生物信息学与系统生物学

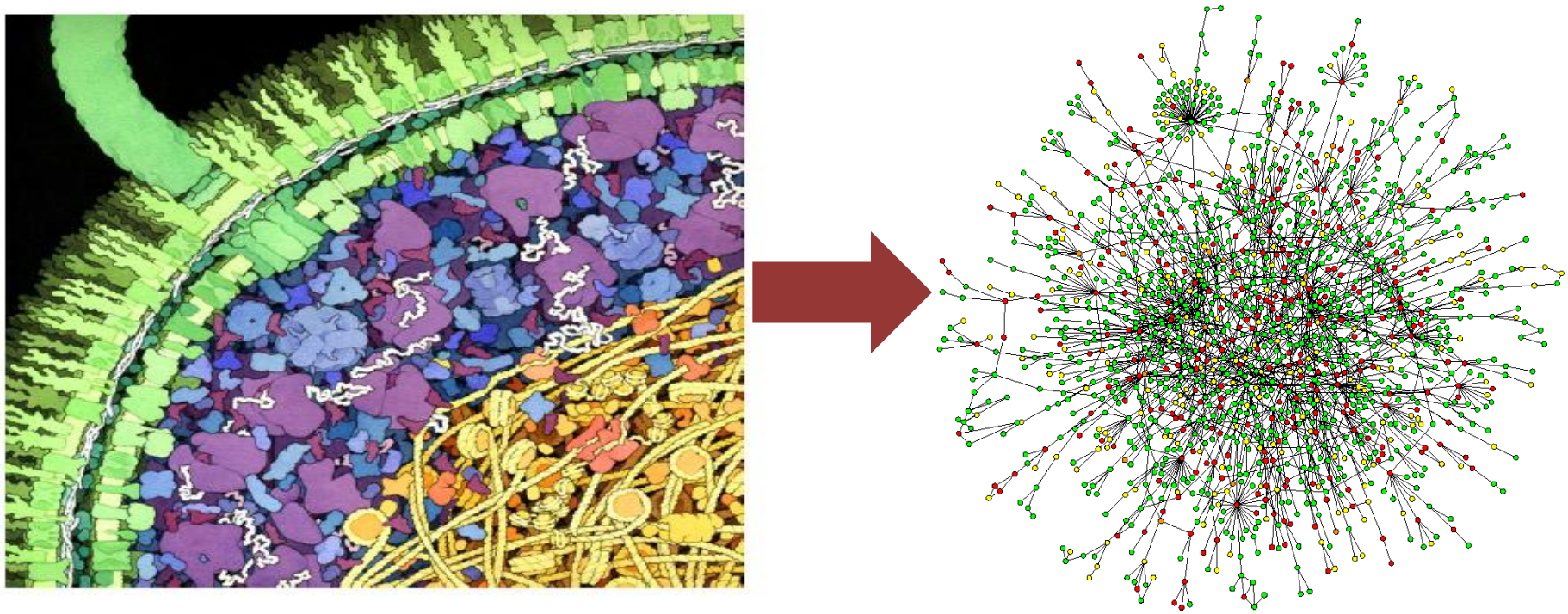
张世华

中国科学院数学与系统科学研究院

Conditional specific pathway or subnetwork identification

Shihua Zhang

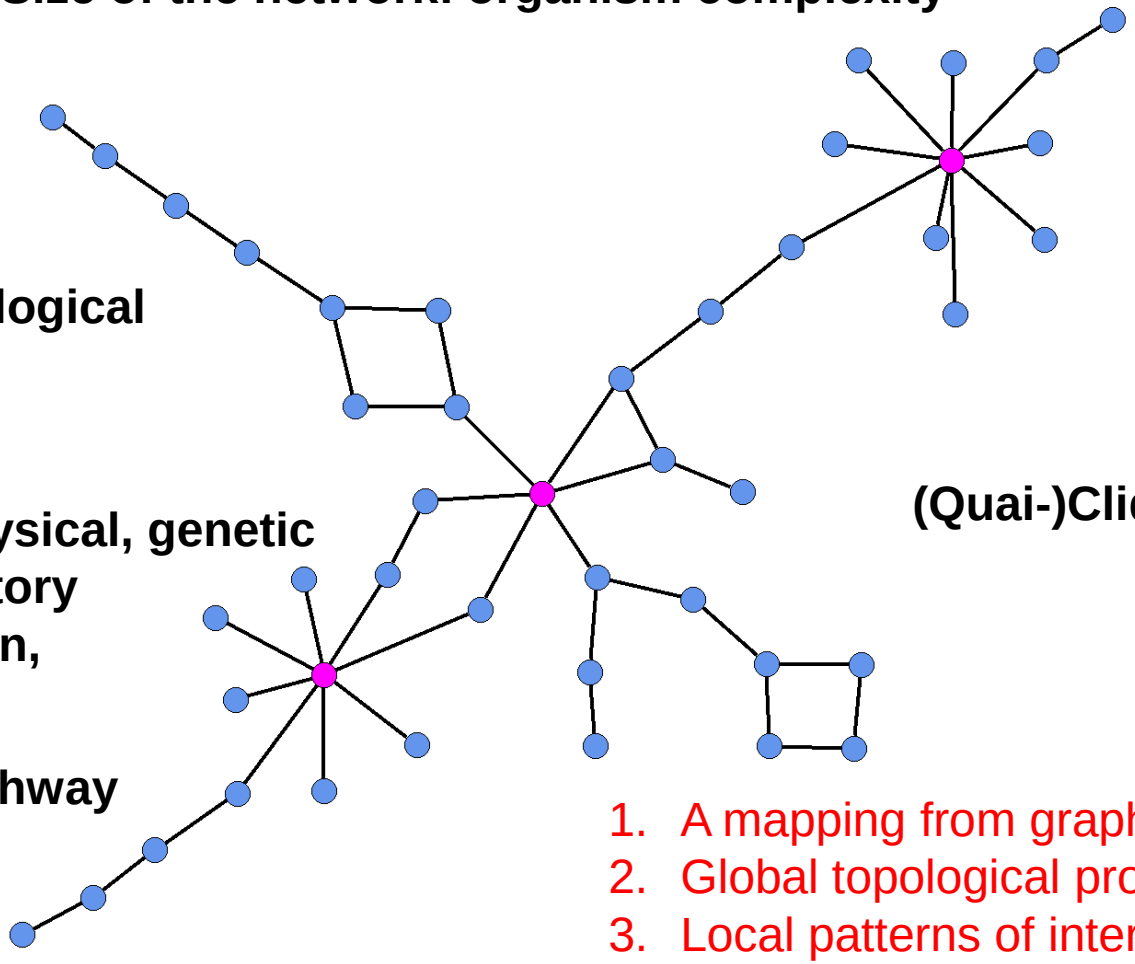
Network systems biology



- Usually graphs are used to represent these complex biological systems
- 1D Vs 3D: 2D representation
- Nodes denote biological molecules and edges denote their relationships

A quick view of network biology

Size of the network: organism complexity



Hub: essential or Evolutionarily conserved molecules

Node: biological molecule

Edge: physical, genetic or regulatory interaction,

(Quai-)Clique: protein complex

Path: pathway

1. A mapping from graph theory to biology
2. Global topological properties
3. Local patterns of interaction

Huge successes

Revealing the large scale organization and evolutionary principles of a cell

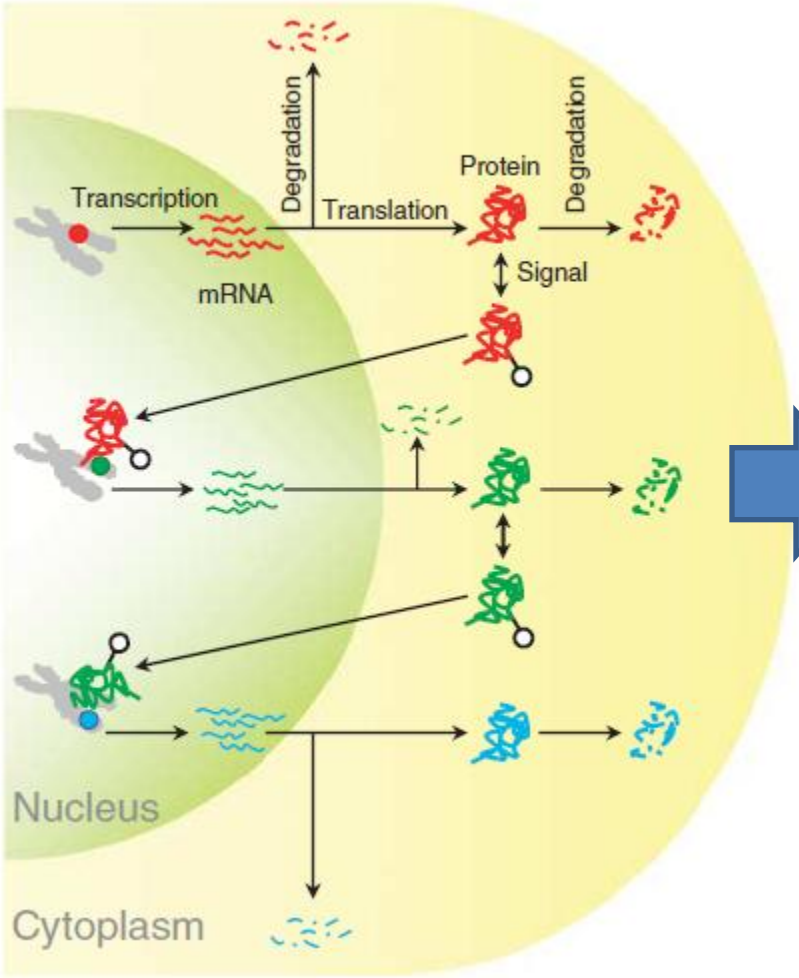
- Cellular networks are scale-free
- High clustering in cellular networks
- Motifs are elementary units of cellular networks
- Hierarchy organization of topological modules
- Modular organization of networks
- Topological, functional and dynamic robustness
- …

Nature Reviews Genetics, 2004

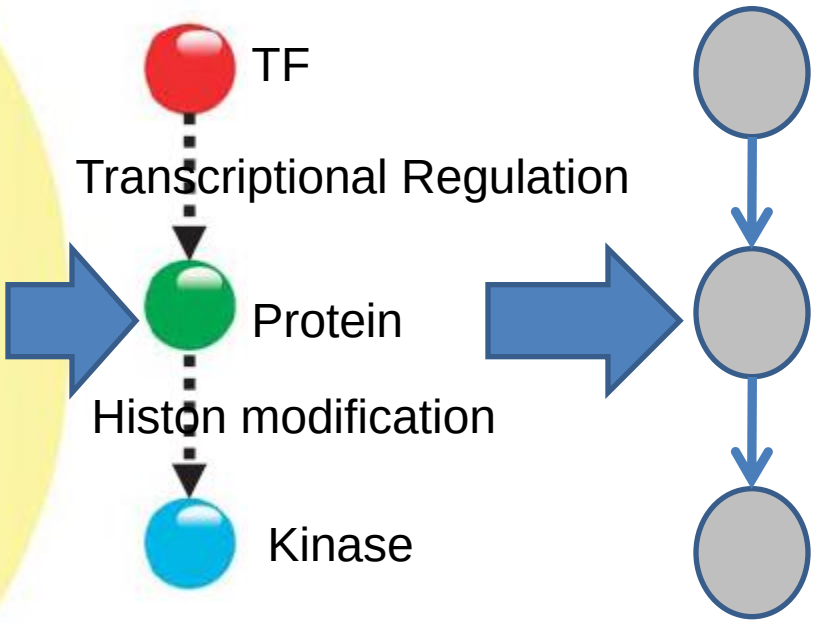
Is it enough to study the whole network?

Observation: Although protein-protein interactions are conveniently represented as nodes and edges in a network, it is important to note that each node in the network represents **several entities** (proteins in different tissues) and events (transcription, translation, degradation, etc) that are compressed in **both space and time**.

Biological complexity of networks



Network representation



Although a series of regulatory events can be conveniently represented as a node in the network, **the dynamics of the entities and the biological processes that make up the node are not captured.**

Molecular Systems Biology 5:294

Subnetwork vs whole network?

- **Observation:** Genome-wide network and subnetwork can be very different.

- **An example:**

1. The current interactome maps cover only a small fraction of the total interactome (3-15%).
2. Basic observation: the current interactome is scale free.
3. **Question:** can we infer that the topology of complete interactome networks is scale free?

Subnetwork?

- Many network-based studies focus on graph theoretical analysis of nodes and edges within a single, global biomolecular network. However, **there exists a high level of chemical and functional heterogeneity** within the underlying biomolecules, biomolecular interactions, and interactome subnetworks.

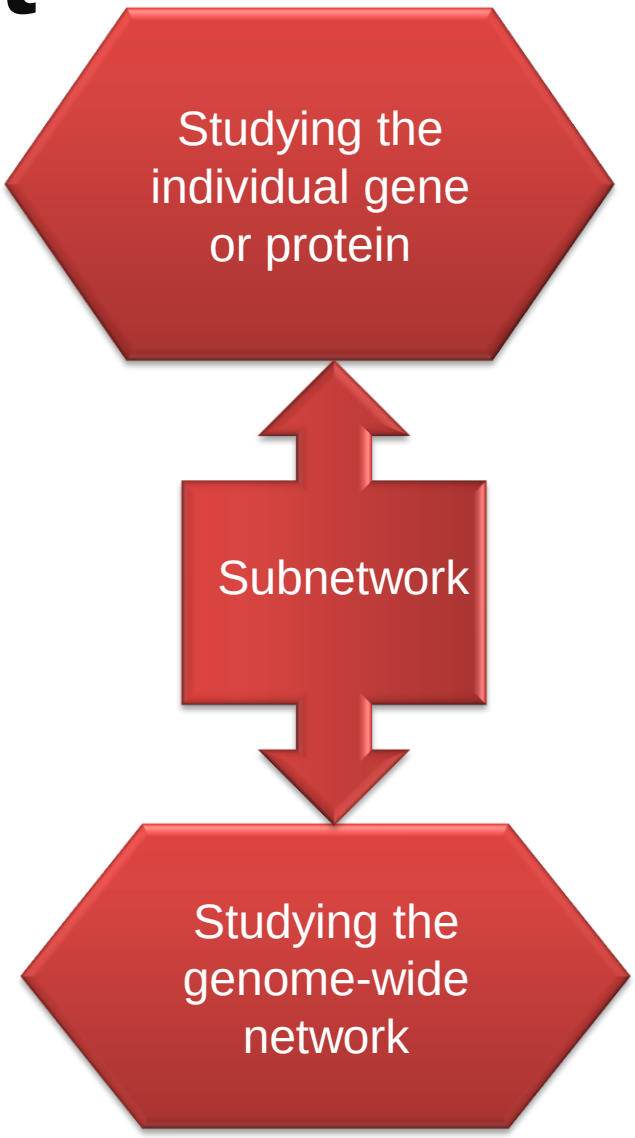
- **It remains an open question** whether or not the global properties of the full interactome extend to these subnetworks.

- In addition, **subnetworks may exhibit unique, emergent properties** that are absent in the conglomeration of the full interactome.

Studying subnetwork is important

- Studying a group of condition specific genes or proteins and their relationships.

- The **concept of subnetwork** is very important and extensively applied in different contexts.



Subnetwork

- Subnetworks can reveal the **complex patterns** of the whole-genome network

Temporal: The temporally conserved or diverse subnetworks

Spatial: Protein complexes depending on the sub-cellular localization

Condition specific context: Subnetwork biomarker for diseases

- Novel subnetwork identification methods that are flexible and efficient are still much needed.

Automatic modeling of signaling pathways from protein-protein interaction networks

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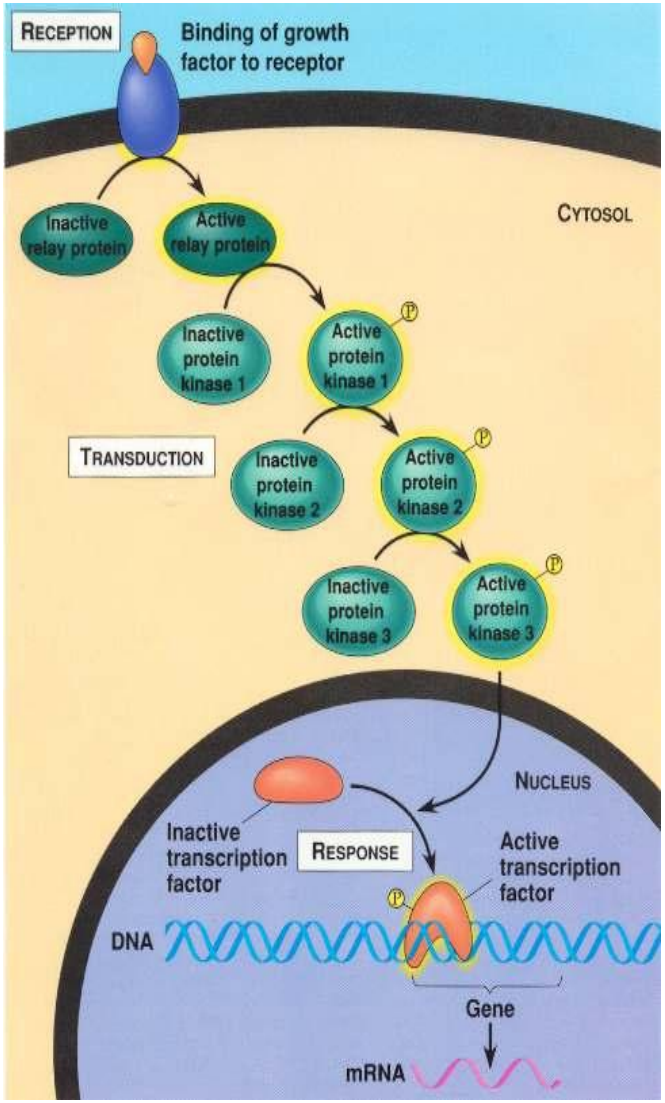
doi:10.1093/nar/gkn145

Uncovering signal transduction networks from high-throughput data by integer linear programming

Xing-Ming Zhao[1,2,3,4], Rui-Sheng Wang[5], Luonan Chen[1,3,4,5] and Kazuyuki Aihara[1,3,*]

[1]ERATO Aihara Complexity Modelling Project, JST, Tokyo 151-0064, Japan, [2]Intelligent Computing Lab, Hefei Institute of Intelligent Machines, Hefei, Anhui, China, [3]Institute of Industrial Science, The University of Tokyo, Tokyo 153-8505, Japan, [4]Institute of Systems Biology, Shanghai University, China and [5]Department of Electrical Engineering and Electronics, Osaka Sangyo University, Osaka 574-8530, Japan

Background



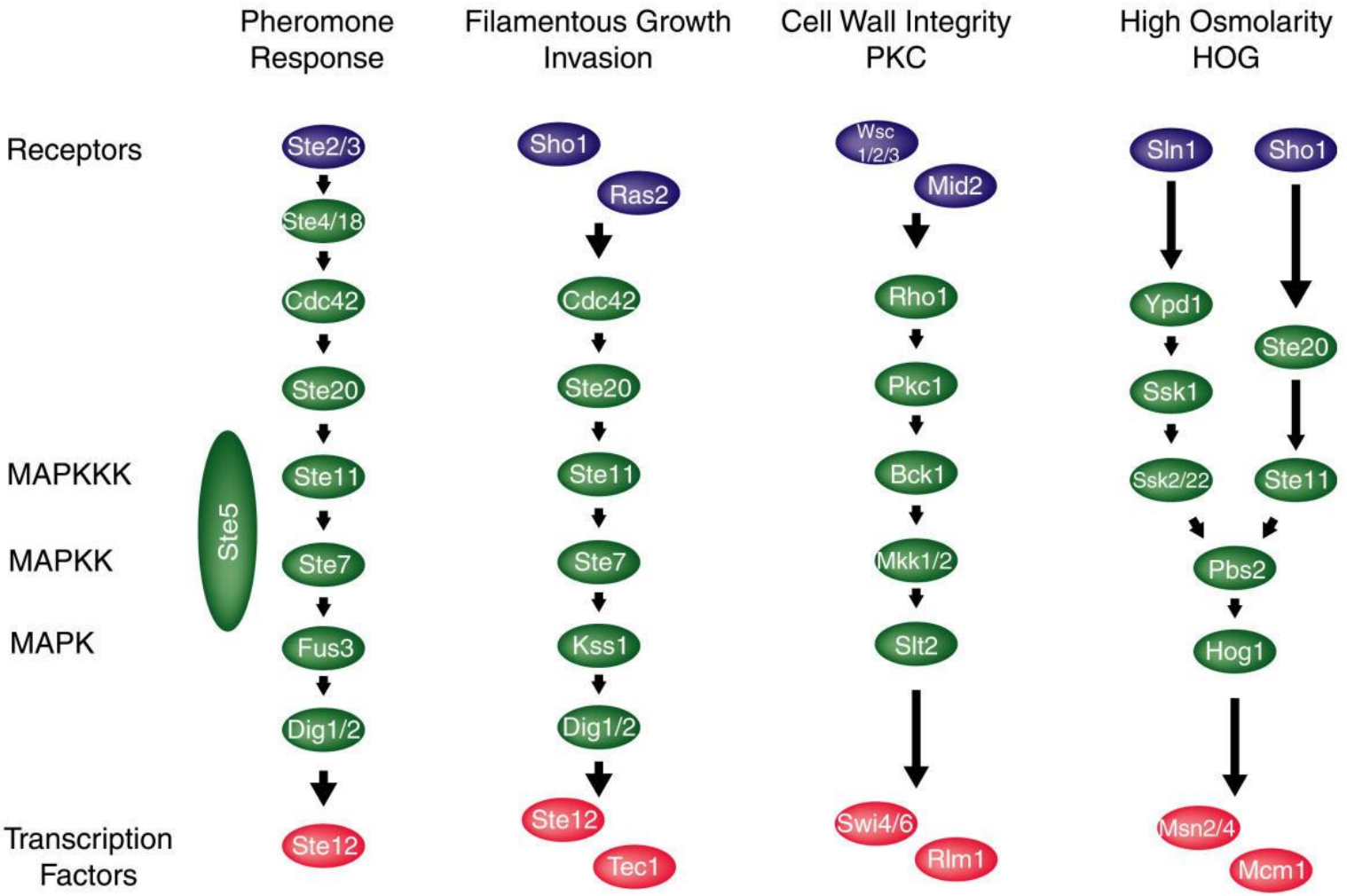
Signal transduction

» Movement of signals from outside the cell to inside; Cells always receive different signals from the physical environment and from other cells. 细菌的群体感应 (quorum sensing)

» Mediate the sensing and processing of stimuli; Many cellular decisions such as proliferation, differentiation, development and other responses to external stimuli are achieved by signal transduction.

» Abnormality in cellular information processing are responsible for diseases such as cancer, heart disease, autoimmunity, and diabetes.

MAPK signal transduction pathways in yeast



Background (cont.)

- Methods for **detecting components** in signaling pathways:
  - Experimental methods:
    - **Knock out** specific genes;
    - Time consuming and expensive;
      - Every reaction and component even in a relatively simple signaling pathway requires a concerted and decades-long effort.
      - Many signaling components and mechanisms are unknown. There is not a lot of kinetic data available with which to create models of pathway component interaction.
  - Computational methods
    - Knowledge based methods;
    - Data based methods.

Background (cont.)

- Knowledge based methods:
  - Modeling pathways by ordinary differential equations;
  - Modeling pathways by Petri net
  - Limited by the scale, lack of kinetic coefficients

- **Data based (our focus):**
  - High-throughput techniques result in large mounts of biological data.
  - Recovering signal transduction pathways and identifying key components from multiple data sources.
    - Large scale.
    - Data dependency.

Previous works

NetSearch algorithm

Steps:

- Potential pathways detected by Depth First Search (DFS) algorithm from PPI network;
- Ranking candidate pathways according to the clustering results on gene expression data.
- The more the elements in candidate pathways overlap with a cluster, the more likely they are true components.

"Automated modelling of signal transduction networks", BMC Bioinformatics 2002, 3:34.

Previous works (cont.)

Ordering the signal pathway with score function

Steps:

- Assume the components in a signaling pathway are known. Only the order of the components is unknown
- Find the candidate pathways by using PPIs, i.e. assign each order a score
- Ordering the signal pathways by using gene expression data (pairwise correlation coefficients).

"A computational approach for ordering signal transduction pathway components from genomics and proteomics data", *BMC Bioinformatics, 5, 158, 2004*

Previous works (cont.)

- Problems lying in the previous works:
  - Individual signaling pathways are identified and then heuristically rank and assemble them into a signal transduction network;
  - Multi-stage tends to lead to local optimal solutions.

- A one-stage method with global optimal solutions is needed.

An idea about recovering signaling networks

- Proteins involving in a same signaling pathway tend to interact with each other.
- The model tries to find a subnetwork with highest sum of edge weights (**there is a tradeoff between the sum of edge weights and the number of edges**) from a **membrane protein** (receptor) to a **transcription factor** in a big protein-protein interaction (PPI) network.
- The extraction process is formulated into **an integer linear programming model**, which will be relaxed into a linear programming in the practical applications

Recovering signaling networks by integer linear programming

$$\text{Minmize}_{\{x_i, y_{ij}\}} \quad S = -\sum_{i=1}^{|V|}\sum_{j=1}^{|V|} w_{ij}y_{ij} + \lambda \sum_{i=1}^{|V|}\sum_{j=1}^{|V|} y_{ij} \qquad 1$$

Subject to

$$y_{ij} \le x_i, \qquad 2$$

$$y_{ij} \le x_j, \qquad 3$$

$$\sum_{j=1}^{|V|} y_{ij} \ge 1, \quad \text{if } i \text{ is either a starting or ending protein,} \qquad 4$$

$$\sum_{j=1}^{|V|} y_{ij} \ge 2x_i, \quad \text{if } i \text{ is not a starting or ending protein,} \qquad 5$$

$$x_i = 1, \quad \text{if } i \text{ is a protein known in STN,} \qquad 6$$

$$x_i \in \{0, 1\},\ i = 1, 2, \ldots, |V|, \qquad 7$$

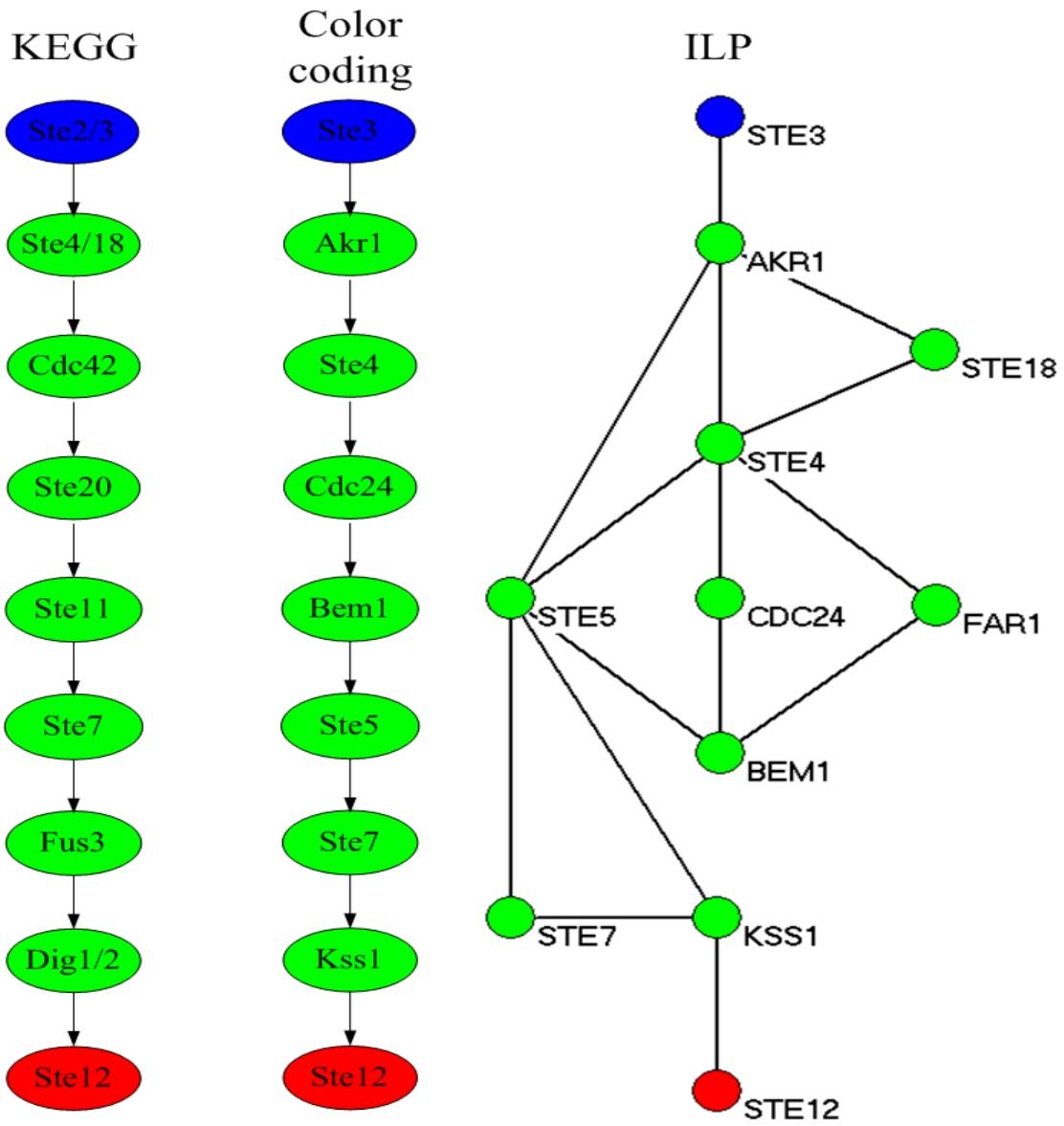
$$y_{ij} \in \{0, 1\},\ i, j = 1, 2, \ldots, |V|, \qquad 8$$

- w_{ij} – PPI strength
- x_i – binary variable for protein i
- y_{ij} – binary variable for protein interaction (i,j)
- λ – penalty parameter
- One step and global model !!!

Experimental results

- Experimental data:
  - Yeast protein interaction network with ~4,500 nodes and ~14,500 edges.
- Pre-process:
  - Find the paths of length 6-8 from the PPI network using the Depth-first search;
  - The reduced network consist of all possible candidate pathways.

Pheromone response (linear path)

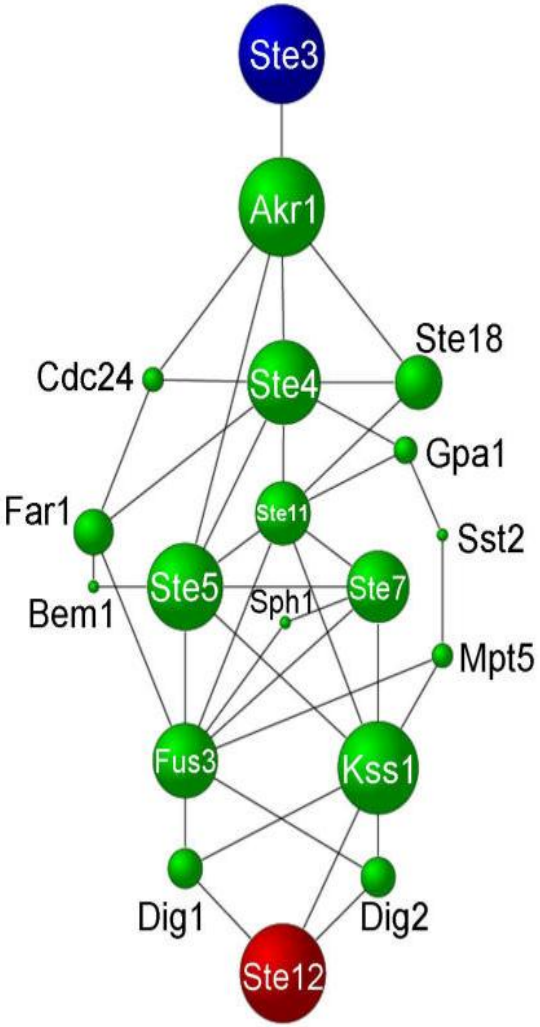


信息素响应

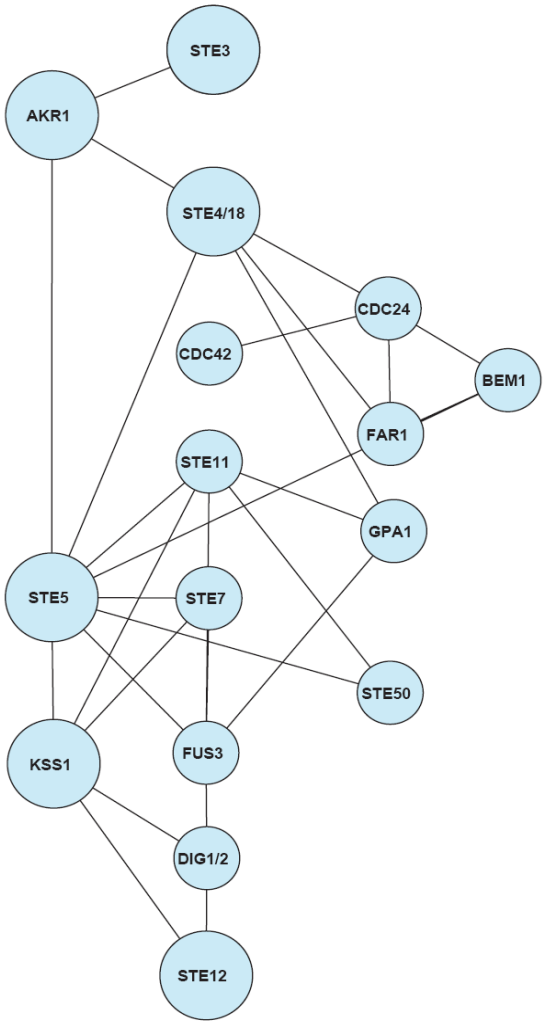
We find additional components. Such redundant mechanisms can compensate single protein disruptions and maintain signal transduction unblocked

Pheromone response (signaling network)

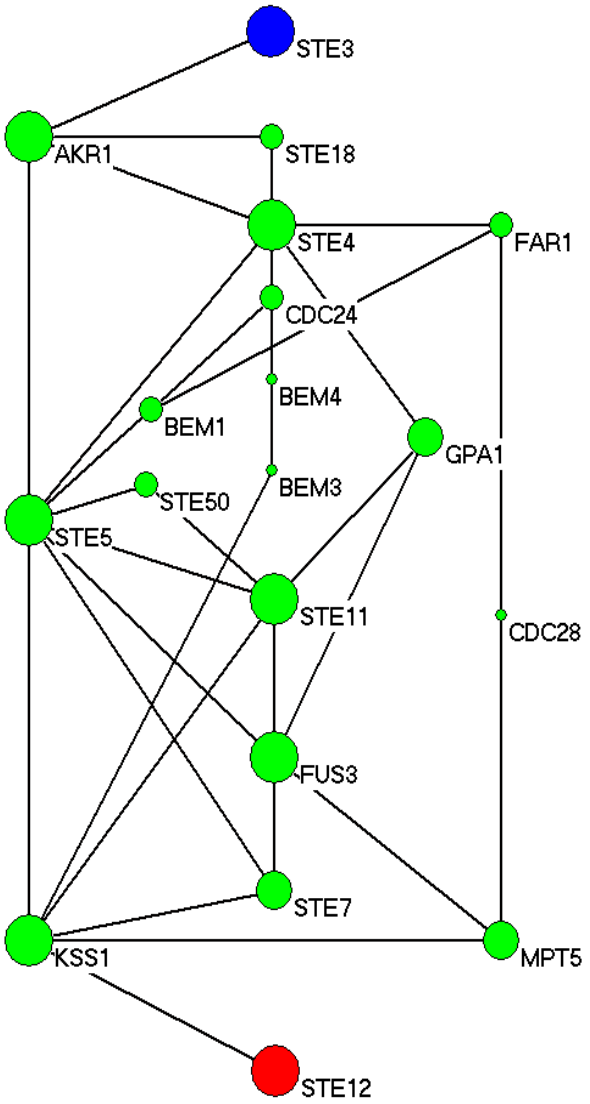
Netsearch



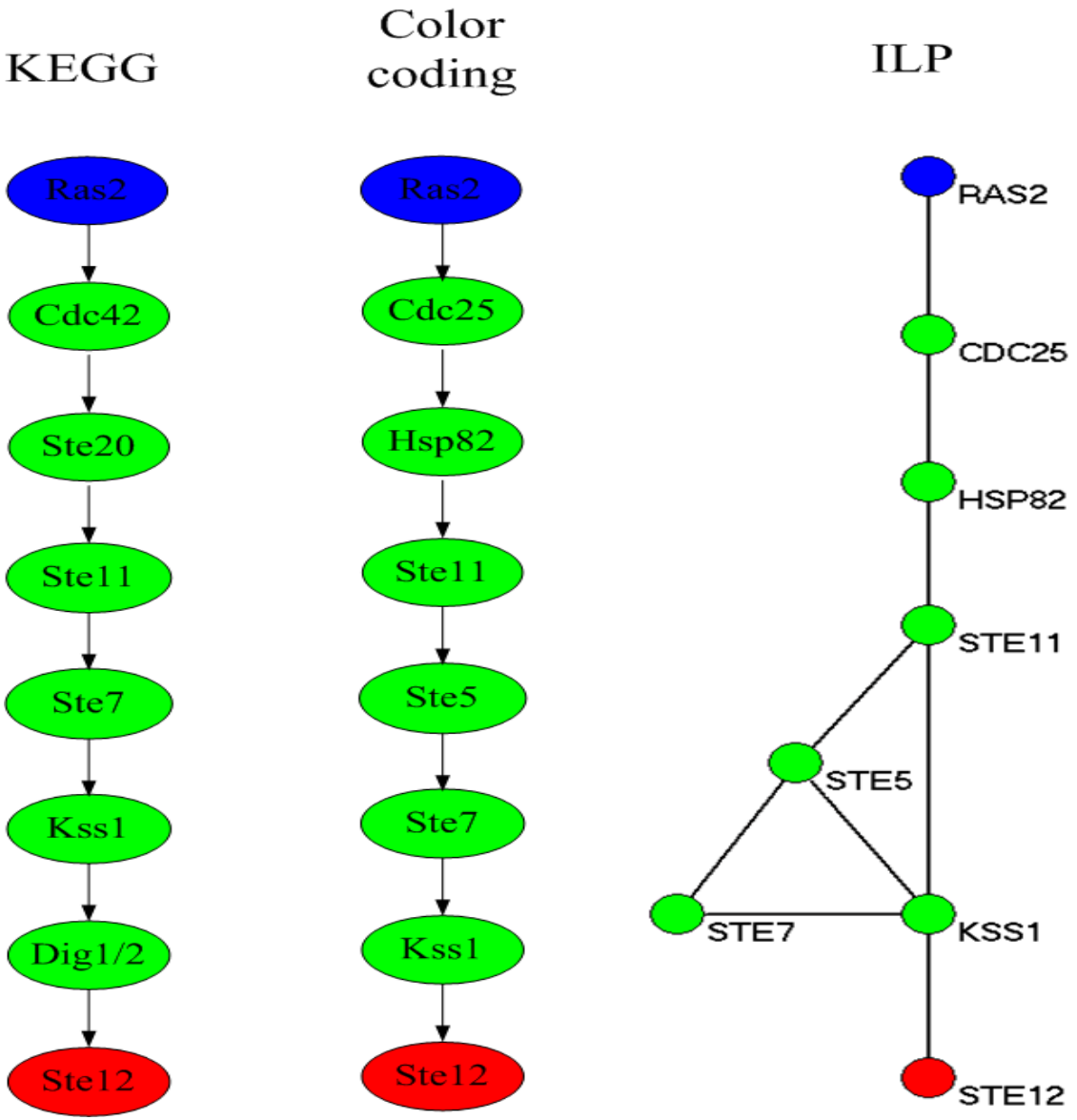
color coding



ILP



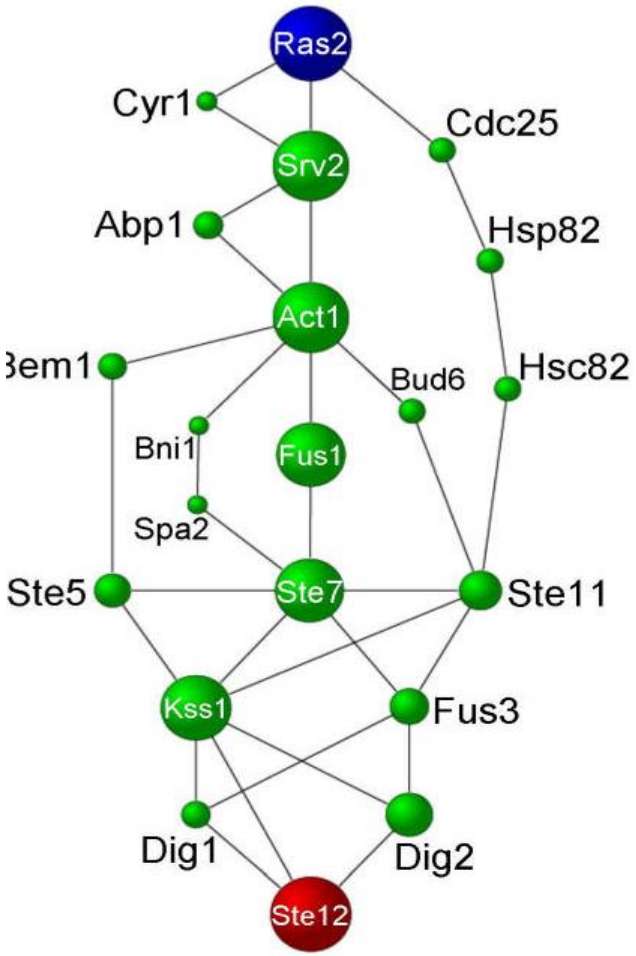
Filamentation pathways (linear path)



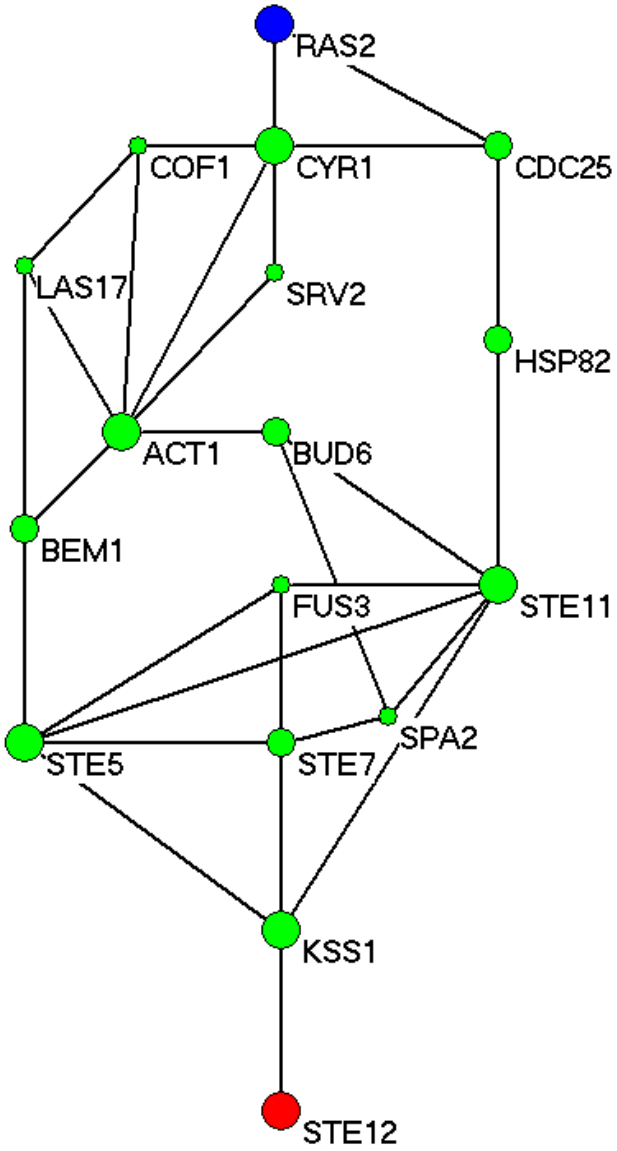
细菌成丝

Filamentation pathways (signaling network)

Netsearch

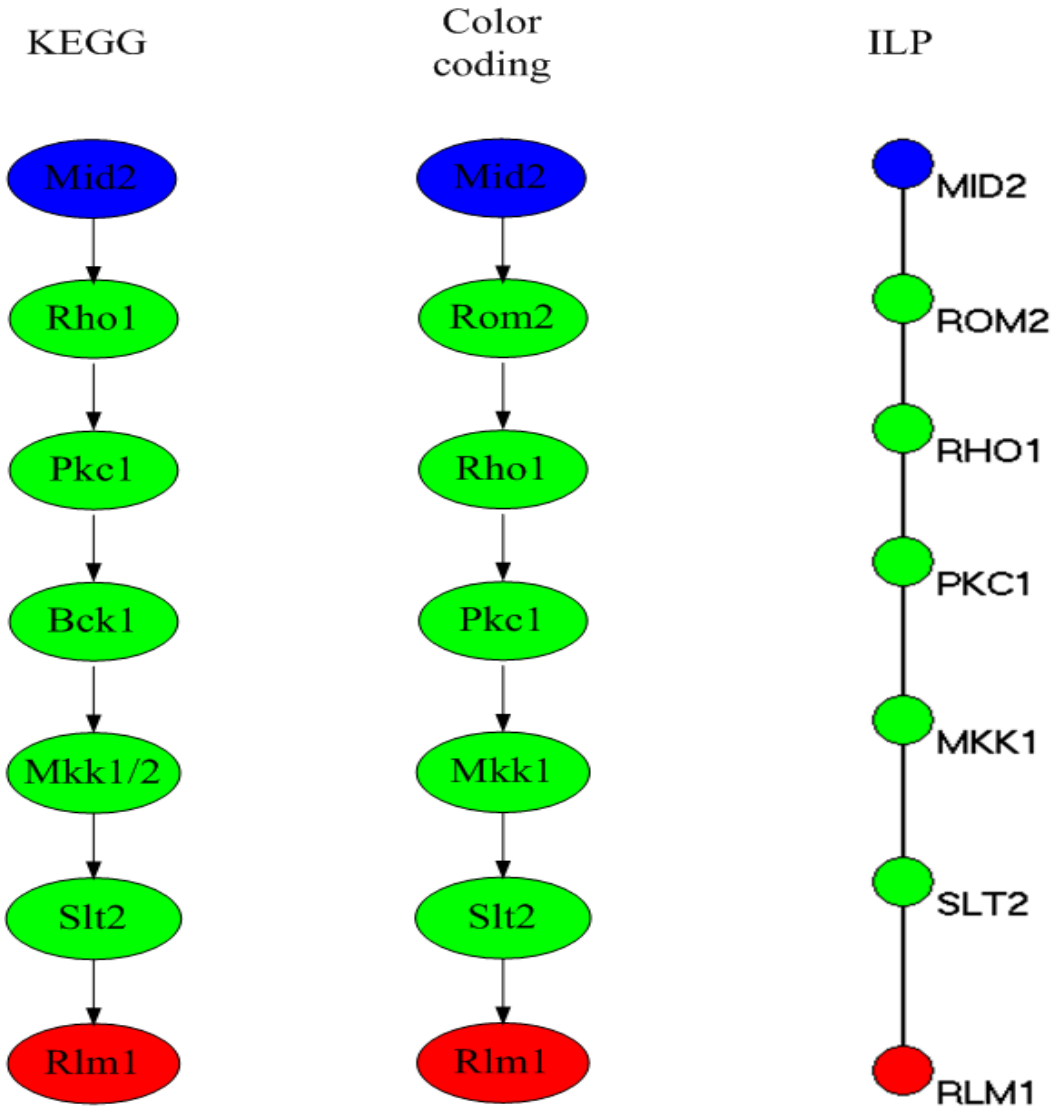


ILP



Cell wall integrity (linear path)

细胞壁



This method can detect the exact pathway that other algorithms found

Discussion

- These results on known yeast MAPK signaling pathways demonstrate that the ILP model can recover the known signaling pathways, and the reconstructed STNs match most parts of those published results

- Compared with existing methods, **this method is much simpler in both algorithm and computation** because it can detect the signaling networks from protein interaction data directly in an integrated and accurate manner

- This method can handle a large scale system without numerical difficulty due to the LP algorithm.

Conclusion and future work

- **Proposed LP algorithm is effective** for inferring the signaling network; It is a one-stage method and does not need heuristic ranking and assembling

- Protein interactions have no timing information. In the future, we will integrate PPIs with gene expression data for signaling network detection, which will make the detection more realistic

- We will also explore the further application of the method to other signaling networks except MAPK pathways.

Qiu *et al. BMC Bioinformatics* 2010, **11**:26
http://www.biomedcentral.com/1471-2105/11/26

BMC Bioinformatics

RESEARCH ARTICLE Open Access

Detecting disease associated modules and prioritizing active genes based on high throughput data

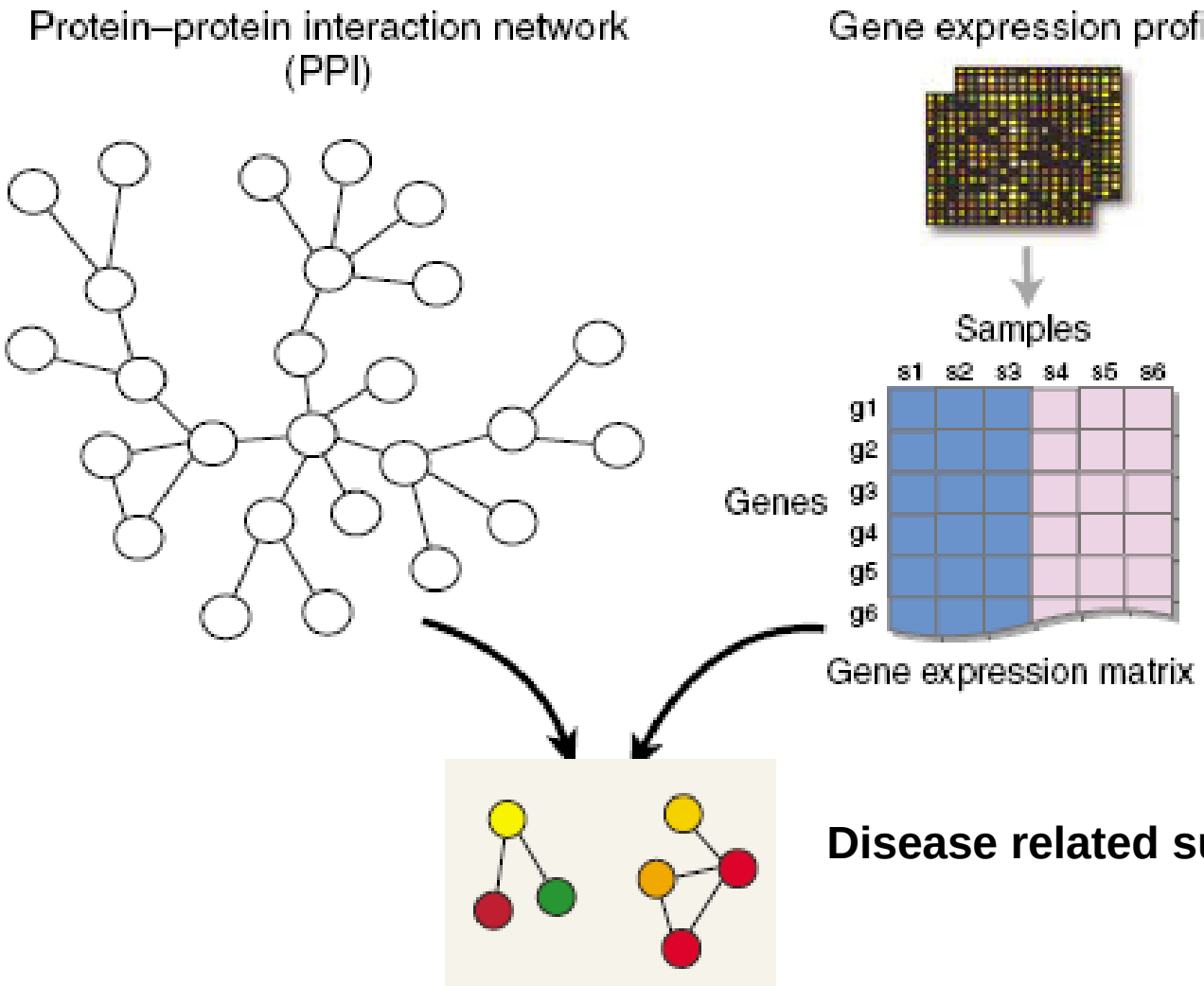
Yu-Qing Qiu[1†], Shihua Zhang[1,2†], Xiang-Sun Zhang[1*], Luonan Chen[3,4*]

Abstract

Background: The accumulation of high-throughput data greatly promotes computational investigation of gene function in the context of complex biological systems. However, a biological function is not simply controlled by an individual gene since genes function in a cooperative manner to achieve biological processes. In the study of human diseases, rather than to discover disease related genes, identifying disease associated pathways and modules becomes an essential problem in the field of systems biology.

Results: In this paper, we propose a novel method to detect disease related gene modules or dysfunctional

Finding the disease related subnetwork



Problem formulation

- Defining response active score f_i for each gene i. ➔$f_i = f(x_i; x_1, x_2, \ldots, x_n)$

$$f(x_i) = \langle u, \phi(x_i) \rangle + b$$

$$u = \sum_{j=1}^{n} \beta_j \phi(x_j)$$

$$k_{ij} = \langle \varphi(x_i), \varphi(x_j) \rangle$$

$$f(x_i) = \sum_{j=1}^{n} \beta_j k_{ij} + b$$

- Defining observed active score w_i for each gene i:

$$w_i = \frac{\mu_{i1} - \mu_{i2}}{\sigma_{i1} + \sigma_{i2}}$$

Problem solution

- Support vector regression (SVR) model:

$$\min \frac{1}{2} || u ||^2 + C * \sum_{i=1}^{n} || f_i - w_i ||^2$$

- It is solved by considering its dual problem (convex quadratic programming)

$$\min \quad \frac{1}{2} \sum_{i,j=1}^{n} (\alpha_i - \alpha_i^*)(\alpha_j - \alpha_j^*) K_{ij}$$

$$-\epsilon \sum_{i=1}^{n} (\alpha + \alpha_i^*) + \sum_{i=1}^{n} w_i (\alpha_i - \alpha_i^*),$$

$$\text{s.t.} \quad \sum_{i=1}^{n} (\alpha_i - \alpha_i^*) = 0,$$

$$\alpha_i, \alpha_i^* \in [0, C^*], i = 1, 2, \ldots, n,$$

To get the condition-specific pathway

- This SVR model is solved by LIBSVM software:

$$VU_f = \{v_i; f_i > \bar{f} + \theta\sigma, i = 1, 2, \ldots, n\}$$

$$VD_f = \{v_i; f_i < \bar{f} - \theta\sigma, i = 1, 2, \ldots, n\}$$

- The induced subnetwork from G forms the up-regulated (down-regulated) pathways.

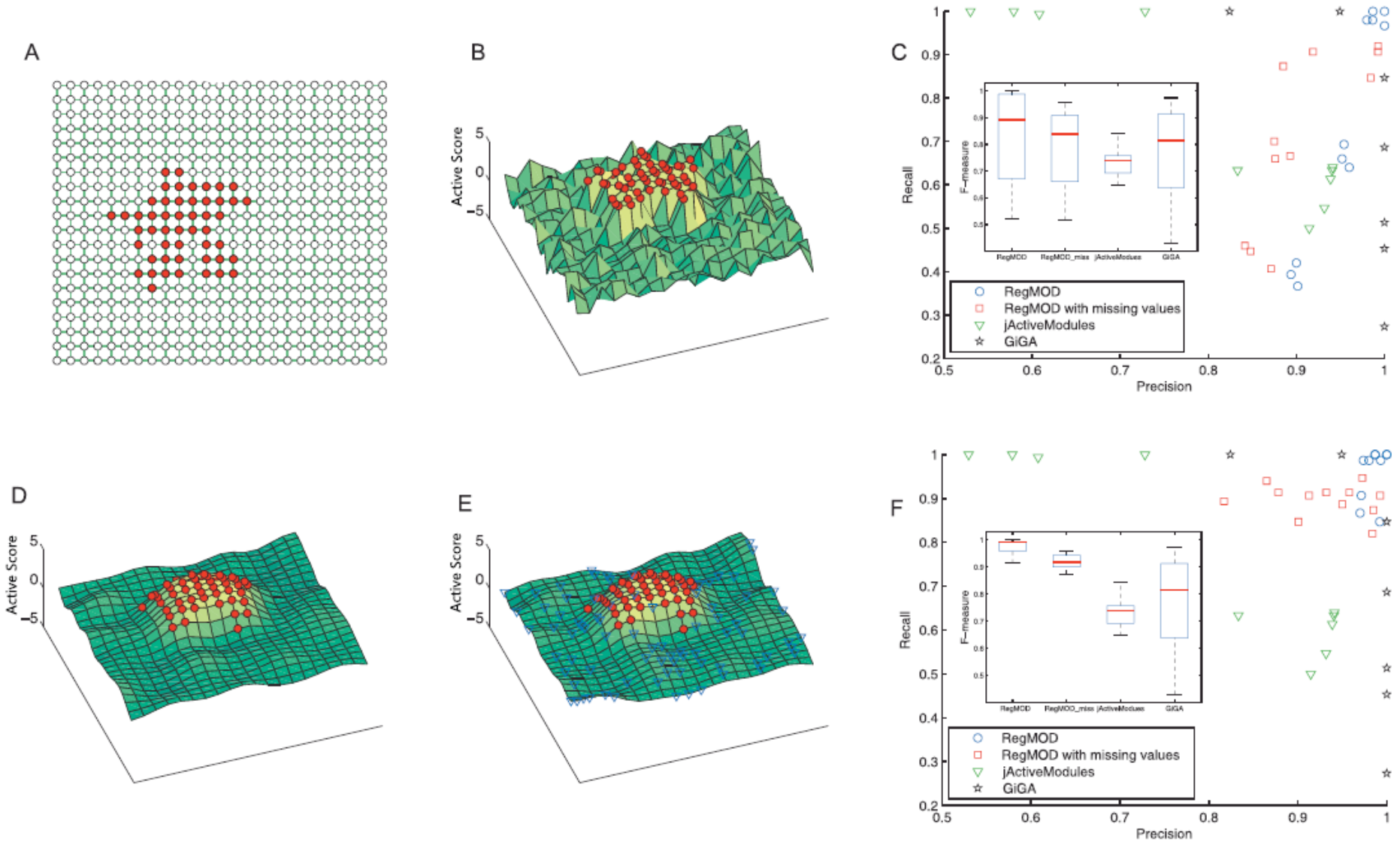
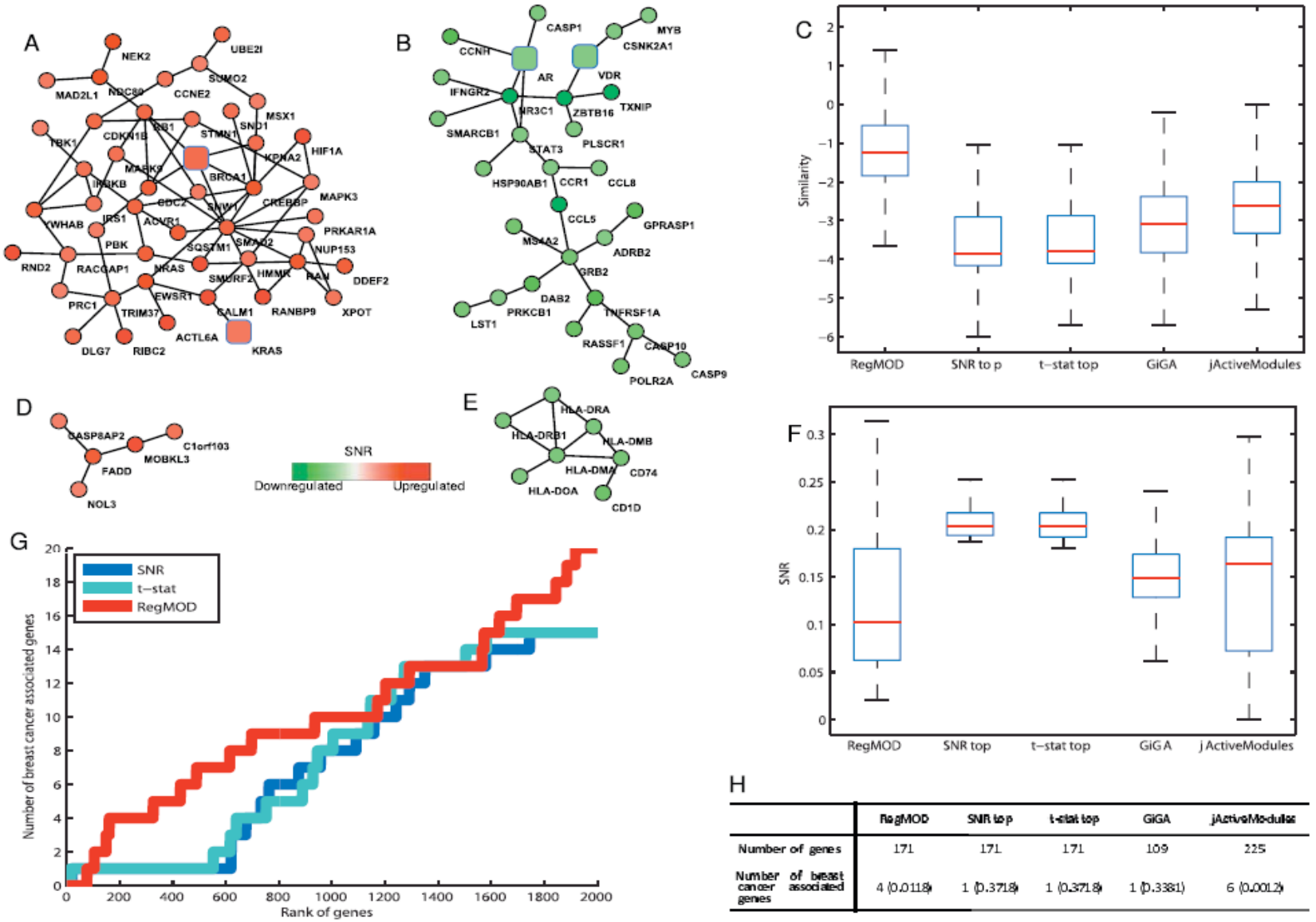


Figure 1 Illustration of the effect of RegMOD. (A) shows the grid network where the red nodes represent the active module. (B) and (D) illustrate the active score surfaces before and after the processing of RegMOD respectively. (E) shows the active score surface obtained by RegMOD when the nodes represented by blue triangle are deleted. In the randomly generated network example, the recall-precision plot and box-plot of F-measure for RegMOD are shown in (C). In the edge-weighted case, the performance is significantly improved. The recall-precision plot and box-plot of F-measure for RegMOD are shown in (F).



H

	RegMOD	SNR top	t-stat top	GiGA	jActiveModules
Number of genes	171	171	171	109	225
Number of breast cancer associated genes	4 (0.0118)	1 (0.3718)	1 (0.3718)	1 (0.3381)	6 (0.0012)

Figure 2 Breast cancer metastasis associated modules identified by RegMOD. The square nodes refer to known breast cancer related genes. (A) and (D) are up-regulated modules BCUM1 and BCUM2 which are related to cell cycle and apoptosis respectively in red color. (B) and (E) are down-regulated modules BCDM1 and BCDM2 which are related to signaling transduction and antigen presentation respectively. (C) and (F) chart the box-plot of the similarity among genes and SNR values of genes involved in active modules found by different methods. The distributions of breast cancer genes on different gene ranking lists are shown in (G). (H) charts the comparison of gene sets' coverage of known breast cancer associated genes using different methods with the significant p-values calculated by hypergeometric distribution.

Optimization model for condition specific subnetwork identification

The Second International Symposium on Optimization and Systems Biology (OSB'08)
Lijiang, China, October 31– November 3, 2008

Condition specific subnetwork identification using an optimization model

Yong Wang[1,2] Yu Xia[1]

[1]Bioinformatics Program, Department of Chemistry, Boston University, Boston, MA 02215, USA
[2]Academy of Mathematics and Systems Science, Chinese Academy of Sciences, Beijing 100080, China

Subnetwork

- Subnetworks can reveal the complex patterns of the whole-genome network

Temporal: The evolutionarily conserved subnetworks

Spatial: Protein complexes depending on the sub-cellular localization

Condition specific context: Subnetwork biomarker for diseases

- Novel subnetwork identification methods that are flexible and efficient are still much needed.

Problem formulation

- Input:

  G=(V,E) is the network with n nodes V_1,V_2. … V_n. We use a symmetric weight matrix W to quantify the connectivity strength (for example, W can be the edge confidence scores for biomolecular interaction or functional linkage networks). $W_{ij} \geq 0$,I,j=1,2…n.

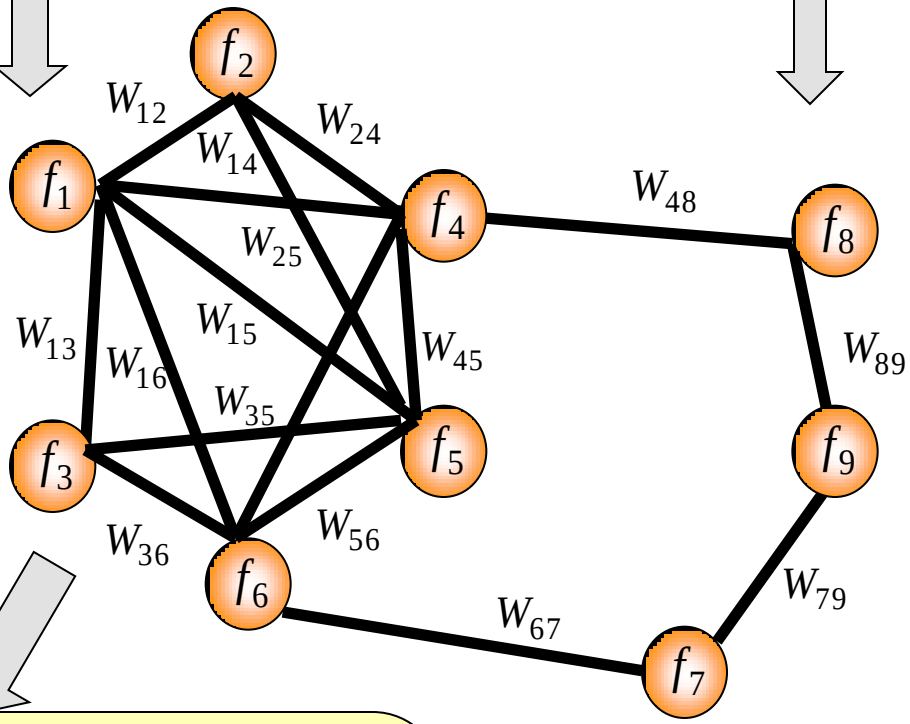
  Every node V_i is associated with a profile (for example gene expression data, or other properties related to the nodes). We consider the simplest case (weight f_i).

- The question:

  Can we find the a group of nodes in this network with similar profiles?

Constructing molecular network G=(V, E) and edge weight Matrix $\{W_{ij}, i,j=1,2,\ldots,n\}$

Assembling condition specific information $f_1, f_2, f_3, \ldots, f_n$ for molecules



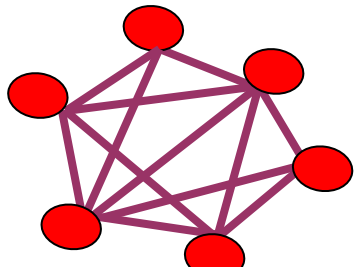
Optimization model

$$\max \quad \sum_i \sum_j W_{ij} x_i x_j + \lambda \sum_i f_i x_i$$

$$s.t. \quad x_1^\beta + x_2^\beta + x_3^\beta + \cdots + x_n^\beta = 1$$

$$x_i \geq 0 \qquad i = 1,2,\cdots,n$$

Condition specific subnetwork



Then we have two objects:

1. Choose **as many as possible edges** within the subnetwork (maximize the interconnectivity within the subnetwork)
2. **Maximize the degree of association** between the subnetwork nodes and the specific condition.
3. We introduce a parameter to integrate them.

- We introduce a **regularization constraint** that limit the number of nodes selected.

1. Parameter ***β*** is introduced to adjust the strength of regularization applied to the variable $x=(x^1,x^2,\ldots,x^n)$
2. When β=2, this is a trust region problem which optimizes a quadratic function
3. When β=1, the L1-type constraint will lead to a sparse solution, i.e., many of the entries will be zeros

Computational complexity

- If we focus only on the first term of objective function, our model can be used to **find the maximum clique in an weighted graph** (the Motzkin-Struss Formalism for computing maximal cliques, Motzkin-Straus Theorem, 1965)
- Both the maximum cardinality and **the maximum weight clique problems** are NP-hard.
- Biomolecular networks are often large in scale. In yeast the protein-protein interaction network is estimated to have about 6,000 nodes and 50,000 interactions.

A fast algorithm for large-scale problem

The KKT condition is:

$$L = -\sum_{\mathrm{i}}\sum_{\mathrm{j}} W_{ij}x_i x_j - \lambda\sum_i f_i x_i + \alpha(x_1^\beta + x_2^\beta + x_3^\beta + \cdots + x_n^\beta - 1) - \sum_i \mu_i x_i$$

$$\frac{\partial L}{\partial x_i} = 0 \Rightarrow \mu_i = -2(WX)_i - \lambda f_i + \alpha\beta x_i^{\beta-1} \qquad i = 1,2,\cdots,n$$

$$\mu_i x_i = 0 \qquad i = 1,2,\cdots,n$$

$$x_{\mathrm{i}} \geq 0, \qquad \mu_i \geq 0 \qquad i = 1,2,\cdots,n$$

$$x_1^\beta + x_2^\beta + x_3^\beta + \cdots + x_n^\beta = 1$$

Then we can use the following iterative algorithm to quickly converge to a local minimum satisfying KKT condition:

$$\alpha = (2X^T WX + \lambda\sum_i f_i x_i) \Big/ \beta$$

$$x_i^{t+1} = (x_i^t \frac{2(WX)_i + \lambda f_i)}{\alpha\beta})^{\frac{1}{\beta}} = (x_i^t \frac{2(WX)_i + \lambda f_i)}{2X^T WX + \lambda\sum_i f_i x_i})^{\frac{1}{\beta}}$$

Please refer the paper for Proof of Convergence!

Notes on the model

- To relax the variable from integer to continuous variable in [0,1], we get a quadratic programming problem. The meaning can be the probability of that node to be a biomarker.

- The hardness of this programming depends on the network structure, maybe many local minimums exist. So careful choose of initial solution is necessary.

- We provide a deterministic way to replace the current heuristic based methods for subnetwork identification.

Type 2 diabetes related subnetwork

- Type 2 diabetes mellitus is a complex disease with profound impact on health and longevity.

- It is estimated to affect more than 150 million people worldwide by the World Health Organization statistics.

Data integration

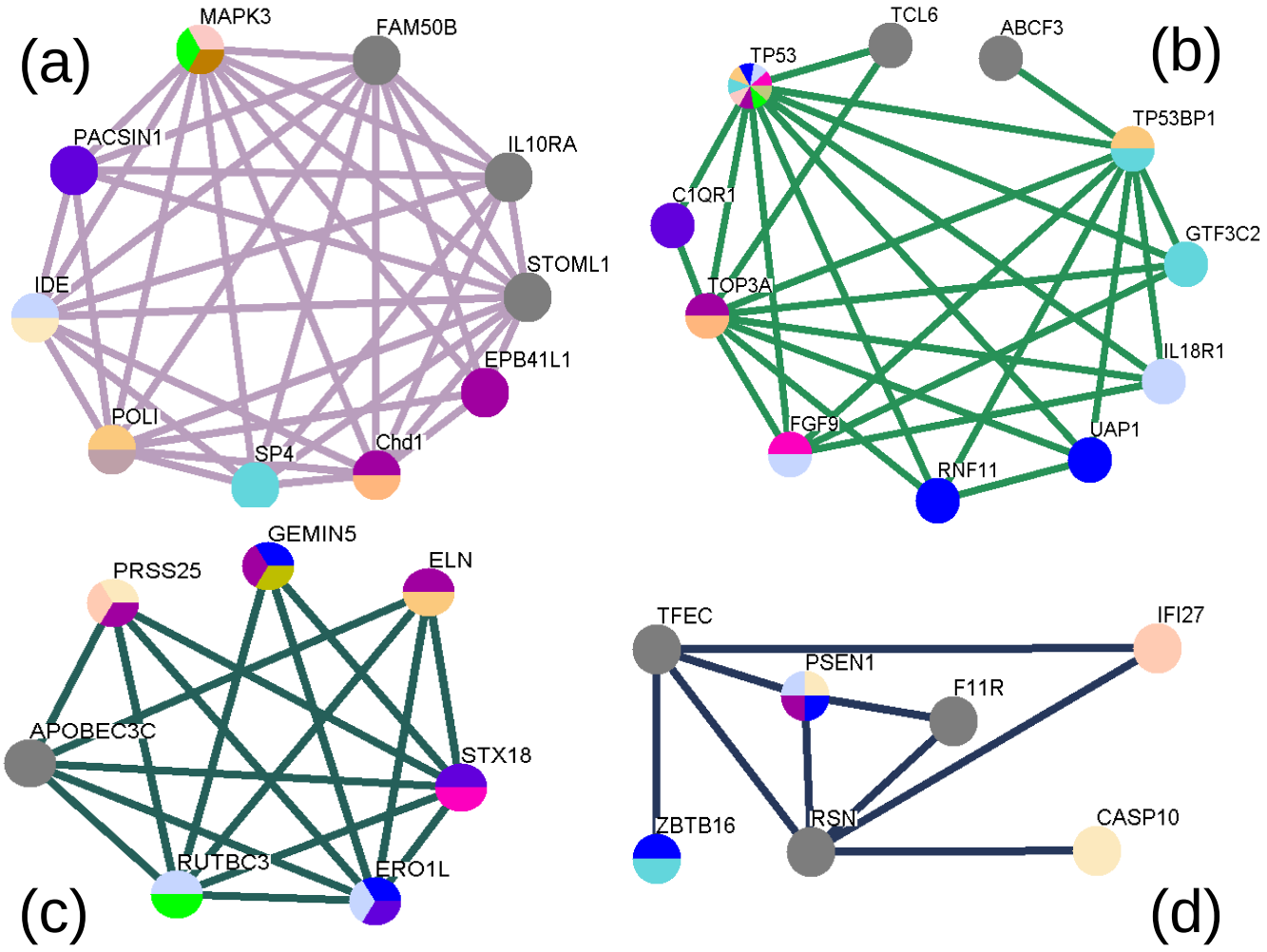
- The basic network is protein interaction network

We assembly the protein-protein interaction data in human have 7,903 proteins and 44,422 interactions. We make the sparse (the percentage of protein pairs that interact is only 0.14%.) denser by considering indirect interaction. In this way, we get a weighted protein-protein interaction network with 724,144 edges (2.3% of all protein pairs, a 16-fold increase in network size).

- Disease related data is confidence of association with T2D

We collected 2503 genes related to T2D and each gene is assigned a confidence score to be T2D candidate gene

Identified subnetworks



They are closely related to insulin-degradation, signal transduction, and metabolism functions.

Why “pilot study”?

- First, the present protein-protein interaction network in human is noisy and far from complete.
- Second, **our basic assumption** is that subnetworks are better biomarkers than single proteins, which needs further experimental and clinical verification especially for complex diseases such as T2D.
- Further research directions include **validation of the effectiveness of subnetwork biomarkers**, and **improvement of the subnetwork identification** algorithm.

Conclusions

- We discuss a general framework to integrate two different kind of data.
- Condition-specific or disease-related subnetworks are important in systems biology.
- a general methodology to deal with it.

Take-home messages

- Subnetwork concept is very important.

- It provides a efficient way to integrate heterogeneous data sources to identify condition-specific pathways (subnetworks)