# Dynamical modelling of biological networks

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Master Bioinformatics - Marseille Luminy

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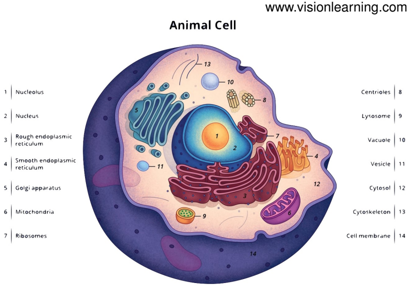
# Cell: the stuctural and functional unit of life




Cells are capable of numerous operations: Movement, Energy supply, Signalling, Growth, Division, Death, Decision making (differentiation), etc.

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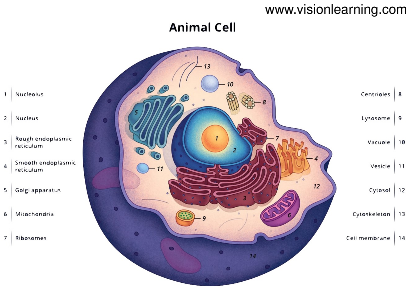
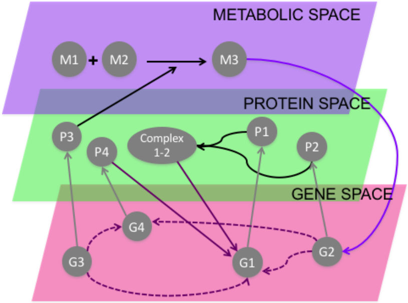


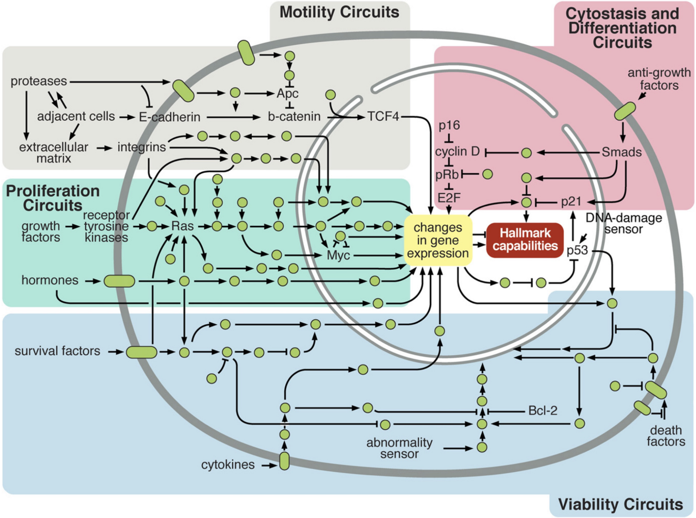

Cells are capable of numerous operations: Movement, Energy supply, Signalling, Growth, Division, Death, Decision making (differentiation), etc.

Heterogeneous interaction networks control and drive these operations

$\rightarrow$ mostly focus on regulatory networks, *i.e.* interactions between genes and their products (proteins): transcriptional and post-transcriptional regulations

## Intracellular Signaling Networks Regulate the Operations of the Cancer Cell

Hanahan & Weinberg (2011) Cell, 144:646-74



# Regulatory network modelling

→ *Use of mathematics to study how genes and proteins interact to produce the complex behaviors of a living cell? (J. Tyson)*

Aims

- Understand the role of individual components and interactions
- Suggest missing components and interactions
- Predict behaviours upon perturbations

Advantages of mathematical and computer tools

- Precise and unambiguous description of network
- *In silico* experiments are cheap and easy!
- A computational model is a generator of predictions

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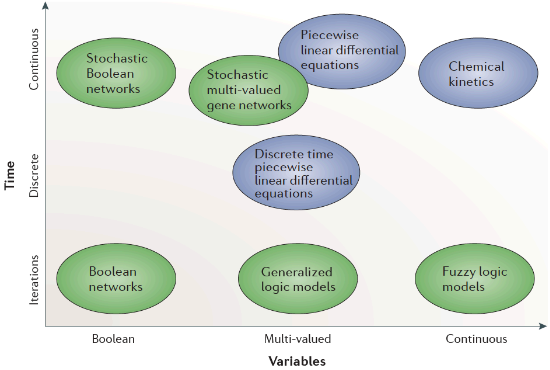
Static *vs* dynamical models of biological networks

- Static models → topology of the networks (nodes and edges)
- Dynamical models → dynamics of the variables associated with the network nodes (nodes, edges, functions)

Plenty of modelling frameworks, spanning different levels of details, e.g.

- Logical models
- Petri nets
- Process algebras
- Constraint-based models
- Ordinary differential equations (ODEs)
- Stochastic master equations
- ...




N. Le Novère 2015

# Ordinary differential equation models of regulatory networks

adapted from H. de Jong

- Concentration of proteins, mRNAs, and other molecules at time-point $t$ represented by continuous variable $x_i(t) \in IR^+$ (concentration level for individual cell or cell population)
- Regulatory interactions, controlling synthesis and degradation, modelled by ODEs
$$\frac{dx}{dt} = \dot{x} = f(x),$$
where $x = [x_1, \ldots x_n]$, and $f(x)$ is **a rate law**
- Well-established theory for modeling gene regulatory networks using ODE models $\rightarrow$ Mathematical specification of rate laws

## Text books


Cornish-Bowden (1995), Fundamentals of Enzyme Kinetics, Portland Press

Heinrich and Schuster (1996), The Regulation of Cellular Systems, Chapman & Hall

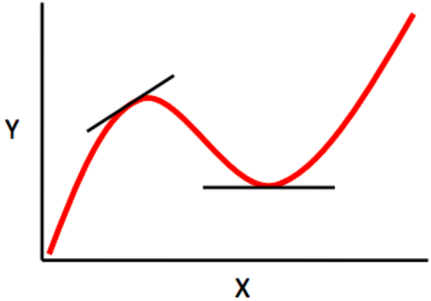
# Ordinary differential equation models

**Interlude!**

adapted from E. Gjini

Mathematical equations used to study time-dependent processes

- A *differential equation* is an algebraic equation involving the function and its derivatives
- A *derivative* is a function representing the change of a dependent variable with respect to an independent variable (slope of a curve)
  - Large derivative: fast change
  - Small derivative: slow change
  - Zero derivative: no change
  - Positive derivative: $Y \uparrow$ if $x \uparrow$
  - Negative derivative: $Y \downarrow$ if $x \uparrow$



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Y(t) : quantity of interest (the dependent variable)
e.g. concentration of a given molecule at time $t$
or level of expression of a gene at time $t$

A continuous function of time $t$ (the independent variable)
The change of $Y$ per unit of time : $dY/dt$ Defined by the limit process:

$$\frac{dY}{dt} = lim_{\Delta t \to 0} \frac{Y(t + \Delta t) - Y(t)}{\Delta t}$$

the derivative of $Y$ with respect to time.

**Interlude!**

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Example of exponential growth: $Y(t)$, number of bacteria over time

$r$: growth rate of the population per unit of time

$$Y(t+dt) \simeq Y(t) + rY(t)dt$$

$$\frac{Y(t+dt)-Y(t)}{dt} \simeq rY(t)$$

$$lim_{dt \to 0} \frac{Y(t+dt)-Y(t)}{dt} \simeq rY(t) \triangleq \frac{dY(t)}{dt} = rY(t)$$

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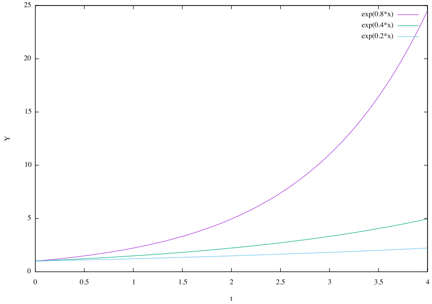
solution: $Y(t) = Y_0 e^{rt}$



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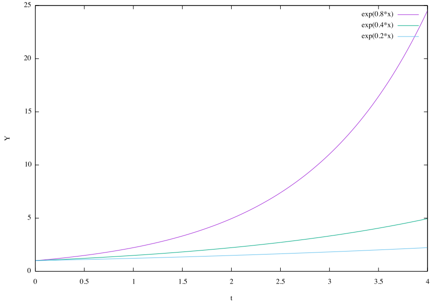


How long to double the population? $\delta$ doubling time

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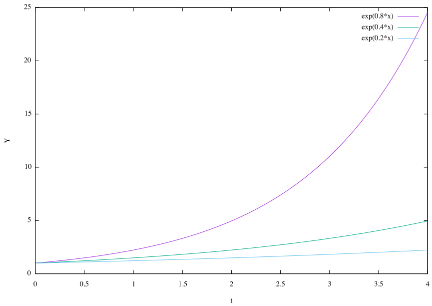
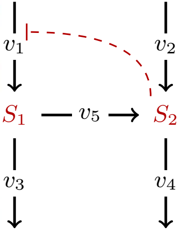



How long to double the population? $\delta$ doubling time $2Y_0 = Y_0 e^{r\delta} \Rightarrow \delta = \frac{ln(2)}{r}$

## Example of a simple reaction network

adapted from B. Ingalls

Reaction rates follow mass action, production of $S_1$ allosteriscally inhibited with a strong cooperative binding of $n$ molecules of $S_2$ ($s_i = [S_i]$):




$$\begin{cases} v_1 = \frac{k_1}{1+(s_2/K)^n},\ v_3 = k_3 s_1,\ v_5 = k_5 s_1 \\ v_2 = k_2,\ v_4 = k_4 s_2 \end{cases}$$

# Ordinary differential equation models

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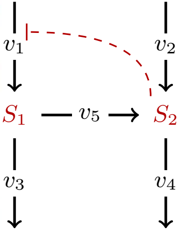


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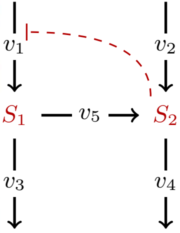


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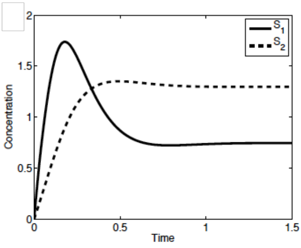
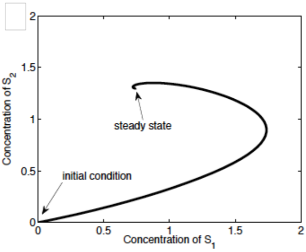
$(\mathrm{conc.time}^{-1})\ \mathrm{k_1} = 20, \mathrm{k_2} = 5, (\mathrm{conc.})\ \mathrm{K} = 1, (\mathrm{time}^{-1})\ \mathrm{k_3} = \mathrm{k_4} = 5, \mathrm{k_5} = 2, \mathrm{and n} = 4,$ arbitrary units




Concentrations plotted against time




Concentration $s_1$ plotted against $s_2$

## Example of a simple reaction network

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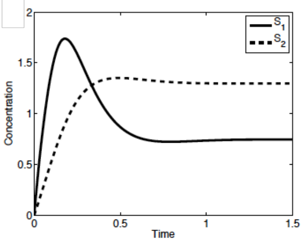


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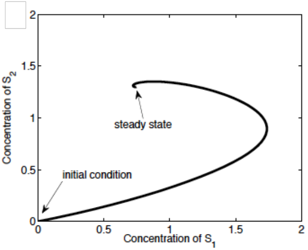


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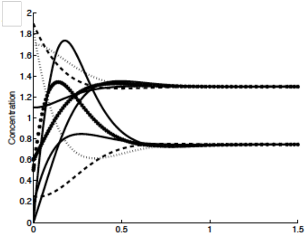
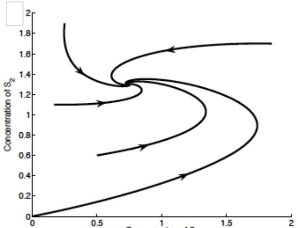
Phase portrait



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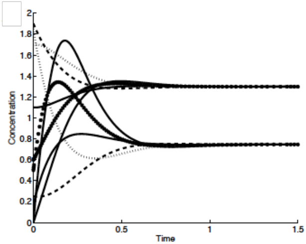
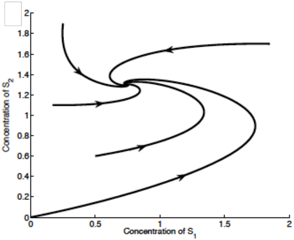
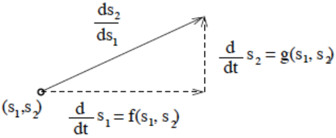


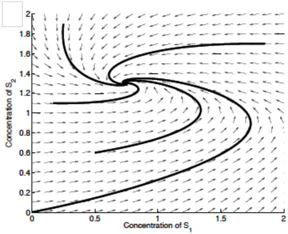




Phase portrait

$$\begin{cases} \frac{ds_1(t)}{dt} = f(s_1(t), s_2(t)) \\ \frac{ds_2(t)}{dt} = g(s_1(t), s_2(t)) \end{cases}$$

The motion in the phase plane at $(s_1, s_2)$ is given by $(f(s_1, s_2), g(s_1, s_2))$




Direction field

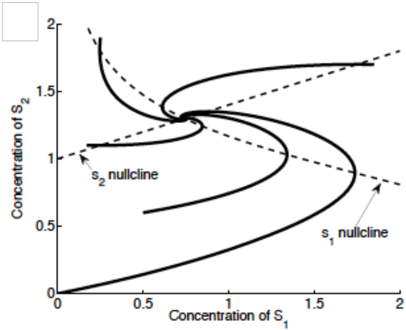
## Example of a simple reaction network

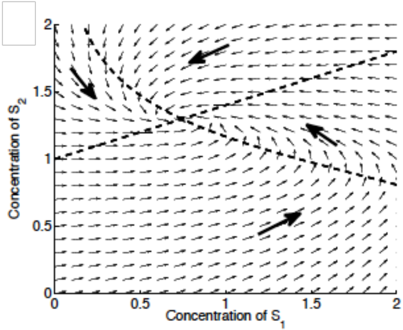
adapted from B. Ingalls

The $s_1$-nullcline (or zero-growth isocline) is the curve $\frac{ds_1}{dt} = 0$

The steady state (or fixed point) of the system is located where all of the nullclines intersect: $\frac{ds_1(t)}{dt} = \frac{ds_2(t)}{dt} = 0$

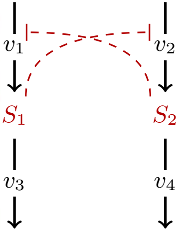
It is stable, because if we move a bit away, the system will return to it.



## Another case of a reaction network

adapted from B. Ingalls




$$\begin{cases} \frac{ds_1(t)}{dt} = \frac{k_1}{1+(s_2(t)/K_2)^{n_1}} - k_3 s_1(t) \\ \frac{ds_2(t)}{dt} = \frac{k_2}{1+(s_1(t)/K_1)^{n_2}} - k_4 s_2(t) \end{cases}$$

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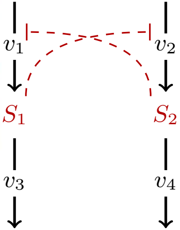


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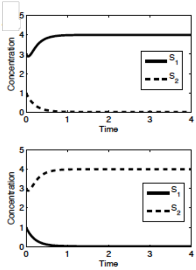
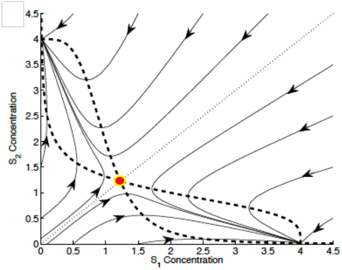
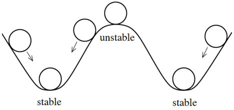
with **balanced** inhibition strength, $k_1 = k_2 = 20$, $K_1 = K_2 = 1$, $k_3 = k_4 = 5$, $n_1 = n_2 = 4$.



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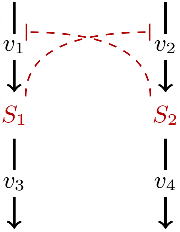


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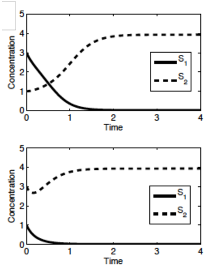
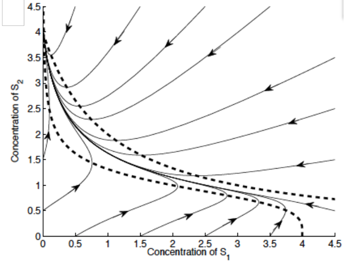
with **unbalanced** inhibition strength, $k_1 = k_2 = 20$, $K_1 = K_2 = 1$, $k_3 = k_4 = 5$, $n_1 = 4$, $n_2 = 1$.



## Exercice

from B. Ingalls

Consider the following system:

$$\begin{cases} \frac{dx(t)}{dt} = -y(t) \\ \frac{dy(t)}{dt} = x(t) \end{cases}$$

What are the nullclines? The steady state?

Sketch the direction field by drawing the direction vectors in the $x - y$ phase plane for $(1,0)$, $(1,1)$, $(0,1)$, $(-1,1)$ $(-1,0)$, $(-1,-1)$, $(0,-1)$, $(1,-1)$.

# Ordinary differential equation models

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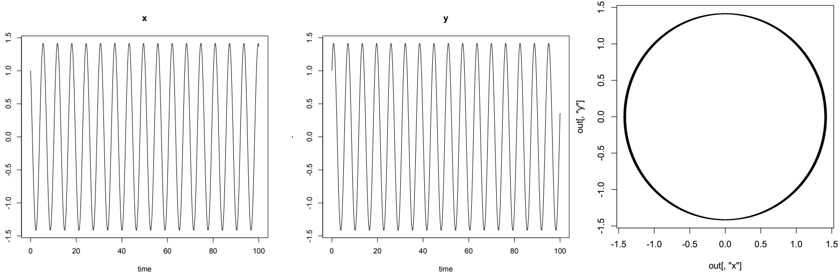
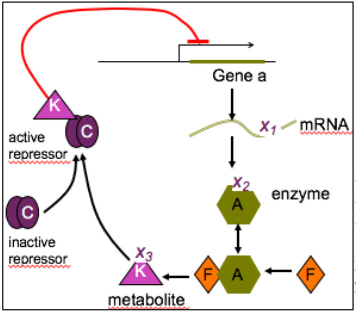


## Example: ODE model of a genetic regulatory system w/ end-product inhibition

from H. de Jong

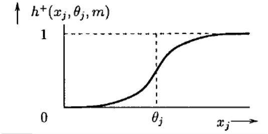



$$\begin{cases} \dfrac{dx_1}{dt} = \kappa_1\, r(x_3) - \gamma_1 x_1 \\[2ex] \dfrac{dx_2}{dt} = \kappa_2\, x_1 - \gamma_2 x_2 \\[2ex] \dfrac{dx_3}{dt} = \kappa_3\, x_2 - \gamma_3 x_3 \end{cases}$$

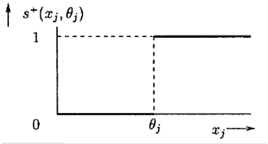
- $x_1$: concentration of mRNA a
- $x_2$: concentration of protein A
- $x_3$: concentration of metabolite K
- $\kappa_i$: production constants
- $\gamma_i$: degradation contants
- $r$: a decreasing non-linear regulatory function ranging from 0 to 1

## Genetic regulatory networks

Non linear regulatory functions




$$h^+(x,\theta,m) = \frac{x^m}{x^m+\theta^m}$$




$$x < \theta,\ s^+(x,\theta) = 0$$
$$x > \theta,\ s^+(x,\theta) = 1$$

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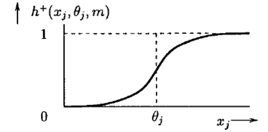
Non linear regulatory functions

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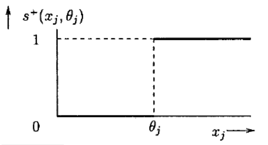


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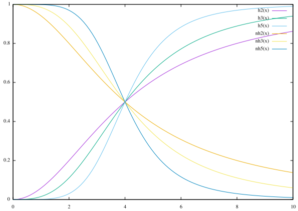


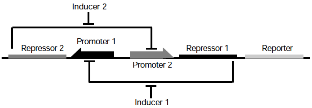

Exercice: Give the expression for the inhibitory Hill function

What is the effect when increasing $m$?

$m$ is called the cooperativity parameter

Gardner *et al.* 2000

## Genetic regulatory networks: the toogle switch




Toggle switch design: Repressor 1 inhibits transcription from Promoter 1 and is induced by Inducer 1. Repressor inhibits transcription from Promoter 2 and is induced by Inducer 2.

$$\frac{du}{dt} = \frac{\alpha_1}{1+v^\beta} - u$$

$$\frac{dv}{dt} = \frac{\alpha_2}{1+u^\gamma} - v$$

- $u$ concentration of rep.1
- $v$ concentration of rep.2
- $\alpha_1$ rate of synthesis of rep. 1
- $\alpha_2$ rate of synthesis of rep. 2
- $\beta$ cooperativity of repression of prom. 2
- $\gamma$ cooperativity of repression of prom. 1

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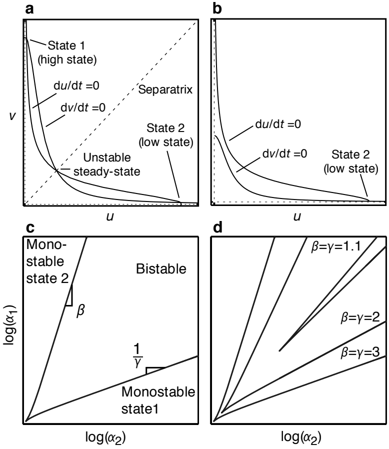
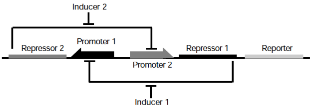



**Figure 2** Geometric structure of the toggle equations. **a**, A bistable toggle network with balanced promoter strengths. **b**, A monostable toggle network with imbalanced promoter strengths. **c**, The bistable region. The lines mark the transition (bifurcation) between bistability and monostability. The slopes of the bifurcation lines are determined by the exponents $\beta$ and $\gamma$ for large $\alpha_1$ and $\alpha_2$. **d**, Reducing the cooperativity of repression ($\beta$ and $\gamma$) reduces the size of the bistable region. Bifurcation lines are illustrated for three different values of $\beta$ and $\gamma$. The bistable region lies inside of each pair of curves.

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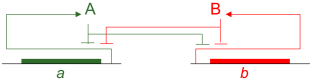
## Exercice: ODE model of a genetic cross-inhibition

adapted from H. de Jong




Can you devise the remaining model equations?

$$\begin{cases} \frac{dx_{ra}}{dt} = \kappa_{ra} h_2^-(x_{pb}, \theta_{pb}) h_2^-(x_{pa}, \theta_{pa}) - \gamma_{ra} x_{ra} \\ \frac{dx_{pa}}{dt} = \\ \frac{dx_{rb}}{dt} = \\ \frac{dx_{pb}}{dt} = \end{cases}$$

$$h_2^-(x, \theta) = \frac{\theta^2}{x^2 + \theta^2}$$

# Ordinary differential equation models

## Exercice: ODE model of a genetic cross-inhibition

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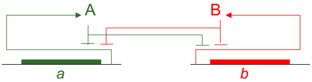


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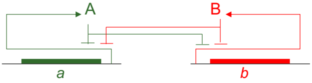
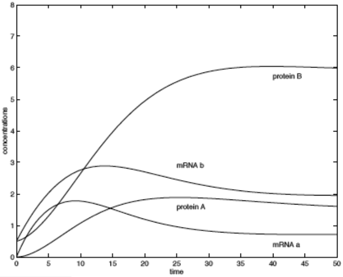



$$\begin{cases} \frac{dx_{ra}}{dt} = \kappa_{ra} h_2^-(x_{pb}, \theta_{pb}) h_2^-(x_{pa}, \theta_{pa}) - \gamma_{ra} x_{ra} \\ \frac{dx_{pa}}{dt} = \kappa_{pa} x_{ra} - \gamma_{pa} x_{pa} \\ \frac{dx_{rb}}{dt} = \kappa_{rb} h_2^-(x_{pa}, \theta_{pa}) h_2^-(x_{pb}, \theta_{pb}) - \gamma_{rb} x_{rb} \\ \frac{dx_{pb}}{dt} = \kappa_{pb} x_{rb} - \gamma_{pb} x_{pb} \end{cases}$$

$$h_2^-(x, \theta) = \frac{\theta^2}{x^2 + \theta^2}$$

# A note on stochastic models

adapted from H. de Jong

- ODEs are valid for homogeneous systems and large numbers of molecules
- Stochasticity arises due to the small number of molecules
- Consider discrete amounts of molecules, homogeneous system, no spatial restrictions

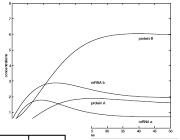
$\beta_j$: transition probability that reaction $j$ brings the system to state $X$,
$\alpha_j$: transition probability to leave state $X$ with the occurrence of reaction $j$

the master equation gives the evolution of $X$

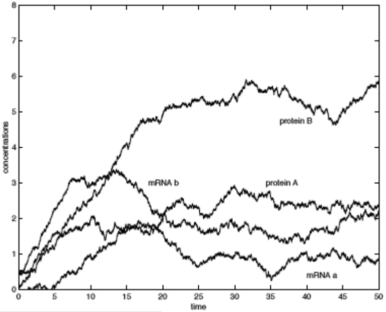
$$\frac{\delta}{\delta t}p(X,t) = \sum_{j=1}^{m}(\beta_j - \alpha_j p(X,t)).$$

hard to solve $\longrightarrow$ stochastic simulation algorithm (Gillespie 77) adapted from H. de Jong

Kierzek et al. 2001 proposed 10 elementary reactions for the transcription and translation of a procaryotic gene

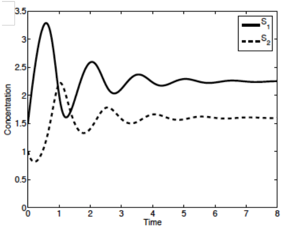


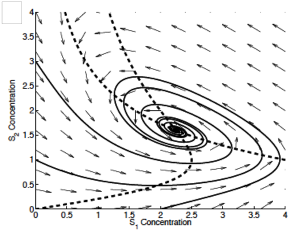
$$
\begin{aligned}
A + A &\longleftrightarrow A_2\\
A_2 + DNA_b &\longleftrightarrow A_2 \cdot DNA_b\\
RNAP + DNA_b &\longleftrightarrow RNAP \cdot DNA_b\\
RNAP \cdot DNA_b &\longrightarrow RNAP + DNA_b\\
&\qquad + RNA_b\\
B + B &\longleftrightarrow B_2\\
B_2 + DNA_b &\longleftrightarrow B_2 \cdot DNA_b\\
B_2 \cdot DNA_b + A_2 &\longleftrightarrow A_2 \cdot B_2 \cdot DNA_b\\
A_2 \cdot DNA_b + B_2 &\longleftrightarrow A_2 \cdot B_2 \cdot DNA_b
\end{aligned}
$$



## Oscillatory behaviours

from B. Ingalls



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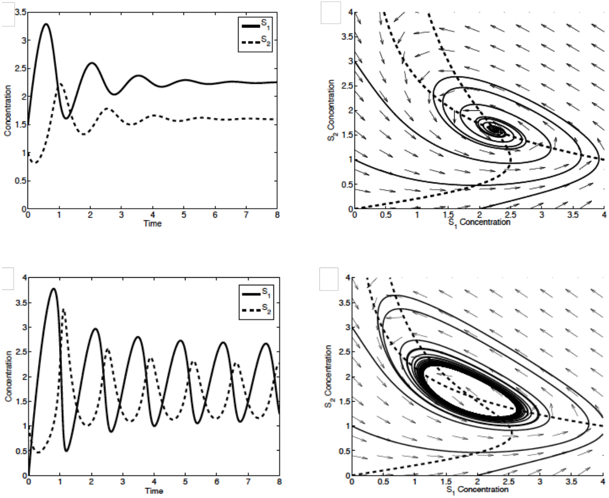

## A note on bifurcation analysis

from B. Ingalls

- Variation in parameter values can cause qualitative changes in long-term system behaviour (e.g. location and/or number of steady states)
- Parameter values at which such changes occur are called bifurcation points

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Exercice:

$$\frac{dx(t)}{dt} = (a-1)x(t)$$

What is the sign of the rate of change $dx/dt$ for positive and negative values of x?
Under which condition the steady state at $x = 0$ is stable?

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Exercice:

$$\frac{dx(t)}{dt} = (a-1)x(t)$$

What is the sign of the rate of change $dx/dt$ for positive and negative values of x?
Under which condition the steady state at $x = 0$ is stable?
the steady state is stable if $a < 1$, unstable if $a > 1$.
The parameter value $a = 1$ is thus a bifurcation point for this system.

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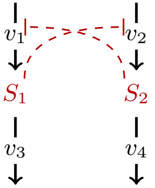


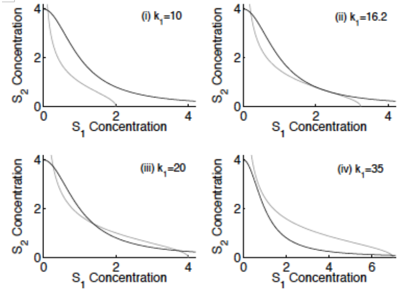


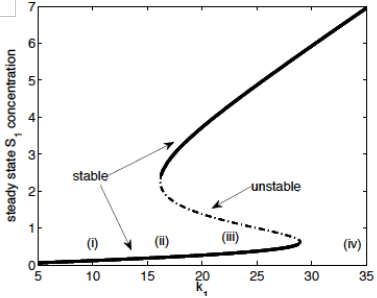

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