

ODEs models in Systems Biology

Lecture 5 & 6

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System Biology

Mathematical modeling

● System Biology

Elementary modules

Examples

- **Systems Biology** = investigates function of genetic, molecular and cellular processes in a systematic way:
→ making (biologically relevant) sense out of data
- why “systems”?
 - ◆ biological processes → mathematical models
 - ◆ many processes simultaneously → systematic methods
- Approach of today: detailed description of **elementary dynamical moduli** for biological processes by means of **ODEs** (Ordinary Differential Equations)
- Inspiration: reaction kinetics
- basic building blocks in constructing networks of interactions for known biochemical pathways

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References for today's material

Mathematical modeling

● System Biology

Elementary modules

Examples

- Leah Edelstein-Keshet "Mathematical Models in Biology" (reprint SIAM 2005)
- Eduardo Sontag "Lecture notes in Mathematical Biology" (lecture Notes available at <http://www.math.rutgers.edu/~sontag>)
- Olaf Wolkenhauer "System Biology" (lecture notes available at <http://www.sbi.uni-rostock.de/teaching.html>)
- J.J. Tyson, K.C. Chen and B. Novak, "Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell", Curr. Opin. Cell Biol. 15:221-231 (2003).



Biological moduli as ODEs

Mathematical modeling

Elementary modules

● Biological moduli as ODEs

- Maltus Law
- Solving ODEs: Matlab
- Qualitative behavior: steady state
- Reaction kinetics
- Elementary reaction kinetics
- Enzyme catalyzed reactions
- Michaelis Menten kinetics
- Competitive inhibition
- Cooperativity
- Sigmoidal responses
- Multistability
- Enzymes and multistability
- Feedback regulation
- Positive feedback
- Negative regulation
- A gene regulatory network
- Other regulatory elements

Examples

- what is a ODE?
Consider x = concentration of a substrate X (e.g. mRNA, protein, small molecule, metabolite, any reagent)
- at time $t + \Delta t$, (Δt small) one can expand in Taylor series

$$x(t + \Delta t) \simeq x(t) + kx(t)\Delta t$$

- in the limit for small times $\lim_{\Delta t \rightarrow 0} \frac{x(t+\Delta t) - x(t)}{\Delta t} =: \frac{dx}{dt}$

$$\implies \boxed{\frac{dx}{dt} = kx}$$

- ◆ 1st order, linear, autonomous ordinary differential equation
- ◆ it involves two different quantities:
 - x = state variable
 - k = parameter (does not describe an elementary component of the process)
- ◆ it describes a **reaction rate**, i.e., how the concentration of X varies with time



Maltus Law

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Examples

■ solving this ODE: Maltus law (1798)

- ◆ separate the variables $\frac{dx}{x} = k dt$
- ◆ integrate both sides

$$\int \frac{dx}{x} = \int k dt$$

$$\ln \frac{x(t)}{x(0)} = k t$$

$$\ln x(t) = \ln x(0) + k t$$

where $x(0) = x_o = \text{constant}$

- ◆ Exponentiating

$$x(t) = x_o e^{kt}$$



Maltus Law

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Elementary modules

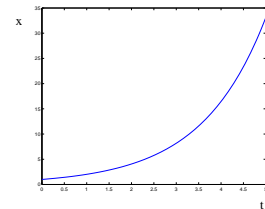
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Examples

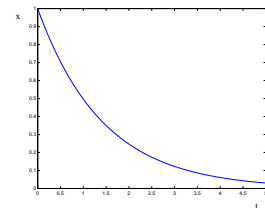
$$x(t) = x_o e^{kt}$$

The characteristic evolution of the Maltus law is exponential and depends on the sign of k

1. $k > 0$ exponential growth



2. $k < 0$ exponential decay





Solving ODEs: Matlab

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Examples

- Apart from simple cases (like Maltus law) there is little chance to find explicit solutions of an ODE or of a system of ODEs. How to proceed then?
- Use a simulator to numerically integrate the ODEs.
- example: Matlab (standard software in all engineering fields)
 - ◆ define a function for the ODE


```
function dzdt = Maltus(t,z,k);
dzdt=k*z;
```
 - ◆ define parameter, initial condition, time interval


```
k = 0.7; % growth constant
x0 = 1; % initial condition
tspan = [0, 5]; % time interval
```
 - ◆ integration routine


```
[t,x] = ode45(@Maltus,tspan,x0,[],k);
```

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Qualitative behavior: steady state

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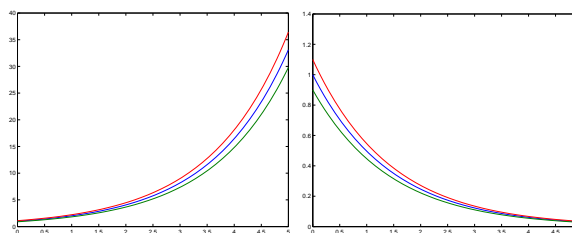
Examples

- what is the long time behavior? $x(\infty) = ???$
- if one is lucky it coincides with the **steady state** solution of the ODE: **steady state(s)** is the value(s) x_{ss} of x for which

$$\frac{dx}{dt} = 0$$

since $dx/dt = 0$, the rate does not change \implies ODE “stays there” forever

- a steady state x_{ss} is said **stable** when changing the initial conditions the steady state remains the same



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Stability of steady states

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Examples

- when is a steady state stable?
- for the Maltus law $dx/dt = kx$

$$\frac{dx}{dt} = 0 \iff x = 0$$

$$1. \ k > 0 : \begin{cases} x(0) = \varepsilon < 0 \implies \frac{dx}{dt} < 0 \\ x(0) = \varepsilon > 0 \implies \frac{dx}{dt} > 0 \end{cases}$$

◆ $\implies x_{ss} = 0$ is unstable

◆ x grows and $\frac{dx}{dt}$ grows \implies unbounded solution

$$2. \ k < 0 : \begin{cases} x(0) = \varepsilon < 0 \implies \frac{dx}{dt} > 0 \\ x(0) = \varepsilon > 0 \implies \frac{dx}{dt} < 0 \end{cases}$$

◆ $\implies x_{ss} = 0$ is stable

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Reaction kinetics

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Examples

- the decay $dx/dt = kx$, $k < 0$ can be seen as a kinetic reaction (in which I am not interested in the product of the degradation):



- to analyze more complex reactions: **law of mass action**

when 2 or more reactants are involved in a reaction step, the reaction rates are proportional to the product of their concentrations

- ◆ justification: macroscopic version of collision theory
- ◆ validity:
 - constant temperature
 - medium must be well-mixed
 - # of molecules must be high

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Elementary reaction kinetics

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Examples

■ bimolecular reaction



ODEs:

$$\begin{aligned} \frac{dx}{dt} &= -kxy \\ \frac{dy}{dt} &= -kxy \\ \frac{dz}{dt} &= kxy \end{aligned}$$

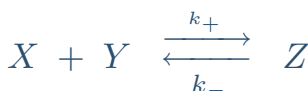
■ dissociation



ODEs:

$$\begin{aligned} \frac{dx}{dt} &= kz \\ \frac{dy}{dt} &= kz \\ \frac{dz}{dt} &= -kz \end{aligned}$$

■ reversible dissociation



ODEs:

$$\begin{aligned} \frac{dx}{dt} &= -k_+xy + k_-z \\ \frac{dy}{dt} &= -k_+xy + k_-z \\ \frac{dz}{dt} &= k_+xy - k_-z \end{aligned}$$

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Elementary reaction kinetics

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Examples

■ conservation laws (e.g. mass conservation) can be used to reduce the number of equations involved:

■ example:

$$\begin{aligned} \frac{dx}{dt} &= -k_+xy + k_-z \\ \frac{dy}{dt} &= -k_+xy + k_-z \\ \frac{dz}{dt} &= k_+xy - k_-z \end{aligned} \Rightarrow \begin{aligned} \frac{d(x+z)}{dt} &= 0 \\ \frac{d(y+z)}{dt} &= 0 \end{aligned} \Rightarrow \begin{aligned} x(t) + z(t) &= x_o + z_o = a_o \\ y(t) + z(t) &= y_o + z_o = b_o \end{aligned}$$

hence the system of 3 ODEs reduces to the scalar ODE

$$\frac{dz}{dt} = k_+(a_o - z)(b_o - z) - k_-z$$

once I solve this ODE (homework: write your Matlab routine) for $z(t)$ I can recover

$$\begin{aligned} x(t) &= a_o - z(t) \\ y(t) &= b_o - z(t) \end{aligned}$$

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Enzyme catalyzed reactions

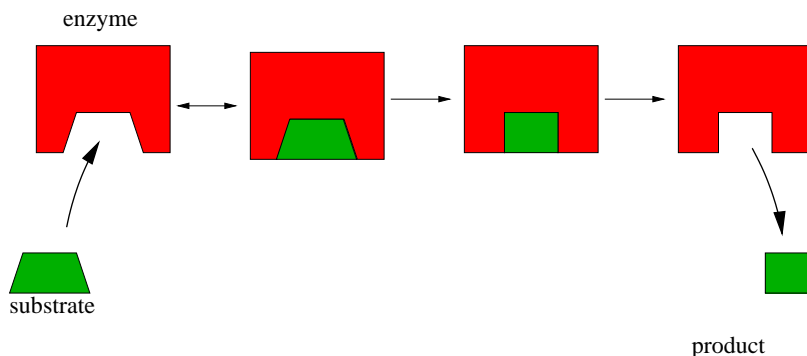
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Examples

- most reactions need to be catalyzed to take place at interesting rates
- enzymes = proteins that convert specific reactants (called substrates) into products while remaining basically unchanged



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Enzyme catalyzed reactions

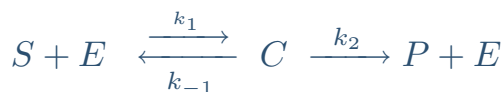
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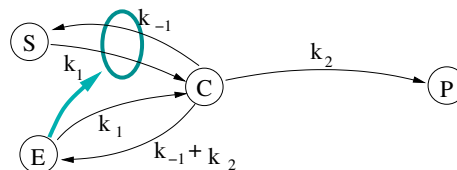
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Examples

- rate of production depends nonlinearly on the concentration of the substrate



- ◆ S = substrate
- ◆ E = enzyme
- ◆ C = complex (" $= [ES]$ ")
- ◆ P = product



- ODEs

$$\begin{aligned} \frac{ds}{dt} &= -k_1 se + k_{-1}c \\ \frac{de}{dt} &= -k_1 se + (k_{-1} + k_2)c \\ \frac{dc}{dt} &= k_1 se - (k_{-1} + k_2)c \\ \frac{dp}{dt} &= k_2c \end{aligned}$$

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Enzyme catalyzed reactions

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Examples

■ simplifications:

- ◆ last equation does not feedback \implies I can ignore it and get $p(t)$ by integration once I have $c(t)$
- ◆ conservation of mass for the enzyme:

$$\frac{de}{dt} + \frac{dc}{dt} = 0 \implies e(t) + c(t) = \text{const} = e_o$$

often at $t = 0$ one has $c(0) = 0$ and $e(0) = e_o$

- ◆ \implies another equation can be eliminated

$$\frac{ds}{dt} = -k_1s(e_o - c) + k_{-1}c$$

$$\frac{dc}{dt} = k_1s(e_o - c) - (k_{-1} + k_2)c$$

■ how do you solve these?

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Michaelis Menten kinetics

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Examples

- quasi steady state approximation: after a transient period in which the enzyme "fills up", the amount of complex C stays (almost) the same:

$$\frac{dc}{dt} = 0 \implies c = \frac{e_o s}{\theta + s} \quad \text{where } \theta = \frac{k_{-1} + k_2}{k_1}$$

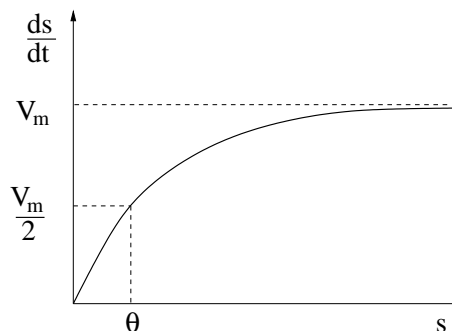
\implies system reduces to a scalar ODE

$$\frac{ds}{dt} = -\frac{V_m s}{\theta + s}$$

where $V_m = k_2 e_o$

- meaning of θ and V_m :

- ◆ V_m = upper bound for $\frac{ds}{dt}$
- ◆ θ = value of s for which $\frac{ds}{dt} = \frac{1}{2} V_m$



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Michaelis Menten kinetics

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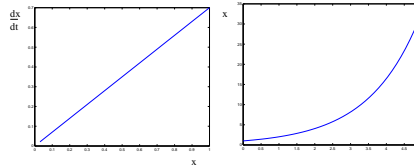
Examples

- meaning of a Michaelis Menten reaction kinetics

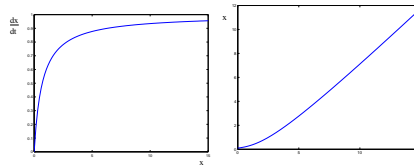
$$\frac{dx}{dt} = \frac{V_m x}{\theta + x}$$

- ◆ it introduces a **saturation** behavior in the dynamics
- ◆ often more realistic than Maltus law even when the substrate is abundant

Maltus law



MM law



“True” vs MM reaction

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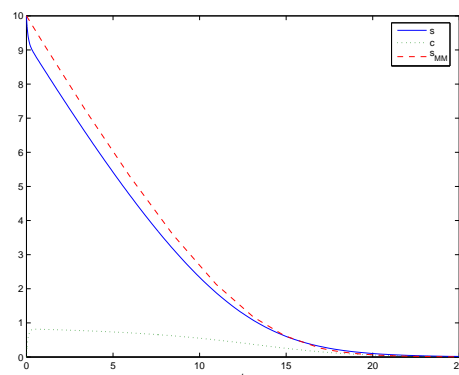
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Examples

- looking again at the ODE, there are 2 time scales
 - ◆ “slow time scale” in which c can be thought of as constant \implies quasi steady state approximation holds
 - ◆ “fast time scale” (in which the approximation does not hold)
- in short: $c(t)$ adjusts very fast to the steady state solution

slow time scale:



- more rigorous analysis: singular perturbation theory



Matlab code used

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Examples

- function for a system of ODEs: same as scalar ODEs

```
% function for enzyme reaction
% with Michaelis-Menten kinetics
% system of 2 ODEs
function dzdt = f_enz_mich_ment1(t,z);
% pass the parameters to the function
global k1 k1m k2 e0
% extract the states from the vector z
s=z(1);
c=z(2);
% ODEs
dsdt=k1m*c-k1*s*(e0-c);
dcdt=k1*s*(e0-c)-(k1m+k2)*c;
% output vector
dzdt=[dsdt; dcdt];
```

- integration routine

```
[t,z] = ode45(@f_enz_mich_ment1,tspan,z0,[]);
```



Competitive inhibition

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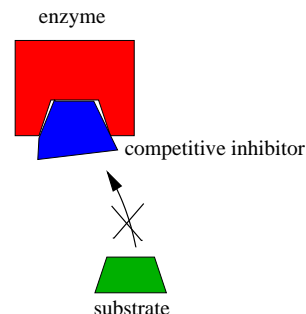
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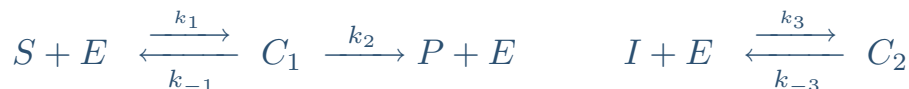
Examples

- A second substrate (called **inhibitor**) can bind to the enzyme, thus preventing the primary substrate from doing it. The result is that no product can be created.

- this is for example a mechanics describing the action of a drug on a receptor (protein on the cell surface that interact with the external world)



- chemical kinetic model





Competitive inhibition

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Examples

■ ODEs

$$\begin{aligned} \frac{ds}{dt} &= -k_1se + k_{-1}c_1 \\ \frac{de}{dt} &= -k_1se - k_3ie + (k_{-1} + k_2)c_1 + k_{-3}c_2 \\ \frac{dc_1}{dt} &= k_1se - (k_{-1} + k_2)c_1 \\ \frac{dc_2}{dt} &= k_3ie - k_{-3}c_2 \\ \frac{di}{dt} &= -k_{-3}ie + k_{-3}c_2 \\ \frac{dp}{dt} &= k_2c_1 \end{aligned}$$

■ reduce #: conservation laws

$$\begin{aligned} c_1 + c_2 + e &= e_o \\ i + c_2 &= i_o \end{aligned} \implies \begin{aligned} \frac{ds}{dt} &= -k_1s(e_o - c_1 - c_2) + k_{-1}c_1 \\ \frac{dc_1}{dt} &= k_1s(e_o - c_1 - c_2) - (k_{-1} + k_2)c_1 \\ \frac{dc_2}{dt} &= k_3(i_o - c_2)(e_o - c_1 - c_2) - k_{-3}c_2 \end{aligned}$$

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Competitive inhibition

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Examples

■ quasi steady state approximation: $\frac{dc_1}{dt} = \frac{dc_2}{dt} = 0$

$$c_1 = \frac{\theta_i e_o s}{\theta_m i + \theta_i s + \theta_m \theta_i}, \quad c_2 = \frac{\theta_m e_o i}{\theta_m i + \theta_i s + \theta_m \theta_i}$$

$$\text{where } \theta_m = \frac{k_{-1} + k_2}{k_1}, \quad \theta_i = \frac{k_{-3}}{k_3}$$

■ product formation rate

$$\frac{dp}{dt} = \frac{V_m s}{\theta_m (1 + i/\theta_i) + s}$$

is smaller than in the no-inhibition case ($i = 0$)

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Cooperativity

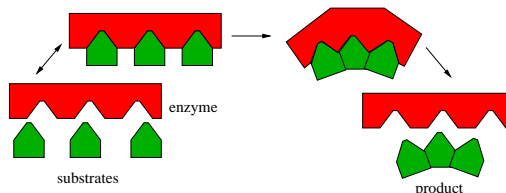
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Elementary modules

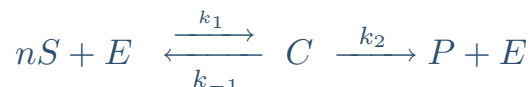
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Examples

- when n molecules of substrate must fit together with the enzyme in order for the reaction to take place



- ex:
 - ◆ ligand binding to cell surface receptors
 - ◆ binding of transcriptor factors to DNA to control gene expression
- kinetics



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Cooperativity

Mathematical modeling

Elementary modules

- Biological models as ODEs
- Maltus Law
- Solving ODEs: Matlab
- Qualitative behavior: steady state
- Reaction kinetics
- Elementary reaction kinetics
- Enzyme catalyzed reactions
- Michaelis Menten kinetics
- Competitive inhibition
- **Cooperativity**
- Sigmoidal responses
- Multistability
- Enzymes and multistability
- Feedback regulation
- Positive feedback
- Negative regulation
- A gene regulatory network
- Other regulatory elements

Examples

- ODEs

$$\begin{aligned} \frac{ds}{dt} &= -k_1 s^n e + n k_{-1} c \\ \frac{de}{dt} &= -k_1 s^n e + (k_{-1} + k_2) c \\ \frac{dc}{dt} &= k_1 s^n e - (k_{-1} + k_2) c \\ \frac{dp}{dt} &= k_2 c \end{aligned}$$

- after the quasi steady state approximation $\frac{dp}{dt} = V_m \frac{s^n}{\theta + s^n}$
- modifying $\theta \rightarrow \theta^n$: **Hill function** $h^+(s, \theta, n)$

$$\frac{dp}{dt} = V_m \frac{s^n}{\theta^n + s^n} =: V_m h^+(s, \theta, n)$$

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Sigmoidal responses

Mathematical modeling

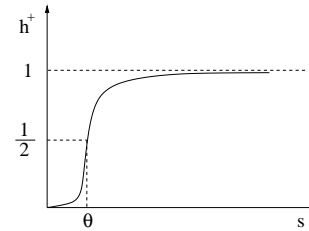
Elementary modules

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- Positive feedback
- Negative regulation
- A gene regulatory network
- Other regulatory elements

Examples

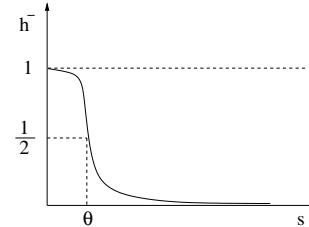
- common modules for saturated growth rate and saturated decay rate
- positive growth

$$h^+(s, \theta, n) = \frac{s^n}{\theta^n + s^n}$$



- negative growth

$$h^-(s, \theta, n) = 1 - \frac{s^n}{\theta^n + s^n} = \frac{\theta^n}{\theta^n + s^n}$$



- θ = threshold
= value of s at which h^\pm reaches 1/2 of the saturation value
- n = Hill parameter

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Hyperbolic vs Sigmoidal responses

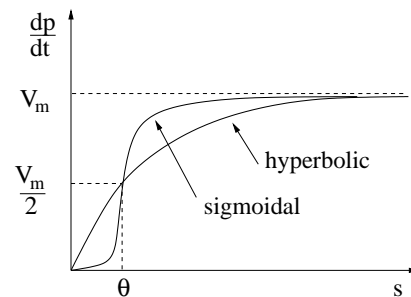
Mathematical modeling

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Examples

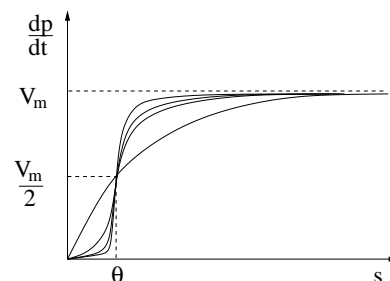
- consider $\frac{dp}{dt} = V_m \frac{s^n}{\theta^n + s^n}$
 - ◆ for $n = 1$ the graph of the formation rate is **hyperbolic**
 - ◆ for $n > 1$ it is **sigmoidal**



- difference:
 - ◆ $n = 1$ graph is concave
 - ◆ for $n > 1$ the graph starts with “concavity up” and finishes with “concavity down”
 ⇒ different stability properties

- when n grows the sharpness of the transition increases

- ⇒ tends to a boolean switch
- ⇒ ultrasensitive response (“all or nothing” behavior)



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Multistability

Mathematical modeling

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Examples

- consider the enzymatic reaction in the quasi steady state approximation

$$\frac{dp}{dt} = V_m \frac{s^n}{\theta^n + s^n}, \quad n \geq 1$$

- assume this is an autocatalytic process: p enhances its own concentration $\implies s = \alpha p$
- add a **degradation rate** = rate at which the product is being used (or naturally degrades, or diffuses, etc.)

$$\frac{dp}{dt} = V_m \frac{(\alpha p)^n}{\theta^n + (\alpha p)^n} - \gamma p, \quad \gamma \geq 0$$

- for simplicity: $\alpha = \gamma = V_m = 1$

$$\frac{dp}{dt} = \frac{p^n}{\theta^n + p^n} - p$$



Multistability

Mathematical modeling

Elementary modules

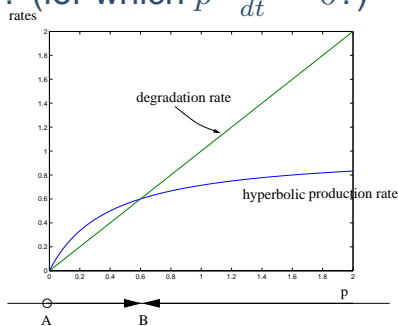
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Examples

- what are the possible steady states? (for which $p \frac{dp}{dt} = 0$?)

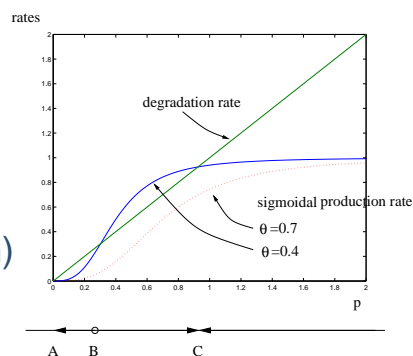
1. hyperbolic case

- ◆ A = unstable equilibrium point
- ◆ B = stable equilibrium point
- $\implies p(t)$ converges uniquely to an intermediate value



2. sigmoidal case

- ◆ A = stable equilibrium point
- ◆ B = unstable equilibrium point
- ◆ C = stable equilibrium point
- $\implies p(t)$ converges either at A or at C depending on the initial condition
- \implies bistability (and a bifurcation)





Enzyme-catalyzed reactions and multistability

G. Craciun, Y. Tang, and Martin Feinberg, Understanding bistability in complex enzyme-driven reaction networks, PNAS 103(23): 8697-8702, 2006

- which enzyme-catalyzed reactions may admit a multiple steady state?



$$\dot{c}_E = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_3 c_E c_{S2} + k_4 c_{ES2} + k_9 c_{ES1S2}$$

$$\dot{c}_{S1} = -k_1 c_E c_{S1} + k_2 c_{ES1} - k_7 c_{S1} c_{ES2} + k_8 c_{ES1S2} + F_{S1} - \xi_{S1} c_{S1}$$

$$\dot{c}_{S2} = -k_3 c_E c_{S2} + k_4 c_{ES2} - k_5 c_{S2} c_{ES1} + k_6 c_{ES1S2} + F_{S2} - \xi_{S2} c_{S2}$$

$$\dot{c}_{ES1} = k_1 c_E c_{S1} - k_2 c_{ES1} - k_5 c_{ES1} c_{S2} + k_6 c_{ES1S2}$$

$$\dot{c}_{ES2} = k_3 c_E c_{S2} - k_4 c_{ES2} - k_7 c_{ES2} c_{S1} + k_8 c_{ES1S2}$$

$$\dot{c}_{ES1S2} = k_5 c_{S2} c_{ES1} + k_7 c_{S1} c_{ES2} - (k_6 + k_8 + k_9) c_{ES1S2}$$

$$\dot{c}_P = k_9 c_{ES1S2} - \xi_P c_P$$

- according to mass-action laws (no quasi steady-state approximation involved) this “has the capacity of a multiple steady state”

Mathematical modeling

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Examples

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Enzyme-catalyzed reactions and multistability

Mathematical modeling

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Examples

1	$E + S \rightleftharpoons ES \rightarrow E + P$	Elementary enzyme catalysis underlying Michaelis-Menten kinetics: $S \rightarrow P$	NO
2	$E + S \rightleftharpoons ES \rightarrow E + P$ $E + I \rightleftharpoons EI$	Elementary enzyme catalysis with competitive inhibition: $S \rightarrow P$	NO
3	$E + S \rightleftharpoons ES \rightarrow E + P$ $ES + I \rightleftharpoons ESI$	Elementary enzyme catalysis with uncompetitive inhibition: $S \rightarrow P$	NO
4	$E + S \rightleftharpoons ES \rightarrow E + P$ $E + I \rightleftharpoons EI$ $ES + I \rightleftharpoons ESI \rightleftharpoons EI + S$	Elementary enzyme catalysis with mixed inhibition: $S \rightarrow P$	YES
5	$E + S1 \rightleftharpoons ES1$ $S2 + ES1 \rightleftharpoons ES1S2 \rightarrow E + P$	Two-substrate enzyme catalysis with ordered substrate-binding: $S1 + S2 \rightarrow P$	NO
6	$E + S1 \rightleftharpoons ES1 \quad E + S2 \rightleftharpoons ES2$ $S2 + ES1 \rightleftharpoons ES1S2 \rightleftharpoons S1 + ES2$ \downarrow $E + P$	Two-substrate enzyme catalysis with unordered substrate-binding: $S1 + S2 \rightarrow P$	YES
7	$S1 + E1 \rightleftharpoons E1S1$ $S2 + E1S1 \rightleftharpoons E1S1S2 \rightarrow P1 + E1$ $S2 + E2 \rightleftharpoons E2S2 \rightarrow 2S1 + E2$	Enzyme-promoted overall reactions: $S1 + S2 \rightarrow P1$ $S2 \rightarrow 2S1$ ($S1 + S2 \rightarrow P1$ with ordered binding.)	NO
8	$S1 + E1 \rightleftharpoons E1S1$ $S2 + E1S1 \rightleftharpoons E1S1S2 \rightarrow P1 + E1$ $S2 + E2 \rightleftharpoons E2S2$ $S3 + E2S2 \rightleftharpoons E2S2S3 \rightarrow P2 + E2$ $S3 + E3 \rightleftharpoons E3S3 \rightarrow 2S1 + E3$	Enzyme-promoted overall reactions: $S1 + S2 \rightarrow P1$ $S2 + S3 \rightarrow P2$ $S3 \rightarrow 2S1$ (Two-substrate reactions all with ordered binding.)	YES
9	$S1 + E1 \rightleftharpoons E1S1$ $S2 + E1S1 \rightleftharpoons E1S1S2 \rightarrow P1 + E1$ $S2 + E2 \rightleftharpoons E2S2$ $S3 + E2S2 \rightleftharpoons E2S2S3 \rightarrow P2 + E2$ $S3 + E3 \rightleftharpoons E3S3$ $S4 + E3S3 \rightleftharpoons E3S3S4 \rightarrow P3 + E3$ $S4 + E4 \rightleftharpoons E4S4 \rightarrow 2S1 + E4$	Enzyme-promoted overall reactions: $S1 + S2 \rightarrow P1$ $S2 + S3 \rightarrow P2$ $S3 + S4 \rightarrow P3$ $S4 \rightarrow 2S1$ (Two-substrate reactions all with ordered binding.)	NO

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Feedback regulation

Mathematical modeling

Elementary modules

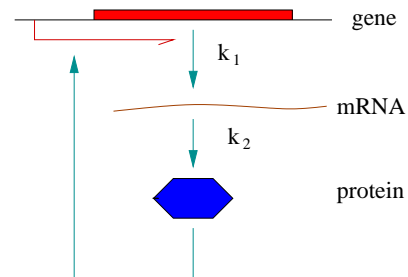
- Biological models as ODEs
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Examples

- autocatalytic reactions: concentration of p modifies $\frac{dp}{dt}$
 - ◆ p regulates itself
 - ◆ p enhances itself \implies positive regulation

- another example of **positive feedback**: gene regulation

- ◆ state variables
 - $x_1 = [\text{mRNA}]$
 - $x_2 = [\text{protein}]$
 - k_1, k_2 production rates
 - γ_1, γ_2 degradation rates



- ◆ ODEs:

$$\begin{aligned} \frac{dx_1}{dt} &= k_1 h^+(x_2, \theta, n) - \gamma_1 x_1 \\ \frac{dx_2}{dt} &= k_2 x_1 - \gamma_2 x_2 \end{aligned}$$

- ◆ assuming this is a stand alone system: is the gene expressed or not at “steady state”?



Positive feedback and multistability

Mathematical modeling

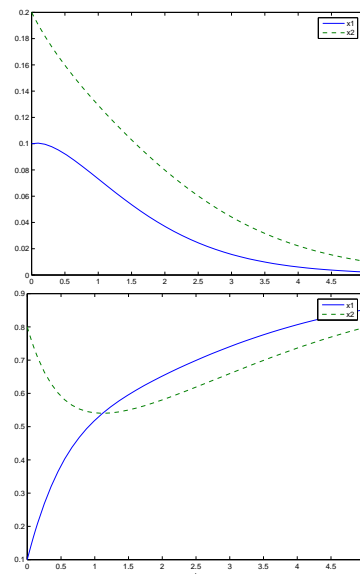
Elementary modules

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Examples

- simulation # 1:
 - ◆ $x_1(0) = 0.1$ (low)
 - ◆ $x_2(0) = 0.2$ (low)

- simulation # 2:
 - ◆ $x_1(0) = 0.1$ (low)
 - ◆ $x_2(0) = 0.8$ (high)



- important in **differentiation** mechanisms



Negative regulation

Mathematical modeling

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- Feedback regulation
- Positive feedback
- **Negative regulation**
- A gene regulatory network
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Examples

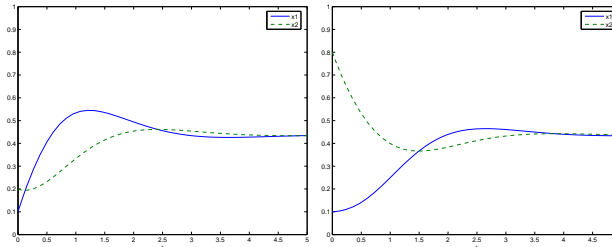
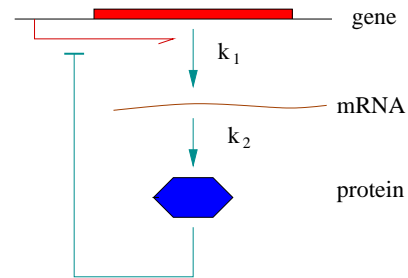
- if instead the protein inhibits the transcription then we have an example of **negative feedback**

- ODEs:

$$\frac{dx_1}{dt} = k_1 h^-(x_2, \theta, n) - \gamma_1 x_1$$

$$\frac{dx_2}{dt} = k_2 x_1 - \gamma_2 x_2$$

- how about “steady state”?



- negative feedback is synonymous of **homeostasis**

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A gene regulatory network

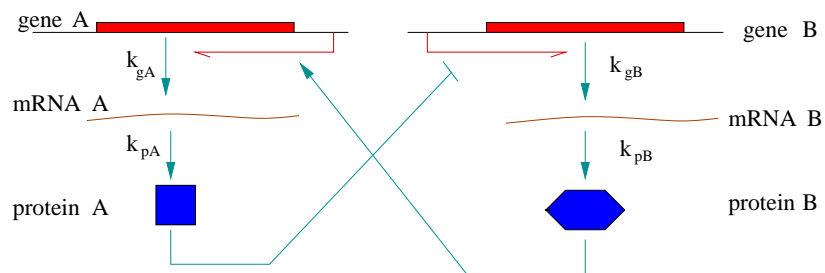
Mathematical modeling

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- **Negative regulation**
- **A gene regulatory network**
- Other regulatory elements

Examples

- the simplest possible gene regulatory **network** is



- ODEs:

$$\frac{dx_{gA}}{dt} = k_{gA} h^+(x_{pB}, \theta_{pB}, n_{pB}) - \gamma_{gA} x_{gA}$$

$$\frac{dx_{gB}}{dt} = k_{gB} h^-(x_{pA}, \theta_{pA}, n_{pA}) - \gamma_{gB} x_{gB}$$

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Other regulatory elements

Mathematical modeling

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Examples

■ delayed regulation

◆ ODEs:

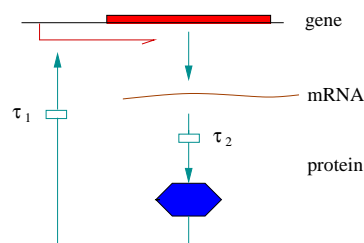
$$\frac{dx_1}{dt} = k_1 h^+(x_2^\tau, \theta, n) - \gamma_1 x_1$$

$$\frac{dx_2}{dt} = k_2 x_1^\tau - \gamma_2 x_2$$

where

$$\blacksquare x_1^\tau = x_1(t - \tau_1)$$

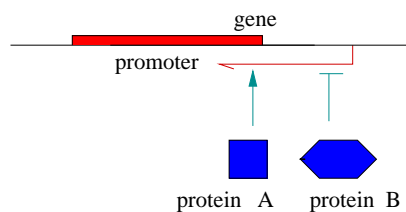
$$\blacksquare x_2^\tau = x_2(t - \tau_2)$$



■ multiple regulation

◆ ODE

$$\frac{dx_g}{dt} = k_g h^+(x_{pA}, \theta_{pA}, n_{pA}) + k_g h^-(x_{pB}, \theta_{pB}, n_{pB}) - \gamma_g x_g$$



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Indirect regulation

Mathematical modeling

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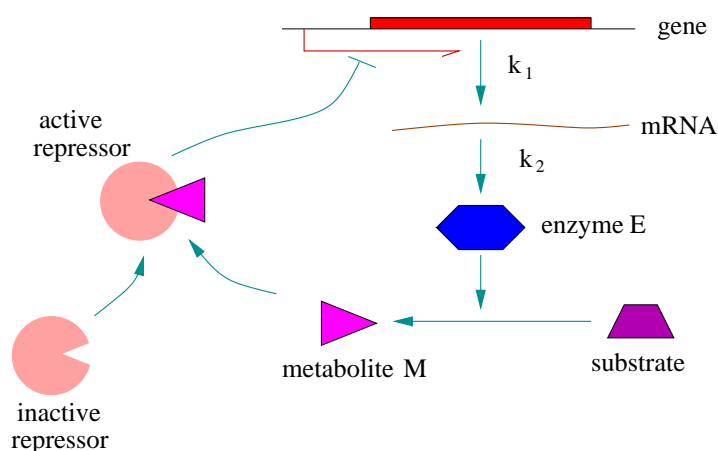
Examples

■ ODE

$$\frac{dx_g}{dt} = k_g h^+(x_M, \theta_M, n_M) - \gamma_g x_g$$

$$\frac{dx_E}{dt} = k_E x_g - \gamma_E x_E$$

$$\frac{dx_M}{dt} = k_M x_E - \gamma_M x_M$$



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Example: autoregulatory negative feedback

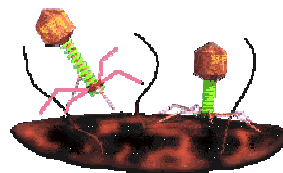
Mathematical modeling

Elementary modules

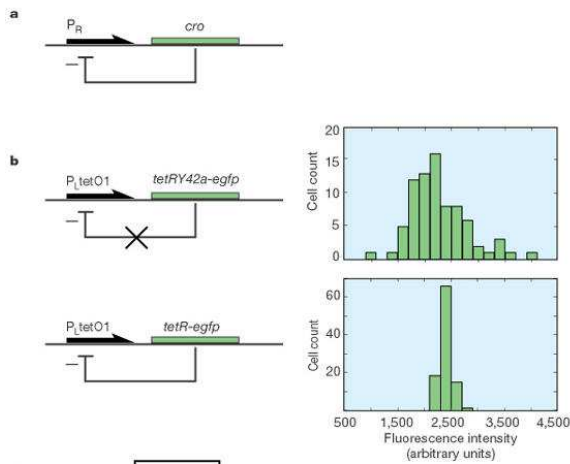
Examples

- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

A. Becskei and L. Serrano *Engineering stability in gene networks by autoregulation*, Nature 405, 590 - 593, 2000
 J. Hasty, D. McMillen, J. Collins *Engineered gene circuits*, Nature 420, 224, 2002



- a: natural negative feedback from bacteriophage λ on E-coli
- b: synthetic negative feedback



Example: repressilator

Mathematical modeling

Elementary modules

Examples

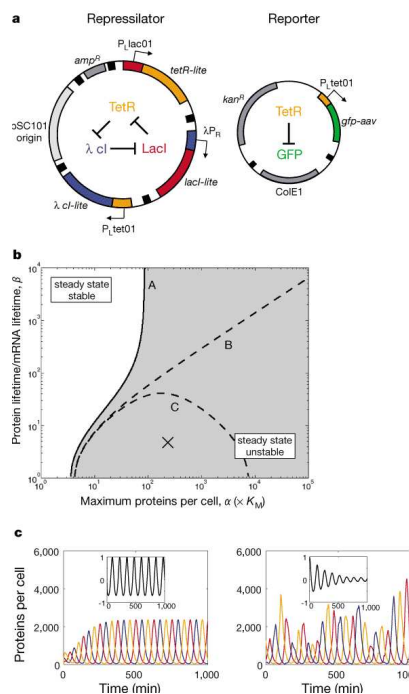
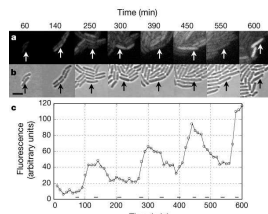
- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

M. B. Elowitz, S. Leibler *A synthetic oscillatory network of transcriptional regulators* Nature 403, 335 - 338, 2000

- model
 - ◆ states
 - m_i = mRNA of cl , $lacI$, $tetR$
 - p_i # of proteins cl , $lacI$, $tetR$
 - ◆ ODEs

$$\frac{dm_i}{dt} = k_{m_i} \frac{\theta_i^2}{\theta_i^2 + p_{i+1}^2} - \gamma_{m_i} m_i + k_{l_i}$$

$$\frac{dp_i}{dt} = k_{p_i} m_i - \mu_i p_i$$





Example: positive feedback

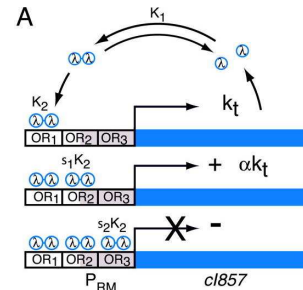
Mathematical modeling

Elementary modules

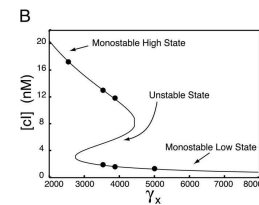
Examples

- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

- genetic switch of the bacteriophage λ
F. J. Isaacs, J. Hasty, C. R. Cantor and J. J. Collins *Prediction and measurement of an autoregulatory genetic module* PNAS, 100:7714-7719, 2003



- gene for the λ repressor (cl857) and its 3 upstream promoters were introduced into E.coli
- the λ repressor is temperature sensitive \implies changing temperature the steady state reached is different
 - ◆ if at most a single repressor binds \implies basal rate (low steady state)
 - ◆ if a repressor protein binds also at OR2 \implies amplification of the transcription
 - ◆ if there is binding to all 3 OR \implies negative feedback again



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Example: positive feedback

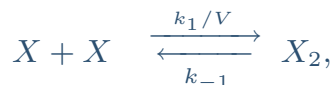
Mathematical modeling

Elementary modules

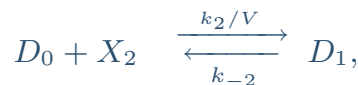
Examples

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- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

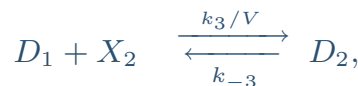
- variables:
 - ◆ X = repressor
 - ◆ X_2 = repressor dimer
 - ◆ D_0, D_1, D_2, D_3 = DNA promoter sites with i dimers bound
- fast reactions: dimerization & binding at the promoter region



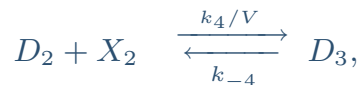
$$x_2 = \frac{k_1}{k_{-1}V} x^2$$



$$d_1 = \frac{k_2}{k_{-2}V} d_0 x_2$$



$$s_2 = \frac{k_3}{k_{-3}V} d_1 x_2$$



$$d_3 = \frac{k_4}{k_{-4}V} d_2 x_2$$

- fast variables: quasi steady state assumption \rightarrow replace with algebraic relations

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Example: positive feedback

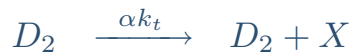
Mathematical modeling

Elementary modules

Examples

- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

- slow, irreversible reactions: transcription, protein degradation



- α = enhancement factor for D_2 transcription (i.e. with OR_1 and OR_2 occupied)
- slowly changing variable of interest: total number of cI molecules (in any form)

$$z = x + 2x_2 + 2d_1 + 4d_2 + 6d_3$$

- ODE

$$\frac{dz}{dt} = \beta(d_0 + d_1) + \alpha\beta d_2 - \gamma_x x, \quad \beta = \tau_0 k_t, \quad \gamma_x = \tau_0 k_d$$

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Example: positive feedback

Mathematical modeling

Elementary modules

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- conservation law: copy number m is constant \implies eliminate d_0

$$m = d_0 + d_1 + d_2 + d_3$$

- up to some parameter reshuffling....

$$\implies d_0 = \frac{m}{1 + cx^2/v^2 + \sigma_1 c^2 x^4/v^4 + \sigma_1 \sigma_2 c^3 x^6/v^6} \simeq \text{const}$$

and (for the full derivation: see PNAS-Supplement)

$$\frac{dz}{dt} = \frac{m\beta(1 + cx^2/v^2 + \alpha\sigma_1 c^2 x^4/v^4)}{1 + cx^2/v^2 + \sigma_1 c^2 x^4/v^4 + \sigma_1 \sigma_2 c^3 x^6/v^6} - \gamma_x x$$

from which the ODE for x is derived

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Example: positive feedback

Mathematical modeling

Elementary modules

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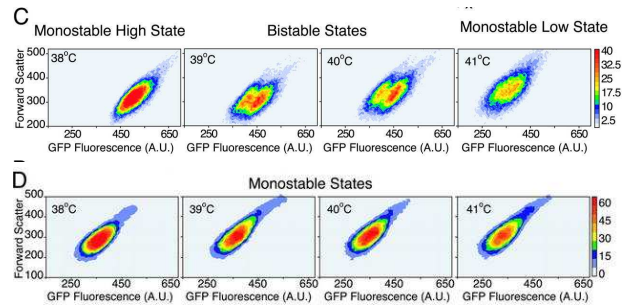
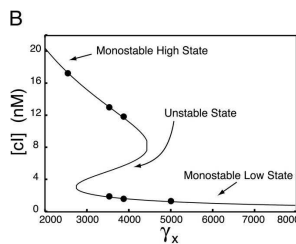
ODEs

$$\begin{aligned} \blacksquare x &= [\lambda] & \frac{dx}{dt} &= \frac{1}{h(x,v)} (\beta f(x,v) - \gamma_x x) \\ \blacksquare g &= [GFP] & \frac{dg}{dt} &= \eta \beta f(x,v) - \gamma_g g \end{aligned}$$

(measured protein)

$$f(x,v) = \frac{m(1 + cx^2/v^2 + \alpha\sigma_1 c^2 x^4/v^4)}{1 + cx^2/v^2 + \sigma_1 c^2 x^4/v^4 + \sigma_1 \sigma_2 c^3 x^6/v^6}$$

$$h(x,v) = 1 + \frac{4c_1 x}{v} + m \frac{4cx/v^2 + 16\sigma_1 c^2 x^3/v^4 + 36\sigma_1 \sigma_2 c^3 x^5/v^6}{1 + cx^2/v^2 + \sigma_1 c^2 x^4/v^4 + \sigma_1 \sigma_2 c^3 x^6/v^6}$$



Example: genetic oscillator

Mathematical modeling

Elementary modules

Examples

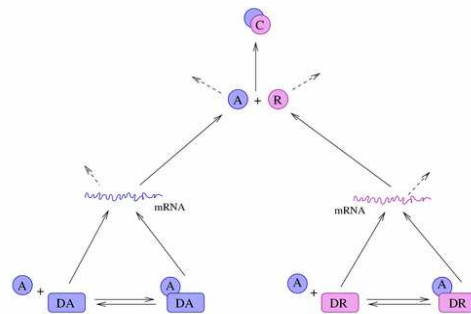
- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

J. M. G. Vilar, H. Y. Kueh, N. Barkai, and S. Leibler, *Mechanisms of noise-resistance in genetic oscillators* PNAS,99:5988-5992, 2002

■ genetic oscillator = example of **circadian clock**

■ variables

- ◆ C = protein complex (inactive)
- ◆ A = activator protein
- ◆ R = repressor protein
- ◆ M_A = activator mRNA
- ◆ M_R = repressor mRNA
- ◆ D_A (D'_A) = activator gene without (with) A bound to the promoter ($D_A + D'_A = 1$)
- ◆ D_R (D'_R) = repressor gene without (with) A bound to the promoter ($D_R + D'_R = 1$)





Example: genetic oscillator

Mathematical modeling

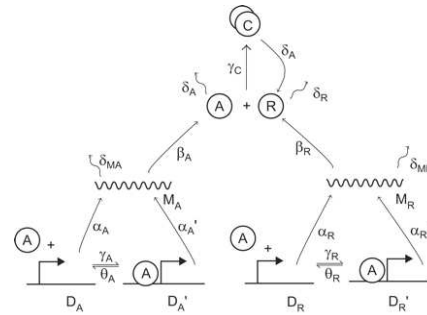
Elementary modules

Examples

- Example: negative feedback
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- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

- A binds to A and R promoters increasing their transcription rates \rightarrow activator
- R "sequesters" A in the complex $C \rightarrow$ repressor

$$\begin{aligned} dD_A/dt &= \theta_A D'_A - \gamma_A D_A A \\ dD_R/dt &= \theta_R D'_R - \gamma_R D_R A \\ dD'_A/dt &= \gamma_A D_A A - \theta_A D'_A \\ dD'_R/dt &= \gamma_R D_R A - \theta_R D'_R \\ dM_A/dt &= \alpha'_A D'_A + \alpha_A D_A - \delta_{M_A} M_A \\ dA/dt &= \beta_A M_A + \theta_A D'_A + \theta_R D'_R \\ &\quad - A(\gamma_A D_A + \gamma_R D_R + \gamma_C C + \delta_A) \\ dM_R/dt &= \alpha'_R D'_R + \alpha_R D_R - \delta_{M_R} M_R \\ dR/dt &= \beta_R M_R - \gamma_C A R + \delta_A C - \delta_R R \\ dC/dt &= \gamma_C A R - \delta_A C, \end{aligned}$$



Example: genetic oscillator

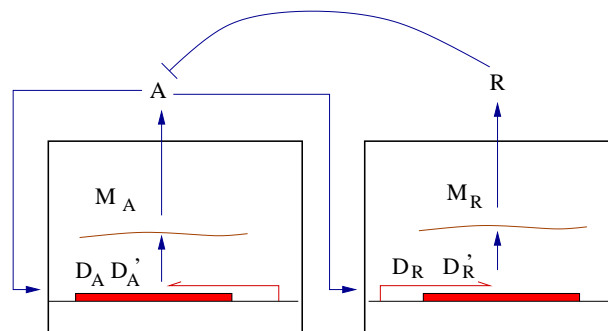
Mathematical modeling

Elementary modules

Examples

- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

- **2 feedback loops:**
 1. A on A : positive feedback
 2. A on R :
 - ◆ positive effect on the transcription of R
 - ◆ negative effect on A (through the complex C formation)



- oscillatory behavior: dynamics of R is slower than the dynamics of A



Example: genetic oscillator

Mathematical modeling

Elementary modules

Examples

- Example: negative feedback
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- to study oscillations: **quasi steady state assumptions**

- ◆ fast variables: $A, M_A, M_R, D_A, D'_A, D_R, D'_R$

- ◆ slow variables: R and C

⇒ reduced dynamical system

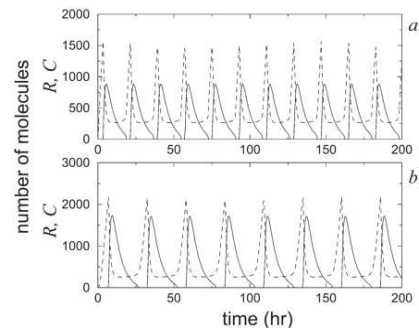
$$\frac{dR}{dt} = \frac{\beta_R}{\delta_{M_R}} \frac{\alpha_R \theta_R + \alpha'_R \gamma_R \tilde{A}(R)}{\theta_R + \gamma_R \tilde{A}(R)} - \gamma_C \tilde{A}(R) R + \delta_{A_C} - \delta_R R$$

$$\frac{dC}{dt} = \gamma_C \tilde{A}(R) R - \delta_{A_C} C$$

such that

$$\tilde{A}(R) = \frac{1}{2} (\alpha'_A \rho(R) - K_d) + \frac{1}{2} \sqrt{(\alpha'_A \rho(R) - K_d)^2 + 4 \alpha_A \rho(R) K_d}$$

- time evolution of R and C in the “true” system and in the reduced system are quite similar
→ good!



Example: genetic oscillator

Mathematical modeling

Elementary modules

Examples

- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
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- limit cycle and stability analysis:

- ◆ for 2-variable systems: \exists of oscillations can be inferred from The **Poincaré-Bendixson theorem**

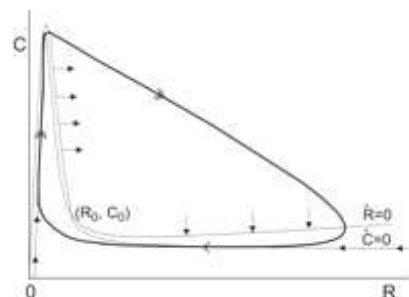
- ◆ **Theorem:** Given a 2-variable system, assume that

1. \exists a region D in the plane s.t. the trajectories that enter D never leave it

2. \nexists stable steady states in D for the system

Then \exists a periodic orbit in D .

- ◆ D : obtained by construction
- ◆ equilibrium: use linear stability analysis, R_o, C_o : is unstable (real part of the eigenvalues is > 0)





Example: modeling yeast cell cycle

Mathematical modeling

Elementary modules

Examples

- Example: negative feedback
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- Software packages

ODEs

Integrative Analysis of Cell Cycle Control

Table 1. Equations

$$\begin{aligned} \frac{d[mass]}{dt} &= k_{in} - k_{out}[mass] \\ \frac{d[Cdh1]}{dt} &= V_{Cdh1} + k_{Cdh1}^{off} [SBF] - [mass] - k_{Cdh1}^{on} [Cdh1] \\ \frac{d[Cdh2]}{dt} &= (k_{Cdh2} + k_{Cdh2}^{off} [MBF]) - [mass] + k_{Cdh2}^{on} [CSP] + k_{Cdh2}^{off} [CS] + k_{Cdh2}^{off} [F5] - (V_{Cdh2} + k_{Cdh2}^{on} [Sic1] + k_{Cdh2}^{off} [Cdh6]) - [Cdh2] \\ \frac{d[Cdh3]}{dt} &= (k_{Cdh3} + k_{Cdh3}^{off} [Mcm1]) - [mass] + k_{Cdh3}^{on} [C2P] + k_{Cdh3}^{off} [C2] + k_{Cdh3}^{off} [F2P] + k_{Cdh3}^{off} [F2] - (V_{Cdh3} + k_{Cdh3}^{on} [Sic1] + k_{Cdh3}^{off} [Cdh6]) - [Cdh3] \\ \frac{d[Sic1]}{dt} &= (k_{Sic1} + k_{Sic1}^{off} [Swi5]) + (V_{Sic1} + k_{Sic1}^{off} [C2]) + (V_{Sic1} + k_{Sic1}^{off} [CS]) + k_{Sic1}^{off} [Cdh14] - [Sic1P] - (k_{Sic1}^{on} [Cdh2] + k_{Sic1}^{off} [Cdh5]) \\ &\quad + V_{Sic1} - [Sic1] \\ \frac{d[Sic1P]}{dt} &= V_{Sic1P} - k_{Sic1P} - (k_{Cdh14} + k_{Sic1P}) + [Sic1P] + V_{Sic1P} - [C2P] + V_{Sic1P} - [CSP] \\ \frac{d[C2]}{dt} &= k_{C2} - k_{C2}^{off} [Cdh5] - [Sic1] + k_{C2}^{on} [Cdh14] - [C2P] - (k_{C2} + V_{C2} + V_{C2}^{off}) - [C2] \\ \frac{d[CSP]}{dt} &= V_{CSP} - [C2] - (k_{Cdh14} + k_{CSP}) + V_{CSP} - [C2P] \\ \frac{d[Cdh6]}{dt} &= (k_{Cdh6} + k_{Cdh6}^{off} [Swi5] + k_{Cdh6}^{off} [SBF]) + (V_{Cdh6} + k_{Cdh6}^{off} [F2]) + (V_{Cdh6} + k_{Cdh6}^{off} [F5]) + k_{Cdh6}^{off} [Cdh14] - [Cdh6P] - (k_{Cdh6}^{on} [Cdh2] \\ &\quad + k_{Cdh6}^{on} [Cdh5] + V_{Cdh6}) - [Cdh6] \\ \frac{d[Cdh6P]}{dt} &= V_{Cdh6P} - (k_{Cdh6} + k_{Cdh6P}) - (k_{Cdh14} + k_{Cdh6P}) + V_{Cdh6P} - [F2P] + V_{Cdh6P} - [F5P] \\ \frac{d[F2]}{dt} &= k_{F2} - k_{F2}^{off} [Cdh5] - [Cdh6] + k_{F2}^{on} [Cdh14] - [F2P] - (k_{F2} + V_{F2} + V_{F2}^{off}) - [F2] \\ \frac{d[F2P]}{dt} &= V_{F2P} - [F2] - (k_{F2} + k_{Cdh14}) + k_{F2} + V_{F2P} - [F2P] \\ \frac{d[F5]}{dt} &= V_{F5} - (F5) - (k_{Cdh14} + k_{F5}) + V_{F5} - [F2P] \\ \frac{d[Swi5]}{dt} &= k_{Swi5} + k_{Swi5}^{off} [Mcm1] - k_{Swi5}^{on} [Cdh14] - (Swi5) - (Swi5) - (k_{Cdh2} + k_{Cdh5}) - [Cdh2] - [Cdh5] \\ \frac{d[APC-F]}{dt} &= \frac{k_{APC-F} - k_{APC-F}^{off} [Cdh2] - (APC-F)}{k_{APC-F}^{on} + 1 + (APC-F)} - \frac{k_{APC-F}}{1 + (APC-F)} \\ \frac{d[Cdh20]}{dt} &= k_{Cdh20} + k_{Cdh20}^{off} [Mcm1] - k_{Cdh20}^{on} [Cdh20] \\ \frac{d[Cdh20P]}{dt} &= (V_{Cdh20} + k_{Cdh20}^{off} [APC-F]) - (Cdh20) - (k_{Cdh20} + k_{Cdh20P}) - [Cdh20] \end{aligned}$$

(continued)

K.C. Chen et al.

Table 1. (Continued)

$$\begin{aligned} \frac{d[Cdh1]}{dt} &= k_{Cdh1} - k_{Cdh1} - [Cdh1] \\ \frac{d[Cdh1]}{dt} &= k_{Cdh1} - k_{Cdh1} - [Cdh1] + \frac{V_{Cdh1} - (k_{Cdh1} - [Cdh1]) - V_{Cdh1} - [Cdh1]}{k_{Cdh1} + (k_{Cdh1})} \\ \frac{d[Tem1]}{dt} &= \frac{k_{Tem1} - (Tem1) - (Tem1)}{k_{Tem1} + (Tem1)} \\ \frac{d[Cdh12]}{dt} &= k_{Cdh12} - (Tem1) - (Tem1) + k_{Cdh12}^{off} [Cdh14] - (Cdh12) - (Cdh12) - k_{Cdh12}^{on} [Cdh15] \\ \frac{d[Cdh14]}{dt} &= k_{Cdh14} - k_{Cdh14} - [Cdh14] \\ \frac{d[Cdh14]}{dt} &= k_{Cdh14} - k_{Cdh14} - [Cdh14] + k_{Cdh14}^{off} [RENT] + [RENTP] + k_{Cdh14}^{off} [RENT] + k_{Cdh14}^{off} [RENTP] - (k_{Cdh14}^{on} [Net1] \\ &\quad + k_{Cdh14}^{off} [Net1P]) - [Cdh14] \\ \frac{d[Net1]}{dt} &= k_{Net1} - k_{Net1} - [Net1] \\ \frac{d[Net1]}{dt} &= k_{Net1} - k_{Net1} - [Net1] + k_{Net1}^{off} [RENT] + k_{Net1}^{off} [RENTP] - k_{Net1}^{on} [Cdh14] - [Net1] + V_{Net1} - [Net1P] - V_{Net1} - [Net1] \\ \frac{d[RENT]}{dt} &= - (k_{Net1} + k_{Cdh14}) [RENT] - k_{Cdh14} [RENT] + k_{Cdh14} - [Cdh14] - [Net1] + V_{Net1} - [RENTP] - V_{Net1} - [RENT] \\ \frac{d[PPX]}{dt} &= k_{PPX} - V_{PPX} - [PPX] \\ \frac{d[Pat1]}{dt} &= k_{Pat1} + k_{Pat1}^{off} [SBF] + k_{Pat1}^{off} [Mcm1] + k_{Pat1}^{off} [PE] - (V_{Pat1} + k_{Cdh14} [Pat1P]) - [Pat1] \\ \frac{d[Pat1]}{dt} &= - k_{Pat1} - [Pat1] - [Pat1P] + (k_{Pat1} + V_{Pat1}) - [PE] \\ \frac{d[OR1]}{dt} &= k_{OR1} - (k_{Cdh5} + k_{Cdh5}^{off} [Cdh5]) + k_{OR1} - [Cdh5] - [OR1] \\ \frac{d[BUD]}{dt} &= k_{BUD} - (k_{BUD} + k_{BUD}^{off} [Cdh2]) + k_{BUD}^{off} [Cdh5] + k_{BUD}^{off} [Cdh5] - k_{BUD}^{on} [BLD] \\ \frac{d[SFN]}{dt} &= k_{SFN} - \frac{[Cdh2]}{k_{SFN} + [Cdh2]} - k_{SFN} - [SFN] \end{aligned}$$

(continued)

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Molecular Biology of the Cell

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Example: modeling yeast cell cycle

Mathematical modeling

Elementary modules

Examples

- Example: negative feedback
- Example: repressilator
- Example: bistability
- Example: Genetic oscillator
- Example: yeast
- Software packages

the model has

- ◆ 36 ODE (mostly nonlinear: quadratic, MM, Goldeberg-Koshland functional)
- ◆ 24 algebraic equations (linear and nonlinear)
- ◆ ~ 130 parameters

simulated behavior:

- ◆ fits the cell cycle of the wild type
- ◆ predicts correctly the phenotype behavior of 120 (out of 131 studied) mutants (obtained by gene inhibition or overexpression)
- ◆ is not crucially sensitive to the values chosen for the parameters

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A few (!) software packages

Mathematical modeling

Elementary modules

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BALSA	BASIS	BIOCHAM	BioCharon	biocyc2SBML
BioGrid	BioModels	BioNetGen	BioPathway Explorer	PathArt
Bio Sketch Pad	BioSens	BioSPICE Dashboard	BioSpreadsheet	BioTapestry
BioUML	BSTLab	CADLIVE	CellDesigner	Cellerator
CeIIIML2SBML	Cellware	CL-SBML	COPASI	Cytoscape
DBsolve	Dizzy	E-CELL	ecellJ	ESS
FluxAnalyzer	Fluxor	Gepasi	INSILICO discovery	JACOBIAN
JDesigner	JWS Online	Karyote&	KEGG2SBML	Kinsolver&
libSBML	MathSBML	MesoRD	MetaboLogica	MetaFluxNet
MMT2	Modesto	Moleculizer	Narrator	NetBuilder
PANTHER Pathway	PathScout	PathwayLab	Pathway Tools	PathwayBuilder
PaVESy	Reactome	ProcessDB	PROTON	psbml
PySCeS	runSBML	SBML ODE Solver	SBMLeditor	SBMLR
SBMLSim	SBMLToolbox	SBToolbox	SClpath	Sigmoid&
SigPath	SIMBA	SimBiology	Simpathica	SimWiz
SmartCell	SRS Pathway Editor	StochSim	STOCKS	TERANODE Suite
Trelis	Virtual Cell	WinSCAMP	XPPAUT	

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One for all: SBML

Mathematical modeling

Elementary modules

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■ SBML= System Biology Markup Language

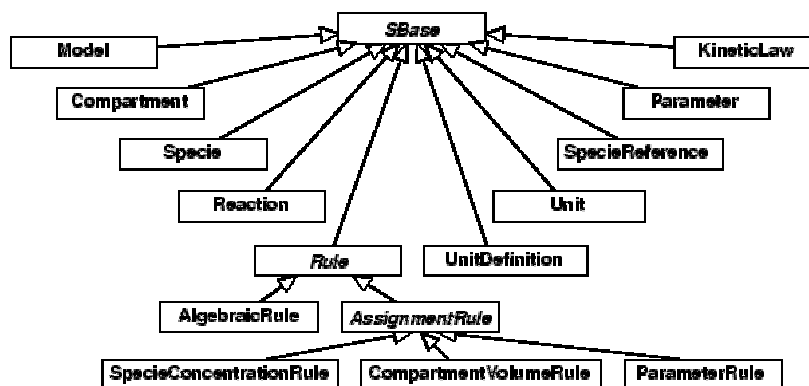
■ made by:

- ◆ Caltech
- ◆ University of Hertfordshire
- ◆ Systems Biology Institute of Japan

```

beginning of model definition
list of unit definitions (optional)
list of compartments
list of species
list of parameters (optional)
list of rules (optional)
list of reactions
end of model definition

```



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