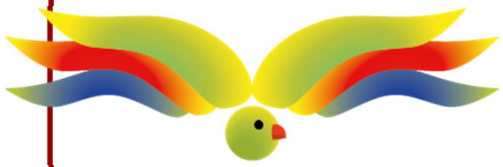

Introductory Course Systems Biology

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University Medical Centre Groningen
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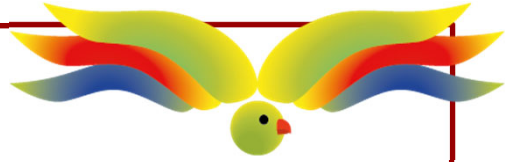
Lorna Morris
Christopher Hardt
LifeGlimmer
Wageningen University
Systems and Synthetic Biology

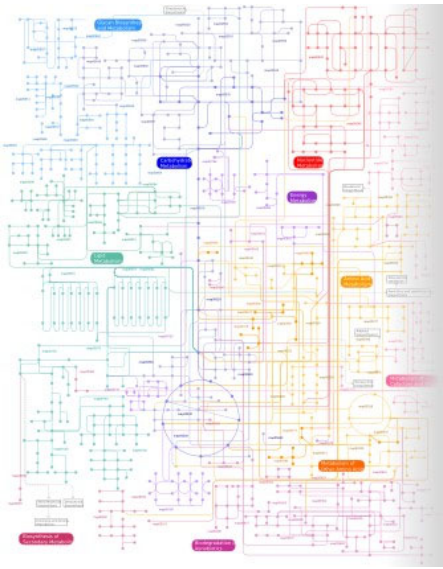
Bettina Warscheid
Silke Oeljeklaus
University of Freiburg
Biochemistry and functional proteomics

MARIE CURIE ACTIONS

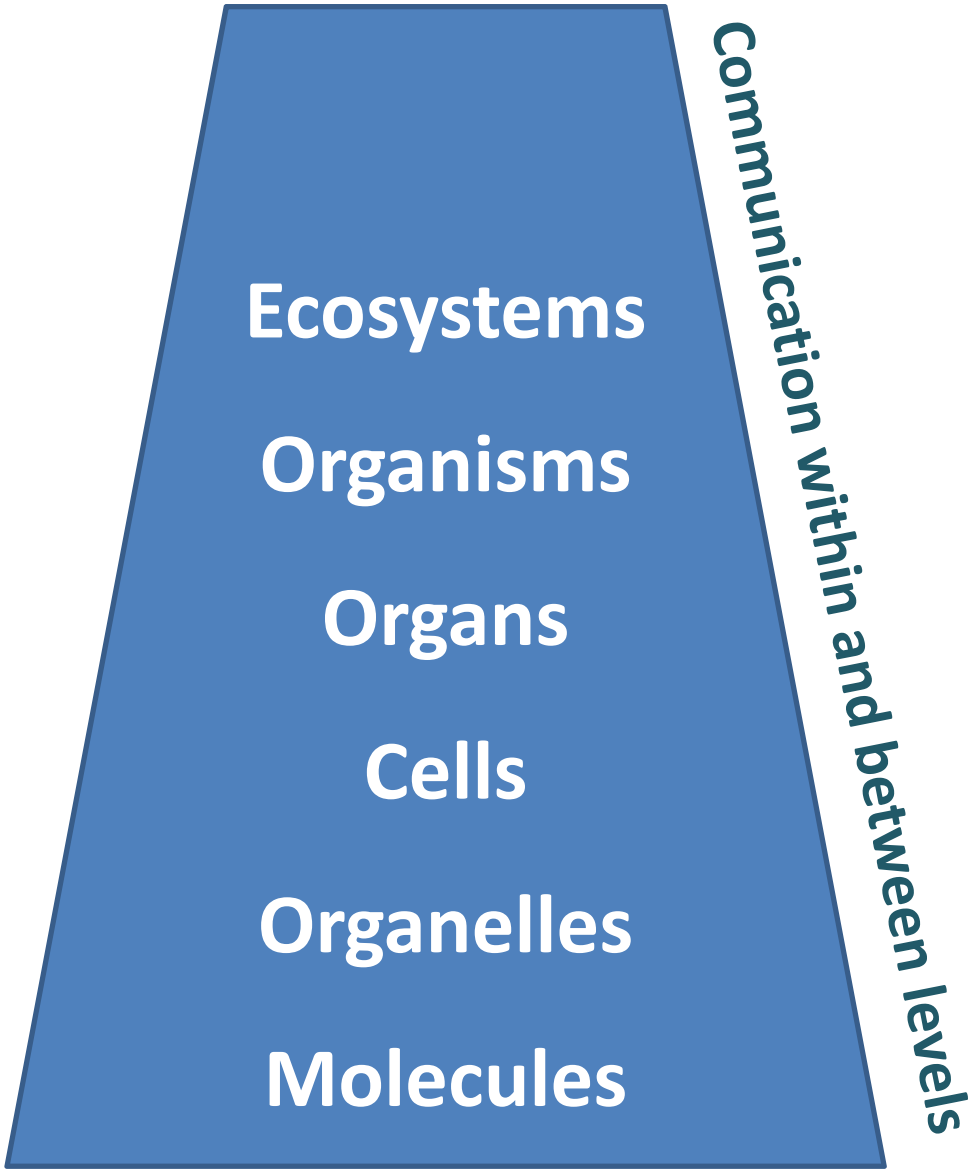
The Menu



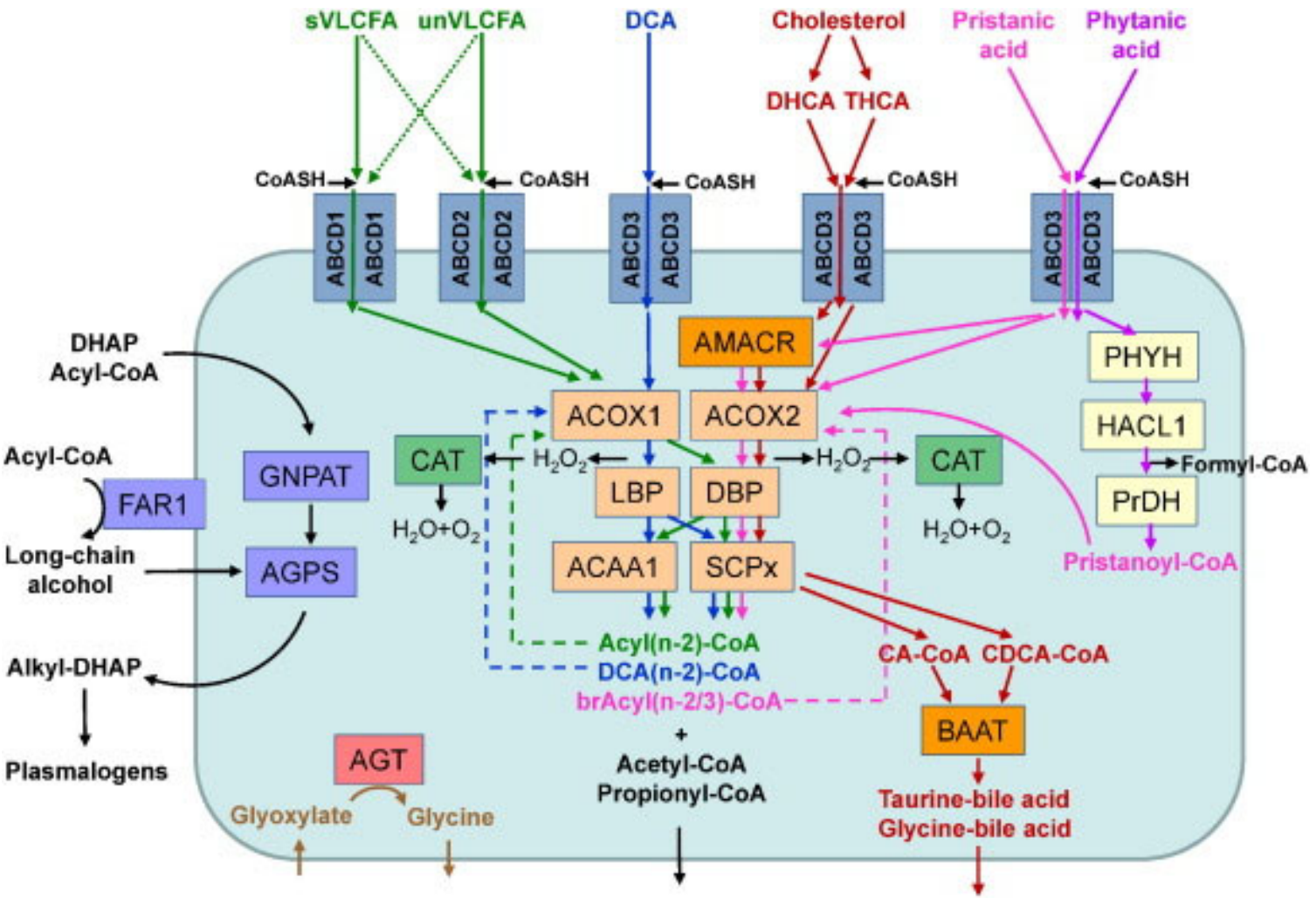
- **Complexity in biology**
- **Systems Biology**
- **Course Outline**



Complexity in Biology

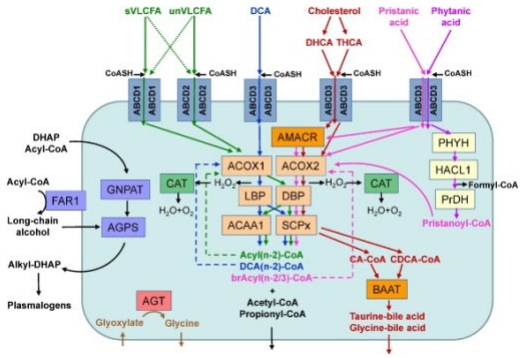


Complexity in PerICo



Waterham, Ferdinandusse & Wanders (2016) BBA 1863, 922-33

Complexity in PerICo

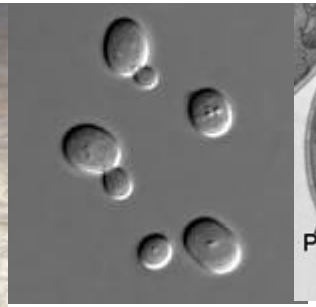


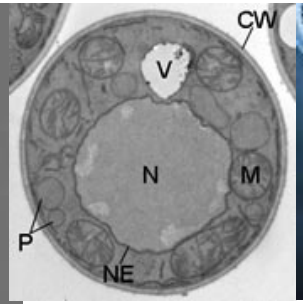
Physical contact
Functional communication

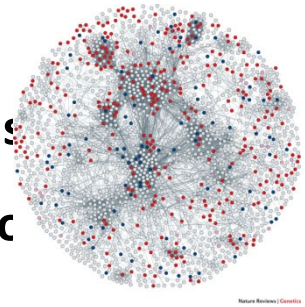
Mitochondria
Vacuole
ER

Systemic implications for health and disease

Reductionism in Biology

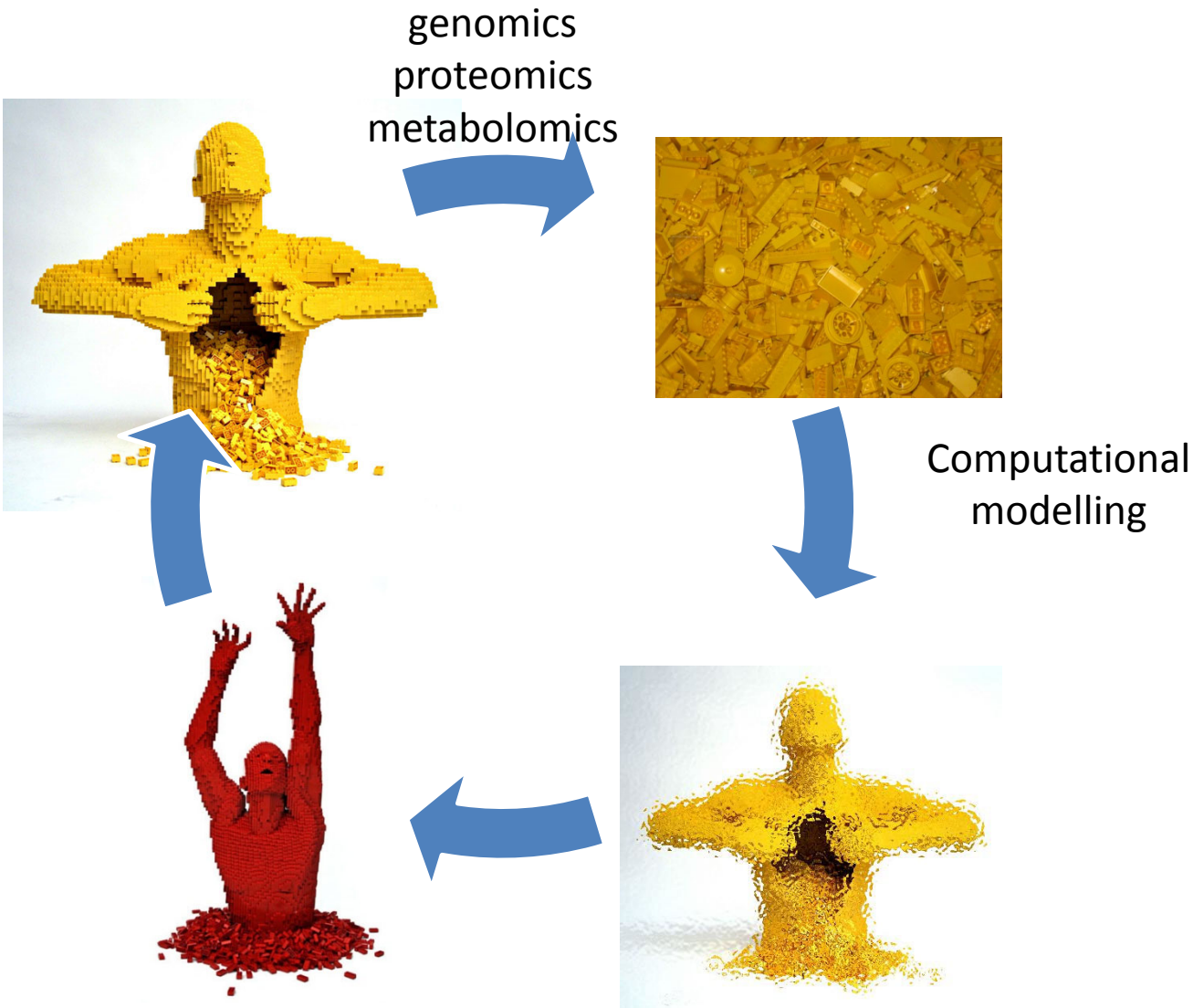




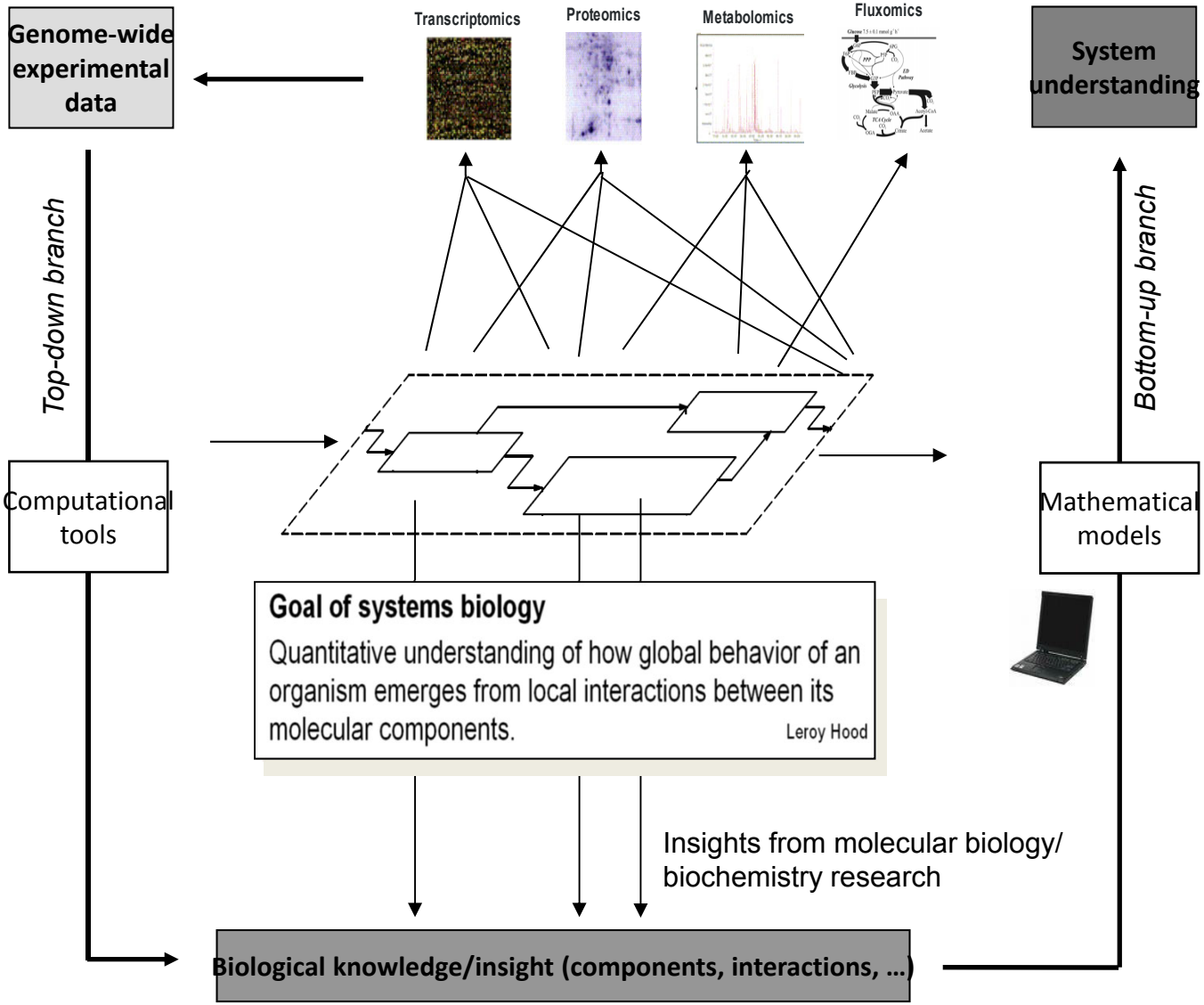


Scientific progress

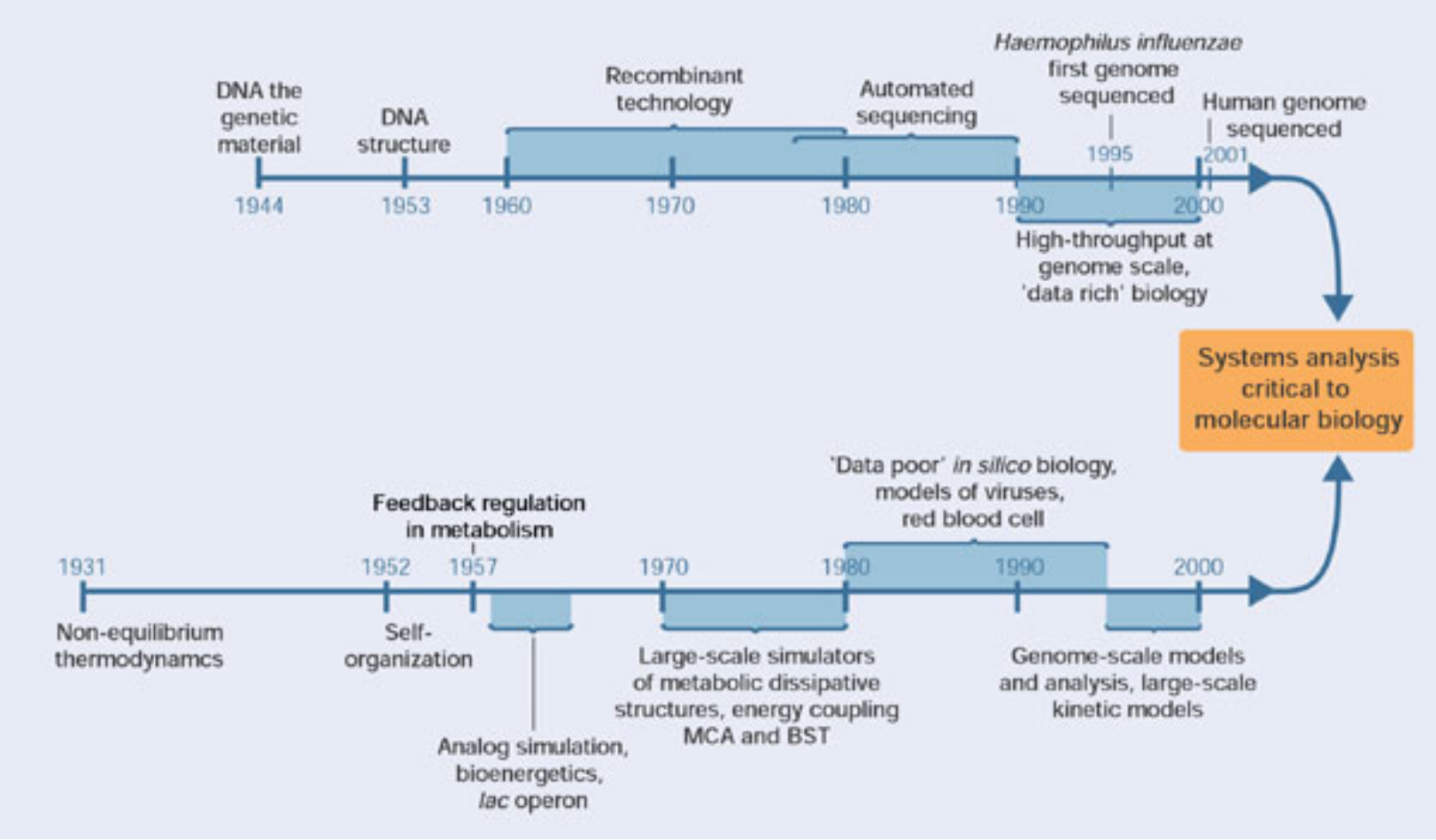
Systems Biology



Top-down & bottom-up



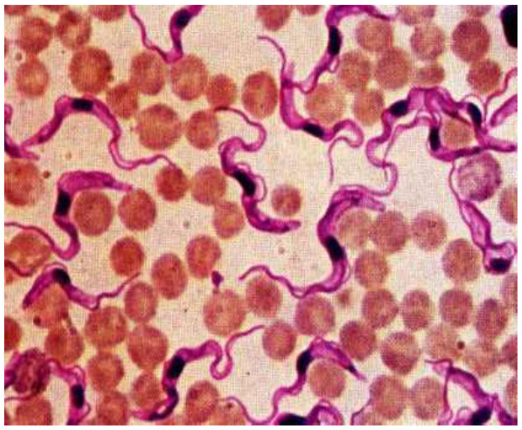
Roots of systems biology

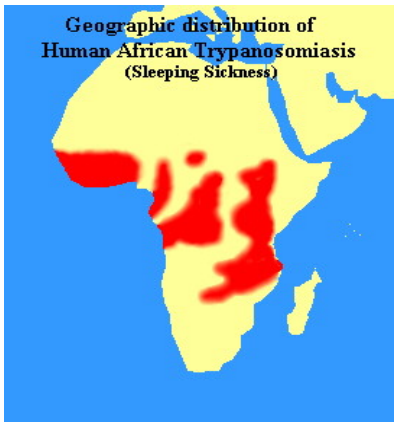


Westerhoff & Palsson (2004) *Nature Biotechnology* 22, 1249 - 1252

My roots in systems biology

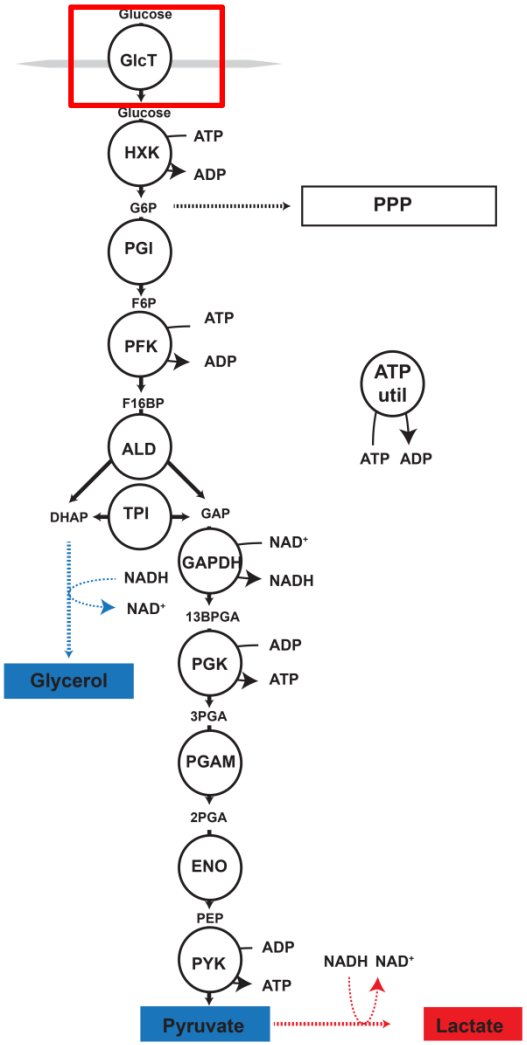
Trypanosoma brucei

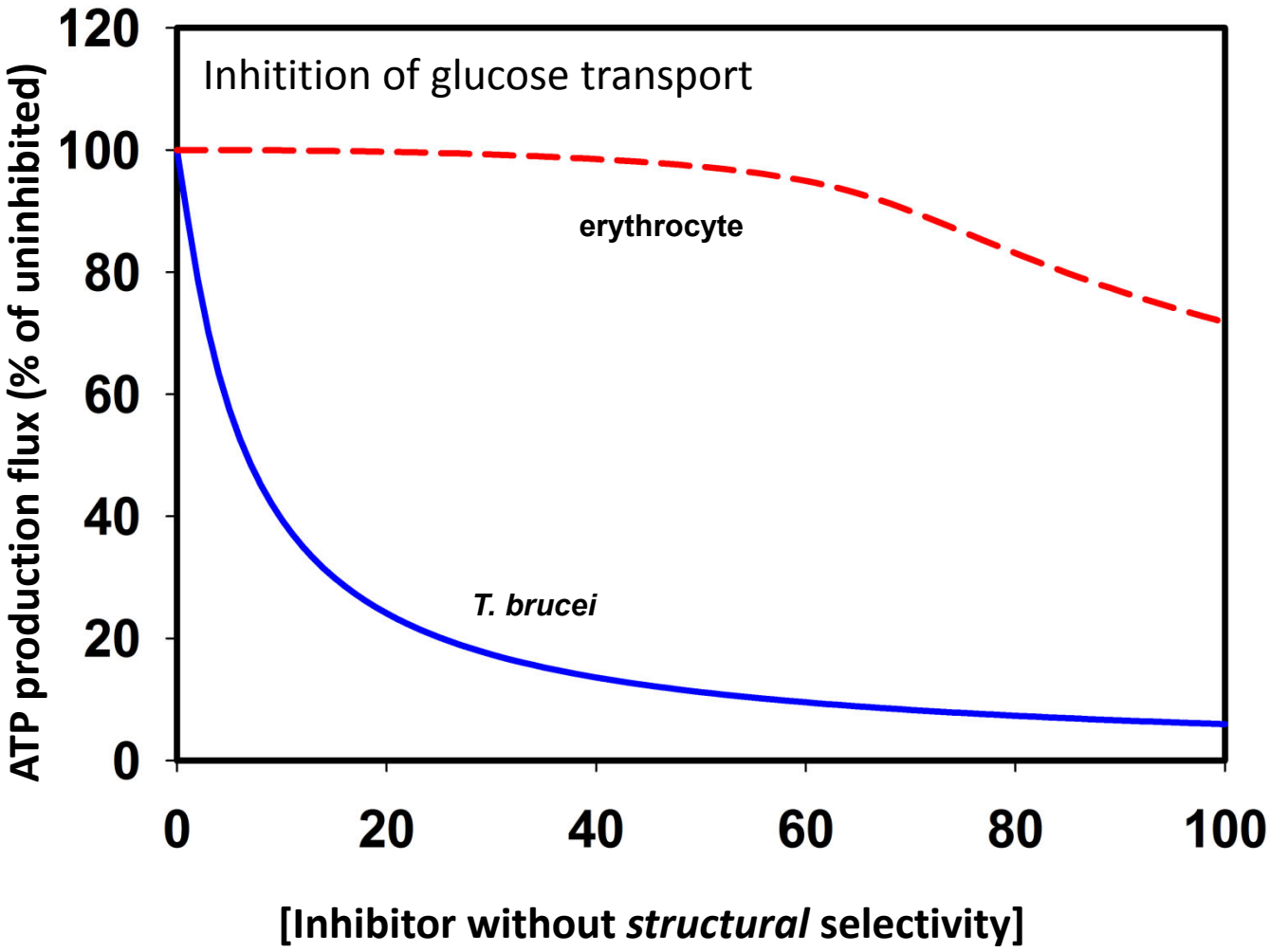




- African sleeping sickness – transmission by tsetse fly
- Disease of cattle and humans
- Fatal if untreated, resistance to current medication
- WHO neglected disease

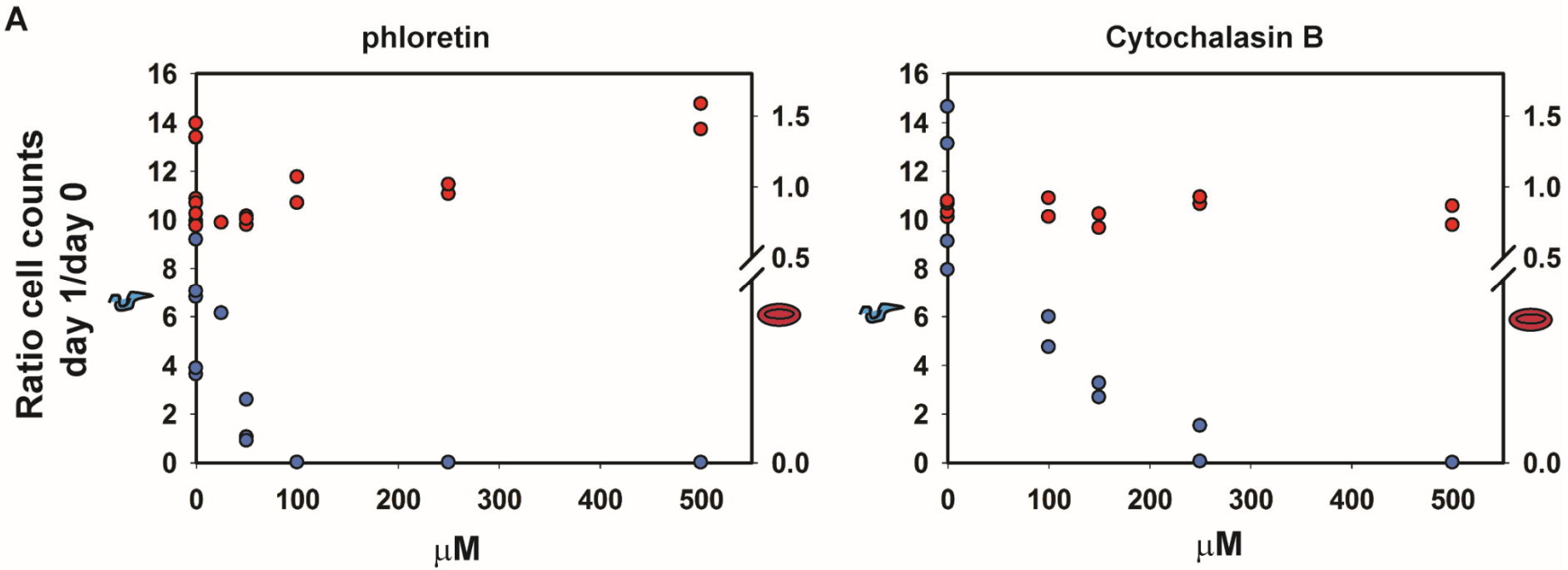
Simulating impact of drugs against glycolysis





Haanstra (2017) Sci Rep. 7:40406

Phloretin and cytochalasin B: non-selective inhibitors of glucose transport



Selectivity through the response of the metabolic network

Haanstra (2017) Sci Rep. 7:40406

Metabolic disease

- Inborn errors of metabolism

  → single-gene mutations, severe paediatric diseases

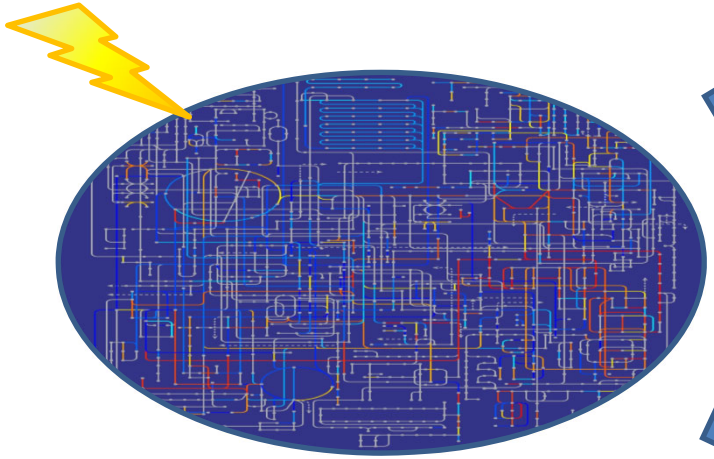
  → systemic impact and treatment

- Multifactorial diseases

  → Multiple factors (mutations, lifestyle, history) leading to disease

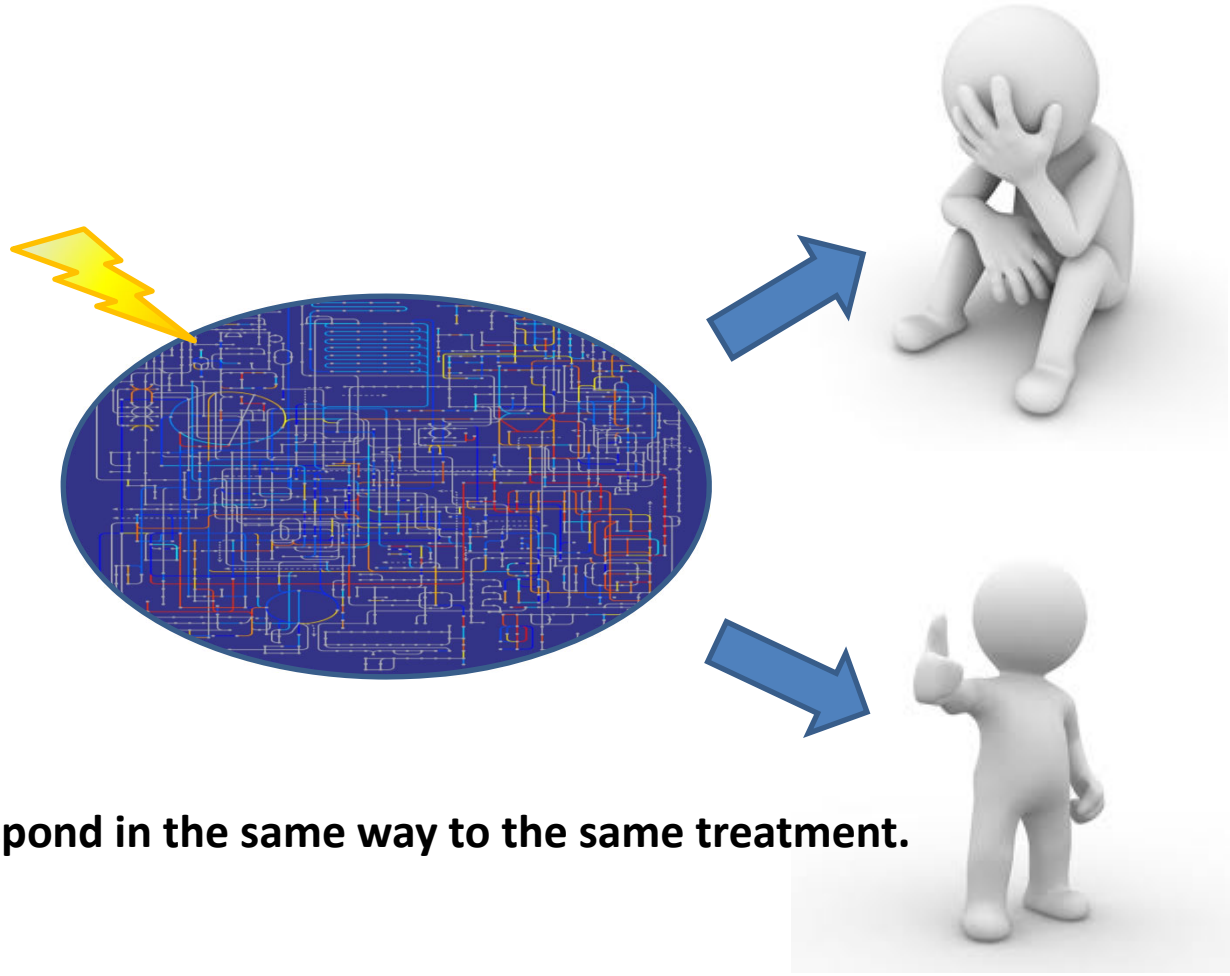
Who is a patient?

Genetic mutation



People with the same ‘ disease’ mutation can show different outcomes

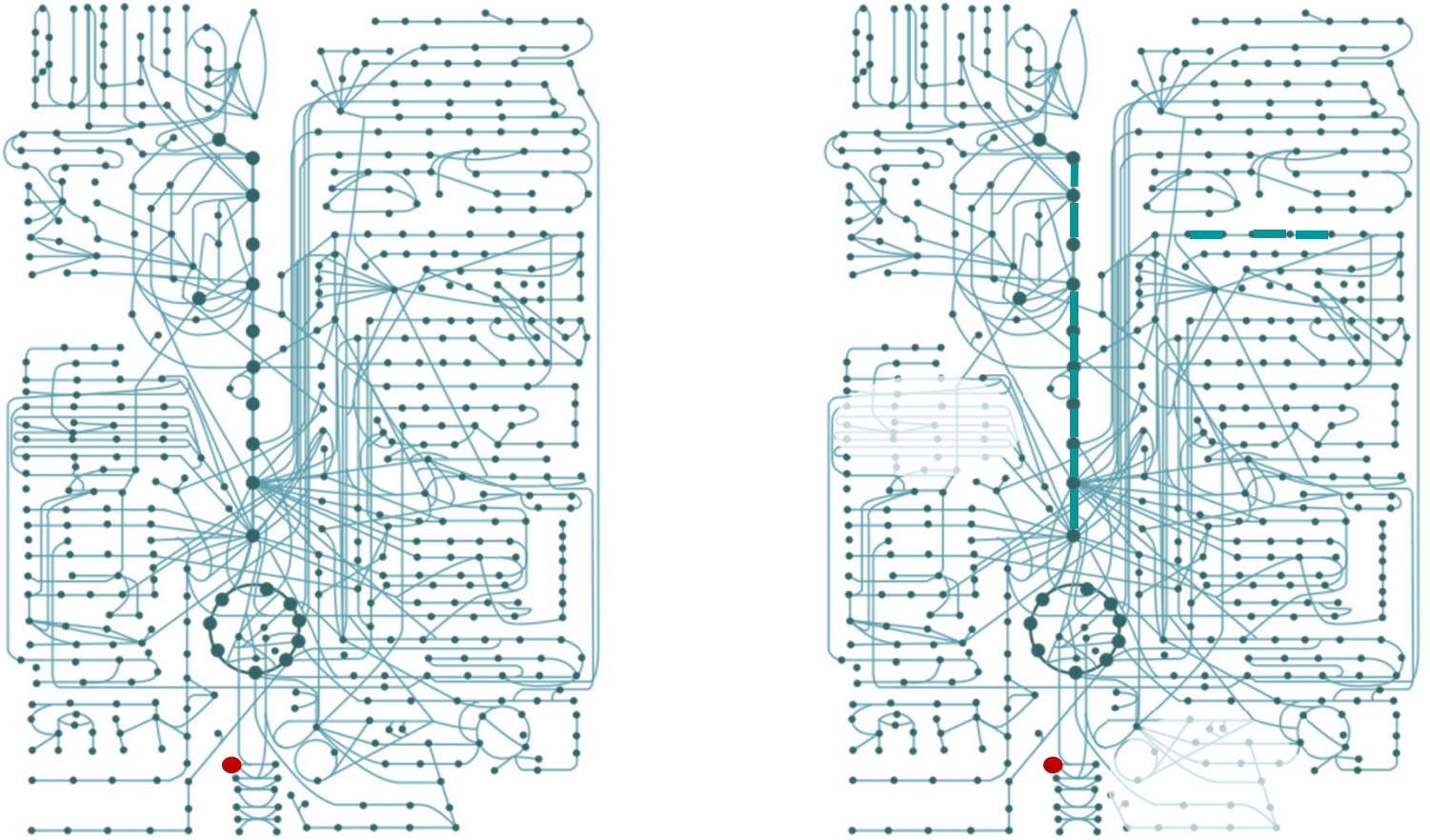
Who benefits from which treatment?



People do not respond in the same way to the same treatment.

Personalized Medicine

- Personalized prognosis: which patient is at risk? Which mutant is a patient?
- Personalized treatment strategy: which diet / medication works best for whom?

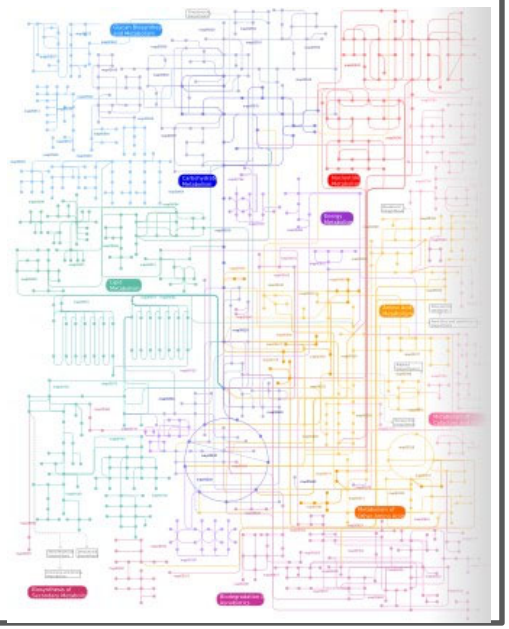


Large, heterogeneous datasets → Computational modelling

Course overview

- **FAIR data management**
- **Proteomics**
- **‘Omics analysis**
- **Computational modelling**

- ***Lectures and hands-on sessions***
- ***Systems Biology in your project***



Dynamic modelling of metabolic networks

Prof. Barbara Bakker (b.m.bakker01@umcg.nl)
University Medical Center Groningen, Laboratory of Pediatrics, Section Systems Medicine of Metabolism and Signaling

The assignments are done with the Copasi software package, which can be downloaded from: http://copasi.org/. The tutorial video's on the Copasi website are very helpful. The tutorial has been tested with Copasi version 4.21, but should work with newer versions as well.

The assignments below are are aimed to:

(i) get acquanted with basic principles of metabolic networks; and
(ii) to get hands-on experience in analysing kinetic models of metabolic networks.

To get an overview of each model, it helps to draw a scheme of the reactions and its regulatory loops.

Assignment 1: A simple 3-enzyme linear pathway

Open Model 1. The model describes a 3-enzyme pathway with reversible Michaelis-Menten kinetics.

a. Inspect the model. Can you find where the stoichiometry, kinetic equations, and kinetic parameters are described?
b. Simulate a time course, using the *Time Course* option under *Tasks*. Does the pathway reach a steady state? How can you see this?
c. Calculate the steady state fluxes and concentration, using the *Steady State* option under *Tasks.* Is the steady state the same as observed in the time course?
d. Alter the initial concentration of the intermediates X_1 and X_2 and calculate a new steady state. Is the steady state the same as before? Can you explain why (not)?
e. Increase the concentration of the substrate S by a factor of 2. Again calculate the steady state. Are the results the same as before? Explain what you observe.
f. Reset S to its original value. Now increase the V_{max} of the first enzyme by 20% and calculate the percentage change of the pathway flux.
g. Reset the V_{max} of the first enzyme and then calculate the effect of increasing the V_{max} of the second and the third enzyme by 20%, one by one. Does it matter which V_{max} you increase? Explain your observations.

Assignment 2: A branched pathway

Open Model2. This model is identical to Model1, except that one enzyme was added.

a. Identify the new enzyme in the model and draw a scheme of the reaction network.
b. Calculate a time course and a steady state. Check that outcome fulfils the steady state requirements. Are the fluxes to the two products different? Can you explain why (not)?

c. Increase the V_{max} of the newly introduced enzyme by 20% and calculate the percentage change of the flux through each individual enzyme. Explain your observations.
d. Now titrate the concentration of P_2 from 0 to 10 mM and calculate the steady enzyme rates and metabolite concentrations as function of $[P_2]$. For this you can use the option *Parameter Scan* in Copasi. Make sure that you collect enough datapoints to obtain a smooth curve, but not too many to avoid lengthy calculations. You will also need to define a new output plot. Explain your observations.

Assignment 3: Feedback strength

Open Model 3 and inspect it.

a. What is different compared to Model 1? Calculate the steady state.
b. How can you increase the feedback strength in this model? Do this and calculate the new steady state. Save your model under a different name. What is the effect on flux and concentrations? To get a good insight in what happens and explore a wide range of feed backstrengths, you best use the option 'Parameter scan' and plot concentrations and flux.

Assignment 4: Identification of drug targets

Open model 'trypanosomce glycolysis + PPP model C – transporters repaired'. This model describes the glycolytic pathway plus the pentose phosphate pathway in the African parasite *Trypanosoma brucei.* This is the version that was published by Kerkhoven et al. (PLoS Comput Biol. 2013;9(12):e1003371, model version C). This network is much more complicated than the toy networks studied before. A detailed reaction scheme is given in Appendix I.

a. Explore the model and identify the main glycolytic reactions. Can you find back the reactions in Appendix I? Which enzymes produce ATP?
b. Under aerobic conditions the flux from Gly-3P splits into a flux to glycerol (GK) and an oxygen-dependent flux back to DHAP (GPO reaction). Compute the fluxes through both reactions and check that they add up to the rate of Gly3P production.
c. Under anaerobic conditions the GPO reaction cannot work. Switch it off by setting its V_{max} to 0. What is the effect on the production of glycerol? And on the production of pyruvate? Explain why the production of pyruvate is affected.
d. *Trypanosoma brucei* causes the deadly sleeping sickness. A good drug target should be essential for a vital flux. Here we focus on the production of ATP. Since glycolysis invests first ATP before there is net production, we use the ATP utilization flux (reaction 19 in the scheme below, reaction 32 ATPu_c in the Copasi file) as a readout of the net ATP production. Test for a couple of reactions, at least including glucose transport (GlcT), hexokinase (HXK) and glyceraldehyde dehydrogenase (GAPDH) if they are essential for net ATP production.
   Hint: you may do this by setting their Vmax value close to zero (e.g. 0.01 % of the original value) and see if the flux changes correspondingly. Alternatively you may titrate their Vmax (option parameter scan) and plot flux against Vmax.
e. In the body it is virtually impossible to completely block an enzyme by chemical inhibition, without causing side effects. To reduce drug dosage, it is therefore of utmost importance to target enzymes with a high flux control coefficient. Compute the flux control coefficients to

quantify the effect of each of the enzymes on the net ATP production flux. The flux control coefficient quantifies the effect of a change of V_{max} of an enzyme on the steady state flux. For instance the flux control coefficient of the enzyme hexokinase is defined as:

$$C_{HK}^{flux} = \frac{dJ}{dV_{max}} \cdot \frac{V_{max}}{J}$$

in which J is the steady-state flux.

Which reaction has the highest flux control coefficient over the net ATP production flux?

Appendix 1: Computational model of glycolysis and pentose-phosphate pathway in *Trypanosoma brucei*

Fig 1 from: Kerkhoven et al. PLoS Comput Biol. 2013;9(12):e1003371

In the course we use model version C, i.e. with the pentose-phosphate pathway included and the ribokinase reaction (reaction 36) to maintain the phosphate balance in the glycososome. The fructose branch was switched off to simulate a situation with glucose as the main energy source. The same model has been used by Haanstra et al (2017) Sci Rep 7:40406, to identify the most effective drug targets. Reaction numbers in the picture below do not correspond to the numbering in the Copasi file.