MODELLING AND SIMULATION

Lesson 9 - SS 2014 – Michel Kana

What do we do in today's lesson?

1. Summary of the previous practice
2. Identifiability Analysis
3. Projects
4. Summary

Summary of the previous practice

Pharmacokinetics modeling

Semester schedule

17ABBMS

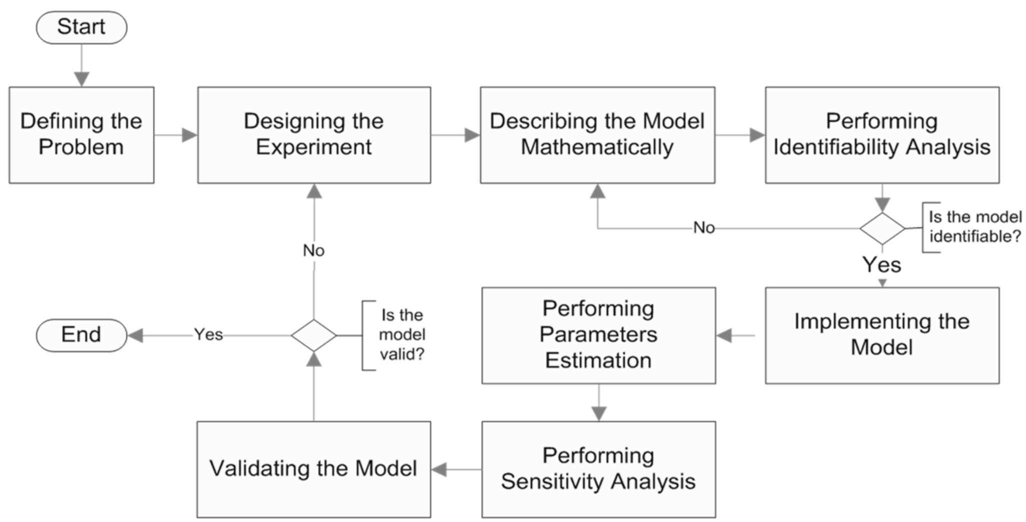
- **Population models**
  - 1th lecture
    Introduction to Mathematical Modeling
  - 2nd lecture
    Models for single specie populations
  - 3rd lecture
    Models for two species populations
  - 4th lecture
    Epidemiology models
- **Compartmental models**
  - 5th lecture
    1 - compartmental models
  - 6th lecture
    More - compartmental models
  - 7th lecture
    More - compartmental models
- **Advanced Topics**
  - 9th lecture Apr 15
    Identifiability analysis
  - 12th lecture May 6
    Identifiability analysis
  - 13th lecture May 13
    Identification of model parameters
  - 14th lecture May 20
    Sensitivity analysis

8th (Apr 8), 10th (Apr 22) and 11th (Apr 29) lessons are postponed
11th (May 1) and 12th (May 8) tutorials are postponed

May 27: final exam, May 29: correction of final exam
June 1: final presentations and grades

Purpose of identifiability analysis

- **Performing identifiability analysis**
  - answers the question if the hidden model parameters are calculable given perfect input-output data
    - example
      - can we estimate the rate of elimination of glucose from the body (k_{11}) and apparent body volume (V_1) if we know the amount of glucose input (u_1) and the glucose concentration in urines (Y_1) ?
      - given u_1 (input) and Y_1 (output), can we calculate k_{11} and V_1 ?
  - if we cannot identify parameters it is advisable to return to the previous stage and readjust the mathematical model and/or the experiment



Purpose of identifiability analysis

- Goal is to find out if the experiment is valid and if the model can fit to the measured data and provide unique values for the model parameters, under the ideal circumstances of noiseless measurements gathered for an infinite amount of time
- **a priori model identifiability** or structural identifiability analysis
  - the model structure is examined before simulating and fitting procedures.
- **posteriori model identifiability** or practical identifiability analysis
  - non-identifiabilities are detected by fitting to data and investigating parameter estimates
  - If a model happens to be structurally non-identifiable then it is also practically non-identifiable.
  - If the model is structurally identifiable, it may nevertheless turn out to be practically non-identifiable.
  - practical identifiability tests can hardly suggest alternative experimental strategies to follow in order to obtain identifiability of the model.

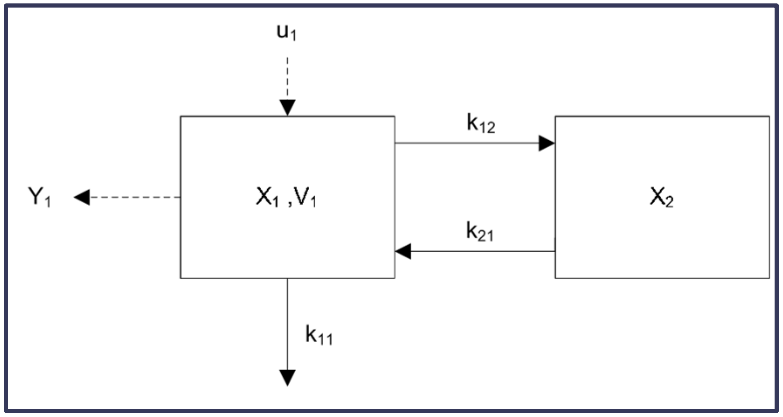
Formal definition of identifiability

- A general dynamic system can be expressed as follows:
  - $\dot{x}(t) = f(t, x(t), u(t), \theta)$
  - $y(t) = h(x(t), u(t), \theta)$
    - Where $u(t)$ is the system input vector, $x(t)$ is the vector of state variables, $y(t)$ is the output vector, θ is the parameters vector
    - θ can be constant, time-varying or a mixture of both
- The system is identifiable if θ can be uniquely determined from the system input $u(t)$ and the system output $y(t)$, otherwise it is unidentifiable
  - The system is globally identifiable if for any input $u(t)$ and any two parameters vectors θ_1 and θ_2 in the whole parameter space, $y(\theta_1) = y(\theta_2)$ holds if and only if $\theta_1 = \theta_2$
  - The system is locally identifiable if for any input $u(t)$ and any two parameters vectors θ_1 and θ_2 in the neighborhood of some point θ_*, $y(\theta_1) = y(\theta_2)$ holds if and only if $\theta_1 = \theta_2$

Structural identifiability with transfer function

- An LTI dynamic system can be expressed as follows:
  - $\dot{x} = A \cdot x + B \cdot u$
  - $y = C \cdot x$
- The Laplace Transform can be used to compute the Transfer Function of the LTI system
  - $C^{-1}\dot{Y} = A.C^{-1}.Y + B.U$
  - $-A.C^{-1}.Y + C^{-1}.\dot{Y} = B.U$
  - $L\{-A.C^{-1}.Y + C^{-1}.\dot{Y}\} = L\{B.U\}$
  - $-A.C^{-1}.L\{Y\} + C^{-1}.L\{\dot{Y}\} = B.L\{U\}$
  - $-A.C^{-1}.L\{Y\} + C^{-1}(s.I.L\{Y\} - Y_0) = B.L\{U\}$
  - $(s.I - A).C^{-1}.L\{Y\} = B.L\{U\}$
  - $\boldsymbol{\frac{L\{Y\}}{L\{U\}} = C.(s.I - A)^{-1}.B}$

Structural identifiability with transfer function



$$X = \begin{bmatrix} X_1 \\ X_2 \end{bmatrix} \quad Y = \begin{bmatrix} Y_1 \\ Y_2 \end{bmatrix} \quad U = \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}$$

$$A = \begin{bmatrix} (-k_{11} - k_{12}) & k_{21} \\ k_{12} & -k_{21} \end{bmatrix}$$

$$\mathrm{B} = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}$$

$$C = \begin{bmatrix} \frac{1}{V_1} & 0 \\ 0 & 0 \end{bmatrix}$$

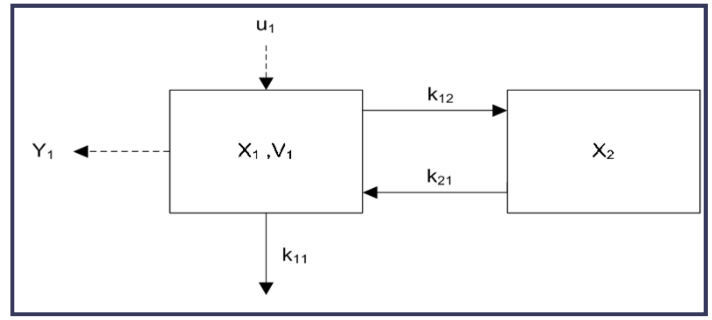
$$\frac{L\{Y\}}{L\{U\}} = C \cdot (s.I - A)^{-1} \cdot \mathrm{B}$$

$$\begin{bmatrix} \frac{L\{Y_1\}}{L\{u_1\}} & \frac{L\{Y_1\}}{L\{u_2\}} \\ \frac{L\{Y_2\}}{L\{u_1\}} & \frac{L\{Y_2\}}{L\{u_2\}} \end{bmatrix} = \begin{bmatrix} \frac{1}{V_1} & 0 \\ 0 & 0 \end{bmatrix} \cdot \begin{bmatrix} s + k_{11} + k_{12} & -k_{21} \\ -k_{12} & s + k_{21} \end{bmatrix}^{-1} \cdot \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix}$$

$$\boldsymbol{\frac{L\{Y_1\}}{L\{u_1\}} = \frac{\frac{1}{V_1} s + \frac{1}{V_1} k_{21}}{s^2 + (k_{11} + k_{12} + k_{21}) s + k_{21} k_{11}}}$$

Structural identifiability with transfer function

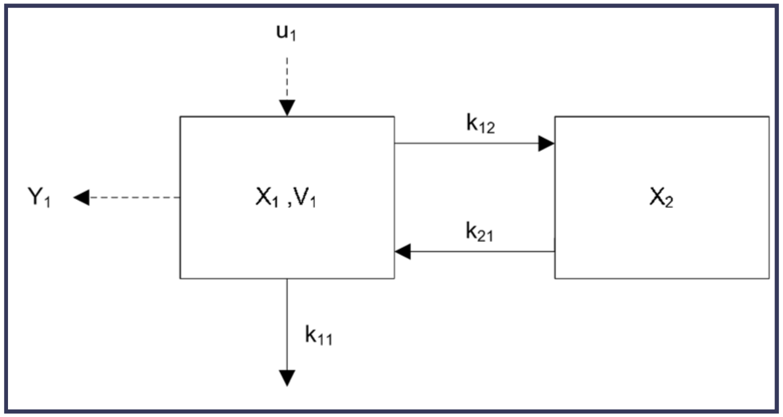
- The transfer function of a LTI system is a ratio of two polynomials.
  - The coefficients $\boldsymbol{a_i}, \boldsymbol{b_i}$ of the polynomials are called observational parameters.
  - The observational parameters are non-linear functions of model parameters.
  - If all model parameters can be uniquely computed from the observational parameters, then the model is identifiable.
  - The identifiability problem reduces to determining the number of solutions in a set of nonlinear algebraic equations.



$$\frac{L\{Y_1\}}{L\{u_1\}} = \frac{\frac{1}{V_1}s + \frac{1}{V_1}k_{21}}{s^2 + (k_{11} + k_{12} + k_{21})s + k_{21}k_{11}}$$

$$\frac{L\{Y\}}{L\{U\}} = \frac{\boldsymbol{a_{n-1} \cdot s^{n-1} + a_{n-2} \cdot s^{n-2} + \cdots + a_1 \cdot s + a_0}}{\boldsymbol{b_n \cdot s^n + b_{n-1} \cdot s^{n-1} + \cdots + b_1 \cdot s + b_0}}$$

Structural identifiability with transfer function



$$\frac{L\{Y_1\}}{L\{u_1\}} = \frac{\frac{1}{V_1}s + \frac{1}{V_1}k_{21}}{s^2 + (k_{11} + k_{12} + k_{21})s + k_{21}k_{11}}$$

Transfer function

$$\begin{cases} a_1 = \dfrac{1}{V_1} \\ a_0 = \dfrac{1}{V_1}k_{21} \\ b_1 = k_{11} + k_{12} + k_{21} \\ b_0 = k_{21}k_{11} \end{cases}$$

Observational parameters

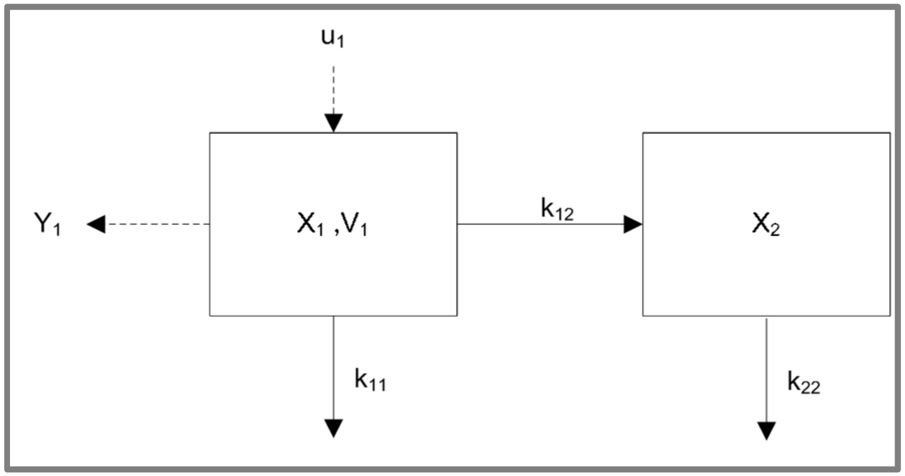
$$\begin{cases} V_1 = \dfrac{1}{a_1} \\ k_{21} = \dfrac{a_0}{a_1} \\ k_{11} = \dfrac{b_0 a_1}{a_0} \\ k_{12} = b_1 - \dfrac{a_0}{a_1} - \dfrac{b_0 a_1}{a_0} \end{cases}$$

Solution to a system of non-linear equations

all model parameters can be uniquely computed from the observational parameters

→ the model is **identifiable**

Structural identifiability with transfer function



$$\frac{L\{Y_1\}}{L\{u_1\}} = \frac{\frac{1}{V_1}s + \frac{1}{V_1}k_{22}}{s^2 + (k_{11}+k_{12}+k_{22})s + k_{22}(k_{11}+k_{12})}$$

Transfer function

$$\begin{cases} a_1 = \dfrac{1}{V_1} \\ a_0 = \dfrac{1}{V_1}k_{22} \\ b_1 = k_{11}+k_{12}+k_{22} \\ b_0 = k_{22}(k_{11}+k_{12}) \end{cases}$$

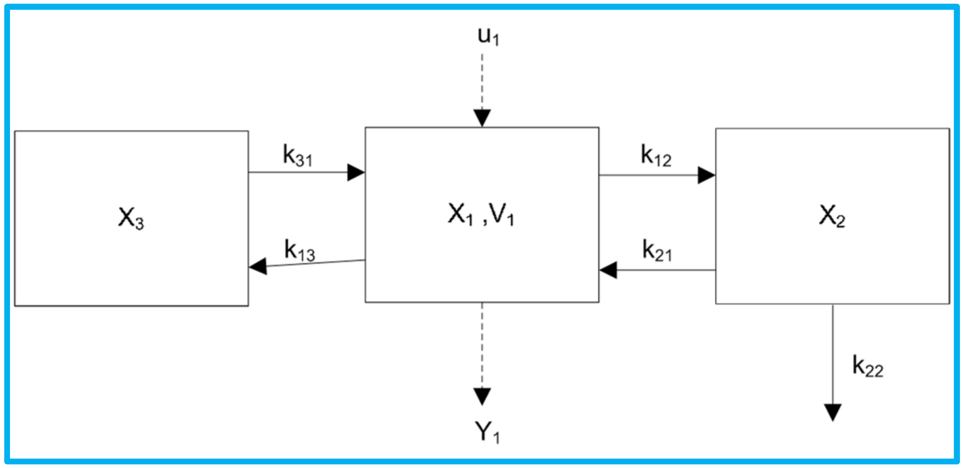
Observational parameters

$$\begin{cases} V_1 = \dfrac{1}{a_1} \\ k_{22} = \dfrac{a_0}{a_1} \\ k_{11}+k_{12} = b_1 - \dfrac{a_0}{a_1} \\ k_{11}+k_{12} = \dfrac{b_0 a_1}{a_0} \end{cases}$$

Solution to a system of non-linear equations

Although V_1 and k_{22} can be uniquely computed from the observational parameters, k_{11} and k_{12} cannot → the model is **unidentifiable**

Structural identifiability with transfer function



$$\frac{\boldsymbol{L}\{\boldsymbol{Y}\}}{\boldsymbol{L}\{\boldsymbol{U}\}} = \frac{\frac{1}{V_1}(s + k_{21} + k_{22})(s + k_{31})}{(s + k_{12} + k_{13})(s + k_{21} + k_{22})(s + k_{31}) - k_{13}k_{31}(s + k_{21} + k_{22}) - k_{12}k_{21}(s + k_{31})}$$

Structural identifiability with similarity transformation

- An LTI dynamic system can be expressed as follows:
  - $\dot{x} = A \cdot x + B \cdot u$
  - $y = C \cdot x$
- The similarity matrix is $S = P^{-1} \cdot A \cdot P$ such that $\dot{x} = S \cdot x + B \cdot u$
  - If the only possible transformation of A is $P = I$, then the system is uniquely and globally identifiable
  - If a finite number of $P \neq I$ can be found, then the system is locally identifiable
  - If no transformation is found, then the system is unidentifiable

Structural identifiability with taylor series

- A general dynamic system can be expressed as follows:
  - $\dot{x}(t) = f(t, x(t), u(t), \theta)$
  - $y(t) = h(x(t), u(t), \theta)$
- Observations $y(t)$ are unique analytic functions of time and so all their derivatives with respect to time ($\dot{y}, \ddot{y}, \dddot{y}$,…) should also be unique
- It is thus possible to represent the observations by the corresponding Taylor series expansion in the vicinity of the initial state t_0 and the uniqueness of this representation will guarantee the structural identifiability of the system
  - $y(t,\theta) = y(t_0,\theta) + t \cdot \dot{y}(t_0,\theta) + \frac{t^2}{2!} \cdot \ddot{y}(t_0,\theta) + \cdots$

Structural identifiability with taylor series

- Taylor series expansion of observations
  - $y(t,\theta) = y(t_0,\theta) + t \cdot \dot{y}(t_0,\theta) + \frac{t^2}{2!} \cdot \ddot{y}(t_0,\theta) + \cdots$
- The idea is to establish a system of non-linear algebraic equations in the parameters, based on the calculation of the Taylor series coefficients, and to check whether the system has a unique solution.
  - Let $a_k(\theta) = \lim_{t \to t_0} \frac{d^k}{dt^k} y(t,\theta)$
  - Then the condition $y(t,\theta) = y(t,\theta_*)$ implies $a_k(\theta) = a_k(\theta_*)$
  - Therefore a sufficient condition for the system to be globally structurally identifiable is:
    - $a_k(\theta) = a_k(\theta_*), k = 0,1,\cdots k_{max} \Longrightarrow \theta = \theta_*$
- This method is not popular in practice because high order of derivatives is needed and the resulting equations are not easy to solve

Homework - Practical identifiability analysis

- Local analyses are based on the computation of local sensitivities, the Fisher Information Matrix, the covariance matrix, or the Hessian of the least-squares function
- Taylor series method
- generating series method
- identifiability *tableaus*
- similarity transformation approach
- differential algebra based method
- direct test method
- implicit function theorem method
- reaction networks