

# A General Framework for Weighted Gene Co-Expression Network Analysis

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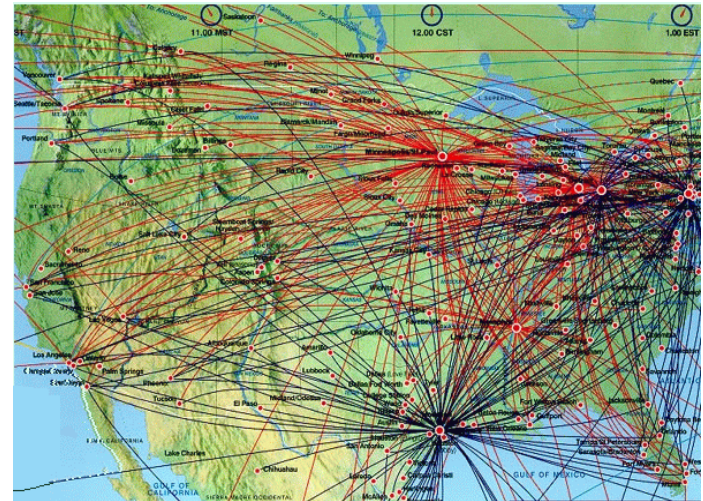
# Content

- Novel statistical approach for analyzing microarray data:
  - weighted gene co-expression network analysis
- Empirical evidence that it matters in practice
  - Application 1: identifying cancer genes
  - Application 2: comparing chimp and human brain

**Does this map tell you  
which cities are  
important?**



**This one does!**



***The nodes with the largest number of links  
(connections) are most important!***

# Background

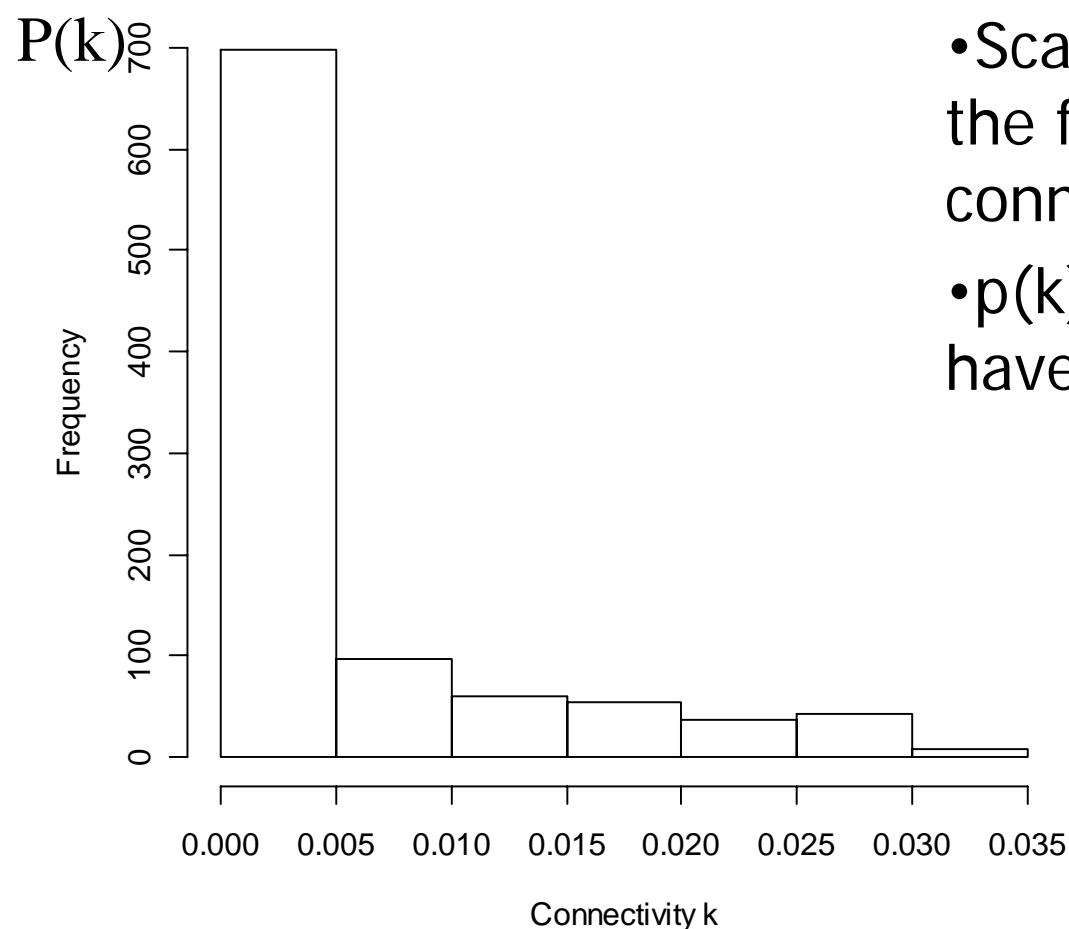
- Network based methods have been found useful in many domains,
  - protein interaction networks
  - the world wide web
  - social interaction networks
  - OUR FOCUS: gene co-expression networks

Scale free topology is a fundamental property of such networks (Barabasi et al)

- It entails the presence of hub nodes that are connected to a large number of other nodes
- Such networks are robust with respect to the random deletion of nodes but are sensitive to the targeted attack on hub nodes
- It has been demonstrated that metabolic networks exhibit scale free topology at least approximately.

# $P(k)$ vs $k$ in scale free networks

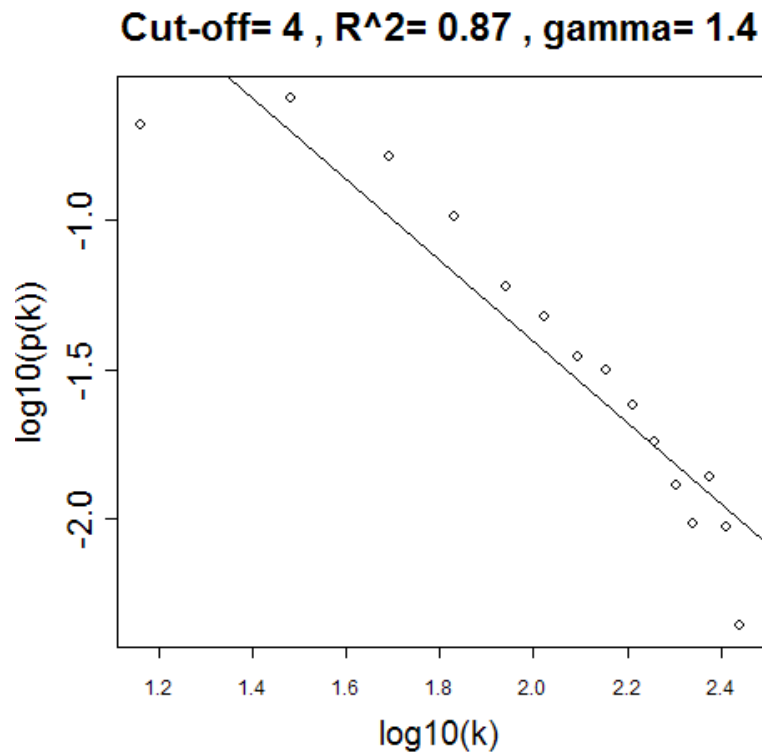
Frequency Distribution of Connectivity



- Scale Free Topology refers to the frequency distribution of the connectivity  $k$
- $p(k)$  = proportion of nodes that have connectivity  $k$

# How to check Scale Free Topology?

Idea: Log transformation  $p(k)$  and  $k$  and look at scatter plots



Linear model fitting  $R^2$   
index can be used to quantify  
goodness of fit

# Generalizing the notion of scale free topology

Motivation of generalizations: using weak general assumptions, we have proven that gene co-expression networks satisfy these distributions approximately.

Barabasi (1999)

$$ScaleFree \hat{=} \log(p(k)) = c_0 + c_1 \log(k)$$

Csanyi-Szendroi (2004)

$$ExponentiallyTruncatedSFT \hat{=} \log(p(k)) = c_0 + c_1 \log(k) + c_2 k$$

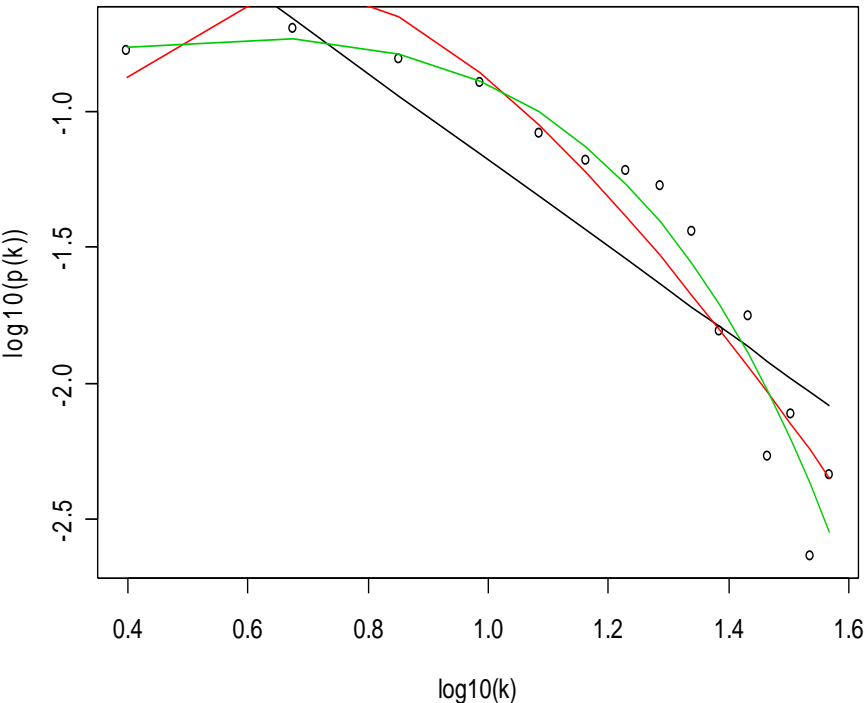
Horvath, Dong (2005)

$$LogLogSFT \hat{=} \log(p(k)) = c_0 + c_1 \log(k) + c_2 \log(\log(k))$$



# Checking Scale Free Topology in the Yeast Network

power=6 , slope= -1.6 , scaleR2= 0.73 , loglogR2= 0.95 , trunc.R^2= 0.9



- Black=Scale Free
- Red=Exp. Truncated
- Green=Log Log SFT

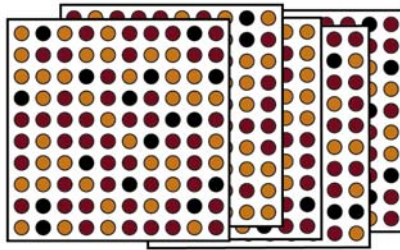
How to define a gene co-expression network?

# Gene Co-expression Networks

- In gene co-expression networks, each gene corresponds to a node.
- Two genes are connected by an edge if their expression values are highly correlated.
- Definition of “high” correlation is somewhat tricky
  - One can use statistical significance...
  - But we propose a criterion for picking threshold parameter: scale free topology criterion.

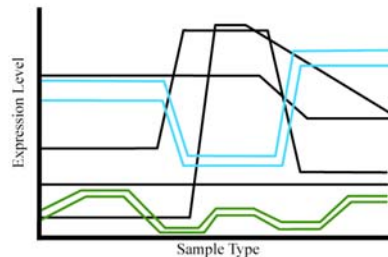
Figure 1

A Array Data



Data contains correlations

B Correlation Analysis



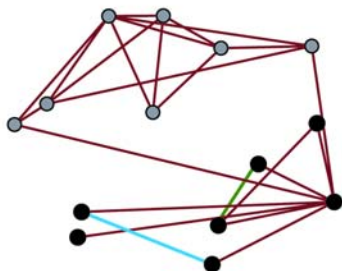
Correlation coefficients for all genes

C Correlation Matrix

	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	G11	G12	G13	G14
G1	1	0.9	0.9	0.9	0.9	0.8	0.9	0.1	0.9	0.1	0.1	0.8	0.2	0.2
G2	0.9	1	0.9	0.3	0.3	0.7	0.0	0.5	0.3	0.1	0.1	0.2	0.4	0.3
G3	0.9	0.9	1	0.9	0.0	0.2	0.5	0.7	0.6	0.5	0.2	0.6	0.1	0.0
G4	0.9	0.3	0.9	1	0.5	0.3	0.6	0.3	0.0	0.5	0.1	0.2	0.2	0.6
G5	0.9	0.3	0.0	0.5	1	0.1	0.6	0.1	0.3	0.3	0.3	0.5	0.2	0.5
G6	0.8	0.7	0.2	0.3	0.1	1	0.9	0.2	0.1	0.1	0.5	0.3	0.1	0.1
G7	0.9	0.0	0.5	0.6	0.6	0.9	1	0.3	0.1	0.5	0.1	0.3	0.5	0.2
G8	0.1	0.5	0.7	0.3	0.1	0.2	0.3	1	0.9	0.9	0.9	0.8	0.9	0.9
G9	0.9	0.3	0.6	0.0	0.3	0.1	0.1	0.9	1	0.8	0.1	0.3	0.5	0.3
G10	0.1	0.1	0.5	0.5	0.3	0.1	0.5	0.9	0.8	1	0.8	1.0	0.2	0.3
G11	0.1	0.1	0.2	0.1	0.3	0.5	0.1	0.9	0.1	0.8	1	0.5	0.8	0.9
G12	0.8	0.2	0.6	0.2	0.5	0.3	0.3	0.8	0.3	1.0	0.5	1	0.8	0.1
G13	0.2	0.4	0.1	0.2	0.2	0.1	0.5	0.8	0.5	0.2	0.8	0.8	1	0.9
G14	0.2	0.3	0.0	0.6	0.5	0.1	0.2	0.9	0.3	0.3	0.9	0.1	0.9	1

Convert into Adjacency Matrix and Network

D Coexpression Network

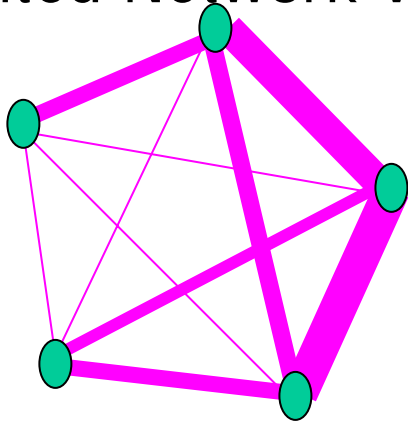


# Steps for constructing a simple, unweighted co-expression network

- A) Microarray gene expression data
- B) Measure concordance of gene expression with a Pearson correlation
- C) The Pearson correlation matrix is dichotomized to arrive at an adjacency matrix. Binary values in the adjacency matrix correspond to an unweighted network.
- D) The adjacency matrix can be visualized by a graph.

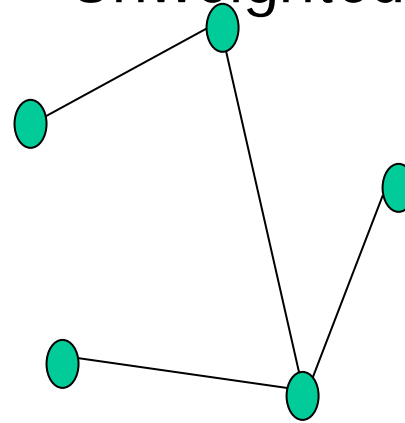
# Our 'holistic' view....

Weighted Network View



- All genes are connected
- Connection Widths=Connection strengths

Unweighted View



- Some genes are connected  
All connections are equal

Hard thresholding may lead to an information loss.

# Mathematical Definition of an Undirected Network

# Network=Adjacency Matrix

- A network can be represented by an adjacency matrix,  $A=[a_{ij}]$ , that encodes whether/how a pair of nodes is connected.
  - A is a symmetric matrix with entries in  $[0,1]$
  - For unweighted network, entries are 1 or 0 depending on whether or not 2 nodes are adjacent (connected)
  - For weighted networks, the adjacency matrix reports the connection strength between gene pairs

# Generalized Connectivity

- Gene connectivity = row sum of the adjacency matrix
  - For unweighted networks=number of direct neighbors
  - For weighted networks= sum of connection strengths to other nodes

$$k_i = \sum_j a_{ij}$$



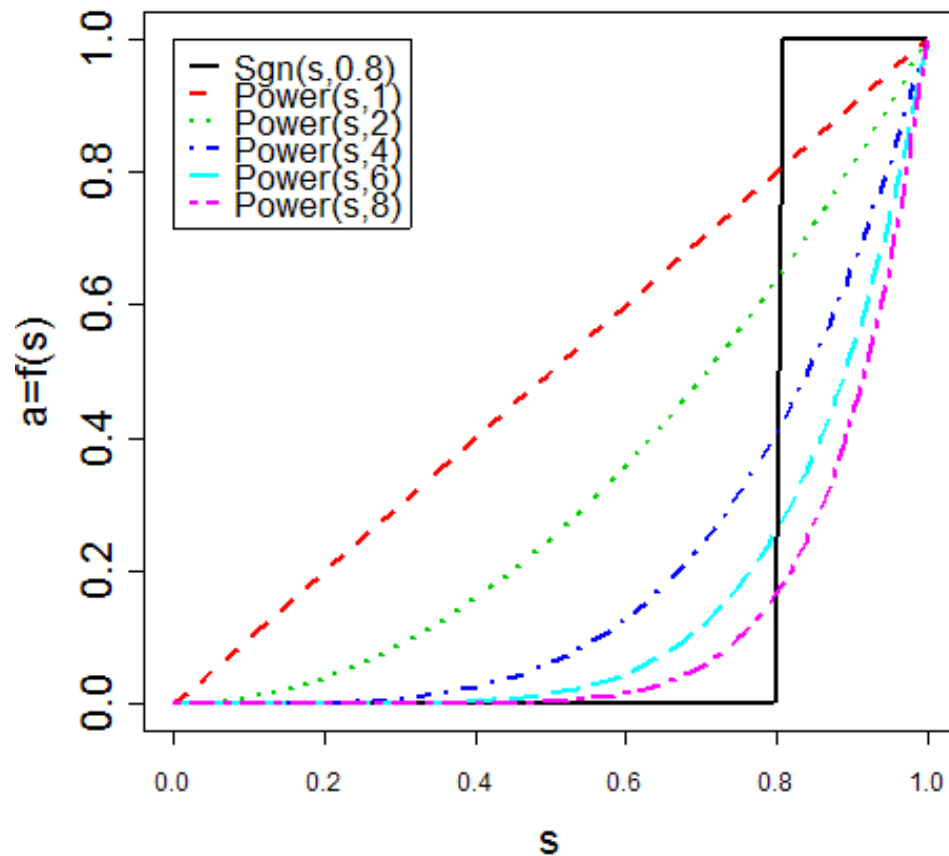
How to construct a  
**weighted** gene co-expression  
network?

# Using an adjacency function to define a network

- Measure co-expression by a similarity  $s(i,j)$  in  $[0,1]$   
e.g. absolute value of the Pearson correlation
- Define an adjacency matrix as  $A(i,j)$  using an adjacency function  $AF(s(i,j))$
- $AF$  is a monotonic function from  $[0,1]$  onto  $[0,1]$
- Here we consider 2 classes of  $AF$ s
  - Step function  $AF(s) = I(s > \tau)$  with parameter  $\tau$   
(unweighted network)
  - Power function  $AF(s) = s^b$  with parameter  $b$
- The choice of the  $AF$  parameters ( $\tau, b$ ) determines the properties of the network.

# Comparing the power adjacency functions with the step function

Adjacency  
=connection strength



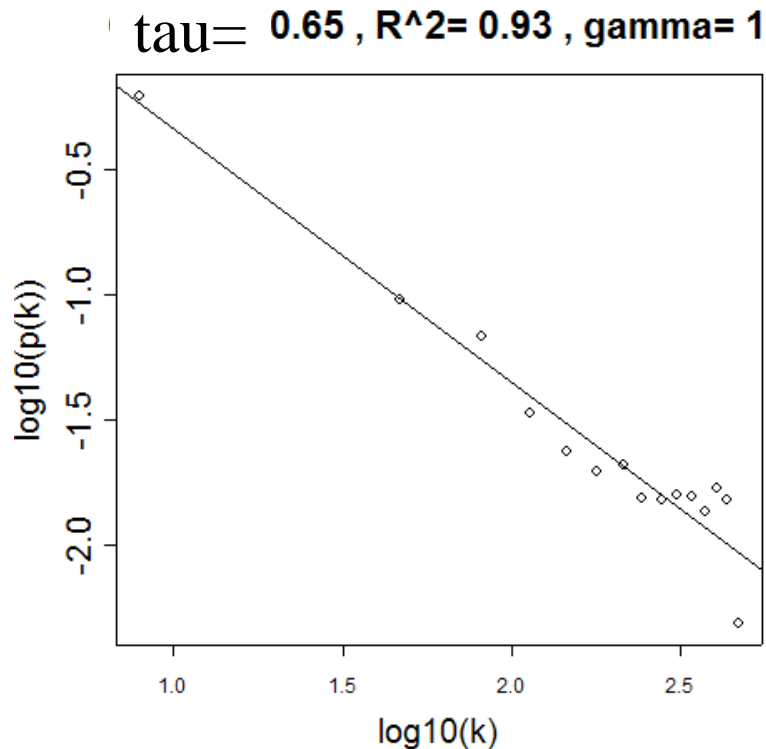
Gene Co-expression Similarity

# The scale free topology criterion for choosing the parameter values of an adjacency function.

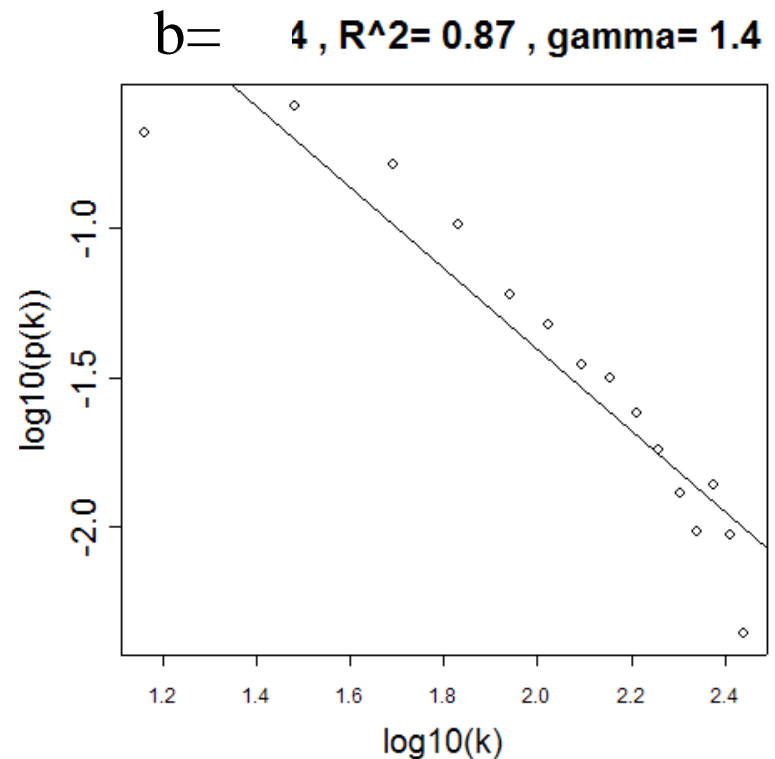
- A) CONSIDER ONLY THOSE PARAMETER VALUES THAT RESULT IN APPROXIMATE SCALE FREE TOPOLOGY
  - B) SELECT THE PARAMETERS THAT RESULT IN THE HIGHEST MEAN NUMBER OF CONNECTIONS
- Criterion A is motivated by the finding that most metabolic networks (including gene co-expression networks, protein-protein interaction networks and cellular networks) have been found to exhibit a scale free topology
  - Criterion B leads to high power for detecting modules (clusters of genes) and hub genes.

# Criterion A is measured by the linear model fitting index $R^2$

Step AF (tau)



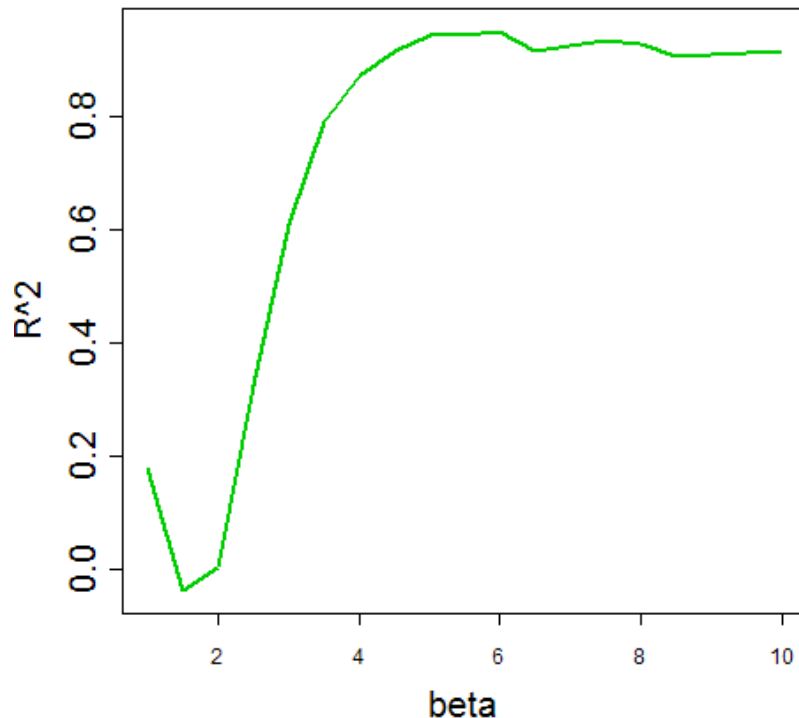
Power AF (b)



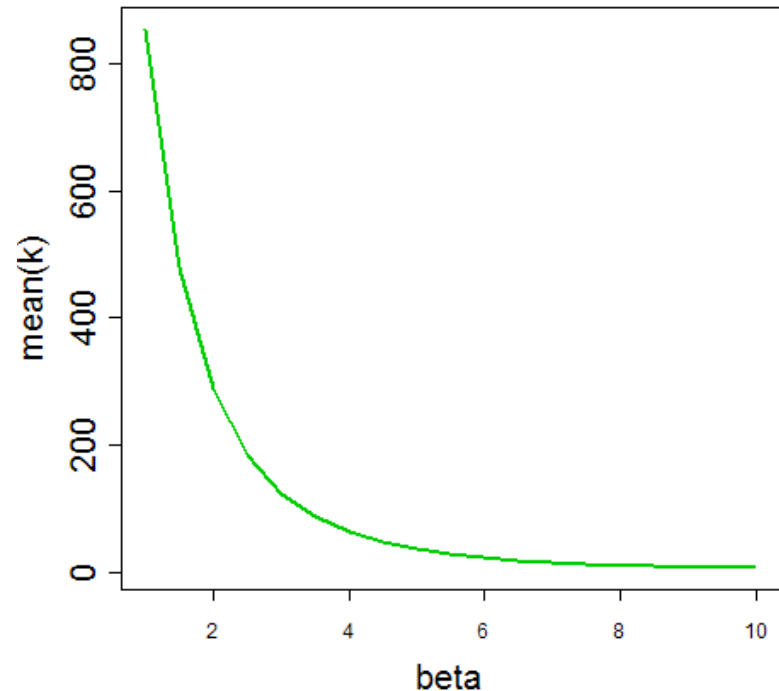
# Trade-off between criterion A ( $R^2$ ) and criterion B (mean no. of connections) when varying the power $b$

Power  $AF(s)=s^b$

criterion A: SFT model fit  $R^2$



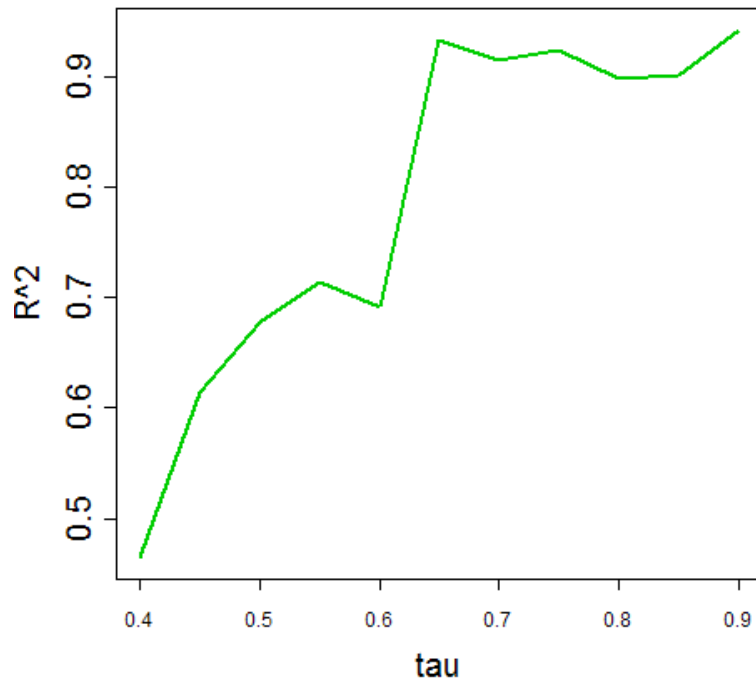
criterion B: mean connectivity



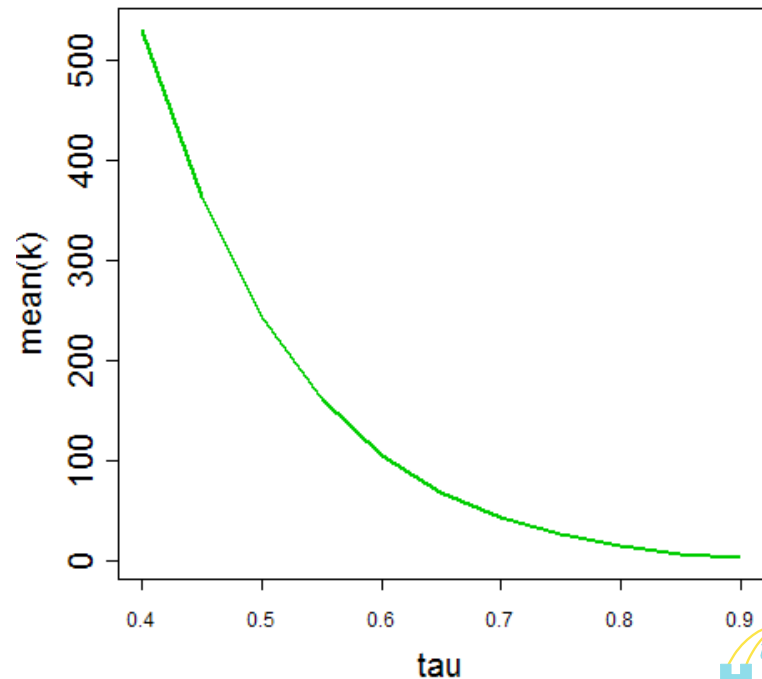
# Trade-off between criterion A and B when varying tau

Step Function:  $I(s > \tau)$

criterion A



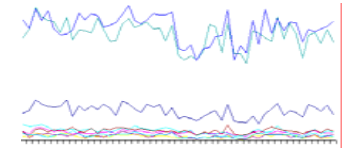
criterion B



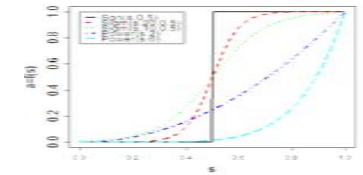
# General Framework for Network Analysis



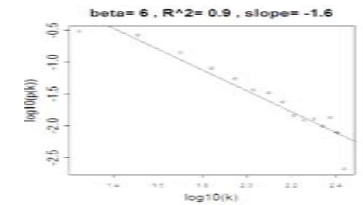
Define a Gene Co-expression Similarity



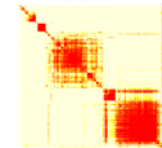
Define a Family of Adjacency Functions



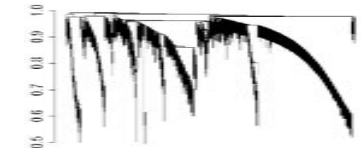
Determine the AF Parameters



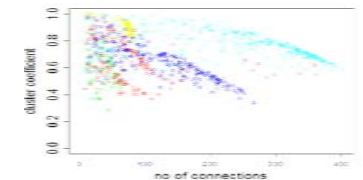
Define a Measure of Node Dissimilarity



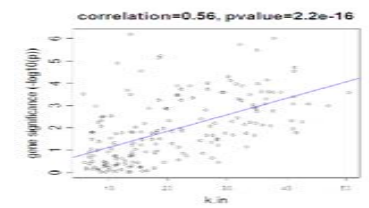
Identify Network Modules (Clustering)



Relate Network Concepts to Each Other



Relate the Network Concepts to External Gene or Sample Information



# How to measure distance in a network?

- Mathematical Answer: Geodesics
  - length of shortest path connecting 2 nodes
- Biological Answer: look at shared neighbors
  - Intuition: if 2 people share the same friends they are close in a social network
  - Use the topological overlap measure based distance proposed by Ravasz et al (2002)

Topological Overlap leads to  
a network distance measure  
(Ravasz et al 2002)

$$TOM_{ij} = \frac{\sum_u a_{iu} a_{uj} + a_{ij}}{\min(k_i, k_j) + 1 - a_{ij}}$$

$$DistTOM_{ij} = 1 - TOM_{ij}$$

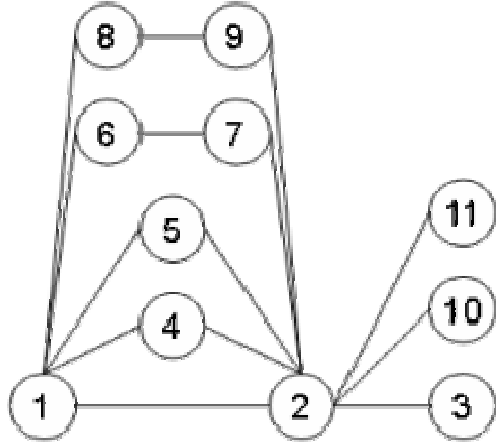
- Generalized in Zhang and Horvath (2005) to the case of weighted networks

# The Generalized Topological Overlap

Andy Yip, S.Horvath

# The general topological overlap matrix

a.



b.

$N_n(i)$	$i = 1$	$i = 2$	$i = 3$
$m = 1$	2,4,5,6,8	1,3,4,5,7,9,10,11	2
$m = 2$	2,3,4,5,6,7,8,9,10,11	1,3,4,5,6,7,8,9,10,11	1,2,4,5,7,9,10,11

c.

$t_g^{[m]}$	$(i, j) = (1, 2)$	$(i, j) = (1, 3)$	$(i, j) = (2, 3)$
$m = 0$	1	0	1
$m = 1$	3/5	1/2	1
$m = 2$	1	7/9	1

$$TOM(i, j) = \frac{|N_1(i) \cap N_1(j)| + a_{ij}}{\min(|N_1(i)|, |N_1(j)|) + 1 - a_{ij}}$$

$N_1(i)$  denotes the set of neighbors of node  $i$

$|\cdot|$  measures the cardinality

We have re-interpreted the TOM measure as the “normalized” proportion of genes that are in both node neighborhoods. This allows for a straightforward generalization to “larger” neighborhoods.

Yip, Horvath (2005)

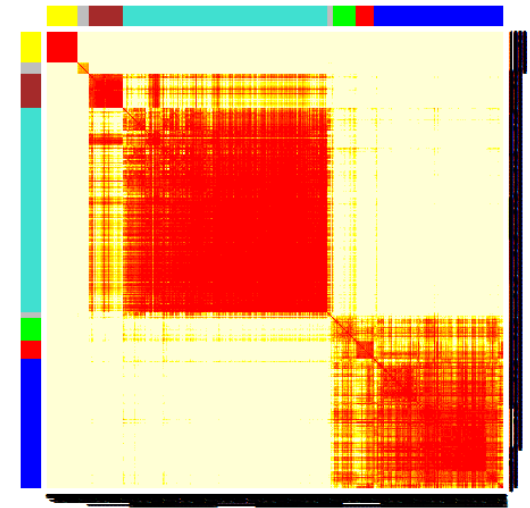
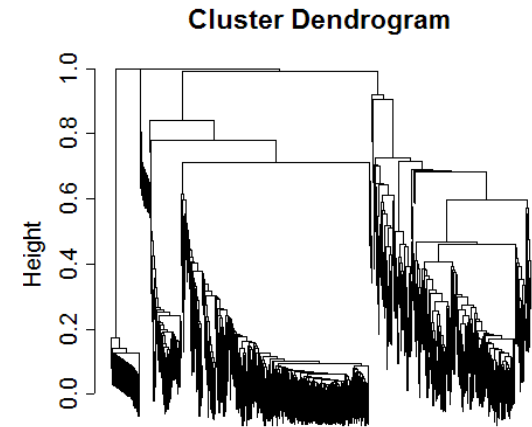
Defining Gene Modules  
=sets of tightly co-regulated genes

# Module Identification based on the notion of topological overlap

- One important aim of metabolic network analysis is to detect subsets of nodes (modules) that are tightly connected to each other.
- We adopt the definition of Ravasz et al (2002): modules are groups of nodes that have high topological overlap.

# Steps for defining gene modules

- Define a dissimilarity measure between the genes.
  - Standard Choice:  $\text{dissim}(i,j)=1-\text{abs}(\text{correlation})$
  - Choice by network community=1-Topological Overlap Matrix (TOM)
    - Used here
- Use the dissimilarity in hierarchical clustering
- Define modules as branches of the hierarchical clustering tree
- Visualize the modules and the clustering results in a heatmap plot



Heatmap

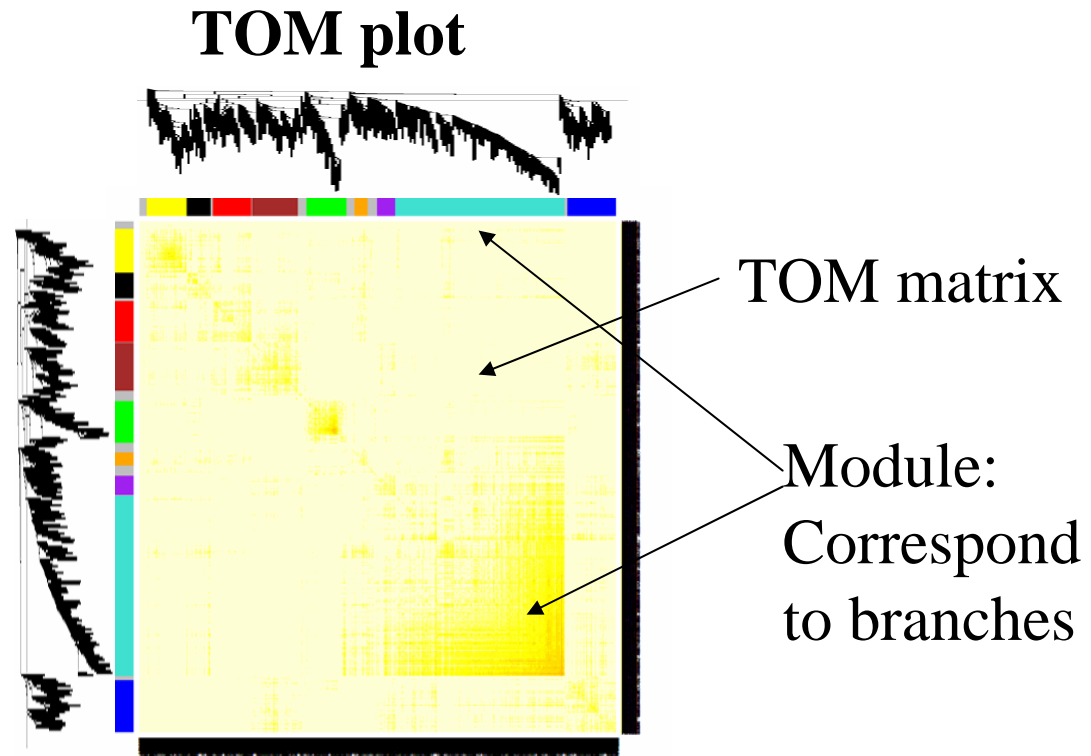


# Using the TOM matrix to cluster genes

- To group nodes with high topological overlap into modules (clusters), we typically use average linkage hierarchical clustering coupled with the TOM distance measure.
- Once a dendrogram is obtained from a hierarchical clustering method, we choose a height cutoff to arrive at a clustering.
  - Here modules correspond to branches of the dendrogram

Genes correspond to  
rows and columns

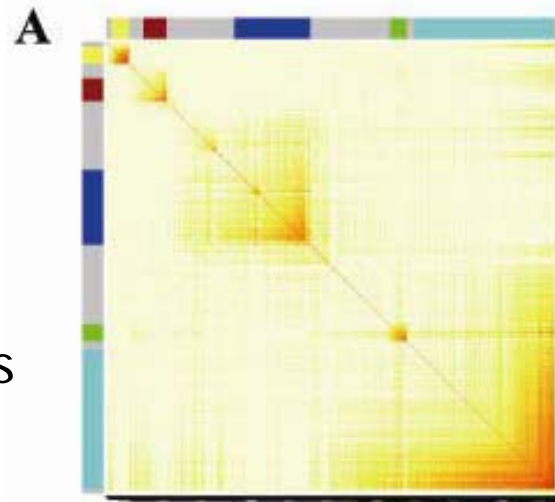
Hierarchical clustering  
dendrogram



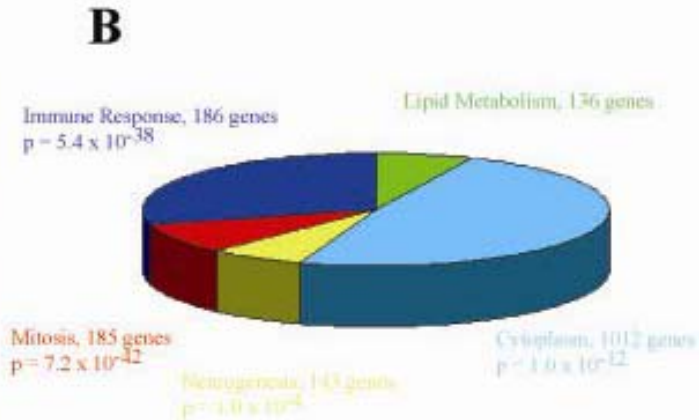
# Different Ways of Depicting Gene Modules

## Topological Overlap Plot

- 1) Rows and columns correspond to genes
- 2) Red boxes along diagonal are modules
- 3) Color bands=modules

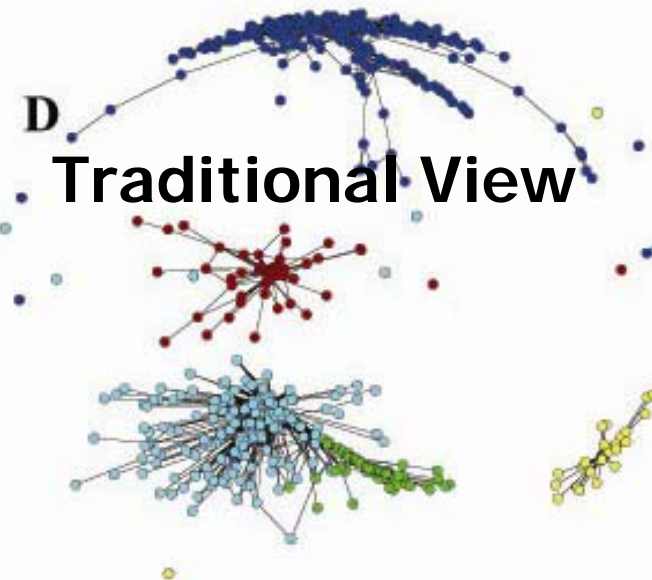
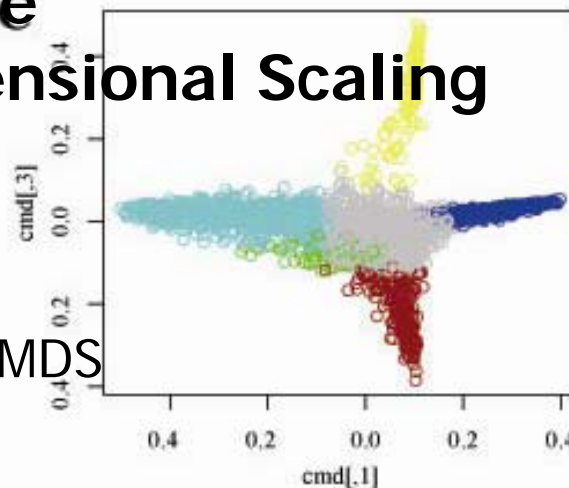


## Gene Functions



## We propose Multi Dimensional Scaling

Idea:  
Use network distance in MDS

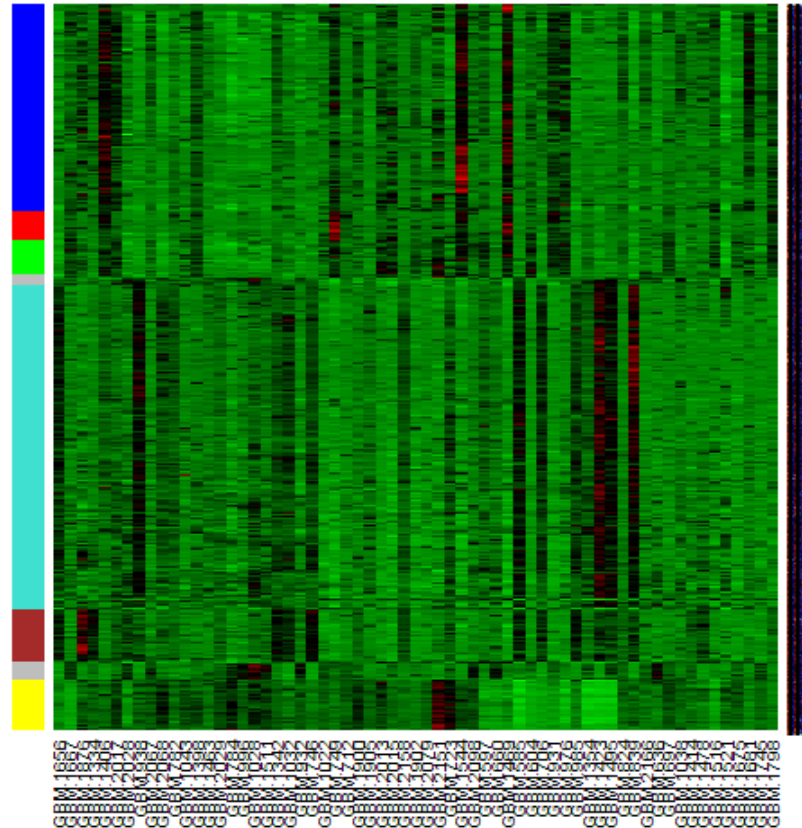


# More traditional view of module

Columns=Brain tissue samples

Rows=Genes

Color band indicates  
module membership

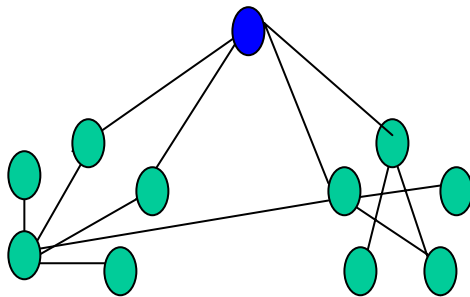


Message: characteristic vertical bands indicate  
tight co-expression of module genes

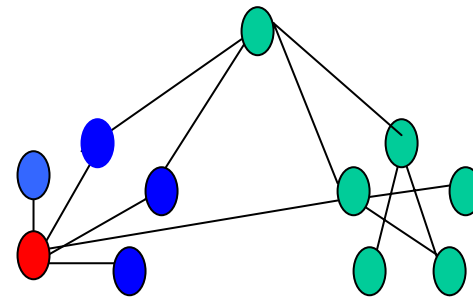
# Module-Centric View of Networks

# Our team (module)-centric view v.s. traditional prima-donna (hub) centric view

- Traditional view based on whole network connectivity



- Module view based on within module connectivity



In many applications, we find that intramodular connectivity is biologically and mathematically more meaningful than whole network connectivity

## Mathematical Facts (Horvath, Dong, Yip 2005)

Hub genes are always module genes in co-expression networks.  
Most module genes have high connectivity.

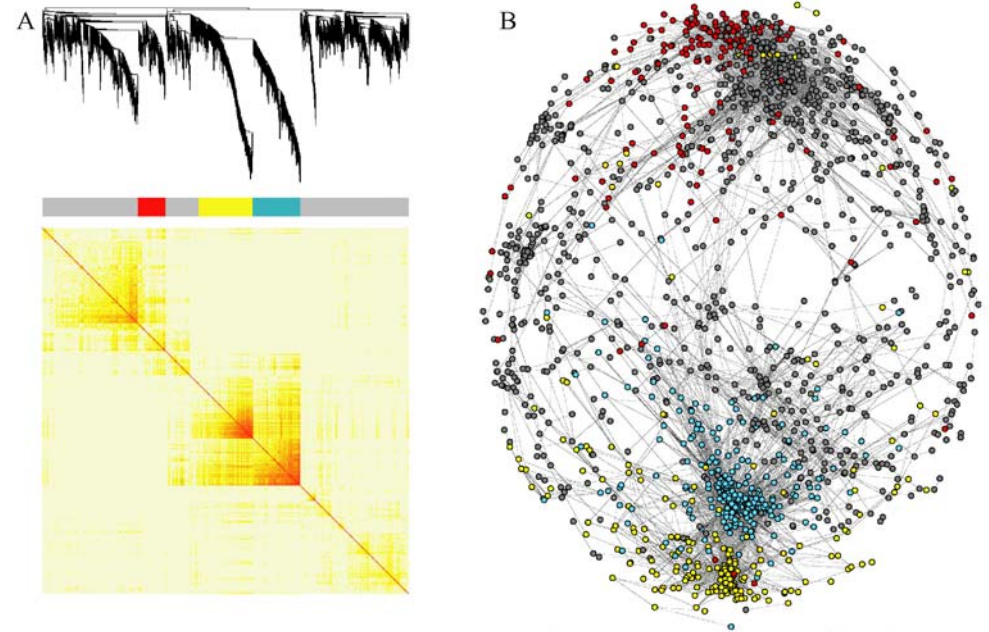
# Yeast Data Analysis

Marc Carlson

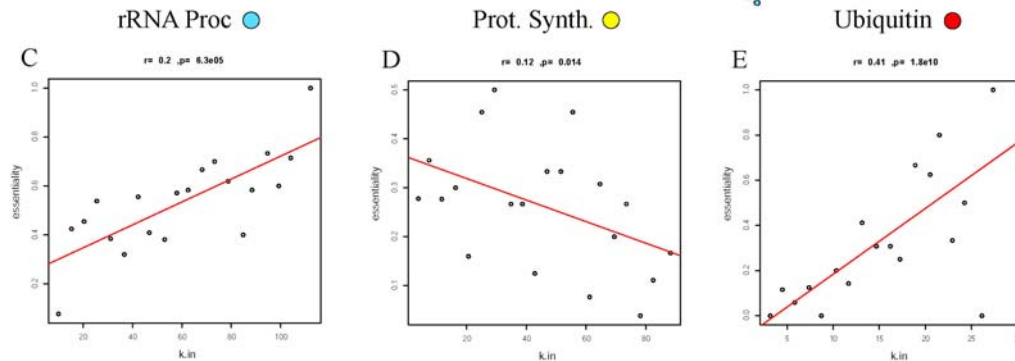
## Findings

- 1) The intramodular connectivities are related to how essential a gene is for yeast survival
- 2) Modules are highly preserved across different data sets
- 3) Hub genes are highly preserved across species

## Within Module Analysis



Prob(Essential)



Connectivity k

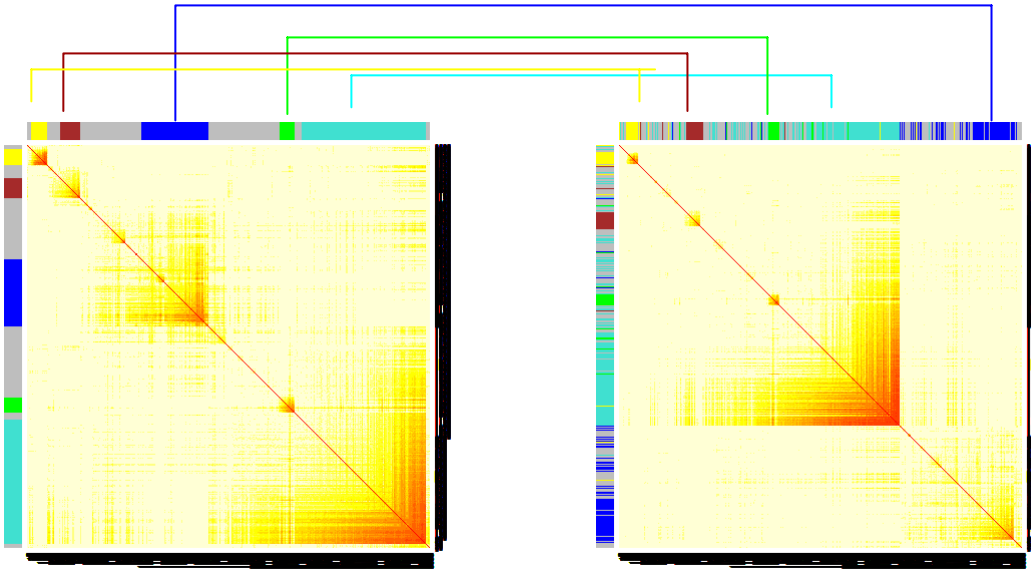
# Hub Genes Predict Survival for Brain Cancer Patients

Mischel PS, Zhang B, et al, Horvath S, Nelson SF.

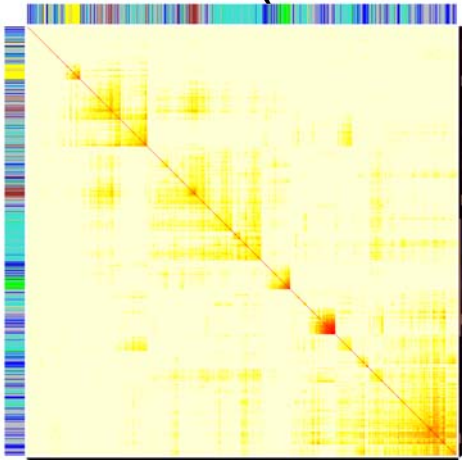
# Module structure is highly preserved across data sets

**55 Brain Tumors**

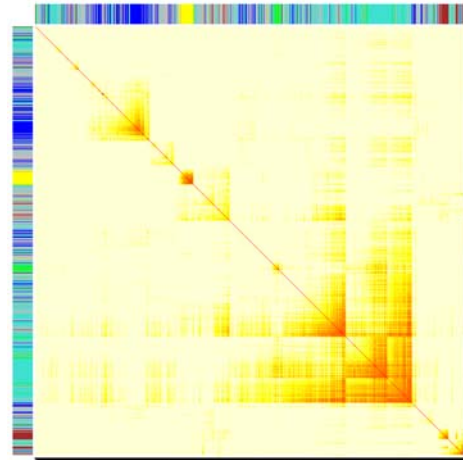
**VALIDATION DATA: 65 Brain Tumors**



**Normal brain (adult + fetal)**



**Normal non-CNS tissues**



Messages:

- 1) Cancer modules can be independently validated
- 2) Modules in brain cancer tissue can also be found in normal, non-brain tissue.

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Insights into the biology of cancer



# Gene prognostic significance

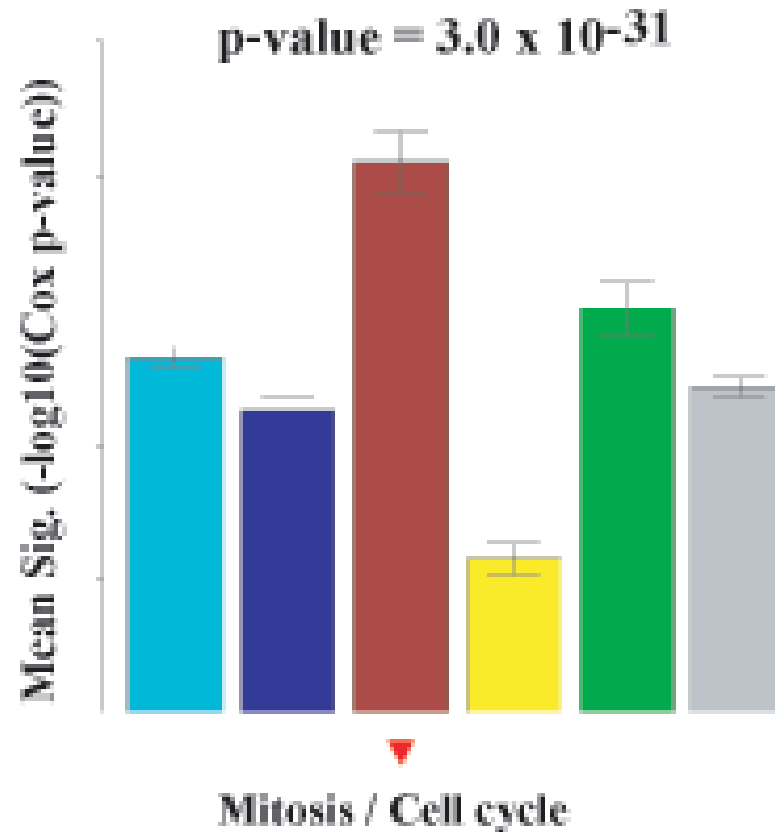
## Definition

- 1) Regress survival time on gene expression information using a univariable Cox regression model
- 2) Obtain the score test p-value
- 3) Gene significance =  $-\log_{10}(\text{p-value})$ 
  - Roughly speaking  
Gene significance ~ no of zeroes in the p-value.

## Goal

Relate gene significance to intramodular connectivity

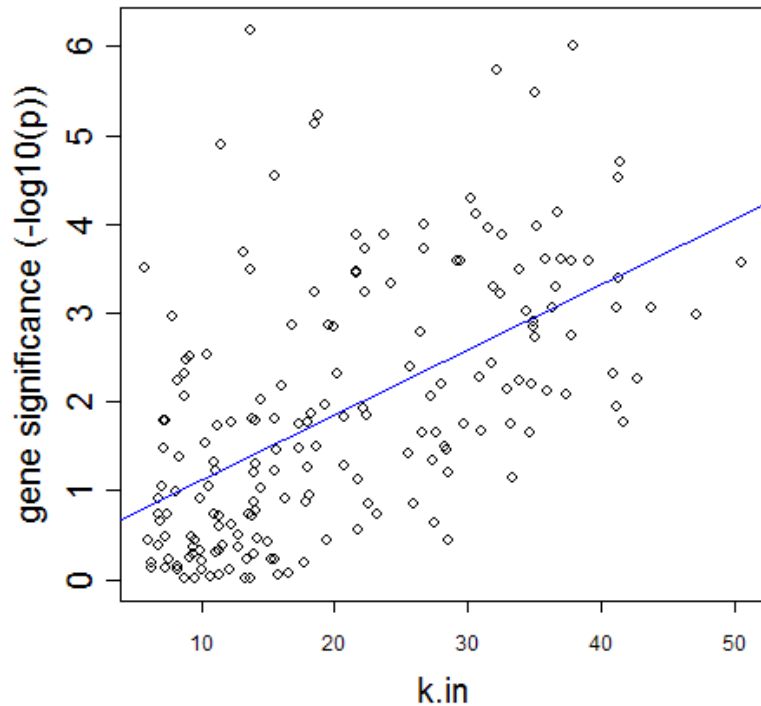
# Mean Prognostic Significance of Module Genes



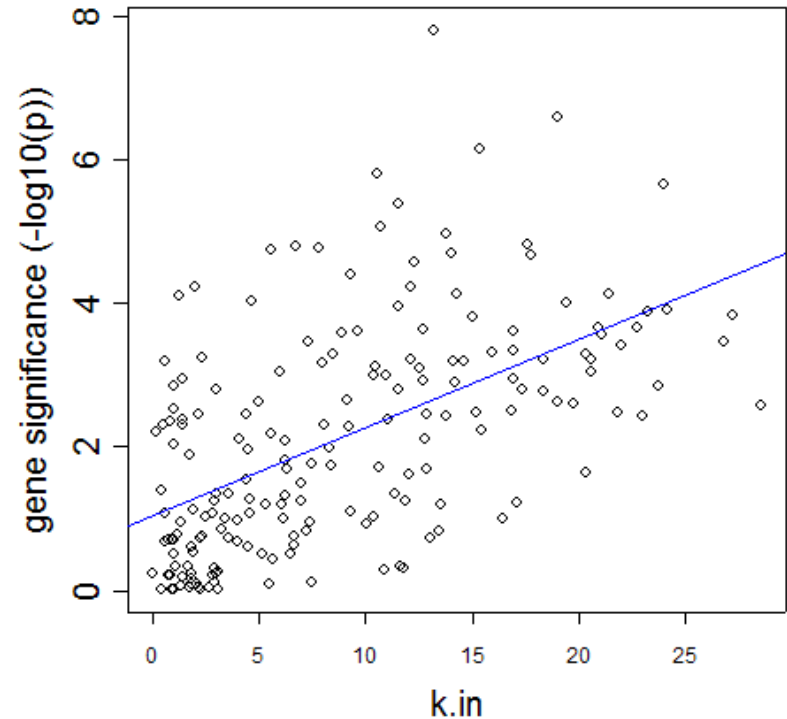
Message: Focus the attention on the brown module genes

# Module hub genes predict cancer survival

1. Intramodular connectivity is highly correlated with gene significance
2. Recall prognostic significance as  $-\log_{10}(\text{Cox-p-value})$



**Test set: 55 samples**  
 **$r = 0.56$ ;  $p = 2.2 \times 10^{-16}$**



**Validation set: 65 samples**  
 **$r = 0.55$ ;  $p = 2.2 \times 10^{-16}$**

The fact that genes with high intramodular connectivity are more likely to be prognostically significant facilitates a novel screening strategy for finding prognostic genes

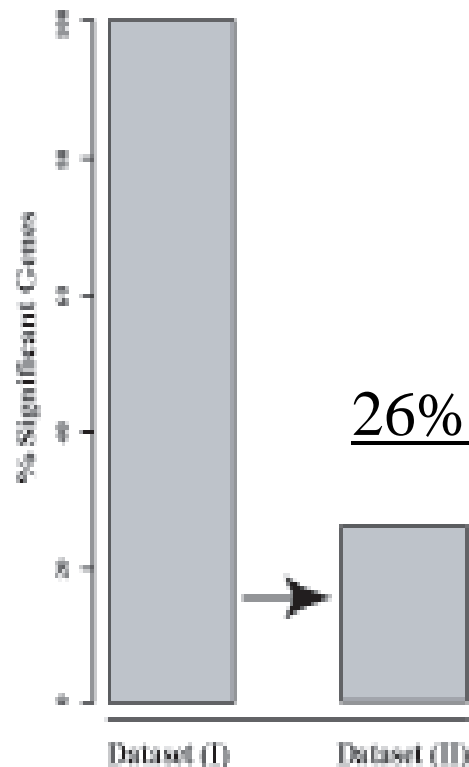
- Focus on those genes with significant Cox regression p-value and high intramodular connectivity.
  - It is essential to take a module centric view: focus on intramodular connectivity of module that is enriched with significant genes.

# Gene screening strategy that makes use of intramodular connectivity is far superior to standard approach

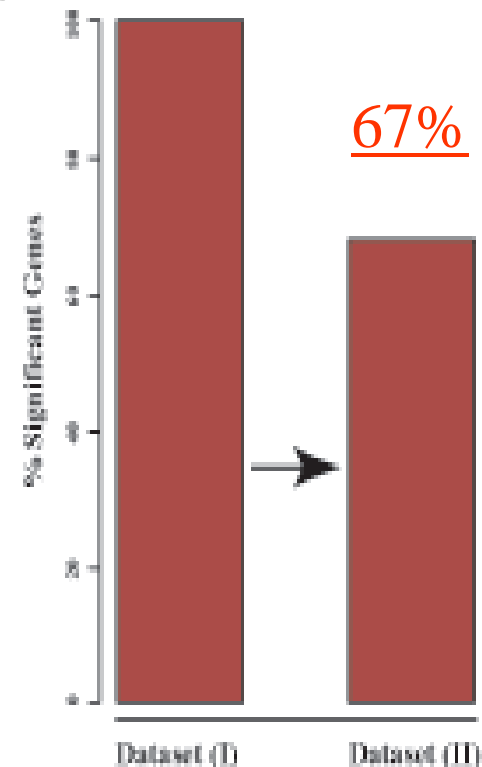
- Validation success rate= proportion of genes with independent test set Cox regression  $p\text{-value} < 0.05$ .
- Validation success rate of network based screening approach (68%)
- Standard approach involving top 300 most significant genes: 26%

# Validation success rate of gene expressions in independent data

300 most significant genes  
(Cox p-value  $< 1.3 \times 10^{-3}$ )



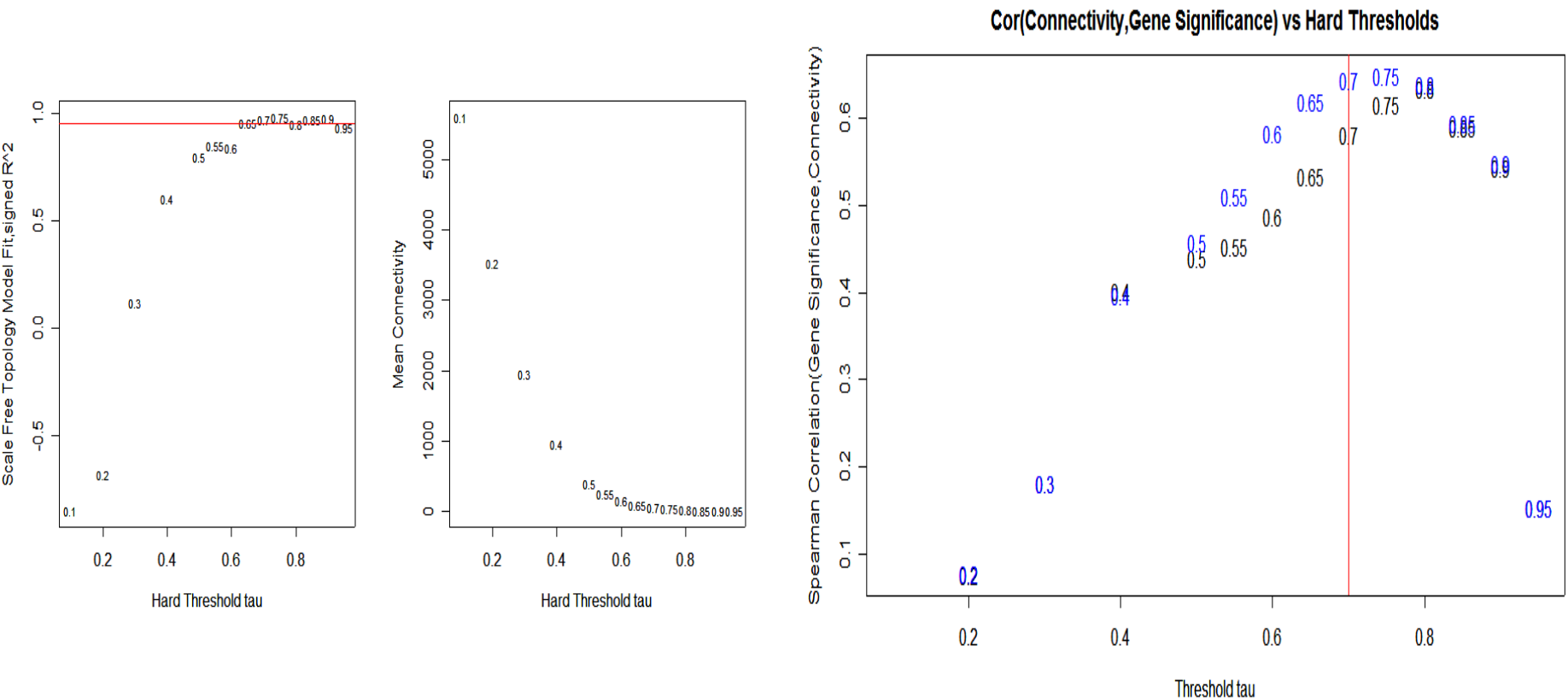
Network based screening  
 $p < 0.05$  and  
high intramodular connectivity



The biological signal is much more robust in weighted than in unweighted networks.

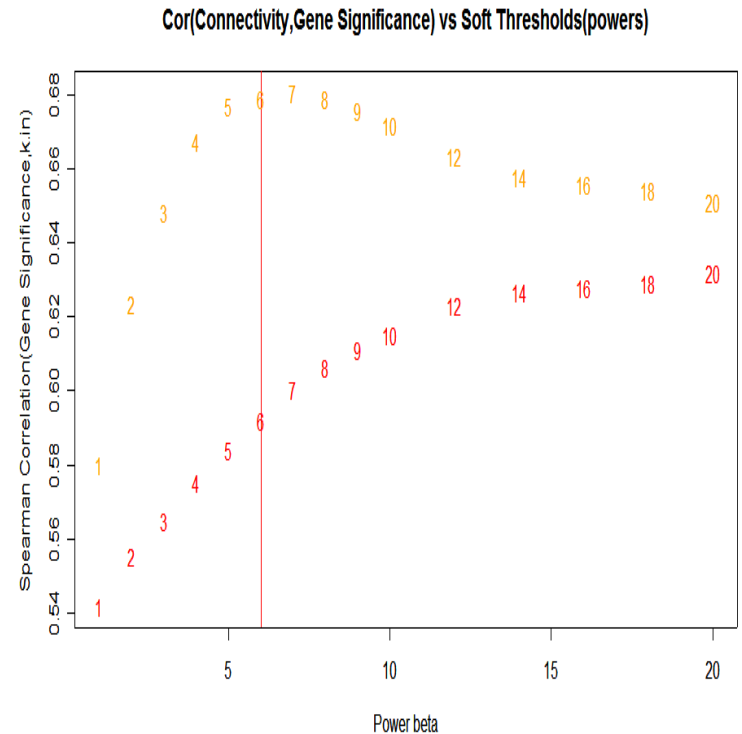
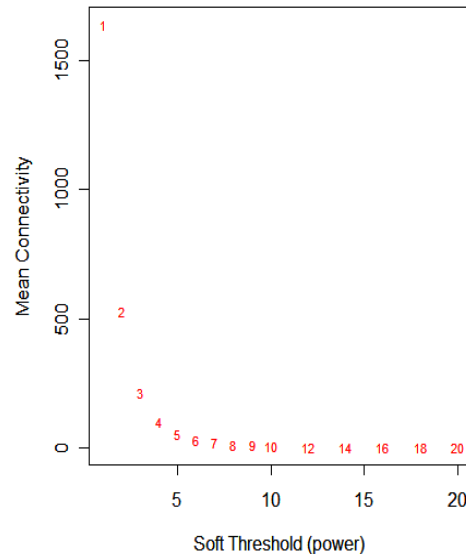
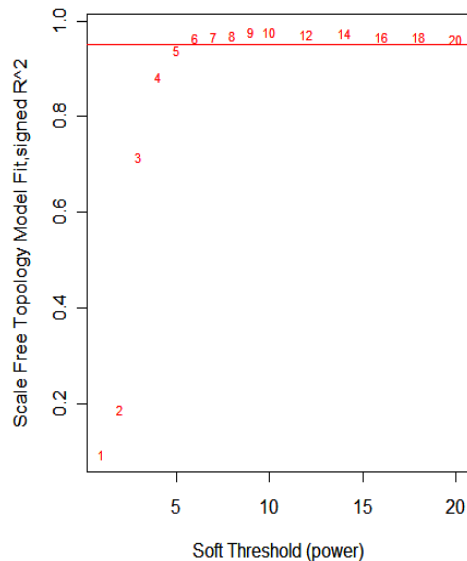
- Biological signal = Spearman correlation between brown intramodular connectivity and prognostic significance,
  - $\text{Biological Signal} = \text{cor}(\text{Gene Signif}, K)$
- Robustness analysis
  - Explore how this biological signal changes as a function of the adjacency function parameters tau (hard thresholding) and b (=power=soft thresholding).

# Scale Free Topology fitting index and biological signals for different hard thresholds





# Scale Free Topology fitting index and biological signals for different SOFT thresholds (powers)



# Soft thresholding leads to more robust results

- The results of soft thresholding are highly robust with respect to the choice of the adjacency function parameter, i.e. the power  $b$
- In contrast, the results of hard thresholding are sensitive to the choice of  $\tau$
- In this application, the biological signal peaks close to the adjacency function parameter that was chosen by the scale free topology criterion.

# Application II

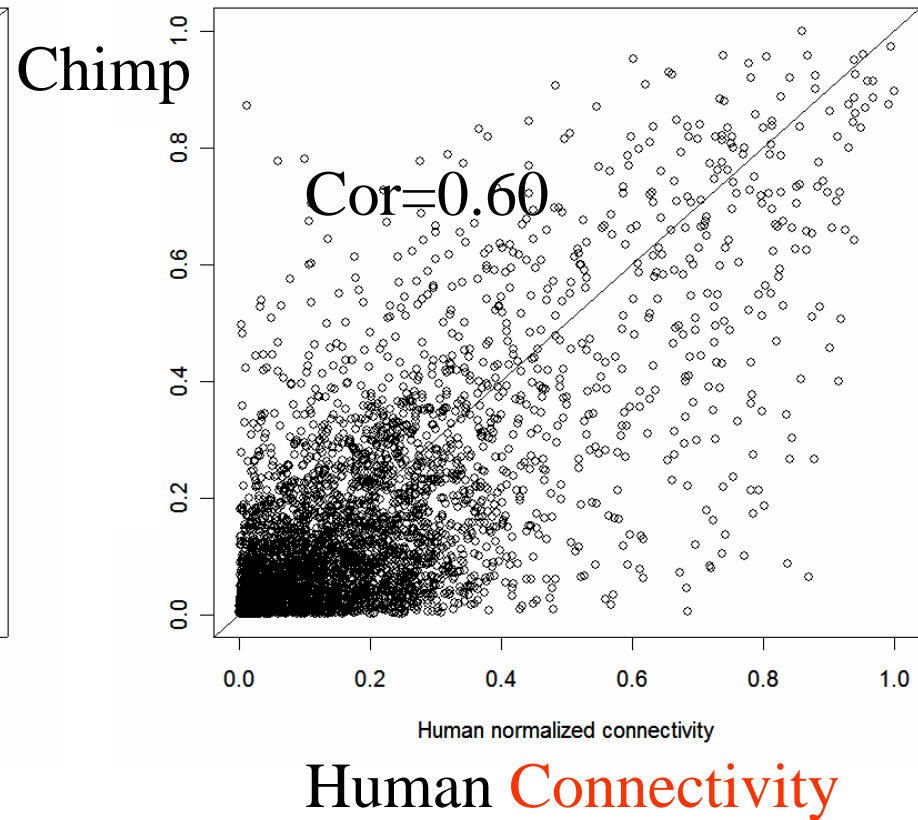
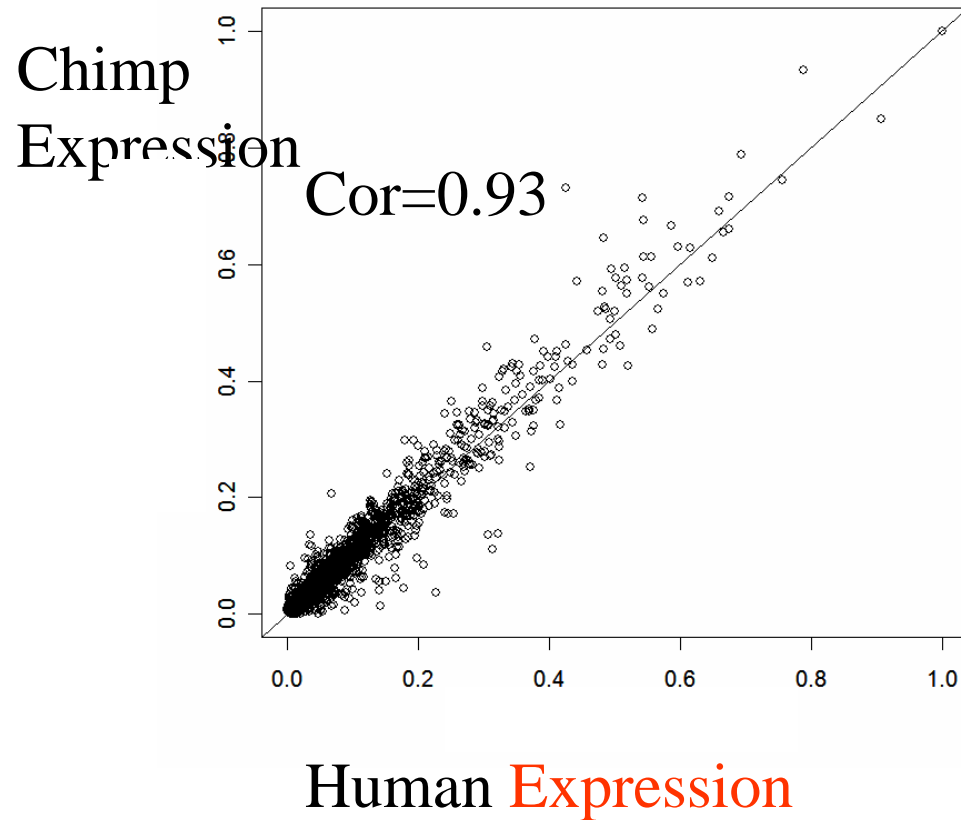
## Comparing Human and Chimp Brains

Mike Oldham, S.Horvath, Dan Geschwind D



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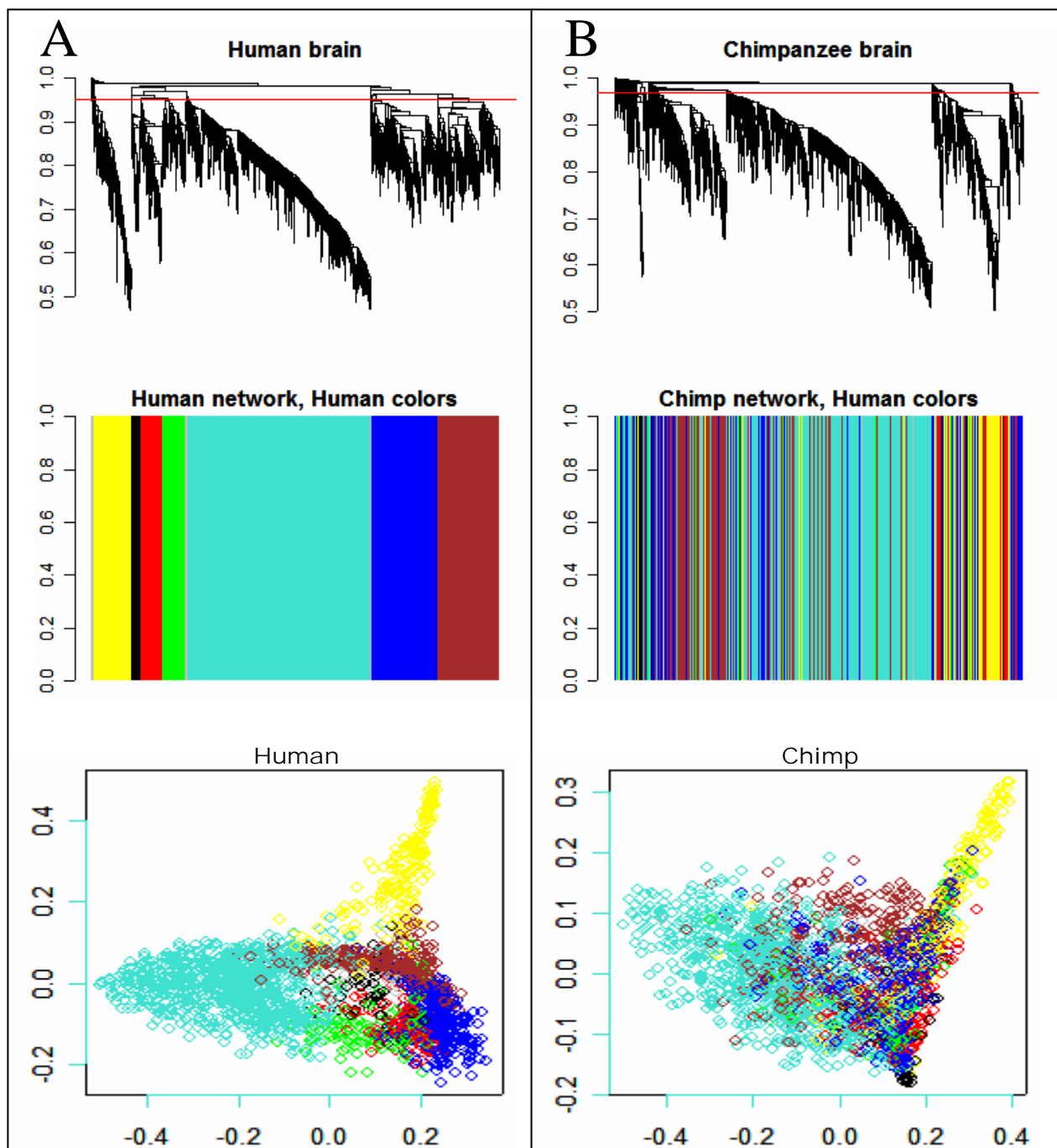
# Gene expression is more strongly preserved than gene connectivity

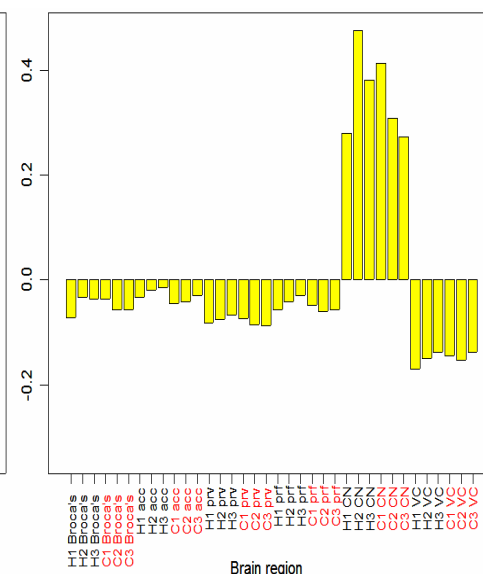
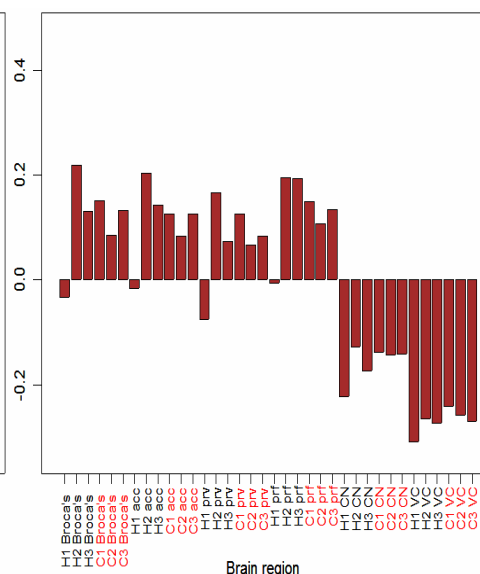
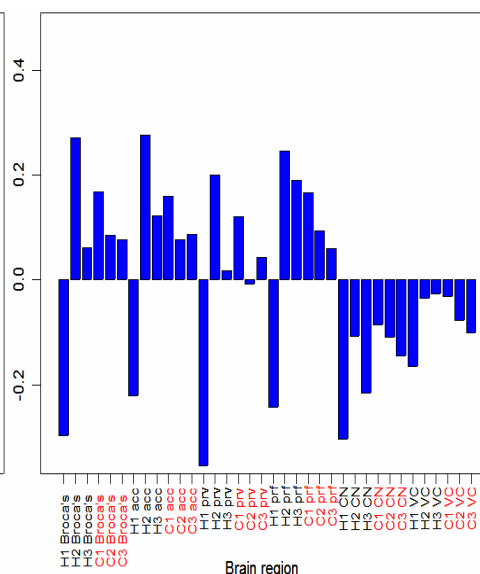
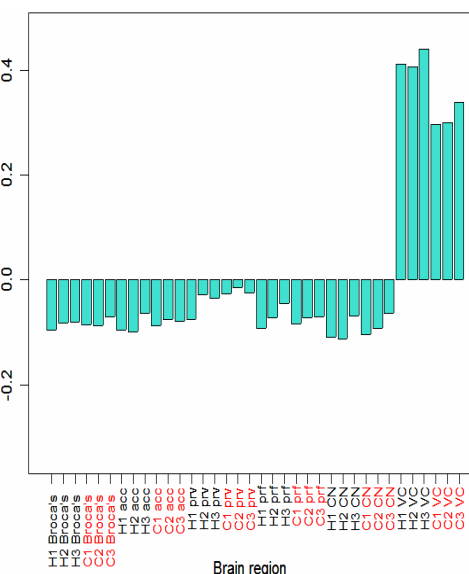
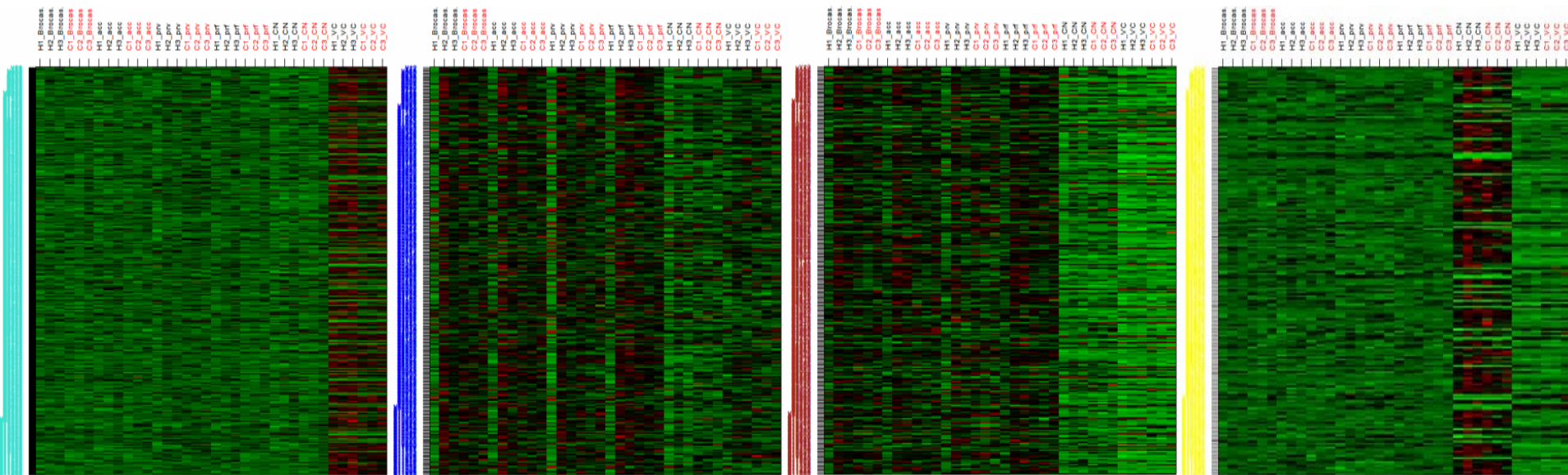


Hypothesis: molecular wiring makes us human

Raw data from Khaitovich *et al.*, 2004

Mike Oldham



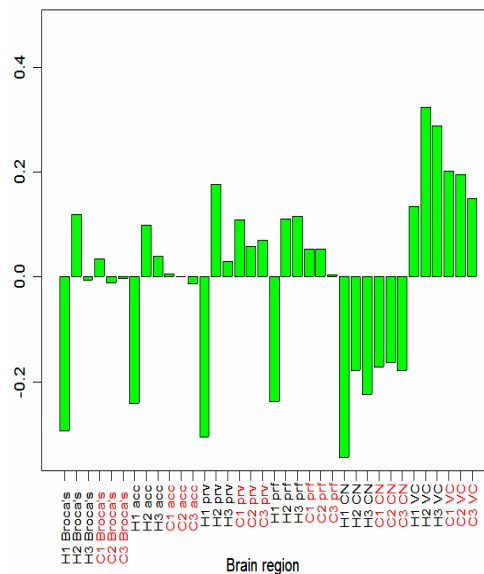
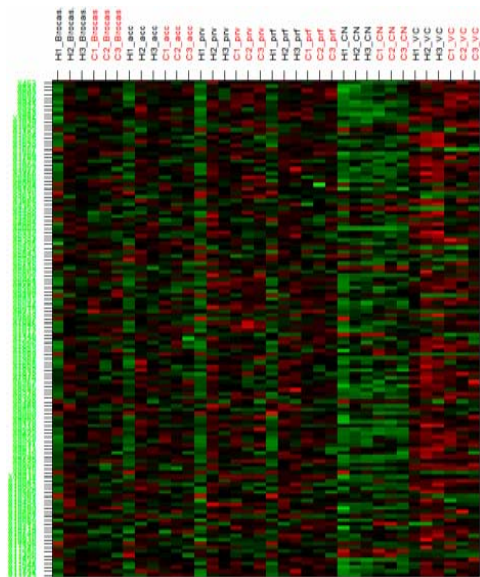


$p = 1.33 \times 10^{-4}$

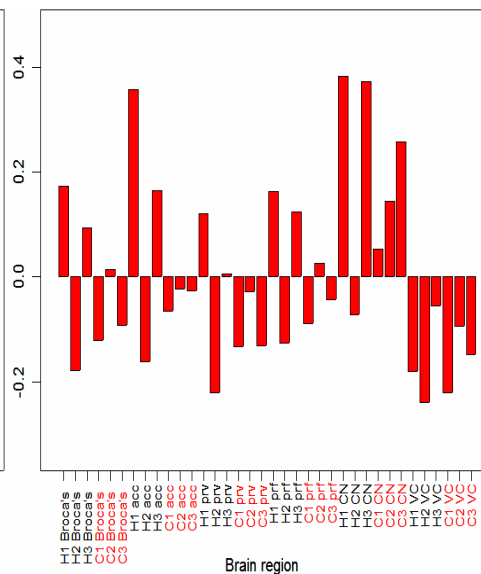
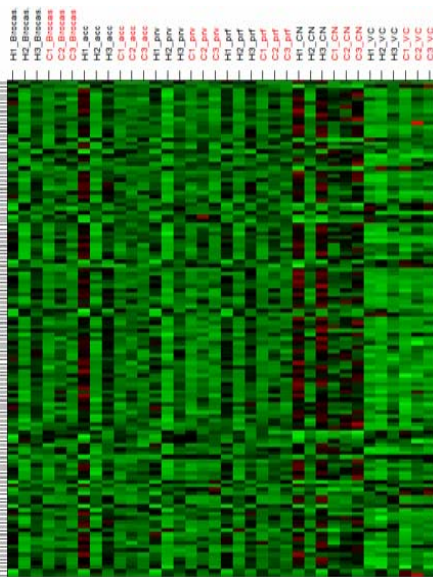
$p = 8.93 \times 10^{-4}$

$p = 1.35 \times 10^{-6}$

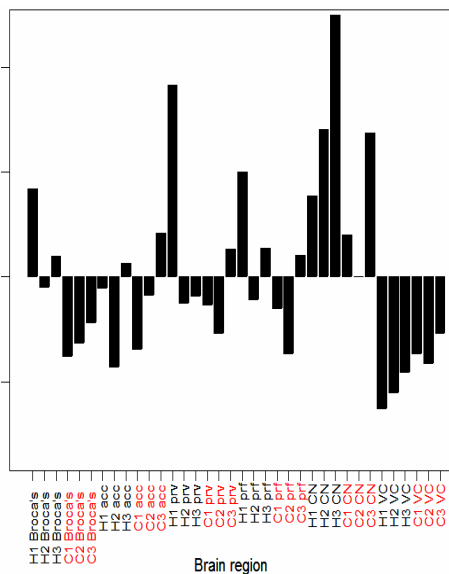
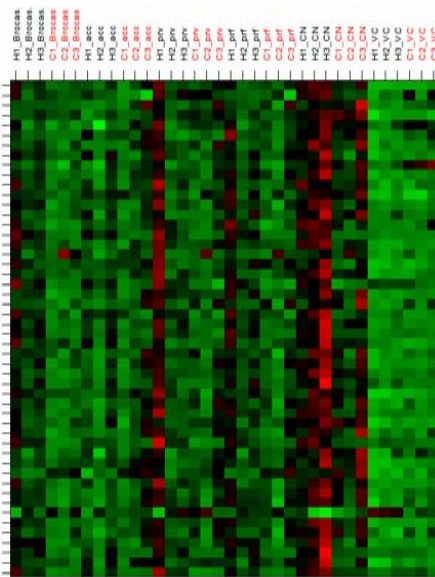
$p = 1.33 \times 10^{-4}$



$p = 2.97 \times 10^{-3}$

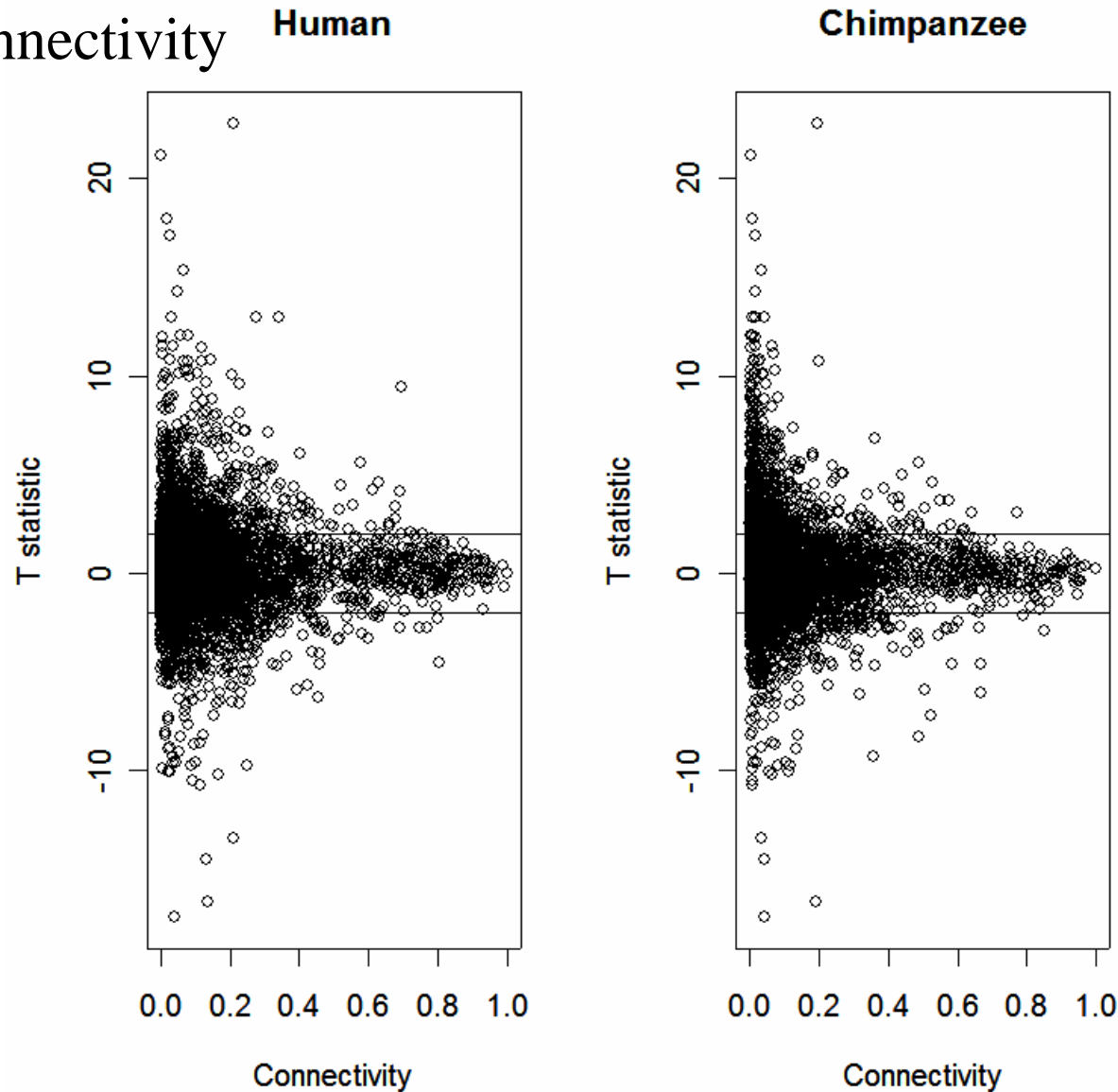


$p = 8.02 \times 10^{-3}$



$p = 2.24 \times 10^{-3}$

# Relationship between T statistic (differential gene expression) and connectivity

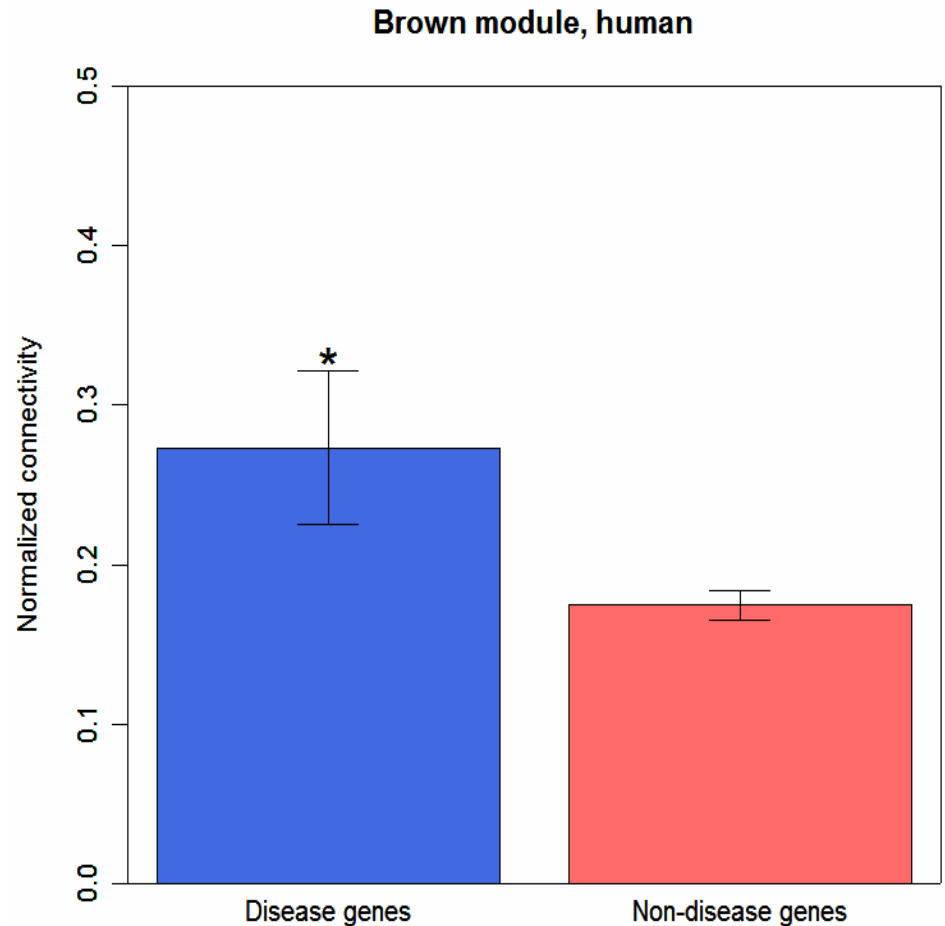


Message: highly connected genes have preserved gene expressions



# Neurodegenerative disease genes have a higher connectivity than non-disease genes.

- Congruent with association between connectivity and lethality in lower organisms
- OMIM database was queried with the term neurodegeneration, yielding genes causing or related to neurodegenerative diseases.



# Conclusions: chimp/human

- Gene **expression** is highly preserved across species brains
- Gene **co-expression** is less preserved
- **Gene modules correspond roughly to brain architecture**
  - Modules that correspond to 'old' architectural features are highly preserved across species
  - Cortex module is not preserved.
- We find evidence that Mendelian disease genes tend to have more connections than anonymous genes.

# Conclusion

- Gene co-expression network analysis can be interpreted as the study of the Pearson correlation matrix.
- Key insight: connectivity can be used to single out important genes.
- Weak relationship with principal or independent component analysis
  - Network methods focus on “local” properties
- Open questions:
  - What is the mathematical meaning of the scale free topology criterion
    - Starting point: noise suppression in modules.
  - Alternative connectivity measures, network distance measures
  - Which and how many genes to target to disrupt a disease module?

# References for this talk

- *Bin Zhang and Steve Horvath (2005) "A General Framework for Weighted Gene Co-Expression Network Analysis", Statistical Applications in Genetics and Molecular Biology: Vol. 4: No. 1, Article 17.*

<http://www.bepress.com/sagmb/vol4/iss1/art17>

- R software tutorials at

<http://www.genetics.ucla.edu/labs/horvath/CoexpressionNetwork/>

- Notion of general topological overlap matrix

<http://www.genetics.ucla.edu/labs/horvath/GTOM/>

- For people who like math, check out

<http://www.genetics.ucla.edu/labs/horvath/ModuleConformity/>

- Cancer network:

*Mischel PS, Zhang B, Carlson M, Fang Z, Freije W, Castro E, Scheck AC, Liao LM, Kornblum HI, Geschwind DH, Cloughesy TF, Horvath S, Nelson SF (2005) A Network Approach to Detecting Individual Prognostic Genes and Therapeutic Targets in Brain Cancer. Submitted.*

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- Chris Plaisier, Access student

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- Stan Nelson, Prof
- Marc Carlson, Postdoc

## **Comparison Human-Chimp**

Dan Geschwind, Prof

Mike Oldham, grad student

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