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, quietly = T, verbose = F) #  install_github("MartinFXP/B-NEM/package")

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$FNrate[j], random$replicates)

##         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 = nIterations)
##             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$single],
##                                 maxStim = 1, maxInhibit = 2, signals = LETTERS[1:random$single])

##             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$single]) {
##                sifMatrix <- rbind(sifMatrix, c("S", "1", k))#, c("S", "-1", k))
##                 for (l in LETTERS[1:random$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, nrow(gtn2) - nrow(res), ncol(gtn2)))
##                  colnames(res2)[(ncol(res)+1):ncol(res2)] <-
##                                      colnames(gtn2)[which(!(colnames(gtn2) %in% colnames(res)))]
##                  rownames(res2)[(nrow(res)+1):nrow(res2)] <-
##                                      rownames(gtn2)[which(!(rownames(gtn2) %in% rownames(res)))]
##                  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)
##              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)

##          }
```

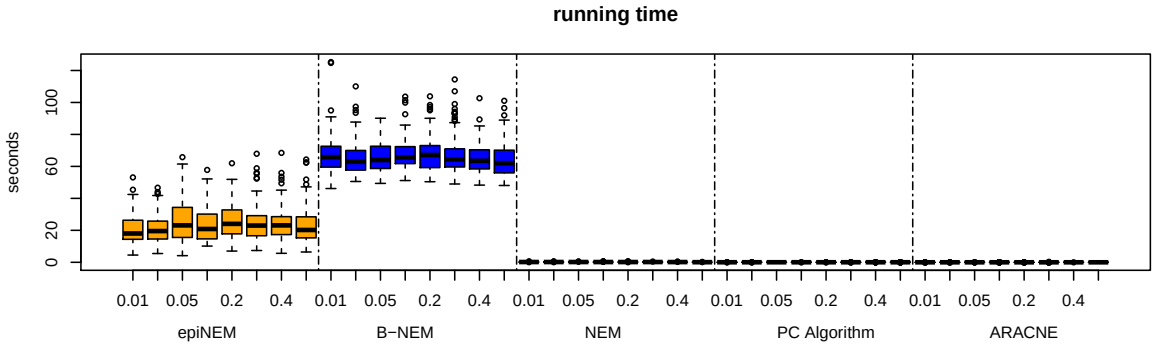
```
##         if (any(c("n", "p", "a") %in% do)) {

##             reddata <- sortedData[, -grep("\\.", colnames(sortedData))]
##             gtnadj <- topology$origModel
##             gtnadj <- gtnadj[order(apply(gtnadj, 1, sum), decreasing = T),
##                                    order(apply(gtnadj, 2, sum), decreasing = F)]
##             gtnadj[lower.tri(gtnadj)] <- gtnadj[upper.tri(gtnadj)]
##             gtnadj <- gtnadj[order(rownames(gtnadj)), order(colnames(gtnadj))]
##             eadj <- topology$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(reddata))[k])])
##             }
##             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")
```

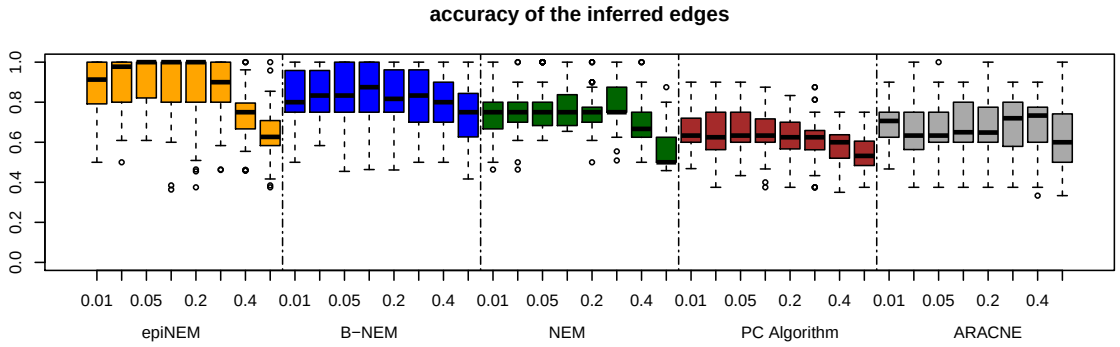
```
##             print(time[4, i, j])

##             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])

##         }

##     }

## }
```

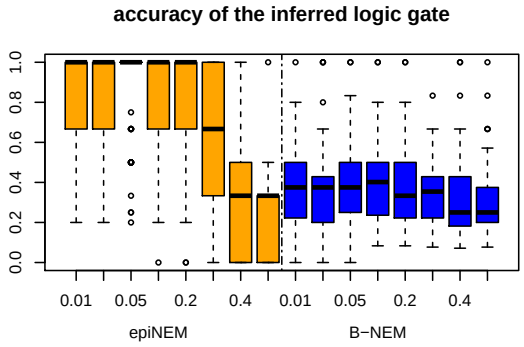
```
data(sim)

colvec <- c(rep("orange", length(noiselvls)), rep("blue", length(noiselvls)),
            rep("darkgreen", length(noiselvls)), rep("brown", length(noiselvls)),
            rep("darkgrey", length(noiselvls)))

acc <- (sens + spec)/2

acc2 <- (sens2 + spec2)/2

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

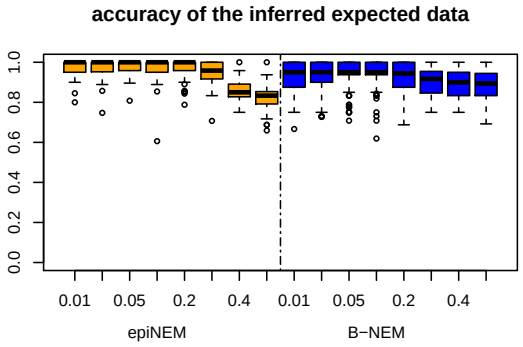
```
layout(m)

timeframe <- as.data.frame(cbind(data.frame(epiNEM = time[1,,]),
                                 data.frame(BNEM = time[2,,]), data.frame(NEM = time[3,,]),
                                 data.frame(Cor = time[4,,]), data.frame(MI = time[5,,])))

colnames(timeframe) <- rep(noiselvls, 5)

boxplot(timeframe, col = colvec, main = "running time", ylab = "seconds")

abline(v=(1:(length(do)-1)*length(noiselvls) + 0.5), col = "black", lty = 6)

axis(1, c(3, 11, 19, 28, 36)+1, c("epiNEM", "B-NEM", "NEM", "PC Algorithm", "ARACNE"),
     tick = F, pos = -25)

accframe2 <- as.data.frame(cbind(data.frame(epiNEM = acc2[1,,]),
                                 data.frame(BNEM = acc2[2,,]), data.frame(NEM = acc2[3,,]),
                                 data.frame(Cor = acc2[4,,]), data.frame(MI = acc2[5,,])))

colnames(accframe2) <- rep(noiselvls, 5)

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

abline(v=(1:(length(do)-1)*length(noiselvls) + 0.5), col = "black", lty = 6)

axis(1, c(3, 11, 19, 28, 36)+1, c("epiNEM", "B-NEM", "NEM", "PC Algorithm", "ARACNE"),
     tick = F, pos = -0.2)

## logical nems:

colvec2 <- c(rep("orange", length(noiselvls)), rep("blue", length(noiselvls)))

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

colnames(logicsframe) <- rep(noiselvls, 2)

boxplot(logicsframe, col = colvec2, main = "accuracy of the inferred logic gate",
        ylim = c(0,1))

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

axis(1, c(3, 11, 19, 28, 36)+1, c("epiNEM", "B-NEM", "NEM", "PC Algorithm", "ARACNE"),
     tick = F, pos = -0.2)

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

colnames(accframe) <- rep(noiselvls, 2)

boxplot(accframe, col = colvec2, main = "accuracy of the inferred expected data",
        ylim = c(0,1))
```

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

axis(1, c(3, 11, 19, 28, 36)+1, c("epiNEM", "B-NEM", "NEM", "PC Algorithm", "ARACNE"),
     tick = F, pos = -0.2)
```







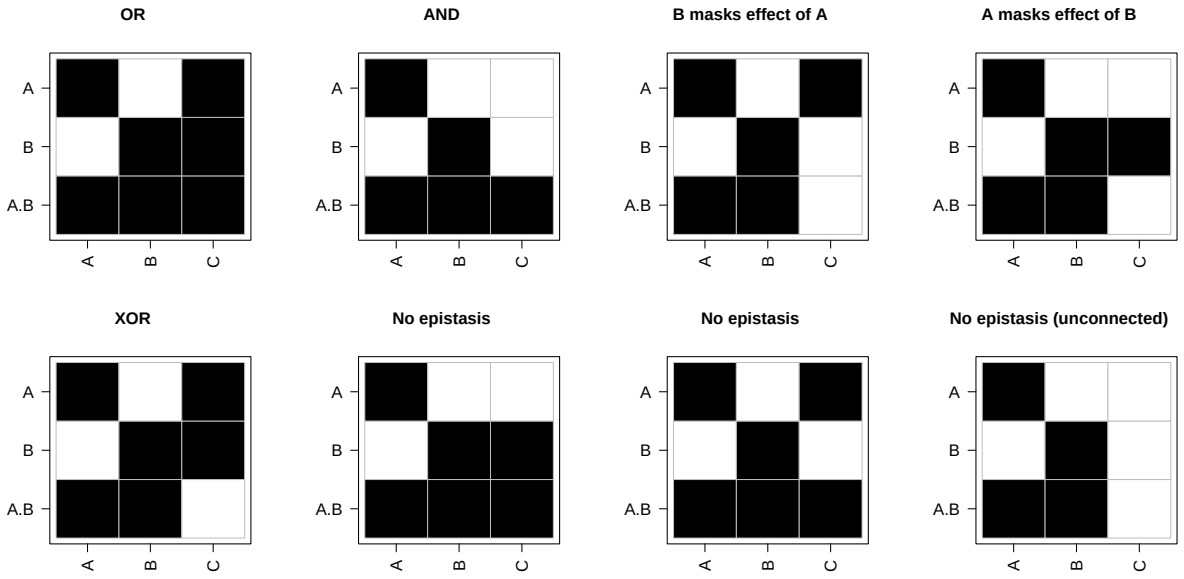


Yeast knockout screens

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])), Colv = F, Rowv = F,
          main = "OR", col = "Greys", sub = "", colorkey = NULL)
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, -1, 1), 3, 3,
                 dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Colv = F, Rowv = F,
          main = "AND", col = "Greys", sub = "", colorkey = NULL)
heatmapOP(matrix(c(1,-1,1,-1,1,1, 1, -1, -1), 3, 3,
                 dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Colv = F, Rowv = F,
          main = "B masks effect of A", col = "Greys", sub = "", colorkey = NULL)
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, 1, -1), 3, 3,
                 dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Colv = F, Rowv = F,
          main = "A masks effect of B", col = "Greys", sub = "", colorkey = NULL)
heatmapOP(matrix(c(1,-1,1,-1,1,1, 1, 1, -1), 3, 3,
                 dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Colv = F, Rowv = F,
          main = "XOR", col = "Greys", sub = "", colorkey = NULL)
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, 1, 1), 3, 3,
                 dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Colv = F, Rowv = F,
          main = "No epistasis", col = "Greys", sub = "", colorkey = NULL)
heatmapOP(matrix(c(1,-1,1,-1,1,1, 1, -1, 1), 3, 3,
                 dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Colv = F, Rowv = F,
          main = "No epistasis", col = "Greys", sub = "", colorkey = NULL)
heatmapOP(matrix(c(1,-1,1,-1,1,1, -1, -1, -1), 3, 3,
                 dimnames = list(c("A", "B", "A.B"), LETTERS[1:3])), Colv = F, Rowv = F,
          main = "No epistasis (unconnected)", col = "Greys", sub = "", colorkey = NULL)
options(warn=0)
```



Wageningen et al., 2010

```
file <-
    "http://www.holstegelab.nl/publications/sv/signaling_redundancy/downloads/DataS1.txt"

data <- read.delim(file)
```

```r
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 <- log2(1.7)

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), ]

dataBinWag <- dataBin

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

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) == 1)
##     for (j in singles) {
##         print(j)
##         if (j %in% doubles.singles) { next() }

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

##         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 {
```

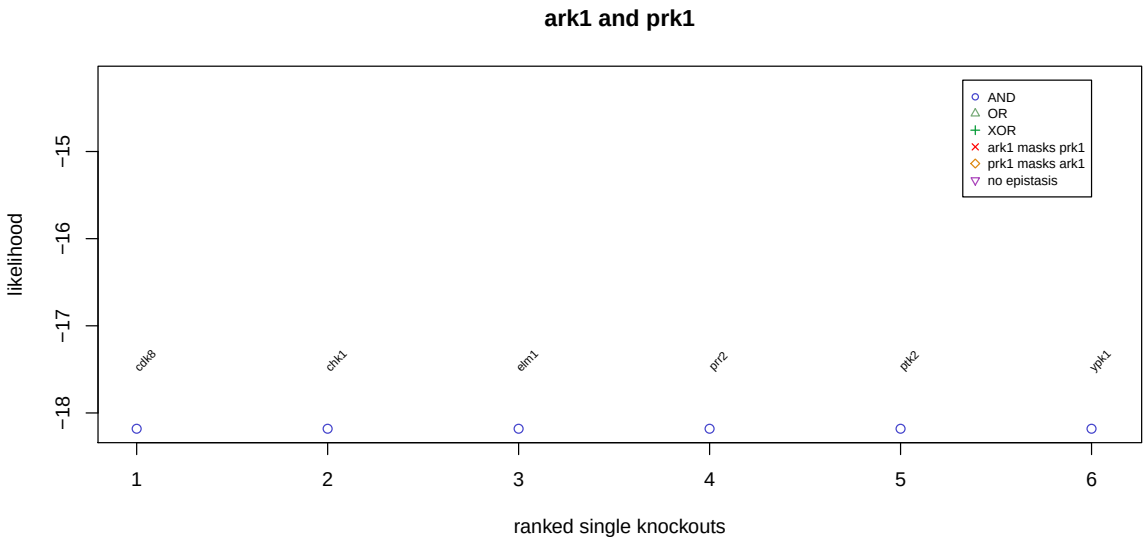
```
##             logicmat[i1, i2] <- "UNCON"
##             llmat[i1, i2] <- -Inf

##         }

##     }

## }
```

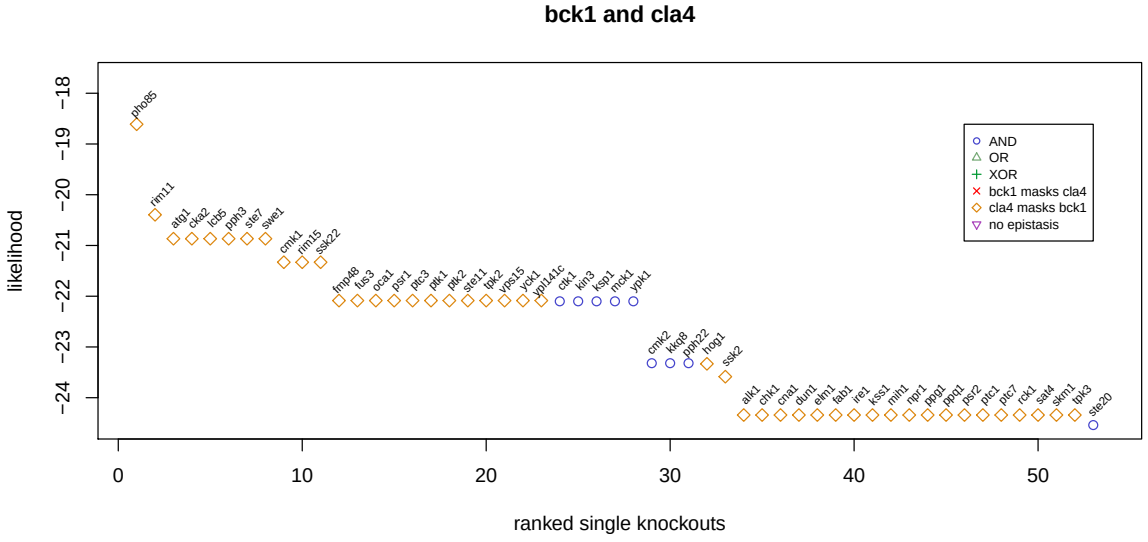
Plot results.

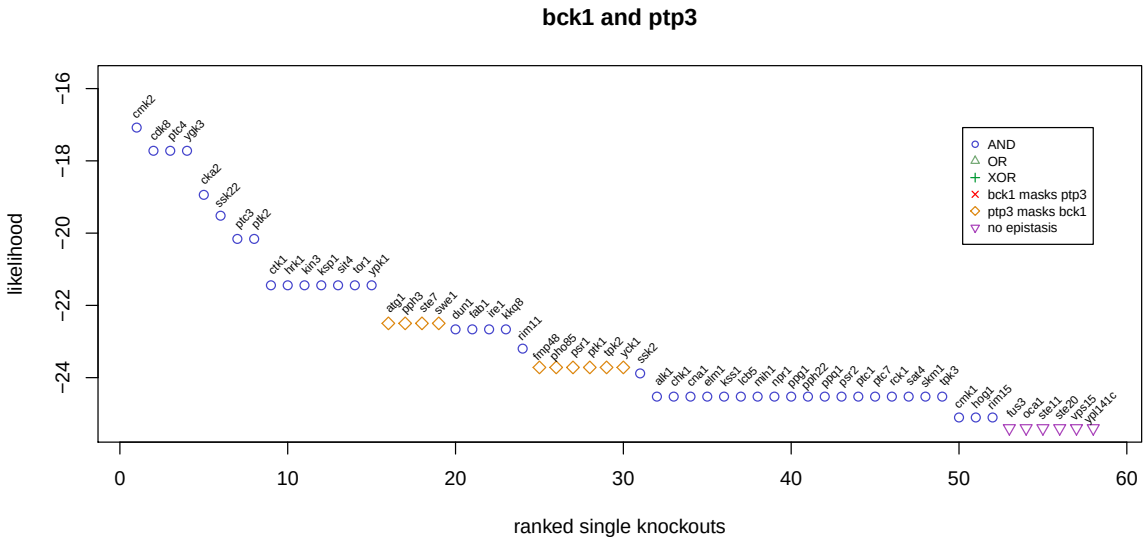
```
palette(c("#4444cc", "#77aa77", "#009933", "#ff0000", "#dd8811", "#aa44bb", "#999900"))

data(wageningen_res)

llmat0 <- wageningen$ll

logicmat0 <- wageningen$logic

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

    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% c("NOINFO", "NOINF"))] <- 7

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

    colvec <- pchvec

    if (all(is.infinite(llvec) == T)) {

        llvec[1:length(llvec)] <- -1000

        margin <- 100
```

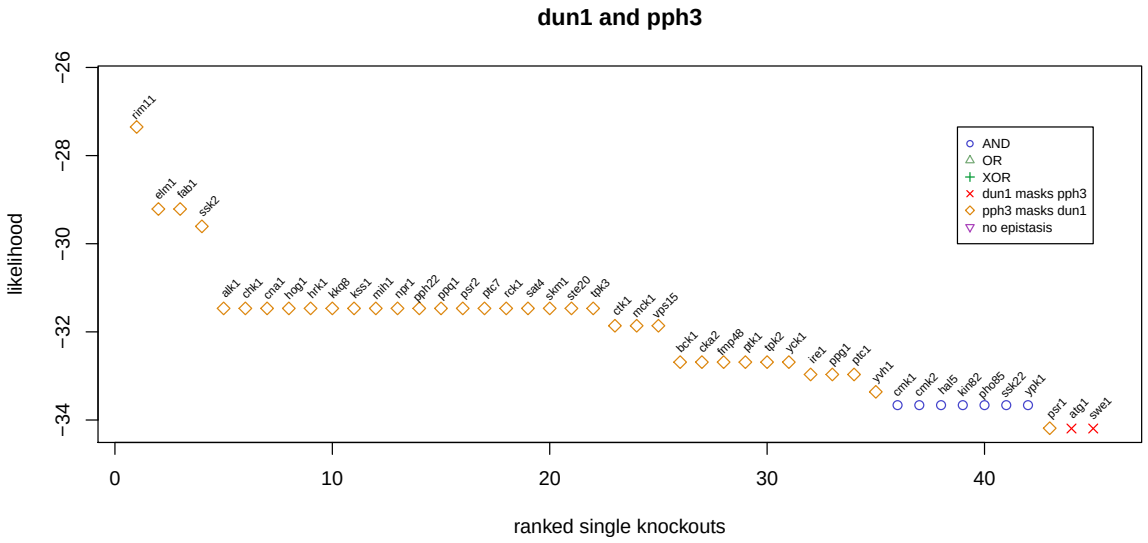
```
    donames <- 30

} else {

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

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

    margin <- abs(max(llvec[1:30], na.rm = T) - min(llvec[1:30], na.rm = T))

    offset <- 0.075

    if (margin == 0) { margin <- 10; offset <- 0.0375 }

    donames <- 30 - sum(is.na(llvec[1:30]) == T)

    if (any(is.na(llvec[1:30]) == T)) { margin2 <- margin*2
    } else { margin2 <- margin }

    llvec[which(is.na(llvec) == T)] <- min(llvec, na.rm = T) - margin

    margin <- margin2

}

if (all(llvec[-(1:30)] - min(llvec[-(1:30)]) == 0)) {

    p2max <- max(llvec[-(1:30)]) + margin

} else {

    p2max <- max(llvec[-(1:30)])

}

mark <- ""
thetop <- sum(!(logicvec %in% c("NOINFO", "NOINF")))
legendx <- length(llvec[1:thetop])
p2max <- max(llvec[1:thetop])
if (p2max == min(llvec[1:thetop])) {
    p2max <- p2max+margin*0.2
}
legendtext <- c("AND", "OR", "XOR", paste(parents[1]," masks ", parents[2], sep = ""),
               paste(parents[2], " masks ", parents[1], sep = ""), "no epistasis")
if (thetop == 0) { next() }
plot = plot(llvec[1:thetop], pch = pchvec[1:thetop], col = colvec[1:thetop],
            ylab = "likelihood", xlab = "ranked single knockouts",
            ylim = c(min(llvec[1:thetop]), max(llvec[1:thetop])+margin*0.2),
            xlim = c(1, thetop+(thetop/100)),
            main = paste(unlist(strsplit(doubles[i], "\\.")), collapse = " and "))
text = text((1:thetop)+(thetop/100), llvec[1:thetop]+(margin*offset),
            labels = names(llvec)[1:thetop], cex = 0.6, srt = 45, pos = 3,
            offset = 0)
```

```
    mtext = mtext(mark, side = 3, line = 1, outer = F, cex = 4, adj = 0)
    legend = legend(legendx, p2max,
                    legend = legendtext,
                    col = 1:6, pch = 1:6, xjust = 1, yjust = 1, cex = 0.7)

}
```

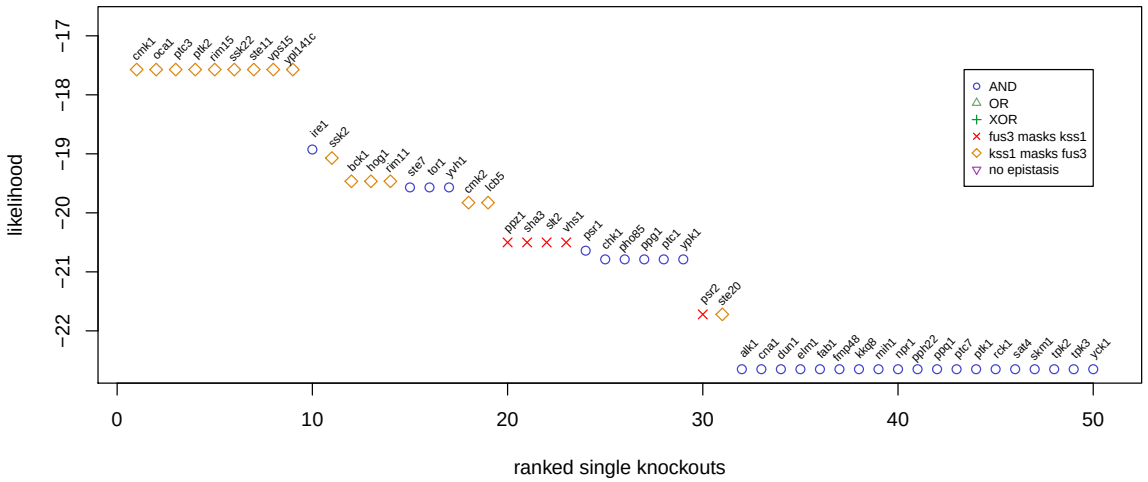




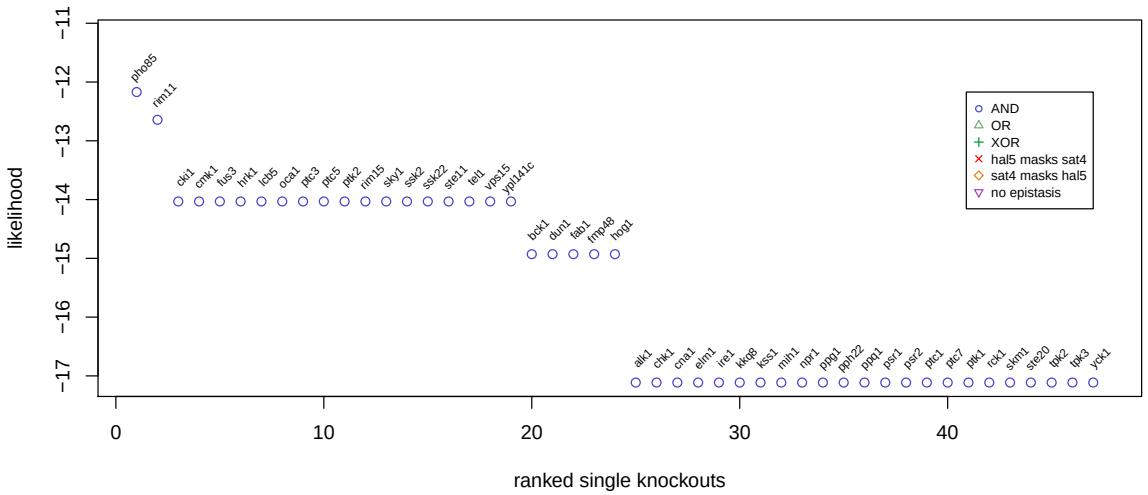

bck1 and ptp3
likelihood
ranked single knockouts
AND
OR
XOR
bck1 masks ptp3
ptp3 masks bck1
no epistasis

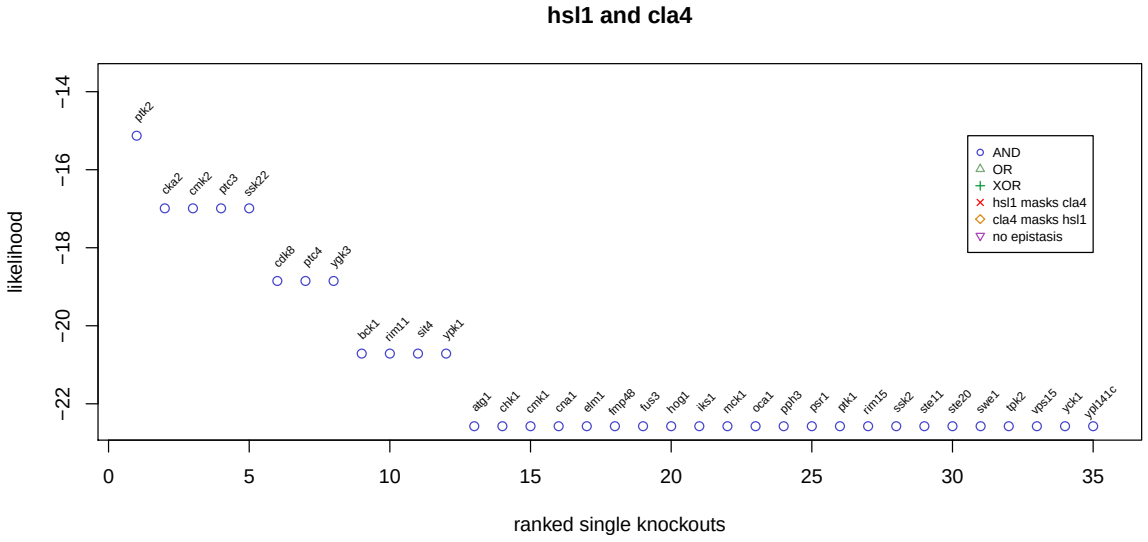

dun1 and pph3
likelihood
ranked single knockouts
AND
OR
XOR
dun1 masks pph3
pph3 masks dun1
no epistasis

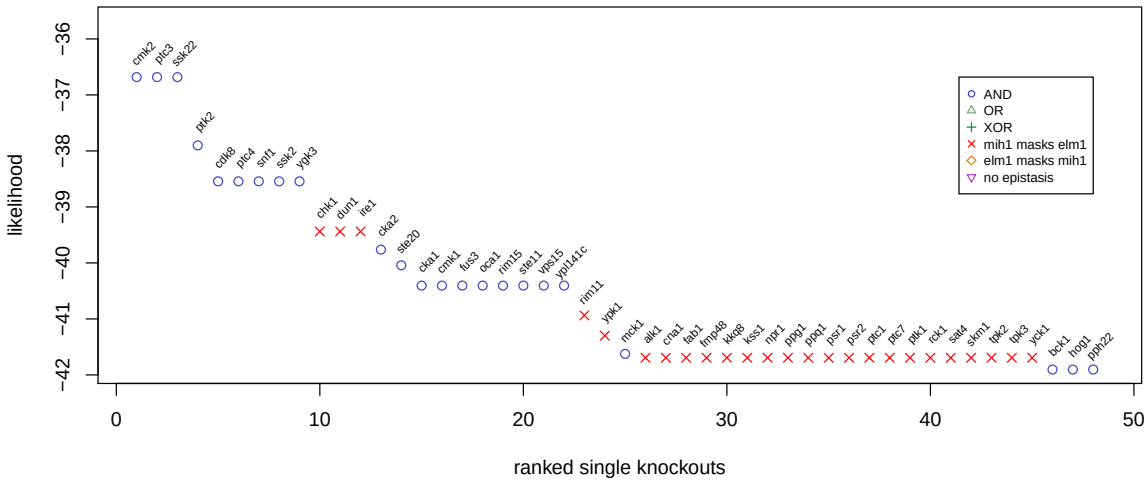
fus3 and kss1

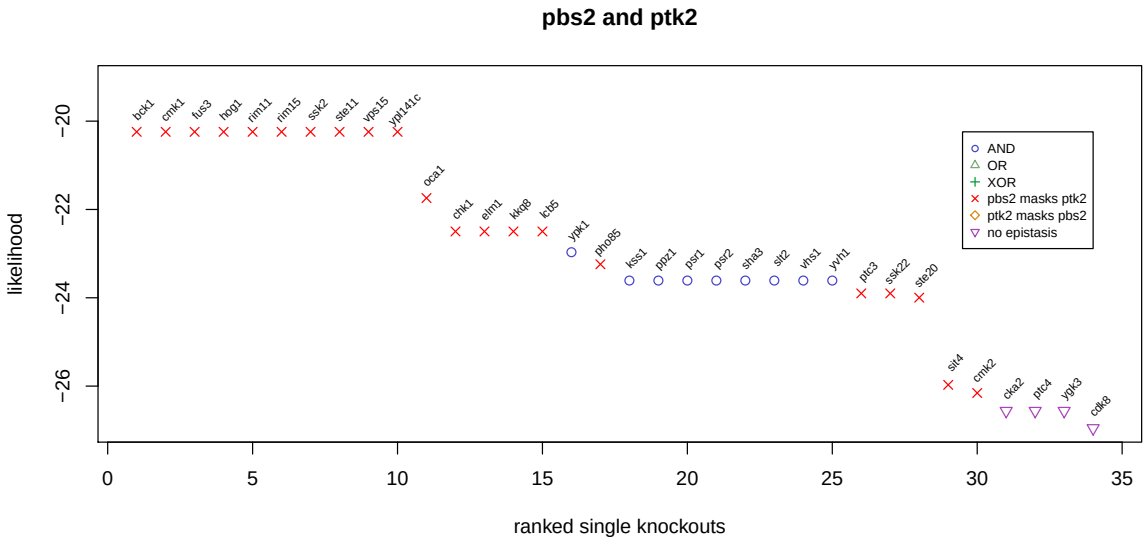


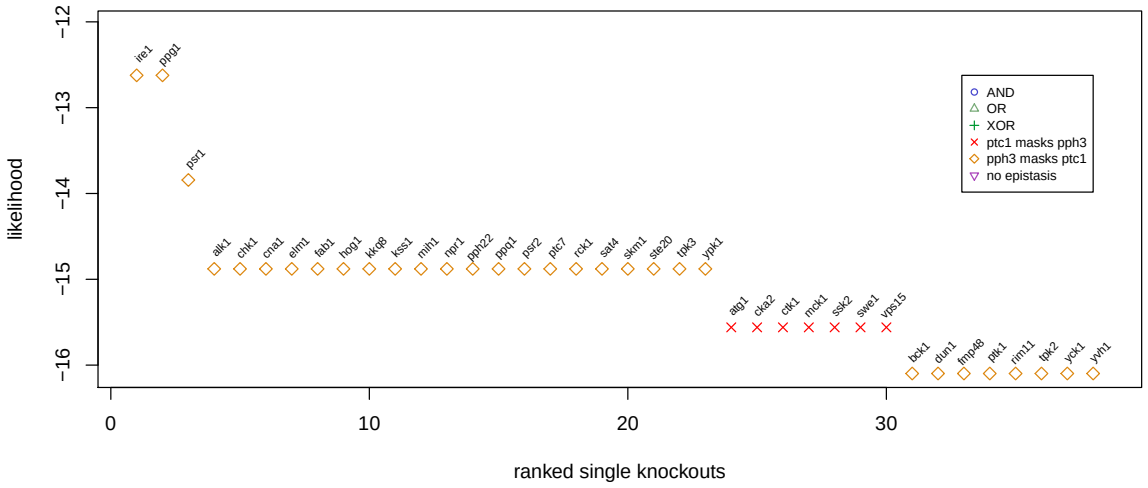
hal5 and sat4



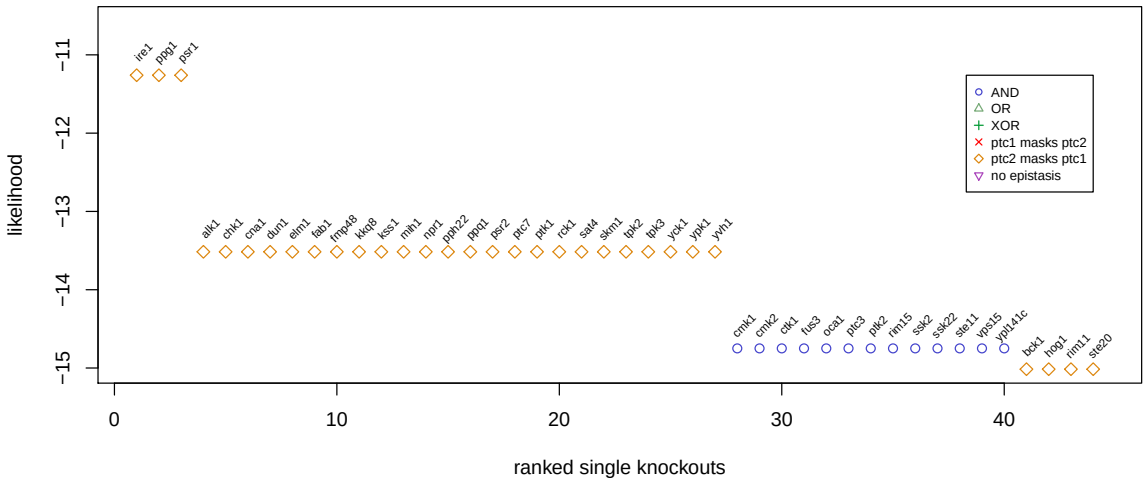

hsl1 and cla4
likelihood
ranked single knockouts
AND
OR
XOR
hsl1 masks cla4
cla4 masks hsl1
no epistasis
ptk2
cka2
cmk2
ptc3
ssk22
cdk8
ptc4
ygk3
bck1
rim11
sit4
ypk1
atg1
chk1
cmk1
cna1
elm1
fmp48
fus3
hog1
iks1
mck1
oca1
pph3
psr1
ptk1
rim15
ssk2
ste11
ste20
swe1
tpk2
vps15
yck1
ydr141c


mih1 and elm1
likelihood
ranked single knockouts
AND
OR
XOR
mih1 masks elm1
elm1 masks mih1
no epistasis
cmk2
ptc3
ssk22
ptk2
cdk8
ptc4
snf1
ssk2
ygk3
chk1
dun1
ire1
cka2
ste20
cka1
cmk1
fus3
oca1
rim15
ste11
vps15
ydl141c
rim11
ypk1
mck1
atk1
cna1
fab1
fmp48
kkq8
kss1
npr1
ppg1
ppq1
psr1
psr2
ptc1
ptc7
ptk1
rck1
sat4
skm1
tpk2
tpk3
yck1
bck1
hog1
pph22

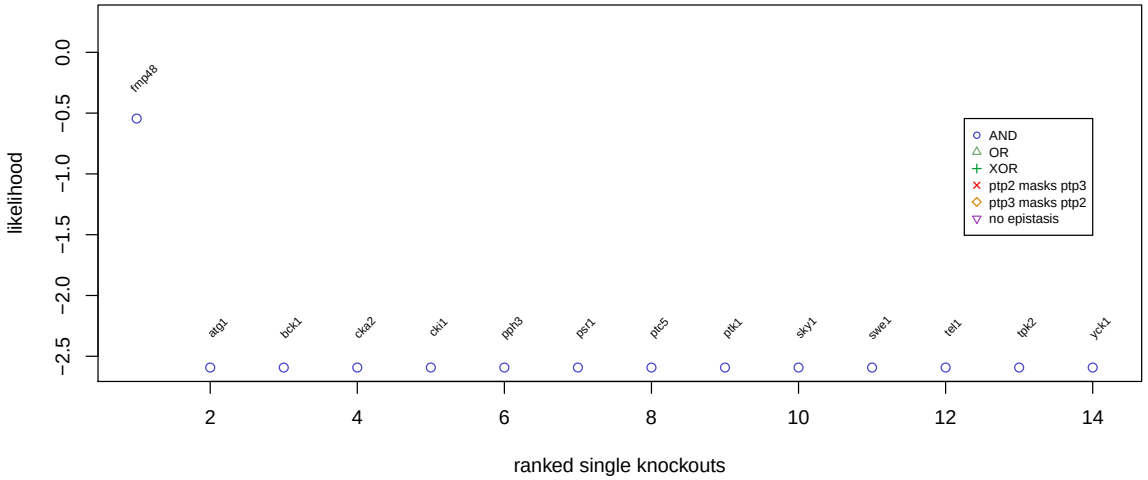

pbs2 and ptk2
likelihood
−20
−22
−24
−26
0
5
10
15
20
25
30
35
ranked single knockouts
bck1
cmk1
lus3
hog1
rim11
rim15
ssk2
ste11
vps15
ypl141c
oca1
chk1
elm1
kkq8
lcb5
ypk1
pho85
kss1
pbz1
psr1
psr2
sha3
slt2
vhs1
yvh1
ptc3
ssk22
ste20
sit4
cmk2
cka2
ptc4
ygk3
ctk3
AND
OR
XOR
pbs2 masks ptk2
ptk2 masks pbs2
no epistasis


ptc1 and pph3
likelihood
−12
−13
−14
−15
−16
0
10
20
30
ranked single knockouts
ire1
ppg1
psr1
alk1
chk1
cna1
elm1
fab1
hog1
kkq8
kss1
mih1
npr1
pph22
ppq1
psr2
ptc7
rck1
sat4
skm1
ste20
tpk3
ypk1
atg1
cka2
ctk1
mck1
ssk2
swe1
vps15
bck1
dun1
fmp48
ptk1
rim11
tpk2
yck1
yvh1
AND
OR
XOR
ptc1 masks pph3
pph3 masks ptc1
no epistasis

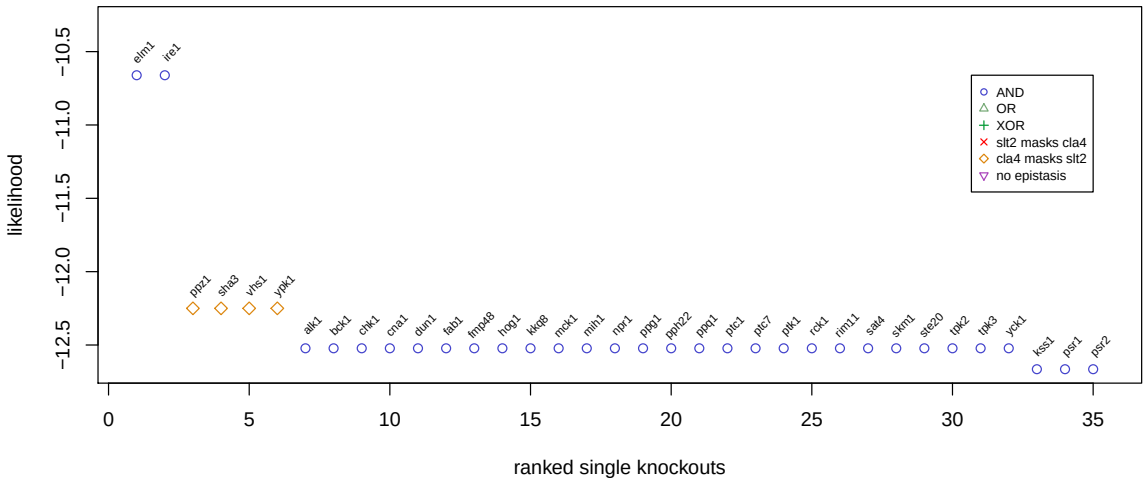
ptc1 and ptc2



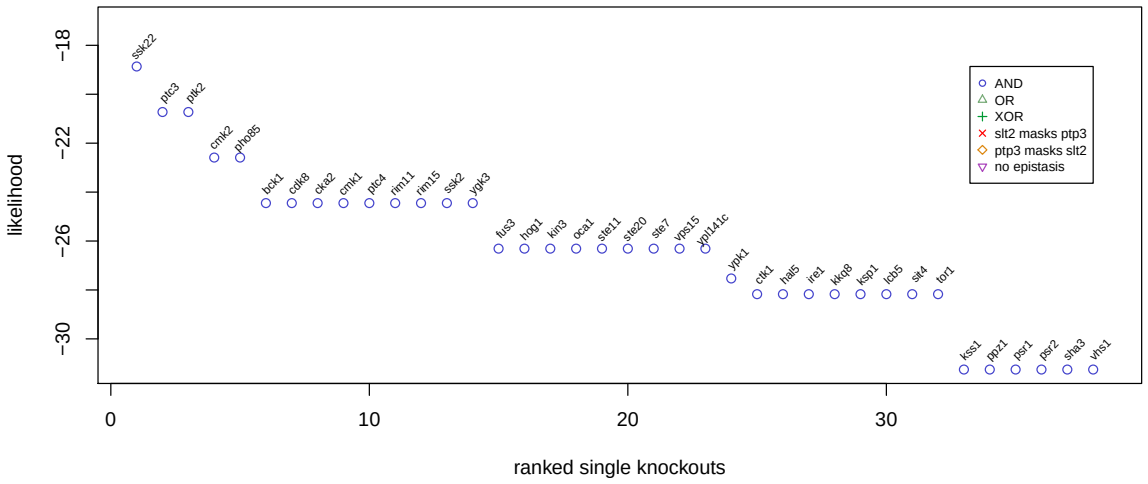
ptp2 and ptp3

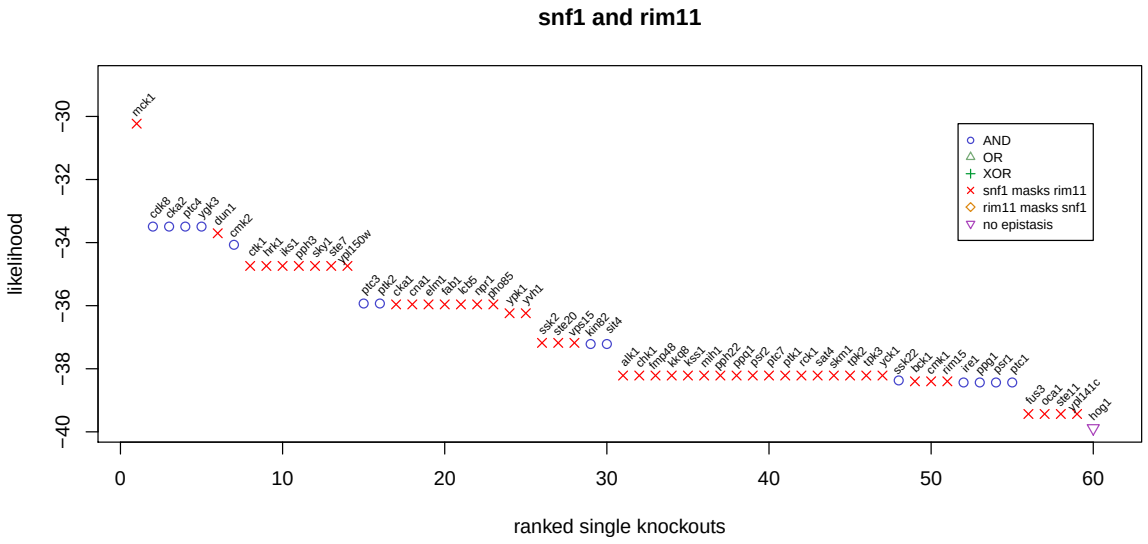


slt2 and cla4



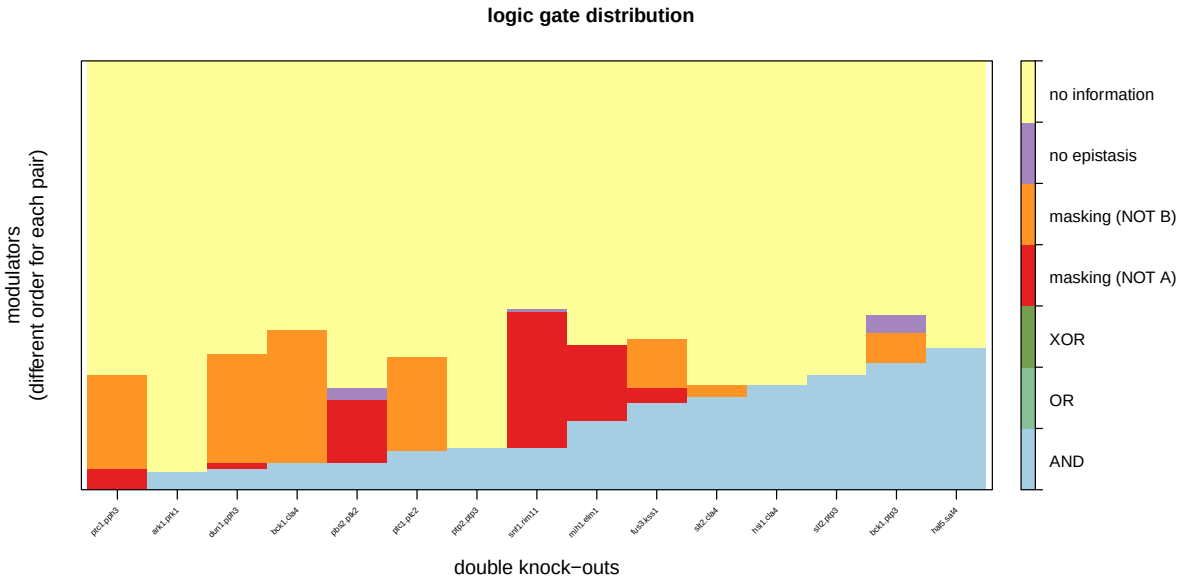
slt2 and ptp3






```
distmat <- wageningen$logic

distmat[which(distmat %in% "AND")] <- 1
distmat[which(distmat %in% "OR")] <- 2
distmat[which(distmat %in% "XOR")] <- 3
distmat[which(distmat %in% "NOEPI")] <- 6
distmat[which(distmat %in% c("NOINFO", "NOINF"))] <- 7

for (i in 1:ncol(distmat)) {

    genes <- unlist(strsplit(colnames(distmat)[i], "\\."))

    distmat[which(distmat[, i] %in%
                  paste(genes[1], " masks the effect of ", genes[2], sep = "")), i] <- 4


    distmat[which(distmat[, i] %in%
                  paste(genes[2], " masks the effect of ", genes[1], sep = "")), i] <- 5

}

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

for (i in 1:ncol(distmat)) {
    distmat[, i] <- rev(sort(distmat[, i]))
}

distmat <- distmat[-which(apply(distmat, 1, sum) == 0), ]

distmat <- distmat[, -which(apply(distmat, 2, max) == 0 | apply(distmat, 2, min) == 7)]

y <- distmat

distmat <- distmat[, order(apply(distmat, 2, function(x) { return(sum(x == 1)) }))]
```

```
y[which(y == 5)] <- 4

rownames(distmat) <- NULL

labeltext <- c("", "no information\n\n\n", "no epistasis\n\n\n","masking (NOT B)\n\n\n",
               "masking (NOT A)\n\n\n", "XOR\n\n\n", "OR\n\n\n", "AND\n\n\n")

heatmapOP(distmat, Colv = F, Rowv = F, main = "logic gate distribution",
          sub = "", col = "Paired", breaks = seq(0.5,7.5, length.out = 8),
          cexRow = 0, cexCol = 0.4, aspect = "fill",
          colorkey = list(space = "right",
                          labels = rev(labeltext), width = 1,
                          at = seq(1.5,7.5, length.out = 8)),
          xlab = "double knock-outs",
          ylab = "modulators\n(different order for each pair)",
          xrot = 45, bordercol = "transparent")
```



Sameith et al., 2015

```
file <-
    "http://www.holstegelab.nl/publications/GSTF_geneticinteractions/downloads/del_mutants_limma.txt"

data <- read.delim(file)

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)
```

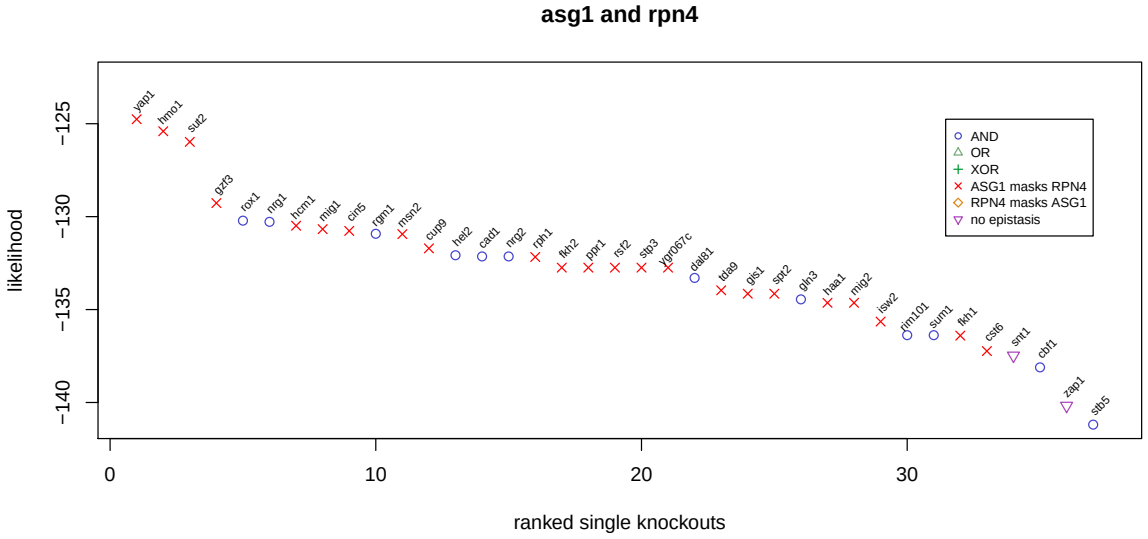
```
dataBin <- dataM

sig <- 0.01

cutoff <- log2(1.5)

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) == 1)
##     for (j in singles) {
##         print(j)
##         if (j %in% doubles.singles) { next() }

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

##         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), ]
##         }
```

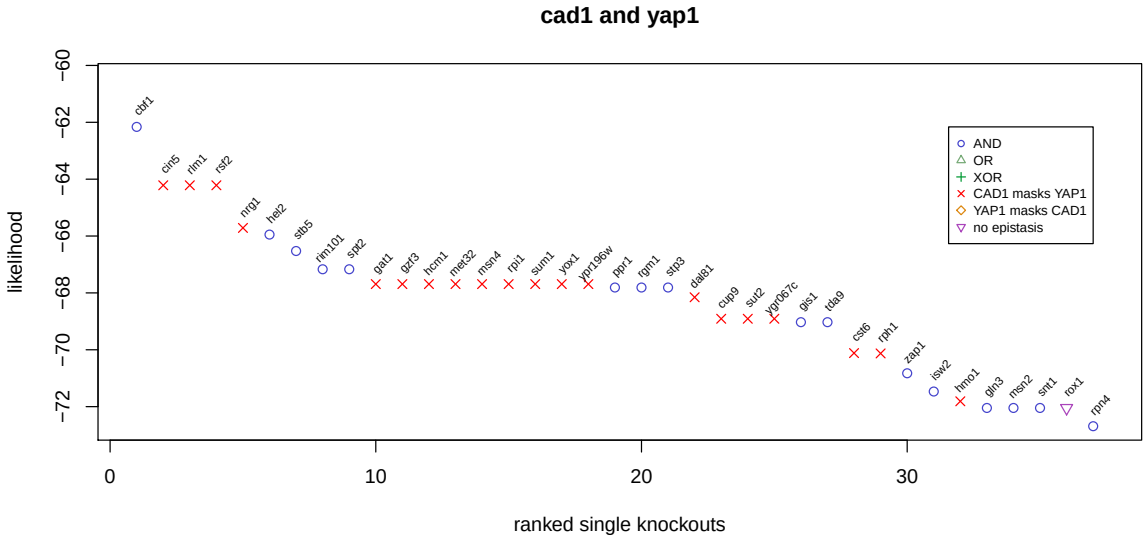
```
##          i1 <- which(singles %in% j)
##          i2 <- which(doubles %in% i)

##          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

##          }

##      }

## }
```

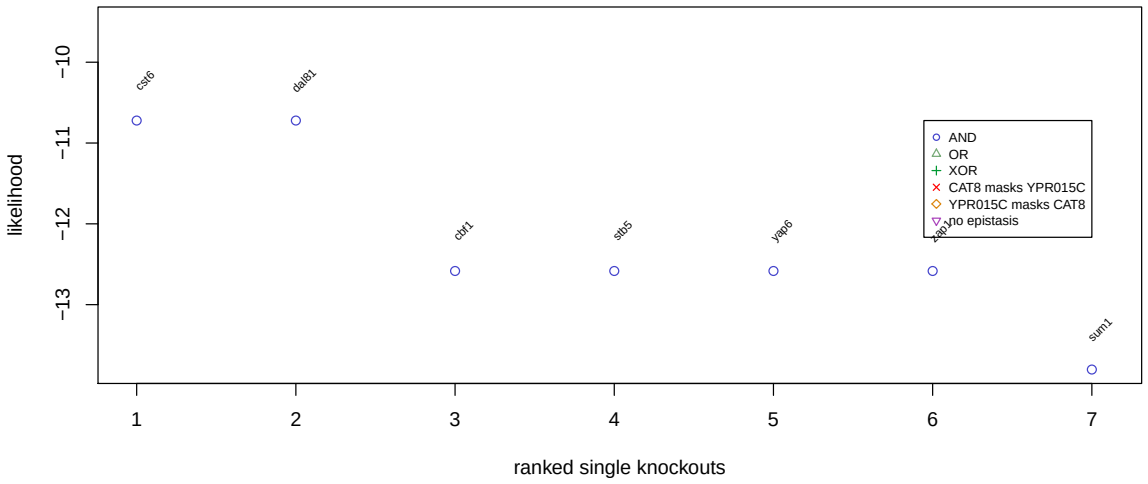
```
data(sameith_res)

llmat0 <- sameith$ll

logicmat0 <- sameith$logic

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

  logicvec <- logicmat0[, i]
```

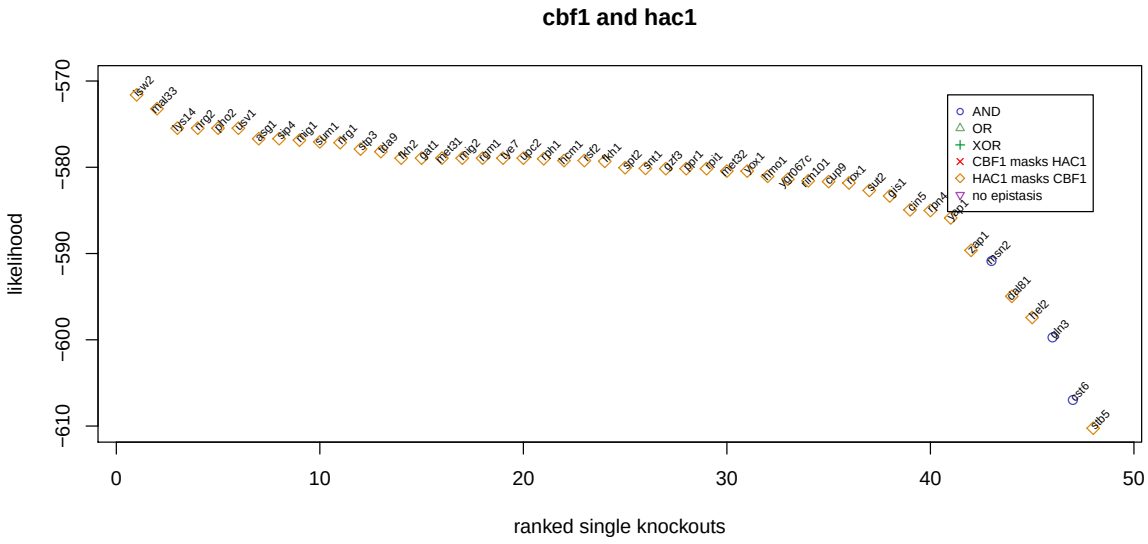
```
llvec <- llmat0[, i]

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% c("NOINFO", "NOINF"))] <- 7

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

  colvec <- pchvec

  if (all(is.infinite(llvec) == T)) {

      llvec[1:length(llvec)] <- -1000

      margin <- 100

      donames <- 30

  } else {

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

      margin <- abs(max(llvec[1:30], na.rm = T) - min(llvec[1:30], na.rm = T))

      if (margin == 0) { margin <- 10 }

      donames <- 30 - sum(is.na(llvec[1:30]) == T)

      if (any(is.na(llvec[1:30]) == T)) { margin2 <- margin*2
      } else { margin2 <- margin }

      llvec[which(is.na(llvec) == T)] <- min(llvec, na.rm = T) - margin

      margin <- margin2

  }

  if (all(llvec[-(1:30)] - min(llvec[-(1:30)]) == 0)) {
```

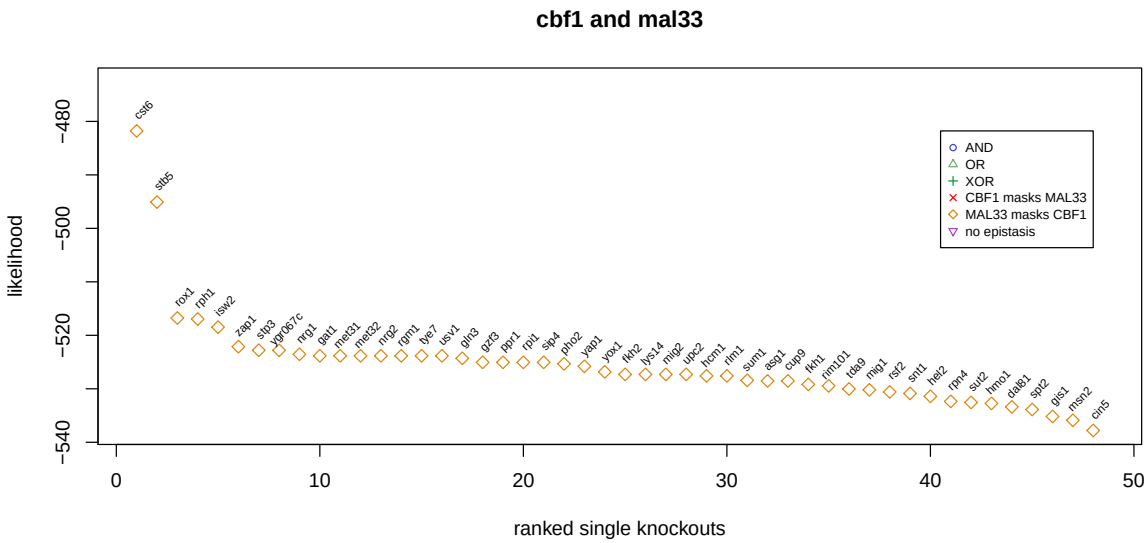
```
        p2max <- max(llvec[-(1:30)]) + margin

    } else {

        p2max <- max(llvec[-(1:30)])

    }

    labeltext <- c("AND", "OR", "XOR", paste(parents[1], " masks ", parents[2], sep = ""),
                   paste(parents[2], " masks ", parents[1], sep = ""), "no epistasis")

    mark <- ""
    pointx <- 10000
    thetop <- sum(!(logicvec %in% c("NOINFO", "NOINF")))
    legendx <- length(llvec[1:thetop])
    p2max <- max(llvec[1:thetop])
    if (p2max == min(llvec[1:thetop])) {
        p2max <- p2max+margin*0.2
    }
    if (thetop == 0) { next() }
    plot = plot(llvec[1:thetop], pch = pchvec[1:thetop], col = colvec[1:thetop],
                ylab = "likelihood", xlab = "ranked single knockouts",
                ylim = c(min(llvec[1:thetop]), max(llvec[1:thetop])+margin*0.2),
                xlim = c(1, thetop+(thetop/100)),
                main = paste(tolower(unlist(strsplit(doubles[i], "\\."))), collapse = " and "))
    text = text((1:thetop)+(thetop/100), llvec[1:thetop]+(margin*offset),
                labels = tolower(names(llvec)[1:thetop]), cex = 0.6, srt = 45, pos = 3, offset = 0)
    mtext = mtext(mark, side = 3, line = 1, outer = F, cex = 4, adj = 0)
    legend = legend(legendx, p2max,
                    legend = labeltext, col = 1:6, pch = 1:6, xjust = 1, yjust = 1, cex = 0.7)

}
```

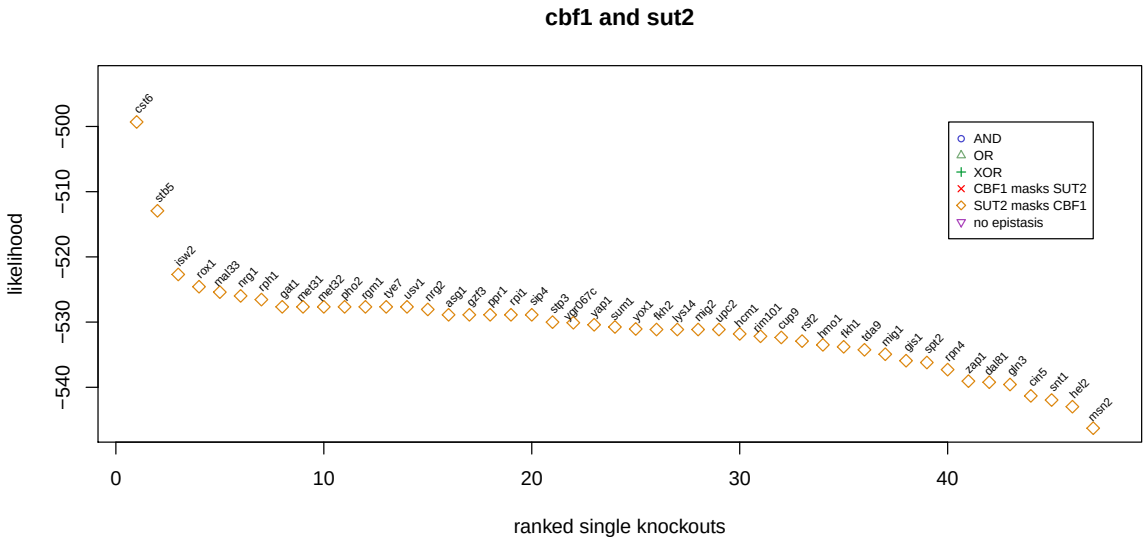


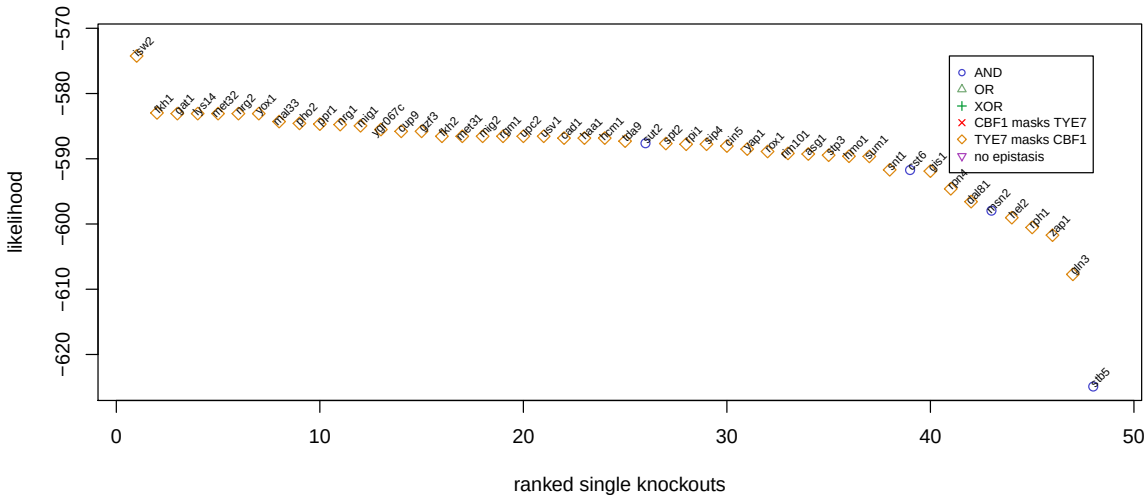

cad1 and yap1
likelihood
−60
−62
−64
−66
−68
−70
−72
0
10
20
30
ranked single knockouts
cbf1
cin5
rlm1
rsf2
nrg1
hst2
stb5
rim101
spt2
gat1
gzf3
hcm1
met32
msn4
rpi1
sum1
yox1
ypr196w
ppr1
fgm1
stp3
dal81
cup9
sut2
ypr067c
gis1
rda9
csi6
rph1
zap1
isw2
hmo1
gln3
msn2
snt1
rox1
rpn4
AND
OR
XOR
CAD1 masks YAP1
YAP1 masks CAD1
no epistasis


cat8 and ypr015c
likelihood
−10
−11
−12
−13
1
2
3
4
5
6
7
ranked single knockouts
csi6
dal81
cbf1
stb5
yap6
zap1
sum1
AND
OR
XOR
CAT8 masks YPR015C
YPR015C masks CAT8
no epistasis

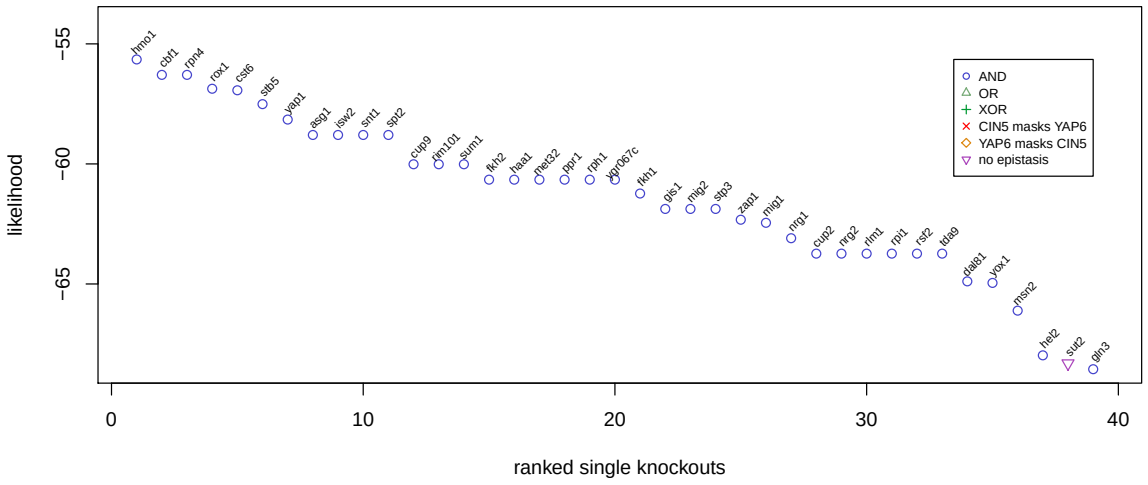

cbf1 and hac1
likelihood
−570
−580
−590
−600
−610
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
CBF1 masks HAC1
HAC1 masks CBF1
no epistasis


cbf1 and mal33
likelihood
−480
−500
−520
−540
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
CBF1 masks MAL33
MAL33 masks CBF1
no epistasis

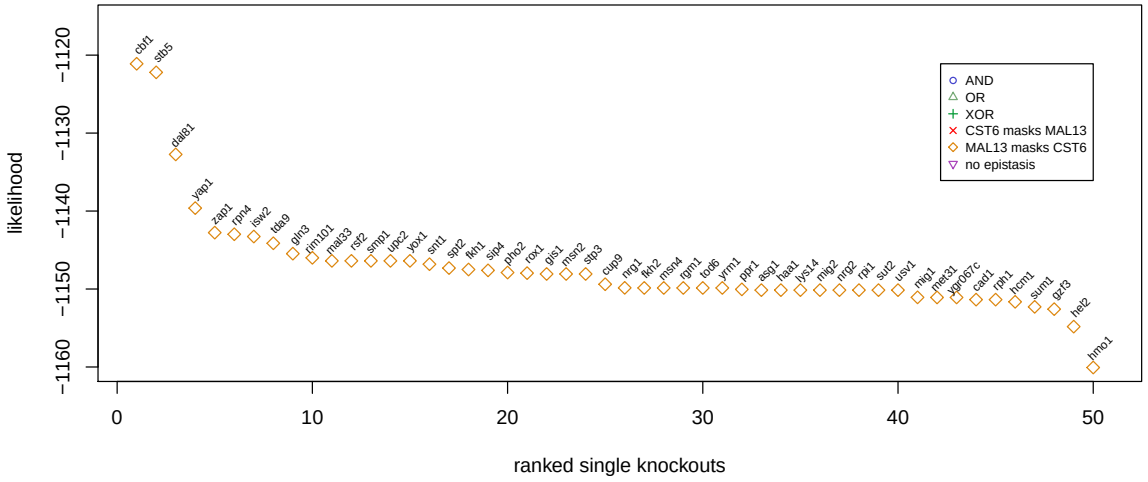

cbf1 and sut2
likelihood
−500
−510
−520
−530
−540
0
10
20
30
40
ranked single knockouts
AND
OR
XOR
CBF1 masks SUT2
SUT2 masks CBF1
no epistasis
csl6
srb5
isw2
rox1
mal33
nrg1
rph1
gat1
met31
met32
pho2
rgm1
tye7
usv1
nrg2
asg1
pzf3
ppr1
rpi1
sip4
stp3
ygr067c
yap1
sum1
yox1
fkh2
lys14
rmp2
upc2
hcm1
rim101
ctp9
rsf2
hmo1
fkh1
tda9
mig1
gis1
spt2
rpn4
zap1
dal81
gln3
cin5
snt1
hir2
msn2


cbf1 and tye7
likelihood
−570
−580
−590
−600
−610
−620
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
CBF1 masks TYE7
TYE7 masks CBF1
no epistasis
isw2
fkh1
gat1
lys14
met32
rmp2
yox1
mal33
pho2
ppr1
nrg1
mig1
ygr067c
ctp9
pzf3
fkh2
met31
nrg2
rgm1
upc2
usv1
cad1
haa1
hcm1
tda9
sut2
spt2
rpi1
sip4
cin5
yap1
rox1
rim101
asg1
stp3
hmo1
stm1
snt1
csl6
gis1
rpn4
dal81
msn2
hir2
rph1
zap1
gln3
srb5

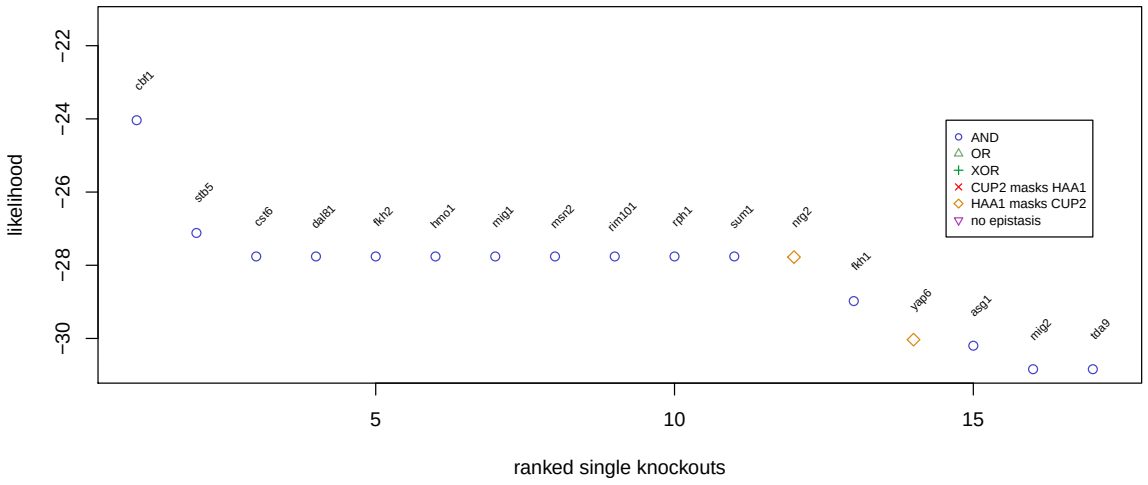
cin5 and yap6



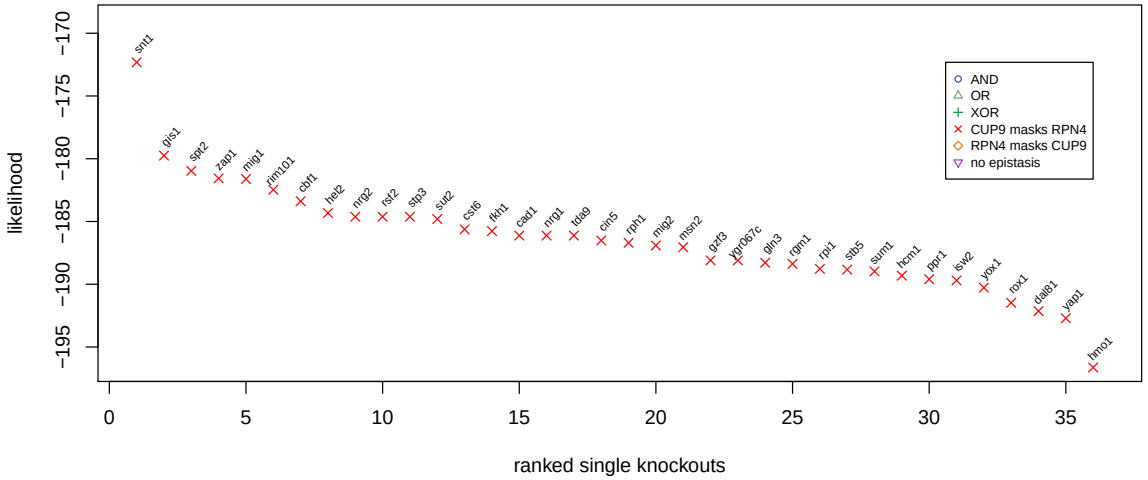
cst6 and mal13

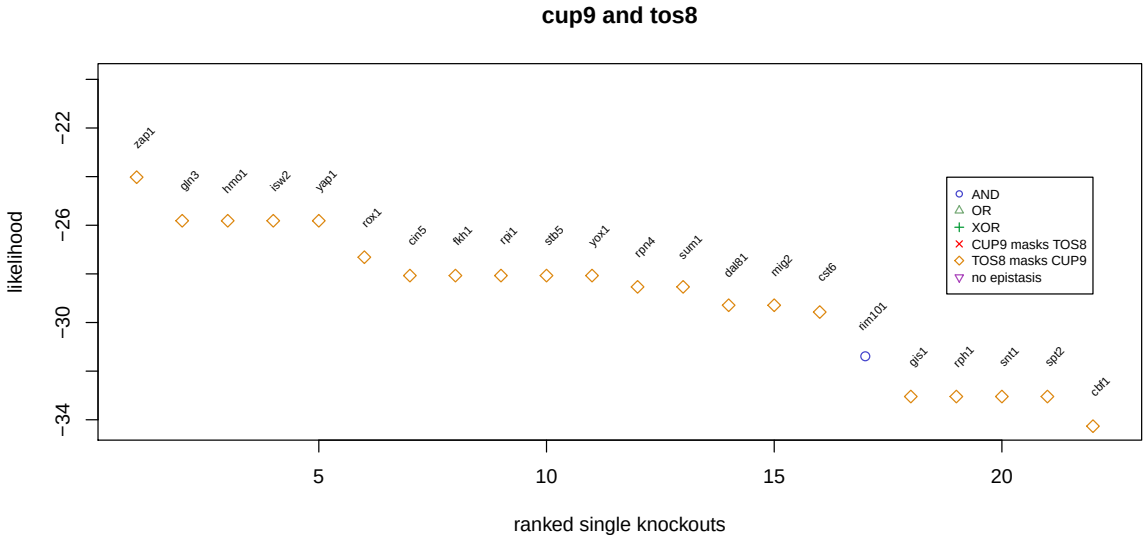


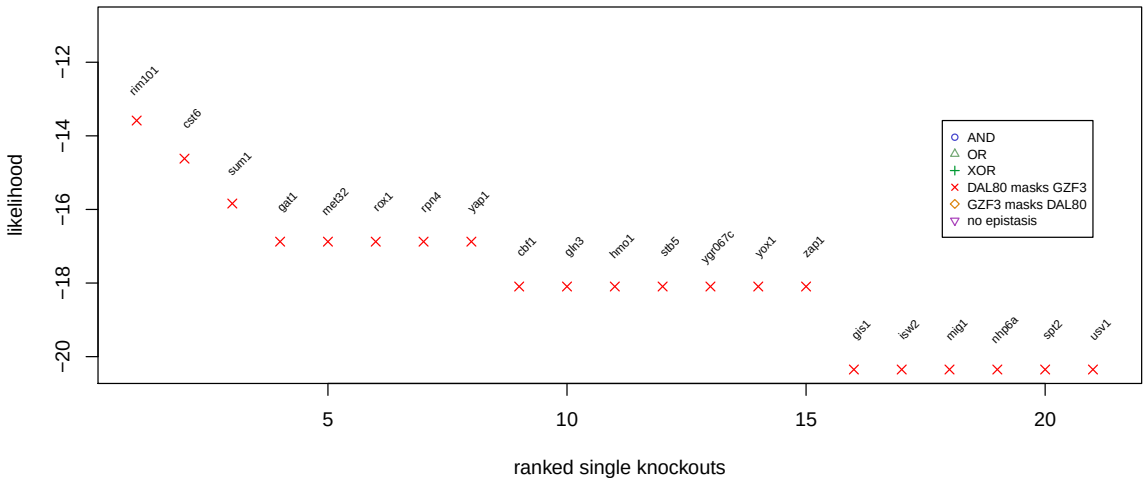
cup2 and haa1

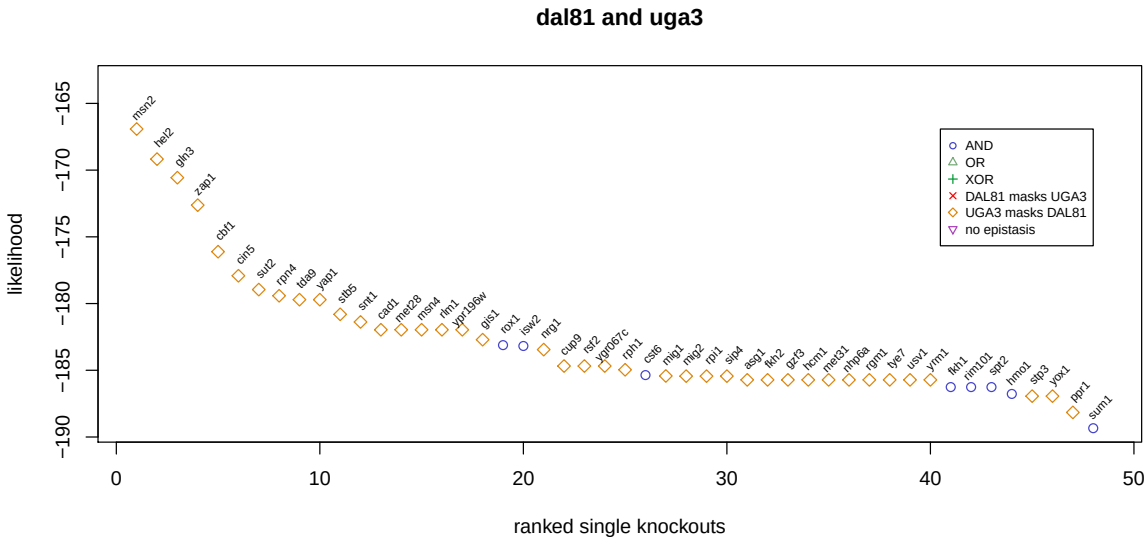


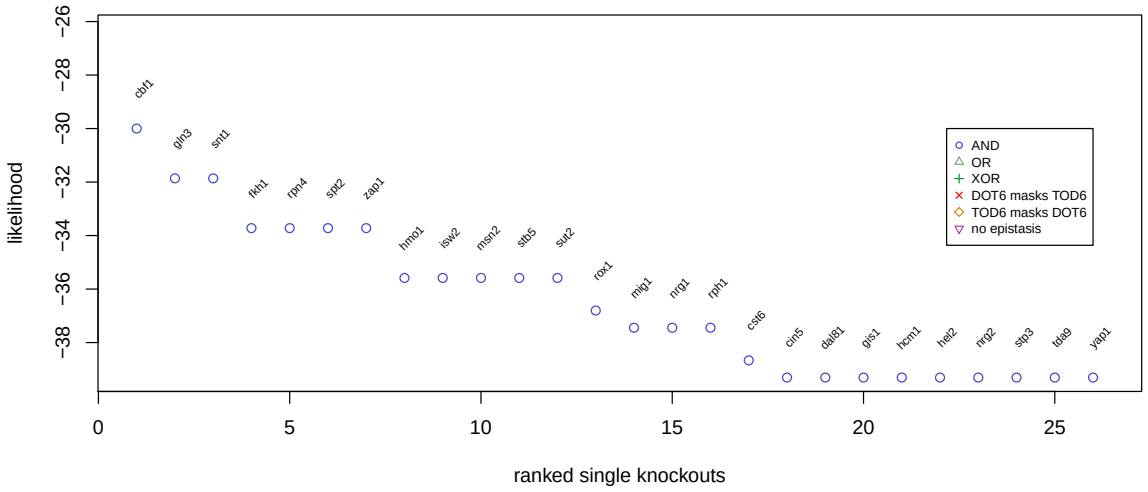
cup9 and rpn4

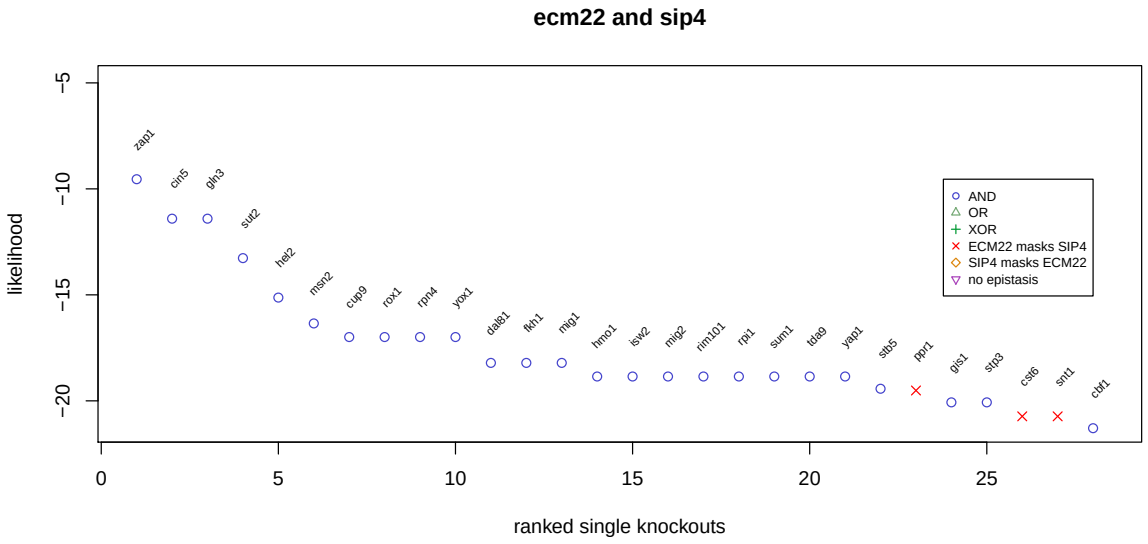


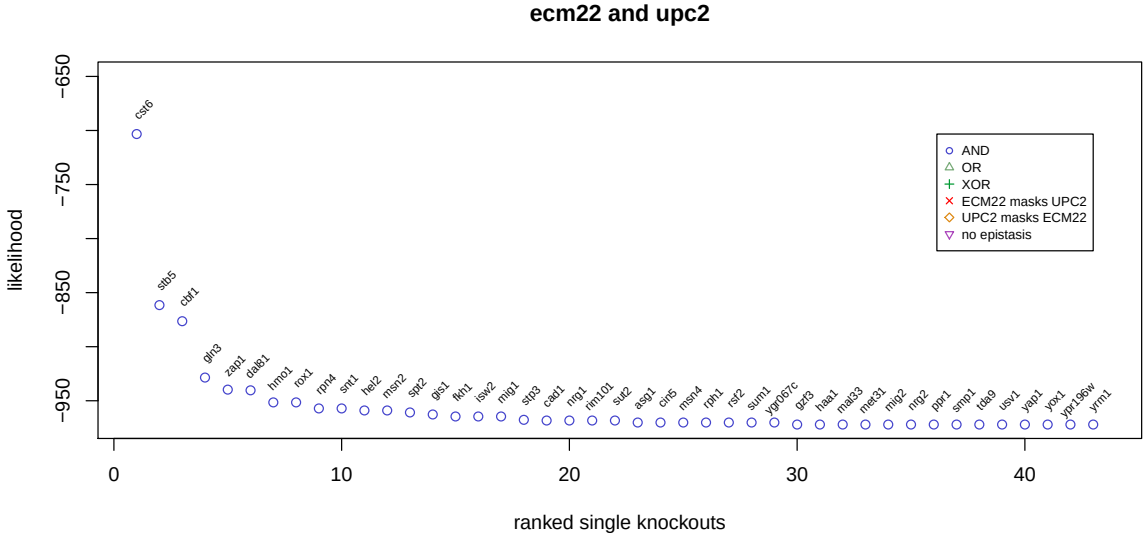

cup9 and tos8
likelihood
−22
−26
−30
−34
zap1
gln3
hmo1
isw2
yap1
rox1
cin5
fkh1
rpi1
stb5
yox1
rpn4
sum1
dal81
mig2
cst6
rim101
gis1
rph1
snt1
spt2
cbf1
5
10
15
20
ranked single knockouts
AND
OR
XOR
CUP9 masks TOS8
TOS8 masks CUP9
no epistasis

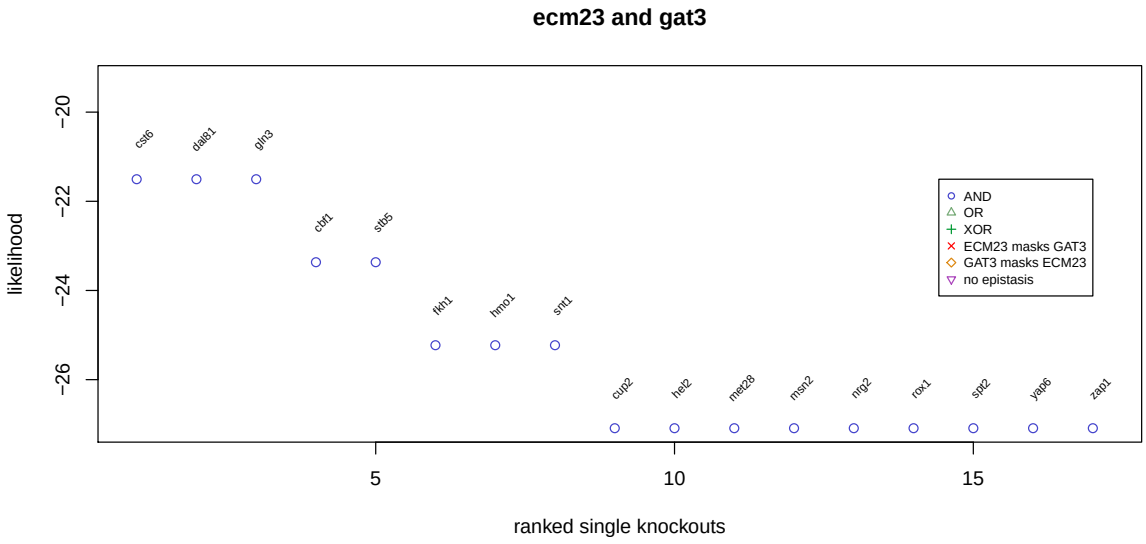

dal80 and gzf3
likelihood
−12
−14
−16
−18
−20
rim101
cst6
sum1
gat1
met32
rox1
rpn4
yap1
cbf1
gln3
hmo1
stb5
ygr067c
yox1
zap1
gis1
isw2
mig1
nhp6a
spt2
usv1
5
10
15
20
ranked single knockouts
AND
OR
XOR
DAL80 masks GZF3
GZF3 masks DAL80
no epistasis

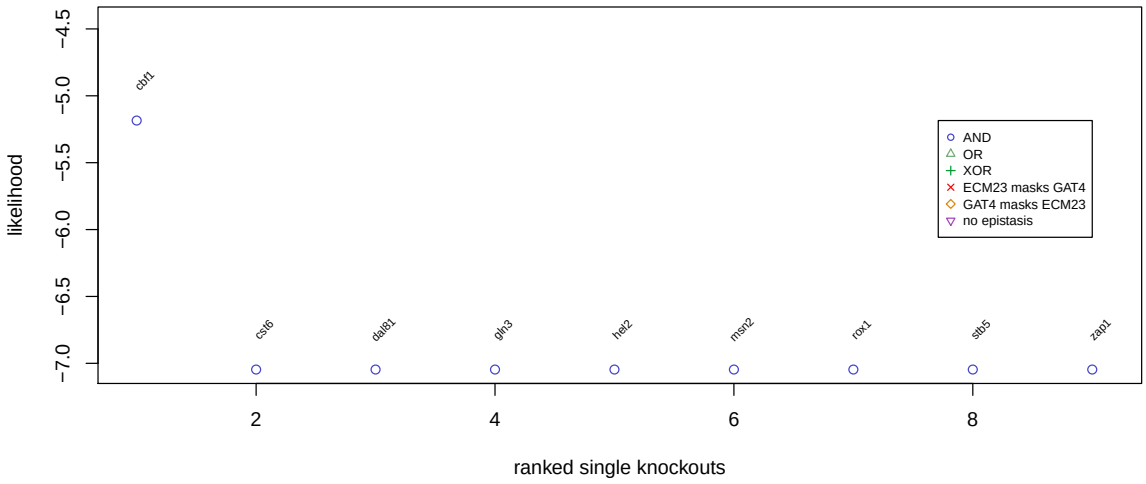

dal81 and uga3
likelihood
−165
−170
−175
−180
−185
−190
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
DAL81 masks UGA3
UGA3 masks DAL81
no epistasis
msn2
hel2
gln3
zap1
cbf1
cin5
sut2
rpn4
tda9
yap1
stb5
snt1
cad1
mar28
msn4
rtm1
ypr196w
gis1
rox1
isw2
nrg1
cup9
rsr2
ygr067c
rph1
csi6
mig1
mig2
rpi1
sip4
asg1
fkh2
gzf3
hcm1
met31
nhp6a
rgm1
tye7
usv1
yrm1
fkh1
rim101
spt2
hmo1
stp3
yox1
ppr1
sum1

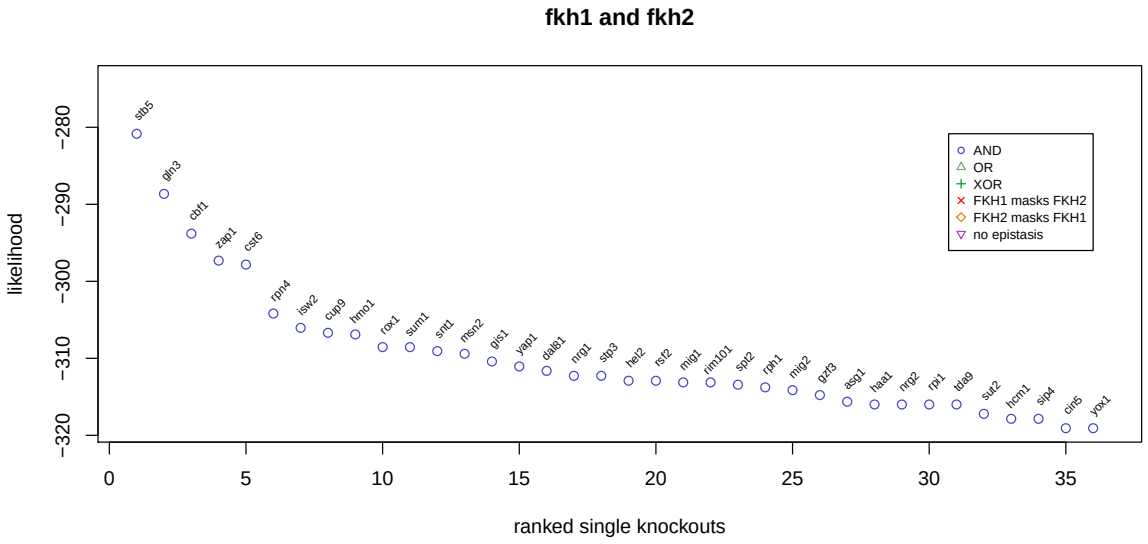

dot6 and tod6
likelihood
−26
−28
−30
−32
−34
−36
−38
0
5
10
15
20
25
ranked single knockouts
AND
OR
XOR
DOT6 masks TOD6
TOD6 masks DOT6
no epistasis
cbf1
gln3
snt1
fkh1
rpn4
spt2
zap1
hmo1
isw2
msn2
stb5
sut2
rox1
mig1
nrg1
rph1
csi6
cin5
dal81
gis1
hcm1
hel2
nrg2
stp3
tda9
yap1

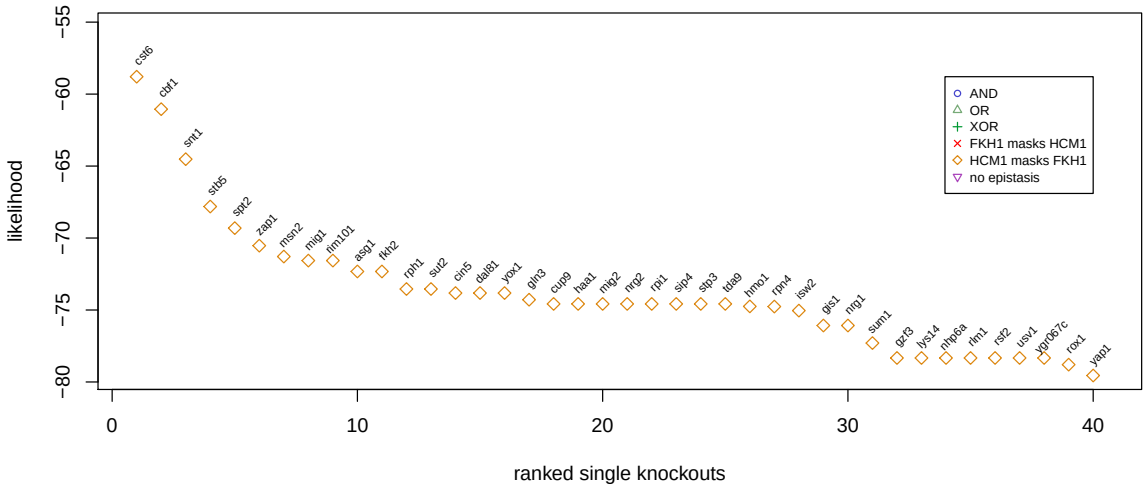

ecm22 and sip4
likelihood
−5
−10
−15
−20
0
5
10
15
20
25
ranked single knockouts
AND
OR
XOR
ECM22 masks SIP4
SIP4 masks ECM22
no epistasis
zap1
cin5
gln3
sut2
hel2
msn2
cup9
rox1
rpn4
yox1
dal81
fkh1
mg1
hmo1
isw2
mig2
rim101
rpi1
sum1
tda9
yap1
stb5
ppr1
gis1
stp3
cst6
snt1
cbf1

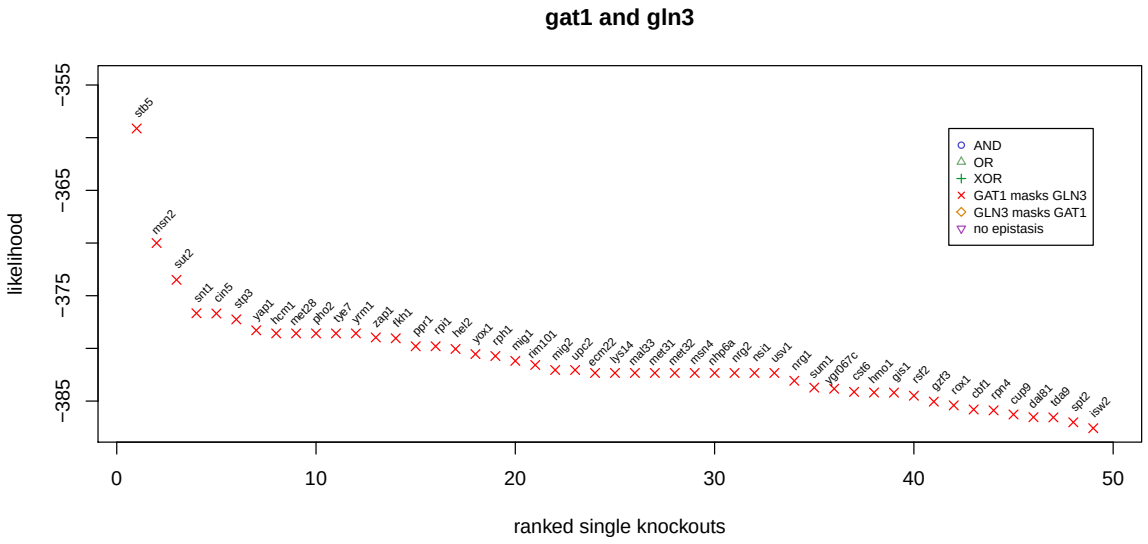

ecm22 and upc2
likelihood
−650
−750
−850
−950
0
10
20
30
40
ranked single knockouts
AND
OR
XOR
ECM22 masks UPC2
UPC2 masks ECM22
no epistasis
cst6
stb5
cbf1
gln3
zap1
dal81
hmo1
rox1
rpn4
snt1
hel2
msn2
spt2
gis1
fkh1
isw2
mig1
stp3
cad1
mg1
rim101
sut2
asg1
cin5
msn4
rph1
rsf2
sum1
ygr067c
gzf3
haa1
mal33
met31
mig2
mg2
ppr1
smp1
tda9
usv1
yap1
yox1
ypr196w
yrm1

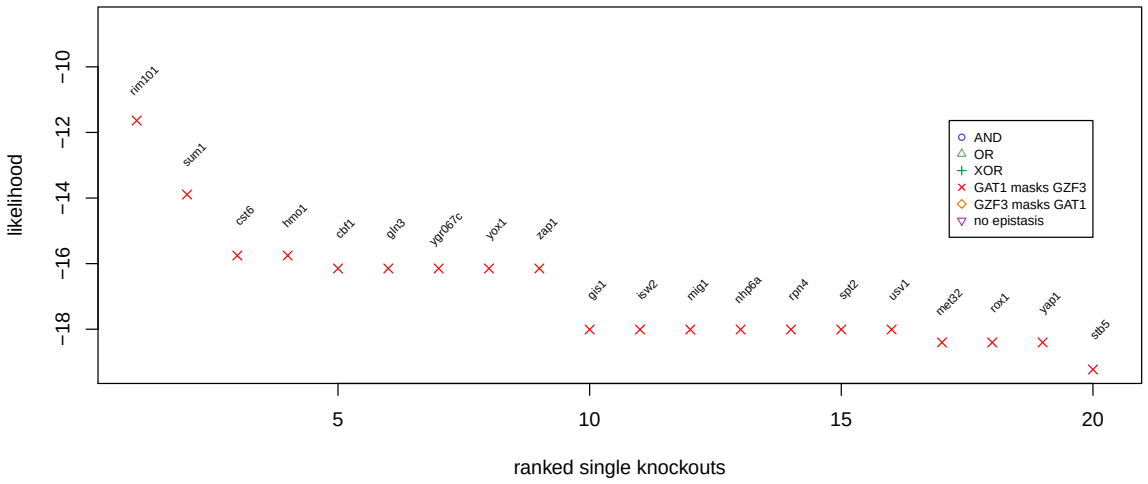

ecm23 and gat3
likelihood
−20
−22
−24
−26
cst6
dal81
gln3
cbf1
stb5
ifxh1
hmo1
srt1
cup2
hel2
met28
msn2
nrg2
rox1
spt2
yap6
zap1
AND
OR
XOR
ECM23 masks GAT3
GAT3 masks ECM23
no epistasis
5
10
15
ranked single knockouts


ecm23 and gat4
likelihood
−4.5
−5.0
−5.5
−6.0
−6.5
−7.0
cbf1
cst6
dal81
gln3
hel2
msn2
rox1
stb5
zap1
AND
OR
XOR
ECM23 masks GAT4
GAT4 masks ECM23
no epistasis
2
4
6
8
ranked single knockouts

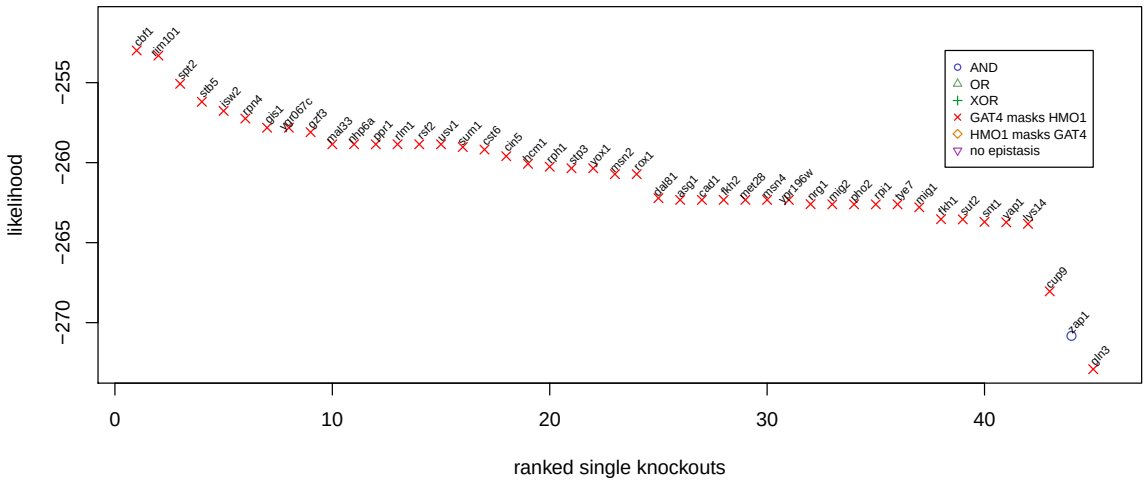

fkh1 and fkh2
likelihood
−280
−290
−300
−310
−320
0
5
10
15
20
25
30
35
ranked single knockouts
AND
OR
XOR
FKH1 masks FKH2
FKH2 masks FKH1
no epistasis
stb5
gln3
cbf1
zap1
cst6
rpn4
isw2
cup9
hmo1
rox1
sum1
snf1
msn2
gis1
yap1
dal81
nrg1
stp3
hel2
rsf2
mig1
rim101
spt2
rph1
mig2
gzf3
asg1
haa1
nrg2
rpi1
tda9
sut2
hcm1
stp4
cin5
yox1


fkh1 and hcm1
likelihood
−55
−60
−65
−70
−75
−80
0
10
20
30
40
ranked single knockouts
AND
OR
XOR
FKH1 masks HCM1
HCM1 masks FKH1
no epistasis
cst6
cbf1
snf1
stb5
spt2
zap1
msn2
mig1
rim101
asg1
fkh2
rph1
sut2
cin5
dal81
yox1
gln3
cup9
haa1
mig2
nrg2
rpi1
stp4
stp3
tda9
hmo1
rpn4
isw2
gis1
nrg1
sum1
gzf3
lys14
rhp6a
rim1
rsf2
usv1
ygr067c
rox1
yap1

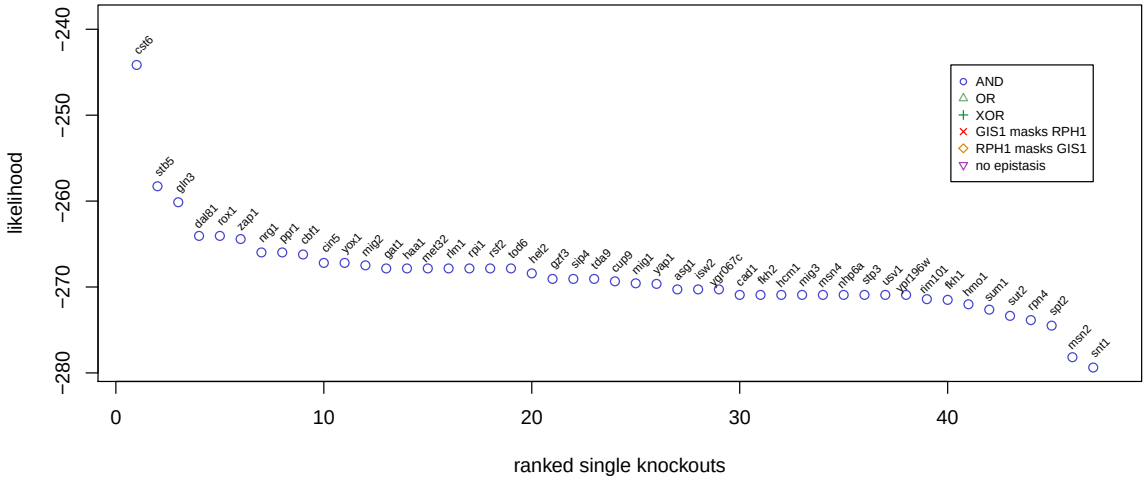

gat1 and gln3
likelihood
−355
−365
−375
−385
0
10
20
30
40
50
ranked single knockouts
stb5
msn2
sut2
snt1
cin5
stp3
yap1
hcm1
met28
pho2
tye7
yrm1
zap1
fkh1
ppr1
rpi1
hel2
yox1
rph1
mig1
nrm101
mig2
upc2
ecm22
lys14
mal33
met31
met32
msn4
nhp6a
mig2
rei1
usv1
nrg1
sum1
ygr067c
cst6
hmo1
gis1
rsf2
gzf3
rox1
cbf1
rpn4
cup9
dal81
tda9
spt2
isw2
AND
OR
XOR
GAT1 masks GLN3
GLN3 masks GAT1
no epistasis

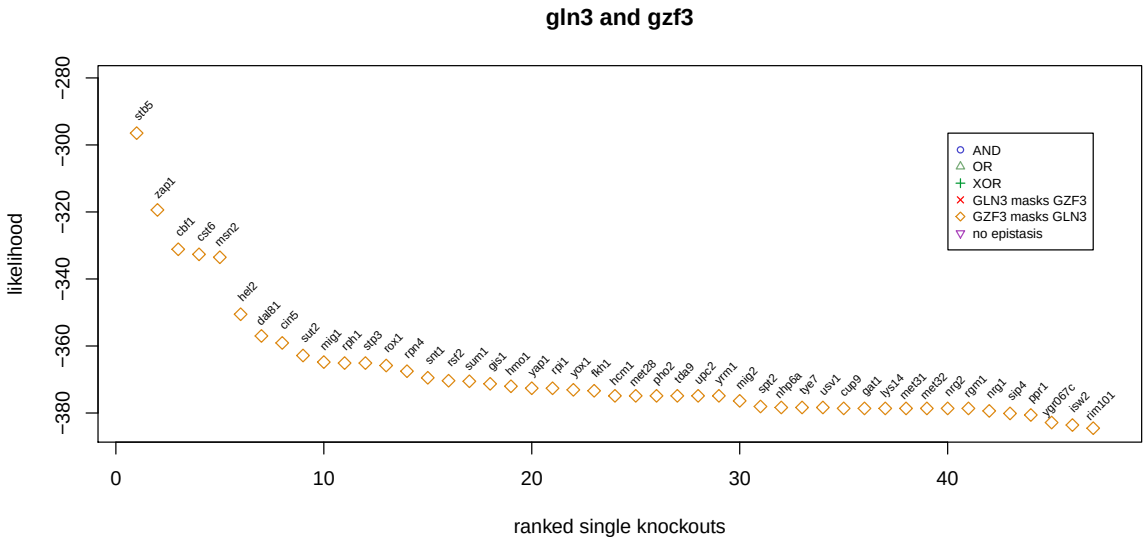

gat1 and gzf3
likelihood
−10
−12
−14
−16
−18
5
10
15
20
ranked single knockouts
nrm101
sum1
cst6
hmo1
cbf1
gln3
ygr067c
yox1
zap1
gis1
isw2
mig1
nhp6a
rpn4
spt2
usv1
met32
rox1
yap1
stb5
AND
OR
XOR
GAT1 masks GZF3
GZF3 masks GAT1
no epistasis

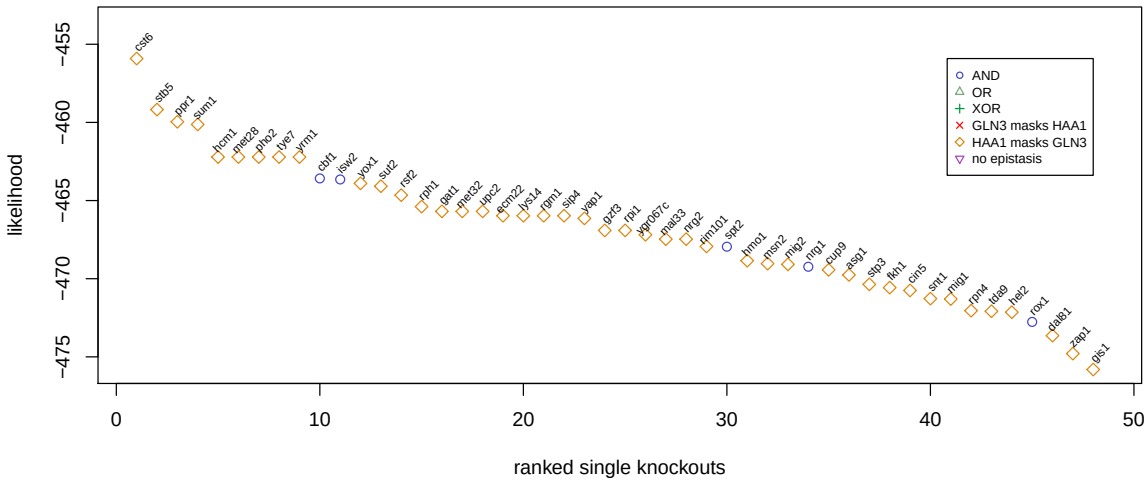
gat4 and hmo1



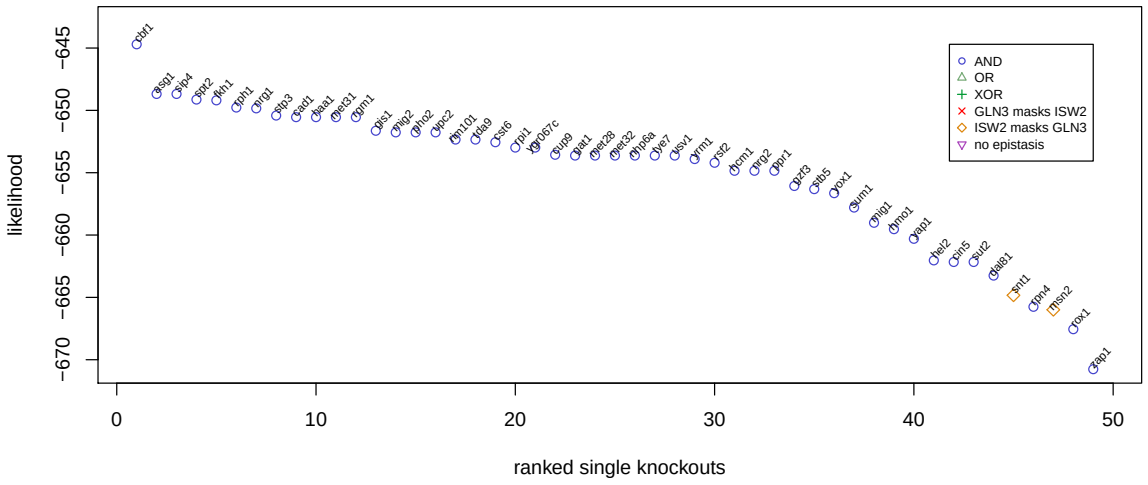
gis1 and rph1



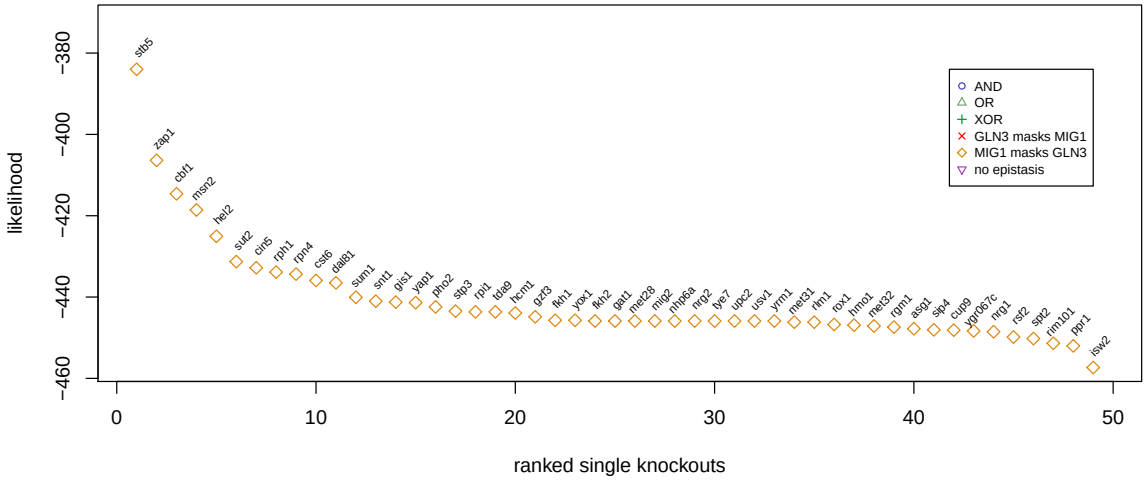

gln3 and gzf3
likelihood
−280
−300
−320
−340
−360
−380
0
10
20
30
40
ranked single knockouts
stb5
zap1
cbf1
cst6
msn2
hel2
dal81
cin5
sut2
mig1
rph1
stp3
rox1
rpn4
snt1
rsf2
sum1
gis1
hmo1
yap1
rpi1
yox1
fkh1
hcm1
met28
pho2
tda9
upc2
yrm1
mig2
spt2
nhp6a
tye7
usv1
cup9
gat1
lys14
met31
met32
nrg2
rgm1
nrg1
sip4
ppr1
ygr067c
isw2
rim101
AND
OR
XOR
GLN3 masks GZF3
GZF3 masks GLN3
no epistasis

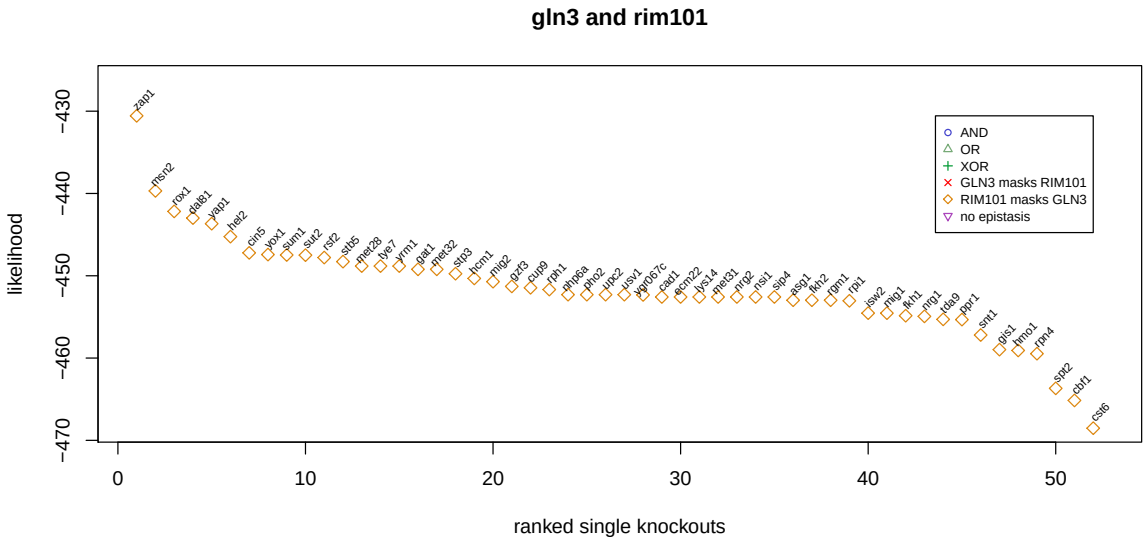

gln3 and haa1
likelihood
−455
−460
−465
−470
−475
0
10
20
30
40
50
ranked single knockouts
cst6
stb5
ppr1
sum1
hcm1
met28
pho2
tye7
yrm1
cbf1
isw2
yox1
sut2
rsf2
rph1
gat1
met32
upc2
ecm22
lys14
rgm1
sip4
yap1
gzf3
rpi1
ygr067c
mal33
nrg2
rim101
skn7
hmo1
msn2
mig2
nrg1
cup9
asg1
stp3
fkh1
cin5
snt1
mig1
rpn4
tda9
hel2
rox1
dal81
zap1
gis1
AND
OR
XOR
GLN3 masks HAA1
HAA1 masks GLN3
no epistasis

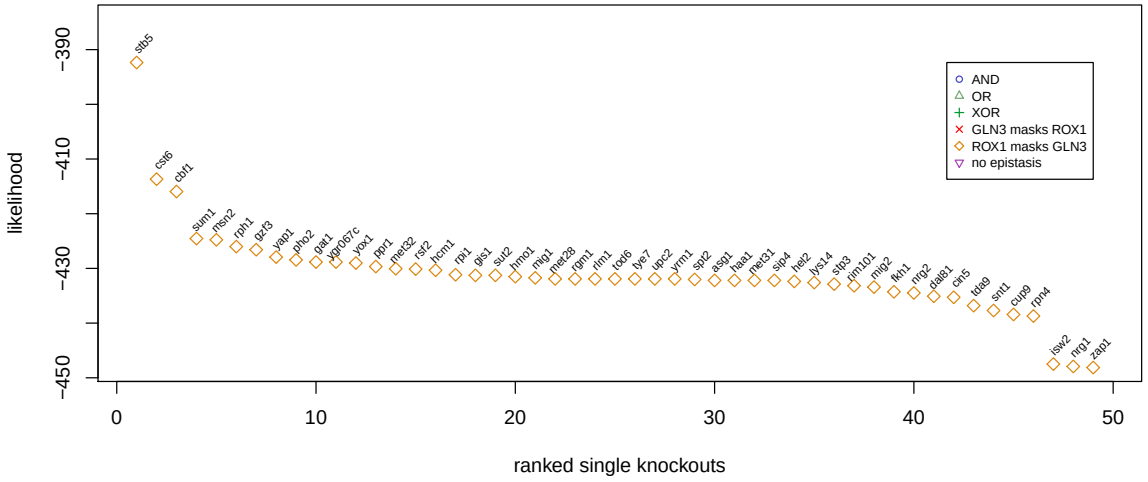
gln3 and isw2

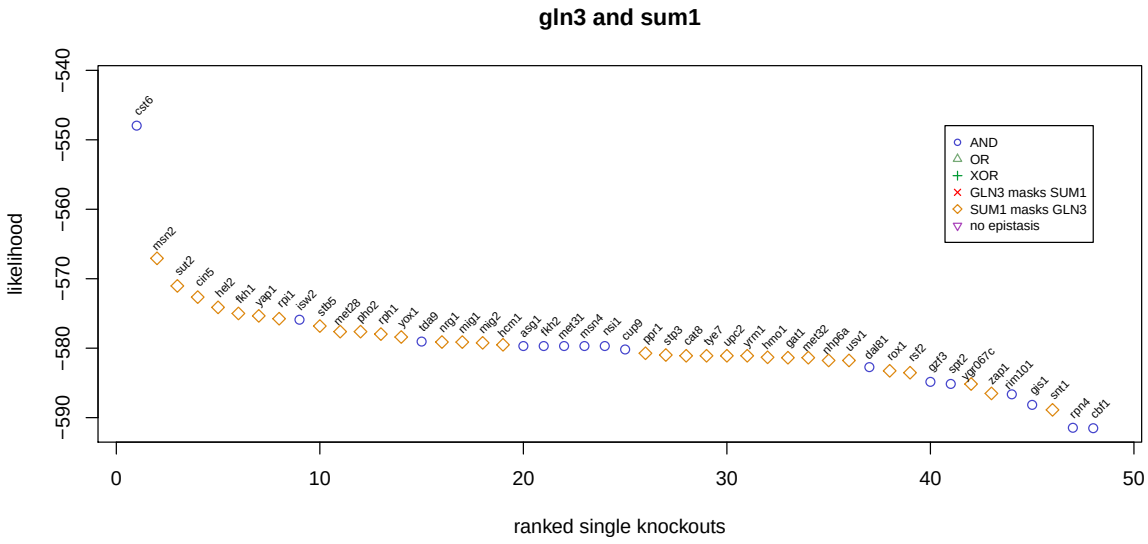


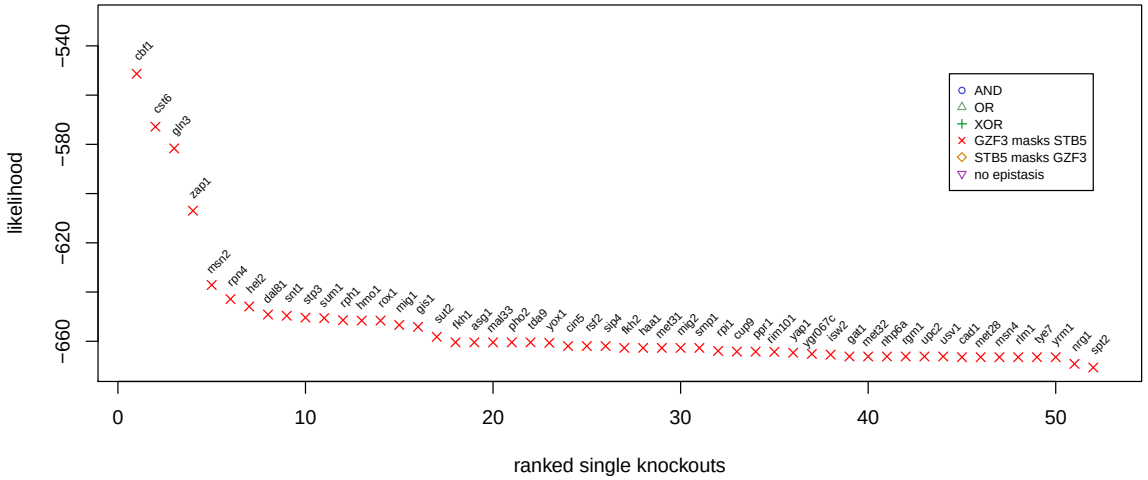
gln3 and mig1

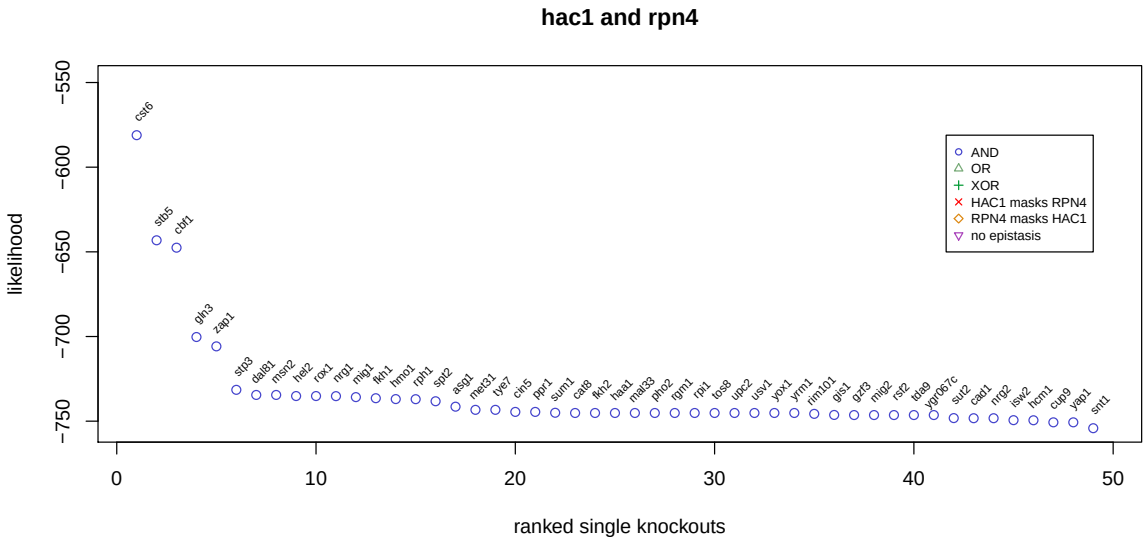


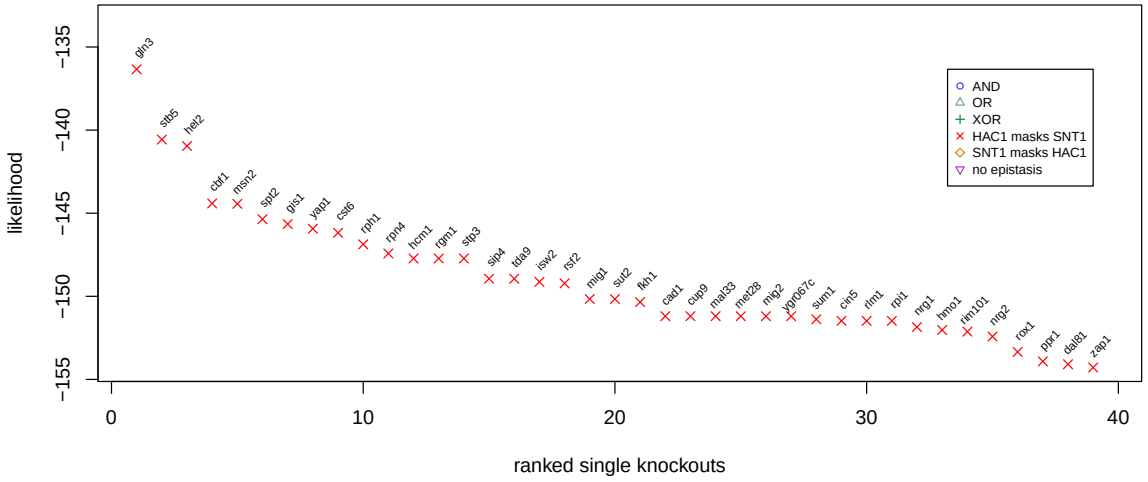

gln3 and rim101
likelihood
−430
−440
−450
−460
−470
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
GLN3 masks RIM101
RIM101 masks GLN3
no epistasis
zap1
rtn2
rox1
dal81
yap1
het2
cin5
vox1
sum1
sut2
rsf2
stb5
met28
tye7
yrm1
gat1
met32
stp3
hcm1
mig2
pzf3
cup9
rph1
ahp6a
pho2
upc2
usv1
ygr067c
cat1
atm22
lys14
met31
mig2
rsi1
sip4
asg1
fkh2
rgm1
rpi1
isw2
mig1
fkh1
nrg1
tda9
ppr1
snt1
gis1
hmo1
rpn4
spt2
cbf1
cst6


gln3 and rox1
likelihood
−390
−410
−430
−450
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
GLN3 masks ROX1
ROX1 masks GLN3
no epistasis
stb5
cst6
cbf1
sum1
rtn2
rph1
pzf3
yap1
pho2
gat1
ygr067c
vox1
ppr1
met32
rsf2
hcm1
rpi1
gis1
sut2
hmo1
mig1
met28
rgm1
rim1
tod6
tye7
upc2
yrm1
spt2
asg1
haa1
met31
sip4
het2
lys14
stp3
rim101
mig2
fkh1
nrg2
dal81
cin5
tda9
snt1
cup9
rpn4
isw2
nrg1
zap1

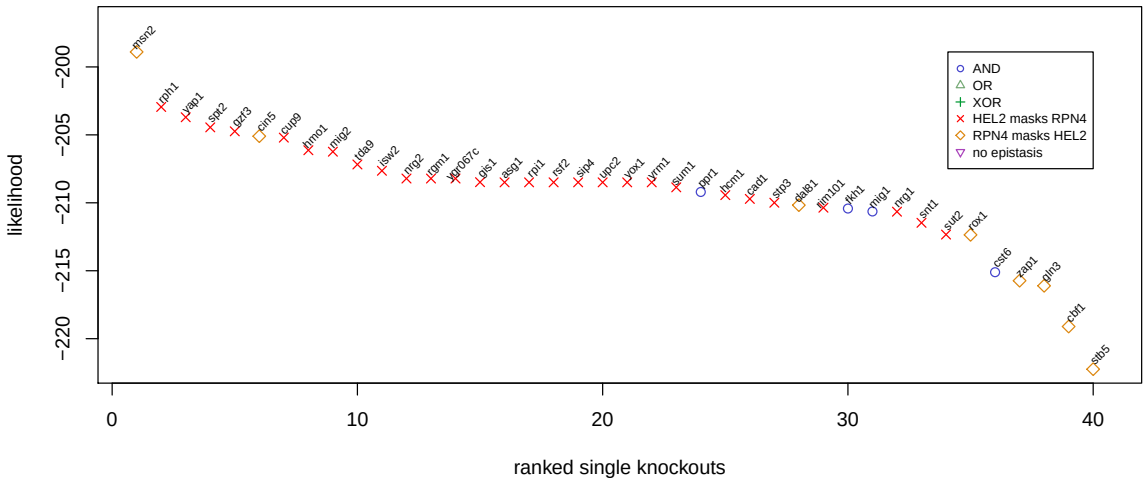

gln3 and sum1
likelihood
−540
−550
−560
−570
−580
−590
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
GLN3 masks SUM1
SUM1 masks GLN3
no epistasis
cst6
msn2
sut2
cin5
het2
fkh1
yap1
rpi1
isw2
stb5
met28
pho2
rph1
yox1
tda9
mig1
mig3
mig2
hcm1
asg1
fkh2
met31
msn4
rsi1
cup9
ppr1
stp3
cat8
tye7
upc2
ynl027c
hmo1
gat1
met32
rhp6a
usv1
dal81
rox1
rsf2
gzf3
spt2
ygr067c
zap1
rim101
gis1
snt1
rpn4
cbf1


gzf3 and stb5
likelihood
−540
−580
−620
−660
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
GZF3 masks STB5
STB5 masks GZF3
no epistasis
cbf1
cst6
gln3
zap1
msn2
rpn4
het2
dal81
snt1
stb3
sum1
rph1
hmo1
rox1
mig1
gis1
sut2
fkh1
asg1
mal33
pho2
tda9
yox1
cin5
rsf2
sip4
fkh2
has1
met31
mig2
smp1
rpi1
cup9
ppr1
rim101
yap1
ygr067c
isw2
gat1
met32
mnl6a
rgm1
upc2
usv1
cad1
met28
msn4
rlm1
tye7
ynl027c
nrg1
spt2

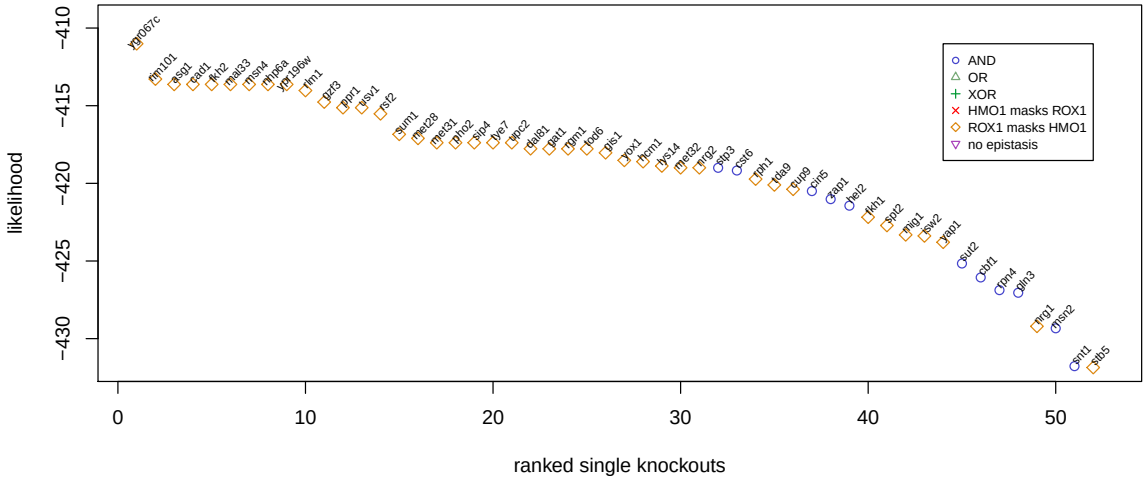

hac1 and rpn4
likelihood
−550
−600
−650
−700
−750
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
HAC1 masks RPN4
RPN4 masks HAC1
no epistasis
cst6
stb5
cbf1
gln3
zap1
stp3
dal81
msn2
hel2
rox1
nrg1
mig1
fkh1
hmo1
rph1
spt2
asg1
met31
rye7
cin5
ppr1
sum1
cat8
fkh2
haa1
mal33
pho2
rgm1
rpi1
tos8
upc2
usv1
yox1
yrm1
rim101
gis1
gzf3
mig2
rsf2
tda9
ygr067c
sut2
cad1
nrg2
isw2
hcm1
cup9
yap1
snt1

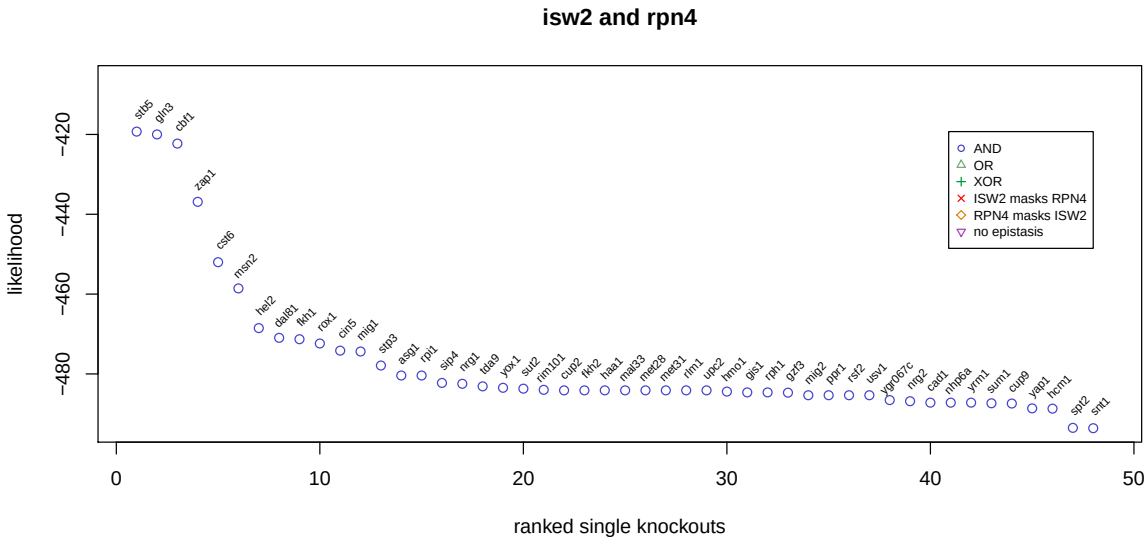

hac1 and snt1
likelihood
−135
−140
−145
−150
−155
0
10
20
30
40
ranked single knockouts
AND
OR
XOR
HAC1 masks SNT1
SNT1 masks HAC1
no epistasis
gln3
stb5
hel2
cbf1
msn2
spt2
gis1
yap1
cst6
rph1
rpn4
hcm1
rgm1
stp3
sip4
tda9
isw2
rsf2
mig1
sut2
fkh1
cad1
cup9
mal33
met28
mig2
ygr067c
sum1
cin5
rlm1
rpi1
nrg1
hmo1
rim101
nrg2
rox1
ppr1
dal81
zap1

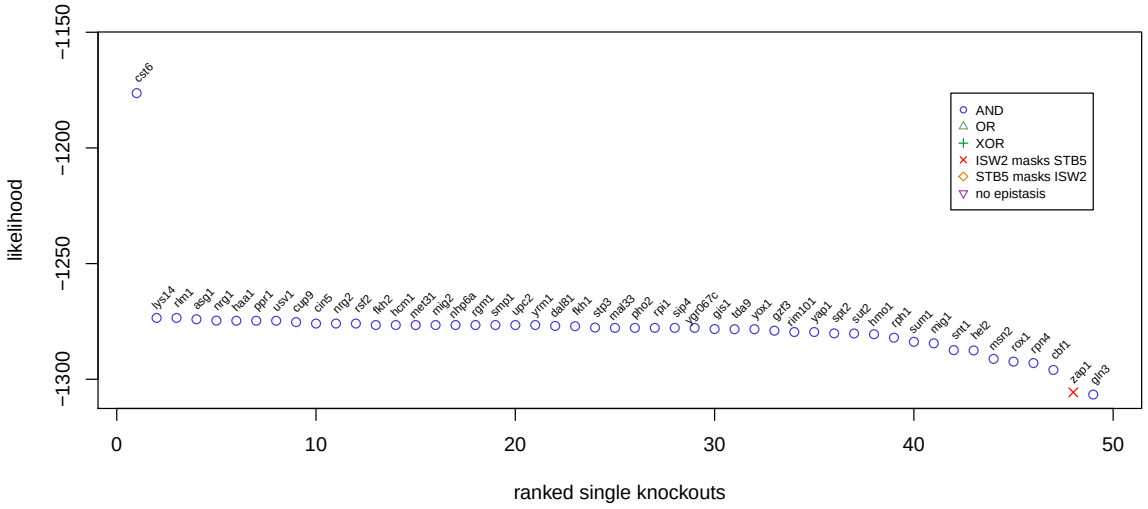
hel2 and rpn4

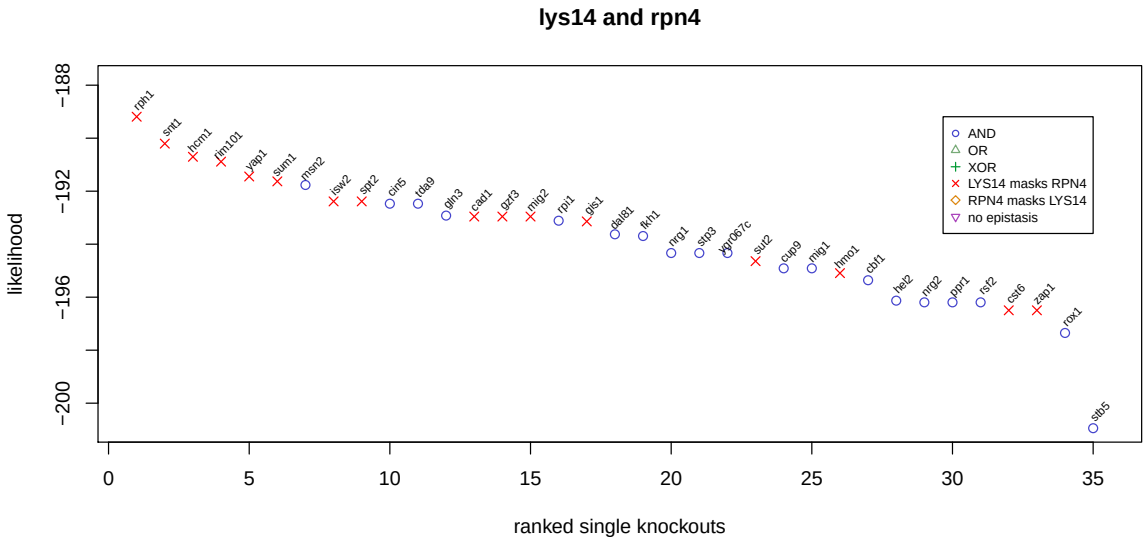


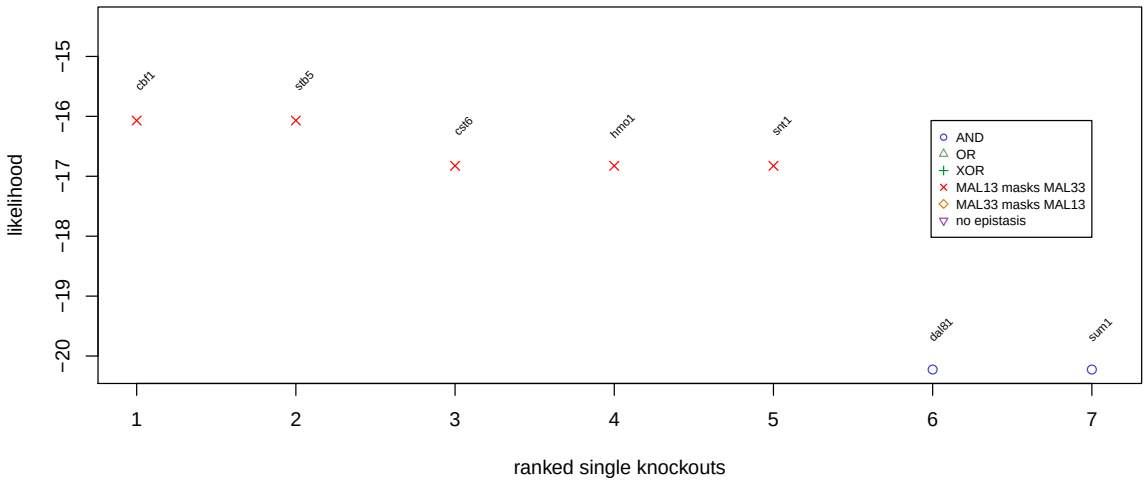
hmo1 and rox1

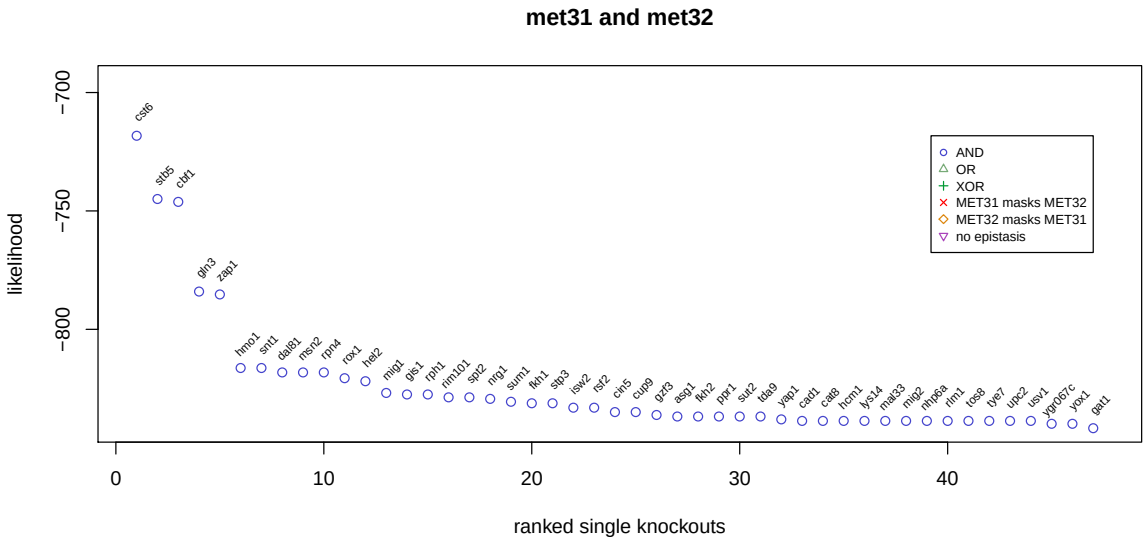


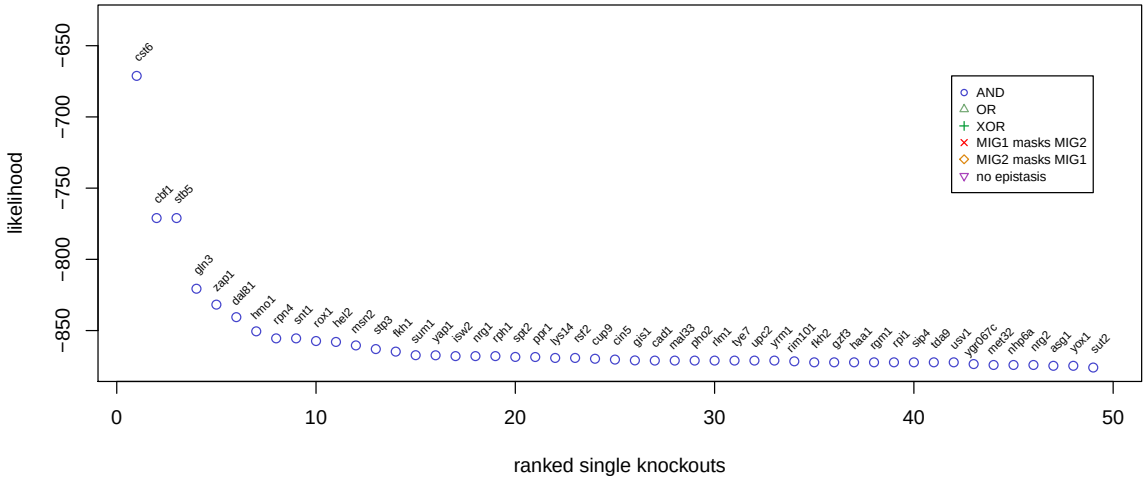

isw2 and rpn4
likelihood
−420
−440
−460
−480
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
ISW2 masks RPN4
RPN4 masks ISW2
no epistasis
stb5
gln3
cbf1
zap1
csf6
msn2
hel2
dal81
fkh1
rox1
cin5
mig1
stp3
asg1
rpi1
sip4
nrg1
tda9
yox1
sut2
rim101
cup2
fkh2
haa1
mal33
met28
met31
rlm1
upc2
hmo1
gis1
rph1
pzf3
mig2
ppr1
rsf2
usv1
ygr067c
nrg2
cad1
nhp6a
yrm1
sum1
cup9
yap1
hcm1
spt2
snt1


isw2 and stb5
likelihood
−1150
−1200
−1250
−1300
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
ISW2 masks STB5
STB5 masks ISW2
no epistasis
csf6
lys14
rlm1
asg1
nrg1
haa1
ppr1
usv1
cup9
cin5
nrg2
rsf2
fkh2
hcm1
met31
mig2
nhp6a
rpn1
smp1
upc2
yrm1
dal81
fkh1
stp3
mal33
pho2
rpi1
sip4
ygr067c
gis1
tda9
yox1
pzf3
rim101
yap1
spt2
sut2
hmo1
rph1
sum1
mig1
snt1
hel2
msn2
rox1
rpn4
cbf1
zap1
gln3

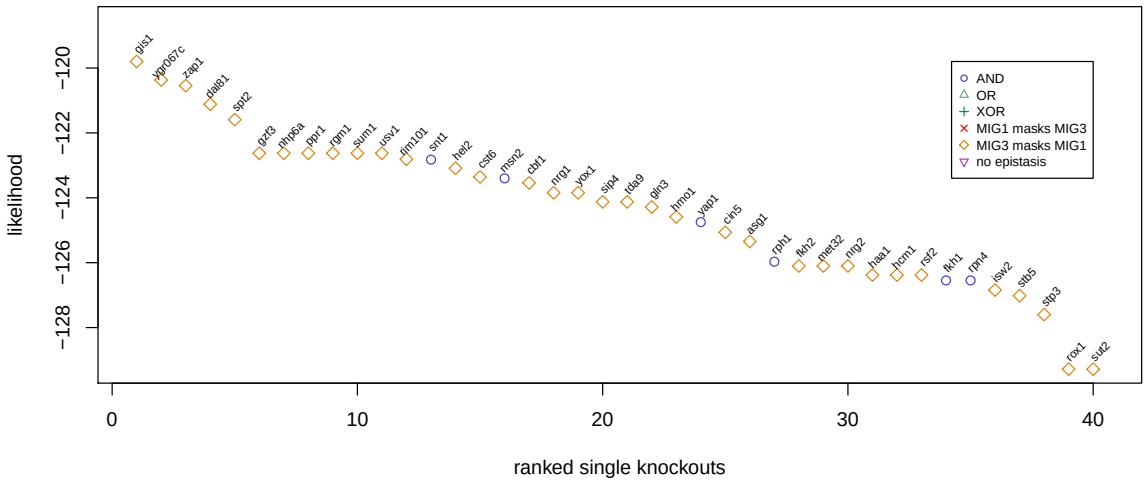

lys14 and rpn4
likelihood
−188
−192
−196
−200
0
5
10
15
20
25
30
35
ranked single knockouts
rpn1
snt1
tbcm1
rtm101
yap1
sum1
msn2
isw2
spt2
cin5
tda9
gln3
cad1
prr3
mig2
rpi1
pbs1
dal81
fkh1
rng1
stp3
ygr067c
sut2
cup9
mig1
hmo1
cbf1
hel2
prg2
ppr1
rsf2
cst6
zap1
rox1
stb5
AND
OR
XOR
LYS14 masks RPN4
RPN4 masks LYS14
no epistasis


mal13 and mal33
likelihood
−15
−16
−17
−18
−19
−20
1
2
3
4
5
6
7
ranked single knockouts
cbf1
stb5
cst6
hmo1
snt1
dal81
sum1
AND
OR
XOR
MAL13 masks MAL33
MAL33 masks MAL13
no epistasis

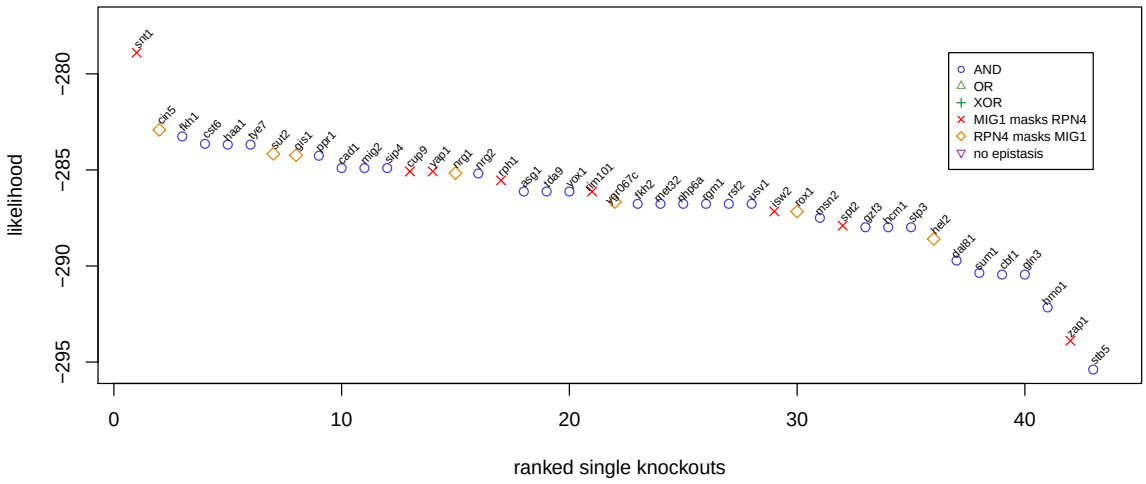

met31 and met32
likelihood
−700
−750
−800
csl6
stb5
cbf1
gln3
zap1
hmo1
snt1
dal81
msn2
rpn4
rox1
hel2
mig1
gis1
rph1
rim101
spt2
nrg1
sum1
fkh1
stp3
isw2
rsf2
cin5
cup9
gzf3
asg1
fkh2
ppr1
sut2
tda9
yap1
cad1
cst8
hcm1
lys14
mal33
mig2
mhp6a
rfm1
toss
tye7
upc2
usv1
ygr067c
yox1
gat1
AND
OR
XOR
MET31 masks MET32
MET32 masks MET31
no epistasis
0
10
20
30
40
ranked single knockouts

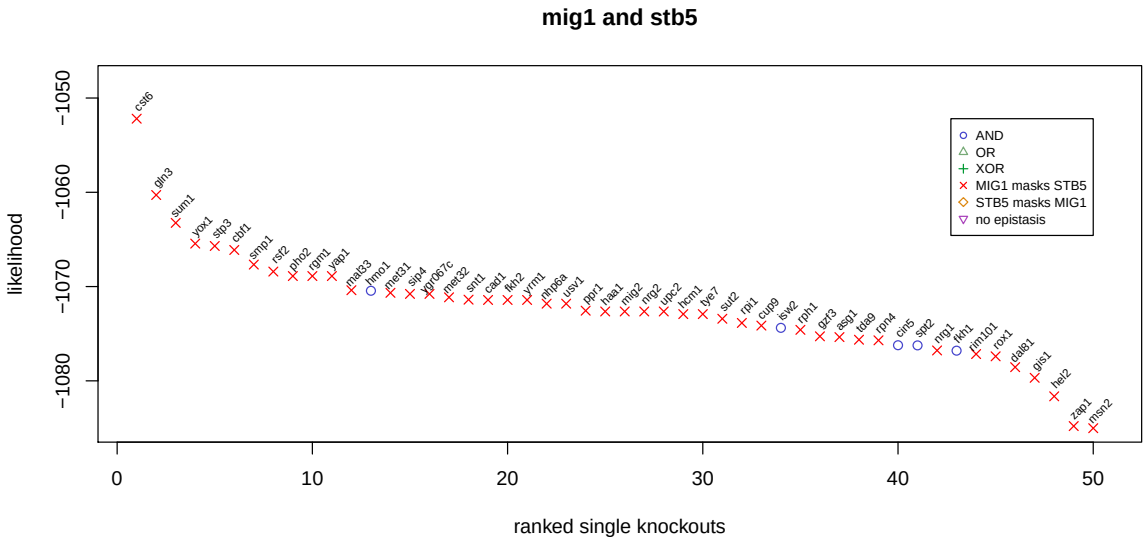

mig1 and mig2
likelihood
−650
−700
−750
−800
−850
csl6
cbf1
stb5
gln3
zap1
dal81
hmo1
rpn4
snt1
rox1
hel2
msn2
stp3
fkh1
sum1
yap1
isw2
nrg1
rph1
spt2
ppr1
lys14
rsf2
cup9
cin5
gis1
cad1
mal33
pho2
rfm1
tye7
upc2
yrm1
rim101
fkh2
gzf3
haa1
rgm1
rpi1
sip4
tda9
usv1
ygr067c
met32
mhp6a
nrg2
asg1
yox1
sut2
AND
OR
XOR
MIG1 masks MIG2
MIG2 masks MIG1
no epistasis
0
10
20
30
40
50
ranked single knockouts

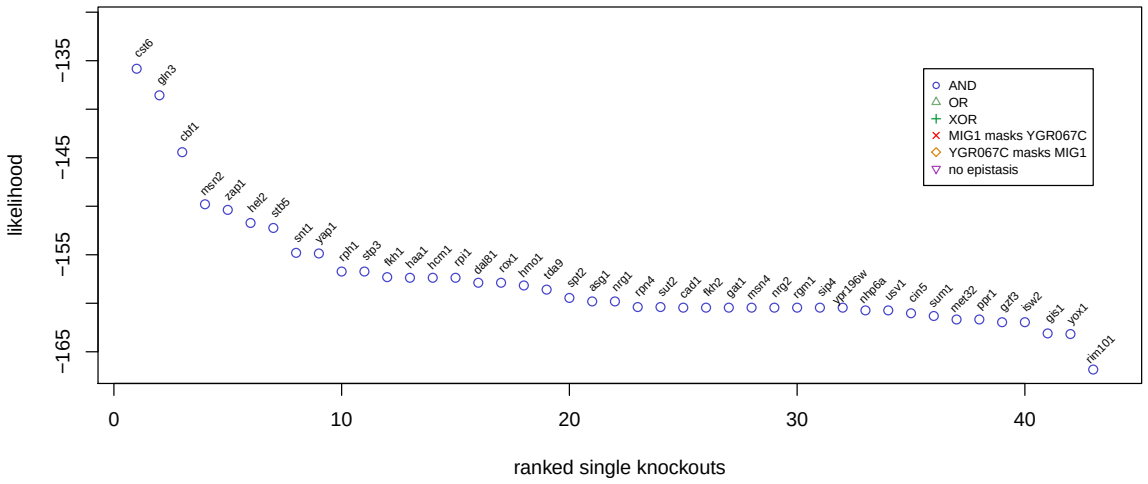
mig1 and mig3



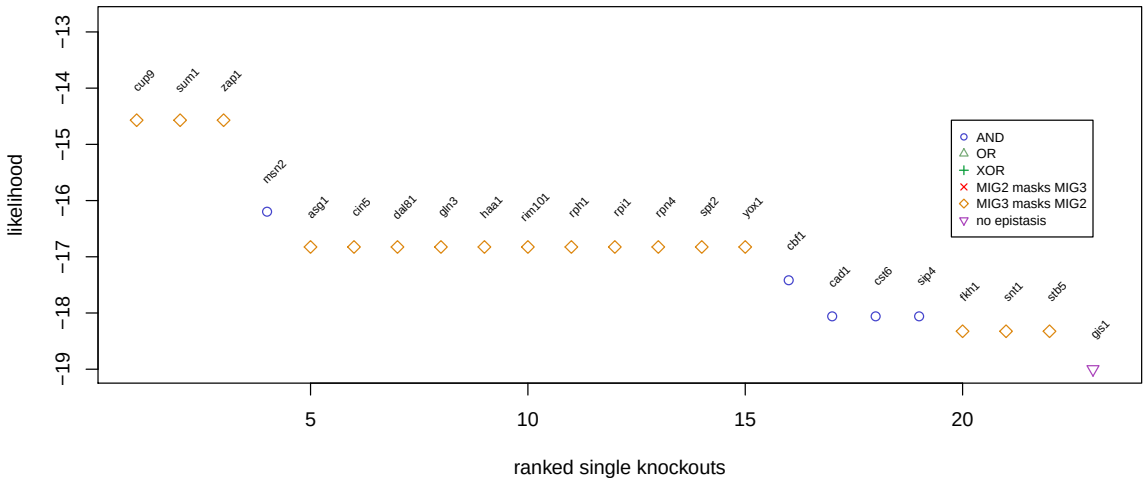
mig1 and rpn4



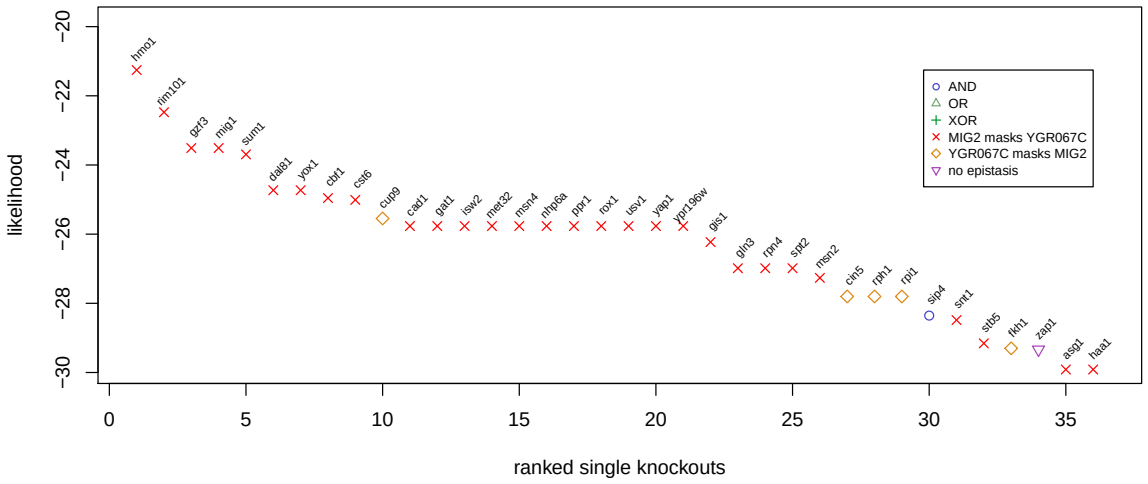

mig1 and stb5
likelihood
−1050
−1060
−1070
−1080
0
10
20
30
40
50
ranked single knockouts
AND
OR
XOR
MIG1 masks STB5
STB5 masks MIG1
no epistasis
csi6
gln3
sum1
yox1
stp3
cbf1
smp1
rsf2
pho2
rgm1
yap1
mal33
hmo1
met31
sip4
ygr067c
met32
snt1
cat1
fkh2
yrm1
rhp6a
usv1
ppr1
haa1
mig2
mg2
upc2
hcm1
tye7
sut2
rpi1
cup9
isw2
rph1
gzf3
asg1
tda9
rpn4
cin5
spt2
nrg1
fkh1
rim101
rox1
dal81
gis1
hel2
zap1
msn2

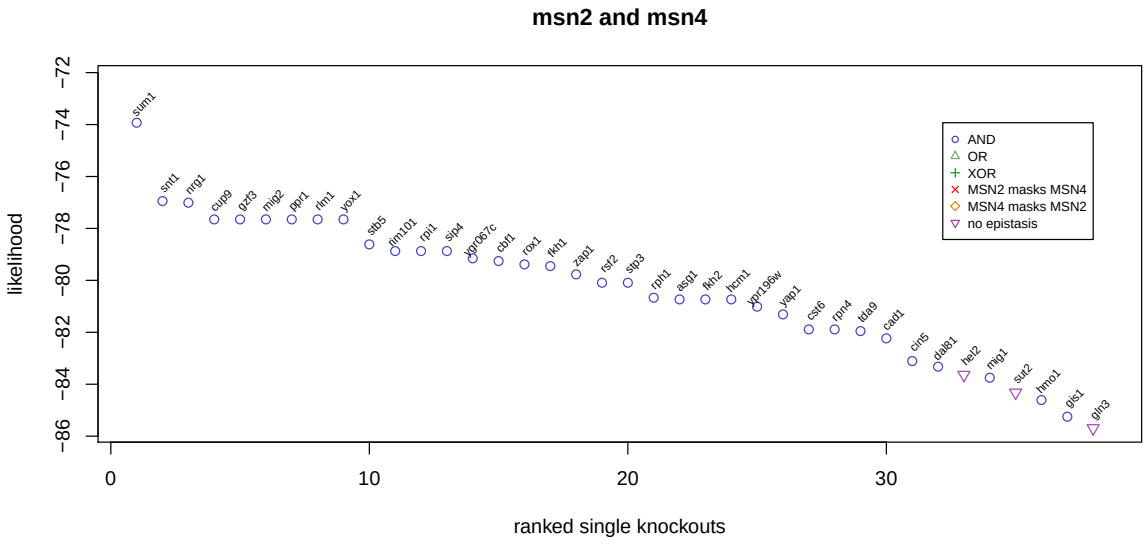

mig1 and ygr067c
likelihood
−135
−145
−155
−165
0
10
20
30
40
ranked single knockouts
AND
OR
XOR
MIG1 masks YGR067C
YGR067C masks MIG1
no epistasis
csi6
gln3
cbf1
msn2
zap1
hel2
stb5
snt1
yap1
rph1
stp3
fkh1
haa1
hcm1
rpi1
dal81
rox1
hmo1
tda9
spt2
asg1
nrg1
rpn4
sut2
cat1
fkh2
gat1
msn4
mg2
rgm1
sip4
ygr196w
rhp6a
usv1
cin5
sum1
met32
ppr1
gzf3
isw2
gis1
yox1
rim101

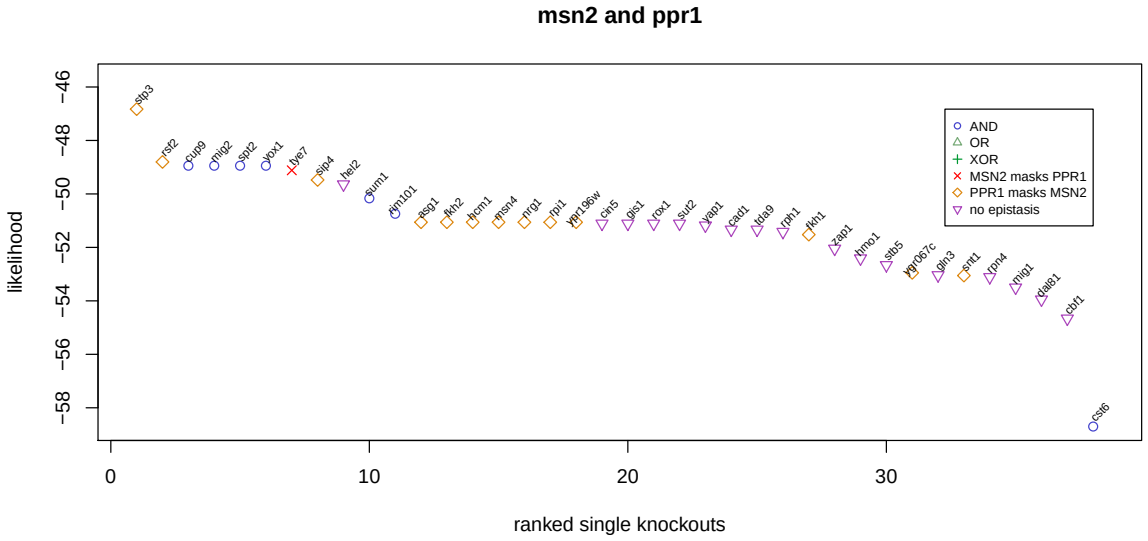
mig2 and mig3

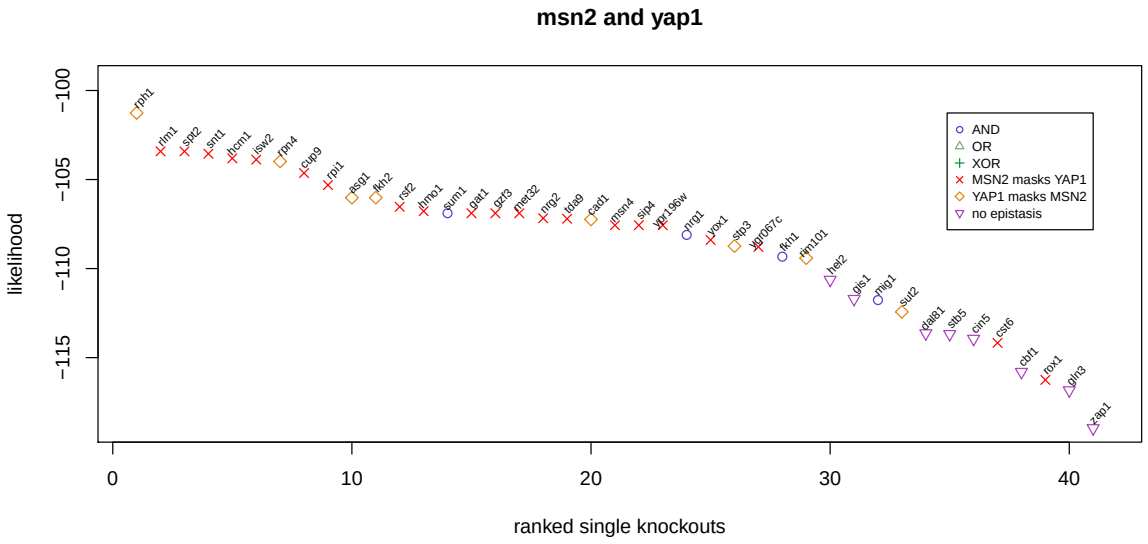


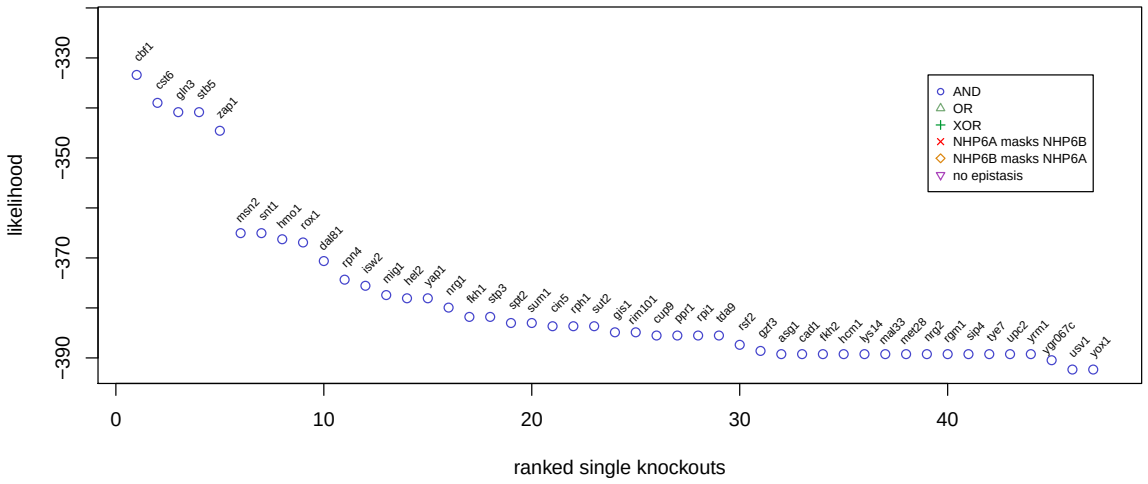
mig2 and ygr067c

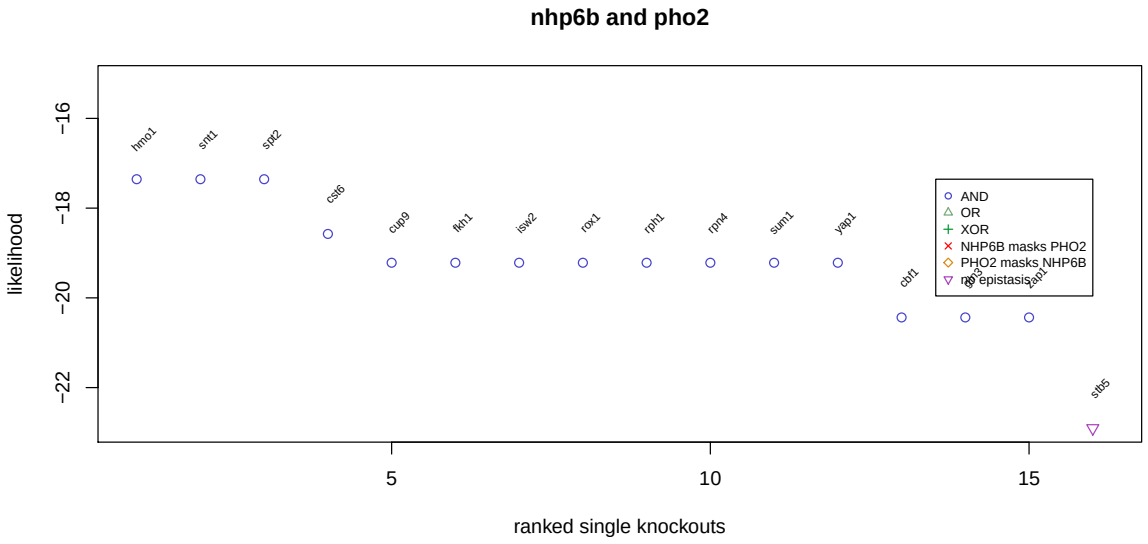


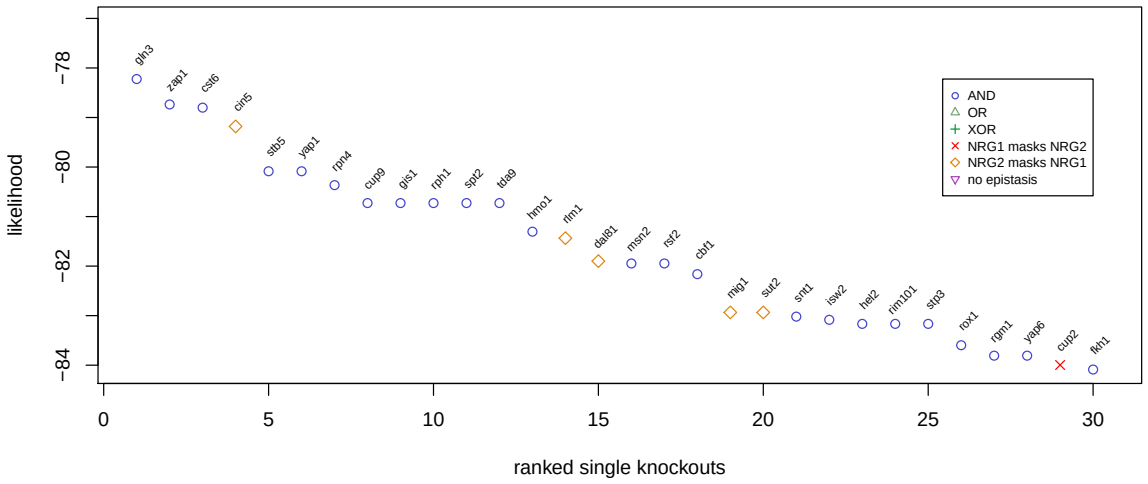

msn2 and msn4
likelihood
−72
−74
−76
−78
−80
−82
−84
−86
0
10
20
30
ranked single knockouts
AND
OR
XOR
MSN2 masks MSN4
MSN4 masks MSN2
no epistasis
sum1
snt1
nrg1
cup9
gzf3
mig2
ppr1
rlm1
yox1
stb5
rim101
rpi1
sip4
ygr067c
cbf1
rox1
fkh1
zap1
rsf2
stp3
rph1
asg1
fkh2
hcm1
ygr196w
yap1
cst6
rpn4
tda9
cad1
cin5
dal81
hel2
mg1
suf2
hmo1
gis1
gln3


msn2 and ppr1
likelihood
−46
−48
−50
−52
−54
−56
−58
0
10
20
30
ranked single knockouts
AND
OR
XOR
MSN2 masks PPR1
PPR1 masks MSN2
no epistasis
stp3
rsf2
cup9
mig2
spt2
yox1
tye7
sip4
hel2
sum1
rim101
asg1
fkh2
hcm1
msn4
nrg1
rpi1
ygr196w
cin5
gis1
rox1
suf2
yap1
cad1
tda9
rph1
fkh1
zap1
hmo1
stb5
ygr067c
gln3
snt1
rpn4
mig1
dal81
cbf1
cst6

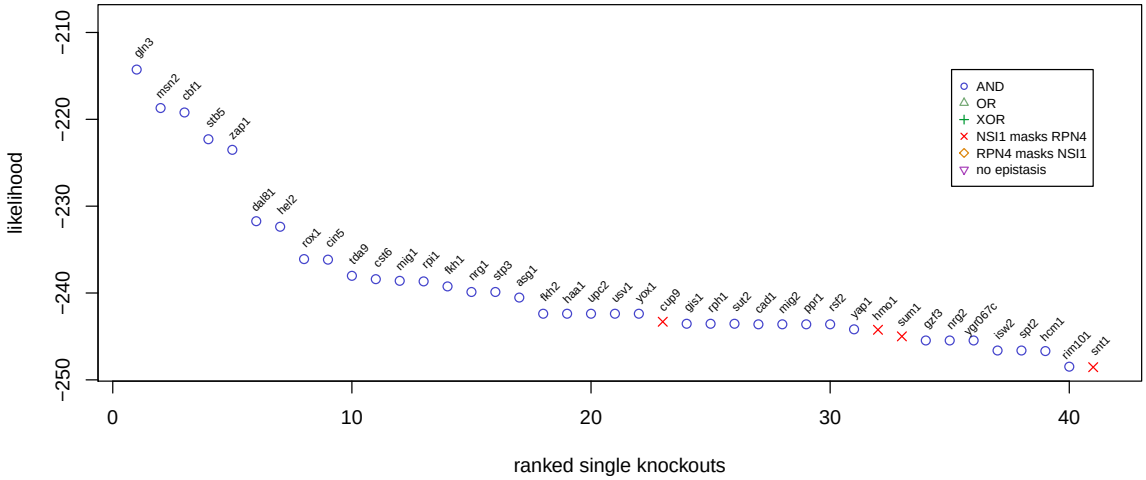

msn2 and yap1
likelihood
−100
−105
−110
−115
0
10
20
30
40
ranked single knockouts
AND
OR
XOR
MSN2 masks YAP1
YAP1 masks MSN2
no epistasis
rph1
rfm1
spt2
snt1
hcm1
isw2
rpn4
cup9
rpi1
asg1
fkh2
rsf2
hmo1
sum1
rgm1
bzf3
met32
nrg2
tda9
cad1
msn4
sip4
ygr196w
nrg1
yox1
stp3
ygr067c
fkh1
rim101
hel2
gis1
nhg1
sut2
dal81
stb5
cin5
csi6
cbf1
rox1
glr3
zap1


nhp6a and nhp6b
likelihood
−330
−350
−370
−390
0
10
20
30
40
ranked single knockouts
AND
OR
XOR
NHP6A masks NHP6B
NHP6B masks NHP6A
no epistasis
cbf1
csi6
glr3
stb5
zap1
msn2
snt1
hmo1
rox1
dal81
rpn4
isw2
mig1
hel2
yap1
nrg1
fkh1
stp3
spt2
sum1
cin5
rph1
sut2
gis1
rim101
cup9
ppr1
rpi1
tda9
rsf2
bzf3
asg1
cad1
fkh2
hcm1
kyl4
mal33
met28
nrg2
rgm1
sip4
uve7
unc2
yrm1
ygr067c
usv1
yox1

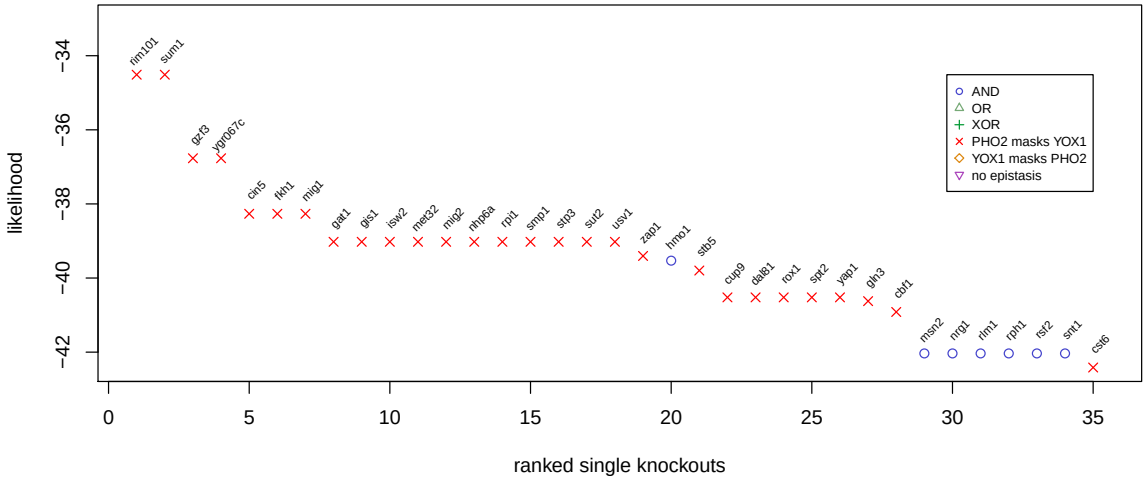

nhp6b and pho2
likelihood
−16
−18
−20
−22
hmo1
snt1
spt2
cst6
cup9
fkh1
isw2
rox1
rph1
rpn4
sum1
yap1
cbf1
stb5
5
10
15
ranked single knockouts
AND
OR
XOR
NHP6B masks PHO2
PHO2 masks NHP6B
no epistasis

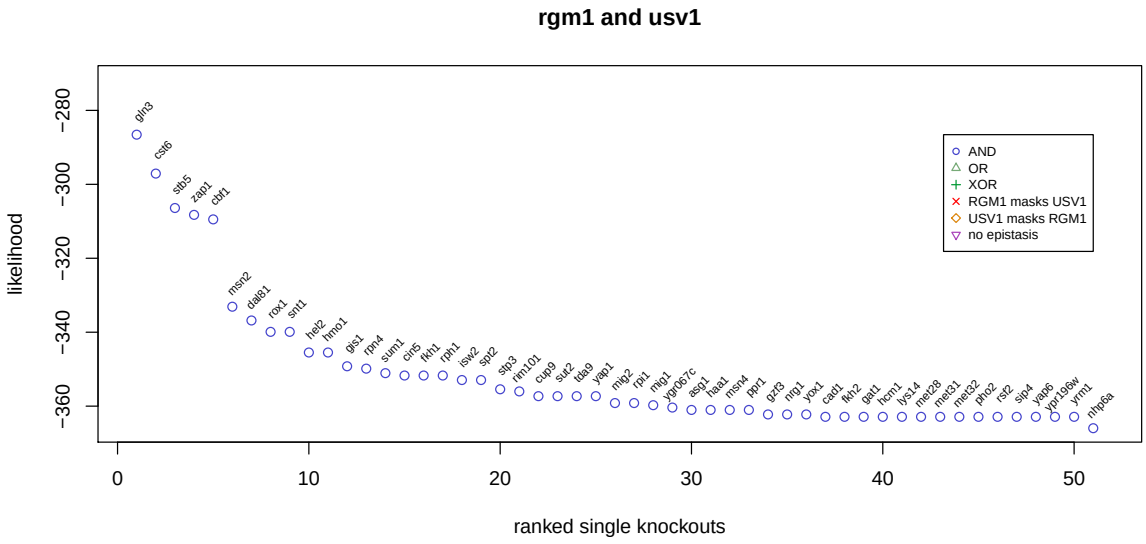

nrg1 and nrg2
likelihood
−78
−80
−82
−84
glh3
zap1
cst6
cin5
stb5
yap1
rpn4
cup9
gis1
rph1
spt2
tda9
hmo1
rim1
dal81
msn2
rsf2
cbf1
mig1
sut2
snt1
isw2
hst2
rim101
stp3
rox1
rgm1
yap6
cup2
fkh1
0
5
10
15
20
25
30
ranked single knockouts
AND
OR
XOR
NRG1 masks NRG2
NRG2 masks NRG1
no epistasis

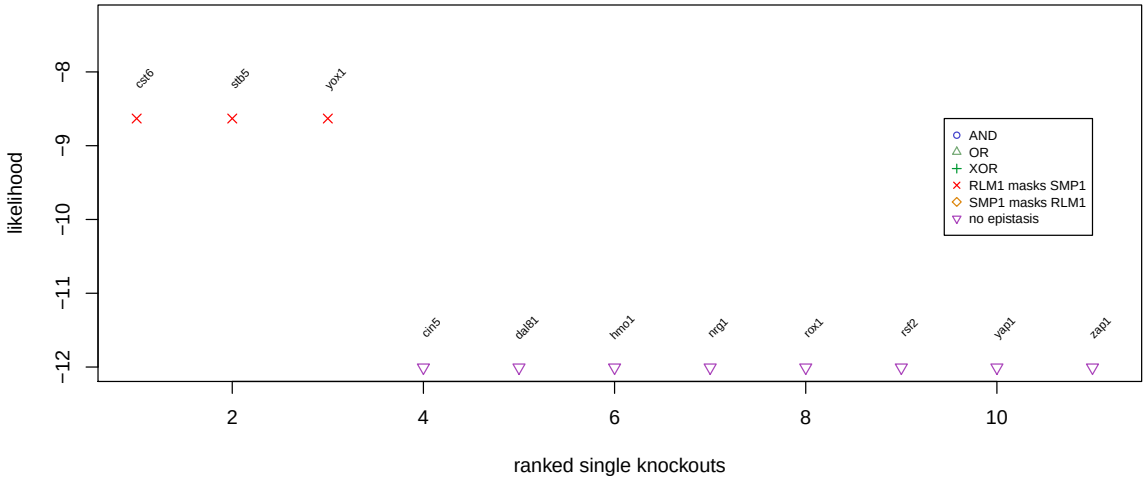
nsi1 and rpn4



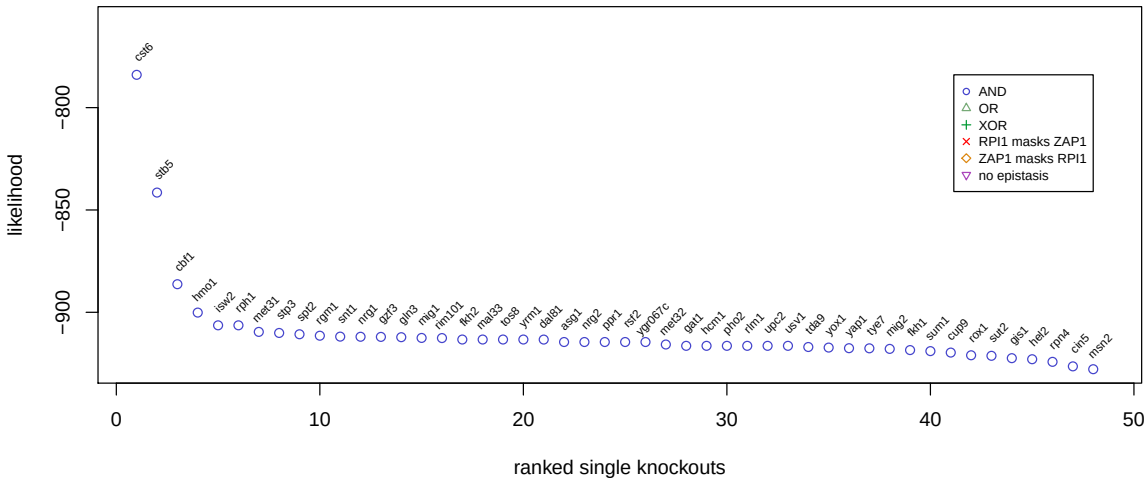
pho2 and yox1



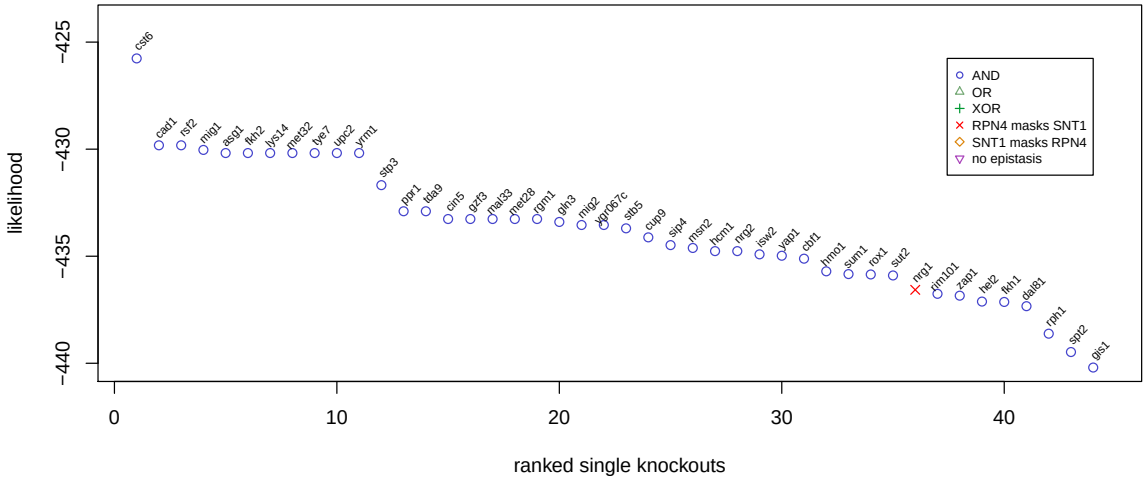

rgm1 and usv1
likelihood
−280
−300
−320
−340
−360
0
10
20
30
40
50
ranked single knockouts
glr3
cst6
stb5
zap1
cht1
msn2
dal81
rox1
snt1
hal2
hmo1
gis1
rpn4
sum1
cin5
fkh1
rph1
isw2
spt2
stp3
rim101
cup9
sut2
tda9
yap1
mg2
rpi1
mig1
ygr067c
asg1
had1
msn4
ppr1
gat3
nrg1
yox1
cad1
fkh2
gat1
hcm1
lys14
met28
met31
met32
pho2
rsf2
sip4
yap6
ypr196w
ynl1
nhp6a
AND
OR
XOR
RGM1 masks USV1
USV1 masks RGM1
no epistasis


rlm1 and smp1
likelihood
−8
−9
−10
−11
−12
2
4
6
8
10
ranked single knockouts
cst6
stb5
yox1
cin5
dal81
hmo1
nrg1
rox1
rsf2
yap1
zap1
AND
OR
XOR
RLM1 masks SMP1
SMP1 masks RLM1
no epistasis

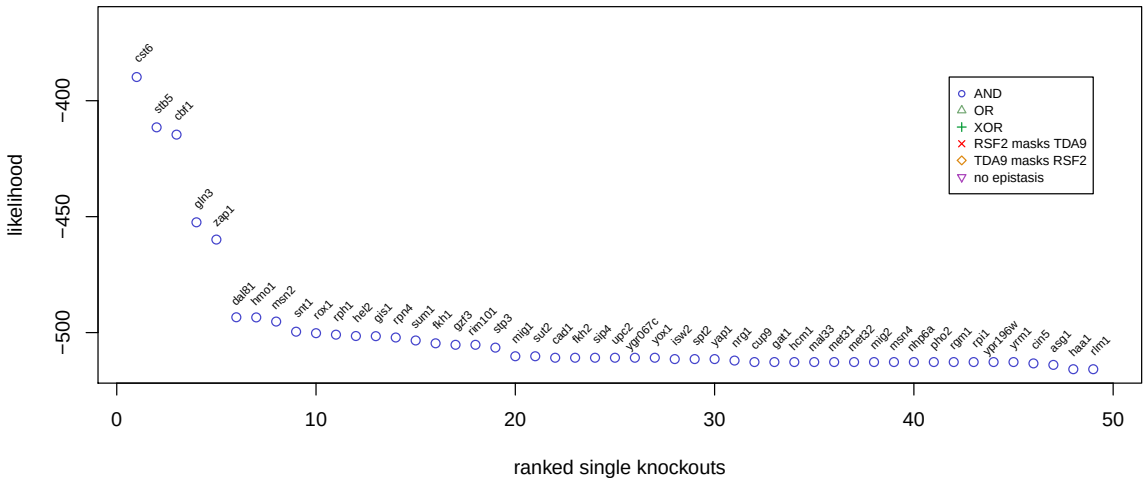
rpi1 and zap1



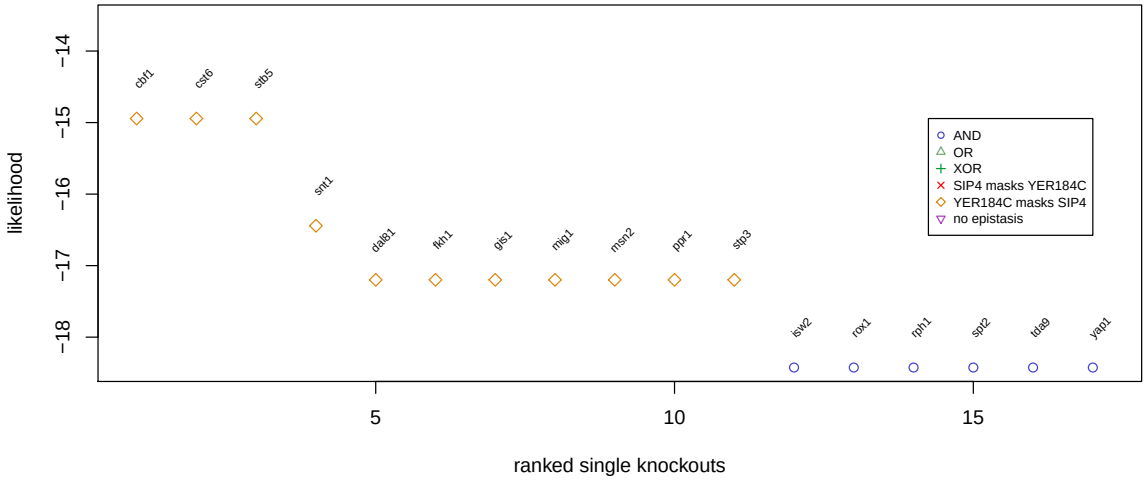
rpn4 and snt1



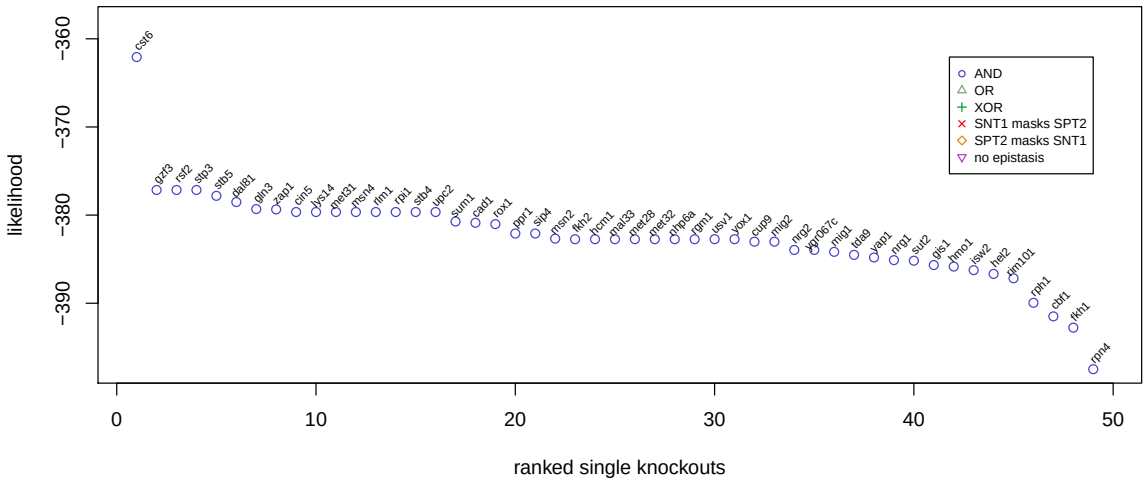
rsf2 and tda9



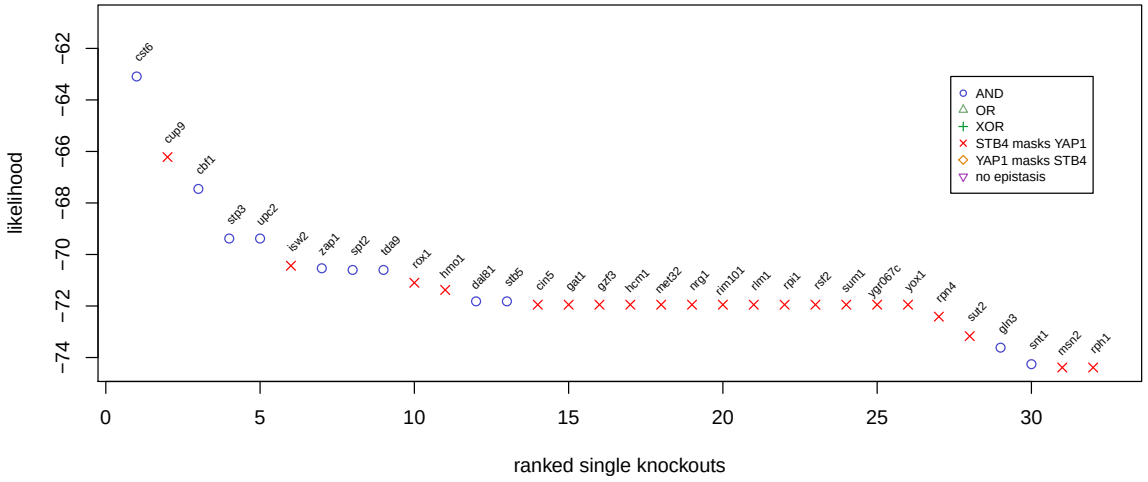
sip4 and yer184c

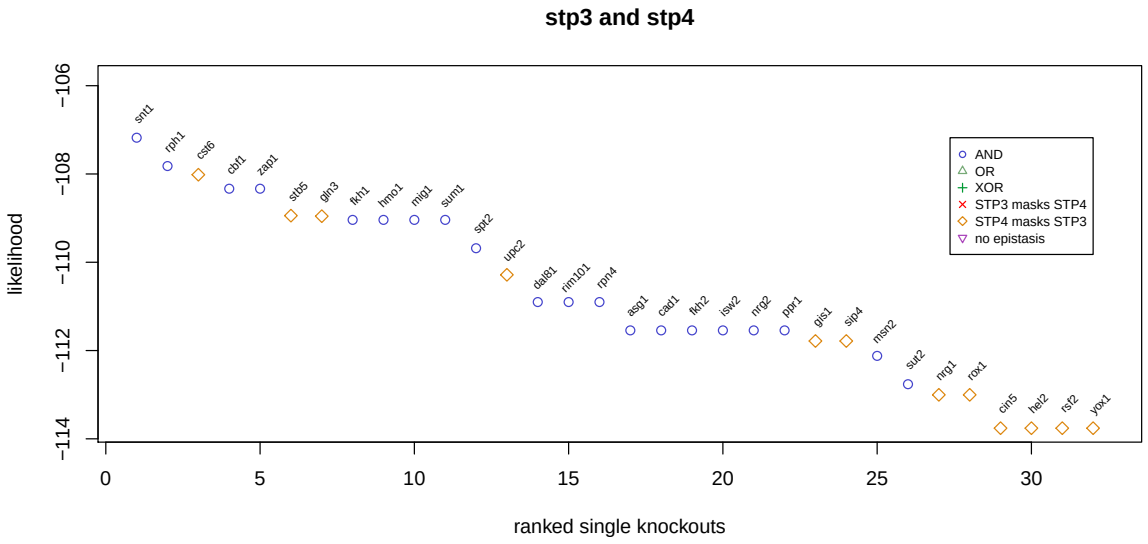


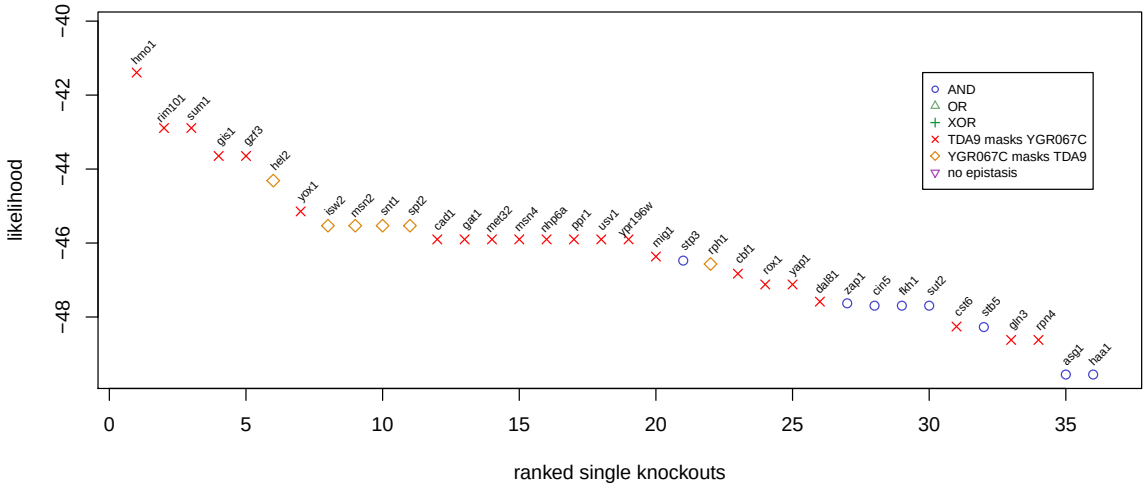
snt1 and spt2

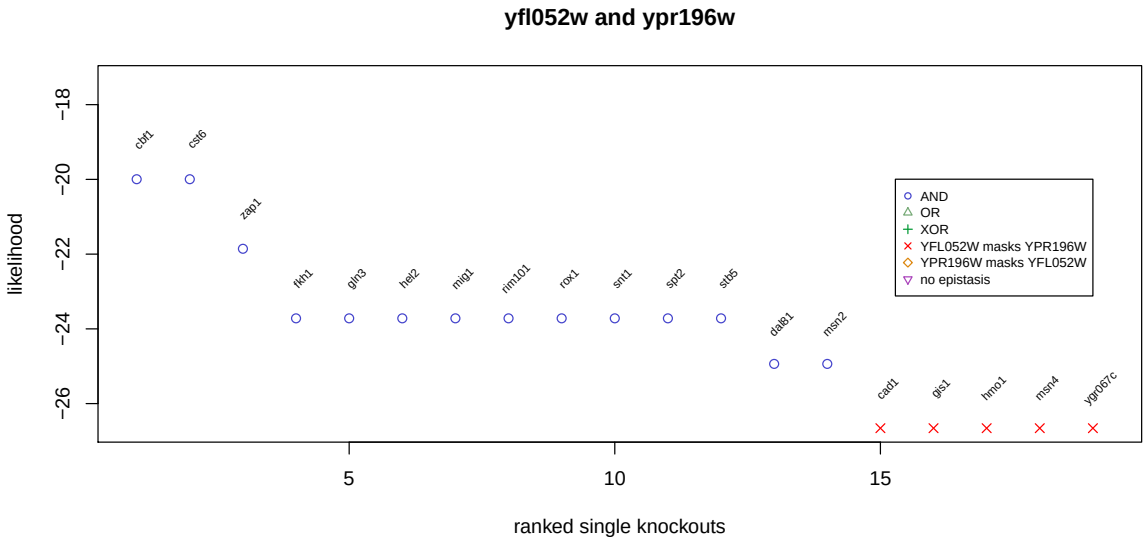


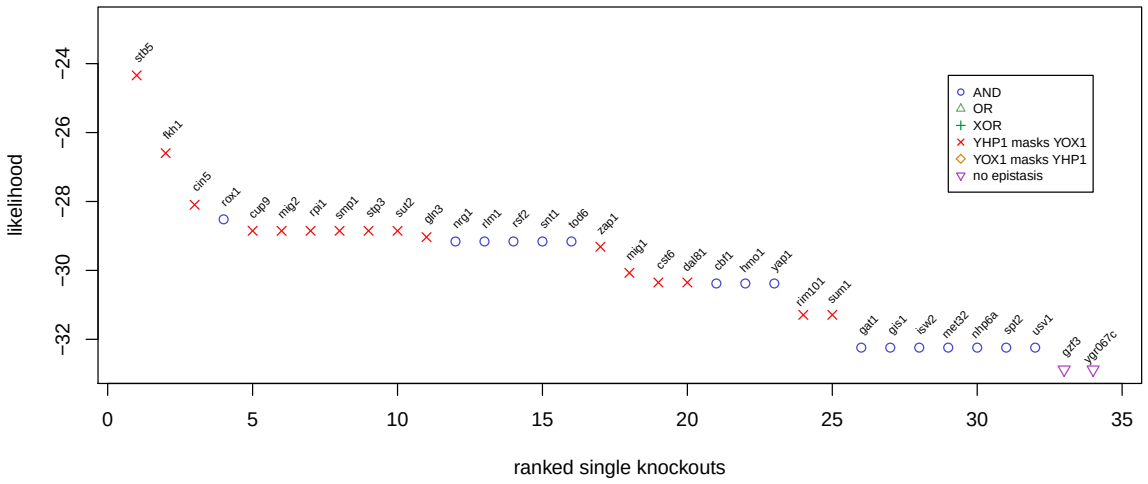
stb4 and yap1

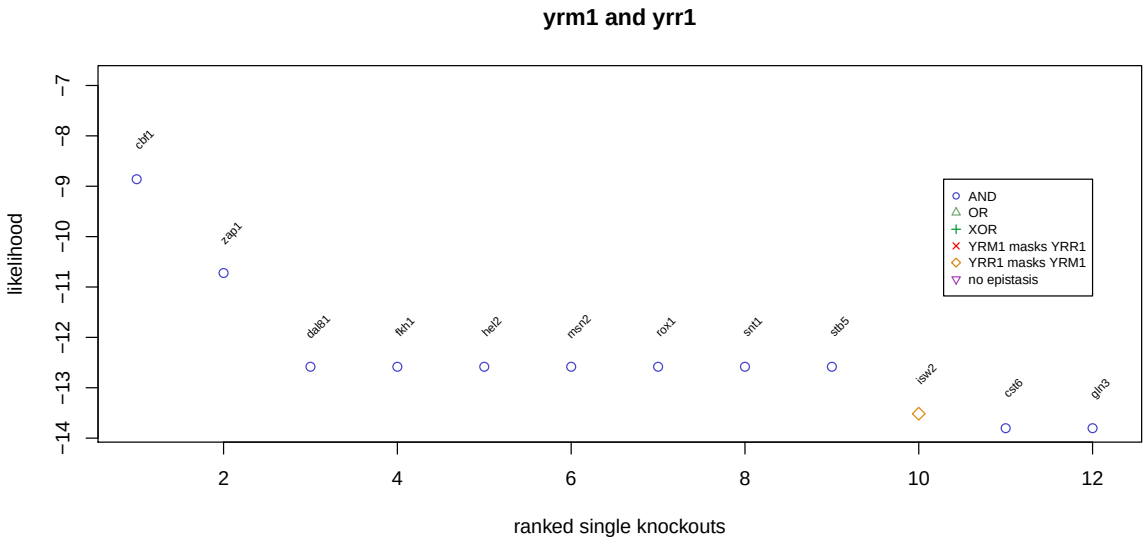



stp3 and stp4
likelihood
−106
−108
−110
−112
−114
0
5
10
15
20
25
30
ranked single knockouts
snt1
rph1
csi6
cbf1
zap1
stb5
glh3
fkh1
hmo1
mig1
sum1
spt2
upc2
dal81
rim101
rpn4
asg1
cad1
fkh2
isw2
nrg2
ppr1
gis1
stp4
msn2
sut2
nrg1
rox1
cin5
hel2
rst2
yox1
AND
OR
XOR
STP3 masks STP4
STP4 masks STP3
no epistasis


tda9 and ygr067c
likelihood
−40
−42
−44
−46
−48
0
5
10
15
20
25
30
35
ranked single knockouts
hmo1
rim101
sum1
gis1
gzf3
hel2
yox1
isw2
msn2
snt1
spt2
cad1
gat1
mes32
msn4
rhp6a
ppr1
usv1
ygr196w
mig1
stp3
rph1
cbf1
rox1
yap1
dal81
zap1
cin5
fkh1
sut2
csi6
stb5
glh3
rpn4
asg1
haa1
AND
OR
XOR
TDA9 masks YGR067C
YGR067C masks TDA9
no epistasis

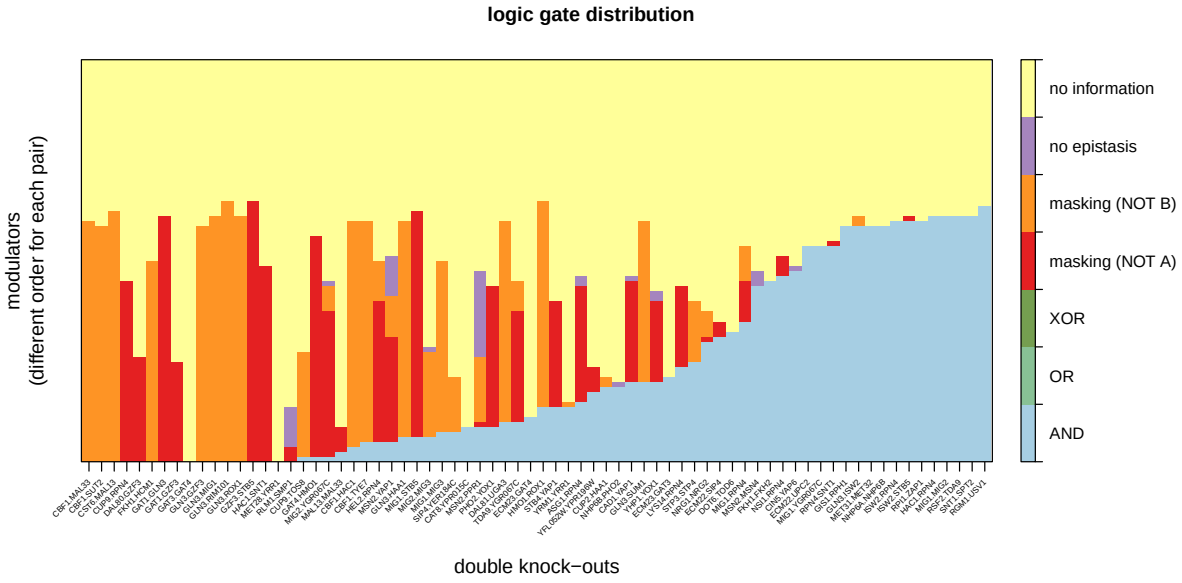

yfl052w and ypr196w
likelihood
−18
−20
−22
−24
−26
cbf1
cst6
zap1
fkh1
gln3
hel2
mig1
rim101
rox1
snt1
spt2
stb5
dal81
msn2
cad1
gis1
hmo1
msn4
ypr067c
AND
OR
XOR
YFL052W masks YPR196W
YPR196W masks YFL052W
no epistasis
5
10
15
ranked single knockouts


yhp1 and yox1
likelihood
−24
−26
−28
−30
−32
stb5
fkh1
cin5
rox1
cup9
mig2
rpi1
smp1
stp3
sut2
gln3
nrg1
rim1
rsf2
snt1
tod6
zap1
mig1
cst6
dal81
cbf1
hmo1
yap1
rim101
sum1
gat1
gis1
isw2
met32
nhp6a
spt2
usv1
pzf3
ypr067c
AND
OR
XOR
YHP1 masks YOX1
YOX1 masks YHP1
no epistasis
0
5
10
15
20
25
30
35
ranked single knockouts




```
distmat <- sameith$logic

distmat[which(distmat %in% "AND")] <- 1
distmat[which(distmat %in% "OR")] <- 2
distmat[which(distmat %in% "XOR")] <- 3
distmat[which(distmat %in% "NOEPI")] <- 6
distmat[which(distmat %in% c("NOINFO", "NOINF"))] <- 7

for (i in 1:ncol(distmat)) {

    genes <- unlist(strsplit(colnames(distmat)[i], "\\."))

    distmat[which(distmat[, i] %in% paste(genes[1], " masks the effect of ",
                                          genes[2], sep = "")), i] <- 4


    distmat[which(distmat[, i] %in% paste(genes[2], " masks the effect of ",
                                          genes[1], sep = "")), i] <- 5

}

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

for (i in 1:ncol(distmat)) {
    distmat[, i] <- rev(sort(distmat[, i]))
}

distmat <- distmat[-which(apply(distmat, 1, sum) == 0), ]

library(bnem)

y <- distmat

distmat <- distmat[, order(apply(distmat, 2, function(x) { return(sum(x == 1)) }))]
```

```
y[which(y == 5)] <- 4

rownames(distmat) <- NULL

labeltext <- c("", "no information\n\n\n", "no epistasis\n\n\n",
               "masking (NOT B)\n\n\n", "masking (NOT A)\n\n\n",
               "XOR\n\n\n", "OR\n\n\n", "AND\n\n\n")

heatmapOP(distmat, Colv = F, Rowv = F, main = "logic gate distribution", sub = "",
          col = "Paired", breaks = seq(0.5,7.5, length.out = 8), cexRow = 0,
          cexCol = 0.4, aspect = "fill",
          colorkey = list(space = "right", labels = rev(labeltext), width = 1,
                          at = seq(1.5,7.5, length.out = 8)),
          xlab = "double knock-outs",
          ylab = "modulators\n(different order for each pair)",
          xrot = 45, bordercol = "transparent")
```



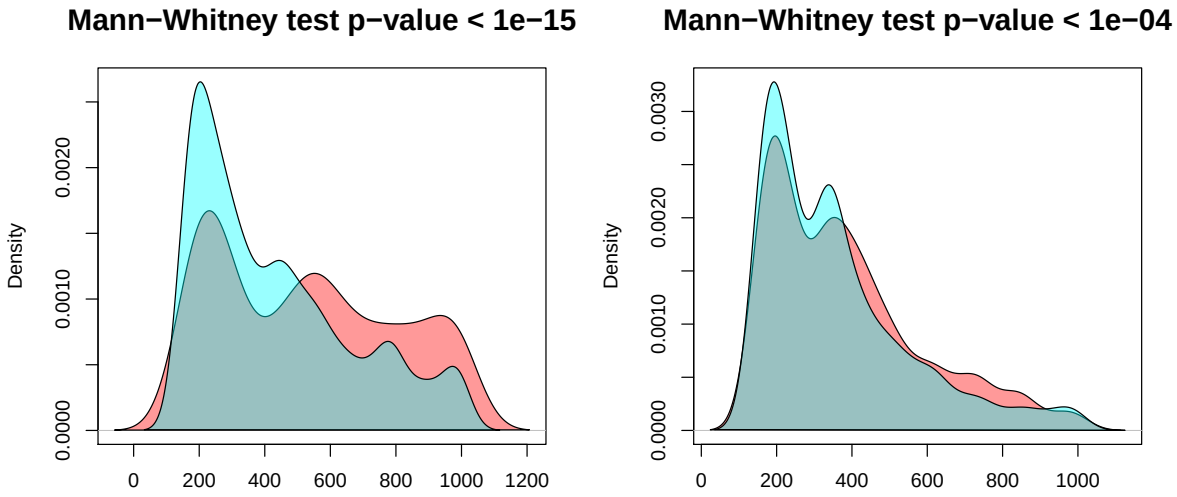
Now we plot the densities of the string-db interaction scores of our identified modulators and a random draw.

```
par(mfrow=c(1,2))

library(STRINGdb)

get_STRING_species(version="10", species_name=NULL)[26, ] # 4932

##    species_id            official_name            compact_name   kingdom type
## 26       4932 Saccharomyces cerevisiae Saccharomyces cerevisiae eukaryota core

string_db <- STRINGdb$new( version="10", species=4932, score_threshold=0,
                           input_directory="~/")

llmat <- wageningen$ll

logicmat <- wageningen$logic
```

```
string.scores <- list()

string.names <- character()

for (i in 1:ncol(llmat)) {

    if (sum(!(llmat[, i] %in% c(0,-Inf))) > 0) {
        top30 <- llmat[, i]
        top30[which(top30 == 0)] <- -Inf
        top30 <- top30[which(!(llmat[, i] %in% c(0,-Inf)))]
        top30 <- top30[order(top30,decreasing = T)[1:min(30, sum(!(llmat[, i]
            %in% c(0,-Inf))))]]

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

        for (j in names(top30)) {
            tmp <- string_db$get_interactions(string_db$mp(c(doubles[1], j)))
            string.scores <- c(string.scores, tmp$combined_score)
            string.names <- c(string.names, paste(sort(c(doubles[1], j)), collapse = "_"))
            tmp <- string_db$get_interactions(string_db$mp(c(doubles[2], j)))
            string.scores <- c(string.scores, tmp$combined_score)
            string.names <- c(string.names, paste(sort(c(doubles[2], j)), collapse = "_"))
        }

    } else {
        next()
    }

}

tmp <- string_db$get_interactions(string_db$mp(unique(unlist(strsplit(colnames(dataBinWag)
                                                                      , "\\."))))))

stsc <- unlist(string.scores)

denspval <- wilcox.test(stsc, unlist(tmp$combined_score), alternative = "greater")$p.value

for (i in 100:1) {

    if (denspval < 10^(-i)) {

        denspval <- paste("< ", 10^(-i), sep = "")

    }

}

plot(density(stsc), col = "#00000000",
     ylim = c(0, max(c(max(density(stsc)$y),max(density(unlist(tmp$combined_score))$y)))),
     main = paste("Mann-Whitney test p-value ", denspval, sep = ""), xlab = "",
     cex.main = 1.5)
polygon(density(stsc), col = "#ff000066")
```

```
lines(density(unlist(tmp$combined_score)), col = "#00000000")
polygon(density(unlist(tmp$combined_score)), col = "#00ffff66")

llmat <- sameith$ll

logicmat <- sameith$logic

string.scores <- list()

string.names <- character()

for (i in 1:ncol(llmat)) {

    if (sum(!(llmat[, i] %in% c(0,-Inf))) > 0) {
        top30 <- llmat[, i]
        top30[which(top30 == 0)] <- -Inf
        top30 <- top30[which(!(llmat[, i] %in% c(0,-Inf)))]
        top30 <- top30[order(top30, decreasing = T)[1:min(30, sum(!(llmat[, i]
            %in% c(0,-Inf))))]]

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

        for (j in names(top30)) {
            tmp <- string_db$get_interactions(string_db$mp(c(doubles[1], j)))
            string.scores <- c(string.scores, tmp$combined_score)
            string.names <- c(string.names, paste(sort(c(doubles[1], j)), collapse = "_"))
            tmp <- string_db$get_interactions(string_db$mp(c(doubles[2], j)))
            string.scores <- c(string.scores, tmp$combined_score)
            string.names <- c(string.names, paste(sort(c(doubles[2], j)), collapse = "_"))
        }

    } else {
        next()
    }

}

tmp <- string_db$get_interactions(string_db$mp(unique(unlist(strsplit(colnames(dataBin)
                                                                      , "\\."))))))

stsc <- unlist(string.scores)

denspval <- wilcox.test(stsc, unlist(tmp$combined_score), alternative = "greater")$p.value

for (i in 100:1) {

    if (denspval < 10^(-i)) {

        denspval <- paste("< ", 10^(-i), sep = "")

    }

}
```

```
plot(density(stsc), col = "#00000000",
     ylim = c(0, max(c(max(density(stsc)$y), max(density(unlist(tmp$combined_score))$y)))),
     main = paste("Mann-Whitney test p-value ", denspval, sep = ""), xlab = "",
     cex.main = 1.5)
polygon(density(stsc), col = "#ff000066")

lines(density(unlist(tmp$combined_score)), col = "#00000000")
polygon(density(unlist(tmp$combined_score)), col = "#00ffff66")
```




```
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] STRINGdb_1.14.0     pcalg_2.4-3         minet_3.32.0        bnem_0.99.0
##  [5] latticeExtra_0.6-28 RColorBrewer_1.1-2  lattice_0.20-34     snowfall_1.84-6.1
##  [9] snow_0.4-2          matrixStats_0.51.0  nem_2.48.0          CellNOptR_1.20.0
## [13] XML_3.98-1.5        Rgraphviz_2.18.0    RCurl_1.95-4.8      bitops_1.0-6
## [17] ggplot2_2.2.0       hash_2.2.6          RBGL_1.50.0         graph_1.52.0
## [21] BiocGenerics_0.20.0 epiNEM_0.99.0       igraph_1.0.1        gtools_3.5.0
## [25] e1071_1.6-7         BoolNet_2.1.3       knitr_1.15.1        devtools_1.12.0
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.8          bdsmatrix_1.3-2      corpcor_1.6.8        png_0.1-7
##  [5] class_7.3-14         assertthat_0.1       digest_0.6.10        gmp_0.5-12
```

```
##  [9] chron_2.3-47         plyr_1.8.4           stats4_3.3.1         RSQLite_1.0.0
## [13] evaluate_0.10        sqldf_0.4-10         highr_0.6            BiocInstaller_1.24.0
## [17] gplots_3.0.1         lazyeval_0.2.0       gdata_2.17.0         gsubfn_0.6-6
## [21] proto_1.0.0          statmod_1.4.26       stringr_1.1.0        munsell_0.4.3
## [25] tibble_1.2           withr_1.0.2          DBI_0.5-1            ggm_2.3
## [29] gtable_0.2.0         magrittr_1.5         scales_0.4.1         KernSmooth_2.23-15
## [33] stringi_1.1.2        limma_3.30.4         robustbase_0.92-6    boot_1.3-18
## [37] fastICA_1.2-0        tools_3.3.1          DEoptimR_1.0-6       sfsmisc_1.1-0
## [41] abind_1.4-5          plotrix_3.6-3        clue_0.3-51          colorspace_1.3-0
## [45] cluster_2.0.5        caTools_1.17.1       memoise_1.0.0
```

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