Simulo
Quick Reference
(November 2017)

Simulation Overview

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

Drug-Disease Model: step by step

Drug Model

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

```
dA0 =  -KA*A0
dA1 =  KA*A0 - KE*A1
C =    A1 / V1
EFF =  Emax*C/(EC50+C)
```

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

```
KA =   0.5
V1 =   10
CL =   4
KE =   CL / V1
Emax = 2
EC50 = 0.3
```

Use the Live View to verify your model implementation

Define variability on model parameters

```
KA =   TVKA * exp(EKA)
V1 =   TVV1 * exp(EV1)
CL =   TVCL * exp(EVCL)
Emax = TVEmax
EC50 = TVEC50
```

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

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

Without parameter uncertainty

```
TVKA = 0.5
TVCL = 4
```

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	S...	OMEGA_KA
ETA_V	Normal	-Inf	Inf	0	S...	OMEGA_V
ETA_CL	Normal	-Inf	Inf	0	S...	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**

```
CL = TVCL * exp(EVCL) * (BW/70)^0.75
V1 = TVV1 * exp(EVV1) * (BW/70)^1
```

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 <- DOSE + 10**

Clinical Trial : step by step

Define number of patients in **Enrollment**

Name	Subjects
Study enrollment	120

Define when treatment and observations happen in **Schedules**

```
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 **Observations**

```
When to observe?
Schedule Rich Sampling

What to observe?
C, C_OBS
```

Add treatments in **Treatments**

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

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`

Define your trial structure in **Protocol**

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

Assign treatments to each group

Launch a simulation in **Simulations**

Add a simulation

Launch the simulation

Analysis of output

```
library(plyr)
setwd("C:/Users/Ruben/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.exprimo.simulo@sgs.com with any questions or comments.

Visit www.exprimo.com/simulo for continued updates, video tutorials and case examples