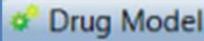


Simulation Overview

1. Drug-Disease model
2. Clinical Trial
3. Analysis of output

Drug-Disease Model: step by step



Define structural equations in the **Structural Equations** section (anything that changes continuously)

$$\begin{aligned} dA_0 &= -KA \cdot A_0 \\ dA_1 &= KA \cdot A_0 - KE \cdot A_1 \\ C &= A_1 / V_1 \\ EFF &= E_{max} \cdot C / (EC_{50} + C) \end{aligned}$$



Add model parameters in the **Model Parameters** section

$$\begin{aligned} KA &= 0.5 \\ V_1 &= 10 \\ CL &= 4 \\ KE &= CL / V_1 \\ E_{max} &= 2 \\ EC_{50} &= 0.3 \end{aligned}$$

Use the Live View to verify your model implementation

Define variability on model parameters

$$\begin{aligned} KA &= TV_{KA} \cdot \exp(E_{KA}) \\ V_1 &= TV_{V1} \cdot \exp(E_{V1}) \\ CL &= TV_{CL} \cdot \exp(E_{VCL}) \\ E_{max} &= TV_{E_{max}} \\ EC_{50} &= TV_{EC_{50}} \end{aligned}$$

Add population estimates in the **Replicate Variability** section

Without parameter uncertainty
 $TV_{KA} = 0.5$
 $TV_{CL} = 4$



To create correlated distributions, drag and drop elements together into a single group

With parameter uncertainty
 Add distributions for all population parameters



| Name | Type | Min | Max | Mean | Sd |
|----------|--------|------|-----|------|-----------|
| THETA_KA | Normal | -Inf | Inf | 1.00 | 0.10*1.00 |
| THETA_V | Normal | -Inf | Inf | 70.0 | 0.12*70 |
| THETA_CL | Normal | -Inf | Inf | 4.00 | 0.31*4 |
| OMEGA_KA | Normal | -Inf | Inf | 0.31 | 0 |
| OMEGA_V | Normal | -Inf | Inf | 0.24 | 0 |
| OMEGA_CL | Normal | -Inf | Inf | 0.35 | 0 |

Add inter-individual variability in the **Subject Variability** section

| Name | Type | Min | Max | Mean | Sd | Variance |
|--------|--------|------|-----|------|----|----------|
| ETA_KA | Normal | -Inf | Inf | 0 | | OMEGA_KA |
| ETA_V | Normal | -Inf | Inf | 0 | | OMEGA_V |
| ETA_CL | Normal | -Inf | Inf | 0 | | OMEGA_CL |

Add Residual Error and the model estimation into **Event Variability**

Event Variability
 ERR (Independent)
 ERR Type=Normal min=-Inf max=Inf mean=0 sd=0.2
 C_OBS A1/V1*exp(ERR)

Use the Live View to verify your model implementation

Sample (or bootstrap) covariates in **Population Covariates**

Population Covariates
 BW (Independent)
 BW Type=Normal min=40 max=150 mean=70 sd=15

And add the effect into **Model Parameters**

$$\begin{aligned} CL &= TV_{CL} \cdot \exp(E_{VCL}) \cdot (BW/70)^{0.75} \\ V_1 &= TV_{V1} \cdot \exp(E_{V1}) \cdot (BW/70)^{1} \end{aligned}$$

Conditional Events

Conditional Events

Uptitrate if too low

Define **Model Parameters** the will influence your simulation

$$DOSE = 50$$

Use DOSE in your treatment

Then define the conditional event

When something is evaluated

As a predefined Schedule
 As an Initial Time and a Frequency

Whether it actually applies

A Boolean expression
 $CONC < 2.5$

The effect

$$DOSE \leftarrow DOSE + 10$$

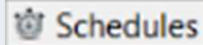
Clinical Trial : step by step

Define number of patients in



| Name | Subjects |
|------------------|----------|
| Study enrollment | 120 |

Define when treatment and observations happen in



Name: **Rich sampling**
 Times: **1; 2; 4; 8; 2d; 3d**
 Repeat every **1w**
 For a duration of **12w**

Base time unit: HOUR

Define when to observe things in



When to observe?
Schedule Rich Sampling

What to observe?
C, C_OBS

Add treatments in



- Add a Study Arm
- Add a Treatment
 When: **Schedule Every day**
 Administer into: **A0**
 Nominal dose: **150**
 Dose adjustment function
3. Function 2 * BW #2mg/kg

Note: add multiple Treatments in a single Study Arm for combination treatments

Define your trial structure in



Add a **Sequence** for every group of patients

Assign treatments to each group

Launch a simulation in



- Add a simulation
- Launch the simulation

Analysis of output

```
library(plyr)
setwd("C:/Users/MyName/Desktop/simulation-
results/MySimulation")
files <- list.files(pattern="*.csv", recursive=T,
full.names=T)
db <- adply(files, 1, read.csv, .id="replicate")
db$file <- files[db$replicate]

library(ggplot2)
db <- subset(db, eventType=="OBS")
ggplot(db, aes(x=t, y=CONC, col=factor(sequence))) +
geom_line(aes(group=subject)) + stat_summary(fun.data =
"mean_cl_boot")
```

Tips and tricks

- Use the Live View to understand the model behaviour, before implementing the Clinical Trial
- Contact us at life.exprimio.simulo@sgs.com with any questions or comments.
- Visit www.exprimio.com/simulo for continued updates, video tutorials and case examples