

PsN and NONMEM7

PsN 4.6.0

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1 Introduction

This version of PsN has been tested with NONMEM 7.1.0, 7.1.2, 7.2.0 and 7.3.0. Not all features of NONMEM 7 are supported. Some will simply be ignored while other may cause errors if used. See details below.

2 Running with an NMQual8 installation of NONMEM

PsN4 supports NMQual8. See [psn_configuration.pdf](#) regarding minor recommended changes in `psn.conf`, and also see the help text for option `-nmqual` in [common_options.pdf](#).

3 Parallel execution of single models in NONMEM 7.2 and higher

PsN4 supports the parallel execution feature of NONMEM. PsN will not check that an mpi daemon is running, or that any other necessary parallelization preparations have been done. Therefore the user must make sure it is possible to run parallel NONMEM with the `nmfe` script before trying to do it through PsN.

It is required that the NONMEM version number 7.2 or later is properly set in `psn.conf`. The parallelization feature is invoked by using PsN option `-parafile=<file>`, and optionally `-nodes=N`, where `<file>` is the name of a NONMEM parafile. PsN will copy the parafile down to the run directory and pass on the name and the nodes option as input to `nmfe`. PsN can currently only handle one parafile at a time. The parafile option is further described in `common_options.pdf`.

A `defaults.pnm` file can be copied down to the NM run directory by setting PsN option `-extra_files`, see `common_options.pdf`.

The `-threads` option does not affect and is not affected by any parallel execution of a single model. The `-threads` option governs how many models PsN will submit for execution (by e.g. `nmfe72`) at a time. The user must ensure that the number of threads multiplied by the number of nodes used for a single model does not exceed what is desired.

If running on a cluster the user must set flags necessary for parallel execution, e.g. `-pe` for SGE, using the existing PsN options, e.g. `-sge_prepend_flags`, `-lsf_options` or `-slurm_prepend_flags`. PsN does not do this automatically.

4 New options to `nmfe72`, `nmfe73`

There is a set of new options to `nmfe72`, e.g. `-xmloff`. These options can be passed on by PsN using option `-nmfe_options`. Option `-nmfe_options` is further described in `common_options.pdf`. If setting option `-nmfe_options=licfile=some_license_file` then the license file must also be set with the PsN option `-extra_files`, unless an absolute path to the license file is given, in which case option `-extra_files` is not needed. See `common_options.pdf` for a description of the `-extra_files` option.

5 New forms of `$$SIGMA` and `$$OMEGA`

In NONMEM 7.2 it is possible to define `$$SIGMA` and `$$OMEGA` in new ways, and indicating this via options `STANDARD/VARIANCE COVARIANCE/CORRELATION` and `CHOLESKY`. PsN does accept these options and will pass them on when creating new models, but the output analysis and updating new models with final estimates from a previous run have not been adapted to these new forms, and updating initial estimates in a model

with final estimates from a previous run will introduce errors, as PsN will put the final VARIANCE/COVARIANCE estimates in \$OMEGA and \$SIGMA without removing the STANDARD/CORRELATION/CHOLESKY options in the control stream. Updating is done by all scripts except execute, sse and parallel_retries. PsN will print a warning when the new \$OMEGA/\$SIGMA options are encountered.

6 Option ORDER in \$ESTIMATION

There is a new option called ORDER in \$EST in NONMEM 7.2. PsN cannot handle any but the default format, and will attempt to remove ORDER if found in \$EST.

7 Supported new records

PsN will accept and handle new records \$SIZES, \$LEVEL, \$ANNEAL, \$PHIS and \$ETAS, \$THETA1 \$THI \$THETAR \$THR \$THETAP \$THETAPV \$OMEGAP \$OMEGAPD \$SIGMAP \$SIGMAPD. However, files set with \$ETAS FILE= or \$PHIS FILE= will not automatically be copied to the directory where NONMEM is run. The user must use PsN option -extra_files to make PsN copy the required files to the NONMEM run directory.

8 Shorthand notation in \$THETA \$OMEGA \$SIGMA

PsN does not support VALUES option in \$OMEGA/\$SIGMA. PsN does not support the new shorthand notation in NM7.3 (xN notation, SAME(n) notation).

9 Control stream in mixed case

In NONMEM 7.2 and higher it is possible to write the control stream in mixed case. PsN does not support this. It is likely that options written in lower case will not be recognized correctly, which can cause errors in scripts which need to modify certain options.

10 New output files in NONMEM 7

PsN handles NONMEM output files .lst .ext .cov .cor .coi .phi .phm .shk .grd .cnv .smt .rmt .imp .npd .npe .npi .fgh .log.xml .xml .cpu .shm .agh.

(The .log.xml file is created by NMQual, if used). The above output files will be retry numbered, and the numbered files will be cleaned if `clean >= 2`.

Only the lst-file will by default be copied back to the calling directory. More files will be copied if the user sets the extensions of those files via the PsN option `-nm_output`. Example: `-nm_output=ext,cov,cor`. Note if the user lets the installation script create a `psn.conf` file then `nm_output` will be set to `-nm_output=ext,cov,cor,coi,phi`

Cleaning of output files: If `clean >= 1` then the following files are removed: LINKC.LNK, compile.lnk, gfortran.txt, ifort.txt, garbage.out, newline, nmexec.set, parafire.set, prcompile.set, prdefault.set, prsame.set, psn.log, rundir.set, runpdir.set, temporaryfile.xml, temp.out, trashfile.xxx, trskip.set, worker.set, xmloff.set, prsizes.f90, licfile.set, background.set, FMSG, FSIZES

If `clean >= 2` then the `temp_dir` subdirectory will be removed.

If `clean >= 3` is set then `worker*` subdirectories are removed when `NM_run` is removed. If the worker subdirectories are called something other than `worker*` then cleaning with `level=3` will fail.

11 Turning off estimation in NONMEM 7

In some scripts PsN turns off estimation in some extra PsN-generated models. It is done in `npc` and `vpc`, in `cdd` if option `-xv` is set, and in `execute` if option `-mirror_plots` is set. With NONMEM5 and NONMEM6 the estimation is easily skipped by setting `MAXEVAL=0`. NONMEM7 however, can have multiple \$ESTIMATIONs and/or estimation methods for which `MAXEVAL` do not apply. Settings in one \$ESTIMATION will by default carry over to the next unless a new setting for the same option is set. This makes it much more complicated to automatically edit the modelfile to skip the estimation step and get correct output of PRED, DV etc.

Of the new estimation methods of NONMEM7, it is most natural to use `IMP` or `IMP MAP` with `EONLY=1` for the purposes for which estimation is turned off. If PsN does not need `ofv` values from the run `NITER=0` can be set. This is true for `vpc`, `npc` and `execute` with `mirror_plots`. If `ofv` values are needed as in `cdd`, `NITER=5-10` is sufficient according to NONMEM7 docu-

mentation. PsN will leave NITER unchanged in most cases (see exception below).

When using NM7, there are two alternatives for the user when running a PsN script that turns off estimation. The first is to make sure 1) that the last \$ESTIMATION has METHOD set to either IMP, IMPMAP or a classical method and 2) that the last \$ESTIMATION is complete, i.e. that all options needed are explicitly set in that record so that none that are needed for that step are carried over from previous \$EST and 3) that PsN is informed of 1 and 2 by setting option -last_est_complete. If option -last_est_complete is set, PsN will do the following to turn off estimation:

1. remove all but the last \$ESTIMATION record
2. If METHOD in last \$EST is classical: set MAXEVAL=0

or If METHOD is IMP or IMPMAP: set EONLY=1. If running vpc, npc or execute with mirror_plots also set NITER=0, otherwise do not change NITER. If METHOD is any other than classical or IMP/IMPMAP then the last \$EST is not changed and a warning is printed.

The second alternative is to let PsN do everything automatically, by not setting option -last_est_complete. Then PsN will collect options (LAPLACIAN, METHOD, ISAMPLE...) from all \$ESTIMATION, removing <OPTION> if NO<OPTION> appears, unsetting LIKELIHOOD if PREDICTION appears, changing the value of ISAMPLE and METHOD if/when they appear again, and so on. PsN addresses the fact that options may be abbreviated in many ways. A number of options are skipped, such as FORMAT and FILE and options which only apply to the BAYES method, see list below. After scanning the options, all \$EST are removed and PsN creates a new one based on the collected options.

- If METHOD is classical (i.e. the last \$EST had a classical method), MAXEVAL=0 is set. The rest of the collected options are appended.
- If METHOD=IMP or IMPMAP, then EONLY=1 is set. If running vpc, npc or execute with mirror_plots also set NITER=0, otherwise do not change NITER. The rest of the collected options, including ISAMPLE if it is set, are appended.
- If METHOD is something other than classical/IMP/IMPMAP, then METHOD is changed to IMP, and EONLY=1 is set. For vpc, npc and

for `mirror_plots` `NITER=0` and `ISAMPLE=1` are set. For `cdd` `NITER` is not changed if it is already set in any of the `$ESTIMATION` steps, otherwise `NITER=10` is set. `ISAMPLE` is left to the default value for `cdd`. The rest of the collected options are appended.

If the option `niter_eonly` is set, PsN will set `NITER` to this value regardless of estimation method and PsN tool (`cdd`, `npc`, `vpc` or `execute`). This option is independent of `last_est_complete`. The following options are skipped when PsN automatically collects options for an `$ESTIMATION` record:

`NOTITLE`, `NOLABEL`, `FORMAT`, `FILE`, `MSFO`, `IACCEPT`, `PACCEPT`, `OACCEPT`,
`NSIGDIGITS`, `SIGDIGITS`, `ISAMPLE_M1`, `ISAMPLE_M2`, `ISAMPLE_M3`,
`NBURN`, `PSAMPLE_M1`, `PSAMPLE_M2`, `PSAMPLE_M3`, `OSAMPLE_M1`,
`OSAMPLE_M2`, `OSAMPLE_M3`, `THETABOUNDTEST`, `NOTHETABOUNDTEST`, `NOTBT`,
`OMEGABOUNDTEST`, `NOOMEGABOUNDTEST`, `NOOBT`, `SIGMABOUNDTEST`,
`NOSIGMABOUNDTEST`, `NOSBT`

Options `MAXEVALS` and `EONLY` are also skipped, since they will be set anyway in later steps.

The `CHAIN` method (reading initial estimates from a rectangular file) will not work with `vpc` or `npc`, because all but the last `$ESTIMATION` are removed as part of turning off estimation. See details, including a workaround, in the section `CHAIN` method. The `cdd` and `execute` scripts will work with `CHAIN`.

12 Raw and additional output, `$ESTIMATION` options

When `NONMEM7` raw and additional output (`ext`, `coi`, `cov`, `cor`, `phi`) files exist, results will be read from these files instead of the `lst`-file. If additional output cannot be found the `lst`-file is used. `NONMEM7` raw and additional output are handled the same way as `lst`-files. These files are numbered by retries and, if set in `nm_output`, copied back to the calling directory.

PsN only accepts default file names and default formatting of the raw and additional output. If any of the options `NOTITLE`, `NOLABEL` or `FILE` is set in any `$ESTIMATION` record, PsN will set the option to the default value in the last `$ESTIMATION`. Only the last `$ESTIMATION` will be changed. If running `sumo` on output with non-default formatting, the run is likely to

fail. If the delimiter is set to something other than spaces (the default) by using `FORMAT` or `DELIM` then PsN output parsing will fail.

In all output, only results (parameter estimates, messages...) from the last `$ESTIMATION` will be presented. The only exception is the `MINIMIZATION SUCCESSFUL` flag, see that section.

13 MINIMIZATION SUCCESSFUL

The message `MINIMIZATION SUCCESSFUL` is important for PsN restart behaviour (see details in `common_options.pdf`) and sumo output, but it only appears for classical estimation methods. The following logic is used for setting the flag `minimization_successful`:

1. Only status of last `$EST` step is considered, except when last `$EST` is `IMP` with `EONLY=1` (see item 7)
2. `BURN-IN/(REDUCED) STATISTICAL PORTION/OPTIMIZATION NOT TESTED` - successful
3. `BURN-IN/(REDUCED) STATISTICAL PORTION/OPTIMIZATION COMPLETED` - successful
4. `BURN-IN/(REDUCED) STATISTICAL PORTION/OPTIMIZATION NOT COMPLETED PRIOR TO USER INTERRUPT` - successful
5. `BURN-IN/(REDUCED) STATISTICAL PORTION/OPTIMIZATION NOT COMPLETED` - failed
6. If any of the two steps in SAEM failed - failed
7. If last `$EST` is `IMP` with `EONLY=1`, the minimization status is determined by the next to last `$EST`

14 Specifying the NONMEM version

The option `nm_version` tells PsN (among other things) which NONMEM-version type of output file to expect. See document `psn_configuration.pdf` for more information on `nm_version` and `psn.conf`.

15 CHAIN method and parallel_retries

There is a PsN script for running a set of copies of a model file with tweaked initial estimates in parallel. The script is called `parallel_retries` and is described in `parallel_retries_userguide.pdf`.

NONMEM 7 can also be used to run a model with tweaked initial estimates. If using the CHAIN method of NONMEM7 and taking initial estimates from an existing file, that filename must be given to PsN with option `-extra_files`, just as a file with a user-written Fortran subroutine. Note: NONMEM does not give an error message if the file with initial estimates is missing. The user must remember to set `-extra_files`, otherwise NONMEM will use the initial estimates in the modelfile without giving any warning.

If the file with adjusted initial estimates is generated by the same modelfile which then uses it, no extra PsN options are needed.

Do not use PsN for running a modelfile with CHAIN as the method of a single \$ESTIMATION step, for example when only generating a file with initial estimates. PsN would change the name of the file where newly generated initial estimates are written. See section Raw and additional output, \$ESTIMATION options.

The PsN option `tweak_inits` will have no effect if CHAIN is used to take initial estimates from a separate file instead of the model specification itself.

The CHAIN method (reading initial estimates from a rectangular file) will not work with `vpc` or `npc`. This is because PsN removes all but the last \$ESTIMATION as part of turning off estimation. It is recommended to generate an `msfo` file with the desired parameter values, and then send this to `npc/vpc` via the existing `-msfo` option. The `cdd` script will work with CHAIN, since there estimation is turned off in newly created modelfiles with initial estimates read from `cdd:s` own runs. Option `mirror_plots` with `execute` will also work with CHAIN, since a separate \$PROBLEM with an \$MSFI record is generated for the simulations.

16 Shrinkage

Shrinkage values are reported as percentages. If option `-shrinkage` is used, PsN will compute `iwres` shrinkage and `eta` shrinkage. Shrinkage is never read from NONMEM output. PsN will compute shrinkage if option `-shrinkage` is set on the command-line.

17 CWRES and iofv

NONMEM7 can output iofv, so that option is turned off when running PsN with NM7. Option -iofv is still available with PsN and NM6. NONMEM7 can usually output also CWRES, but not in all cases, so PsN option -cwres is always enabled.