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From Machine Learning to Learning Machines - A Perspective toward Personalized Medicine

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Outline of the talk

- Introduction
- Learning Machines: A Bottom-up Approach with a Network
- Analysis of Networks
- From Networks to Personalized Medicine

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Introduction

The Interactomes

- Molecular Networks
  - Protein-protein Interaction Networks
  - Metabolic Networks
  - Regulatory Networks - TF-gene Networks
  - Post-translational Networks - Kinase-substrate Networks
  - RNA Networks - TF-miRNA Networks, miRNA-gene Networks
- Phenotypic Networks
  - Co-expression Networks
  - Genetic Networks
- What is a Disease Network?

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Disease Genes (A Snapshot from 2007)

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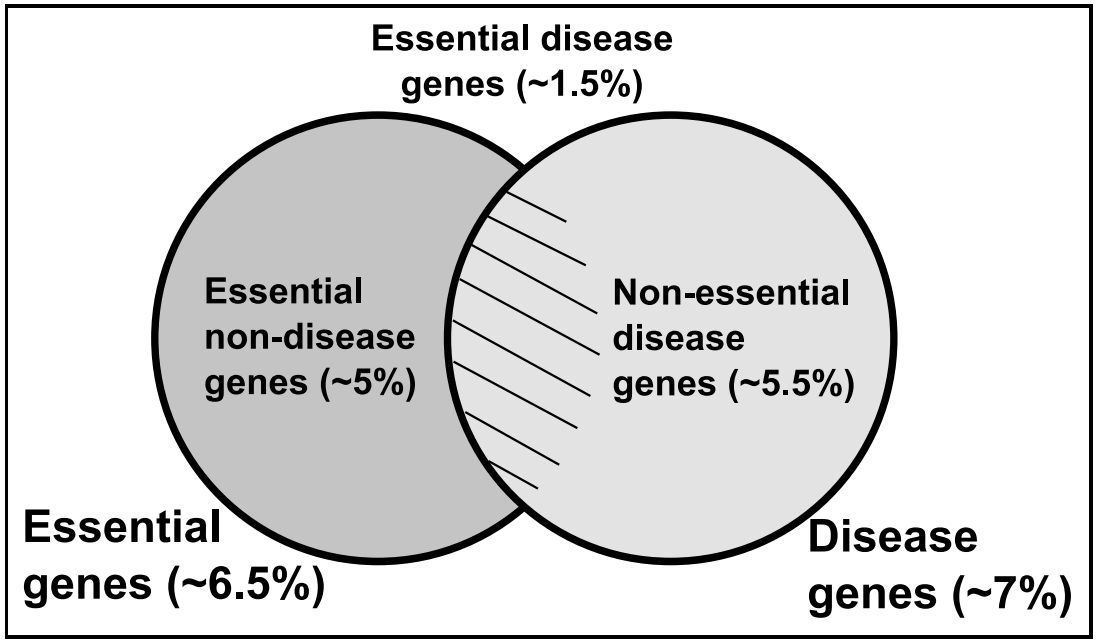

- Less than 10% of human genes are known to have association with specific diseases [Barabási, 2011].
- Of these ∼19% are known to be oncogenes (November 16, 2011; Cancer Genome Project).

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Learning Machines: A Bottom-up Approach with a Network

A Framework of Co-expression Analysis

- Co-expression
- Differential Expression
- Differential Co-expression
- Co-expression Dynamics

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Co-expression

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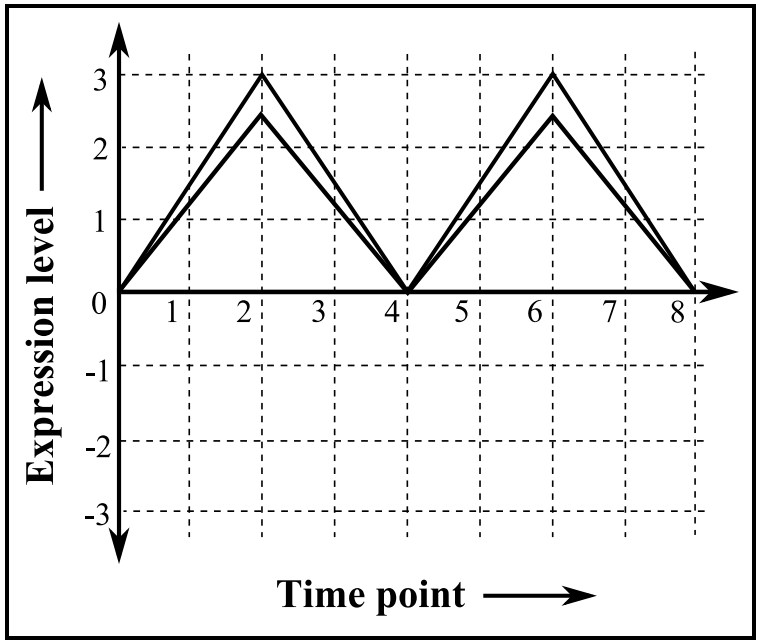
Definition

Pairwise similarity pattern (spatial or temporal) of expression vectors.



- Different statistical measures [Bandyopadhyay, 2011].

Differential Expression

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Definition

Varying patterns (spatial or temporal) of expression vectors in different phenotypes.

- SAM, t-test, etc.

Differential Co-expression

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Definition

Pairwise varying dependence (spatial or temporal) between expression vectors in different phenotypes.

- On/off case and gap/subsitution case [Dettling, 2005].

Co-expression Dynamics

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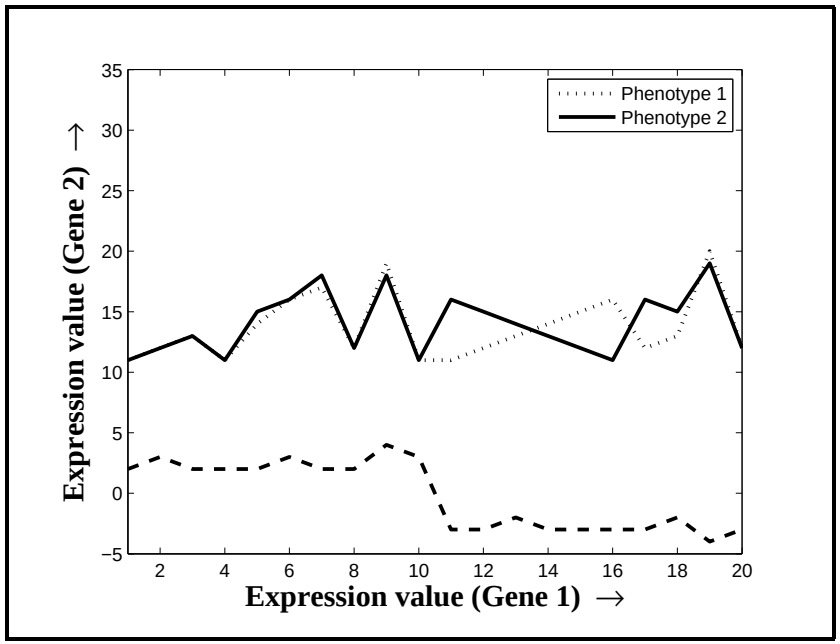
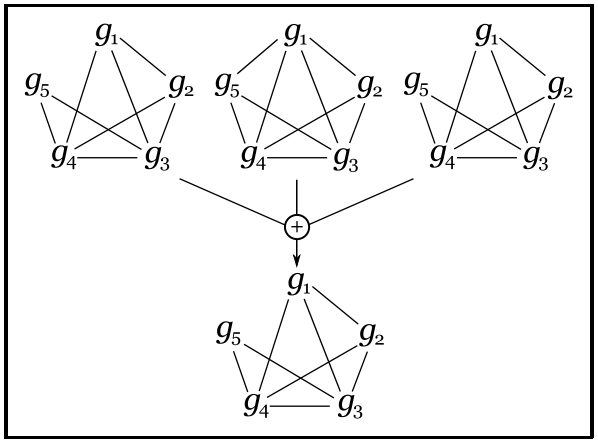
Definition

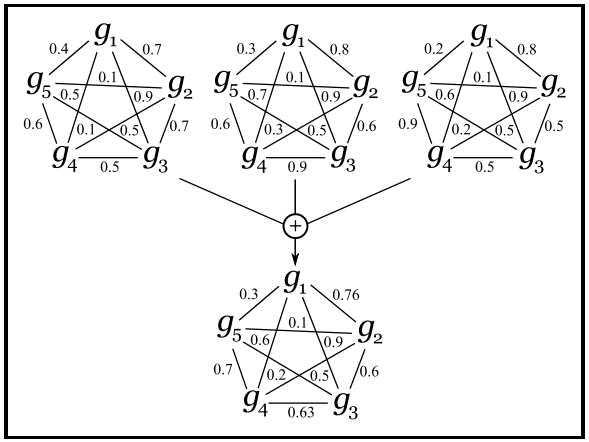
Pairwise varying dependence (spatial or temporal) between expression vectors based on another expression vector.



[Li, 2002].

Making Networks Robust by Integration





Supervised Approach

$$LS = \ln \frac{P(L|E)/\sim P(L|E)}{P(L)/\sim P(L)}$$

$P(L|E)$ and $\sim P(L|E)$ are the observed linkage frequencies of annotated genes operating in the same and in different pathways, respectively, whereas $P(L)$ and $\sim P(L)$ are the prior annotations [Lee, 2004].

Unsupervised Approach

$$W_c(i,j) = \sqrt[\alpha]{\sum_{k=1}^{n} \xi_k(i,j) W_k(i,j)^\alpha}$$

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Analysis of Networks

Understanding the Diseasome

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Hypotheses

Degree: Disease biomolecules avoid hubs

Modularity: Biomolecules specific to a disease form modules

Sharing: Diseases having common biomolecules show phenotypic similarity

Closeness: Causal pathways coincide with the connectors of known disease-subnetworks

Differential Co-expression to Module Finding

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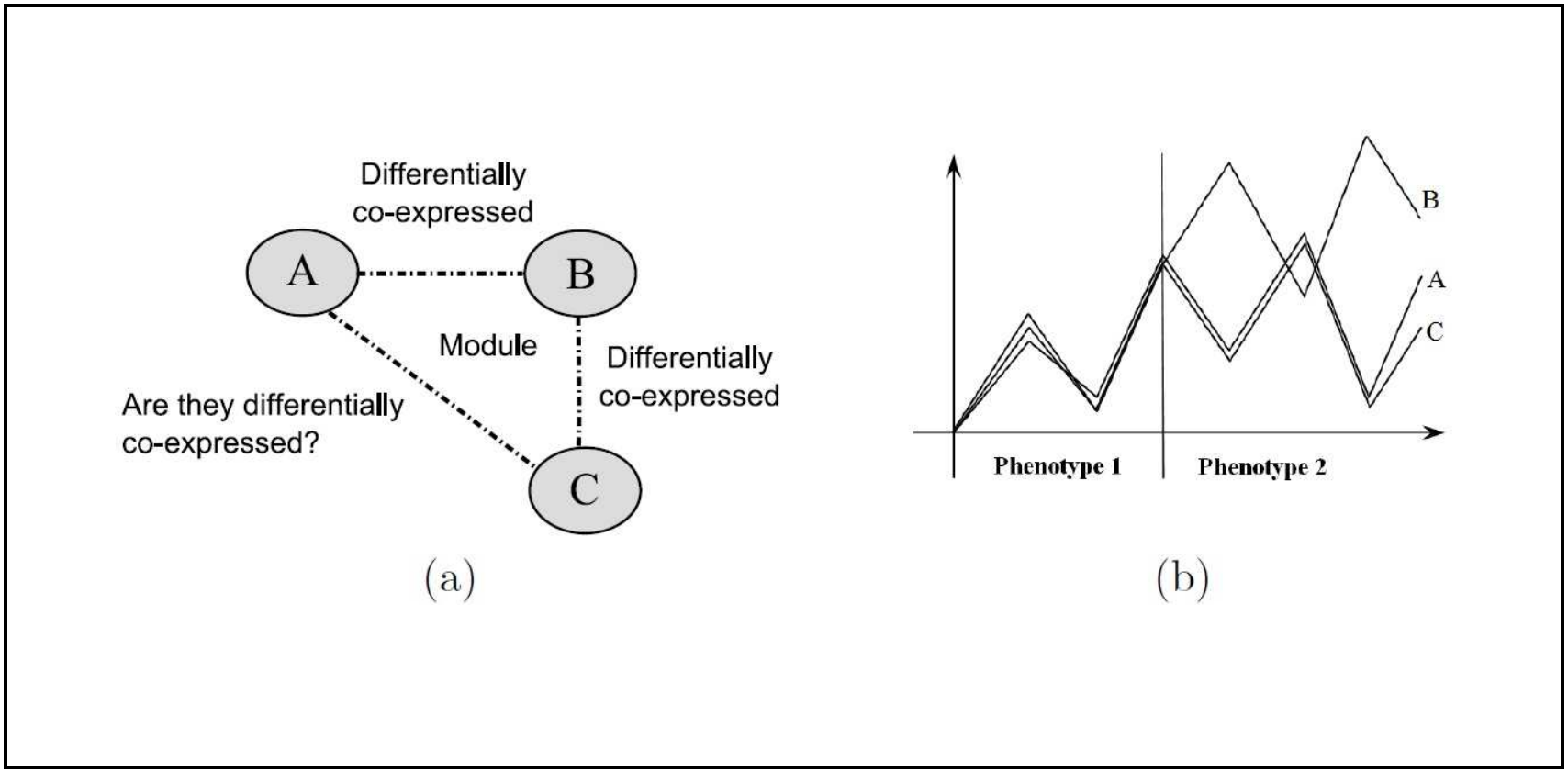
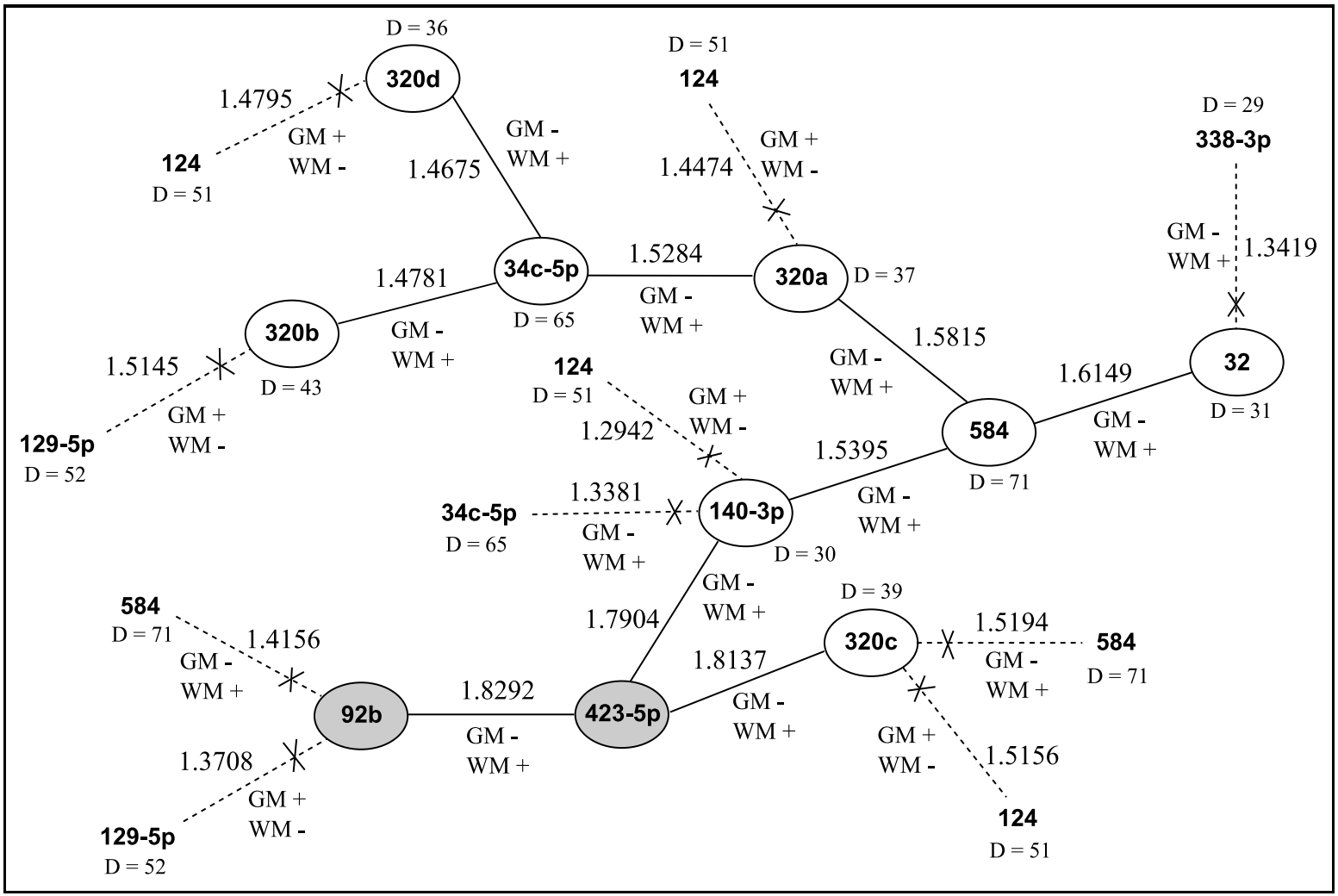


Differentially Co-expressed Switching Tree



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How to Define an Association as Dense?

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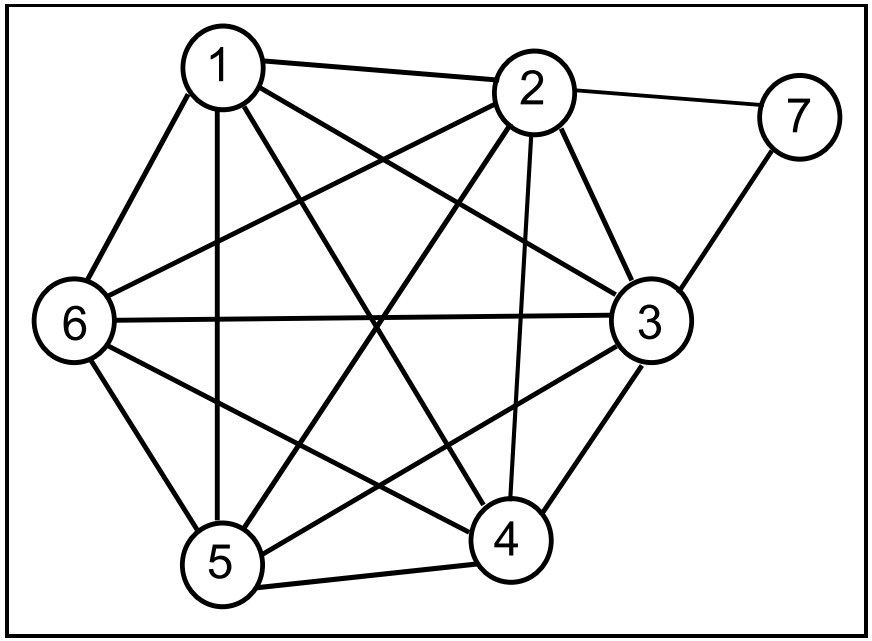

Density $= 17/21 \sim 0.81$

Minimum participation density $= 2/6 \sim 0.33$

A Dense Module

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Association density of a vertex

Given a weighted *graph* $G = (V, E, \Omega)$, the association density, μ_{v_i/V^N}, of a vertex v_i of G with respect to a vertexlet V^N (such that $v_i \notin V^N$), is defined as the ratio of the sum of the edge weights between v_i and each of the vertices belonging to V^N, and the cardinality of the set V^N. Thus, the association density of a vertex v_i with respect to the vertexlet V^N is computed as $\mu_{v_i/V^N} = \frac{\sum_{v_j \in V^N} \Omega_{v_i v_j}}{N}$.

Association density of a vertexlet

The association density of a vertexlet V^N is defined to be the minimum of the association density of every vertex belonging to the vertexlet with respect to the vertexlets of order $(N-1)$. So, the association density of a vertexlet V^N is given by $\mu_{V^N} = \min_{v_i \in V^N} \left(\mu_{v_i/V^N - \{v_i\}} \right)$.

Regulatory Network Analysis

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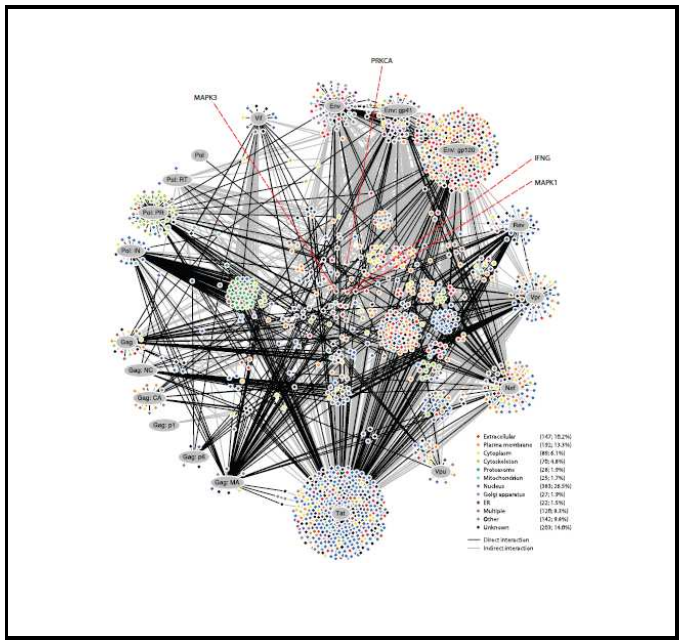

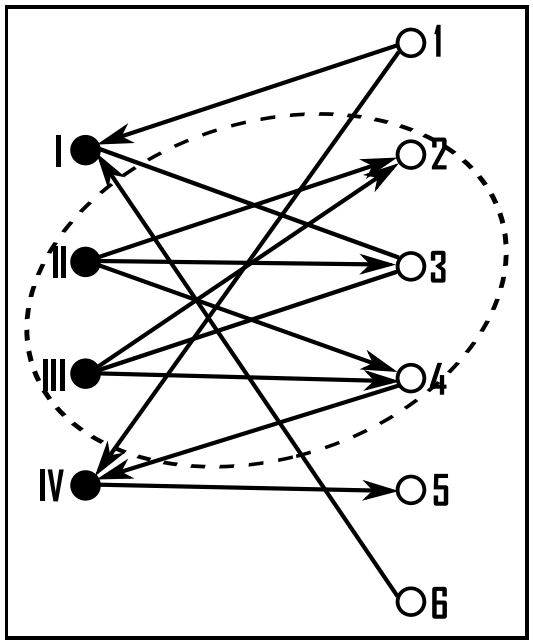

[Ptak, 2008].

DBClique

A DBClique is a fully connected subgraph $G' = (V_1', V_2', E') \subseteq G$ of a directed bipartite graph G such that either $i \in V_1', j \in V_2', \forall (i,j) \in E'$ or $i \in V_2', j \in V_1', \forall (i,j) \in E'$.

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	Endogenous	**Exogenous**
TF combinations	complex	simple
Path length	long	short
TF outdegree	Low	High
Significant motifs	FFLs	single input
TF interconnectedness	High	Low

Table: Topological properties of Networks.

[Luscombe, 2004].

Strengthening the Network Analysis

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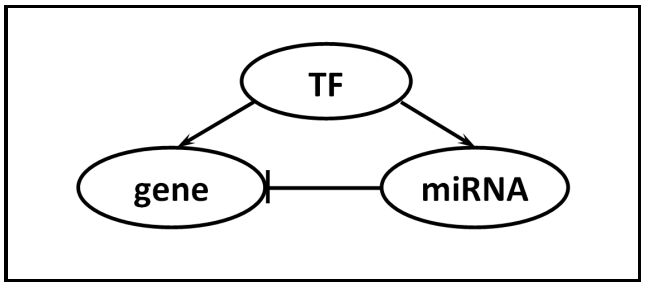
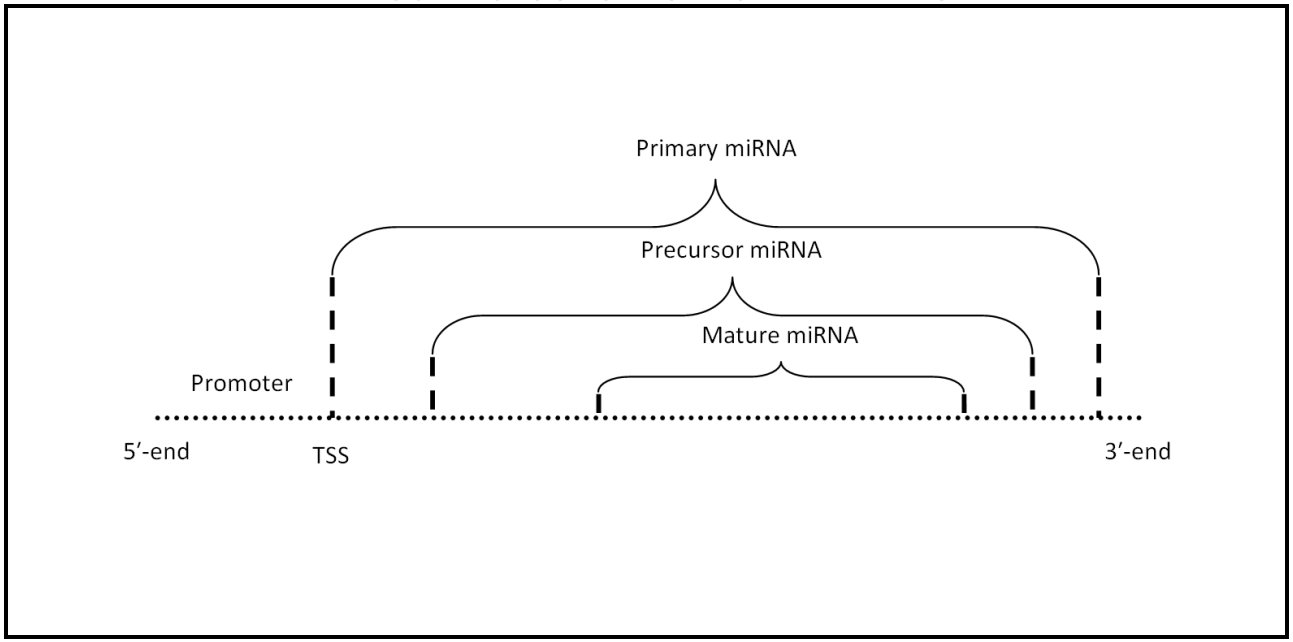


Activities of small RNAs



Transcriptional regulation of miRNAs

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From Networks to Personalized Medicine

Drugs and Biomarkers

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How?

- Prepare integrative network models
- Correlate network dynamics and states to the phenotype and patient disease data
- Identify potential multi-node signatures

A test case of cancer metastasis is proposed pursuing the 'seed and soil' principle [Erler, 2009].

More focus on aberrations and pathways

- Identify the genetic aberrations and the master regulators that drive proliferation, survival, metastasis, and drug resistance
- Model the adaptive/feedback mechanisms that thwart the efficacy of potent drugs
- Predict additional target pathways for combinatorial drug treatment

[Ray, 2010, Pe'er, 2011].

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