Optimal rejection regions for testing multiple binary endpoints in small samples

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Possible aims of a study with multiple endpoints

(1) Show effect in all endpoints
- Reject all H_i
- Endpoints are co-primary

(2) Reject the global null-hypothesis of no effect in any EP
- Need not involve conclusions on individual EPs

(3) Identify efficacious endpoints
- Reject some H_i
- Multiple testing problem

(4) Show non-inferiority for some EP and superiority for at least one EP
- Might be considered as minimal condition for an improved treatment

What is the problem with small sample sizes?

- Asymptotic distibution may not reflect true distributions with sufficient accuracy
- Low precision of nuisance parameter estimates
- Limited model complexity/risk of overfitting
- Low power

Testing binary endpoints

- $H_0 : p_1 = p_2$ or equivalently $H_0 : OR = 1$
  - p_1, p_2 proportions in treatment and placebo group
  - n sample size per group
- Large sample sizes:
  - Asymptotic z-test
  - Under H_0, $Z = \sqrt{n}\frac{\hat{p}_T - \hat{p}_C}{\sqrt{2\hat{p}_0(1-\hat{p}_0)}} \xrightarrow{d} N(0,1)$
  - Uses central limit theorem and consistent estimate for p_0
- Small sample sizes:
  - Under H_0, $n\hat{p}_1, n\hat{p}_2 \sim Binom(n, p_0)$
  - Can find the exact distribution of $\hat{p}_1 - \hat{p}_2$ for given p_0
  - Difficulty: p_0 is unkown
- Conditional test
  - Table row margins are a sufficient statistic for p_0
  - Conditional on the margins the data do not depend on p_0

Fisher's Exact Test

- Null hypothesis H_0 : Odds ratio ≤ 1
- Test statistic T is the number of successes in the treatment group
- Conditional on margins, T has hypergeometric distribution under H_0
- The test may be quite conservative (due to discreteness)

Example Data

	Trt	**Ctrl**	Sum
Succ.	**3**	1	4
Fail	2	4	6
Sum	5	5	

Observed T = 3

Null distribution of T

k	**P(T=k)**
0	0.0238
1	0.2381
2	0.4762
3	0.2381
4	0.0238

Rejection region (k = 4)

p-value = 0.2619 (k = 3, 4)

Multiple Fisher Tests

- Consider two endpoints, A and B
- Four possible outcomes: No success, Success A only, Success B only, Success for A and B
- Global null-hypothesis: $H_0 : OR_A \leq 1$ and $OR_B \leq 1$
- Simple approach: Two marginal Fisher tests at level $\alpha/2$
- May be very conservative

Example Data

	Trt	**Ctrl**	Sum
AB	8	3	9
A	3	2	5
B	2	3	5
Fail	2	7	11
Sum	15	15	

Marginal Table EP A

	Trt	**Ctrl**	Sum
Succ.	**11**	5	16
Fail	4	10	14
Sum	15	15	

T_A = 11

p = 0.033 > 0.0125

Marginal Table EP B

	Trt	**Ctrl**	Sum
Succ.	**10**	6	16
Fail	5	9	14
Sum	15	15	

T_B = 10

p = 0.1362 > 0.0125

Idea: Use conditional joint distribution of the test statistics

	Trt	**Ctrl**	Sum
AB	x_1	y_1	a
A	x_2	y_2	b
B	x_3	y_3	c
Fail	x_4	y_4	d
Sum	n	m	N

- Fixed sample size per group n, m
- $X \sim Mult(n, p_{X_1}, p_{X_2}, p_{X_3}, p_{X_4})$,
- $Y \sim Mult(m, p_{Y_1}, p_{Y_2}, p_{Y_3}, p_{Y_4})$
- X, Y independent.
- $P(X_1 = x_1, X_2 = x_2, X_3 = x_3, X_4 = x_4 |$ $X_1 + Y_1 = a, X_2 + Y_2 = b, X_3 + Y_3 = c, X_4 + Y_4 = d) \propto$ $\propto \prod_{i=1}^{4} \frac{1}{x_i! y_i!} \left(\frac{p_{X_i}}{p_{Y_i}} \right)^{x_i}$
- Use this to find conditional joint distribution of the test statistics $T_A = x_1 + x_2$, $T_B = x_1 + x_3$
- Consider the point null-hypothesis $H_0 : p_{x_i} = p_{y_i}, \forall i = 1, ..., 4$
- Or any alternative specified through $p_{X_i}/p_{Y_i}, i = 1, ..., 4$

Conditional joint distribution under H_0

Joint distribution of T_A and T_B

Probabilities in %, rounded to 1 decimal digit. Entries "0" are small but positive.

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	**0**	**0**	**0.4**	**2.8**	**10.3**	**22.1**	**28.5**	**22.1**	**10.3**	**2.8**	**0.4**	**0**	**0**	**0**	**100**
15										**0**	**0**					**0**
14									**0**	**0**	**0**	**0**				**0**
13								**0**	**0**	**0**	**0**	**0**	**0**			**0**
12							**0**	**0.1**	**0.1**	**0.1**	**0.1**	**0**	**0**	**0**		**0.4**
11						**0**	**0.3**	**0.7**	**0.9**	**0.6**	**0.2**	**0.1**	**0**	**0**	**0**	**2.8**
10					**0**	**0.4**	**1.5**	**2.8**	**3**	**1.8**	**0.6**	**0.1**	**0**	**0**	**0**	**10.3**
9				**0**	**0.3**	**1.5**	**4.1**	**6.4**	**5.8**	**3**	**0.9**	**0.1**	**0**	**0**		**22.1**
8			**0**	**0.1**	**0.7**	**2.8**	**6.4**	**8.4**	**6.4**	**2.8**	**0.7**	**0.1**	**0**			**28.5**
7		**0**	**0**	**0.1**	**0.9**	**3**	**5.8**	**6.4**	**4.1**	**1.5**	**0.3**	**0**				**22.1**
6	**0**	**0**	**0**	**0.1**	**0.6**	**1.8**	**3**	**2.8**	**1.5**	**0.4**	**0**					**10.3**
5	**0**	**0**	**0**	**0.1**	**0.2**	**0.6**	**0.9**	**0.7**	**0.3**	**0**						**2.8**
4		**0**	**0**	**0**	**0.1**	**0.1**	**0.1**	**0.1**	**0**							**0.4**
3			**0**	**0**	**0**	**0**	**0**	**0**								**0**
2				**0**	**0**	**0**	**0**									**0**
1					**0**	**0**										**0**

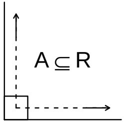
Under alternative of specific success probabilities

Succ. probs. for EP A and B: Treatment 0.7, 0.4, control 0.25, 0.25, correlation between endpoints 0.5

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	**0**	**0**	**0**	**0**	**0**	**0.1**	**0.6**	**3.6**	**13**	**27.4**	**31.8**	**18.6**	**4.6**	**0.3**	**100**
15										**0**	**0**					**0**
14									**0**	**0**	**0**	**0**				**0**
13								**0**	**0**	**0.1**	**0.3**	**0.4**	**0.2**			**0.9**
12							**0**	**0**	**0.1**	**0.6**	**1.7**	**2.4**	**1.5**	**0.3**		**6.8**
11						**0**	**0**	**0**	**0.4**	**2**	**5.2**	**7.2**	**5**	**1.5**	**0.1**	**21.5**
10					**0**	**0**	**0**	**0.1**	**0.9**	**3.6**	**8.4**	**10.6**	**6.9**	**2**	**0.2**	**32.7**
9				**0**	**0**	**0**	**0**	**0.2**	**1.1**	**3.7**	**7.4**	**8**	**4.1**	**0.8**		**25.2**
8			**0**	**0**	**0**	**0**	**0**	**0.1**	**0.7**	**2.2**	**3.5**	**2.8**	**0.9**			**10.3**
7		**0**	**0**	**0**	**0**	**0**	**0**	**0.1**	**0.3**	**0.7**	**0.8**	**0.4**				**2.3**
6	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0.1**	**0.1**	**0.1**					**0.3**
5	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**						**0**
4		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**							**0**
3			**0**	**0**	**0**	**0**	**0**	**0**								**0**
2				**0**	**0**	**0**	**0**									**0**
1					**0**	**0**										**0**

Definition of valid rejection regions

- A valid rejection region $R \in \mathbb{N} \times \mathbb{N}$ must satisfy
  - (i) Under H_0, $P((T_A, T_B) \in R) \leq \alpha$
  - (ii) If $(t_1, t_2) \in R$ then $A = \{(s_1, s_2) \in \mathbb{N} \times \mathbb{N} : s_1 \geq t_1, 2_2 \geq t_2\} \subseteq R$



- Condition (i) ensures level α control.
- Condition (ii) prevents implausible results and ensures larger power for larger effects.
- Reject H_0 if $(T_A, T_B) \in R$

Bonferroni rejection region for the example

Bonferroni rejection region

T_B																
	0	0	0.03	0.43	2.82	10.34	22.15	28.48	22.15	10.34	2.82	0.43	0.03	0	0	100
15										0	0					0
14									0	0	0	0				0
13								0	0.01	0.01	0.01	0	0			0.03
12							0.02	0.08	0.14	0.12	0.05	0.01	0	0		0.43
11						0.04	0.26	0.69	0.9	0.63	0.24	0.05	0.01	0	0	2.82
10					0.04	0.38	1.46	2.83	3.03	1.84	0.63	0.12	0.01	0	0	10.34
9				0.02	0.26	1.46	4.11	6.43	5.79	3.03	0.9	0.14	0.01	0		22.15
8			0	0.08	0.69	2.83	6.43	8.41	6.43	2.83	0.69	0.08	0			28.48
7		0	0.01	0.14	0.9	3.03	5.79	6.43	4.11	1.46	0.26	0.02				22.15
6	0	0	0.01	0.12	0.63	1.84	3.03	2.83	1.46	0.38	0.04					10.34
5	0	0	0.01	0.05	0.24	0.63	0.9	0.69	0.26	0.04						2.82
4		0	0	0.01	0.05	0.12	0.14	0.08	0.02							0.43
3			0	0	0.01	0.01	0.01	0								0.03
2				0	0	0	0									0
1					0	0										0
T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	

Alpha = 2.5 %; Level = 0.909 %; Area = 34

Aims: Use joint distribution to ...

- Find rejection region with maximal power for a specified alternative
- Also find rejection regions with
  - Maximal alpha exploitation
  - Maximal area
- Study special cases of exact p-value combination tests
  - $C = min(p_1, p_2)$
  - $C = p_1 * p_2$
  - Reject H_0 if c greater or equal the α quantile of the exact conditional null-distribution of C.
- Calculate power for Bonferroni related tests
  - Bonferroni
  - Tarone test: Test at level α/m. m is the number of tests that can become significant at level α/m. Choose m as large as possible. May add unused alpha to some individual tests.

Optimal rejection regions

An optimal rejection region R can be found as solution of

- $P((T_A, T_B) \in R) \rightarrow max$, under a specified alternative (maximal power)
- subject to conditions (i) and (ii)

Similarly we can optimize either

- $P((T_A, T_B) \in R) \rightarrow max$, under H_0 (maximal α)

or

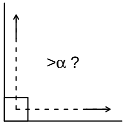
- $|R| \rightarrow max$ (maximal area)

This is a binary optimization problem, since each point (t_1, t_2) is either element of R or not element of R.

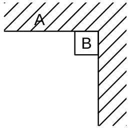
Optimization preprocessing

Size of search space is of order 2^n, preprocessing useful

1. Exclude points $(t_1, t_2) : P\{(s_1, s_2) : s_1 \geq t_1, s_2 \geq t_2\} > \alpha$



2. For all points $B = (t_1, t_2)$ get largest region A meeting condition (ii) without that point



If $P(A) + P(B) \leq \alpha$, $B \in R$ for sure

Preprocessing result example

Preprocessing

Excluded: Black, Remaining search space: Red, Included: Green

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0	0.4	2.8	10.3	22.1	28.5	22.1	10.3	2.8	0.4	0	0	0	100
15										0	0					0
14									0	0	0	0				0
13								0	0	0	0	0	0			0
12							0	0.1	0.1	0.1	0.1	0	0	0		0.4
11						0	0.3	0.7	0.9	0.6	0.2	0.1	0	0	0	2.8
10					0	0.4	1.5	2.8	3	1.8	0.6	0.1	0	0	0	10.3
9				0	0.3	1.5	4.1	6.4	5.8	3	0.9	0.1	0	0		22.1
8			0	0.1	0.7	2.8	6.4	8.4	6.4	2.8	0.7	0.1	0			28.5
7		0	0	0.1	0.9	3	5.8	6.4	4.1	1.5	0.3	0				22.1
6	0	0	0	0.1	0.6	1.8	3	2.8	1.5	0.4	0					10.3
5	0	0	0	0.1	0.2	0.6	0.9	0.7	0.3	0						2.8
4		0	0	0	0.1	0.1	0.1	0.1	0							0.4
3			0	0	0	0	0	0								0
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 3.591 %; Area = 16

Actual opimization as binary linear program

- Solution is of type $x = (0, 1, 0, \dots)$
- Objective function can be power, alpha, area
- γ_i contribution of element x_i to the objective function
- Find R, such that $\gamma^T x \rightarrow max$, s.t. conditions (i) and (ii)
- Condition (ii) imposes $x_i \leq x_j$ for certain pairs i, j
- Constraint matrix for linear program:

$$\begin{pmatrix} 1 & 1 & 1 & 1 & \dots & 1 \\ 1 & -1 & 0 & 0 & \dots & 0 \\ 1 & 0 & -1 & 0 & \dots & 0 \\ 0 & 1 & 0 & -1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix} x \leq \begin{pmatrix} \alpha \\ 0 \\ 0 \\ 0 \\ \vdots \end{pmatrix}$$

- Use LP solver (branch and bound algorithm)

Result: Maximal power rejection region

Region with maximal power for specified alternative

Succ. probs. EP A, EP B: Trtm. 0.7, 0.4, Contr. 0.25, 0.25. Common correlation 0.5

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	**0**	**0.03**	**0.43**	**2.82**	**10.34**	**22.15**	**28.48**	**22.15**	**10.34**	**2.82**	**0.43**	**0.03**	**0**	**0**	**100**
15										0	0					0
14									0	0	0	0				0
13								0	0.01	0.01	0.01	0	0			0.03
12							0.02	0.08	0.14	0.12	0.05	0.01	0	0		0.43
11						0.04	0.26	0.69	0.9	0.63	0.24	0.05	0.01	0	0	2.82
10					0.04	0.38	1.46	2.83	3.03	1.84	0.63	0.12	0.01	0	0	10.34
9				0.02	0.26	1.46	4.11	6.43	5.79	3.03	0.9	0.14	0.01	0		22.15
8			0	0.08	0.69	2.83	6.43	8.41	6.43	2.83	0.69	0.08	0			28.48
7		0	0.01	0.14	0.9	3.03	5.79	6.43	4.11	1.46	0.26	0.02				22.15
6	0	0	0.01	0.12	0.63	1.84	3.03	2.83	1.46	0.38	0.04					10.34
5	0	0	0.01	0.05	0.24	0.63	0.9	0.69	0.26	0.04						2.82
4		0	0	0.01	0.05	0.12	0.14	0.08	0.02							0.43
3			0	0	0.01	0.01	0.01	0								0.03
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 2.442 %; Area = 34

Maximal alpha rejection region

Rejection region with maximal alpha (red area)

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0.03	0.43	2.82	10.34	22.15	28.48	22.15	10.34	2.82	0.43	0.03	0	0	100
15										0	0					0
14									0	0	0	0				0
13								0	0.01	0.01	0.01	0	0			0.03
12							0.02	0.08	0.14	0.12	0.05	0.01	0	0		0.43
11						0.04	0.26	0.69	0.9	0.63	0.24	0.05	0.01	0	0	2.82
10					0.04	0.38	1.46	2.83	3.03	1.84	0.63	0.12	0.01	0	0	10.34
9				0.02	0.26	1.46	4.11	6.43	5.79	3.03	0.9	0.14	0.01	0		22.15
8			0	0.08	0.69	2.83	6.43	8.41	6.43	2.83	0.69	0.08	0			28.48
7		0	0.01	0.14	0.9	3.03	5.79	6.43	4.11	1.46	0.26	0.02				22.15
6	0	0	0.01	0.12	0.63	1.84	3.03	2.83	1.46	0.38	0.04					10.34
5	0	0	0.01	0.05	0.24	0.63	0.9	0.69	0.26	0.04						2.82
4		0	0	0.01	0.05	0.12	0.14	0.08	0.02							0.43
3			0	0	0.01	0.01	0.01	0								0.03
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 2.486 %; Area = 33

Maximal area rejection region

Region with maximal area

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0.03	0.43	2.82	10.34	22.15	28.48	22.15	10.34	2.82	0.43	0.03	0	0	100
15										0	0					0
14									0	0	0	0				0
13								0	0.01	0.01	0.01	0	0			0.03
12							0.02	0.08	0.14	0.12	0.05	0.01	0	0		0.43
11						0.04	0.26	0.69	0.9	0.63	0.24	0.05	0.01	0	0	2.82
10					0.04	0.38	1.46	2.83	3.03	1.84	0.63	0.12	0.01	0	0	10.34
9				0.02	0.26	1.46	4.11	6.43	5.79	3.03	0.9	0.14	0.01	0		22.15
8			0	0.08	0.69	2.83	6.43	8.41	6.43	2.83	0.69	0.08	0			28.48
7		0	0.01	0.14	0.9	3.03	5.79	6.43	4.11	1.46	0.26	0.02				22.15
6	0	0	0.01	0.12	0.63	1.84	3.03	2.83	1.46	0.38	0.04					10.34
5	0	0	0.01	0.05	0.24	0.63	0.9	0.69	0.26	0.04						2.82
4		0	0	0.01	0.05	0.12	0.14	0.08	0.02							0.43
3			0	0	0.01	0.01	0.01	0								0.03
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 2.42 %; Area = 37

$C = p_1 p_2$ rejection region

C=p_1p_2 rejection region

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0.03	0.43	2.82	10.34	22.15	28.48	22.15	10.34	2.82	0.43	0.03	0	0	100
15										0	0					0
14									0	0	0	0				0
13								0	0.01	0.01	0.01	0	0			0.03
12							0.02	0.08	0.14	0.12	0.05	0.01	0	0		0.43
11						0.04	0.26	0.69	0.9	0.63	0.24	0.05	0.01	0	0	2.82
10					0.04	0.38	1.46	2.83	3.03	1.84	0.63	0.12	0.01	0	0	10.34
9				0.02	0.26	1.46	4.11	6.43	5.79	3.03	0.9	0.14	0.01	0		22.15
8			0	0.08	0.69	2.83	6.43	8.41	6.43	2.83	0.69	0.08	0			28.48
7		0	0.01	0.14	0.9	3.03	5.79	6.43	4.11	1.46	0.26	0.02				22.15
6	0	0	0.01	0.12	0.63	1.84	3.03	2.83	1.46	0.38	0.04					10.34
5	0	0	0.01	0.05	0.24	0.63	0.9	0.69	0.26	0.04						2.82
4		0	0	0.01	0.05	0.12	0.14	0.08	0.02							0.43
3			0	0	0.01	0.01	0.01	0								0.03
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 2.42 %; Area = 37

$C = min(p_1, p_2)$ rejection region

C=min(p_1,p_2) rejection region

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0.03	0.43	2.82	10.34	22.15	28.48	22.15	10.34	2.82	0.43	0.03	0	0	100
15										0	0					0
14									0	0	0	0				0
13								0	0.01	0.01	0.01	0	0			0.03
12							0.02	0.08	0.14	0.12	0.05	0.01	0	0		0.43
11						0.04	0.26	0.69	0.9	0.63	0.24	0.05	0.01	0	0	2.82
10					0.04	0.38	1.46	2.83	3.03	1.84	0.63	0.12	0.01	0	0	10.34
9				0.02	0.26	1.46	4.11	6.43	5.79	3.03	0.9	0.14	0.01	0		22.15
8			0	0.08	0.69	2.83	6.43	8.41	6.43	2.83	0.69	0.08	0			28.48
7		0	0.01	0.14	0.9	3.03	5.79	6.43	4.11	1.46	0.26	0.02				22.15
6	0	0	0.01	0.12	0.63	1.84	3.03	2.83	1.46	0.38	0.04					10.34
5	0	0	0.01	0.05	0.24	0.63	0.9	0.69	0.26	0.04						2.82
4		0	0	0.01	0.05	0.12	0.14	0.08	0.02							0.43
3			0	0	0.01	0.01	0.01	0								0.03
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 0.909 %; Area = 34

Tarone rejection region

Tarone rejection region

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0.03	0.43	2.82	10.34	22.15	28.48	22.15	10.34	2.82	0.43	0.03	0	0	100
15										0	0					0
14									0	0	0	0				0
13								0	0.01	0.01	0.01	0	0			0.03
12							0.02	0.08	0.14	0.12	0.05	0.01	0	0		0.43
11						0.04	0.26	0.69	0.9	0.63	0.24	0.05	0.01	0	0	2.82
10					0.04	0.38	1.46	2.83	3.03	1.84	0.63	0.12	0.01	0	0	10.34
9				0.02	0.26	1.46	4.11	6.43	5.79	3.03	0.9	0.14	0.01	0		22.15
8			0	0.08	0.69	2.83	6.43	8.41	6.43	2.83	0.69	0.08	0			28.48
7		0	0.01	0.14	0.9	3.03	5.79	6.43	4.11	1.46	0.26	0.02				22.15
6	0	0	0.01	0.12	0.63	1.84	3.03	2.83	1.46	0.38	0.04					10.34
5	0	0	0.01	0.05	0.24	0.63	0.9	0.69	0.26	0.04						2.82
4		0	0	0.01	0.05	0.12	0.14	0.08	0.02							0.43
3			0	0	0.01	0.01	0.01	0								0.03
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 0.909 %; Area = 34

Power of Bonferroni rejection region = 58%

Power for Bonferroni region

Succ. probs. EP A, EP B: Trtm. 0.7, 0.4, Contr. 0.25, 0.25. Common correlation 0.5

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0	0	0	0	0.06	0.59	3.59	13.03	27.41	31.79	18.57	4.61	0.33	100
15										0	0					0
14									0	0.01	0.02	0.02				0.05
13								0	0.01	0.1	0.29	0.37	0.16			0.93
12							0	0.01	0.11	0.61	1.72	2.42	1.55	0.34		6.76
11						0	0	0.05	0.43	2.01	5.19	7.18	4.98	1.51	0.14	21.5
10					0	0	0.01	0.12	0.89	3.63	8.38	10.62	6.89	1.98	0.19	32.71
9				0	0	0	0.02	0.18	1.06	3.71	7.4	7.96	4.12	0.79		25.23
8			0	0	0	0	0.02	0.14	0.73	2.16	3.51	2.84	0.88			10.27
7		0	0	0	0	0	0.01	0.07	0.29	0.69	0.82	0.38				2.26
6	0	0	0	0	0	0	0	0.02	0.06	0.11	0.07					0.27
5	0	0	0	0	0	0	0	0	0.01	0.01						0.02
4		0	0	0	0	0	0	0	0							0
3			0	0	0	0	0	0								0
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 58.191 %; Area = 34

Power for maximal alpha region = 63%

Power for maximal alpha region

Succ. probs. EP A, EP B: Trtm. 0.7, 0.4, Contr. 0.25, 0.25. Common correlation 0.5

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0	0	0	0	0.06	0.59	3.59	13.03	27.41	31.79	18.57	4.61	0.33	100
15										0	0					0
14									0	0.01	0.02	0.02				0.05
13								0	0.01	0.1	0.29	0.37	0.16			0.93
12							0	0.01	0.11	0.61	1.72	2.42	1.55	0.34		6.76
11						0	0	0.05	0.43	2.01	5.19	7.18	4.98	1.51	0.14	21.5
10					0	0	0.01	0.12	0.89	3.63	8.38	10.62	6.89	1.98	0.19	32.71
9				0	0	0	0.02	0.18	1.06	3.71	7.4	7.96	4.12	0.79		25.23
8			0	0	0	0	0.02	0.14	0.73	2.16	3.51	2.84	0.88			10.27
7		0	0	0	0	0	0.01	0.07	0.29	0.69	0.82	0.38				2.26
6	0	0	0	0	0	0	0	0.02	0.06	0.11	0.07					0.27
5	0	0	0	0	0	0	0	0	0.01	0.01						0.02
4		0	0	0	0	0	0	0	0							0
3			0	0	0	0	0	0								0
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 62.597 %; Area = 33

Power for maximal area region = 73%

Power for maximal area region

Succ. probs. EP A, EP B: Trtm. 0.7, 0.4, Contr. 0.25, 0.25. Common correlation 0.5

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	**0**	**0**	**0**	**0**	**0**	**0.06**	**0.59**	**3.59**	**13.03**	**27.41**	**31.79**	**18.57**	**4.61**	**0.33**	**100**
15										0	0					0
14									0	0.01	0.02	0.02				0.05
13								0	0.01	0.1	0.29	0.37	0.16			0.93
12							0	0.01	0.11	0.61	1.72	2.42	1.55	0.34		6.76
11						0	0	0.05	0.43	2.01	5.19	7.18	4.98	1.51	0.14	21.5
10					0	0	0.01	0.12	0.89	3.63	8.38	10.62	6.89	1.98	0.19	32.71
9				0	0	0	0.02	0.18	1.06	3.71	7.4	7.96	4.12	0.79		25.23
8			0	0	0	0	0.02	0.14	0.73	2.16	3.51	2.84	0.88			10.27
7		0	0	0	0	0	0.01	0.07	0.29	0.69	0.82	0.38				2.26
6	0	0	0	0	0	0	0	0.02	0.06	0.11	0.07					0.27
5	0	0	0	0	0	0	0	0	0.01	0.01						0.02
4		0	0	0	0	0	0	0	0							0
3			0	0	0	0	0	0								0
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 73.775 %; Area = 37

Maximal power = 79%

Power for maximal power region

Succ. probs. EP A, EP B: Trtm. 0.7, 0.4, Contr. 0.25, 0.25. Common correlation 0.5

T_B \ T_A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
	0	0	0	0	0	0	0.06	0.59	3.59	13.03	27.41	31.79	18.57	4.61	0.33	100
15										0	0					0
14									0	0.01	0.02	0.02				0.05
13								0	0.01	0.1	0.29	0.37	0.16			0.93
12							0	0.01	0.11	0.61	1.72	2.42	1.55	0.34		6.76
11						0	0	0.05	0.43	2.01	5.19	7.18	4.98	1.51	0.14	21.5
10					0	0	0.01	0.12	0.89	3.63	8.38	10.62	6.89	1.98	0.19	32.71
9				0	0	0	0.02	0.18	1.06	3.71	7.4	7.96	4.12	0.79		25.23
8			0	0	0	0	0.02	0.14	0.73	2.16	3.51	2.84	0.88			10.27
7		0	0	0	0	0	0.01	0.07	0.29	0.69	0.82	0.38				2.26
6	0	0	0	0	0	0	0	0.02	0.06	0.11	0.07					0.27
5	0	0	0	0	0	0	0	0	0.01	0.01						0.02
4		0	0	0	0	0	0	0	0							0
3			0	0	0	0	0	0								0
2				0	0	0	0									0
1					0	0										0

Alpha = 2.5 %; Level = 79.046 %; Area = 34

Exact power (%) for different alternatives

n=15 per group

	Succ. prob. treat.		Optimize			Combine p-values		Bonferroni-related		Simplifications		
Corr.	**EP A**	**EP B**	**Power**	**Area**	**Alpha**	**p1*p2**	**minP**	**Tarone**	**Bonf.**	**Collapse**	**Only A**	**Only B**
0	0.25	0.25	2.4	2.2	2.4	2.0	1.3	1.4	0.8	0.8	0.9	0.9
0	0.75	0.25	76.8	67.8	52.5	69.9	67.5	67.7	55.0	39.7	67.5	0.9
0	0.75	0.5	87.8	81.6	77.0	84.0	70.8	72.1	59.8	58.3	67.5	15.7
0	0.75	0.75	97.7	95.7	95.4	96.8	87.4	88.2	79.6	79.6	67.5	67.5
0.5	0.25	0.25	2.4	2.2	2.4	2.0	1.3	1.4	0.8	0.8	0.9	0.9
0.5	0.75	0.25	75.0	66.6	51.3	67.4	67.5	67.7	55.0	39.0	67.5	0.9
0.5	0.75	0.5	85.3	79.1	74.6	81.1	70.3	71.3	59.1	54.8	67.5	15.7
0.5	0.75	0.75	96.4	94.3	94.2	95.5	86.5	86.9	78.1	76.7	67.5	67.5

Success probability control = 0.25 for both EP

- For these scenarios, maximal power test is 0.9 to 7.3 % points better than next best test
- Maximizing alpha is not sole the key to good power
- $C = p_1 p_2$ and maximal area test similar
- Tarone and minP very similar
- Simplifications have least power

Non-inferiority - superiority tests

What if we want to show non-inferiority for both EP and superiority in the sense of the global null-hypothesis for some EP?

- Find optimal rejection region for global superiority test within the rejection region of the non-inferiority test.
- Problem: At the moment the optimal test is designed for a point null-hypothesis
- Type-I-error rate control for more general null-hypothesis $H_0 : OR_1 \leq 1$ AND $OR_2 \leq 1$?

Discussion

- Exact conditional tests useful for small sample inference
- Example of two binary endpoints
- Can get optimal rejection region for a specified alternative
  - Generalizations to more endpoints no problem in principle
  - But optimization run-time may be non-polynomial
- Level of significance close to nominal level
  - Not sole determinant of good power
  - Behavior under other than point null-hypothesis remains to be analyzed
- Exact joint distribution can be used to study other tests
  - Maxmial power test can be used as benchmark
- Further restictions can be implemented, e.g. as suggested for non-inferiority - superiority test

Literature

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Agresti, A. (2002). Categorical data analysis. A John Wiley and Sons, Inc. Publication, Hoboken, New Jersey, USA.

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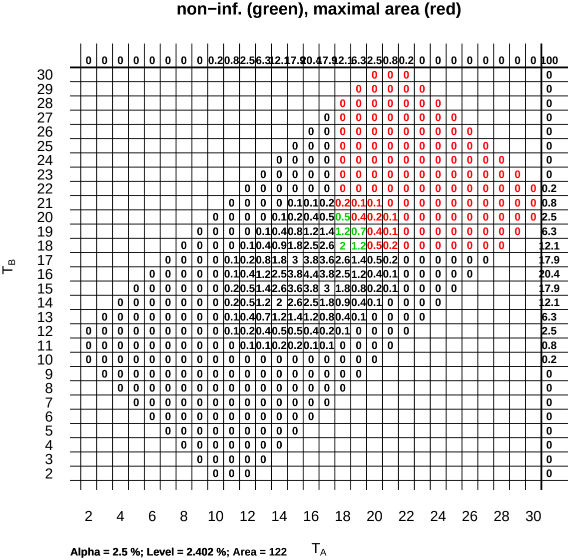
Exact power (%) for different alternatives

n=10 per group

	Succ. prob. treat.		Optimize			Combine p-values		Bonferroni-related		Simplifications		
Corr.	**EP A**	**EP B**	**Power**	**Area**	**Alpha**	**p1*p2**	**minP**	**Tarone**	**Bonf.**	**Collapse**	**Only A**	**Only B**
0	0.25	0.25	2.0	1.9	2.0	1.7	0.9	0.9	0.4	0.6	0.5	0.5
0	0.75	0.25	54.1	47.2	41.3	48.4	42.2	42.3	41.6	22.0	42.1	0.5
0	0.75	0.5	69.1	62.0	61.0	63.0	46.6	46.6	45.7	34.2	42.1	8.6
0	0.75	0.75	87.5	83.4	84.1	84.5	66.3	66.3	65.8	51.6	42.1	42.1
0.5	0.25	0.25	2.0	1.9	2.0	1.7	0.9	0.9	0.4	0.6	0.5	0.5
0.5	0.75	0.25	51.8	45.6	39.4	46.8	42.2	42.3	41.6	21.7	42.1	0.5
0.5	0.75	0.5	65.5	59.1	57.8	59.7	46.1	46.1	45.1	31.9	42.1	8.6
0.5	0.75	0.75	84.1	80.7	81.4	81.2	64.8	64.8	64.3	49.4	42.1	42.1

Non-inferiority - superiority maximal area



Non-inferiority - superiority $C = p_1 p_2$