An Introduction of Some Methods in Learning Gene Association Networks

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Overview

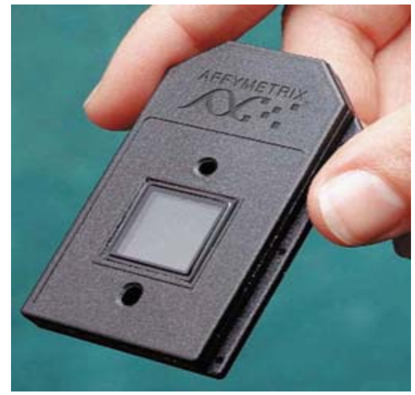
- Motivation
- Naïve Method
- Graphical Lasso

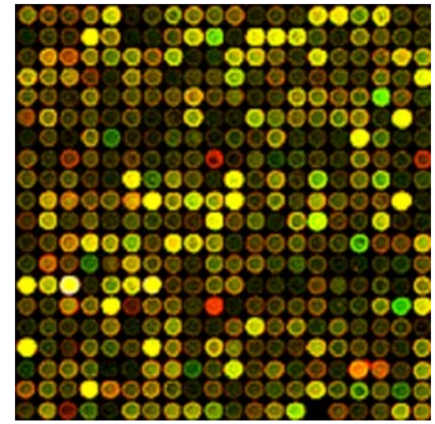
Motivation

- Genes are never isolated
- Want to study them in a systematic way
- A good way to look at their interactions : build gene association networks

Data

- Microarrays
  - Traditional technology
  - Data are noisy





- RNA-Seq
  - Appears recently
  - Data are more accurate

*Pictures are found from internet, unauthorized

Data

- Data Matrix X $\quad \mathrm{X} \in R^{p \times n}$
  - p : number of genes
  - n : number of samples
  - $p >> n$

Goal

- Build a undirected graph
  - Describing relationship between genes

- As simple as possible

Naïve Method

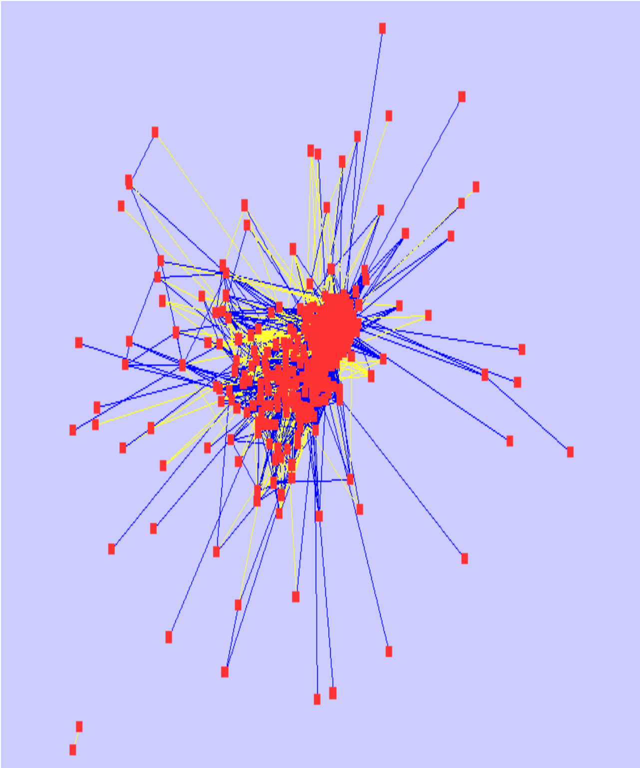
- For each pair of genes
  - Calculate Pearson Correlation Coefficient

$$\rho(X,Y) = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_{i=1}^{n}(x_i - \bar{x})^2}\sqrt{\sum_{i=1}^{n}(y_i - \bar{y})^2}}$$

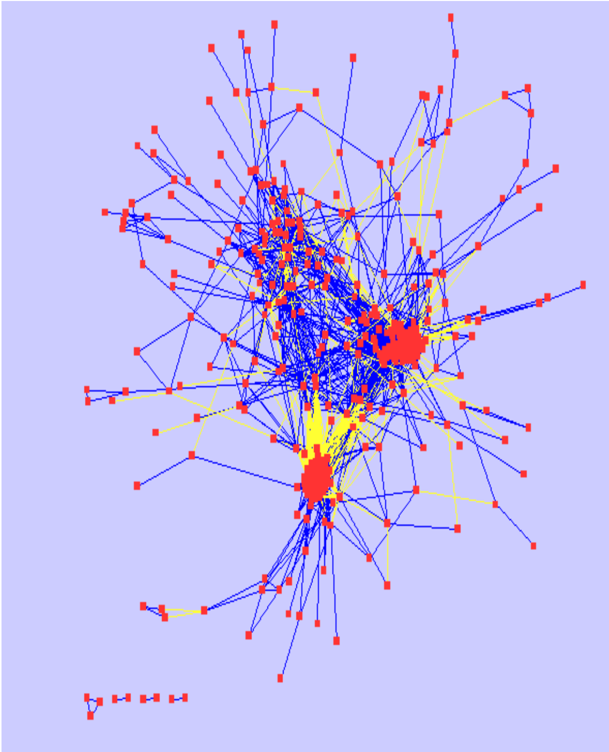
  - Calculate P value
    - Permutation Tests
    - t-distribution
- Control False Discovery Rate (FDR)

Example Networks

Based on 431 mitosis cell cycle related microarray probe sets



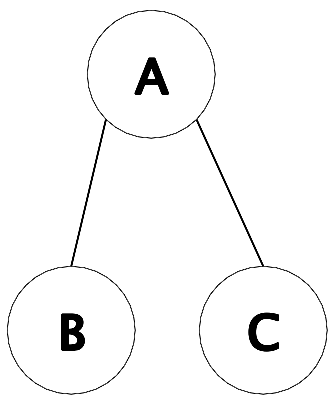
Normal Leukocyte



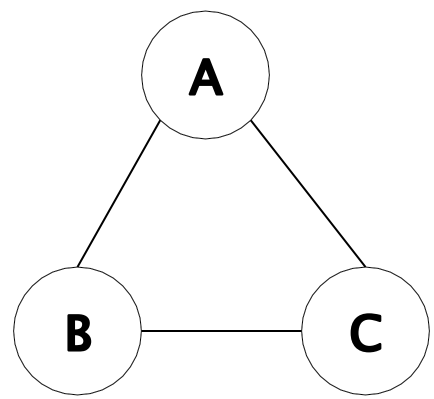
Acute myeloid leukemia

Drawback

- If B, C depend on A, but are conditionally independent given A
  - Say gene A regulates gene B and C
  - Naïve method tends to connect B and C, too!



We want



Naïve method builds

Gaussian Graphical Model

- Assume each sample is sampled from a multivariate Gaussian distribution $N(\mu, \Sigma)$.

$$N(x|\mu, \Sigma) = \frac{1}{(2\pi)^{p/2}} \frac{1}{|\Sigma|^{1/2}} \exp\{-\frac{1}{2}(x-\mu)^T \Sigma^{-1} (x-\mu)\}$$

- Let $\Theta = \Sigma^{-1}$. This is precision matrix
  - If θ_{ij} is 0, variable i & j are conditionally independent given all other variables
  - Otherwise, connect i and j in the graph

Graphical Lasso
[Friedman et al. 2008]

- Friedman, J., Hastie, T. and Tibshirani, R. (2008). Sparse inverse covariance estimation with the graphical lasso. *Biostatistics* 9, 432–441.
- Assume μ is fixed, say $\mu = 0$
- Let $S = \frac{1}{n} X X^T$
- Want to maximize penalized log-likelihood

$$\log\det\Theta - \mathrm{tr}(S\Theta) - \rho\|\Theta\|_1$$

Graphical Lasso

- Define W $= \Theta^{-1}$
- The subgradient equation is

$$W - S - \rho \cdot \Gamma = 0$$

$$\Gamma_{ij} = \begin{cases} sgn(\theta_{ij}), & \theta_{ij} \neq 0 \\ \gamma_{ij} \in [-1,1], & \theta_{ij} = 0 \end{cases}$$

- Partition W as follows:

$$\begin{pmatrix} W_{11} & w_{12} \\ w_{12}^T & w_{22} \end{pmatrix} \begin{pmatrix} \Theta_{11} & \theta_{12} \\ \theta_{12}^T & \theta_{22} \end{pmatrix} = \begin{pmatrix} I & 0 \\ 0^T & 1 \end{pmatrix}$$

Graphical Lasso

- Assume W_{11} is known, we can find w_{12} by solving

$$\min_{\beta}\{\frac{1}{2}\left\|W_{11}^{1/2}\beta - W_{11}^{-1/2}s_{12}\right\|^2 + \rho\|\beta\|_1\} \quad (*)$$

- w_{12} is given by

$$w_{12} = W_{11}\hat{\beta}, \qquad \hat{\beta} \text{ solves } (*).$$

- (*) is a lasso problem!

Graphical Lasso

- To show it, the upper right block of penalized log-likelihood's subgradient equation is

$$w_{12} - s_{12} - \rho \cdot \gamma_{12} = 0$$

- The subgradient equation of (*) is

$$W_{11}\beta - s_{12} + \rho \cdot \nu = 0$$

$$\nu_i = \begin{cases} sgn(\beta_i), & \beta_i \neq 0 \\ \nu_i \in [-1,1], & \beta_i = 0 \end{cases}$$

Graphical Lasso

- Algorithm
  - Start with $W = S + \rho I$
  - For j = 1,2,…,p,1,2,…,p
    - Permute jth diagonal item to the lower right corner of W
    - Solve the lasso problem (*) and get $w_{12} = W_{11}\hat{\beta}$
    - Recover the corresponding row and column with w_{12}
  - Continue until convergence

Some Related References

- P. Ravikumar, G. Raskutti, M. Wainwright, B. Yu (2008) Model selection in Gaussian graphical models: high-dimensional consistency of l1-regularized MLE. *In Advances in Neural Information Processing Systems* (NIPS) 21, 2008.

Q&A

- Thanks!