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

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Introduction

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)
```

```r
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))
```

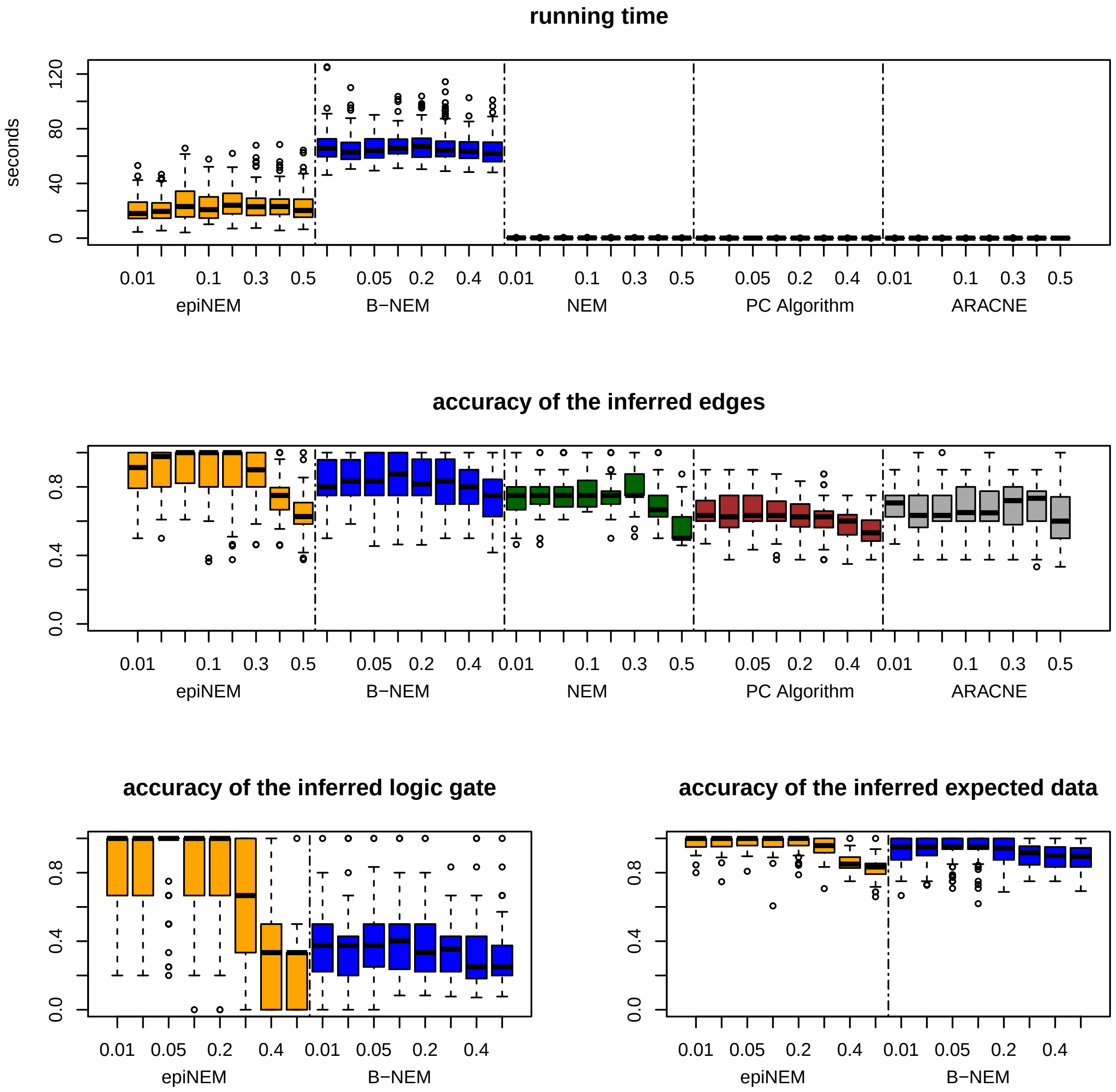
```r
for (i in 1:runs) {

    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)

    }
```

```r
        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)
```


running time

accuracy of the inferred edges

accuracy of the inferred logic gate

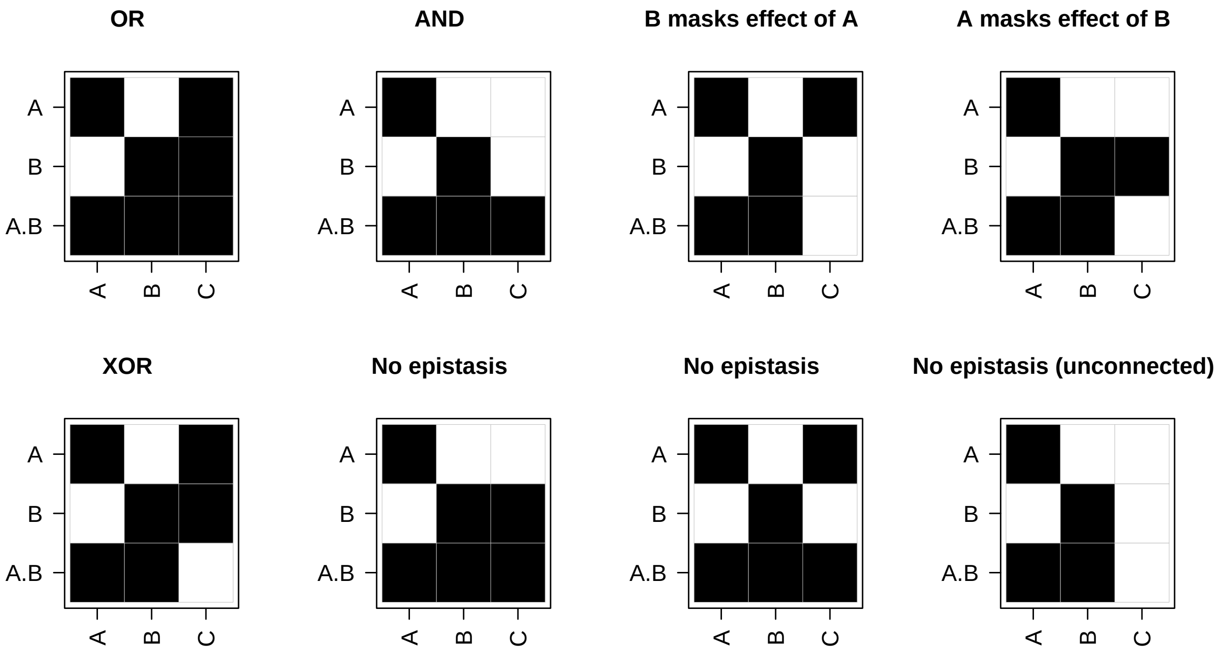
accuracy of the inferred expected data

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:

```r
a1 <- 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)
a2 <- 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)
a3 <- 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)
a4 <- 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)
a5 <- 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)
a6 <- 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)
a7 <- 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)
a8 <- 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)
print(a5, position = c(0,0, .25, .5), more = TRUE)
print(a6, position = c(.25,0, .5, .5), more = TRUE)
print(a7, position = c(.5,0, .75, .5), more = TRUE)
print(a8, position = c(.75,0, 1, .5), more = TRUE)
print(a1, position = c(0,.5, .25, 1), more = TRUE)
print(a2, position = c(.25,.5, .5, 1), more = TRUE)
print(a3, position = c(.5,.5, .75, 1), more = TRUE)
print(a4, position = c(.75,.5, 1, 1))
```



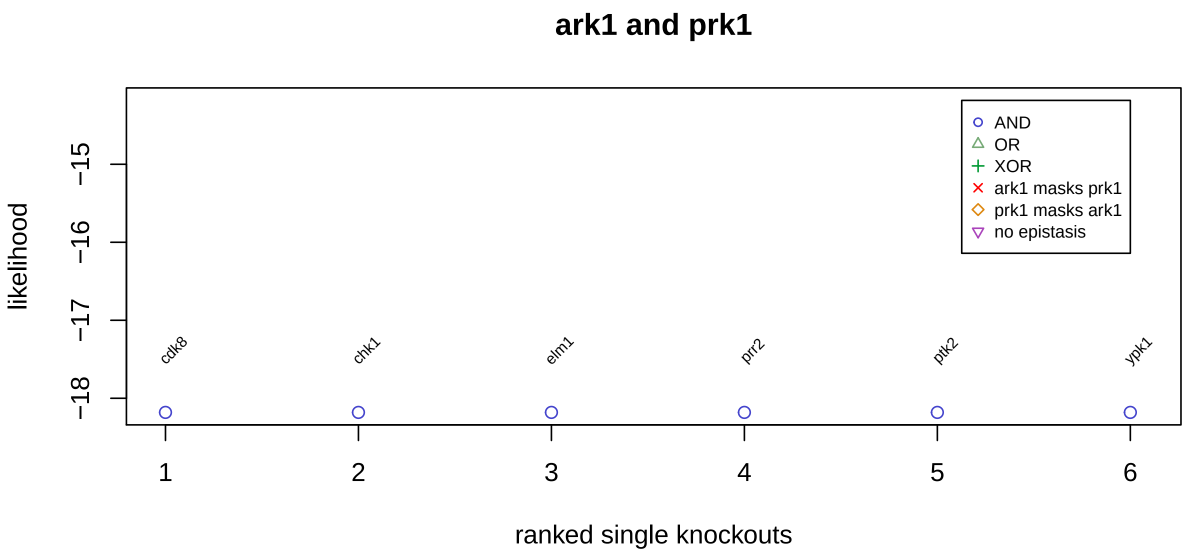
Wageningen et al., 2010

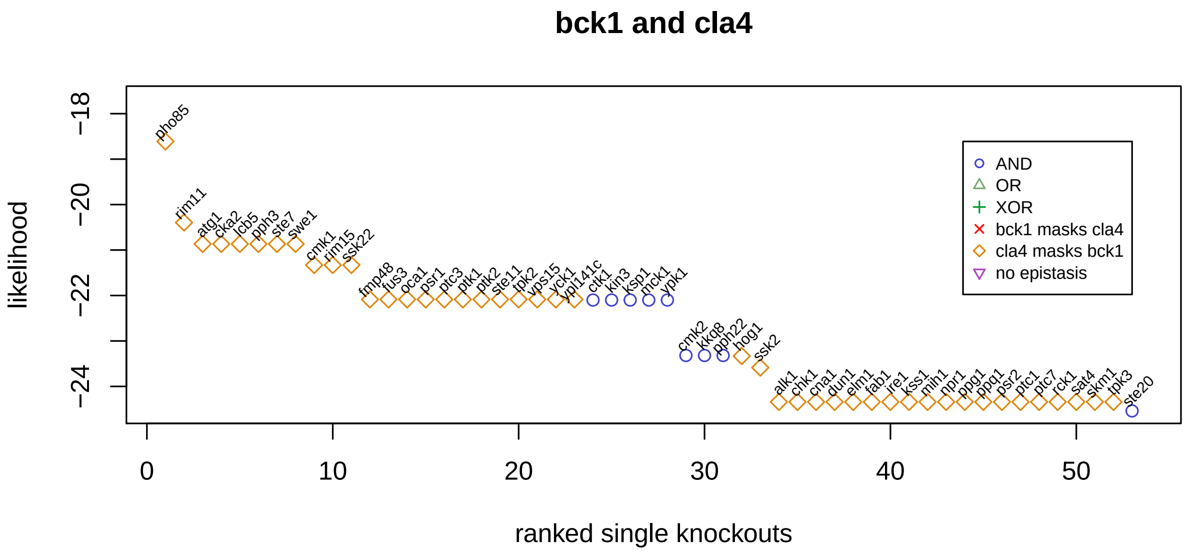
```
file <-
    "http://www.holstegelab.nl/publications/sv/signaling_redundancy/downloads/DataS1.txt"

data <- read.delim(file)

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
```

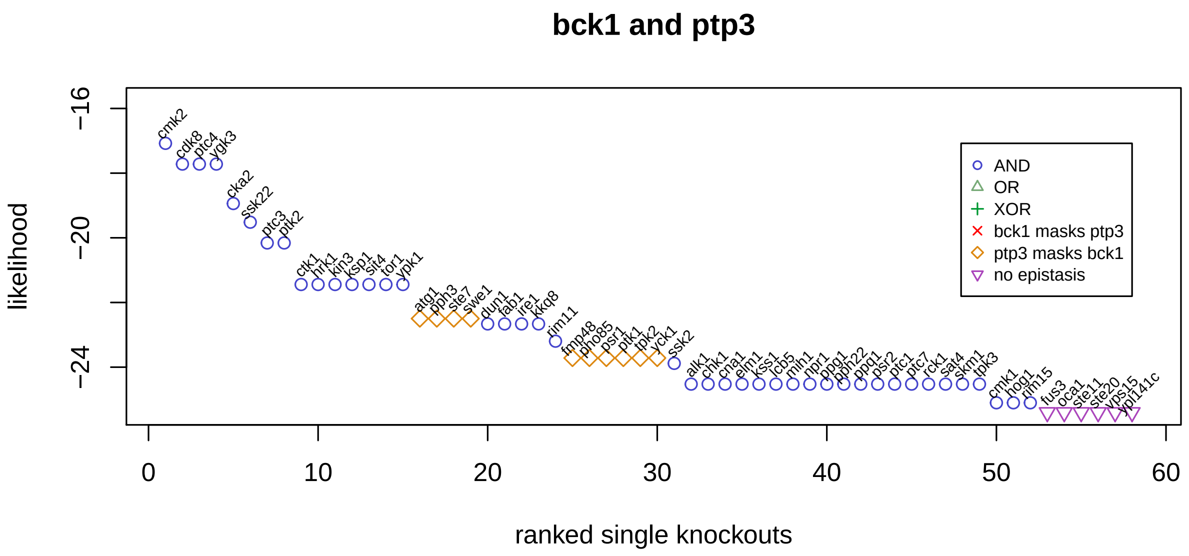
```
dataBin <- dataBin[-which(apply(dataBin, 1, max) == 0), ]

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) {
    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

        }

    }

}
```

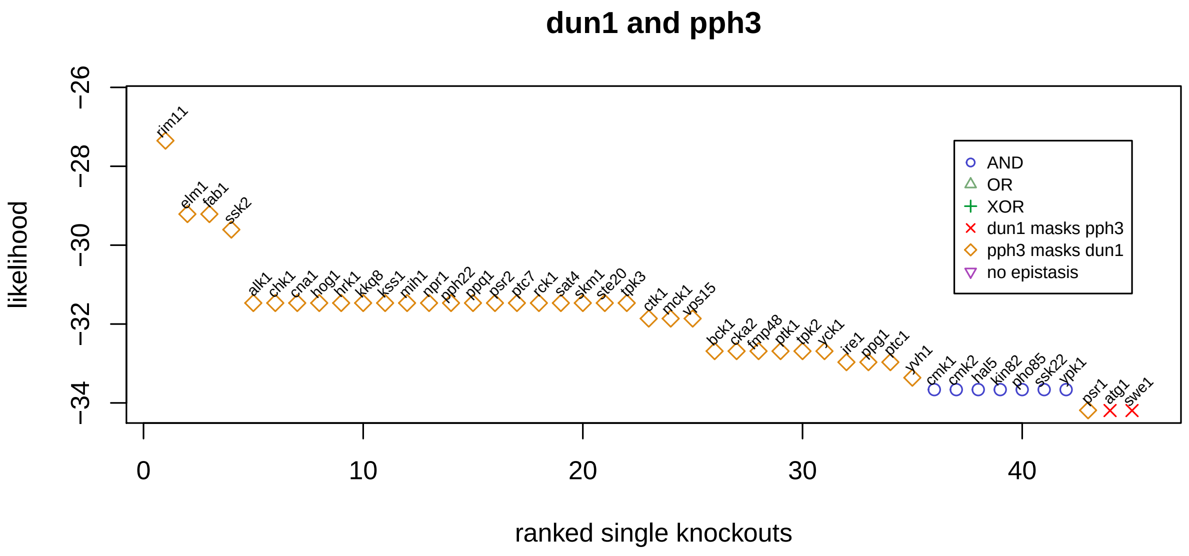
```
palette(c("#4444cc", "#77aa77", "#009933", "#ff0000", "#dd8811", "#aa44bb", "#999900"))

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)

}
```


ark1 and prk1
likelihood
−15
−16
−17
−18
ranked single knockouts
1
2
3
4
5
6
cdk8
chk1
elm1
prr2
ptk2
ypk1
○ AND
△ OR
+ XOR
× ark1 masks prk1
◇ prk1 masks ark1
▽ no epistasis

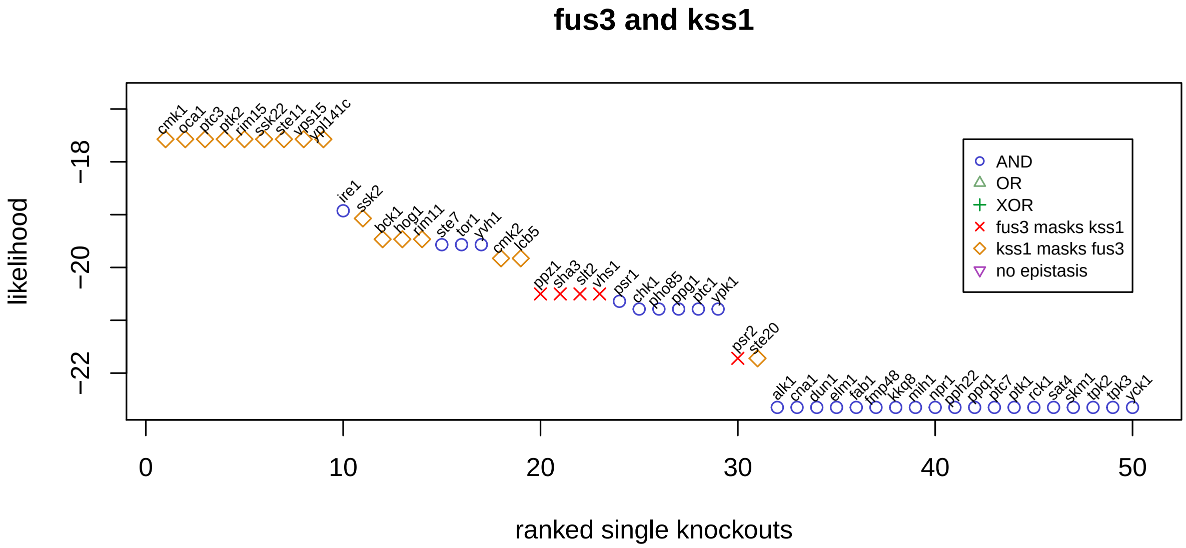

bck1 and cla4
likelihood
−18
−20
−22
−24
ranked single knockouts
0
10
20
30
40
50
pho85
rim11
atg1
cka2
lcb5
pph3
ste7
swe1
cmk1
rim15
ssk22
fmp48
fus3
oca1
psr1
ptc3
ptk1
ptk2
ste11
tpk2
vps15
yck1
ypl141c
ctk1
kin3
ksp1
mck1
ypk1
cmk2
kkq8
pph22
hog1
ssk2
alk1
chk1
cna1
dun1
elm1
fab1
ire1
kss1
mih1
npr1
ppg1
ppq1
psr2
ptc1
ptc7
rck1
sat4
skm1
tpk3
ste20
○ AND
△ OR
+ XOR
× bck1 masks cla4
◇ cla4 masks bck1
▽ no epistasis



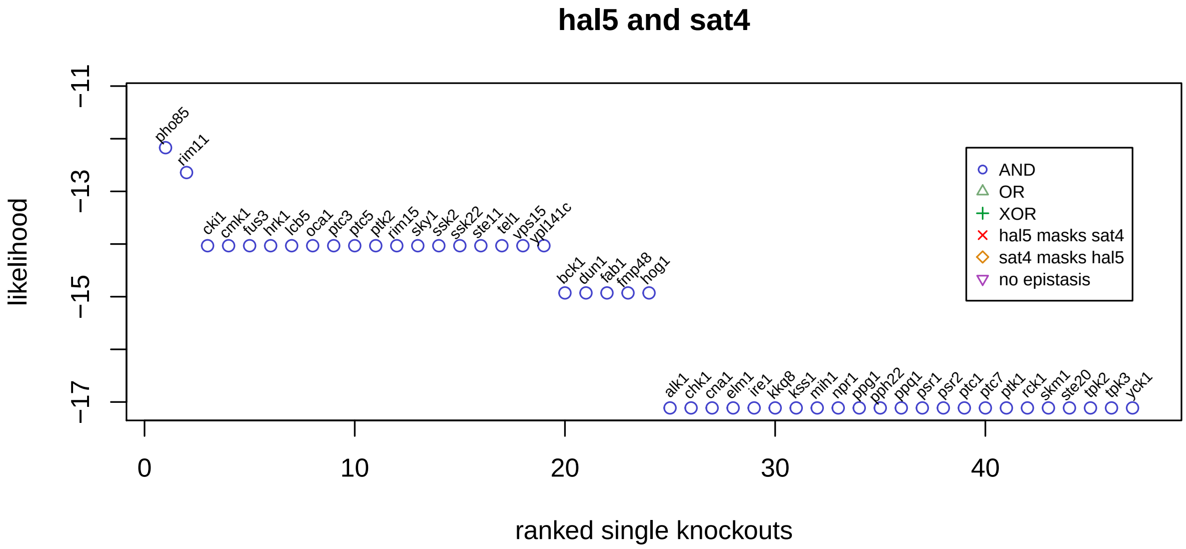
bck1 and ptp3



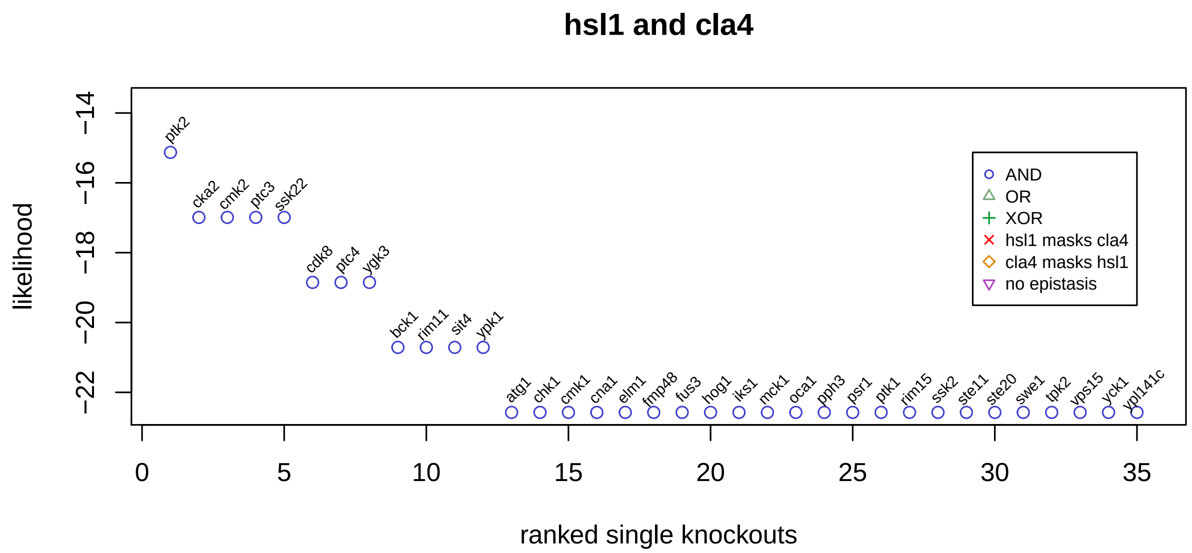
dun1 and pph3

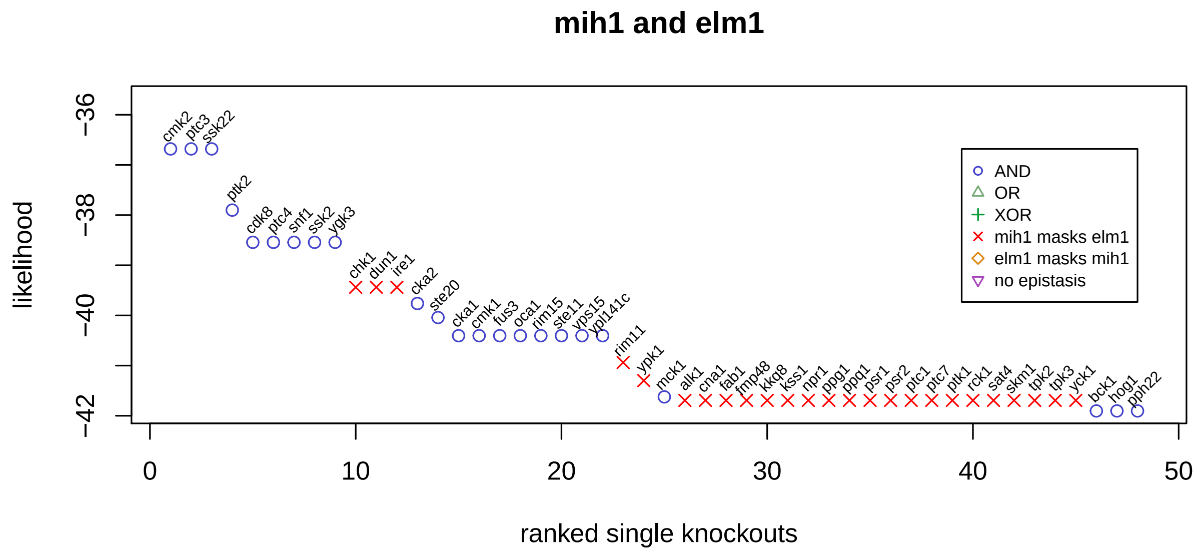


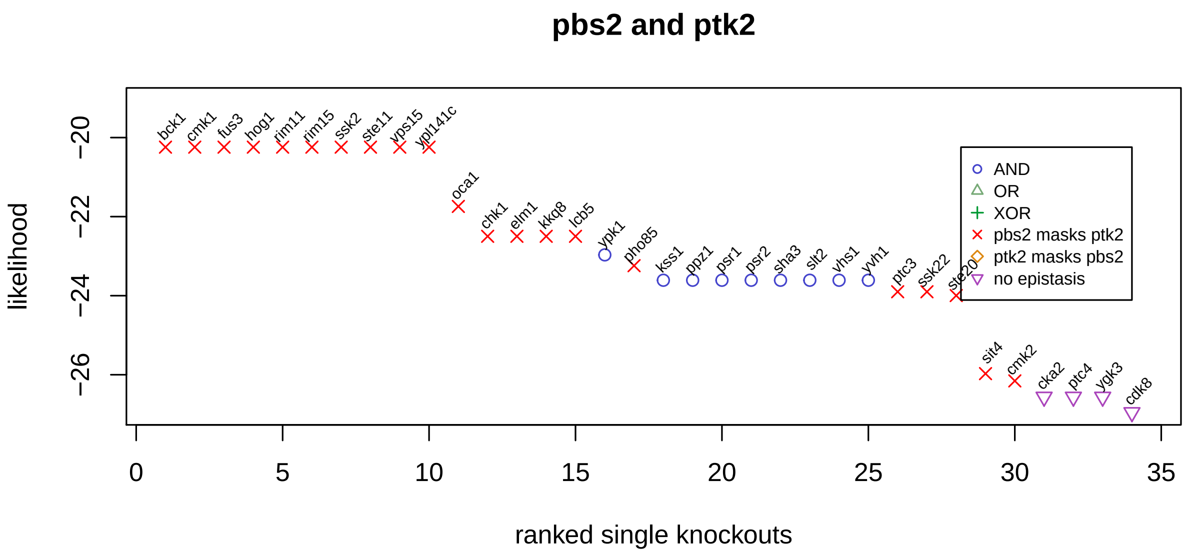
fus3 and kss1

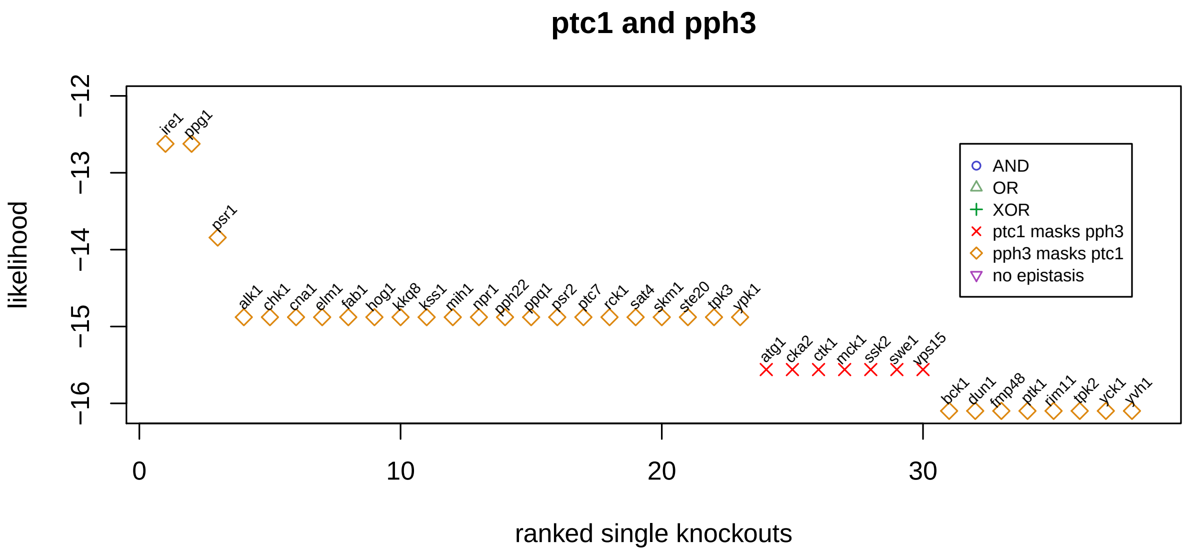


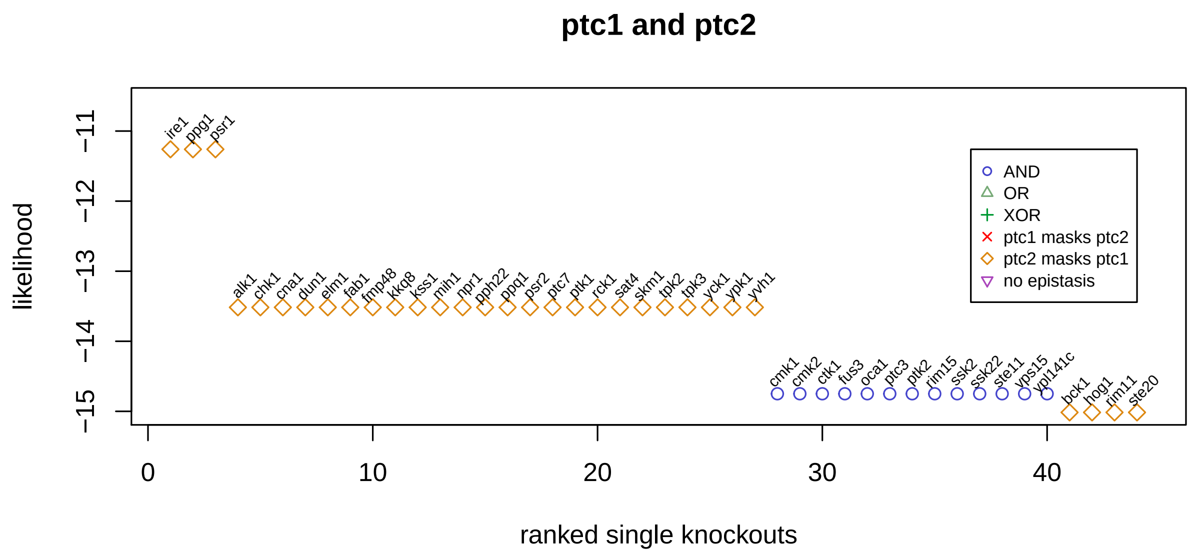
hal5 and sat4

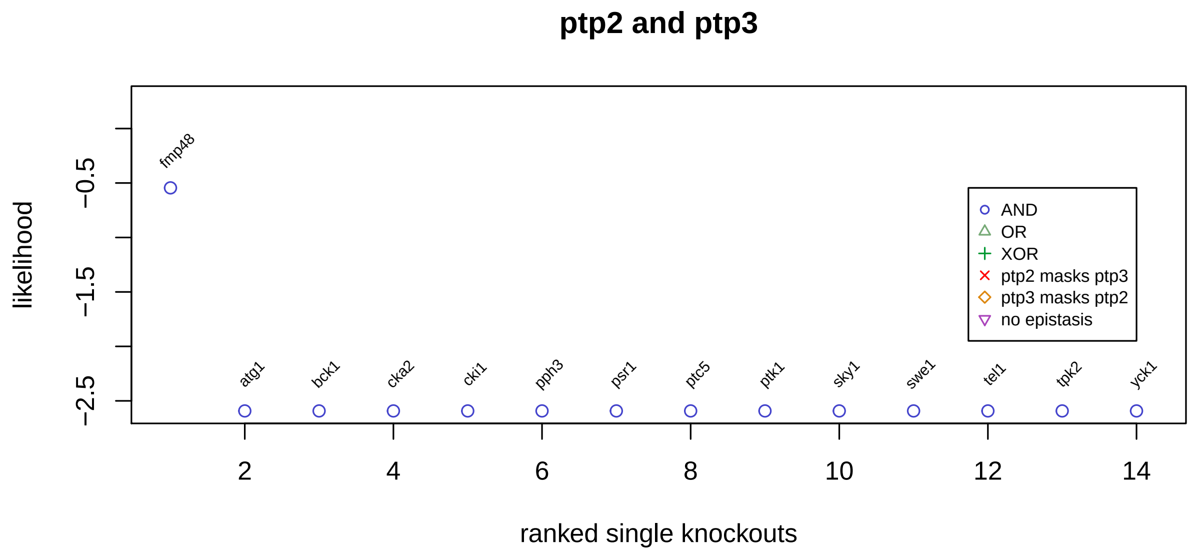

hsl1 and cla4
likelihood
−14
−16
−18
−20
−22
ranked single knockouts
0
5
10
15
20
25
30
35
ptk2
cka2
cmk2
ptc3
ssk22
cdk8
ptc4
ygk3
bck1
rim11
sit4
ypk1
atg1
chk1
cmk1
cna1
elm1
fmp48
fus3
hog1
iks1
mck1
oca1
pph3
psr1
ptk1
rim15
ssk2
ste11
ste20
swe1
tpk2
vps15
yck1
ypl141c
○ AND
△ OR
+ XOR
× hsl1 masks cla4
◇ cla4 masks hsl1
▽ no epistasis

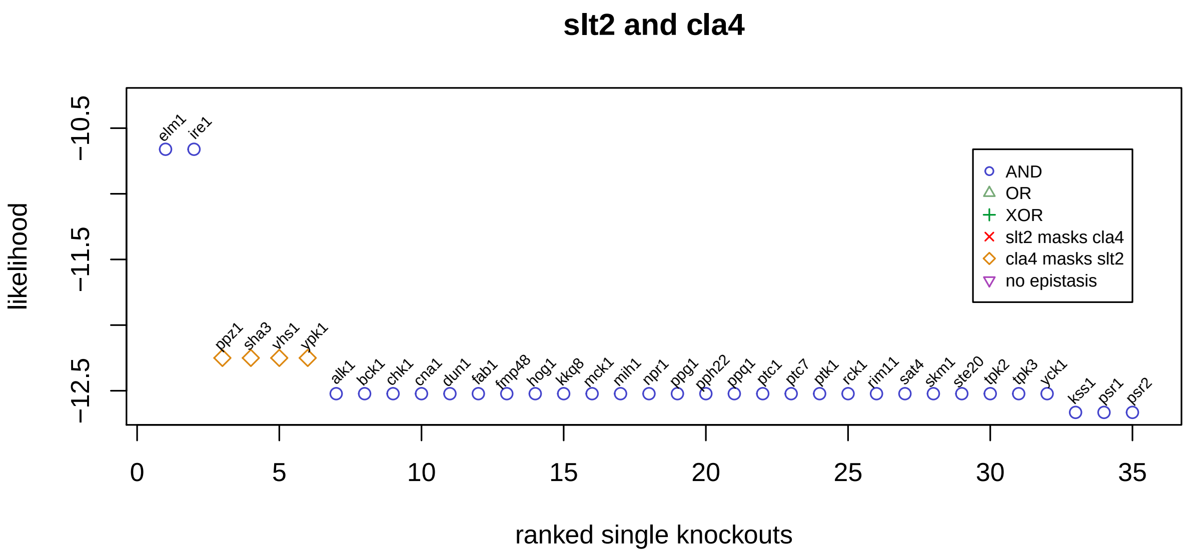

mih1 and elm1
likelihood
−36
−38
−40
−42
ranked single knockouts
0
10
20
30
40
50
cmk2
ptc3
ssk22
ptk2
cdk8
ptc4
snf1
ssk2
ygk3
chk1
dun1
ire1
cka2
ste20
cka1
cmk1
fus3
oca1
rim15
ste11
vps15
ypl141c
rim11
ypk1
mck1
alk1
cna1
fab1
fmp48
kkq8
kss1
npr1
ppg1
ppq1
psr1
psr2
ptc1
ptc7
ptk1
rck1
sat4
skm1
tpk2
tpk3
yck1
bck1
hog1
pph22
○ AND
△ OR
+ XOR
× mih1 masks elm1
◇ elm1 masks mih1
▽ no epistasis

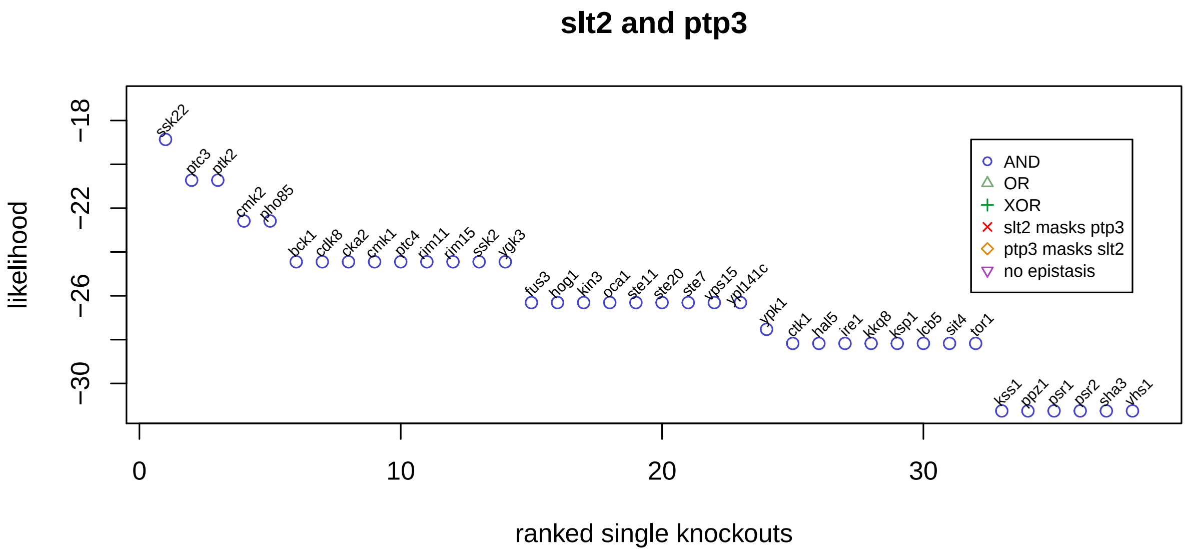

pbs2 and ptk2
likelihood
−20
−22
−24
−26
ranked single knockouts
0
5
10
15
20
25
30
35
bck1
cmk1
fus3
hog1
rim11
rim15
ssk2
ste11
vps15
ypl141c
oca1
chk1
elm1
kkq8
lcb5
ypk1
pho85
kss1
ppz1
psr1
psr2
sha3
slt2
vhs1
yvh1
ptc3
ssk22
ste20
sit4
cmk2
cka2
ptc4
ygk3
cdk8
○ AND
△ OR
+ XOR
× pbs2 masks ptk2
◇ ptk2 masks pbs2
▽ no epistasis

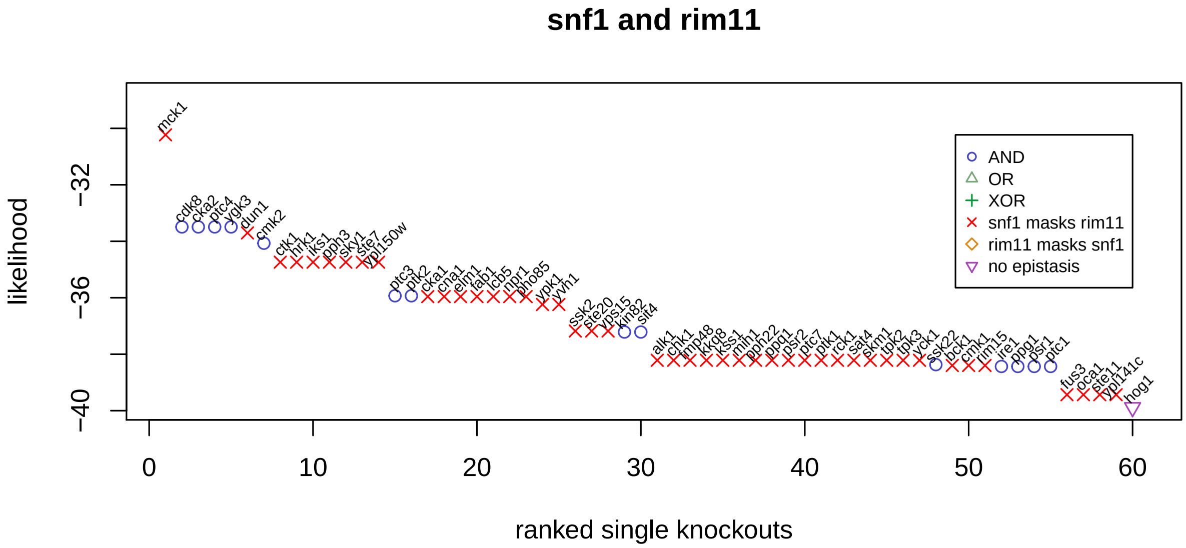

ptc1 and pph3
likelihood
−12
−13
−14
−15
−16
ranked single knockouts
0
10
20
30
ire1
ppg1
psr1
alk1
chk1
cna1
elm1
fab1
hog1
kkq8
kss1
mih1
npr1
pph22
ppq1
psr2
ptc7
rck1
sat4
skm1
ste20
tpk3
ypk1
atg1
cka2
ctk1
mck1
ssk2
swe1
vps15
bck1
dun1
fmp48
ptk1
rim11
tpk2
yck1
yvh1
○ AND
△ OR
+ XOR
× ptc1 masks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


ptc1 and ptc2
likelihood
−11
−12
−13
−14
−15
ranked single knockouts
0
10
20
30
40
ire1
ppg1
psr1
alk1
chk1
cna1
dun1
elm1
fab1
fmp48
kkq8
kss1
mih1
npr1
pph22
ppq1
psr2
ptc7
ptk1
rck1
sat4
skm1
tpk2
tpk3
yck1
ypk1
yvh1
cmk1
cmk2
ctk1
fus3
oca1
ptc3
ptk2
rim15
ssk2
ssk22
ste11
vps15
ypl141c
bck1
hog1
rim11
ste20
○ AND
△ OR
+ XOR
× ptc1 masks ptc2
◇ ptc2 masks ptc1
▽ no epistasis


ptp2 and ptp3
likelihood
−0.5
−1.5
−2.5
ranked single knockouts
2
4
6
8
10
12
14
fmp48
atg1
bck1
cka2
cki1
pph3
psr1
ptc5
ptk1
sky1
swe1
tel1
tpk2
yck1
○ AND
△ OR
+ XOR
× ptp2 masks ptp3
◇ ptp3 masks ptp2
▽ no epistasis

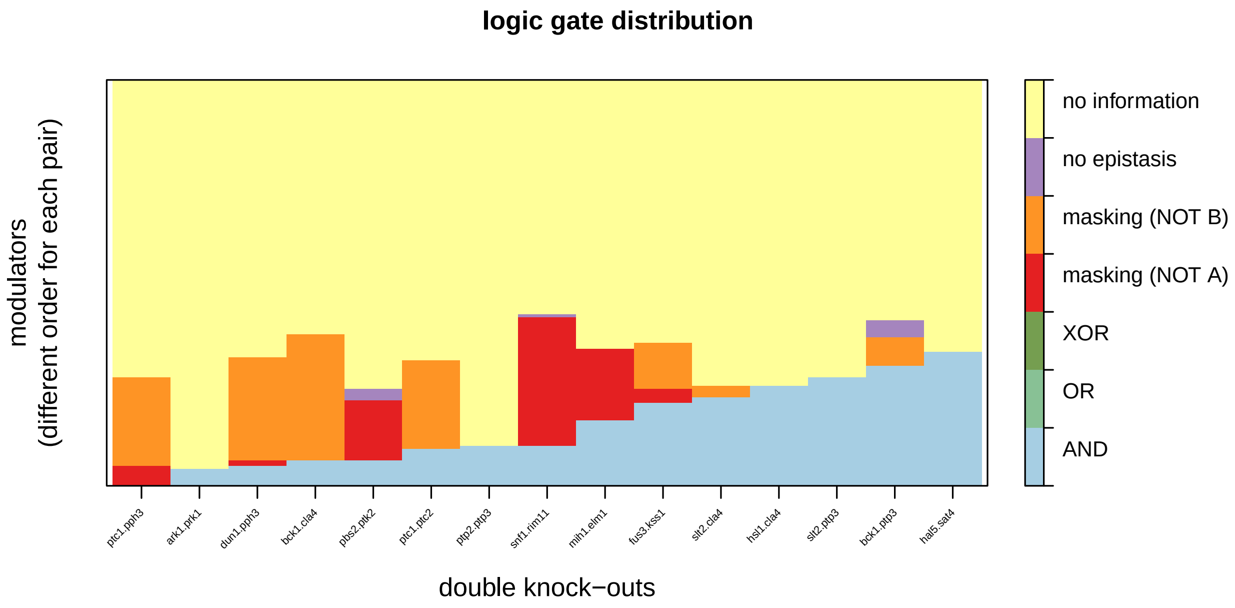

slt2 and cla4


slt2 and ptp3



```r
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

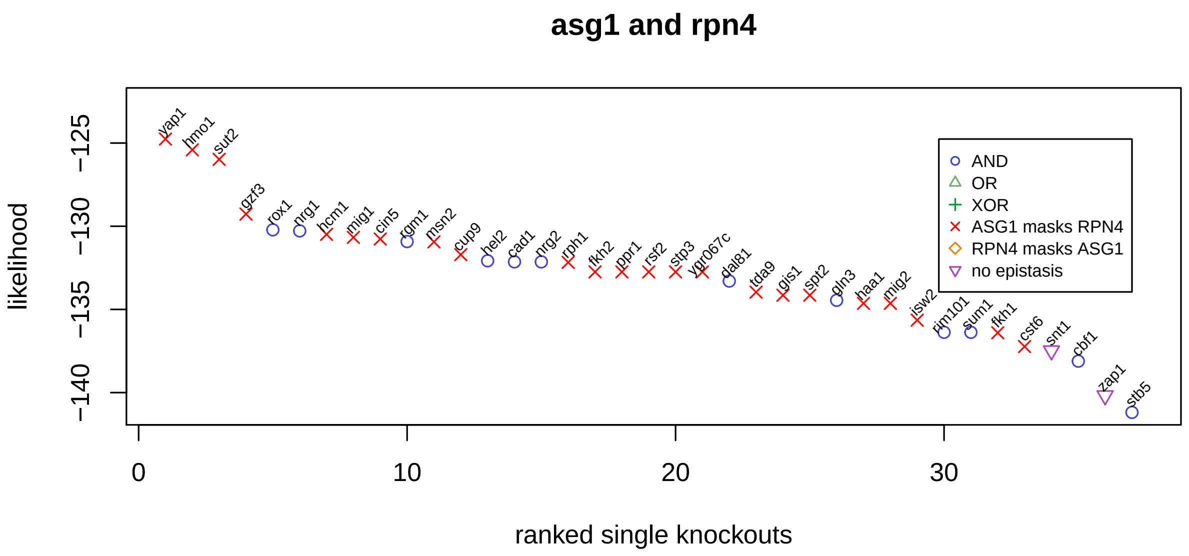
```
file <- paste("http://www.holstegelab.nl/publications/GSTF_geneticinteractions/",
              "downloads/del_mutants_limma.txt", sep = "")

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)
```

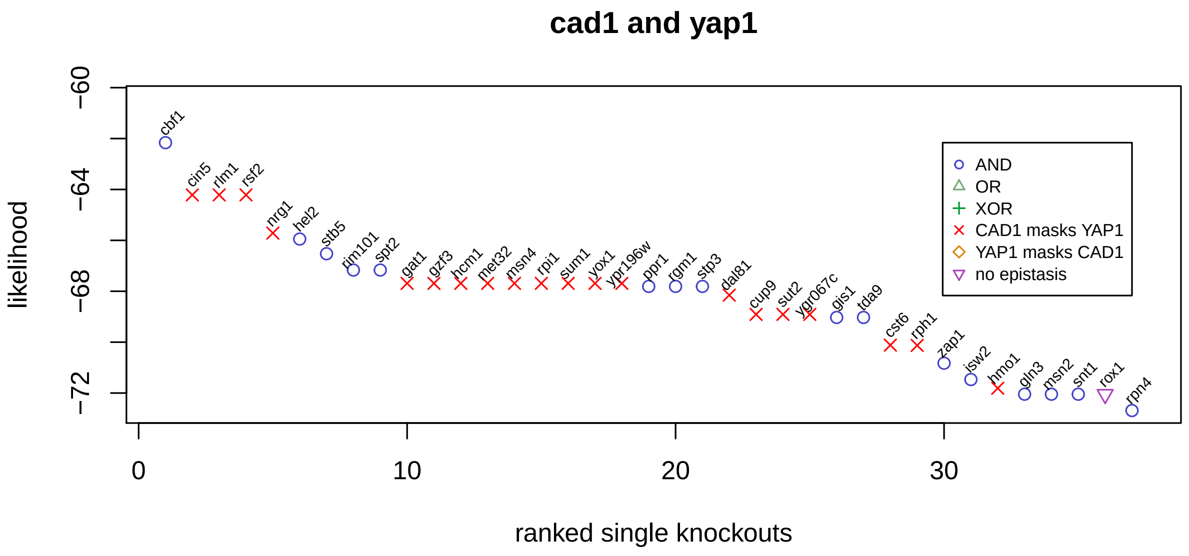
```
dataP <- data[-1, which(data[1, ] %in% "p.value")]

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)
```

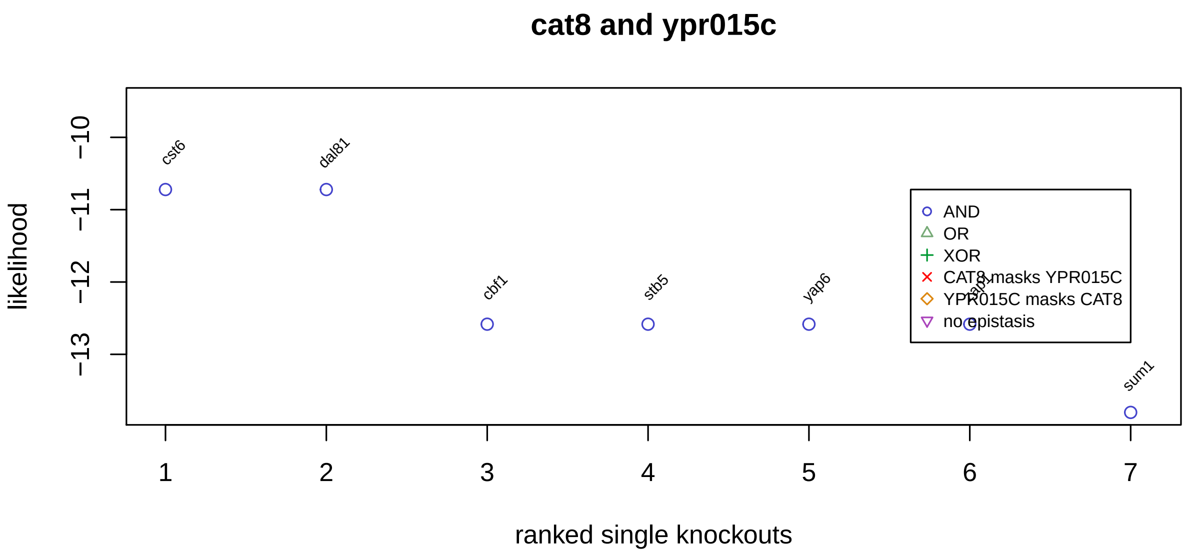
```
for (i in doubles[set]) {
    print(i)
    doubles.singles <- unlist(strsplit(i, "\\."))
    egenes <- which(apply(dataBin[,
              which(colnames(dataBin) %in% c(i, doubles.singles))], 1, max) == 1)
    for (j in singles) {
        print(j)
        if (j %in% doubles.singles) { next() }

        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

        }

    }

}
```

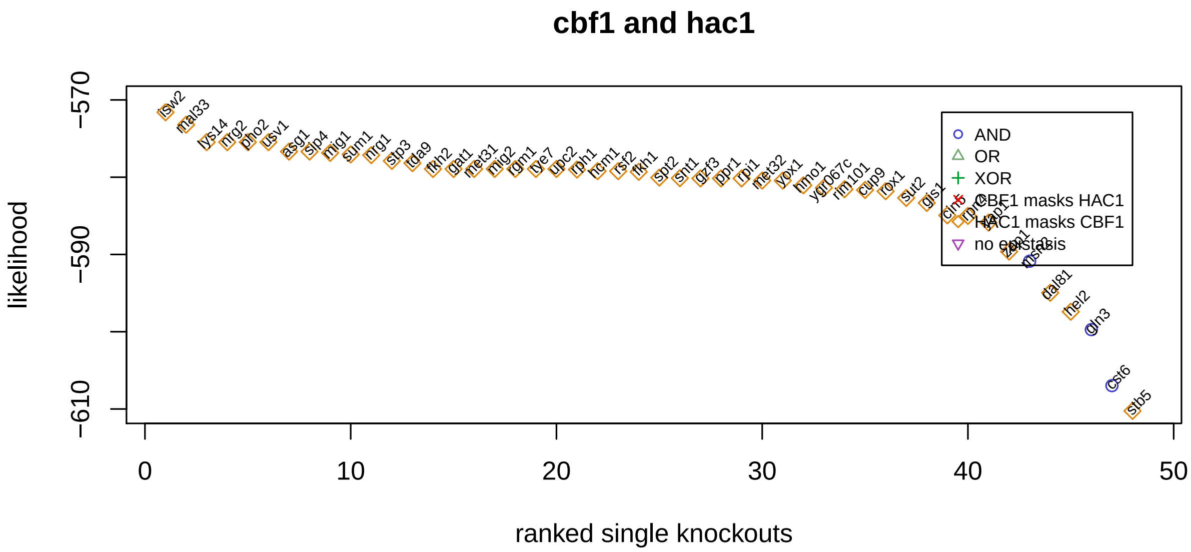
```
data(sameith_res)

llmat0 <- sameith$ll

logicmat0 <- sameith$logic
```

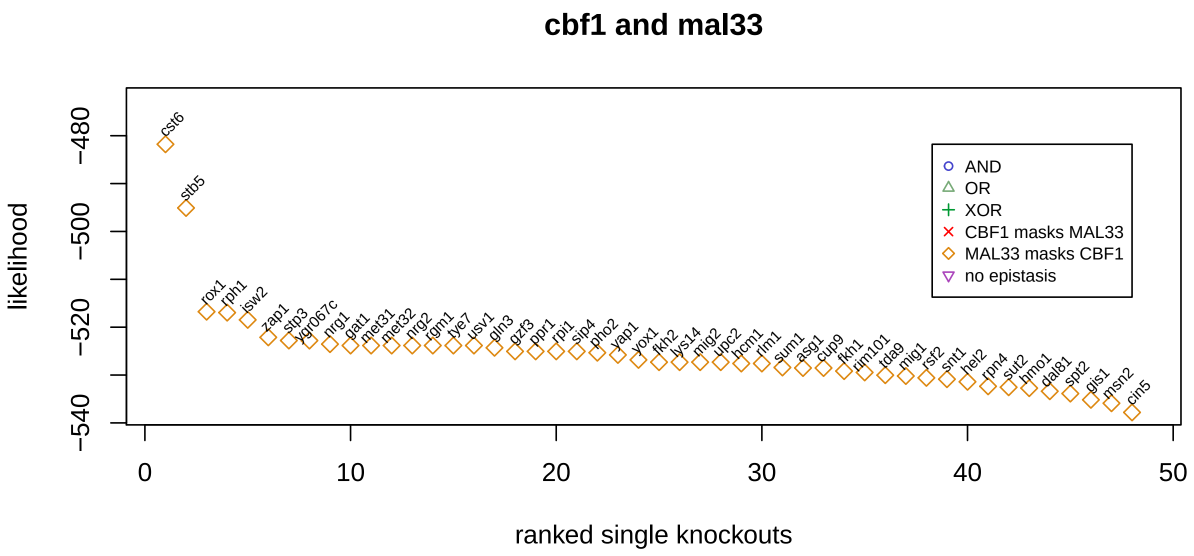
```r
for (i in 1:length(doubles)) {

  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)

}
```

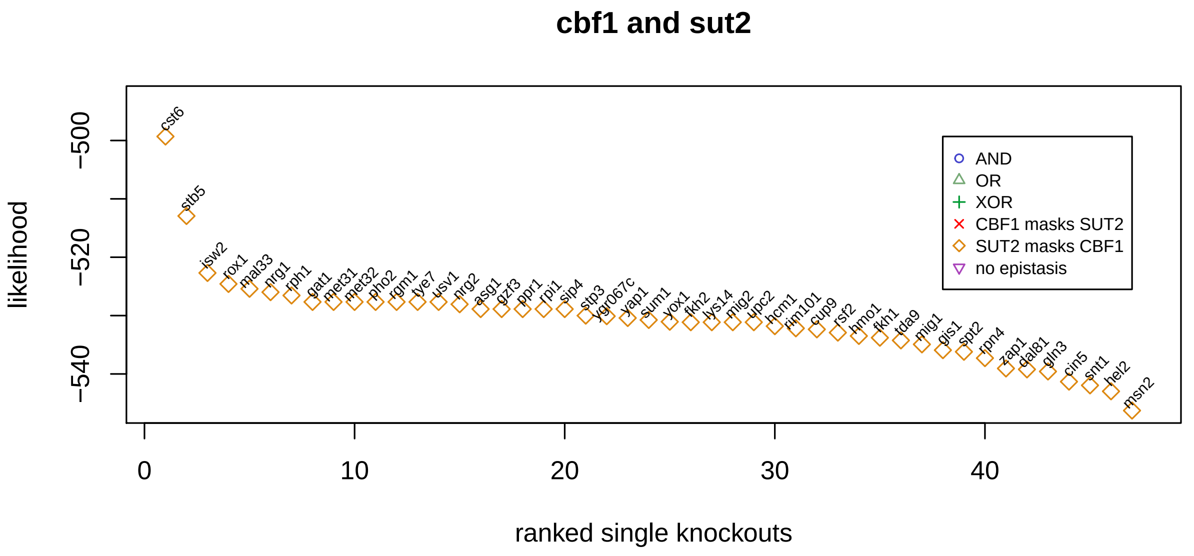

asg1 and rpn4
likelihood
−125
−130
−135
−140
0
10
20
30
ranked single knockouts
yap1
hmo1
sut2
gzf3
rox1
nrg1
hcm1
mig1
cin5
rgm1
msn2
cup9
hel2
cad1
nrg2
rph1
fkh2
ppr1
rsf2
stp3
ygr067c
dal81
tda9
gis1
spt2
gln3
haa1
mig2
isw2
rim101
sum1
fkh1
cst6
snt1
cbf1
zap1
stb5
○ AND
△ OR
+ XOR
× ASG1 masks RPN4
◇ RPN4 masks ASG1
▽ no epistasis

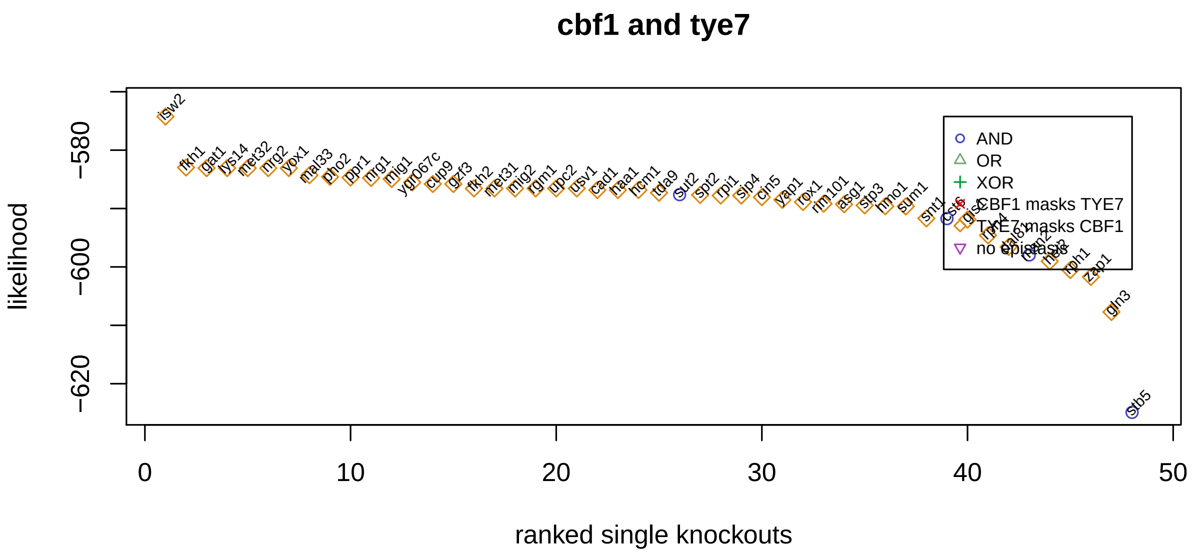

cad1 and yap1
likelihood
−60
−64
−68
−72
0
10
20
30
ranked single knockouts
cbf1
cin5
rlm1
rsf2
nrg1
hel2
stb5
rim101
spt2
gat1
gzf3
hcm1
met32
msn4
rpi1
sum1
yox1
ypr196w
ppr1
rgm1
stp3
dal81
cup9
sut2
ygr067c
gis1
tda9
cst6
rph1
zap1
isw2
hmo1
gln3
msn2
snt1
rox1
rpn4
○ AND
△ OR
+ XOR
× CAD1 masks YAP1
◇ YAP1 masks CAD1
▽ no epistasis

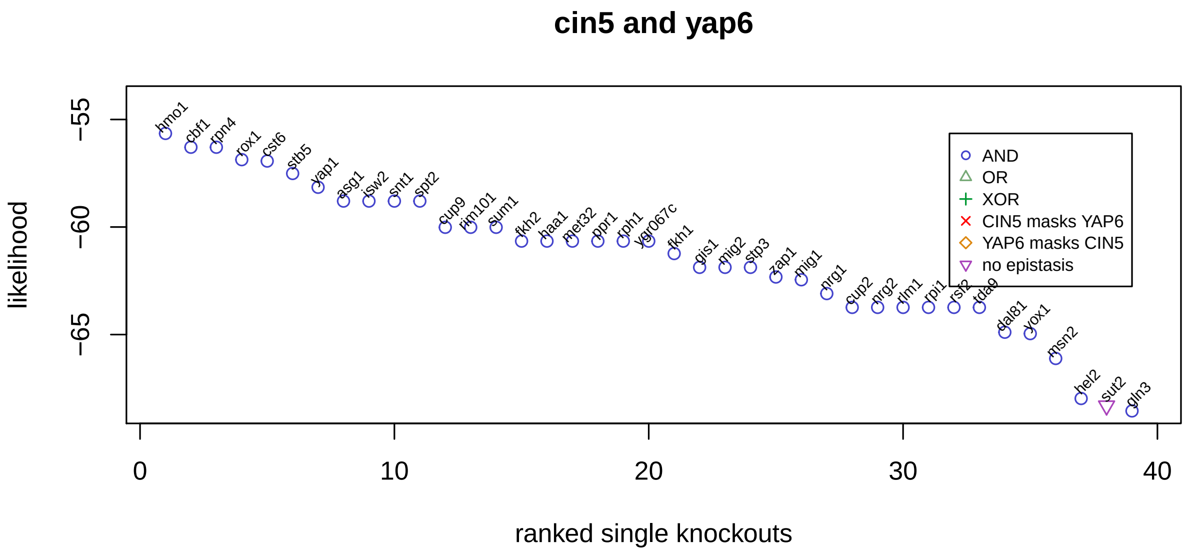

cat8 and ypr015c
likelihood
−10
−11
−12
−13
ranked single knockouts
1
2
3
4
5
6
7
cst6
dal81
cbf1
stb5
yap6
rap1
sum1
AND
OR
XOR
CAT8 masks YPR015C
YPR015C masks CAT8
no epistasis

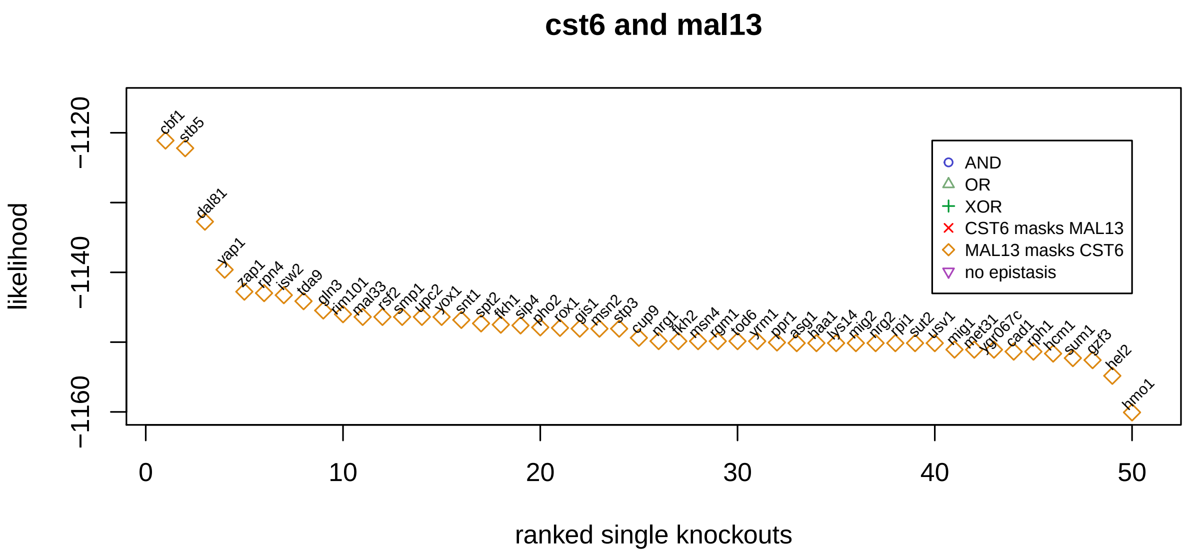

cbf1 and hac1
likelihood
−570
−590
−610
ranked single knockouts
0
10
20
30
40
50
isw2
mal33
lys14
nrg2
pho2
usv1
asg1
sip4
mig1
sum1
nrg1
stp3
tda9
fkh2
gat1
met31
mig2
rgm1
tye7
upc2
rph1
hcm1
rsf2
fkh1
spt2
snt1
gzf3
ppr1
rpi1
met32
yox1
hmo1
ygr067c
rim101
cup9
rox1
sut2
gis1
cin5
rpn4
hap1
zap1
msn2
dal81
hel2
gln3
cst6
stb5
AND
OR
XOR
CBF1 masks HAC1
HAC1 masks CBF1
no epistasis

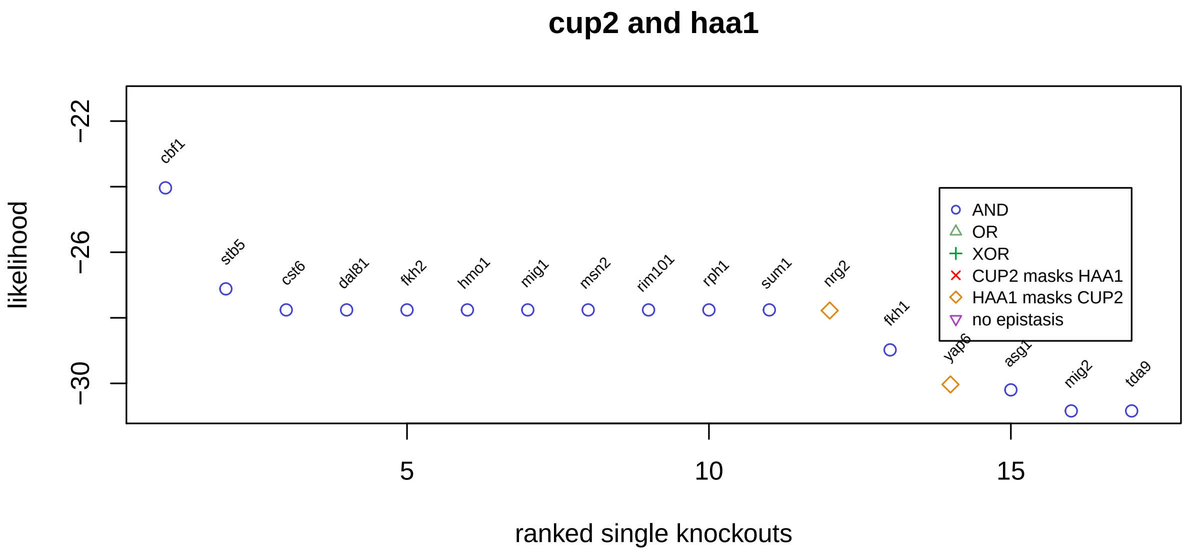

cbf1 and mal33
likelihood
−480
−500
−520
−540
0
10
20
30
40
50
ranked single knockouts
○ AND
△ OR
+ XOR
× CBF1 masks MAL33
◇ MAL33 masks CBF1
▽ no epistasis
cst6
stb5
rox1
rph1
isw2
zap1
stp3
ygr067c
nrg1
gat1
met31
met32
nrg2
rgm1
tye7
usv1
gln3
gzf3
ppr1
rpi1
sip4
pho2
yap1
yox1
fkh2
lys14
mig2
upc2
hcm1
rlm1
sum1
asg1
cup9
fkh1
rim101
tda9
mig1
rsf2
snt1
hel2
rpn4
sut2
hmo1
dal81
spt2
gis1
msn2
cin5

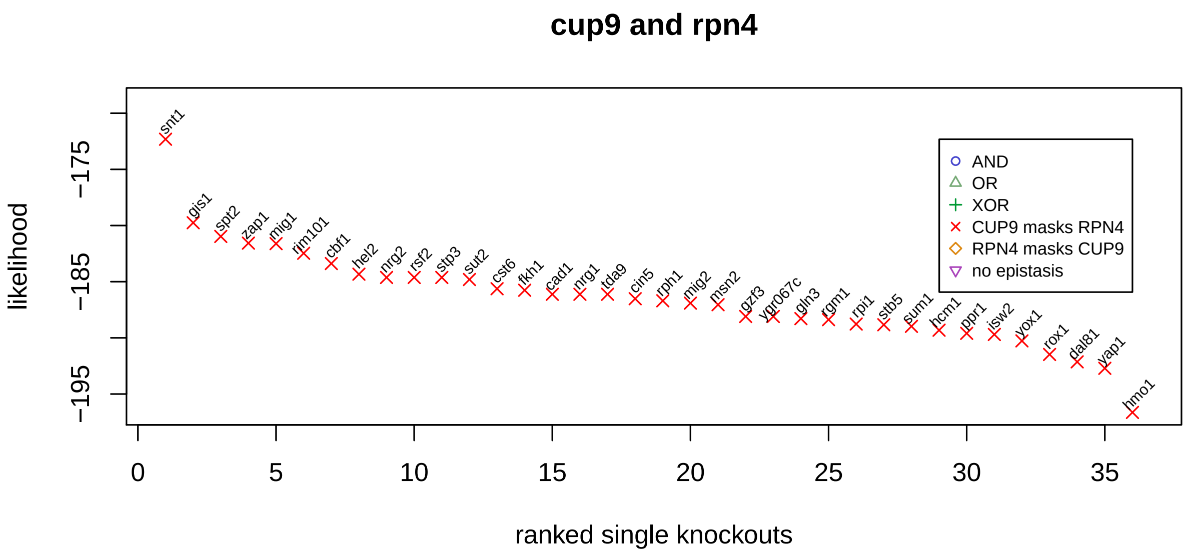

cbf1 and sut2
likelihood
−500
−520
−540
0
10
20
30
40
ranked single knockouts
○ AND
△ OR
+ XOR
× CBF1 masks SUT2
◇ SUT2 masks CBF1
▽ no epistasis
cst6
stb5
isw2
rox1
mal33
nrg1
rph1
gat1
met31
met32
pho2
rgm1
tye7
usv1
nrg2
asg1
gzf3
ppr1
rpi1
sip4
stp3
ygr067c
yap1
sum1
yox1
fkh2
lys14
mig2
upc2
hcm1
rim101
cup9
rsf2
hmo1
fkh1
tda9
mig1
gis1
spt2
rpn4
zap1
dal81
gln3
cin5
snt1
hel2
msn2

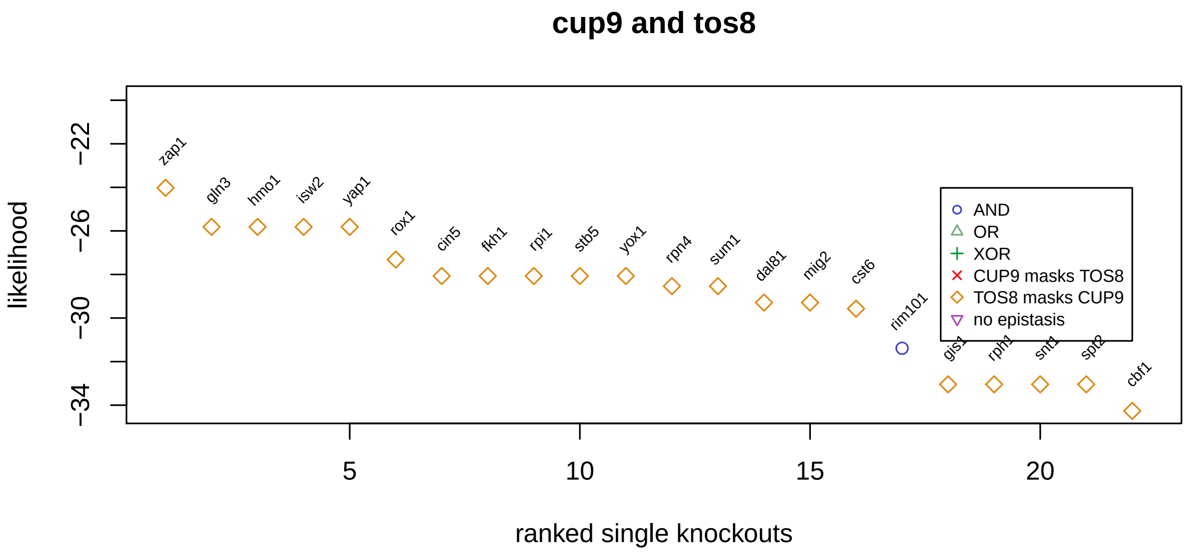

cbf1 and tye7
likelihood
−580
−600
−620
ranked single knockouts
0
10
20
30
40
50
AND
OR
XOR
CBF1 masks TYE7
TYE7 masks CBF1
no epistasis
isw2
fkh1
gat1
lys14
met32
nrg2
yox1
mal33
pho2
ppr1
nrg1
mig1
ygr067c
cup9
gzf3
fkh2
met31
mig2
rgm1
upc2
usv1
cad1
haa1
hcm1
tda9
sut2
spt2
rpi1
sip4
cin5
yap1
rox1
rim101
asg1
stp3
hmo1
sum1
snt1
cst6
gis1
rpn4
dal81
msn2
hel2
rph1
zap1
gln3
stb5

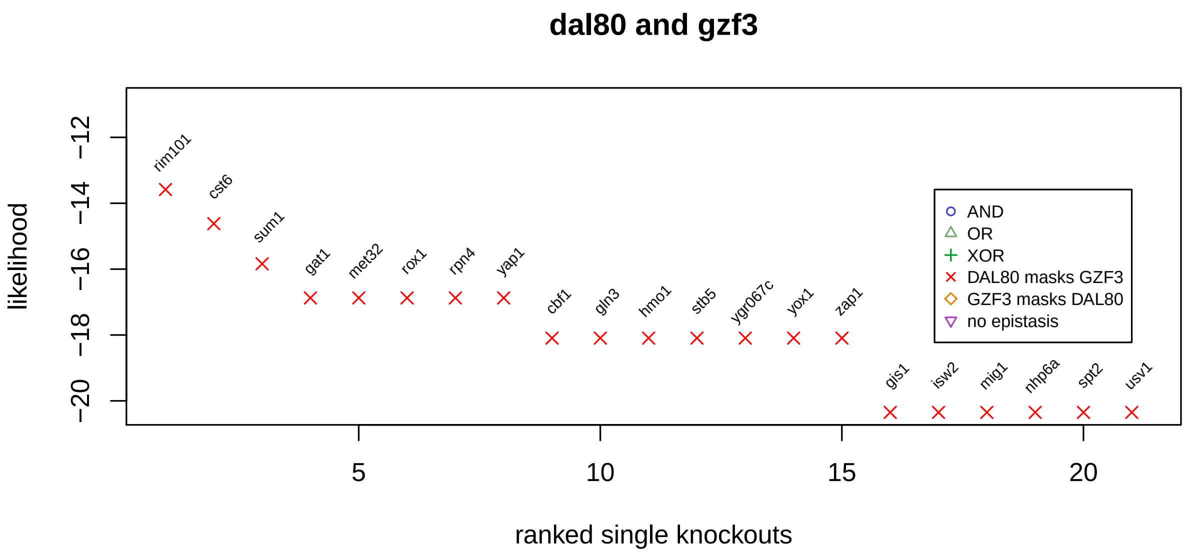

cin5 and yap6
likelihood
−55
−60
−65
ranked single knockouts
0
10
20
30
40
AND
OR
XOR
CIN5 masks YAP6
YAP6 masks CIN5
no epistasis
hmo1
cbf1
rpn4
rox1
cst6
stb5
yap1
asg1
isw2
snt1
spt2
cup9
rim101
sum1
fkh2
haa1
met32
ppr1
rph1
ygr067c
fkh1
gis1
mig2
stp3
zap1
mig1
nrg1
cup2
nrg2
tlm1
rpi1
rsf2
tda9
dal81
yox1
msn2
hel2
sut2
gln3

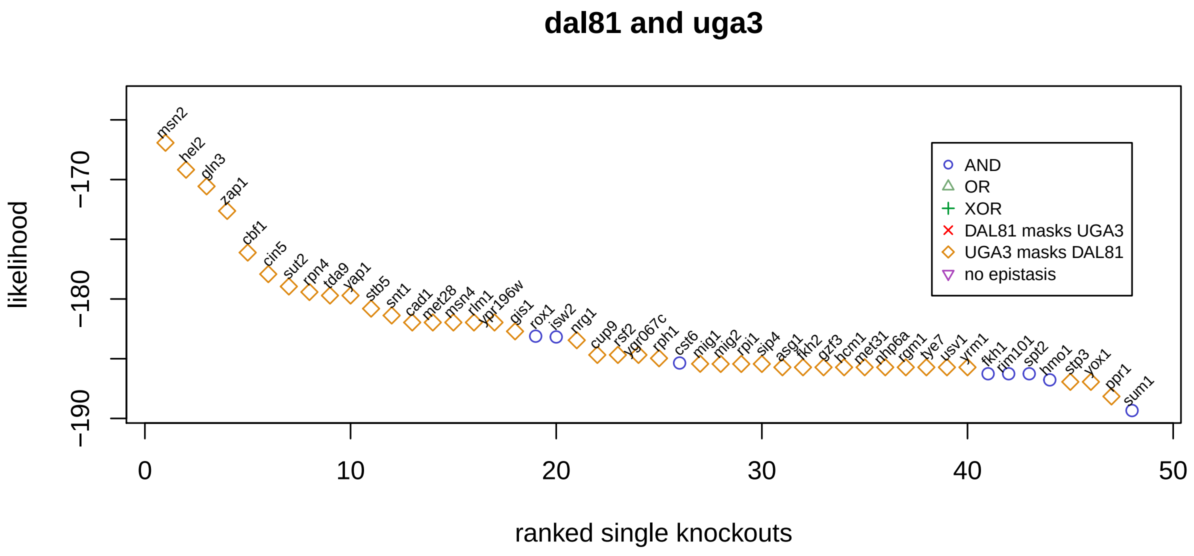

cst6 and mal13
likelihood
−1120
−1140
−1160
0
10
20
30
40
50
ranked single knockouts
○ AND
△ OR
+ XOR
× CST6 masks MAL13
◇ MAL13 masks CST6
▽ no epistasis
cbf1
stb5
dal81
yap1
zap1
rpn4
isw2
tda9
gln3
rim101
mal33
rsf2
smp1
upc2
yox1
snt1
spt2
fkh1
sip4
pho2
rox1
gis1
msn2
stp3
cup9
nrg1
fkh2
msn4
rgm1
tod6
yrm1
ppr1
asg1
haa1
lys14
mig2
nrg2
rpi1
sut2
usv1
mig1
met31
ygr067c
cad1
rph1
hcm1
sum1
gzf3
hel2
hmo1

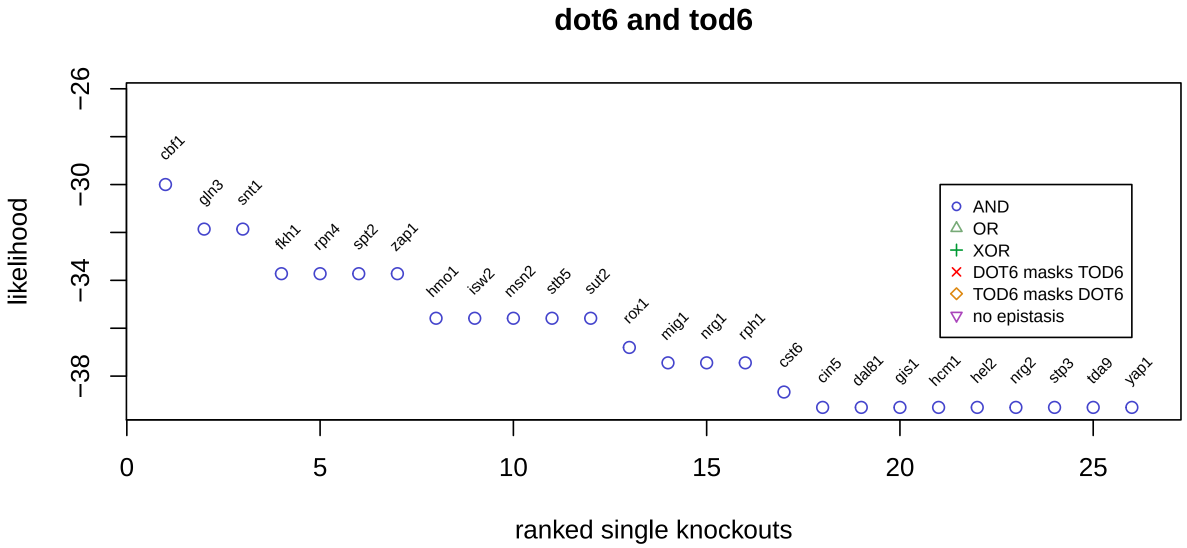

cup2 and haa1
likelihood
−22
−26
−30
5
10
15
ranked single knockouts
○ AND
△ OR
+ XOR
× CUP2 masks HAA1
◇ HAA1 masks CUP2
▽ no epistasis
cbf1
stb5
cst6
dal81
fkh2
hmo1
mig1
msn2
rim101
rph1
sum1
nrg2
fkh1
yap6
asg1
mig2
tda9

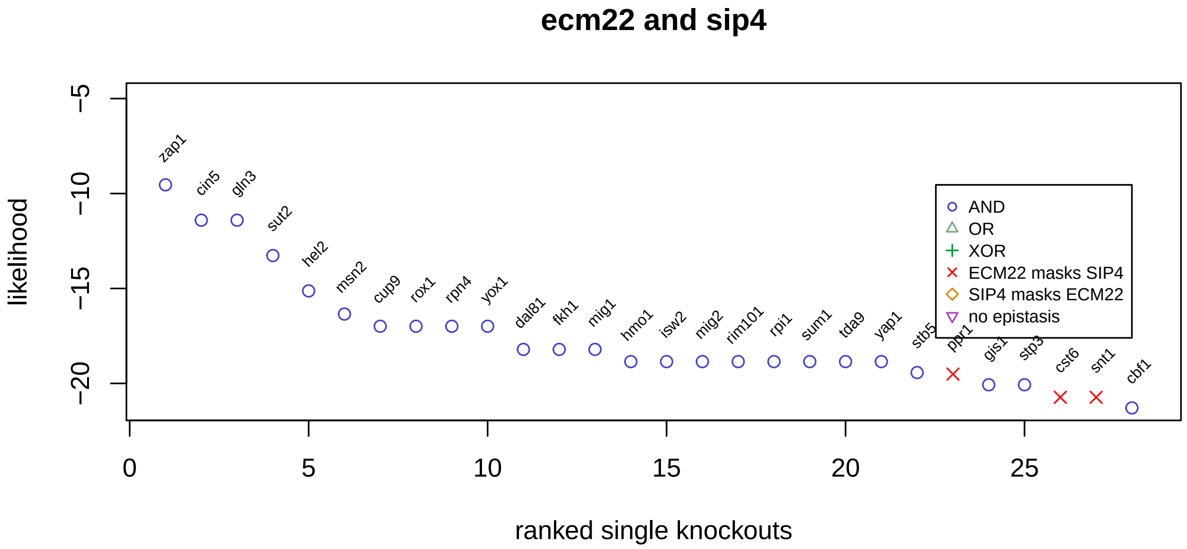

cup9 and rpn4
likelihood
−175
−185
−195
0
5
10
15
20
25
30
35
ranked single knockouts
snt1
gis1
spt2
zap1
mig1
rim101
cbf1
hel2
nrg2
rsf2
stp3
sut2
cst6
fkh1
cad1
nrg1
tda9
cin5
rph1
mig2
msn2
gzf3
ygr067c
gln3
rgm1
rpi1
stb5
sum1
hcm1
ppr1
isw2
yox1
rox1
dal81
yap1
hmo1
AND
OR
XOR
CUP9 masks RPN4
RPN4 masks CUP9
no epistasis

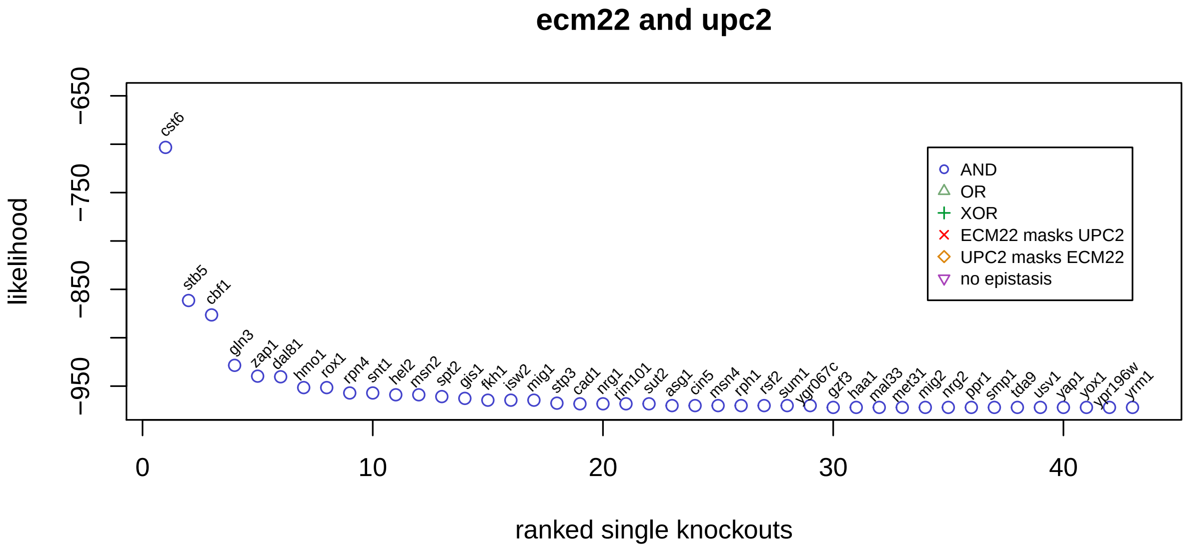

cup9 and tos8
likelihood
−22
−26
−30
−34
5
10
15
20
ranked single knockouts
zap1
gln3
hmo1
isw2
yap1
rox1
cin5
fkh1
rpi1
stb5
yox1
rpn4
sum1
dal81
mig2
cst6
rim101
gis1
rph1
snt1
spt2
cbf1
AND
OR
XOR
CUP9 masks TOS8
TOS8 masks CUP9
no epistasis


dal80 and gzf3

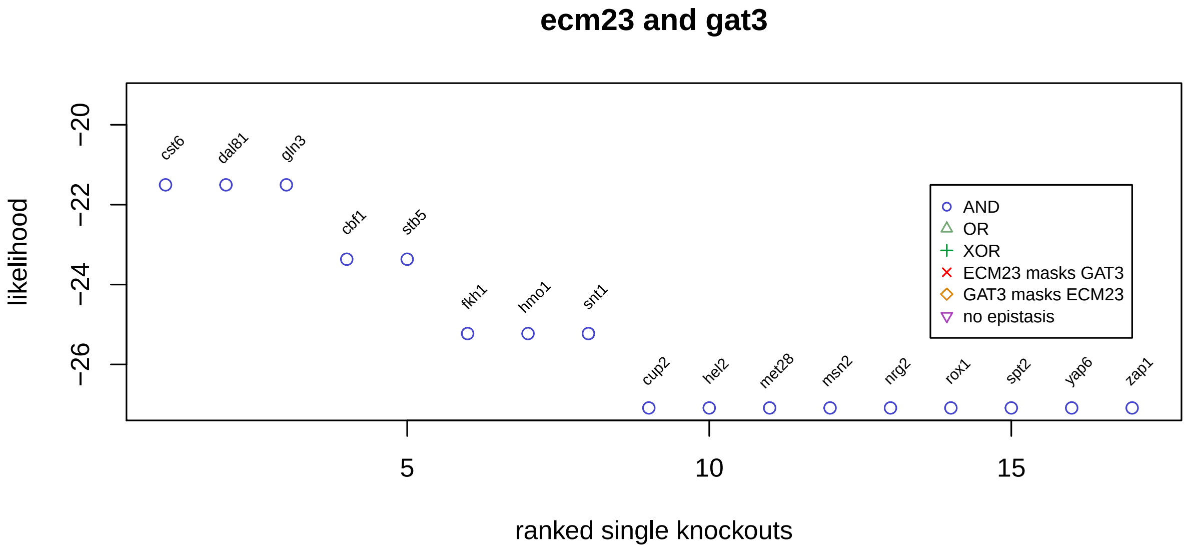

dal81 and uga3


dot6 and tod6

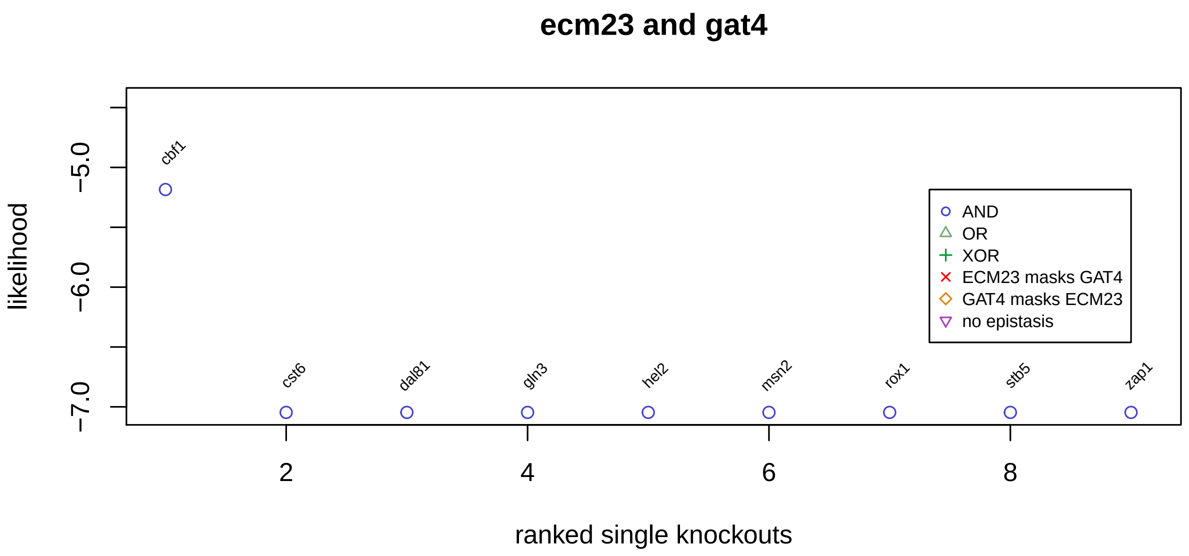

ecm22 and sip4

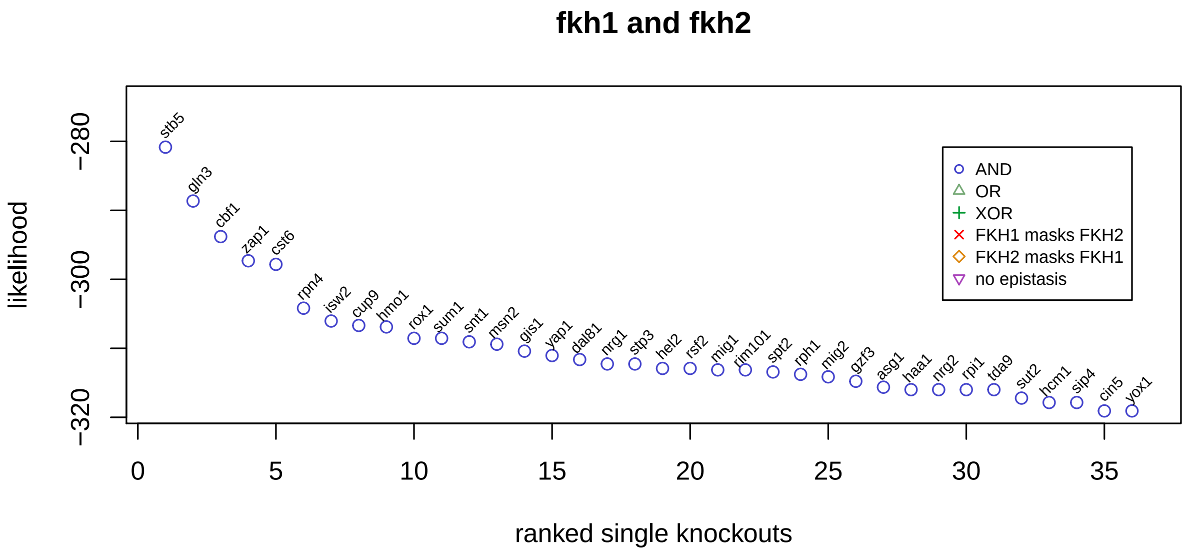


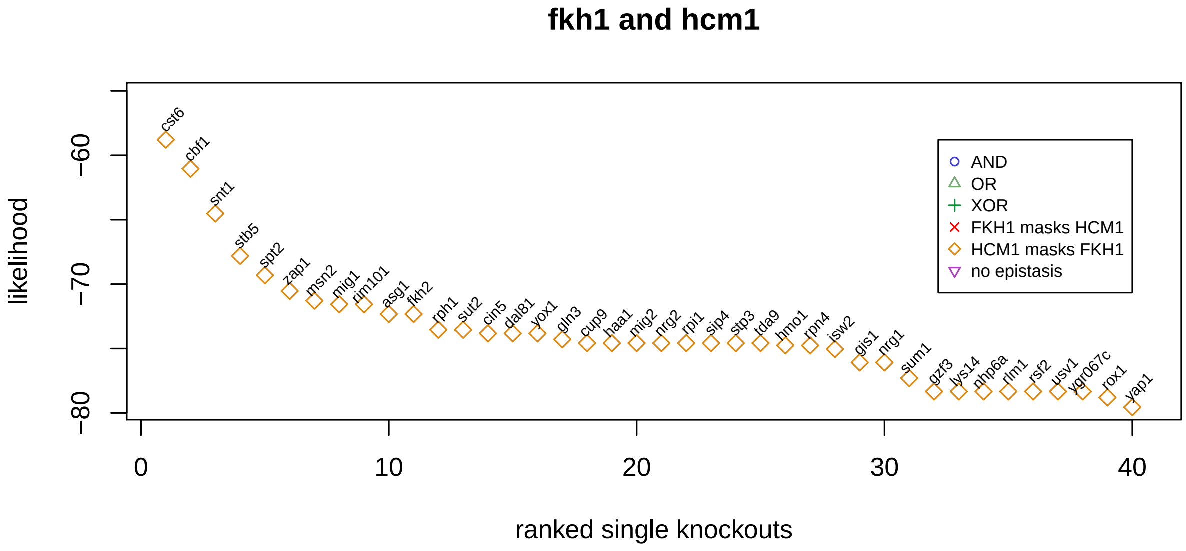
ecm22 and upc2

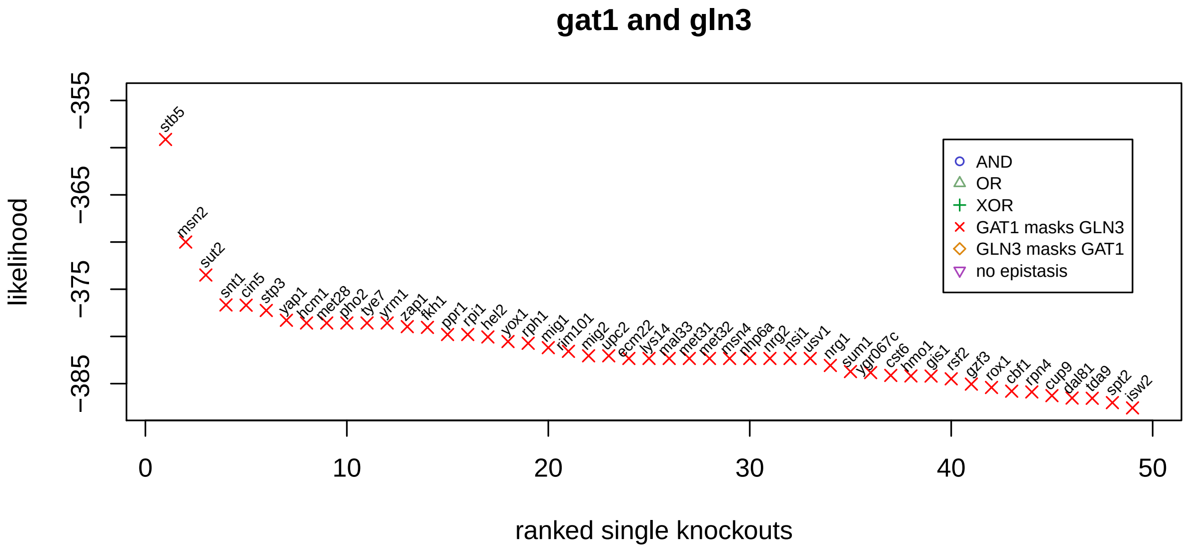


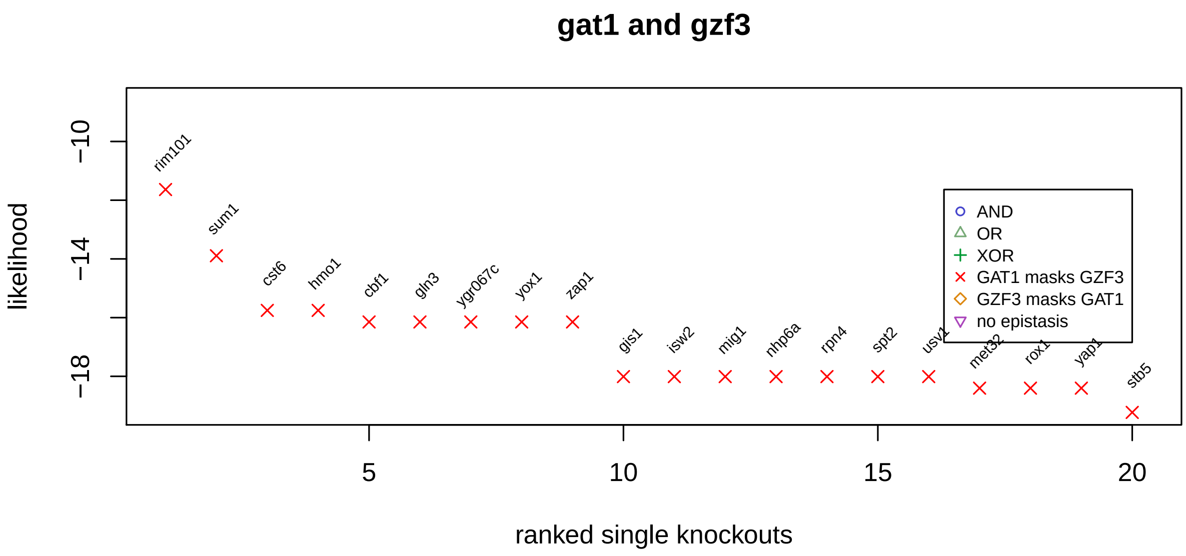
ecm23 and gat3

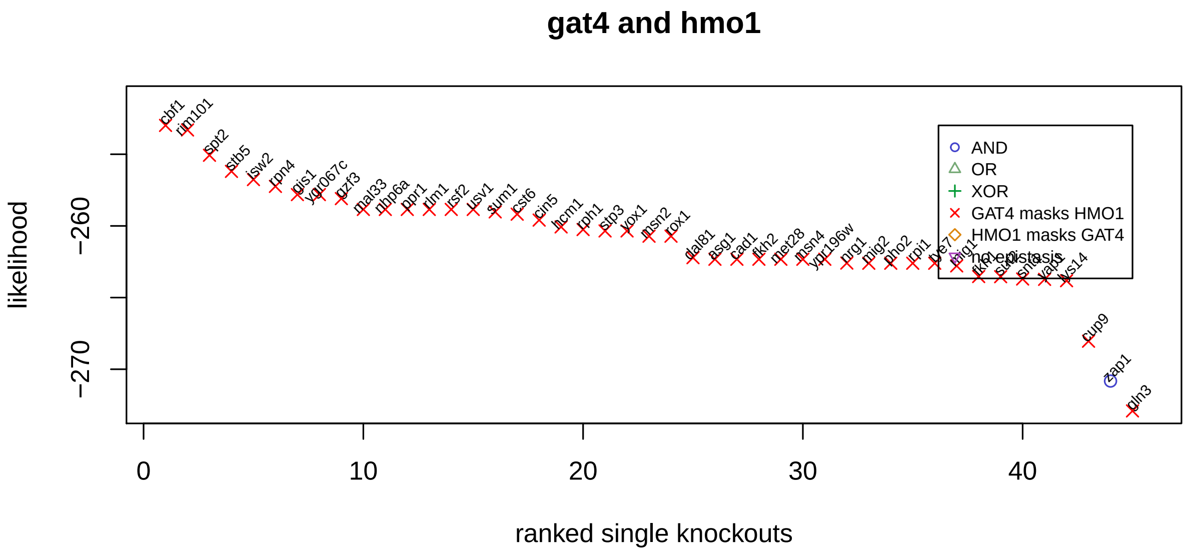

ecm23 and gat4
likelihood
−5.0
−6.0
−7.0
ranked single knockouts
2
4
6
8
cbf1
cst6
dal81
gln3
hel2
msn2
rox1
stb5
zap1
○ AND
△ OR
+ XOR
× ECM23 masks GAT4
◇ GAT4 masks ECM23
▽ no epistasis

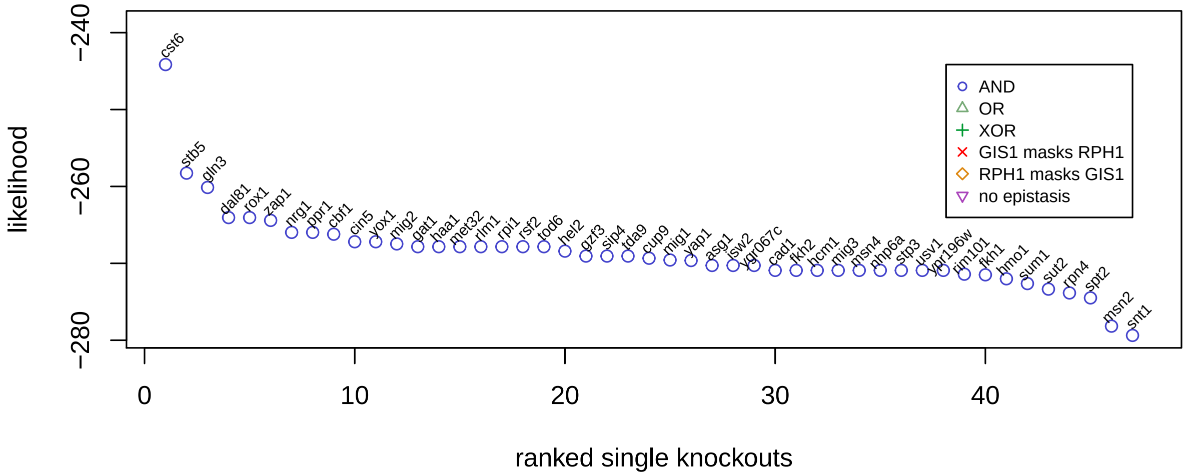

fkh1 and fkh2
likelihood
−280
−300
−320
ranked single knockouts
0
5
10
15
20
25
30
35
stb5
gln3
cbf1
zap1
cst6
rpn4
isw2
cup9
hmo1
rox1
sum1
snt1
msn2
gis1
yap1
dal81
nrg1
stp3
hel2
rsf2
mig1
rim101
spt2
rph1
mig2
gzf3
asg1
haa1
nrg2
rpi1
tda9
sut2
hcm1
sip4
cin5
yox1
○ AND
△ OR
+ XOR
× FKH1 masks FKH2
◇ FKH2 masks FKH1
▽ no epistasis


fkh1 and hcm1
likelihood
−60
−70
−80
0
10
20
30
40
ranked single knockouts
○ AND
△ OR
+ XOR
× FKH1 masks HCM1
◇ HCM1 masks FKH1
▽ no epistasis
cst6
cbf1
snt1
stb5
spt2
zap1
msn2
mig1
rim101
asg1
fkh2
rph1
sut2
cin5
dal81
yox1
gln3
cup9
haa1
mig2
nrg2
rpi1
sip4
stp3
tda9
hmo1
rpn4
isw2
gis1
nrg1
sum1
gzf3
lys14
nhp6a
rlm1
rsf2
usv1
ygr067c
rox1
yap1

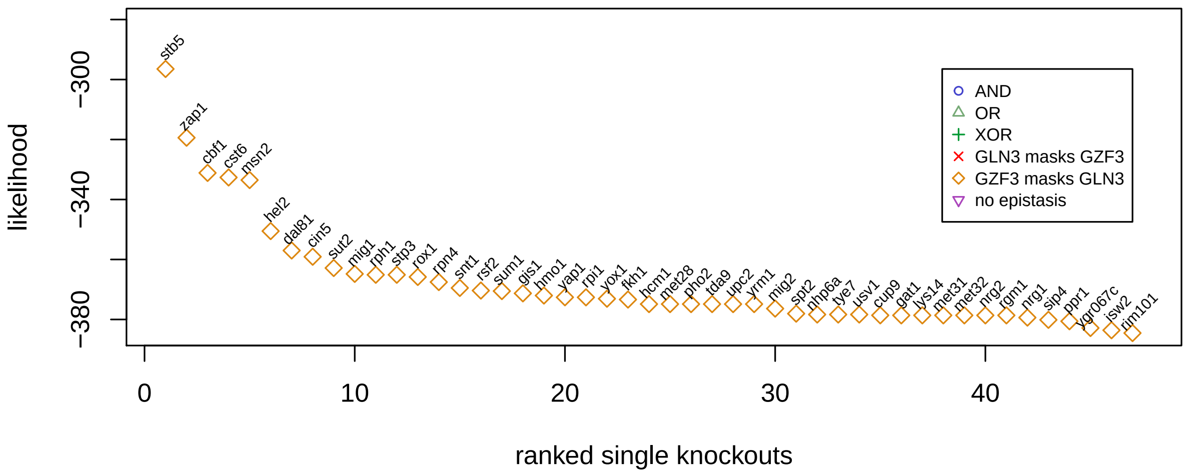

gat1 and gln3
likelihood
−355
−365
−375
−385
0
10
20
30
40
50
ranked single knockouts
○ AND
△ OR
+ XOR
× GAT1 masks GLN3
◇ GLN3 masks GAT1
▽ no epistasis
stb5
msn2
sut2
snt1
cin5
stp3
yap1
hcm1
met28
pho2
tye7
yrm1
zap1
fkh1
ppr1
rpi1
hel2
yox1
rph1
mig1
rim101
mig2
upc2
ecm22
lys14
mal33
met31
met32
msn4
nhp6a
nrg2
nsi1
usv1
nrg1
sum1
ygr067c
cst6
hmo1
gis1
rsf2
gzf3
rox1
cbf1
rpn4
cup9
dal81
tda9
spt2
isw2


gat1 and gzf3
likelihood
−10
−14
−18
ranked single knockouts
5
10
15
20
rim101
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

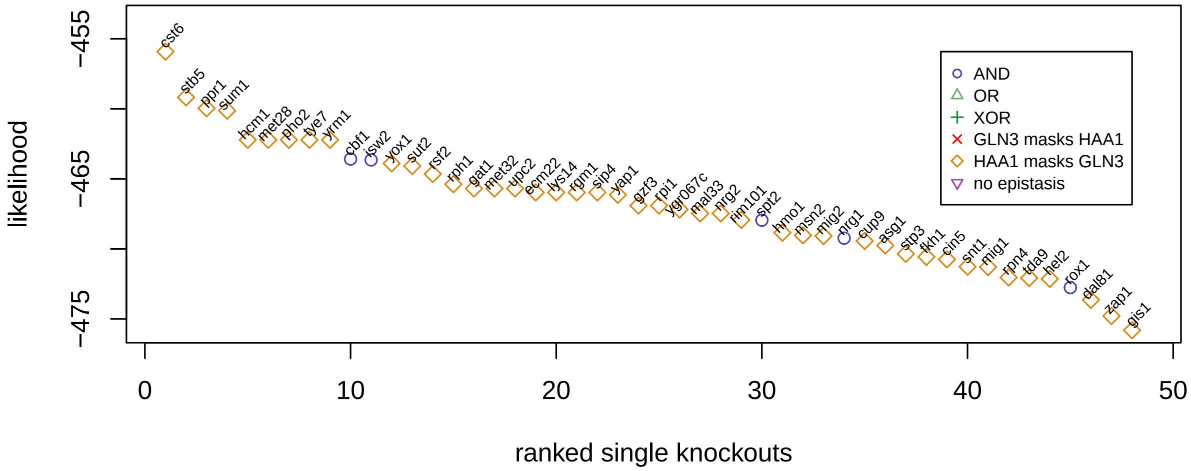

gat4 and hmo1
likelihood
−260
−270
ranked single knockouts
0
10
20
30
40
cbf1
rim101
spt2
stb5
isw2
rpn4
gis1
ygr067c
gzf3
mal33
nhp6a
ppr1
rlm1
rsf2
usv1
sum1
cst6
cin5
hcm1
rph1
stp3
yox1
msn2
rox1
dal81
asg1
cad1
fkh2
met28
msn4
ypr196w
nrg1
mig2
pho2
rpi1
tye7
fkh1
sut1
yap1
lys14
cup9
zap1
gln3
○ AND
△ OR
+ XOR
× GAT4 masks HMO1
◇ HMO1 masks GAT4
▽ no epistasis

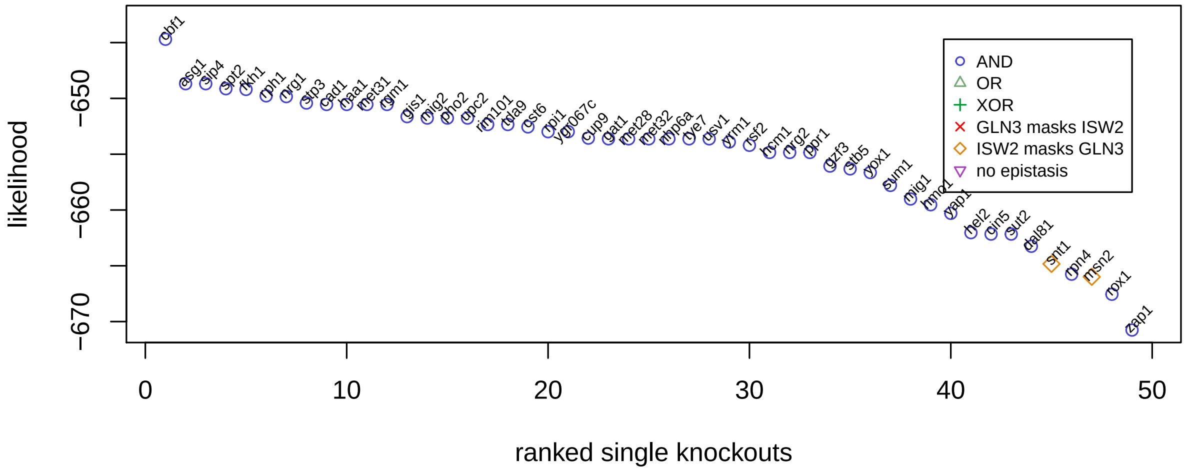


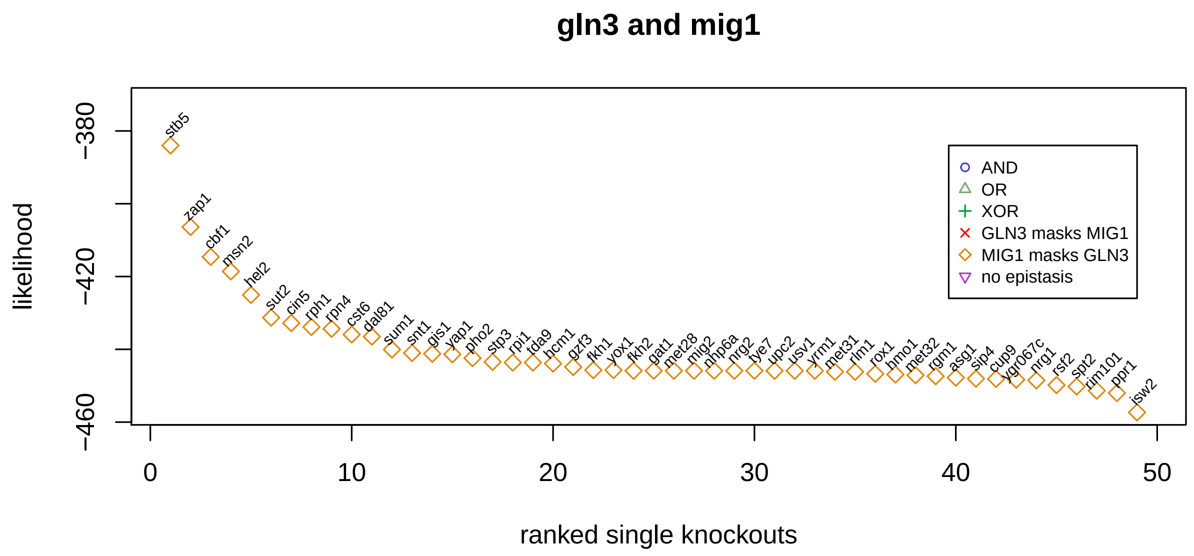
gis1 and rph1



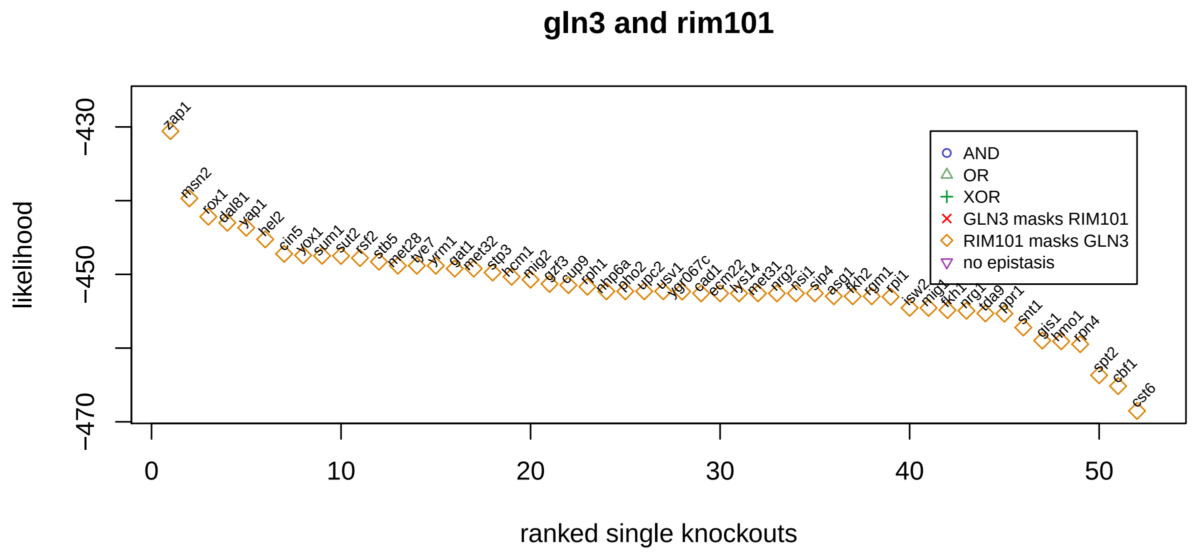
gln3 and gzf3


gln3 and haa1

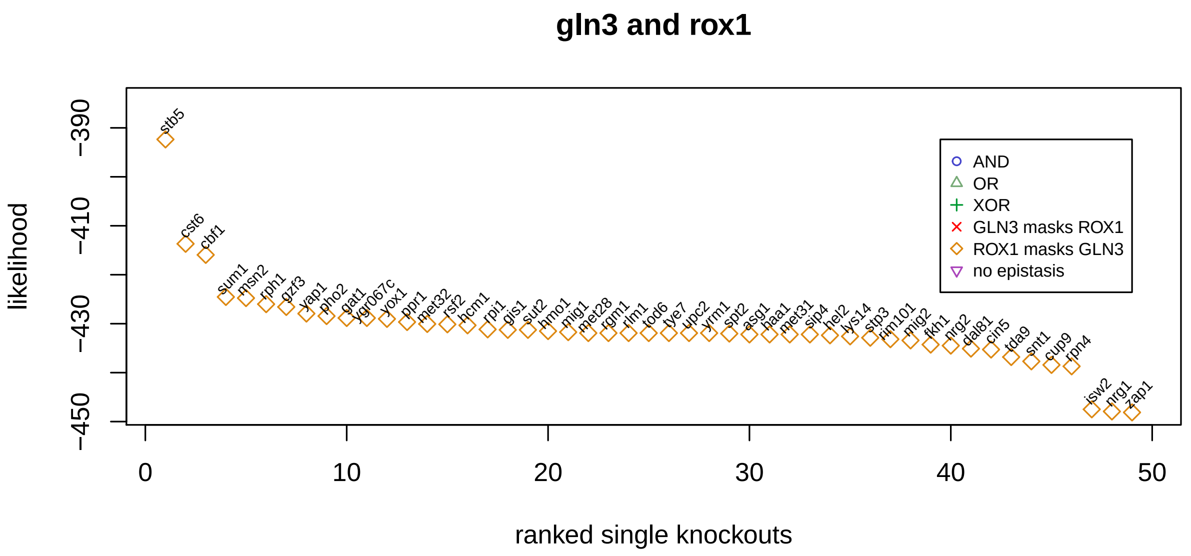

gln3 and isw2

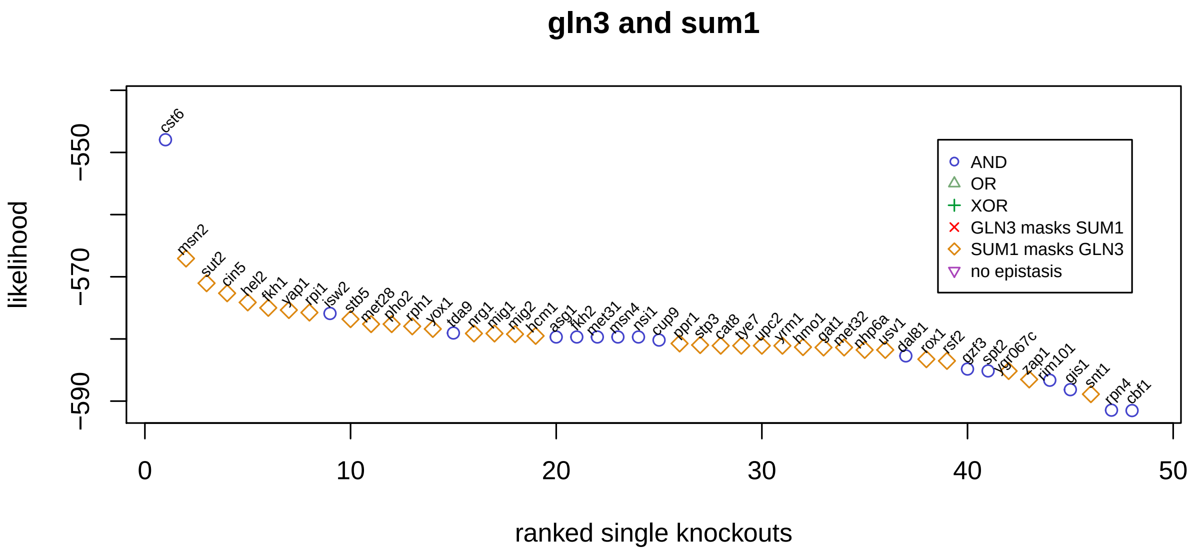


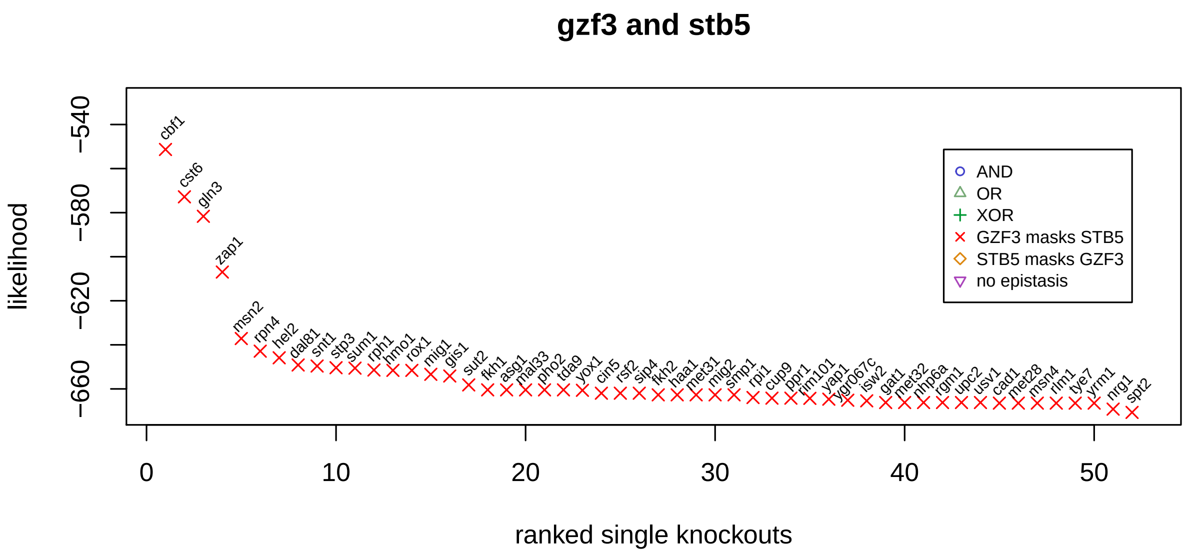
gln3 and mig1

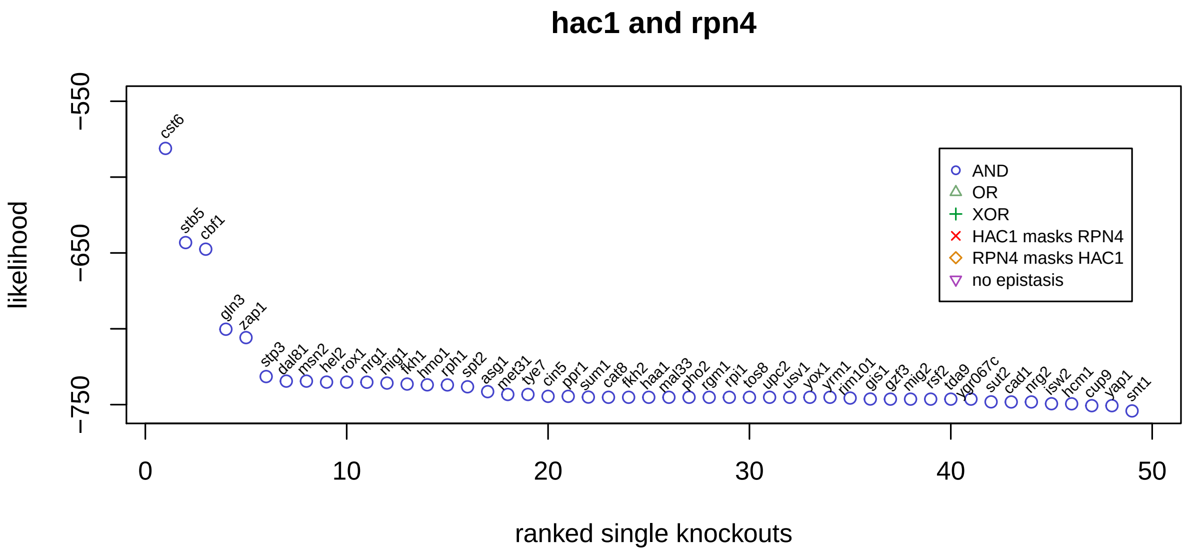


gln3 and rim101

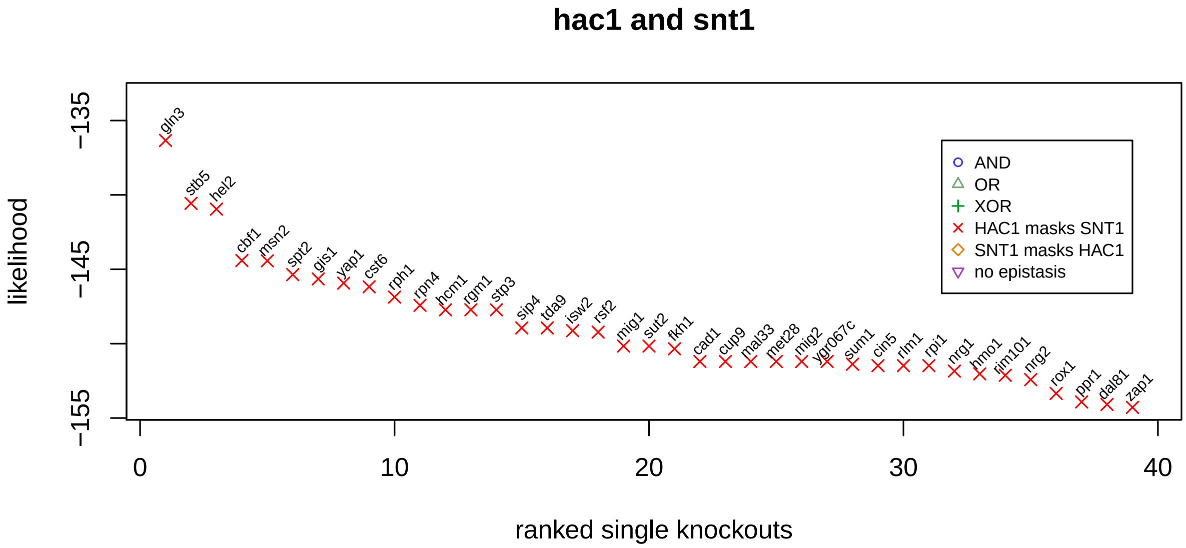

gln3 and rox1
likelihood
−390
−410
−430
−450
0
10
20
30
40
50
ranked single knockouts
○ AND
△ OR
+ XOR
× GLN3 masks ROX1
◇ ROX1 masks GLN3
▽ no epistasis
stb5
cst6
cbf1
sum1
msn2
rph1
gzf3
yap1
pho2
gat1
ygr067c
yox1
ppr1
met32
rsf2
hcm1
rpi1
gis1
sut2
hmo1
mig1
met28
rgm1
rlm1
tod6
tye7
upc2
yrm1
spt2
asg1
haa1
met31
sip4
hel2
lys14
stp3
rim101
mig2
fkh1
nrg2
dal81
cin5
tda9
snt1
cup9
rpn4
isw2
nrg1
zap1


gln3 and sum1
likelihood
−550
−570
−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
hel2
fkh1
yap1
rpi1
isw2
stb5
met28
pho2
rph1
yox1
tda9
nrg1
mig1
mig2
hcm1
asg1
fkh2
met31
msn4
nsi1
cup9
ppr1
stp3
cat8
tye7
upc2
yrm1
hmo1
gat1
met32
nhp6a
usv1
dal81
rox1
rsf2
gzf3
spt2
ygr067c
zap1
rim101
gis1
snt1
rpn4
cbf1

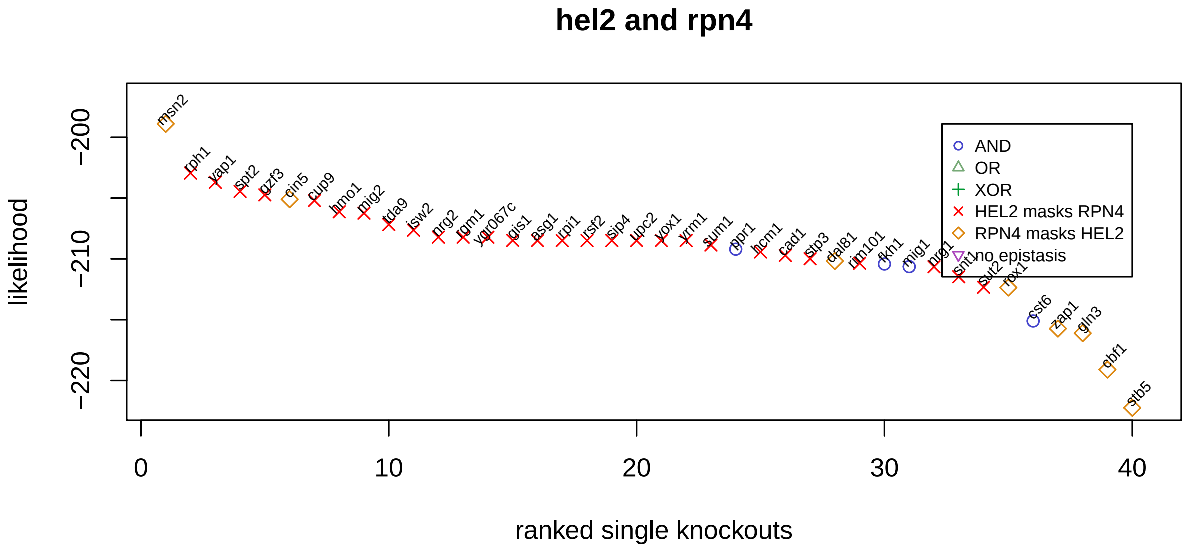

gzf3 and stb5
likelihood
−540
−580
−620
−660
ranked single knockouts
0
10
20
30
40
50
○ AND
△ OR
+ XOR
× GZF3 masks STB5
◇ STB5 masks GZF3
▽ no epistasis
cbf1
cst6
gln3
zap1
msn2
rpn4
hel2
dal81
snt1
stp3
sum1
rph1
hmo1
rox1
mig1
gis1
sut2
fkh1
asg1
mal33
pho2
tda9
yox1
cin5
rsf2
sip4
fkh2
haa1
met31
mig2
smp1
rpi1
cup9
ppr1
rim101
yap1
ygr067c
isw2
gat1
met32
nhp6a
rgm1
upc2
usv1
cad1
met28
msn4
rlm1
tye7
yrm1
nrg1
spt2

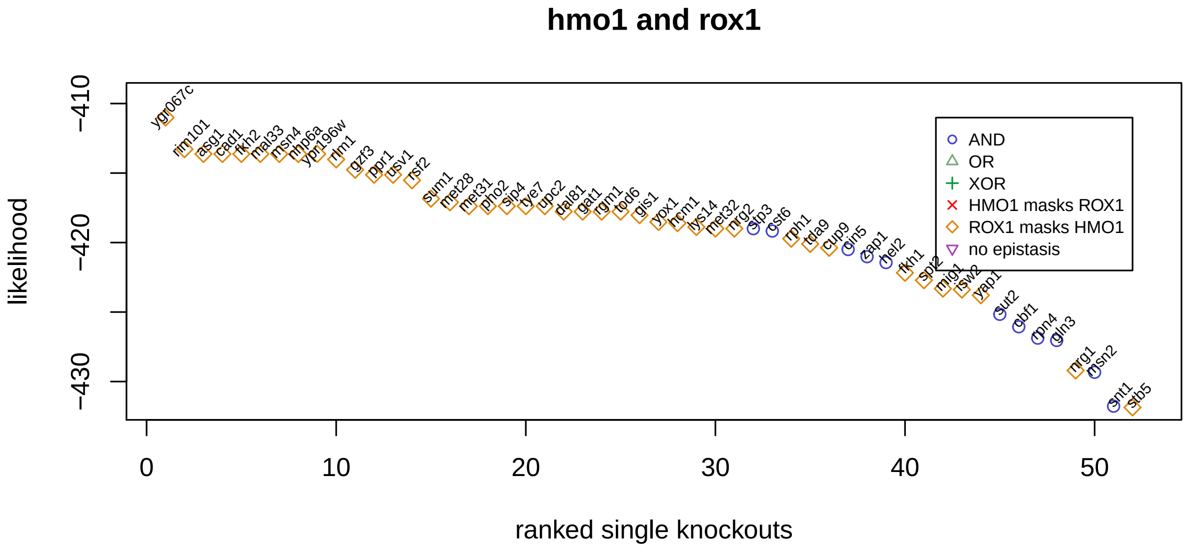

hac1 and rpn4
likelihood
−550
−650
−750
ranked single knockouts
0
10
20
30
40
50
○ AND
△ OR
+ XOR
× HAC1 masks RPN4
◇ RPN4 masks HAC1
▽ no epistasis
cst6
stb5
cbf1
gln3
zap1
stp3
dal81
msn2
hel2
rox1
nrg1
mig1
fkh1
hmo1
rph1
spt2
asg1
met31
tye7
cin5
ppr1
sum1
cat8
fkh2
haa1
mal33
pho2
rgm1
rpi1
tos8
upc2
usv1
yox1
yrm1
rim101
gis1
gzf3
mig2
rsf2
tda9
ygr067c
sut2
cad1
nrg2
isw2
hcm1
cup9
yap1
snt1

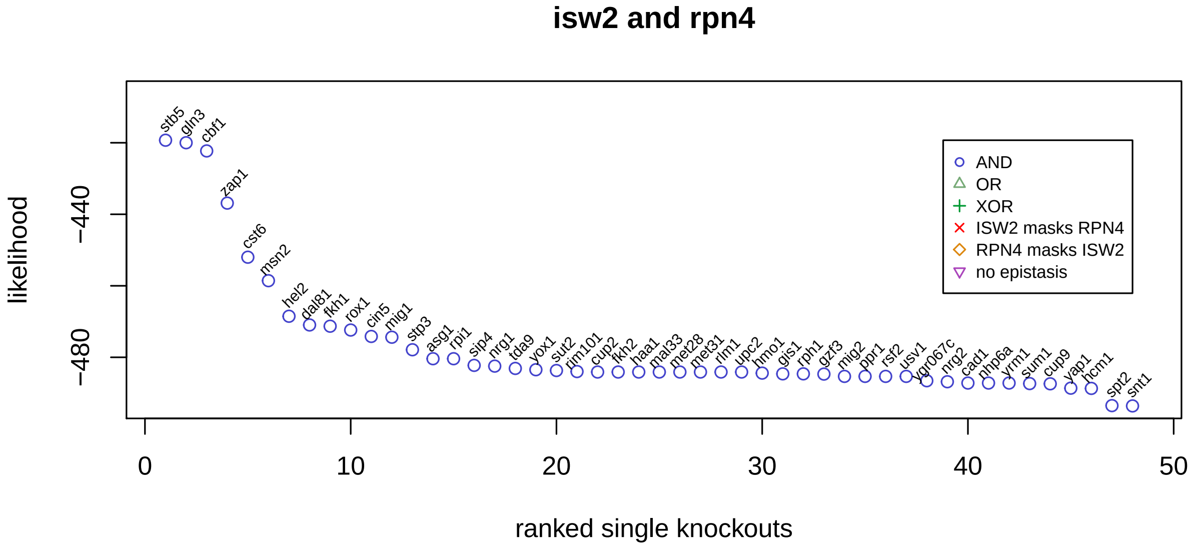
hac1 and snt1

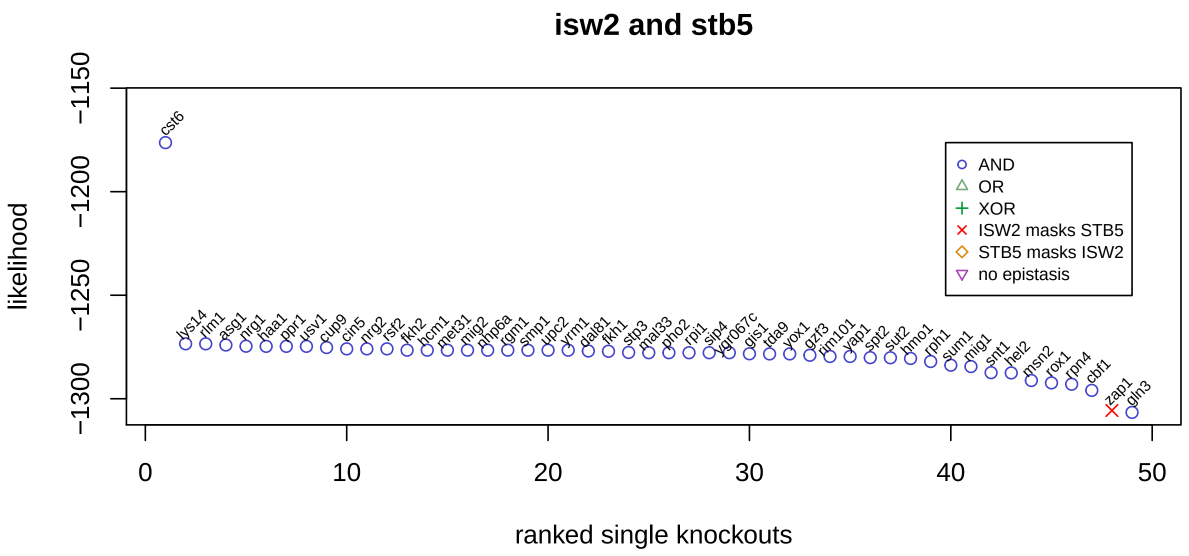


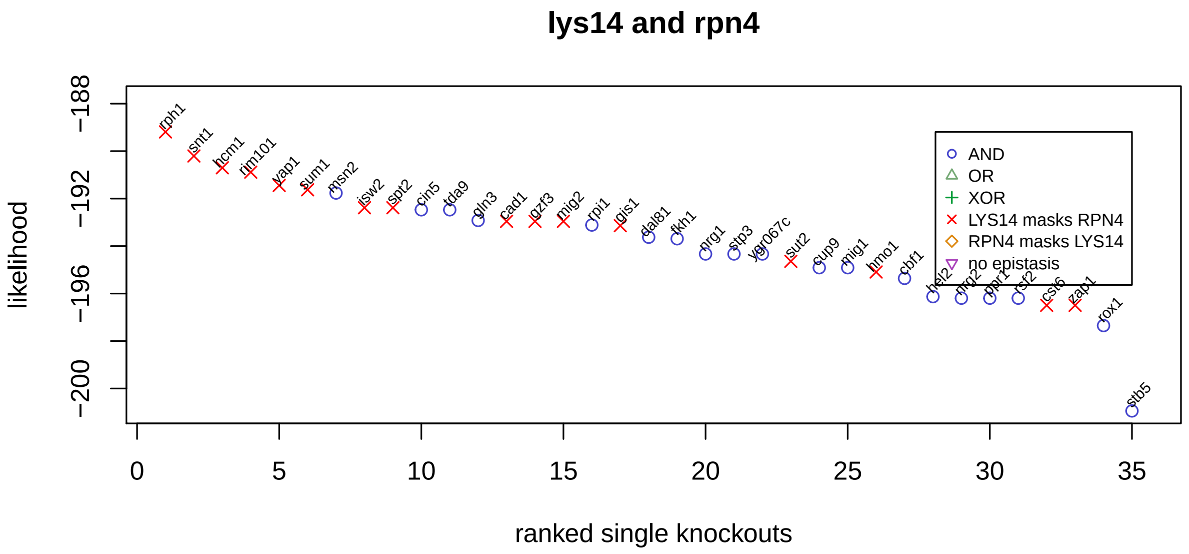
hel2 and rpn4

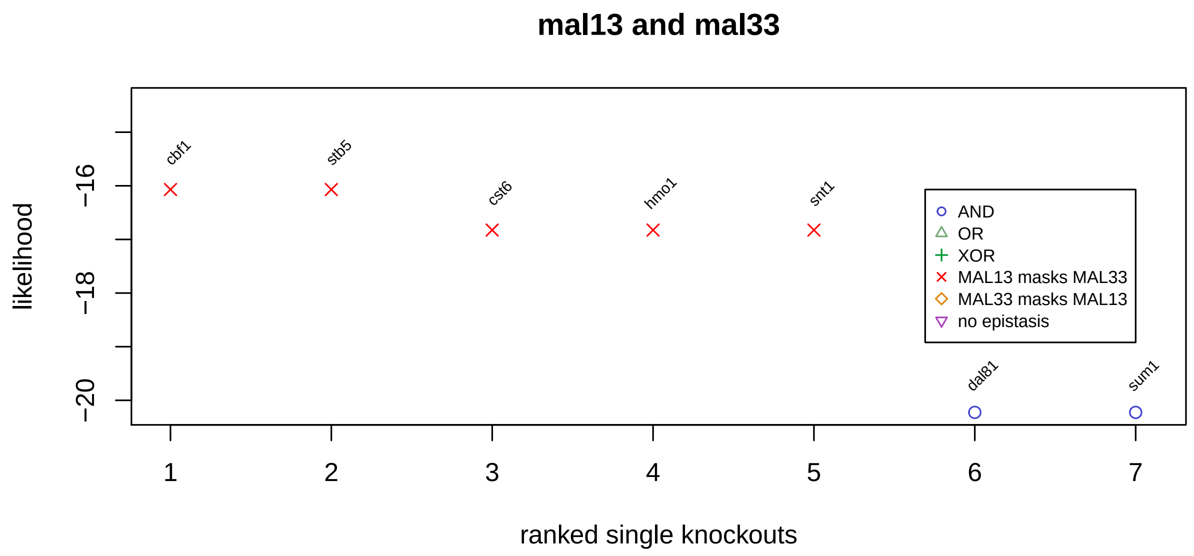



hmo1 and rox1
likelihood
−410
−420
−430
ranked single knockouts
0
10
20
30
40
50
AND
OR
XOR
HMO1 masks ROX1
ROX1 masks HMO1
no epistasis
ygr067c
rim101
asg1
cad1
fkh2
mal33
msn4
nhp6a
ypr196w
rlm1
gzf3
ppr1
usv1
rsf2
sum1
met28
met31
pho2
sip4
tye7
upc2
dal81
gat1
rgm1
tod6
gis1
yox1
hcm1
lys14
met32
nrg2
stp3
cst6
rph1
tda9
cup9
cin5
zap1
hel2
fkh1
spt2
mig1
isw2
yap1
sut2
cbf1
rpn4
gln3
nrg1
msn2
snt1
stb5

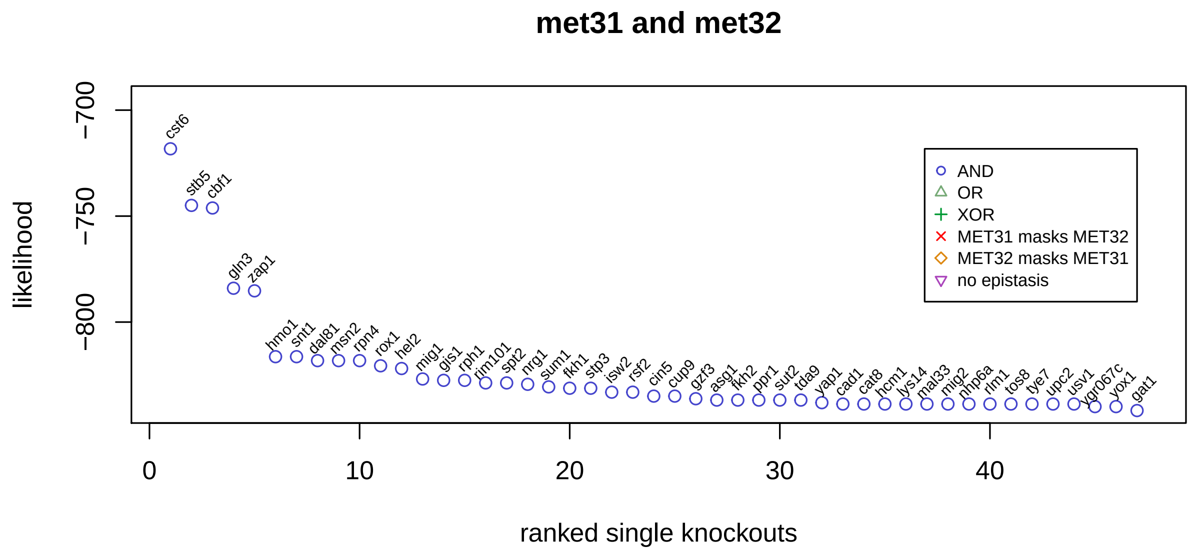

isw2 and rpn4
likelihood
−440
−480
ranked single knockouts
0
10
20
30
40
50
AND
OR
XOR
ISW2 masks RPN4
RPN4 masks ISW2
no epistasis
stb5
gln3
cbf1
zap1
cst6
msn2
hel2
dal81
fkh1
rox1
cin5
mig1
stp3
asg1
rpi1
sip4
nrg1
tda9
yox1
sut2
rim101
cup2
fkh2
haa1
mal33
met28
met31
rlm1
upc2
hmo1
gis1
rph1
gzf3
mig2
ppr1
rsf2
usv1
ygr067c
nrg2
cad1
nhp6a
yrm1
sum1
cup9
yap1
hcm1
spt2
snt1


isw2 and stb5
likelihood
−1150
−1200
−1250
−1300
ranked single knockouts
0
10
20
30
40
50
○ AND
△ OR
+ XOR
× ISW2 masks STB5
◇ STB5 masks ISW2
▽ no epistasis
cst6
lys14
rlm1
asg1
nrg1
haa1
ppr1
usv1
cup9
cin5
nrg2
rsf2
fkh2
hcm1
met31
mig2
nhp6a
rgm1
smp1
upc2
yrm1
dal81
fkh1
stp3
mal33
pho2
rpi1
sip4
ygr067c
gis1
tda9
yox1
gzf3
rim101
yap1
spt2
sut2
hmo1
rph1
sum1
mig1
snt1
hel2
msn2
rox1
rpn4
cbf1
zap1
gln3

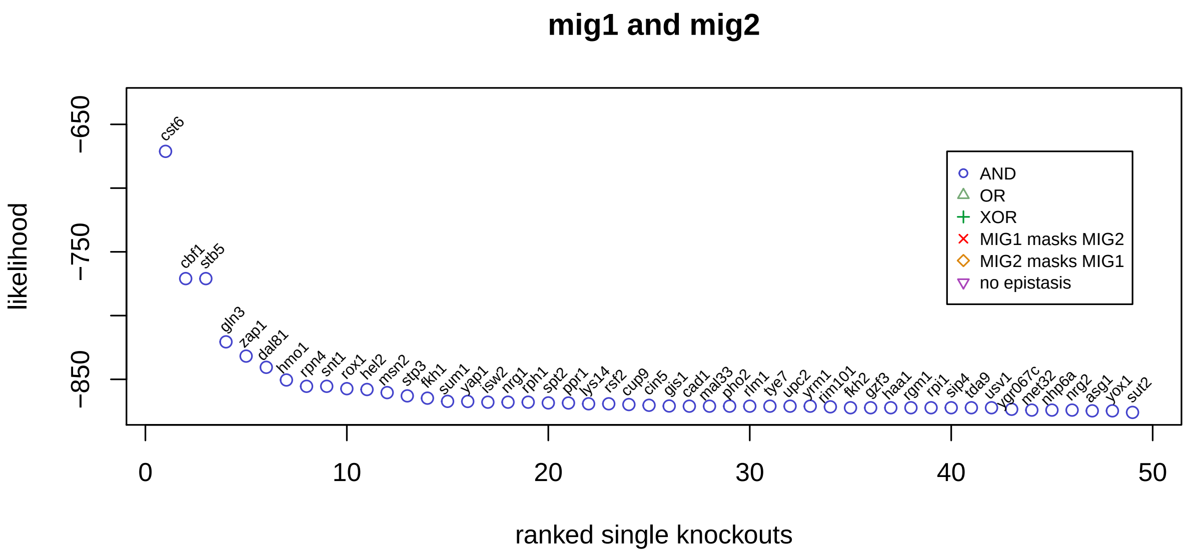

lys14 and rpn4
likelihood
−188
−192
−196
−200
ranked single knockouts
0
5
10
15
20
25
30
35
○ AND
△ OR
+ XOR
× LYS14 masks RPN4
◇ RPN4 masks LYS14
▽ no epistasis
rph1
snt1
hcm1
rim101
yap1
sum1
msn2
isw2
spt2
cin5
tda9
gln3
cad1
gzf3
mig2
rpi1
gis1
dal81
fkh1
nrg1
stp3
ygr067c
sut2
cup9
mig1
hmo1
cbf1
hel2
nrg2
ppr1
rsf2
cst6
zap1
rox1
stb5

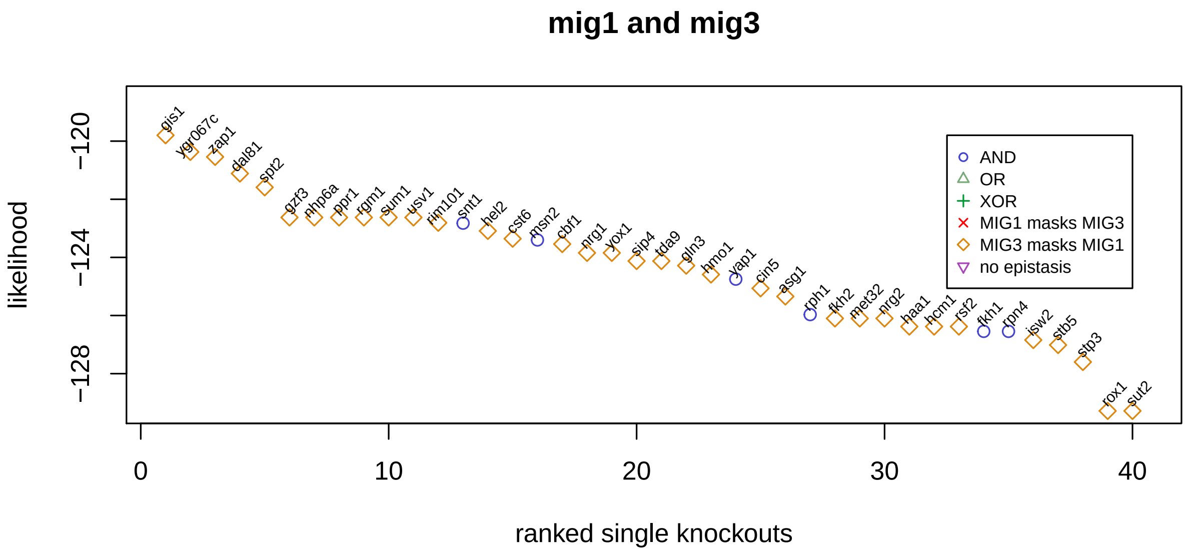


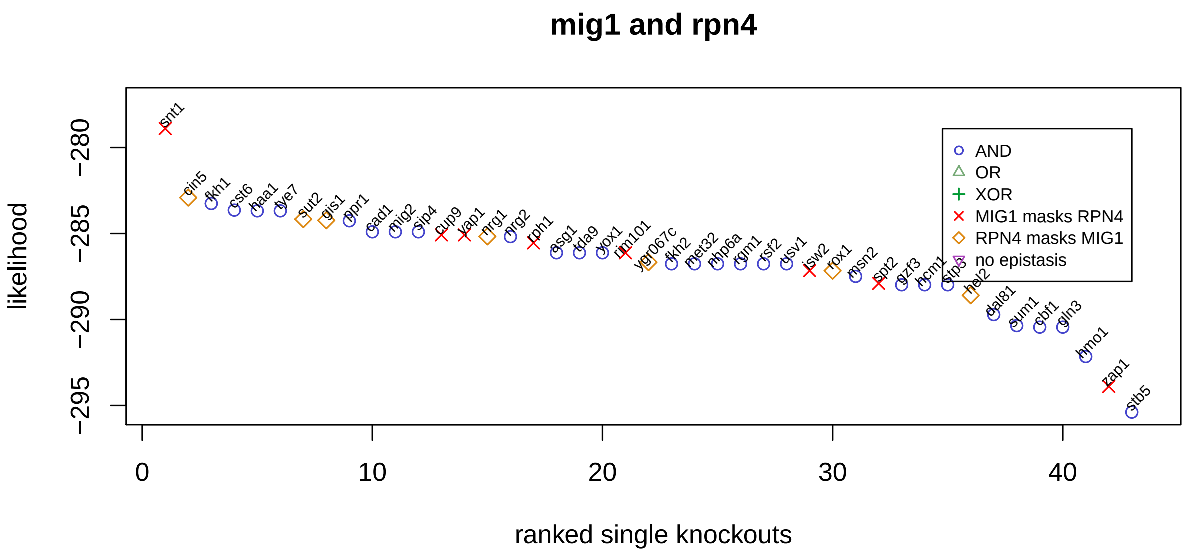
mal13 and mal33



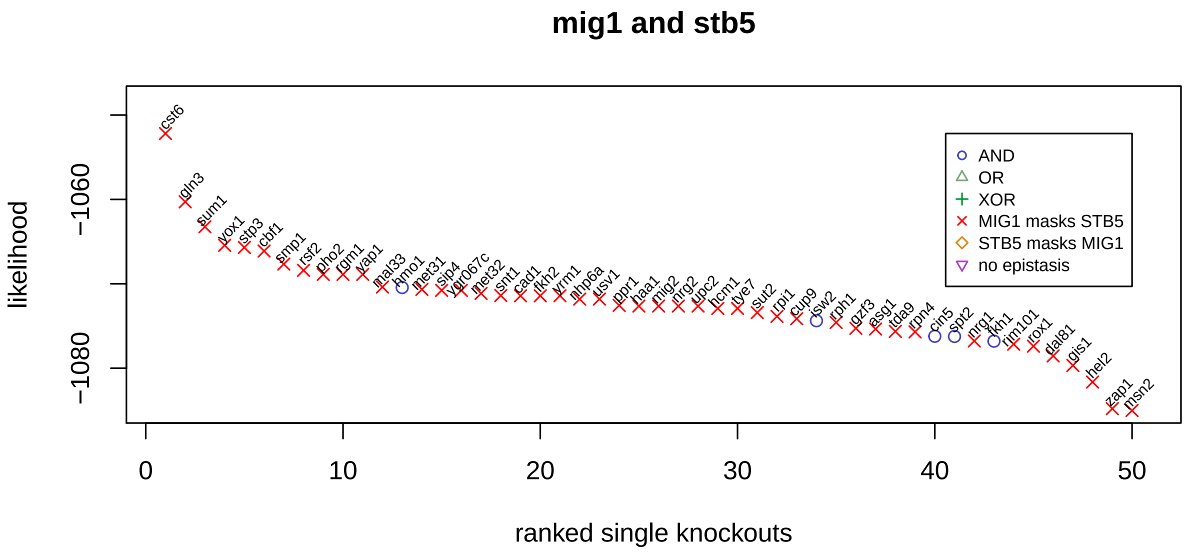
met31 and met32


mig1 and mig2
likelihood
−650
−750
−850
ranked single knockouts
0
10
20
30
40
50
○ AND
△ OR
+ XOR
× MIG1 masks MIG2
◇ MIG2 masks MIG1
▽ no epistasis
cst6
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
rlm1
tye7
upc2
yrm1
rim101
fkh2
gzf3
haa1
rgm1
rpi1
sip4
tda9
usv1
ygr067c
met32
nhp6a
nrg2
asg1
yox1
sut2

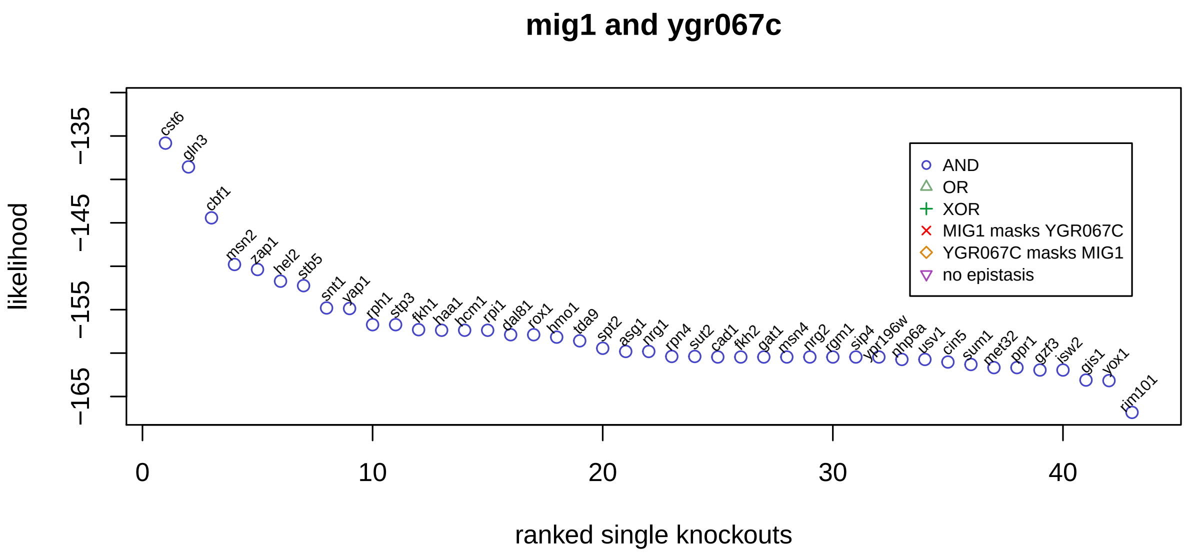

mig1 and mig3
likelihood
−120
−124
−128
ranked single knockouts
0
10
20
30
40
○ AND
△ OR
+ XOR
× MIG1 masks MIG3
◇ MIG3 masks MIG1
▽ no epistasis
gis1
ygr067c
zap1
dal81
spt2
gzf3
nhp6a
ppr1
rgm1
sum1
usv1
rim101
snt1
hel2
cst6
msn2
cbf1
nrg1
yox1
sip4
tda9
gln3
hmo1
yap1
cin5
asg1
rph1
fkh2
met32
nrg2
haa1
hcm1
rsf2
fkh1
rpn4
isw2
stb5
stp3
rox1
sut2



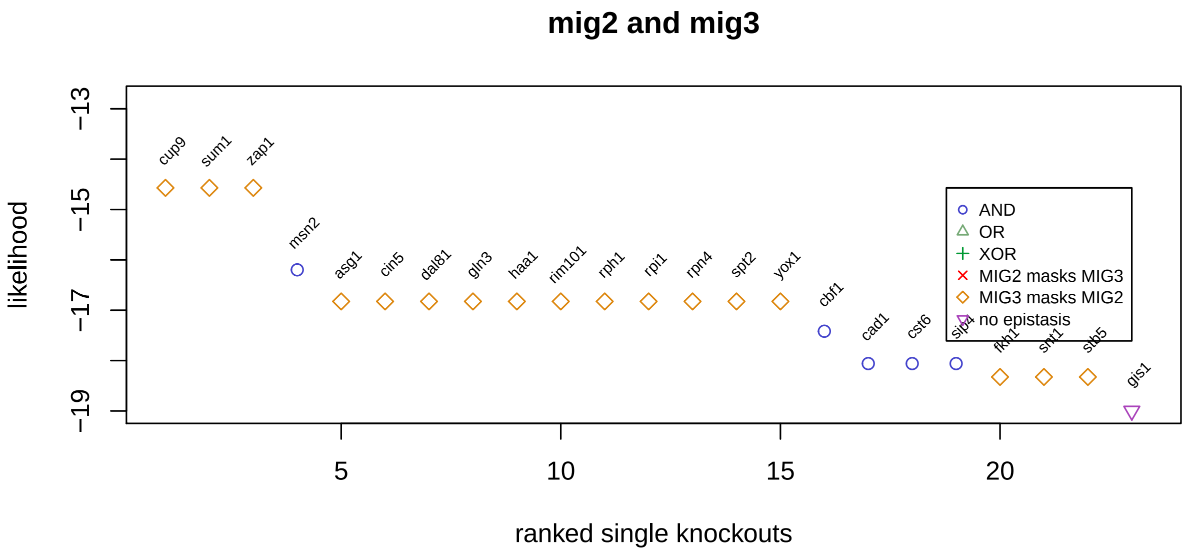
mig1 and rpn4



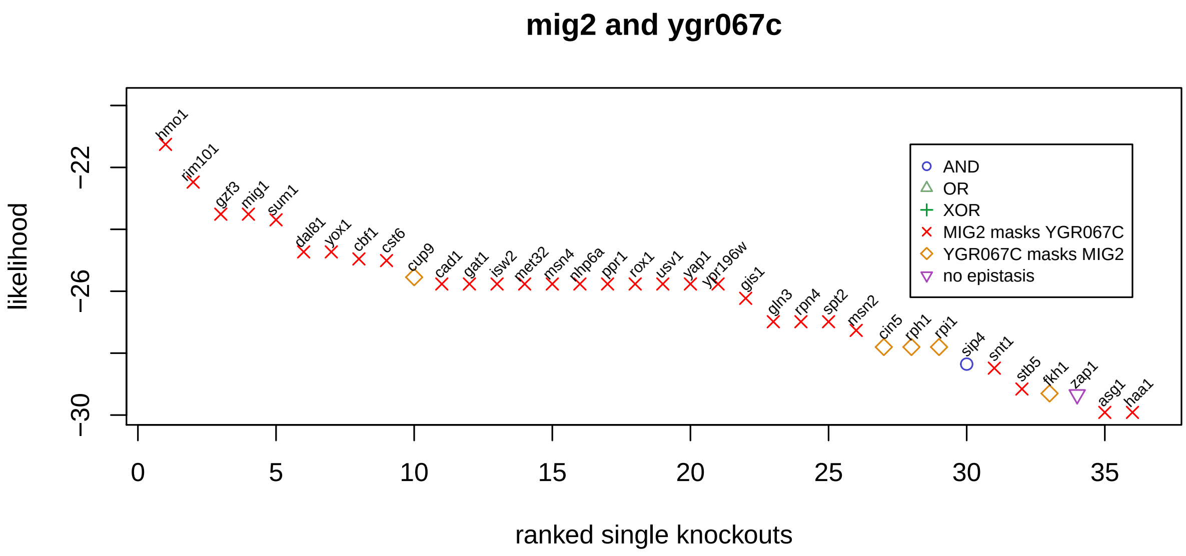
mig1 and stb5

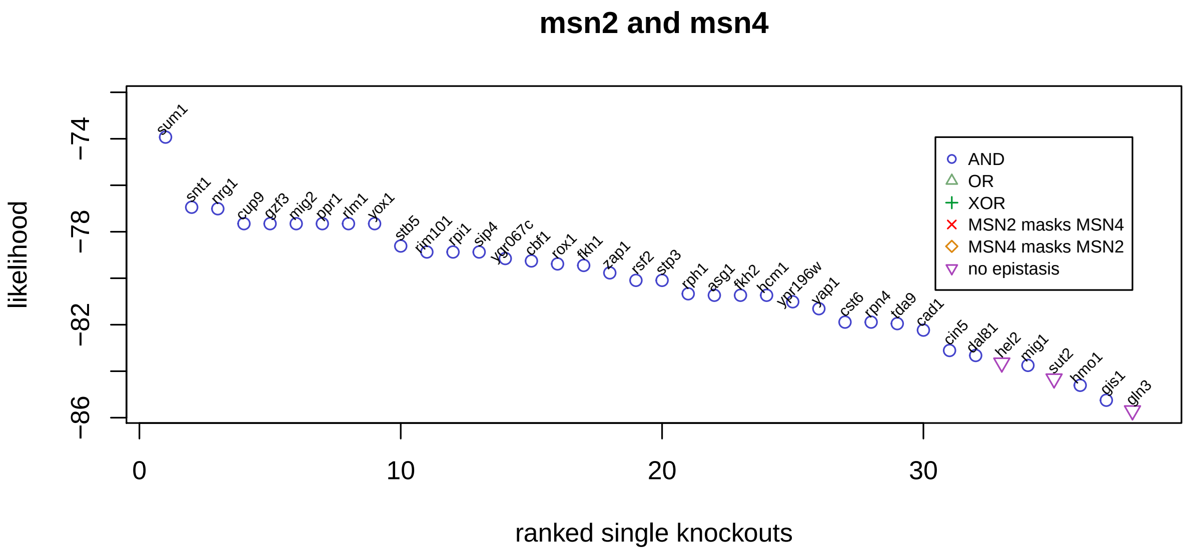


mig1 and ygr067c

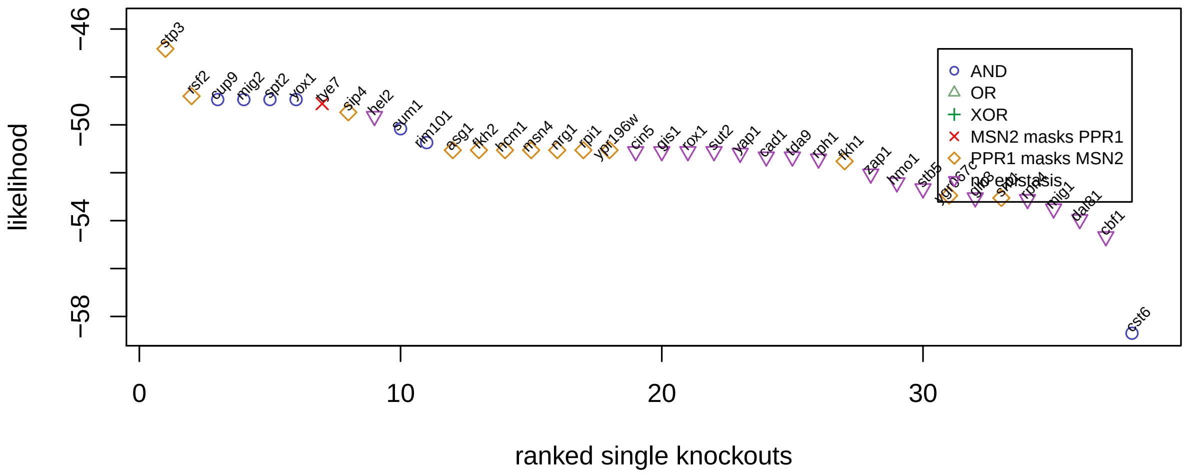


mig2 and mig3

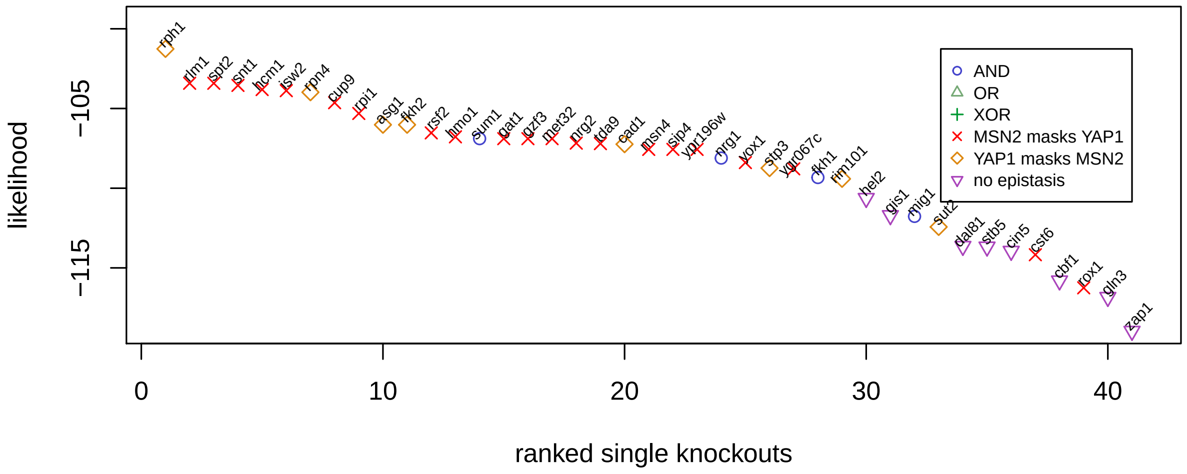

mig2 and ygr067c
likelihood
−22
−26
−30
0
5
10
15
20
25
30
35
ranked single knockouts
hmo1
rim101
gzf3
mig1
sum1
dal81
yox1
cbf1
cst6
cup9
cad1
gat1
isw2
met32
msn4
nhp6a
ppr1
rox1
usv1
yap1
ypr196w
gis1
gln3
rpn4
spt2
msn2
cin5
rph1
rpi1
sip4
snt1
stb5
fkh1
zap1
asg1
haa1
○ AND
△ OR
+ XOR
× MIG2 masks YGR067C
◇ YGR067C masks MIG2
▽ no epistasis

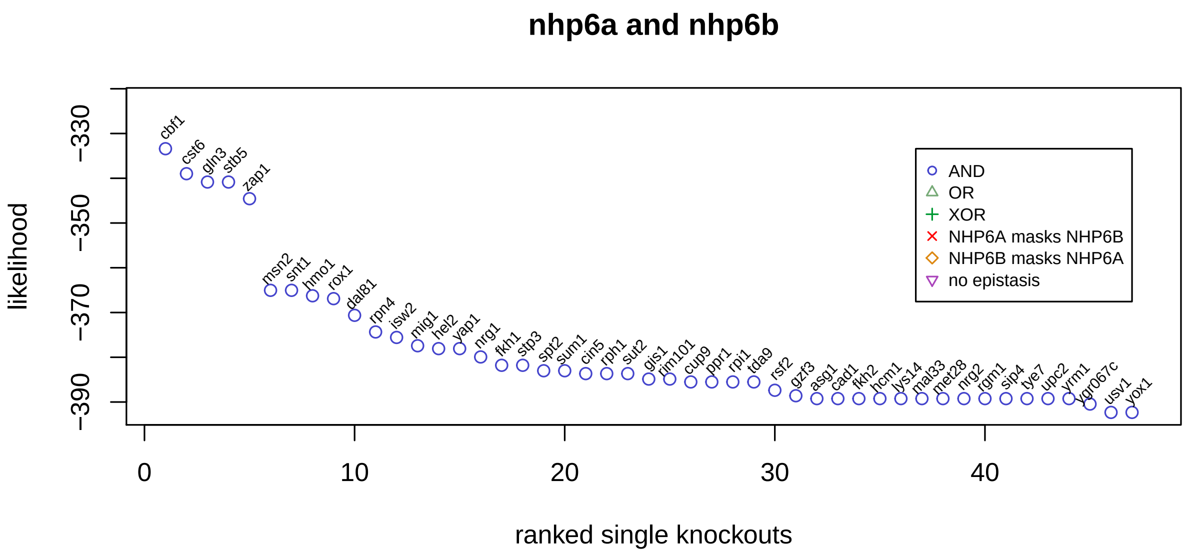

msn2 and msn4
likelihood
−74
−78
−82
−86
0
10
20
30
ranked single knockouts
sum1
snt1
nrg1
cup9
gzf3
mig2
ppr1
rlm1
yox1
stb5
rim101
rpi1
sip4
ygr067c
cbf1
rox1
fkh1
zap1
rsf2
stp3
rph1
asg1
fkh2
hcm1
ypr196w
yap1
cst6
rpn4
tda9
cad1
cin5
dal81
hel2
mig1
sut2
hmo1
gis1
gln3
○ AND
△ OR
+ XOR
× MSN2 masks MSN4
◇ MSN4 masks MSN2
▽ no epistasis

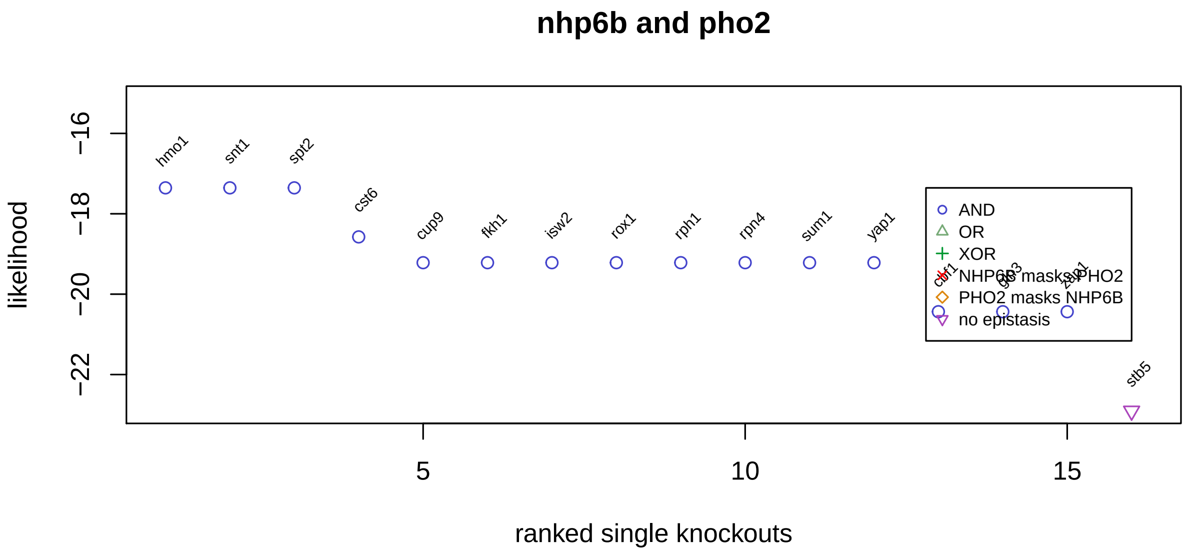
msn2 and ppr1

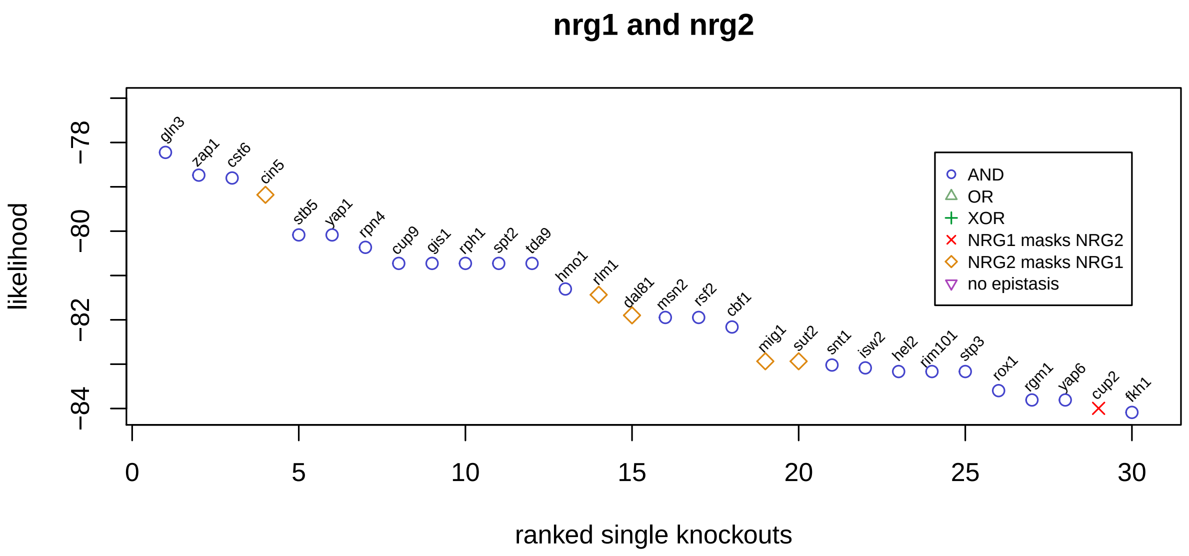


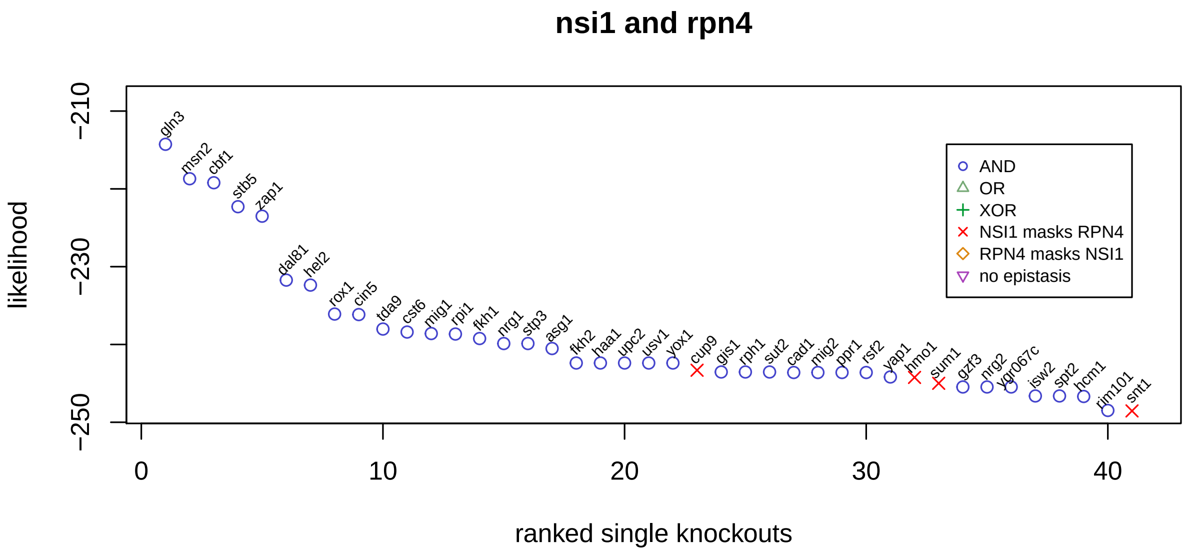
msn2 and yap1

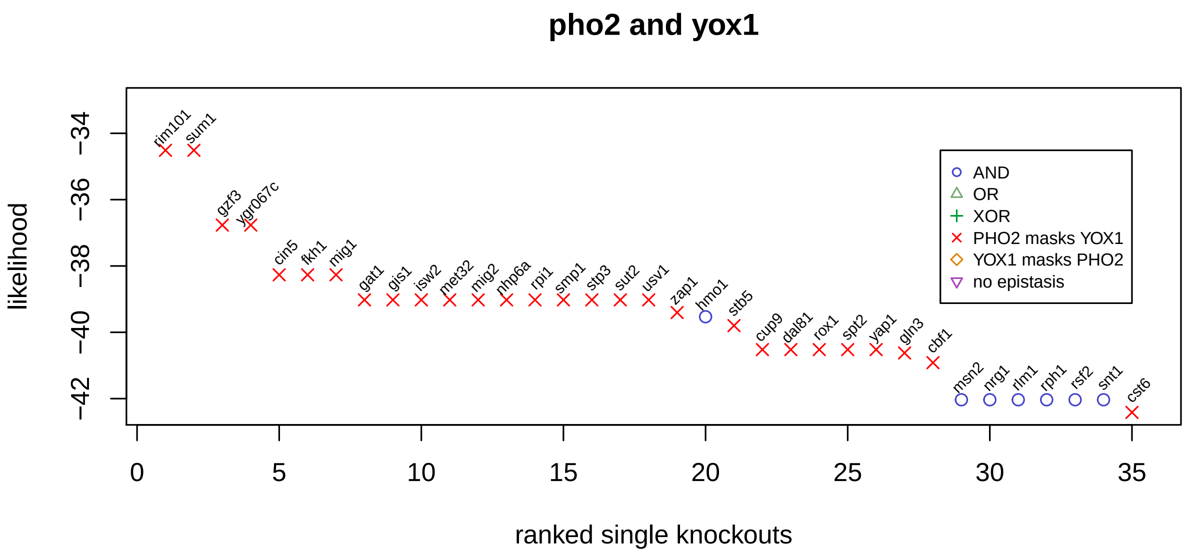


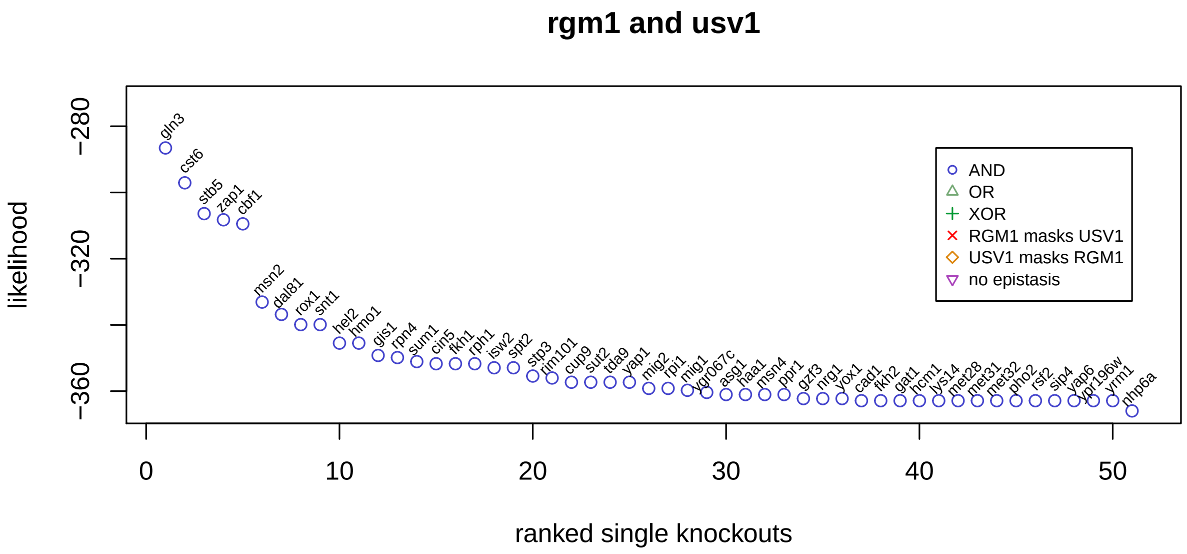

nhp6a and nhp6b
likelihood
−330
−350
−370
−390
ranked single knockouts
0
10
20
30
40
cbf1
cst6
gln3
stb5
zap1
msn2
snt1
hmo1
rox1
dal81
rpn4
isw2
mig1
hel2
yap1
nrg1
fkh1
stp3
spt2
sum1
cin5
rph1
sut2
gis1
rim101
cup9
ppr1
rpi1
tda9
rsf2
gzf3
asg1
cad1
fkh2
hcm1
lys14
mal33
met28
nrg2
rgm1
sip4
tye7
upc2
yrm1
ygr067c
usv1
yox1
AND
OR
XOR
NHP6A masks NHP6B
NHP6B masks NHP6A
no epistasis

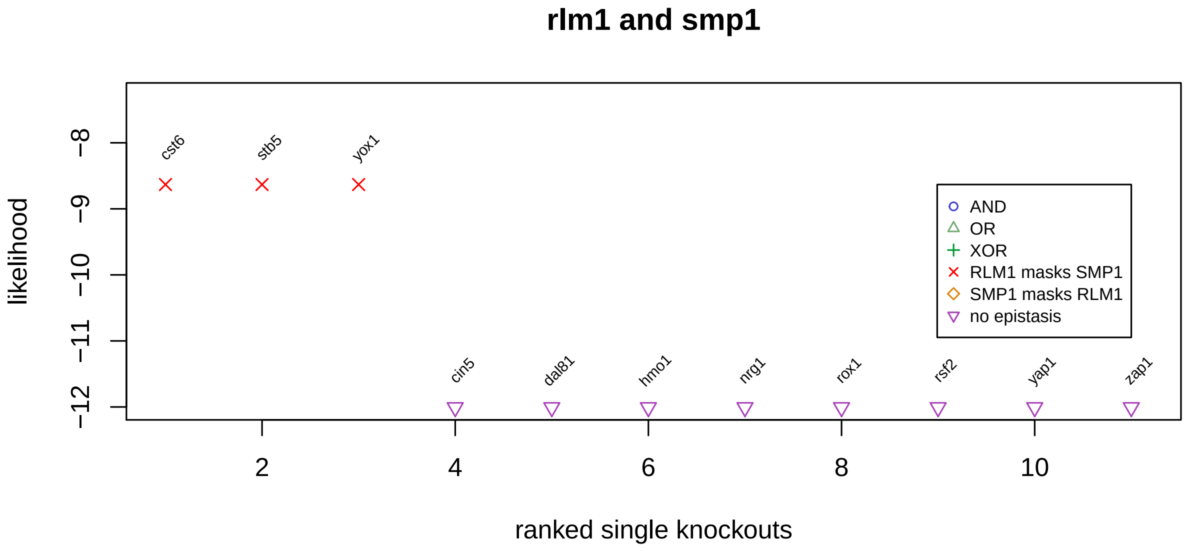

nhp6b and pho2
likelihood
−16
−18
−20
−22
ranked single knockouts
5
10
15
hmo1
snt1
spt2
cst6
cup9
fkh1
isw2
rox1
rph1
rpn4
sum1
yap1
cbf1
gln3
zap1
stb5
AND
OR
XOR
NHP6B masks PHO2
PHO2 masks NHP6B
no epistasis

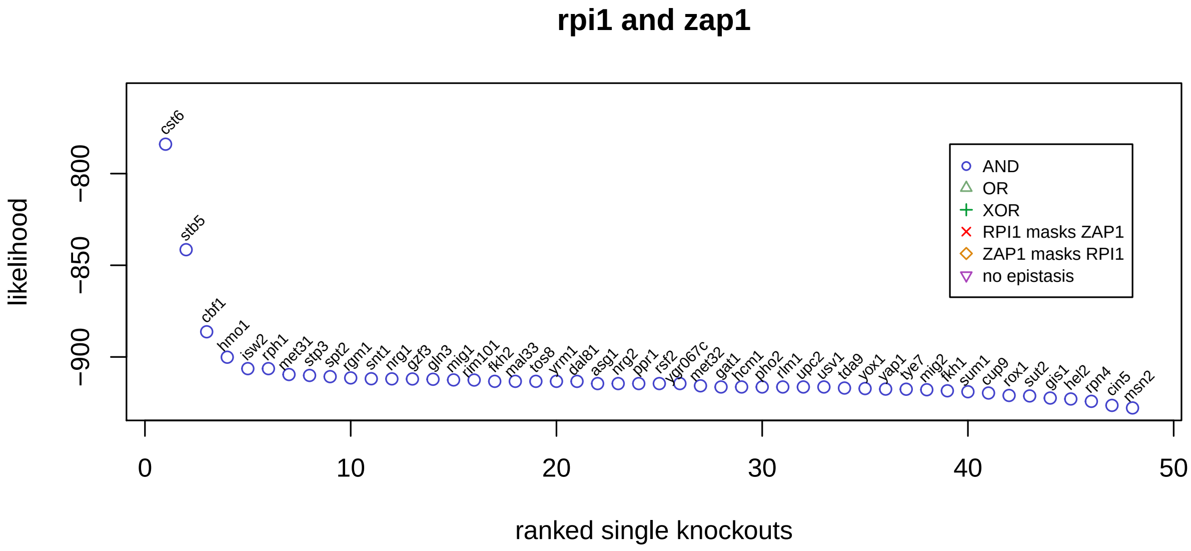

nrg1 and nrg2
likelihood
−78
−80
−82
−84
0
5
10
15
20
25
30
ranked single knockouts
gln3
zap1
cst6
cin5
stb5
yap1
rpn4
cup9
gis1
rph1
spt2
tda9
hmo1
rlm1
dal81
msn2
rsf2
cbf1
mig1
sut2
snt1
isw2
hel2
rim101
stp3
rox1
rgm1
yap6
cup2
fkh1
○ AND
△ OR
+ XOR
× NRG1 masks NRG2
◇ NRG2 masks NRG1
▽ no epistasis

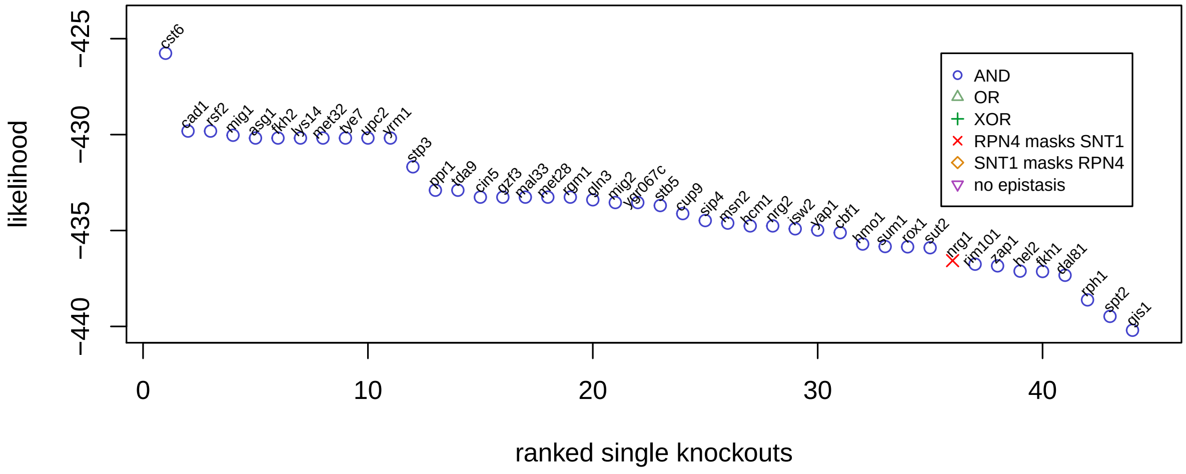

nsi1 and rpn4
likelihood
−210
−230
−250
0
10
20
30
40
ranked single knockouts
gln3
msn2
cbf1
stb5
zap1
dal81
hel2
rox1
cin5
tda9
cst6
mig1
rpi1
fkh1
nrg1
stp3
asg1
fkh2
haa1
upc2
usv1
yox1
cup9
gis1
rph1
sut2
cad1
mig2
ppr1
rsf2
yap1
hmo1
sum1
gzf3
nrg2
ygr067c
isw2
spt2
hcm1
rim101
snt1
○ AND
△ OR
+ XOR
× NSI1 masks RPN4
◇ RPN4 masks NSI1
▽ no epistasis


pho2 and yox1
likelihood
−34
−36
−38
−40
−42
ranked single knockouts
0
5
10
15
20
25
30
35
○ AND
△ OR
+ XOR
× PHO2 masks YOX1
◇ YOX1 masks PHO2
▽ no epistasis
rim101
sum1
gzf3
ygr067c
cin5
fkh1
mig1
gat1
gis1
isw2
met32
mig2
nhp6a
rpi1
smp1
stp3
sut2
usv1
zap1
hmo1
stb5
cup9
dal81
rox1
spt2
yap1
gln3
cbf1
msn2
nrg1
rlm1
rph1
rsf2
snt1
cst6

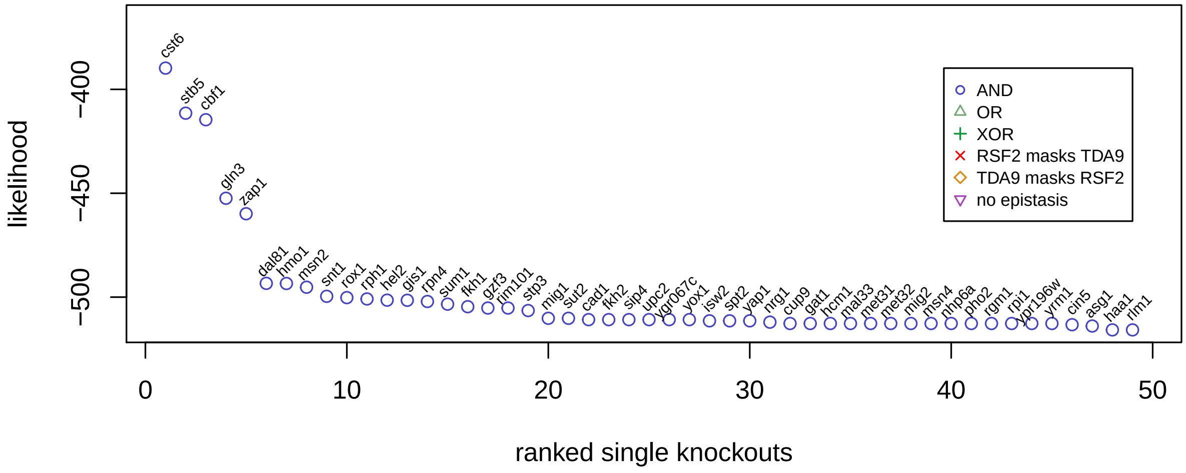

rgm1 and usv1
likelihood
−280
−320
−360
ranked single knockouts
0
10
20
30
40
50
○ AND
△ OR
+ XOR
× RGM1 masks USV1
◇ USV1 masks RGM1
▽ no epistasis
gln3
cst6
stb5
zap1
cbf1
msn2
dal81
rox1
snt1
hel2
hmo1
gis1
rpn4
sum1
cin5
fkh1
rph1
isw2
spt2
stp3
rim101
cup9
sut2
tda9
yap1
mig2
rpi1
mig1
ygr067c
asg1
haa1
msn4
ppr1
gzf3
nrg1
yox1
cad1
fkh2
gat1
hcm1
lys14
met28
met31
met32
pho2
rsf2
sip4
yap6
ypr196w
yrm1
nhp6a


rlm1 and smp1

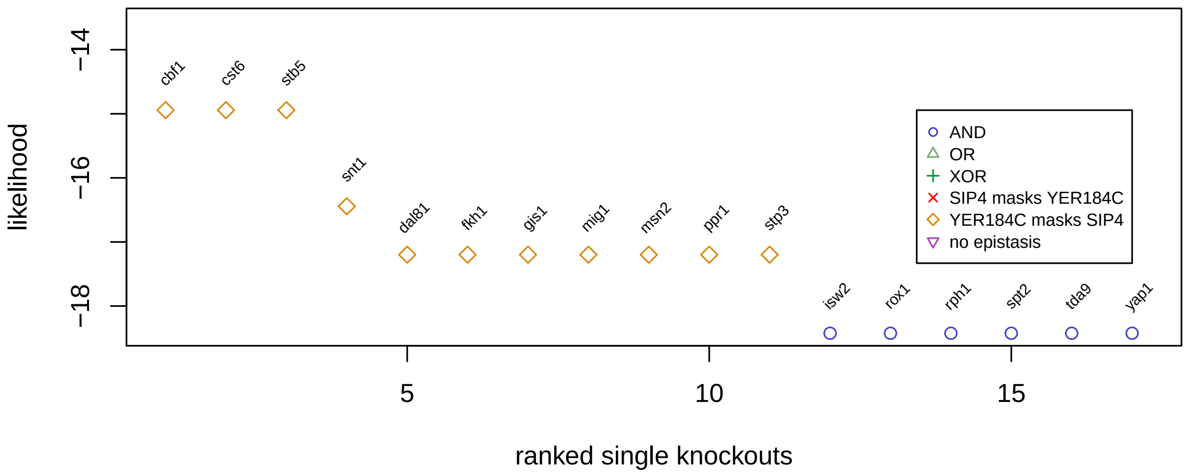

rpi1 and zap1



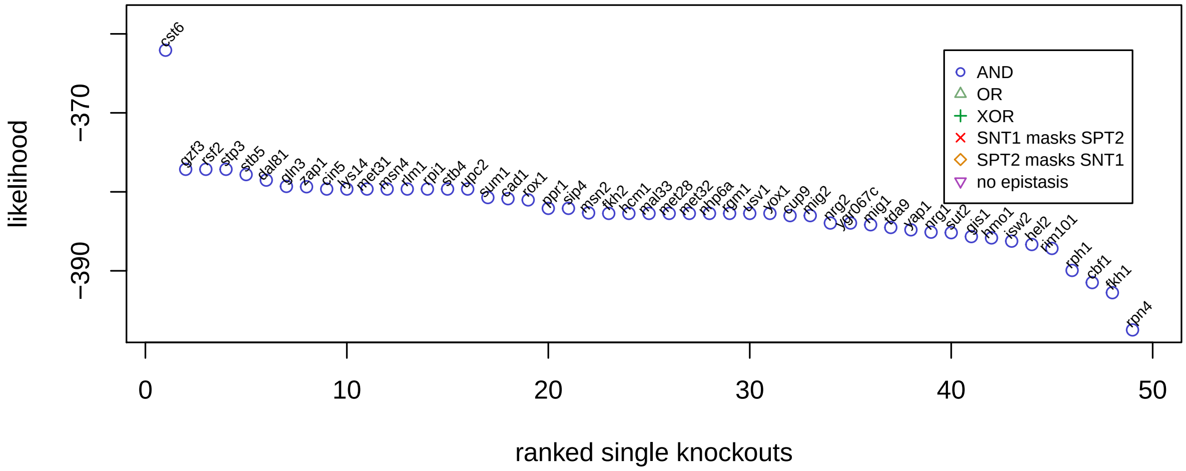
rpn4 and snt1



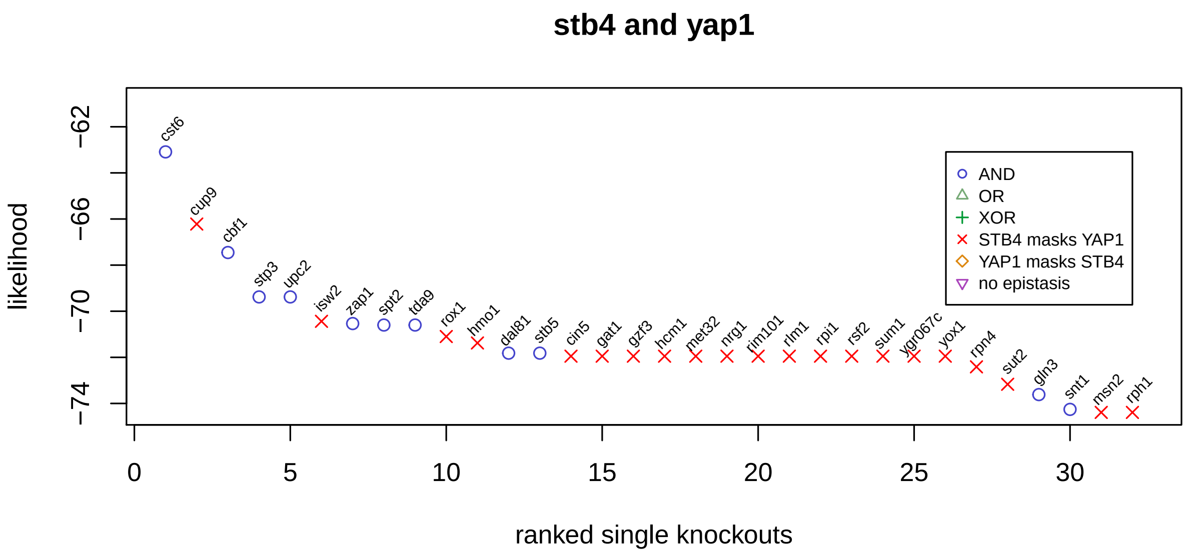
rsf2 and tda9

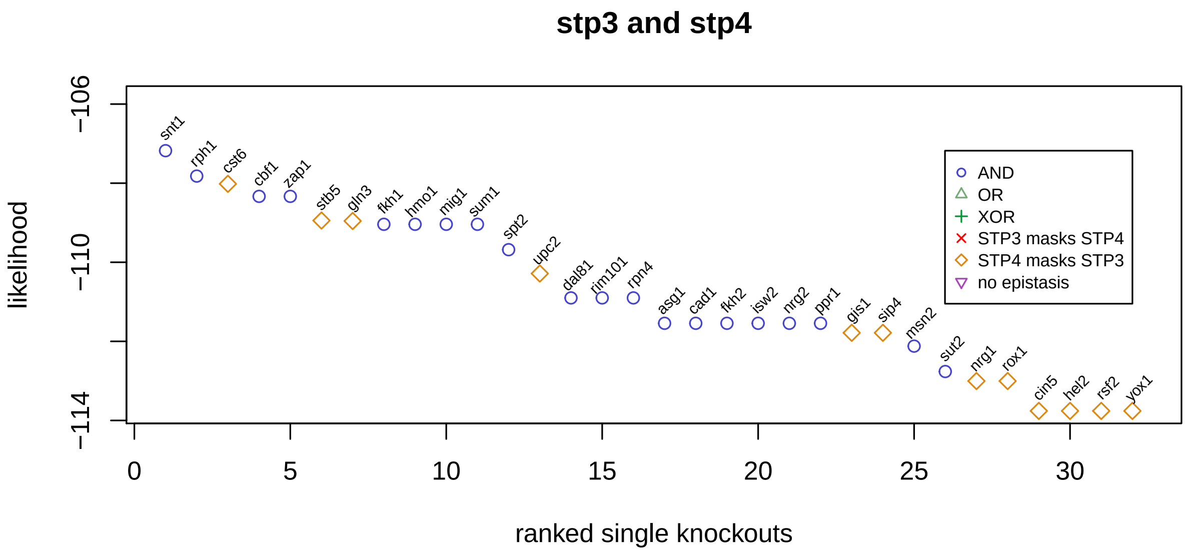


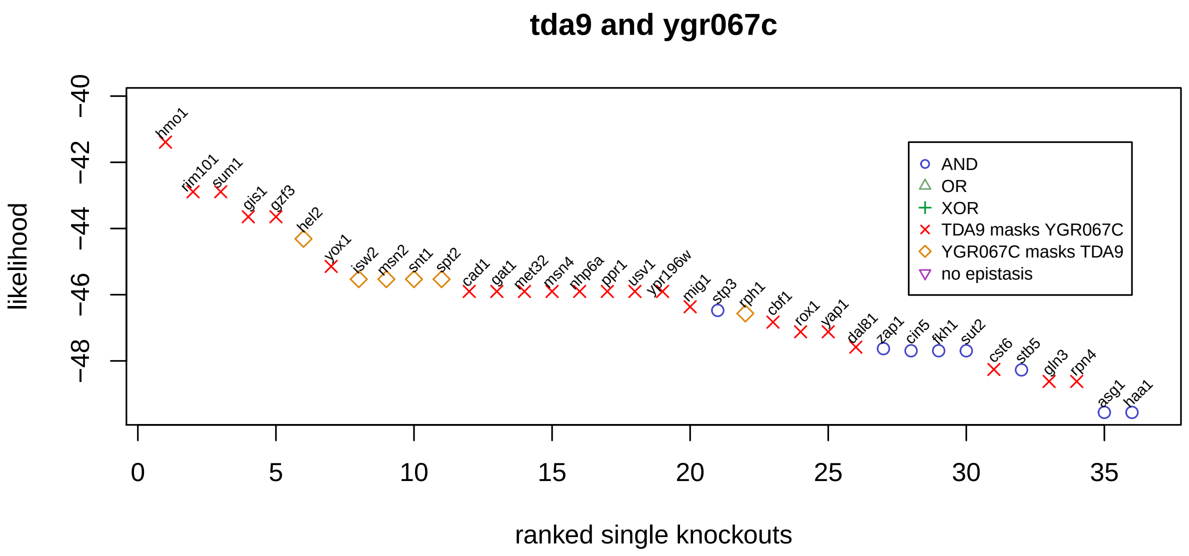
sip4 and yer184c

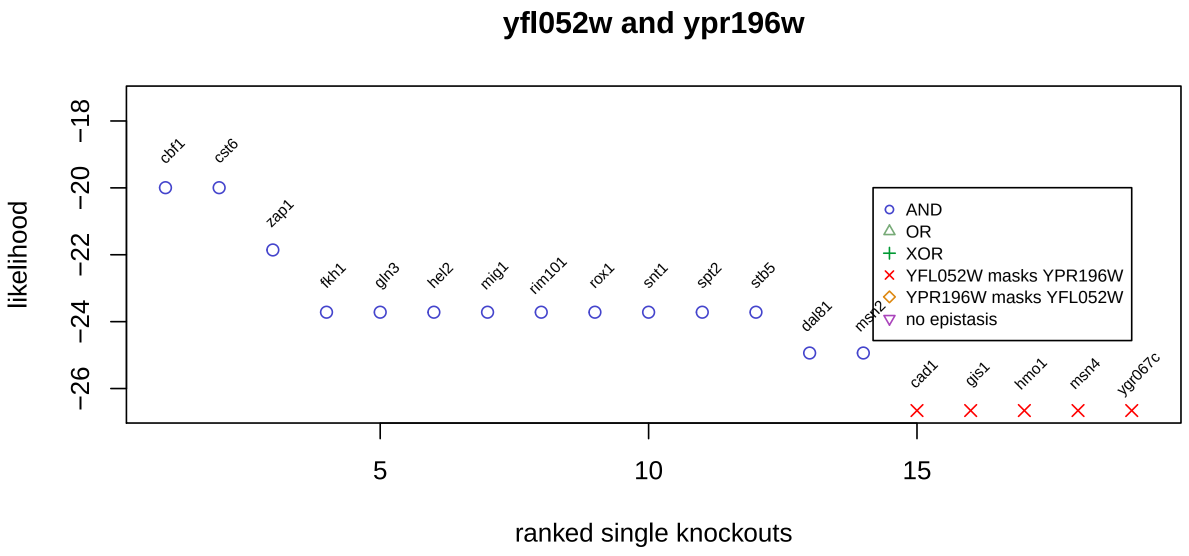


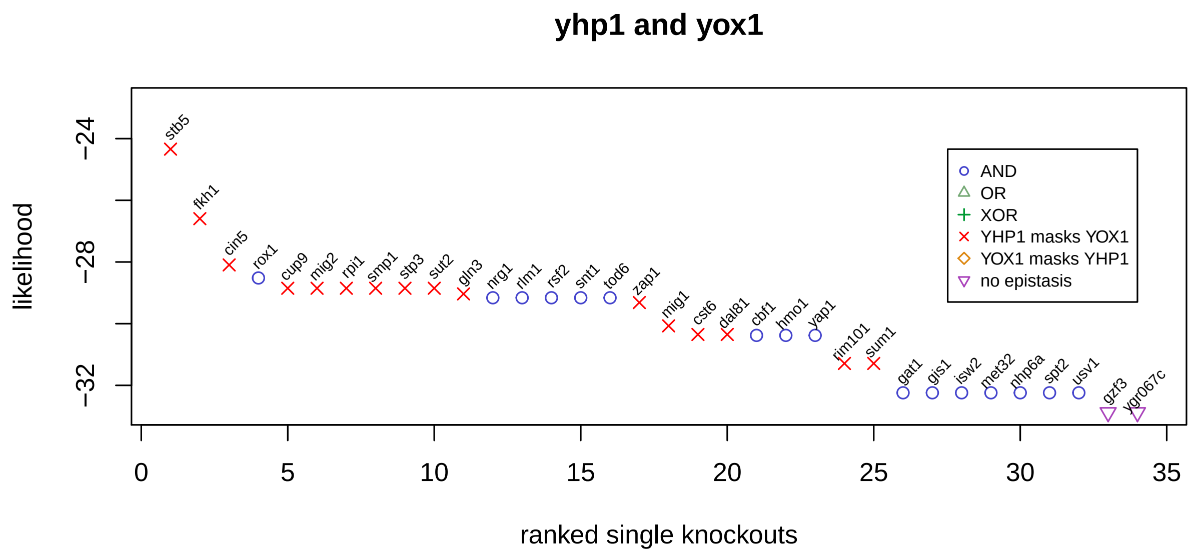
snt1 and spt2

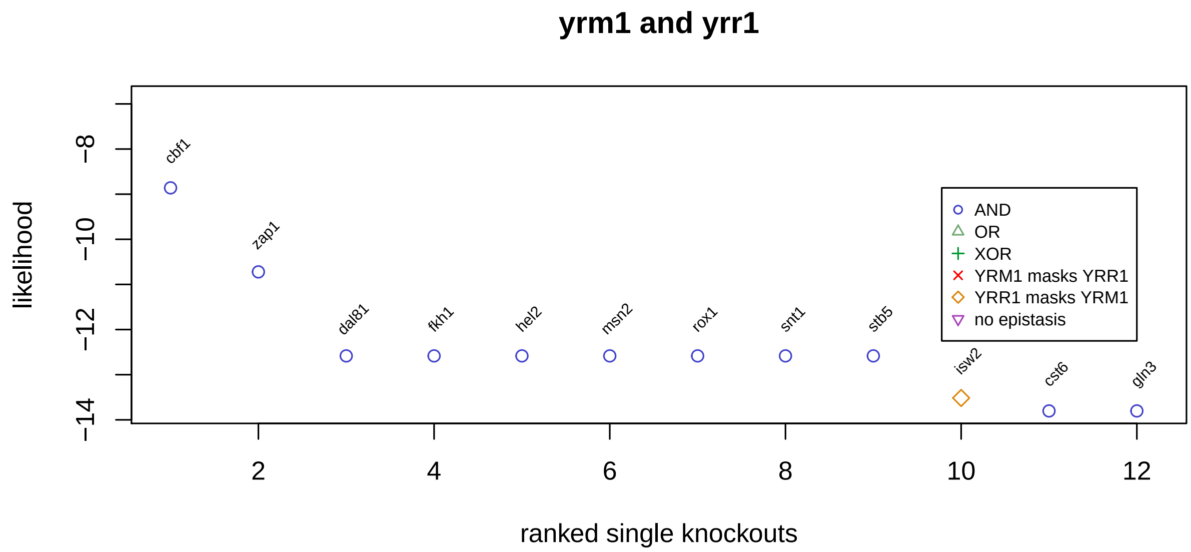

stb4 and yap1
likelihood
−62
−66
−70
−74
ranked single knockouts
0
5
10
15
20
25
30
○ AND
△ OR
+ XOR
× STB4 masks YAP1
◇ YAP1 masks STB4
▽ no epistasis
cst6
cup9
cbf1
stp3
upc2
isw2
zap1
spt2
tda9
rox1
hmo1
dal81
stb5
cin5
gat1
gzf3
hcm1
met32
nrg1
rim101
rlm1
rpi1
rsf2
sum1
ygr067c
yox1
rpn4
sut2
gln3
snt1
msn2
rph1


stp3 and stp4
likelihood
−106
−110
−114
ranked single knockouts
0
5
10
15
20
25
30
○ AND
△ OR
+ XOR
× STP3 masks STP4
◇ STP4 masks STP3
▽ no epistasis
snt1
rph1
cst6
cbf1
zap1
stb5
gln3
fkh1
hmo1
mig1
sum1
spt2
upc2
dal81
rim101
rpn4
asg1
cad1
fkh2
isw2
nrg2
ppr1
gis1
sip4
msn2
sut2
nrg1
rox1
cin5
hel2
rsf2
yox1

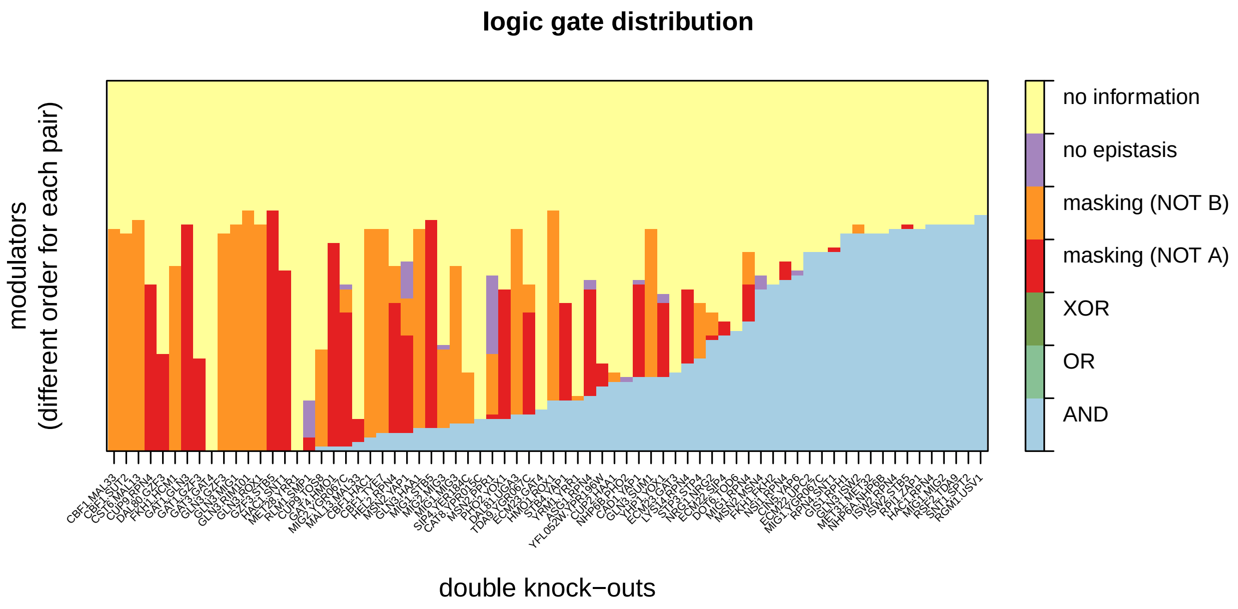

tda9 and ygr067c
likelihood
−40
−42
−44
−46
−48
0
5
10
15
20
25
30
35
ranked single knockouts
hmo1
rim101
sum1
gis1
gzf3
hel2
yox1
isw2
msn2
snt1
spt2
cad1
gat1
met32
msn4
nhp6a
ppr1
usv1
ypr196w
mig1
stp3
rph1
cbf1
rox1
yap1
dal81
zap1
cin5
fkh1
sut2
cst6
stb5
gln3
rpn4
asg1
haa1
AND
OR
XOR
TDA9 masks YGR067C
YGR067C masks TDA9
no epistasis


yfl052w and ypr196w
likelihood
−18
−20
−22
−24
−26
5
10
15
ranked single knockouts
cbf1
cst6
zap1
fkh1
gln3
hel2
mig1
rim101
rox1
snt1
spt2
stb5
dal81
msn2
cad1
gis1
hmo1
msn4
ygr067c
AND
OR
XOR
YFL052W masks YPR196W
YPR196W masks YFL052W
no epistasis


yhp1 and yox1


yrm1 and yrr1

```
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.

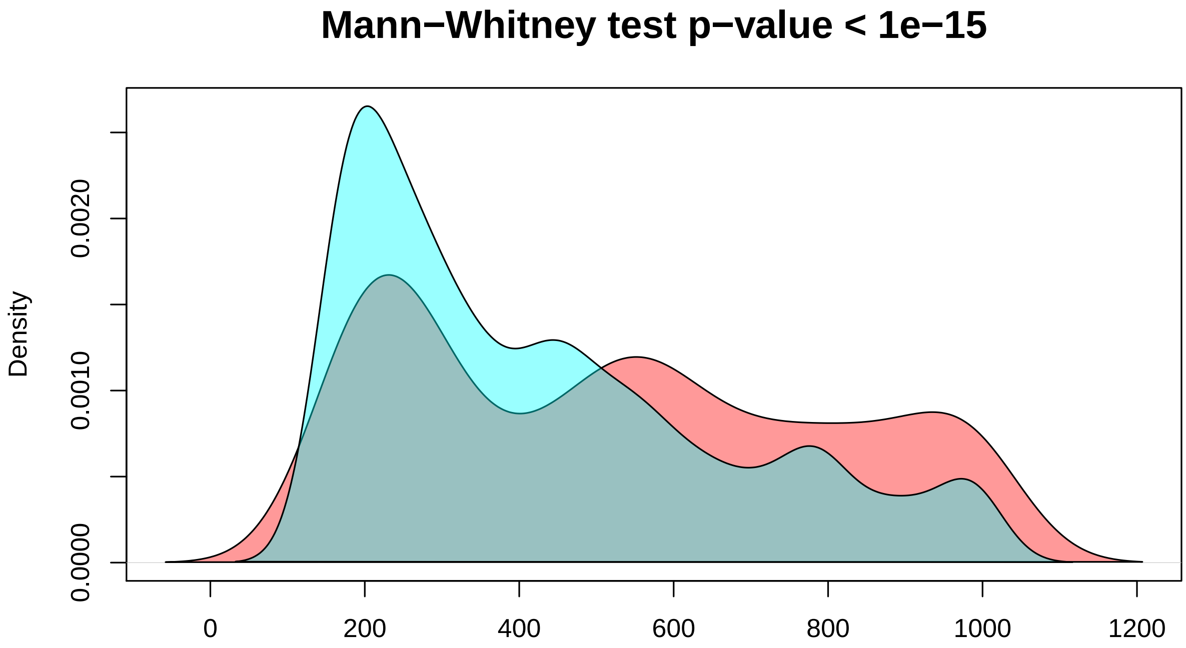
```
par(mfrow=c(1,2))

library(STRINGdb)

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

```
##    species_id            official_name             compact_name   kingdom
## 26       4932 Saccharomyces cerevisiae Saccharomyces cerevisiae eukaryota
##    type
## 26 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()
    }

}
```

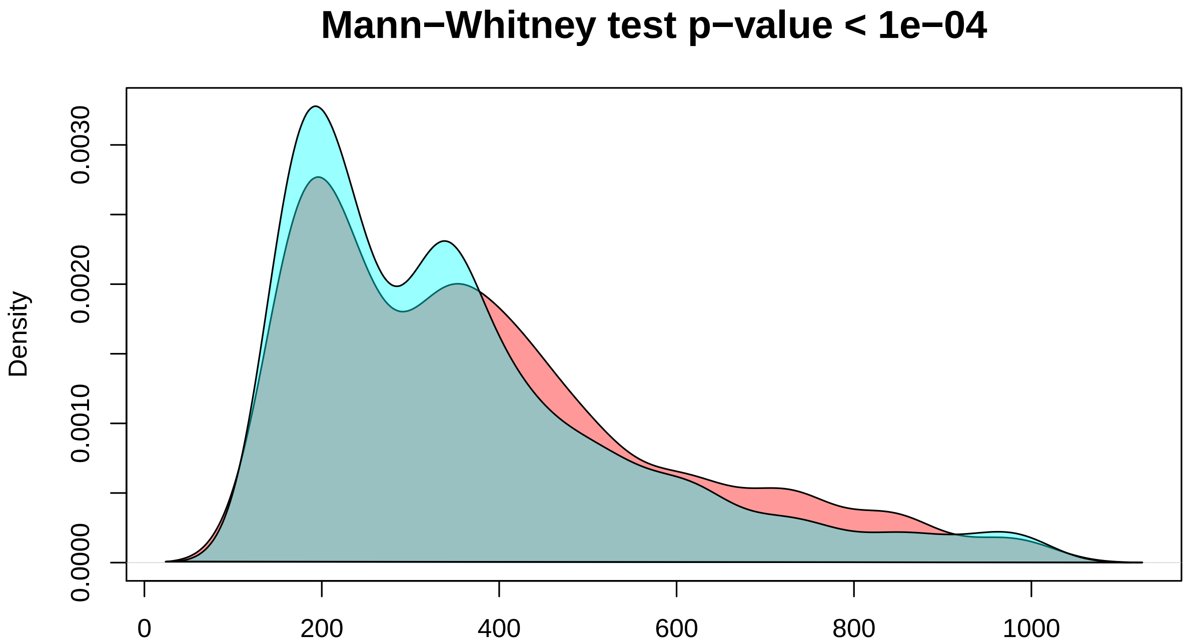
```
data(wageningen_string)

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.scores2 <- list()

string.names2 <- 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.scores2 <- c(string.scores2, tmp$combined_score)
            string.names2 <- c(string.names2, paste(sort(c(doubles[1], j)), collapse = "_"))
            tmp <- string_db$get_interactions(string_db$mp(c(doubles[2], j)))
            string.scores2 <- c(string.scores2, tmp$combined_score)
            string.names2 <- c(string.names2, paste(sort(c(doubles[2], j)), collapse = "_"))
        }
    } else {
        next()
    }

}
```

```
data(sameith_string)

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

stsc <- unlist(string.scores2)

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")
```



```r
sessionInfo()
```

```
## R version 3.3.2 (2016-10-31)
## Platform: x86_64-apple-darwin13.4.0 (64-bit)
## Running under: OS X El Capitan 10.11.5
##
## locale:
## [1] C/UTF-8/C/C/C/C
##
## attached base packages:
## [1] grid      parallel  stats     graphics  grDevices utils     datasets
## [8] methods   base
##
## other attached packages:
##  [1] bnem_0.99.0         latticeExtra_0.6-28 RColorBrewer_1.1-2
##  [4] lattice_0.20-34     snowfall_1.84-6.1   snow_0.4-2
##  [7] matrixStats_0.51.0  nem_2.48.0          CellNOptR_1.20.0
## [10] XML_3.98-1.5        Rgraphviz_2.18.0    RCurl_1.95-4.8
## [13] bitops_1.0-6        ggplot2_2.2.0       hash_2.2.6
## [16] RBGL_1.50.0         graph_1.52.0        BiocGenerics_0.20.0
## [19] devtools_1.12.0     STRINGdb_1.14.0     minet_3.32.0
## [22] pcalg_2.4-3         roxygen2_5.0.1      epiNEM_0.99.0
## [25] knitr_1.15.1        igraph_1.0.1        gtools_3.5.0
## [28] e1071_1.6-7         BoolNet_2.1.3
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.8          bdsmatrix_1.3-2      corpcor_1.6.8
##  [4] png_0.1-7            class_7.3-14         assertthat_0.1
##  [7] rprojroot_1.1       digest_0.6.10       gmp_0.5-12
## [10] plyr_1.8.4          chron_2.3-47        backports_1.0.4
## [13] stats4_3.3.2        RSQLite_1.0.0       evaluate_0.10
## [16] sqldf_0.4-10        BiocInstaller_1.24.0 gplots_3.0.1
## [19] lazyeval_0.2.0      gdata_2.17.0        rmarkdown_1.3
## [22] gsubfn_0.6-6        proto_1.0.0         statmod_1.4.26
## [25] stringr_1.1.0       munsell_0.4.3       htmltools_0.3.5
## [28] tcltk_3.3.2         tibble_1.2          withr_1.0.2
## [31] ggm_2.3             gtable_0.2.0        DBI_0.5-1
## [34] magrittr_1.5        scales_0.4.1        KernSmooth_2.23-15
## [37] stringi_1.1.2       limma_3.30.4        robustbase_0.92-6
## [40] boot_1.3-18         fastICA_1.2-0       tools_3.3.2
## [43] DEoptimR_1.0-6      sfsmisc_1.1-0       abind_1.4-5
## [46] plotrix_3.6-3       yaml_2.1.14         clue_0.3-51
## [49] colorspace_1.3-0    cluster_2.0.5       caTools_1.17.1
## [52] memoise_1.0.0
```

Reference:

Martin Pirkl, Madeline Diekmann, Marlies van der Wees, Niko Beerenwinkel, Holger Fröhlich, Florian Markowetz. Inferring Modulators of Genetic Interactions with Epistatic Nested Effects Models. submitted.