BIOLOGY
Bioinformatics 1

Systems Biology

an Introduction

16.11.2023 – 10:15 to 11:45

Eberhard Korsching

complex-systems.uni-muenster.de

How to become a theoretical biologist ?

Studies in i.a. chemistry / biochemistry / biology
interests in physics / applied mathematics / statistics

grow

PhD in a wet-lab situation
e.g. biochemistry / immunohistochemistry /
cell biology / behavioral biology etc.
with the thoughtful application of theoretical methods

wet lab

Get associated with a life science topic,
be part of scientific networks,
gather work experience and get a broad overview
in theoretical sciences ...

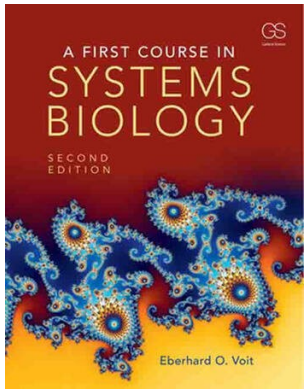
postdoc

Extend promising concepts ...

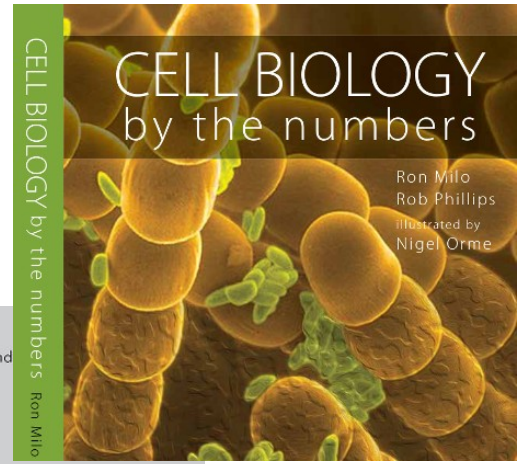
theory lab
in close cooperation with a
wet lab

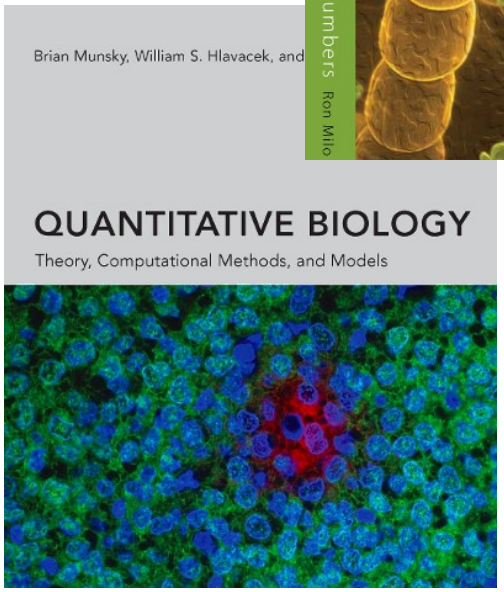
Resources

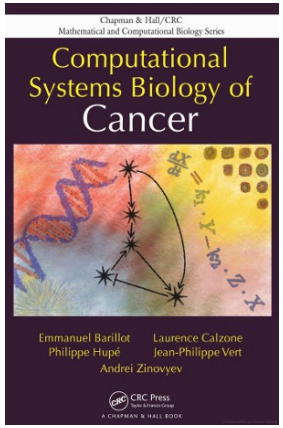
Internet resources : no science area is better represented on the web than the theoretical sciences

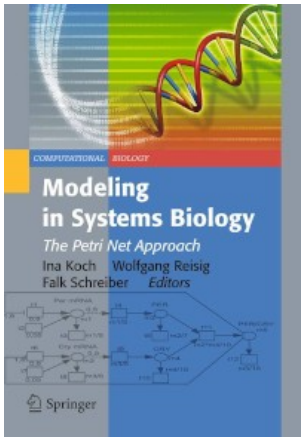


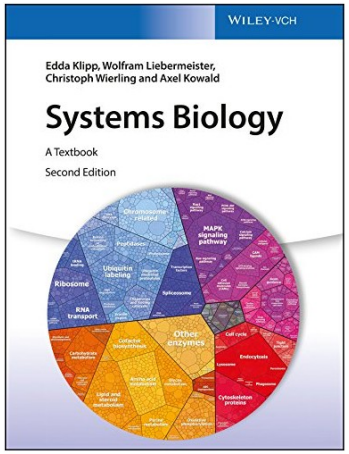
get inspired











discover topics


An Introduction to Systems Biology
Design Principles of Biological Circuits
Uri Alon
Systems Biology
A Textbook
A First Course in Systems Biology
Eberhard O. Voit
An Introduction to Computational Systems Biology
Systems Biology
Constraint-based Reconstruction and Analysis
Bernhard O. Palsson
Networks
An Introduction
M.E.J. Newman
Mathematical Modeling in Systems Biology
An Introduction
Brian P. Ingalls
Handbook of Systems Biology
Concepts and Insights
The Logic of Chance
The Nature and Origin of Biological Evolution
Eugene V. Koonin
George E. Mobus
Michael C. Kalton
Principles of Systems Science
Springer
Systems Biology of Cell Signaling
Recurring Themes and Quantitative Models
James E. Ferrell, Jr.
Joseph DiStefano III
Dynamic Systems Biology Modeling and Simulation
Collective Behavior in Systems Biology
A Primer on Modeling Infrastructure
Assaf Steinschneider
Introduction to Computational Biology
Maps, sequences and genomes
Interdisciplinary Sciences
Michael S. Waterman
Jinzhi Lei
Systems Biology
Modeling, Analysis, and Simulation
Springer
WenJun Zhang
Fundamentals of Network Biology
Michael G. Katze, Editor
Systems Biology
Springer
SYS BIO
Systems Biology
Isidore Rigoutsos and Gregory Stephanopoulos
Systems Biology
Simulation of Dynamic Network States
Bernhard Ø. Palsson
Shalini Singh, Editor
Machine Learning and Systems Biology in Genomics and Health
Springer
Alan Garfinkel · Jane Shevtsov · Yina Guo
Modeling Life
The Mathematics of Biological Systems
Springer
Systems Biology
Topological Data Analysis for Genomics and Evolution
Topology in Biology
Raúl Rabadán and Andrew J. Blumberg
Jinhu Lü
Pei Wang
Modeling and Analysis of Bio-molecular Networks
Springer
Noor Ahmad Shaik
Khalid Rehman Hakeem
Babajan Banaganapalli · Ramu Elango
Editors
Essentials of Bioinformatics, Volume I
Understanding Bioinformatics: Genes to Proteins
Springer
Sara Green, Editor
Philosophy of Systems Biology
Perspectives from Scientists and Philosophers
Springer
Wiley Series
Systems Biology
Networks
Mark Newman
Fundamentals of Systems Biology
From Synthetic Circuits to Whole-cell Models
Markus W. Covert
Nikolaus Rajewsky
Stefan Junga
Jan Ranftszewski
Editors
Systems Biology
Springer
Yoram Vodovotz
Gary An
Editors
Complex Systems and Computational Biology Approaches to Acute Inflammation
A Framework for Model-based Precision Medicine
Second Edition
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Ali Navid, Editor
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Editor-in-Chief
Joseph J. Barchi Jr.
Springer Protocols
Ramnata Tomar, Editor
Immuno-informatics
Synthetic Biology
A Primer
CRC Focus Series
Computational Biology Series
Systems-level Modelling of Microbial Communities
Theory and Practice
Aarthi Ravikrishnan
Karthik Raman
CRC Press
Physical Models of Living Systems
Philip Nelson
Robustness and Evolvability in Living Systems
Andreas Wagner
Systems Biology:
Introduction to Pathway Modeling
Eberhard O. Voit
Systems Biology
A Very Short Introduction
Oxford

even more ...

What are we going to talk about?

- **T**erm definitions & some first orientation
- **W**hat is a biological network? - and how we might use it...
- **A**pplication example
  from experimental data to results...
- **I**mportant technologies
  and spotlights
  on how systems biology is applied...

Introduction

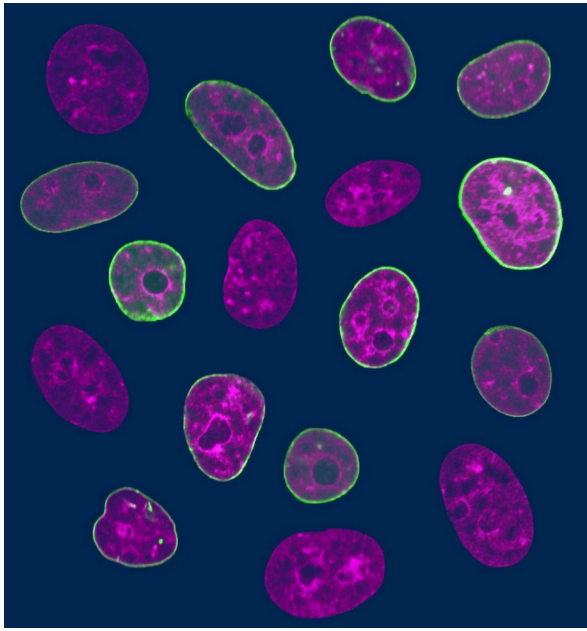
Definitions

&

Overview

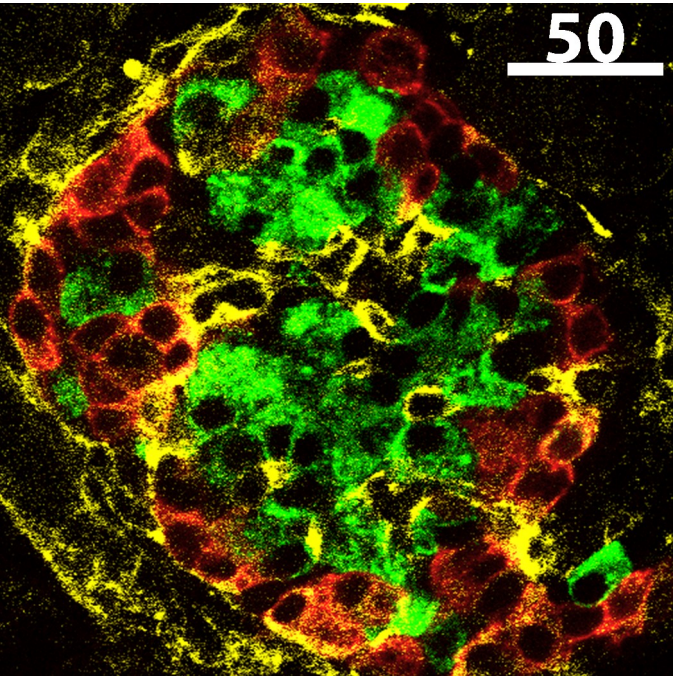
What is systems biology?

Mainly focusing on one cell
and their cellular states,
sometimes on parts of a cell,
and sometimes on all the cells
forming tissues/organs ...



Human cell nuclei with fluorescently labeled chromatin (purple) and nuclear envelope (green). Image credit: Fang-Yi Chu & Alexandra Zidovska, N.Y. University.

https://doi.org/10.1371/journal.pone.0007739.g004
Neonatal pancreas, mice: Endocrine-cells coated with a layer of extracellular matrix. Immunohistochemical staining for Insulin (green), glucagon (red) and collagen IV (yellow) - 50 µm scale bar.



... tries to explain the
interaction (mechanisms) of
all molecules forming and
maintaining a cell
and their self developed
micro environment ...

Our focus : molecule quantities

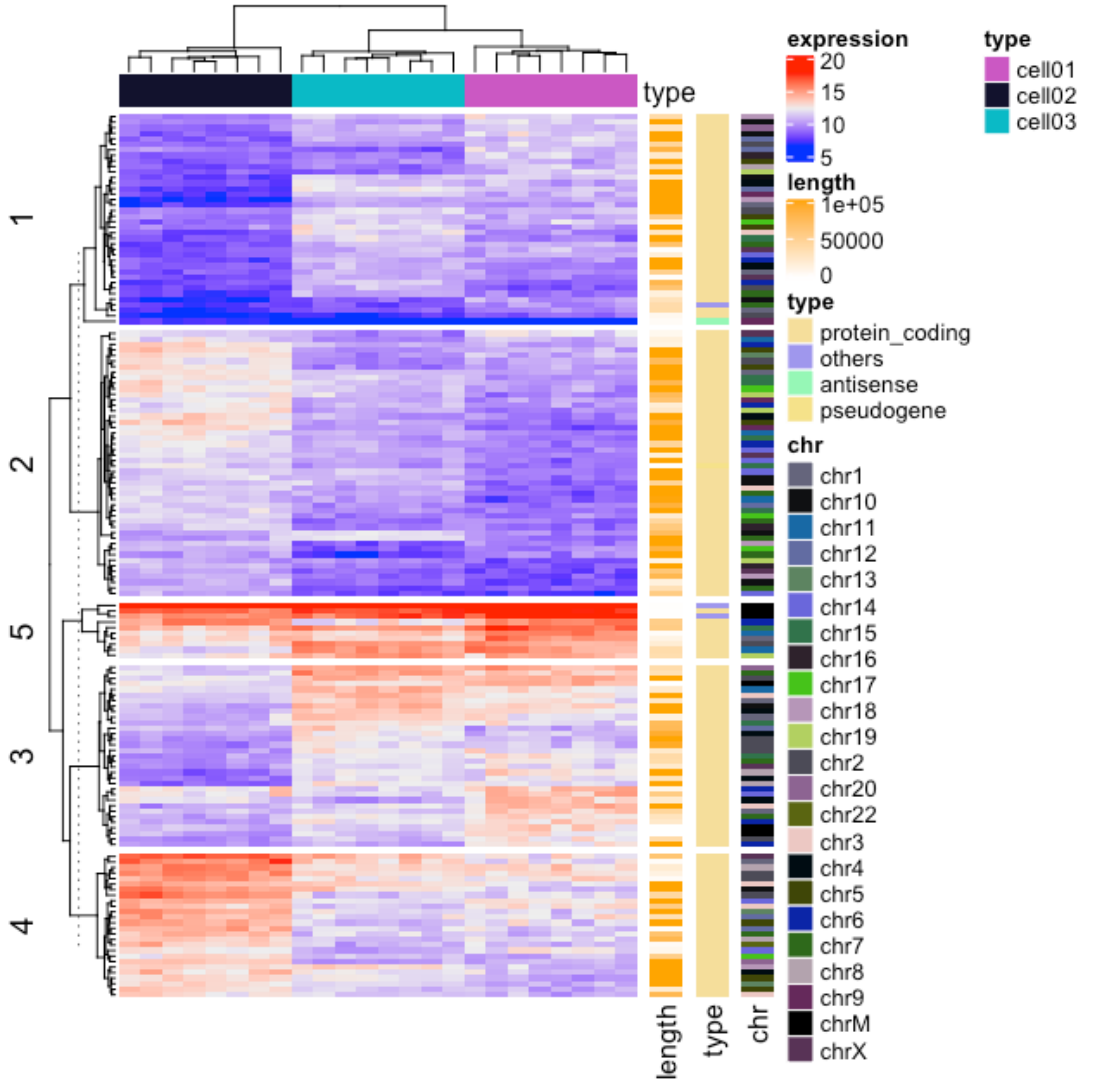
Even more specific:

gene expression

protein expression

no (larger) complexes,
no (smaller) fragments,
and no atoms

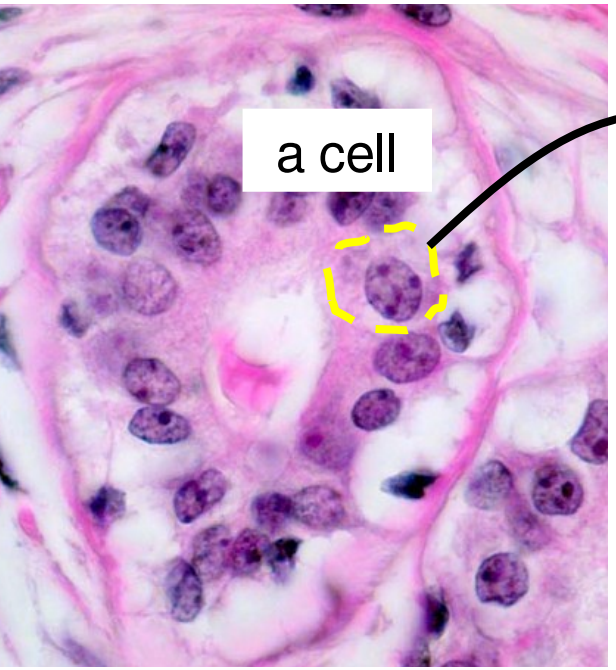
so, many objects are excluded

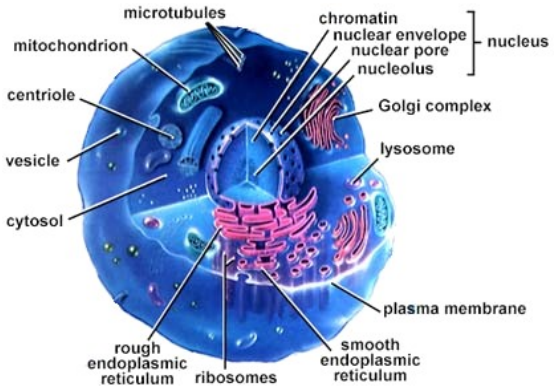


gene expression

https://www.datanovia.com/en/lessons/heatmap-in-r-static-and-interactive-visualization/

Systems biology is highly complex





a model

The human cell has a diameter of app. 10-40 µm - the human body app. 10^{13} cells.

ESTIMATES for the complexity of a *human* cell

About $25 * 10^{9}$ human hemoglobin macromolecules (64 kDa or ku) fit in the volume of a human cell

Likely $>10^{5}$ basic types of macromolecules
DNA, RNAs, proteins, glycans, fragments, ...

More details on models

Biological objects can be described by a logical notation
of properties, rules and states,
often in a mathematical way forming a model of observations.

consider additionally

- A biological object can be investigated
  by means of different experimental methods
  which might or might not conform with a certain model

- Each biological object/process can be described by various models

- The choice of a model depends on the problem, the purpose,
  and the intention of the investigator

- The process of modeling has to reflect essential properties of the system

Model development

What is important to consider?

- Review of the existing publications associated with a certain topic

- What types of data are available for this research question?

- What type of confidence is associated with the data :

  this means, fetch additional information on the creation and limitations of the experimental data (really important)

Working with models - have a concept

- Identify the specific questions that shall be answered
- Build a stringent hypothesis before you start

Implementation of a model

- Select the level of abstraction
  (molecular, cellular, physiological, phenotypical,
  disease related, ...)

- Methodological approaches: e.g. deterministic or stochastic

- Variable types: discrete or continuous

Establish controls for the model, e.g. :

- Robustness / sensitivity analysis
  e.g. test the probability to be able to
  distinguish two different model groups

- Data randomization should show different results

Section summary

You got some insight on

- what kind of idea is behind systems biology

- what might be meant by using the term model

Have in mind

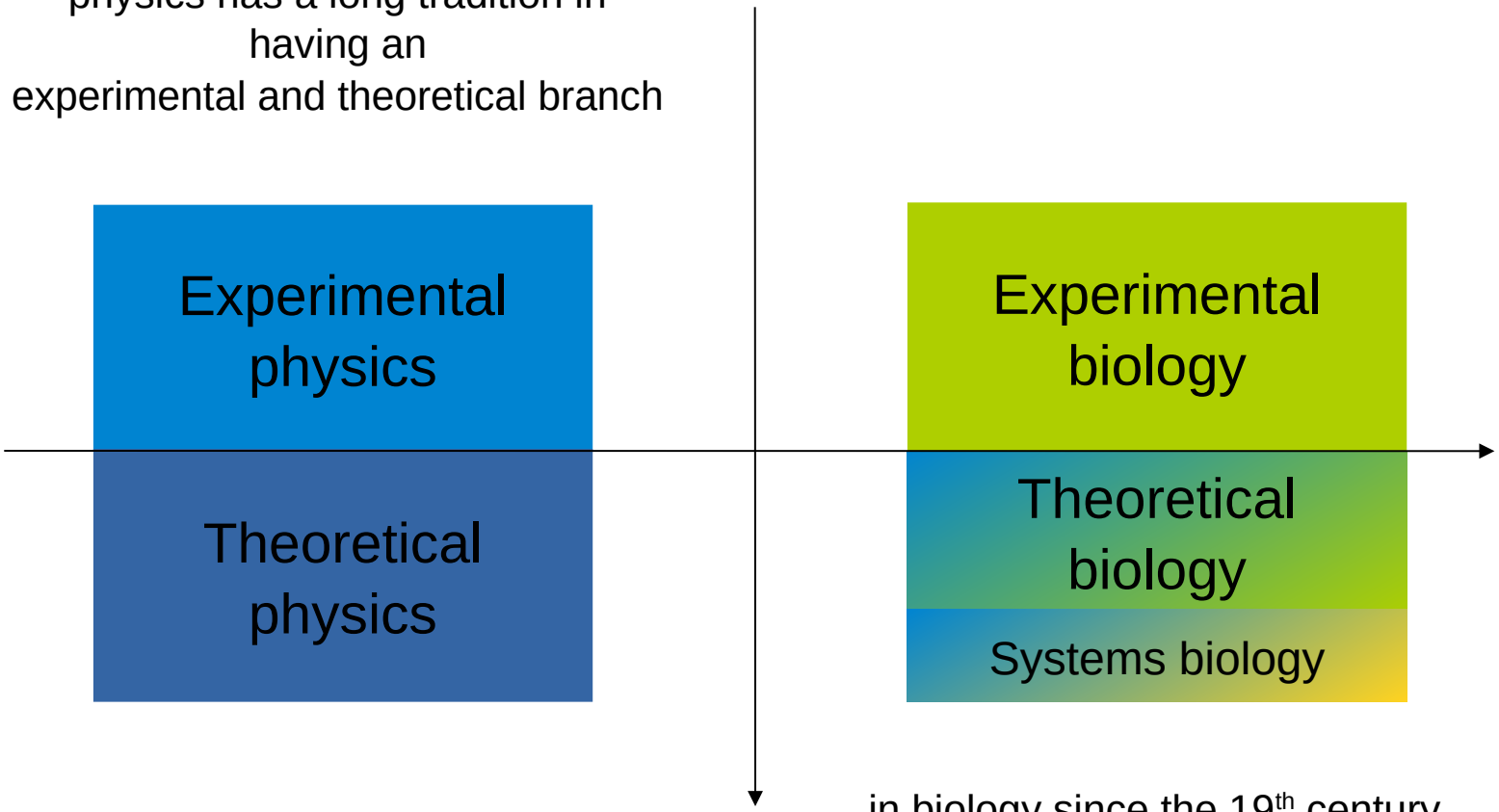
--> A model is the basis of every research question
and
indispensable for doing systems biology

some more notes on

systems biology

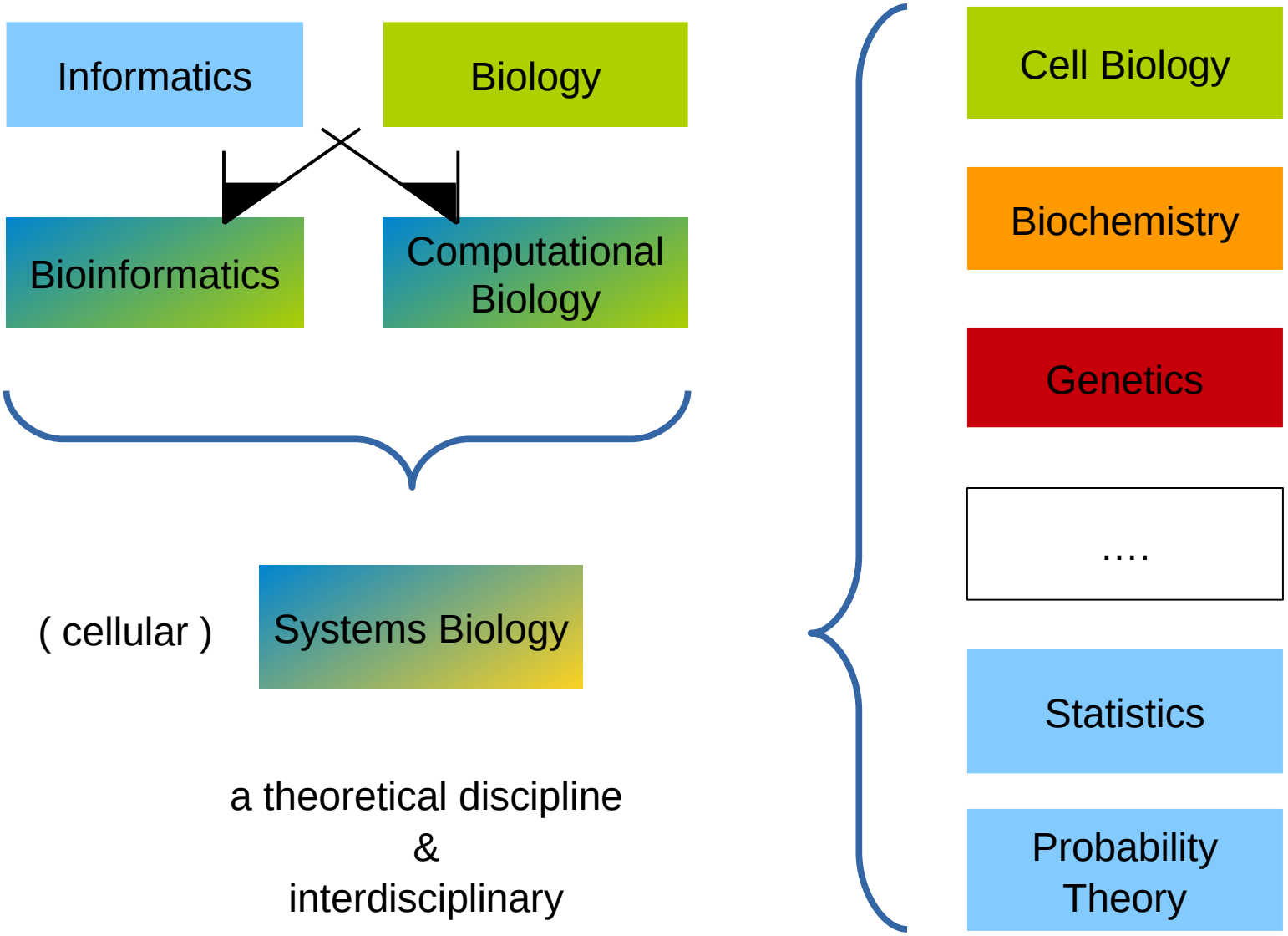
The evolution of systems biology

physics has a long tradition in having an experimental and theoretical branch



in biology since the 19th century the theoretical fields develop more rapidly

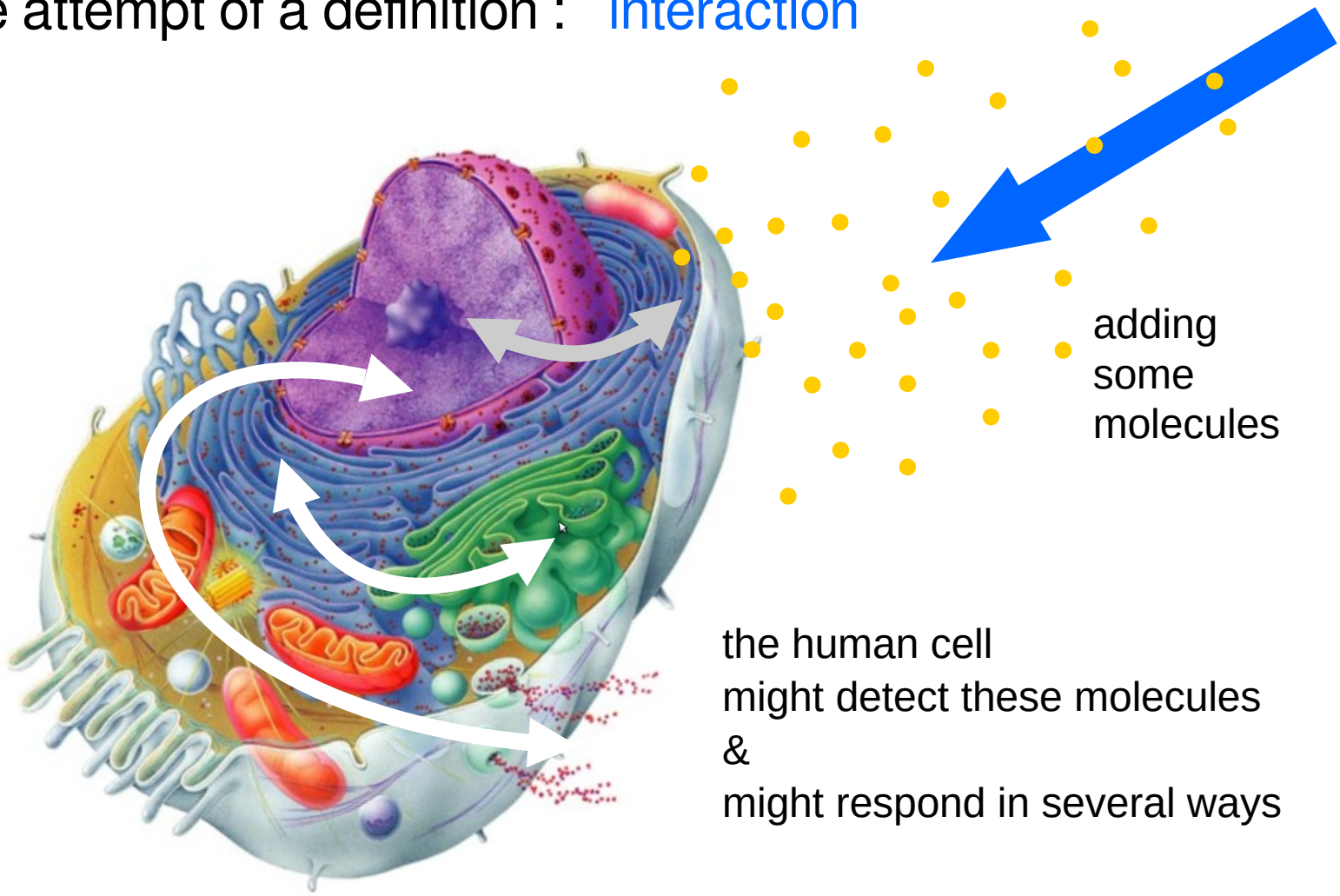
Systems biology - scientific fields



Systems biology

a schematic view

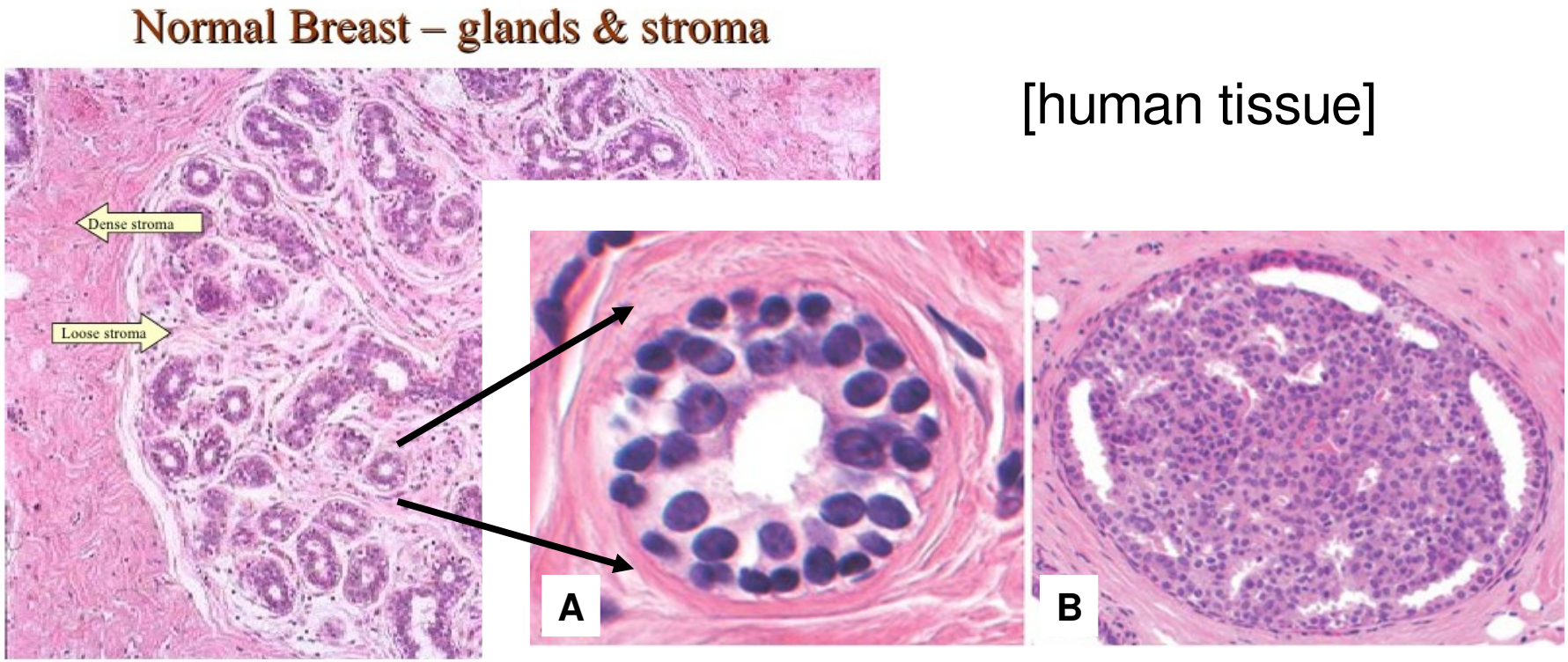
One attempt of a definition : interaction



adding some molecules

the human cell
might detect these molecules
&
might respond in several ways

A microscopic view



[human tissue]

A --> B : systemic change

A – Normal
A normal duct has a myoepithelial cell layer and a single luminal cell layer

B - Epithelial hyperplasia
The lumen is filled with a heterogeneous population of cells of slightly different morphology

A molecular view

again schematic

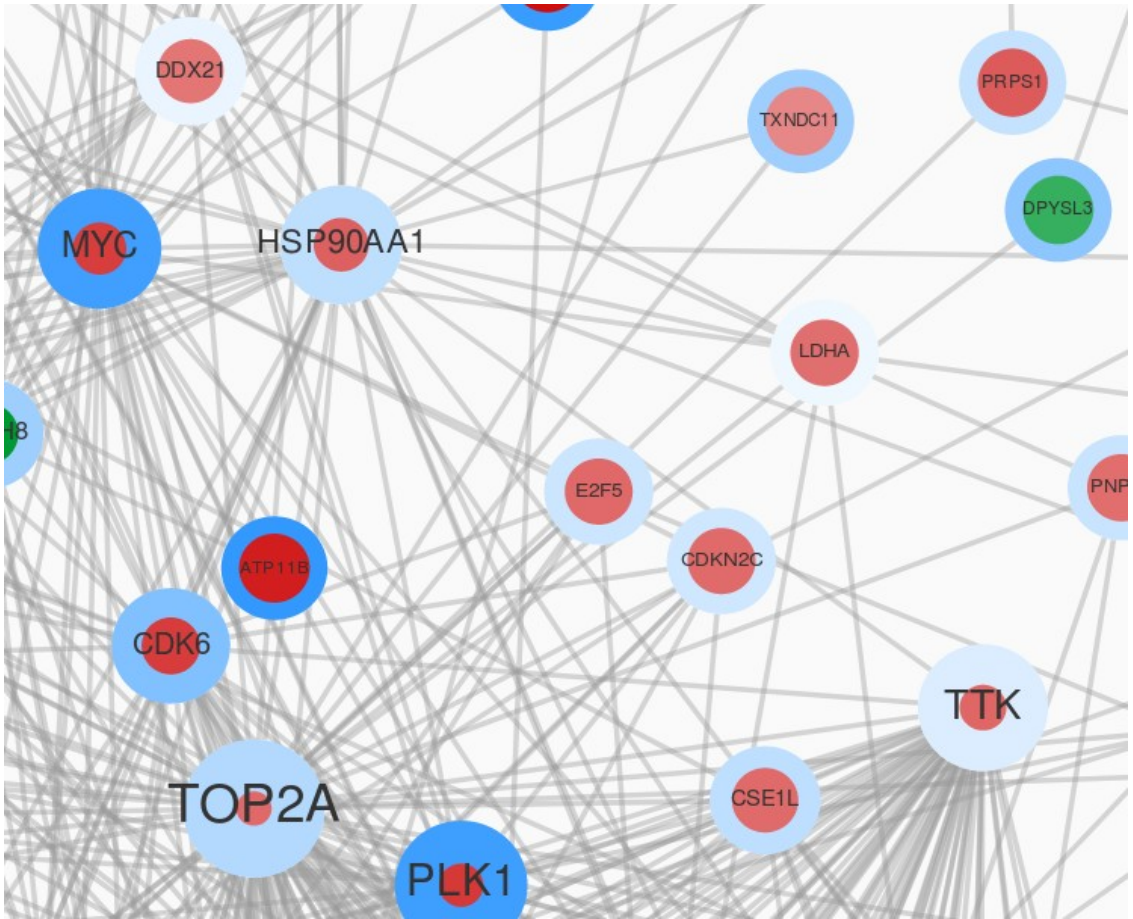
by a graph (c.f. --> 'graph theory')

composed of nodes / vertices and edges / arcs

which visualize

relations

between
parts
of the system

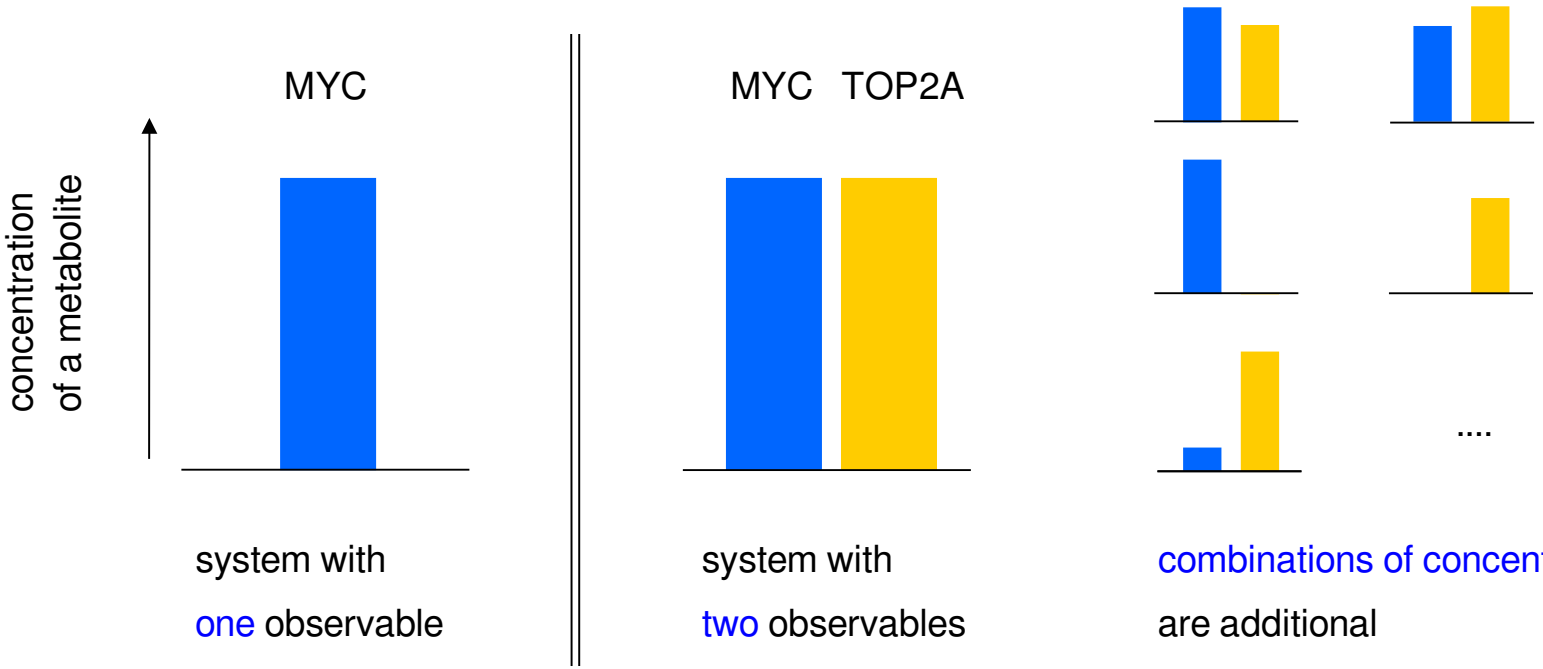


This is leads to a different definition

for systems biology

"The whole is more than the sum of the parts"

gene expression example:



system with one observable

system with two observables

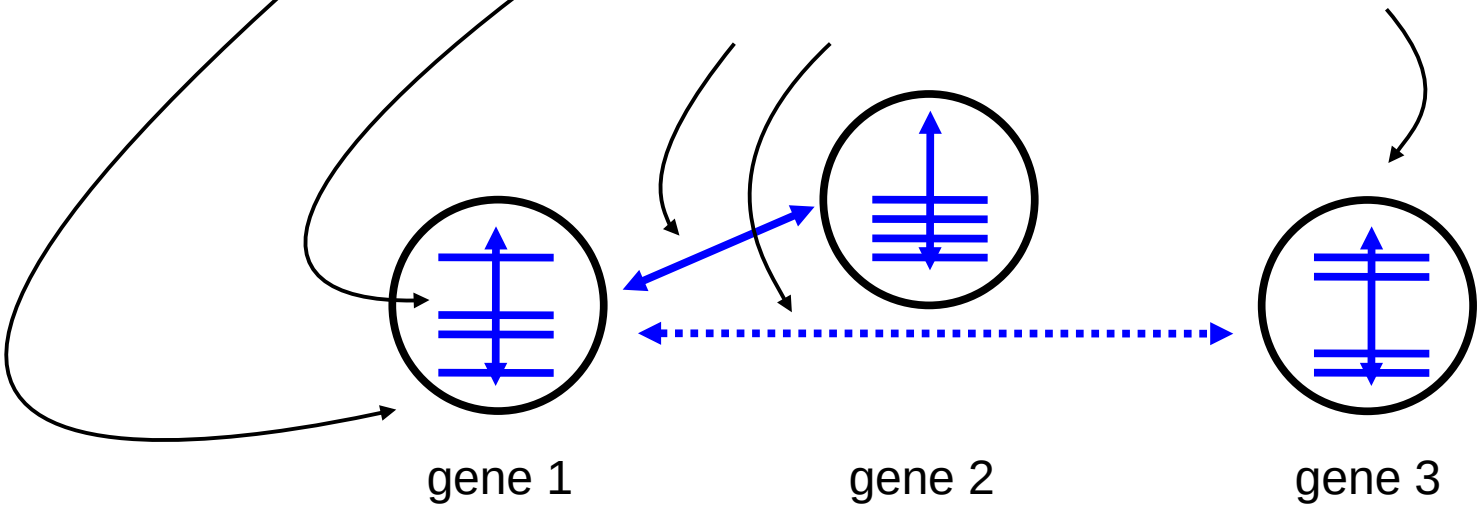
combinations of concentrations are additional information

check molecules in e.g. https://www.genecards.org

Section summary

Systems biology tries primarily to model the dynamic parts of a cell :
the cellular mechanisms

So mechanisms can be **represented**
by nodes (with states)
and transitions between states
and interaction between nodes



further methods useful

in

systems biology

Lingua franca

an elaborated handling of complex systems needs

modeling/ computing platforms

the **language** of the life science community is often **R**

scientists who come from engineering disciplines
tend to use e.g. **Julia**

and those in the physics community
may be more familiar with e.g. **SAGE**

from the perspective of biology

Systems biology

… deals with the analysis of all (known/relevant) interactions between the components of a cellular system

… tries to explain and to predict cellular behavior

… emerged with the appearance of the high-throughput technologies

massive parallel measurements of molecular observables

High-throughput technologies

- Genome-, transcriptome-, **sequencing**, ...

you already heard about that in the last lessons ...

- Tissue-, peptide-, protein **microarrays** ...

Characterized by a highly parallel measurement of concentrations or numbers of system compounds

appearing or disappearing or changing due to different physiological conditions ...

Section summary

So, high-throughput technologies

are measuring states of the system

and this data will be analyzed

by a computing platform & language

More details on interactions

- Biochemical reactions between molecular factors
- Physical binding (without chemical reactions)
  to establish a molecular complex, - a membrane, etc.

Those interactions are forming a **biological network**
which can be analyzed by different **network models**,

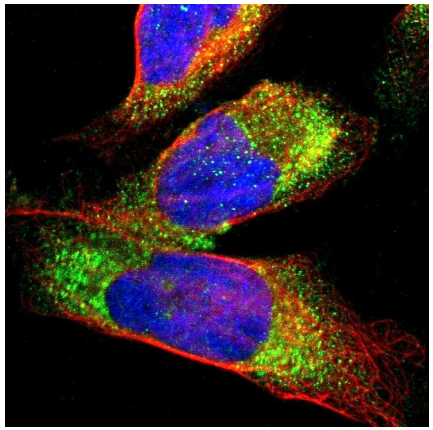
e.g. :

reaction networks (Petri nets ...)
looking on properties like reaction kinetics, stoichiometry, ...

co-expression networks
comparing expression trends over time and between genes

Mid-term summary

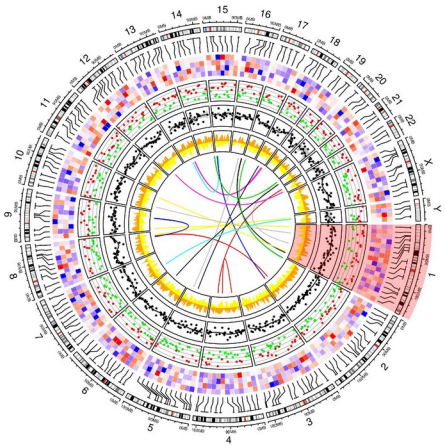
Disassembling a system into components



Assembling components to a model system

Components Biology

HT analytical chemistry:
- genomics
- transcriptomics
- proteomics
  etc.



Systems Biology

Integrative analysis:
- bioinformatics
- computer simulation

--> both approaches are necessary for a mechanistic understanding

concept from the book B.O. Palsson

Main section

Introducing some basic graph theoretical ideas
discussing measurement options
pointing to some limitations
showing a real world experiment

Presenting an expression analysis:
protein co-expression

More methods

- single cell sequencing
- microRNA - mRNA networks
- Petri nets
- gene co-expression networks

Outlook on further topics - systems biology is huge ...

What is a network ?

Abstract definition: interconnected nodes

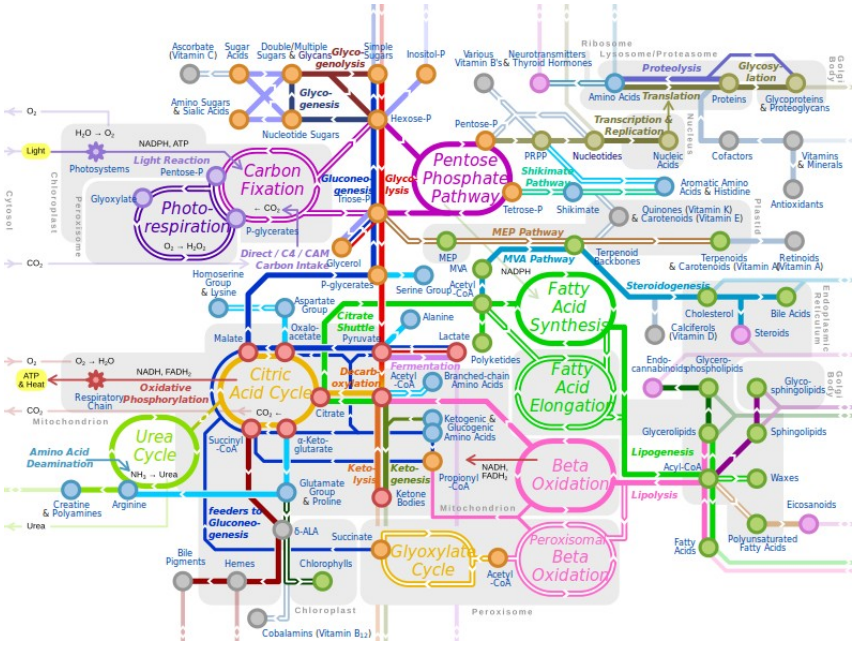
'interconnect' means : sharing something

e.g. inter-/ or changing information or physical objects

in biology, e.g.

metabolic reactions

to transport energy
to build macromolecules
to degrade macromolecules
to transport information



https://en.wikipedia.org/wiki/Metabolic_pathway

Different networks - different perspectives

Protein-protein interaction networks (PPI, sometimes also peptide-peptide interaction)
primary network - e.g. transcription pre-initiation complex, cell structure forming, signaling

Metabolic networks
primary network - e.g. databases : KEGG (Japan), ExPASy (Swiss) Biochemical Pathways

Genetic interaction networks
meta network - e.g. observe pattern of mutations and associate with disease types

Gene / transcriptional regulatory networks
primary network - cellular control on structure and function, e.g. cellular differentiation, morphogenesis

Cell signaling networks
primary network - cell communication plays a role in e.g. body development, immunity

Gene / protein expression networks
meta network - observe expression pattern and associate e.g. with disease function

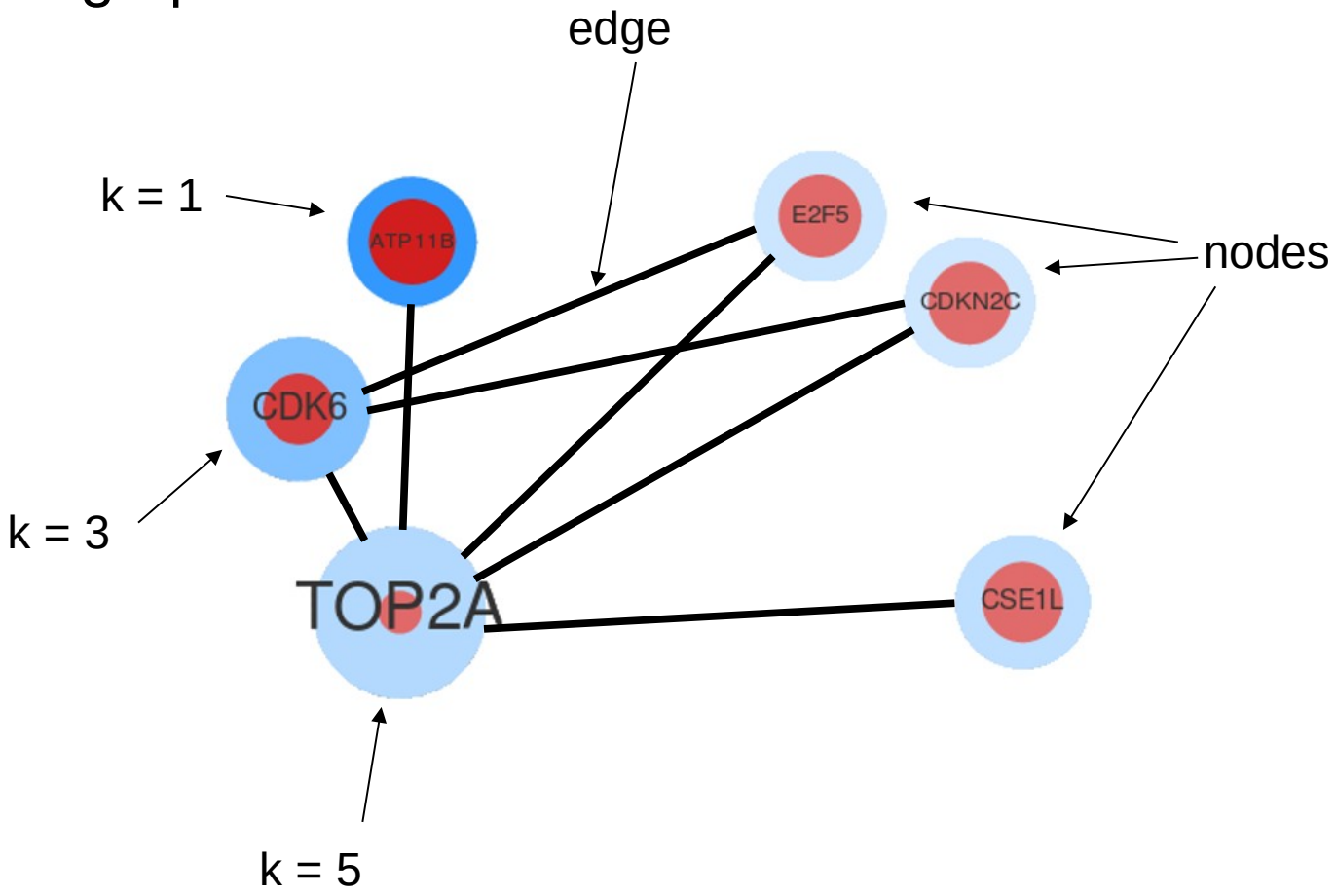
Neural networks - a primary network or in the case of AI networks a meta network

Ecological networks - meta network - e.g. ecological interactions between species

....

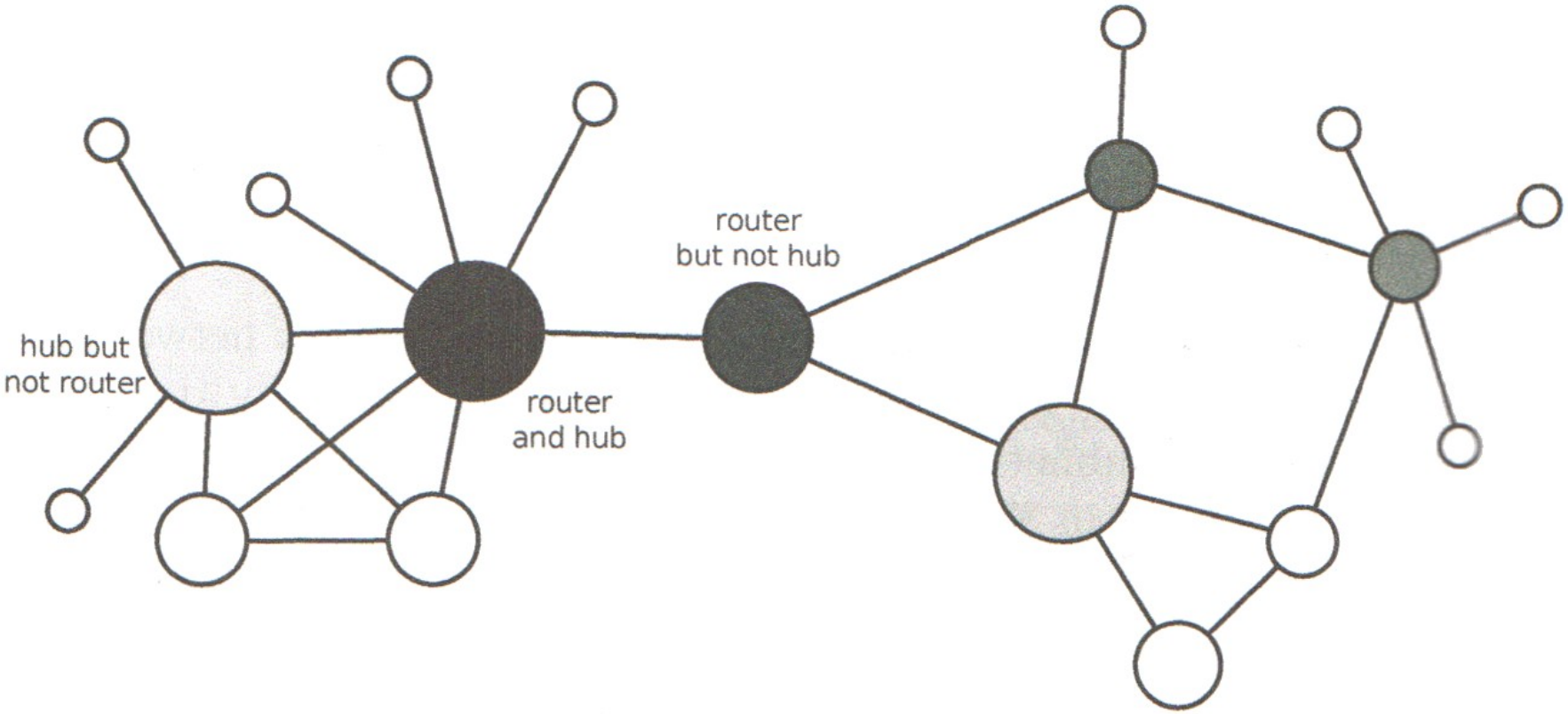
Some details on networks means some details on graphs

a simplified graph

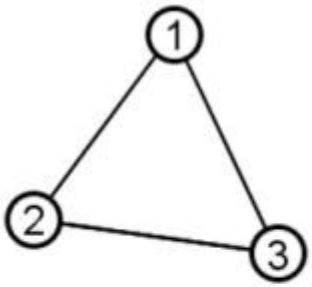


k := node degree

Hubs & Routers



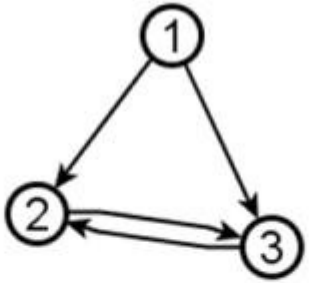
Directed versus undirected graphs



Undirected graph (V_1, E_1)

$V_1 = \{1,2,3\}$

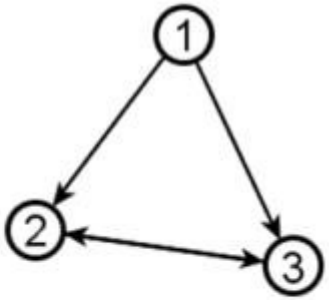
$E_1 = \{\{1,2\},\{2,3\},\{3,1\}\}$



Directed graph (V_2, E_2)

$V_2 = \{1,2,3\}$

$E_2 = \{(1,2),(2,3),(3,2),(1,3)\}$



Easier way to draw

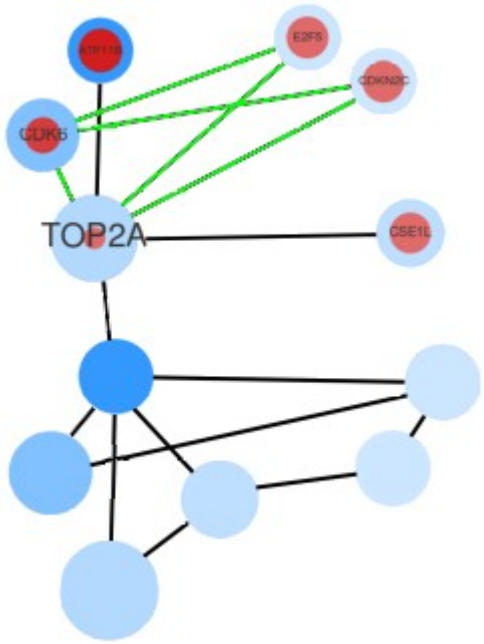
directed graph (V_2, E_2)

V := vertex / pl. vertices (nodes)

E := edges

Network properties

Node degree distribution
number of direct neighbors
per node



Subgraphs / motifs

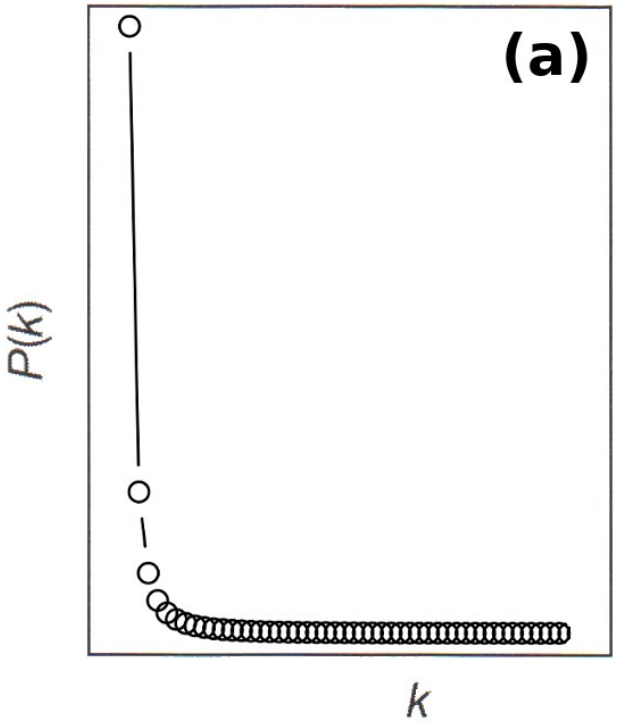
Betweenness-Centrality
BC: number of shortest path
through a node (bridge function)

Assortativity
high degree nodes directly
connected to other
high degree nodes

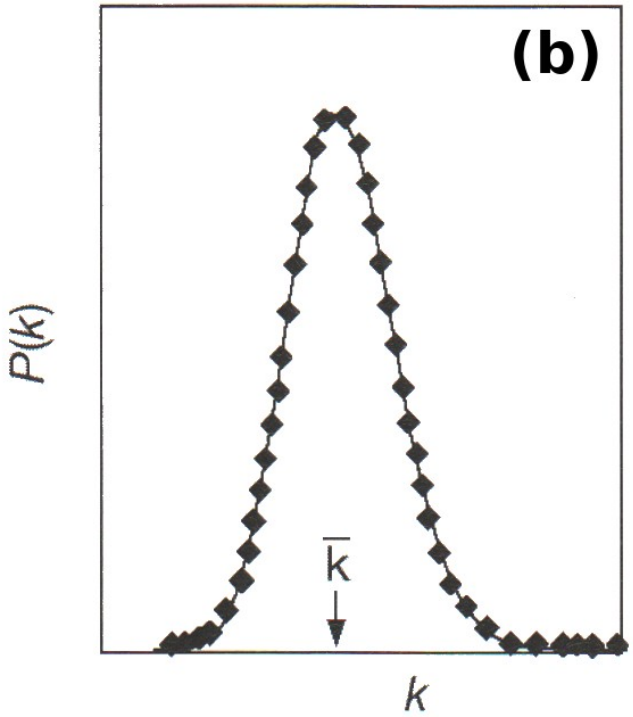
Real world 'node degree' distributions

k := observed node degrees

power law distributed



biological networks



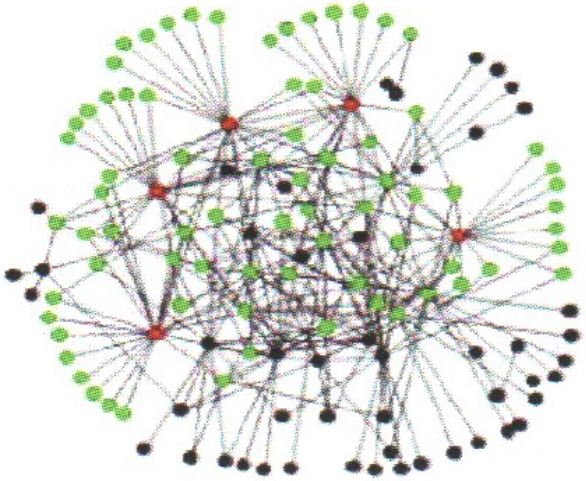
other networks

Poisson like distributed

Shape of the network

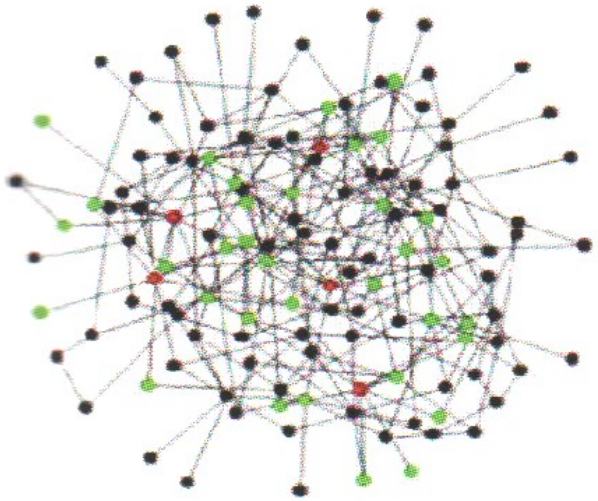
Power law or

Scale-free network



biological networks

Random network

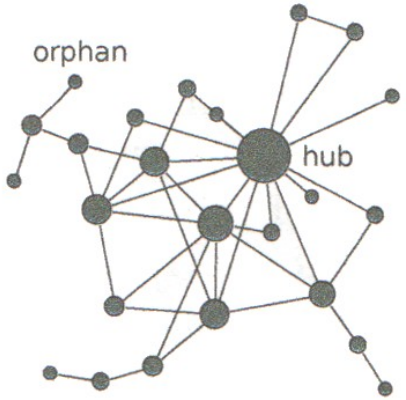


might be useful sometimes as a control

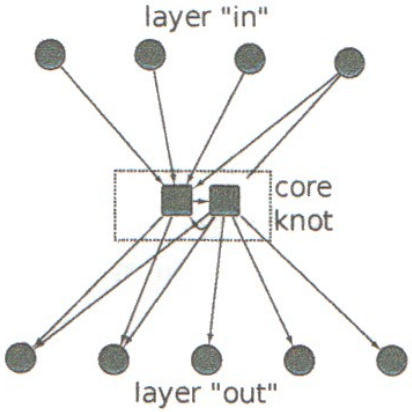
Network types

Power law or

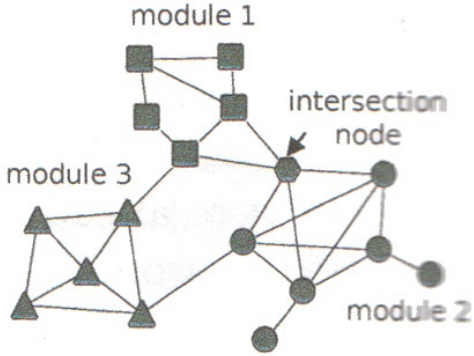
A - scale free



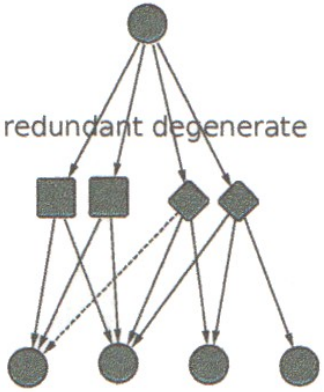
B - layered



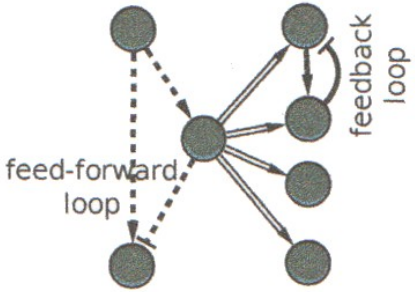
C - modularity



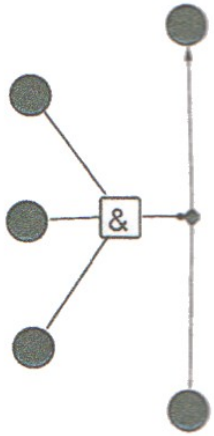
D - redundancy
overlapping diversity



E - motif - subnetwork

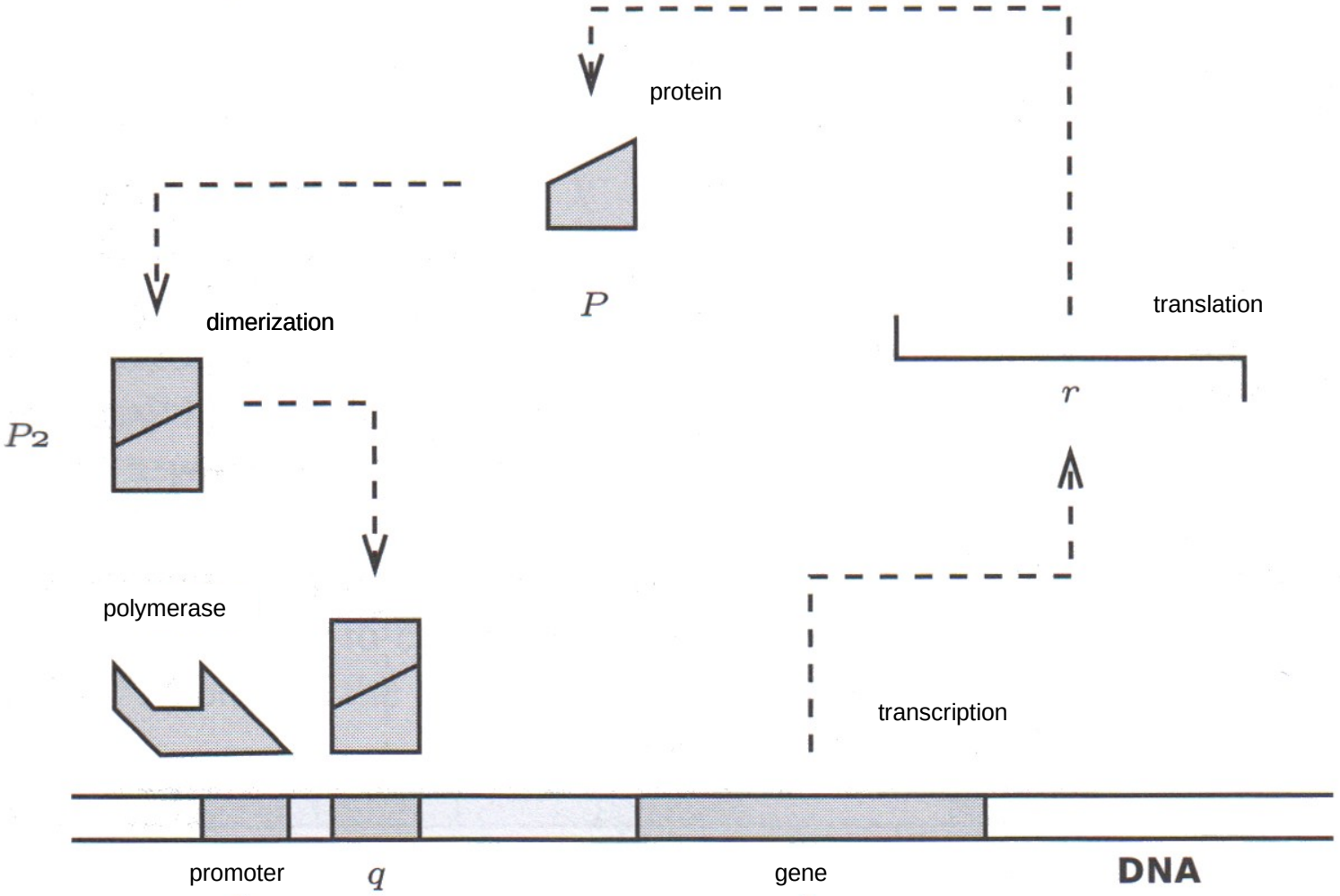


F - cooperativity

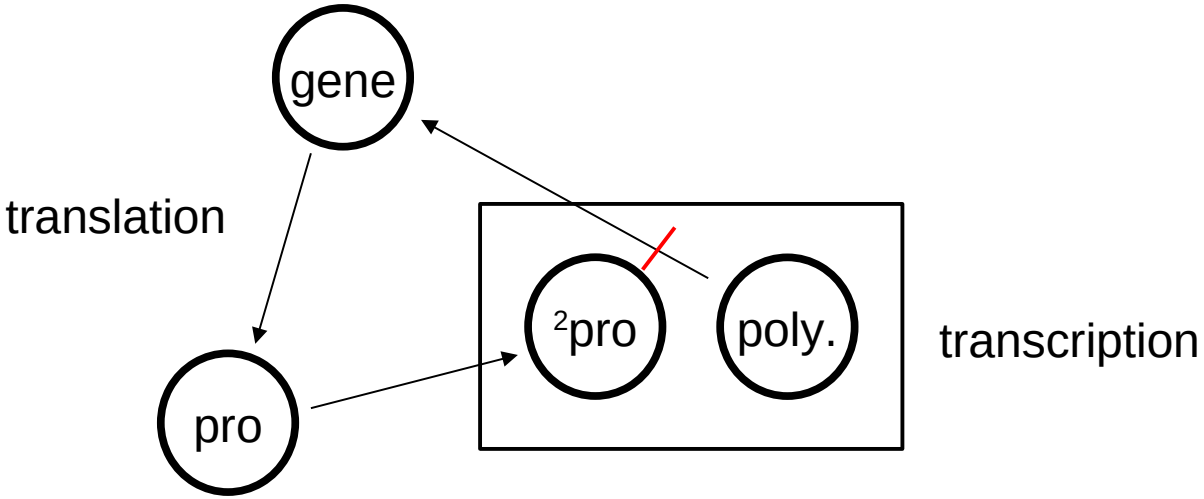


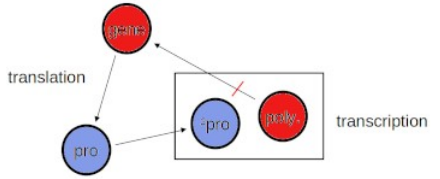
Join graph theory with biology (I)

Prokaryotic auto-regulatory feedback loop.



Translation into a graph



1


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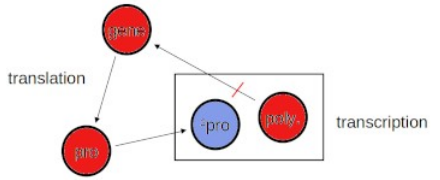
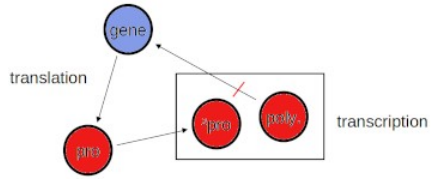
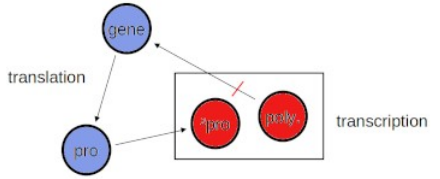


3


4


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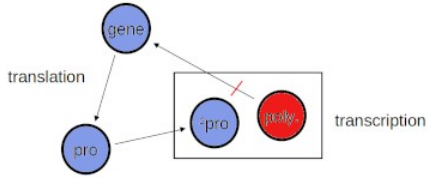
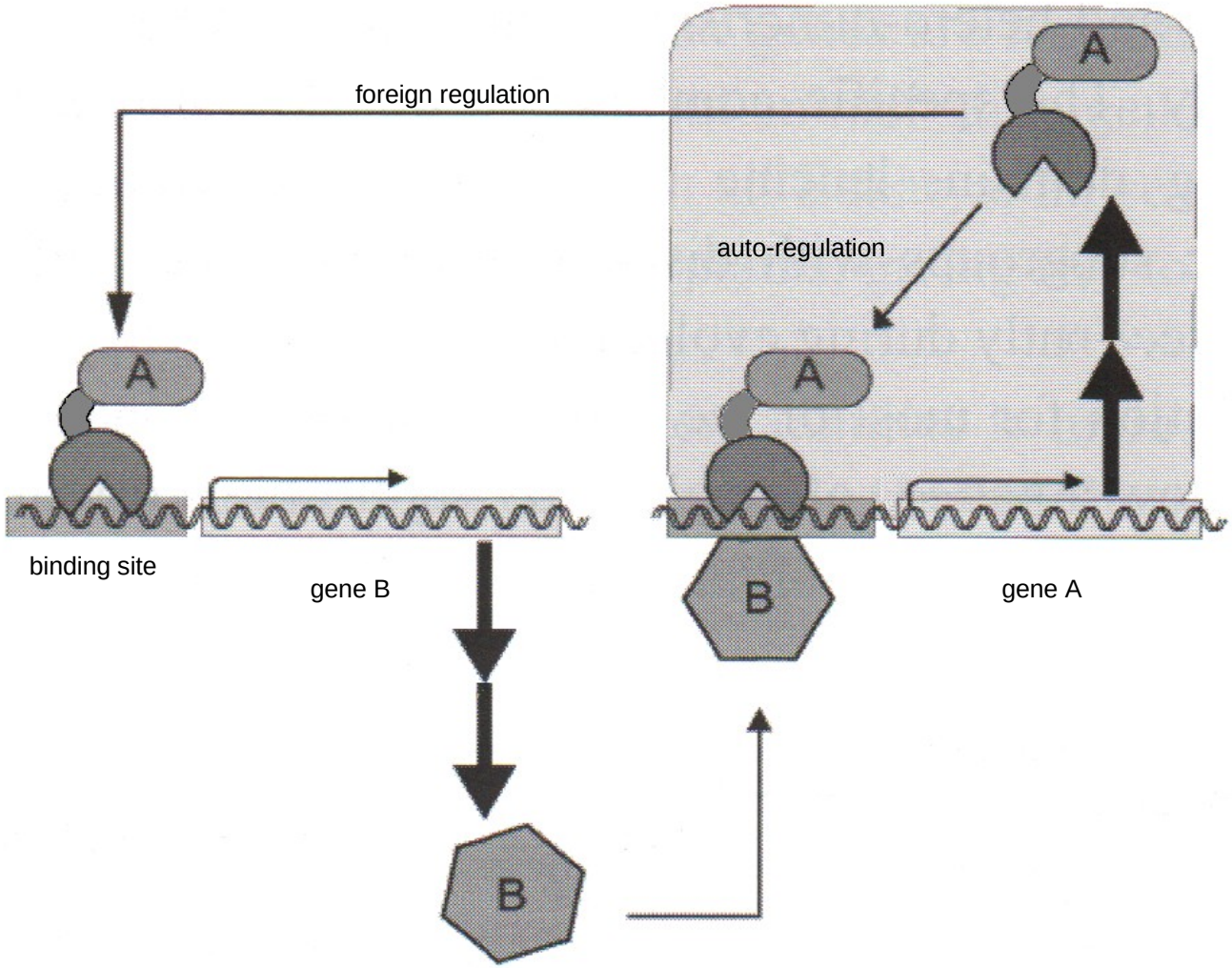


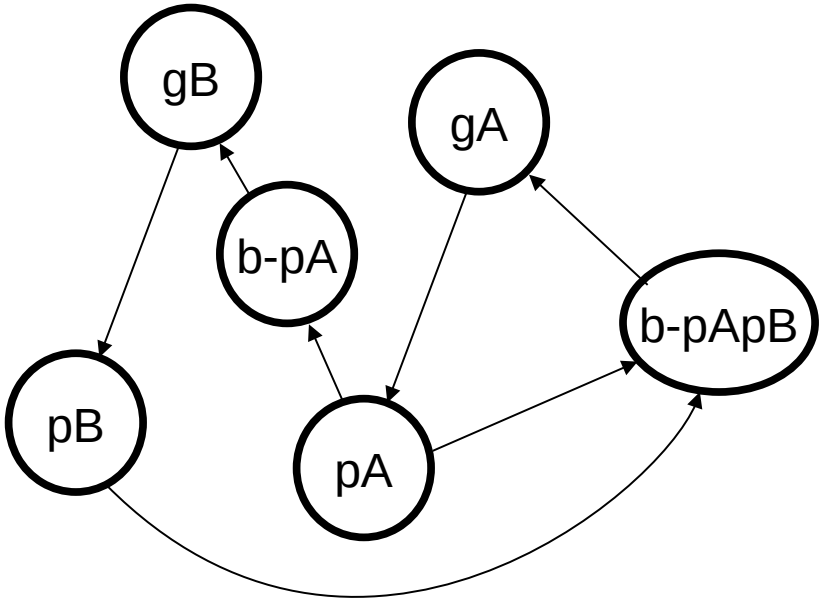
red: high expression
blue: low expression

Join graph theory with biology (II)

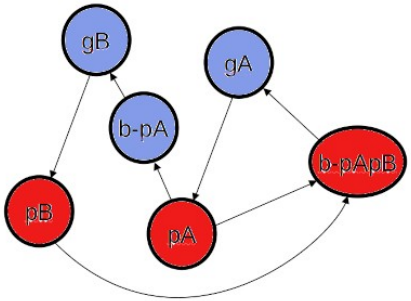
Example of an eukaryotic transcription factor activity.



Translation into a graph

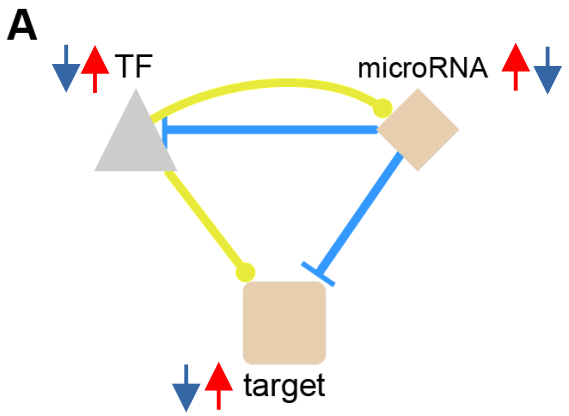


only the start situation is shown here



red: high expression
blue: low expression

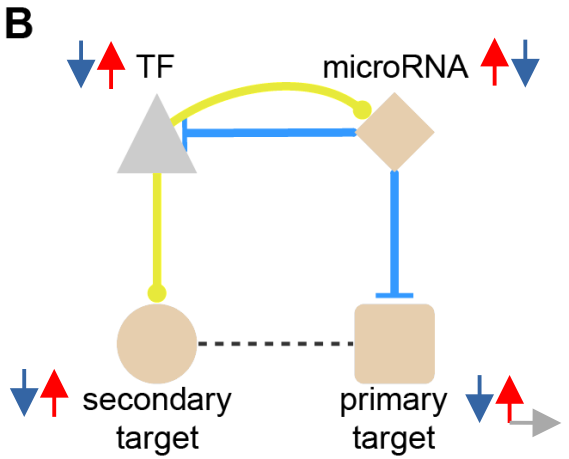
Research example



Research question:
Which motif **A** or **B**
is more relevant in
our situation of interest ?

TF : transcription factor

Target : gene



measured : mRNA + microRNA expression

filtering with database information:
TF- + microRNA targets

PLoS Comput Biol. 2013;9(8):e1003210. doi: 10.1371/journal.pcbi.1003210

Section summary

- we have learned some basics on the cellular networks
- we have learned some facts on graphs, motifs and the visualization of models
- we translated biology into graphs and vice versa

Measurements

The basis for calculating networks

is qualitative and/or quantitative information

on systemic properties
which are interaction information
or could be interpreted as such

so, we need measurements ...

Protein expression measurements

The chosen method:

Immunohistology

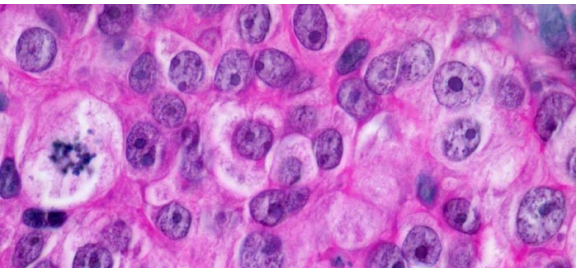
means, we creating ultra thin sections of a frozen
or paraffin embedded tissue sample

these sections will be stained:

all sections:
with a stain for the tissue structure

each individual section:
with a stain specific only for the selected protein

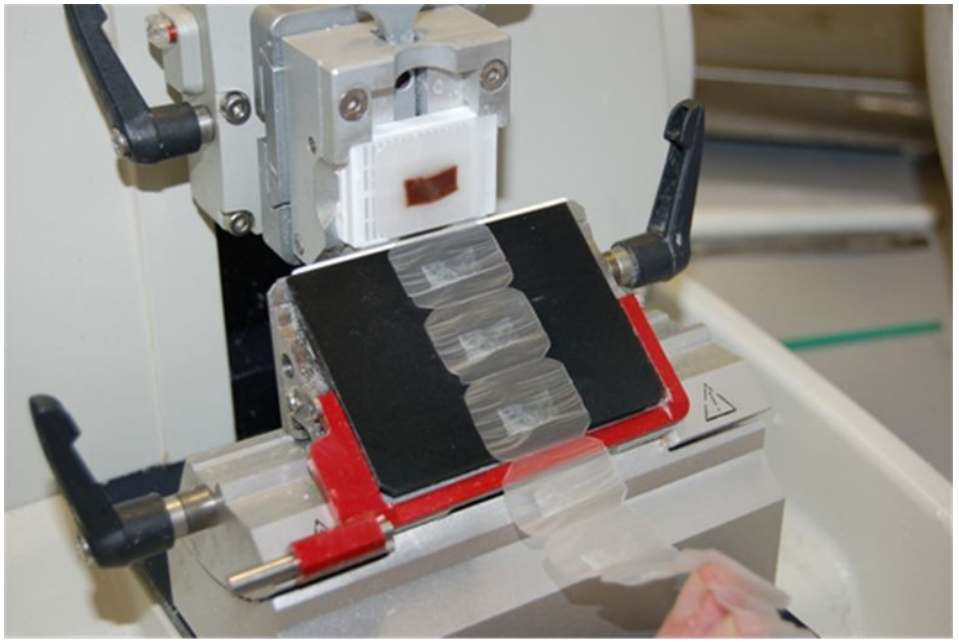
Immunohistology - create sections



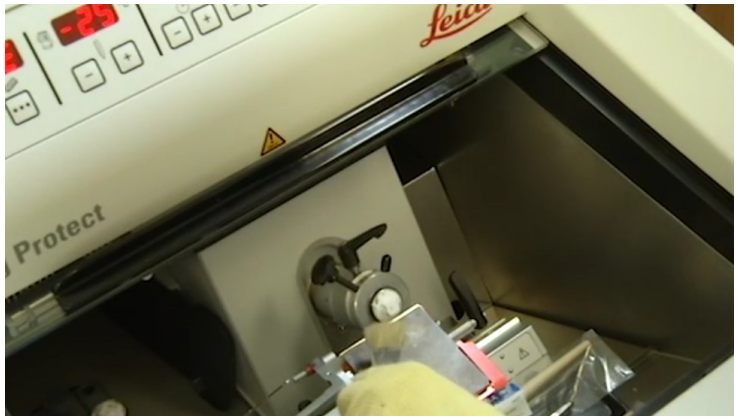
sections - approx. 4 µm thick

and an area between 1 mm^2 and 1 cm^2

Microtome



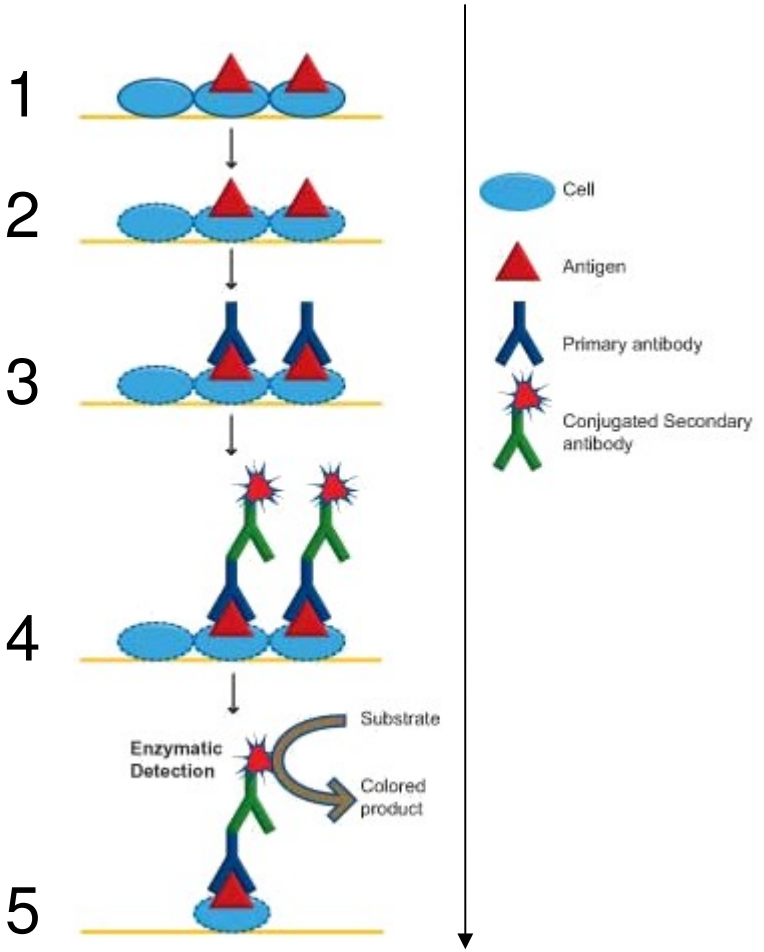
Cryotome



How to stain these sections ?

- H&E stain is for showing tissue structure

- Immunostaining is to visualize specific macromolecules by using antibodies directed against these molecules

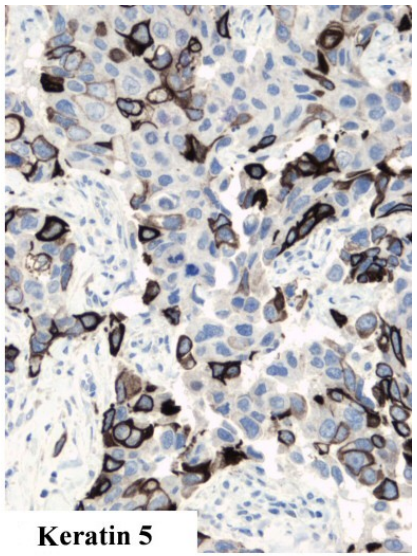


http://www.abcam.com - modified

How to measure protein expression ?

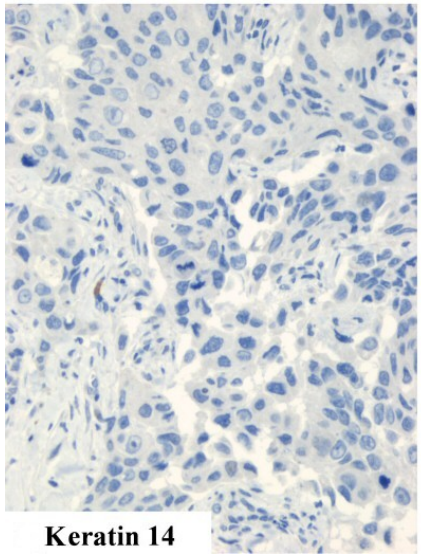
basal
breast cancer

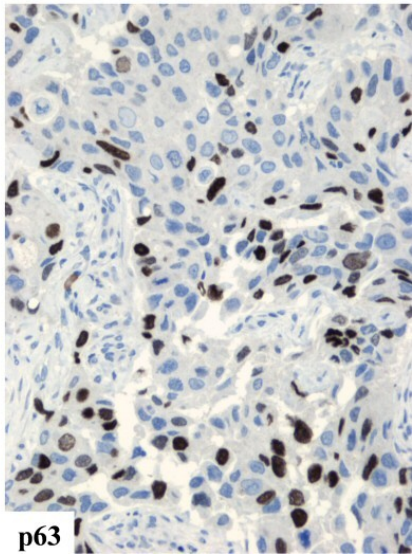
K5/p63 positive
K14 negative



2

0





2

One way is
to count total cells
in a certain sector,

note down positivitity,

note down the strength of
the staining per cell,

and calculate the final
score value

The result for each sector
is a single number ranging
e.g.

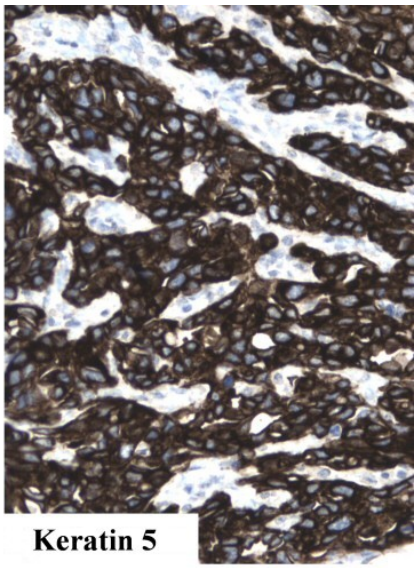
from 0 (negative)
to 3 (strongly positive)

Modern Pathology 2005 Oct;18(10):1321-8

It might look different for other sub-types

basal
breast cancer

K5/K14 positive
p63 negative

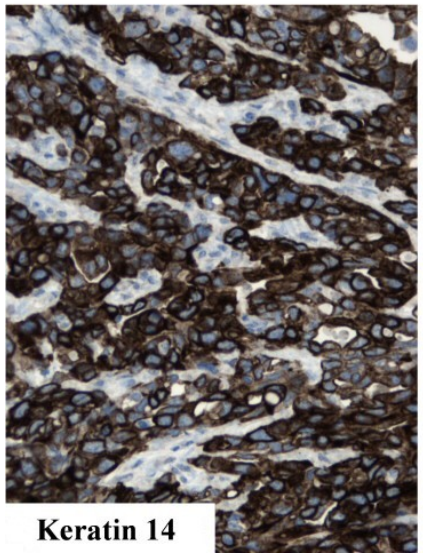


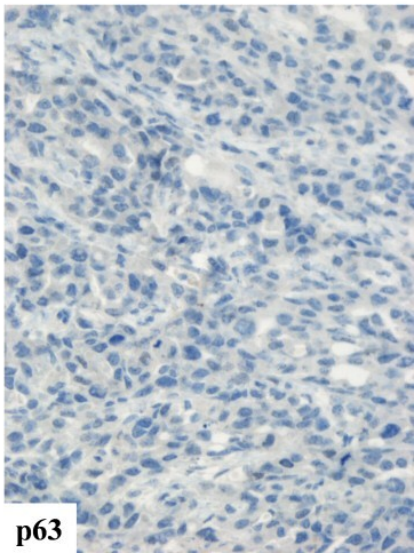
3

which represent almost 9% of invasive ductal breast cancers

mostly aggressive
hormone receptor negative
grade III tumors

3



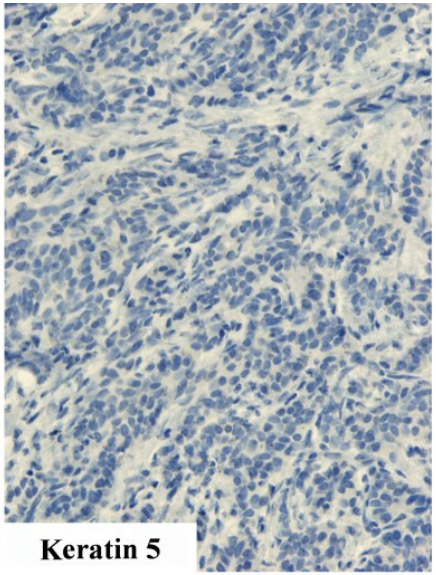


0

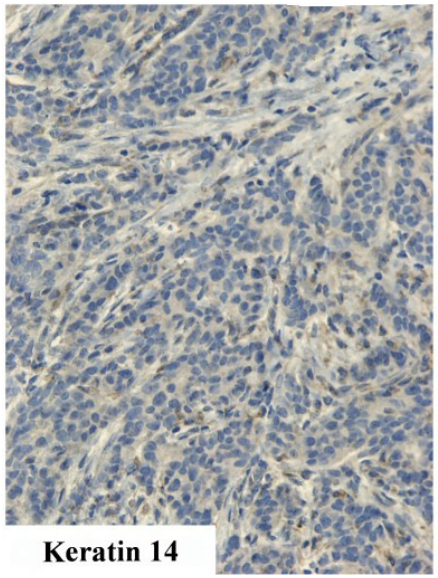
Another cancer subtype

basal
breast cancer

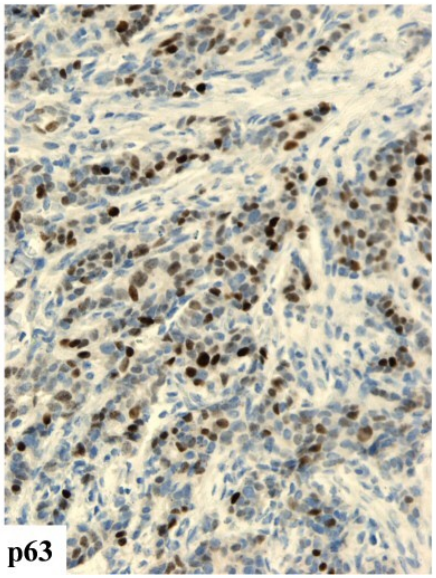
p63 positive
K5/K14 negative



0



0



1

Transcription factor p63-positive tumors are rare

and

showed in this case
no overlap to

K5/K14-positive tumors

Gene expression measurements

Pick a piece of tissue which owns predominantly a certain cell type of interest (cells of interest > 70 %)

Dissolve the tissue and separate the molecule class of interest

Take appropriate technologies (RNAseq, expression microarrays) to generate signals of expression strength

Drawback in this case:

- loss of information (spatial information, morphology)
- cell type mixture of unknown composition ...

Section summary

- we have learned some basics on
  protein measurements (immunohistology)

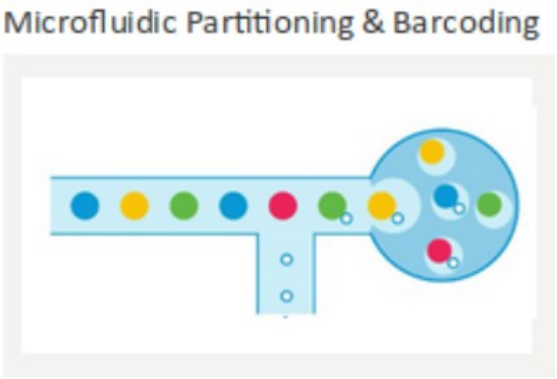
- and conventional mRNA measurements

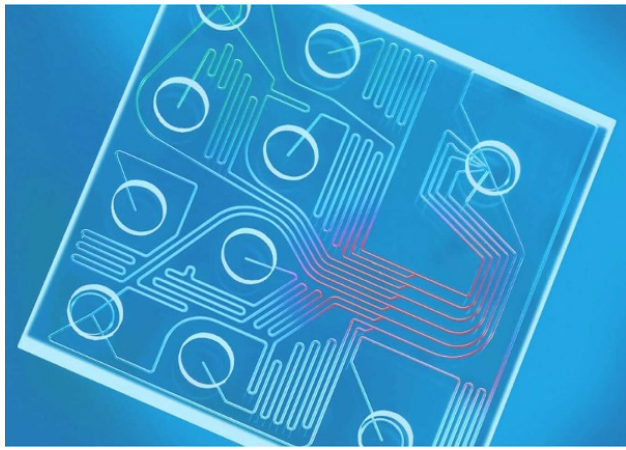
Advanced methods: Single cell omics

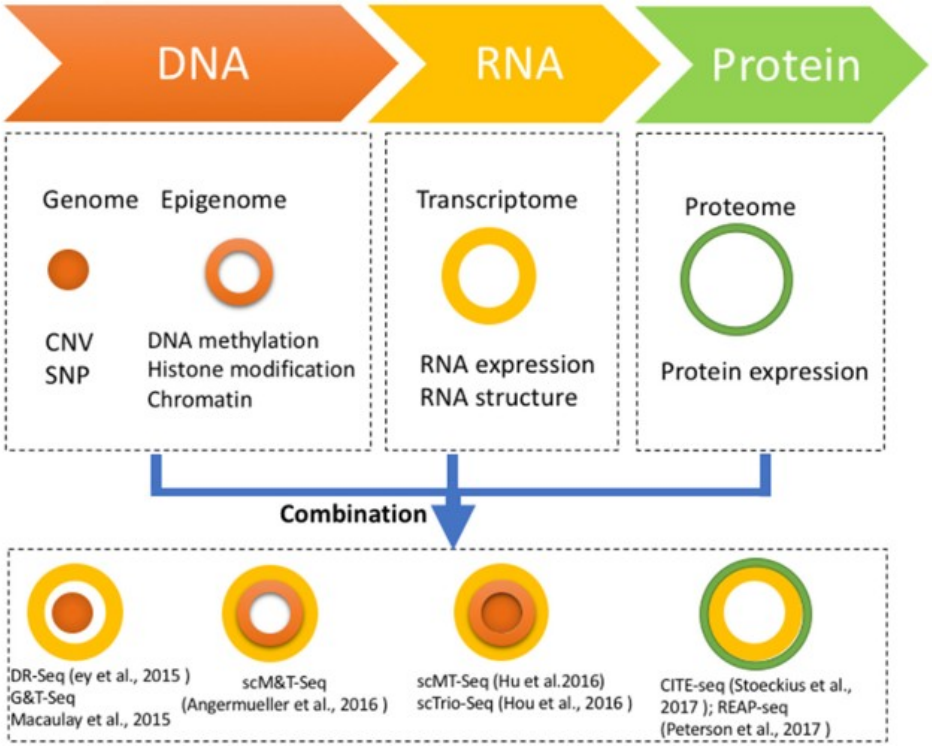
Separate cells,

and measure the expressom

and further features **by sequencing**



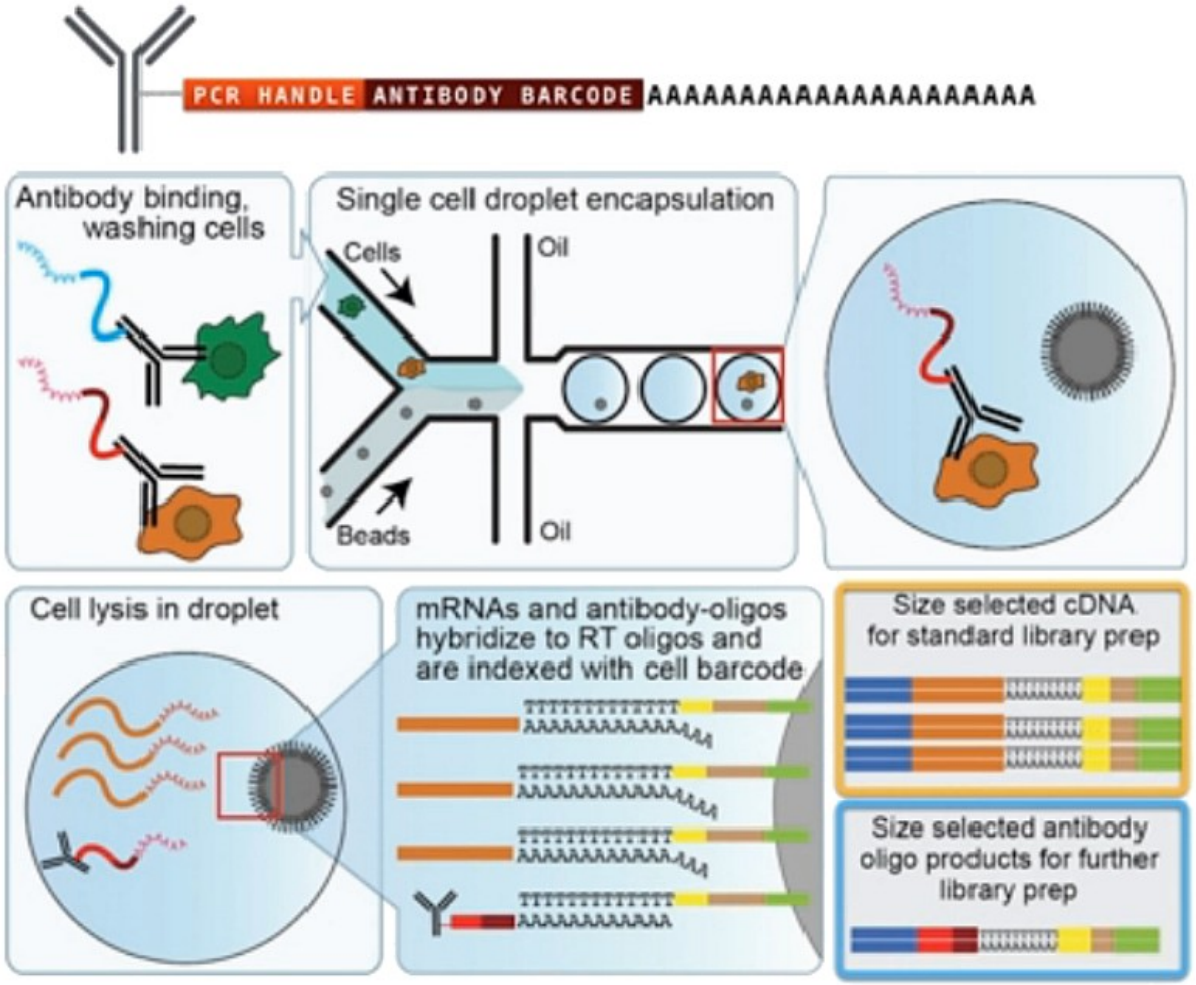




Youjin Hu et al., Frontiers in Cell and Developmental Biology, April 2018, Vol 6

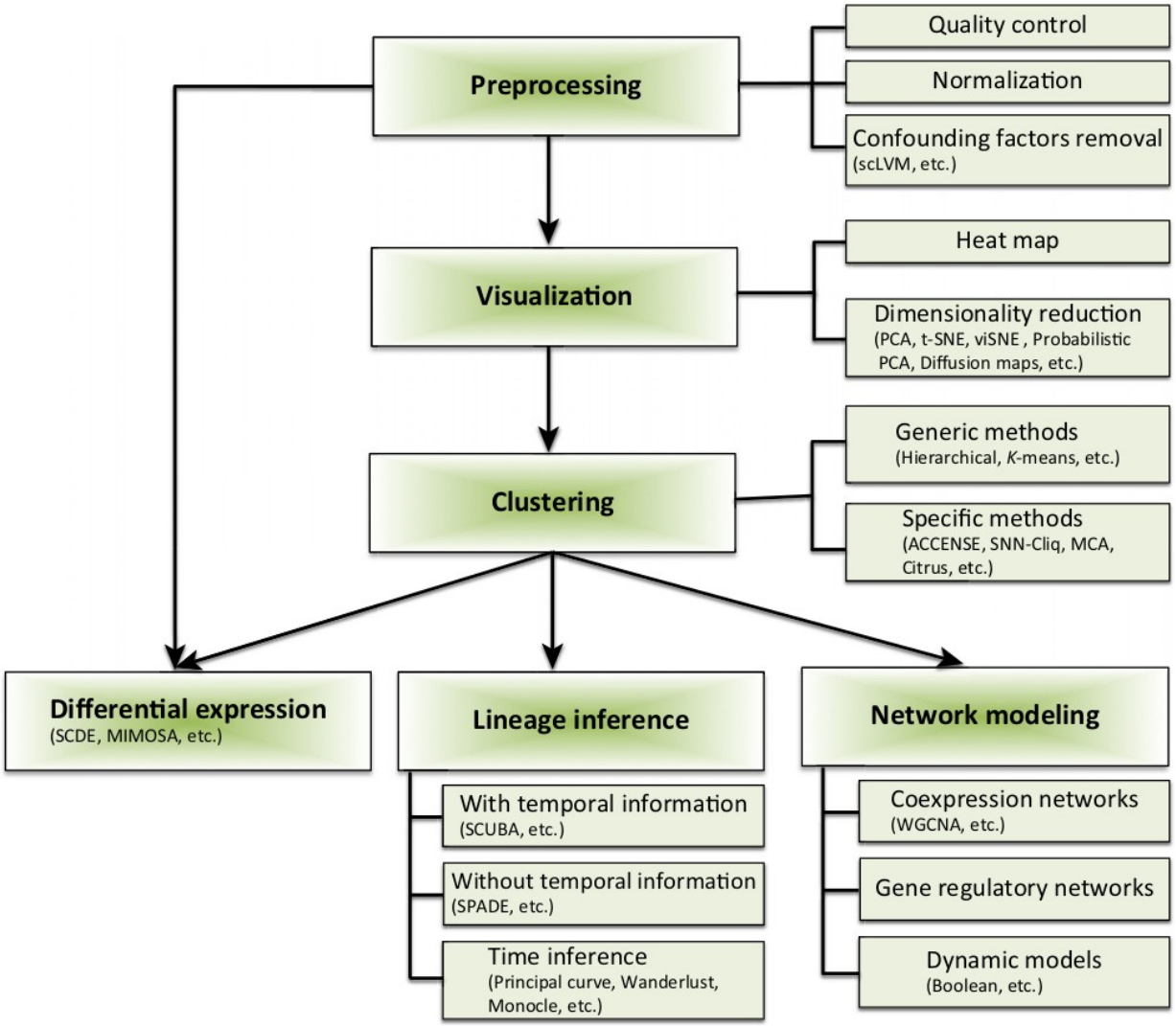
Protein detection by scRNA-seq

cellular indexing of transcriptomes and epitopes



Stoeckius et al., Nature Methods, 14(9), 2017

Flowchart : Single-Cell Data Analysis



Saadatpour et al., Trends in Genetics, October 2015, Vol. 31, No. 10

Measurement summary

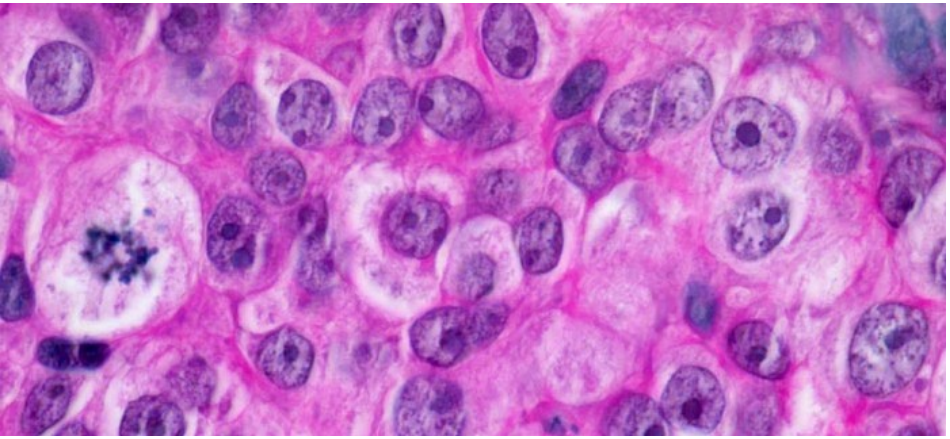
Every method has its limitations
be aware of that, be critical on the quality of your lab results

Translating measurements into data is an important step
and has again a big impact on the results

NOTE: Like in *laboratory experiments* also
theoretical experiments usually termed '**analysis**'
need controls
to verify the stability of the generated results

Drawing good conclusions is bound to careful considerations and high data quality

A co-expression example



invasive ductal carcinoma
HE stained

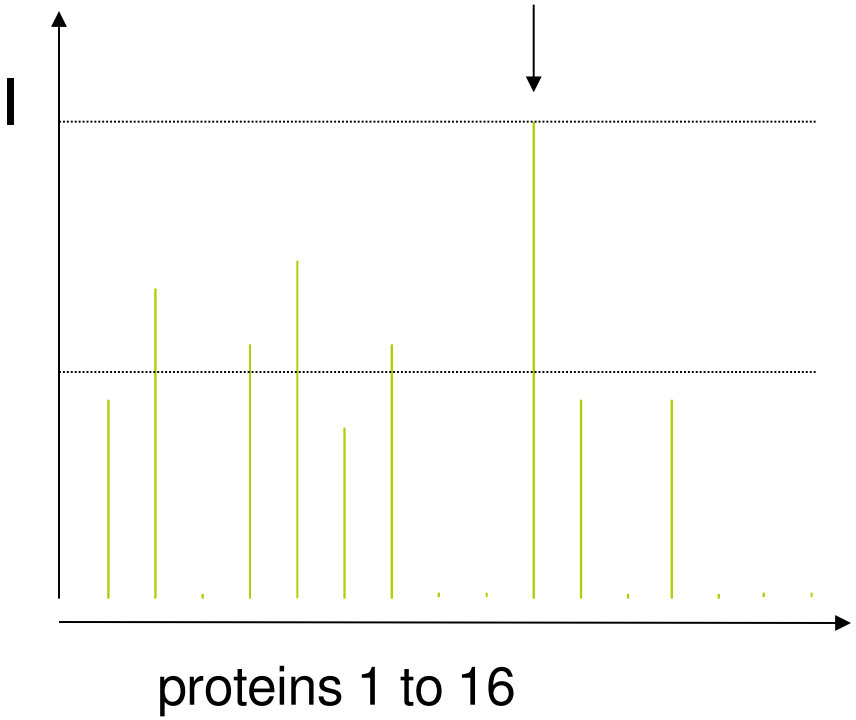
One physiological situation

Objective

analyze molecular **dependencies**
based on **one** condition

What to measure in this example ?

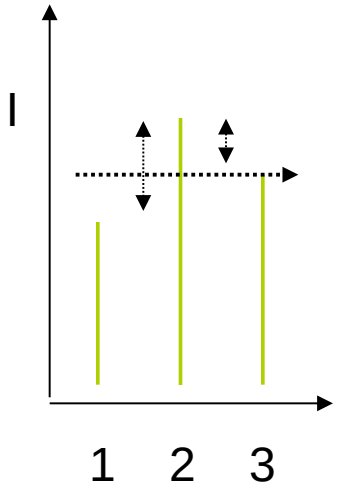
16 different proteins and their expression



one patient sample
of a tissue with
ductal invasive carcinoma

--> we measure
a pattern of 16 protein
expression values

How stable is the measurement ?



If we have one measurement,
we own some uncertainty
that the next measurements is exactly equal

do at least 3-5 replicate measurements
more is better

NOTE:
there are statistical rules
to decide how many replicates are necessary
to get a certain precision

How to come to dependencies ?

At this point we only measured one patient sample
with 16 protein expressions

this is **not sufficient** to see a **dependency**
between our 16 proteins

the term dependency
implies a further type of information

In our case this additional information will result from
measuring many patients
of the same disease situation
slightly varying the basic situation

Score data based on raw signals

16 proteins

640 patient samples

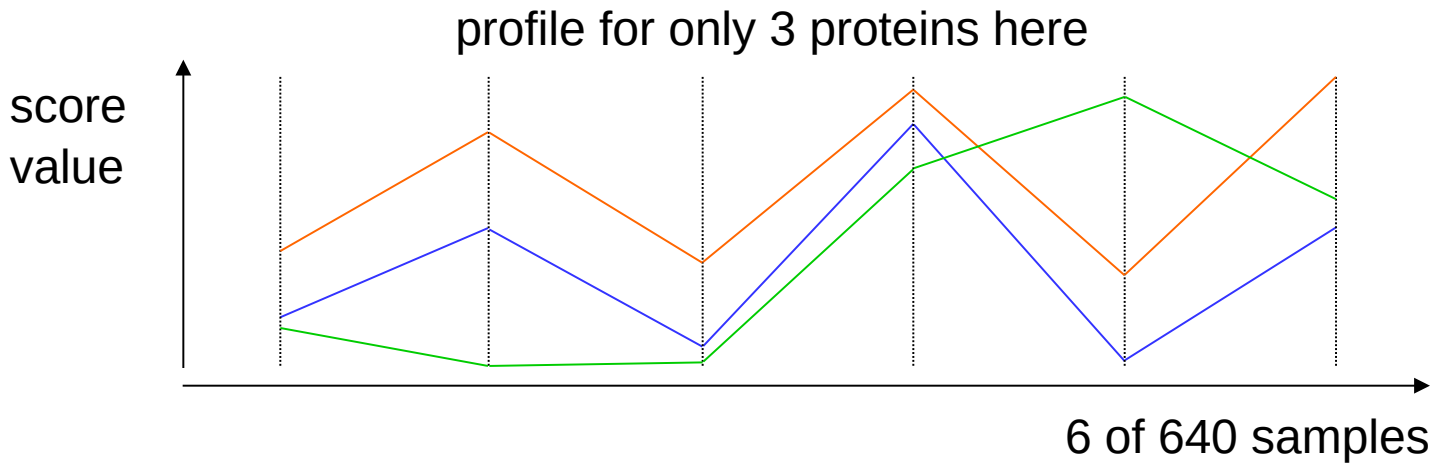
A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
RowNames	K5	K8-18	K19	EGFR	K14	EMA	ERBB2	VIM	p53	BCL2	CyclinD1	K1	K10	ER	PR	KI67
1	1	4	4	1	1	4	1	1	1	2	2	1	1	4	4	3
2	1	4	4	1	1	4	3	1	1	2	4	1	1	4	4	1
3	1	4	4	1	1	3	1	1	1	1	3	1	1	4	4	2
4	1	4	4	1	1	4	4	1	2	1	3	1	1	4	4	3
5	1	4	4	1	1	4	2	1	1	3	4	1	1	4	4	2
6	1	4	4	1	1	4	2	1	1	2	3	1	1	4	4	2
7	1	4	4	1	1	4	1	1	1	2	2	1	1	4	4	1
8	1	4	4	1	1	4	1	1	2	2	3	1	1	4	4	2
9	1	4	4	1	1	3	1	1	1	4	3	1	1	4	4	2
10	1	4	4	1	1	4	2	1	2	2	4	1	1	4	1	2
11	1	3	3	1	1	4	4	1	2	1	1	1	1	4	1	1
12	1	4	4	1	1	4	1	1	1	2	2	1	1	4	4	2
13	1	2	4	2.5	1	4	2	1	1	1	2	1	1	1	1	4
14	1	4	4	1	1	3	3	1	1	3	3	1	1	4	4	1
15	1	4	4	1	1	4	1	2.5	2	2	3	1	1	4	4	4
16	1	4	4	1	1	4	1	1	1	1	4	1	1	4	4	4
17	1	4	4	1	1	4	1	1	1	3	4	1	1	4	4	1
18	1	4	4	1	1	4	1	1	1	1	4	1	1	4	4	1
19	1	3	3	1	1	4	3	1	2	3	3	1	1	4	1	3
20	1	4	4	1	1	4	4	1	3	2	3	1	1	4	4	3
21	1	4	3	1	1	4	1	1	1	1	3	1	1	4	4	3
22	1	4	3	1	1	4	2	1	2	2	4	1	1	4	4	2
23	1	4	4	1	1	4	1	1	1	2	2	1	1	1	1	2
24	1	3	4	1	1	4	1	1	1	2	2	1	1	4	4	1
25	1	3	4	1	1	3	1	1	1	2	3	1	1	4	4	1
26	1	3	3	4	2	3	1	1	4	1	1	1	1	1	1	4
27	1	4	4	1	1	4	1	1	1	3	2	1	1	4	4	1
28	1	3	4	1	1	4	1	1	1	1	3	1	1	4	4	4
29	4	4	4	1	1	3	1	1	1	2	1	1	1	4	4	1
30	1	4	4	1	1	4	2	1	1	4	4	1	1	4	1	2

score sheet

Entering the first analysis step

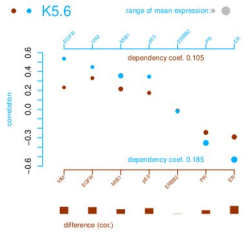
Applying a proximity measure between each of the protein columns

Purpose: how similar or dissimilar is the protein expression



Result: in this example protein 'red' and 'blue' is more similar and 'green' more dissimilar to 'red/blue'

Analyze dependencies



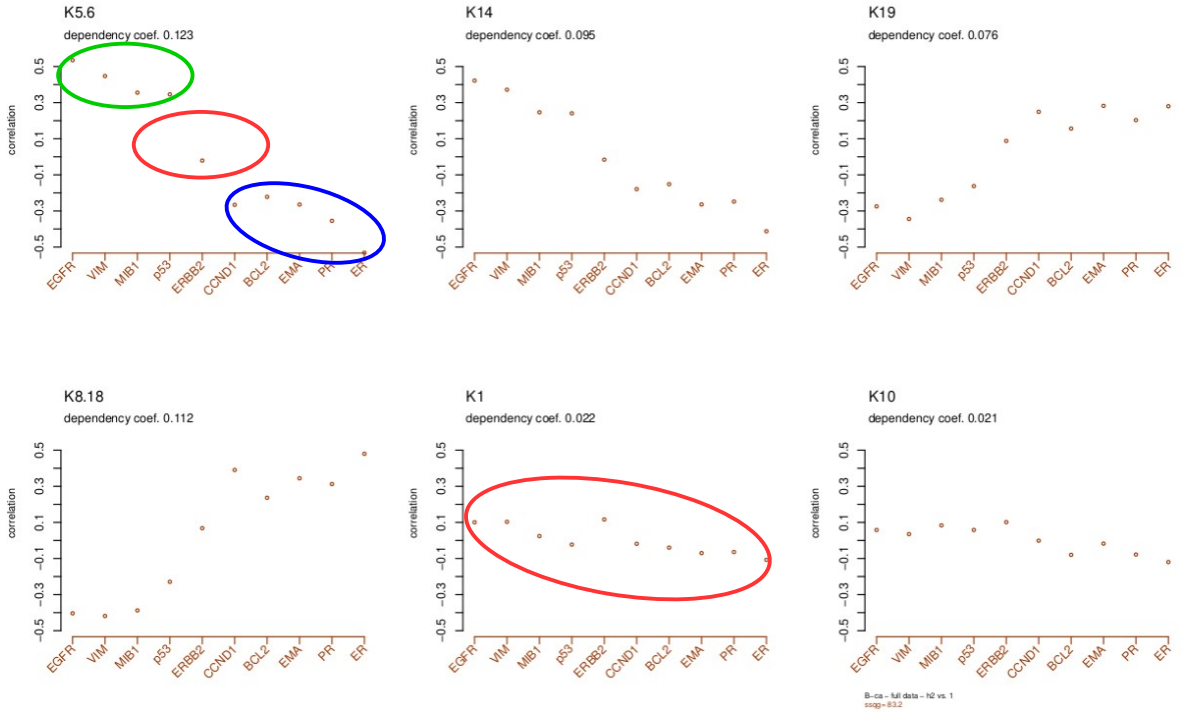
1) splitting the factors into **partitions**

K5-6 | K14 | K19 | K8-18 | K1 | K10 — reference group

EGFR, VIM, KI-67, p53, ERBB2, Cyclin-D1, BCL-2, EMA, PR, ER — test group

2) generalized **regression**

3) **optimal order** of proximity values across **all** partitions denotes the dependency



- synergistic co-expression
- no (or weak) dependency
- antagonistic co-expression

Histopathology. 2015 Dec;67(6):888-97, Cancer Inform. 2016 Jun 29;15:143-9

Section summary

The basic assumption in this approach is
that all molecular factors belong to a
cellular system in one physiological condition

therefore
if one factor is tuned, many others are also tuned
as a systemic consequence

Every patient owns a slightly different network

The superposition of all network variants
is exposing the dependencies

Spotlights

on networks,

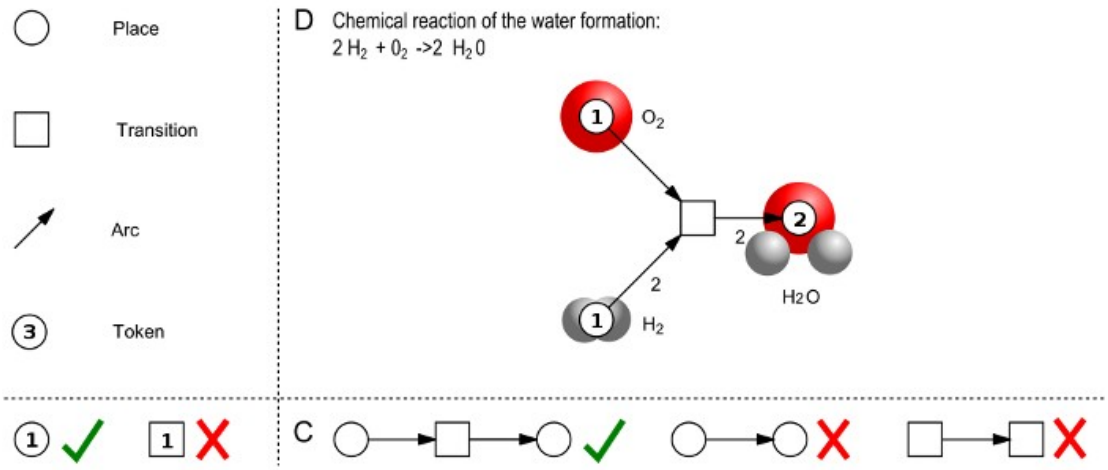
databases,

and advanced application scenarios

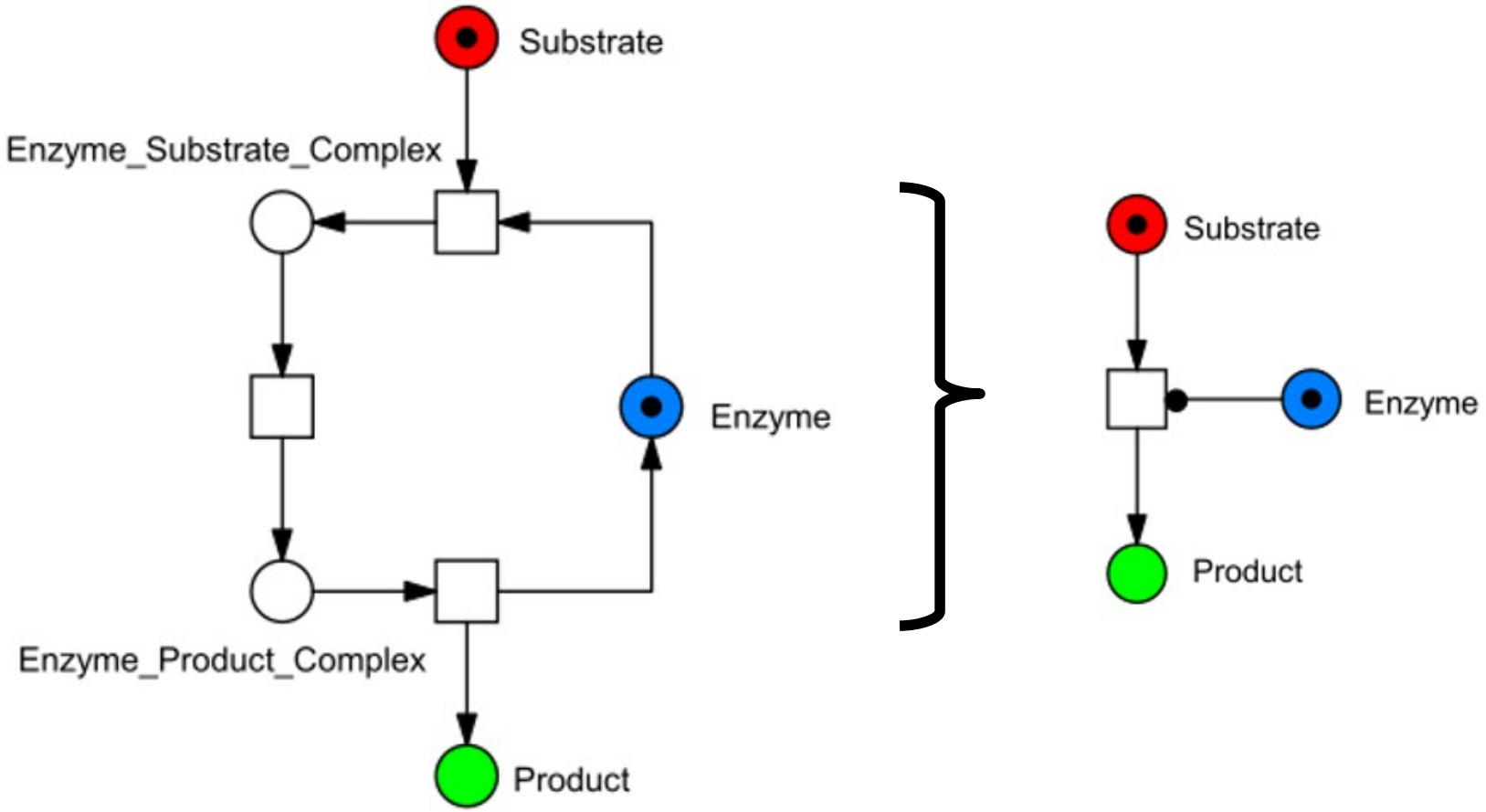
Petri net

‘Petri nets’ are used as a formal and
graphical language
for modeling systems

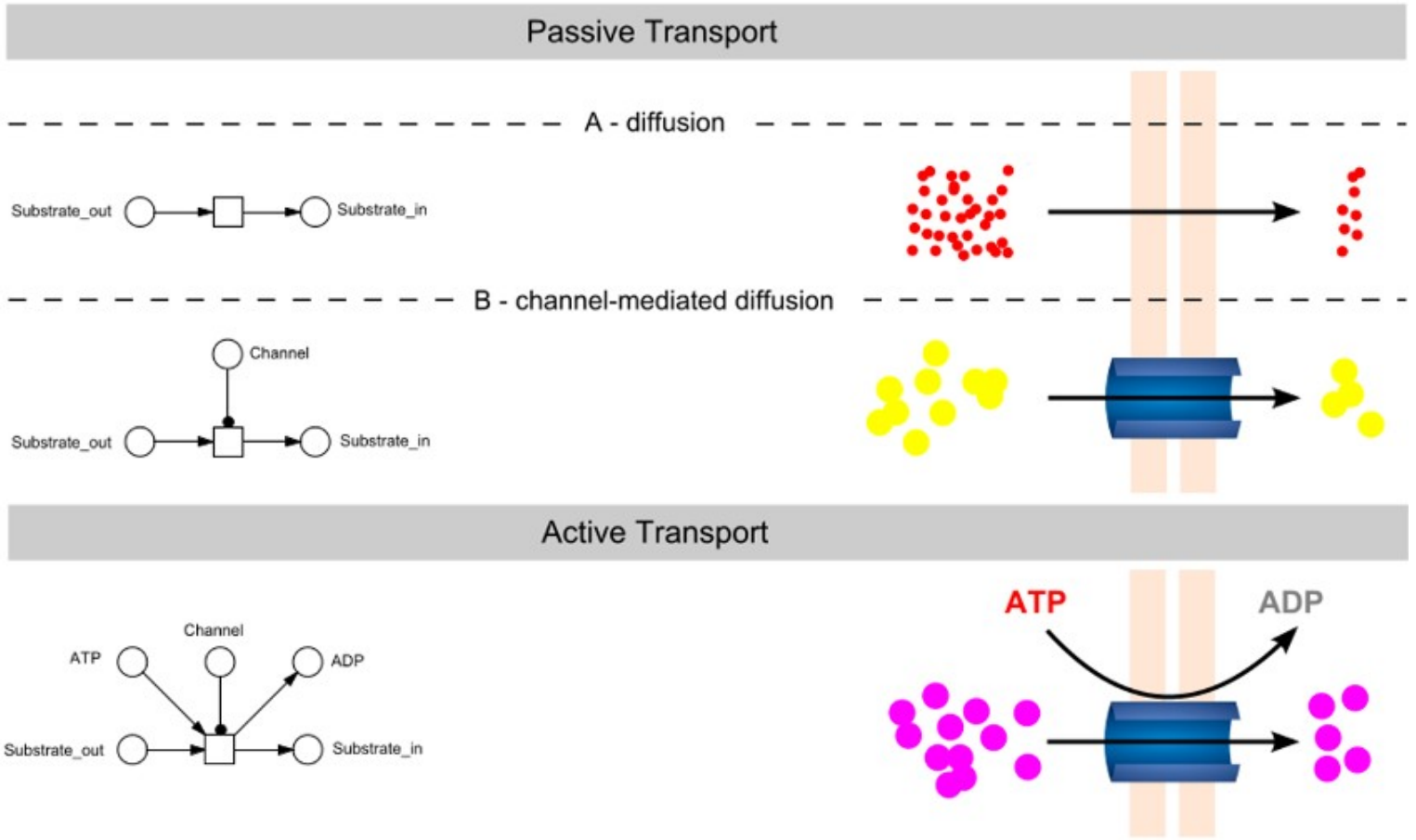
A Petri net is represented by a directed, finite, bipartite graph,
typically without isolated nodes



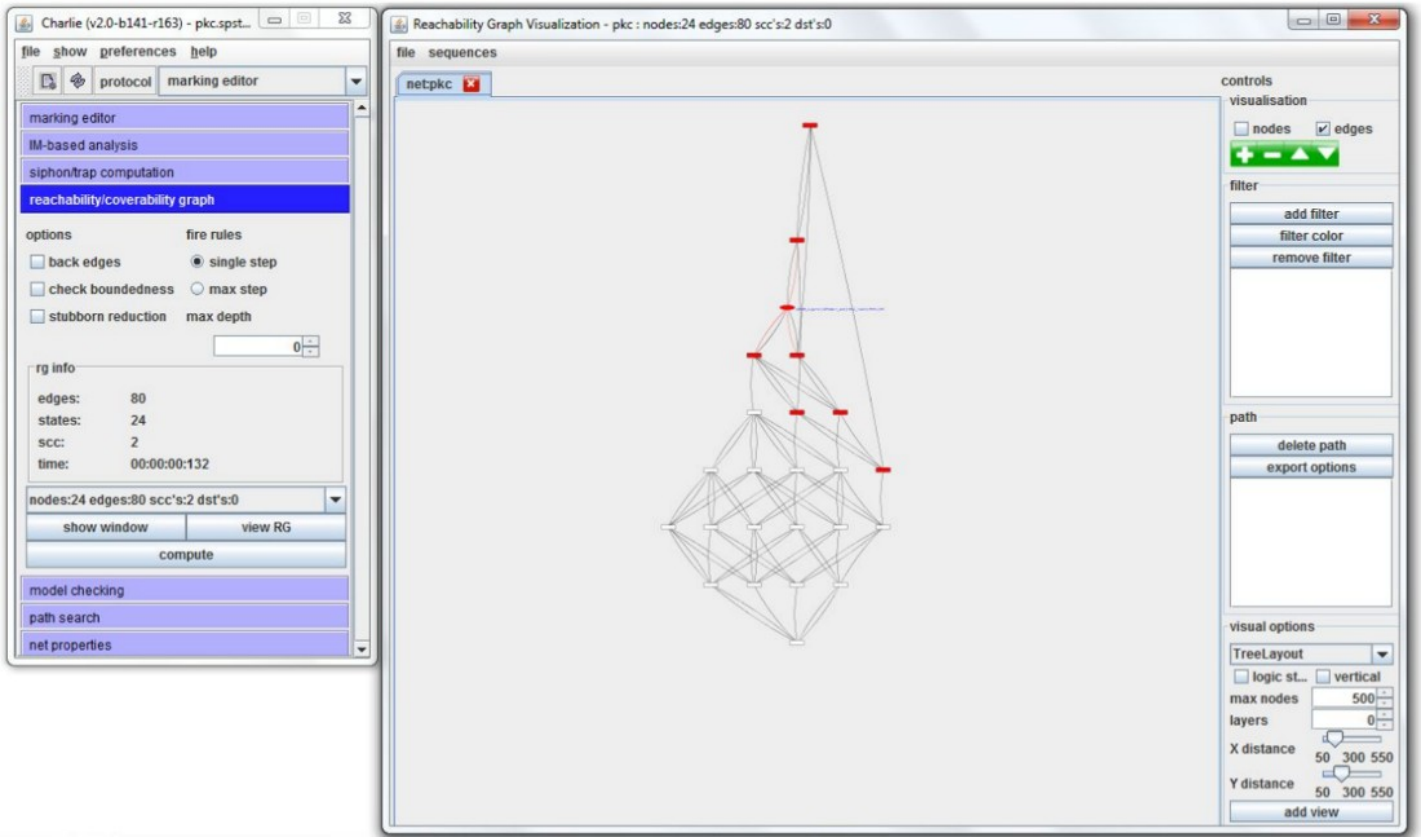
Scheme for an enzymatic reaction



Membrane transport



Tools to work with



Download & Credits
http://www-dssz.informatik.tu-cottbus.de/DSSZ/Software/Software

The scientific biography behind that: Monika Heiner

WGCNA - R package

Gene co-expression networks

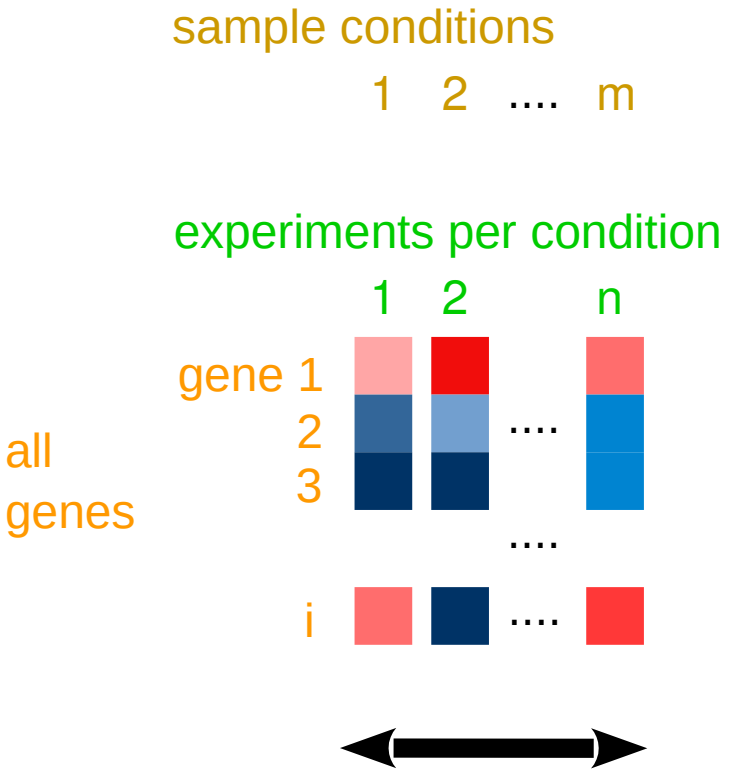
but instead - as before - over proteins
(many different patients, but of one condition)

here now over genes
in many different conditions
(e.g. a certain cell type treated with different agents)

objective : find gene modules
that differentiate these conditions

BMC Bioinformatics. 2008 Dec 29;9:559. doi: 10.1186/1471-2105-9-559

How does it work ?



Pearson correlation of gene profiles (rows)

The outcome is a number of modules (groups) of genes

each module with a typical expression profile

is assumed to share a specific biological context

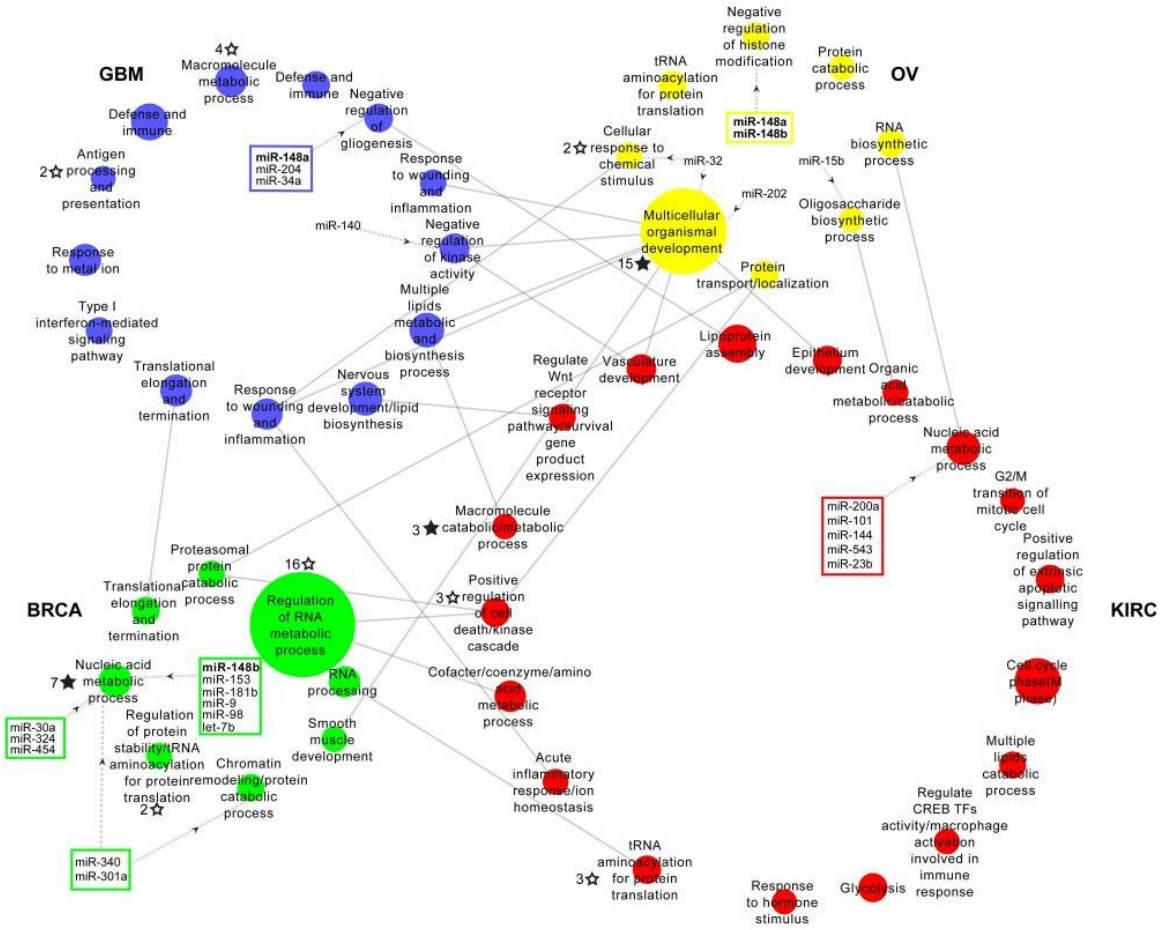
The modules might explain the network difference between the tested biological conditions

WGCNA - example of use

GBM - glioblastoma
OV - ovarian adenocarcinoma
BRCA - invasive breast carcinoma
KIRC - kidney carcinoma

The 47 prognostic modules
are plotted in four circles, each
representing one cancer type

Grey lines:
conservation correspondence
between different cancer types



Nat Commun. 2014;5:3231. doi: 10.1038/ncomms4231

Databases

Some core databases

Chemical reaction constants database

http://kinetics.nist.gov/kinetics/welcome.jsp

Biochemical reaction kinetics database

http://sabio.villa-bosch.de/

http://www.ebi.ac.uk/biomodels/

microRNA database

http://www.mirbase.org/

Genome database

http://www.internationalgenome.org/

EBI database

http://www.ebi.ac.uk/

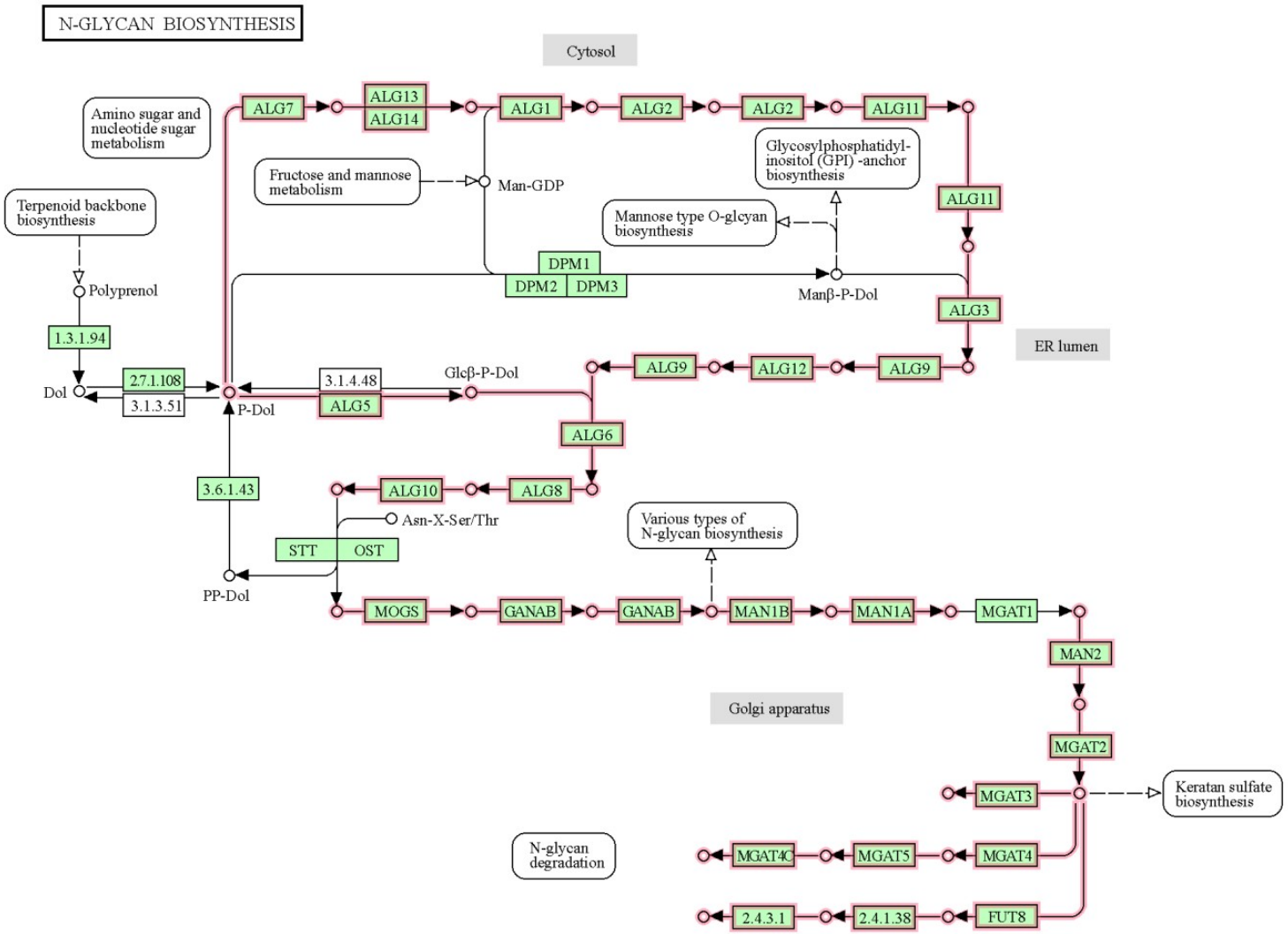
NCBI database

https://www.ncbi.nlm.nih.gov/

Pathway database

http://www.genome.jp/

Pathway database : KEGG

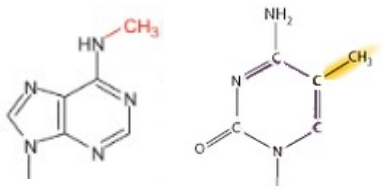


Homosapiens (hsa)

N-glycans or asparagine-linked glycans

are major constituents of glycoproteins in eukaryotes

Epigenetics



A C

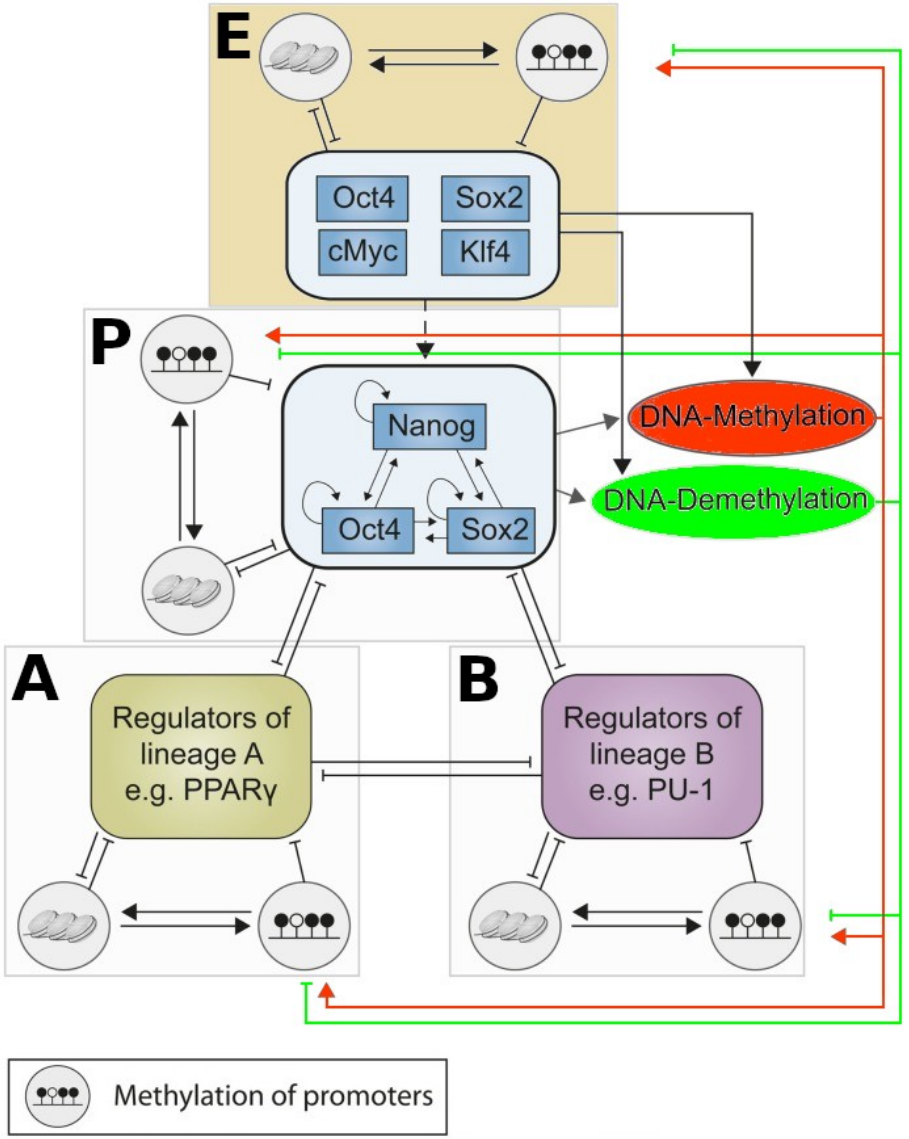
Methylation targets

Somatic Cell Reprogramming

Transcriptional regulators that account for the activation of a certain cell state
are combined into a module.

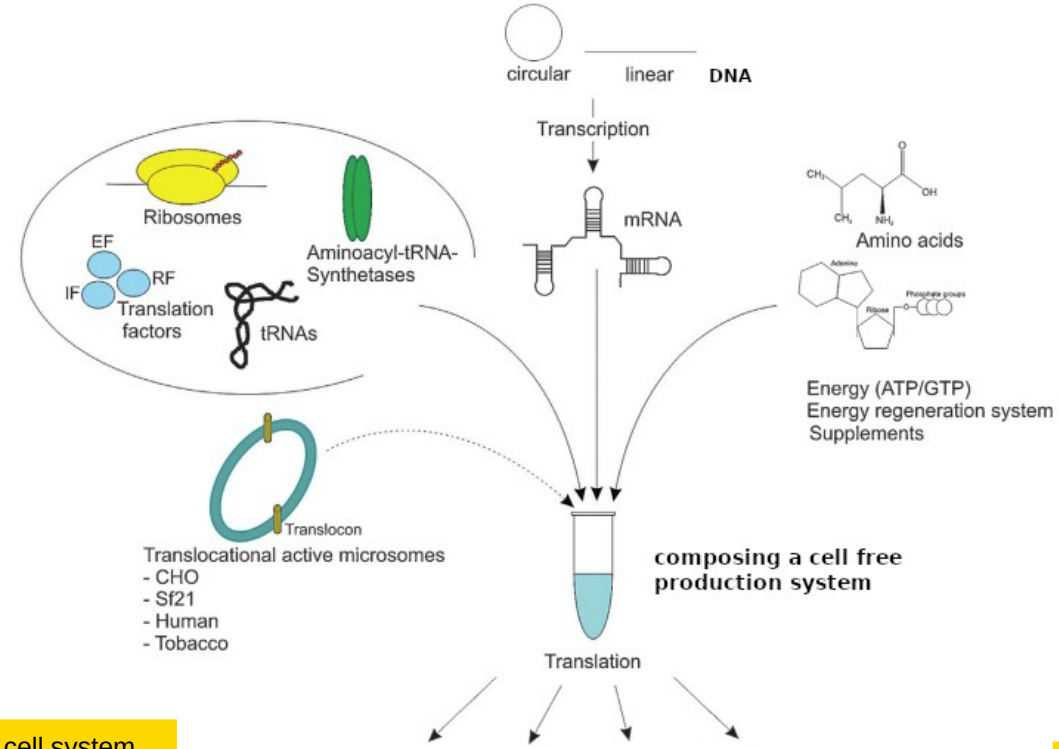
Four modules:
2 different **differentiation** modules A and B,
the **pluripotency** P,
and the **exogenous reprogramming genes** E.

Each module is governed by the activity of the other modules as well as its epigenetic states.



Front Physiol. 2012 Jun 27;3:216. doi: 10.3389/fphys.2012.00216

Synthetic biology



cell system	Soluble proteins	Disulfide proteins	Membrane proteins	Glycoproteins
Archae / Protozoa	✓			
E.coli	✓	✓ Redoxsystem necessary	✓ Detergents/ liposomes/nanodiscs/ refolding processes necessary	
Wheat Germ	✓	✓ Optimized system necessary	✓ Detergents and liposomes are necessary	
Yeast	✓			✓ Addition of microsomes
Rabbit Reticulocyte	✓	✓ Addition of exogenous microsomes necessary	✓ Addition of exogenous microsomes necessary	✓ Addition of exogenous microsomes necessary
Tobacco	✓	✓	✓	✓
Insect	✓	✓ Redoxsystem necessary	✓	✓
CHO / Human	✓		✓	✓

target protein types

production feasible

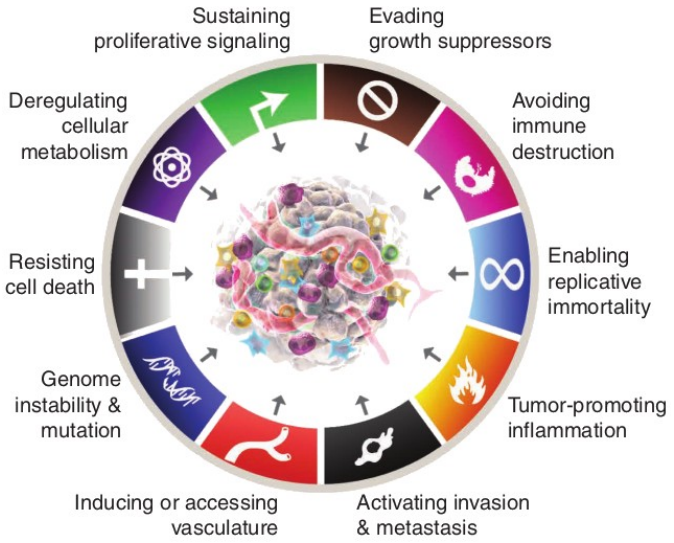
Chinese hamster ovary (CHO) cells

Cell-Free Protein Synthesis - https://doi.org/10.1002/cbic.201500340

https://doi.org/10.1016/j.copbio.2019.05.003 , https://doi.org/10.1002/0471142727.mb1630s108

Evolutionary Systems Biology

Cancer stem cells follow
their own evolutionary process,
which
results in an escape
from the
multi-cellular control mechanisms.



The hallmarks of cancer
are indicators on this way.

Hanahan & Weinberg, Cell, 2011, 144(5), Hanahan, Cancer Discov 2022, 12(3)

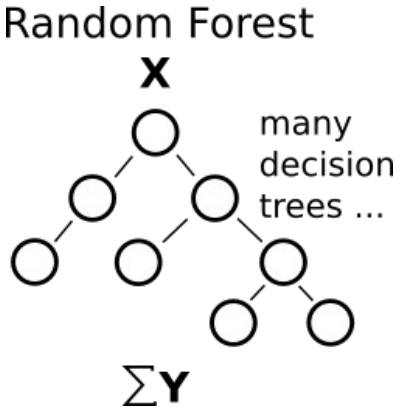
A teaser for the next lecture

Is **artificial intelligence (AI)**
the next big thing in systems biology ?

It depends ...

AI is still based on known **ideas**.

Therefore it might be still **limited**
for detecting
new concepts in biological systems.



Take home message

- Systems biology
  is mapping massive parallel measurements
  into systemic models
  and is trying to explain
  the behavior of complex biological systems

- The methodology of systems biology
  still needs attention
  and more elaborated concepts