

STRUCTURE & FUNCTION OF METABOLIC NETWORKS

Petter Holme

KTH, CSC, Computational Biology

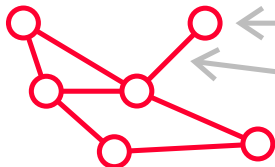
Oktober 10, 2007, SBC seminar series

<http://www.csc.kth.se/~pholme/>



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nodes, vertices, links, edges



vertex, node, site, actor, agent

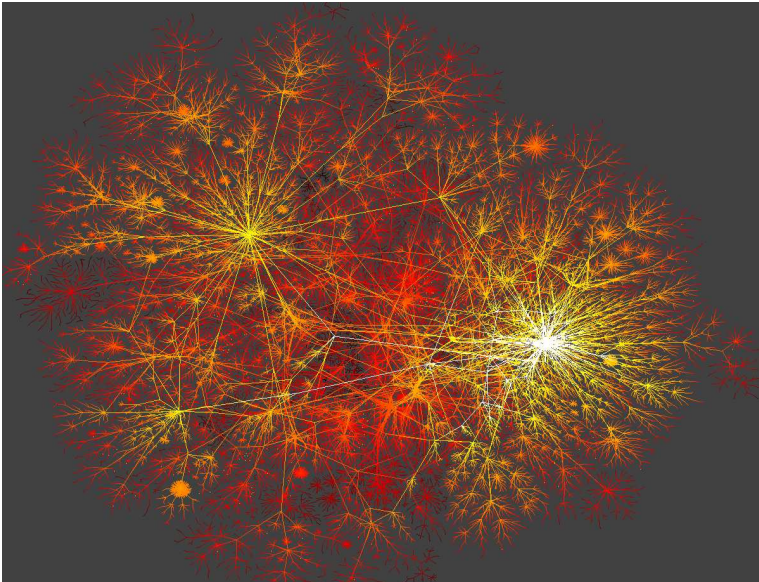
edge, link, tie, bond, arc

number of neighbors = *degree*



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examples: internet



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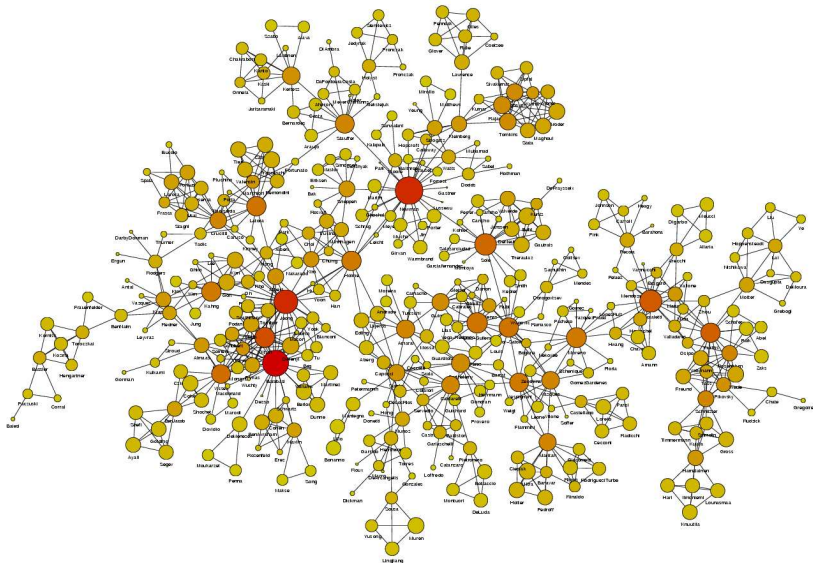
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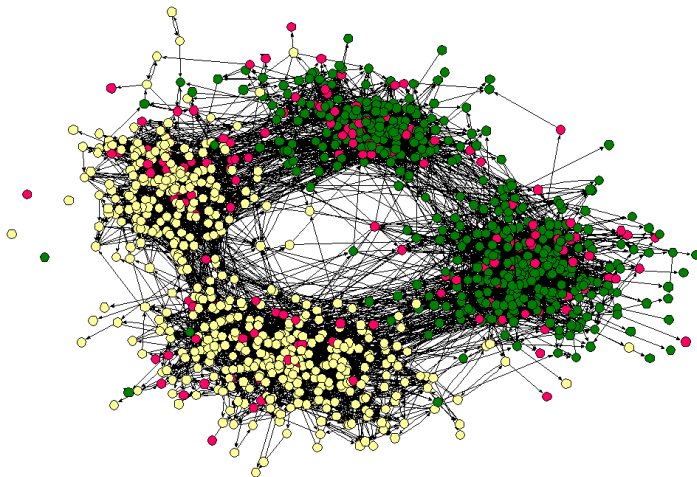


examples: scientific collaborations



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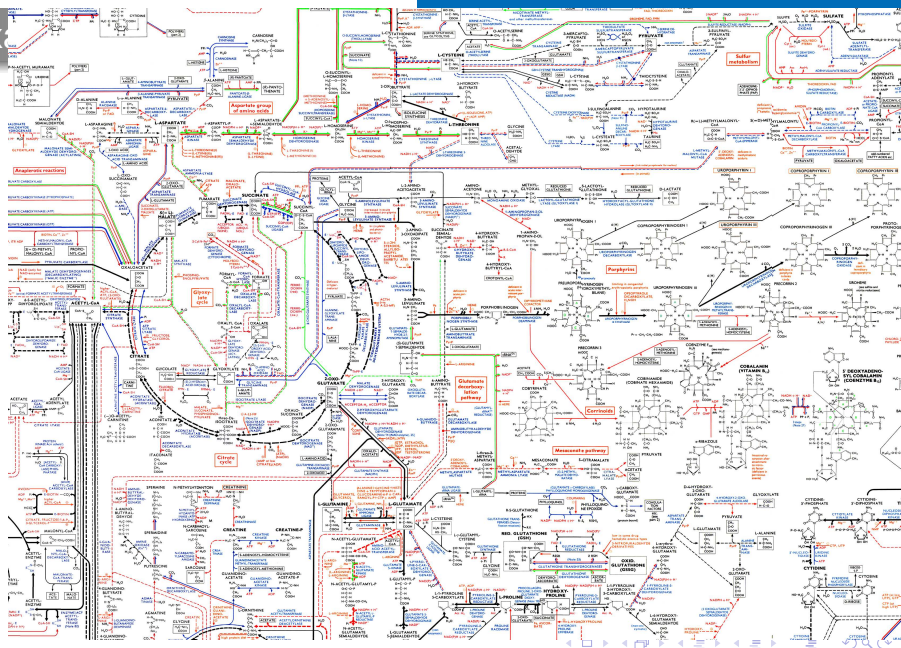
examples: friendship



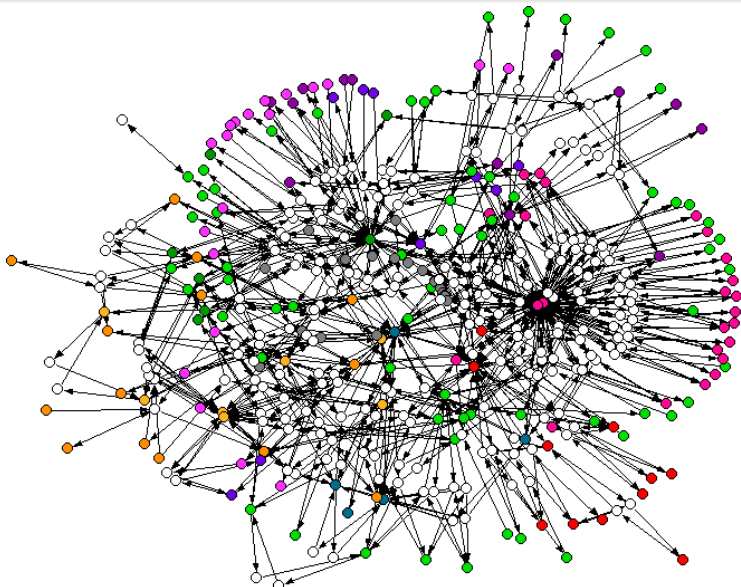
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introduction to complex networks
metabolic networks

ex



examples: metabolism



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STRUCTURE & FUNCTION OF METABOLIC NETWORKS



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what systems can be modeled as networks?

- items are coupled pairwise
- the network is relatively sparse (the average degree is constant)
- there is a dynamic system on the network
- the time scale of this dynamics is faster than the dynamics of network evolution



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what is network structure?

- how the network differs a random network
- **to be more precise:** how the network differs from a null model



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network null-models

- Network structures are always relative . . .
- . . . one has to be clear about what to compare with . . . a null model
- *Null model 1*: random graphs (Poisson random graphs, Erdős-Rényi graphs)
- *Null model 2*: random graphs constrained to the set of degrees of the original graph



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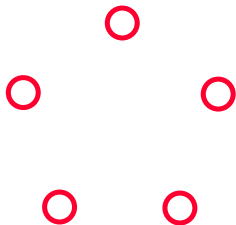


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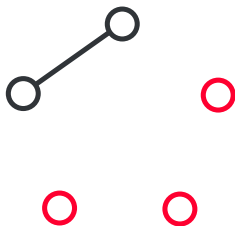
random graphs



for each pair of vertices,
with probability p , add an edge



random graphs

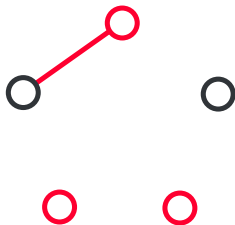


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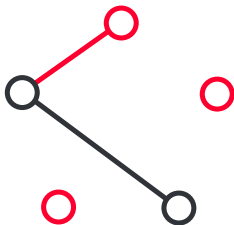


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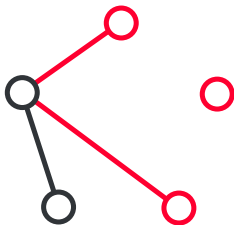


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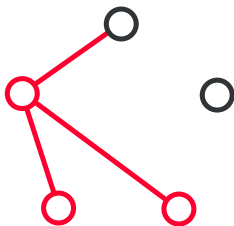


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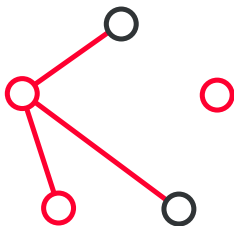


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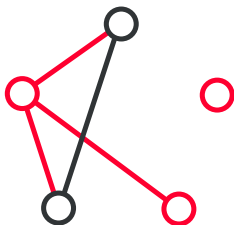


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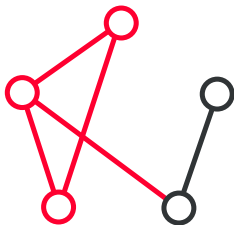


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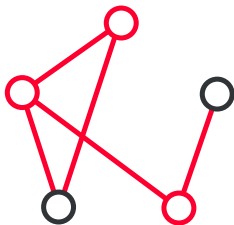


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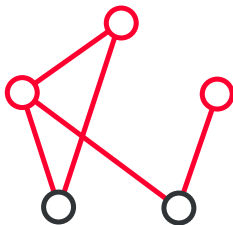


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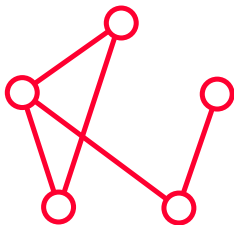


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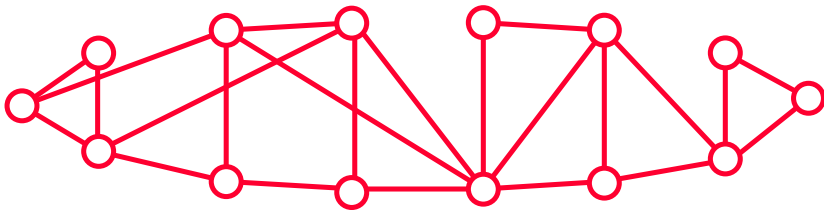


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random rewiring

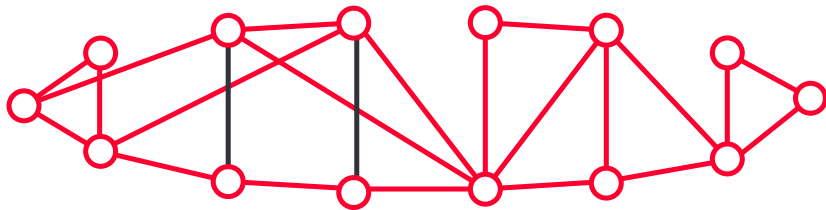


start from the original graph
choose edge pairs, and swap them



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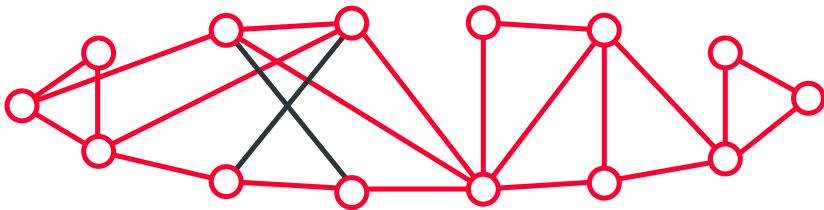


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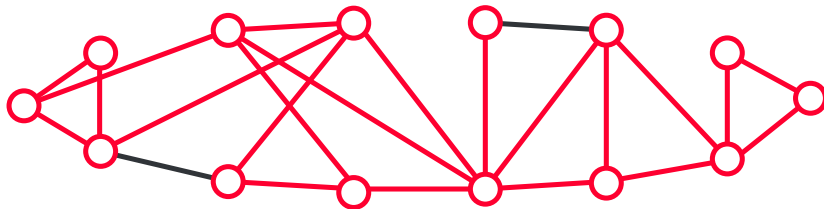


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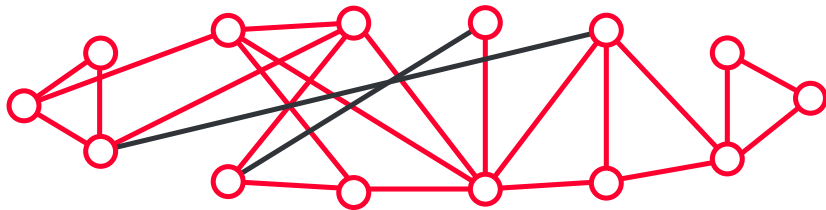


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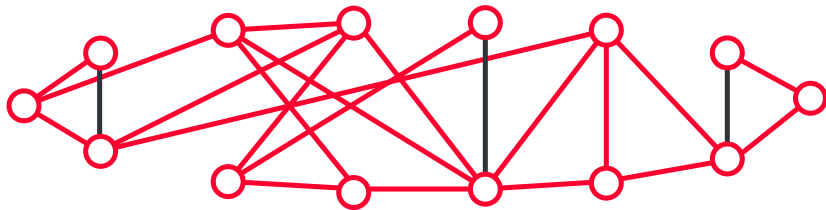


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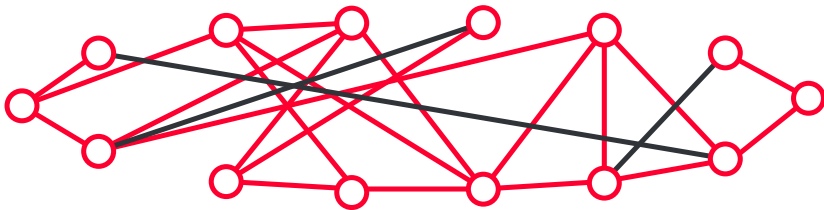


start from the original graph
edge triples can be swapped too



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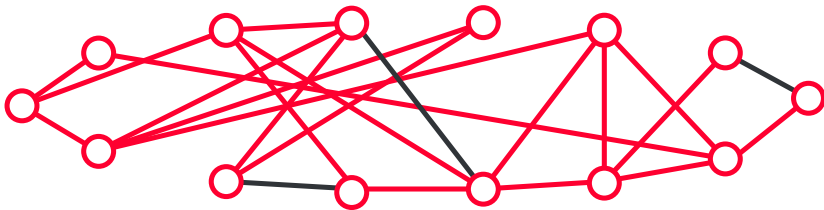


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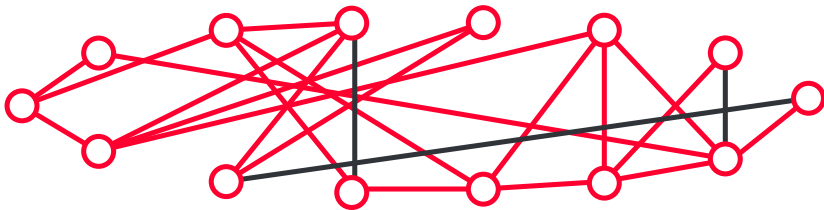


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the dogmas of network science

- real networks have both structure and randomness
- the network structure relates to the function of the network



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what is network science?

- Constructing relevant measures of network structure.
- Measuring structure of real networks, and elucidating correlations between the quantities.
- Why do real networks have the structure they have? Modeling the evolution of networks.
- How does the topology affect dynamic systems on the network.
- How can we control network topology to get some desirable dynamic property.



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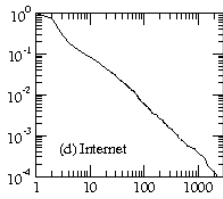
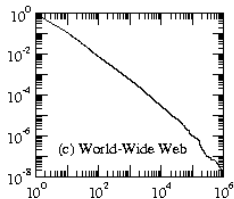
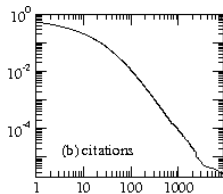
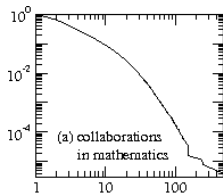


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degree distribution

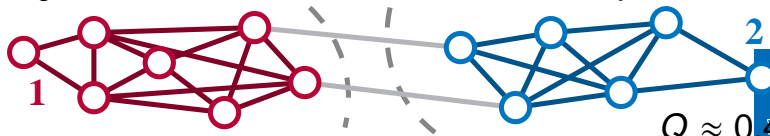


modularity (of a partition)

Definition

$$Q = \sum_i \left[e_{ii} - \left(\sum_j e_{ij} \right)^2 \right] \quad (1)$$

the sum is over the a partition into clusters and e_{ij} is the fraction of edges that leads between vertices of cluster i and j



modularity (of a graph)

Definition

$$\hat{Q}(G) = \max_{\text{partitions}} Q \quad (2)$$

(null model: random graphs)

Definition

$$\hat{Q}(G) = \max_{\text{partitions}} Q - \left\langle \max_{\text{partitions}} Q \right\rangle \quad (3)$$

(null model: random graphs with the same degree sequence)



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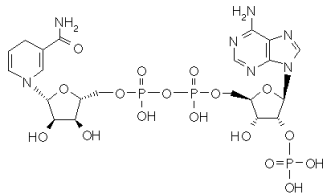
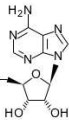
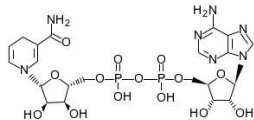
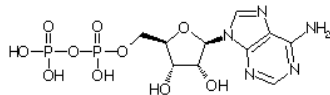
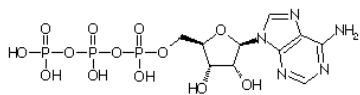
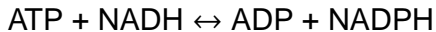
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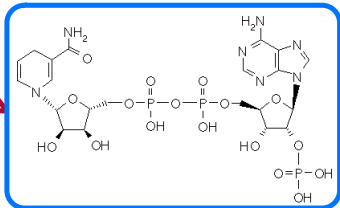
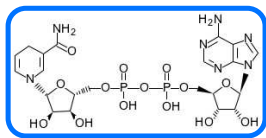
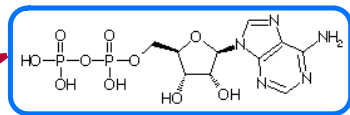
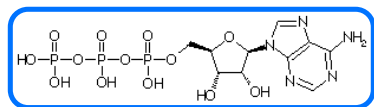
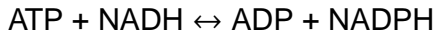
(null model: random graphs with the same degree sequence)



representations



representations



vertices: substrates

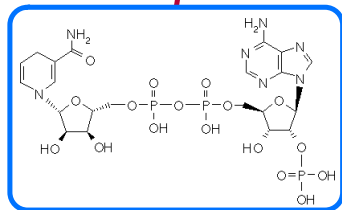
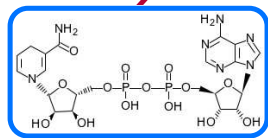
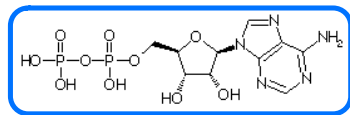
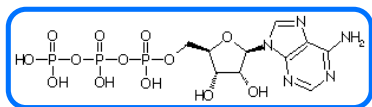
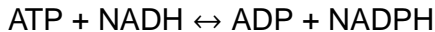
edges: between products / substrates

on different sides



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representations

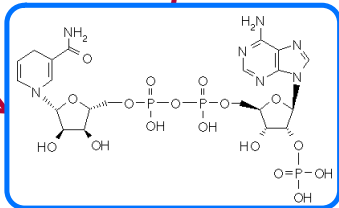
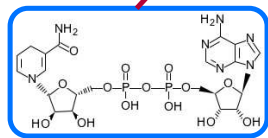
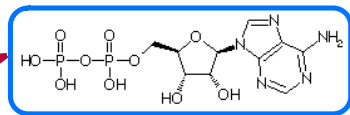
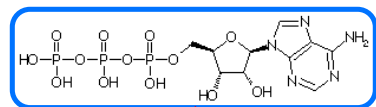
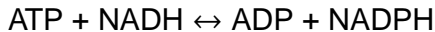


vertices: substrates

edges: between products / substrates

on the same side

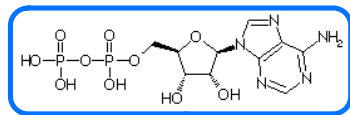
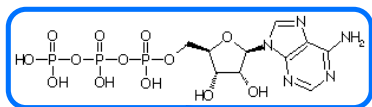
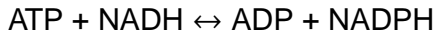
representations



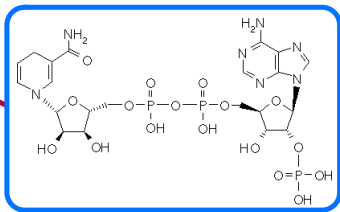
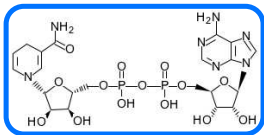
vertices: substrates

edges: between all products / substrates

representations



NADH kinase

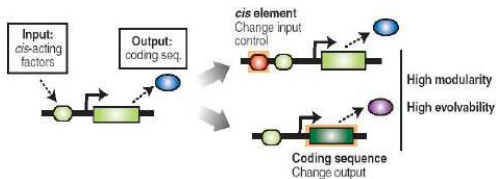


vertices: substrates + enzymes (reactions)

edges: between substance / reaction vertices



modularity (the biological idea)

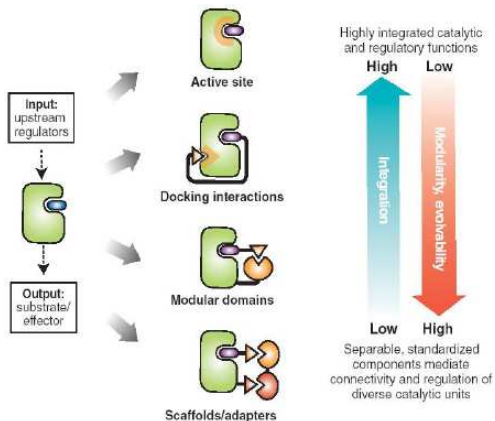


(Bhattacharyya *et al.*, 2006, *Annu Rev Biochem* **75**, pp. 655–80)



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modularity (the biological idea)



(Bhattacharyya *et al.*, 2006, *Annu. Rev. Biochem.* **75**, pp. 655–80)



modularity and robustness

- robustness—*sensitivity of a relevant dynamic system on the network* to perturbations
- in spreading of harmful things (like disease), modularity increases robustness
- in other systems where a flow is needed throughout the networks, modularity might decrease robustness



modularity and robustness

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- in spreading of harmful things (like disease), modularity increases robustness
- in other systems where a flow is needed throughout the networks, modularity might decrease robustness



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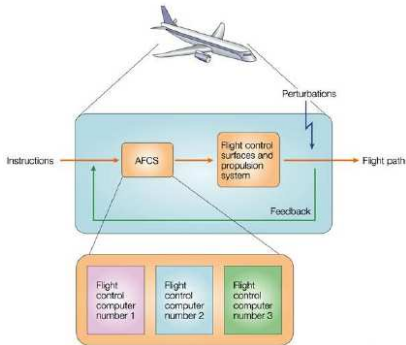
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modularity and robustness

robustness by redundancy



(Kitano, 2004, Nat. Rev. Genet. **5**, pp. 826–837.)



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modularity and robustness

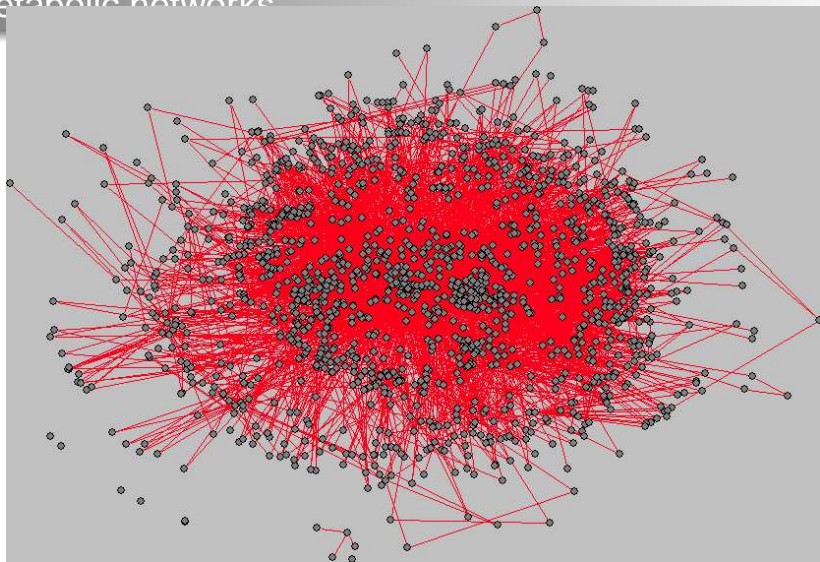
distributed robustness (A. Wagner):

In distributed robustness, many parts of a system contribute to its function, but all of these parts have different roles. When one part fails or is changed through mutations, other parts can compensate for this failure, but not simply by standing in for the failed part.

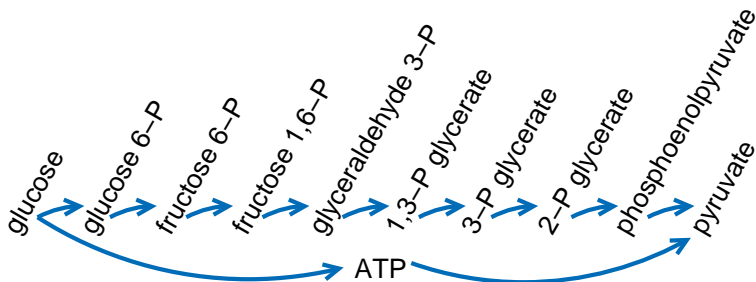


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metabolic networks



currency metabolites



currency metabolites

Wagner & Fell, 2001	Schuster <i>et al.</i> , 2002	Ma & Zeng, 2003
ATP	ATP	ATP
ADP	ADP	ADP
NADP	NADP	NADP
NADPH	NADPH	
NAD		NAD
NADH		
	P_i	P_i
	H ₂ O	H ₂ O
	H ⁺	
	PP _i	
	CMP	
		CO ₂
		O ₂
		NH ₃



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currency metabolites (a definition)

- 1 currency metabolites have high degree
- 2 they make not meaningful shortcuts
- 3 i.e. tie together distant parts of the network
- 4 i.e. tie different modules together

. . . let's turn this around to a definition . . .



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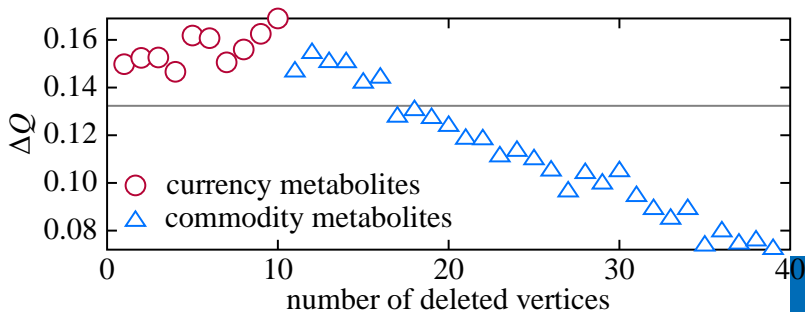
Definition

Remove vertices in order of (currently) highest degree. The set of removed vertices that gives the network the highest modularity is the set of currency metabolites.



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human currency metabolites



detected currency metabolites

Wagner & Fell, 2001

ATP
ADP
NADP
NADPH
NAD
NADH

Schuster *et al.*, 2002

ATP
ADP
NADP
NADPH

P_i
H₂O
H⁺
PP_i
CMP

Ma & Zeng, 2003

ATP
ADP
NADP

NAD

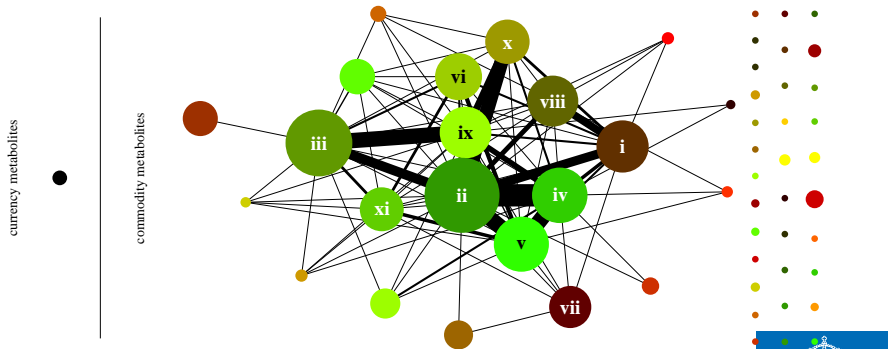
P_i
H₂O

CO₂
O₂
NH₃



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modularity and robustness



- | | | |
|---|---|---------------------------------|
| i. nitrogen metabolism | ii. amino acid metabolism / protein synthesis | iii. sugar metabolism |
| iv. citric acid cycle / porphyrin synthesis | v. fatty acid metabolism | vi. steroid metabolism |
| vii. metabolism of xenobiotics | viii. tyrosine and tryptamine metabolism | ix. DNA metabolism / glycolysis |
| x. nucleoside / nucleotide metabolism | xi. glycerophospholipid and arachidonic acid metabolism | |



different organisms

organism	samples	nodes	edges	c. m.	modularity
animals	5	1621	4662	6.2	0.157
plants	1	1561	4302	1	0.144
fungi	2	1281	3654	1.5	0.150
bacteria	99	1050	2739	1.7	0.140



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conclusions

- proposed graph based definition of currency metabolites
- metabolic networks *are* modular, but not so much
- the reason they are not more modular might be give robustness

(Huss & Holme, 2007, IET Syst. Biol. 1, pp. 280–5.)



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