

Mathematical modelling dynamics of biological systems

ODE models of signal transduction

Centre for Biological Modelling
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27-30/09/2016

Concepts

**What is systems
biology?**



**What are mathematical
models and what for?**



**Mathematical descriptions of the time
behaviour of a spatially homogenous
chemical system: ODE models**



**Systems biology modelling: (Part of
an) integrative model of the response
of yeast to osmotic shock**



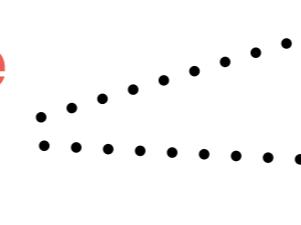
Presentation

Simple examples and exercises

Presentation

Exercises

**Simulations
with python**

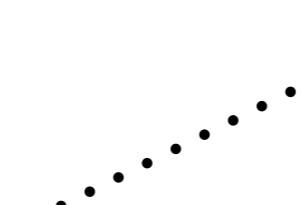


Presentation

Modelling the MAP kinase cascade
module



Modelling the transcription module



Connecting the two modules

Schedule

Time	Tuesday	Wednesday	Thursday	Friday
9:00-1:00	Reminder of Python, array manipulation and relevant libraries for modelling	What is systems biology? What are mathematical models and what for? ODE models of simple systems and parameter estimation	Systems biology modelling: Integrative model of the response of yeast to osmotic shock - Modelling the MAP kinase cascade module	Open session
2:00-4:30	Open session	Open session	Open session	Open session

What is systems biology?

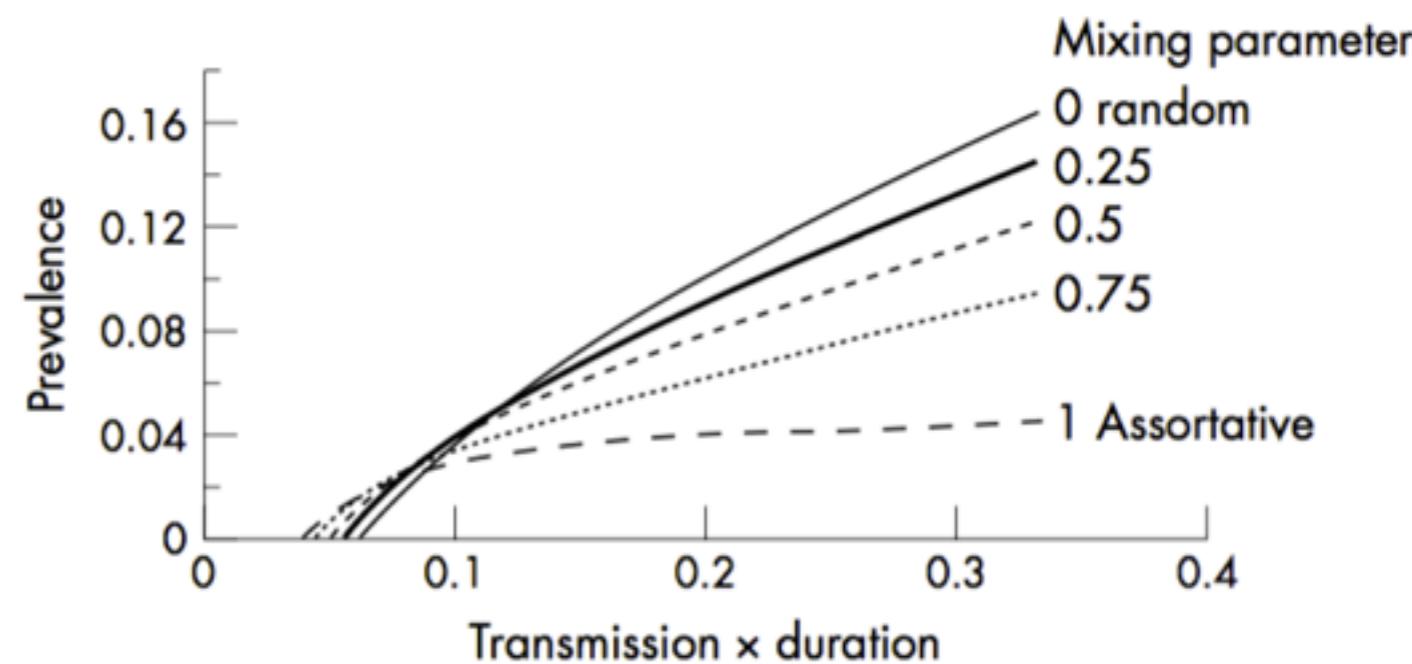
Systems Biology is the study of the *emerging* properties of a biological system, taking into account all the *necessary* constituents, their *relationships* and their *dynamics*

Modelling the spread of HIV in a society

Necessary constituents?

- ✓ Susceptible
- ✓ Infected/infective
- ✓ Recovered/no longer susceptible
- ✗ Number of chimps in the zoo?

Emerging properties



Relationships

- ✓ The number of contacts that are sufficient for an infectious individual to spread the disease
- ✓ The speed of recovery of an infected individual
- ✓ The population: is large/small, well-mixed/segregated and homo/heterogenous
- ✓ Migration patterns
- ✗ General hygiene of the city?

What is a mathematical model?

Wikipedia (April 17th 2013): “A mathematical model is a description of a **system** using **mathematical** concepts and language.”

variables

[x]

Vmax

Kd

EC₅₀

length

t_{1/2}

relationships

$$K_d = \frac{[A] \cdot [B]}{[AB]}$$

$$d[X]/dt = k \cdot [Y]^2$$

$$\sum_i [X]_i - F(t) = 0$$

$$k(t) \sim N(k, \sigma^2)$$

If mass_t > threshold
then mass_{t+Δt} = 0.5 · mass

constraints

[x]>0

Energy conservation

Boundary conditions
(v < upper limit)

Objective functions
(maximise ATP)

Initial conditions

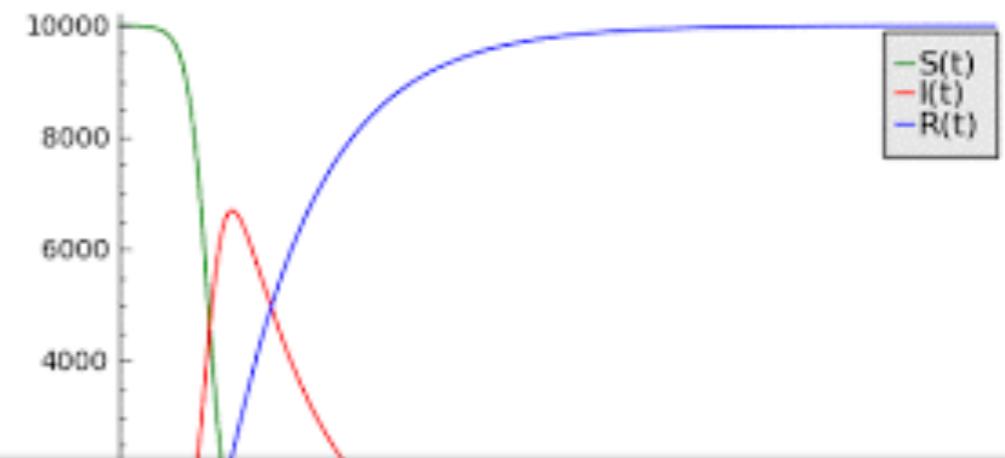
Different types: Dynamical models, logical models, rule-based models, multi-agent models, statistical models, etc.

Modelling the spread of HIV in a society

Necessary constituents?

- ✓ Susceptible - S
- ✓ Infected/infective - I
- ✓ Recovered/no longer susceptible - R

Emerging properties



Naming variables carefully is very important!!

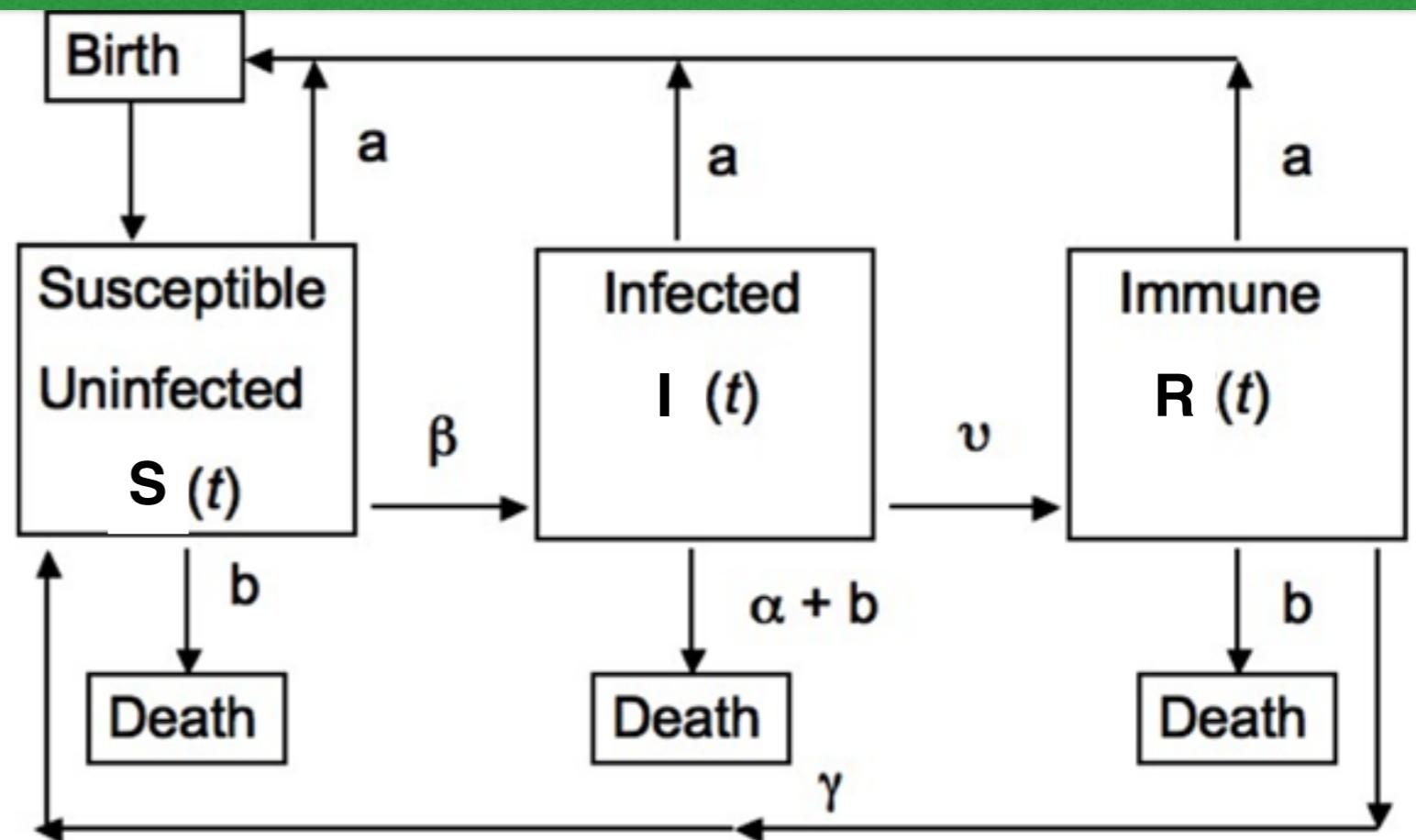
Relationships

$$\frac{dS}{dt} = -\beta \frac{SI}{N}$$

$$\frac{dI}{dt} = \beta \frac{SI}{N} - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

$$N = S + I + R$$

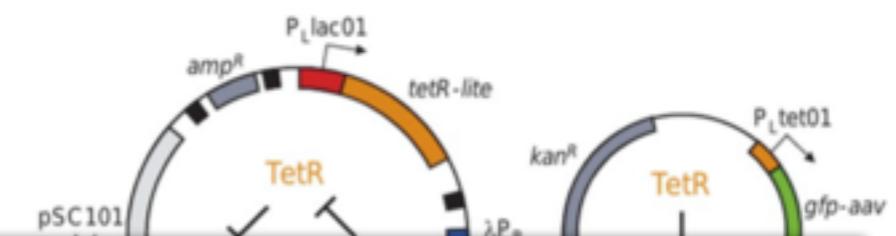
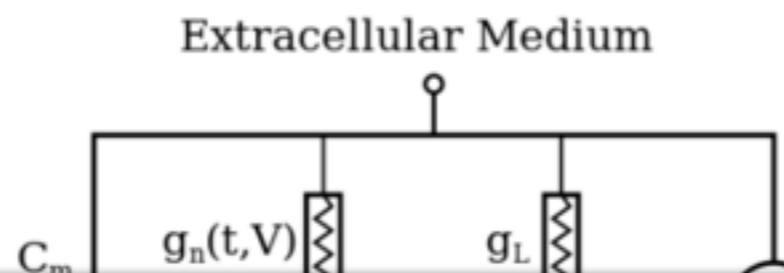


Why using mathematical models?

Describe

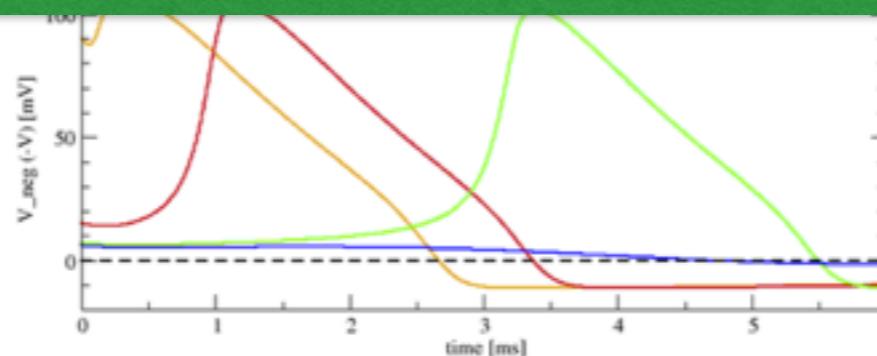
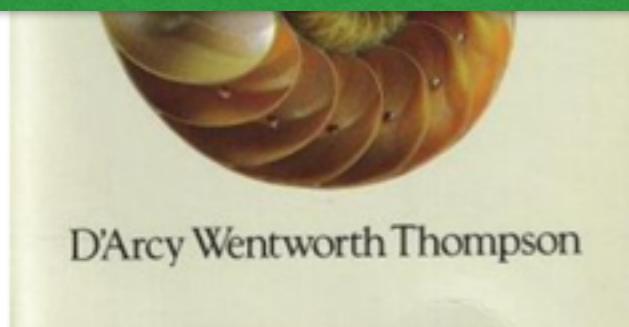
Explain

Predict



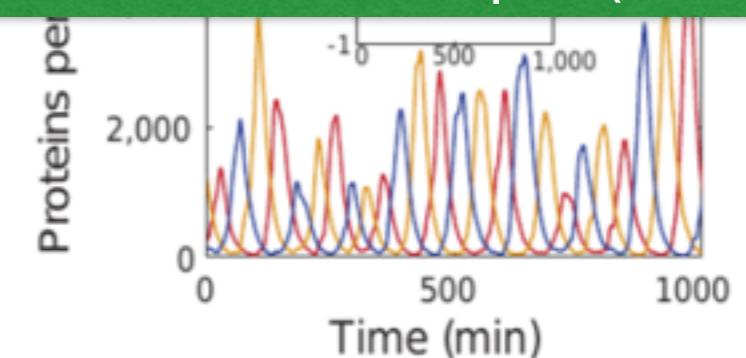
"Not unique! Several system structures may generate the same properties."

Michael Stumpf (ICL)



1917

1952



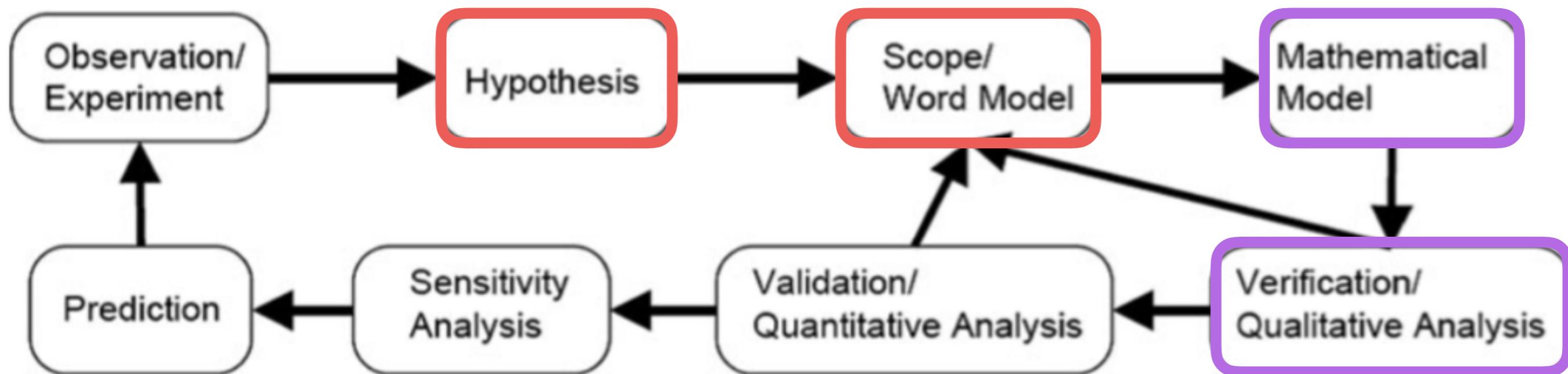
2000

Why using mathematical models?

Mathematical modelling can be very helpful for discovering and understanding biological processes and organisation principles, because:

- it forces the investigator to formulate hypotheses and insights in a clear-cut and formal way
- it may allow for the representation and evaluation of system compounds that are experimentally not accessible
- it allows to explore many scenarios or parameter values in less time and cheaper than in experiments
- it may help to extract structural dependencies or mathematical and physical relation that are hard to find by biological intuition, e.g. + and - loops

Process of mathematical modelling in biology



The following steps are/not considered:

- Define network structure.
- Analyse the network structure.
- **Describe dynamics with a mathematical model, e.g., set of ODEs.**
- Estimate parameters.
- Qualitative analysis of the model
- Test model against data (does the output describes data input satisfactorily?).
- Test model against new experimental scenarios.
- Sensitivity analysis
- Make predictions for hitherto untested (but in principle testable) scenarios.

Mathematical descriptions of
the time behaviour of a spatially
homogenous chemical system

Deterministic mathematical description of the time behaviour of a spatially homogenous chemical system

Assumptions:

1. chemical reactions are **continuous** rate processes
 2. chemical reactions are a **predictable** process, based only on the initial conditions
- **governed** by a set of coupled, ordinary differential equations (**ODEs**)

Deterministic vs stochastic

The time evolution of a chemical system is regarded as not having fluctuations.

1. chemical reactions are **continuous** rate processes
 2. chemical reactions are a **predictable** process, based only on the initial conditions
- **governed** by a set of coupled, ordinary differential equations (**ODEs**)

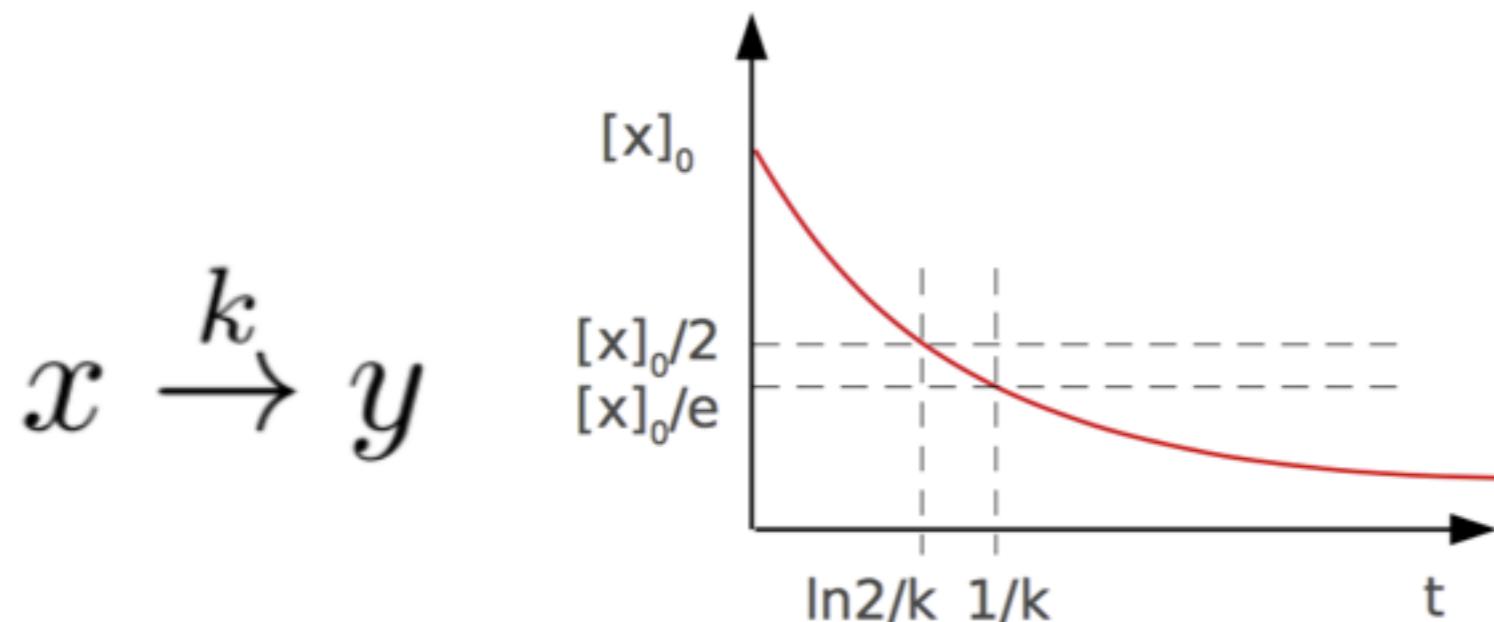
The time evolution of a chemical system is regarded as having inherent fluctuations. Chemical reactions are

1. **kind of a (discrete) random-walk process** (not a continuous process) because molecular population levels obviously can change only by discrete integer amounts
2. **not a deterministic process:** to predict the exact molecular population levels at some future time, the precise positions and velocities of all the molecules in the system need to be taken into account, but this is just too hard. Instead, implement randomness.
 - is governed by a single differential-difference equation (the “**master equation**”)

Differential Equations

A differential equation is a mathematical equation that relates some function with its derivatives.

(In biology) the **functions** represent **physical quantities**, the **derivatives** represent their **rates of change**, and the **equation** defines a **relationship** between the two.



$$\frac{d[x](t)}{dt} = -1 \cdot k \cdot [x](t)$$

Law of Mass Action

Waage and Guldberg (1864)



$$v = k \cdot \prod_i [X_i]^{n_i}$$

activity

rate-constant

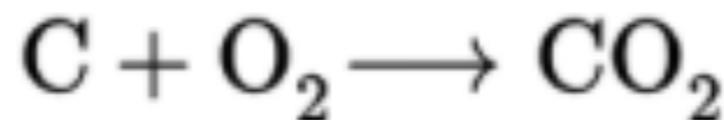
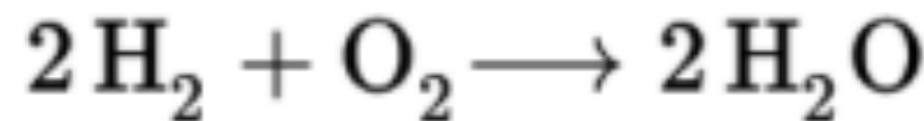
velocity

stoichiometry

The equation $v = k \cdot \prod_i [X_i]^{n_i}$ is centered. Four lines extend from its components to the words above them: 'activity' (green) points to the $[X_i]$ term, 'rate-constant' (red) points to the k , 'velocity' (grey) points to the v , and 'stoichiometry' (blue) points to the n_i .

When the numbers of catalyst and substrate molecules are usually in the same order of magnitude, using mass action kinetics would make sense, since the reaction depends on those concentrations.

Writing the differential equations for combustion



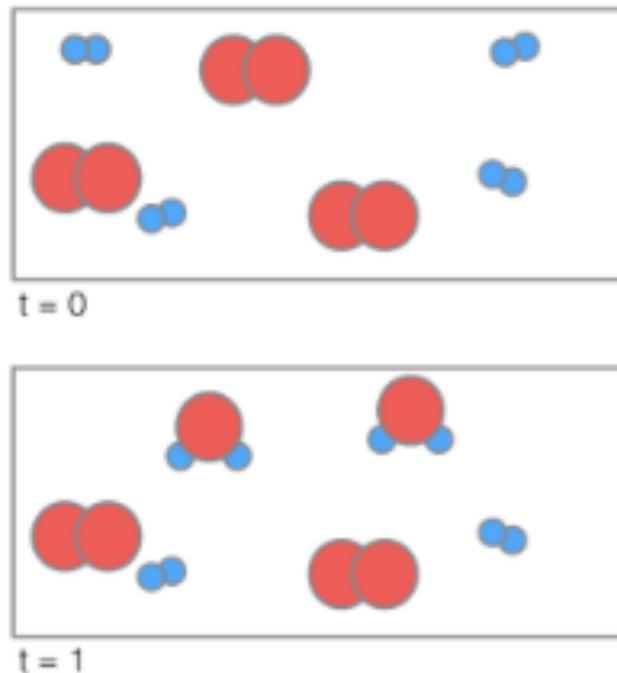
Since all of these concentrations will not in general remain constant, they can be written as a function of time:

$$[\text{H}_2](t), [\text{O}_2](t), [\text{H}_2\text{O}](t), [\text{C}](t), [\text{CO}_2](t)$$

For computational purposes, write the system as a vector:

$$y(t) = \begin{pmatrix} [\text{H}_2](t) \\ [\text{O}_2](t) \\ [\text{H}_2\text{O}](t) \\ [\text{C}](t) \\ [\text{CO}_2](t) \end{pmatrix} \quad \dot{y} \equiv \frac{dy}{dt} = \begin{pmatrix} \frac{d[\text{H}_2]}{dt} \\ \frac{d[\text{O}_2]}{dt} \\ \frac{d[\text{H}_2\text{O}]}{dt} \\ \frac{d[\text{C}]}{dt} \\ \frac{d[\text{CO}_2]}{dt} \end{pmatrix}$$

Writing the differential equations for combustion



$$\begin{aligned}[H_2] &= 4 \\ [O_2] &= 3 \\ [H_2O] &= 0\end{aligned}$$

The rate of this reaction is the speed at which you loose 2 H_2 's or 1 O_2 or you gain 2 H_2O 's.

$$\begin{aligned}[H_2] &= 2 \\ [O_2] &= 2 \\ [H_2O] &= 2\end{aligned}$$

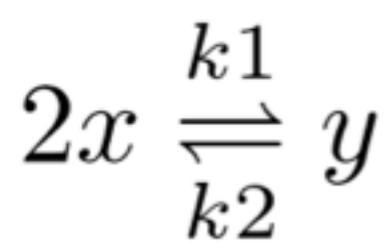
$$rate_{R1} = -\frac{1}{2} * \frac{d[H_2]}{dt} = -\frac{d[O_2]}{dt} = +\frac{1}{2} * \frac{d[H_2O]}{dt}$$

assuming mass action:

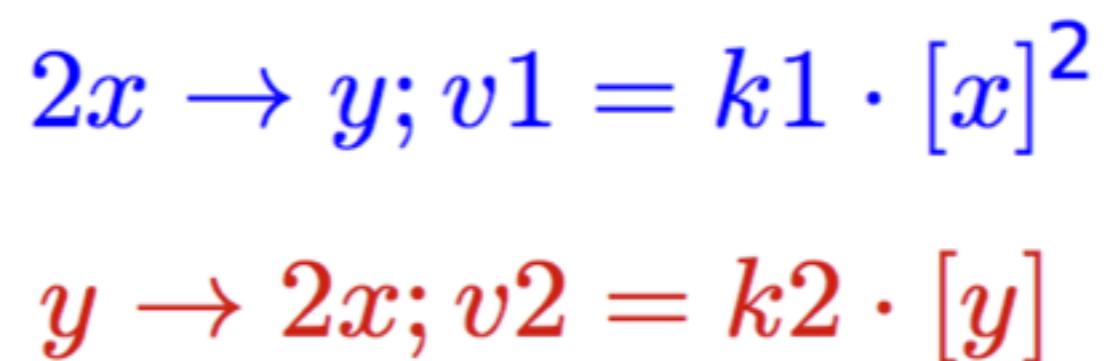
$$rate_{R1} = k_1 [H_2]^2 [O_2]$$

$$\dot{y} = \Gamma * V = \begin{pmatrix} & R1 & R2 \\ H_2 & -2 & 0 \\ O_2 & -1 & -1 \\ H_2O & 2 & 0 \\ C & 0 & -1 \\ CO_2 & 0 & 1 \end{pmatrix} * \begin{pmatrix} R1 : & k_1 * [H_2]^2 * [O_2] \\ R2 : & k_2 * [C] * [O_2] \end{pmatrix} = \begin{pmatrix} \frac{d[H_2]}{dt} = -2 * k_1 * [H_2]^2 * [O_2] \\ \frac{d[O_2]}{dt} = -k_1 * [H_2]^2 * [O_2] - k_2 * [C] * [O_2] \\ \frac{d[H_2O]}{dt} = 2 * k_1 * [H_2]^2 * [O_2] \\ \frac{d[C]}{dt} = -k_2 * [C] * [O_2] \\ \frac{d[CO_2]}{dt} = k_2 * [C] * [O_2] \end{pmatrix}$$

Reversible reaction



is equivalent to



$$\frac{d[x]}{dt} =$$

$$\frac{d[y]}{dt} =$$

Example of an enzymatic reaction

Michaelis–Menten kinetics

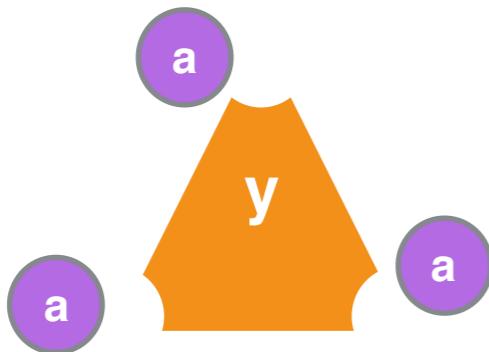


where **Vmax** represents the maximum rate achieved by the system, at maximum saturation of the substrate concentration

KM is the substrate concentration at which the reaction rate is half of Vmax

A **precondition for the application of Michaelis-Menten kinetics** is that the amount of enzyme and substrate differ by several orders of magnitude e.g. nM for enzyme compared to mM for the substrate

Phenomenological ultrasensitivity

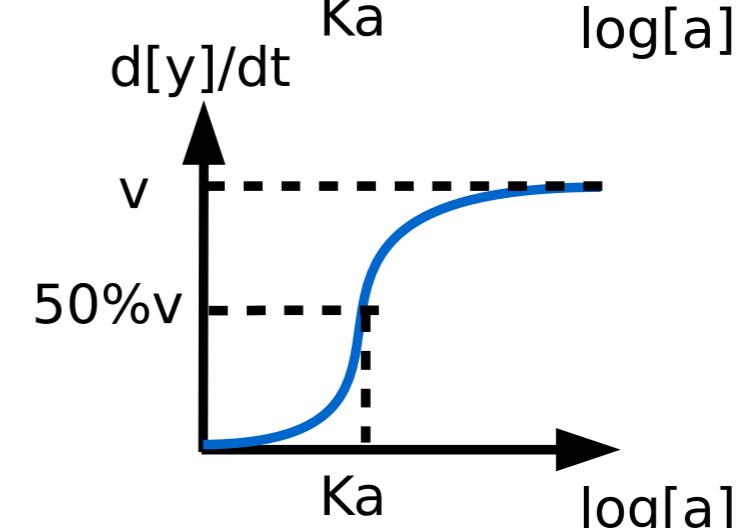
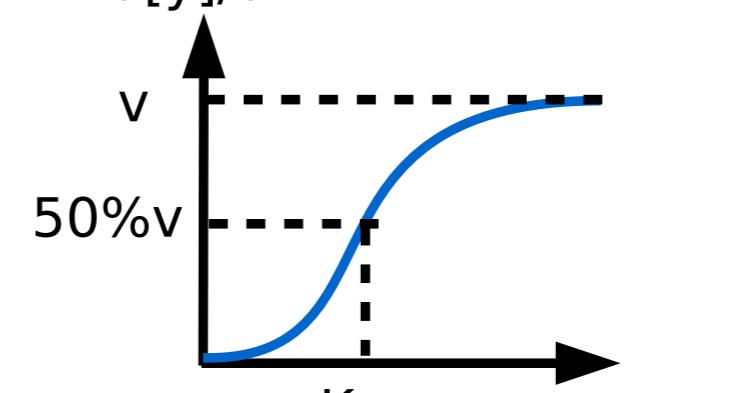
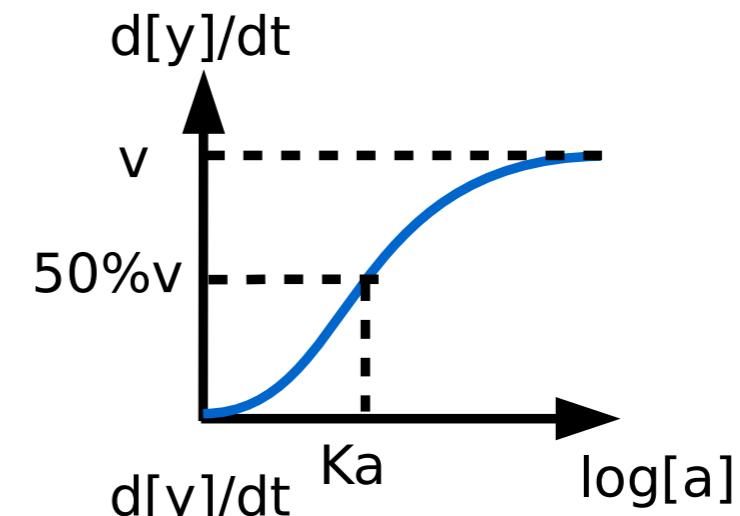


$$\frac{d[y]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$

$$\frac{d[y]}{dt} = v \cdot \frac{[a]^2}{Ka^2 + [a]^2}$$

$$\frac{d[y]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n}$$

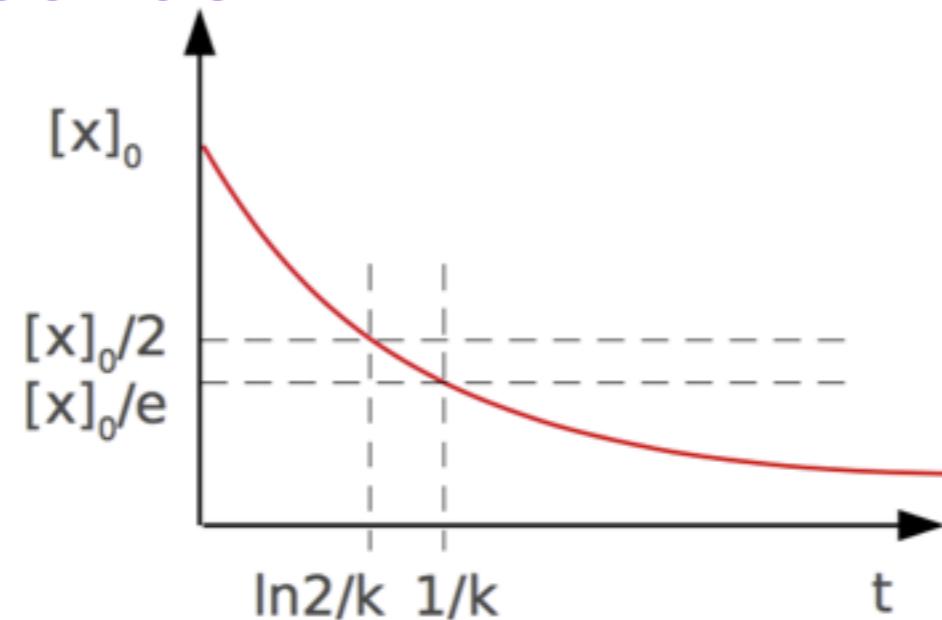
Hill function



(In biology) the **functions** represent **physical quantities**, the **derivatives** represent their **rates of change**, and the **equation** defines a **relationship** between the two.

Describe

$$x \xrightarrow{k} y$$



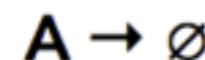
Explain

$$\frac{d[x]^{(t)}}{dt} = -1 \cdot k \cdot [x]^{(t)}$$

Exercises:

1. Write an ODE model of each of these systems
 - use mass action
2. Simulate the model in python

Decay:



Equilibrium:



Enzymatic reaction: $S + E \rightarrow SE$ $SE \rightarrow S + E$ $SE \rightarrow E + P$

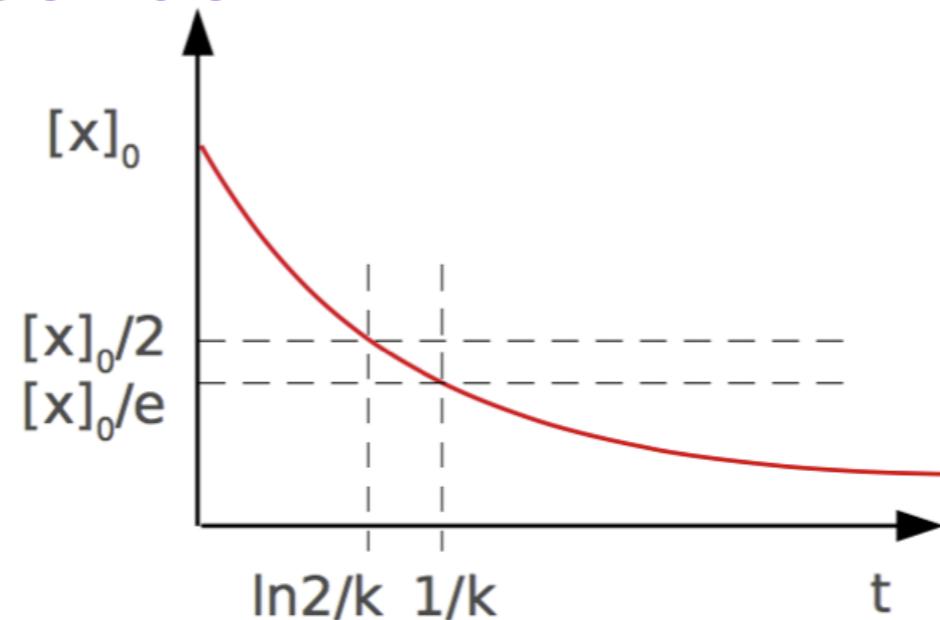
Gene expression (central dogma):

Reactions: $G \rightarrow G + M$ $M \rightarrow M + P$ $M \rightarrow \emptyset$ $P \rightarrow \emptyset$

(In biology) the **functions** represent **physical quantities**, the **derivatives** represent their **rates of change**, and the **equation** defines a **relationship between the two**.

Describe

$$x \xrightarrow{k} y$$



Explain

$$\frac{d[x](t)}{dt} = -k \cdot [x](t)$$

Predict

$$x(t) =$$

?

Analytical (exact) solution

$$x(t) = [x]_0 \cdot e^{-kt}$$

Numerical approximation
to solution

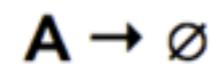
Others



Exercises:

1. Simulate the systems below using python and `scipy.integrate.odeint`

Decay:



Equilibrium:



Enzymatic reaction: $S + E \rightarrow SE$ $SE \rightarrow S + E$ $SE \rightarrow E + P$

Gene expression (central dogma):

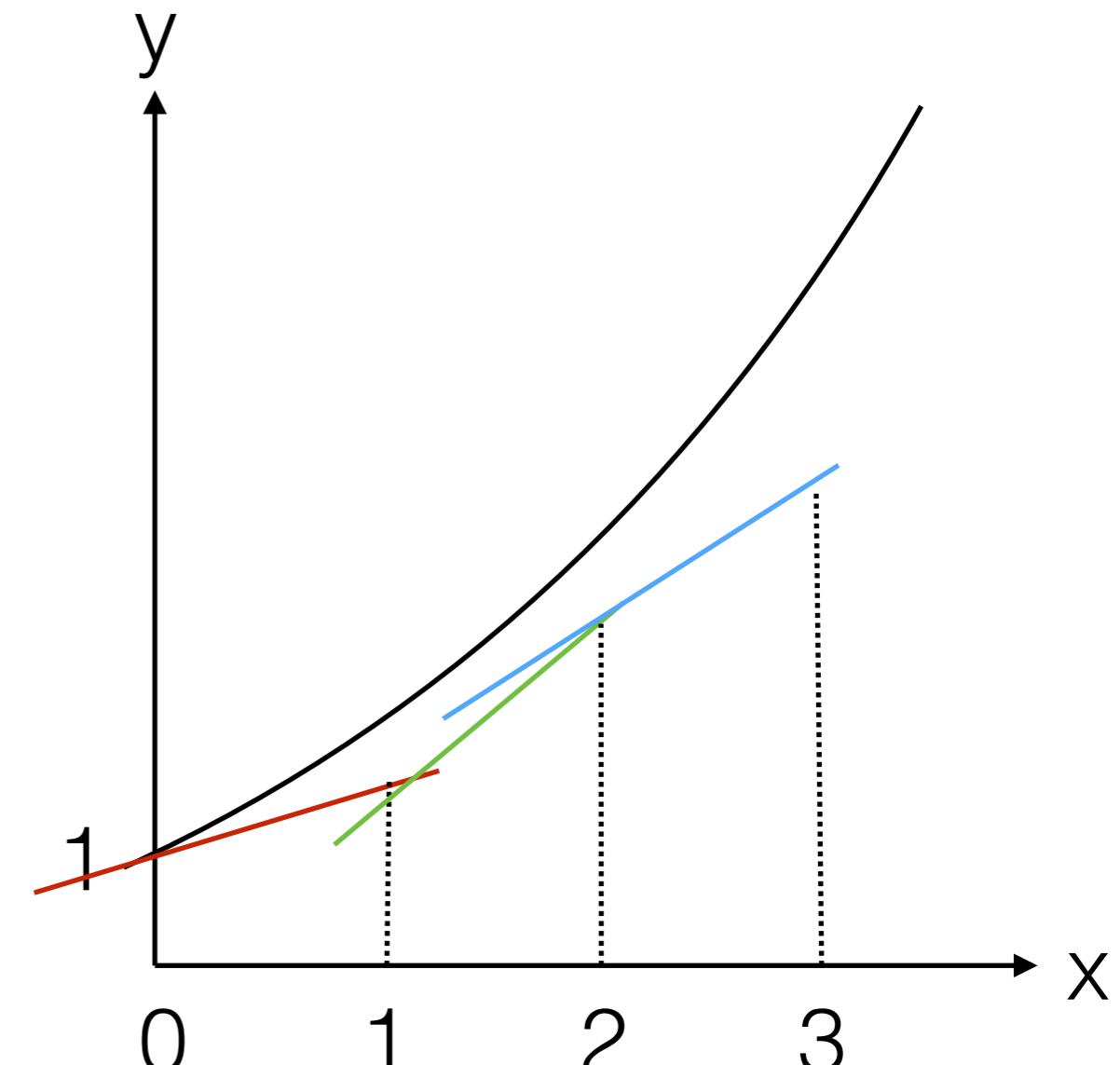
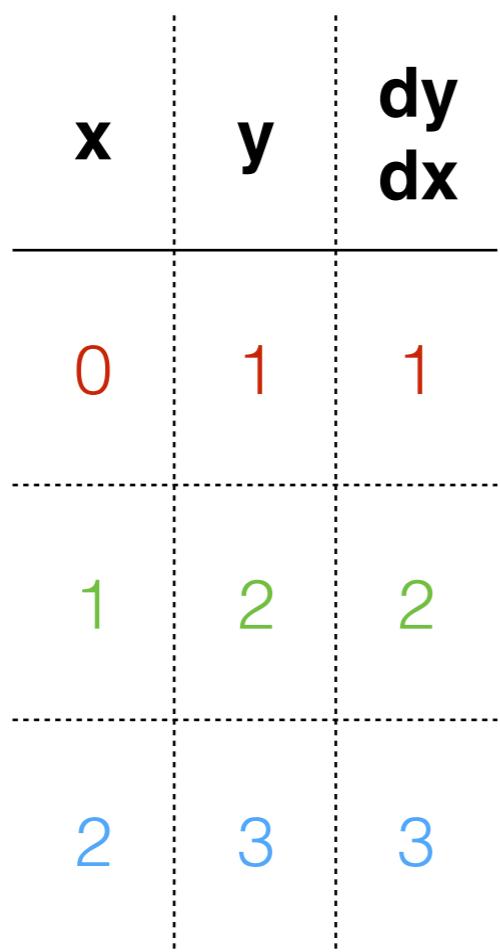
Reactions: $G \rightarrow G + M$ $M \rightarrow M + P$ $M \rightarrow \emptyset$ $P \rightarrow \emptyset$

Euler's method

$$\frac{dy}{dt} = y$$

$$y(0) = 1$$

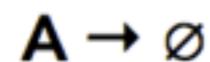
$$Dx = 1$$



Exercises:

1. Simulate one of the systems below using the Euler method

Decay:



Equilibrium:



Enzymatic reaction: $S + E \rightarrow SE$ $SE \rightarrow S + E$ $SE \rightarrow E + P$

Gene expression (central dogma):

Reactions: $G \rightarrow G + M$ $M \rightarrow M + P$ $M \rightarrow \emptyset$ $P \rightarrow \emptyset$

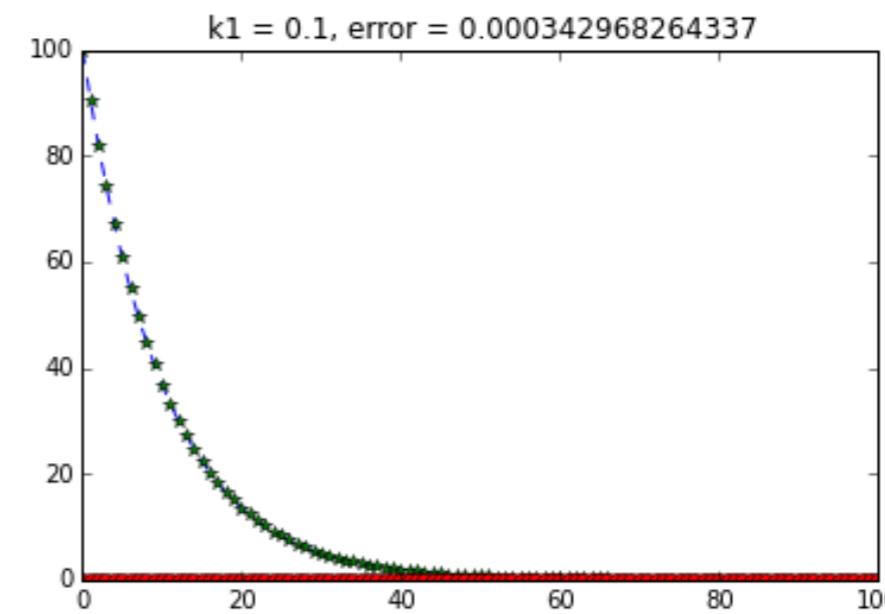
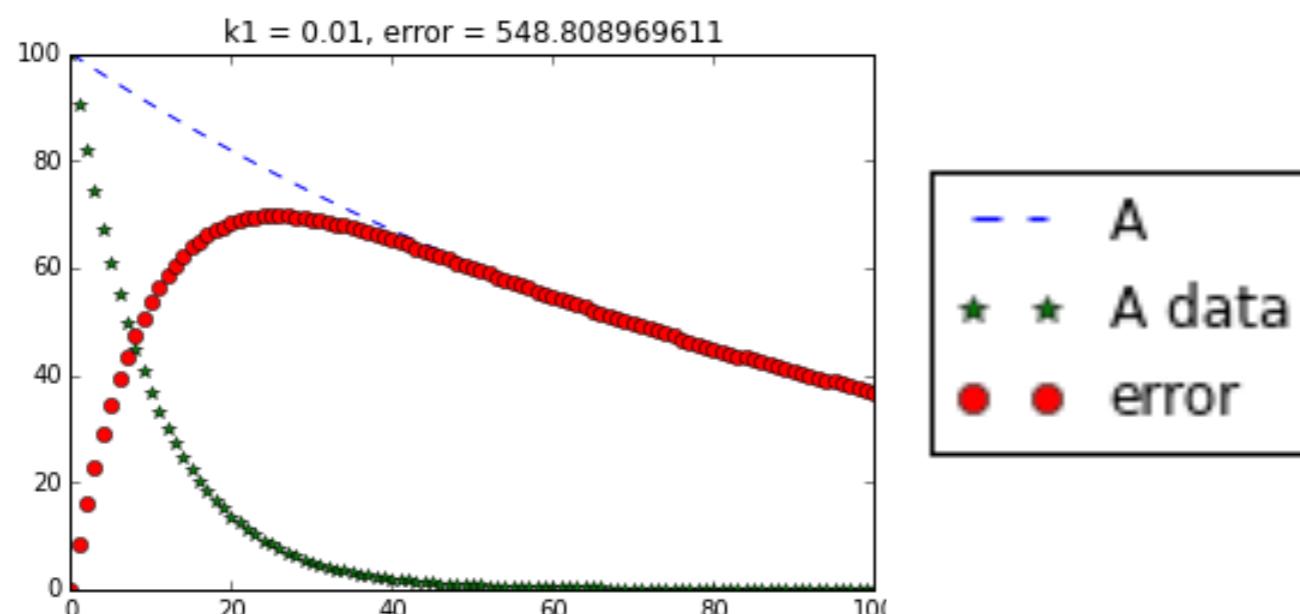
Parameter estimation by fitting data

Parameter estimation is the attempt to determine the values of the kinetic constants or other parameter values of a specific model from experimental data.

In practice, the idea is to minimise the sum of squared distances of time course experimental data and simulation results as:

$$\sum_{i,j,k} (x_i(t_k) - y_{i,j}(t_k))^2$$

where index `i` runs over all compounds, index `j` over all experiments, and index `k` over all measurement time points.



Modelling the response
of yeast to osmotic shock

Definitions

Osmosis is the movement of water molecules from a region of lower solute concentration to a region of higher solute concentration.

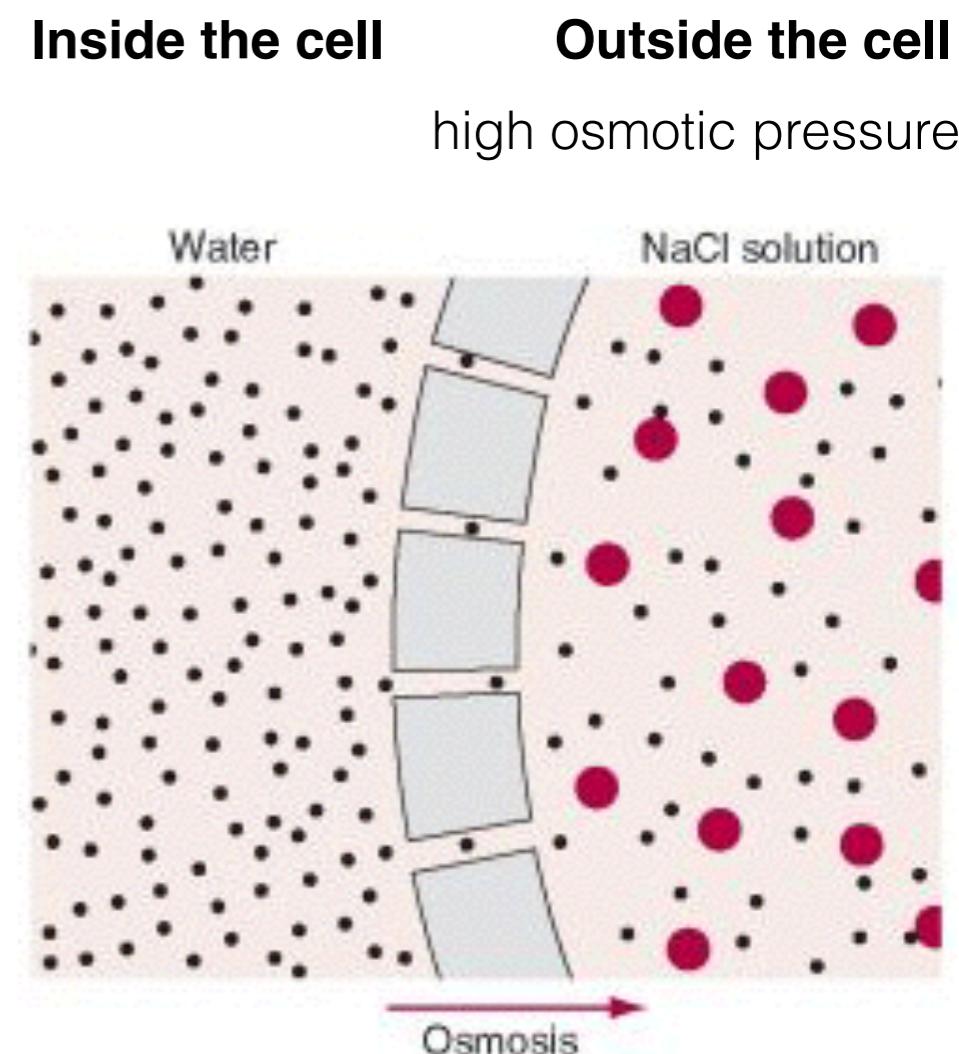
Osmotic pressure is caused by a change in solute concentration.

For example, an increase in solute concentration outside of the cell causes an increase in the **external osmotic pressure**.

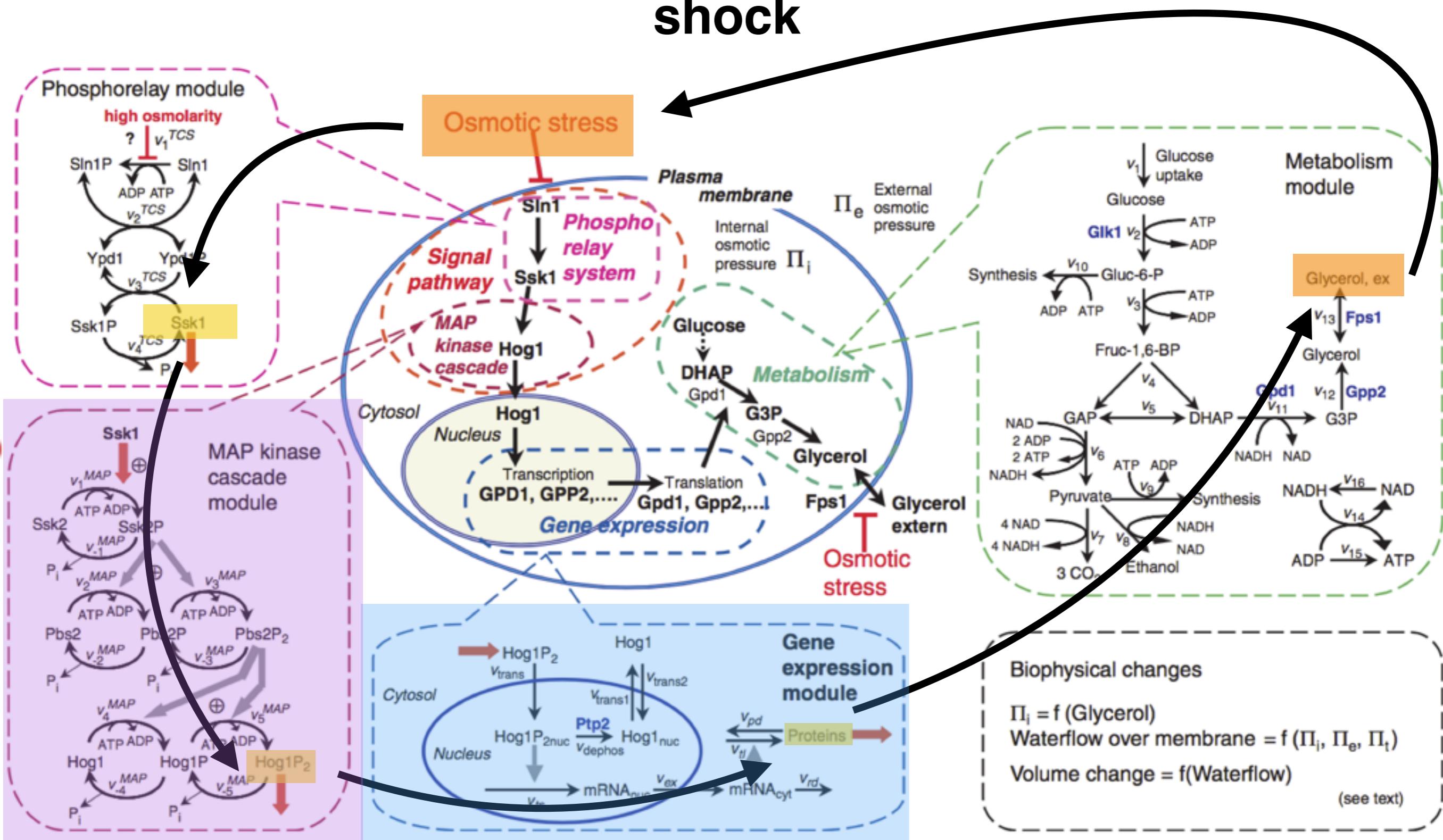
Turgor pressure can be viewed as the amount of pressure being exerted on the cell membrane and is dependent on the internal and external osmotic pressures.

An outflow of water molecules from the cell will cause a cell to lose volume, which in turn will decrease the turgor pressure.

Osmotic shock leads to a quick increase in the external osmotic pressure and a sharp decrease in the turgor pressure of the cell.



Integrative model of the response of yeast to osmotic shock

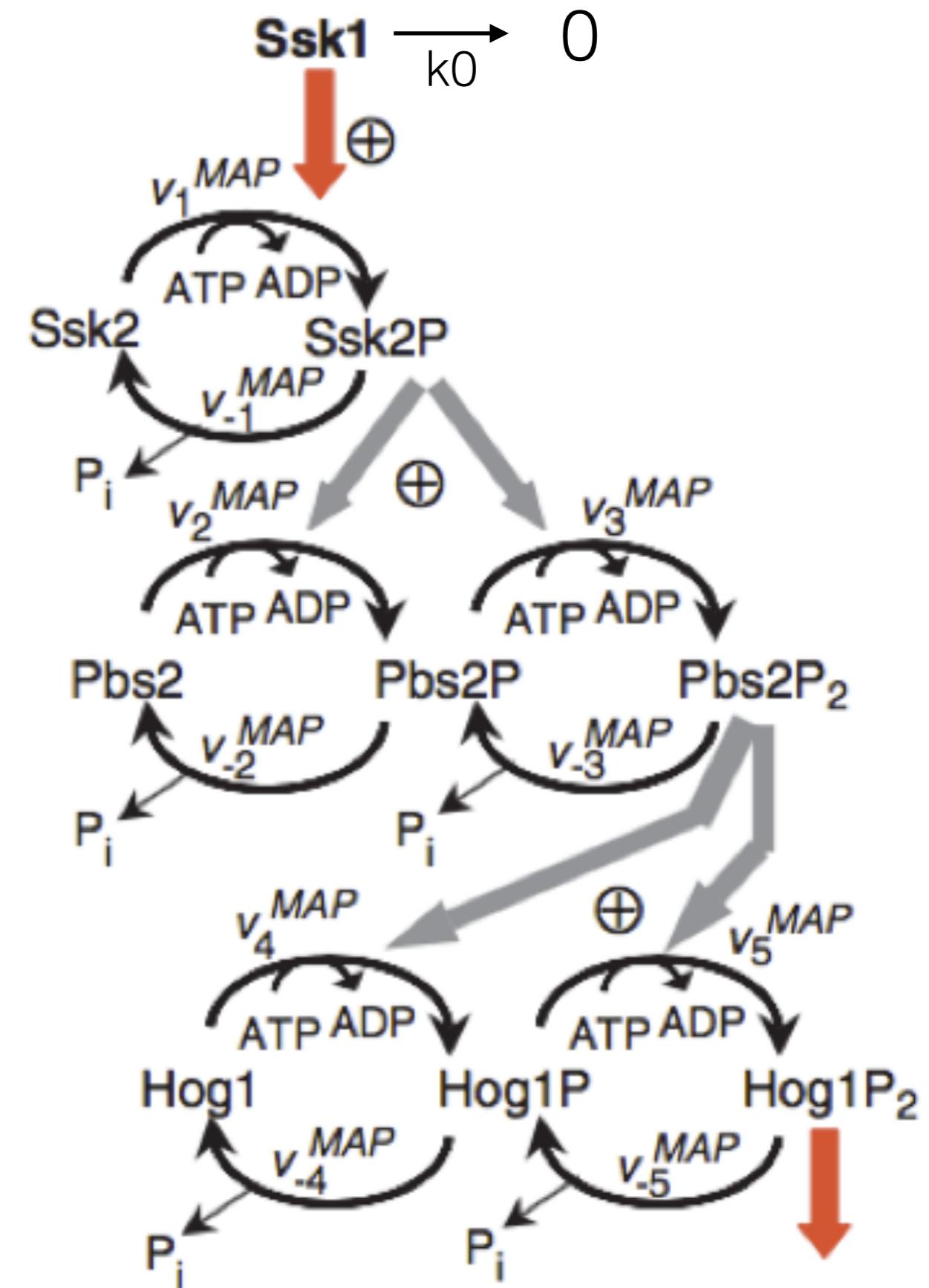
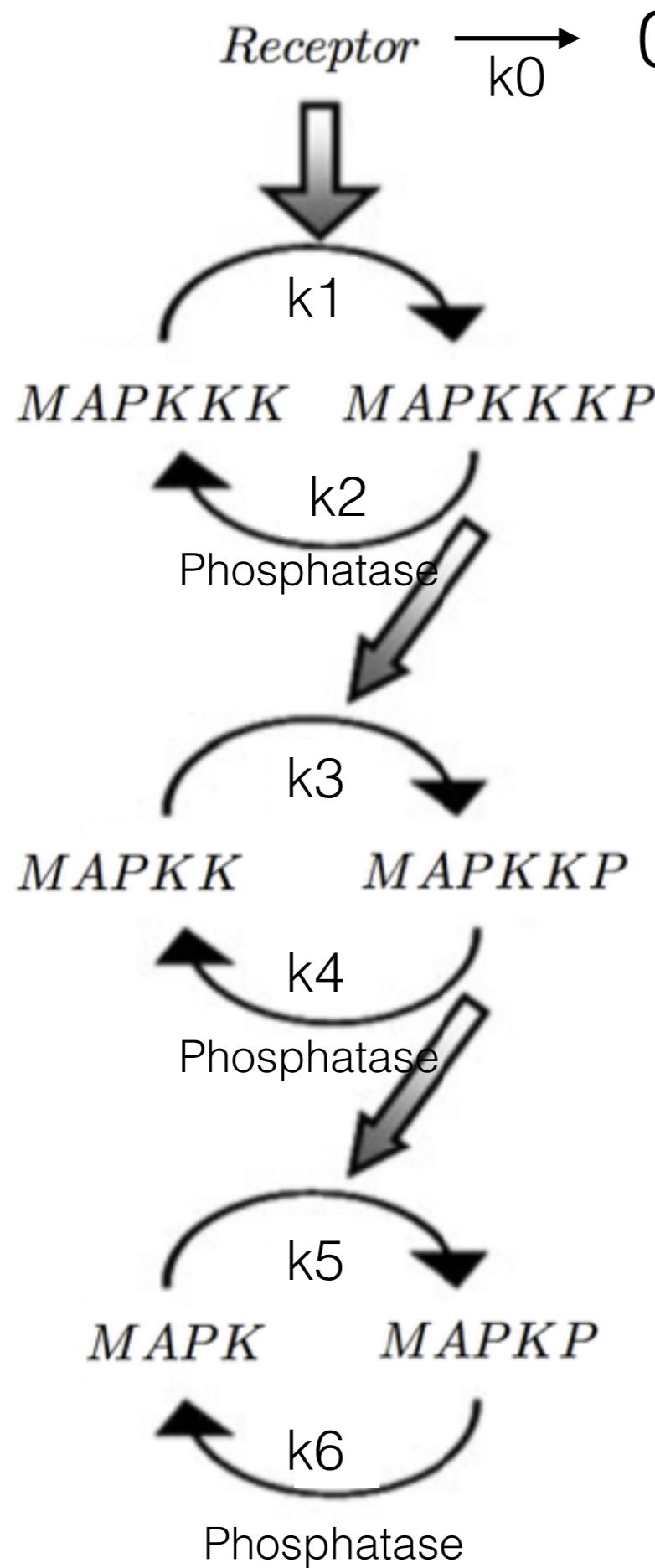


Edda Klipp et al.

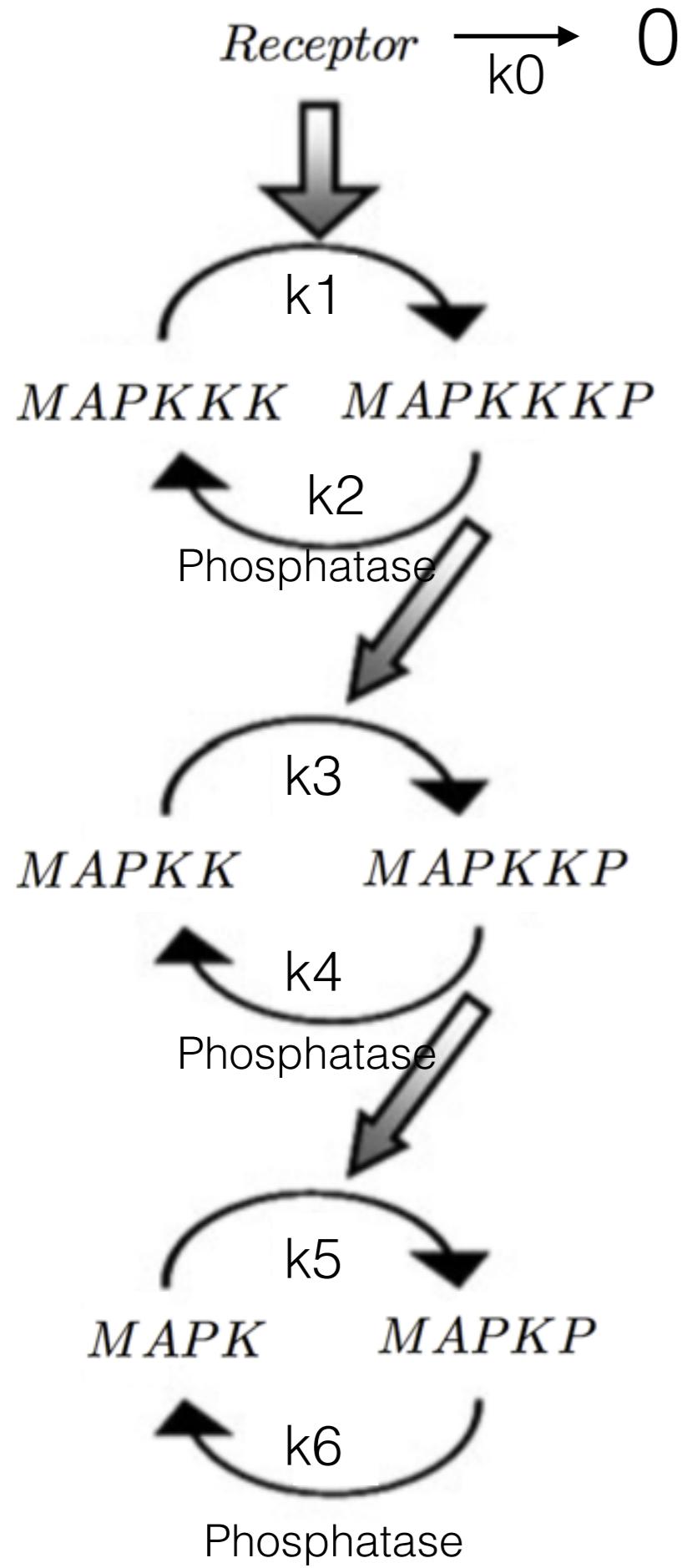
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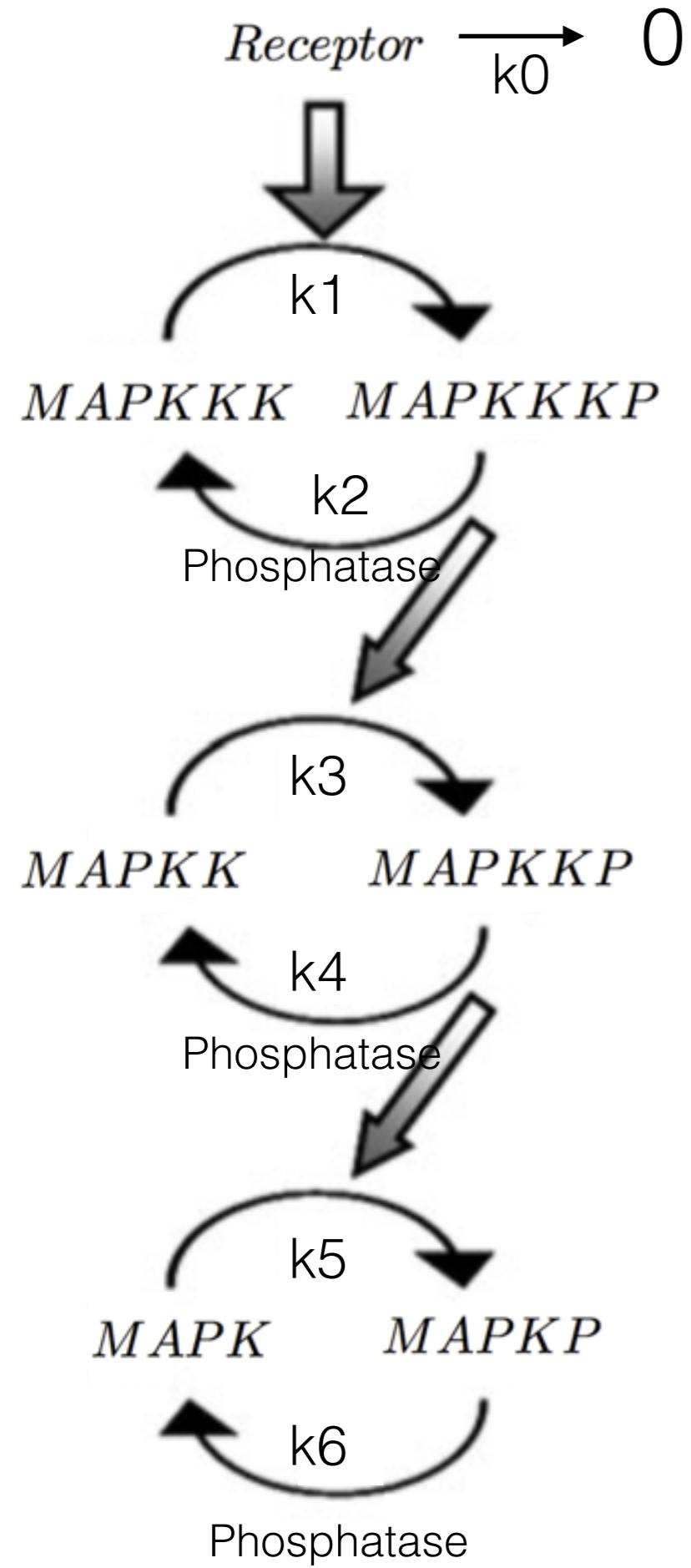
Modelling the MAP kinase cascade

Two models of the MAP kinase cascade

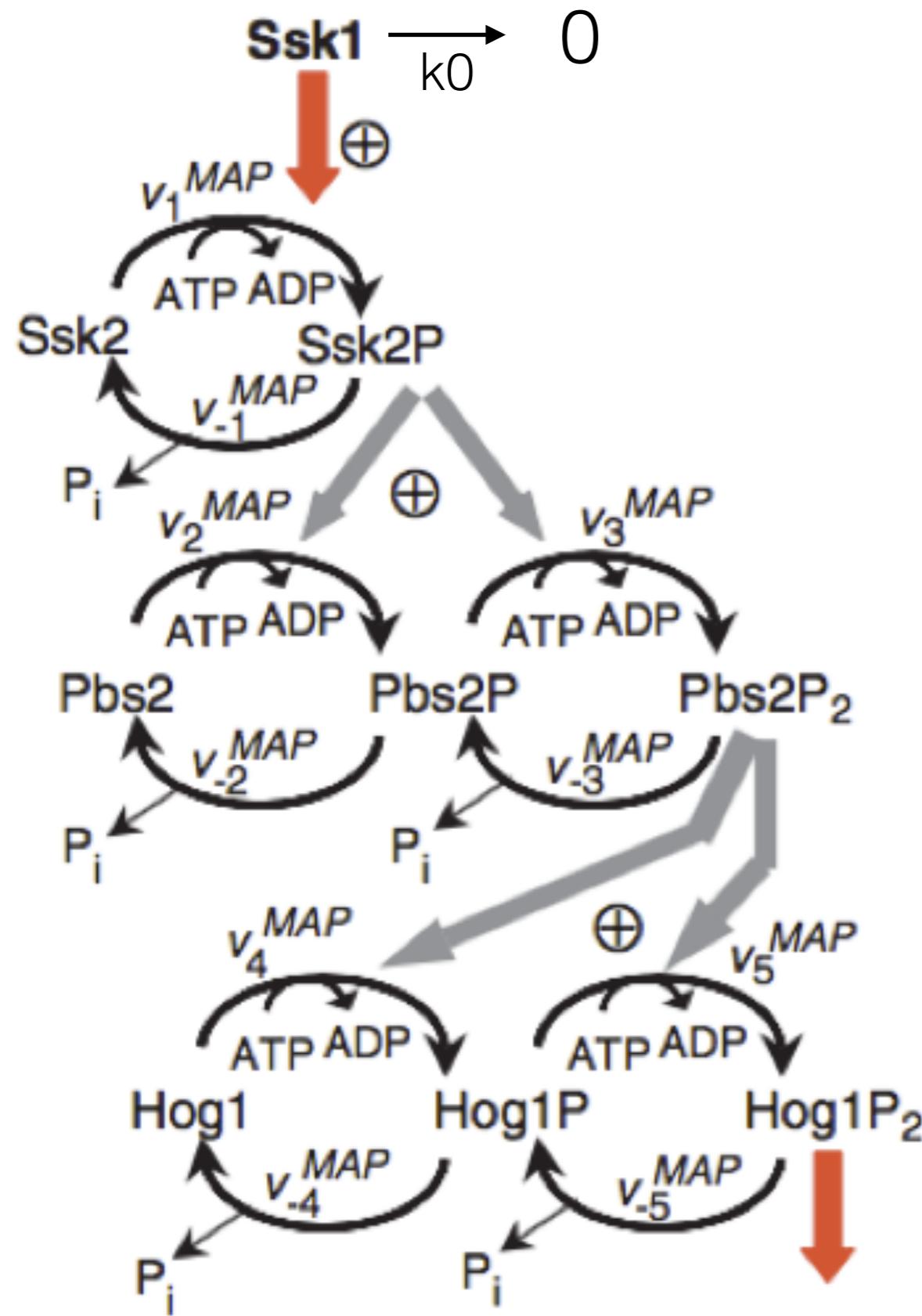


Mathematical model



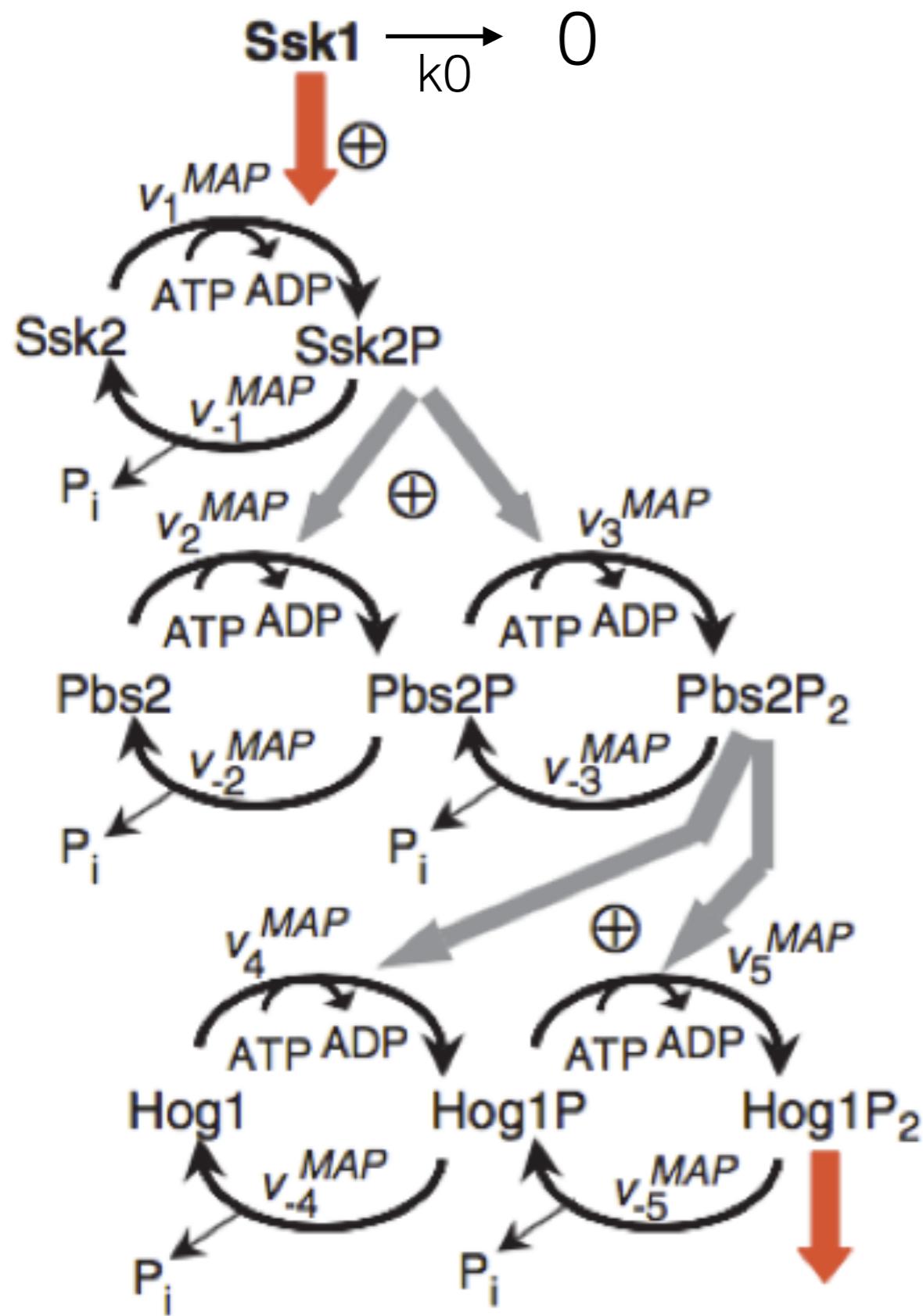


Exercises
in Jupyter notebook

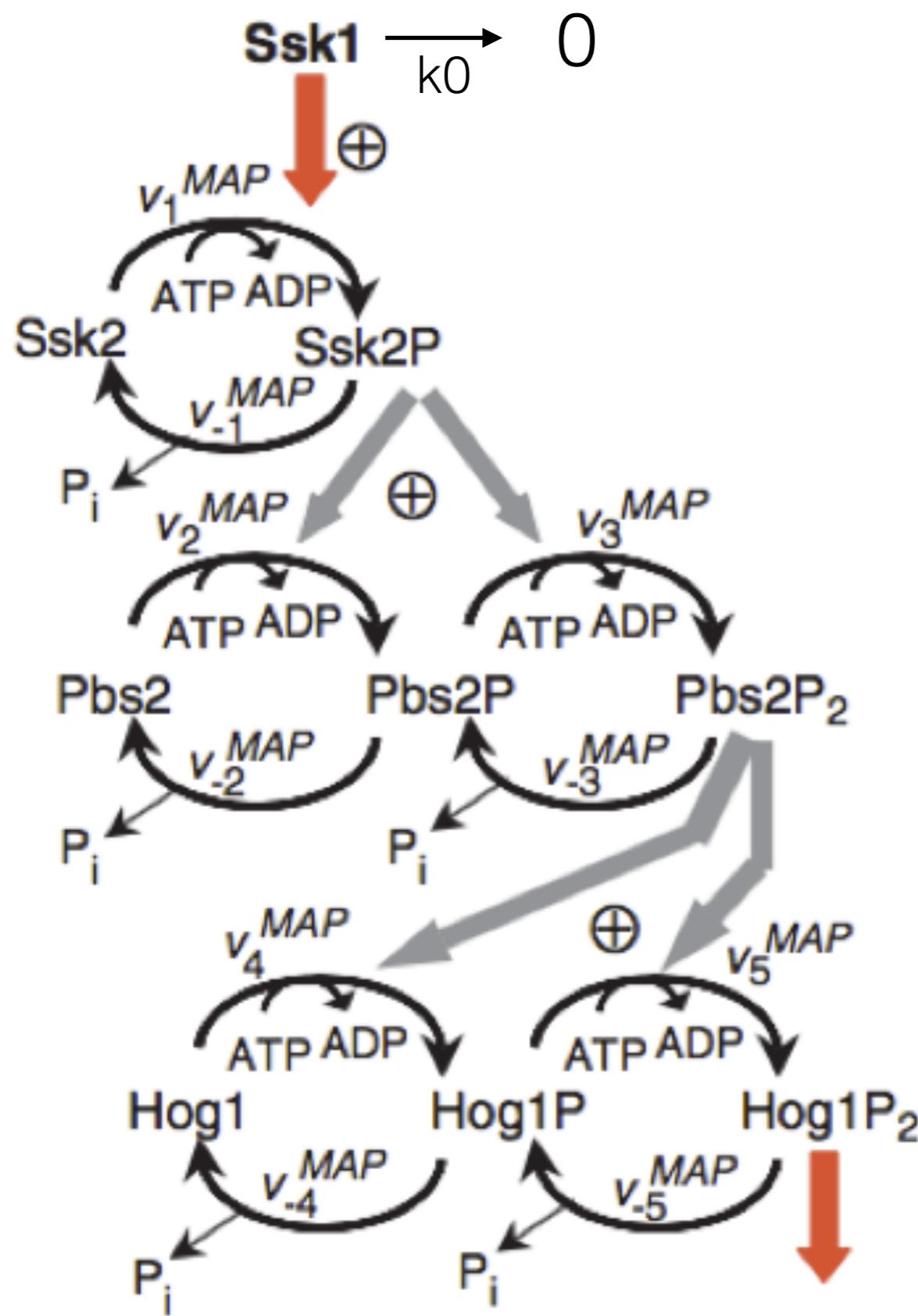


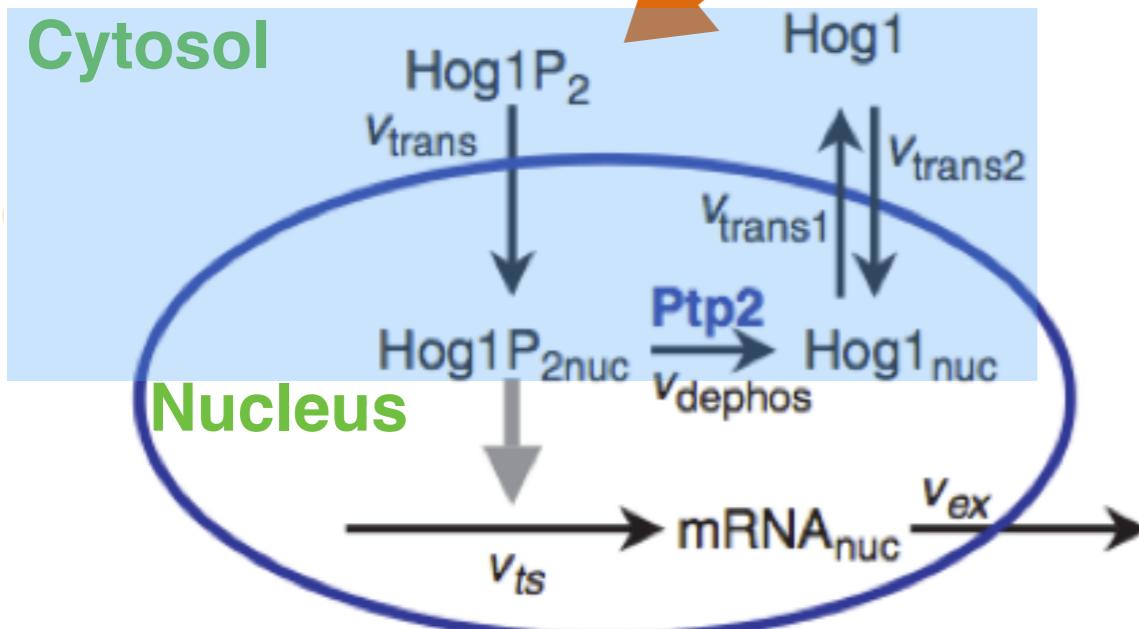
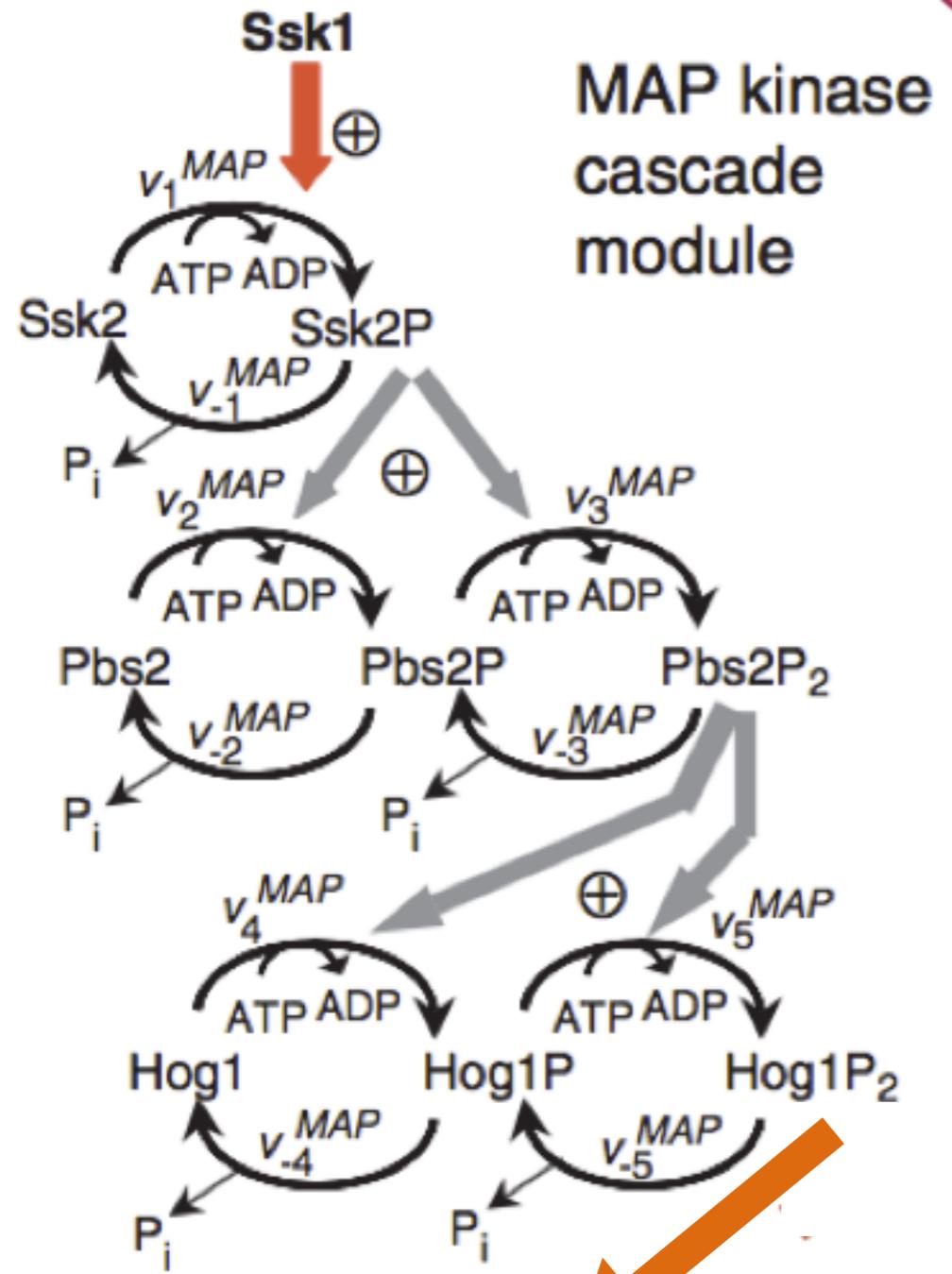
Exercises
in Jupyter notebook

Mathematical model - velocity of reactions



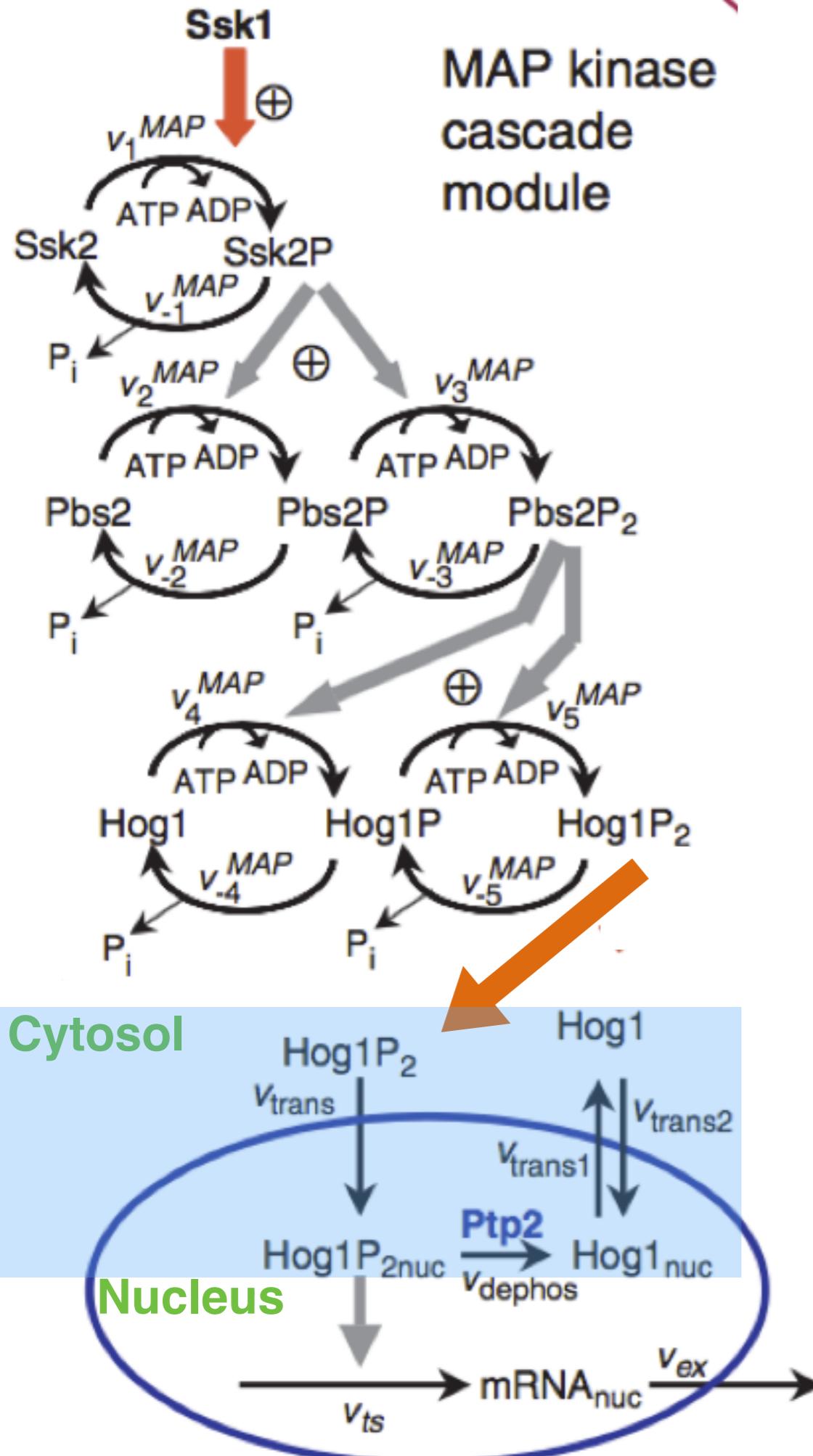
Mathematical model - rate of change of concentrations

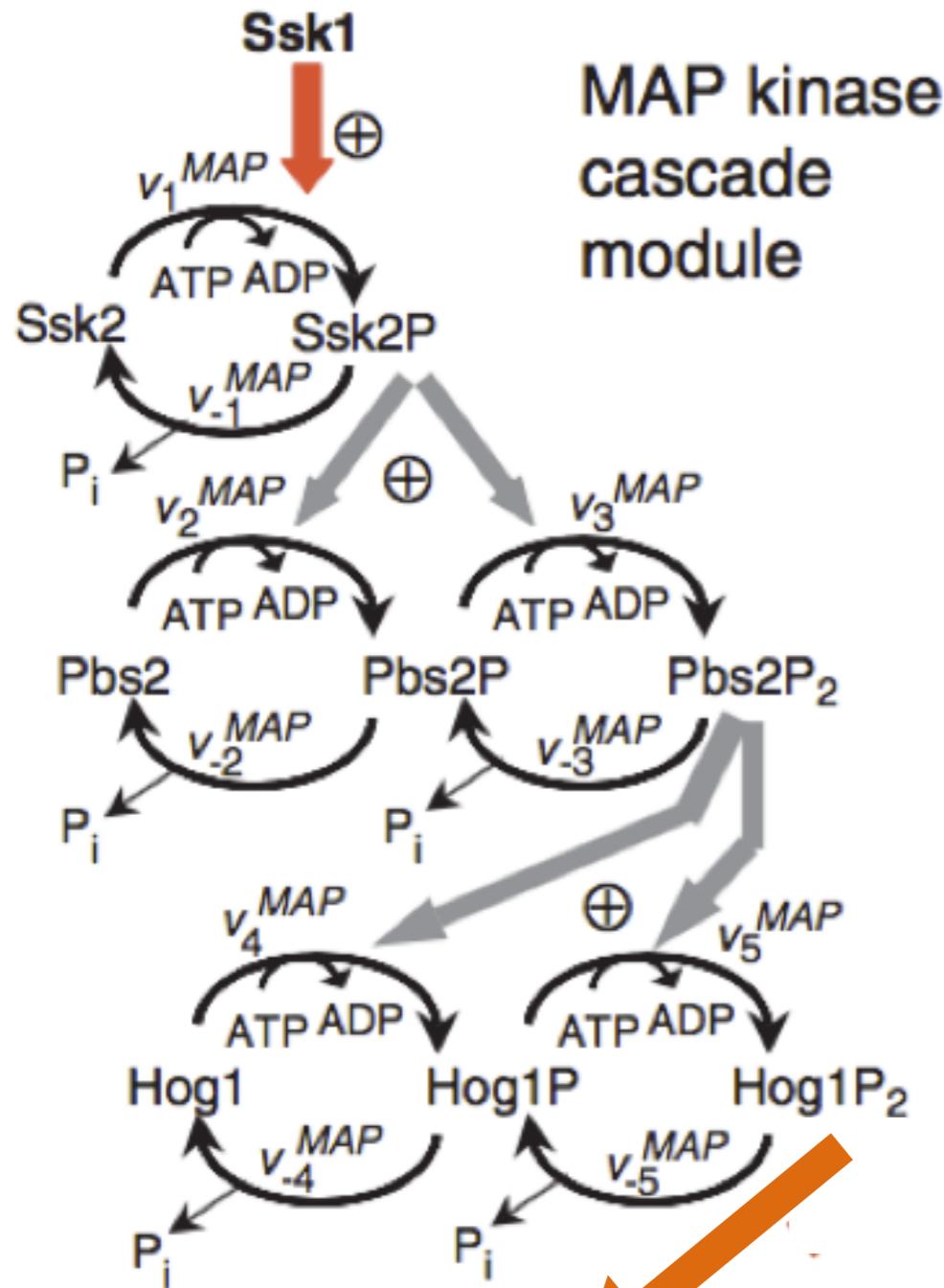




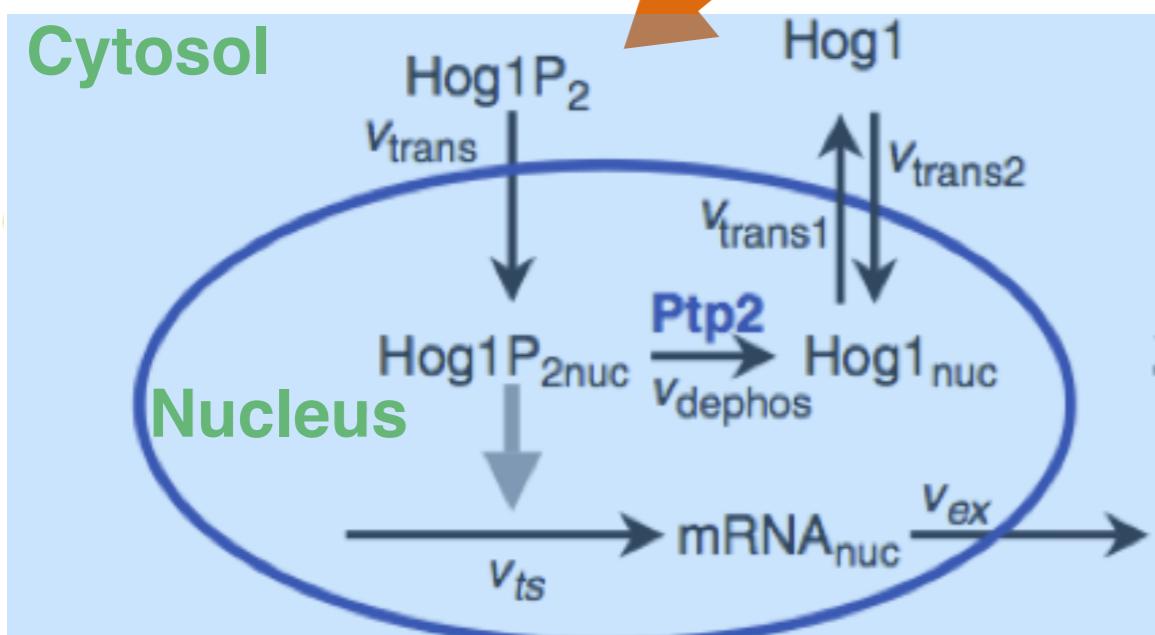
Exercises
in Jupyter notebook

Mathematical model

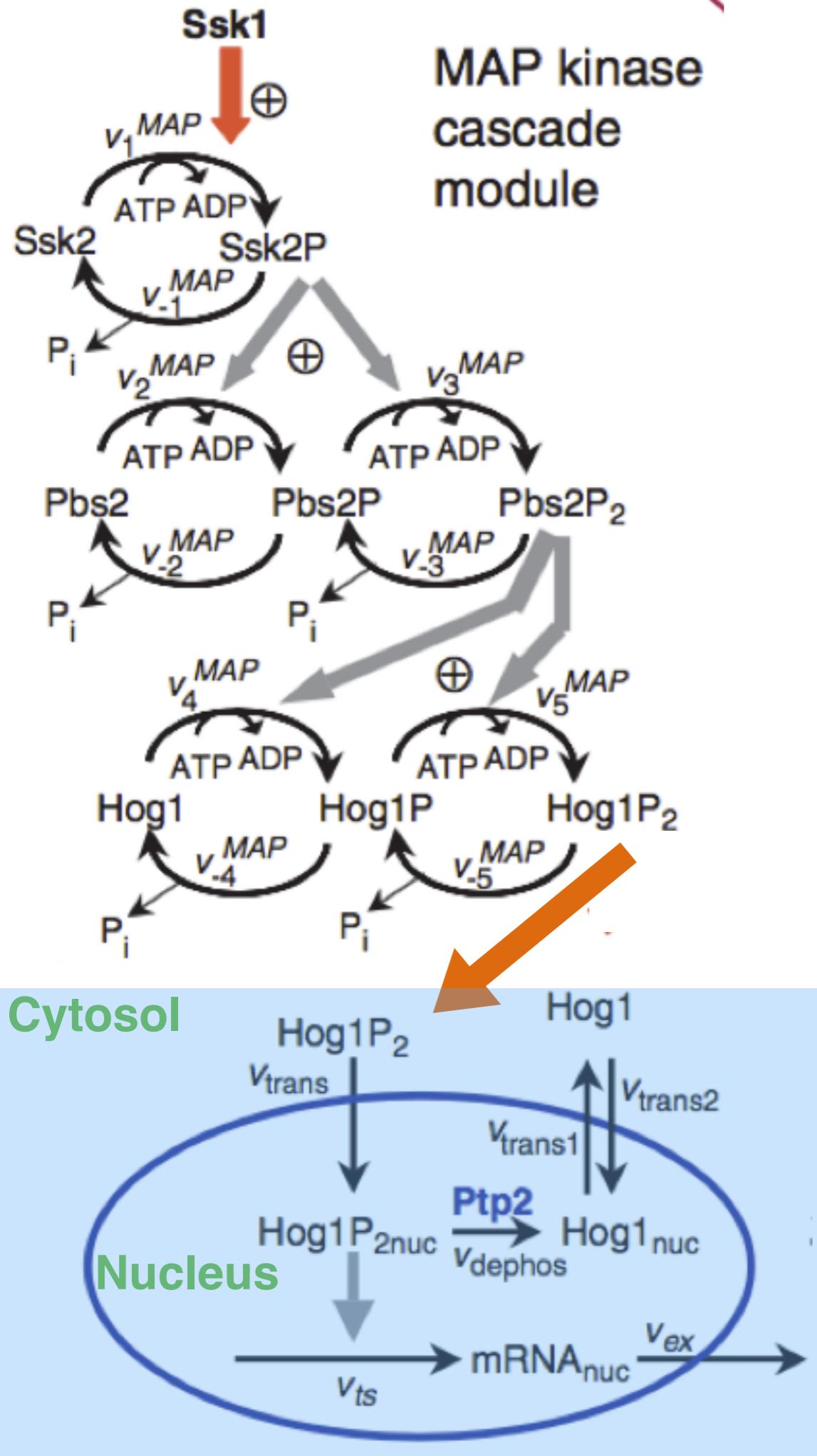




Exercises in Jupyter notebook



Mathematical model



What's next?

Sensitivity analysis

Predictions