# Neighbor_net analysis

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**Abstract**

This package is indented to be the R implementation of the method introduced in [1]. Neighbor_net analysis aims to take advantage of the prior knowledge of gene-gene interactions and idetifies the putative mechanisms at play in the given condition (e.g. a disease, a treatment, etc.). The captured network can be useful for the prediction of mechanisms of action of drugs or the responses of an organism to a specific impact.

## 1 Neighbor_net analysis

Neighbor_net (`neighborNet`) is a tool to identify the active mechanism involved in an investigated phenotype. This method uses two sources of data: one is the experiment data and the other is the gene-gene interactions knowledge.

### 1.1 Gene-gene interaction knowledge

Neighbor_net can accept any gene-gene interaction information obtained from different databases. The data has to be converted to a list format. Each element in the list represents the neighborhood of one gene.

We provided an example that includes the interactions exist in KEGG[2] and HPRD [3] databases.

```
> load(system.file("extdata/listofgenes.RData", package = "NeighborNet"))
```

The `listofgenes` is a list including the neighbors of the genes in the analysis:

```
> head(listofgenes)

$`216`
[1] "216"

$`3679`
[1] "3679" "1134" "1398" "1399" "5747" "6714" "60"   "71"   "9564"

$`55607`
[1] "55607" "71"    "5575"  "5504"  "84687" "5499"  "6198"

$`5552`
[1] "5552"  "960"   "5196"  "56893" "6449"  "3002"  "213"
```

```
$`2886`
 [1] "2886" "2064" "3815" "2065" "2885" "7010" "5747" "9020" "1956" "3643"
[11] "5979"

$`5058`
 [1] "5058"   "2064"   "5335"   "5604"   "660"    "9459"   "4690"   "4638"
 [9] "3984"   "5879"   "5829"   "668"    "4771"   "10095"  "9181"   "1457"
[17] "1459"   "985"    "998"    "4086"   "4087"   "4089"   "57154"  "7046"
[25] "58480"  "6853"   "1277"   "5580"   "58"     "572"    "10818"  "9815"
[33] "7048"   "2316"   "2099"   "2308"   "834"    "5894"   "9020"   "5605"
[41] "10746"  "4215"   "5609"   "6416"   "2317"   "2318"   "7074"   "340156"
[49] "85366"  "91807"  "3985"   "8874"
```

### 1.2 Experiment data

As an example, we provided five pre-processed data sets from GEO (GSE4183, GSE9348, GSE21510, GSE32323, GSEl8671).

These data study the expression change between colorectal cancer and normal patients. The data was preprocessed using the *limma* package. Only probe sets with a gene associated to them have been kept.

```
> load(system.file("extdata/dataColorectal4183.RData", package = "NeighborNet"))
> load(system.file("extdata/dataColorectal9348.RData", package = "NeighborNet"))
> load(system.file("extdata/dataColorectal21510.RData", package = "NeighborNet"))
> load(system.file("extdata/dataColorectal32323.RData", package = "NeighborNet"))
> load(system.file("extdata/dataColorectal8671.RData", package = "NeighborNet"))
> head(dataColorectal4183)

     adj.P.Val    logFC EntrezID
1 0.0005849192 2.165550    27253
2 0.0005849192 1.993385     7450
3 0.0005849192 1.402015      857
4 0.0015330474 1.887886    25937
5 0.0015330474 2.220579    29767
6 0.0015330474 3.536515      285
```

The next step is to select the genes that are differentially expressed, with p-value lower than 1% and absolute fold change more than 1.5.

```
> pvThreshold <- 0.01
> foldThreshold <- 1.5
> de1 <- dataColorectal4183$EntrezID [
+   dataColorectal4183$adj.P.Val < pvThreshold &
+   abs(dataColorectal4183$logFC) > foldThreshold
+ ]
> de2 <- dataColorectal9348$EntrezID [
+   dataColorectal9348$adj.P.Val < pvThreshold &
+   abs(dataColorectal9348$logFC) > foldThreshold
+ ]
```

```
> de3 <- dataColorectal21510$EntrezID [
+   dataColorectal21510$adj.P.Val < pvThreshold &
+   abs(dataColorectal21510$logFC) > foldThreshold
+ ]
> de4 <- dataColorectal32323$EntrezID [
+   dataColorectal32323$adj.P.Val < pvThreshold &
+   abs(dataColorectal32323$logFC) > foldThreshold
+ ]
> de5 <- dataColorectal8671$EntrezID [
+   dataColorectal8671$adj.P.Val < pvThreshold &
+   abs(dataColorectal8671$logFC) > foldThreshold
+ ]
>
```

Later, the differentialy expressed genes from different datasets should be combined together:

```
> de <- unique( c(de1,de2,de3,de4,de5))
```

The reference contains all the genes measured in the analysis:

```
> ref <- unique( c(
+   dataColorectal4183$EntrezID,
+   dataColorectal9348$EntrezID,
+   dataColorectal21510$EntrezID,
+   dataColorectal32323$EntrezID,
+   dataColorectal8671$EntrezID
+ ))
> head(ref)

[1] "27253" "7450"  "857"   "25937" "29767" "285"
```

### 1.3 Neighbor_net analysis and resulted network

We have all the input fot Neighbor_net analysis.

- the gene-gene knowledge in a list format -`listofgenes`
- the experiment data -`de` and -`ref`

```
> library("NeighborNet")
> library("graph")
> sig_genes <- neighborNet(de = de, ref = ref, listofgenes=listofgenes)
> sig_genes

A graphNEL graph with undirected edges
Number of Nodes = 144
Number of Edges = 251
```

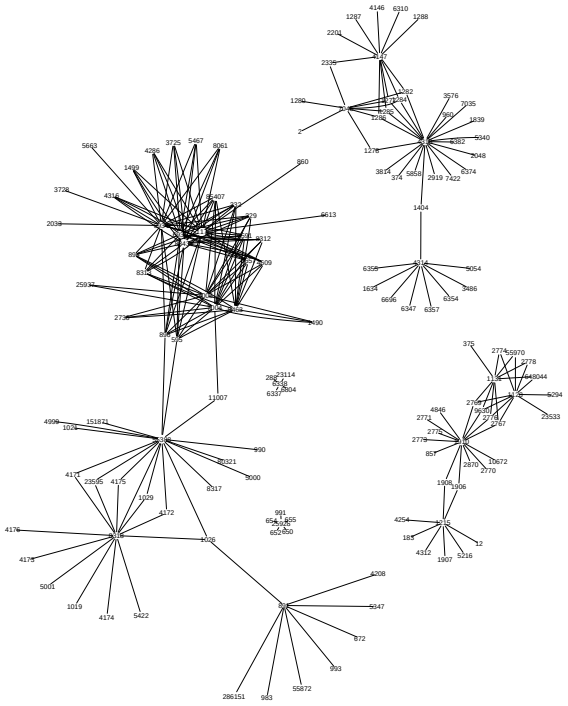

Figure 1: The active network that describes the putative mechanism involved in colorectal cancer.

### 1.4 Graphical representation of results

To visualize the identified network use the function `plot`(see Fig. 1):

```
> require("graph")
> attrs <- list(node= list(fontsize=40,fixedsize= FALSE),graph=list(overlap=FALSE), edge=list(l
> nAttr <- list()
> nAttr$color <- c(rep("white",length(nodes(sig_genes))))
> names(nAttr$color) <- nodes(sig_genes)
> plot(sig_genes)
```

## References


[1] S. Ansari, M. Donato, N. Saberian, and S. Draghici. An approach to infer putative disease-specific mechanisms using neighboring gene networks. *Bioinformatics*, page btx097, 2017.

[2] M. Kanehisa and S. Goto. KEGG: kyoto encyclopedia of genes and genomes. *Nucleic Acids Research*, 28(1):27–30, 2000.

[3] S. Peri, J. D. Navarro, R. Amanchy, T. Z. Kristiansen, C. K. Jonnalagadda, V. Surendranath, V. Niranjan, B. Muthusamy, T. Gandhi, M. Gronborg, et al. Development of human protein reference database as an initial platform for approaching systems biology in humans. *Genome Research*, 13(10):2363–2371, 2003.