

# Experimental Design for Pop – PK Modeling



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# Introduction

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- ❑ Most pharmaceutical companies including Merck have been using the standard empirical design to select blood sampling times for obtaining Pop-PK parameters, which is lack of systematic evaluation and optimization.
- ❑ D-optimal design has been a useful tool for design of experiments applied mostly in manufactory process. We propose a new strategy that links the d-optimal design with the PK modeling so that the quality of PK parameter estimates is a function of a design: the number of concentrations measured per subject, the timing of each blood sample, and the number of subjects.
- ❑ This new strategy can be executed in two stages. First, a preliminary study is done to estimate the Pop-PK model. Based on the results, a D-optimal design is used to optimize blood sampling times for the second stage.
- ❑ Simulations showed that the optimized sampling times enable us to draw fewer blood samples without sacrificing the precision obtained with a standard empirical design.

# Background

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- A phase I study has been done to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of a investigational compound.
- PK sampling schemes are needed in some phase II studies.
- We would like to use the phase I PK data and the Pop-PK constructed to guide the selection of PK sampling times in phase II studies so that the PK parameters can be estimated more efficiently.

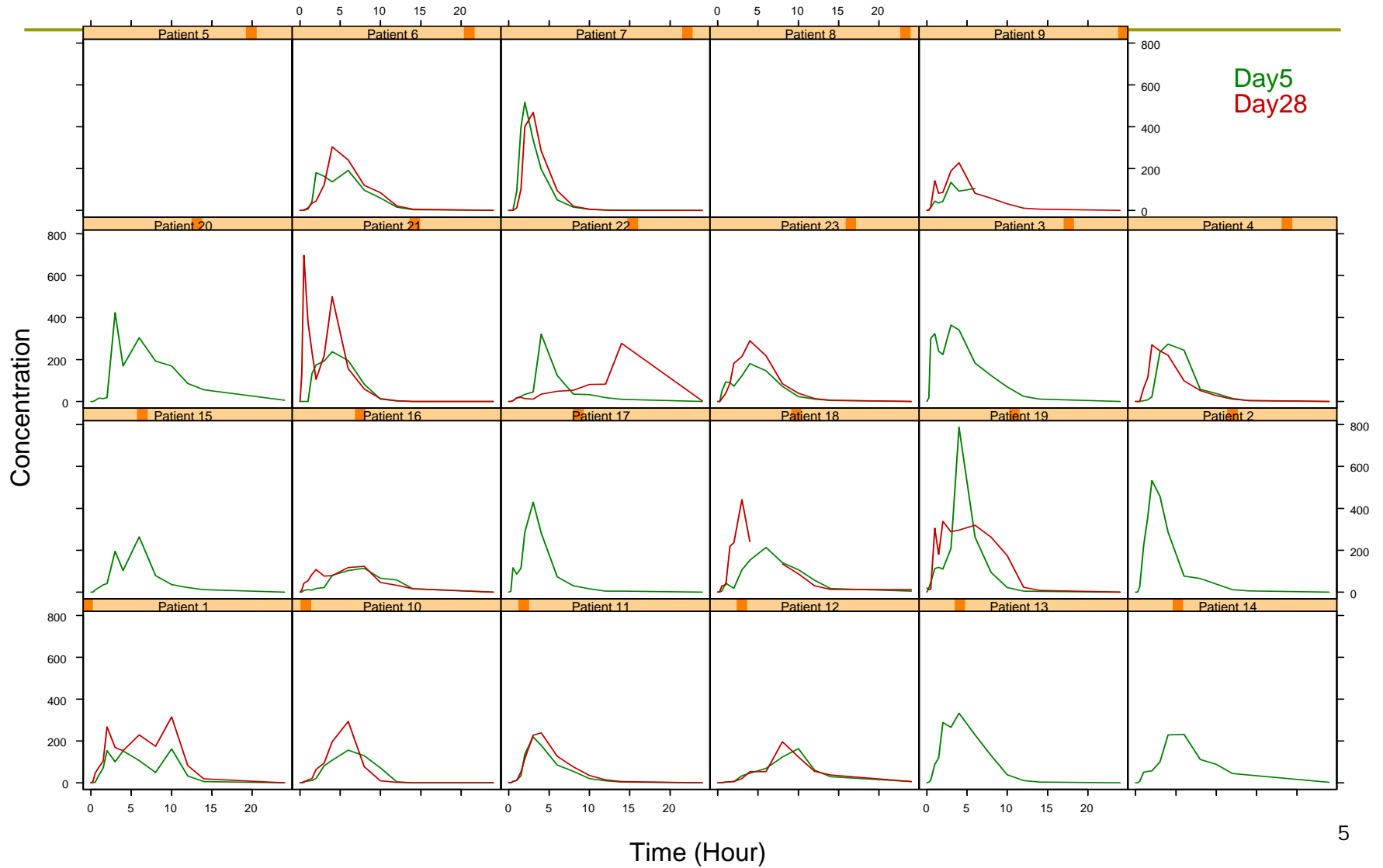
# Design of Phase I study

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Patients received a single oral dose in the fasted state on Day 1 with pharmacokinetic sampling for 48 hours post-dose. Following a washout of at least 4 days, patients received a single oral dose following by a standard high-fat meal on Day 5 with blood samples collected for 48 hours post-dose. Patients received oral doses daily from Days 7 through 27. On day 28, patients received a single dose following by a standard high-fat meal with blood samples collected for 24 hours post-dose.

Time	Day1	Day2	Day3	Day4	Day5	Day6	Day 7-27	Day28
PK-Collection	Y	N	N	N	Y	N	N	Y
Meal	Fasted				Fed			Fed
Dose	400mg q.d.	N	N	N	400mg q.d.	N	400mg q.d.	400mg q.d.

# Data Profile



# First-Order 1-Compartment Base Model (Extravascular Administration)

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$$C_{ij}(t_{ij}) = f(t_{ij}, k_{a_i}, V_i, Cl_i, d_i)(1 + e_{ij}) + \varepsilon_{ij}$$
$$= \left[ \frac{k_{a_i} \cdot d_i}{V_i k_{a_i} - Cl_i} \left( e^{-(Cl_i/V_i)t_{ij}} - e^{-k_{a_i}t_{ij}} \right) \right] (1 + e_{ij}) + \varepsilon_{ij}$$

where

$$\text{Log}(k_{a_i}) \sim N(\text{Log}(k_a), \sigma_{k_a}^2),$$

$$\text{Log}(Cl_i) \sim N(\text{Log}(Cl), \sigma_{cl}^2),$$

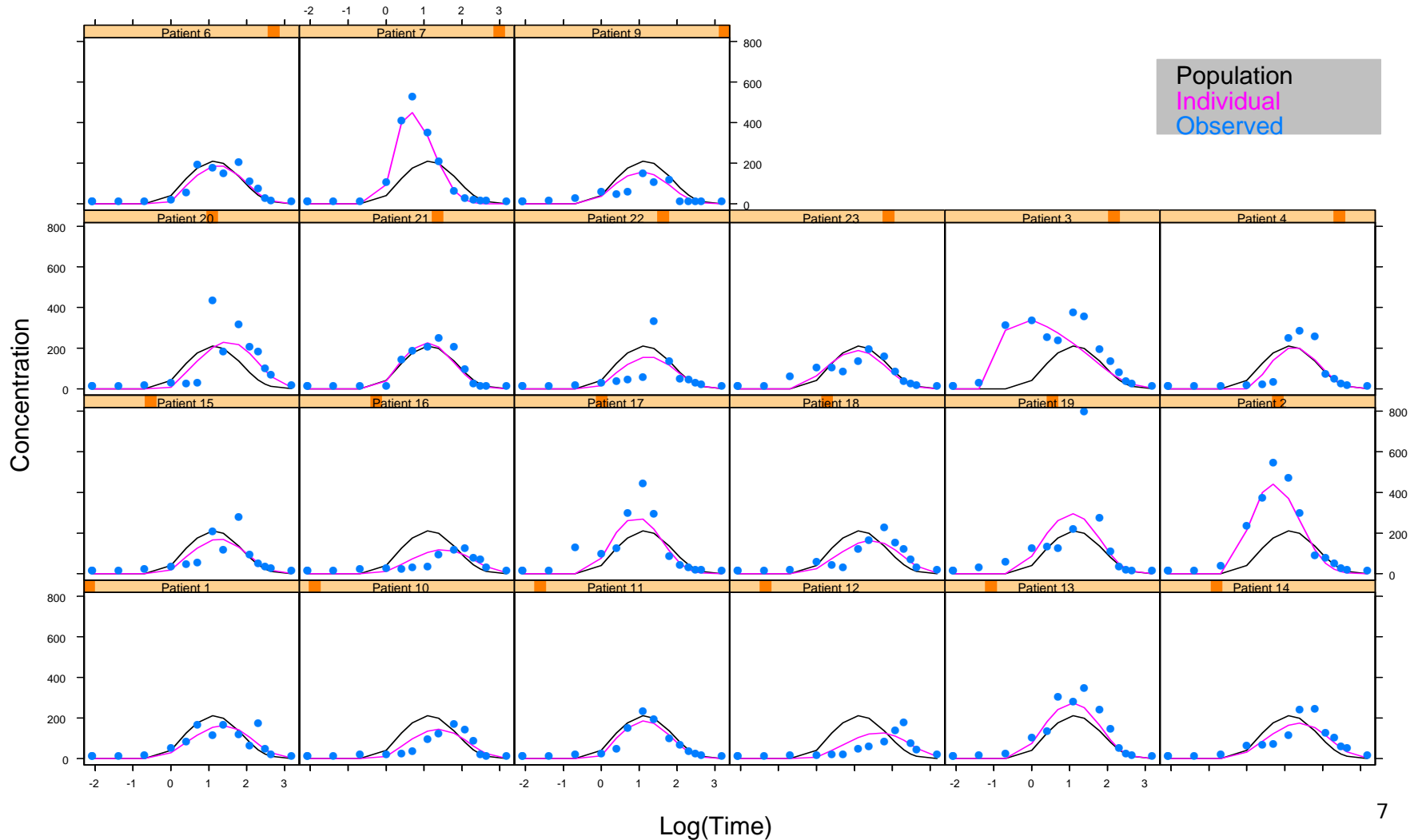
$$\text{Log}(V_i) \sim N(\text{Log}(V), \sigma_v^2),$$

$$e_{ij} \sim N(0, \sigma_e^2),$$

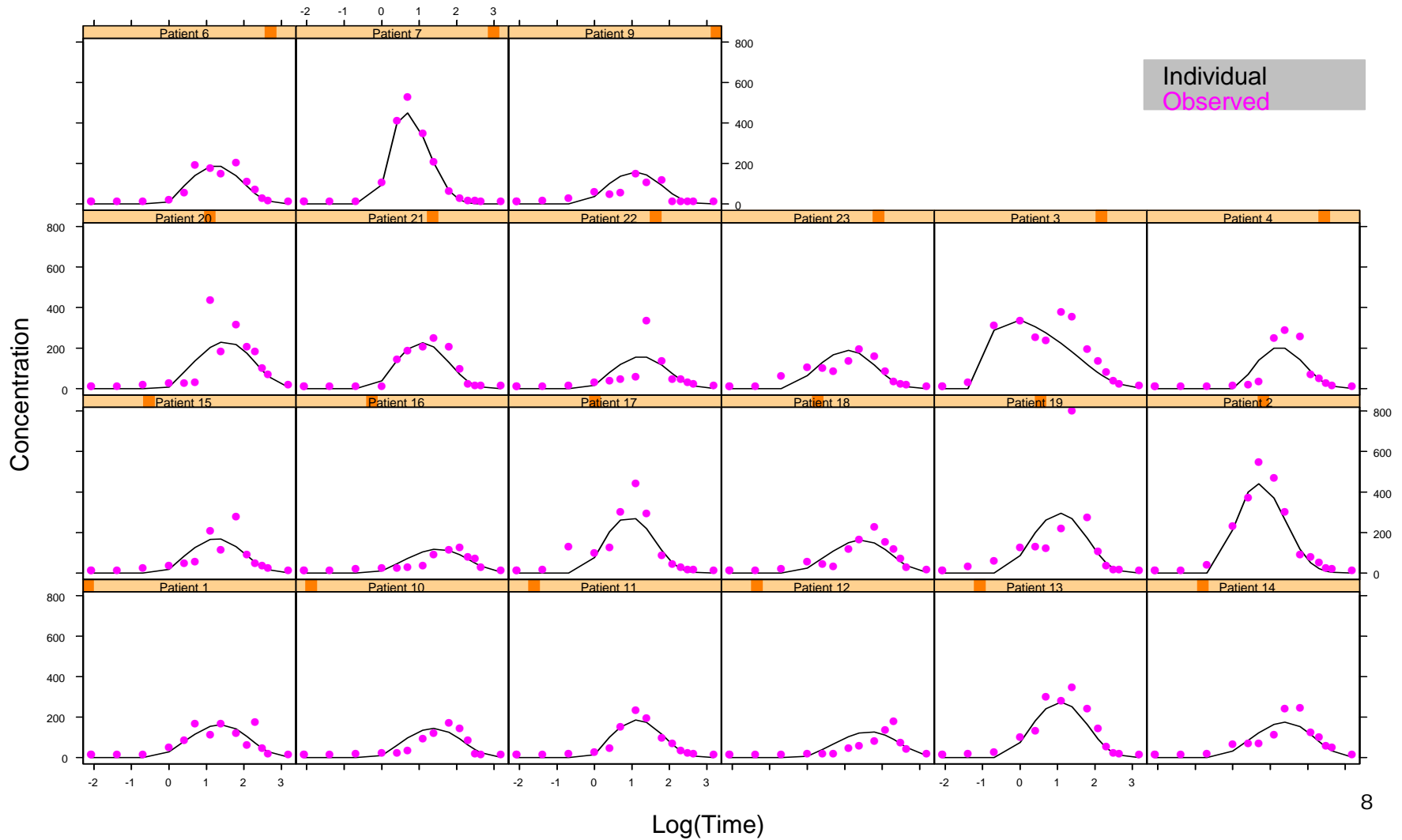
$$\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2).$$

- The patients' demographic information, gender, race, age, weight, and height, were included as covariates in the modeling.
- Nonlinear Mixed Effects Models MLE estimation implemented using NONMEM.

# Estimations for Population & Individuals at Day 5

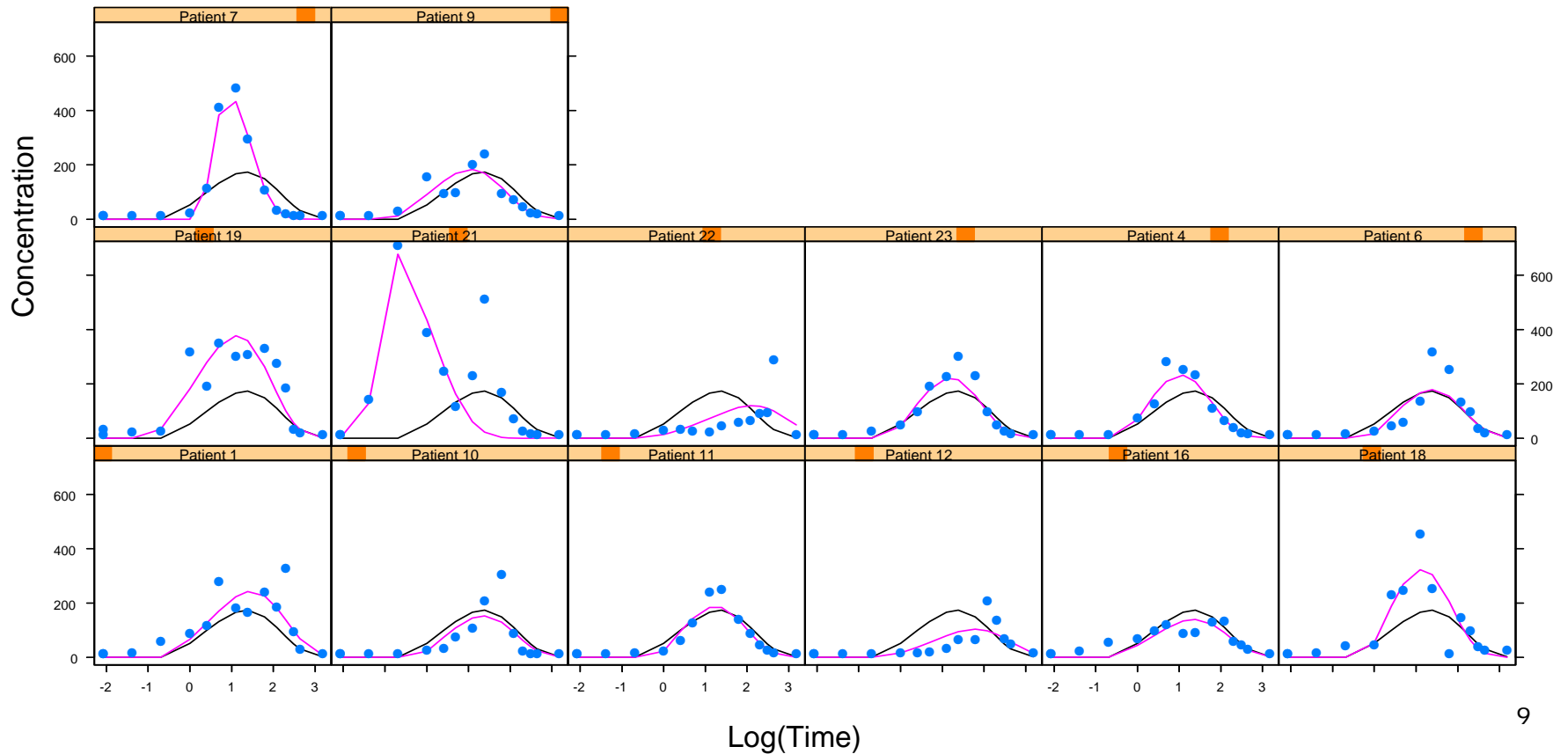


# Estimations for Individuals Only at Day 5



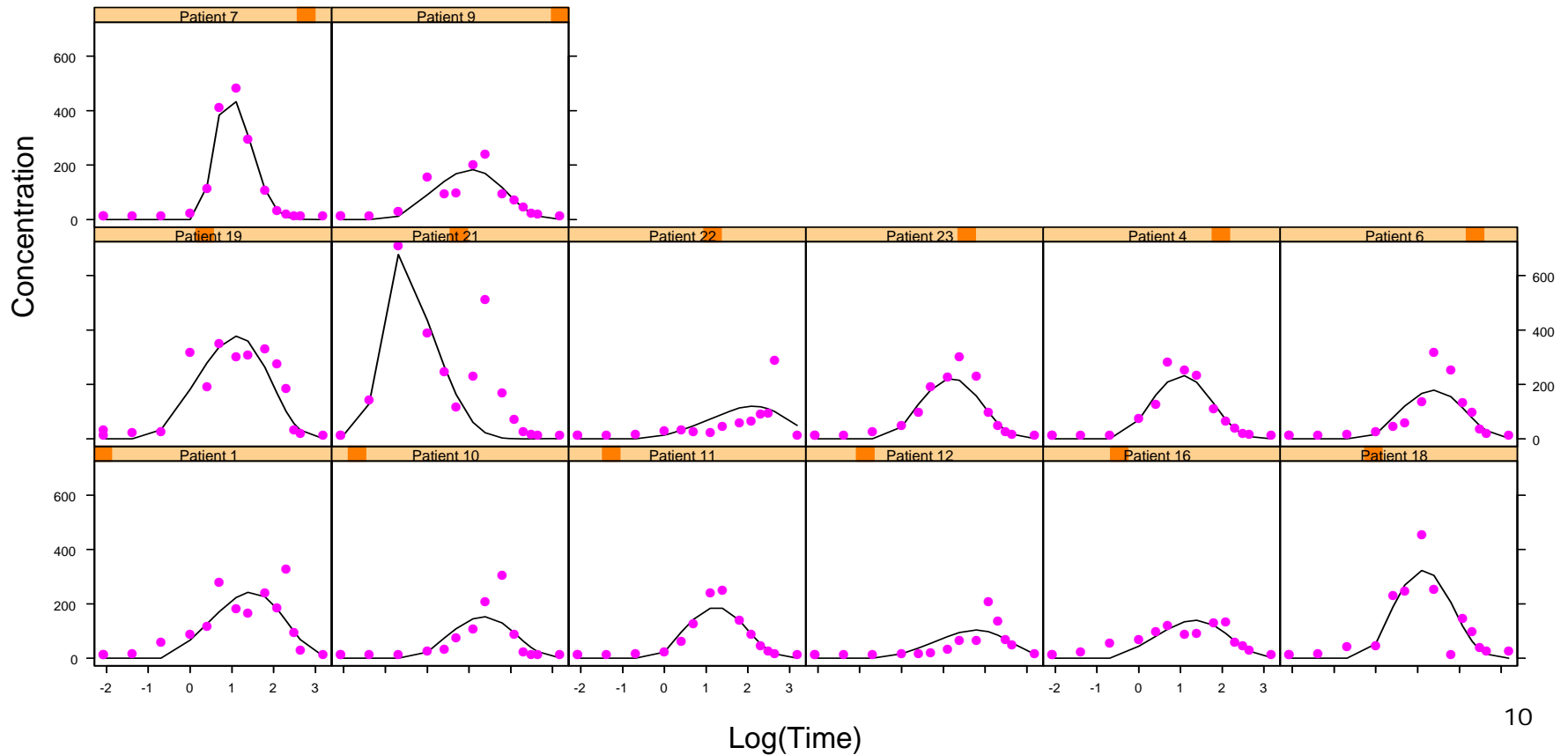
# Estimations for Population & Individuals at Day 28

Population  
Individual  
Observed

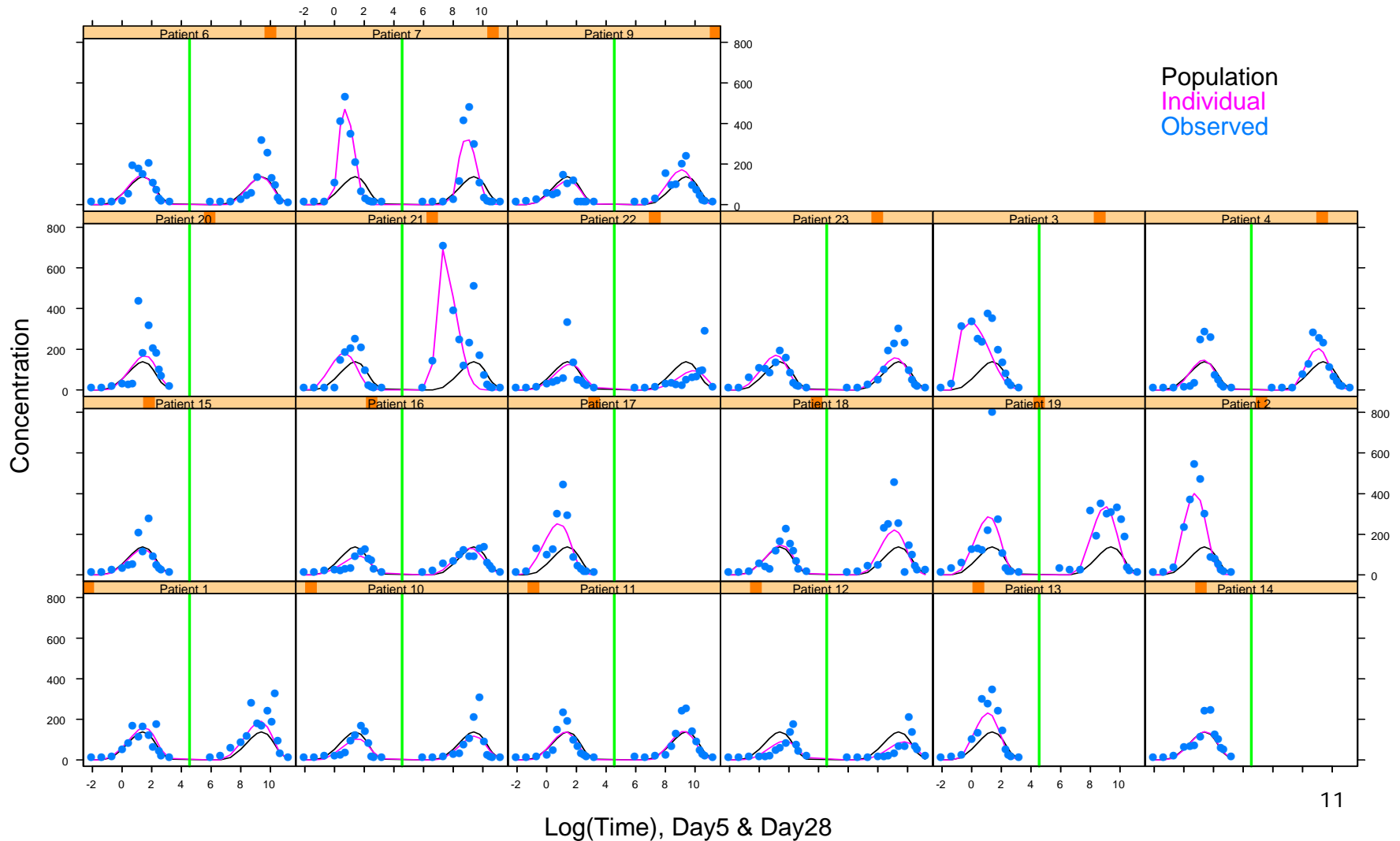


# Estimations for Individuals Only at Day 28

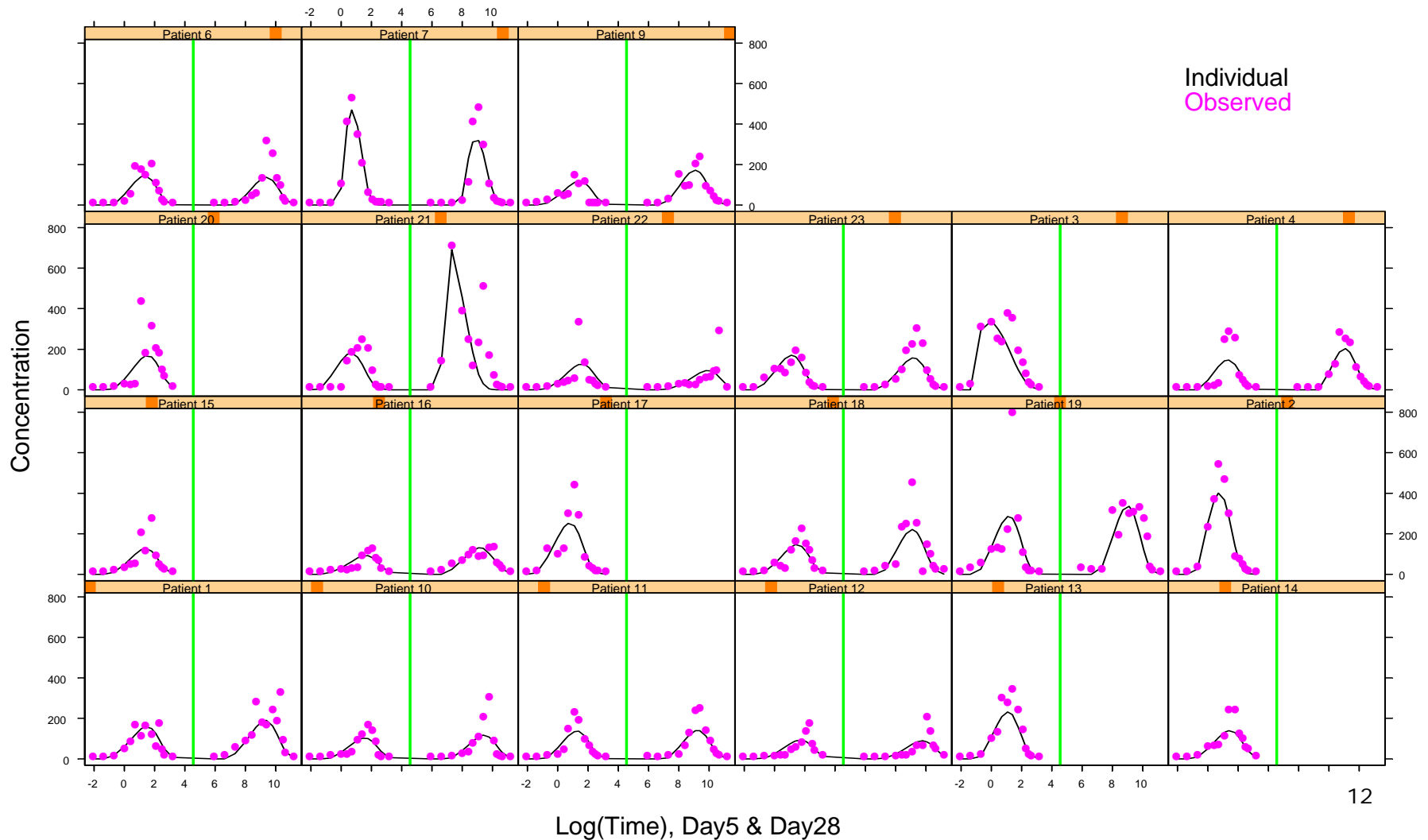
Individual  
Observed



# Estimations of Population & Individuals for Days 5 & 28



# Estimations of Individuals Only for Days 5&28



# Model Fitting Results

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- One compartment parameters estimates:
  - $CL = 0.282$
  - $V = 1.05$
  - $Ka = 0.263$
  - $Lag = 0.377$  (a time lag was found and considered into the model)
  
- Inter-individual variability
  - $\omega_{CL}^2 = 0.0616$
  - $\omega_V^2 = 1.07$
  - $\omega_{Ka}^2 = 0.373$
  - $\omega_{Lag}^2 = 0.126$
  
- Residual variability
  - $\sigma_e^2 = 0.601$
  - $\sigma_\varepsilon^2 = 174$

# D-optimal Design

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- Fisher's Information Matrix

$$M_F(\Psi, t) = E\left(\frac{\partial^2 l(\Psi; y)}{\partial \Psi \partial \Psi^T}\right) = \sum_{i=1}^N E\left(\frac{\partial^2 l(\Psi; y_i)}{\partial \Psi \partial \Psi^T}\right) = \sum_{i=1}^N M_F(\Psi, t_i)$$

- $l(\Psi; y_i)$  is the log-likelihood of the vector of observation  $y_i$  of the subject  $i$  with the population parameters  $\Psi$ .
- D-Optimality:

$$|M_F(\Psi, t^*)| = \max_t |M_F(\Psi, t)|$$

# Why D-optimal Designs?

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- Cramér–Rao bound

Let  $T(y)$  be an unbiased estimator for  $\Psi$

$$\text{Cov}(T(y)) \geq [M_F(\Psi, t)]^{-1}$$

And in general ( $T(y)$  may not be unbiased)

$$\text{Cov}(T(y)) \geq \frac{\partial \Psi}{\partial \Psi_i} [M_F(\Psi, t)]^{-1} \left( \frac{\partial \Psi}{\partial \Psi_i} \right)^T$$

- D-Optimal Designs Controls the Variance of the estimates!
- But...

# Problems of D-optimal Designs

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- D-optimal Designs do not consider the bias of the estimation, which is common in nonlinear mixed effects model fitting.
- D-optimal Designs only control the lower bound of the variance.

# Procedure of Searching D-optimal Designs

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- Get a population pharmacokinetics model, using historical data;
- Set the total number of sampling times, the number per subject and a finite set of admissible times;
- Some algorithms and software can be utilized to find the D-optimal design, e.g., WinPOPT and PFIM.

# Using Simulation to Evaluate D-optimal Designs

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Always Evaluate D-optimal Designs by Simulation!

- ❑ Simulate PK data using D-optimal time points, based on a known population PK model;
- ❑ Evaluate population PK parameters' estimates properties, using the simulated data;
- ❑ Compare the estimates from D-optimal sampling schemes, with other sampling schemes.

# D-optimal Designs

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- *D*-optimal designs are generated by WINPOPT based on a pre-specified model.
  
- Pre-specified model (final covariate multiple-dose model):
  - $CL = 0.282$
  - $V = 1.05$
  - $Ka = 0.263$
  - $Lag = 0.377$
  
- D-Optimal 2 Day collections:
  - Day 1: 2.5, 2.75, 5, 8;
  - Day X ( $X > 1$ ): 0.5, 1.5, 7, 8.

# Evaluation of D-optimal Designs

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Two types of criteria are considered

- Parameter estimate MSE Criteria, e.g.,

$$MSE(\hat{AUC}) = E(\hat{AUC} - AUC)^2$$

MSE can be estimated in Simulation by

$$\hat{MSE}(\hat{AUC}) = \frac{1}{p} \sum_{i=1}^p (\hat{AUC}_i - AUC)^2$$

- Power to conclude PK parameter is bio-equivalent to a target value. In Simulation, this can be approximated by

$$P(0.8 \leq \frac{AUC_i}{AUC} \leq 1.25 | \frac{AUC_i}{AUC} = 1)$$

# Two Designs Compared

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Compare D-optimal Designs with the equal-spaced (log-scale) designs

- D-optimal Designs

Day 1: 2.5, 2.75, 5, 8;

Day X ( $X > 1$ ): 0.5, 1.5, 7, 8.

- Equal-spaced Designs

Day 1: 1, 2, 4, 8;

Day X ( $X > 1$ ): 1, 2, 4, 8.

# Simulation

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- ❑ Simulate PK data with sample size  $N$  using D-optimal time points, based on a known population PK model.
- ❑ Estimate population AUC and its corresponding variance, using the simulated data.
- ❑ Repeated the steps 1) and 2)  $M$  times where  $M$  is large enough. Then calculate MSE and the probability of AUC estimate is bioequivalent to the theoretical AUC
- ❑ Repeat steps 1) to 3) for the equal-spaced (on log scale) sample scheme. Then calculate the corresponding MSE and the probability of AUC estimate is bioequivalent to the theoretical AUC value.
- ❑ Compare the MSEs and probabilities from two sampling schemes.
- ❑ Repeat steps the above steps by using different  $N$

# Results

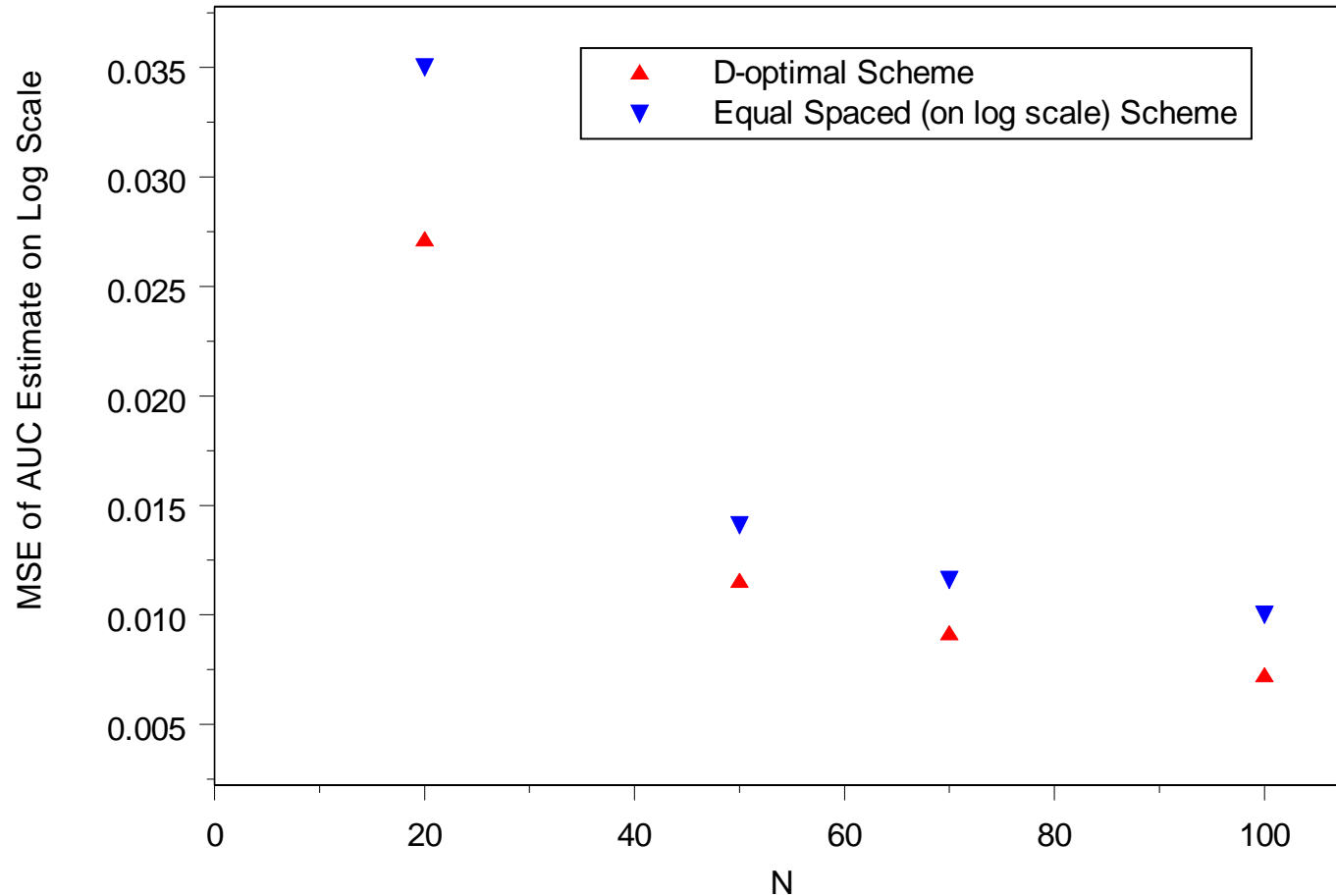
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Table Simulation Results Comparing Two Different PK Sampling Schemes

Sample Size	Design Scheme	AUC estimate MSE (on log-scale)	Power to Conclude Bioequivalence
20	D-optimal	0.0271	0.928
	Equal-Spaced	0.0350	0.915
50	D-optimal	0.0115	0.990
	Equal-Spaced	0.0141	0.970
70	D-optimal	0.0091	0.997
	Equal-Spaced	0.0116	0.993
100	D-optimal	0.0072	1.000
	Equal-Spaced	0.0100	0.997

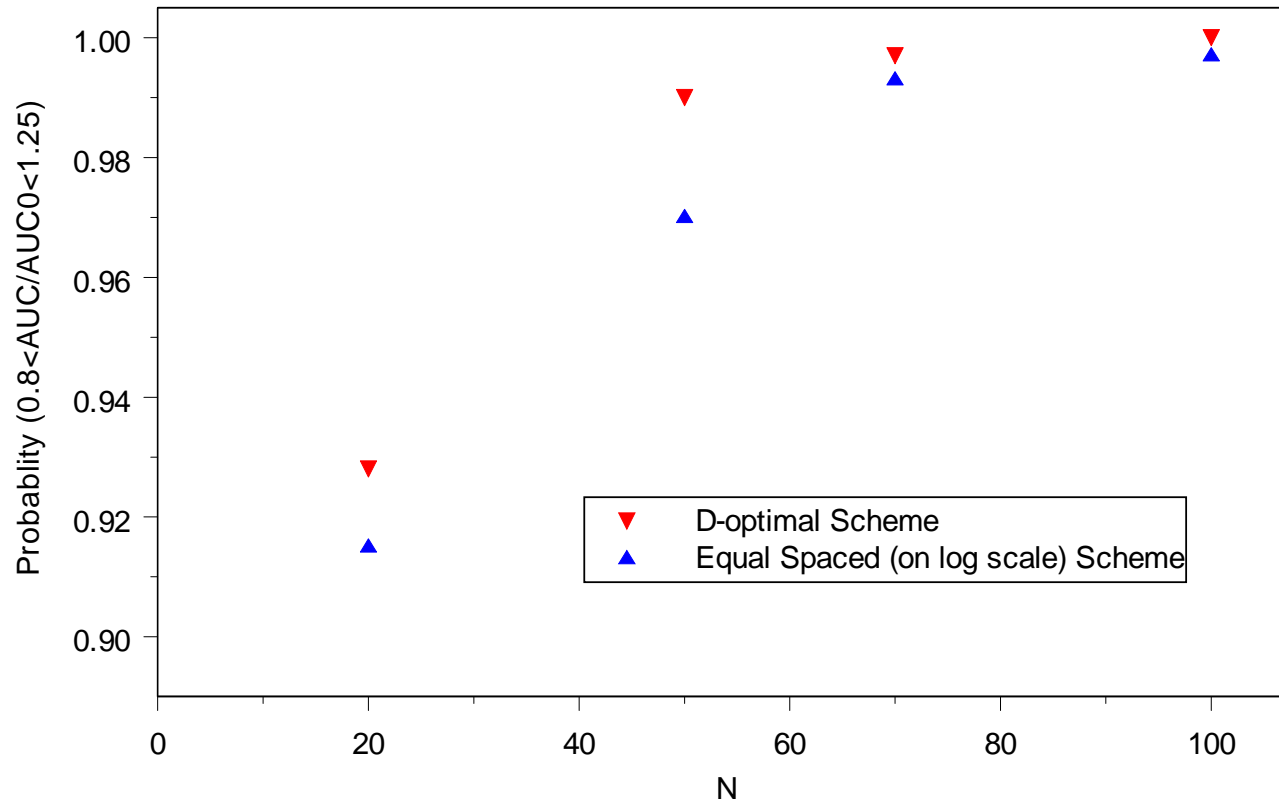
# Results (Continued)

Figure 1 Comparison between Two Sampling Schemes - MSE



# Results (Continued)

Figure 2 Comparison between Two Sampling Schemes  
- Bioequivalence to the Target



# Summary

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- A strategic practice is explained in detail how to incorporate Pop-PK and optimal sparse sampling into late stage clinical trial development.
- Historical Data -> Pop-PK modeling -> Optimal Designs -> Evaluation  
in an adaptive procedure in the life cycle of development.
- Only Sparse PK sampling
- Better Estimation of PK parameters – Better Statistical Properties.

# Future Research

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- ❑ Other optimal criteria in the nonlinear mixed modeling setting.
- ❑ Theoretical proof for the good statistical properties of optimal designs.
- ❑ Large enough number of Simulations
- ❑ Consider the uncertainty of Pop-PK models – Incorporate Hierarchical Structure of parameters.