

Additional file 2

This R-script simulates the density of the p-gain for metabolite concentrations M_1 and M_2 .

Input variables:

kor_M1_M2	correlation of M_1 and M_2
kor_M1_ratio	correlation of M_1 and the metabolite ratio M_1/M_2
kor_M2_ratio	correlation of M_2 and the metabolite ratio M_1/M_2
alpha	significance level

Function:

```
p.gain.simulation<-function(kor_M1_M2, kor_M1_ratio, kor_M2_ratio,
alpha)
{
  library(copula)
  korrel<-c(kor_M1_M2, kor_M1_ratio, kor_M2_ratio)
  norm.cop<-normalCopula(korrel^3, dim=3, dispstr="un")

  pval1.l<-pval2.l<-pval3.l<-NULL
  for(j in 1:100)
  {
    test<-rcopula(norm.cop, 5000)
    IVNTR1<- qnorm((rank(test[,1], na.last="keep")-
      0.5)/sum(!is.na(test[,1])))
    IVNTR2<- qnorm((rank(test[,2], na.last="keep")-
      0.5)/sum(!is.na(test[,2])))
    IVNTR3<- qnorm((rank(test[,3], na.last="keep")-
      0.5)/sum(!is.na(test[,3])))

    pval1<-pval2<-pval3<-rep(NA, 1000)
    for(i in 1:1000)
    {
      var1<-runif(5000,min=0, max=1)
      pval1[i]<-summary(lm(IVNTR1~var1))$coefficients[2,4]
      pval2[i]<-summary(lm(IVNTR2~var1))$coefficients[2,4]
      pval3[i]<-summary(lm(IVNTR3~var1))$coefficients[2,4]
    }
    pval1.l<-c(pval1.l, pval1)
    pval2.l<-c(pval2.l, pval2)
    pval3.l<-c(pval3.l, pval3)
  }

  test2<-cbind(apply(cbind(pval1.l, pval2.l),1,min), pval3.l)
  pgain<-test2[,1]/test2[,2]
  pgain.order<-pgain[order(pgain, decreasing=TRUE)]
  print(pgain.order[length(pgain)*alpha])
}
```