SOFTWARE FOR OPTIMAL DESIGN IN POPULATION PKPD: A COMPARISON

France Mentré[1], Stephen Duffull[2], Ivelina Gueorguieva[3], Andy Hooker[4], Sergei Leonov[5], Kayode Ogungbenro[6], Sylvie Retout[1]

1. INSERM U738, University Paris 7, Paris, France
2. School of Pharmacy, University of Otago, Dunedin, New Zealand
3. Global PK/PD, Lilly Research Centre, Windlesham, UK
4. Dpt of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden
5. GlaxoSmithKline Pharmaceuticals, Collegeville, PA, USA
6. Center for Applied Pharmacokinetic Research, School of Pharmacy, University of Manchester, Manchester, UK

OUTLINE

1. Population design
2. Software tools
3. Comparison
4. Conclusions

1. POPULATION DESIGN

Population PK/PD

- Population PK/PD studies increasingly performed during drug development
- Several methods/software for maximum likelihood estimation of population parameters using NonLinear Mixed Effects Models (NLMEM)
  - NONMEM
  - Splus/R: nmle, SAS: Proc NLINMIX
  - MCMC estimation methods: SAEM (MONOLIX), MC-PEM,…
- Problem beforehand: choice of population design
  - number of patients?
  - number of sampling times?
  - sampling times?
- Recommendations on design in the FDA guidance

Statistical estimation

Statistics:

1. Inference
2. Planning

1. Inference
   - hypothesis testing
   - **estimation**
   - prediction
2. Planning = find ‘optimal’ design given
   - objective (e.g.: estimation)
   - statistical method (e.g.: maximum likelihood)
   - experimental constraints
   - some prior knowledge on expected results (e.g.: models and parameters)

Evaluation of population designs

- Compare designs
  - predicted standard errors of each population parameter
- Optimal design
  - smallest estimation variance
  - greatest information in the data
- Two approaches
  - simulation studies
  - mathematical derivation of the Fisher Information matrix (MF)
    - Cramer-Rao inequality: MF^{-1} is the lower bound of the estimation variance

Fisher Information Matrix

- Problem in NLMEM because no analytical expression of the likelihood
  - Evaluation of MF using first order linearisation
    - first paper: Mentré, Mallet & Baccar, *Biometrika*, 1997
    - (see other references at the end)

- Since first theoretical work
  - Several statistical developments by different teams
  - Applications in drug development, in clinical pharmacology
  - Several software tools

Population Optimum Design of Experiments (PoDe)

- Creation of a multidisciplinary group: PODE
  - initiated by Barbara Bogacka (School of Mathematical Sciences, University of London)
  - discuss theory of optimum experimental design in NLMEM and their application in drug development

  www.maths.qmul.ac.uk/~bb/PODE/PODE2007.html

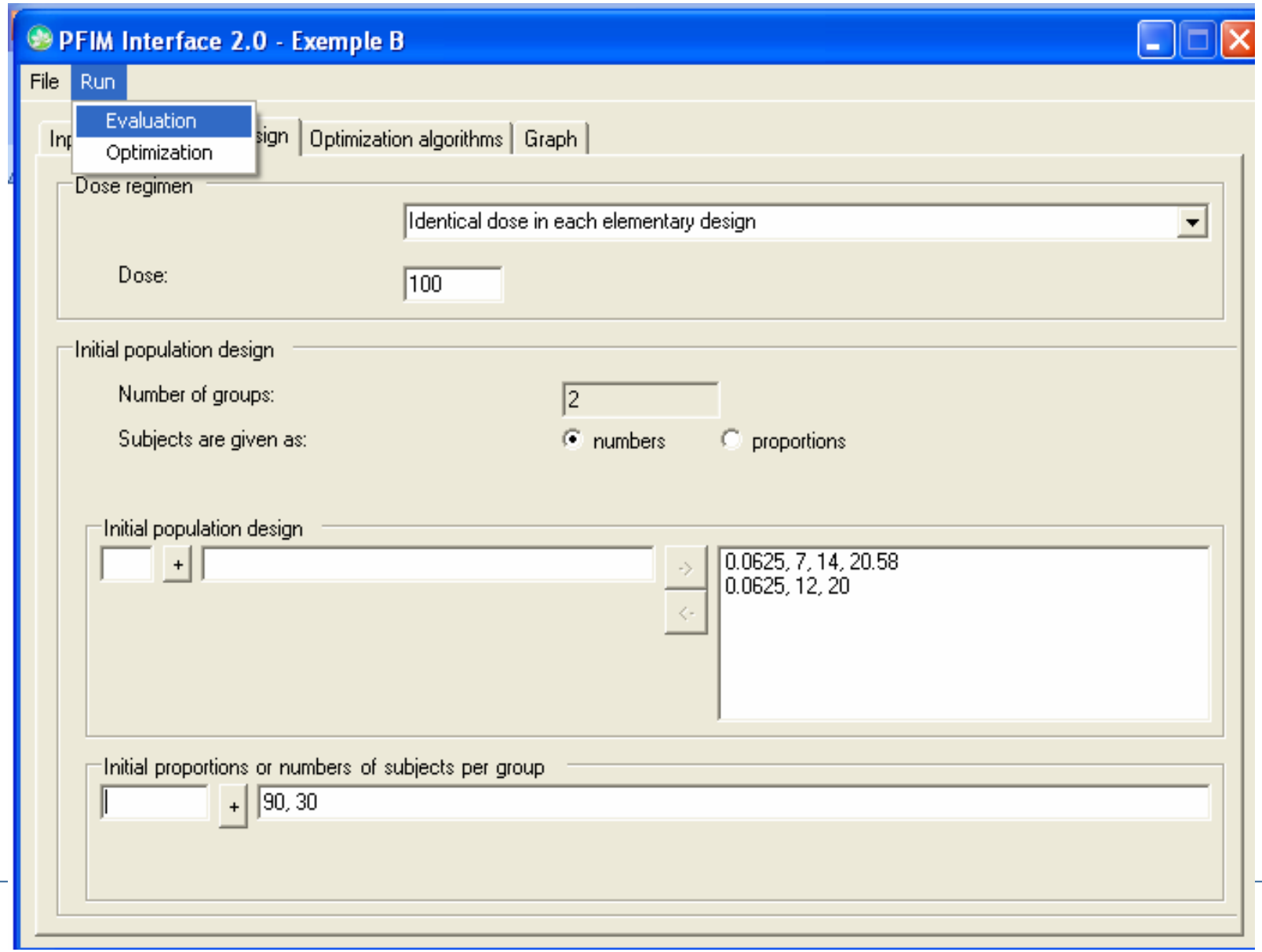
- One day workshop
  - May 2006: London, University of London (B. Bogacka)
  - May 2007: Sandwich, Pfizer (P. Johnson)
    - special session on software tools and their statistical methodology

2. SOFTWARE TOOLS (alphabetical order)

PFIM and PFIM interface

- Developed by Sylvie Retout and France Mentré
  - INSERM & University Paris 7
  - Other participants: Emmanuelle Comets, Hervé Le Nagard, Caroline Bazzoli
- Population Fisher Information Matrix
- Use R
- Available at www.pfim.biostat.fr
- History of PFIM
  - 2001: PFIM 1.1 similar in Splus and Matlab (S. Duffull)
  - 2003: PFIM 2.1 and PFIMOPT 1.0
  - June 2007: PFIM Interface 2.0 (evaluation and optimisation)
  - Soon PFIM 3 (beta version) and PFIM Interface 3

PFIM Interface 2.0

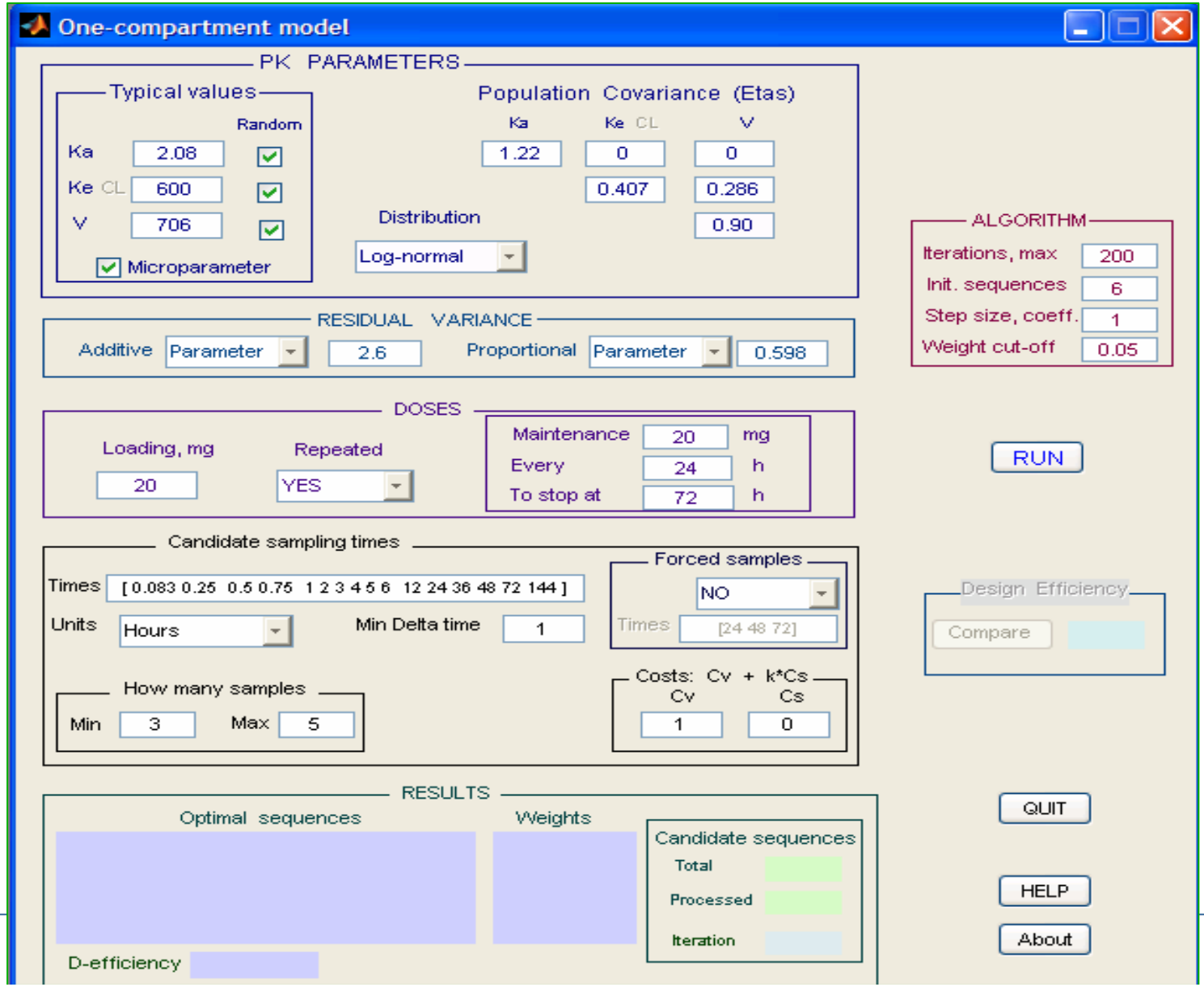


PkStaMP

- Developed by Sergei Leonov
  - Research Statistics Unit, GlaxoSmithKline
  - Other participants: Bob Gagnon, Brian McHugh, Valerii Fedorov
- Sampling Times Allocation - Matlab Platform
- Or STand Alone - Matlab Platform
  - (no need of Matlab)
  - free Matlab Component Runtime environment

- Not available outside GSK

PkStaMP


One-compartment model
PK PARAMETERS
Typical values
Random
Ka 2.08
Ke CL 600
V 706
Microparameter
Population Covariance (Etas)
Ka Ke CL V
1.22 0 0
0.407 0.286
0.90
Distribution
Log-normal
ALGORITHM
Iterations, max 200
Init. sequences 6
Step size, coeff. 1
Weight cut-off 0.05
RESIDUAL VARIANCE
Additive Parameter 2.6
Proportional Parameter 0.598
DOSES
Loading, mg 20
Repeated YES
Maintenance 20 mg
Every 24 h
To stop at 72 h
RUN
Candidate sampling times
Times [0.083 0.25 0.5 0.75 1 2 3 4 5 6 12 24 36 48 72 144]
Units Hours
Min Delta time 1
Forced samples
NO
Times [24 48 72]
Design Efficiency
Compare
How many samples
Min 3 Max 5
Costs: Cv + k*Cs
Cv 1
Cs 0
RESULTS
Optimal sequences
Weights
Candidate sequences
Total
Processed
Iteration
D-efficiency
QUIT
HELP
About

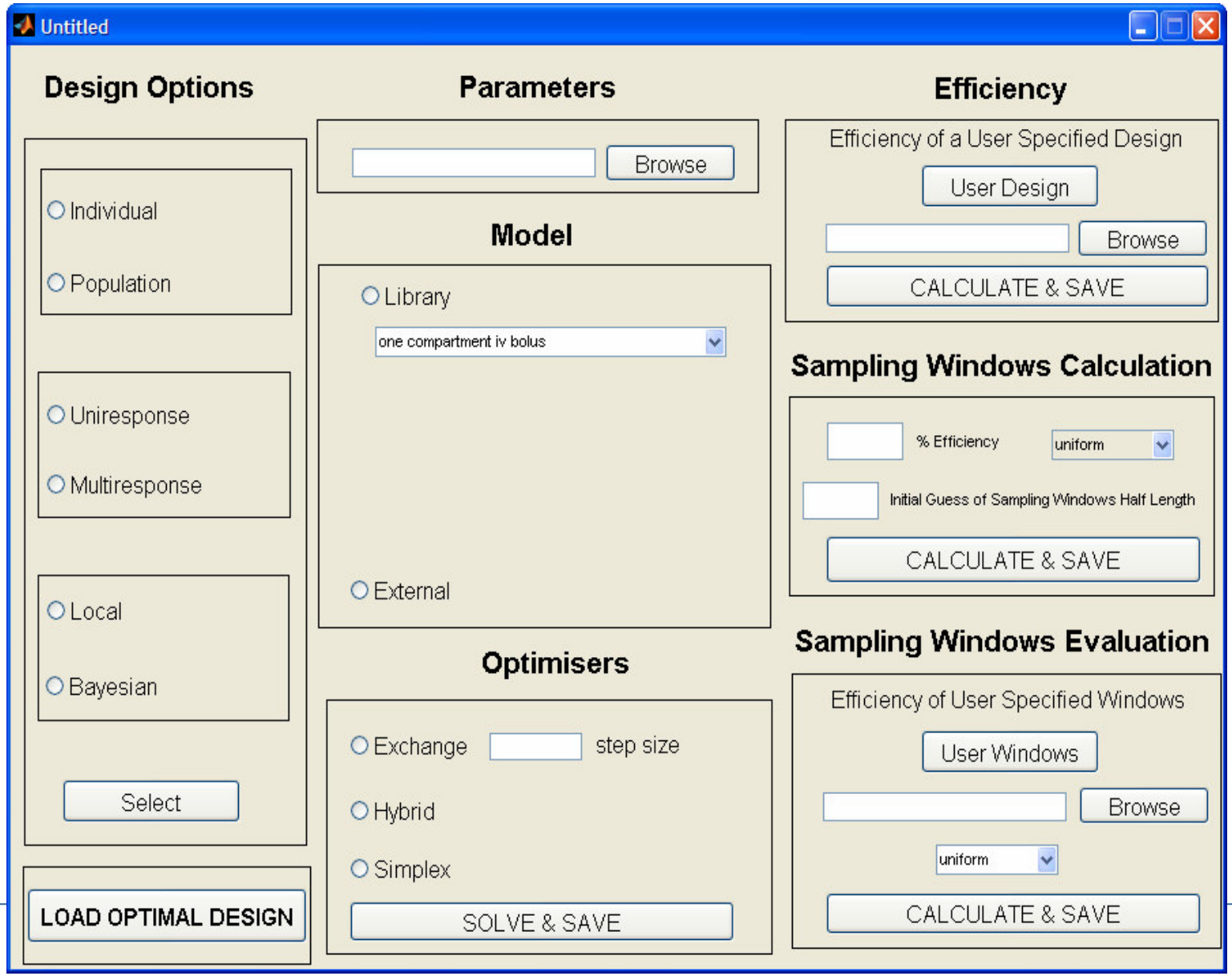
PopDes

The University of Manchester

MANCHESTER 1824

- Developed by Kayode Ogungbenro, Ivelina Gueorguieva and Leon Aarons
  - CAPKR, University of Manchester
- Population Design
- Matlab platform
- Available at www.capkr.man.ac.uk/PopDes
- Since April 2007 (on website)

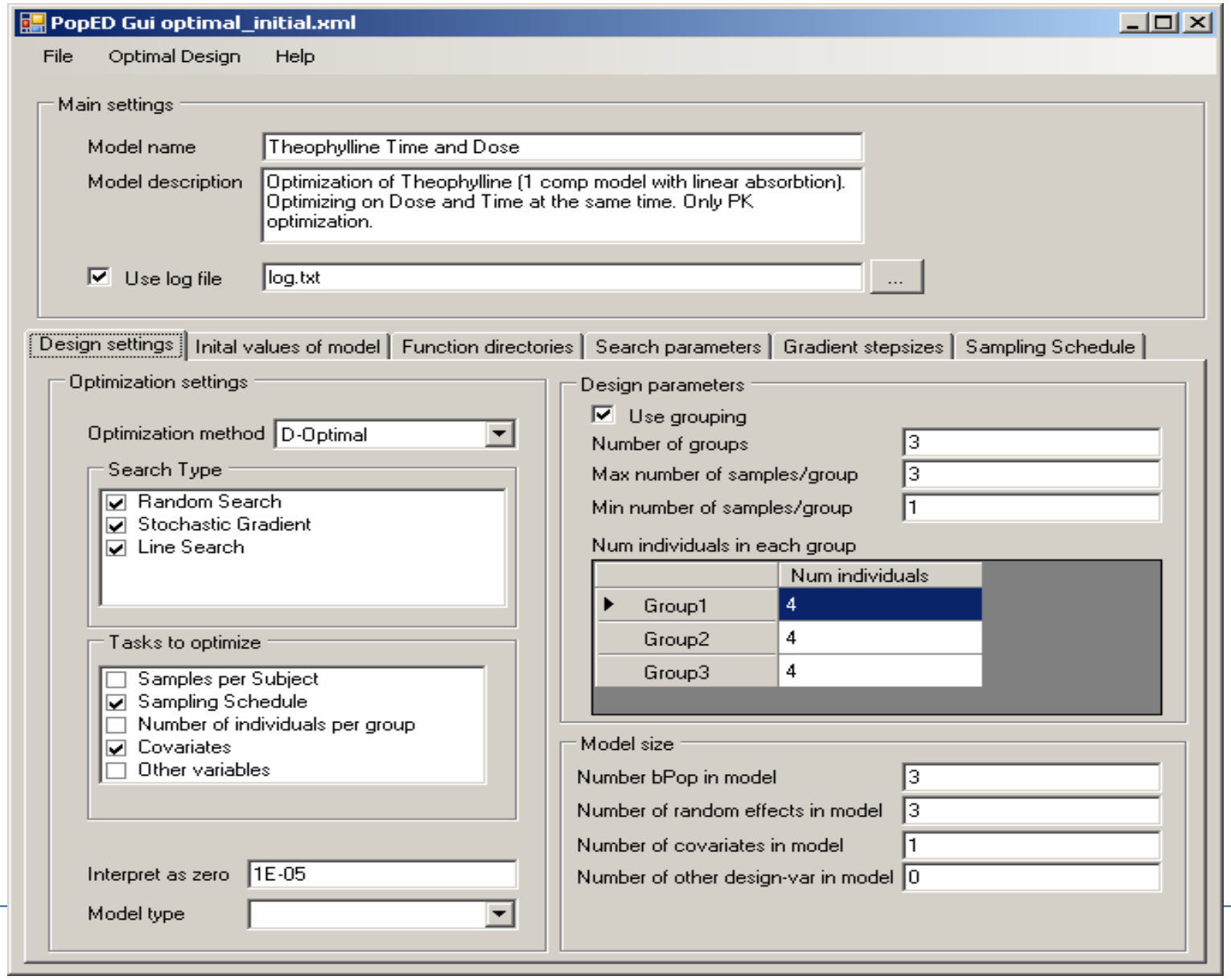
PopDes


Untitled
Design Options
Individual
Population
Uniresponse
Multiresponse
Local
Bayesian
Select
LOAD OPTIMAL DESIGN
Parameters
Browse
Model
Library
one compartment iv bolus
External
Optimisers
Exchange
step size
Hybrid
Simplex
SOLVE & SAVE
Efficiency
Efficiency of a User Specified Design
User Design
Browse
CALCULATE & SAVE
Sampling Windows Calculation
% Efficiency
uniform
Initial Guess of Sampling Windows Half Length
CALCULATE & SAVE
Sampling Windows Evaluation
Efficiency of User Specified Windows
User Windows
Browse
uniform
CALCULATE & SAVE

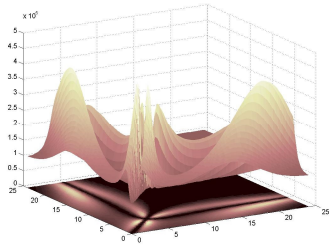
PopED

- Developed by Andy Hooker, Joakim Nyberg, Mats Karlsson
  - Uppsala University
- Population optimal Experimental Design
- Matlab platform
  - O-matrix with previous versions (University of Washington, Paolo Vicini)
- Matlab version available
  - by request andrew.hooker@farmbio.uu.se
  - soon (July 2007) from www.sourceforge.net
- Previous O-matrix version available
  - depts.washington.edu/rfpk/rd/software_popED.html
  - since March 2003

PopED

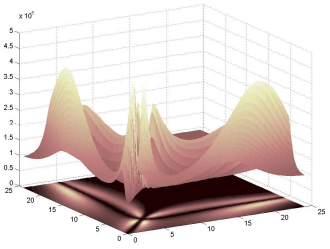

PopED Gui optimal_initial.xml
File
Optimal Design
Help
Main settings
Model name
Theophylline Time and Dose
Model description
Optimization of Theophylline (1 comp model with linear absorbtion). Optimizing on Dose and Time at the same time. Only PK optimization.
Use log file
log.txt
...
Design settings
Inital values of model
Function directories
Search parameters
Gradient stepsizes
Sampling Schedule
Optimization settings
Optimization method
D-Optimal
Search Type
Random Search
Stochastic Gradient
Line Search
Tasks to optimize
Samples per Subject
Sampling Schedule
Number of individuals per group
Covariates
Other variables
Interpret as zero
1E-05
Model type
Design parameters
Use grouping
Number of groups
3
Max number of samples/group
3
Min number of samples/group
1
Num individuals in each group
Num individuals
Group1
4
Group2
4
Group3
4
Model size
Number bPop in model
3
Number of random effects in model
3
Number of covariates in model
1
Number of other design-var in model
0

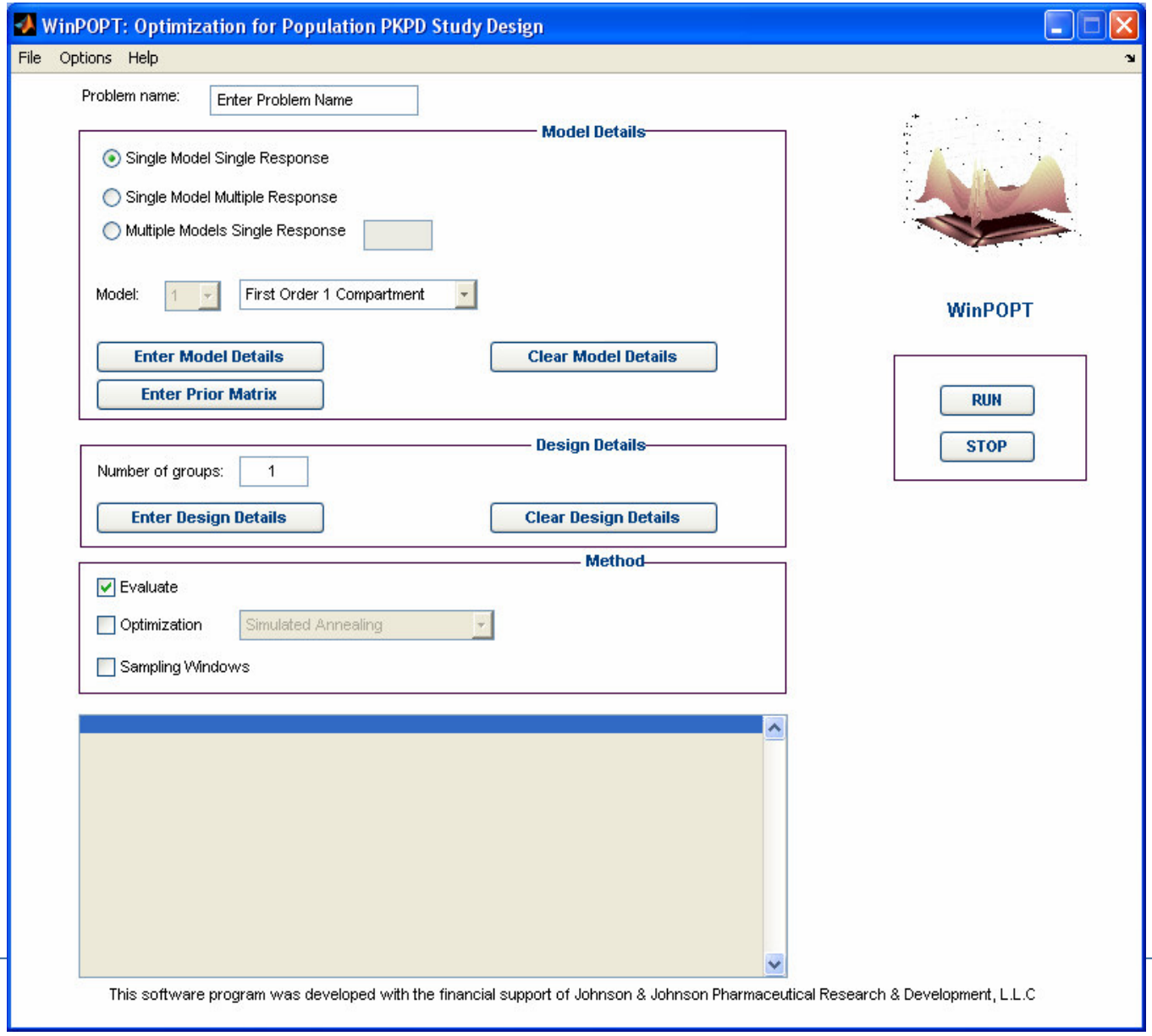
POPT and WinPOPT



- Developed by Stephen Duffull
  - University of Otago (NZ), University of Queensland, Johnson & Johnson
  - Other participants: Nick Denman, Hui Kimko, John Eccleston
- Matlab platform
- For WinPOPT:
  - stand alone version (no need of Matlab)
  - free Matlab Component Runtime environment
- Available at www.winpopt.com
- POPT: since July 2003
- WinPOPT: since March 2006

WinPOPT




WinPOPT: Optimization for Population PKPD Study Design
File
Options
Help
Problem name:
Enter Problem Name
Model Details
Single Model Single Response
Single Model Multiple Response
Multiple Models Single Response
Model:
1
First Order 1 Compartment
Enter Model Details
Clear Model Details
Enter Prior Matrix
Design Details
Number of groups:
1
Enter Design Details
Clear Design Details
Method
Evaluate
Optimization
Simulated Annealing
Sampling Windows
WinPOPT
RUN
STOP
This software program was developed with the financial support of Johnson & Johnson Pharmaceutical Research & Development, L.L.C

3. COMPARISON

Summary done by France Mentré from slides at PoDe2007 based on currently available versions (June 2007)

Language, availability, interface, models…

	PFIM	PFIM Int.	PkStaMP	PopDes	PopED	POPT	WinPOPT
Authors	Retout	Retout	Leonov	Ogungbenro	Hooker	Duffull	Duffull
Language	R	R	Matlab CR	Matlab	Matlab O matrix	Matlab	Matlab CR
Available on website	Yes	Yes	No	Yes	Yes	Yes	Yes
GUI	No	Yes	Yes	Yes	Yes	No	Yes
Library of PK models	No	Yes	Yes	Yes	Yes	Yes	Yes
Multi response models	No*	No*	Yes	Yes	Yes	Yes	Yes

Evaluation of information matrix

	PFIM	PFIM Int.	PkStaMP	PopDes	PopED	POPT	WinPOPT
Analytical derivatives	Yes	Yes	No	No	Yes	No	No
ODE Models	No	Yes	No	Yes	Yes	Yes	Yes
Off-diagonal terms in MF	Yes	No	*Yes*	Yes	Yes	No	No
Full covariance matrix Ω	No	No	Yes	Yes	No	No	No
Designs differ across responses	-	-	No	Yes	Yes	Yes	Yes

Optimisation

	PFIM	PFIM Int.	PkStaMP	PopDes	PopED	POPT	WinPOPT
Exact Design	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Design	Yes	Yes	Yes	No	No	Yes	No
Constraints	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Algorithm	Simplex Fedorov - Wynn	Simplex Fedorov - Wynn	Fedorov - Wynn	Simpex Exchange	Stochastic gradient	Simulated annealing Exchange	Simulated annealing Exchange
Design Structure	Yes	Yes	Yes	Yes	Yes	Yes	No
Bayesian design (ED)	No	No	No	No	Yes	Yes	No
Sampling Windows	No	No	No	Yes	Yes	Yes	Yes

Future developments

- All software tools have ongoing development that should fill the gap with the others
- Some have other specific features
  - See documentation or slides at PoDe2007
- Other statistical developments
  - Models with covariates
  - Models with inter-occasion variability
  - …
- Main limitation
  - First-order approximation
    - simulation results: closer to FOCE and SAEM than to FO
  - Exact evaluation of MF: stochastic approach or Gaussian quadrature

4. CONCLUSIONS

Conclusion of PoDe2007 Meeting

1. Start a distribution list: PopDesign
   - organised by S. Duffull
   - to register: http://lists.otago.ac.nz/listinfo/popdesign
   - to send an email: popdesign@lists.otago.ac.nz
   - any questions/comments on design in NLMEM and software tools
   - answers by all members of PoDe

2. Start a discussion 'Would it be possible to combine all software tools in one for future developments?'
   - to be organised by A. Hooker & F. Mentré
   - role of nlme consortium?

Conclusion

- Results of population PK/PD analyses increasingly used
  - in drug labeling
  - in test of covariates
  - for clinical trial simulation

  ➔ Informative studies with small estimation error
- Evaluation and comparison of population designs without simulation using statistical approach
- Results show that design may CONSIDERABLY affect precision of estimation

SPARSE-SAMPLING DESIGN = BEST INFORMATION NEEDED

- Several software tools available: no excuses!
  - define good population designs (ethical/financial reasons)
  - anticipate fatal population designs

Several Methodological References (1)

- PFIM
  - Mentré F, Mallet A, Baccar D. Optimal design in random-effects regression models. *Biometrika,* 1997, 84: 429-442.
  - Mentré F, Dubruc C, Thénot JP. Population pharmacokinetic analysis and optimization of the experimental design for mizolastine solution in children. *J Pharmacokinet Pharmacodyn*, 2001, 28:299-319.
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  - Retout S, Mentré F, Bruno R. Fisher information matrix for nonlinear mixed-effects models: evaluation and application for optimal design of enoxaparin population pharmacokinetics. *Stat Med*, 2002, 21: 2623-2639.
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  - Retout S, Mentré F. Optimisation of individual and population designs using Splus. *J Pharmacokinet Pharmacodyn*, 2003, 30: 417-443.
  - Retout S, Comets E, Samson A, Mentré F. Design in nonlinear mixed effects models: optimization using the Fedorov-Wynn algorithm and power of the Wald test for binary covariates. *Stat Med*, 2007 (in press).

Several Methodological References (2)

- PkStaMP
  - Fedorov VV, Gagnon R, Leonov S. Design of experiments with unknown parameters
  - in variance. *Appl Stoch Models Bus Ind,* 2002,18: 207-218.
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Several Methodological References (3)

- PopDES
  - Ogungbenro K, Graham G, Gueorguieva I, Aarons L. The use of a modified Fedorov exchange algorithm to optimise sampling times for population pharmacokinetic experiments. *Comput Methods Programs Biomed*, 2005, 80: 115-125.
  - Gueorguieva I, Aarons L, Ogungbenro K, Jorga KM, Rodgers T, Rowland M. Optimal design for multivariate response pharmacokinetic models. *J Pharmacokinet Pharmacodyn*, 2006, 33: 97-124.
  - Gueorguieva I, Ogungbenro K, Graham G, Glatt S, Aarons L. A program for individual and population optimal design for univariate and multivariate response pharmacokinetic-pharmacodynamic models. *Comput Methods Programs Biomed*, 2007, 86: 51-61.
  - Ogungbenro K, Gueorguieva I, Majid O, Graham G, Aarons L. Optimal design for multiresponse pharmacokinetic-pharmacodynamic models: dealing with unbalanced designs. *J Pharmacokinet Pharmacodyn*, 2007, 34: 313-331.
  - Ogungbenro K, Graham G, Gueorguieva I, Aarons L. Incorporating Correlation in Interindividual Variability for the Optimal Design of Multiresponse Pharmacokinetic Experiments. *J Biopharm Stat*, 2007 (in press).

Several Methodological References (4)

- PopED
  - Hooker A, Foracchia M, Dodds MG, Vicini P. An evaluation of population kinetic d-optimal designs via pharmacokinetic simulations. *Ann Biomed Eng,* 2003, 31: 98-111.
  - Foracchia M, Hooker A, Vicini P, Ruggeri A. PopED, a software for optimal experimental design in population kinetics. *Comput Methods Programs Biomed*, 2004, 74: 29-46.
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Several Methodological References (5)

- POPT/ WinPOPT
  - Duffull SB, Mentré F, Aarons L. Optimal design of a population pharmacodynamic experiment for ivabradine. *Pharm Res*, 2001, 18:83-89.
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  - Duffull SB, Waterhouse TH, Eccleston JA. Some considerations on the design of population pharmacokinetic studies. *J Pharmacokinetic Pharmacodyn*, 2005, 32:441-457.
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