Supplementary Material: Use of MONOLIX software version 2.4 for analysis by NLMEM of crossover bioequivalence trials

In our study, we simulate crossover data and analyse them by nonlinear mixed effects model using the SAEM algorithm implemented in the MONOLIX software version 2.4. MONOLIX is a graphical user interface software. To fit the data by MONOLIX, we use a datafile with a certain format. Each type of information of the datafile (concentration, sampling time, dose...) corresponds to a tag in MONOLIX. To simplify the use of MONOLIX, the column names in the datafile often correspond to a MONOLIX tag. A dot corresponds to a missing value. For crossover trial bioequivalence analysis, the datafile contains the following columns (with the corresponding MONOLIX tag):

- subject identification (`ID`),
- observed drug concentration (`DV`),
- sampling time (`TIME`), zero usually corresponding to the drug administration,
- individual administered dose (`DOSE`),
- indicator for dose administration (`MDV`),
- period covariate (or occasion, `OCC`),
- treatment covariate (`CAT`, generic tag for categorical covariates),

Table 1 displays the first two subjects of a file for a dataset simulated under $H_{0;80\%}$ and $S_{l,l}$ with the sparse design. The different column names are described above. The column `treat` corresponds to the treatment covariate.

ID	TIME	DV	DOSE	MDV	OCC	treat
1	0	.	4	1	1	R
1	0.25	2.55	.	0	1	R
1	3.35	7.32	.	0	1	R
1	24	1.06	.	0	1	R
1	0	.	4	1	2	T
1	0.25	4.25	.	0	2	T
1	3.35	8.76	.	0	2	T
1	24	1.7	.	0	2	T
2	0	.	4	1	1	R
2	0.25	2.93	.	0	1	R
2	3.35	6.91	.	0	1	R
2	24	1.06	.	0	1	R
2	0	.	4	1	2	T
2	0.25	2.81	.	0	2	T
2	3.35	9.75	.	0	2	T
2	24	1.9	.	0	2	T

Table 1: Example of a file for a dataset simulated under $H_{0;80\%}$ and $S_{l,l}$ with the sparse design. Only the information of the first two subjects are displayed

The Figure 1 displays the main MONOLIX window. In the main window, the user specifies the model for the between-subject variability, the covariates which do not change with periods, and the error model. The user also specifies the initial values for parameter estimation and different parameters for the algorithms (the SAEM algorithm for NLMEM parameter estimation, the importance sampling algorithm for log-likelihood estimation...).

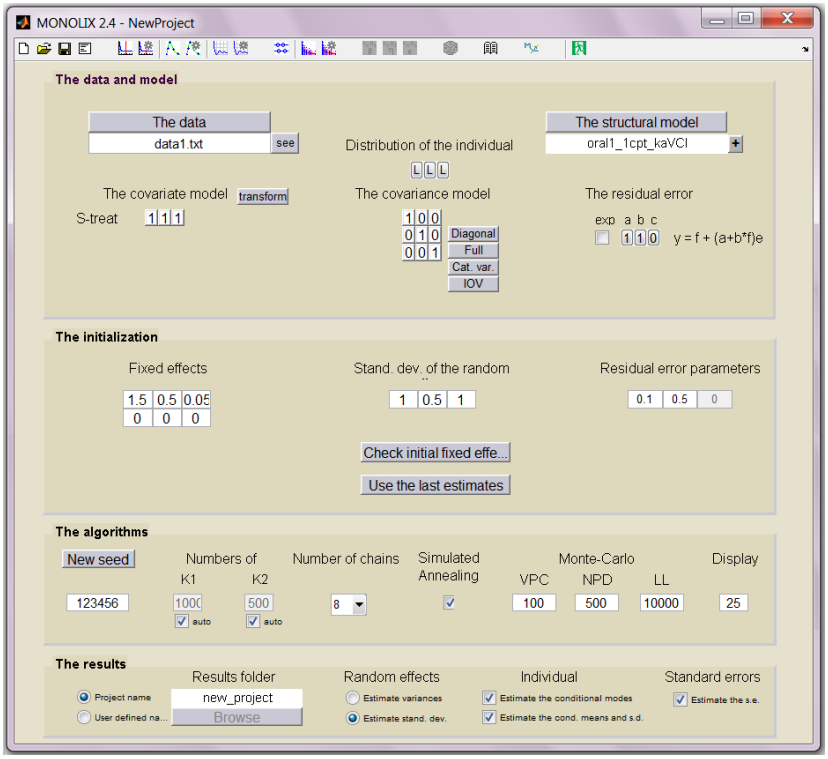

Figure 1: Main window of the graphical user interface software MONOLIX version 2.4

When the MONOLIX tag `OCC` is used in the dataset, it is possible to also define the model for the within-subject variability (or inter-occasion variability, IOV, in MONOLIX), and covariates which change with periods as the treatment and period covariates. These information are displayed in the IOV window as shown in Figure 2.

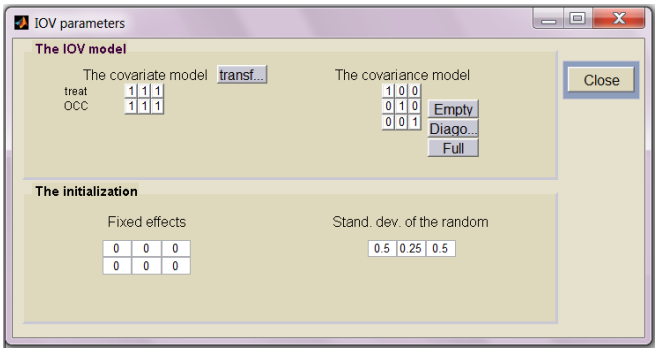

Figure 2: IOV window of the graphical user interface software MONOLIX version 2.4.

For the model-based bioequivalence analysis, we use a NLMEM including treatment, period but also sequence effects. The sequence covariate is created automatically by MONOLIX. As the column name for the treatment covariate is `treat`, the sequence covariate is denoted `S-treat`. It is displayed in the up left of the main MONOLIX window.

After specifying all needed information, the NLMEM parameter estimation is performed using the button panel on the top of the main MONOLIX window (fifth button from the left). All the parameters required for a project are saved in a binary MAT-file, as a structure array named `s`. Using the complete MATLAB version, the estimation of the NLMEM parameters (`saemmlx_iov`), of their standard errors (i.e. the Fisher information matrix estimate, `fisher_info_iov`) and of the log-likelihood (`lvraismlx_iov`) can be runned without the graphical user interface using this structure array. This is particulary useful for the estimation of several simulated datasets. In that case, a MATLAB script can be written to perform the different estimations using a "`for`" loop. This is how we proceed for our simulation study. More details and scripts are available upon request to the corresponding author.