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

CHAPT V : Population PKs

❶ Description of variabilities. Classification of problems. Single and two-stage methods. Covariates.

❷ Preliminary choices in the TS methods : parametric and nonparametric approaches. The Normal and Lognormal cases. The kernel functions : smoothing effects.

❸ SS methods : working spaces, distribution hypotheses. Parametric (NONMEM) and nonparametric (NPML) methods.

❹ Comparison of SS and TS methods. The NP - TS approach. MAP estimators in population studies : balance.

❺ The information theory : entropy, uncertainty. Number of patterns. Detection of outliers.

❻ Real-time processing : recursive and sequential approaches. Influential covariates. Estimation of missing data. Bioequivalence. Time- and dose-dependence.

❼ Properties and applications of the TS - NP approach using MAP. Elaborated schemes.

Functional scheme - Chapt V

Studies during drug development

- PK information is obtained from :
  - ★ healthy volunteers (experimental PKs, drug development, preclinical and phase I),
  - ★ patients (clinical PKs, drug treatment, phases II and III).
- The problem : Individual PKs characterize both :
  - ★ the subject, and
  - ★ the drug.

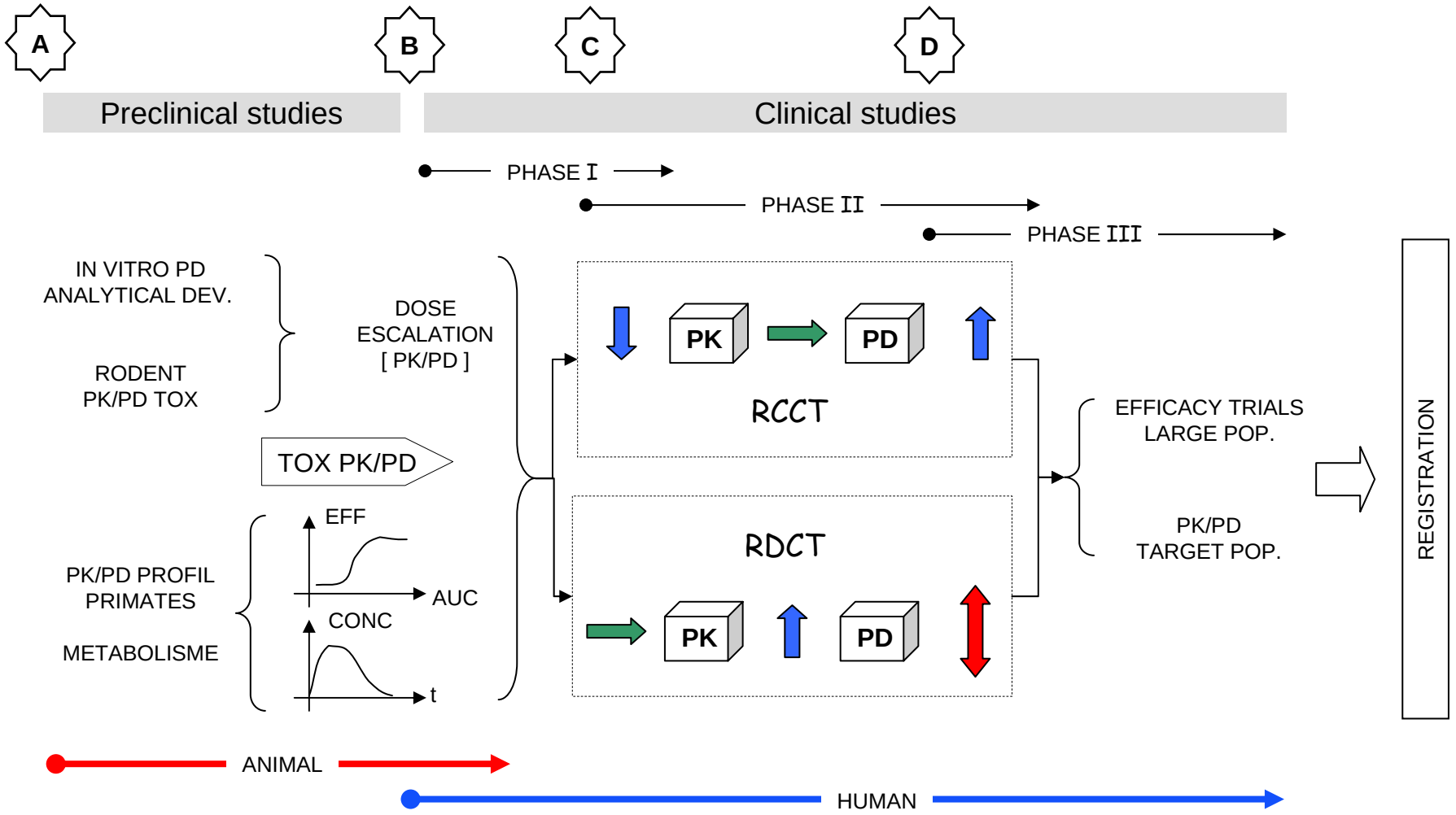
$$CL(\text{drug},\text{indv}) \rightarrow \int_{\text{indv}} CL(\text{drug},\text{indv})\,d(\text{indv}) = CL(\text{drug})$$

- The solution :

Compile individual PKs to obtain :

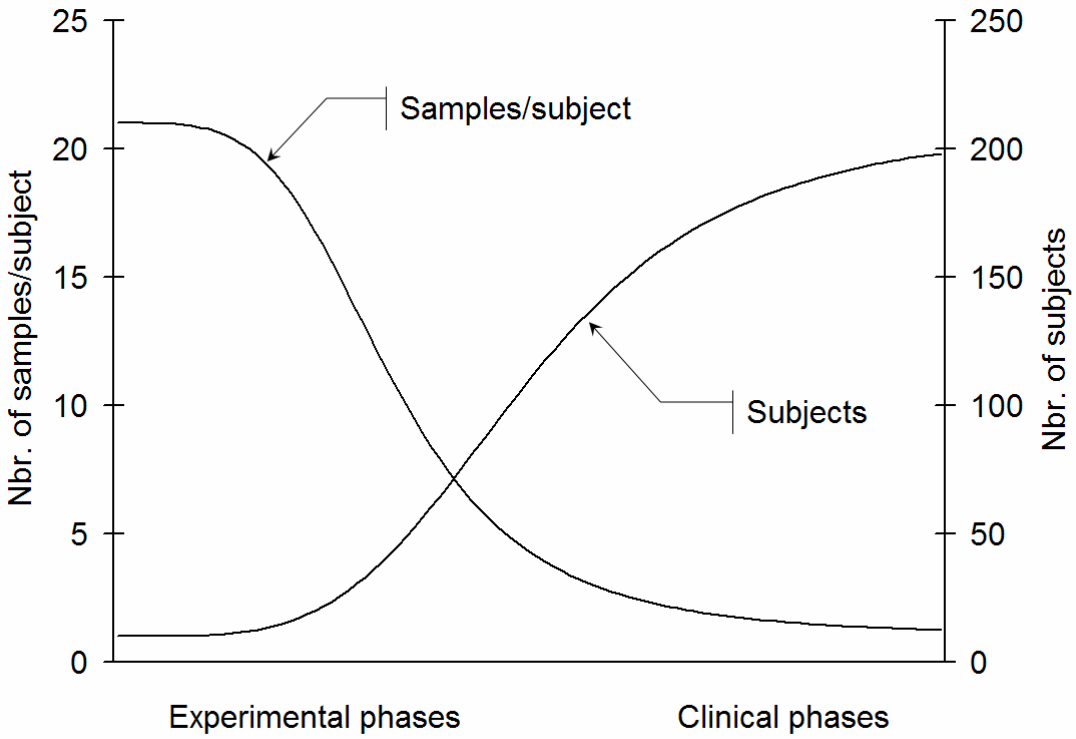
- ★ patient characteristics and pull-out only the drug properties (ex : high CL, etc)
- ★ drug characteristics and recognize patient's status (ex : renal impairment, etc)

The phases of drug development



Classification of problems

- PK data bases during drug development
  - ☐ Preclinical and phase I : Experimental PKs
    - ★ Individual kinetics well documented,
    - ★ data rich situation,
    - ★ two-stage (TS) methods.
  - ☐ Phases II and III : Clinical PKs
    - ★ few samples per patient,
    - ★ sparse data situation,
    - ★ single-stage (SS) methods.



Density estimation

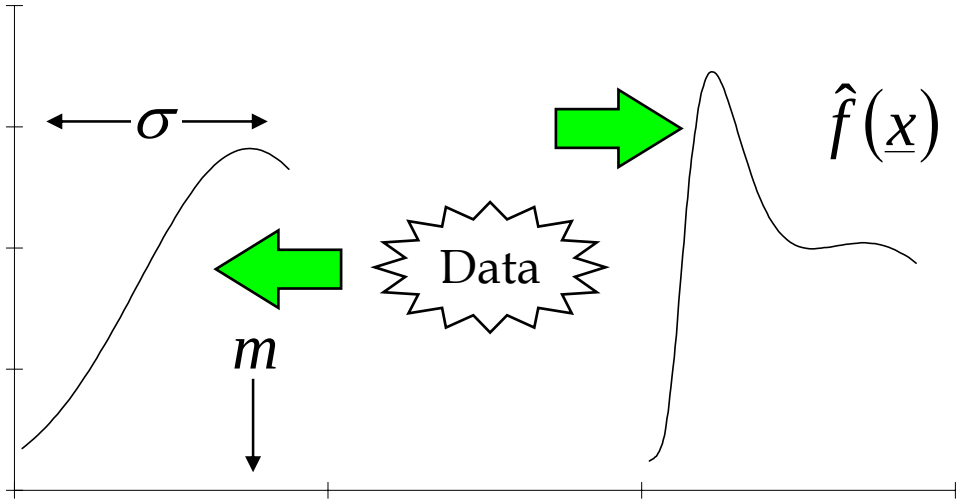
- Density estimation ➡ the construction of an estimate $\hat{f}(x)$ of the density function $f(x)$ from the available data.

- Approaches to density estimation

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

    Ex : the normal density :

$$X \sim N(m, \sigma^2)$$



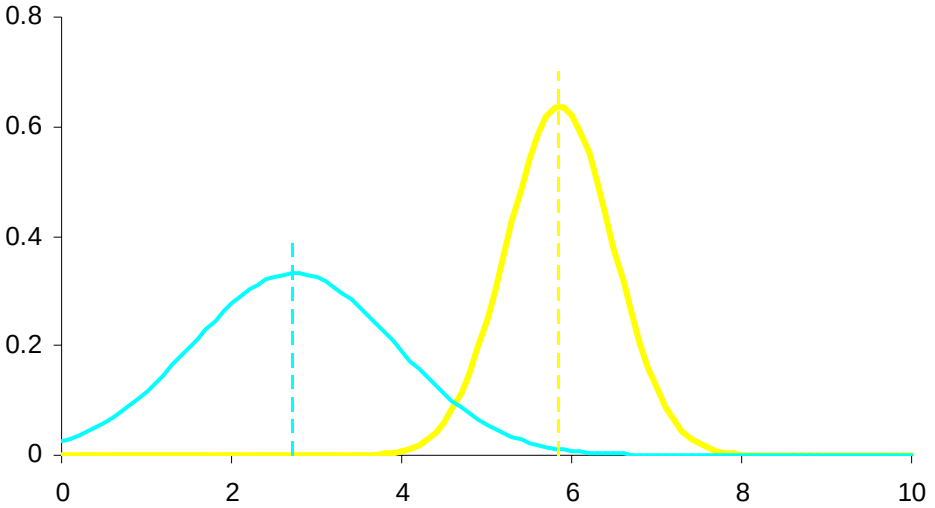
  - ☐ Nonparametric : distribution free of structure and parameters.

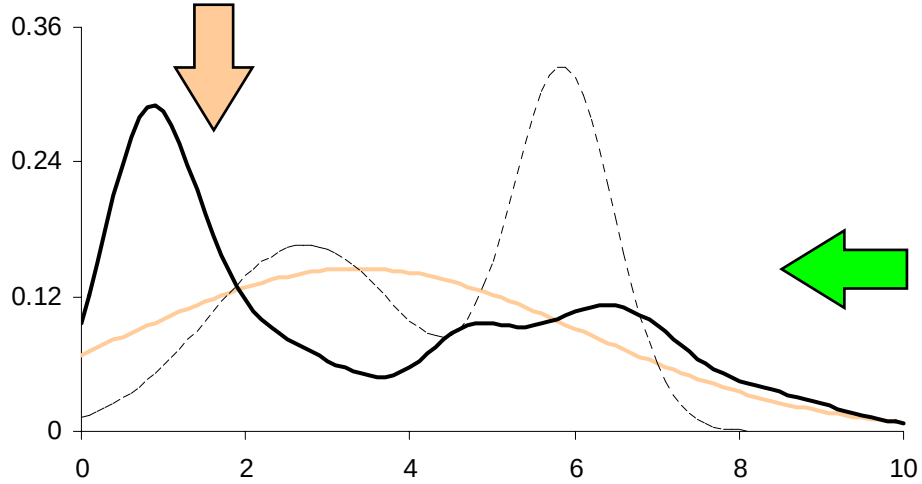
Parametric vs. nonparametric PDF

Smoothing = 2.5

n°	CL	s.e.m.	Kernel window
1	0.78	0.22	
2	5.86	0.25	0.625
3	2.73	0.48	1.2
4	2.16	0.38	
5	0.79	0.33	
6	0.72	0.18	
7	4.71	0.22	
8	8.02	0.43	
9	1.16	0.23	
10	6.73	0.25	

mean	3.37
std	2.75
CV	81.69





Compile

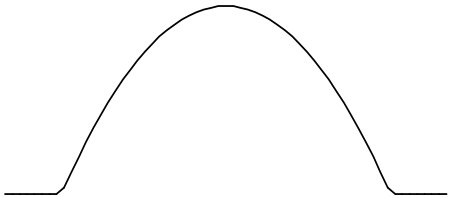
$$\hat{f}(x;s) = \frac{1}{n} \cdot \sum_{j=1}^{n} k\left(\frac{x - \hat{x}_j}{s \cdot p_j}\right)$$

What is a kernel ?

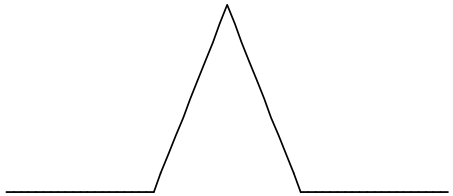
- Elementary functions $k(x)$ with :

$$\int_{\underline{x}} k(\underline{x}) \cdot d\underline{x} = 1$$

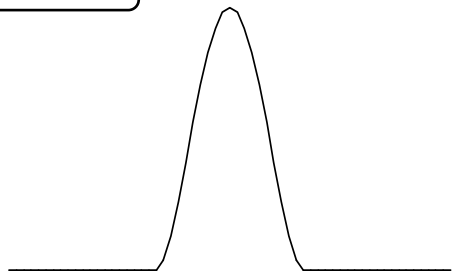
Epanechnikov



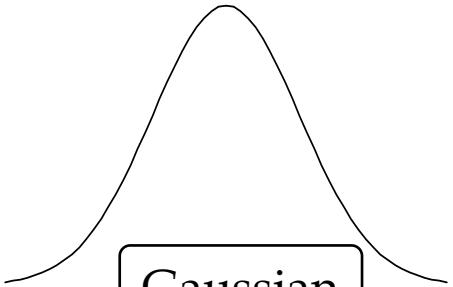
Triangular



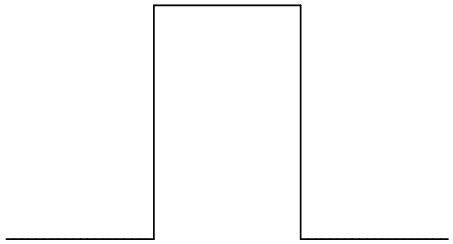
Biweight



Gaussian

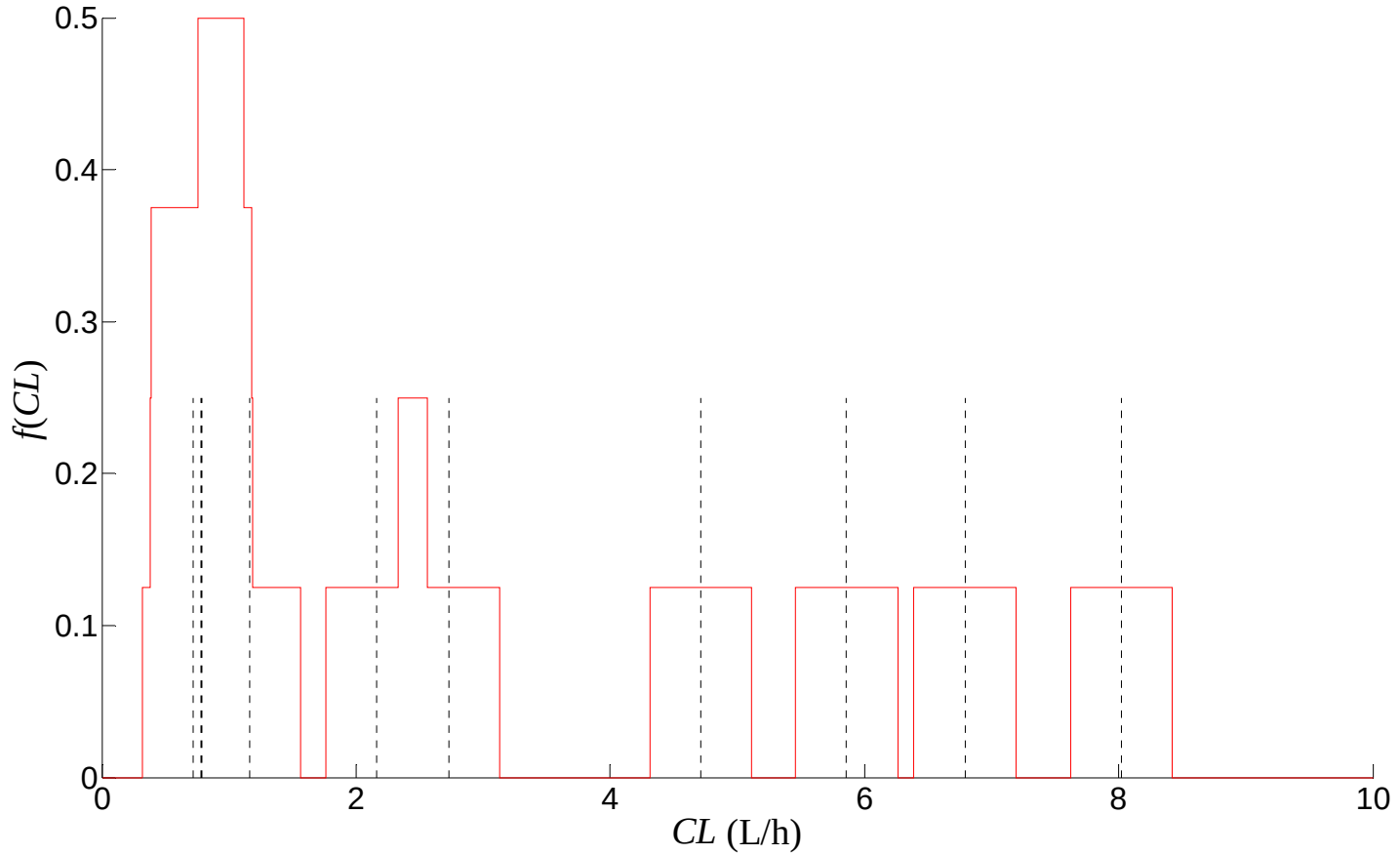


Rectangular



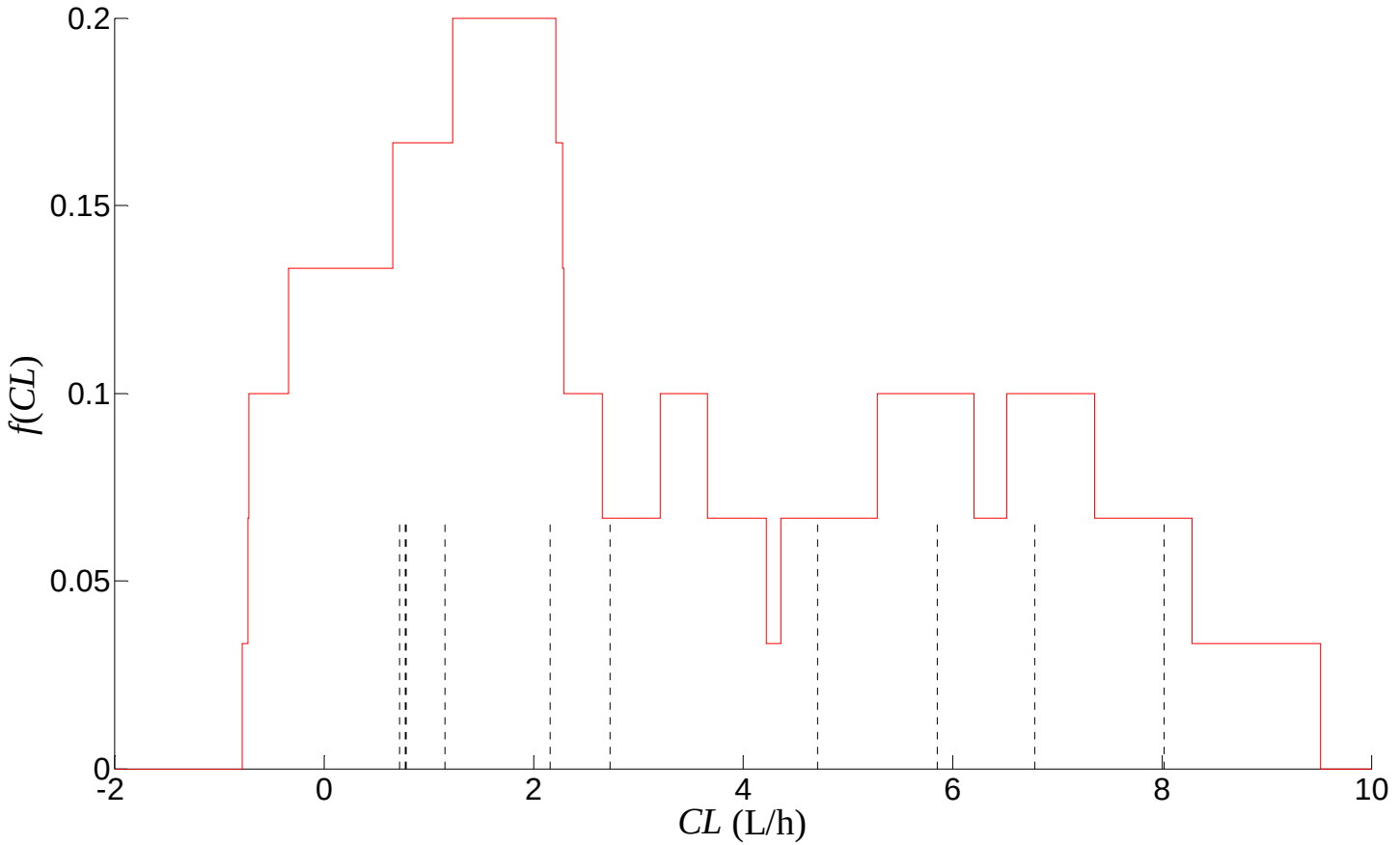
Low smoothing or ...

- Rectangular kernel (histograms) : window width $s_R = 0.8$



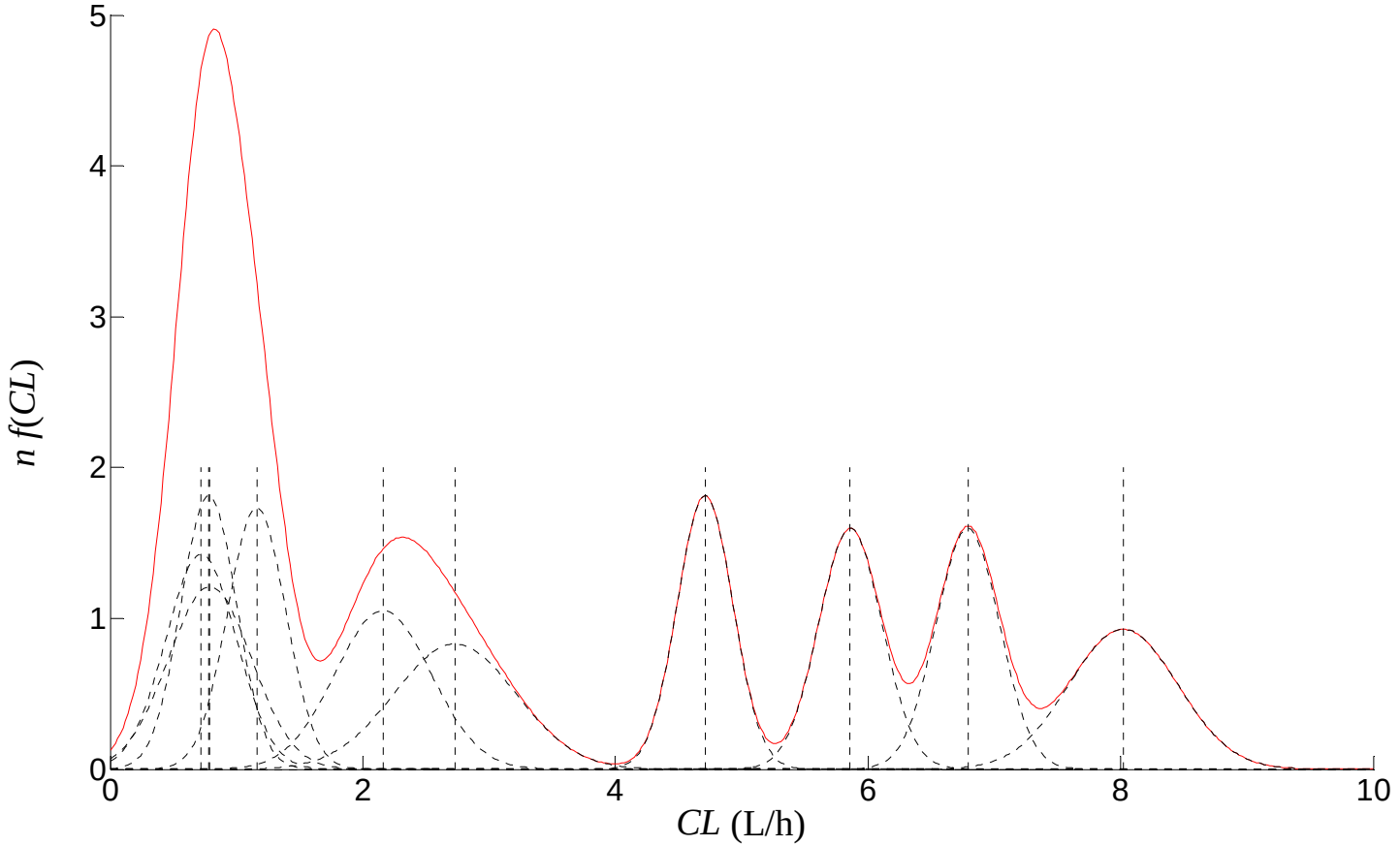
… or high smoothing ?

- Rectangular kernel (histograms) : window width $s_R = 3$



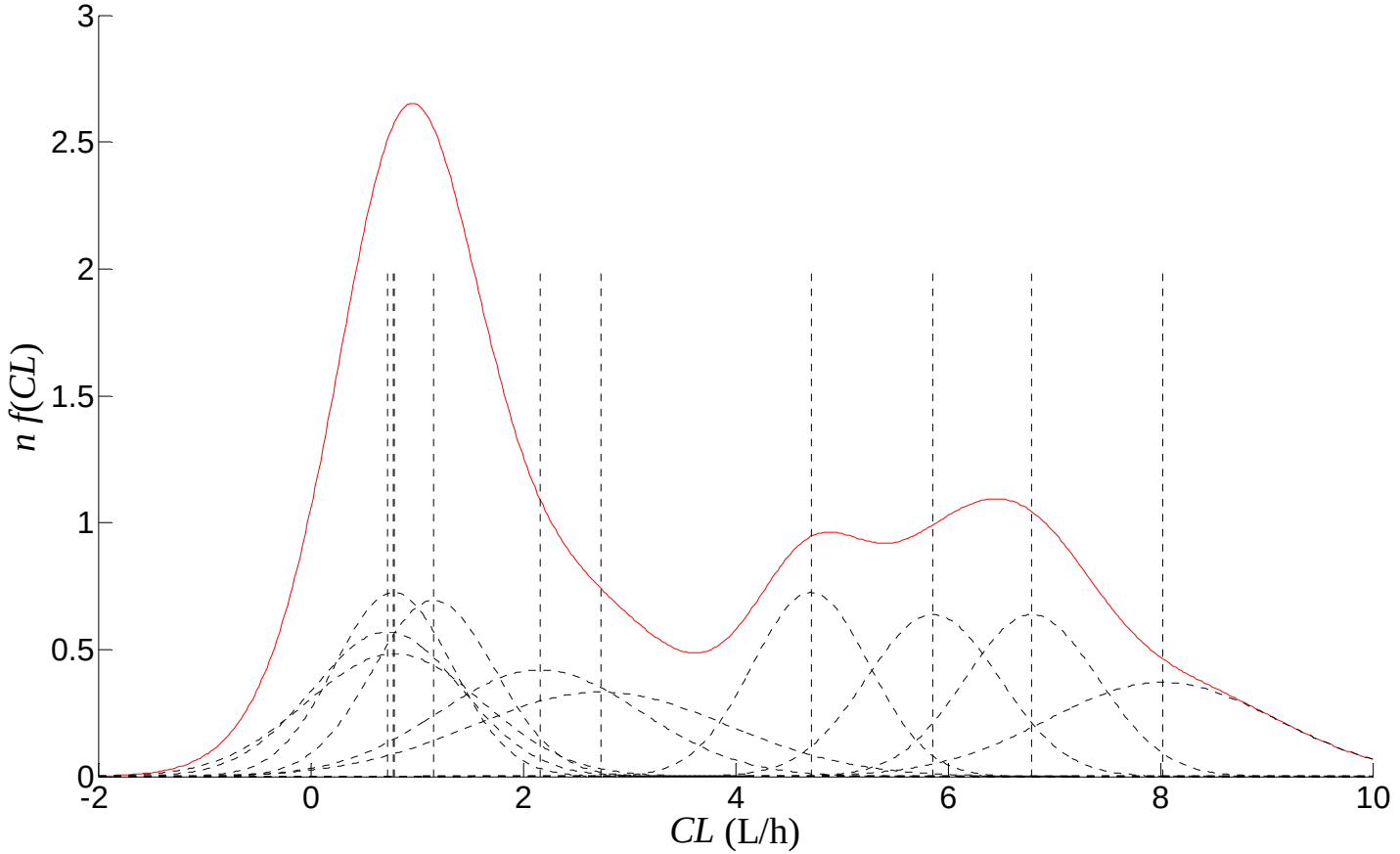
Adaptive smoothing - 1

- Gaussian kernel, low smoothing $s_G = 1.0 \cdot [\text{precision of estimates}]$



Adaptive smoothing - 2

- Gaussian kernel, high smoothing $s_G = 2.5 \cdot [\text{precision of estimates}]$

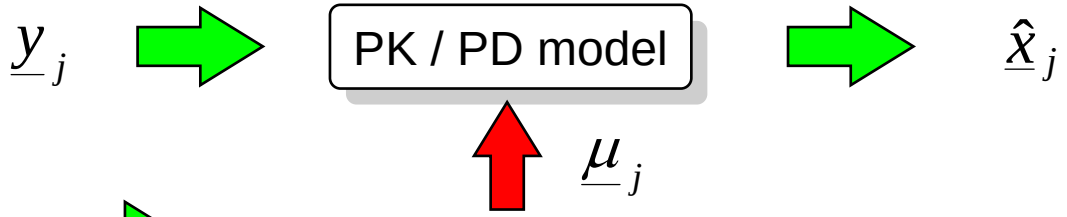


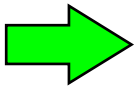
Density estimation in PKs

- 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.

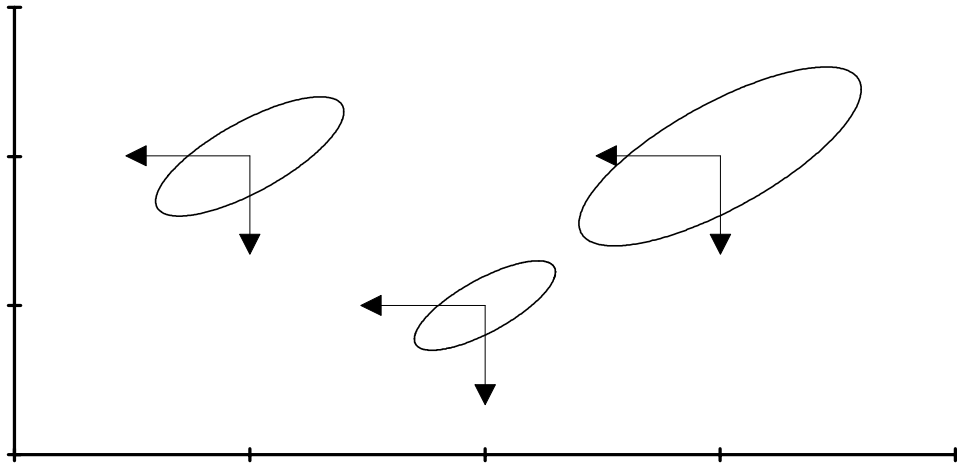
Choices in the TS methods

- In the first stage : Obtain the training data over n individuals :

$$\left\{ \underline{\hat{x}}_j \, , \underline{\mu}_j ; \; j = 1, n \right\}$$

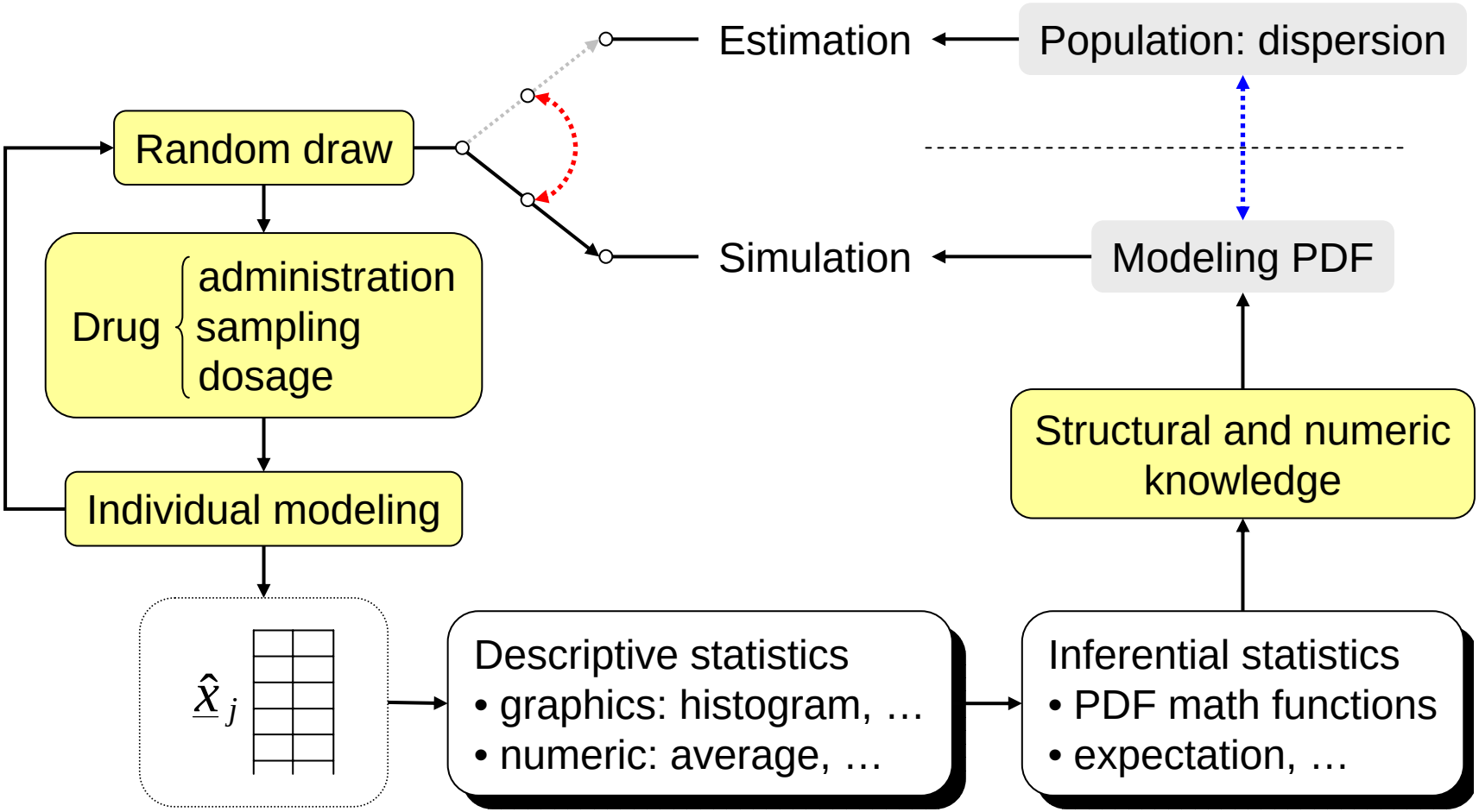
  - If MLE is used, we can obtain the precision of estimates in a matrix P_j .
    - ★ record P_j in the training data base :

$$\left\{ \underline{\hat{x}}_j , \underline{\mu}_j , P_j ; \; j = 1, n \right\}$$



- In the second stage : Obtain $\hat{f}\left(\underline{x}\right)$ from the training data by using a parametric or nonparametric approach.

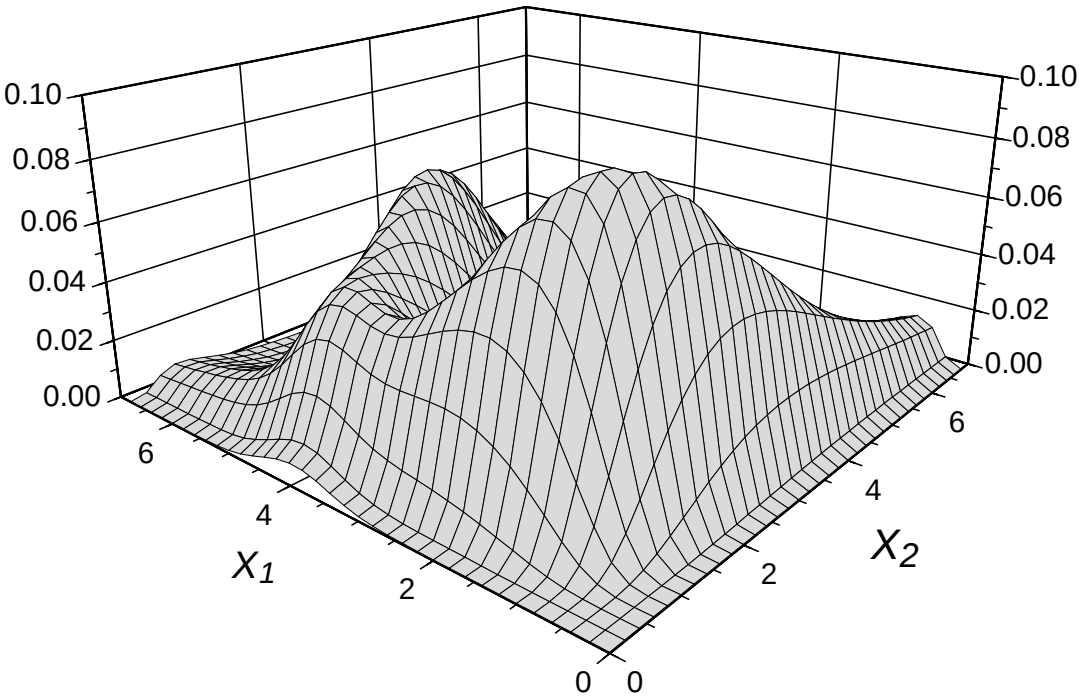
Simulations evaluating performances



The theoretical density

- Characteristics : Mixture of NO (0.3) and LN (0.7)

  - NO : - mean $\begin{bmatrix} 5 & 3 \end{bmatrix}$
    - dispersion $\begin{bmatrix} 0.5 & 0.7 \\ 0.7 & 2 \end{bmatrix}$
  - LN : - mean $\begin{bmatrix} 0.5 & 0.75 \end{bmatrix}$
    - dispersion $\begin{bmatrix} 0.5 & -0.3 \\ -0.3 & 0.5 \end{bmatrix}$
  - Number of samples : 50



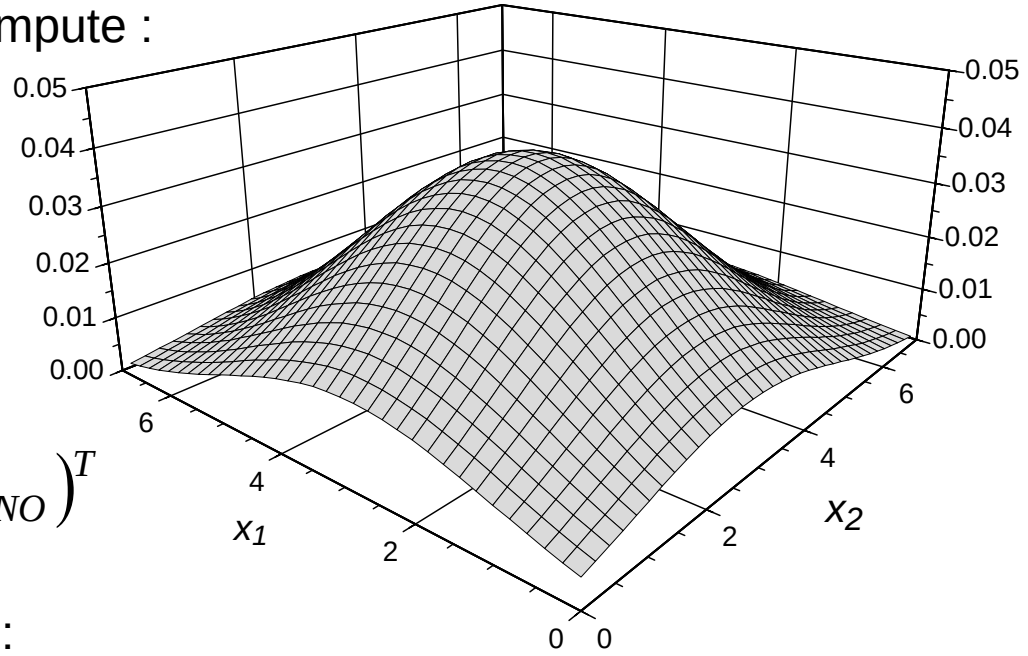
Parametric distributions in TS - 1

- The normal (NO) case
  - From training data $\left\{ \hat{\underline{x}}_j \; ; \; j = 1, n \right\}$ compute :
    1. the mean vector :

$$\underline{x}_{NO} = n^{-1} \cdot \sum \hat{\underline{x}}_j$$

    2. the dispersion matrix :

$$D_{NO} = n^{-1} \cdot \sum \left(\hat{\underline{x}}_j - \underline{x}_{NO} \right) \cdot \left(\hat{\underline{x}}_j - \underline{x}_{NO} \right)^T$$



  - The multivariate NO density function is :

$$\hat{f}_{NO}\left(\underline{x}\right) = \left(2\pi\right)^{-p/2} \cdot \left| D_{NO} \right|^{-1/2} \cdot \exp\left[-1/2 \cdot \left(\underline{x} - \underline{x}_{NO} \right)^T \cdot D_{NO}^{-1} \cdot \left(\underline{x} - \underline{x}_{NO} \right) \right]$$

Parametric distributions in TS - 2

- The log-normal (LN) case
  - From training data $\left\{ \underline{\hat{x}}_j \; ; \; j = 1, n \right\}$ compute :
    1. the p-dimensional vectors $\underline{\ln x}_j$:

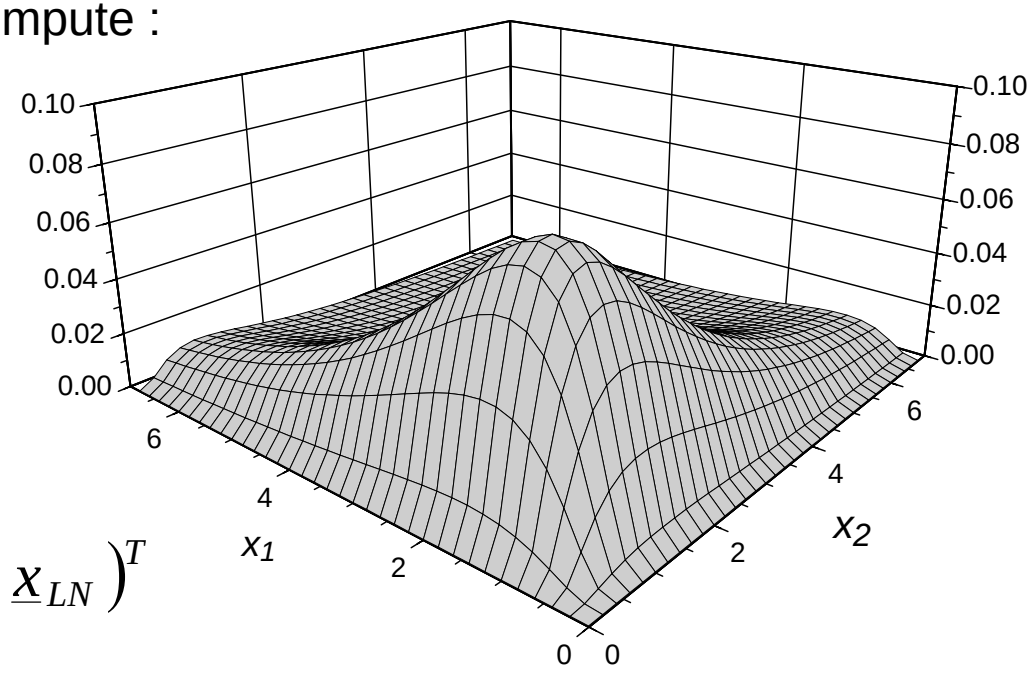
$$\underline{\ln \hat{x}}_j^{\,T} = \left[\ln \hat{x}_{1j} \; \ldots \ln \hat{x}_{pj} \right]$$

    2. the mean vector :

$$\underline{x}_{LN} = n^{-1} \cdot \sum \underline{\ln \hat{x}}_j$$

    3. the dispersion matrix :

$$D_{LN} = n^{-1} \cdot \sum \left(\underline{\ln \hat{x}}_j - \underline{x}_{LN} \right) \cdot \left(\underline{\ln \hat{x}}_j - \underline{x}_{LN} \right)^T$$



  - The multivariate LN density function is :

$$\hat{f}_{LN}(\underline{x}) = (2\pi)^{-p/2} \cdot |D_{LN}|^{-1/2} \cdot \left[1 / \prod x_s \right] \cdot \exp\left[-1/2 \cdot \left(\underline{\ln x} - \underline{x}_{LN} \right)^T \cdot D_{LN}^{-1} \cdot \left(\underline{\ln x} - \underline{x}_{LN} \right) \right]$$

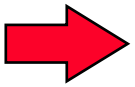
Nonparametric distributions in TS

- The kernel approach
  - The estimated density is the average of kernels over the n available individuals.

$$\hat{f}(\underline{x};s) = n^{-1} \cdot s^{-p} \cdot \sum_{j=1}^{n} k\left[\left(\underline{x} - \underline{\hat{x}}_j\right)/s\right]$$

  - The kernels may be weighted by the precision matrix P_j of individual estimates $\underline{\hat{x}}_j$.
  - Nonparametric approach using normal kernels :

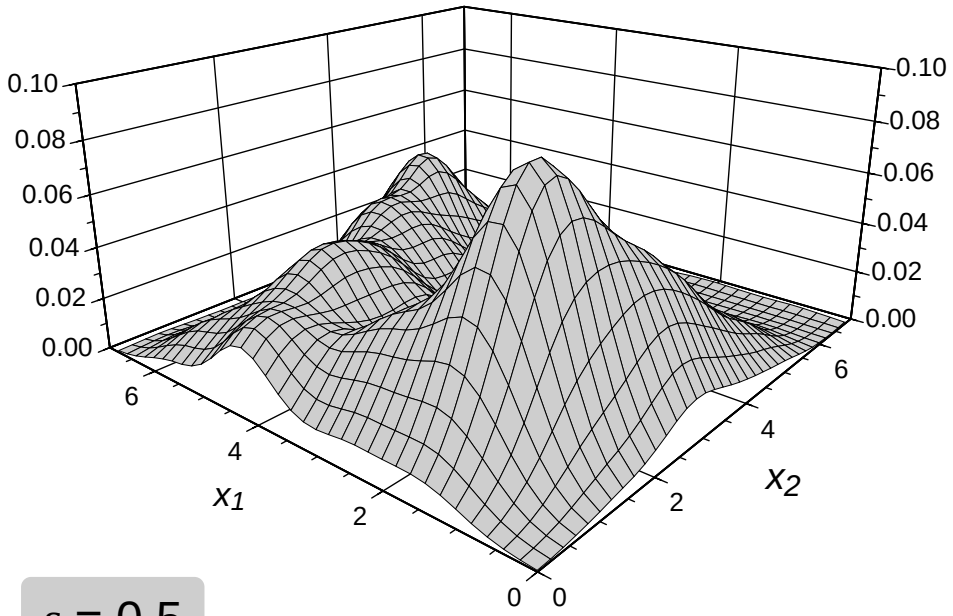
$$\hat{f}(\underline{x};s) = n^{-1} \cdot (2\pi)^{-p/2} \cdot s^{-p} \cdot \sum_{j=1}^{n} \left|P_j\right|^{-1/2} \cdot \exp\left[-1/2 \cdot s^{-2} \left(\underline{x} - \underline{\hat{x}}_j\right)^T \cdot P_j^{-1} \cdot \left(\underline{x} - \underline{\hat{x}}_j\right)\right]$$



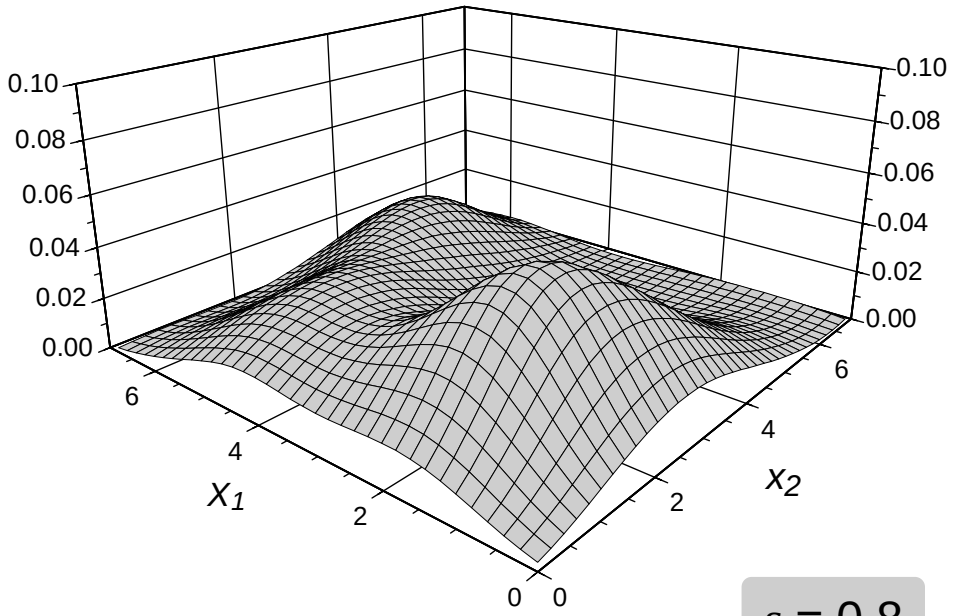
With enough patterns, we converge to an arbitrarily complicated unknown density.

Smoothing effects

- The window width s is a smoothing parameter
  - ★ It controls the size and the shape of the kernel functions,
  - ★ It is adjustable and its choice is critical.



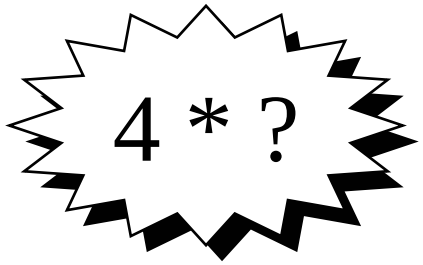
$s = 0.5$



$s = 0.8$

Fundamental questions

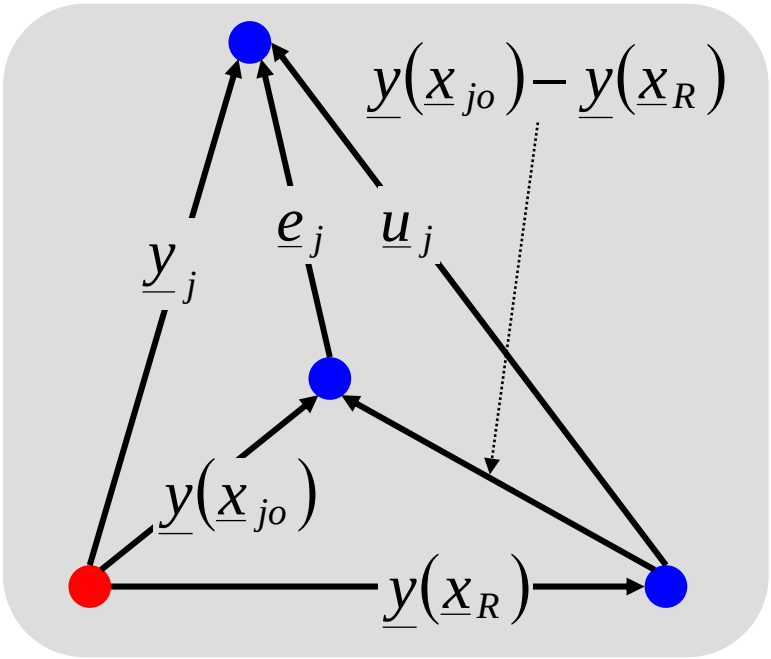
- Q1 - Available data are sufficient to describe the actual dispersion ?
- Q2 - What is the PDF model of dispersion of parameters ?
- Q3 - Are there individuals that exhibit atypical PK/PD behavior ?
- Q4 - What are the influential covariates ?



SS methods, working spaces

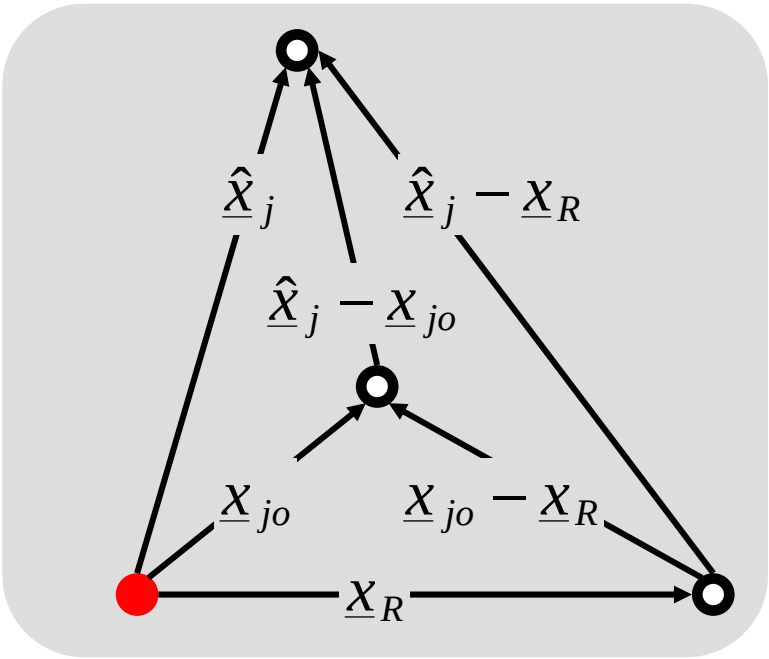
- The correspondence between output and parameter spaces

Output space



NL model

Parameter space



Distribution hypotheses

m_j-dimensional observations	p-dimensional parameter vectors
$\underline{y}_j$ $\underline{e}_j \sim \mathrm{N}_{m_j}\left(\underline{0}, \mathrm{I}_j \cdot \sigma^2\right)$ (H1)	$\underline{\hat{x}}_j$: individual estimation $\underline{\hat{x}}_j - \underline{x}_{jo}$: shift for measurement error
$\underline{u}_j$ $\underline{y}(\underline{x}_R)$	$\underline{\hat{x}}_j - \underline{x}_R$: shift of estimates / reference $\underline{x}_R$: to be estimated
$\underline{y}(\underline{x}_{jo})$ $\left[\underline{y}(\underline{x}_{jo}) - \underline{y}(\underline{x}_R)\right]$	$\underline{x}_{jo} \sim N_p(\underline{x}_R, D_R)$ (H2) (unknown) $\underline{x}_{jo} - \underline{x}_R \sim N_p(\underline{0}, D_R)$ (H2')

Precision

Dispersion

- Problem : Given $\left\{ \underline{y}_j \; ; j = 1, n \right\}$, compute $\left\{ \underline{x}_R, D_R, \sigma^2 \right\}$
  in a single stage without estimating $\underline{x}_j$

Parametric approach in SS

- NONlinear Mixed Effect Modeling (NONMEM)

  ☐ Main features :

  ★ The model is linearized to transfer hypotheses :

  Parameter space — **H2** → Output space

  ★ The reference x_R becomes a model implying the covariates : structural model

  e.g. $$CL_j = x_{1R} + \mu_j \cdot x_{2R}$$

  ☐ Practical use :

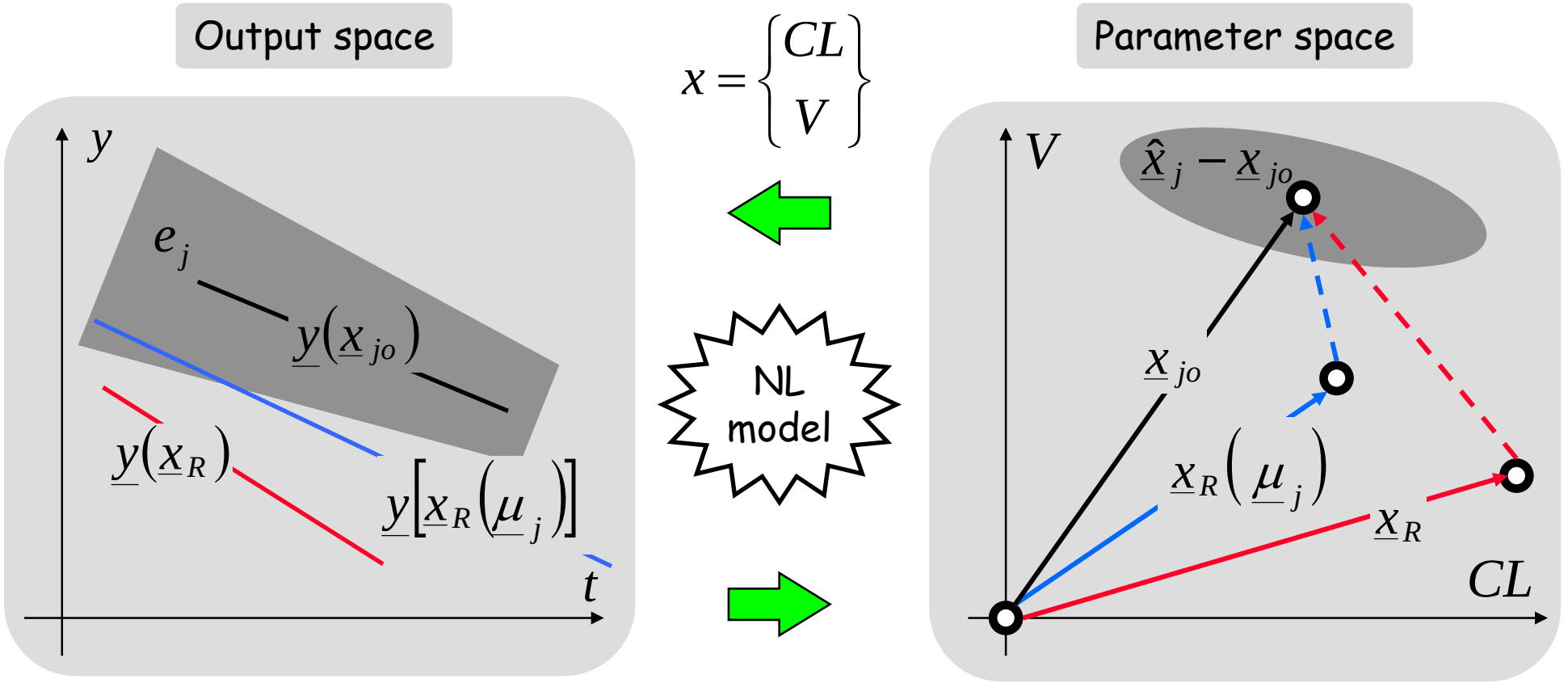
  ★ Estimate : { parameters of the structural model, D_R and σ^2 }.

  ★ Perform many 'runs' to select : ❶ the most appropriate structural model,

  ❷ the influential covariates.

Linearization and covariates

- The NONMEM principle

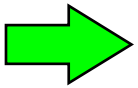


Nonparametric approach in SS

- 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 :
      - ❶ locations in the parameter space, and
      - ❷ associated weights.
  - ☐ Practical use :
    - ★ accepts missing data,
    - ★ considers covariates as corrupted by a random error with small variance,
    - ★ automatically derives marginal and conditional densities.

Discrete solution

ind	observed conc.			
1	t_{11}/y_{11}	t_{12}/y_{12}		m_1
2	t_{21}/y_{21}			m_2
...	...			...
j	t_{j1}/y_{j1}	t_{j2}/y_{j2}	t_{j3}/y_{j3}	m_j
...	...			...
n	t_{n1}/y_{n2}			m_n

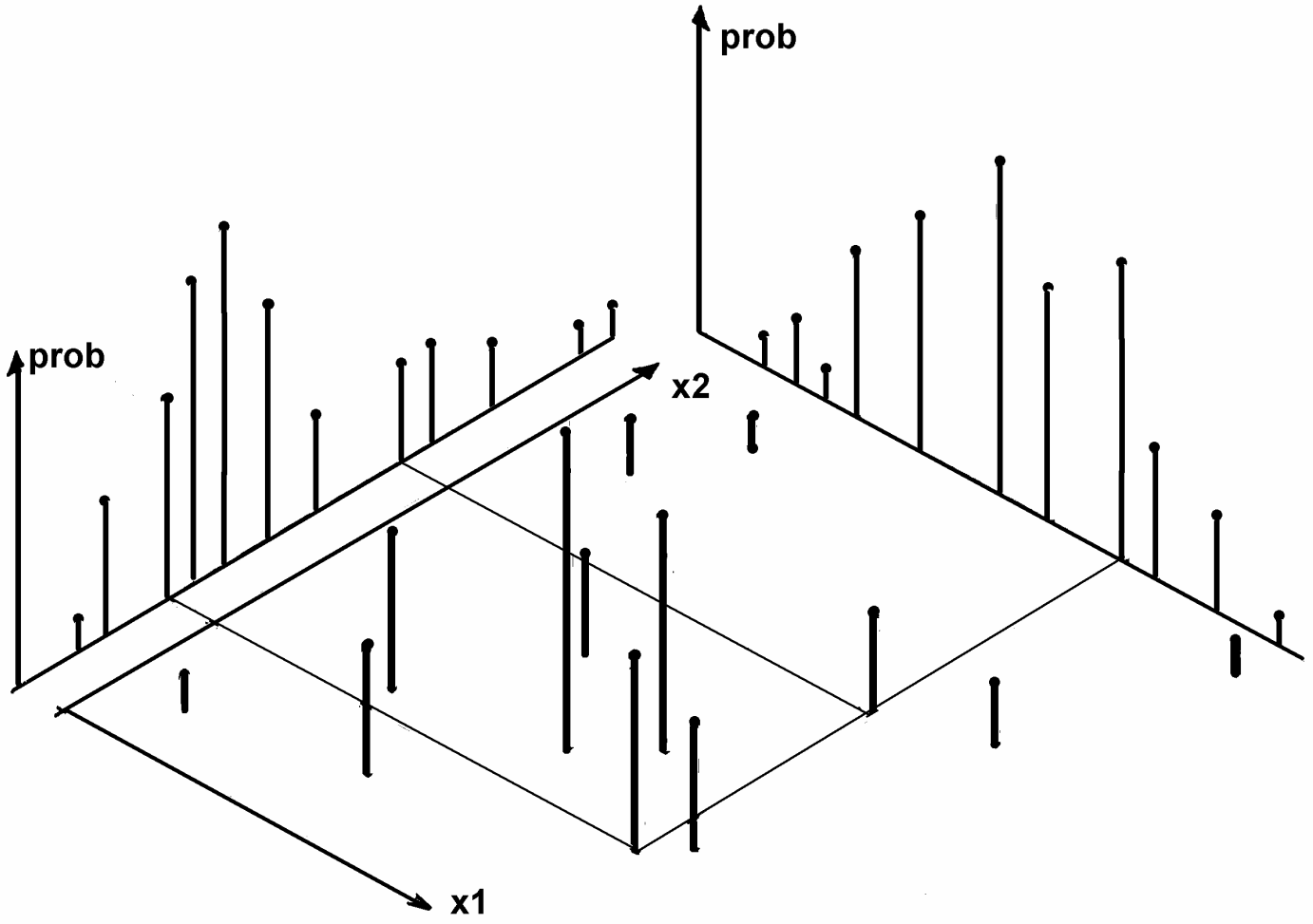


S-ind	weight	locations		
1	w_1	x_{11}	...	x_{1p}
2	w_2	x_{21}	...	x_{2p}
...	...	...	...	...
k	w_k	x_{k1}	...	x_{kp}
...	...	...	...	...
n'	$w_{n'}$	$x_{n'1}$	...	$x_{n'p}$

with $n' \le n$ and $\sum_{k=1}^{n'} w_k = 1$

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.



Single- vs. two-stage methods

- TS methods :
  - ★need, for the first stage, several individual observations,
  - ★require simpler mathematical background than the SS methods.

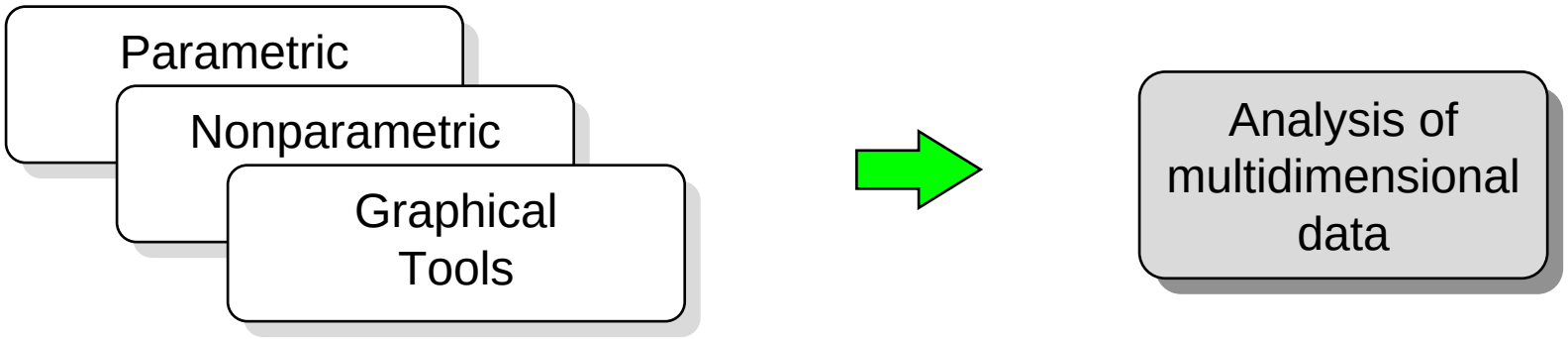
  Because :
  - ★perform PK modeling (precision analysis) in the first stage,
  - ★estimate density (dispersion analysis) in the second stage.

- SS methods :
  - ★use sophisticated mathematical and statistical framework,
  - ★require huge computer hardware and long CPU time.

  Because :
  - ★they work simultaneously on the output and parameter spaces,
  - ★transition between these spaces is done by a nonlinear model.

The nonparametric TS kernel approach has proved simple and flexible

Parametric vs. nonparametric approaches



- Definitions for nonparametric estimators
  - Heuristic : It works for a large class of $f(\underline{x})$.
  - Elegant :

In $f(x)$, the influence of x_j ...

...should vanish (nonparametric) ...

... if $|x - x_j| > \xi$ for any $\xi > 0$

... does not vanish (parametric) ...

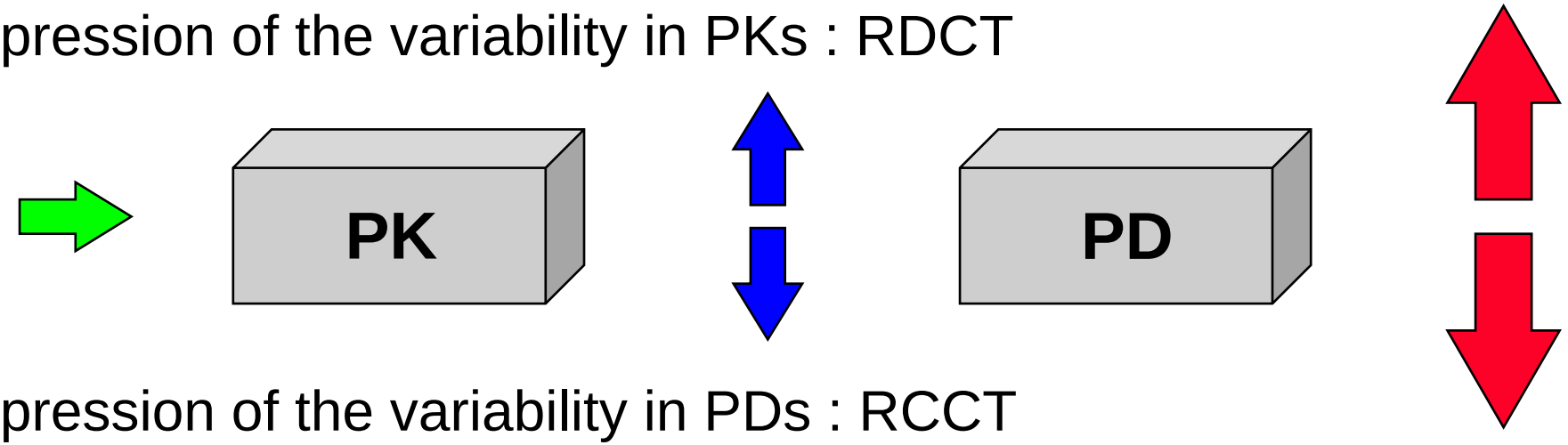
Contribution of population studies

- Preclinical studies:
  - ★ Extrapolation: animal ⇒ 1st dose in man,
  - ★ Dose escalation.
- Phase I:
  - ★ PK extrapolation: healthy volunteers ⇒ patient,
  - ★ Design: Control variable (RDCT / RCCT).
- Phases II and III:
  - ★ Individual drug adjustment,
  - ★ Clinical trial simulations integrating defaults in practice.
- Marketing:
  - ★ Post-marketing labeling, PK/PD advice, ...

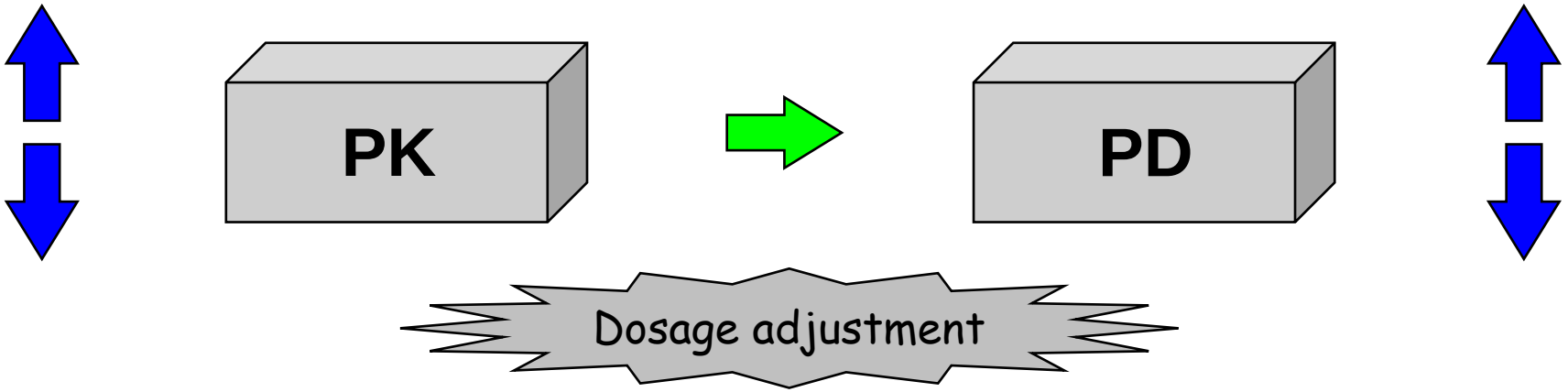
⇒ Early integration of population studies:
★ increases the reliability on drug information,
★ decreases the nbr of needed clinical studies, and
thus, allows a low-expensive and short-time drug development.

RDCT and RCCT

- Expression of the variability in PKs : RDCT



- Expression of the variability in PDs : RCCT



Covariates and variability - Gentamycin

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

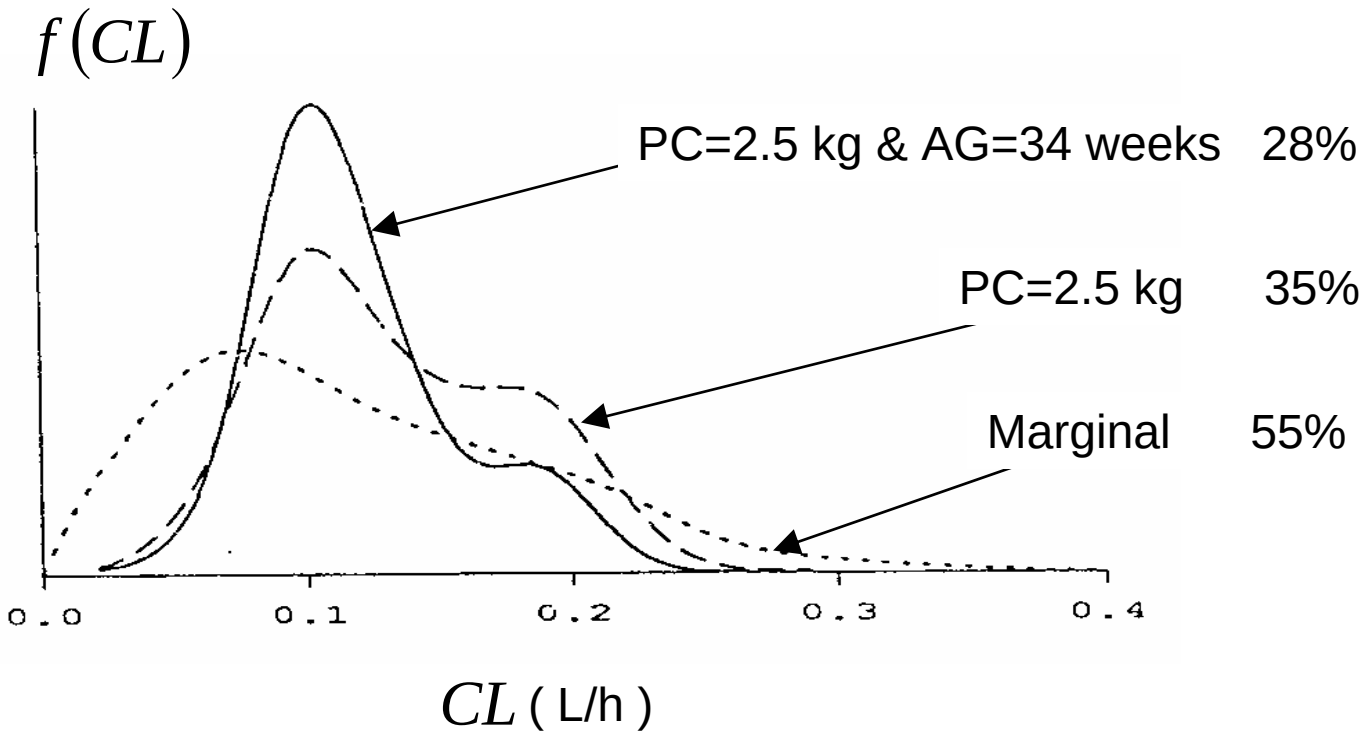
- PK results :

	$\bar{x}$	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



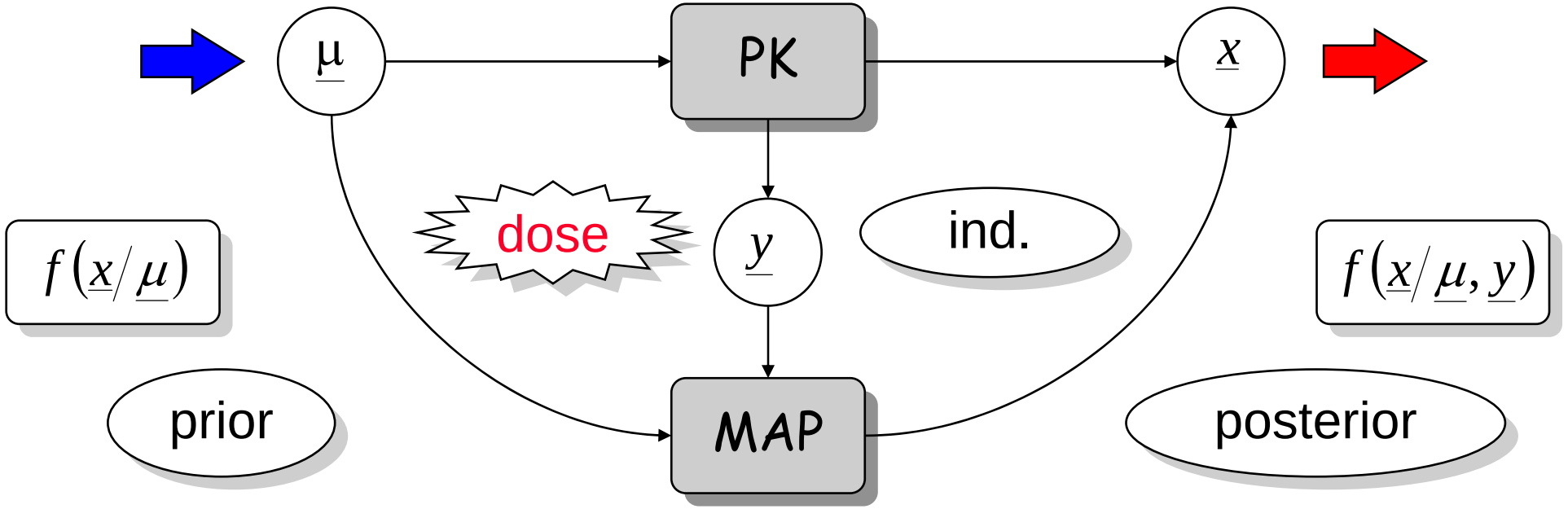
Elaborated MAP schemes

1°) $\underline{x}$ can be approximated without performing PK experiment :

★ select the mode of $f(\underline{x}/\underline{\mu})$.

2°) Perform PK experiment, observe $\underline{y}$:

★ select the mode of $f(\underline{x}/\underline{\mu},\underline{y})$, with $f(\underline{x}/\underline{\mu})$ as prior.



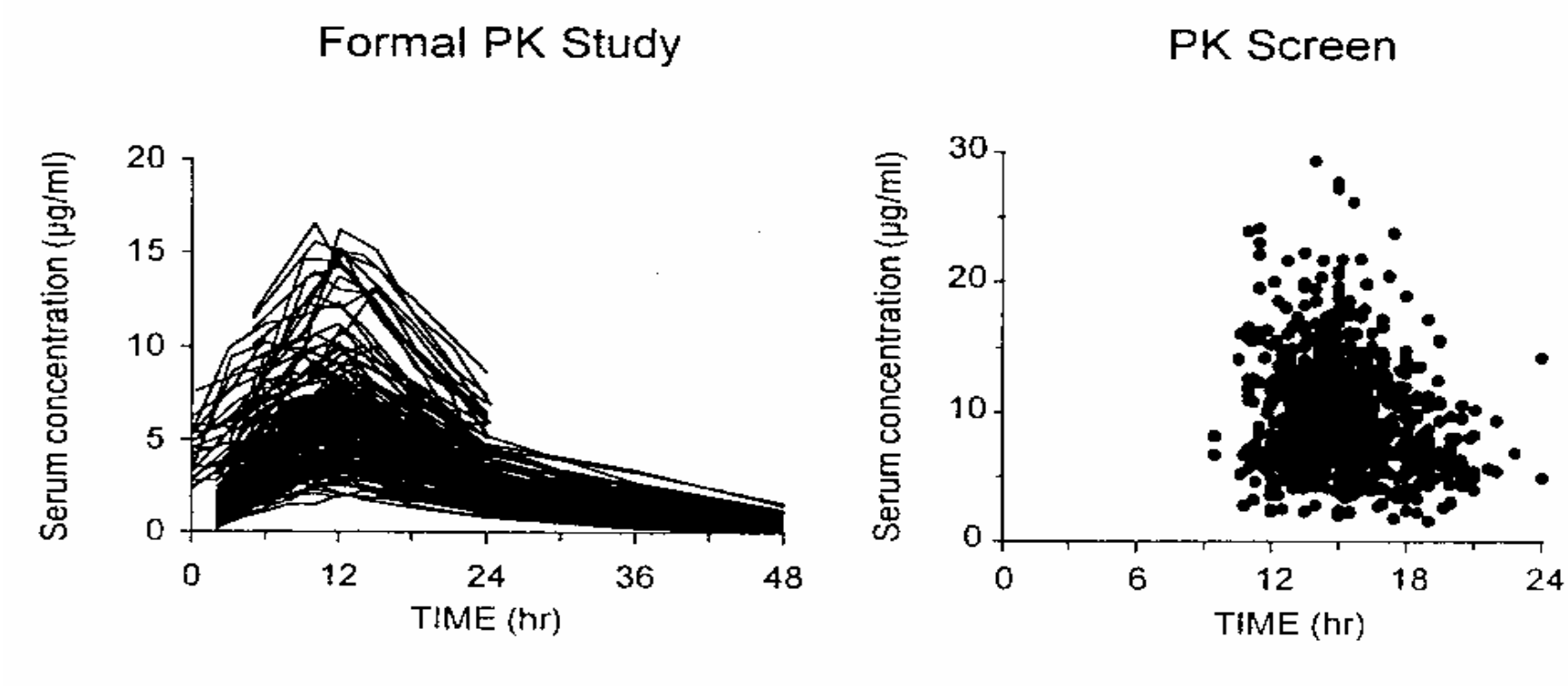
Post-marketing labeling - Theophylline

- Post-marketing study (Japan), sustained release preparation.
  - ☐ Without new experiments: compile the available studies in man !
    - ✓ 1 Phase I: ★ 131 healthy volunteers ★ « rich » data
    - ✓ 2 Phase II: } ★ 306 patients with chronic asthma ★ « sparse » data
    - ✓ 4 Phase III: }
    - ● Age: [9 , (43) , 82],
    - ● 20 children,
    - ● 12 volunteers with overnight fasting,
    - ● 15 patients having hepatic dysfunction,
    - ● 75 people aged > 65 years,
    - ● 65 smokers.
  - ☐ Population PK analysis:
    - ★ 1 cpt model,
    - ★ 1st order process.

		$\bar{x}$	%
k_a	(h^{-1})	0.077	19
CL/F_a	(L/h/kg)	0.054	31
V/F_a	(L/kg)	0.320	29

PK data

☐ 1 dosing with the evening meal to have C_{MAX} the next day morning (10 h later)



Post-marketing recommendations

- Dosage adjustment using covariates:

[body weight - severity of illness - smoking habit - age]

ASTHMA	Mild, Moderate			
SMOKING	Yes	No	Yes	No
AGE	Age<65		Age≥65	
LIVER Func	Normal			
BW 40kg	400mg			
45kg	400 - 600 mg			
50kg				
55kg				
60kg				
65kg	600 - 800mg			
70kg				
75kg				
80kg	800mg			

ASTHMA	Severe			
SMOKING	Yes	No	Yes	No
AGE	Age<65		Age≥65	
LIVER Func	Normal			
BW 40kg	400mg			
45kg				
50kg				
55kg	400 - 600mg			
60kg				
65kg				
70kg	600 - 800mg			
75kg				
80kg				

Information tools

- The amount of information ⇒ associated with a :
  - density $f(\underline{x})$:

$$I(f) = \int_{R^p} f(\underline{x}) \ln[f(\underline{x})] \, \mathrm{d}\,\underline{x}$$

  - sample of size n drawn from an unknown density approximated by $\hat{f}(\underline{x})$:

$$I_S(\hat{f}, n) = n^{-1} \cdot \sum_{j=1}^{n} \ln[\hat{f}(\underline{\hat{x}}_j)]$$

- To evaluate $I_S(\hat{f}, n)$:
  1. obtain $\hat{f}(\underline{x})$ from the $\{ \underline{\hat{x}}_j \; ; \; j = 1, n \}$ data,

     by using TS or SS methods and parametric or nonparametric approaches.
  2. average $\ln \hat{f}(\underline{\hat{x}}_j)$ over the n data.

Information and population studies

- Information indexes :
  - ★ evaluate the randomness (uncertainty) of $\underline{X}$,
  - ★ may be computed for joint, marginal and conditional densities,
  - ★ to be used to control better the second-stage.

- Use $I_S\left(\hat{f}, n\right)$ to answer the fundamental questions
  - ☐ If $f\left(\underline{x}\right)$ is a prior, the scalar $I_S\left(\hat{f}, n\right)$ measures the dispersion of $\underline{\hat{x}}$'s.

- Example on real data
  - ☐ Antidepressant drug : oral 50 or 100 mg / 93 volunteers, 6 to 15 samples / subject.
  - ☐ PK modeling : one-cpt
  - ☐ 3 covariates recorded

$$\left[V^{-1} \quad k_e \quad k_a \quad age \quad weight \quad height\right] \times 93$$

Q1 : Number of individuals

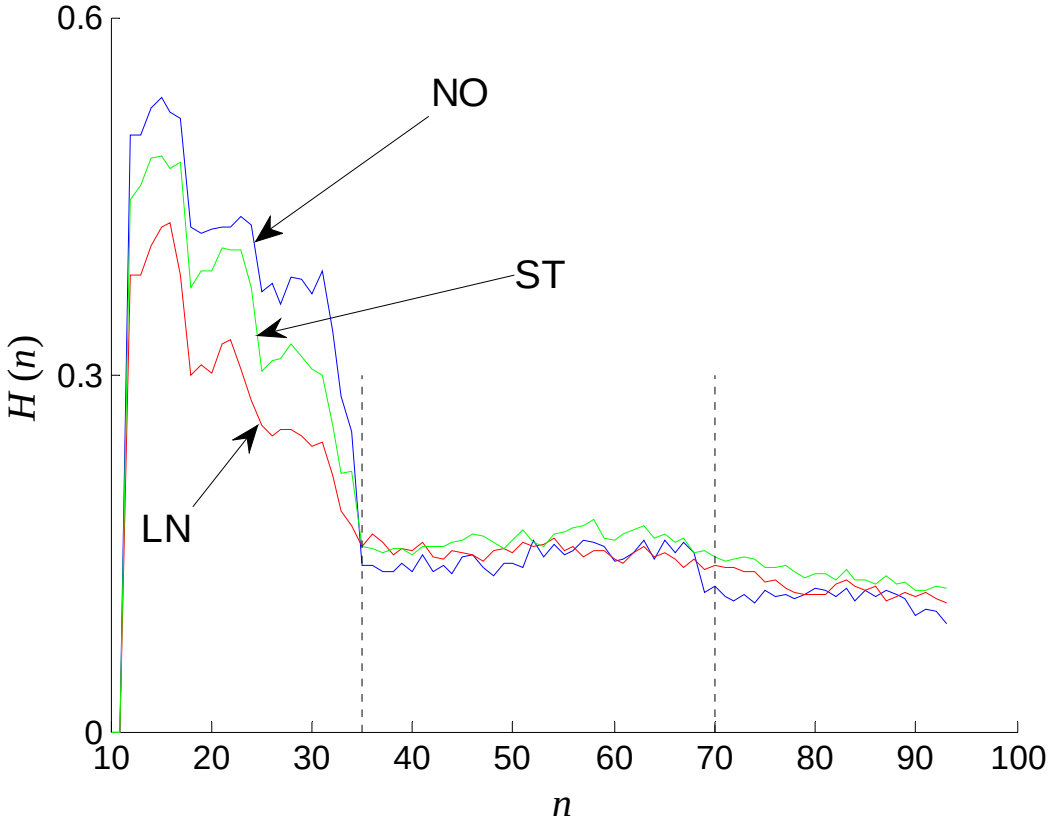
- Evaluate the metrics :

$$H(n) = \mathrm{iqr}\left[I_S\left(\hat{f}, n\right)\right] / \mathrm{med}\left[I_S\left(\hat{f}, n\right)\right]$$

  - For several $\hat{f}$ and as a function of n

- Bootstrap :
  - Obtain median and inter-quartile range for each $I_S\left(\hat{f}, n\right)$.

- Results (empirical) :
  - Compile at least $n = 35$.
  - Stabilization for $n > 70$.



Q2 : Selection of the PDF model

- For a given PDF model $f(\underline{x})$:

$$I_S(\hat{f}, n)$$

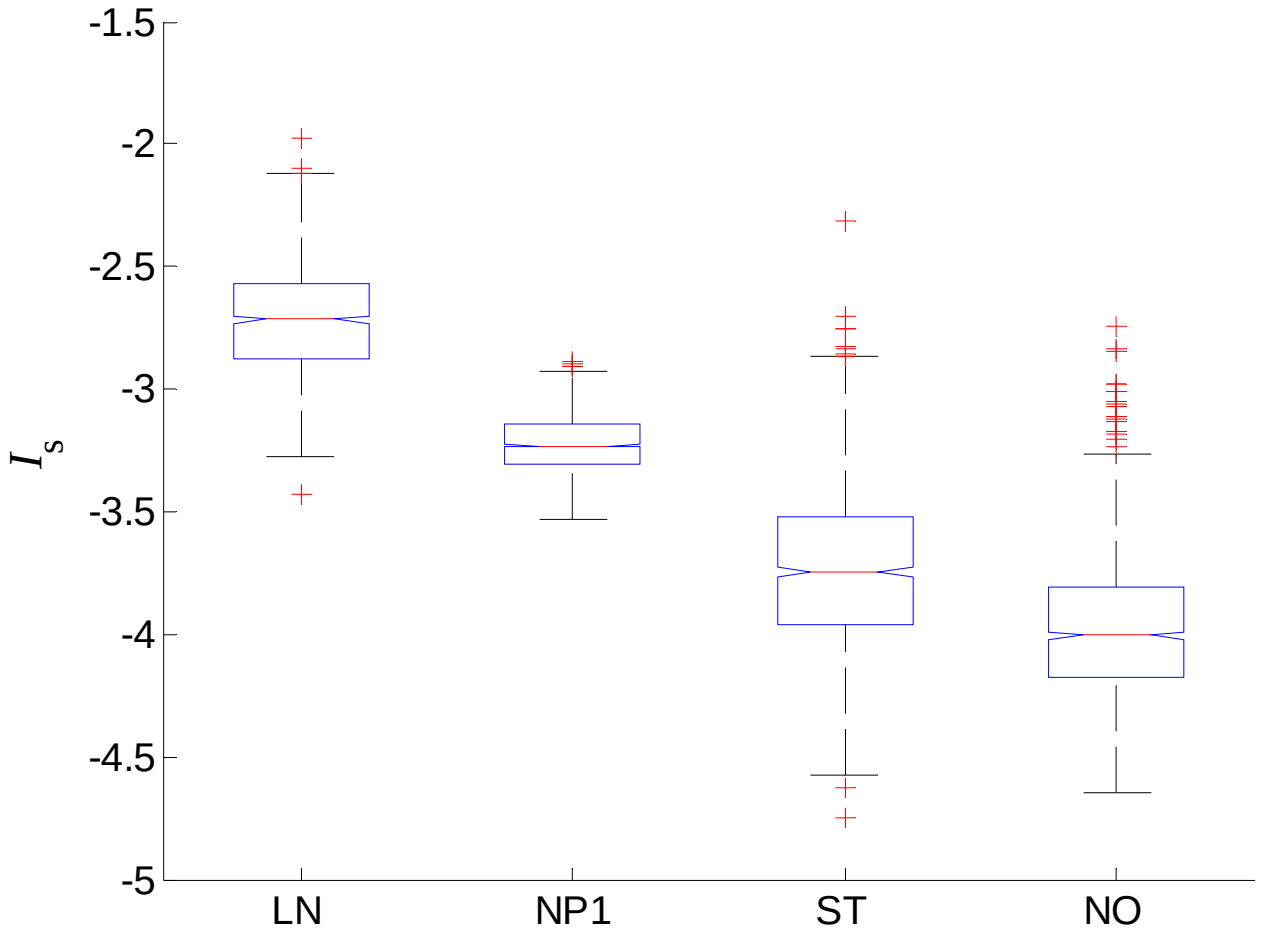
may be considered as the log-likelihood of the given model $\hat{f}(\underline{x})$ on the $\underline{\hat{x}}_j$ data .

- Try several models:
  - ☐ parametric or
  - ☐ nonparametric and

select the most likely one, that having the highest I_S w.r.t. the $\underline{\hat{x}}_j$ data

- Bootstrap :
  - ☐ Obtain median and inter-quartile range of $I_S(\hat{f}, n)$ for each $f(\underline{x})$ model.

The LN model is the best



Q3 : Detecting atypical individuals

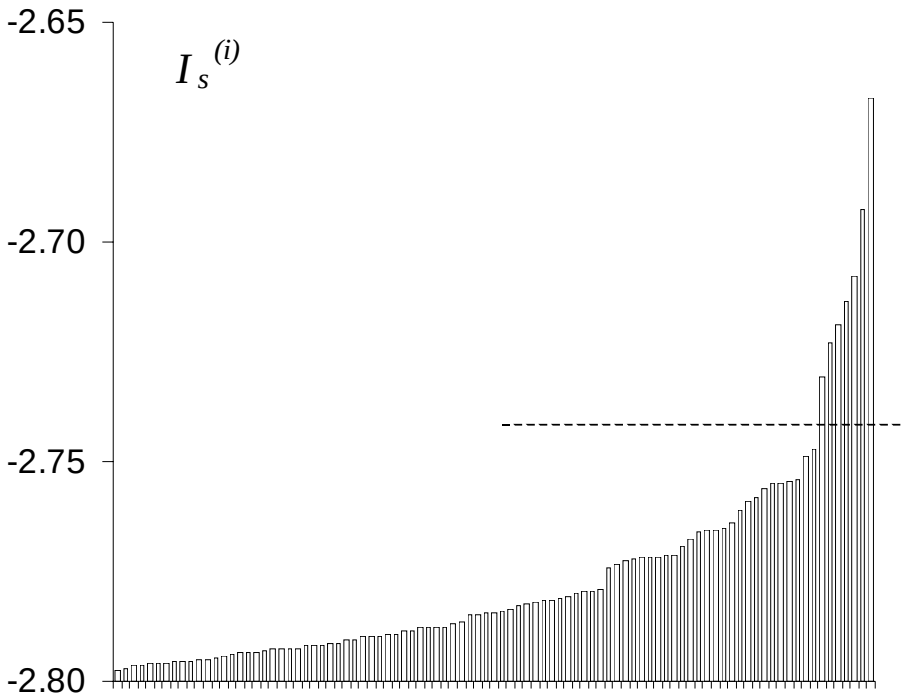
- "Leave-one-out" technique:
  - evaluate the information brought by a given individual j by computing the amount of information on n data without the j-th individual:

$$I_S^{(j)}\left(\hat{f}, n\right) = (n-1)^{-1} \cdot \sum_{\substack{r=1 \\ r \neq j}}^{n} \ln \hat{f}\left(\underline{\hat{x}}_r\right)$$

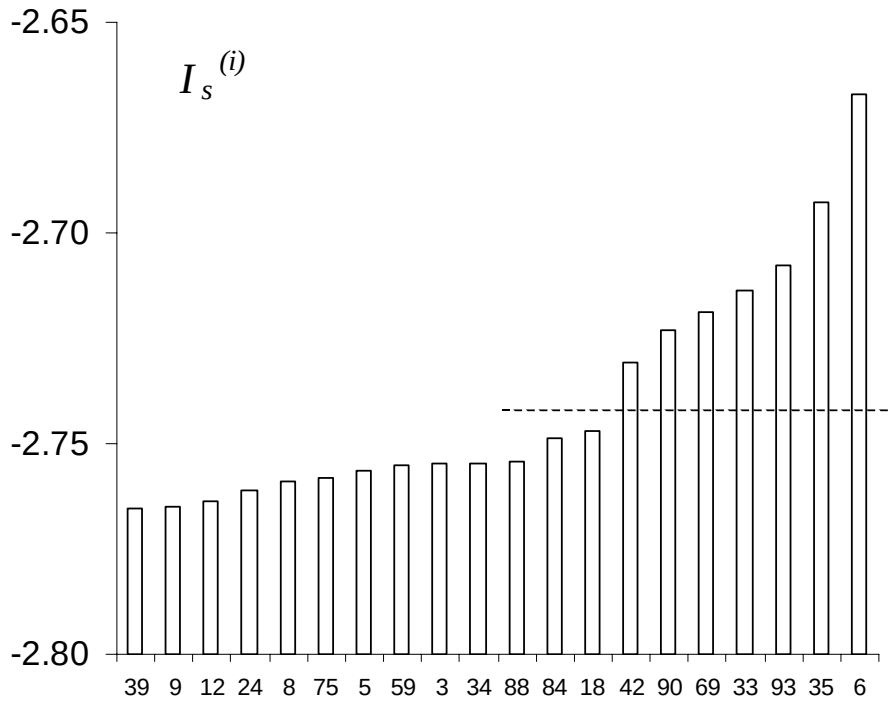
- Sort individuals according their $I_S^{(j)}$ scores:

Individuals associated with high $I_S^{(j)}$ may be considered as atypical individuals

7 atypical individuals



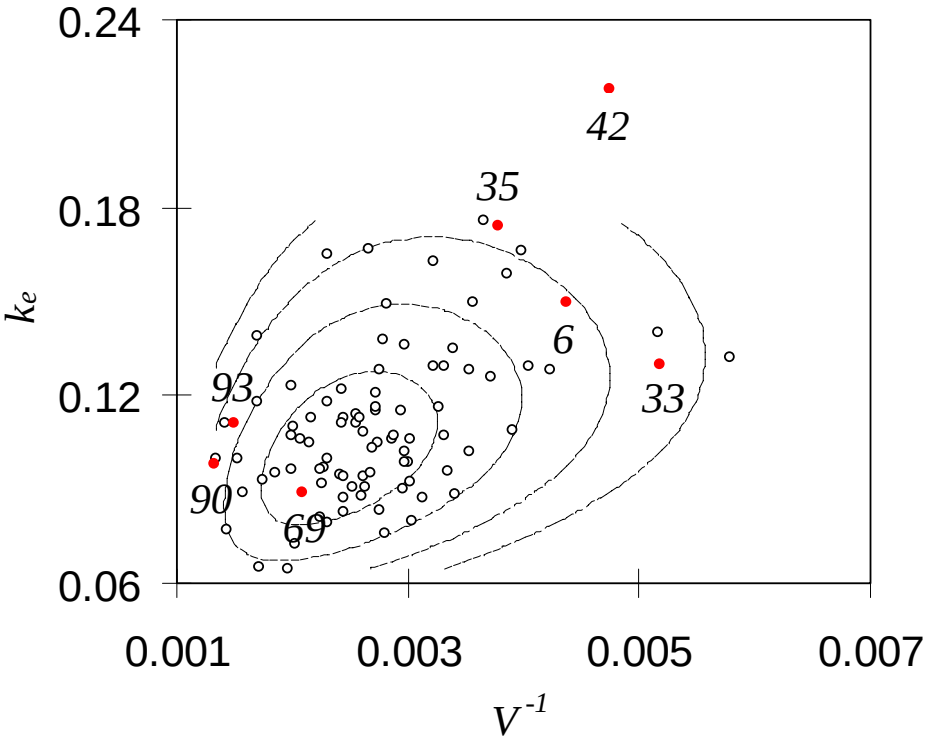
Sorted individuals

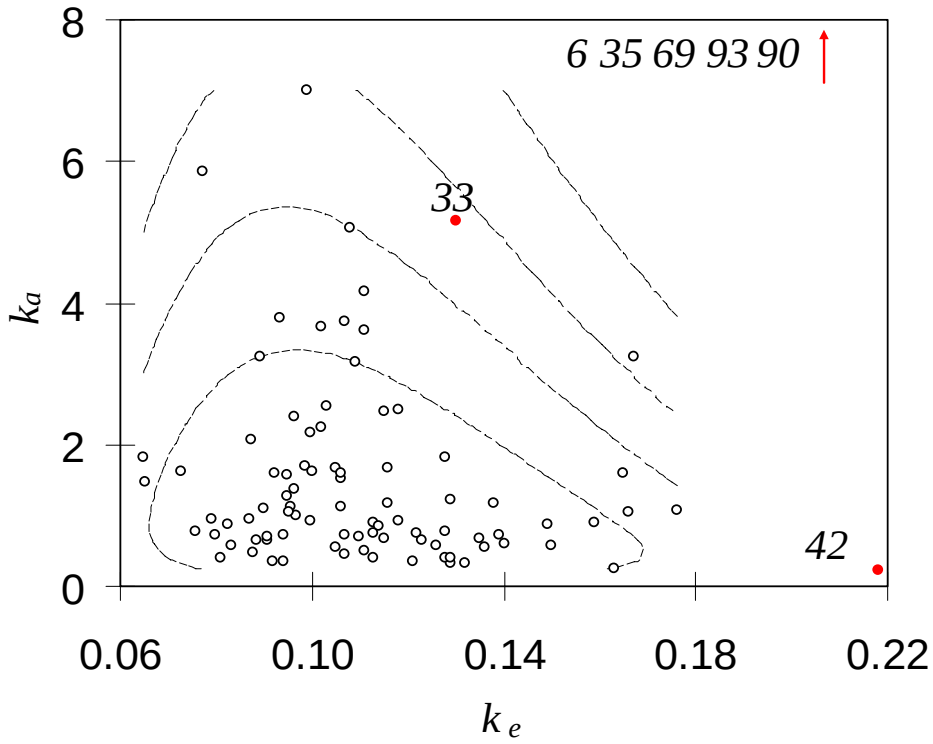


The last 20 sorted individuals

LN PDF in the parameter space

- Contour plots and atypical subjects





★ LN PDF was obtained without discarding atypical subjects.

Q4 : Screening influential covariates

- Examine the amount of information brought by their knowledge
  - The conditional information $I_C^{(k)}$ of the kinetic parameters $\underline{X}$, given a covariate μ_k:

$$I_C^{(k)} = I_S\left(\hat{f}_{\underline{X},\mu_k}, n\right) - I_S\left(\hat{f}_{\mu_k}, n\right)$$

    is the information expected for the kinetic parameters $\underline{X}$ if covariate μ_k is known.

  - The mutual information $I_M^{(ik)}$ between a given kinetic parameter X_i and a given covariate μ_k :

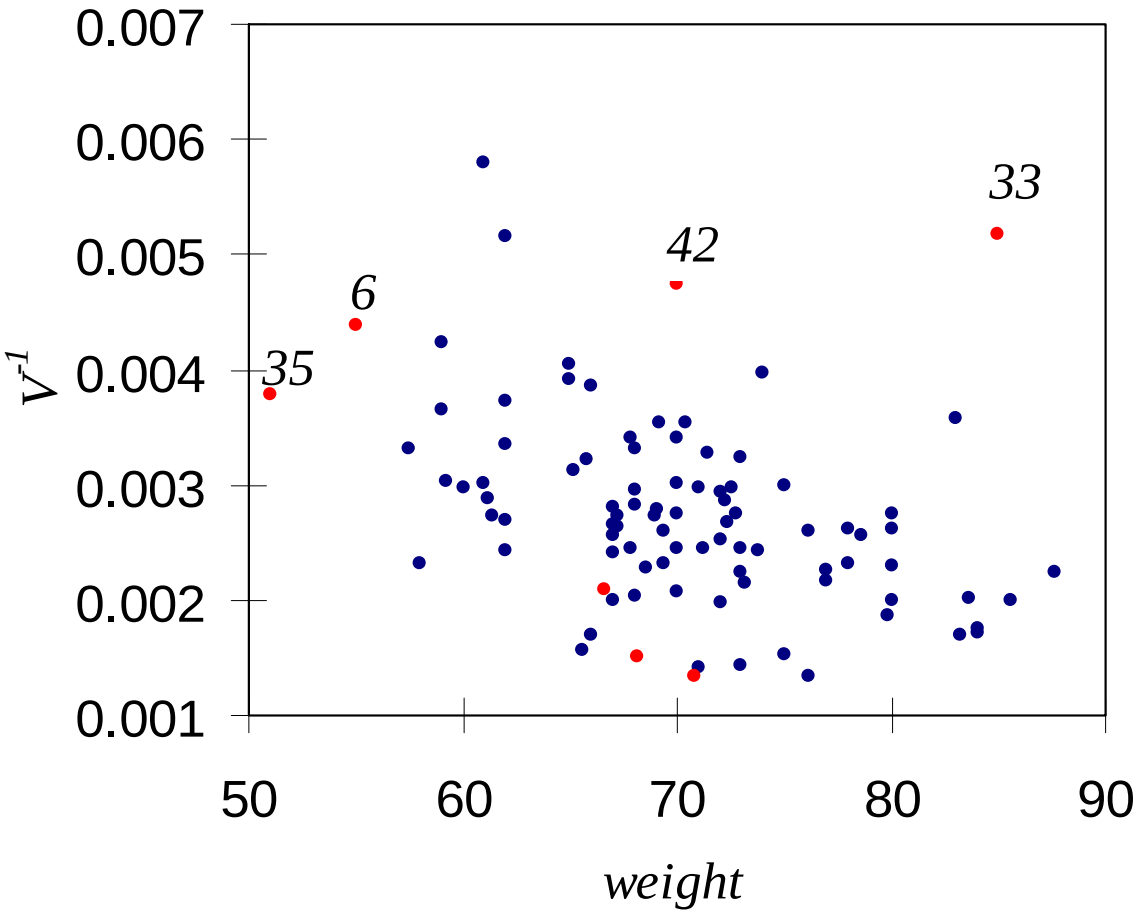
$$I_M^{(ik)} = I_S\left(\hat{f}_{X_i,\mu_k}, n\right) - I_S\left(\hat{f}_{X_i}, n\right) - I_S\left(\hat{f}_{\mu_k}, n\right)$$

    ★ Map $I_M^{(ik)}$ on the interval [0,1] by: $\delta^{(ik)} = \left[1 - \exp\left(-2 \cdot I_M^{(ik)}\right)\right]^{1/2}$

Influential covariates are that associated with the highest $I_C^{(k)}$ or $I_M^{(ik)}$

Influential covariates : weight, age

☐ Screen covariates by comparing $I_C^{(k)}$ obtained for each one : $I_C^{(weight)} > I_C^{(age)} > I_C^{(height)}$



Information and PK studies

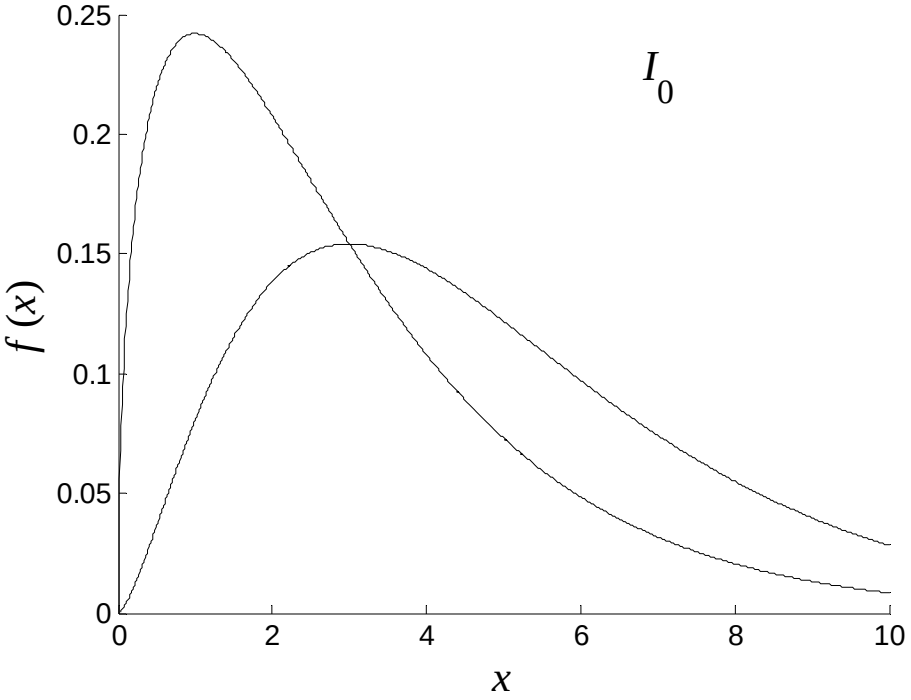
- Apply tools from information theory :
  - If the PDF is prior $f(\underline{x})$, $I_0 \equiv I(f)$ measures the dispersion of $\underline{X}$;
  - If the PDF is a posterior $f(\underline{x}/\underline{y})$, $I_1 \equiv I(f, \underline{y})$ evaluates the amount of information on $\underline{X}$ provided by $\underline{y}$.
- These indexes :
  - express the concept of : - disorder or entropy, and
    - variability, i.e., dispersion I_0 and precision I_1,

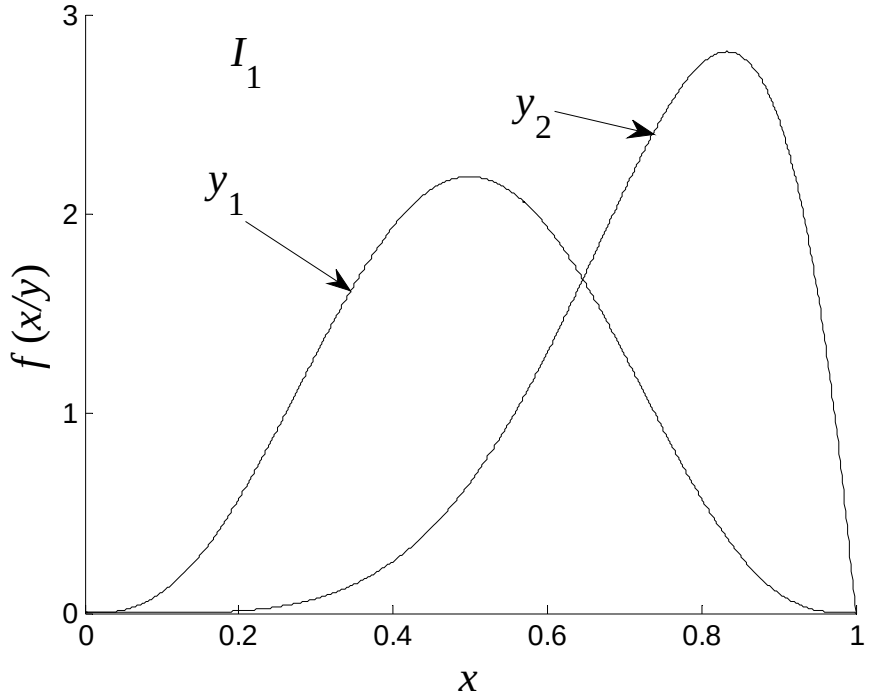
Control MAP performances by means of I_0 and I_1 balance

  - supply quantitative criteria to select the experiments to be performed,
  - allow unified approach for the analysis of problems.

Information indexes

- Apply the information tools :
  - ★ <u>prior</u> : select $f(\underline{x})$ for which I_0 is the lowest (detect sub-populations) ;
  - ★ <u>posterior</u> : select the experiment y for which I_1 is the highest.

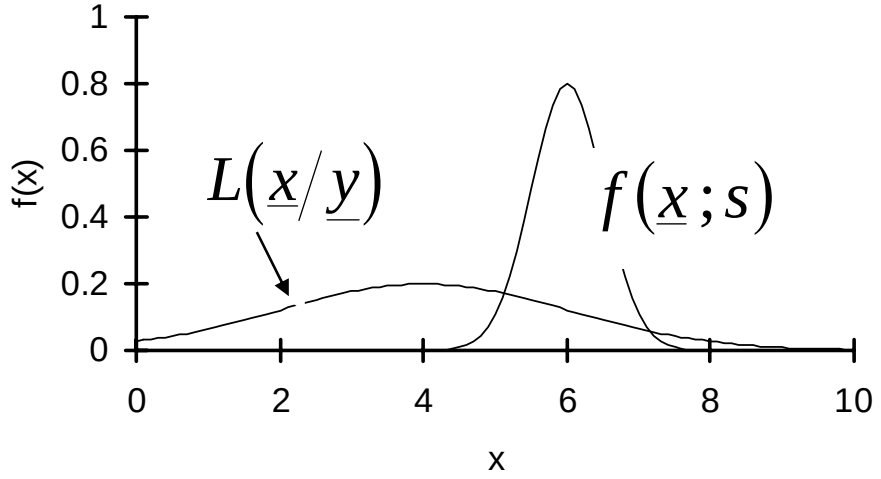




MAP estimators and population studies

- Remember the formula : $\hat{\underline{x}}_B = \arg\max\left\{ \ln f\left(\underline{x}; s\right) + \ln L\left(\underline{x}/\underline{y}\right) \right\}$

- Optimize the formula of MAP to improve its performance :



Ex : the MAP converge towards

a fixed point (mode of the prior)

- Balance MAP by means of the :

★quality of analytical method,
★number and location of sampling times,
★smoothing prior by means of *s*.

Properties of the kernel approach

- The nonparametric TS approach supplies the joint :

$$f\left(\underline{x}, \underline{\mu}\,; s\right)$$

- From the joint , it is easy to derive :
  - ★ marginals $f\left(\underline{x}\,; s\right)$ and
  - ★ conditionals $f\left(\underline{x} \,/\, \underline{\mu}\,; s\right)$

- Estimation of missing data from conditionals.
- Objective information indexes are available to control operations.
- All computations are made with analytic expressions : no iterative schemes, quick evaluations.
- Smoothing capabilities for MAP balancing.

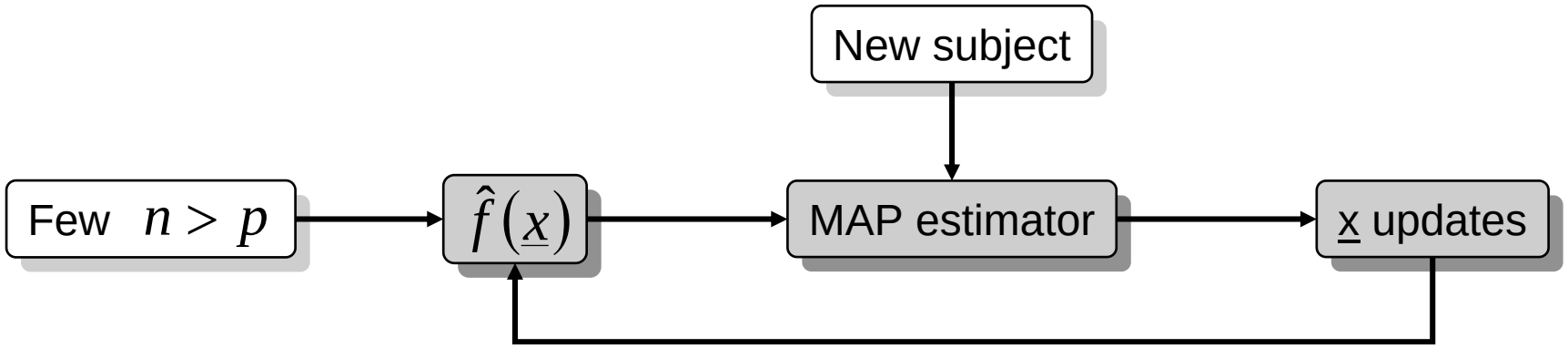
Real-time data processing

- If the prior is not informative : $I_0 << I_1$

  Conceive a sequential MAP learning procedure :

  ★ start with only few patterns to form an index group and then,

  ★ use MAP and periodic updates of $\hat{f}(\underline{x})$ as the number of patterns increases.



- Note : It is of interest to develop recursive formula for the NP $\hat{f}(\underline{x})$ estimation in order to occupy moderate memory when huge amounts of data are involved.

Future developments

- Notes :
  - Nonparametric PDF are proscribed for Q1 (size of data set) and Q3 (atypical patterns).
  - For statistical tests, use parametric PDFs.
  - SS methods and information tools :
    - ★ after Bayesian individualization, questions Q1 to Q4 are still present.
- Some questions remain :
  - Derive statistics for the metrics H .
  - Determine the best smoothing s for nonparametric PDFs.
  - Control the number of subjects before or after the PDF model is established ?
  - Software implementation.