Platform for adaptive optimal design of nonlinear mixed effect models

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Model based drug development
Outline

• Robust optimal design
• Adaptive optimal design (AOD)
• Platform for testing and performing AOD trials (DDMORE)
• Exploring AOD
  – Pediatric bridging studies (PK)
Robust optimal design

• Standard optimal design requires knowledge about the underlying model and parameter values for that model

\[ FIM(\text{models }_{\text{fixed}}, \text{parameters }_{\text{fixed}}, \text{design}) \]

• What if we don’t know the model or we don’t have a good guess for the parameters of a model?
Robust optimal design (2)

- Assume your parameters have distributions
  - (“E-family”, e.g. ElnD)
- Problems if:
  - Distribution does not overlap the true value
  - One region of parameter values “drive” the design

Robust optimal design (3)

• Incorporate multiple models into your optimization

\[ \Psi_{P-D} = \arg \max_{\xi} \left( \sum_{i} \log \left( |FIM(\xi, \Phi_i)^{\alpha_i} \left| p_i \right| \right) \right) \]

m=model #, \( \alpha_i \) = weighting and \( p_i \) = # of parameters

• Problems if:
  – “true” model is not one of the candidate models.
  – Parameters are not near the “truth”

Hooker and Vicini, J. AAPS, 2005
Waterhouse and Duffull, JPKPD, 2005
Problems with robust design

• If you have too much uncertainty or too many potential models:
  – Rich design covering entire design space is needed

• Are there other ways to deal with uncertainty?
Adaptive Optimal Designs (AOD)

• Another type of robust design

• Adapt and update your understanding of the system (the model) at intermediate steps within a trial, then re-optimize
Some previous work with AOD

- A recent survey has found that for 10 European pharmaceutical companies the importance of AOD for NLMEM was ranked, on average, 4 on a scale of 5 (Mentre et al. CPT:PSP, 2013).
- Previous work has demonstrated the usefulness of AOD in
  - PET occupancy studies (Zamuner et al. CPT, 2010).
  - population PK in children (Dumont et al. PAGE, 2012).
Design of future studies 1

Model guesses $M_{G0}$
Param. guesses $P_0$
Param. uncertainty $P_{se,0}$
Prior$_0$ = FIM$_0$

Optimal Design

Design ($Q_1$)

STUDY

Cohort 1

Data ($Y_1$)
Prior$_0$

Estimation

Possible models ($M_1$)
Estimates ($P_1$, $P_{se,1}$)
Obs. FIM (FIM$_{obs,1}$)

Stop criterion achieved?

…

Design of future studies 2

$M_1$, $P_1$, $P_{se,1}$
FIM$_{obs,1}$, Prior$_1$
New model guesses $M_{G,2}$

Optimal Design

Design ($Q_2$)

STUDY

Cohort 2

Data ($Y_2 \pm Y_1$)
Prior$_1$

Estimation

Possible models ($M_2$)
Estimates ($P_2$, $P_{se,2}$)
Obs. FIM (FIM$_{obs,2}$)

Stop criterion achieved?

…

Design of future studies $N_c$

$M_{Nc-1}$, $P_{Nc-1}$, $P_{se,Nc-1}$
FIM$_{obs,Nc-1}$, Prior$_{Nc-1}$
$M_{G,Nc-1}$

Optimal Design

Design ($Q_{Nc}$)

STUDY

Cohort $N_c$

Data ($Y_1 \pm Y_1 \ldots Y_{Nc-1}$)
Prior$_{Nc-1}$

Estimation

Possible models ($M_{Nc}$)
Estimates ($P_{Nc}$, $P_{se,Nc}$)
Obs. FIM (FIM$_{obs,Nc}$)

Stop criterion achieved?

…
AOD the good and the bad

• Good
  – Allows for adjustment of uncertainty in models and parameters
  – Adjustment in misspecification if present

• Bad
  – If you are not wrong from the beginning then adaptations may just introduce error.
  – Adjustments being driven by a small group of patients…may lead to bias.
PLATFORM FOR TESTING AND PERFORMING AOD TRIALS (DDMORE)
Design of future studies 1

Model guesses $M_G^0$
Param. guesses $P_0$
Param. uncertainty $P_{se,0}$
Prior $\text{Prior}_0 = \text{FIM}_0$

Optimal Design
Design $(Q_1)$

STUDY

Cohort 1
Data $(Y_1)$
Prior $\text{Prior}_0$

Estimation
Possible models $(M_1)$
Estimates $(P_1, P_{se,1})$
Obs. FIM $(\text{FIM}_{obs,1})$

Stop criterion achieved?

Design of future studies 2

$M_1, P_1, P_{se,1}$
FIM$_{obs,1}$, $\text{Prior}_1$
New model guesses $M_{G,2}$

Optimal Design
Design $(Q_2)$

STUDY

Cohort 2
Data $(Y_2 \pm Y_1)$
Prior $\text{Prior}_1$

Estimation
Possible models $(M_2)$
Estimates $(P_2, P_{se,2})$
Obs. FIM $(\text{FIM}_{obs,2})$

Stop criterion achieved?

Design of future studies $N_c$

$M_{Nc-1}, P_{Nc-1}, P_{se,Nc-1}$
FIM$_{obs,Nc-1}$, $\text{Prior}_{Nc-1}$
$M_{G,Nc-1}$

Optimal Design
Design $(Q_{Nc})$

STUDY

Cohort $N_c$
Data $(Y_1 \pm Y_1 \ldots Y_{Nc-1})$
Prior $\text{Prior}_{Nc-1}$

Estimation
Possible models $(M_{Nc})$
Estimates $(P_{Nc}, P_{se,Nc})$
Obs. FIM $(\text{FIM}_{obs,Nc})$

Stop criterion achieved?
Design of future studies 1

Model guesses $M_{G0}$
Param. guesses $P_0$
Param. uncertainty $P_{se,0}$
Prior$_0$=FIM$_0$

Design ($Q_1$)

**PopED**

Cohort 1

Data ($Y_1$)
Prior$_0$

Estimation
Possible models ($M_1$)
Estimates ($P_1$, $P_{se,1}$)
Obs. FIM (FIM$_{obs,1}$)

Stop criterion achieved?

Design of future studies 2

$M_1$, $P_1$, $P_{se,1}$
FIM$_{obs,1}$, Prior$_1$
New model guesses $M_{G,2}$

Design ($Q_2$)

**PopED**

Cohort 2

Data ($Y_2$ ± $Y_1$)
Prior$_1$

Estimation
Possible models ($M_2$)
Estimates ($P_2$, $P_{se,2}$)
Obs. FIM (FIM$_{obs,2}$)

Stop criterion achieved?

Design of future studies $N_c$

$M_{Nc-1}$, $P_{Nc-1}$, $P_{se,Nc-1}$
FIM$_{obs,Nc-1}$, Prior$_{Nc-1}$
$M_{G,Nc-1}$

Design ($Q_{Nc}$)

**PopED**

Cohort $N_c$

Data ($Y_1$ ± $Y_1$ … $Y_{Nc-1}$)
Prior$_{Nc-1}$

Estimation
Possible models ($M_{Nc}$)
Estimates ($P_{Nc}$, $P_{se,Nc}$)
Obs. FIM (FIM$_{obs,Nc}$)

Stop criterion achieved?

…
Design of future studies 1

Model guesses $M_{G0}$
Param. guesses $P_0$
Param. uncertainty $P_{se,0}$
Prior$_0$=FIM$_0$

$\rightarrow$ PopED
Design $(Q_1)$

Cohort 1
Data $(Y_1)$
Prior$_0$

$\rightarrow$ NONMEM (PsN)
Possible models $(M_1)$
Estimates $(P_{1}, P_{se,1})$
Obs. FIM (FIM$_{obs,1}$)

Stop criterion achieved?

Design of future studies 2

$M_1$, $P_1$, $P_{se,1}$
FIM$_{obs,1}$, Prior$_1$
New model guesses $M_{G,2}$

$\rightarrow$ PopED
Design $(Q_2)$

Cohort 2
Data $(Y_2 \pm Y_1)$
Prior$_1$

$\rightarrow$ NONMEM (PsN)
Possible models $(M_2)$
Estimates $(P_2, P_{se,2})$
Obs. FIM (FIM$_{obs,2}$)

Stop criterion achieved?

Design of future studies $N_c$

$M_{Nc-1}$, $P_{Nc-1}$, $P_{se,Nc-1}$
FIM$_{obs,Nc-1}$, Prior$_{Nc-1}$

$\rightarrow$ PopED
Design $(Q_{Nc})$

Cohort $N_c$
Data $(Y_1 \pm Y_1 \ldots Y_{Nc-1})$
Prior$_{Nc}$

$\rightarrow$ NONMEM (PsN)
Possible models $(M_{Nc})$
Estimates $(P_{Nc}, P_{se,Nc})$
Obs. FIM (FIM$_{obs,Nc}$)

Stop criterion achieved?
Design of future studies 1
Model guesses $M_{G0}$
Param. guesses $P_0$
Param. uncertainty $P_{se,0}$
Prior$_0$ = FIM$_0$

PopED
Design ($Q_1$)

Study
Cohort 1
Possible models ($M_1$)
Estimates ($P_1$, $P_{se,1}$)
Obs. FIM (FIM$_{obs,1}$)

Stop criterion achieved?

Design of future studies 2
$M_1$, $P_1$, $P_{se,1}$
FIM$_{obs,1}$, Prior$_1$
New model guesses $M_{new}$

PopED
Design ($Q_{new}$)

Study
Cohort 2
Data ($Y_2 \pm Y_1$)
Prior$_1$

NONMEM (PsN)
Possible models ($M_2$)
Estimates ($P_2$, $P_{se,2}$)
Obs. FIM (FIM$_{obs,2}$)

Stop criterion achieved?

...
Design of future studies 1
Model guesses $M_{G0}$
Param. guesses $P_0$
Param. uncertainty $P_{se,0}$
Prior$_0$ = FIM$_0$

PopED

Design ($Q_1$)

Cohort 1
Data $(Y_1)$
Prior$_0$

NONMEM (PsN)
Possible models ($M_1$)
Estimates ($P_{1,1}$, $P_{se,1}$)
Obs. FIM (FIM$_{obs,1}$)

Stop criterion achieved?

Simulate data NONMEM (PsN)

Cohort 2
Data $(Y_2 \pm Y_1)$
Prior$_1$

NONMEM (PsN)
Possible models ($M_2$)
Estimates ($P_{2,1}$, $P_{se,2}$)
Obs. FIM (FIM$_{obs,2}$)

Stop criterion achieved?

Cohort $N_c$
Data $(Y_1 \pm Y_1 \ldots Y_{N_c-1})$
Prior$_{N_c-1}$

NONMEM (PsN)
Possible models ($M_{Nc}$)
Estimates ($P_{Nc,1}$, $P_{se,Nc}$)
Obs. FIM (FIM$_{obs,Nc}$)

Stop criterion achieved?

...
Evaluating AODs – Multiple simulations

- Simulate entire process many times (R and PsN)
- Evaluate results in some way (R and PsN)

Design of future studies 1

- Model guesses $M_{G0}$
- Param. guesses $P_0$
- Param. uncertainty $P_{se,0}$
- Prior $= \text{FIM}_0$

- Design ($Q_1$)

- PopED

- Simulate data NONMEM (PsN)

Cohort 1

- Data ($Y_1$)
- Prior $= \text{Prior}_0$

- NONMEM (PsN)

- Possible models ($M_1$)
- Estimates ($P_{1r}, P_{se,1}$)
- Obs. FIM ($\text{FIM}_{\text{obs},1}$)

Stop criterion achieved?

Design of future studies 2

- $M_1, P_1, P_{se,1}$
- FIM$_{\text{obs},1}$, Prior$_1$
- New model guesses $M_{G2}$

- Design ($Q_2$)

- PopED

- Simulate data NONMEM (PsN)

Cohort 2

- Data ($Y_2 \pm Y_1$)
- Prior $= \text{Prior}_1$

- NONMEM (PsN)

- Possible models ($M_2$)
- Estimates ($P_{2r}, P_{se,2}$)
- Obs. FIM ($\text{FIM}_{\text{obs},2}$)

Stop criterion achieved?

Design of future studies $N_c$

- $M_{Nc-1}, P_{Nc-1}, P_{se,Nc-1}$
- FIM$_{\text{obs},Nc-1}$, Prior$_{Nc-1}$
- New model guesses $M_{G,Nc-1}$

- Design ($Q_{Nc}$)

- PopED

- Simulate data NONMEM (PsN)

Cohort $N_c$

- Data ($Y_1 \pm Y_1 \ldots Y_{Nc-1}$)
- Prior $= \text{Prior}_{Nc-1}$

- NONMEM (PsN)

- Possible models ($M_{Nc}$)
- Estimates ($P_{Nc}, P_{se,Nc}$)
- Obs. FIM ($\text{FIM}_{\text{obs},Nc}$)

Stop criterion achieved?

• Simulate entire process many times (R and PsN)
• Evaluate results in some way (R and PsN)
For the coming example

- Simulate entire process many times (R and PsN)

- Evaluate results in some way (R and PsN)
PopED

- Optimal experimental design software
- Flexible description of models
- Flexible description of design space
- Flexible design optimization
- Written in Matlab

poped.sf.net

PsN

- Perl Speaks NONMEM
- Aids in running nonmem
- Automatic evaluation of complex statistical techniques
- Extraction of important results from NONMEM

psn.sf.net
AOD prototype

- Modular so that the calls to PopED, PsN and NONMEM can be switched out for other programs.
- General so that “any” model (and adaptation) can be used.
- DDMoRe (www.ddmore.eu)
  - Platform for AOD
  - Investigate optimal strategies for AOD

Van Hasselt and Hooker, PAGE, 2013

Veronese et al. AODware: a model-based application for optimal and adaptive optimal experimental design exploration, ACOP, 2013
Exploring AOD – Pediatric PK bridging studies

• Several model types to describe PK changes in children
  – Empirical: \( CL_i = CL_{std,i} \cdot \left( \frac{WT_i}{70} \right)^\theta \cdot ... \)
  – Holfordian: \( CL_i = CL_{std,i} \cdot \left( \frac{WT_i}{70} \right)^{0.75} \cdot \frac{PMA_i^\gamma}{PMA_i^\gamma + TM_{50}^\gamma} \cdot F_{organ,i} \cdot ... \)
  – PBPK ...

Pediatric PK bridging study

• For this example we chose a somewhat simplistic approach:

\[ y_{ij} = \frac{DOSE_i}{V_i} e^{\left(\frac{CL_i}{V_i}\right)t_{ij}} \cdot (1 + \epsilon_{1ij}) + \epsilon_{2ij} \]

\[ CL_i = CL_{BASE,i} + \frac{CL_{MAX} \cdot WT_i^\gamma}{WT^{50^\gamma} + WT_i^\gamma} \]

\[ V_i = V_{STD,i} \cdot \left(\frac{WT_i}{70}\right) \]

\[ CL_{BASE,i}, \ V_{STD,i} \in \text{LogNormal} \]

\[ DOSE_i = 1000 \cdot \left(\frac{WT_i}{70}\right) \]
Pediatric bridging study

- Cohorts optimized on
  - Weights to include in cohort
  - Sampling times.

- Compared the performance of two study design approaches:
  - Fixed optimized design (D-optimal)
  - Adaptive optimized designs (D-optimal).

- For each design approach we evaluated:
  - Different levels of parameter misspecification

- The resulting study designs were evaluated based on:
  - Parameter bias and precision
  - Predicted exposure (AUC).
Fixed D-optimal design with misspecification of WT50

Prior: WT50 = 5
Truth: WT50 = 25
Fixed D-optimal design with misspecification of WT50

Prior: WT50 = 5
Truth: WT50 = 25
Fixed D-optimal design with misspecification of WT50

Prior: WT50 = 5  
Truth: WT50 = 25
Fixed D-optimal design with misspecification of WT50
Adaptive D-optimal design with misspecification of WT50

Prior: WT50 = 5
Truth: WT50 = 25
Adaptive D-optimal design with misspecification of WT50

Prior: WT50 = 5
Truth: WT50 = 25

Cohort 1

Clearance

Prior: WT50 = 5
Truth: WT50 = 25
Adaptive D-optimal design with misspecification of WT50
Adaptive D-optimal design with misspecification of WT50
Adaptive D-optimal design with misspecification of WT50
Adaptive D-optimal design with misspecification of WT50
Adaptive D-optimal design with misspecification of WT50
REE (%) of Parameter estimates
REE (%) of Parameter estimates

![Graph showing REE (%) of Parameter estimates for AOD and FIXED-OD parameters.]

- AOD parameters: thCl, thE50, thHill, thMax, thV
- FIXED-OD parameters: thCl, thE50, thHill, thMax, thV
Prediction of AUC for a fixed dose
No Misspecification

AOD

Parameter

REE (%)
No Misspecification
EMAX misspecification

Prior: EMAX = 0.01
Truth: EMAX = 2
EMAX misspecification

Prior: EMAX = 0.01
Truth: EMAX = 2
Comparing different AOD strategies.
Comparing different AOD strategies (2).
Conclusions

• We successfully developed an initial implementation of a modular and flexible AOD computational platform, which will be available as freeware when released.

• In many cases AOD can improve parameter precision and accommodate for initial model misspecification compared to standard optimal design techniques.

• If no adaptation is needed or if the adaptation process is not carefully chosen a decrease in parameter precision or even parameter bias can be introduced, demonstrating the need for prior investigation, through simulation, of the AOD process.
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