Evaluation of a Random Sparse Sampling Design

An Assessment of Power and Bias Using Simulation

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Introduction

- Obtain PK information in a phase III out-patient trial in the targeted patient population
- Integrate PK sub-study into overall trial using a convenient, sparse sampling design
  - Minimize burden on patient and clinic
  - Ensure adequate power to assess patient factors
  - Ensure design adequacy by minimizing design- and model-induced bias
- Simulation is a valuable tool to address these concerns
- Based on previously presented/published work
  - DIA Annual Meeting, 1999
  - ASCPT Annual Meeting, 2000
  - Kowalski & Hutmacher, *Stats. in Med*. 2001;20:75-91

Objectives

- Power to assess covariate effects
  - Detect a 40 percent reduction in CL/F (ΔCL= -40%) in an arbitrary sub-population of clinically meaningful size (e.g., 5 or 10%)
- Evaluate bias in key parameters (e.g., CL/F)
  - Sparse designs can fail to support the model complexity of phase I (dense sampling)
  - Bias in the estimates can be induced by choice of design/model
    - Are estimates still interpretable with phase I?

Simulation Components: Data Sets

- Index data set
  - Single dose healthy volunteer study
    - 3 dose levels
    - 50 subjects per dose
    - Dense sampling
- Validation data set
  - Multiple dose healthy volunteer study
    - 3 BID + 1 QD dose regimens
    - 8 subjects per dose regimen
    - 24 hour single dose lead-in
    - Dense sampling during single dose lead-in and at steady-state

Simulation Components: PPK Model

- Two-compartment model with lagged first-order absorption
- Interindividual variability model
  - $\theta_i = \theta_o \exp(\eta_i)$
    - θ_i := individual's parameter vector (CL/F, V/F, …)
    - θ_o := population's typical value vector
    - η_i := random effect vector ~(0, Ω)
- Intraindividual variability model
  - $y = f(y \mid \eta) + f(y \mid \eta)\,\varepsilon_1 + \varepsilon_2$
    - y := observed concentration data
    - $f(y|\eta)$:= individual model prediction
    - ε_k := proportional + additive residual errors ~(0, σ_k^2)

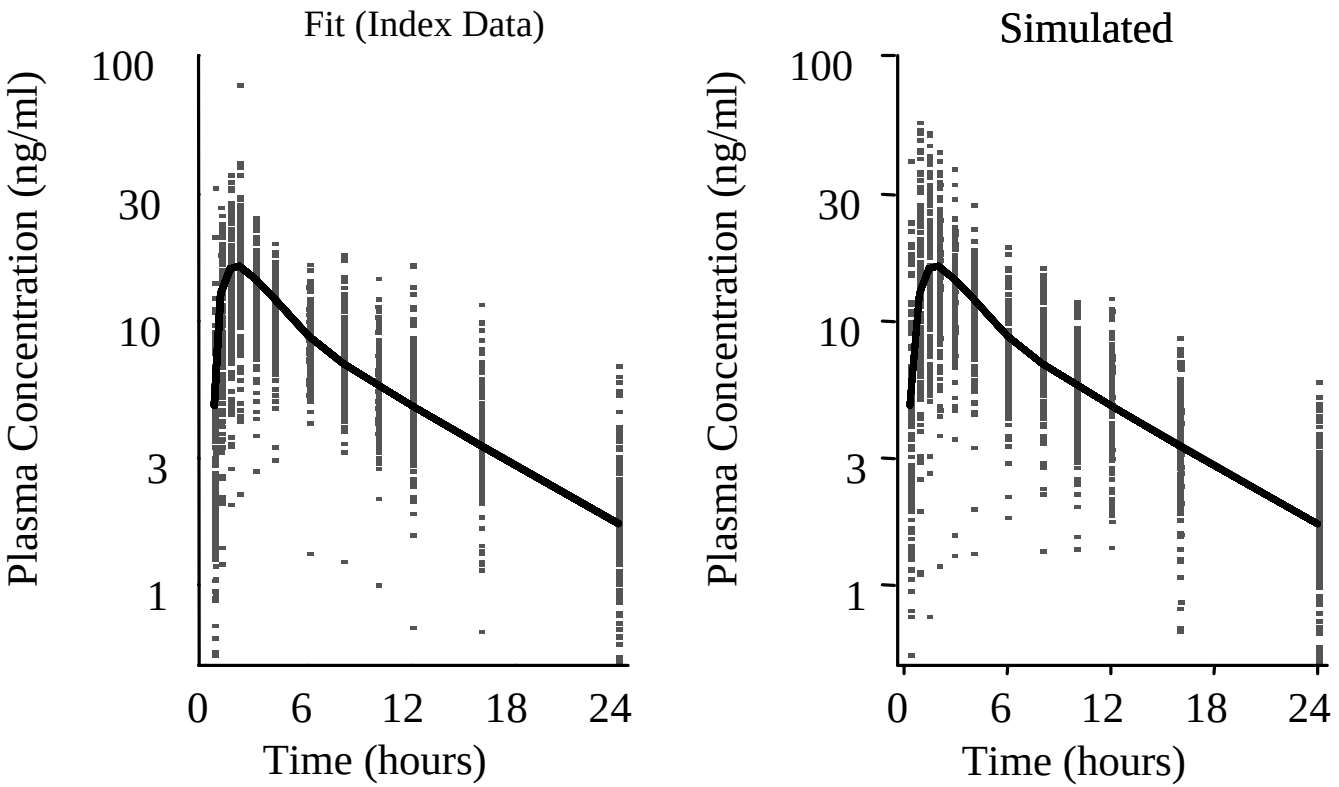
PPK Model Parameter Estimates

Parameter	Estimate	%CV	Interindividual Correlations					
			T_{lag}	k_a	CL	V_1	Q	V_2
T_{lag} (hr)	0.318	34.8	1					
k_a (1/hr)	0.799	69.3	0.397	1				
CL (L/hr)	6.10	35.4	0	0	1			
V_1 (L)	26.6	61.7	0	0	0.669	1		
Q (L/hr)	11.4	37.0	0	0	0	0	1	
V_2 (L)	33.6	22.4	0	0	0	0	1[a]	1

σ_1 = 19.5 (%CV), σ_2 = 3.54 ng/ml

a. $\eta^{V2} = \phi\eta^{Q}$

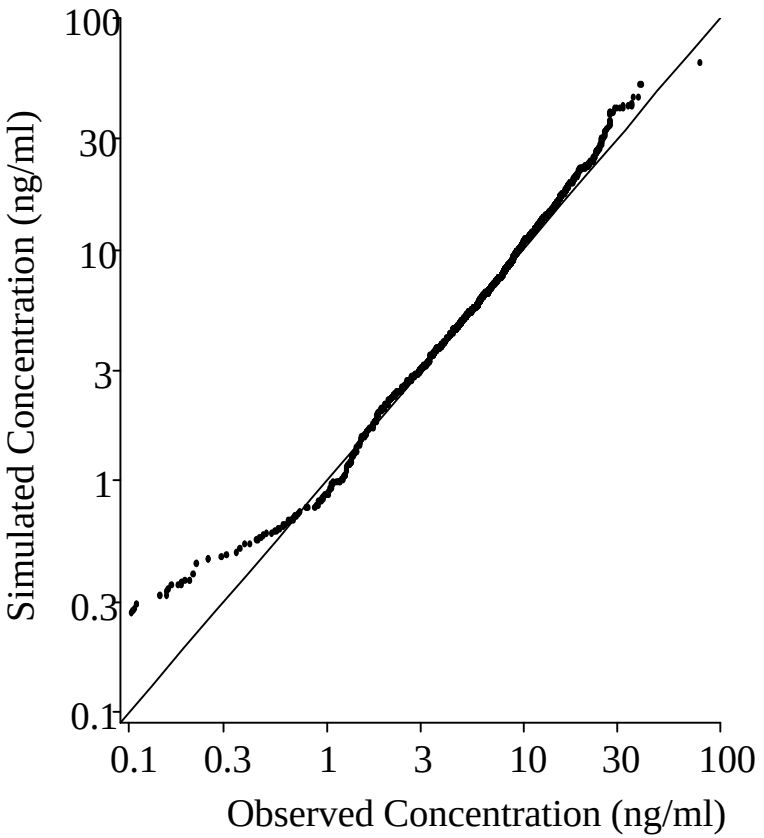
Fit (Index Data) & Simulated Data



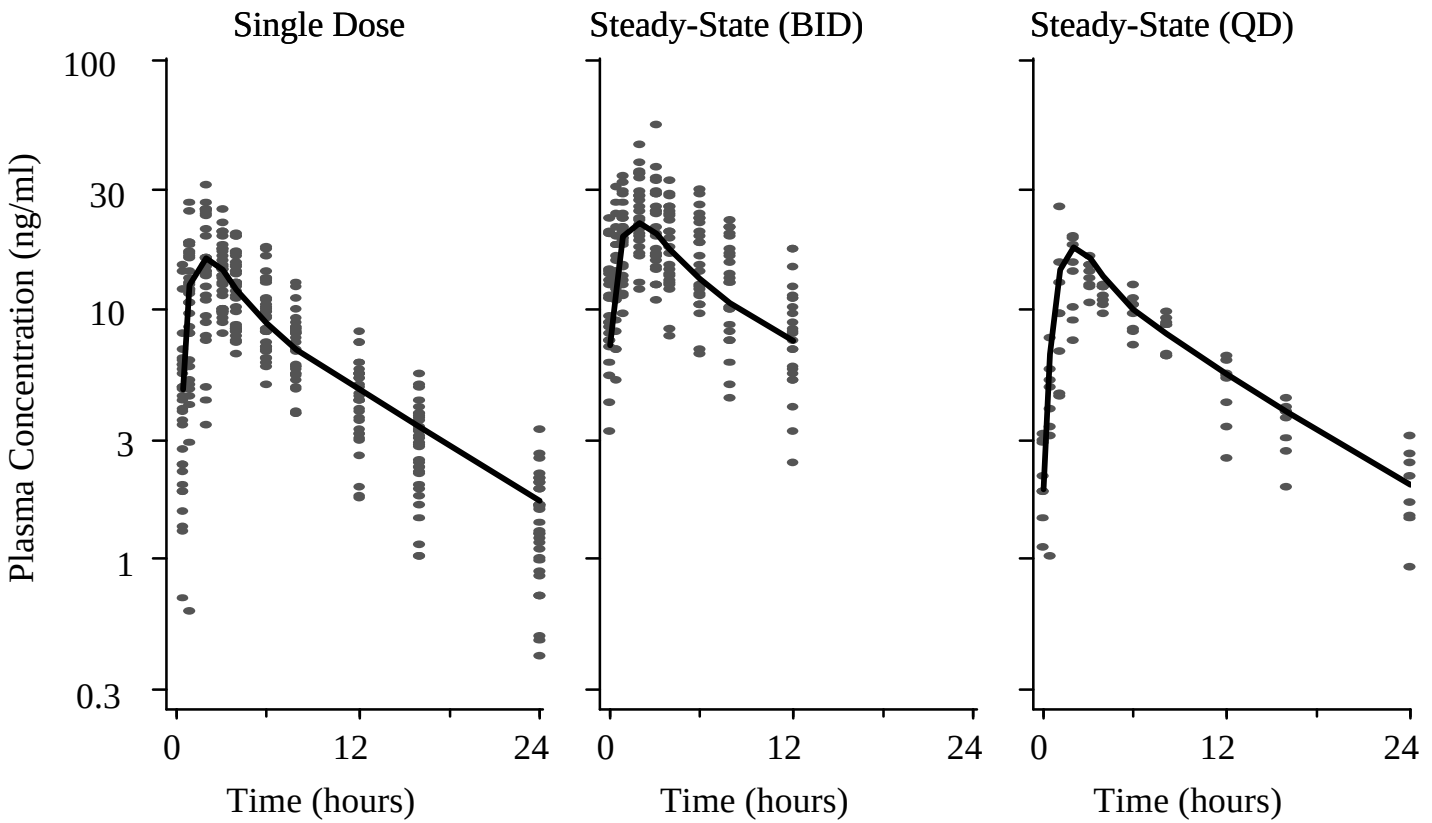
Note: Concentrations scaled by dose.

Q-Q Plot of Obs. Vs. Sim. (SD PPK)

- Simulate PK data
  - Parameters estimated from index data set
    - $\eta \sim N(0, \Omega)$
    - $\varepsilon_k \sim N(0, \sigma_k^2)$, k=1,2
  - Condition on index data set design (regimens and times)
- Assess distribution similarities
  - Merge observed (index) and simulated data sets by order statistics (rankings)
  - Construct quantile-quantile plot



MD Prediction (Validation Data)



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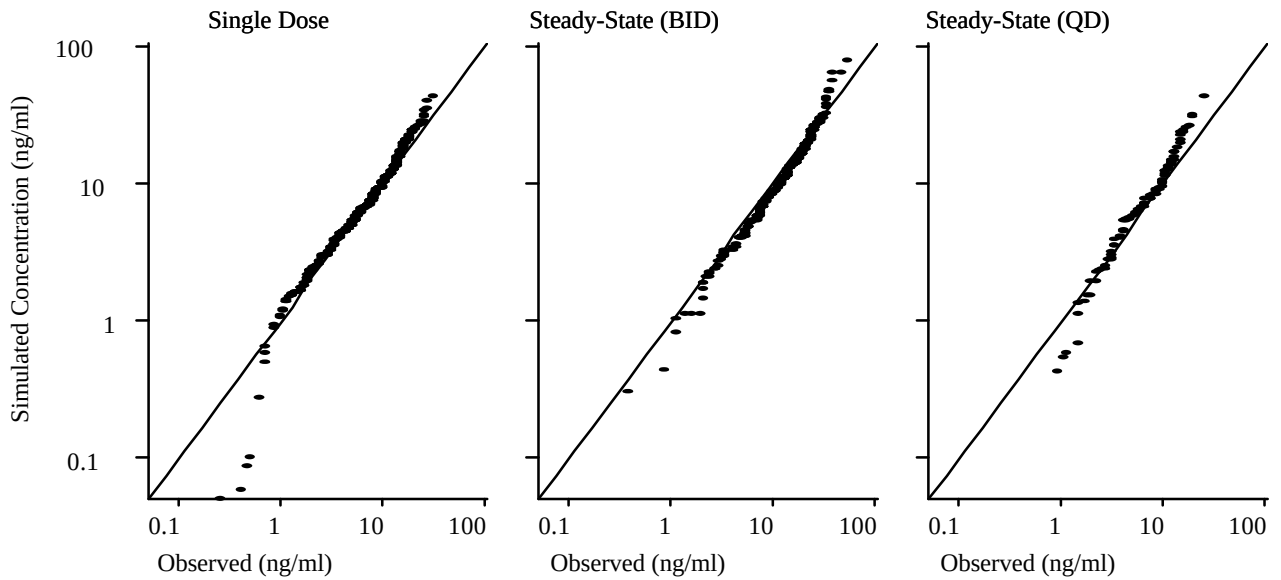
Q-Q Plot of Obs. Vs. Sim. (MD PPK)

- Simulate PK Data
  - Parameters estimated from index data set
  - Condition on validation data set design (regimens and times)
- Construct Q-Q plot

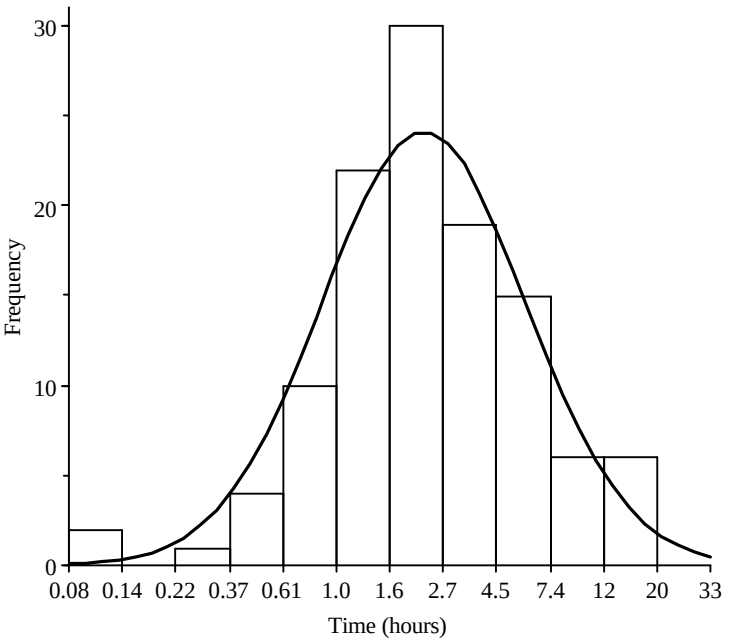


Simulation Components: Phase III PPK Sub-study Design

- Double-blind, placebo-controlled, five-arm study
  - Placebo
  - Investigational drug (3 dose groups)
  - Active comparator
- PK sub-study sampling
  - 2 samples per visit
  - 2 visits (steady-state)
- Morning dose prior to visit
  - Time of first sample (t) is random
  - Second sample taken 1 hour later (t+1)

Sampling Time Distribution

- Model sampling times from another drug
  - Same patient population
  - Similar design
- Time of first sample (t) is approx. log-normal
  - log(t) ~ N(0.82, 0.95)
  - Geom. Mean = 2.27 hr

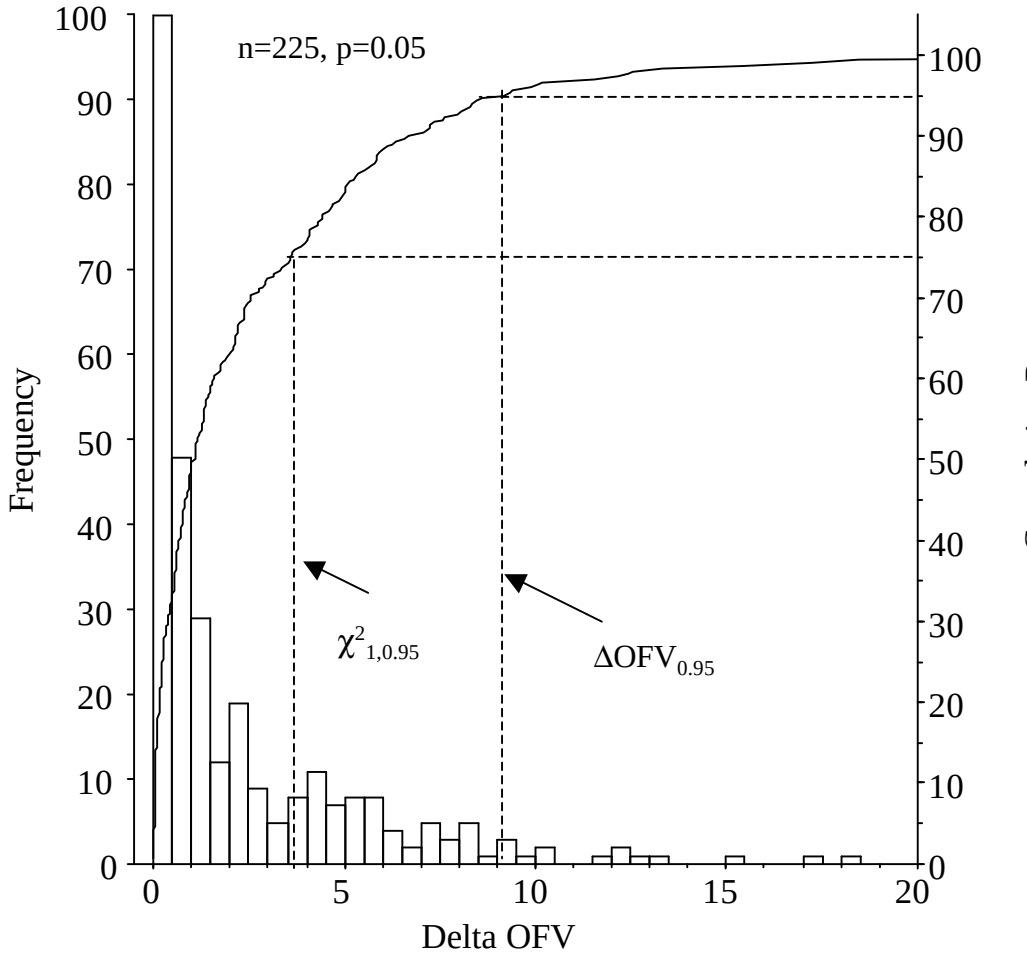


Simulation Plan

- Design components
  - Sample times: t, t+1 hr at each of 2 visits
    - log(t) ~ N(0.82, 0.95)
  - Sample size: n=150, 225 (50, 75 pts./dose)
  - Subpopulation size: p=5, 10%
    - Pop(p) ~ Bernoulli(p)
- Design can only support a one-comp. model
- Simulation study to evaluate:
  - Type I error rate (ie., maintain α=0.05)
  - Power to detect a 40% decrease in CL/F in Pop(p)
  - Bias in parameter estimates

Simulation Evaluation: Type I Error Calibration

- N=300 data sets simulated under null
  - ΔCL = 0% for Pop(p)
- Fit base (reduc.) model (ΔCL=0%)
- Fit full model (ΔCL est.)
- Calculate test statistic
  - $\Delta OFV = OFV_r - OFV_f$
- Estimation: FOCE



Type I Error Calibration

Sample Size (n)	Subpopulation Size (p)	Type I Error[a] (α, %)	5th Upper Percentile[b] ($\Delta OFV_{0.95}$)
150 (50/dose)	0.05	17.3	8.45
	0.10	20.0	10.5
225 (75/dose)	0.05	24.0	9.25
	0.10	23.3	12.2

a. Based on $\chi^2_{1,0.95} = 3.84$

b. From empirical distribution of simulated test statistics (ΔOFV) under the null.

Simulation Evaluation: Power

- N=300 data sets simulated under the alternative
  - ΔCL = -40% for Pop(p)
- Fit base model (ΔCL = 0%) for each data set
- Fit full model (ΔCL est.) for each data set
- Calculate power:
  - Uncalibrated: %power = 100$\times$(# ΔOFV > 3.84)/N
  - Calibrated: %power = 100 $\times$(# ΔOFV > $\Delta OFV_{0.95}$)/N
- Estimation: FOCE (NONMEM V)

Simulation Results: %Power

Sample Size (n)	Subpopulation Size (p)	Power (%)	
		Uncalibrated[a]	Calibrated[b]
150	0.05	86.3	73.0
(50/dose)	0.10	98.3	91.0
225	0.05	94.0	84.3
(75/dose)	0.10	99.3	96.7

a. Based on $\chi^2_{1,0.95} = 3.84$

b. Based on $\Delta OFV_{0.95}$

Recommended Design: n=225, p=0.05

Simulation Results: %Bias

- %Bias = $100\times(\theta_i - \theta)/\theta$
  - θ_i := 1-cmt estimate for i^{th} simulated data set
  - θ := 2-cmt true parameter
- Fixed effects accurately estimated except k_a
- Interindividual variability downward biased
- Residual variability upward biased

Recommended Design: n=225, p=0.05

Parameter	%Bias (mean ± SE)
Fixed Effects	
k_a (1/hr)	132 ± 3
CL (L/hr)	1.92 ± 0.32
ΔCL	6.48 ± 0.98
V_{ss} (L)	0.197 ± 0.809
IIV Parameters	
ω-k_a	-3.73 ± 0.88
ω-CL	-33.0 + 0.5
ω-V_{ss}	-19.6 ± 0.6
Residual Var.	
σ_1 (%CV)	37.7 ± 0.5

Conclusions

- A simpler misspecified model supported by sparse data can result in accurate fixed effects estimates of key parameters
  - Mean %BIAS for CL, ΔCL, and Vss <10%
- Type I error rates for LRTs of covariate effects (e.g., ΔCL) can be inflated even though the effects may be accurately estimated
  - Estimated α's ranged from 17.3 – 24.0%
  - ΔOFV critical values to maintain α=5% ranged from 8.45 – 12.2 (ie., greater than the Chi-square critical value of 3.84)
- Power can be adjusted based on calibration of the ΔOFV statistics simulated under the null to maintain proper α

Final Remarks

- Simulation is a valuable tool for assessing inferential properties of PPK sub-studies
  - Assess power for significance tests on covariate effects
  - Assess effects of model misspecification (bias) on parameter estimation
- Notable simulation features not addressed:
  - Influence of uncertainty in simulation model parameter estimates
  - Sensitivity to model/design assumptions
    - Patients could have different population means and/or increased IIV relative to healthy volunteers
    - Degrees of compliance could be evaluated