Tools for Systems biology modeling and data exchange

Magdeburg, 2023

Introduction to Modeling using COPASI

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Introduction to COPASI and how to use it to:

- Model a biochemical/biological system
- Simulate and analyse it
- Perform parameter estimation with experimental data
- CopasiSE and scripting

Block 1 – Setting up a model

- Finding models in databases
- Using SBML-files in COPASI
- Looking at the model structure using COPASI
- Modifying the model/setting it up

Why modeling?

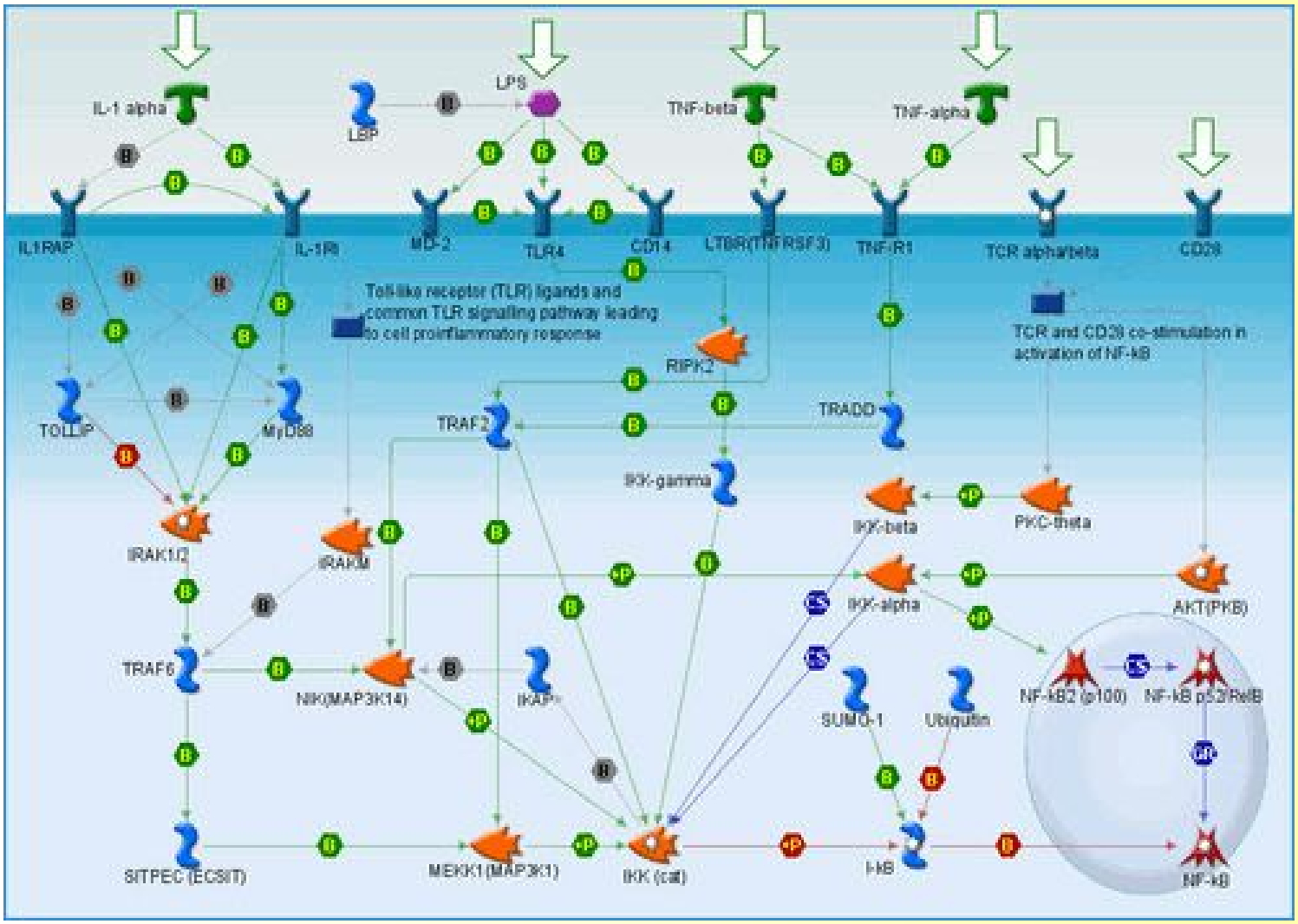
If we have a model and can

- reproduce experimental results
- justify the modeling choices
- do correct predictions

we have an indication that we have some understanding of the system

we save some experiments

Why modeling?

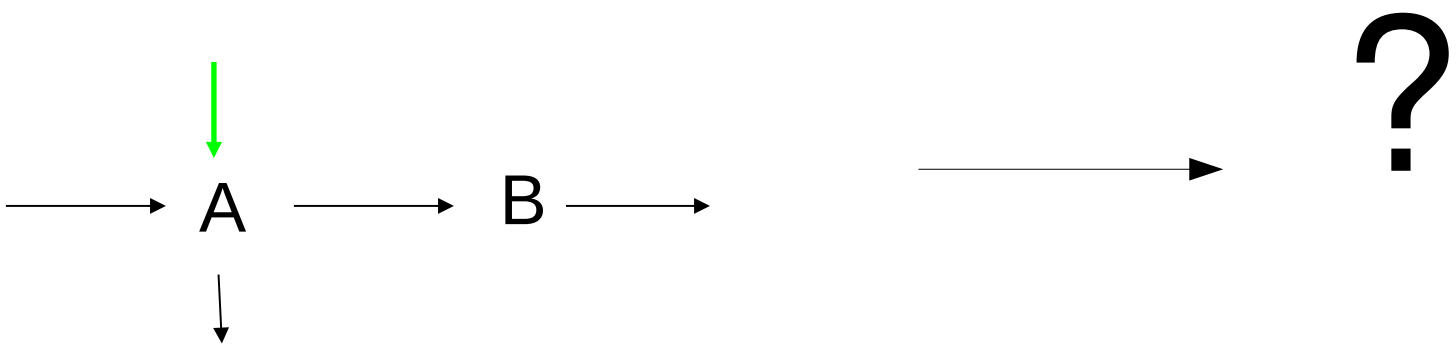


- complexity
- nonlinearity
- non-intuitive behaviour

From: http://pathwaymaps.com/maps/411/

Computer model are necessary

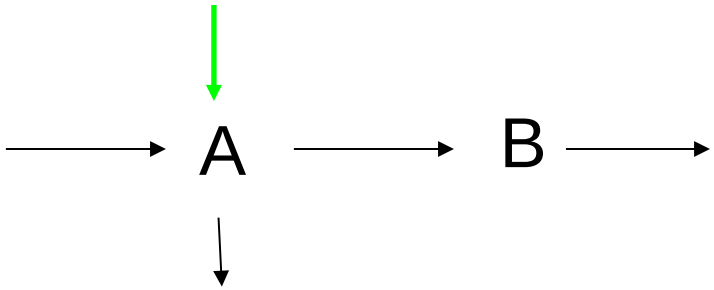
Example:

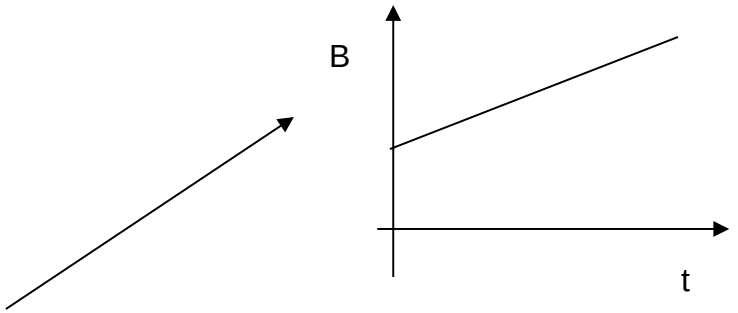


What happens to B, if I add more A?

Computer model are necessary

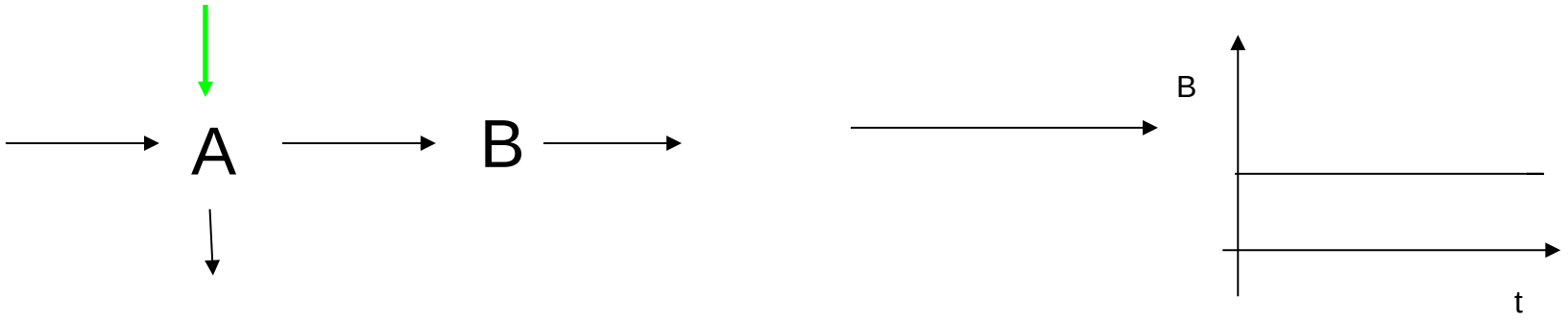
Example:





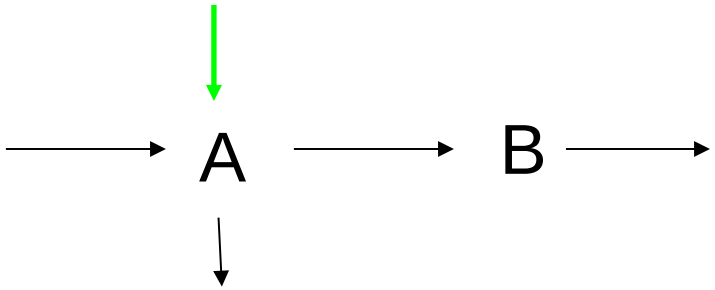
Computer model are necessary

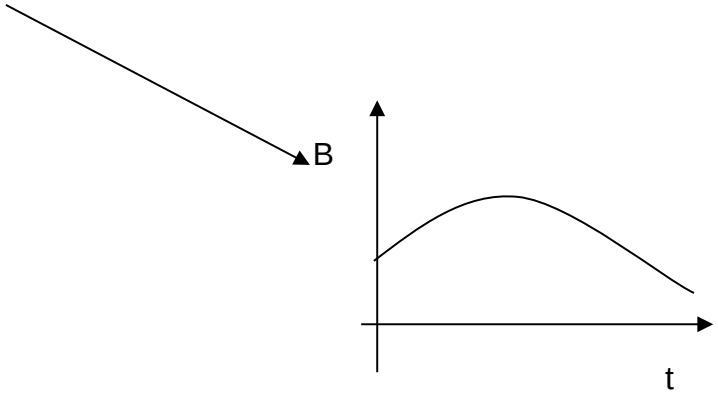
Example:



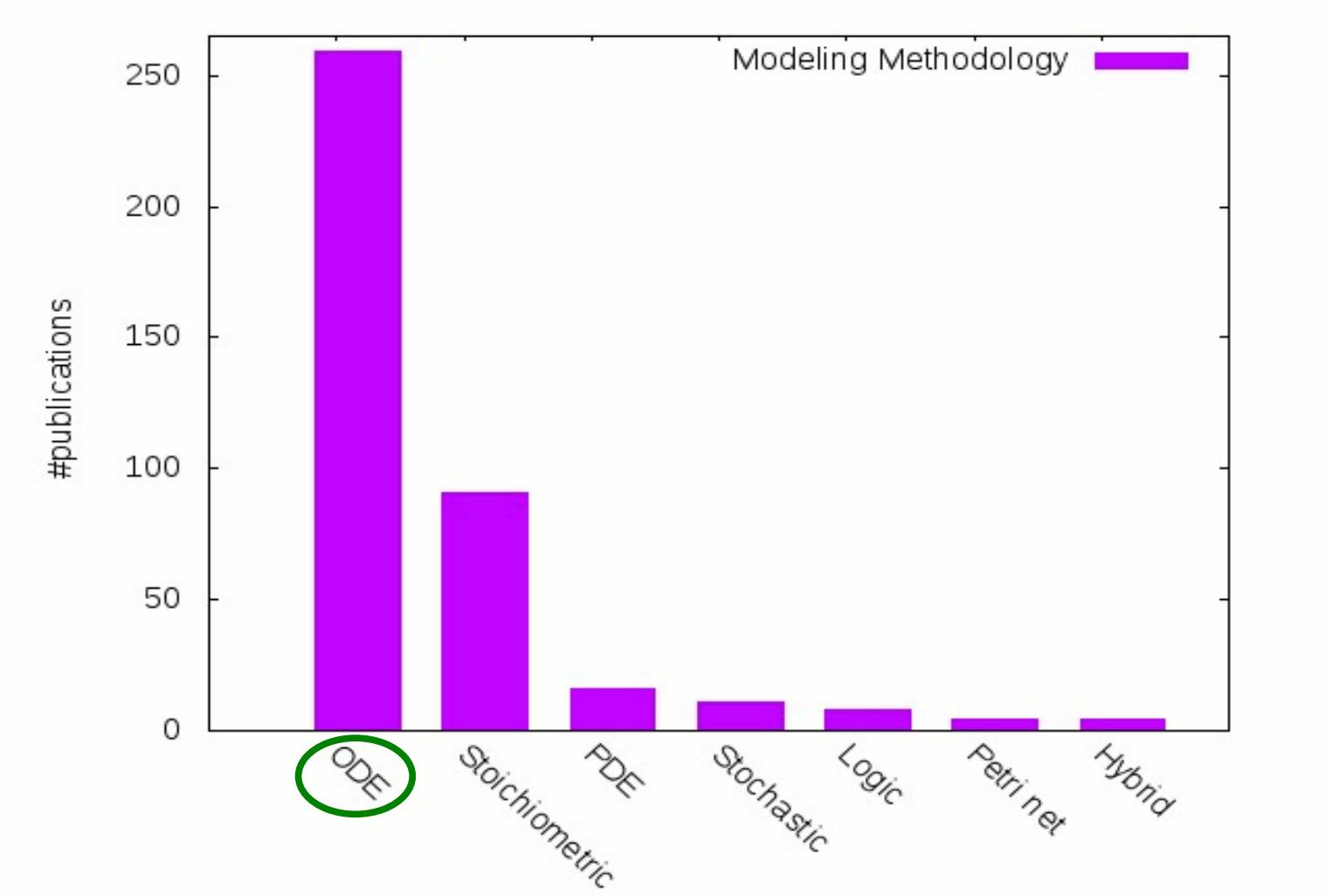
Computer model are necessary

Example:



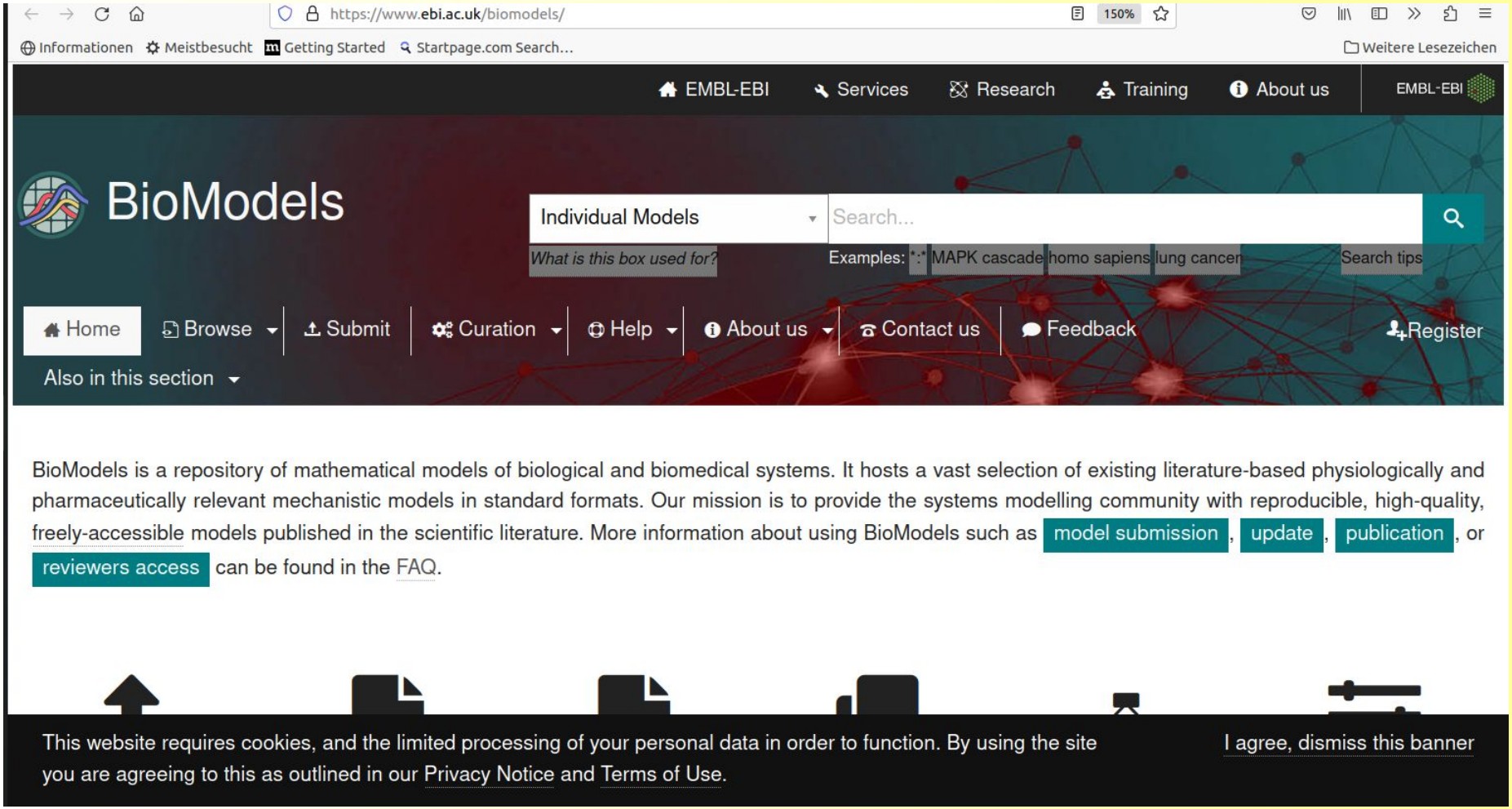


Usage of different model formalisms (cellular scale)



Hübner, Sahle and Kummer, FEBS Journal, 2011, Review

Biomodels – a database for Biomodels



Model exchange with SBML

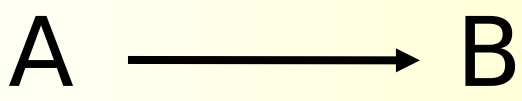
- Different software tools have different strengths and a different file format!
- In order to facilitate the exchange of biochemical models between the tools SBML was designed
- SBML is a XML based file format
- It contains all necessary elements to describe a biochemical model mathematically
- Only the model, not the simulation/analysis strategies are exchanged

Practice

COPASI – a modeling software

- Implement a model of only one reaction: G6P → F6P
- Load a model of glycolysis by Teusink et al.
- Look at the model structure and understand it

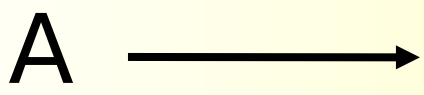
Modeling – a **very** simple example



1st order reaction or radioactive decay

Writing the ODEs

starting with the reaction equation



we arrive at the differential equation

$$\frac{d[A]}{dt} = -1 \cdot \nu_1$$

rate of change,
can also be written as
dA/dt, $\dot{A}$, A´

stoichiometry

reaction speed

...

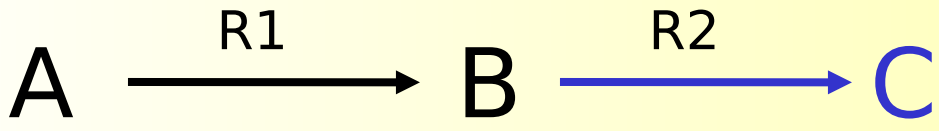
and for [B]:

$$\mathrm{dA/dt} = -1 \cdot v_1$$

$$\mathrm{dB/dt} = +1 \cdot v_1$$

...

adding the second step:



$$\mathrm{dA/dt} = -1 \cdot v_1$$

$$\mathrm{dB/dt} = +1 \cdot v_1 \; -1 \cdot v_2$$

$$\mathrm{dC/dt} = +1 \cdot v_2$$

adding the kinetics

Now we need to specify the reaction kinetics: Mass action

$$v_1 = k_1 \cdot A$$

and

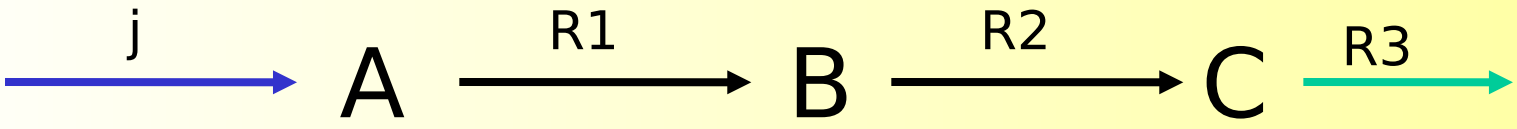
$$v_2 = k_2 \cdot B$$

$$\mathrm{dA/dt} = -1 \cdot k_1 \cdot A$$

$$\mathrm{dB/dt} = +1 \cdot k_1 \cdot A - 1 \cdot k_2 \cdot B$$

$$\mathrm{dC/dt} = +1 \cdot k_2 \cdot B$$

closed/open system

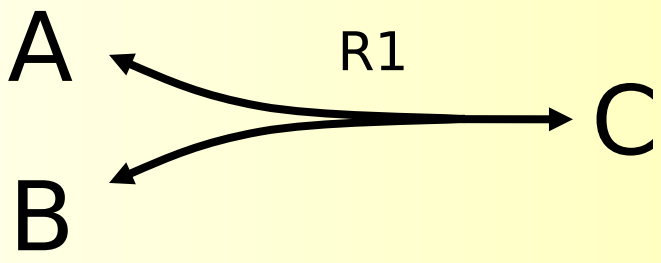


$$\mathrm{dA/dt} = -1 \cdot k_1 \cdot A + j$$

$$\mathrm{dB/dt} = +1 \cdot k_1 \cdot A - 1 \cdot k_2 \cdot B$$

$$\mathrm{dC/dt} = +1 \cdot k_2 \cdot \mathrm{B} - \mathrm{k_3} \cdot C$$

reversible/higher order reactions



$$\mathrm{dA/dt} = -1 \cdot k_1 \cdot A \cdot \mathrm{B} + \mathrm{k_{-1}} \cdot C$$

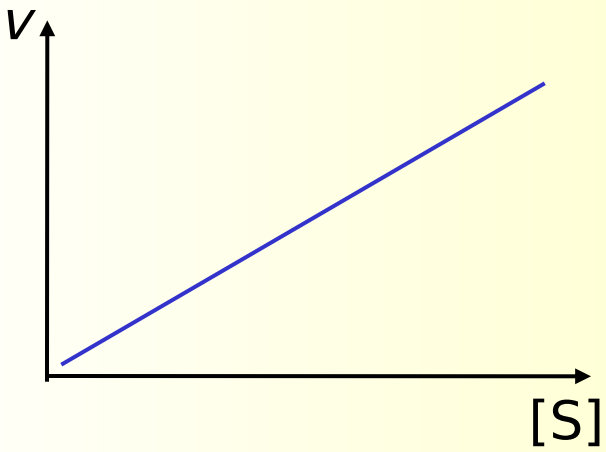
$$\mathrm{dB/dt} = -1 \cdot k_1 \cdot A \cdot B + \mathrm{k_{-1}} \cdot C$$

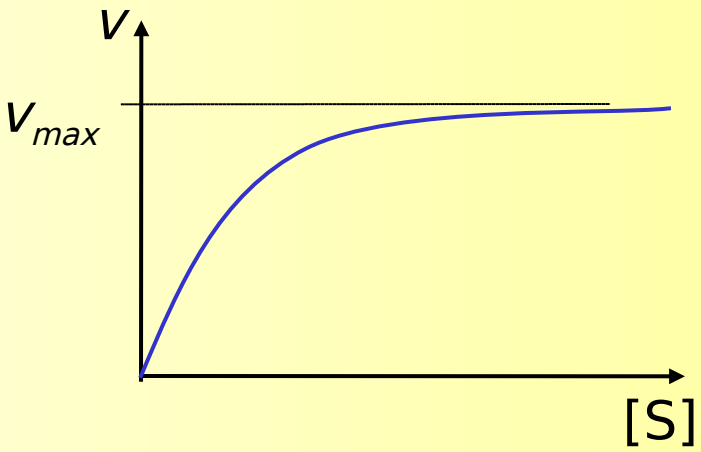
$$\mathrm{dC/dt} = +1 \cdot k_1 \cdot A \cdot \mathrm{B} - \mathrm{k_{-1}} \cdot C$$

a reversible reaction can be modeled as a combination of a forward and a backward reaction.

All reactions are reversible!

Enzyme kinetics





first order mass action:

more substrate
->faster reaction

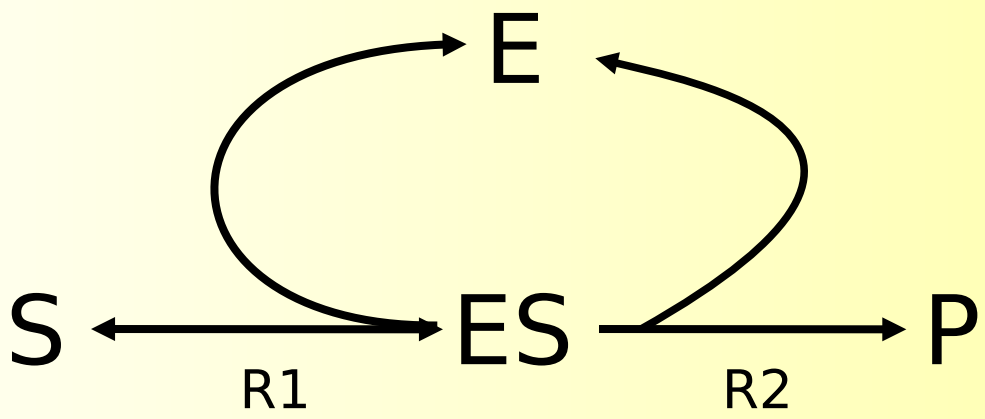
enzyme kinetics:

the enzyme has finite capacity to catalyze the reaction

-> v_{max}

Michaelis-Menten/Briggs-Haldane kinetics

we create a model of what we think happens in a simple enzymatic reaction:



differential equation for the detailed enzyme reaction:

$$dS/dt = -k_1 \cdot S \cdot E + k_{-1} \cdot ES$$

$$dE/dt = -k_1 \cdot S \cdot E + k_{-1} \cdot ES + k_2 \cdot ES$$

$$dES/dt = +k_1 \cdot S \cdot E - k_{-1} \cdot ES - k_2 \cdot ES$$

$$dP/dt = +k_2 \cdot ES$$

conserved entities: The total enzyme concentration can in many cases be considered constant: $E + ES = E_0 = \text{constant}$

Assumptions: fast equilibrium of ES formation and S in excess compared to E:

$$v = \frac{k_2 \cdot S \cdot E_0}{K_M + S} = \frac{v_{max} \cdot S}{K_M + S}$$

Enzyme Kinetics - PingPong-Mechanism

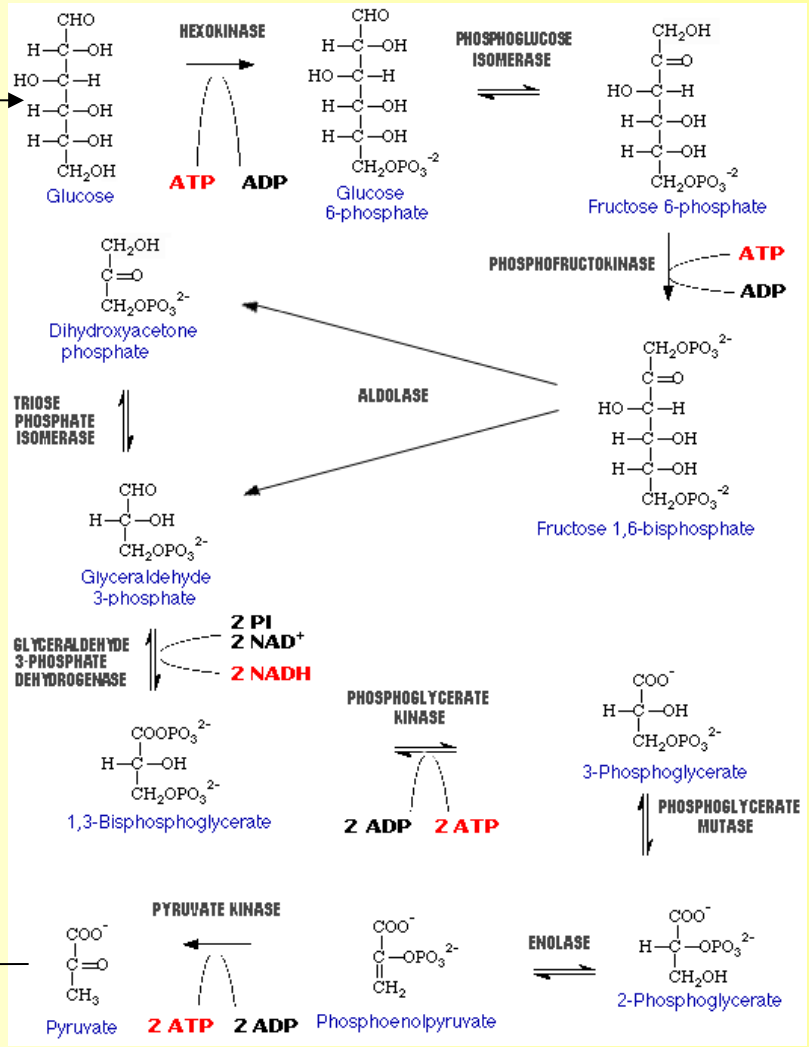
E + S1 <==> ES1 ----> E* + P1 <===> ES2 ------> E + P2

Analogous procedure:

$$V = V1 * \frac{S1 * S2}{\left(KmS2 * S1 + KmS1 * S2 + S1 * S2 \right)}$$

Example: Glycolysis

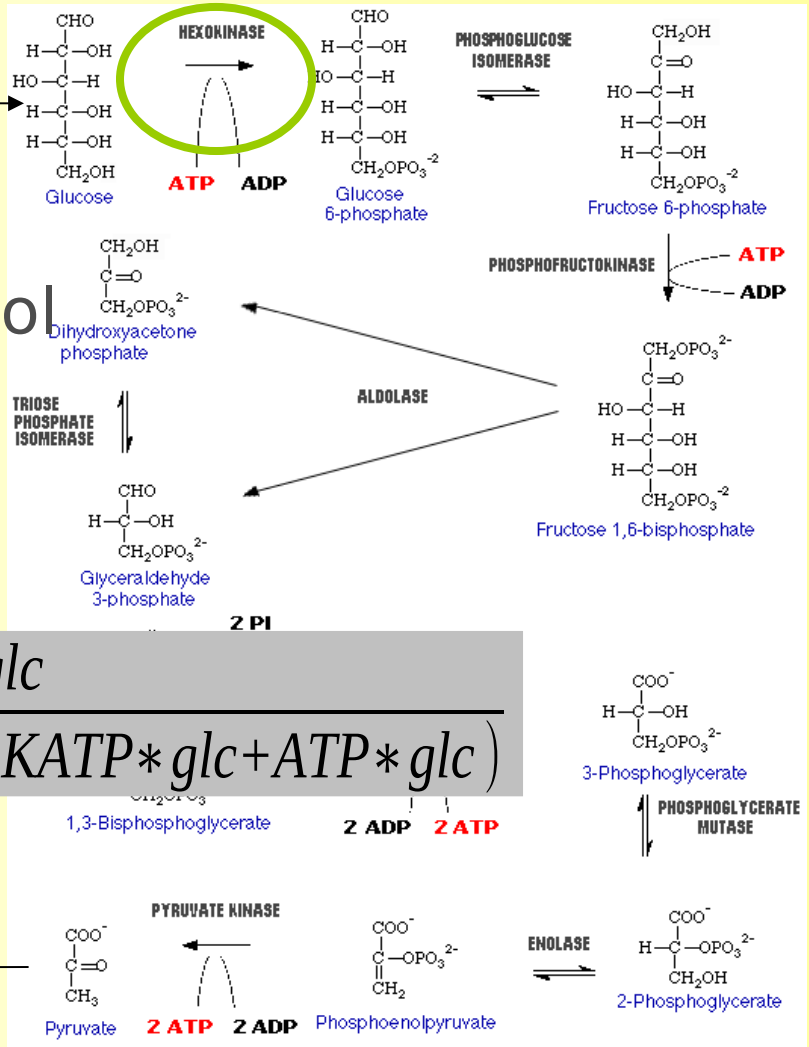
$$glc' = v_{trans} - v_{hk}$$
$$g6p' = v_{hk} - v_{pgi}$$
$$f6p' = v_{pgi} - v_{pfk}$$
$$f16p' = v_{pfk} - v_{ald}$$
$$dhap' = v_{ald} - v_{ti}$$
$$gap' = v_{ald} + v_{ti} - v_{gpdh}$$
$$bpg' = v_{gpdh} - v_{pgk}$$
$$p3g' = v_{pgk} - v_{pgm}$$
$$p2g' = v_{pgm} - v_{eno}$$
$$pp' = v_{eno} - v_{pyk}$$
$$py' = v_{pyk} - v_{py}$$



Example: Glycolysis

V_{hk}

- MM for 2 non-competing substrates
- Often ATP as constant pool

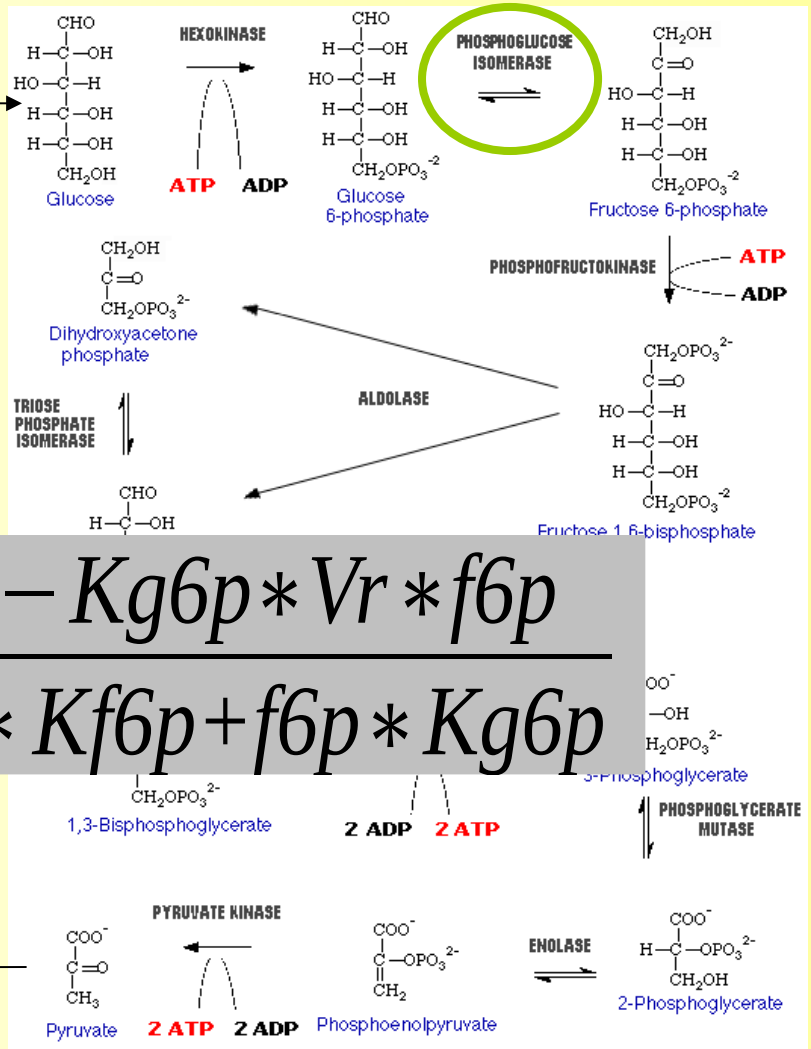


$$vhk = Vhk * \frac{ATP * glc}{(KATP * Kglc + Kglc * ATP + KATP * glc + ATP * glc)}$$

Example: Glycolysis

v_{pgi}

- Reaction strongly reversible
- reversible MM



$$vpgi = \frac{Kf6p * Vhin * g6p - Kg6p * Vr * f6p}{Kg6p * Kf6p + g6p * Kf6p + f6p * Kg6p}$$

Generality of these principles

- valid not only for metabolic pathways
- valid not only for enzymatic reaction
- valid for signalling systems
- valid for genetic networks etc.

Practice

Looking at the ODEs

- Have a look at the ODE version of your model(s) in COPASI
- Change the kinetics of your one enzyme model to Michaelis-Menten and check again

Block 2 – Simulation

- Integration of ODEs
- Numerical algorithms
- Running simulations
- Plotting the results
- Using sliders

Simulation: Solving the ODEs

For simple cases, it is possible to analytically solve the equations:

$$\frac{d[A]}{dt} = -k_1 \cdot [A] \quad \longrightarrow \quad [A](t) = [A](0) \cdot e^{-k_1 \cdot t}$$

It is easy to compute [A] for any time t directly.

This is not possible for most biochemical models!

Numerical solution of the ODEs using Euler

$$\frac{d[A]}{dt} = -k_1 \cdot [A]$$

$$[A](t+\Delta t) = [A](t) + \Delta t \cdot \left(-k_1 \cdot [A](t)\right)$$

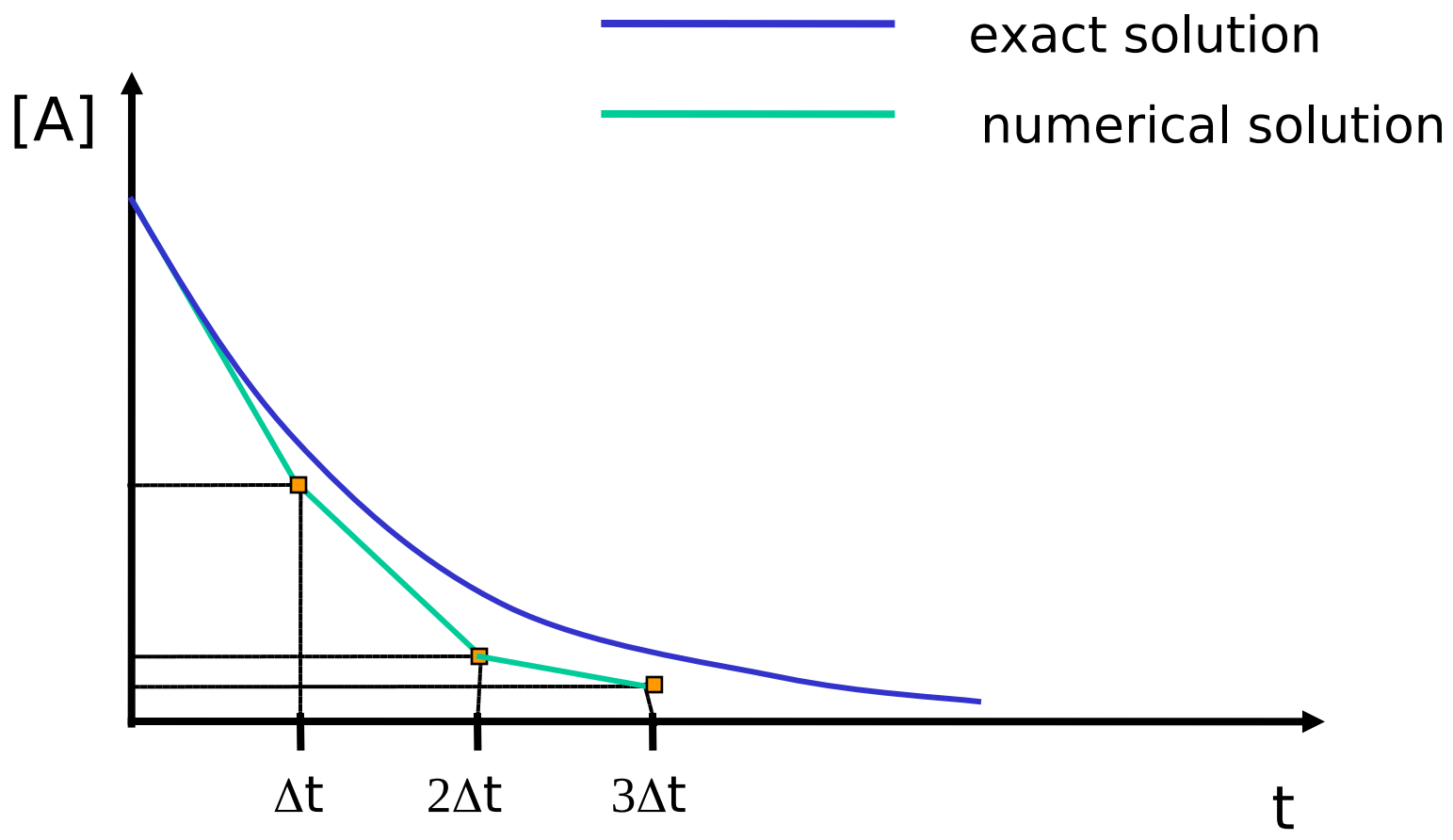
new value of [A]

old value of [A]

time step

rate of change
(right side of the ODE)

Euler



Improving numerical solutions:

- Methods that produce smaller errors per time step (e.g. Runge-Kutta)
- Automatic determination of step-sizes
- Methods that can deal with stiff systems
- Compare results!

Simulating the Models

By numerical integration of the systems equations using a stiff solver, e.g. LSODA

If particle numbers low -> stochastic methods (not covered in this course)

Practice

Run a simulation....

- Run a simulation and plot the result using the output assistant
- Manually vary a parameter and see the impact:
  - For the toy model, you can e.g. change initial concentrations of the species G6P and F6P
  - For the glycolysis model you can try to change the parameter you think will impact the model behaviour a lot
- Do the same by using sliders

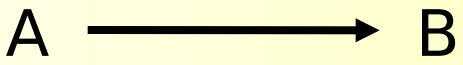
Block 3 – Steady states

- Definition of a steady state
- Algorithms to compute steady states
- Run a steady state computation
- Using parameter scans

Steady States

If the rate of change of all variables (concentrations) in an open system is zero we have a steady state.

If the rate of change of all variables in a closed system is zero we have an equilibrium.



Steady states can have different stability properties.

Computing the Steady State

- Simplest possibility: Simulation.
  Disadvantage: Rather high computational costs

- Newton-Algorithm
  Can compute steady state quite efficiently and precise

Computing the Steady State

Right side of the ODEs has to be zero.

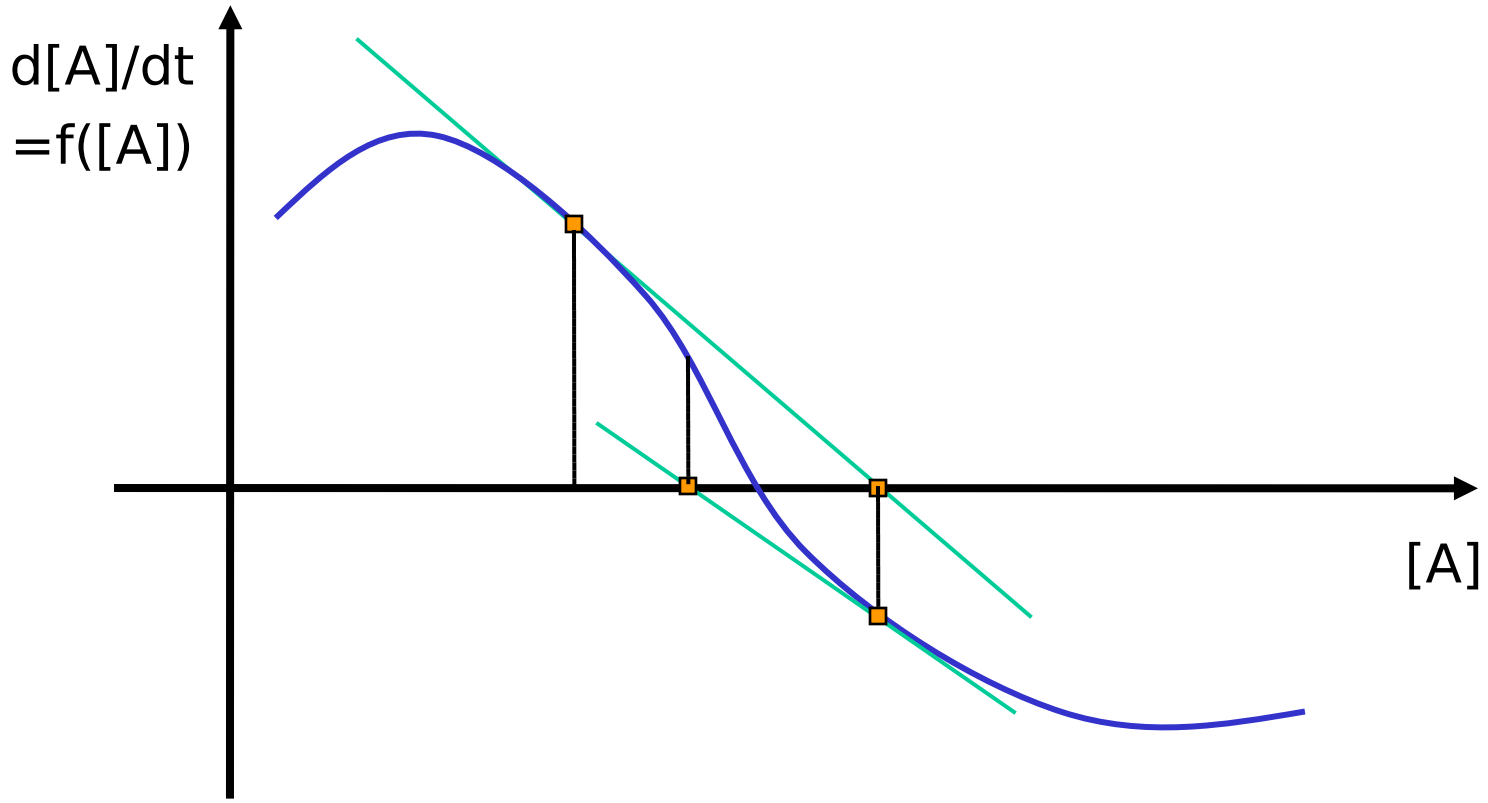
$d[A]/dt = f([A])$

Steady State:

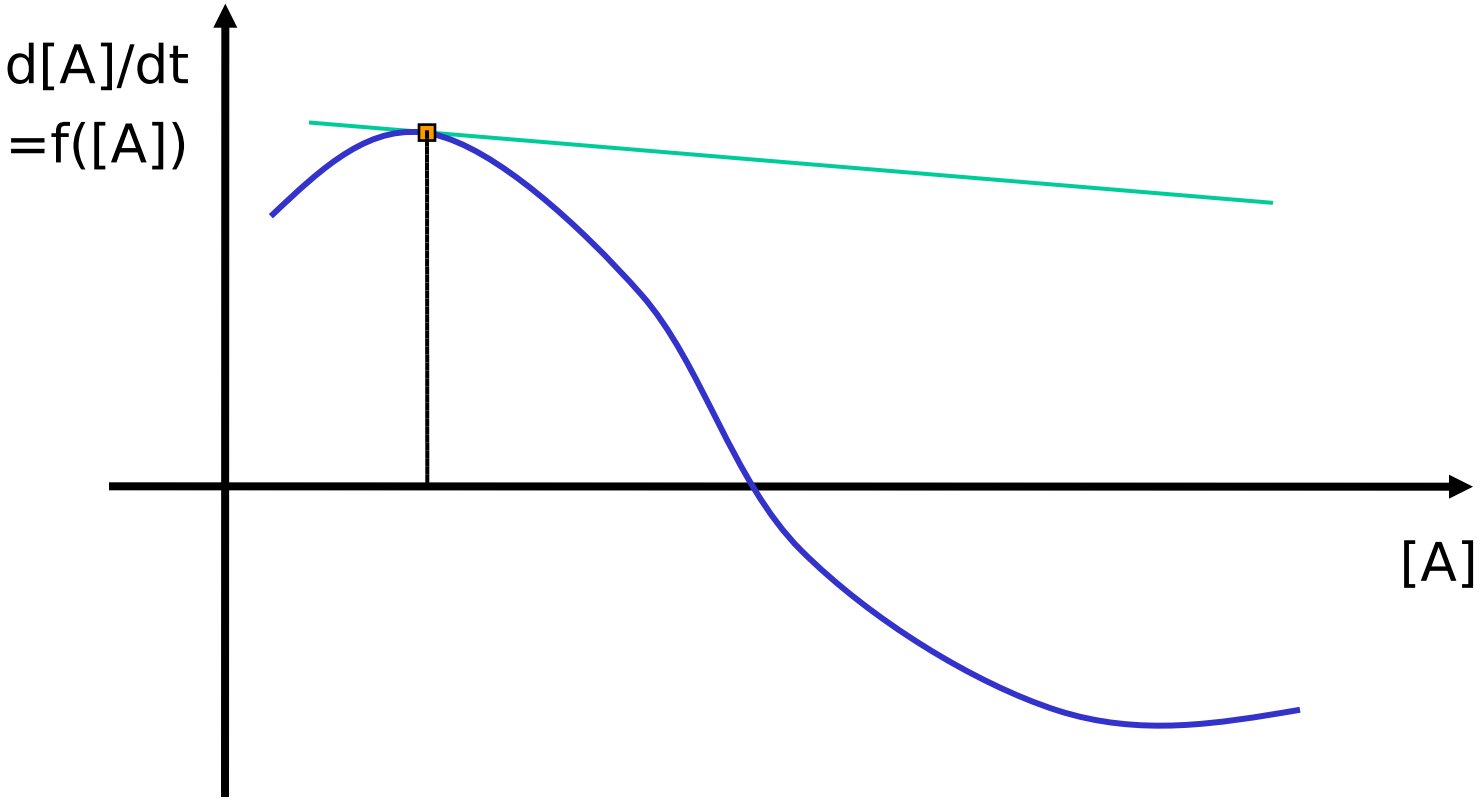
$f([A]) = 0$

Newton

$$[A]_{i+1} = [A]_i - \frac{f([A]_i)}{f'([A]_i)}$$



Problems of the Newton-Algorithm



Practice

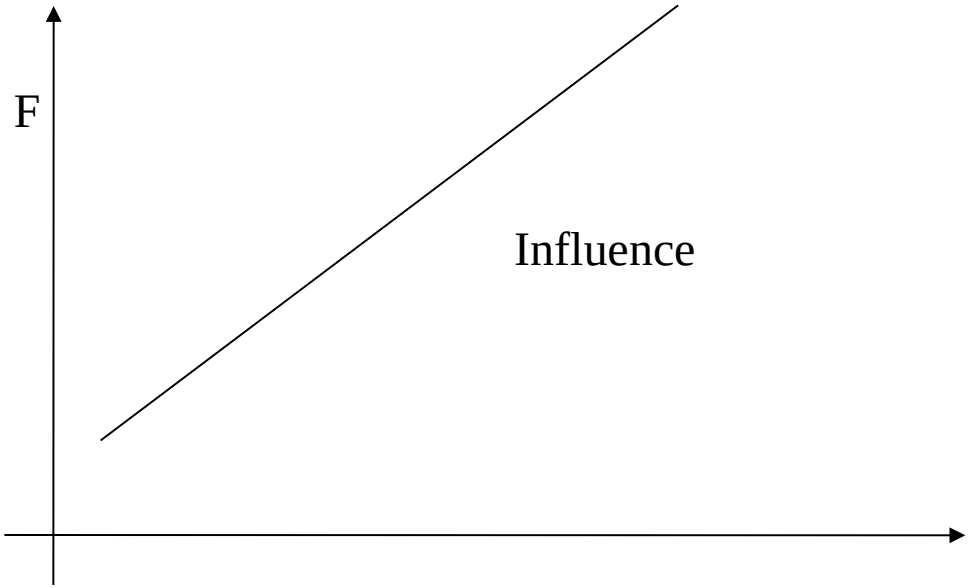
Run a steady state analysis....

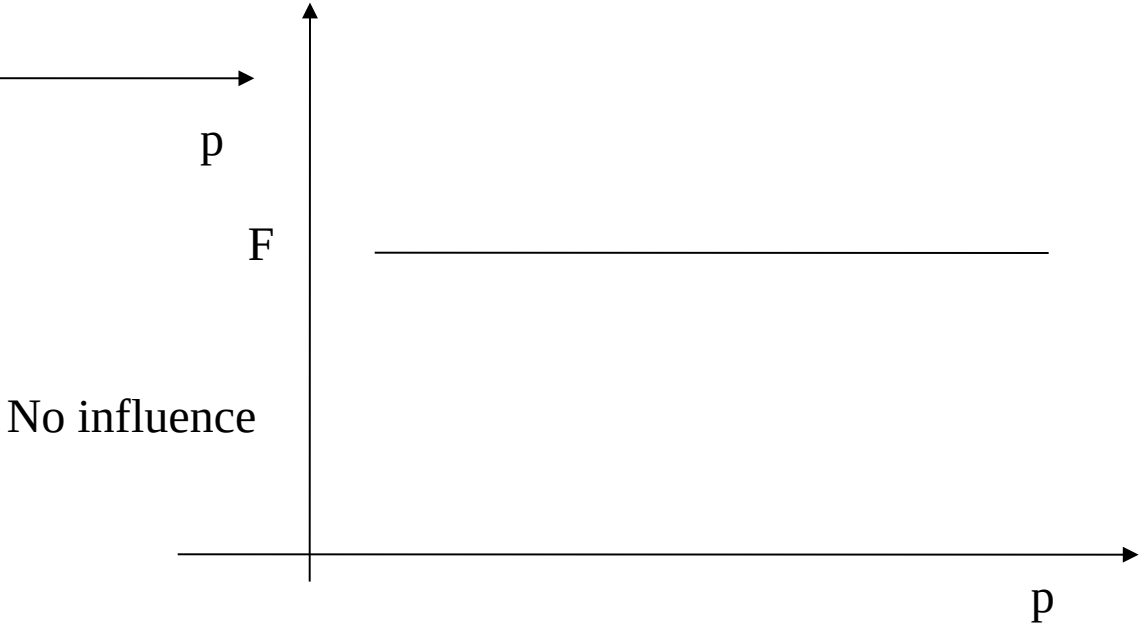
- Implement in- and efflux for your one-enzyme model
- Run a steady state analysis and compare the results of integration and Newton for both models
- Use a parameter scan to see the dependency of the steady state on parameters

Block 4: Sensitivities

- Used to answer questions like: How much influence does a specific parameter has on the behaviour of the system?
- What are the most relevant reactions determining the flux through my system?
- Is it important to know this specific parameter for certain?

How to measure influence....





MCA (only in steady state)

Dependencies are described mathematically using partial derivatives.

$$c_x^y = \left(\frac{x}{y} \frac{\Delta y}{\Delta x} \right)_{\Delta x \to 0} \quad c_x^y = \frac{x}{y} \frac{\delta y}{\delta x} = \frac{\delta \ln y}{\delta \ln x}$$

Coefficients

The MCA defines so-called coefficients – numerical values which describe the impact of a pertubation on different system variables.

Two types of coefficients are used:

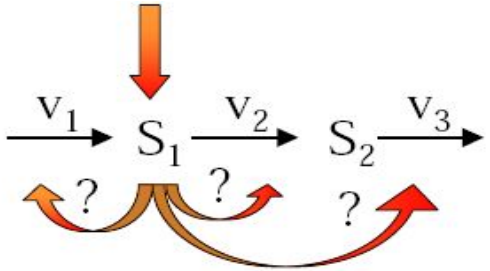
Local:

Influence on one single reaction without considering the system

Global:

Influence on system's properties like ss-levels

ε-Elasticity:



Elasticity coefficient of reaction k relative to metabolite S_i

$$\varepsilon_i^k = \frac{\partial v_k}{\partial S_i}\frac{S_i}{v_k} = \frac{\partial \ln v_k}{\partial \ln S_i}$$

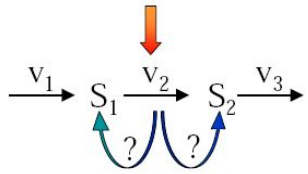
How much impact do changes of the metabolite concentration S_i have on the reaction rate v_k?

Partial derivative
(sensitivity of the rate ***v*** of reaction ***k*** to changes in the concentration of metabolite $\boldsymbol{S_i}$)

Scaling factor
(we are interested in relative changes). This yields a coefficient which is independent from the original values of $\boldsymbol{S_i}$ and $\boldsymbol{v_k}$.

The derivative can be directly calculated from the kinetic law.

Concentration Control Coefficient



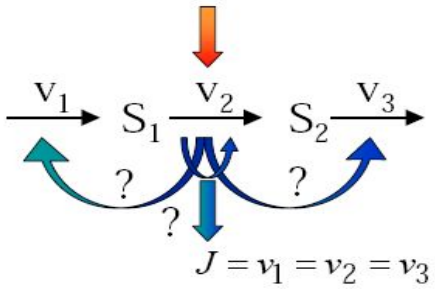
Control coefficient of the steady state concentration of metabolite S_i relative to a pertubation in reaction *k*

$$C_k^{S_i} = \frac{\partial S_i}{\partial v_k}\frac{\partial p}{\partial p}\frac{v_k}{S_i} = \frac{\partial S_i}{\partial v_k}\frac{v_k}{S_i} = \frac{\partial \ln S_i}{\partial \ln v_k}$$

How much impact do changes of a single reaction rate have on the steady state concentrations of the metabolites?

This derivative cannot be directly calculated from the kinetic law since the steady state alteration of the entire system has to be taken into account.

Flux Control Coefficient



Control Coefficient of the steady state flux *J* of the reaction *j* relative to a pertubation in the rate *v* of reaction *k*

$$C_k^{J_j} = \frac{\partial J_j}{\partial v_k}\frac{\partial p}{\partial p}\frac{v_k}{J_j} = \frac{\partial J_j}{\partial v_k}\frac{v_k}{J_j} = \frac{\partial \ln J_j}{\partial \ln v_k}$$

How much impact do changes of a single reaction rate have on the steady state flux of (another) reaction?

This derivative cannot be directly calculated from the kinetic law since the steady state alteration of the entire system has to be taken into account.

Unscaled coefficients

In some cases it is useful to consider the coefficients non-scaled.

Example: In case the steady state value (concentration, flux) or a parameter value equals zero scaling becomes impossible (division by zero is not defined).

Practice

Sensitivities

- Analyse your models using MCA
- Where are sensitive points in your model
- Does that make sense to you in the biological context?