Increasing the efficiency of the covariate search algorithm in the SCM

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Objectives

To compare the efficiency of the legacy SCM covariate search algorithm [1] to the new SCM+ algorithm available in the publically available PsNplus package (www.pharmetheus.com/psnplus).

Background

- The scm is a commonly used tool for covariate modelling.
- The scm often has long runtimes and extensive output.
- PsN+ is an independent addon to PsN which aims to supplement the core functionality of PsN to streamline day-to-day analysis tasks.
- SCM+ is a part of PsN+ and implements a number of run-time reducing tweaks to the legacy SCM algorithm.
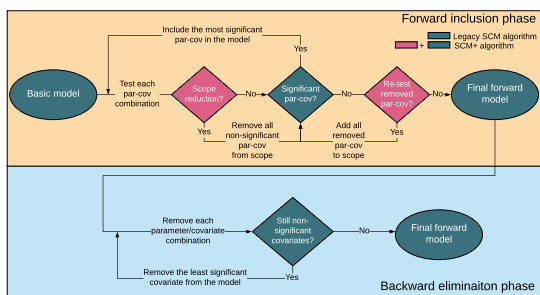

Figure 1. The SCM (green) and adaptive scope part of the SCM+ (pink) algorithms

Methods

Two real data examples were used for the comparison
- Both are phase 3 pharmacokinetic data sets (n=1628 and n=370)
- The first model was implemented using differential equations [3] and the second model included inter-occasion variability from 9 occasions.
- The search scope for the two data sets included 24 and 57 parameter-covariate relationships, respectively.
- Performance was measured as the total run-times when executed on the same system.
- The computational resources were assigned so that all par-cov in the first forward step could be executed in parallell.

Results

- The final SCM and SCM+ results were identical in the two examples, although the path to the final model was different in example two (Table 1).
- The run times for SCM were 4.5 h and 13.5 h for example 1 and 2, respectively, while the corresponding run times for SCM+ were 2.5 h and 6.5 h.

Figure 2. Summary of the scm+ analysis for example 2. The table was generated using the PsNplus command 'scmreport –ofv_table'.

Step	Covariate	Parameter	SCM state	Base OFV	New OFV	ΔOFV	p-value
Forward 1	STUD	F1	2	–421.42	–483.67	62.26	0.01
Forward 2	FOOD	ALAG1	2	–483.67	–515.36	31.68	0.01
Forward 3	FOOD	KA	2	–515.36	–535.16	19.8	0.01
Forward 4	SEX	V3	2	–535.16	–547.96	12.8	0.01
Forward 5	DIAB	CL	2	–547.96	–558.11	10.15	0.01
Forward 6				Removed covariates are re-tested			
Forward 7	SEX	V2	2	–558.11	–569.3	11.2	0.01
Forward 8	BALAT	KA	5	–569.3	–576.25	6.95	0.01
Forward 9							
Backward 1	BALAT	KA	1	–576.25	–569.3	–6.95	0.001
Backward 2	DIAB	CL	1	–569.3	–559.4	–9.9	0.001
Backward 3							
Final included	FOOD	ALAG1	2				
Final included	STUD	F1	2	The final parameter-covariates relations are identical to the ones identified by the legacy SCM algorithm.			
Final included	FOOD	KA	2				
Final included	SEX	V2	2				
Final included	SEX	V3	2				

Conclusions

The SCM+ algorithm may reduce the run-times for covariate searches by more than 50% compared to the legacy SCM This is accomplished by reducing the number of times that non-significant par-cov combinations are tested and by basing the covariate selection decisions on different, but for the task at hand more relevant, convergence criteria, compared to the default criteria in NONMEM.

Methods

The basic SCM algorithm proceeds in a Forward inclusion phase and a Backward elimination phase (Figure 1). The the forward phase each parameter-covariate (par-cov) combination in the scope are tested one at a time. The par-cov that yields the largest drop in OFV, provided it is significant, is retained in the model. The remaining par-cov are then tested again in the updated model and the one with the largest drop in OFV (assuming significance) is retained. This stepwise inclusion proceeds until no more significant par-cov can be identified. The Backward elimination removes par-cov from the Forward model in a stepwise fashion at a stricter significance level. Once all remaining par-cov are significant, the final model has been established.

The SCM+ algorithm

The SCM+ algorithm increase the efficiency of the legacy SCM algorithm through:

Adaptive scope reduction: Parameter-covariate relations that have not shown promise in early steps are not tested in later steps. However, before proceeding to the backward elimination phase, the removed parameter-covariate relations are re-tested. (Figure 1).

Limit the number of function evaluations: To avoid excessive iterations without improvement in OFV, the max no of function evaluations are limited (default to 1.2 times the function evaluations used in the base model).

Alternative termination criteria: Since the SCM is only concerned with changes in OFV, the CTYPE=4 criteria is used instead of the default.

Enforcing appropriate numerical settings for differential equations: With $DES, SIGL, TOL and NSIG are set to 6, 6, and 2, respectively, to keep the numerical precision the same as with ADVAN1-4.

Table 2. Summary of the scm+ analysis for example 1. The table was generated using the PsNplus command 'scmreport'.

Model	Number of times tested	N OK terminations	N local minima	N failed runs	Step Selected	Step Stashed	Step Readded	Backstep Removed
CLAGE-5	6	6	0	0		3	7	
CLCRCL-5	2	2	0	0	2			
CLDOSE-2	3	3	0	0	3			
CLRACE-2	4	4	0	0	4			3
CLSEX-2	2	2	0	0	7	1	7	
CLSTUT-2	4	4	0	0		1	7	
KMAGE-5	4	4	0	0		1	7	
KMRACE-2	4	4	0	0		1	7	
KMSEX-2	4	4	0	0		1	7	
KMSTUT-2	4	4	0	0		1	7	
V1AGE-5	4	4	0	0		1	7	
V1DOSE-2	4	4	0	0		1	7	
V1RACE-2	8	8	0	0		5	7	
V1SEX-2	1	1	0	0	1			
V1STUT-2	4	4	0	0		1	7	
V2AGE-5	4	4	0	0		1	7	
V2DOSE-2	7	7	0	0		4	7	
V2RACE-2	4	4	0	0		1	7	
V2SEX-2	5	5	0	0		2	7	
V2STUT-2	5	5	0	0	5			2
VMAGE-5	4	4	0	0		1	7	
VMRACE-2	4	4	0	0		1	7	
VMSEX-2	4	4	0	0		1	7	
VMSTUT-2	3	3	0	0	8	1	7	1

References

[1] Jonsson EN and Karlsson MO, PharmRes (15), 1998., [2] Lindbom L, Ribbing J and Jonsson EN., Comp Meth Prog Biomed 75 (2), 2004., [3] Jonsson EN et al, Br J Clin Pharm 81 (4) 2015.

Acknowledgments

The hand out will contain a description of the control options for scm+ and possibly some additional information about companion PsNplus commands scmreport and monitor.