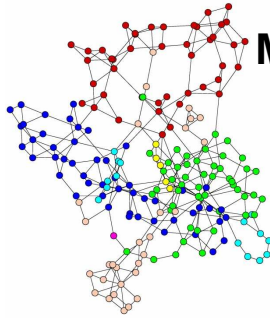# Mathematical Biology:
Metabolic Network Analysis

*Interdisciplinary lecture series
for Bioinformatics, Mathematics,
Biology and/or Life Science & Technology*

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Universiteit Leiden

Mathematisch Instituut

Modeling (bio-)chemical reaction networks

One aspect that distinguishes bio(logical) chemistry from general chemistry:

- The chemical compounds used by biological systems represent only a tiny fraction of all possible chemical carbon-based compounds with molecular mass in the same range:

estimated: $\sim 10^3 - 10^4$ out of $\sim 10^{60}$

(Ch.M. Dobson (2004). Chemical space and biology, *Nature* **432**, 824-828)

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What to model? Why? How?

- Be aware of purpose of mathematical modelling:

  What questions should be answered by the model and its *subsequent analysis and/or simulation*?

  Determines the *type of model* used, *level of detail*, or 'complexity', of the model

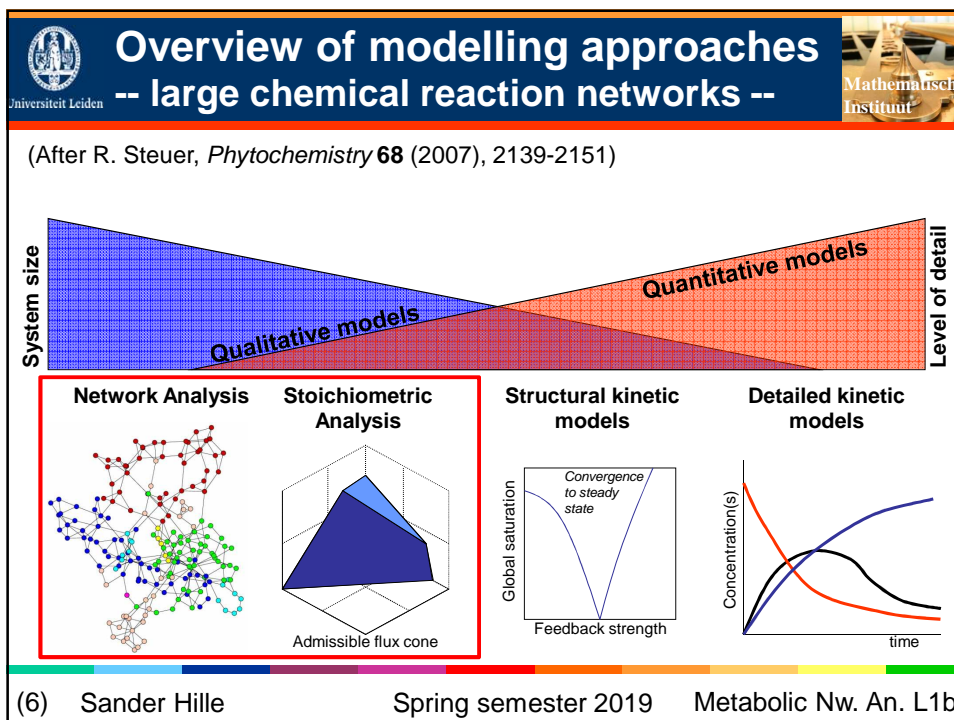(4) Sander Hille   Spring semester 2019   Metabolic Nw. An. L1b

Types of modelling

our focus →

	Qualitative	*Quantitative*
Predictive	• Fair level of realistic detail • targeted at providing detailed **insight** in changes in behaviour or **optimal control**	• *In silicon* version of reality • used to **predict** development of a system with appropriate accuracy • all relevant processes must be known in detail
Explorative	*('Toy models')* • (Highly) simplified system view • targeted at **understanding** particular aspects of the system	• Fair level of realistic detail • targeted at **discovering** detailed realistic structure of the system

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Overview of modelling approaches
-- large chemical reaction networks --

(After R. Steuer, *Phytochemistry* **68** (2007), 2139-2151)

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A hierarchical organisation (of metabolism) has been defined *based on man-made concepts* in order to better understand functioning of metabolism

> *'traditional' hierarchy*
> (found in most textbooks)

In contrast, graph theoretical results allow to introduce a *network-based hierarchy*.

> *'Network-based approach'* ⟵ ***our focus***

Goal: to obtain an *unbiased* -- objective -- hierarchy in the system, derived (solely) from its intrinsic structure

---

Metabolism:

The set of chemical reactions that occur in living organisms in order to maintain life.

Nutrients
- sugars
- cellulose
- proteins
- fats
- ...

Structural components
- proteins (e.g. enzymes)
- membranes
- RNA / DNA
- organelles
- ...

Metabolism

Metabolism:

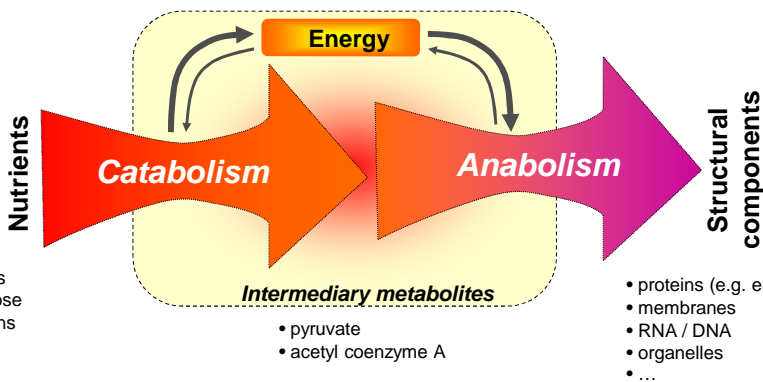The set of chemical reactions that occur in living organisms in order to maintain life.

Energy

Nutrients

Catabolism

Anabolism

Structural components

Intermediary metabolites

- sugars
- cellulose
- proteins
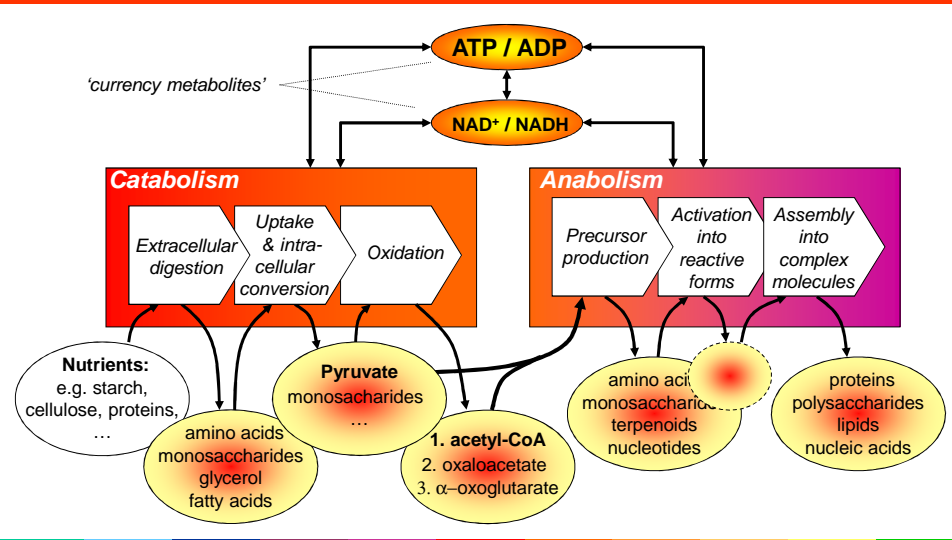- fats
- …

- pyruvate
- acetyl coenzyme A

- proteins (e.g. enzymes)
- membranes
- RNA / DNA
- organelles
- …

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Metabolism
-- detailed process view --

'currency metabolites'

ATP / ADP

NAD⁺ / NADH

Catabolism

Extracellular digestion

Uptake & intra-cellular conversion

Oxidation

Anabolism

Precursor production

Activation into reactive forms

Assembly into complex molecules

Nutrients:
e.g. starch, cellulose, proteins, …

amino acids
monosaccharides
glycerol
fatty acids

Pyruvate
monosacharides
…

1. acetyl-CoA
2. oxaloacetate
3. α–oxoglutarate

amino acids
monosaccharides
terpenoids
nucleotides

proteins
polysaccharides
lipids
nucleic acids

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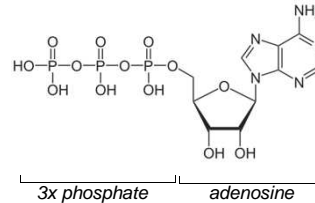
5

Metabolism
-- Currency metabolites --

ADP / ATP:

*A*denosine *D*i-(*T*ri-)*P*hosphate

Function: Transport of energy within cells
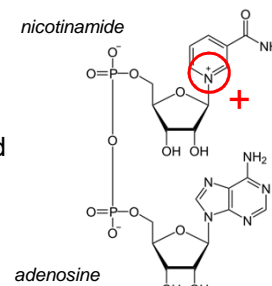e.g. for metabolism; phosphate donor

3x phosphate *adenosine*

NAD$^+$ / NADH:

*N*icotinamide *A*denosine *D*inucleotide

Function: Transfer of electrons from one compound
to another in redox reactions

NAD$^+$: oxidizing agent, accepts electrons
NADH: reducing agent, donates electrons

nicotinamide

adenosine

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Metabolism
-- Reduction and oxidation of NAD$^+$/NADH --

Reduction

Oxidation

$$NAD^+ + H^+ + 2e^- \rightleftharpoons NADH$$
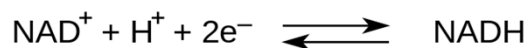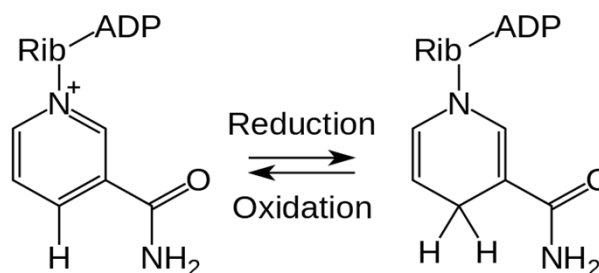
Oxidation: the loss of electrons by a molecule, atom or ion
Reduction: the gain of electrons by a molecule, atom or ion

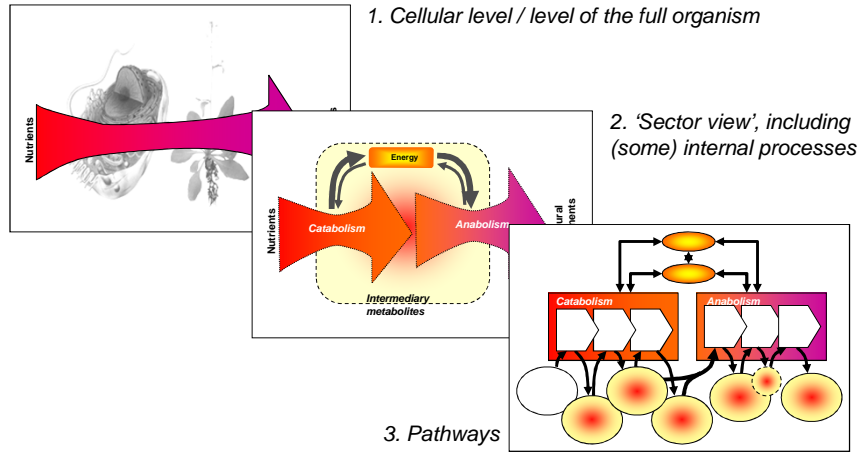(12) Sander Hille   Spring semester 2019   Metabolic Nw. An. L1b

Levels of modelling
-- a traditional hierarchy --

A 'traditional hierarchy':

1. *Cellular level / level of the full organism*

2. *'Sector view', including (some) internal processes*

3. *Pathways*

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Levels of modelling
-- a traditional hierarchy --

A 'traditional hierarchy':

3. *Pathways*

4. *Modules of (high-level) chemical reactions* (e.g. glycolysis, Calvin cycle …)

5. *Detailed chemistry*
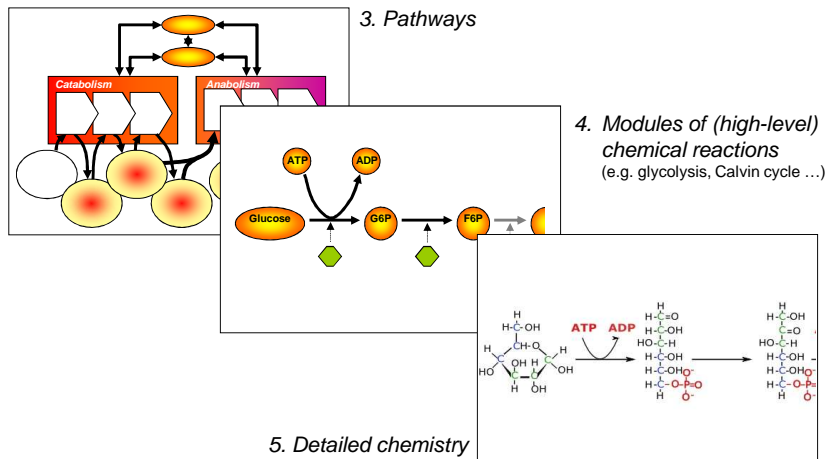
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Examples of (parts of) metabolic networks

Metabolic networks
-- example: photosynthesis --
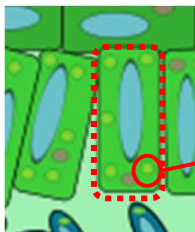

Cell with chloroplasts

Cross section

Cuticula
Boven-epidermis
Palisade parenchym
Spons-parenchym
Onder-epidermis
$CO_2 \uparrow \downarrow O_2$
Huidmondje
Xyleem
Floëem
Nerf

Metabolic networks
-- example: photosynthesis --
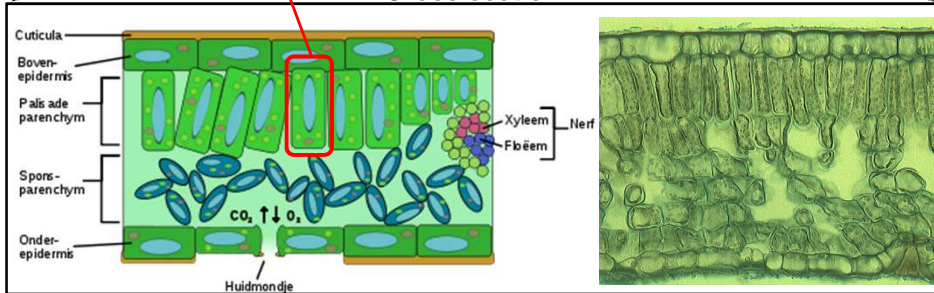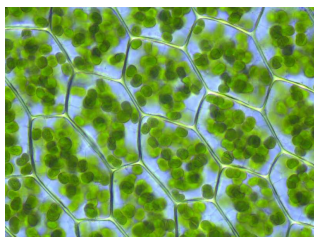
Chloroplasts in a moss, *Plagiomnium affine*
(Photo: Kristian Peters)
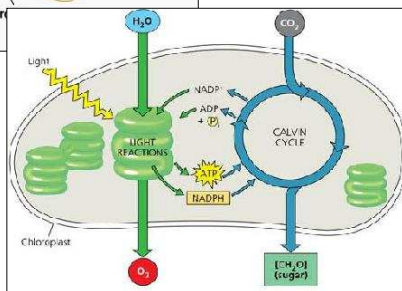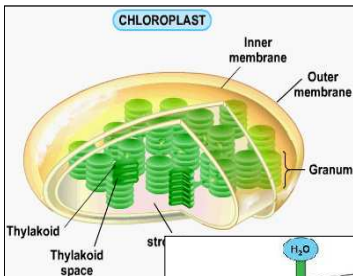
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Metabolic networks
-- example: glycolysis --

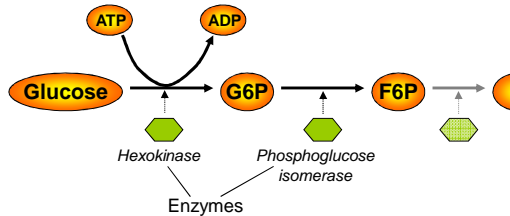*(http://www.biologyclass.net/pathways.html)*
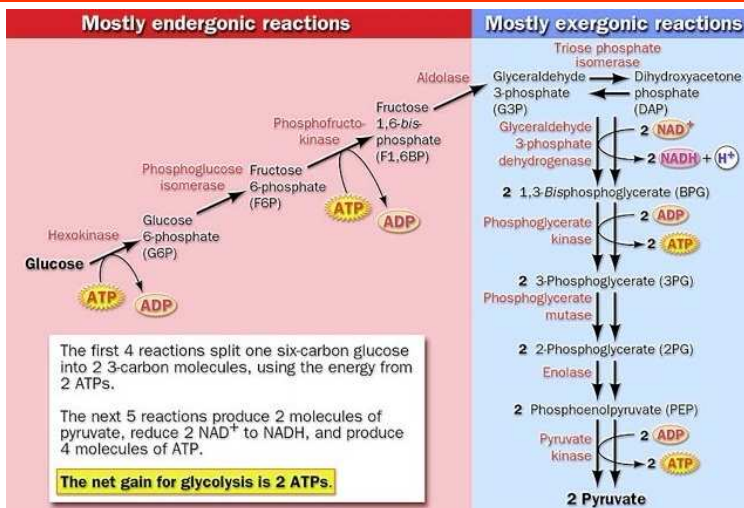
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Metabolic networks
-- some characteristics --

- **Almost all reactions are catalyzed by enzymes**

Glucose → G6P → F6P

ATP → ADP

Hexokinase *Phosphoglucose isomerase*

Enzymes

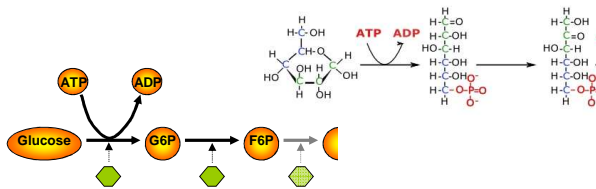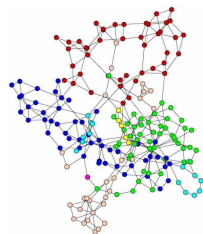**Example of an enzyme**
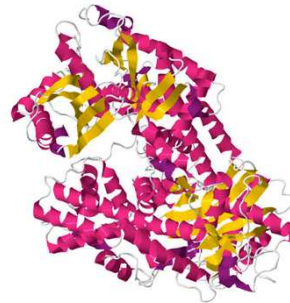
Crystal structure of hexokinase

- **Some reactions do not (hardly) occur in their absence**

  Although chemically:
  Principle of microscopic reversability

- **Large number of (substrate) molecules**
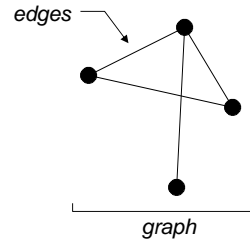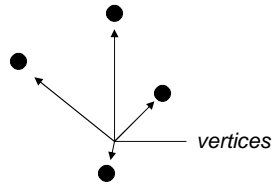
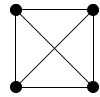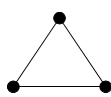# Chemical reaction networks viewed as mathematical graphs

Graph representations
-- some basic mathematical terminology --
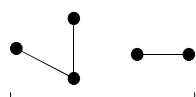
An **undirected graph** G is an ordered pair (V,E) of a finite collection of *vertices* V (or 'nodes') together with a set E of two-point subsets of V, the *edges* (or 'lines').

Other examples:
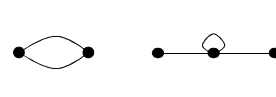

Complete graphs   *Disconnected graph*   *Graphs with cycle and with self-loops*

Graph representations
-- some basic mathematical terminology --

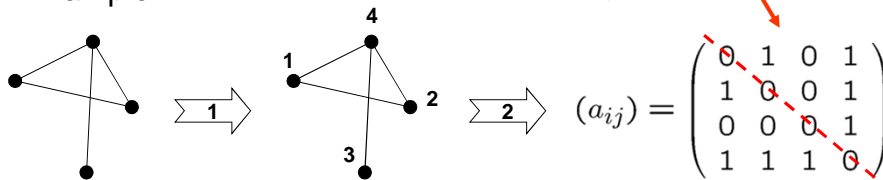A graph G=(V,E) can be represented by a matrix, the *adjacency matrix* of G, in the following manner:

1. Label the vertices by natural numbers 1,2, ... , n

2. The adjacency matrix is the n$\times$ n matrix with coefficients

$$a_{ij} = \begin{cases} 1, & \text{when } \{i,j\} \in E \\ 0, & \text{otherwise.} \end{cases}$$

Example:

Note: symmetric!

$$(a_{ij}) = \begin{pmatrix} 0 & 1 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ 1 & 1 & 1 & 0 \end{pmatrix}$$

A **bipartite graph** is a graph G=(V,E) such that the set of vertices is the disjoint union of two subsets V_1 and V_2, such that there are no edges connecting vertices within each of these subsets.
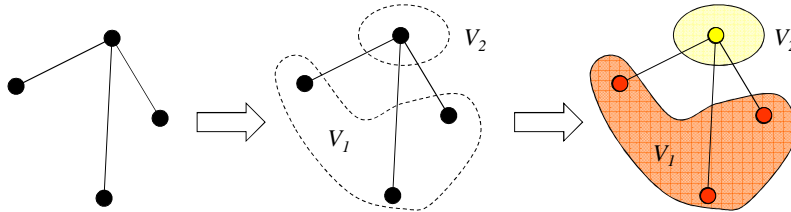
A bipartite graph

In a bipartite graph the vertices can be colloured in such a way that no two vertices of the same collour are connected through an edge.

A **bipartite graph** is a graph G=(V,E) such that the set of vertices is the disjoint union of two subsets V_1 and V_2, such that there are no edges connecting vertices within each of these subsets.
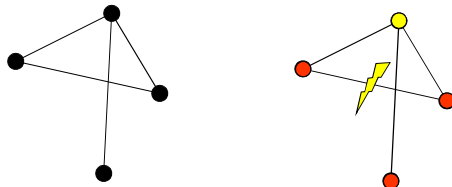
Not a bipartite graph

A **directed graph** G is an ordered pair (V,A) of a collection of *vertices* V (or 'nodes') together with a set $A \subset V \times V$ of ordered pairs of vertices, called *arrows* (or 'directed edges', 'arcs').

v_0 — v_1

Two paths from v_0 to v_1 of length 4

A directed graph
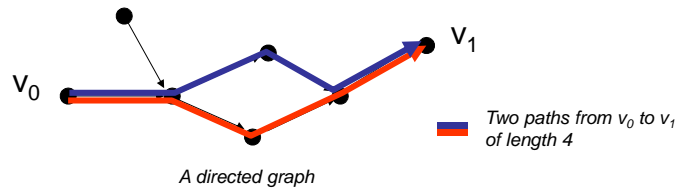
A **path** of length n from $v_0 \in V$ to $v_1 \in V$ is a sequence of arrows in A, $a_1, \ldots, a_n$ such that a_1 starts in v_0, a_n ends in v_1 and the end point of a_i is the starting point of a_{i+1}.
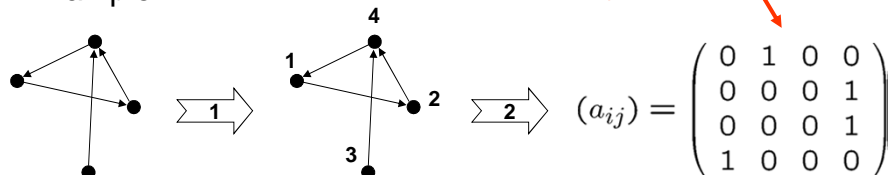

An adjacency matrix can be defined for a directed graph G=(V,A) similarly to that for an undirected graph:

● The adjacency matrix of a directed graph with n vertices is the n×n matrix with coefficients

$$a_{ij} = \begin{cases} 1, & \text{when } (i,j) \in A \\ 0, & \text{otherwise.} \end{cases}$$

Example:

Note: asymmetric!

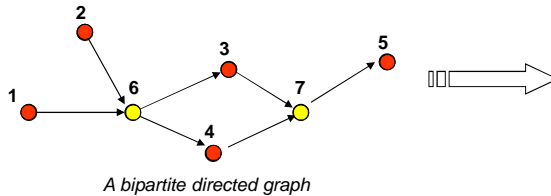$$(a_{ij}) = \begin{pmatrix} 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

Graph representations
-- some basic mathematical terminology --

The concept of a bipartite graph can be applied to directed graphs also…

A bipartite directed graph

- Directed bipartite graphs have a specially structured adjaceny matrix…

- Hence may be coded more efficiently …

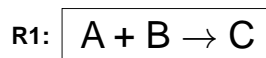(27) Sander Hille   Spring semester 2019   Metabolic Nw. An. L1b

Graph representations
of chemical reaction networks

Bipartite directed graphs can be used to model chemical reaction networks:

Chemical reaction:
(unidirectional)

R1: $A + B \rightarrow C$

Bipartite graph:
(directed graph)

- Substrate / product
- Chemical reaction

Ambigious…

also

Substrate graph:
(directed graph)

Arrow between substrate / products when connected through a reaction

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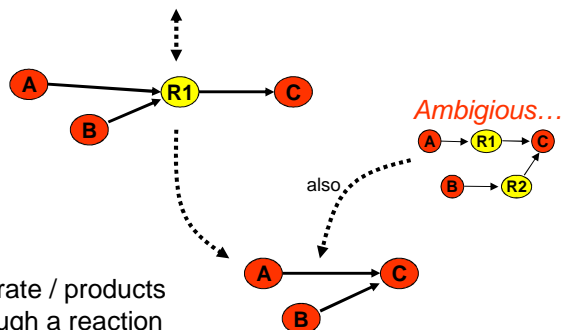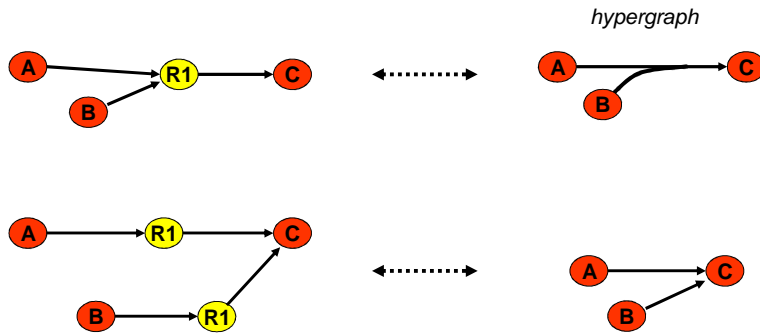
Graph representations of chemical reaction networks

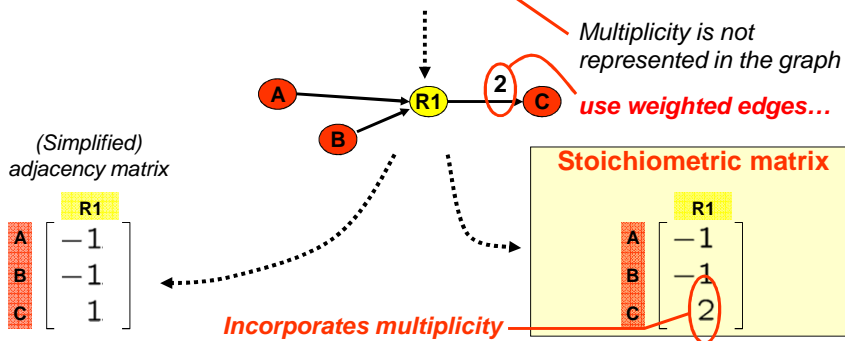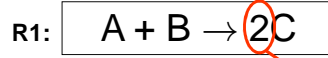Ambiguity in substrate graphs may be circumvented by using *hypergraph* notation…

hypergraph

Graph representations of chemical reaction networks

Another ambiguity is present even in bipartite graphs associated to chemical reactions…

Chemical reaction:
(unidirectional)

R1: $A + B \rightarrow 2C$

Multiplicity is not represented in the graph

use weighted edges…

(Simplified) adjacency matrix

$$\begin{array}{c} A \\ B \\ C \end{array} \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}$$

Stoichiometric matrix

$$\begin{array}{c} A \\ B \\ C \end{array} \begin{bmatrix} -1 \\ -1 \\ 2 \end{bmatrix}$$

Incorporates multiplicity

Graph representations of chemical reaction networks

Multiple chemical reactions:
(unidirectional)

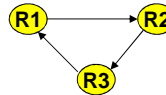R1: $A + B \rightarrow C$

R2: $C \rightarrow D + E$

R3: $D \rightarrow B$
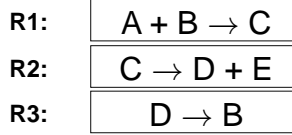
Bipartite graph:
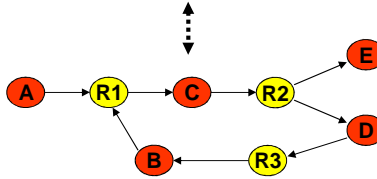
Reaction graph:

Arrow from a reaction to another when the endpoint uses a product of the first as a substrate

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Network Analysis

Summarising:

Chemical reaction network

Detailed network graph
(Bipartite directed graph)

Substrate graph

Reaction graph
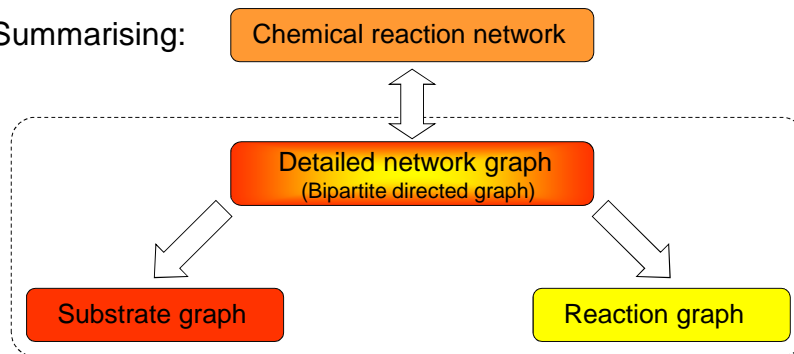
May use nodes of different shapes instead of collours to distinguish compounds from reaction:

Network Analysis

Summarising:

Chemical reaction network

Detailed network graph
(Bipartite directed graph)

Substrate graph

Reaction graph
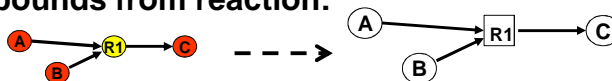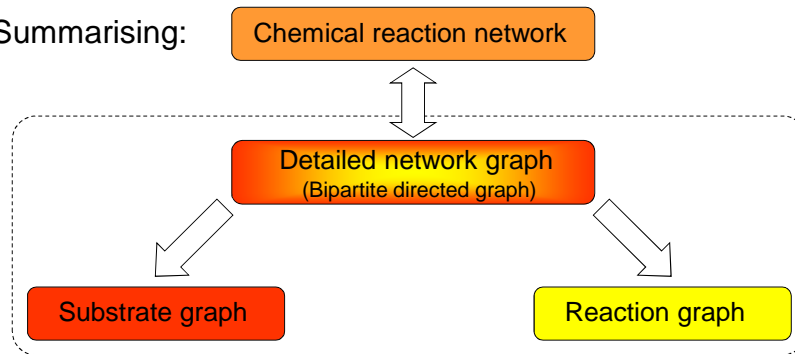
Network Analysis is the term used in the literature for studying the properties of these graphs.

'Network statistics'

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