Network modularity, currency metabolites and graph representations of metabolism

Petter Holme

KTH, CSC, Computational Biology

December 17, 2007, Mathematics for biological networks

ROYAL INSTITUTE
OF TECHNOLOGY

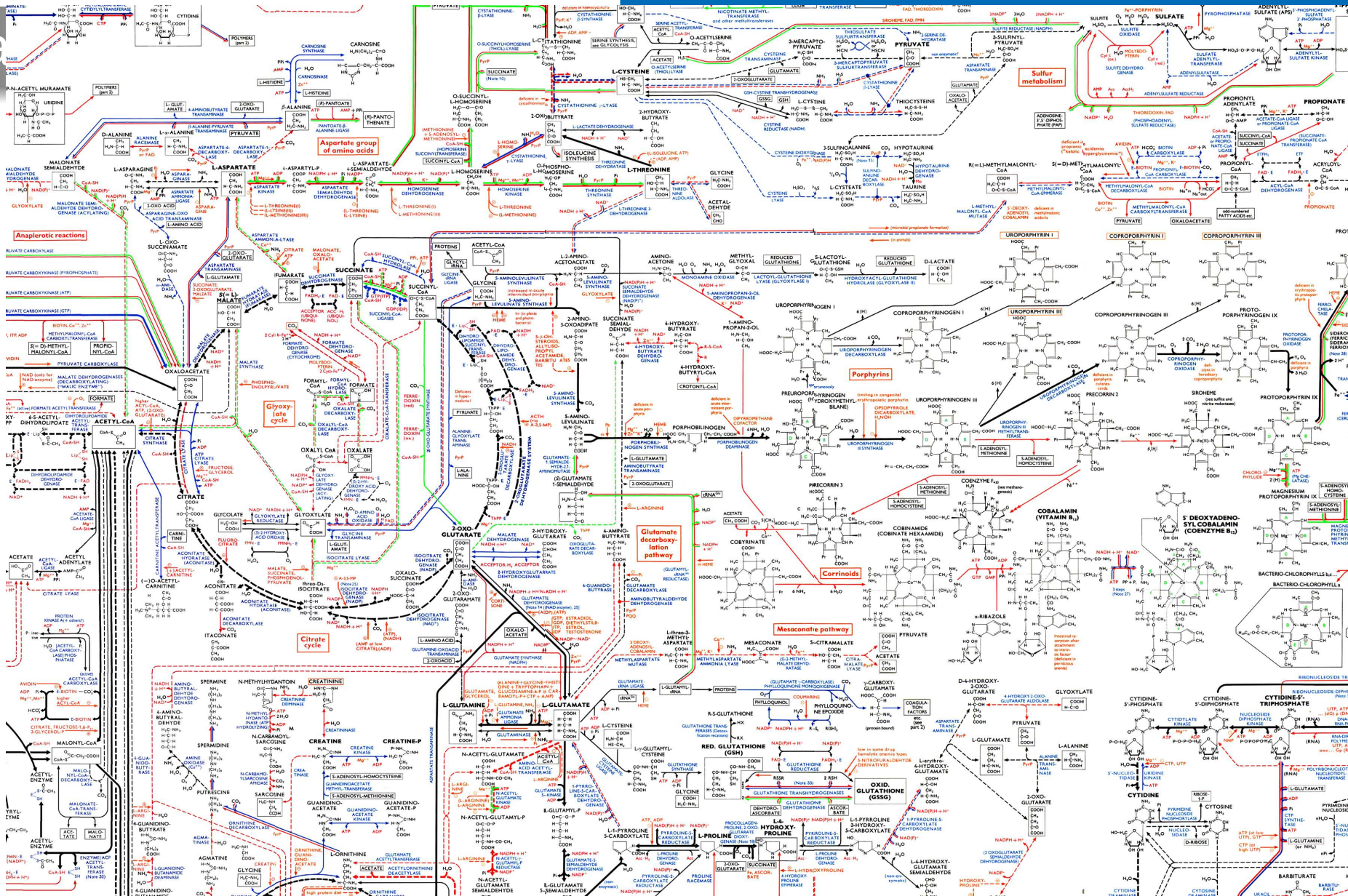
metabolic networks, intro

networks (physicist style?)

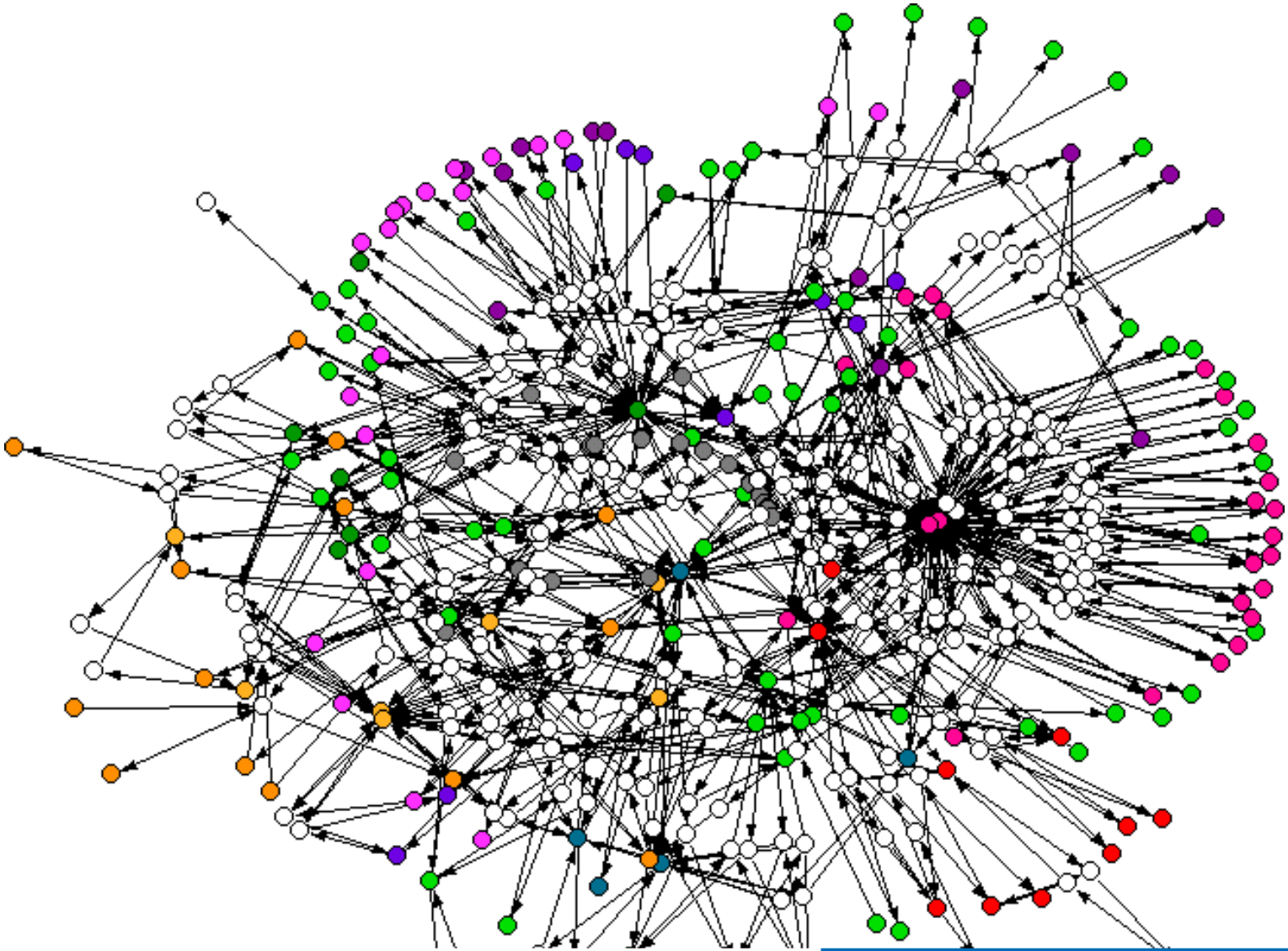
modularity & currency metabolites

subnetwork hierarchies

wa

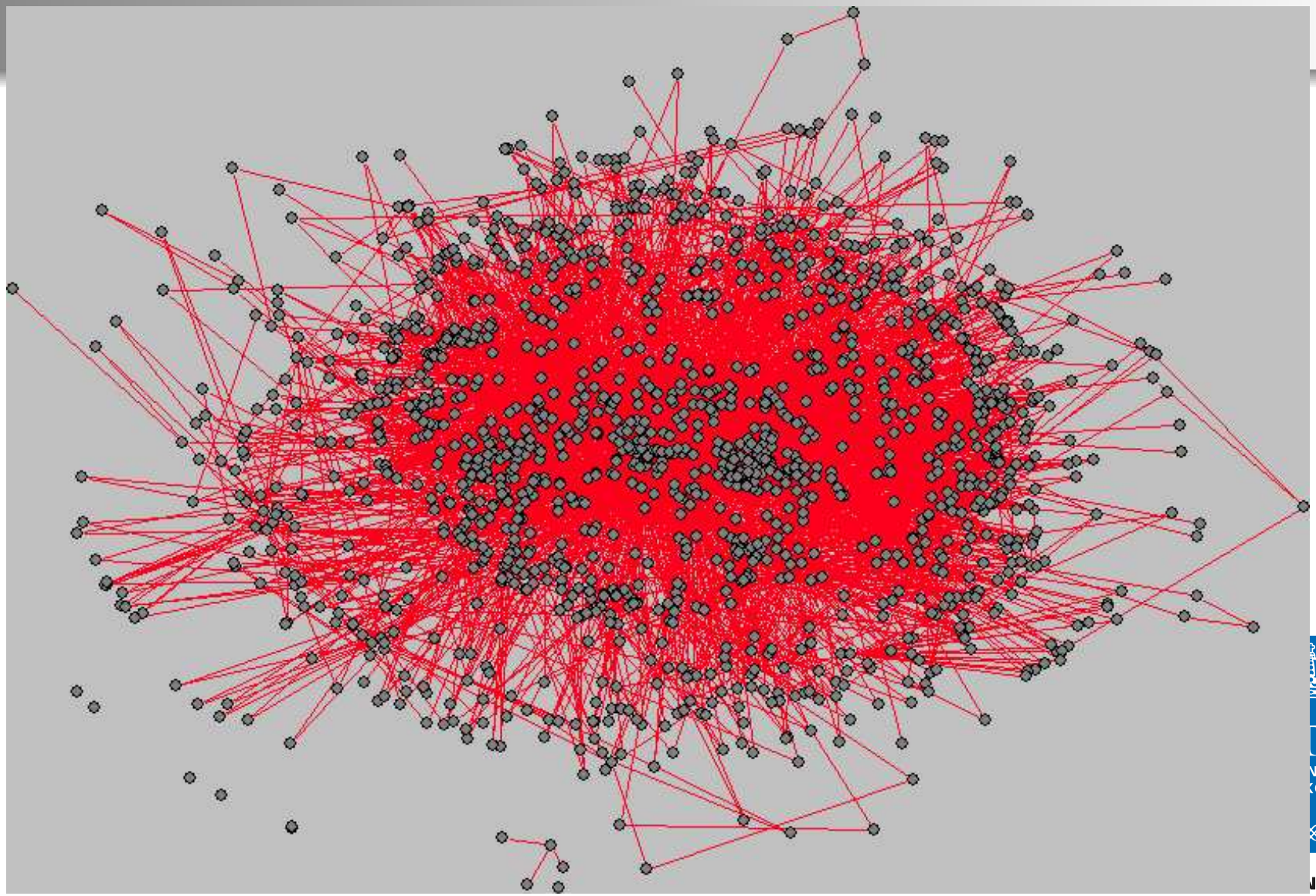


B. burgdorferi, 2000



ROYAL INSTITUTE OF TECHNOLOGY

hu



complex network studies

. . . of biochemical networks. What questions can we ask?

- how can the large-scale organization be characterized?
- are there any universal features over different species?
- do the differences tell us something about evolution?
- can we identify functional modules?
- . . the functions of molecules?

ROYAL INSTITUTE
OF TECHNOLOGY

complex network studies

. . . of biochemical networks. What questions can we ask?

- how can the large-scale organization be characterized?
- are there any universal features over different species?
- do the differences tell us something about evolution?
- can we identify functional modules?
- . . the functions of molecules?

ROYAL INSTITUTE
OF TECHNOLOGY

complex network studies

. . . of biochemical networks. What questions can we ask?

- how can the large-scale organization be characterized?
- are there any universal features over different species?
- do the differences tell us something about evolution?
- can we identify functional modules?
- . . the functions of molecules?

ROYAL INSTITUTE
OF TECHNOLOGY

complex network studies

. . . of biochemical networks. What questions can we ask?

- how can the large-scale organization be characterized?
- are there any universal features over different species?
- do the differences tell us something about evolution?
- can we identify functional modules?
- . . the functions of molecules?

ROYAL INSTITUTE
OF TECHNOLOGY

complex network studies

. . . of biochemical networks. What questions can we ask?

- how can the large-scale organization be characterized?
- are there any universal features over different species?
- do the differences tell us something about evolution?
- can we identify functional modules?
- . . the functions of molecules?

ROYAL INSTITUTE
OF TECHNOLOGY

complex network studies

. . . of biochemical networks. What questions can we ask?

- how can the large-scale organization be characterized?
- are there any universal features over different species?
- do the differences tell us something about evolution?
- can we identify functional modules?
- . . the functions of molecules?

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

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

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

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

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

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

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

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

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

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

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

- items are, naturally, coupled pairwise MAYBE?
- the network is relatively sparse (the average degree is constant) ALMOST TRUE
- there is a dynamic system on the network TRUE!
- the time scale of this dynamics is faster than the dynamics of network evolution **TRUE!**

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

- items are, naturally, coupled pairwise MAYBE?
- the network is relatively sparse (the average degree is constant) ALMOST TRUE
- there is a dynamic system on the network **TRUE!**
- the time scale of this dynamics is faster than the dynamics of network evolution **TRUE!**

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

What systems can be analyzed with complex network methods?

- items are, naturally, coupled pairwise MAYBE?
- the network is relatively sparse (the average degree is constant) **ALMOST TRUE**
- there is a dynamic system on the network **TRUE!**
- the time scale of this dynamics is faster than the dynamics of network evolution **TRUE!**

ROYAL INSTITUTE
OF TECHNOLOGY

what systems?

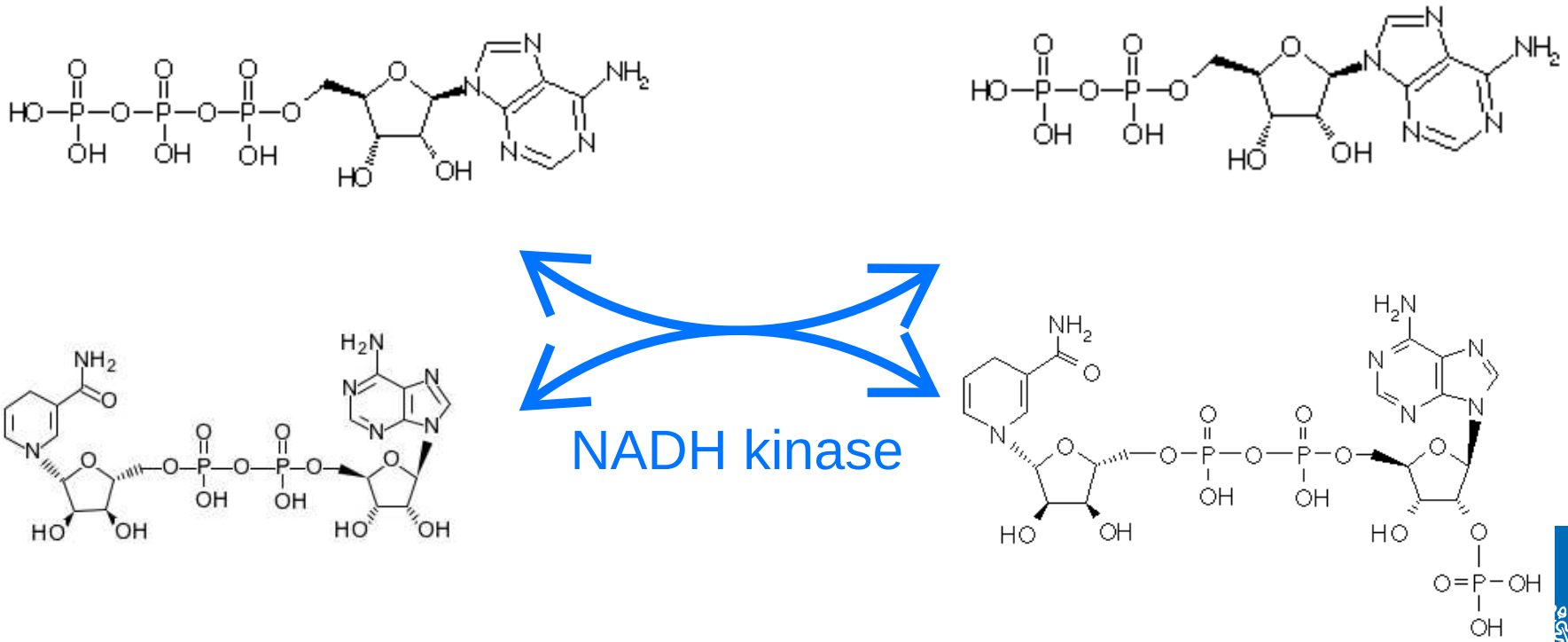
What systems can be analyzed with complex network methods?

- items are, naturally, coupled pairwise **MAYBE?**
- the network is relatively sparse (the average degree is constant) **ALMOST TRUE**
- there is a dynamic system on the network **TRUE!**
- the time scale of this dynamics is faster than the dynamics of network evolution **TRUE!**

ROYAL INSTITUTE
OF TECHNOLOGY

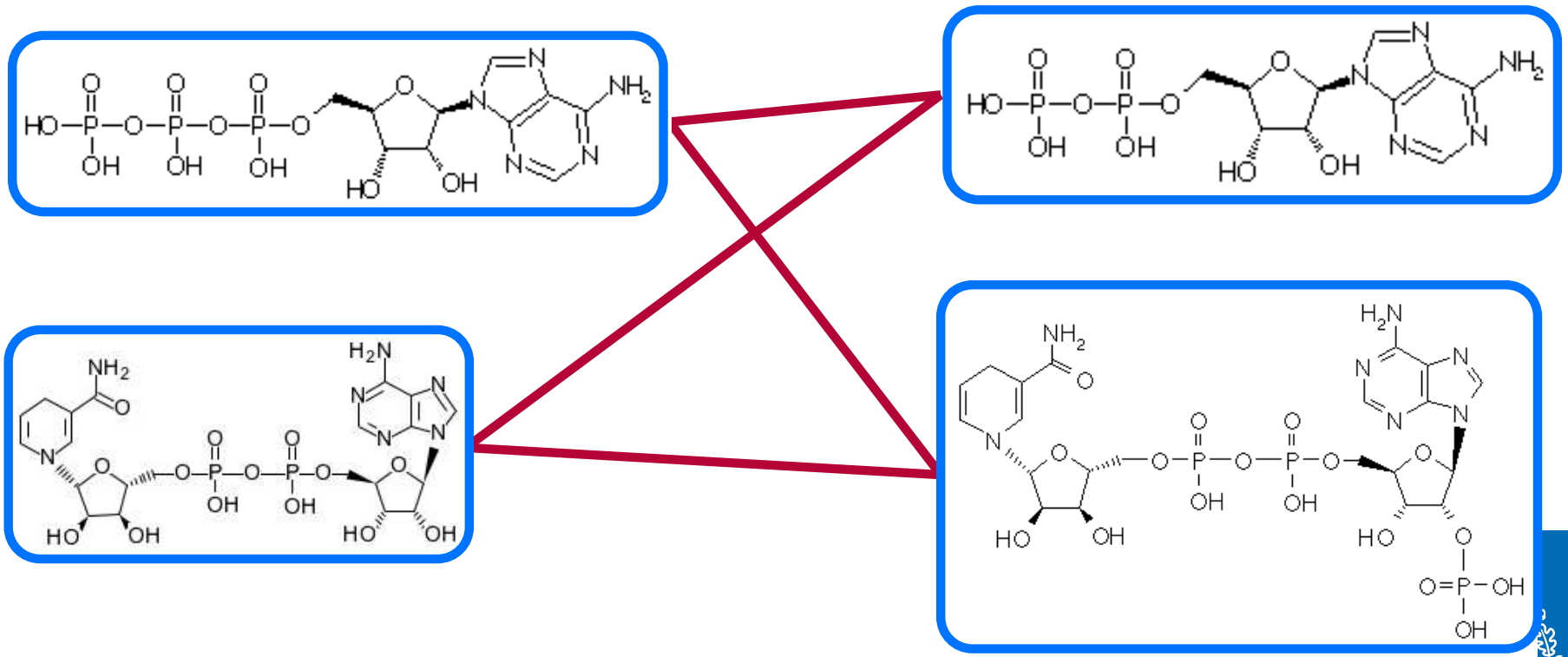
representations

ATP + NADH ↔ ADP + NADPH



representations

ATP + NADH ↔ ADP + NADPH

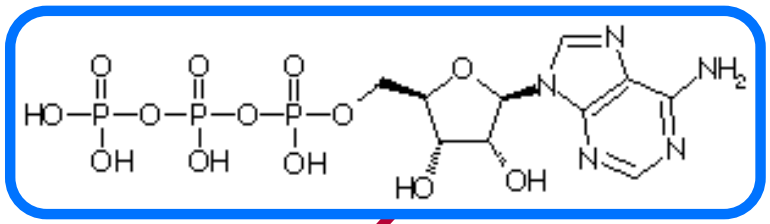


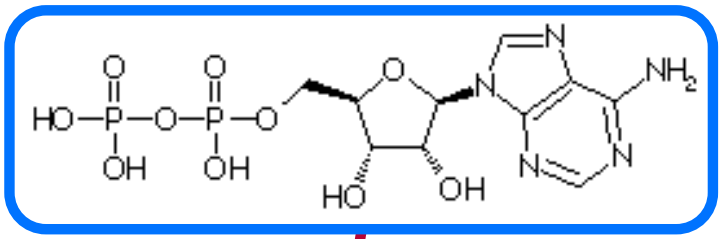
vertices: substrates

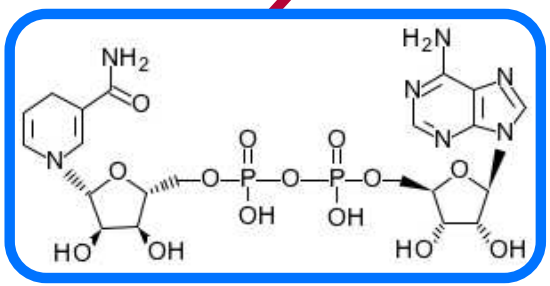
edges: between products / substrates

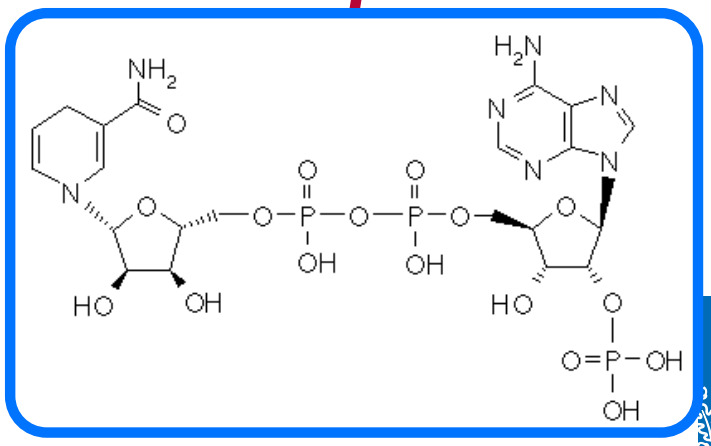
representations

ATP + NADH ↔ ADP + NADPH







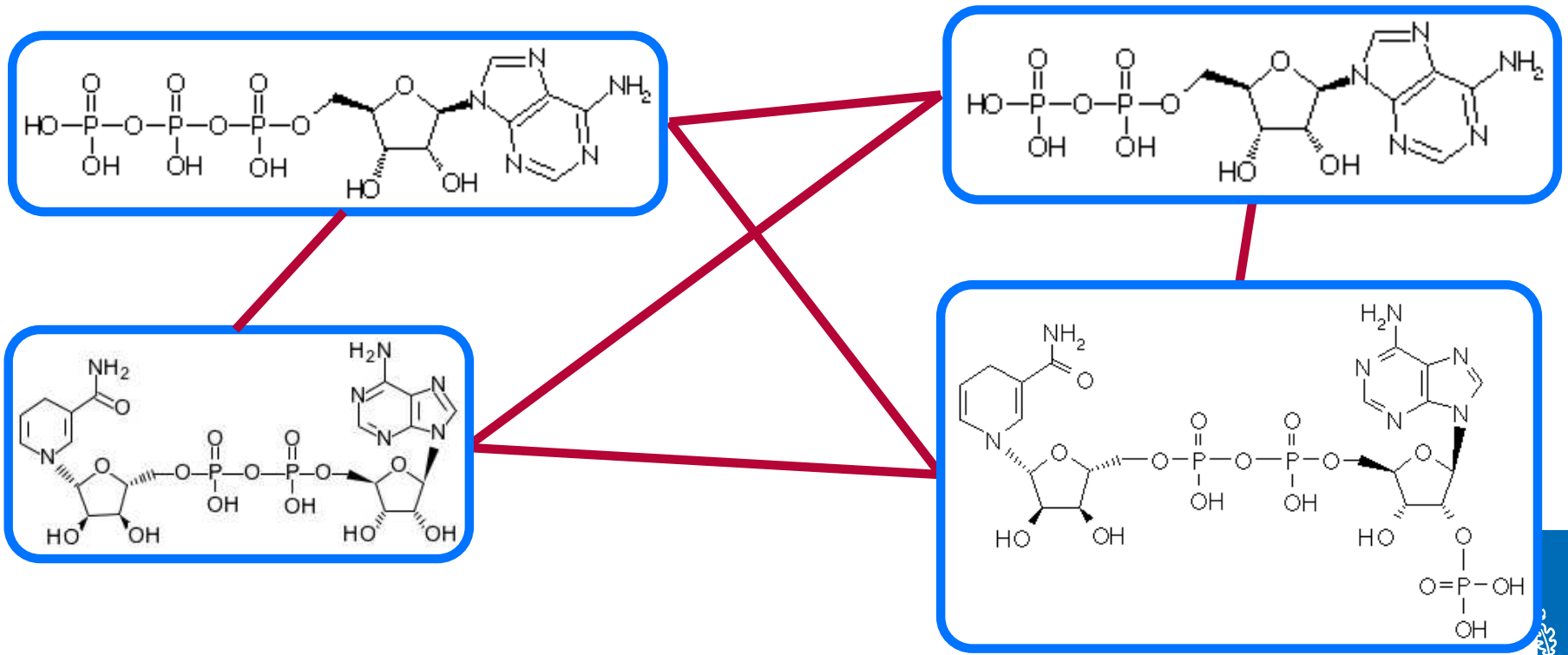


vertices: substrates

edges: between products / substrates

representations

ATP + NADH ↔ ADP + NADPH

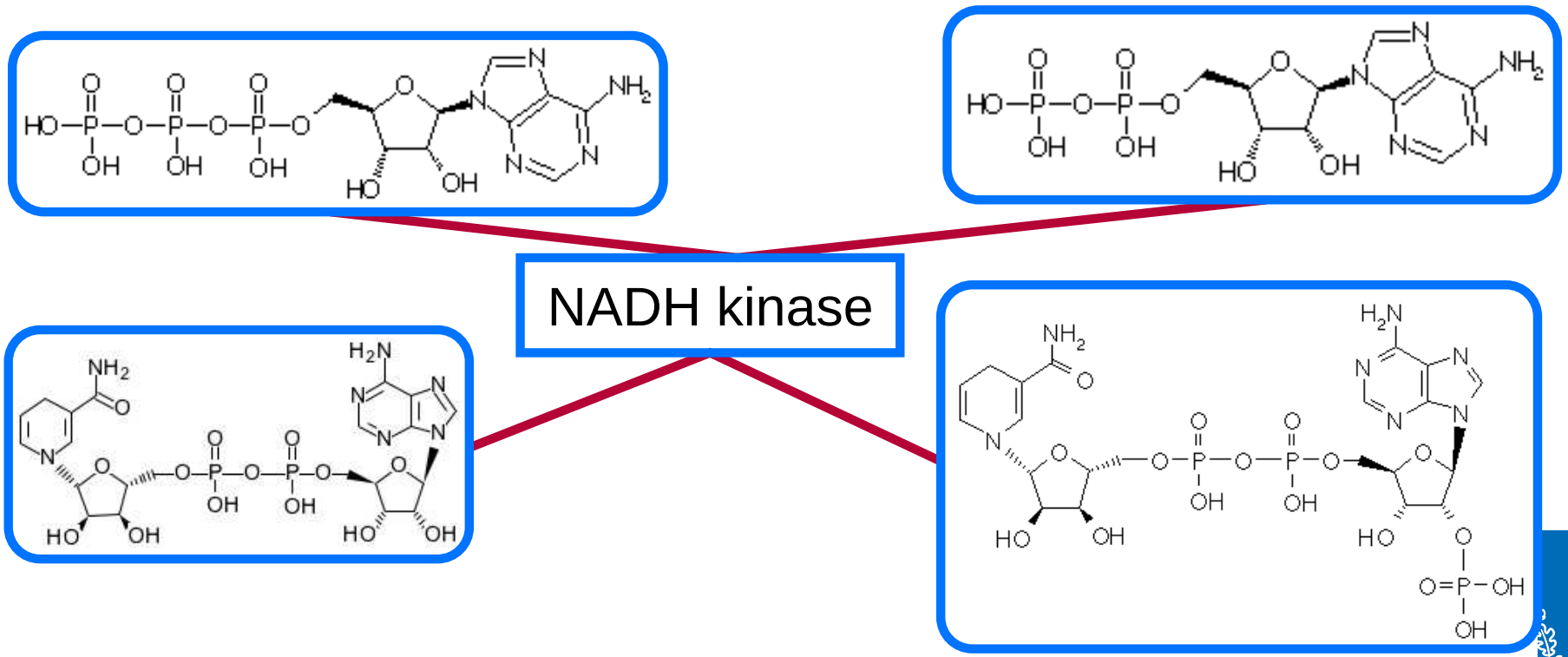


vertices: substrates

edges: between all products / substrates

representations

ATP + NADH ↔ ADP + NADPH



vertices: substrates + enzymes (reactions)

edges: between substance / reaction vertices

representations

- different representations, give different information
- most common representation = substance graphs—following atoms, the number of conversions between two molecules are small $\Leftrightarrow$ the graph distance is small

ROYAL INSTITUTE
OF TECHNOLOGY

representations

- different representations, give different information
- most common representation = substance graphs—following atoms, the number of conversions between two molecules are small $\Leftrightarrow$ the graph distance is small

ROYAL INSTITUTE
OF TECHNOLOGY

representations

- different representations, give different information
- most common representation = substance graphs—following atoms, the number of conversions between two molecules are small $\Leftrightarrow$ the graph distance is small

ROYAL INSTITUTE
OF TECHNOLOGY

what is network structure?

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

ROYAL INSTITUTE
OF TECHNOLOGY

what is network structure?

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

ROYAL INSTITUTE
OF TECHNOLOGY

what is network structure?

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

network null-models

- Network structures are relative . . .
- . . . so 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

ROYAL INSTITUTE
OF TECHNOLOGY

network null-models

- Network structures are relative . . .
- . . . so 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

ROYAL INSTITUTE
OF TECHNOLOGY

network null-models

- Network structures are relative . . .
- . . . so 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

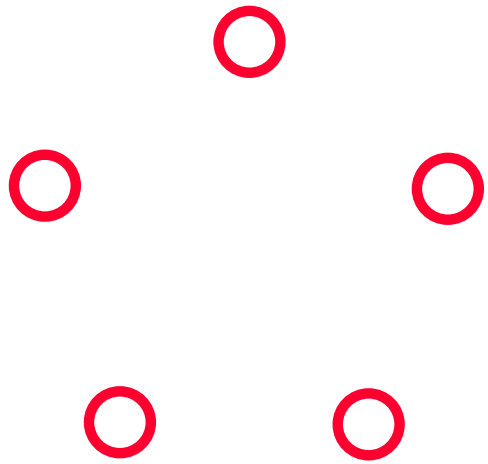
ROYAL INSTITUTE
OF TECHNOLOGY

network null-models

- Network structures are relative . . .
- . . . so 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

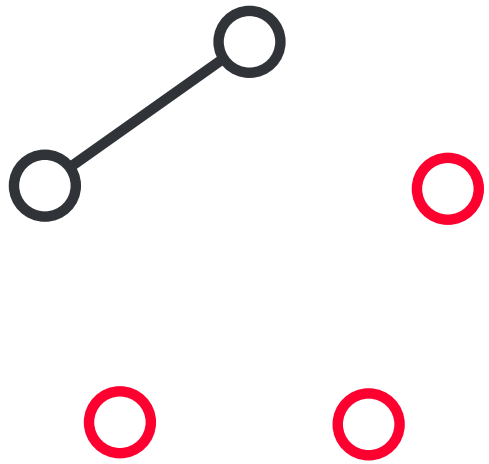
ROYAL INSTITUTE
OF TECHNOLOGY

random graphs



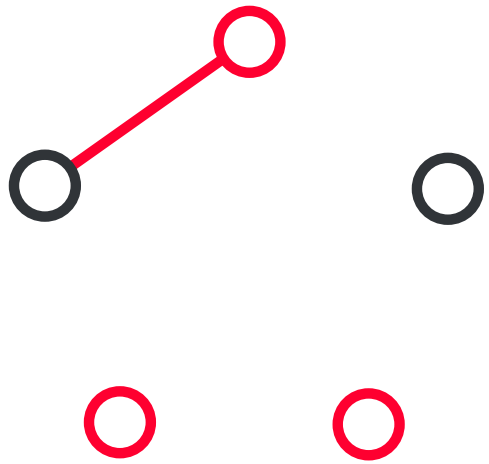
for each pair of vertices,
with probability p, add an edge

random graphs



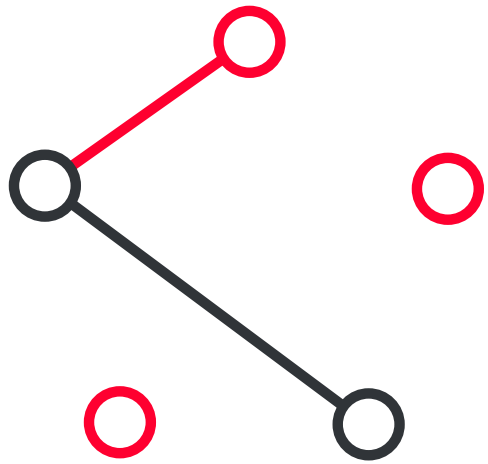
for each pair of vertices,
with probability p, add an edge

random graphs



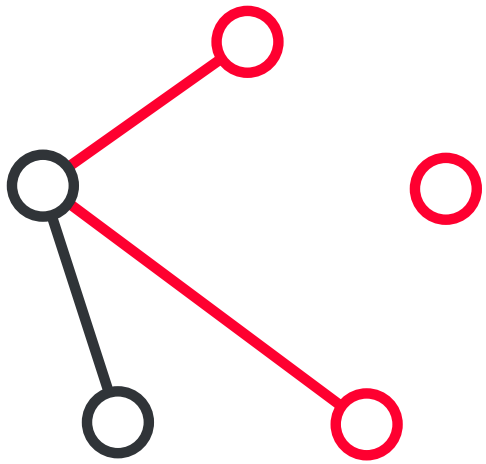
for each pair of vertices,
with probability p, add an edge

random graphs



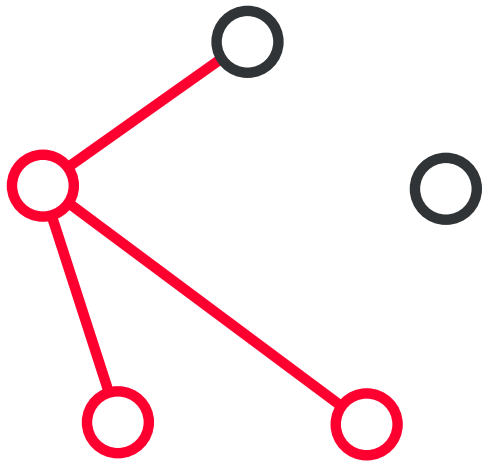
for each pair of vertices,
with probability p, add an edge

random graphs



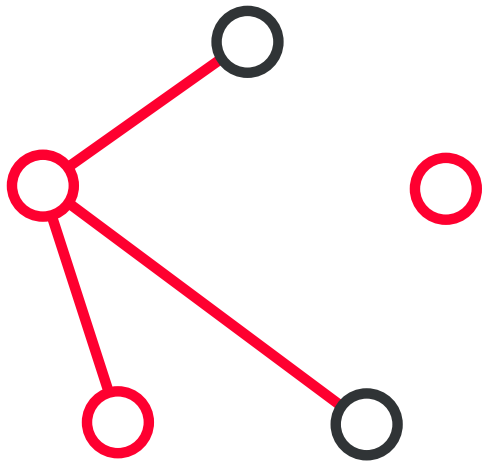
for each pair of vertices,
with probability p, add an edge

random graphs



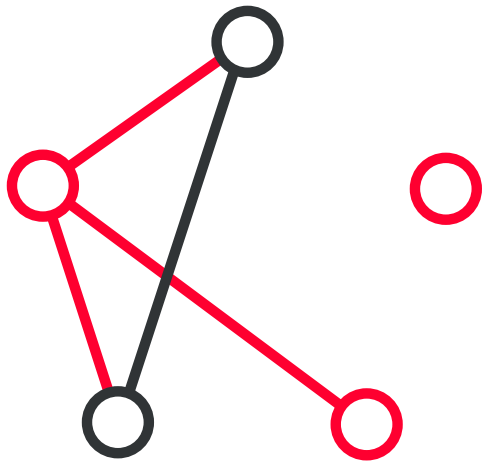
for each pair of vertices,
with probability p, add an edge

random graphs



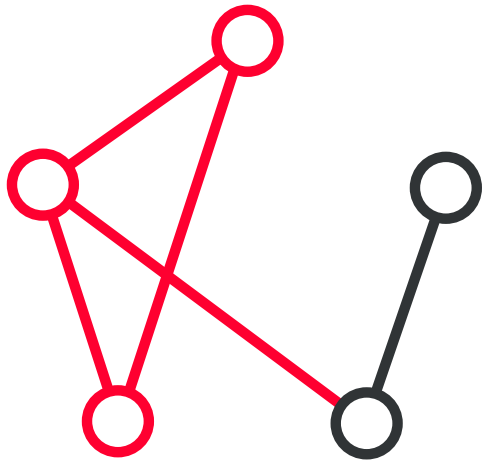
for each pair of vertices,
with probability p, add an edge

random graphs



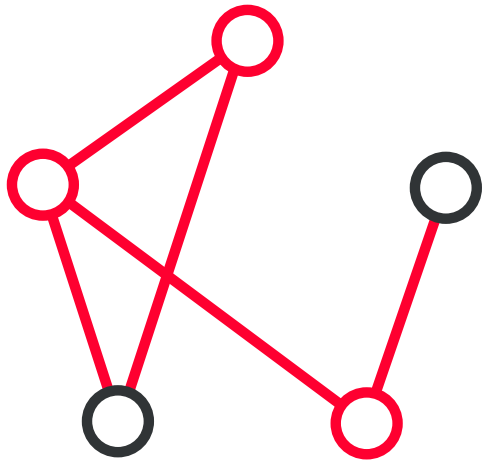
for each pair of vertices,
with probability p, add an edge

random graphs



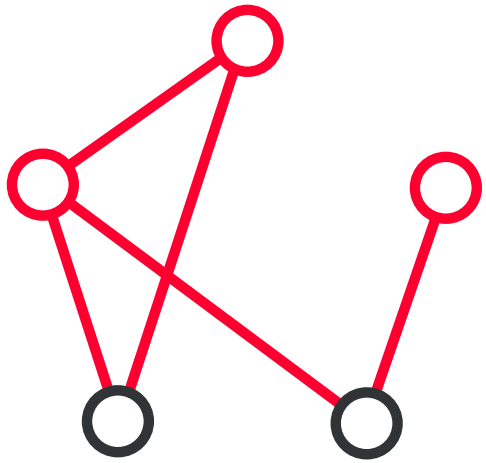
for each pair of vertices,
with probability p, add an edge

random graphs



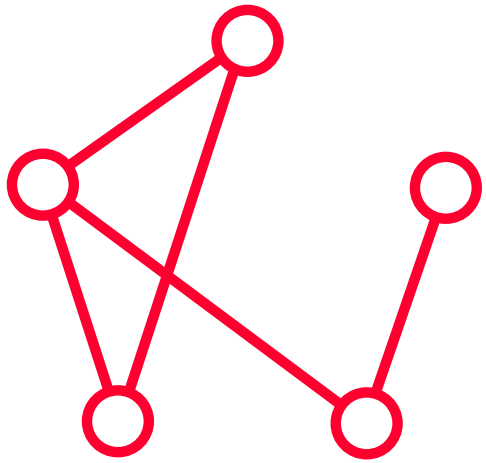
for each pair of vertices,
with probability p, add an edge

random graphs



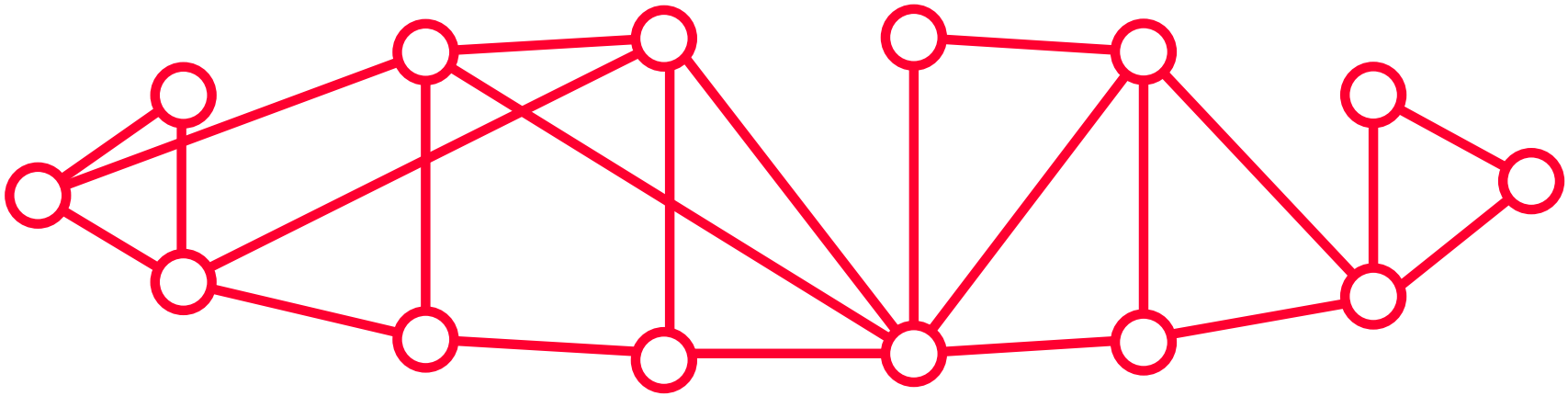
for each pair of vertices,
with probability p, add an edge

random graphs



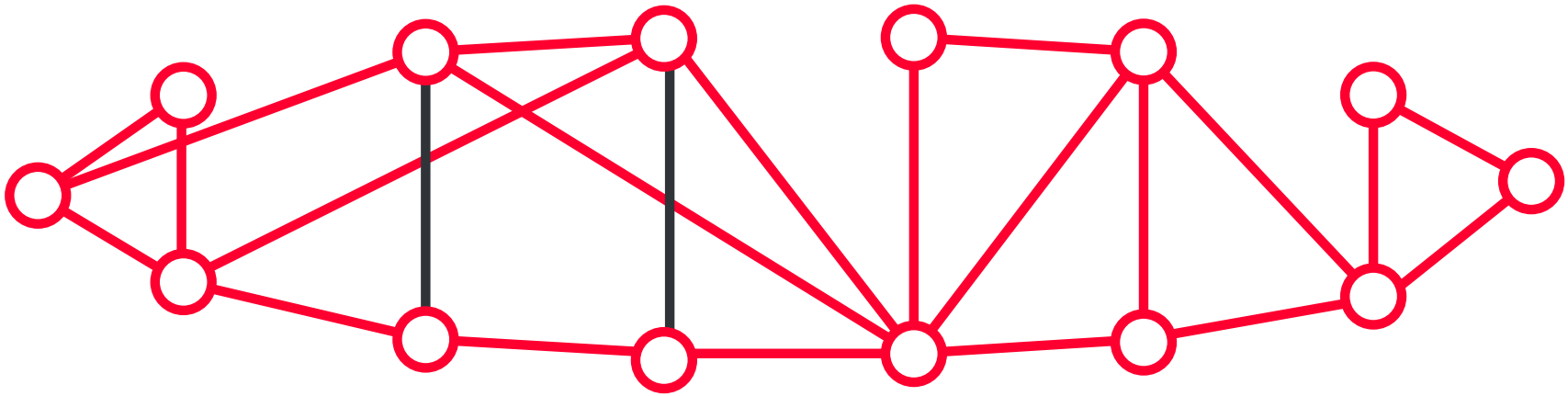
for each pair of vertices,
with probability p, add an edge

random rewiring



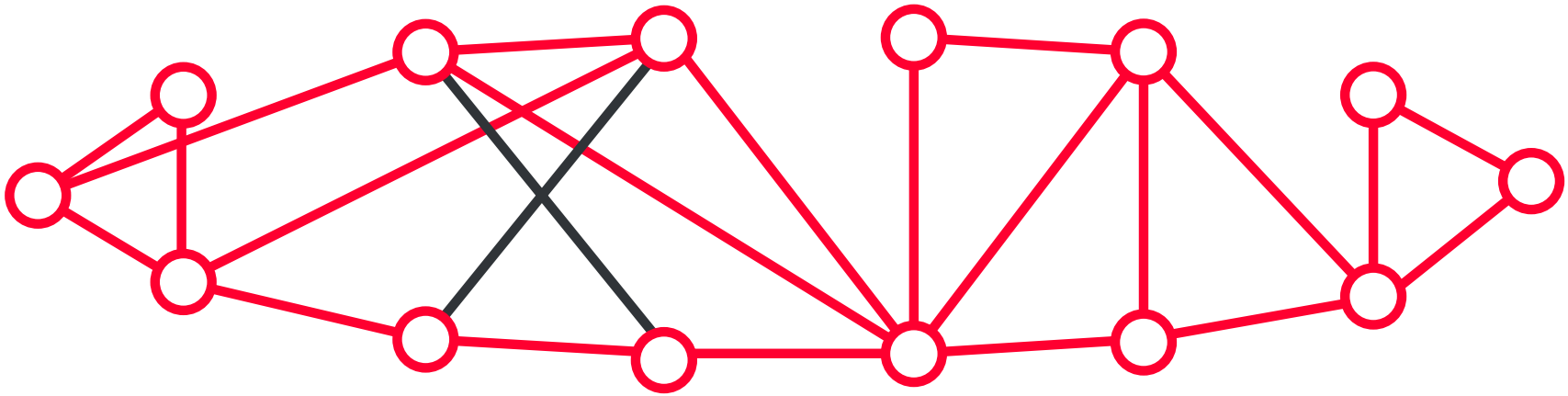
start from the original graph
choose edge pairs, and swap them

random rewiring



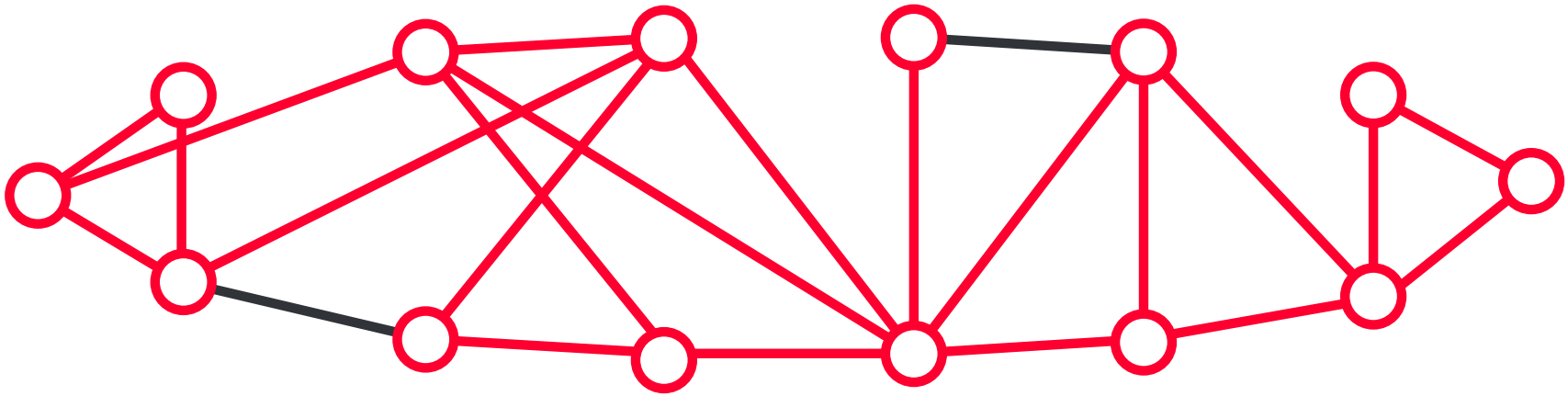
start from the original graph
choose edge pairs, and swap them

random rewiring



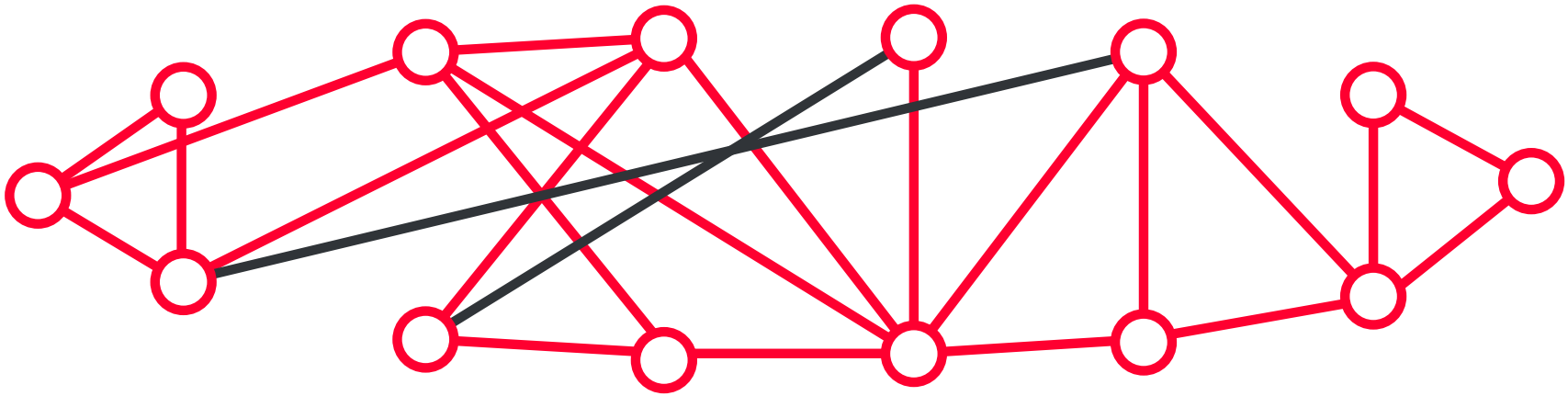
start from the original graph
choose edge pairs, and swap them

random rewiring



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

random rewiring



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

the dogmas of network science

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

ROYAL INSTITUTE
OF TECHNOLOGY

the dogmas of network science

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

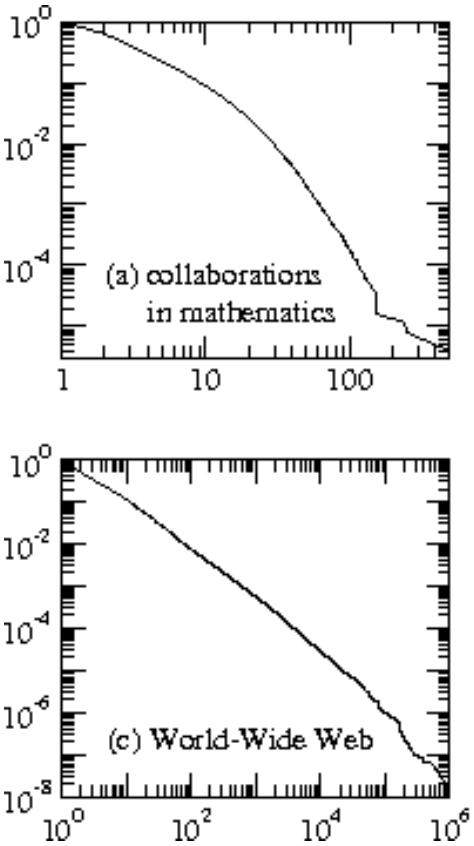
ROYAL INSTITUTE
OF TECHNOLOGY

the dogmas of network science

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

ROYAL INSTITUTE
OF TECHNOLOGY

degree distribution



network structure of metabolism

- Power-law degree distributions.
- Increasing average degree.
- Network modularity?

ROYAL INSTITUTE
OF TECHNOLOGY

network structure of metabolism

- Power-law degree distributions.
- Increasing average degree.
- Network modularity?

ROYAL INSTITUTE
OF TECHNOLOGY

network structure of metabolism

- Power-law degree distributions.
- Increasing average degree.
- Network modularity?

network structure of metabolism

- Power-law degree distributions.
- Increasing average degree.
- Network modularity?

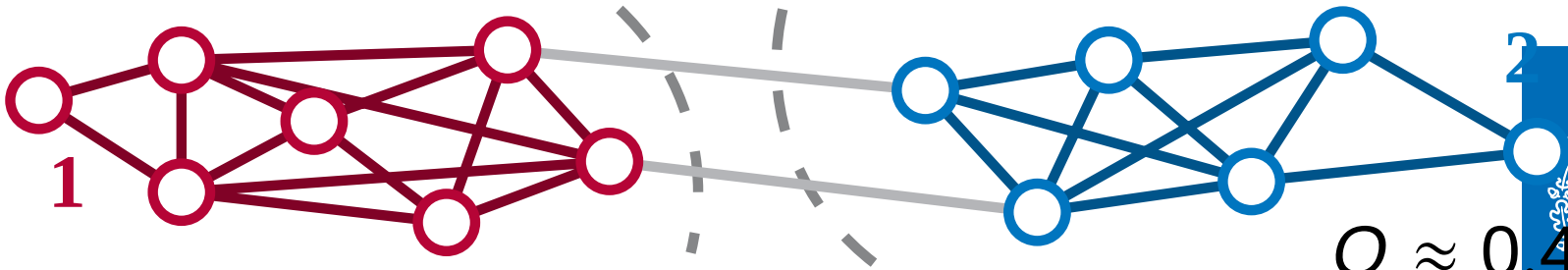
ROYAL INSTITUTE
OF TECHNOLOGY

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

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

(null model: random graphs)

Definition

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

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

modularity (of a graph)

Definition

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

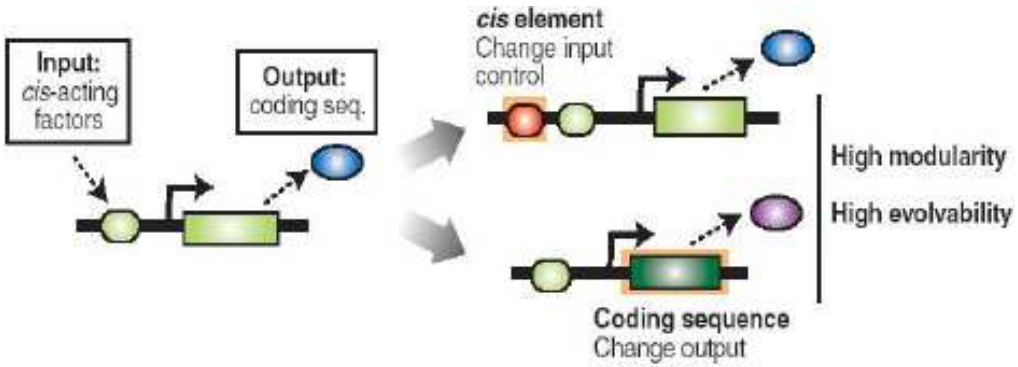
(null model: random graphs)

Definition

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

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

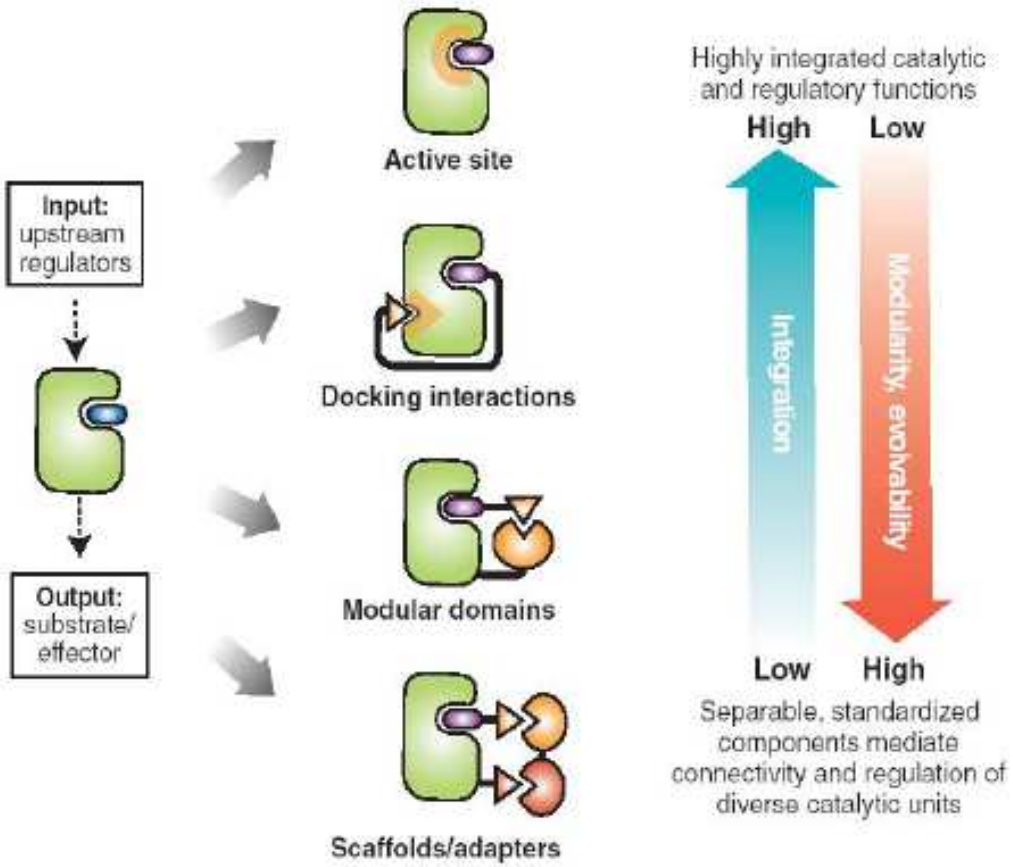
modularity (the biological idea)



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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity (the biological idea)



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

KTH VETENSKAP OCH KONST
ROYAL INSTITUTE OF TECHNOLOGY

modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

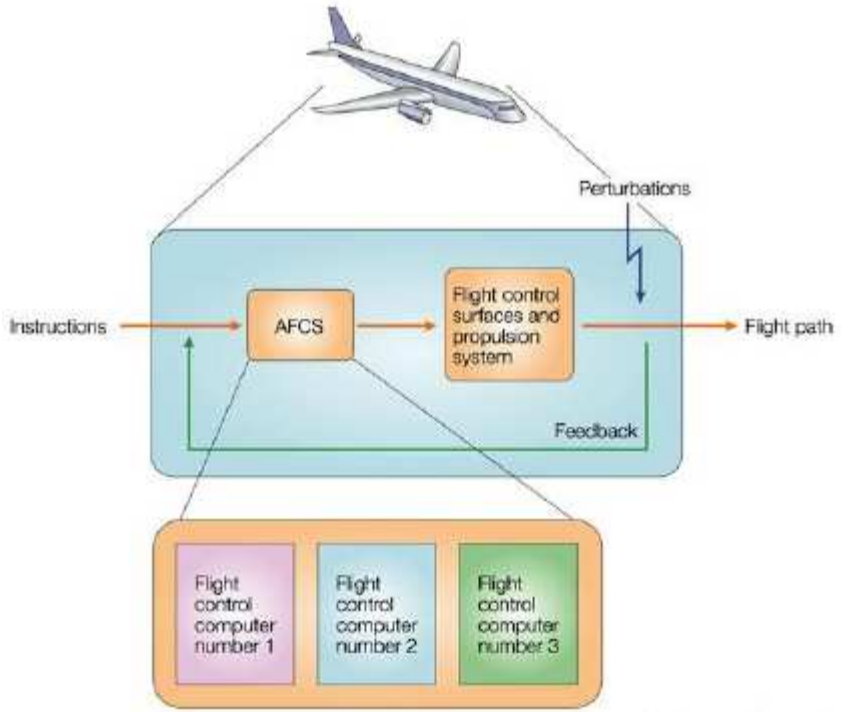
modularity and robustness

- robustness—sensitivity *of a relevant dynamic system on the network* to perturbations
- perturbations = changes in:
  - network topology
  - concentrations
  - delays in periodic input
- 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

ROYAL INSTITUTE
OF TECHNOLOGY

modularity and robustness

modular redundancy



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

ROYAL INSTITUTE OF TECHNOLOGY

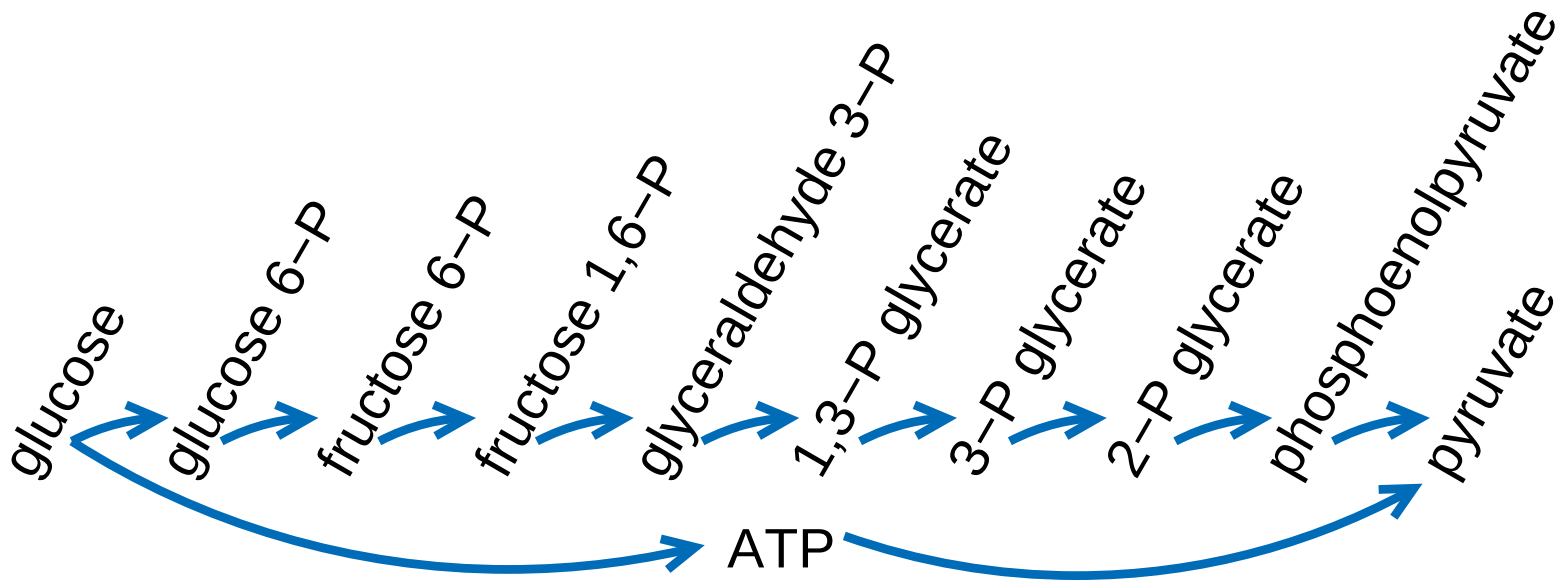
modularity and robustness

distributed redundancy (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.*

ROYAL INSTITUTE
OF TECHNOLOGY

currency metabolites



currency metabolites

Wagner & Fell, 2001	Schuster *et al.*, 2002	Ma & Zeng, 2003
ATP	ATP	ATP
ADP	ADP	ADP
NADP	NADP	NADP
NADPH	NADPH	
NAD		NAD
NADH		
	P_i	P_i
	H_2O	H_2O
	H^+	
	PP_i	
	CMP	
		CO_2
		O_2
		NH_3

ROYAL INSTITUTE
OF TECHNOLOGY

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 . . .

ROYAL INSTITUTE
OF TECHNOLOGY

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 . . .

ROYAL INSTITUTE
OF TECHNOLOGY

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 . . .

ROYAL INSTITUTE
OF TECHNOLOGY

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 . . .

ROYAL INSTITUTE
OF TECHNOLOGY

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 . . .

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

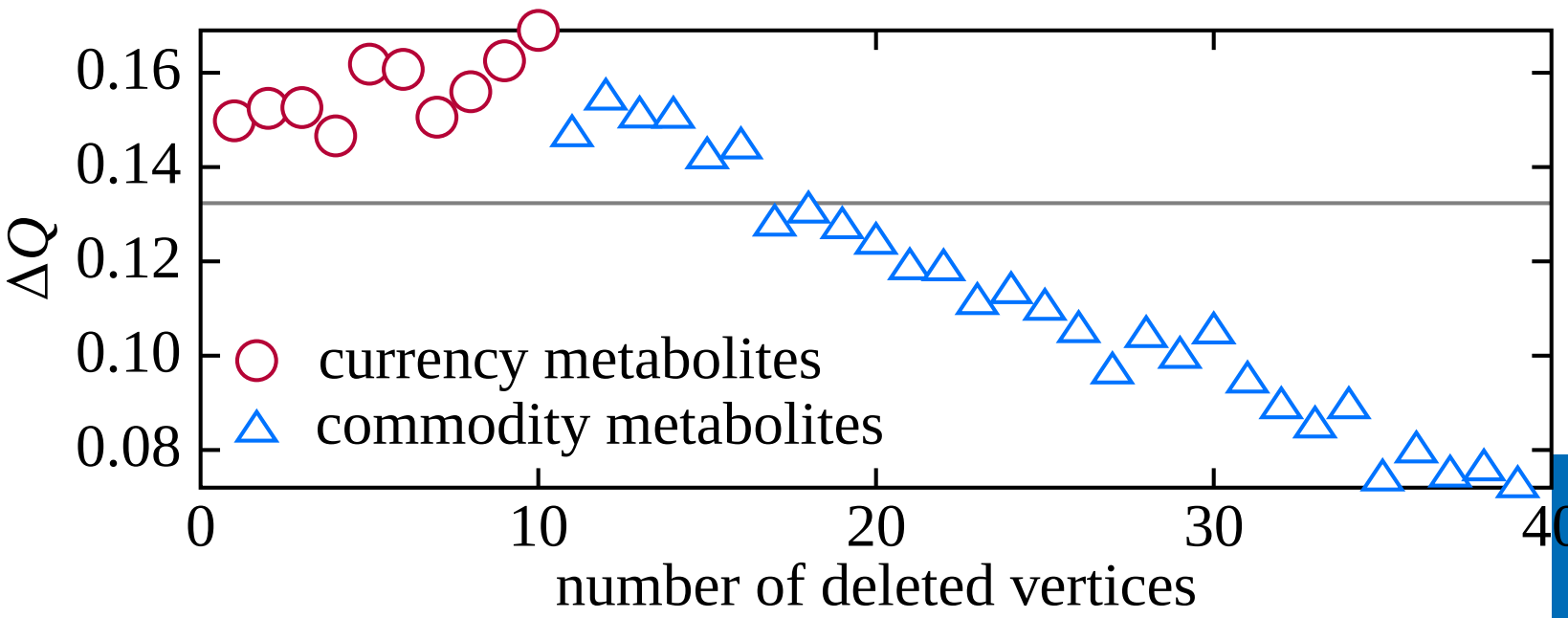
. . . let's turn this around to a definition . . .

currency metabolites (a definition)

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.

human currency metabolites

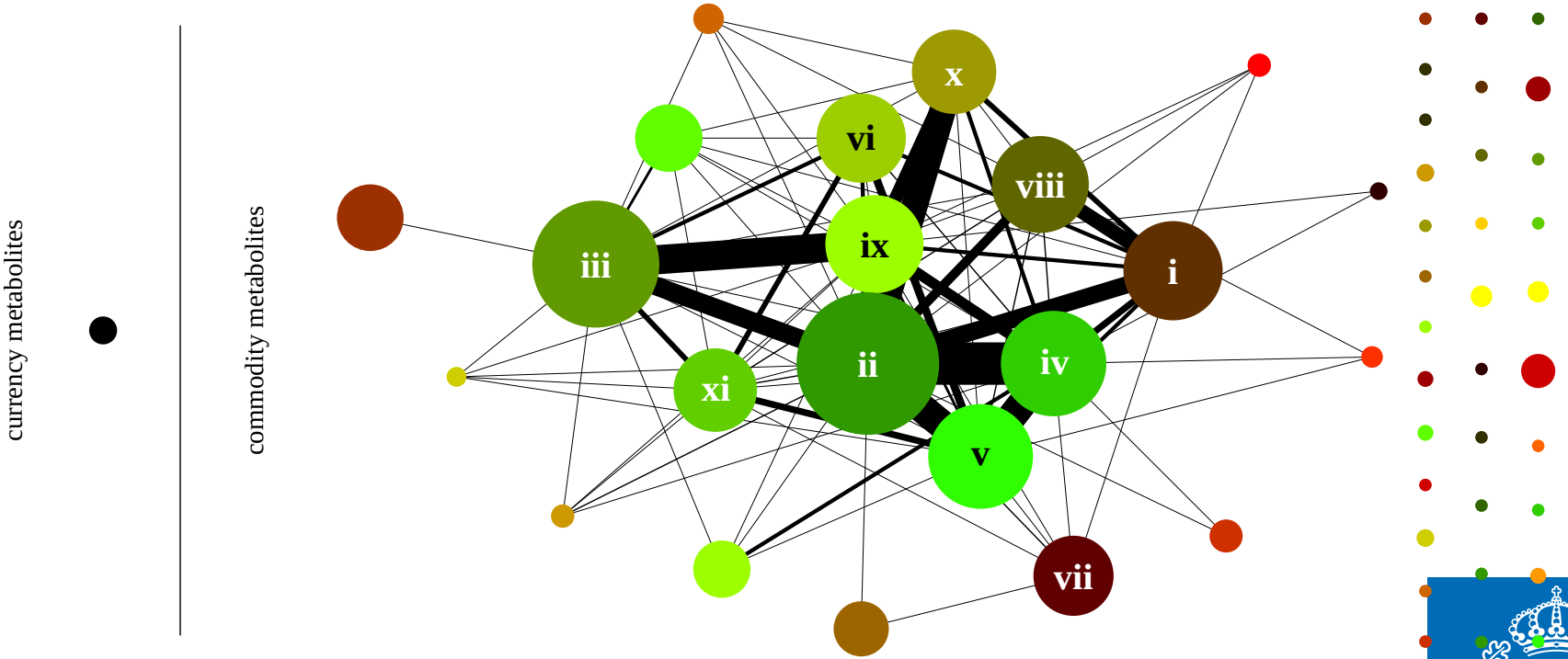


detected currency metabolites

Wagner & Fell, 2001	Schuster *et al.*, 2002	Ma & Zeng, 2003
ATP	**ATP**	**ATP**
ADP	**ADP**	**ADP**
NADP	**NADP**	**NADP**
NADPH	**NADPH**	
NAD		**NAD**
NADH		
	P_i	P_i
	H_2O	**H_2O**
	H^+	
	PP_i	
	CMP	
		CO_2
		O_2
		NH_3

ROYAL INSTITUTE
OF TECHNOLOGY

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

ROYAL INSTITUTE
OF TECHNOLOGY

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.)

ROYAL INSTITUTE
OF TECHNOLOGY

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.)

ROYAL INSTITUTE
OF TECHNOLOGY

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.)

ROYAL INSTITUTE
OF TECHNOLOGY

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.)

ROYAL INSTITUTE
OF TECHNOLOGY

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

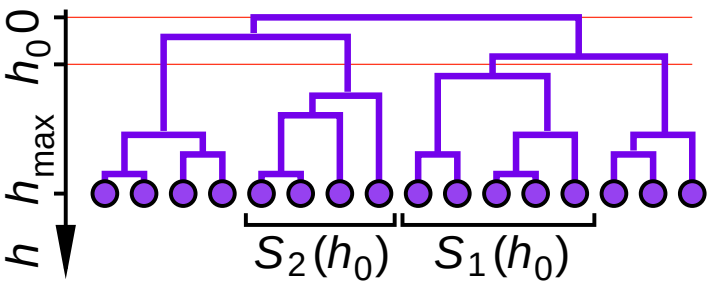
(Huss & Holme, 2007, IET Syst. Biol. **1**, pp. 280–5.)

ROYAL INSTITUTE
OF TECHNOLOGY

subnetwork hierarchies

P. Holme, M. Huss & H. Jeong, 2003, Bioinformatics **19**, pp. 532–8.

- Start with a directed bipartite networks, with both reaction and substance vertices (keep the currency metabolites).
- Iteratively remove the reaction vertices with the highest *betweenness* (fraction of shortest paths passing through a vertex).
- Study the dendrogram of this process.

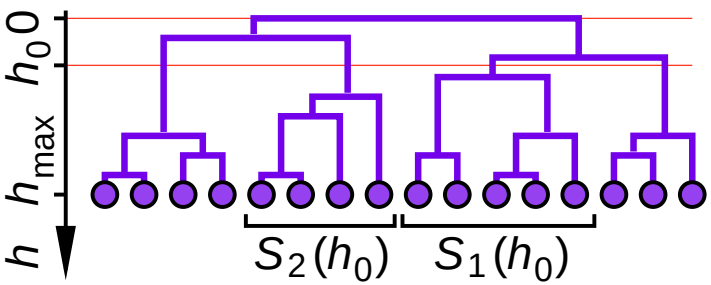


ROYAL INSTITUTE OF TECHNOLOGY

subnetwork hierarchies

P. Holme, M. Huss & H. Jeong, 2003, Bioinformatics **19**, pp. 532–8.

- Start with a directed bipartite networks, with both reaction and substance vertices (keep the currency metabolites).
- Iteratively remove the reaction vertices with the highest *betweenness* (fraction of shortest paths passing through a vertex).
- Study the dendrogram of this process.

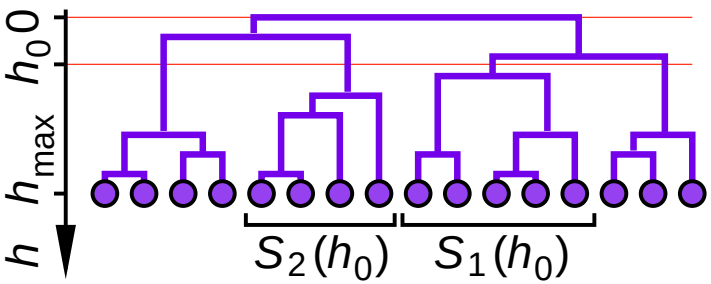


ROYAL INSTITUTE OF TECHNOLOGY

subnetwork hierarchies

P. Holme, M. Huss & H. Jeong, 2003, Bioinformatics **19**, pp. 532–8.

- Start with a directed bipartite networks, with both reaction and substance vertices (keep the currency metabolites).
- Iteratively remove the reaction vertices with the highest *betweenness* (fraction of shortest paths passing through a vertex).
- Study the dendrogram of this process.

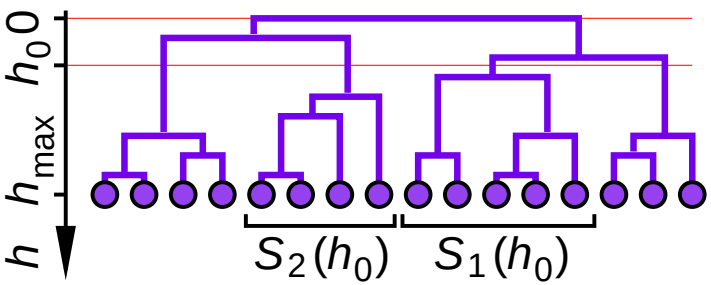


ROYAL INSTITUTE OF TECHNOLOGY

subnetwork hierarchies

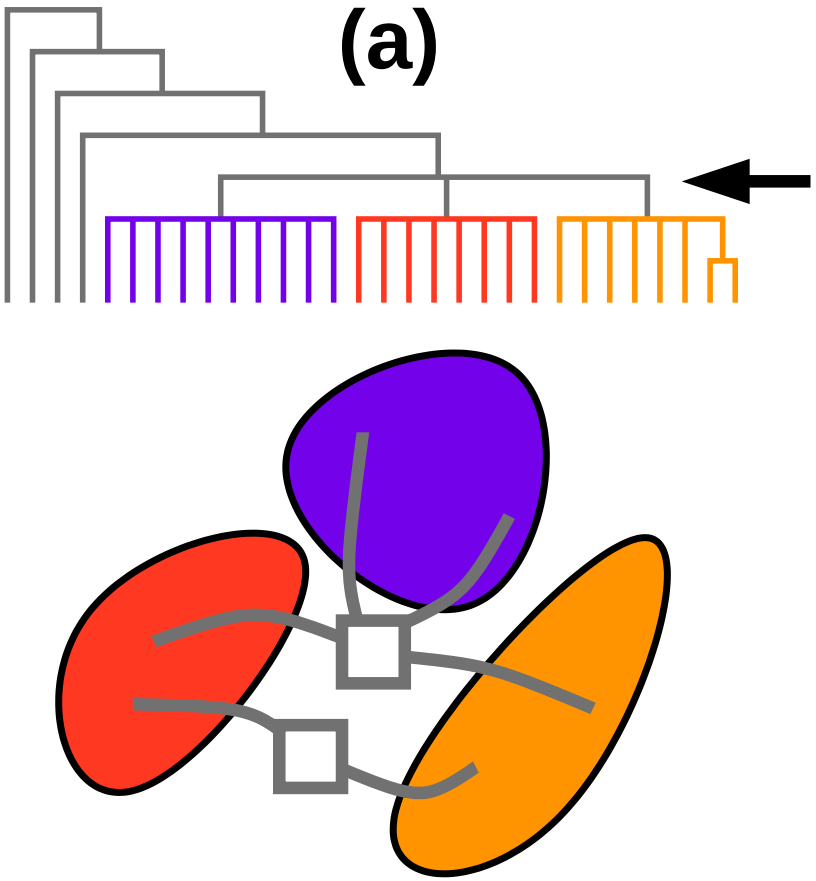
P. Holme, M. Huss & H. Jeong, 2003, Bioinformatics **19**, pp. 532–8.

- Start with a directed bipartite networks, with both reaction and substance vertices (keep the currency metabolites).
- Iteratively remove the reaction vertices with the highest *betweenness* (fraction of shortest paths passing through a vertex).
- Study the dendrogram of this process.



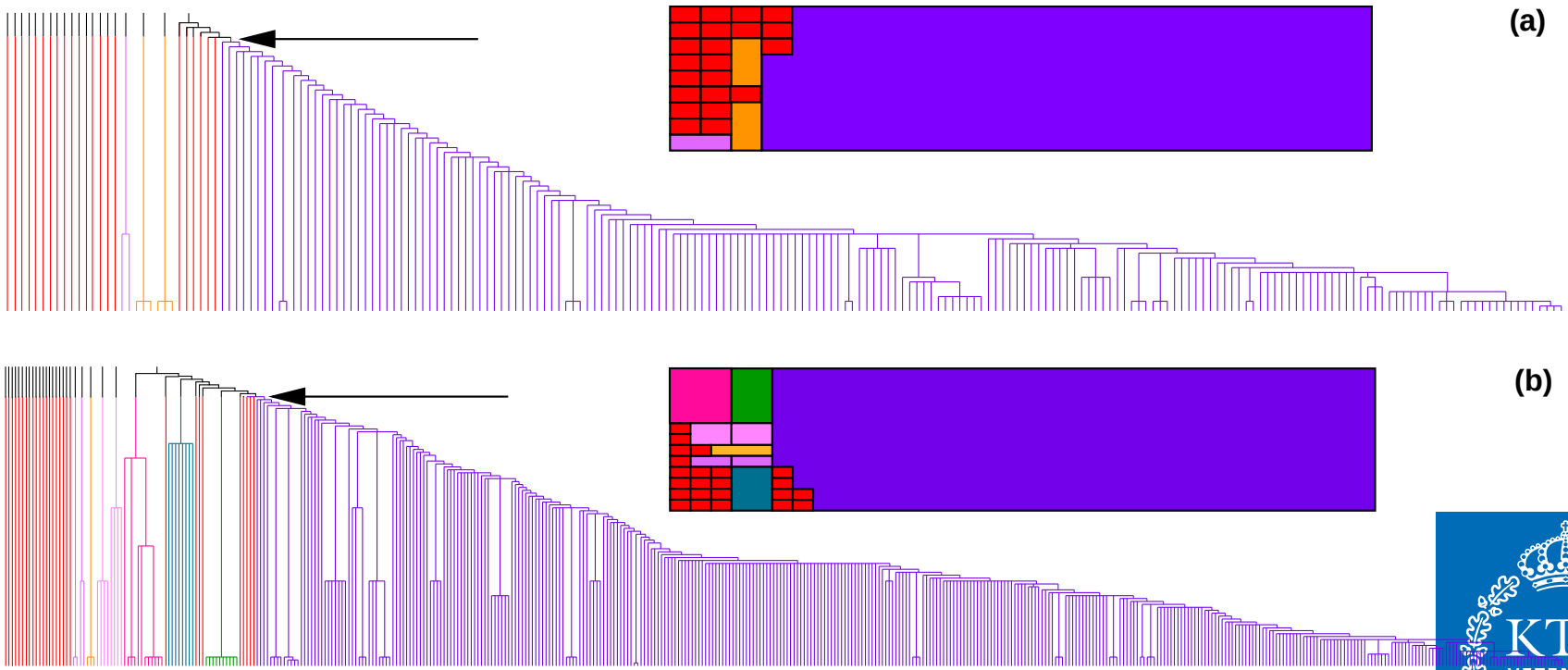
ROYAL INSTITUTE OF TECHNOLOGY

shell- vs community-type ordering

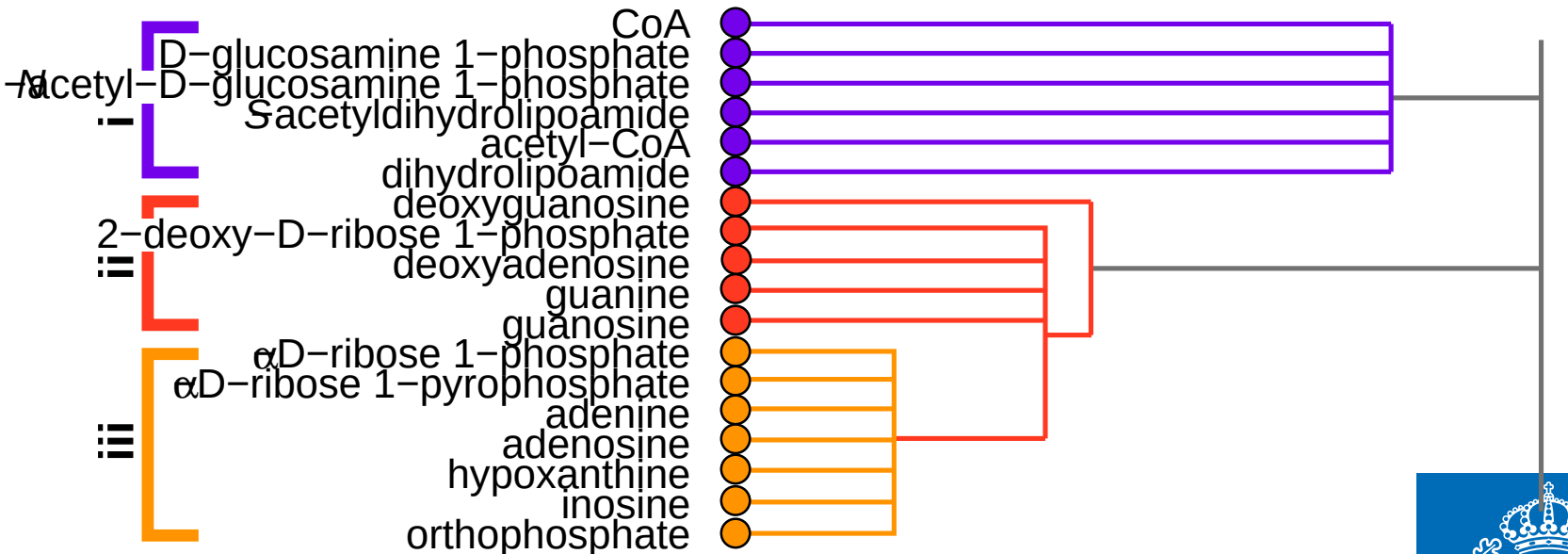


ROYAL INSTITUTE
OF TECHNOLOGY

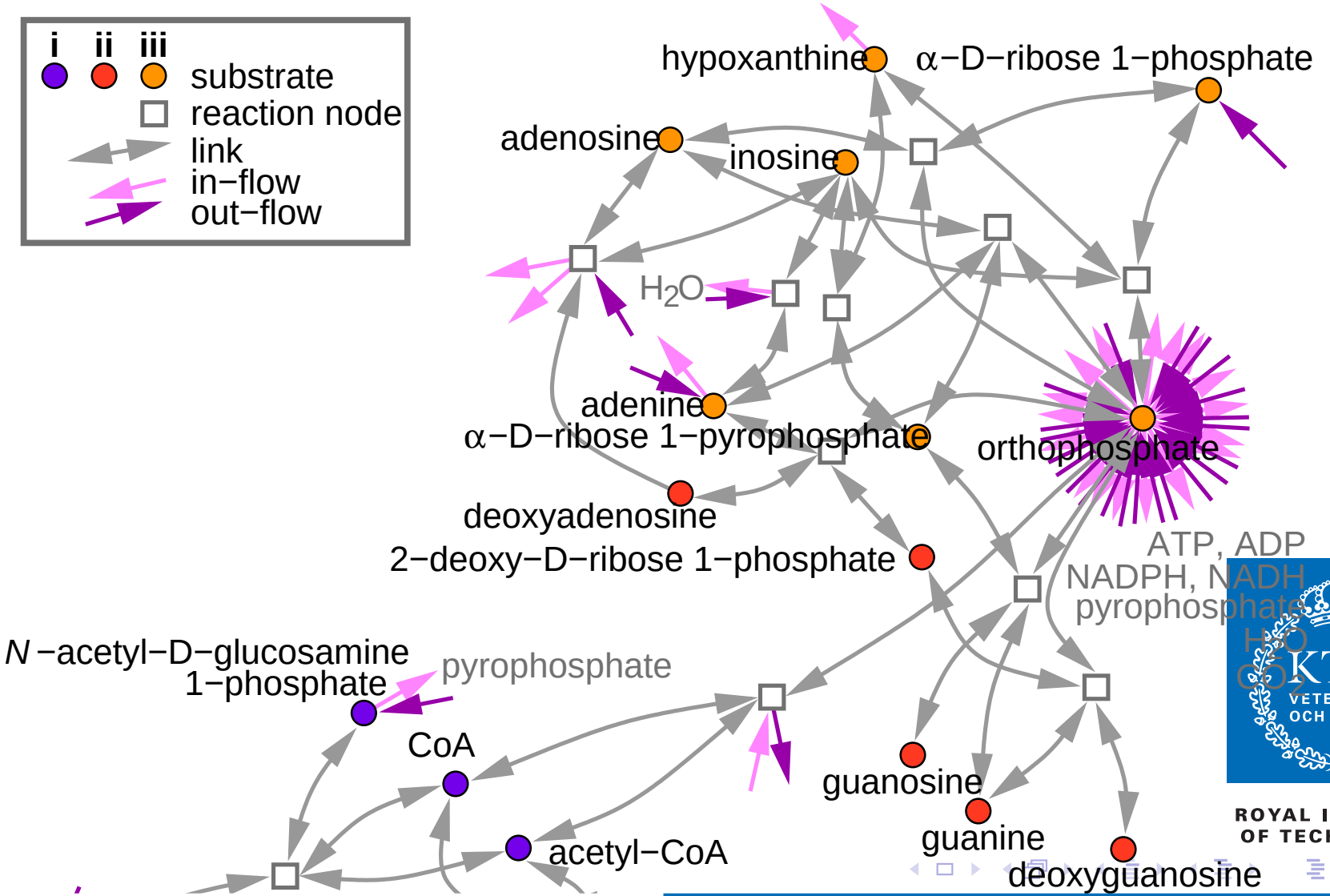
dendrogram



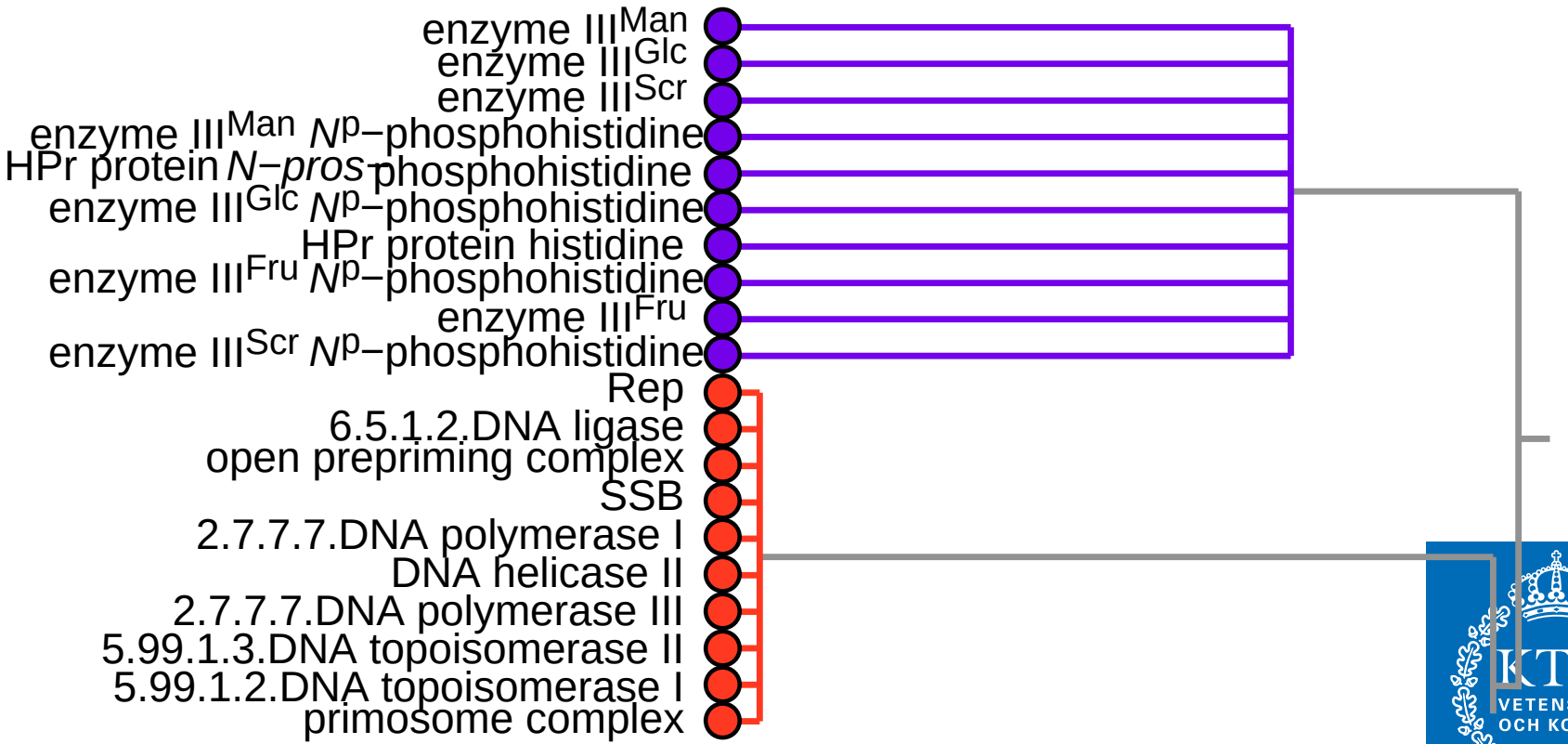
modules


CoA
D−glucosamine 1−phosphate
N−acetyl−D−glucosamine 1−phosphate
S−acetyldihydrolipoamide
acetyl−CoA
dihydrolipoamide
deoxyguanosine
2−deoxy−D−ribose 1−phosphate
deoxyadenosine
guanine
guanosine
αD−ribose 1−phosphate
αD−ribose 1−pyrophosphate
adenine
adenosine
hypoxanthine
inosine
orthophosphate

modules

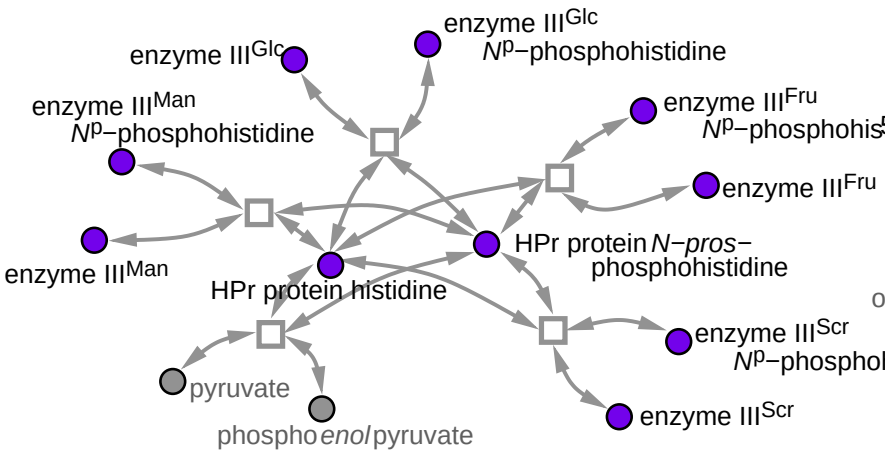

i ii iii
substrate
reaction node
link
in−flow
out−flow
hypoxanthine
α−D−ribose 1−phosphate
adenosine
inosine
H2O
adenine
α−D−ribose 1−pyrophosphate
orthophosphate
deoxyadenosine
2−deoxy−D−ribose 1−phosphate
ATP, ADP
NADPH, NADH
pyrophosphate
H2O
CO2
N−acetyl−D−glucosamine
1−phosphate
pyrophosphate
CoA
acetyl−CoA
guanosine
guanine
deoxyguanosine

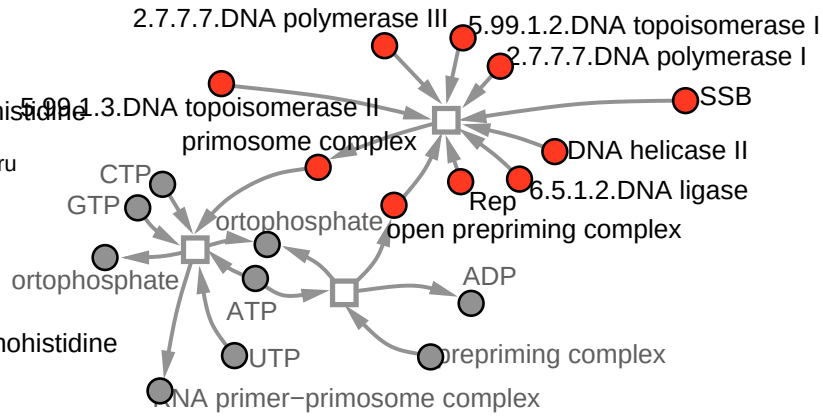
modules



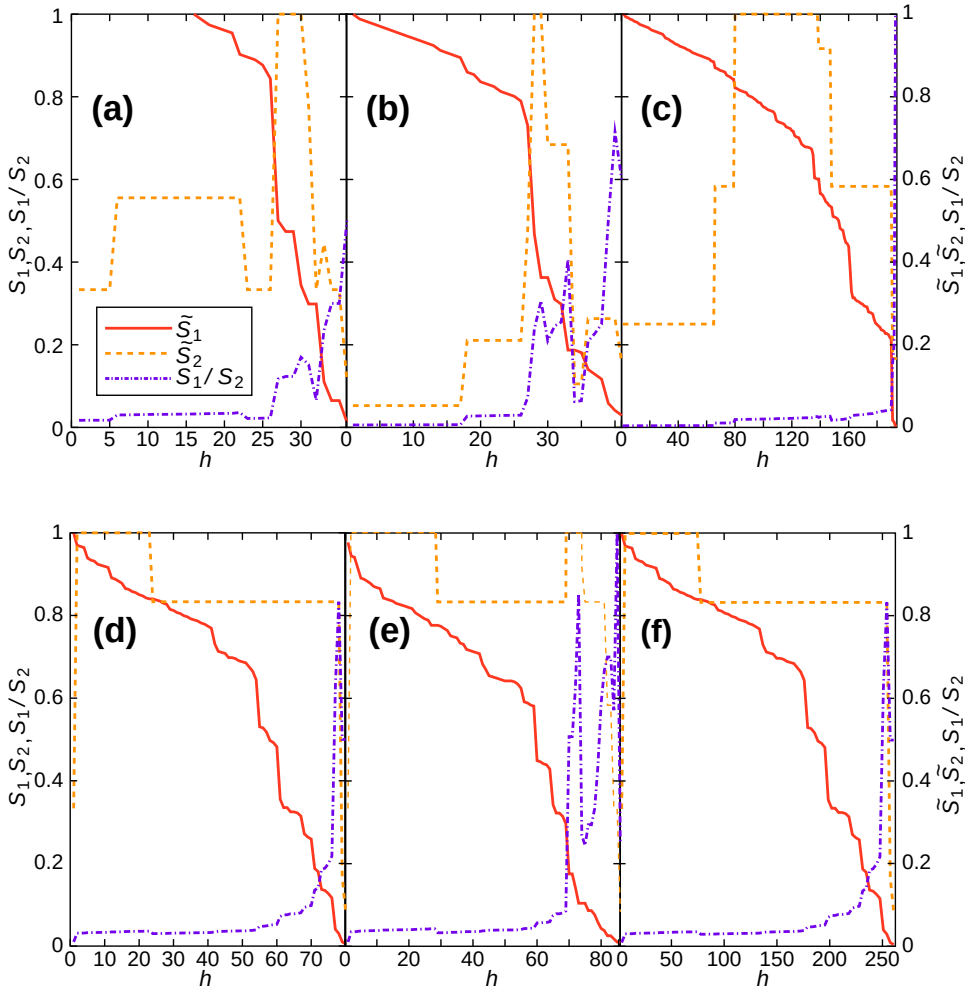
ROYAL INSTITUTE
OF TECHNOLOGY

modules


enzyme III^Glc
enzyme III^Glc N^p−phosphohistidine
enzyme III^Man N^p−phosphohistidine
enzyme III^Fru N^p−phosphohistidine
enzyme III^Fru
enzyme III^Man
HPr protein N−pros− phosphohistidine
HPr protein histidine
enzyme III^Scr N^p−phosphohistidine
pyruvate
enzyme III^Scr
phospho enol pyruvate


2.7.7.7.DNA polymerase III
5.99.1.2.DNA topoisomerase I
2.7.7.7.DNA polymerase I
5.99.1.3.DNA topoisomerase II
SSB
primosome complex
DNA helicase II
CTP
GTP
Rep
6.5.1.2.DNA ligase
ortophosphate
open prepriming complex
ortophosphate
ADP
ATP
UTP
prepriming complex
DNA primer−primosome complex

dentrogram statistics



conclusions

- Shell- rather than community-type ordering
- A few, seemingly clear, modules

ROYAL INSTITUTE
OF TECHNOLOGY

conclusions

- Shell- rather than community-type ordering
- A few, seemingly clear, modules

ROYAL INSTITUTE
OF TECHNOLOGY

conclusions

- Shell- rather than community-type ordering
- A few, seemingly clear, modules

ROYAL INSTITUTE
OF TECHNOLOGY