Getting started with Optimal Design for NLME model

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Aim

Present the challenges & questions that newbies face when getting started into the field of optimal design

My Background

- Pharmacist by training
- PhD in Pharmacometrics in 2013:
  - PKPD modelling of therapeutic proteins in preclinical stages
- 2 years postdoc
  - Pharmacometric models to foster a rational use of oncological drugs
  - Education & Training working group at DDMoRe
- Ongoing project with a Pharma Industry:
  - Goal: Explore how modelling and optimal design can improve preclinical experiments of xenograft mice for anticancer treatment

Where do I start?

- No regular courses available
- There is a distribution list, but not online searchable
- Available books, but not specific to nlme
  - "Optimal Design for non linear response models" Federov & Leonov
- Learning relies on :
  - Existing publications,
  - UserGuides and examples
  - Presentations from PODE meetings
  - Supports from colleagues working on Optimal Design

Some general concepts…

- Optimal balance between the design variables (e.g. sample size, sampling times…) with respect to certain statistical criterion

- Relies on the FIM to describe the informativeness of a design:
  - the inverse of the FIM is the lower bound of the variance-covariance matrix of any unbiased estimators of parameters (Cramer-Rao inequality)

- Minimising the variance (maximising the FIM) corresponds to maximising the information

- Prior information regarding the model and the parameters is needed

Software Selection

- Recent publication comparing implemented features and reproducibility of results[1]

Feature	PFIM	PkStaMp	Software PopDes	PopED	POPT
Language	R	Matlab	Matlab	Matlab FreeMat	Matlab FreeMat
Available on website	✓		✓	✓	✓
Library of PKPD models	✓	✓	✓	✓	✓
User-defined models	✓	✓	✓	✓	✓
Multiresponse models	✓	✓	✓	✓	✓
Designs differ across responses	✓	✓	✓	✓	✓
ODE models	✓	✓	✓	✓	✓
Full FIM	✓	✓	✓	✓	–
Full covariance matrix for Ω	–	✓	✓	✓	–
Full covariance matrix for Σ	–	–	✓	✓	–
IOV	✓	–	✓	✓	–
Discrete covariates/power	✓/✓	–	✓/–	✓/✓	✓/–

- PopED and PFIM available for R

[1] Nyberg *et al.* BJCP (2014)

Time to get started!

Input requirements

- PFIM:
  - Structural model definition in an independent R file
  - Pre-defined input file where parameters, design and task features are defined
- PopED
  - No pre-defined template
  - Set of functions for the structural model, the parameters and variability model, and the residual error function
  - PopED database calling above functions, specifying parameter value and including design information
  - Tasks are package functions

Model implementation

- PFIM and PopED implement the model as an R function suitable for the solver R package 'deSolve'.
- Model code similar, but not directly interchangeable:
- Different ways of encoding dosing

  - POPED:
    - the dose, dose time, dose interval can be considered covariates
    - easily manipulated
  - PFIM:
    - Large library of PK models
    - Dose can be easily modified when using analytical solutions
    - dose interval and dose time are defined as function arguments

Model implementation

PFIM

```
formED<-function(t,y,p){
  …
  n <- t%/%tau

  multiple_oral <- function(ka,k10,V,dose,n,tau,t){
    if (n<tdose_start){return(0)}
    if(n>=tdose_start & n<=tdose_end){return((dose/V)*(ka/(ka-k10))*(exp(-
k10*(t-n*tau))-exp(-ka*(t-n*tau))) +multiple_oral(ka,k10,V,dose,n-1,tau,t))}
    if (n>tdose_end){return(multiple_oral(ka,k10,V,dose,n-1,tau,t))}
  }

  C1 <-multiple_oral(ka,k10,V,dose=dose1,n,tau,t)

  w <- y[1]+y[2]+y[3]+y[4]

  yd1 <- (KP*y[1]/(1+((KP/KL)*w)^psi)^(psi^-1)) -KD*C1*y[1]
  yd2 <- EDRUG1*y[1]-KTR*y[2]
  yd3 <- KTR*(y[2]-y[3])
  yd4 <- KTR*(y[3]-y[4])

return(list(c(yd1,yd2,yd3,yd4),c(w)))}
}
```

Model implementation

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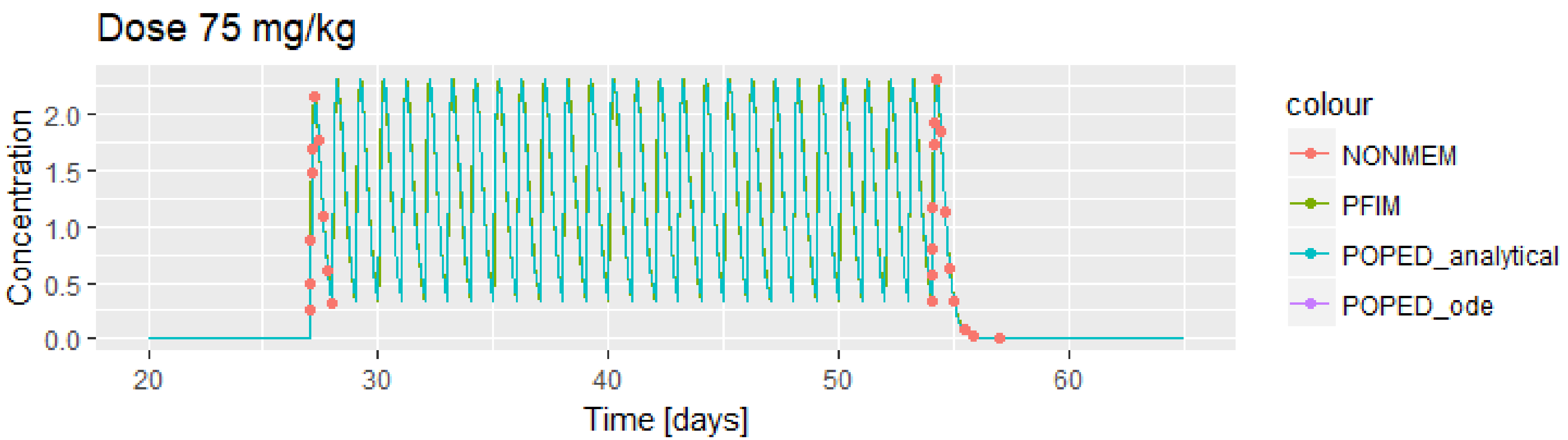
PFIM

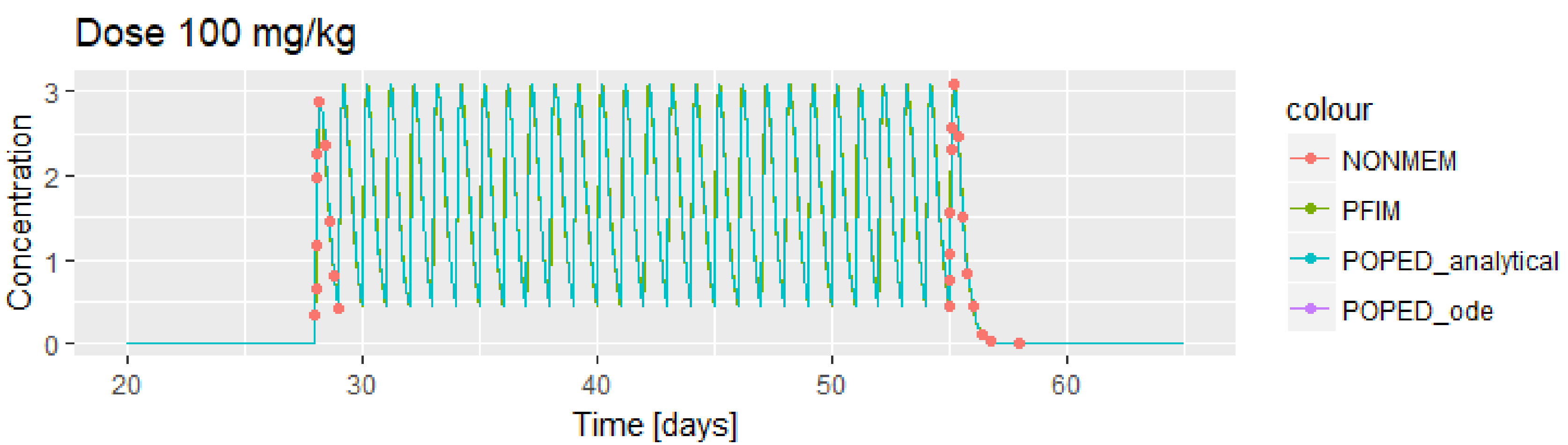
```
formED<-function(t,y,p){
  …
  C1 <-multiple_oral(ka,k10,V,dose=dose1,n,tau,t)
  C2 <- multiple_oral(ka,k10,V,dose=dose2,n,tau,t)

  w1 <- y[1]+y[2]+y[3]+y[4]
  w2 <- y[5]+y[6]+y[7]+y[8]
  w <- w1 + w2

  yd1 <- (KP*y[1]/(1+((KP/KL)*w1)^psi)^(psi^-1)) -KD*C1*y[1]
  yd2 <- EDRUG1*y[1]-KTR*y[2]
  yd3 <- KTR*(y[2]-y[3])
  yd4 <- KTR*(y[3]-y[4])

  yd5 <- (KP*y[5]/(1+((KP/KL)*w2)^psi)^(psi^-1)) -KD*C2*y[1]
  yd6 <- EDRUG1*y[5]-KTR*y[6]
  yd7 <- KTR*(y[6]-y[7])
  yd8 <- KTR*(y[7]-y[8])

return(list(c(yd1,yd2,yd3,yd4,yd5,yd6,yd7,yd8),c(w)))}
}
```

*Adapted from Giulia Lestini code

Model implementation

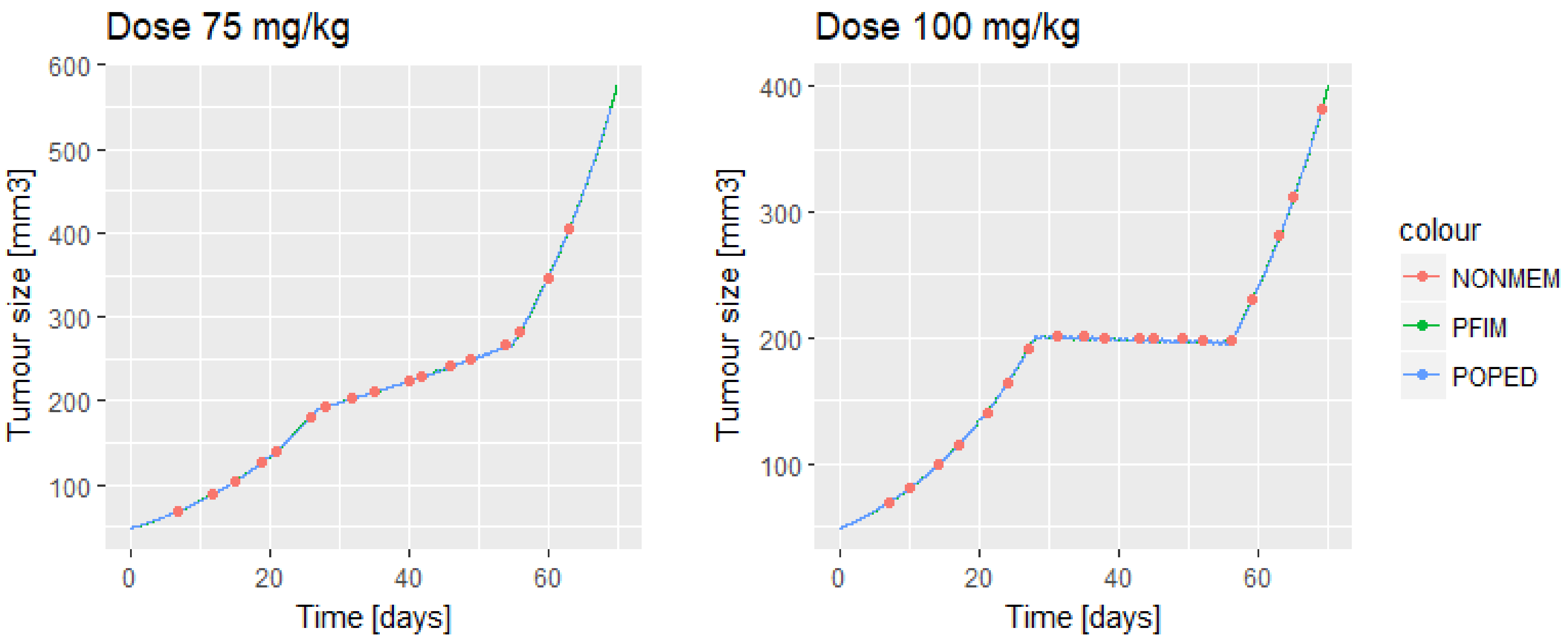
Validation





Model implementation

Validation



Design evaluation

- Based on the computation of the FIM to retrieve RSE
- Two expressions of the FIM
  - Full FIM
  - Block diagonal FIM
- Block showed a better performance

Parameter	Block diagonal FIM	Full FIM	Simulations	
	PFIM/PkStaMp/PopDes/PopED/POPT	PFIM/PkStaMp/PopDes/PopED	NONMEM	MONOLIX
β_{ka}	13.9	4.8	13.6	13.8
$\beta_{CL/F}$	4.7	3.6	4.9	4.8
$\beta_{V/F}$	2.8	2.6	2.7	2.8
ω^2_{ka}	25.8	26.5	26.6	28.1
$\omega^2_{CL/F}$	25.6	26.3	26.1	26.6
$\omega^2_{V/F}$	30.3	30.9	32.4	30.8
σ^2	11.2	12.4	10.9	11.0

From Nyberg *et al*. BJCP (2014)

Can be foreseen situations where this is not the case?

Design evaluation

- No analytical expression for the FIM
- Different approximations available:
  - FO / FOCE / FOCEI / FOI

Parameter	Block diagonal FIM	Full FIM	Simulations	
	PFIM/PkStaMp/PopDes/PopED/POPT	PFIM/PkStaMp/PopDes/PopED	NONMEM	MONOLIX
β_{ka}	13.9	4.8	13.6	13.8
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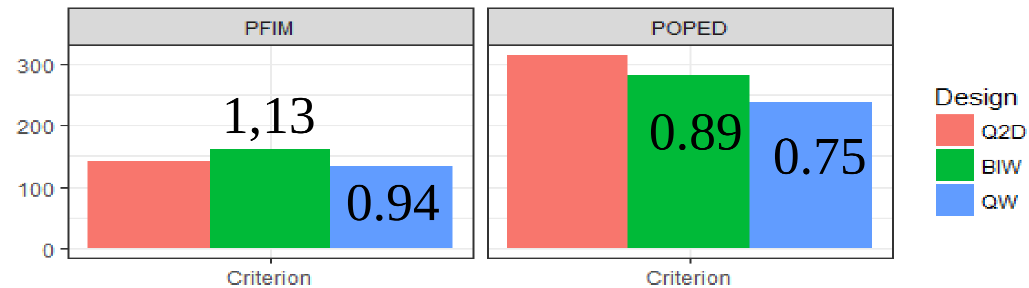
From Nyberg *et al.* BJCP (2014)

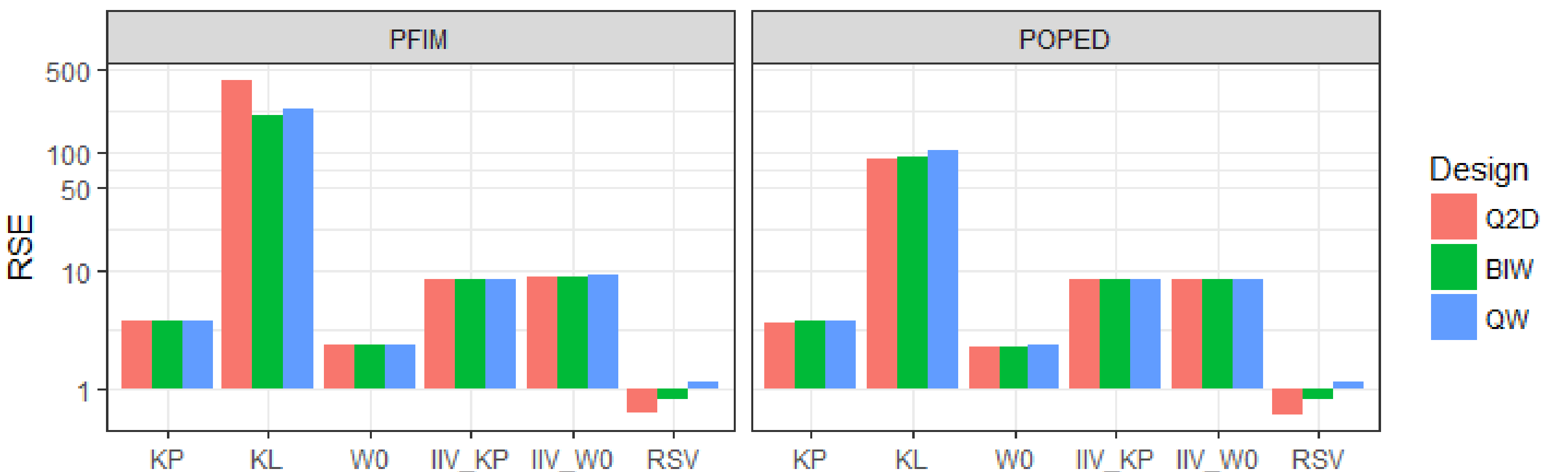
When shall we use the other approximation methods?

Design evaluation: interpreting the results

- Expected RSE
- Criterion: $|\mathrm{FIM}|^{1/\dim(\varphi)}$
- Efficacy criterion: $\mathrm{Criterion}_{\mathrm{REF}}/\mathrm{Criterion}_{\mathrm{NEW}}$

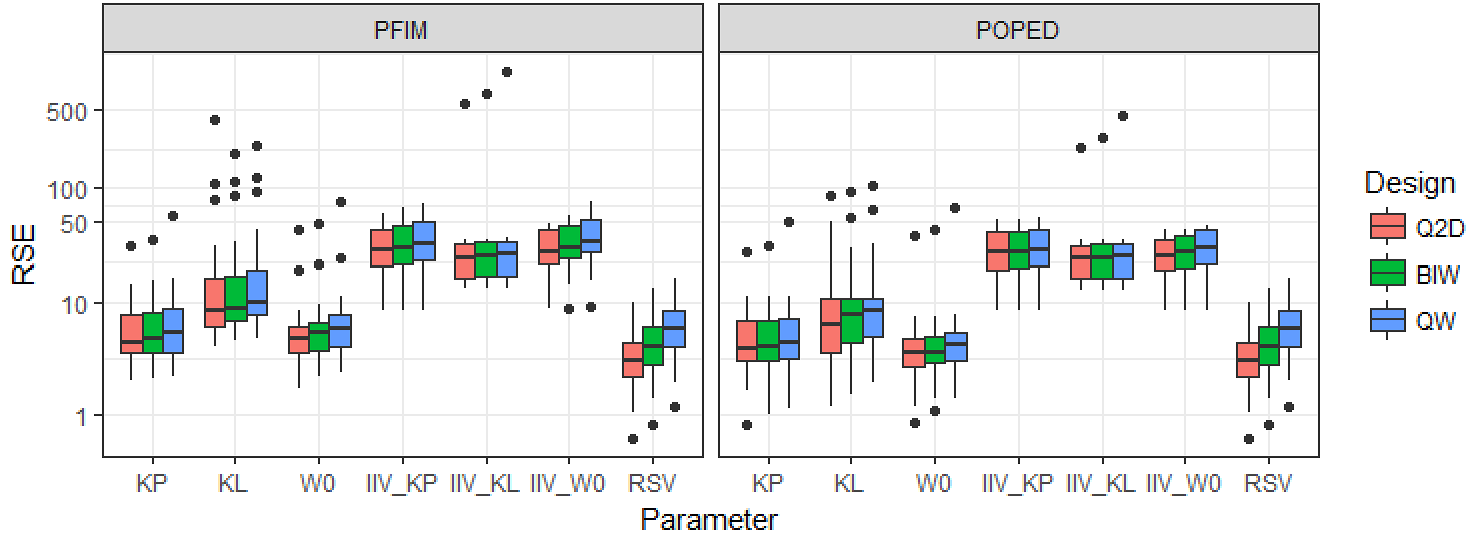


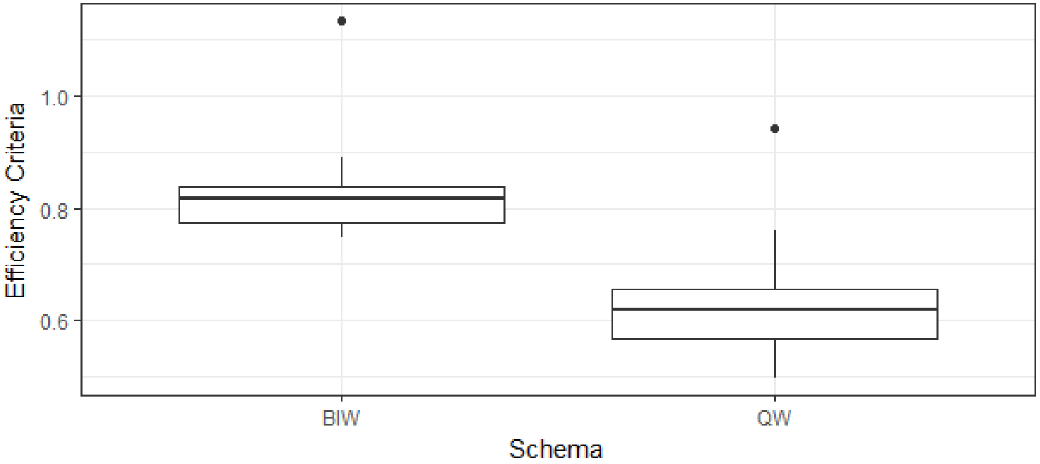
Is there a generalised/ statistical cut off ?



Design evaluation: interpreting the results

- Example:





Optimisation

- Goal is to minimise the variance (i.e maximise the information
- Different optimality criteria based on the information matrix are available
  - D-Optimality criteria frequently used:
    - maximise the determinant of the FIM

When shall we use other optimality criteria?

Optimisation

- Different algorithms implemented:
  - PopED:
    - Adaptive Random Search
    - Line Search
    - L-BFGS-B
    - Gene search
  - PFIM:
    - Simplex: fix designs
    - Fedorov - Wynn: - Optimise statistical designs

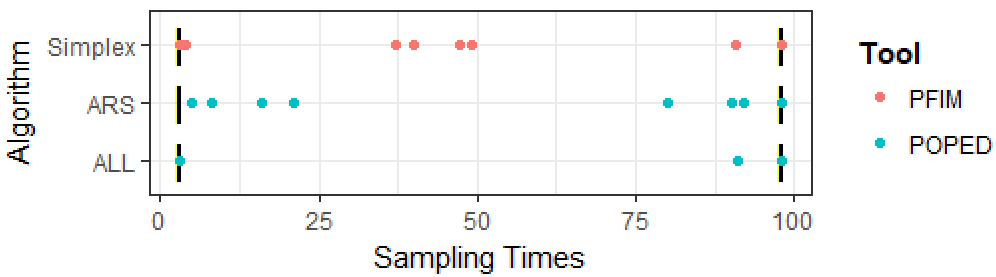
Is there any rule regarding when to select which?

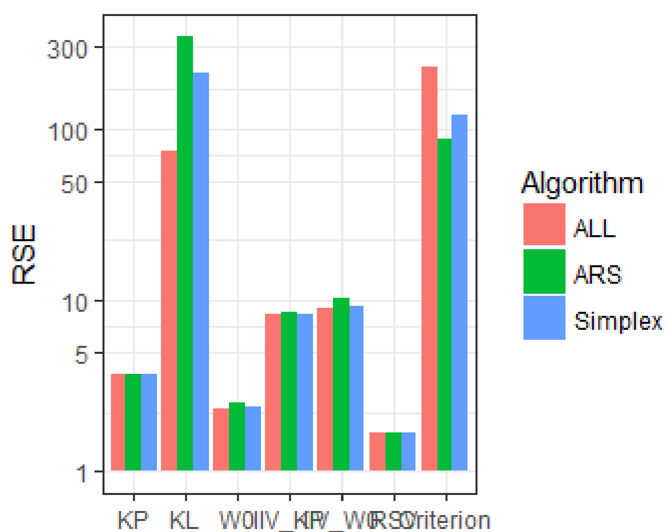
Optimisation: results evaluation

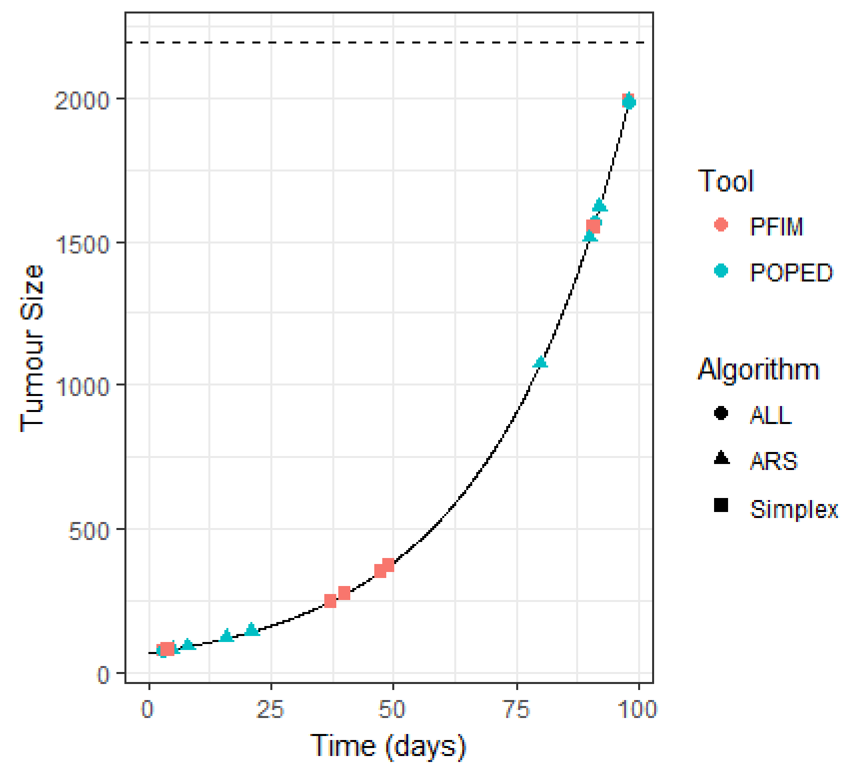
An example using the Simeoni Model:

Optimise only sampling times for unperturbed growth (n=8)

Sampling time window: 3-98 days







Conclusions

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- There is a growing interest in incorporating Optimal Design on our regular M&S workflows
- Getting started in Optimal Design is not easy
- PODE workshop provides a great platform to share and learn, but can get too technical for newbies
- Inclusion of model code and input information as appendix in publications would be extremely helpful
- Didactic material and courses tailored for pharmacometricians are required

Bibliography

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THANK
YOU