

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

**Kayode Ogungbenro and Leon Aarons
Centre for Applied Pharmacokinetic Research
School of Pharmacy and Pharmaceutical Sciences
The University of Manchester
Manchester, UK**

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)

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

Mixed Effects (Population)

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

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

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

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

$$\Psi = [\theta_1, \dots, \theta_p, \sigma_1^2, \sigma_2^2] \leftarrow F(\Psi, \xi_i) = E \left(-\frac{\partial^2 l(\Psi; y_i)}{\partial \Psi \partial \Psi^T} \right)$$

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

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

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

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

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

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

FIM – Individual and Population Multivariate

Fixed Effects (Individual)

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

$$j = 1, \dots, n, m = 1, \dots, M$$

$$y = [y'_1, y'_2, \dots, y'_M]$$

Mixed Effects (Population)

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

$$j = 1, \dots, n, m = 1, \dots, M, i = 1, \dots, N$$

$$y_i = [y'_{i1}, y'_{i2}, \dots, y'_{iM}]$$

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

$$\Sigma = \{\tau_{qm}\}_{1 \leq q, m \leq M}$$

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

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

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

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

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

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

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

FIM – Individual and Population Multivariate

Fixed Effects (Individual)

Mixed Effects (Population)

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

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

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

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

$$\zeta = [\sigma_{11}^2, \dots, \sigma_{1M}^2, \sigma_{21}^2, \dots, \sigma_{2M}^2]$$

$$\Psi = [\theta_1, \dots, \theta_p, \sigma_{11}^2, \dots, \sigma_{1M}^2, \sigma_{21}^2, \dots, \sigma_{2M}^2]$$

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

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

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

$$J_a = [J'_{a1}, J'_{a2}, \dots, J'_{aM}]$$

$$J_{am} = \frac{\partial f_m(\Psi, \xi_i)}{\partial \Psi_a}$$

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

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

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

The screenshot shows the PopDes software interface with the following components and callouts:

- 1**: Points to the **Design Options** section on the left.
- 2**: Points to the **Parameters** section at the top center.
- 3**: Points to the **Model** section in the middle.
- 4**: Points to the **Optimisers** section at the top right.
- 5**: Points to the **Efficiency** section in the middle right.
- 6**: Points to the **Sampling windows** section at the bottom right.

The interface includes the following sections:

- Design Options**: Radio buttons for Individual, Population (selected), Univariate, Multivariate, Local (selected), and Bayesian. A **Select** button is at the bottom.
- Parameters**: A text field containing `required_param.dat` and a **Browse** button.
- Model**: Radio buttons for Library and External. The Library section has a list box with the following items: one compartment first order abso, one compartment iv bolus, one compartment first order abso (highlighted), one compartment zero order abso, one compartment infusion, two compartment iv bolus, two compartment first order abso, two compartment zero order abso, two compartment infusion, and three compartment iv bolus.
- Optimisers**: Radio buttons for Exchange, Hybrid, and Simplex (selected). A **SOLVE & SAVE** button is below.
- Efficiency**: A section titled "Efficiency of a user specified design" with a text field, a **Browse** button, and a **Calculate & Save** button.
- Sampling windows**: A section with a text field, a **% Efficiency** label, a dropdown menu set to "uniform", and a **Calculate & Save** button.

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)

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

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

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

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

Parameters

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

$$\Omega = \begin{bmatrix} \Omega_{Cl} & \Omega_{ClV} & 0 & 0 \\ \Omega_{ClV} & \Omega_V & 0 & 0 \\ 0 & 0 & \Omega_{e50} & \Omega_{e50emax} \\ 0 & 0 & \Omega_{e50emax} & \Omega_{emax} \end{bmatrix}$$

$$\sigma^2 = [\sigma_{PK1}^2, \sigma_{PK2}^2, \sigma_{PD1}^2]$$

(4)

(6)

(3)

12

Example

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

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

[Correlation Cl and $V = 0.6$, e_{50} and $e_{max} 0.7$]

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

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)

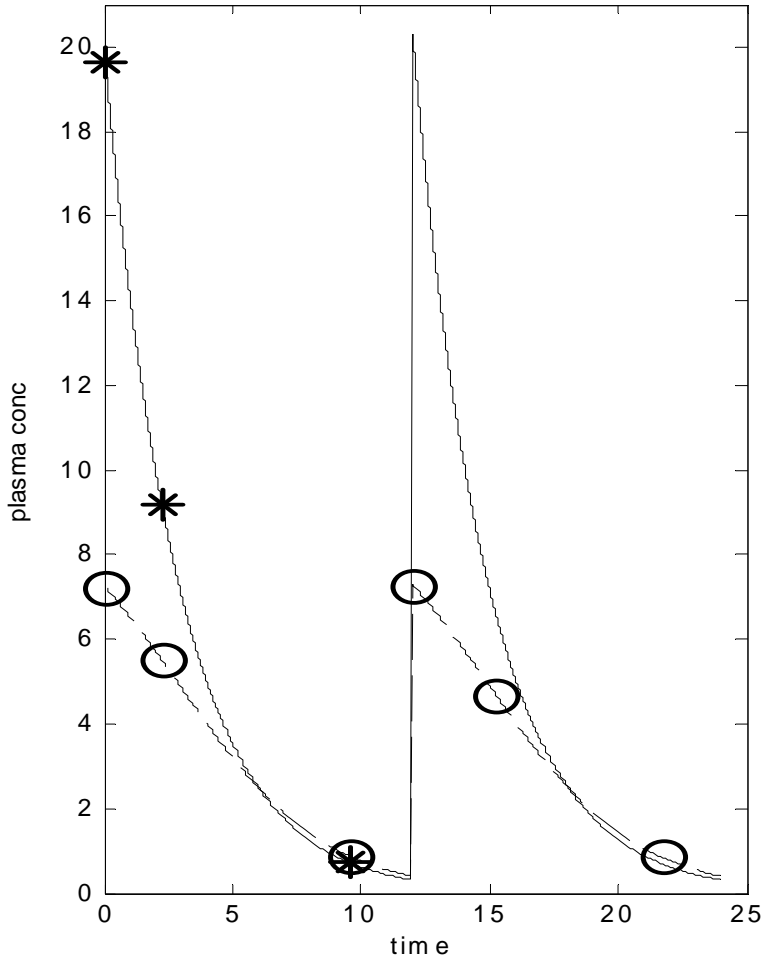
$$RE = \Psi_{est} - \Psi_{true} / \Psi_{true}$$

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

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

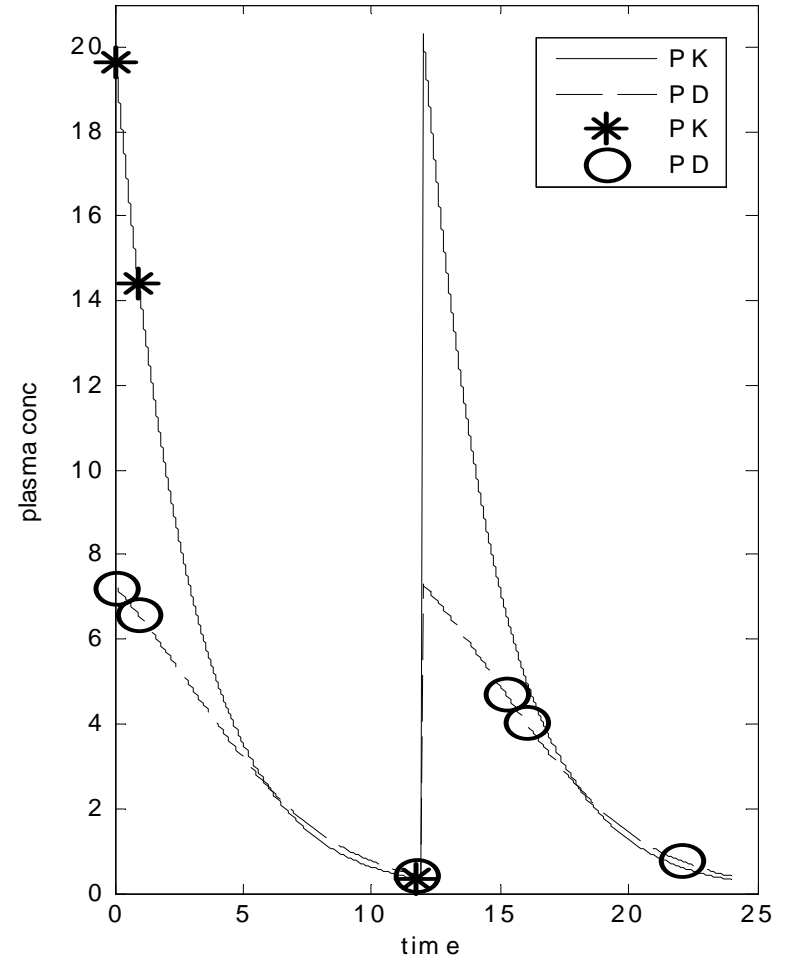
Results - Optimisation

Omega with diagonal elements



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

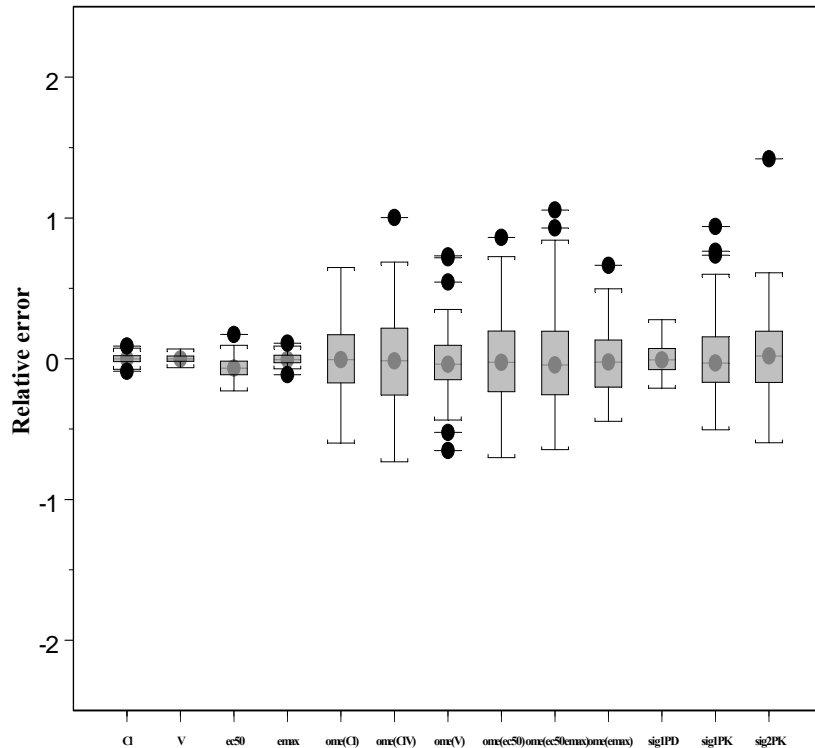
Omega without diagonal elements



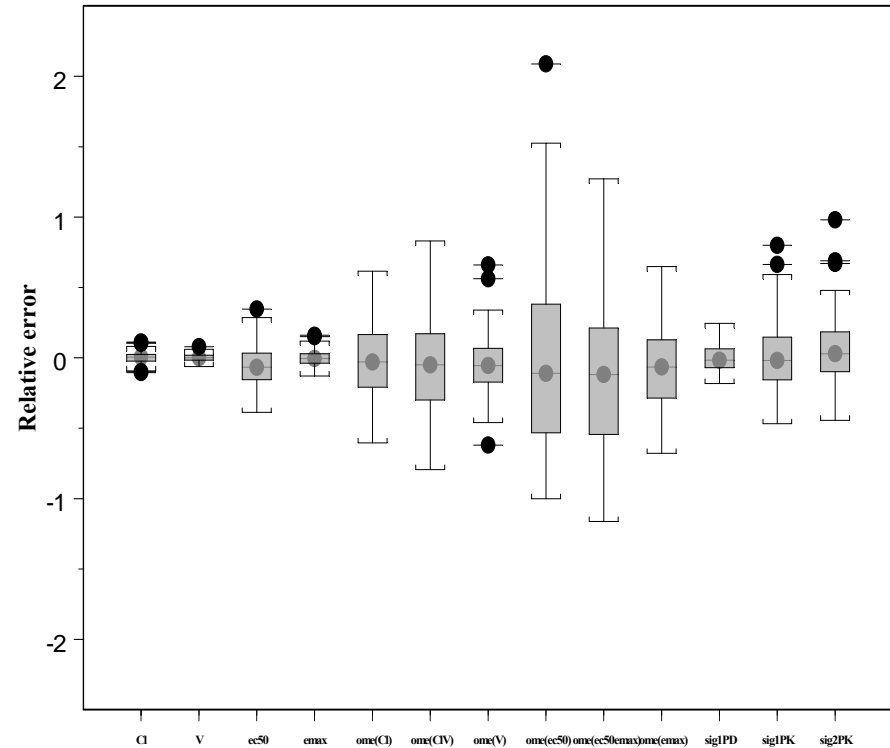
0.05, 0.95, 11.7, 15.2, 16, 22 hr

Results - Simulation

Omega with off diagonal elements



Omega without off diagonal elements

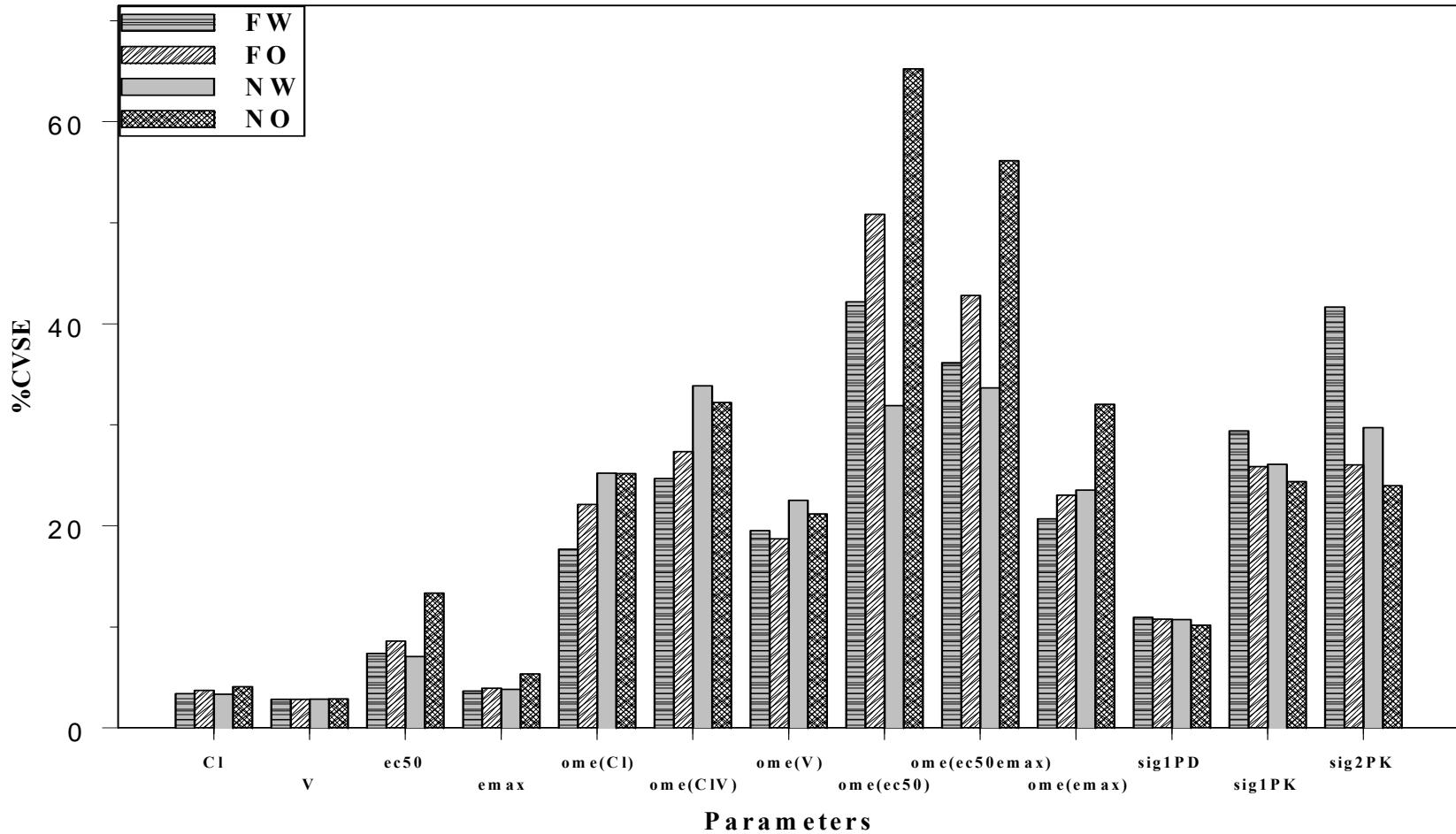


Results - Simulation

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

Results - Simulation

Percentage coefficient of variation of the standard errors



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