CTD Lab Exercise

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I. Generate background knowledge graph.

I.I: Manually build graphs from adjacency matrices.

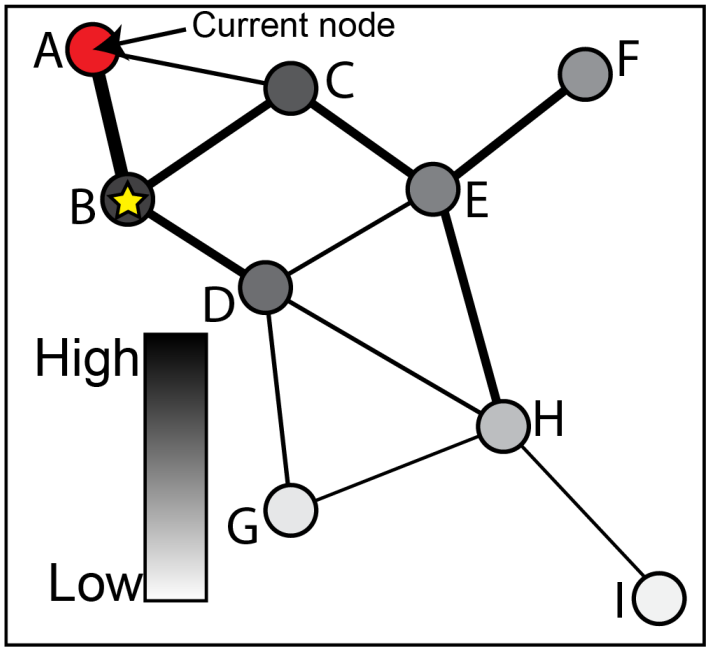


Figure 1: Cartoon of example network

```
adj_mat = rbind(c(0,3,1,0,0,0,0,0,0), #A's neighbors
                c(3,0,2,2,0,0,0,0,0), #B's neighbors
                c(1,2,0,0,2,0,0,0,0), #C's neighbors
                c(0,2,0,0,1,0,1,1,0), #D's neighbors
                c(0,0,2,1,0,2,0,2,0), #E's neighbors
                c(0,0,0,0,2,0,0,0,0), #F's neighbors
                c(0,0,0,1,0,0,0,1,0), #G's neighbors
                c(0,0,0,1,2,0,1,0,1), #H's neighbors
                c(0,0,0,0,0,0,0,1,0) #I's neighbors
                )
rownames(adj_mat) = c("A", "B", "C", "D", "E", "F", "G", "H", "I")
```

```r
colnames(adj_mat) = c("A", "B", "C", "D", "E", "F", "G", "H", "I")
# Convert adjacency matrices to igrpah objects for all three graphs.
ig = graph.adjacency(adj_mat, mode="undirected", weighted=TRUE,
                         add.colnames = "name")
print(ig)
```

```
## IGRAPH a0c85b6 UNW- 9 12 --
## + attr: name (v/c), weight (e/n)
## + edges from a0c85b6 (vertex names):
##  [1] A--B A--C B--C B--D C--E D--E D--G D--H E--F E--H G--H H--I
```

I.II: Learn a graph from data.

Note all code chunks in sections I - IV may rely on lines in previous code chunks, so do not empty your environment between code chunks.

```r
# Load the Miller2015_Heparin dataset
data(Miller2015)
# Only include metabolites that are present in >90% reference samples.
fil.rate=as.numeric(Miller2015$`Times identifed in all 200 samples`[-1])/200
names(fil.rate) = rownames(Miller2015)[-1]
data_mx = Miller2015[,grep("IEM_", colnames(Miller2015))]
data_mx = data_mx[which(fil.rate>0.90), ]
dim(data_mx)
```

```
## [1] 620 186
```

```r
# Remove any metabolites where any profile has a z-score > 1000.
# These are likely imputed raw values that were not z-scored.
rmMets = names(which(apply(data_mx, 1, function(i) any(i>20))))
if (length(rmMets)>0) {
    data_mx = data_mx[-which(rownames(data_mx) %in% rmMets),]
}
dim(data_mx)
```

```
## [1] 196 186
```

```r
# Get data from all patients with Argininemia
diags = Miller2015["diagnosis", grep("IEM", colnames(Miller2015))]
arg_data = data_mx[,which(diags=="Argininemia")]
# Add surrogate disease and surrogate reference profiles based on 1 standard
# deviation around profiles from real patients to improve rank of matrix when
# learning Gaussian Markov Random Field network on data. While surrogate
# profiles are not required, they tend to learn less complex networks
# (i.e., networks with less edges) and in faster time.
ind = which(diags=="No biochemical genetic diagnosis")
arg_data=data.surrogateProfiles(arg_data, 1, ref_data = data_mx[,ind])
dim(arg_data)
```

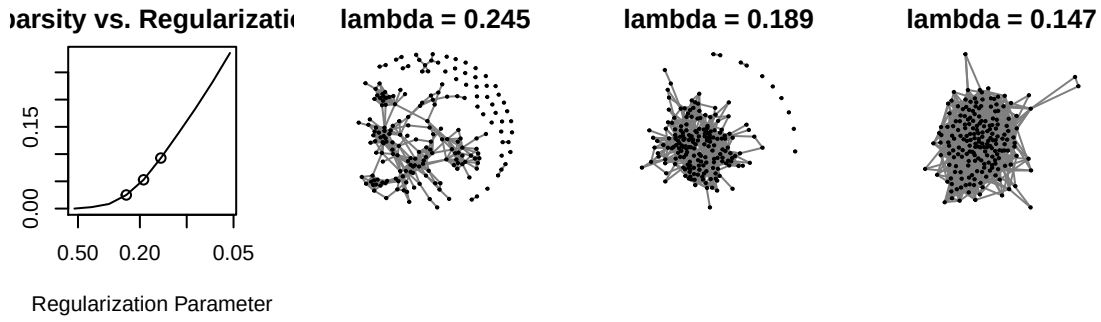
```
## [1]  196 1872
```

```r
# Learn a Gaussian Markov Random Field model using the Graphical LASSO in
# the R package "huge".
# Select the regularization parameter based on the "STARS" stability
# estimate.
require(huge)
```

```
#This will take 30 seconds - 1 minute.
arg = huge(t(arg_data), method="glasso")
```

```
## Conducting the graphical lasso (glasso) wtih lossless screening....in progress: 9%Conducting the grap
## Conducting the graphical lasso (glasso)....done.
```

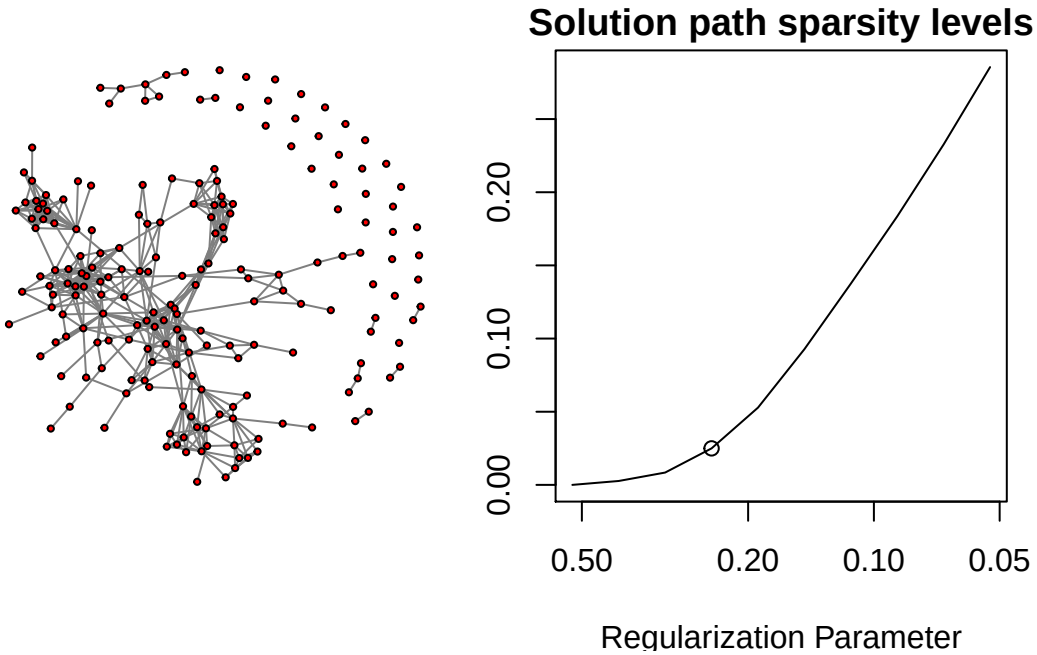
```
plot(arg)
```




```
# This will take several minutes. For a faster option, you can use the
# "ebic" criterion instead of "stars", but we recommend "stars".
arg.select = huge.select(arg, criterion="stars")
```

```
## Conducting Subsampling....in progress:5% Conducting Subsampling....in progress:10% Conducting Subsamp
```

```
plot(arg.select)
```




```
# This is the regularization parameter the STARS method selected.
print(arg.select$opt.lambda)
```

```
## [1] 0.244638
```

```
# This is the corresponding inverse of the covariance matrix that corresponds
# to the selected regularization level.
arg_icov = as.matrix(arg.select$opt.icov)
# Remove all "self" edges, as we are not interested in self-relationships.
diag(arg_icov) = 0
rownames(arg_icov) = rownames(arg_data)
colnames(arg_icov) = rownames(arg_data)
# Convert adjacency matrices to an igraph object.
ig_arg = graph.adjacency(arg_icov, mode="undirected", weighted=TRUE,
                         add.colnames="name")
print(ig_arg)
```

```
## IGRAPH 6e0daf1 UNW- 196 477 --
## + attr: name (v/c), weight (e/n)
## + edges from 6e0daf1 (vertex names):
##  [1] 1-arachidonoyl-gpc (20:4)   --1-docosahexaenoyl-gpc (22:6)
##  [2] 1-arachidonoyl-gpc (20:4)   --1-eicosatrienoyl-gpc (20:3)
##  [3] 1-arachidonoyl-gpc (20:4)   --2-arachidonoyl-gpc (20:4)
##  [4] 1-arachidonoyl-gpc (20:4)   --2-eicosatrienoyl-gpc (20:3)
##  [5] 1-arachidonoyl-gpc (20:4)   --2-oleoyl-gpc (18:1)
##  [6] 1-arachidonoyl-gpc (20:4)   --2-stearoyl-gpc (18:0)
##  [7] 1-arachidonoyl-gpc (20:4)   --x - 13478
```

```
##  [8] 1-docosahexaenoyl-gpc (22:6)--2-arachidonoyl-gpc (20:4)
## + ... omitted several edges
```

II. The Probability Diffusion Algorithm

II.I From a starting node.

Run the following code, then go to the directory, and open all diffusionEventMovie*.png files all at once. Starting from the first image, view how the probability diffusion algorithm works to diffuse 100% probability to the rest of the graph. Be sure to pay attention to the recursion level listed in the title of each image, to imagine where in the call stack the algorithm is at the captured time the image was generated.

```
G=vector(mode="list", length=length(V(ig)$name))
G[1:length(G)] = 0
names(G) = c("A", "B", "C", "D", "E", "F", "G", "H", "I")
startNode = "A"
visitedNodes = startNode
coords = layout.fruchterman.reingold(ig)
.GlobalEnv$imgNum = 1
G_new = graph.diffuseP1(p1=1.0, sn=startNode, G=G, vNodes=visitedNodes,
                        thresholdDiff=0.01, adj_mat=adj_mat, verbose=TRUE,
                        out_dir = sprintf("%s/images", getwd()),
                        r_level = 1, coords = coords)
```

```
## [1] "prob. to diffuse:1.000000 sn: A, visitedNodes: A"
## [1] "child#1 B got 0.750000"
## [1] "took 0.375000 from child#1:B to send"
## [1] "   prob. to diffuse:0.375000 sn: B, visitedNodes: A, B"
## [1] "   child#1 C got 0.187500"
## [1] "   took 0.093750 from child#1:C to send"
## [1] "      prob. to diffuse:0.093750 sn: C, visitedNodes: A, B, C"
## [1] "      child#1 E got 0.093750"
## [1] "      took 0.046875 from child#1:E to send"
## [1] "         prob. to diffuse:0.046875 sn: E, visitedNodes: A, B, C, E"
## [1] "         child#1 D got 0.009375"
## [1] "         child#2 F got 0.018750"
## [1] "         child#3 H got 0.018750"
## [1] "   child#2 D got 0.187500"
## [1] "   took 0.093750 from child#2:D to send"
## [1] "      prob. to diffuse:0.093750 sn: D, visitedNodes: A, B, D"
## [1] "      child#1 E got 0.031250"
## [1] "      took 0.015625 from child#1:E to send"
## [1] "         prob. to diffuse:0.015625 sn: E, visitedNodes: A, B, D, E"
```

```
## [1] "         child#1 C got 0.005208"
## [1] "         child#2 F got 0.005208"
## [1] "         child#3 H got 0.005208"
## [1] "      child#2 G got 0.031250"
## [1] "      took 0.015625 from child#2:G to send"
## [1] "         prob. to diffuse:0.015625 sn: G, visitedNodes: A, B, D, G"
## [1] "         child#1 H got 0.015625"
## [1] "      child#3 H got 0.031250"
## [1] "      took 0.015625 from child#3:H to send"
## [1] "         prob. to diffuse:0.015625 sn: H, visitedNodes: A, B, D, H"
## [1] "         child#1 E got 0.007812"
## [1] "         child#2 G got 0.003906"
## [1] "         child#3 I got 0.003906"
## [1] "child#2 C got 0.250000"
## [1] "took 0.125000 from child#2:C to send"
## [1] "   prob. to diffuse:0.125000 sn: C, visitedNodes: A, C"
## [1] "   child#1 B got 0.062500"
## [1] "   took 0.031250 from child#1:B to send"
## [1] "      prob. to diffuse:0.031250 sn: B, visitedNodes: A, C, B"
## [1] "      child#1 D got 0.031250"
## [1] "      took 0.015625 from child#1:D to send"
## [1] "         prob. to diffuse:0.015625 sn: D, visitedNodes: A, C, B, D"
## [1] "         child#1 E got 0.005208"
## [1] "         child#2 G got 0.005208"
## [1] "         child#3 H got 0.005208"
## [1] "   child#2 E got 0.062500"
## [1] "   took 0.031250 from child#2:E to send"
## [1] "      prob. to diffuse:0.031250 sn: E, visitedNodes: A, C, E"
## [1] "      child#1 D got 0.006250"
## [1] "      child#2 F got 0.012500"
## [1] "      child#3 H got 0.012500"
```

```r
# Inherited probabilities across all nodes should add to 1.
sum(unlist(G_new))
```

```
## [1] 1
```

```r
# Which node inherited the highest probability from startNode?
G_new[which.max(G_new)]
```

```
## $B
## [1] 0.40625
```

II.II From a starting node, after visiting previous nodes.

Now, delete all diffusionEventMovie*.png files from your current directory, and run the following code. View the new image stack in the same way we did previously.

```
# Now let's see how the probability diffusion algorithm diffuses probability
# after B has been "stepped" into.
visitedNodes = c("A", "B")
startNode = "B"
.GlobalEnv$imgNum=1
G_new = graph.diffuseP1(p1=1.0, sn=startNode, G, vNodes=visitedNodes,
                        thresholdDiff=0.01, adj_mat, TRUE,
                        out_dir = sprintf("%s/images", getwd()),
                        1, coords)
```

```
## [1] "prob. to diffuse:1.000000 sn: B, visitedNodes: A, B"
## [1] "child#1 C got 0.500000"
## [1] "took 0.250000 from child#1:C to send"
## [1] "   prob. to diffuse:0.250000 sn: C, visitedNodes: A, B, C"
## [1] "   child#1 E got 0.250000"
## [1] "   took 0.125000 from child#1:E to send"
## [1] "      prob. to diffuse:0.125000 sn: E, visitedNodes: A, B, C, E"
## [1] "      child#1 D got 0.025000"
## [1] "      took 0.012500 from child#1:D to send"
## [1] "         prob. to diffuse:0.012500 sn: D, visitedNodes: A, B, C, E, D"
## [1] "         child#1 G got 0.006250"
## [1] "         child#2 H got 0.006250"
## [1] "      child#2 F got 0.050000"
## [1] "      took 0.025000 from child#2:F to send"
## [1] "         prob. to diffuse:0.025000 sn: F, visitedNodes: A, B, C, E, F"
## [1] "         child#1 D got 0.008333"
## [1] "         child#2 H got 0.016667"
## [1] "      child#3 H got 0.050000"
## [1] "      took 0.025000 from child#3:H to send"
## [1] "         prob. to diffuse:0.025000 sn: H, visitedNodes: A, B, C, E, H"
## [1] "         child#1 D got 0.008333"
## [1] "         child#2 G got 0.008333"
## [1] "         child#3 I got 0.008333"
## [1] "child#2 D got 0.500000"
```

```
## [1] "took 0.250000 from child#2:D to send"
## [1] "   prob. to diffuse:0.250000 sn: D, visitedNodes: A, B, D"
## [1] "   child#1 E got 0.083333"
## [1] "   took 0.041667 from child#1:E to send"
## [1] "      prob. to diffuse:0.041667 sn: E, visitedNodes: A, B, D, E"
## [1] "      child#1 C got 0.013889"
## [1] "      child#2 F got 0.013889"
## [1] "      child#3 H got 0.013889"
## [1] "   child#2 G got 0.083333"
## [1] "   took 0.041667 from child#2:G to send"
## [1] "      prob. to diffuse:0.041667 sn: G, visitedNodes: A, B, D, G"
## [1] "      child#1 H got 0.041667"
## [1] "      took 0.020833 from child#1:H to send"
## [1] "         prob. to diffuse:0.020833 sn: H, visitedNodes: A, B, D, G, H"
## [1] "         child#1 E got 0.013889"
## [1] "         child#2 I got 0.006944"
## [1] "   child#3 H got 0.083333"
## [1] "   took 0.041667 from child#3:H to send"
## [1] "      prob. to diffuse:0.041667 sn: H, visitedNodes: A, B, D, H"
## [1] "      child#1 E got 0.020833"
## [1] "      took 0.010417 from child#1:E to send"
## [1] "         prob. to diffuse:0.010417 sn: E, visitedNodes: A, B, D, H, E"
## [1] "         child#1 C got 0.005208"
## [1] "         child#2 F got 0.005208"
## [1] "      child#2 G got 0.010417"
## [1] "      child#3 I got 0.010417"
```

```
# Inherited probabilities across all nodes should add to 1.
sum(unlist(G_new))
```

```
## [1] 1
```

```
# Which node inherited the highest probability from startNode?
G_new[which.max(G_new)]
```

```
## $D
## [1] 0.2791667
```

II.III Diffusing through visited nodes, based on connectivity.

Sometimes the startNode is "stranded" by a bunch of visited nodes. The diffusion algorithm diffuses "through" visited nodes, so that nodes in the same connected component can be prioritized over nodes in a different

connected component, or "island nodes" (e.g. in the below code snippet, "I" is an island node). This only works currently for nodes 2 hops away from the current startNode, however.

```
adj_mat = rbind(c(0,1,2,0,0,0,0,0,0), #A's neighbors
                c(1,0,3,0,0,0,0,0,0), #B's neighbors
                c(2,3,0,0,1,0,0,0,0), #C's neighbors
                c(0,0,0,0,0,0,1,1,0), #D's neighbors
                c(0,0,1,0,0,1,0,0,0), #E's neighbors
                c(0,0,0,0,1,0,0,0,0), #F's neighbors
                c(0,0,0,1,0,0,0,1,0), #G's neighbors
                c(0,0,0,1,0,0,1,0,0), #H's neighbors
                c(0,0,0,0,0,0,0,0,0) #I's neighbors
                )
rownames(adj_mat) = c("A", "B", "C", "D", "E", "F", "G", "H", "I")
colnames(adj_mat) = c("A", "B", "C", "D", "E", "F", "G", "H", "I")
# Convert adjacency matrices to igrpah objects for all three graphs.
ig = graph.adjacency(adj_mat, mode="undirected", weighted=TRUE,
                         add.colnames = "name")
coords = layout.fruchterman.reingold(ig)
print(ig)
```

```
## IGRAPH 822ec7a UNW- 9 8 --
## + attr: name (v/c), weight (e/n)
## + edges from 822ec7a (vertex names):
## [1] A--B A--C B--C C--E D--G D--H E--F G--H
```

```
# Now let's see how the probability diffusion algorithm diffuses probability
# after B has been "stepped" into "C" and then "A". As you can see, startNode
# "A" is surrounded by visited nodes "B" and "C". It needs to be smart enough
# to weigh "E" and "F" before "D", "H", "G" and "I".
visitedNodes = c("B", "C", "A")
startNode = "A"
.GlobalEnv$imgNum = 1
G_new = graph.diffuseP1(p1=1.0, sn=startNode, G, vNodes=visitedNodes,
                         thresholdDiff=0.01, adj_mat, TRUE,
                         out_dir = sprintf("%s/images", getwd()),
                         1, coords)
```

```
## [1] "prob. to diffuse:1.000000 sn: A, visitedNodes: B, C, A"
## [1] "child#1 E got 1.000000"
## [1] "took 0.500000 from child#1:E to send"
## [1] "   prob. to diffuse:0.500000 sn: E, visitedNodes: B, C, A, E"
## [1] "   child#1 F got 0.500000"
## [1] "   took 0.250000 from child#1:F to send"
## [1] "      prob. to diffuse:0.250000 sn: F, visitedNodes: B, C, A, E, F"
## [1] "F is singleton or stranded by visited n.bors"
## [1] "Diffuse p1 uniformly amongst all unvisited nodes."
```

```
# Inherited probabilities across all nodes should add to 1.
sum(unlist(G_new))
```

```
## [1] 1
```

```
# Which node inherited the highest probability from startNode?
G_new[which.max(G_new)]
```

```
## $E
## [1] 0.5
```

III. The Network Encoding Algorithms

III.I Multi-Node Diffusion Encoding

```
# The multi-node network walker tends to overfit on the network and is more
# computationally intensive/slow compared to the single-node network walker.
# It is therefore not recommended that you use this network walker over the
# single-node network walker. However, it is unclear if this network walker
# can be beneficial in some circumstances or application areas. We include
# it as an experimental feature only.
adj_mat = rbind(c(0,3,1,0,0,0,0,0,0), #A's neighbors
                c(3,0,2,2,0,0,0,0,0), #B's neighbors
                c(1,2,0,0,2,0,0,0,0), #C's neighbors
                c(0,2,0,0,1,0,1,1,0), #D's neighbors
                c(0,0,2,1,0,2,0,2,0), #E's neighbors
                c(0,0,0,0,2,0,0,0,0), #F's neighbors
                c(0,0,0,1,0,0,0,1,0), #G's neighbors
                c(0,0,0,1,2,0,1,0,1), #H's neighbors
                c(0,0,0,0,0,0,0,1,0) #I's neighbors
                )
rownames(adj_mat) = c("A", "B", "C", "D", "E", "F", "G", "H", "I")
colnames(adj_mat) = c("A", "B", "C", "D", "E", "F", "G", "H", "I")
# Convert adjacency matrices to igrpah objects for all three graphs.
ig = graph.adjacency(adj_mat, mode="undirected", weighted=TRUE,
                         add.colnames = "name")
coords = layout.fruchterman.reingold(ig)
print(ig)
```

```
## IGRAPH 5fa1ca2 UNW- 9 12 --
## + attr: name (v/c), weight (e/n)
## + edges from 5fa1ca2 (vertex names):
##  [1] A--B A--C B--C B--D C--E D--E D--G D--H E--F E--H G--H H--I
```

```
# Generate PNGs to animate the multi-node encoding node ranks.
ranks = multiNode.getNodeRanks(S = c("A", "B"), G, p1=1.0,
                               thresholdDiff=0.01, adj_mat,
                               log2(length(G)), FALSE,
                               out_dir = sprintf("%s/images", getwd()),
                               TRUE, coords)
# Get node ranks as list object, with no images generated
ranks = multiNode.getNodeRanks(S = c("A", "B"), G, p1=1.0,
                               thresholdDiff=0.01, adj_mat,
                               log2(length(G)), FALSE)
```

III.II Single-Node Diffusion Encoding

```
# This network walker tends to avoid overfitting. Of further note, since
# single-node network walker is not parameterized by the subset being
# encoded, you can pre-compute node rankingsusing dynamic programming.
# Pre-computing node ranks enables quick encoding of thousands of subsets
# at a time (see The Encoding Process).
S = c("A", "B")
out_dir=sprintf("%s/images",getwd())
# Generate PNGs to animate the single-node encoding node ranks.
ranks = list()
for (n in seq_len(length(S))) {
    ind = which(names(G)==S[n])
    ranks[[n]]=singleNode.getNodeRanksN(ind,G,p1=1.0,thresholdDiff=0.01,
                                        adj_mat,S=S,num.misses=log2(length(G)),
                                        FALSE,out_dir,TRUE, coords)
}
names(ranks) = S
# Get node ranks as list object, with no images generated
S = c("A", "B")
ranks = list()
for (n in 1:length(S)) {
    ind = which(names(G)==S[n])
    ranks[[n]]=singleNode.getNodeRanksN(ind,G,p1=1.0,thresholdDiff=0.01,
                                        adj_mat,S=S,
                                        num.misses=log2(length(G)),FALSE)
}
names(ranks) = S
```

IV. The Encoding Process

We're going to go back to our data using the Arginase deficiency network model, and the Miller et al (2015) dataset. ## IV.0 Re-define the Arginase deficiency network model

```
print(ig_arg)
```

```
## IGRAPH 6e0daf1 UNW- 196 477 --
## + attr: name (v/c), weight (e/n)
## + edges from 6e0daf1 (vertex names):
##  [1] 1-arachidonoyl-gpc (20:4)   --1-docosahexaenoyl-gpc (22:6)
##  [2] 1-arachidonoyl-gpc (20:4)   --1-eicosatrienoyl-gpc (20:3)
##  [3] 1-arachidonoyl-gpc (20:4)   --2-arachidonoyl-gpc (20:4)
##  [4] 1-arachidonoyl-gpc (20:4)   --2-eicosatrienoyl-gpc (20:3)
##  [5] 1-arachidonoyl-gpc (20:4)   --2-oleoyl-gpc (18:1)
##  [6] 1-arachidonoyl-gpc (20:4)   --2-stearoyl-gpc (18:0)
##  [7] 1-arachidonoyl-gpc (20:4)   --x - 13478
##  [8] 1-docosahexaenoyl-gpc (22:6)--2-arachidonoyl-gpc (20:4)
## + ... omitted several edges
```

```
adj_mat = as.matrix(get.adjacency(ig_arg, attr="weight"))
G=vector(mode="list", length=length(V(ig_arg)$name))
G[1:length(G)] = 0
names(G) = V(ig_arg)$name
```

IV.I Choose your node subset.

```
# Maximum subset size to inspect
kmx=15
# Get our node subset associated with the $KMX highest perturbed (up or down)
# in our first Arginase deficiency sample.
S_arg = sort(abs(arg_data[,1]), decreasing=TRUE)[1:kmx]
print(S_arg)
```

```
##                           x - 11381                           x - 13481
##                            4.197347                            3.510904
##                      2-aminobutyrate                       dihydroorotate
##                            3.122232                            3.117244
##           2-arachidonoyl-gpc (20:4) 2-linoleoylglycerol (2-monolinolein)
##                            2.942611                            2.862771
##         1-docosahexaenoyl-gpc (22:6)                           x - 13478
##                            2.754610                            2.741754
##                           x - 12792      gamma-glutamyl-2-aminobutyrate
##                            2.707036                            2.661916
##           1-arachidonoyl-gpc (20:4)                           x - 17001
##                            2.653048                            2.586215
##                           x - 18914               prolylhydroxyproline
##                            2.573498                            2.537495
##               1-stearoyl-gpc (18:0)
##                            2.246071
```

IV.II Get k node permutations.

```
# Get the single-node encoding node ranks starting from each node in the subset
# S_arg.
ranks = list()
for (n in 1:length(S_arg)) {
    ind = which(names(G)==names(S_arg)[n])
    ranks[[n]]=singleNode.getNodeRanksN(ind,G,p1=1.0,thresholdDiff=0.01,
                                        adj_mat,S=names(S_arg),
                                        num.misses=log2(length(G)),TRUE)
}
```

```
## [1] "Node ranking 128 of 196."
## [1] "Node ranking 157 of 196."
## [1] "Node ranking 19 of 196."
## [1] "Node ranking 60 of 196."
## [1] "Node ranking 21 of 196."
## [1] "Node ranking 28 of 196."
## [1] "Node ranking 2 of 196."
## [1] "Node ranking 156 of 196."
## [1] "Node ranking 149 of 196."
## [1] "Node ranking 63 of 196."
## [1] "Node ranking 1 of 196."
## [1] "Node ranking 170 of 196."
## [1] "Node ranking 188 of 196."
## [1] "Node ranking 103 of 196."
## [1] "Node ranking 17 of 196."
```

```
names(ranks) = names(S_arg)
```

IV.III Convert to bitstrings.

```
# Get the bitstrings associated with the patient's perturbed metabolites in
# "S_arg" based on the node ranks calculated in the previous step, "ranks".
ptBSbyK = mle.getPtBSbyK(names(S_arg), ranks)
```

IV.IV Get encoding length of minimum length codeword.

```
ptID = colnames(arg_data)[1]
ind = which(colnames(arg_data) %in% names(diags))
data_mx.pvals=apply(arg_data[,ind], c(1,2),
                    function(i) 2*pnorm(abs(i), lower.tail=FALSE))
res = mle.getEncodingLength(ptBSbyK, t(data_mx.pvals), ptID, G)
ind.mx = which.max(res$d.score)
res[ind.mx,]
```

```
##   patientID optimalBS subsetSize opt.T
## 6  IEM_1006  TTT0T0TT          6     6
##                                       varPvalue fishers.Info  IS.null
## 6 1.0e-02/2.7e-05/4.5e-04/9.7e-03/8.0e-03/3.3e-03     35.32494 36.08495
##     IS.alt d.score
## 6 14.61471   21.47
```

IV.V Get probability of node subset.

```
# This is the lower bound of the probability associated with the metabolites
# in S_arg. The higher the probability relative to a random set of the same
# size, the more tightly connected the metabolite set is.
2^-res[ind.mx,"IS.alt"]
```

```
## [1] 3.985969e-05
```

```
# Note the probability printed above may seem low, but there are
# log2(length(G), kmx) outcomes that probability is assigned between.
# We should expect a probability for a node set of size kmx in a length(G)
# network to have probability:
2^-(log2(choose(length(G), kmx)))
```

```
## [1] 9.359992e-23
```

```
# You'll notice the probability associated with the metabolite set we encoded,
# S_arg, is orders of magnitude higher than a uniform probability model. This
# implies the metabolites in S_arg are  connected in the network ig_arg more
# than is expected by chance.
```

IV.V Get p-value of variable length encoding vs. fixed length encoding.

```
# You can interpret the probability assigned to this metabolite set by
# comparing it to a null encoding algorithm, which uses fixed-length codes
# for all metabolites in the set. The "d.score" is the difference in bitlength
# between the null and alternative encoding models. Using the Algorithmic
# Significance theorem, we can estimate the upper bounds on a p-value by
# 2^-d.score.
2^-res[ind.mx,"d.score"]
```

```
## [1] 3.442595e-07
```

```
# All metabolites in S_arg
names(S_arg)
```

```
##  [1] "x - 11381"
##  [2] "x - 13481"
##  [3] "2-aminobutyrate"
##  [4] "dihydroorotate"
##  [5] "2-arachidonoyl-gpc (20:4)"
##  [6] "2-linoleoylglycerol (2-monolinolein)"
##  [7] "1-docosahexaenoyl-gpc (22:6)"
##  [8] "x - 13478"
##  [9] "x - 12792"
## [10] "gamma-glutamyl-2-aminobutyrate"
## [11] "1-arachidonoyl-gpc (20:4)"
## [12] "x - 17001"
## [13] "x - 18914"
## [14] "prolylhydroxyproline"
## [15] "1-stearoyl-gpc (18:0)"
```

```
# Which metabolites were in the 8 metabolite subset of patient IEM_1006's
# top 15 perturbed metabolites that had the above p-value?
ptBSbyK[[ind.mx]] # all metabolites in the bitstring
```

```
##                 x - 18914                 x - 11381                 x - 13481
##                         1                         1                         1
##                 x - 12798                 x - 17001                 x - 16581
##                         0                         1                         0
## 1-arachidonoyl-gpc (20:4) 2-arachidonoyl-gpc (20:4)
##                         1                         1
```

```
# just the F metabolites that are in S_arg that were were "found"
names(which(ptBSbyK[[ind.mx]]==1))
```

```
## [1] "x - 18914"                 "x - 11381"
## [3] "x - 13481"                 "x - 17001"
## [5] "1-arachidonoyl-gpc (20:4)" "2-arachidonoyl-gpc (20:4)"
```

V. Patient Distances, Single-Node Encoding Recommended

```
data_mx=arg_data[,which(colnames(arg_data) %in% names(diags))]
data_mx=data_mx[,1:8]
S_arg=c()
```

```
for (pt in 1:ncol(data_mx)) {
    ptID=colnames(data_mx)[pt]
    S_arg=c(S_arg,names(sort(abs(data_mx[,pt]),decreasing=TRUE)[1:kmx]))
}
S_arg = unique(S_arg)
# Pre-computing node ranks from all perturbed metabolites across all patients
# is the overhead we have to pay for when using this mutual information-based
# similarity metric, but will pay off when we go to compute several pairwise
# calculations of similarity.
# It feels like a lot of overhead when run serially, but when run in parallel
# (recommended) (e.g., a computing cluster) this finishes in minutes.
ranks=list()
for (n in 1:length(S_arg)) {
    print(sprintf("Node ranks for perturbed metabolite %d/%d.",
                  n, length(S_arg)))
    ind=which(names(G)==S_arg[n])
    ranks[[n]]=singleNode.getNodeRanksN(ind,G,p1=1.0,thresholdDiff=0.01,
                                        adj_mat,S=S_arg,
                                        num.misses=log2(length(G)),TRUE)
}
```

```
## [1] "Node ranks for perturbed metabolite 1/87."
## [1] "Node ranking 128 of 196."
## [1] "Node ranks for perturbed metabolite 2/87."
## [1] "Node ranking 157 of 196."
## [1] "Node ranks for perturbed metabolite 3/87."
## [1] "Node ranking 19 of 196."
## [1] "Node ranks for perturbed metabolite 4/87."
## [1] "Node ranking 60 of 196."
## [1] "Node ranks for perturbed metabolite 5/87."
## [1] "Node ranking 21 of 196."
## [1] "Node ranks for perturbed metabolite 6/87."
## [1] "Node ranking 28 of 196."
## [1] "Node ranks for perturbed metabolite 7/87."
## [1] "Node ranking 2 of 196."
## [1] "Node ranks for perturbed metabolite 8/87."
## [1] "Node ranking 156 of 196."
## [1] "Node ranks for perturbed metabolite 9/87."
## [1] "Node ranking 149 of 196."
## [1] "Node ranks for perturbed metabolite 10/87."
## [1] "Node ranking 63 of 196."
## [1] "Node ranks for perturbed metabolite 11/87."
## [1] "Node ranking 1 of 196."
## [1] "Node ranks for perturbed metabolite 12/87."
## [1] "Node ranking 170 of 196."
## [1] "Node ranks for perturbed metabolite 13/87."
## [1] "Node ranking 188 of 196."
## [1] "Node ranks for perturbed metabolite 14/87."
## [1] "Node ranking 103 of 196."
## [1] "Node ranks for perturbed metabolite 15/87."
## [1] "Node ranking 17 of 196."
## [1] "Node ranks for perturbed metabolite 16/87."
## [1] "Node ranking 87 of 196."
## [1] "Node ranks for perturbed metabolite 17/87."
```

```
## [1] "Node ranking 32 of 196."
## [1] "Node ranks for perturbed metabolite 18/87."
## [1] "Node ranking 104 of 196."
## [1] "Node ranks for perturbed metabolite 19/87."
## [1] "Node ranking 49 of 196."
## [1] "Node ranks for perturbed metabolite 20/87."
## [1] "Node ranking 164 of 196."
## [1] "Node ranks for perturbed metabolite 21/87."
## [1] "Node ranking 192 of 196."
## [1] "Node ranks for perturbed metabolite 22/87."
## [1] "Node ranking 74 of 196."
## [1] "Node ranks for perturbed metabolite 23/87."
## [1] "Node ranking 43 of 196."
## [1] "Node ranks for perturbed metabolite 24/87."
## [1] "Node ranking 88 of 196."
## [1] "Node ranks for perturbed metabolite 25/87."
## [1] "Node ranking 76 of 196."
## [1] "Node ranks for perturbed metabolite 26/87."
## [1] "Node ranking 51 of 196."
## [1] "Node ranks for perturbed metabolite 27/87."
## [1] "Node ranking 136 of 196."
## [1] "Node ranks for perturbed metabolite 28/87."
## [1] "Node ranking 142 of 196."
## [1] "Node ranks for perturbed metabolite 29/87."
## [1] "Node ranking 195 of 196."
## [1] "Node ranks for perturbed metabolite 30/87."
## [1] "Node ranking 92 of 196."
## [1] "Node ranks for perturbed metabolite 31/87."
## [1] "Node ranking 129 of 196."
## [1] "Node ranks for perturbed metabolite 32/87."
## [1] "Node ranking 7 of 196."
## [1] "Node ranks for perturbed metabolite 33/87."
## [1] "Node ranking 187 of 196."
## [1] "Node ranks for perturbed metabolite 34/87."
## [1] "Node ranking 25 of 196."
## [1] "Node ranks for perturbed metabolite 35/87."
## [1] "Node ranking 110 of 196."
## [1] "Node ranks for perturbed metabolite 36/87."
## [1] "Node ranking 89 of 196."
## [1] "Node ranks for perturbed metabolite 37/87."
## [1] "Node ranking 141 of 196."
## [1] "Node ranks for perturbed metabolite 38/87."
## [1] "Node ranking 193 of 196."
## [1] "Node ranks for perturbed metabolite 39/87."
## [1] "Node ranking 150 of 196."
## [1] "Node ranks for perturbed metabolite 40/87."
## [1] "Node ranking 127 of 196."
## [1] "Node ranks for perturbed metabolite 41/87."
## [1] "Node ranking 191 of 196."
## [1] "Node ranks for perturbed metabolite 42/87."
## [1] "Node ranking 179 of 196."
## [1] "Node ranks for perturbed metabolite 43/87."
## [1] "Node ranking 90 of 196."
## [1] "Node ranks for perturbed metabolite 44/87."
```

```
## [1] "Node ranking 108 of 196."
## [1] "Node ranks for perturbed metabolite 45/87."
## [1] "Node ranking 172 of 196."
## [1] "Node ranks for perturbed metabolite 46/87."
## [1] "Node ranking 93 of 196."
## [1] "Node ranks for perturbed metabolite 47/87."
## [1] "Node ranking 67 of 196."
## [1] "Node ranks for perturbed metabolite 48/87."
## [1] "Node ranking 59 of 196."
## [1] "Node ranks for perturbed metabolite 49/87."
## [1] "Node ranking 38 of 196."
## [1] "Node ranks for perturbed metabolite 50/87."
## [1] "Node ranking 68 of 196."
## [1] "Node ranks for perturbed metabolite 51/87."
## [1] "Node ranking 35 of 196."
## [1] "Node ranks for perturbed metabolite 52/87."
## [1] "Node ranking 91 of 196."
## [1] "Node ranks for perturbed metabolite 53/87."
## [1] "Node ranking 22 of 196."
## [1] "Node ranks for perturbed metabolite 54/87."
## [1] "Node ranking 86 of 196."
## [1] "Node ranks for perturbed metabolite 55/87."
## [1] "Node ranking 135 of 196."
## [1] "Node ranks for perturbed metabolite 56/87."
## [1] "Node ranking 112 of 196."
## [1] "Node ranks for perturbed metabolite 57/87."
## [1] "Node ranking 36 of 196."
## [1] "Node ranks for perturbed metabolite 58/87."
## [1] "Node ranking 30 of 196."
## [1] "Node ranks for perturbed metabolite 59/87."
## [1] "Node ranking 100 of 196."
## [1] "Node ranks for perturbed metabolite 60/87."
## [1] "Node ranking 45 of 196."
## [1] "Node ranks for perturbed metabolite 61/87."
## [1] "Node ranking 83 of 196."
## [1] "Node ranks for perturbed metabolite 62/87."
## [1] "Node ranking 34 of 196."
## [1] "Node ranks for perturbed metabolite 63/87."
## [1] "Node ranking 143 of 196."
## [1] "Node ranks for perturbed metabolite 64/87."
## [1] "Node ranking 70 of 196."
## [1] "Node ranks for perturbed metabolite 65/87."
## [1] "Node ranking 148 of 196."
## [1] "Node ranks for perturbed metabolite 66/87."
## [1] "Node ranking 99 of 196."
## [1] "Node ranks for perturbed metabolite 67/87."
## [1] "Node ranking 80 of 196."
## [1] "Node ranks for perturbed metabolite 68/87."
## [1] "Node ranking 181 of 196."
## [1] "Node ranks for perturbed metabolite 69/87."
## [1] "Node ranking 180 of 196."
## [1] "Node ranks for perturbed metabolite 70/87."
## [1] "Node ranking 66 of 196."
## [1] "Node ranks for perturbed metabolite 71/87."
```

```
## [1] "Node ranking 166 of 196."
## [1] "Node ranks for perturbed metabolite 72/87."
## [1] "Node ranking 61 of 196."
## [1] "Node ranks for perturbed metabolite 73/87."
## [1] "Node ranking 169 of 196."
## [1] "Node ranks for perturbed metabolite 74/87."
## [1] "Node ranking 122 of 196."
## [1] "Node ranks for perturbed metabolite 75/87."
## [1] "Node ranking 39 of 196."
## [1] "Node ranks for perturbed metabolite 76/87."
## [1] "Node ranking 125 of 196."
## [1] "Node ranks for perturbed metabolite 77/87."
## [1] "Node ranking 146 of 196."
## [1] "Node ranks for perturbed metabolite 78/87."
## [1] "Node ranking 177 of 196."
## [1] "Node ranks for perturbed metabolite 79/87."
## [1] "Node ranking 71 of 196."
## [1] "Node ranks for perturbed metabolite 80/87."
## [1] "Node ranking 131 of 196."
## [1] "Node ranks for perturbed metabolite 81/87."
## [1] "Node ranking 75 of 196."
## [1] "Node ranks for perturbed metabolite 82/87."
## [1] "Node ranking 155 of 196."
## [1] "Node ranks for perturbed metabolite 83/87."
## [1] "Node ranking 84 of 196."
## [1] "Node ranks for perturbed metabolite 84/87."
## [1] "Node ranking 3 of 196."
## [1] "Node ranks for perturbed metabolite 85/87."
## [1] "Node ranking 8 of 196."
## [1] "Node ranks for perturbed metabolite 86/87."
## [1] "Node ranking 11 of 196."
## [1] "Node ranks for perturbed metabolite 87/87."
## [1] "Node ranking 4 of 196."
```

```
names(ranks)=S_arg
# Calculate patient bitstrings
ptBSbyK=list()
for (pt in 1:ncol(data_mx)) {
    ptID=colnames(data_mx)[pt]
    S_pt=names(sort(abs(data_mx[,pt]),decreasing=TRUE)[1:kmx])
    ptBSbyK[[ptID]]=mle.getPtBSbyK(S_pt, ranks)
}
# Now perform mutual information-based patient similarity scoring
res = list()
t = list(ncd=matrix(NA, nrow=ncol(data_mx), ncol=ncol(data_mx)))
rownames(t$ncd) = colnames(data_mx)
colnames(t$ncd) = colnames(data_mx)
for (i in 1:kmx) { res[[i]] = t }
for (pt in 1:ncol(data_mx)) {
    print(sprintf("Patient %d vs...", pt))
    ptID=colnames(data_mx)[pt]
    for (pt2 in pt:ncol(data_mx)) {
        print(sprintf("Patient %d.", pt2))
        ptID2=colnames(data_mx)[pt2]
```

```
        # Because we pre-computed node ranks for all perturbed metabolites
        # across our 8 patients, this will complete very quickly.
        tmp = mle.getPtDist(ptBSbyK[[ptID]],ptID,ptBSbyK[[ptID2]],ptID2,
                            data_mx,ranks,p1=1.0,thresholdDiff=0.01,adj_mat)
        for (k in 1:kmx) {
            res[[k]]$ncd[ptID, ptID2] = tmp$NCD[k]
            res[[k]]$ncd[ptID2, ptID] = tmp$NCD[k]
        }
    }
}
```

```
## [1] "Patient 1 vs..."
## [1] "Patient 1."
## [1] "Patient 2."
## [1] "Patient 3."
## [1] "Patient 4."
## [1] "Patient 5."
## [1] "Patient 6."
## [1] "Patient 7."
## [1] "Patient 8."
## [1] "Patient 2 vs..."
## [1] "Patient 2."
## [1] "Patient 3."
## [1] "Patient 4."
## [1] "Patient 5."
## [1] "Patient 6."
## [1] "Patient 7."
## [1] "Patient 8."
## [1] "Patient 3 vs..."
## [1] "Patient 3."
## [1] "Patient 4."
## [1] "Patient 5."
## [1] "Patient 6."
## [1] "Patient 7."
## [1] "Patient 8."
## [1] "Patient 4 vs..."
## [1] "Patient 4."
## [1] "Patient 5."
## [1] "Patient 6."
## [1] "Patient 7."
## [1] "Patient 8."
## [1] "Patient 5 vs..."
## [1] "Patient 5."
## [1] "Patient 6."
## [1] "Patient 7."
## [1] "Patient 8."
## [1] "Patient 6 vs..."
## [1] "Patient 6."
## [1] "Patient 7."
## [1] "Patient 8."
## [1] "Patient 7 vs..."
## [1] "Patient 7."
## [1] "Patient 8."
## [1] "Patient 8 vs..."
```

```
## [1] "Patient 8."
```

VI. Visualizations

```
# Multi-dimensional scaling
plot.mdsDist = function(patientDist, diagnoses, k, diag) {
    if (!(k %in% c(2,3))) {
        print("K must be either 2-dimensions or 3-dimensions.")
        return(0)
    }
    if (is.null(diagnoses)) {
        print("To view patient clusters, please provide clinical labels.")
        return(0)
    }
    fitDist = cmdscale(patientDist, eig=FALSE, k=k)
    x = round(fitDist[,1], 2)
    y = round(fitDist[,2], 2)
    if (k==3) {
        z=round(fitDist[,3], 2)
        df=data.frame(x=x,y=y,z=z,color=diagnoses,label=colnames(patientDist))
        p=plot_ly(df,x=~x,y=~y,z=~z,color=~color,text=~label,
                  marker=list(size=20))
    } else {
        df=data.frame(x=x,y=y,color=diagnoses,label=colnames(patientDist))
        p=plot_ly(df,x=~x,y=~y,color=~color,text=~label,
                  marker=list(size=20))
    }
    return(p)
}
# K-nearest neighbors
plot.knnDist = function(patientDist, diagnoses, diag) {
    diagnoses = diagnoses[colnames(patientDist)]
    # Add a GREEN edge between patient nodes if k nearest neighbor is
    # correct diagnosis (either TP or TN)
    # Add a RED edge between patient nodes if k nearest neighbor is
    # incorrect diagnosis (either FP or FN)
    tp = 0
    fp = 0
    tn = 0
    fn = 0
    ig = make_empty_graph(n=ncol(patientDist), directed=TRUE)
    V(ig)$name = colnames(patientDist)
    for (pt1 in 1:length(diagnoses)) {
        diag_pt1 = diagnoses[pt1]
        ind = sort(patientDist[pt1,-pt1], decreasing = FALSE)
        ind = ind[which(ind==min(ind))]
        diag_pt_ind = diagnoses[which(names(diagnoses) %in% names(ind))]
        if (any(diag_pt_ind==diag) && diag_pt1==diag) { # True positive
            tp=tp + 1
            ind=ind[which(diag_pt_ind==diag)]
            ig=add.edges(ig,
                         edges=c(colnames(patientDist)[pt1],names(ind[1])),
```

```
                        attr=list(color="green", lty=1))
        } else if (diag_pt_ind!=diag && diag_pt1!=diag) { # True negative
            tn=tn + 1
            ig=add.edges(ig,
                        edges=c(colnames(patientDist)[pt1],names(ind[1])),
                        attr=list(color="green", lty=1))
        } else if (diag_pt_ind==diag && diag_pt1!=diag) { # False positive
            fp=fp + 1
            ig=add.edges(ig,
                        edges=c(colnames(patientDist)[pt1],names(ind[1])),
                        attr=list(color="red", lty=1))
        } else { # False negative
            fn=fn + 1
            ig=add.edges(ig,
                        edges=c(colnames(patientDist)[pt1],names(ind[1])),
                        attr=list(color="red", lty=1))
        }
    }
    print(sprintf("Tp = %d, Tn= %d, Fp = %d, Fn=%d", tp, tn, fp, fn))
    sens = tp / (tp+fn)
    spec = tn / (tn+fp)
    print(sprintf("Sens = %.2f, Spec= %.2f", sens, spec))
    V(ig)$label = rep("", length(V(ig)$name))
    return(ig)
}

# If you have diagnostic labels associated with the colnames(data_mx),
# send them using diagnoses parameter
res_ncd = lapply(res, function(i) i$ncd)
ncd = mle.getMinPtDistance(res_ncd)
dd = colnames(data_mx)
dd[which(dd %in% names(diags)[which(diags=="Argininemia")])] = "ARG"
dd[which(dd %in% names(diags)[which(diags!="Argininemia")])] = "negCntl"
names(dd) = colnames(res[[1]]$ncd)

require(plotly)
```

```
## Loading required package: plotly
## Loading required package: ggplot2
##
## Attaching package: 'plotly'
## The following object is masked from 'package:ggplot2':
##
##     last_plot
## The following object is masked from 'package:igraph':
##
##     groups
## The following object is masked from 'package:stats':
##
##     filter
## The following object is masked from 'package:graphics':
```

```
##
##     layout
```

```
require(gplots)
```

```
## Loading required package: gplots
```

```
##
## Attaching package: 'gplots'
```

```
## The following object is masked from 'package:stats':
##
##     lowess
```

```
require(RColorBrewer)
```

```
## Loading required package: RColorBrewer
```

```
colnames(ncd)=colnames(res[[1]]$ncd)
rownames(ncd)=colnames(res[[1]]$ncd)
p=plot.mdsDist(ncd, dd, k=2, NULL)
p
```

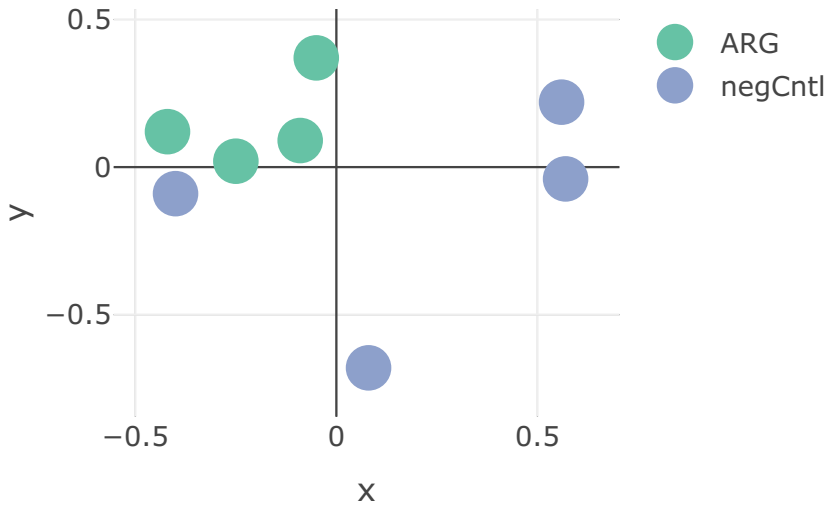
```
## No trace type specified:
##   Based on info supplied, a 'scatter' trace seems appropriate.
##   Read more about this trace type -> https://plot.ly/r/reference/#scatter
```

```
## No scatter mode specifed:
##   Setting the mode to markers
##   Read more about this attribute -> https://plot.ly/r/reference/#scatter-mode
```

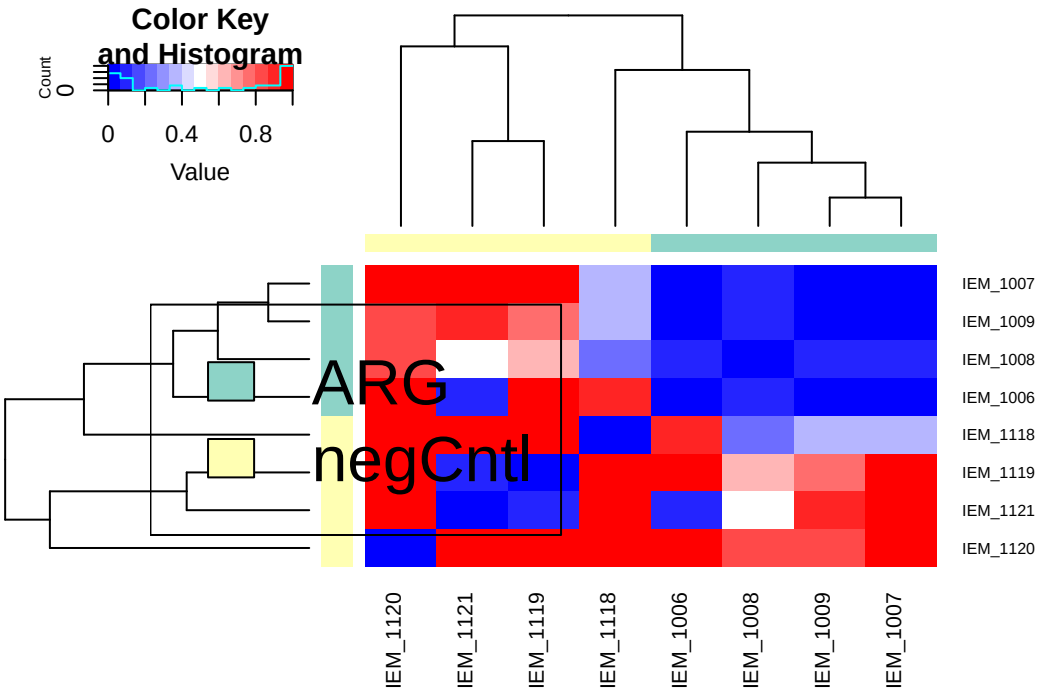
```
## Warning: `arrange_()` is deprecated as of dplyr 0.7.0.
## Please use `arrange()` instead.
## See vignette('programming') for more help
## This warning is displayed once every 8 hours.
## Call `lifecycle::last_warnings()` to see where this warning was generated.
```

```
## Warning in RColorBrewer::brewer.pal(N, "Set2"): minimal value for n is 3, returning requested palett
```

```
## Warning in RColorBrewer::brewer.pal(N, "Set2"): minimal value for n is 3, returning requested palett
```




```
# Hierarchical clustering
dd_f = as.numeric(as.factor(as.character(dd)))
heatmap.2(x=ncd,dendrogram="both", Rowv=TRUE,Colv=TRUE,
          ColSideColors=c(brewer.pal(12,"Set3"),brewer.pal(9,"BrBG"))[dd_f],
          RowSideColors=c(brewer.pal(12,"Set3"),brewer.pal(9,"BrBG"))[dd_f],
          cexRow=0.75,cexCol=1, margins=c(12,12), trace="none", key=TRUE,
          col=bluered, notecol="black")
legend("left", legend=unique(sort(as.character(dd))),
        fill=c(brewer.pal(12,"Set3"), brewer.pal(9,"BrBG")), cex=2)
```




```
# K-NN
ig=plot.knnDist(ncd, dd, diag="ARG")
```

```
## [1] "Tp = 4, Tn= 2, Fp = 2, Fn=0"
## [1] "Sens = 1.00, Spec= 0.50"
```

```
grps=list()
grps[[1]]=names(dd)[which(dd=="ARG")]
grps[[2]]=names(dd)[which(dd!="ARG")]
names(grps)=names(table(dd))
plot.igraph(ig, mark.groups=grps, mark.col=c("white", "black"),
            layout=layout.circle, edge.width=3, edge.arrow.size=0.5)
```