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A general method for optimal design of individual and population univariate and multivariate pharmacokinetic experiments

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Introduction

- PK – Time course of concentration of drug and metabolites in body fluids
- PD – Collection of data to characterise pharmacological effects
  - surrogate marker, biomarker, enzyme activity or clinical endpoints
- Pharmacokinetic study – Univariate or Multivariate
  - Univariate – PK, PD
  - Multivariate – PK/PD, drug and metabolites, multi-drug (cancer and tuberculosis), multi-organ (WBPBPK)
- Pharmacokinetic multivariate study
  - Balanced
  - Unbalanced

Introduction

- Population pharmacokinetics (PPK) is widely used in drug development
- PPK study design – Elementary designs, sampling times, number of subjects
- Optimal PPK study design gives the best parameter estimates
- Two approaches to optimal design of PPK
  - Simulation
  - Model (FIM)– Cramer-Rao inequality, inverse of FIM lower bound of the variance-covariance of any unbiased estimator of the parameters
    - Prior knowledge about parameter/variability values - previous studies, pilot study
    - Optimise some criterion function of likelihood within given constraints, D-optimality: Minimise uncertainty associated with parameter estimates

Introduction - FIM

- Theory of experimental design – Fisher, 1920 Rothamsted Agricultural Experimental Station
  - Considerable amount of work on methodology and application especially in engineering
- PK models present peculiar problem - nonlinear models
  - Individual univariate PK models – FIM is defined
  - Individual multivariate – FIM is defined for balanced design
  - Population univariate – FIM is defined
  - Population multivariate - FIM is defined for balanced design

Aim

- Develop a general method for individual and population univariate and multivariate PK models that will address existing problems such
  - Unbalanced design – Individual and population multivariate
  - Covariance terms (off diagonal elements) in the omega – Population multivariate

FIM – Individual and Population Univariate

Fixed Effects (Individual)

$$y_j = f(\theta, t_j) + \varepsilon_j \quad j = 1,...n$$

Mixed Effects (Population)

$$y_{ij} = f(\theta_i, t_{ij}) + \varepsilon_{ij} \qquad j = 1,...n, i = 1,...., N$$

$$g(\theta, b_i) = \theta + b_i$$

$$\Omega = \begin{bmatrix} \omega_{11} & \omega_{12} & . \\ \omega_{12} & \omega_{22} & . \\ . & . & \omega_{pp} \end{bmatrix}$$

$$n_\omega = p(p+1)/2$$

$$F(\Psi, \xi_i) = E\left(-\frac{\partial^2 l(\Psi; y_i)}{\partial \Psi \partial \Psi^T}\right)$$

$$\Psi = [\theta_1,...., \theta_p, \sigma_1^2, \sigma_2^2]$$

$$\Psi = [\theta_1,...., \theta_p, \omega_{11}, \omega_{12},...., \omega_{1p}, \omega_{22}, \omega_{23},..., \omega_{2p}, \omega_{pp}, \sigma_1^2, \sigma_2^2]$$

$$F(\theta, \xi)_{ab} = \frac{\partial f(\theta, \xi)}{\partial \Psi_a}^T V^{-1} \frac{\partial f(\theta, \xi)}{\partial \Psi_b} + \frac{1}{2} tr\left(\frac{\partial V}{\partial \Psi_a} V^{-1} \frac{\partial V}{\partial \Psi_b} V^{-1}\right)$$

$$(p+2) \times (p+2)$$

$$V = diag(\sigma_1^2 + \sigma_2^2 f(\theta, \xi)^2)$$

$$(p + n_\omega + 2) \times (p + n_\omega + 2)$$

$$V \cong \frac{\partial f^T(\beta, \xi_i)}{\partial b^T} \Omega \frac{\partial f(\beta, \xi_i)}{\partial b^T} + diag(\sigma_1^2 + \sigma_2^2 f(\theta, \xi_i)^2)$$

FIM – Individual and Population Multivariate

Fixed Effects (Individual)

$$y_{mj} = f_m(\theta, t_j) + \varepsilon_{mj}$$

$$j = 1,...n, m = 1,...., M$$

$$y = \left[y_1^{'}, y_2^{'}, ..., y_M^{'}\right]^{'}$$

Mixed Effects (Population)

$$y_{imj} = f_m(\theta_i, t_{ij}) + \varepsilon_{imj}$$

$$j = 1,...n, m = 1,...., M, i = 1,...., N$$

$$y_i = \left[y_{i1}^{'}, y_{i2}^{'}, ..., y_{iM}^{'}\right]^{'}$$

$$\varepsilon_m \rightarrow \sigma_{m1}, \sigma_{m2}$$

$$\Sigma = \left\{\tau_{qm}\right\}_{1 \le q,m \le M}$$

$$\varepsilon \sim MVN(0, V)$$

$$V = \begin{bmatrix} V_{11} & . & V_{1M} \\ . & . & . \\ V_{M1} & . & V_{MM} \end{bmatrix} (M*n) \times (M*n)$$

$$\varepsilon_i \sim MVN(0, R_i)$$

$$R_i = \begin{bmatrix} R_{11} & . & R_{1M} \\ . & . & . \\ R_{M1} & . & R_{MM} \end{bmatrix} \quad (M*n) \times (M*n)$$

$$V_{qm}, R_{qm} \rightarrow n \times n$$

$$V_{qm}(j,l)\Big|_{j=l} = \left\{\tau_{qm^*} \sqrt{\left(\sigma_{q1}^2 + (\sigma_{q2}^2 * f_q(\theta, t_j)^2)\right) * \left(\sigma_{m1}^2 + (\sigma_{m2}^2 * f_m(\theta, t_j)^2)\right)}\right\}_{\substack{1 \le q,m \le M \\ 1 \le j,l \le n}}$$

$$V_{qm}(j,l)\Big|_{j \ne l} = \{0\}_{\substack{1 \le q,m \le M \\ 1 \le j,l \le n}}$$

FIM – Individual and Population Multivariate

Fixed Effects (Individual)

Mixed Effects (Population)

$$F(\Psi,\xi_i) = E\left(-\frac{\partial^2 l(\Psi;y_i)}{\partial\Psi\partial\Psi^T}\right)$$

$$\Psi = \left[\theta_1,.....,\theta_p,\sigma^2_{11},.....,\sigma^2_{1M},\sigma^2_{21},.....,\sigma^2_{2M}\right]$$

$$\Psi = [\theta',\Pi',\zeta']$$

$$\theta = [\theta_1,.....\theta_p]$$

$$\Pi = \left[\omega_{11},...,\omega_{1p},\omega_{22},...,\omega_{2p},\omega_{33},...,\omega_{3p},...,\omega_{pp}\right]$$

$$\zeta = \left[\sigma^2_{11},.....,\sigma^2_{1M},\sigma^2_{21},.....,\sigma^2_{2M}\right]$$

,

$$F(\Psi,\xi_i)_{az} = \left\{J_a{}^T V^{-1} J_z + \frac{1}{2} tr\left(\frac{\partial V}{\partial\Psi_a} V^{-1} \frac{\partial V}{\partial\Psi_z} V^{-1}\right)\right\}$$

$$(p+2*M)\times(p+2*M)$$

$$(p+n_\omega+2*M)\times(p+n_\omega+2*M)$$

$$J_a = \left[J'_{a1},J'_{a2},.....,J'_{aM}\right] \quad J_{am} = \frac{\partial f_m(\Psi,\xi_i)}{\partial\Psi_a}$$

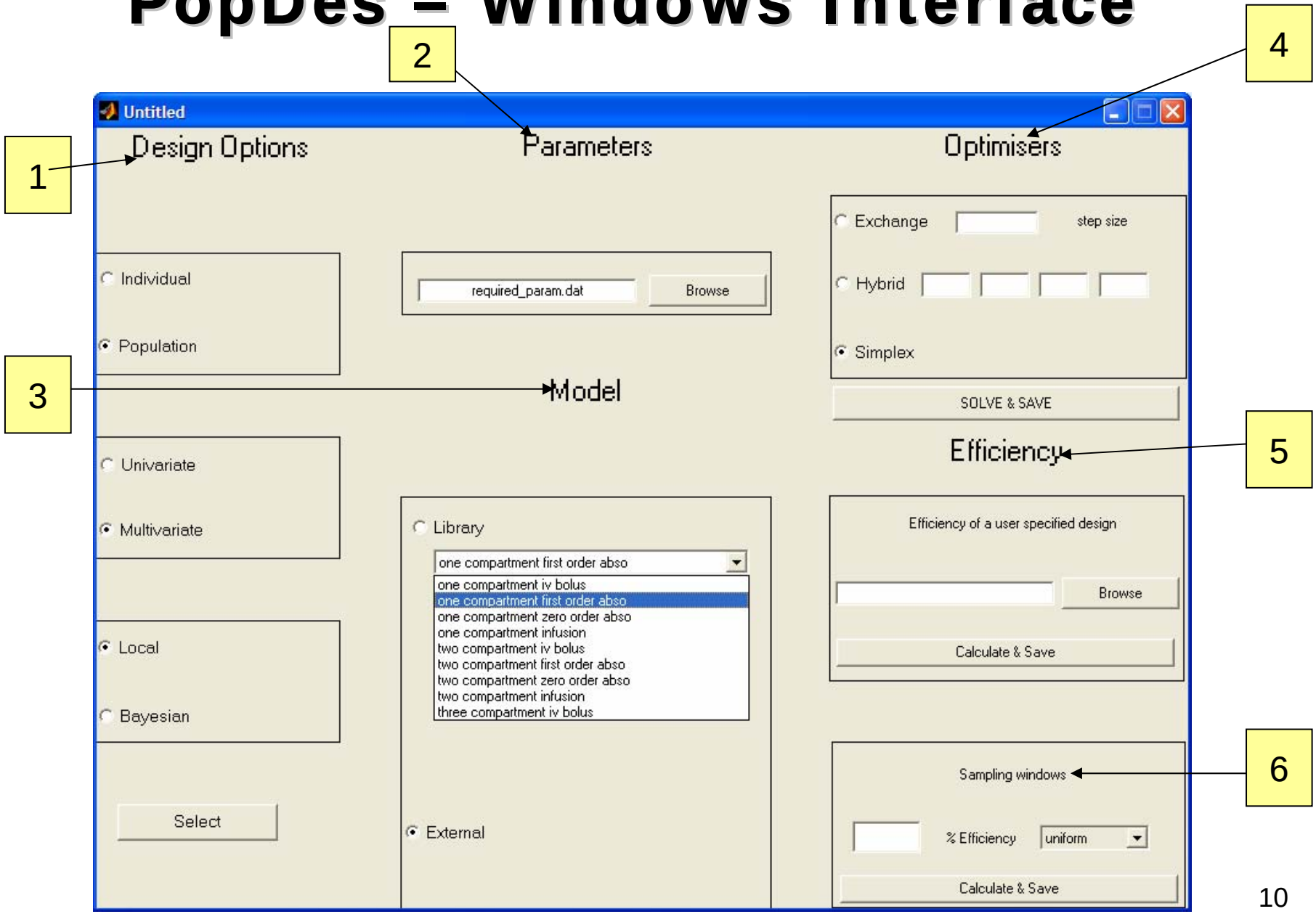
$$V = Var(y_i) \cong U'\Omega U + R$$

$$U_k = \left[U'_{k1},U'_{k2},.....,U'_{kM}\right] \text{and} \, U_{km} = \left.\frac{\partial f_m^T(\theta,b_i,\xi_i)}{\partial b_i}\right|_{b_i=0}$$

FIM – Univariate and Multivariate

- Expressions for unbalanced designs have been developed
- Expressions incorporated into sampling windows determination
- Full omega matrix has been accounted for in the expressions
- These expressions have been implemented in PopDes
  - Balanced design
  - Diagonal omega matrix

PopDes – Windows Interface



PopDes - Options

Design	Local/Bayesian		Model		Optimisation	Efficiency	Sampling Windows
	Local	Bayesian	Library	External			
Individual Univariate	√	√	√	√	√	√	-
Individual Multivariate	√	√	-	√	√	√	-
Population Univariate	√	-	√	√	√	√	√
Population Multivariate	√	-	-	√	√	√	√

Key: √ means that function is available and – (dash) means function is not available for the design.

Example

PK/PD Model (2 responses)

$$y_{PKij_{PK}} = f_{PK}(\theta_i, t_{ij_{PK}}) + \varepsilon_{PKij_{PK}} \qquad \varepsilon_{PKij_{PK}} \rightarrow \sigma_{PK1}, \sigma_{PK2}$$

$$f_{PK}(\theta_i, t_{ij_{PK}}) = \frac{Dose}{V_i} e^{\left(Cl_i * t_{ij_{PK}} / V\right)}$$ ⇒ One cmpt IV bolus model

$$y_{PDij_{PK}} = f_{PD}(\theta_i, t_{ij_{PD}}) + \varepsilon_{PDij_{PD}} \qquad \varepsilon_{PDij_{PD}} \rightarrow \sigma_{PD1}$$

$$f_{PD}(\theta_i, t_{ij_{PD}}) = \frac{emax_i * f_{PK}(\theta_i, t_{ij_{PD}})}{e50_i + f_{PK}(\theta_i, t_{ij_{PD}})}$$ ⇒ Emax model

Parameters

$$\theta = [Cl, V, emax, e50]$$

$$\Omega = \begin{bmatrix} \Omega_{Cl} & \Omega_{ClV} & 0 & 0 \\ \Omega_{ClV} & \Omega_{V} & 0 & 0 \\ 0 & 0 & \Omega_{e50} & \Omega_{e50e\max} \\ 0 & 0 & \Omega_{e50e\max} & \Omega_{emax} \end{bmatrix}$$

$$\sigma^2 = \left[\sigma^2_{PK1}, \sigma^2_{PK2}, \sigma^2_{PD1}\right]$$

(4) (6) (3)

Example

$$\theta_i = \theta e^{b_i} \longrightarrow \text{Exponential IIV}$$

$$\theta = [3.46, 10, 7.5, 10] \qquad \Omega = \begin{bmatrix} 0.0625 & 0.03 & 0 & 0 \\ 0.03 & 0.04 & 0 & 0 \\ 0 & 0 & 0.16 & 0.07 \\ 0 & 0 & 0.07 & 0.0625 \end{bmatrix} \qquad \sigma^2 = [0.25, 0.1, 0.09]$$

[Correlation *Cl* and *V* =0.6, *e50* and *emax* 0.7]

$$\Sigma = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \longrightarrow \text{No correlation between responses}$$

Dose=200mg every 12 hours

One group of 50 subjects

Sampling designs: 3 PK and PD sample (same time) after the first dose, 3 PD samples after the second dose (9 samples, 3 PK and 6 PD

Example

Optimisation: Modified Fedorov exchange algorithm, step size 0.05

Optimisation: Two designs; with and without off diagonal elements

Simulation and Estimation: Two designs, NONMEM (FOCE/LAPLACE) - 100

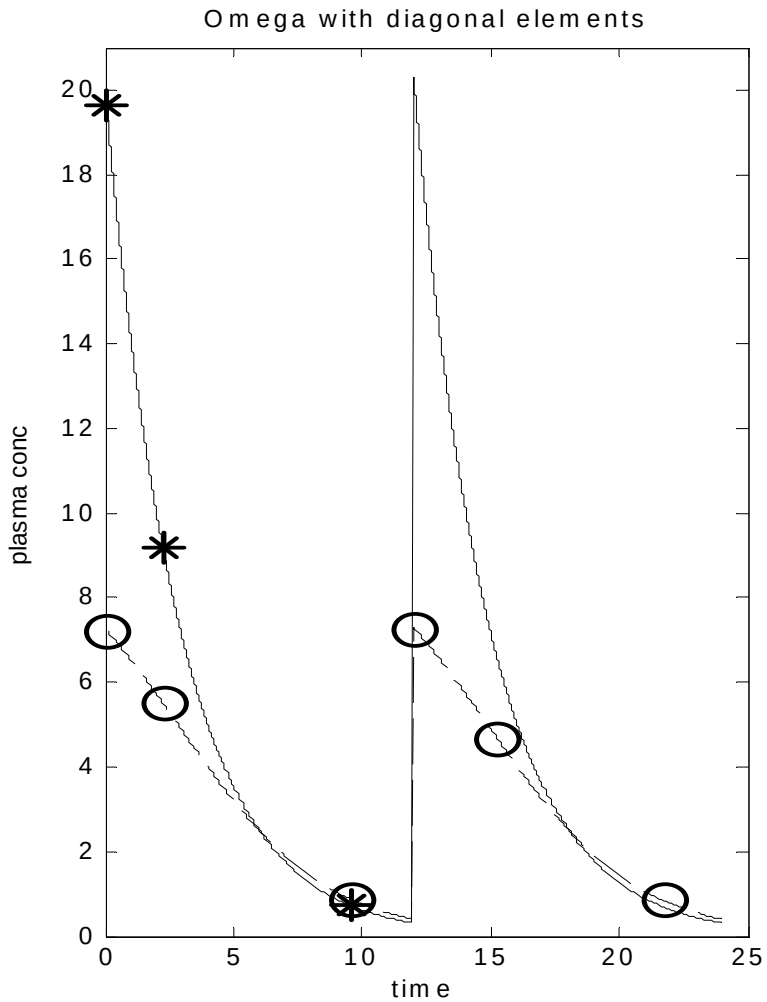
Statistics: Relative error (RE), % mean relative error (bias)
% root mean square error (precision)

$$RE = \Psi_{est} - \Psi_{true} / \Psi_{true}$$

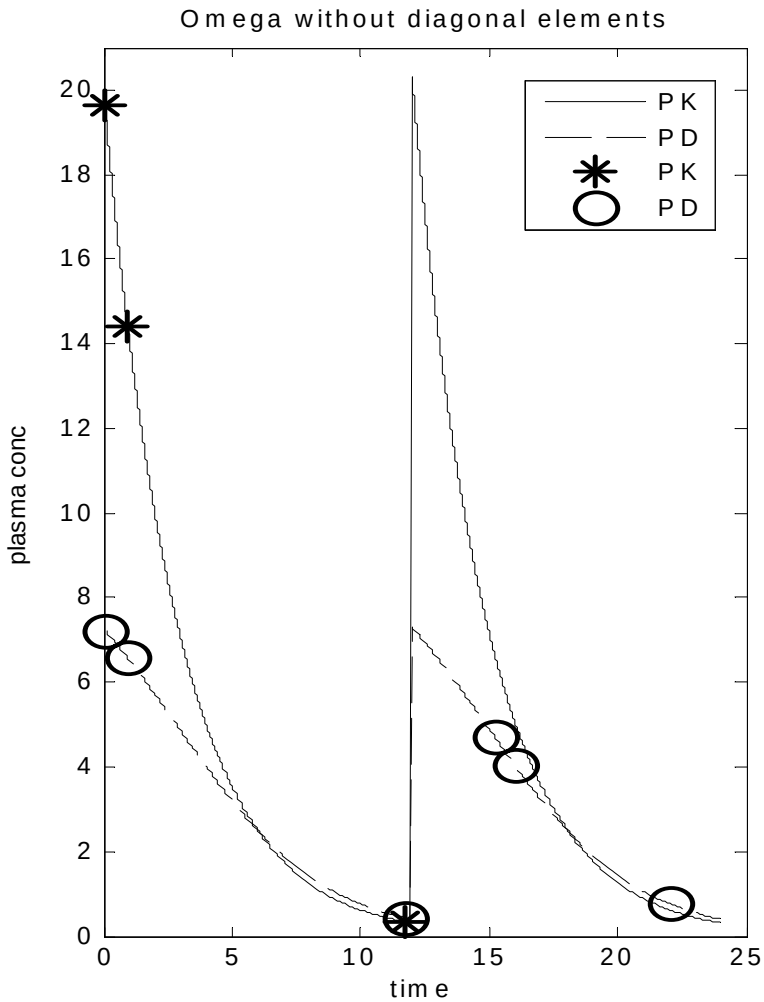
$$\%MRE = \frac{1}{n}\left(\sum_{j=1}^{n}\left(\frac{\Psi_{est_i} - \Psi_{true}}{\Psi_{true}} * 100\right)\right)$$

$$\%RMSE = \left[\frac{1}{n}\left(\sum_{j=1}^{n}\Psi_{est_i} - \Psi_{true}\right)^2\right]^{\frac{1}{2}} * 100$$

Results - Optimisation

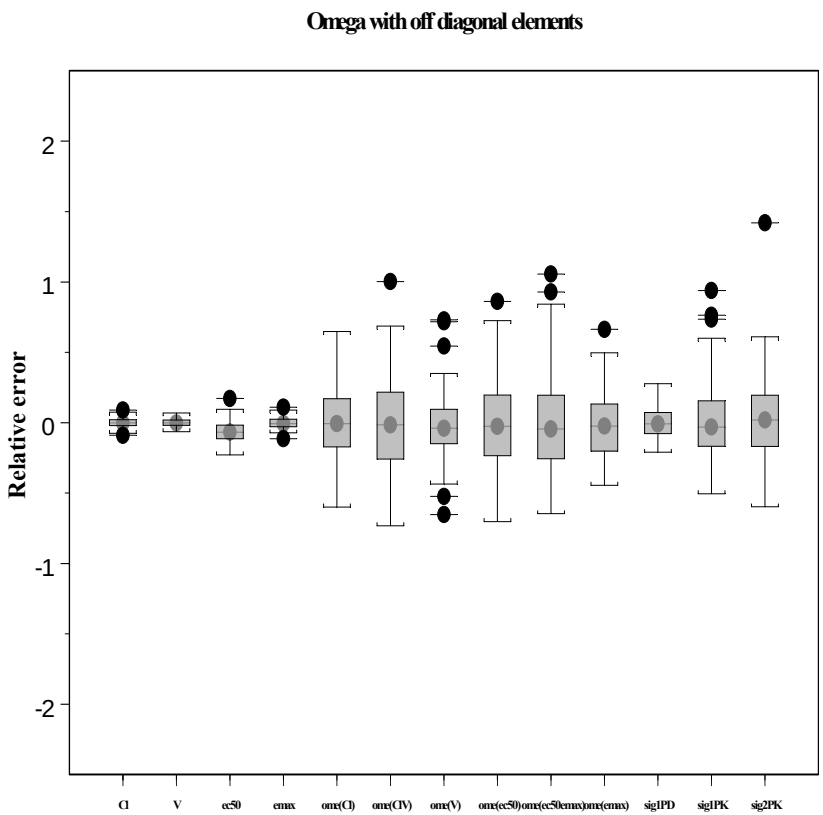


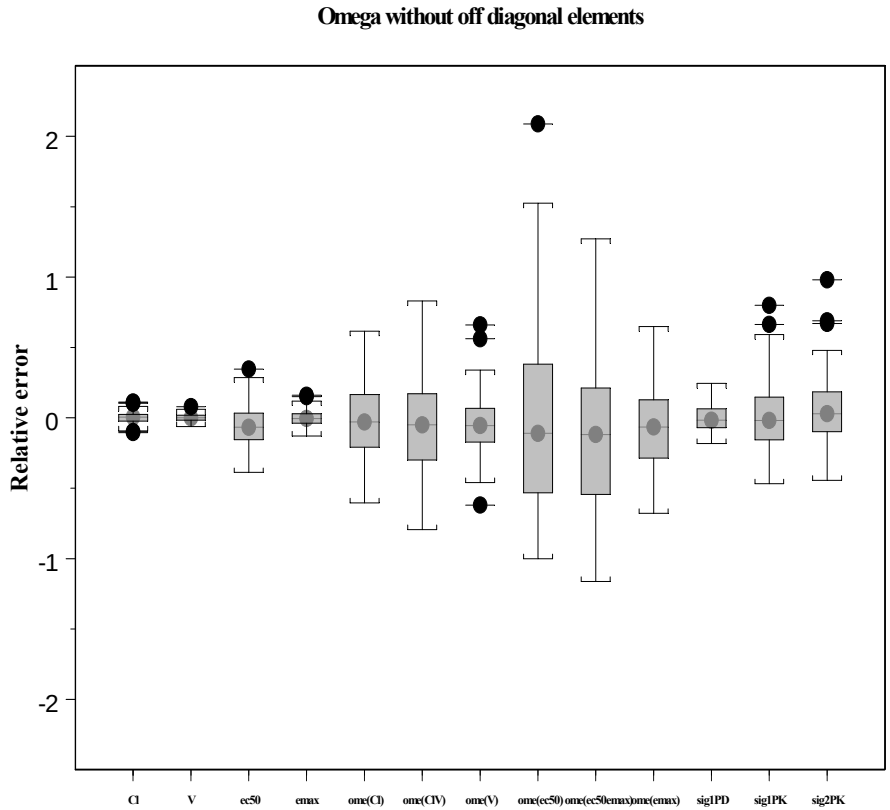
0.05,2.25,9.6,12.05,15.25,21.75 hr



0.05,0.95,11.7,15.2,16,22 hr

Results - Simulation

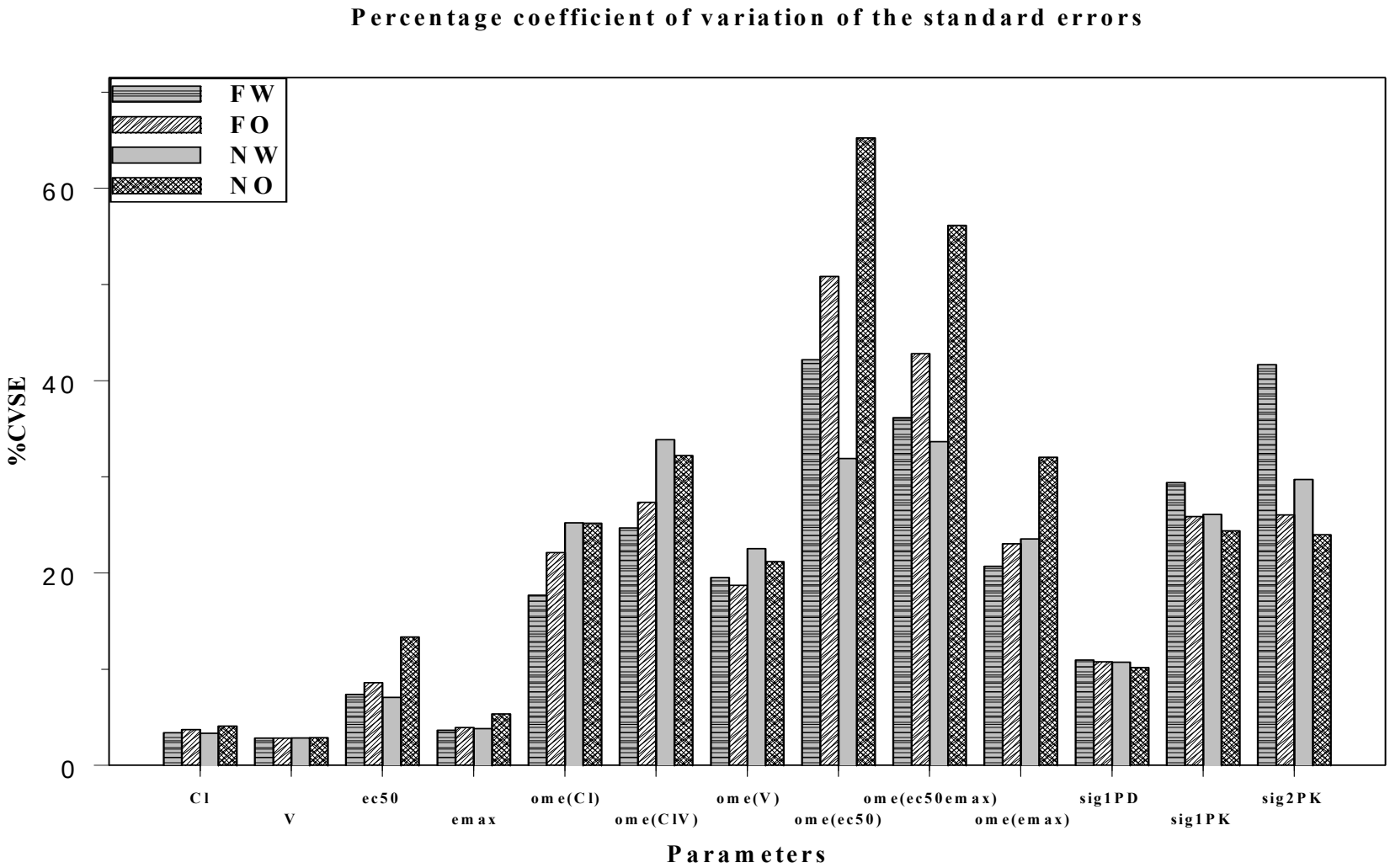




Results - Simulation

Parameters	%MRE		%RMSE	
	NW	NO	NW	NO
Cl	0.17	0.35	11.56	14.18
V	0.08	0.08	28.62	29.04
ec50	-6.61	-5.68	72.55	108.49
emax	-0.33	-0.08	38.44	53.49
ome(*Cl*)	0.82	-1.82	1.57	1.57
ome(*ClV*)	-1.77	-6.24	1.01	0.98
ome(*V*)	-2.08	-4.85	0.90	0.87
ome(*ec50*)	-1.44	-6.09	5.09	10.43
ome(*ec50emax*)	-0.91	-8.04	2.35	3.95
ome(*emax*)	-0.84	-5.16	1.47	2.02
sig1PK	2.42	6.10	0.30	0.25
sig2PK	2.16	1.04	6.52	6.07
sig1PD	0.40	-0.24	0.96	0.91

Results - Simulation



Summary

- A general method that deals with
  - unbalanced problem in population multivariate problem has been described
  - as well as off diagonal elements in the omega matrix
- The FIM can be used for
  - optimisation – D,c,A,G optimality
  - Bayesian
  - Sampling windows determination
- The CVSE are within the NONMEM range