Multiple Comparisons for Correlated Outcomes in Clinical Trials

When multiple outcomes are obtained from clinical trials, the most common approach in the medical literature is to analyze each outcome separately, presenting multiple p-values and an overall subject conclusion. However, it is well known that the excessive use of multiple significance tests can substantially increase the chance of false positive findings (type I error). On possible solution is to control a predefined error rate such as Family Error Rate (FER) in the strong sense, i.e., the probability of rejecting falsely at least one true individual null hypothesis, irrespective of which and how many of the individual null hypotheses are in fact true. Bonferroni method controls FER in the strong sense and is easy to apply. However when outcomes are correlated, Bonferroni method appears to be too conservative. We consider k normally distributed outcomes, each with known variance, for which all possible pairs have known correlation ρ_{ij} within each of two treatment groups. Then for given α, k, and ρ_{ij} we can derive numerically that the "nominal" value α* for individual tests which controls for FER at α under the null hypothesis. The MATLAB function multicompare calculates α* and the corresponding critical values as outputs. These can easily be extended to g (g >2) treatment groups and analysis of covariance for g (g ≥ 2) groups.

Example

In a study, investigators wish to determine the difference of physical performance between two groups of older overweight women. Three measures are taken as primary outcomes: muscle quality, muscle power and SPPB. Based on some preliminary data, the outcomes appear to be roughly normally distributed and the correlation matrix is obtained as following:

$$\begin{bmatrix} 1 & 0.53 & -0.05 \\ 0.53 & 1 & 0.43 \\ -0.05 & -0.43 & 1 \end{bmatrix}$$

We wish to perform two-sided t-test controlling for FER at 0.05.

Data Structure

The required inputs for the multicompare function are: correlation matrix (k by k matrix), desired FER or overall α (scalar), test type (two-sided or one-sided) (scalar: 1 or 2).

Output

Exact "nominal" significance level α* and corresponding critical value.

Example Codes:

```
% Specify Correlation Matrix;
sigma = [1  0.53 -0.05
         0.53  1  0.43
        -0.05  0.43  1];
% Specify FER, here 0.05;
% Specify test type, here 2-sided;
% Calculate alpha* and corresponding critical value;
[alpha cvalue] = multicompare(sigma,0.05,2)
```

Example output:

```
alpha =

    0.0181

cvalue =

    2.3638
```

So the “nominal” significance level for individual test is 0.0181 for the above test and the corresponding critical value is 2.3638. Note that, Bonferroni procedure will give each of the three individual tests significance level of 0.0167 by assuming independence.

Look-up Tables

However, when does Bonferroni method become conservative for correlated outcomes? It is difficult to take arbitrary correlation structure and distribution of the data. We consider k normal outcomes with equal correlations ρ among all outcomes for two group comparisons. Assume all the outcomes are standardized (mean = 0 and variance = 1) and the correlations among outcomes are known. For one-sided test, we set FER = 0.05 and 0.025. This reproduces Pocock’s table with more ρs added.

Reference

Pocock SJ, Geller NL and Tsiatis AA (1987) The analysis of multiple endpoints in clinical trials. Biometrics 43: 487-498.

Article Link: http://www.jstor.org/stable/2531989?origin=crossref

Table 1 Bonferroni correction and the exact “nominal” significance level α*, with corresponding critical value to control FER at α = 0.05, for k = 2, 3, … , 10 normally distributed outcomes and equal correlations ρ within each of two treatment groups.

K		Bonferroni	ρ (\rho)													
			0	0.1	0.3	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	0.99
2	Critical value	1.9600	1.9545	1.9508	1.9385	1.9163	1.9086	1.8997	1.8893	1.8773	1.8631	1.8460	1.8249	1.7976	1.7581	1.6987
	α*	0.0250	0.0253	0.0255	0.0263	0.0277	0.0282	0.0287	0.0294	0.0302	0.0312	0.0324	0.0340	0.0361	0.0394	0.0447
3	Critical value	2.1280	2.1212	2.1158	2.0969	2.0621	2.0499	2.0358	2.0195	2.0005	1.9783	1.9516	1.9189	1.8767	1.8162	1.7259
	α*	0.0167	0.0170	0.0172	0.0180	0.0196	0.0202	0.0209	0.0217	0.0227	0.0239	0.0255	0.0275	0.0303	0.0347	0.0422
4	Critical value	2.2414	2.2340	2.2276	2.2041	2.1602	2.1446	2.1271	2.1069	2.0831	2.0555	2.0218	1.9809	1.9285	1.8541	1.7435
	α*	0.0125	0.0127	0.0130	0.0138	0.0154	0.0160	0.0167	0.0176	0.0186	0.0199	0.0216	0.0238	0.0269	0.0319	0.0406
5	Critical value	2.3263	2.3187	2.3116	2.2847	2.2337	2.2161	2.1953	2.1715	2.1446	2.1122	2.0740	2.0271	1.9677	1.8821	1.7565
	α*	0.0100	0.0102	0.0104	0.0112	0.0128	0.0133	0.0141	0.0149	0.0160	0.0173	0.0190	0.0213	0.0246	0.0299	0.0395
6	Critical value	2.3940	2.3862	2.3785	2.3491	2.2924	2.2723	2.2494	2.2232	2.1926	2.1573	2.1151	2.0632	1.9980	1.9042	1.7664
	α*	0.0083	0.0085	0.0087	0.0094	0.0109	0.0115	0.0122	0.0131	0.0142	0.0155	0.0172	0.0195	0.0229	0.0284	0.0387
7	Critical value	2.4500	2.4421	2.4337	2.4019	2.3402	2.3190	2.2938	2.2661	2.2326	2.1943	2.1490	2.0932	2.0223	1.9222	1.7749
	α*	0.0071	0.0073	0.0075	0.0082	0.0096	0.0102	0.0109	0.0117	0.0128	0.0141	0.0158	0.0182	0.0216	0.0273	0.0380
8	Critical value	2.4977	2.4898	2.4813	2.4475	2.3814	2.3586	2.3315	2.3013	2.2669	2.2260	2.1773	2.1186	2.0435	1.9379	1.7819
	α*	0.0063	0.0064	0.0065	0.0072	0.0086	0.0092	0.0099	0.0107	0.0117	0.0130	0.0147	0.0171	0.0205	0.0263	0.0374
9	Critical value	2.5392	2.5312	2.5224	2.4866	2.4170	2.3928	2.3647	2.3326	2.2962	2.2531	2.2021	2.1409	2.0615	1.9505	1.7883
	α*	0.0056	0.0057	0.0058	0.0064	0.0078	0.0084	0.0090	0.0098	0.0108	0.0121	0.0138	0.0161	0.0196	0.0256	0.0369
10	Critical value	2.5758	2.5679	2.5583	2.5213	2.4482	2.4228	2.3938	2.3602	2.3220	2.2773	2.2238	2.1596	2.0776	1.9620	1.7932
	α*	0.0050	0.0051	0.0053	0.0058	0.0072	0.0077	0.0083	0.0091	0.0101	0.0114	0.0131	0.0154	0.0189	0.0249	0.0365

Table 2 Bonferroni correction and the exact "nominal" significance level α*, with corresponding critical value to control FER at α = 0.025, for k = 2, 3, … , 10 normally distributed outcomes and equal correlations ρ within each of two treatment groups.

K		Bonferroni	ρ												
			0	0.1	0.3	0.5	0.55	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.95	0.99
2	Critical value	2.2414	2.2390	2.2368	2.2287	2.2121	2.2060	2.1987	2.1901	2.1799	2.1676	2.1524	2.1334	2.1081	2.0709	2.0133
	α*	0.0125	0.0126	0.0126	0.0129	0.0135	0.0137	0.0139	0.0143	0.0146	0.0151	0.0157	0.0164	0.0175	0.0192	0.0220
3	Critical value	2.3940	2.3909	2.3878	2.3753	2.3490	2.3391	2.3276	2.3139	2.2976	2.2781	2.2543	2.2245	2.1853	2.1280	2.0403
	α*	0.0083	0.0084	0.0085	0.0088	0.0094	0.0097	0.0100	0.0103	0.0108	0.0114	0.0121	0.0131	0.0144	0.0167	0.0207
4	Critical value	2.4977	2.4943	2.4907	2.4752	2.4417	2.4290	2.4148	2.3972	2.3764	2.3521	2.3220	2.2854	2.2365	2.1650	2.0573
	α*	0.0063	0.0063	0.0064	0.0067	0.0073	0.0076	0.0079	0.0083	0.0087	0.0093	0.0101	0.0111	0.0127	0.0152	0.0198
5	Critical value	2.5758	2.5723	2.5684	2.5500	2.5111	2.4974	2.4804	2.4593	2.4364	2.4073	2.3727	2.3299	2.2745	2.1933	2.0704
	α*	0.0050	0.0051	0.0051	0.0054	0.0060	0.0063	0.0066	0.0070	0.0074	0.0080	0.0088	0.0099	0.0115	0.0141	0.0192
6	Critical value	2.6383	2.6347	2.6302	2.6103	2.5673	2.5510	2.5317	2.5092	2.4826	2.4511	2.4128	2.3658	2.3047	2.2145	2.0809
	α*	0.0042	0.0042	0.0043	0.0045	0.0051	0.0054	0.0057	0.0061	0.0065	0.0071	0.0079	0.0090	0.0106	0.0134	0.0187
7	Critical value	2.6901	2.6865	2.6818	2.6608	2.6133	2.5956	2.5744	2.5507	2.5225	2.4873	2.4459	2.3954	2.3286	2.2332	2.0893
	α*	0.0036	0.0036	0.0037	0.0039	0.0045	0.0047	0.0050	0.0054	0.0058	0.0064	0.0072	0.0083	0.0099	0.0128	0.0183
8	Critical value	2.7344	2.7307	2.7258	2.7033	2.6513	2.6337	2.6114	2.5848	2.5538	2.5178	2.4738	2.4195	2.3494	2.2486	2.0957
	α*	0.0031	0.0032	0.0032	0.0034	0.0040	0.0042	0.0045	0.0049	0.0053	0.0059	0.0067	0.0078	0.0094	0.0123	0.0181
9	Critical value	2.7729	2.7693	2.7644	2.7398	2.6862	2.6659	2.6428	2.6150	2.5824	2.5437	2.4978	2.4407	2.3664	2.2608	2.1027
	α*	0.0028	0.0028	0.0029	0.0031	0.0036	0.0038	0.0041	0.0045	0.0049	0.0055	0.0062	0.0073	0.0090	0.0119	0.0177
10	Critical value	2.8070	2.8034	2.7981	2.7735	2.7154	2.6952	2.6705	2.6424	2.6079	2.5680	2.5192	2.4591	2.3837	2.2718	2.1083
	α*	0.0025	0.0025	0.0026	0.0028	0.0033	0.0035	0.0038	0.0041	0.0046	0.0051	0.0059	0.0070	0.0086	0.0115	0.0175