Design of population PK/PD studies: approximation of the individual Fisher information matrix

Sergei Leonov

(*fmr GlaxoSmithKline, ftr Vertex*)

DAE02: Optimum Design for Mixed Effects Models

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Outline

- PODE workshops
- Population optimal design software tools
  - Types of problems they address
  - Comparison, whether their outputs match
- Approximation options for Fisher information matrix

Optimal design for population PK/PD models

- PODE Workshop created in 2006

  Population Optimum Design of Experiments

  - Theory of optimal experimental design for nonlinear mixed effects models and its applications in drug development
- Discussion of population optimal design software started in 2007, continued in 2008-2011

Population optimal design software

Five tools available

- PFIM (developed in INSERM, Universitè Paris 7, France)
- PkStaMp (GlaxoSmithKline, Collegeville, U.S.A.)
- PopDes (CAPKR, University of Manchester, UK)
- PopED (Uppsala University, Sweden)
- WinPOPT (University of Otago, New Zealand)

Main application areas:

pharmacokinetics (PK) and pharmacodynamics (PD)

Comparison of population design tools

- Key: Fisher information matrix of a properly defined *single observational unit* (*individual patient*)

- Calculation of individual matrix $\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$
  - *Identical* under the same assumptions for all tools (benchmark examples)

- Differences: selection of sampling sequences, algorithmic details, libraries of models, types of approximation….

- More from France Mentré

Pharmacokinetics (PK)

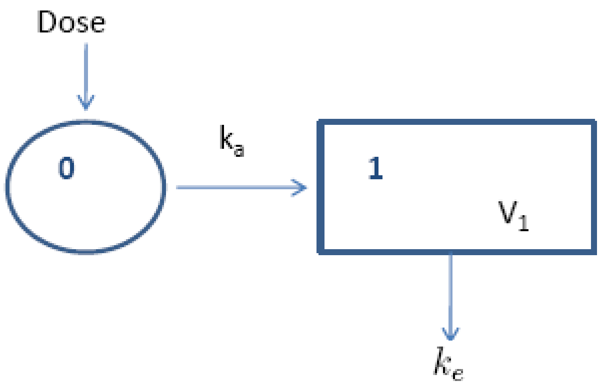
- PK: how drug propagates in patient's body
  - Dose → concentration
- PK studies: at different phases of drug development
- Models:
  - Compartmental, systems of ODE
  - Non-compartmental (AUC, Tmax, Cmax)

Example:

One-compartment model, 1st order absorption and linear elimination

$$\begin{cases} \dot{f}_0(t) = -k_a f_0(t) \\ \dot{f}_1(t) = k_a f_0(t) - k_e f_1(t) \end{cases}$$

$$f_0(t_i) = f_0(t_i - 0) + D_i, \quad f_0(0) = D_0, \quad f_1(0) = 0.$$



Pharmacodynamics (PD)

- PK: what body does to the drug
- PD: what drug does to the body, progression of clinical endpoint (concentration → effect)
  - Drop in blood pressure for hypertensive patients
  - Reduction in the number of “bad” cells
  - Tumor shrinkage
- Popular PD model: E_{max} (sigmoidal-shaped curve, multi-parameter logistic model)

Design of population PK/PD studies

- What we select/optimize (*control*):
  - Location of sampling times
  - Number of sampling times per patient
  - Number of patients enrolled
- Optimal population designs:
  - Optimal: with respect to precision of parameter estimates
  - Goal: *find the most informative sampling times*

Nonlinear models, multiple responses

- Predictor $\mathbf{x} = (x_1, x_2, \ldots, x_k)$ - sequence of sampling times,
- Measurements $\mathbf{Y} = [y(x_1), \ldots, y(x_k)]$ - vector,
- Response $\boldsymbol{\eta}(\mathbf{x}, \boldsymbol{\theta}) = [\eta(x_1, \boldsymbol{\theta}), \ldots, \eta(x_k, \boldsymbol{\theta})]$ - vector

Key: $\boldsymbol{\mu}(\mathbf{x}, \boldsymbol{\theta})$ - information matrix of a k-dimensional sequence $\mathbf{x}$

Optimal designs

Information matrix : n_i patients on seq. $\mathbf{x}_i$ $\Longrightarrow$ $\mathbf{M}_N(\boldsymbol{\theta}) = \sum_{i=1}^{N} n_i \, \boldsymbol{\mu}(\mathbf{x}_i, \boldsymbol{\theta})$

Variance of the MLE: $\mathbf{Var}(\hat{\boldsymbol{\theta}}) \approx \mathbf{M}_N^{-1}(\boldsymbol{\theta})$

$\mathbf{M}(\xi, \boldsymbol{\theta}) = \frac{\mathbf{M}_N(\boldsymbol{\theta})}{N} = \sum_i w_i \boldsymbol{\mu}(\mathbf{x}_i, \boldsymbol{\theta})$ - normalized information, per observation

$\xi = \{w_i, \mathbf{x}_i\}$ - normalized design; $w_i = n_i / N$ - weights

$\mathbf{D}(\xi, \boldsymbol{\theta}) = \mathbf{M}^{-1}(\xi, \boldsymbol{\theta})$ - normalized variance-covariance matrix

Optimal designs (cont.)

Criterion of optimality $\Psi[\mathbf{D}(\xi, \boldsymbol{\theta})] \rightarrow \min_{\xi}$: minimization wrt

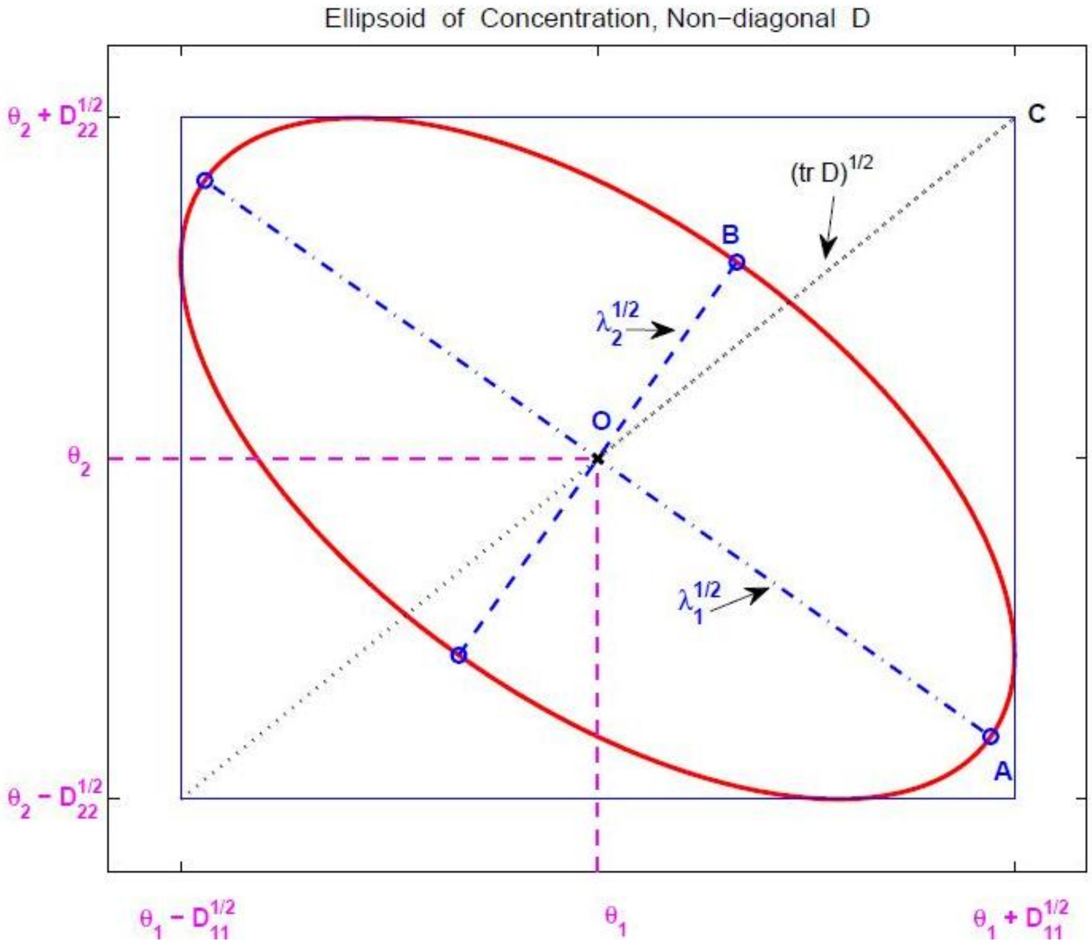
- weights w_i, $0 \leq w_i \leq 1$, $\Sigma_i w_i = 1$ (continuous designs)
- admissible sampling sequences $\mathbf{x}_i \in \mathbf{X}$ - design region.

Locally D-optimal designs: $\Psi = |\mathbf{D}(\xi, \boldsymbol{\theta})|$

Equivalence Theorem: *Kiefer, Wolfowitz (1960), Fedorov (1972)* -

Background for algorithms: Fedorov (1969,72) – Wynn (1970)
Backward step: Atwood (1973)

Optimality criteria, ellipse $(\boldsymbol{\theta} - \boldsymbol{\theta}^*)^T \mathbf{D}^{-1} (\boldsymbol{\theta} - \boldsymbol{\theta}^*) \leq 1$



D-criterion: $|\mathbf{D}| = \lambda_1 \cdot \lambda_2 = (OA \cdot OB)^2$; area (V) = $\pi (\lambda_1 \cdot \lambda_2)^{1/2}$

E-criterion: $\lambda_1 = (OA)^2$

A-criterion: tr $\mathbf{D} = \lambda_1 + \lambda_2 = (OC)^2 = D_{11} + D_{22}$

Mixed effects model model

- γ - *response parameters* (rate constants)
- γ_i - parameters of patient i (sampled from population):

  normal, $\gamma_i \sim N(\gamma^0, \Omega)$, or log-normal ($\gamma^0$ - "typical values")

- Data $y(x_{ij}) = \eta(x_{ij}, \gamma_i)\left[1 + \varepsilon_{ij}^p\right] + \varepsilon_{ij}^a, \quad j = 1, \ldots, k_i.$ (1)

  $\varepsilon_{ij}^a \sim N(0, \sigma_a^2), \quad \varepsilon_{ij}^p \sim N(0, \sigma_p^2)$

- Combined vector of parameters: $\theta = (\gamma^0;\ \Omega;\ \sigma_A^2,\ \sigma_P^2)$

Example: one-compartment model, single dose D at $x = 0$,

$$\eta(x, \gamma) = \frac{D k_a}{V(k_a - k_e)} \left(e^{-k_e x} - e^{-k_a x}\right), \quad \gamma = (k_a, k_e, V)^T$$

Information matrix for sequence x

(1) Gaussian $\mathbf{Y}$: $\mathbf{E}[\mathbf{Y}|\mathbf{x}] = \boldsymbol{\eta}(\mathbf{x},\boldsymbol{\theta})$, $\mathbf{Var}[\mathbf{Y}|\mathbf{x}] = \mathbf{S}(\mathbf{x},\boldsymbol{\theta})$

$\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$ - information matrix of a single (k-dimensional) sequence $\mathbf{x}$:

$$\mu_{\alpha\beta}(\mathbf{x},\boldsymbol{\theta}) = \frac{\partial\boldsymbol{\eta}}{\partial\theta_\alpha}\mathbf{S}^{-1}\frac{\partial\boldsymbol{\eta}}{\partial\theta_\beta} + \frac{1}{2}\,\mathrm{tr}\left[\mathbf{S}^{-1}\frac{\partial\mathbf{S}}{\partial\theta_\alpha}\mathbf{S}^{-1}\frac{\partial\mathbf{S}}{\partial\theta_\beta}\right],$$

$\mathbf{S} = \mathbf{S}(\mathbf{x},\boldsymbol{\theta})$, $\boldsymbol{\eta} = \boldsymbol{\eta}(\mathbf{x},\boldsymbol{\theta})$ [*Muirhead (1982), Magnus and Neudecker (1988)*]

(2) First-order approximation of variance matrix $\mathbf{S}$, model (1): for normal $\boldsymbol{\gamma}$

$$S(\mathbf{x},\boldsymbol{\theta}) \simeq \mathbf{F}\,\boldsymbol{\Omega}\,\mathbf{F}^T + \sigma_P^2\,\mathrm{Diag}[\boldsymbol{\eta}(\mathbf{x},\boldsymbol{\theta})\,\boldsymbol{\eta}^T(\mathbf{x},\boldsymbol{\theta}) + \mathbf{F}\,\boldsymbol{\Omega}\,\mathbf{F}^T] + \sigma_A^2\mathbf{I}_k,$$

$$\mathbf{F} = \mathbf{F}(\mathbf{x},\boldsymbol{\gamma}^0) = \left[\frac{\partial\boldsymbol{\eta}(\mathbf{x},\boldsymbol{\theta})}{\partial\gamma_\alpha}\right]\Bigg|_{\boldsymbol{\gamma}=\boldsymbol{\gamma}^0} \; - \; (k \times m_\gamma) \text{ matrix}$$

Retout, Mentré (2003), Gagnon, Leonov (2005)

Design region X

PkStaMp: Sampling Times Allocation (STand-Alone Application), Matlab Platform

Specific type of constraint (design region)

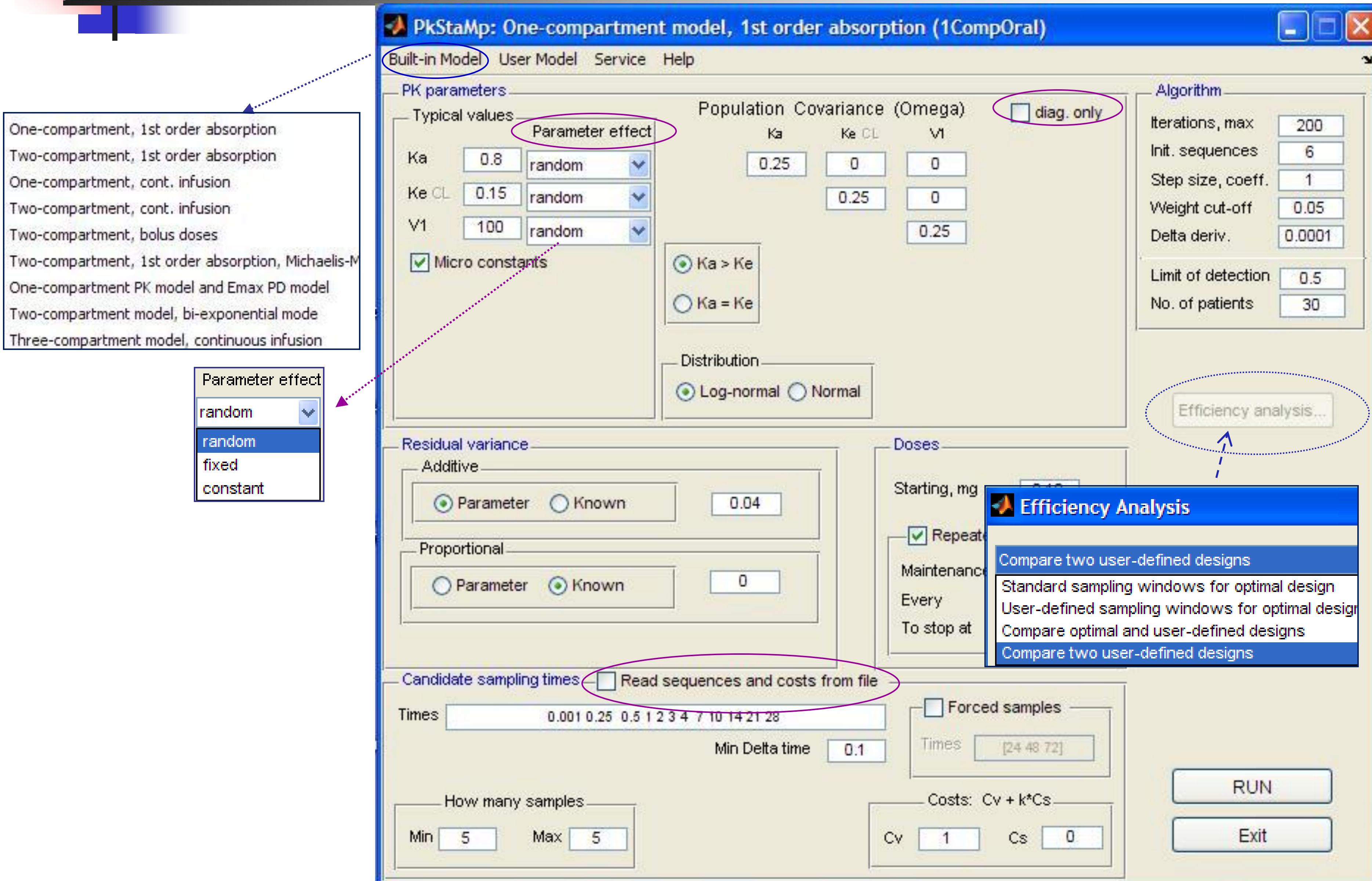
Selection of sampling sequences:

- Option 1: specify
  - All candidate times $(x_1, x_2, \ldots, x_K)$
  - Number of sampling times per patient $k \in [k_{min}, k_{max}]$
  - Lag between samples: $x_{i,j+1} - x_{i,j} \geq \Delta$
- Option 2: pre-specify an arbitrary set of candidate sequences in a file

$$\Downarrow$$

Design region $\mathbf{X} = \{\mathbf{x}_i = (x_{i,1}, \ldots, x_{i,k_i})\}$

Typical screen: one-compartment,1st order absorption



More complex setting: cost-based designs

Measurements at $\mathbf{x_i}$ associated with cost $c(\mathbf{x_i})$,

$$\sum_i n_i c(\mathbf{x}_i) \leq \mathcal{C} \implies \mathbf{M}_C(\boldsymbol{\theta}) = \sum_{i=1}^{n} \frac{n_i}{\mathcal{C}} \boldsymbol{\mu}(\mathbf{x_i}, \boldsymbol{\theta}) = \sum_i \tilde{w}_i \, \tilde{\boldsymbol{\mu}}(\mathbf{x_i}, \boldsymbol{\theta}),$$

Information matrix normalized by total cost $\mathcal{C}$,

$\tilde{w}_i = n_i c(\mathbf{x_i})/\mathcal{C}$; $\tilde{\boldsymbol{\mu}}(\mathbf{x_i}, \boldsymbol{\theta}) = \boldsymbol{\mu}(\mathbf{x_i}, \boldsymbol{\theta})/c(\mathbf{x_i}) \implies$ same framework,

same algorithms

Costs in design problems: *Elfving (1952), Cook, Fedorov (1995),*

Mentré, Mallet, Baccar (1997), Fedorov, Gagnon, Leonov (2002)

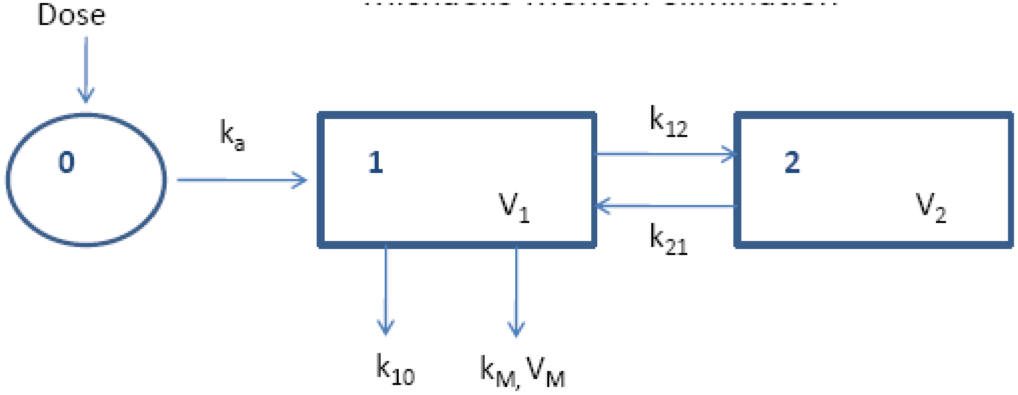
In PkStaMp: (a) Cost $c(\mathbf{x})$ proportional to # of samples in sequence **x**, or
(b) Entered by user for each candidate sampling sequence

More complex models: nonlinear kinetics

Two-compartment model, 1st order absorption,

Michaelis-Menten elimination: no analytical solution (ODE solver)

$$\begin{cases} \dot{f}_0(t) &= -k_a f_0(t) \\ \dot{f}_1(t) &= k_a f_0(t) \quad -(k_{12}+k_e) f_1(t) - \frac{(V_m/V) f_1(t)}{k_m + f_1(t)/V} \quad + k_{21} \; f_2(t) \\ \dot{f}_2(t) &= k_{12} \; f_1(t) \quad - k_{21} \; f_2(t), \end{cases}$$

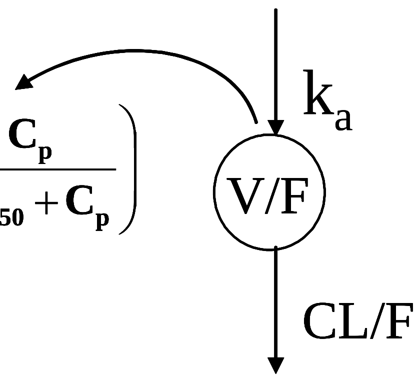


More complex models: combined PK/PD model

One-compartment PK and Emax PD model

Final PK/PD Model

$$E = E_o \cdot \left(1 - \frac{C_p}{IC_{50} + C_p}\right)$$



k_a: first-order absorption rate constant (h^{-1})
V/F: apparent volume of distribution (L)
CL/F: apparent systemic clearance (L/h)
E_o: PD endpoint at baseline (nM/min/mL)
IC_{50}: Drug X plasma concentration causing 50% inhibition of PD endpoint (ng/mL)

PK and PD compartments measured, in general, at different times

Another benchmark test: HCV

Proposed by France Mentré, Spring 2011: combination drug for treating chronic hepatitis C (HCV) infection

$$\begin{cases} \dot{f}_0(t) = -k_a f_0(t) + r(t) \\ \dot{f}_1(t) = k_a f_0(t) - k_e f_1(t) \\ \eta_1(t) = f_1(t)/V_1 \end{cases}$$

PK: parameters (k_a, k_e, V_1), response η_1 (continuous infusion term $r(t)$)

$$\begin{cases} \dot{g}_1(t) = -C_2 g_1(t) - C_1 g_1(t) g_3(t) + C_3 \\ \dot{g}_2(t) = -\delta g_2(t) + C_1 g_1(t) g_3(t) \\ \dot{g}_3(t) = C_4 \left[1 - \frac{1}{1+(EC_{50}/\eta_1)^n}\right] g_2(t) - c g_3(t) \\ \eta_2(t) = \log_{10} g_3(t) \end{cases}$$

$g_1(t)$ - "target cells", $g_2(t)$ - infected cells, $g_3(t)$ - viral particles (load)

PD: parameters (δ, EC_{50}, n, c), response η_2

HCV example: user-defined option

Design to be tested

- 12 sampling times for each patient
- Same times for PK and PD endpoints

Parameterization

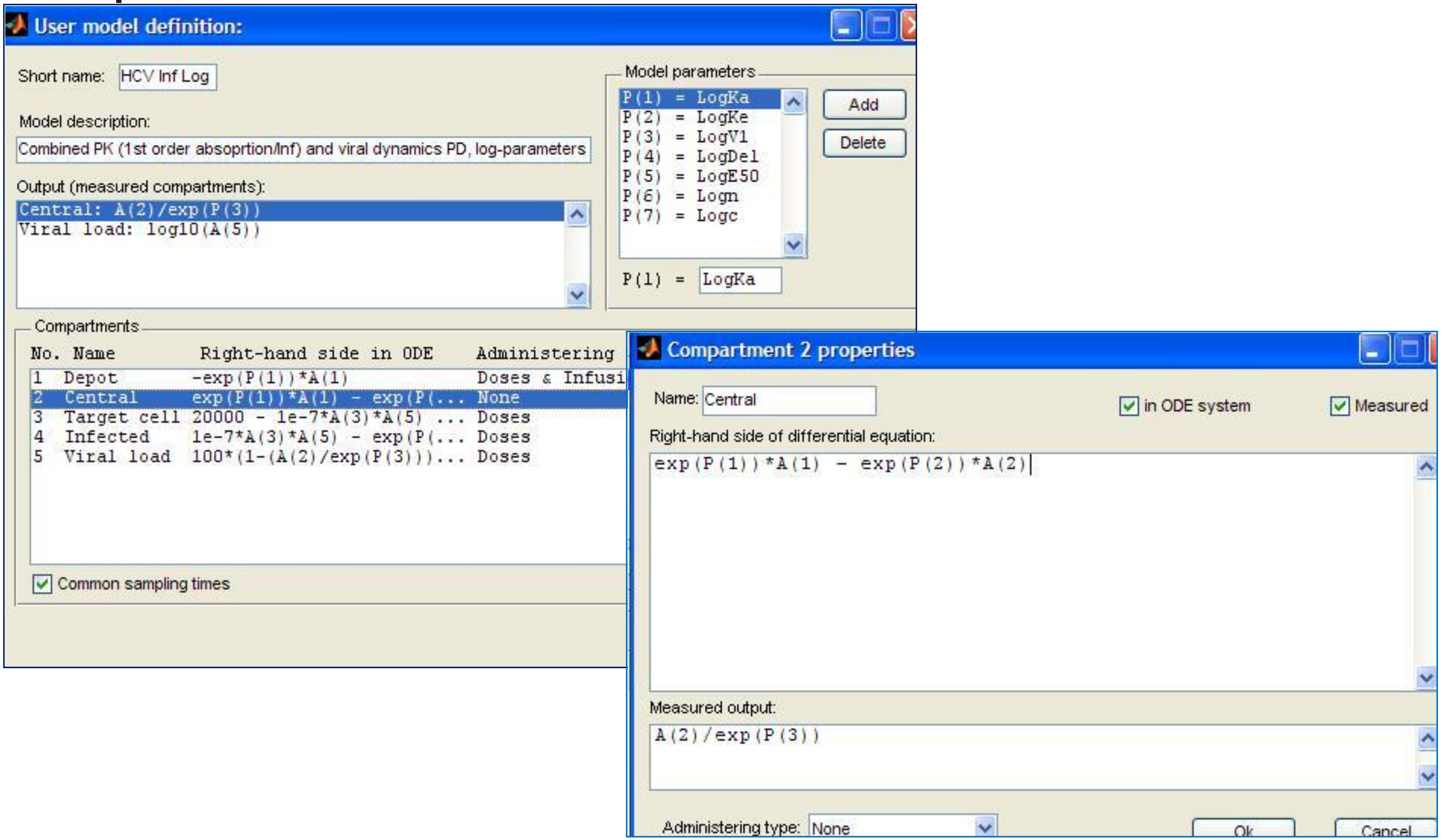
- Log-parameters
- Normal population distribution
- Diagonal population covariance matrix

User-defined option and last 2+ years of PkStaMp development:

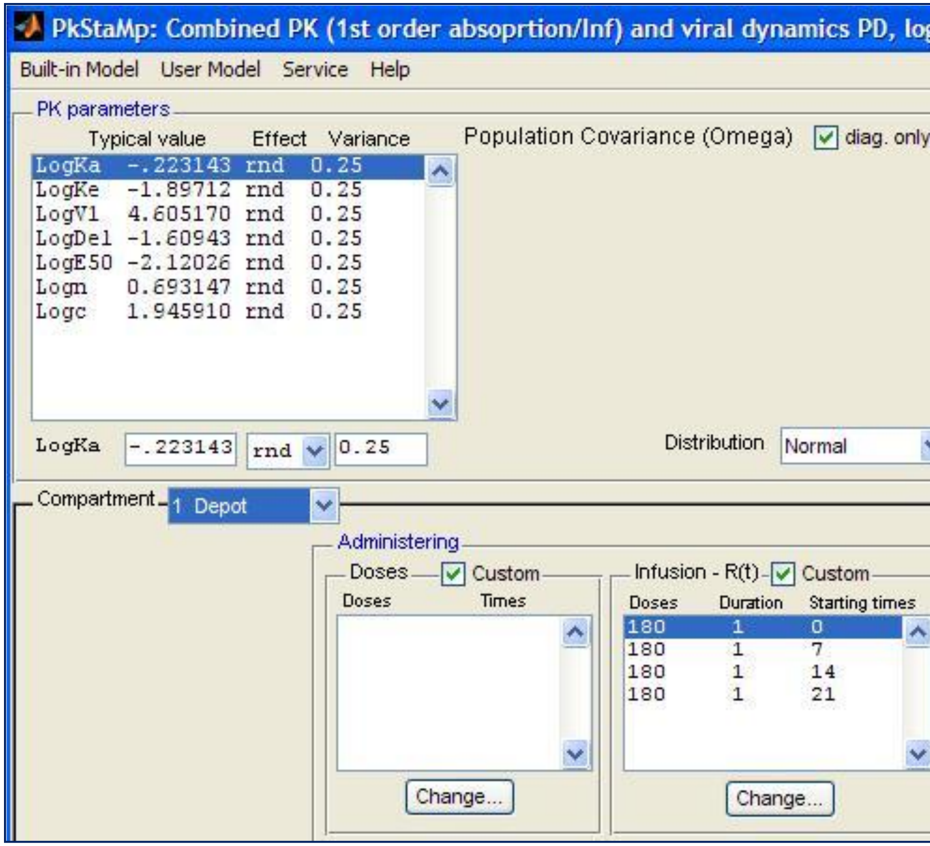
collaboration with Dr. Alexander Aliev (Institute for Systems Analysis, Russian Academy of Sciences, Moscow)

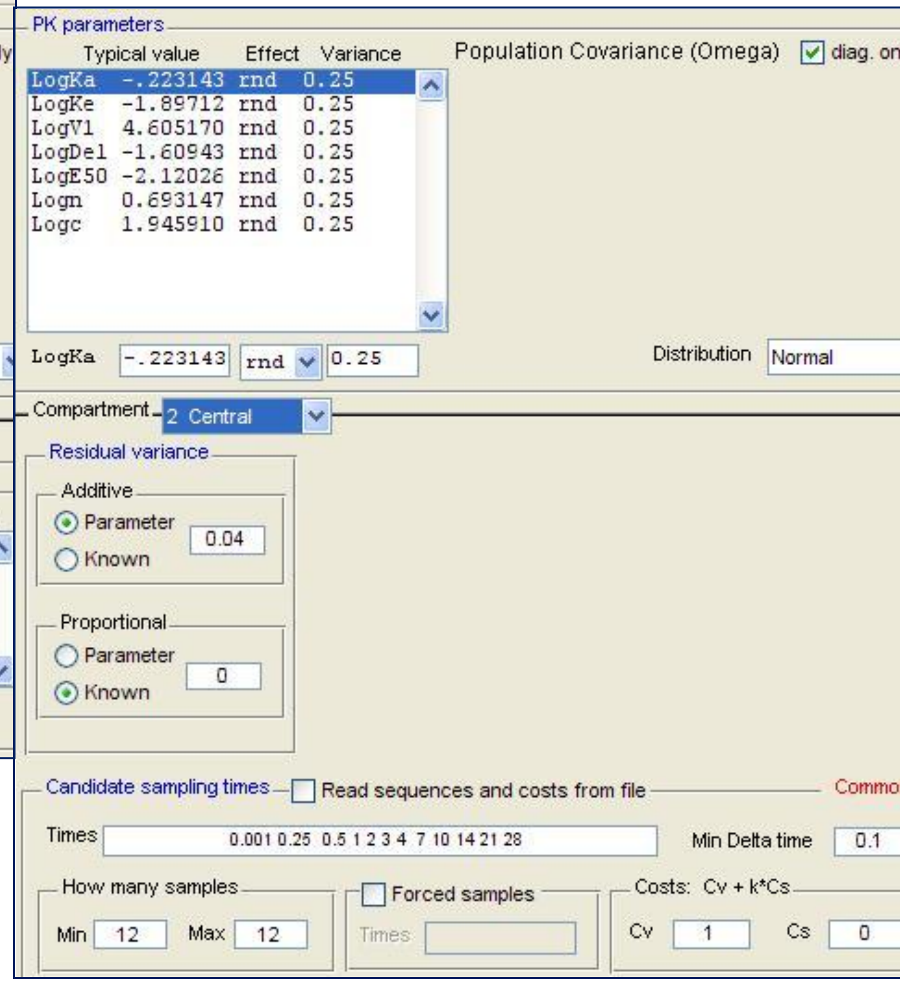
- "Arbitrary" system of ODE, and/or
- "Arbitrary" closed-form solution
- "Arbitrary" number of compartments

Model specification



Parameters, dosing (1), sampling (2)





PODE 2009-2010 comparison

Goal: compare FIM for a particular model/sampling sequence

Model: one-compartment, 1st order absorption, single dose $D = 70$ mg

Response parameters $\gamma = (k_a, CL, V)$, $k_e = CL/V$

Individual parameters $\gamma_i = \gamma^0 e^{\xi_i}$, $\xi_i \sim \mathcal{N}(\mathbf{0}, \mathbf{\Omega})$

$$\gamma^0 = (1, 0.15, 8), \; \mathbf{\Omega} = diag(0.6, 0.07, 0.02)$$

Measurements: $y_{ij} = \eta(\gamma_i, x_{ij}) \, [1 + \varepsilon_{M,ij}]$,

$$\{x_{ij}\} \equiv \mathbf{x} = (0.5, 1, 2, 6, 24, 36, 72, 120) \text{ hours}$$

$$\varepsilon_{M,ij} \sim \mathcal{N}(0, \sigma_M^2), \; \sigma_M^2 = 0.01; \; i = 1, \ldots, 32; \; j = 1, \ldots, 8$$

Combined parameter $\boldsymbol{\theta} = (k_a^0, \; CL^0, \; V^0; \; \omega_{k_a}^2, \; \omega_{CL}^2, \; \omega_V^2; \; \sigma_M^2)$

PODE 2009-2010 comparison (cont.)

Information matrix $\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$: block form, *Retout and Mentré (2003)*

$$\boldsymbol{\mu} = \left\{ \begin{matrix} \mathbf{A} & \mathbf{C} \\ \mathbf{C}^T & \mathbf{B} \end{matrix} \right\},$$

$$\begin{aligned} \mathbf{A} &= \mathbf{F}^T\,\mathbf{S}^{-1}\,\mathbf{F} + \tfrac{1}{2}\,\mathrm{tr}\ \ \text{(derivatives wrt } \gamma_\alpha\text{)} \\ \mathbf{C} &= \tfrac{1}{2}\,\mathrm{tr}\ \ \text{(mixed derivatives wrt } \gamma_\alpha \text{ and } [\omega_\beta^2, \sigma_M^2]\text{)} \\ \mathbf{B} &= \tfrac{1}{2}\,\mathrm{tr}\ \ \text{(derivatives wrt } [\omega_\beta^2, \sigma_M^2]\text{)} \end{aligned}$$

$\boldsymbol{\mu}(\mathbf{x},\boldsymbol{\theta})$ - information matrix of a single (k-dimensional) sequence $\mathbf{x}$:

$$\mu_{\alpha\beta}(\mathbf{x},\boldsymbol{\theta}) = \frac{\partial\boldsymbol{\eta}}{\partial\theta_\alpha}\,\mathbf{S}^{-1}\,\frac{\partial\boldsymbol{\eta}}{\partial\theta_\beta} + \frac{1}{2}\,\mathrm{tr}\left[\mathbf{S}^{-1}\,\frac{\partial\mathbf{S}}{\partial\theta_\alpha}\,\mathbf{S}^{-1}\,\frac{\partial\mathbf{S}}{\partial\theta_\beta}\right],$$

PODE 2009-2010 comparison (cont.)

- Compared $Var_a = [\mu(\boldsymbol{x},\boldsymbol{\theta})]^{-1}$ produced by different tools: identical results under the same assumptions
- Compared Var_a and Var_e : empirical variance-covariance matrix (Monte Carlo + estimation in NONMEM and Monolix):
  - If block **C** “excluded” (**C** = **0**), and 2nd term in **A** removed, then analytical results (1st order approximation) and Var_e are very close
  - If block **C** and 2nd term in **A** are both kept, then there is a visible difference for some elements of *Var*

Approximation options

Individual parameters, log-normal distribution:

$$\gamma_i = e^{\xi_i}, \ \xi_i \sim \mathcal{N}(\mathbf{0}, \mathbf{\Omega}),$$

- *1st-order approximation*, $\mathbf{E}\xi_i = 0, \ \mathbf{Var}(\xi_i) = V \implies$

$$\mathbf{E}_\xi(e^{\xi_i}) \simeq 1, \qquad \mathbf{Var}_\xi(e^{\xi_i}) \simeq V$$

- *Exact moments*: $\mathbf{E}_\xi(e^{\xi_i}) = e^{V/2}, \ \ \mathbf{Var}_\xi(e^{\xi_i}) = e^V(e^V - 1).$

- $V = 0.6 \implies \mathbf{E}_{1st} = 1, \ \mathbf{E}_{exact} = 1.35; \ \mathbf{Var}_{1st} = 0.6, \mathbf{Var}_{exact} = 1.50$

Parameter k_a

Approximation options (cont.)

2^{nd} - order approximation for mean/variance

$$\mathbf{E}_{\boldsymbol{\theta}}[\eta(x,\gamma_i)] \approx \eta(x,\boldsymbol{\gamma}^0) + \frac{1}{2}\,\mathrm{tr}\left[\mathbf{H}(\boldsymbol{\gamma}^0)\boldsymbol{\Omega}\right] ,$$

$$\mathbf{H}(\gamma^0) = \left[\frac{\partial^2\eta(x,\boldsymbol{\gamma})}{\partial\gamma_\alpha\,\partial\gamma_\beta}\right]\Bigg|_{\boldsymbol{\gamma}=\boldsymbol{\gamma}^0} \quad etc \quad \Longrightarrow$$

Numerically may be rather tedious

- All derivatives calculated numerically (central differences)
- Derivatives of variance $\boldsymbol{S}$ require second derivatives of η
- With 2^{nd} order approximation: fourth derivatives…..

Approximation options (cont.)

Calculation of mean/variance via Monte Carlo:

$$\widehat{\eta}(x_j) = \widehat{\mathbf{E}}_{\boldsymbol{\theta}}(y_{ij}) = \frac{1}{N}\sum_{i=1}^{N} y(x_{ij}) \ ,$$

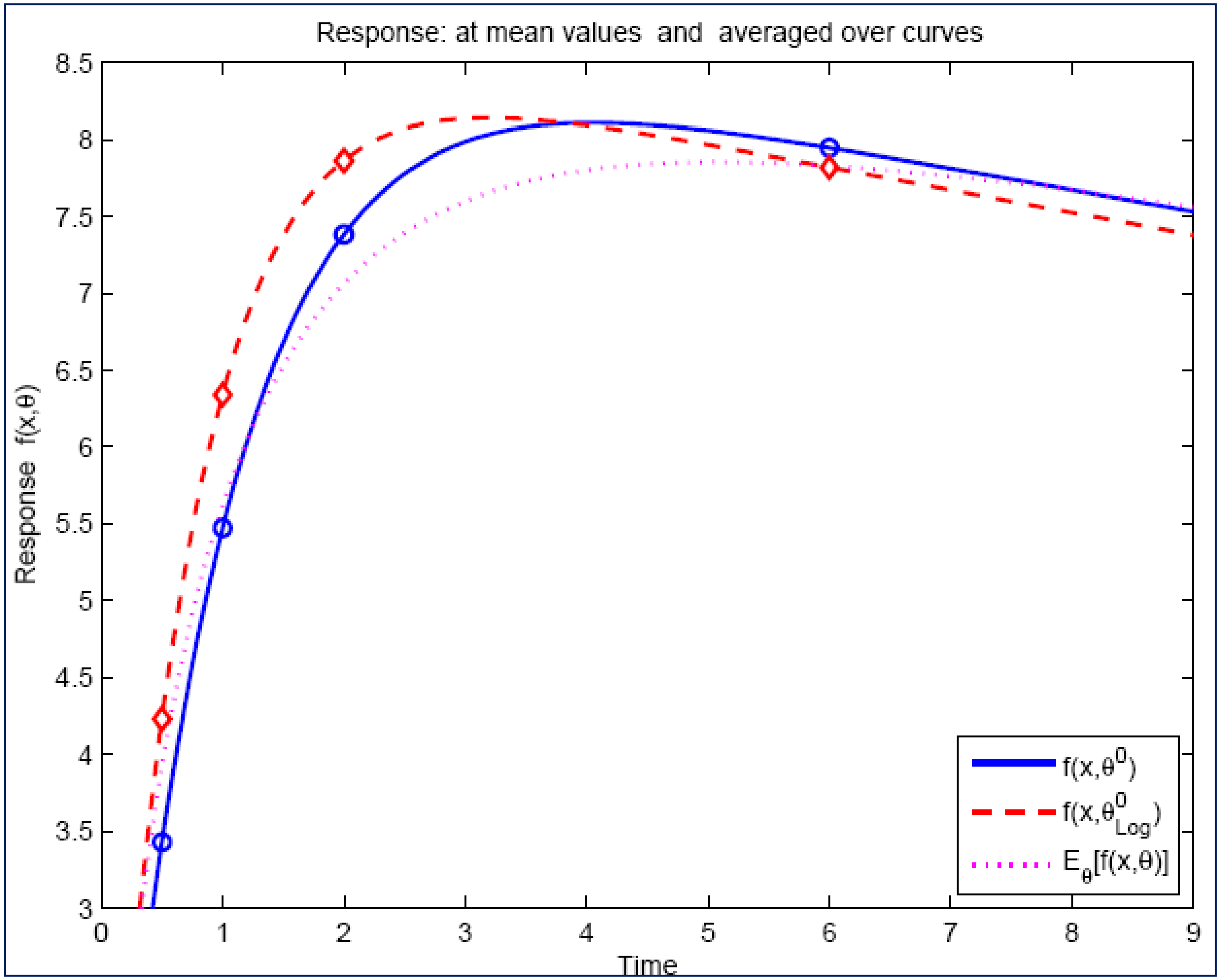
$$\widehat{S}(x_j) = \widehat{\mathbf{Var}}_{\boldsymbol{\theta}}(y_{ij}) = \frac{1}{N}\sum_{i=1}^{N}[y(x_{ij}) - \widehat{\eta}(x_j)]^2 \ \Longrightarrow$$

Numerically straightforward: OK if normal approximation is "reasonable"

FOCE: *Lindstrom, Bates* (1990)

Mielke, Schwabe (2010)

Approximation options (cont.)



Mean response curves for one-compartment model example

- Solid - 1st order approximation
- Dashed - computed at mean values of log-normal distribution,
- Dotted - Monte Carlo average

Approximation options

- Measures of nonlinearity:
  - *Curvature measures, intrinsic* vs *parameter effects*
  - *Bates and Watts* (1988), *Pázman* (1986), *Ratkowsky* (1983)

- Simulation studies for PK/PD, *Merlé and Tod* (2001)
  - Criteria values may be substantially affected by linearization
  - Designs and relative efficiencies are often <u>not</u>

- PODE 2009-2011 comparison/simulation studies:
  - Linearization (1st order) very crude, but performed reasonably well without block **C** (?)

Optimal design for PK/PD

- Chaloner and Verdinelli (1995), “Bayesian experimental design”, *Stat.Science*
  - There is a rich related literature, mostly non-Bayesian, on design for complex PK and biological models… With a few exceptions, this important work is not in the mainstream statistics literature…

Concluding remarks

Goals of population optimal design

- Find most informative sampling times
- Validate the quality of standard/alternative designs (optimal design as a reference/benchmarking)
- Test robustness of optimal designs (sampling windows)
- Reduce number of samples with “minimal” loss of precision
  - Example: from 16 sampling times – to 8 most informative

    D-efficiency Eff = $\left(|\mathbf{M}(\xi^*_8)| \,/\, |\mathbf{M}(\xi_{16})| \right)^{1/m} = 0.85$ (only 15% lost)
- May incorporate costs

Approximation options?

References

- Aliev, A., Fedorov, V., Leonov, S., McHugh, B. (2009). PkStaMp library for optimization of sampling schemes for PK/PD models. In: Ermakov, S.M., Melas, V.B., Pepelyshev, A.N. (Eds). *Proceedings of the 6th St. Petersburg Workshop on Simulation*, St. Petersburg, VVM com. Ltd, Vol.1, 368-374.
- Atwood, C.L.(1973). Sequences converging to D-optimal designs of experiments, *Ann. Stat*. **1**, 342-352.
- Bates, D.M., Watts, D.G. (1988). *Nonlinear Regression Analysis and Its Applications.* Wiley, New York.
- Chaloner, K.(1984). Optimal Bayesian experimental design for linear models. *Ann. Stat.,* **12**, 283-300.
- Chaloner, K. Verdinelli, I. (1995) Bayesian experimental design: a review. *Statistical Science,* **10**, 273-204.
- Elfving, G. (1952). Optimum allocation in linear regression theory, *Ann. Math. Statist*., **23**, 255-262.
- Fedorov, V.V., Gagnon, R., Leonov, S., Wu, Y. (2007). Optimal design of experiments in pharmaceutical applications. In: Dmitrienko, A., Chuang-Stein, C., D'Agostino, R. (Eds), *Pharmaceutical Statistics Using SAS.* SAS Press, Cary, NC, pp. 151-195.
- Fedorov, V.V., and Hackl, P. (1997). *Model-Oriented Design of Experiments*. Springer, NY
- Gagnon, R., and Leonov, S.L. (2005). Optimal population designs for PK models with serial sampling. *J. Biopharm. Stat*., **15** (1), 143-163.
- Graham, G., Aarons, L. (2006). Optimum blood sampling windows for parameter estimation in population pharmacokinetics experiments. *Stat. Med*., **25**, 4004-4019.
- Lindstrom, M.J., Bates, D.M. (1990). Nonlinear mixed effects models for repeated measures data. *Biometrics*, **46**, 673-687.

References

- Magnus, J.R., Neudecker, H. (1988). *Matrix Differential Calculus with Applications in Statistics and Econometrics*, Wiley, NY.
- Mentré, F., Duffull, S., Gueorguieva, I., Hooker, A., Leonov, S., Ogungbenro, K., Retout, S. (2007). Software for optimal design in population pharmacokinetics and pharmacodynamics: a comparison. In: Abstracts of the PAGE Annual Meeting. ISSN 1871-6032, http://www.page-meeting.org/?abstract=1179
- Mentré, F., Mallet, A., Baccar, D. (1997). Optimal design in random-effects regression models, *Biometrika*, **84** (2), 429-442.
- Merlé, Y., Tod, M. (2001) . Impact of pharmacokinetic-pharmacodynamic model linearization on the accuracy of population information matrix and optimal design. *J. Pharmacokin. Pharmacodyn.*, **28** (4), 363-388.
- Mielke, T., Schwabe, R. (2010). Some considerations on the Fisher information in nonlinear mixed effects models. In: Giovagnoli A, Atkinson AC, Torsney B (Eds) *mODa 9 – Advances in Model-Oriented Design and Analysis*. Physica-Verlag/Springer, Berlin, pp. 129-136.
- Pázman, A. (1986). *Foundations of Optimum Experimental Design*. Reidel, Dordrecht.
- Ratkowsky, D.A. (1990). *Handbook of Nonlinear Regression Models*. Marcel Dekker, New York.
- Retout, S., Mentrè, F. (2003). Further developments of the Fisher information matrix in nonlinear mixed effects models with evaluation in population pharmacokinetics. *J. Biopharm. Stat*., **13** (2), 209-227.
- Wynn, H.P. (1970) The sequential generation of D-optimal experimental designs. *Ann. Math. Statist.*, **41**, 1655-1664.