

A scenic view of a town with colorful buildings and snow-capped mountains in the background. The buildings are multi-story, with various colors including orange, yellow, green, and white. The mountains are large and rugged, covered in snow, and set against a clear blue sky. The text "An introduction to modelling of biological systems" is overlaid in the center of the image.

# An introduction to modelling of biological systems



# Overview

## **Part I - Kinetic modeling**

- What is modelling about?
- Kinetic models of biochemical pathways
- Simulation and dynamic behaviour
- Model fitting

## **Part II - Constraint-based modelling**

- Network reconstruction
- Flux Balance Analysis (FBA)

## **Part III - Other dynamical cell models**

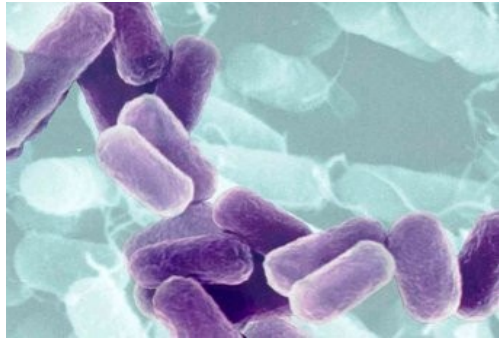
- Whole-cell models
- Gene expression models
- Stochastic simulation
- Spatial simulation models
- Model formats and tools

## **Part IV - Data analysis and regression**

- Principal Component Analysis
- Clustering
- Linear regression

## **Blackboard session (Wednesday / Thursday)**

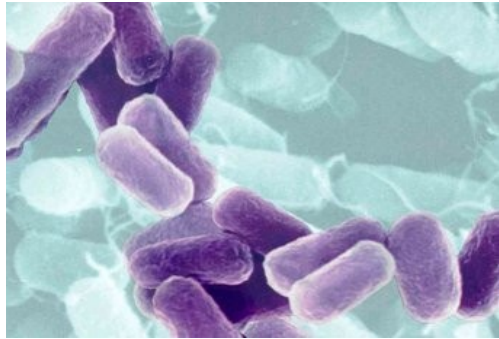
- Advanced kinetic modelling and enzyme costs



How can a living cell emerge from sugar, water, and a couple of salts?

Minimal Medium for *E. coli*

Glucose	5 g/l
Na <sub>2</sub> HPO <sub>4</sub>	6 g/l
KH <sub>2</sub> PO <sub>4</sub>	3 g/l
NH <sub>4</sub> Cl	1 g/l
NaCl	0.5 g/l
MgSO <sub>4</sub>	0.12 g/l
CaCl <sub>2</sub>	0.01 g/l



How can a living cell emerge from sugar, water, and a couple of salts?

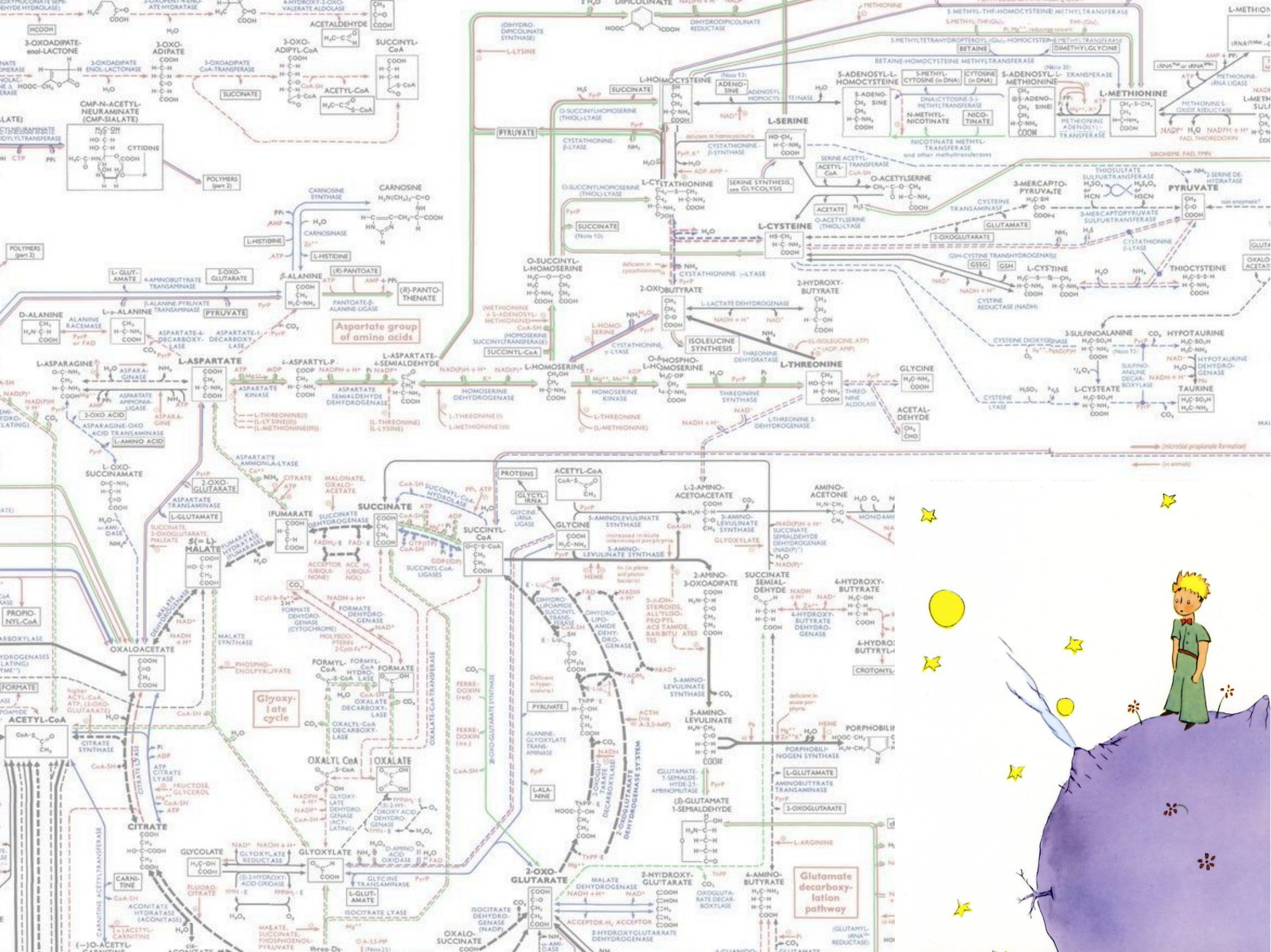
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$\text{MgSO}_4$	0.12 g/l
$\text{CaCl}_2$	0.01 g/l

L'essentiel est invisible pour les yeux.





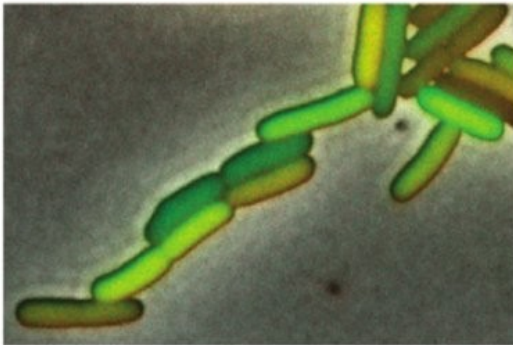


From pictures of cells to mathematical models

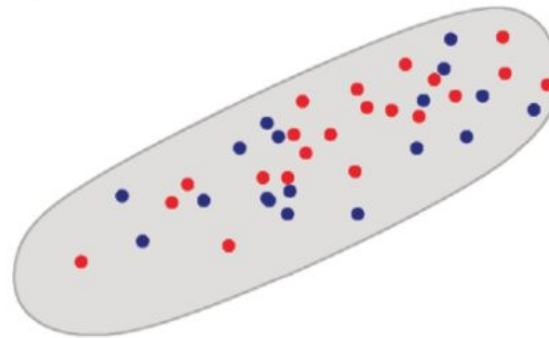


# Simulation models are simple pictures of cells, in a mathematical form

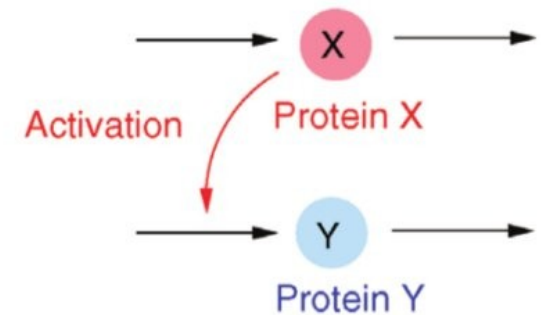
**(a)** Biological system



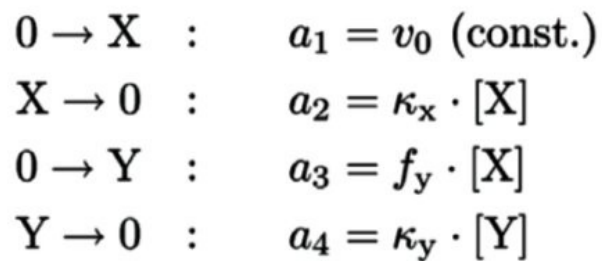
**(b)** Mental model



**(c)** Model scheme



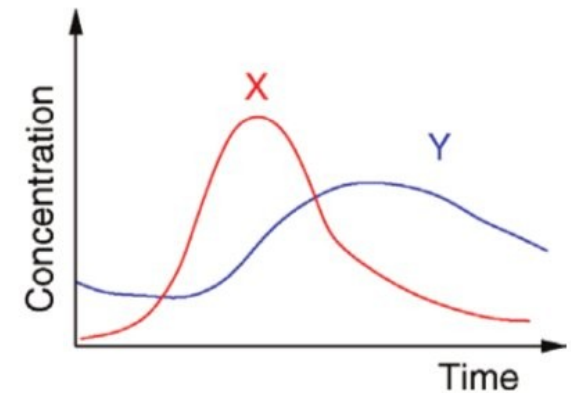
**(d)** Process model



**(e)** Dynamical model

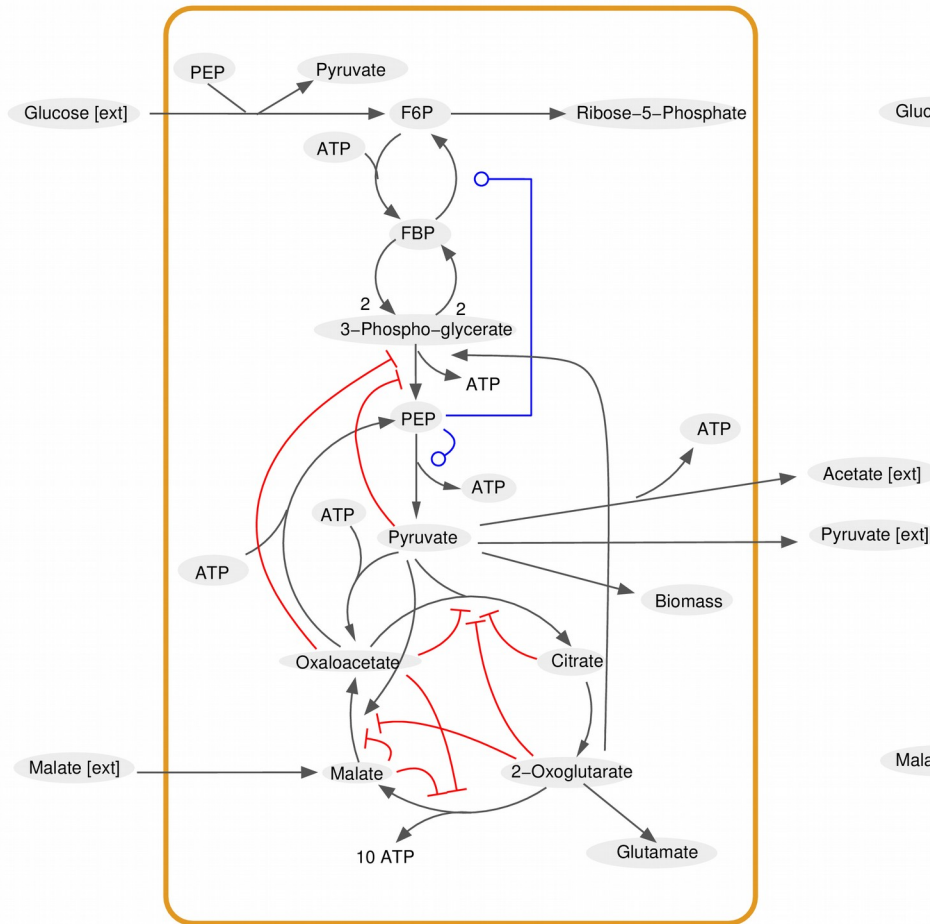
$$\begin{aligned}
 dx/dt & = v_0 - \kappa_x x \\
 dy/dt & = f_y x - \kappa_y y \\
 x(0) & = x_0 \\
 y(0) & = y_0
 \end{aligned}$$

**(f)** Quantitative results

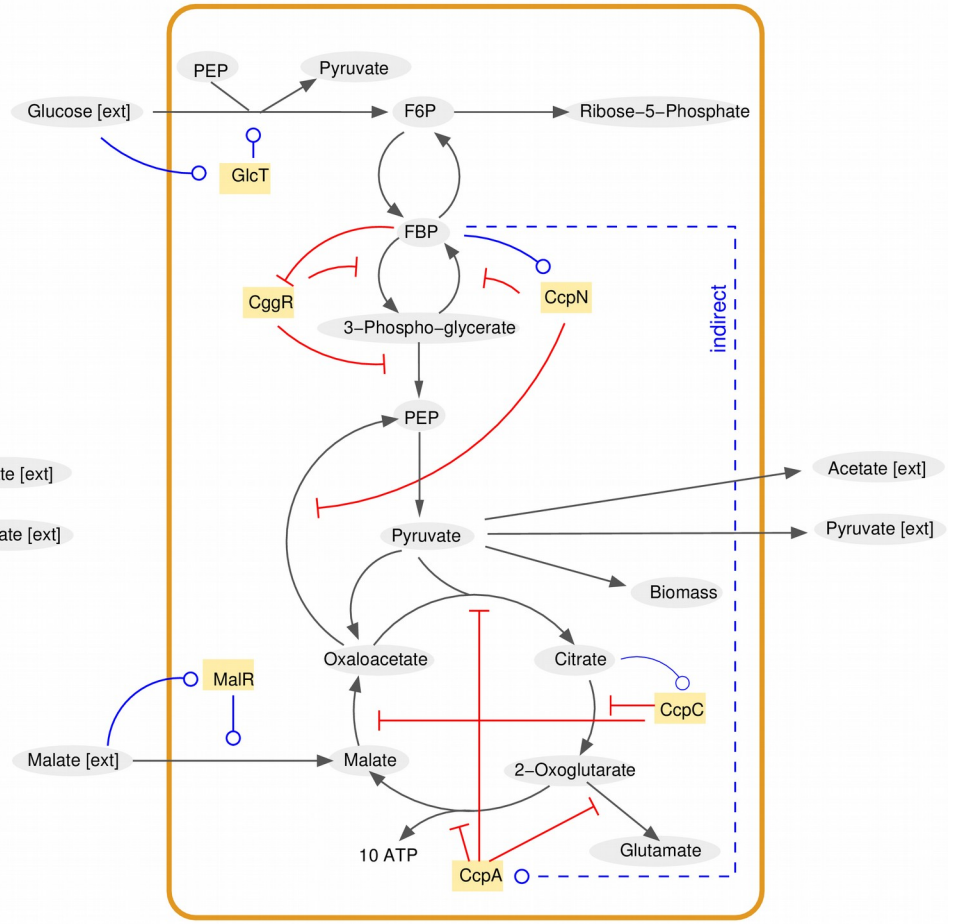


# How can we translate network schemes into simulation models?

(a) Allosteric regulation



(b) Transcriptional regulation



Metabolite      Reaction      Activation/induction

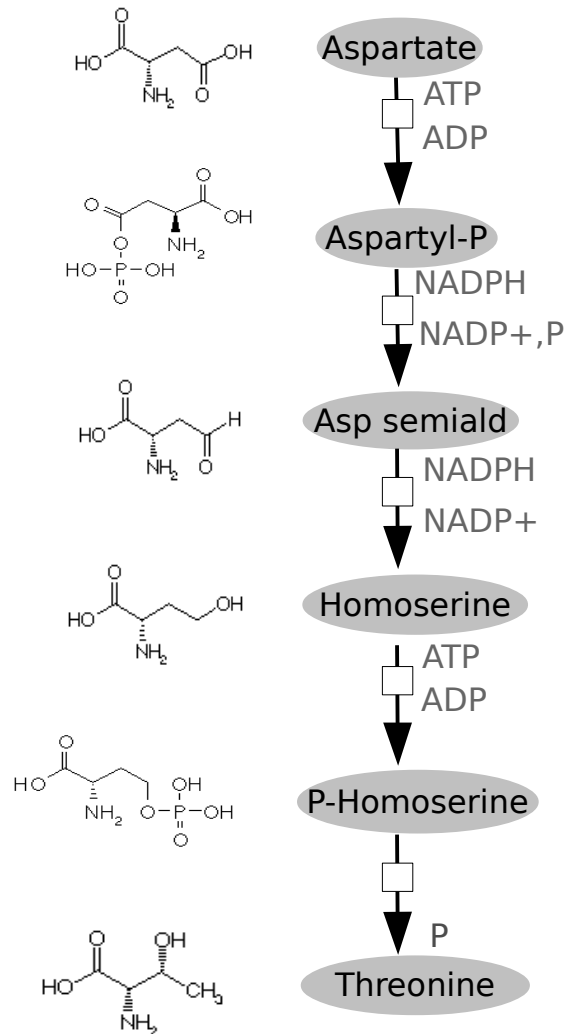
Inhibition/repression      Transcription factor



# What aspects of a pathway do we want to model?

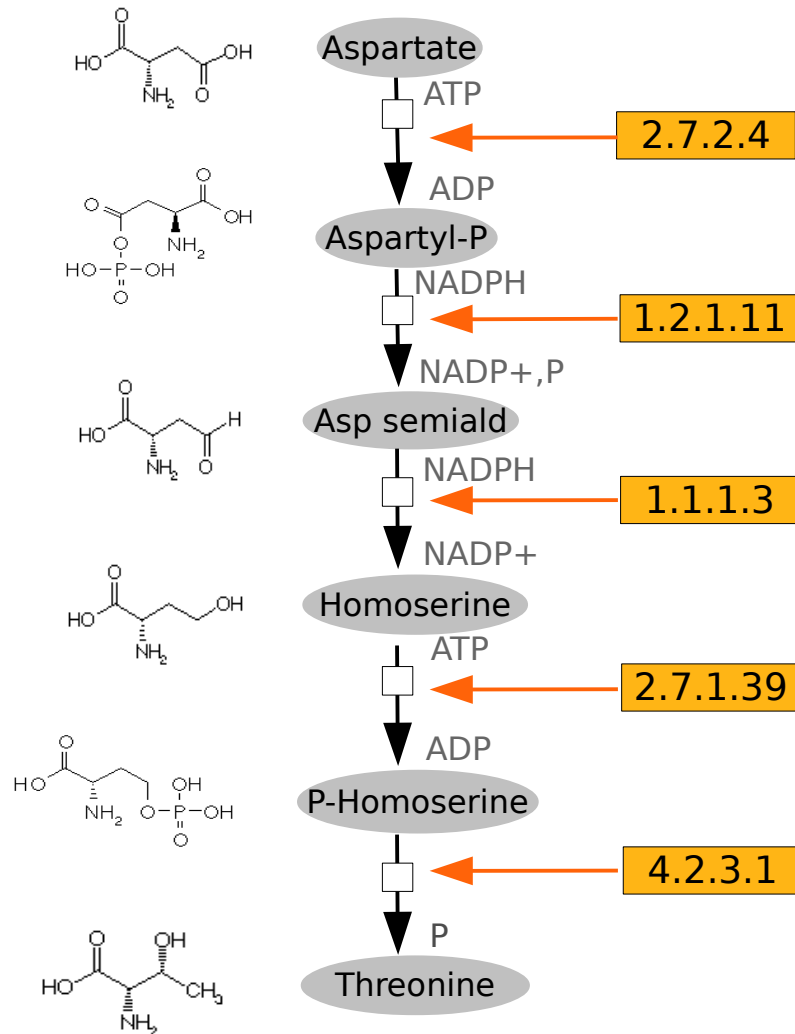
## Metabolites

## Reactions

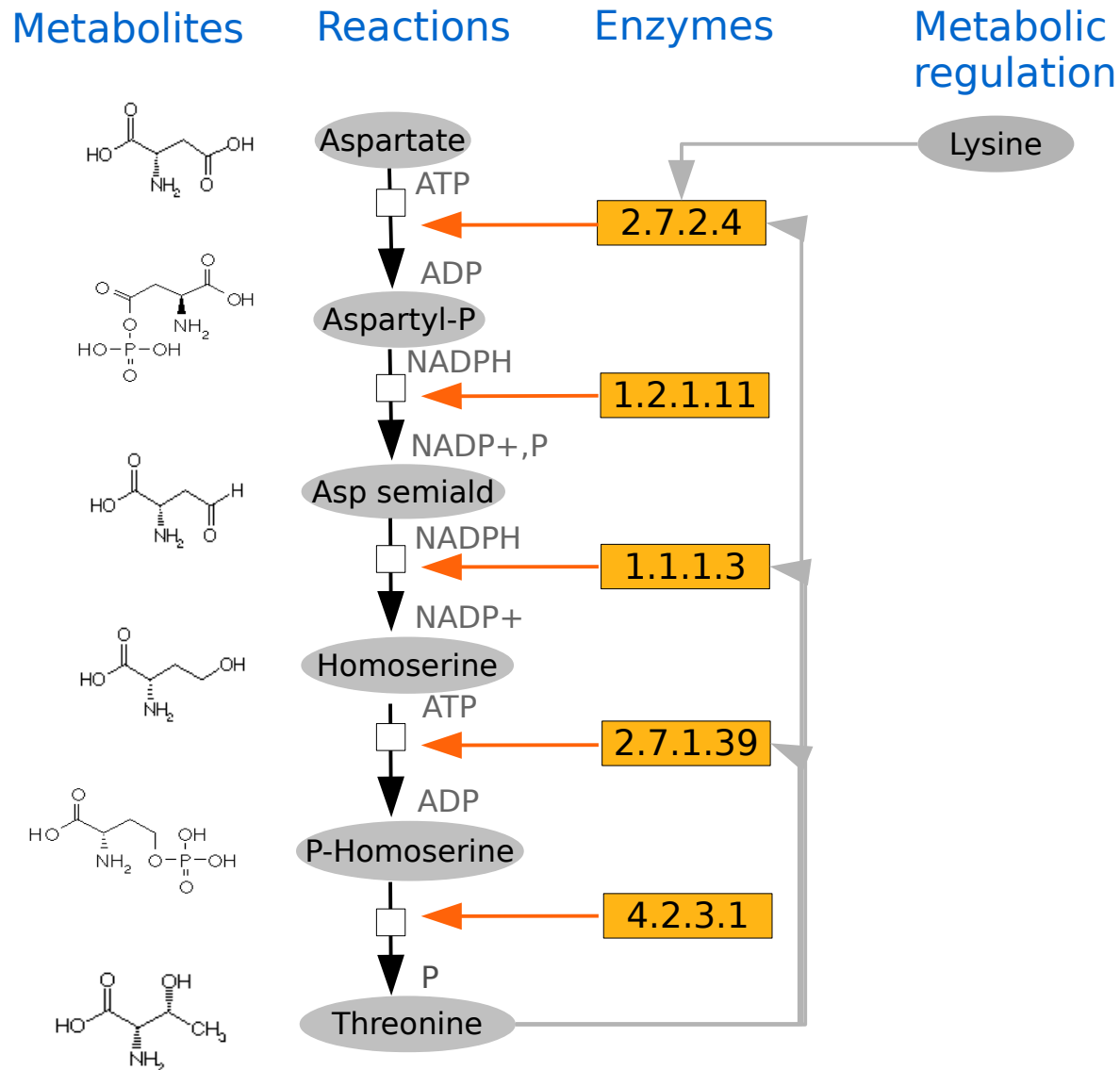


# What aspects of a pathway do we want to model?

Metabolites      Reactions      Enzymes

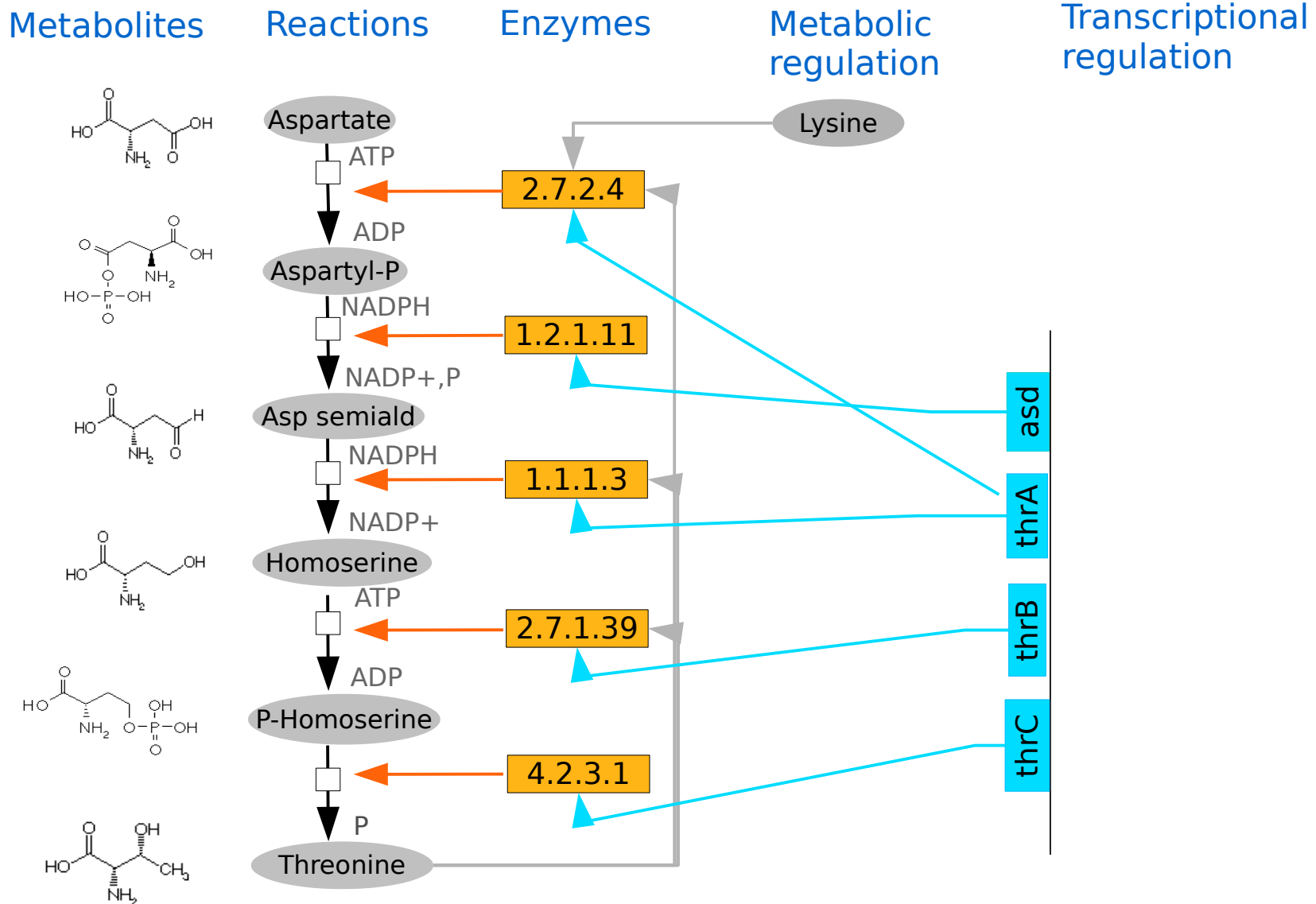


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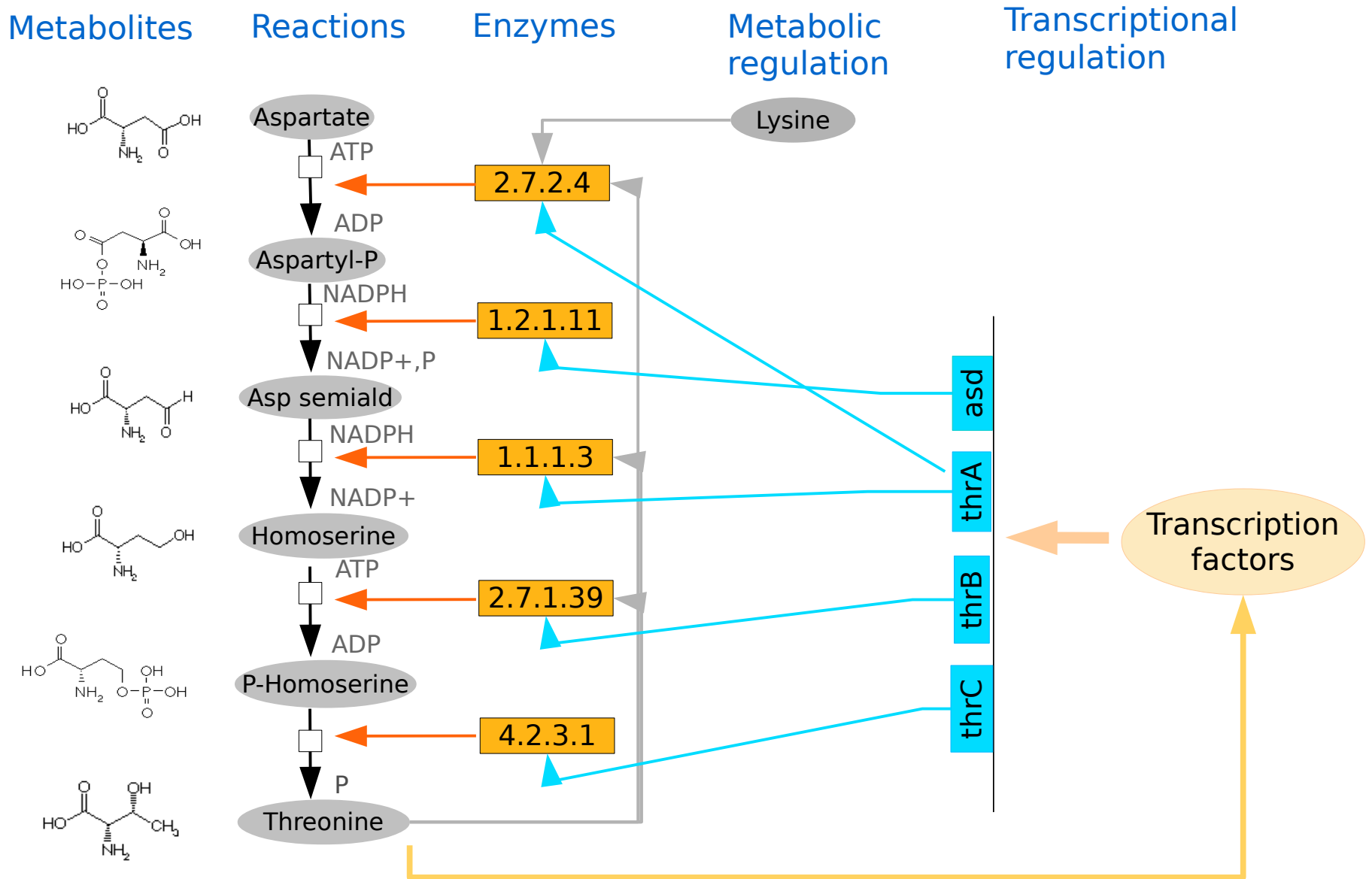




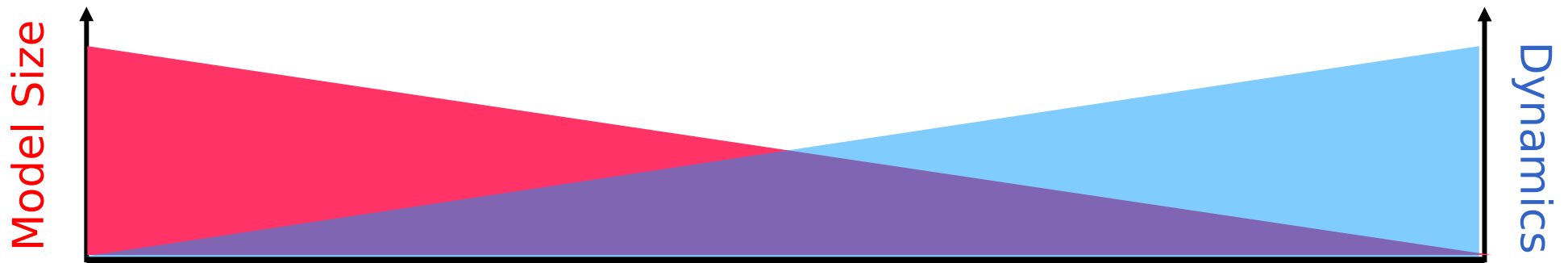
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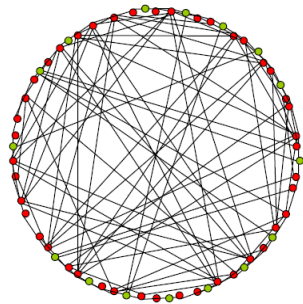
# What aspects of a pathway do we want to model?



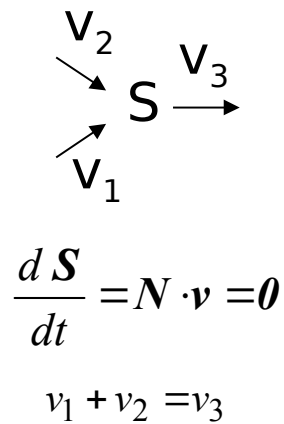
# Modelling approaches cover different levels of complexity



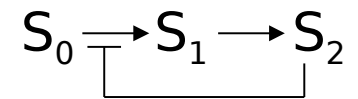
Topological Analysis



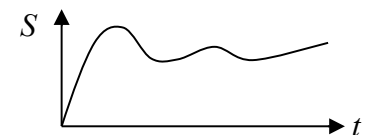
Flux Balance Analysis



Kinetic modeling

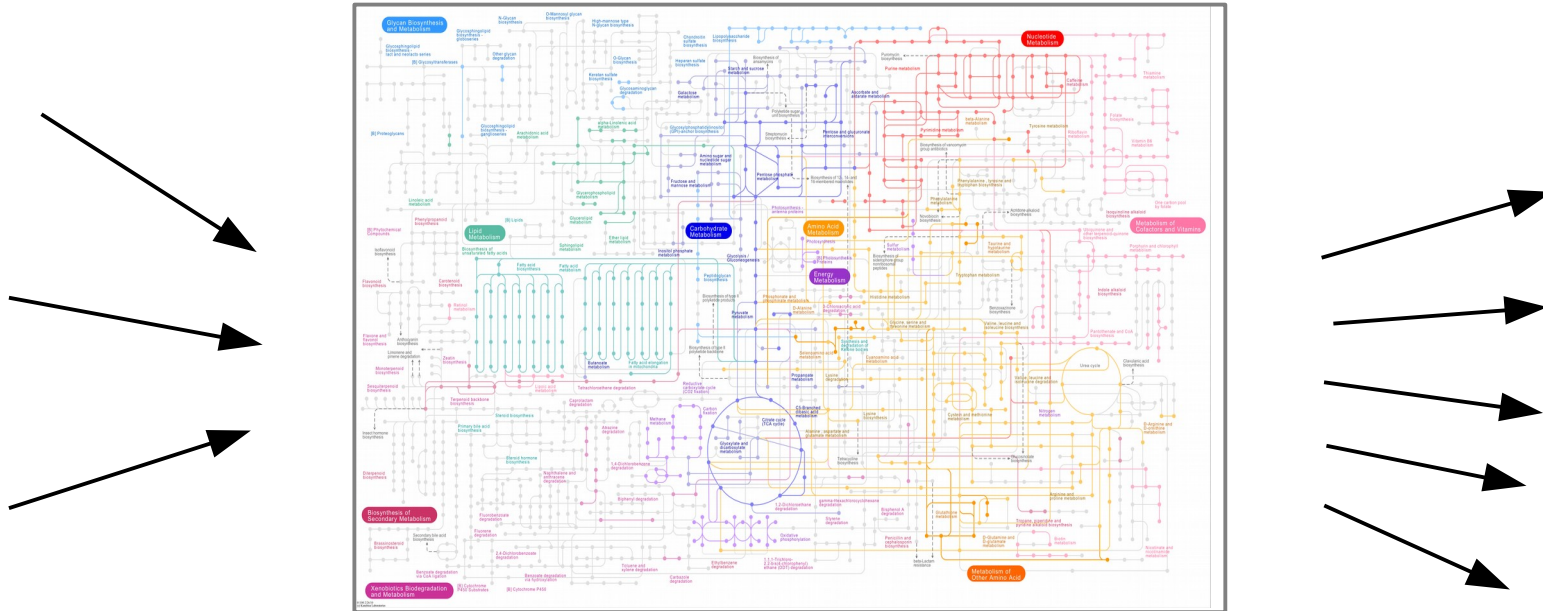


$$\frac{dS}{dt} = N \cdot v(S, p)$$





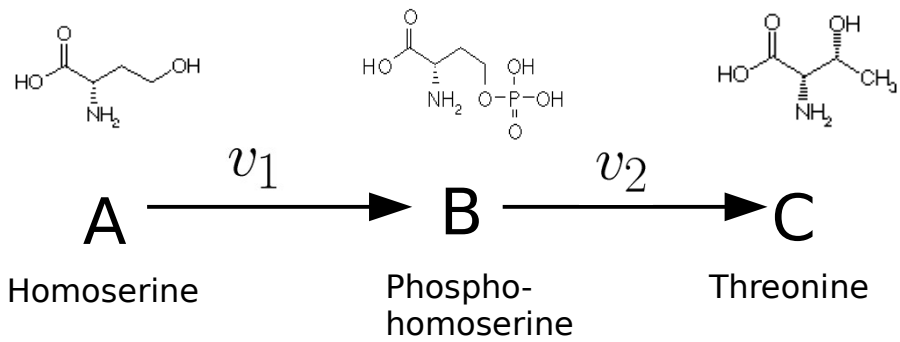
# What kinds of questions do we want to answer?



- What compounds can the cell produce, and on what media can it survive?
- What do the metabolic fluxes look like?
- How do fluxes and metabolite levels respond to varying conditions?
- How would a mutation change the cell state?
- How big are the differences between individual cells?
- ...
- How can we answer all these questions with limited data?

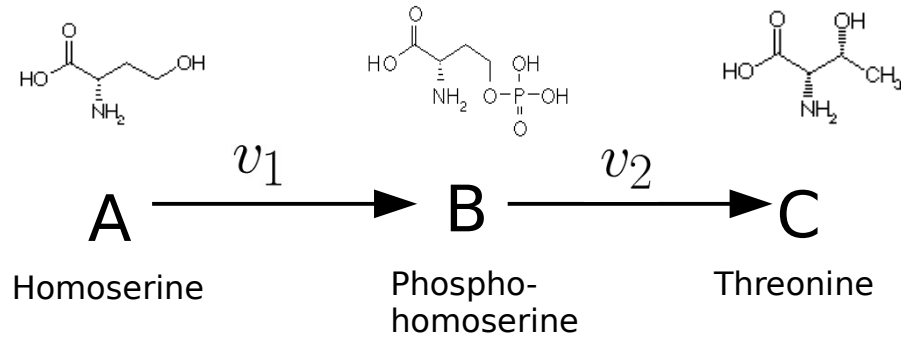
# Kinetic models of metabolic pathways

# Kinetic models describe the dynamics of biochemical reactions





# Kinetic models describe the dynamics of biochemical reactions



Kinetic rate law: “mass-action kinetics”  
How often does the reaction occur per time ?

$$v_1(a, b) = k_{1+} a - k_{1-} b$$

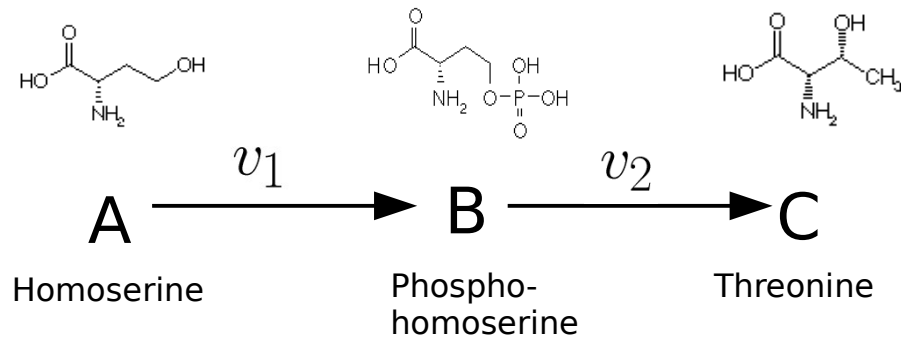
$$v_2(b, c) = k_{2+} b - k_{2-} c$$

↑  
reaction rate

↑  
kinetic  
constant

↑  
metabolite  
concentration

# Kinetic models describe the dynamics of biochemical reactions



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↑  
reaction rate

↑  
kinetic constant

↑  
metabolite concentration

System equations

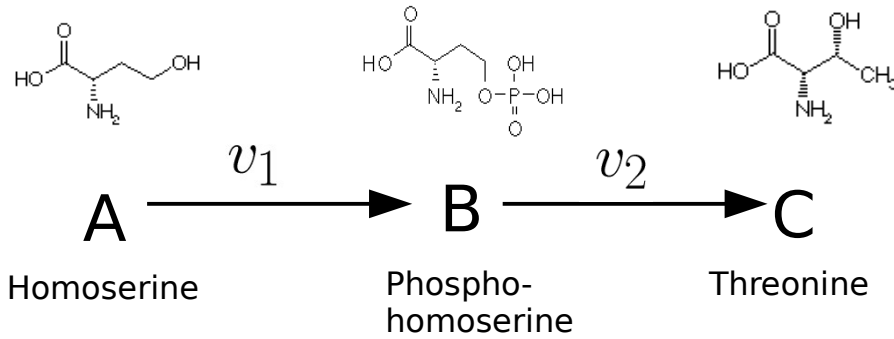
How do the concentrations change over time?

$$da/dt = -v_1$$

$$db/dt = v_1 - v_2$$

$$dc/dt = v_2$$

# Kinetic models describe the dynamics of biochemical reactions



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↑ reaction rate                      ↑ kinetic constant                      ↑ metabolite concentration

concentration change

stoichiometric coefficient

kinetic rate law (reaction rate)

$$\frac{ds_i}{dt} = \sum_l n_{il} v_l(s, k)$$

metabolite concentrations

kinetic parameters, enzyme concentrations

System equations

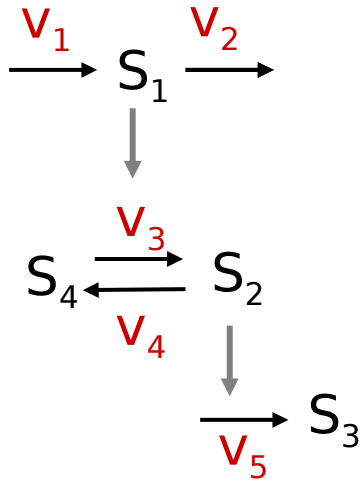
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# System equations – a more complicated example



Differential equations (ODEs)

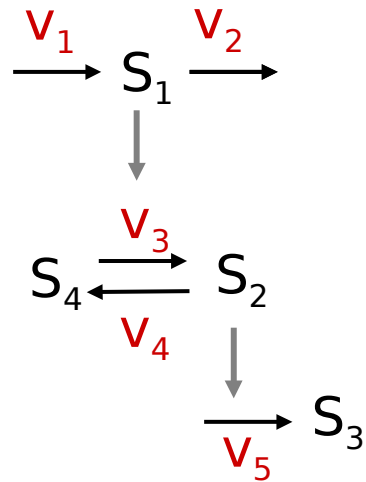
$$d[S_1]/dt = v_1 - v_2$$

$$d[S_2]/dt = v_3 - v_4$$

$$d[S_3]/dt = v_5$$

$$d[S_4]/dt = -v_3 + v_4$$

# System equations – a more complicated example



Metabolite  
Concentrations

$$\mathbf{s} = \begin{pmatrix} S_1 \\ S_2 \\ S_3 \\ S_4 \end{pmatrix}$$

Reaction rates

$$\mathbf{v} = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix}$$

Stoichiometric Matrix

$$\mathbf{N} = \begin{matrix} & v_1 & v_2 & v_3 & v_4 & v_5 \\ \begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 1 & 0 \end{pmatrix} & S_1 \\ & S_2 \\ & S_3 \\ & S_4 \end{matrix}$$

Differential equations (ODEs)

$$d[S_1]/dt = v_1 - v_2$$

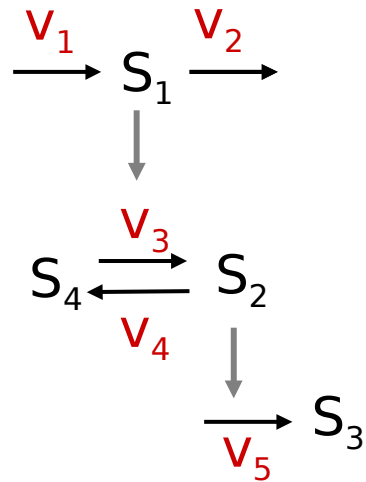
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Differential equations (ODEs)

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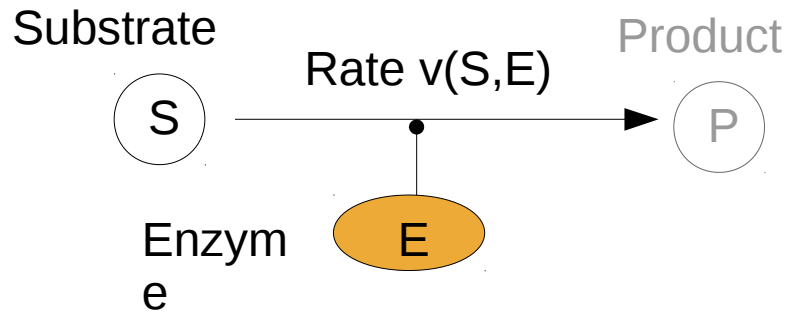
$$d[S_3]/dt = v_5$$

$$d[S_4]/dt = -v_3 + v_4$$

$$N \times \vec{v} = \vec{d[S]/dt}$$

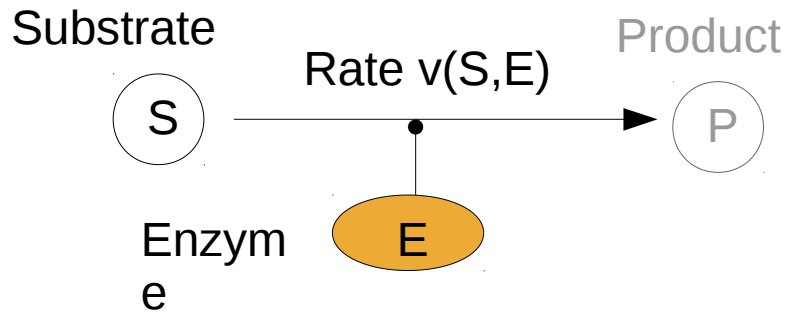
$$\begin{pmatrix} 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & -1 & 1 & 0 \end{pmatrix} \times \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix} = \begin{pmatrix} v_1 - v_2 + 0 + 0 + 0 \\ 0 + 0 + v_3 - v_4 + 0 \\ 0 + 0 + 0 + 0 + v_5 \\ 0 + 0 - v_3 + v_4 + 0 \end{pmatrix}$$

# The irreversible Michaelis-Menten rate law

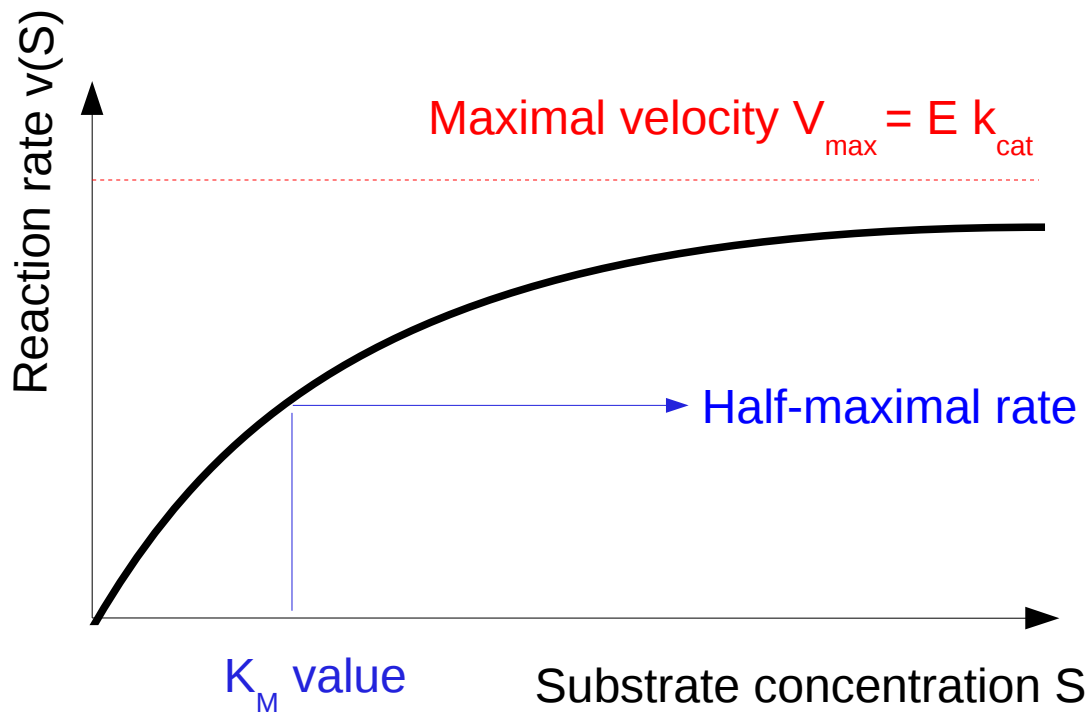


$$v(S, E) = \underbrace{E k_{\text{cat}}}_{V_{\text{max}}} \frac{S}{S + K_M}$$

# The irreversible Michaelis-Menten rate law



$$v(S, E) = \underbrace{E k_{\text{cat}}}_{V_{\text{max}}} \frac{S}{S + K_M}$$



## Variables:

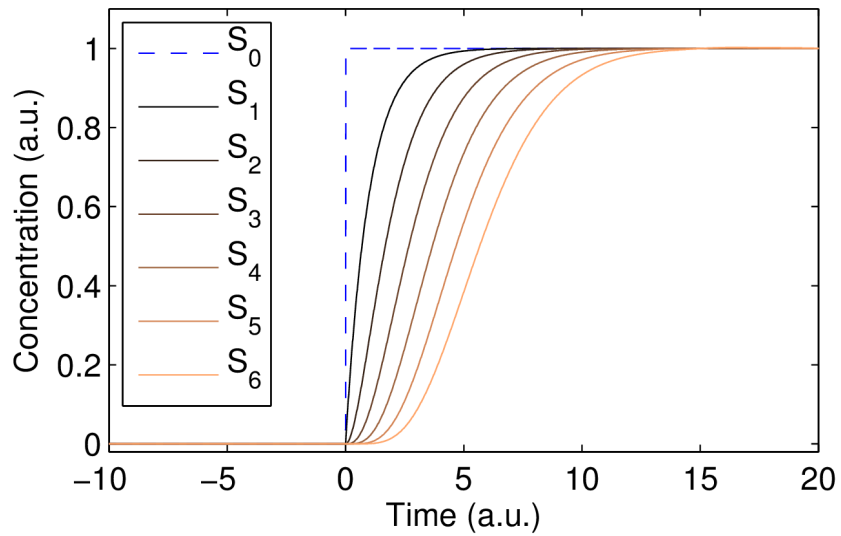
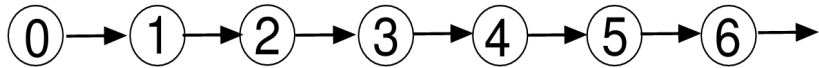
- Substrate concentration  $s$
- Enzyme concentration  $E$

## Parameters:

- $K_M$  value (in mM): inverse binding affinity
- Catalytic constant  $k_{\text{cat}}$  (in 1/s)  
Maximal number of conversions per time and enzyme molecule

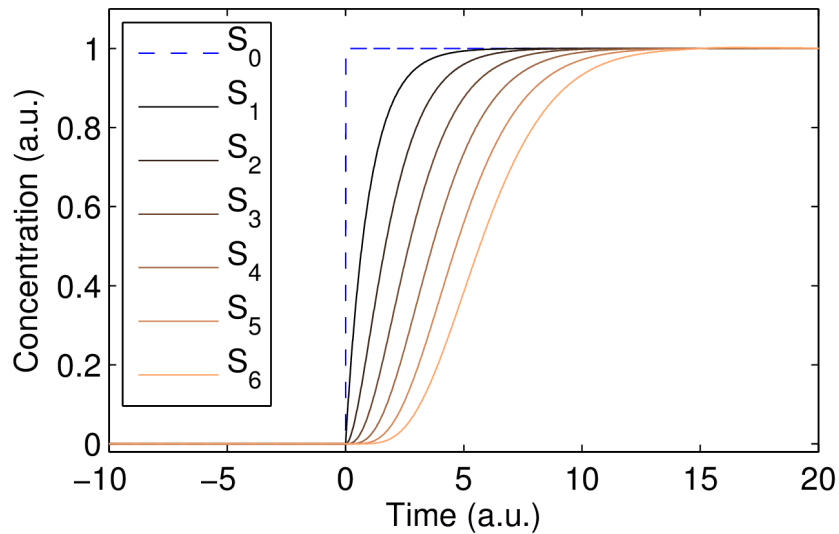
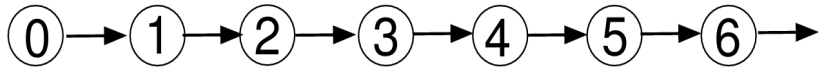
# Dynamic behaviour and steady states

Differential equations describe the change in a moment - numerical integration yields the overall behaviour in time





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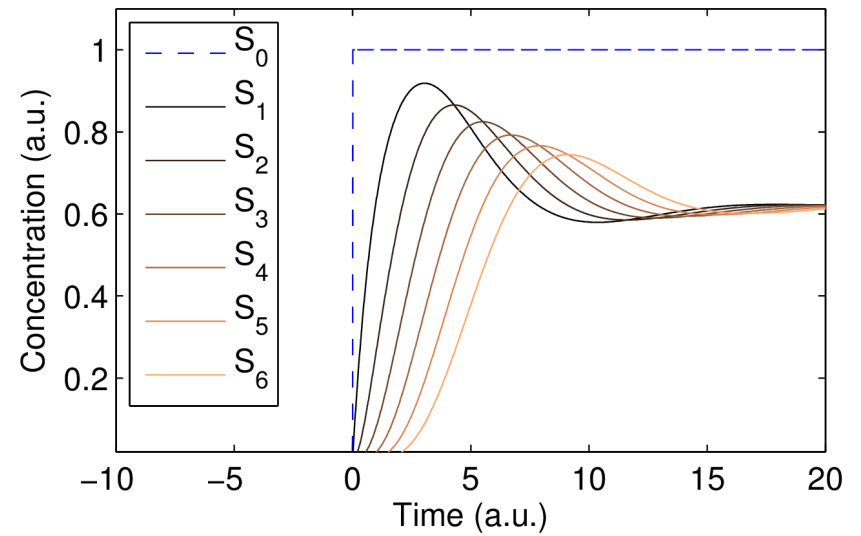
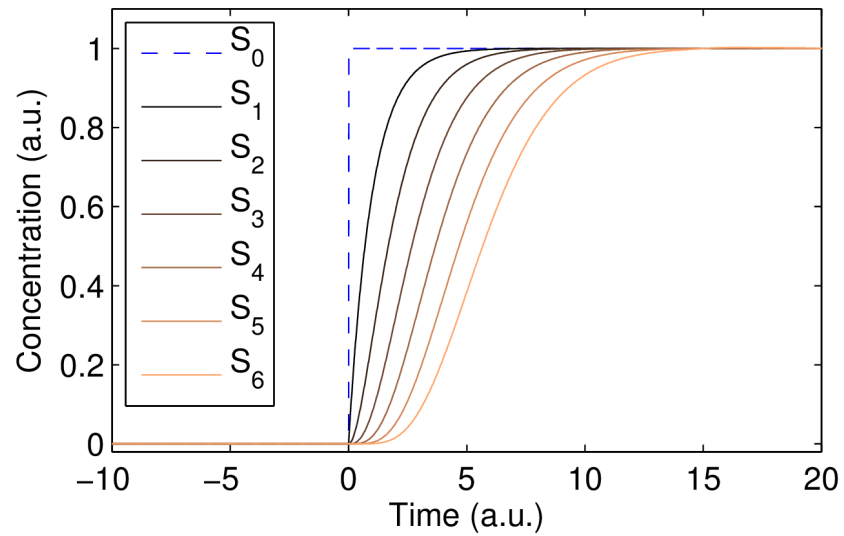
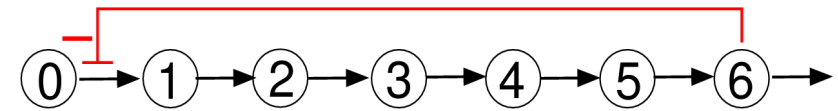
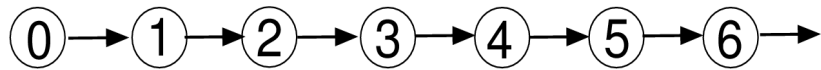
A simple way to solve differential equations numerically (“Euler method”)

- Consider fixed, small time step!
- Start with initial values  $s(t=0)$
- Use the updating rule:

$$s(t + \Delta t) = s(t) + \frac{ds}{dt} \Delta t$$

- Repeat the last step many times

Dynamic behaviour depends on small details of a model



In steady states, all substance levels remain constant in time

Stationarity condition in kinetic models

$$\frac{dc}{dt} = Nv = 0$$

Condition on the flux vector  
Kinetic rate laws do not play a role!

External metabolites (e.g. extracellular or buffered)

→ Treated as fixed parameters

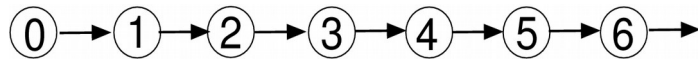
Intracellular metabolites (dynamic)

→ Concentration varies due to chemical reactions

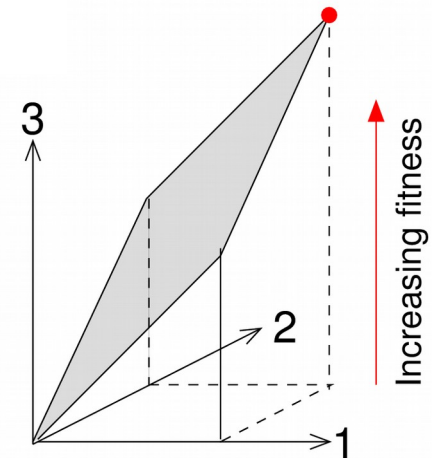
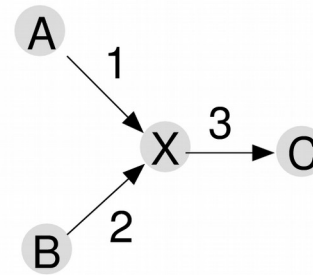
Stationary (=steady) state

A state in which all variables remain constant in time

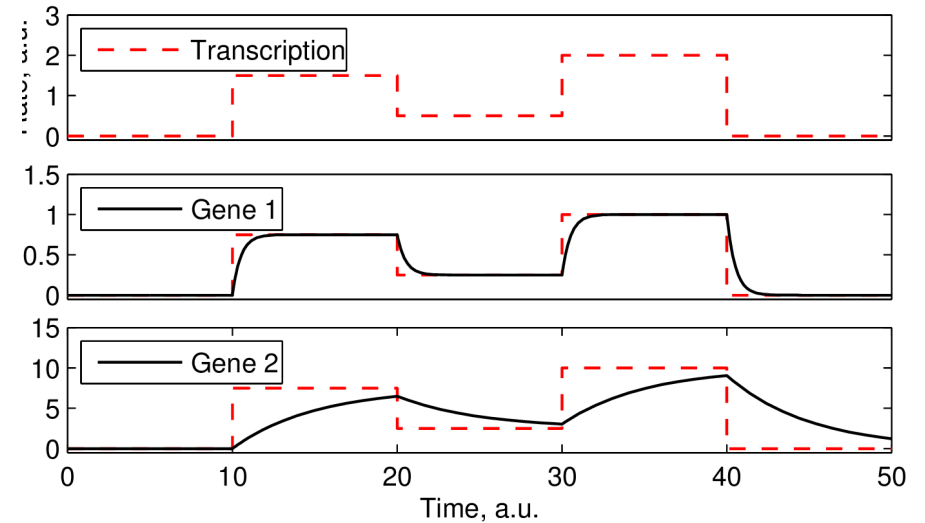
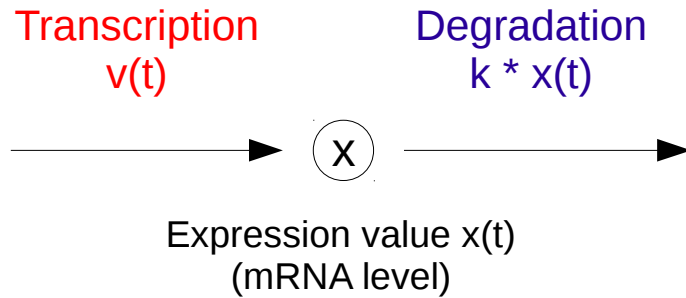
Linear pathway



Branch point



# An example: transcription rate and mRNA expression level



## Exercise 1:

Write down the differential equation for  $x$

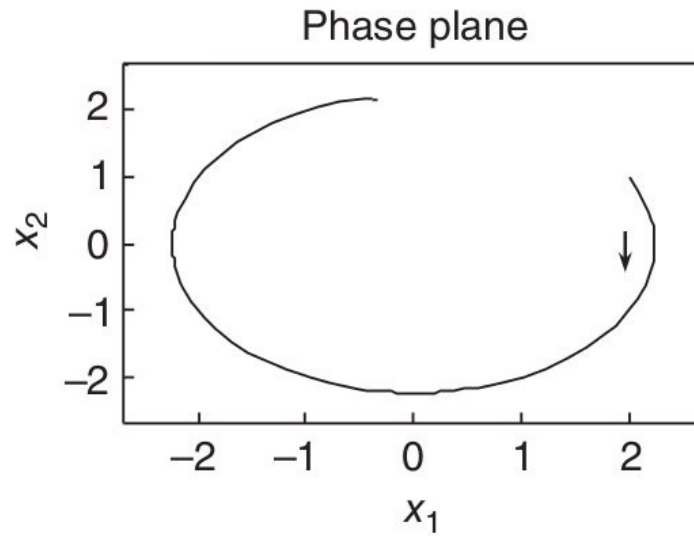
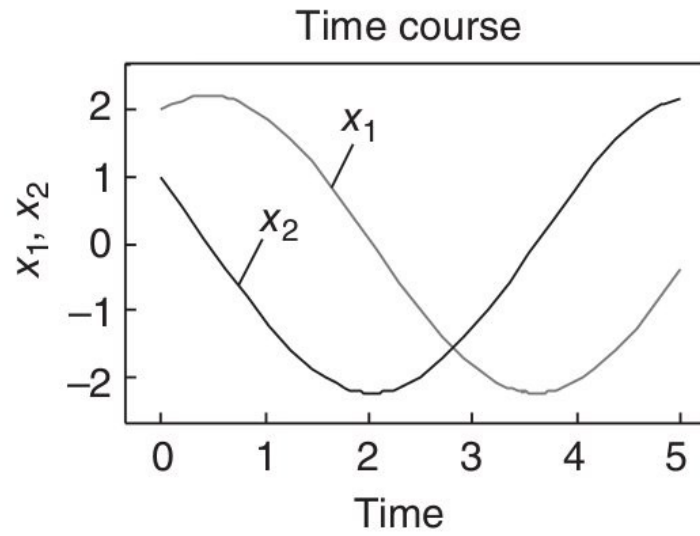
## Exercise 2:

Solve the equation. Assume that  $x(0) = 10$  nM,  $k = 1$  /min, and  $v(t) = 0$ .

## Exercise 3:

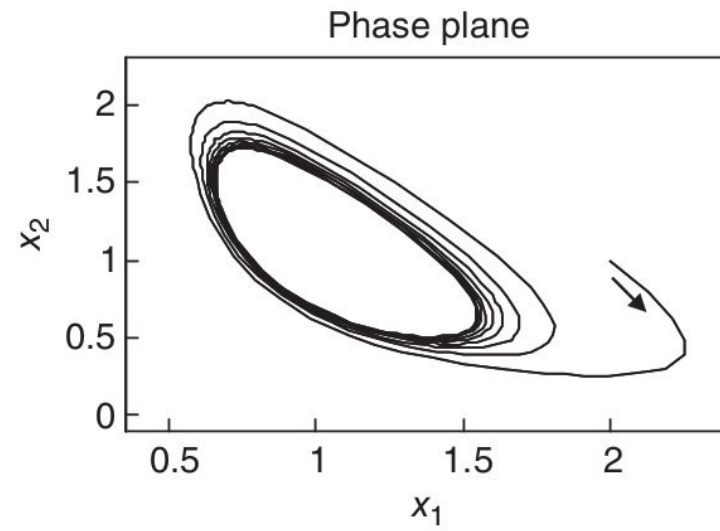
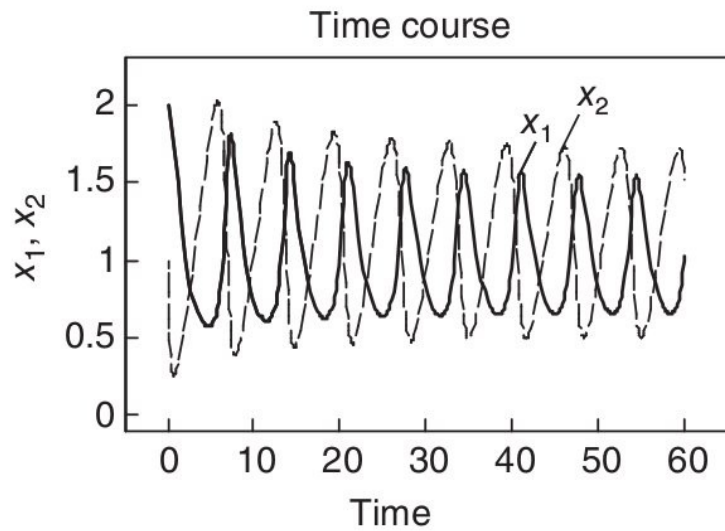
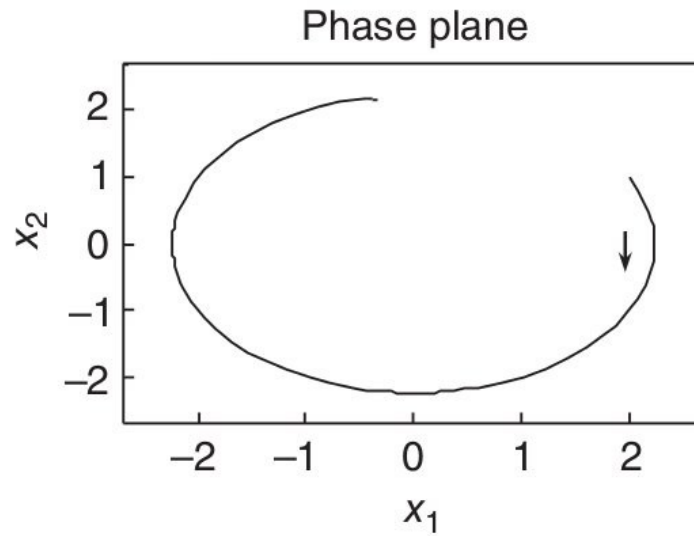
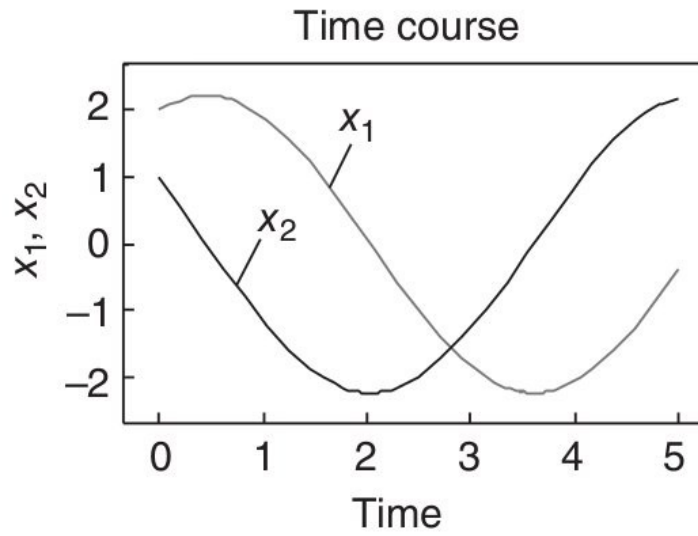
Assume a constant  $v(t) = 20$  nM/s,  $k=0.1$  / min, and determine the steady-state value of  $x$ .

# Dynamic behaviour in time and in phase space

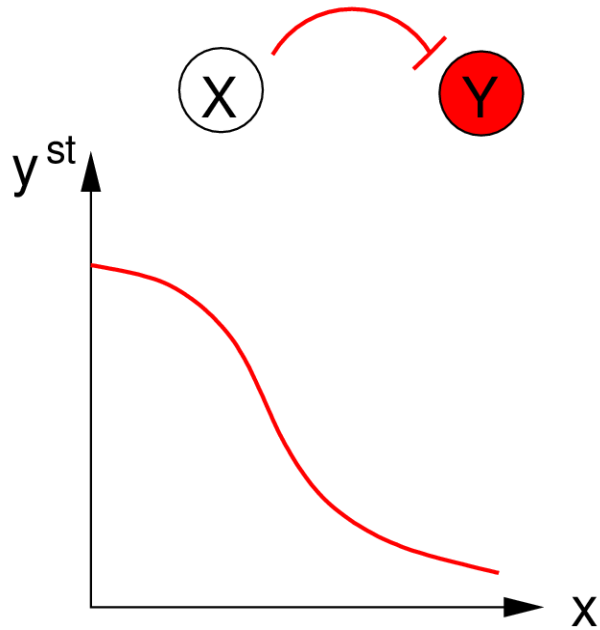




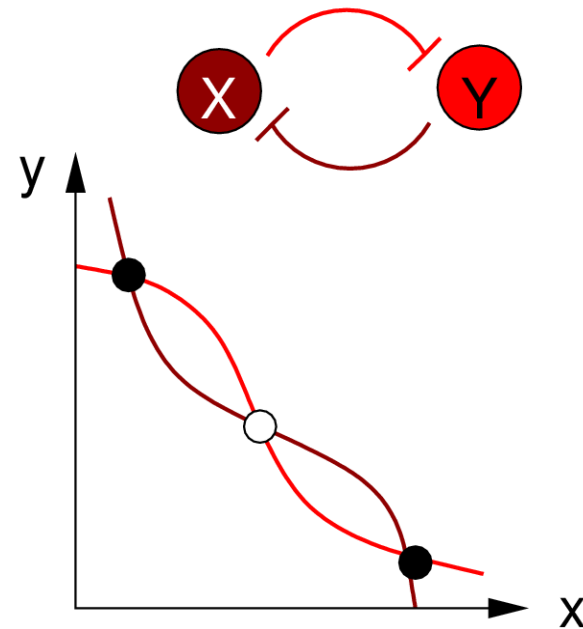
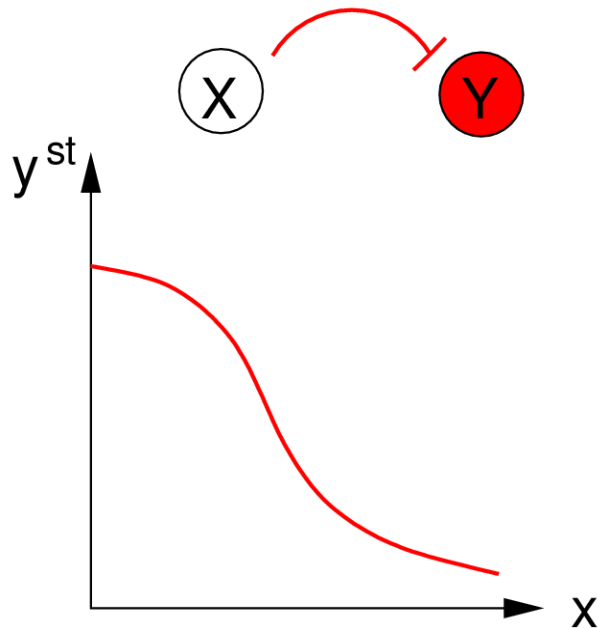
# Dynamic behaviour in time and in phase space



Mutual inhibition can lead to bistability  
as a systemic behaviour



Mutual inhibition can lead to bistability as a systemic behaviour



Metabolic control:  
quantifying the effects of parameter changes

# Metabolic control analysis studies the systemic effects of local parameter perturbations

Parameter change  
higher substrate supply?

$$\Delta p_m$$



Metabolic change  
altered concentrations?  
redirected fluxes?

$$\Delta s_i \approx R_{p_m}^{s_i} \Delta p_m$$

# Metabolic control analysis studies the systemic effects of local parameter perturbations

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higher substrate supply?

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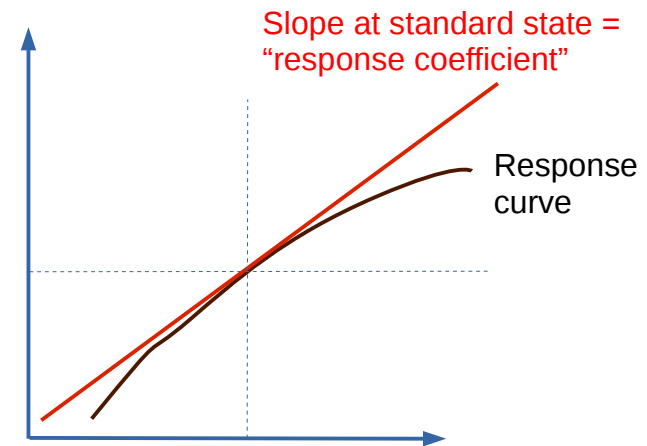
$$\Delta s_i \approx R_{p_m}^{s_i} \Delta p_m$$

## 1. Stationary concentrations $s(p)$

$$\text{Solution of } 0 = N v(s(p), p)$$

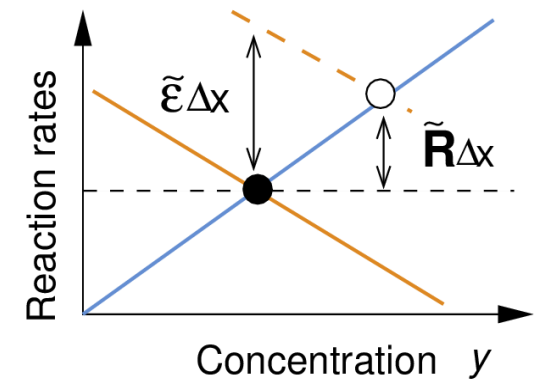
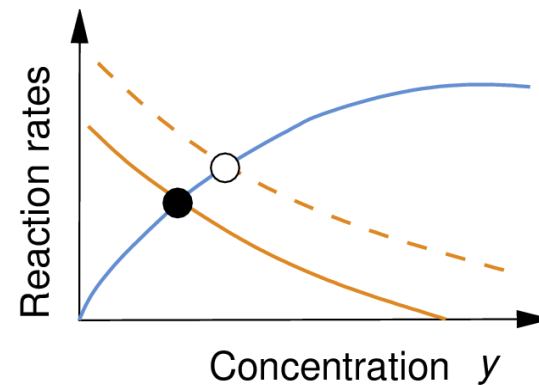
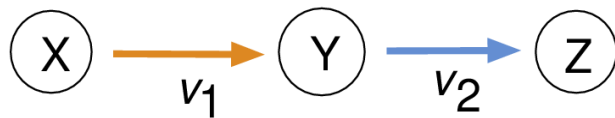
## 2. Response coefficients

Systemic effect:  
flux or concentration



Local cause:  
e.g., single enzyme level

Local perturbations, in the long run,  
change the entire metabolic state



Two types of sensitivities in metabolic control analysis:

- Reaction elasticities
- Response (or control) coefficients

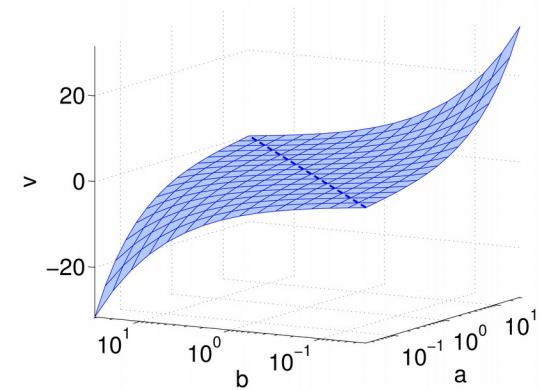
Model parameters, variability,  
and model structure



A problem in kinetic modelling: each enzyme is different !!

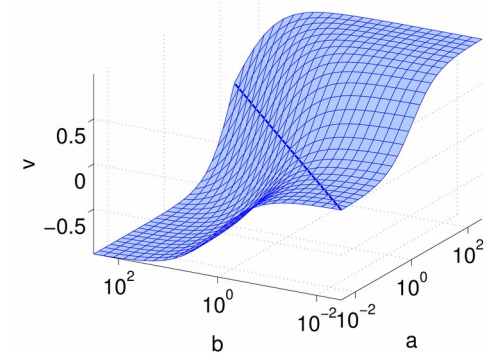
Reversible mass-action kinetics (non-enzymatic)

$$v = k_+ a - k_- b$$



Reversible Michaelis-Menten kinetics

$$v = \frac{v_+^{\max}(a/k_A^M) - v_-^{\max}(b/k_B^M)}{1 + (a/k_A^M) + (b/k_B^M)}$$

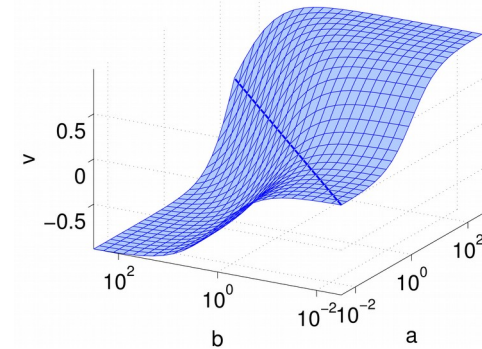


How can we obtain all the necessary parameters ??

Another problem: parameters may depend on each other!

### Reversible Michaelis-Menten kinetics

$$v = \frac{v_+^{\max}(a/k_A^M) - v_-^{\max}(b/k_B^M)}{1 + (a/k_A^M) + (b/k_B^M)}$$



### Thermodynamic constraints

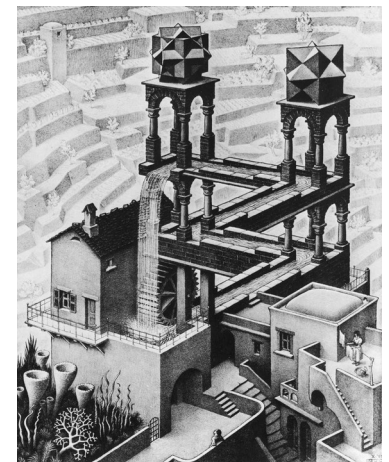
Thermodynamic laws lead to dependencies between kinetic parameters

#### Chemical equilibrium

$$0 = v(a^{\text{eq}}, b^{\text{eq}}) = v_+^{\max} \frac{a^{\text{eq}}}{k_A^M} - v_-^{\max} \frac{b^{\text{eq}}}{k_B^M}$$

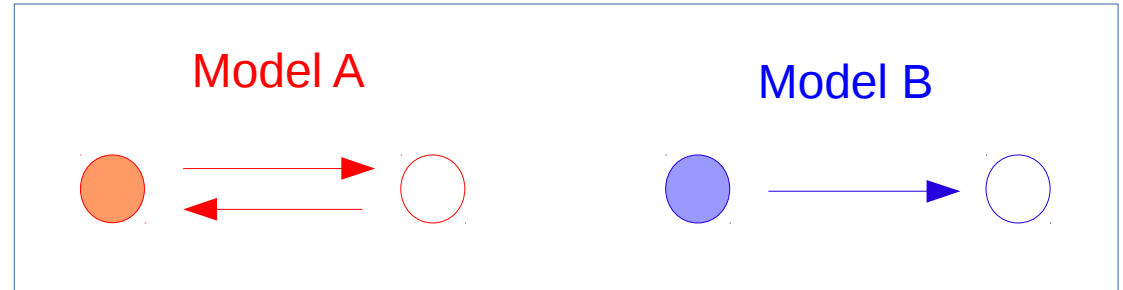
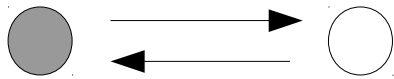
#### Haldane relationship

$$k^{\text{eq}} = \frac{b^{\text{eq}}}{a^{\text{eq}}} = \frac{v_+^{\max} k_B^M}{v_-^{\max} k_A^M}$$

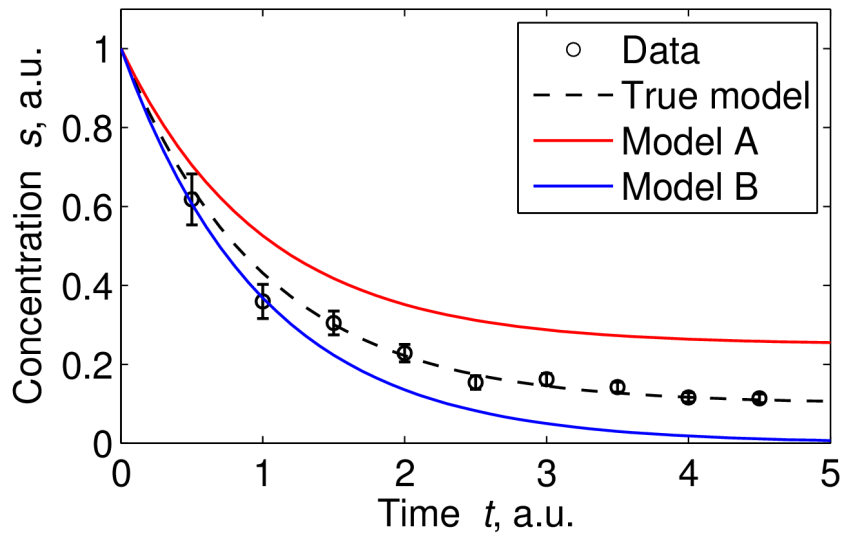


# How can we choose between two models?

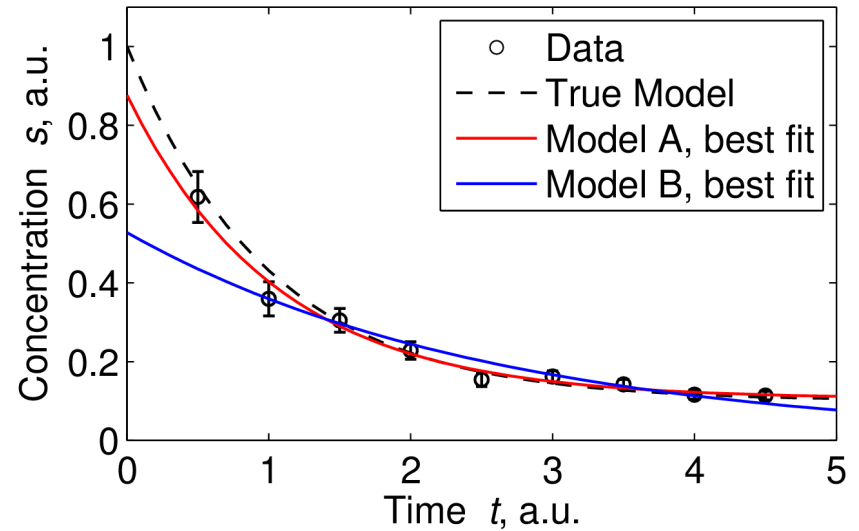
True model (unknown)



Models before parameter fitting



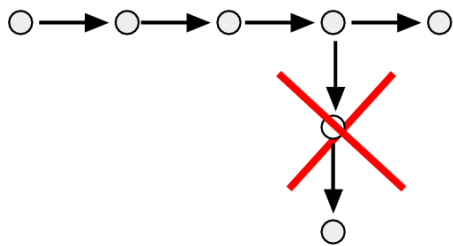
Models after parameter fitting



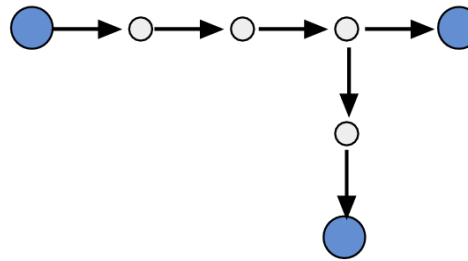
Some methods for model selection: Cross-validation – “Selection criteria” – Bayesian model selection

# How models can be simplified (hopefully, without losing too much accuracy)

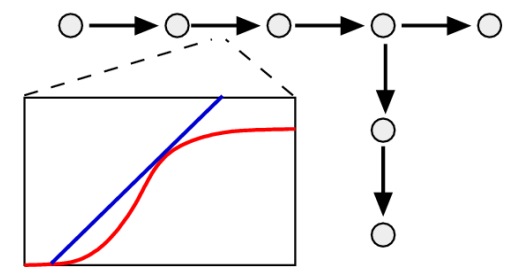
(a) Omit elements



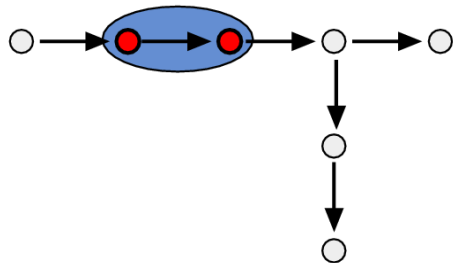
(b) Fix elements



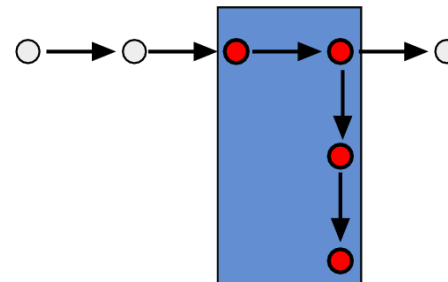
(c) Simplify formulae



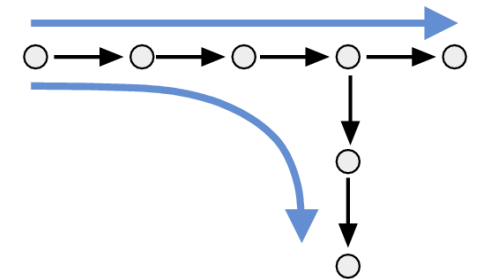
(d) Lump elements



(e) Dynamic black box model

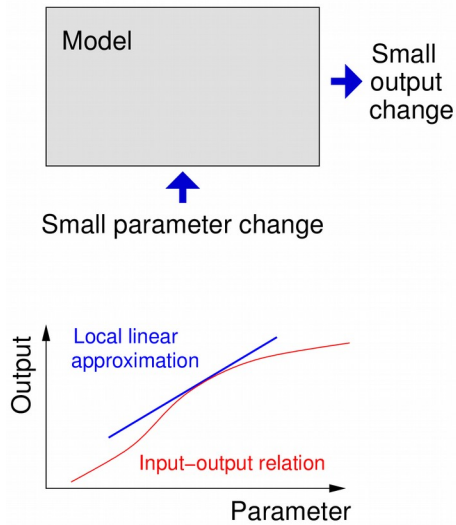


(f) Global flux modes

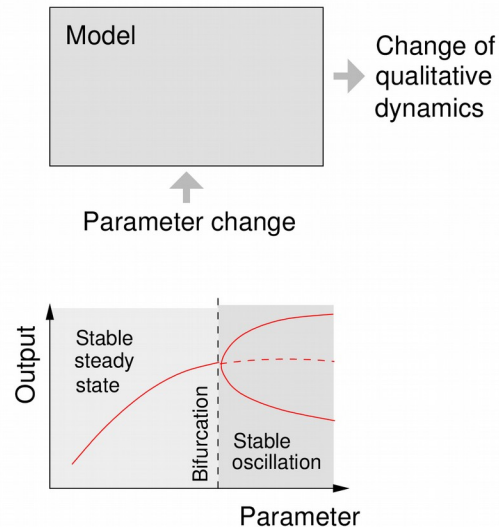


# Variability and uncertainty of parameters can be mathematically described

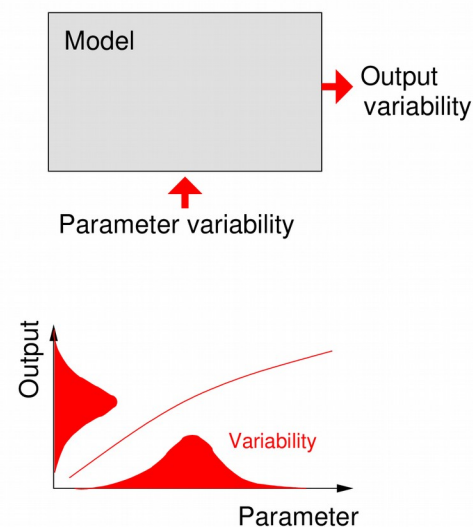
(a) Local sensitivity analysis



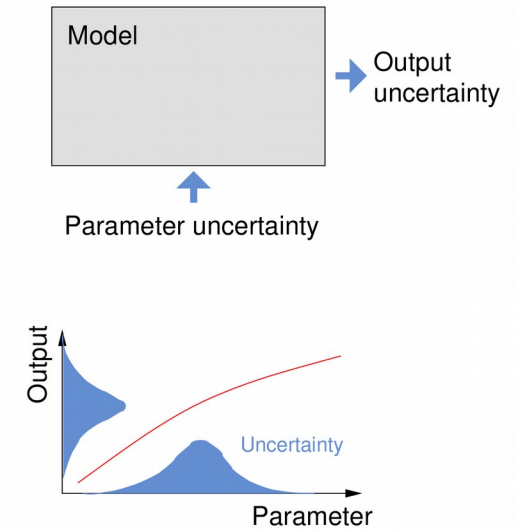
(b) Bifurcation analysis



(c) Variability analysis



(d) Uncertainty analysis



Some questions we might care about:

- What parameters have a strong effect on model behaviour?
- What model outputs are strongly affected?
- Under what parameter changes does the qualitative behaviour change, and how?
- If a parameter varies between cells, how much variation do we expect in the model output?
- If we are uncertain about a parameter, how uncertain will we be about model outputs?

Thank you !

