Simultaneous inference of correlated marginal tests using intersection-union or union-intersection test principle

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Abstract

Two main approaches in simultaneous inference are intersection-union tests and union-intersection tests. For intersection-union hypotheses, the classical IUT based on marginal p-values and the all-in-alternative UIT are compared. Depending on correlation, number of marginal tests and patterns of the alternative the inherent power loss of the aiaUIT seems to be acceptable, considering its advantage, namely the availability of simple-to-interpret simultaneous confidence interval.

1 Introduction

Although the majority of multiple testing is based on the union-intersection test (UIT) principle, some applications exist which use the complementary intersection-union test (IUT) principle, e.g. the analysis of multiple correlated primary endpoints [6], [8], or fixed dose combinations [12].

Simultaneous inference considering $j$ elementary hypotheses of interest with related correlated test statistics $T_j$ and compatible p-value $p_j$ based therefore on two main principles (under some conditions): intersection-union tests (IUT) and union-intersection tests (UIT).

Their global $H_0$'s are:

UIT: $H_0 = \bigcap_{j \in J} H_{0,j}$ and $T_{max} = \max(T_1, ..., T_j, ..., T_J)$ or $p_{min} = \min(p_1, ..., p_j, ..., p_J)$

IUT: $H_0 = \bigcup_{j \in J} H_{0,j}$ and $T_{min} = \min(T_1, ..., T_j, ..., T_J)$ or $p_{max} = \max(p_1, ..., p_j, ..., p_J)$

Assuming uncorrelated tests, their behavior under $H_0$ seems to be related:

UIT: $H_A : \exists (\text{any } j) p_j < \alpha/J$

IUT: $H_A : \forall (p_1, ..., p_j, ..., p_J) < \alpha$

whereas considering the more general and more realistic case of correlated tests:

UIT: $H_A : \exists (\text{any } j) T_j < t_{J, df, R, \alpha}$

IUT: $H_A : \forall (p_1, ..., p_j, ..., p_J) < \alpha$

I.e. the IUT can be used for the correlated case as well. A related solution based on the multivariate $t$ distribution exists [3], but the consequence is that the joint test rejects global $H_0$ even when some elementary tests remain still under $H_0$ which seem to be hard to interpret in most applications.

The second argument is that UIT based on $\alpha$-adjustment, where IUT does not. The second argument is a bit superficial, since both tests are conservative as dimension $J$ increases, the IUT just about the 'and... and' condition. An essential difference is that due to the Gabriel theorem [2] the UIT makes individual decisions available, the IUT however provide only the global decision. This is an essential disadvantage for some applications. An alternative is the use of the all-in-the-alternative UITs (aiaUIT) instead of classical IUT tests discussed in the following. Related is the concept of all-pairs power [9] or complete...
power UIT approach \[13\] \[^7\].

Looking more closely at \(H_0\) formulation, the UIT under \(H_1\) is formulated for all possible patterns of individual decisions: from exactly one test under \(H^A\) to exactly all tests or all partitions in between. Assuming \(J = 4\) for example, the following elementary outcomes are possible under UIT’s \(H_A^J\):

\[
\begin{align*}
H^J_1, H^J_2, H^J_3, H^J_4 \\
H_{10}, H_{20}, H_{30}, H_{40} \\
H_{10}, H_{20}, H_{30}, H_{40} \\
H_{A1}, H_{A2}, H_{A3}, H_{A4} \\
H_{A1}, H_{A2}, H_{A3}, H_{A4} \\
H_{A1}, H_{A2}, H_{A3}, H_{A4} \\
H_{A1}, H_{A2}, H_{A3}, H_{A4} \\
H_{A1}, H_{A2}, H_{A3}, H_{A4} \\
H_{A1}, H_{A2}, H_{A3}, H_{A4}
\end{align*}
\]

The last set reveals the same conclusion like an IUT, but it provides individual outcomes, such as simultaneous confidence interval or adjusted p-values. This property can be used applying an UIT in an IUT hypothesis scenario. The question is, how high is the inherent power loss? This is answered by a simulation study with different scenarios in the following section considering the correlation between the test as a primary criterion, the pattern of individual \(H^A_{j+}\) and the number and kind of tests.

## 2 Simulation studies

The primary interest is the comparison of classical IUT with the aitaiUT under \(H_0\) and patterns of \(H^A\) by means of the power ratio (RR) (as a rough empirical measure of a Pitman efficiency)

### 2.1 IUT for two correlated primary endpoints

In phase II-III randomized clinical trials sometime two primary endpoints occur. The benefit of the drug is demonstrated, exactly if both endpoints are under the alternative, using the classic IUT as \(max(p_j)\)-test.

| \(n_1\) | \(n_2\) | \(m_1\) | \(m_2\) | \(\rho \) | \(RR\) |
|---|---|---|---|---|---|
| 10 | 20 | 1.0 | 1.0 | 0.0 | 0.0 |
| 20 | 20 | 1.0 | 1.0 | 1.0 | 0.0 |
| 10 | 10 | 1.0 | 1.0 | 0.0 | 0.0 |
| 10 | 10 | 1.0 | 1.0 | 1.0 | 0.0 |

Table 1: Simulated power for 2 correlated endpoints in 2-sample design
The power loss, represented by RR, becomes smaller, the higher the correlation between the tests and the more similar the elementary powers (e1,e2) are.

2.2 IUT for three correlated primary endpoints

The question whether the loss of power decreases with increasing number of elementary tests (due to the considerable conservatism of the classical IUT) is answered on the one hand with 3 and 4 endpoints in the two-sample design and on the other hand for 3 endpoints and two simultaneous treatment contrasts. For the global UIT and giaUIT the multiple marginal model approach [10] was used for this multiple endpoints scenario [5] (see the R-code in the Appendix).

Table 2: Simulated power for 3 correlated endpoints in 2-sample design

2.3 IUT for four correlated endpoints

Table 3: Simulated power for 4 correlated endpoints in 2-sample design
2.4 Global IUT for both three correlated endpoints when claiming at least non-inferiority of standard with two new treatments

Table 4: Simulated power for 3 correlated endpoints in 3-sample design

3 Analysis of an example

The availability of real data with multiple treatments and multiple primary endpoints is challenging. Therefore, the data of a dose-finding study to reduce lipids [1] are adapted by means of simulation (assumed $\rho = 0.8$). For both endpoints percentage change of triglyceride vs. baseline and percentage change of cholesterol after 4 weeks as well as the placebo and the three doses 5, 20, 80 mg, the data used here are included in the Appendix and visualized by means of a boxplot:

![Boxplot of simulated data for dose-finding study with two primary endpoints EP1 and EP2](image)

To obtain comparable tests, the multiple endpoint Dunnett test [5] and univariate k-sample contrasts dose vs. placebo were used.
Table 5: p-values: marginal vs. aiaUIT-adjusted in the dose finding study

The (not too realistic) hypothesis that all doses and both endpoints are effective is tested using classical IUT and the new aiaUIT, with adjusted p-values (max(p)-approach) resulting to: $p_{\text{IUT}}^\text{max} = 0.68$, $p_{\text{aiaUIT}}^\text{max} = 0.34$

Of course, the marginal p-values (of the IUT-test) are in principle smaller than those of the aiaUIT. But both tests lead to the same conclusion: rejection of the global IUT hypothesis. The decisive advantage of the aiaUIT test can be seen in Figure 2 with the simulated confidence limits. Without further complicated assumption ([11]) one can evaluate the changes of the individual contrasts - this is not possible with the classical IUT by definition:

![Figure 2: Simultaneous confidence limits for the aiaUIT](image)

4 Conclusions

For the classical intersection-union hypotheses, one can always use the advantages of the complete power UIT as an alternative to the classical IUT, i.e. the additional availability of elementary decisions, special simultaneous confidence intervals, but combined with an inherent power loss. This power loss becomes smaller (and thus more tolerable given the advantages in a sense of aesthetics and power considerations in multiple testing [11]) the more elementary tests are included in the hypothesis family and the more highly correlated these tests are, vice versa. Both test principles are conservative, although with the IUT this becomes extreme as the number of elementary tests increases. The power is high if all elementary tests are appropriately in the alternative. And it becomes low if at least one is under $H_0$ or close to $H_0$. Prerequisite is that the multivariate t-distribution with suitable correlation structure for the various max-T tests is numerically available, which is the case in the CRAN packages multcomp and mvtnorm, whereas classical IUT based on simple univariate distributions for the elementary tests.
References

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5 Appendix I: R-code for simulation

```r
### GUT vs. IUT for 3 correlated endpoints in 3 sample design: gaussian

# library(tukeytrend); library(multcomp); library(ferret); library(glmulti)
# library(CombinePValue); library(robustHD); library(simstudy); library(npmv)

all3DU=function(sims,n1,n2, n3,ma1,ma2,ma3, mb1, mb2, mb3,mc1,mc2,mc3,sa,sb,sc,rho)
{
  set.seed(17051949)
  tw = replicate(sims, {
    n<-c(n1,n2,n3); dose<-c("C", "D1", "D2"); Dose = rep(dose, n);
    corMatABC <- matrix(c(1, rho, rho, rho, 1, rho, rho, rho, 1), nrow = 3)
    sdat1 <- genCorData(n1,mu =c(ma1,mb1, mc1), sigma =c(sa,sb,sc), corMatrix = corMatABC)
    sdat2 <- genCorData(n2,mu =c(ma2,mb2, mc2), sigma =c(sa,sb,sc), corMatrix = corMatABC)
    sdat3 <- genCorData(n3,mu =c(ma3,mb3, mc3), sigma =c(sa,sb,sc), corMatrix = corMatABC)
    simdat<-data.frame(Dose = as.factor(Dose), response= rbind(sdat1,sdat2, sdat3))
    colnames(simdat)<-c("Dose", "id", "Y1", "Y2", "Y3")
    fita <- lm(Y1~Dose, data = simdat) # Endpoint a
    fitb <- lm(Y2~Dose, data = simdat) # Endpoint b
    fitc <- lm(Y3~Dose, data = simdat) # Endpoint c
    dfA<-anova(fita)$Df[2] # lm df
    multT <-summary(glht(mmm(E1=fita,E2=fitb, E3=fitc),
                      mlf(mcp(Dose ="Dunnett")), alternative="greater", df=dfA)) ### mmm
    MA <-summary(glht(fita,mcp(Dose ="Dunnett"), alternative="greater", df=dfA))
    MB <-summary(glht(fitb,mcp(Dose ="Dunnett"), alternative="greater", df=dfA))
    MC <-summary(glht(fitc,mcp(Dose ="Dunnett"), alternative="greater", df=dfA))
    c(mm=multT$test$pvalues,
    ma=MA$test$pvalues,# univar 1 sided
    mb=MB$test$pvalues,
    mc=MC$test$pvalues)
  })
  erg= as.data.frame(t(tw))
  estall=length(which(erg$mm1<0.05 & erg$mm2<0.05 & erg$mm3<0.05&
    erg$mm4<0.05 & erg$mm5<0.05 & erg$mm6<0.05))/sims
  estUI=length(which(erg$mm1<0.05| erg$mm2<0.05 | erg$mm3<0.05|
    erg$mm4<0.05 | erg$mm5<0.05 | erg$mm6<0.05))/sims
}
```

### R-code for simulation

```r
library(tukeytrend); library(multcomp); library(glmulti)
library(CombinePValue); library(robustHD); library(simstudy); library(npmv)

all3DU=function(sims,n1,n2, n3,ma1,ma2,ma3, mb1, mb2, mb3,mc1,mc2,mc3,sa,sb,sc,rho)
{
  set.seed(17051949)
  tw = replicate(sims, {
    n<-c(n1,n2,n3); dose<-c("C", "D1", "D2"); Dose = rep(dose, n);
    corMatABC <- matrix(c(1, rho, rho, rho, 1, rho, rho, rho, 1), nrow = 3)
    sdat1 <- genCorData(n1,mu =c(ma1,mb1, mc1), sigma =c(sa,sb,sc), corMatrix = corMatABC)
    sdat2 <- genCorData(n2,mu =c(ma2,mb2, mc2), sigma =c(sa,sb,sc), corMatrix = corMatABC)
    sdat3 <- genCorData(n3,mu =c(ma3,mb3, mc3), sigma =c(sa,sb,sc), corMatrix = corMatABC)
    simdat<-data.frame(Dose = as.factor(Dose), response= rbind(sdat1,sdat2, sdat3))
    colnames(simdat)<-c("Dose", "id", "Y1", "Y2", "Y3")
    fita <- lm(Y1~Dose, data = simdat) # Endpoint a
    fitb <- lm(Y2~Dose, data = simdat) # Endpoint b
    fitc <- lm(Y3~Dose, data = simdat) # Endpoint c
    dfA<-anova(fita)$Df[2] # lm df
    multT <-summary(glht(mmm(E1=fita,E2=fitb, E3=fitc),
                      mlf(mcp(Dose ="Dunnett")), alternative="greater", df=dfA)) ### mmm
    MA <-summary(glht(fita,mcp(Dose ="Dunnett"), alternative="greater", df=dfA))
    MB <-summary(glht(fitb,mcp(Dose ="Dunnett"), alternative="greater", df=dfA))
    MC <-summary(glht(fitc,mcp(Dose ="Dunnett"), alternative="greater", df=dfA))
    c(mm=multT$test$pvalues,
    ma=MA$test$pvalues,# univar 1 sided
    mb=MB$test$pvalues,
    mc=MC$test$pvalues)
  })
  erg= as.data.frame(t(tw))
  estall=length(which(erg$mm1<0.05 & erg$mm2<0.05 & erg$mm3<0.05&
    erg$mm4<0.05 & erg$mm5<0.05 & erg$mm6<0.05))/sims
  estUI=length(which(erg$mm1<0.05| erg$mm2<0.05 | erg$mm3<0.05|
    erg$mm4<0.05 | erg$mm5<0.05 | erg$mm6<0.05))/sims
}
```
library(multcomp)
library(sandwich)
fits <- lm(Y1 ~ Dose, data = simDF) # Endpoint a
fitsb <- lm(Y2 ~ Dose, data = simDF) # Endpoint b

simDF <- cbind(multT$test$pvalue, MAu$test$pvalue, MBu$test$pvalue)

MAu <- summary(glht(fita, mcp(Dose = "Dunnett"), alternative = "greater", df = dfA, vcov = sandwich), univariate())

plot(glht(mmm(T1 = fita, T2 = fitb), mlf(mcp(Dose = "Dunnett")), alternative = "greater", df = dfA, vcov = sandwich)) ### mmm

Mmu <- summary(glht(fits, mpileup(Coe = "Bonferroni"), alternative = "greater", df = dfA, vcov = sandwich), univariate())

Mmu <- summary(glht(fits, mpileup(Coe = "Bonferroni"), alternative = "greater", df = dfA, vcov = sandwich), univariate())

print(shapiro.test(rescale))

6 Appendix II: R-code for simulated data example

```r
library(multcomp)
library(sandwich)
fits <- lm(Y1 ~ Dose, data = simDF) # Endpoint a
fitsb <- lm(Y2 ~ Dose, data = simDF) # Endpoint b

simDF <- cbind(multT$test$pvalue, MAu$test$pvalue, MBu$test$pvalue)

MAu <- summary(glht(fita, mcp(Dose = "Dunnett"), alternative = "greater", df = dfA, vcov = sandwich), univariate())

plot(glht(mmm(T1 = fita, T2 = fitb), mlf(mcp(Dose = "Dunnett")), alternative = "greater", df = dfA, vcov = sandwich)) ### mmm

Mmu <- summary(glht(fits, mpileup(Coe = "Bonferroni"), alternative = "greater", df = dfA, vcov = sandwich), univariate())

print(shapiro.test(rescale))
```
