

# 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 1.2 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 1.2 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=1.2

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 four 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.

**-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. 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 -parafle 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.