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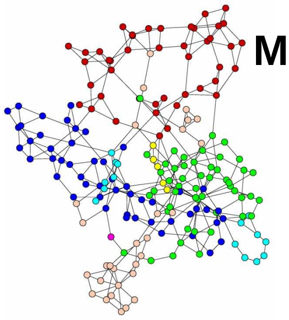

Mathematical Biology: Metabolic Network Analysis

Lecture 2 *(12th February 2019)***:**
Modeling Metabolic Networks II

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Spring semester 2019

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Summary of last week

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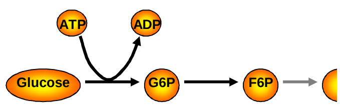
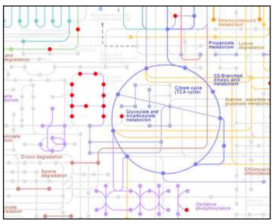
Modeling of (bio)chemical reaction networks:

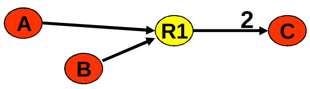
0.) Hypergraph representation
(Usual description in biochemistry)





1.) Weighted bi-partite graph representation

R1: $A + B \to 2C$



$\Longleftrightarrow$

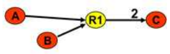
	R1
A	-1
B	-1
C	2

Stoichiometric matrix

Summary of last week

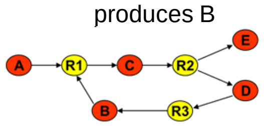
Modeling of (bio)chemical reaction networks:

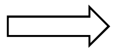
1.) Weighted **bi-partite graph** **representation**

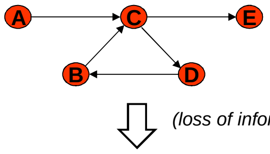


2.) (Directed) **substrate graph**

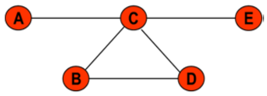
Nodes: the chemical compounds involved
Edges: arrow from A to B for each reaction that uses A as substrate and produces B







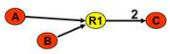
2b.) (Undirected) **substrate graph**



Summary of last week

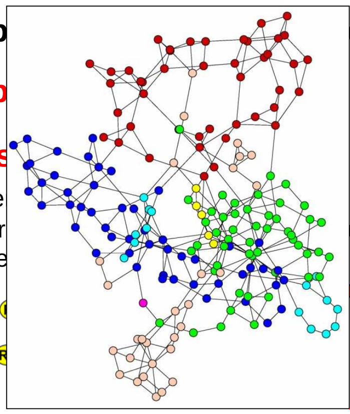
Modeling of (b ... etworks:

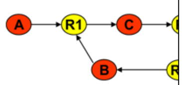
1.) Weighted b ... ntation

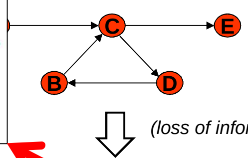


2.) (Directed) s

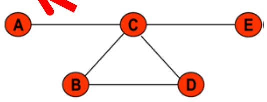
Nodes: the che
Edges: arrow fr ... uses A as substrate and
produce







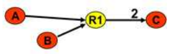
2b.) (Undirected) **substrate graph**



Summary of last week

Modeling of (bio)chemical reaction networks:

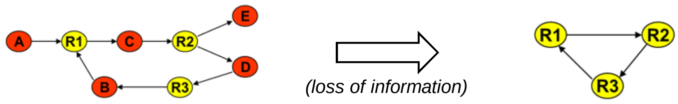
1.) Weighted bi-partite graph representation



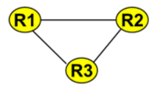
2.) (Undirected / directed) substrate graph

3.) (Directed) Reaction graph

Nodes: the chemical reactions involved
Edges: arrow from R1 to R2 if reaction R2 uses a product of reaction R1 as substrate



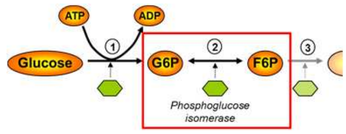
3b.) (Undirected) Reaction graph



An additional network model

(from the general Chemical Reaction Network Theory: CRNT)

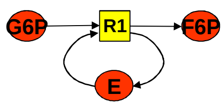
4.) CRNT network model



Issue: e.g. catalyzed reactions

$G6P + E \rightarrow F6P + E$

E: enzyme – catalyst, here phosphoglucose isomerase



	R1
G6P	-1
F6P	1
E	0

Stoichiometric matrix

No net change in amount of E !!

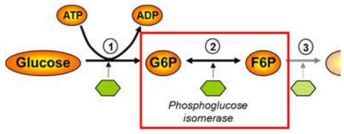
An additional network model

(from the general Chemical Reaction Network Theory: CRNT)

4.) CRNT network model

Issue: e.g. catalyzed reactions

G6P + E $\rightarrow$ F6P + E



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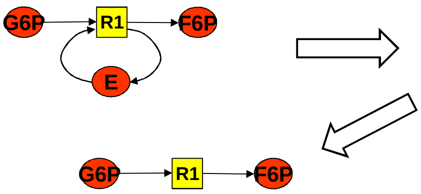

	R1
G6P	-1
F6P	1
E	0

Stoichiometric matrix

Ambiguity !!

An additional network model

(from the general Chemical Reaction Network Theory: CRNT)

4.) CRNT network model

A ***chemical reaction network*** is a triple $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ of finite sets:

1. $\mathcal{S} = \{X_1, X_2, \ldots, X_m\}$ is the set of basic ***species*** / molecules that undergo chemical transitions
2. $\mathcal{C} \subset \mathbb{N}_0^m$ is the set of all ***complexes***, i.e. all combinations of species (together with their multiplicities) that are either substrate or product of a reaction.
3. $\mathcal{R} = \{R_1, R_2, \ldots, R_r\} \subset \mathcal{C} \times \mathcal{C}$ is the set of all ***reactions***, i.e. all transitions between complexes that are possible.

$$R_i : \quad \sum_{j=1}^{m} y_{ij} X_j \quad \longrightarrow \quad \sum_{j=1}^{m} y'_{ij} X_j$$

$$y_i = (y_{ij})_j \in \mathcal{C} \qquad y'_i = (y'_{ij})_j \in \mathcal{C}$$

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An additional network model

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(from the general Chemical Reaction Network Theory: CRNT)

4.) CRNT network model

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$$R_i = (y_i, y_i') : \quad \sum_{j=1}^{m} y_{ij} X_j \longrightarrow \sum_{j=1}^{m} y'_{ij} X_j$$

$$y_i = (y_{ij})_j \in \mathcal{C} \qquad y_i' = (y'_{ij})_j \in \mathcal{C}$$

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An additional network model

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(from the general Chemical Reaction Network Theory: CRNT)

4.) CRNT network model

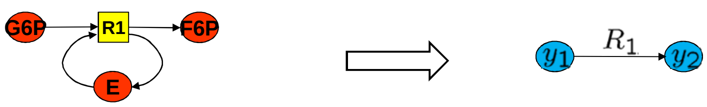
Nodes: the complexes in $\mathcal{C}$
Arrows: the reactions in $\mathcal{R}$

$X_1 = \text{G6P}$
$X_2 = \text{F6P}$
$X_3 = \text{E}$

G6P + E $\rightarrow$ F6P + E

$$\mathcal{C} = \{\text{G6P} + \text{E}, \text{F6P} + \text{E}\}$$
$$= \{y_1, y_2\}$$

$$y_1 = (1, 0, 1)$$
$$y_2 = (0, 1, 1)$$



An additional network model

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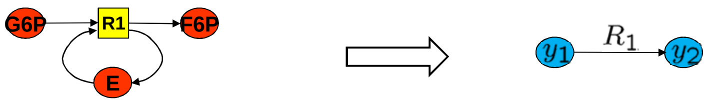
(from the general Chemical Reaction Network Theory: CRNT)

4.) CRNT network model

-- Provides an unambiguous representation of any chemical reaction network

-- Characteristics of the graph representation relate to possible dynamics of the reaction network
('Feinberg's deficiency-one theorem')

-- The graph representation is hard to interpret in terms of chemical transitions of species, however…



An additional network model

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(from the general Chemical Reaction Network Theory: CRNT)

4.) CRNT network model

-- Provides an unambiguous representation of any chemical reaction network

-- Characteristics of the graph representation relate to possible dynamics of the reaction network
('Feinberg's deficiency-one theorem')

-- The graph representation is hard to interpret in terms of chemical transitions of species

There is no need for a CRNT network model if one does not include the catalysts in a metabolic network model

… so we do not, and model with bi-partite graphs

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Elementary biochemical reactions

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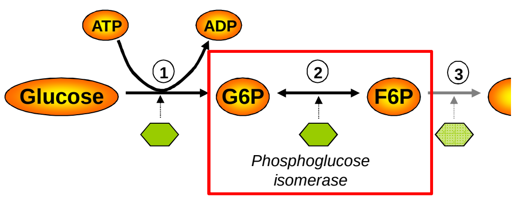
Elementary biochemical reactions
-- 1. Isomerases --

Three types of elementary biochemical reactions:

1.) ***Isomeric reactions***, ('subgroup reorganisation')

Isomer: chemical compound with the same molecular formula, but different structural formula

Example: in glycolysis…

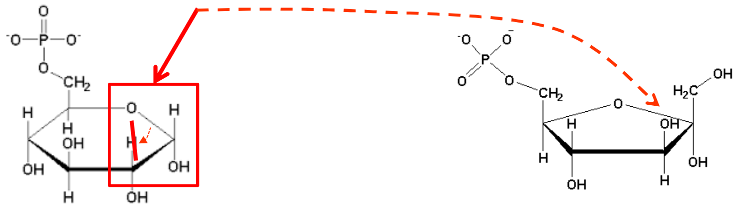


Elementary biochemical reactions
-- 1. Isomerases --

Three types of elementary biochemical reactions:

1.) ***Isomeric reactions***, ('subgroup reorganisation')

G6P F6P



α-D-glucose-6-phosphate *β-D-fructose-6-phosphate*

$C_6H_{13}O_9P$ ← *Same molecular formula* → $C_6H_{13}O_9P$

Elementary biochemical reactions
-- 1. Isomerases --

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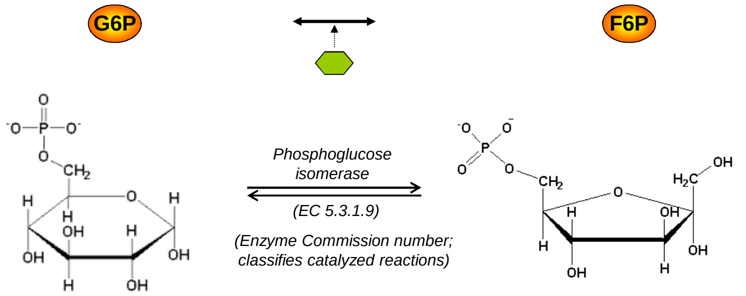
G6P F6P



α-D-glucose-6-phosphate *β-D-fructose-6-phosphate*

Isomerase: Enzyme that changes the structural formula of a compound, not its molecular formula

Elementary biochemical reactions
-- 1. Isomerases --

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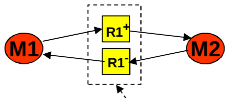
Three types of elementary biochemical reactions:

1.) ***Isomeric reactions***, ('subgroup reorganisation')

Modelling:

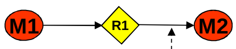
(a)



*(pair of unidirectional (**irreversible**) reactions)*

Labelling '+'/'-' indicates that the same enzyme catalyzes both forward (+) and backward (-) reactions

(b)



*(introduce new class of **reversible** reactions, catalyzed by the same enzyme)*

Arrow indicates the choice of positive direction ('forward reaction')

('*Tripartite graph*')

Elementary biochemical reactions
-- 1. Isomerases --

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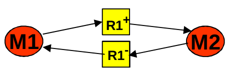
Three types of elementary biochemical reactions:

1.) ***Isomeric reactions***, ('subgroup reorganisation')

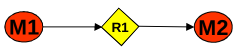
Stoichiometric matrix:

(a)



	$R1^+$	$R1^-$
M1	-1	1
M2	1	-1

(b)



	R1
M1	-1
M2	1

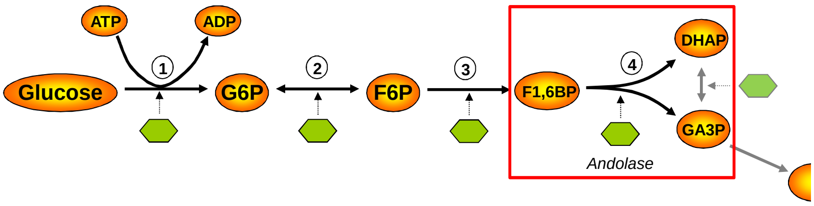
Elementary biochemical reactions
-- 2. Bimolecular association / dissociation --

Three types of elementary biochemical reactions:

2.) ***Bimolecular association or dissociation***, ('splitting')

$M_1 + M_2 \rightarrow M_3$ or $M_1 \rightarrow M_2 + M_3$

Example: again in glycolysis…



… or starch production (polymerisation)

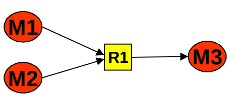
Elementary biochemical reactions
-- 2. Bimolecular association / dissociation --

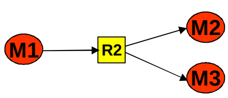
Three types of elementary biochemical reactions:

2.) ***Bimolecular association or dissociation***, ('splitting')

$M_1 + M_2 \rightarrow M_3$ or $M_1 \rightarrow M_2 + M_3$

Modelling:





Stoichiometric matrix:

	R1
M1	−1
M2	−1
M3	1

	R2
M1	−1
M2	1
M3	1

Elementary biochemical reactions
-- 3. Co-factor coupled reactions --

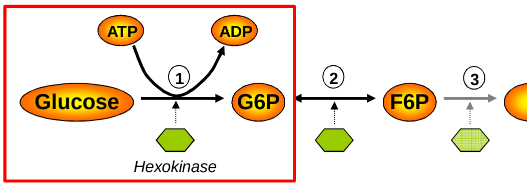
Three types of elementary biochemical reactions:

3.) ***Co-factor coupled reactions***, ('carrier mediated')

A moiety P is 'donated' by a carrier (co-factor) C to an accepting compound A

$$A + CP \rightarrow AP + C$$

Example: again in glycolysis… -- *phosphorylation* --



Elementary biochemical reactions
-- 3. Co-factor coupled reactions --

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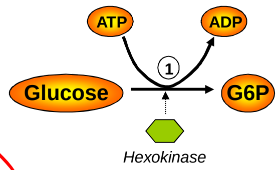
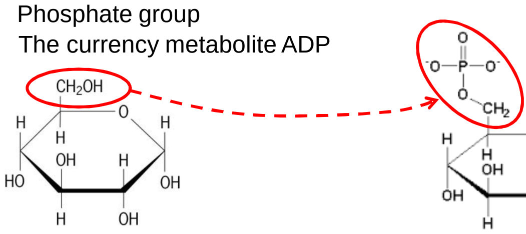


A: Glucose
P: Phosphate group
C: The currency metabolite ADP



D-glucose *α-D-glucose-6-phosphate*

Elementary biochemical reactions
-- 3. Co-factor coupled reactions --

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Three types of elementary biochemical reactions:

3.) ***Co-factor coupled reactions***, ('carrier mediated')

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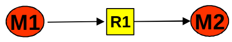
$$A + CP \rightarrow AP + C$$

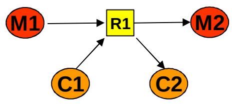
Modelling: (M1 = A; M2 = AP)

(a)



(Carrier/currency metabolites is not explicitly modelled, e.g. energy balance is not important)

(b)



(Carrier/currency metabolites are explicitly modelled, e.g. energy balance is taken into account)

(C1 = CP; C2 = C: currency metabolites)
(e.g. ATP / ADP)

Elementary biochemical reactions
-- 3. Co-factor coupled reactions --

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Three types of elementary biochemical reactions:

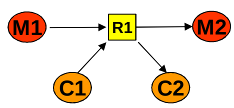
3.) ***Co-factor coupled reactions***, ('carrier mediated')

A moiety P is 'donated' by a carrier (co-factor) C to an accepting compound A

Stoichiometric matrix:

	R1
M1	-1
M2	1
C1	-1
C2	1

(b)



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Note: further classification
-- types of metabolites / reactions --

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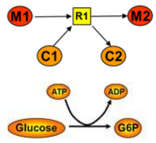
So, two types of metabolites may be identified in model:



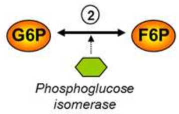
-- Specific metabolites M1 M2

-- Currency metabolites (ADP / ATP, NAD$^+$ / NADH) C1 C2

And two types of reactions:

-- Irreversible reactions R1

-- Reversible reactions (catalyzed by the same enzyme) R1



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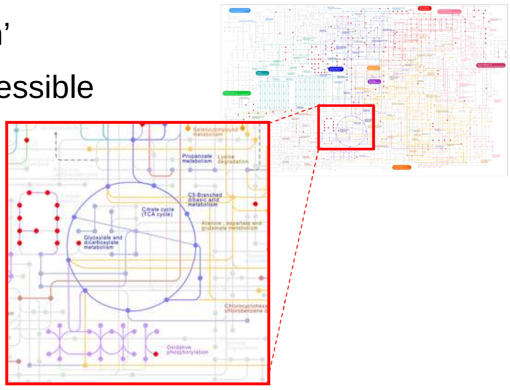
Modularisation and virtual and physical compartmentation

Modularisation

Often one is interested in modeling only part of an organism’s metabolic network:

- -- ‘Reductionist approach’
- -- Full network is not accessible computationally



Modularisation

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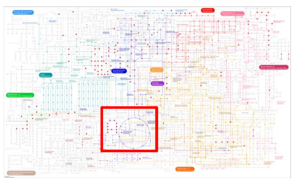
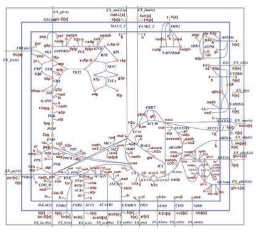


- -- Part of the network may be sufficient for studying research question of interest

So one (subjectively) selects a subnetwork: a **module**



(simplified E.coli metabolic model)

Modularisation

-- example: glycolytic pathway --

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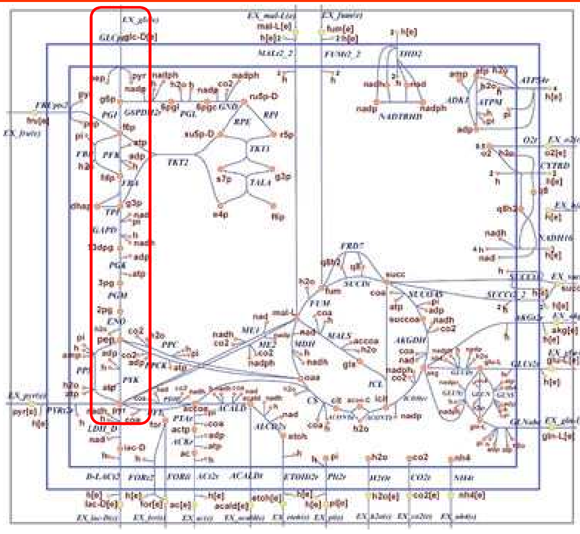

Orth, Fleming, and Palsson (2010) '*Reconstruction and Use of Microbial Metabolic Networks: the Core Escherichia coli Metabolic Model as an Educational Guide*'

Modularisation

-- example: glycolytic pathway --

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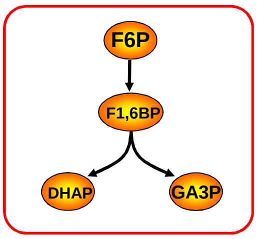
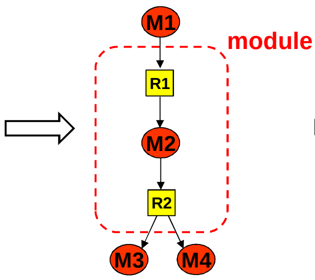
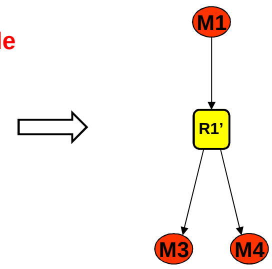


(Hypergraph representation)

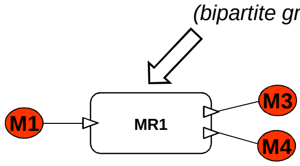




(bipartite graph representation)

*(bipartite graph representation with non-elementary - **modular** - reaction)*

Or



'Modular reaction'

Modularisation
-- example: glycolytic pathway --

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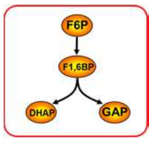
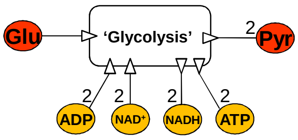


The **function** of modular reaction 1 is:

-- ‘*to transform one* M1 (F6P) *into one* M3 (DHAP) *and one* M4 (GA3P)’

Glycolytic pathway / glycolysis:



The **function** of glycolysis is:

-- ‘*to transform one glucose into two pyruvate (central metabolite), together with a net gain of two ATP (energy) and two NADH (redox power) (currency metabolites)*

(25) Sander Hille Spring semester 2019 Metabolic Nw. An. L2

Modularisation
-- example: glycolytic pathway --

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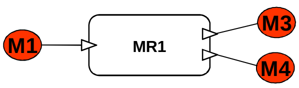
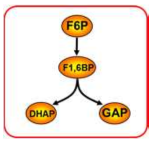
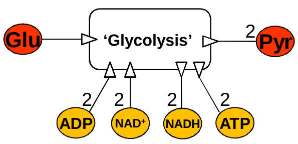




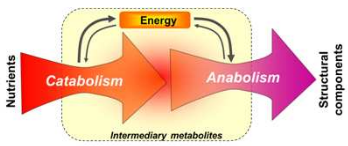
The **function** of modular reaction 1 is:

-- ‘*to transform one* M1 (F6P) *into one* M3 (DHAP) *and one* M4 (GAP)’

Glycolytic pathway / glycolysis:

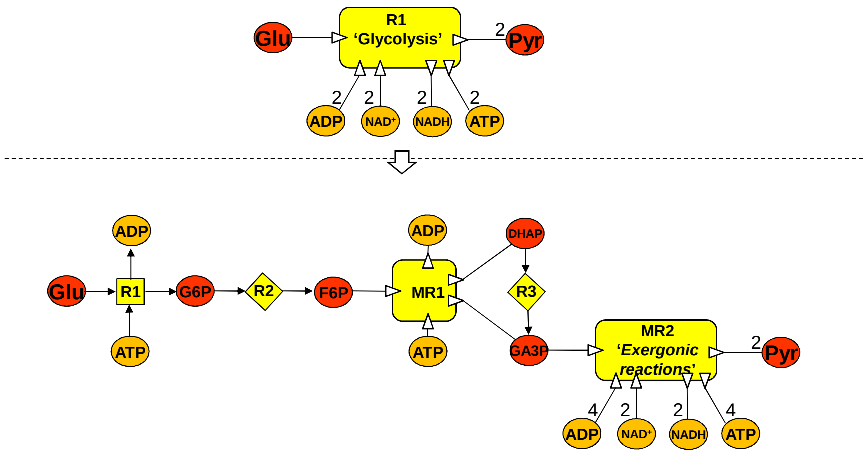


Recall ‘catabolism’:

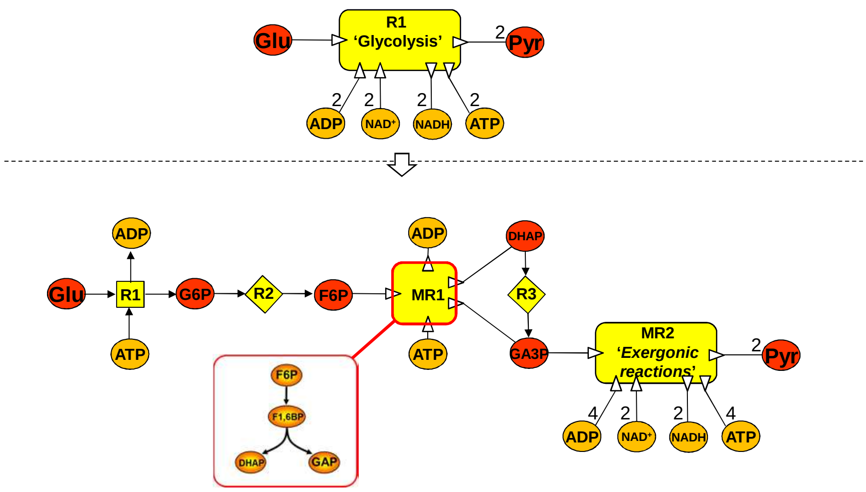


(25) Sander Hille Spring semester 2019 Metabolic Nw. An. L2

Modularisation
-- a hierarchy of network models --



Modularisation
-- a hierarchy of network models --



Modularisation
-- a hierarchy of network models --

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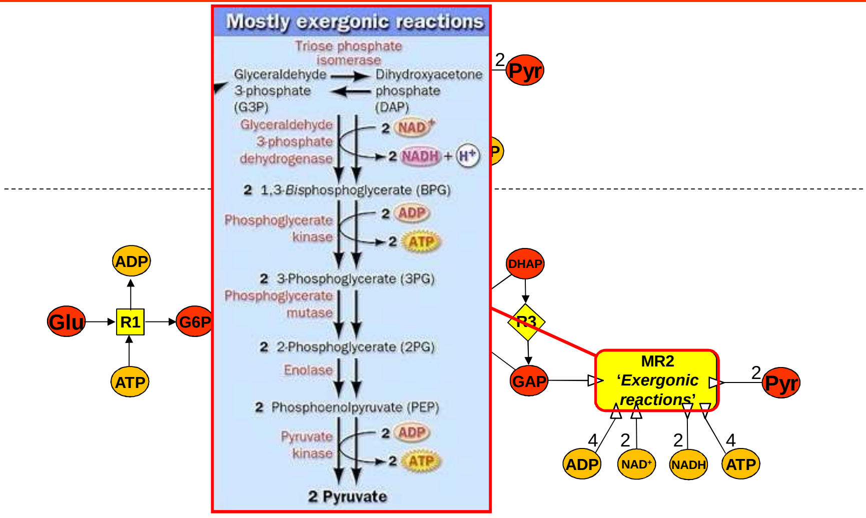

Modularisation
-- a hierarchy of network models --

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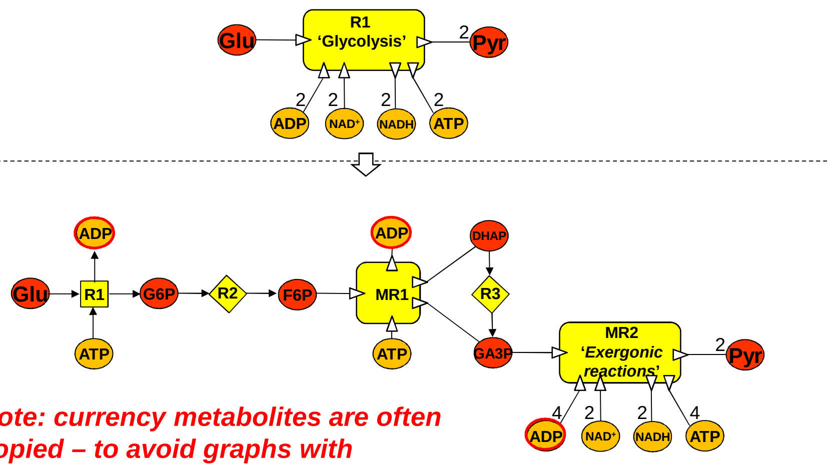
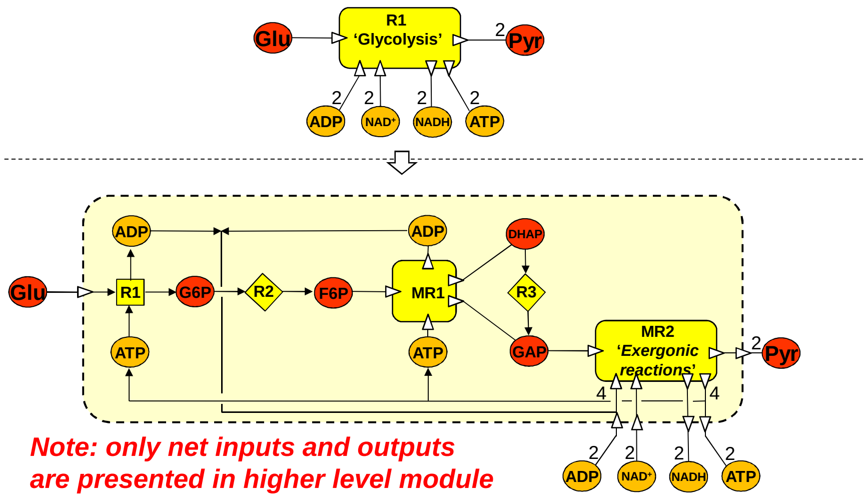


Note: currency metabolites are often copied – to avoid graphs with complex connections…

Modularisation

-- a hierarchy of network models --



Note: only net inputs and outputs are presented in higher level module

Exchange reactions

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Exchange reactions

-- transport over membranes --

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Cells are enclosed by the cell membrane and cell wall.

Metabolites (nutrients) must cross this barrier.

Cells may have many internal compartments and membranes too…

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Compartmentation

-- Nature's diversity --

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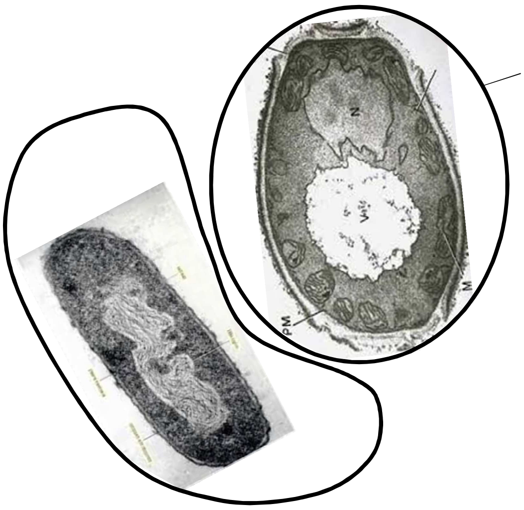
Prokaryotes

Unicellular;
No internal compartments in cells



Eukaryotes

Compartmentalized cells with (many) organelles,
e.g. nucleus

Compartmentation
-- Nature's diversity --

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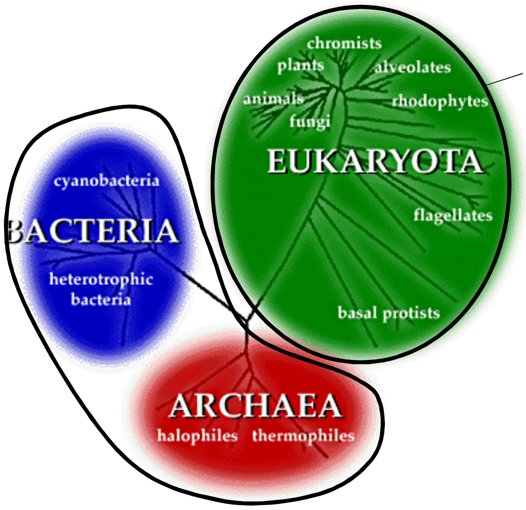
Prokaryotes

Unicellular;
No internal compartments in cells



Eukaryotes

Compartmentalized cells with (many) organelles, e.g. nucleus

Source: Introduction to the Archaea (http://www.ucmp.berkeley.edu/archaea/archaea.html)

Compartmentation
-- Nature's diversity --

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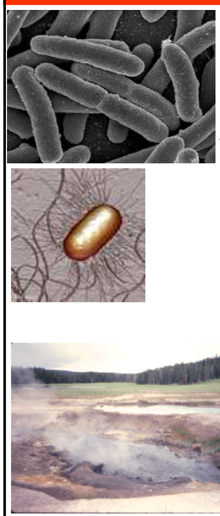
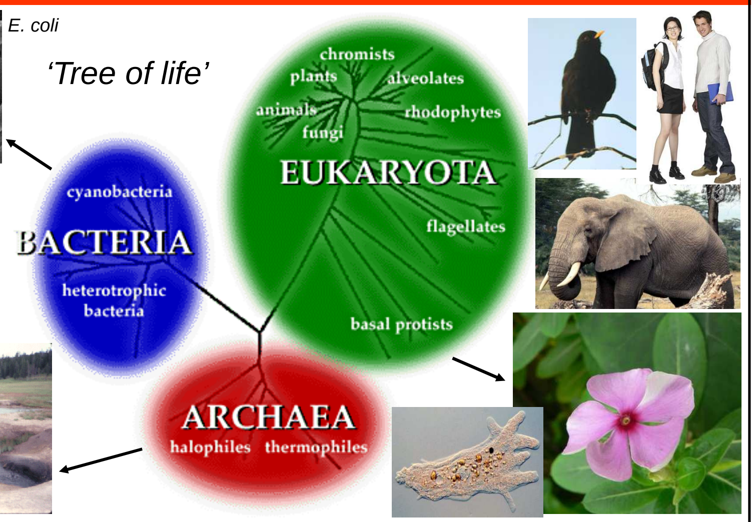
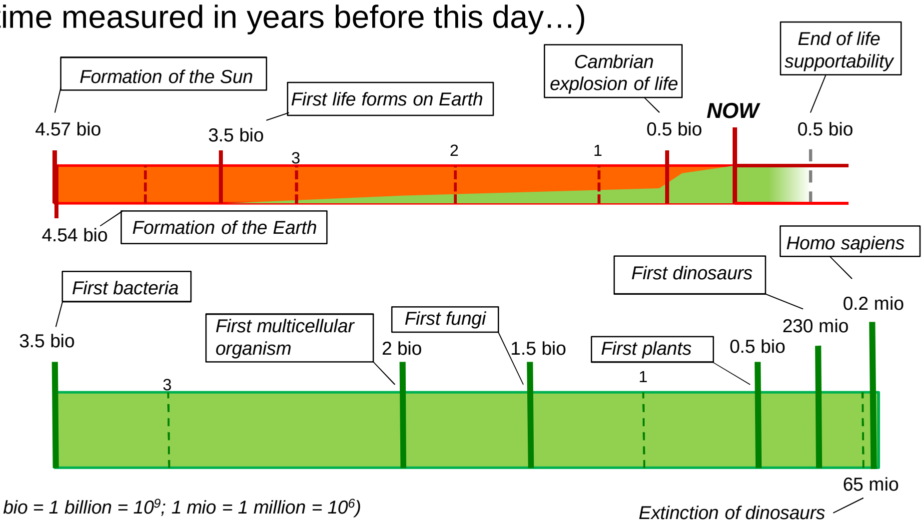




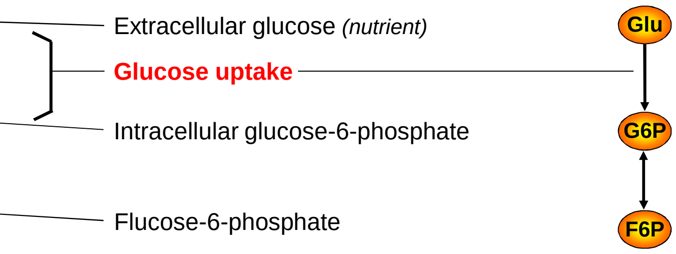
Source: Introduction to the Archaea (http://www.ucmp.berkeley.edu/archaea/archaea.html)

A history of life
(and the solar system)

(time measured in years before this day…)



Exchange reaction
-- example: glycolytic pathway --



Nutrients have to cross the cell membrane !!

Cell membranes

- **Consist of a phospholipid bilayer with various proteins**
- **Fluid-like structure!**

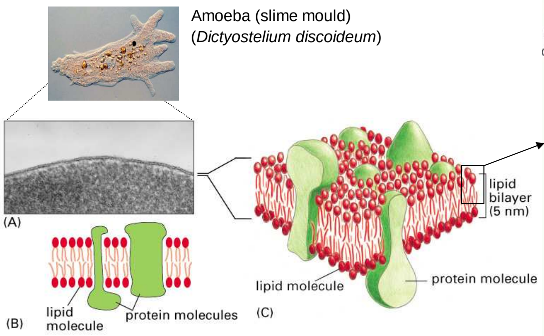
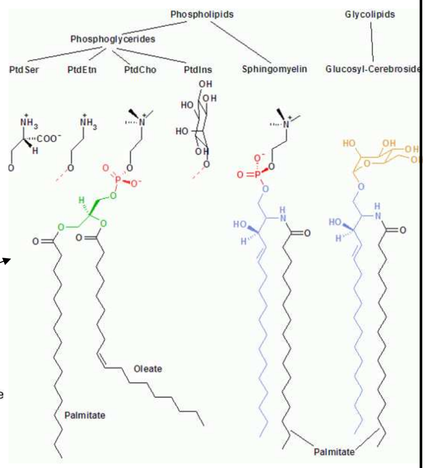
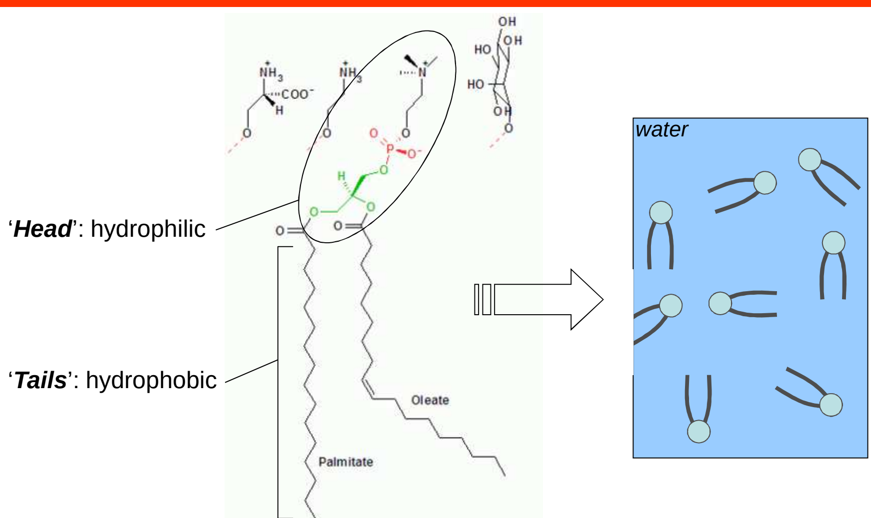


Figure 10–1. Molecular Biology of the Cell, 4th Edition.



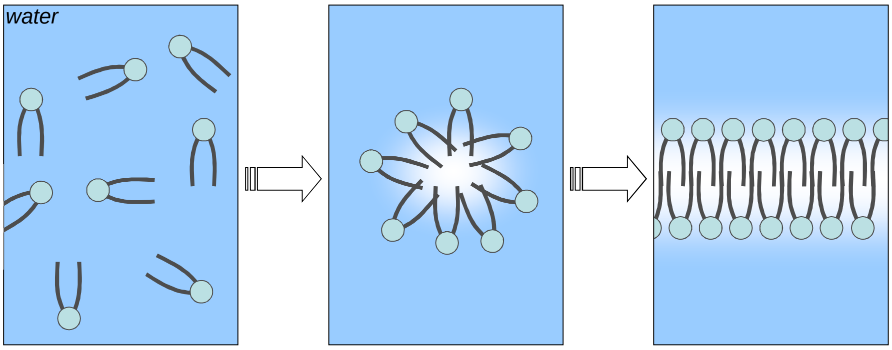
Membrane lipids (Borislav Mitev)

Cell membranes



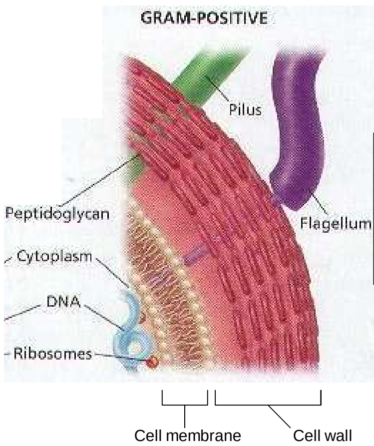
Membrane lipid(s) (Borislav Mitev)

Cell membranes

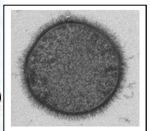


Diversity in bacteria
-- different membrane structures --

Gram-negative and Gram-positive bacteria



Examples:
Bacillus anthraxis



Bacillus subtilis

Listeria …

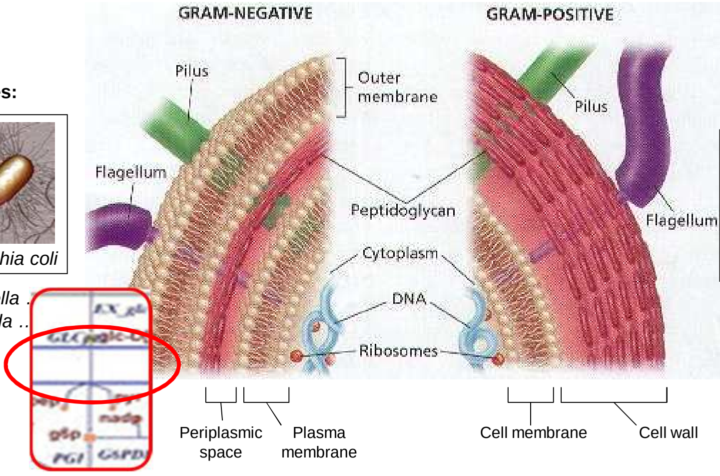
Diversity in bacteria
-- different membrane structures --

Gram-negative and Gram-positive bacteria

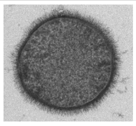
Examples:

Escherichia coli

Salmonella …
Legionella …



Examples:
Bacillus anthraxis

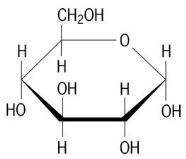


Bacillus subtilis

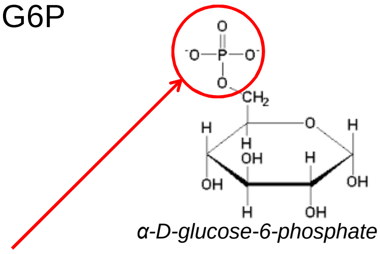
Listeria …

A real-life example
-- Glucose uptake by *E. coli* --

- Glucose dissolves in plasma membrane and can enter the cell through diffusion (and leak away…)
- There is also an active uptake mechanism, directly converting glucose into G6P



D-glucose

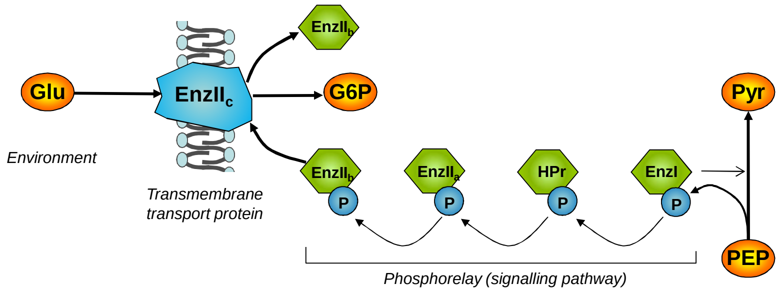


α-D-glucose-6-phosphate (G6P)

- The anion *(negative ion)* G6P can hardly diffuse through the charged plasma membrane.

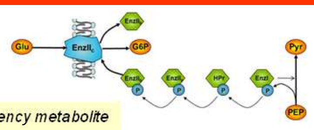
A real-life example
-- Glucose uptake by *E. coli* --

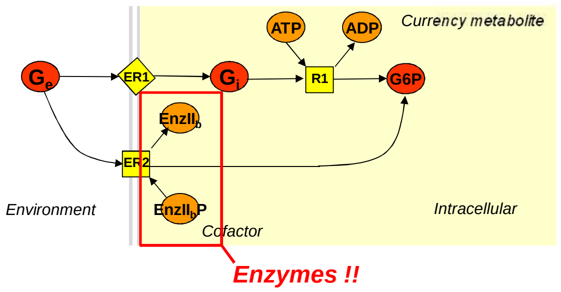
Cartoon of the active uptake mechanism:



A real-life example
-- Glucose uptake by *E. coli* --

Metabolic network model
for glucose uptake in *E. coli*:





ER1: Diffusive uptake of glucose through cell membrane ('*uptake is positive*')
(ER = '*Exchange reaction*' – exchange between compartments)

ER2: Active glucose uptake through cell membrane through EnzII$_c$

R1: Conversion catalyzed by hexokinase

A real-life example
-- Glucose uptake by *E. coli* --

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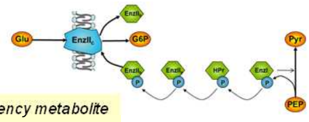
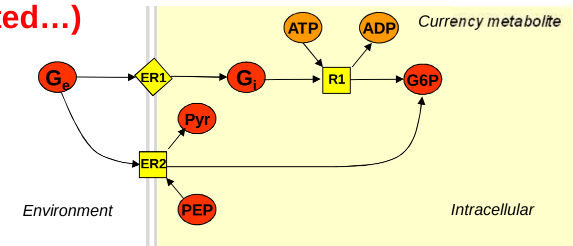
Metabolic network model
for glucose uptake in *E. coli*
(Corrected…)





Signaling molecules / enzymes have been removed

ER1: Diffusive uptake of glucose through cell membrane ('*uptake is positive*')
(ER = '*Exchange reaction*' – exchange between compartments)

ER2: Active glucose uptake through cell membrane through $EnzII_c$

R1: Conversion catalyzed by hexokinase

A real-life example
-- Glucose uptake by *E. coli* --

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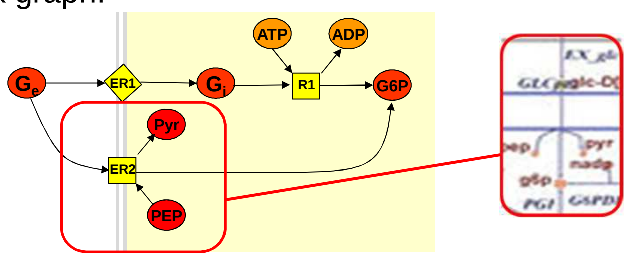
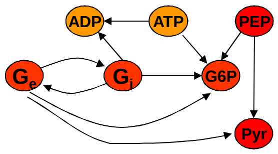
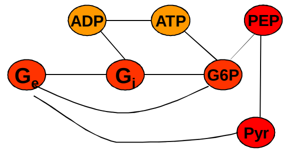
Detailed network graph:



Substrate graph:



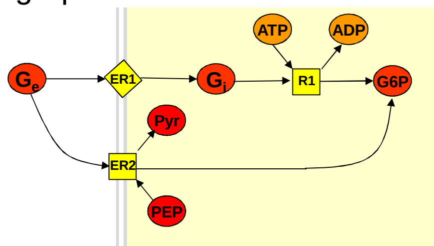
(directed)



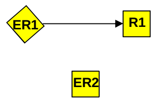
(undirected)

A real-life example
-- Glucose uptake by *E. coli* --

Detailed network graph:



Reaction graph:



(R1 uses a product of ER1 (namely G_i); ER2 does not use any products of the other reactions, nor does ER1 or R1 from ER2)

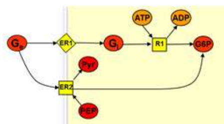
Summary
-- types of reactions --

Types of reactions:

-- Irreversible or reversible reactions

-- Internal or exchange reactions

Exchange reactions transport (and possibly transform) metabolites over membranes that separate physical compartments



Glucose uptake

… or are internal reactions that are part of the virtual boundary of a module (= virtual compartment)