Open Systems Pharmacology

MoBi and R-Toolbox

April 2021

- OSP software landscape
- PK-Sim vs. MoBi: when to use
- MoBi: Overview
- MoBi: modeling concepts
  - Building blocks
  - „Generic“ modeling
- R-Toolbox

OSP software landscape

Import

Excel® CSV
NONMEM® SBML

Export

Excel® CSV
PDF JSON

Modeling Tools

PK-Sim®
PBPK modeling & simulation

MoBi®
Biological modeling & simulation

Qualification Framework

OSP Model exchange format (**PKML**)

R packages

- Reporting Engine
- Plot-Library (TLF)
- PI (in dev.)

…

OSP Toolboxes / Interfaces

R (statistical computing)

Matlab (technical computing)
Deprecated!

Validation/Automation Tools

- Installation Validator
- Command Line Interface (CLI)

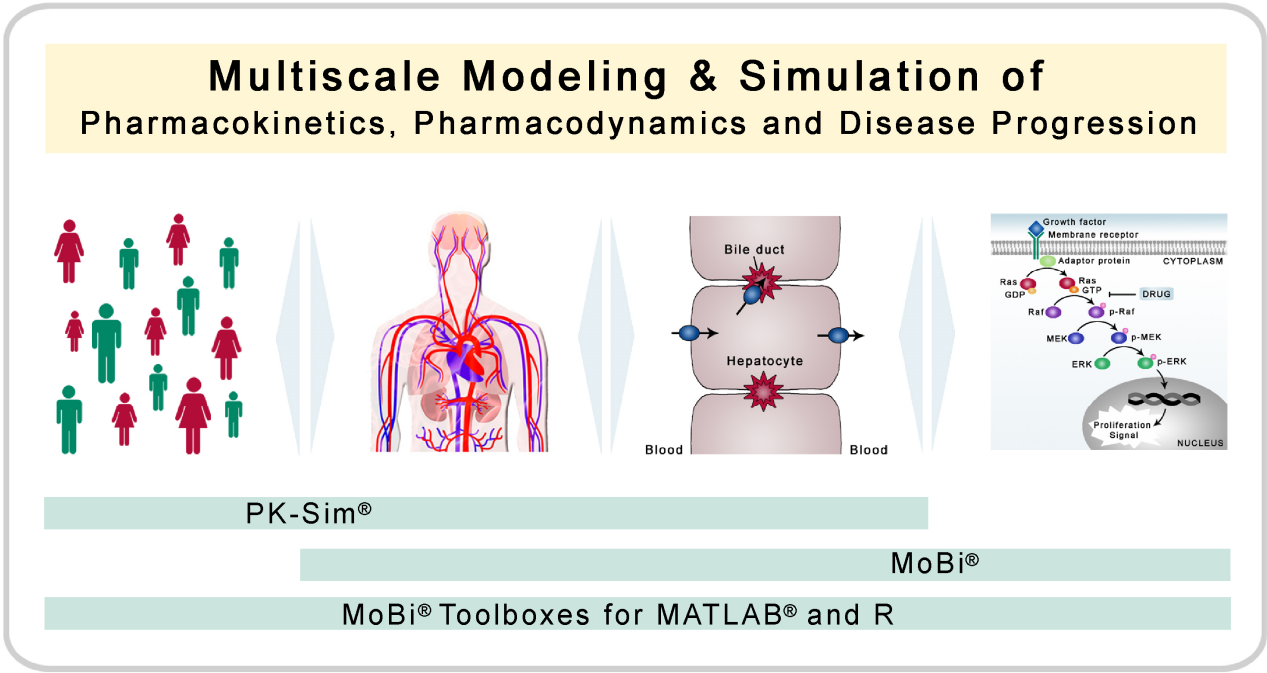
…

OSP Modeling Tools: PK-Sim and MoBi

- PK-Sim® is a comprehensive software tool for **whole-body physiologically based pharmacokinetic (PBPK) modeling**.
- Like most PBPK modeling tools, **PK-Sim® is designed for use by non-modeling experts and only allows for minor structural model modifications**.
- It enables rapid access to all relevant anatomical and physiological parameters for humans and common laboratory animals contained in the integrated database.
- Users can access different PBPK calculation methods, which enables fast and efficient model building and parameterization.
- PK-Sim® offers different model structures to choose from, e.g., to account for important differences between small and large molecules.
- More importantly, PK-Sim® is fully compatible with the expert modeling software tool MoBi®, thereby allowing full access to all model details including the option for extensive model modifications and extensions.

OSP Modeling Tools: PK-Sim and MoBi

- MoBi® is a systems biology software tool for multiscale physiological modeling and simulation.
  - Within the restrictions of ordinary differential equations, almost any kind of (biological) model can be imported or set up from scratch.
  - Examples include biochemical reaction networks, compartmental disease progression models, or PBPK/PD models.
  - However, de novo development of a PBPK model, for example, is very cumbersome such that the preferred procedure is to import them from PK-Sim®.



PK-Sim vs. MoBi: main features

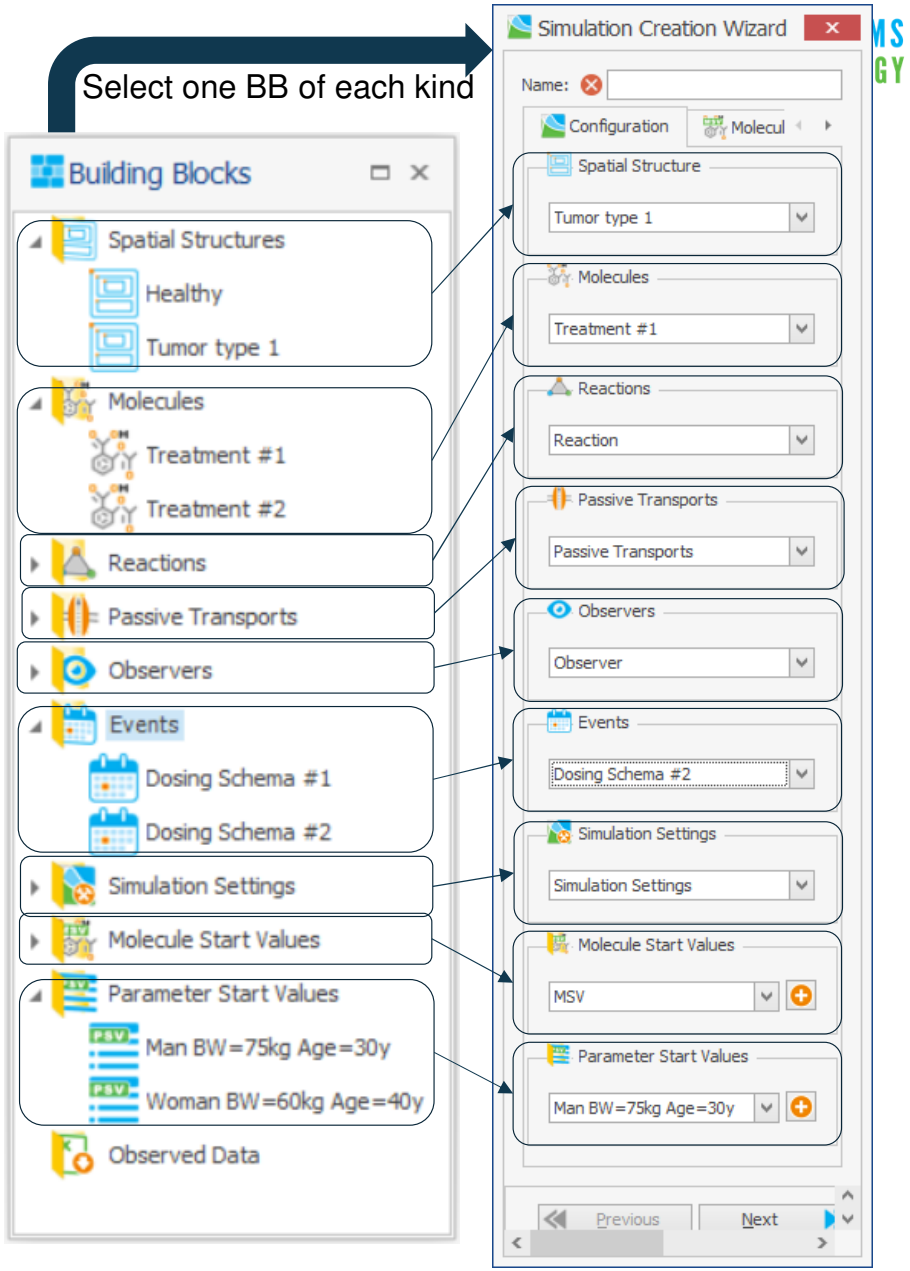
	PK-Sim	MoBi
Integrated databases with: - anatomical and physiological properties of humans and laboratory animals - protein expressions - whole-body model structures for small molecules and biologics - prediction models for tissue partition coeff. / cellular and intestinal permeabilities(*)	X	(*)X
Template library for: - optional processes (DDI / metabolizing pathways / active transporter / protein binding) - food effects / administration protocols / formulations	X	
Creating of individuals and populations	X	
Building Block (BB) Concept: Simulation creation by simple combining of previously defined BBs	X	X
Visualization: plotting of all calculated time courses	X	X
Visualization: population plots (Box-Whisker, Range, Scatter, ..)	X	
Fully integrated Parameter Identification (PI) Toolbox	X	X
Sensitivity Analysis (SA) of PK-Parameters (AUC, Cmax, …) vs. simulation parameters.	X	X
Built-in working journal for manual annotation of models and simulations	X	X
„No limits“ modeling: modify formulas, change structure beyond templates, …		**X**

When will we use MoBi® ?

- Changes in parameters that are not accessible in PK-Sim® .
- Structural physiological changes (e.g., adding an organ).
- PK-PD modeling (e.g., tumor growth and growth inhibition).
- Modeling of metabolic or signaling networks (non-PK models), in vivo and in vitro scenarios.
- … (and many more)

MoBi: Building Block Concept

- MoBi® uses **building blocks (BB)** that are grouped into:
  - Spatial Structures
  - Molecules
  - Reactions
  - Passive Transports
  - Observers
  - Events
  - Molecule Start Values
  - Parameter Start Values
  - Observed Data
- Building blocks out of the above-mentioned groups can be combined to generate models.
- The advantage of building blocks is that they can be reused.
- For example, a different set of parameter start values may define a new scenario, situation, or individual.



Export from PK-Sim® to MoBi®: Where to find what

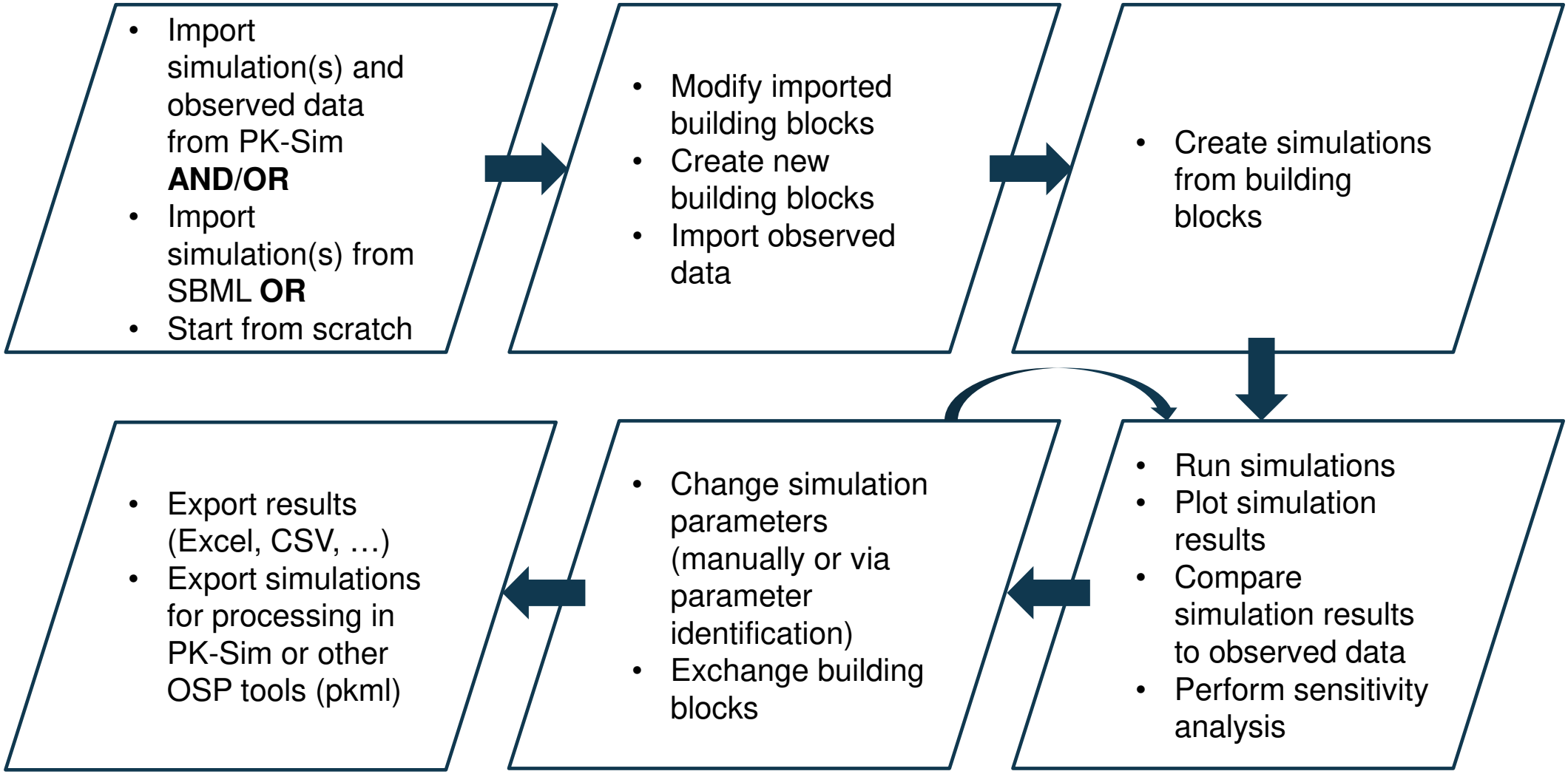
Building blocks in PK-Sim®

- Individuals
- Populations
- Compounds
- Formulations
- Administration Protocols
- Events
- Observed Data
- Observers

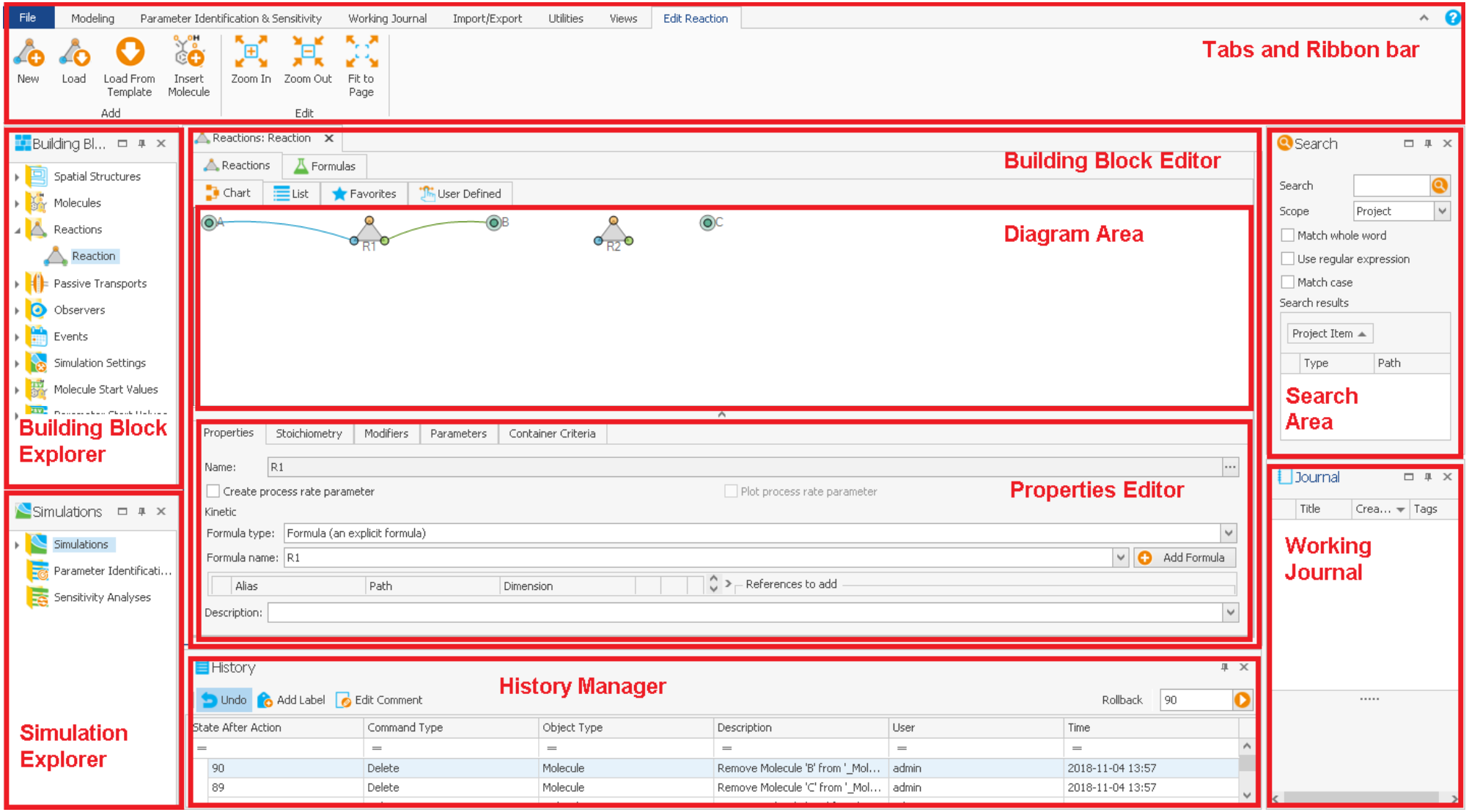
Building blocks in MoBi®

- Spatial structure
- Molecules
- Reactions
- Passive Transports
- Observers
- Events
- Simulation Settings
- Molecule Start Values
- Parameter Start Values
- Observed Data

MoBi: Workflow



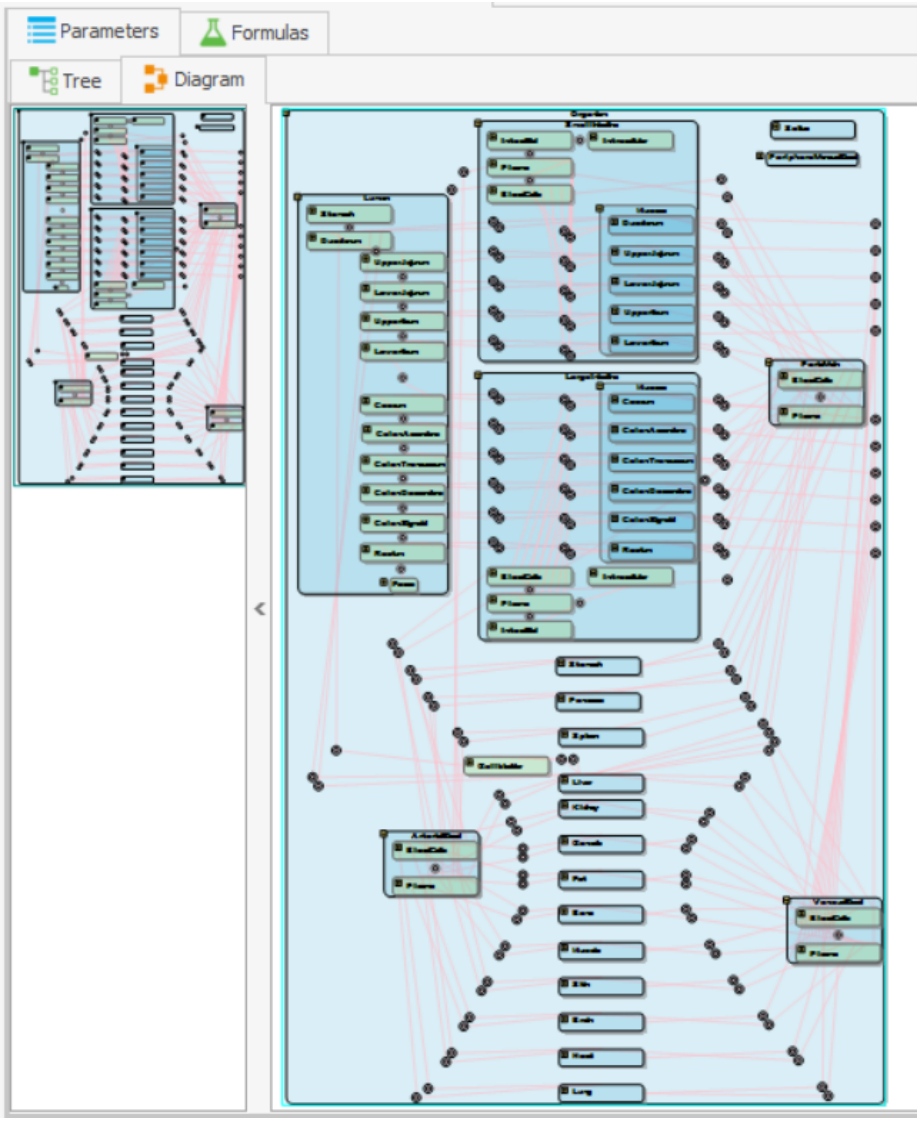
MoBi: Quick Tour



MoBi: Modeling concepts

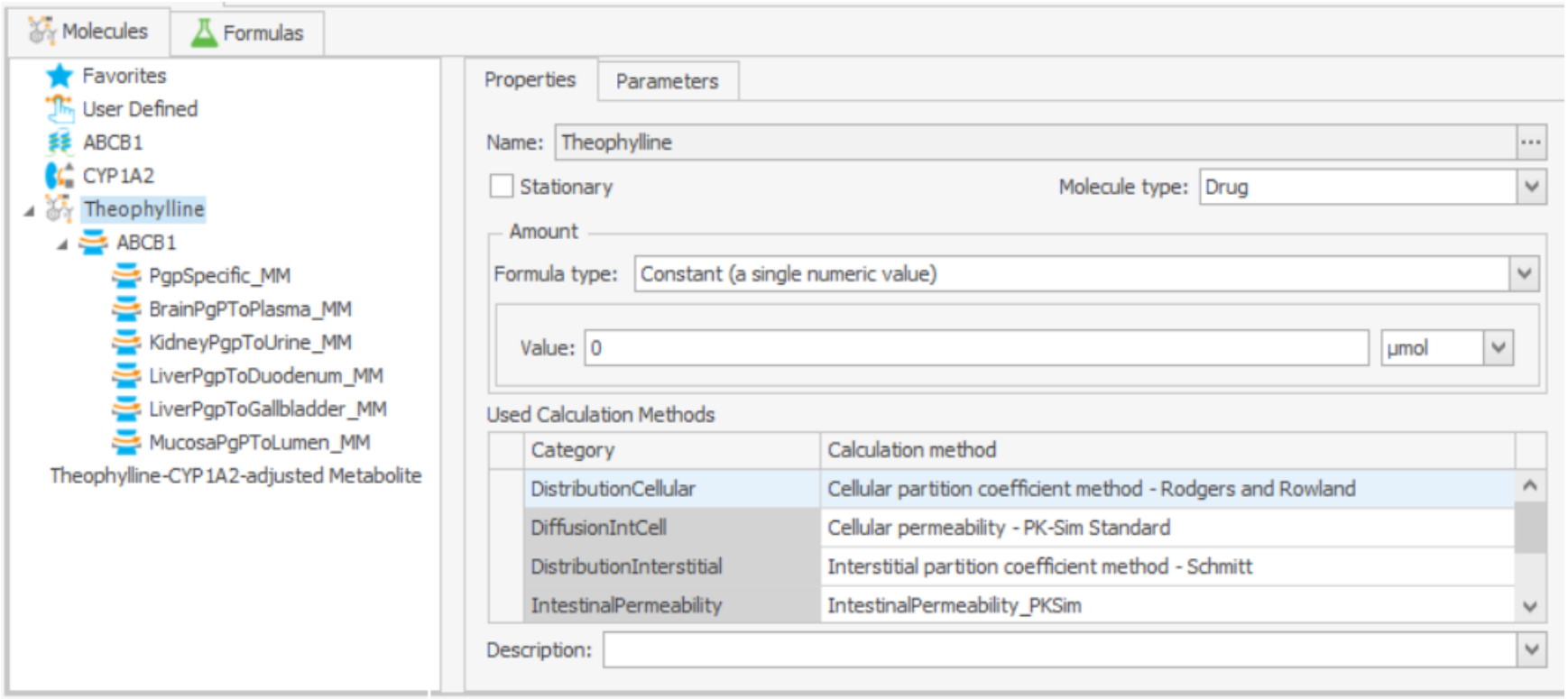
Spatial Structure: define and connect model compartments

- A spatial structure can be an organism consisting of organs, cells and other substructures. Alternatively, it can be a laboratory setup, like a test tube.
- Containers of a spatial structure can be defined as **Physical**, which may contain molecules in the simulation. They can also be defined as Logical, meaning they do not represent a real container with molecules but instead just representing a grouping of sub-containers.
- Any container may have parameters associated with it. They can describe physical or biological properties of the container that are required for processes like transports or reactions (e.g., *Volume*, *pH*, …)
- Containers are connected via **Neighborhoods**
- Containers and neighborhoods may be labelled with **tags**. These tags, together with the name given to a container or neighborhood, may be used for selectively enabling observers, active or passive transports, or events.



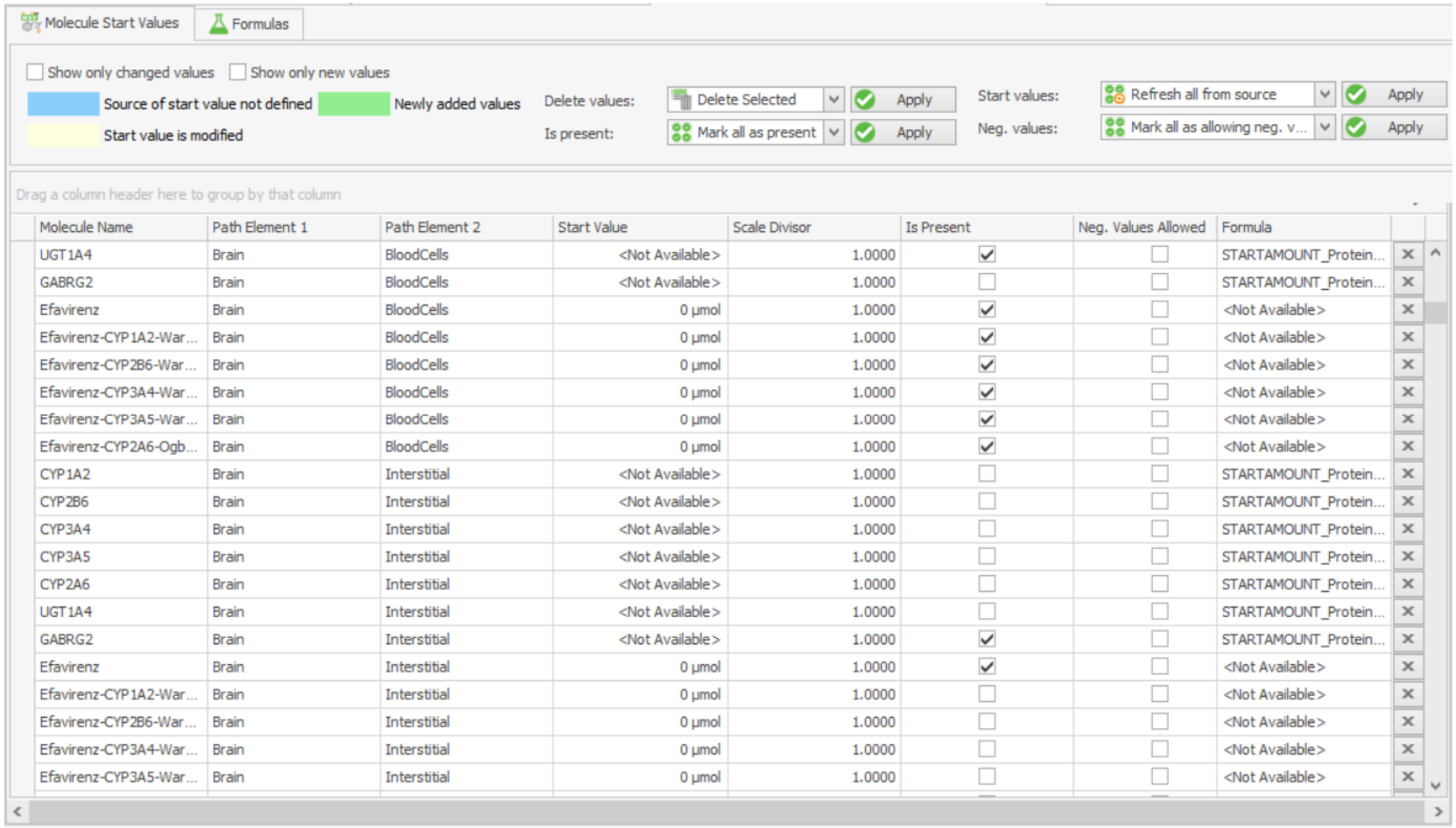
Molecules:

- Mostly, molecules will be chemical or biological compounds and can either be quantified by amount or by concentration.
- It is important to specify whether a molecule may move freely through all containers of a model, which is the default setting, or if it is stationary, i.e., it is immobilized in the current container. In the latter case, for example, the molecule may represent a membrane-bound receptor protein.



Molecule Start Values

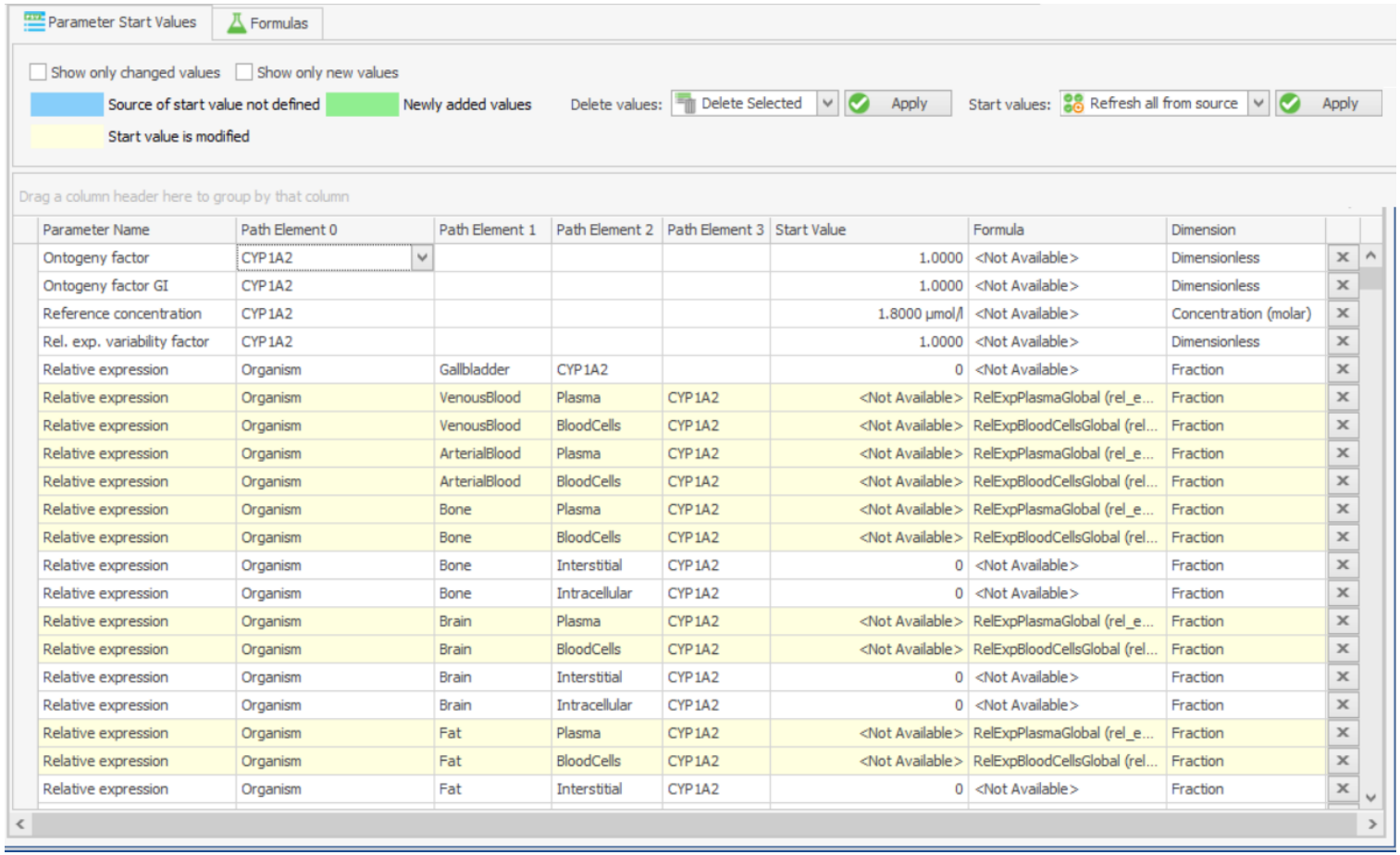
- This building block defines the initial amounts or concentration of all molecules in the model.
- If you want to exclude a specific molecule from a specific container, de-select the "is present" checkbox.



Molecule Name	Path Element 1	Path Element 2	Start Value	Scale Divisor	Is Present	Neg. Values Allowed	Formula
UGT1A4	Brain	BloodCells	<Not Available>	1.0000	☑	☐	STARTAMOUNT_Protein...
GABRG2	Brain	BloodCells	<Not Available>	1.0000	☐	☐	STARTAMOUNT_Protein...
Efavirenz	Brain	BloodCells	0 µmol	1.0000	☑	☐	<Not Available>
Efavirenz-CYP1A2-War...	Brain	BloodCells	0 µmol	1.0000	☑	☐	<Not Available>
Efavirenz-CYP2B6-War...	Brain	BloodCells	0 µmol	1.0000	☑	☐	<Not Available>
Efavirenz-CYP3A4-War...	Brain	BloodCells	0 µmol	1.0000	☑	☐	<Not Available>
Efavirenz-CYP3A5-War...	Brain	BloodCells	0 µmol	1.0000	☑	☐	<Not Available>
Efavirenz-CYP2A6-Ogb...	Brain	BloodCells	0 µmol	1.0000	☑	☐	<Not Available>
CYP1A2	Brain	Interstitial	<Not Available>	1.0000	☐	☐	STARTAMOUNT_Protein...
CYP2B6	Brain	Interstitial	<Not Available>	1.0000	☐	☐	STARTAMOUNT_Protein...
CYP3A4	Brain	Interstitial	<Not Available>	1.0000	☐	☐	STARTAMOUNT_Protein...
CYP3A5	Brain	Interstitial	<Not Available>	1.0000	☐	☐	STARTAMOUNT_Protein...
CYP2A6	Brain	Interstitial	<Not Available>	1.0000	☐	☐	STARTAMOUNT_Protein...
UGT1A4	Brain	Interstitial	<Not Available>	1.0000	☐	☐	STARTAMOUNT_Protein...
GABRG2	Brain	Interstitial	<Not Available>	1.0000	☑	☐	STARTAMOUNT_Protein...
Efavirenz	Brain	Interstitial	0 µmol	1.0000	☑	☐	<Not Available>
Efavirenz-CYP1A2-War...	Brain	Interstitial	0 µmol	1.0000	☐	☐	<Not Available>
Efavirenz-CYP2B6-War...	Brain	Interstitial	0 µmol	1.0000	☐	☐	<Not Available>
Efavirenz-CYP3A4-War...	Brain	Interstitial	0 µmol	1.0000	☐	☐	<Not Available>
Efavirenz-CYP3A5-War...	Brain	Interstitial	0 µmol	1.0000	☐	☐	<Not Available>

Parameter Start Values

- This building block defines the start values of the parameters in the model.
- This allows for the setting of specific physiological parameters if different individuals, species or patient subgroups are to be considered.



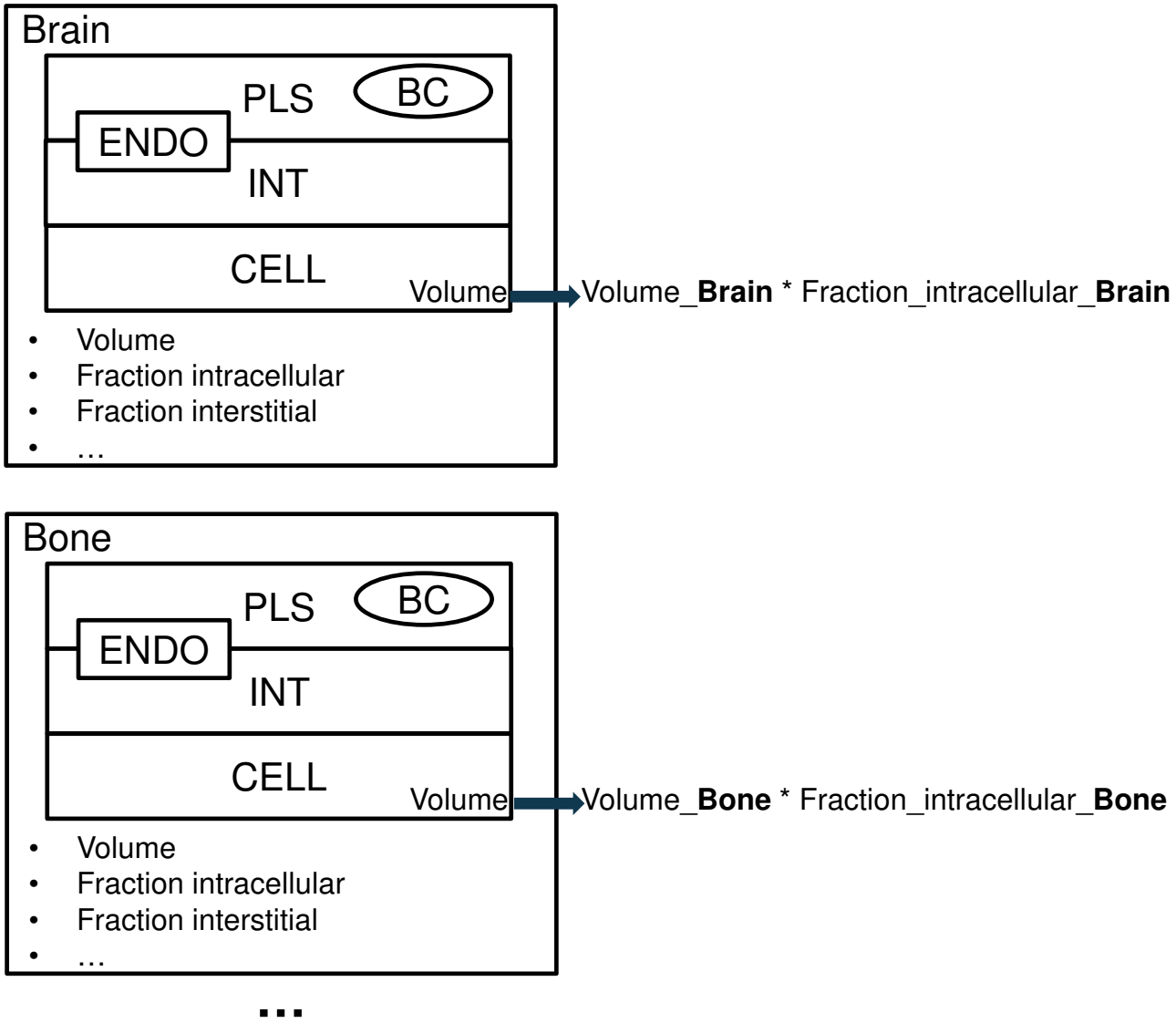
Parameter Name	Path Element 0	Path Element 1	Path Element 2	Path Element 3	Start Value	Formula	Dimension
Ontogeny factor	CYP1A2				1.0000	<Not Available>	Dimensionless
Ontogeny factor GI	CYP1A2				1.0000	<Not Available>	Dimensionless
Reference concentration	CYP1A2				1.8000 µmol/l	<Not Available>	Concentration (molar)
Rel. exp. variability factor	CYP1A2				1.0000	<Not Available>	Dimensionless
Relative expression	Organism	Gallbladder	CYP1A2		0	<Not Available>	Fraction
Relative expression	Organism	VenousBlood	Plasma	CYP1A2	<Not Available>	RelExpPlasmaGlobal (rel_e...	Fraction
Relative expression	Organism	VenousBlood	BloodCells	CYP1A2	<Not Available>	RelExpBloodCellsGlobal (rel...	Fraction
Relative expression	Organism	ArterialBlood	Plasma	CYP1A2	<Not Available>	RelExpPlasmaGlobal (rel_e...	Fraction
Relative expression	Organism	ArterialBlood	BloodCells	CYP1A2	<Not Available>	RelExpBloodCellsGlobal (rel...	Fraction
Relative expression	Organism	Bone	Plasma	CYP1A2	<Not Available>	RelExpPlasmaGlobal (rel_e...	Fraction
Relative expression	Organism	Bone	BloodCells	CYP1A2	<Not Available>	RelExpBloodCellsGlobal (rel...	Fraction
Relative expression	Organism	Bone	Interstitial	CYP1A2	0	<Not Available>	Fraction
Relative expression	Organism	Bone	Intracellular	CYP1A2	0	<Not Available>	Fraction
Relative expression	Organism	Brain	Plasma	CYP1A2	<Not Available>	RelExpPlasmaGlobal (rel_e...	Fraction
Relative expression	Organism	Brain	BloodCells	CYP1A2	<Not Available>	RelExpBloodCellsGlobal (rel...	Fraction
Relative expression	Organism	Brain	Interstitial	CYP1A2	0	<Not Available>	Fraction
Relative expression	Organism	Brain	Intracellular	CYP1A2	0	<Not Available>	Fraction
Relative expression	Organism	Fat	Plasma	CYP1A2	<Not Available>	RelExpPlasmaGlobal (rel_e...	Fraction
Relative expression	Organism	Fat	BloodCells	CYP1A2	<Not Available>	RelExpBloodCellsGlobal (rel...	Fraction
Relative expression	Organism	Fat	Interstitial	CYP1A2	0	<Not Available>	Fraction

„Generic“ modeling: Formulas in building blocks

- Example 1: compartment volume of the intracellular space in a tissue organ is defined by the product of the **organ volume** and the **fraction of intracellular space** of the organ

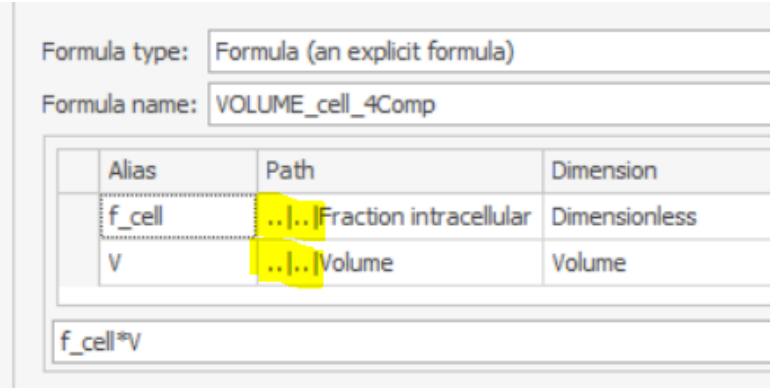
- This could be defined by a separate formula in each tissue organ

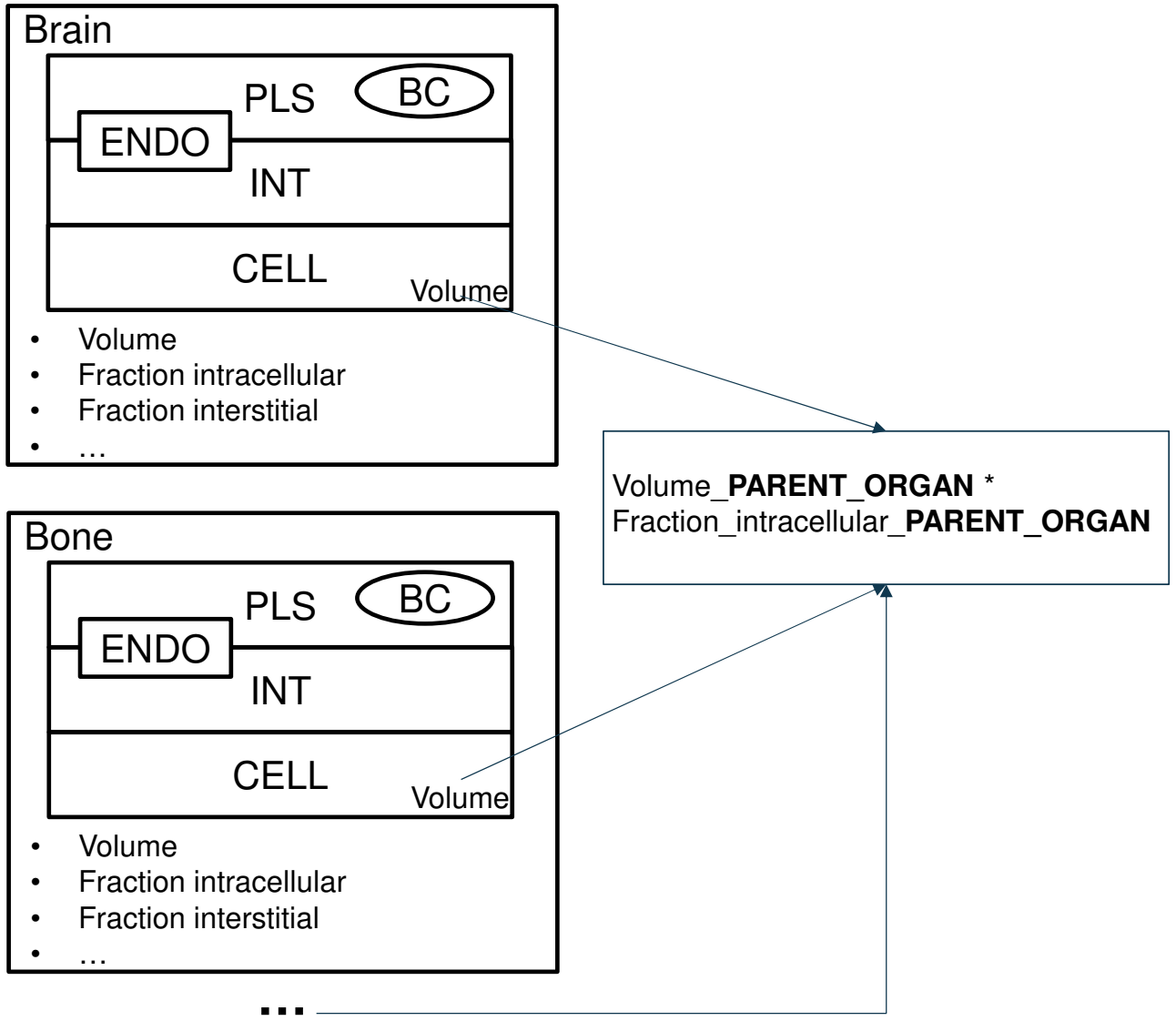
- Disadvantages
  - N formulas need to be defined (one per tissue organ)
  - If a modification of intracellular volume definition is required: N formulas need to be adjusted



„Generic“ modeling: Formulas in building blocks

- Better solution: ONE formula shared between all tissue organs – possible due to the usage of **“generic” reference**s to the formula items





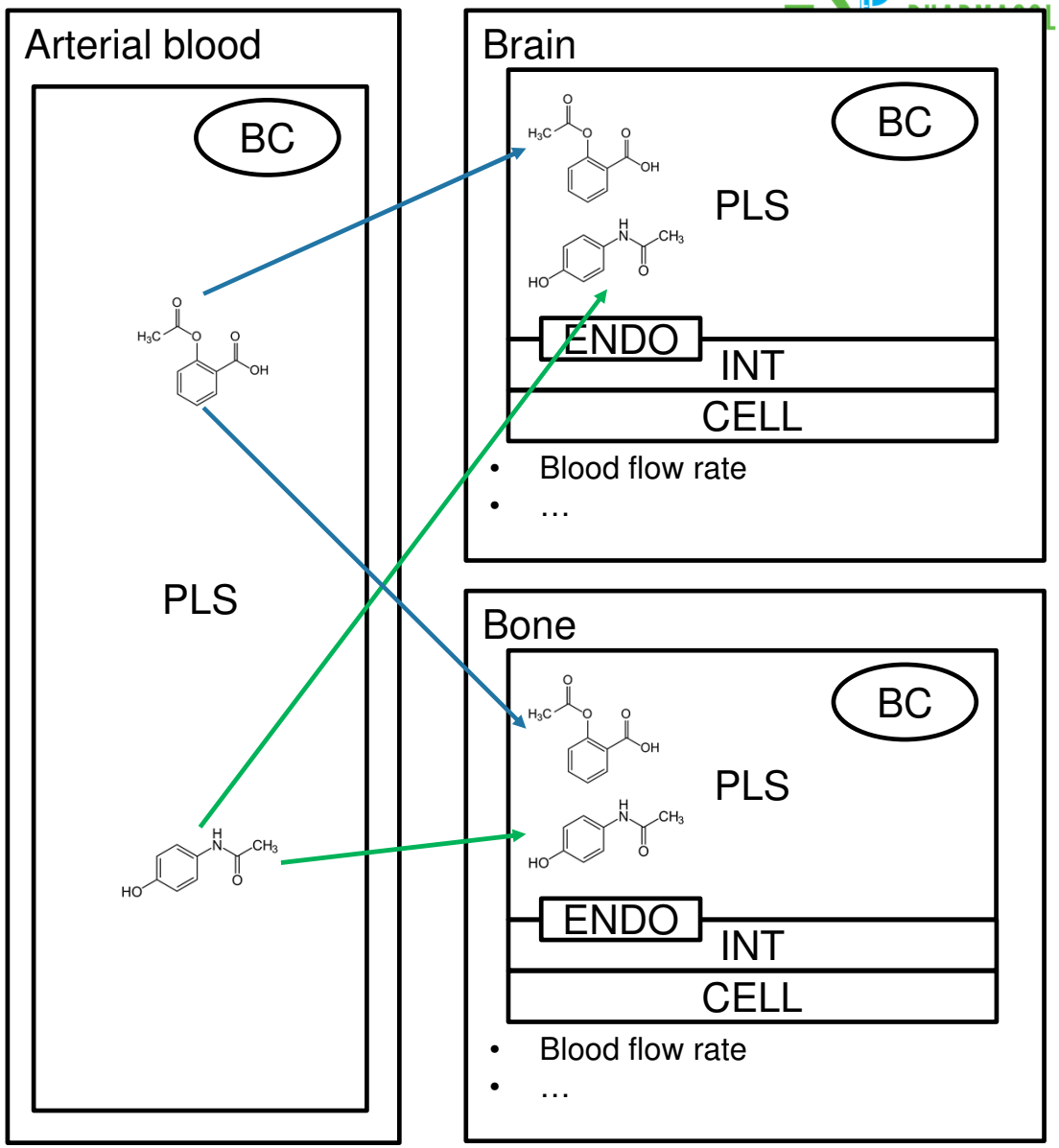
„Generic“ modeling: Formulas

- Example 2: Blood flow (passive) transports from arterial blood plasma to (tissue) organs plasma:
  - N tissue organs
  - M transported molecules
  - But just one formula for the transport rate!

```
Blood_Flow_rate_TARGET_ORGAN  *
Concentration_SOURCE_MOLECULE *
(1 - Hematocrit)
```

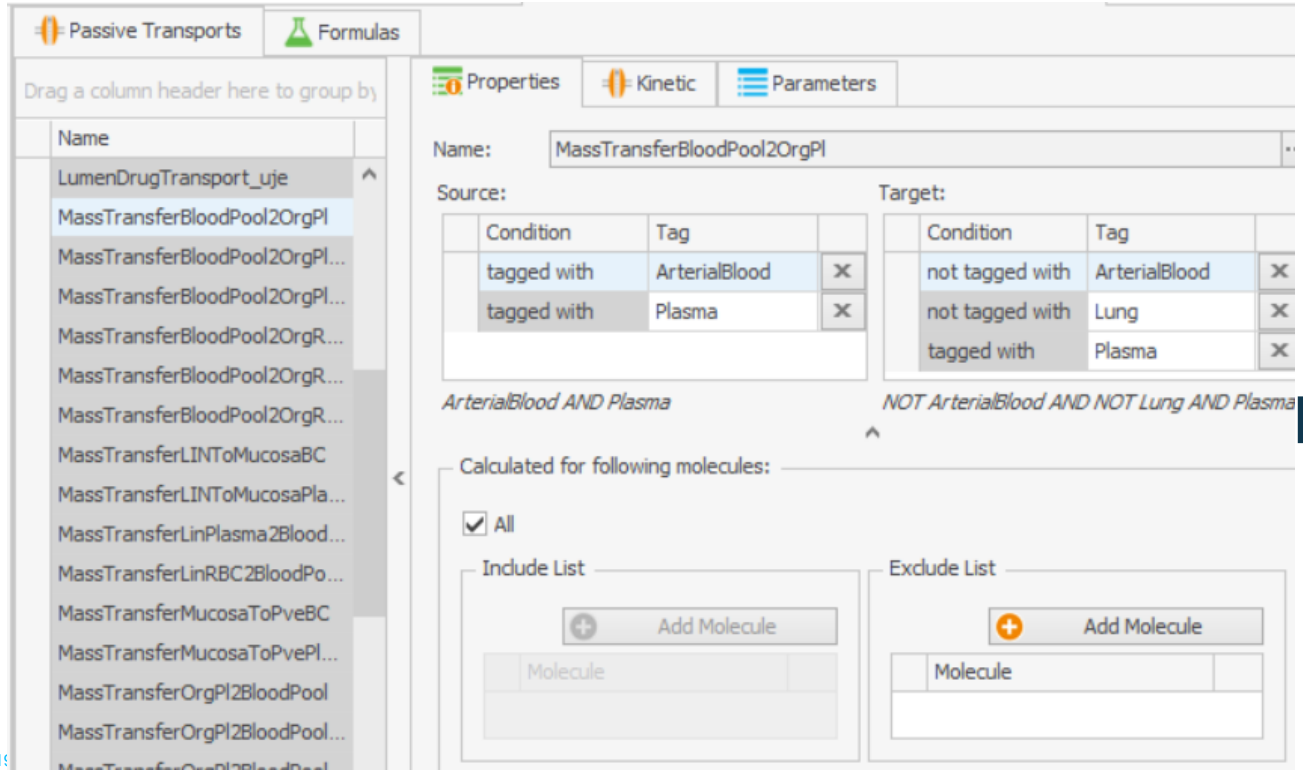
Alias	Path	Dimension
Q	TARGET|..|Blood flow rate	Flow
C_pls	SOURCE|MOLECULE|Concentration	Concentration (molar)
HCT	Organism|Hematocrit	Dimensionless

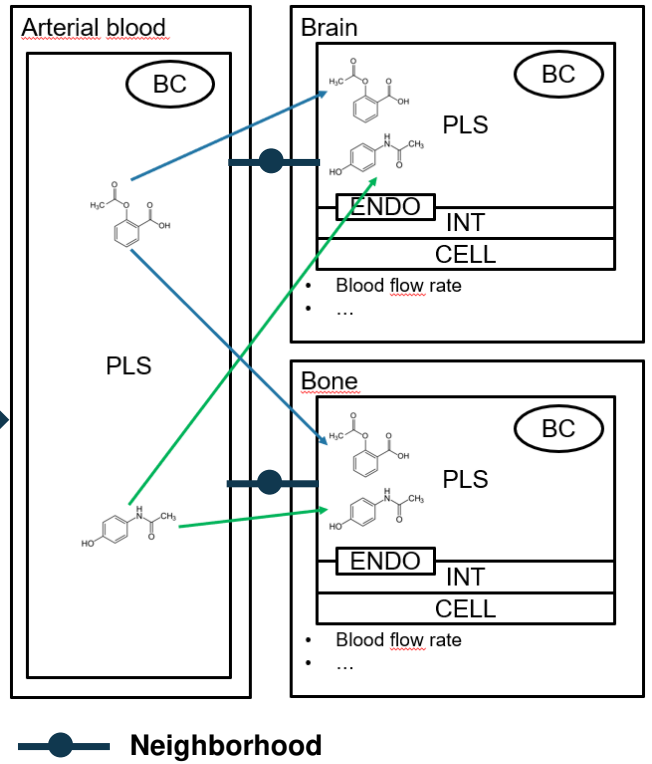
Q*(1-HCT)*C_pls



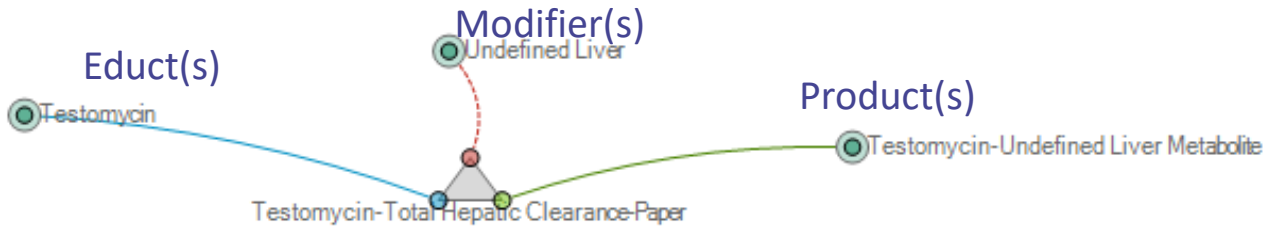
Passive Transports

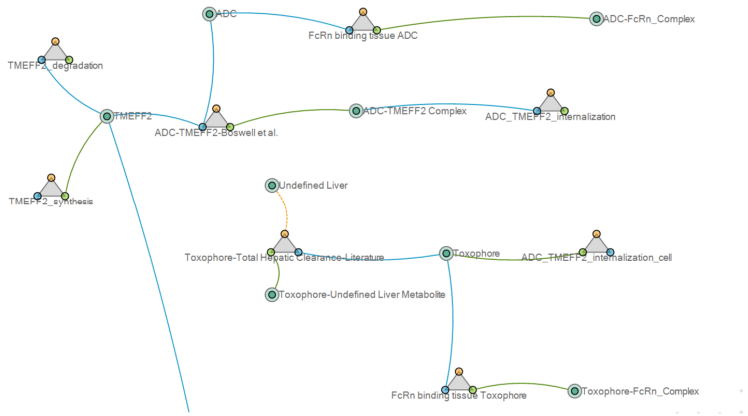
- Passive transports will affect non-stationary molecules. Examples are passive diffusion, the flow of body fluids like blood, or perfusion processes.
- A passive transport is defined by source and target, while the transport rate is defined by a kinetic formula.
- Often, it is desired to define transport processes by a generic type of equation, e.g., in all organs from blood to interstitial space. This is done by selecting the corresponding **container tag conditions**.



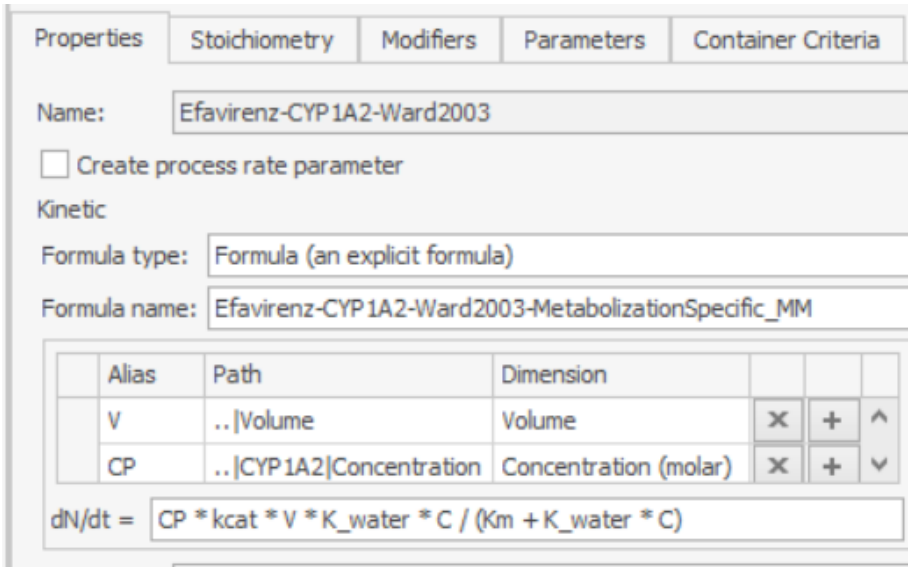


Reactions and reaction networks





- In a Reactions building block, all (bio-)chemical reactions which are of interest for the current project are defined.
- A reaction is defined by lists of reaction partners (educts, products and modifiers), stoichiometry and reaction rate
- Reactions are defined **independent of the location** and take place wherever all reaction partners are present in non-zero amounts.
  - Can be restricted by **container criteria**



Further Building Blocks

- **Observers**: An observer which can be displayed in a chart is an output derived from one or several molecules or parameters by a defined formula.
- **Events** (and Applications):
  - An **event** is used to change an entity, like the amount of molecules or a reaction rate, when a given condition is met. Examples: food intake, sports activities, …
  - An application will be (in almost all cases) will be created within PK-Sim® and then transferred to MoBi®
- **Simulation Settings** include some additional setting like
  - *output time intervals* for which results should be generated
  - Numerical settings of the (ODE) solver
  - output selections (quantities which will be shown in charts)
  - (Default) chart templates
- **Observed data**: experimental data can be imported and used in VPC-plots, for (automated) parameter identification etc.

OSP R-Toolbox

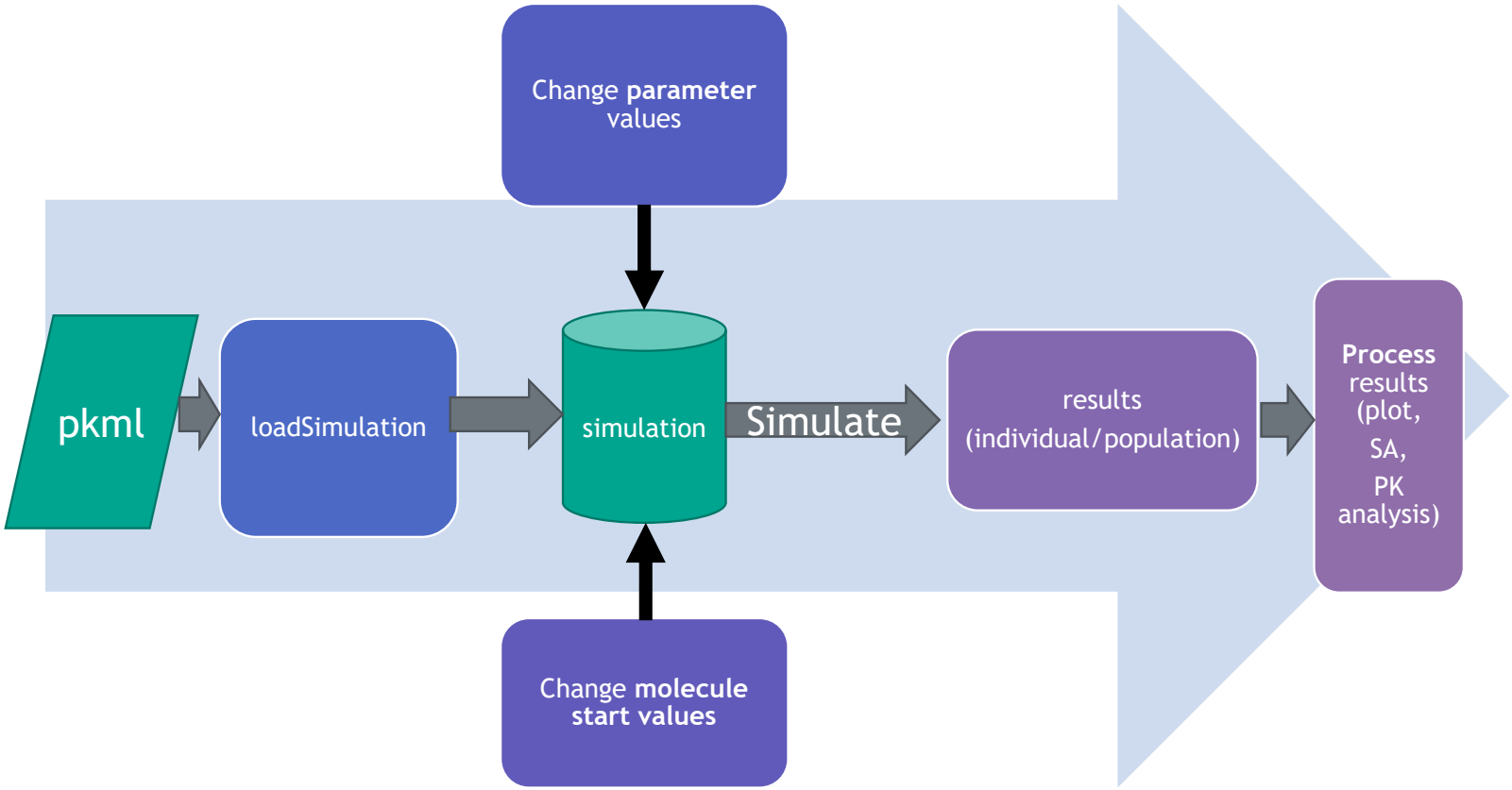
R-Toolbox: main features

- R-Toolbox provides methods to read, manipulate, and simulate (and write) pkml models
  - Change *values* of *parameters* and *start values* of *molecules*
  - Get simulated results as vector of values
  - But: You CANNOT change the structure or equations of the model!
- Creation of individuals and populations
- Individual and Population simulations
- PK-analysis (**user-defined** PK-parameters can be easily created)
- Sensitivity analysis
- Supports Windows and Linux (runs **standalone** - OSP Suite Installation not required)

R-Toolbox: motivation

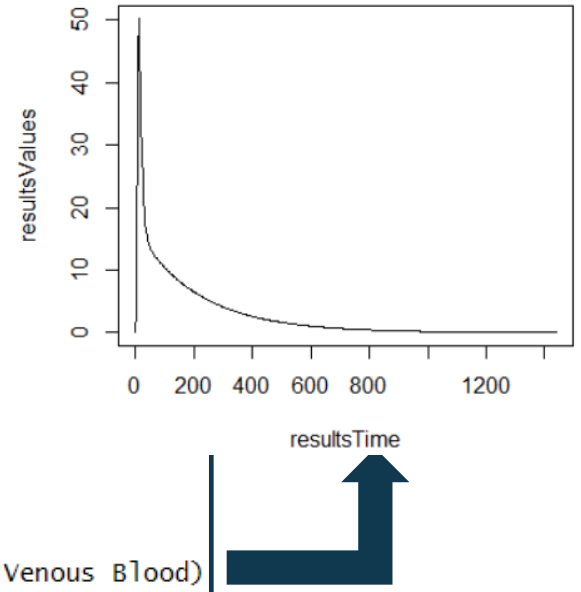
- Why use R with OSPS?
  - *Flexibility* and *reproducibility* – create figures that are fit for your objective
  - *Automation* – create your own workflows
  - *Advanced parameter identification* – use advanced algorithms, objective functions…
  - *Save time!* - parallel simulations (incl. ready to use **Docker container**, allowing simple plug&play into HPC/Cloud environments (e.g., Amazon Web Services (**AWS**)) via the **Docker** technology)

General Workflow



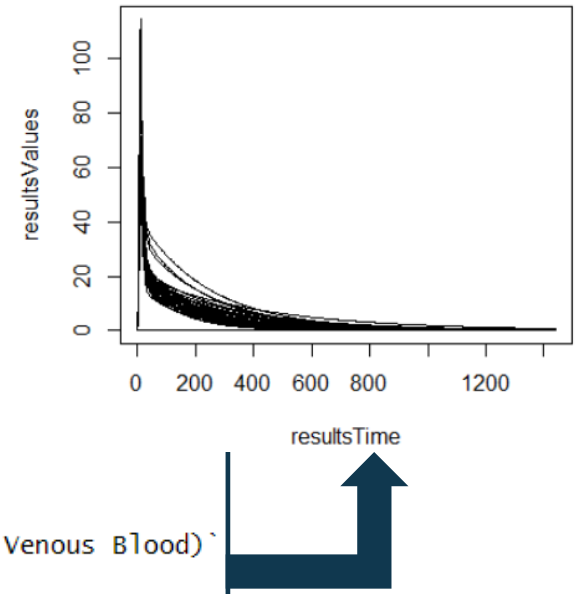
Example 1: run individual simulation, change parameters

```r
library(ospsuite)

# Load simulation
sim <- loadSimulation("Aciclovir.pkml")

# Change parameter value (liver volume)
liverVolume <- getParameter("Organism|Liver|Volume", sim)
print(liverVolume)
#> Parameter:
#>   Path: Organism|Liver|Volume
#>   Value: 2.1675 [l]
#>   isDistributed: TRUE
#>   isStateVariable: FALSE
setParameterValues(liverVolume, 1)
print(liverVolume)
#> Parameter:
#>   Path: Organism|Liver|Volume
#>   Value: 1.00 [l]
#>   isDistributed: TRUE
#>   isStateVariable: FALSE

# Run simulation
simulationResults <- runSimulation(simulation = sim)

# Get the first simulated output and plot it
resultsPath <- simulationResults$allQuantityPaths[[1]]
print(resultsPath)
#> [1] "Organism|PeripheralVenousBlood|Aciclovir|Plasma (Peripheral Venous Blood)"
resultsData <- getOutputValues(simulationResults, quantitiesOrPaths = resultsPath)
resultsTime <- resultsData$data$Time
resultsValues <- resultsData$data$`Organism|PeripheralVenousBlood|Aciclovir|Plasma (Peripheral Venous Blood)`
plot(resultsTime, resultsValues, type = "l")
```



Example 2: create population, run population simulation

```r
library(ospsuite)

# Create population from population characteristics
populationCharacteristics <- createPopulationCharacteristics(
                                species = Species$Human,
                                population = HumanPopulation$Asian_Tanaka_1996,
                                numberOfIndividuals = 50,
                                proportionOfFemales = 50,
                                weightMin = 30, weightMax = 98, weightUnit = "kg",
                                heightMin = NULL, heightMax = NULL,
                                ageMin = 0, ageMax = 80, ageUnit = "year(s)")

myPopulation <- createPopulation(populationCharacteristics = populationCharacteristics)

# Load simulation
sim <- loadSimulation("Aciclovir.pkml")

# Run population simulation
populationResults <- runSimulation(simulation = sim, population = myPopulation)
print(populationResults)
#> SimulationResults:
#>   Number of individuals: 50

# Get the first simulated output and plot it
resultsPath <- populationResults$allQuantityPaths[[1]]
print(resultsPath)
#> [1] "Organism|PeripheralVenousBlood|Aciclovir|Plasma (Peripheral Venous Blood)"
resultsData <- getOutputValues(populationResults, quantitiesOrPaths = resultsPath)
resultsTime <- resultsData$data$Time
resultsValues <- resultsData$data$`Organism|PeripheralVenousBlood|Aciclovir|Plasma (Peripheral Venous Blood)`
plot(resultsTime, resultsValues, type = "l")
```

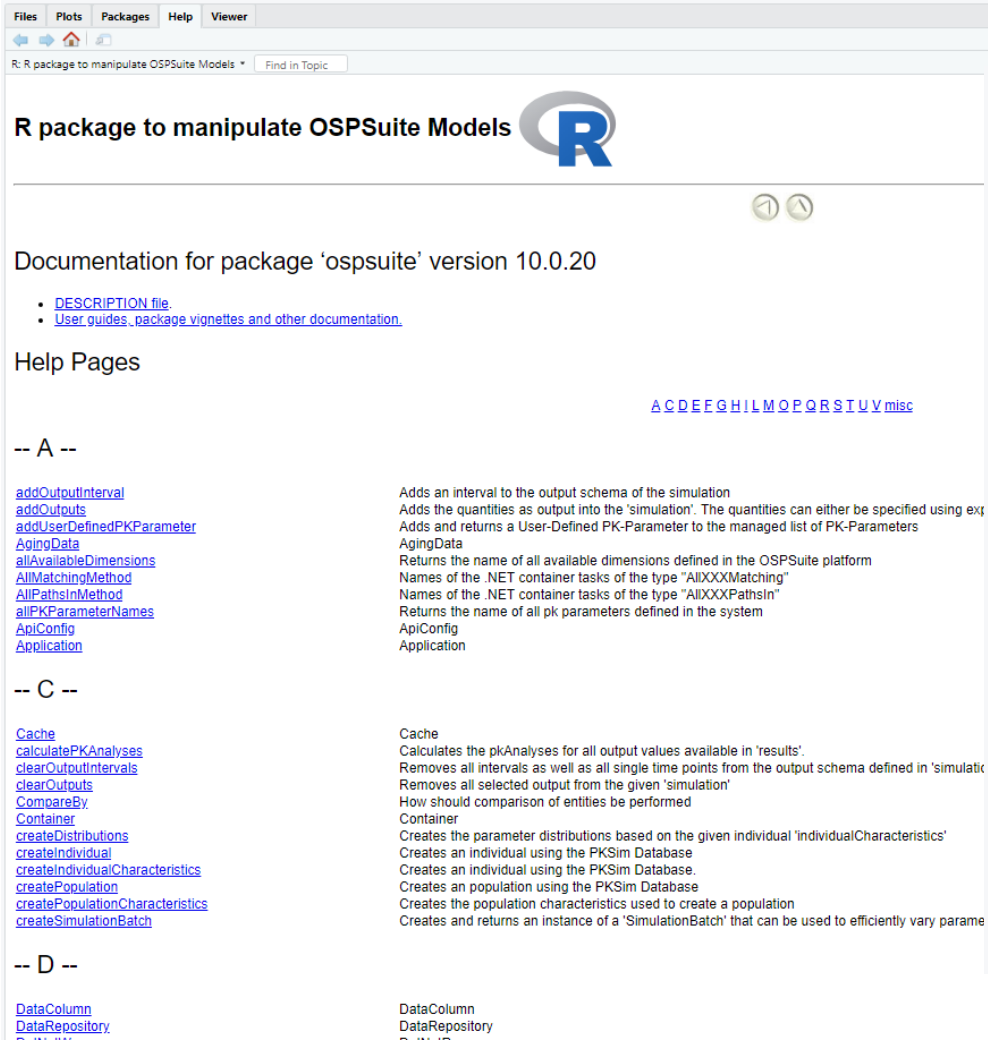


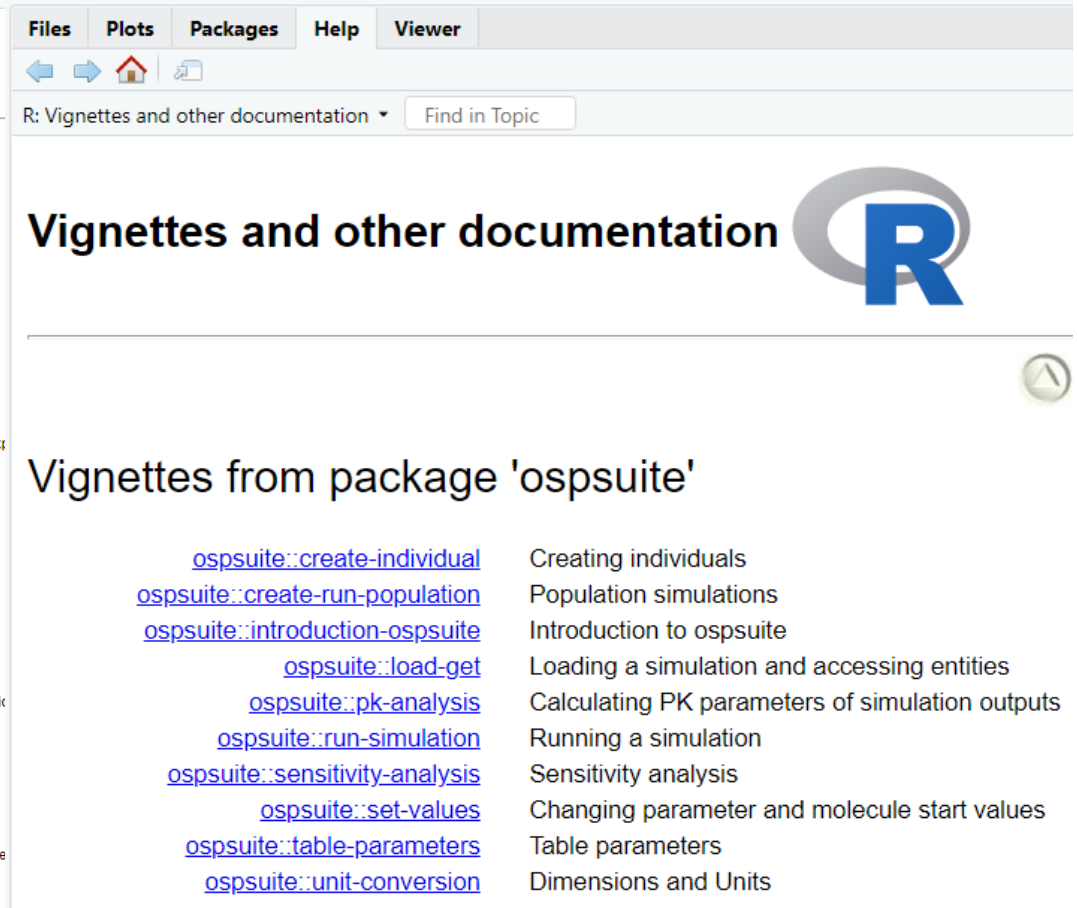
Example 3: Calculate pk values in a population simulation

```
library(ospsuite)

# Create population from population characteristics
populationCharacteristics <- createPopulationCharacteristics(
  species = Species$Human,
  population = HumanPopulation$Asian_Tanaka_1996,
  numberOfIndividuals = 50,
  proportionOfFemales = 50,
  weightMin = 30, weightMax = 98, weightUnit = "kg",
  heightMin = NULL, heightMax = NULL,
  ageMin = 0, ageMax = 80, ageUnit = "year(s)")

myPopulation <- createPopulation(populationCharacteristics = populationCharacteristics)

# Load simulation
sim <- loadSimulation("Aciclovir.pkml")

# Run population simulation
populationResults <- runSimulation(simulation = sim, population = myPopulation)

# Calculate PK-analyses
pkAnalysis <- calculatePKAnalyses(results = populationResults)

# print available PK parameter names
pkAnalysis$allPKParameterNames
#>   [1] "C_max"      "C_max_norm"      "t_max"   "C_tEnd"    "AUC_tEnd"                "AUC_tEnd_norm"
#>   [7] "AUC_inf"    "AUC_inf_norm"    "MRT"     "Thalf"     "FractionAucLastToInf"    "CL"
#>   [13] "Vss"       "Vd"

# Get C_max parameter
c_max <- pkAnalysis$pKParameterFor(quantityPath = resultsPath, pkParameter = "C_max")
print(c_max)
#>   Organism|PeripheralVenousBlood|Aciclovir|Plasma (Peripheral Venous Blood): C_max
#>   Dimension: Concentration (molar)
#>   Unit: µmol/l
c_max$values
#>   [1]  56.58231  53.85415  55.56487  53.30254  54.23650  59.40544  96.93449  54.66903  59.37316  60.1951
#>   [15]  52.09306 106.74448  80.44911  66.90536 102.34718  58.16575  58.75869  66.63985  83.09749  53.540
#>   [29]  66.23164  65.73529  72.27832  63.65108  60.89072  69.34486  61.48062  74.38184  71.07183  63.598
#>   [43]  66.29802  61.69744  57.31629  60.77491  78.32831  61.15554  78.40282  81.85518
```

Documentation

https://docs.open-systems-pharmacology.org/working-with-r/r-introduction





OPEN SYSTEMS PHARMACOLOGY

Questions?