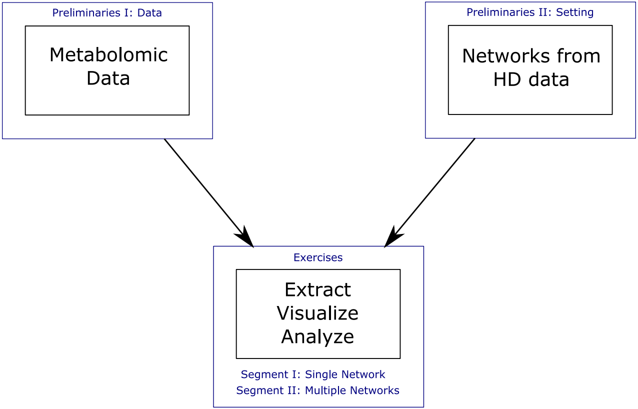
rags2ridges
Network Modeling of High-Dimensional Data

Carel F.W. Peeters
Dept. of Epidemiology & Biostatistics
VU University medical center, Amsterdam
cf.peeters@vumc.nl

Multi-Omics Analysis Workshop
Amsterdam, The Netherlands
November 23, 2017

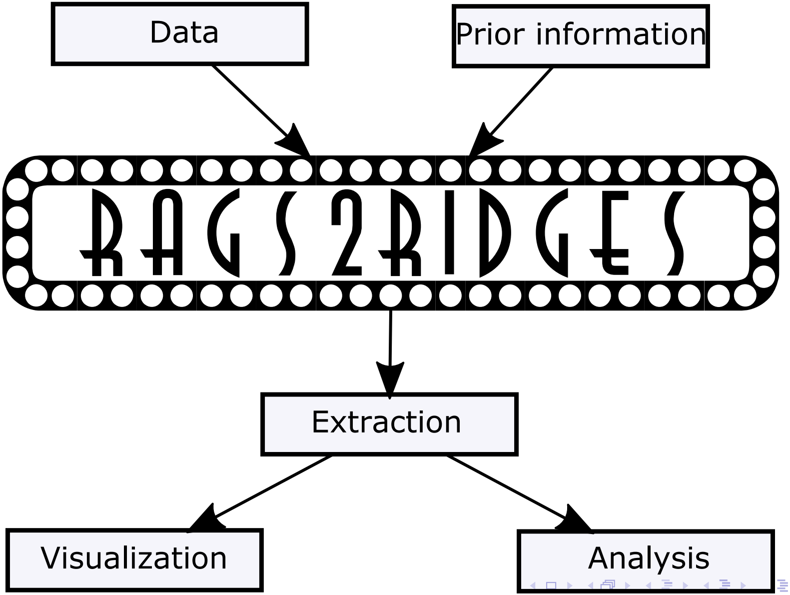
Overview



Materials

- These slides: Contain explanation theory/methodology and exercises
- `rags2ridges_Practical.HTML`: Contains solutions to exercises with additional explanations
- `NetworksExercises.R`: Contains bare solutions to exercises

ragsridges: One-Stop-Go



Omics and omics data

-ome

A totality of some (molecular biological) sort

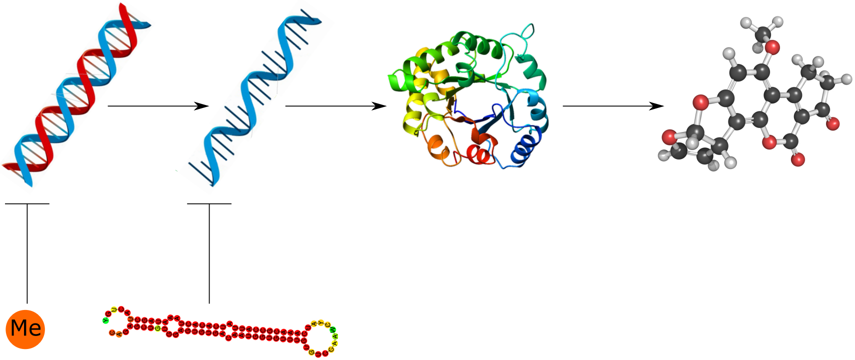
-omics

Collective quantification of some pool of molecular molecules

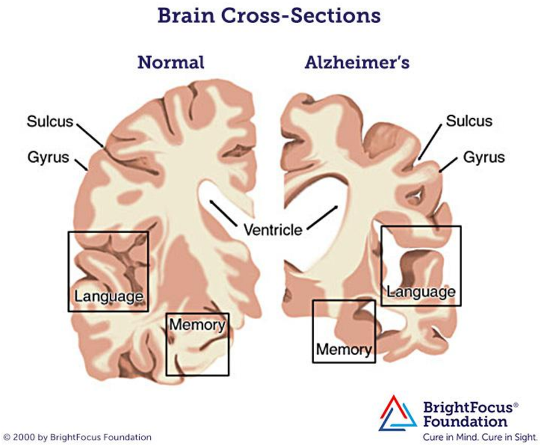
Genomics

The omics of the genome (of some organism)

The omic cascade



Alzheimer's Disease



Metabolite quantification

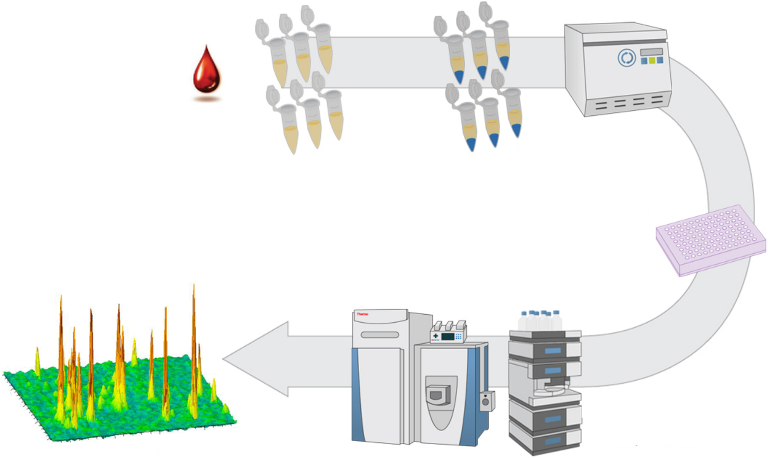


Illustration adapted from: http://planetorbitrap.com/untargeted-metabolomics#.Vzw6yfmLRaQ &

http://metabolomicsplatform.com/metabolomics-overview/

Metabolomic Data

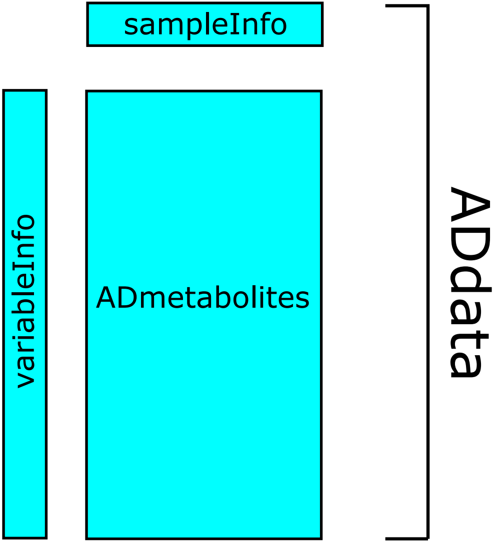
Variables (features)

Observations	1	2	3	4	5	…	p
1	y_{11}	y_{12}	y_{13}	y_{14}	y_{15}	…	y_{1p}
2	y_{21}	y_{22}	y_{23}	y_{24}	y_{25}	…	y_{2p}
3	y_{31}	y_{32}	y_{33}	y_{34}	y_{35}	…	y_{3p}
⋮	⋮	⋮	⋮	⋮	⋮		⋮
n	y_{n1}	y_{n2}	y_{n3}	y_{n4}	y_{n5}	…	y_{np}

- Amines
- Lipids
- Organic Acids
- Oxidative Stress

$p = 230$: 53 Amines, 116 Lipids, 22 Organic acids, 39 Oxidative stress compounds
$n = 127$: 40 AD class 1, 87 AD class 2

Metabolomic Data Objects



Exercise 1: Get acquainted with the data

```
## Set working directory
setwd("")

## Needed libraries
library(rags2ridges)
```

Invoke data

```
data(ADdata)
```

Which objects?

```
objects()
```

Simple exploration objects

```
head()
```

Gaussian graphical modeling

Graphical modeling

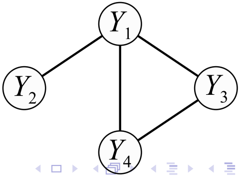
Class of models using graphs to express conditional (in)dependence relations between random variables

Gaussian setting

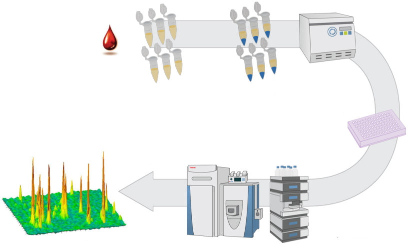
- Vertices: Correspond to random variables with normal distribution
- Edges: Correspond to the dependence structure
- Say $\mathbf{y} \sim \mathcal{N}_p(\mathbf{0}, \mathbf{\Sigma})$, and define $\mathbf{\Sigma}^{-1} \equiv \mathbf{\Omega}$. Then, for $a, b \in$ vertex set V, $a \neq b$

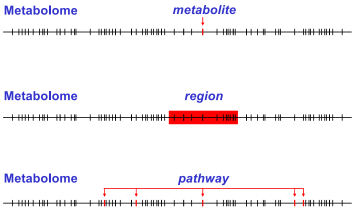
$$-\frac{\omega_{ab}}{\sqrt{\omega_{aa}\omega_{bb}}} = 0 \iff \omega_{ab} = 0 \iff a \perp\!\!\!\perp b | V \setminus \{a, b\} \iff a \not- b$$

$$\begin{bmatrix} \omega_{11} & \omega_{12} & \omega_{13} & \omega_{14} \\ \omega_{21} & \omega_{22} & 0 & 0 \\ \omega_{31} & 0 & \omega_{33} & \omega_{34} \\ \omega_{41} & 0 & \omega_{43} & \omega_{44} \end{bmatrix}$$



Challenge





Problem

- Let $\mathbf{S} \equiv \hat{\boldsymbol{\Sigma}}$ denote the sample covariance matrix on $\mathbf{y}_i$
- When $p \approx n$ or $p > n$, $\mathbf{S}$ is ill-behaved or singular
- The precision $\mathbf{S}^{-1} \equiv \hat{\boldsymbol{\Omega}}$ is then undefined

ℓ_2-Penalization: Proper ridge

Maximize

$$\underbrace{\ln|\boldsymbol{\Omega}| - \mathrm{tr}(\mathbf{S}\boldsymbol{\Omega})}_{\text{log}-\text{likelihood}} - \underbrace{\frac{\lambda}{2}\|\boldsymbol{\Omega} - \mathbf{T}\|_2^2}_{\ell_2-\text{penalty}}$$

- $\mathbf{T}$ denotes a p.d. symmetric target matrix
- $\lambda \in (0, \infty)$ denotes a penalty parameter

Analytic penalized ML estimator

$$\hat{\boldsymbol{\Omega}}(\lambda) = \left\{ \left[\lambda \mathbf{I}_p + \frac{1}{4}(\mathbf{S} - \lambda\mathbf{T})^2 \right]^{1/2} + \frac{1}{2}(\mathbf{S} - \lambda\mathbf{T}) \right\}^{-1}$$

Properties

Behavior

i. $\hat{\mathbf{\Omega}}(\lambda) \succ 0$, for all $\lambda \in (0, \infty)$;

ii. $\lim_{\lambda \to 0^+} \hat{\mathbf{\Omega}}(\lambda) = \mathbf{S}^{-1}$ if $p < n$;

iii. $\lim_{\lambda \to \infty} \hat{\mathbf{\Omega}}(\lambda) = \mathbf{T}$.

Consistency

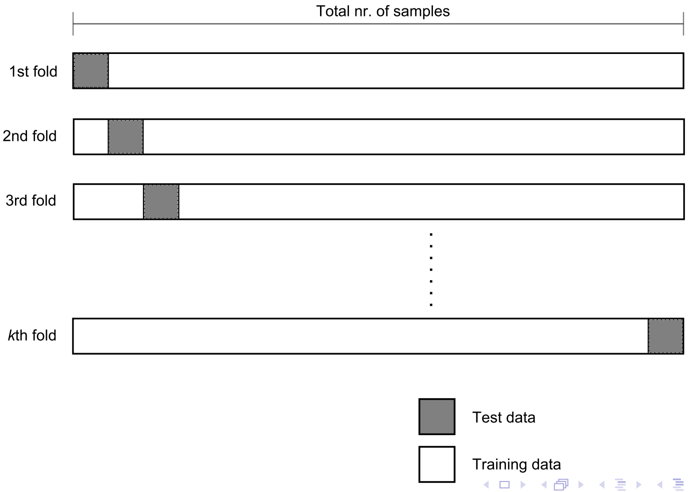
i. $\lim_{n \to \infty} \mathbb{E}\left[\hat{\mathbf{\Omega}}_n(\lambda_n)\right] \longrightarrow \lim_{n \to \infty} \mathbb{E}\left(\mathbf{S}_n^{-1}\right) = \mathbf{\Omega}$;

ii. $\lim_{n \to \infty} \mathbb{E}\left(\|\hat{\mathbf{\Omega}}_n(\lambda_n) - \mathbf{\Omega}\|_F^2\right) = 0$.

Choosing the penalty value

K-fold cross-validation (CV)

Single iteration of K-fold CV



Choosing the penalty value

K-fold CV score

$$\varphi^K(\lambda) = \sum_{k=1}^{K} n_k \left\{ -\ln |\hat{\mathbf{\Omega}}(\lambda)_{-k}| + \mathrm{tr}[\hat{\mathbf{\Omega}}(\lambda)_{-k}\mathbf{S}_k] \right\},$$

n_k is the size of subset k, for $k = 1, \ldots, K$ disjoint subsets;
$\mathbf{S}_k$ denotes the sample covariance matrix on *kth* test set;
$\hat{\mathbf{\Omega}}(\lambda)_{-k}$ denotes the estimated regularized precision matrix on kth training set

Choose

$\lambda^* = \arg\min_{\lambda \in \mathbb{R}^+} \varphi^K(\lambda)$

Efficiency

- Implementation uses `C++` at its core
- Makes use of a root-finding (Brent) algorithm
- Utilizes rotational equivariance property when possible

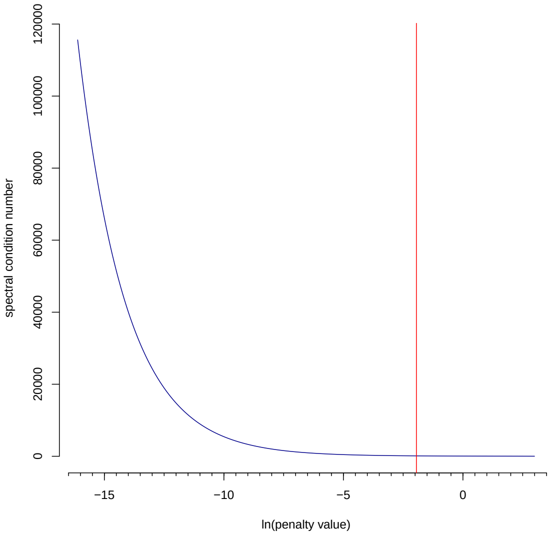
Exercise 2: Find an optimal precision matrix for the Class 2 AD data

```
optPenalty.kCVauto(Y,                 ⟵ data (matrix)
                   lambdaMin,         ⟵ min. λ
                   lambdaMax,         ⟵ max. λ
                   target)            ⟵ T (use default.target())
```

Returns list object

- `$optLambda`: Optimal penalty parameter
- `$optPrec`: Precision estimate under optimal penalty parameter

Assessing the Conditioning of the Estimate: Condition Number Plot

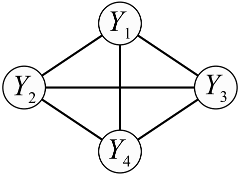


Exercise 3: Assess the conditioning of the optimal precision matrix

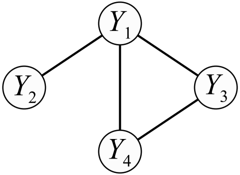
```
CNplot(S,              ←—— covariance matrix data
       lambdaMin,      ←—— min. λ
       lambdaMax,      ←—— max. λ
       step,           ←—— coarseness grid
       target,         ←—— T
       vertical,       ←—— logical
       value)
```

Support Determination

$$\begin{bmatrix} \omega_{11} & \omega_{12} & \omega_{13} & \omega_{14} \\ \omega_{21} & \omega_{22} & \omega_{23} & \omega_{24} \\ \omega_{31} & \omega_{32} & \omega_{33} & \omega_{34} \\ \omega_{41} & \omega_{42} & \omega_{43} & \omega_{44} \end{bmatrix}$$



$$\begin{bmatrix} \omega_{11} & \omega_{12} & \omega_{13} & \omega_{14} \\ \omega_{21} & \omega_{22} & 0 & 0 \\ \omega_{31} & 0 & \omega_{33} & \omega_{34} \\ \omega_{41} & 0 & \omega_{43} & \omega_{44} \end{bmatrix}$$



Support determination

Scaling

$\hat{\mathbf{P}}(\lambda)$: Regularized precision estimate scaled to partial correlation form

Assume

Nonredundant coefficients (indexed by $j < j'$) follow a mixture distribution:

$$f\left\{[\hat{\mathbf{P}}(\lambda^*)]_{jj'}\right\} = \eta_0 f_0\left\{[\hat{\mathbf{P}}(\lambda^*)]_{jj'};\kappa\right\} + (1-\eta_0)f_{\mathcal{E}}\left\{[\hat{\mathbf{P}}(\lambda^*)]_{jj'}\right\}$$

- $\eta_0 \in [0,1]$ is the mixture weight
- $f_0\{\cdot\}$ denotes the distribution of a null-edge
- $f_{\mathcal{E}}\{\cdot\}$ denotes the distribution of a present edge
- κ denotes degrees of freedom

Determine

$$P\left(Y_j \not\to Y_{j'} | [\hat{\mathbf{P}}(\lambda^*)]_{jj'}\right) = \frac{\hat{\eta}_0 f_0\left\{[\hat{\mathbf{P}}(\lambda^*)]_{jj'};\hat{\kappa}\right\}}{\hat{\eta}_0 f_0\left\{[\hat{\mathbf{P}}(\lambda^*)]_{jj'};\hat{\kappa}\right\} + (1-\hat{\eta}_0)\hat{f}_{\mathcal{E}}\left\{[\hat{\mathbf{P}}(\lambda^*)]_{jj'}\right\}}$$

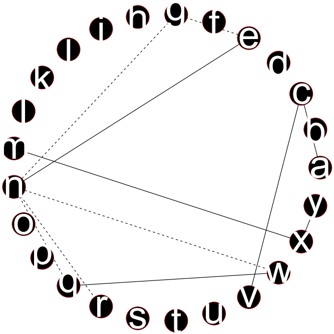
Exercise 4: Extract a network from the optimal precision matrix by retaining elements whose posterior probability of being present $\geq$ .999

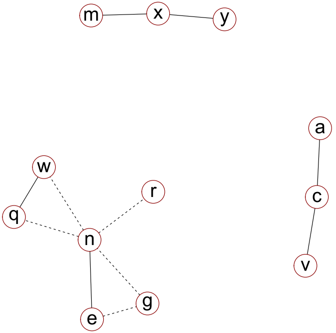
```
sparsify(P,           ←—— estimated precision matrix
         threshold,   ←—— type: "localFDR", "top"
         FDRcut)      ←—— cut-off for 1 - lFDR
```

Returns list object

- `$sparsePrecision`: Sparsified precision matrix
- `$sparseParCor`: Sparsified partial correlation matrix

Visualization





Things to Consider

- Layout
- Size of vertices
- colorings
- ...

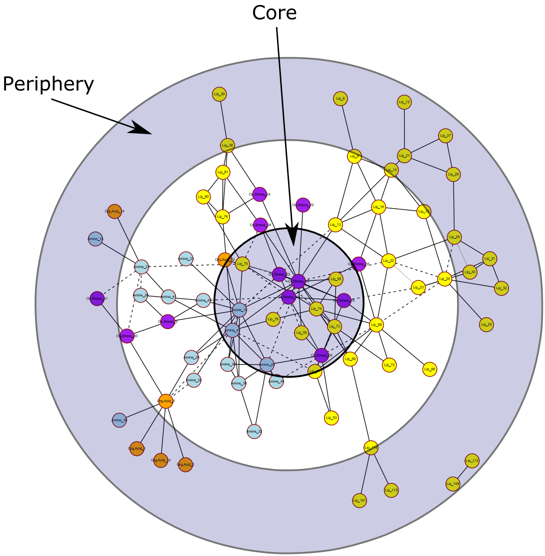
Exercise 5: Visualize the extracted network

`Ugraph(M,`	⟵ sparse matrix to be visualized
`type,`	⟵ `"plain", "fancy", "weighted"`
`lay,`	⟵ specifies layout
`Vsize,`	⟵ size of vertices
`Vcex,`	⟵ size vertex labels
`Vcolor,`	⟵ vertex color
`VBcolor,`	⟵ vertex boundary color
`VLcolor,`	⟵ color vertex labels
`prune,`	⟵ removes unconnected vertices?
`...)`	

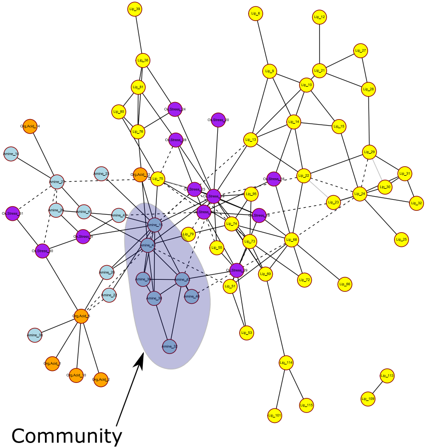
Returns matrix object

Containing the coordinates of the vertices in the given graph/network

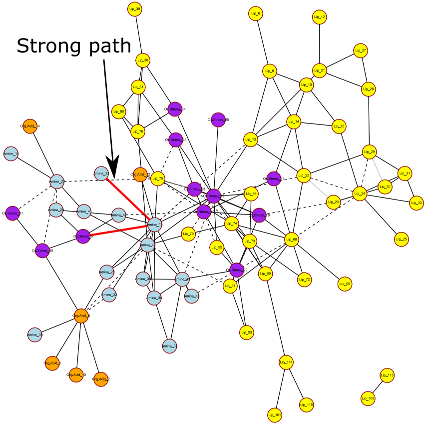
Analysis: Global Level



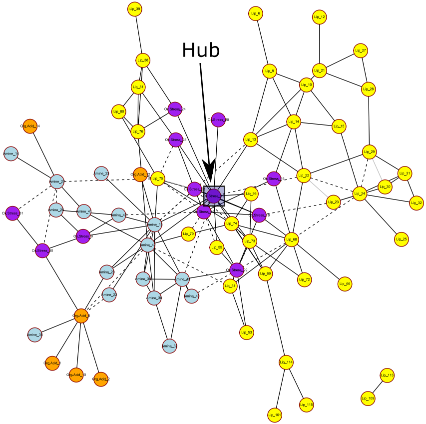
Analysis: Group Level



Analysis: Path Level



Analysis: Node Level



Node-Level Analysis: Centrality

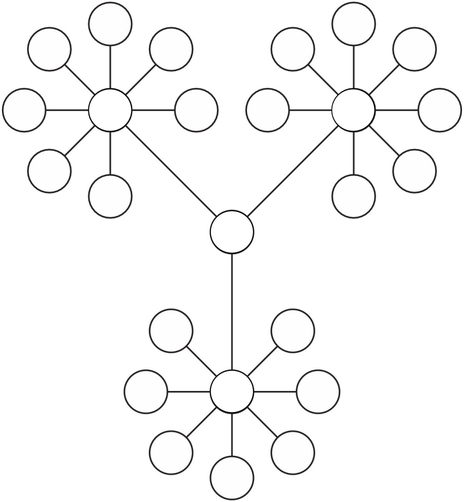


Illustration adapted from: http://shareablespaces.blogspot.nl/2010/03/social-networking-tools.html

Node-Level Analysis: Degree Centrality

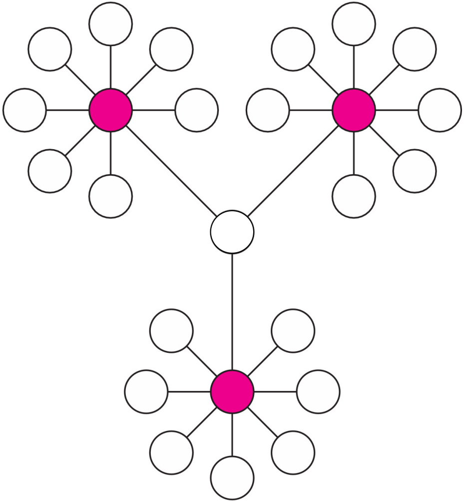


Illustration adapted from: http://shareablespaces.blogspot.nl/2010/03/social-networking-tools.html

Node-Level Analysis: Betweenness Centrality

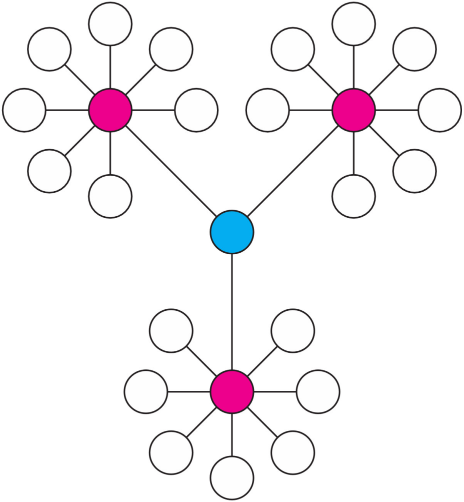


Illustration adapted from: http://shareablespaces.blogspot.nl/2010/03/social-networking-tools.html

Exercise 6: Find the nodes with the top degree and betweenness centralities

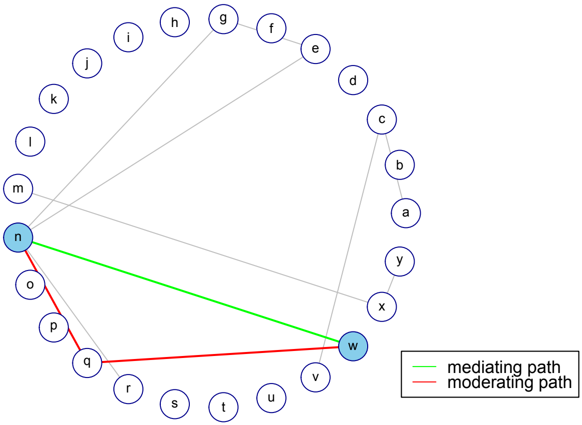
```
GGMnetworkStats(sparseP)
```

sparse matrix

Returns list object

- `$degree`: Degree centrality
- `$betweenness`: Betweenness centrality
- ...

Path-Level Analysis: Mediating and Moderating Paths



Exercise 7: Find 2 strongest paths between Amines 1 and 2

```
GGMpathStats(P0,    ← sparse precision matrix
             node1, ← endpoint 1
             node2, ← endpoint 2
             graph, ← logical, should graph be produced?
             ...)   ← arguments passed to Ugraph
```

Returns list object

- `$pathStats`: Matrix specifying paths
- ...

Group-Level Analysis: Finding Communities

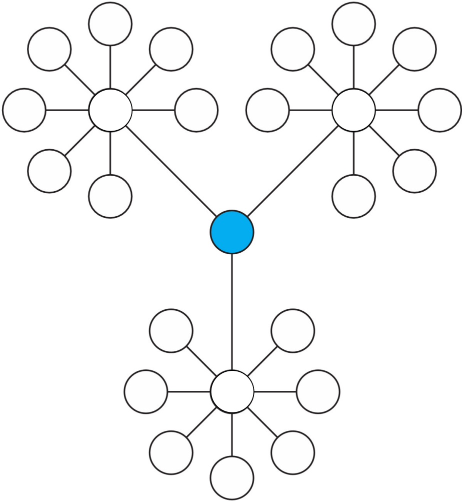


Illustration adapted from: http://shareablespaces.blogspot.nl/2010/03/social-networking-tools.html

Group-Level Analysis: Finding Communities

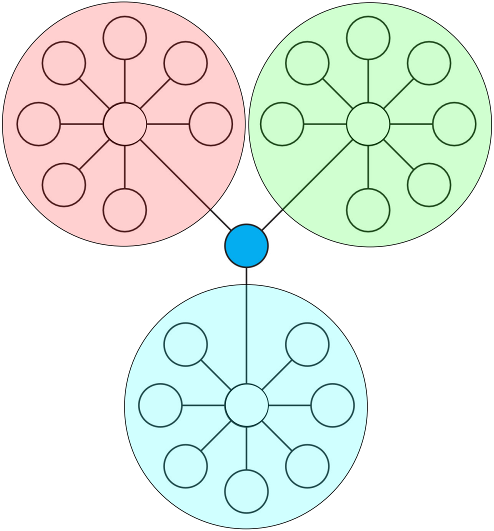


Illustration adapted from: http://shareablespaces.blogspot.nl/2010/03/social-networking-tools.html

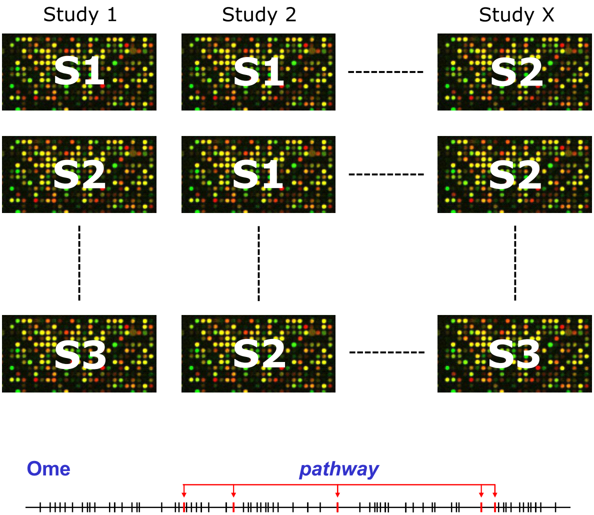
Exercise 8: Find and visualize communities for the extracted network

```
Communities(P,          <-- sparse matrix
            graph,      <-- logical, if TRUE, then graph is given
            lay,
            Vsize,
            Vcex,
            Vcolor,         arguments Ugraph
            VBcolor,
            VLcolor,
            main)
```

Returns list object

- `$membership`: Community membership for each feature
- `$modularityscore`: Modularity score

Multiple data classes



Situation

Data

- G classes of $(n_g \times p)$-dimensional data
- Classes defined by data sets and/or (subtypes of) diseases

Assumption

Precision matrices of constituent classes chiefly share the same structure but potentially differ in a number of locations of interest

Desire

Integrative or meta-analytic Gaussian graphical modeling

Targeted fused ridge estimation: General Formulation

Maximize

$$\underbrace{\mathcal{L}(\{\mathbf{\Omega}_g\};\{\mathbf{S}_g\})}_{\text{log-likelihood}} - \sum_g \underbrace{\frac{\lambda_{gg}}{2}\left\|\mathbf{\Omega}_g - \mathbf{T}_g\right\|_F^2}_{\text{ridge-penalty}} - \sum_{g_1,g_2} \underbrace{\frac{\lambda_{g_1g_2}}{4}\left\|(\mathbf{\Omega}_{g_1} - \mathbf{T}_{g_1}) - (\mathbf{\Omega}_{g_2} - \mathbf{T}_{g_2})\right\|_F^2}_{\text{fusion-penalty}}$$

- $\mathbf{T}_g$ indicate class-specific target matrices
- $\lambda_{gg} \in (0, \infty)$ denote class-specific ridge penalty parameters
- $\lambda_{g_1g_2} \in [0, \infty)$ denote pair-specific fusion penalty parameters, $\lambda_{g_1g_2} = \lambda_{g_2g_1}$

Penalty matrix

All penalties can be collected into a non-negative symmetric matrix $\mathbf{\Lambda} = [\lambda_{g_1g_2}]$

Targeted fused ridge estimation

Maximizing argument for class g_0

$$\hat{\mathbf{\Omega}}_{g_0}(\mathbf{\Lambda}, \{\mathbf{\Omega}_g\}_{g \neq g_0}) = \left\{ \left[\bar{\lambda}_{g_0} \mathbf{I}_p + \frac{1}{4} (\bar{\mathbf{S}}_{g_0} - \bar{\lambda}_{g_0} \mathbf{T}_{g_0})^2 \right]^{1/2} + \frac{1}{2} (\bar{\mathbf{S}}_{g_0} - \bar{\lambda}_{g_0} \mathbf{T}_{g_0}) \right\}^{-1},$$

where

$$\bar{\mathbf{S}}_{g_0} = \mathbf{S}_{g_0} - \sum_{g \neq g_0} \frac{\lambda_{gg_0}}{n_{g_0}} (\mathbf{\Omega}_g - \mathbf{T}_g), \quad \text{and} \quad \bar{\lambda}_{g_0} = \frac{\sum_g \lambda_{gg_0}}{n_{g_0}}$$

Properties

Behavior

i. $\hat{\mathbf{\Omega}}_g \succ \mathbf{0}$ for all $\lambda_{gg} \in (0, \infty)$;

ii. $\lim\limits_{\lambda_{gg} \to 0^+} \hat{\mathbf{\Omega}}_g = \mathbf{S}_g^{-1}$ if $\sum_{g' \neq g} \lambda_{gg'} = 0$ and $p \leq n_g$;

iii. $\lim\limits_{\lambda_{gg} \to \infty} \hat{\mathbf{\Omega}}_g = \mathbf{T}_g$ if $\lambda_{gg'} < \infty$ for all $g' \neq g$;

iv. $\lim\limits_{\lambda_{g_1 g_2} \to \infty} (\hat{\mathbf{\Omega}}_{g_1} - \mathbf{T}_{g_1}) = \lim\limits_{\lambda_{g_1 g_2} \to \infty} (\hat{\mathbf{\Omega}}_{g_2} - \mathbf{T}_{g_2})$ if $\lambda_{g_1' g_2'} < \infty$ for all $\{g_1', g_2'\} \neq \{g_1, g_2\}$.

Block coordinate ascent

Input:
Sufficient data: $(\mathbf{S}_1, n_1), \ldots, (\mathbf{S}_G, n_G)$
Penalty matrix: $\mathbf{\Lambda}$
Convergence criterion: $\varepsilon > 0$
Output:
Estimates: $\hat{\mathbf{\Omega}}_1, \ldots, \hat{\mathbf{\Omega}}_G$
procedure $\textsc{ridgeP.fused}(\mathbf{S}_1, \ldots, \mathbf{S}_G, n_1, \ldots, n_G, \mathbf{\Lambda}, \varepsilon)$
    Initialize: $\hat{\mathbf{\Omega}}_g^{(0)}$ for all g.
    for $c = 1, 2, 3, \ldots$ **do**
        for $g = 1, 2, \ldots, G$ **do**
            Update $\hat{\mathbf{\Omega}}_g^{(c)} := \hat{\mathbf{\Omega}}_g\left(\mathbf{\Lambda}, \hat{\mathbf{\Omega}}_1^{(c)}, \ldots, \hat{\mathbf{\Omega}}_{g-1}^{(c)}, \hat{\mathbf{\Omega}}_{g+1}^{(c-1)}, \ldots, \hat{\mathbf{\Omega}}_G^{(c-1)}\right)$
        end for
        if $\max_g \left\{ \frac{\|\hat{\mathbf{\Omega}}_g^{(c)} - \hat{\mathbf{\Omega}}_g^{(c-1)}\|_F^2}{\|\hat{\mathbf{\Omega}}_g^{(c)}\|_F^2} \right\} < \varepsilon$ **then**
            return $\left(\hat{\mathbf{\Omega}}_1^{(c)}, \ldots, \hat{\mathbf{\Omega}}_G^{(c)}\right)$
        end if
    end for
end procedure

Functional analogues

Core	Fused
`ridgeP`	`ridgeP.fused`
`optPenalty`	`optPenalty.fused`
`sparsify`	`sparsify.fused`
`GGMnetworkStats`	`GGMnetworkStats.fused`
`GGMpathStats`	`GGMpathStats.fused`

Exercise 9: Construct lists of class-specific target and data matrices

```
## Subset
ADclass1 <- ADmetabolites[, sampleInfo$ApoEClass == "Class 1"]
ADclass2 <- ADmetabolites[, sampleInfo$ApoEClass == "Class 2"]

## Transpose and scale data
ADclass1 <- scale(t(ADclass1))
ADclass2 <- scale(t(ADclass2))

## Correlations for subsets
rAD1 <- cor(ADclass1)
rAD2 <- cor(ADclass2)

## Constructing list of correlation matrices
Rlist = list(rAD1 = rAD1, rAD2 = rAD2)
samps = c(dim(ADclass1)[1], dim(ADclass2)[1])

## Constructing list of target matrices and data
Tlist <- default.target.fused(Slist = Rlist, ns = samps, type = "DUPV")
Ylist <- list(AD1data = ADclass1, AD2data = ADclass2)
```

Exercise 10: Find optimal precision matrices for Class 1 and Class 2 AD data

```
optPenalty.fused(Ylist,      ←— list of data matrices
                 Tlist,      ←— list of target matrices
                 cv.method)  ←— CV method: choose LOOCV
```

Returns list object

- `$lambda.unique`: Optimal penalty parameters
- `$Plist`: List of precision matrices under optimal penalty parameters
- ...

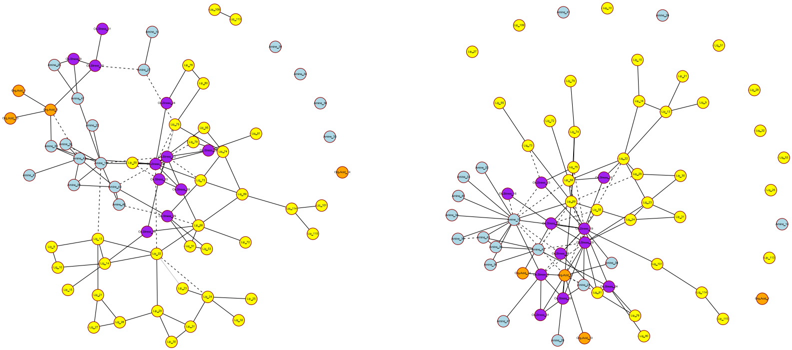
Exercise 11: Extract class-specific networks on the basis of local FDR thresholding

```
sparsify.fused(Plist,       ←—— list of estimated precision matrices
               threshold,   ←—— type: "localFDR", "top"
               FDRcut)      ←—— cut-off for 1 - lFDR
```

Returns list object for each class

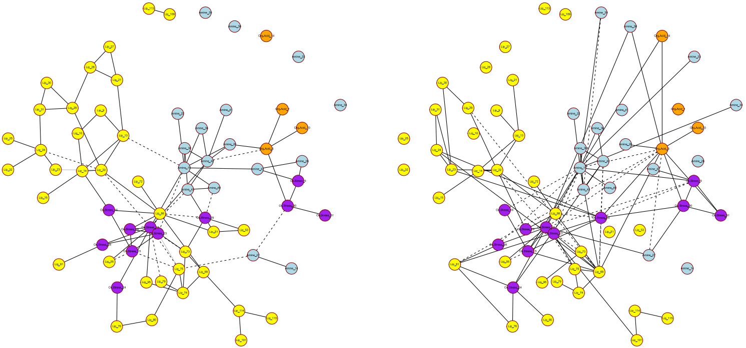
- `$sparsePrecision`: Sparsified precision matrix
- `$sparseParCor`: Sparsified partial correlation matrix

Visualization



Two class-specific networks, independently visualized with the FR algorithm

Visualization



Coordinate retainment supports visual comparison

Same two class-specific networks, visualized with the same node-coordinates

Exercise 12: Visualize the retained networks in the same coordinates

```
Ugraph(M,
        type,
        lay,
        coords,
        Vsize,
        Vcex,
        Vcolor,
        VBcolor,
        VLcolor,
        prune
        ...)
```

if `lay = NULL`, then
layout according to coordinates

Returns matrix object

- Containing coordinates of layout

Tips

- Use the `union` function.
- Use coordinates return object.

Exercise 13: Compare the top node-degrees for the class-specific networks

```
GGMnetworkStats.fused(Plist)
```

A list of sparse matrices

Returns `data.frame`

Names of `Plist` are prefixed to column-names

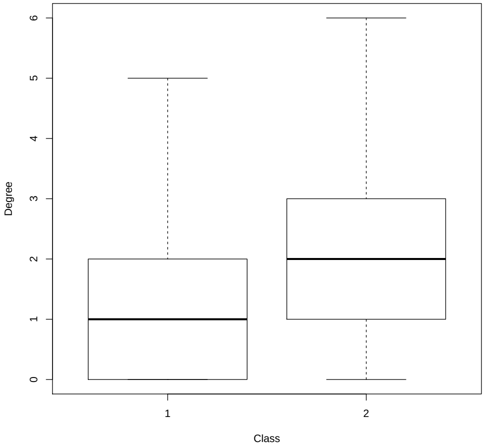
Exercise 14: Find and visualize communities for the class-specific networks

```
Communities(P,          <-- sparse matrix
            graph,      <-- logical, if TRUE, then graph is given
            lay,
            Vsize,
            Vcex,
            Vcolor,         arguments Ugraph
            VBcolor,
            VLcolor,
            main)
```

Returns list object

- `$membership`: Community membership for each feature
- `$modularityscore`: Modularity score

Global Analysis: Degree Distributions



Global Analysis: Entropy

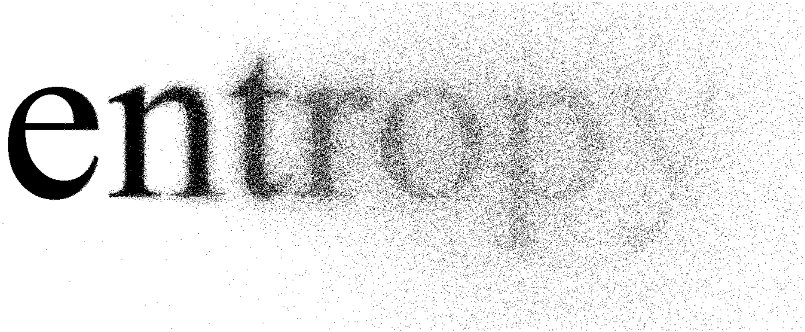


Illustration adapted from: http://creepypasta.wikia.com/wiki/Entropy

Exercise 15: Compare either the degree distributions or the entropies for the class-specific networks

Comparing degree distributions

Can be done with simple test, such as the Wilcoxon Signed Rank Test

Comparing entropies

```
library(sigaR)

entropyTest(Y,       ←—— data matrix, samples in rows
            id,      ←—— class indicator (coded 0,1)
            nPerm,   ←—— number of permutations
            method)  ←—— distributional assumption: use "knn"
```

Entropy test returns test information

`summary()`

- Brent, R.P. (1971). "An Algorithm with Guaranteed Convergence for Finding a Zero of a Function". Computer Journal, 14: 422-425.
- Csardi, G. & Nepusz, T. (2006). "The igraph software package for complex network research". InterJournal, Complex Systems 1695. http://igraph.sf.net
- Fruchterman, T.M.J. & Reingold, E.M. (1991). "Graph Drawing by Force-Directed Placement". Software: Practice & Experience, 21: 1129-1164.
- Jones, B. & West, M. (2005). "Covariance Decomposition in Undirected Gaussian Graphical Models". Biometrika, 92: 779-786.
- Newman, M.E.J. (2010). Networks: an introduction. Oxford University Press.
- Newman, M.E.J. & Girvan, M. (2004). "Finding and evaluating community structure in networks". Physical Review E, 69: 026113.
- Schäfer, J. & Strimmer, K. (2005a). "A shrinkage approach to large-scale covariance matrix estimation and implications for functional genomics". Statistical Applications in Genetics and Molecular Biology, 4: art. 32.
- Schäfer, J. & Strimmer, K. (2005b). "An empirical Bayes approach to inferring large-scale gene association networks". Bioinformatics, 21: 754764.
- van Wieringen, W.N. & van der Vaart, A.W. (2011). "Statistical analysis of the cancer cells molecular entropy using high-throughput data". Bioinformatics, 27: 556-563.

Manual/Download

- Peeters, C.F.W., Bilgrau, A.E., & van Wieringen, W.N. (2017). "rags2ridges: Ridge Estimation of Precision Matrices from High-Dimensional Data". R package, version 2.2. URL: https://cran.r-project.org/package=rags2ridges.

Theory/Methodology

- Bilgrau*, A.E., Peeters*, C.F.W., Eriksen, P.S., Bøgsted, M., & van Wieringen, W.N. (2015). "Targeted Fused Ridge Estimation of Inverse Covariance Matrices from Multiple High-Dimensional Data Classes". arXiv:1509.07982v1 [stat.ME].
- Peeters, C.F.W., van Wieringen, W.N., & van de Wiel, M.A. (in preparation). "Directed Cyclic Mixed Graph Modeling for High-Dimensional Omic Data Integration".
- van Wieringen, W.N. & Peeters, C.F.W. (2016). "Ridge Estimation of Inverse Covariance Matrices from High-Dimensional Data". Computational Statistics & Data Analysis, 103: 284-303. arXiv:1403.0904v3 [stat.ME].

Software

- Peeters, C.F.W., van de Wiel, M.A., & van Wieringen, W.N. (2016) "The Spectral Condition Number Plot for Regularization Parameter Determination". arXiv:1608.04123v1 [stat.CO].
- van Wieringen, W.N. & Peeters, C.F.W. (2015). "Application of a New Ridge Estimator of the Inverse Covariance Matrix to the Reconstruction of Gene-Gene Interaction Networks". In: di Serio, C., Lio, P., Nonis, A., and Tagliaferri, R. (Eds.) 'Computational Intelligence Methods for Bioinformatics and Biostatistics'. Lecture Notes in Computer Science, vol. 8623. Springer, pp. 170–179.