

Addendum to Manual of MW\Pharm

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KinPop: Iterative two-stage Bayesian population procedure

A completely new module 'KinPop' has been added to MW\Pharm. KinPop performs a population pharmacokinetic analysis by an 'Iterative two-stage Bayesian population procedure' (ITSB).

The ITSB procedure in KinPop is similar to that described by Prévost (ref. 1), which has been used also by others (ref. 2-6). It has been demonstrated that the ITSB procedure performs well in comparison to other methods including standard two-stage (STS), global two-stage (GTS), and nonlinear mixed-effect modelling (NONMEM) (ref. 2-5).

The ITSB procedure is close to the method in the program IT2B, the 'front end' program of NPEM2 in USC*PACK (ref. 7). Details of the procedures in IT2B have not been published.

An example of the practical use is given in ref. 6.

An overview of the various methods for population analysis can be found in ref. 8.

For a detailed description of several procedures, and a comparison by Monte Carlo simulation, see ref. 2-5.

Principle

The principle of ITSB may be understood from the following scheme:

Assume a reasonable set of population data (e.g. from STS):
means and SDs (or complete variance-covariance matrix).

Step 1 Perform Bayesian analysis on each subjects separately

Step 2 Calculate new set of population data
means and SDs (or complete variance-covariance matrix)

Repeat steps 1 and 2 until convergence is reached.

(in KinPop, each repetition of steps 1 and 2 is called a 'cycle').

If convergence is reached, the assumed population data, as used in step 1, are equal to the population data obtained in step 2.

It can be shown by Monte Carlo simulation (see elsewhere) that this procedure provides accurate and precise estimates of the means and SDs (or complete variance-covariance matrix) of the population.

The final outcome is not dependent on the initial set of population means and SDs (or complete variance-covariance matrix). However, small insignificant differences will occur due to rounding off and the stop criteria. In exceptional cases the procedure may converge to a different solution (local minimum). The 'optimal' solution is the parameter set with the highest value for the summed log-likelihood.

To diminish the risk of convergence in a local minimum, it is advised to start the analysis with a reasonable set of initial estimates. Also, one may start the analysis with a different set of initial estimates.

User manual

KinPop can be started via the KinMenu (Main menu option 8, 3).

1 Make patient selection file

First, a selection of patient records must be made. The patient database window is shown (similar to that in the Main menu, option 1), and patients can be selected by pressing the Space bar. Marked patients are indicated in **bold**. After <F1> or <F10> the patient selection is saved automatically to a file. A previously saved patient selection can be loaded and modified.

2 Load patient selection file

A previously saved patient selection can be loaded. This option is also useful for resetting all values to their original values before restarting a population analysis.

3 Load drug data

The data of the selected drug, which is read from the **first** patient of the patient selection, are shown and can be changed if necessary.

The following drug data are used during the population analysis:

- population mean values and SDs of model parameters are used as initial estimates of the population means and SDs. Missing SDs are replaced automatically by the corresponding population mean (CV 100%).

(KinPop does not check whether or not the data of each patient refers to the same drug; this must be done by the user!)

- SD assay error
- distribution of assay error (normal or log-normal)
- distribution of parameters (see option 4)

4 Parameters distribution

Normal distribution or log-normal distribution.

The choice made here is similar to that in the medication screen (after <PgDn>, last line).

In general, a log-normal distribution is more suited than a normal distribution for pharmacokinetic parameters. The actual distribution can be checked in the output after the fitting procedure.

Even more important than the choice between normal and log-normal distribution is that Bayesian forecasting should be performed with the same type of distribution as was used for

the generation of the population data. The type of distribution is saved with the population data (see below).

5 New population parameters based on

Options:

- mean \forall sd
- median and df(mean) (see below option 9, and manual of NPEM2)

The option 'means \forall sd' is the default and more natural choice. In the manual of NPEM2, Prof. R. Jelliffe advises the use of 'median and df(mean)' as the best population values to be used in Bayesian forecasting. However, using this option, the calculation may converge less efficiently (see below).

6 Output to file

Intermediate and final results of calculations can be saved in a text file if a filename is chosen (extension 'PRT').

This may be useful for checking irregularities, but is not necessary for normal procedures (default: results not saved in a text file).

7 Mode

KinPop will stop to allow user interaction or to show intermediate results:

- 1 interactive mode
- 2 pause after each patient and after each cycle
- 3 pause after each cycle
- 4 automatic mode (does not pause)

The automatic mode is the default setting.

8 Stop criterion

KinPop stops the iterative procedure if the relative change of each of the calculated population values is less than the stop criterion (default is 0.0001).

9 Start KinPop (Iterative two-stage procedure)

First the screen of the fitting procedure of the medication history (similar to that of option 5 of Main menu) is shown. The entries and selections are now used for all patients (except for the interactive mode, see option 7).

If 'Bayes' is set OFF, KinPop performs a standard two-stage procedure (STS).

If a parameter is set 'fixed', its value will not be fitted, and the population value will be kept at its initial value.

Initial individual parameter estimates are ignored. For each patient and for each cycle, the initial parameter values are set equal to the population mean.

After <F10> the correlation matrix between the population parameters is shown. A detailed description is given below. Default: all correlations are '0' and 'fixed'.

After again <F10> the iterative analysis starts. The screen shows the progress in the current cycle number, current patient, and parameter set of current patient.

If the stop criterion is reached, or if the calculation is interrupted by the user by pressing <F1>, the results are shown (see below).

The new population values (means and SDs) are copied automatically to the medication screen. To save these values, e.g. for future Bayesian forecasting, the drug data have to be save to the database by <Ctrl><s> in the medication screen (option 3 in KinPop, or option 2 in Main menu). To keep old values as well, choose a new name for the drug.

Overview of results shown on successive screens:

Table 1

- old population values (initial values of Bayesian procedure)

- new population values (shown in yellow):

mean	(for log-normal distribution: geometric mean)
sd	(for log-normal distribution: log-sd * mean)
median	median of individual parameters.
df(mean)	average value of DF ₅₀ and DF ₉₅ .
df50	(DF ₅₀) standard deviation of a (log-)normal distribution which has the same values for the 25- and 75-percentiles as the actual distribution (see also manual of NPEM2).
df95	(DF ₉₅) idem, for the 2.5- and 97.5-percentiles.
minimum	minimum value of individual parameters.
maximum	maximum value of individual parameters.
skewness	skewness of the distribution (a true (log-)normal distribution gives a value 0; a negative value indicates a skewness to the left, a positive value to the right).
kurtosis	kurtosis of the distribution (a measure of the degree of similarity with the shape of a (log-)normal distribution; a true (log-)normal distribution has a value of 3).

Also the summed 'log-likelihood' of all patients is given.

Table 2

- Correlation matrix of the individual patient parameters (Covar_{j,k} is calculated as given below, without the factor Covar_{j,k}(i) in the equation).

- Correlation matrix of the population parameters 'calculated' (Covar_{j,k} is calculated as given below).

- Correlation matrix of the 'actual' population parameters, including fixed values replacing the 'calculated' values Covar_{j,k}; This is the correlation matrix of the population parameters which is used during the Bayesian fit procedure, and is copied to the medication screen (and can be saved to the drug database).

Graphs

- For each parameter a histogram of the individual values of each patient. This allows an 'eye judgement' of the actual parameter distribution (e.g. 'about normal', 'about log-normal', 'bimodal').

The graph is scaled automatically, but the scaling can be changed, including the number of bars. The X-axis is scaled logarithmically if a log-normal distribution is chosen (see option 4). For comparison, also the frequency distribution the (log-)normal distribution corresponding to the calculated population parameters is shown.

- For each combination of two parameters a scatterplot: for each patient a circle is plotted . This allows an 'eye judgement' of the joint distribution of both parameters, e.g. correlation and clustering.

For comparison, also the boundaries of the 50% and 95% probabilities corresponding to the calculated distribution and correlation of both parameters are shown, i.e. the 50% and 95% of the patients should lie within these boundaries.

- The change of the calculated population parameters during the iterative procedure. Parameter values are scaled relative to the initial value.

- Idem, for the calculated standard deviations of the population parameters. Parameter values are scaled relative to the initial value.

- Idem, for the correlation coefficients between the calculated parameters (actual values).

- Idem, for the summed 'log-likelihood' (actual value).

Table 3

For all selected patients the individual parameter values.

Showing the results can be interrupted by pressing <F1>.

All results are shown again after pressing <a> in the KinPop menu.

Description of the procedures

Method **mean** \forall **SD**

The population values of the pharmacokinetic parameters are calculated as the mean of the individual parameters of N patients (j).

The standard deviations of the population values are calculated as the square root of the variance ($Covar_{j,j}$).

The covariance matrix of the population parameters is calculated from:

$$Covar_{j,k} = \frac{\sum_{i=1}^N [(P_j(i) - P_j)(P_k(i) - P_k) + Covar_{j,k}(i)]}{N - 1}$$

where

$Covar_{j,k}$	covariance of population parameters j and k
N	number of patients
$P_j(i)$	values of parameter j in patient i
\bar{P}_j	mean value of parameter j (in N patients)

$Covar_{j,k}(i)$ covariance of parameters j and k in patient i

In case of a log-normal distribution of the parameter, the values P_j refer to the logarithm (base e) of the parameter value.

The standard error of parameter j in patient i, as shown after fitting of each patient is equal to the square root of $Covar_{j,j}(i)$.

Note:

The individual parameter estimates obtained by the Bayesian procedure are different from the estimates of that parameter obtained with 'Bayes OFF'. The parameter values are moved into the direction of the population mean, and represent the most likely values given the measurement for that patient and given the distribution of the parameter in the population; this is the Bayesian principle. The less information is obtained for the individual patient, the more the parameter for that patient is moved to the population mean. The more information is obtained for the individual patient, the more the parameter for that patient moves to the value which would be obtained with 'Bayes OFF'.

As a result, the standard deviation of the individual parameter values is not an unbiased estimate of the population standard deviation: it is too small.

By taking into account the term $Covar_{j,k}(i)$ in the equation given above, an unbiased estimate of the interindividual standard deviation is obtained.

The correlation matrix of the population parameters is calculated from:

$$r_{j,k} = \frac{Covar_{j,k}}{\sqrt{(Covar_{j,j} Covar_{k,k})}}$$

where

$r_{j,k}$ correlation coefficient between parameters j and k

Method **median** \forall **DF_{mean}**

The population values of the pharmacokinetic parameters are calculated as the median of N patients.

The standard deviations of the population parameters are calculated from:

$$SD_j = \sqrt{(DF_{mean})^2 + \frac{\sum_{i=1}^N Covar_{j,j}(i)}{N-1}}$$

where

SD_j standard deviation of parameter j

DF_{mean} average value of DF_{50} and DF_{95}

DF_{50} standard deviation of a normal distribution which has the same values for the 25- and 75-percentiles as the actual distribution (similar values are used in the NPEM2 program of USC*PACK)

DF_{95} idem for 2.5 and 97.5 percentiles

The correlation matrix of the population parameters is calculated as indicated for the method 'mean \sqrt{sd} '.

Correlation between population parameters

ITSB can be performed in various ways with respect to the correlation between population parameters:

(A) Assuming NO CORRELATION between the population parameters. In this case the 'classical' Bayesian fitting is applied.

The correlations between the population parameters are calculated from the individual patient parameters and shown on the screen, but these values are not used or copied to the medication screen.

(B) Assuming a KNOWN (fixed) CORRELATION between the population parameters. The Bayesian fitting procedure takes this correlation into account.

Before the iterative procedure starts, the fixed values for the correlations can be entered and set 'fixed'.

As in case A), the correlations between the population parameters are also calculated from the individual patient parameters and shown on the screen, but these values are not used or copied to the medication screen.

(C) Assuming an UNKNOWN CORRELATION between the population parameters. ITSB estimates the correlation during the iterative procedure. The Bayesian fitting procedure takes this correlation into account.

Before the iterative procedure starts, initial values can be entered (a value '0' is the most objective choice), and set 'variable'.

If appropriate, some correlations can be set 'variable' and others 'fixed' (see under B).

The correlations between the population parameters are calculated from the above equation ($\text{Covar}_{j,k}$). The values are shown with the results, and are copied to the medication screen.

The boundaries for correlations are -0.999 to +0.999 (see below).

Method C) performs the analysis with less assumptions than methods B) and C). As a result of the increased flexibility, irregularities may occur occasionally. In exceptional cases, the correlation between two parameters increases, and may approach -1 or +1 (for technical reasons the actual boundaries in the program are -0.999 and +0.999). Such extremely high correlations are unlikely, and should be regarded carefully.

References:

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