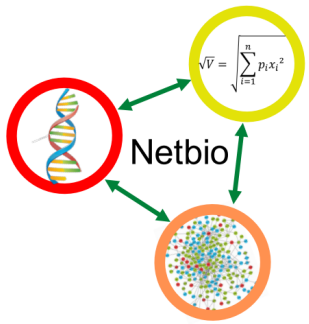
Networks: what? what for? how?



https://mia.toulouse.inra.fr/NETBIO

Julien Chiquet, Étienne Delannoy, Marie-Laure Martin-Magniette, Françoise Monéger, Guillem Rigaill & Nathalie Villa-Vialaneix

NETBIO, Paris - November 9th 2017

Outline

1. What are networks/graphs?

2. What are networks useful for in biology?
   - Visualization
   - Simple analyses based on network topology
   - More advanced analyses based on network topology
   - Biological interaction models

3. How to build networks?

Outline

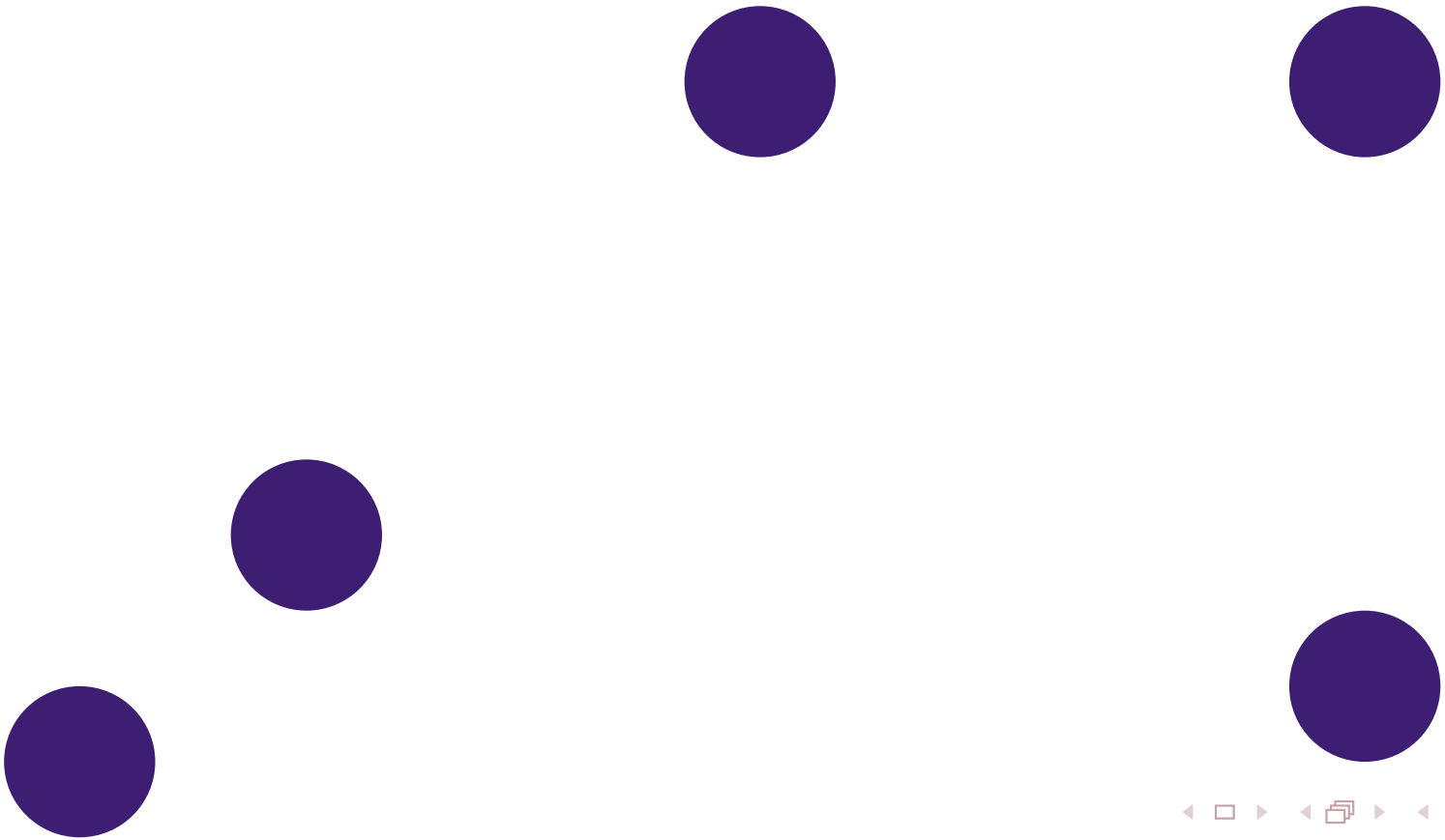
What is a graph? *graphe*

Mathematical object used to model **relational data between entities**.

What is a graph? *graphe*

Mathematical object used to model **relational data between entities**.

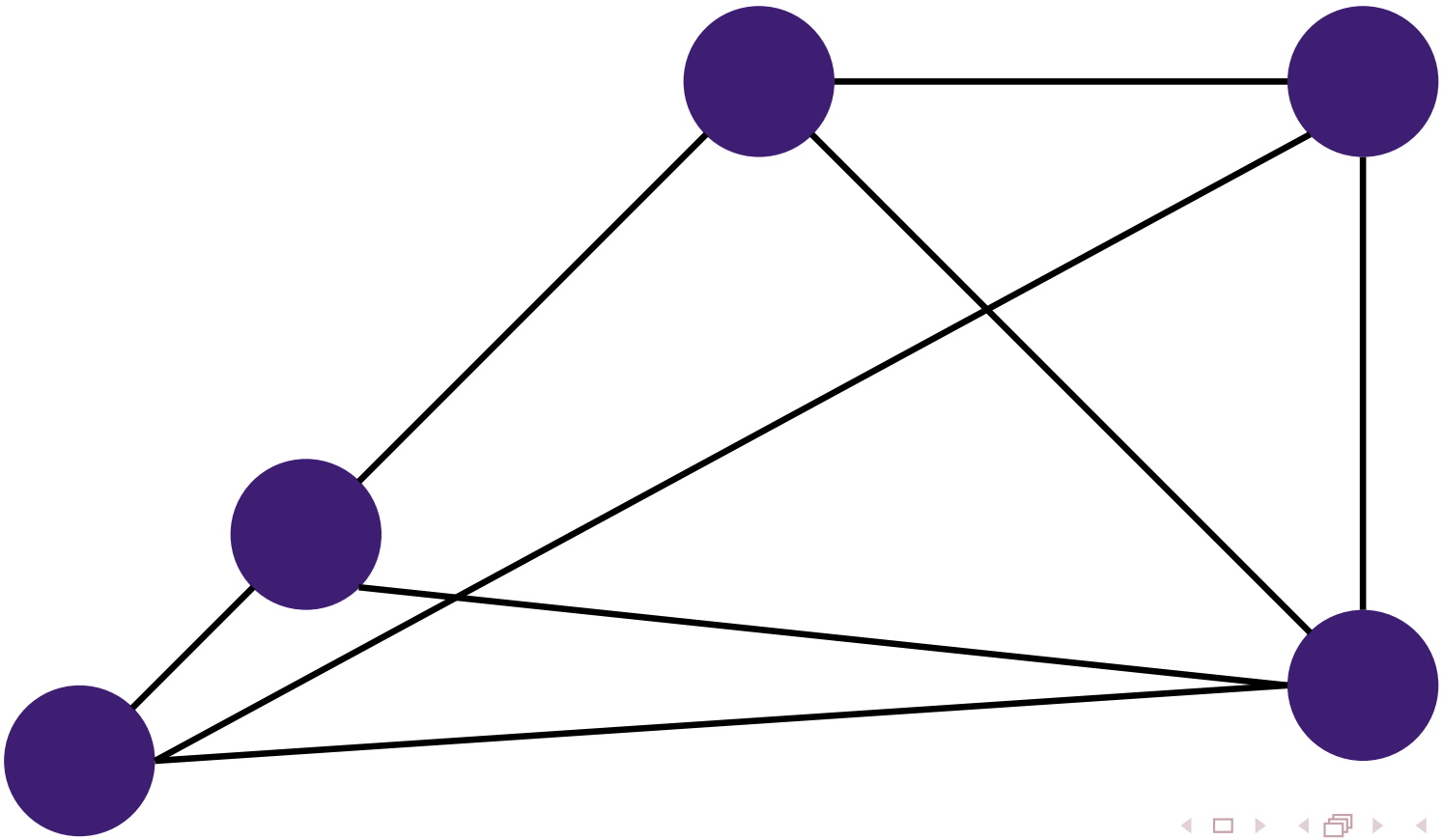
The entities are called **nodes** or **vertices**
nœuds/sommets



What is a graph? *graphe*

Mathematical object used to model **relational data between entities**.

A relation between two entities is modeled by an **edge**
arête



Graphs are a way to represent biological knowledge

Nodes can be...

genes, mRNAs, proteins, small RNAs, hormones, metabolites, species, populations, individuals, ...

Graphs are a way to represent biological knowledge

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genes, mRNAs, proteins, small RNAs, hormones, metabolites, species, populations, individuals, ... Additional information can be attached to these nodes (GO term, protein family, functional motifs, cis-regulatory motifs, ...)

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Nodes can be...

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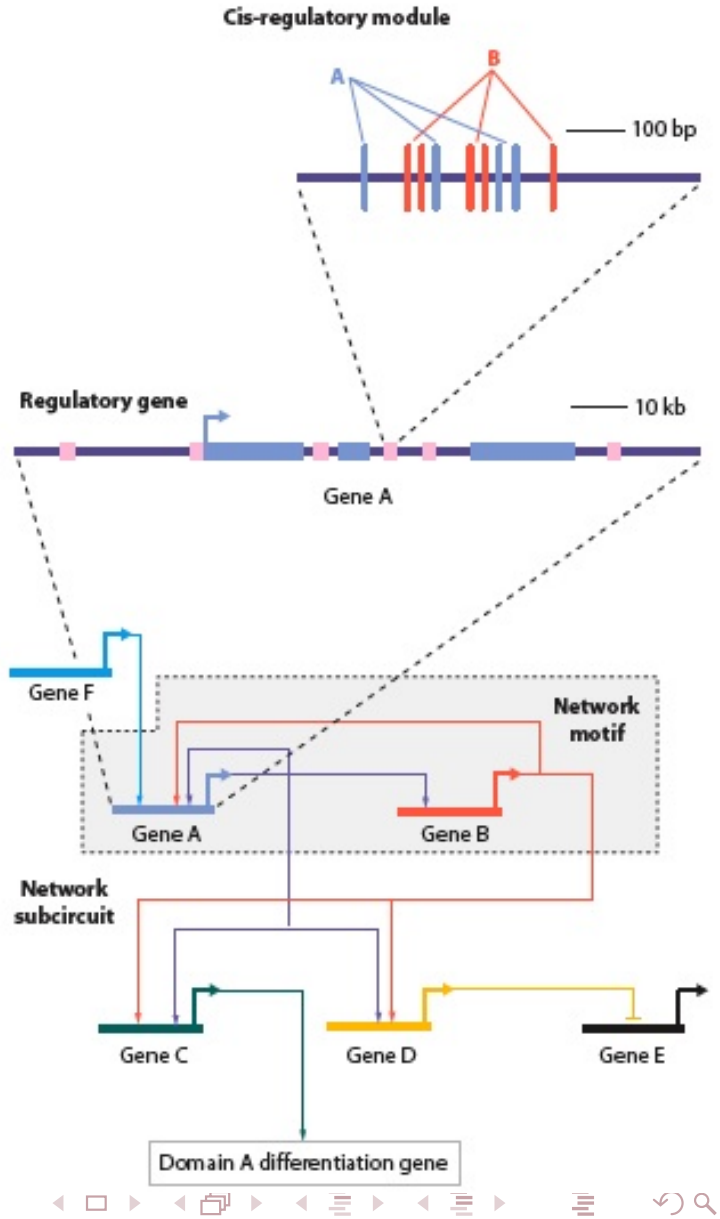
Relations can be...

- molecular regulation (transcriptional regulation, phosphorylation, acetylation, ...)
- molecular interaction (protein-protein, protein-siRNA, ...)
- enzymatic reactions
- genetic interactions (when gene A is mutated, gene B expression is up-regulated)
- co-localisation (genomic, sub-cellular, cellular, ...)
- co-occurence (when two entities are systematically found together)

Example of a molecular network with molecular regulation

Nodes are **genes**
Relations are **transcriptional regulations**

[de Leon and Davidson, 2006]



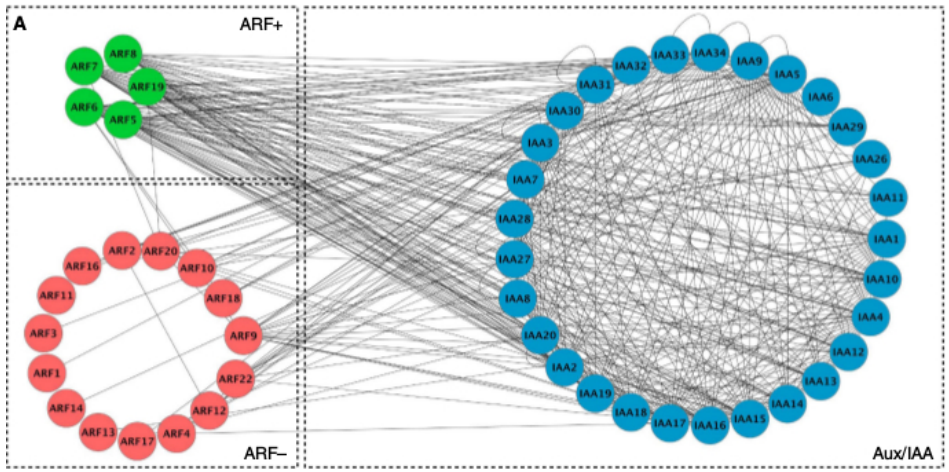
Example of a molecular network with physical interactions

Nodes are **proteins**
Relations are **physical interactions (Y2H)**

made from data in

[*Arabidopsis* Interactome Mapping Consortium, 2011]

[Vernoux et al., 2011]



Example of a metabolic network

Nodes are **metabolites**
Relations are **enzymatic reactions**

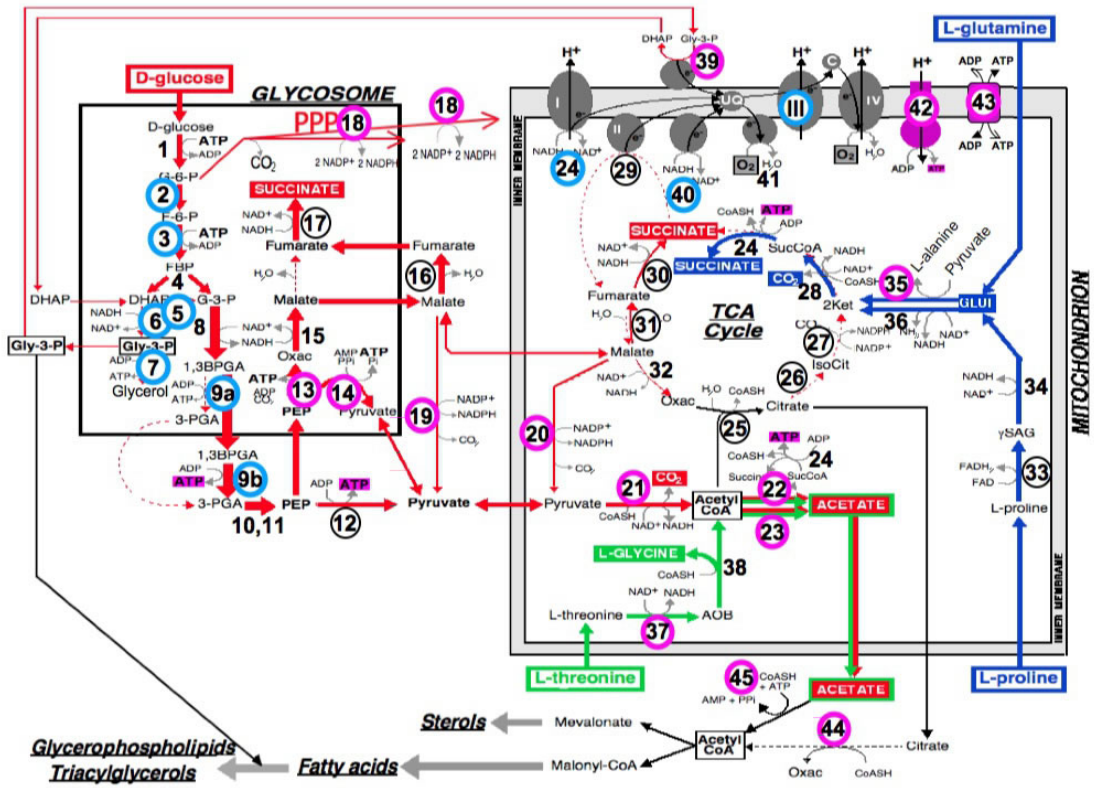
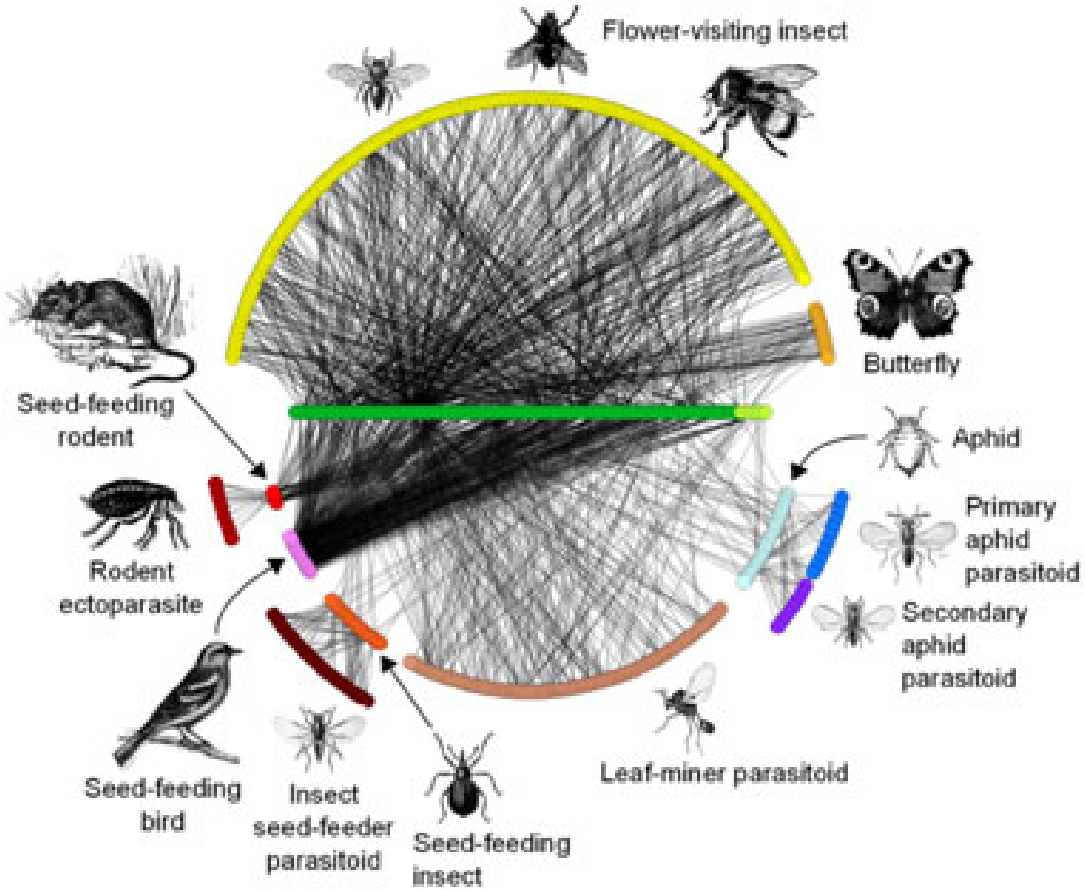


Image taken from Project "Trypanosome" (F. Bringaud - iMET team, RMSB, Bordeaux)

Example of an ecologic network

Nodes are **species**
Relations are **trophic links**



[The QUINTESSENCE Consortium, 2016]

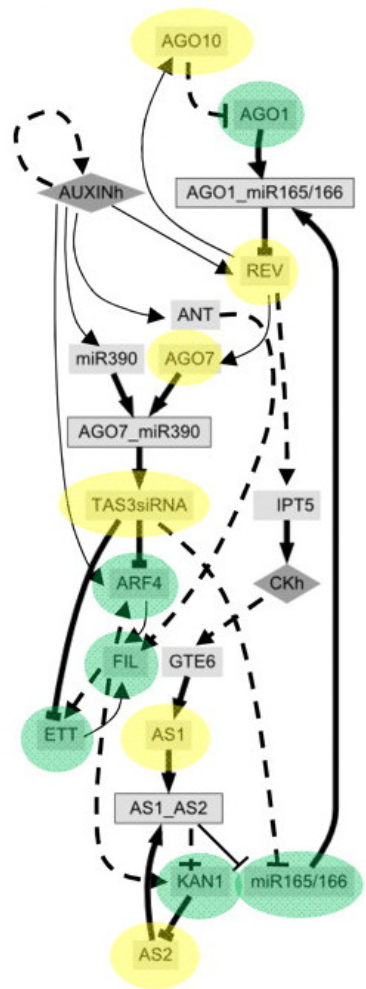
Example of a molecular network with heterogeneous information

Nodes

- shapes represent the nature of the entities
- colors indicate tissue localisation

Edges are direct molecular relations of different types

- reliability: bold, dashed, normal lines
- inhibition or activation: T-line or arrow



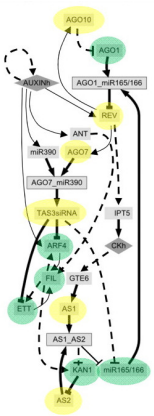
[La Rota et al., 2011]

What is a model?

Model: simplified representation of reality

What is a model?

Model: simplified representation of reality

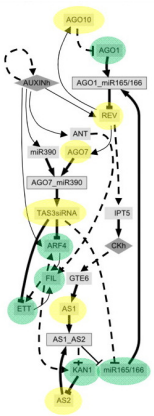


Biological model

simplified representation of a biological process

What is a model?

Model: simplified representation of reality

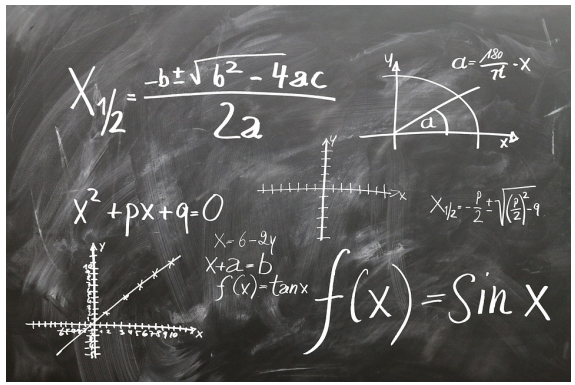


Biological model

simplified representation of a biological process

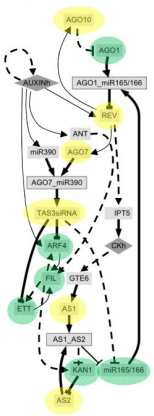
Mathematical model

- simplified description of a system using mathematical concepts
- in particular, **statistical models** represent the data-generating process



What is a model?

Model: simplified representation of reality



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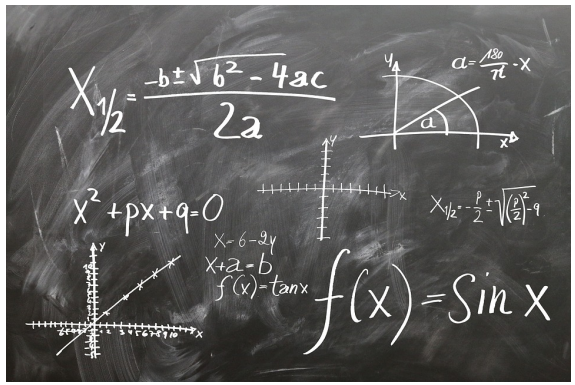


biological interaction model = biological network + mathematical model

Outline

Outline

Advantages and drawbacks of network visualization

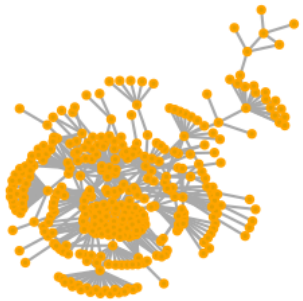
Visualization helps understand the network macro-structure and provides an **intuitive understanding** of the network.

Advantages and drawbacks of network visualization

Visualization helps understand the network macro-structure and provides an **intuitive understanding** of the network.

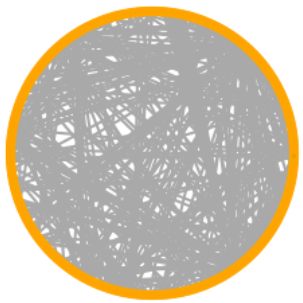
But all network visualizations are subjective and can mislead the person looking at it if not careful. **[Shen-Orr et al., 2002]** *Escherichia coli* transcriptional regulation network

Kamada Kawaï

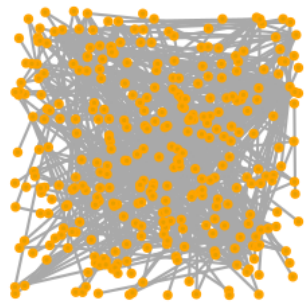


Fruchterman Reingold

circle



random



How to represent networks?

Many different algorithms that often produce solutions that are not unique (integrate some randomness)

Most popular: **force directed placement algorithms**

- Fruchterman & Reingold **[Fruchterman and Reingold, 1991]**
- Kamada & Kawaï **[Kamada and Kawai, 1989]**

Such algorithms are computationally extensive and hard to use with large networks (more than a few thousands nodes)

Another useful layout

- attribute circle layout (quick but can be hard to read)

Network visualization software

(not only for biological networks)

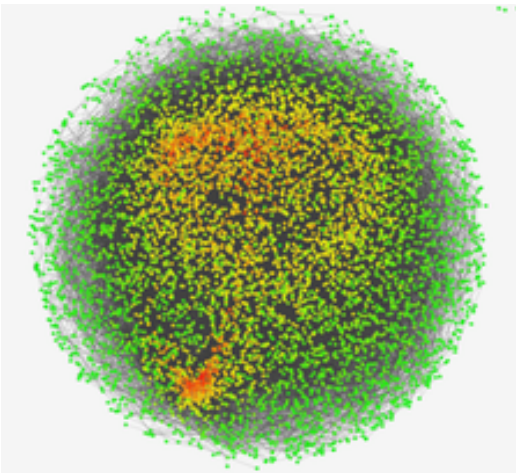
- **NetworkX** (python library, not really interactive but produces javascript) https://networkx.github.io
-  **igraph** (python and R libraries, not really interactive) http://igraph.org
-  **Tulip** (interactive) http://tulip.labri.fr
-  **Cytoscape** (interactive) http://cytoscape.org
-  **Gephi** (interactive) gephi.org
- ...

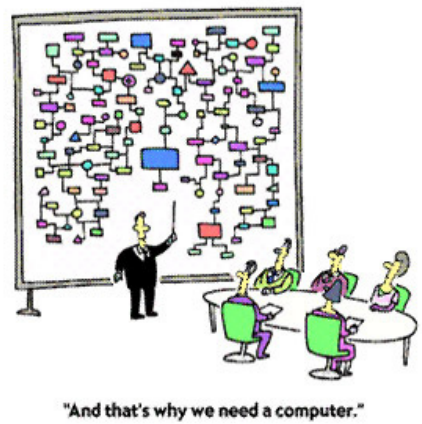
Outline

What is network topology?

Network topology

- study of the **network global and local structure**
- produces **numerical summaries** $\Rightarrow$ biological interpretation





Credits: S.M.H. Oloomi, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=35247515 (network)

and AJC1, CC BY-NC-SA 2.0, https://www.flickr.com/photos/ajc1/4830932578 (biology)

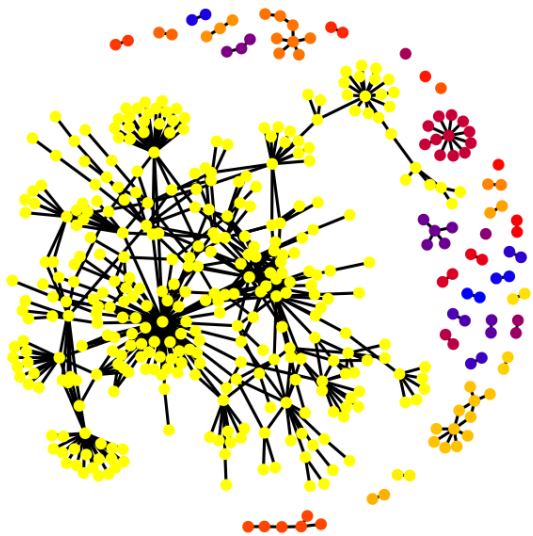
What is network topology?

Network topology

- study of the **network global and local structure**
- produces **numerical summaries** $\Rightarrow$ biological interpretation

connected components are the connected subgraphs, *i.e.*, parts of the graph in which any node can be reached from any other node by a path

composantes connexes



34 connected components

[Shen-Orr et al., 2002] *Escherichia coli* transcriptional regulation network

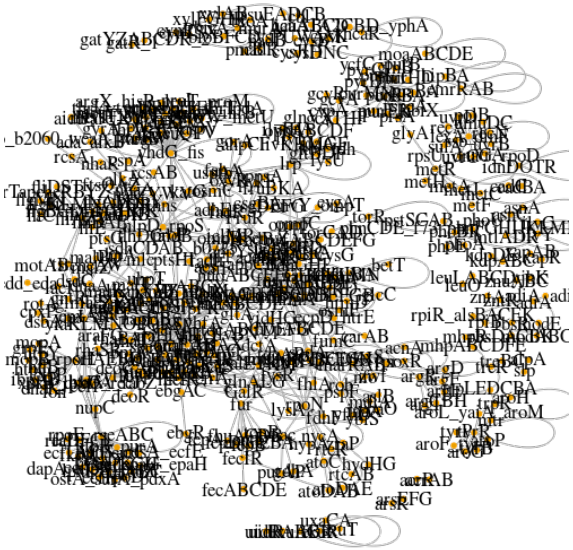
Global characteristics

(mainly used for comparisons between networks or with random graphs having common characteristics with the real network)

Density *densité*

Number of edges divided by the number of pairs of nodes.

[Shen-Orr et al., 2002] *Escherichia coli* transcriptional regulation network: 423 nodes, 578 edges.
Density: $\sim 0.64\%$



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molecular systems biology

REPORT

Survival of the sparsest: robust gene networks are parsimonious

Robert D Leclerc

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Biological gene networks appear to be dynamically robust to mutation, stochasticity, and changes in the environment and also appear to be sparsely connected. Studies with computational models, however, have suggested that denser gene networks evolve to be more dynamically robust than sparser networks. We resolve this discrepancy by showing that misassumptions about how to

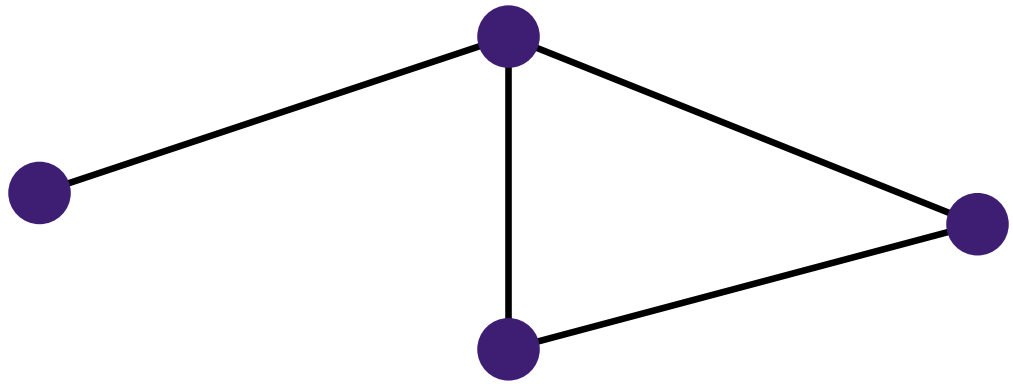
[Leclerc, 2008]: biological networks are generally sparsely connected (*S. cerevisiae*, *E. coli*, *D. melanogaster* transcriptional regulatory network densities < 0.1): evolutionary advantage for preserving robustness?

Global characteristics

(mainly used for comparisons between networks or with random graphs having common characteristics with the real network)

Transitivity *transitivité*

Number of triangles divided by the number of triplets connected by at least two edges.



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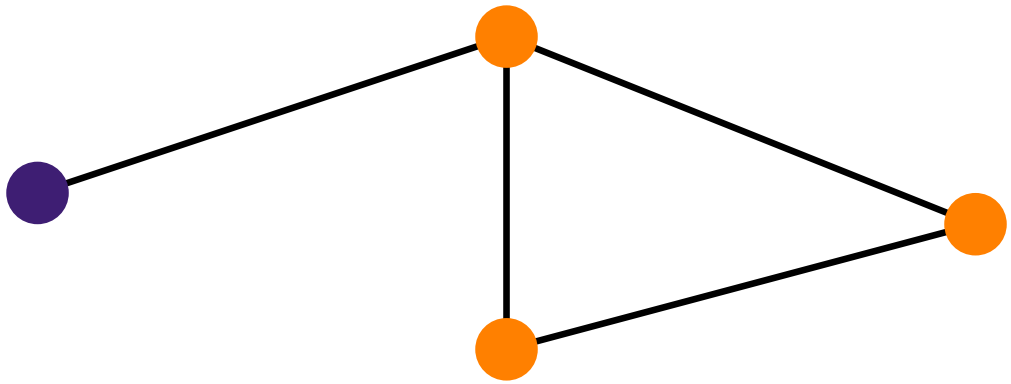

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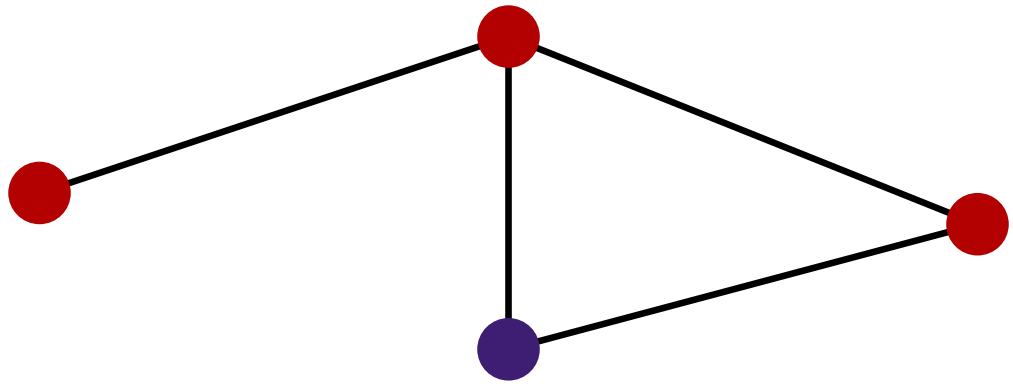

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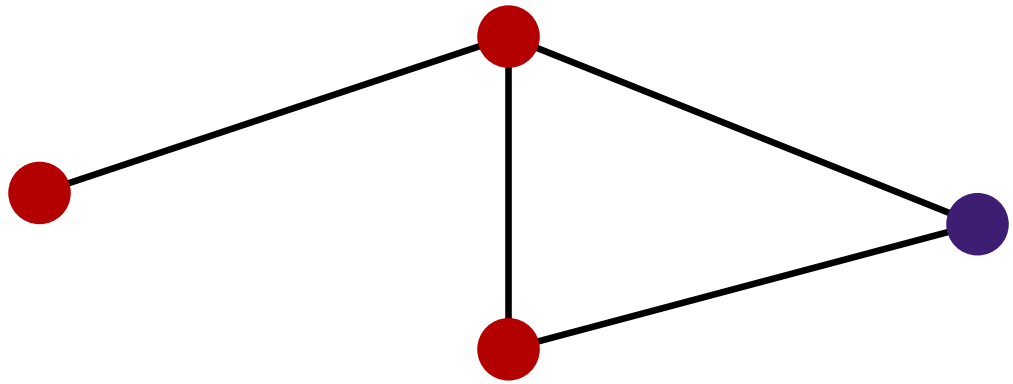


Transitivity is equal to 1/3. Density is equal to $\frac{4}{4\times 3/2} = 2/3$

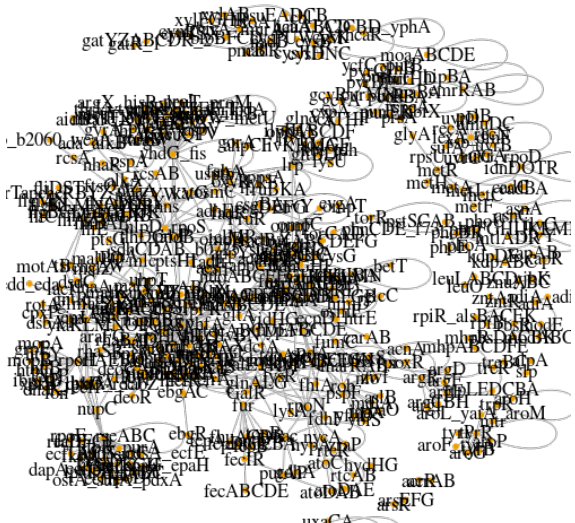
Global characteristics

(mainly used for comparisons between networks or with random graphs having common characteristics with the real network)

Transitivity *transitivité*

Number of triangles divided by the number of triplets connected by at least two edges.

[Shen-Orr et al., 2002] *Escherichia coli* transcriptional regulation network. Transitivity: $\sim 2.38\%$ $\gg$ density



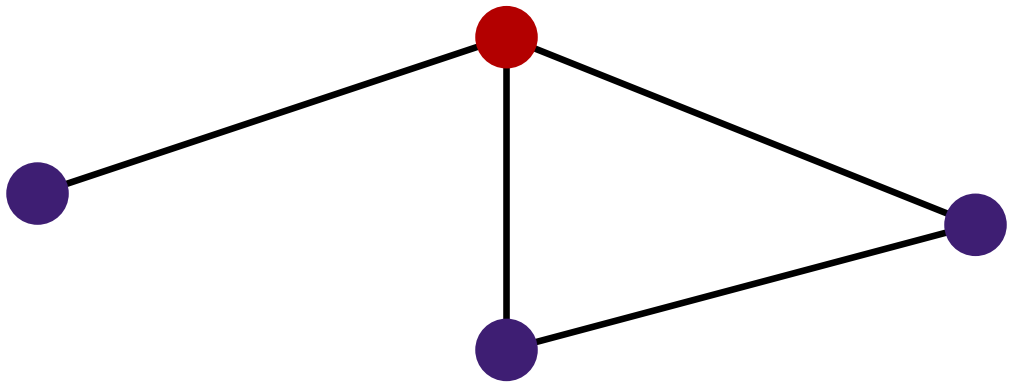
Comparaison with random graphs *(same number of nodes and edges, edges distributed at random between pairs of nodes)*: average transitivity is $\sim 0.63\%$.

$\Rightarrow$ strong local density in *Escherichia coli* transcriptional regulation network ("modularity" structure).

Key measures for other numerical characteristics

Node degree *degré*

number of edges adjacent to a given node or number of neighbors of the node



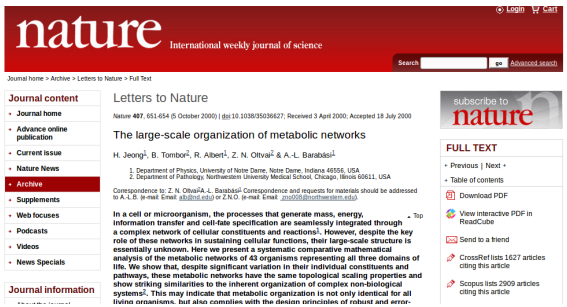
The degree of the red node is equal to 3.

Key measures for other numerical characteristics

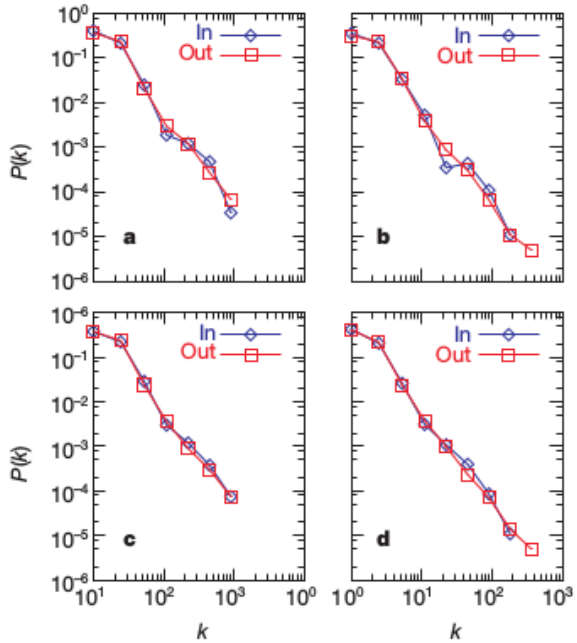
Node degree *degré*

number of edges adjacent to a given node or number of neighbors of the node

[Jeong et al., 2000] shows that degree distribution in metabolomic networks is "scale-free"



frequency of nodes having a degree of k $\sim k^{-\gamma}$ (highly skewed distributions)

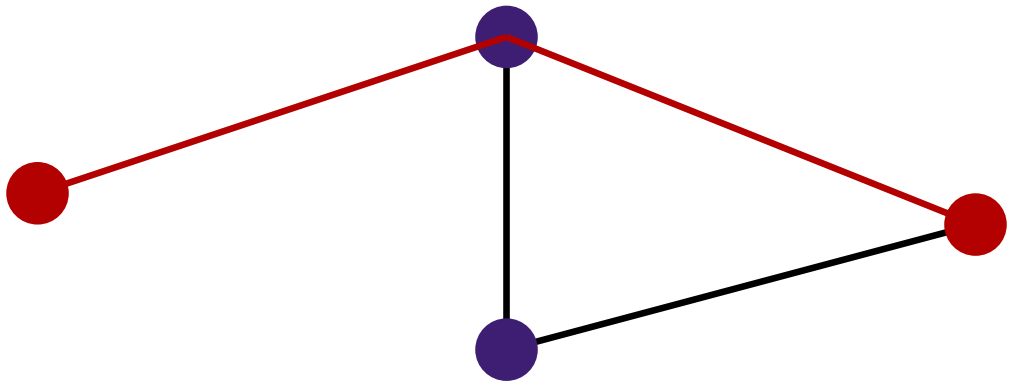


Archaeoglobus fulgidus, *E. coli*, *Caenorhabditis elegans* and average over 43 organisms

Key measures for other numerical characteristics

Shortest path length (between two nodes)

minimal number of edges needed to reach a node from the other node through a path along the edges of the network

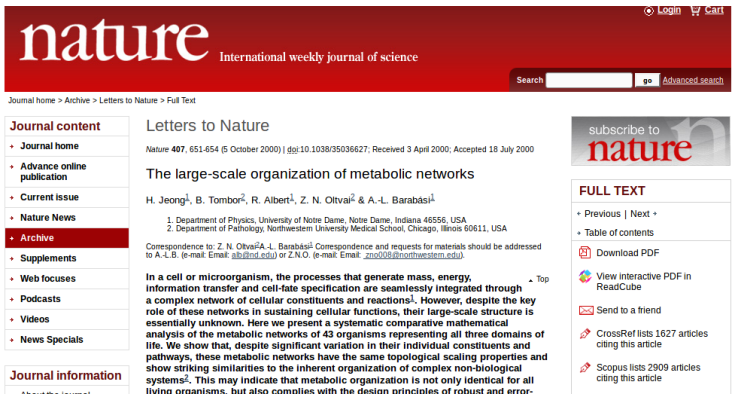


The shortest path length between red nodes is equal to 2.

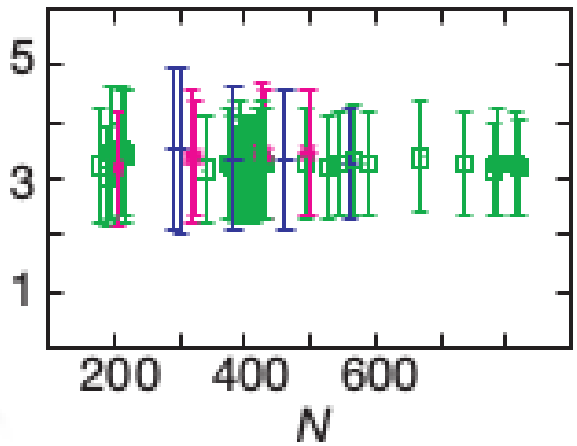
Key measures for other numerical characteristics

Shortest path length (between two nodes)

minimal number of edges needed to reach a node from the other node through a path along the edges of the network



[Jeong et al., 2000] shows that shortest path length distribution is similar accross 43 species in metabolomic networks

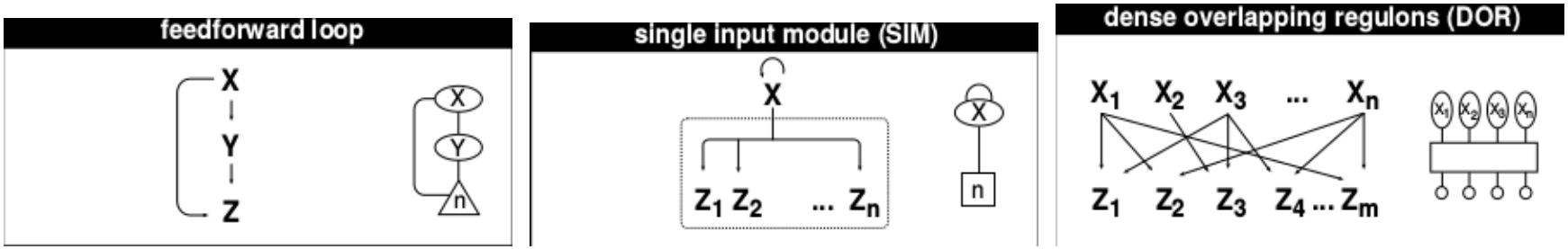


observed average shortest path lengths is smaller than in random graph with uniform distribution of edges

Outline

Network motifs

[Shen-Orr et al., 2002] showed that some **specific motifs**



are found significantly more often in *Escherichia coli* transcription network than in random networks with the same degree distribution.

Network motifs

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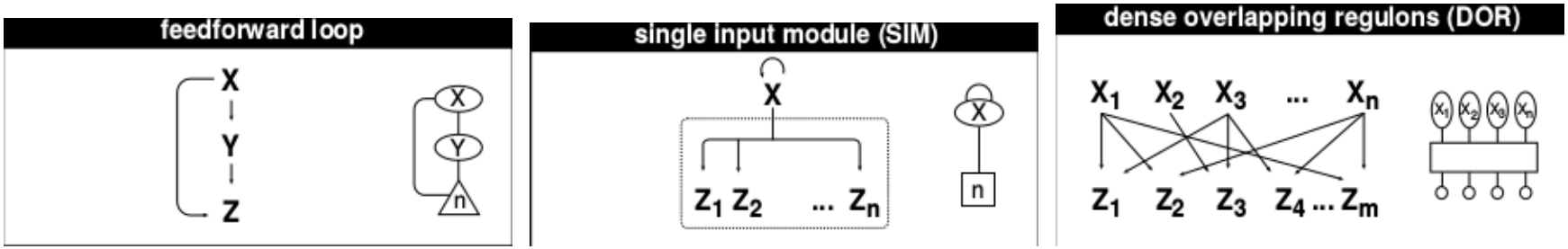
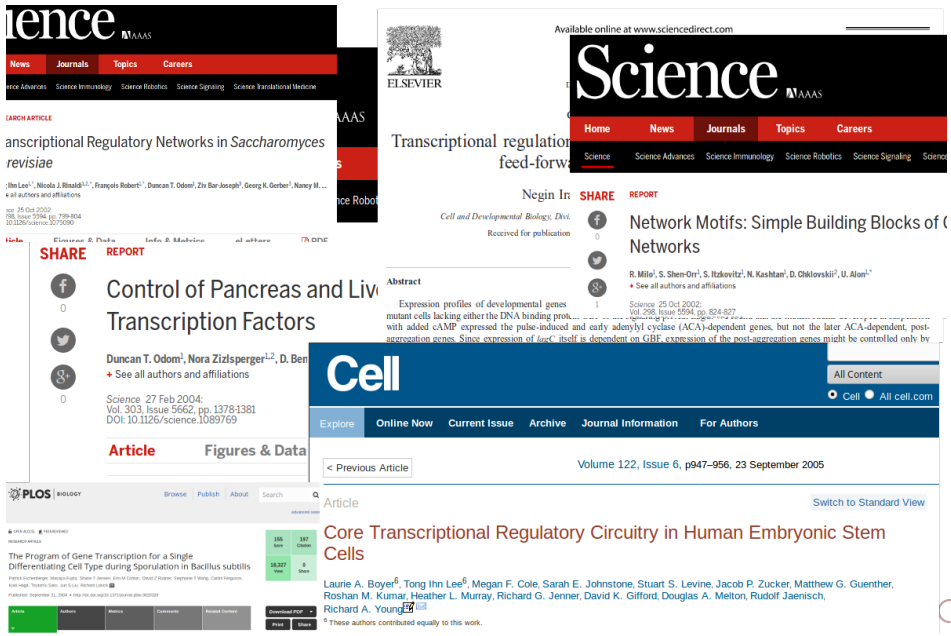


are found significantly more often in *Escherichia coli* transcription network than in random networks with the same degree distribution.

[Milo et al., 2002,
Lee et al., 2002,
Eichenberger et al., 2004,
Odom et al., 2004,
Boyer et al., 2005,
Iranfar et al., 2006] show similar conclusion in various species (bacteria, yeast, higher organisms)



Node clustering *classification*

Cluster nodes into groups that are **densely connected** and share **few links** (comparatively) **with the other groups**. Clusters are often called **communities** *communautés* (social sciences) or **modules** *modules* (biology). **[Fortunato, 2010]**

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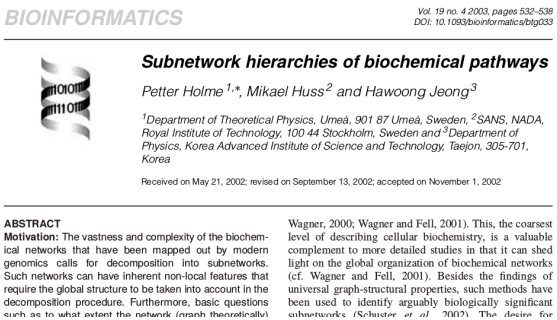
Simplification of a large complex network



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Subnetwork hierarchies of biochemical pathways

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Received on May 21, 2002; revised on September 13, 2002; accepted on November 1, 2002

ABSTRACT

Motivation: The vastness and complexity of the biochemical networks that have been mapped out by modern genomics calls for decomposition into subnetworks. Such networks can have inherent non-local features that require the global structure to be taken into account in the decomposition procedure. Furthermore, basic questions such as to what extent the network (graph theoretically)

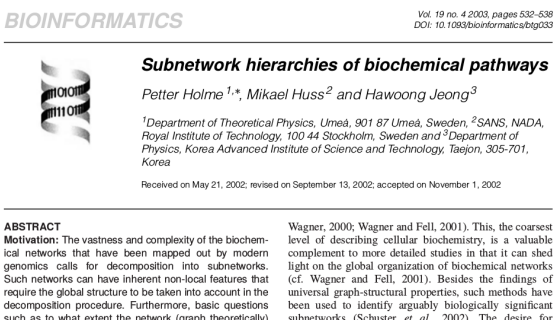
Wagner, 2000; Wagner and Fell, 2001). This, the coarsest level of describing cellular biochemistry, is a valuable complement to more detailed studies in that it can shed light on the global organization of biochemical networks (cf. Wagner and Fell, 2001). Besides the findings of universal graph-structural properties, such methods have been used to identify arguably biologically significant subnetworks (Schuster *et al.*, 2002). The desire for

[Holme et al., 2003] use clustering of metabolic networks to provide a simplified overview of the whole network and meaningful clusters

Node clustering *classification*

Cluster nodes into groups that are **densely connected** and share **few links** (comparatively) **with the other groups**. Clusters are often called **communities** *communautés* (social sciences) or **modules** *modules* (biology). **[Fortunato, 2010]**

Simplification of a large complex network



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Subnetwork hierarchies of biochemical pathways

Petter Holme [1,*], Mikael Huss [2] and Hawoong Jeong [3]

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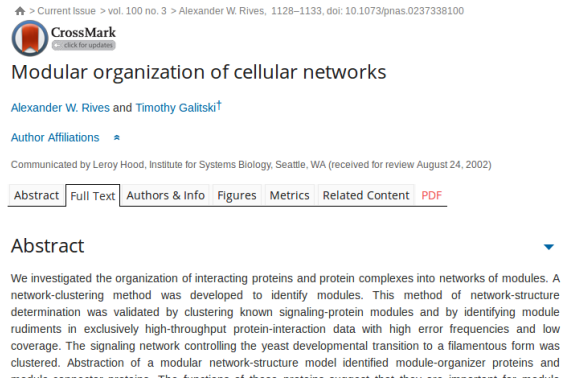
ABSTRACT

Motivation: The vastness and complexity of the biochemical networks that have been mapped out by modern genomics calls for decomposition into subnetworks. Such networks can have inherent non-local features that require the global structure to be taken into account in the decomposition procedure. Furthermore, basic questions

Wagner, 2000; Wagner and Fell, 2001). This, the coarsest level of describing cellular biochemistry, is a valuable complement to more detailed studies in that it can shed light on the global organization of biochemical networks (cf. Wagner and Fell, 2001). Besides the findings of universal graph-structural properties, such methods have been used to identify arguably biologically significant

[Holme et al., 2003] use clustering of metabolic networks to provide a simplified overview of the whole network and meaningful clusters

Identify key groups or key genes



> Current Issue > vol. 100 no. 3 > Alexander W. Rives, 1128–1133, doi: 10.1073/pnas.0237338100

CrossMark

Modular organization of cellular networks

Alexander W. Rives and Timothy Galitski†

Author Affiliations

Communicated by Leroy Hood, Institute for Systems Biology, Seattle, WA (received for review August 24, 2002)

Abstract | Full Text | Authors & Info | Figures | Metrics | Related Content | PDF

Abstract

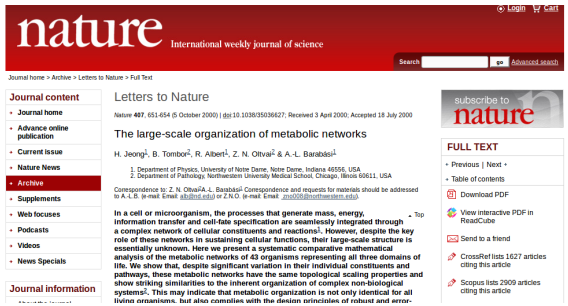
We investigated the organization of interacting proteins and protein complexes into networks of modules. A network-clustering method was developed to identify modules. This method of network-structure determination was validated by clustering known signaling-protein modules and by identifying module rudiments in exclusively high-throughput protein-interaction data with high error frequencies and low coverage. The signaling network controlling the yeast developmental transition to a filamentous form was clustered. Abstraction of a modular network-structure model identified module-organizer proteins and

[Rives and Galitski, 2003] use clustering in PPI network of yeast and found that proteins mostly interacting with members of their own cluster are often essential proteins.

Extracting important nodes

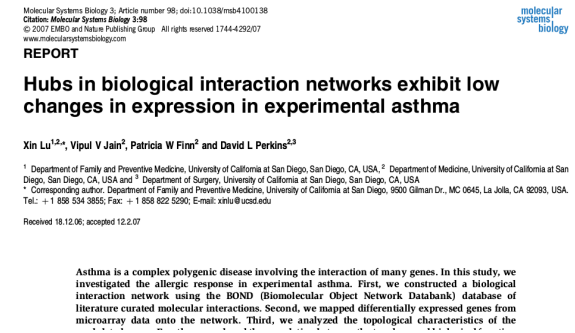
Hubs

Nodes with a high degree are called **hubs**: measure of the node popularity.



[Jeong et al., 2000] show that the hubs are practically identical in metabolic networks among many species

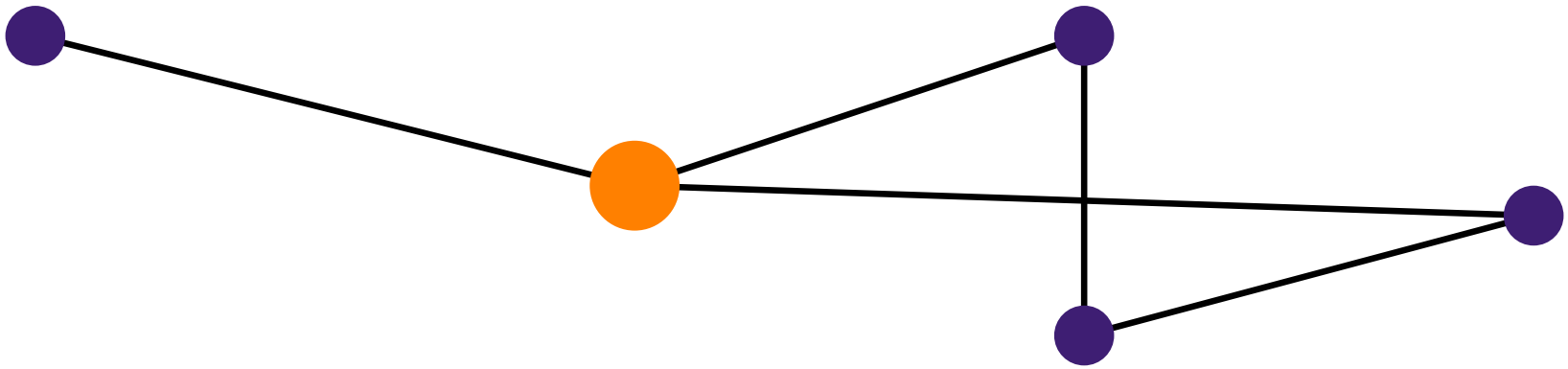
[Lu et al., 2007] show that hubs have low changes in expression and have significantly different functions than peripherical nodes



Extracting important nodes

Betweenness (of a node) *centralité*

number of shortest paths between all pairs of nodes that pass through the node. Betweenness is a centrality measure (nodes that are likely to disconnect the network if removed).



The orange node's degree is equal to 3, its betweenness to 4.

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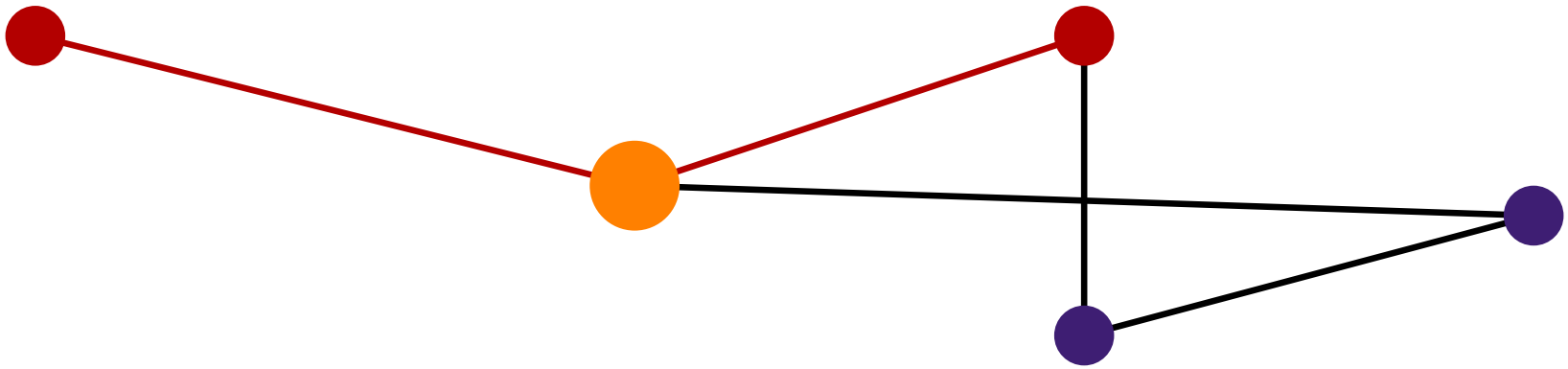

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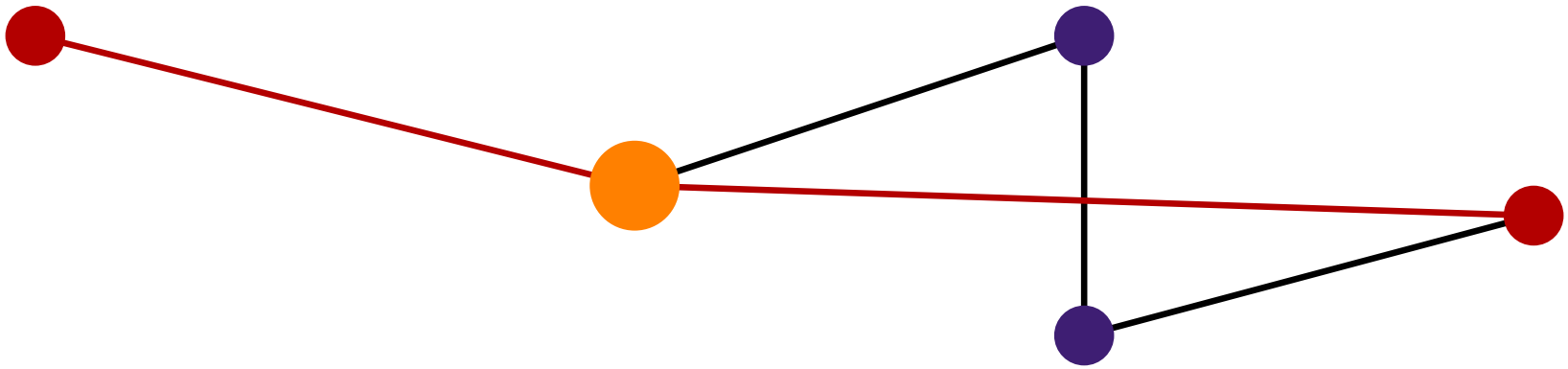

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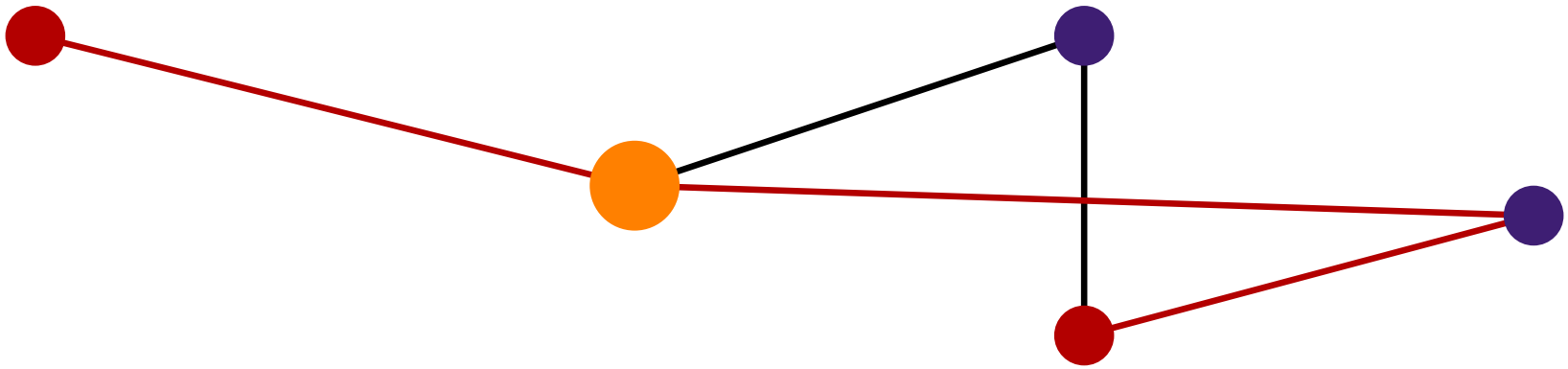

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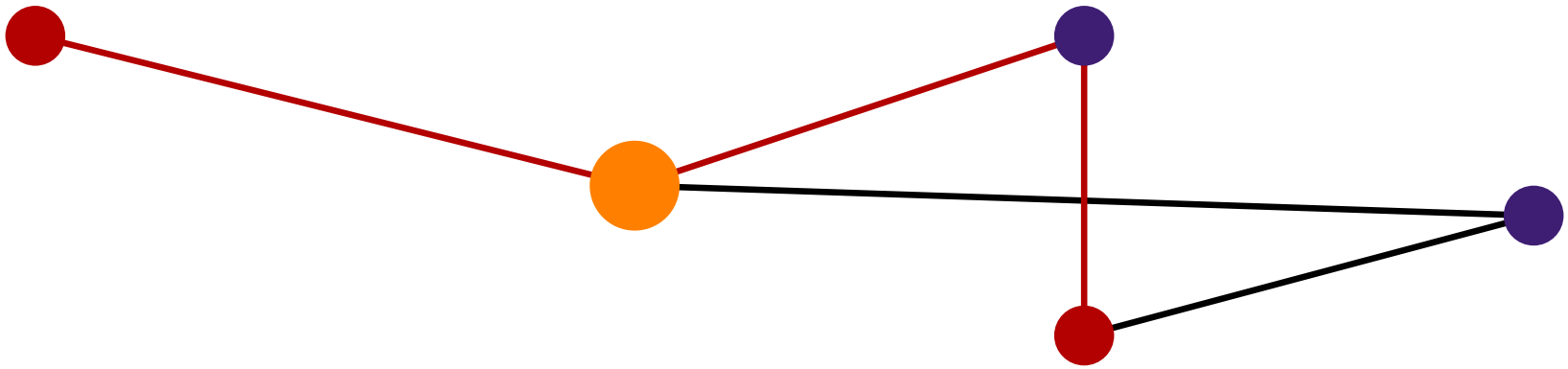

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The Importance of Bottlenecks in Protein Networks: Correlation with Gene Essentiality and Expression Dynamics

Haiyuan Yu[1,2,3☯], Philip M. Kim[1☯], Emmett Sprecher[1,4], Valery Trifonov[5], Mark Gerstein[1,4,5*]

1 Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut, United States of America, 2 Department of Genetics, Harvard Medical School, Boston, Massachusetts, United States of America, 3 Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States of America, 4 Program in Computational Biology and Bioinformatics, Yale University, New Haven, Connecticut, United States of America, 5 Department of Computer Science, Yale University, New Haven, Connecticut, United States of America

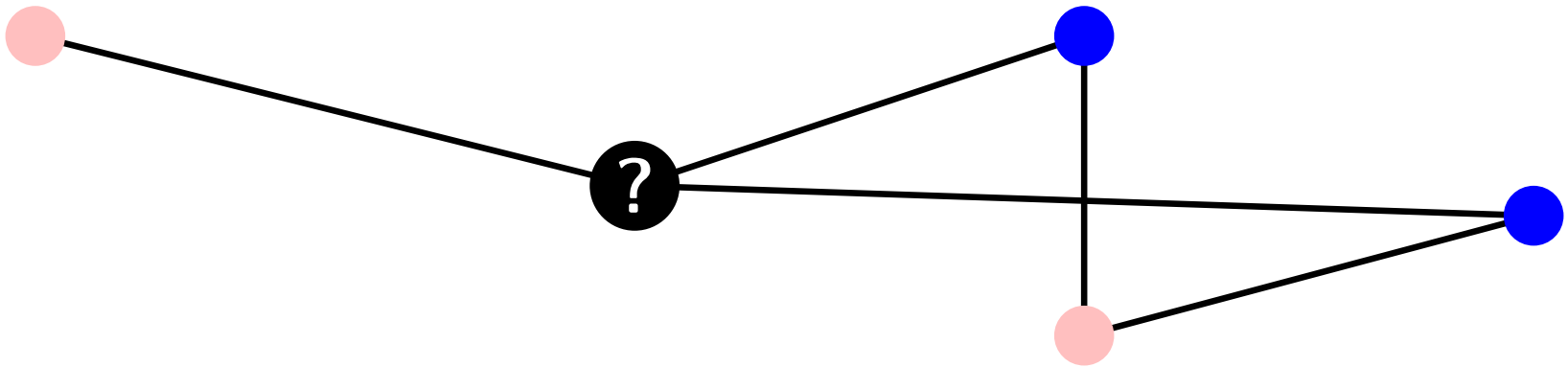
It has been a long-standing goal in systems biology to find relations between the topological properties and functional features of protein networks. However, most of the focus in network studies has been on highly connected proteins ("hubs"). As a complementary notion, it is possible to define bottlenecks as proteins with a high betweenness centrality (i.e., network nodes that have many "shortest paths" going through them, analogous to major bridges and tunnels on a highway map). Bottlenecks are, in fact, key connector proteins with surprising functional and dynamic properties. In particular, they are more likely to be essential proteins. In fact, in regulatory and other directed networks, betweenness (i.e., "bottleneck-ness") is a much more significant indicator of essentiality than degree (i.e.,

[Yu et al., 2007] show that nodes with high betweenness in PPI networks are key connector proteins and are more likely to be essential proteins.

Outline

Principle of status prediction based on a biological network

Available data: a network in which nodes are labeled by (incomplete) information (*e.g.*, GO term, disease status...)
Question: complete the information of nodes with unknown status



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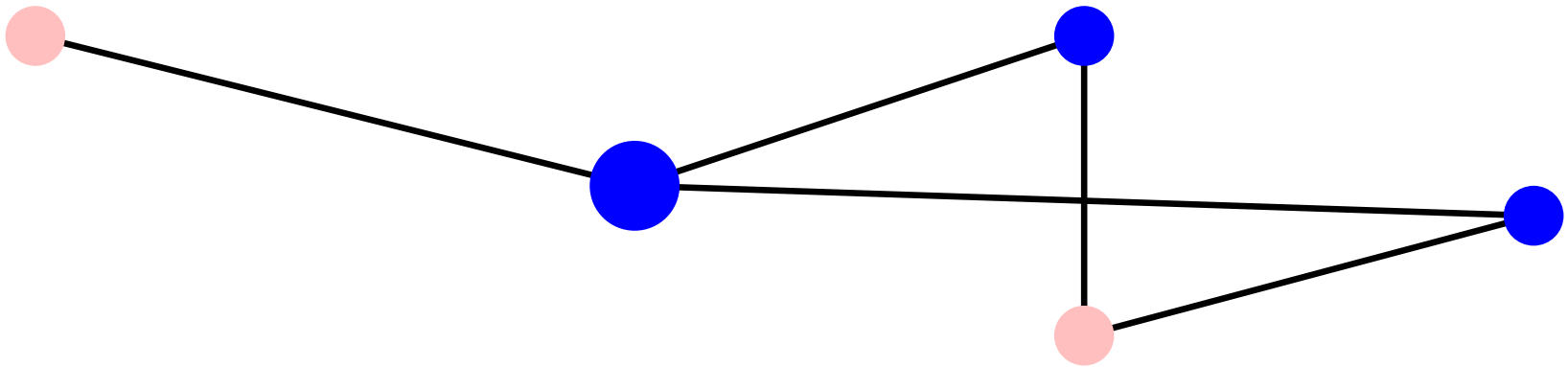
Solution: Rule based on a majority vote among the neighbours. If the score is greater than a given threshold, then status is selected.
[Zaag, 2016]



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Available data: a set of gene expression profiles and a gene network (on the same genes)
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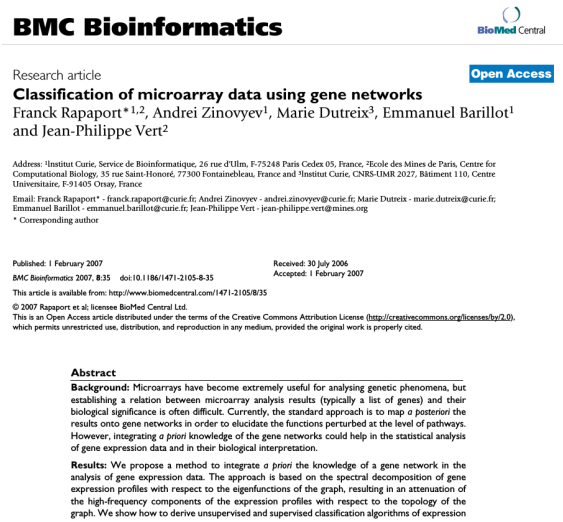
[Rapaport et al., 2007] using the network knowledge improves the results by producing solutions that have **similar contributions for genes connected by the network**

regression model with **network based penalization**



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Classification of microarray data using gene networks

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Email: Franck Rapaport* - franck.rapaport@curie.fr; Andrei Zinovyev - andrei.zinovyev@curie.fr; Marie Dutreix - marie.dutreix@curie.fr; Emmanuel Barillot - emmanuel.barillot@curie.fr; Jean-Philippe Vert - jean-philippe.vert@mines.org

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Abstract

Background: Microarrays have become extremely useful for analysing genetic phenomena, but establishing a relation between microarray analysis results (typically a list of genes) and their biological significance is often difficult. Currently, the standard approach is to map *a posteriori* the results onto gene networks in order to elucidate the functions perturbed at the level of pathways. However, integrating *a priori* knowledge of the gene networks could help in the statistical analysis of gene expression data and in their biological interpretation.

Results: We propose a method to integrate *a priori* the knowledge of a gene network in the analysis of gene expression data. The approach is based on the spectral decomposition of gene expression profiles with respect to the eigenfunctions of the graph, resulting in an attenuation of the high-frequency components of the expression profiles with respect to the topology of the graph. We show how to derive unsupervised and supervised classification algorithms of expression

Differential expression using a graph

Available data: a set of gene expression obtained in two conditions and a gene network (on the same genes)
Question: find genes that are differentially expressed between the two conditions

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independant tests and multiple test corrections

But: multiple test corrections are made for independant tests and genes are strongly correlated

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But: multiple test corrections are made for independant tests and genes are strongly correlated

using the network (T. Ha's Thesis "A multivariate learning penalized method for a joined inference of gene expression levels and gene regulatory networks")

a regression model for incorporating the information on gene dependency structure provided by the network into the differential analysis

Outline

Standard methods for network inference

- bibliographic (expert based) inference (automatic language processing, ontology, text mining, ...) **[Huang and Lu, 2016]**
  Advantages: uses large expertise knowledge from biological databases

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  Advantages: can handle interactions with **yet unknown genes** and deal with data collected in **specific conditions**
  Most widely used methods: relevance network, **Gaussian graphical models** (GGM), Bayesian models
  [Pearl, 1998, Pearl and Russel, 2002, Scutari, 2010] (R package bnlearn)

Correlation networks and GGM

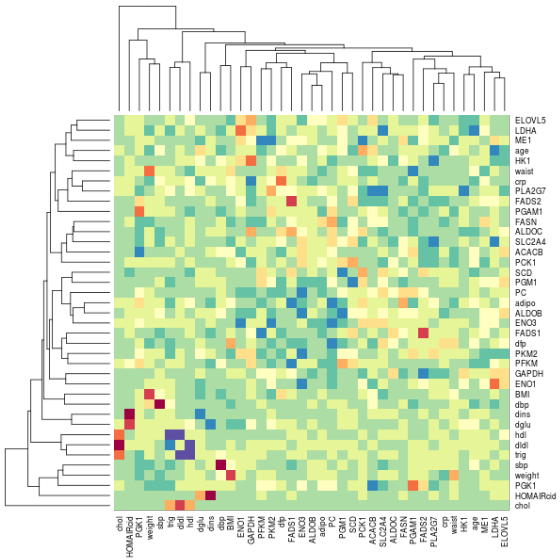
Data: gene expression data

$$\underbrace{\left\{ X = \begin{pmatrix} \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & x_i^j & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \end{pmatrix} \right.}_{\text{variables (selected gene expressions), } p}$$

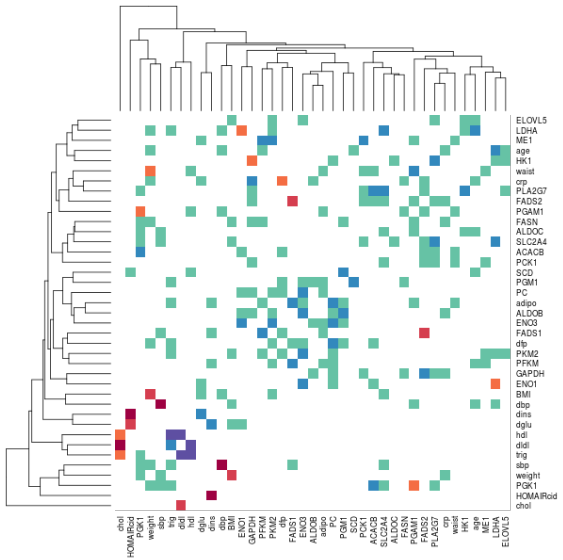
individuals
$n \simeq 30/50$

Using *correlations*: relevance network [Butte and Kohane, 1999, Butte and Kohane, 2000]

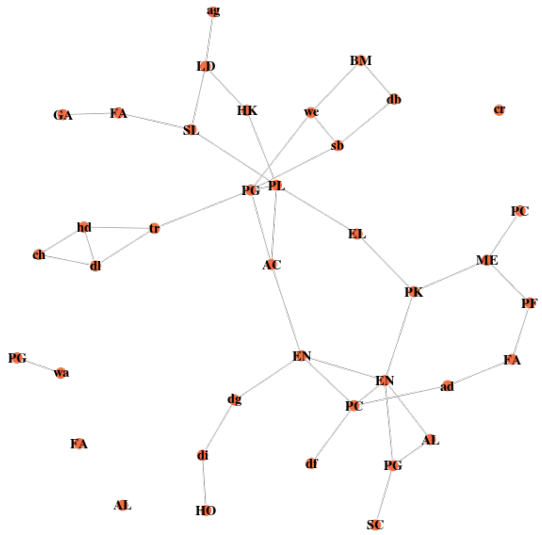
First (naive) approach: calculate correlations between expressions for all pairs of genes, threshold the smallest ones and build the network.



"Correlations"

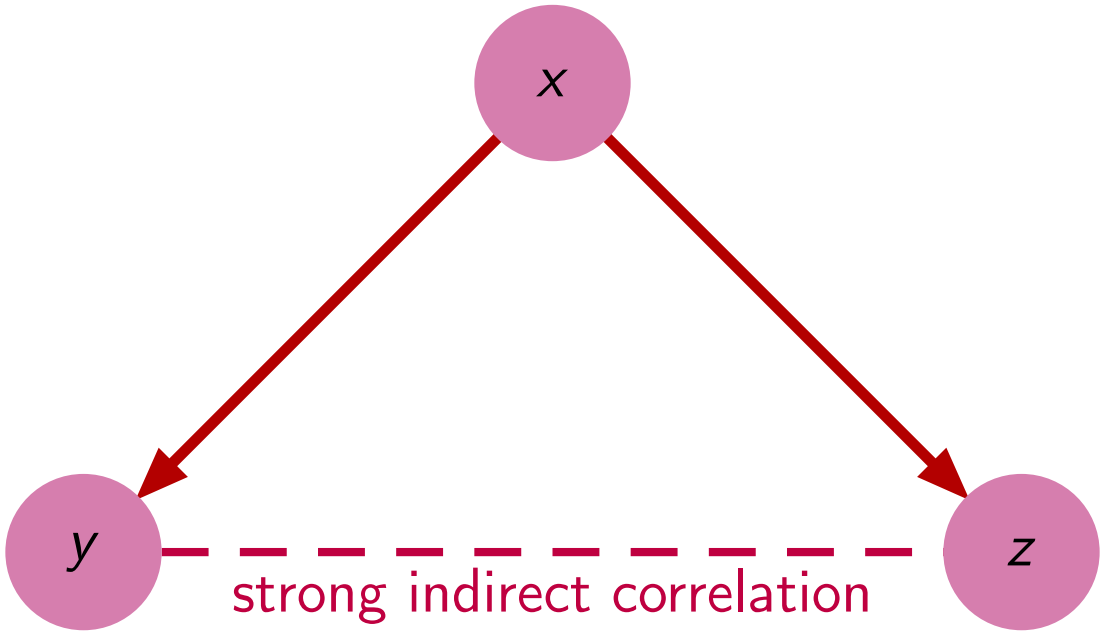


Thresholding



Graph

But correlation is not causality...




```
set.seed(2807); x <- runif(100)
y <- 2*x+1+rnorm(100,0,0.1); cor(x,y); [1] 0.9988261
z <- 2*x+1+rnorm(100,0,0.1); cor(x,z); [1] 0.998751
cor(y,z); [1] 0.9971105
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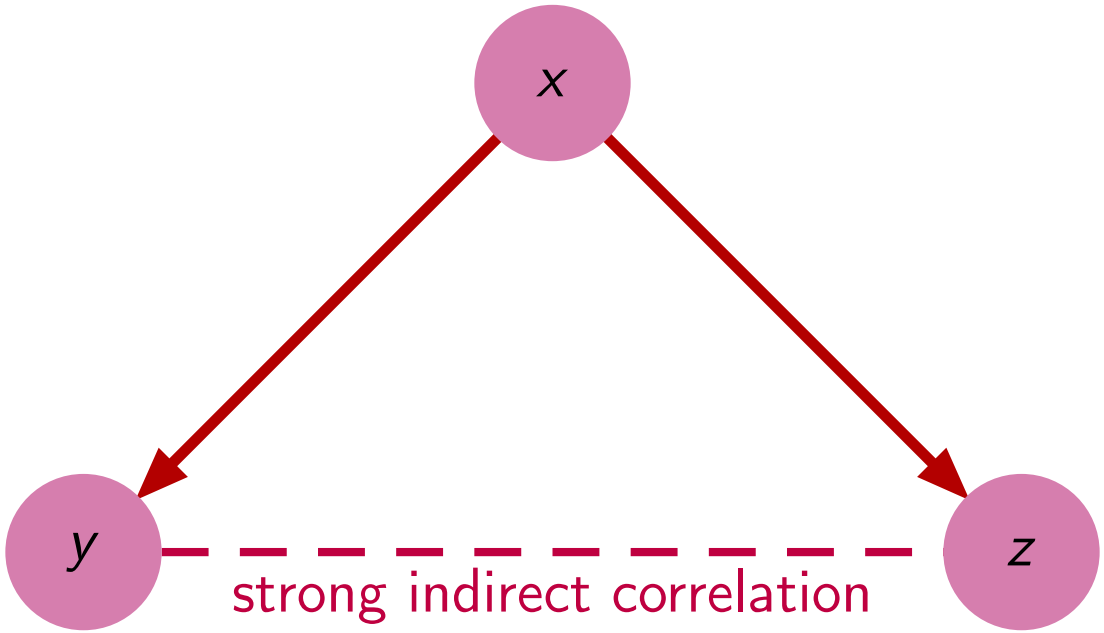


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# Partial correlation
cor(lm(y~x)$residuals,lm(z~x)$residuals) [1] -0.1933699
```

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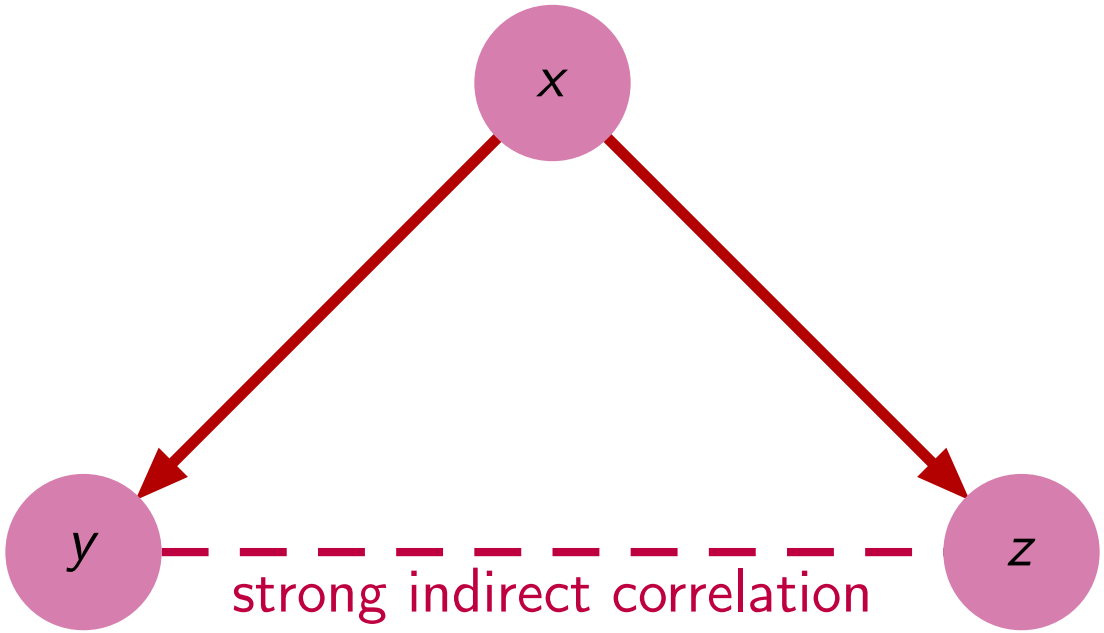

Networks are built using **partial correlations**, i.e., correlations between gene expressions **knowing the expression of all the other genes** (residual correlations).

GGM

Assumptions: $(X_i)_{i=1,\dots,n}$ are i.i.d. Gaussian random variables $\mathcal{N}(0, \Sigma)$ (gene expression)

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GGM definition

- **Partial correlation formulation**

$$j \longleftrightarrow j' (\text{genes } j \text{ and } j' \text{ are linked}) \Leftrightarrow \mathbb{C}\text{or}\left(X^j, X^{j'} | (X^k)_{k \neq j,j'}\right) \neq 0$$

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- **Regression formulation**

$$X^j = \sum_{j'\neq j} \beta_{jj'} X^{j'} + \epsilon \qquad \beta_{jj'} \neq 0 \Leftrightarrow j \longleftrightarrow j' (\text{genes } j \text{ and } j' \text{ are linked})$$

Mathematical background

Theoretically: If $X \sim \mathcal{N}(0, \Sigma)$ then for $S = \Sigma^{-1}$

- partial correlation formulation

$$\mathbb{C}\text{or}\left(X^j, X^{j'} | (X^k)_{k \neq j,j'}\right) = -\frac{S_{jj'}}{\sqrt{S_{jj} S_{j'j'}}}$$

- regression formulation

$$\beta_{jj'} = -\frac{S_{jj'}}{S_{jj}}$$

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In practice:

- Since p (number of genes) is often large compared to n (number of samples), S **is hard to estimate**.
- After the estimation, entries of S are not null $\Rightarrow$ How to **select the "largest" entries in** S?

Some solutions

1. Seminal work
   [Schäfer and Strimmer, 2005a, Schäfer and Strimmer, 2005b]
   (implemented in the R package GeneNet)
   - Estimation of S: regularization for inversion of Σ
   - Edge selection: Bayesian approach

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2. Sparse approach
   [Friedman et al., 2008, Meinshausen and Bühlmann, 2006]
   (implemented in the R package huge)
   - estimation and selection performed together
   - uses the regression framework in which a "sparse" penalty is added (LASSO or Graphical LASSO)

Important notices

- **ultra-high dimensionality**: if p is the number of genes, n the number of samples and k the (true) number of edges of a network, ultra-high dimensionality means that $k\left[1+\log\left(\frac{p(p-1)/2}{k}\right)\right]$ is "large" compared to n

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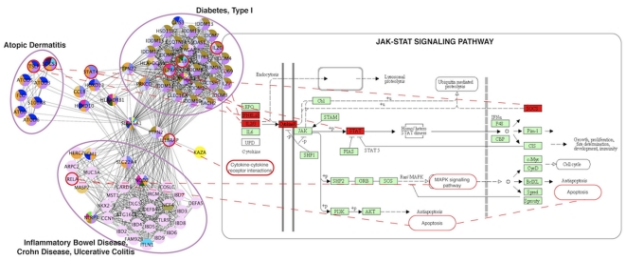
- **applicability**: Gaussian models are well designed for microarray datasets. However, **extension to RNA-seq data is non trivial** and still under development.

Take home message...

networks are useful to model complex systems



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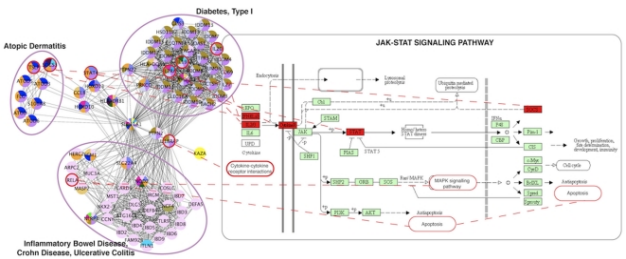
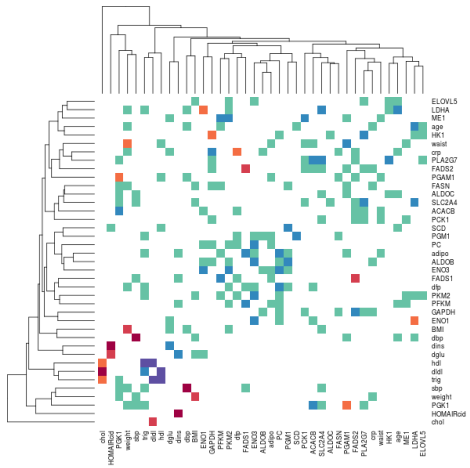
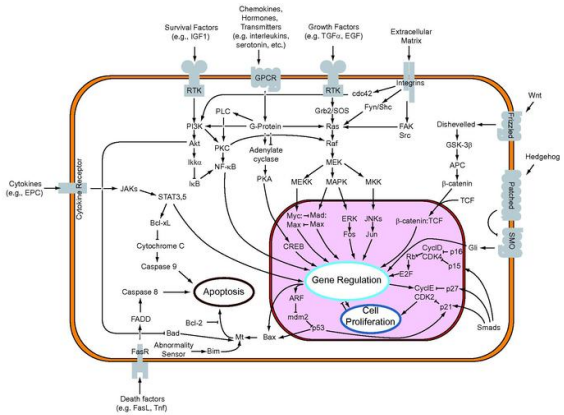


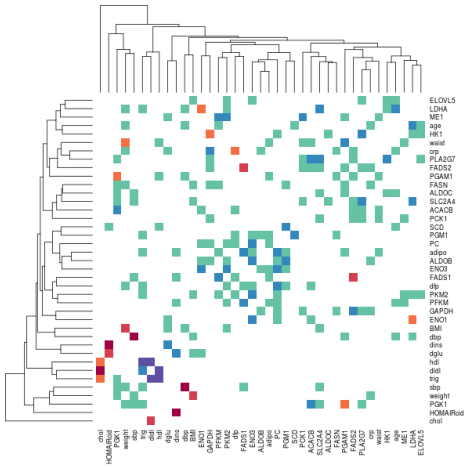


networks can be built with various approaches that define what they can be used for

Take home message...



networks are useful information that can be integrated in biological models to improve knowledge



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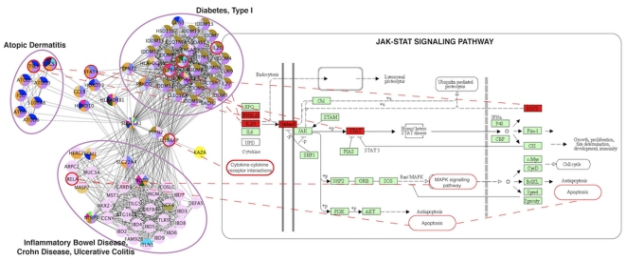

networks can be built with various approaches that define what they can be used for

References

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