



## What is PopED 2

PopED is an Optimal Experimental Design tool for Non-Linear Mixed Effect Models [1]. Key features of PopED include the ability to assume distributions around model parameter values (ED-optimal design), the optimization over multiple possible models as well as the optimization of design parameters other than sampling times (doses, infusion lengths, sizes of experiments, etc.). PopED consists of two parts, the Graphical User Interface (GUI) written in C# .NET and the script part written in MATLAB, both are open source freely available at <http://poped.sf.net>

## Features of PopED 2

- Expectation (global) optimal design (ED) & local optimal design (D)
- Optimization on multiple response models
- Optimization on other discrete or continuous design variables, e.g. doses, study length, number of individuals etc.
- Optimize on Cost/Penalty functions
- User defined distributions (ED-distributions)
- User defined response models, residual models and interindividual variability models
- Fisher Information Matrix (FIM) based on, first order (FO) approximation, first order conditional (FOCE) approximation or first order conditional with interaction (FOCEI) approximation
- Include inter occasion variability (IOV)
- Correlation between interindividual variability (IIV) parameters
- Differential equation models (ODE) with closed form solutions solver for linear ODEs, memory solvers and Matlab solvers
- Criteria available: A, D, In D, D<sub>s</sub>, all as global and local criteria with the possibility to fix parameters
- Analytic derivatives or complex differentiation in the calculation of FIM
- Optimization algorithms: Random Search, Stochastic Gradient, Line Search or Modified Exchange Algorithm
- Extensible model template library with 1-3 compartment models + various model examples
- Grouping of sample times and other design variables between design groups and design responses
- Latin Hypercube sampling for conditional approximations and global designs

## The PopED 2 graphical users interface (GUI)

- GUI written in C# .NET
- Communicates with MATLAB via XML files and/or COM server.
- Allows for development of optimal design input files without the need for MATLAB.
- Optimal calculations (in MATLAB) can be run on a server.

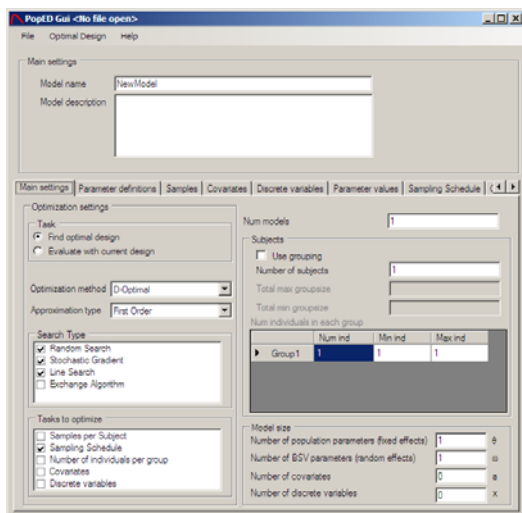


Figure 2. PopED GUI main window.

## Tools in PopED 2

- Typical value plot of the models
- Simulation tool for the models
  - Creation of simulated data file (Comma Separated file, CSV)
  - Simulate with different levels of randomness, i.e. with/without ED-uncertainty, with/without residual variability and with/without interindividual variability
  - Plot data or prediction interval (Visual Predictive Check)

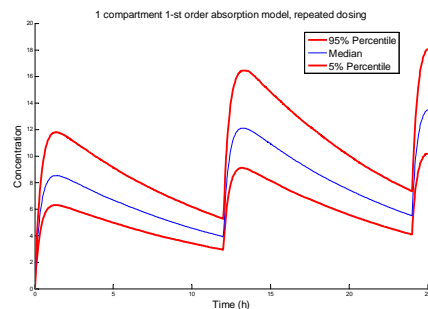


Figure 1. A simulation in PopED showing the median and the 5 and 95 % percentiles. The simulation is done without residual variability and simulated with 1000 individuals at 1000 time points each.

- 3 dimensional plot of parts of the FIM surface
  - x, y – axis could be any design variable, e.g. sample times, covariates, discrete variables or group sizes
  - z-axis could be the criterion function, the normalized criterion function, the efficiency or a coefficient of variation of any parameter in the FIM

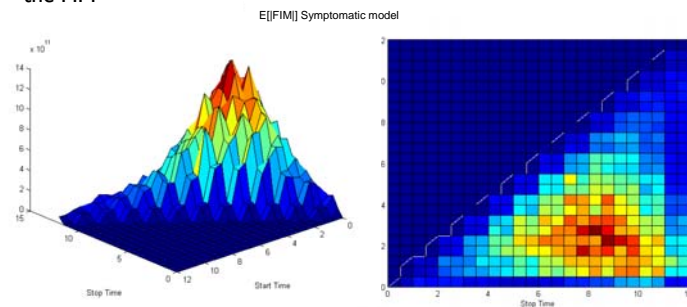


Figure 3. 3d surface, left panel, and viewed from above (right panel) of the start time versus the stop time of a disease progression study for a drug with a symptomatic effect. The colors represent the E[[FIM]], red color indicates more information. The ED uncertainty were 15% of the slope parameter in the symptomatic linear disease progression model.

- Tool to calculate sampling, covariates and discrete variables – windows
- Plot optimization results, e.g. the optimal sample times, doses etc.

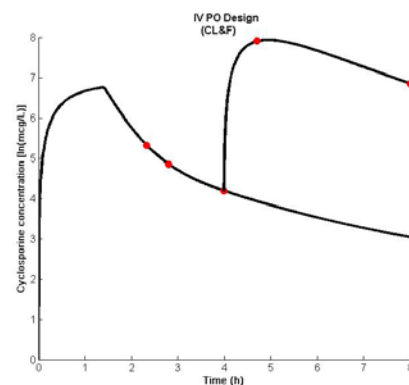


Figure 4. Optimization results for a Cyclosporine population model with an infusion followed by an oral dose, optimized for precision of the individual parameters (CL and F). The figure shows the optimal sample times (red dots) as well as the profiles for a typical patient after an optimal dose. The optimized infusion length is also visible in the figure.

## Reference:

1. Foracchia, M., et al., POPED, a software for optimal experiment design in population kinetics. *Comput Methods Programs Biomed.* 2004, 74(1): p. 29-46.