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Expanding the reach of optimal design and the PODE community

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Perspectives

- Easier to use
  - Interoperability
  - Shiny apps – ISOP server, running both PFIM and POPED?
- In drug development … extrapolation, interim analysis,
- OD – more use of uncertainty in model and parameter space, MBAOD.

Introduction to Model Description Language:

a new pharmacometric standard

Material prepared by:
Mike K Smith, Stuart Moodie & Zinnia P Parra-Guillen

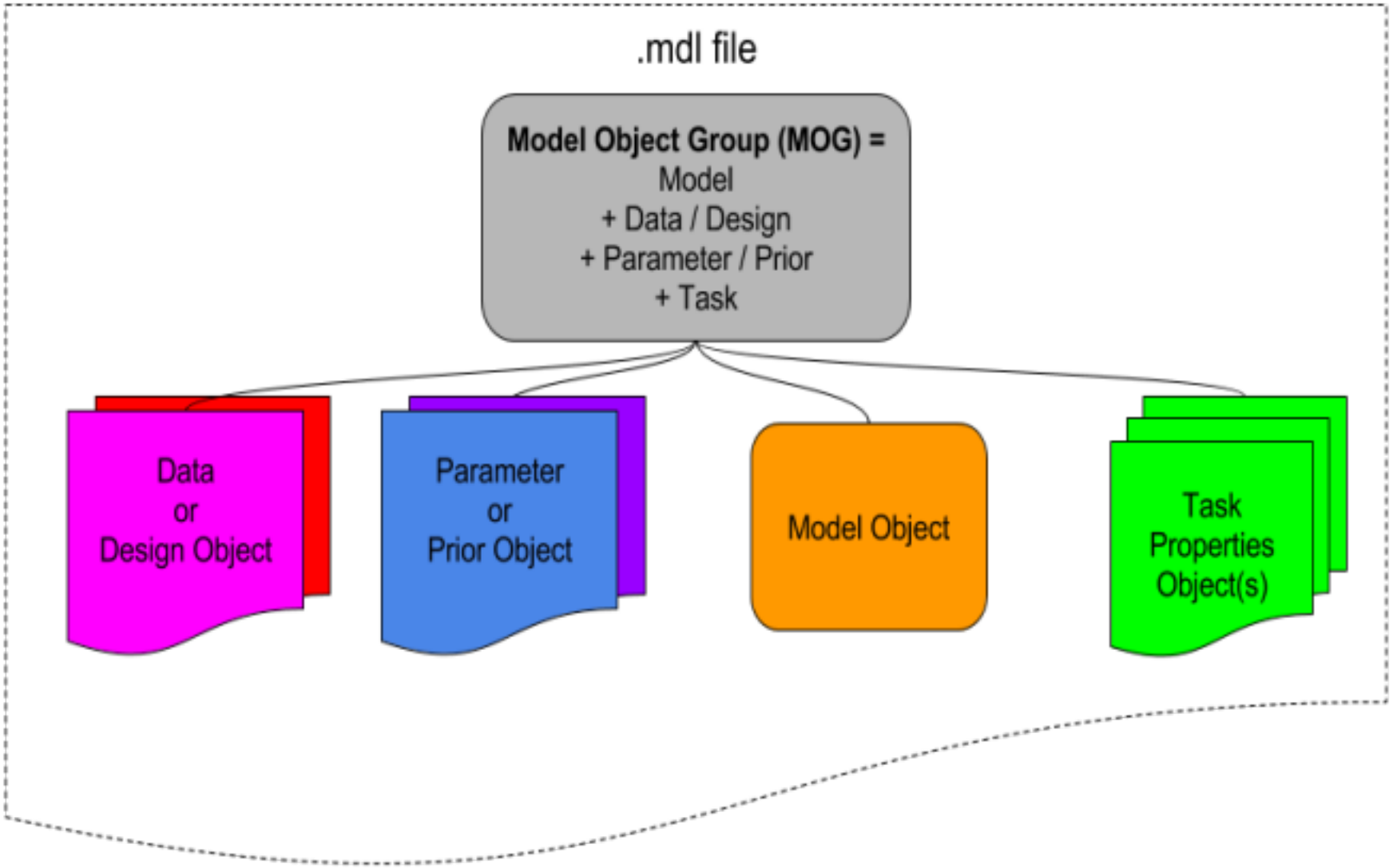
On behalf of the DDMoRe consortium

Modularity – example workflow

- **Estimation** = Data + Parameters + **MODEL** + Monolix Task Properties
- **Bayesian estimation** = Data + Priors + **MODEL** + BUGS Task
- **VPC** = Data + Final Parameters + **MODEL** + NONMEM Task Properties
- **Prediction / simulation** = Design + Final Parameters + **MODEL** + Simulation Task Properties
- **Optimal design / evaluation** = Design + Final Parameters + **MODEL** + PFIM / PopED Task Properties

Model Description Language

Structure



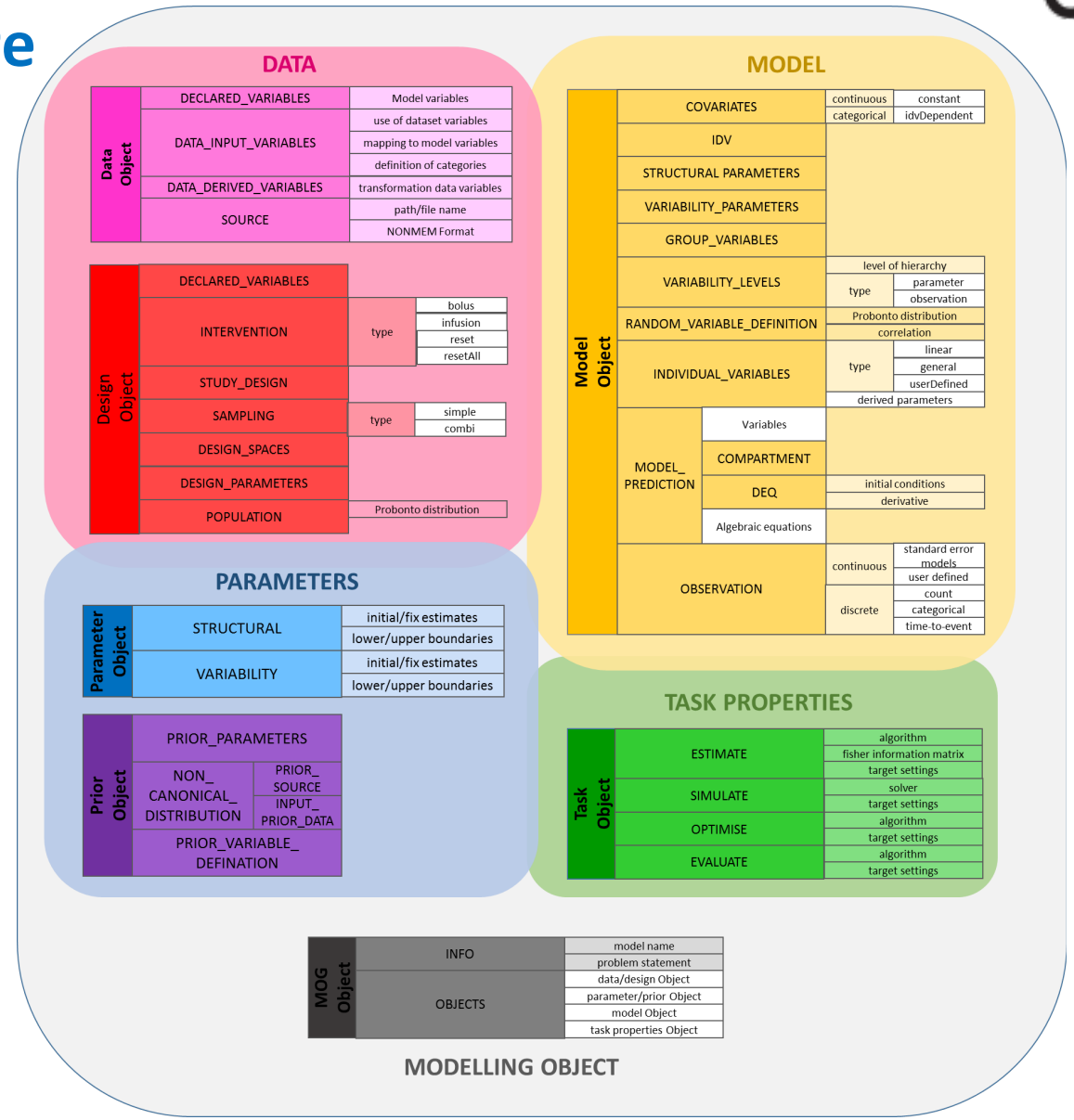
Model Description Language

Definition

- ***Human*** readable and writable language
- ***Standards*** to describe pharmacometric models and tasks
  - Consistent description of models
  - Facilitate communication and understanding across pharmacometricians and disciplines
- Target tool ***independent***
  - Eliminate (as much as possible) target software specific “tricks”
- ***Modular*** structure
  - Define in a single text file
  - Flexibility, re-usability and interchange

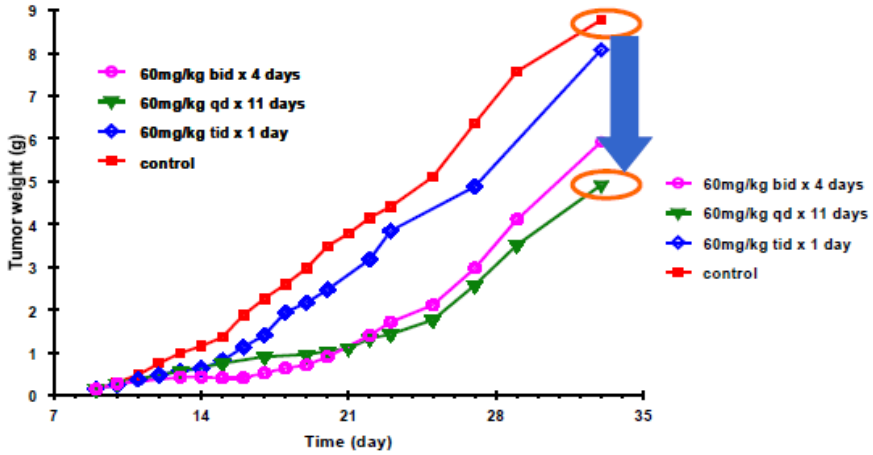
Model Description Language

Structure



Tumour growth model - Simeoni

- Efficacy of most of the drugs approved for oncology have been first tested in xenograf models
- *In vivo* preclinical experiment
  - Drug + control arms
  - 6-10 mice
  - Tumour cells inoculated at Day 0
  - Drug administered when certain tumour size has been reached
  - Tumour size measured at regular intervals until ~ Day 40



Simeoni model - Model Object

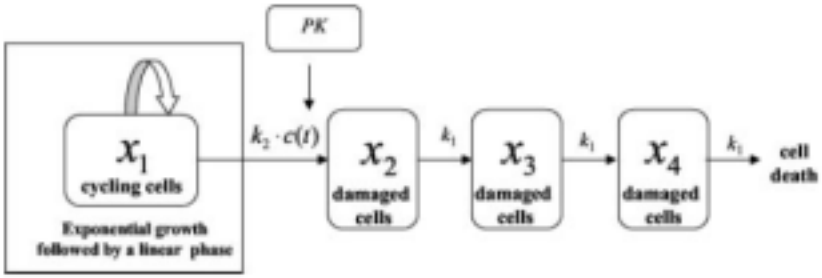


Fig. 1. Scheme of the pharmacokinetic (*PK*)-pharmacodynamic model. k_1, first-order rate constant of transit; k_2, measure of drug potency; $c(t)$, plasma concentration of the anticancer agent.

$$\frac{dQ1}{dt} = K21 \cdot Q2 - (K10 + K12) \cdot Q1$$

$$\frac{dQ2}{dt} = K12 \cdot Q1 - K21 \cdot Q2$$

$$\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_1(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\psi}\right]^{1/\psi}} - k_2 \cdot c(t) \cdot x_1(t)$$

$$\frac{dx_2(t)}{dt} = k_2 \cdot c(t) \cdot x_1(t) - k_1 \cdot x_2(t)$$

$$\frac{dx_3(t)}{dt} = k_1 \cdot [x_2(t) - x_3(t)]$$

$$\frac{dx_4(t)}{dt} = k_1 \cdot [x_3(t) - x_4(t)]$$

$$w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$$

with

$$x_1(0) = w_0, x_2(0) = x_3(0) = x_4(0) = 0$$

and

$$c(t) = 0 \qquad 0 < t \leq t_0$$

Simeoni *et al.* Cancer Res 2004

Simeoni model - Model Object

```
MODEL_PREDICTION{
 DEQ{
 # PK model
 C=Q1/V1
 Q1:{deriv=K21*Q2-(K10+K12)*Q1, init=0}
 Q2:{deriv=K12*Q1-K21*Q2, init=0}

 # TGI model
 X1:{deriv=(LAMBDA0*X1/
     ((1+(WTOT*LAMBDA0/LAMBDA1)^PSI)^(1/PSI)))
     - K2*C*X1, init=W0}

 X2:{deriv=K2*C*X1-K1*X2, init=0}

 X3:{deriv=K1*X2-K1*X3, init=0}

 X4:{deriv=K1*X3-K1*X4, init=0}

 WTOT=X1+X2+X3+X4

    }
}
```

$$\frac{dQ1}{dt} = K21 \cdot Q2 - (K10 + K12) \cdot Q1$$

$$\frac{dQ2}{dt} = K12 \cdot Q1 - K21 \cdot Q2$$

$$\frac{dx_1(t)}{dt} = \frac{\lambda_0 \cdot x_1(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\psi}\right]^{1/\psi}} - k_2 \cdot c(t) \cdot x_1(t)$$

$$\frac{dx_2(t)}{dt} = k_2 \cdot c(t) \cdot x_1(t) - k_1 \cdot x_2(t)$$

$$\frac{dx_3(t)}{dt} = k_1 \cdot [x_2(t) - x_3(t)]$$

$$\frac{dx_4(t)}{dt} = k_1 \cdot [x_3(t) - x_4(t)]$$

$$w(t) = x_1(t) + x_2(t) + x_3(t) + x_4(t)$$

with

$$x_1(0) = w_0, x_2(0) = x_3(0) = x_4(0) = 0$$

and

$$c(t) = 0 \qquad 0 < t \leq t_0$$

Simeoni *et al.* Cancer Res 2004

Simeoni model – Design Object

```
simeoni2004_design = designObj{

DECLARED_VARIABLES{
  Q1::dosingTarget  Y::continuousObs}

INTERVENTION{
   treated : {type is bolus, input=Q1, amount=120, doseTime=0}
   control : {type is bolus, input=Q1, amount=0, doseTime=0}
}

SAMPLING{
 sampleControl : {type is simple, sampleTime=[0,4,36,40],
                  outcome = Y}
 sampleTreated : {type is simple, sampleTime=[0,20,55,60],
                  outcome = Y}
}

                        STUDY_DESIGN{
                    treatedArm : {armSize = 1,
                 interventionSequence = {admin=treated, start=0},
                samplingSequence = {sample=sampleTreated,start=0}}

                    controlArm : {armSize = 1,
                 interventionSequence = {admin=control, start=0},
                 samplingSequence={sample=sampleControl,start=0}}
                                }}
```

Declare variables defined in the model object, and ist type

Define dosing schedule to evaluate

Define the sampling times and variables

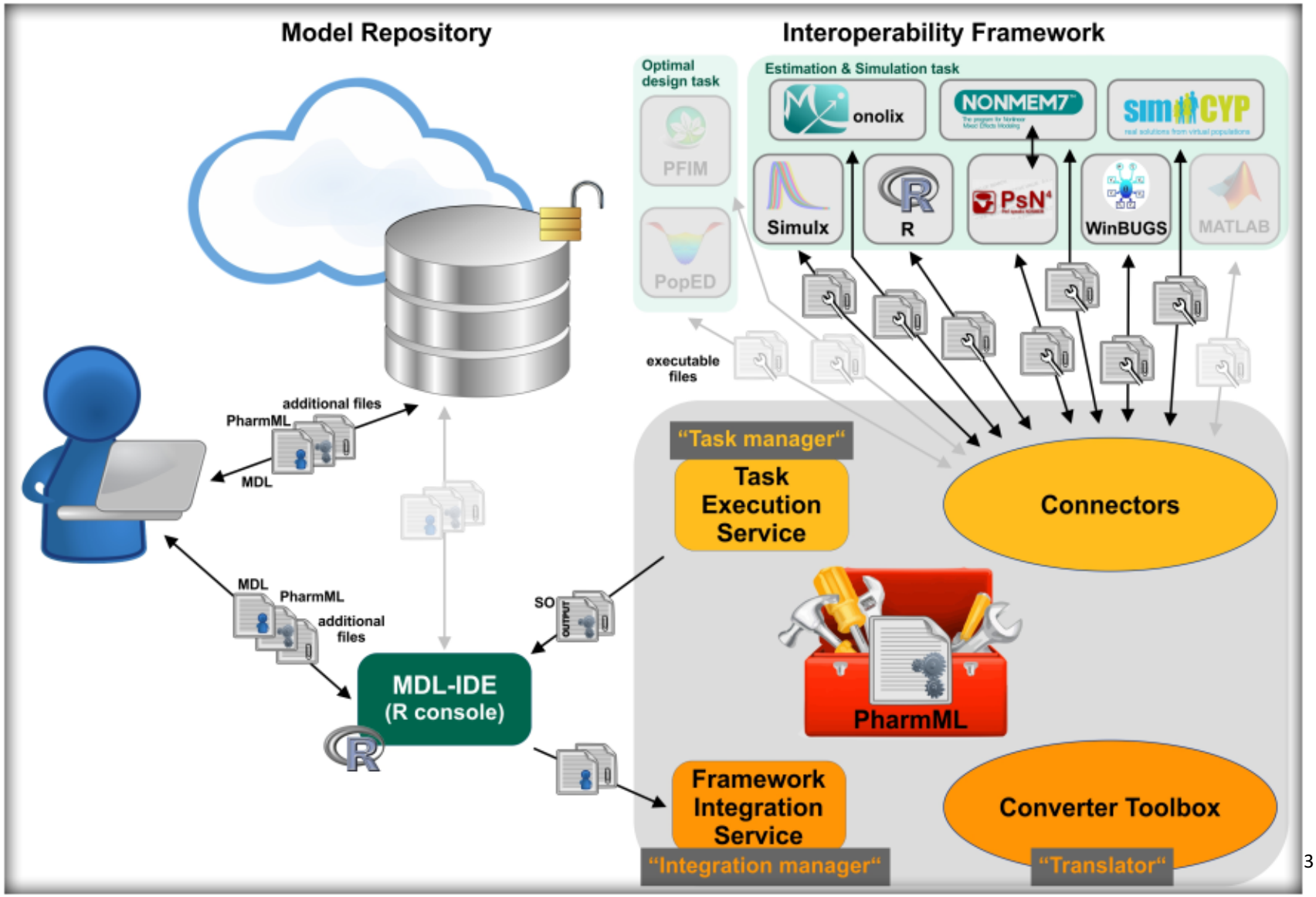
Define the size of the study groups and link them to their intervation and sampling schema

Simeoni model – Task Properties

```
simeoni2004_NONMEM_task = taskObj{
            ESTIMATE {
            set algo is foce
                }
                }

simeoni2004_Monolix_task = taskObj{
            ESTIMATE {
            set algo is saem
                }
                }

 simeoni2004_BUGS_task = taskObj{
            ESTIMATE {
            set algo is mcmc
                }
                }

  simeoni2004_Evaltask = taskObj{
            EVALUATE {
                }
                }
```

Specify some properties regarding the task to be performed

How can I use my MDL model?



Pharmacometric Workflow - HOW?

“ddmore” R package

ddmore R package
- R functions

- The different set of functions within the ddmore package allows the user to:
  1. Retrieve and modify different elements of a .mdl file
  2. Apply “methods”
  3. Define and execute M&S tasks using a MOG
  4. Query and extract information from the Standard Output (SO) object
  5. Create input for other tools

→ All these tasks can be integrated in a single R script

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Design evaluation using MDL and PopED

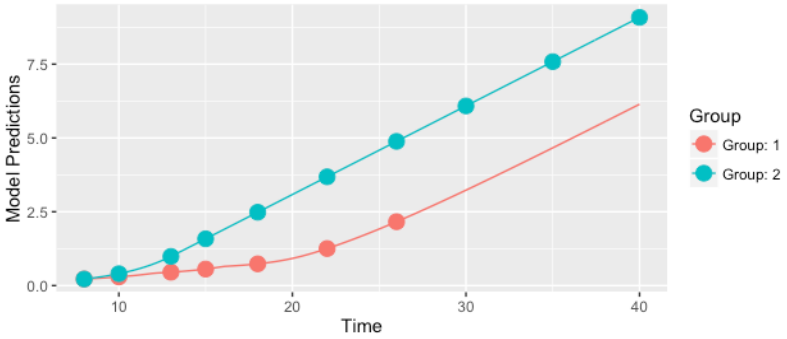
PopED function as.poped takes a PharmML file and creates a poped.db database object ready for use with PopED. We can then use PopED functions directly (natively) in R.

```
library(PopED)

mdlfile <- "Simeoni_PAGE_Evaluation_PFIM.mdl"
pharmMLFile <- as.PharmML(mdlfile)
as.poped(pharmMLFile)
```

create plot of model without variability

```
plot_model_prediction(poped.db)
```



evaluate initial design

```
FIM <- evaluate.fim(poped.db)
```

```
get_rse(FIM,poped.db)
```

```
##     bpop[1]     bpop[2]     bpop[3]     bpop[4]     bpop[5]     bpop[6]
##   25.250685   10.185474    7.905951  453.676408   55.984215    7.045591
```

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Design evaluation using MDL and PopED

```
mdlfile.PFIM <- "Simeoni_PAGE_Evaluation_PFIM.mdl"
```

```
pharmmlfile.PFIM <- as.PharmML(mdlfile.PFIM)
```

```
runPFIM(pharmmlfile=pharmmlfile.PFIM, jarLocation=file.path(ddmore:::DDMORE.checkConfigurat
```

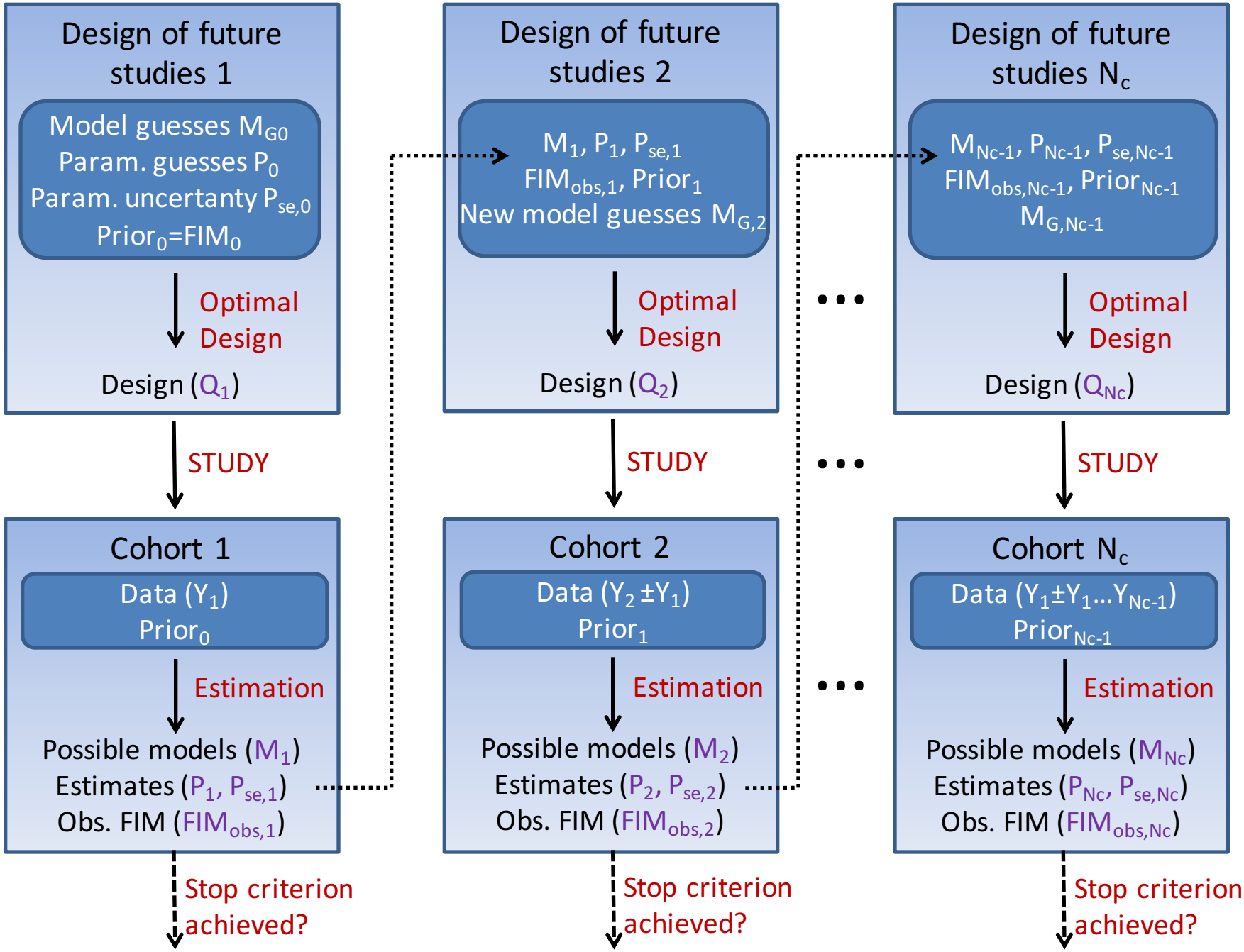
```
## [1] "java -jar C:/SEE/distrib-20160604a/pfim.jar -p C:/SEE/PFIM4.0/program -i C:\\SEE\\M
```

```
readLines(file.path(getwd(),"PFIM","stdout.out"))
```

```
##   [1] "PFIM 4.0 "
##   [2] " "
##   [3] "Project:  Generated from MDL. MOG ID: outputMog"
##   [4] " "
##   [5] "Date:  Mon Jun 06 17:16:48 2016"
##   [6] " "
##   [7] ""
##   [8] " "
##   [9] "*************************** INPUT SUMMARY *********************************"
##  [10] " "
```

Pharmacometric Workflow

- Exploratory data analysis
- Estimation:
  - NONMEM
  - Monolix
  - WinBUGS
- Comparison of estimates
- Diagnostics in Xpose
- VPC
- Prediction / Simulation using simulx
- Evaluate design using PFIM
- Evaluate design using PopED


Design of future studies 1
Model guesses M_{G0}
Param. guesses P_0
Param. uncertanty $P_{se,0}$
$Prior_0=FIM_0$
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?

Resources

- YouTube clips for installation and testing of demonstrator:
  - https://www.youtube.com/playlist?list=PL_GGUkhbiP3t0Q7wTqkQdMAw7yuC8xWa-
- MDL User Guide documentation:
  - http://ddmore.eu/instructions/user-guides

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Inter-operability in R

- Model description of NLMEs
  - PopED
  - PFIM
  - The ***deSolve*** package, with the possibility to compile models in c++ with great speed improvements.
  - The ***PKPDsim*** package [1]
  - The ***mrgsolve*** package [2]

- Optimization methods
- Parallelization methods

1. https://github.com/ronkeizer/PKPDsim
2. https://github.com/metrumresearchgroup/mrgsolve

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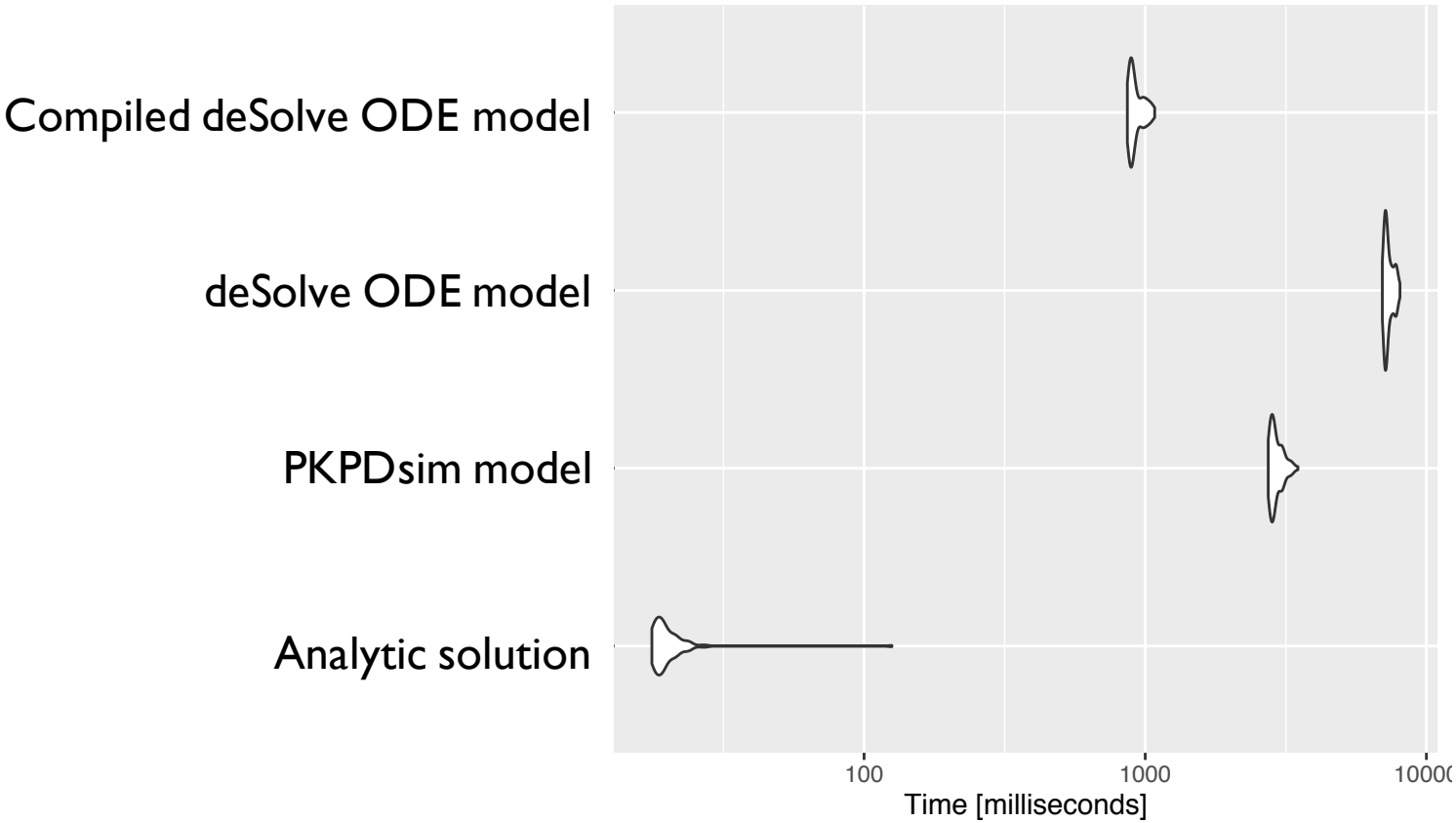
Comparing the speed of model implementations (FIM evaluation)



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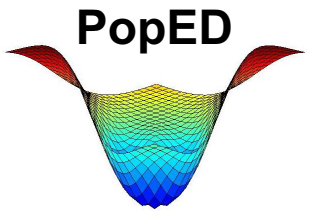
Software



poped.sf.net

https://github.com/andrewhooker/PopED

- Optimal experimental design software
- Flexible description of models
- Flexible description of design space
- Flexible design optimization
- Robust design critera
- Written in R (Package available via CRAN)

MBAOD – R package to perform MBAOD

https://github.com/andrewhooker/MBAOD

PopED lite - OD software for preclinical animal studies

http://www.bluetree.me/PopED_lite.html

Shiny apps in R

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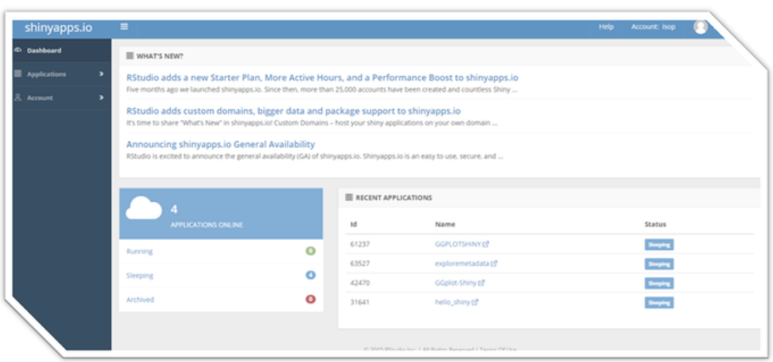
Model Based Applications: The ISoP Shiny Server.

Pharmacometricians are often asked by the teams they work with to explore various scenarios with our models, simulations and analyses. In most cases, the pharmacometrician, in his role as a data analyst, needs to rerun analyses, and re-represent the results, often in multiple iterations.

Shiny is a web application framework for R that can remove the step between the data analyst and the users of model results. The R package Shiny allows for easy development of web-based applications for those using R-based workflows. Shiny applications can be launched from R, or the files used can be stored on a server and launched without the need for the end user to have or be proficient in R. Basic R Shiny app development is fun and easy for even someone with limited R skills. It allows pharmacometricians to share their work with others, and empowers non-quantitative team members to explore data and analyses in real-time.

What is the ISOP Shiny Server?

ISoP, supported by the ISOP technology committee, and RStudio, has made available a Shiny server for ISOP members to host their Pharmacometric related applications.



Pasted image897x419 79.7 KB

What Applications are Suitable for the Server?

Applications for working with datasets, visualizing models and modeling results, and simple model-based simulations applications are all suitable for the Shiny server. Applications must utilize non-proprietary code and data, and other materials. Applications that require excessively long run times may not be suitable.

Examples

Explore Meta Data3

This is an R Shiny Demo for pharmacometric applications. It allows you to change the settings and assumptions underlying your exploratory data analysis on the fly. Try to generate the dose-

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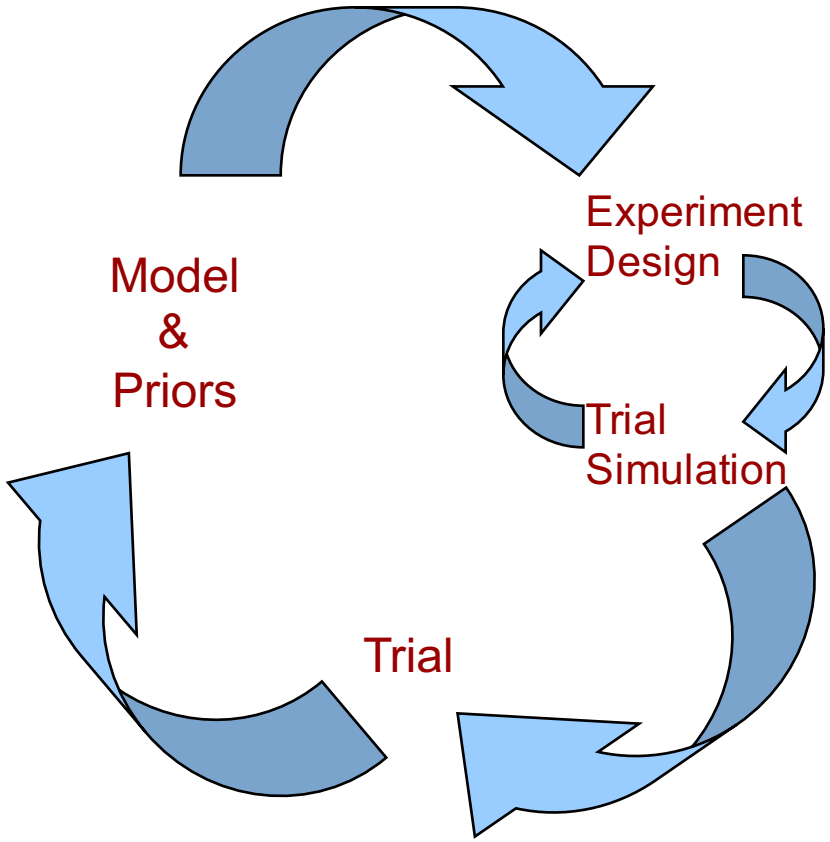
Model based drug development



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Advantages of pharmacometric approaches

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e23; doi:10.1038/psp.2012.24

www.nature.com/psp

ORIGINAL ARTICLE

Comparisons of Analysis Methods for Proof-of-Concept Trials

KE Karlsson[1], C Vong[1], M Bergstrand[1], EN Jonsson[1,2] and MO Karlsson[1]

Drug development struggles with high costs
accentuated by many stakeholders in drug dev
drug development. Two simulated examples,
compare a pharmacometric model–based anal
investigated examples and scenarios, the conv
80% power. For a scenario with a parallel des
conventional and pharmacometric approach w
the model-based power depend on the model
was demonstrated to permit drastic streamlini
CPT: Pharmacometrics & Systems Pharmacology

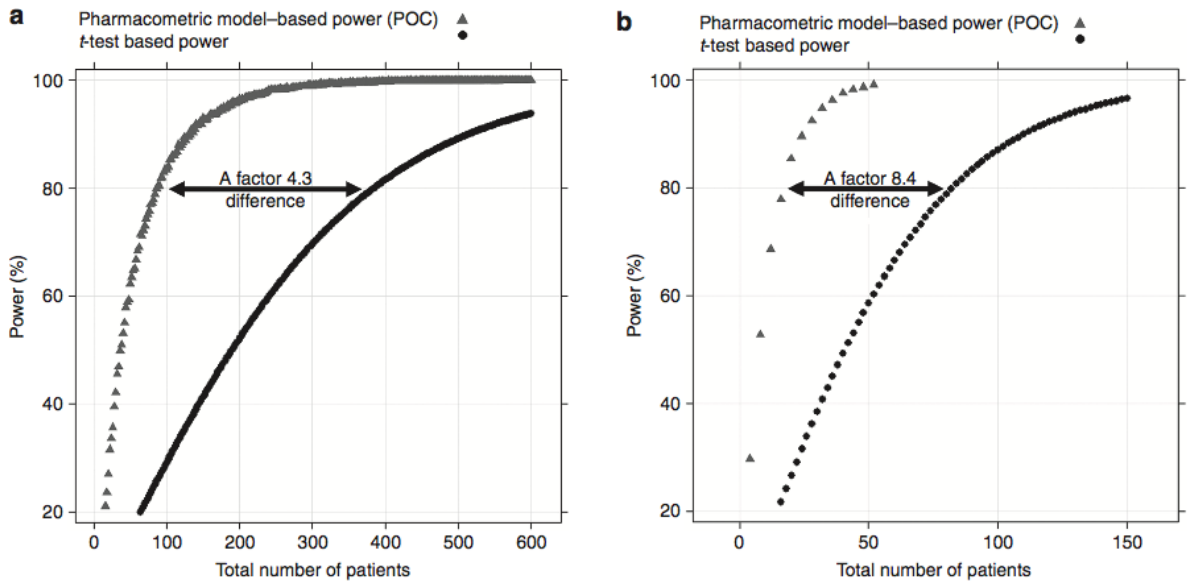

Figure 3 Power curve comparison between the pharmacometric model–based power (gray triangles) and the *t*-test based power (black diamonds), for the proof-of-concept scenario. (**a**) The power curves for the stroke example in which the difference in study size is a factor of 4.3 (90 vs. 388 total number of patients) is displayed. (**b**) In the diabetes example, the difference in study size was 8.4-fold (10 vs. 84 total number of patients) in favor of the pharmacometric approach.

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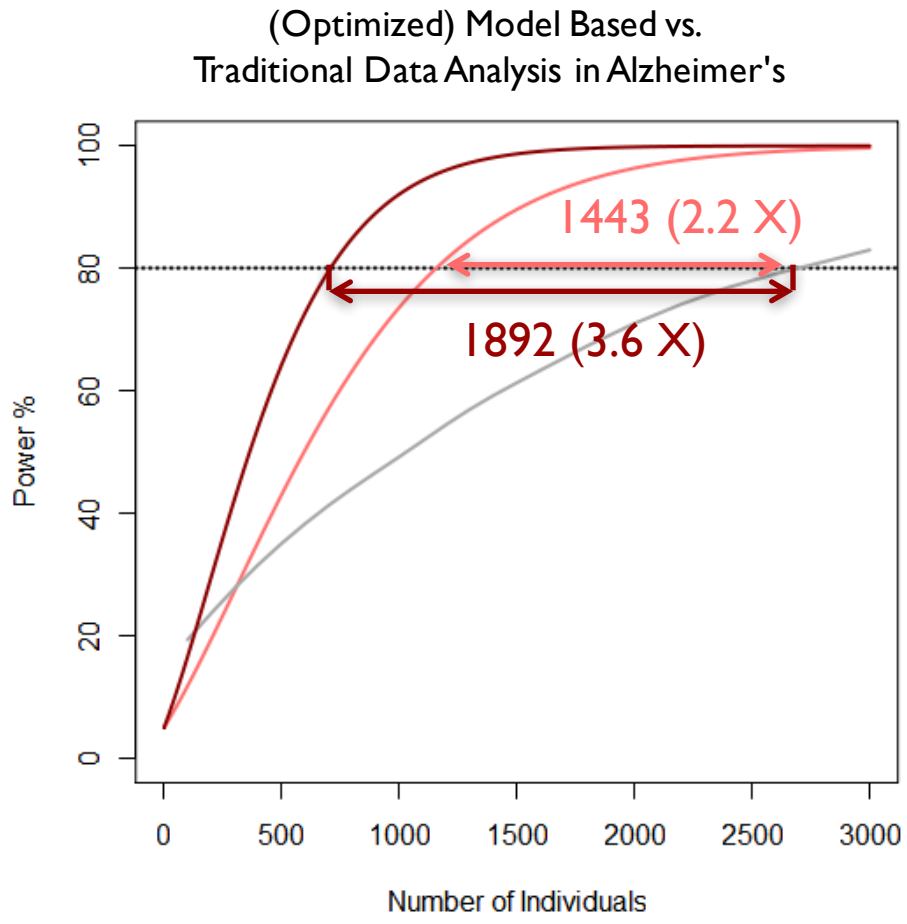
Advantages of optimal design of experiments



Model-Based Analysis (Optimized for power)

Model-Based Analysis (Default Design)

Traditional Analysis (Unstructured MMRM model, LSMeans)

Hooker et al., Model-based Trial Optimization for Phase II and III designs in Alzheimer's Disease, ACOP, 2011

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Potential problems with a model based approach

- Estimation – Building models on measured data can lead to bias.
  - One solution: model averaging
- Simulation / optimization – Using a misspecified model may give poor information and poor designs
  - One solution: model based adaptive optimal design

- Putting the two together: model averaged adaptive optimal design

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Averaged model based decision making for dose selection studies

Yasunori Aoki*, Bengt Hamrén+, Daniel Röshammar+, and Andrew C. Hooker*

Aoki, et al., PAGE, 2014.

Hooker et al. EMA workshop on the importance of dose finding and dose selection. 2014.

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+Quantitative Clinical Pharmacology, AstraZeneca R&D Mölndal, Sweden

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Model Averaging: General principle

- We would like to:
  - Use population pharmacometric models for longitudinal data (nonlinear mixed effects models)
  - Avoid model building to avoid problems of potential model bias
    (pre-specified models, model averaging)
  - Test for a drug effect using population model based approaches
  - Incorporate uncertainty in both model structure and estimated model parameters in dose selection.

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Comparison of model averaging to Traditional Model Based Approach (single model approach) and a traditional statistical analysis

Analysis Result

Analysis of PhIIb study data recommends ____mg in the upcoming PhIII study

with ____% probability of achieving an effect higher than the target effect.

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Placebo Model

Placebo Model + Linear

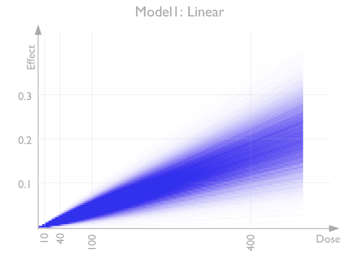
Placebo Model + Log-linear

Placebo Model + Emax

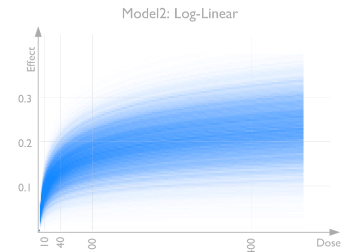
Placebo Model + Sigmoidal

Bootstrap or COV matrix

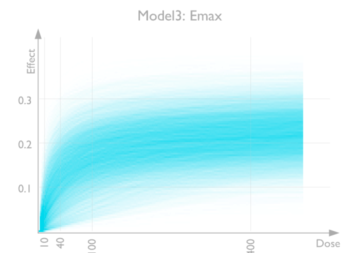
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$\vdots$$



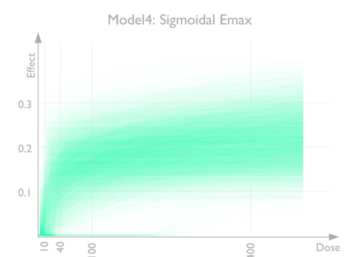
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$\vdots$$



$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$\vdots$$

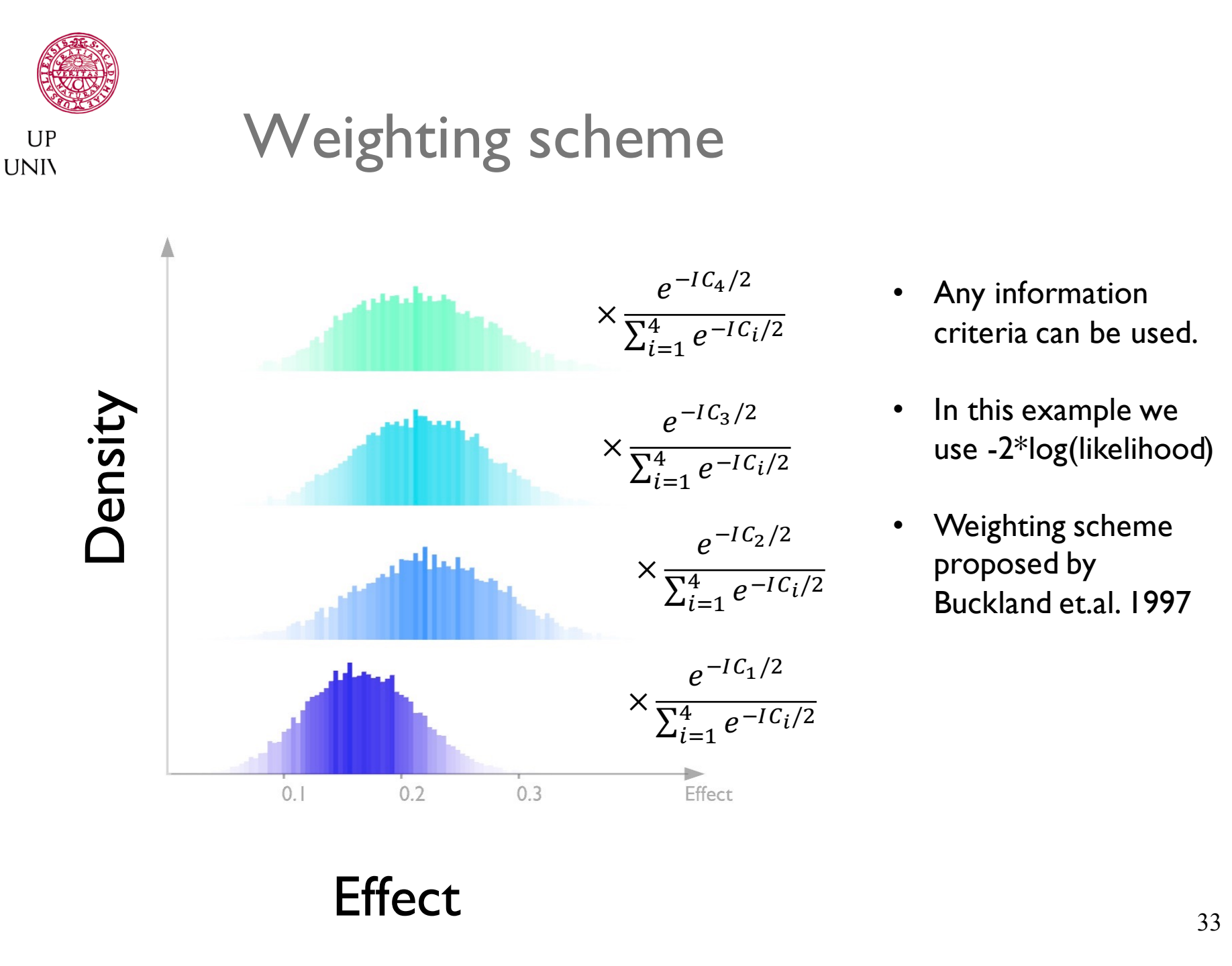


$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$(\theta_1, \theta_2, ..., \omega_1, \omega_2, ..., \sigma_1, \sigma_2)$$
$$\vdots$$



\+

PhIIb clinical trial data



Weighting scheme

- Any information criteria can be used.
- In this example we use -2*log(likelihood)
- Weighting scheme proposed by Buckland et.al. 1997

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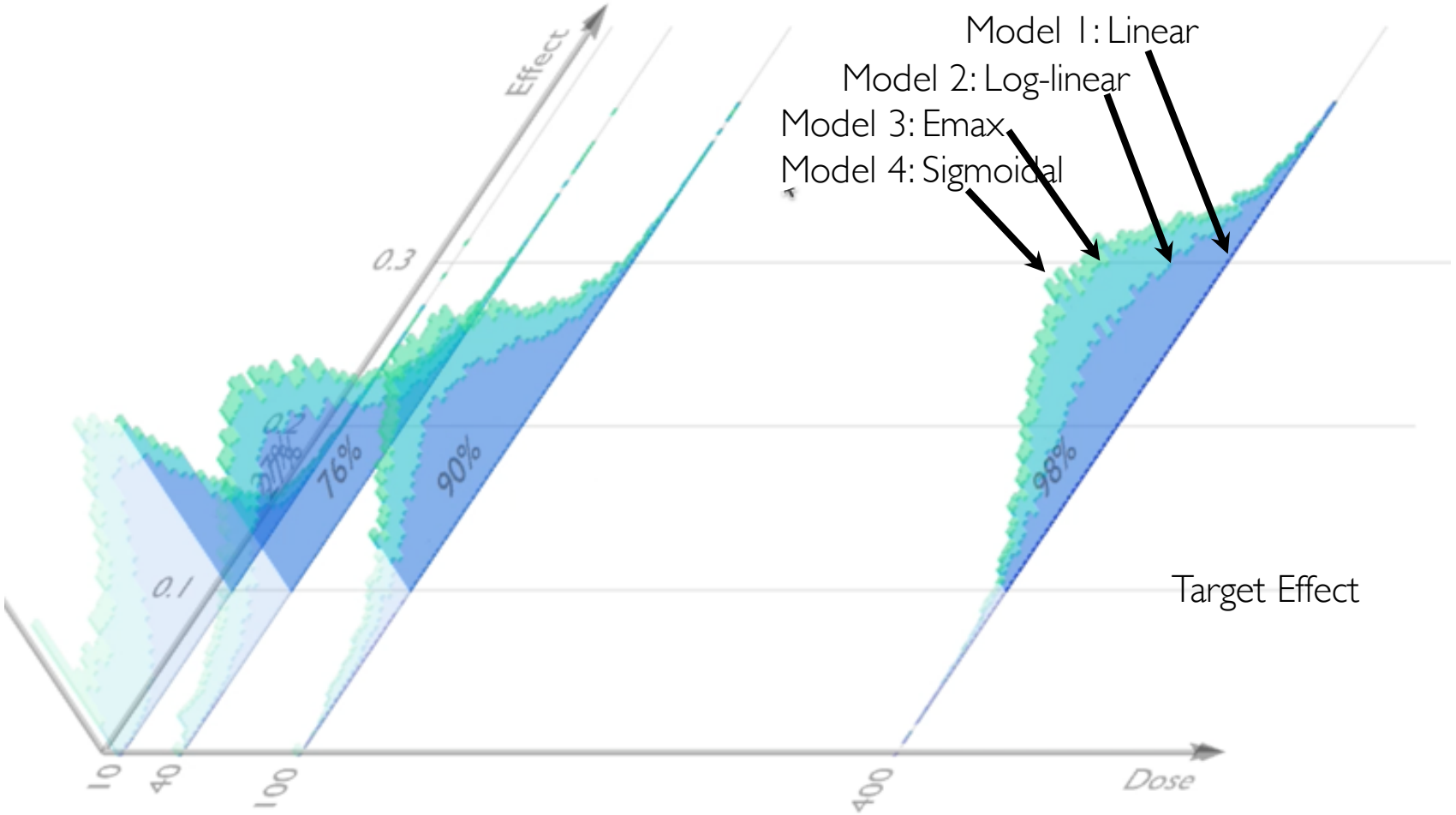
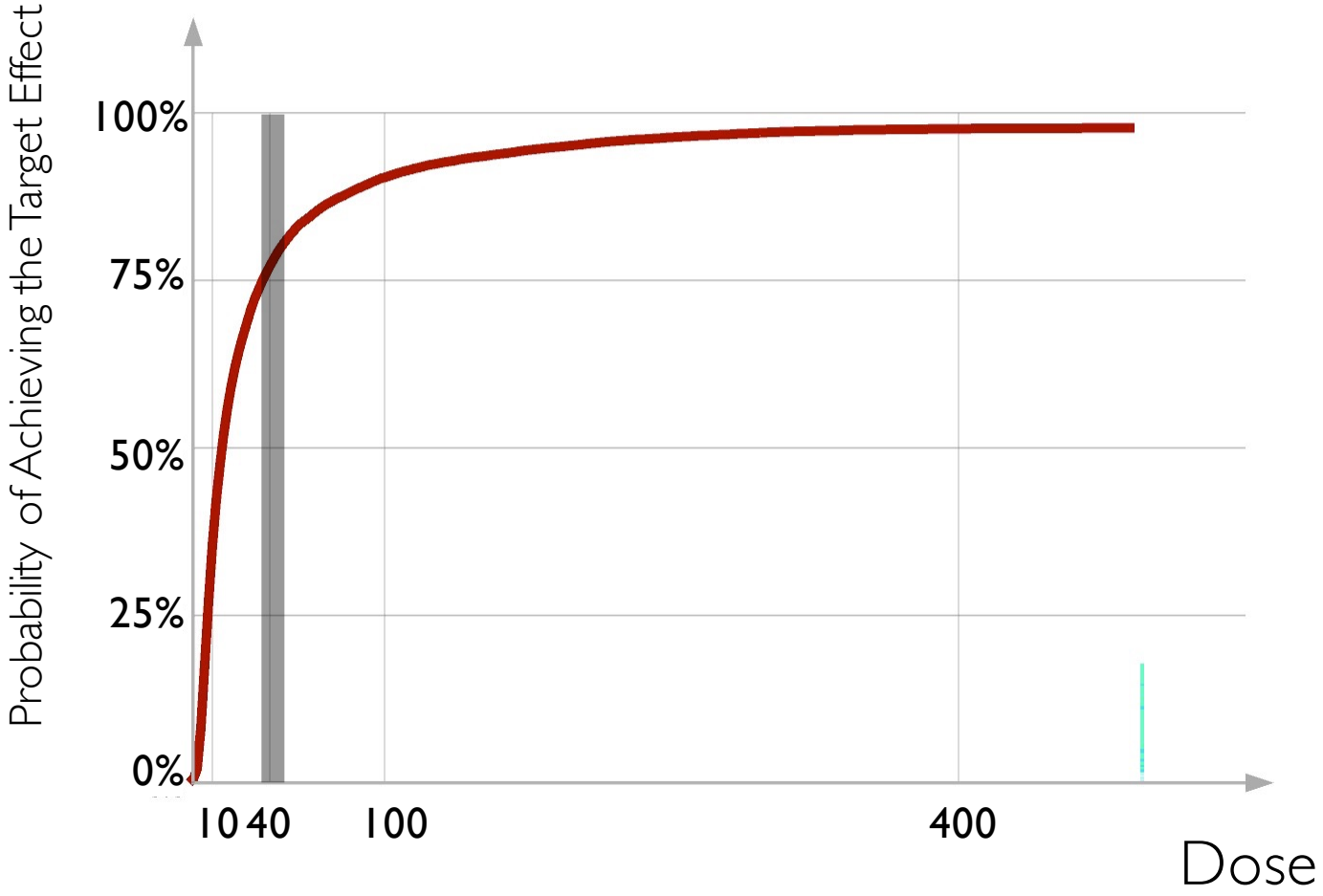
Our model averaging methodology combines both the parameter estimation uncertainty and model structure uncertainty to quantify overall uncertainty



Probability of Success based on Quantified Overall Uncertainty



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Simulation Studies based on AZD 1981

	Frequencies of making the correct dose selection		
	Study Protocol (ANOVA + Averaged Effect)	Averaged Model Based	
Case 1 correct dose = 10mg	582	788	35% improvement
Case 2 correct dose = 40mg	361	592	64% improvement
Case 3 correct dose = 100mg	312	432	38% improvement
Case 4 correct dose = 400mg	402	519	29% improvement

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Type – I error rates

	Frequencies of making the correct dose selection	
	Study Protocol (ANOVA + Averaged Effect)	Averaged Model Based
Simulation Study 6 correct decision = "stop"	**98 %**	**95 %**

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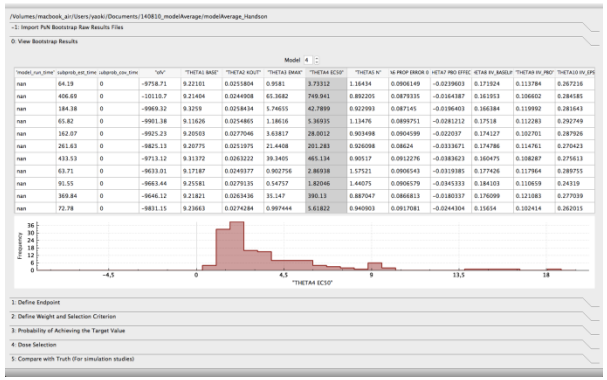
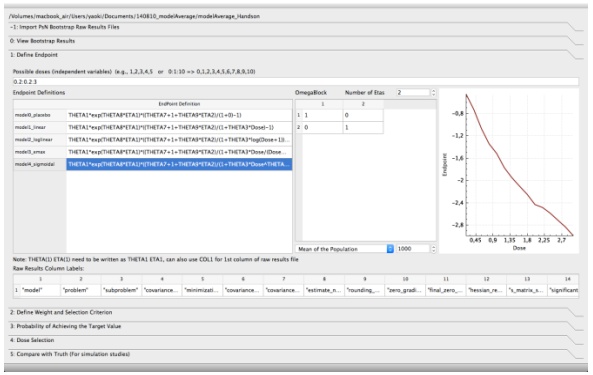
Software modelAVERAGE available on www.bluetree.me

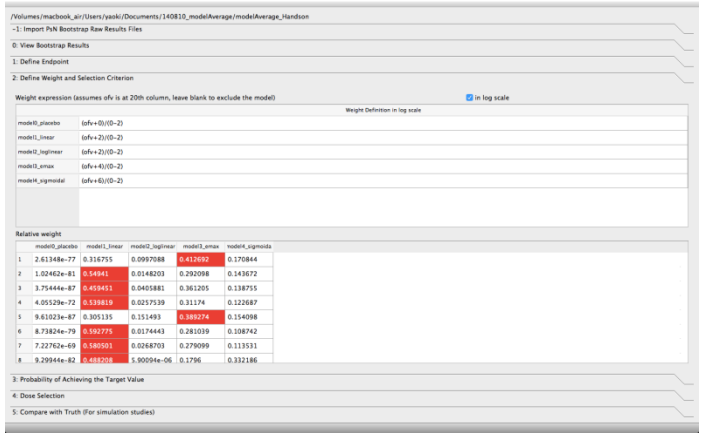
1: import bootstrap results from candidate models (will be automated in the future version of PsN)



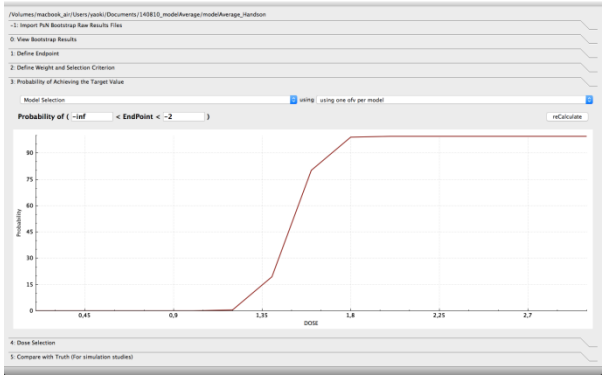
2: define endpoint



3: define weighting scheme



4: obtain the probability of success v.s. dose plot



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ADAPTIVE OPTIMAL DESIGN

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Robust optimal design

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

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

- **What if we don't know the model or we don't have a good guess for the parameters of a model?**

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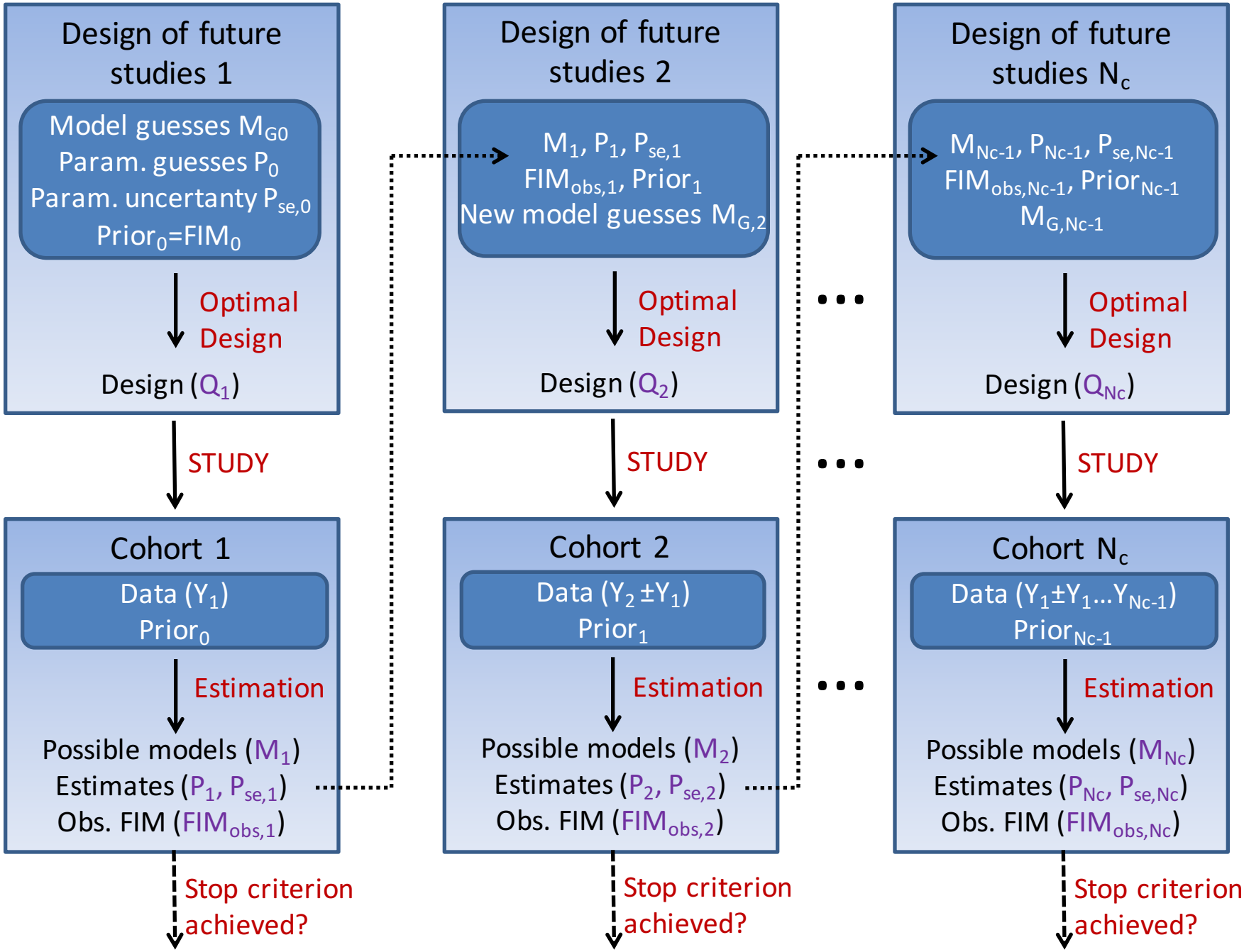
Model based adaptive optimal designs (MBAOD)

- A type of robust design
- Adapt and update your understanding of the system (the model) at intermediate steps within a trial, then re-optimize


Design of future studies 1
Model guesses M_{G0}
Param. guesses P_0
Param. uncertanty $P_{se,0}$
$Prior_0=FIM_0$
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?

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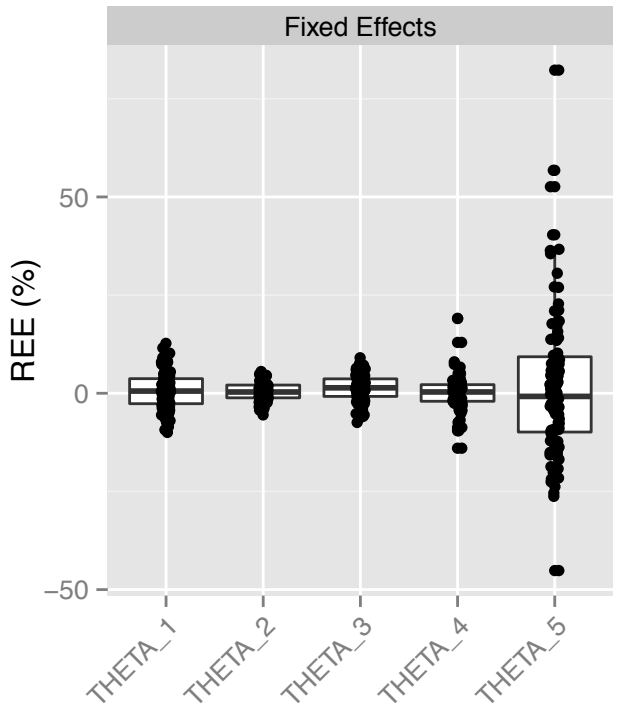
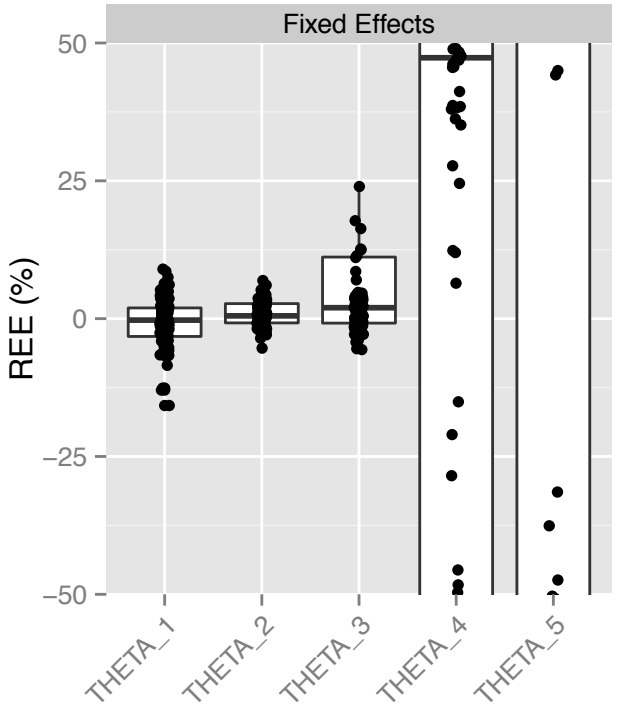
With initial misspecification in your model MBAOD can adapt

MBAOD



Fixed-OD with model misspecification



Hooker et al. ACOP 2013

MBAOD using FDA stopping criteria in children bridging studies

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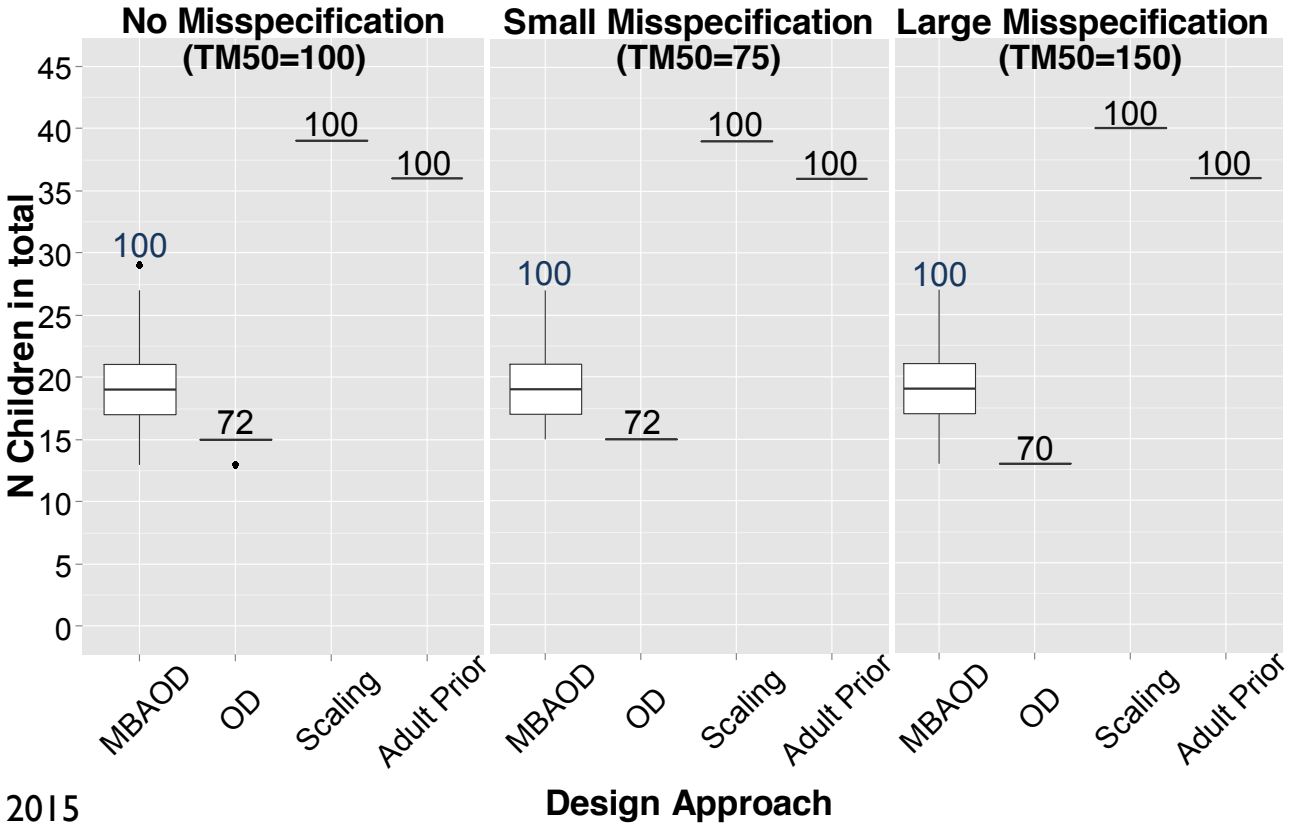
Results

Total Number of Children and Power



Strömberg et al., PAGE, 2015

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Robust adaptive optimal design

- Incorporate multiple models into your optimization

$$\Psi_{P-D} = \arg\max_{\xi}\left(\sum_{i}^{m}\log\left(\left|FIM(\xi,\Phi^{\{i\}})\right|^{\frac{\alpha_i}{p_i}}\right)\right)$$

m=model #, α_i = weighting and p_i = # of parameters

- Weight the models using results from model averaging

Waterhouse and Duffull, JPKPD, 2005

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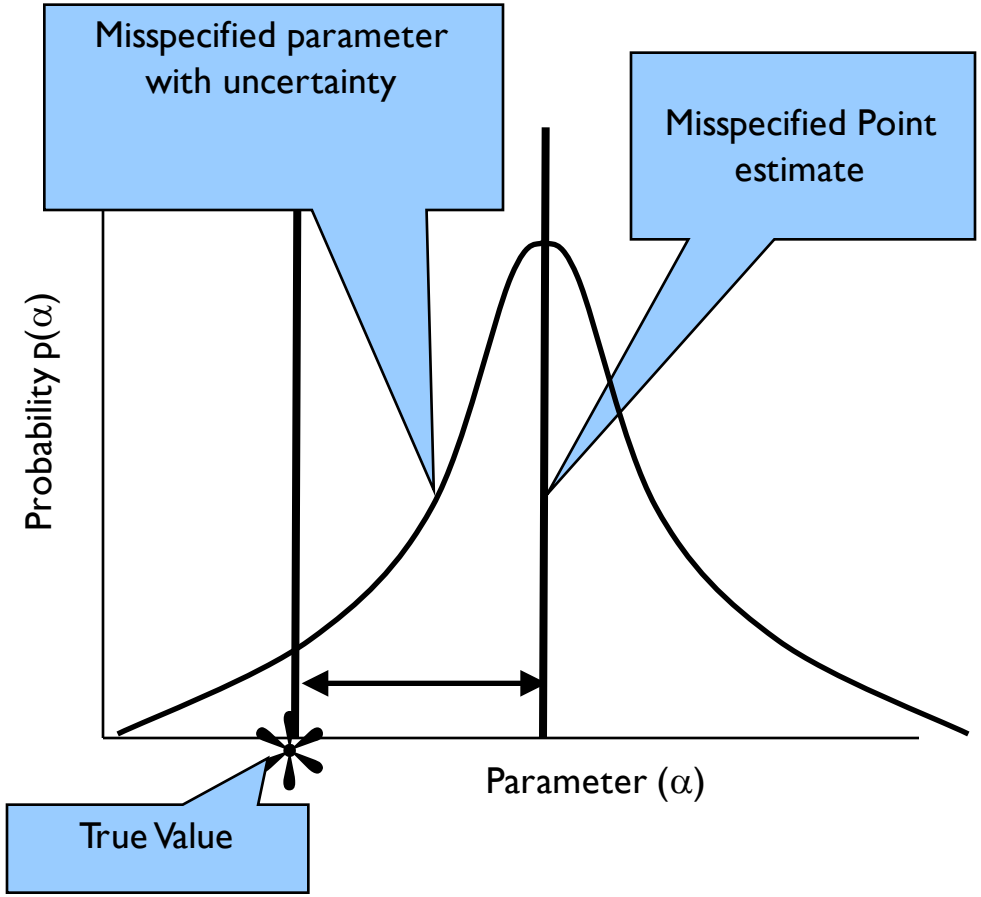
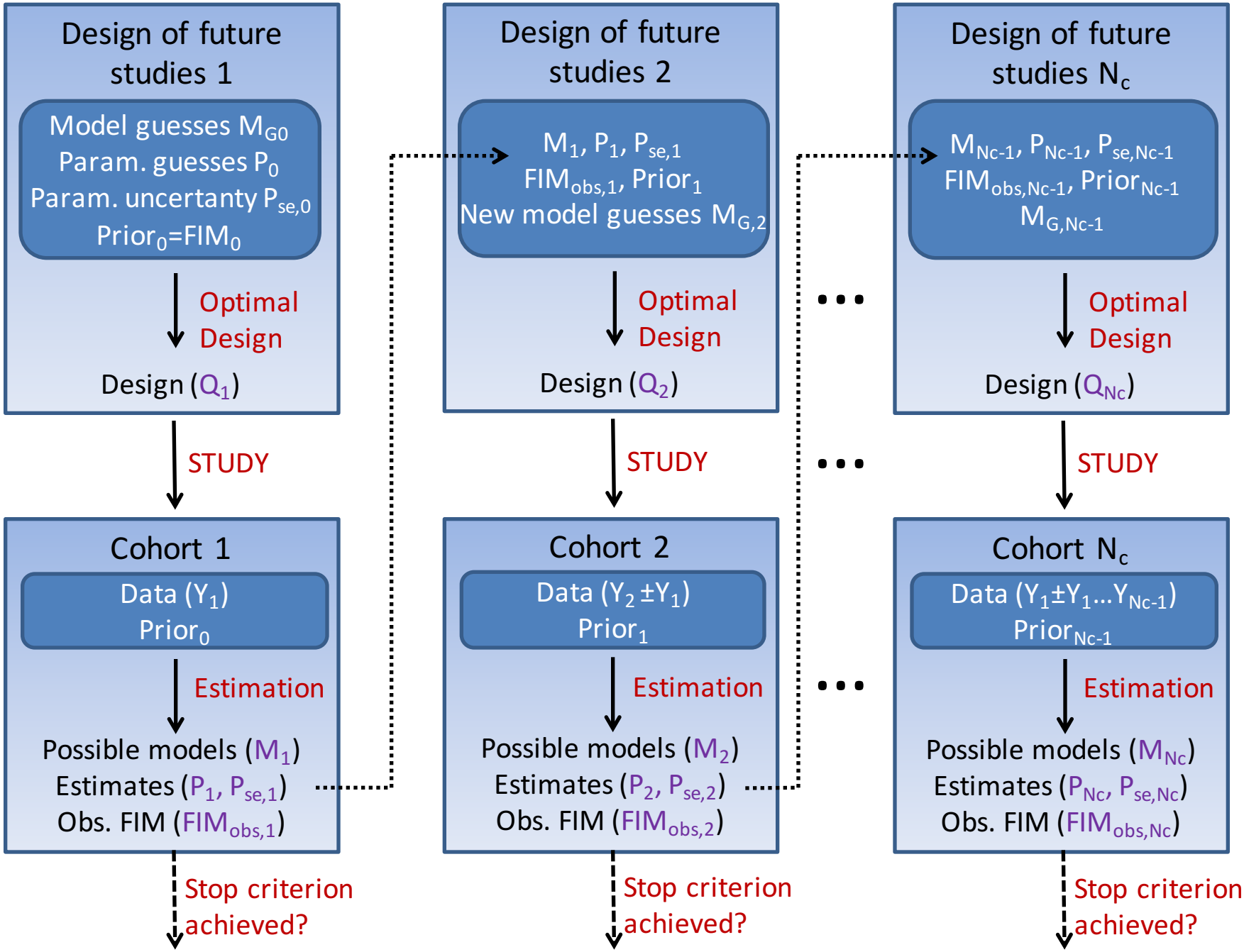
Robust adaptive optimal designs

- Assume your parameters have distributions
  - ("E-family", e.g. ElnD)



M.G. Dodds, A. Hooker and P. Vicini. *J Pharmacokinet Pharmacodyn*, 32(1):33-64, 2005.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Comparison of model averaging to MCP-MOD

- Testing for drug effect
  - Using the likelihood ratio test for each model, instead of contrast tests
  - Allows for incorporation of covariate adjusted dosing and dose-concentration-effect modelling.
- Our model averaging takes into account uncertainty in models and parameter estimates and uses predicted drug effect as the parameter of interest
- MCP-MOD does not specify the "MOD" method following the selection of the candidate models using contrast testing, hence our methodology can be used together with MCP-MOD.