Two-stage adaptive designs in nonlinear mixed-effects models: an evaluation by simulation for a pharmacokinetic (PK) and pharmacodynamic (PD) model in oncology

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CONTEXT

Optimal design in population PKPD is based on prior information on the models and on the parameters. Adaptive designs [1,2] are a promising alternative to local or robust designs [3]. Two-stage designs are easier to implement than fully adaptive designs and can be as efficient [4].

OBJECTIVES

- To compare by simulation one and two-stage designs using a PKPD model in oncology
- To study the influence of the size of each cohort in two-stage designs

METHODS

Two-Stage design

Assumptions
- prior information about the parameters and model available
- same elementary design ξ for all patients in each cohort

Notation
- M_F= Population Fisher Information Matrix
- Ψ^0 : prior parameters
- Ψ^* : true parameters
- ξ^0: optimized design obtained with Ψ^0 for N_1 subjects
- $\hat{\Psi}_1$: estimated parameters from data Y_1 with design ξ^0 and N_1 subjects
- ξ^2: optimized design obtained with $\hat{\Psi}_1$ for N_2 subjects
- $\hat{\Psi}_2$: estimated parameters from data Y_1 and Y_2 (obtained with design ξ^2 for N_2 subjects)

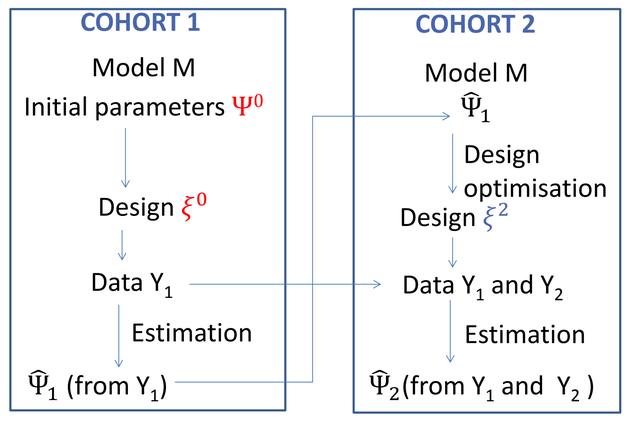


Figure 1: *Two-stage design*

Design optimisation

First stage: from a priori Ψ^0, ξ^0 maximizes determinant of

$$M_F(\Psi^0, N_1\,\xi) = N_1\, M_F(\Psi^0, \xi)$$

Second stage: using estimated $\hat{\Psi}_1$, ξ^2 maximizes determinant of

$$M_F(\hat{\Psi}_1, N_1\,\xi^0 + N_2\,\xi) = N_1\, M_F(\hat{\Psi}_1, \xi^0) + N_2\, M_F(\hat{\Psi}_1, \xi)$$

NB: this procedure is implemented in PFIM 4.0 released in April 2014 [7, 8]

PKPD Model

- Model developed for a novel oral transforming growth factor β (TGF – β) inhibitor [5,6]
- PK parameters: ka, V, CL
- PD parameters: kout, IC50
- True parameters Ψ^* in Table 1
- Prior parameters $\Psi^0 \neq \Psi^*$: CL=40 L/h (× 4), kout=2 h^{-1} (× 10)

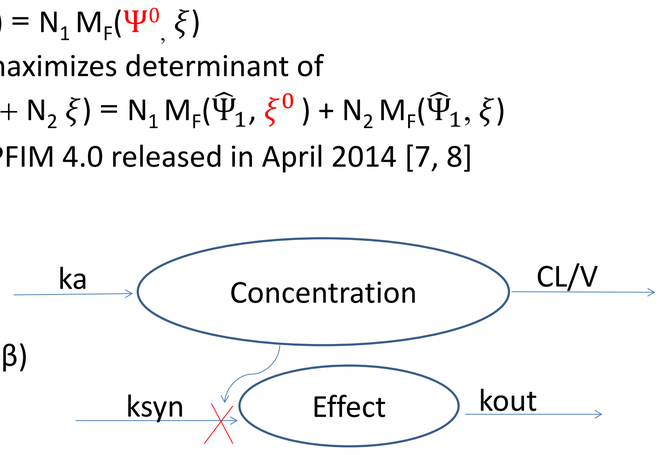


Figure 2: *PKPD Model*

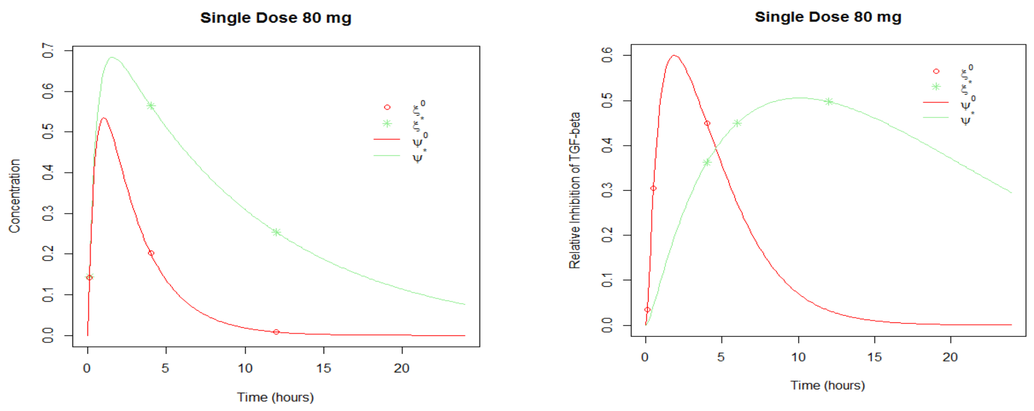


Figure 3: *Simulated PK (left) and PD (right) models with parameters Ψ^0 and Ψ^**

Evaluated designs

- N= 50 patients

One-stage designs
- Rich design, n=6 sampling times: $\xi_{rich} = (0.1, 0.5, 1.5, 4, 6, 12)$
- Sparse designs, n=3 sampling times among the 6 of ξ_{rich}:
  - $\xi^0 = \{\xi^0_{PK} = (0.1, 4, 12); \xi^0_{PD} = (0.5, 1.5, 4)\}$ (D-optimal for Ψ^0)
  - $\xi^* = \{\xi^*_{PK} = (0.1, 4, 12);\ \xi^*_{PD} = (4, 6, 12)\}$ (D-optimal for Ψ^*)
  - mixed design ξ^{0*} (N_1=25 patients with ξ^0; N_2=25 patients with ξ^*)

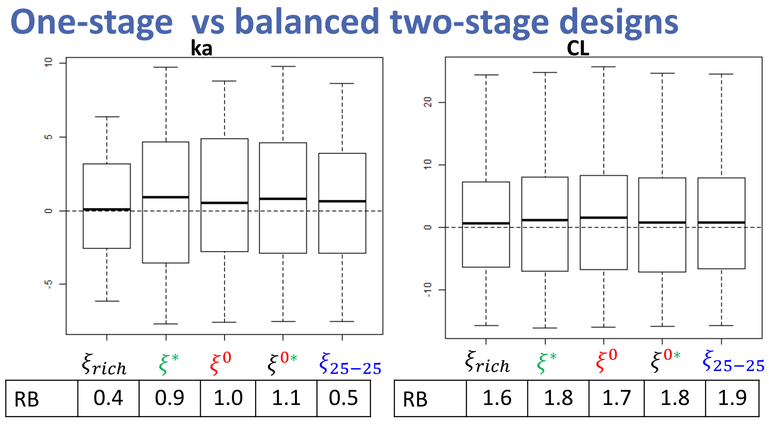
Two-stage designs
- Balanced: ξ_{25-25} (N_1= N_2 =25)
- Various sizes for cohorts 1 and 2: ξ_{10-40} , ξ_{15-35} , ξ_{35-15} , ξ_{40-10}

Clinical Trial Simulation

- For each design: 100 data sets simulated with Ψ^*
- For two-stage design: optimisation of ξ^2 from estimated $\hat{\Psi}_1$
- Parameters estimation: SAEM algorithm in MONOLIX 4.3
  - 5 chains, initial estimates: Ψ^0
- Comparison of designs from 100 estimated $\hat{\Psi}_2$: Relative Estimation Error (REE), Relative Bias (RB) and Relative Root Mean Squared Error (RRMSE)

RESULTS

One-stage vs balanced two-stage designs

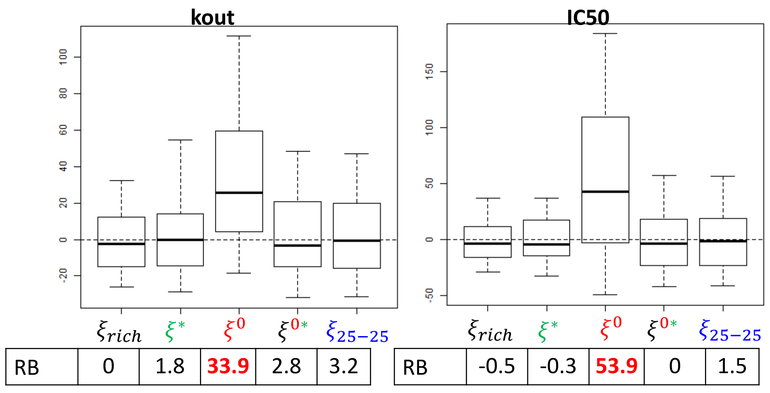


RB	0.4	0.9	1.0	1.1	0.5

RB	1.6	1.8	1.7	1.8	1.9

- For PK, good results for all designs

Figure 4: *Boxplot of REE for ka and CL and relative bias (RB)*



RB	0	1.8	33.9	2.8	3.2

RB	-0.5	-0.3	53.9	0	1.5

- For PD, REE and RB are very high with ξ^0 compared with the other designs
- For the two-stage design ξ_{25-25} results of REE and RB are close to those of ξ^*

Figure 5: *Boxplot of REE for kout and IC50 and relative bias (RB)*

		RRMSE % (standardized RRMSE)			
Parameters	Ψ^*	ξ^*	ξ^0	ξ^{0*}	ξ_{25-25}
$k_a(\mathrm{h}^{-1})$	2	5.8	5.6 (0.97)	5.7 (0.98)	5.0 (0.86)
$V\ (L)$	100	9.9	9.9 (1.00)	9.9 (1.00)	9.3 (0.94)
$CL(L/h)$	10	12.5	12.4 (0.99)	12.5 (1.00)	12.5 (1.00)
ω^2_V	0.49	22.7	22.5 (0.99)	22.5 (0.99)	22.2 (0.98)
ω^2_{CL}	0.49	24.3	24.5 (1.01)	24.2 (1.00)	24.1 (0.99)
$\sigma_{slope.PK}$	0.2	10.2	10.2 (1.00)	10.0 (0.98)	9.9 (0.97)
$k_{out}(\mathrm{h}^{-1})$	0.2	23.2	54.5 (2.35)	25.6 (1.10)	24.3 (1.05)
$IC_{50}(\mathrm{mg/L})$	0.3	22.1	91.1 (4.12)	30.4 (1.38)	30.3 (1.37)
$\omega^2_{k_{out}}$	0.49	72.9	59.9 (0.82)	59.5 (0.82)	61.2 (0.84)
ω^2_{IC50}	0.49	72.4	709.9 (9.81)	95.7 (1.32)	99.0 (1.37)
$\sigma_{inter.PD}$	0.2	7.2	6.5 (0.90)	6.5 (0.90)	6.3 (0.88)
Mean Standardized RRMSE		1.00	2.18	1.04	1.02

- Relative RRMSE shows again good results of the two-stage design ξ_{25-25}, except somehow for IC50 and ω^2_{IC50} but much better than those of ξ^0

Table 1: *RRMSE of final estimated parameters from N_1+N_2=50 patients*

Influence of the size of each cohort in two-stage design

		RRMSE % (standardized RRMSE)				
Parameters	Ψ^*	ξ_{10-40}	ξ_{15-35}	ξ_{25-25}	ξ_{35-15}	ξ_{40-10}
$k_a(\mathrm{h}^{-1})$	2	5.5 (0.95)	5.6 (0.97)	5.0 (0.86)	5.3 (0.91)	5.6 (0.97)
$V\ (L)$	100	9.4 (0.95)	9.7 (0.98)	9.3 (0.94)	9.5 (0.96)	9.7 (0.98)
$CL(L/h)$	10	12.4 (0.99)	12.5 (1.00)	12.5 (1.00)	12.5 (1.00)	12.5 (1.00)
ω^2_V	0.49	22.3 (0.98)	22.0 (0.97)	22.2 (0.98)	22.1 (0.97)	22.2 (0.98)
ω^2_{CL}	0.49	23.9 (0.98)	24.5 (1.01)	24.1 (0.99)	23.9 (0.98)	24.9 (1.02)
$\sigma_{slope.PK}$	0.2	10.7 (1.05)	10.0 (0.98)	9.9 (0.97)	9.9 (0.97)	9.9 (0.97)
$k_{out}(\mathrm{h}^{-1})$	0.2	28.7 (1.24)	26.2 (1.13)	24.3 (1.05)	32.2 (1.39)	33.3 (1.44)
$IC_{50}(\mathrm{mg/L})$	0.3	49.1 (2.22)	36.0 (1.63)	30.3 (1.37)	45.7 (2.07)	57.0 (2.58)
$\omega^2_{k_{out}}$	0.49	60.0 (0.82)	63.4 (0.87)	61.2 (0.84)	59.3 (0.81)	63.3 (0.87)
ω^2_{IC50}	0.49	104.5 (1.44)	102.4 (1.41)	99.0 (1.37)	197.7 (2.73)	247.2 (3.41)
$\sigma_{inter.PD}$	0.2	6.3 (0.88)	6.8 (0.94)	6.3 (0.88)	6.5 (0.90)	6.5 (0.90)
Mean Standardized RRMSE		1.14	1.08	1.02	1.25	1.37

- From the RRMSE, the balanced two-stage design (ξ_{25-25}) performed better compared to the other different two-stage designs

Table 2: *RRMSE of final estimated parameters from N_1+N_2=50 patients for the balanced and unbalanced cohort size two-stage designs*

	ξ_{10-40}	ξ_{15-35}	ξ_{25-25}	ξ_{35-15}	ξ_{40-10}
# dif designs	12	8	6	6	6
# data-set with design $\xi^2 = \xi^*$	24	36	49	47	45

- After the first stage, the design ξ_{25-25} is the one with the greatest number of optimal elementary designs ξ^2 equals to ξ^*

Table 3: *Optimal designs ξ^2 obtained after the first stage*

CONCLUSIONS

- With the balanced two-stage design ξ_{25-25} , results are very close to those of the one-stage design using true parameters (Ψ^*) and are much better than those using wrong prior parameters (Ψ^0)
- The balanced ξ_{25-25} was the best two-stage design compared to unbalanced cohort size, especially if the second cohort was of small size
- Perspectives
  - to compare two-stage design with three-stage and five-stage designs
  - to use robust approach for first stage
  - to expand the approach for dose-finding

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Acknowledgment: The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115156, resources of which are composed of financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. The DDMoRe project is also financially supported by contributions from Academic and SME partners. This work does not necessarily represent the view of all DDMoRe partners.