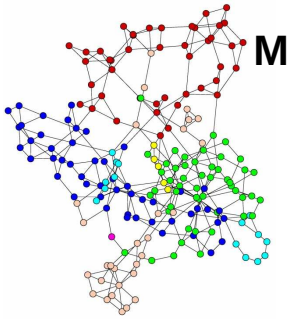
Universiteit Leiden



Mathematical Biology: Metabolic Network Analysis

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

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Snellius, Niels Bohrweg 1, room 401

Mathematisch Instituut

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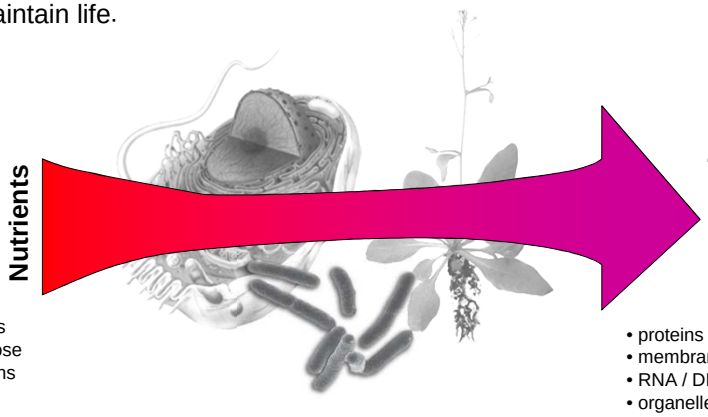
Metabolism

Metabolism:

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

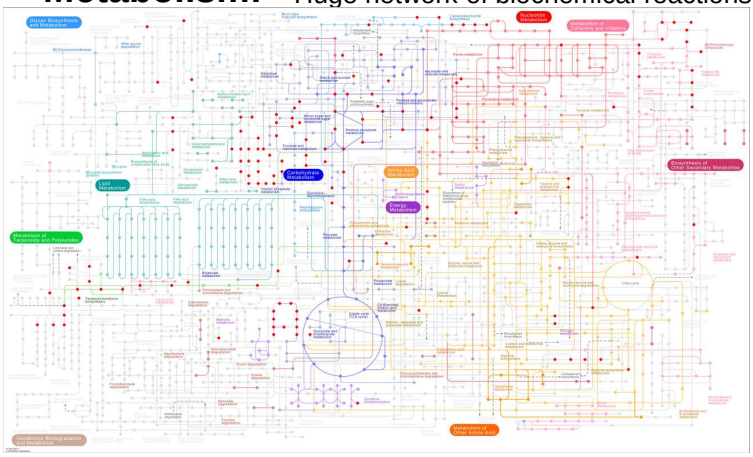


- sugars
- cellulose
- proteins
- fats
- …

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

A real-life example
-- Metabolism of *E. coli* --

Metabolism: Huge network of biochemical reactions



Model *i*AF1260
For *E. coli* strain K12-MG1655

~ 2077 reactions

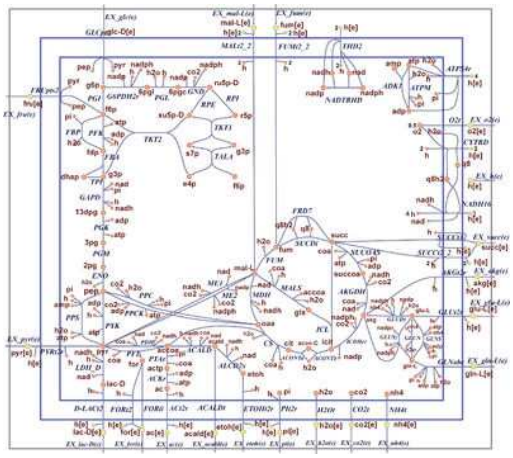
~ 1039 metabolites (= chemical compounds)

Feist et al., Mol. Syst. Biol. 3 (2007):121

Reconstruction of metabolic network of E. coli from KEGG database

A real-life example
-- Metabolism of *E. coli* --

Metabolism: (Huge) network of biochemical reactions



***E.coli* core model**

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

Key questions

- What functions can an organism's metabolism perform in transforming nutrients into structural components?
- How does it function under particular environmental conditions, i.e. nutrient availability?
- How do mutations / genetic engineering alter these?

Course objectives

- **Provide a mathematical framework for modeling metabolic networks**
  - Graph representation (similar to Petri nets)
  - Stoichiometric matrix
- **Use framework and algorithm(s) to compute all possible functions of the network**
  - Elementary Flux Modes (EFMs)
  - Extreme Currents (ECs), and their relationship to EFMs
  - (Extreme Pathways)
- **Use framework to compute optimal functioning of the network**
  - By means of Flux Balance Analysis (FBA)
  - By means of EFMs

Course objectives

- **Understand the approach(es) to and issues with mathematical modelling of metabolic networks**
- **Perform analyses of such models by hand and using computational (software) tools**
- **Understand the results that are given by these tools and the algorithms used to obtain them**
- **Be able to read the current research literature on this topic**
- **Know issues of method that arise when studying:**
  - Unicellular eukaryotes, instead of bacteria
  - Higher organisms, instead of unicellular ones
  - Signalling or regulatory networks, instead of metabolic…

Biological topics:

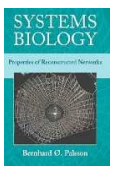
- **Prokaryotes versus eukaryotes** (the '*tree of life*')
- **Primary versus secondary metabolism**
- **Details of metabolism:**
  -- biochemically (enzymes)
  -- structurally (central metabolites, currency metabolites)
- **Compartmentation, membranes and transport**
- **Other important networks in cells:**
  -- signaling networks
  -- regulatory networks

Mathematical & computational topics:

- Elementary graph theory
- Elementary linear algebra and differential equations
- Theory of convex sets in finite dim. vector spaces
- Analysis of functions on convex sets: Convex analysis
- Some concepts & techniques specific to MNA
- Algorithms (for EFMs)
- Bit of programming in Matlab / Python
- Software tool(s) for MNA (e.g. CellNet Analyzer)

Literature

- **Lecture notes and slides**
  - The material will become available on *http://pub.math.leidenuniv.nl/~hillesc/*
- **Auxiliary research and review papers**
  - Download from electronic library, using ULCN login name and password
- **Notes written on the blackboard**



Bernhard Ø. Palsson:
Systems Biology; Properties of Reconstructed Networks.
Cambridge University Press, 2006.
(ISBN-13: 978-0-521-85903-5)

Examination

- **2 homework assignments** — 2x 15% = 30%
- **Individually written essay** — 30%
  (on a research question, based on 1-3 research papers, studied in a team)
- **Team presentation** — 10%
  (on the the studied papers)
- **Written exam** — 30%

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