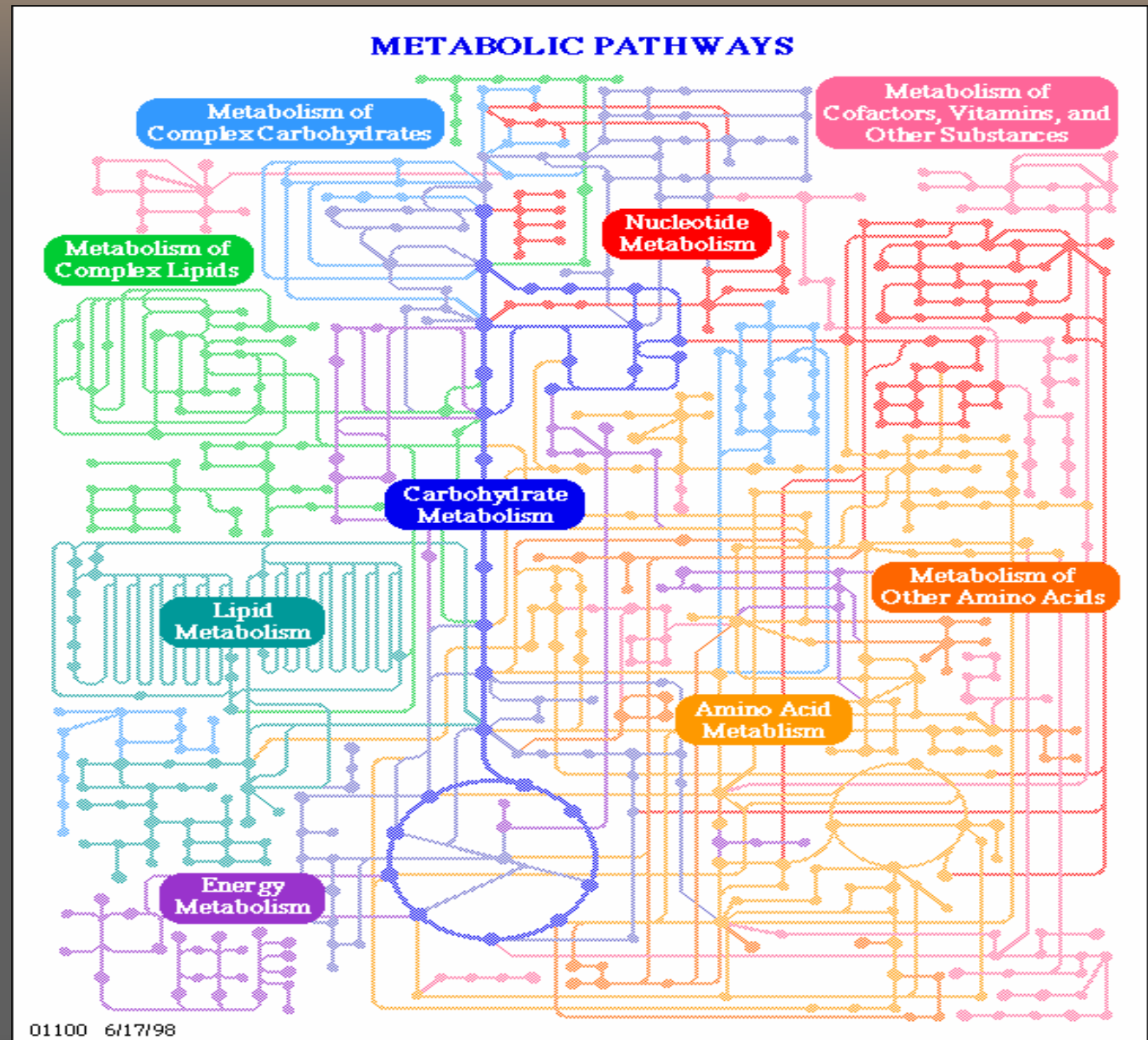
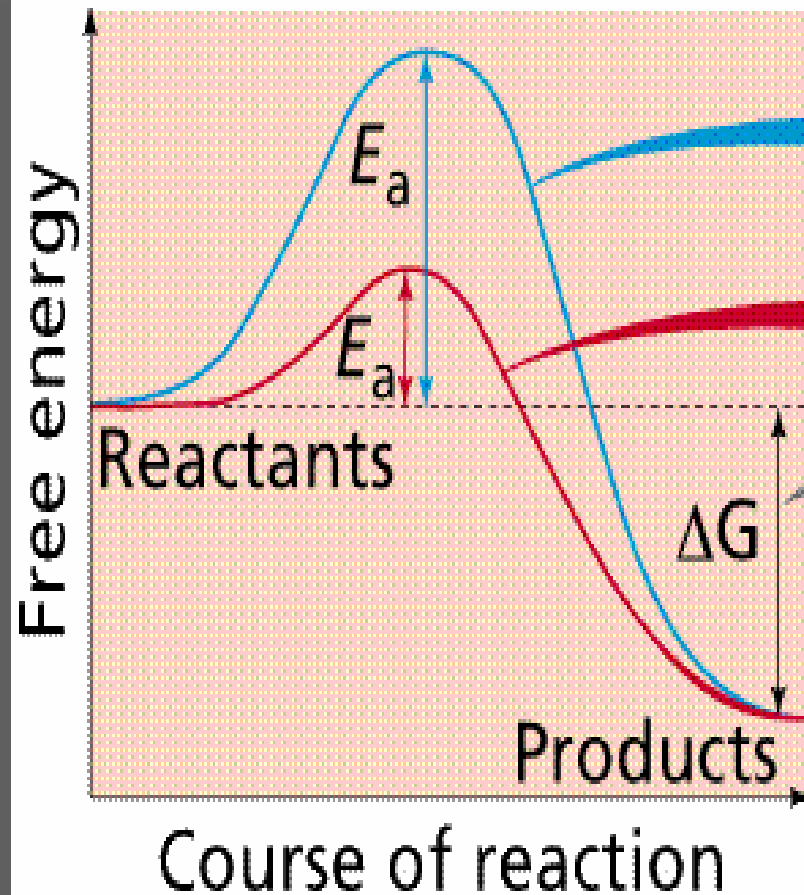


# Metabolic Networks

- ⇒ Molecular circuitry of a cell
- ⇒ Catabolism
- ⇒ Anabolism
- ⇒ Directed graph



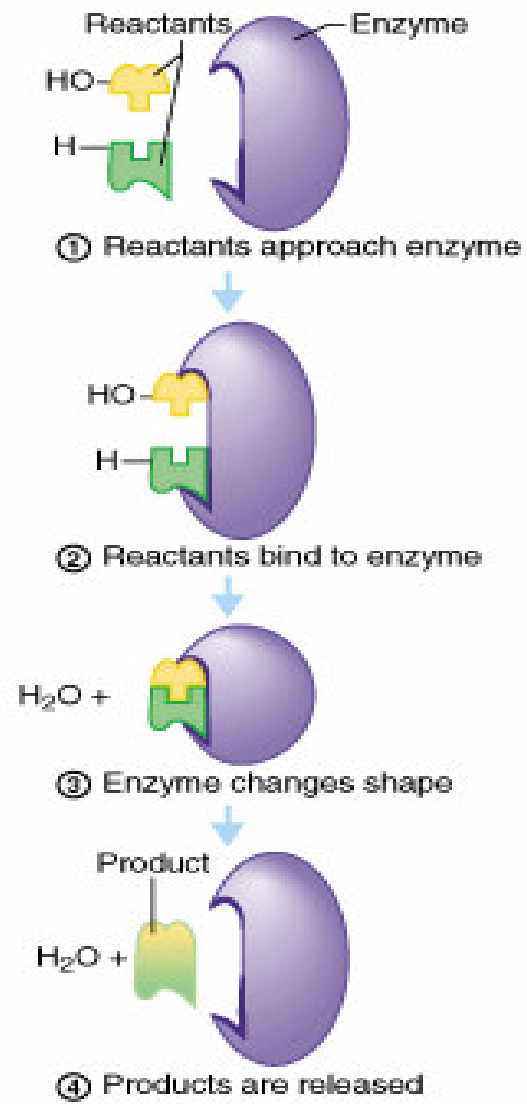
# Enzyme Function



An **uncatalyzed reaction** requires a higher activation energy than does a **catalyzed reaction**

There is no difference in free energy between catalyzed and uncatalyzed reactions

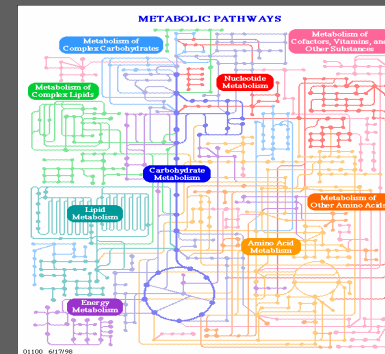
# Enzymes



# Cell as a “Computer”

Regulatory genes

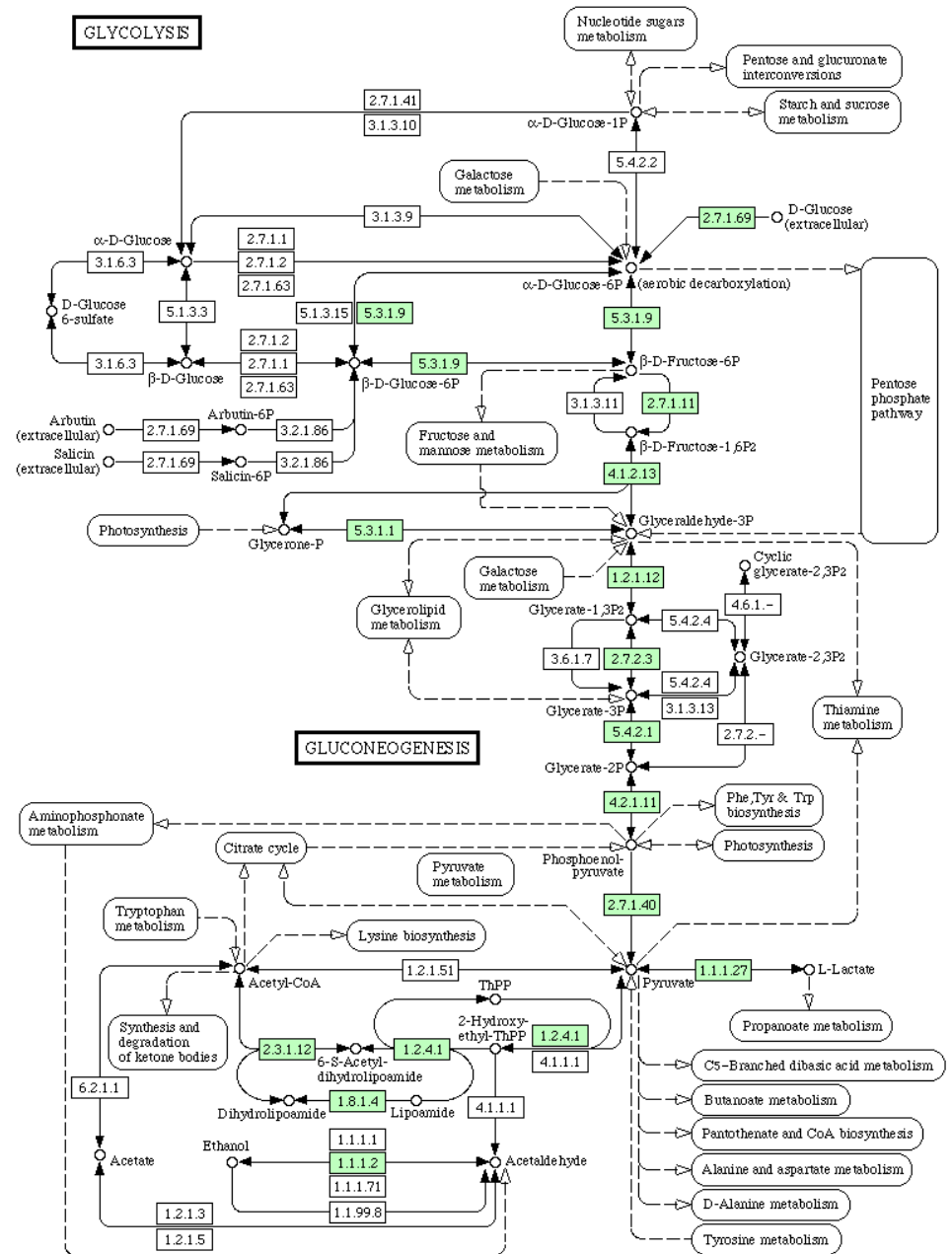
*“Operating System”*



*“System resources”*

# KEGG database

Directed graph



# Enzyme Nomenclature (EC)

EC 1.x.x.x Oxireductases: transfer of hydrogen or electrons

EC 2.x.x.x Transferases: transference of atoms

EC 3.x.x.x Hydrolases: addition or removal of water

EC 4.x.x.x Lyases: cleavage or addition of double bonds

EC 5.x.x.x Isomerases: rearrangement of atoms

EC 6.x.x.x Ligases: formation of covalent bonds

Example: 2.1.1.1

2. Transferases

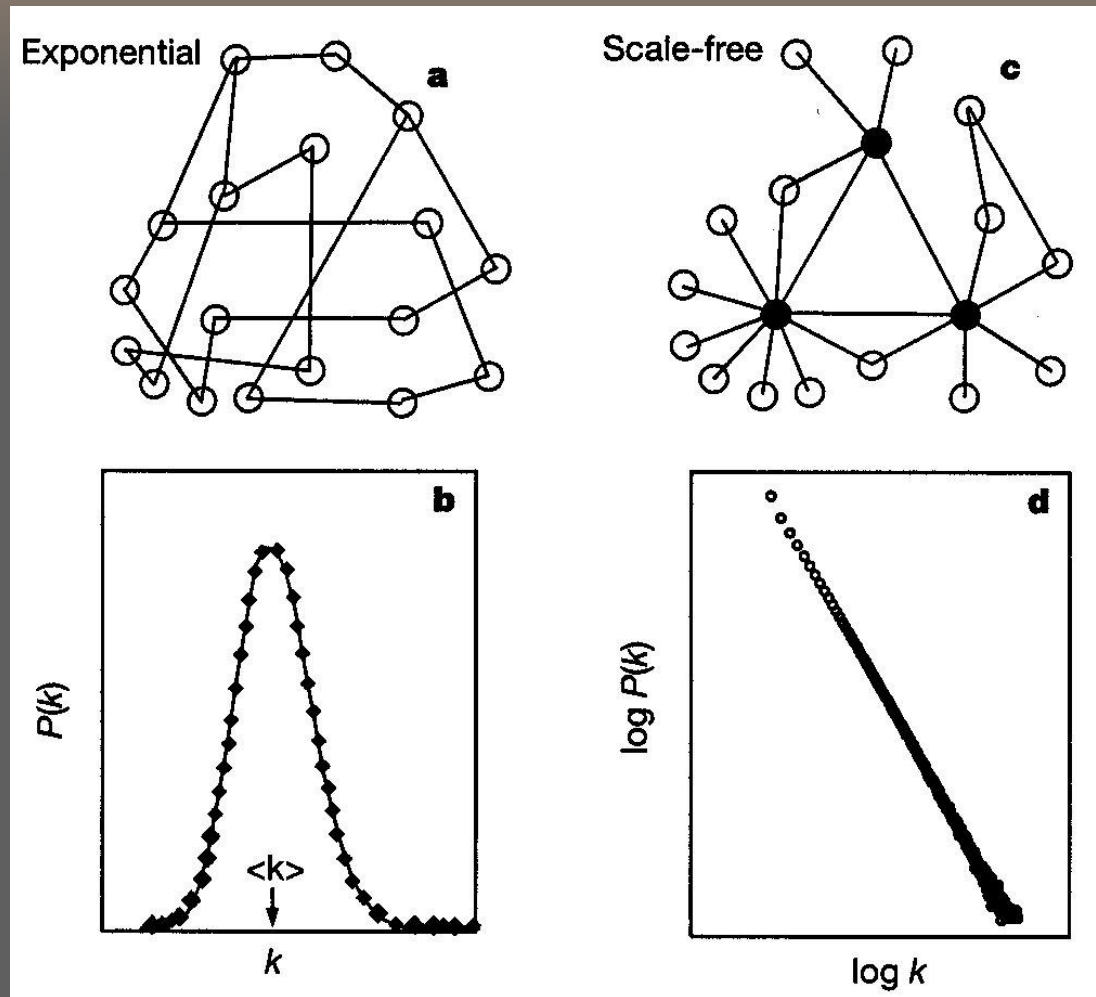
2.1. Transferring One-Carbon Groups

2.1.1. Methyltransferases

2.1.1.1 nicotinamide N-methyltransferase

# Metabolic Graphs

- ⇒ Modeling metabolism is complex
- ⇒ Graphs capture causality
- ⇒ Structure of complex systems
- ⇒ Water, ATP, ADP



$$P(k) \sim e^{-k}$$

(Poisson)

$$P(k) \sim k^{-\gamma}$$

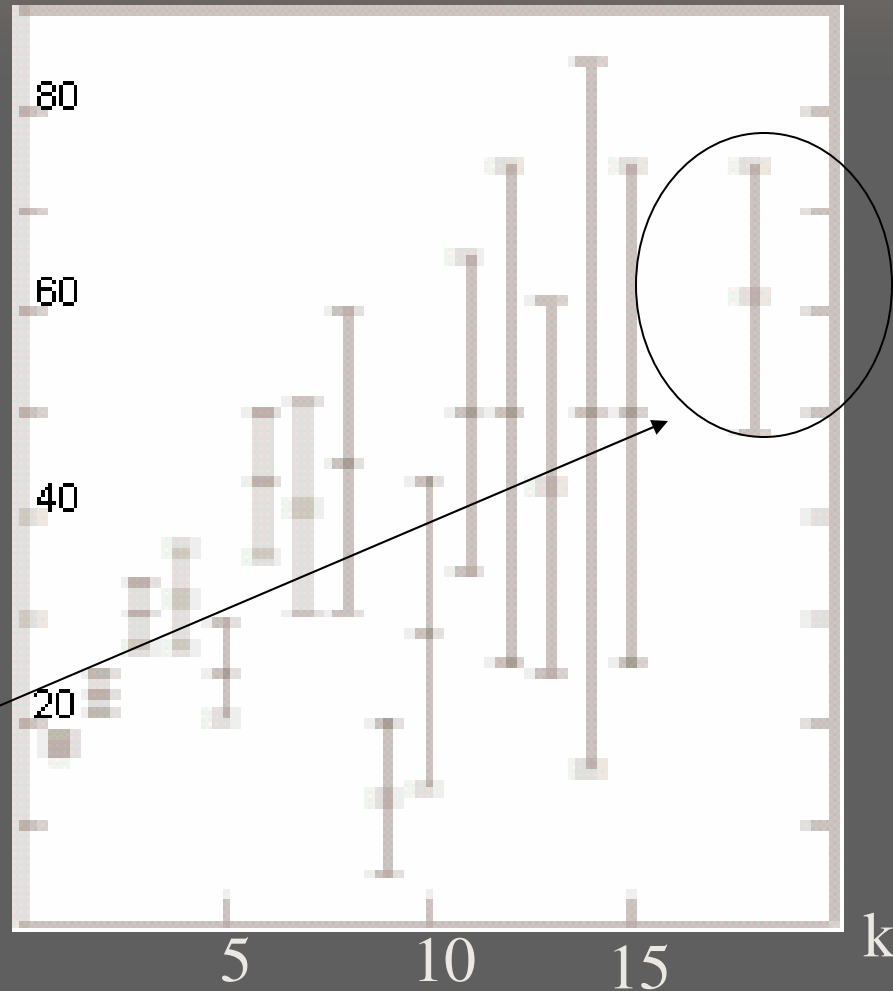
# Protein Networks

Percentage of essential proteins of *S. cerevisiae*

1870 proteins  
2240 interactions

$k < 6$  (93%)  
21% essential

$k > 15$  (0.7%)  
62% non-essential



# Relevance of Network Topology ?

- ⇒ Network anatomy is related to function!  
(Strogatz)

# Importance and topology ?

importance



topology

metabolites



connectivity

phys. interac.

proteins



||

enzymes



?

damage

# *Escherichia coli*

Can we determine the important enzymes from the graph?  
Importance = lethality

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## ***Essentiality and damage in metabolic networks***

*Ney Lemke, Fabiana Herédia, Cláudia K. Barcellos,  
Adriana N. dos Reis and José C. M. Mombach*

*Laboratório de Bioinformática e Biologia Computacional, Centro de Ciências  
Exatas e Tecnológicas, Universidade do Vale do Rio dos Sinos,  
93022-000 São Leopoldo, RS, Brazil*

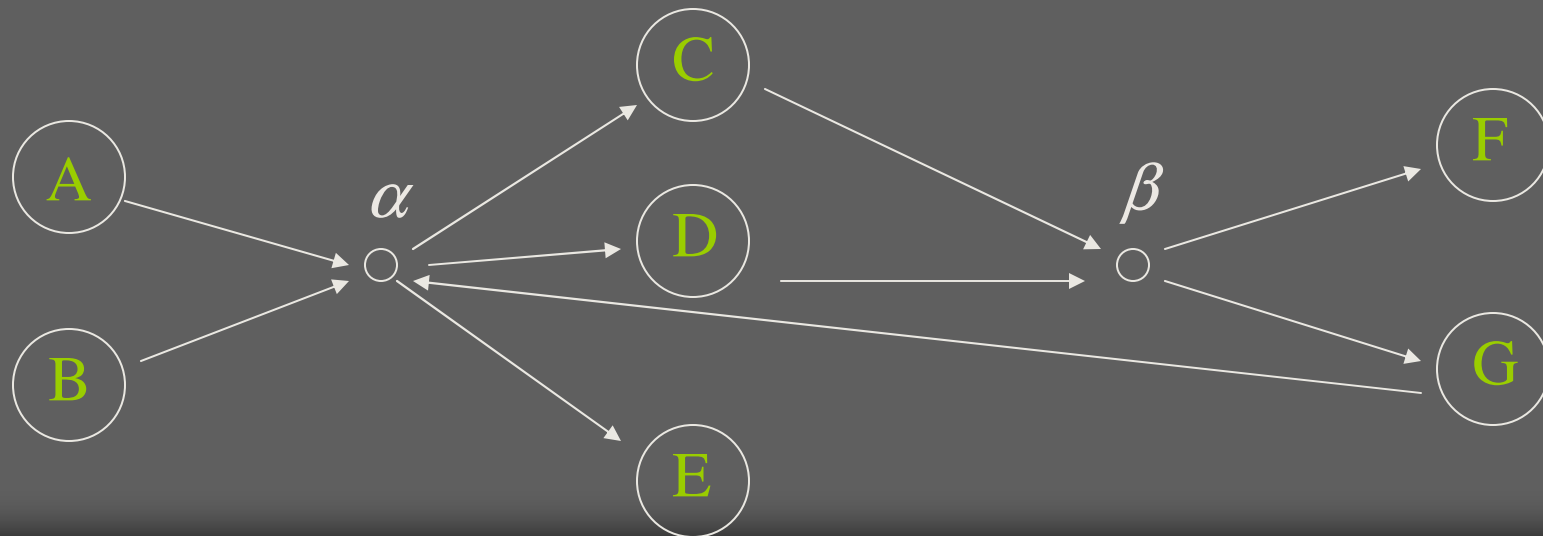
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### **ABSTRACT**

Understanding the architecture of physiological functions from annotated genome sequences is a major task for postgenomic biology. From the annotated genome sequence of the microbe

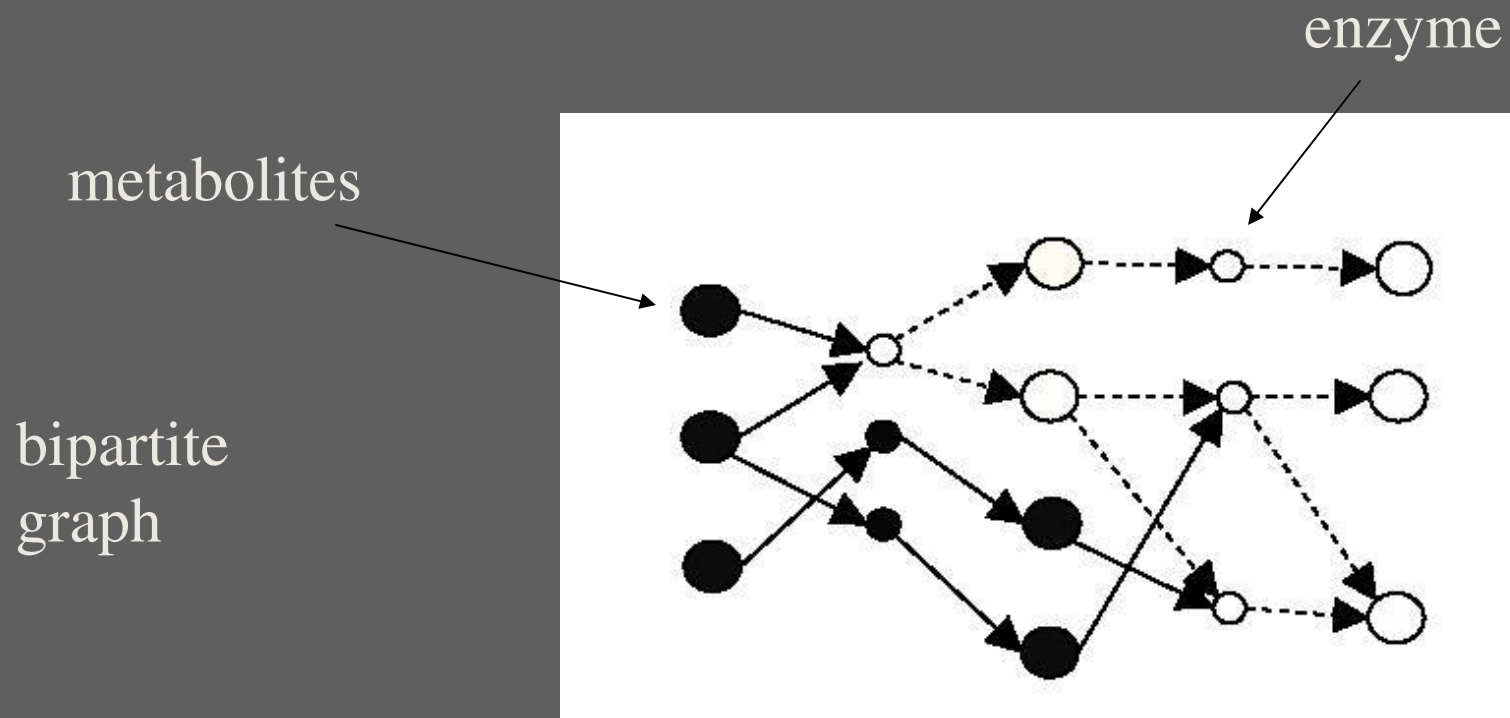
forms the metabolic network. Developing realistic models for metabolic networks is still beyond our capabilities, since the experimental determination of the set of kinetic parameters that characterize each of the hundreds of reactions in a cell

# Bipartite Graph Representation



# Damage ( $d$ )

⇒ Number of metabolites (nodes) removed from the network



We consider only reactions involved in the small molecule metabolism.



Small molecule metabolism is a subset of the complete metabolism that excludes DNA replication and protein synthesis reactions (large molecules).

## Building the metabolic network:

\* collect all annotated EC numbers for the organism and corresponding reactions in the corresponding metabolic map using the KEGG database



Inconsistencies in data are common  
since annotation is error prone

Analysis of metabolic network

## Examples of inconsistencies:

- \* a reaction may require a metabolite that is not produced by any other reaction or is not available from an external source, then the reaction is excluded:

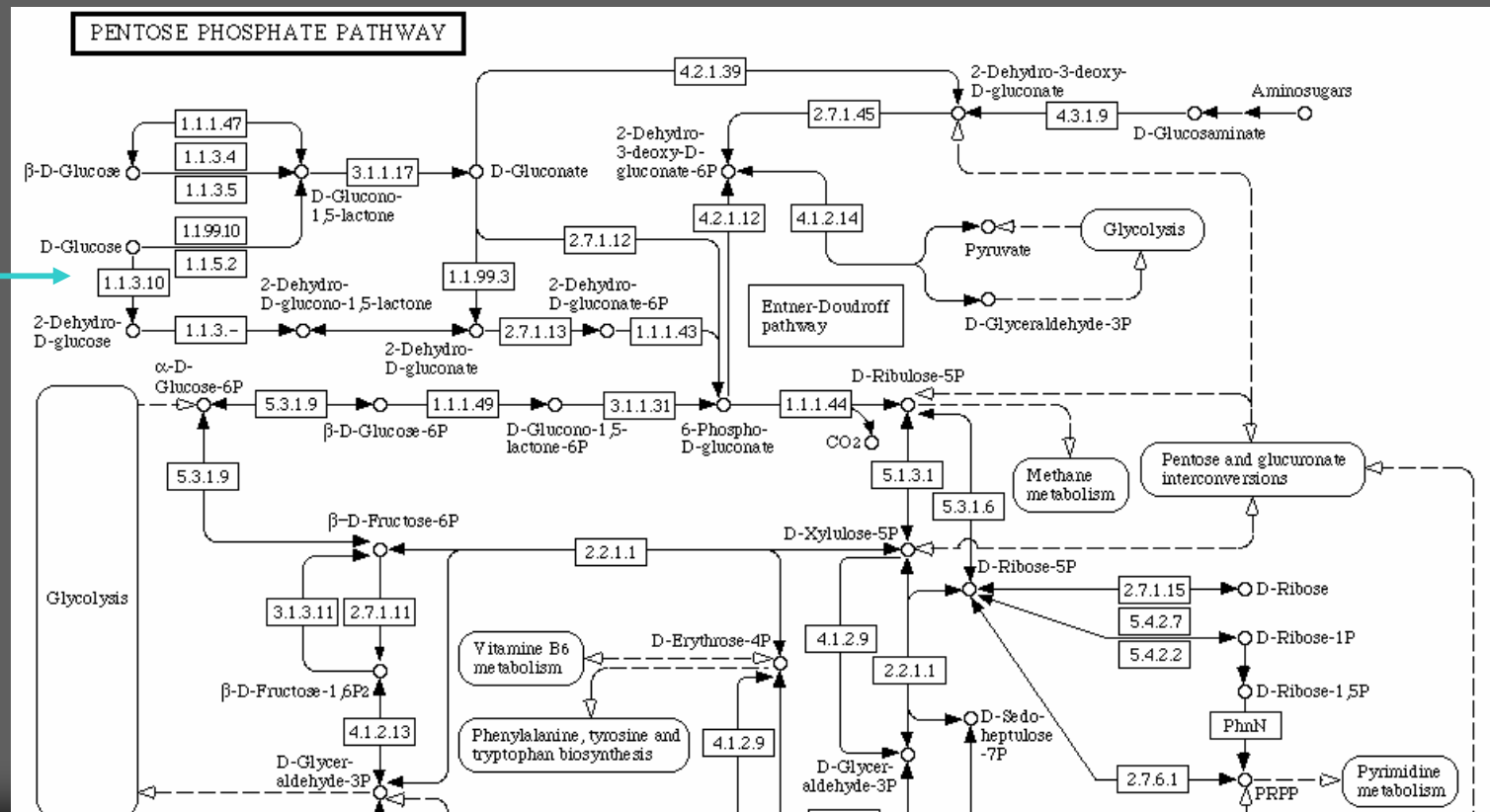
- \* some reactions require metabolites that are not produced inside the cell, however if what is produced is used in other reactions, we determine all external metabolites required and use them as inputs for the simulation

\* in the Kegg database the same reaction is showed with different directions (reversible or irreversible):

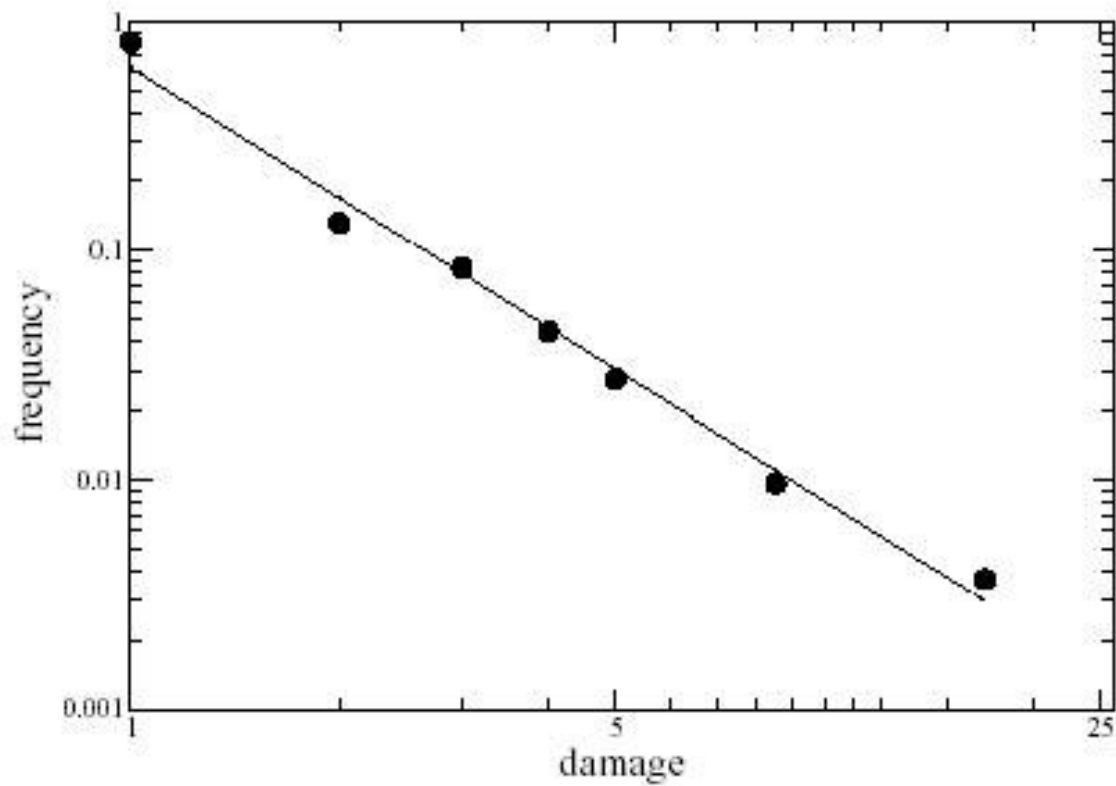


Map Pentose Phosphate Pathway (in archive .txt)

R00302 1.1.3.10 D-Glucose + O<sub>2</sub> ⇌ 2-Dehydro-D-glucose + H<sub>2</sub>O<sub>2</sub>



# Damage Frequency



$d < 5$ : 91%

$d \geq 5$ : 9%

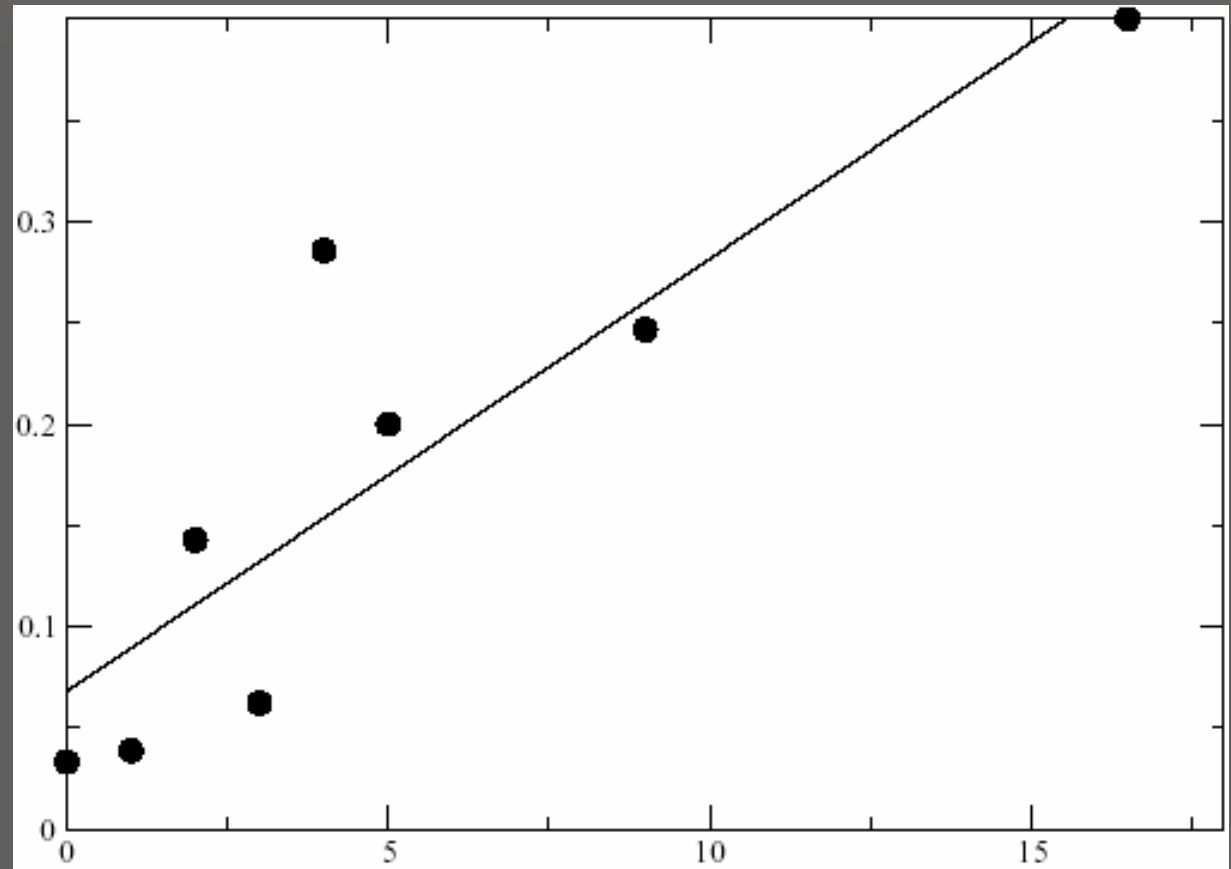
# # Essential Enzymes vs. *d*

Fraction

Correlation

F-test

P-value = 0.0228



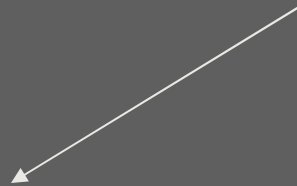
damage

# Another Statistical Significance

Two groups:

$d < 5$ : 91%  $\rightarrow$  50% of not essentials

$d \geq 5$ : 9%  $\rightarrow$  50% of essentials



$$P(9\% ; 50\% \text{ of essentials}) = 10^{-7}$$

# 10 Enzymes Highest Damage

Enzyme	<i>d</i>	<i>E</i>	Product
Ribose-phosphate pyrophosphokinase	22	E	Phosphoribosyl pyrophosphate
3-dehydroquinate dehydratase	21	N	Dehydroshikimate
Phosphoglucosamine mutase	20	E	Glucosamine 1-phosphate
Shikimate 5-dehydrogenase	20	N	Shikimate
UDP-N-acetylglucosamine pyrophosphorylase	19	E	UDP N-acetyl glucosamine
3-phosphoshikimate 1-carboxyvinyltransferase	18	N	3-Phosphate-shikimate
Acetyl-CoA carboxylase carboxyl transferase	18	E	Malonyl-CoA
Malonyl CoA-acyl carrier protein transacylase	17	E	Malonyl-ACP
3-oxoacyl-[acyl-carrier-protein] synthase	17	E	Acetyl-ACP
Chorismate synthase	17	N	Chorismate

High damage, not essential => present in culture medium (?)

low damage, essential => not metabolism

# Analysis

- ⇒ In general → connect different maps
- ⇒ Highest damage enzyme → PRPP initial product for 4 different maps
- ⇒ 4 enzymes → production de chorismate, aromatic aminoacids, folate e ubiquinone
- ⇒ 5 enzymes → biosynthesis of cell wall (attractive targets)