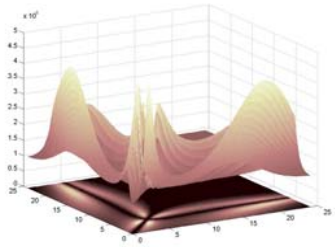
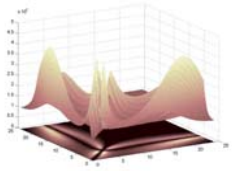


Walking With WinPOPT

www.winpopt.com

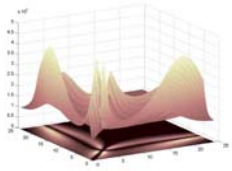
Stephen Duffull



WinPOPT Engine

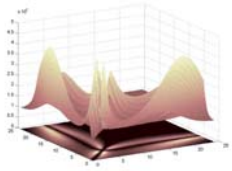
- WinPOPT is a Windows interface for POPT (v3)
- POPT is a set of MATLAB routines that provides extensibility to the application PFIM 1.2(i)
- PFIM is a MATLAB (.m) and SPLUS (.ssc) application for evaluating the Fisher information matrix for any given design
- PFIM was co-developed by France Mentre, Sylvie Retout and Stephen Duffull

- WinPOPT (C) copyright Stephen Duffull ver 1.1, Feb; 2nd 2006
- POPT (C) copyright Stephen Duffull ver 3.0, Oct; 5th 2003
- PFIM_M (C) copyright Stephen Duffull ver 1.2(i) May; 28th 2003



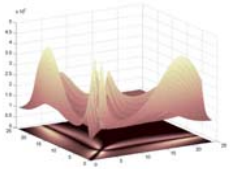
WinPOPT

- WinPOPT is a Windows GUI optimal design program
- It was developed in MATLAB but does not require MATLAB to run
- WinPOPT can run as either standalone or over a Network
- It is released with MCRInstaller which is an executable file that installs a MATLAB Component Runtime environment – this needs only be installed once.
- All releases of MATLAB will run under the same MCRInstaller file
- WinPOPT can be downloaded with the MCRInstaller including a 110 page user manual and a full range of worked examples

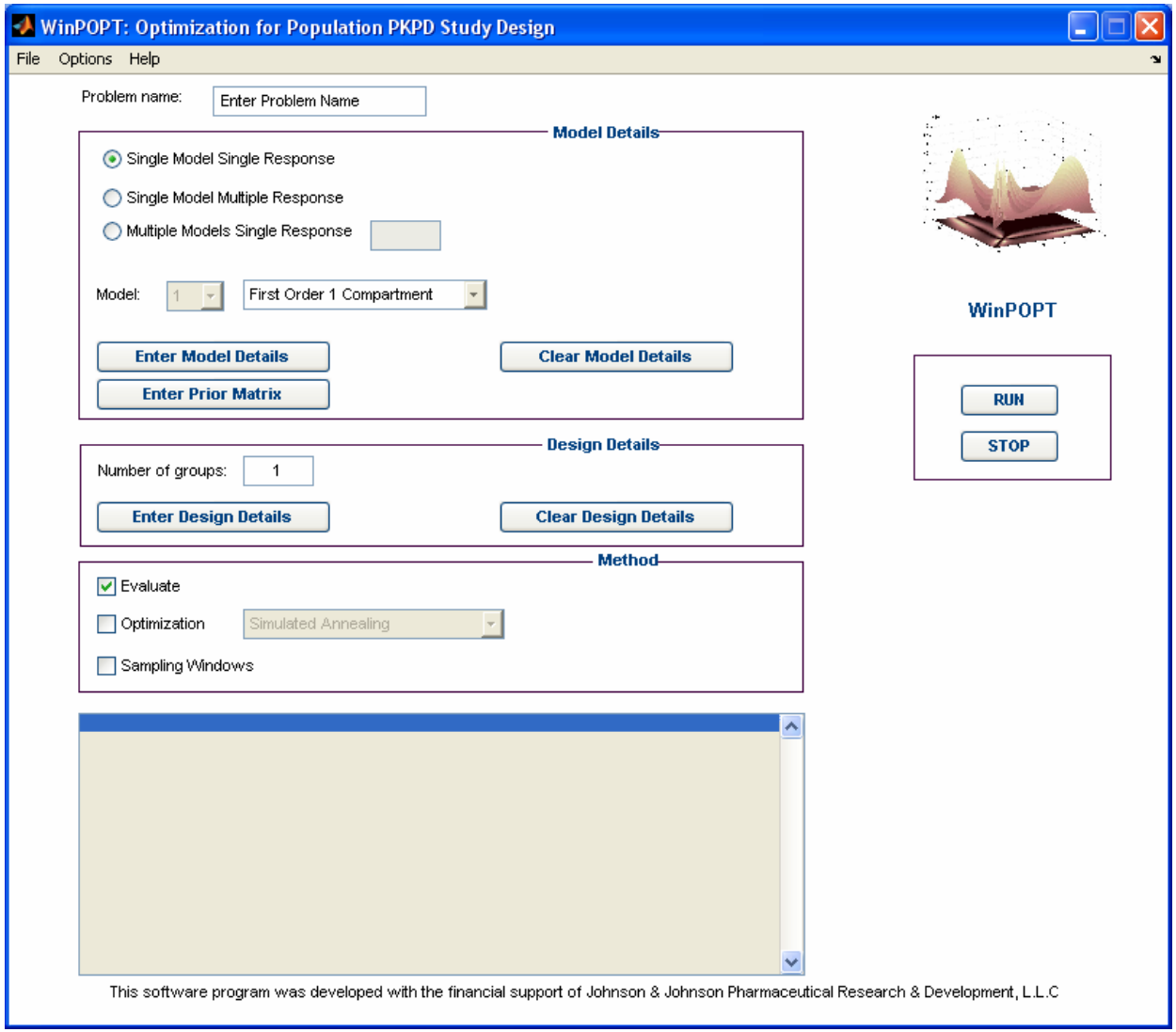


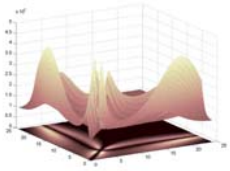
WinPOPT Availability

- WinPOPT is GNU licensed freeware
- It is available as compiled code free of charge
- POPT is available as uncompiled script files free of charge
- WinPOPT use
  - Registration = 52 researchers from 42 institutions from around the world (3rd May 07)
  - Software support is available for technical and design enquiries

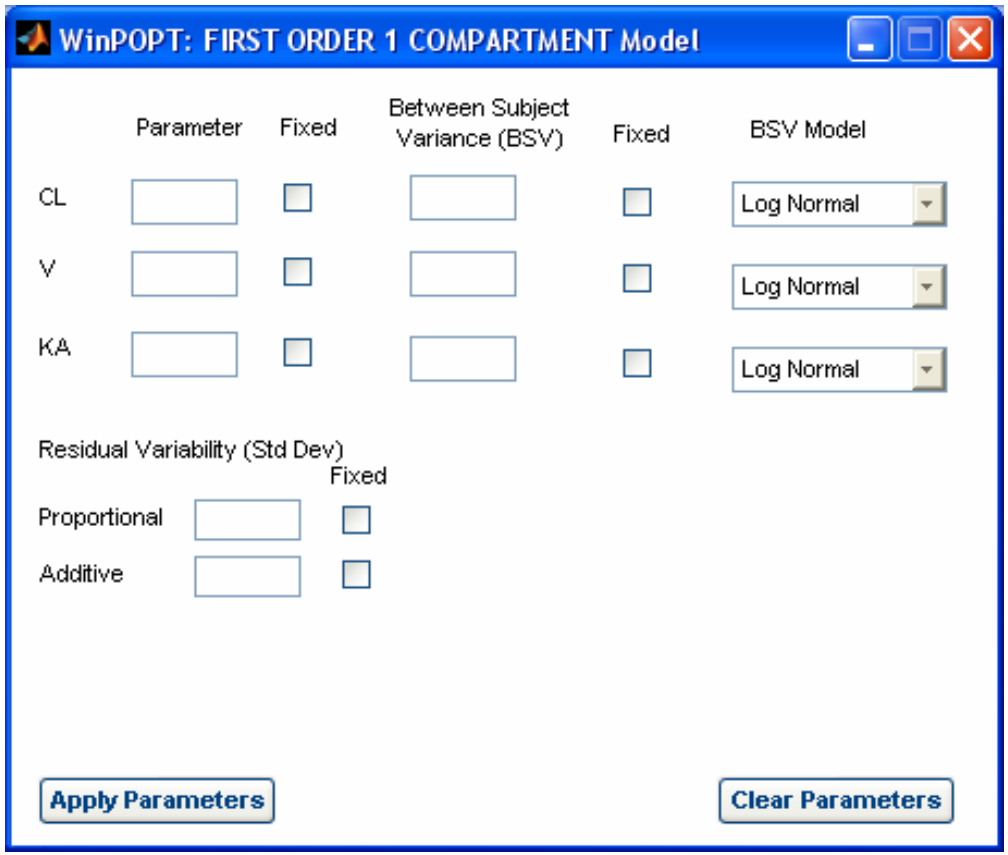


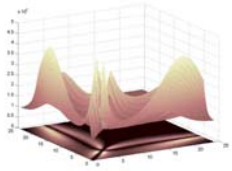
WinPOPT interface



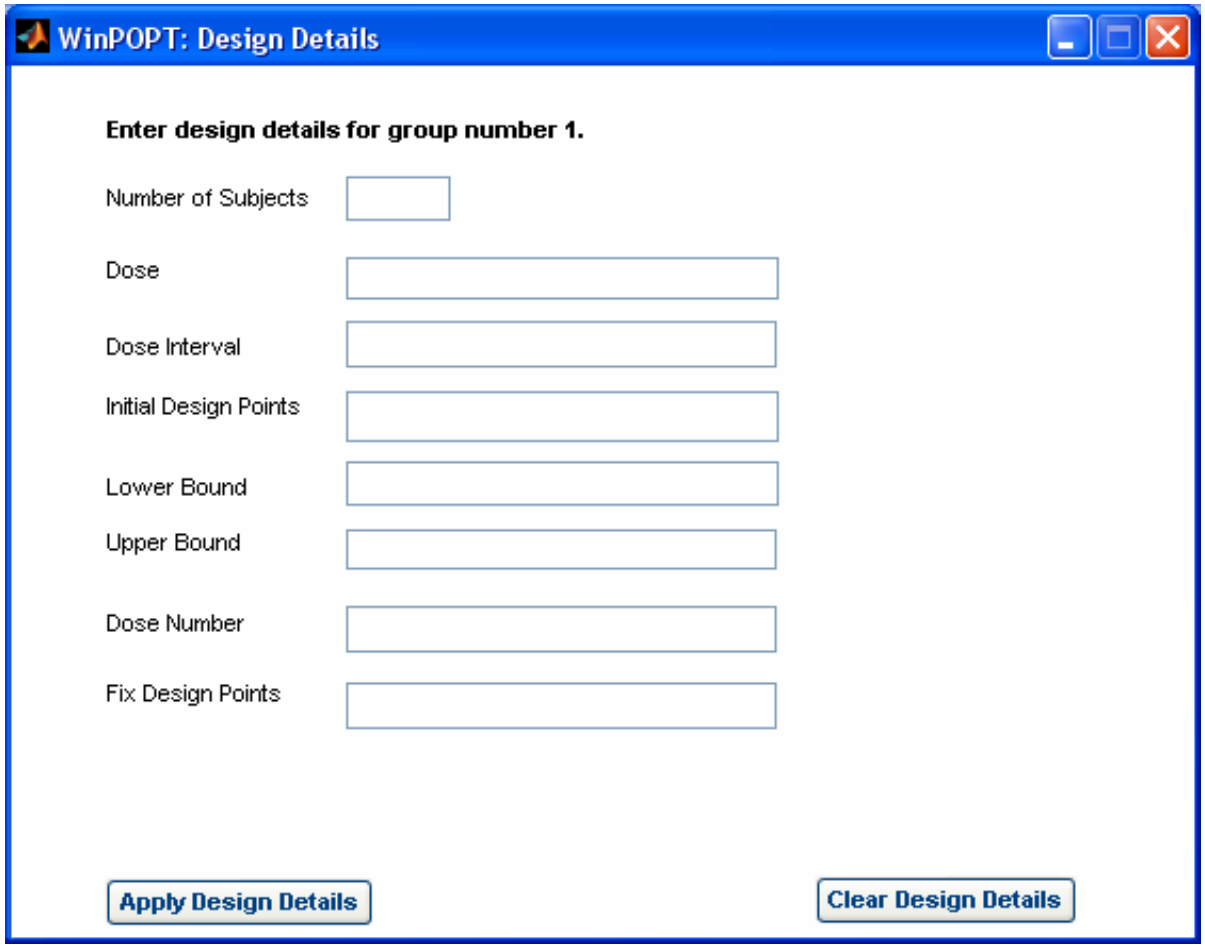


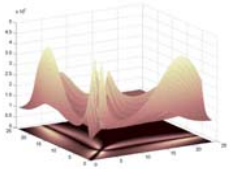
Specify model details GUI



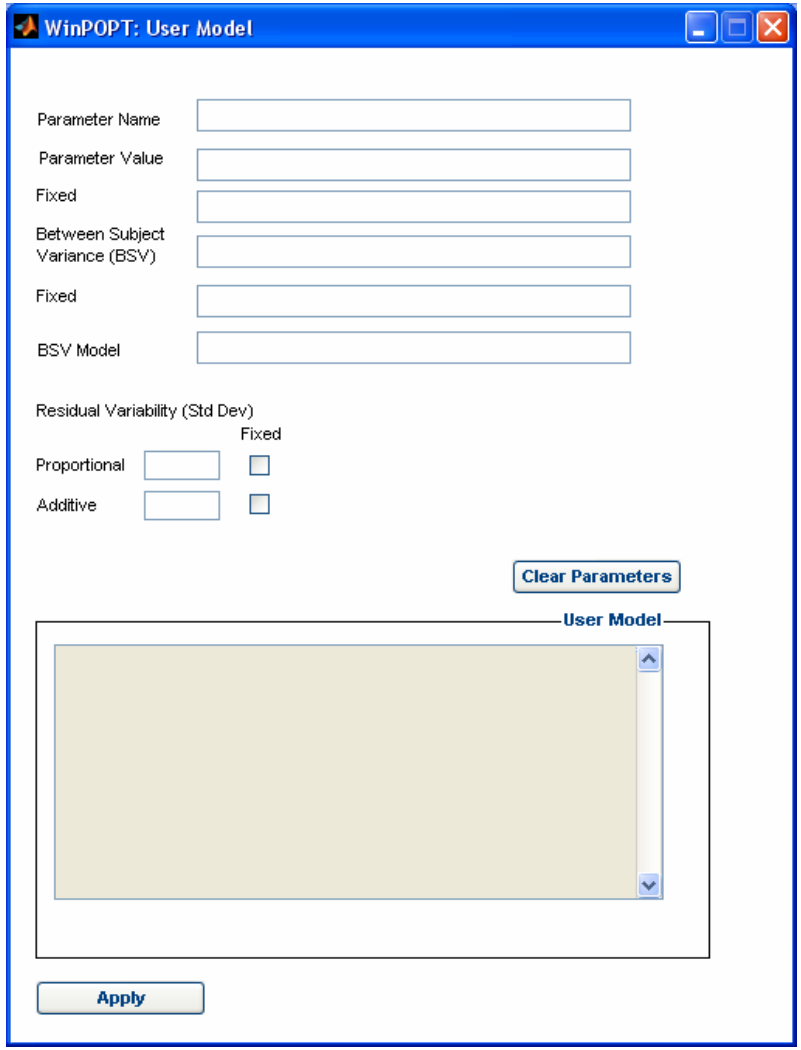


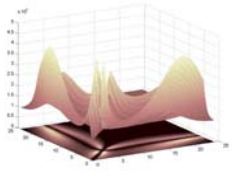
Specify Design GUI





Specify user defined model GUI

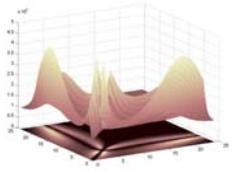




WinPOPT and POPT

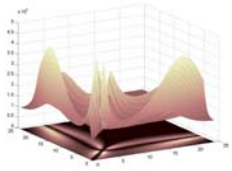
- Future WinPOPT development will include most POPT features
- Further and extensive development of WinPOPT is planned including different approximations to the information matrix

- In this talk (W) refers to WinPOPT and (P) refers to POPT



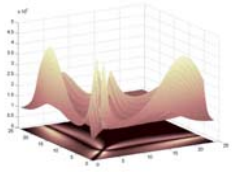
Pre-written Models

- Library (W only)
  - 1 & 2 compartment zero order input and first order input models with first order output
- Examples (W, P)
  - 3 compartment with zero order input and first order output
  - SMMR (1 and 2 compartment)
  - MMSR (closed form and ODE)
  - 1 compartment MM model



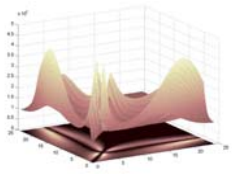
User defined models

- Any model that can be written in closed form including
  - Incorporation of complex numbers (W,P)
- Any model that can be written as an ODE including
  - Single and multiple dose solutions (W,P)
  - Ability to change integrator settings on-the-fly (P)



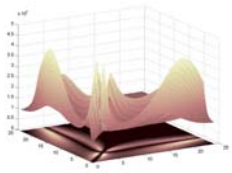
Model combinations supported

- Model structures supported automatically
  - SMSR
  - SMMR
  - MMSR
- Treat any parameter from any model as a fixed constant so the design does not optimize for it (W,P)
- Random effects may be normal or log normal for each parameter from any model (W,P)



Determination of the Information Matrix

- Based on a first order linearisation of the model about the random effects (as per Retout & Mentré)
- Off diagonal elements of OMEGA (covariance matrix of between subject effects) and SIGMA (covariance matrix of residual effects) are not currently allowed
- Variance of the occasion effects are also not currently allowed



Population Fisher Information Matrix (PFIM)

$$PFIM \approx \frac{1}{2}\begin{bmatrix} A(E,V) & C(E,V) \\ C^T(E,V) & B(E,V) \end{bmatrix}$$

$$A(E,V) = 2\frac{\partial E}{\partial \theta_m}^T V^{-1}\frac{\partial E}{\partial \theta_n} \quad m,n = 1...p$$

$$B(E,V) = tr\left(\frac{\partial V}{\partial \psi_m}V^{-1}\frac{\partial V}{\partial \psi_n}V^{-1}\right) \quad m,n = 1...p(+2), \quad \boldsymbol{\psi} = (\boldsymbol{\omega}^T, \boldsymbol{\sigma}^T)^T$$

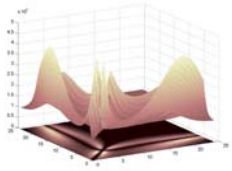
$$C(E,V) = tr\left(\frac{\partial V}{\partial \theta_m}V^{-1}\frac{\partial V}{\partial \psi_n}V^{-1}\right)$$

As a simplification $C(E,V)$ is set to a matrix of zeros

$$E = R \quad (\text{model response})$$

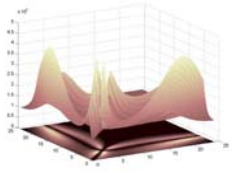
$$V = \frac{\partial E}{\partial \theta_m}\boldsymbol{\Omega}\frac{\partial E}{\partial \theta_n}^T + \boldsymbol{\Sigma}$$

Retout et al. Stat Med 2002; 21:2623-2639



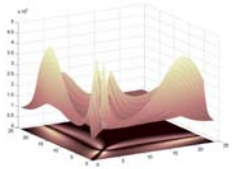
Optimization criteria

- D-optimality (W,P)
- Product D-optimality (W,P)
- ED-optimality (P)



Optimization algorithms

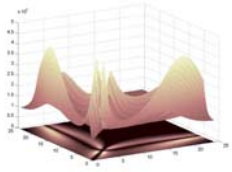
- Evaluation only (W,P)
- Exchange k=1 (W,P)
- Exchange k=2 (P)
- Simulated annealing (normal and fast methods) (W,P)



Design structures supported

$$\Xi = \begin{bmatrix} \boldsymbol{\xi}_1 & \cdots & \boldsymbol{\xi}_N \\ w_1 & \cdots & w_N \end{bmatrix}, \quad \boldsymbol{\xi} = \begin{bmatrix} x_1 & \cdots & x_n \\ v_1 & \cdots & v_n \end{bmatrix}$$

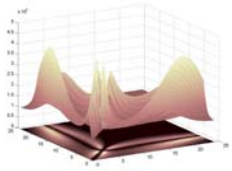
- If w, x, v are treated as continuous (C), discrete (D) or fixed (F) then…
  - FDD (W,P)
  - FCD (W,P)
  - CCD (P)



Design Constraints

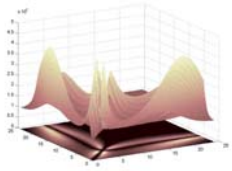
- Any sample can be specified to be taken from any dose (first or steady state …) or clinic visit (W,P)
- Different upper and lower bounds can be put on each sampling time to constrain the design search (W,P)
- All sampling times to be the same for all elementary designs (W,P)
- Two sets of sampling times over > 2 elementary designs (P)
- All times on an occasion to be identical over all elementary designs (P) while all other samples allowed to be optimised
  - Occasion can be defined as a treatment period or as a defined duration of time within a treatment period

- … <<many more>> …



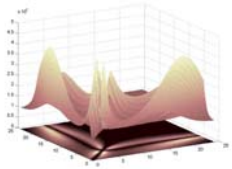
Sampling Windows

- MC sampling for joint design windows (W,P)
- Define
  - minimum efficiency of windows
  - Initial estimates of windows
  - Percentile of windows to report



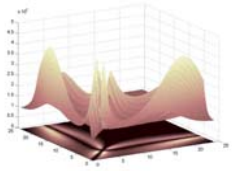
Unbalanced multiple response models

- You can specify any type of design you like (W,P)
  - e.g. both responses taken at the same set of times
  - response 1 taken at different times to response 2
- Utilise an EVID data item that specifies the system is reset after a specified dose (P)



Correlations between random effects

- Not allowed at this stage (future development)

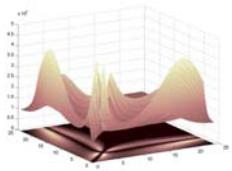


Additional extensibility

- Formal incorporation of prior information (W,P)
- Fixed sampling times (W,P)
- Lockout (W,P)
- Writes NONMEM data template (W,P)
- Produces graph of model responses with optimal sampling times (W)
- Estimates individual information matrix and population simultaneously (P)
- FOCE (P)
- Incorporation of covariates – ED-optimality (P)
- Treating sampling times as a random variable (P)
- Single or multiple dose (W,P)
- Multiple ascending dose structures (P)

Outputs (W)

- User specifies directory for outputs
- Design specification file
- Result file (ascii or as Word document)
- Full design-model Matlab file so that the design can be recreated after closing WinPOPT
- Print model and design output
- Print model responses to Excel compatible file
- Create NONMEM data template file (ID, TIME, AMT …) for simulation-estimation (W,P)



WinPOPT Development Team

- Stephen Duffull (University of Otago)
- Nick Denman (University of Queensland)
- Hui C Kimko (J&J PRD)
- John Eccleston (University of Queensland)