New Model-Based Bioequivalence Statistical Approaches for Pharmacokinetic Studies with Sparse Sampling

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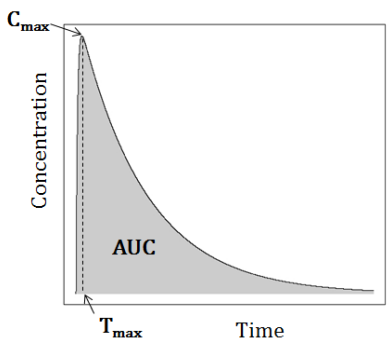
Bioequivalence (BE) studies

- **BE**: The difference in the pharmacokinetic (PK) of two formulations of a given drug does not exceed a predefined threshold (usually $\delta = \log(1.25)$)
- **Parallel studies** preferable for drugs with **long half-life**: $N/2$ subjects receive reference treatment (R), $N/2$ subjects receive test treatment (T)
- **Non-Compartmental Approach (NCA)** based BE:
  - Individual NCA estimates of AUC_i and Cmax_i
  - Let $\beta_{AUC} = \text{mean}(\log(AUC_{iT})) - \text{mean}(\log(AUC_{iR}))$
    $\beta_{Cmax} = \text{mean}(\log(Cmax_{iT})) - \text{mean}(\log(Cmax_{iR}))$



pros	cons
⋆ Reproductible	⋆ **Require more than 10 samples per subject**
⋆ Few assumptions	⋆ Not appropriate for complex models

- **Two one-sided tests (TOST)** [1] **at level $\alpha = 5\%$ on β_{AUC} and β_{Cmax}**:
  Reject of H_0 (= BE significant) if
  - $(\beta - \delta)/SE(\beta) \leq -z_{1-\alpha}$ and $(\beta + \delta)/SE(\beta) \geq z_{1-\alpha}$, with $z_{1-\alpha}$: $(1-\alpha)\%$ quantile of the normal distribution **or**
  - $CI(\beta)_{1-2\alpha\%} \in [-\delta; \delta]$ (CI: Confidence Interval)

[1] Schuirmann, *J Pharmacokinet Pharmacodyn*, 1987.

Model based (MB) BE

Non linear mixed effect model (NLMEM):
y_{ij}: concentration for subject i at sampling time j

$$y_{ij} = f(t_{ij}, \phi_i) + g(t_{ij}, \phi_i)\epsilon_{ij}$$

$$\log(\phi_{il}) = \log(\lambda_l) + \beta_l Tr_i + \eta_{il} \text{ where}$$

- β_l: Test treatment effect on the log of a PK parameter $l = (1, \ldots, p)$
- λ_l: l^{th} element of the vector of fixed effects
- Tr_i: vector of indicator for treatment group
- $\eta_{il} \sim \mathcal{N}(0, \omega_l)$: between subject random effect for parameter l
- $\epsilon_{ij} \sim \mathcal{N}(0, 1)$: residual error
- combined error model $g(t_{ij}, \phi_i) = a + b \times f(t_{ij}, \phi_i)$

Vector of population parameters: $\boldsymbol{\theta = (\lambda, \beta, \omega, a, b)}$

- Estimation of θ using SAEM algorithm [2]
- Estimation of $SE(\theta)$ from observed Fisher information matrix Σ

[2] Kuhn et Lavielle. *Comput Stat Data Anal*, 2005.

MBBE

- AUC and Cmax: secondary parameters of the NLMEM
  - β_{AUC} and β_{Cmax} functions of vectors λ and β
  - $SE(\beta_{AUC})$ and $SE(\beta_{Cmax})$ obtained using the delta method [3]
- **TOST at level $\alpha = 5\%$ or 90%CI on β_{AUC} and β_{Cmax}**

pros	cons
⋆ Require few samples per subject	⋆ **SE under estimated on sparse designs ⇒ Type I error inflation** [4]

- **Objectives: Development, evaluation and comparison of new model-based (MB) statistical approaches for sparse design BE studies**
  - Parametric random effect and residual bootstrap
  - Full distribution estimation using `Stan` [5]

[3] Oelhert *The American Statistician*, 1992.

[4] Dubois et al. *Stat in Med*, 2011.

[5] Stan development team, Rstan, 2012.

MBBE parametric random effect and residual bootstrap

Principle [6]

1. Estimation of θ and Σ with saemix
2. Drawing of $b = 1, \ldots, B$ (B=250) matrices of random effects of size N x p from $\mathcal{N}(0, \hat{\Omega})$
3. Drawing of vector of residual errors of size $\sum_{i=1}^{N} n_i$ from $\mathcal{N}(0, 1)$
4. Simulation of the B vectors of responses
5. Fit the B new data sets with saemix to get the B estimates θ_b and β_b
6. Derive 90%*CIs* on β_{Cmax} and β_{AUC} from the 5th and 95th percentiles of the serie $\hat{\beta}_b$

[6] Thai et al, *J Pharmacokinet Pharmacodyn*, 2014.

MBBE full distribution using Stan

Principle [7]

1. Estimation of θ and η_i with saemix
2. Full distribution in `Stan` [5]
   - Initialize HMC chain at estimates from step 1
   - Draw 1 chain of 1000 (including 100 burning) samples in *a posteriori* distributions of λ, β,ω,a, b
   - out of the B=900 samples derive 90%CI on β_{Cmax} and β_{AUC}

Stan model:

- Default distributions on fixed effects λ, β
- Non-informative priors on ω, a, b

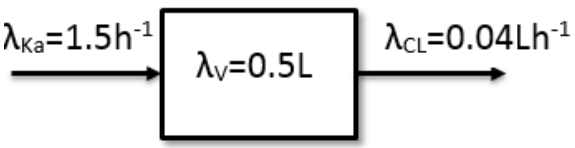
```
omega_vec ~ cauchy(0,2.5);
a ~ cauchy(0,2.5);
b ~ cauchy(0,2.5);
```

[5] Stan development team, Rstan, 2012.

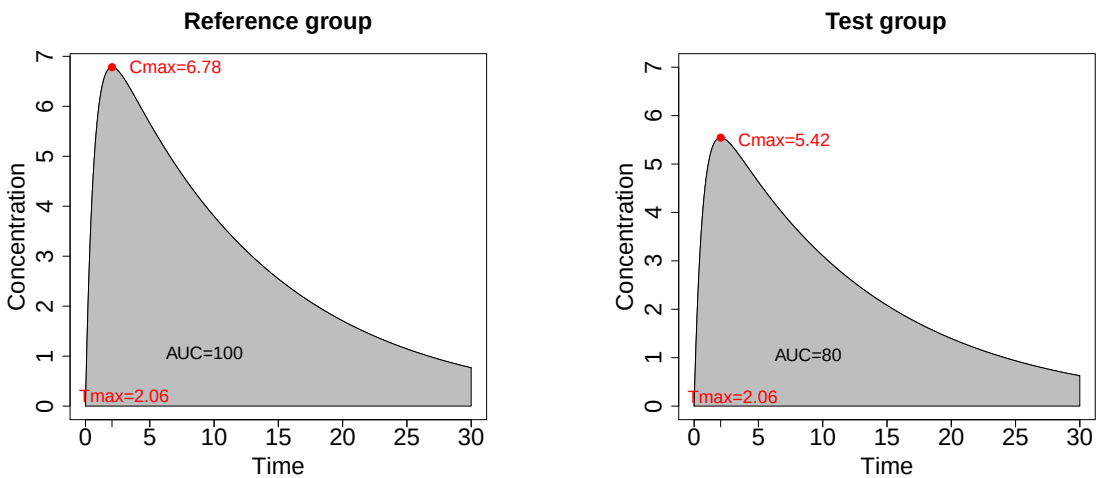
[7] Ueckert et al. *ACOP*, 2015.

PK model

- PK model of concentrations of the anti-asthmatic drug theophylline [2]
- Parallel design: N_R=N_T=20
- One-compartment model with first-order absorption and first-order elimination. Dose=4mg



- Covariate effects in test treatment group: $\beta_V = \beta_{Cl} = \log(1.25)$, $\beta_{Ka} = 0$



- Residual variability: a=0.1 mg/L, b=10%
- Random effects for BSV only:

ω_{k_a} (%)	$\omega_{V/F}$ (%)	$\omega_{CL/F}$ (%)
22	11	22

Simulation scenarios

- 500 simulated data sets for each of the 4 scenarios

Design	N	Sampling times (hours)	Hypothesis	$\beta_{CL} = \beta_V$
Rich	40	n=10, $t = (0.25, 0.5, 1, 2, 3.5, 5, 7, 9, 12, 24)$	H_0	log(1.25)
			H_1	log(1)
Sparse	40	n=3, $t = (0.25, 3.35, 24)$	H_0	log(1.25)
			H_1	log(1)

Under H_0: $\beta_{AUC} = \beta_{Cmax} = \log(0.8)$,
Under H_1: $\beta_{AUC} = \beta_{Cmax} = \log(1) = 0$

- Evaluation:
  - Type I error ($IP_{95\%}(0.05) = [0.033; 0.073]$)
  - Power
  - Computing times

Type I error and power estimates

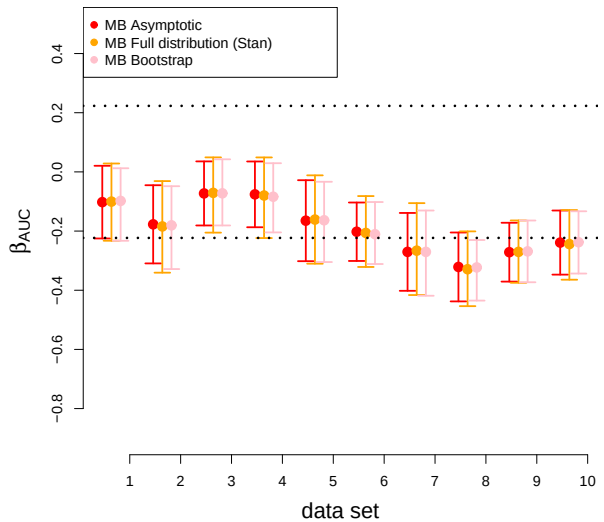
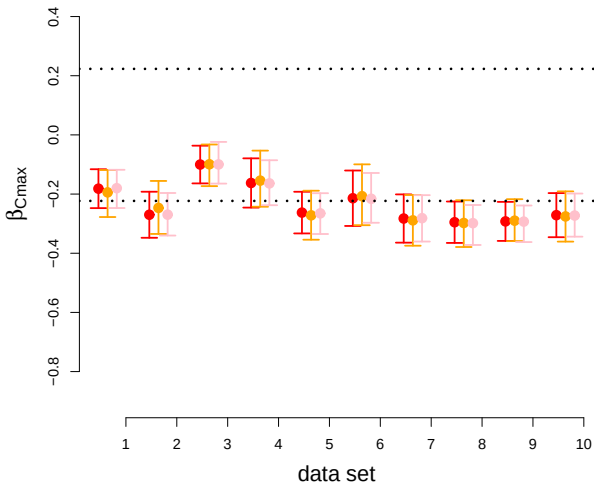
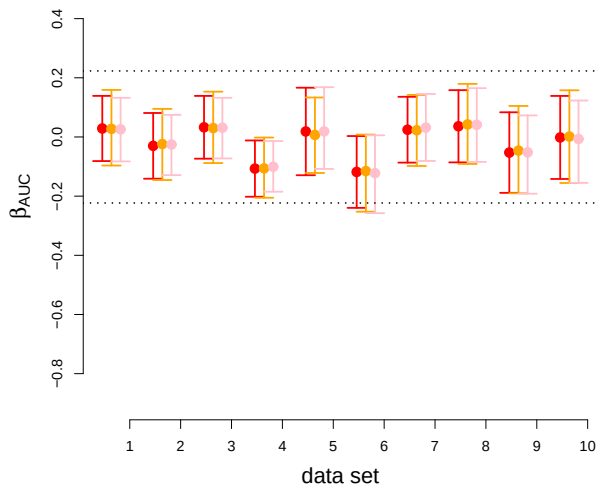
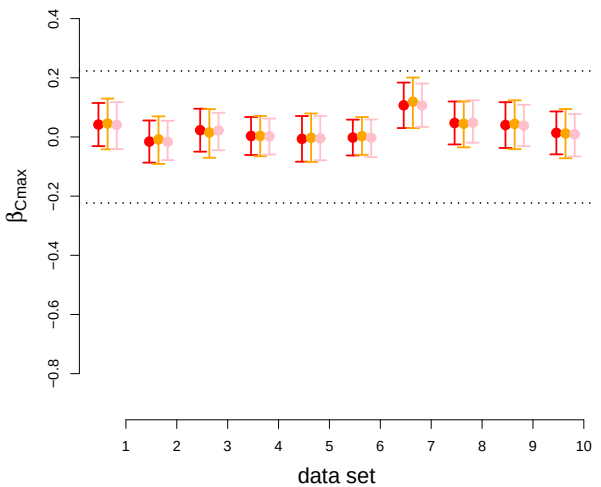
	NCA	MB Asymptotic SE	MB Bootstrap CI	MB Full distribution CI
Mean computing time for 1 data set	15 sec	15 sec	43 min	5 min

	Rich design			
	NCA	MB Asymptotic SE	MB Bootstrap CI	MB Full distribution CI
Type I error β_{AUC}	0.058	0.056	0.062	0.040
Type I error β_{Cmax}	0.062	0.058	0.064	0.044
Power β_{AUC}	0.814	0.830	0.832	0.762
Power β_{Cmax}	0.998	1.000	1.000	0.962

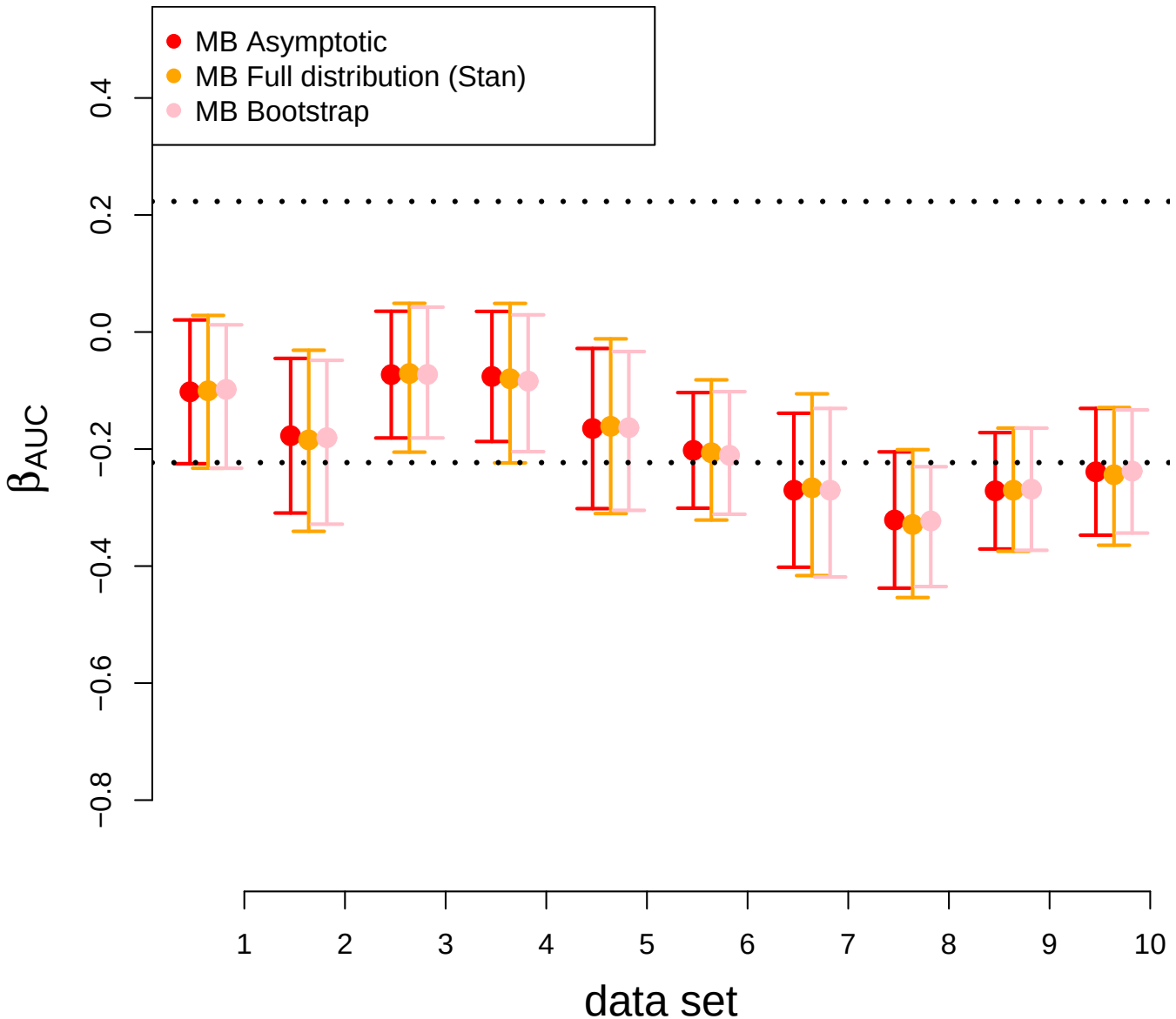
	Sparse design			
	NCA	MB Asymptotic SE	MB Bootstrap CI	MB Full distribution CI
Type I error β_{AUC}	-	0.076	0.074	0.060
Type I error β_{Cmax}	-	0.066	0.068	0.050
Power β_{AUC}	-	0.910	0.916	0.868
Power β_{Cmax}	-	1.000	1.000	0.992

$IP_{95\%}(0.05) = [0.033; 0.073]$ with 500 simulated data sets

90% CI(β) on sparse design

	β_{AUC}	β_{Cmax}
H_0		
H_1		

90% CI(β) on sparse design, under H0

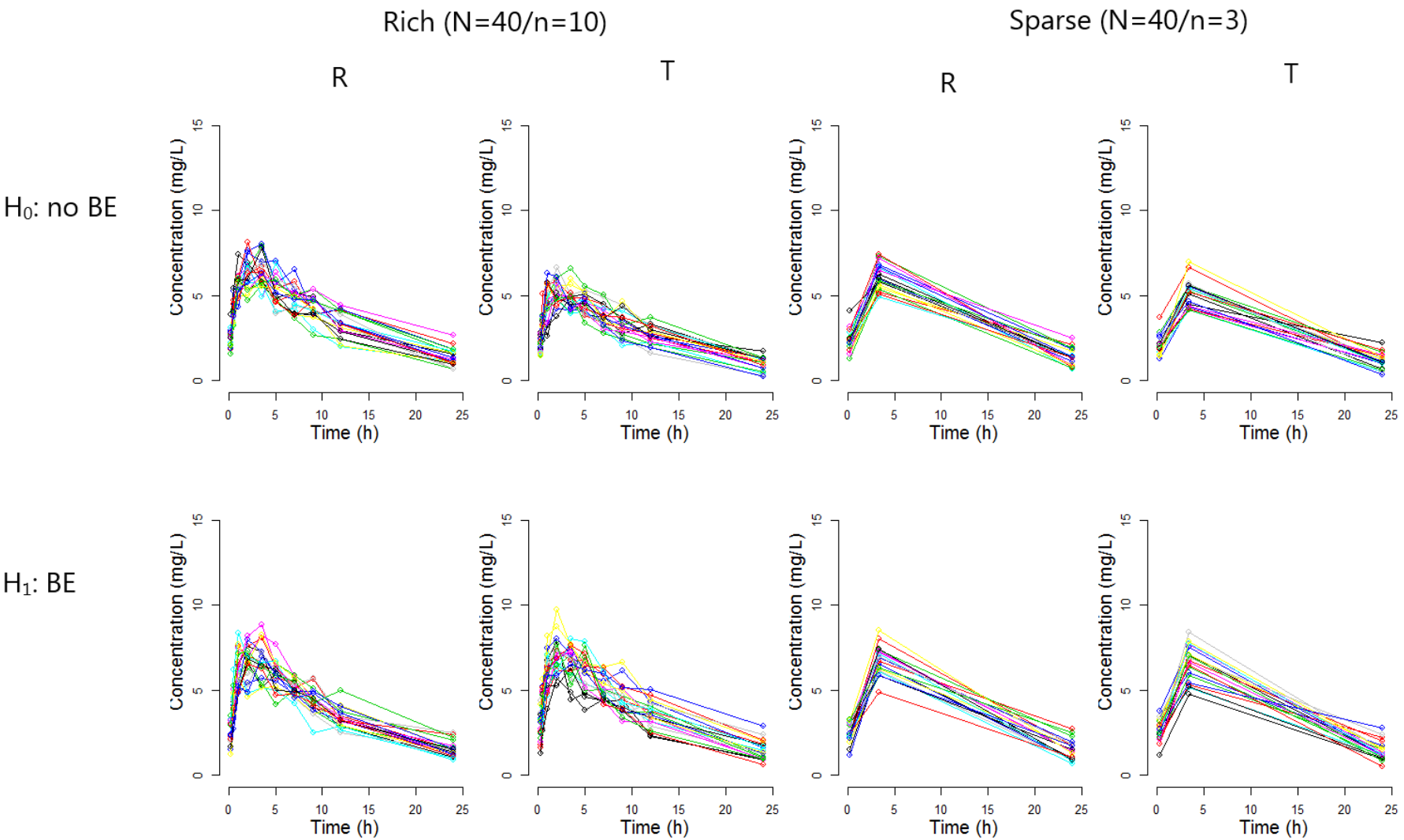


Conclusion

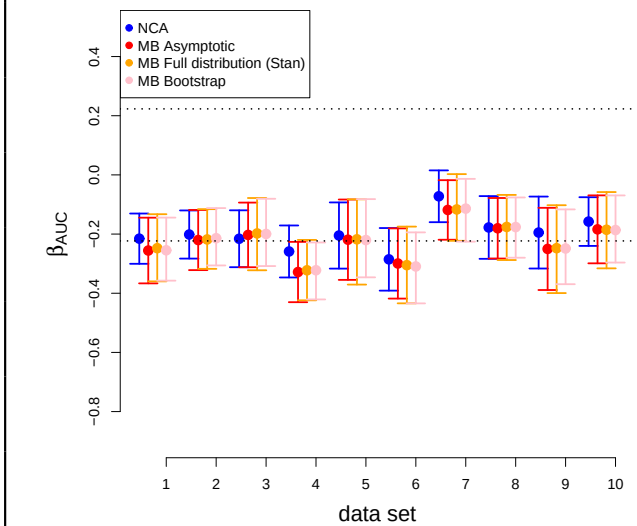
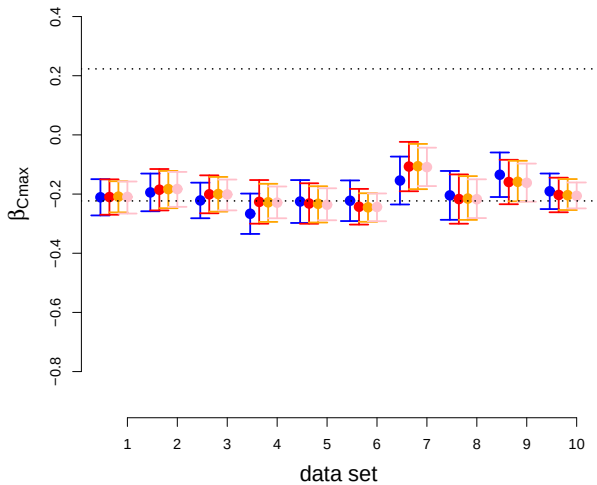
- Implementation of new methods for MBBE using parametric bootstrap and full distribution sampled in Stan
- Correction of MB TOST with asymptotic SE on sparse design using full distribution sampled in Stan
  - faster than bootstrap
- Perspective: implementation of the methods for 2-period 2-sequence crossover BE studies (accounting for within-subjects variability)

Thank you

Simulation scenarios



90% CI(β) on rich design

	β_{AUC}	β_{Cmax}
H_0		
H_1