MANCHESTER 1824

The University of Manchester

Pharmacokinetic and Pharmacodynamic Modelling

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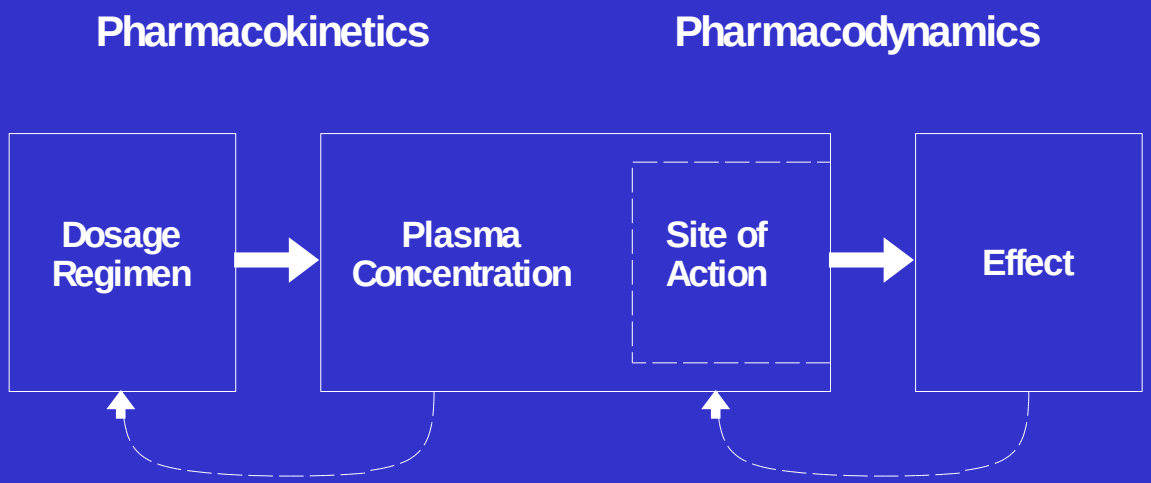
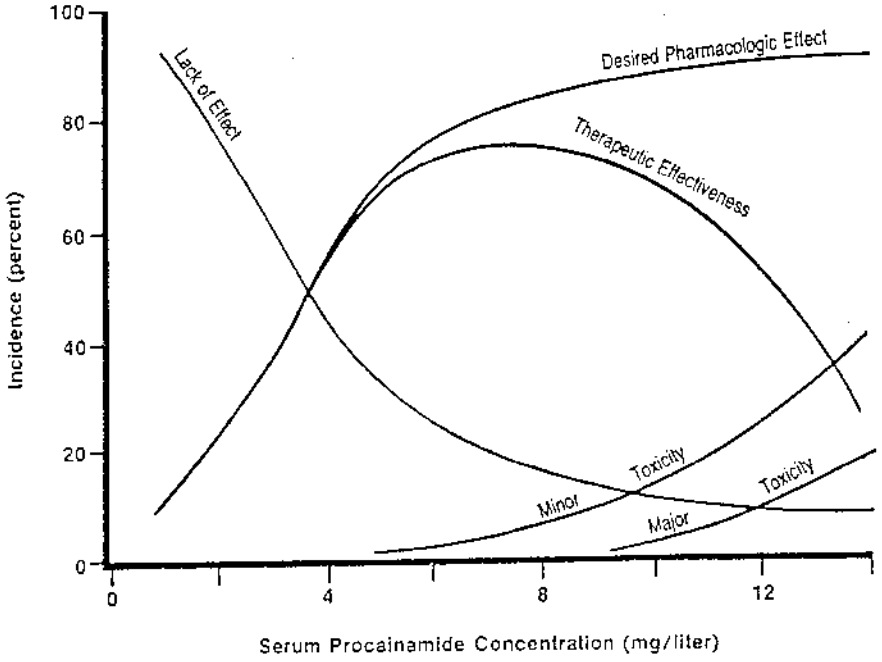
Pharmacokinetics
and
Pharmacodynamics

Clinical Pharmacokinetics





9–6. Schematic representation of the incidence of desired pharmacologic effect (suppression of arrhythmias), of effect, minor and major side effects, and therapeutic effectiveness (desired pharmacologic effect minus ity) as a function of procainamide concentration in serum. (From Rowland, M., and Tozer, T.N.[8])

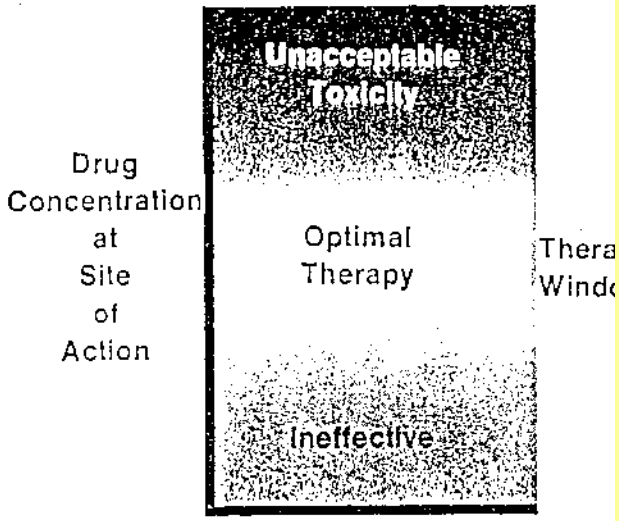
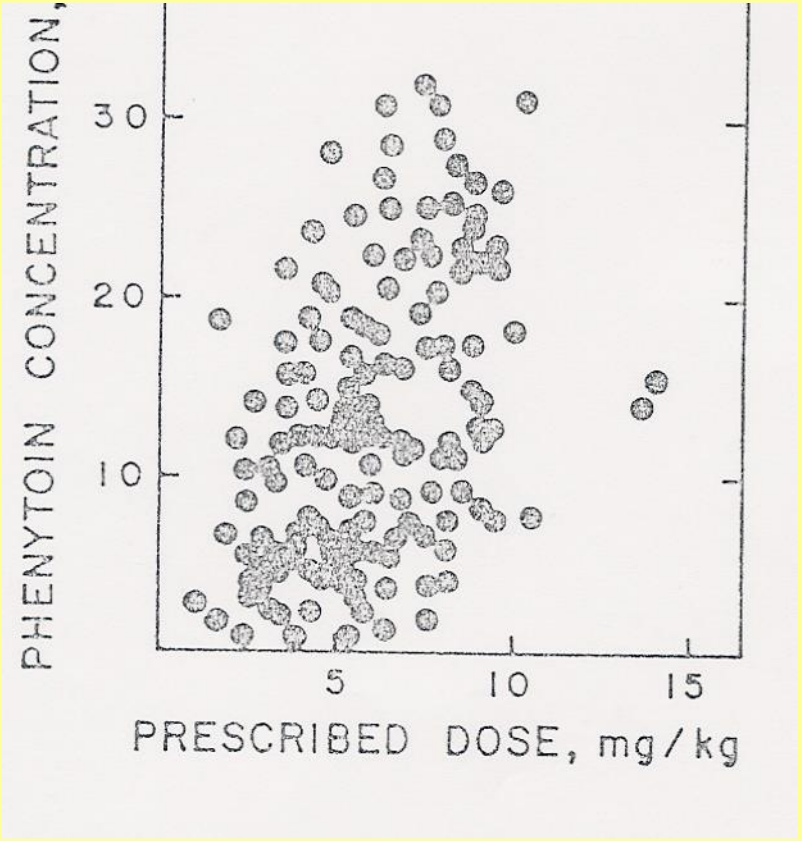


Figure 1-2. *Between certain limits of concen lies a region associated with therapeutic su the therapeutic window.*


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

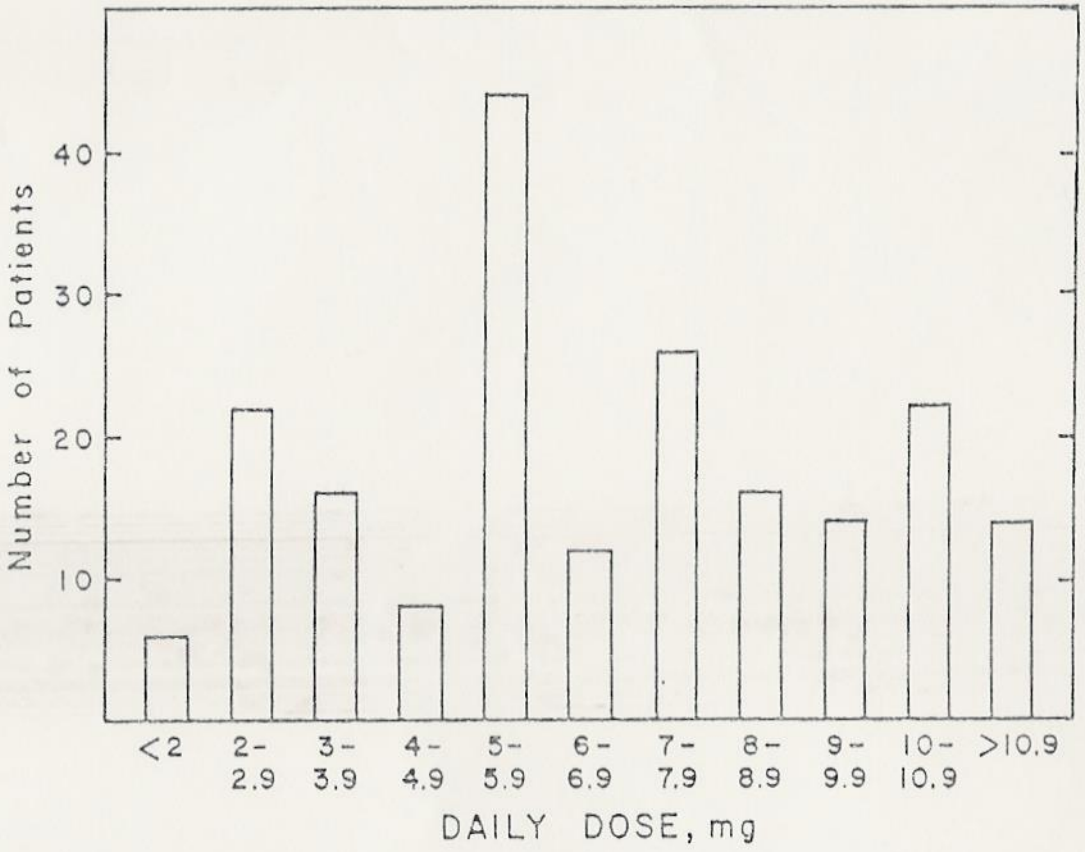


Fig. 8–1. Distribution of doses of warfarin in 200 patients during chronic therapy. (Data from Koch-Weser.[1])

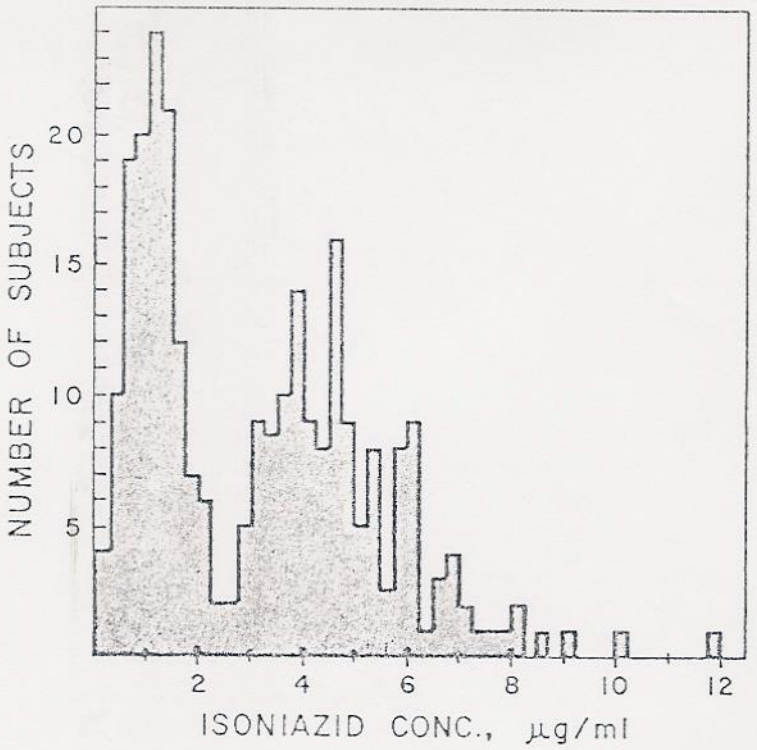


Fig. 7–6. Isoniazid concentration in plasma, 6 hr after oral administration of the same dose to 267 individuals. (Data from Evans, Manely and McKusick.[52])

Pharmacokinetics and Pharmacodynamics in Drug Development

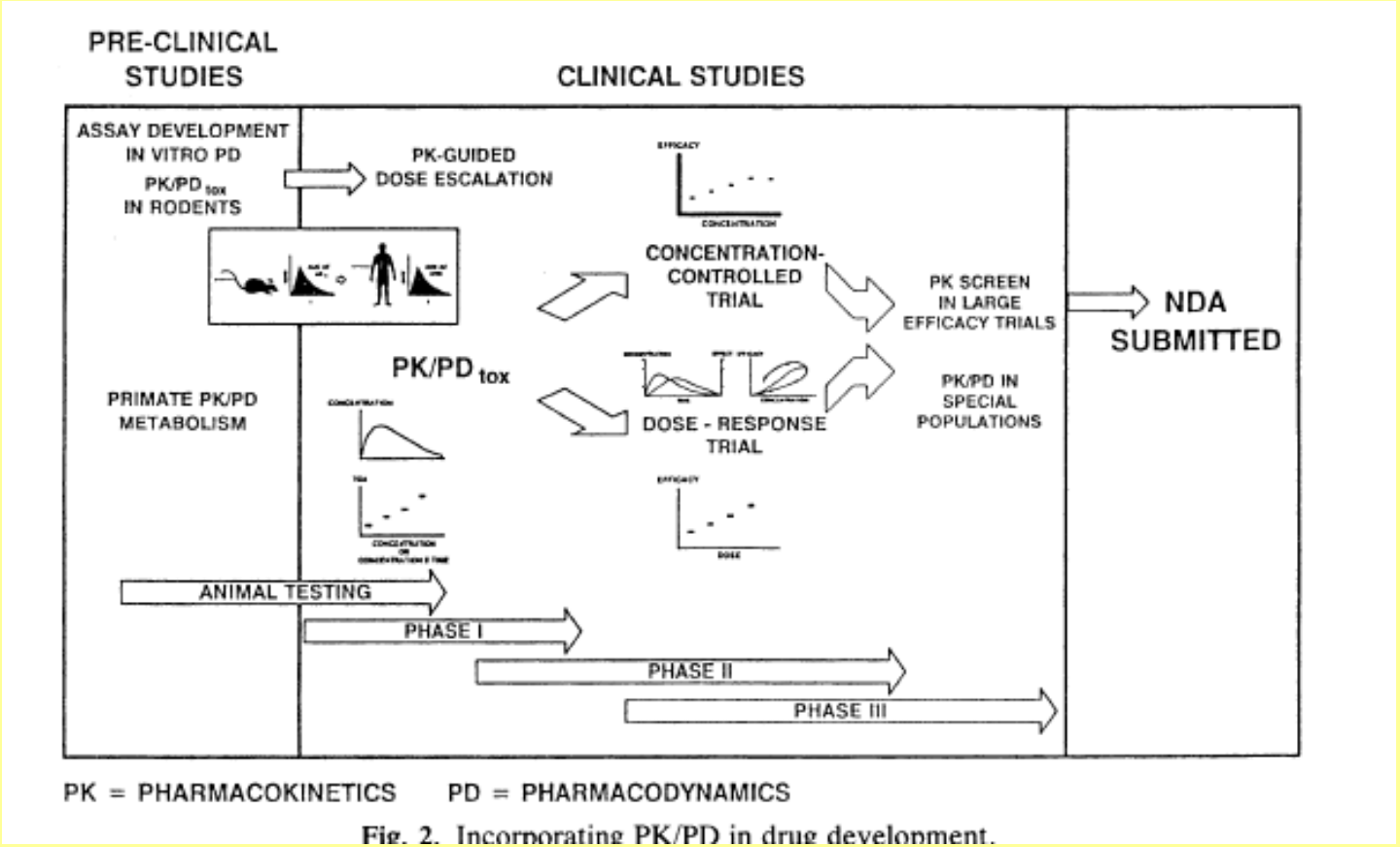


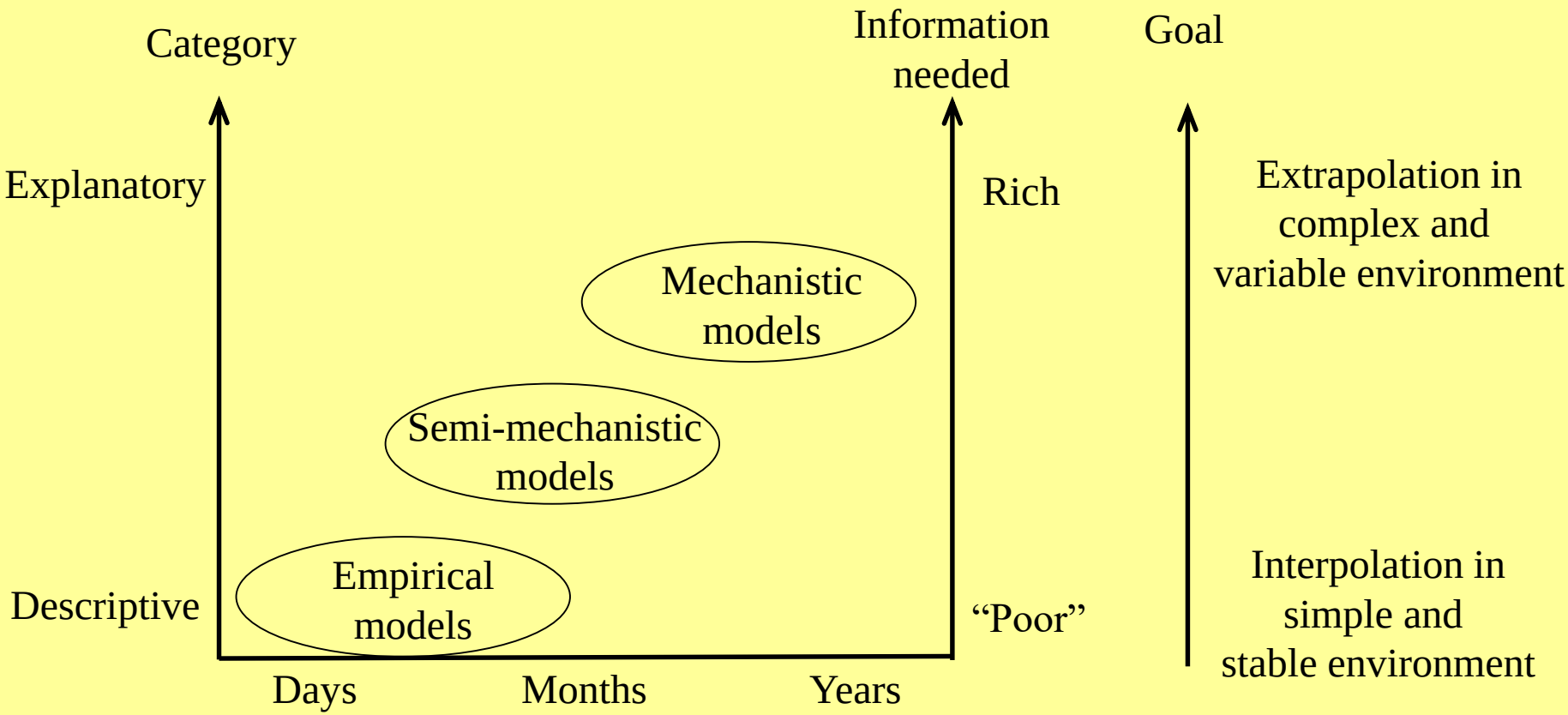
Fig. 2. Incorporating PK/PD in drug development.

Opportunities for Integration of Pharmacokinetics, Pharmacodynamics and Toxicokinetics in Rational Drug Development

Peck *et al.* Pharm.Res. 9: 826 (1992)

Models

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



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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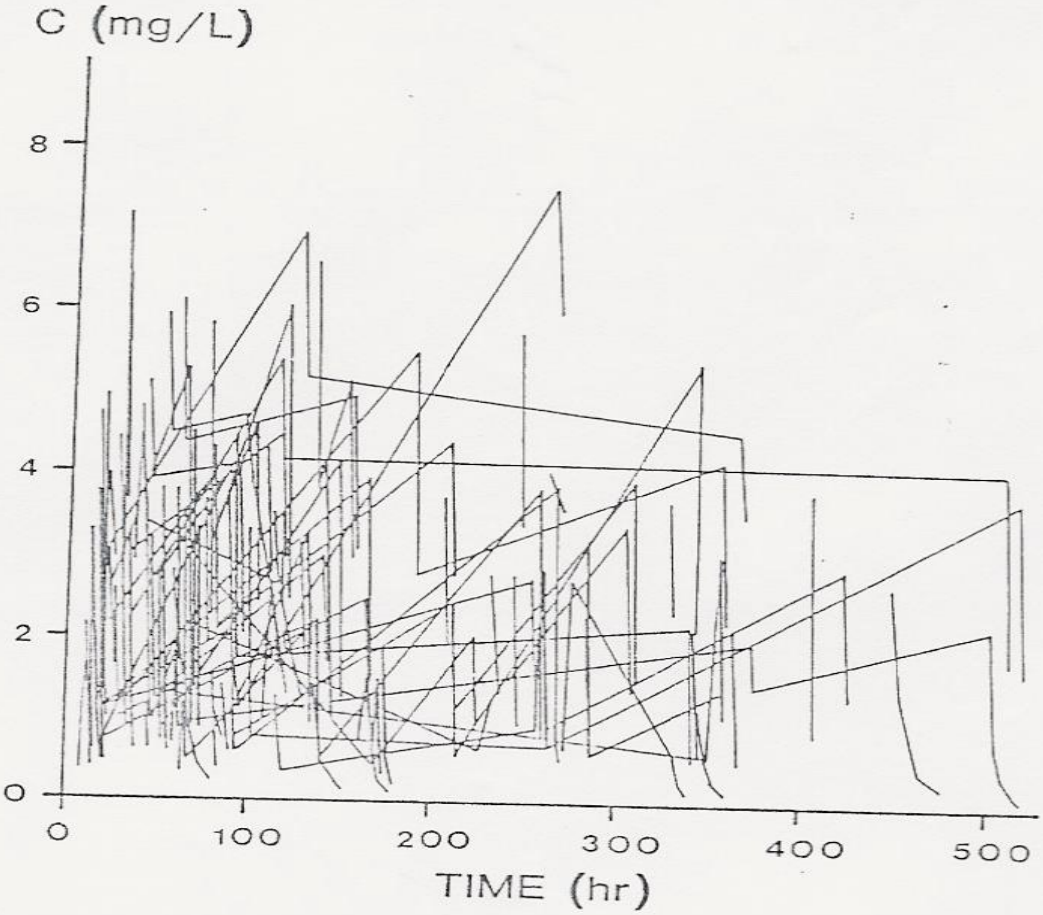
Population study

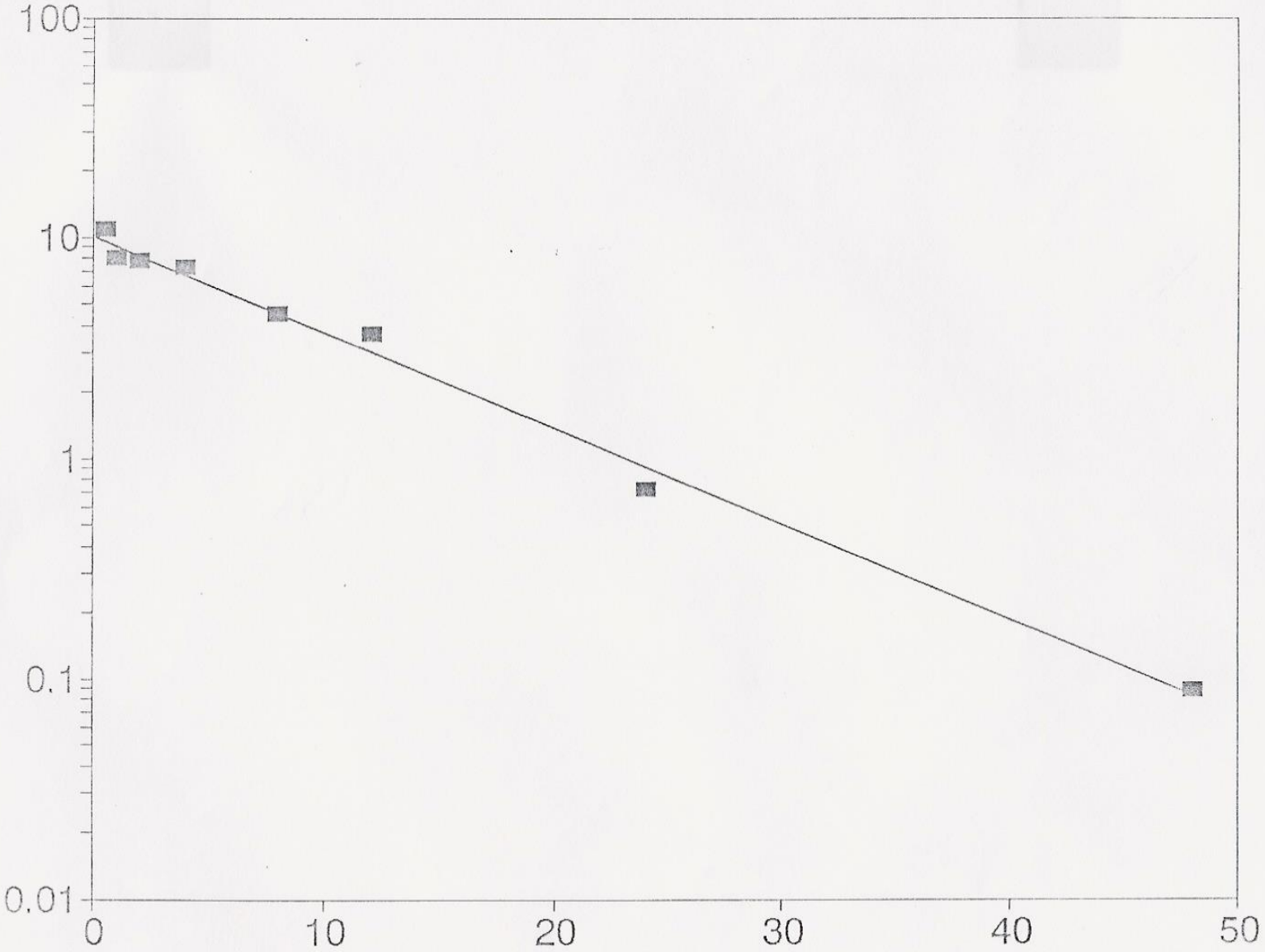
- .numbers are large
- .subjects are heterogeneous - often patients
- .study control is difficult - maybe multicentre observational
- .sparse data

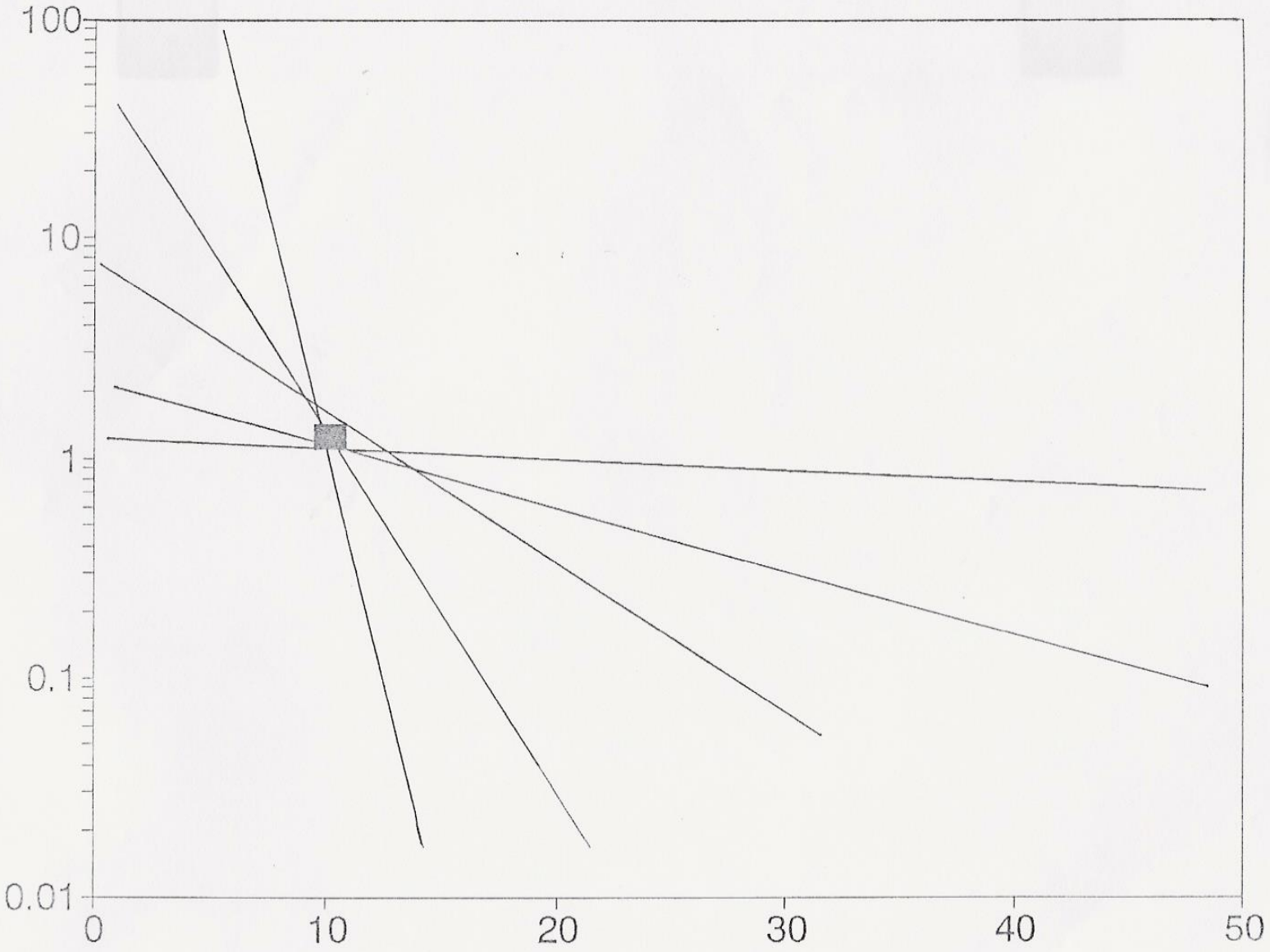
1731 doses
322 concentrations



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	

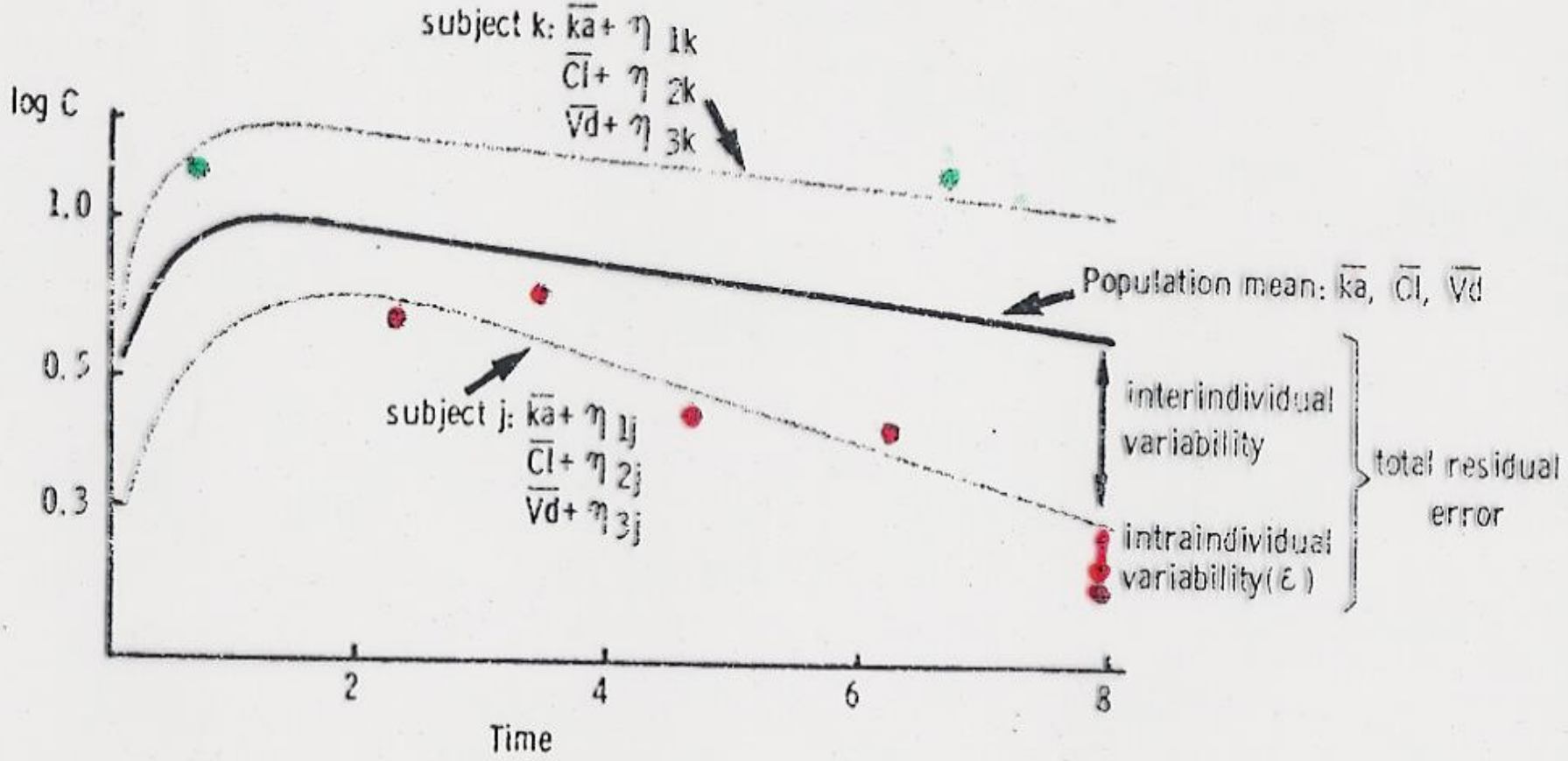

100
10
1
0.1
0.01
0
10
20
30
40
50

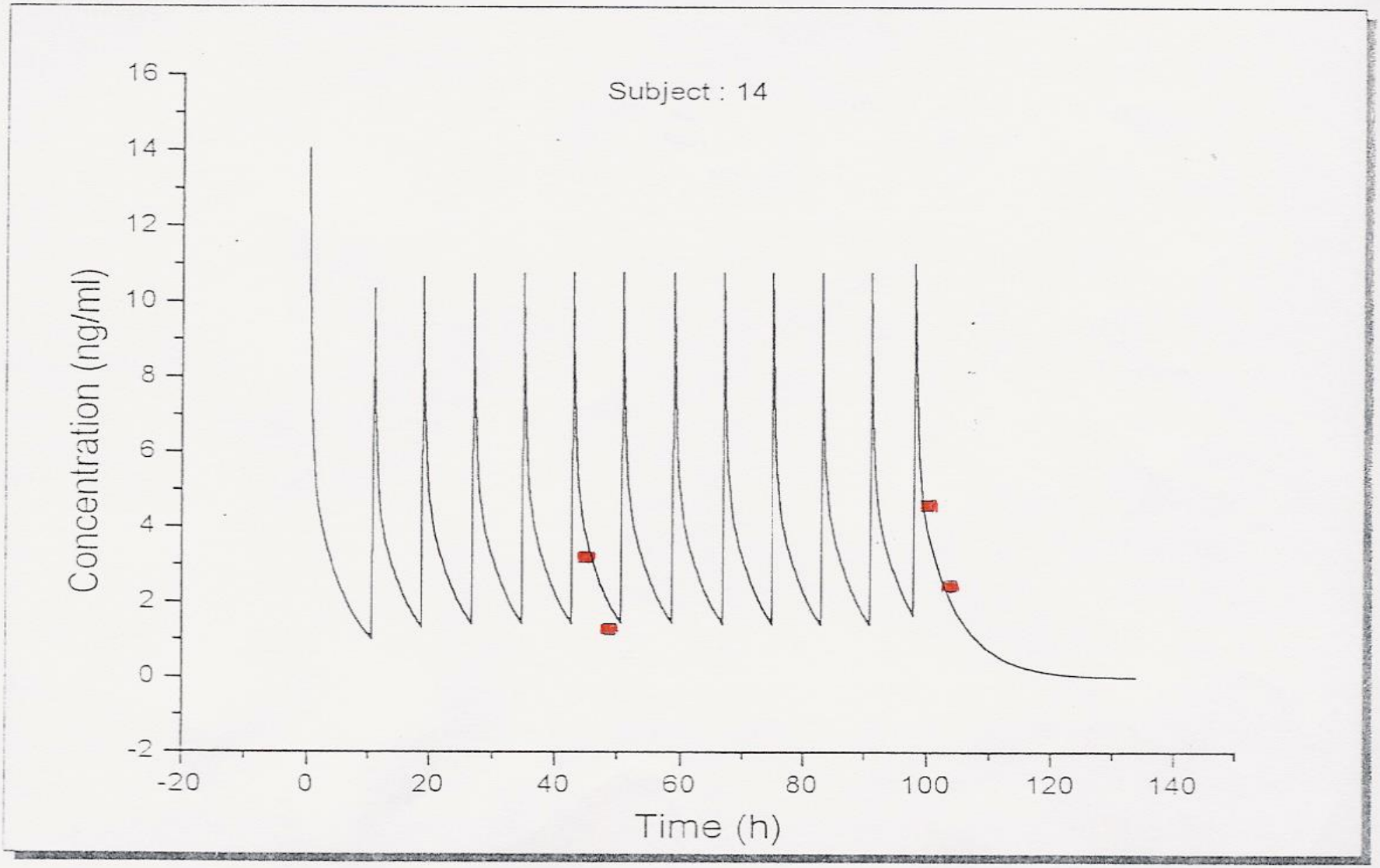

100
10
1
0.1
0.01
0
10
20
30
40
50

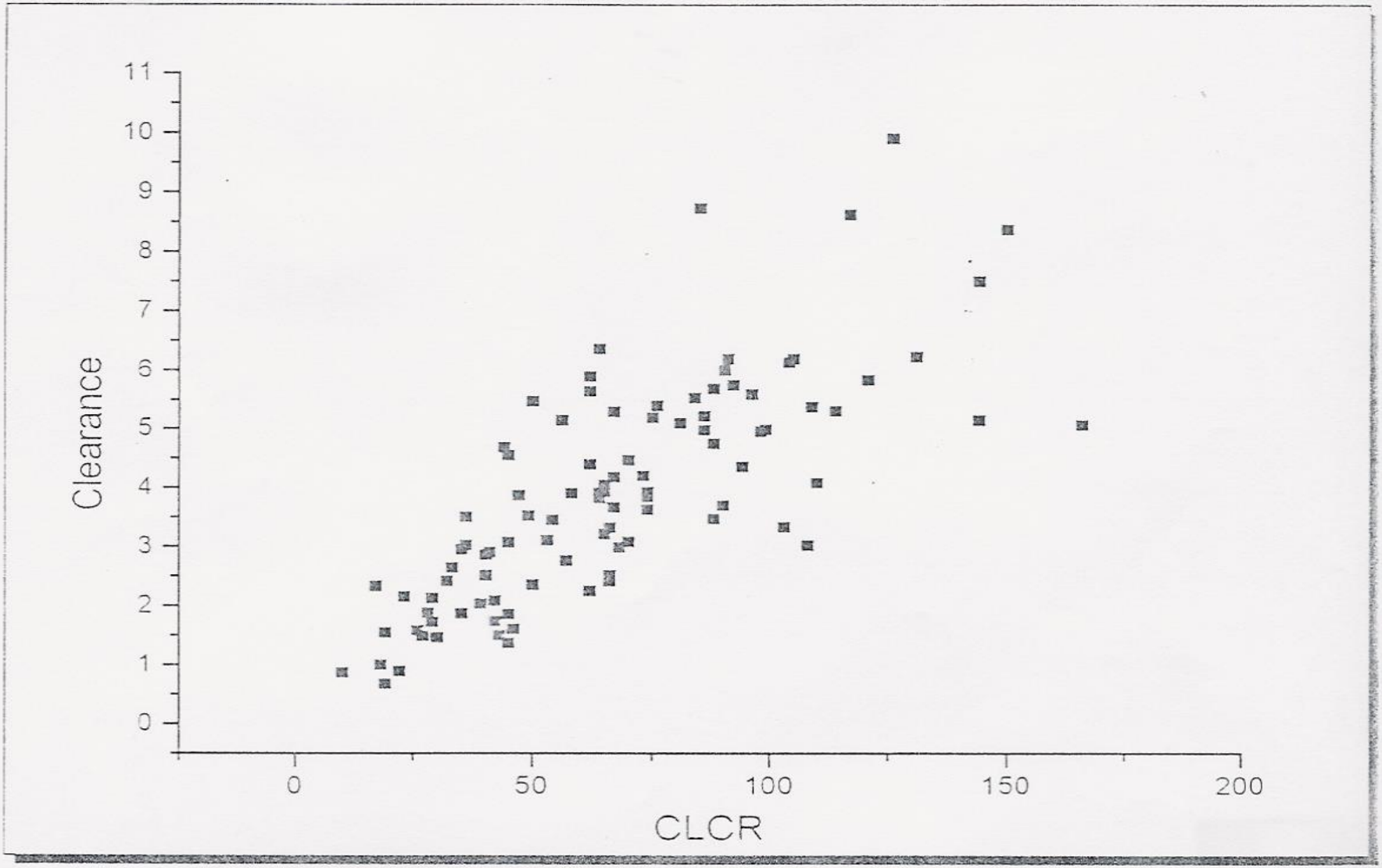
Intelligent Analysis of Unavailable Data

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".


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:

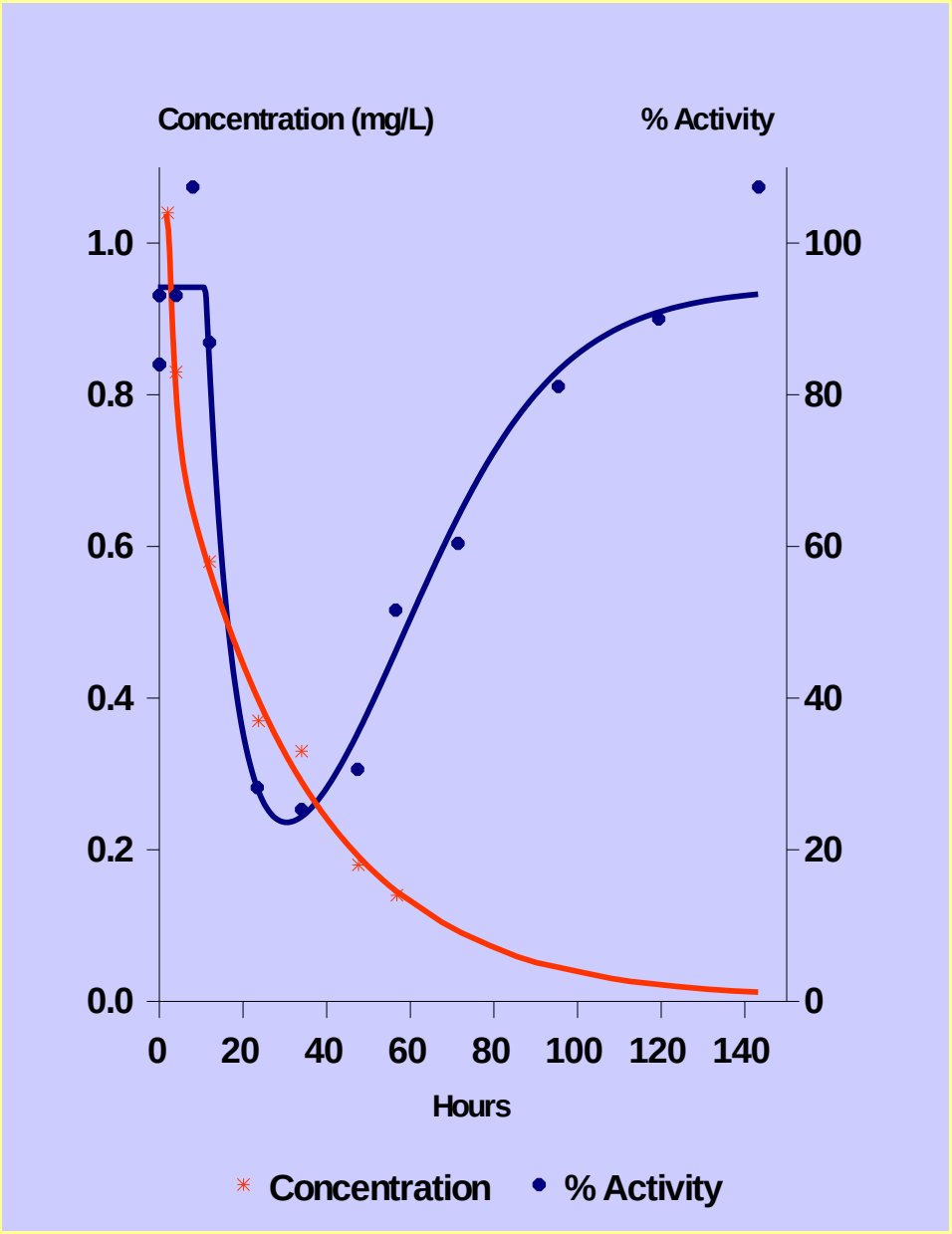
n	**48 normal subjects**
weight (kg)	**66-75**
age (yr)	**20-27**
sex	**male**

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)

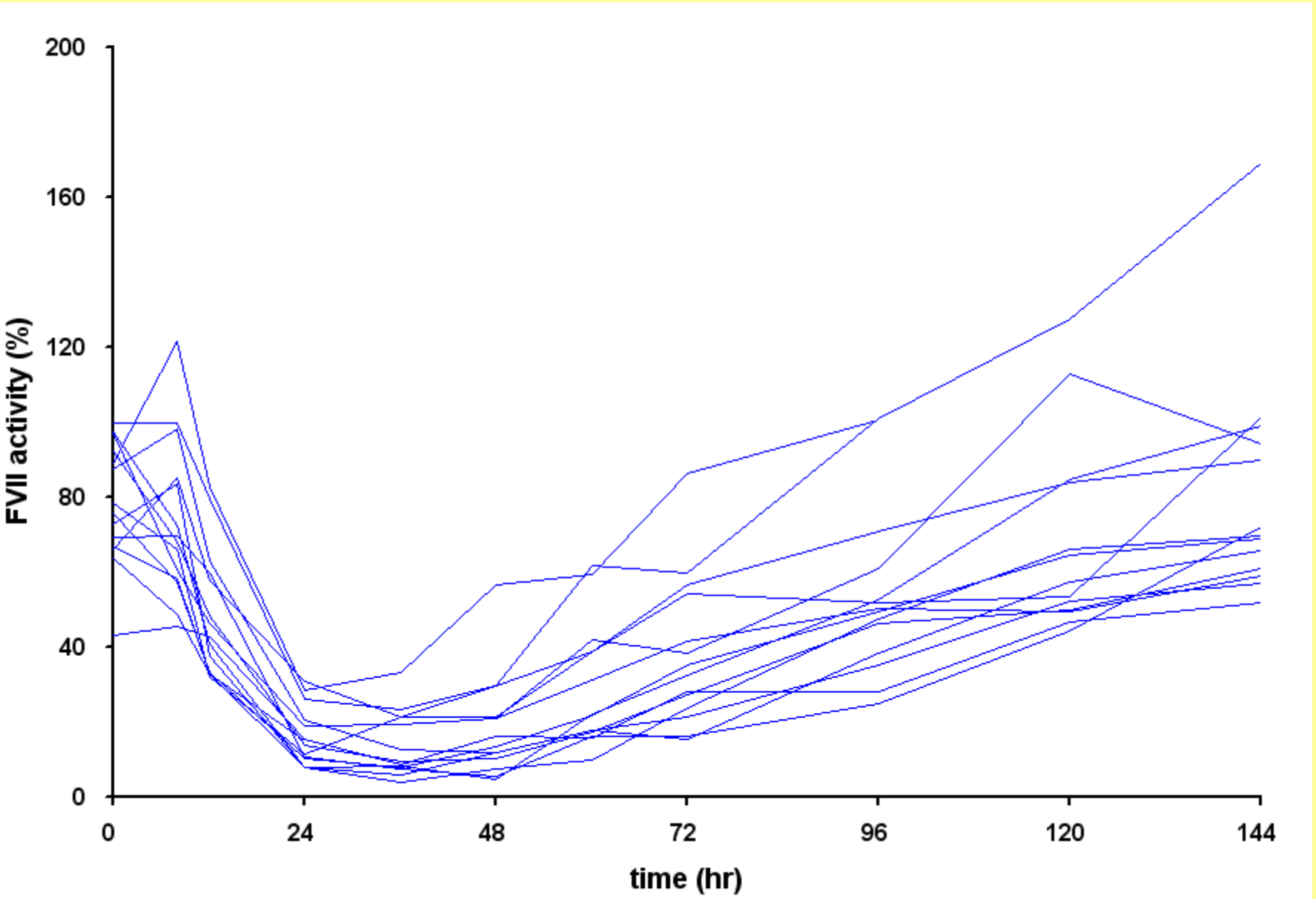

Concentration (mg/L)
% Activity
1.0
0.8
0.6
0.4
0.2
0.0
100
80
60
40
20
0
0
20
40
60
80
100
120
140
Hours
Concentration
% Activity

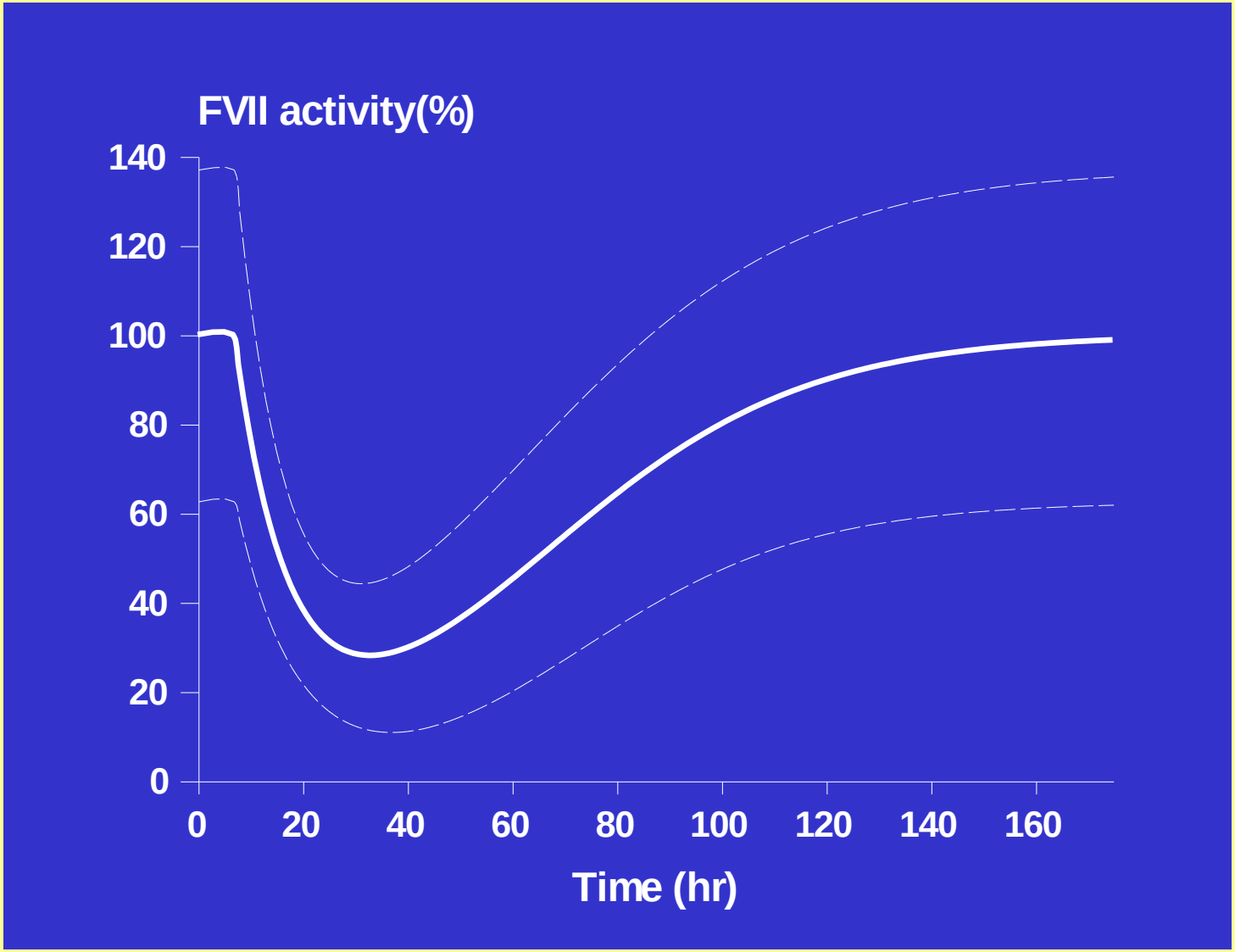
PHARMACODYNAMIC MODEL

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)

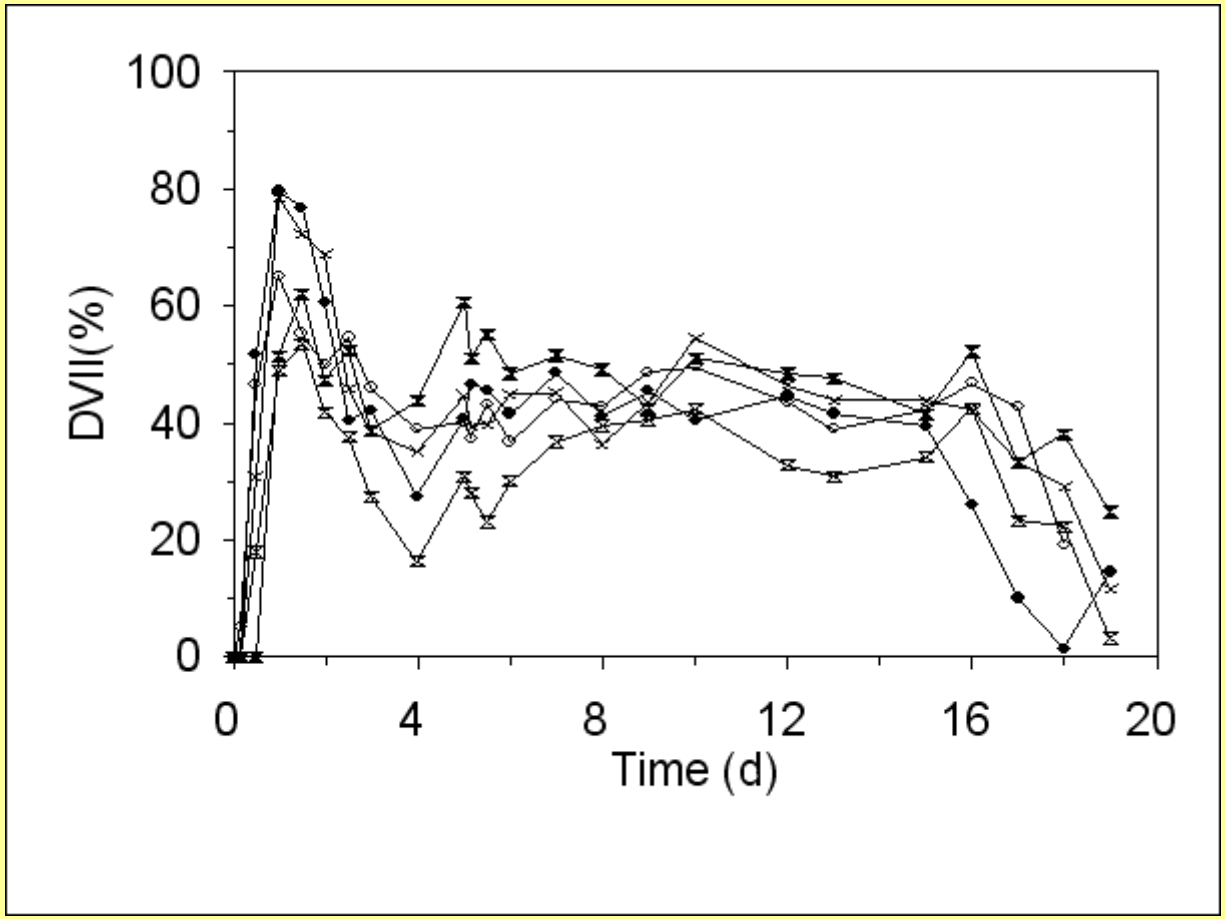
Prospective study

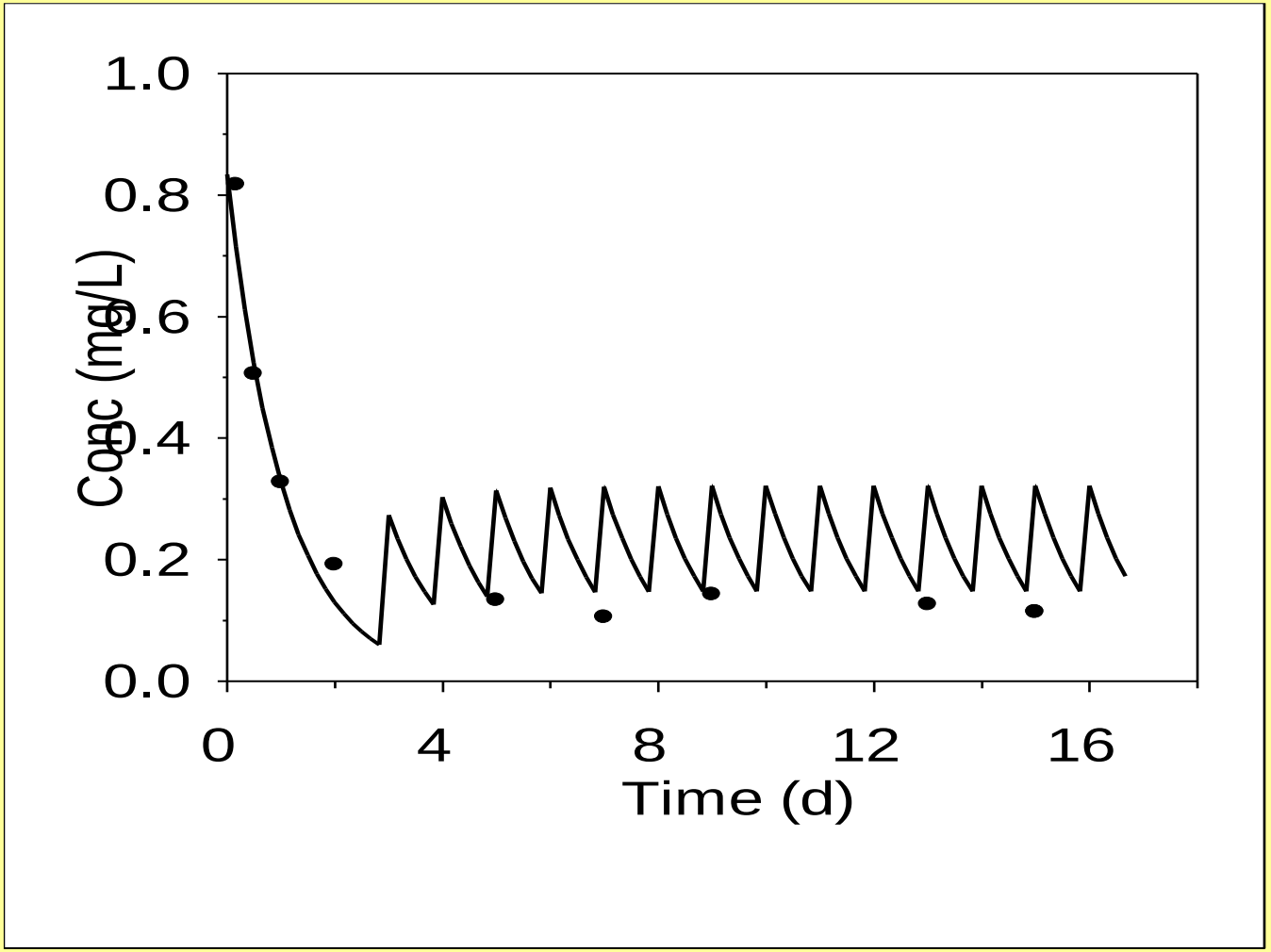
n	**5 normal male volunteers**
Study design	**15mg single dose followed by maintenance dosing from day 3 to day 16 designed to achieve 50% of clotting factor activity**
Maintenance dose	$DM/\tau = k_s \bullet V_s \bullet C_{50,s}$

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)

Some applications of Modelling

Pharmacogenetics and Pharmacokinetics

- Change in focus from description to prediction
- Result = Growth in search for useful covariates
- What are covariates?
  - Demographic
  - Clinical
- Why are they important?
  - Help to describe between and within subject variability
  - Increase prediction accuracy
- Pharmacogenetics
  - Study of how genotype/phenotype effects PK/PD response
  - New covariates to help explain differences. May have been previously partially captured by covariates such as ethnicity

Warfarin and CYP2C9

- **The response of individuals to warfarin has been shown to vary widely between individuals**
- **CYP2C9 is the major enzyme involved in S-warfarin metabolism and the polymorphic differences in expression may help to explain the variability in warfarin response**
- **The CYP2C9*2 allele is expressed in approximately 12% of individuals and CYP2C9*3 in 5%**

Previous studies have shown that:

- **CYP2C9 genotype accounted for 19.8% of the variability in maintenance dose (Hillman, et al., 2004)**
- **VKORC1 and CYP2C9 genetic variants combined are able to account for about a third of the between subject variability (D'Andrea, et al., 2005)**
- **The following covariates accounted for significant variability in response; age (14.6%), body surface area (7.5%), male sex (4.7%) and cardiac valve replacement (5.4%) (Hillman, et al., 2004).**

Drug Interactions

- Population PK studies can potentially be used to study drug-drug interactions in routinely obtained, and hence relevant, clinical data

- However
  - Power may be poor as study is not designed
  - Dosing history of interacting drugs may be poor or absent
  - Probably no drug levels of interacting drugs
  - Drug combinations likely to be heterogeneous

- For important interactions be guided by *in vitro* studies and use classical designs
- Stratification in population studies may help

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!