MANCHESTER 1824

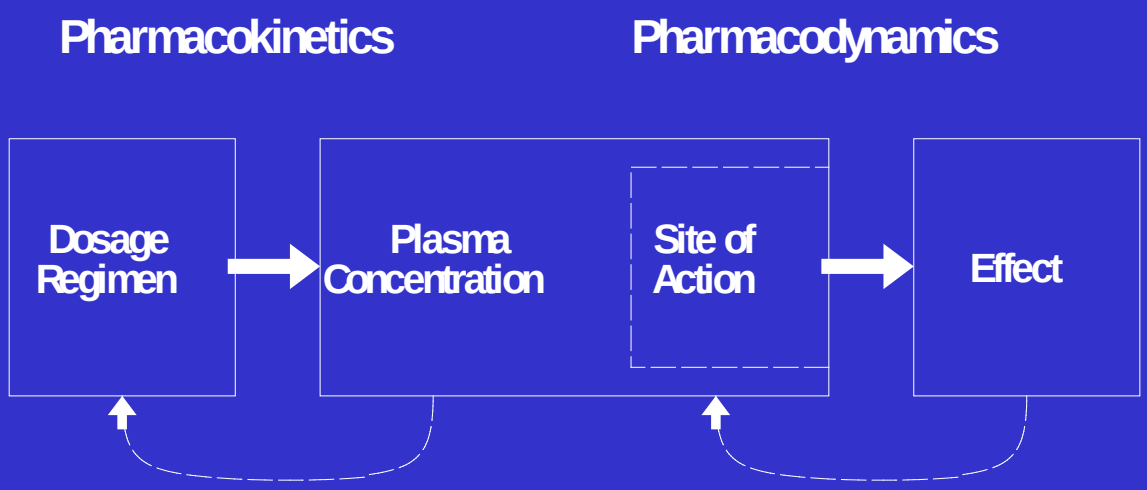
The University of Manchester

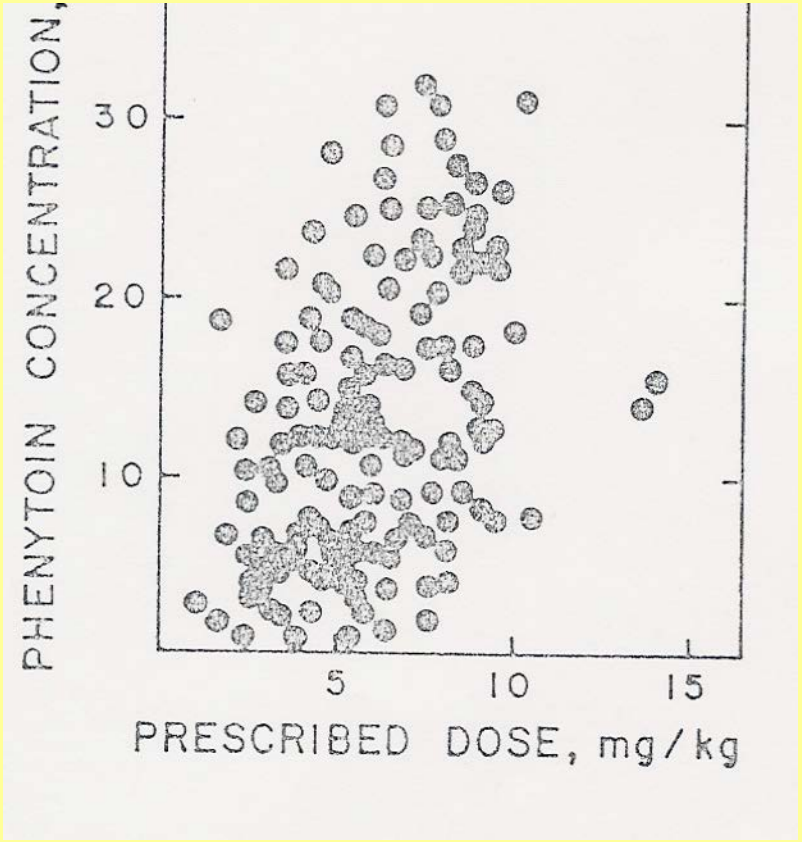
Population Pharmacokinetics and Pharmacodynamics as a Tool in Drug Development

Leon Aarons
Manchester Pharmacy School
University of Manchester

Pharmacokinetics
and
Pharmacodynamics

Clinical Pharmacokinetics




PHENYTOIN CONCENTRATION,
30
20
10
5
10
15
PRESCRIBED DOSE, mg/kg

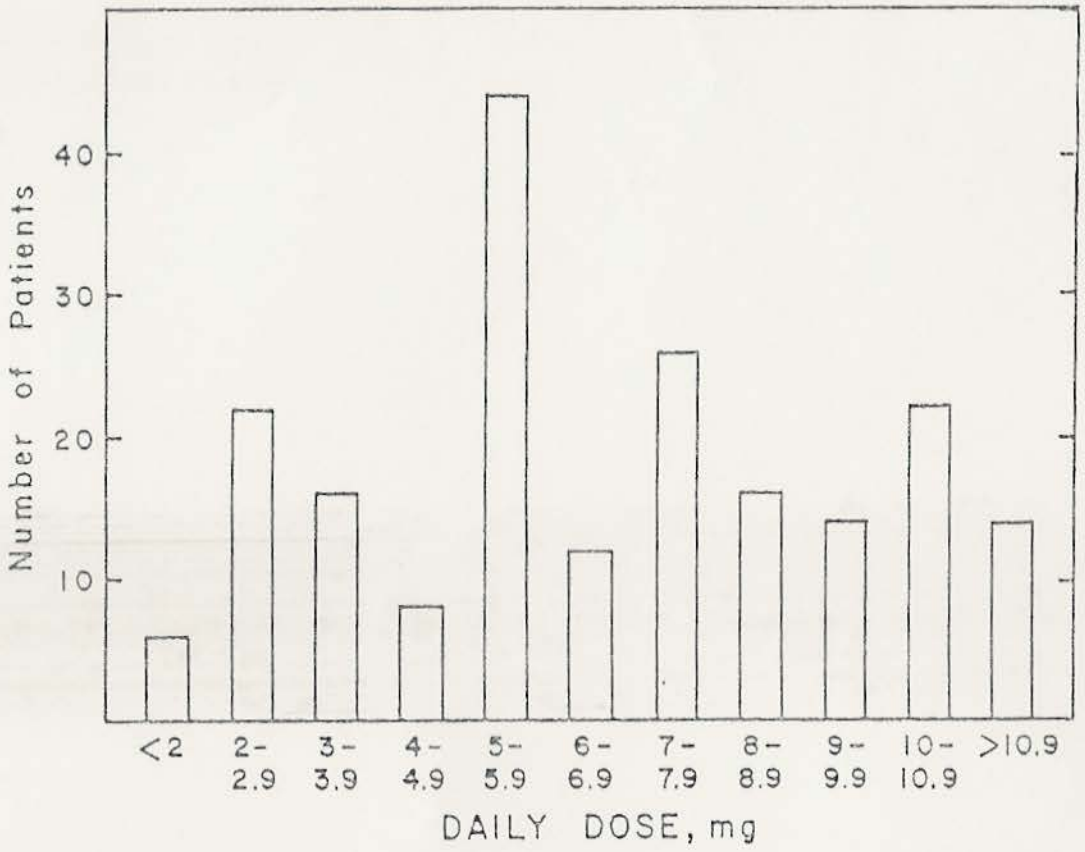


Fig. 8–1. Distribution of doses of warfarin in 200 patients during chronic therapy. (Data from Koch-Weser.[1])

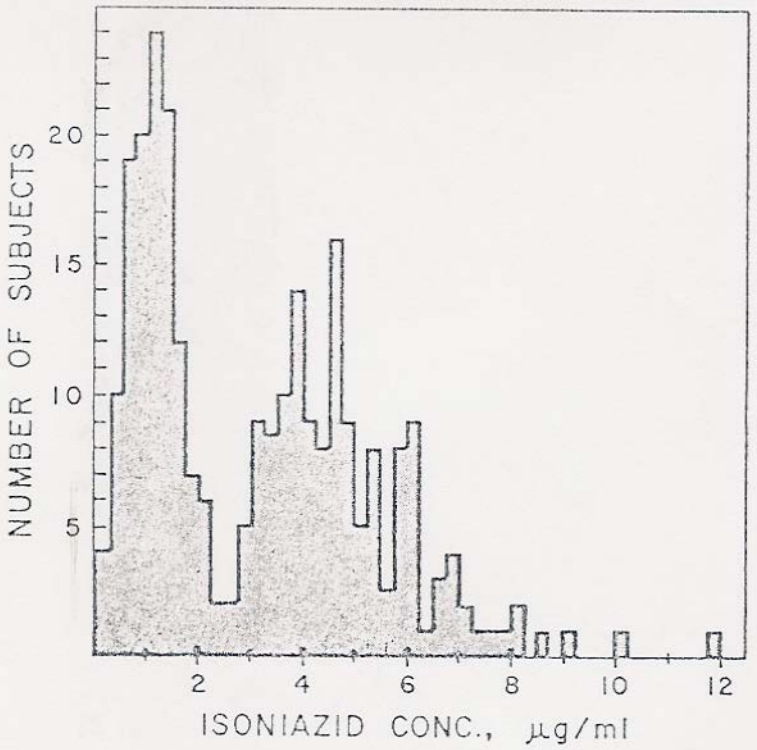
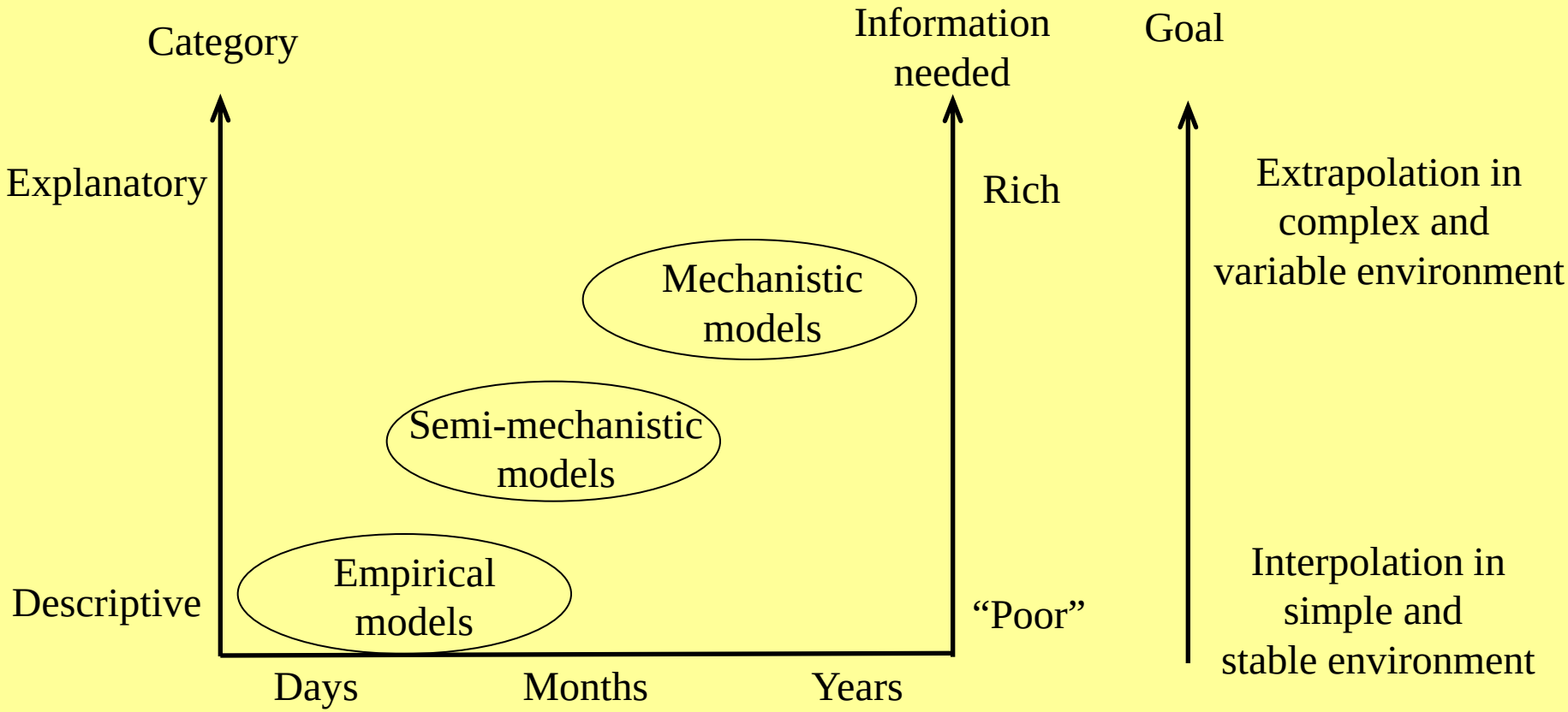
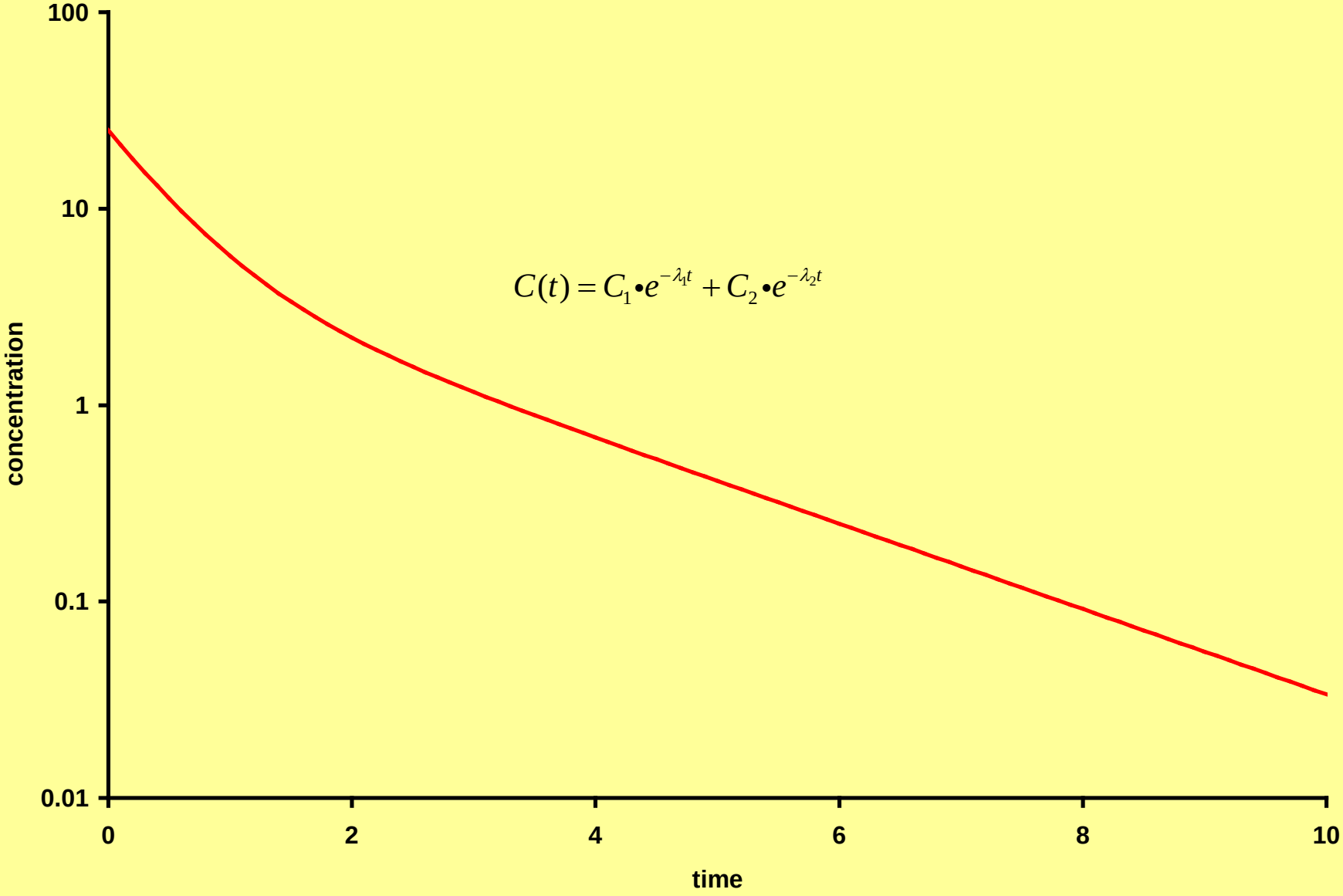


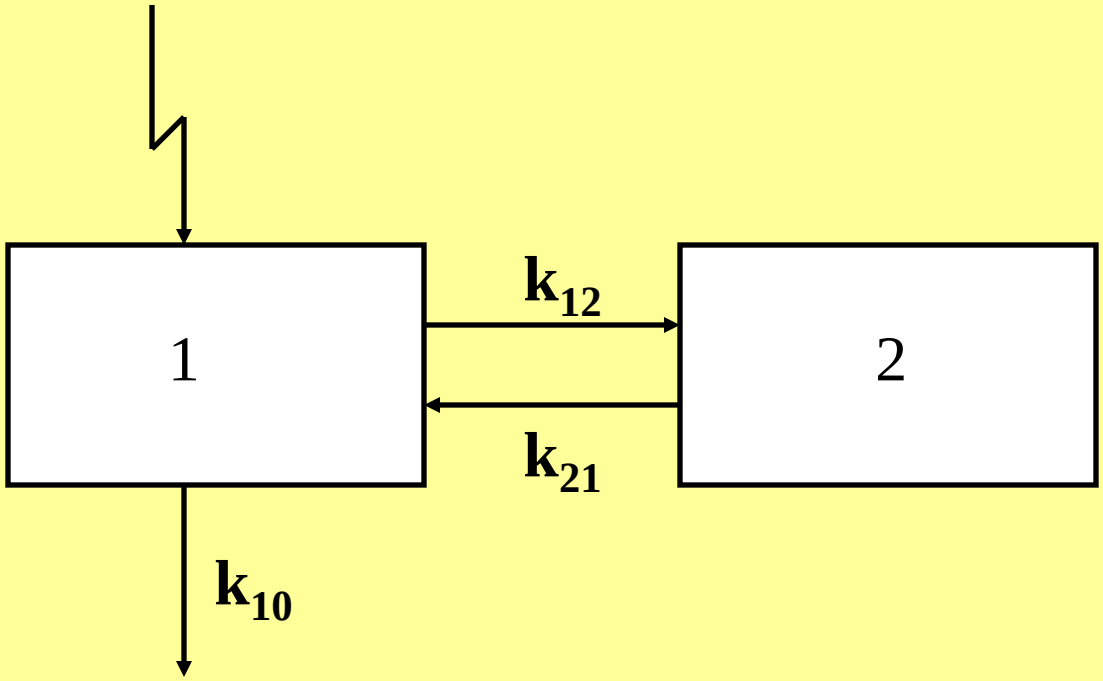
Fig. 7–6. Isoniazid concentration in plasma, 6 hr after oral administration of the same dose to 267 individuals. (Data from Evans, Manely and McKusick.[52])

Models

The type of model to be developed should be driven by the available information and the goal of the simulations



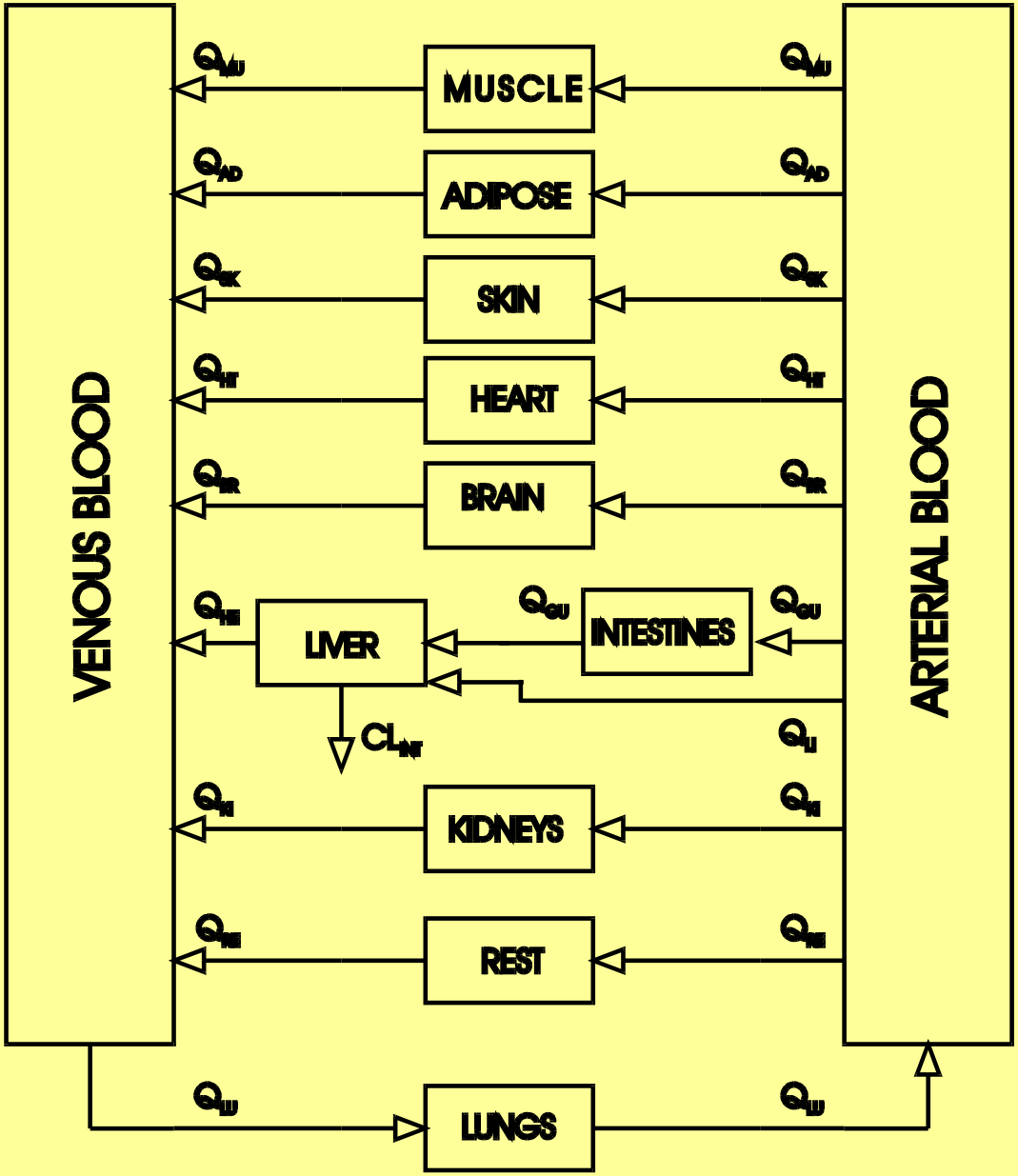

100
10
1
0.1
0.01
concentration
$C(t) = C_1 \bullet e^{-\lambda_1 t} + C_2 \bullet e^{-\lambda_2 t}$
0
2
4
6
8
10
time



$$V_1 \bullet \frac{dC_1(t)}{dt} = -k_{12}V_1C_1(t) - k_{10}V_1C_1(t) + k_{21}V_2C_2(t)$$

$$V_2 \bullet \frac{dC_2(t)}{dt} = k_{12}V_1C_1(t) - k_{21}V_2C_2(t)$$

PBPK MODEL


VENOUS BLOOD
ARTERIAL BLOOD
MUSCLE
ADIPOSE
SKIN
HEART
BRAIN
LIVER
INTESTINES
KIDNEYS
REST
LUNGS
Q_{MU}
Q_{AD}
Q_{SK}
Q_{HT}
Q_{BR}
Q_{HE}
Q_{GU}
Q_{LI}
Q_{KI}
Q_{RE}
Q_{LU}
CL_{INT}

$$Kp_H \bullet V_H \bullet \frac{dC_{out,H}(t)}{dt} = Q_H \bullet C_A(t) - Q_H \bullet C_{out,H}(t) - CL_{\text{int}} \bullet Kp_H \bullet C_{out,H}(t)$$

Pharmacokinetic Study Design

POPULATION PHARMACOKINETICS/ PHARMACODYNAMICS

Estimating the pharmacokinetic/pharmacodynamic similarity and differences between individuals from measurements of drug levels in biological fluids (often blood) and pharmacological effect of subjects or patients arising from some population of interest

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Classical pharmacokinetic/pharmacodynamic study

- .numbers are small
- .subjects are homogeneous - often volunteers
- .studies are well controlled - experimental
- .sufficient data per individual

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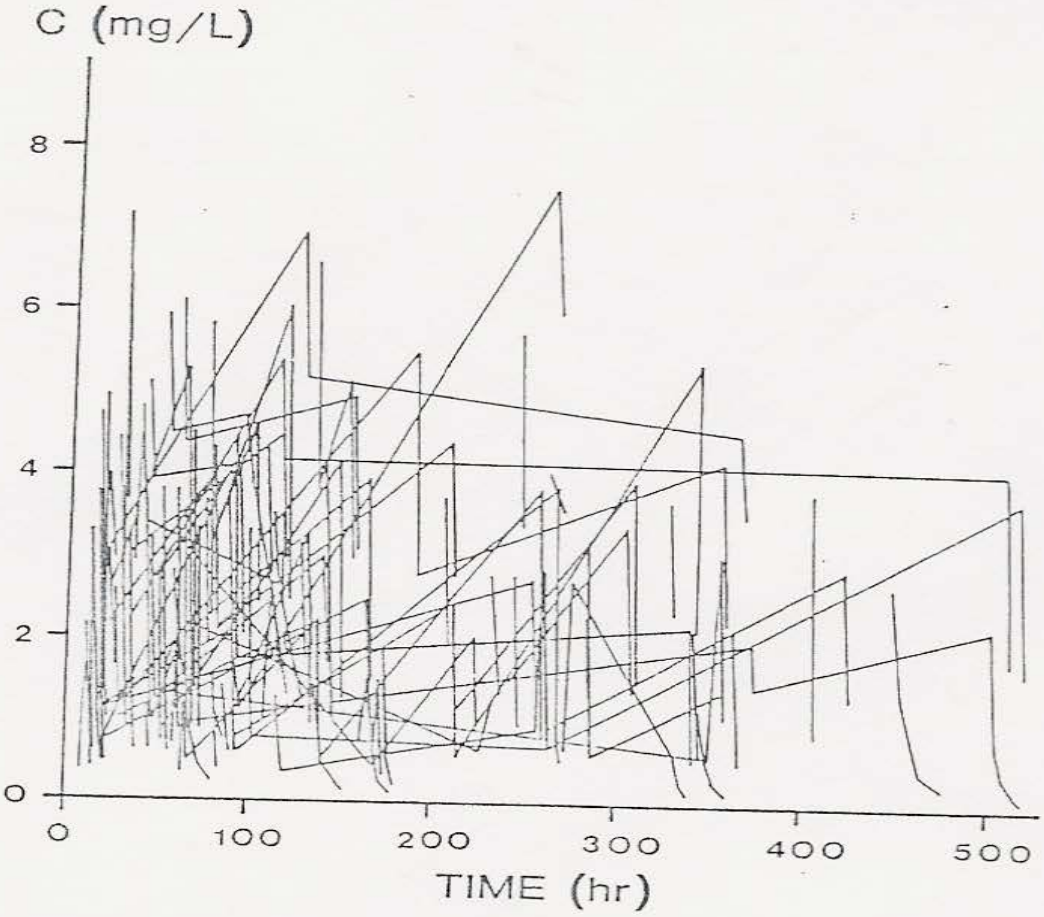
Population study

- .numbers are large
- .subjects are heterogeneous - often patients
- .study control is difficult - maybe multicentre observational
- .sparse data

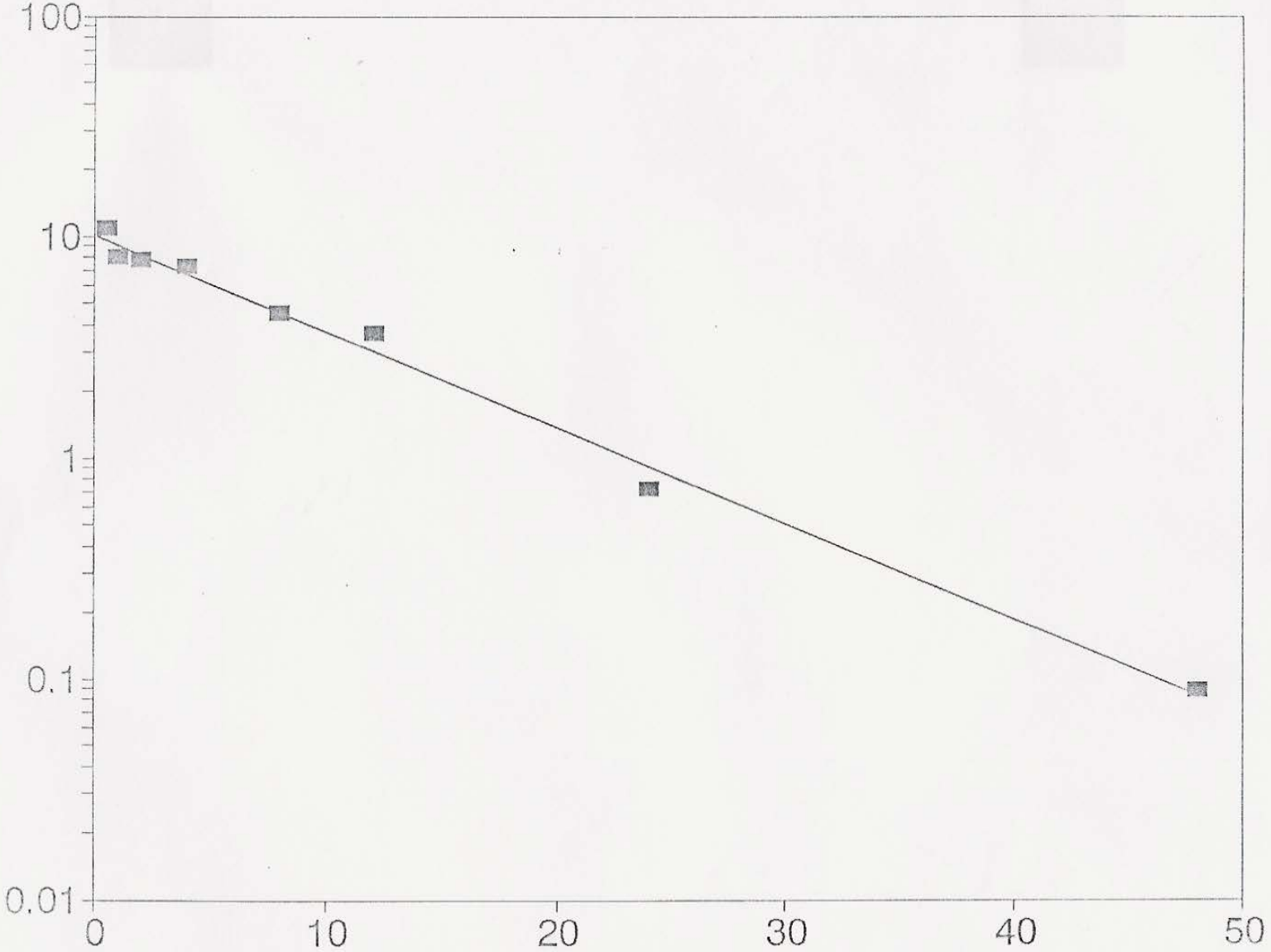
Sparse Data

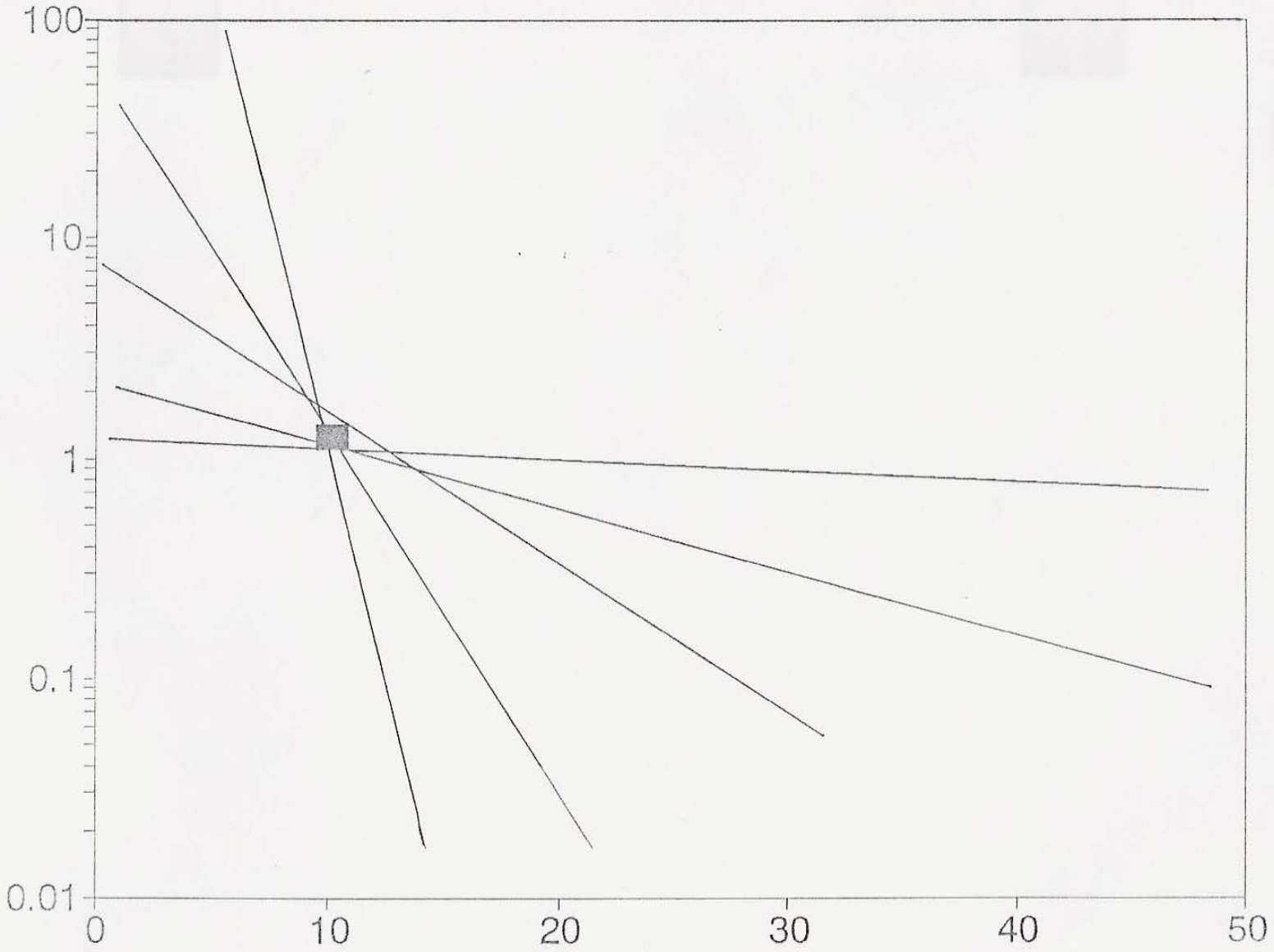
1731 doses
322 concentrations



Tobramycin study

Objective:	**to establish dosage regimen guidelines to maintain maximum efficacy (Cmax > 6 mg/L) and minimum toxicity (Cav < 4 mg/L) in a majority of patients**	
Patients:	**n**	**97 (after pruning)**
	body weight (kg)	**42-120**
	age (yr)	**16-85**
	sex (M/F)	**52/45**
	creatinine clearance (ml/min)	**10-166**
	indication	**variety of infection**
Study design:	**no design - routine TDM**	
	dosage - 20 to 140 mg every 8 to 24 hr	
	number of concentrations per individual 1-9 (median 2)	
	duration of therapy - 14 to 520 hr	


100
10
1
0.1
0.01
0
10
20
30
40
50


100
10
1
0.1
0.01
0
10
20
30
40
50

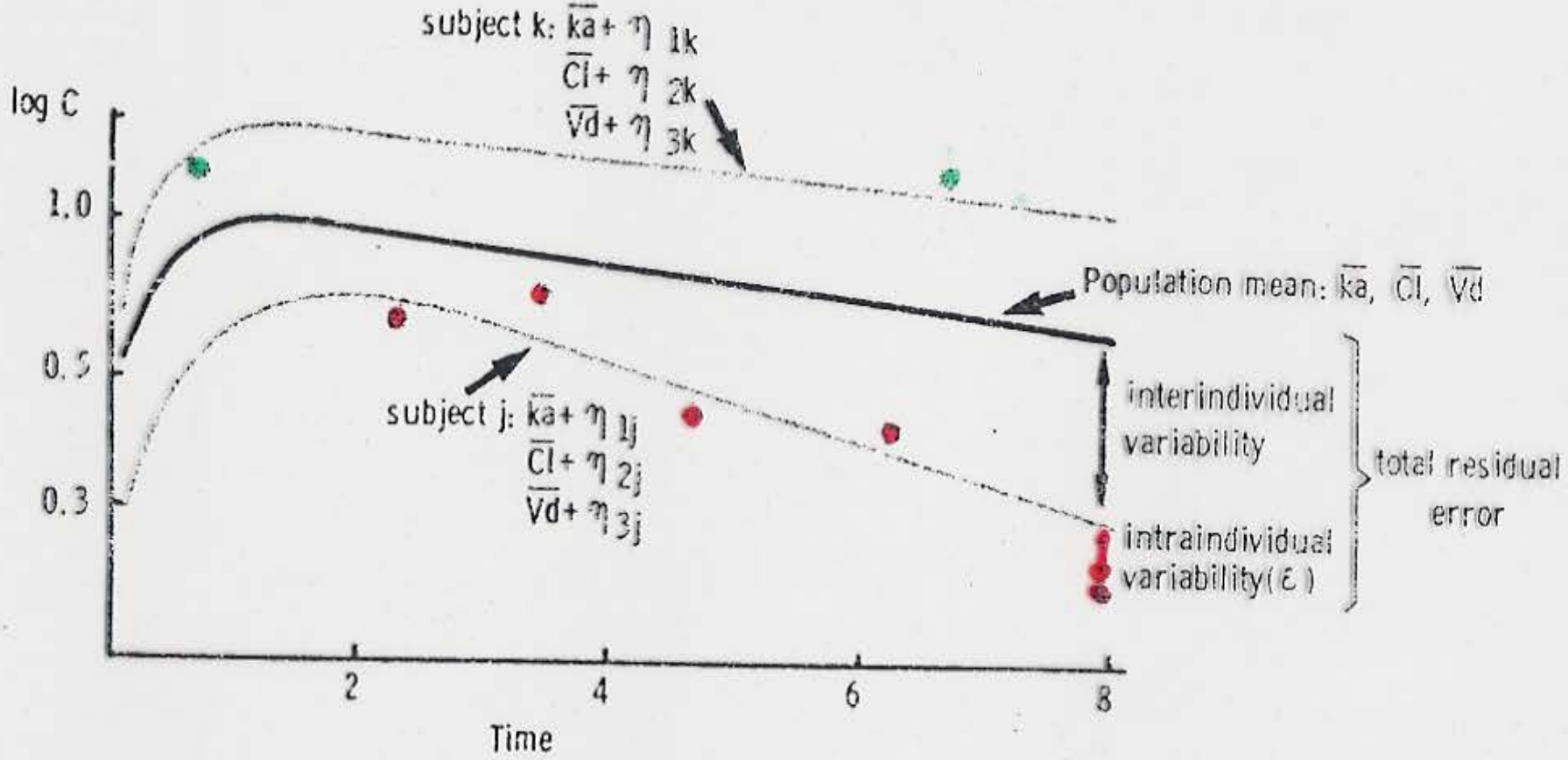
Intelligent Analysis of Unavailable Data

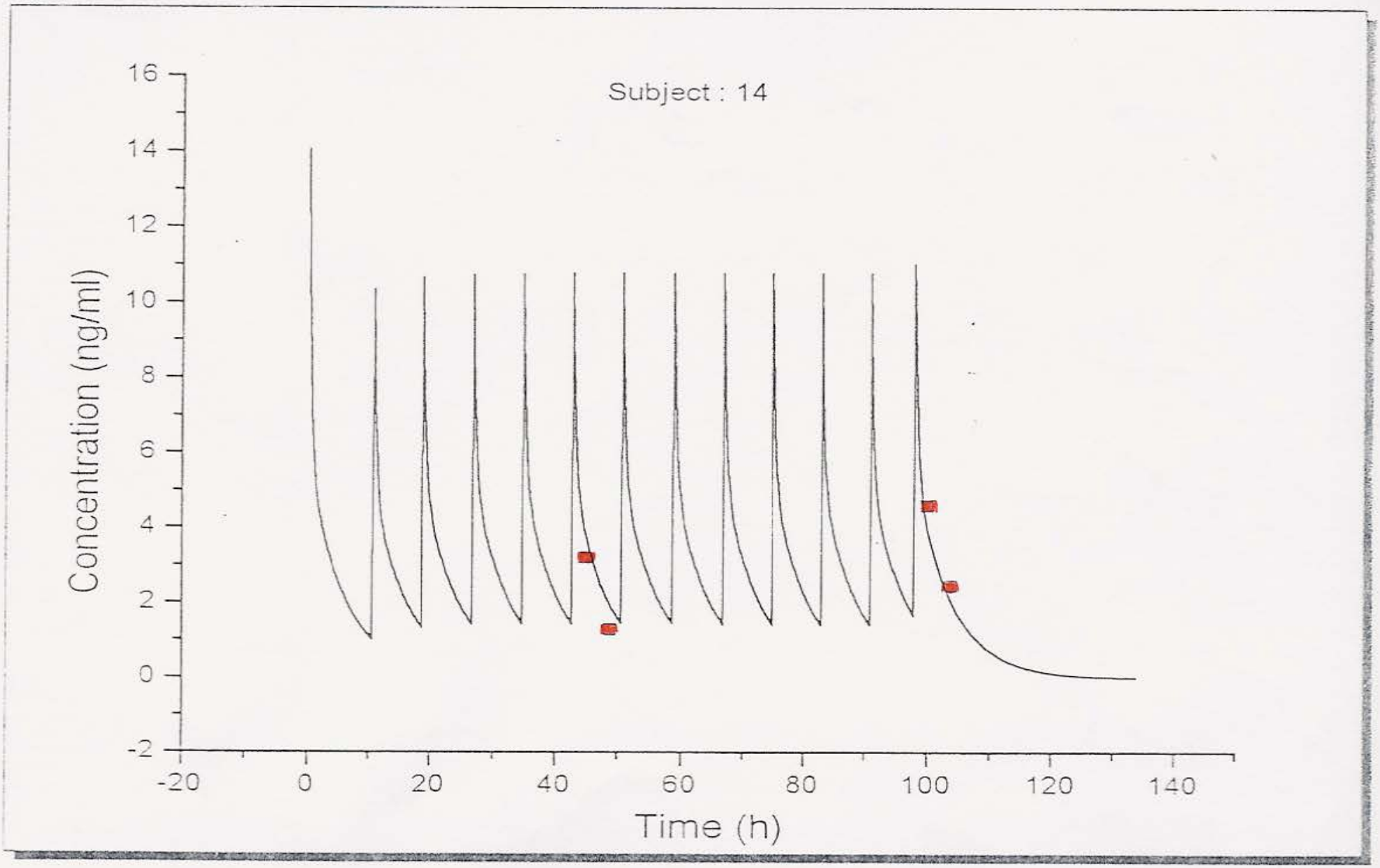
Sum Huan Else, J.Irreprod.Res. 28, 28-29 (1983).

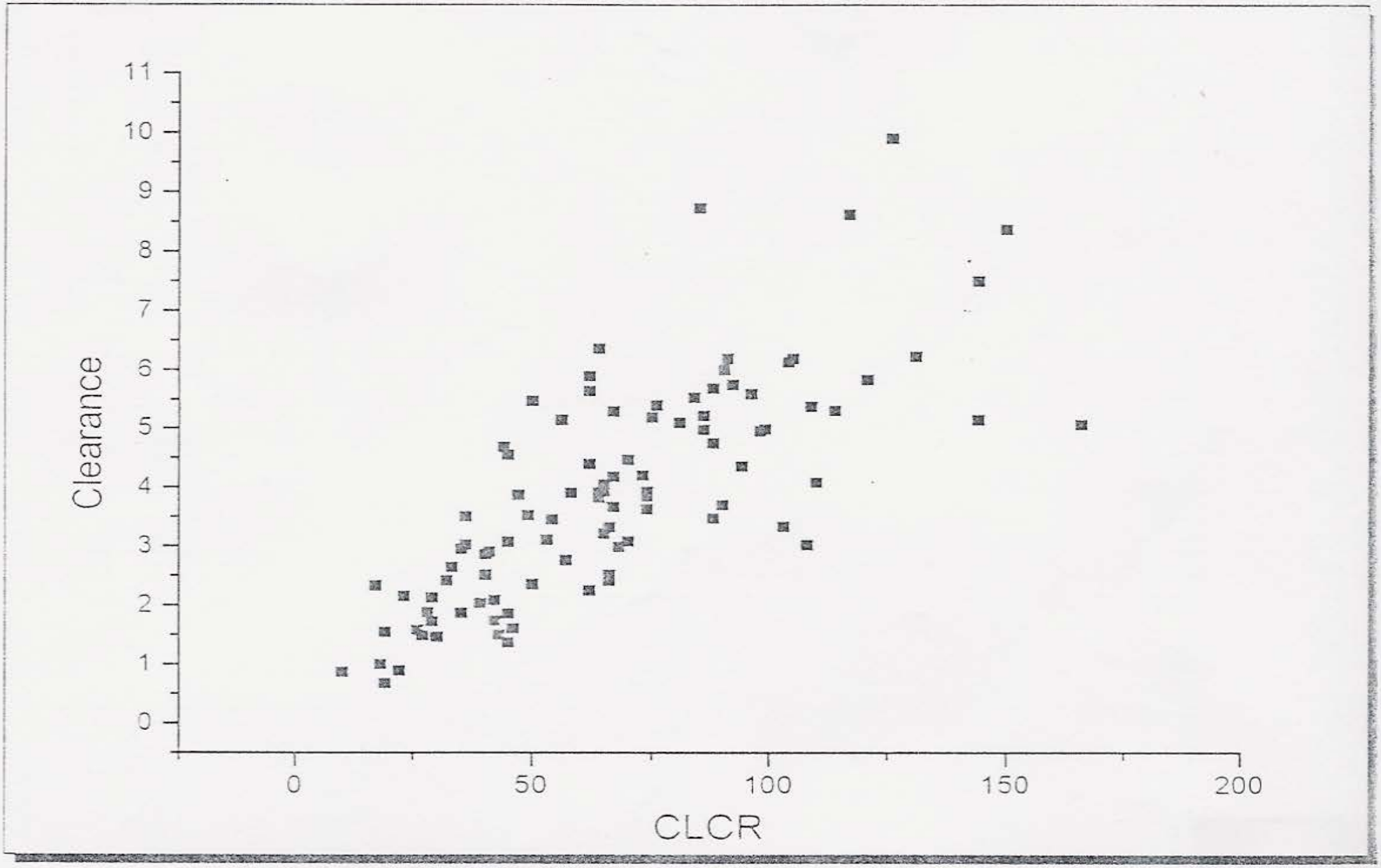
"The inexperienced or naïve analyst might perceive the lack of data to be a minor handicap. The fact of the matter is that a superfluity of data is extremely confining, imposing extreme constraints on the technique, imagination and creativity of the analyst. On the other hand, a lack of data permits full exercise of one's talents and abilities. The ideal situation is to have absolutely no data available at all".

Why?

- **It seeks to obtain relevant pharmacokinetic information in patients who are representative of the target population to be treated with the drug**
- **It recognizes variability as an important feature that should be identified and measured during drug development and evaluation**
- **It seeks to explain variability by identifying factors of demographic, pathophysiological, environmental or drug-related origin that may influence the pharmacokinetic behavior of a drug**
- **It seeks to quantitatively estimate the magnitude of the unexplained variability in the patient population**


subject k: $\overline{ka} + \eta_{1k}$
$\overline{Cl} + \eta_{2k}$
$\overline{Vd} + \eta_{3k}$
log C
1.0
0.5
0.3
Population mean: $\overline{ka}$, $\overline{Cl}$, $\overline{Vd}$
subject j: $\overline{ka} + \eta_{1j}$
$\overline{Cl} + \eta_{2j}$
$\overline{Vd} + \eta_{3j}$
interindividual variability
intraindividual variability(ε)
total residual error
2
4
6
8
Time


Subject : 14
Concentration (ng/ml)
16
14
12
10
8
6
4
2
0
-2
-20
0
20
40
60
80
100
120
140
Time (h)


Clearance
11
10
9
8
7
6
5
4
3
2
1
0
0
50
100
150
200
CLCR

Warfarin study

Objective:

to predict warfarin maintenance dose requirements to achieve a desired degree of anticoagulation based on measurements obtained after a sungle dose of warfarin

Data:

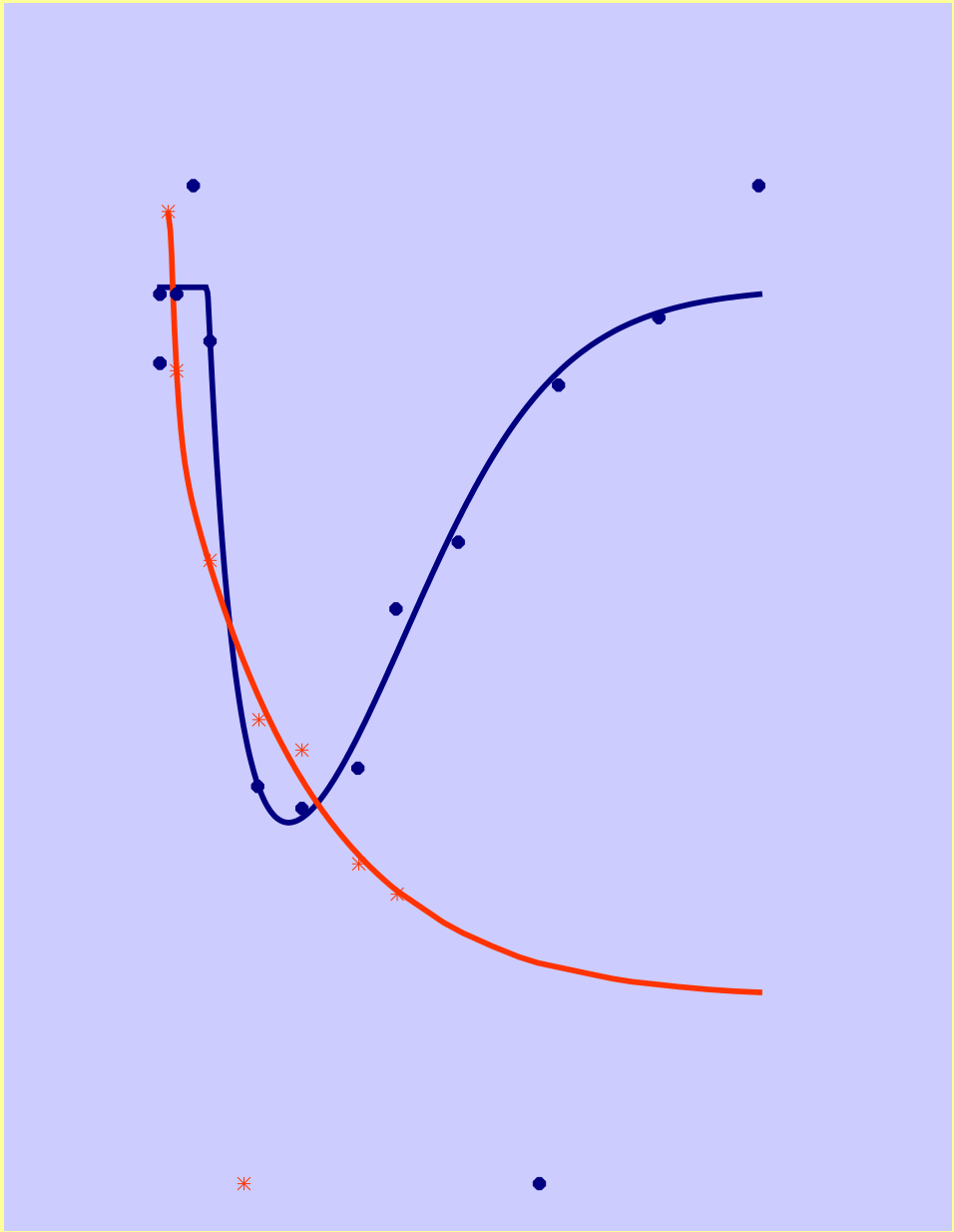
n	**48 normal subjects**
weight (kg)	**66-75**
age (yr)	**20-27**
sex	**male**

Study design:

25mg single dose of racemic warfarin
14 blood samples (0-168 hr)

Measurements:

R and S warfarin (HPLC)
Prothrombin time (Quick one stage)
Factor VII (chromogenic method)

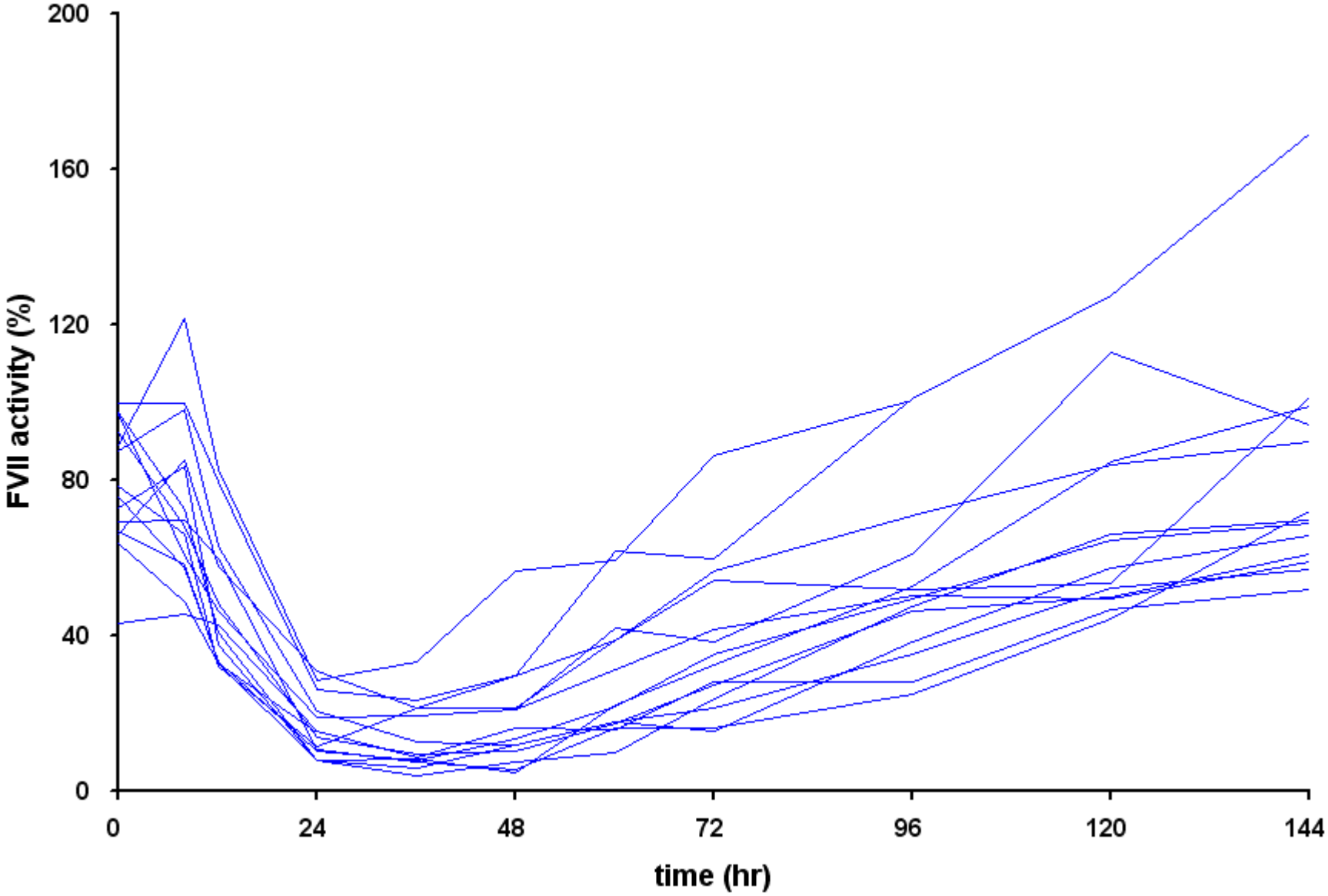


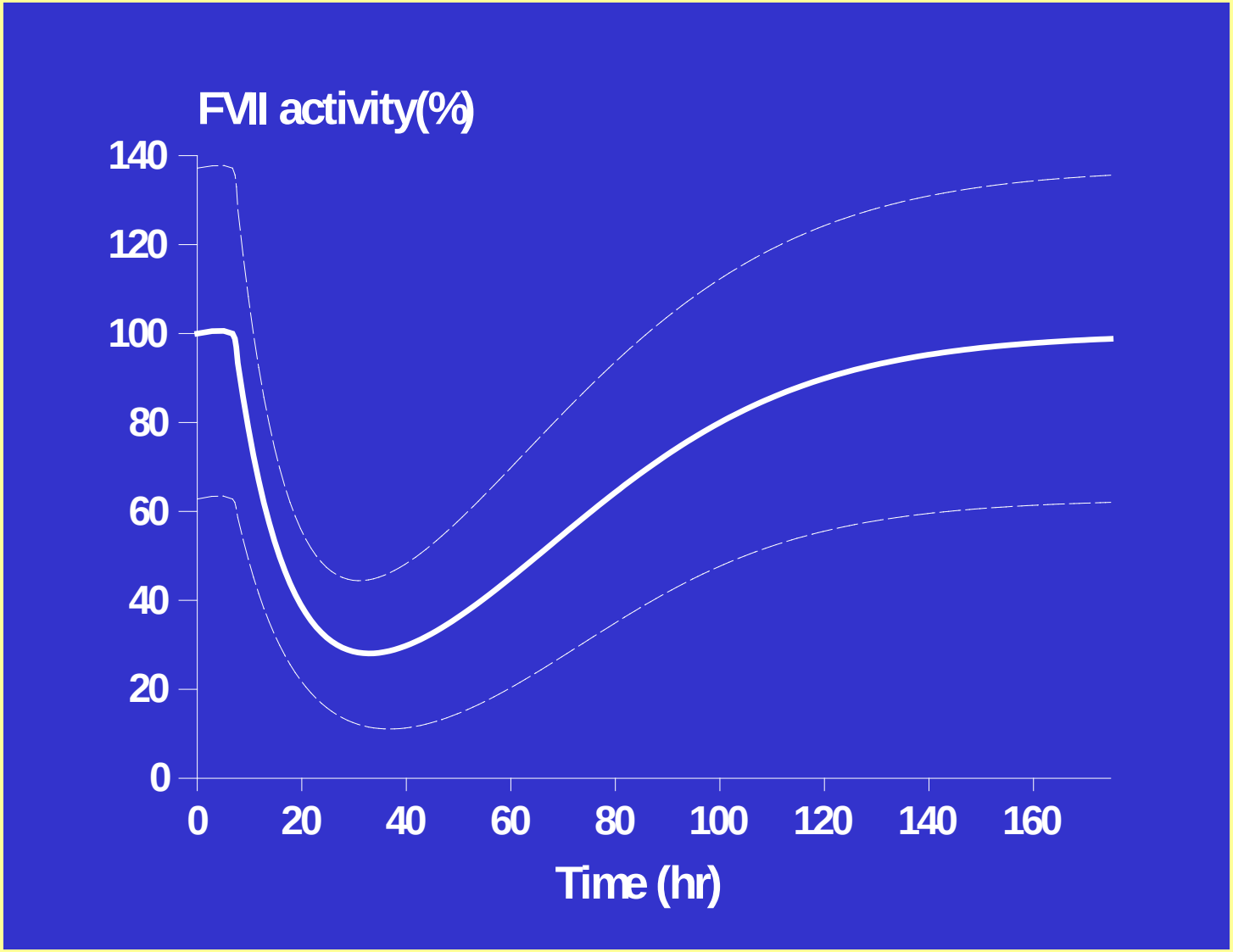
PHARMACODYNAMIC MODEL

rate of change of clotting activity = rate of clotting factor synthesis - rate of clotting factor degradation

$$\frac{dCA(t)}{dt} = k_d \left[\frac{CA_{norm}}{1 + \left(\frac{C_s(t)}{C_{50,s}} \right)^{\gamma}} - CA(t) \right]$$

k_d = clotting factor degradation rate constant
CA_{norm} = normal clotting activity
$C_{50,s}$ = drug concentration giving 50% of maximum effect
γ = slope factor
$C_s(t)$ = plasma concentration of s enantiomer


200
160
120
80
40
0
FVII activity (%)
0
24
48
72
96
120
144
time (hr)


FVII activity(%)
140
120
100
80
60
40
20
0
0
20
40
60
80
100
120
140
160
Time (hr)

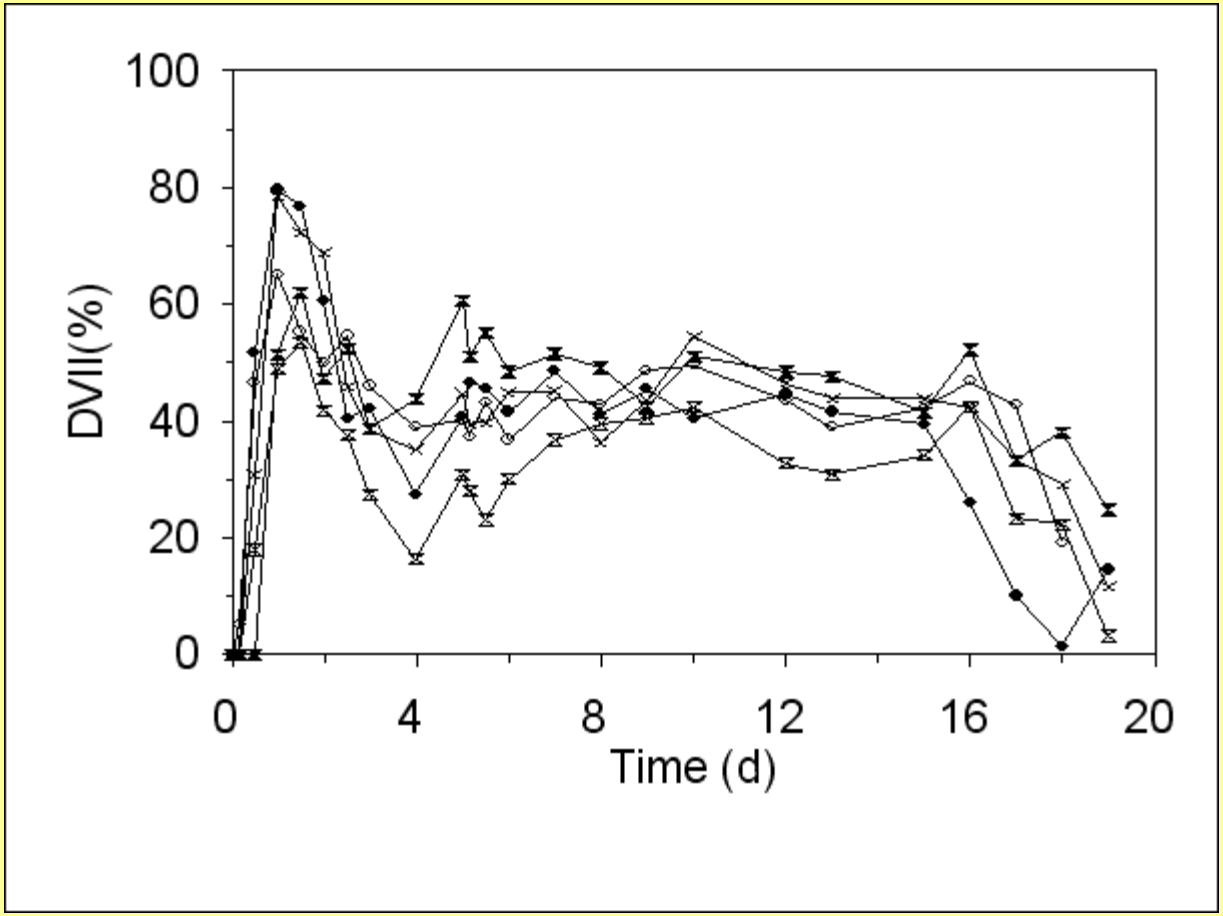
Prospective study

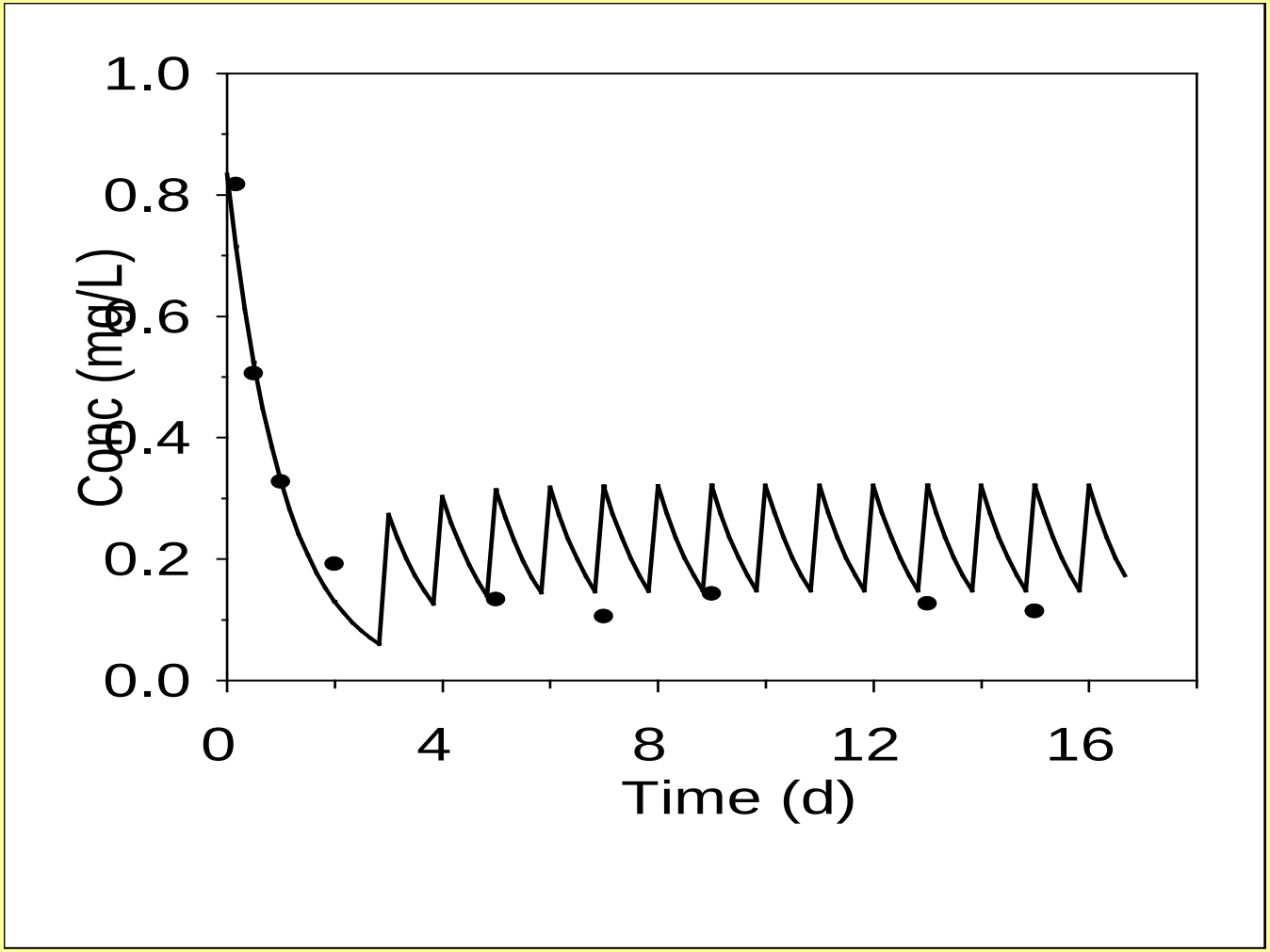
n	**5 normal male volunteers**
Study design	**15mg single dose followed by maintenance dosing from day 3 to day 16 designed to achieve 50% of clotting factor activity**
Maintenance dose	$DM/\tau = k_s \bullet V_s \bullet C_{50,s}$

Dose prediction

$$\Phi_i = \sum_{k=1}^{nparm} \frac{(\log \hat{p}_k - \log p_{k,i})^2}{cv(\hat{p}_k)^2} + \sum_{j=1}^{nobs_i} \frac{(\log y_{j,i} - \log f_{j,i})^2}{cv(y_{j,i})^2}$$

pharmacokinetic parameters set to population values


100
80
60
40
20
0
DVII(%)
0
4
8
12
16
20
Time (d)

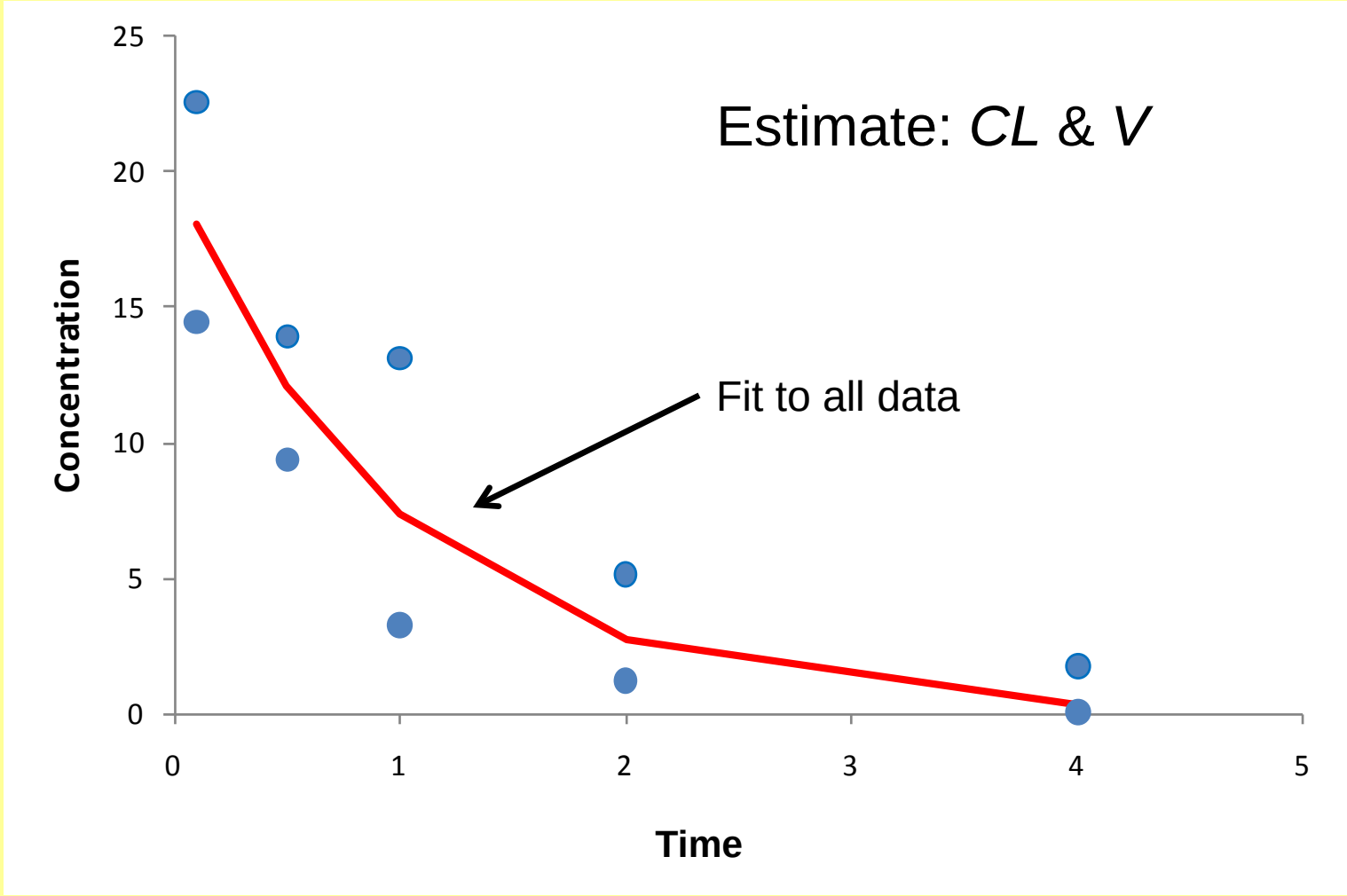

1.0
0.8
0.6
0.4
0.2
0.0
Conc (mg/L)
0
4
8
12
16
Time (d)

Approaches for population analysis

- Naïve pooled data approach
- 2-stage approach
- A fully population approach

Naïve Pooled Data Approach

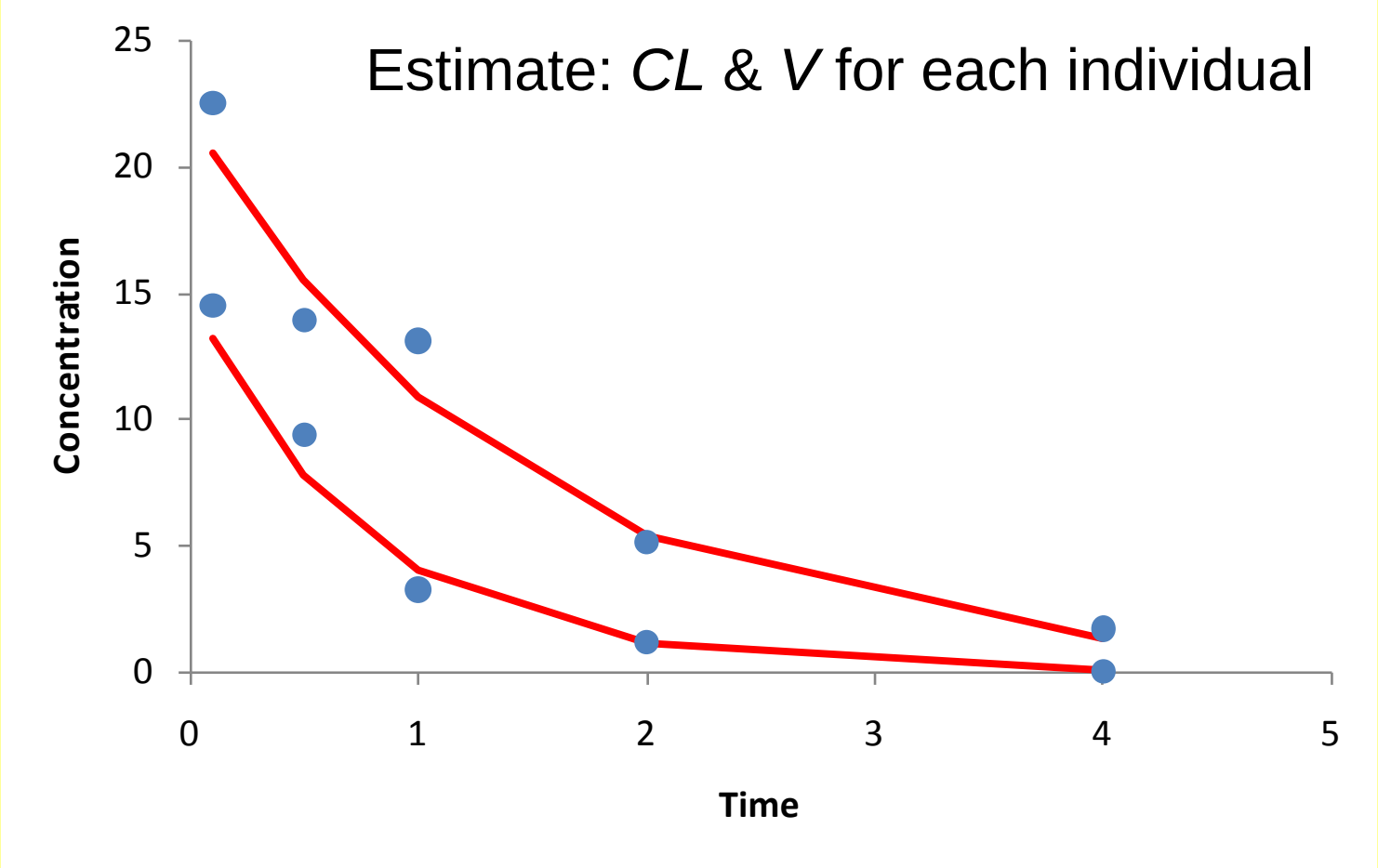
- Estimate parameters for the model assuming all data arise from a single individual
- Can be biased
  - If individuals have different amounts of data
  - If model very nonlinear
- No estimation of variability components
- Influential factors on PK cannot be ascertained


Estimate: CL & V
Fit to all data
Concentration
Time
25
20
15
10
5
0
0
1
2
3
4
5

Two-Stage Approach

- The “traditional” approach for PK analyses
- Model the PK of each subject’s data (Stage 1)
- Obtain summary statistics, e.g. mean value of clearance (Stage 2)
  - Between-subject variance is overestimated because estimation of the parameters includes residual error
  - Assumes all individuals contribute equally
  - Is not helpful for identifying sources of variability (e.g. renal function)
  - Essentially unusable where there are “sparse” data

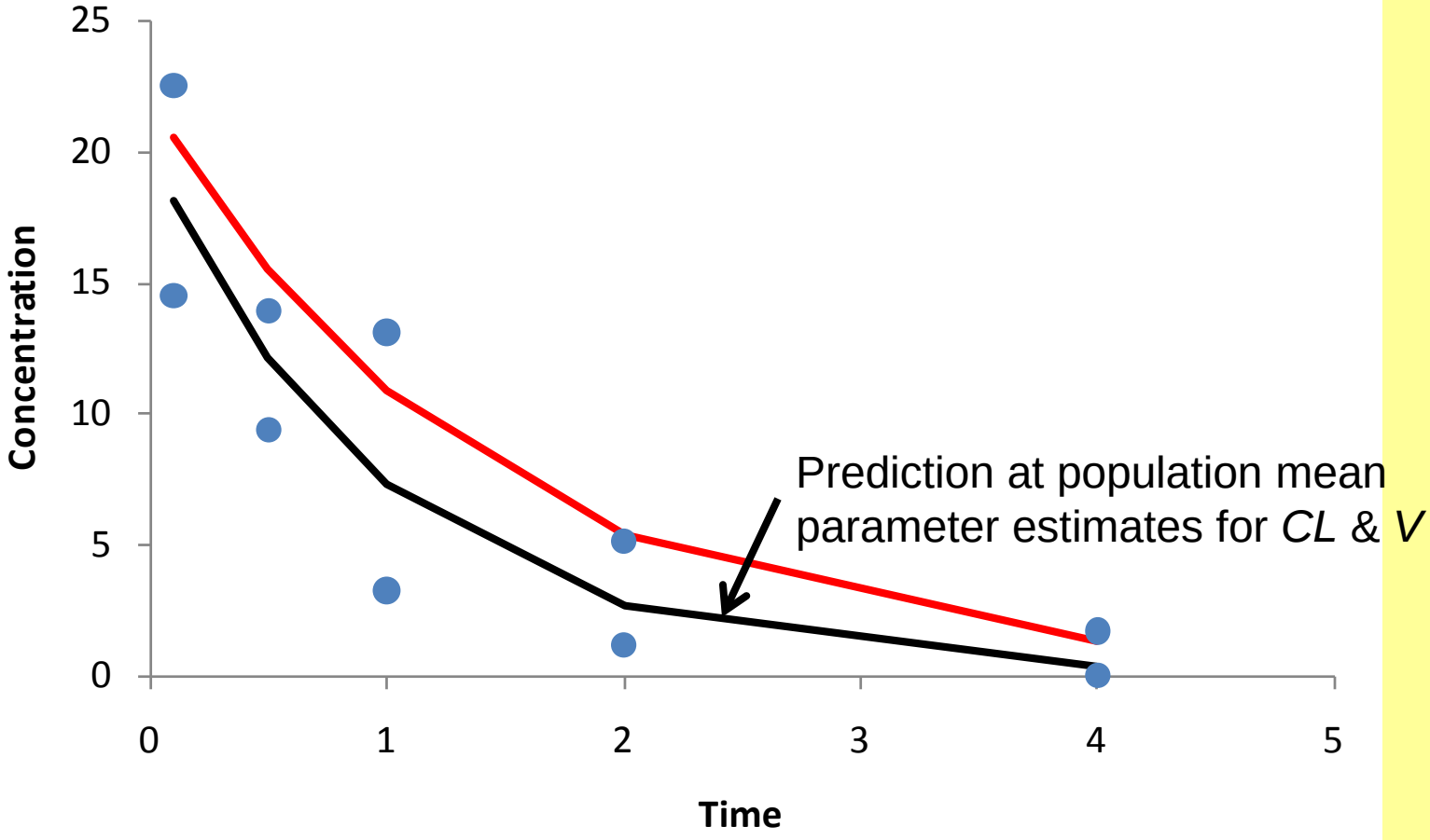
Two-Stage Approach



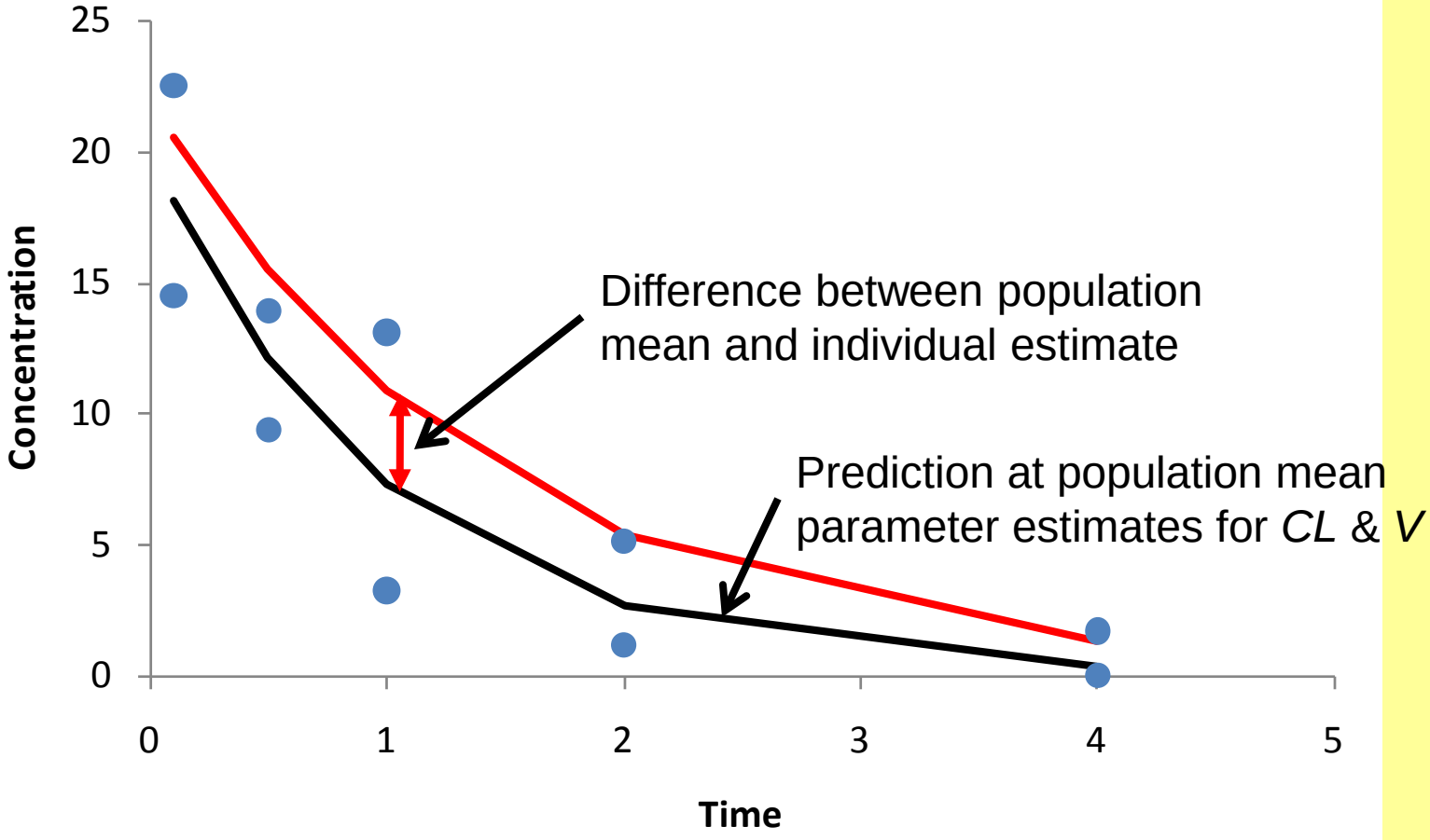
The population approach

- Estimate the overall mean parameters and the variability between individuals as well as the residual variability
- The “standard” population analytical approach
- Sparse/rich, unbalanced/unstructured data
- Considers the population (rather than the individual) as the unit for the PK analysis
- “Individuality” of the subjects is maintained

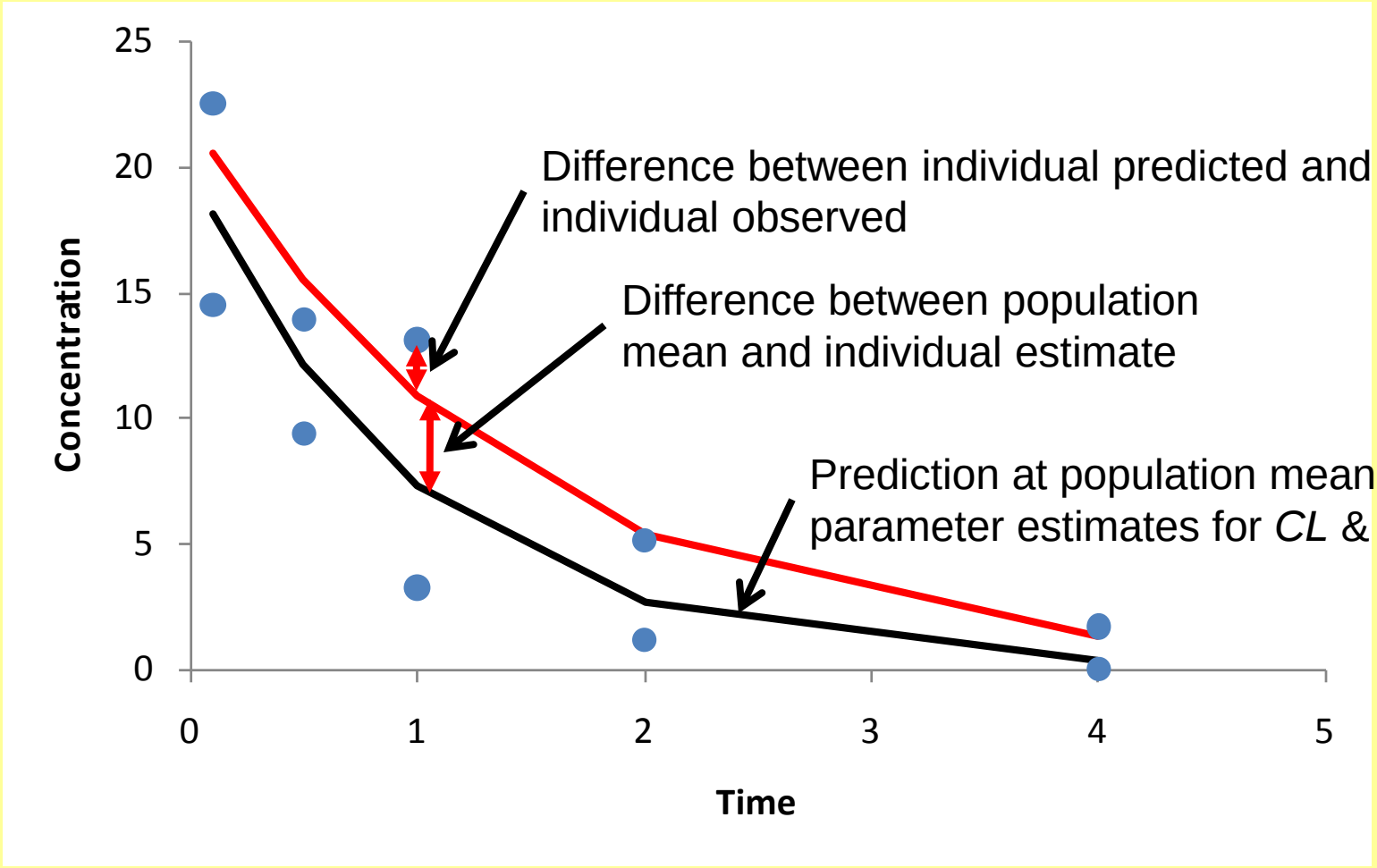
The population approach



The population approach



The population approach



Variability

- Two levels
  - Variability between people (heterogeneity)
  - Uncertainty about the observations (residual unexplained variability)

Heterogeneity
(Between Subject Variance [BSV])

- There are two sources of heterogeneity between patients
  - Predictable = BSVP
  - Unpredictable (random) = BSVR
- Predictable variability can arise from (examples):
  - differences in renal function
  - differences in body size and composition
- The population parameter variability (PPV) in the population is therefore the sum of these two sources:

$$PPV = BSVR + BSVP$$

Residual unexplained variability
[RUV]

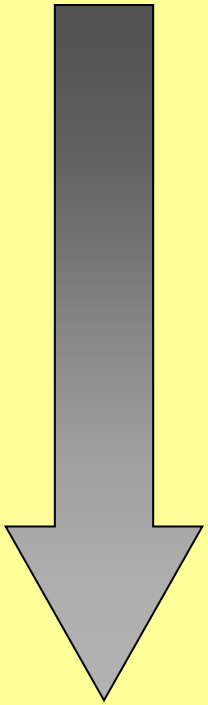
- This is the variability of the observed concentration around the model predicted
- The observed will seldom equal the model predicted due to many process such as assay error

Nonlinear mixed effects modelling

- Nonlinear: almost (if not all) PK and PKPD models are nonlinear in the parameters
- The population approach is interested in the mean parameter values (“fixed effects”) as well as the variability between and within individuals (“random effects”)
- Combining fixed and random effects is termed “mixed effects”
- Essentially all population PK studies are therefore examples of nonlinear mixed effects modelling

Software for Population Analyses

Decreasing
Market Share



- NONMEM ($$)
- Monolix (free/$$)
- WinBUGS (free)
- SAS proc nlmixed ($$$)
- Phoenix nlme (free/$$$)
- S-ADAPT MC-PEM (free)
- NPEM (free)
- P-Pharm ($?)
- NPML (dead?)

Not used to
any extent

Role of Modelling and Simulation in Phase I Drug Development

L. Aarons, M. Karlsson, F. Mentré,

F. Rombout, J.-L. Steimer, A. van Peer

COST B15

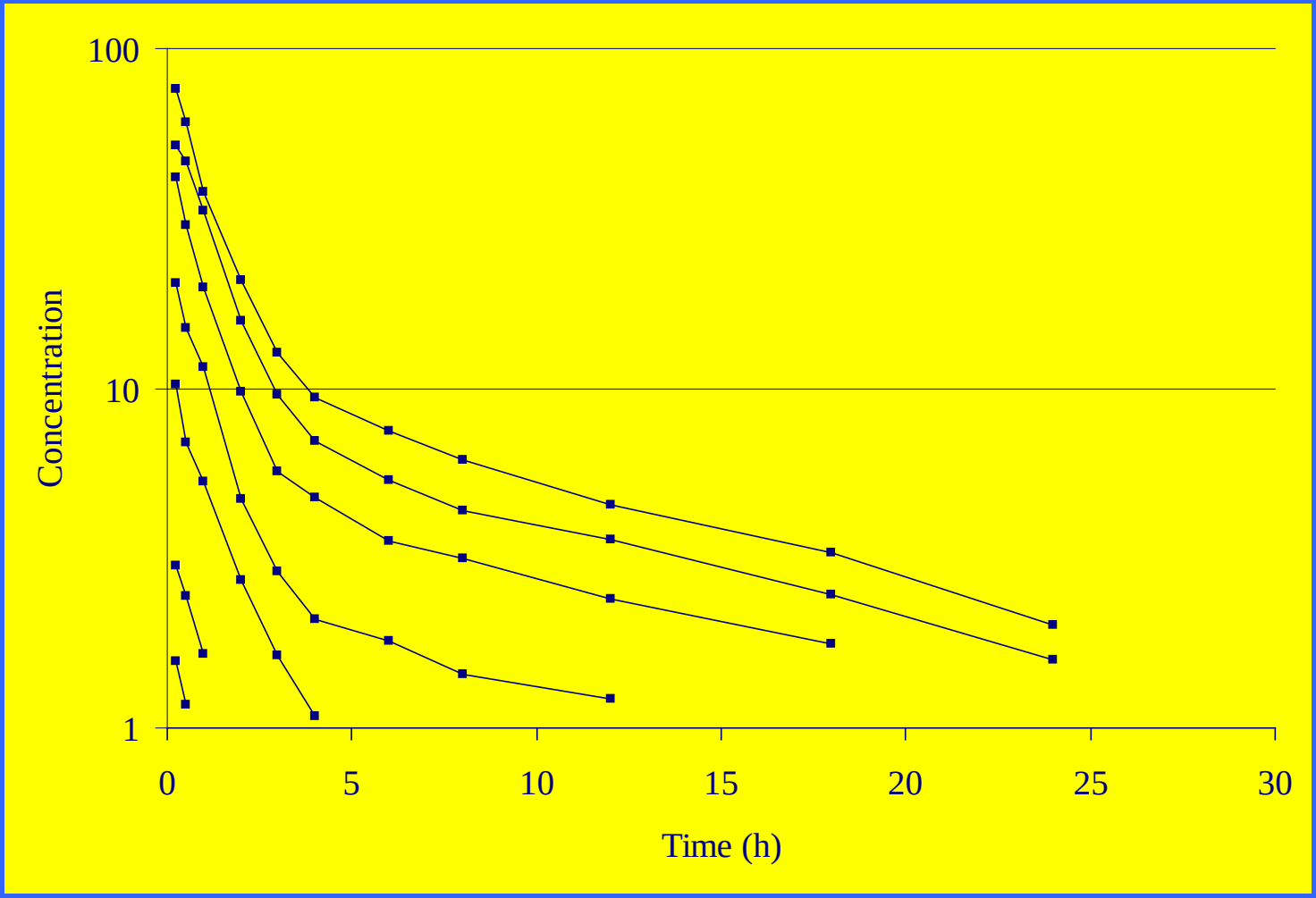
Brussels January 10-11, 2000

When is the population approach useful?

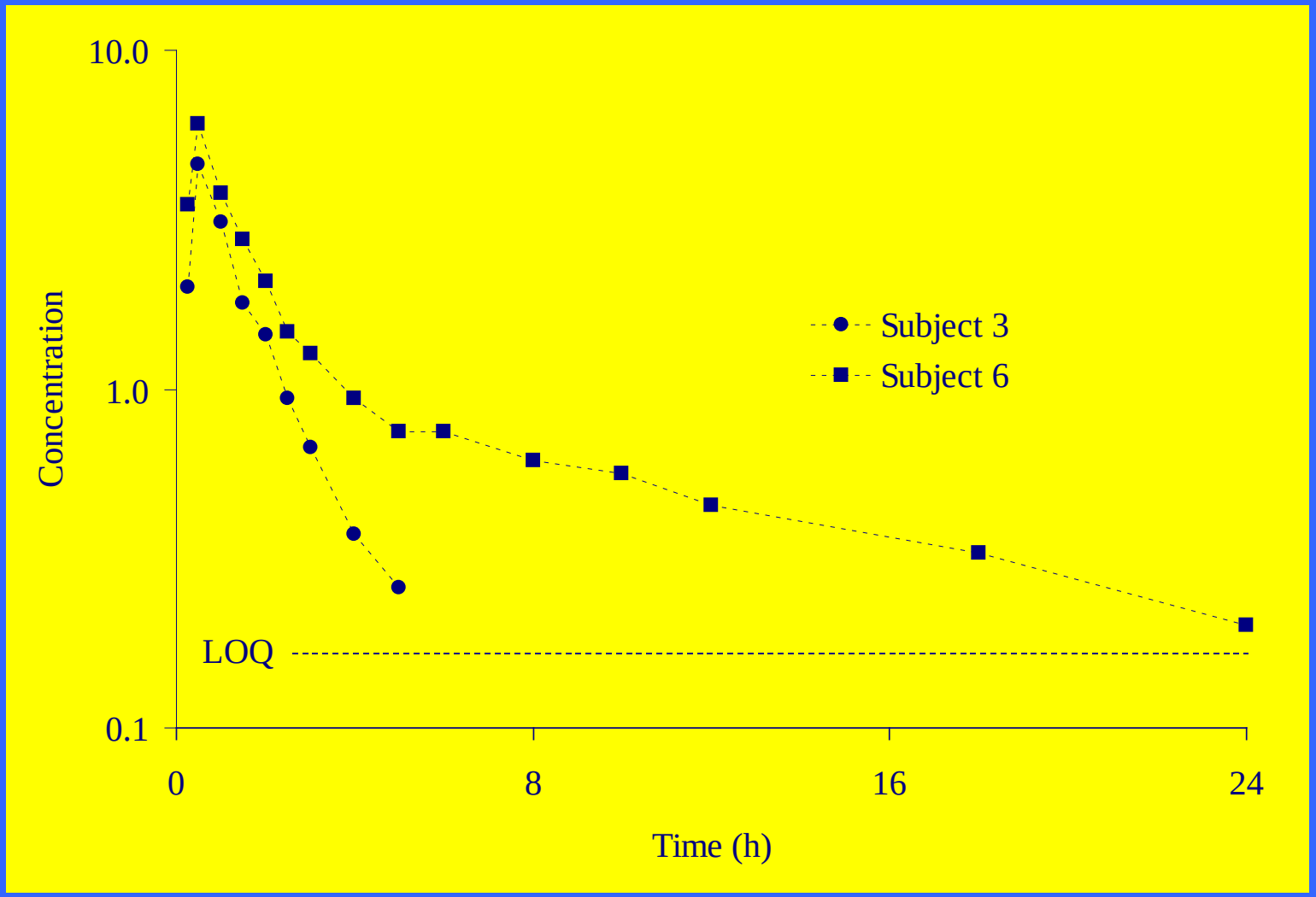
Essentially it is (almost) always useful

- In particular if there are few observations per patient e.g.
  - Outpatients or phase III studies
  - Intensive and emergency care
  - Elderly
  - Children, including premature infants
- When you want to learn about sources of variability
- When you want to develop a model to predict future patient responses
- When you want to use the model to simulate various dosing scenarios
- ...

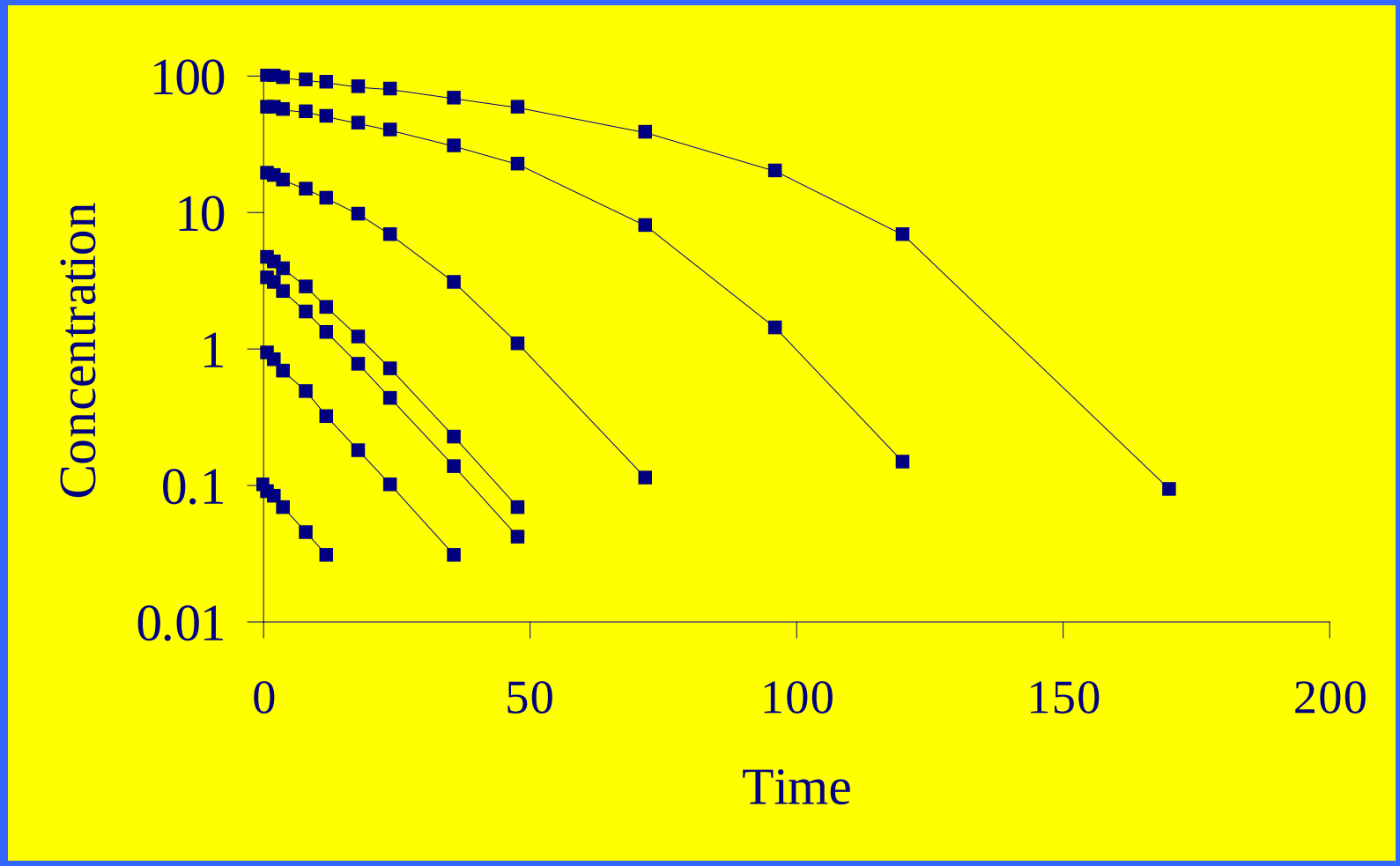
Tolerability studies



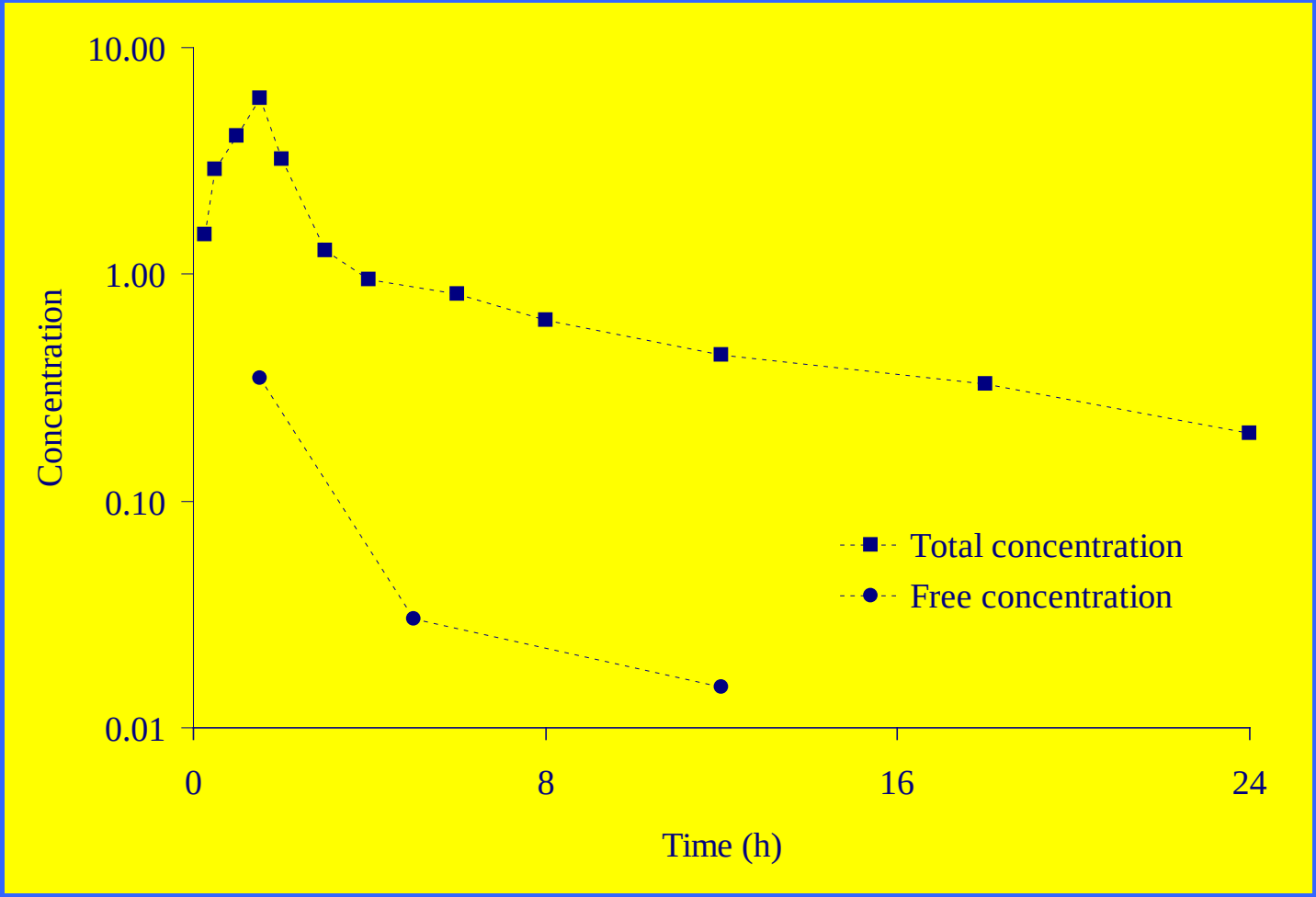
Unbalance and confounding



Non-linear PK



Rich + sparse data



Summary

- PK/PD is model driven
- PK/PD models aid the interpretation of pharmacological data and can be used prospectively to design subsequent studies **learning/confirming**
- Nonlinear mixed effects modelling allows data from a variety of unbalanced, sparse designs to be analysed
- Software for nonlinear mixed effects modelling is now widely available -

  even for amateurs!