A Nonlinear Model Based Method for Steady-state Assessment

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Outline

- Introduction
  - Pharmacokinetics and pharmaceutical research
  - Definition & Existing methods
- Method development
  - Pharmacokinetic Modeling
  - Decision rules to determine steady-state
    - Is steady-state attained at the end of dosing?
    - At what time is steady-state reached?
- Simulation
  - Performance of the proposed method
  - Comparison to other existing methods
- Concluding remarks

Introduction

Pharmacokinetics : Font 40 Definition

Pharmacokinetics (PK)

what the body does to the drug

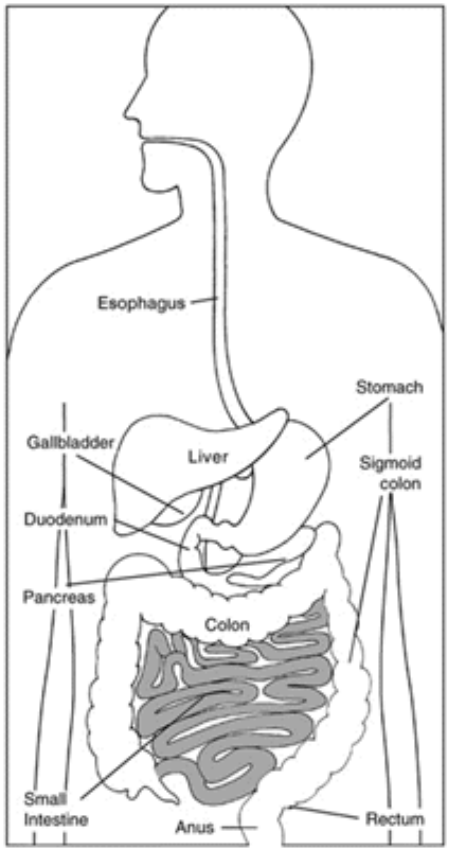
Pharmacodynamics (PD)

what the drug does to the body

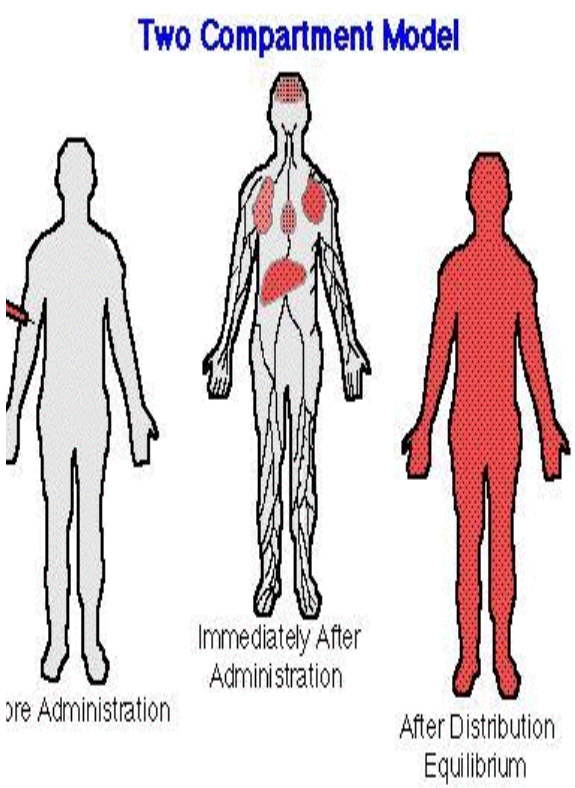
Pharmacokinetics : Font 14 Definition

Pharmacokinetics: **The quantitative study and characterization of the time course of drug absorption, distribution, metabolism, and excretion.**

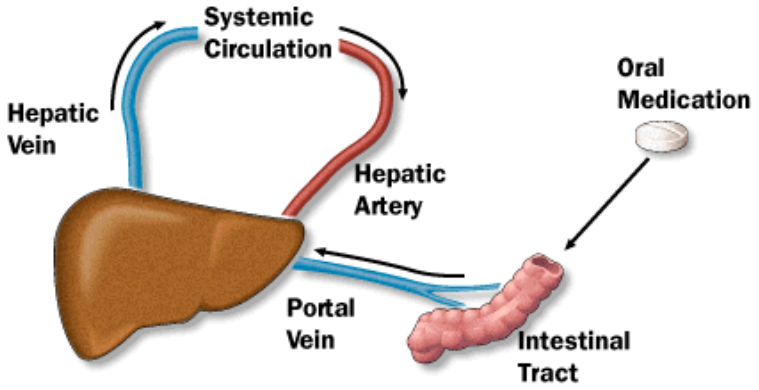
Absorption

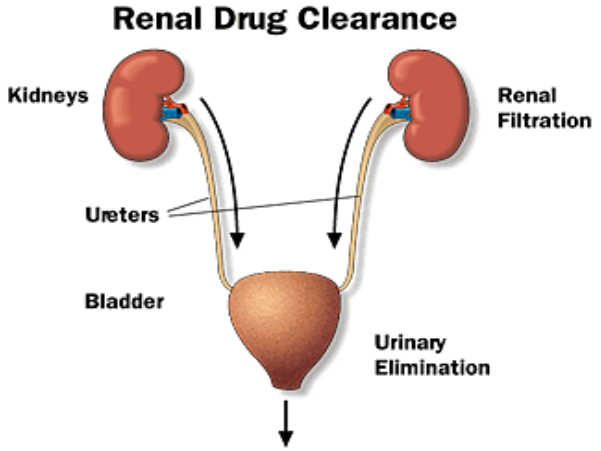


Distribution



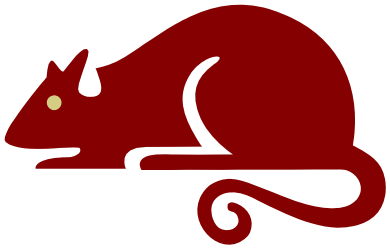
Metabolism & Excretion





Pharmacokinetics in Pharmaceutical Research

Preclinical



- Rate of absorption
- Extent of absorption
- Rate of elimination
- Metabolites
- Etc

What to expect in humans

Clinical
Phase I trials

Phase I Design questions:

- Length of dosing period
- Length of washout period
- Time points of blood sample collections
- Doses to be tested

Pharmacokinetics in Pharmaceutical Research

Phase I

Pharmacokinetic Parameters :

- **Volume of distribution**
- **Clearance**
- **Cmax**
- **Tmax**
- **AUC**
- **Half life**
- **etc**

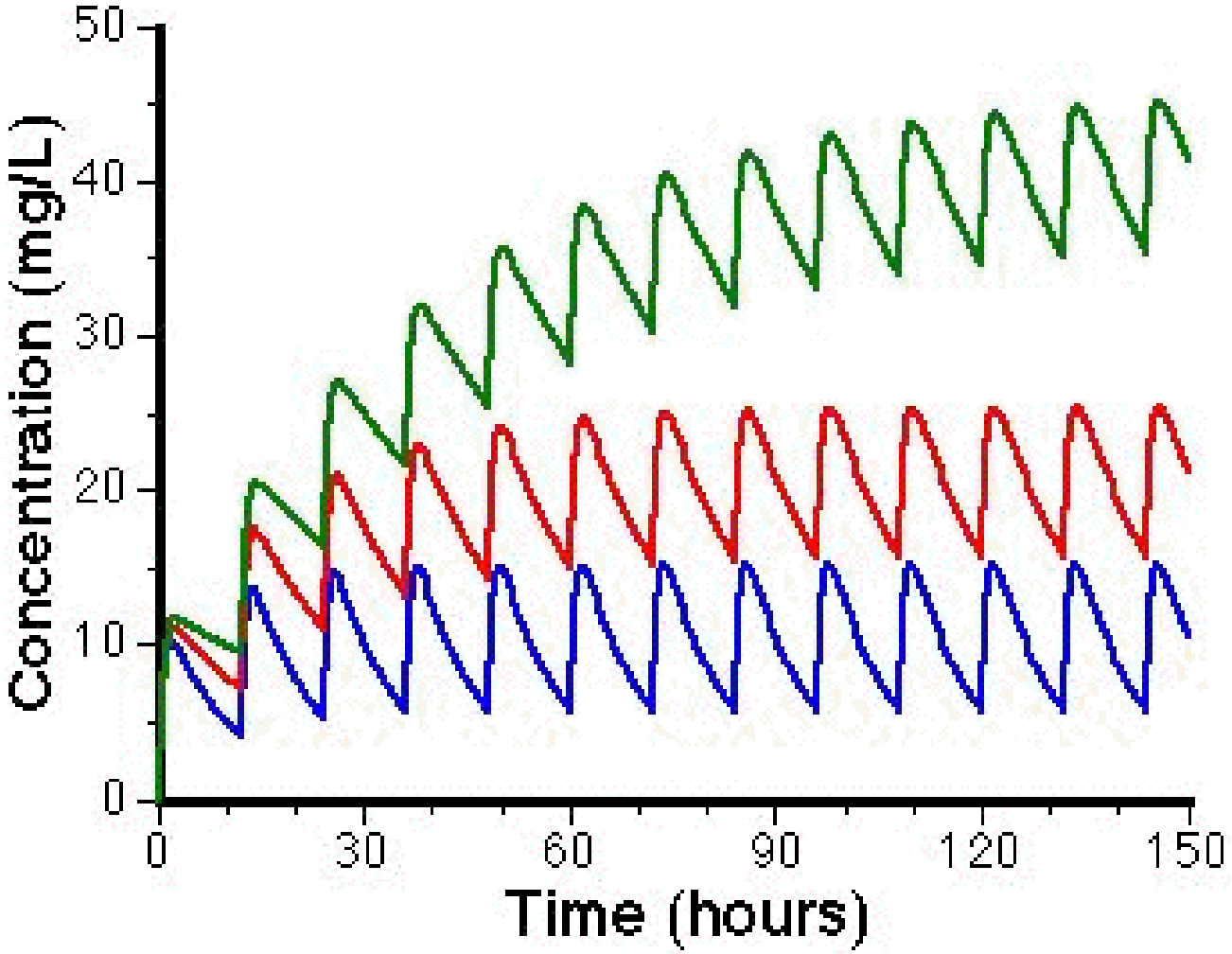
Help Determine

Dose regimen

Phase II, III, IV

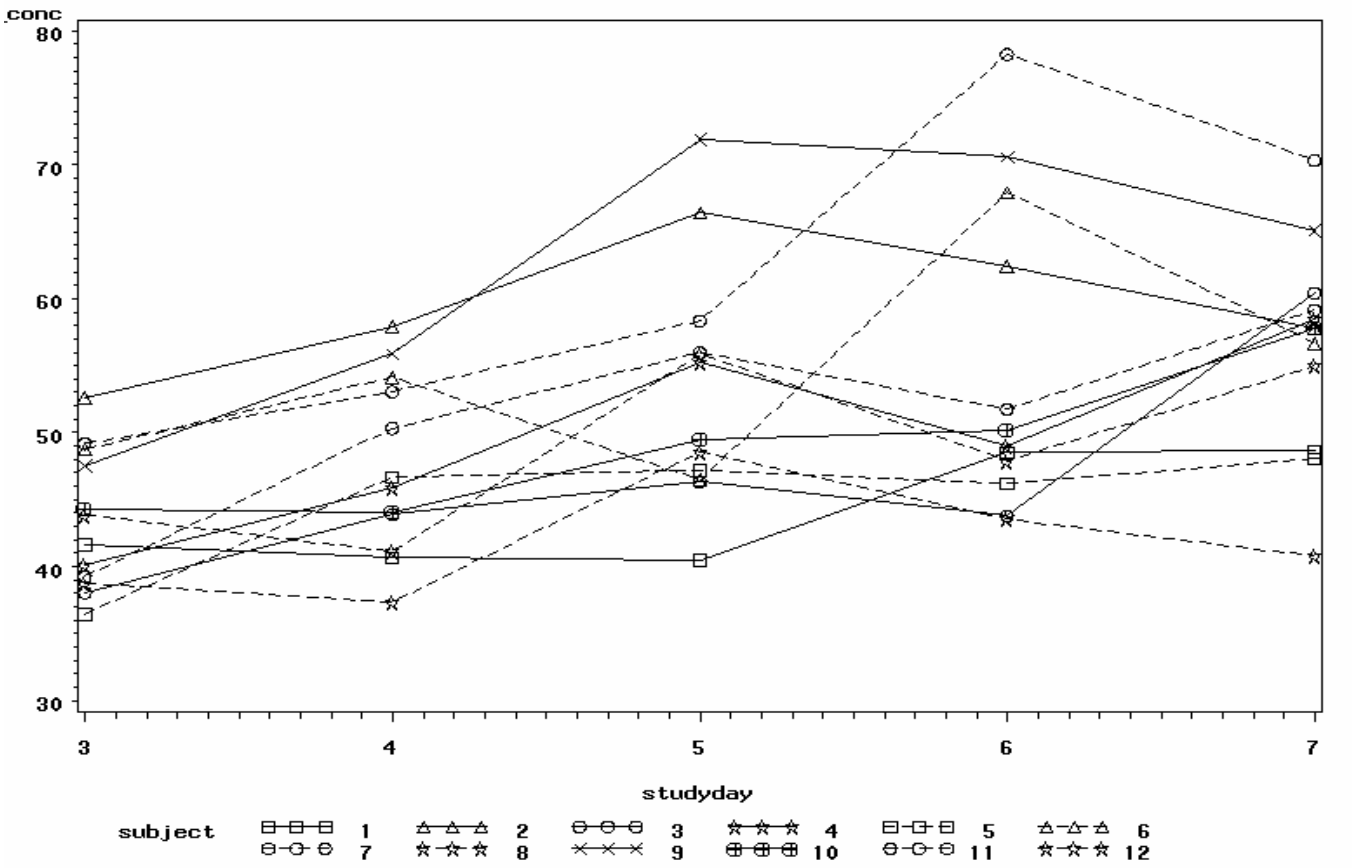
- **Therapeutic dose**
- **Dosing frequency**
- **With/without food**
- **Dose adjustment in special subpopulations**
- **Drug-drug interaction**

Problem Background
Pharmacokinetics in multiple dosing setting



Example Problem

Example : 12 subjects, trough conc on day 3, 4, 5, 6 and 7.



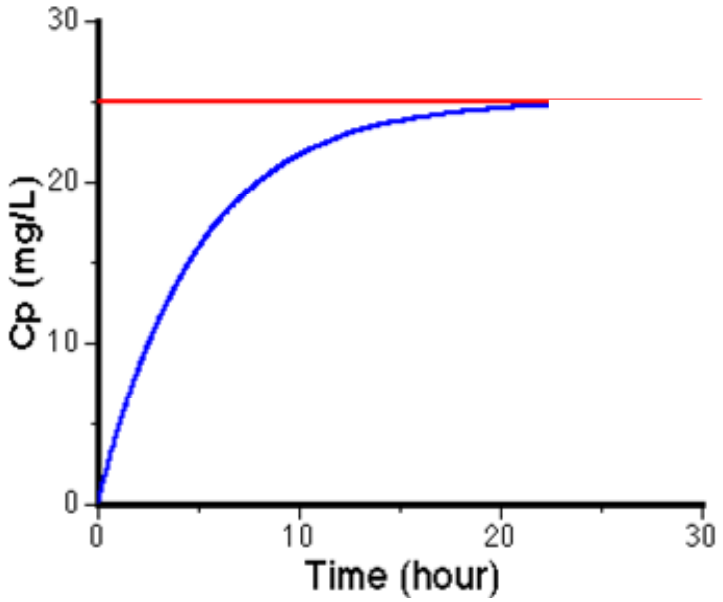
Why evaluating steady-state?

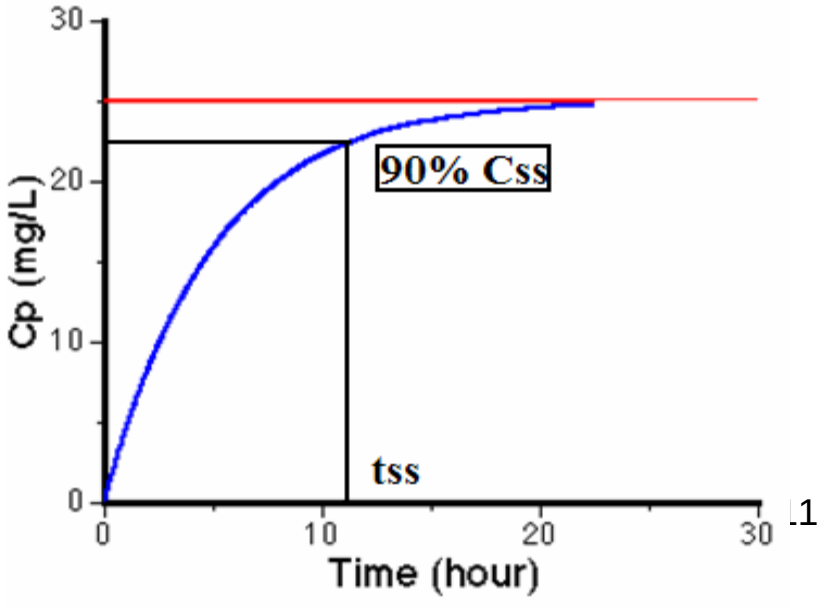
- Therapeutically relevant
- Certain PK concepts apply to SS (e.g, intrinsic clearance, protein binding, enzyme systems)
- Influence of internal/external factors on exposure of chronically administered drug is most relevant at SS; most importantly, in drug-drug interaction (DDI) studies.
- Constitute well controlled study

Steady-state definition

- ***Theoretical*** : the equilibrium condition reached when the amount of drug admitted into the kinetic system over time exactly equals the amount of drug eliminated by the system over that same period of time. (**rate in = rate out**)

- ***Practical*** : "From a clinical perspective, 90% of the theoretical steady state value is often used as a practical definition"
  - Rowland M, Tozer TN. Clinical pharmacokinetics: Concepts and applications.





Existing methods in practice
Analysis of Variance (ANOVA)

- Difference test :

  "each vs last" test

  Day 6 vs Day 7

  Day 5 vs Day 7

  ……..

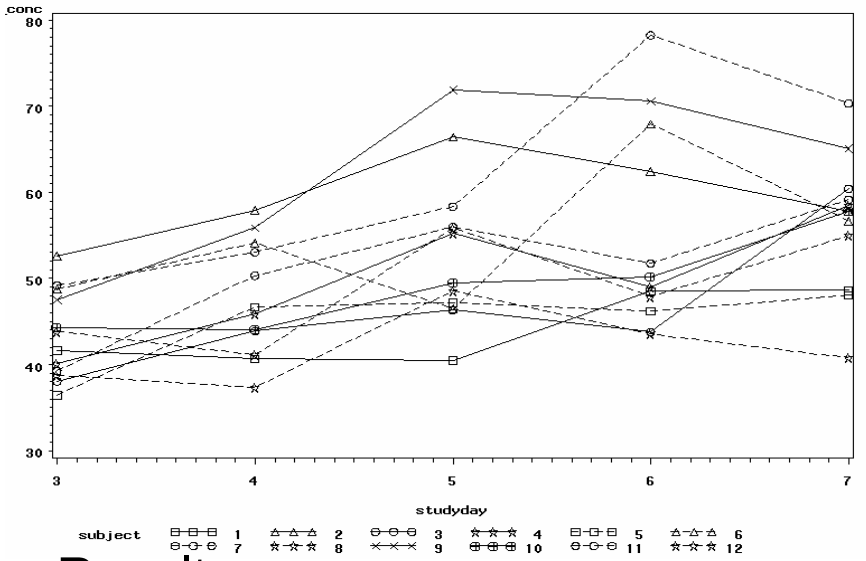
  "Helmert test

  Day 6 vs Day 7

  Day 5 vs (Day 6 + Day 7)/2

- Equivalence test : 90% CI of geometric mean ratio wholly contained in (0.8, 1.25).

Example : 12 subjects, trough conc on day 3, 4, 5, 6 and 7.



Results :

Day	N	Least-Squares Geometric Mean	Ratio Versus Day 7 (90% CI) [p-Value]	Helmert Test (90% CI) [p-Value]
5	11	79.22	1.17(1.09, 1.25)[.001]	1.15(1.08, 1.26)[.012]
6	11	88.64	1.04(0.97, 1.12)[.319]	1.04(0.97, 1.12)[.319]
7	11	92.31		

Pros and Cons of ANOVA method

Advantages :

- PK model free
- Easily implemented

Disadvantages :

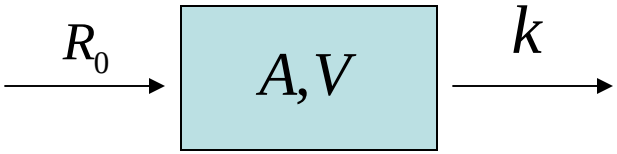
- Qualitatively :
  - Not related to practical definition (90% of asymptotic steady state)
  - Estimated date restricted to actual sampling day
  - Yes/no responses. If no, no guidance on future studies
  - Can not determine individual steady state
- Quantitatively :
  - Will come back at Simulation

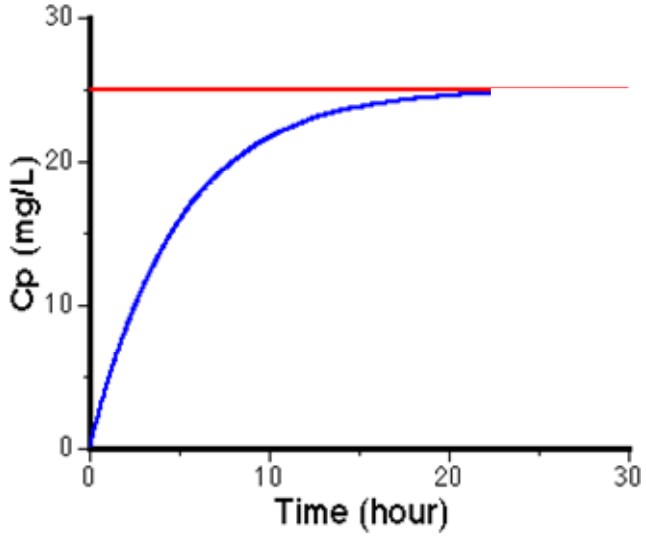
Method Development

1. PK modeling

2. Decision rules

PK modeling - Case I : constant IV infusion





Notations

A : amount

V : volume

k : elimination rate constant

R_0 : infusion rate

Derivation :

$$\frac{dA}{dt} = R_0 - kA$$

$$\Rightarrow A_{(t)} = \frac{R_0}{k}\left(1 - e^{-kt}\right)$$

$$\Rightarrow C_{P(t)} = \frac{A_{(t)}}{V} = \frac{R_0}{V \cdot k}\left(1 - e^{-kt}\right)$$

$$\Rightarrow C_{P(t)} = C_{SS}\left(1 - e^{-kt}\right)$$

PK modeling - Case II : Multiple IV bolus

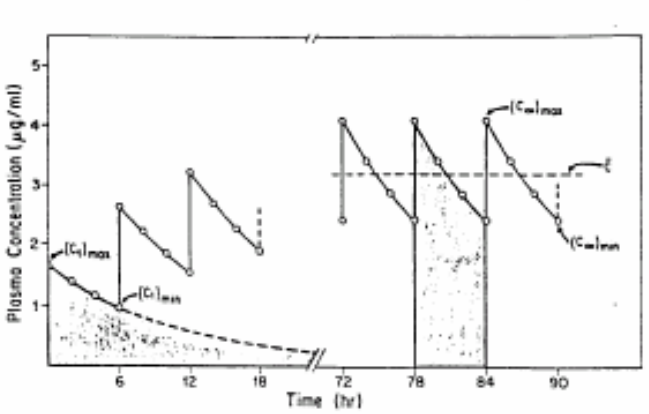
Suppose dosing interval is τ .

$$A(t) = A_0 \cdot e^{-k \cdot t}$$

Immediately following first dose,

$$A(0) = A_0$$

Immediately following the second dose,



$$A(\tau) = A_0 + A_0 e^{-k\tau} = A_0(1+q)$$

….

Following N-th dosing, by law of superpositioning :

$$A((n-1)\tau) = A_0(1+q+\cdots q^{n-1}) = \frac{A_0(1-q^n)}{1-q}$$

$$C_{P,trough}((n-1)\tau) = \frac{A_0}{V(1-q)}(1-q^n) = C_{SS,trough}(1-e^{-k \cdot n\tau})$$

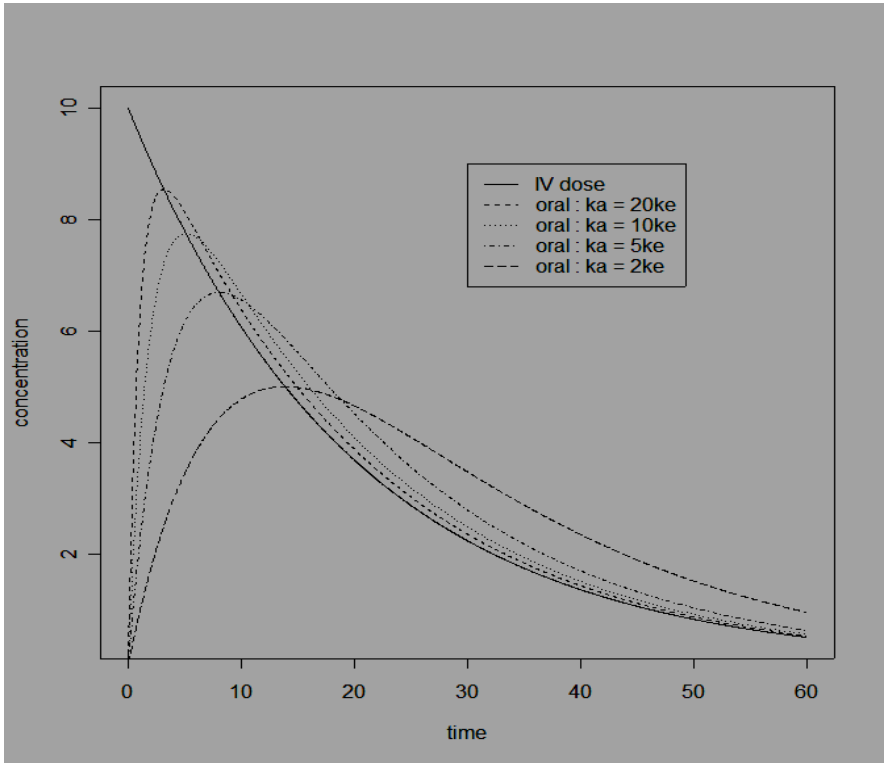
PK modeling – Case III : multiple oral dosing

$$A = \frac{A_0 \cdot k_a}{(k_a - k_e)}\left(e^{-k_e t} - e^{-k_a t}\right)$$

- When $k_a >> k_e$, the terminal elimination phase nearly identical to that of iv bolus dosing, the same model holds
- In general($k_a > k_e, k_a = k_e, k_a < k_e$)

$$C_{P,trough}((n-1)\tau) = C_{SS,trough}(1 - e^{-k^* \cdot n\tau})$$

where $k^* = g(k_a, k_e, \tau)$



Model Assumptions and Concepts

- **Assumptions :** if PK is linear with time and dose, then $C_{P,trough}$ can be described as

$$C_{P,trough}(t) = C_{SS,trough}(1 - e^{-k \cdot t})$$

- **Measure of steady-state:** $f = \dfrac{C_{P,trough}(t)}{C_{SS,trough}} = 1 - e^{-k \cdot t}$

- **f as a function of half-life :** $t_{1/2} = \ln(2)/k$

$$f(t_{1/2}) = 1 - e^{-k \cdot t_{1/2}} = 0.5$$
$$f(2t_{1/2}) = 1 - e^{-k \cdot 2\ln(2)/k} = 0.75$$
$$\cdots$$
$$f(5t_{1/2}) = 0.97$$
$$f(7t_{1/2}) = 0.99$$

So, steady-state can be reasonably assumed at 5 to 7 half-life of time

Non-linear mixed effect Model expression

For individual $i = 1, \cdots s$; dosing $j = 1, \cdots l$; trough plasma concentration after jth dosing

$$C_{i,j} = [C_{SS,trough} e^{\alpha_i}](1 - e^{-[ke^{\beta_i}]j\tau}) e^{\varepsilon_{ij}}$$

Where

Random error ~ $\varepsilon_{i,j} \sim N(0, \sigma_\varepsilon^2)$

Random subject effect ~ $(\alpha_i, \beta_i) \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_\alpha^2 & \sigma_{\alpha\beta} \\ \sigma_{\alpha\beta} & \sigma_\beta^2 \end{pmatrix}\right)$

Principles of Decision rules

To answer two central questions :

- Is steady-state attained at the end of dosing?
- At what time is steady-state reached?

Decision Rule #1
Hypothesis testing – SS attained?

SS is reached, if, after the n-th dosing

$$f_{n\tau} = 1 - e^{-k \cdot n\tau} \geq 0.9$$

Thus, statistical hypothesis of SS attainment is set at :

$$H_o : f_{n\tau} \geq 0.9 \quad vs \quad H_a : f_{n\tau} < 0.9$$

Equivalently,

$$H_o : e^{-k \cdot n\tau} \leq 0.1 \quad vs \quad H_a : e^{-k \cdot n\tau} > 0.1$$

Suppose k can be estimated by $\hat{k}$. By δ-method, when $\hat{k} \in N(\mu_k, {\delta_k}^2)$, then

$$e^{-\hat{k} \cdot n\tau} \in N(e^{-\mu_k \cdot n\tau}, (n\tau \cdot e^{-\mu_k \cdot n\tau} \cdot \delta_q)^2)$$

Test statistics can be formed

$$T = \frac{e^{-\hat{k} \cdot n\tau} - 0.1}{n\tau \cdot e^{-\hat{k} \cdot n\tau} \cdot \hat{se}_k}$$

which, when $e^{-k \cdot n\tau} = 0.1$, $T \in N(0,1)$,reject H0 when $T > Z_\alpha$, where Z_α is the $(1-\alpha)$ - th quantile of standard normal distribution

Decision Rule #2
estimating time to reach steady-state

As

$$f = \frac{C_{P,trough}(t)}{C_{SS,trough}} = 1 - e^{-k \cdot t}$$

Time to reach steady-state can be estimated as

$$\hat{t}_{SS} = \frac{\ln(1-f)}{-\hat{k}} \text{ when } f = 0.9$$

By delta-method, if $\hat{k} \in N(\mu_k, \delta_k{}^2)$

Then $$\hat{t}_{SS} = \frac{\ln(1-f)}{-\hat{k}} \in N\left(\frac{\ln(1-f)}{-\mu_k}, \left(\frac{\ln(1-f)}{\mu_k^2}\delta_k\right)^2\right)$$

CI of $\hat{t}_{SS}$ can be calculated.

Corollary : SS can be determine alternatively when $100(1-\alpha)\%$ upper boundary of $\hat{t}_{SS}$ is less than the time of the last dosing

$$\hat{t}_{SS} + z_{1-\alpha} \frac{\ln(1-f)}{\hat{k}^2} \hat{se}_k < l\tau$$

A similar method by Hoffman et al

Hoffman et al, *Pharmaceut. Statist*. 2005; **4**: 15–24

Modeling is the same but decision rule is different

$$C_{i,j} = [C_{SS,trough} e^{\alpha_i}](1 - e^{-[ke^{\beta_i}]j\tau})e^{\varepsilon_{ij}}$$

$$\bar{t}_f = \frac{ln(1-f)}{-\bar{k}} \qquad \bar{t}_{if} = \frac{ln(1-f)}{-\bar{k}_i}$$

Decision rule is different : " We suggest that both the 50th percentile (for average steady state) and the 90th percentile (for individual steady state) of the subject-specific predicted values be reported."

Example : By Hoffman's method

- Design: 4 dose groups, 6 subject each,
- Length of study : QD for 20 days;
- Measurements : C_{trough} on D1,2,3,4,6,13,19,20

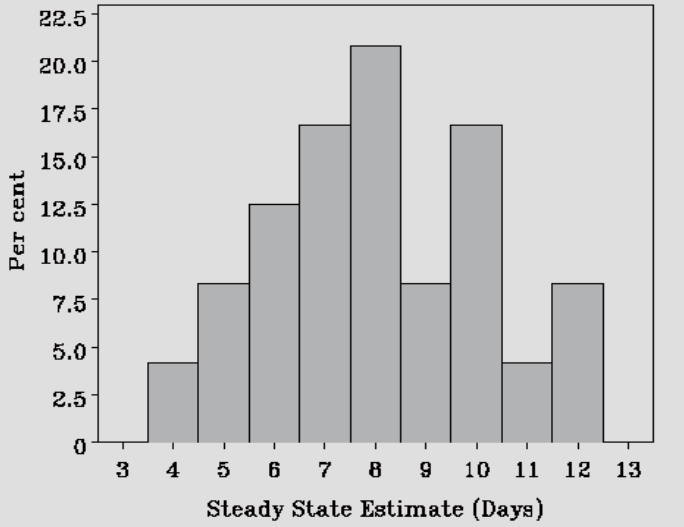


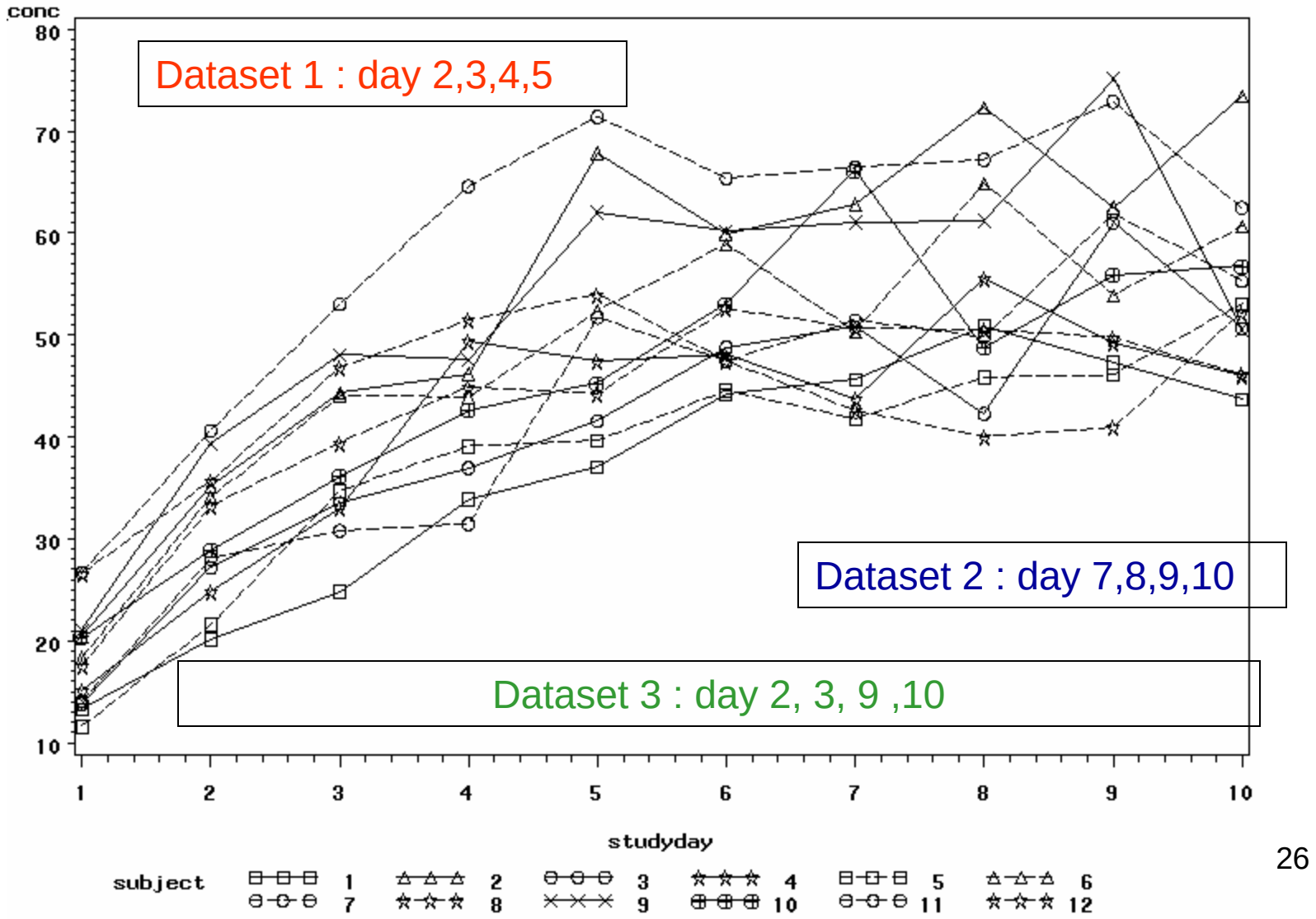
Figure 2. Histogram of subject-specific steady state estimates from fitted model.

Table II. Estimates and 95% confidence intervals for 50th and 90th percentiles of predicted day of steady state.

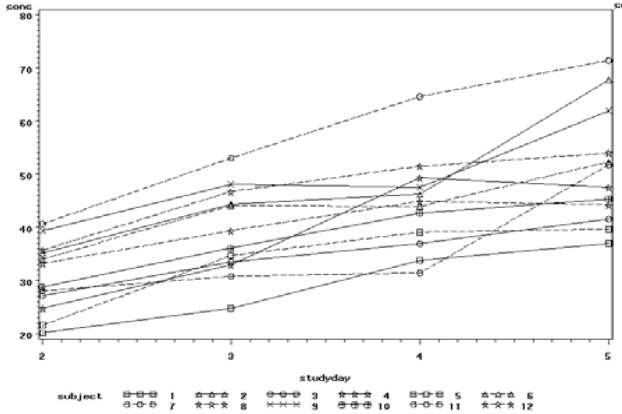
Percentile	Estimate	95% CI
90th	11.0	(9.5, 12.4)
50th	7.7	(7.0, 9.5)

Simulation

Simulation : single dataset

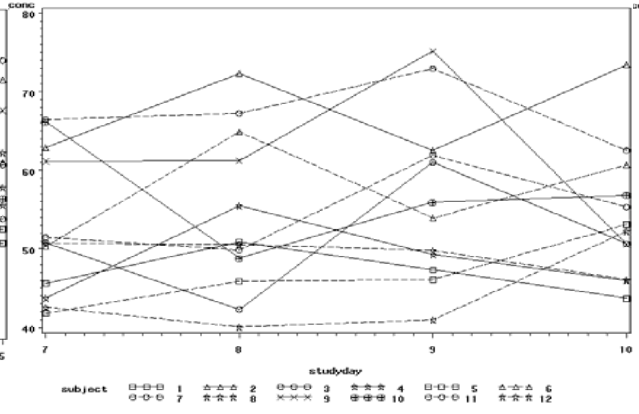


Dataset 1 : day 2,3,4,5



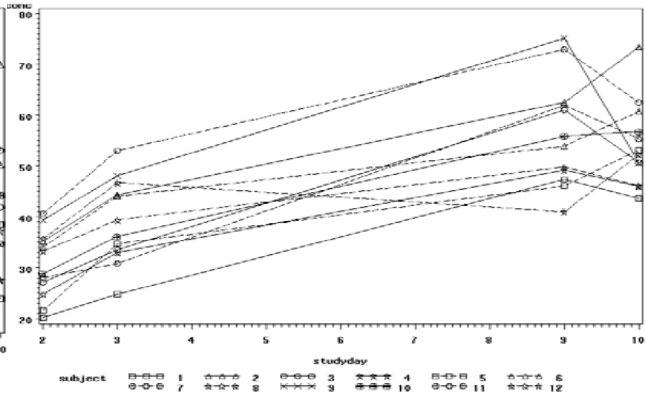
Parameters	"true" value	Estimates(se)
n	12	
day	2,3,4,5	
$\log(C_{SS})$	4	4.1004(0.06139)
k	0.4	0.3811(0.04421)
σ_ε	0.1	0.0880(0.01082)
σ_α	0.1	0.1695(0.04438)
σ_β	0.4	0.4782(0.04950)
$\sigma_{\alpha\beta}$	0	-0.0450(0.0237)
t_{SS}	5	6.0422(0.70)
90% t_{SS} U_bound		6.716 (>5)
f_1	0.9	0.851238
T		1.4830
Deny SS?		No

Dataset 2 : day 7,8,9,10



Parameters	"true" value	Estimates(se)
n	12	
day	7,8,9,10	
$\log(C_{SS})$	4	4.1371 (0.1129)
k	0.4	0.3969 (0.2089)
σ_ε	0.1	0.09562 (0.01095)
σ_α	0.1	0.1945 (0.07481)
σ_β	0.4	0.4883(0.3512)
$\sigma_{\alpha\beta}$	0	-0.09311 (0.09044)
t_{SS}	5	5.8013(3.05)
90% t_{SS} U_bound		18.5979 (>10)
f_1	0.990	0.9811
T		-2.0549
Deny SS?		No

Dataset 3 : day 2, 3, 9 ,10



Parameters	"true" value	Estimates(se)
n	12	
day	2, 3 , 9 , 10	
$\log(C_{SS})$	4	4.0415 (0.04001)
k	0.4	0.3663 (0.03079)
σ_ε	0.1	0.09449 (0.01314)
σ_α	0.1	0.1099 (0.03127)
σ_β	0.4	0.3989 (0.08068)
$\sigma_{\alpha\beta}$	0	-0.01383 (0.01109)
t_{SS}	5	6.2836(0.53)
90% t_{SS} U_bound		6.6687 (<10)
f_1	0.990	0.9743
T		-9.4139
Deny SS?		No

Simulation – Performance of the proposed method

k_e =0.461(reaching steady state on Day 5); C_{SS} =100, $\tau = 1$, multiple dosing up to 7 days.

CV indicates both within-subject CV and between-subject CV in C_{SS} and k_e. When CV=10%, $\sigma_e = \sigma_\alpha = \sigma_\beta$ =0.10; when CV=25%, $\sigma_e = \sigma_\alpha = \sigma_\beta$ =0.246; when CV=50%, $\sigma_e = \sigma_\alpha = \sigma_\beta = 0.472$.

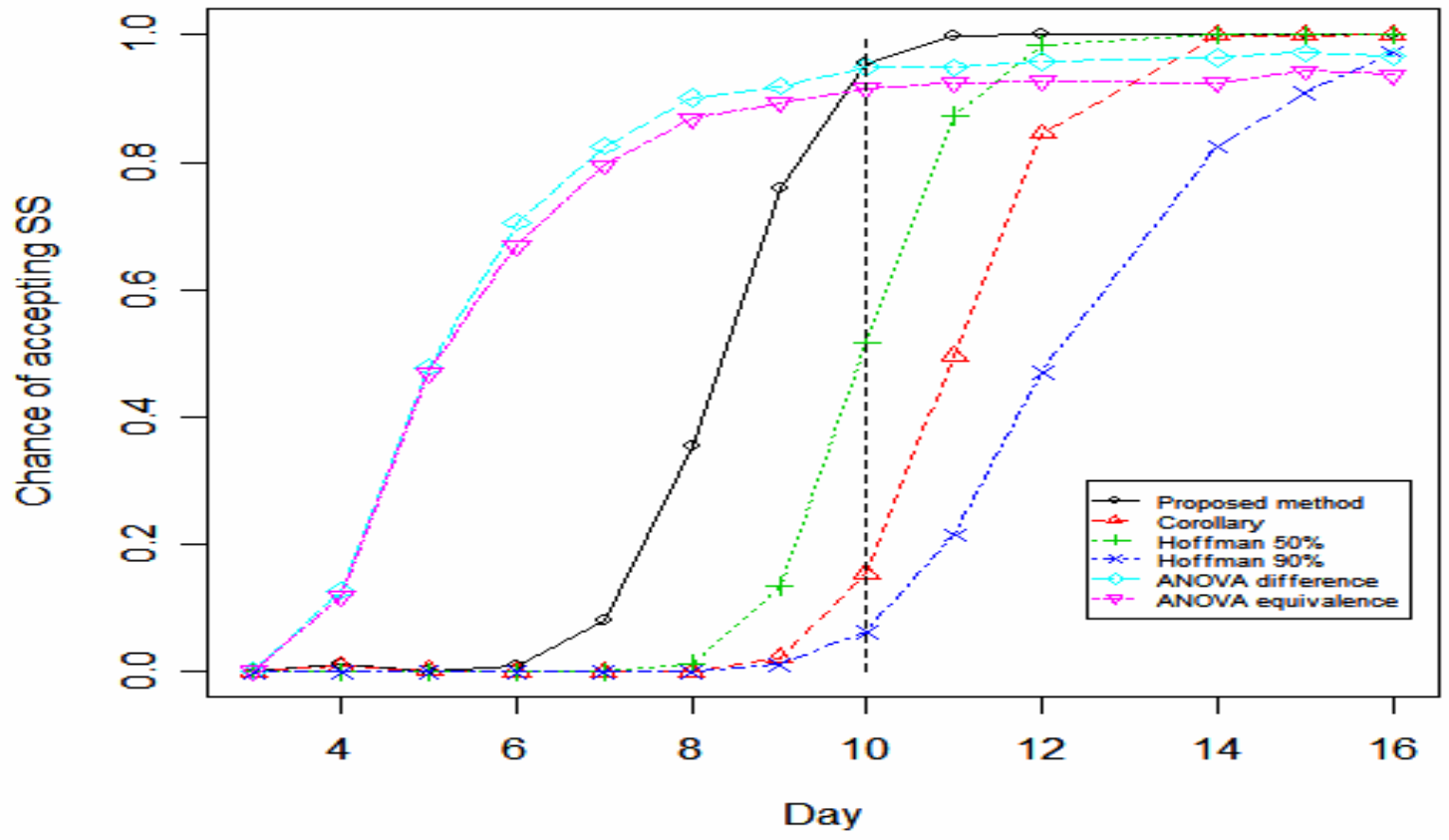
Parameter		Parameter estimators					Decision rules			Hoffman's	
N	CV*	$\hat{k}_e$	$\hat{C}_{SS}$	$\hat{\sigma}_\alpha$	$\hat{\sigma}_\beta$	$\hat{\sigma}_e$	$\hat{t}_{SS}$	$\hat{se}(\hat{t}_{SS})$	PSS_7	P_{H50}	P_{H90}
8	10%	0.460	100.0	0.101	0.114	0.083	5.04	0.36	1.00	1.00	0.90
16		0.461	100.5	0.099	0.121	0.088	5.02	0.28	1.00	1.00	0.98
32		0.459	100.2	0.096	0.099	0.096	5.03	0.20	1.00	1.00	0.99
8	25%	0.466	101.5	0.249	0.300	0.203	5.14	0.94	0.99	0.95	0.51
16		0.459	102.2	0.249	0.315	0.218	5.14	0.74	1.00	0.99	0.52
32		0.464	100.5	0.250	0.250	0.238	5.01	0.50	1.00	1.00	0.82
8	50%	0.521	114.2	0.475	0.564	0.412	5.97	5.29	0.98	0.85	0.40
16		0.500	104.3	0.487	0.598	0.418	5.10	1.75	1.00	0.84	0.39
32		0.471	102.8	0.482	0.528	0.454	5.10	1.14	1.00	0.97	0.47

PSS_7 is the percentage of concluding steady state among simulation replications.

P_{H50} is percentage of steady state conclusion under Hoffman's rule, using 50% percentile criteria, P_{H90} using 90% percentile criteria

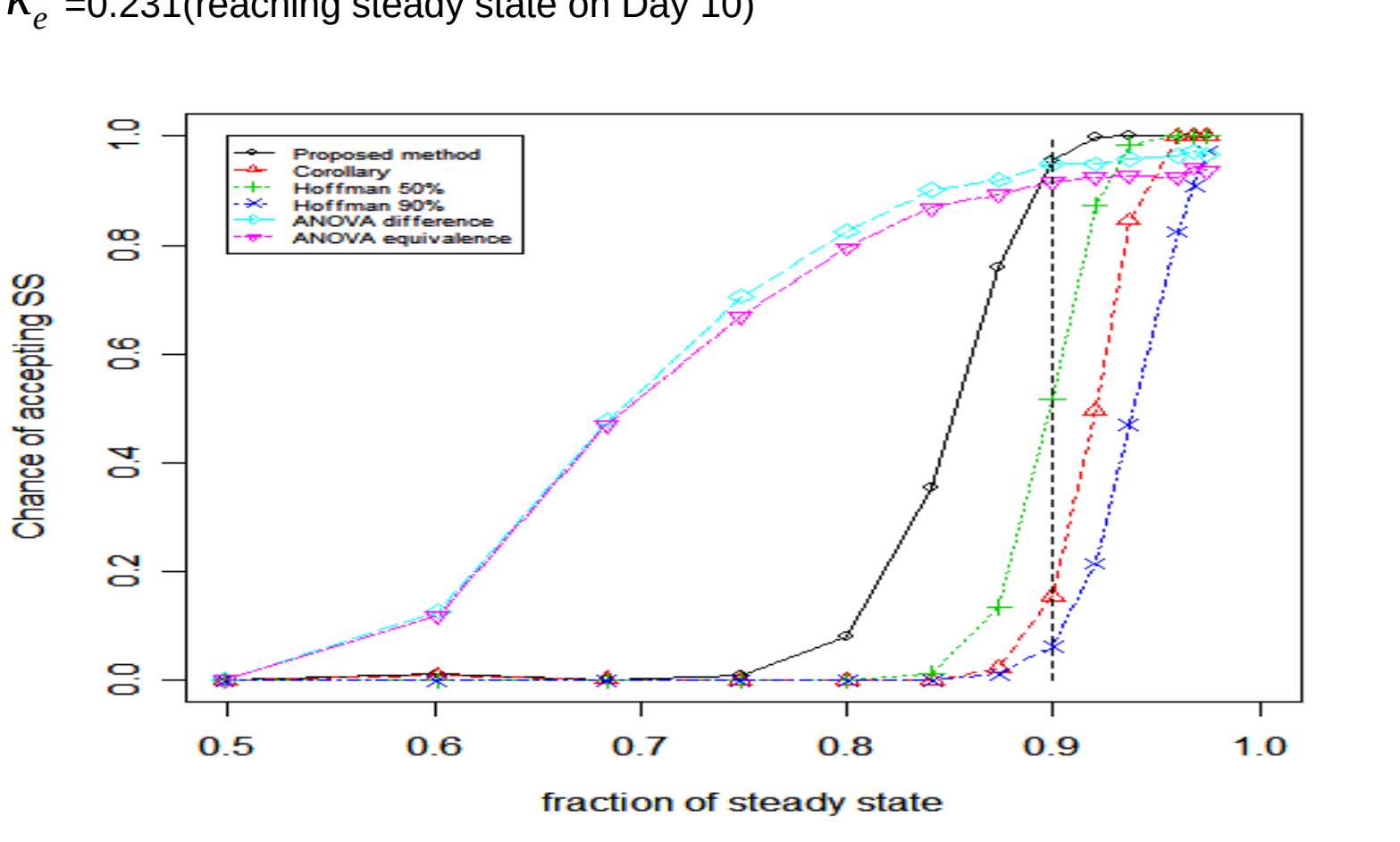
Comparison to existing methods

k_e =0.231(reaching steady state on Day 10)

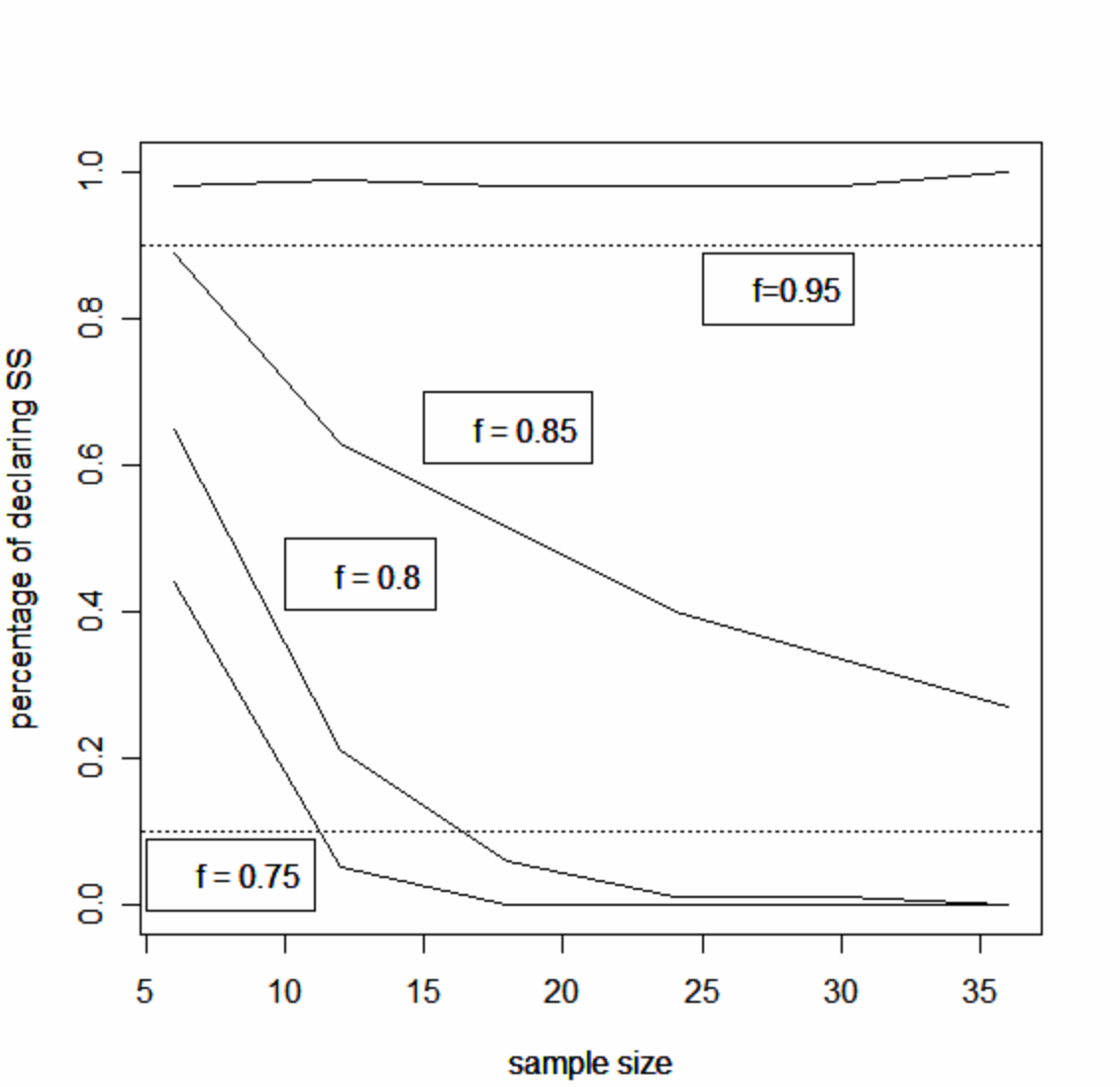


Comparison to existing methods

k_e =0.231(reaching steady state on Day 10)



Sample Size Selection



Concluding Remarks

- Proposed method yields unbiased estimators of nonlinear model parameters, and both decision rules perform satisfactorily in determining SS and estimating tss, given sufficient data.
- ANOVA-based method declares steady-state prematurely (when the fraction f is far below 0.9), while Hoffman's method is on the conservative side.
- Proposed method is less sensitive to the influence of sample size and variability than other existing methods.
- When datasets include only days toward steady-state(the plateau part of the curve), estimation of k and tss can become less precise. (Caveat : when designing the study, plan on obtaining trough plasma concentration on both early and late days relative to steady state)
- A monogram can be constructed to guide the sample size selection to ensure power and type I error.

Thank you!

Questions?