FACULTÉ DE PHARMACIE DE MARSEILLE
UNIVERSITÉ DE LA MÉDITERRANÉE AIX-MARSEILLE II

CHAPT I : Processes and models

Ευχενής Απλότης - Σωστός Μεγαλείο

❶ Description of the functional scheme. Topics in modern PKs. Modeling. Species of mathematical models.

❸ Mathematical modeling. Characterization : structure. Estimation : parameters.

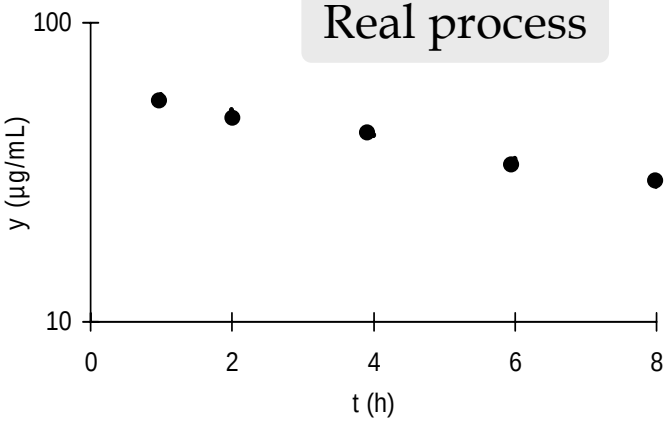
❹ Checking identifiability : structural and parametric identifiability. Choose the best model : the parsimony principle. Redundancy, misspecification.

❺ Dynamic functional scheme. Nonlinear models : iterations, parameter convergence. Residual error. Data processing in batch and in real-time.

❻ Observation and parametric spaces. Validation : analysis of residuals, sensitivity analysis. Modeling extensions in PKs.

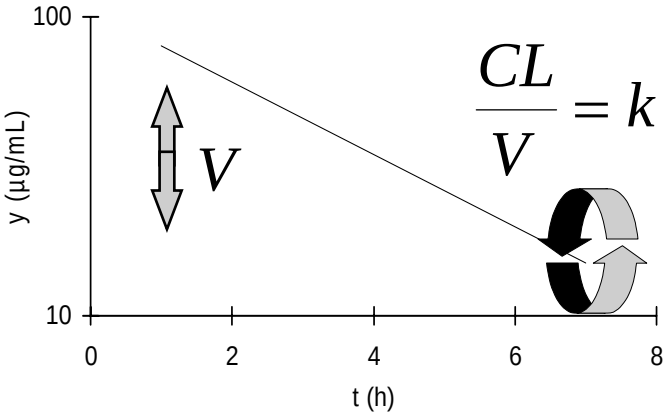
❼ Building and using models : identification, simulation, dosage adjustment. Synthesis of main tasks. Modeling advantages.

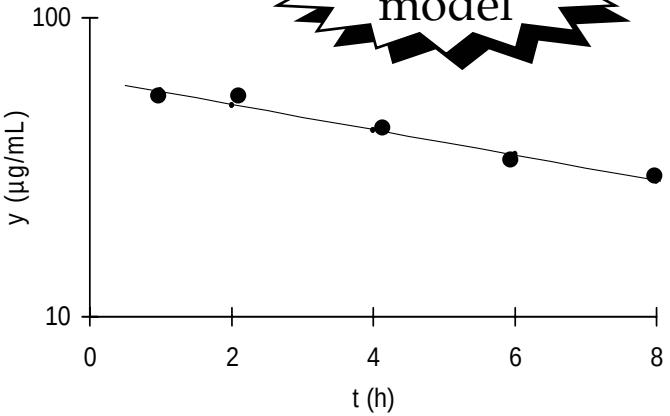
Real process and mathematical model



Math. model

$$y(t) = \frac{D}{V} \cdot \exp\left[-\frac{CL}{V} \cdot t\right]$$





$\hat{V} = 16$ L

$\hat{k} = 0.1$ h^{-1}

Standardize observations

- Example: Administer the same dose to 2 different subjects and compare kinetics.

Sampling times (h)		1	2	6	12
Real sampling times (h) / Subject n° 1		0.975	2.06	6.12	-
Conc.	#	y_{11}	y_{12}	y_{13}	-
Real sampling times (h) / Subject n° 2		1.03	2.0	5.9	12.06
Conc.	#	y_{21}	y_{22}	y_{23}	y_{24}

  - Heterogeneity in real sampling: the comparison is not possible.
  - ✓ Compare the kinetics out of the « world » of concentrations.

- Transformation: → Use a mathematical model smoothing observations and computing PK parameters

  - ☐ Compare PK parameters.

Functional scheme

Topics in modern PKs

- PK process :
  - ★ Classical PKs : analyze physiology, drug characteristics, biopharmacy, etc.
- Mathematical models :
  - ★ PK : structural and parametric aspects. Error : variance models.
- Equivalence criterion :
  - ★ Bayesian, maximum likelihood estimators.
- Nonlinear programming :
  - ★ Iterative methods, heuristic algorithms, quasi-Newton methods.
- A priori information :
  - ★ Population approaches, parametric and nonparametric methods.

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Modeling

- Models : Dialectic, mental, physical, mathematical, etc.
- Elements : Structural and parametric knowledge, state variable.
- Goals : Model is proposed to be efficient for a specified action : recognition, control, simulation, etc.
- Validation : Experimental and statistical tools.
- Applications in : engineering (fast dynamics),
  : biology, sociology, economics, PKs (slow dynamics),
  : physics, astronomy, PDs (mixed dynamics).
- Ex. : Tourist map of the city of Marseille.

Mathematical modeling

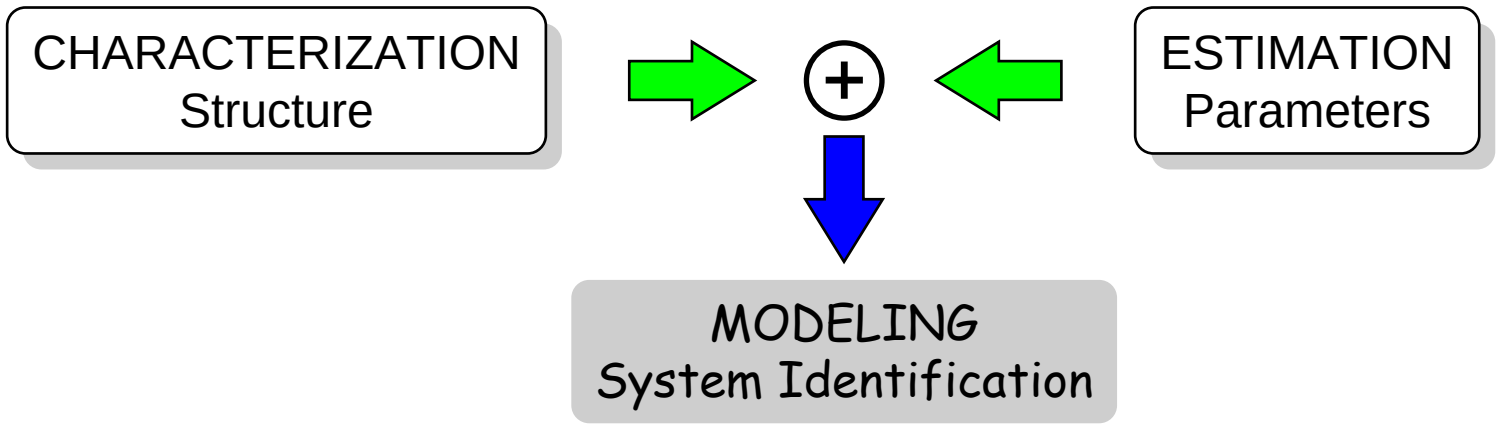
- Models are defined by :

  - their structure (number and connectivity of compartments, etc) expressed by mathematical operations involving adjustable parameters :

  ★ **Ex** : 1-cpt, $y(t) = \frac{D}{V} \cdot \exp\left[-\frac{CL}{V} \cdot t\right]$

  exponential structure, parameters : $\underline{x} = [V, CL]$

  - the numerical value of parameters used : $[V, CL] = [16\ \text{L},\ 1.6\ \text{L} \cdot \text{h}^{-1}]$



Matrix definitions

- Definition of terms
  - An array of numbers written as below is called a matrix of order $m \times n$.
  - Square matrix if $m = n$.
  - Column vector if $n = 1$.
  - Row vector if $m = 1$.
  - Scalar if $m = n = 1$.
  - A square matrix may be :
    - ★ Diagonal if $a_{ij} = 0 \quad i \neq j$, or
    - ★ Symmetric if $a_{ij} = a_{ji}$, or etc.
  - A diagonal matrix with $a_{ii} = 1 \quad i = 1, n$ is the identity matrix I.

$$A = \begin{bmatrix} a_{11} & a_{12} & \dots & a_{1n} \\ a_{21} & a_{22} & \dots & a_{2n} \\ \dots & \dots & \dots & \dots \\ a_{m1} & a_{m2} & \dots & a_{mn} \end{bmatrix}$$

- Notation : matrix A (cap), matrix element a (lower), vector $\underline{a}$ (lower, underlined).

Matrix algebra

- Transposition : $A \quad m \times n \qquad C = A^T \quad n \times m \qquad c_{ij} = a_{ji}$
- Addition : $A, B \quad m \times n \qquad C = A + B \quad m \times n \qquad c_{ij} = a_{ij} + b_{ij}$
- Multiplication : $A \quad m \times n$, $B \quad n \times q \qquad C = A \cdot B \quad m \times q \qquad c_{ij} = \sum_{k=1}^{n} a_{ik} \cdot b_{kj}$
- Square matrix :
  - Determinant (characteristic scalar) : $|A|$ Ex. $|A| = a_{11} \cdot a_{22} - a_{12} \cdot a_{21}$ for $n = 2$
  - Inversion : $C = A^{-1} \qquad C \cdot A = A \cdot C = I \qquad c_{ij} = (-1)^{i+j} \dfrac{|A^T|_{i,j}}{|A|}$
- Rules : $(A \cdot B)^T = B^T \cdot A^T \qquad (A \cdot B)^{-1} = B^{-1} \cdot A^{-1} \qquad |A^{-1}| = (|A|)^{-1}$

Operators : Analytic geometry - 1

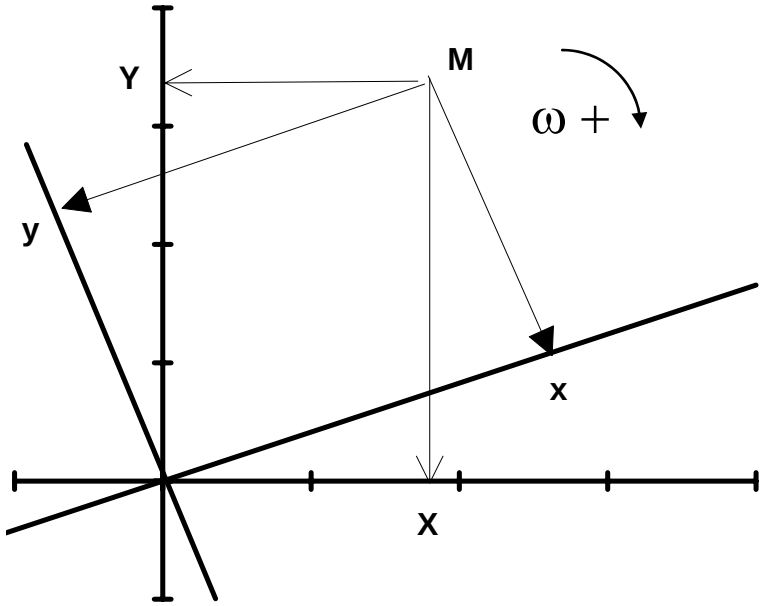
☐ Rotation of rectangular coordinate system :

★ Rotation angle ω

★ $[X, Y]$: old and $[x, y]$: new coordinates

$$x = X \cdot \cos\omega + Y \cdot \sin\omega$$

$$y = -X \cdot \sin\omega + Y \cdot \cos\omega$$



☐ Matrix form :

$$\begin{Bmatrix} x \\ y \end{Bmatrix} = \begin{bmatrix} \cos\omega & \sin\omega \\ -\sin\omega & \cos\omega \end{bmatrix} \cdot \begin{Bmatrix} X \\ Y \end{Bmatrix}$$

★ or $\underline{c}_{new} = \Omega \cdot \underline{c}_{old}$

☐ Matrix inversion : $\underline{c}_{old} = \Omega^{-1} \cdot \underline{c}_{new}$ with $\Omega^{-1} = \begin{bmatrix} \cos\omega & -\sin\omega \\ \sin\omega & \cos\omega \end{bmatrix}$

Operators : Analytic geometry - 2

☐ Conversion of rectangular to polar system :

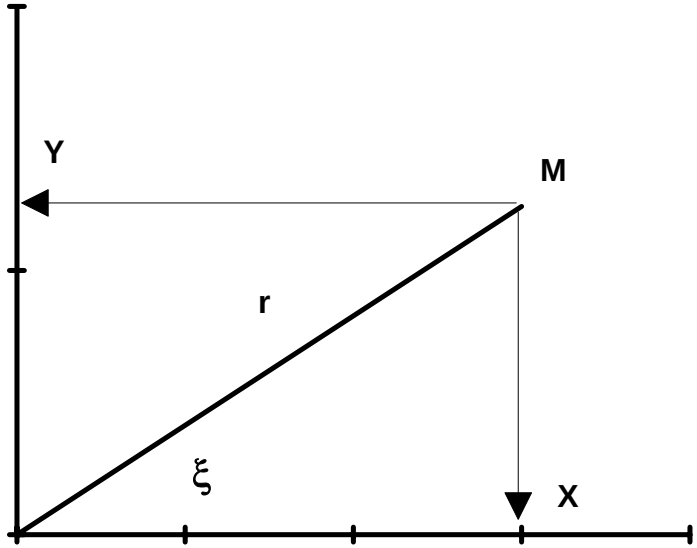
$$r = \sqrt{X^2 + Y^2}$$

$$\xi = \arctan\left(Y / X\right)$$

★ Inversely :

$$X = r \cdot \cos\xi$$

$$Y = r \cdot \sin\xi$$



☐ Impossible to link

$$\begin{Bmatrix} r \\ \xi \end{Bmatrix} \text{ and } \begin{Bmatrix} X \\ Y \end{Bmatrix}$$ by a matrix operator.

☐ The conversion relations are nonlinear.

Linear operators

☐ Let :

1°) $e_1(t)$ → **T** → $s_1(t)$

2°) $e_2(t)$ → **T** → $s_2(t)$

☐ For the input combination :

$g \cdot e_1(t) + h \cdot e_2(t)$ → **T** → ?

☐ The operator T is linear, if and only if : ? $= g \cdot s_1(t) + h \cdot s_2(t)$

PK example - 1

- For the 1-cpt model : $$y(t) = \frac{D}{V} \cdot \exp\left[-\frac{CL}{V} \cdot t\right]$$

associate : - ❶ $y(t)$ to $s(t)$ and
- ❷ D to $e(t)$.

- The model is a linear operator because :

when $D_1 \Rightarrow y_1(t) = \frac{D_1}{V} \cdot \exp\left[-\frac{CL}{V} \cdot t\right]$ and $D_2 \Rightarrow y_2(t) = \frac{D_2}{V} \cdot \exp\left[-\frac{CL}{V} \cdot t\right]$

then ⇒ $g \cdot D_1 + h \cdot D_2 \Rightarrow \frac{g \cdot D_1 + h \cdot D_2}{V} \cdot \exp\left[-\frac{CL}{V} \cdot t\right] = g \cdot y_1(t) + h \cdot y_2(t)$

PK linearity (proportionality)

PK example - 2

- For the 1-cpt model : $$y(t) = \frac{D}{V} \cdot \exp\left[-\frac{CL}{V} \cdot t \right]$$

associate : - ❶ $y(t)$ to $s(t)$ and
- ❷ CL to $e(t)$.

☐ The model is a nonlinear operator because :

when $CL_1 \Rightarrow y_1(t) = \frac{D}{V} \cdot \exp\left[-\frac{CL_1}{V} \cdot t \right]$ and $CL_2 \Rightarrow y_2(t) = \frac{D}{V} \cdot \exp\left[-\frac{CL_2}{V} \cdot t \right]$

then ⇒ $g \cdot CL_1 + h \cdot CL_2 \Rightarrow \frac{D}{V} \cdot \exp\left[-\frac{g \cdot CL_1 + h \cdot CL_2}{V} \cdot t \right] \neq g \cdot y_1(t) + h \cdot y_2(t)$

Parametric nonlinearity

Choose the best model

Rule 1 : The model should be a necessary and sufficient description of the real process :

★ necessary : good fitting on observed data.

★ sufficient : without redundancy of parameters in the structure.

Rule 2 : The model structure should be parsimonious :

★ to adequately represent the real process.

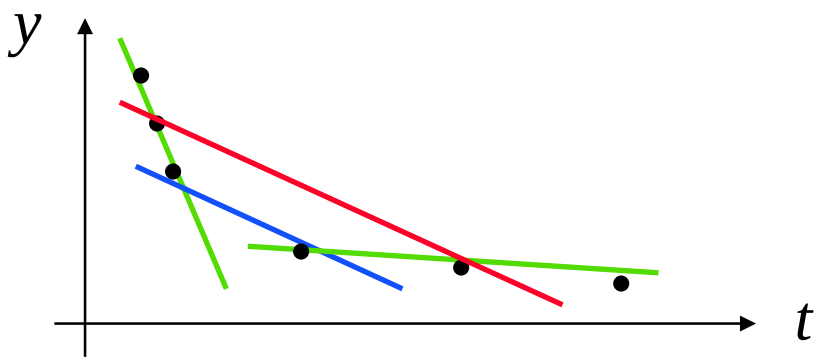
★ by containing the smallest number of parameters.

☐ **Ex** :

★ 1-cpt model is misspecified**.**

★ 3-cpt model is redundant**.**

★ 2-cpt is the best model.



Fotemustine neutrophil toxicity

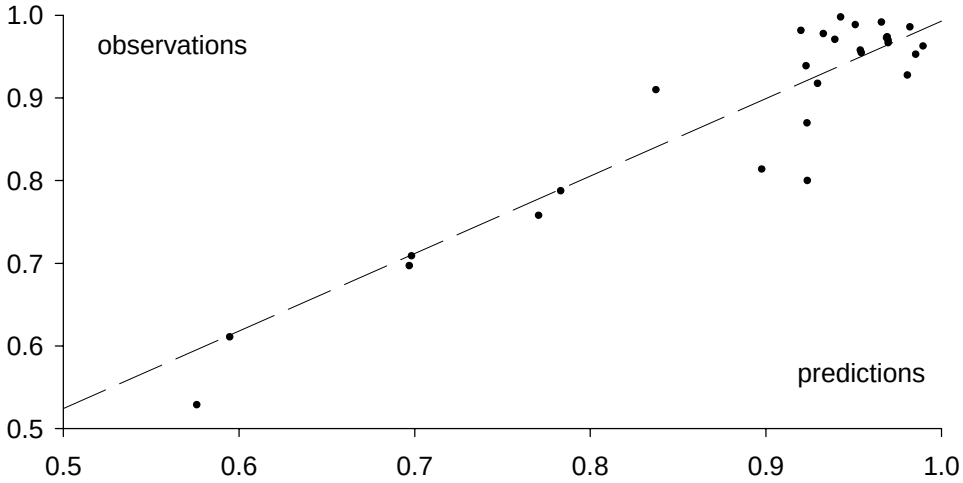
- Observations:
  - relative count: $$y_i = \left.\frac{pretreatment - nadir}{pretreatment}\right|_i \qquad i = 1, n \quad n = 29$$
- Predictions:
  - Logistic model: $$y_{Mi} = \frac{e^{z_i}}{1 + e^{z_i}} \quad \text{with} \quad z_i = \sum_{k=1}^{p} g_{ik} \cdot x_k \qquad k = 1, p \quad p = 14$$

    data → g_{ik} ; model parameters → x_k
    - e.g. $$z_i = x_1 + D_i \cdot x_2 + CL_i \cdot x_3 + BSA_i \cdot x_4 + ... + (weight)_i \cdot x_p$$
    - data for individual i : $$\underline{g}_i = [1 \quad D_i \quad CL_i \quad BSA_i \quad ... \quad (weight)_i]$$
- Problem: obtain numeric values for the model parameters ⇒ fit y_{Mi} to y_i .
- Application: Predict toxicity y_{Mo} for a new individual o with given data $\underline{d}_o$.

Indexes for the goodness of fit

- Regression line : $y_i = a \cdot y_{Mi} + b + e_i$

  ★ correlation coefficient R



- Coefficient of determination : R^2

$$R^2 = 1 - \frac{\mathrm{var}(y_i - y_{Mi})}{\mathrm{var}(y_i - \bar{y})}$$

★ is the part of data variability

(with respect to the average $\bar{y}$) explained by the model.

- Root Mean Squared Error :

$$RMSE = \sqrt{\frac{1}{n-p}\sum_{i=1}^{n} w_i^2 \cdot (y_i - y_{Mi})^2}$$

★ $RMSE$ takes into account the sample tail, n, the number of model parameters, p, and the closeness of predictions y_{Mi} to the observations y_i .

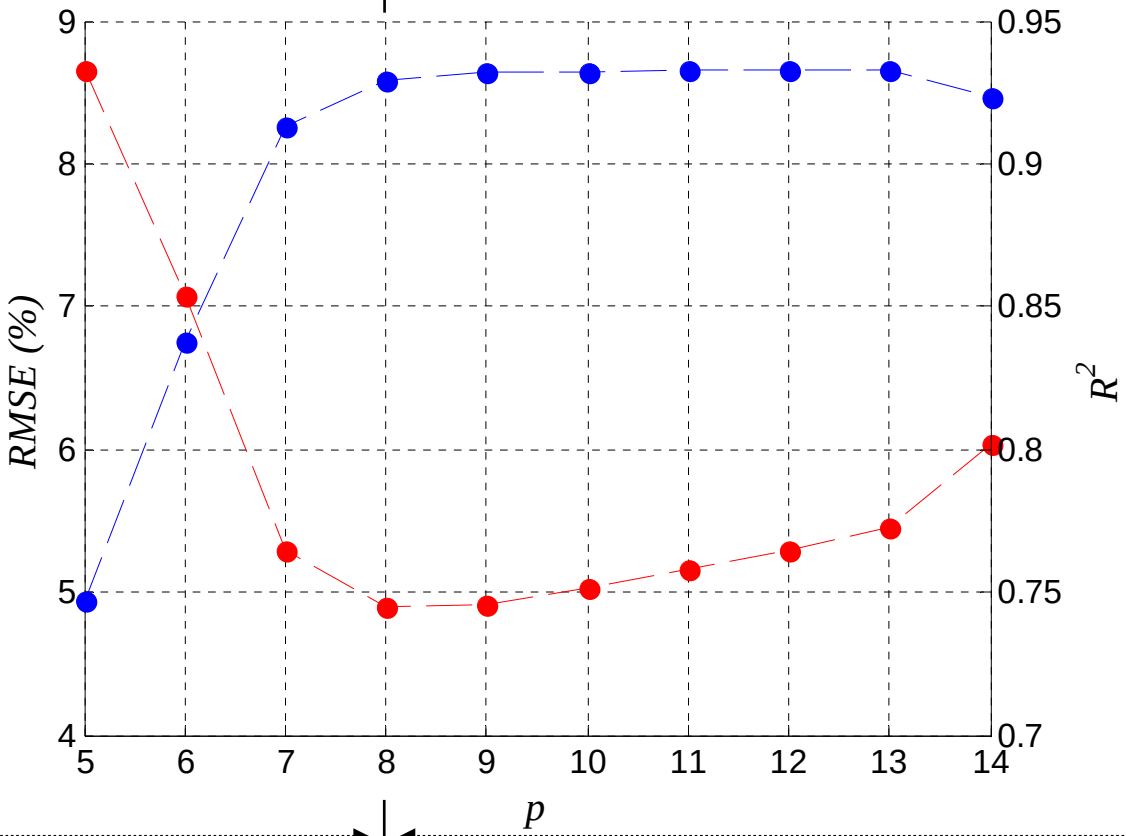
Reduce the model structure

	p									
CV	14	13	12	11	10	9	8	7	6	5
x_1	0.69	0.75	0.73	0.46	0.15	0.14	0.13	0.15	0.19	0.22
x_2	0.35	0.20	0.19	0.18	0.13	0.09	0.08	0.08	0.12	0.14
x_3	-2.71	-4.13	-3.29	*	*	*	*	*	*	*
x_4	0.60	0.33	0.30	0.26	0.24	0.22	0.21	0.15	0.23	0.33
x_5	-2.56	13.75	*	*	*	*	*	*	*	*
x_6	-3.27	2.61	2.51	3.67	*					
x_7	1.87	-2.50	-2.32	-2.36	-2.81					
x_8	1.36	0.71	0.70	0.67	0.39	0.35	0.34	0.25	*	*
x_9	0.84	0.66	0.64	0.54	0.52	0.42	0.37	0.20	0.20	0.27
x_{10}	1.69	0.79	0.77	0.67	0.57	0.51	0.52	*	*	*
x_{11}	7.67	*	*	*	*	*	*	*	*	*
x_{12}	-1.66	-2.08	-0.98	-1.01	-1.00	-1.09	*	*	*	*
x_{13}	-4.49	-0.69	-0.62	-0.60	-0.52	-0.23	-0.23	-0.17	-0.26	*
x_{14}	-1.66	-0.77	-0.69	-0.68	-0.62	-0.34	-0.29	-0.20	-0.23	-0.32
$RMSE$ (%)	6.04	5.46	5.30	5.16	5.03	4.92	4.90	5.30	7.08	8.66

Largest coefficient of variation CV

Redundancy, misspecification

Misspecification
High RMSE
NC non-satisfied



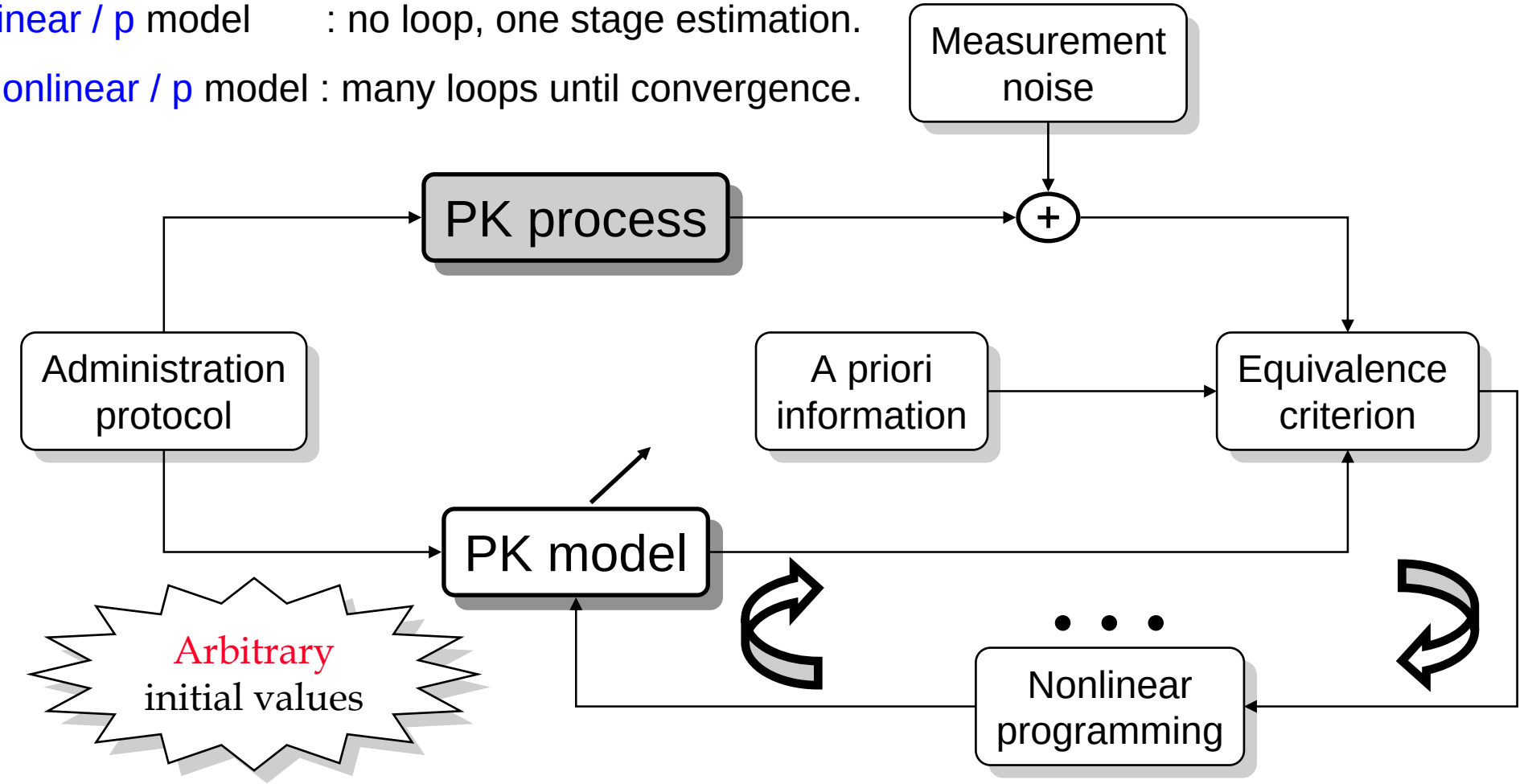
Redundancy
Increasing RMSE
SC not-satisfied

- Attention : R^2, the squared correlation coefficient, does not detect redundancy !

Functional scheme (dynamic)

Linear / p model : no loop, one stage estimation.

Nonlinear / p model : many loops until convergence.

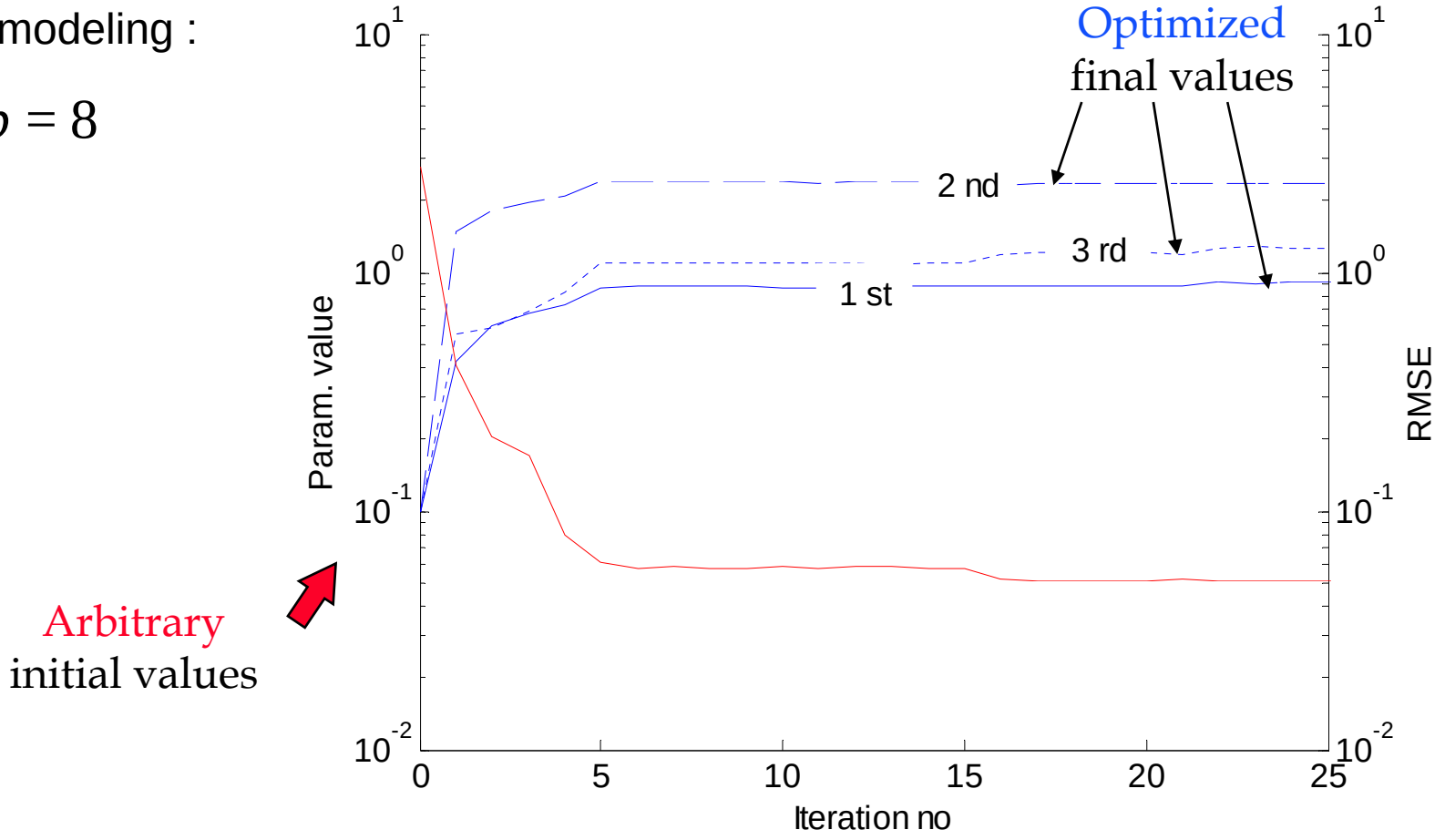


Iterations, parameter convergence

- Ex : Fotemustine neutrophil toxicity :

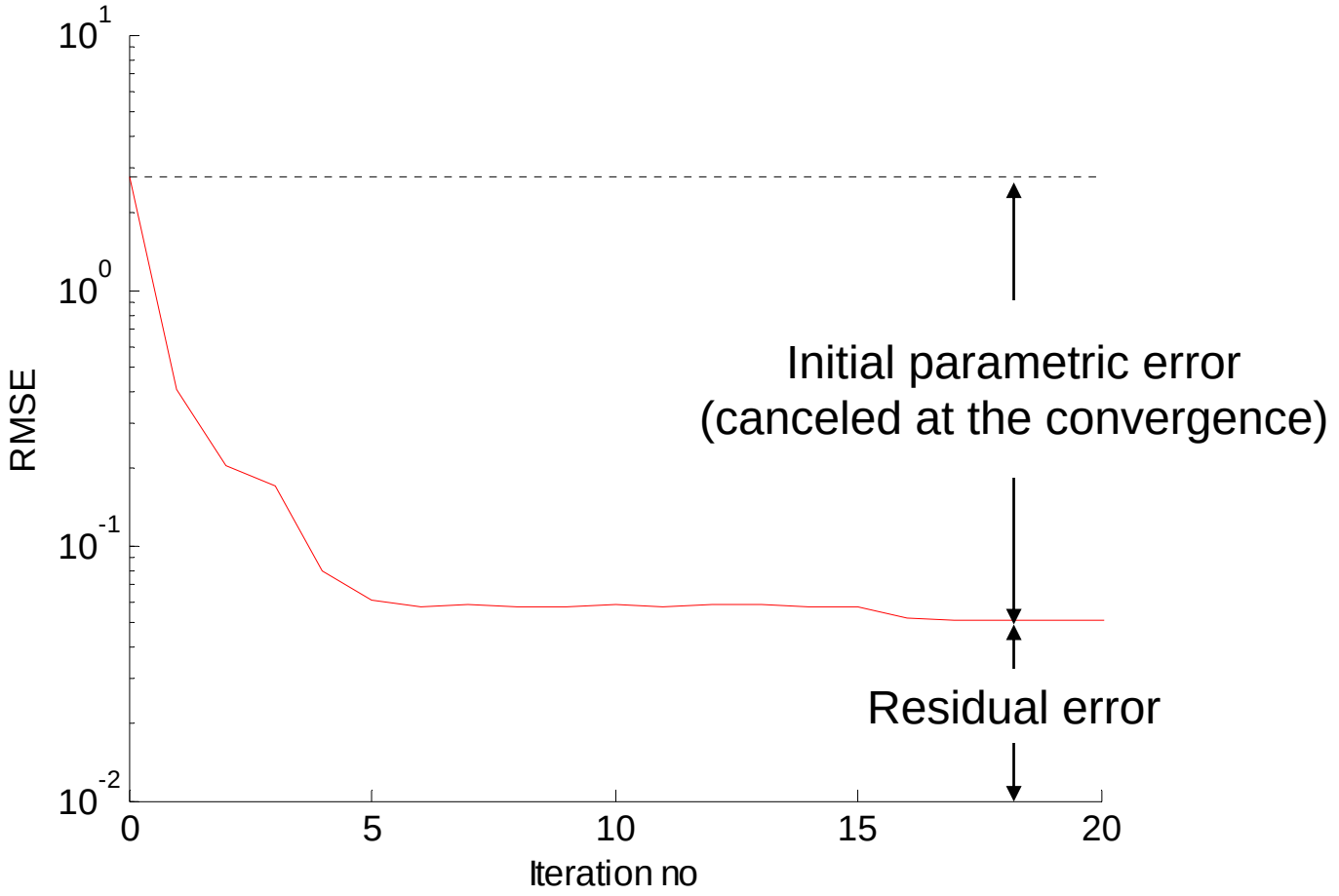
Nonlinear modeling :

$n = 29,\ p = 8$



Errors in the functional scheme

- The existing errors :
  - ❶ experimental,
  - ❷ structural,
  - ❸ parametric.
- Residual error :
  - ★ experimental,
  - ★ structural (model misspecification).



Linear modeling

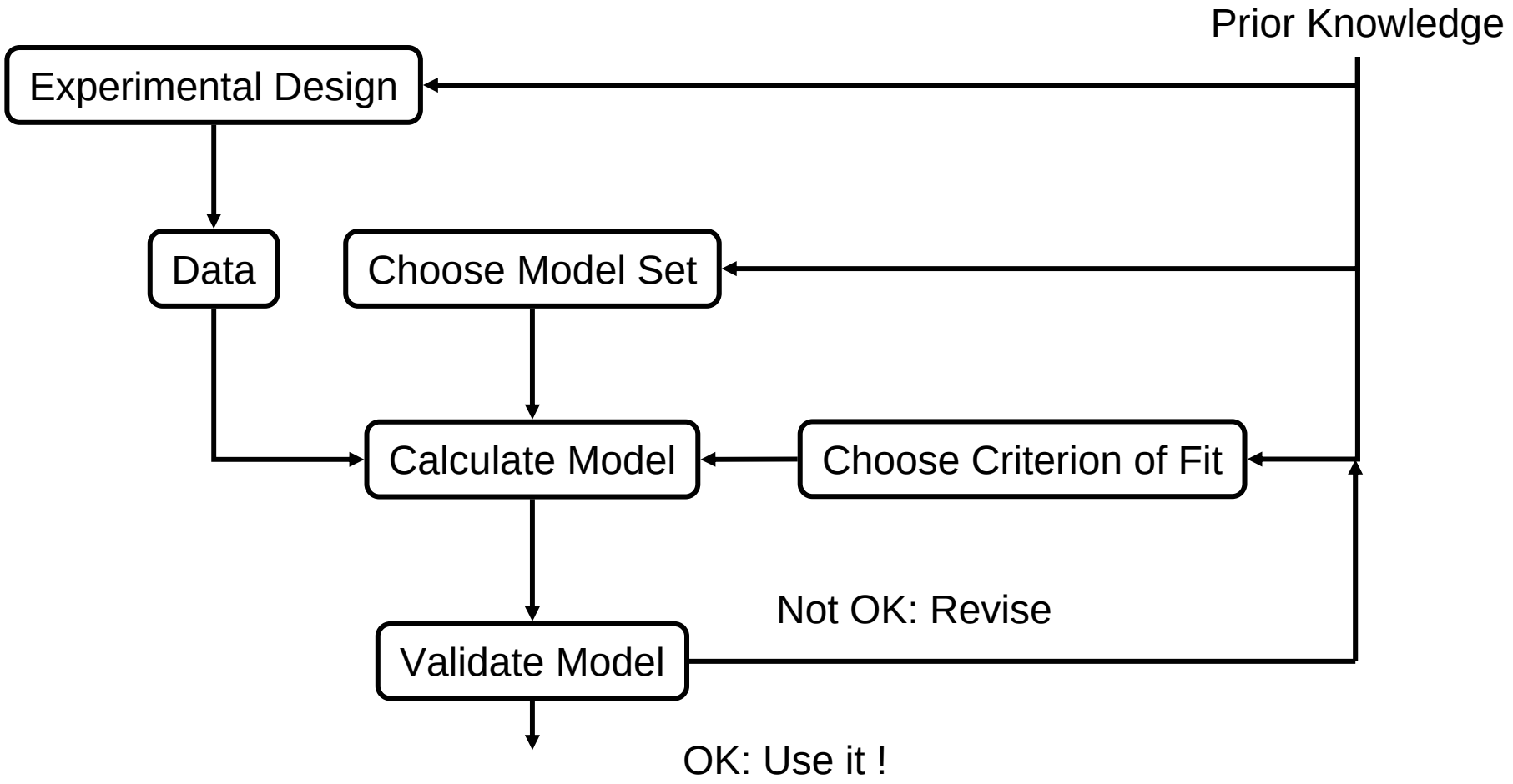
- Alternative model for fotemustine
  - Re-write the logistic model $e^{z_i} = \frac{y_{Mi}}{1-y_{Mi}}$ or $z_i = \log\frac{y_{Mi}}{1-y_{Mi}} = \underline{g}_i^T \cdot \underline{x}$
  - Transform the data and set $v_i \equiv \log\frac{y_i}{1-y_i}$
  - Find $\hat{\underline{x}} = \arg\min RMSE = \arg\min\left[(\underline{v} - G\cdot\underline{x})^T \cdot W \cdot (\underline{v} - G\cdot\underline{x})\right]$ with

$$\underline{v}^T = [v_1 \quad \ldots \quad v_i \quad \ldots \quad v_n] \qquad W = diag(w_i^2) \qquad G^T = [\underline{g}_1 \quad \ldots \quad \underline{g}_i \quad \ldots \quad \underline{g}_n]$$

  - Solving $\frac{\partial RMSE}{\partial \underline{x}} = 0$ leads to $\hat{\underline{x}} = (G^T \cdot W \cdot G)^{-1} \cdot G^T \cdot W \cdot \underline{v}$

Because the model is linear, no iterations needed !

The system identification loop



Real-time processing of data

- Data processing :
  - ☐ In batch or off-line : Wait until the last observation for all data processing.
    - ★ { m observations } - 1 data processing
  - ☐ Sequentially or in real-time : Perform modeling while observations are available.
    - ★ { 1 observation - 1 datum processing } x { m times }

Warning :

❶ In the first stages, the lack of individual information should be offset by the a priori information (population studies).

❷ As the number of individual samples increases, the prior information can be forget.

Bayesian estimation

Equivalence criterion, real-time

- Indexing : m observation times i; individual j associated with p parameters prm_j.
- Equivalence criterion : Intra-kinetic weighting

$$SE = \sum_i w_i \cdot \left[\mathrm{obs}_i - \mathrm{pred}_i\left(\mathrm{prm}_j\right) \right]^2$$

- Bayesian attractor : Inter-kinetic weighting
  - In real-time when $m < p$, SE leads to infinite solutions.

Select the most appealing solution by using an attractor with :
center of attraction ave and force of attraction D

$$prior = D \cdot \left(\mathrm{prm}_j - \mathrm{ave}\right)^2$$

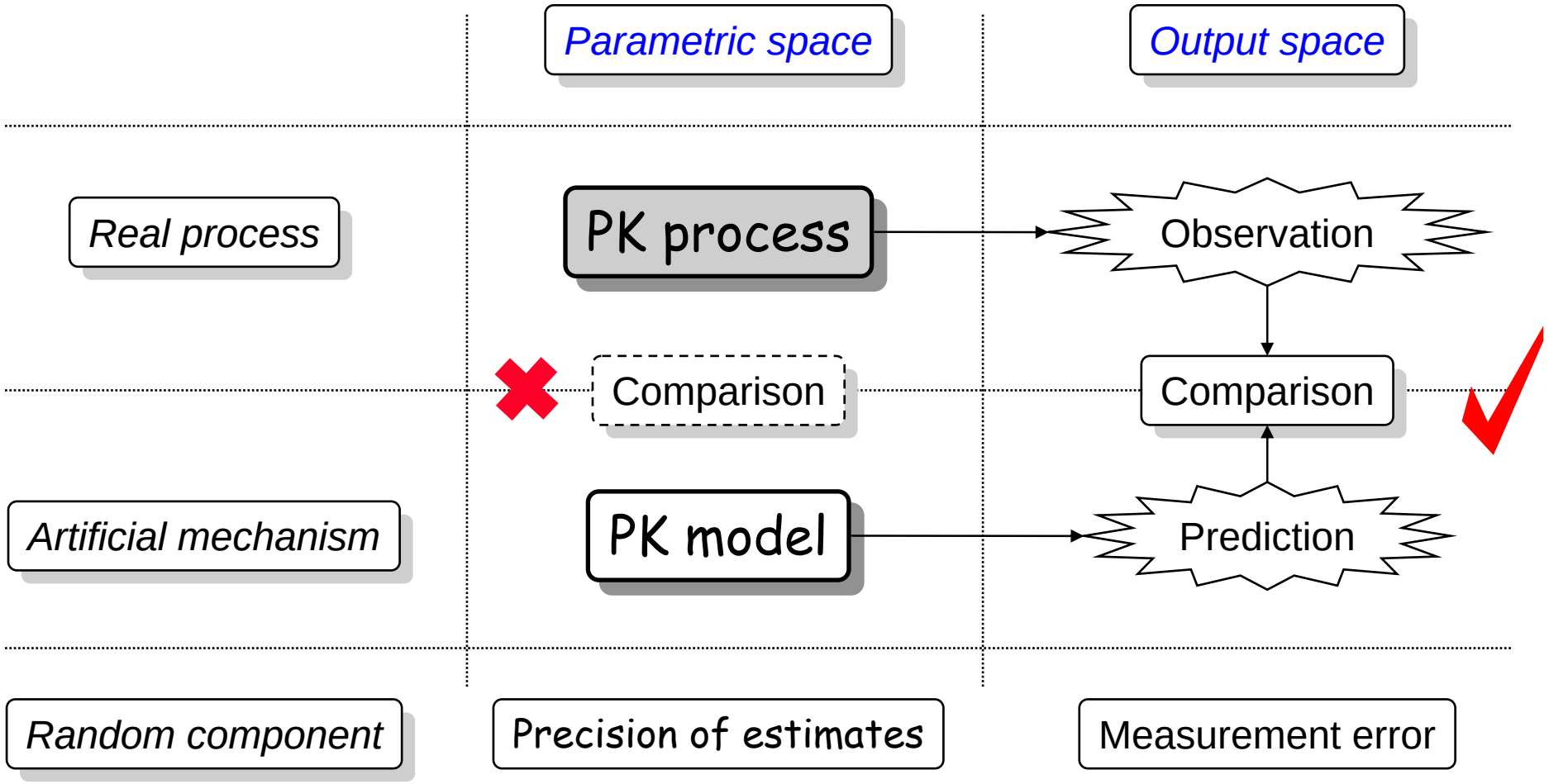
- Combine criteria to obtain prm_j : ⇒ $\ln\left(prior\right) + \ln\left(SE\right)$

Bayesian estimation

- It analyzes only a few samples per patient :
  - ★ Respect of the ethical constraints,
  - ★ Reduction of the cost of the PK analysis.
- It requires :
  - ★ Obtaining the prior $f\left(\underline{x}\right)$.
  - ★ Balancing the population and the individual information :

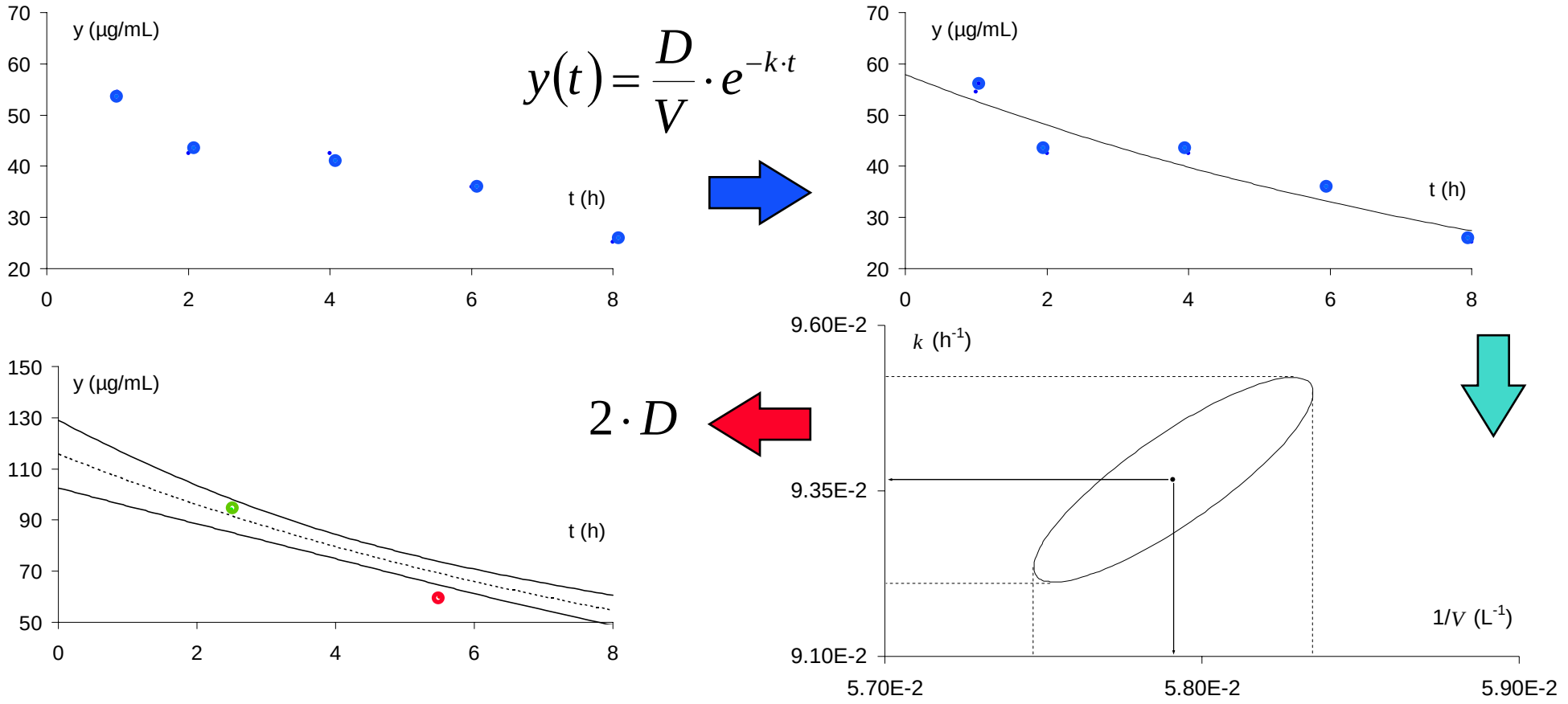
    → *balance the prior and likelihood terms*
  - ★ Operating with : staffs having a good experience and high specialized health professionals.
- It may be used in a feedback loop :
  - ★ Efficient data analyses.

Parametric and output spaces



Observation vs. parametric space

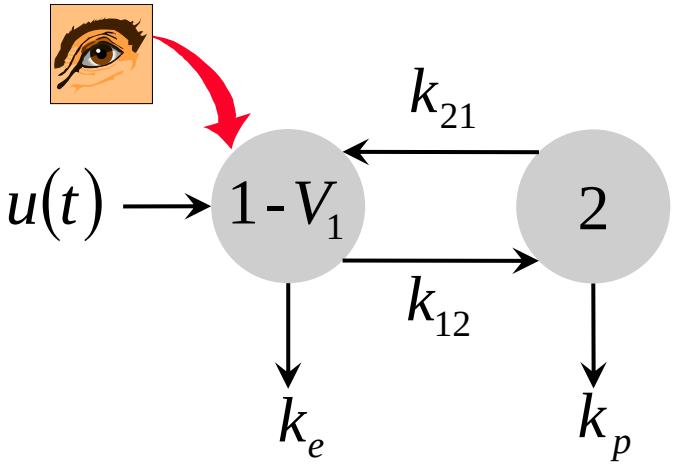
- Confidence regions and corridors



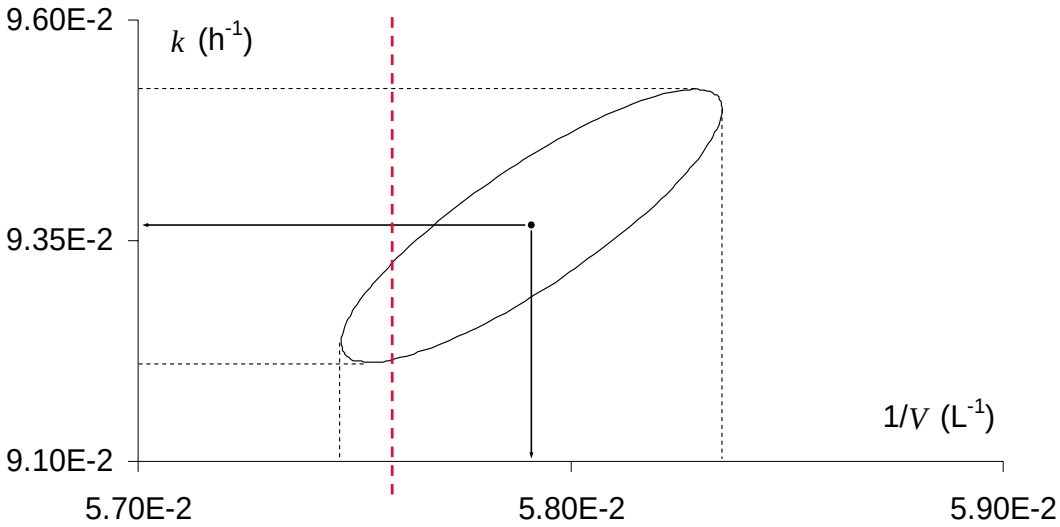
Checking identifiability

- Structural identifiability : given a hypothetical structure with unknown parameters, and a set of proposed experiments (not measurements !), would the unknown parameters be uniquely determinable from these experiments ?

- Parametric identifiability : estimating the parameters from measurements with errors and optimize sampling designs.



k_p : structural **non-identifiable**



Non-consistent V estimate

Structural identifiability ... (1)

- Analysis of the 2-cpt model.
  - Associate an elimination way k_p from the 2nd cpt.
  - Administer the D amount of drug by T h infusion.
  - Obtain analytic expression of $y_{M1}(t)$: sum of 2 exponential terms.

$$y_{M1}(t) = \frac{D}{T} \cdot \sum_{j=1}^{2} \frac{A_{1j}}{a_j} \cdot \left[e^{-a_j \cdot (t-T) \cdot u(t-T)} - e^{-a_j \cdot t} \right]$$

  - Express A_1, A_2, a_1, a_2 as functions of $V_1, k_e, k_p, k_{12}, k_{21}$.

$$A_1 = \frac{1}{V_1} \cdot \frac{k_p + k_{21} - a_1}{a_2 - a_1} \qquad a_1 + a_2 = k_e + k_{12} + k_p + k_{21}$$

$$A_2 = \frac{1}{V_1} \cdot \frac{k_p + k_{21} - a_2}{a_1 - a_2} \qquad a_1 \cdot a_2 = k_e \cdot (k_p + k_{21}) + k_{12} \cdot k_p$$

$4 : A_{1j}, a_j$
$5 : V, k$

Structural identifiability … (2)

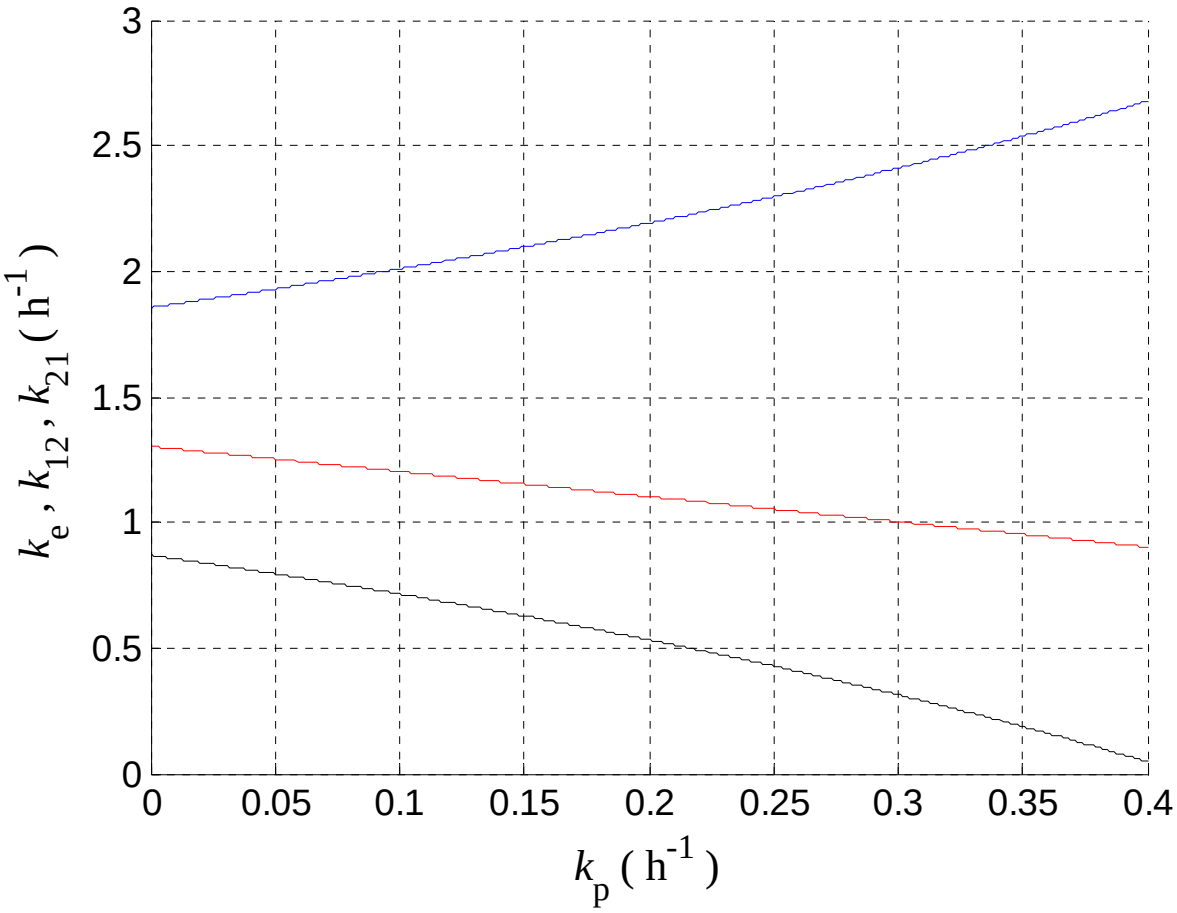
- Synthesis : Identify the 2-cpt model from real data

❶ Estimate 4 A_1, A_2, a_1, a_2

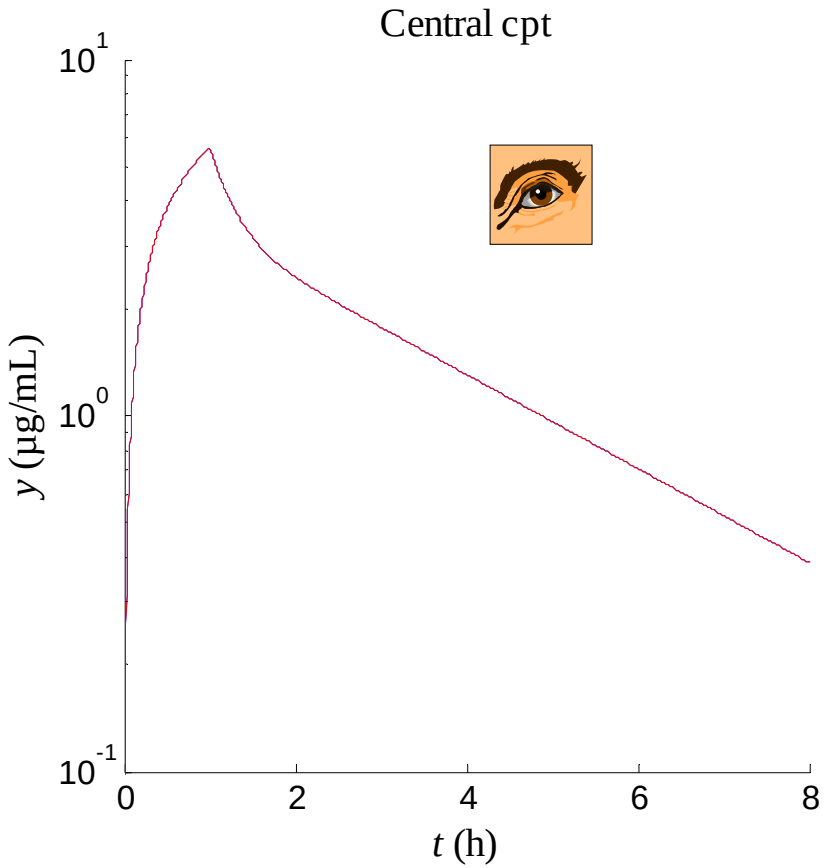
❷ Compute 5 $V_1, k_e, k_p, k_{12}, k_{21}$

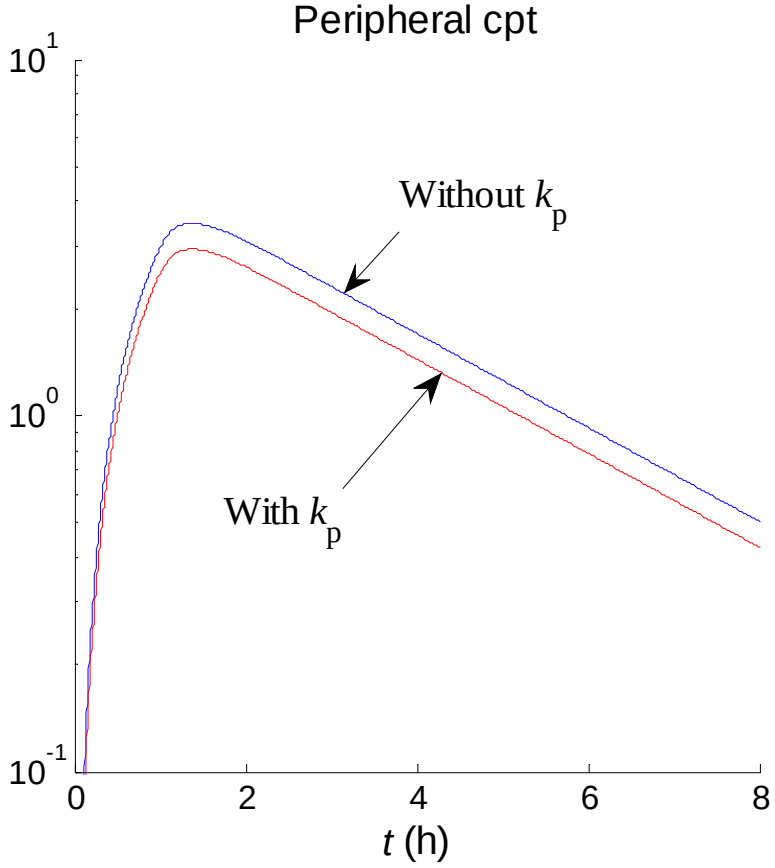
The model is structurally not identifiable

The same time-series $y_{M1}(t)$ is obtained from this plot with any combination of k_e, k_p, k_{12}, k_{21}



Simulations





Overall notes

- Modeling extensions in PKs :

  Repeated dose (multi-input) and simultaneous observation of several kinetics (multi-output systems), model the error process.

- Validation :

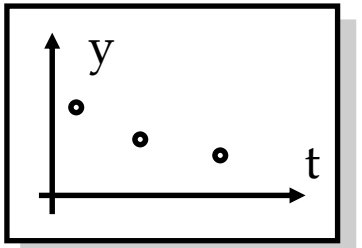
  Check whether the model is "good enough", whether it is valid for its purpose :
  { statistical tests, confidence intervals, sensitivity analysis, analysis of residuals, information concepts, new experiments }

- Remember :

The model is not an exact description of the real process.
The success of modeling depends on the richness of available knowledge.
The model never explains, but only describes the available observations.

Building and using models

Real Process



Time schedule
+
Drug amounts

Functional properties

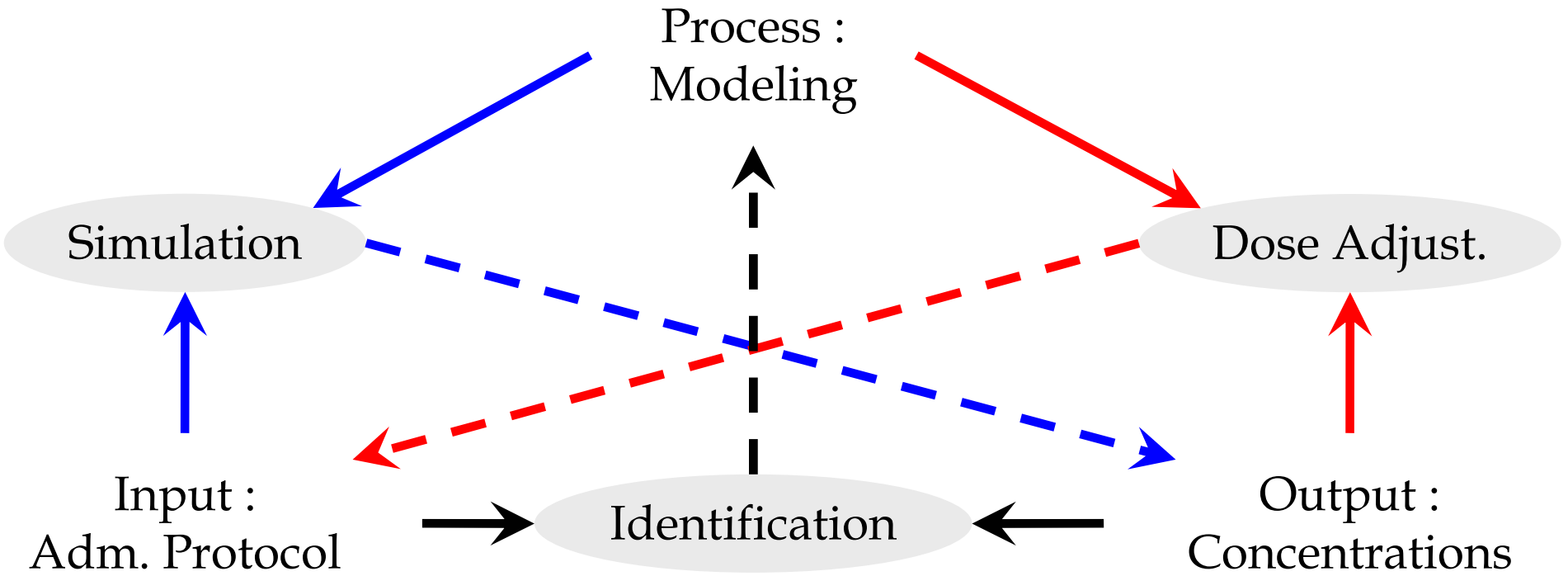
Observations, or Predictions, or Clinical Constraints

Dosage adjustment

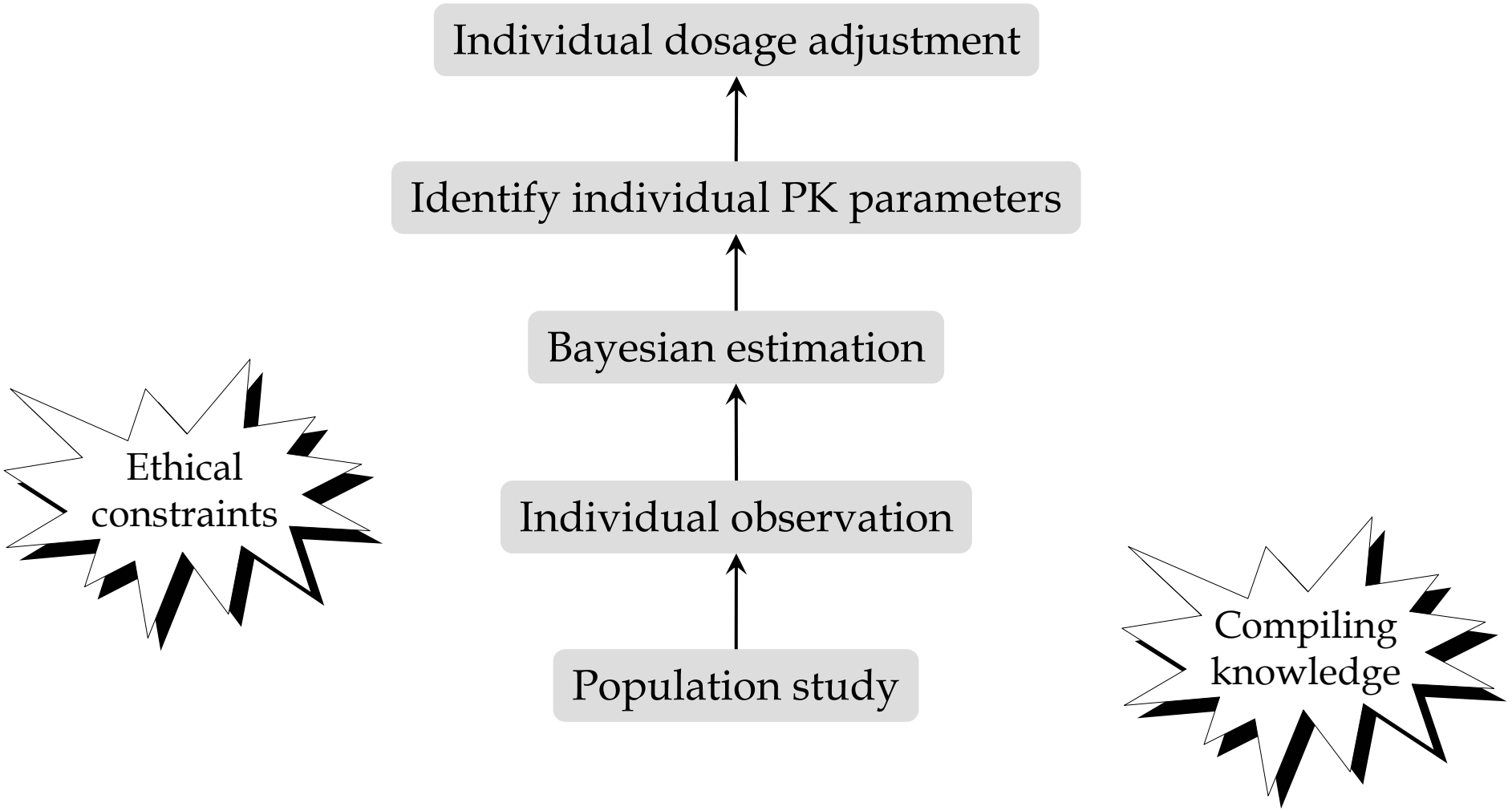
$$\sum_{j=1}^{L} A_{ij} \cdot \exp\left(-a_j \cdot t\right)$$

Simulation

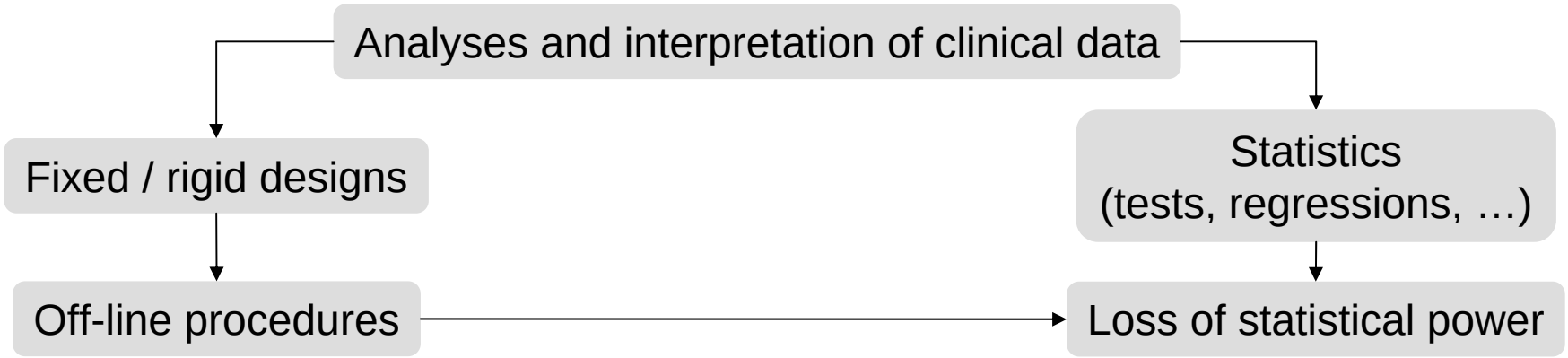
Devil's Triangle

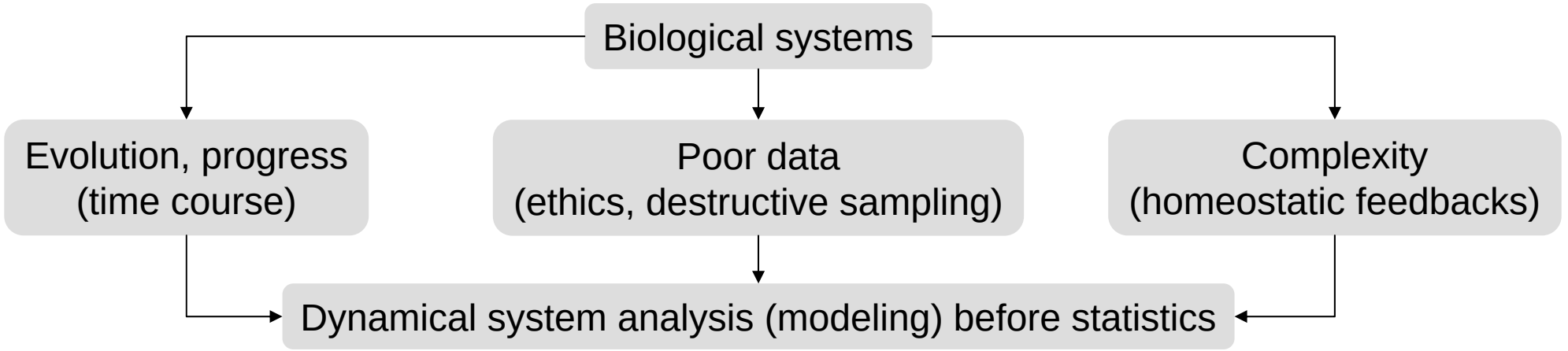


Functional flowchart



Traditional vs. modern techniques





Modeling advantages

- Advantages :
  1. Discovery of the fundamental properties of PK process by drug assay in blood or urinary samples.
  2. Data standardization : series of observations made for different administration and sampling protocols can be expressed in a standard base, the PK parameters.
  3. Data reduction : a large number of data can be reduced to a few PK parameters.
  4. Ethical individual recognition : combine in a Bayesian estimator the population and individual information supplied by few samples.
- Modeling allows :
  - ★ Prediction and control of the true process state.
  - ★ Optimization of the sampling protocol and population studies.
  - ★ Description, comparison, discrimination and classification of individuals.

Processes and models

- Biological systems :
  - Preserve integral functionality of the real process. Avoid experiments leading to :
    - ★ breakdown the feedback mechanisms or
    - ★ excessively stimulate the process in order to record quantifiable observations.
- Analysis by modeling :
  - Even approximate representation, the model must rely with the fundamental functional properties of the real process.
  - The model is able to manage complex situations. It performs efficient evaluation of multiple scenarios for :
    - ★ Optimization of subsequent experiments,
    - ★ Adjustment of inputs to control outputs.