Lectures (9-10):

ODEs Models for Biological Systems

9.1 System Biology

- Systems Biology = investigates function of genetic, molecular and cellular processes in a systematic way: →making (biologically relevant) sense out of data
- why "systems"?
 - \circ biological processes \rightarrow mathematical models
 - \circ many processes simultaneously \rightarrow 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

9.2 Biological moduli as ODEs

• what is a ODE?

Consider x = concentration of a substrate X (e.g. mRNA, protein, small molecule, metabolite, any reagent)

• at time t + Δ t, (Δ t small) one can expand in Taylor series

$$\mathbf{x}(t + \Delta t) \simeq \mathbf{x}(t) + \mathbf{k}\mathbf{x}(t)\Delta t$$

$$\lim_{\Delta t \to 0} \frac{x(t + \Delta t) - x(t)}{\Delta t} =: \frac{dx}{dt}$$

• in the limit for small times

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

- 1st order, linear, autonomous ordinary differential equation
- it involves two different quantities:

 \circ x = state variable

- \circ 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.

9.3 Maltus Law



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





2. $\mathbf{k} < \mathbf{0}$ exponential decay



9.4 Solving ODEs: Matlab

- 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: ANSYS CFD, Matlab (standard software in all engineering fields)
- define a function for the ODE

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function dzdt = Maltus(t,z,k);
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- 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);

9.5 Qualitative behavior: steady state

- 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) *xss* of x for which

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

since dx=dt = 0, the rate does not change \rightarrow ODE "stays

there" forever

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



• for the Maltus law dx=dt = kx

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

 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):

$$X \xrightarrow{k} \longrightarrow$$

- 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:
 - o constant temperature
 - o medium must be well-mixed
 - # of molecules must be high
- bimolecular reaction

$$X + Y \xrightarrow{k} Z$$
 ODEs: $\frac{\frac{dx}{dt} = -k x y}{\frac{dy}{dt} = -k x y}$
 $\frac{\frac{dz}{dt} = k x y}{\frac{dz}{dt} = k x y}$

• dissociation

$$Z \xrightarrow{k} X + Y \qquad \text{ODEs:} \qquad \begin{array}{c} \frac{dx}{dt} = k \ z \\ \frac{dy}{dt} = k \ z \\ \frac{dz}{dt} = -k \ z \end{array}$$

• reversible dissociation

$$X + Y \xrightarrow[k_{-}]{k_{+}} Z \qquad \text{ODEs:} \quad \begin{array}{l} \frac{dx}{dt} = -k_{+}xy + k_{-}z\\ \frac{dy}{dt} = -k_{+}xy + k_{-}z\\ \frac{dz}{dt} = k_{+}xy - k_{-}z \end{array}$$

9.6 Elementary reaction kinetics

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

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

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

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

9.7 Enzyme catalyzed reactions

- 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



9.8 Enzyme catalyzed reactions

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



9.9 Enzyme catalyzed reactions

- simplifications:
- last equation does not feedback =) 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 $e(0) = e_0$

• \rightarrow another equation can be eliminated

$$\frac{ds}{dt} = -k_1 s(e_o - c) + k_{-1} c$$

$$\frac{dc}{dt} = k_1 s(e_o - c) - (k_{-1} + k_2) c$$

• how do you solve these?

9.10 Michaelis Menten kinetics

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

$$rac{dc}{dt} = 0 \qquad \Longrightarrow \quad c = rac{e_o s}{ heta + s} \qquad \mbox{where} \ \ heta = rac{k_{-1} + k_2}{k_1}$$

 \rightarrow system reduces to a scalar ODE



• meaning of a Michaelis Menten reaction kinetics

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

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



9.11 "True" vs MM reaction

- looking again at the ODE, there are 2 time scales
- "slow time scale" in which c can be thought of as constant → 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

9.12 Matlab code used

- 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 \boldsymbol{z}
 - s=z(1);
 - c=z(2);
 - % ODEs
 - dsdt=k1m*c-k1*s*(e0-c);

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dcdt=k1*s*(e0-c)-(k1m+k2)*c;
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- % output vector
- dzdt=[dsdt; dcdt];
- integration routine
 - [t,z] = ode45(@f enz mich ment1,tspan,z0,[]);