

Modeling drug dynamics in clinical settings

- ① Modeling, simulation and control
- ② Estimation, modeling in PKs, population studies
- ③ Dosage adjustment in current PKs : Gentamycin, Methotrexate, Amikacin
- ④ Tracking a reference signal : Isosorbite dinitrate and metabolite kinetics
- ⑤ Optimal control in clinical PKs : Minimal transient time

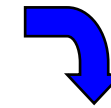
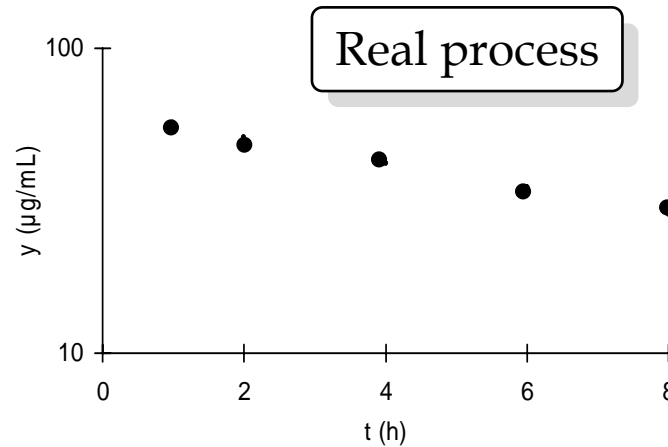
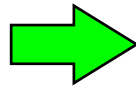
<http://pharmapk.pharmacie.univ-mrs.fr/>

Outline

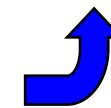
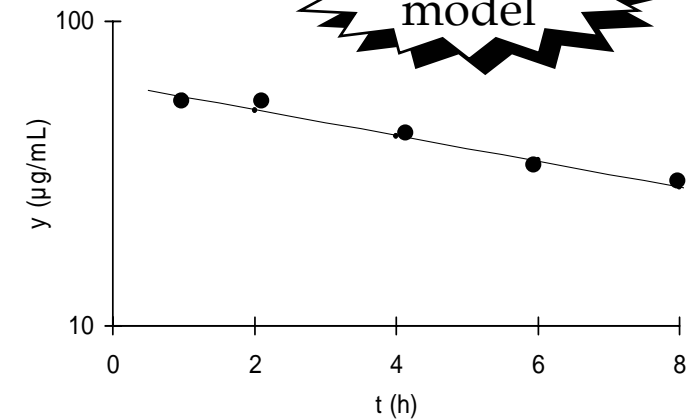


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Real process and mathematical model



Fitted model

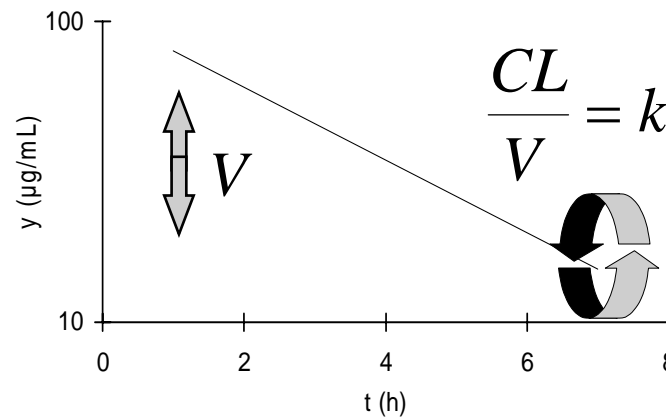


$$\hat{V} = 16 \text{ L}$$

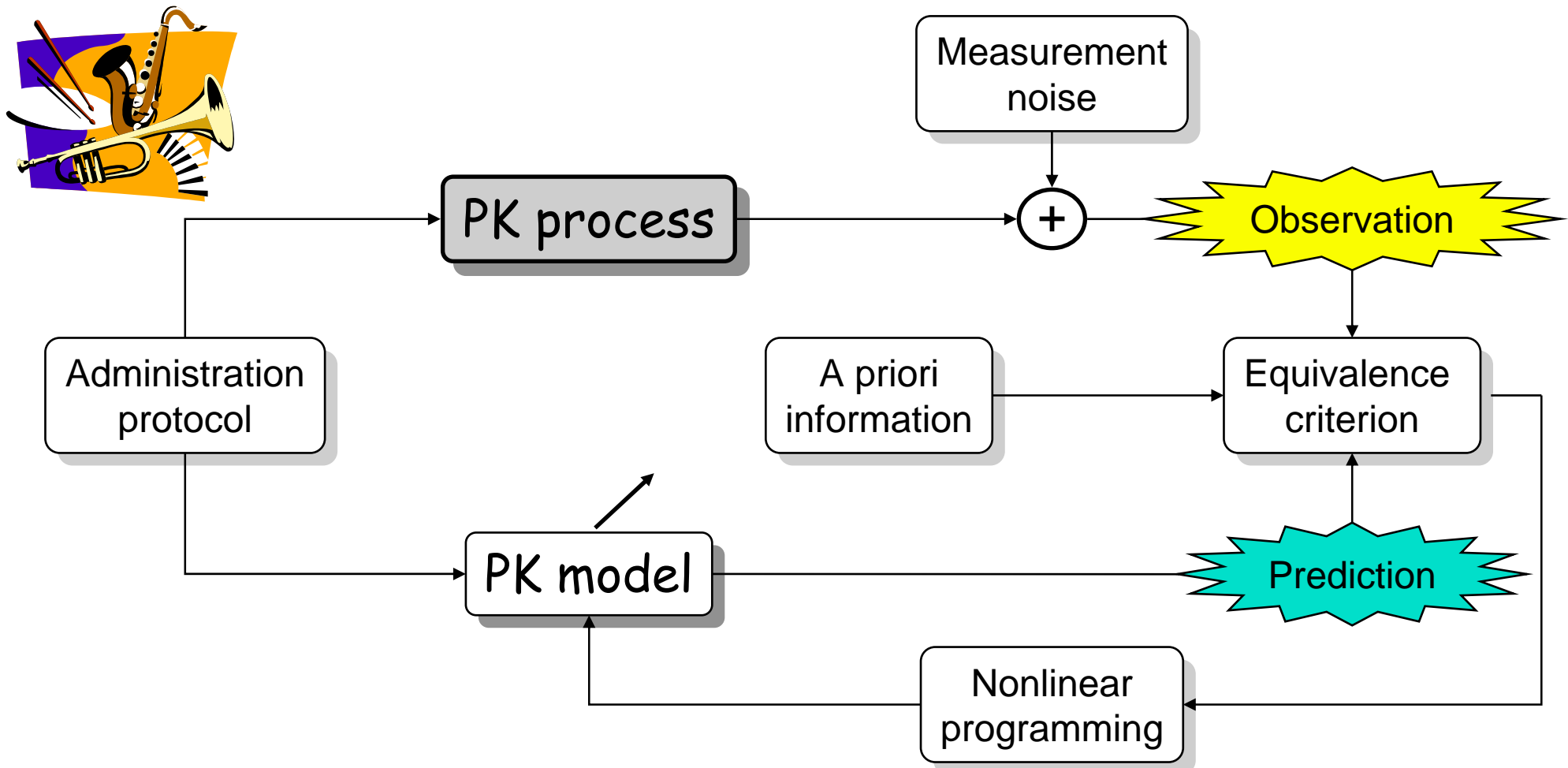
$$\hat{k} = 0.1 \text{ h}^{-1}$$

Math. model

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



Functional scheme

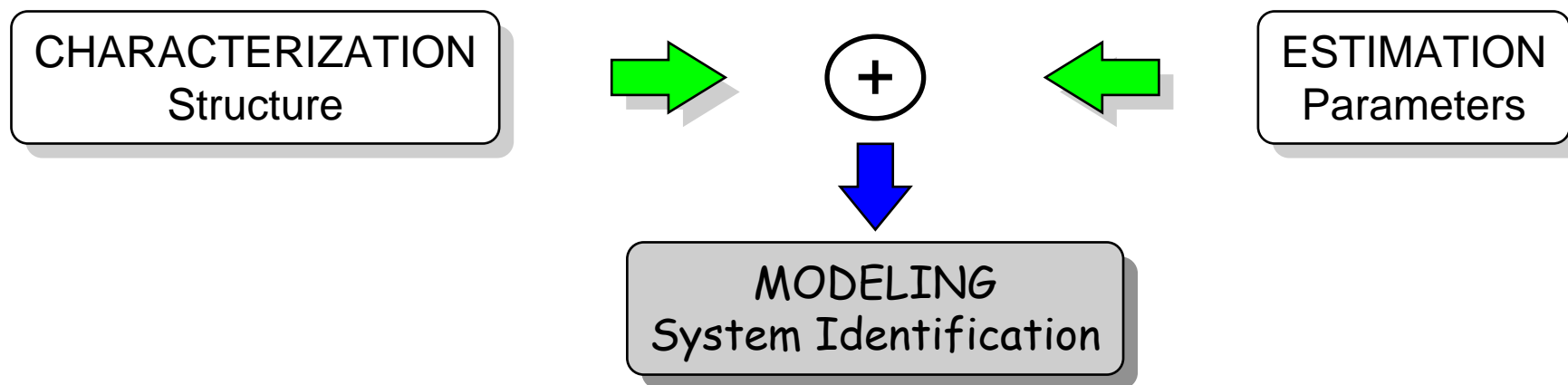


● Models are defined by :

- 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 : $[V, CL] = [16 \text{ L}, 1.6 \text{ L} \cdot \text{h}^{-1}]$



Choose the best model



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

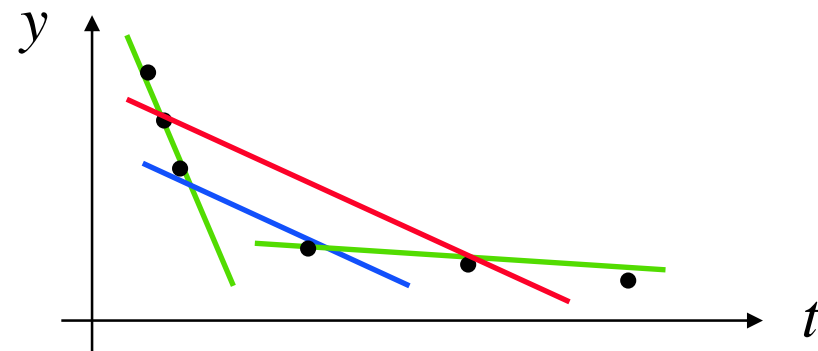
- ★ necessary : good fitting on observed data.
- ★ sufficient : without redundancy of parameters in the structure.

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.



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

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

- Bayesian attractor : **Inter-kinetic** weighting

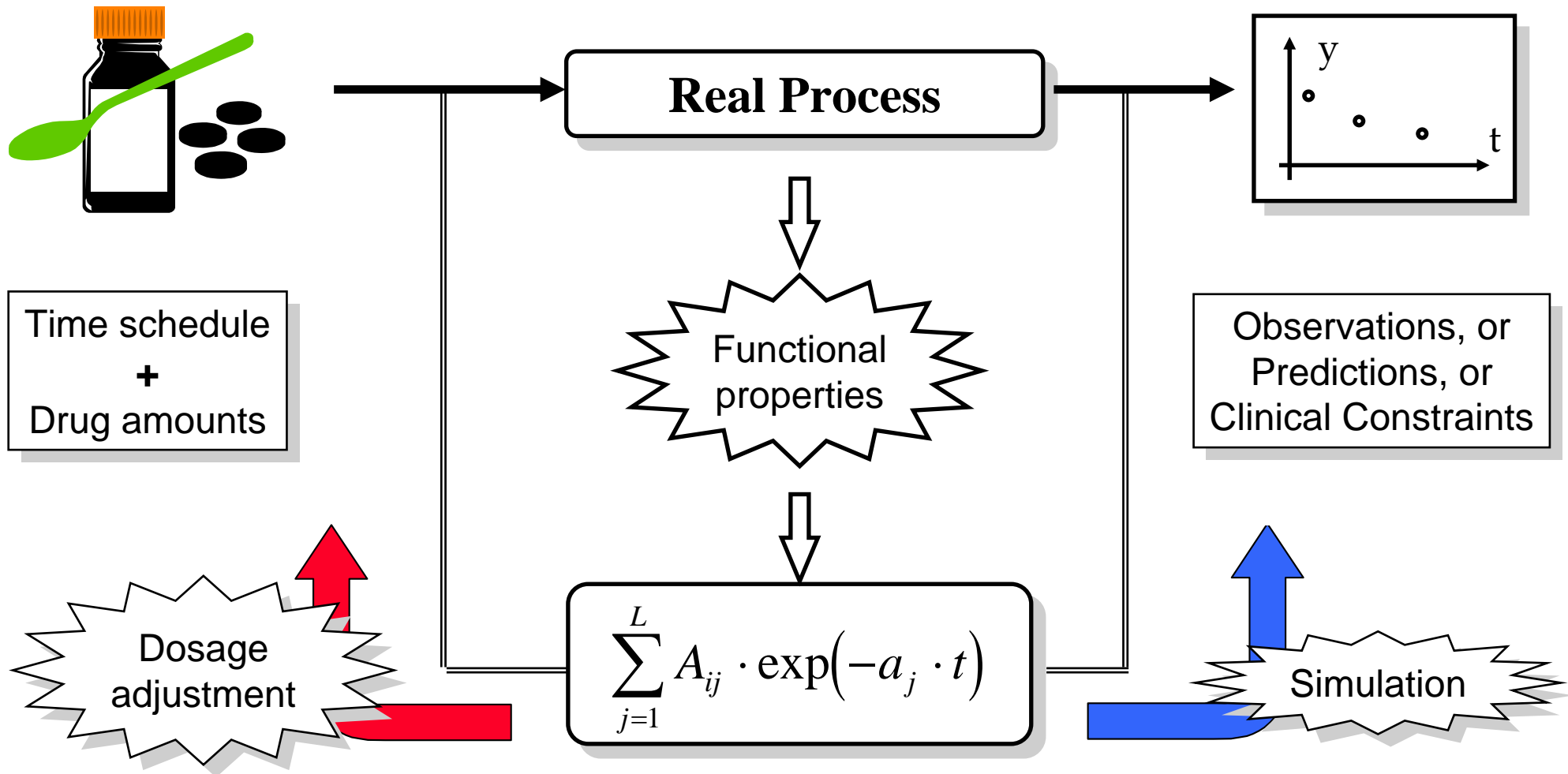
□ In real-time when $m < p$, SE leads to infinite solutions.

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

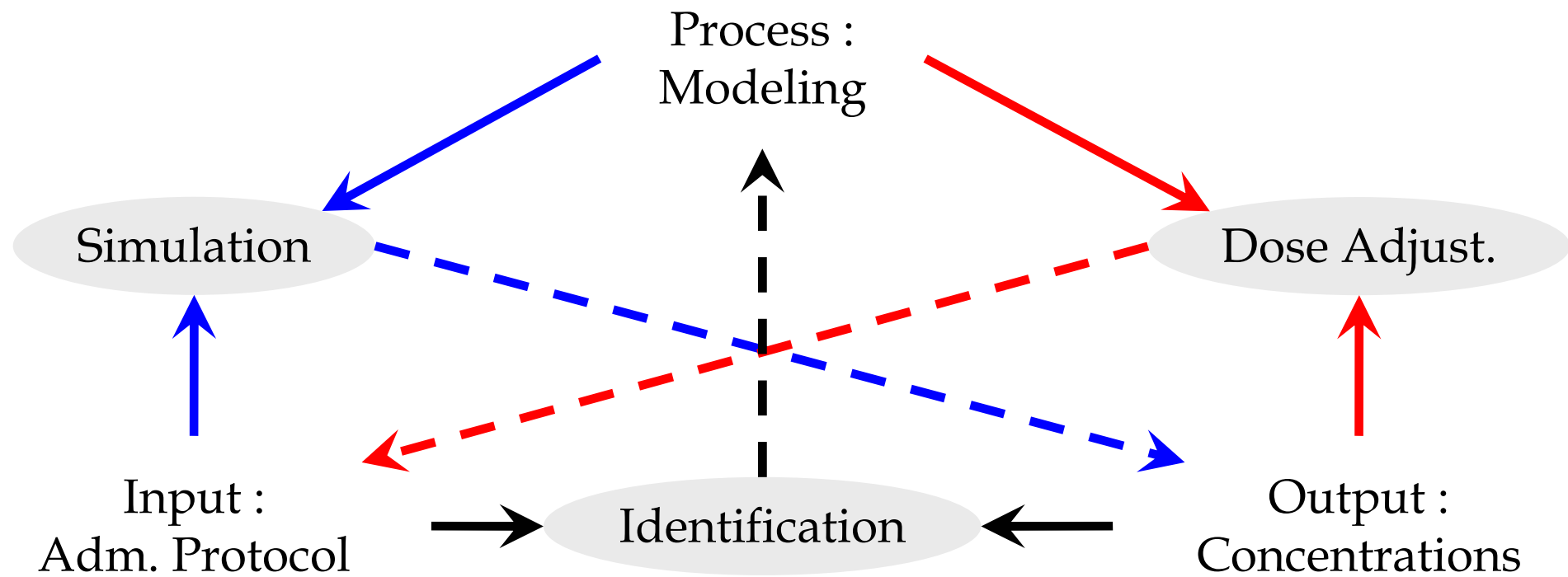
$$\text{prior} = D \cdot (\text{ave} - \text{prm}_j)^2$$

- Combine criteria to obtain prm_j :  $\ln(\text{prior}) + \ln(SE)$

Building and using models



Devil's Triangle



Modeling advantages



● Advantages :

- ① **Discover 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 real process state.
- ★ Optimization of the sampling protocol and population studies.
- ★ Description, comparison, discrimination and classification of individuals.

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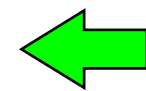
Optimal estimation

Estimation is the operation of assigning a **numerical** values to unknown parameters, based on noise-corrupted observations.

● Organization of the variables :

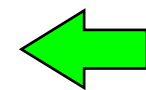
- The observed drug concentrations over time, \underline{y} (m – dimensional vector).
- The random parameters to be estimated, \underline{x} (p – dimensional vector).
- Consider the joint pdf $f(\underline{x}, \underline{y})$ and then :
 - ★ the marginal $f(\underline{x})$ is called **prior** pdf [the marginal $f(\underline{y})$ is not of interest].
 - ★ the conditional $f(\underline{x}/\underline{y})$ is called **posterior** pdf :

$$\hat{x}_B = \arg \max \{ f(\underline{x}/\underline{y}) \}$$

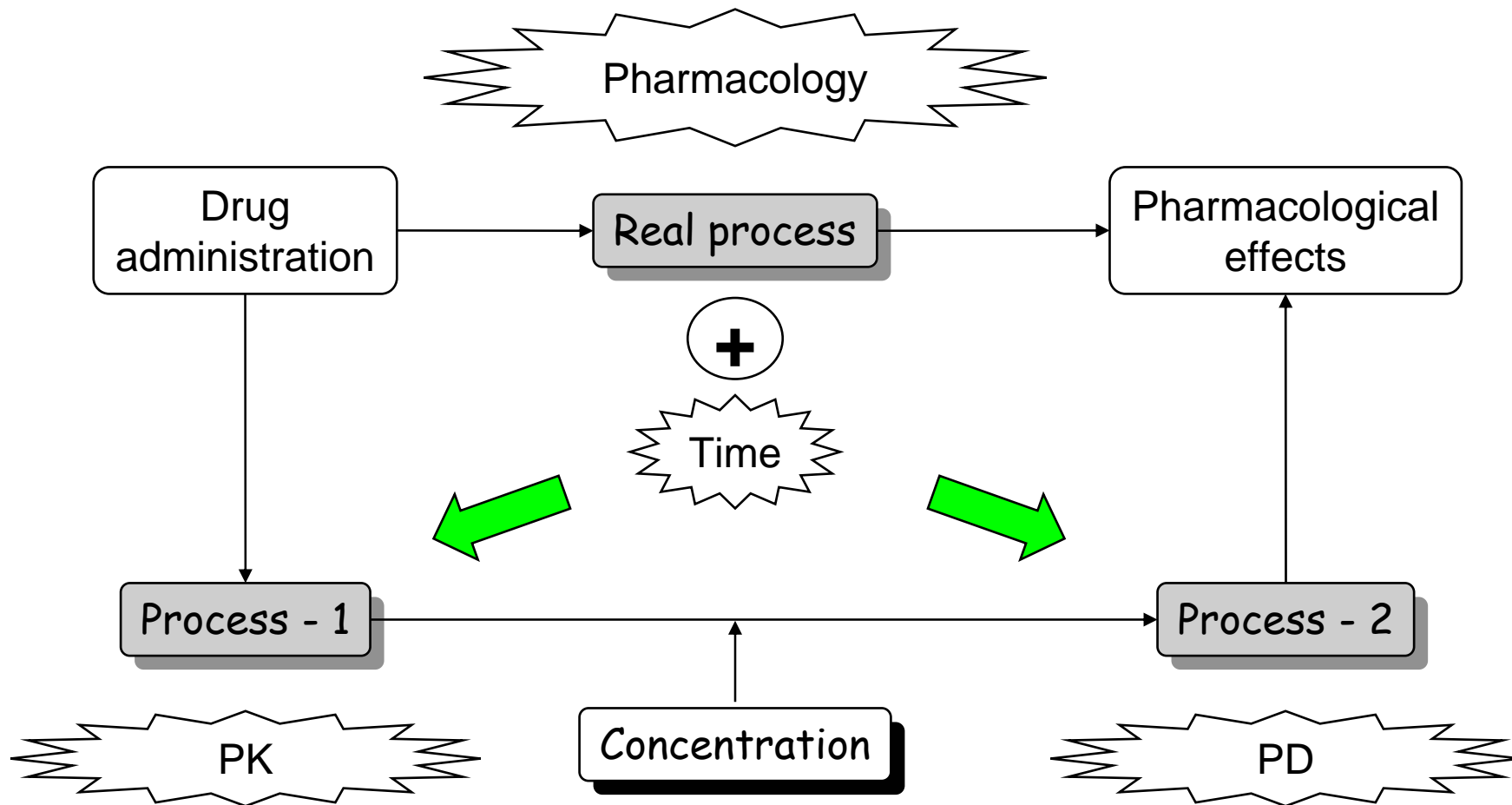


- ★ the conditional $f(\underline{y}/\underline{x})$ leads to the **likelihood** function :

$$\hat{x}_L = \arg \max \{ f(\underline{y}/\underline{x}) \}$$

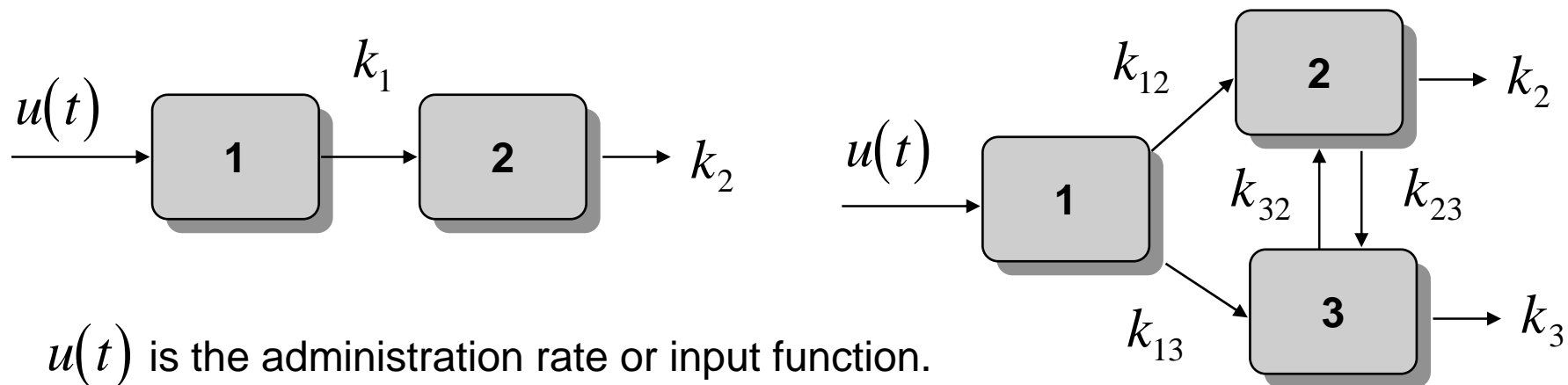


The context



Space and compartments

- **Biological space** : may be well-stirred (homogeneous, ex. blood stream) or under-stirred (heterogeneous, ex. intracellular space).
- **Compartment** : is a biological space that acts kinetically like a distinct, homogeneous, well-stirred amount of material.
- **Compartmental models** : is a model which is made up of a finite number of compartments, and the compartments interact by exchanging material.



Linear modeling and ...

- Draw and connect compartments :

- Volumes of distribution V_i characterizes the size of the compartment (units : volume).
- Transfer rate constants k_{ij} connect compartments among them (units : time⁻¹).

- Mathematic description :

- Modeling each connection pathway by **first-order** unit processes :

$$\left\{ \begin{array}{l} \frac{dq}{dt} = -k_{ij} \cdot q \\ \left[\frac{dq/q}{dt} \right] = -k_{ij} \end{array} \right.$$

The elimination rate from a given compartment is proportional to the amount of material in this compartment

*The **relative** decrease of material from a given compartment per unit time is constant*

- ★ Transfer rate constants k_{ij} are involved in a first-order (linear) unit process.
- ★ For the sampled compartments introduce the volumes of distribution V_i .

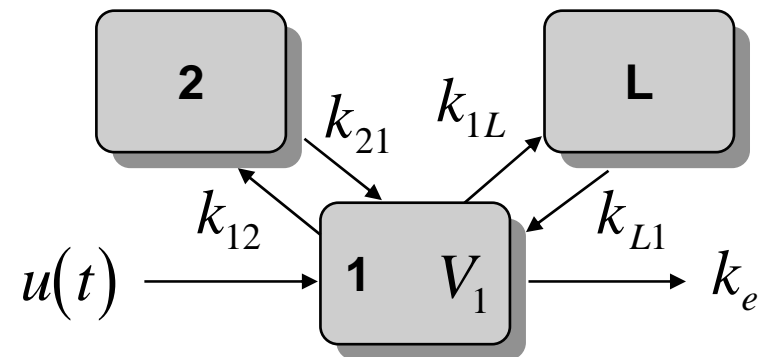
... compartmental configurations

● The commonly used structure : open mammillary models

- ❶ The material is **distributed** and **eliminated from** the central cpt.
- ❷ No exchanges among peripheral cpts.
- ❸ Observations are made in the central cpt.

□ The nbr of parameters in DE is **twice** L :

★ V_1 , k_e and $k_{1i} - k_{i1}$ pairs.



● Note : If peripheral cpts are not sampled, the corresponding V_i cannot be evaluated.

To assess a **fictitious** volume, assume flux equality, then :

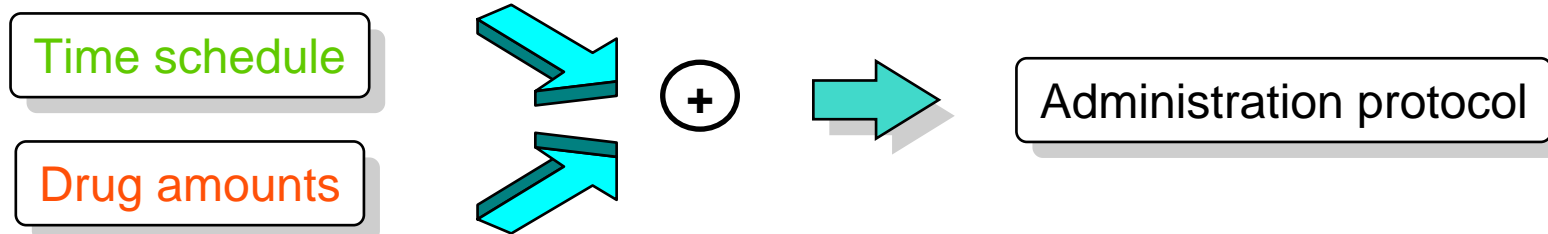
$$V_i = (k_{1i}/k_{i1}) \cdot V_1 \quad i = 2, L \quad \text{and the total} \quad V_T = V_1 \cdot \left[1 + \sum_{i=2}^L (k_{1i}/k_{i1}) \right]$$

● Clearance definitions :

- ★ **Internal** : The capacity of a live organism (e.g. liters of drug distribution volume) to eliminate the drug per time unit : $CL = V_1 \cdot k_e$
- ★ **External** : The proportionality constant between D and its image at output, the area under the time-concentration curve : $CL = (D/AUC)$

● Administration protocols :

- ★ **Intra-** (bolus IV or infusion) and **extravascular** (oral or intramuscular) routes have been considered in **single** or **repeated** dose protocols.
- ★ Factors defining an administration protocol :



Studies during drug development



- PK information is obtained from :

- ★ healthy volunteers (**experimental** PKs, drug development, phases I and II), or
- ★ patients (**clinical** PKs, drug treatment, phases III and IV).

- The problem : Individual PKs characterize both :

- ★ the subject, and
- ★ the drug.

- The solution :

Compile individual PKs to obtain :

- ★ patient characteristics and **pull-out** only the drug properties (ex : high CL, etc)
- ★ drug characteristics and **recognize** patient's status (ex : renal insufficiency, etc)

Classification of problems

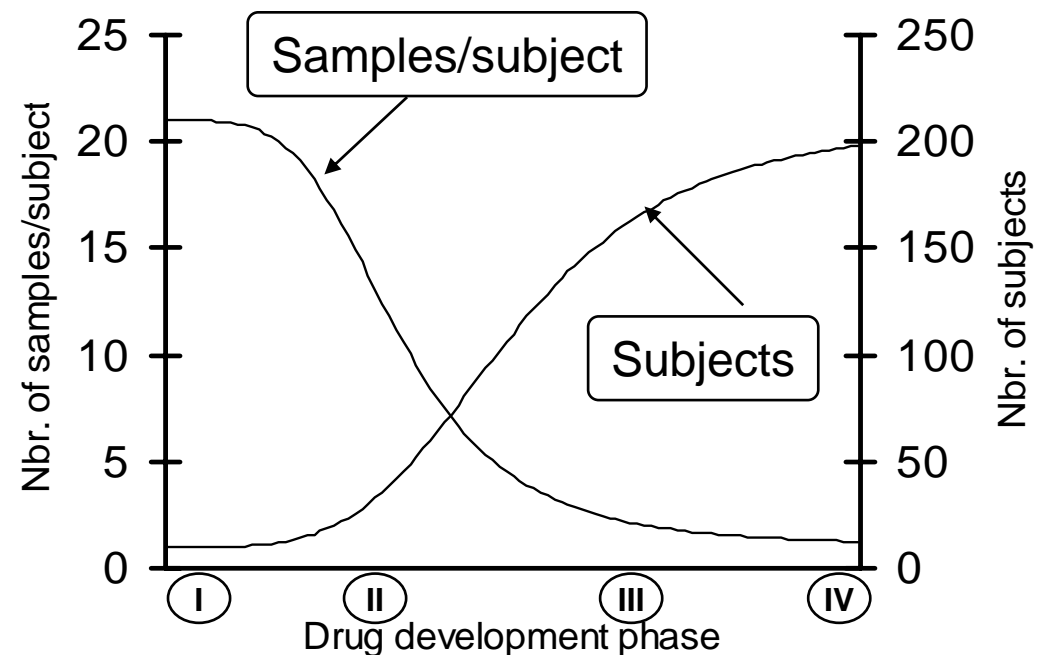
● PK data bases during drug development

□ Phases I, II : Experimental PKs

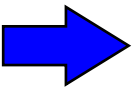
- ★ Individual kinetics well documented,
- ★ **data rich** situation,
- ★ two-stage (**TS**) methods.

□ Phases III, IV : Clinical PKs

- ★ few samples per patient,
- ★ **sparse data** situation,
- ★ single-stage (**SS**) methods.



Density estimation

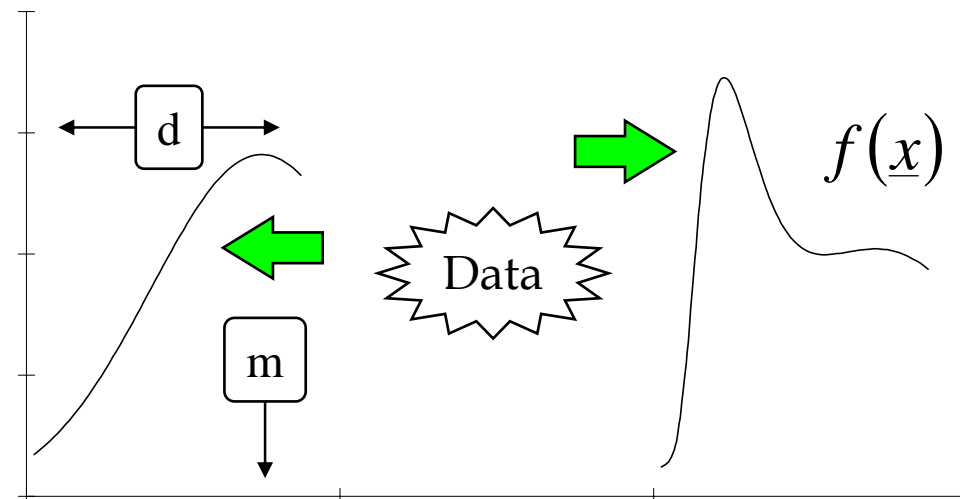
- Density estimation  the construction of an estimate $f(\underline{x})$ of the density function $\varphi(\underline{x})$ from the available data.

- Approaches to density estimation

- **Parametric** : given structure with parameters to be computed from the available data.

Ex : the normal density :

$$\sim N(m, d^2)$$



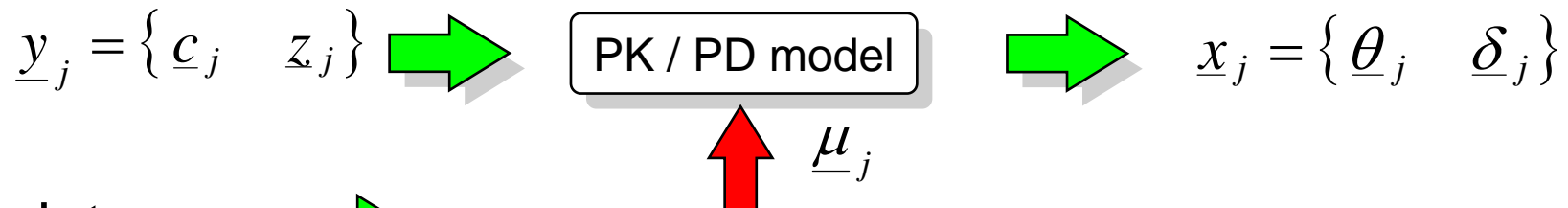
- **Nonparametric** : distribution free of structure and parameters.

Density estimation in PKs

- **Classification** : Cross approaches for density estimation and, TS and SS methods.

	TS	SS
parametric	Normal, Log-normal	NONMEM
nonparametric	Kernel approach	NPML
available data	training data	observed data

- **Training data in TS methods** :



- **Covariates** $\underline{\mu}_j$  demographic, physiological and biological variables commonly available in a well established data base.
Covariates can influence PK and PD processes.

Nonparametric approach in SS

● Non Parametric Maximum Likelihood (NPML)

□ Main features :

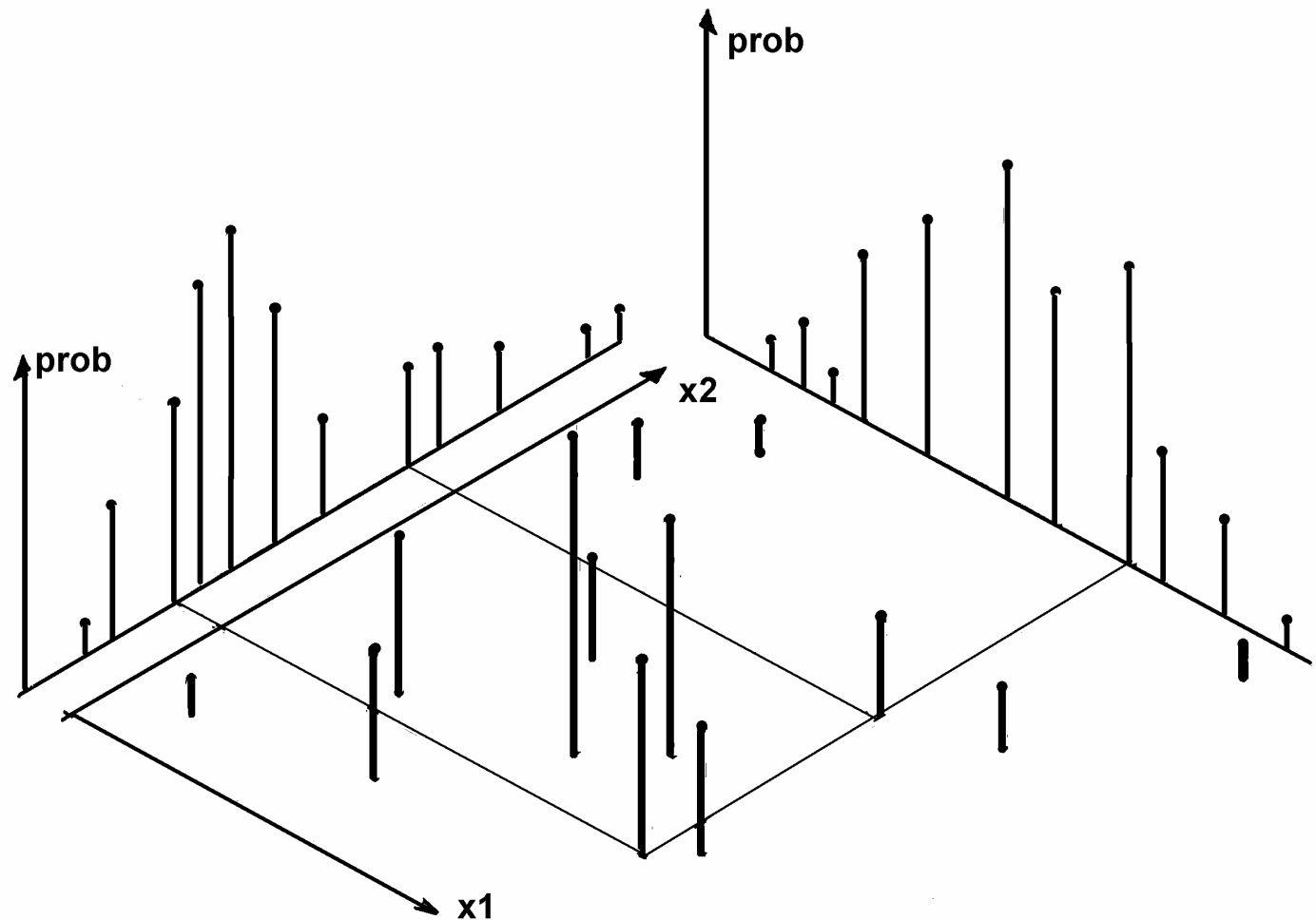
- ★ assumes **exact** knowledge for the measurement error model σ^2 .
- ★ estimates the interindividual variability in a **discrete** form (even for continuous random variables), by supplying a set of geometrical characteristics. They are defined by :
 - ① locations in the parameter space, and
 - ② associated weights.

□ Practical use :

- ★ accepts missing data,
- ★ considers covariates as corrupted by a random error with small variance,
- ★ automatically derives marginal and conditional densities.

3D graph for NPML

- Discrete form :
 - ★ $p = 2 : x_1, x_2$
- Locations :
 - ★ (x_1, x_2) coordinates of spikes.
- Weights :
 - ★ Heights of spikes.
- Univariate prob :
 - ★ Marginal distributions.

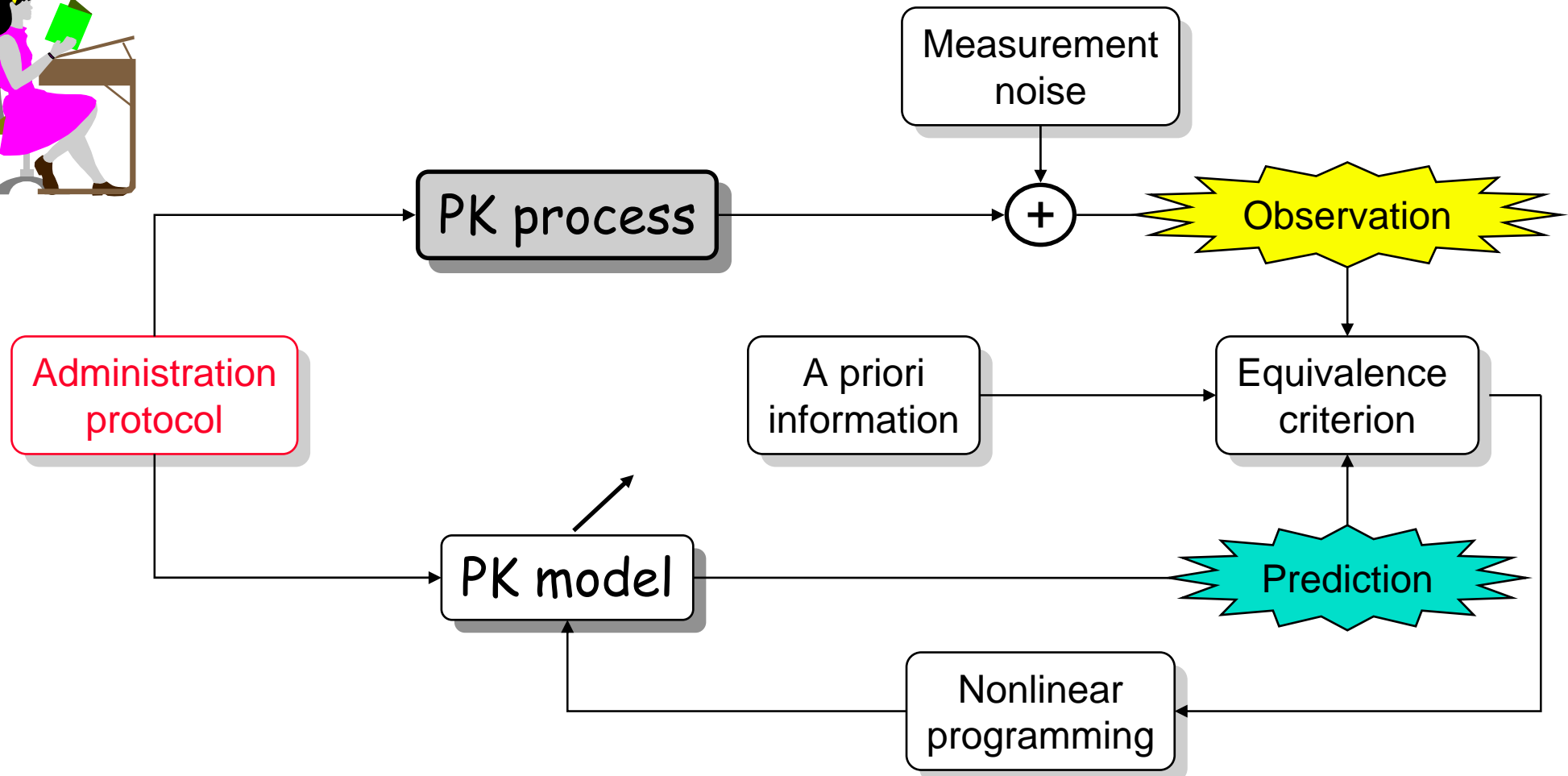


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Dosage adjustment



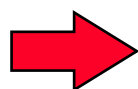
Covariates and variability - Gentamycin

● Data:

- ★ $n = 113$ new-borns,
- ★ infusion of 2 to 3 mg,
- ★ $m = 1$ or 2 samples / child.
- ★ PC: [0.76 , 4.26 kg],
- ★ every 12 h,
- ★ AG: [26 , 41 weeks],
- ★ for 1 to 3 d,

● PK results :

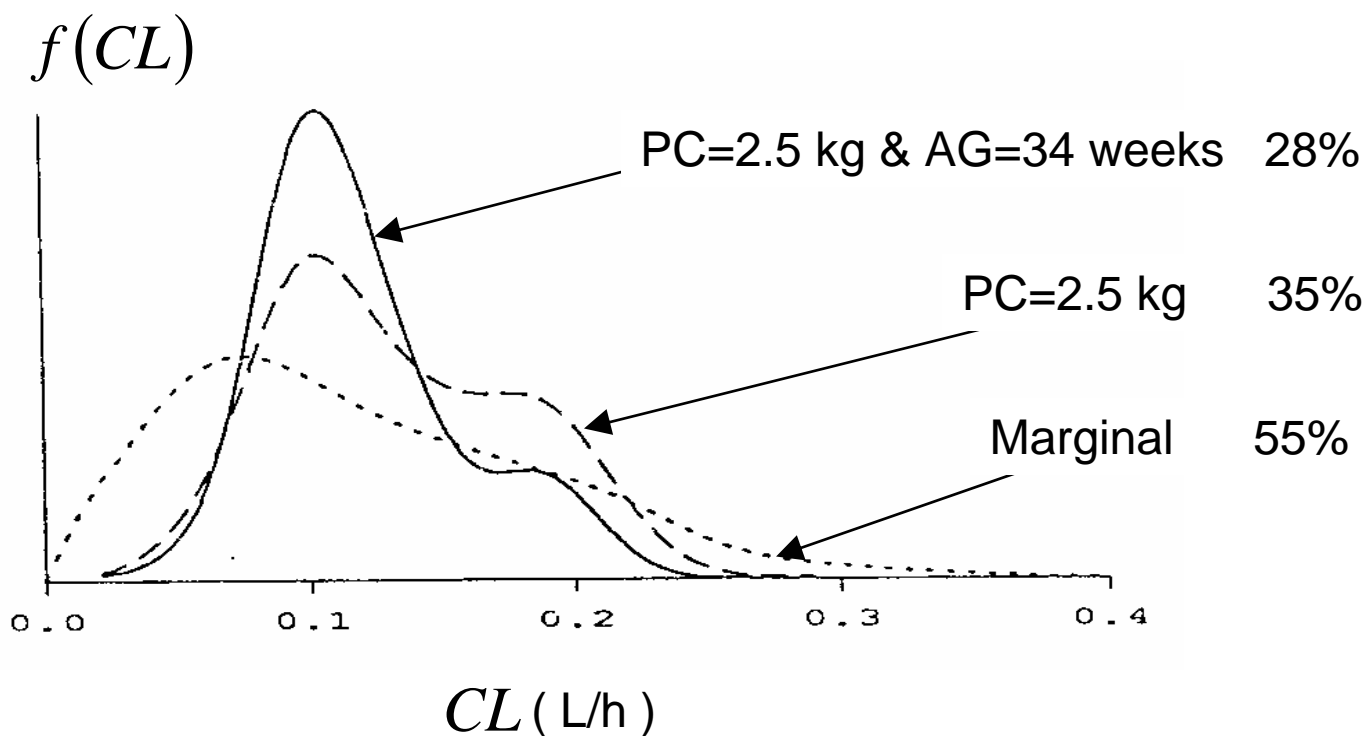
	\bar{x}	s	%
CL (L/h)	0.116	0.063	55
V (L)	1.1	0.51	46



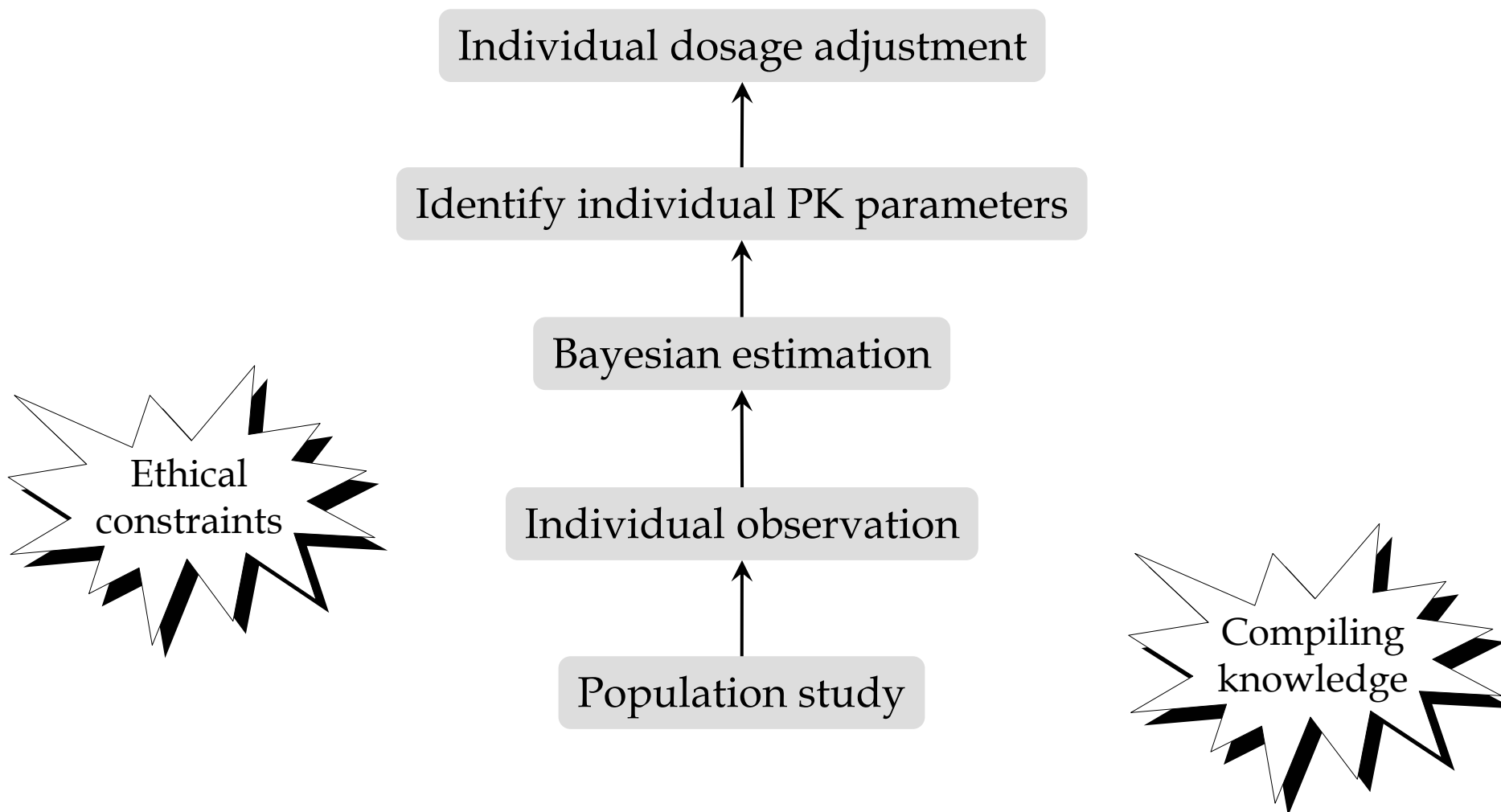
High inter-individual variability,
individualize PK parameters !

Conditional density (CL)

- The density of CL is influenced by PC & AG covariates



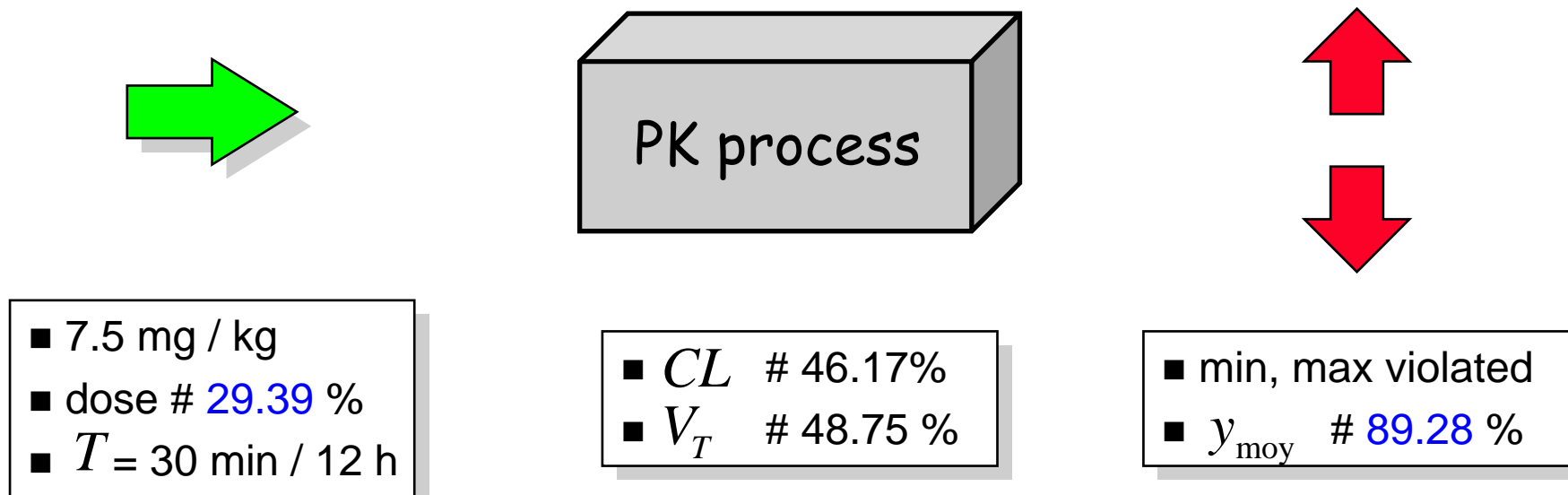
Functional flowchart



Before the dosage adjustment...

● Goal : Safely administer drugs having :

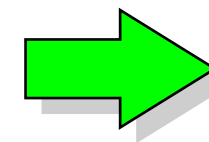
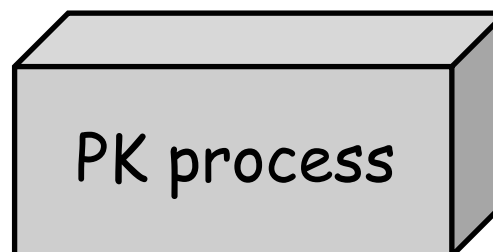
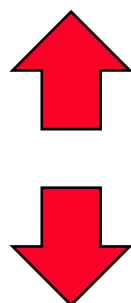
★ **narrow** therapeutic window + **wide** inter-individual dispersion.



The observed variability is an **image** of the inter-individual dispersion

... after the dosage adjustment

Obtain individual PK parameters and, then use highly variable inputs to **offset** the dispersion of the process parameters

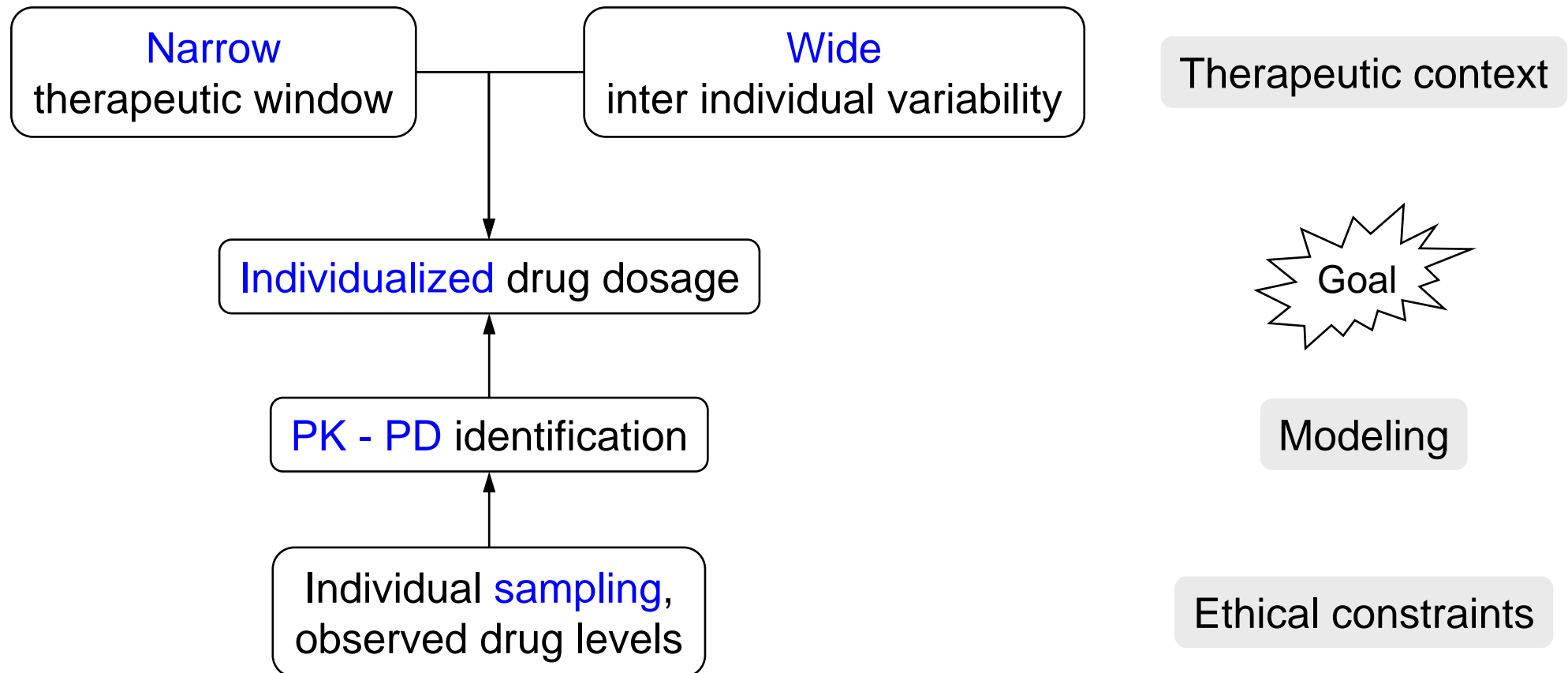


- load dose # 49.39 %
- maint. - # 46.19 %
- $T = [1-8] \text{ h} / [8-48] \text{ h}$

- CL # 46.17%
- V_T # 48.75 %

- min, max respected
- $y_{\text{moy}} < 5 \%$

Why and how dosage adjustment



Naive dosage adjustment



- Hypotheses :
 - linear PK systems,
 - concentrations are directly related to the individual pharmacological response.
- Goal : concentration profile inside the therapeutic **window** (assumed known !).
- Possible solutions :

	Time schedule	Drug amounts
1st problem	<i>Set</i>	Compute
2nd #	Compute	<i>Set</i>

- ★ the 1st problem has a simple solution using the **PK linearity** property ;
- ★ the 2nd problem is more complex and requires tools from **control theory**.

Optimal conditions

- **Optimality (1) :** For a given route and schedule of drug administrations, the adjustment will be said **optimal** if :

★ minimum levels $y_{\min} > C_{\text{eff}}$

★ mean levels $y_{\text{moy}} = C_{\text{ave}}$

★ maximum levels $y_{\max} < C_{\text{tox}}$



for **each administration**.

- **Steps :**

❶ Set C_{eff} C_{ave} C_{tox} ;

❷ Identify individual PK parameters \underline{x} ;

❸ **Propose** a time-schedule for drug administration ;

❹ Specify the t_{\min} and t_{\max} for each administration ;

❺ Compute : $y_{\min} = y_{Mi}(t_{\min}, \underline{x})$ $y_{\text{moy}} = y_{Mi}(\underline{x})$ $y_{\max} = y_{Mi}(t_{\max}, \underline{x})$.

The solution

● Computation :

□ Using linearity, **factorize** y_{\min} y_{moy} y_{\max} expressions as :

$$\star y_{\min} = D_{\min} \cdot g(t_{\min}, \underline{x}) > C_{\text{eff}}$$

$$\star y_{\text{moy}} = D_{\text{moy}} \cdot g(\underline{x}) = C_{\text{ave}}$$

$$\star y_{\max} = D_{\max} \cdot g(t_{\max}, \underline{x}) < C_{\text{tox}}$$

□ **Solve** these inequalities to obtain the optimal amounts D_{\min} , D_{moy} and D_{\max} .

□ Actual choice :

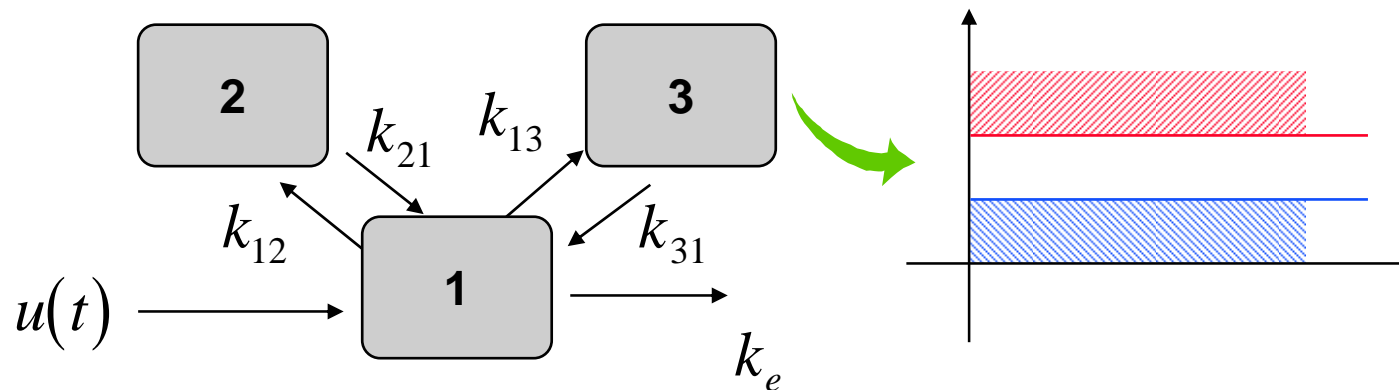
$$D_{\min} < D_{\text{OPT}} \approx D_{\text{moy}} < D_{\max}$$

Warning :

If no reliable solution can be found (ex : $D_{\min} > D_{\max}$) a new time-schedule is proposed and the procedure is **repeated**.

Options :

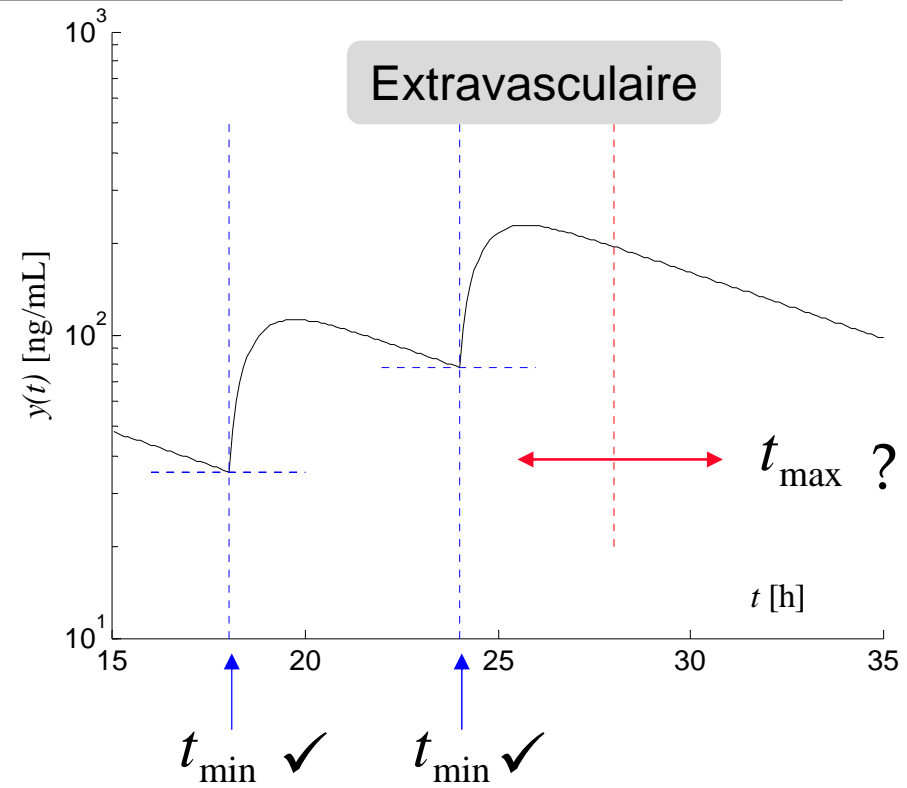
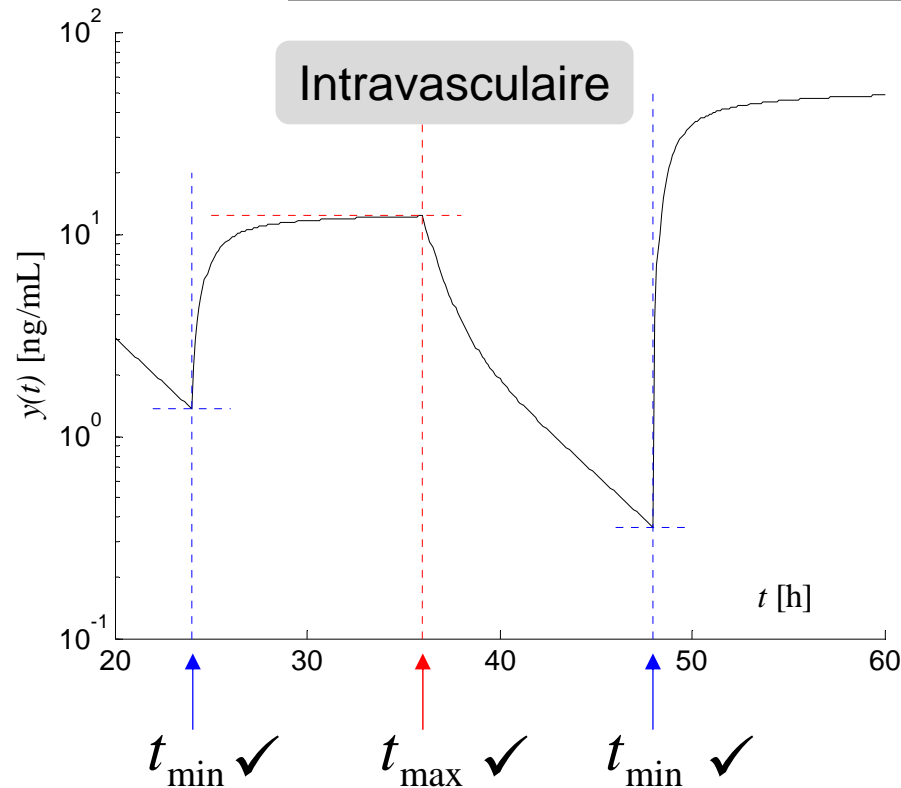
- Possible association of constraints with a peripheral compartment, as for the central.



- The basic approach is adapted to :

- ★ **long-term** treatment (static) : optimize **at the stationary state**, and
- ★ **emergency** treatment (dynamic) : adapt **as soon as possible**, (ex : loading and maintenance amounts).

Determine times of extrema



- t_{\min} before a new administration,
- t_{\max} at the end of infusion,

- t_{\min} before a new administration,
- compute t_{\max} as solution of a **transcendental** equation (using iterative algorithms).

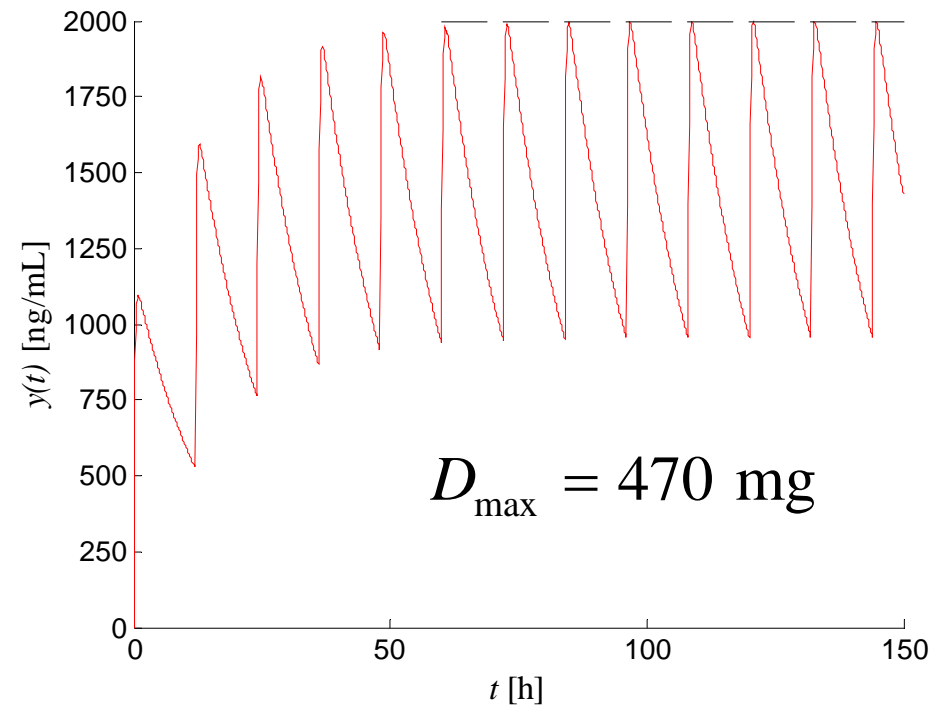
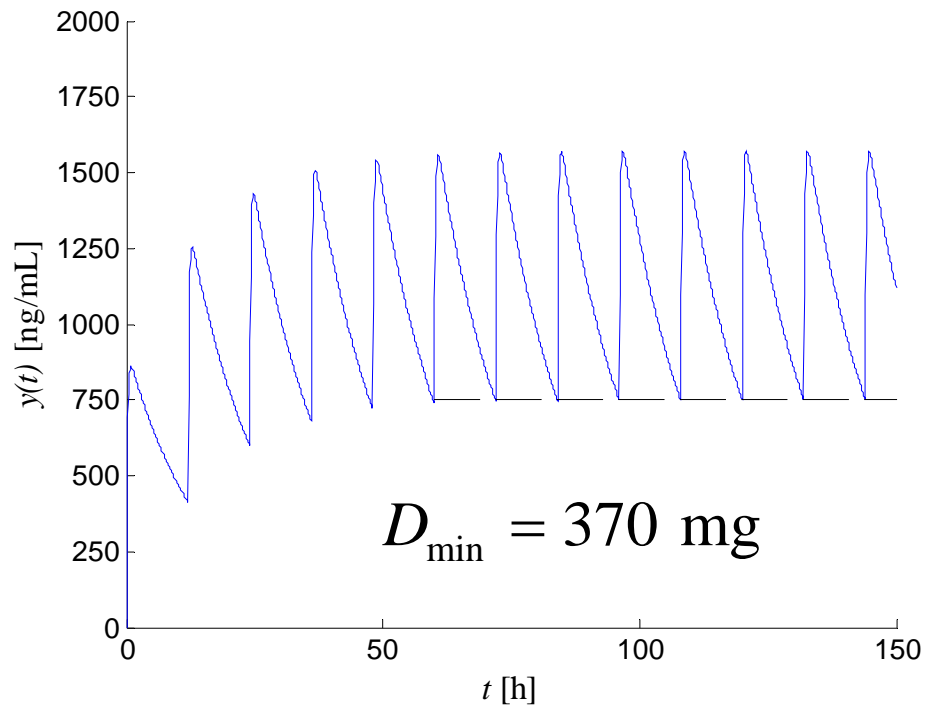
Static dosage

● Let :

$$1^{\circ}) C_{\min} = 750 \text{ ng} \cdot \text{mL}^{-1} \quad C_{\max} = 2 \text{ } \mu\text{g} \cdot \text{mL}^{-1} ,$$

$$2^{\circ}) V_1 = 406 \text{ L} \quad k_e = 0.067 \text{ h}^{-1} \quad k_a = 4.85 \text{ h}^{-1} ,$$

3^o) 12-h regular dosage schedule.



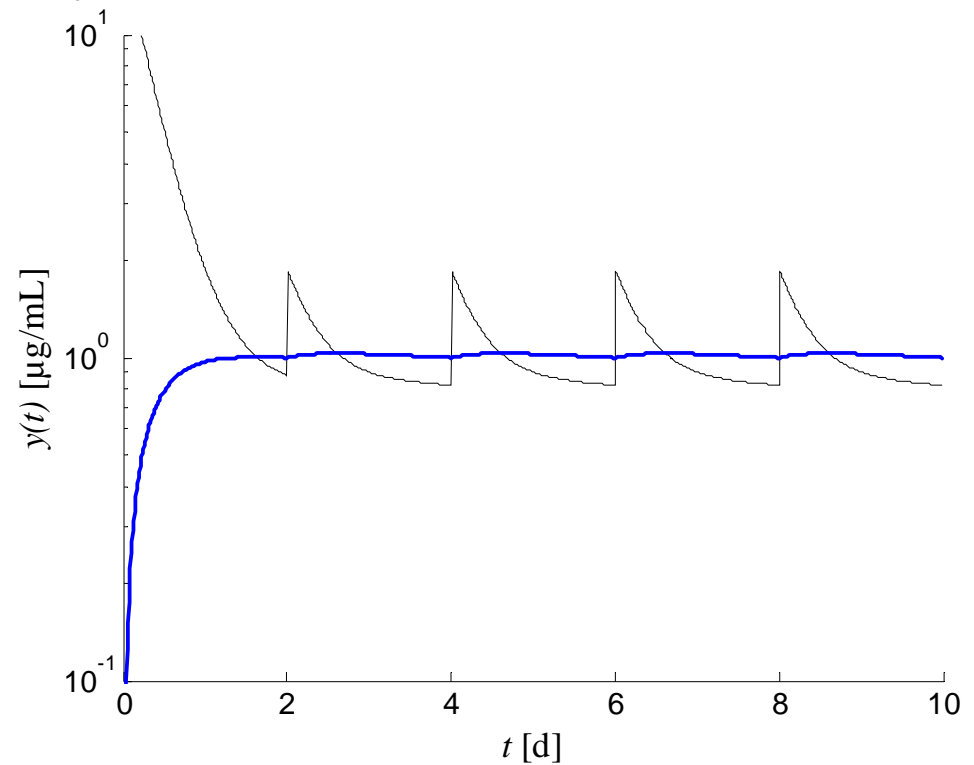
Dynamic dosage



- Let :
- 1°) $C_{\min} = 1 \mu\text{g} \cdot \text{mL}^{-1}$ in the **peripheral** compartment,
 - 2°) $V_1 = 400 \text{ L}$ $k_e = 0.509 \text{ d}^{-1}$ $k_{12} = 2.17 \text{ d}^{-1}$ $k_{21} = 0.165 \text{ d}^{-1}$,
 - 3°) 15-min infusions every 2 days.

Administer in the **central** cpt :

- a loading dose of 7.192 g at d0,
- a transition dose of 390 mg at d2,
- maintenance doses of 415 mg / 2 d.



Real data - Methotrexate

- **Goal** : For an individual (i), reach $P = 15 \mu\text{M} \cdot \text{L}^{-1}$ at the steady state by infusion.

- ① **Compute** an infusion rate using the mean population :

$$CL_{\text{moy}} = 7.167 \text{ L} \cdot \text{h}^{-1} \quad R_0 = CL_{\text{moy}} \cdot P = 0.1075 \text{ mM} \cdot \text{h}^{-1}$$

- ② **Begin** the infusion for the i -th

individual with R_0 : *Discrepancy*
{ P target / actual levels }.

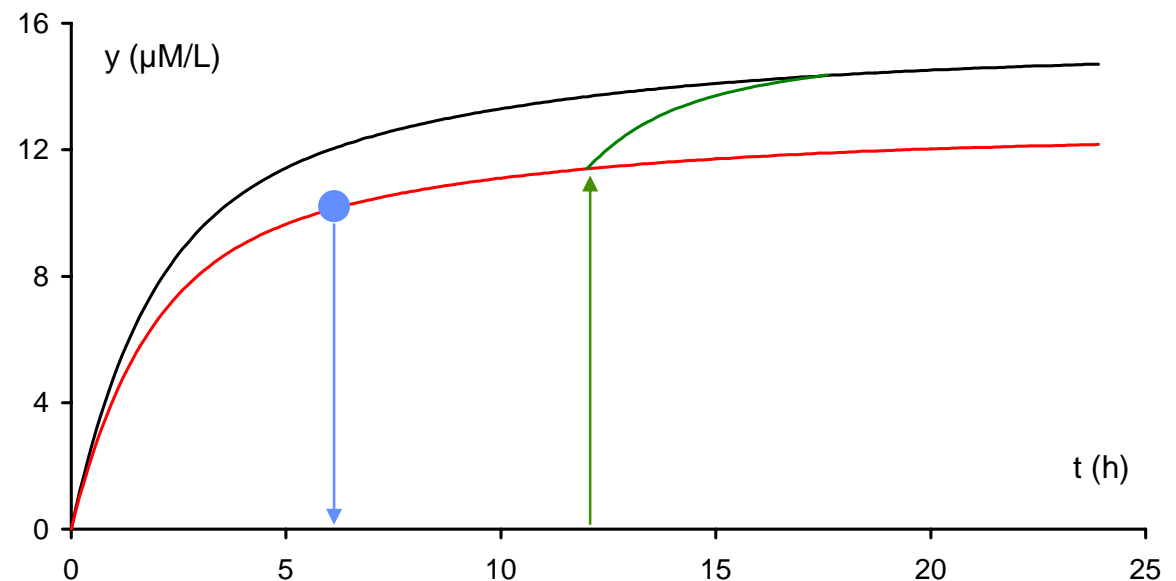
- ③ **Sample** at 6 h, assay, estimate

using MAP $CL_i = 8.675 \text{ L} \cdot \text{h}^{-1}$

Compute $R_i = 0.134 \text{ mM} \cdot \text{h}^{-1}$

- ④ **Stop** the infusion with R_0 at 12 h

and begin a new one with R_i .



Real data - Amikacin

- Intravenous infusion. Std protocol : Dose = 7.5 mg/kg, $T = 30$ min.
- Goals : $y_{\min} < C_{\text{toxA}} = 3$ $y_{\text{moy}} = C_{\text{ave}} \approx 8$ $y_{\max} < C_{\text{toxR}} = 25 \mu\text{g} \cdot \text{mL}^{-1}$

- ① MAP identification : 525 mg, 3 samples :

$$V_1 = 8.39 \text{ L} \quad k_e = 1.145 \text{ h}^{-1}$$

$$k_{12} = 1.38 \text{ h}^{-1} \quad k_{21} = 0.833 \text{ h}^{-1}$$

- ② Observation interval :

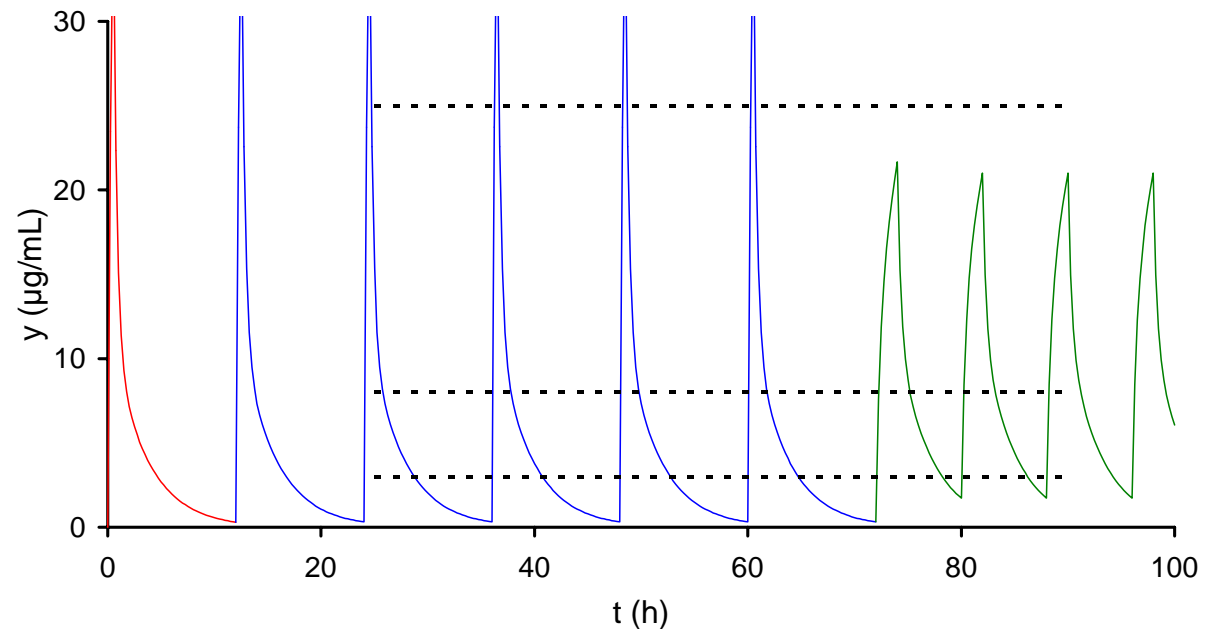
$$\square [T = 0.5 \text{ h} / 12\text{h}] * 6$$

- ③ Adjusted dosage at 72 h :

$$\square \text{Schedule} : [T = 2\text{h} / 8\text{h}]$$

$$\square \text{Load and maintenance}$$

doses = 658 and 615 mg.





Outline



- ① Modeling, simulation and control
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- ⑤ Optimal control in clinical PKs : Minimal transient time

Tracking a reference signal

● Administration protocol :

- ★ schedule : $0 < t_1 < \dots < t_k < \dots < t_N = T$  set
- ★ amounts : $D_1 \quad \dots \quad D_k \quad \dots \quad D_N$  unknown

★ T is the treatment duration and N the number of administrations.

● Optimality (2) :

□ Compute $D_k, k = 1, \dots, N$ such that $y_{\bullet}(t)$ follows the reference signal $s_R(t)$.

★ solve the NLP problem : $\hat{\underline{D}} = \arg \min \left\{ \int_0^T [y_{\bullet}(t, \underline{D}) - s_R(t)]^2 \cdot dt \right\}$

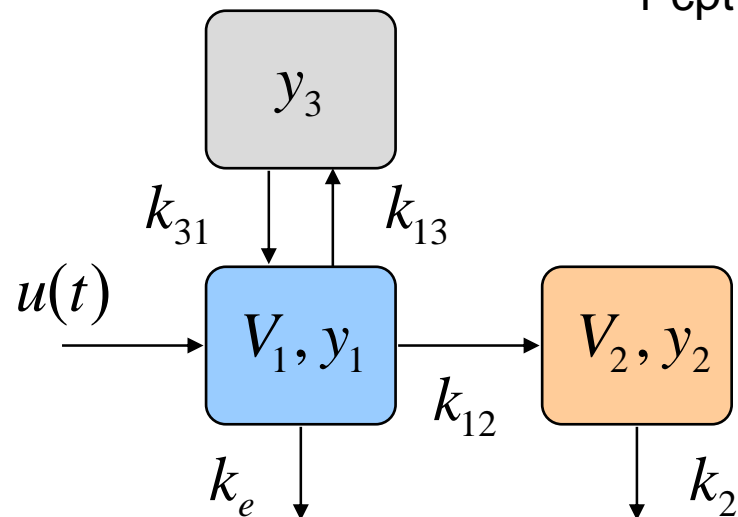
★ associated with possible constraints on drug levels.



Multi - output system identification

● Analysis of time-concentration curves of ISDN :

- administration : 2.5 mg infused during 1.75 h,
- sampling : 15 blood samples over 8 h,
- analytical assay : ISDN and 2-ISMN levels obtained by capillary GC,
- structural cpt model : - 2 cpt for ISDN (y_1 for the central, y_3 for the peripheral cpt),
- 1 cpt for 2-ISMN (y_2).



$$\frac{dy_1}{dt} = -(k_e + k_{12}) \cdot y_1 - k_{13} \cdot (y_1 - y_3) + \frac{u(t)}{V_1}$$

$$\frac{dy_2}{dt} = k_{12} \cdot \frac{V_1}{V_2} \cdot y_1 - k_2 \cdot y_2$$

$$\frac{dy_3}{dt} = k_{31} \cdot (y_1 - y_3)$$

Estimation of parameters and fitting

- Obtain predicted levels by numerical integration (Runge-Kutta).
- Estimate unknown model parameters by using the multi - output MLE criterion.

$$\frac{1}{V_1} = 0.0134 \text{ L}^{-1}$$

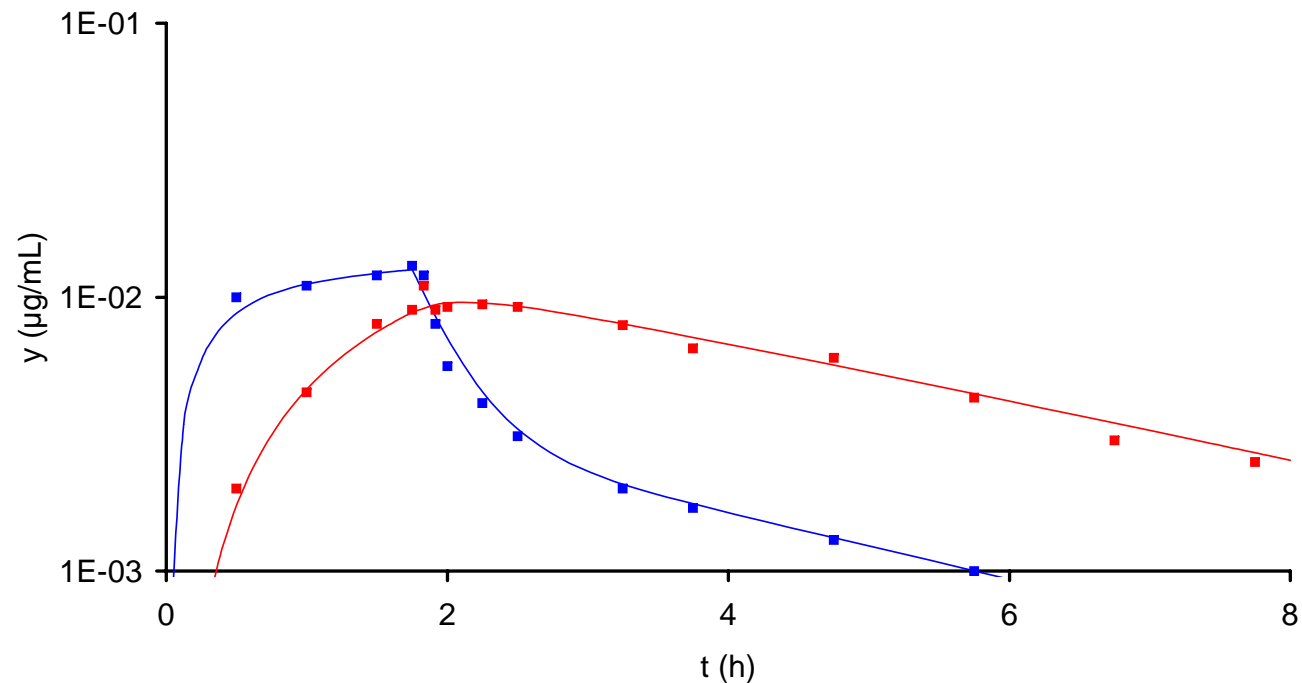
$$k_e + k_{12} = 1.914 \text{ h}^{-1}$$

$$k_{12} \cdot \frac{V_1}{V_2} = 0.692 \text{ h}^{-1}$$

$$k_2 = 0.4 \text{ h}^{-1}$$

$$k_{13} = 1.151 \text{ h}^{-1}$$

$$k_{31} = 0.473 \text{ h}^{-1}$$

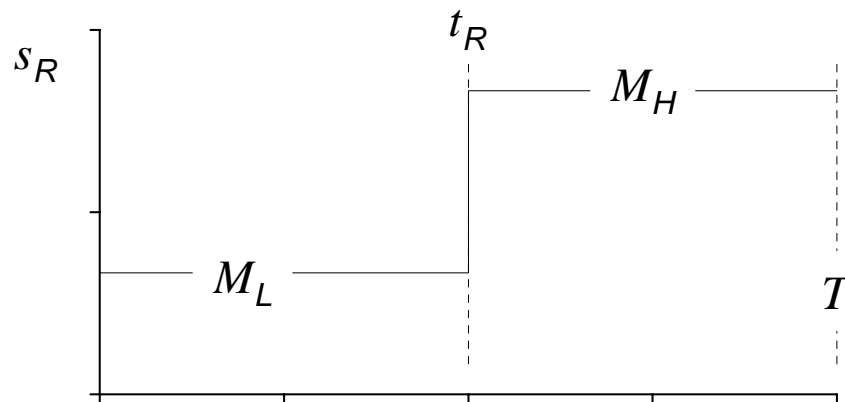


$$RMSE(y_1) = 7\%, \quad RMSE(y_2) = 13.5\%$$

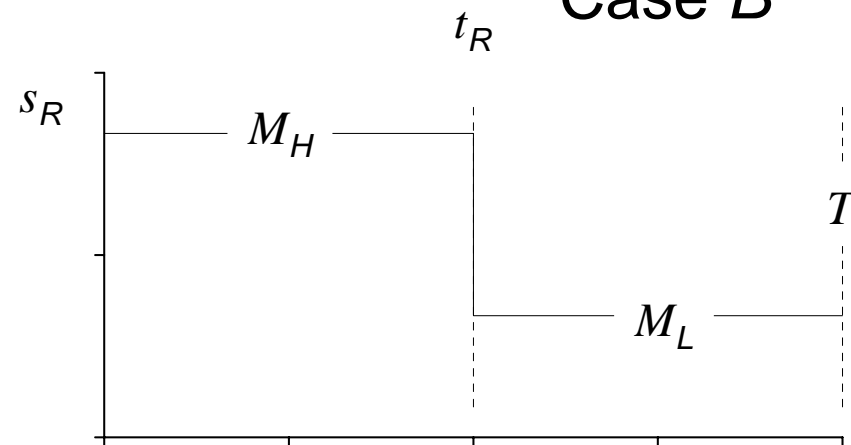
Compute the optimal doses

- Control metabolite levels : $y_{\bullet} \equiv y_2$
- Schedule characteristics : $T = 24 \text{ h}$, $t_k - t_{k-1} = 2 \text{ h}$, $k = 1, \dots, 12$
- Reference signal : $[M_L, M_H] = [20, 50 \text{ ng} \cdot \text{mL}^{-1}]$ $t_R = T/2$

Case A



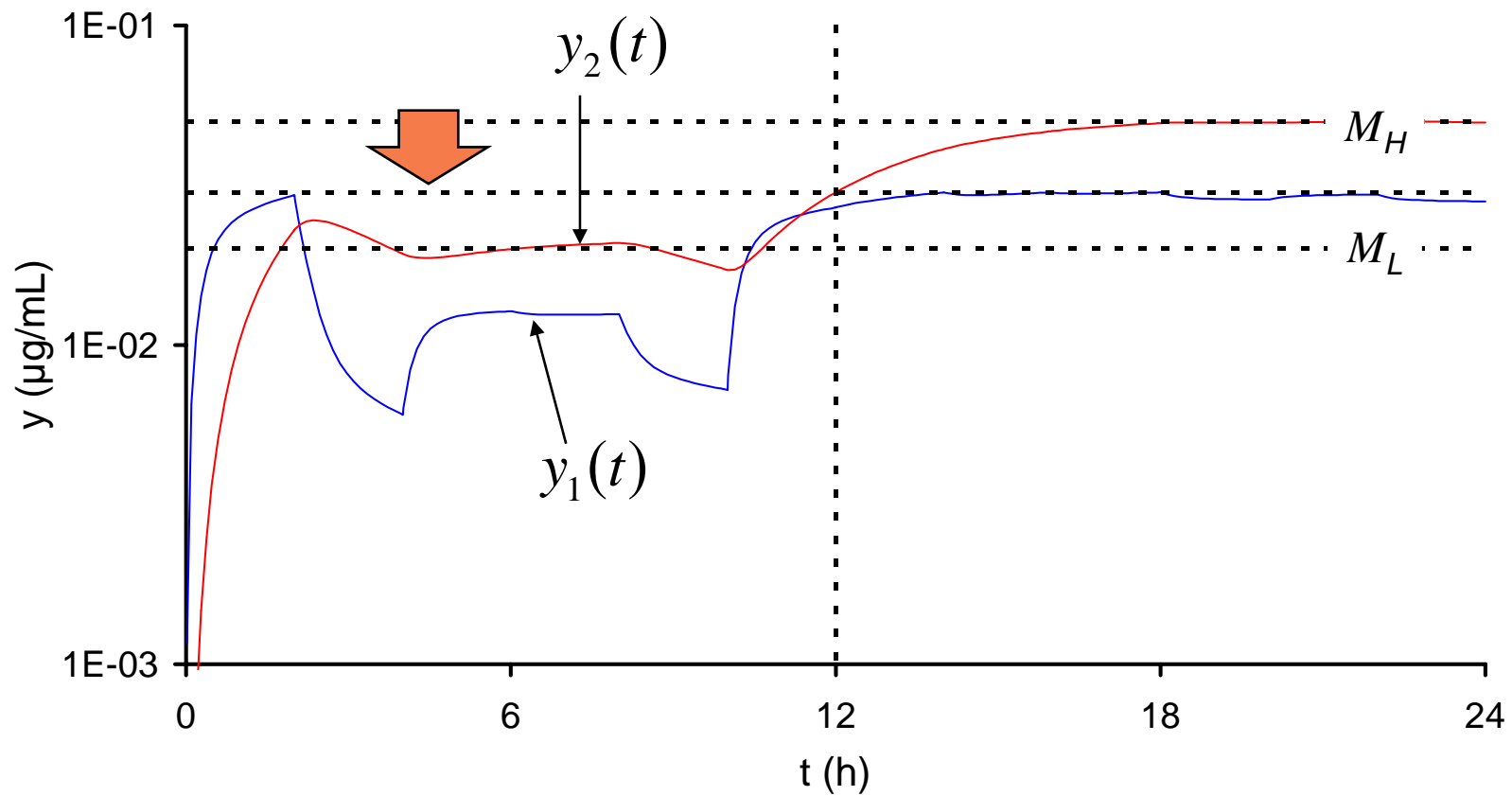
Case B



□ Constraint on y_1 levels : $y_1(t) \leq 30 \text{ ng} \cdot \text{mL}^{-1}$

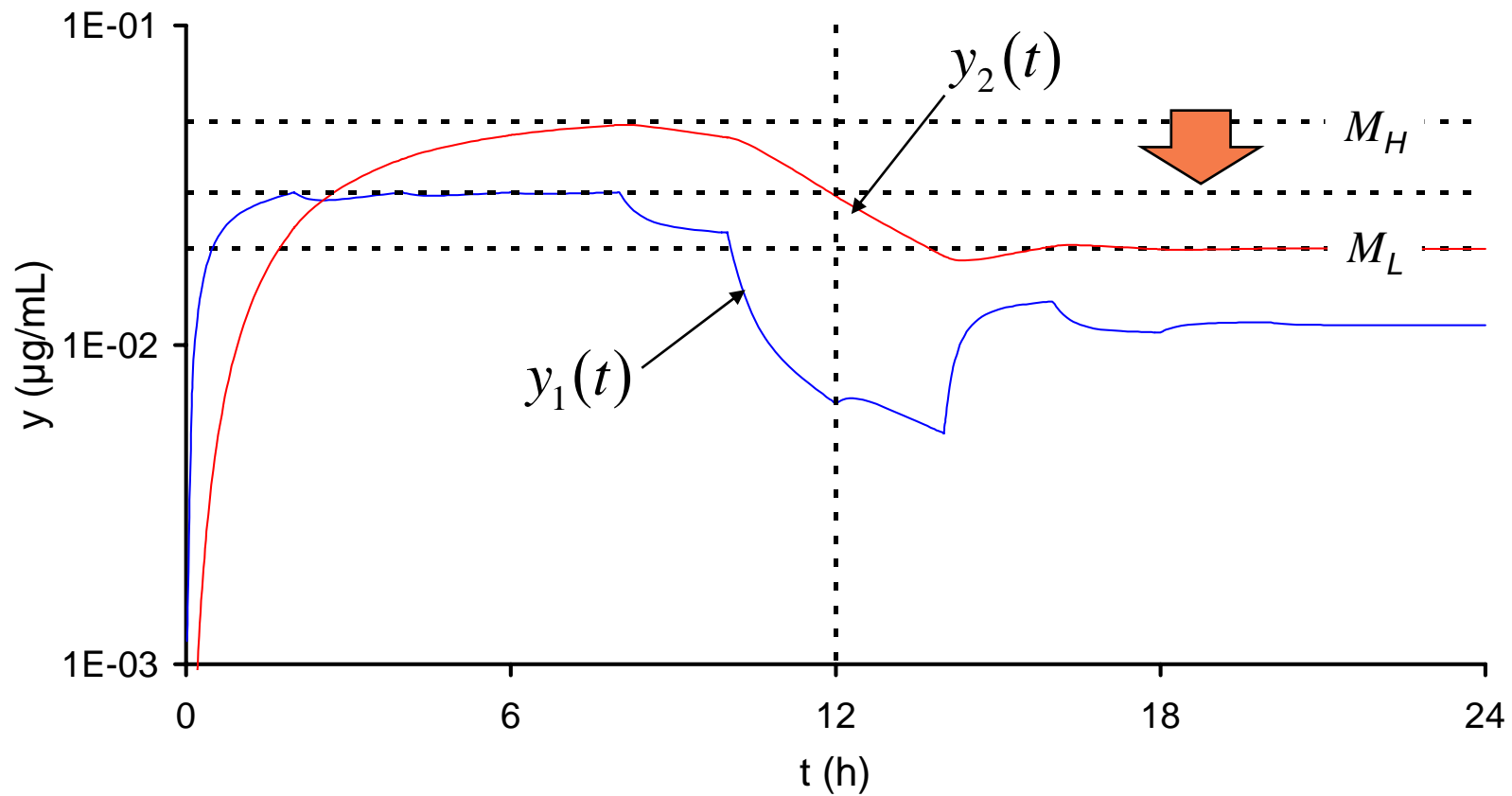
Adjusted levels - Case A

- $y_1(t)$ levels are constrained at 2 h and, from 14 to 18 h.



Adjusted levels - Case B

- $y_1(t)$ levels are constrained from 2 up to 8 h.



Optimal drug inputs

● Total amount :

❶ Case A : 82.37 mg

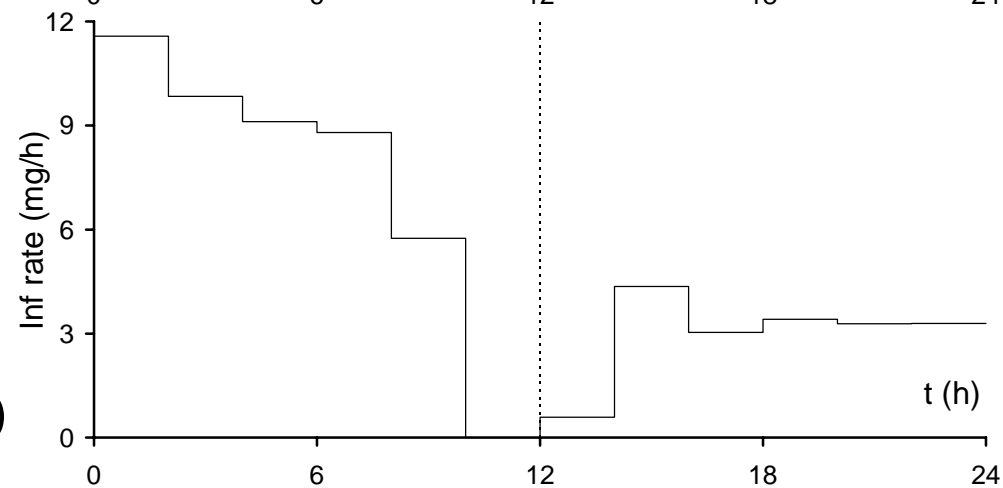
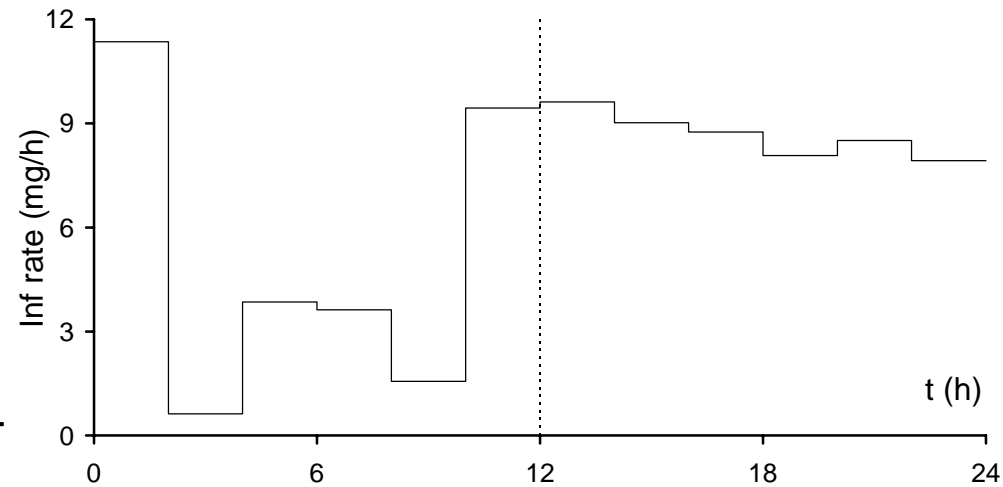
$$M_L \longrightarrow M_H$$

$$\int_0^T [y.(t, \underline{D}) - s_R(t)]^2 \cdot dt = 1.084$$

❷ Case B : 63.04 mg

$$M_H \longrightarrow M_L$$

$$\int_0^T [y.(t, \underline{D}) - s_R(t)]^2 \cdot dt = 1.890$$



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The mathematical model

- PKs described by ordinary differential equations :

$$\dot{\underline{y}}(t) = A(\underline{x}) \cdot \underline{y}(t) + \underline{c}(\underline{x}) \cdot u(t)$$

- 1 L : nbr. of compartments,
 - 2 $\underline{y}(t)$: the state vector,
 - 3 $u(t)$: scalar control (dosage regimen),
 - 4 \underline{x} : the PK parameters, assumed known from identification.
- 1 State : $y_j(t) \geq 0, \quad j = 1, \dots, L$
 - 2 Control : $C_{\text{inf}} \leq u(t) \leq C_{\text{sup}}$
- 1 intra-vascular : $0 \leq u(t) \leq R_{\text{max}}$.
 - 2 extra-vascular : $0 \leq u(t) \leq D_{\text{max}}$.

The state space

- Pairs of states define graphically
- $\underline{y}(t)$ are coordinates in the state space
- Motion of $\underline{y}(t)$

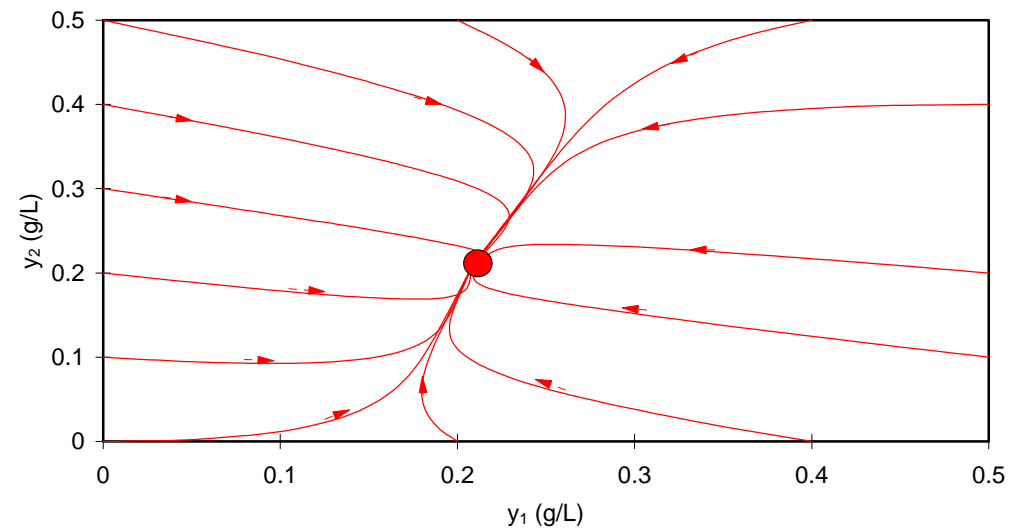
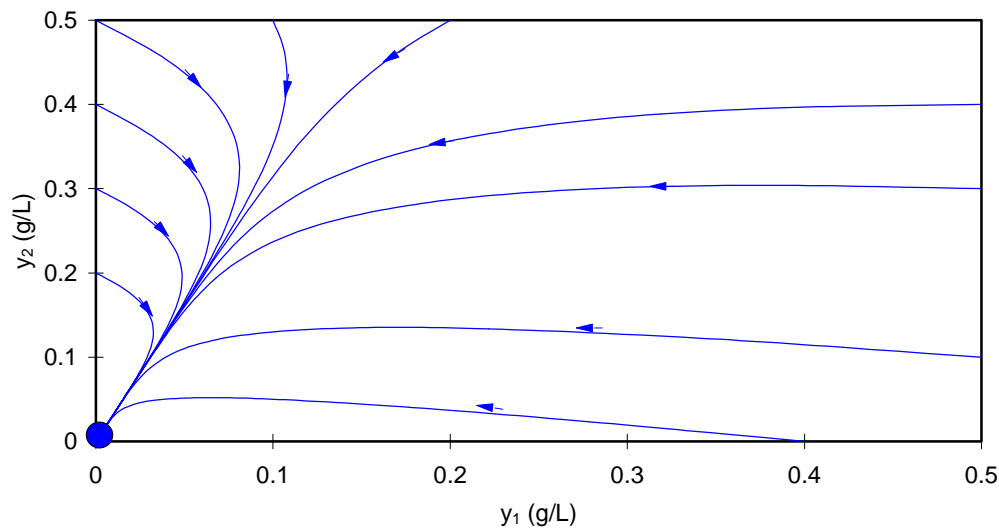
: *state space.*

: *describing point.*

: *state trajectory.*

$u(t) = 0$ ● : the origin

$u(t) = R_{\max}$ ● : the steady-state



The fastest transition

● Controllability and optimality :

□ PK systems are stable and controllable.

□ Controllability :

★ define first the **reachable** area and then, by means of an appropriate $u(t)$,

★ drive the system from \underline{y}_i to \underline{y}_f in a finite time : $t_0 = t_f - t_i$.

● Optimality (3) : From \underline{y}_i reach \underline{y}_f **in minimal time**, i.e. :

Optimize the functional $u(t)$: $\hat{u}(t) = fcn \min\{t_0\}$

Goal - 3

● Optimal control :

★ It is a bang-bang process : $\hat{u}(t)$ lies either on C_{inf} , or on C_{sup} .

★ The number of switches between C_{inf} and C_{sup} is equal to $L - 1$.

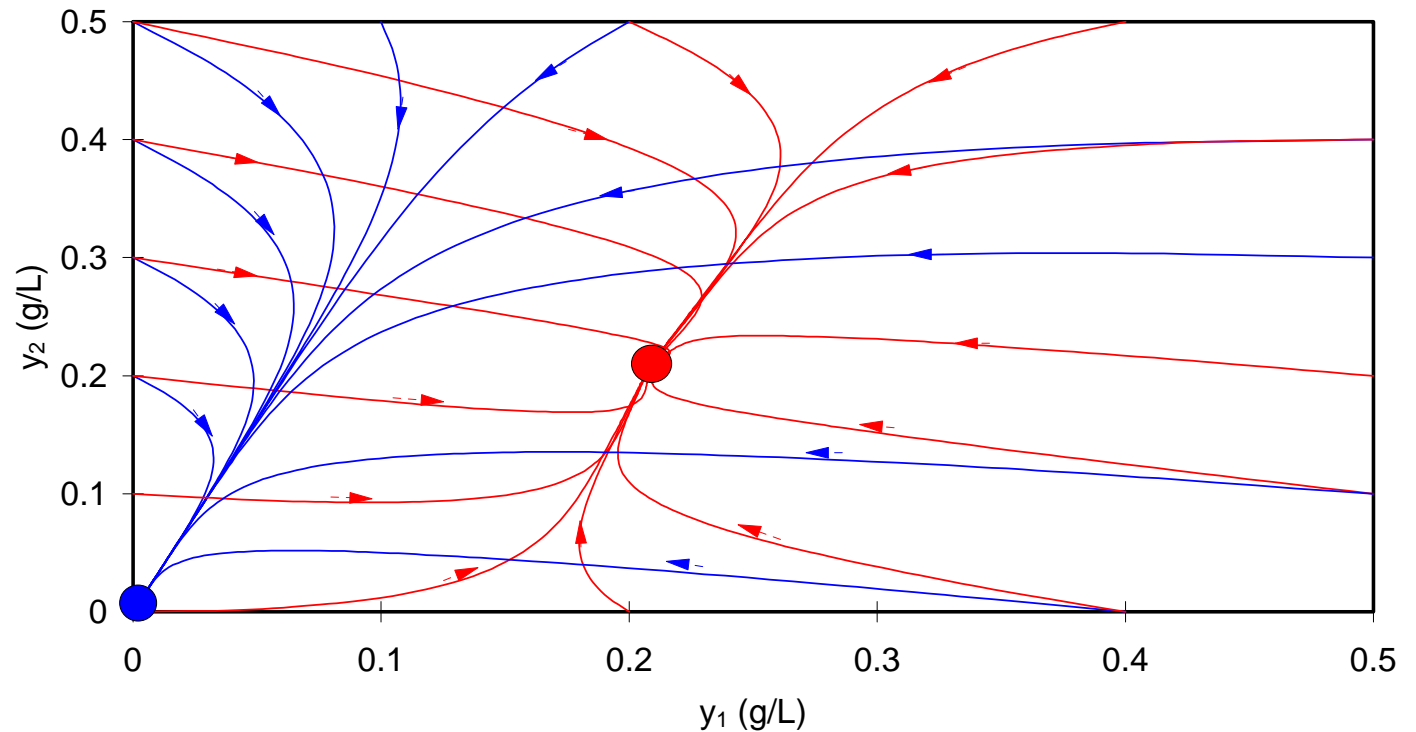
The system trajectories

- The trajectories are parametric forms which depends on the time : the elapsed time between two points of the trajectory is **known**.
- Read the transient time in order to reach prescribed levels in a **minimal** time.

□ Combination of :

$$u(t) = 0$$

$$u(t) = R_{\max}$$



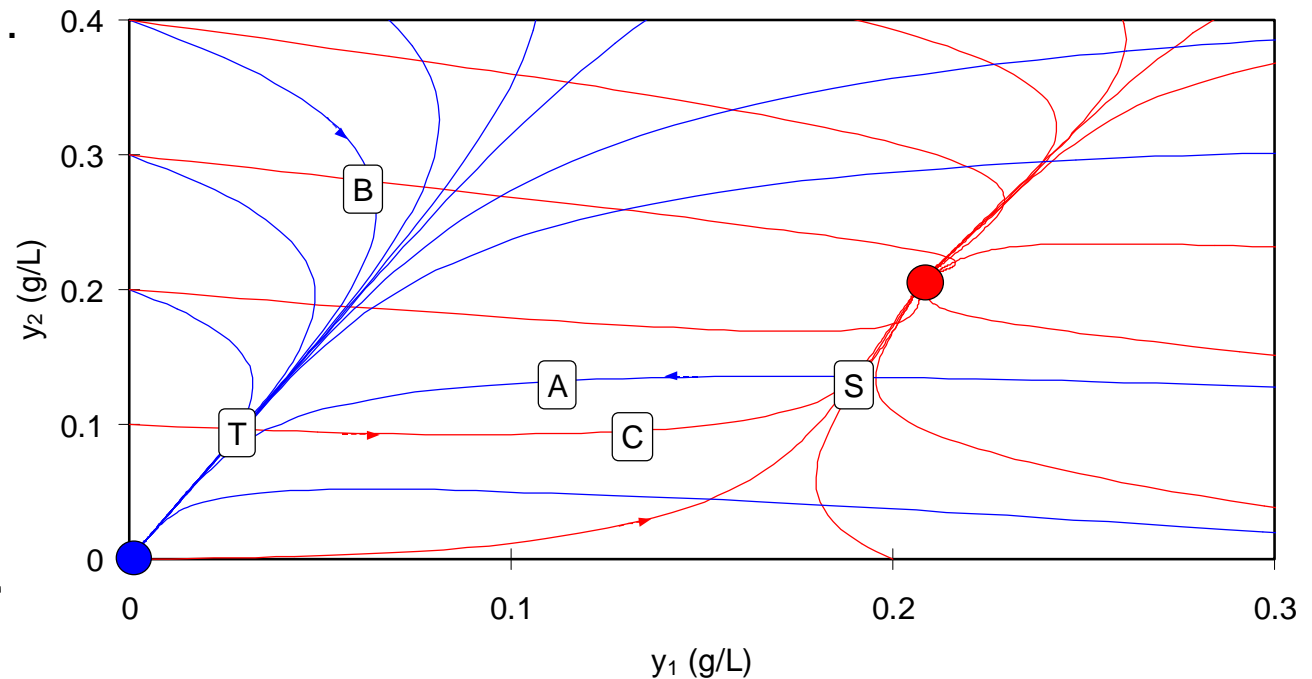
Performing the fastest transition

● Reach A from the origin :

- Mark the trajectories : ❶ from the origin to ● ; and ❷ from A to ● .
- Find intersection S and read the t_S .
- Infuse at R_{\max} , until t_S .

● Reach C from B :

- Mark the trajectories :
 - ❶ from B to ● ; and
 - ❷ from C to ● .
- Find T and read t_T .
- Infuse at R_{\max} , from t_T until C is reached.

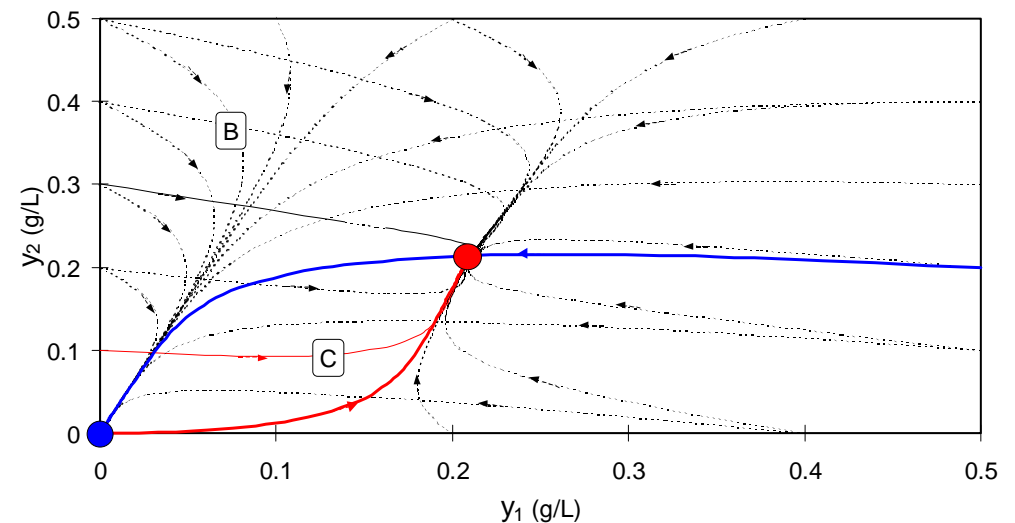
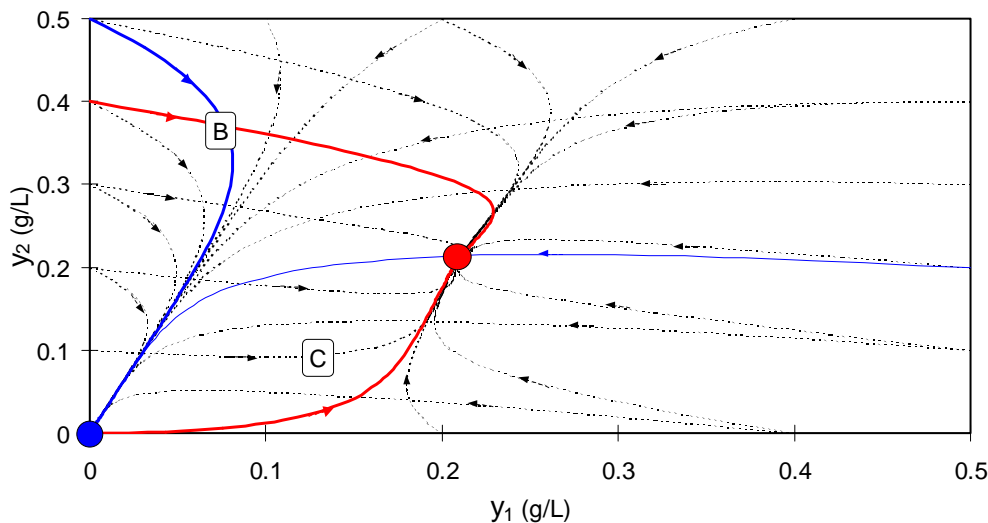


The reachable area

- Definition :** The **largest** closed domain in the state plane bounded by the trajectories going through :
 - 1°) \underline{y}_i , and obtained by the minimal and maximal infusion rates ;
 - 2°) the origin, and obtained by the maximal infusion rate ;
 - 3°) the steady state, and obtained by the minimal infusion rate.

C is reachable from B

B is not reachable from C



Optimal control - example

- Two compartment linear model :

➔ 1 switching time t_s

$$R_{\max} = 2 \text{ g} \cdot \text{h}^{-1}$$

- Estimated PK parameters :

$$V_1 = 11.51 \text{ L}$$

$$k_e = 0.695 \text{ h}^{-1}$$

$$k_{12} = 0.175 \text{ h}^{-1}$$

$$k_{21} = 0.230 \text{ h}^{-1}$$

- Goal :

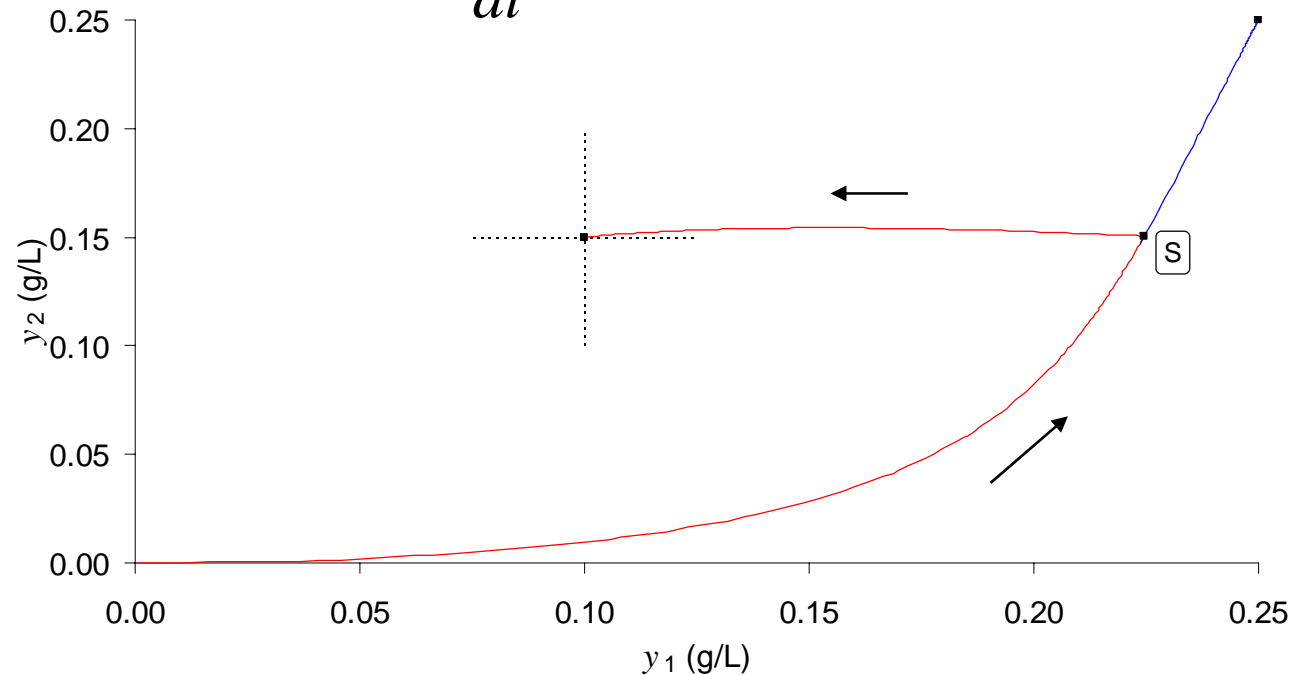
From the origin reach :

$$(0.10, 0.15) \text{ g} \cdot \text{L}^{-1}$$

$$y_1(t) \geq 0.07 \text{ g} \cdot \text{L}^{-1}$$

$$\frac{dy_1}{dt} = -(k_e + k_{12}) \cdot y_1 + k_{12} \cdot y_2 + \frac{u(t)}{V_1}$$

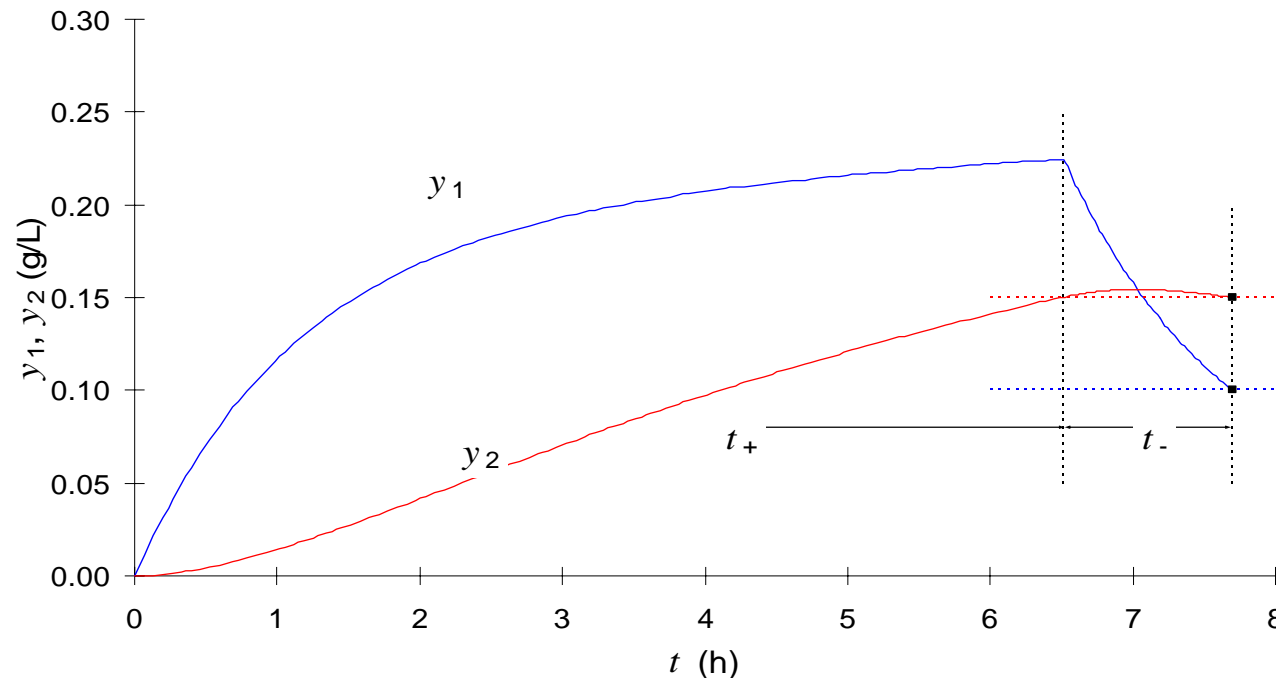
$$\frac{dy_2}{dt} = k_{21} \cdot (y_1 - y_2)$$



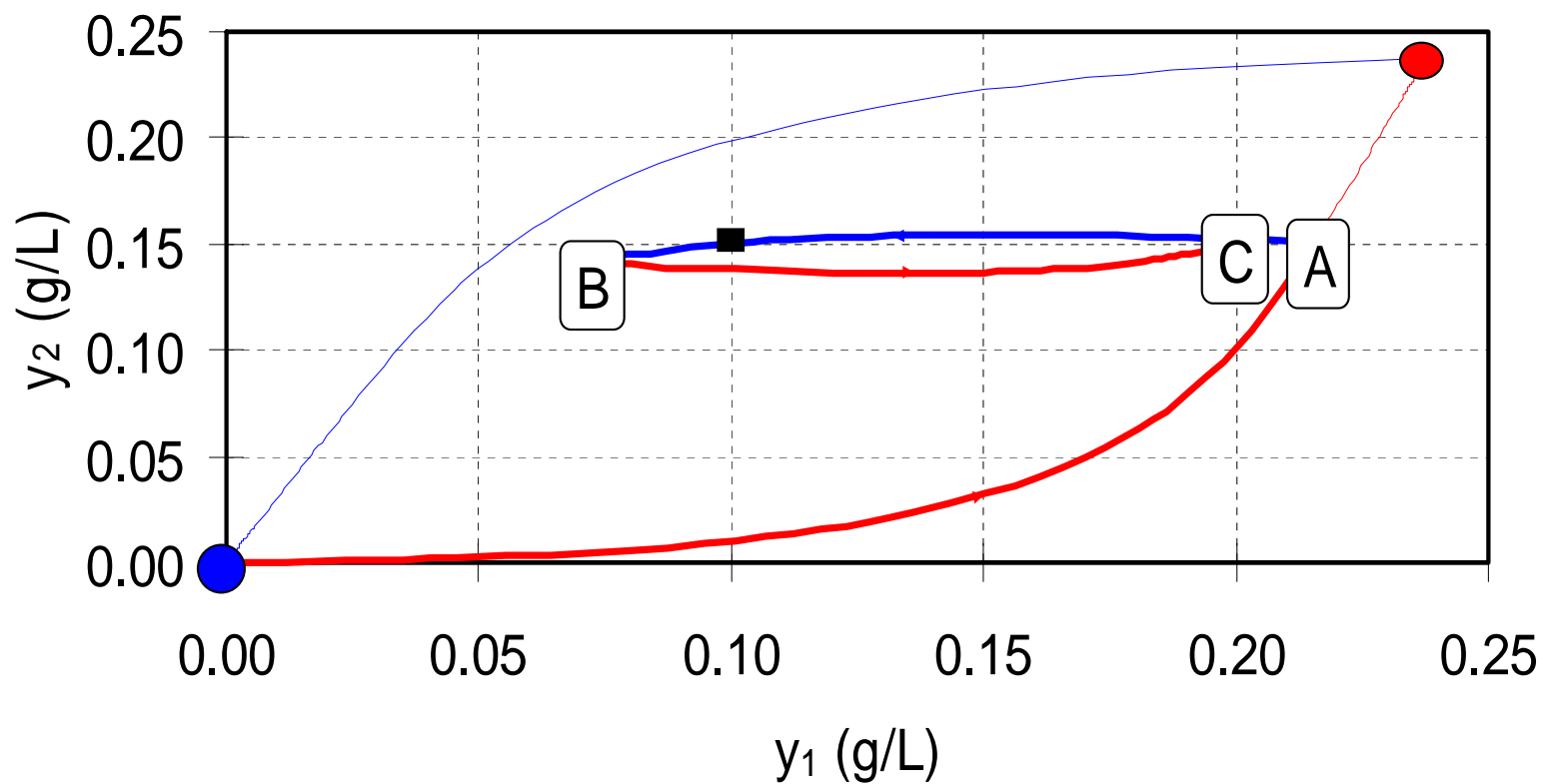
The optimal time-courses

● The optimal control :

- Intravenous infusion at $R_{\max} = 2 \text{ g} \cdot \text{h}^{-1}$ with : $t_s = t_+ = 6.52 \text{ h}$ $t_- = 1.18 \text{ h}$
- $t_0 = t_+ + t_- = 7.70 \text{ h}$ is the fastest transition from $(0,0) \rightarrow (0.10,0.15) \text{ g} \cdot \text{L}^{-1}$



Repeated optimal control



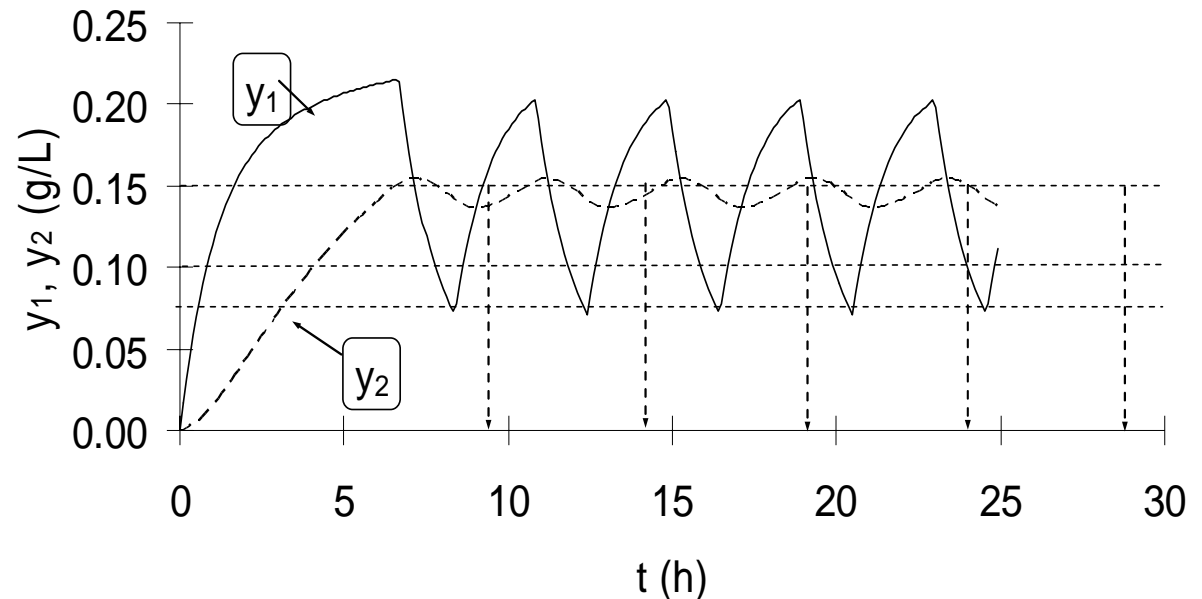
The optimal time-courses

- Intravenous infusion :

$$R_{\max} = 2 \text{ g} \cdot \text{h}^{-1}$$

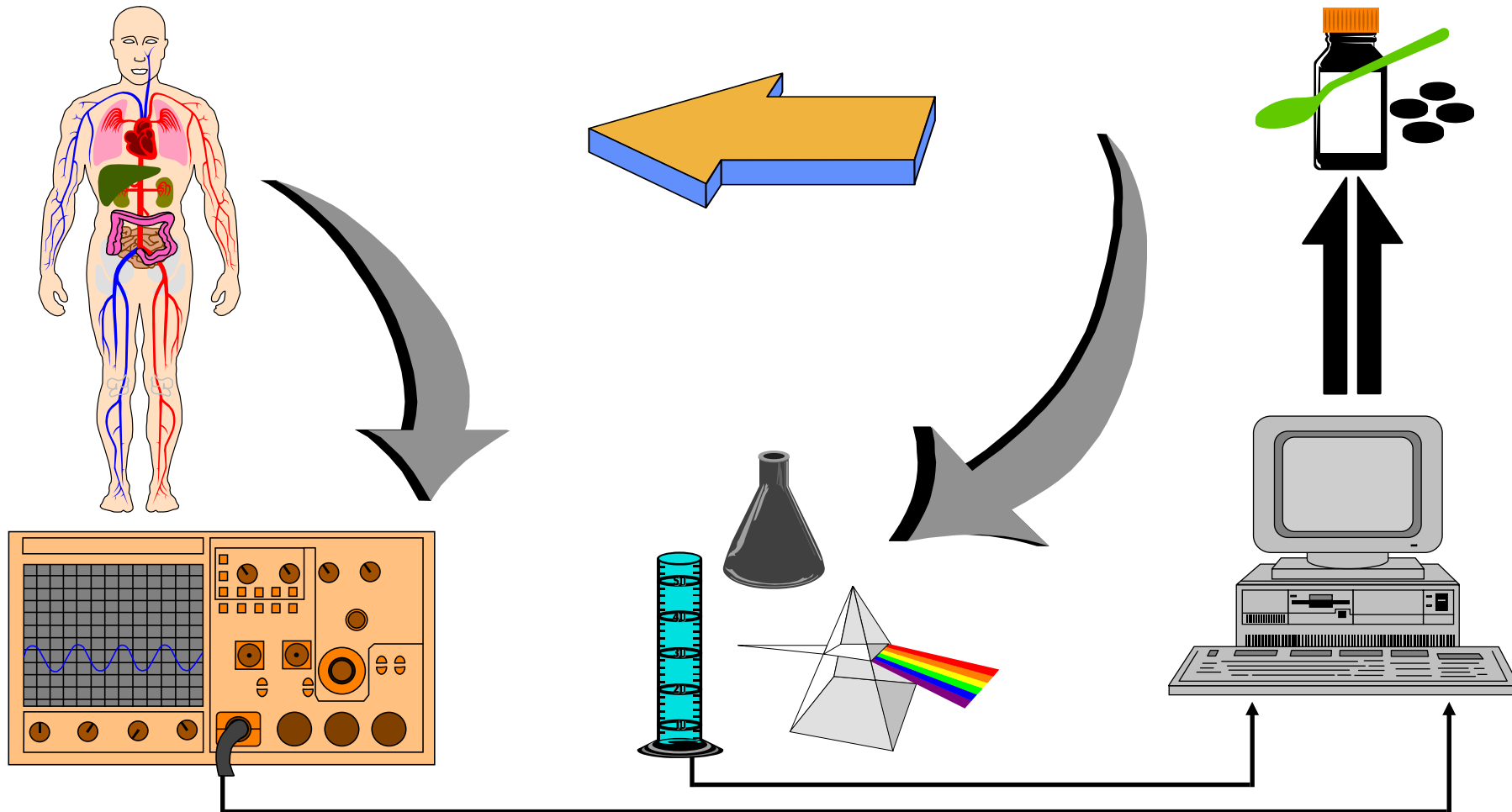
$$t_S = 6.69 \text{ h} \quad t_0 = 7.77 \text{ h}$$

- After the first period, administer R_{\max} every 4 h, with infusions of 2.5 h of duration.

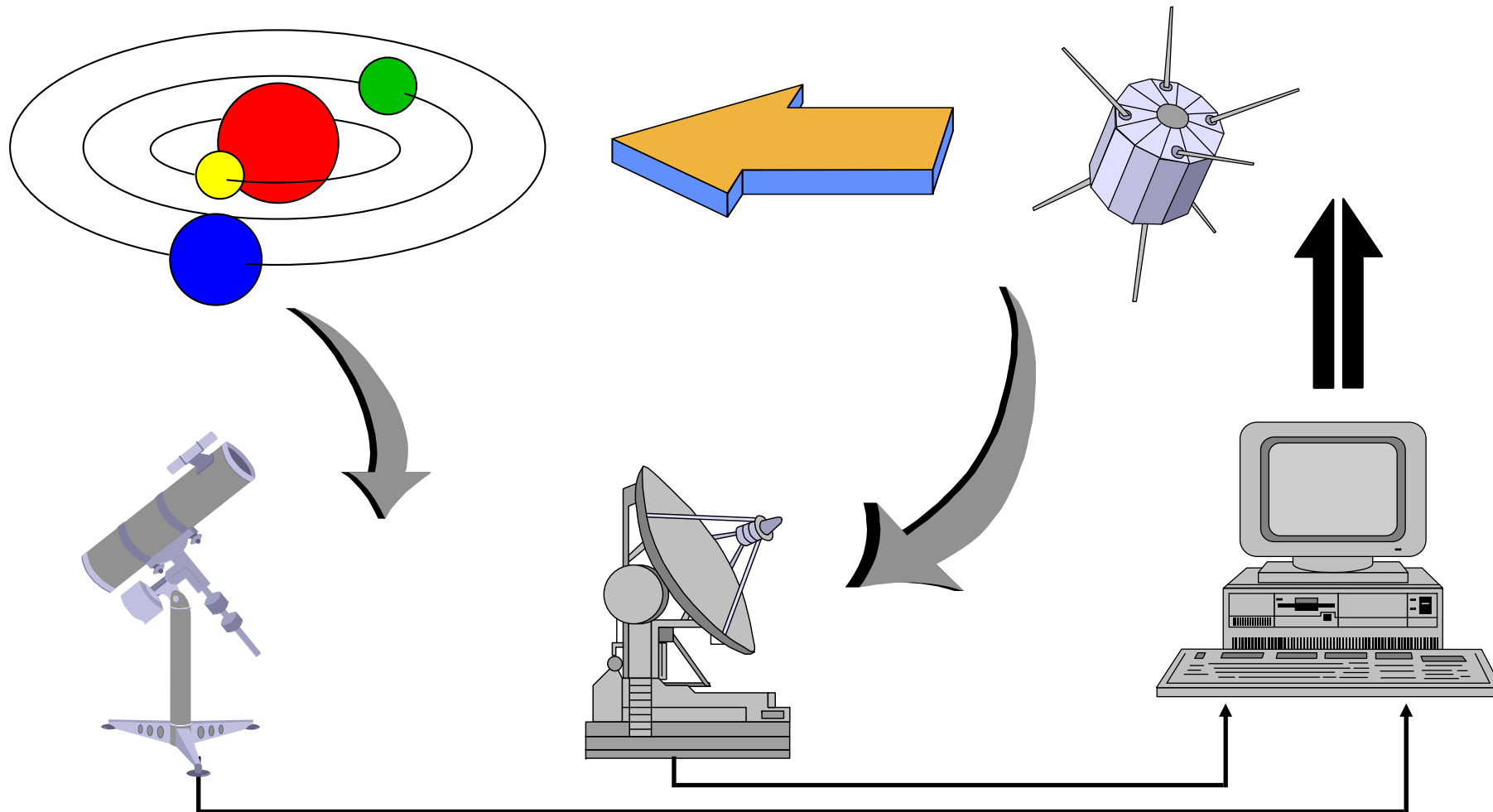


- Optimal control of drug combination : when one drug is the **principal** agent having the pharmacological action and the other is a **controller**, use a model involving independent additive and multiplicative control terms to design optimal **bilinear** inputs.

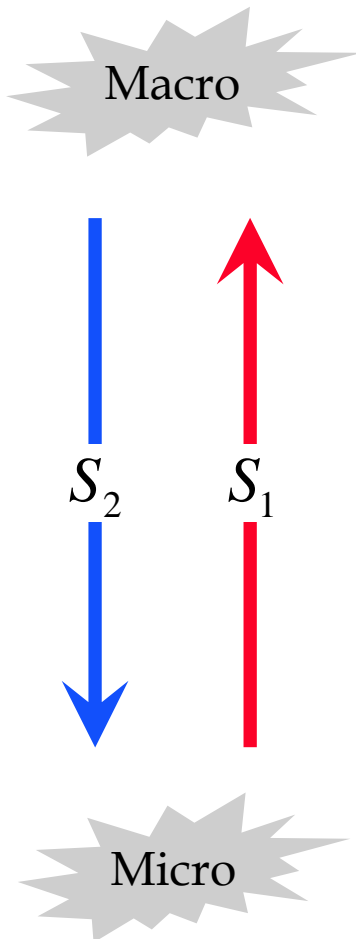
Clinical PKs



Space voyager



Strategies in modeling architecture



S_1 « **Bottom-up** » approach:
Details of the component parts and connectivity of them.
Incorporate in a complex model all the available biologic information.
Observations from non in-vivo experiments.
DRAWBACK : Difficulties to apply in clinical practice.

S_2 « **Top-down** » approach:
Functional representation of the entire process.
Start with a simple model. If it lacks to fit with in-vivo observations,
integrate progressively available biological information.
AVANTAGE : Direct clinical applications.