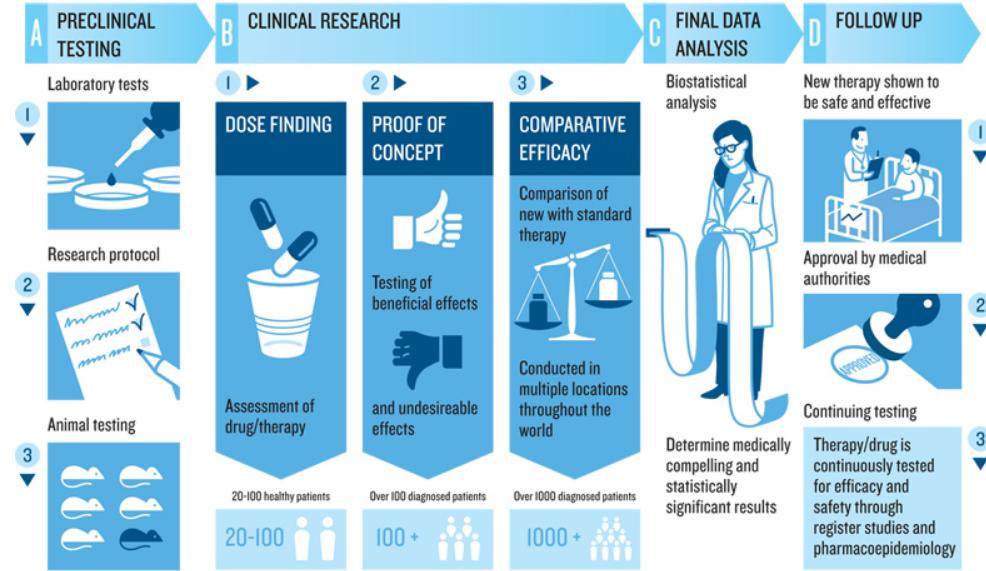


Pharmacometrics : **Nonlinear mixed effect models in** **Statistics**

**Department of Statistics
Ewha Womans University
Eun-Kyung Lee♪**

Clinical Trials

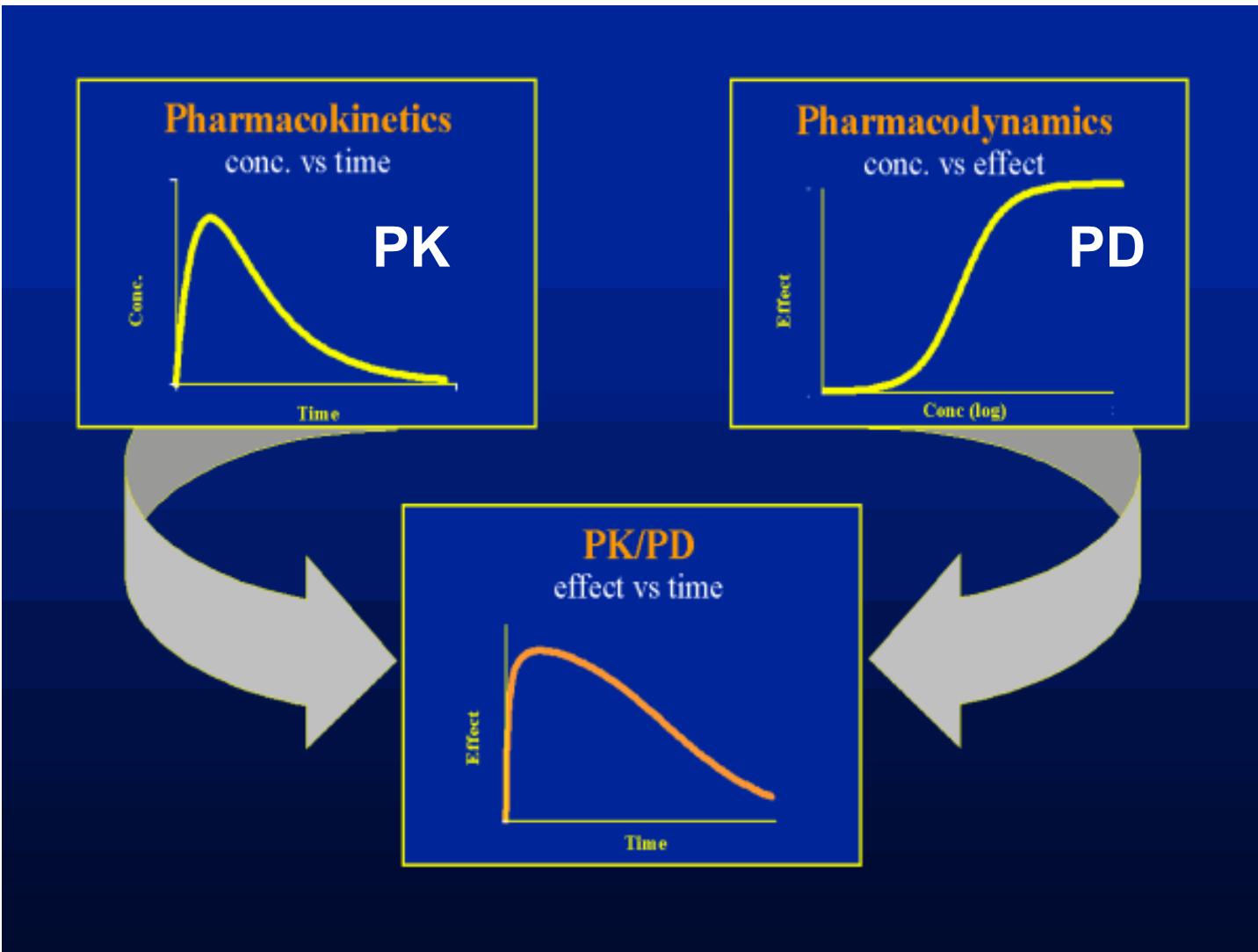


- Preclinical trial: animal study
- Phase I trial: First in human, small number of healthy volunteers, dose finding
- Phase II/III trial: First in patient. Large number of patients. Prepare for FDA approval

Phase I clinical trial

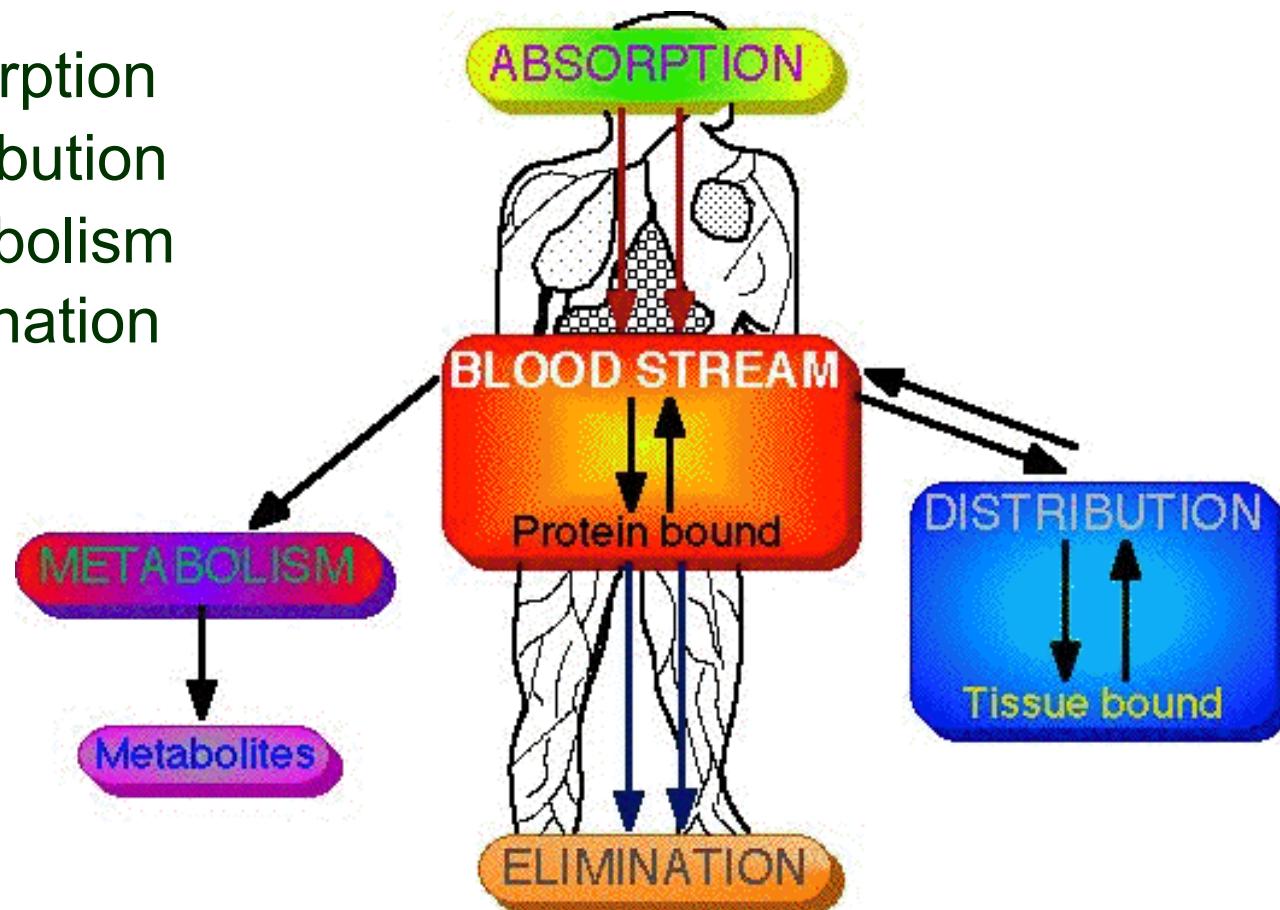
- first in human
- small number of healthy volunteers, usually 10~20
- Purpose
 - find the right dose for human
 - check toxicity
- After administration, collect the following information
 - Cp: the drug concentration in blood
 - Time: usually for 24 hours
 - Effect: the effect of drug
 - (eg. Blood pressure for hypertension drug)

Pharmacometrics

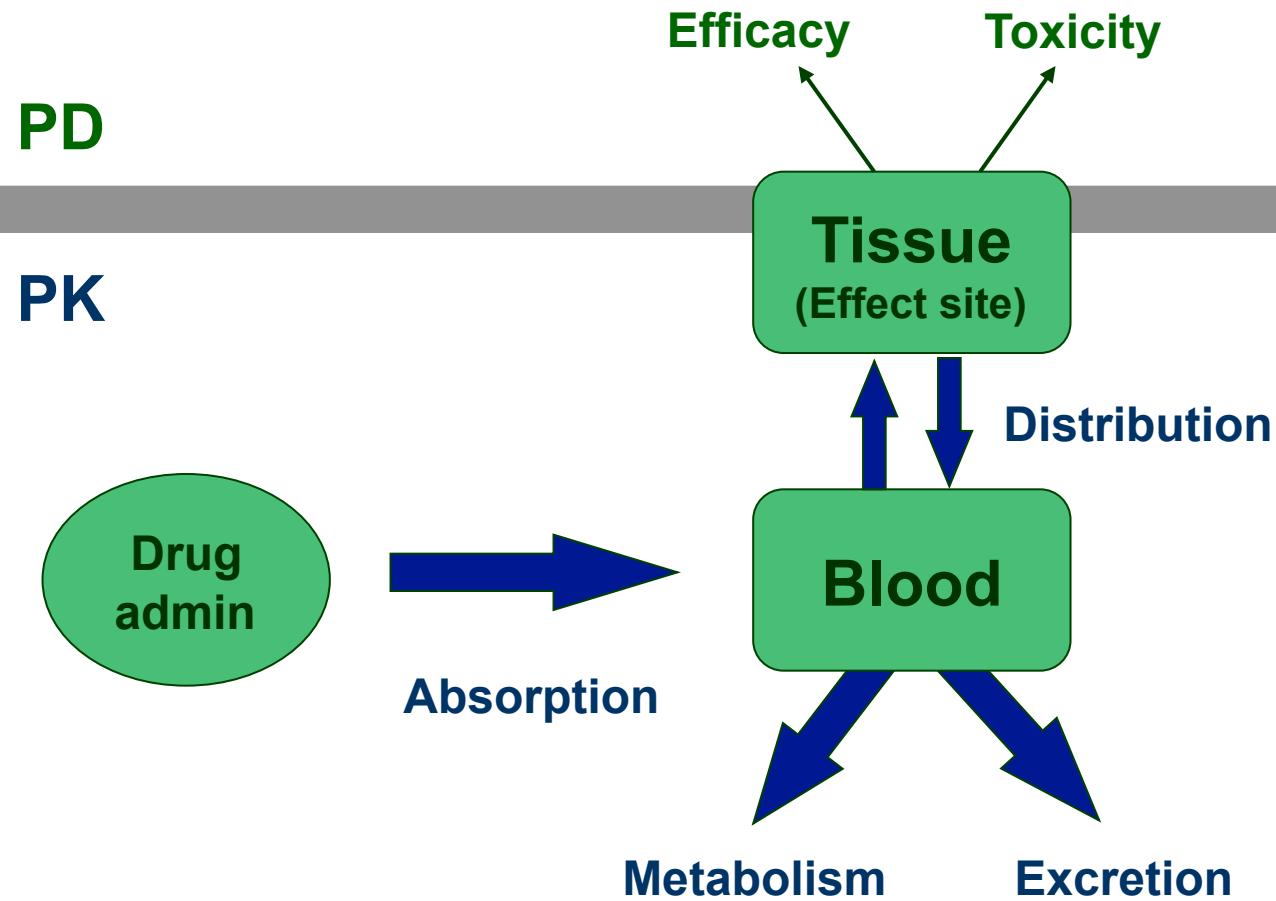


Schematics of PK

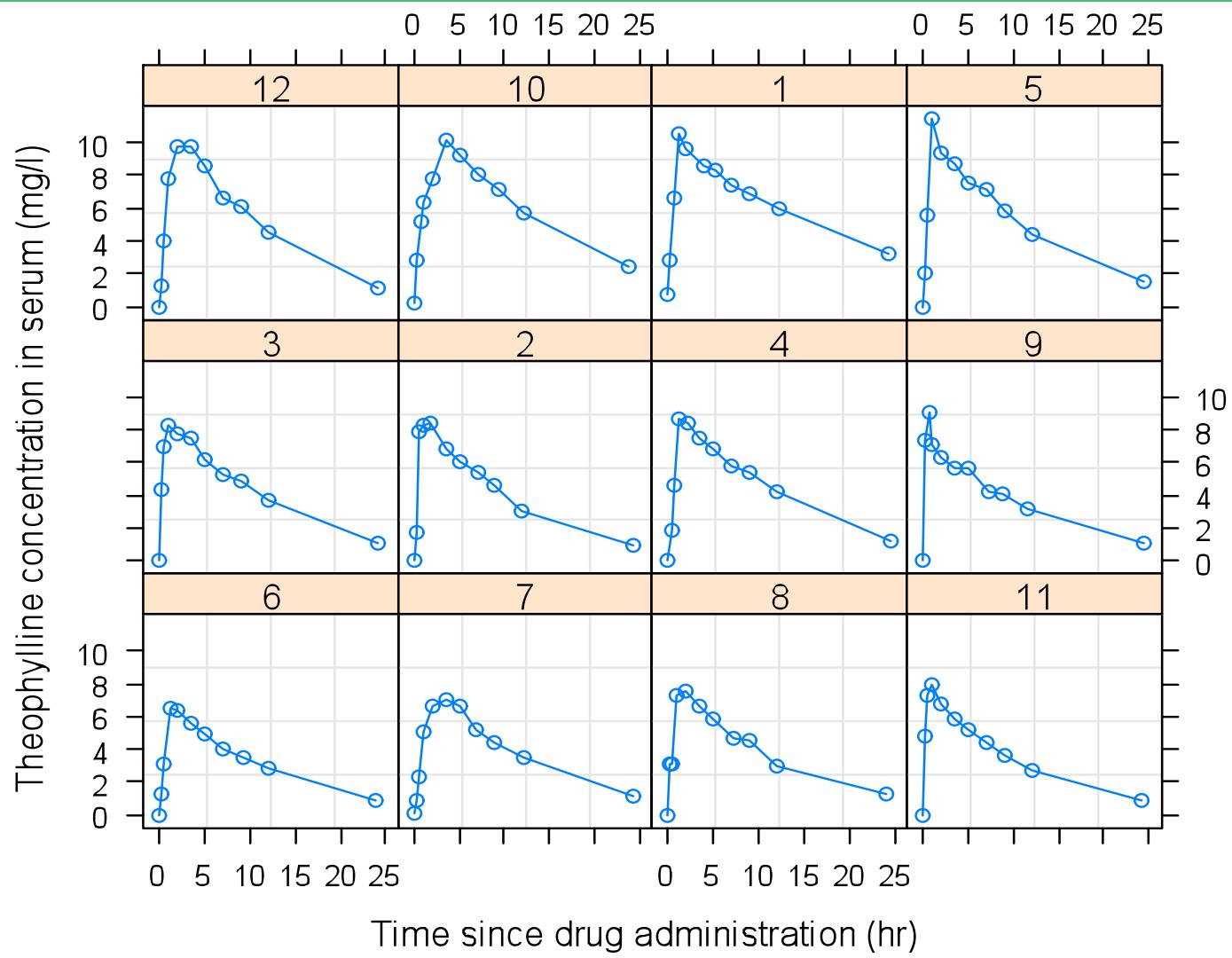
Absorption
Distribution
Metabolism
Elimination



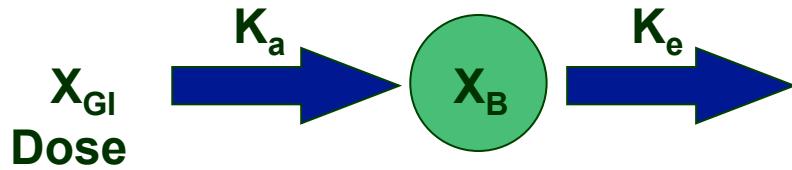
Schematics of PK and PD



Theophylline



One-comp model: oral admin. with 1st order absorp.



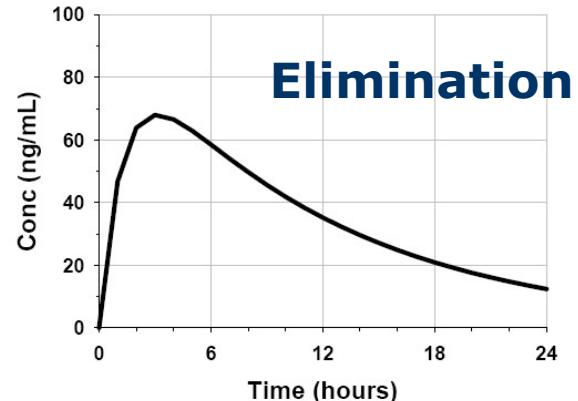
$$\frac{dX_{GI}}{dt} = -K_a X_{GI}, \quad \frac{dX_B}{dt} = K_a X_{GI} - K_e X_B$$

$$K_e = \frac{Cl}{V}$$

$$C = \frac{dose \cdot K_a}{V(K_a - K_e)} \left(e^{-K_e \cdot time} - e^{-K_a \cdot time} \right)$$

Data : C_t , t, dose

Parameters : K_a , K_e , V



K_a : 1st order constant absorption rate

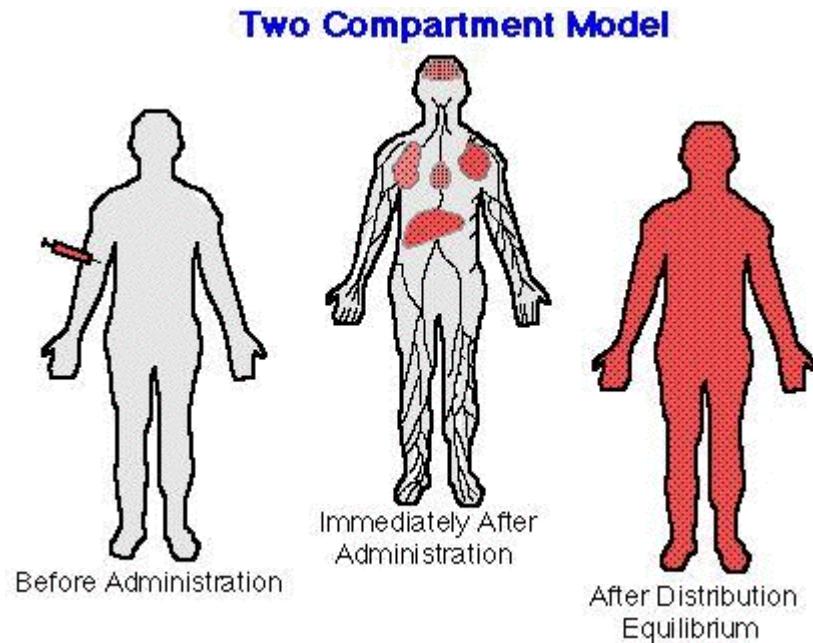
K_e : elimination constant rate

V : volume of distribution

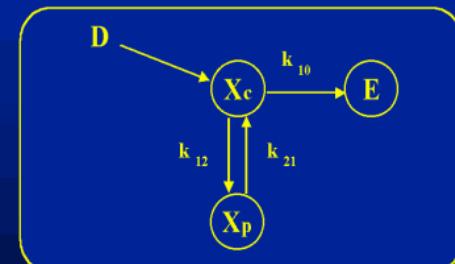
(theoretical volume that total amount of admin. drug would have to occupy to provide the same concentration; large V , more diluted in the blood)

Cl : clearance

two-comp model



Two-compartment model



Dose

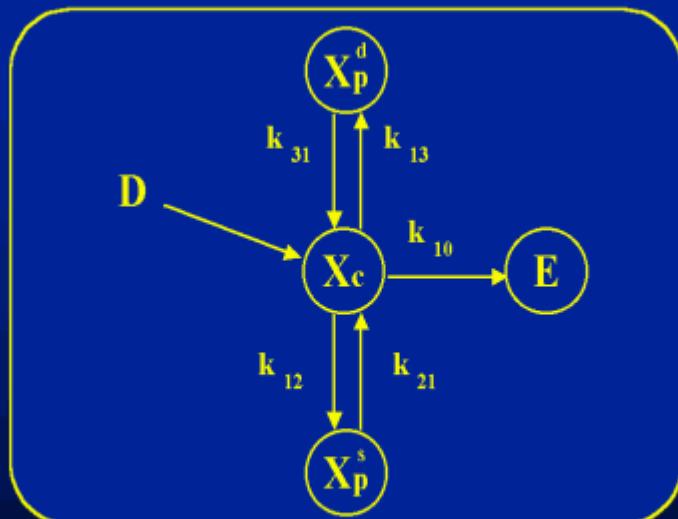
X_c Drug in the central compartment

X_p Drug in the peripheral compartment

Drug eliminated

three-comp model

Three-compartment model



D Dose

E Drug eliminated

X_c Drug in the central compartment

X_{ps} Drug in the shallow peripheral compartment

X_{pd} Drug in the deep peripheral compartment

Population approach

1. Structural sub-model

- Overall trend using fixed-effect parameters

$$C = \frac{dose \cdot K_a}{V(K_a - K_e)} \left(e^{-K_e \cdot time} - e^{-K_a \cdot time} \right)$$

Population approach

2. Statistical sub-model

1) Intra-individual variability

$$C_j = \frac{dose \cdot K_a}{V(K_a - K_e)} \left(e^{-K_e \cdot time_j} - e^{-K_a \cdot time_j} \right) + \varepsilon_j$$

$$\varepsilon_j \sim N(0, \sigma^2)$$

Population approach

2) Inter-individual variability

$$C_{ij} = \frac{dose_i \cdot K_{ai}}{V_i(K_{ai} - K_{ei})} \left(e^{-K_{ei} \cdot time_{ij}} - e^{-K_{ai} \cdot time_{ij}} \right) + \varepsilon_{ij}$$

$$K_{ai} = K_a \exp(\eta_{1i})$$

C_{ij} : concentration of

$$V_i = V \exp(\eta_{2i})$$

the i th patient and the j th timepoint

$$K_{ei} = K_e \exp(\eta_{3i})$$

K_{ai} : absorption rate of the i th patient

$$\begin{pmatrix} \eta_{1i} \\ \eta_{2i} \\ \eta_{3i} \end{pmatrix} \sim N(0, \Omega)$$

V_i : volume of distribution of the i th patient

$$\varepsilon_{ij} \sim N(0, \sigma^2)$$

K_{ei} : elimination constant rate of the
 i th patient

Population approach

3. Covariance sub-model

- The relationship between covariate and model parameter

$$K_{ai} = K_a \exp(\alpha_1 x_{1i} + \eta_{1i})$$

$$V_i = V \exp(\alpha_2 x_{2i} + \eta_{2i})$$

$$K_{ei} = K_e \exp(\alpha_3 x_{1i} + \eta_{3i})$$

→ Nonlinear mixed effect model with covariates

PK Model

- Individual level model

$$y_{ij} = f(D_i, t_{ij}, \beta_i) + e_{ij}, \quad i = 1, \dots, m, \quad j = 1, \dots, n_i$$

→ $y_i = f(D_i, t_i, \beta_i) + e_i, \quad i = 1, \dots, m$
 $e_i \sim N_{n_i}(0, \sigma^2 I_{n_i})$

- Population level model

$$\beta_i = d(x_i, \theta, \eta_i) \quad i = 1, \dots, m$$

$$\eta_i \sim N_p(0, \Omega)$$

y_{ij} : measurement of i^{th} subject at time t_{ij}

D_i : dose

t_{ij} : time

x_i : covariates(weight, height, age, etc)

θ : PK parameter(V, CL, Ka, etc)

Estimation Methods in NONMEM

- linear approximation approach
 - First order method (FO)
 - First order conditional method (FOCE)
 - Laplacian method (Laplacian)
- EM algorithm based approach
 - Iterative two stage (ITS)
 - Important Sampling method (IMP)
 - IMP assisted by mode a posteriori (IMPMAP)
 - Stochastic approximation EM(SAEM)
- Bayesian approach

References for estimation methods

- Dempster, A. P., Laird N., and Rubin, D. B (1977) Maximum likelihood from incomplete data via the EM algorithm
- Laird, N. M. and Ware, J. H (1982) Random-effects models for longitudinal data
- Wu, C. F. (1983) On the convergence properties of the EM algorithm
- Lindstrom, M.J., and Bates, D. M(1988) Newton-Raphson and EM algorithms for linear mixed effects models for repeated-measures data
- Delyon, B., Laville, M., and Moulines, E.(1990) Convergence of a stochastic approximation version of the EM algorithm
- Lindstrom, M.J., and Bates, D.M(1990) Non-linear mixed-effects models for repeated-measures data
- Wolfinger, R. (1993) Laplace's approximation for nonlinear model
- Pinheiro, J.C. and Bates, D.M (1994) Approximations to the loglikelihood function in the non-linear mixed effect model
- Davidian, M and Giltinan, D. M (1995) Nonlinear Models for Repeated Measurement Data
- Walker, S (1996) An EM algorithm for Nonlinear Random Effects Models
- Kuhn, E., and Lavielle, M. (2004) Coupling a stochastic approximation version of EM with a MCMC procedure
- Kuhn, E., and Lavielle, M.(2005) Maximum likelihood estimation in nonlinear mixed effects models
- Lavielle, M., and Meza, C. (2007) A parameter expansion version of the SAEM algorithm
- Meza, C., Jaffrezic, F., and Foulley, J-L (2007) REML estimation of variance parameters in nonlinear mixed effects models using the SAEM algorithm

Results from NONMEM fitting

1. Estimates of parameters

- PK/PD population parameter $\hat{\theta}$
- Inter-individual variability $\hat{\Omega}$
- Intra-individual variability $\hat{\sigma}^2$

2. Predictions

- PRED: predictive values without random effect (when $\eta_i = 0$)
- EBE: empirical Bayesian estimate of η_i
- IPRED: individual level predicted values (when $\eta_i = \hat{\eta}_i$)

3. Residuals

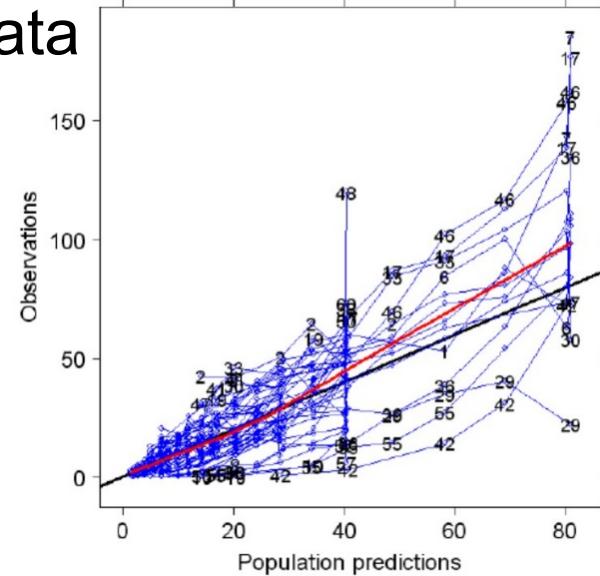
- RES: residuals
- WRES: weighted residuals(for FO method)
- CWRES: conditional weighted residual (for FOCE method)

4. Covariates, TIME, DV, ...

Graphical Method: Prediction-based(1)

1. Prediction-based : PRED, IPRED, etc.

- **PRED vs DV(obs) plot** with
 - line of identity (black line)
 - lines between points for an individual
 - ID values for “outer edges” of data
 - Regression line (red line)
- **IPRED vs DV plot**



Source: Intermediate NONMEM 7 Workshop, 2010, Seoul, Korea

Graphical Method: Residual-based(1)

2. Residual-based : RES, WRES, CWRES, etc.

WRES (weighted residual) : use for FO method

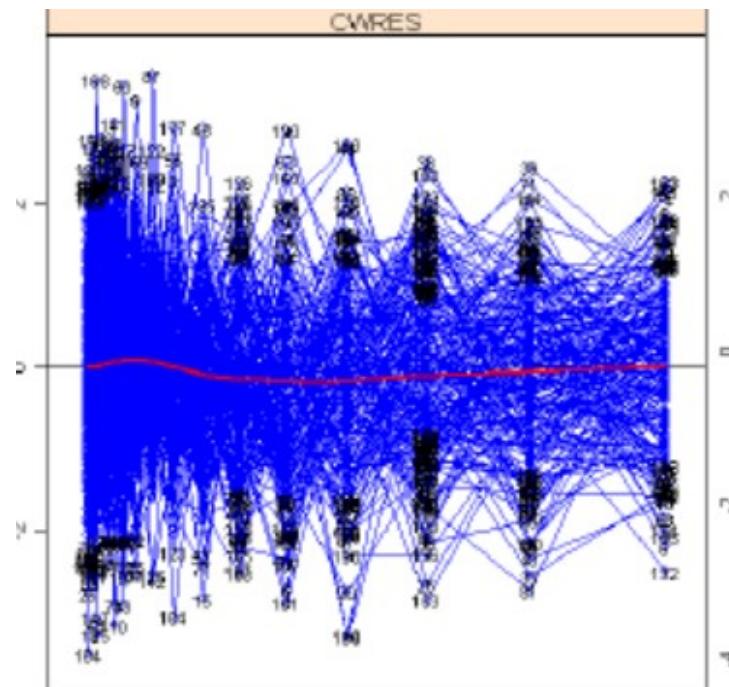
$$WRES_i = \left(y_i - E_{FO}(y_i) \right)^T \left(Var_{FO}(y_i) \right)^{-1} \left(y_i - E_{FO}(y_i) \right) \\ \sim N(\mathbf{0}, \mathbf{I})$$

CWRES (conditional WRES) : use for FOCE method

$$CWRES_i = \left(y_i - E_{FOCE}(y_i) \right)^T \left(Var_{FOCE}(y_i) \right)^{-1} \left(y_i - E_{FOCE}(y_i) \right) \\ \sim N(\mathbf{0}, \mathbf{I})$$

Graphical Method: Residual-based(2)

- **TIME vs. residual plot** with
 - lines between points for an individual
 - ID values for “outer edges” of data
 - line of $y=0$ (black line)
 - lowess line line (red line)
- **PRED vs. residual plot**
- **Covariate vs. residual plot**



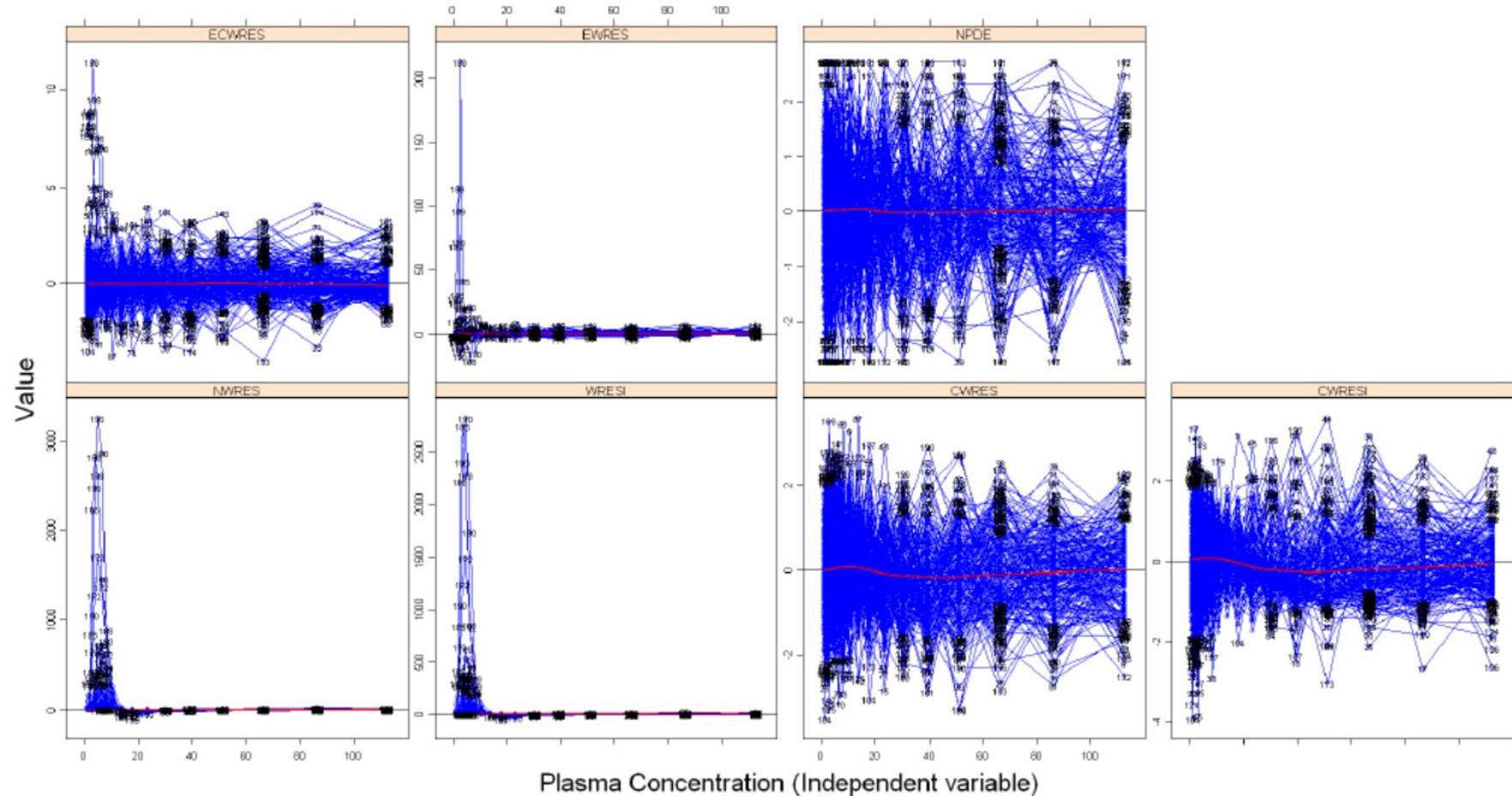
Source: Intermediate NONMEM 7 Workshop, 2010, Seoul, Korea

Graphical Method: Residual-based(3)

- Estimation method vs. prediction/residual in NONMEM

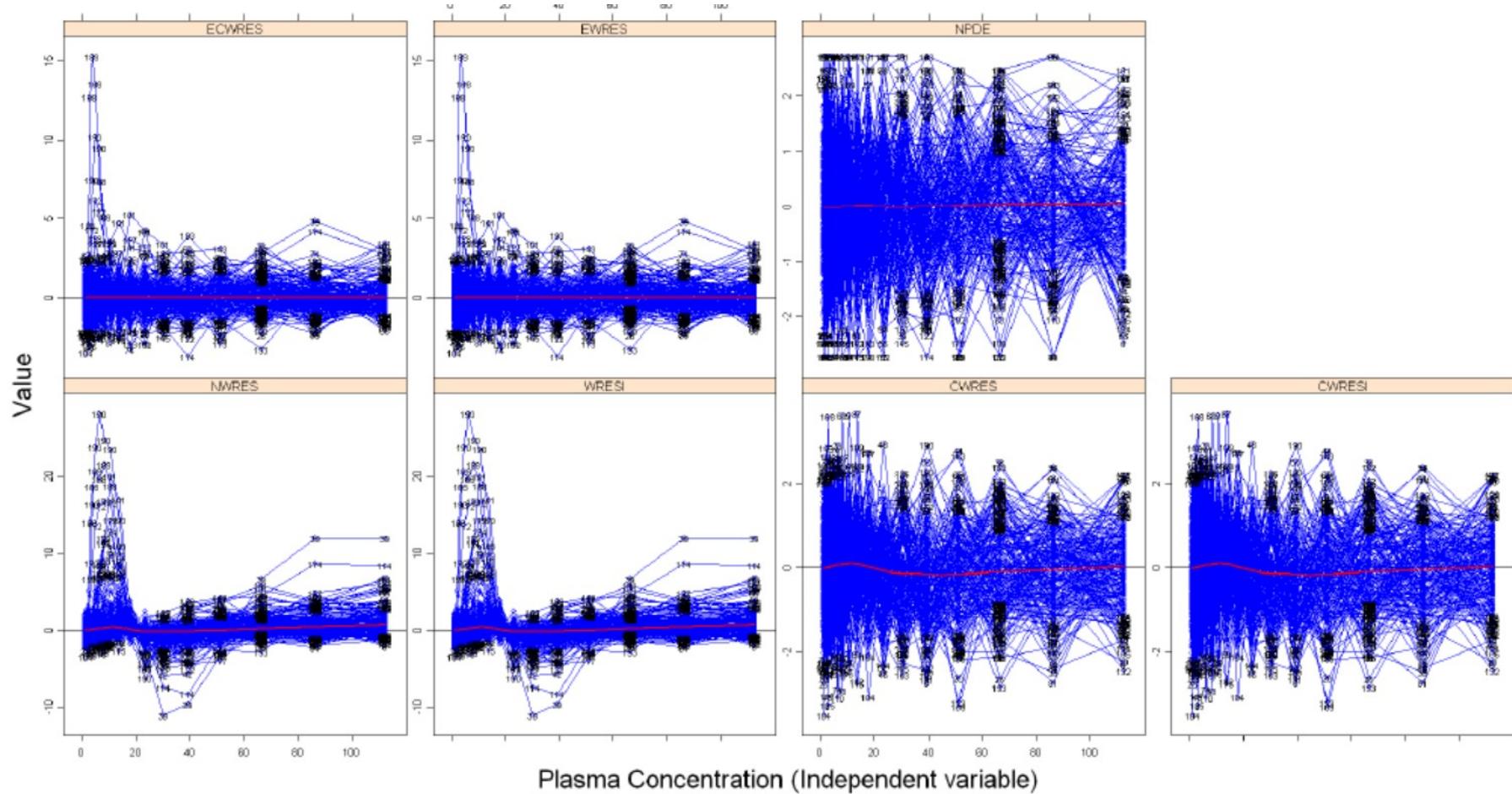
Estimation method	PRED	RES	Weighted RES
FO	NPRED	NRES	NWRES
FO INTER	PREDI	RESI	WRESI
FOCE	CPRED	CRES	CWRES
FOCE INTER	CPREDI	CRESI	CWRESI
MC based	EPRED	ERES	ECWRES
MC based INTER	EPRED	ERES	EWRES
MC based			NPDE

Graphical Method: Residual-based(4)



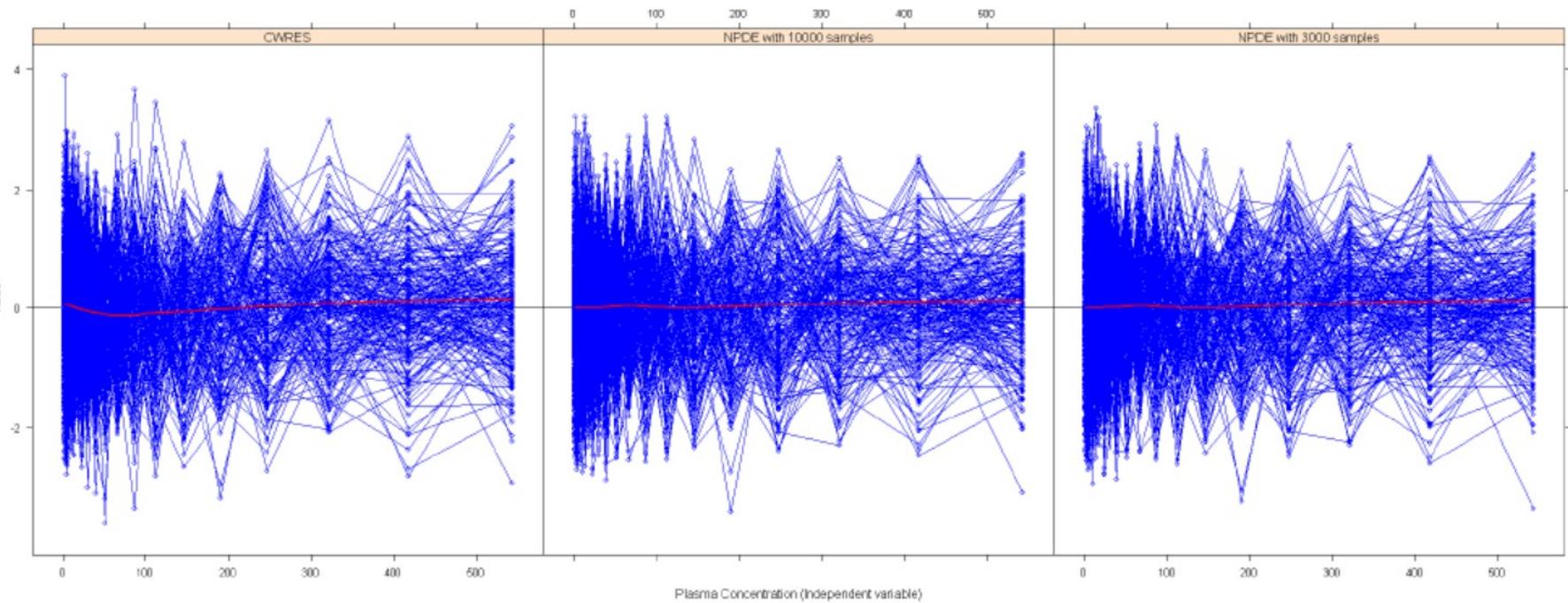
Source: Intermediate NONMEM 7 Workshop, 2010, Seoul, Korea

Graphical Method: Residual-based(5)



Source: Intermediate NONMEM 7 Workshop, 2010, Seoul, Korea

Graphical Method: Residual-based(6)



Var(CWRES)=0.9966

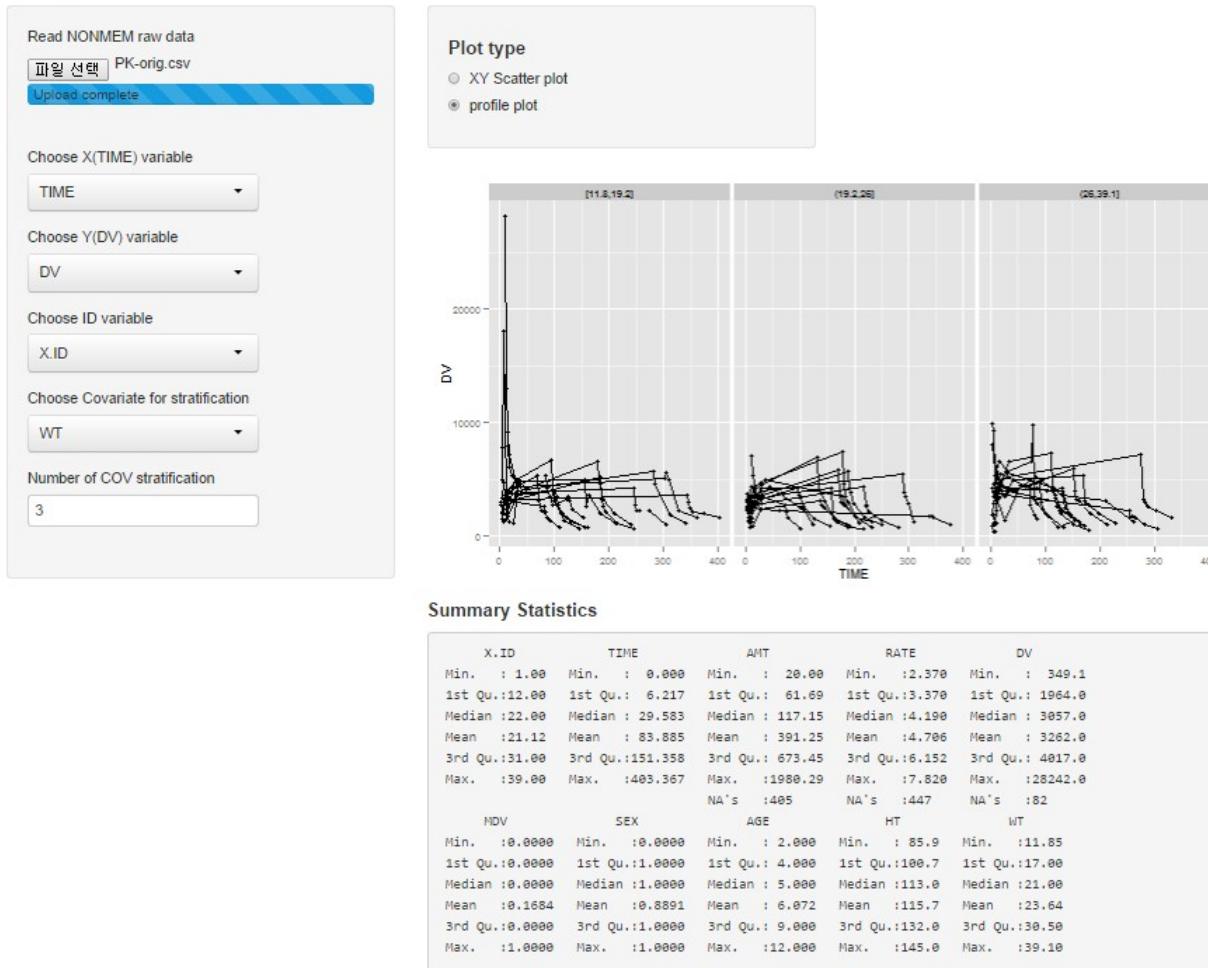
3,000 samples
Var(NPDE)=0.9894

10,000 samples
Var(NPDE)=0.9907

Source: Intermediate NONMEM 7 Workshop, 2010, Seoul, Korea

Shiny : Explore NONMEM data

Explore NONMEM data



Shiny : Explore NONMEM output

Explore NONMEM output

Read NONMEM raw data

NM-output.dat
Upload complete

Choose ID variable

ID

Choose X variable

TIME

Choose Y variable(points)

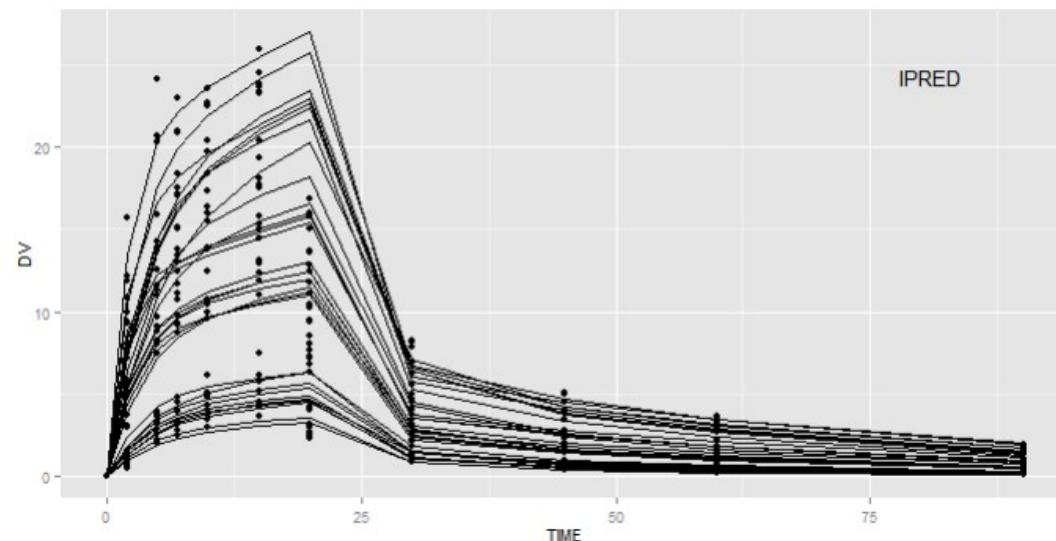
DV

Choose Y variable(line)

IPRED

Options

lowess
 y=0
 y=x



Shiny : Explore NONMEM output

Explore NONMEM output

Read NONMEM raw data

NM-output.dat
Upload complete

Choose ID variable

ID

Choose X variable

TIME

Choose Y variable(points)

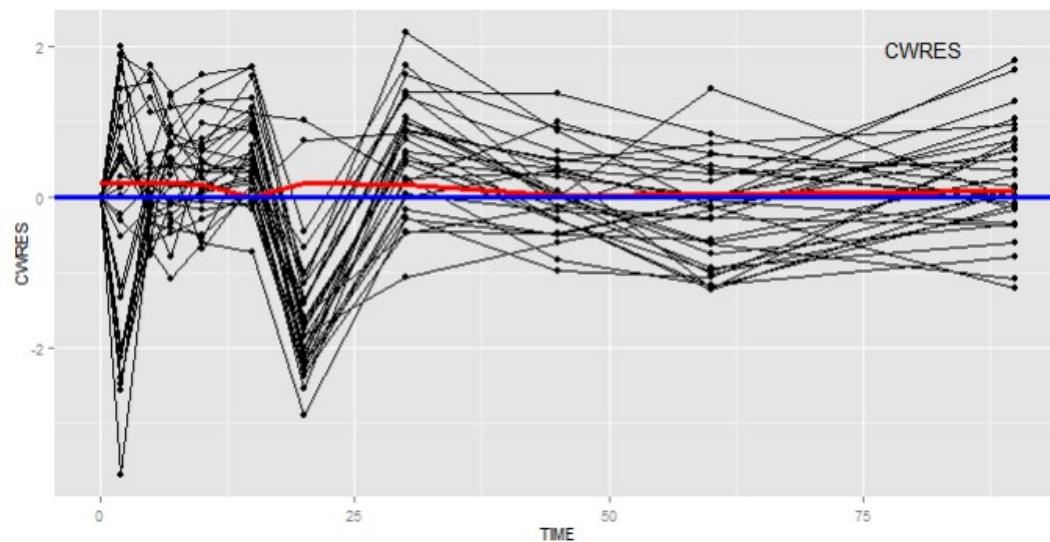
CWRES

Choose Y variable(line)

CWRES

Options

lowess
 y=0
 y=x



Theophylline

Explore NONMEM output

Read NONMEM raw data

test-1-PRED.dat

Upload complete

Choose ID variable

ID

Choose X variable

TIME

Choose Y variable(points)

DV

Choose Y variable(line)

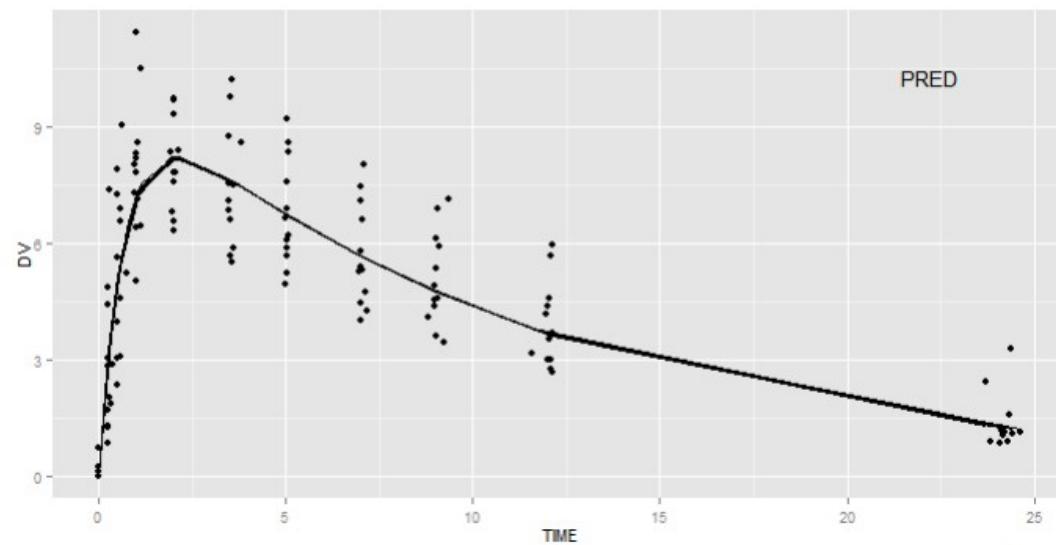
PRED

Options

lowess

y=0

y=x



Theophylline

Explore NONMEM output

Read NONMEM raw data

test-1-PRED.dat

Upload complete

Choose ID variable

ID

Choose X variable

TIME

Choose Y variable(points)

CWRES

Choose Y variable(line)

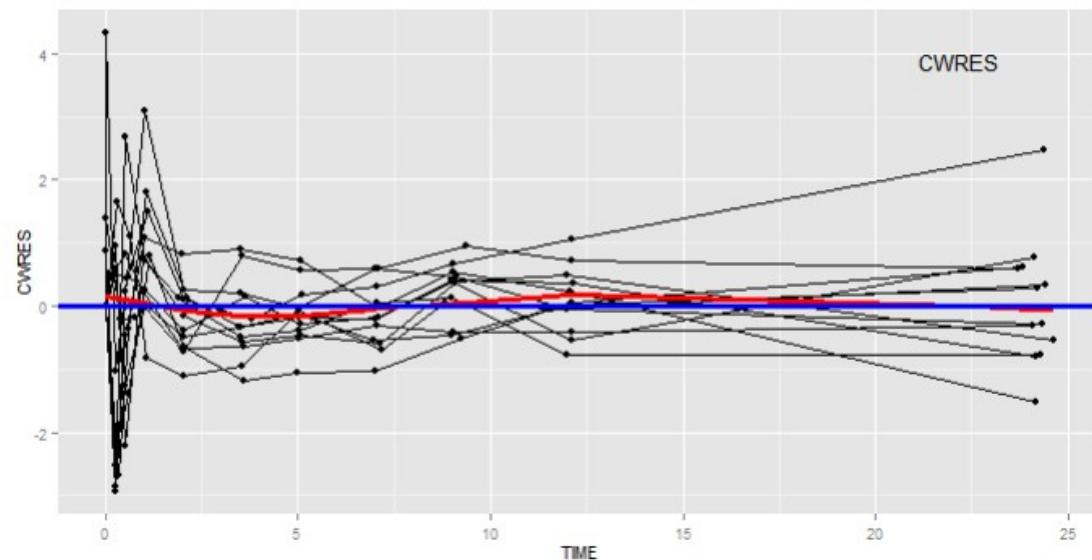
CWRES

Options

lowess

y=0

y=x



Graphical Method: Simulation-based(1)

Data

Y_{ij} : observed value, i th subject j th observation

t_{ij} : observed time of i th subject j th observation

\mathbf{x}_i : covariates of i th subject $i = 1, \dots, m$, $j = 1, \dots, n_i$

Model

$$Y_{ij} = f(\boldsymbol{\theta}_i, t_{ij})(1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$$

$$\boldsymbol{\theta}_i = g(\mathbf{x}_i, \boldsymbol{\theta}) + \boldsymbol{\eta}_i \quad \text{or} \quad \boldsymbol{\theta}_i = g(\mathbf{x}_i, \boldsymbol{\theta})e^{\boldsymbol{\eta}_i}$$

$$\varepsilon_{1ij} \sim N(0, \sigma_1^2), \quad \varepsilon_{2ij} \sim N(0, \sigma_2^2), \quad \boldsymbol{\eta}_i \sim N_q(\mathbf{0}, \boldsymbol{\Omega})$$

→ Estimate $\boldsymbol{\theta}, \boldsymbol{\Omega}, \sigma_1^2, \sigma_2^2$

Graphical Method: Simulation-based(2)

Simulated data from model

$\hat{\theta}, \hat{\Omega}, \hat{\sigma}_1^2, \hat{\sigma}_2^2$: estimates of $\theta, \Omega, \sigma_1^2, \sigma_2^2$

Simulate data from

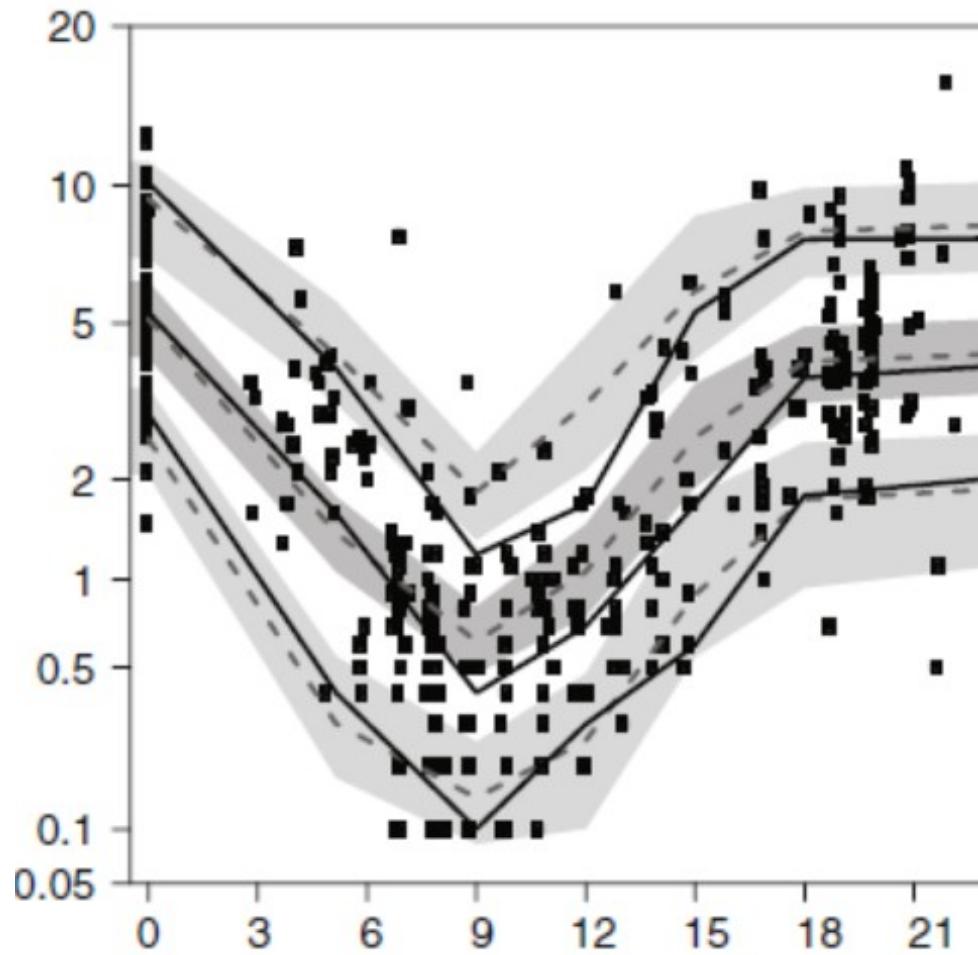
$$Y_{ij} = f(\hat{\theta}_i, t_{ij})(1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$$

$$\hat{\theta}_i = g(\mathbf{x}_i, \hat{\theta}) + \eta_i \quad \text{or} \quad \hat{\theta}_i = g(\mathbf{x}_i, \hat{\theta})e^{\eta_i}$$

$$\varepsilon_{1ij} \sim N(0, \hat{\sigma}_1^2), \quad \varepsilon_{2ij} \sim N(0, \hat{\sigma}_2^2), \quad \eta_i \sim N_q(\mathbf{0}, \hat{\Omega})$$

→ $Y_{ij}^{sim(k)} \quad i = 1, \dots, m, \quad j = 1, \dots, n_i \quad k = 1, \dots, K$

VPC : example

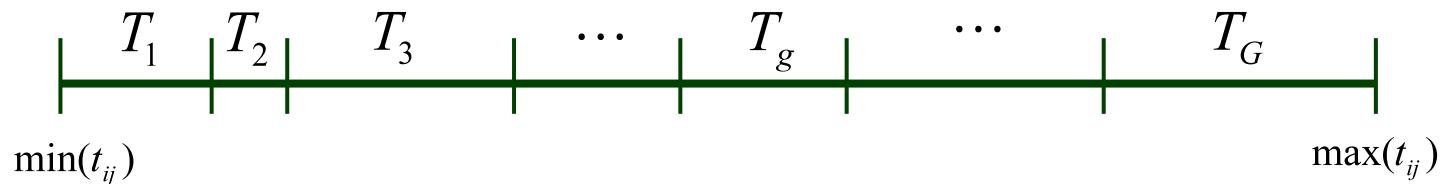


Source: <http://www.page-meeting.org/?abstract=1434>

VPC : Visual Predictive Checks (1)

Step 1: Binning TIME data

Make G intervals with $\{t_{ij} \mid i = 1, \dots, m, j = 1, \dots, n_i\}$



- Binning strategy
 - Have similar amount of data in each bin
 - No need binning if observation times are same between subjects

VPC : Visual Predictive Checks (2)

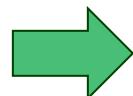
Step 2: find PI of the original data

Find 5%, 50%, 95% percentile of

$$\{Y_{ij} \mid t_{ij} \in T_g, i = 1, \dots, m, j = 1, \dots, n_i\} \text{ for each } g=1, \dots, G$$

Also find median(50%percentile) of

$$\{t_{ij} \mid t_{ij} \in T_g, i = 1, \dots, m, j = 1, \dots, n_i\} \text{ for each } g=1, \dots, G$$



g	med(t _{ij})	5% percentile	50% percentile	95% percentile
1				
2	t_g	$Y_g^{5\%}$	$Y_g^{50\%}$	$Y_g^{95\%}$
...				

* Prediction Interval(PI) of each bin is 5% percentile and 95% percentile

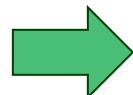
VPC : Visual Predictive Checks (3)

Step 3: find PI of the simulation data

Find 5%, 50%, 95% percentile of

$$\{Y_{ij}^{sim(k)} \mid t_{ij} \in T_g, i = 1, \dots, m, j = 1, \dots, n_i, k = 1, \dots, K\}$$

for each $g=1, \dots, G$



g	5% percentile	50% percentile	95% percentile
1			
2	$Y_g^{sim,5\%}$	$Y_g^{sim,50\%}$	$Y_g^{sim,95\%}$
...			
G			

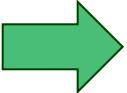
VPC : Visual Predictive Checks (4)

Step 4: find CI of 5%, 50%, and 95% percentile of the simulation data (1)

Find 5%, 50%, 95% percentile of

$$\{Y_{ij}^{sim(k)} \mid t_{ij} \in T_g, i = 1, \dots, m, j = 1, \dots, n_i\}$$

for each $g=1, \dots, G$ and each $k=1, \dots, K$

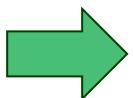


		5% percentile				50% percentile				95% percentile						
		k	1	2	...	K	k	1	2	...	K	k	1	2	...	K
		g					g					g				
		1					1					1				
		2		$Y_{gk}^{5\%}$			2		$Y_{gk}^{50\%}$			2		$Y_{gk}^{95\%}$		
					
		G					G					G				

VPC : Visual Predictive Checks (5)

Step 4: find CI of 5%, 50%, and 95% percentile of the simulation data (2)

		5% percentile				
		k	1	2	...	K
g						
1						
2				$Y_{gk}^{5\%}$		
...						
G						



Find 2.5% and 97.5% percentile
of $\{Y_{gk}^{5\%} \mid k = 1, \dots, K_i\}$

CI of 5% percentile of the simulation data

g	2.5% percentile	97.5% percentile
1		
2	$LY_g^{sim, 5\%}$	$UY_g^{sim, 5\%}$
...		
G		

VPC : Visual Predictive Checks (6)

- * Repeat this procedure for 50% and 95% percentile

CI of 50% percentile of the simulation data

g	2.5% percentile	97.5% percentile
1		
2	$LY_g^{sim,50\%}$	$UY_g^{sim,50\%}$
...		
G		

CI of 95% percentile of the simulation data

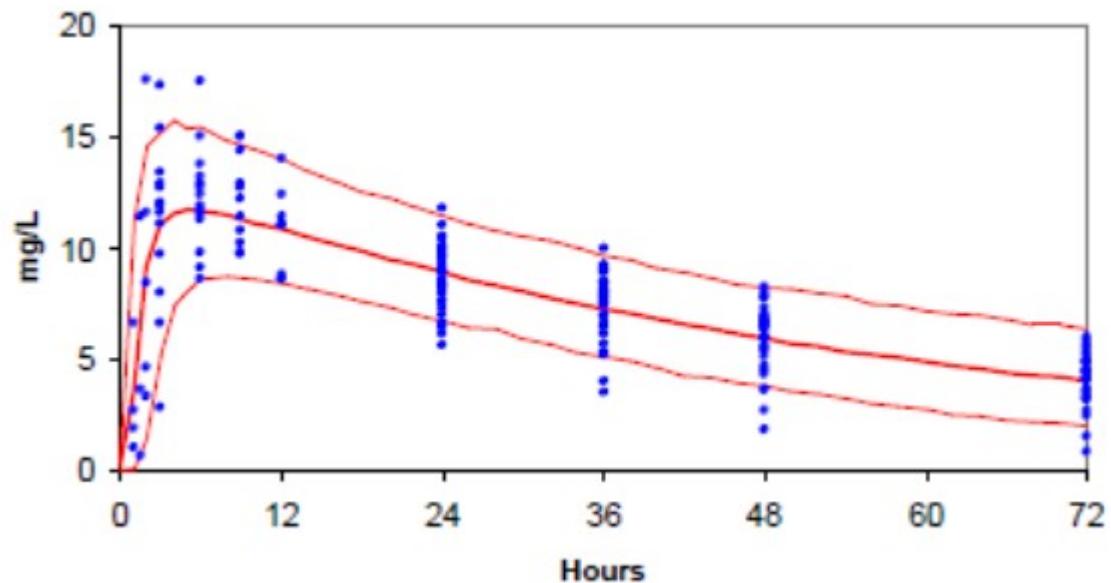
g	2.5% percentile	97.5% percentile
1		
2	$LY_g^{sim,95\%}$	$UY_g^{sim,95\%}$
...		
G		

VPC : Visual Predictive Checks (7)

Scatter VPC

Make scatter plot of t_{ij} and y_{ij} with 3 lines

- t_g vs. $Y_g^{5\%}$
- t_g vs. $Y_g^{50\%}$
- t_g vs. $Y_g^{95\%}$



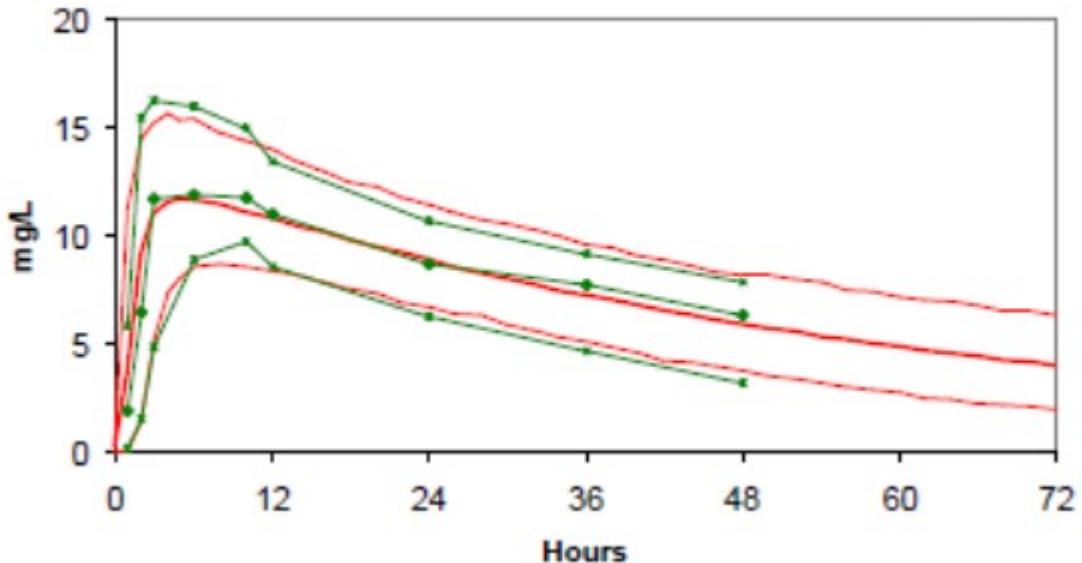
Source: <http://www.page-meeting.org/?abstract=1434>

VPC : Visual Predictive Checks (8)

Percentile VPC

Make plot with 6 lines

- t_g vs. $Y_g^{5\%}$
- t_g vs. $Y_g^{50\%}$
- t_g vs. $Y_g^{95\%}$
- t_g vs. $Y_g^{sim,5\%}$
- t_g vs. $Y_g^{sim,50\%}$
- t_g vs. $Y_g^{sim,95\%}$



Source: <http://www.page-meeting.org/?abstract=1434>

VPC : Visual Predictive Checks (9)

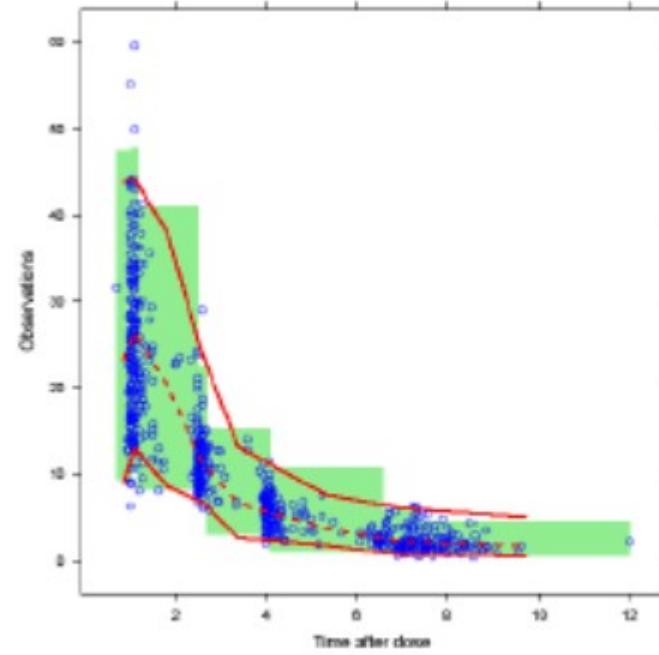
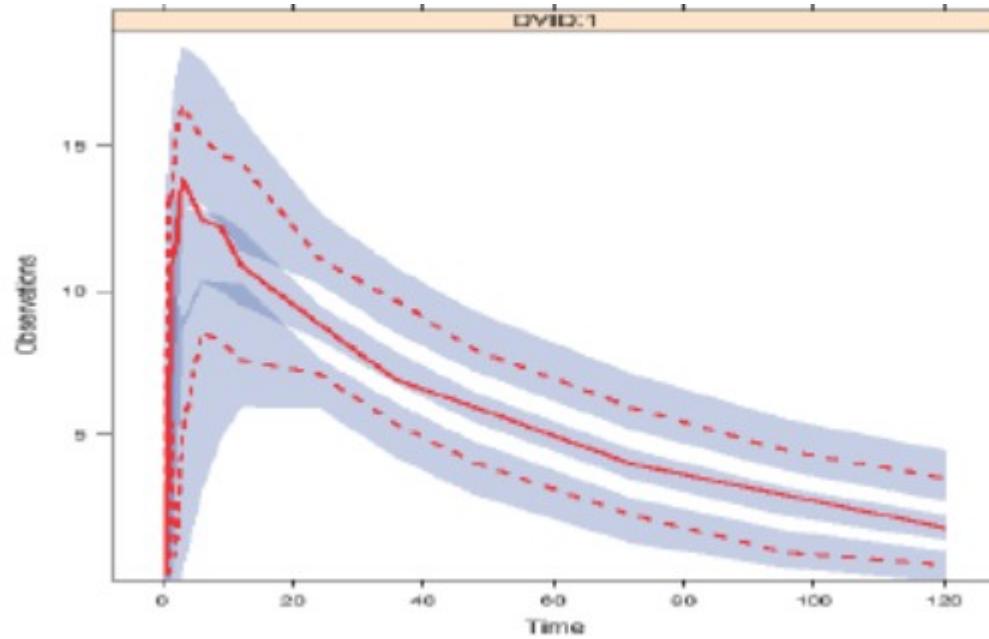
Confidence Interval VPC

Make plot with 3 lines and 3 areas

- t_g vs. $Y_g^{5\%}$: line
- t_g vs. $Y_g^{50\%}$: line
- t_g vs. $Y_g^{95\%}$: line
- t_g vs. $LY_g^{sim,5\%}$ and $UY_g^{sim,5\%}$: area
- t_g vs. $LY_g^{sim,50\%}$ and $UY_g^{sim,50\%}$: area
- t_g vs. $LY_g^{sim,95\%}$ and $UY_g^{sim,95\%}$: area

VPC : Visual Predictive Checks (10)

Confidence Interval VPC



Source: <http://www.page-meeting.org/?abstract=1434>

VPC : Visual Predictive Checks (11)

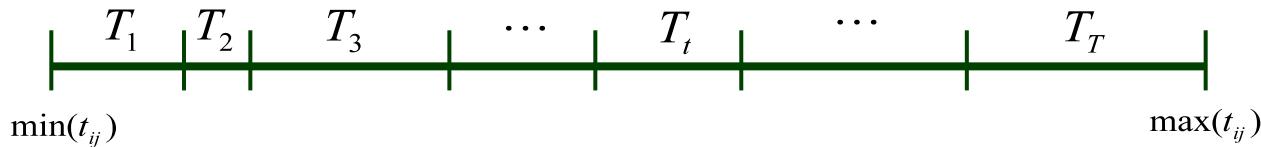
Handle covariate in VPC

- Need to use stratification of covariate
- For each strata, draw VPC plot
- Pros
 - Allows subset of data/model to be inspected
 - Can increase resolution of model misspecification
- Cons
 - Can dilute the signal
 - Multiple plot makes diagnostics complex
- Use prediction correction

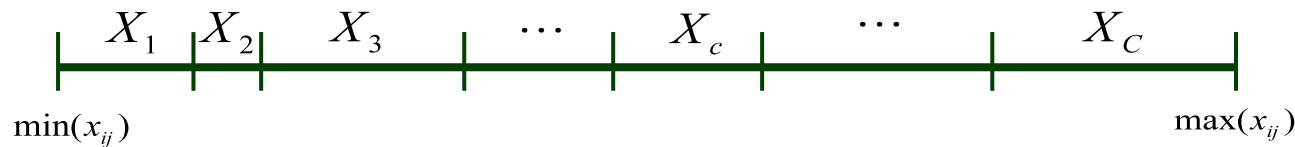
Prediction Correction (1)

Step 1: Binning TIME/Covariate data

Make T intervals with $\{t_{ij} \mid i = 1, \dots, m, j = 1, \dots, n_i\}$



Make C intervals with $\{x_{ij} \mid i = 1, \dots, m, j = 1, \dots, n_i\}$



Overall number of bins:
 $G = T * C$

c	t	T_1	T_2	\dots	T_T
x_1	G_1	G_2	\dots	G_T	
x_2		G_{T+1}			
\dots		\dots			
x_C			\dots	G_G	

Prediction Correction (2)

Step 2: Calculate pcVPC(prediction-corrected VPC)

$$pcY_{ij} = lb_{ij} + (Y_{ij} - lb_{ij}) \left(\frac{\tilde{PRED}_{bin,g} - lb_{ij}}{PRED_{ij} - lb_{ij}} \right)$$

$$pcY_{ij}^{sim(k)} = lb_{ij} + (Y_{ij}^{sim(k)} - lb_{ij}) \left(\frac{\tilde{PRED}_{bin,g} - lb_{ij}}{PRED_{ij} - lb_{ij}} \right)$$

where lb_{ij} : lower bound of y_{ij} from PRED

$\tilde{PRED}_{bin,g}$: med(PRED_{ij} in bin g)

$PRED_{ij}$: typical model prediction

Prediction Correction (3)

Step 3: calculate pvcVPC(prediction- and variability-corrected VPC)

$$pvcY_{ij} = \tilde{PRED}_{bin,g} + (pcY_{ij} - \tilde{PRED}_{bin,g}) \left(\frac{\tilde{sd}(pcY_{ij})_{bin,g}}{sd(pcY_{ij})} \right)$$

$$pvcY_{ij}^{sim(k)} = \tilde{PRED}_{bin,g} + (pcY_{ij}^{sim(k)} - \tilde{PRED}_{bin,g}) \left(\frac{\tilde{sd}(pcY_{ij})_{bin,g}}{sd(pcY_{ij})} \right)$$

where $pc\bar{Y}_{ij}^{sim} = \frac{1}{K} \sum_{k=1}^K pcY_{ij}^{sim(k)}$

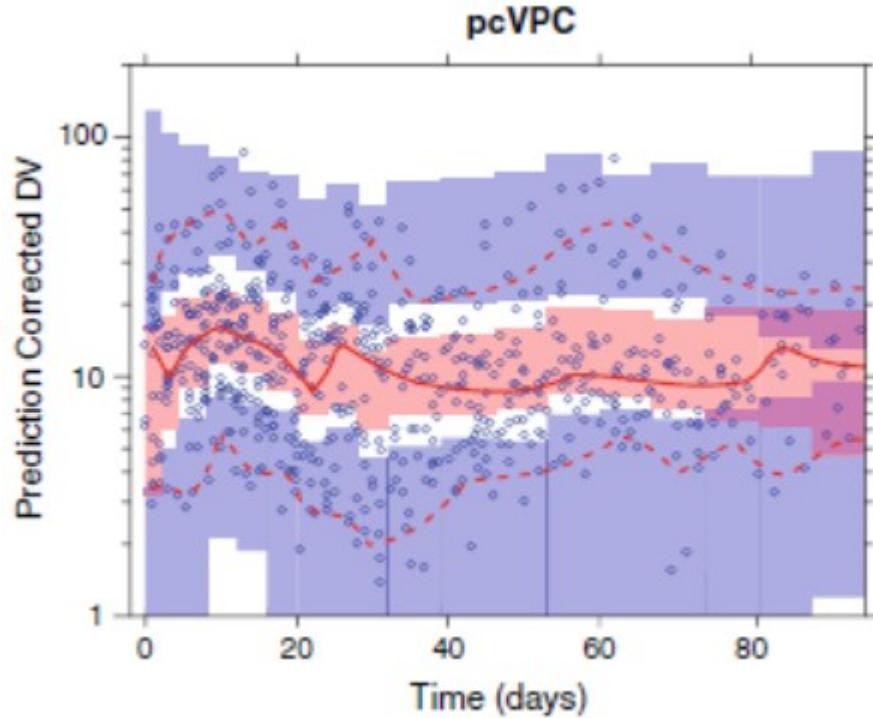
$$sd(pcY_{ij}) = \sqrt{\frac{1}{K-1} \sum_{k=1}^K (pcY_{ij}^{sim(k)} - pc\bar{Y}_{ij}^{sim})^2}$$

$$\tilde{sd}(pcY_{ij})_{bin,g} = median(sd(pcY_{ij}) \text{ in bin } g)$$

Prediction Correction (4)

Step 4: plot pcVPC and pvcVPC

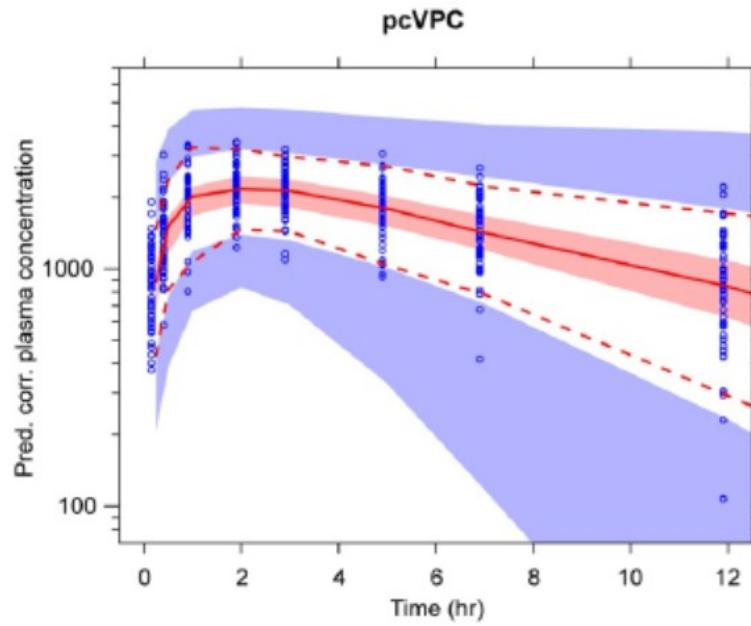
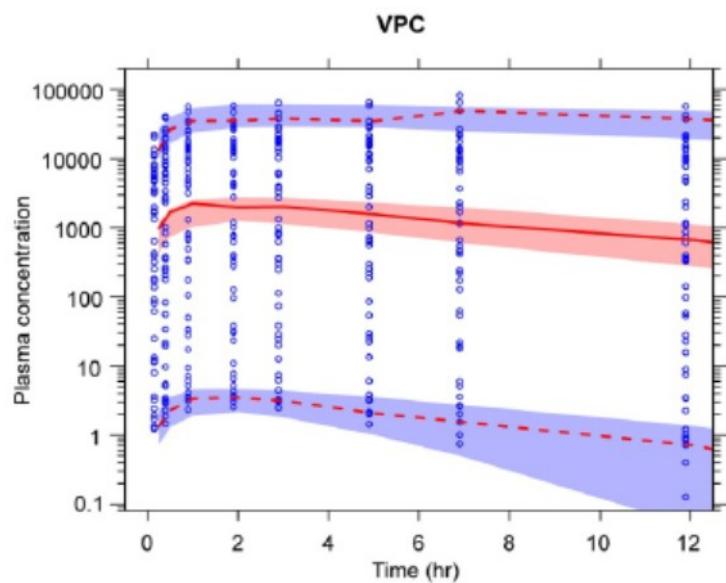
- Combine all bins and draw one plot in the same manner of VPC
- Use pcY_{ij} / $pvcY_{ij}$ instead of Y_{ij}



Source: AAPS Journal(2013), Vol.13(2) 143-151

Prediction Correction (4)

VPC vs. pcVPC



Source: AAPS Journal(2013), Vol.13(2) 143-151

QVPC/BVPC (1)

Data

Y_{ij} : observed value, i th subject j th observation
(including missing) $i = 1, \dots, m, \quad j = 1, \dots, n_i$

t_{ij} : observed time of i th subject j th observation

$$N = \sum_i n_i = N_a + N_u \quad \begin{aligned} N_a &: \# \text{ of available data} \\ N_u &: \# \text{ of missing data} \end{aligned}$$

Rearranged Data

$$Y_{i^*, t}^R \quad t \in \text{unique} \left\{ t_{ij}, i = 1, \dots, m, j = 1, \dots, n_i \right\}$$

$$i^* = 1, \dots, N_t = 1, \dots, n_{a,t}, n_{a,t} + 1, \dots, N_t$$

$$\sum_t N_t = \sum_t (n_{a,t} + n_{u,t}) = N \quad \sum_t n_{a,t} = N_a, \quad \sum_t n_{u,t} = N_u$$

QVPC/BVPC(2)

Simulated Data from model

$$Y_{i^*, t}^{R, sim(k)} \quad k = 1, \dots, K \\ i^* = 1, \dots, n_{a,t} \\ t \in \text{unique} \left\{ t_{ij}, i = 1, \dots, m, j = 1, \dots, n_i \right\}$$

Bootstrap sample from data

$$Y_{i^*, t}^{R, B(k)} \quad k = 1, \dots, K \\ i^* = 1, \dots, n_{a,t} \\ t \in \text{unique} \left\{ t_{ij}, i = 1, \dots, m, j = 1, \dots, n_i \right\}$$

QVPC/BVPC(3)

Quantified VPC

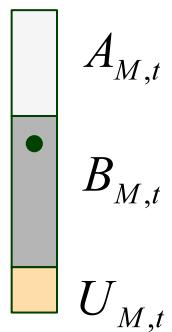
1. Find $M_t = \text{median} \left\{ Y_{i^*,t}^{R,\text{sim}(k)}, i^* = 1, \dots, n_{a,t}, k = 1, \dots, K \right\}$

2. Calculate

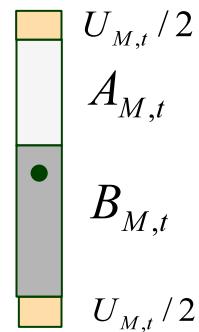
$$A_{M,t} = \sum_{i^*} I(Y_{i^*,t}^R \geq M_t) / N * 100, \quad B_{M,t} = \sum_{i^*} I(Y_{i^*,t}^R < M_t) / N * 100$$

$$U_{M,t} = 100 - (A_{M,t} + B_{M,t})$$

3. For each t, draw parallel boxes

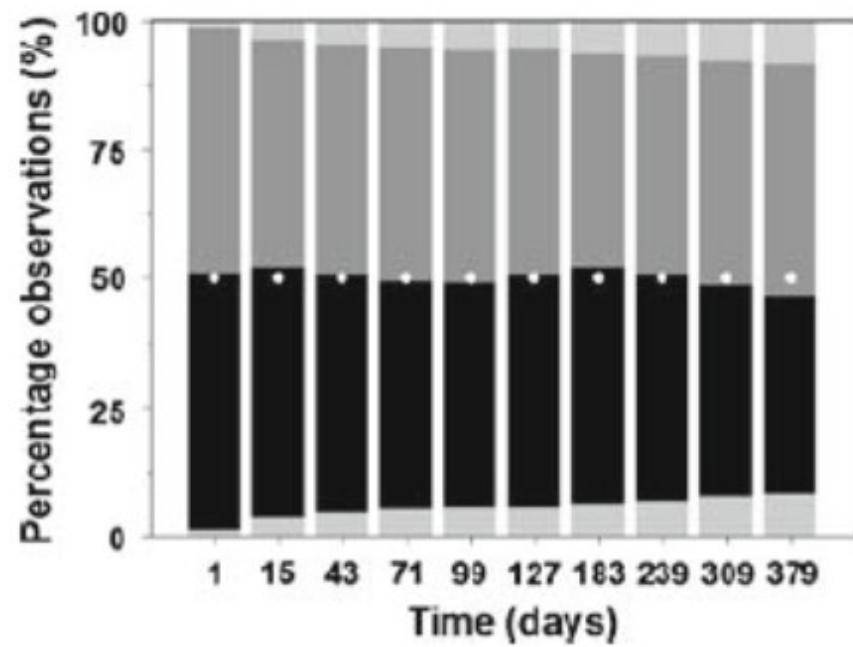
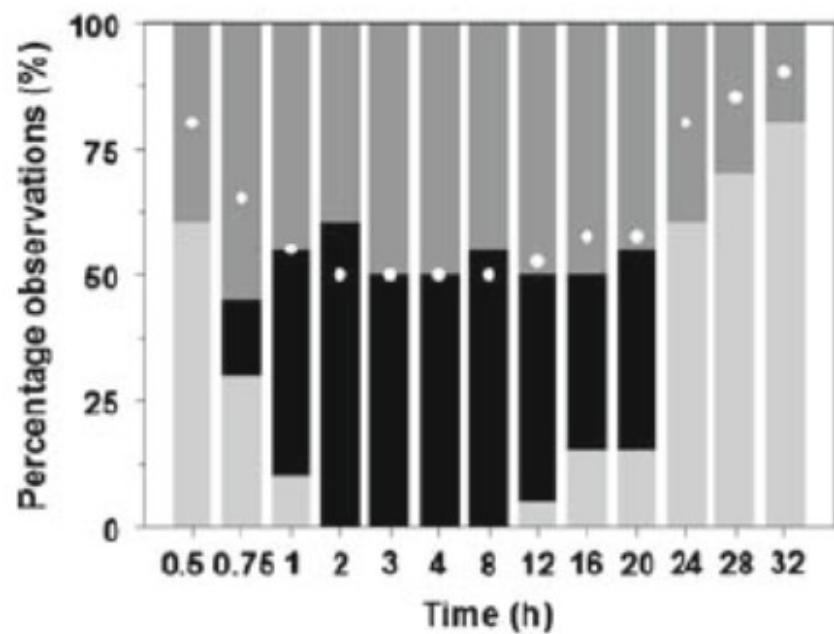


or



QVPC/BVPC(3)

Quantified VPC



Source: J. Pharmacokinet Pharmacodyn(2008), Vol.35:185-202

QVPC/BVPC(4)

Bootstrap VPC

1. If $N_u \neq 0$, impute $Y_{i^*,t}^{R,B(k)}$ with $\min/\max \{Y_{i^*,t}^R, i = 1, \dots, n_{a,t}\}$
 $i^* = n_{a,t} + 1, \dots, n_t$
2. Find $\text{median} \{Y_{i^*,t}^{R,B(k)}, i^* = 1, \dots, N_t\}$ for each t and k

	k	1	2	...	K
t					
1					
2			Y_{tk}^{med}		
...					

QVPC/BVPC(5)

Bootstrap VPC

3. Find 5%, 50%, 95% percentile of

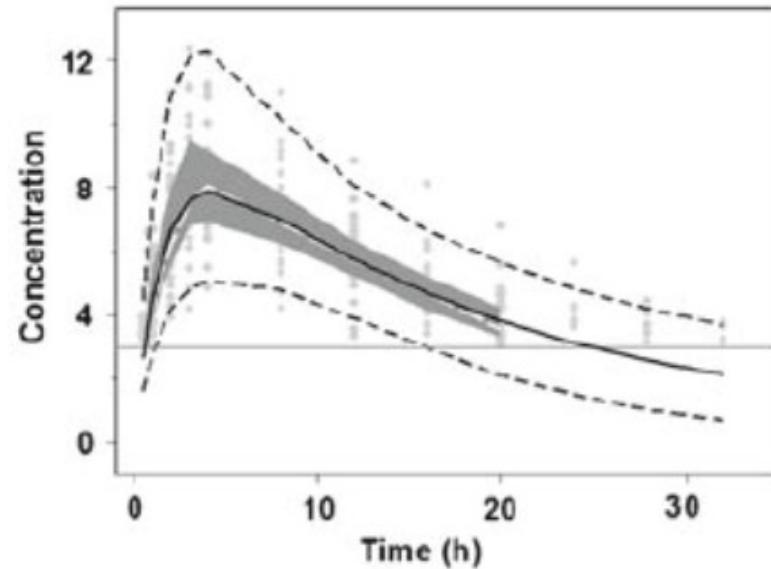
$$\left\{ Y_{t,k}^{med}, k = 1, \dots, K, t \in \text{unique} \left\{ t_{ij}, i = 1, \dots, m, j = 1, \dots, n_i \right\} \right\}$$

t	5% percentile	50% percentile	95% percentile
1			
2	$Y_t^{5\%}$	$Y_t^{50\%}$	$Y_t^{95\%}$
...			

QVPC/BVPC(6)

Bootstrap VPC

4. Draw scatter VPC plot
and draw area with $(t, Y_t^{5\%})$ and $(t, Y_t^{95\%})$
and draw line with $(t, Y_t^{50\%})$



Shiny : Visual Predictive Check

Visual Predictive Check

Original data
 PK-orig.csv
Upload complete

Simulation data
 PK-sim.csv
Upload complete

Number of simulation

Original data with PRED
 PK-orig-pred.csv
Upload complete

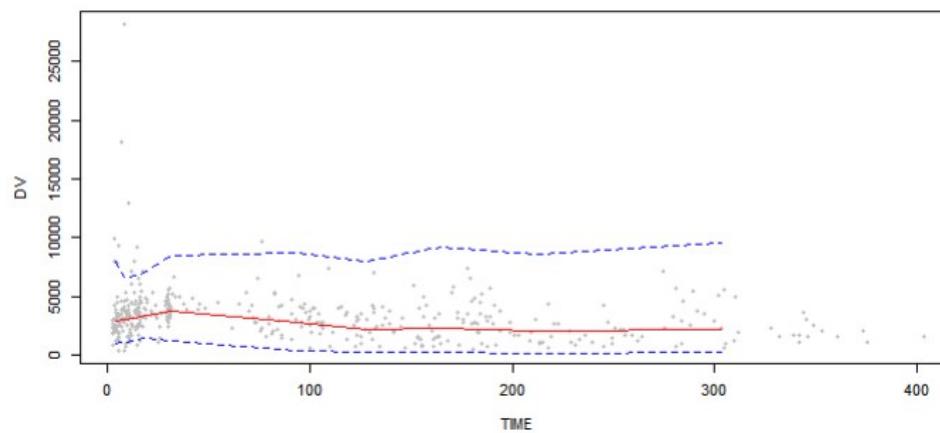
VPC type

- Scatter VPC
- Percentile VPC
- Confidence Interval VPC
- QVPC
- pcVPC
- pvcVPC

Number of TIME stratification

Choose one covariate

Number of COV stratification



Shiny : Visual Predictive Check

Visual Predictive Check

Original data

[파일 선택] PK-orig.csv

Upload complete

Simulation data

[파일 선택] PK-sim.csv

Upload complete

Number of simulation

100

Original data with PRED

[파일 선택] PK-orig-pred.csv

Upload complete

VPC type

- Scatter VPC
- Percentile VPC
- Confidence Interval VPC
- QVPC
- pcVPC
- pvcVPC

Number of TIME stratification

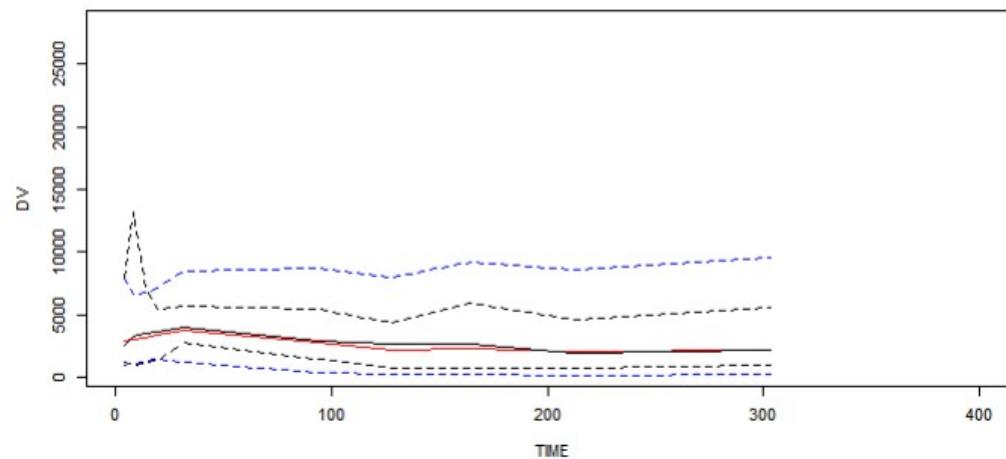
10

Choose one covariate

NONE

Number of COV stratification

0



Shiny : Visual Predictive Check

Visual Predictive Check

Original data
 PK-orig.csv
Upload complete

Simulation data
 PK-sim.csv
Upload complete

Number of simulation
100

Original data with PRED
 PK-orig-pred.csv
Upload complete

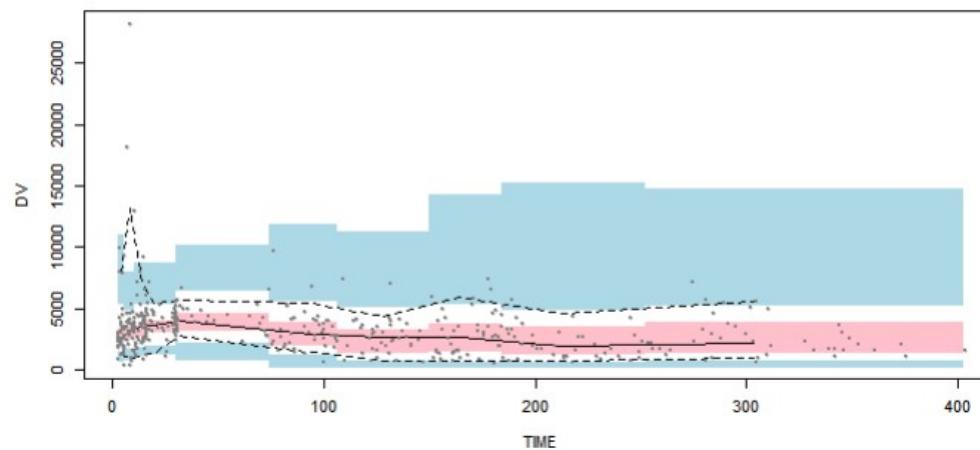
VPC type

- Scatter VPC
- Percentile VPC
- Confidence Interval VPC
- QVPC
- pcVPC
- pvcVPC

Number of TIME stratification
10

Choose one covariate

Number of COV stratification
0



Shiny : Visual Predictive Check

Visual Predictive Check

Original data
 PK-orig.csv
Upload complete

Simulation data
 PK-sim.csv
Upload complete

Number of simulation
100

Original data with PRED
 PK-orig-pred.csv
Upload complete

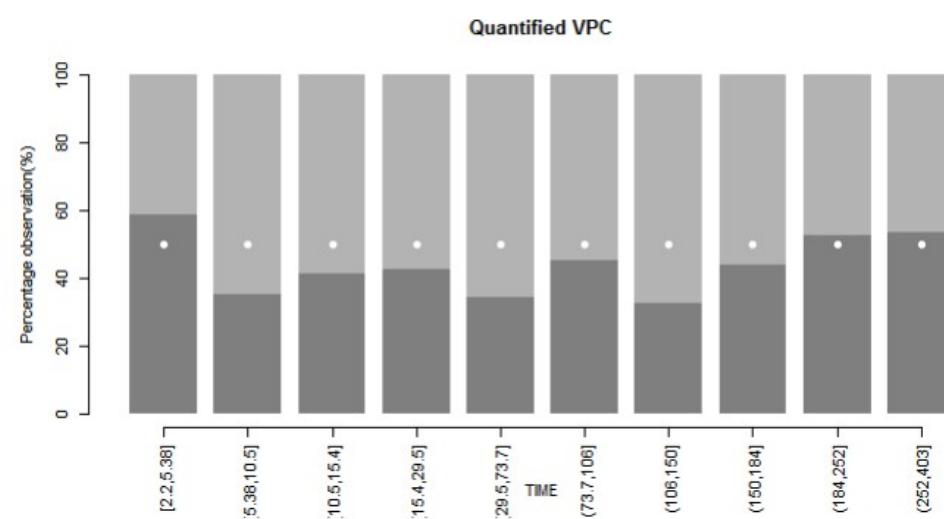
VPC type

- Scatter VPC
- Percentile VPC
- Confidence Interval VPC
- QVPC
- pcVPC
- pvcVPC

Number of TIME stratification
10

Choose one covariate
NONE

Number of COV stratification
0



Shiny : Visual Predictive Check

Visual Predictive Check

Original data
 PK-orig.csv

Simulation data
 PK-sim.csv

Number of simulation
100

Original data with PRED
 PK-orig-pred.csv

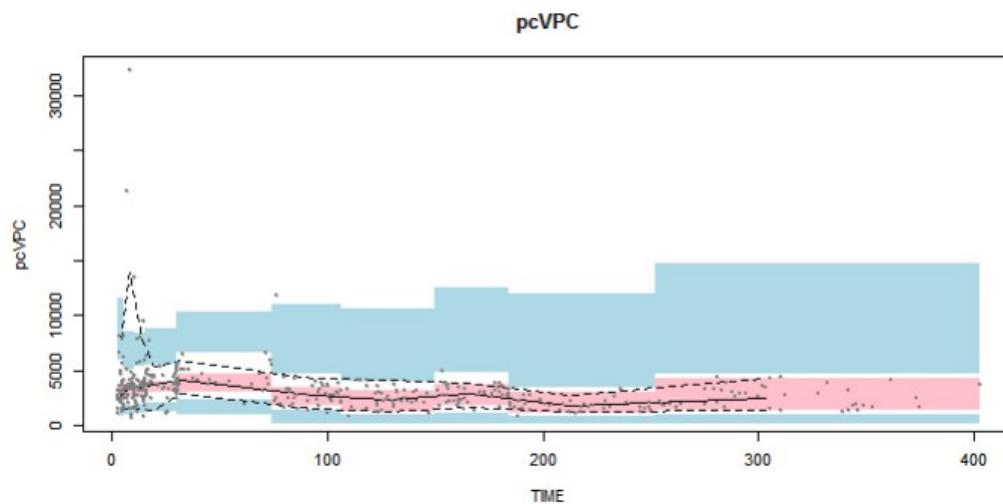
VPC type

- Scatter VPC
- Percentile VPC
- Confidence Interval VPC
- QVPC
- pcVPC
- pvcVPC

Number of TIME stratification
10

Choose one covariate

Number of COV stratification
0



Shiny : Visual Predictive Check

Visual Predictive Check

Original data
 PK-orig.csv

Simulation data
 PK-sim.csv

Number of simulation
100

Original data with PRED
 PK-orig-pred.csv

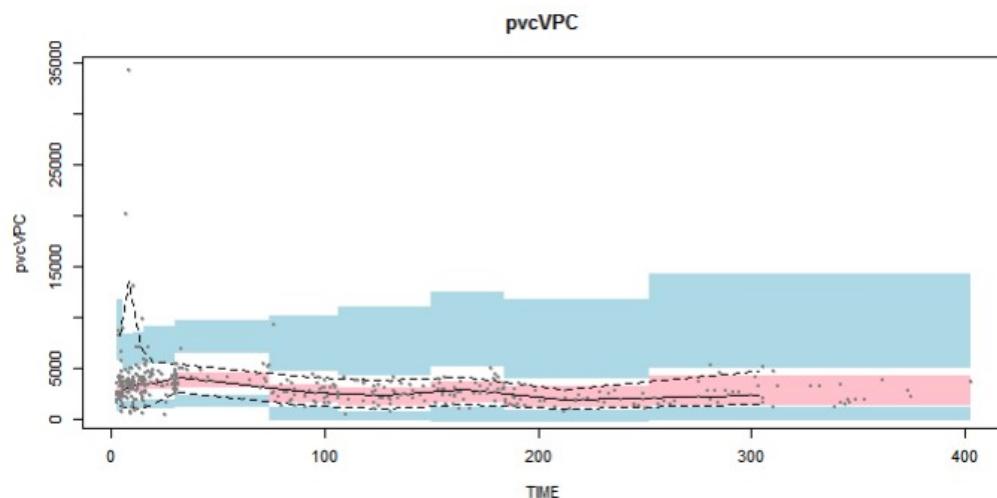
VPC type

- Scatter VPC
- Percentile VPC
- Confidence Interval VPC
- QVPC
- pcVPC
- pvcVPC

Number of TIME stratification
10

Choose one covariate

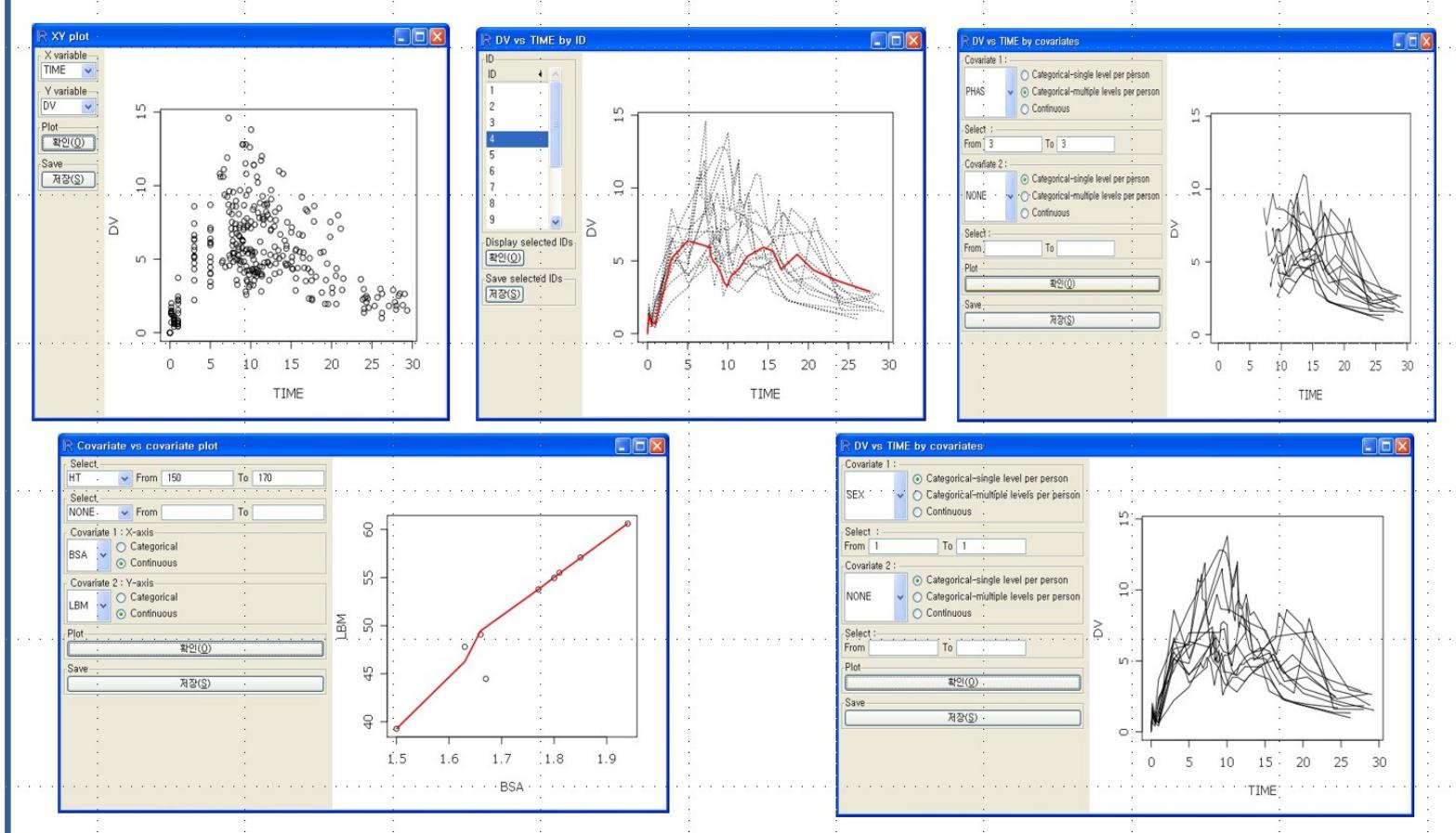
Number of COV stratification
2



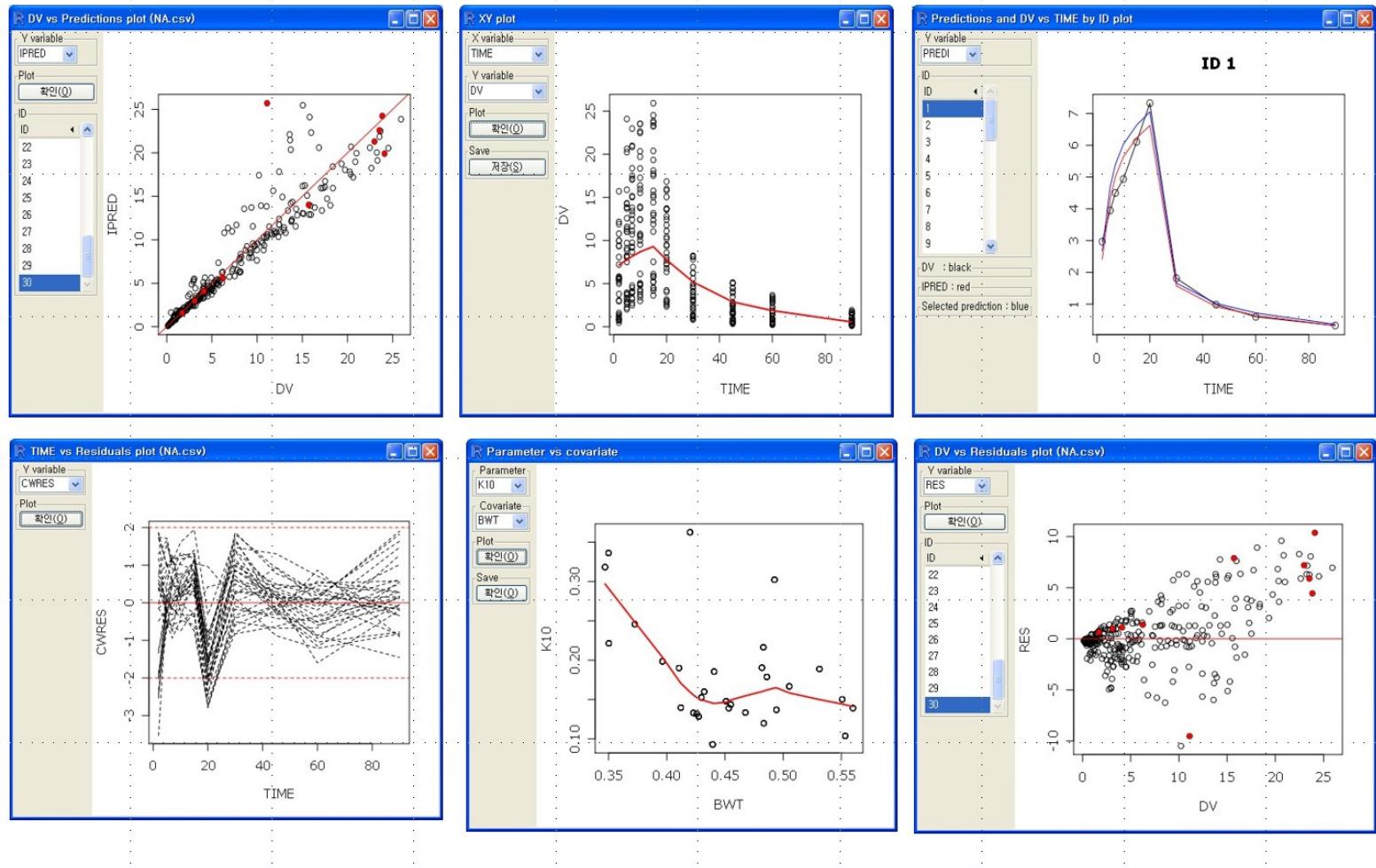
fit4NM main GUI

R GUI for NONMEM												
Run number	Date	Time	MIN	COV	OFV	AIC	AICc	SBC	Condition number	Parents	Model description	
1001	2010-09-09	오후 11:06	SUCCESSFUL	OK	254,184	292,184	294,53	365,156	-17541229385307346	ROOT		
1002	2010-09-09	오후 11:55	SUCCESSFUL	OK	184,047	222,047	224,507	294,172	-38311688311688320	ROOT		
100201	2010-09-11	오후 09:12	TERMINATED	NONE	251,677	289,677	292,145	361,744	NA	1002		
100202	2010-09-11	오후 09:30	SUCCESSFUL	NONE	246,488	284,488	286,964	356,497	NA	1002		
100203	2010-09-11	오후 09:38	SUCCESSFUL	NONE	199,7	237,7	240,184	309,651	NA	1002		
100204	2010-09-11	오후 10:15	SUCCESSFUL	OK	193,81	231,81	234,302	303,703	-18787128712871288	1002		
1002041	2010-09-11	오후 10:28	SUCCESSFUL	NONE	186,136	226,136	228,899	301,813	NA	100204		
1002042	2010-09-11	오후 10:32	TERMINATED	NONE	193,815	233,815	236,578	309,492	NA	100204		
1002043	2010-09-11	오후 10:39	SUCCESSFUL	OK	195,038	233,038	235,53	304,931	-1.72e+16	100204		
100211	2010-09-12	PM 04:23	SUCCESSFUL	NONE	186,148	224,148	226,673	295,805	NA	1002		
1002111	2010-09-12	PM 04:30	SUCCESSFUL	OK	185,465	223,465	225,99	295,122	-12692307692307692	100211		
1002112	2010-09-12	PM 04:37	SUCCESSFUL	OK	186,148	222,148	224,413	290,034	-16992084432717680	100211		

Plots



Plots



Calculate elapsed time Join / Split data

Calculate elapsed time

Open reference time file #ID, DATE0 (yyyy-mm-dd), TIME0 (h:mm:ss) : F:\Rpackage-test\#Data\#DataManipulation\#CalcElapsedTime\setTIME.csv

Select data folder #ID, DATE (yyyy-mm-dd), TIME (h:mm:ss)... after data split by ID

Select time unit: secs

Calculate and save as csv

setTIME

#ID	TIME0
1	2010-06-23 14:08
2	2010-06-23 14:08
3	2010-06-23 14:09

elapsedtime-result

#ID	TIME	BIS	SQI
1	-20	97.5	34.3
2	-15	97.4	30
3	-10	97.3	34.3
4	-5	97.2	31.4
5	0	97.1	27.1
6	5	97.1	27.1
7	10	97	32.9
8	15	96.1	47.1
9	20	95.6	51.9
10	25	94.7	57.1

DATE0

#ID	TIME	BIS	SQI	DATE
2	14:07:55	97.5	34.3	2010-06-23
3	14:08:00	97.4	30	2010-06-23
4	14:08:05	97.3	34.3	2010-06-23
5	14:08:10	97.2	31.4	2010-06-23
6	14:08:15	97.1	27.1	2010-06-23
7	14:08:20	97.1	27.1	2010-06-23

Join / Split data

Left side: Input CSV files (l211-1, l211-2)

Right side: Output CSV files (l211-3, l211-4)

Process: Join / Split

Join / Split dialog box:

- Level 1: X.ID
- Level 2: NONE
- Split: 확인(O)

l211-1

#ID	TIME	AMT	RATE	DV	MOV	LWD	BNT
1	1	0	5/053	0.25265	0	1	0/053
3	1	5		3.9524	0	0	0/053
4	1	7		4.09444	0	0	0/053
5	1	10		4.3053	0	0	0/053
6	1	40		0.32739	0	0	0/053
7	2	0	4/833	0.24165	0	1	0/4833

l211-2

#ID	TIME	AMT	RATE	DV	MOV	LWD	BNT
2	1	0	5/053	0.25265	0	1	0/053
3	1	2		2.96671	0	0	0/053
4	1	5		3.9524	0	0	0/053
5	1	7		4.09444	0	0	0/053
6	1	10		4.3053	0	0	0/053
7	1	15		6.10644	0	0	0/053
8	1	20					
9	1	30					
10	1	45					
11	1	60					
12	1	90					

l211-3

#ID	TIME	AMT	RATE	DV	MOV	LWD	BNT
2	2	0	4/833	0.24165	0	1	0/4833
3	2	2	NA	1.0773	0	0	0/4833
4	2	5	NA	2.83252	0	0	0/4833
5	2	7	NA	4.04699	0	0	0/4833
6	2	10	NA	6.12401	0	0	0/4833
7	2	15	NA	7.1582	0	0	0/4833
8	2	20	NA	7.32311	0	0	0/4833
9	2	30	NA	1.834703	0	0	0/4833
10	2	45	NA	0.082682	0	0	0/4833
11	2	60	NA	0.59827	0	0	0/4833
12	2	90	NA	0.32739	0	0	0/4833

l211-4

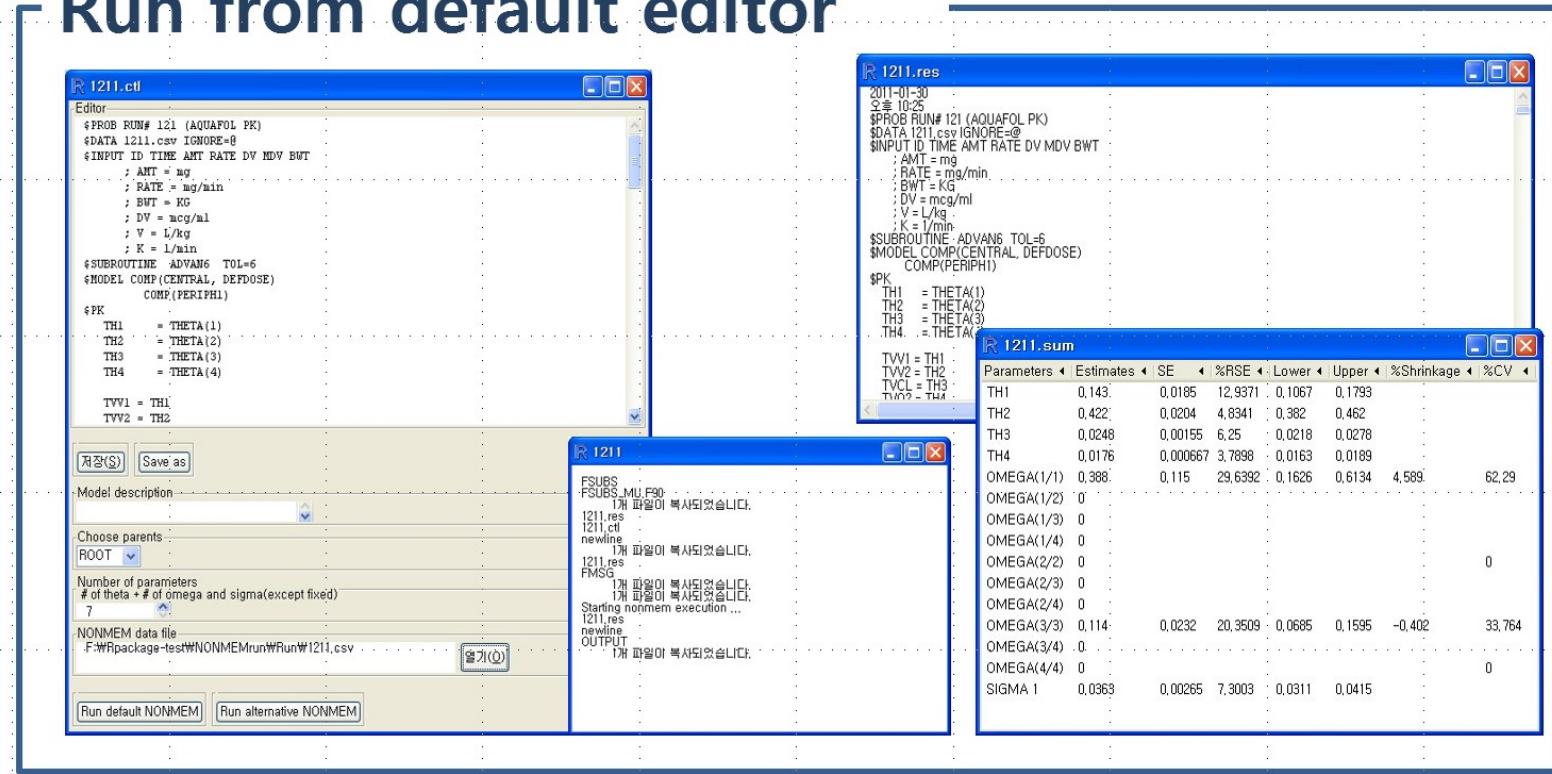
#ID	TIME	AMT	RATE	DV	MOV	LWD	BNT
2	1	0	5/053	0.25265	0	1	0/053
3	1	2	NA	3.9524	0	0	0/053
4	1	5	NA	4.09444	0	0	0/053
5	1	7	NA	4.3053	0	0	0/053
6	1	10	NA	6.10644	0	0	0/053
7	1	15	NA	7.1582	0	0	0/053
8	1	20	NA	7.32311	0	0	0/053
9	1	30	NA	1.834703	0	0	0/053
10	1	45	NA	0.082682	0	0	0/053
11	1	60	NA	0.59827	0	0	0/053
12	1	90	NA	0.32739	0	0	0/053

Create NONMEM data

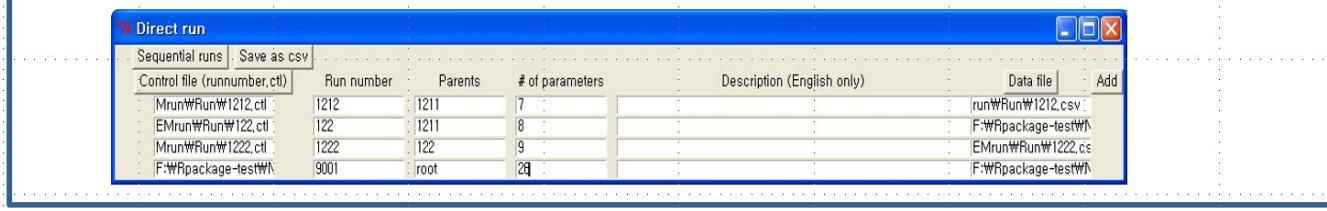
The screenshot shows the RStudio interface with four windows:

- Aquafo_PK**: A data frame with columns #ID, TIME, AMT, RATE, DUR, DRUG, DV, and M.
- Demog**: A data frame with columns #ID, AGE, SEX, HT, WT, BSA, and LBM.
- DV1**: A data frame with columns #ID, TIME, and DV.
- NM data preparation for PREDPP**: A dialog box for selecting datasets:
 - Demographics (#ID, covariates): F:\Rpackage-test\#Data\#NONMEM data\#Demog.csv
 - iPK (#ID, iPK): F:\Rpackage-test\#Data\#NONMEM data\#Adm.csv
 - Dosing (#ID, TIME (elapse), AMT, RATE): F:\Rpackage-test\#Data\#NONMEM data\#Dosing.csv
 - DV (#ID, TIME (elapse), DV): F:\Rpackage-test\#Data\#NONMEM data\#DV1.csv
 Buttons include Select, Combine, and Save.
- nonmem-final**: A data frame combining all selected data into a single structure with columns #ID, TIME, AMT, RATE, DUR, DRUG, DV, MDV, AGE, SEX, HT, WT, BSA, and LBM.

Run from default editor



Direct run

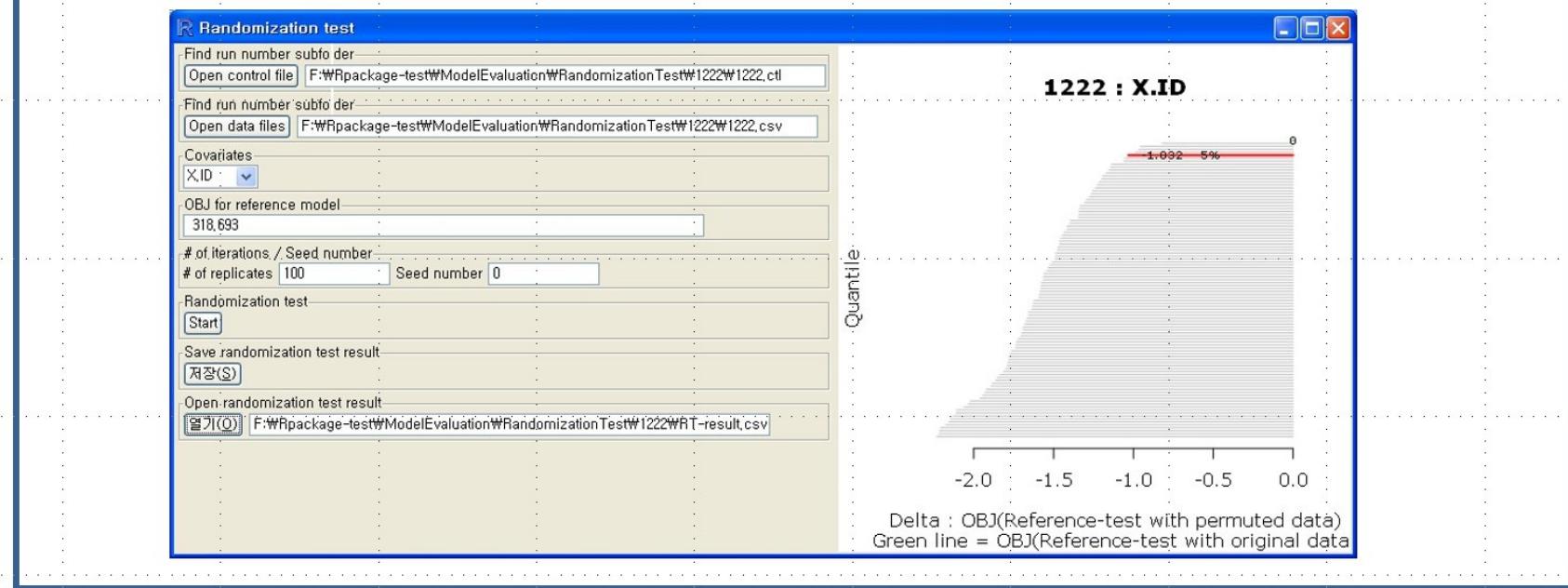


Bootstrap

The screenshot shows the R Bootstrap interface with two windows. The left window is the 'Bootstrap' dialog, which includes fields for 'Open control file' (F:\Rpackage-test\ModelEvaluation\Bootstrap\1211\1211.ctl), 'Open data files' (F:\Rpackage-test\ModelEvaluation\Bootstrap\1211\1211.csv), 'Number of bootstrap replicates / Seed number' (# of replicates: 100, Seed number: 0), and buttons for 'Start bootstrap', 'Save bootstrap raw data as csv', 'Save bootstrap summary data as csv', and 'Summary data from joined bootstrap raw data file (Prob,Obj,Min,COV,EST,SE)'. The right window is the 'Bootstrap Summary' table, which displays statistical estimates for various parameters across two conditions: 'All' and 'Min success'. The table includes columns for Condition, Parameter, Estimates, Mean, SD, Median, 2.5%, and 97.5%.

Condition	Parameter	Estimates	Mean	SD	Median	2.5%	97.5%
All	THETA(1)	0.143	0.14077	0.018374804334834	0.1395	0.10995	0.179
	THETA(2)	0.422	0.42207	0.01954908610848	0.422	0.3869	0.459575
	THETA(3)	0.0248	0.024732	0.00156915051328205	0.02455	0.021595	0.0277575
	THETA(4)	0.0176	0.01757	0.000646904048901264	0.0176	0.0164475	0.0189
	OMEGA(1/1)	0.388	0.41605	0.106709212632303	0.422	0.222025	0.65175
	OMEGA(1/2)	0	0	0	0	0	0
	OMEGA(1/3)	0	0	0	0	0	0
	OMEGA(1/4)	0	0	0	0	0	0
	OMEGA(2/2)	0	0	0	0	0	0
	OMEGA(2/3)	0	0	0	0	0	0
	OMEGA(2/4)	0	0	0	0	0	0
	OMEGA(3/3)	0.114	0.11526	0.0235477936516054	0.1135	0.0747125	0.164725
	OMEGA(3/4)	0	0	0	0	0	0
	OMEGA(4/4)	0	0	0	0	0	0
	SIGMA(1/1)	0.0363	0.036557	0.00265578293037827	0.03615	0.032295	0.0419525
Min success	THETA(1)	0.143	0.14077	0.018374804334834	0.1395	0.10995	0.179
	THETA(2)	0.422	0.42207	0.01954908610848	0.422	0.3869	0.459575
	THETA(3)	0.0248	0.024732	0.00156915051328205	0.02455	0.021595	0.0277575
	THETA(4)	0.0176	0.01757	0.000646904048901264	0.0176	0.0164475	0.0189
	OMEGA(1/1)	0.388	0.41605	0.106709212632303	0.422	0.222025	0.65175
	OMEGA(1/2)	0	0	0	0	0	0
	OMEGA(1/3)	0	0	0	0	0	0
	OMEGA(1/4)	0	0	0	0	0	0
	OMEGA(2/2)	0	0	0	0	0	0
	OMEGA(2/3)	0	0	0	0	0	0
	OMEGA(2/4)	0	0	0	0	0	0
	OMEGA(3/3)	0.114	0.11526	0.0235477936516054	0.1135	0.0747125	0.164725
	OMEGA(3/4)	0	0	0	0	0	0
	OMEGA(4/4)	0	0	0	0	0	0
	SIGMA(1/1)	0.0363	0.036557	0.00265578293037827	0.03615	0.032295	0.0419525

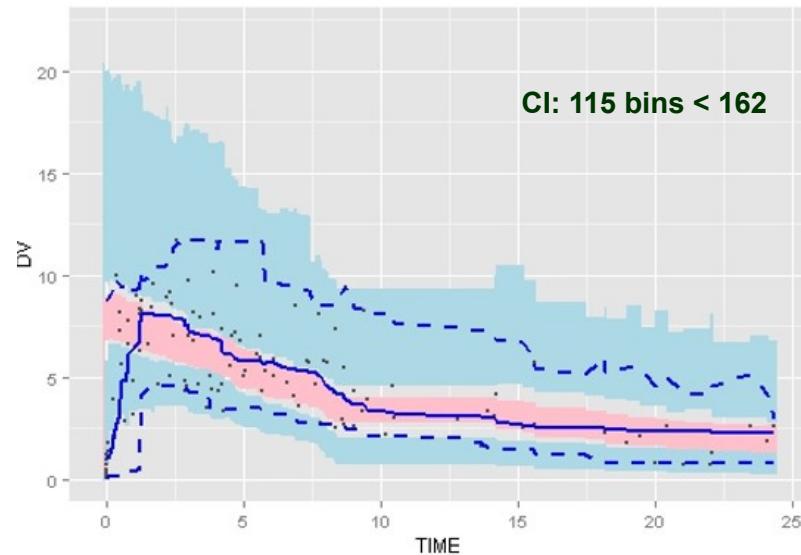
Randomization test



asVPC: example (6)

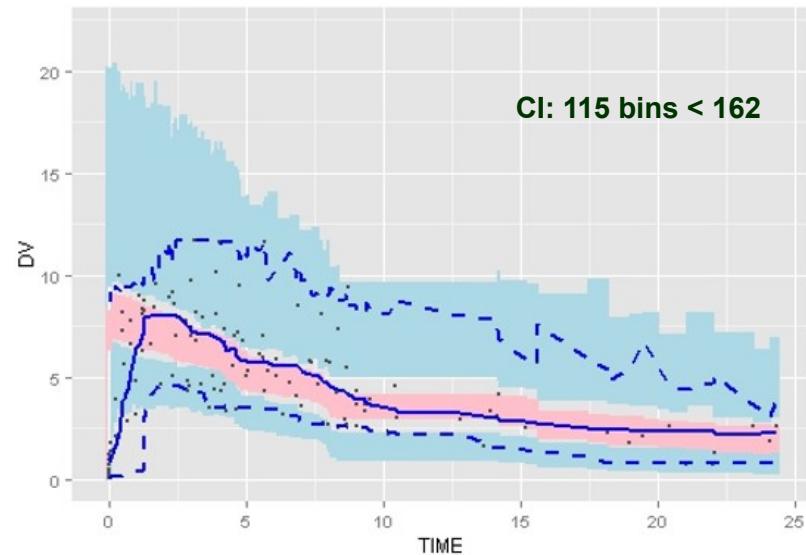
Bin-related weights

(a) # of bin=9/# of shifted=18



Distance-related weights

(b) # of bin=9/# of shifted=18



References

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Questions





Thank You !