Mean Squared Error as Criterion for Sampling Schedule Optimization for Individual Dose Targeting in Busulfan

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Introduction:

Individual **MAP** Estimator (uses population prior)

Known to introduce bias (shrinkage towards parameter mean) in the estimate for an individual → **Optimal Individual MAP Schedule?**

Proposed Design Criterion: Mean Squared Error

$$MSE = \frac{1}{M}\sum_{j=1}^{M}\left(\hat{\theta}_j - \bar{\theta}\right)^2$$

$\bar{\theta}$ = true individual parameter value
$\hat{\theta}_j$ = individual estimate for error replicate j

$$MSE = \underbrace{\left(\frac{1}{M}\sum_{j=1}^{M}\left(\hat{\theta}_j - \bar{\theta}\right)\right)^2}_{me^2} + \underbrace{\frac{1}{M}\sum_{j=1}^{M}\left(\left(\hat{\theta}_j - \bar{\theta}\right) - \frac{1}{M}\sum_{j=1}^{M}\left(\hat{\theta}_j - \bar{\theta}\right)\right)^2}_{pev}$$

Mean prediction error (me) A measure of "bias"

Prediction error variance (pev) A measure of "precision"

D-optimality criterion also a measure of precision

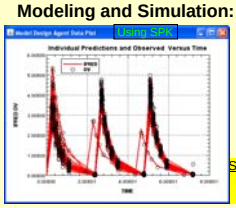
Proposed individual estimation design criterion: MSE – accounts for precision and bias

Most optimal design software for both individual (ADAPT II) and population (PFIM, WinPopt, popED) experimental design is based on D-optimality design criterion (determinant of Fischer information matrix; a measure of precision only).

MAP = maximum *a posteriori* estimation (*i.e.* MLE with population prior).

MSE; see e.g. [1] and [2]

Modeling and Simulation:



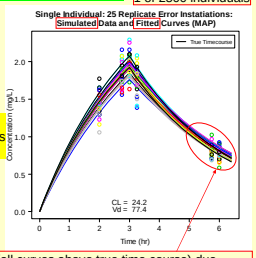
Population mixed-effect modeling of IV Busulfan
First order kinetics with three hour infusion
42 individuals

CL ~ LN(12.2 L/h, 31.1% CV)
Vd ~ LN(49.3 L, 29.5% CV)
Corr(CL,VD) = 0.9

RUV: 0.06 SD & 8.3% CV

Simulation:
N=1000-2500 simulated subjects
M=15-25 error replicates

1 of 2500 individuals



Bias (all curves above true time course) due to parameter "shrinkage" toward population values

Re-estimation (MAP):
nls function in R implemented with
– population prior and
– rotation to incorporate full covariance [as in 3]

Optimal Individual MAP Schedule?

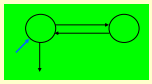
MSE criterion (precision and bias):
MSE computed:
– for each parameter (CL and Vd)
– scaled $(MSE/\bar{\theta}^2)$ and averaged
– for each individual
– on each potential time schedule

Figure of merit: Mean MSE (over all individuals)

D-optimality criterion (precision):
Determinant of the Fisher Information Matrix (FIM)
Computed in R as 1/det(vcov)
– for each replicate
– for each individual (as mean over replicates)
– on each potential time schedule
(vcov – covariance matrix of model parameters returned from the nls)

Figure of merit: Median det(FIM) (over all individuals)

Bonus Example: Fludarabine Sampling Schedule Optimization



Population Model:

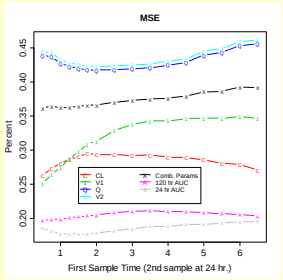
		Correlations		
		CL	V1	Q
CL ~ LN(11.3 L/h,	39% CV)			
V1 ~ LN(58.1 L,	40% CV)	0.8		
Q ~ LN(16.2 L/h,	46% CV)	0[a]	0.3[b]	
V2 ~ LN(85.2,	47% CV)	0[a]	0.3[b]	1[a]

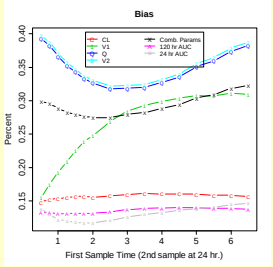
(a – correlations assumed by construction)
(b – correlations equal by construction)

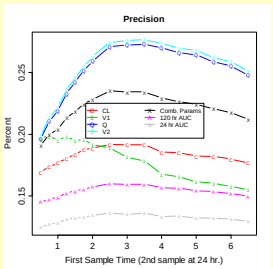
RUV: 0.016 SD & 23.7% CV

Optimal Individual MAP Schedule?

Compare criteria:
– for each parameter
– All params. combined
– 24 hour AUC
– 120 hour AUC
Plotted as:
– root mean MSE
– root me^2 (bias)
– root pev (precision)







Bias, precision and MSE of AUC follows similar trend as for combined parameters

Objective 1: Illustration of MSE-optimality vs. D-optimality:

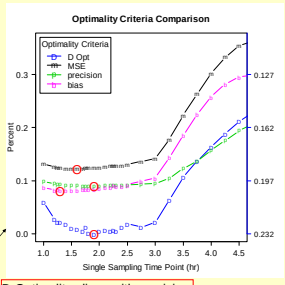
Single time point schedule (in 0 – 6 hrs)

Kinetic and statistical Model:
Adapted IV Busulfan kinetics Model

CL ~ LN(12.2 L/h, 10% CV)
Vd ~ LN(49.3 L, 50% CV)
Corr(CL,VD) = 0.2
RUV: 0.06 SD & 8.3% CV

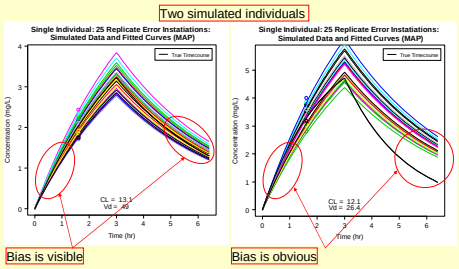
Optimal Individual MAP Schedule?

Compare criteria:
Plotted as:
– root mean MSE
– root me^2 (bias)
– root pev (precision)
– det(FIM) (D-Opt) (inverted scale on rhs)



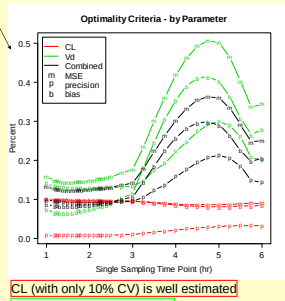
D-Optimality aligns with precision
Bias and precision contribute ~equally to MSE

Two simulated individuals



Bias is visible

Bias is obvious



CL (with only 10% CV) is well estimated
Vd (with 50% CV) dominates

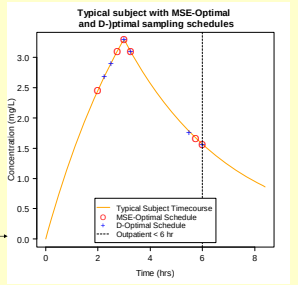
Objective 2: Rich sampling optimal outpatient schedule for Individual Busulfan TDM

Outpatient sampling <6 hrs from infusion initiation

Rich sampling: 6 time points (0-6 hrs)
- Samples at 3, 3.25, 6 hrs fixed (by clinician)
- Sampling on ¼, ½, ¾ and full hour only
- Single sample per time point only

Optimal Individual MAP Schedule?

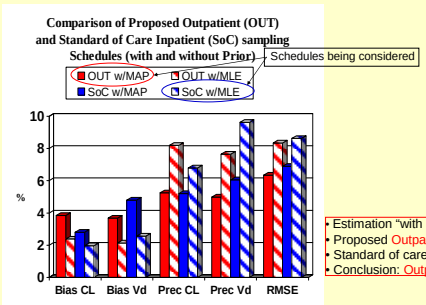
Rich sampling:
MSE and D –Optimal schedules similar (as expected)



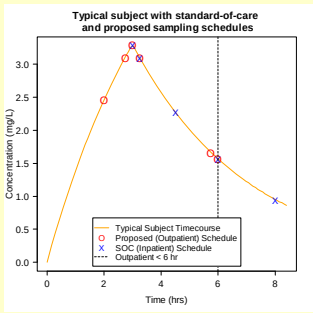
Objective 3: Comparison of Outpatient schedule with Standard of Care (Inpatient)

Proposed Outpatient Schedule with MAP Estimation
vs.
Inpatient Schedule (Standard of Care) with MLE Estimation

Optimal Individual MAP or MLE Schedule?



- Estimation "with prior" (MAP) increased bias but improved precision.
- Proposed Outpatient schedule with MAP had lowest MSE
- Standard of care schedule with MLE had the highest MSE
- Conclusion: Outpatient sampling is feasible



Conclusions: MSE-optimality vs. D-optimality Criteria:

Individual MAP estimator biased:
Extent of bias determined by number of samples (well known) as well as sampling schedule

→ **Optimal Individual MAP Schedule?**

MSE as optimality criterion:
- Accounts for bias and precision
- Requires simulation/re-estimation

D-optimality criterion:
- Accounts for precision only
- Does not require simulation

References:
[1] Sheiner LB and Beal SL (1981) Some suggestions for measuring predictive performance. J. Pharmacokinetics and Biopharmaceutics 9:4:503-512
[2] Monteleone JPR and Duffull SB. (2003) Choice of best design. In Kimko HC and Duffull SB Eds. Simulation for designing clinical trials. Taylor and Francis Group, NY, New York.
[3]. Callegari T, Caumo A, and Cobelli C (2002) Generalization of Map Estimation in SAAM II: Validation Against ADAPT II in a Glucose Model Case Study Annals of Biomed Eng