1 Overview

The scmplus program is a wrapper around the scm script that reduces the number of times that insignificant parameter-covariate relations are retested. The insignificant runs are often the most unstable and difficult to estimate, and they take a considerable amount of computing time. The method used is called Adaptive Scope Reduction.

1.1 Overview of basic scm algorithm

The basic scm algorithm proceeds in a Forward inclusion phase and a Backward elimination phase. In 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.

1.2 Summary of improvements in scmplus

The scmplus algorithm increases the efficiency of the legacy scm algorithm through the following changes:

1.2.1 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 parameter-covariate relations are re-tested.

Specifically, after each step set with scmplus option -scope_reduction_steps, scmplus will stash all relations that are insignificant according to option -p_cutoff. Option -keep_local_min can be used to further control which relations are stashed. When the reduced scope forward search is finished, either because all relations have been included or because no more relations are significant, scmplus will retest the stashed relations provided that option -retest_stashed_relations is set. If any of the retested relations is found to be significant, the forward inclusion phase will proceed as with the regular scm.

1.2.2 Limit the number of function evaluations

To avoid excessive iterations without improvement in OFV, the max no of function evaluations are limited (default to 3.1 times the function evaluations used in the base model). This feature is invoked with option -maxevals.

1.2.3 Only run NONMEM estimation step

By default, scmplus will drop $COVARIANCE and $TABLE from the model. Options -keep_covariance and -keep_tables can be used to turn off this feature.

1.2.4 Alternative termination criteria

Since the scm is only concerned with changes in OFV, the CTYPE=4 criteria is used instead of the default. This feature is invoked with option -ctype4.

1.2.5 Appropriate numerical settings

With ADVAN 6, 8, 9 and 13, scmplus requires SIGL to be set. This feature can be turned off with option -ignore_no_sigl.

2 Input and options

The scmplus program depends on the scm tool of PsN, and all scm options apply also to scmplus, with the exception of -linearize. Please refer to scm_userguide.pdf for help on scm options.

Example:

```
scmplus run101.scm -scope_reduction_steps=1,2,3 -p_cutoff=0.05
```

2.1 Required input

An scm configuration file is required on the command-line. The format of the configuration file follows the format of the scm configuration file exactly. The input model must be set in the configuration file, it cannot be given on the scmplus commandline.

No other option is required.

2.2 Optional input

These options are specific to scmplus, and they can only be given on the command-line, not in the scm configuration file.

-scope_reduction_steps = *comma-separated list of integers*
: Comma-separated list of steps after which to perform scope reduction. Default 1 (after first step only). To perform scope reduction after every forward step set -scope_reduction_steps=all To never perform scope reduction set -scope_reduction_steps=none

-retest_stashed_relations
: Default set. Unset with -no-retest_stashed_relations. If set then parameter-covariate relations that were stashed in scope reduction will be retested at the end of the forward search.

-p_cutoff = *number*
: Cutoff p-value in scope reduction. Default is equal to p_forward, which in turn has default value 0.05 if not set in the scm config file.

-keep_local_min
: Default set. Unset with -no-keep_local_min. If set then candidate models that terminated with local minimum are kept in scope reduction.

-keep_covariance
: By default the $COVARIANCE record will be deleted from the models, to save run time. If option -keep_covariance is set, the $COVARIANCE record will be kept.

-keep_tables
: By default all $TABLE will be deleted from the models. If option -keep_tables is set, all $TABLE will be kept.

−maxevals = *number*
Default 3.1 in scmplus. If set to a decimal number, and the estimation method is classical, $EST MAXEVALS will be set to that number times the actual number of function evaluations in the base model, rounded down to the nearest integer and capped at 9999. If set to an integer smaller than 10000 will be interpreted as the new value of $EST MAXEVALS. A warning will be printed if the new integer value is less than or equal to 10. If set to an integer equal to or larger than 9999 then this option will be ignored by scmplus and passed on to common_options maxevals (see documentation for common options).

−ctype4
Default set, unset with -no-ctype4. If -ctype4 is set, and a classical estimation method is used, scmplus will ensure CTYPE=4 is set in $EST

−ignore_no_sigl
Default not set. If not set, scmplus will stop with an error message if SIGL is not set in $EST and ADVAN 6,8,9 or 13 is used. If set, and SIGL is not set, a warning will be printed but scmplus will run.

−fast
Default not set. If -fast is set, the scmplus defaults for options -ctype4, -retest_stashed_relations, -scope_reduction_steps and -maxevals will change to -ctype4 set, -retest_stashed_relations unset, -scope_reduction_steps=all and -maxevals=3.1
If any of those options are set individually, the individual setting will override the -fast defaults.

−etas
Default not set. If -etas is set, and a classical estimation method is used, scmplus will ensure record $ETAS is used in the model, that FILE is set to the phi-file of the base model of the current iteration, and that MCETA in $EST is set to at least 1.

−base_ofv = *number*
Only applicable when included_relations is set in the scm config file. Use this value as the ofv of the base model with included relations, i.e. do not run the base model with included relations but use this value instead.

−setup_only
Default not set. If -setup_only is set, scmplus will setup everything but not start the scm run.

2.3 Some common PsN-options useful with scmplus

For a complete list see common_options.pdf, or psn_options -h on the commandline.

−h or -?
Print a list of available options and exit.

−help
With -help all programs will print a longer help message. If an option name is given as argument, help will be printed for this option. If no option is specified, help text for all options will be printed.

−clean = *integer*
Default is 1. The clean option can take six different values:

0 Nothing is removed

1 NONMEM binary and intermediate files except INTER are removed, and files specified with option -extra_files.

2 model and output files generated by PsN restarts are removed, and data files in the NM_run directory, and (if option -nmqual is used) the xml-formatted NONMEM output.

3 All NM_run directories are completely removed. If the PsN tool has created modelfit_dir:s inside the main run directory, these will also be removed.

4 All NM_run directories and all m1 directories are completely removed.

5 The entire run directory is removed. This is only useful for execute. The lst-file will be copied even if the run failed.

−directory = *string*

Default scmplus_dirN, where N will start at 1 and be increased by one each time you run the script. The directory option sets the directory in which PsN

will run NONMEM and where PsN-generated output files will be stored. You do not have to create the directory, it will be done for you. If you set -directory to a the name of a directory that already exists, PsN will run in the existing directory, except for scm, boot_scm and xv_scm that cannot be started in an existing directory.

−model_subdir

Use an alternative directory structure for PsN. An extra directory level unique to each model is introduced between the calling directory and the rundirectory. More information about this option can be found in PsN.pdf.

−nm_version = *string*

Default is 'default'. If you have more than one NONMEM version installed you can use option -nm_version to choose which one to use, as long as it is

defined in the [nm_versions] section in psn.conf, see psn_configuration.pdf for details. You can check which versions are defined, without opening psn.conf, using the command

```
psn -nm_versions
```

−seed = *string*

You can set your own random seed to make PsN runs reproducible. The random seed is a string, so both -seed=12345 and -seed=JustinBieber are valid. It is important to know that because of the way the Perl pseudo-random number generator works, for two similar string seeds the random sequences may be identical. This is the case e.g. with the two different seeds 123 and 122. From limited tests it seems as if the final character is ignored and a work around to be sure to set different seeds would be to add a dummy final character. Setting the same seed guarantees the same sequence, but setting two slightly different seeds does not guarantee two different random sequences, that must be verified.

−threads = *integer*

Default is 5 (if the default psn.conf is used). Use the threads option to enable parallel execution of multiple models.

This option decides how many models PsN will run at the same time, and it is completely independent of whether the individual models are run with serial NONMEM or parallel NONMEM. If you want to run a single model in parallel you must use options -parafile and -nodes. On a desktop computer it is recommended to not set -threads higher the number of CPUs in the system plus one. You can specify more threads, but it will probably not increase the performance. If you are running on a computer cluster, you should consult your system administrator to find out how many threads you can specify.

−version

Prints the PsN version number of the tool, and then exit.