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Application relevant shrinkage metrics

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Objective

To illustrate how relevant shrinkage metrics can be derived for secondary parameters such as AUC and C_{max} and how that shrinkage may affect a sequential PKPD analysis

About shrinkage

- Rada Savic and Mats Karlsson first introduced the concept of ETA and EPSILON shrinkage in connection to the 2007 PAGE meeting [1,2,3]
- Publications on shrinkage has primarily focused on the impact of shrinkage on model diagnostics and strategies to overcome that [2,3,4,5]
- Recently there is also a proposed method to overcome the issue with ETA-shrinkage for TDM applications [6]

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Quantifying Shrinkage

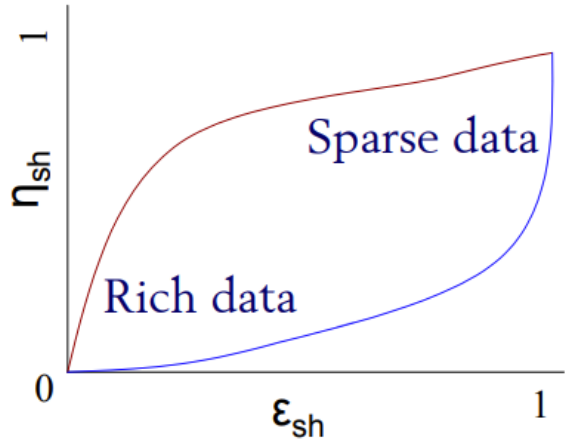
1. ETA shrinkage

$$\eta_{sh} = 1 - \frac{SD(\hat{\eta}_{ph})}{\omega}$$

2. EPSILON shrinkage

$$\varepsilon_{sh} = 1 - SD(IWRES)$$

How do these values change with information content?



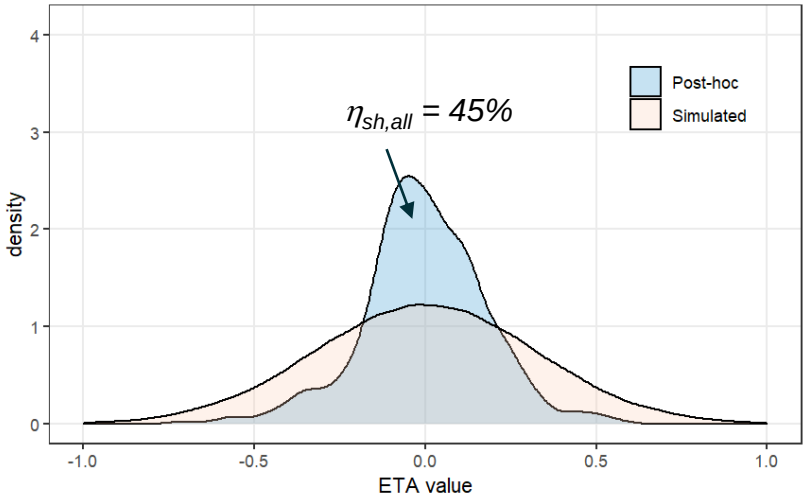
[1] Savic RM, Karlsson MO. PAGE 16 (2007) Abstr 1087 [www.page-meeting.org/?abstract=1087]
[2] Karlsson MO, Savic RM. Diagnosing model diagnostics. Clin Pharmacol Ther. 2007
[3] Savic RM, Karlsson MO. Importance of shrinkage in empirical bayes estimates for diagnostics: problems and solutions. AAPS J. 2009
[4] Xu XS et al. Shrinkage in nonlinear mixed-effects population models: quantification, influencing factors, and impact. AAPS J. 2012
[5] Lavielle, Marc, Benjamin Ribba. Enhanced Method for Diagnosing Pharmacometric Models: Random Sampling from Conditional Distributions. Pharm Res. 2016
[6] Baklouti, Sarah et al. "De-Shrinking" EBEs: The Solution for Bayesian Therapeutic Drug Monitoring. Clinical pharmacokinetics 2022

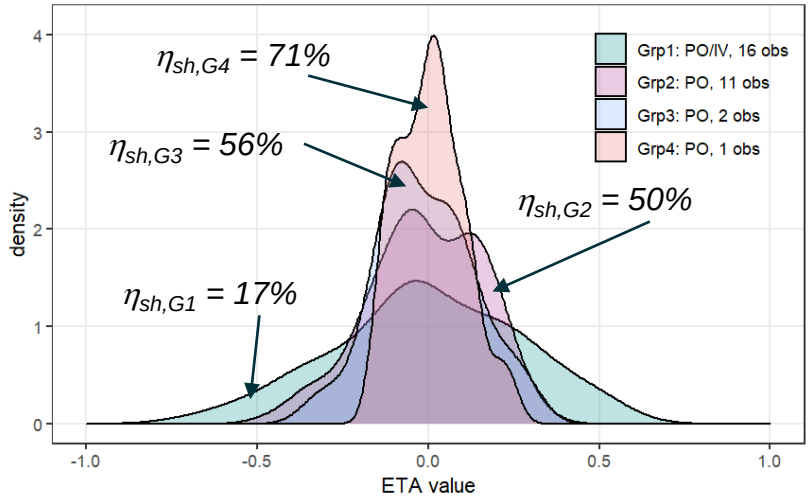
Common misconceptions regarding ETA shrinkage (1/2)

- The traditional definition of ETA shrinkage and typical way of reporting it, is in fact a mean shrinkage for all individuals* in the analysis dataset [7]

$$\eta_{sh} = \frac{\sum \eta_{sh,i}}{n}$$

- The shrinkage for a specific individual ($\eta_{sh,i}$) is dependent on the design (e.g. timing/number of obs., dosing), the applied model, but also the underlying “true” model parameters.
- Under normal circumstances the individual shrinkage is difficult to assess. However, differences in shrinkage between different subgroups e.g. different study design and/or characteristics can easily be assessed.





[7] Combes FP, Retout S, Frey N, Mentré F. Prediction of shrinkage of individual parameters using the bayesian information matrix in non-linear mixed effect models with evaluation in pharmacokinetics. Pharm Res. 2013

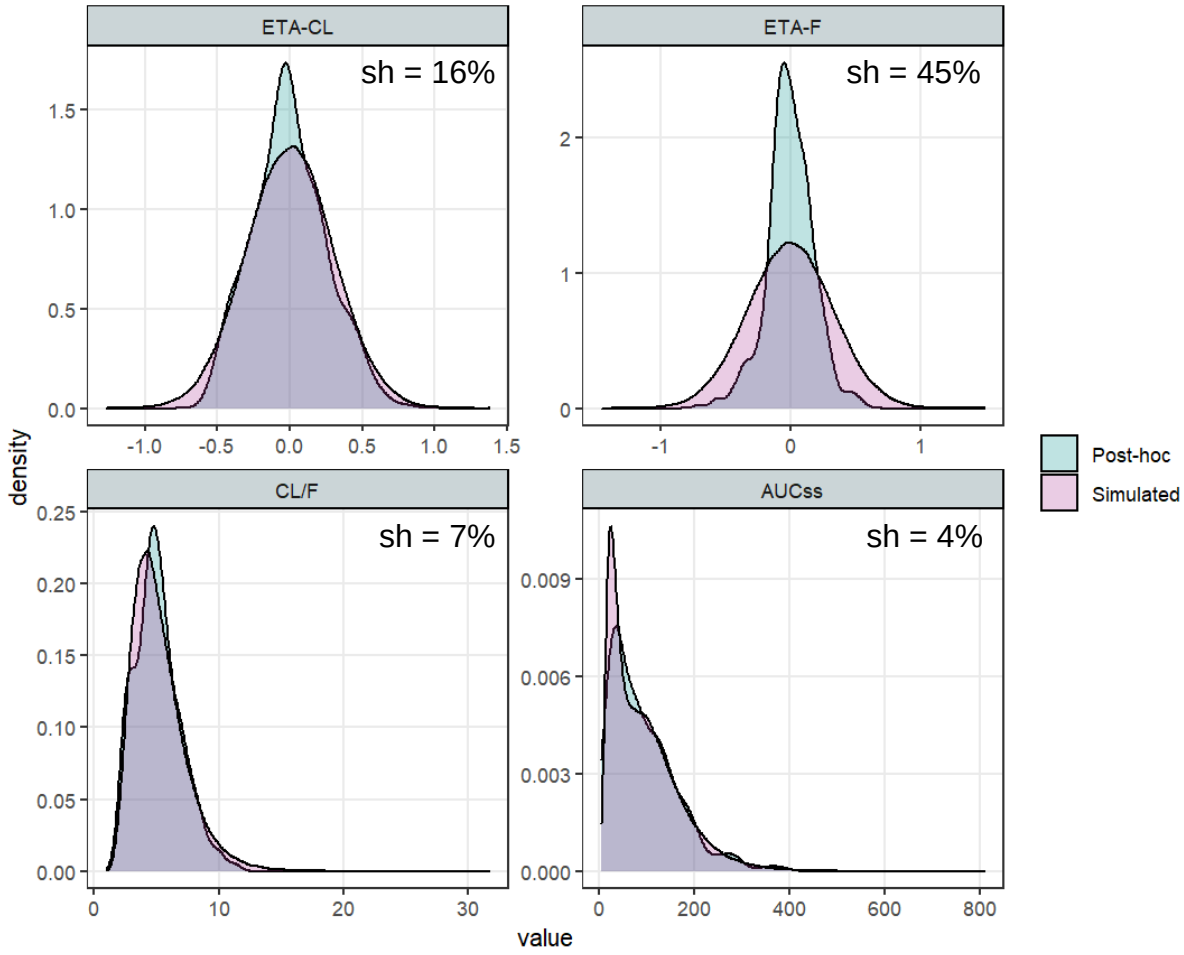
**Individuals are in this case used to exemplify the common case when ETAs are used to reflect inter-individual variability (IIV)*

Common misconceptions regarding ETA shrinkage (2/2)

"In general, shrinkage indicates that the model is over-parameterized for the data that is available. The first recommendation is to simplify the model ..."
[Quote on "what-is-shrinkage"]

- I disagree with this and similar statements. High shrinkage is not by itself a reason to simplify the model at the cost of a worse model fit.

- High ETA shrinkage has been suggested to introduce bias for sequential PKPD analyses [4,8]
  - While this can be true under some circumstances, this presentation aims to demonstrate that the ETA shrinkage per se isn't a good metric to evaluate this.



[4] Xu XS et al. Shrinkage in nonlinear mixed-effects population models: quantification, influencing factors, and impact. AAPS J. 2012
[8] Lacroix, B D et al. Evaluation of IPPSE, an alternative method for sequential population PKPD analysis. JPKPD. 2012.

Shrinkage for secondary parameters

- Shrinkage can be derived for secondary model parameters that depend at least partly on one or more ETAs

$$SP_{sh}(\%) = 100 \times \left(1 - \frac{SD\left(log\left(SP_{post-hoc}\right)\right)}{SD\left(log\left(SP_{simulated}\right)\right)}\right)$$

Where SP_{sh} is the % shrinkage for the secondary parameters, SP, calculated based on the standard deviation for the log of the post-hoc estimates ($SP_{post-hoc}$) and the corresponding simulated parameters ($SP_{simulated}$) with the estimated model parameters.

- Examples of secondary model parameters of interest that can be derived via analytical expressions and through integration:
  - PK: CL/F, V/F, $t_{½}$ etc.
  - Exposure: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, AUC_{ss}, C_{av}, C_{max}, $C_{max,ss}$, C_{min}, C(t), T>MIC,
  - PD: nadir, stead-state response

- The secondary parameters can be used for sub-group comparisons and/or sequential analysis e.g. exposure response.

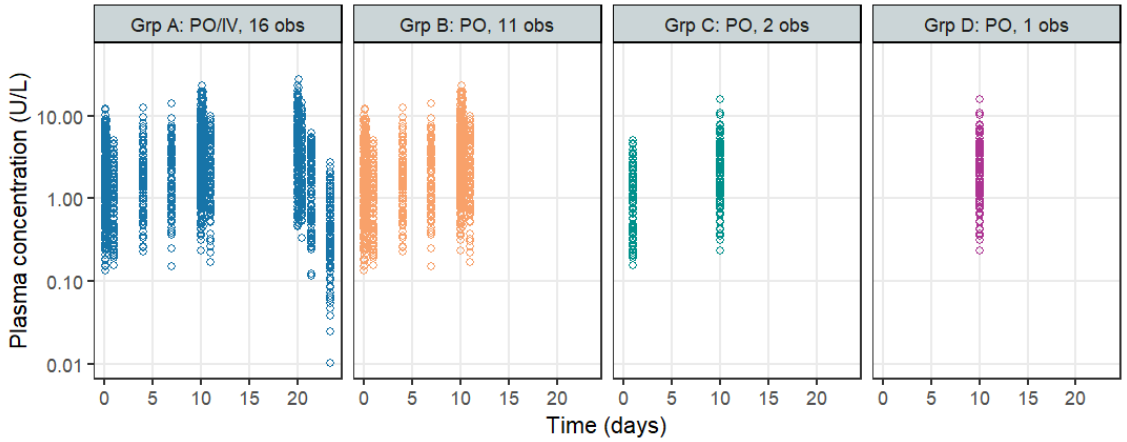
Simulated examples

- 1-compartment PK model with first order abs. with fix allometric scaling for disposition parameters

Parameter	Typical value	IIV (variance)
CL (L/h)	2.5	0.1
Vc (L)	100	0.2
K_a (h-1)	1.5	0.4
F	0.5	0.15*

* On the logit scale

- 4 different design sub-groups (100 subjects/group)



Note: Simulated PK data for SC1

- Uniform weight range from 40 to 100 kg
- 3 continuous drug response variables with linear exposure-response (slope = 1, intercept = 0):
  - $R1 \propto AUC_{ss}$
  - $R2 \propto C_{max,ss}$
  - $R3 \propto C_{max,dose1}$
- Three scenarios (SC)
  - **SC1:** Five different dose levels (100 mg, 200 mg, 400 mg, 600 mg and 800 mg) was studied, with equal allocations to each dose
  - **SC2:** 400 mg doses for all subjects
  - **SC3:** As SC2 but without the weight covariate in the PK model used for re-estimation

Shrinkage by subgroup and scenario

Scenario	Group	ETA-CL	ETA-Vc	ETA-ka	ETA-F	CL	Vc	CL/F	Vc/F	ka	F	AUC_{ss}	$C_{max,ss}$	$C_{max,dose1}$
SC1	Grp A	9.5	6.7	26.0	16.5	8.6	-1.8	3.6	-2.6	26.0	15.7	2.2	0.0	-4.4
	Grp B	14.5	8.4	29.9	49.6	10.7	-1.3	3.4	-3.6	29.9	48.9	3.1	0.2	-5.7
	Grp C	18.9	23.1	96.3	56.2	12.6	8.2	6.6	7.3	96.3	56.5	4.2	2.2	-0.8
	Grp D	21.5	56.1	97.0	70.5	14.9	33.3	12.6	39.3	97.0	71.1	6.3	6.2	10.4
SC2	Grp A	9.5	6.7	26.0	16.5	8.6	-1.8	3.6	-2.6	26.0	15.7	3.6	3.9	-2.1
	Grp B	14.5	8.4	29.9	49.6	10.7	-1.3	3.4	-3.6	29.9	48.9	3.4	2.1	-3.4
	Grp C	18.9	23.1	96.3	56.2	12.6	8.2	6.6	7.3	96.3	56.5	6.6	6.9	7.5
	Grp D	21.5	56.1	97.0	70.5	14.9	33.3	12.6	39.3	97.0	71.1	12.6	21.9	40.4
SC3	Grp A	6.0	1.0	26.0	21.0	6.0	1.0	2.6	-0.3	26.0	21.1	2.6	-1.0	-1.0
	Grp B	16.4	7.5	30.4	41.9	16.4	7.5	3.0	-0.5	30.4	41.2	3.0	-2.0	-1.3
	Grp C	17.5	22.1	96.7	47.4	17.5	22.1	5.6	16.3	96.7	47.3	5.6	8.2	15.6
	Grp D	22.6	61.8	97.6	68.3	22.6	61.8	17.7	71.4	97.6	69.3	17.7	39.5	75.3

<5%
5% - 25%
25% - 50%
>50%

- ETA-shrinkage increase with sparser sampling (Grp A → D)
- Parameters CL & V less shrunk than ETA-CL and ETA-Vc due to variability explained by weight covariate
- CL/F and Vc/F less shrunk than underlying parameters CL, Vc and F. Due to CL/F and Vc/F having a higher degree of identifiability.

- For SC1: AUC_{ss} is less shrunk than CL/F due to part of variability explained by difference in dose.
- For SC2 and SC3 (single dose level) the shrinkage in AUC_{ss} and CL/F is identical.
- Even in cases when ETA-shrinkage is very high the shrinkage in exposure metrics such as AUC_{ss}, $C_{max,ss}$ and $C_{max,dose1}$ can be relatively low.

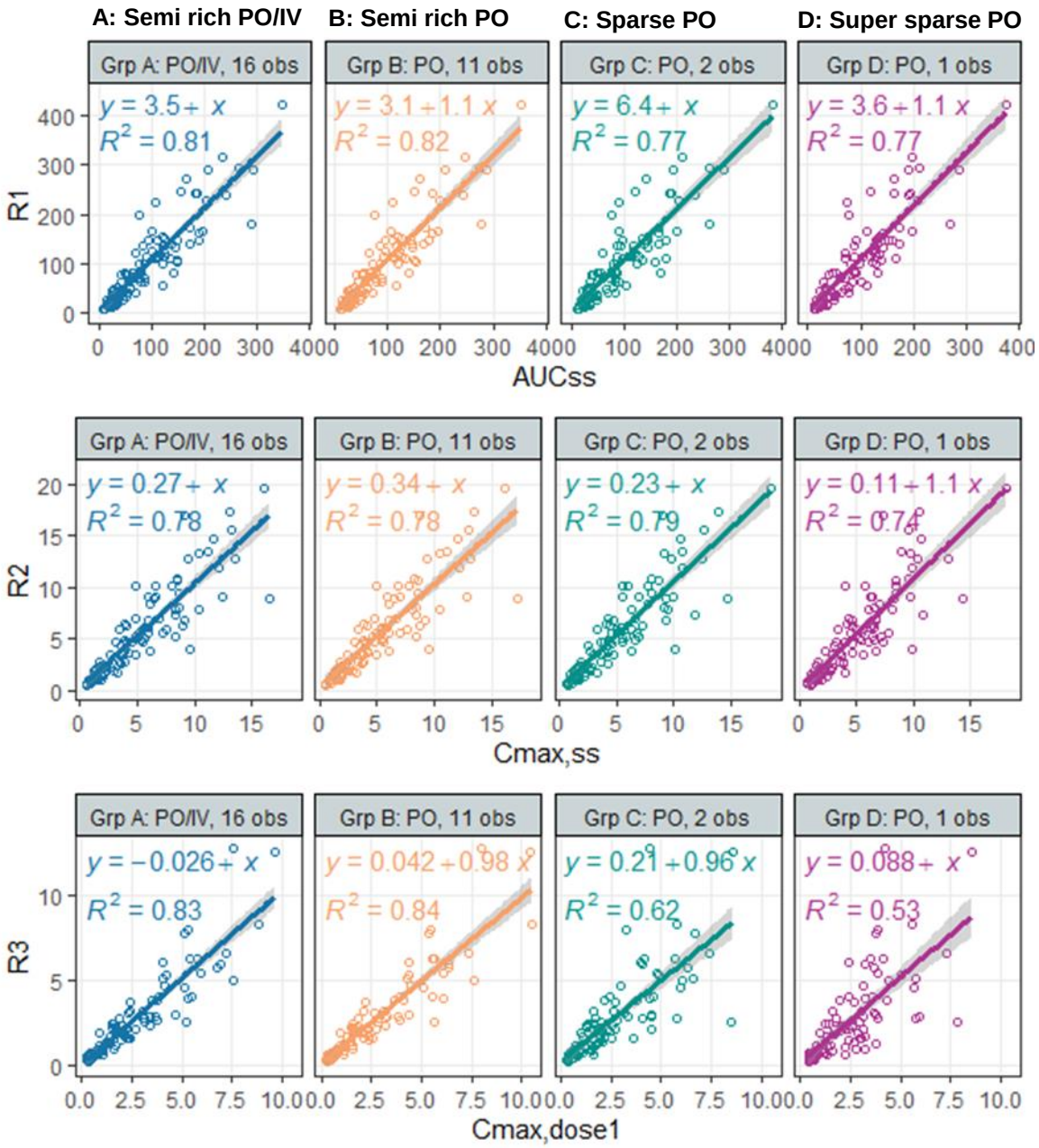
Exposure-response - SC1

(SC1 => Five dose levels + weight covariate)

Results

Scenario	Group	Shrinkage		
		AUC_{ss}	$C_{max,ss}$	$C_{max,dose1}$
CS1	Grp A	2.2	0.0	-4.4
	Grp B	3.1	0.2	-5.7
	Grp C	4.2	2.2	-0.8
	Grp D	6.3	6.2	10.4

- No meaningful bias in E-R parameters for any of the sub-groups (confidence interval included the true value)
- For the sub-groups with sparse sampling the higher shrinkage correlated with lower R^2 and higher uncertainty for the estimated E-R parameters



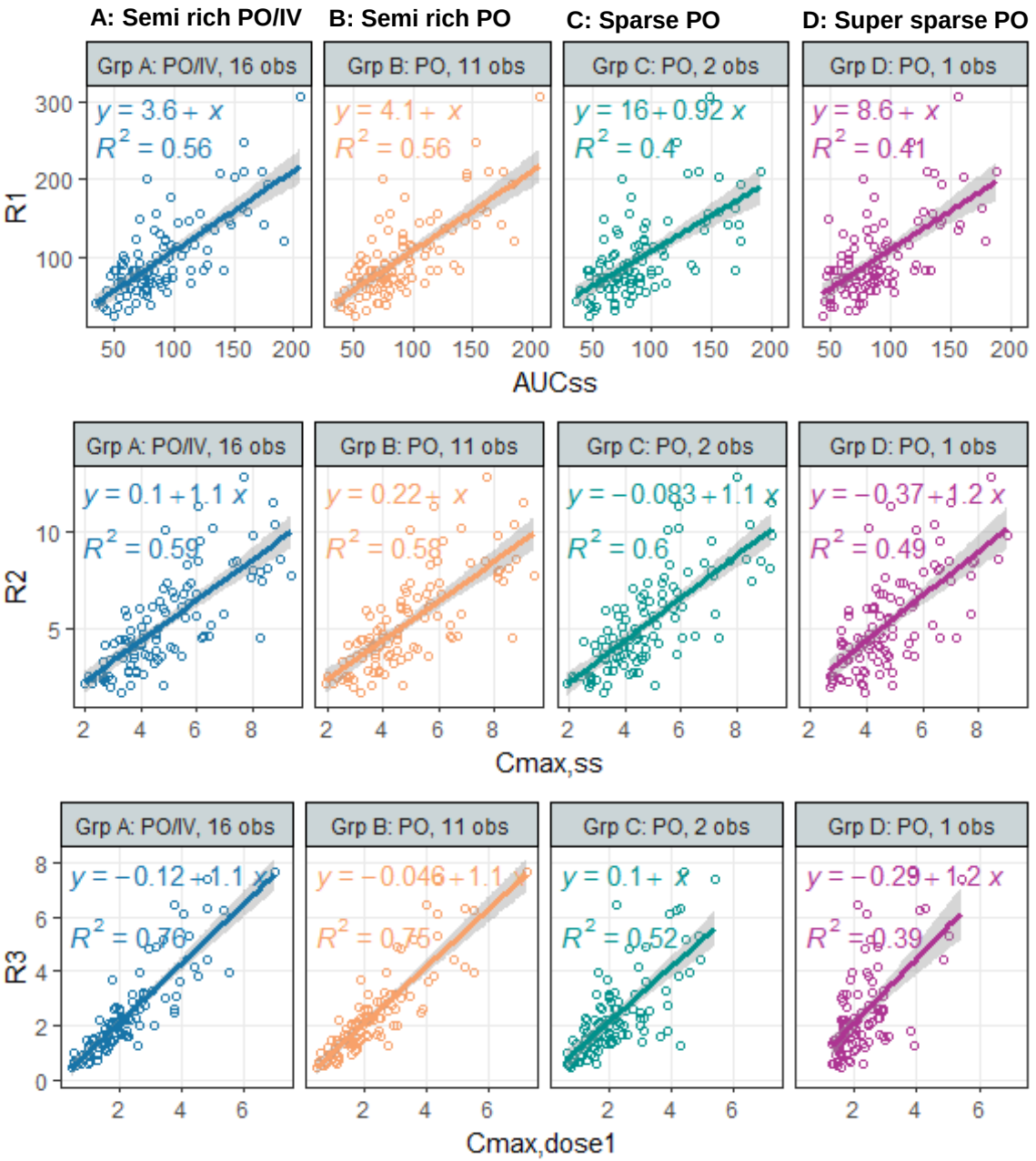
Exposure-response - SC2

(SC2 => One dose level + weight covariate)

Results

Scenario	Group	Shrinkage		
		AUC_{ss}	$C_{max,ss}$	$C_{max,dose1}$
CS2	Grp A	3.6	3.9	-2.1
	Grp B	3.4	2.1	-3.4
	Grp C	6.6	6.9	7.5
	Grp D	12.6	21.9	40.4

- No meaningful bias in E-R parameters for any of the sub-groups (confidence interval included the true value)
- For the sub-groups with sparse sampling the higher shrinkage correlated with lower R^2 and higher uncertainty for the estimated E-R parameters



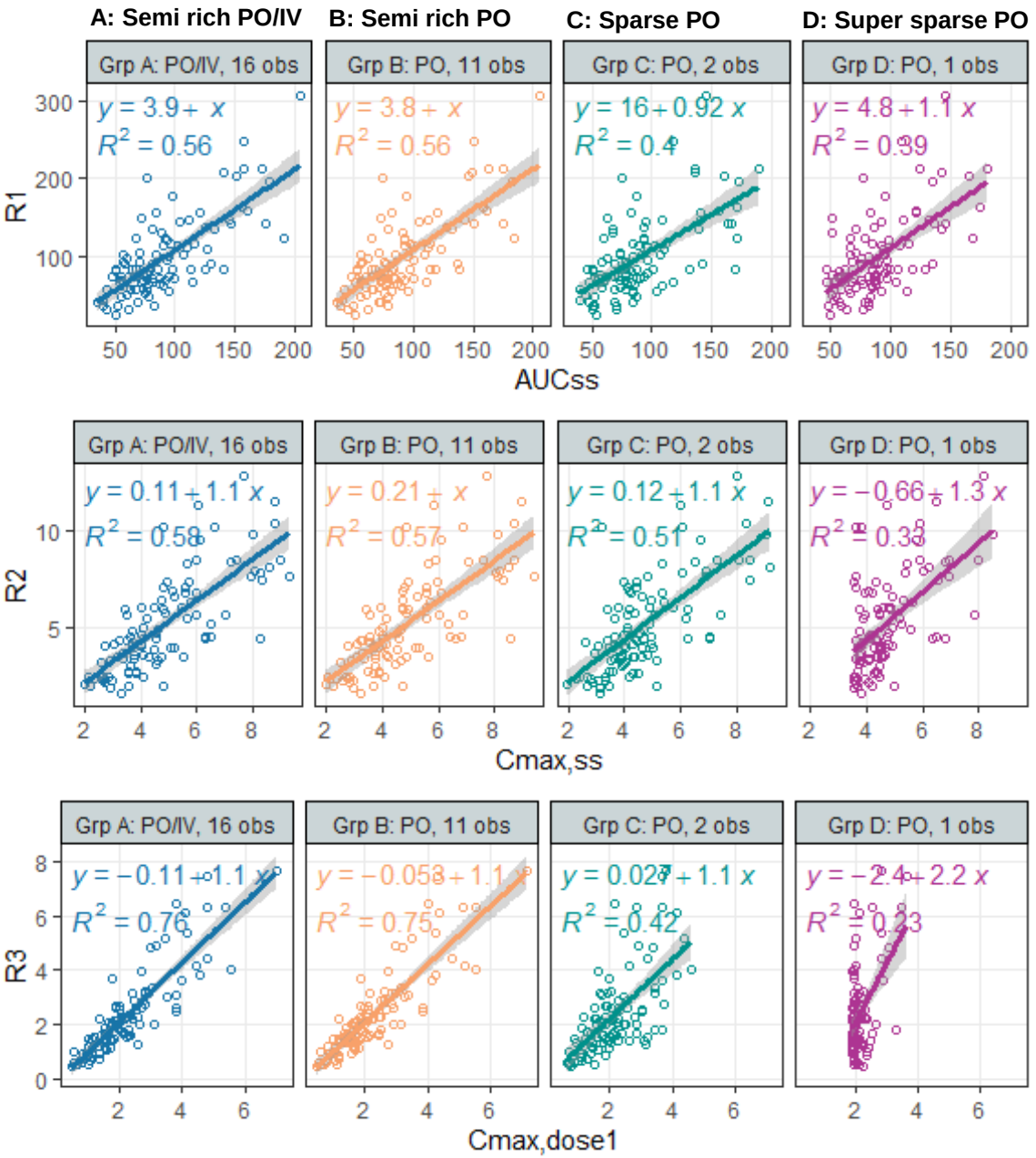
Exposure-response - SC3

(SC3 => One dose level + no weight covariate)

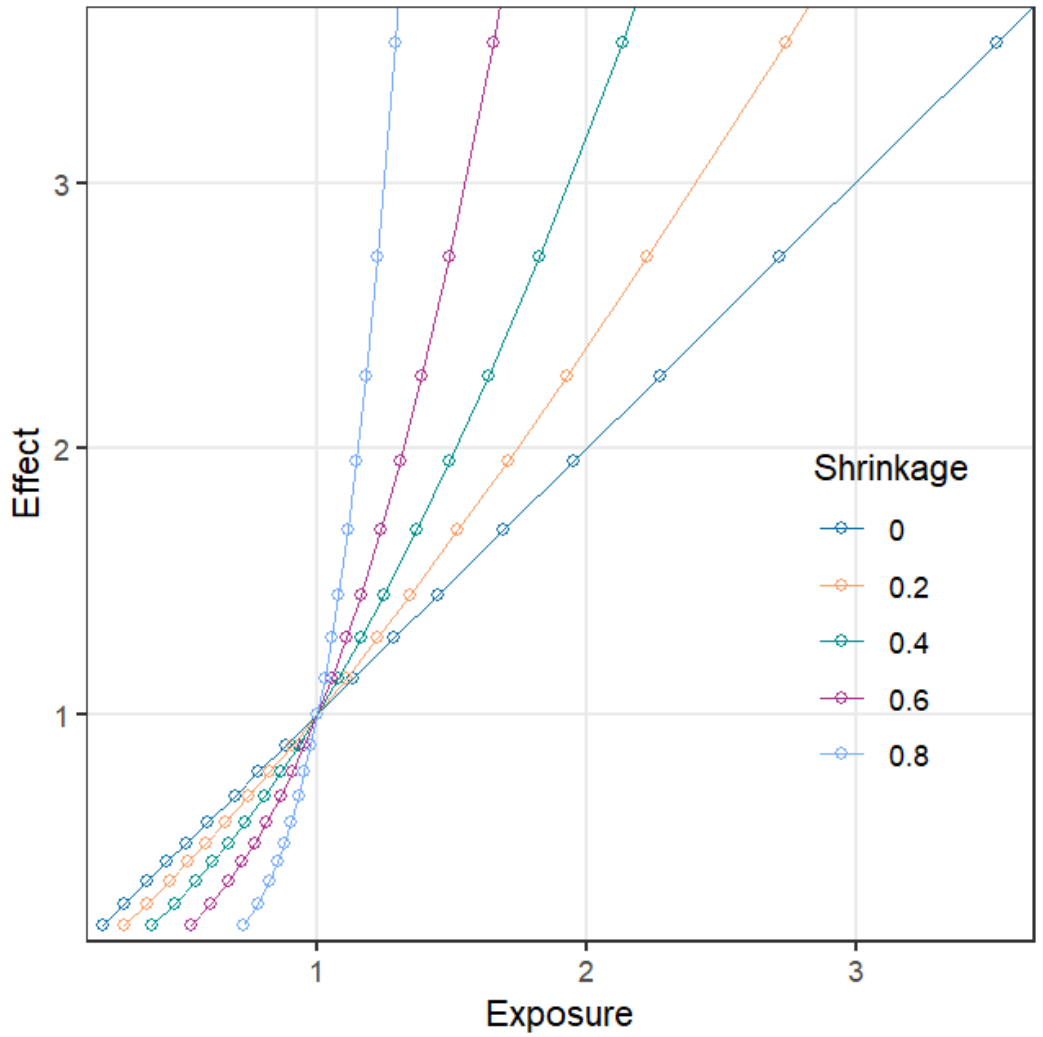
Results

Scenario	Group	Shrinkage		
		AUC_{ss}	$C_{max,ss}$	$C_{max,dose1}$
CS3	Grp A	2.6	-1.0	-1.0
	Grp B	3.0	-2.0	-1.3
	Grp C	5.6	8.2	15.6
	Grp D	17.7	39.5	75.3

- No meaningful bias in E-R parameters for sub-groups A,B and C or for subgroup D with AUC_{ss} or $C_{max,ss}$ as the exposure metric (R1 & R2)
- The Grp D design resulted in biased E-R estimates with $C_{max,dose1}$ as the exposure metric
  - Intercept: -2.4 (95%CI: -4.1, -0.6)
  - Slope: 2.2 (95%CI: 1.4, 3.0)



Principal effect of shrinkage in exposure metrics on E-R assessment



- Hypothetical example A:
  - True linear E-R relationship
  - Perfectly symmetrical shrinkage affecting all exposure estimates the same (0%, 20%, 40%, 60% or 80% shrinkage)

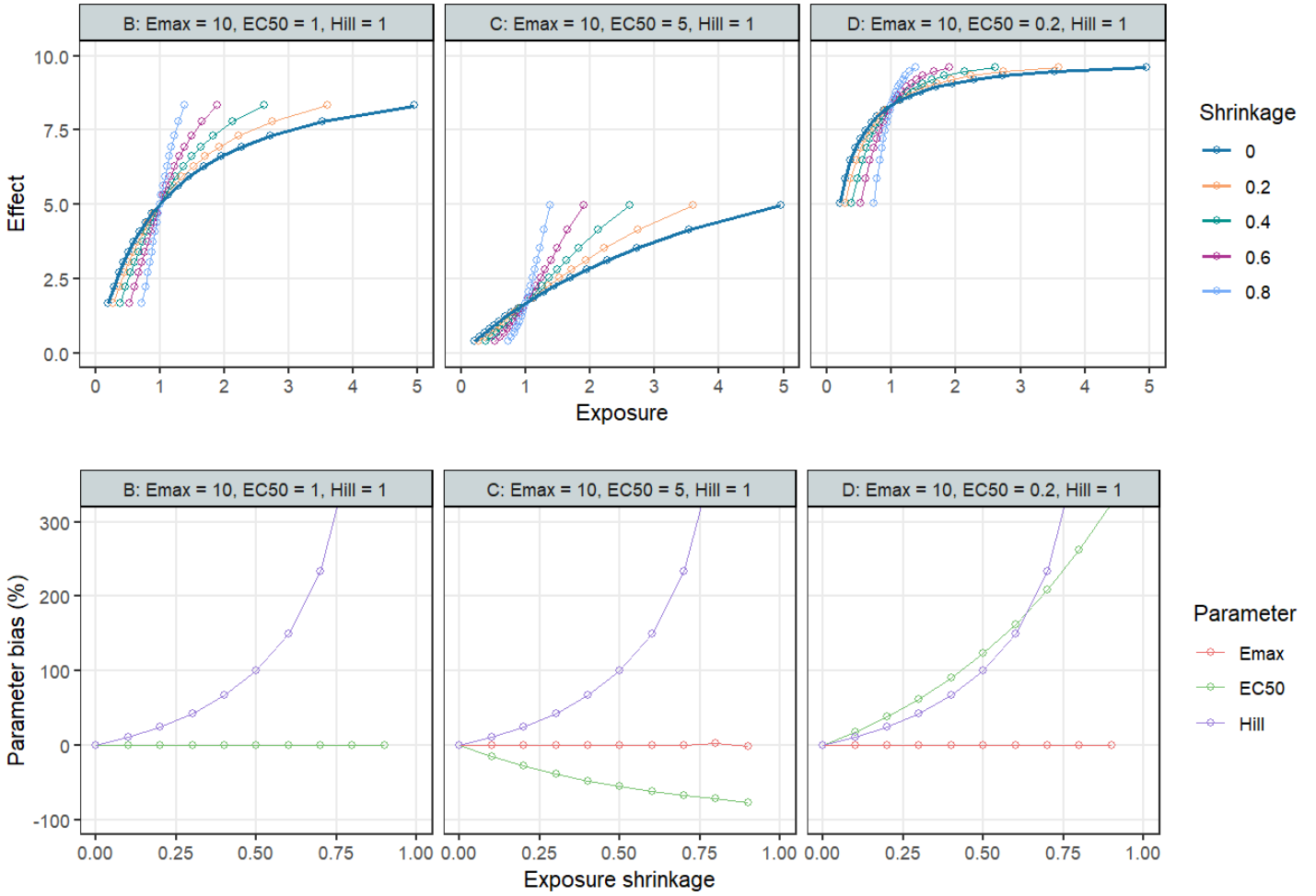
⇨ Increasing shrinkage results in bias towards a steeper E-R slope

⇨ Increasing shrinkage results in a distorted shape of the E-R relationship towards a power function

$$Effect \propto Exposure^{\theta_{power}}$$

Shrinkage = 0 => θ_{power} = 1
Shrinkage = 0.2 => θ_{power} = 1.25
Shrinkage = 0.4 => θ_{power} = 1.67
Shrinkage = 0.6 => θ_{power} = 2.50
Shrinkage = 0.8 => θ_{power} = 5.00

Principal effect of shrinkage in exposure metrics on E-R assessment



- Hypothetical example B/C/D
  - True underlying Emax relationships (true param. in panel header)
  - Shrinkage as for A

⇨ Increasing shrinkage results in bias towards steeper E-R relationships i.e. Hill coefficient ↑

⇨ True EC_{50} > Observed Exposures results in negative bias for EC_{50} estimate

⇨ True EC_{50} < Observed Exposures results in positive bias for EC_{50} estimate

Conclusions

- ETA-shrinkage is not a good metric to judge the validity of a sequential PKPD analysis approach. Shrinkage for the exposure parameter of interest is a better metric to consider.
- Even with very sparse PK sampling the shrinkage in exposure parameters can often be sufficiently low to allow for an unbiased sequential PKPD analysis approach
- When shrinkage for the exposure parameter of interest is high (~ >25%)* E-R parameters estimated with a sequential PKPD analysis approach can be substantially biased
- Simulation/re-estimation approaches can be used to evaluate if a specific study design will allow for an unbiased sequential PKPD analysis
  - ⇨ Design informative studies
  - ⇨ Device efficient and accurate analysis approaches

**Note: should not be interpreted as shrinkage >25% always result in biased E-R parameters (see examples) but that this may warrant more investigation e.g. simulation/re-estimation to evaluate*

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