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

Unité d'Enseignement III i-1

Études de population

- Introduction : Variabilités
- Approches et méthodes
- Analyses de population
- Exemple clinique

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

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Introduction : Principes de base

- Variabilité intra – individuelle : Modélisation.
- Variabilité inter – individuelle : Relations « dose - réponse ».
- DCCT vs. CCCT.
- Adaptation de posologie.

Standardisation des observations

- Exemple: Administrer la même dose chez 2 sujets et comparer les cinétiques.

Protocole de prélev. (h)		1	2	6	12
Temps réels prélev. (h) / Sujet n° 1		0.975	2.06	6.12	-
Conc.	#	y_{11}	y_{12}	y_{13}	-
Temps réels prélev. (h) / Sujet n° 2		1.03	2.0	5.9	12.06
Conc.	#	y_{21}	y_{22}	y_{23}	y_{24}

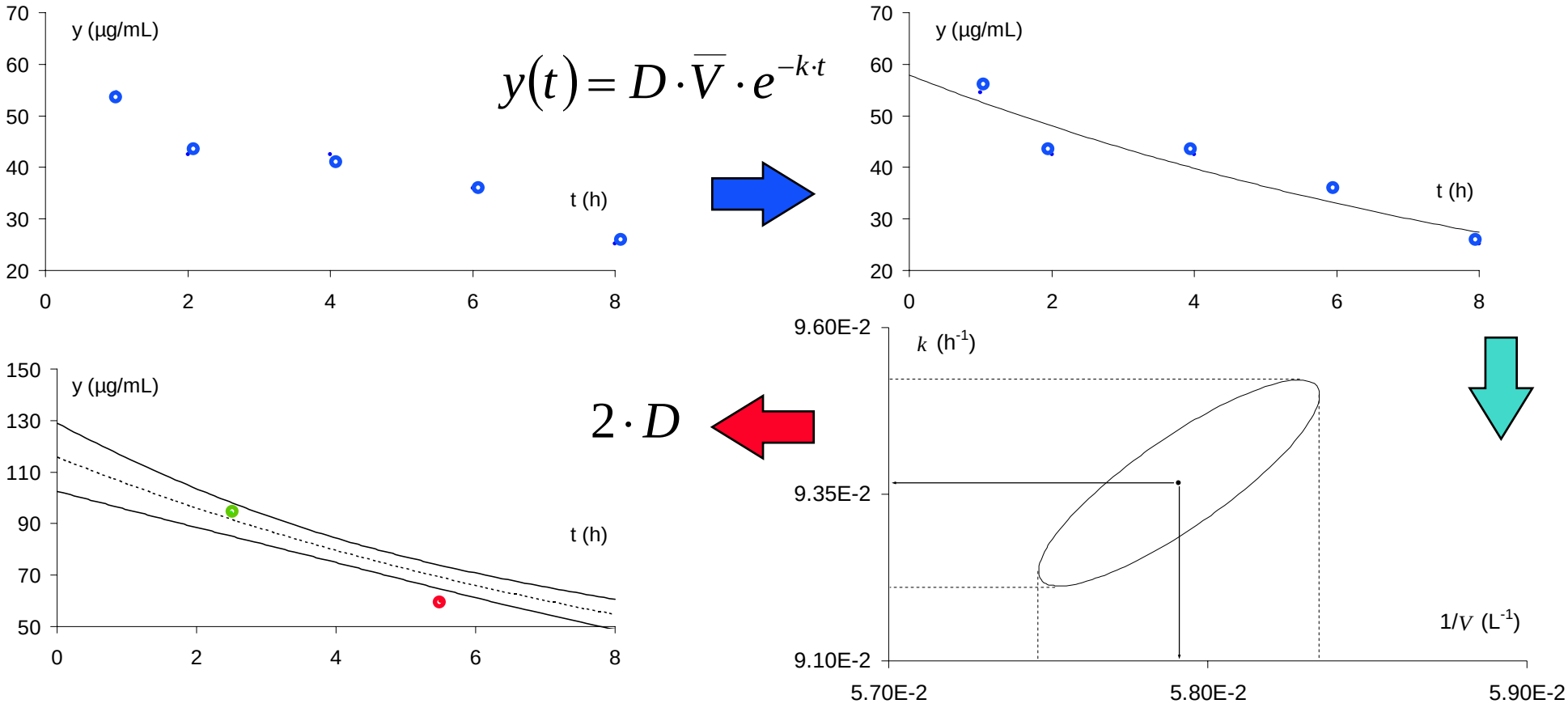
  - Hétérogénéité du protocole, comparaison impossible.
  - ✓ Faire la comparaison en dehors du « monde » des concentrations.

- Transformation: ⇒ Utiliser un modèle mathématique qui lissera les observations et calculera les paramètres PK

  - ☐ Comparer les paramètres PK.

Variabilité intra - individuelle

- Régions et couloirs de confiance



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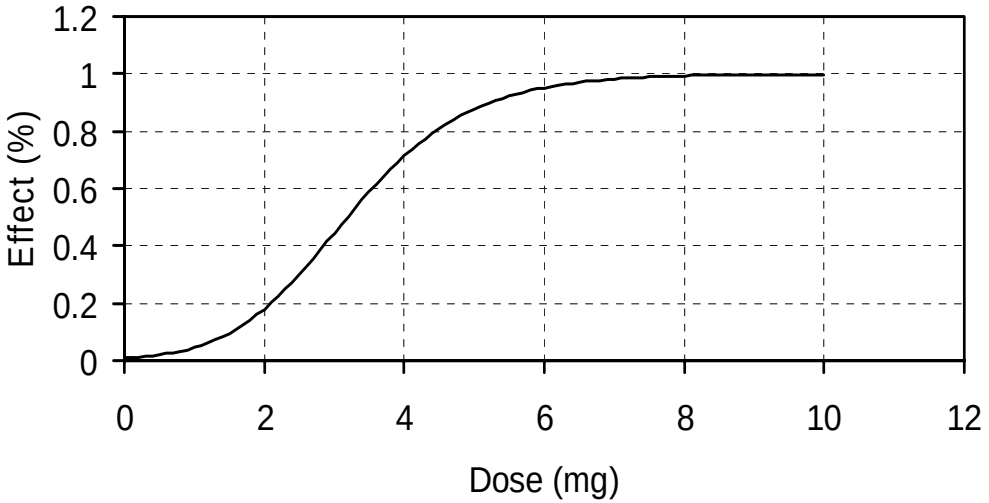
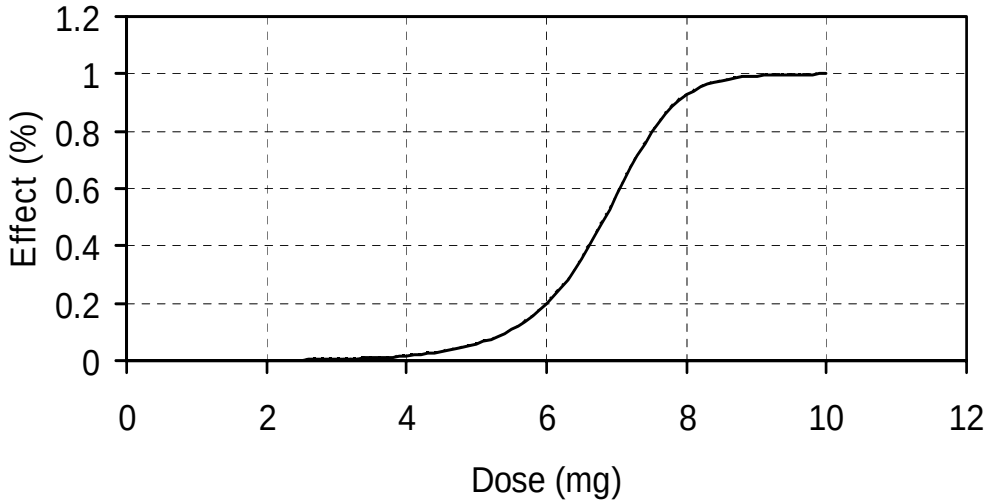
La relation « dose - réponse »

- Etudier les relations :

dose - efficacité

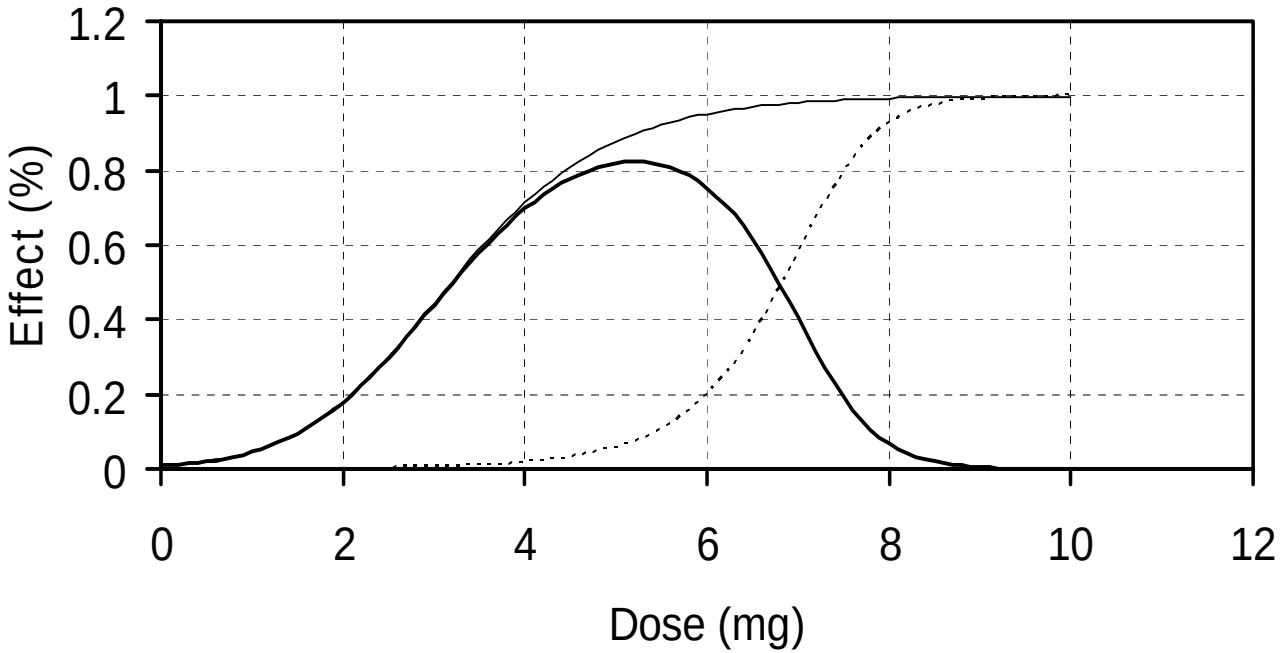


dose - toxicité



Le rapport [bénéfice / risque]

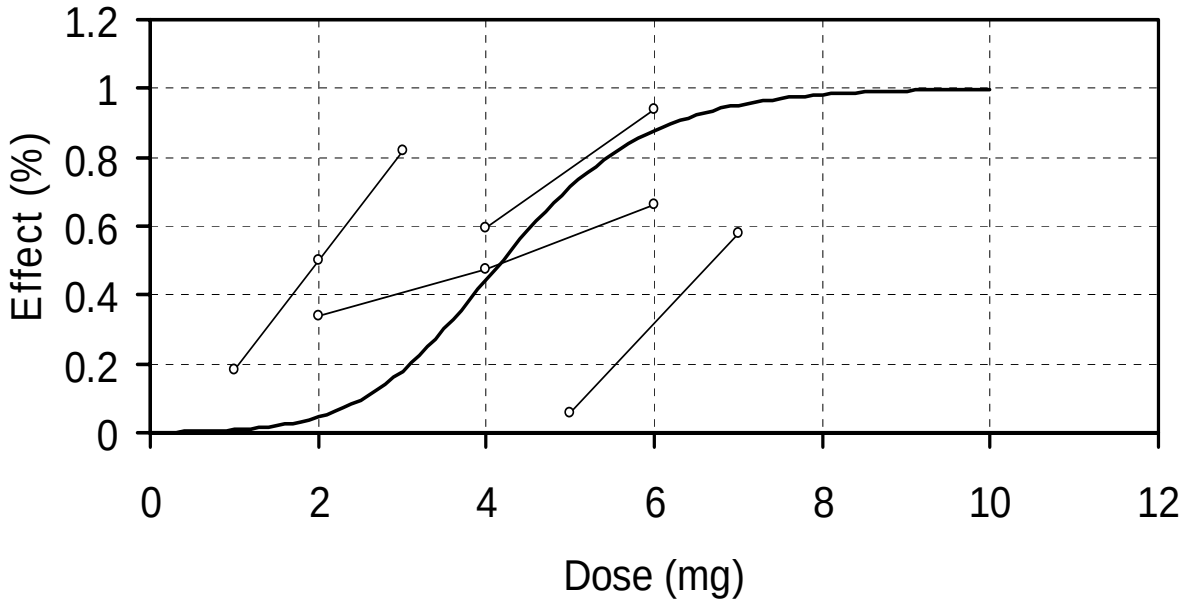
- Etablir les relations « dose - bénéfice » and « dose - risque » :



- Optimiser le protocole d'administration du médicament :
  - ☐ Choisir le contrôle (dose) maximisant le rapport [bénéfice / risque].

La réalité

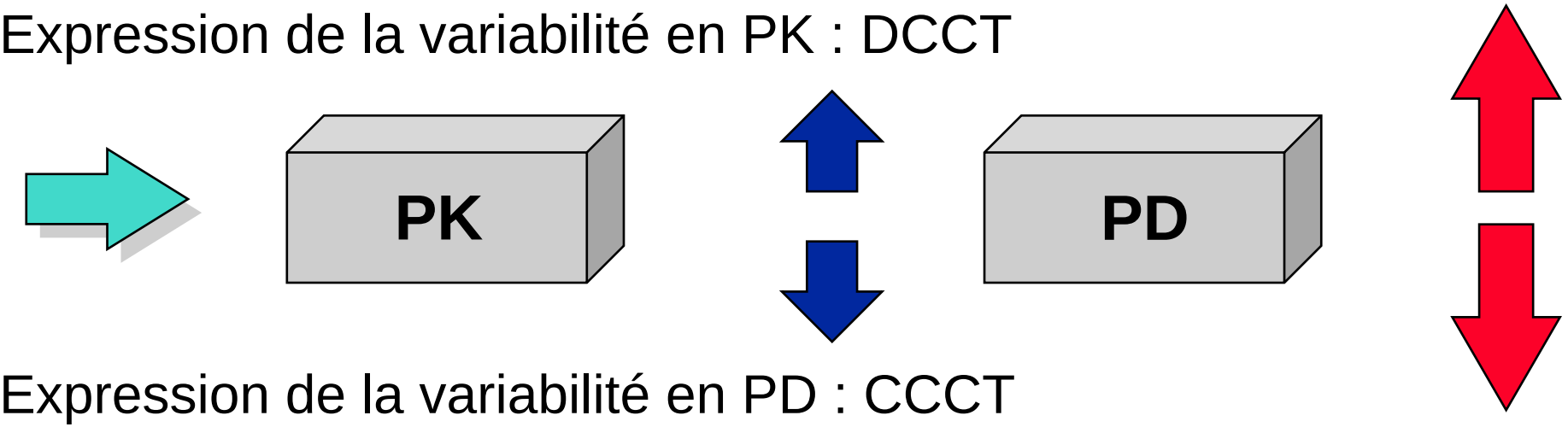
- La relation « dose - réponse » lisse hautement les données



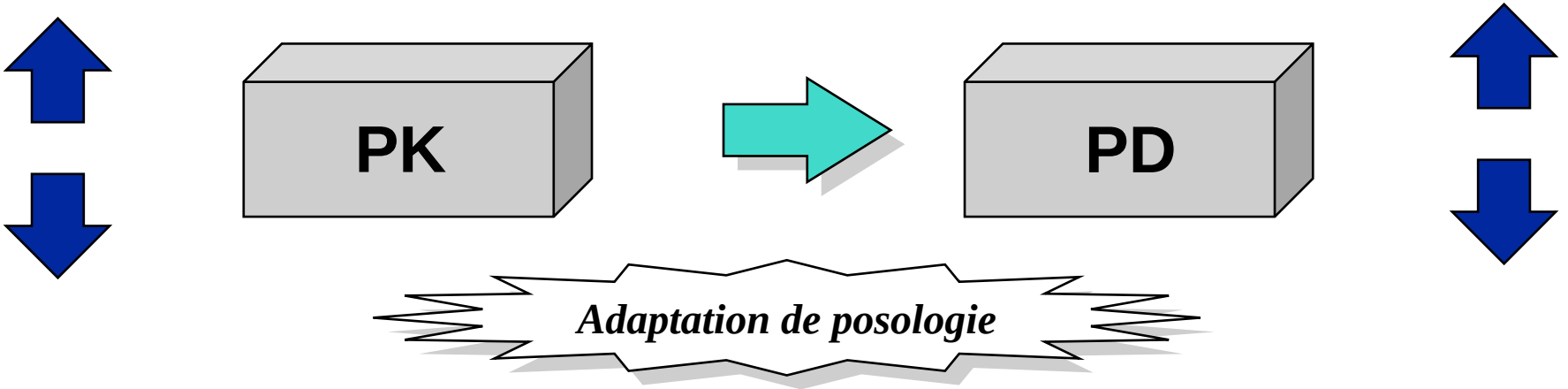
- ☐ Variabilité inter - individuelle importante :
  - ★ La qualité de la prédiction (à partir de la relation « dose - réponse » obtenue sur un groupe de sujets) diminue quand la variabilité augmente.

DCCT et CCCT

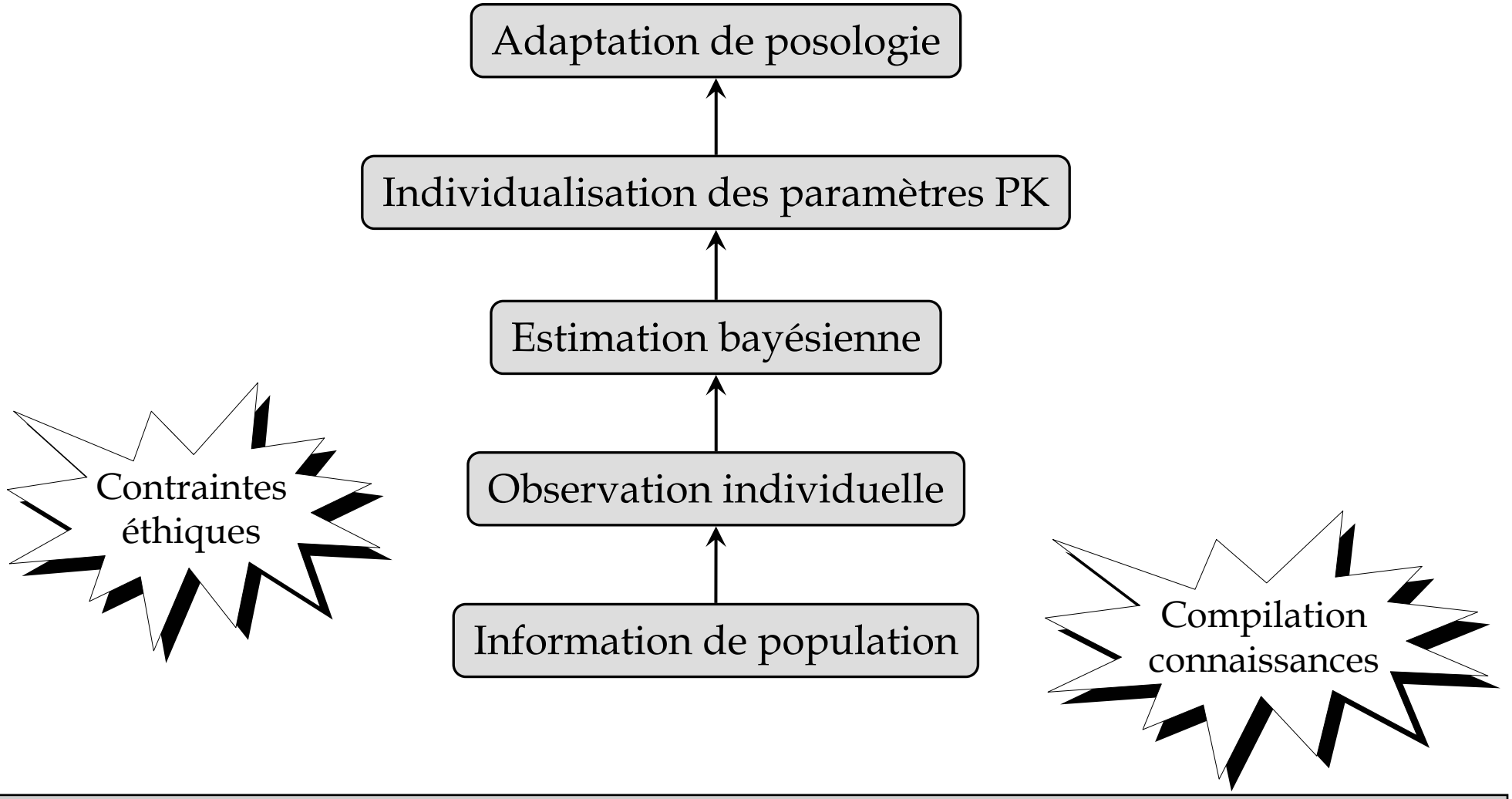
- Expression de la variabilité en PK : DCCT



- Expression de la variabilité en PD : CCCT



Organigramme opératoire



Contribution des approches de population

- Etudes précliniques:
  - ★ Extrapolation: animal ⟹ 1e dose chez l'homme,
  - ★ Escalade de doses.
- Phase I:
  - ★ Extrapolation PK: volontaire sain ⟹ patient,
  - ★ Planification: variable de contrôle (DCCT / CCCT).
- Phases II et III:
  - ★ Individualisation des posologies,
  - ★ Simulations des essais intégrant les imperfections en pratique: compliance, perdus de vue, etc.
- Commercialisation:
  - ★ Etiquetage utile (individualisation), conseils PK/PD.

⟹ L'intégration précoce des études de population peut:
- ★ augmenter la fiabilité de l'information sur le médicament,
- ★ diminuer le nombre d'études cliniques, et

ainsi permettre un développement plus rapide et moins coûteux

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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.

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

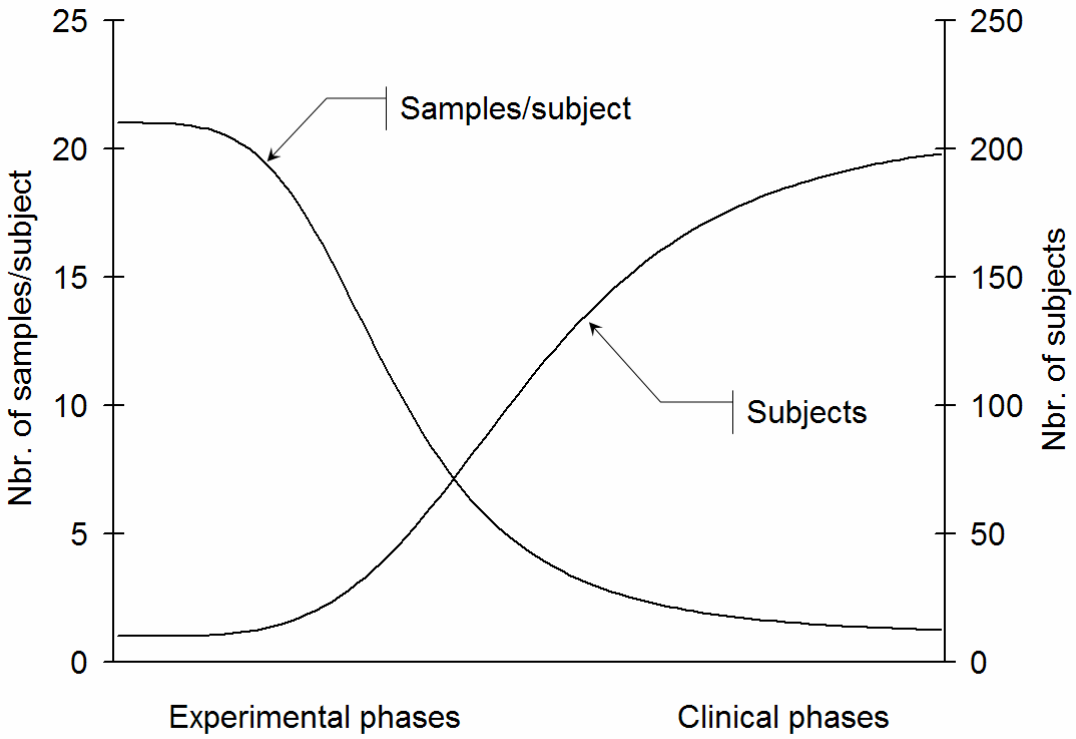
- The solution :

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 insufficiency, etc)

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

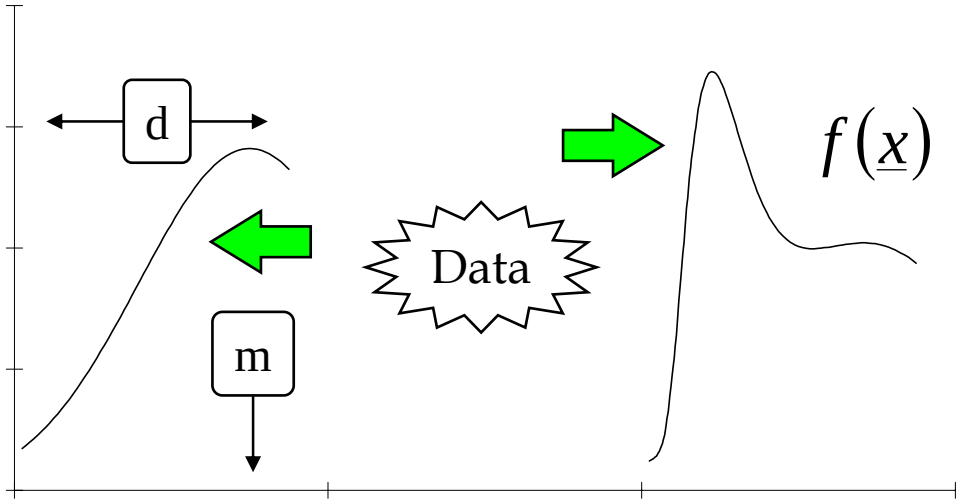
- Density estimation ➡ the construction of an estimate $f(\underline{x})$ of the density function $\varphi(\underline{x})$ from the available data.

- Approaches to density estimation

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

    Ex : the normal density :

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



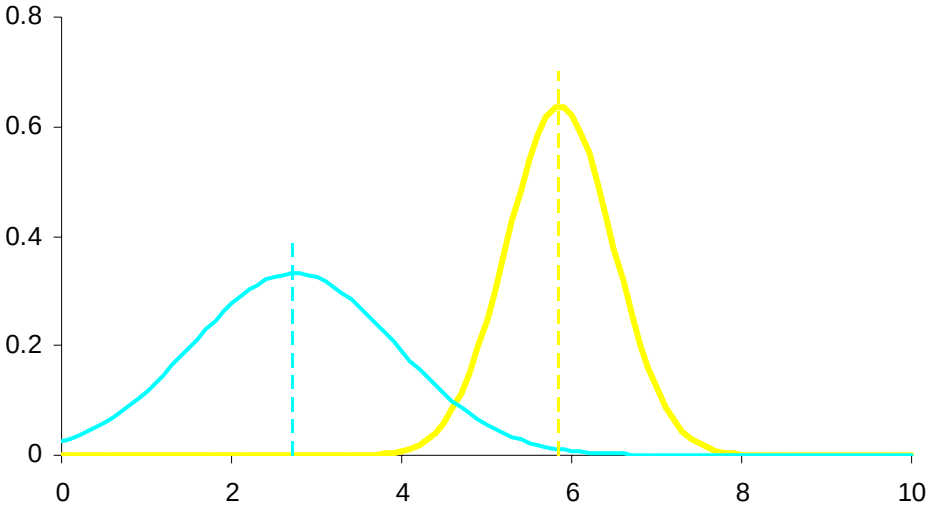
  - ☐ Nonparametric : distribution free of structure and parameters.

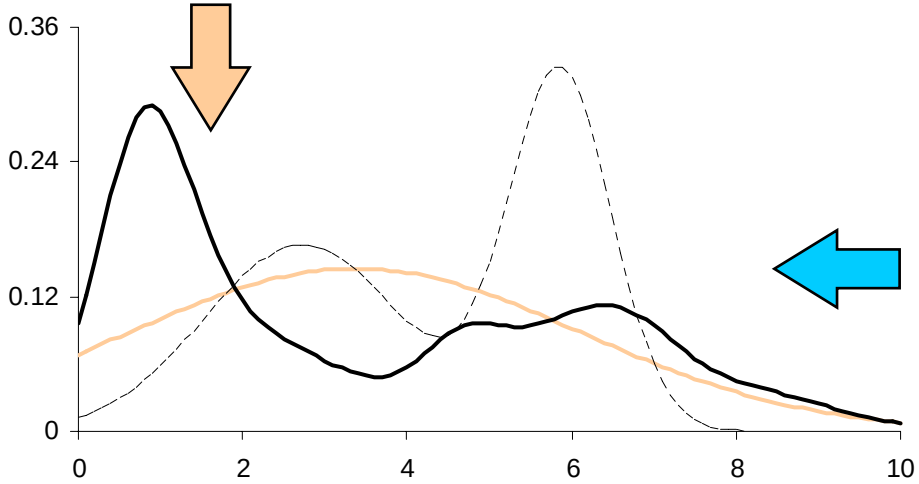
Parametric vs. nonparametric pdf

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

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

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 :

$$\underline{y}_j = \{\underline{c}_j \quad \underline{z}_j\} \Rightarrow \boxed{\text{PK / PD model}} \Rightarrow \underline{x}_j = \{\underline{\theta}_j \quad \underline{\delta}_j\}$$

$$\underline{\mu}_j \uparrow \boxed{\text{PK / PD model}}$$

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

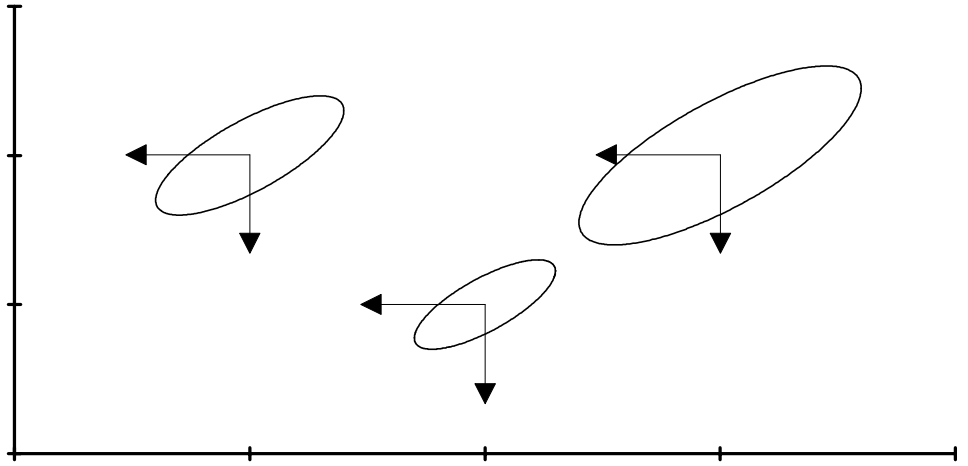
Choices in the TS methods

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

$$\underline{x}_j^T = \left[\underline{\mu}_j, \underline{\theta}_j, \delta_j\right]^T \qquad \left\{ \underline{x}_j \; ; \; j = 1, n \right\}$$

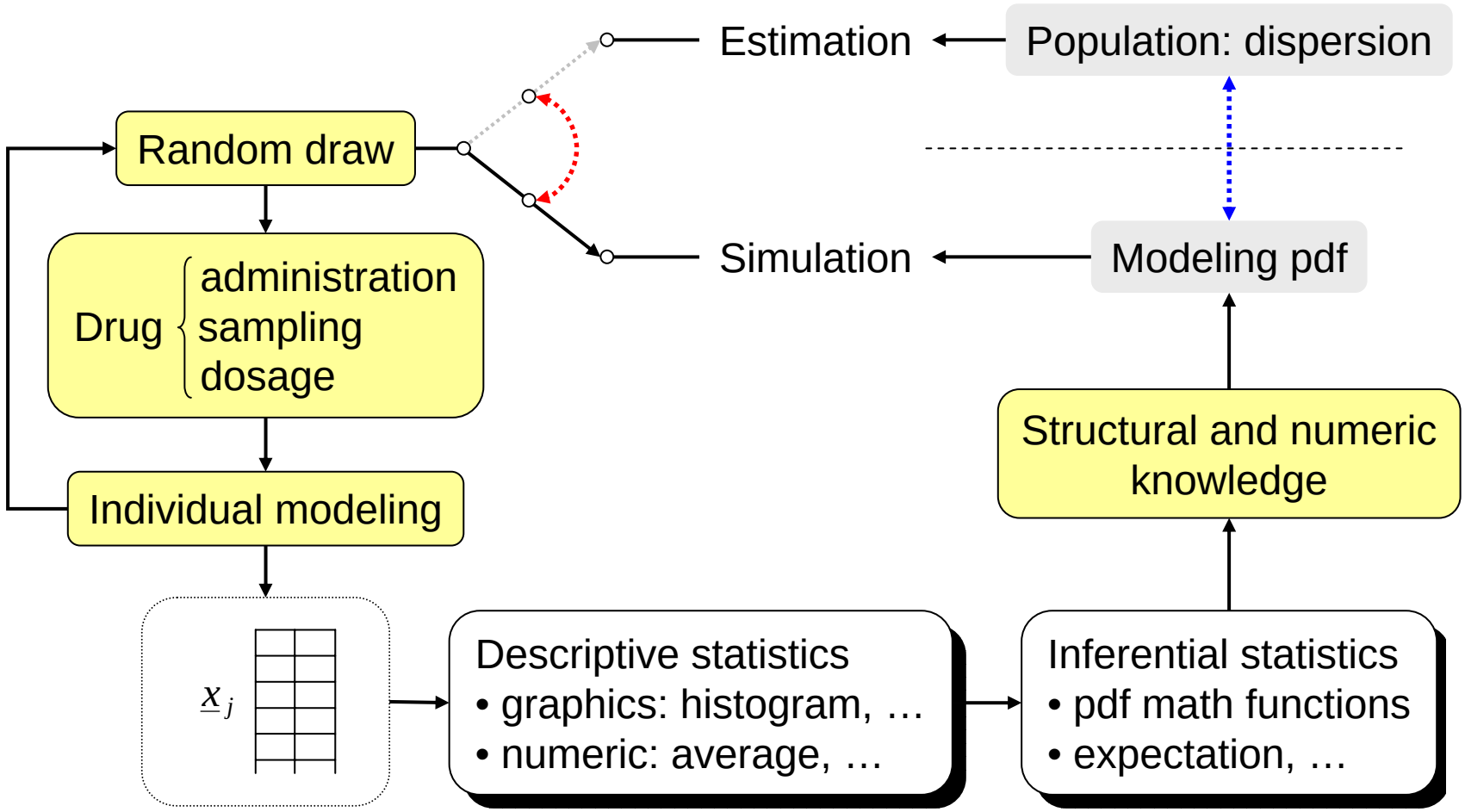
- If **MLE** is used, we can obtain the **precision** of estimates in a matrix P_j .
  - ★ record P_j in the training data base :

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



- In the second stage : Estimate $\varphi(\underline{x})$ 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)

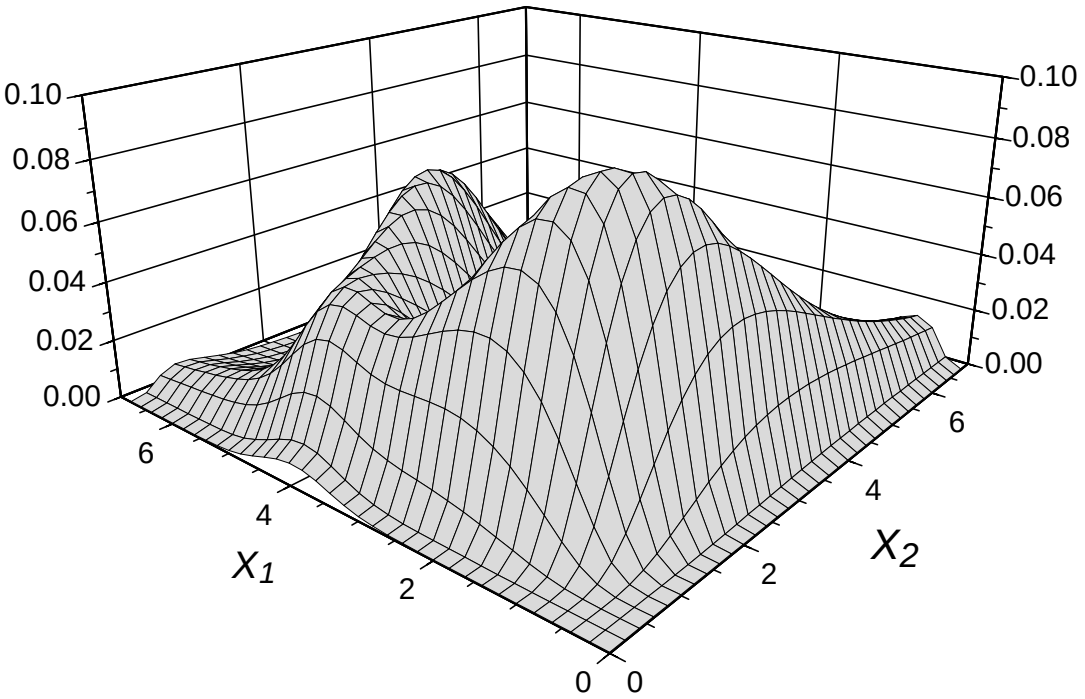
  - NO : - mean $\begin{bmatrix} 5 & 3 \end{bmatrix}$

    - 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



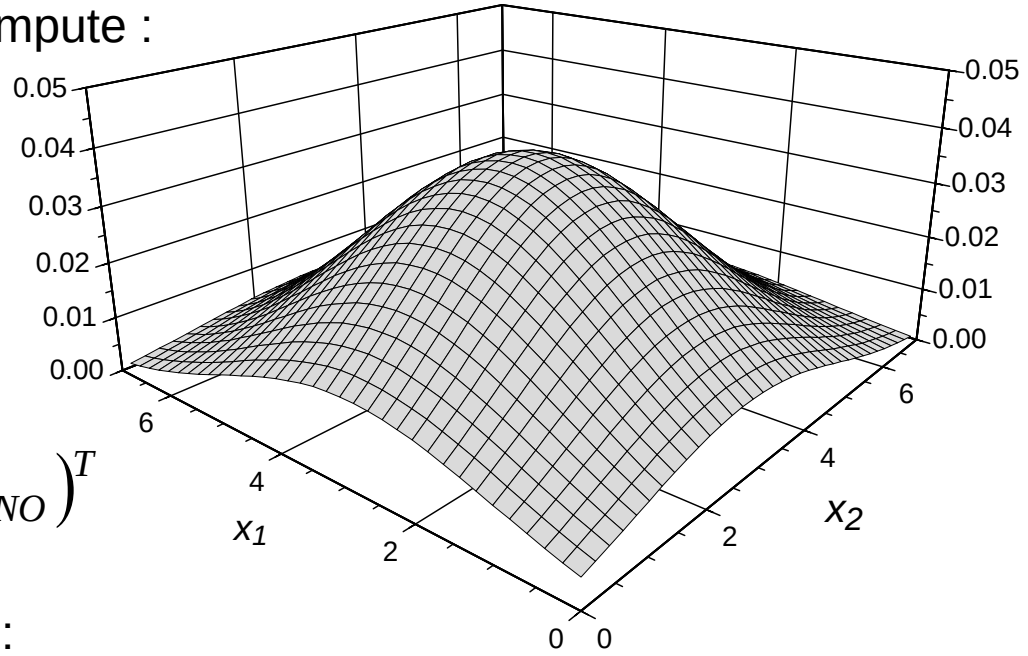
Parametric distributions in TS - 1

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

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

    2. the dispersion matrix :

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



  - The multivariate NO density function is :

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

Parametric distributions in TS - 2

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

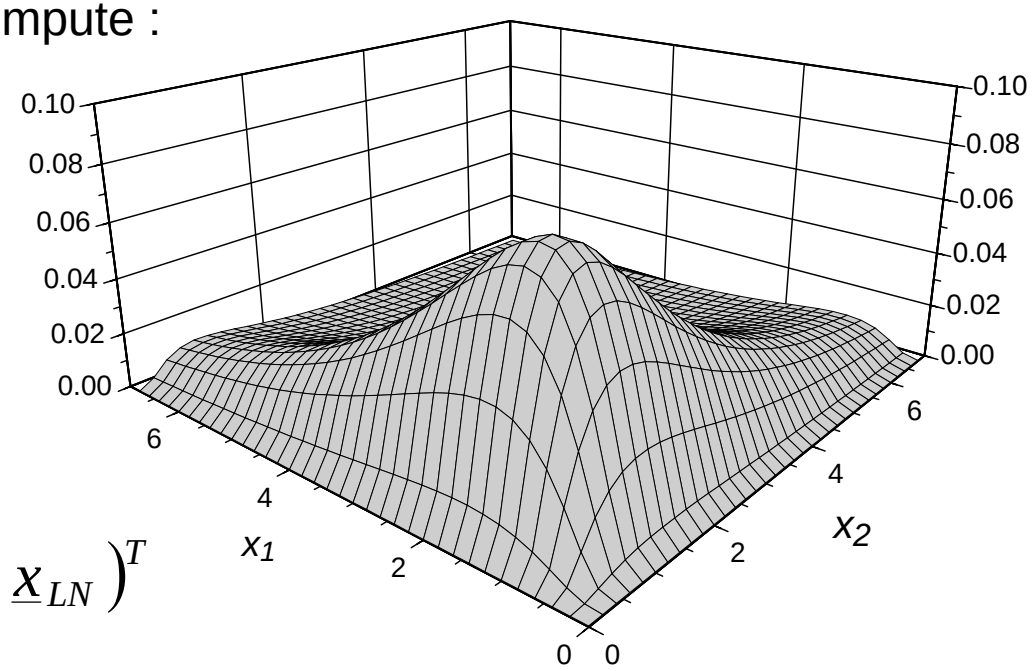
$$\underline{\ln x}_j^{\,T} = \left[\ln x_{1j} \; \ldots \ln x_{pj} \right]$$

    2. the mean vector :

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

    3. the dispersion matrix :

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



  - The multivariate LN density function is :

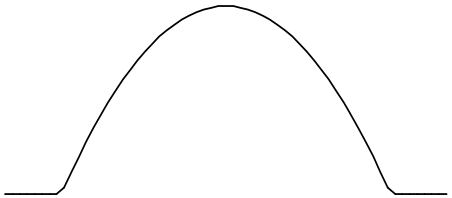
$$f_{LN}(\underline{x}) = (2\pi)^{-p/2} \cdot |D_{LN}|^{-1/2} \cdot \left[1 / \prod x_s \right] \cdot \exp\left[-1/2 \cdot \left(\underline{\ln x} - \underline{x}_{LN} \right)^T \cdot D_{LN}^{-1} \cdot \left(\underline{\ln x} - \underline{x}_{LN} \right) \right]$$

What is a kernel ?

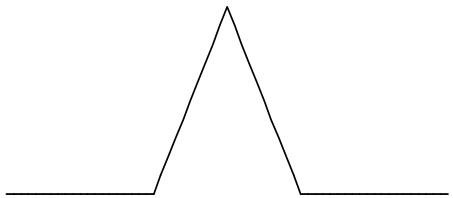
- Elementary functions $k(x)$ with :

$$\int_{-\infty}^{+\infty} k(\underline{x}) \cdot d\underline{x} = 1$$

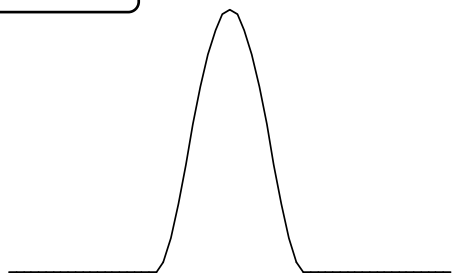
Epanechnikov



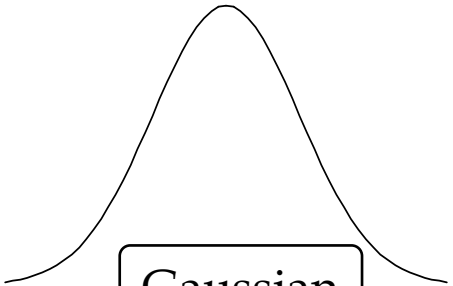
Triangular



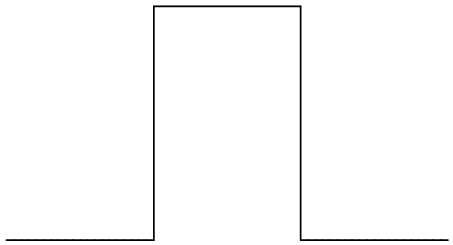
Biweight



Gaussian

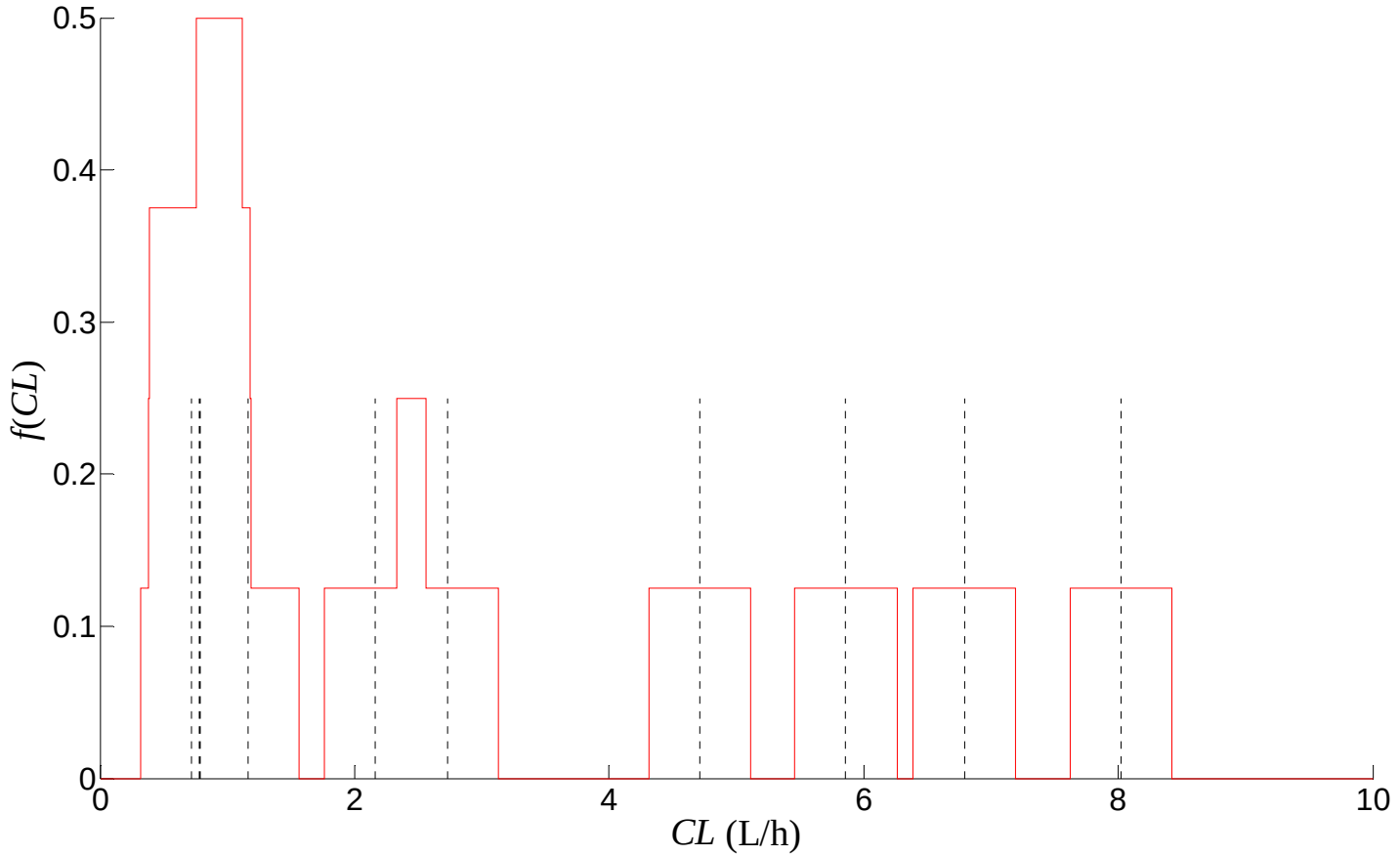


Rectangular



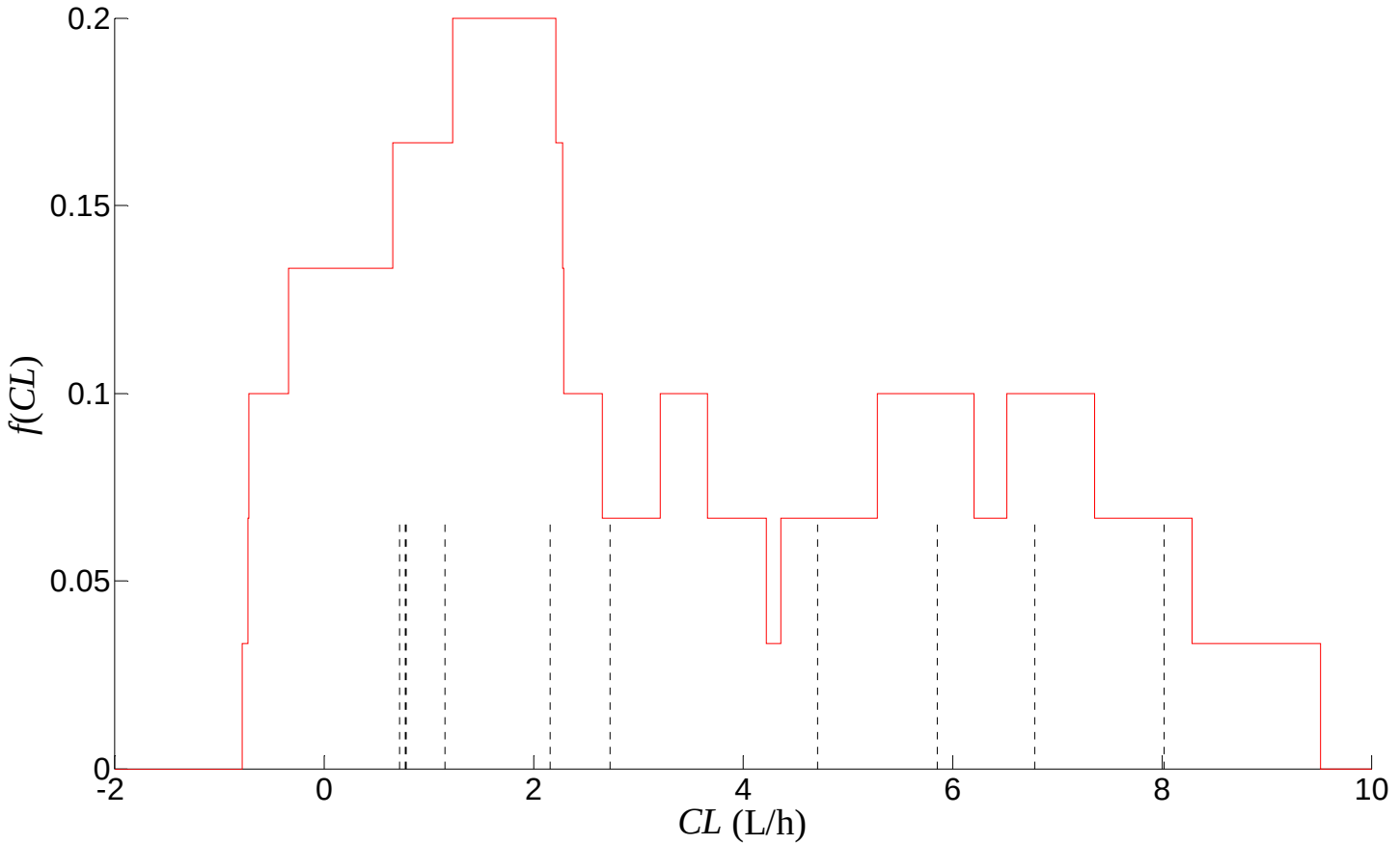
Low smoothing or …

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



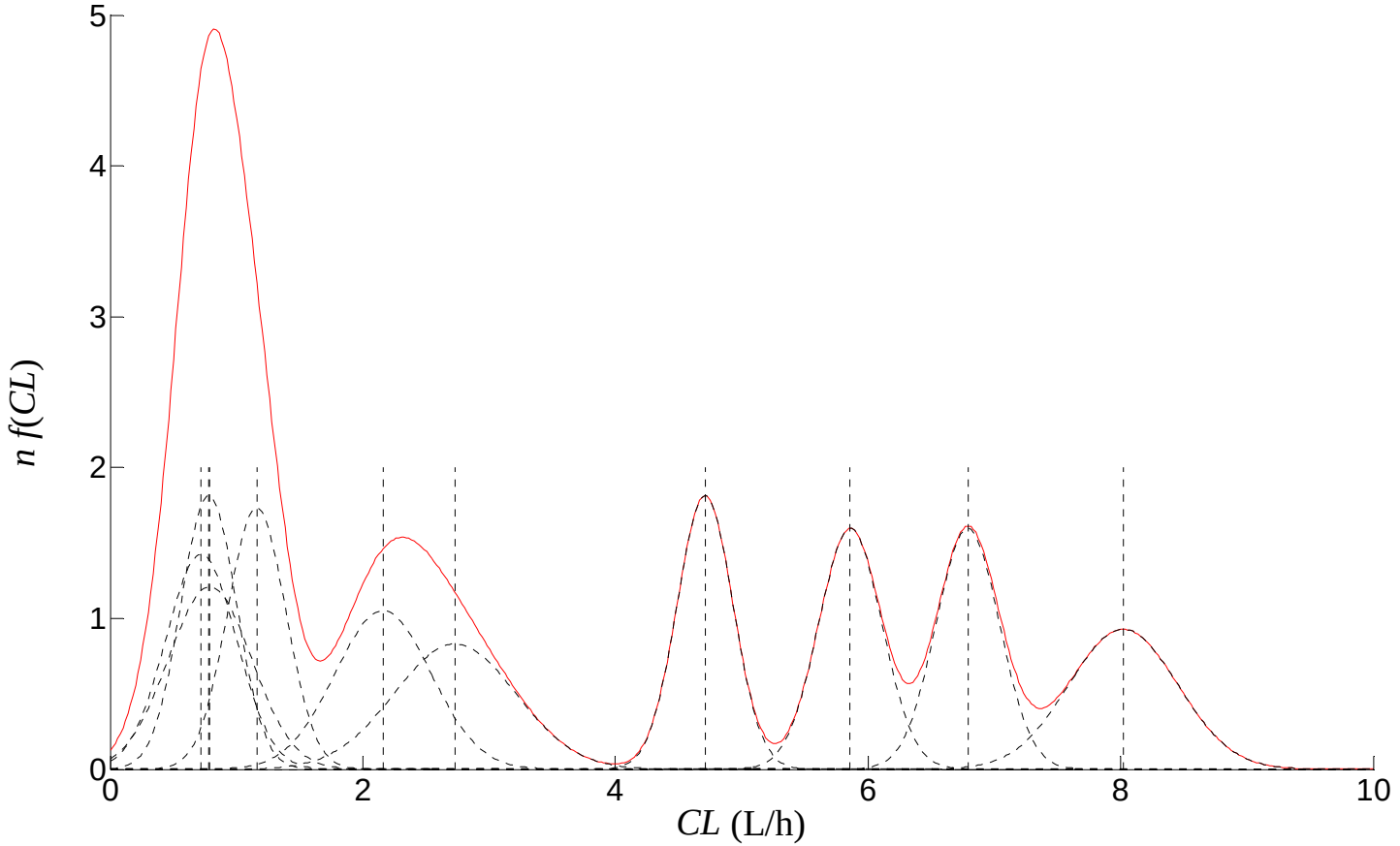
… or high smoothing ?

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



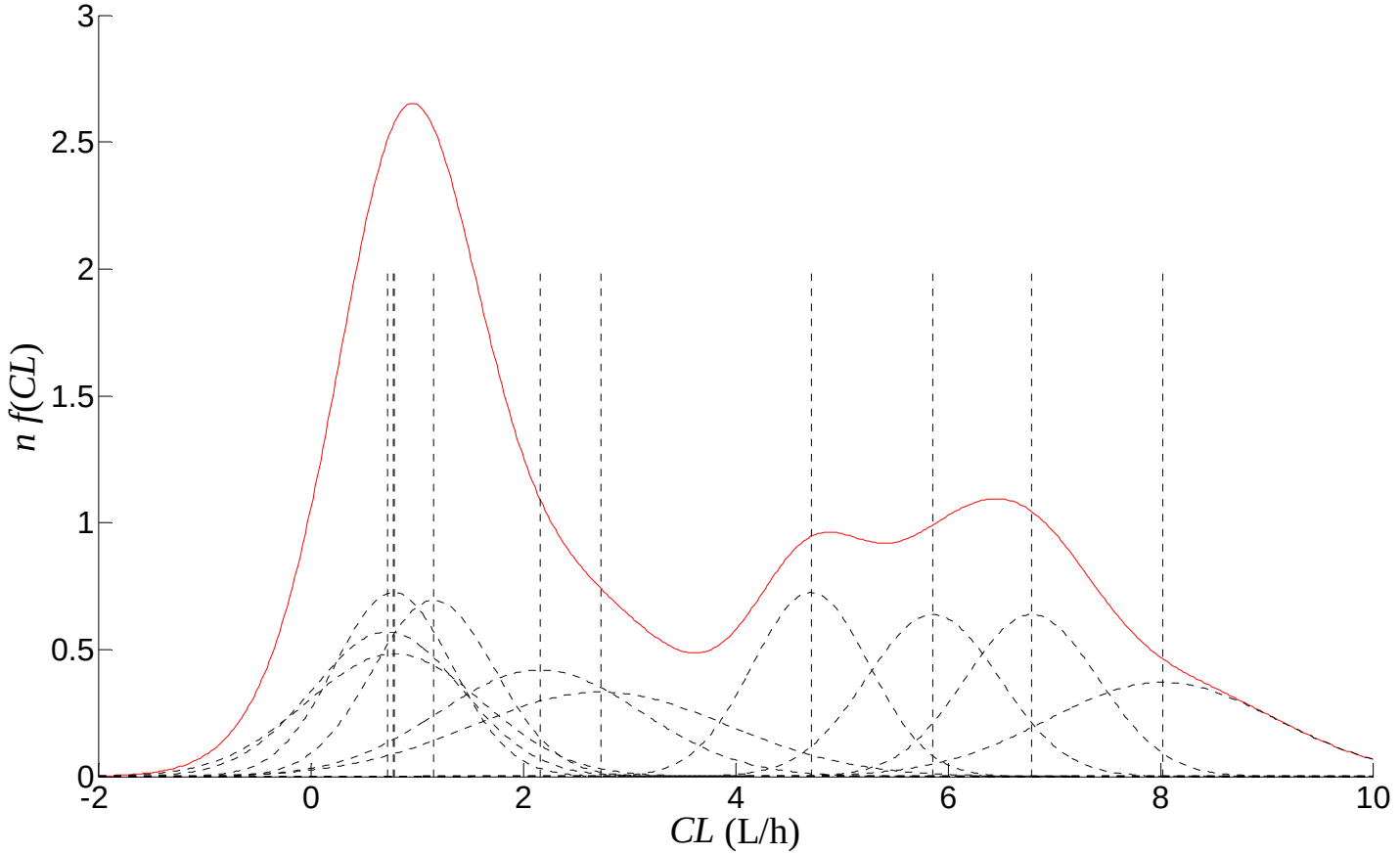
Adaptive smoothing - 1

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



Adaptive smoothing - 2

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



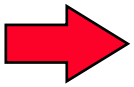
Nonparametric distributions in TS

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

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

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

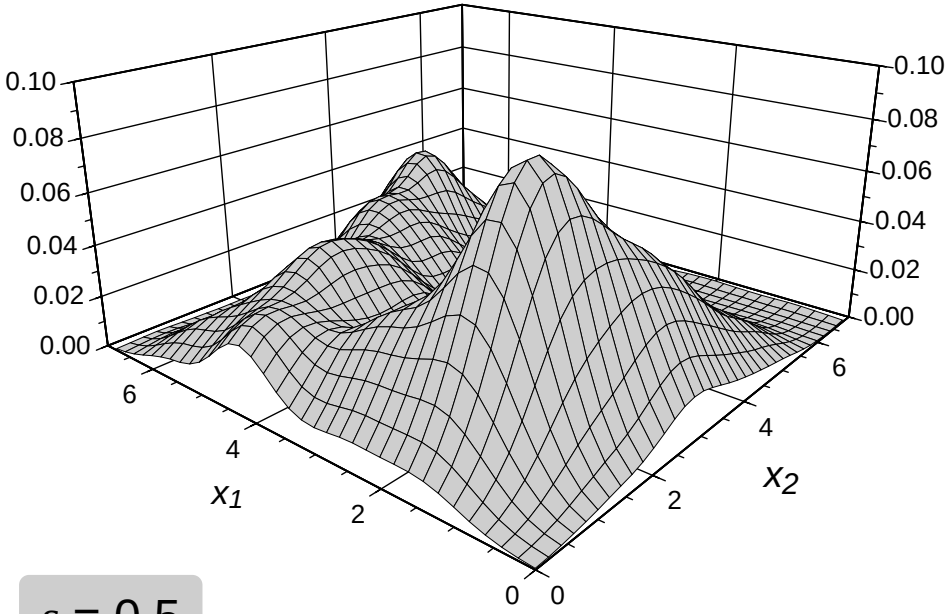
$$f(\underline{x}, s) = n^{-1} \cdot (2\pi)^{-p/2} \cdot s^{-p} \cdot \sum_{j=1}^{n} \left|P_j\right|^{-1/2} \cdot \exp\left[-1/2 \cdot s^{-2} \left(\underline{x} - \underline{x}_j\right)^T \cdot P_j^{-1} \cdot \left(\underline{x} - \underline{x}_j\right)\right]$$



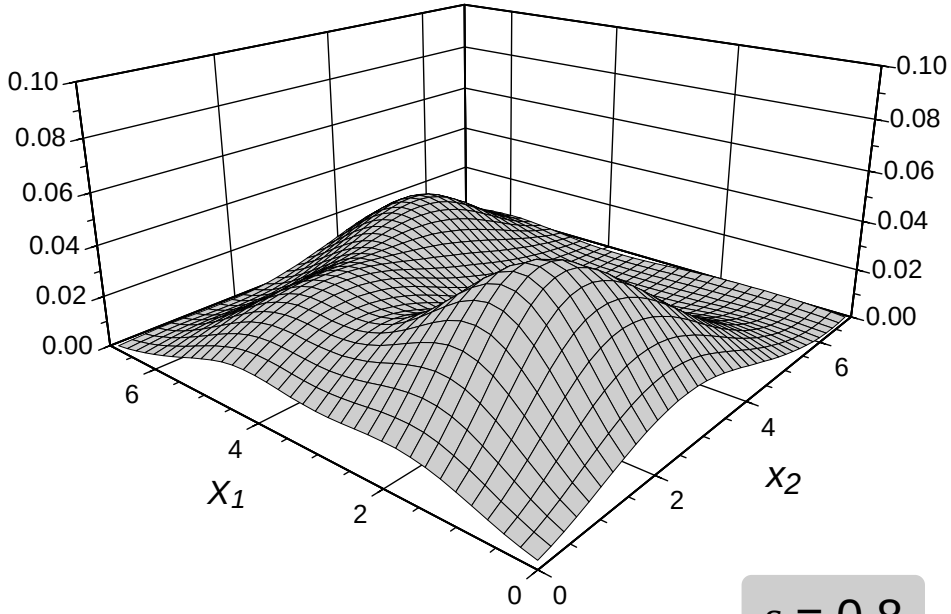
With enough patterns, we converge to an arbitrarily complicated unknown density.

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.



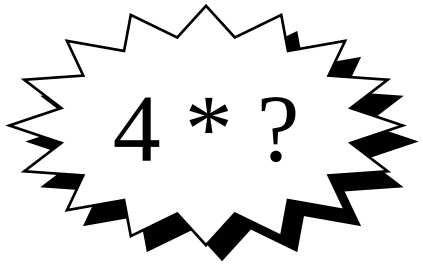
s = 0.5



s = 0.8

Fundamental questions

- Q1 - Available data are sufficient to describe the actual variability ?
- 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 ?



Information tools

- The amount of information ⇨ associated with a :
  - ❶ density $\varphi(\underline{x})$:

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

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

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

- These indexes :
  - ★ evaluate the dispersion associated with $\underline{x}$,
  - ★ may be computed for joint, marginal and conditional densities,
  - ★ to be used to control better the second-stage.

Information and population studies

- Use $I_S(f,n)$ to answer the fundamental questions
  - If $\varphi(\underline{x})$ is a prior, the scalar $I_S(f,n)$ measures the dispersion of $\underline{x}$'s.
  - Elaborate charts giving $I_S(f,n)$ as a function of included subjects n in the study.
  - Bootstrap : Obtain median and inter-quartile range for each n .

- 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

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

Selection of the pdf model

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

$$I_S(f, n)$$

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

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

select the most likely one, that having the highest I_S with respect to the $\underline{x}_j$ data

- Technique : Bootstrap
  - ☐ Obtain median and inter-quartile range for each model.

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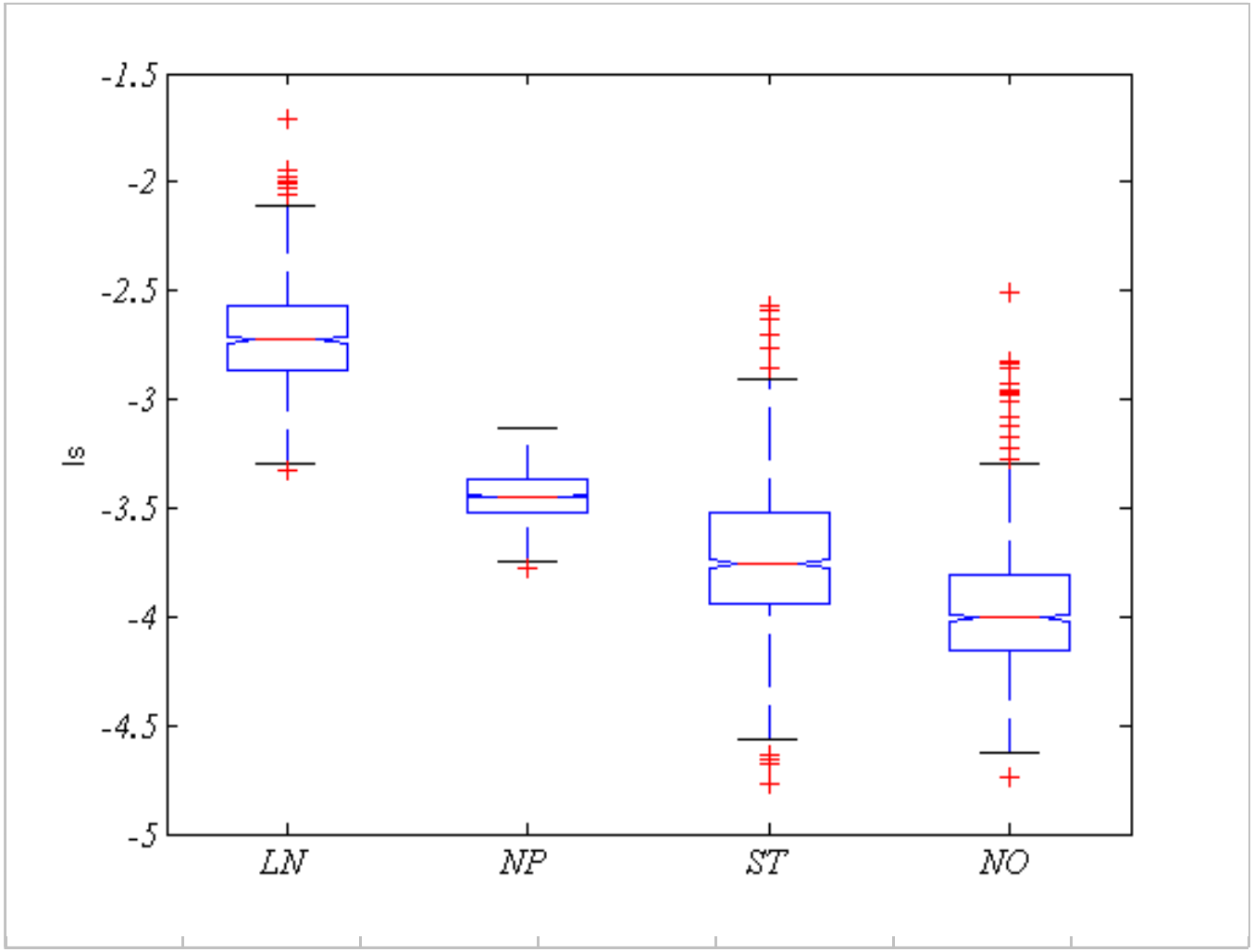
The LN model is the best



Detecting atypical individuals

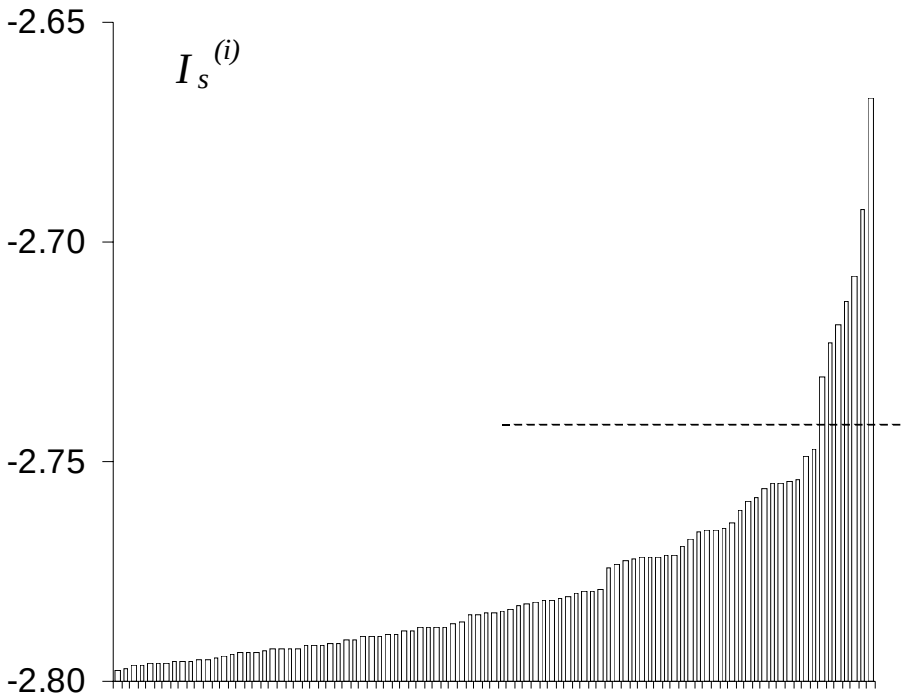
- "Leave-one-out" technique:
  - evaluate the information brought by a given individual j by computing the amount of information on n data without the j-th individual:

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

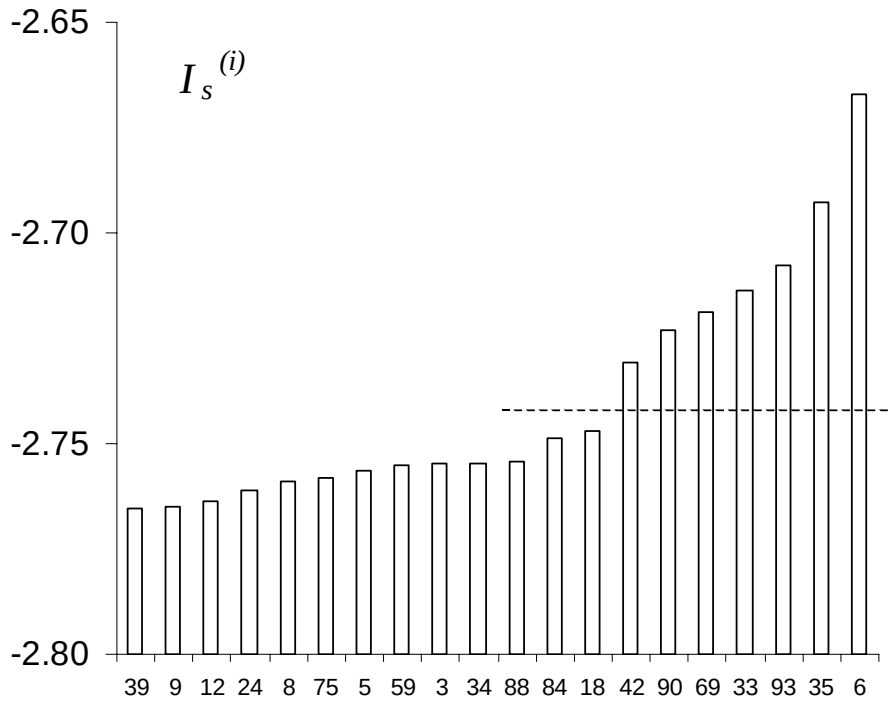
- Sort individuals according their $I_S^{(j)}$ scores:

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

7 atypical individuals



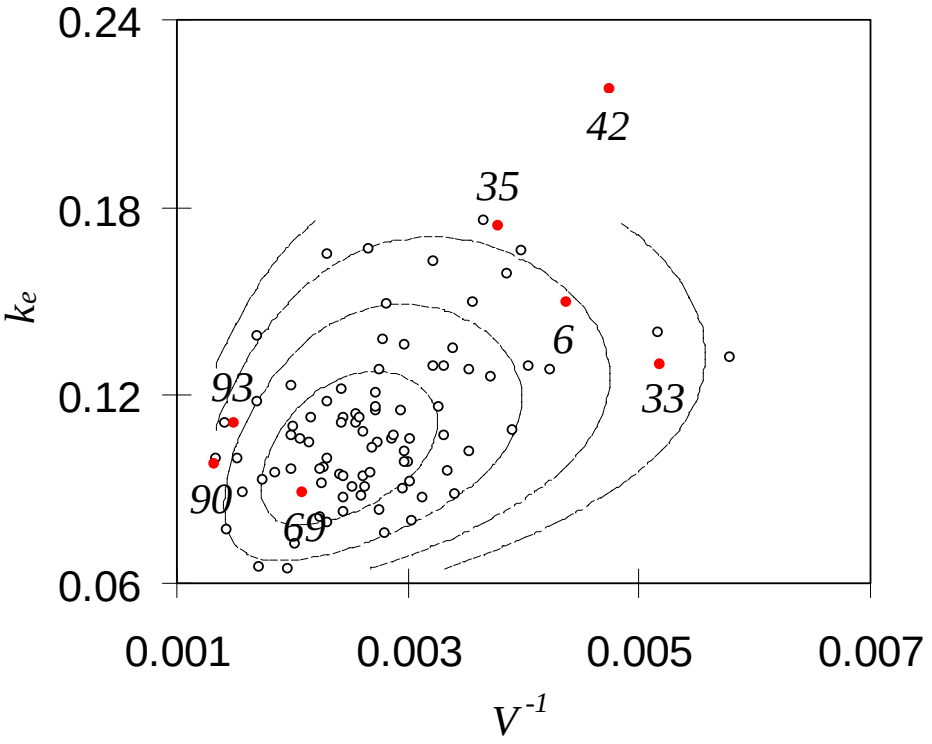
Sorted individuals

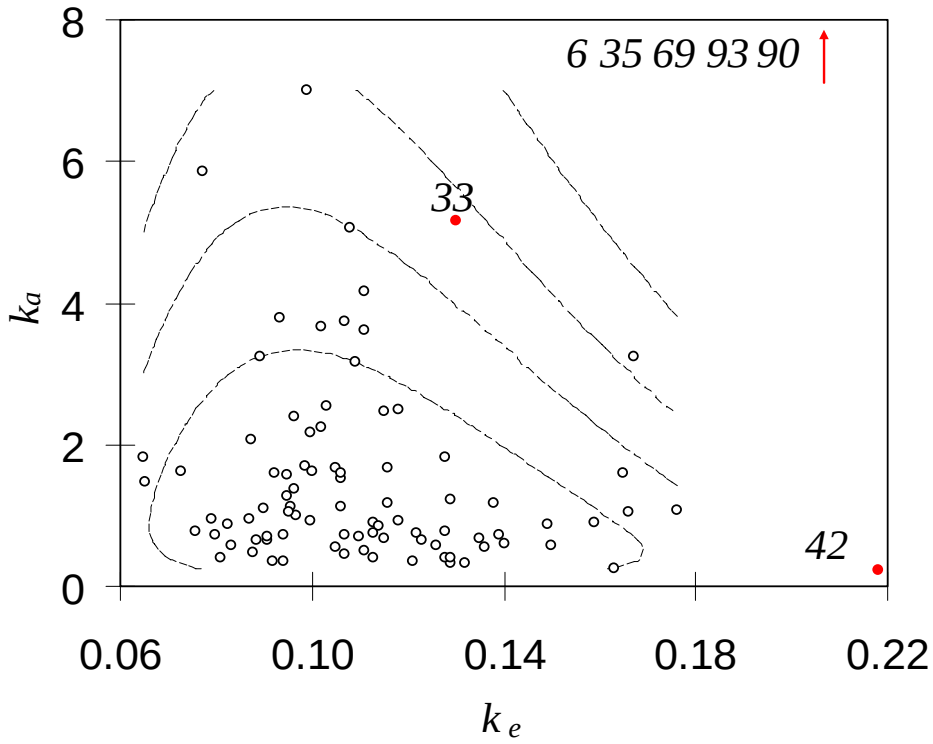


The last 20 sorted individuals

LN pdf in the parameter space

- Contour plots and atypical subjects





★ *LN* pdf was obtained without discarding atypical subjects.

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:

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

    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 :

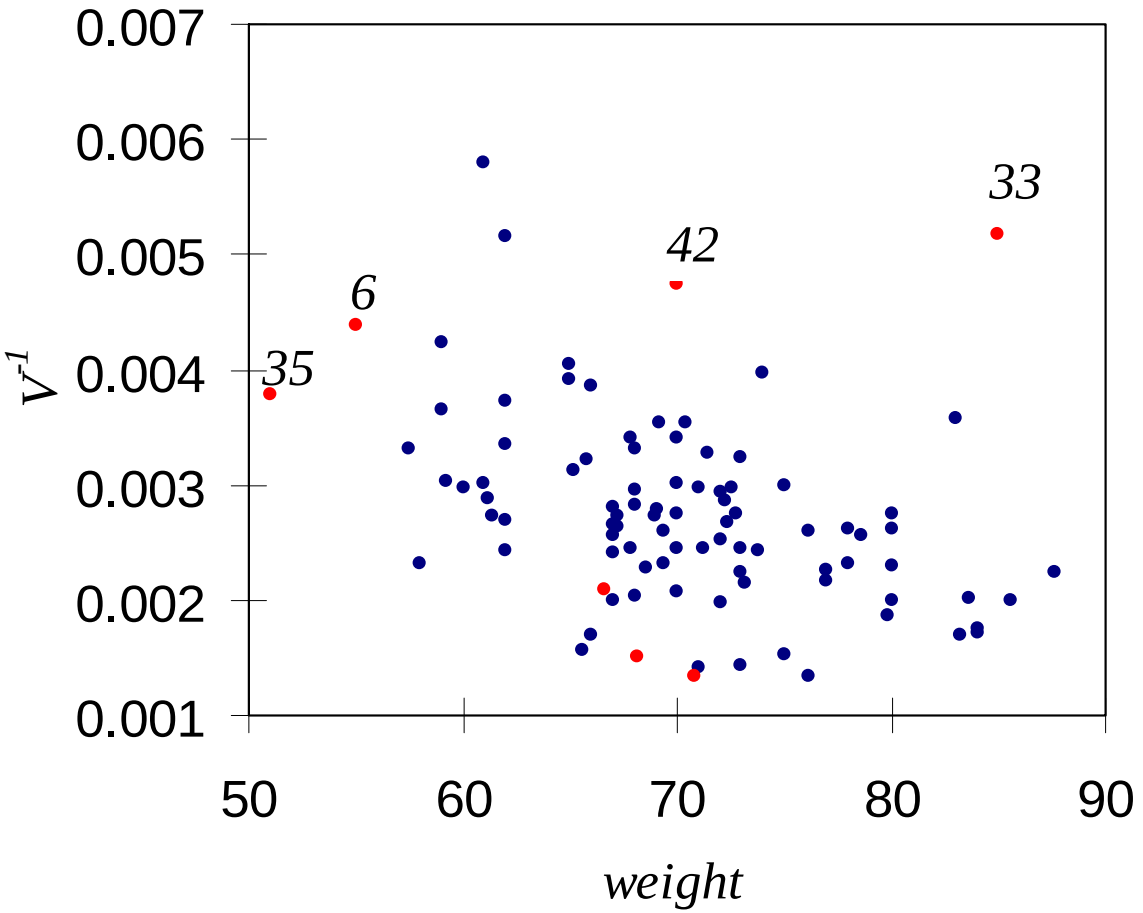
$$I_M^{(ik)} = I_S\left(f_{X_i,\mu_k}, n\right) - I_S\left(f_{X_i}, n\right) - I_S\left(f_{\mu_k}, n\right)$$

    ★ 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 $I_M^{(ik)}$

Weight and age are influential covariates

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



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