Session 11.3.1

Computational Genomics, Gene Expression, and Genetic Networks I

8:50-10:20, Sept 2, Room 3E

Finding Co-clusters of Genes and Clinical Parameters

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Linking Genes with Clinical Traits

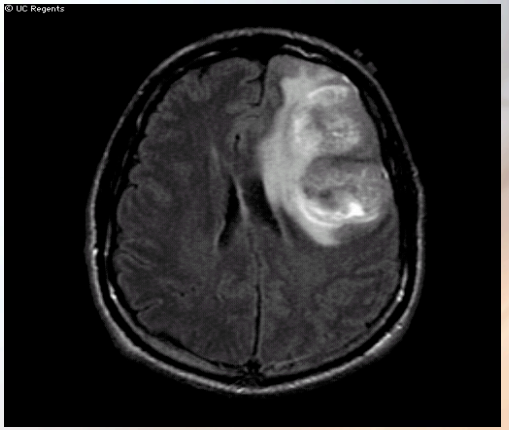
- Given specific clinical traits of interest, to determine which genes are responsible
- Can have a major impact on clinical diagnosis and prognosis
- Typically done by correlating gene expression with trait measurement
  - DNA microarray technology
    - Enables us to monitor expression levels of thousands of genes simultaneously
    - Sparked development of new methods

Correlation Analysis

- Compute the Pearson correlation coefficient between trait vector and gene expression vector

Patients

Trait 1	0.6	0.7	0.8	0.9	1.0
Trait 2	0.4	0.5	0.6	0.5	0.4
:					

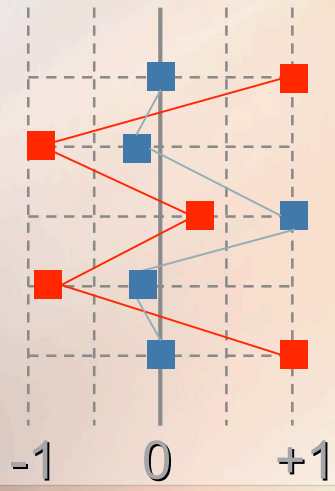


(Nardini *et al.*, 2004)

Genes

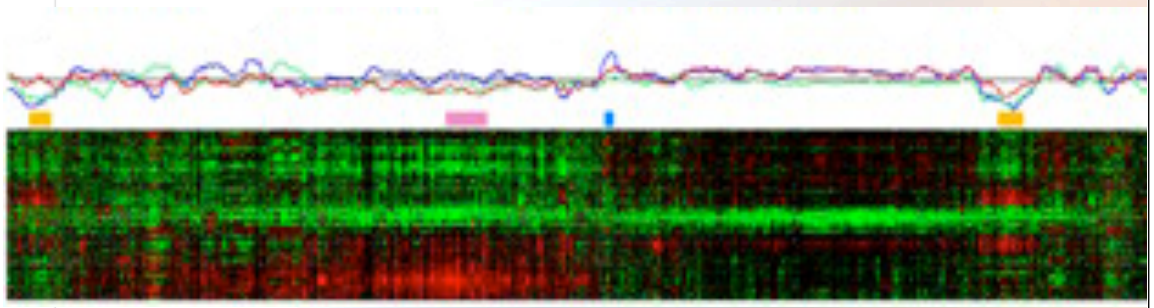
0.1	0.2	0.3	0.4	0.5
0.5	0.4	0.3	0.2	0.2
0.5	0.6	0.7	0.8	0.5
0.8	0.7	0.6	0.4	0.5
1.0	1.1	1.2	1.3	1.4

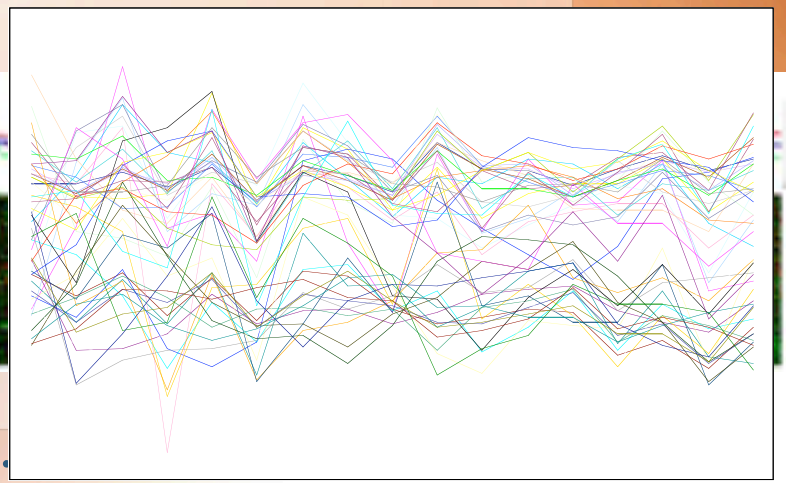
Patients



Challenges

- As the number of clinical traits increases, the inspection method breaks down
  - We need a systematic approach
- The values of clinical traits are not necessarily continuous or numeric
  - We need a more generalized statistic than the Pearson correlation coefficient

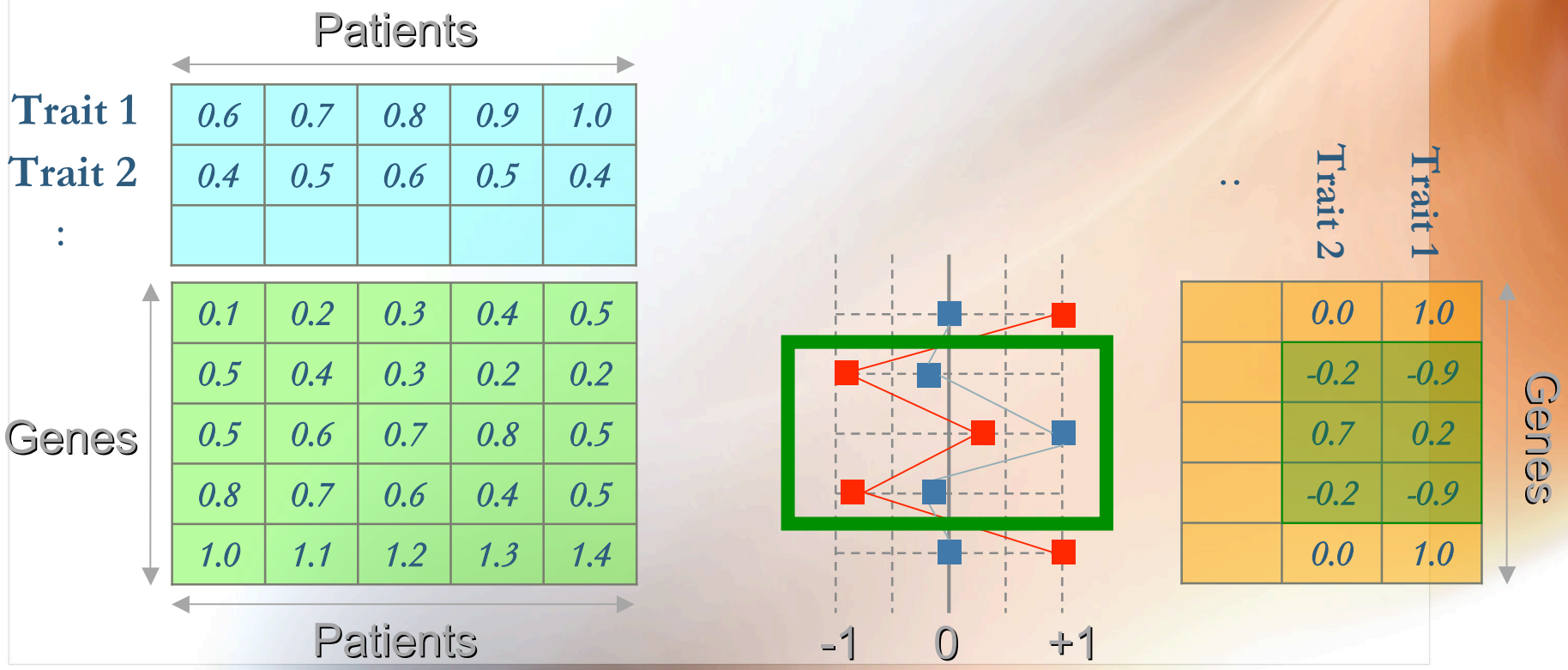




Lapointe, Jacques et al. (2004) Proc. Natl. Acad.

Our Approach

- Construct a "correlation matrix"
  - Use the *SAM* statistic (Tusher *et al.*, 2001)
- Find local structures in that matrix
  - Use the technique of *co-clustering*



Co-clustering

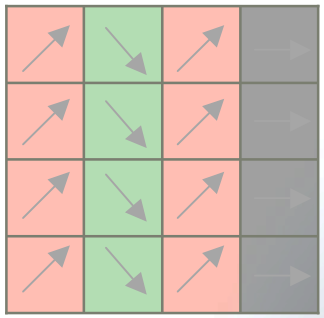
- Simultaneous clustering of rows and columns in a data matrix
  - Co-clusters are represented by a submatrix
  - Co-clusters can overlap with each other
- Various applications in data mining
  - Text mining: word-document
  - Gene expression analysis: gene-patient
- Computationally challenging
  - Can be reduced to the problem of finding maximum edge bicliques

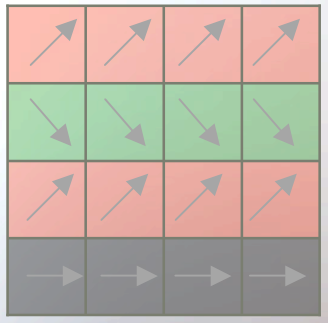
Examples of Co-clusters

1	1	1	1
1	1	1	1
1	1	1	1
1	1	1	1

1	1	1	1
2	2	2	2
3	3	3	3
4	4	4	4

1	2	3	4
1	2	3	4
1	2	3	4
1	2	3	4





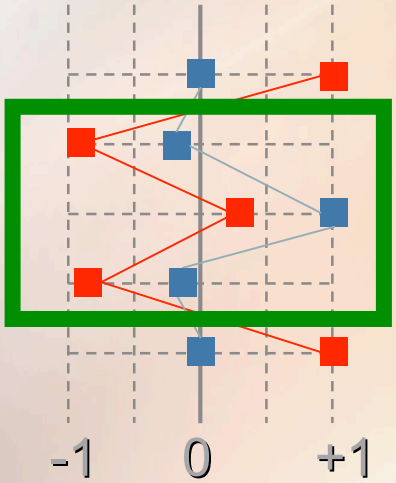
- All constant
  - Hartigan, 1972
  - Tibshirani *et al.*, 1999
- Constant rows/columns
  - Getz *et al.*, 2000
  - Califano *et al.*, 2000
  - Segal *et al.*, 2001
- Common trend
  - Cheng and Church, 2000
  - Wang *et al.*, 2002
  - Kluger *et al.*, 2003
  - Ben-Dor *et al.*, 2002
  - Tanay *et al.*, 2002

Definition

- *Co-cluster* of genes and clinical traits
  - A submatrix of the correlation matrix
  - For any pair of column vectors, the inter-column distance is less than a threshold

..	Trait 2	Trait 1
	0.0	1.0
	-0.2	-0.9
	0.7	0.2
	-0.2	-0.9
	0.0	1.0

Genes



Measuring Inter-column Distance

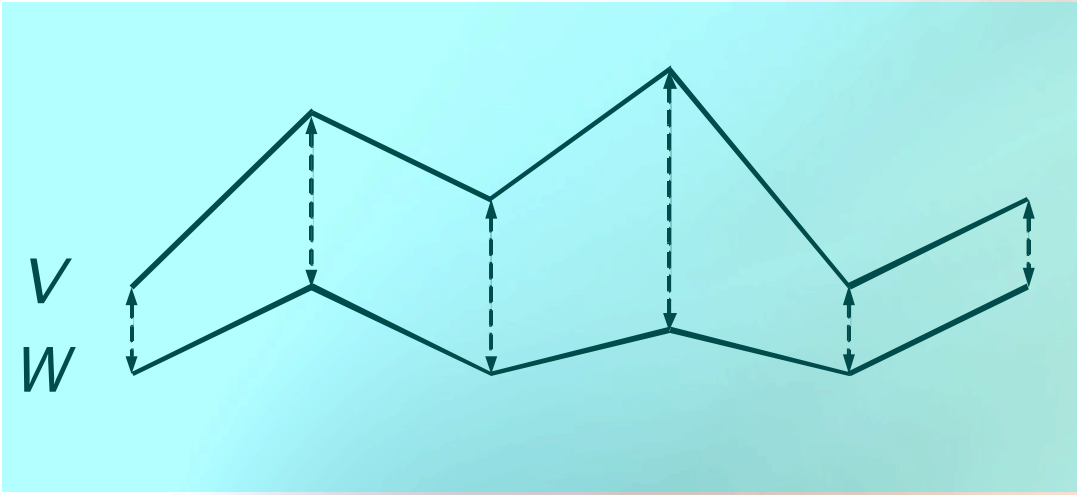
- For a vector V

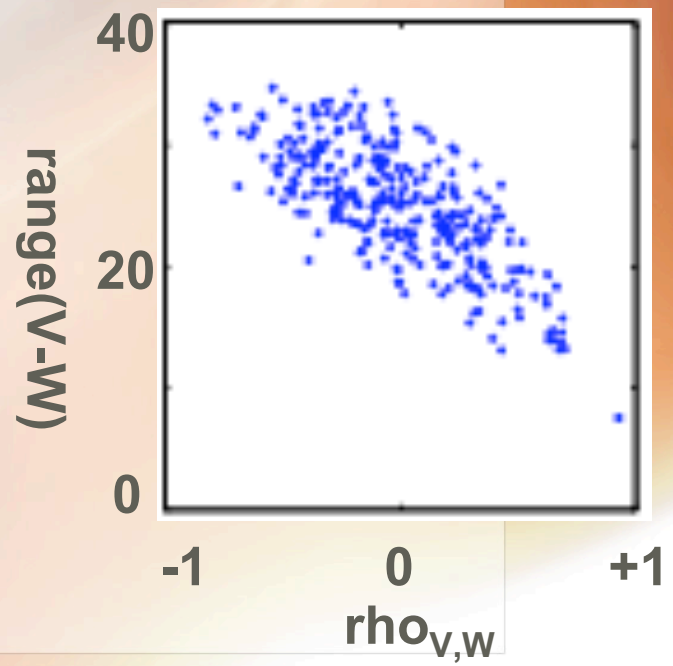
$$range(V) = max(V) - min(V)$$

- For two vectors V and W

$$distance(V, W) = range(V - W) \leq \tau$$

- Rationale
  - Computational efficiency



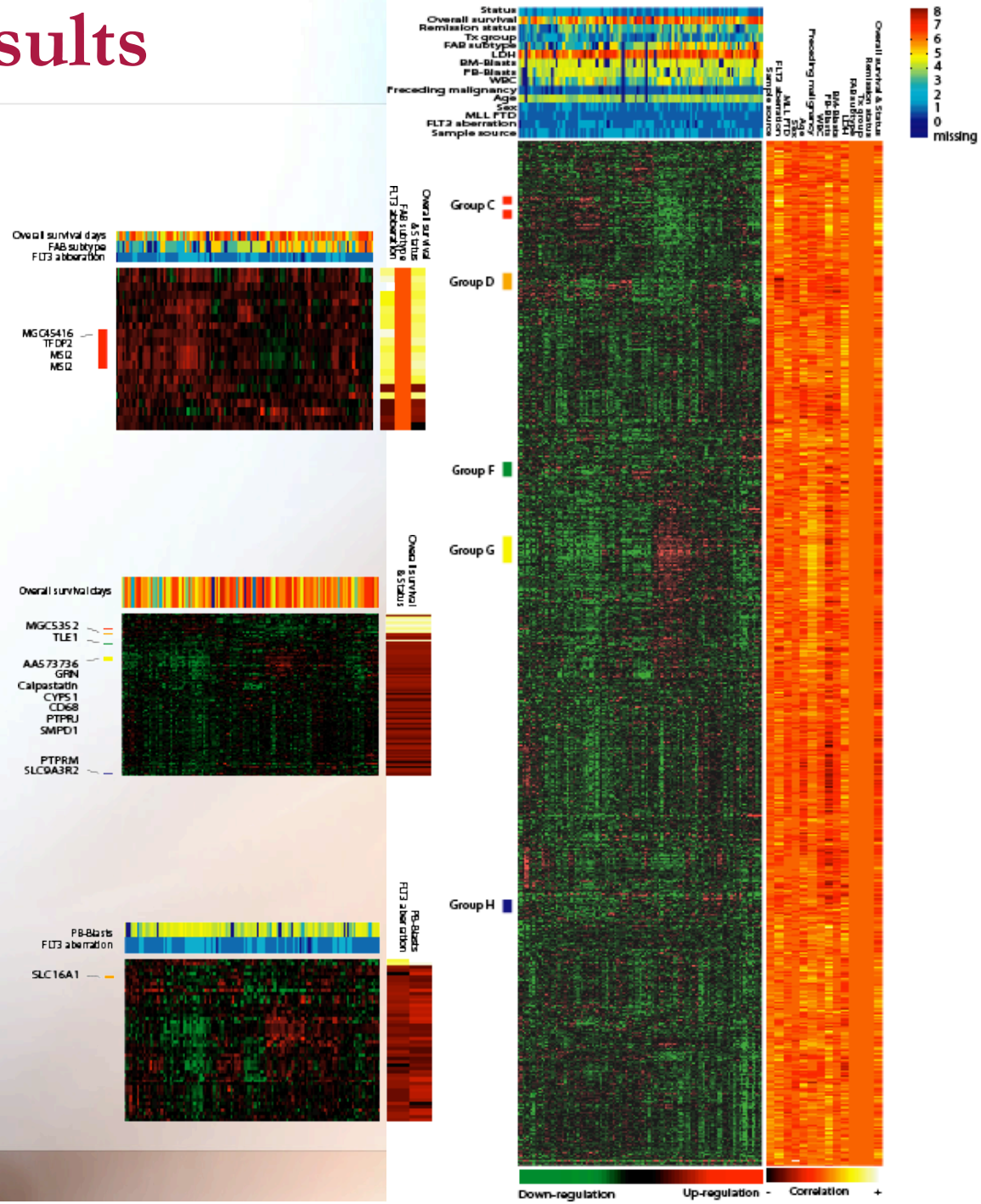


Our Co-clustering Method

- Input
  - A matrix of clinical traits
  - A gene expression matrix
- Output
  - Co-clusters of genes and traits
- Two-step process
  - Step 1: Find "seed" co-clusters
  - Step 2: Merge seeds to find co-clusters
- Can find all the co-clusters
  - That satisfy specific input conditions
  - That are statistically significant

Experimental Results

- AML data set
  - Bullinger *et al.*, 2004
  - 6283 genes
  - 119 patients
  - 15 clinical traits
- 43 GT co-clusters



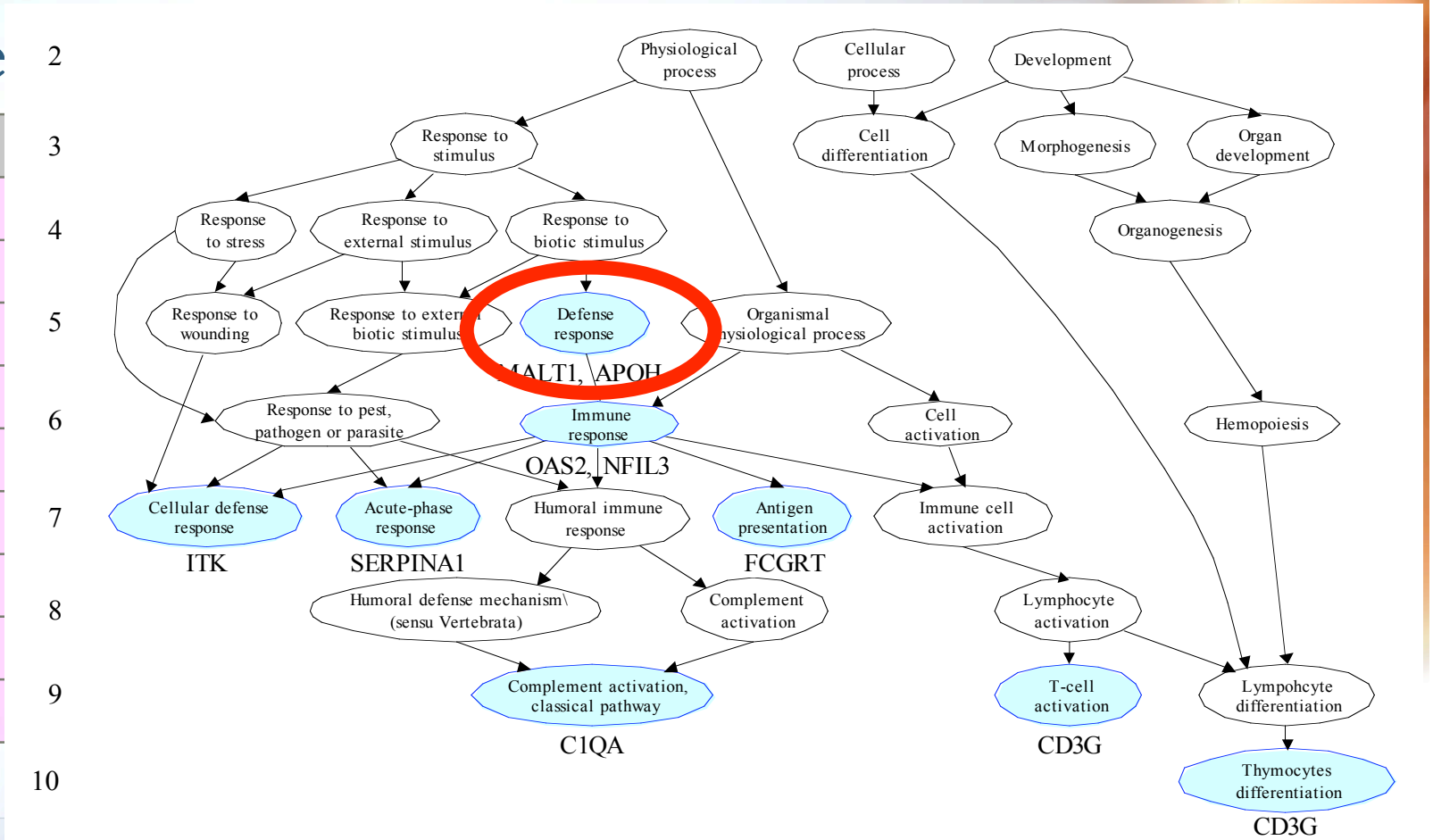
Biological Validation

- "Survival" with TGFB1/2 and CD1a
  - Riedl *et al.*, 1997, Jcobsen *et al.*, 1996, Weisberg *et al.*, 20

Item	Value
GO term	Defense response
Corrected p-value	0.0359

- Gene

Gene
MALT1
NFIL3
APOH
FCGRT
SERPINA1
C1QA
OAS2
ITK
CD3G



Summary

- Linking genes and clinical traits
  - Can lead to a major impact on diagnosis
  - DNA microarray opened a door for new methods
- Our approach
  - Construct a correlation matrix
  - Find co-clusters of genes and traits appearing on the correlation matrix
- Experimental results
  - Tested with AML data set
  - Successfully identify 43 co-clusters

Thank You!