Description of UseCase models in MDL

A set of UseCases (UCs) has been prepared to illustrate how different modelling features can be implemented in the Model Description Language or MDL. These UseCases are located in the "models" folder under the UseCasesDemo project pre-configured in the MDL-IDE.

All of the UCs included can be converted to PharmML, and downstream conversion for execution in target tools is also supported for most of them. For these UCs, R scripts demonstrating how these UC models can be used in M&S workflows involving several target tools are available in the "scripts" folder - also located under the UseCasesDemo project.

The key characteristics represented in each UC are summarized in Table I, which also shows which UCs have R scripts available, and which of these are considered interoperable – meaning that estimation is possible in both NONMEM and Monolix. Even if not shown in the R scripts, several of these UCs can also be run in WinBUGS if you add suitable prior and task objects. More specifically, for all of the UCs marked with '+ WB' in Table I, valid WinBUGS code can be produced. However, for some models/priors you can experience numerical difficulties due to limitations in WinBUGS.

More detailed descriptions of the UCs with R scripts available are given in the following sections, and instructions on how to run the R scripts are given in the last section of this document.

Included in the UseCasesDemo project are also UCs specifically for estimation in WinBUGS and optimal design using PFIM and PopED. MDL files and R scripts for these UCs are located in the 'Priors' and 'Design' subfolders of the 'models' and 'scripts' folders in the UseCasesDemo project.

Table I: Brief description of UseCases (UCs)

UC ID	Data file	Description	R script available	Inter-operable
UC1	warfarin_conc.csv	PK model, single oral dose, ODEs	YES	YES + WB
UC1_1	warfarin_conc.csv	UC1 + extended task properties	YES	YES + WB
UC2	warfarin_conc.csv	PK model, single oral dose, analytical solution	YES	YES + WB
UC2_1	warfarin_conc.csv	UC2 + DATA_DERIVED_VARIABLES for DoseTime (DT)	YES	YES
UC2_2	warfarin_conc _analytic.csv	UC2 + Dose (D) and DoseTime (DT) as DATA_INPUT_VARIABLES	YES	YES
UC3	warfarin_conc_pca.csv	Simultaneous PKPD model	YES	YES + WB
UC3_1	warfarin_conc_pca _PKparam.csv	UC3 + individual PK parameters as DATA_INPUT_VARIABLES	YES	YES
UC4	warfarin_infusion _oral.csv	PK model, multiple administration routes, ODEs	YES	YES
UC4_1	warfarin_infusion _oral.csv	UC4 + COMPARTMENTs instead of ODEs	YES	YES + WB
UC4_2	warfarin_infusion _oral.csv	UC4 + COMPARTMENT input (depot / direct) to ODEs	YES	YES + WB
UC4_3	warfarin_infusion _oral.csv	UC4 + COMPARTMENT input (direct / direct) to ODEs	YES	Monolix only + WB
UC5	warfarin_conc_sexf.csv	PK model with a categorical covariate and covariate transformations	YES	YES + WB
UC5_1	warfarin_conc_sexf.csv	UC5 + GROUP_VARIABLE fixed effects + INDIVIDUAL_VARIABLEs as equations	NO	Not tested
UC5_2	warfarin_conc_sexf.csv	UC5 + GROUP_VARIABLE fixed effects + “general” INDIVIDUAL_VARIABLEs.	NO	Not tested
UC6	warfarin_conc.csv	PK model with correlation between random effects	YES	YES + WB
UC6_1	warfarin_conc.csv	UC6 + pairwise correlation (instead of covariance) in Model Object.	NO	Not tested
UC6_2	warfarin_conc.csv	UC6 + MultivariateNormal distribution for random effects.	NO	Not tested
UC6_3	warfarin_conc.csv	UC6 + Multivariate Student T distribution for random effects.	NO	Not tested
UC7	warfarin_conc_cmt.csv	PK model, single oral dose, expressed using COMPARTMENTs	YES	YES + WB
UC8	warfarin_conc_bov_P4 _sort.csv	PK model with inter-occasion variability	YES	YES
UC8_1	warfarin_conc_bov_P4 _sort.csv	UC8 + GROUP_VARIABLE definition of fixed effects	NO	Not tested

UC ID	Data file	Description	R script available	Inter-operable
UC9	warfarin_infusion.csv	PK model, IV infusion, expressed using COMPARTMENTs	YES	YES + WB
UC10	warfarin_conc_cmt.csv	PK model, two compartments, expressed using COMPARTMENTS (CL, VC, VP, Q)	YES	YES + WB
UC10_1	warfarin_conc_cmt.csv	UC10 + parameterised as V, K, K23, K32.	NO	Not tested
UC11	count.csv	Poisson count data model	YES	YES
UC11_1	count.csv	UC11 + Negative Binomial distribution for outcome.	NO	Not tested
UC12	binary.csv	Binary outcome data (Bernoulli distribution for outcome)	NO	Not tested
UC12_1	binary.csv	UC12 + Binomial distribution for outcome (with n=1)	NO	Not tested
UC12_2	binomial.csv	UC12 + Binomial outcome with n taken from DATA_INPUT_VARIABLES	NO	Not tested
UC13	category.csv	Categorical outcome data (unordered)	NO	Not tested
UC13_1	category.csv	UC13 + ordered categorical	NO	Not tested
UC14	warfarin_TTE_exact.csv	Time to event data, exact/right-censored	YES	YES
UC14_1	warfarin_TTE_exact.csv	UC14 + ODE for integration of the hazard	YES	Monolix only
UC14_2	warfarin_TTE_exact.csv	UC14 + ODE for integration of the hazard	YES	NONMEM only
UC15	warfarin_conc_lnDV.csv	Model of log-transformed data	NO	Not tested
UC15_1	warfarin_conc_lnDV.csv	UC15 + user-defined error model.	NO	Not tested
UC16	warfarin_conc_blq.csv	BLQ handling	NO	Not tested
UC17	warfarin_conc_SS.csv	Steady state dosing	YES	YES
UC17_1	warfarin_conc _SSADDL.csv	UC17 + ADDL in DATA_INPUT_VARIABLES	YES	NONMEM only
UC19	warfarin_conc_ Parent_Metabolite.csv	L2 - correlated EPS for modelling parent and metabolite data	NO	Not tested
UC20	warfarin_conc.csv	Transit compartment model	NO	Not tested
UC21	warfarin_conc.csv	Mixture model	NO	Not tested
UC21_1	warfarin_conc.csv	UC21 + RANDOM_VARIABLE_DEFINITION cat. cov. to describe mixture population.	NO	Not tested
UC22	warfarin_conc_cmt.csv	Latent compartment PK model	NO	Not tested
UC23	warfarin_conc.csv	Model with conditional assignment in observation model	NO	Not tested

UseCase1

Warfarin population pharmacokinetic model using ordinary differential equations (ODEs)

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AMT : Total drug administered [mg]
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

Structural model:

- 1 compartment model using ODE (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

<u>Inter-individual variability:</u>

- Exponential model for V, CL, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL and V random variables expressed in correlation scale

<u>Residual error model:</u>

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase1_1

Variant of UseCase1 with extended task properties.

This variant has the same dosing regimen, data set, structural model, covariate model, and variability model as UseCase1, but contains three (more detailed) task objects:

- SAEM_task with specific TARGET_SETTINGS for SAEM estimation in NONMEM or Monolix
- BUGS_task with specific TARGET_SETTINGS for MCMC estimation in WinBUGS
- FOCEI_task with specific TARGET_SETTINGS for FOCEI estimation in NONMEM.

UseCase2

Warfarin population pharmacokinetic model using analytical solution

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AMT : Total drug administered [mg]
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

Structural model:

- 1 compartment model using analytical solution (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\mathrm{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \mathrm{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for V, CL, k_a and TLAG expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \quad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL and V random variables expressed in correlation scale

Residual error model:

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \quad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase2_1

Variant of UseCase2 with calculation of dosing time in DATA_DERIVED_VARIABLES.

This variant has the same dosing regimen, data set, structural model, covariate model, and variability model as UseCase2, except that dosing time (DT) is calculated in DATA_DERIVED_VARIABLES and used instead of time (T) in the MODEL_PREDICTION.

UseCase2_2

Variant of UseCase2 where dose amount and dosing time are passed in from the data set.

This variant has the same dosing regimen, structural model, covariate model, and variability model as UseCase2, but uses a different data set with dose amount (D) and dosing time (DT) as extra columns.

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- DT : Dosing time [h]
- WT : Patient's weight [kg]
- D : Total drug administered [mg]
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

UseCase3

Population pharmacokinetic and pharmacodynamic model to describe warfarin PK and PCA response

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AGE [years]
- SEX (0: female, 1: male)
- AMT : Total drug administered [mg]
- DVID : Dependent variable identifier (0: dose, 1:PK measurement, 2: PD measurement)
- DV : Warfarin concentration [mg/L] or PCA measurement
- MDV : Missing dependent variable (0: observation, 1: dosing record)

Structural model:

PK model

- 1 compartment model specified with COMPARTMENTs (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

PD model

- Indirect response model
- 0 order synthesis (RCPA) and 1st order elimination (KPCA)
- Inhibitory effect of drug concentration on RPCA (synthesis) using an Emax model (EMAX, C50)

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for V, CL, k_a, TLAG (this last fix to 0.1), PCA0, C50 and TEQ (ln(2)/KPCA) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Linear model for EMAX

$$\theta_i$$

- Correlation between CL and V random variables expressed in correlation scale

Residual error model:

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \quad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var(y_{i,j}) = g^2$$

- Combined error model for warfarin

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

- Additive error model for PCA

$$g = RUV\_ADD$$

UseCase3_1

Variant of UseCase3, where only the PCA response is fitted, given the individual estimates of the PK model parameters, i.e. the PD part of a sequential PKPD model fit, using the IPP approach.

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AGE [years]
- SEX (0: female, 1: male)
- AMT : Total drug administered [mg]
- DVID : Dependent variable identifier (0: dose, 2: PD measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- CL : Individual estimate of CL [L/h]
- V : Individual estimate of V [L]
- KA : Individual estimate of KA [1/h]
- TLAG : Individual estimate of TLAG [h]

Structural model:

PK model

- 1 compartment model specified with COMPARTMENTs (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process
- Individual estimates from previous PK model fit used as input (IPP approach)

PD model

- Indirect response model
- 0 order synthesis (RCPA) and 1st order elimination (KPCA)
- Inhibitory effect of drug concentration on RPCA (synthesis) using an Emax model (EMAX, C50)

Covariate model:

- None.

Variability model:

Inter-individual variability:

- Exponential model for PCA0, C50 and TEQ (ln(2)/KPCA) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Linear model for EMAX

$$\theta_i$$

Residual error model:

- Additive error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \qquad var(y_{i,j}) = g^2$$

$$g = RUV\_ADD$$

UseCase4

Warfarin population pharmacokinetic model for multiple dosing via different administration routes

Dosing regimen: intravenous infusion followed by oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AMT : Total drug administered [mg]
- RATE : Infusion rate [mg/h]
- CMT : Compartment number (1: absorption compartment, 2: central compartment)
- DV : Warfarin concentration [mg/L]
- logtWT : Log transformed patient's body weight standardised to 70 kg
- MDV : Missing dependent variable (0: observation, 1: dosing record)

Structural model:

- 1 compartment model using ODE (V, CL, k_a, TLAG, FORAL)
- 1st order absorption process with lag time and bioavailability for oral administration
- 0 order input for intravenous infusion
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

<u>Inter-individual variability:</u>

- Exponential model for V, CL, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Logit model for FORAL expressed as standard deviation

$$logit(\theta_i) = logit(\theta)$$

- Correlation between CL and V random variables expressed in correlation scale

<u>Residual error model:</u>

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase4_1

Variant of UseCase4 using COMPARTMENTs

This variant has the same dosing regimen, data set, structural model, covariate model, and variability model as UseCase4, except that COMPARTMENTs are used to specify the structural model in MODEL_PREDICTION.

UseCase4_2

Variant of UseCase4 using a combination of COMPARTMENTs and ODEs

This variant has the same dosing regimen, data set, structural model, covariate model, and variability model as UseCase4, except that in MODEL_PREDICTION a COMPARTMENT construct with ‘type is depot’ is used to specify the target compartment, bioavailability and lag time for the oral dose and a COMPARTMENT construct with ‘type is direct’is used to specify the target compartment for the iv dose. This variant only has one ODE specified (the central compartment), because ‘type is depot’ implicitly gives the extra depot ODE.

UseCase4_3

Variant of UseCase4 using a combination of COMPARTMENTs and ODEs

This variant has the same dosing regimen, data set, structural model, covariate model, and variability model as UseCase4, except that MODEL_PREDICTION two COMPARTMENT constructs with ‘type is direct’ are used to specify the target compartment, bioavailability and lag time for the oral dose and the target compartment for the iv dose. This variant has two ODEs specified (the depot compartment and central compartment), because ‘type is direct’ does not imply extra ODEs.

UseCase5

Warfarin population pharmacokinetic model incorporating categorical and transformed covariates

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AGE [years]
- SEXF (0: male, 1: female)
- AMT : Total drug administered [mg]
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)

Structural model:

- 1 compartment model using COMPARTMENTs (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles
- SEX and AGE on CL with an exponential model

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \times e^{\beta_{SEX=1}} \times e^{\beta(AGE-40)} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for V, CL, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL and V random variables expressed in correlation scale

Residual error model:

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase6

Warfarin population pharmacokinetic model with correlation block

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AMT : Total drug administered [mg]
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

Structural model:

- 1 compartment model using COMPARTMENTs (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for V, CL, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL, V and k_a random variables expressed in correlation scale

Residual error model:

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase7

Warfarin population pharmacokinetic model using COMPARTMENTs

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AMT : Total drug administered [mg]
- CMT : Compartment number (1: absorption compartment)
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

Structural model:

- 1 compartment model using COMPARTMENTs (V, CL, k_a, TLAG, FORAL)
- 1st order absorption process with lag time and bioavailability (fixed to 1)
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

<u>Inter-individual variability:</u>

- Exponential model for V, CL, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL and V random variables expressed in correlation scale

<u>Residual error model:</u>

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase8

Warfarin population pharmacokinetic model with between occasion variability (BOV)

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AGE [years]
- SEX (0: female, 1: male)
- AMT : Total drug administered [mg]
- OCC : Occasion identifier (1: 1st occasion , 2: 2nd occasion)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)

Structural model:

- 1 compartment model using COMPARTMENTs (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for V, CL, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

Between occasion variability:

- Between occasion variability on V and CL
- Correlation between CL and V between occasion random variables expressed in correlation scale

Residual error model:

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase9

Warfarin population pharmacokinetic model

Dosing regimen: intravenous infusion

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AMT : Total drug administered [mg]
- RATE : Infusion rate [mg/h]
- DV : Warfarin concentration [mg/L]
- logtWT : Log transformed patient's body weight standardised to 70 kg

Structural model:

- 1 compartment model using COMPARTMENT (V, CL)
- 0 order input
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for V and CL expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL and V random variables expressed in correlation scale

Residual error model:

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase10

Two-compartment warfarin population pharmacokinetic model using COMPARTMENTs

Dosing regimen: single oral administration

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AMT : Total drug administered [mg]
- CMT : Compartment number (1: absorption compartment)
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

Structural model:

- 2 compartment model using COMPARTMENTs (VC, CL, VP, Q, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

Covariate model:

- WT on CL and VC following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_VC} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for VC, CL, VP, Q, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL and VC random variables expressed in correlation scale

Residual error model:

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase11

Poisson count data model

Dosing regimen: NA

Dataset:

- ID : Patient identifier (n=100)
- TIME [h]
- CP : Drug concentration acting as covariate [mg/L]
- DV : Number of counts
- MDV : missing dependent variable (0: observation, 1: dosing record)

Statistical model:

- Poisson distribution model

Covariate model:

- Linear effect of drug concentration on baseline count parameter on the logarithmic domain to ensure parameter positivity

Variability model:

Inter-individual variability:

- Exponential model for baseline count parameter expressed as variance

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

UseCase14

Time to event model for exact and right censored information

Dosing regimen: NA

Dataset (only mentioning the columns used in the model):

- ID : Patient identifier (n=32)
- TIME [h]
- TRT : Treatment identifier
- DV : Event identifier (0: no event or right censored, 1: event at exact time)

Statistical model:

- Constant hazard model

Covariate model:

- Proportional covariate model of treatment on the baseline hazard

UseCase14_1

Variant of UseCase14 using an ODE for integration of the hazard function

This variant has the same data set, statistical model and covariate model as UseCase14, but shows how to use an ODE (here with derivative 0) for integration of the hazard function.

The treatment covariate effect is implemented in the MODEL_PREDICTION in this case.

UseCase14_2

Variant of UseCase14 using an ODE for integration of the hazard function

This variant has the same data set, statistical model and covariate model as UseCase14, but shows how to use an ODE (here with derivative 0) for integration of the hazard function.

The treatment effect is implemented in the GROUP_VARIABLES in this case.

UseCase17

Warfarin population pharmacokinetic model at steady-state using SS and II

Dosing regimen: multiple oral administrations

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AGE [years]
- SEX (0: female, 1: male)
- AMT : Total drug administered [mg]
- SS : Steady-state
- II : Dosing interval
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

Structural model:

- 1 compartment model using COMPARTMENTs (V, CL, k_a, TLAG)
- 1st order absorption process with lag time
- 1st order elimination process

Covariate model:

- WT on CL and V following allometric principles

$$\text{POP\_CL} \times \left(\frac{WT}{70}\right)^{0.75} \qquad \text{POP\_V} \times \left(\frac{WT}{70}\right)^{1}$$

Variability model:

Inter-individual variability:

- Exponential model for V, CL, k_a and TLAG (this last fix to 0.1) expressed as standard deviation

$$\theta_i = \theta \times e\exp\left(\eta_{\theta_i}\right) \qquad \eta_{\theta_i} \sim \mathcal{N}(0, \omega_\theta)$$

- Correlation between CL and V random variables expressed in correlation scale

Residual error model:

- Combined error model

$$y_{i,j} = IPRED + g \times \varepsilon_{i,j} \qquad \varepsilon_{i,j} \sim \mathcal{N}(0,1) \quad var\left(y_{i,j}\right) = g^2$$

$$g = RUV\_ADD + RUV\_PROP \times IPRED$$

UseCase17_1

Variant of UseCase17 using ADDL.

This variant has the same dosing regimen, structural model, covariate model, and variability model as UseCase17, but uses a different data set with ADDL in addition to SS and II.

Dataset:

- ID : Patient identifier (n=32)
- TIME [h]
- WT : Patient's weight [kg]
- AGE [years]
- SEX (0: female, 1: male)
- AMT : Total drug administered [mg]
- SS : Steady-state
- ADDL : Additional doses
- II : Dosing interval
- DVID : Dependent variable identifier (0: dose, 1:PK measurement)
- DV : Warfarin concentration [mg/L]
- MDV : Missing dependent variable (0: observation, 1: dosing record)
- logtWT : Log transformed patient's body weight standardised to 70 kg

Implementing M&S workflows using the ddmore R package

Along with the collection of UC models in MDL, a set of R scripts (located in the 'scripts' sub-folder of the UseCasesDemo project) have been prepared to illustrate how these models can be used in M&S workflows with the "ddmore" R package:

- Initialisation of the R console
- Reading and parsing MDL files in R
- Exploratory graphical analysis of the data
- Parameter estimation with Monolix
- Evaluation of the model executed in Monolix using Xpose
- Parameter estimation of the same model with NONMEM
- Evaluation of the model executed in NONMEM using Xpose
- Changing estimation method to FOCEI and re-estimation of the model via PsN
- Bootstrap in PsN to evaluate parameter precision
- Performing a Visual Predictive Check (VPC) in PsN using MLE values from NONMEM
- Simulating new observed values using the simulx function in the mlxR package
- Performing Bayesian estimation in WinBUGS (scripts in 'Priors' sub-folder)
- Performing optimal design in PFIM or PopED (scripts in 'Design' sub-folder)

Please note that R scripts are not available for all UCs, and there are also some cases were not all of the above-mentioned steps are included. All the R scripts have been commented to guide users through the code and provide information regarding the new 'ddmore' R functions. Additional information about the functions can be obtained from the R help by typing the name of the function after "?" (e.g. ? as.PharmML) or by directly navigating through the help files.

Execution of R scripts

There are different ways of executing the R scripts. It is recommended to run the scripts line by line to get familiarised with the different functions and the output produced. However, given that execution of some tasks might take several minutes and in some cases up to an hour, two alternative mechanisms are possible: (i) the "source" option and (ii) the "spin" function of the knitr R package.

To run the R script line by line:

- Navigate to the ./scripts subfolder
- Open the relevant file in the MDL-IDE editor by double-clicking. Select any code lines you wish to execute by marking them with your cursor, and press CTRL+R+R to execute them. You can also modify the code to explore different options.
- Execution has ended once the cursor in the console appears highlighted in blue again

When using this option, and depending upon the command executed, the results will be returned to your workspace (e.g. folder containing the results of an estimation in Monolix, generation of pdf files), to your console (e.g. information of the estimation process, evaluation of the results) or to the R graphics window (e.g. plot of data).

To run the R script via source:

- Navigate to the ./scripts subfolder
- Right click on the R file named you wish to execute. Then select --> "Run as" --> "R script in R submitting directly".
- Execution has ended once the cursor in the console appears highlighted in blue again

This option will also return information as if the code would have been run line by line.

To run the R script via the spin function:

- load the knitr library, e.g. library(knitr)
- Spin the file using the full path to the R script, e.g.
  spin(file.path(Sys.getenv("MDLIDE_WORKSPACE_HOME"),
  "UseCasesDemo","scripts","UC2_Prod5.R"))
- Execution has ended once the cursor in the console appears highlighted in blue again

This option will return the results to your workspace, and will also generate an html report collecting all the commands and their respective output.

If you have any question or experience any problem while executing the R scripts, do not hesitate to contact us via the DDMoRe Forum (http://www.ddmore.eu/forum).