Pharmetheus

Efficient and relevant stepwise covariate model building for pharmacometrics

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Objectives

To evaluate SCM+[1] with and without stage-wise filtering and compare them to the legacy SCM approach in terms of efficiency and ability to identify relevant covariates.

Background

The stepwise covariate model (SCM)[2] building procedure is the most common method for covariate model development[3].

Despite its advantages, the traditional SCM method is known to have long runtimes and sub-optimal ability to select relevant covariates.

Methods

SCM+[1]

Builds on the legacy SCM algorithm[2] but introduces adaptive scope reduction (ASR, Figure 1) and optimized estimation settings (CTYPE=4 instead of default settings and the MAXEVAL is set dynamically to 3.1 times the number of function evaluations used by the base model).

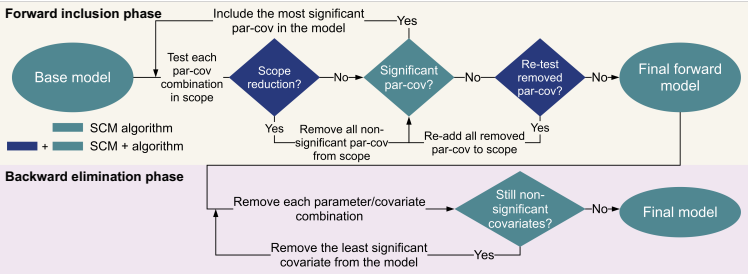

Figure 1. *Overview of the SCM algorithm, with and without adaptive scope reduction (ASR).*

Stage-wise filtering

The covariates are classified into three groups: Mechanistic, Structural and Exploratory.

Mechanistic: Have a known impact on one or more parameters of the model.

Structural: Have a strong rationale to impact one or more model parameters.

Exploratory: Are neither mechanistic nor structural and are explored for hypothesis-generating reasons.

Stage-wise filtering proceeds in 3 phases:

1. Addition of mechanistic covariates to the base model without testing.
2. Stepwise inclusion (SCM+) of structural covariates
3. Stepwise inclusion (SCM+) of exploratory covariates.

The 3 covariate categories are hierarchical, meaning that a structural covariate cannot replace a mechanistic covariate, and an exploratory covariate cannot replace a structural or mechanistic covariate.

Data

Data for 13 covariates was simulated using the conditional distribution method[4] for three studies, two Phase 1 and one Phase 3 study, in a hypothesized Phase 3 setting, in total 560 subjects. Pharmacokinetic data was simulated using a one compartment model in which WT, diet, CYP2D6, NCI (liver function category), formulation and CRCL were included as covariates at various strengths. A total of 100 data sets were simulated and analyzed. (See supplementary information.)

Conclusions

- The two SCM+ methods were considerably more efficient than the traditional SCM both in terms of run-time and computational burden.
- SCM+ with stage-wise filtering selected the highest number of relevant covariates.

Results

SCM+ and SCM+ with stage-wise filtering were considerably more efficient than the legacy SCM (Figure 2):

- The number of function evaluations was reduced by 70% and 76%, respectively.
- The number of executed models was reduced by 44% and 70%, respectively.

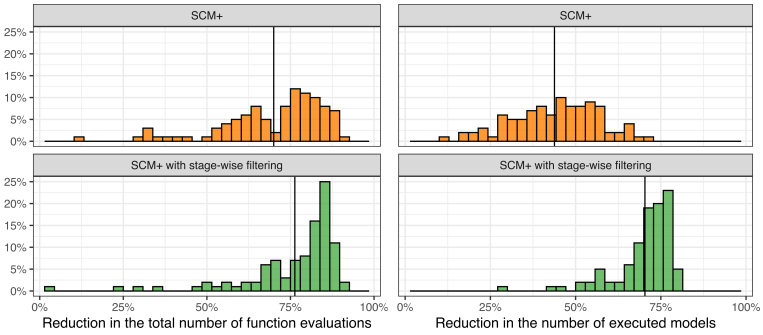

Figure 2. *Reduction in number of function evaluations and number of executed models for SCM+ or SCM+ with stage-wise filtering versus SCM. Solid line is the median within each panel.*

SCM+ with stage-wise filtering selected the highest number of true covariate coefficients (8.0 on average) compared to the SCM (5.1) and SCM+ (5.1) approaches (Table 1).

The SCM and SCM+ were in all aspects comparable in their ability to identify covariates.

All approaches had low selection frequencies of related and unrelated covariate-parameter relationships (Table 1).

Table 1. *Number of included covariate coefficients and covariate-parameter relations.*

	(n=100)	Mean number of covariate coefficients [Min,Max]	Mean number of covariate-parameter relations [Min,Max]
Total	SCM	5.51 [3,9]	5.45 [3,9]
	SCM+	5.61 [3,9]	5.54 [3,9]
	SCM+ with stage-wise filtering	8.63 [8,11]	6.63 [6,9]
True*	SCM	5.06 [2,8]	5 [2,8]
	SCM+	5.11 [2,8]	5.04 [2,8]
	SCM+ with stage-wise filtering	8.03 [7,10]	6.03 [5,8]
Related**	SCM	0.32 [0,1]	0.32 [0,1]
	SCM+	0.28 [0,2]	0.28 [0,2]
	SCM+ with stage-wise filtering	0.41 [0,1]	0.41 [0,1]
Unrelated**	SCM	0.13 [0,1]	0.13 [0,1]
	SCM+	0.22 [0,3]	0.22 [0,3]
	SCM+ with stage-wise filtering	0.19 [0,2]	0.19 [0,2]

*The total number of true covariate coefficients is 14 and of true covariate-parameter relations is 10.

**To acknowledge the fact that "false" covariates due to their correlations to "true" covariates can still be predictive, the covariates were classified as being either True, Related ([corr| > 0.5) or Unrelated ([corr| < 0.5).

References

1. Jonsson, E. N., Harling, K, PAGE 27 (2018) Abstr 8429 [www.page-meeting.org/?abstract=8429]
2. Jonsson and & Karlsson PharmRes 1998;15:1463–1468
3. Hutmacher and Kowalski Br. J. Clin. Pharmacol. 2015;79:132–147
4. Smania and Jonsson, CPT PSP 2021; 10:330–339

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Supplementary material

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Simulation setup

The intention with the simulation setup was to create a non-trivial data set that more closely resembles a real-world situation than most simulated data sets used in methodological research do. N=100 simulated data sets were created.

Data for 13 covariates was simulated using the conditional distribution method[4] (Table 2), for three studies (a Phase 1 cross-over food effect study n=30, a Phase 1 study with 30 healthy volunteers that were either poor or normal CYP2D6 metabolizers and a Phase 3 repeated dosing study with 500 subjects randomized to low, middle or high dose of the drug.

Plasma PK samples were simulated in NONMEM from a one-compartment model with linear elimination and sequential zero and first-order absorption. Elimination was simulated by including both hepatic and renal components. The renal contribution to elimination was regulated by the parameter fe, set to 0.4 for the typical subjects.

WT was included on hepatic clearance (CL) and volume of distribution (V) with allometric constants of, respectively, 0.75 and 1.

Diet was a strong covariate on absorption, affecting the first-order absorption rate constant (KA), zero-order absorption duration, and relative bioavailability (Frel).

CYP2D6 and NCI were intermediate covariates on hepatic CL and Frel. The effect size of CYP2D6 genotype was set so that CYP2D6 was responsible for 50% of the hepatic CL (assuming hepatic extraction ratio of 0.35).

Formulation was a weak-intermediate covariate on Frel.

CRCL was a weak covariate on renal CL.

Analysis of the simulated data

The estimation model had a different and simpler structure than the simulation model since not all components of the simulation model were identifiable based on the simulated data.

The base estimation model was a one-compartment model with linear elimination. Only total CL was modeled. The sequential zero and first-order absorption was parameterized in terms of mean absorption time (MAT). MAT was estimated as two fractions: one for the zero-order absorption (Eq 1) and one for the first-order absorption (Eq 2).

$$Dur_{0-orderabs} = MAT \cdot f_{0-orderabs} \qquad (1)$$

$$k_a = \frac{1}{(MAT \cdot (1 - f_{0-orderabs}))} \qquad (2)$$

Covariate categories with 10 or fewer subjects were merged with the most common category or nearest category.

Categorical covariates were binarized so that each level became a yes/no covariate ("one-hot encoding").

In the SCM and SCM+ analysis, covariate pairs that had an absolute correlation >0.6 were reduced so that only one of the covariates was used in the analysis.

With stage-wise filtering, the correlation filter was only used for the exploratory covariates.

Analysis of the simulated data (continuation)

The covariates tested with the SCM, SCM+, and SCM+ with stage-wise filtering are listed in Table 2 according to their classification; the specific settings used for the comparison of the 3 approaches are listed in Table 3.

***Table** 2. Covariates tested in the traditional SCM, SCM+, and SCM+ with stage-wise filtering.*

Category	Parameter	SCM and SCM+	Stage-wise filtering
Mechanistic	CL	None	WT*, genotype
	V		WT*
Structural	CL	None	CRCL
	MAT		Diet, formulation, genotype
	F_{rel}		Diet, formulation, genotype
Exploratory	CL	CRCL, Age, AST, ALT, BILI, sex, race, ethnicity, NCI, CYP2D6 genotype, WT	Age, AST, ALT, BILI, sex, race, ethnicity, NCI
	V	Age, AST, ALT, BILI, sex, race, ethnicity, NCI, WT	Age, AST, ALT, BILI, sex, race, ethnicity, NCI
	MAT	Age, AST, ALT, BILI, diet, sex, race, ethnicity, NCI, genotype, formulation	Age, AST, ALT, BILI, sex, race, ethnicity, NCI
	F_{rel}	Age, AST, ALT, BILI, diet, sex, race, ethnicity, NCI, genotype, formulation	Age, AST, ALT, BILI, sex, race, ethnicity, NCI

*Fixed to the standard allometric exponents. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin; CL, clearance; CRCL, creatinine clearance; Frel relative bioavailability; MAT, mean absorption time; NCI, National Cancer Institute – in reference to liver function classification; V, volume of distribution; WT, body weight.

***Table** 3. Settings and handling of covariates adopted, in each simulated dataset, for the 3 SCM approaches compared.*

	SCM (n=100)*	SCM+ (n=100)*	SCM+ with stage-wise filtering (n=100)*
Covariate-parameter relationships in base model	none	none	Weight on CL and V, with fixed allometric exponents (respectively 0.75 and 1); CYP2D6 genotype on CL
Stage-wise filtering	No	No	Yes
Inclusion of covariates with absolute correlation coefficient >0.6	Only one of the covariates is included	Only one of the covariates is included	If mechanistic or structural covariates: both covariates are tested; if exploratory covariates: one of the covariates is omitted
P-value forward selection	0.01	0.01	0.01
P-value backward elimination	0.001	0.001	0.001
Adaptive scope reduction applied to all forward steps (threshold p-value)	No	Yes (0.01)	Yes (0.01)
Retesting of all stashed relationships	No	Yes	Yes
General estimation settings applied	Those of the base model	CTYPE=4 criterion[a]; maximum number of function evaluations (MAXEVAL in NONMEM) set to 3.1 times the function evaluations used by the base model.	CTYPE=4 criterion[a]; maximum number of function evaluations (MAXEVAL in NONMEM) set to 3.1 times the function evaluations used by the base model

References

1. Jonsson, E. N., Harling, K, PAGE 27 (2018) Abstr 8429 [www.page-meeting.org/?abstract=8429]
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