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Standardized Visual Predictive Check in Model Evaluation

- Methodology and Applications

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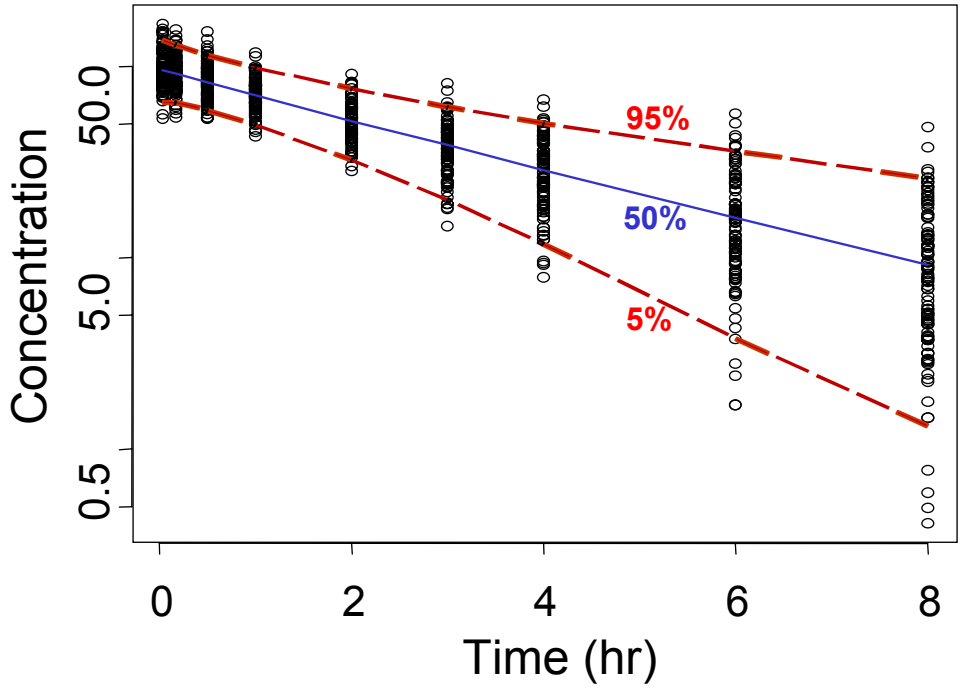
Visual Predictive Check
- What are the limitations?

Visual Predictive Check (VPC)

- Visual inspection of whether the model can resemble the data from which it was derived



Θ – fixed effect

Ω,σ – random effects

90% interval of simulated observations vs time plot with actual observation overlaid

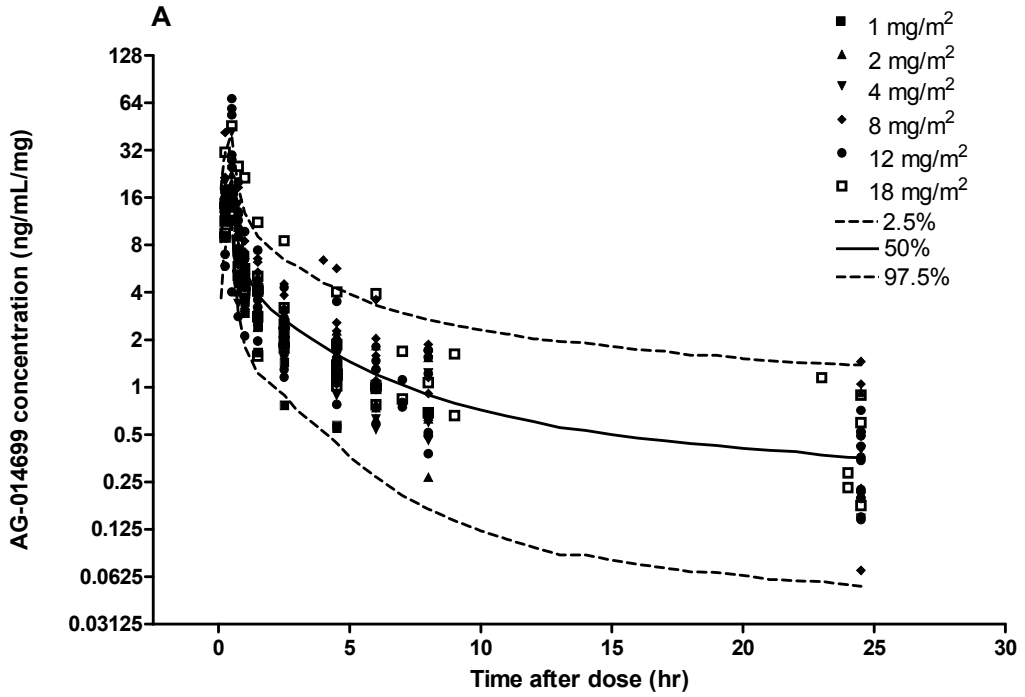
What is the Problem?

The case

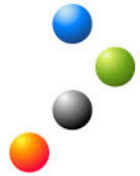
- **FIP dose escalation study for AG-014699**
- **Six Cohorts**
  - 1 mg/m^2 (n=3)
  - 2 mg/m^2 (n=3)
  - 4 mg/m^2 (n=3)
  - 8 mg/m^2 (n=3)
  - 12 mg/m^2 (n=12)
  - 18 mg/m^2 (n=6)
- **PK and PK/PD modeling were conducted**
  - PK is described by a 3 compartment linear model
  - PD is described by Emax model (non-linear)
  - Body Surface Area (BSA) is not a covariate on PK or PD parameters

VPC for PK Model

- **Dose-normalized VPC for PK**
  - PK is linear
  - VPC based on dose-normalized concentration



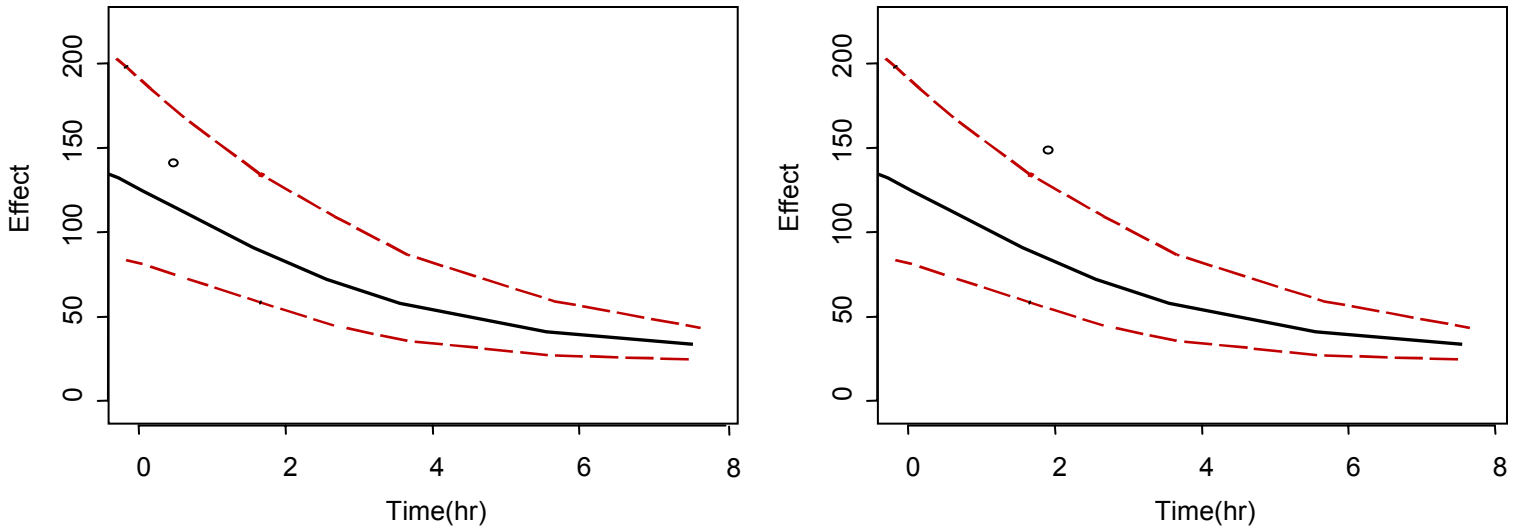
What Can We Do for the PD Model?



- **Dose-normalized VPC?**
  - PD is Non-linear (not applicable)
- **VPC for each dose group (stratified VPC)?**
  - Very limited number of subjects (N=3 for most groups)
  - Body surface area (BSA)-based dosing, total doses are still not the same even within the same dose group (BSA is not a covariate for any PK/PD parameters)

What Can We Do Then ?

- Determine the percentile of each observation in the marginal distribution of model-simulated observations using the same design template (dosing method in this case)



- Evaluate the distribution of observation percentiles

Standardized Visual Predictive Check (SVPC)

- 1000 data sets are simulated using the final model based on the original data set
- The percentile (P_{ij}) of *j*-th observation for the *i*-th patient is calculated by:

$$P_{ij} = \frac{1}{1001}(1 + \sum_{k=1}^{1000} \delta_{ij,k})$$

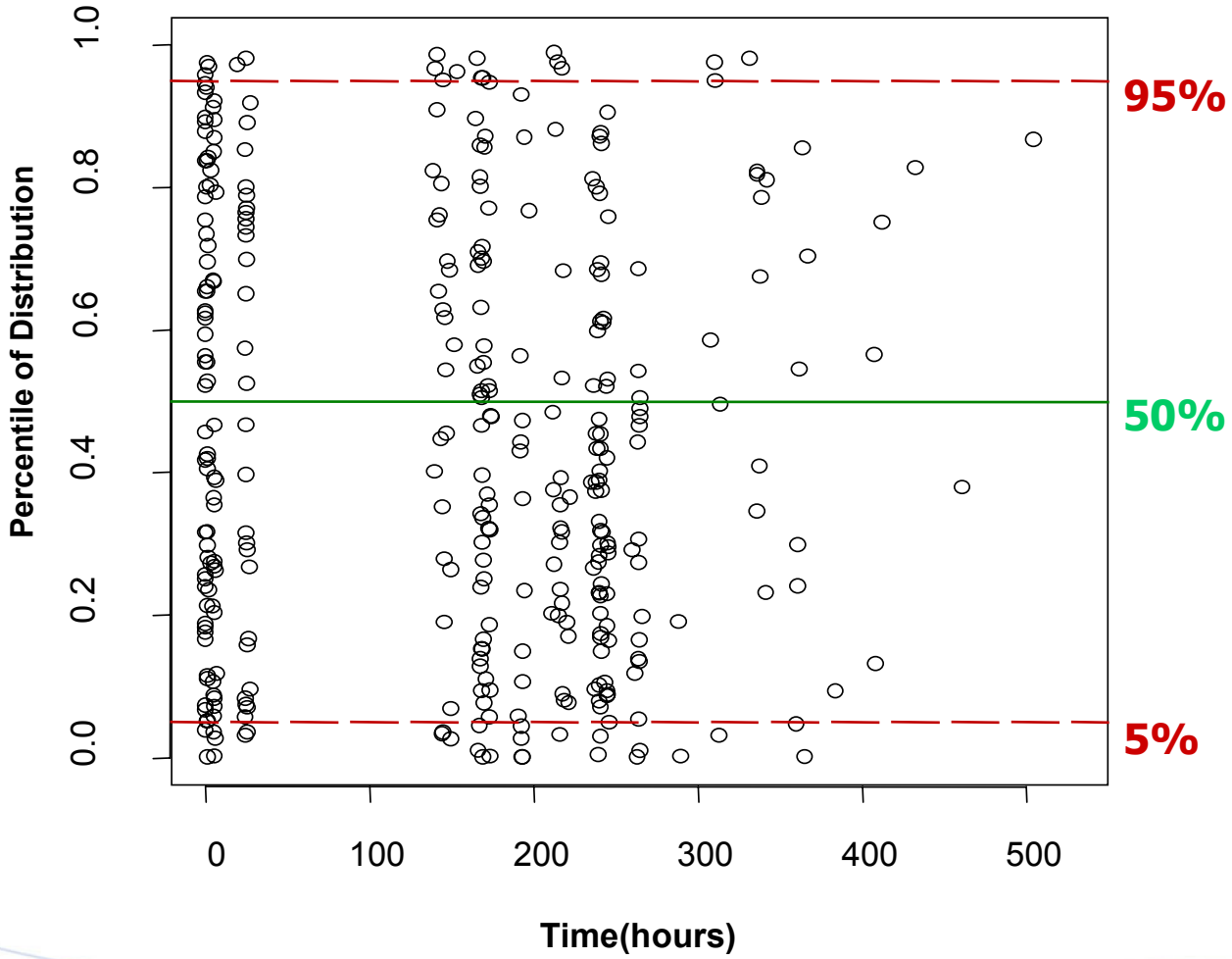
$\delta_{ij,k}$= 1 if $y_{ij} > y'_{ij,k}$, otherwise, $\delta_{ij,k}$= 0

y_{ij}: the actual *j*-th observation for the *i*-th individual

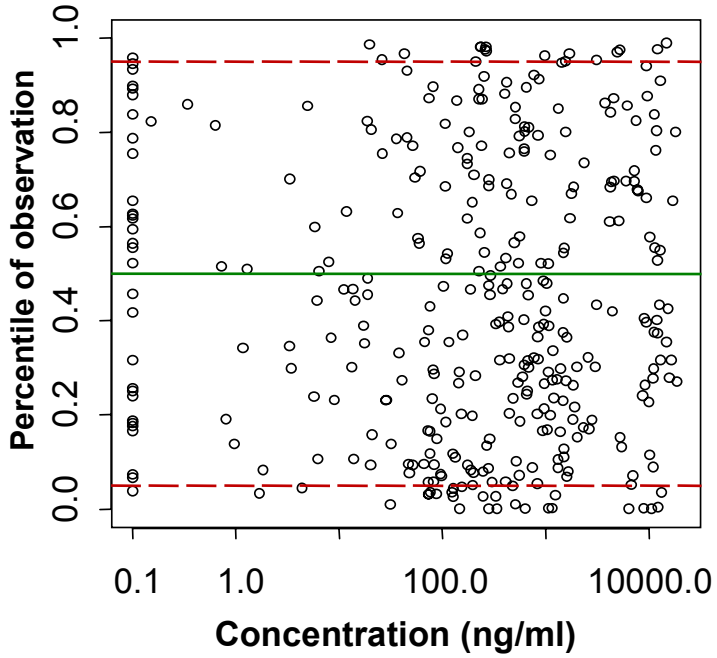
$y'_{ij,k}$: the *k*-th simulated observation corresponding to y_{ij}

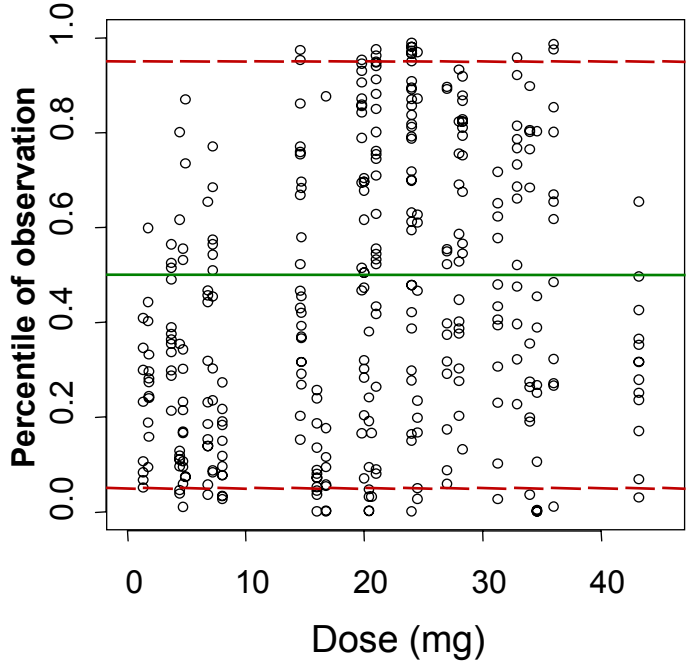
- P_{ij} should be uniformly distributed between [0,1] if the model and population parameter estimates are adequate
- Plot P_{ij} vs. covariate (such as time) for all observations and evaluate their distribution

SVPC Plot for AG-014699 PD model



SVPC Plot for AG-014699 PD model Covariate Evaluation





Questions

- Has the VPC been performed adequately
- Under what situations VPC is not applicable
- When SVPC should be used

Simulation Study (1)

Nonlinear kinetics with mg/kg dosing

- Study Design
  - 100 subjects
  - Single IV bolus dose on mg/kg basis
- Model
  - PK: One compartment model with no covariate effect
  - PD: Immediate effect model (E = Emax*C/(EC50 +C))
- Data
  - PK and PD data sets were simulated based on pre-defined population PK and PD parameters (observed data)
- Estimation
  - PK: True model
  - PD
    - True
    - False model (E = slope*C)
- Predictive
  - Set NSUBPROB = 10 to get 1000 simulated observations for each time point

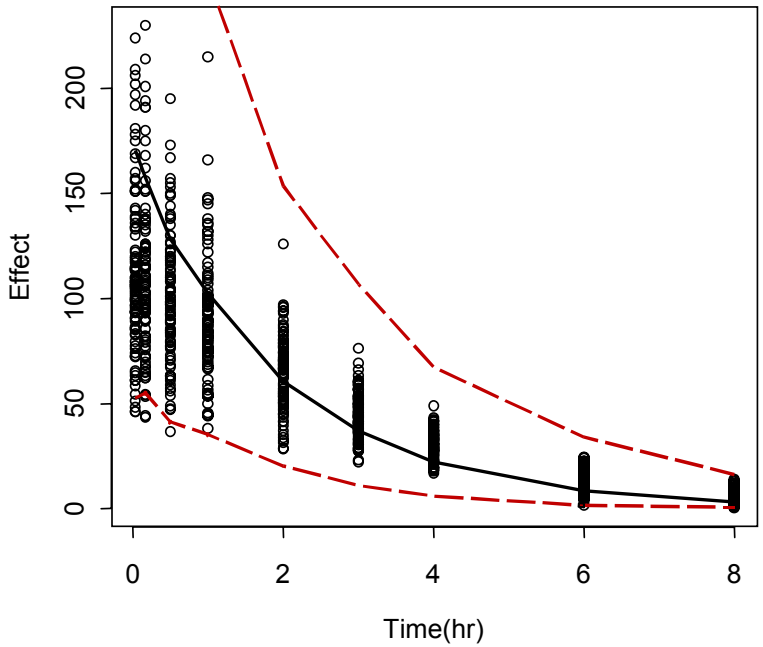
Simulation Study (1)

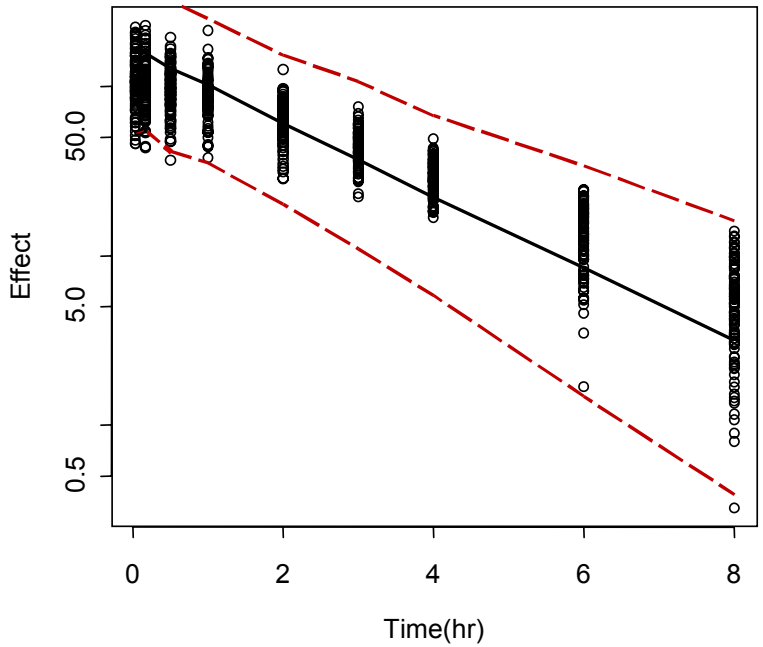
Nonlinear kinetics with body weight (WT) as covariate on CL

- Study Design
  - 100 subjects
  - Single IV bolus fixed dose
- Model
  - PK: One compartment model with WT effect on CL
  - PD: Immediate effect model (E = Emax*C/(EC50 +C))
- Data
  - PK and PD data sets were simulated based on pre-defined population PK and PD parameters (observed data)
- Estimation
  - PK: True model
  - PD
    - True
    - False model (E = slope*C)
- Visual Predictive Check
  - Set NSUBPROB = 10 to get 1000 simulated observations for each time point

False PD model

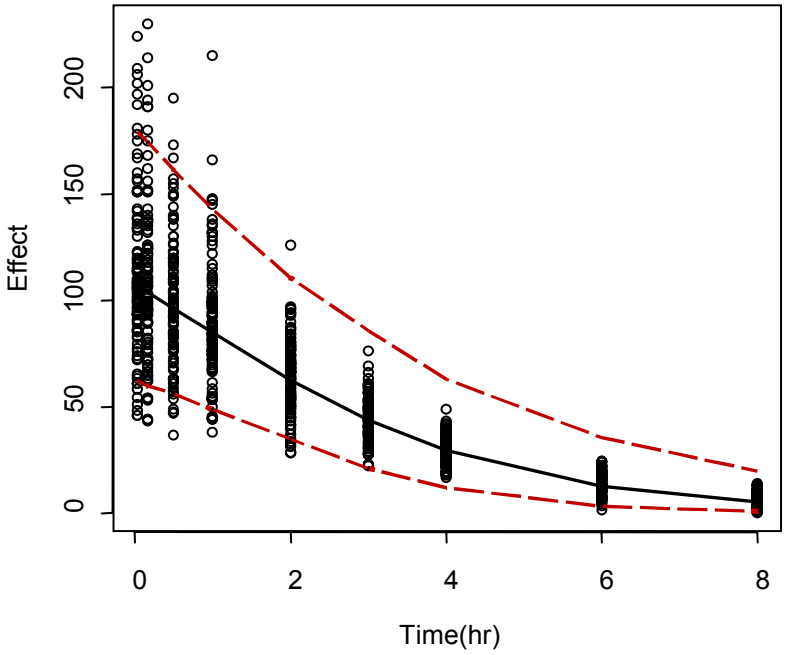
E = Slope *C

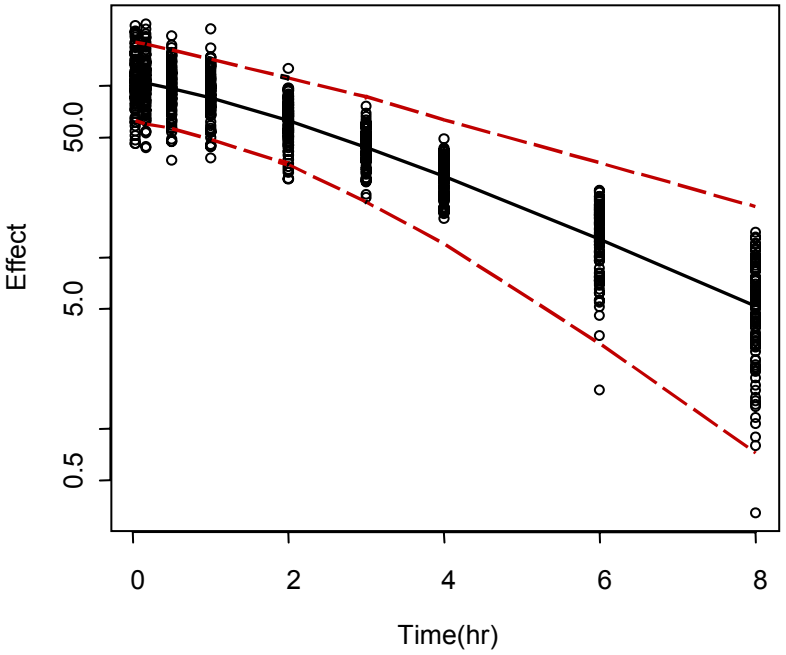




True PD model

$$E = E_{max} * C/(EC_{50} + C)$$

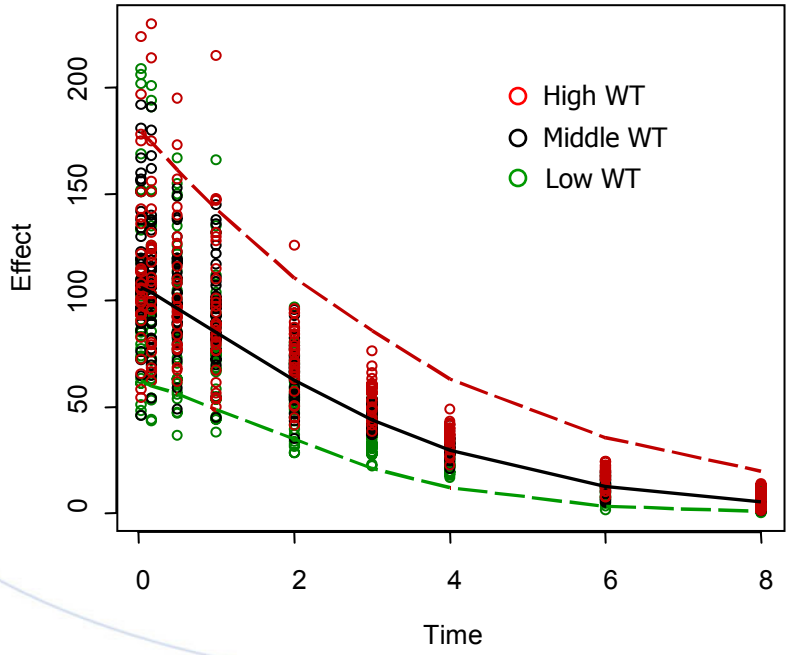


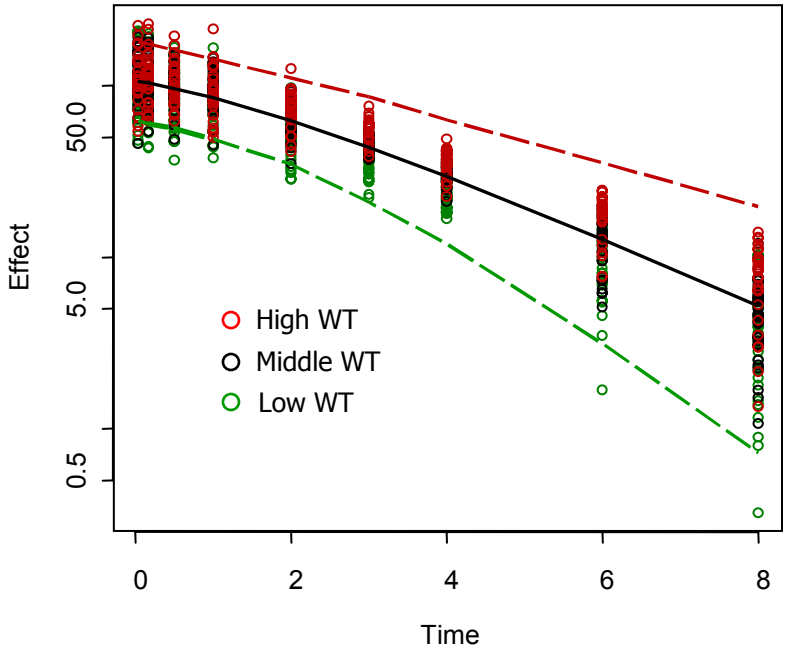


True PD Model – VPC

$$E = Emax*C/(EC_{50} + C)$$

- Body weight (WT)-based dosing
- Individuals were grouped into high, middle and low WT range

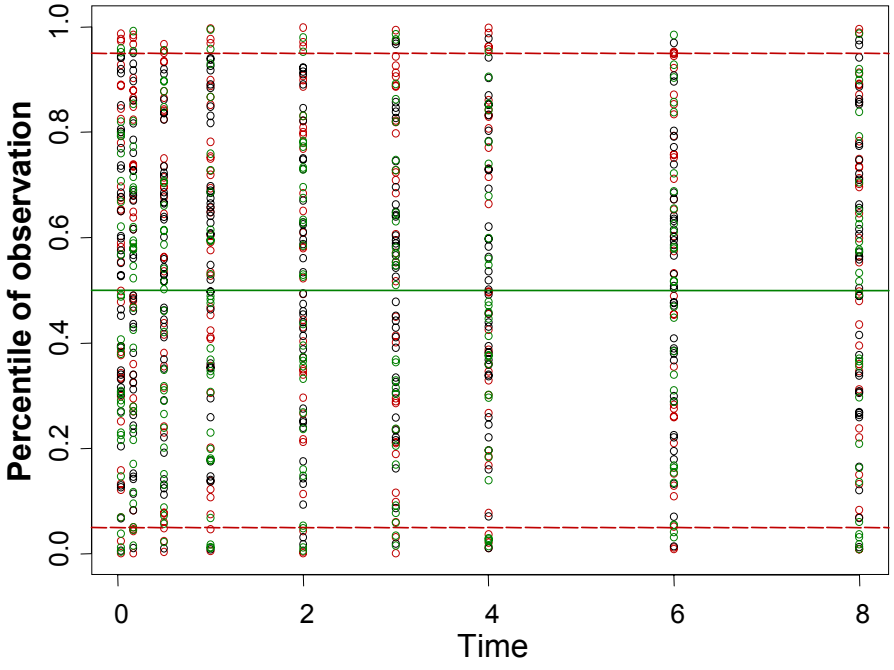




SVPC

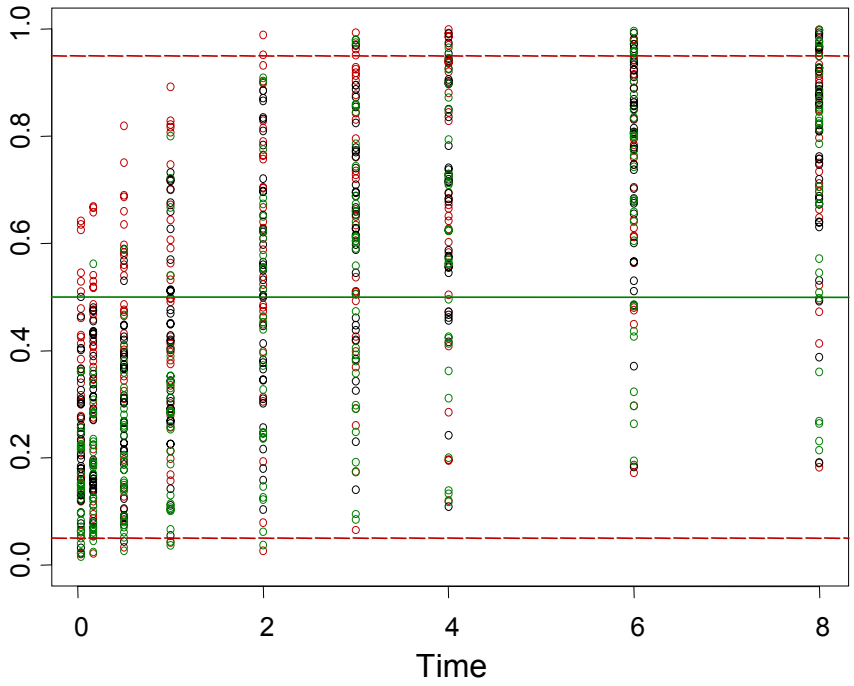
True PD model

E = Emax*C/(EC_{50} +C)



False PD model

E = Slope *C



Low WT Middle WT High WT

Simulation Study (2)

WT as a covariate for CL

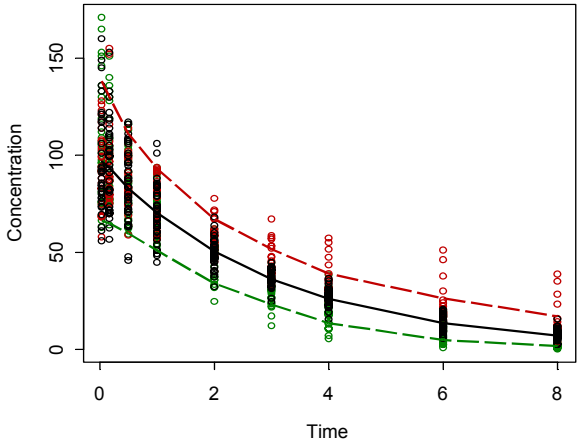
- Study Design
  - 100 subjects
  - Single IV bolus dose (fixed dose)
- Model
  - PK: One compartment model with WT as covariate for CL

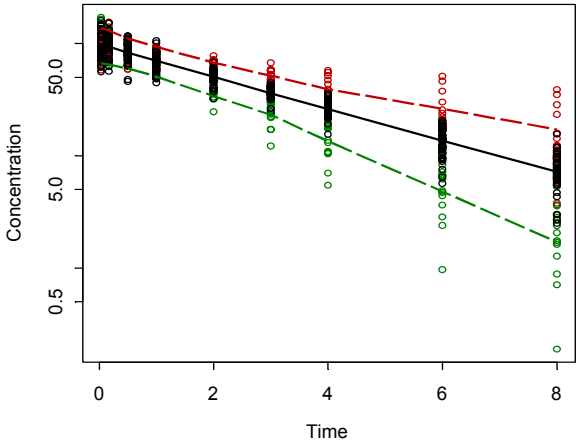
$$Cl = \theta*(WT/WT_{median})^{0.75}$$

- Data
  - PK data set was simulated based on pre-defined population PK parameters (observed data)
- Estimation
  - True model (Ω_{Cl}=10%)
  - False model (Ω_{Cl}=25%)
- Visual Predictive check
  - Set NSUBPROB = 10 to get 1000 simulated observations for each time point

VPC Plots

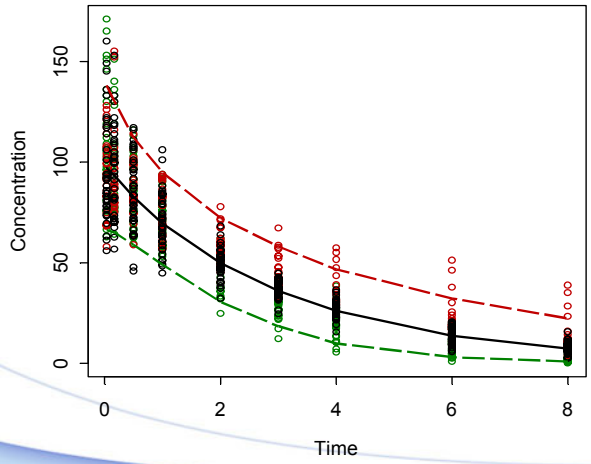
Correct Estimate: Ω_{Cl}=10%

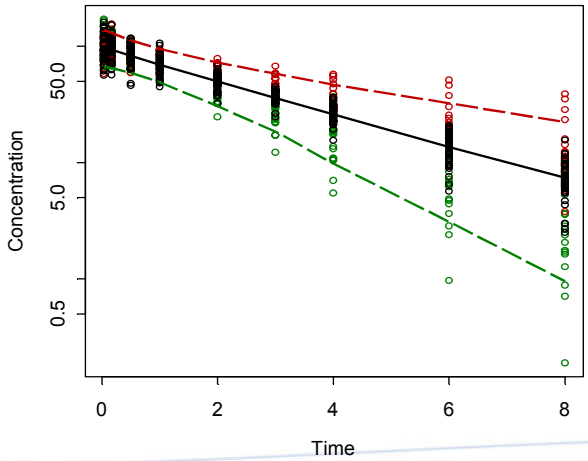




Individuals were grouped based on the covariate (WT) values into high, middle and low WT range

Wrong Estimate: Ω_{Cl}=25%

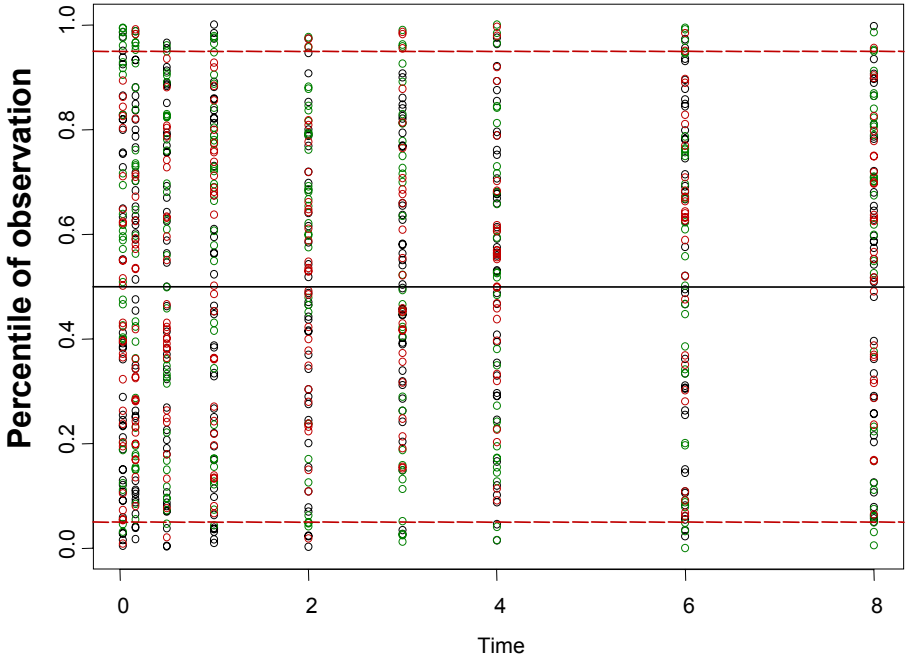




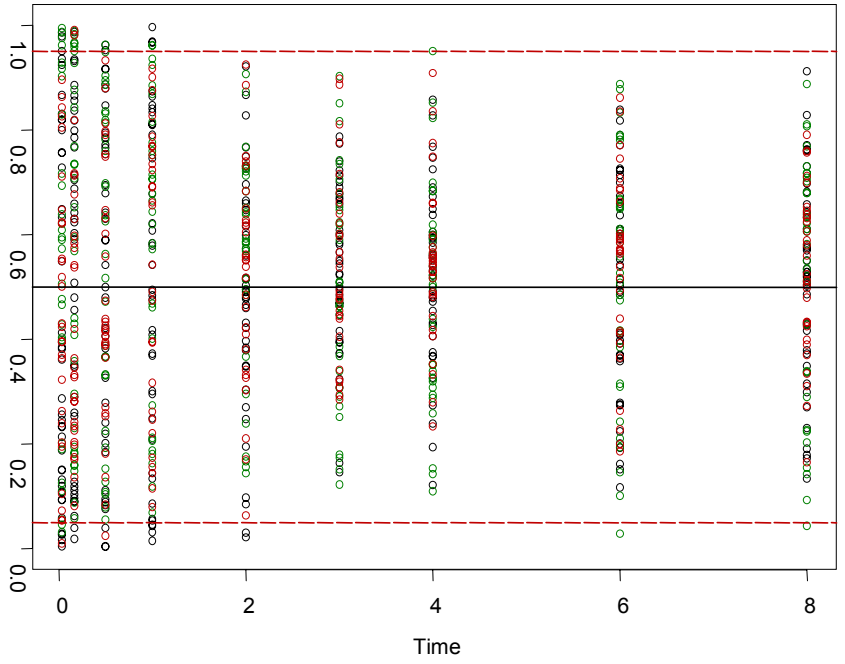
- **Low WT**
- **Middle WT**
- **High WT**

SVPC Plots

True model: Ω_{Cl}=10%



False model: Ω_{Cl}=25%



Low WT **Middle WT** **High WT**

VPC When There is a Covariate Effect

- **It is not adequate to conduct VPC using the final model with there is covariate effect**

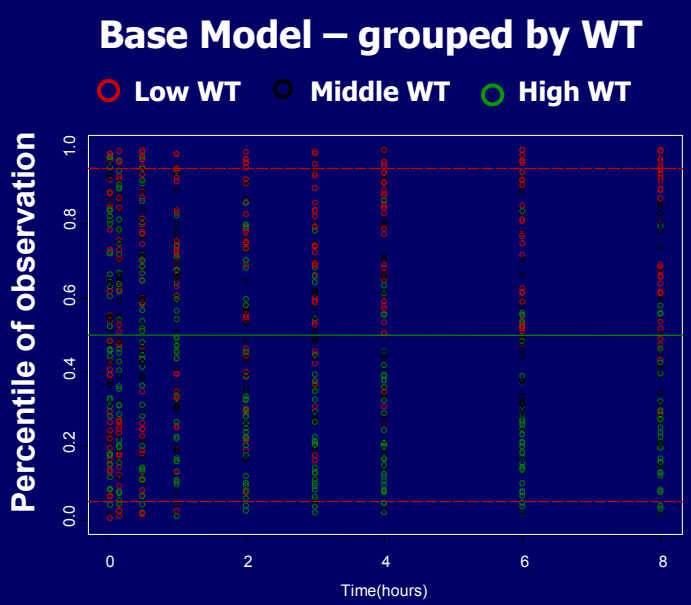
- **Categorical**
  - Stratify for each covariate

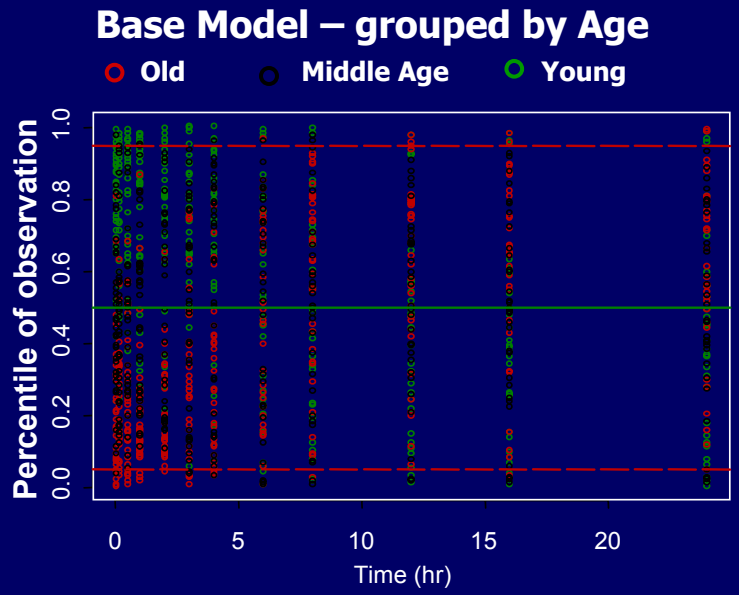
- **More than one covariate**
  - Stratification may not be possible if the number of subjects per group is small
  - By stratifying the data, each plot can only present partial information thus the overall picture may not be easily visualized. When the number of plot increases, information in each plot deminishes

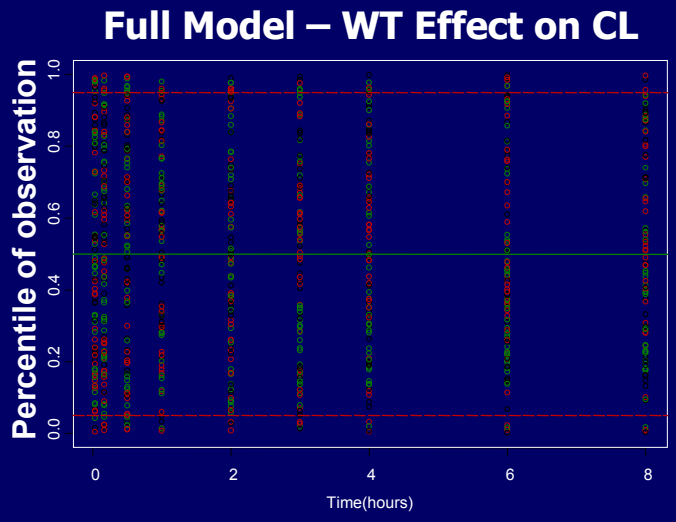
- **Continuous**
  - Can not be stratified

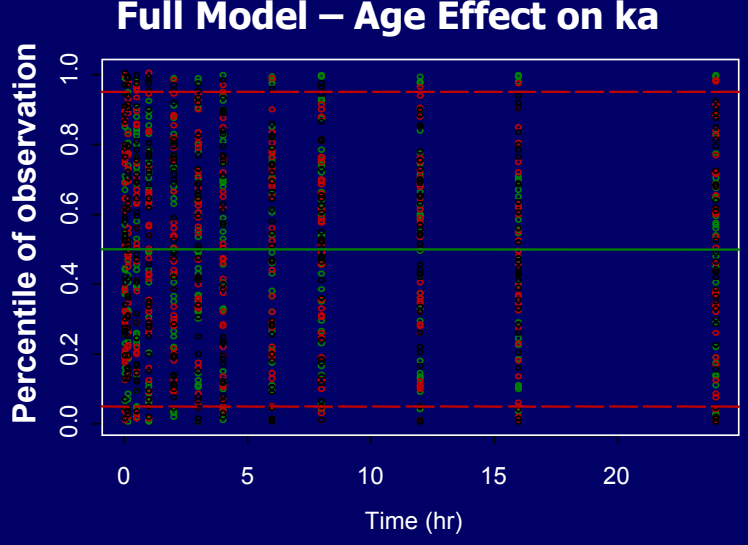
Applications of SVPC

Covariate Effect Evaluation - SVPC for the Base Model



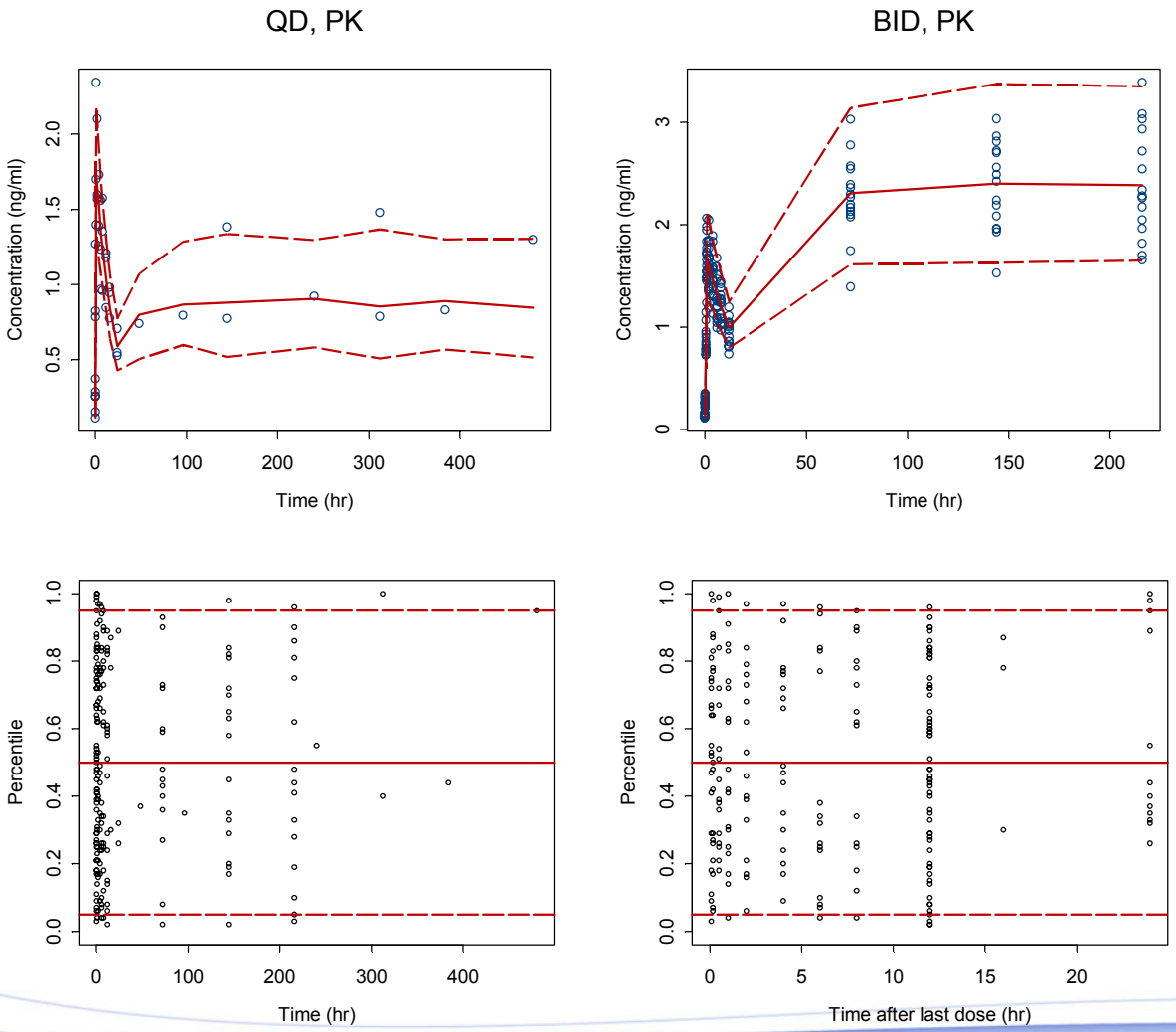






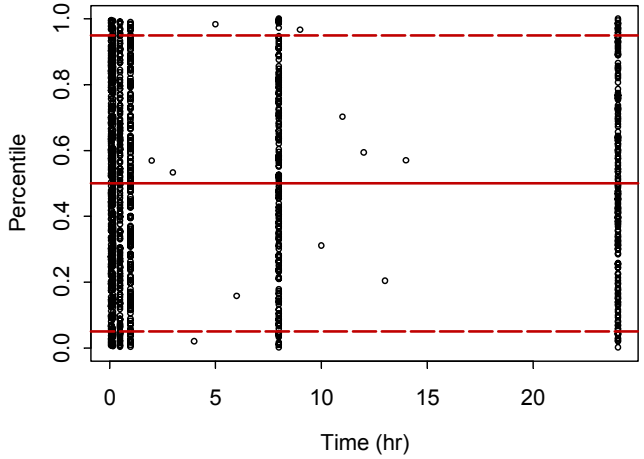
Applications of SVPC

Study Design Varies Among Subjects/During Study

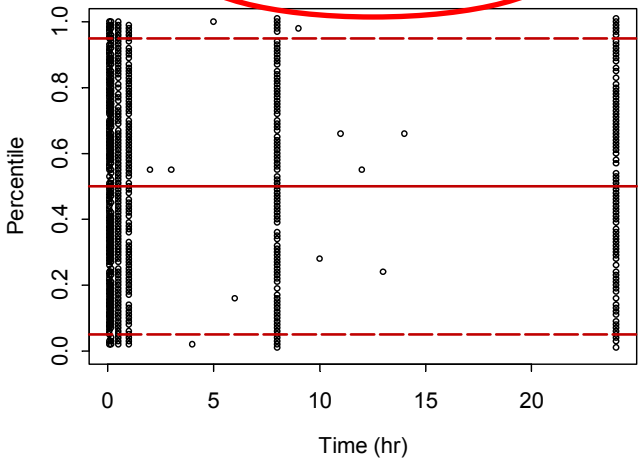


Number of sub-problems in NONMEM Run for SVPC

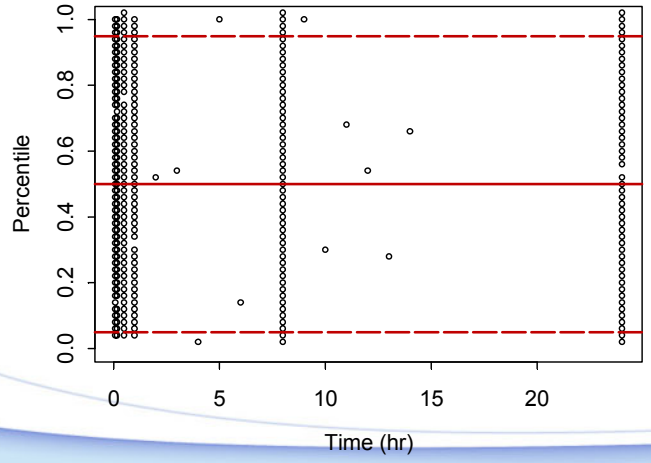
1000 times



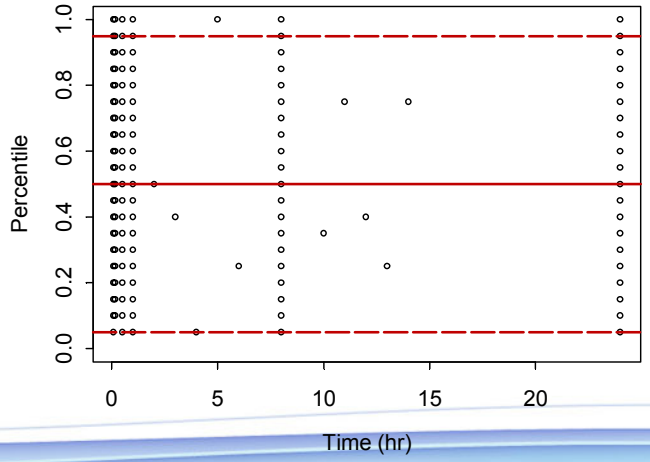
100 times



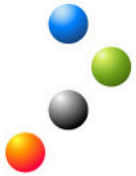
50 times



20 times



CONCLUSIONS



- Common VPC approach is inadequate in many cases
- VPC is only applicable when profiles for all subjects are supposed to be the same when Ω and σ are set to 0 unless data can be stratified by influential covariates and or study design
- SVPC filters out all covariate effects and other study design differences thus can be used in all cases
- In addition to the information provided by VPC, SVPC can be used to identify the covariate effect over the time course

CONCLUSIONS

- **Situations when VPC is not feasible but SVPC can be used**
  - Patients received individualized dose or there are a small number of patients per dose group and PK or PD is nonlinear thus observations can not be normalized for dose
  - There are multiple categorical covariate effects on PK or PD parameters
  - Covariate is a continuous variable which made stratification impossible
  - Study design and execution varies among individuals, such as adaptive design, difference in dosing schedule, dose changes and dosing time varies during study, protocol violations
  - Different concomitant medicines and food intake among individuals when there are drug-drug interactions and food effect on PK

Acknowledgment

Shuzhong Zhang