

MCMP user guide

PsN 4.6.0

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1 Introduction

MCMP – Monte-Carlo Mapped Power [1] – is a tool for power computations. The method is based on the use of individual Objective Function Values (iOFV) and aims to provide a fast and accurate prediction of the power and sample size relationship without any need for adjustment of the significance criterion. The principle of the method is as follows:

1. a large dataset (e.g. 1000 individuals) is simulated with a full model, or a separate simulation model if model misspecification will be taken into account.
2. the full and reduced models are re-estimated with this data set
3. *iOFV*:s are extracted from the NONMEM .phi-files, and for each subject the difference in *iOFV* between the full and reduced model is computed ($\Delta iOFV$)
4. $\Delta iOFV$:s are sampled according to the design for which power is to be calculated and a starting sample size (N)
5. the $\Delta iOFV$ sum for each sample is calculated ($\sum_i \Delta iOFV$)
6. steps 4 and 5 are repeated many times
7. the percentage of $\sum_i \Delta iOFV$ greater than the significance criterion (e.g. 3.84 for one degree of freedom and $\alpha = 0.05$) is taken as the power for sample size N,

- steps 4-7 are repeated with increasing N to provide the power at all sample sizes of interest.

Example

```
mcnp -full_model=mod1.mod -stratify_on=DOSE -reduced_model=mod2.mod -seed=123
```

2 Input and options

2.1 Mcmp-specific input

-simulation_model = *sim.mod*

The filename of the simulation model, optional. Default is the `-full_model` filename. PsN will modify this model, removing \$EST and adding \$SIM, if it is not already a simulation model. If both `-table_reduced` and `-table_full` are specified, then option `-simulation_model` will be ignored. Cannot be used with option `-simdata`.

-full_model = *full.mod*

The filename of the full model is required, unless `-table_full` (see below) is used. This must be an estimation model.

-reduced_model = *red.mod*

The name of the reduced model is required, unless `-table_reduced` (see below) is used. This must be an estimation model.

-stratify_on = *column*

The name of the variable to stratify on, optional. Must be all uppercase and (unless NM7) at most 4 characters. Unless `-table_strata` is specified, the variable must be possible to request in \$TABLE, i.e. either present in \$INPUT or defined in \$PK/\$PRED/\$ERROR. PsN does not check that the variable is defined. If `-reduced_model` is specified then PsN will set \$TABLE there, otherwise \$TABLE will be set in the full model. The stratification table will not be generated from the simulation model. PsN will set \$TABLE ID `<stratify_on>` FIRSTONLY NOAPPEND NOPRINT ONEHEADER FILE=strata.tab

- curve**
Set by default. Can be disabled with `-no-curve`. This option controls whether the complete power curve up to the target power should be generated, or if the program should only compute the sample size required to achieve the target power.
- start_size = N**
First total sample size (sum of samples from all strata) to test. Optional, default is $3 \times \text{increment}$ (see below).
- increment = N**
Optional, default is the number of strata (1 if stratification is not used). Only consider setting this option if the stratification groups do not have equal size (the design is not balanced). Option `-increment` is the stepsize for the total sample size (sum of samples from all strata), i.e. the distance on the x-axis between the points in a total sample size vs. power plot. See section Discussion on strata sample sizes for a more detailed discussion of this option.
- max_size = N**
The largest total sample size to plot for, optional, default equal to number of individuals in dataset.
- target_power = X**
Default 98. If the whole power curve is generated (option `-curve` is set), the computations will stop when the computed power exceeds the target power 3 times in a row, even if `max_size` is not reached. If option `curve` is not set, then the program determines the sample size only for the target power.
- table_full = *filename***
Optional. The name of the table containing `iofv` for the full model. If this option is used, PsN will skip the estimation of the full model and read the table directly instead. For this option, `iotab` tables generated using PsN with option `-iofv` and `NONMEM6` will work, as well as `.phi`-files generated with `NONMEM7`. Files generated in other ways must follow the following rules: There must be exactly one row per individual, all other lines (headers) must start with a non-number,

the columns must be space or tab separated, and iofv must come in the last column.

-table_reduced = *filename*

Optional. The name of the table containing iofv for the reduced model. If this option is used, PsN will skip the estimation of the reduced model and read the table directly instead. The file must have the format defined above in the -table_full help text.

-simdata = *filename*

Optional. The name of a previously generated file with simulated data. Cannot be used together with option -simulation_model. If this option is set, no simulation will be performed by mcmp. Instead the file simdata will be used as the datafile when estimating the full and reduced model.

-table_strata = *filename*

Optional unless both -table_full and -table_reduced is used and stratify_on is set, then required. Table with stratification column. Must have only one row per individual, i.e. for example generated in NONMEM with FIRSONLY (see option -stratify_on), and must have a header with ID and stratification variable name. Option -table_strata may be used even if neither of -table_full or -table_reduced are used, then the stratification column in -table_strata will be used instead of a table generated from the estimation of the full or reduced model.

-n_bootstrap = N

Optional, default 10000. The number of bootstrapped delta- θ 's to generate for each total sample size.

-df = N

Optional, default 1. The number of degrees of freedom for the chi-square test. Allowed values are 1-20. PsN will compute the power for significance levels 20%, 15%, 10%, 5%, 1% and 0.1% for the number of degrees of freedom.

-significance_level

Optional, default 5 (percent). Permitted values are 20, 15, 10, 5, 1 and 0.1. Convergence check will be based on critical ofv for this significance level.

-critical_ofv

Optional, no default. If specified, -critical_ofv will override the setting of -df. PsN will work with positive values internally (delta_ofv=reduced-full, check if delta_ofv > critical_ofv), but will automatically change the sign if the user gives a negative value.

2.2 Some important common PsN options

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

-h or -?

Print the 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.

-directory = 'string'

Default mcmp_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.

-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.

-clean = *'integer'*

Default 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.

-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
```

-threads = *'integer'*

Default 5 (if default PsN config file 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.

2.3 Auto-generated R-plots from PsN

PsN can automatically generate R plots to visualize results for mcmp, using a default template found in the R-scripts subdirectory of the installation directory. The user can also create a custom template, see more details in section “Auto-generated R-plots from PsN” in common_options.pdf.

The default mcmp template requires the R libraries ggplot2 and plyr. If the packages are not installed no pdf will be generated, see the .Rout file in the main run directory for error messages.

-rplots = level

-rplots<0 means R script is not generated

-rplots=0 (default) means R script is generated but not run

-rplots=1 means basic plots are generated

-rplots=2 means basic and extended plots are generated

Troubleshooting

If no pdf was generated even if a template file is available and the appropriate options were set, check the .Rout-file in the main run directory for error messages. If no .Rout-file exists then check that R is properly installed, and that either command 'R' is available or that R is configured in psn.conf.

Basic plots

A basic mcmp rplot will be generated in file PsN_mcmp_plots.pdf if option -rplots is set >0, and the general rplots conditions fulfilled, see above. The basic plot is the mcmp-generated power curve for the significance level chosen

with option `-significance_level`, with a mark at the sample size required for 80% power.

Extended plots

Extended `mcmp` `rplots` will be generated in file `PsN_mcmp_plots.pdf` if option `-rplots` is set `>1`, and the general `rplots` conditions fulfilled, see above.

The first extended plot shows a power versus sample size parametric power estimation (PPE) curve together with the `mcmp`-generated power curve for the significance level chosen with option `-significance_level`. Parametric power estimation allows to generate data for full power versus sample size curve(s) based on simulation and reestimation with full and reduced models performed with a single sample size. The procedure is described in [2].

The second extended plot is the the `mcmp`-generated power curves for each of the significance levels, with a mark of the sample size required for 80% power.

The third extended plot is a histogram of the individual full-reduced `delta-ofv`.

3 Output

The output from each `mcmp` is `mcmp_results.csv` which contains a table with header `total_X,power at 20%,power at 15%,power at 10%,power at 5%,power at 1%,power at 0.1%`, (headers for `N` from each stratum). One row for each total sample size (`total_X`). The table can be plotted in excel. The results are also printed to screen as they are produced, and the user can terminate the run with `Ctrl-C` if the obtained power is deemed sufficient. The file `mcmp_results.csv` will contain the values that were computed before the interruption. If `mcmp` is rerun the previous result file will be copied and kept.

4 Known bugs

If estimation of the full and/or reduced model fails but `NONMEM 7` still produces a `.phi`-file with the initial individual `ofv`-values, then `PsN` will not

detect the failed estimation but continue to bootstrap from the .phi-file. Then the power curves will be completely wrong.

5 Recovering a crashed/stopped mcmp

If the simulation finished but none of the estimations finished, then start over in a new run directory but use option `-simdata` with the dataset from the simulation step. If one or two of the estimations finished, then start in new directory using option `-table_reduced` and/or `-table_full` and possibly `-table_strata`.

6 Discussion on strata sample sizes

The `increment` and `start_size` options may seem complicated, so here is a detailed background to the design of those options in PsN.

We start with some examples to explain a method which is not implemented in PsN. When the design is perfectly balanced, choosing the number of individuals to sample from each stratum in each iteration is trivial. It is more complicated to define an algorithm that works in all cases with any design. Consider the following three cases:

1. $N_{total} = 400$ where $N_A = 200$ and $N_B = 200$
2. $N_{total} = 400$ where $N_A = 100$ and $N_B = 300$
3. $N_{total} = 424$ where $N_A = 233$ and $N_B = 191$

It is easy to see that the ideal sampling scheme in case 1 is to take 1 individual from each stratum in the first iteration, 2 from each in the second iteration, and so on. Then the 1:1 balance is perfect in every iteration. The increment, the increase of the total sample size in each iteration, is 2 in this case.

Case 2 is also simple, take 1 individual from stratum A and 3 from stratum B in the first iteration, 2 from stratum A and 6 from stratum B in the second iteration and so on, thus always preserving the 1:3 relation of the group sizes.

Case 3 is more difficult and it is not obvious what the best strategy is.

The implicit strategy in for case 1 and 2 is the following algorithm:

1. Find the greatest common divisor D of the strata sizes.

2. In each iteration, increase the sample size from stratum A with N_A/D and from stratum B with N_B/D

For case 1 $D=200$ and $N_A/D=N_B/D=1$ and for case 2 $D=100$, $N_A/D=1$ and $N_B/D=3$. For case 3 it turns out the greatest common divisor is 1, giving a useless strategy since it is not okay to sample 233+191 individuals in the first iteration. Hence finding the greatest common divisor is not a strategy which is suitable to implement in PsN.

PsN must be able to handle all cases, keep as good a balance as possible between the strata regardless of their original sizes, make small enough increases in the sample sizes to give a good power plot and allow the user to affect the sampling strategy as much as possible without making the input options too complicated.

PsN uses the following algorithm:

1. Compute the desired total sample size $X_{desired_{total}} = start_size + (i-1) * increment$, where $i, i=1,2,3...$ is the iteration number, increment has default equal the number of strata but can be set by the user, and start_size has default $3 * increment$ but can be set by the user.
2. Compute the number of individuals X_i to sample from stratum i using the following formula: $X_i = round_to_nearest_integer(X_{desired_{total}} * N_i / N_{total})$.

With the formula in step 2 stratum i 's fraction of the total sample size will always be as close as possible to the fraction of stratum i in the original population. The rounding is necessary since the division often has a non-zero remainder, and it is important to note that the actual total sample size $X_{actual_{total}}$, which is the sum of the individual sample sizes X_i , can differ slightly from $X_{desired_{total}}$ because of the necessary rounding. If the increment is small it can happen that $X_{actual_{total}}$ is the same in two consecutive iterations, without there being any error. PsN always reports $X_{actual_{total}}$ in all output. $X_{desired_{total}}$ is an internal variable and is never displayed.

If the user has a dataset as case 2 ($N_{total}=400$ where $N_A=100$ and $N_B=300$) the user can set increment to 4 (1+3) which would give a perfect relation between the strata sample sizes in each iteration, since according to PsN's algorithm stratum A will always get $100/400=1/4$ of the samples and stratum B $300/400=3/4$ of the samples and $X_{desired_{total}}$ would always be a multiple of 4. If the user leaves increment to the default = the number of strata, then the results would still be acceptable. In every other iteration the relation

would be perfect ($X_{desired_{total}}$ is a multiple of 4). In the rest of the iterations the actual relation would deviate slightly, e.g. if $X_{desired_{total}}=10$ then $XA= \text{round}(10*100/400)=3$ and $XB= \text{round}(10*300/400)=8$ giving $X_{actual_{total}}=3+8=11$, but the larger the total sample size is the smaller the deviation will be.

The user can also choose to set `start_size` to manipulate the sample sizes, but it is recommended not to set this option to anything other than a multiple of increment.

7 Technical overview of algorithm

1. If NONMEM6 is used, then the `iofv` option to PsN is set automatically. If NONMEM7 is used, no extra settings are needed.
2. PsN checks that the requirements on the options are fulfilled (see list of options above).
3. Look-up critical `ofv` if not given on command-line, then make sure sign is +.
4. Unless option `simdata` is given, or both `table_reduced` and `table_full` are given, simulate the simulation model with a random number seed in `$SIM` which set by PsN.
5. If `-reduced_model` is specified, PsN will add a `$TABLE` to the first `$PROBLEM` with ID `<stratify_on>` `FIRSTONLY NOAPPEND ONEHEADER NOPRINT FILE=strata.tab`. PsN does not check that it is possible to request `<stratify_on>` in `$TABLE`, so it is the responsibility of the user to either have it in `$INPUT` or define it in `$PK/$PRED/$ERROR`.
6. If `-reduced_model` is not specified but `-full_model` is, then PsN will add a `$TABLE` to the first `$PROBLEM` with ID `<stratify_on>` `FIRSTONLY NOAPPEND ONEHEADER NOPRINT FILE=strata.tab`.
7. In both the reduced and full model, set `$DATA` to the simulated data file.
8. Estimate the reduced model unless `-table_reduced` is specified.
9. Estimate the full model unless `-table_full` is specified.

10. Extract iofv-values from full and reduced iofv-tables, and subtract to create delta-iofv-vector.
11. Stratify delta-iofv-table based on strata.tab/-table_stratify.
12. Loop over total sample size starting on -start_size and incrementing with -increment in each step, continuing as long as total sample size does not exceed -max_size. For each total sample size and each stratum, compute the number of samples to draw from this stratum using the formula $Z = \text{round}(total.sample.size \cdot \frac{n.individuals.in.stratum}{n.individuals.in.total})$. Draw Z samples from the stratum, randomly with replacement. Repeat n_bootstrap times, sum delta_iofv for the samples from all strata to generate n_bootstrap delta_ofv:s. Compute percentage of delta_ofv > critical_ofv=power. In output table, write line with total_sample_size, power, sample_sizes from each stratum. Halt if power exceeds target_power % three times in a row.

References

- [1] Camille Vong, Martin Bergstrand, Joakim Nyberg, and Mats O. Karlsson. “Rapid sample size calculations for a defined likelihood ratio test-based power in mixed effects models”. In: *AAPS J. 2012 Jun; 14(2): 176–186* (2012).
- [2] S. Ueckert, M. O. Karlsson, and A. C. Hooker. “Accelerating Monte Carlo power studies through parametric power estimation”. In: *J Pharmacokinetic Pharmacodyn 43(2):223-234* (2016).