Epistatic Nested Effects Models
Inferring mixed epistatis from indirect measurements of knockout screens.

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This package is an extension of the classic Nested Effects Models provided in package *nem*. Nested Effects Models is a pathway reconstruction method, which takes into account effects of downstream genes. Those effects are observed for every knockout of a pathway gene, and the nested structure of observed effects can then be used to reconstruct the pathway structure. However, classic Nested Effects Models do not account for double knockouts. In this package *epiNEM*, one additional layer of complexity is added. For every two genes, acting on one gene together, the relationship is evaluated and added to the model as a logic gate. Genetic relationships are represented by the logics OR (no relationship), AND (functional overlap), NOT (masking or inhibiting) and XOR (mutual prevention from acting on gene C).

Loading epiNEM

```
## install.packages("devtools", verbose = F, quiet = T)

library(devtools)

## install_github("cbg-ethz/epiNEM", quiet = T)

library(epiNEM)
```

Simulations

We compare epiNEM to several network inference methods.

```
library(bnem) #  install_github("MartinFXP/B-NEM/package")

## Loading required package:  CellNOptR
## Loading required package:  RBGL
## Loading required package:  graph
## Loading required package:  BiocGenerics
## Loading required package:  parallel
##
## Attaching package:  'BiocGenerics'
## The following objects are masked from 'package:parallel':
##
##    clusterApply, clusterApplyLB, clusterCall, clusterEvalQ, clusterExport,
```

```
##     clusterMap, parApply, parCapply, parLapply, parLapplyLB, parRapply,
##     parSapply, parSapplyLB
## The following objects are masked from 'package:igraph':
##
##     normalize, union
## The following objects are masked from 'package:stats':
##
##     IQR, mad, xtabs
## The following objects are masked from 'package:base':
##
##     Filter, Find, Map, Position, Reduce, anyDuplicated, append, as.data.frame,
##     cbind, colnames, do.call, duplicated, eval, evalq, get, grep, grepl,
##     intersect, is.unsorted, lapply, lengths, mapply, match, mget, order, paste,
##     pmax, pmax.int, pmin, pmin.int, rank, rbind, rownames, sapply, setdiff,
##     sort, table, tapply, union, unique, unsplit
##
## Attaching package:  'graph'
## The following objects are masked from 'package:igraph':
##
##     degree, edges, intersection
##
## Attaching package:  'RBGL'
## The following objects are masked from 'package:igraph':
##
##     bfs, dfs, transitivity
## The following object is masked from 'package:e1071':
##
##     extractPath
## Loading required package:  hash
## hash-2.2.6 provided by Decision Patterns
## Loading required package:  ggplot2
## Loading required package:  RCurl
## Loading required package:  bitops
## Loading required package:  Rgraphviz
## Loading required package:  grid
## Loading required package:  XML
##
## Attaching package:  'XML'
## The following object is masked from 'package:graph':
##
##     addNode
## Loading required package:  nem
##
## Attaching package:  'nem'
## The following object is masked from 'package:RBGL':
##
##     transitive.closure
## Loading required package:  matrixStats
## matrixStats v0.51.0 (2016-10-08) successfully loaded.  See ?matrixStats for help.
## Loading required package:  snowfall
## Loading required package:  snow
##
## Attaching package:  'snow'
```

```
## The following objects are masked from 'package:BiocGenerics':
##
##     clusterApply, clusterApplyLB, clusterCall, clusterEvalQ, clusterExport,
##     clusterMap, clusterSplit, parApply, parCapply, parLapply, parRapply,
##     parSapply
## The following objects are masked from 'package:parallel':
##
##     clusterApply, clusterApplyLB, clusterCall, clusterEvalQ, clusterExport,
##     clusterMap, clusterSplit, makeCluster, parApply, parCapply, parLapply,
##     parRapply, parSapply, splitIndices, stopCluster
## Loading required package:  latticeExtra
## Loading required package:  lattice
## Loading required package:  RColorBrewer
##
## Attaching package:  'latticeExtra'
## The following object is masked from 'package:ggplot2':
##
##     layer
```

```
library(nem)
```

```
library(minet)
```

```
library(pcalg)
```

```
runs <- 100
```

```
noiselvls <- c(0.01, 0.025, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5)
```

```
random <- list(FPrate = 0.1, FNrate = noiselvls, single = 4, double = 1, reporters = 100, replicates = 3
```

```
spec <- sens  <- logics <- array(0, dim = c(2, runs, length(noiselvls)))
```

```
sens2 <- spec2 <- time <- array(0, dim = c(5, runs, length(noiselvls)))
```

```
do <- c("n", "p", "a")
```

```
do <- c("e", "b", do)
```

```
popSize <- 100
```

```
maxTime <- F
```

```
forcelogic <- T
```

```
epinemsearch <- "greedy"
```

```
nIterations <- 3
```

```
bnemsearch <- "genetic"
```

```
parallel <- NULL
```

```
logicgate <- matrix("", runs, length(noiselvls))

edgenr <- matrix(0, runs, length(noiselvls))

## for (i in 1:runs) {

##     print(paste("run ", i, sep = ""))

##     for (j in 1:length(noiselvls)) {

##         print(paste("noiselvl ", j, sep = ""))

##         topology <- CreateTopology(random$single, random$double, force = forcelogic)

##         topology <- unlist(unique(topology), recursive = FALSE)

##         extTopology <- ExtendTopology(topology$model, random$reporters)

##         sortedData <- GenerateData(topology$model, extTopology, random$FPrate, random$FNrate[j], rand

##         logicgate[i, j] <- paste(topology$logics, collapse = "_")

##         edgenr[i, j] <- sum(topology$origModel == 1)

##         if ("e" %in% do) {
##             print("epiNEM")

##             start <- Sys.time()
##             TriplModel <- epiNEM(filename = sortedData, method = epinemsearch, nIterations = nIterat
##             time[1, i, j] <- difftime(Sys.time(), start, units = "secs")
##             print(time[1, i, j])

##             tp <- sum(topology$model == 1 & TriplModel$model == 1)
##             tn <- sum(topology$model == 0 & TriplModel$model == 0)
##             fp <- sum(topology$model == 0 & TriplModel$model == 1)
##             fn <- sum(topology$model == 1 & TriplModel$model == 0)
##             sens[1, i, j] <- tp/(tp+fn)
##             spec[1, i, j] <- tn/(tn+fp)
##             tp <- sum(topology$origModel == 1 & TriplModel$origModel == 1)
##             tn <- sum(topology$origModel == 0 & TriplModel$origModel == 0)
##             fp <- sum(topology$origModel == 0 & TriplModel$origModel == 1)
##             fn <- sum(topology$origModel == 1 & TriplModel$origModel == 0)
##             sens2[1, i, j] <- tp/(tp+fn)
##             spec2[1, i, j] <- tn/(tn+fp)
##             tp <- 0
##             for (k in 1:length(topology$column)) {
##                 for (l in 1:length(TriplModel$column)) {
##                     if (topology$column[k] == TriplModel$column[l]) {
##                         if (topology$logics[k] %in% TriplModel$logics[l]) {
##                             tp <- tp + 1
##                         }
##                     }
##                 }
```

```
##             }
##             logics[1, i, j] <- tp/(length(topology$logics) + length(TriplModel$logics) - tp)
##             print(sens[1, i, j])
##             print(spec[1, i, j])
##             print(sens2[1, i, j])
##             print(spec2[1, i, j])
##             print(logics[1, i, j])

##         }

##         if ("b" %in% do) {
##             print("B-NEM")

##             gtn <- epi2bg(topology)

##             fc <- cbind(Ctrl_vs_S = -1, epi2bg(sortedData))*(-1)

##             bnemnoise <- sample(1:nrow(fc), floor(nrow(fc)*random$FNrate[j]))

##             fc[bnemnoise, 1] <- 0

##             ers <- t(topology$model)*(-1)
##             colnames(ers) <- paste("S_vs_S_", gsub("\\.", "_", colnames(ers)), sep = "")
##             ers <- cbind(Ctrl_vs_S = 1, ers)
##             ers <- ers[, order(colnames(ers))]

##             CNOlist <- dummyCNOlist(stimuli = "S", inhibitors = LETTERS[1:random$single], maxStim =

##             parents <- unique(unlist(strsplit(colnames(sortedData)[grep("\\.", colnames(sortedData))]

##             nodes <- unique(colnames(sortedData)[-grep("\\.", colnames(sortedData))])

##             child <- nodes[-which(nodes %in% parents)]

##             sifMatrix <- NULL
##             for (k in LETTERS[1:random$single]) {
##                sifMatrix <- rbind(sifMatrix, c("S", "1", k))#, c("S", "-1", k)) # bnem can set a pri
##                 for (l in LETTERS[1:random$single]) {
##                     if (k %in% l) { next() }
##                     if (k %in% parents) {
##                         sifMatrix <- rbind(sifMatrix, c(k, "1", l), c(k, "-1", l))
##                     } else {
##                         sifMatrix <- rbind(sifMatrix, c(k, "1", l))
##                     }

##             randfile <- paste("pkn_", as.numeric(Sys.time()), sep = "")
##             write.table(sifMatrix, file = randfile, sep = "\t",
##                         row.names = FALSE, col.names = FALSE, quote = FALSE)
##             PKN <- readSIF(randfile)
##             unlink(randfile)

##             model <- preprocessing(CNOlist, PKN)
```

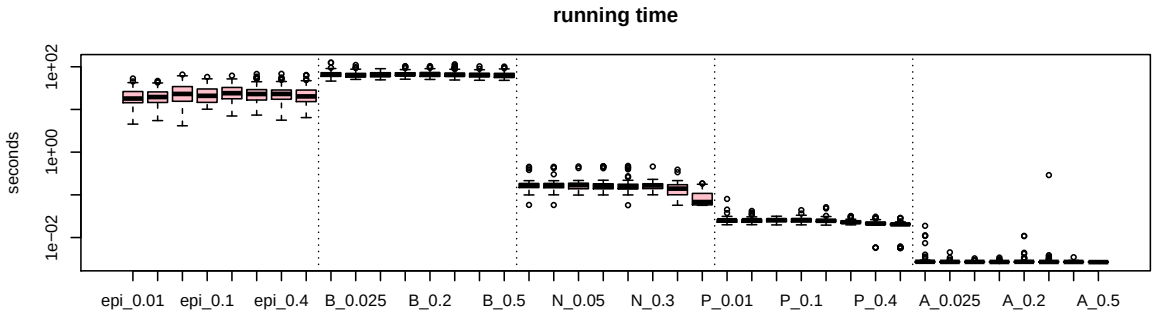
```
##             initBstring <- absorption(rep(1, length(model$reacID)), model)

##             if (maxTime) { maxTime2 <- time[1, i, j] } else { maxTime2 <- Inf }

##             start <- Sys.time()
##             bga <- bnem(search = bnemsearch,
##                         fc=fc,
##                         CNOlist=CNOlist,
##                         model=model,
##                         initBstring=initBstring,
##                         draw = F,
##                         verbose = F,
##                         popSize = popSize,
##                         maxTime = maxTime2,
##                         parallel = parallel
##                         )
##             time[2, i, j] <- difftime(Sys.time(), start, units = "secs")
##             print(time[2, i, j])

##             ers2 <- computeFc(CNOlist, t(simulateStatesRecursive(CNOlist, model, bga$bString)))
##             ers2 <- ers2[, unique(colnames(fc))]
##             ers2 <- ers2[, order(colnames(ers2))]

##             tp <- sum(ers == -1 & ers2 == -1)
##             tn <- sum(ers == 0 & ers2 == 0)
##             fn <- sum(ers == -1 & ers2 == 0)
##             fp <- sum(ers == 0 & ers2 == -1)
##             sens[2, i, j] <- tp/(tp+fn)
##             spec[2, i, j] <- tn/(tn+fp)
##             gtn2 <- abs(dnf2adj(gtn))
##             if (length(grep("S", rownames(gtn2))) > 0) {
##                 gtn2 <- gtn2[-grep("S", rownames(gtn2)), -grep("S", colnames(gtn2))]
##             }
##             gtn2 <- gtn2[order(rownames(gtn2)), order(colnames(gtn2))]
##             res <- abs(dnf2adj(bga$graph))
##             if (length(grep("S", rownames(res))) > 0) {
##                 res <- as.matrix(res[-grep("S", rownames(res)), -grep("S", colnames(res))])
##             }
##             if (dim(res)[1] == 1) {
##                 colnames(res) <- rownames(res) <- gsub(".*=", "", bga$graph)
##             } else {
##                 res <- res[order(rownames(res)), order(colnames(res))]
##             }
##             if (nrow(res) < nrow(gtn2)) {
##                 res2 <- rbind(cbind(res, matrix(0, nrow(res), nrow(gtn2) - nrow(res))), matrix(0, nr
##                 colnames(res2)[(ncol(res)+1):ncol(res2)] <- colnames(gtn2)[which(!(colnames(gtn2) %i
##                 rownames(res2)[(nrow(res)+1):nrow(res2)] <- rownames(gtn2)[which(!(rownames(gtn2) %i
##                 res2 <- res2[order(rownames(res2)), order(colnames(res2))]
##                 res <- res2
##             }
##             diag(gtn2) <- diag(res) <- 0
##             tp <- sum(gtn2 == 1 & res == 1)
##             tn <- sum(gtn2 == 0 & res == 0)
```

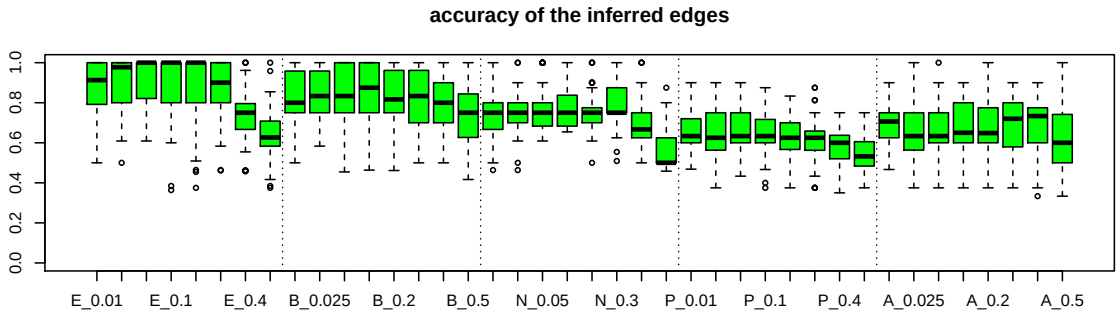
```
##              fn <- sum(gtn2 == 1 & res == 0)
##              fp <- sum(gtn2 == 0 & res == 1)
##              sens2[2, i, j] <- tp/(tp+fn)
##              spec2[2, i, j] <- tn/(tn+fp)
##              tp <- sum(bga$graph %in% gtn)
##              logics[2, i, j] <- tp/(length(gtn) + length(bga$graph) - tp) # (tp/(tp+fn) + tn/(tn+fp))/
##              print(sens[2, i, j])
##              print(spec[2, i, j])
##              print(sens2[2, i, j])
##              print(spec2[2, i, j])
##              print(logics[2, i, j])

##              print(bga$graph)
##              print(gtn)

##          }

##          if (any(c("n", "p", "a") %in% do)) {

##              reddata <- sortedData[, -grep("\\.", colnames(sortedData))]
##              gtnadj <- topology$origModel
##              gtnadj <- gtnadj[order(apply(gtnadj, 1, sum), decreasing = T), order(apply(gtnadj, 2, su
##              gtnadj[lower.tri(gtnadj)] <- gtnadj[upper.tri(gtnadj)]
##              gtnadj <- gtnadj[order(rownames(gtnadj)), order(colnames(gtnadj))]
##              eadj <- topology$origModel
##              eadj <- eadj[order(rownames(eadj)), order(colnames(eadj))]
##              reddata2 <- matrix(0, nrow(reddata)*random$replicates, length(unique(colnames(reddata))),
##              for (k in 1:length(unique(colnames(reddata)))) {
##                  reddata2[, k] <- as.vector(reddata[, which(colnames(reddata) %in% unique(colnames(red
##              }
##              colnames(reddata2) <- unique(colnames(reddata))

##          }

##          if ("n" %in% do) {
##              print("NEM")

##              start <- Sys.time()
##              if (epinemsearch %in% "greedy") {
##                  nemres <- nem(reddata, inference = "nem.greedy")
##              } else {
##                  nemres <- nem(reddata, inference = "search")
##              }
##              nadj <- transitive.reduction(graph2adj(nemres$graph))
##              time[3, i, j] <- difftime(Sys.time(), start, units = "secs")
##              print(time[3, i, j])

##              tp <- sum(eadj  == 1 & nadj == 1)
##              tn <- sum(eadj == 0 & nadj == 0)
##              fp <- sum(eadj == 0 & nadj == 1)
##              fn <- sum(eadj == 1 & nadj == 0)
##              sens2[3, i, j] <- tp/(tp+fn)
##              spec2[3, i, j] <- tn/(tn+fp)
```

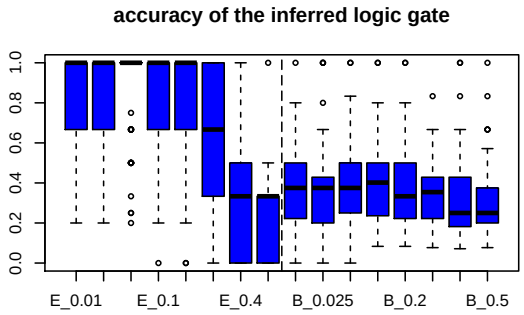
```
##             print(sens2[3, i, j])
##             print(spec2[3, i, j])

##         }

##         if ("p" %in% do) {
##             print("PCalg")

##             start <- Sys.time()
##             pc.fit <- pc(suffStat = list(C = cor(reddata2), n = nrow(reddata2)),
##                   indepTest = gaussCItest, ## indep.test: partial correlations
##                   alpha=0.05, labels = colnames(reddata2), verbose = F)
##             pcadj <- graph2adj(pc.fit@graph)
##             time[4, i, j] <- difftime(Sys.time(), start, units = "secs")
##             print(time[4, i, j])

##             tp <- sum(gtnadj == 1 & pcadj == 1)
##             tn <- sum(gtnadj  == 0 & pcadj == 0)
##             fp <- sum(gtnadj == 0 & pcadj == 1)
##             fn <- sum(gtnadj == 1 & pcadj == 0)
##             sens2[4, i, j] <- tp/(tp+fn)
##             spec2[4, i, j] <- tn/(tn+fp)
##             print(sens2[4, i, j])
##             print(spec2[4, i, j])

##         }

##         if ("a" %in% do) {
##             print("Aracne")

##             start <- Sys.time()
##             ares <- build.mim(reddata2)
##             ares <- aracne(ares)
##             ares <- disc(ares, 0)
##             ares <- ares[order(rownames(ares)), order(colnames(ares))]
##             nas <- which(is.na(ares) == T)
##             ares[nas] <- 0
##             diag(ares) <- 0
##             time[5, i, j] <- difftime(Sys.time(), start, units = "secs")
##             print(time[5, i, j])

##             tp <- sum(gtnadj == 1 & ares == 1)
##             tn <- sum(gtnadj == 0 & ares == 0)
##             fp <- sum(gtnadj == 0 & ares == 1)
##             fn <- sum(gtnadj == 1 & ares == 0)
##             sens2[5, i, j] <- tp/(tp+fn)
##             spec2[5, i, j] <- tn/(tn+fp)
##             print(sens2[5, i, j])
##             print(spec2[5, i, j])

##         }

##     }
```

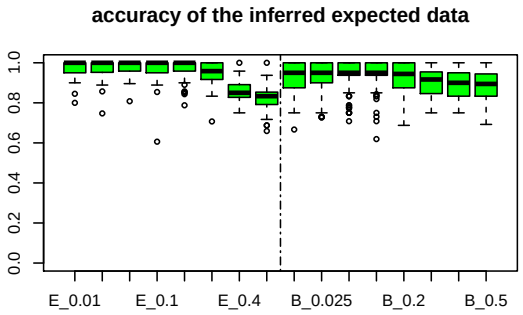
```
## }
```

```
data(sim)

acc <- (sens + spec)/2

acc2 <- (sens2 + spec2)/2

m <- rbind(c(1,1), c(2,2), c(3,4))

layout(m)

timeframe <- as.data.frame(cbind(data.frame(epiNEM = time[1,,]), data.frame(BNEM = time[2,,]), data.fra

colnames(timeframe) <- c(paste(rep("epi", length(noiselvls)), noiselvls, sep = "_"), paste(rep("B", leng

boxplot(timeframe, col = "pink", main = "running time", ylab = "seconds", log = "y")

abline(v=(1:(length(do)-1)*length(noiselvls) + 0.5), col = "black", lty = 3)

accframe2 <- as.data.frame(cbind(data.frame(epiNEM = acc2[1,,]), data.frame(BNEM = acc2[2,,]), data.fra

colnames(accframe2) <- c(paste(rep("E", length(noiselvls)), noiselvls, sep = "_"), paste(rep("B", lengt

boxplot(accframe2, col = "green", main = "accuracy of the inferred edges", ylim = c(0,1))

abline(v=(1:(length(do)-1)*length(noiselvls) + 0.5), col = "black", lty = 3)

logicsframe <- as.data.frame(cbind(data.frame(epiNEM = logics[1,,]), data.frame(BNEM = logics[2,,])))

colnames(logicsframe) <- c(paste(rep("E", length(noiselvls)), noiselvls, sep = "_"), paste(rep("B", leng

boxplot(logicsframe, col = "blue", main = "accuracy of the inferred logic gate", ylim = c(0,1))

abline(v=length(noiselvls)+0.5, col = "black", lty = 5)

accframe <- as.data.frame(cbind(data.frame(epiNEM = acc[1,,]), data.frame(BNEM = acc[2,,])))

colnames(accframe) <- c(paste(rep("E", length(noiselvls)), noiselvls, sep = "_"), paste(rep("B", length

boxplot(accframe, col = "green", main = "accuracy of the inferred expected data", ylim = c(0,1))

abline(v=length(noiselvls)+0.5, col = "black", lty = 6)
```









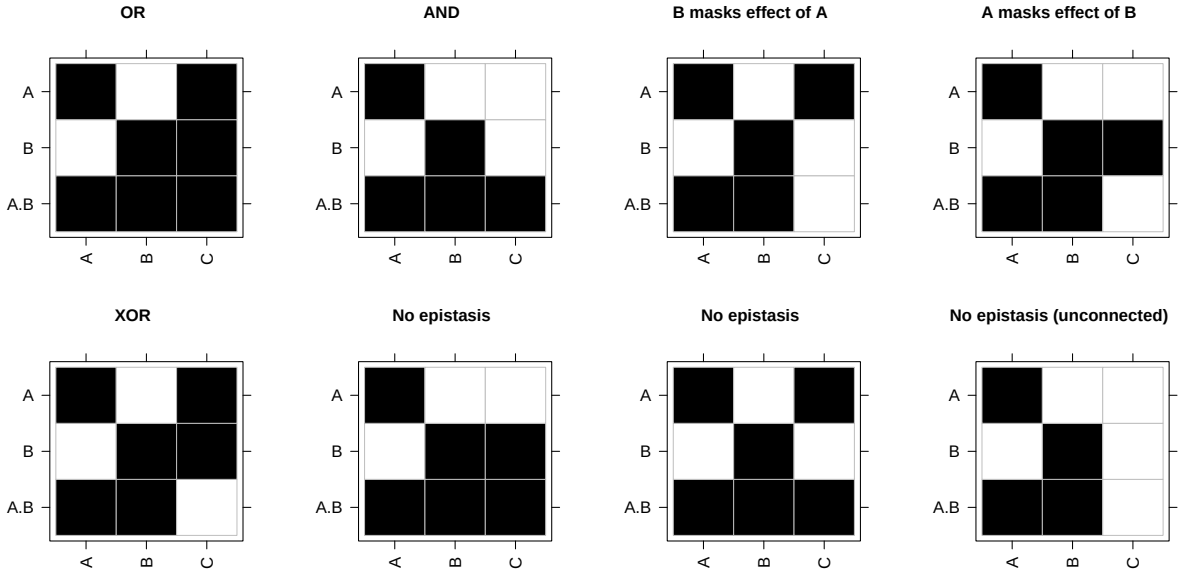
Yeast knockout screens

In this section we analyse previously published yeast knockout screens. The screens consist of gene expression data derived from double and single knockout mutants. We use epiNEM on each double mutant combined with each single mutant.

The results of the knockout screens have been annotated according to the following legend:

```
options(warn=-1)
heatmapOP(matrix(c(1,-1,1,-1,1,1, 1, 1, 1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Co
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, -1, 1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])),
heatmapOP(matrix(c(1,-1,1,-1,1,1, 1, -1, -1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])),
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, 1, -1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])),
heatmapOP(matrix(c(1,-1,1,-1,1,1, 1, 1, -1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), C
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, 1, 1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), C
```

```
heatmapOP(matrix(c(1,-1,1,-1,1,1, 1, -1, 1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), C
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, -1, -1), 3, 3, dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])),
options(warn=0)
```



Wageningen et al., 2010

```
data <- read.delim("http://www.holstegelab.nl/publications/sv/signaling_redundancy/downloads/DataS1.txt"

dataM <- data[-(1:2), (1+(1:(324/2))*2)]

dataP <- data[-(1:2), (2+(1:(324/2))*2)]

dataM <- dataM[-1, ]

dataP <- dataP[-1, ]

dataM <- apply(dataM, c(1,2), as.numeric)

dataP <- apply(dataP, c(1,2), as.numeric)

dataBin <- dataM

sig <- 0.05

cutoff <- 0.7

dataBin[which(dataP < sig & dataP > 0 & abs(dataM) >= cutoff)] <- 1

dataBin[which(dataP >= sig | dataP == 0 | abs(dataM) < cutoff)] <- 0 # why do you throw away p-values w

dataBin <- dataBin[-which(apply(dataBin, 1, max) == 0), ]

genelist <- toupper(c('hsl1', 'cla4', 'gin4', 'swe1', 'hsl1.cla4'))
```

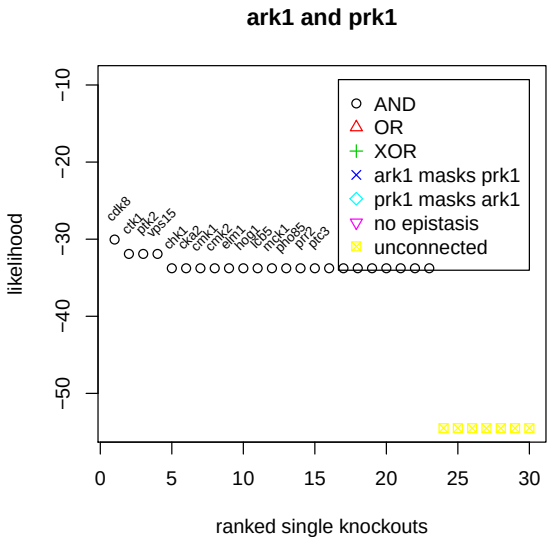
```
read_in_genes <- function(genes){
    return(unlist(lapply(genes, function(x) {paste(x, '.del.vs..wt.1', sep='')})))
}

single <- read_in_genes(genelist)

colnames(dataBin) <- gsub(".del.vs..wt", "", colnames(dataBin))

colnames(dataBin) <- gsub(".del", "", colnames(dataBin))

doubles <- colnames(dataBin)[grep("\\.", colnames(dataBin))]

doubles <- sort(doubles[-grep("vs", doubles)])

doubles.genes <- unique(unlist(strsplit(doubles, "\\.")))

singles <- colnames(dataBin)[-grep("\\.", colnames(dataBin))]

singles <- unique(sort(singles))

llmat <- logicmat <- matrix(0, length(singles), length(doubles))

rownames(llmat) <- rownames(logicmat) <- singles

colnames(llmat) <- colnames(logicmat) <- doubles

globalgenes <- which(apply(dataBin, 1, max) == 1)

## for (i in doubles[set]) {
##     if (which(doubles %in% i) == 8) { next() }
##     print(i)
##     doubles.singles <- unlist(strsplit(i, "\\."))
##     egenes <- which(apply(dataBin[, which(colnames(dataBin) %in% c(i, doubles.singles))], 1, max) ==
##     for (j in singles) {
##         print(j)
##         if (j %in% doubles.singles) { next() }

##         dataTmp <- dataBin[, grep(paste(paste("^", c(i, j, doubles.singles), "$", sep = ""), collaps

##         if (path %in% "fixed_set") {
##             dataTmp <- dataTmp[egenes, ]
##         }
##         if (path %in% "global") {
##             dataTmp <- dataTmp[globalgenes, ]
##         }
##         if (path %in% "") {
##             dataTmp <- dataTmp[which(apply(dataTmp, 1, max) == 1), ]
##         }

##         i1 <- which(singles %in% j)
##         i2 <- which(doubles %in% i)

##         if (!(is.null(dim(dataTmp)))) {
```

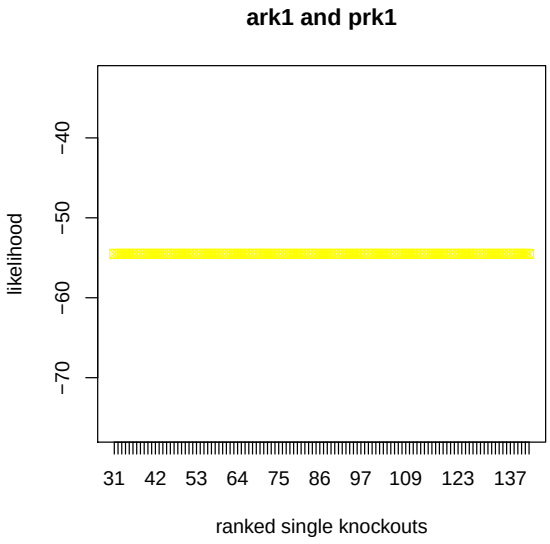
```
##             if (any(dataTmp[, j] != 0)) {

##                 epires <- epiNEM(dataTmp, method = "exhaustive")

##                 tmp <- epires$logics
##                 if ("OR" %in% tmp) {
##                     if (sum(epires$origModel[, j]) != 2) {
##                         tmp <- "NOEPI"
##                     } else {
##                         if (all(tmp %in% "OR")) {
##                             tmp <- "OR"
##                         } else {
##                             tmp <- tmp[which(!(tmp %in% "OR"))]
##                         }
##                     }
##                 }

##                 logicmat[i1, i2] <- tmp
##                 llmat[i1, i2] <- epires$score

##             } else {

##                 logicmat[i1, i2] <- "UNCON"
##                 llmat[i1, i2] <- -Inf

##             }

##         } else {

##             logicmat[i1, i2] <- "UNCON"
##             llmat[i1, i2] <- -Inf

##         }

##     }

## }
```

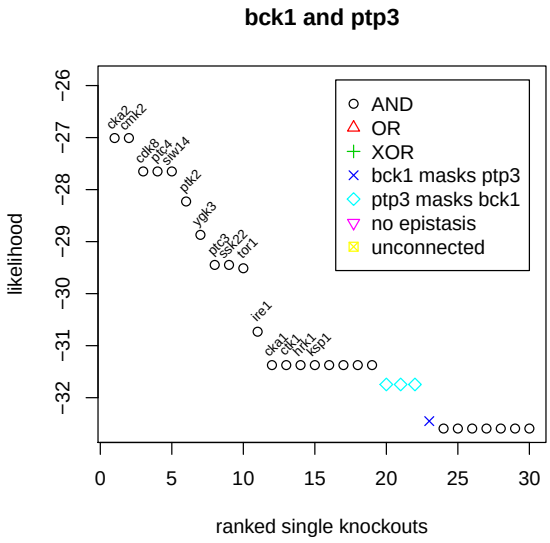
Plot results.

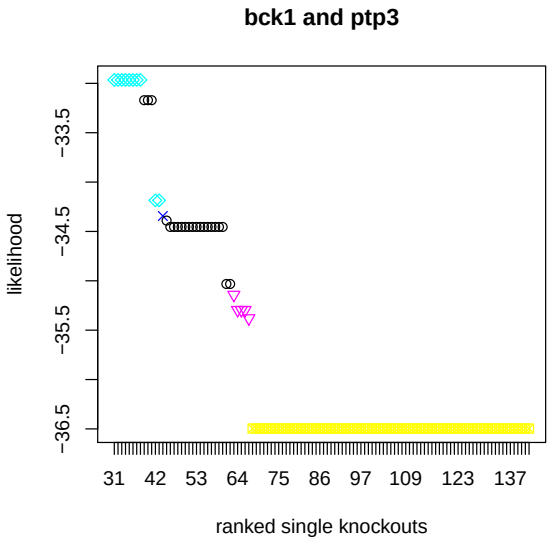
```
data(wageningen_res)

llmat0 <- wageningen$ll

logicmat0 <- wageningen$logic

paperdoubles <- c(4, 9, 17)

for (i in 1:length(doubles)) {

    if (!(doubles[i] %in% c("ark1.prk1", "prk1.ark1", "ptp2.ptp3", "ptp3.ptp2", "bck1.ptp3", "ptp3.bck1"

    if (i %in% 8) { next() }
```

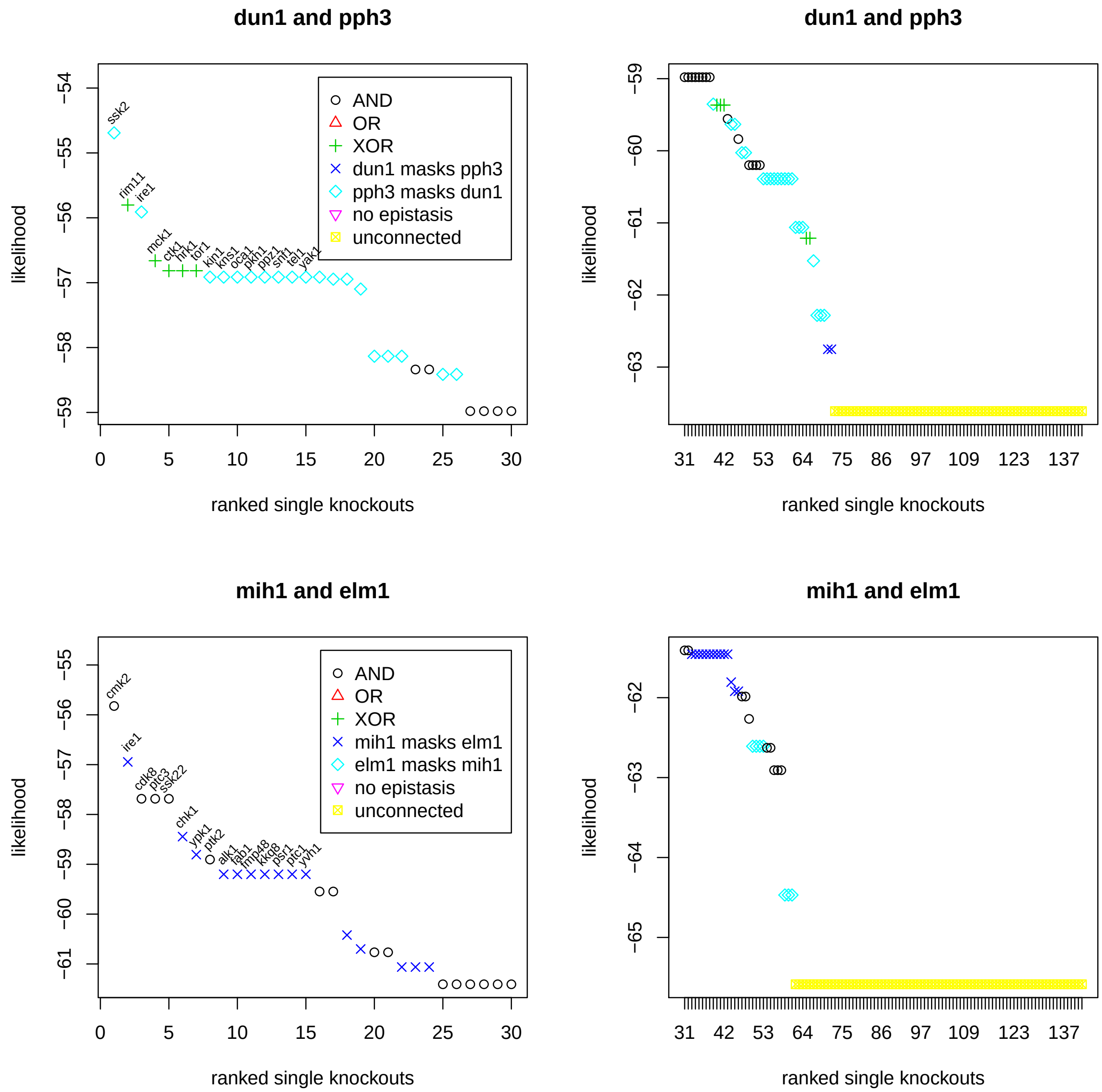
```
    logicvec <- logicmat0[, i]

    llvec <- llmat0[, i]

    logicvec <- logicvec[order(llvec, decreasing = T)]

    llvec <- llvec[order(llvec, decreasing = T)]

    parents <- unlist(strsplit(doubles[i], "\\."))

    pchvec <- numeric(length(llvec))

    pchvec[which(logicvec %in% "AND")] <- 1
    pchvec[which(logicvec %in% "OR")] <- 2
    pchvec[which(logicvec %in% "XOR")] <- 3
    pchvec[grep(paste("^", parents[1], sep = ""), logicvec)] <- 4
    pchvec[grep(paste("^", parents[2], sep = ""), logicvec)] <- 5
    pchvec[which(logicvec %in% "NOEPI")] <- 6
    pchvec[which(logicvec %in% "UNCON")] <- 7

    logicvec <- logicvec[-which(logicvec %in% "0")]
    pchvec <- pchvec[-which(pchvec == 0)]
    llvec <- llvec[-which(llvec == 0)]

    colvec <- pchvec

    llvec[which(is.infinite(llvec) == T)] <- Inf

    llvec[which(is.infinite(llvec) == T)] <- min(llvec) - 100

    if (all(is.infinite(llvec) == T)) { llvec[1:length(llvec)] <- -1000 }

    margin <- abs(max(llvec[1:30]) - min(llvec[1:30]))*0.2

    llvec[which(llvec == min(llvec))] <- min(llvec) + 100 - margin

    par(mfrow=c(1,2))
    plot(llvec[1:30], pch = pchvec[1:30], col = colvec[1:30], ylab = "likelihood", xlab = "ranked single
    legend(30, max(llvec)+margin, legend = c("AND", "OR", "XOR", paste(parents[1], " masks ", parents[2]
    text((1:30)+0.5, llvec[1:30]+(margin*0.1), labels = c(names(llvec)[1:15], rep("", 15)), cex = 0.7, p
    plot(llvec[-(1:30)], pch = pchvec[-(1:30)], col = colvec[-(1:30)], ylab = "likelihood", xlab = "rank
    axis(1, at = 1:length(llvec[-(1:30)]), labels = 31:length(llvec))

}
```

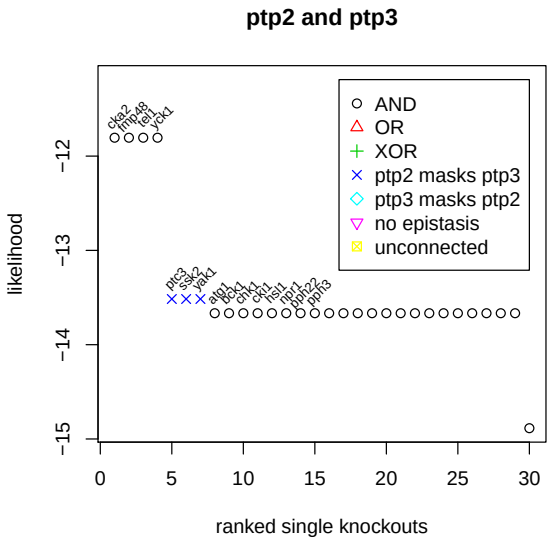

ark1 and prk1
likelihood
ranked single knockouts
AND
OR
XOR
ark1 masks prk1
prk1 masks ark1
no epistasis
unconnected

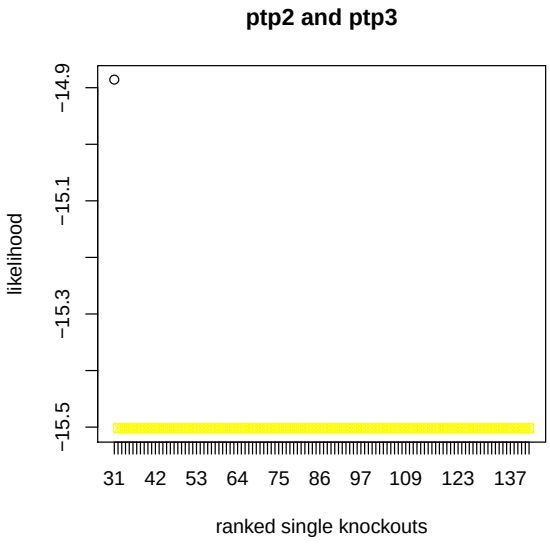

ark1 and prk1
likelihood
ranked single knockouts

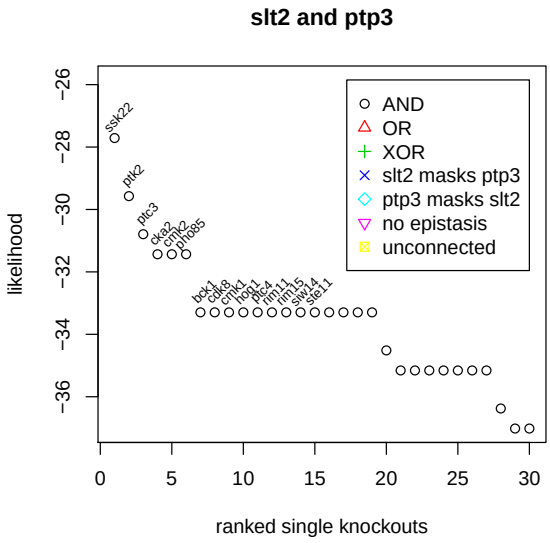

bck1 and ptp3
likelihood
ranked single knockouts
AND
OR
XOR
bck1 masks ptp3
ptp3 masks bck1
no epistasis
unconnected

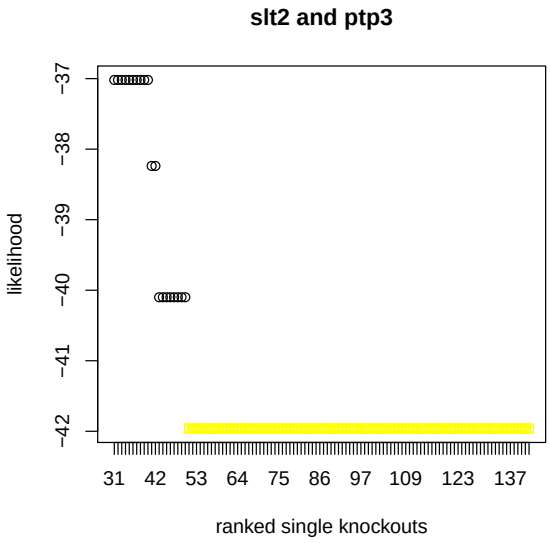

bck1 and ptp3
likelihood
ranked single knockouts

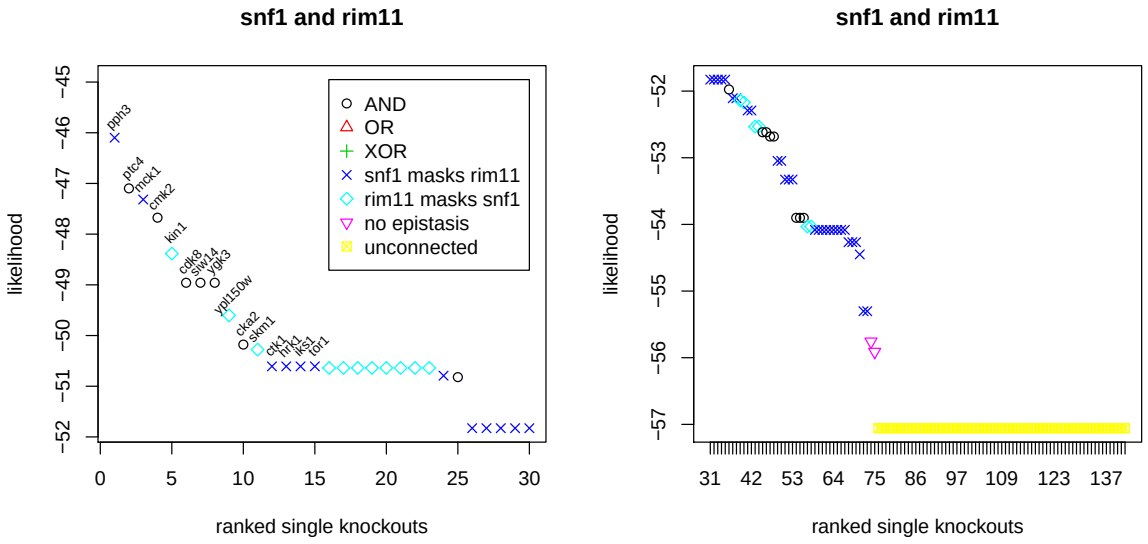

dun1 and pph3
likelihood
ranked single knockouts
AND
OR
XOR
dun1 masks pph3
pph3 masks dun1
no epistasis
unconnected
mih1 and elm1
mih1 masks elm1
elm1 masks mih1


ptp2 and ptp3
likelihood
ranked single knockouts
AND
OR
XOR
ptp2 masks ptp3
ptp3 masks ptp2
no epistasis
unconnected
cka2
mtp48
tel1
vck1
ptc3
ssk2
yak1
atg1
bck1
cmk1
ckl1
rsl1
npr1
bph22
pph3


ptp2 and ptp3
likelihood
ranked single knockouts


slt2 and ptp3
likelihood
ranked single knockouts
AND
OR
XOR
slt2 masks ptp3
ptp3 masks slt2
no epistasis
unconnected
ssk22
ptk2
ptc3
cka2
cmk2
pho85
bck1
cdk8
cmk1
hog1
ptc4
rim11
rim15
swi4
ste11


slt2 and ptp3
likelihood
ranked single knockouts



Sameith et al., 2015

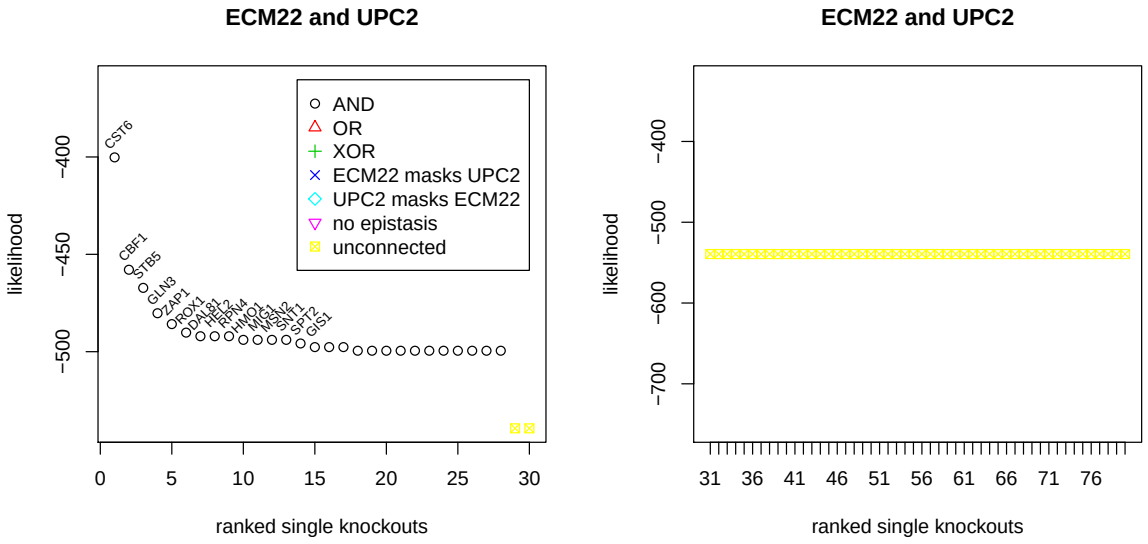
```
data <- read.delim("http://www.holstegelab.nl/publications/GSTF_geneticinteractions/downloads/del_mutant

data <- apply(data, c(1,2), as.character)

dataM <- data[-1, which(data[1, ] %in% "M")]

dataM <- apply(dataM, c(1,2), as.numeric)

dataP <- data[-1, which(data[1, ] %in% "p.value")]

dataP <- apply(dataP, c(1,2), as.numeric)

dataBin <- dataM

sig <- 0.05

cutoff <- 0.7

dataBin[which(dataP < sig & dataP > 0 & abs(dataM) >= cutoff)] <- 1

dataBin[which(dataP >= sig | dataP == 0 | abs(dataM) < cutoff)] <- 0

dataBin <- dataBin[-which(apply(dataBin, 1, max) == 0), ]

colnames(dataBin) <- gsub("\\.\\.\\.", "\\.", colnames(dataBin))

## big screen:

doubles <- colnames(dataBin)[grep("\\.", colnames(dataBin))]

doubles.genes <- unique(unlist(strsplit(doubles, "\\.")))
```

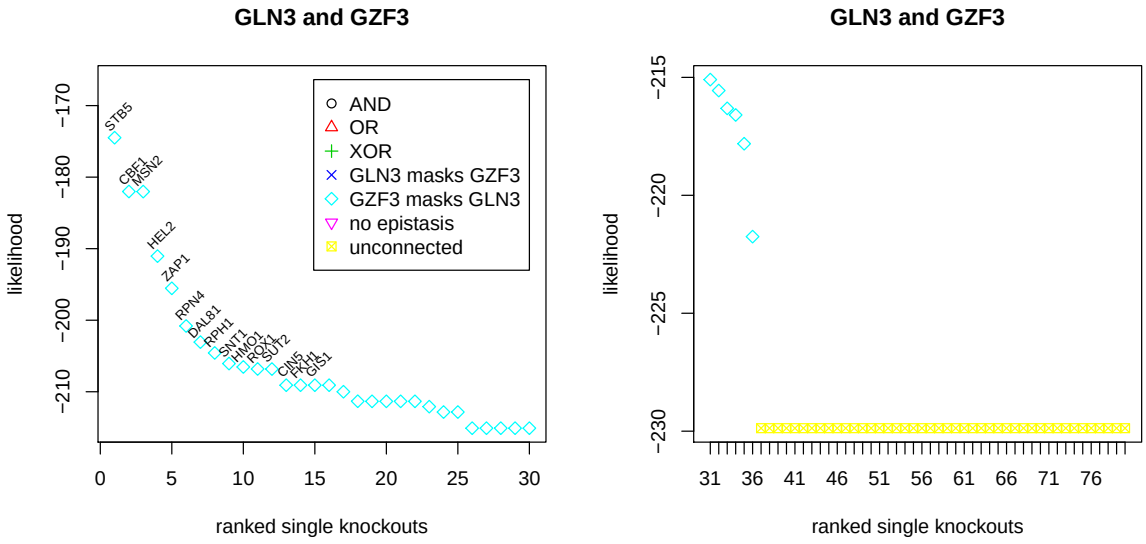
```
singles <- colnames(dataBin)[-grep("\\.", colnames(dataBin))]

singles <- unique(sort(singles))

llmat <- logicmat <- matrix(0, length(singles), length(doubles))

rownames(llmat) <- rownames(logicmat) <- singles

colnames(llmat) <- colnames(logicmat) <- doubles

globalgenes <- which(apply(dataBin, 1, max) == 1)

## for (i in doubles[set]) {
##     print(i)
##     doubles.singles <- unlist(strsplit(i, "\\."))
##     egenes <- which(apply(dataBin[, which(colnames(dataBin) %in% c(i, doubles.singles))], 1, max) ==
##     for (j in singles) {
##         print(j)
##         if (j %in% doubles.singles) { next() }

##         dataTmp <- dataBin[, grep(paste(paste("^", c(i, j, doubles.singles), "$", sep = ""), collaps

##         if (path %in% "fixed_set") {
##             dataTmp <- dataTmp[egenes, ]
##         }
##         if (path %in% "global") {
##             dataTmp <- dataTmp[globalgenes, ]
##         }
##         if (path %in% "") {
##             dataTmp <- dataTmp[which(apply(dataTmp, 1, max) == 1), ]
##         }

##         i1 <- which(singles %in% j)
##         i2 <- which(doubles %in% i)

##         if (!(is.null(dim(dataTmp)))) {

##             if (any(dataTmp[, j] != 0)) {

##                 epires <- epiNEM(dataTmp, method = "exhaustive")

##                 tmp <- epires$logics
##                 if ("OR" %in% tmp) {
##                     if (sum(epires$origModel[, j]) != 2) {
##                         tmp <- "NOEPI"
##                     } else {
##                         if (all(tmp %in% "OR")) {
##                             tmp <- "OR"
##                         } else {
##                             tmp <- tmp[which(!(tmp %in% "OR"))]
##                         }
##                     }
##                 }
```

```
##                 logicmat[i1, i2] <- tmp
##                 llmat[i1, i2] <- epires$score

##             } else {

##                 logicmat[i1, i2] <- "UNCON"
##                 llmat[i1, i2] <- -Inf

##             }

##         } else {

##             logicmat[i1, i2] <- "UNCON"
##             llmat[i1, i2] <- -Inf

##         }

##     }

## }
```

```
data(sameith_res)

llmat0 <- sameith$ll

logicmat0 <- sameith$logic

paperdoubles <- c(4, 9, 17)

for (i in 1:length(doubles)) {

    if (!(doubles[i] %in% c("ECM22.UPC2", "GLN3.GZF3"))) { next() }

    if (i %in% 8) { next() }

    logicvec <- logicmat0[, i]

    llvec <- llmat0[, i]

    logicvec <- logicvec[order(llvec, decreasing = T)]

    llvec <- llvec[order(llvec, decreasing = T)]

    parents <- unlist(strsplit(doubles[i], "\\."))

    pchvec <- numeric(length(llvec))

    pchvec[which(logicvec %in% "AND")] <- 1
    pchvec[which(logicvec %in% "OR")] <- 2
    pchvec[which(logicvec %in% "XOR")] <- 3
    pchvec[grep(paste("^", parents[1], sep = ""), logicvec)] <- 4
    pchvec[grep(paste("^", parents[2], sep = ""), logicvec)] <- 5
    pchvec[which(logicvec %in% "NOEPI")] <- 6
```

```
    pchvec[which(logicvec %in% "UNCON")] <- 7

    logicvec <- logicvec[-which(logicvec %in% "0")]
    pchvec <- pchvec[-which(pchvec == 0)]
    llvec <- llvec[-which(llvec == 0)]

    colvec <- pchvec

    llvec[which(is.infinite(llvec) == T)] <- Inf

    llvec[which(is.infinite(llvec) == T)] <- min(llvec) - 100

    if (all(is.infinite(llvec) == T)) { llvec[1:length(llvec)] <- -1000 }

    margin <- abs(max(llvec[1:30]) - min(llvec[1:30]))*0.2

    llvec[which(llvec == min(llvec))] <- min(llvec) + 100 - margin

    par(mfrow=c(1,2))
    plot(llvec[1:30], pch = pchvec[1:30], col = colvec[1:30], ylab = "likelihood", xlab = "ranked single
    legend(30, max(llvec)+margin, legend = c("AND", "OR", "XOR", paste(parents[1], " masks ", parents[2
    text((1:30)+0.5, llvec[1:30]+(margin*0.1), labels = c(names(llvec)[1:15], rep("", 15)), cex = 0.7, p
    plot(llvec[-(1:30)], pch = pchvec[-(1:30)], col = colvec[-(1:30)], ylab = "likelihood", xlab = "rank
    axis(1, at = 1:length(llvec[-(1:30)]), labels = 31:length(llvec))

}
```






```
sessionInfo()

## R version 3.3.1 (2016-06-21)
## Platform: x86_64-apple-darwin13.4.0 (64-bit)
## Running under: OS X 10.11.5 (El Capitan)
##
## locale:
## [1] C/UTF-8/C/C/C/C
##
## attached base packages:
## [1] grid      parallel  stats     graphics  grDevices utils     datasets  methods
## [9] base
##
## other attached packages:
##  [1] pcalg_2.4-3         minet_3.30.0        bnem_1.0            latticeExtra_0.6-28
##  [5] RColorBrewer_1.1-2  lattice_0.20-34     snowfall_1.84-6.1   snow_0.4-2
##  [9] matrixStats_0.51.0  nem_2.46.0          CellNOptR_1.18.0    XML_3.98-1.4
## [13] Rgraphviz_2.16.0    RCurl_1.95-4.8      bitops_1.0-6        ggplot2_2.1.0
## [17] hash_2.2.6          RBGL_1.48.1         graph_1.50.0        BiocGenerics_0.18.0
## [21] devtools_1.12.0     epiNEM_1.0          knitr_1.14          igraph_1.0.1
## [25] gtools_3.5.0        e1071_1.6-7         BoolNet_2.1.1       roxygen2_5.0.1
##
## loaded via a namespace (and not attached):
##  [1] statmod_1.4.26       colorspace_1.2-7     stats4_3.3.1         fastICA_1.2-0
##  [5] gmp_0.5-12           withr_1.0.2          plyr_1.8.4           robustbase_0.92-6
##  [9] stringr_1.1.0        munsell_0.4.3        gtable_0.2.0         bdsmatrix_1.3-2
## [13] memoise_1.0.0        evaluate_0.10        ggm_2.3              BiocInstaller_1.22.3
## [17] class_7.3-14         highr_0.6            DEoptimR_1.0-6       Rcpp_0.12.7
## [21] corpcor_1.6.8        scales_0.4.0         formatR_1.4          limma_3.28.21
## [25] plotrix_3.6-3        abind_1.4-5          digest_0.6.10        stringi_1.1.2
## [29] clue_0.3-51          tools_3.3.1          magrittr_1.5         cluster_2.0.5
## [33] boot_1.3-18          sfsmisc_1.1-0
```

References: