



DDMoRe Standalone Execution Environment (SEE)

Version 2.0.0

Features and Known Issues

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1 Introduction and overview of the release

This is the Official Public Release of the MDL IDE and Interoperability Framework.

The purpose of the release is to allow access to the General Public to assess the deployment, features and usability of the system.

2 Interoperability framework features by release

		Beta release SEE Version 1.2.0 December 11 th 2015	Official release SEE Version 2.0.0 August 22 nd 2016
High-level overview			
Language standards		MDL draft 7	MDL v. 1.0
		PharmML v. 0.6.1	PharmML v. 0.8.1
Key software components		MDL-IDE v. 1.3.0	MDL-IDE v. 1.5.0
		Monolix v. 4.3.2	Monolix v. 4.3.2
		NONMEM v. 7.3	NONMEM v. 7.3
		R v. 3.0.3	R v. 3.0.3
		Xpose v. 4.5.3	Xpose v. 4.5.3
		PsN v. 4.4.8	PsN v. 4.4.8
		Simulx v. 2.1.1 (mlxR) / 1.1.0 (mlxLibrary)	Simulx v. 2.1.1 (mlxR) / 1.1.0 (mlxLibrary)
			BlackBox 1.5 / WinBUGS 1.4.3 / WBDev / PKPD Model Library 1.2
		PFIM v. 4.0	
		PopED v. 0.3.0	
Distribution/deployment			
Stand-alone execution environment		x	x
Integration within existing IT infrastructure possible			x
Features/tasks			
Estimation	Monolix	x	x
	NONMEM	x	x
	WinBUGS		x
Graphical diagnostics	R (user-defined)	x	x
	Xpose	x	x
Re-sampling/simulation-based diagnostics	Bootstrap in PsN	x	x
	VPC in PsN	x	x
Simulation	SimCyp		x
	Simulx	x	x
Optimal design	PFIM		x
	PopED		x

		Beta release SEE Version 1.2.0 December 11 th 2015	Official release SEE Version 2.0.0 August 22 nd 2016
Models supported			
Outcome types	Continuous	x	x
	Binary		⁻¹
	Count	x	²
	Categorical		⁻¹
	Time-to-event	x	³
Ways to describe the model	ODEs	x	⁴
	Analytical solutions	x	⁵
	Short-hand macro notation	x	⁶
Admin./dosing support	Single or multiple dosing	x	x
	Multiple admin. routes	x	x
	Zero- or first-order input	x	x
	Steady-state dosing	x	x
Variability model types	Inter-individual variability	x	x
	Inter-occasion variability	x	⁷
	Higher levels of variability		⁻⁸
	Correlated random effects	x	x
	Prior distributions		⁹
	Mixture models		⁻¹⁰
Covariate types	Continuous	x	x
	Categorical (binary only)	x	x

¹ Models for binary or categorical data can be specified in MDL and translated to PharmML, but downstream execution in target tools is not currently supported.

² Models for count data can be specified in MDL and translated to PharmML, but downstream execution in target tools is only supported for models of the Poisson type, and not all for WinBUGS.

³ Models for time-to-event data can be specified in MDL and translated to PharmML, but downstream execution in target tools is only supported for the exact/right-censored type, and not at all for WinBUGS.

⁴ Resolves to: ADVAN 13 + \$DES in NONMEM; ODEs in Monolix; ODEs in WinBUGS.

⁵ Resolves to: \$PRED in NONMEM; analytical solution in Monolix; analytical solution in WinBUGS.

⁶ Resolves to: ADVAN 1-4/10-12 or ADVAN 13 + \$DES in NONMEM; PK macros in Monolix; ODEs in WinBUGS.

⁷ Inter-occasion variability is not supported for WinBUGS.

⁸ Models with higher levels of variability can be specified in MDL and translated to PharmML, but downstream execution in target tools is not currently supported.

⁹ Models with prior distributions can be specified in MDL and translated to PharmML, but downstream execution is only possible for model types supported by WinBUGS.

¹⁰ Mixture models can be specified in MDL and translated to PharmML, but downstream execution in target tools is currently not supported.

3 Known issues with the current release

The following are either known issues revealed during ad-hoc testing or areas of functionality that are known to be incomplete in the current release.

SEE installation issues

1. Installation of the SEE into a path containing spaces or special characters will result in failures when attempting to execute any third-party tools. Installing the SEE into a path without spaces or special characters will resolve the problem. Similarly, installation of the SEE into a deeply-nested folder will cause path length issues, usually when copying execution output files back to the workspace project directory, so it is strongly suggested that the recommended location mentioned in the Installation Guide is used.
2. An issue with a utility specifically provided for use on Acer machines (abFiles: <http://www.acer.com/ac/en/US/content/byoc-consumer>) has been seen. This utility contains a program called 'start' which may interfere with the in-built 'start' command used in Windows. The workaround is to ensure that this program is not referenced anywhere on the Windows PATH. The manifestation of the problem is that the background services won't start up, meaning that a lot of the framework functionality is not available.

InstallationTest issues

3. When comparing InstallationTest_Aug2016.html with InstallationTest_Aug2016_reference.html, minor discrepancies have been seen for the PopED results. Specifically, the values for the last two parameters D[1,1] and D[2,2] from get_rse(FIM,poped.db) as well as the corresponding elements of the FIM may be interchanged, but this is not a problem as long as the reported values are the same.

MDL IDE issues

4. There have been instances observed where memory has been exhausted on a 4GB RAM environment with multiple projects loaded. Restarting the MDL IDE resolved the problem.
5. Auto completion of MDL code is not fully functional for all language elements.

R console issues

6. There have been instances observed where the R Console has hung and eventually an error ('RMI - R server not found') was displayed. Restarting the R Console resolved the problem.
7. The R console has been seen to 'disappear' following an MDL-IDE shutdown, possibly related to attempting to move the workspace. Restarting the IDE resolved the issue. In any case, attempting to use a workspace other than the default may work to some extent but with limited functionality, primarily in that the R console and attendant servers will not automatically start up.

General issues with execution of tasks

8. The error messages produced in the R console when failures occur in task execution can be cryptic or not specific enough to be helpful. To identify the root cause, the contents of the relevant files within the working directory or workspace directory may need to be examined.
9. It is not possible to cancel 'in-progress' jobs. Execution will continue in the background, even if control is returned to the R console.
10. The parsing of standard output into the R environment can produce a number of warning messages if the third-party tool has not populated the object as expected.

Issues for specific target tools

NONMEM

11. For models with BOV, some BOV variability parameters not defined in MDL (but used internally in NONMEM) are returned in the standard output.
12. If a CMT column is used in the data set to identify doses to multiple compartments, the number in the CMT column must map to the appropriate ODE. If COMPARTMENTS are used in combination with ODEs to define structural models, the user should keep in mind that the extra ODEs derived from the COMPARTMENTS will be placed first in the list.
13. A bug has been identified, when a COMPARTMENT construct with "type is direct" is used in combination with ODEs for oral administration (UC4_3). This can be avoided by using "type is depot", which implicitly gives the dose to a depot compartment (UC4_2).

Monolix

14. In some cases, when using a proportionalError model, the residual error parameters are not being returned in the standard output.
15. There is a bug in the current version of Monolix, which means that the ADDL data item is not handled properly for models with steady-state dosing.

Xpose

16. When creating an Xpose database using as.xpdb, the DVID column, if present in the data set, is not taken into account, and predictions and observed data may therefore be incorrectly matched. This may for example be an issue for simultaneous PKPD models in Monolix.
17. For BOV models (UC8), the occasion label OCC is not populated in the Xpose database, which means that plots have panel label "NA: 1". This is easily fixed by editing the Xpose database object directly in R (e.g. `nm.xpdb@Labels$OCC <- "OCC"`) to change the label.
18. It is not possible to create an Xpose database object following all model executions. One example is for discrete data models.

PsN

19. After a bootstrap execution, the order of the parameters in the output may be different from the order defined in the MDL model.
20. If variability parameters are specified on a standard deviation scale, the bootstrap process will run properly, but the summary statistics will be returned on a variance scale.

WinBUGS

21. There have been instances, where WinBUGS does not execute due to problems with user permissions. The exact cause is unknown and no workaround is available yet.

22. Three of the UseCases in the 'Priors' folder (example331, UseCase1_PRIOR, UseCase1_PRIOR_Cauchy) cannot be estimated in WinBUGS due to a limitation of WinBUGS.

Simulx

23. It is not yet possible to use models involving categorical covariates for simulation in Simulx.

Interoperability issues and things to consider in MDL code

Data Object

DATA_INPUT_VARIABLES

24. If time is used as idv, the variable name used in the MDL needs to be TIME. Otherwise the SO is not correctly populated for Monolix.

25. If covariates are used in the model, the name given to the covariate in MDL needs to match the name in the data set header, taking also into account lower or upper cases, because Monolix uses the header name to retrieve the covariate information.

26. Standard NONMEM ignore statements are not supported in the current version. Any data processing needs to be done before using the data set for a task in Monolix or NONMEM. Special treatment of the header row for NONMEM is not needed since a logic to ignore that row is automatically implemented.

DATA_DERIVED_VARIABLES

27. Data derived variables are only partially supported by the WinBUGS converter. Variables defined with "use is doseTime" or "use is doseInterval" are not allowed.

Parameter Object

STRUCTURAL

28. Structural parameters without IIV need to be redefined in the INDIVIDUAL_PARAMETER block. Otherwise they are not correctly translated for Monolix.

29. Lag time parameters do not have a keyword that can be recognized by the target tools, unless COMPARTMENTS are used to define the structural model. This means that the lag time mechanism has to be explicitly defined in the model and estimation of IIV is not supported when using FOCE or FOCEI in NONMEM.

30. Bioavailability parameters do not have a keyword that can be recognized by the target tools, unless COMPARTMENTS are used to define the structural model. This means that bioavailability has to be implemented in the model equations. This also implies that bioavailability cannot be used to scale/define the initial amount in a compartment (common practice in previous versions of NONMEM to initialise compartments).

VARIABILITY

31. The name used for the "use is varlevel" variable cannot contain an underscore when using NONMEM.

Model Object

GROUP_VARIABLES

32. Any statement (definition of variables or transformation of covariates) placed into GROUP_VARIABLES will make the model incompatible with Monolix.

33. Monolix only supports the linear or "linear after transformation" relation between time invariant covariates, structural parameters and random effects ("type is linear" definition

of individual parameters). No other transformation of the structural parameters will be compatible with Monolix.

INDIVIDUAL_VARIABLES

34. To be compatible with Monolix, INDIVIDUAL_VARIABLES may only contain two types of statements:

- “Type is linear” declarations of individual parameters.
- Simple assignments to define parameters without IIV (e.g. BASE=POP_BASE). Non-IIV parameters defined through simple assignments are assumed to be normally distributed, i.e. they can become negative. If positivity is desired, a type 3 definition has to be used, and IIV fixed to 0.

MODEL_PREDICTION

35. To be compatible with Monolix, any variable used in MODEL_PREDICTION must be either:

- The independent variable.
- Defined in MODEL_PREDICTION.
- Declared in INDIVIDUAL_VARIABLES in the way stated above.
- Defined as a covariate in MDL.
- Defined as a DATA_DERIVED_VARIABLE.

This implies in particular that STRUCTURAL_PARAMETERS, VARIABILITY_PARAMETERS, and random variables defined in RANDOM_VARIABLES_DEFINITION cannot be used in MODEL_PREDICTION.

OBSERVATION

36. Only standard residual error model functions are supported. This means that equation based assignments are not supported in this block.

37. For Monolix compatibility, different observation types have to use different STRUCTURAL_PARAMETERS and random variables.

Prior Object

38. The WinBUGS converter does not support non-parametric and empirical distributions, meaning that the NonParametric and MultiNonParametric distributions in MDL are not supported.

39. WinBUGS has limited support of some multivariate distributions, such as the Wishart distribution. In particular, as reported in the WinBUGS manual “Dirichlet and Wishart distributions may only be used as conjugate priors and must have known parameters (although there does exist a trick for allowing unknown Dirichlet parameters); in contrast, multinomial distributions may not be used as priors and the order N of the distribution must be known; multivariate normal and Student-t distributions can be used anywhere in the graph (i.e. as prior or likelihood) and there are no restrictions regarding their parameters. See the Constraints on using certain distributions section of the WinBUGS user’s guide.”