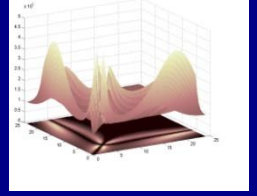

An Approach for Identifiability of Population Pharmacokinetic-Pharmacodynamic Models

Vittal Shivva[1]*, Julia Korell[1,2], Ian Tucker[1], Stephen Duffull[1]

[1]School of Pharmacy, University of Otago, Dunedin, New Zealand
[2]Department of Pharmaceutical Biosciences, Uppsala University, Sweden

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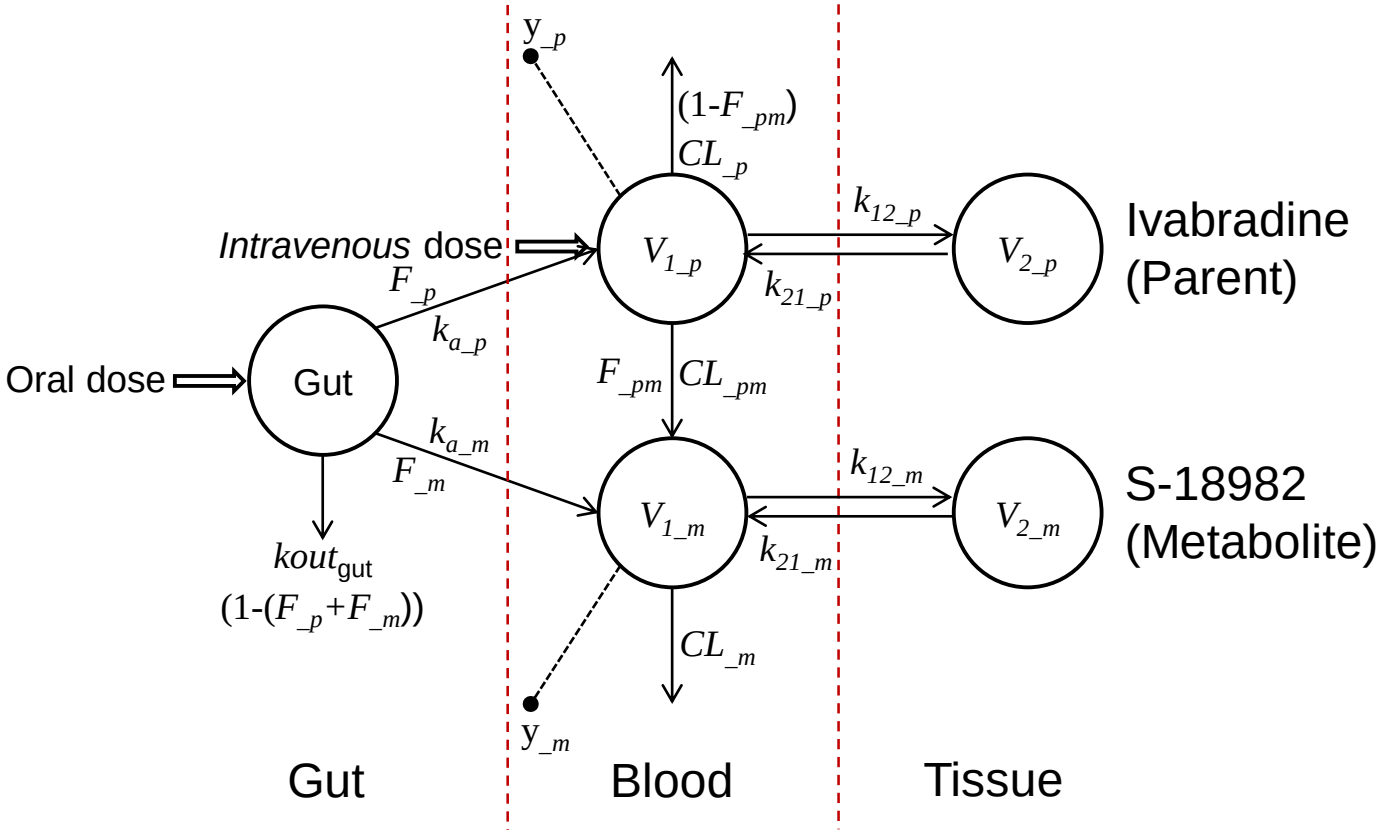
Example PK model

- Combined parent-metabolite PK model of ivabradine[1,2]
- Bradycardiac agent for prevention of myocardial ischemia



- Issues with this model - difficulties in estimating the parameters

[1]Duffull *et al.* (2000). *Eur. J. Pharm. Sci.* 10(4):285-294; [2]Evans *et al.* (2001). *J. Pharmacokin. Pharmacodyn.* 28(1):93-105

Identifiability

- Structural identifiability: Whether the parameters in a model have unique solutions given a perfect input-output data[3]
  - *Structurally globally identifiable*: All parameters have unique solutions
  - *Structurally locally identifiable*: One or more parameters have a finite number of alternate solutions
  - *Structurally unidentifiable*: One or more parameters have an infinite number of alternate solutions
- Deterministic identifiability: Whether the parameters in a model can be estimated precisely given data that contains random noise[4]

[3]Godfrey *et al.* (1980). *J. Pharmacokin. Biopharm.* 8(6):633-648
[4]Foo LK and Duffull SB (2011). *Optimal design of PK-PD studies*. Springer US. 175-193

Available approaches

- *Structural identifiability analysis*:
  - Mathematical approaches
    - Laplace transformation approach
    - Similarity transformation approach
    - Differential algebra
  - Software
    - DAISY[5]
    - GenSSI[6]
- *Deterministic identifiability analysis*: No special software is available, any optimal design software can be used

[5]Bellu *et al*. (2007). *Comput. Methods Programs Biomed.* 88(1):52-61; [6]Chis *et al.* (2011). *Bioinformatics.* 27(18):2610-2611

Motivating context

- Structural and deterministic identifiability are not simultaneously assessed
- Formal methods for assessing identifiability of random effects parameters in population models do not exist in the literature

Aim & Objectives

Aim: To develop an informal approach that can serve as a unified method for assessing structural and deterministic identifiability of population PKPD models based on an information theoretic framework

Objectives:

1. To develop a criterion for identifiability analysis of models
2. To evaluate the criterion for testing identifiability
3. To explore the criterion for testing identifiability of random effects parameters in population PK models
4. To apply the criterion for identifiability analysis of the practical example PK model

Objective 1

Criterion for identifiability analysis

Fisher Information Matrix

- Structure of a PK model

$$\mathbf{y} = f\left(D,\boldsymbol{\xi},\boldsymbol{\theta}\right)+\boldsymbol{\varepsilon};\ \boldsymbol{\varepsilon} \overset{iid}{\sim} N\left(0,\sigma^2\right)$$

- Sensitivity matrix (Jacobian matrix $\mathbf{J}$) with first partial derivatives

$$\mathbf{J} = \begin{bmatrix} \dfrac{\partial f\left(D,\xi_1,\boldsymbol{\theta}\right)}{\partial\theta_1} & \cdots & \dfrac{\partial f\left(D,\xi_1,\boldsymbol{\theta}\right)}{\partial\theta_p} \\ \vdots & \ddots & \vdots \\ \dfrac{\partial f\left(D,\xi_n,\boldsymbol{\theta}\right)}{\partial\theta_1} & \cdots & \dfrac{\partial f\left(D,\xi_n,\boldsymbol{\theta}\right)}{\partial\theta_p} \end{bmatrix}$$

- Variance-covariance matrix

$$\boldsymbol{\Sigma} = \sigma^2 \cdot \mathbf{I}_n \rightarrow \begin{bmatrix} \sigma_1^2 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & \sigma_n^2 \end{bmatrix}$$

- Fisher Information Matrix ($\mathbf{M_F}$) for the fixed effects model

$$\mathbf{M_F}\left(D,\boldsymbol{\xi},\boldsymbol{\theta},\boldsymbol{\Sigma}\right) = \mathbf{J}^{\mathbf{T}} \cdot \boldsymbol{\Sigma}^{-1} \cdot \mathbf{J}$$

Criterion for identifiability analysis

- Mathematical basis of the criterion - determinant of $\mathbf{M_F}$ ($|\mathbf{M_F}|$)

- Criterion for fixed effects models

$$\forall \boldsymbol{\xi} : \left|\mathbf{M_F}(D,\boldsymbol{\xi},\boldsymbol{\theta},\boldsymbol{\Sigma})\right|_{\lim \sigma^2 \to 0} = \infty, \text{ where } n > p,\ \xi_i \neq \xi_j \text{ ; for all } i \neq j$$

- Criterion for mixed effects models

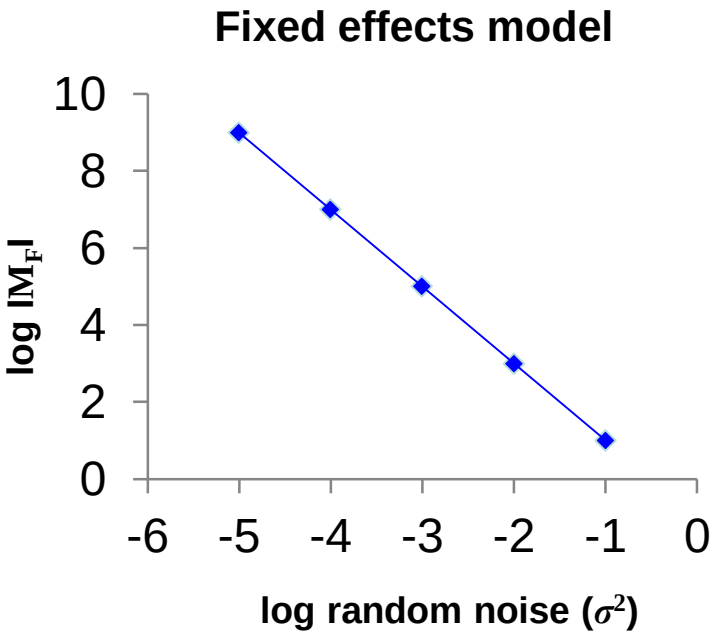
$$\forall \boldsymbol{\xi} : \left|\mathbf{M_F}(D,\boldsymbol{\xi},\boldsymbol{\theta},\boldsymbol{\Omega},\boldsymbol{\Sigma})\right|_{\lim \sigma^2 \to 0} = \boldsymbol{\Psi}, \text{ where } n > p,\ \xi_i \neq \xi_j \text{ ; for all } i \neq j$$

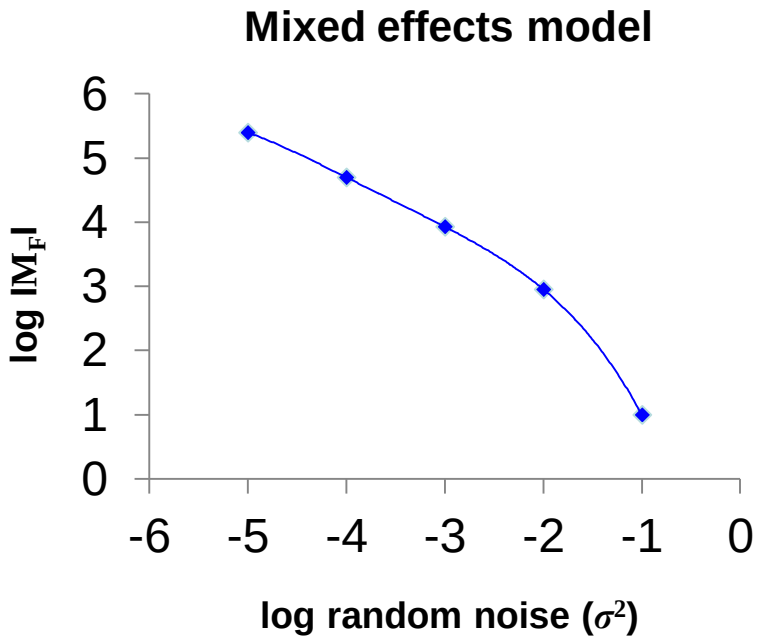
$$\text{here } 0 < \boldsymbol{\Psi} < \infty,\ \boldsymbol{\Psi} = f(\mathbf{V});\ \mathbf{V} \approx \mathbf{J}^{\mathbf{T}}.\boldsymbol{\Omega}.\mathbf{J} + \boldsymbol{\Sigma}$$

Identifiable PK model

Two conditions are needed for identifiability

- log $|\mathbf{M_F}|$ should have continuous relationship with log random noise
- $|\mathbf{M_F}|$ should approach infinity (or non-infinite asymptote for mixed effects models) as noise approaches zero





Objective 2

Evaluation of the criterion for testing identifiability

Methods

- Models tested: One compartment first order input PK models (fixed effects)
  - Bateman model

$$f\left(D,\xi_j,\boldsymbol{\theta}\right)=\frac{D\cdot F\cdot k_a}{V\cdot\left(k_a-k\right)}\left(\exp\left(-k\cdot t_j\right)-\exp\left(-k_a\cdot t_j\right)\right)$$

$$k=\frac{CL}{V}$$

Parameters in the model: V, CL, k_a and F

  - Dost model

$$f\left(D,\xi_j,\boldsymbol{\theta}\right)=\frac{D\cdot F\cdot k^*\cdot t_j}{V}\left(\exp\left(-k^*\cdot t_j\right)\right)$$

Parameters in the model: V, k^* and F

Methods

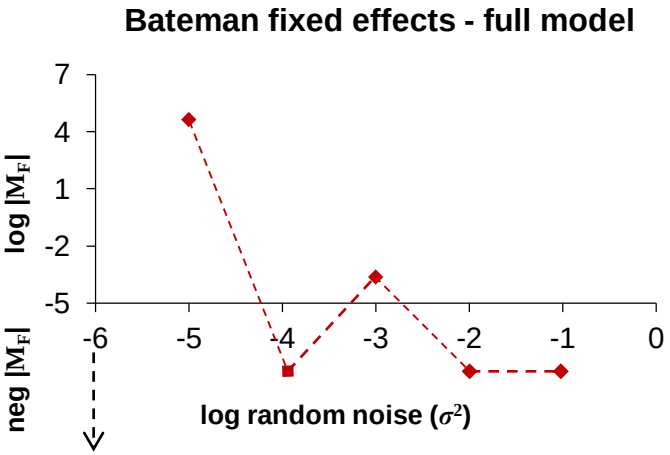
- Study design: Generic study design with sampling times 0, 0.25, 0.5, 0.75, 1, 2, 4, 8, 12, 18 and 24 h post dose

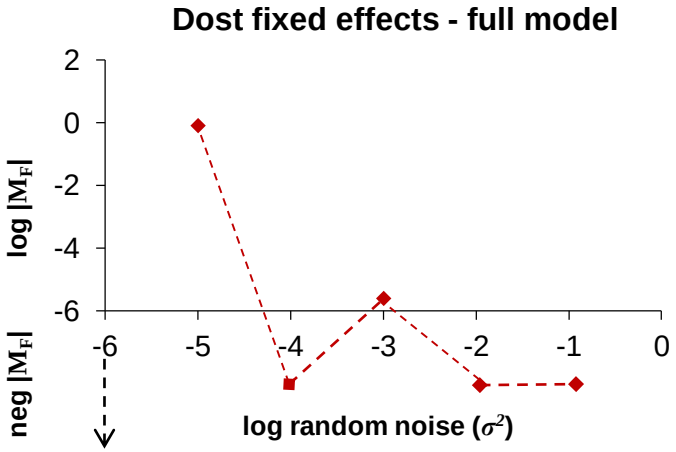
- Dose and parameter values:
  - Dose = 100 mg (for all models)
  - V = 20 L, CL = 4 L.h^{-1}, k_a = 1 h^{-1} and F = 1 (Bateman)
  - V = 20 L, k^* = 0.5 h^{-1} and F = 1 (Dost)

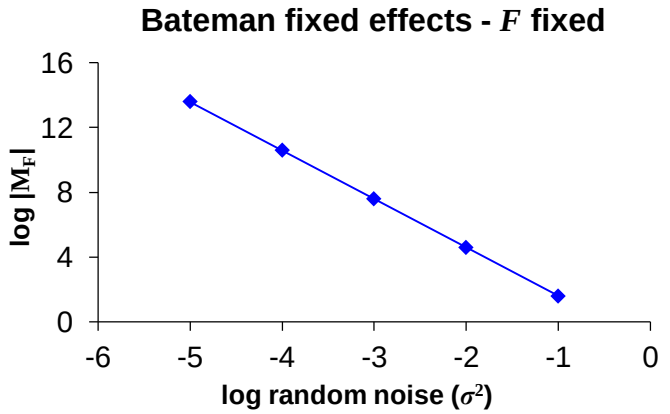
- Random noise assumed in the observed data
  - σ^2 = 0.00001 to 0.1

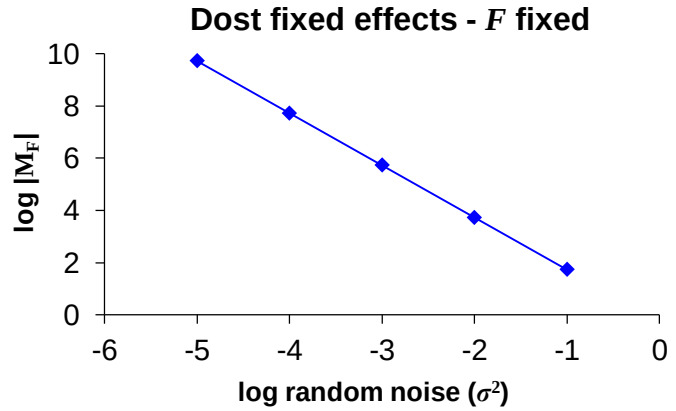
- Software: MatlabR2011a

Results









- Full models - unidentifiable (discontinuous relationship)
- F fixed in the models - identifiable (continuous relationship)

Objective 3

Exploration of the criterion for population PK model

Methods

- Structure of the population PK model (mixed effects model)

  Two stage hierarchical models

  – Model for the data (structural model)

$$y_{ij} = f\left(D_i, \xi_{ij}, \boldsymbol{\theta}_{\mathbf{i}}\right) + \varepsilon_{ij} \; ; \; \varepsilon_{ij} \overset{iid}{\sim} N\left(0, \sigma^2\right)$$

  – Model for heterogeneity (covariate model)

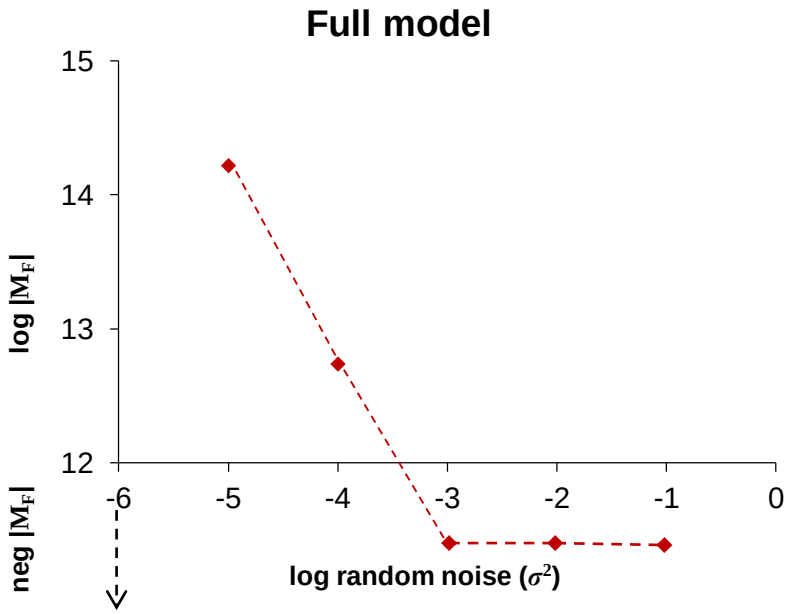
$$\boldsymbol{\theta}_{\mathbf{i}} = g\left(\mathbf{Z}_{\mathbf{i}}, \boldsymbol{\theta}_{\mathbf{pop}}\right)\exp\left(\boldsymbol{\eta}_{\mathbf{i}}\right); \; \boldsymbol{\eta}_{\mathbf{i}} \overset{iid}{\sim} N\left(0, \boldsymbol{\Omega}\right)$$

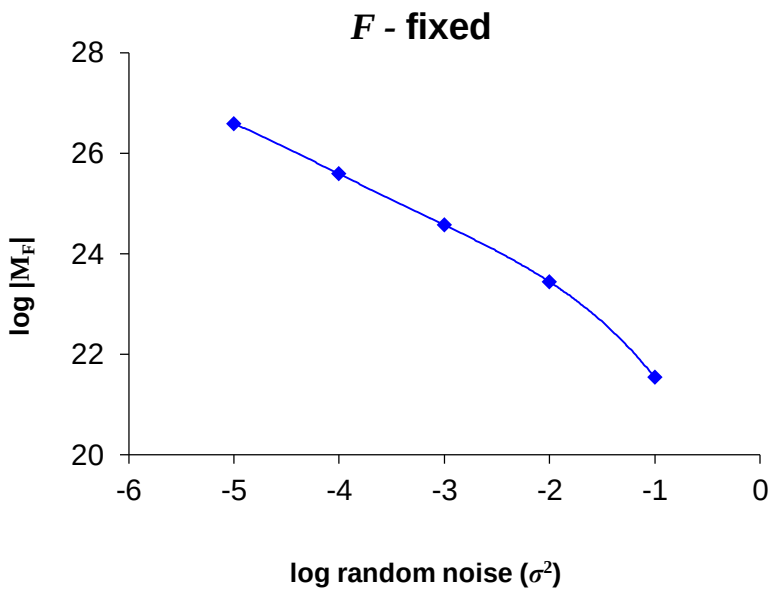
- Models tested
  – Bateman & Dost

Methods

- Study design, dose & random noise in the data: as in the fixed effects model
- Parameters & size of the population:
  - Fixed effects: as in the fixed effects models
  - Random effects: log normal variance of 0.1 was assumed for all parameters (only diagonal elements of Ω were considered)
  - Population size: 100 subjects
- Software: Population OPTimal design (POPT)

Bateman model

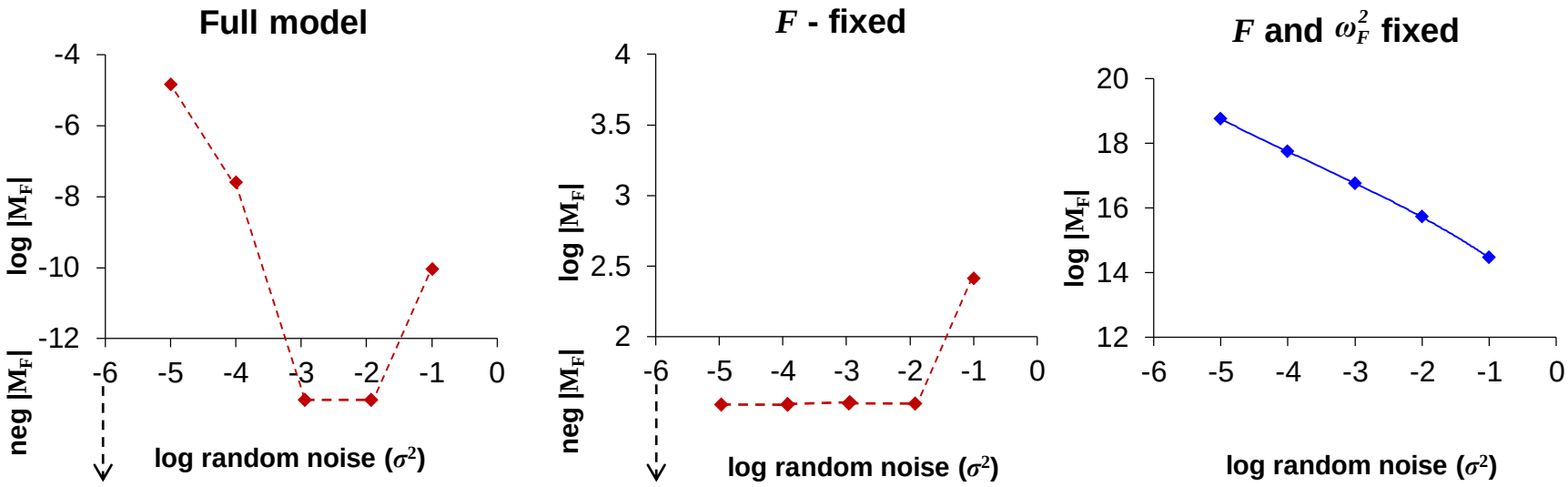




- Full population model - unidentifiable
- Fixed effects - F was unidentifiable

N.B. Random effects - all parameters were identifiable

Dost model



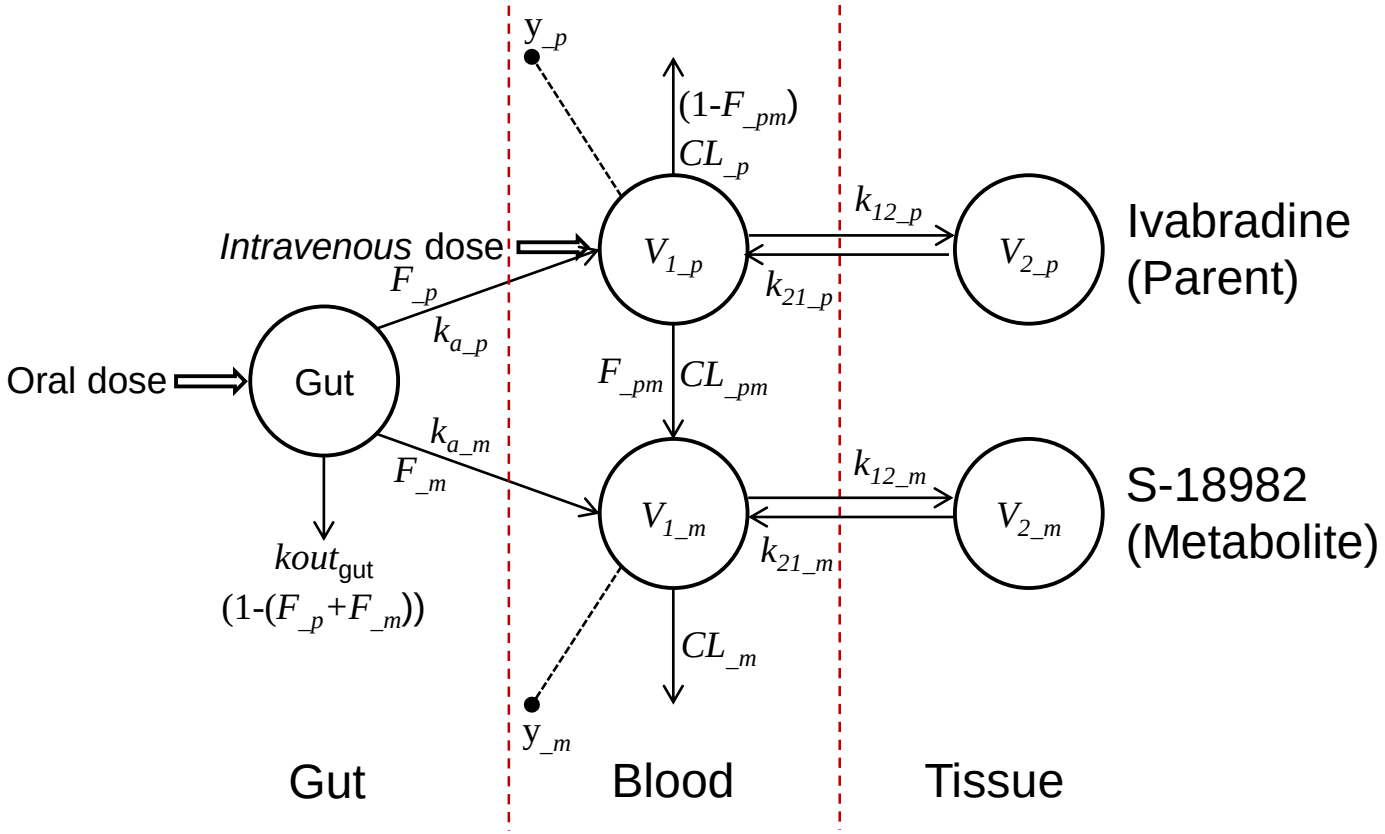
- Full population model - unidentifiable
- Fixed effects - F was unidentifiable
- Random effects - ω_F^2 was unidentifiable

Objective 4

Application of the criterion
for the practical example PK model

Example PK model

Combined parent-metabolite PK model of ivabradine



Oral PK model

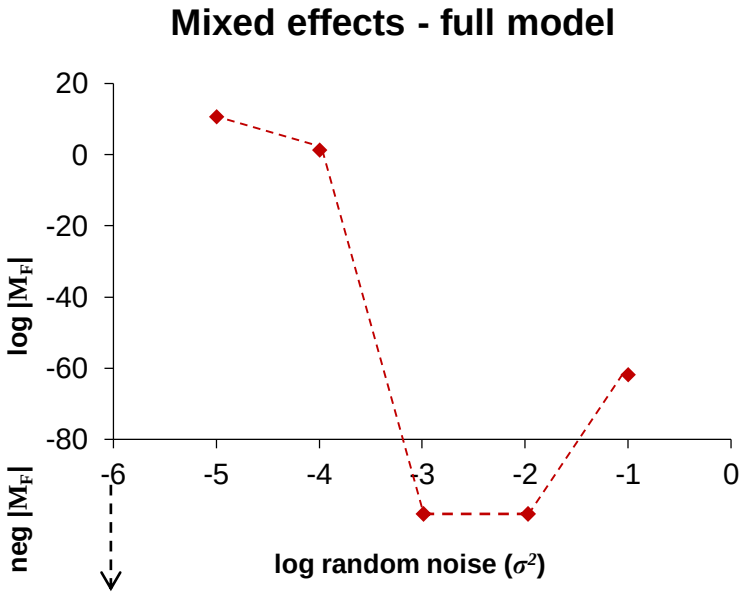
- Two linked two compartment parent-metabolite PK model

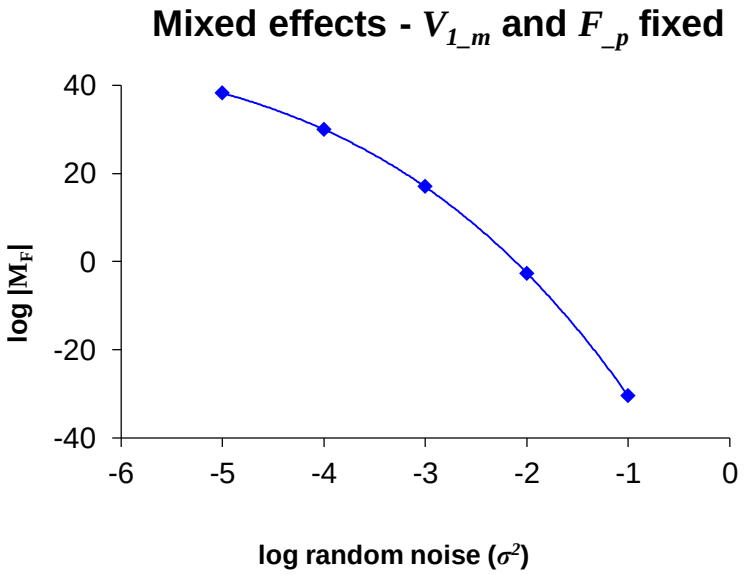
- Parameters:
  - $CL_{\_p}$, V_{1_p}, $Q_{\_p}$, V_{2_p}, $CL_{\_pm}$, $F_{\_pm}$, k_{a_p}, $F_{\_p}$, $CL_{\_m}$, V_{1_m}, $Q_{\_m}$, V_{2_m}, k_{a_m}, $F_{\_m}$
  - Population parameter values for the assessment are from the literature[1]

- Study design, dose, random noise and population size
  - As described in the simple example models

[1]Duffull *et al.* (2000). *Eur. J. Pharm. Sci.* 10(4):285-294

Oral PK model





- Full population model - unidentifiable
- Fixed effects - V_{1_m} and $F_{\_p}$ were unidentifiable (comparable to the literature data[2])

N.B. Random effects - all parameters were identifiable

[2]Evans *et al.* (2001). *J. Pharmacokin. Pharmacodyn.* 28(1):93-105

Discussion

- The approach was able to assess the identifiability of the simple and practical example PK models
- The approach provides an informal way of assessing the identifiability of random effects parameters in population models
- Random effects parameters may or may not follow the same rule as fixed effects parameters for identifiability
- Assessment of deterministic identifiability is straight forward given the diagonal elements of inverse of $\mathbf{M}_{\mathbf{F}}$

Discussion

- A range of the random noise needs to be tested in assessing identifiability
  - Current assessment used 5 different values for the variance of random noise ranging from 10^{-5} to 10^{-1}

- Simple, practical approach and any optimal design software (PFIM, PopED & PopDes) can be used

➢ This informal approach can serve as a unified method for assessing structural and deterministic identifiability of population PKPD models

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Thank you!

Coagulation Network Model