Open Systems Pharmacology Suite - 10 Installation Validation

User1

October 19, 2021

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Chapter 1

Installation Validation Results

Overall Validation Result

Valid

1.1 Validation Summary

Run Duration

Start time: 2021-10-19 03:39 End time: 2021-10-19 04:40

Validation performed in 01h:00m:27s:920ms

Input Configuration Folder

 $C: \label{lem:condition} C: \label{lem:condition} Pharmacology \label{lem:condition} In tallation \label{lem:condition} Validator \label{lem:condition} 10.0 \label{lem:condition} In puts \label{lem:condition} Batch Files \label{lem:condition} Files \label{lem:condition} Pharmacology \label{lem$

Local Outputs Location

Application Versions

PK-Sim Version 10.0.256 MoBi Version 10.0.122

Language Settings

English (Germany) (en-DE)

Computer Name

DESKTOP-CF7981D

Operating System

Windows 10 Enterprise

Architecture

x64

Running on Virtual Machine

Yes

Running on Terminal Session

No

1.2 Comparison Results

Overall Comparison Result

Valid

Installation Folder

 $C:\ \ Program Data \ \ Open \ Systems \ Pharmacology \ \ Installation \ \ Validator \ \ \ \ \ Batch Files$

Computed Folder

1.2.1 Valid Simulations (155/155)

 $Simulation: Beagle_SingleORAL_Dissolved-Beagle_SingleORAL_Dissolved$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|drug|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 0

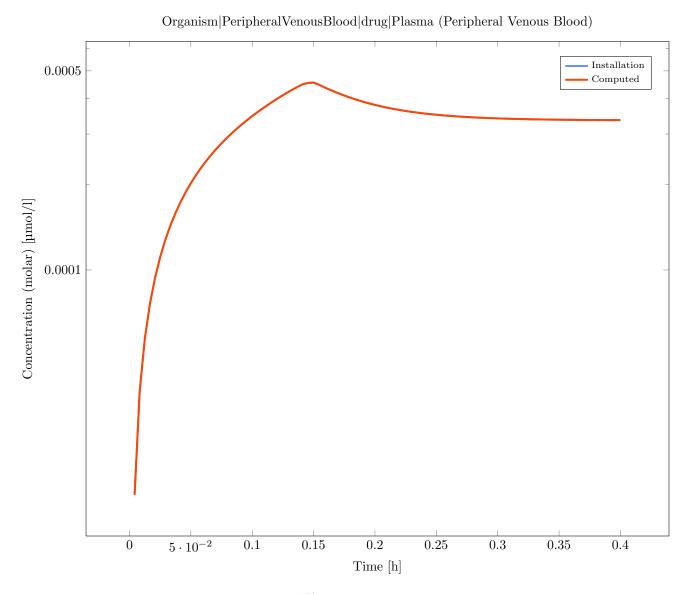
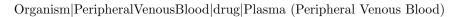


Figure 1.1

 $\label{lem:simpleORAL_Dissolved_Beagle_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5\\ Result of the validation: Valid$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: $\mathbf 0$



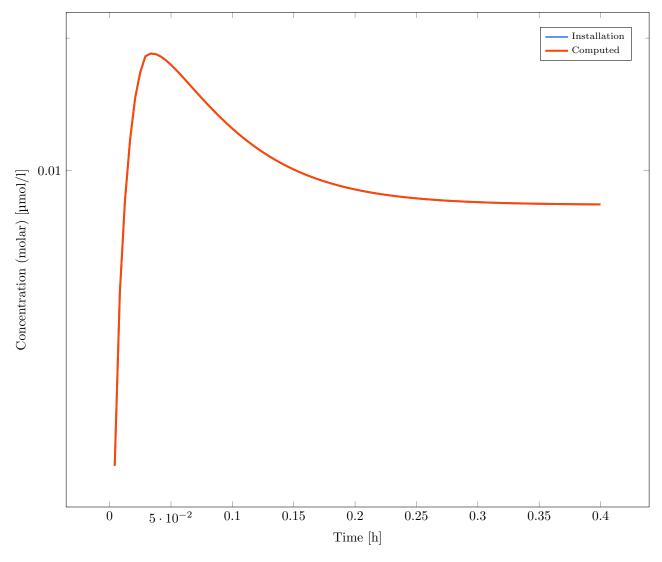


Figure 1.2

 $\label{lem:simulation:beagle_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_--5 \\ Result of the validation: Valid$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: $\mathbf 0$

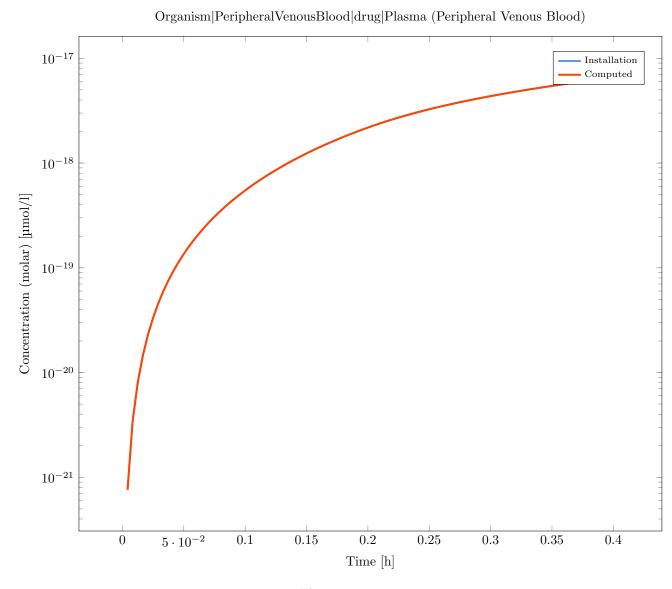
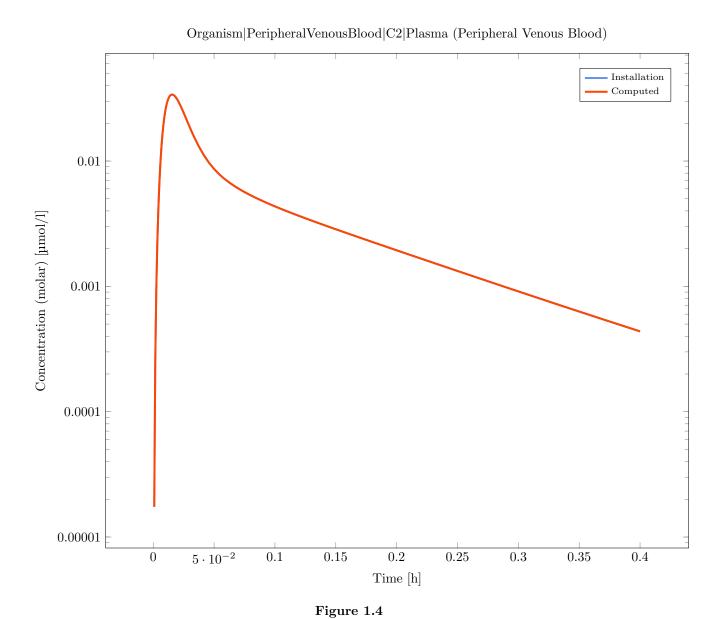


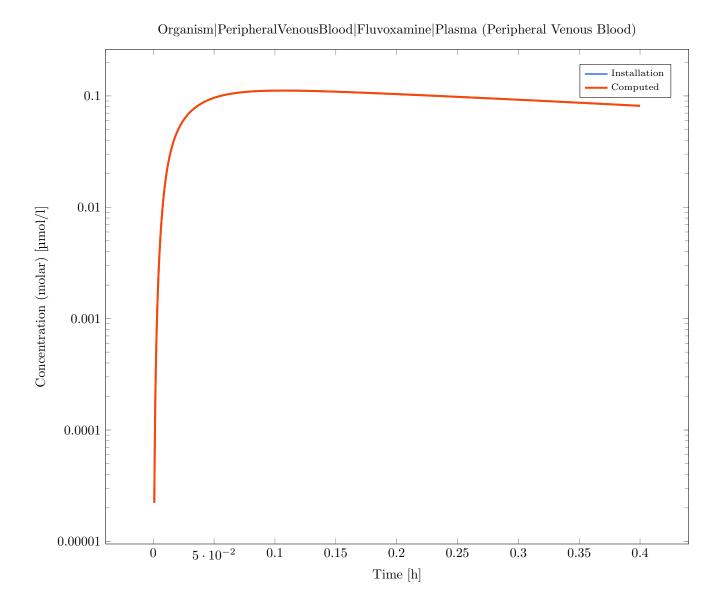
Figure 1.3

 ${\bf Simulation:\ DDI_Multiple Combinations\hbox{--}01_MM_Competitive_Competitive} \\ {\bf Result\ of\ the\ validation:\ Valid}$

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: 3.84E-4



Output Path: Organism |Peripheral Venous
Blood |Fluvoxamine |Plasma (Peripheral Venous Blood)
 Deviation: 2.00E-4



Output Path: Organism |Peripheral Venous
Blood |Itraconazole |Plasma (Peripheral Venous Blood)
 Deviation: 2.44E-4

Figure 1.5

Organism|PeripheralVenousBlood|Itraconazole|Plasma (Peripheral Venous Blood)

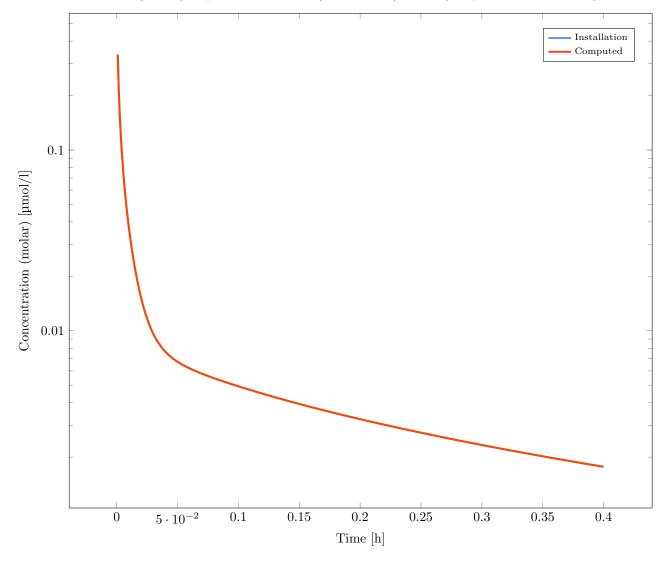


Figure 1.6

 ${\bf Simulation:\ DDI_Multiple Combinations-02_MM_Uncompetitive_Uncompetitive_Result\ of\ the\ validation:\ Valid}$

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: 3.78E-4

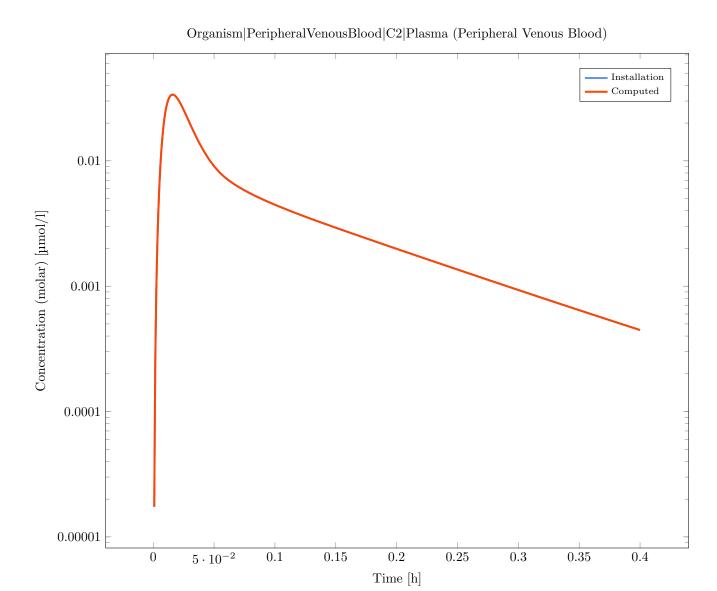


Figure 1.7

 $Output\ Path:\ Organism|PeripheralVenousBlood|Uncompetitive_CYP3A4_1|Plasma\ (PeripheralVenous\ Blood)$

Deviation: 3.60E-4

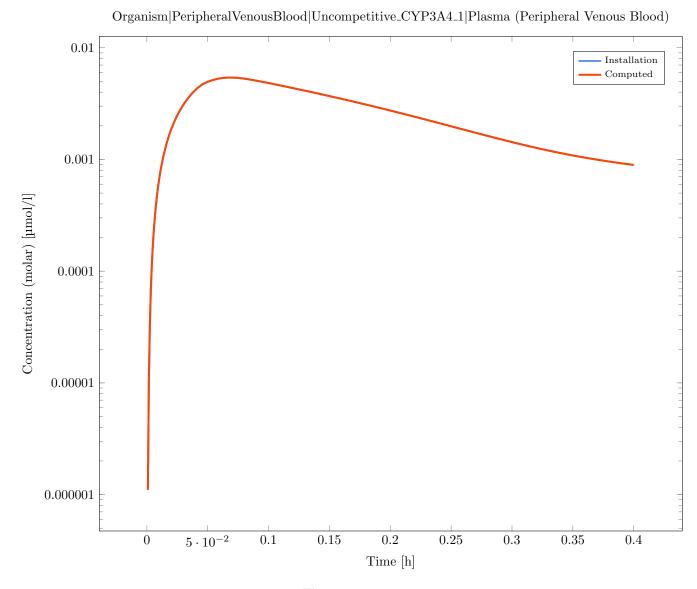
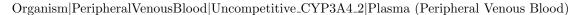


Figure 1.8

 $Output\ Path:\ Organism|PeripheralVenousBlood|Uncompetitive_CYP3A4_2|Plasma\ (PeripheralVenous\ Blood)$

Deviation: 3.69E-4



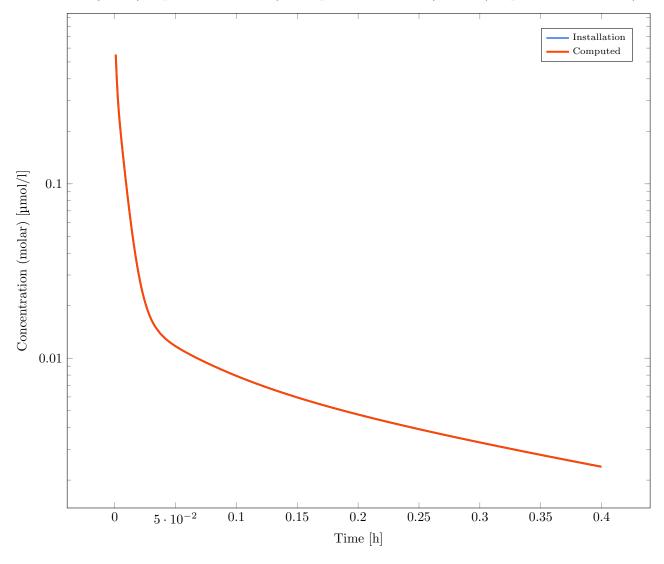


Figure 1.9

 ${\bf Simulation:\ DDI_Multiple Combinations-03_MM_Noncompetitive_N$

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: 3.59E-4

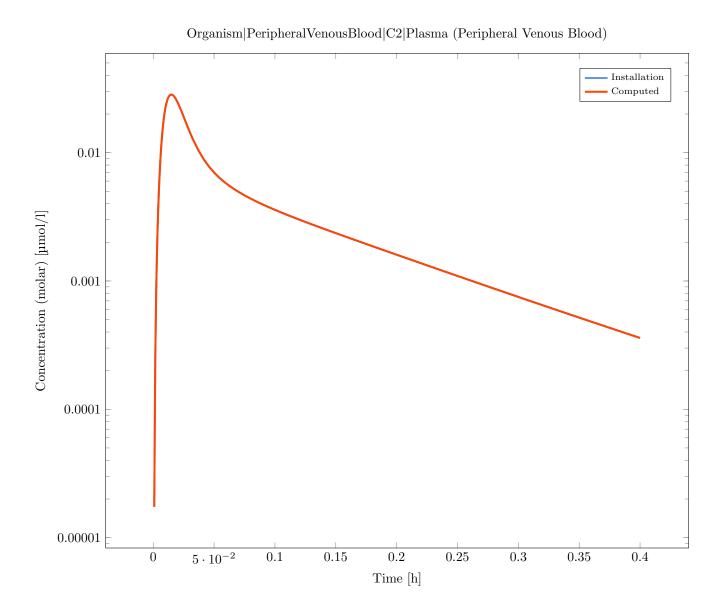


Figure 1.10

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.69E-4

Organism|PeripheralVenousBlood|Noncompetitive_CYP3A4_1|Plasma (Peripheral Venous Blood)

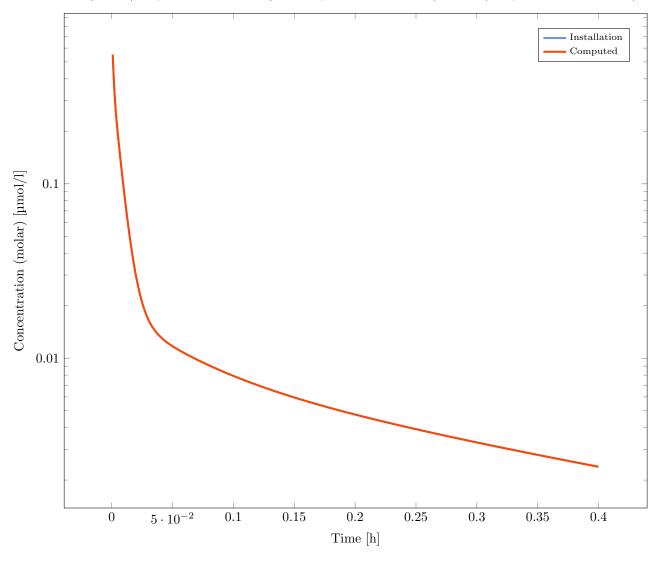


Figure 1.11

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_2|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.12E-4

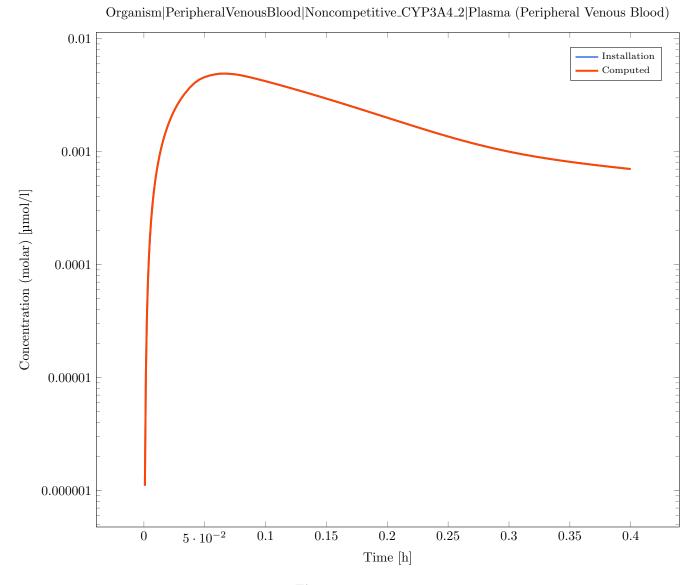


Figure 1.12

 $Simulation: \ DDI_MultipleCombinations-04_MM_Mixed_Mixed$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C2|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.82E-4

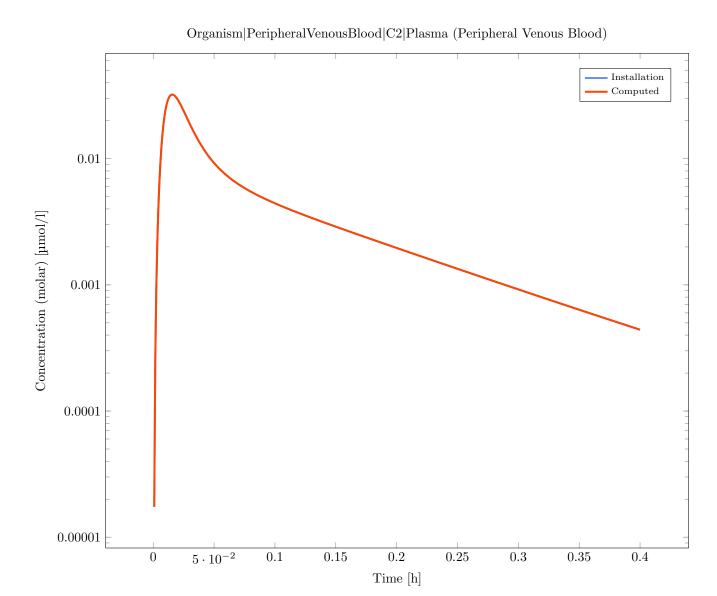


Figure 1.13

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_1|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 3.15E-4

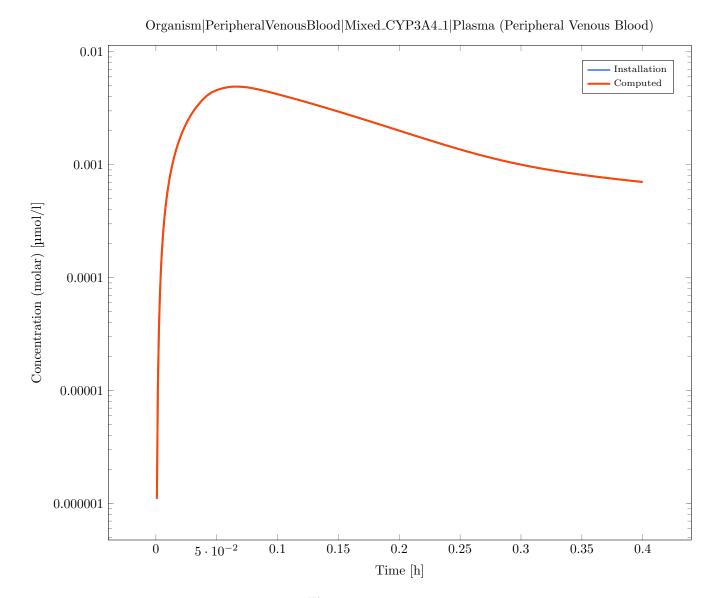


Figure 1.14

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_2|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 3.68E-4



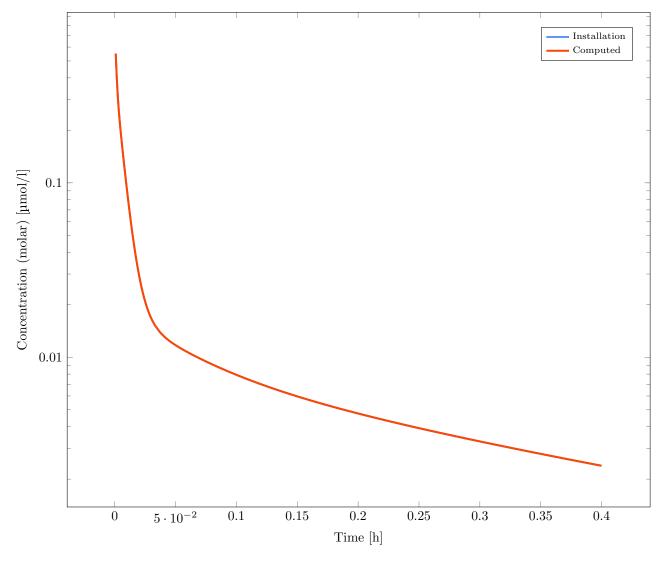


Figure 1.15

Simulation: DDI_MultipleCombinations-05_MM_Mechanismbased_Mechanismbased Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: $3.69\hbox{E-}4$

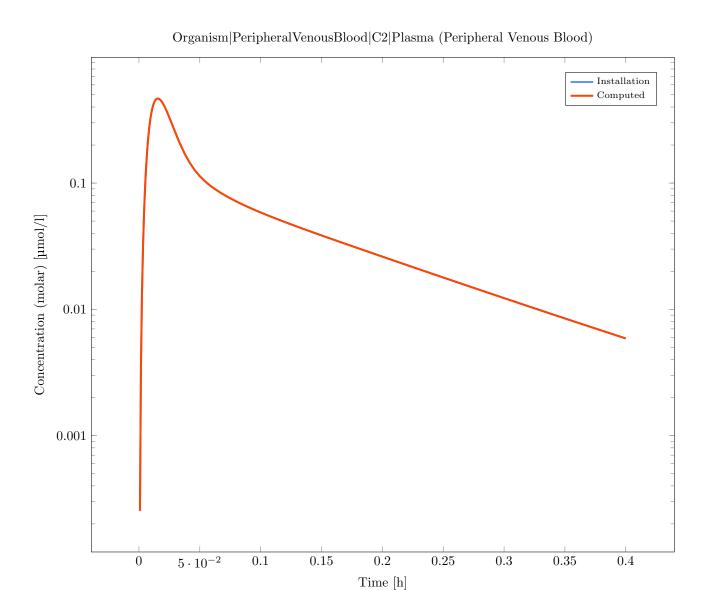
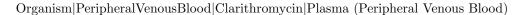


Figure 1.16

Output Path: Organism |Peripheral Venous
Blood |Clarithromycin |Plasma (Peripheral Venous Blood)
 Deviation: 2.03E-4



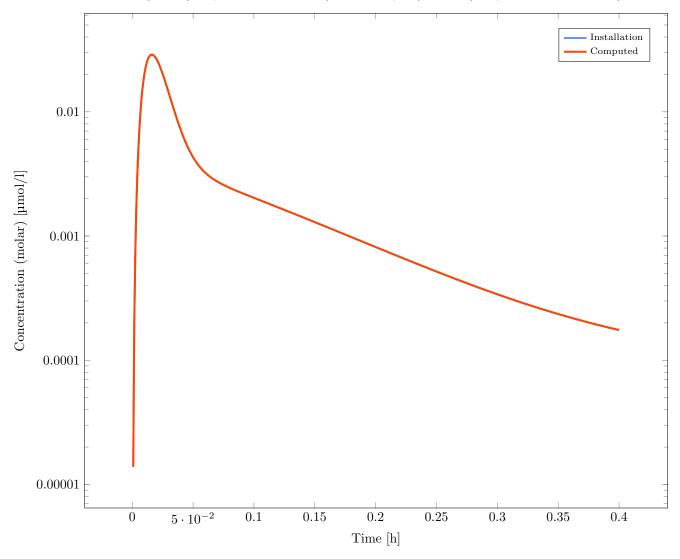


Figure 1.17

Output Path: Organism |PeripheralVenousBlood | Erythromycin |Plasma (Peripheral Venous Blood)
 Deviation: 3.62E-4

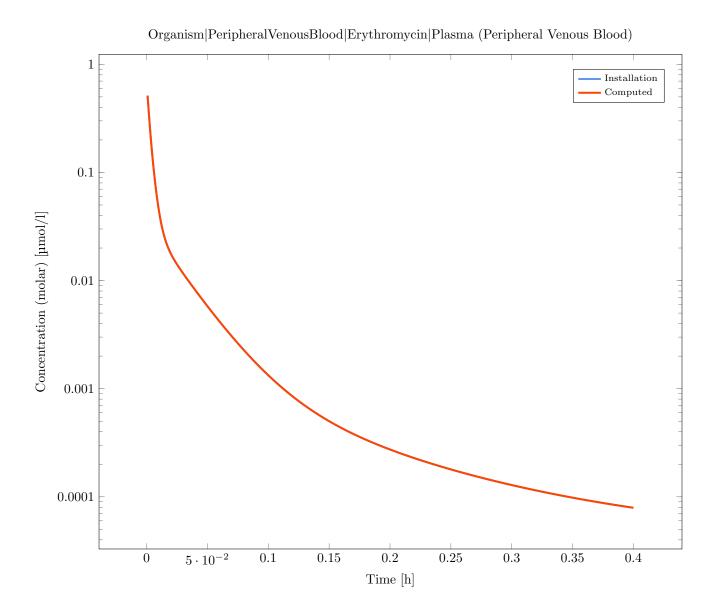


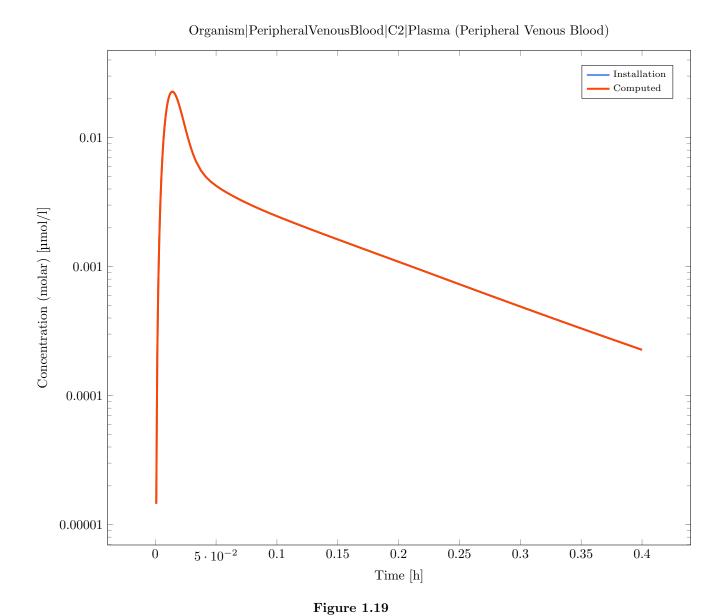
Figure 1.18

 $Simulation: \ DDI_Multiple Combinations-06_MM_Induction_Induction$

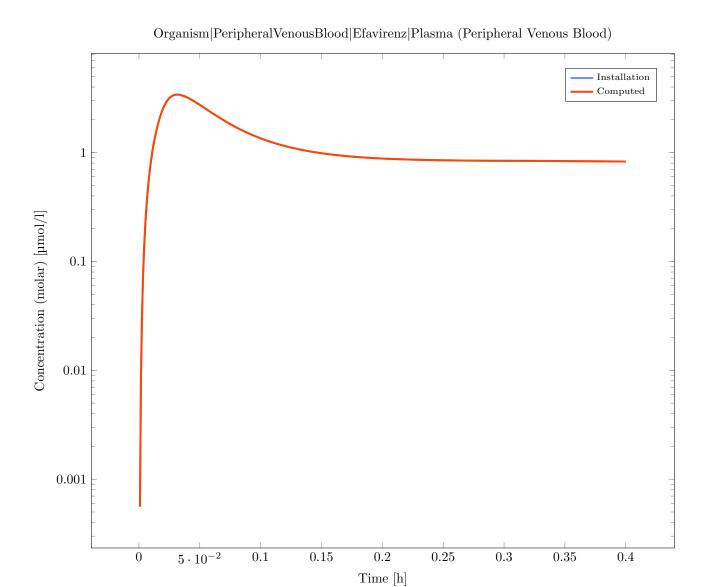
Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C2|Plasma (Peripheral Venous Blood)

Deviation: 3.14E-4



Output Path: Organism |Peripheral Venous
Blood |Efavirenz |Plasma (Peripheral Venous Blood)
 Deviation: 1.71E-4



out Path: Organism|PerinheralVenousBlood|Bifamnicin|Plasma (Perinheral Venous B

Figure 1.20

Output Path: Organism |Peripheral Venous
Blood |Rifampicin |Plasma (Peripheral Venous Blood)
 Deviation: 3.68E-4

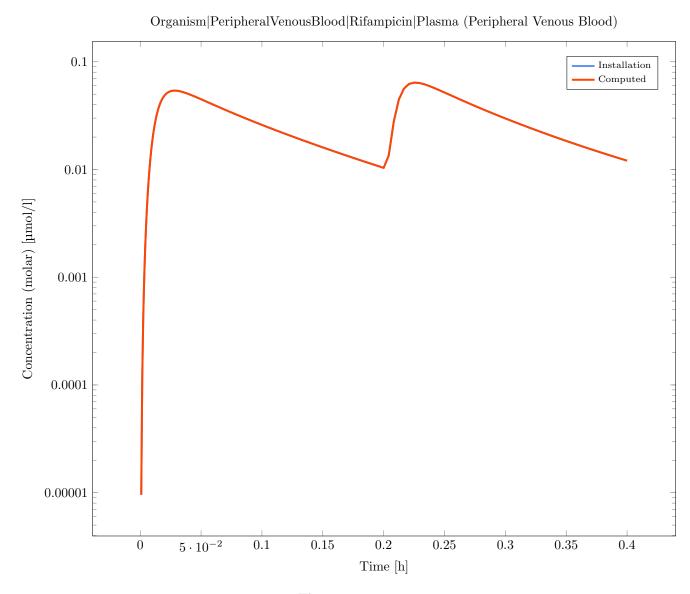
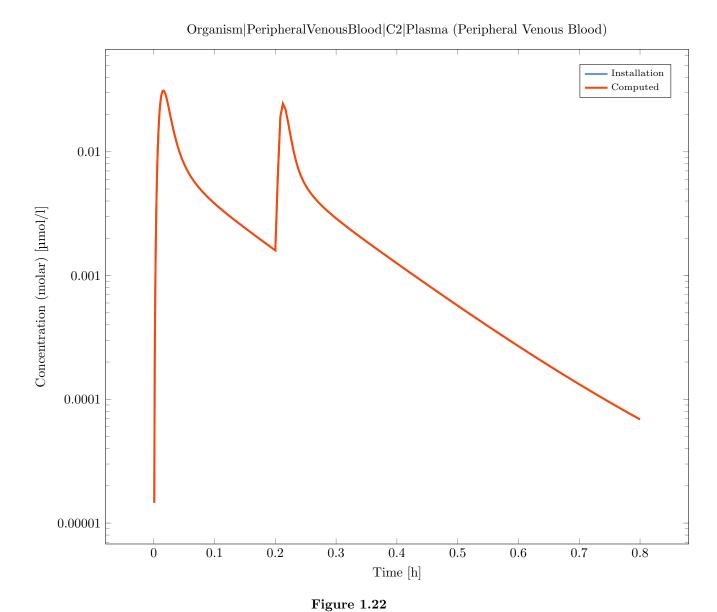


Figure 1.21

Simulation: DDI_MultipleCombinations-07_MM_Competitive_Competitive_Mechanismbased_Mechanismbased Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: 3.29E-4



Output Path: Organism |Peripheral Venous
Blood |Clarithromycin |Plasma (Peripheral Venous Blood)
 Deviation: 2.13E-4

Concentration (molar) $[\mu]$

0.001

0.0001

0.00001

0

0.1

0.2

Organism|PeripheralVenousBlood|Clarithromycin|Plasma (Peripheral Venous Blood) — Installation — Computed

Figure 1.23

0.4

Time [h]

0.5

0.6

0.7

0.8

0.3

Output Path: Organism |Peripheral Venous
Blood |Erythromycin |Plasma (Peripheral Venous Blood)
 Deviation: 6.56E-4

Organism|PeripheralVenousBlood|Erythromycin|Plasma (Peripheral Venous Blood)

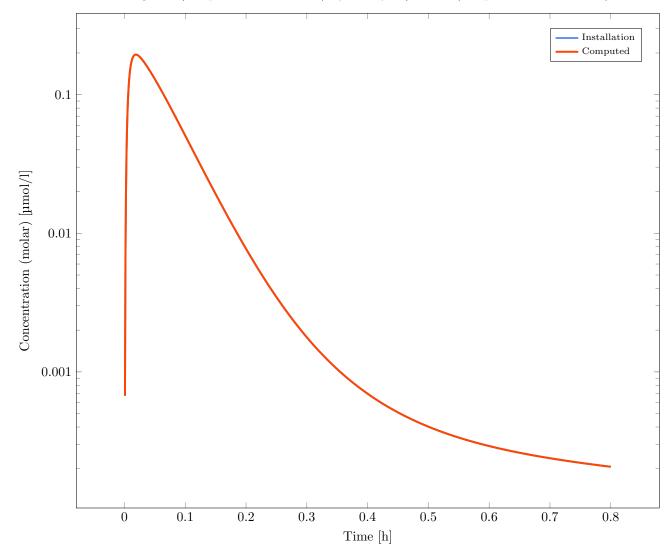


Figure 1.24

Output Path: Organism |Peripheral Venous
Blood |Itraconazole |Plasma (Peripheral Venous Blood)
 Deviation: 3.28E-4

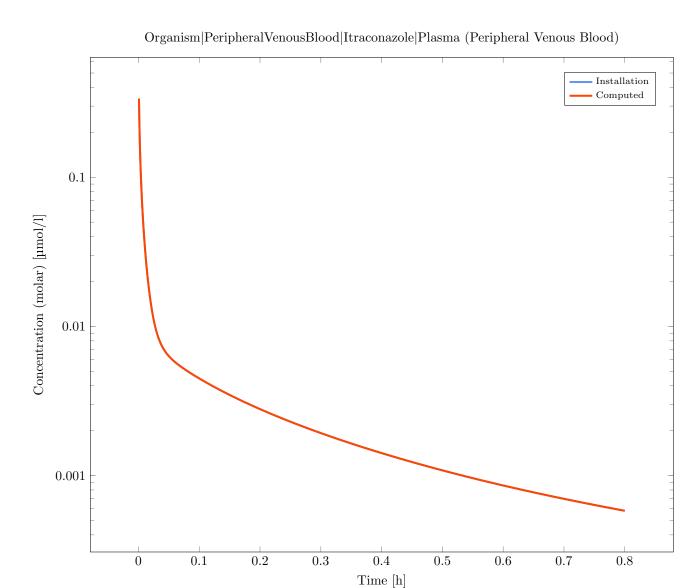


Figure 1.25

Output Path: Organism |Peripheral Venous
Blood |Rifampicin |Plasma (Peripheral Venous Blood)
 Deviation: $4.68 \hbox{E-}4$

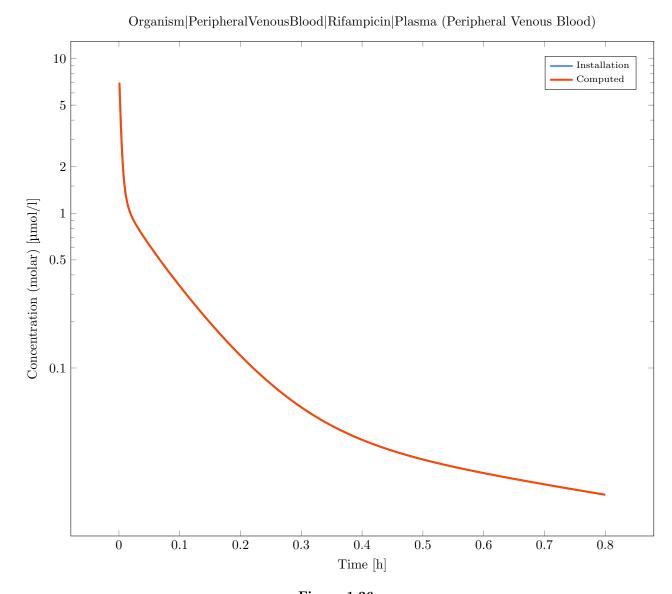


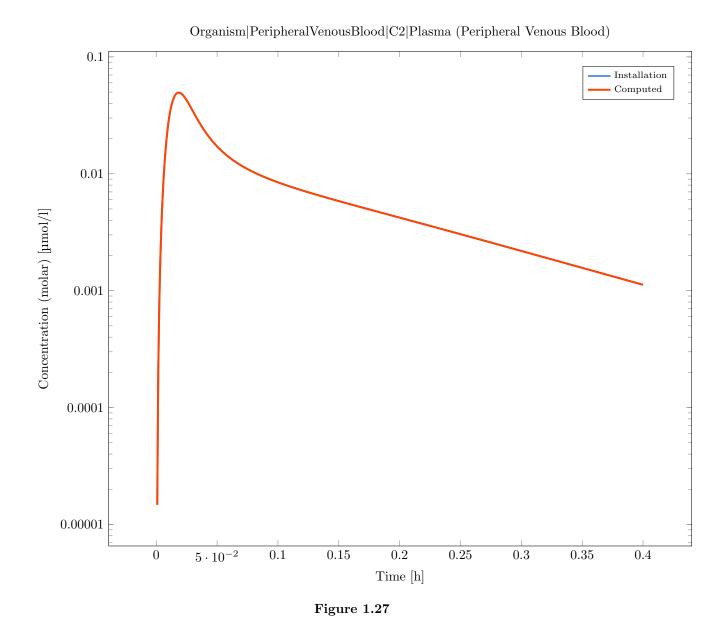
Figure 1.26

 $Simulation: \ DDI_Multiple Combinations - 08_MM_Uncompetitive_Uncompetitive_Mechanism based_Mechanism based$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C2|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 6.00E-4



Output Path: Organism|PeripheralVenousBlood|MechanismBased_4|Plasma (Peripheral Venous

Blood) Deviation: 6.17E-4

Organism|PeripheralVenousBlood|MechanismBased_4|Plasma (Peripheral Venous Blood)

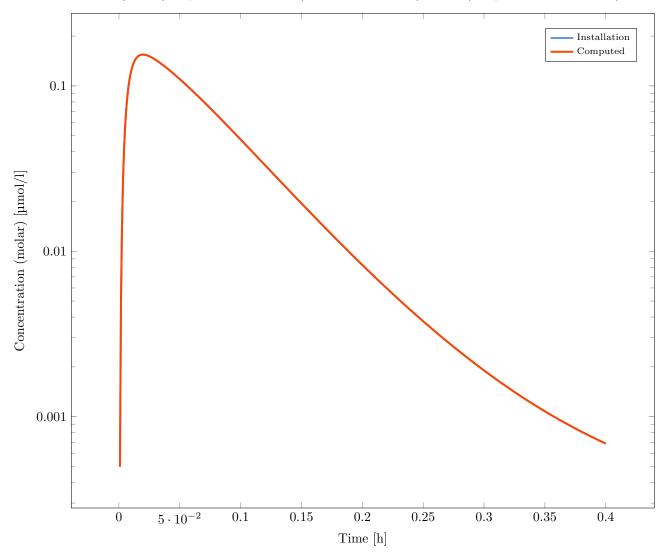
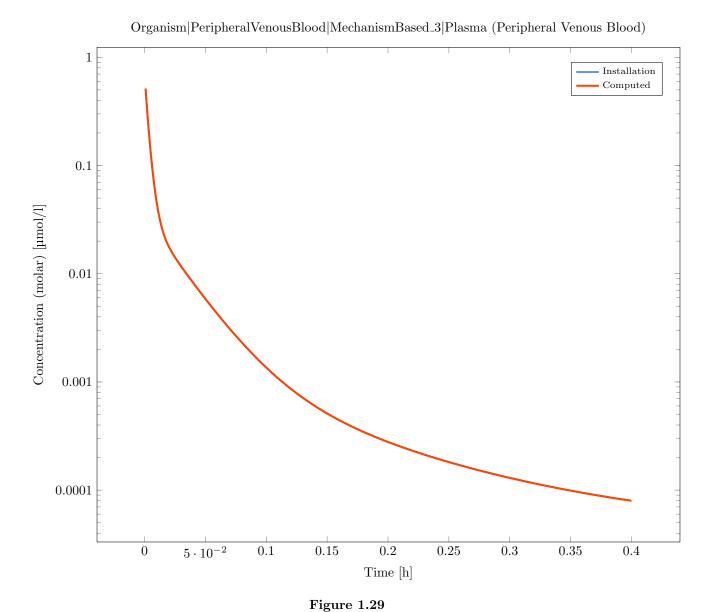


Figure 1.28

 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.67E-4



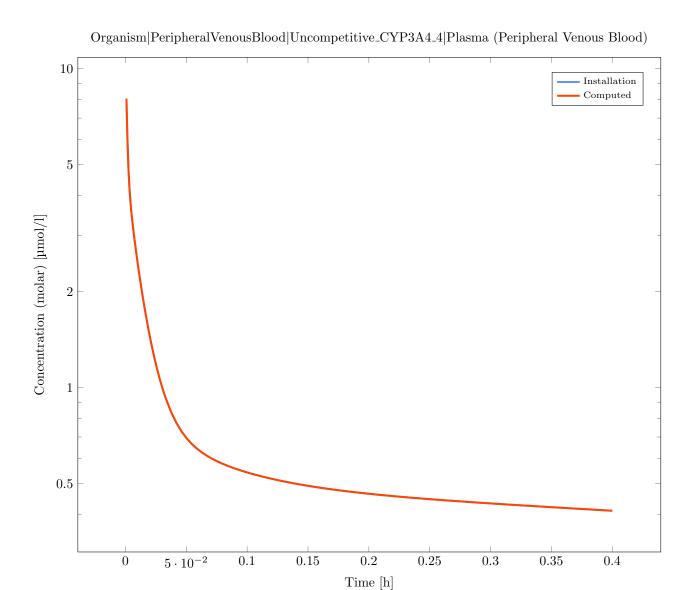
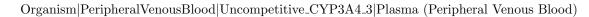


Figure 1.30

 $Output\ Path:\ Organism|PeripheralVenousBlood|Uncompetitive_CYP3A4_3|Plasma\ (PeripheralVenous\ Blood)$

Deviation: 1.08E-4



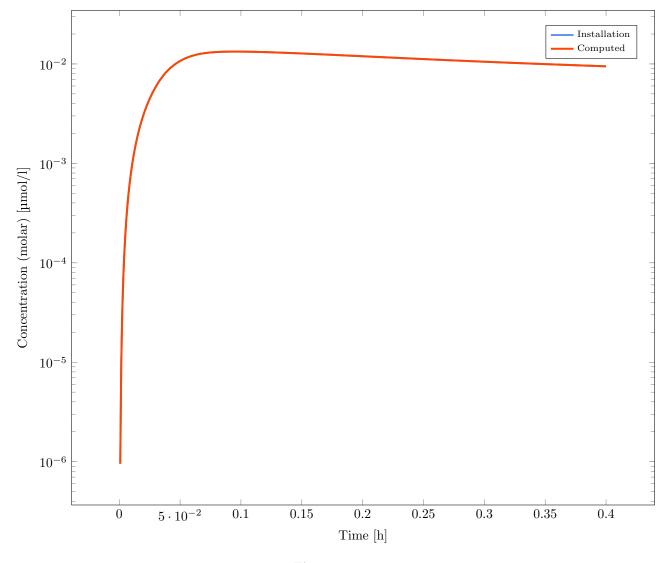


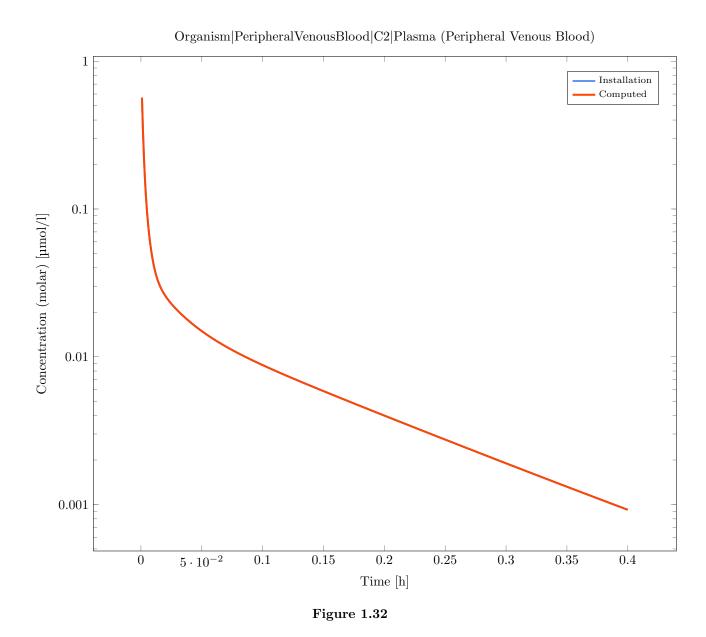
Figure 1.31

 $Simulation: \ DDI_Multiple Combinations - 09_MM_Noncompetitive_Noncompetitive_Mechanism based_Mechanism based$

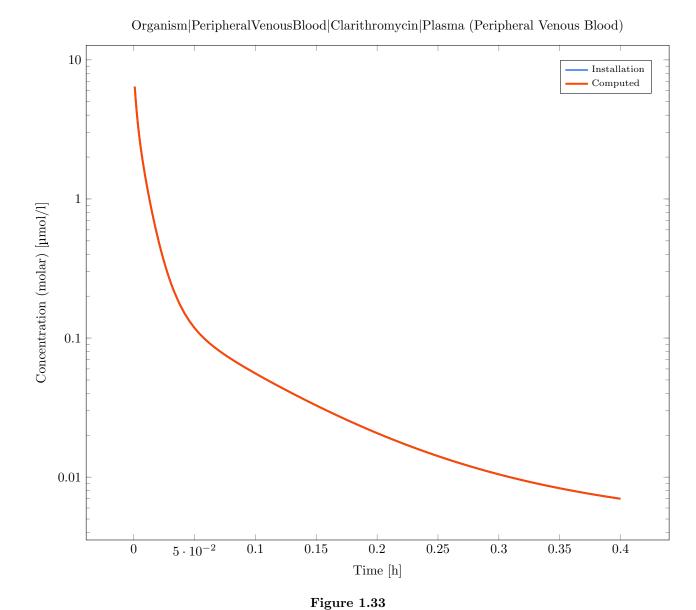
Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C2|Plasma (Peripheral Venous Blood)

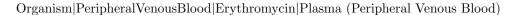
Deviation: 3.15E-4



Output Path: Organism |Peripheral Venous
Blood |Clarithromycin |Plasma (Peripheral Venous Blood)
 Deviation: 2.89E-4



Output Path: Organism|PeripheralVenousBlood|Erythromycin|Plasma (Peripheral Venous Blood)
Deviation: 8.48E-4



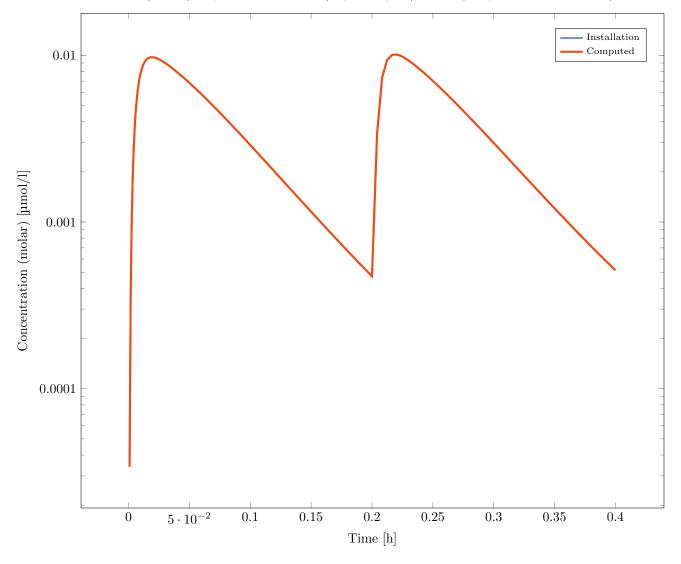


Figure 1.34

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.33E-4



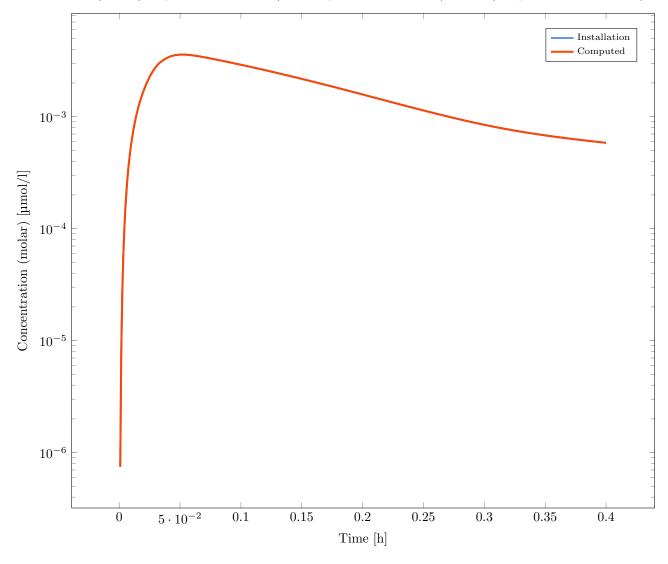


Figure 1.35

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_2|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.32E-4

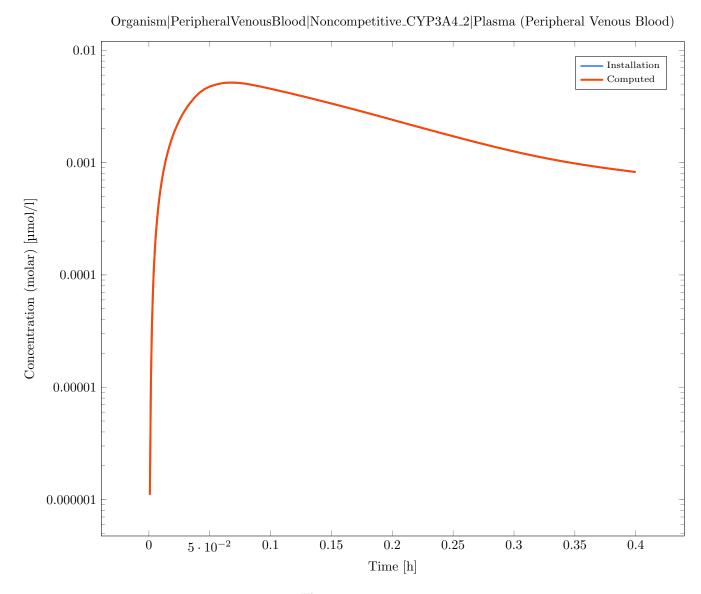


Figure 1.36

 ${\bf Simulation:\ DDI_Multiple Combinations-10_MM_Mixed_Mixed_Mechanismbased_Mech$

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: $4.93\hbox{E-}4$

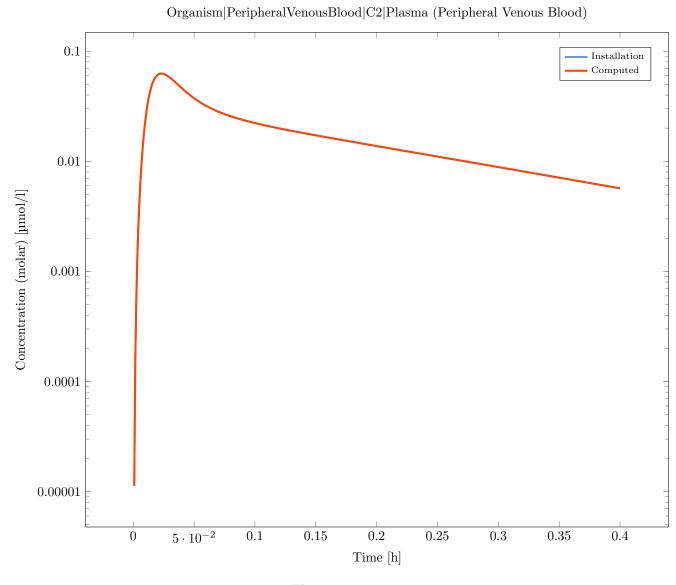


Figure 1.37

 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_4|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 5.67E-4

Organism|PeripheralVenousBlood|MechanismBased_4|Plasma (Peripheral Venous Blood)

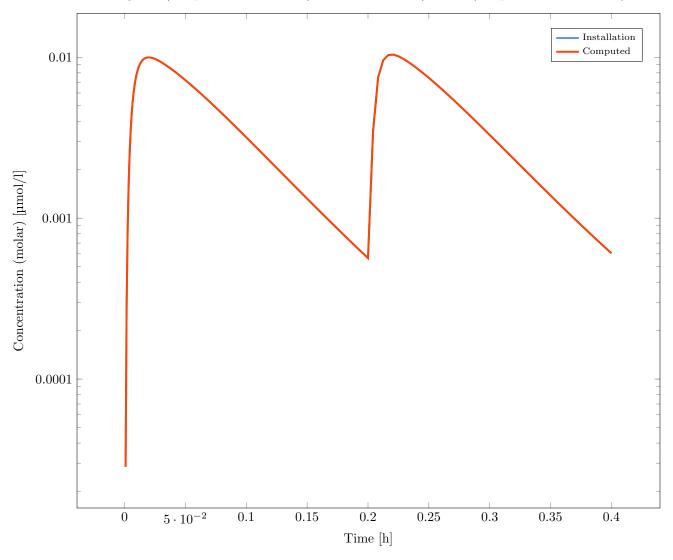


Figure 1.38

 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 5.93E-4

$Organism | Peripheral Venous Blood | Mechanism Based_3 | Plasma \ (Peripheral Venous Blood)$

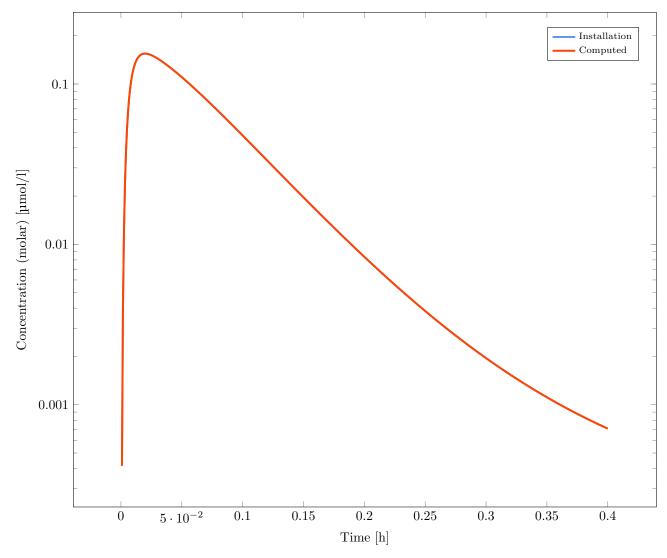
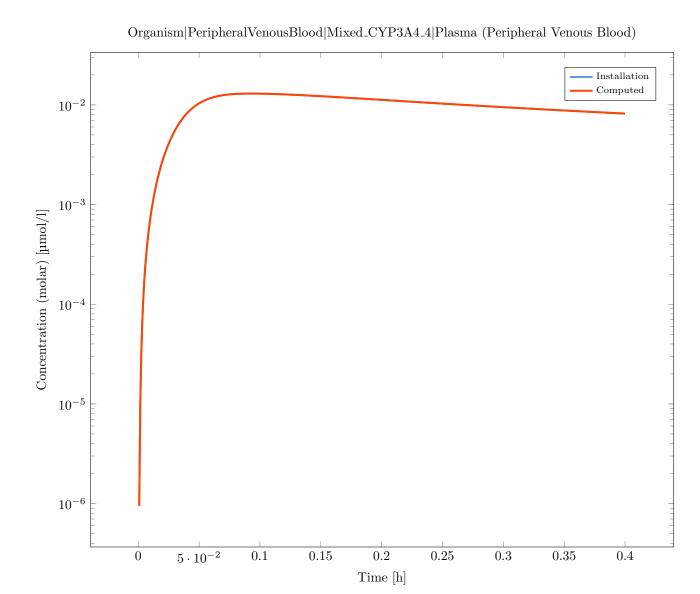


Figure 1.39

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_4|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 1.18E-4



 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_3|Plasma\ (Peripheral\ VenousBlood)$

Figure 1.40

Deviation: 1.69E-4

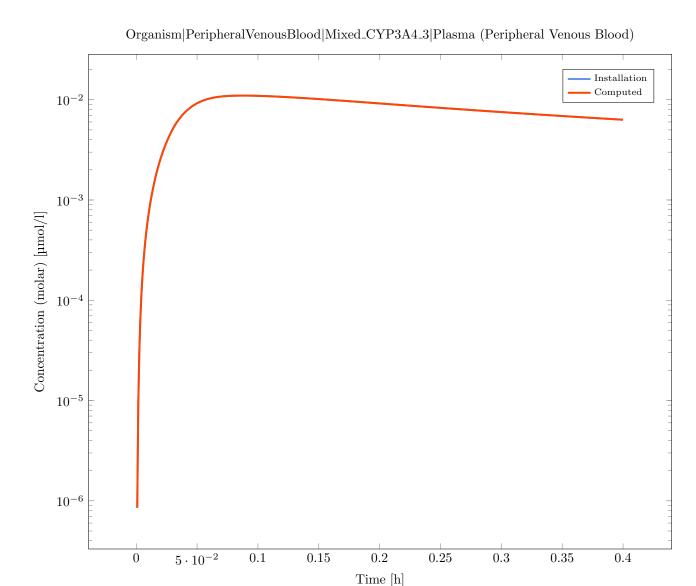


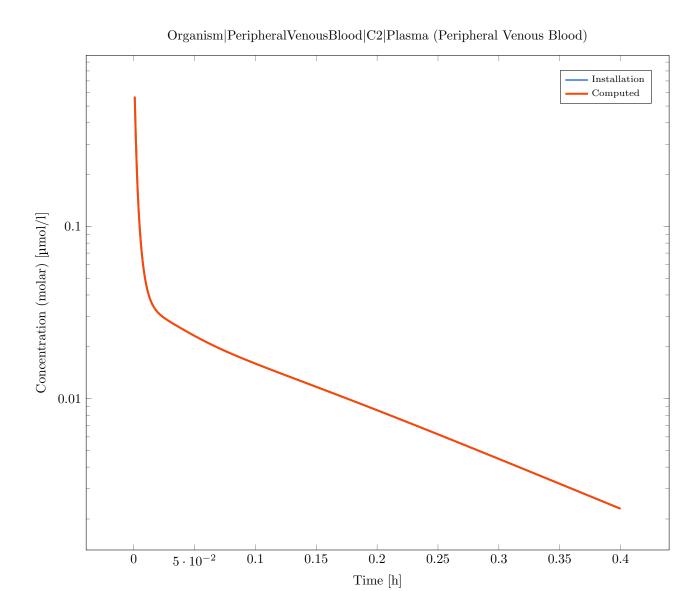
Figure 1.41

 $Simulation: \begin{tabular}{ll} DDI_Multiple Combinations-11_MM_Mechanism based_Mechanism based_Induction_Induction \end{tabular}$

Result of the validation: Valid

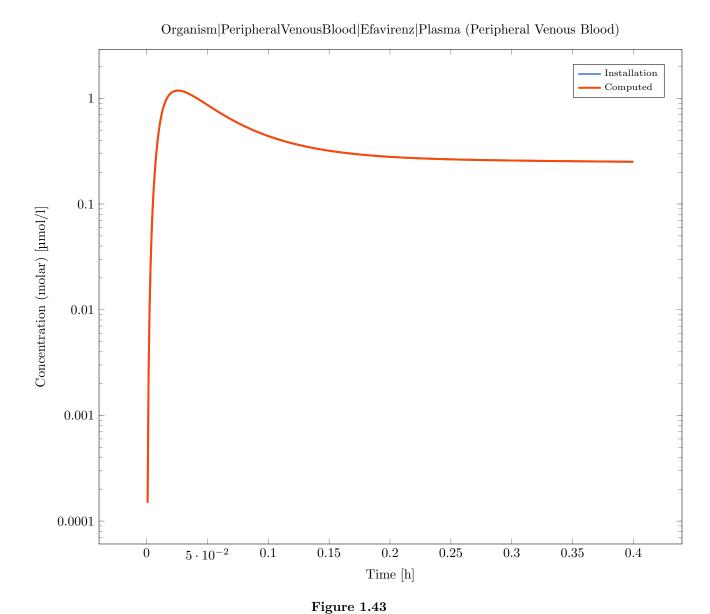
Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: $5.06\hbox{E-}4$

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Output Path: Organism |Peripheral Venous
Blood |Efavirenz |Plasma (Peripheral Venous Blood) Deviation:
 $1.75 \pm .4$

Figure 1.42



 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 5.99E-4

Organism|PeripheralVenousBlood|MechanismBased_3|Plasma (Peripheral Venous Blood)

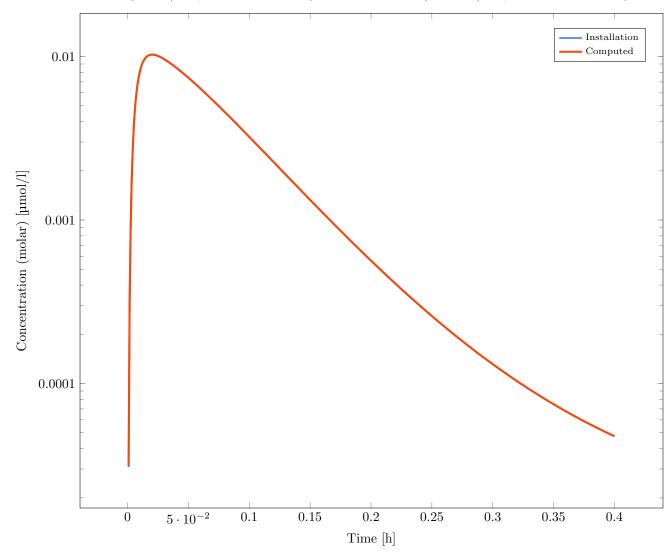


Figure 1.44

 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_4|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 6.01E-4

Organism|PeripheralVenousBlood|MechanismBased_4|Plasma (Peripheral Venous Blood)

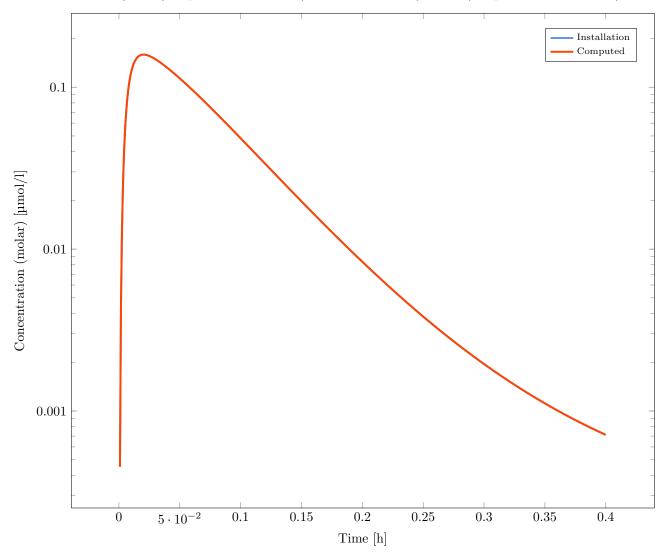


Figure 1.45

Output Path: Organism |Peripheral Venous
Blood |Rifampicin |Plasma (Peripheral Venous Blood)
 Deviation: $4.51 \hbox{E-}4$

$\label{eq:constraint} Organism | Peripheral Venous Blood) \\ Rifampicin | Plasma \; (Peripheral Venous Blood) \\$

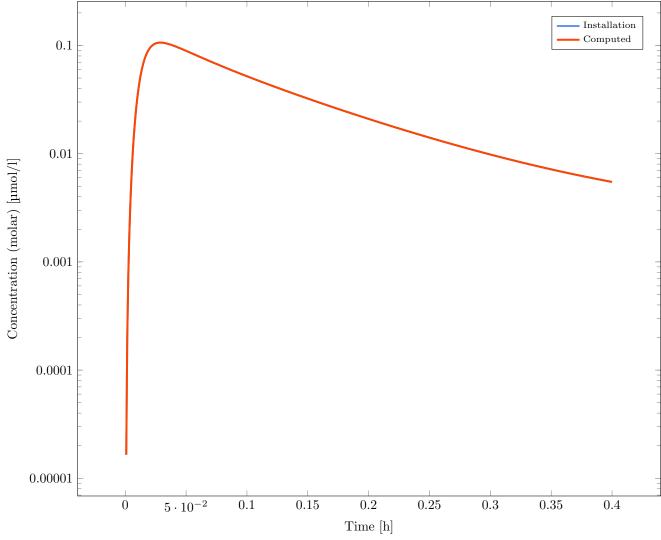


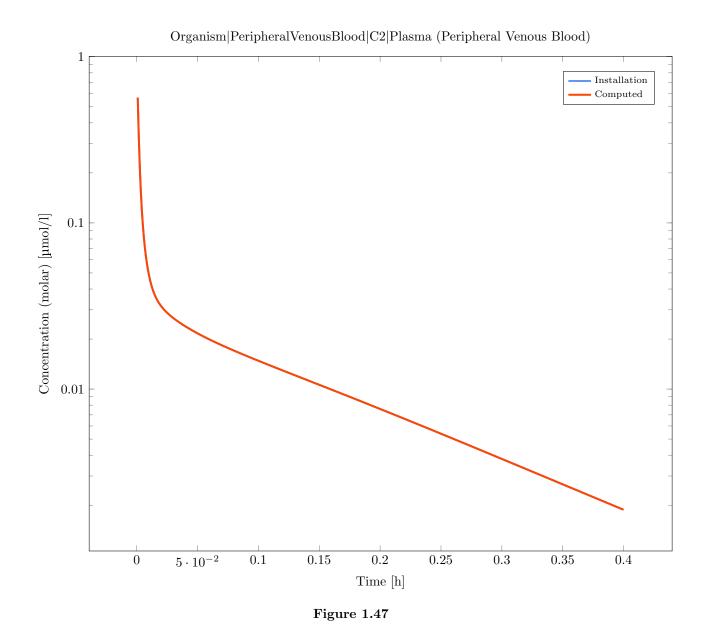
Figure 1.46

 $Simulation: \ DDI_MultipleCombinations-12_MM_All_DDI_Types$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C2|Plasma (Peripheral Venous Blood)

Deviation: 5.63E-4



Output Path: Organism |Peripheral Venous
Blood |Efavirenz |Plasma (Peripheral Venous Blood)
 Deviation: $1.92 \hbox{E-}4$

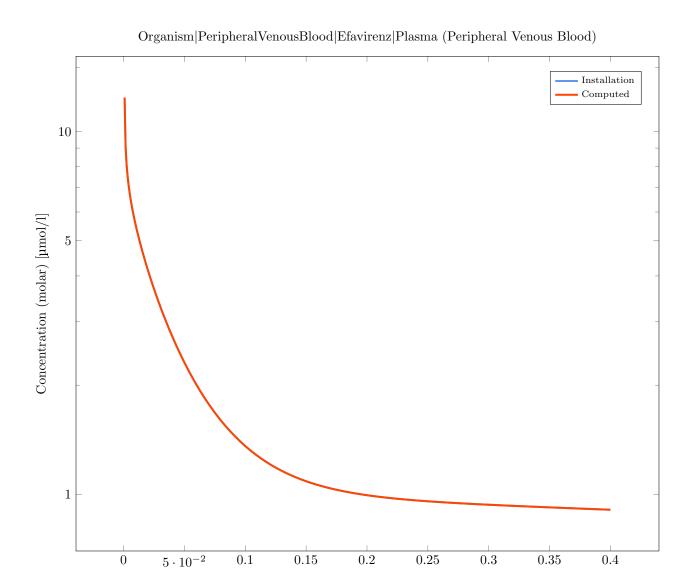
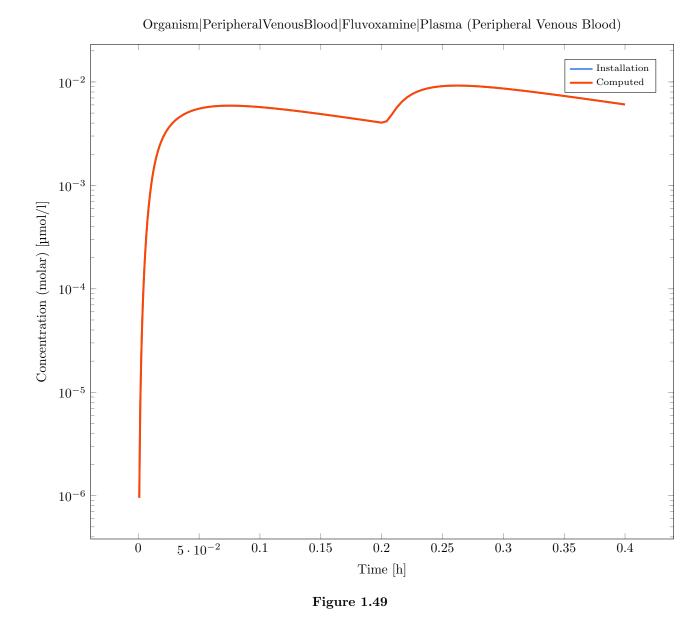


Figure 1.48

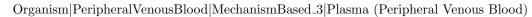
Time [h]

Output Path: Organism |Peripheral Venous
Blood |Fluvoxamine |Plasma (Peripheral Venous Blood)
 Deviation: 3.13E-4



 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 5.87E-4



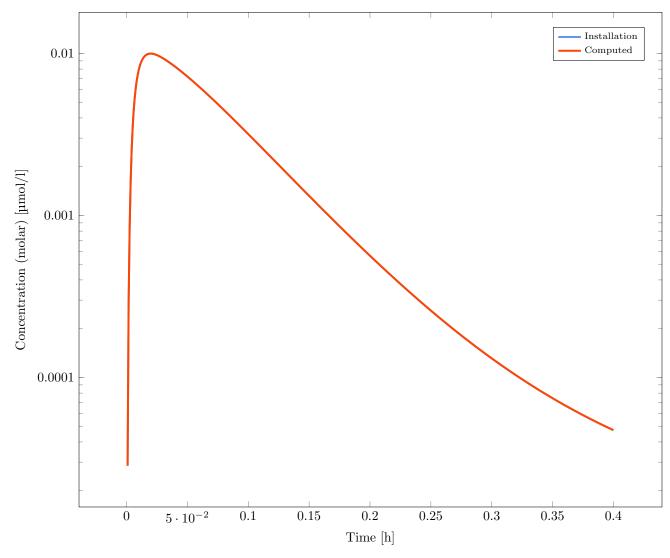


Figure 1.50

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_3|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 4.12E-4

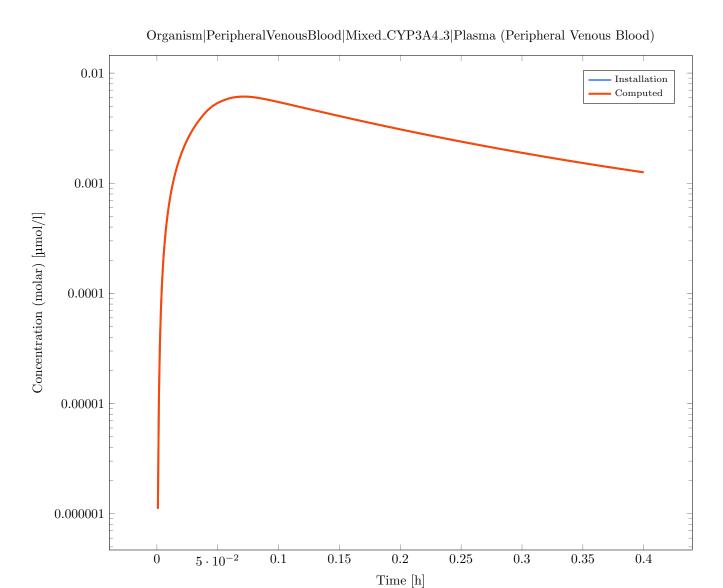
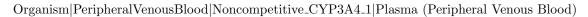


Figure 1.51

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 4.86E-4



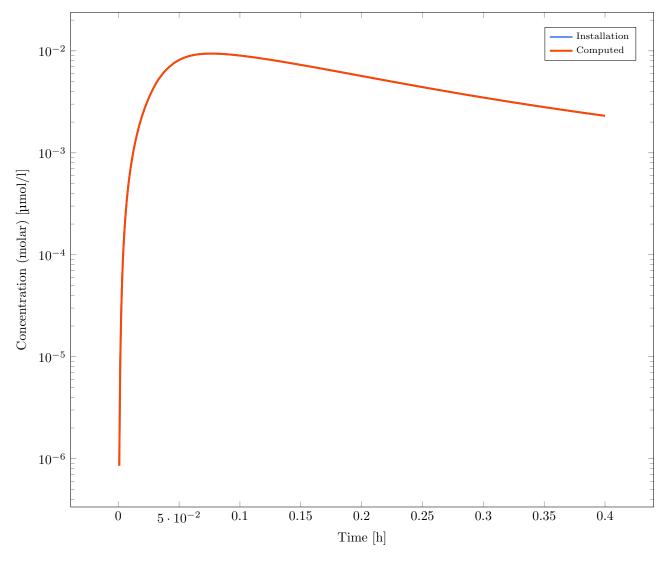


Figure 1.52

 $Output\ Path:\ Organism|PeripheralVenousBlood|Uncompetitive_CYP3A4_3|Plasma\ (PeripheralVenous\ Blood)$

Deviation: 5.05E-4

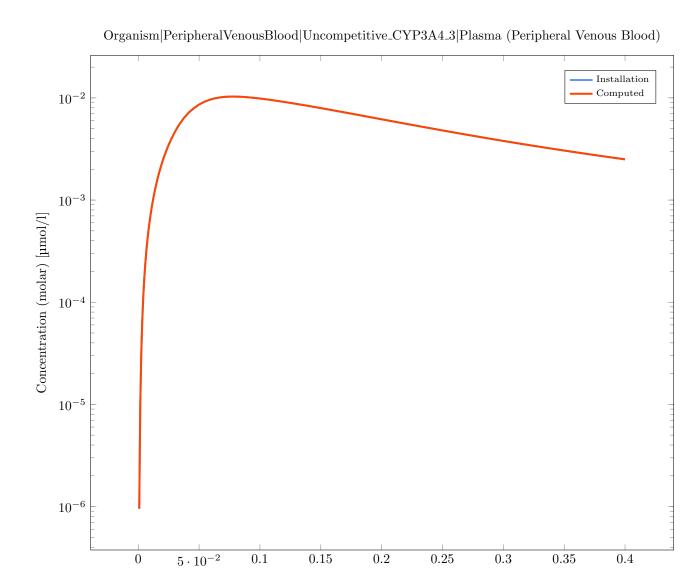
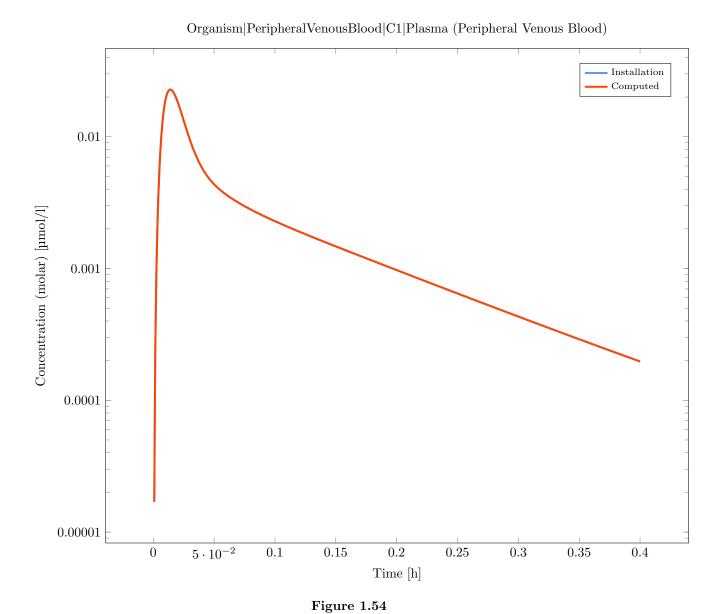


Figure 1.53

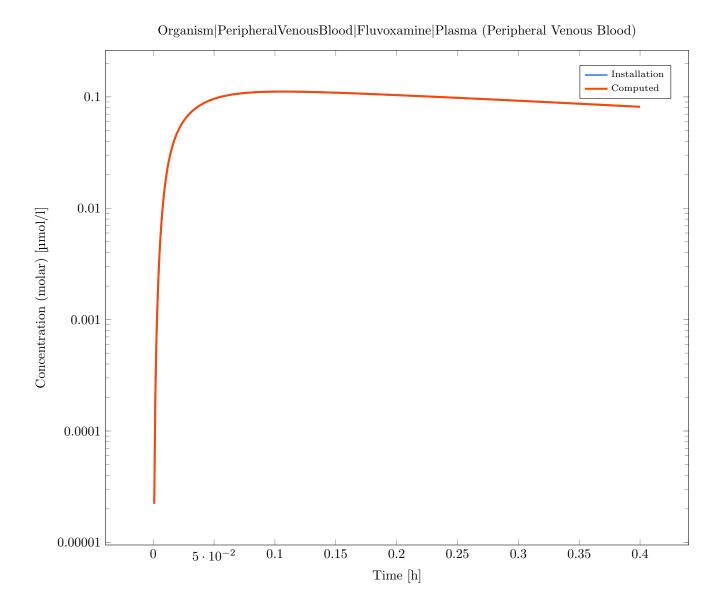
Time [h]

 ${\bf Simulation:\ DDI_Multiple Combinations-21_1st_Competitive_Competitive_Result\ of\ the\ validation:\ Valid}$

Output Path: Organism |Peripheral Venous
Blood |C1 |Plasma (Peripheral Venous Blood)
 Deviation: 2.97E-4



Output Path: Organism |Peripheral Venous
Blood |Fluvoxamine |Plasma (Peripheral Venous Blood)
 Deviation: 2.00E-4



Output Path: Organism|PeripheralVenousBlood|Itraconazole|Plasma (Peripheral Venous Blood)

Figure 1.55

Deviation: 2.44E-4

Installation Computed 0.1 Concentration (molar) [µmol/l] 0.01

Organism|PeripheralVenousBlood|Itraconazole|Plasma (Peripheral Venous Blood)

Figure 1.56

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

Simulation: DDI_MultipleCombinations-23_1st_Noncompetitive_Noncompetitive Result of the validation: Valid

0.1

 $5 \cdot 10^{-2}$

 $Output\ Path:\ Organism | Peripheral Venous Blood | Noncompetitive_CYP3A4_1 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Noncompetitive_CYP3A4_1 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Noncompetitive_CYP3A4_1 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Noncompetitive_CYP3A4_1 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Noncompetitive_CYP3A4_1 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Noncompetitive_CYP3A4_1 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Noncompetitive_CYP3A4_1 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Peripheral Venous Blood$ Venous Blood)

Deviation: 3.68E-4

0

Organism|PeripheralVenousBlood|Noncompetitive_CYP3A4_1|Plasma (Peripheral Venous Blood)

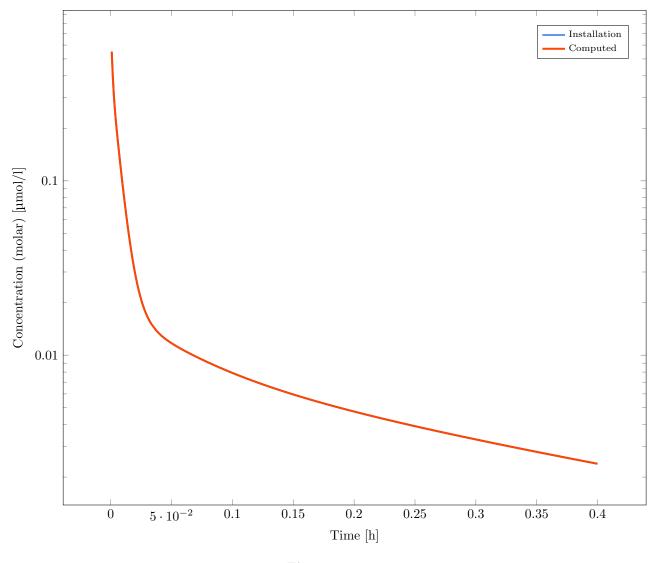


Figure 1.57

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_2|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.13E-4

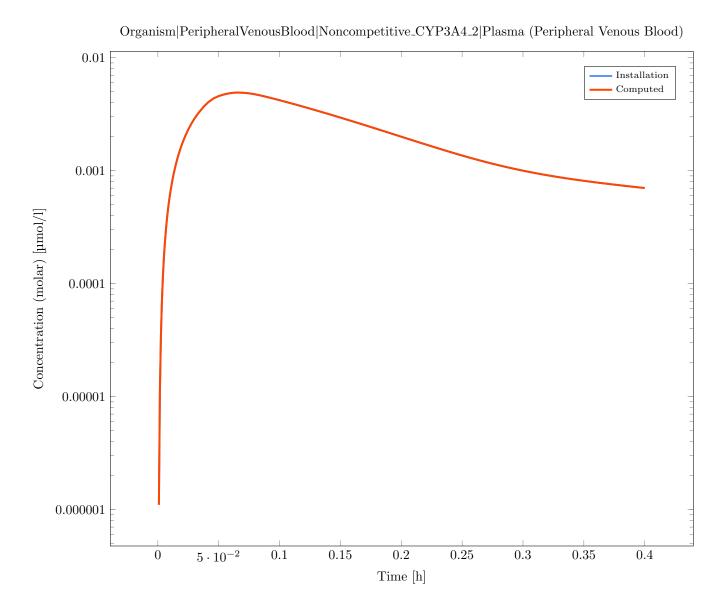


Figure 1.58

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 2.64E-4

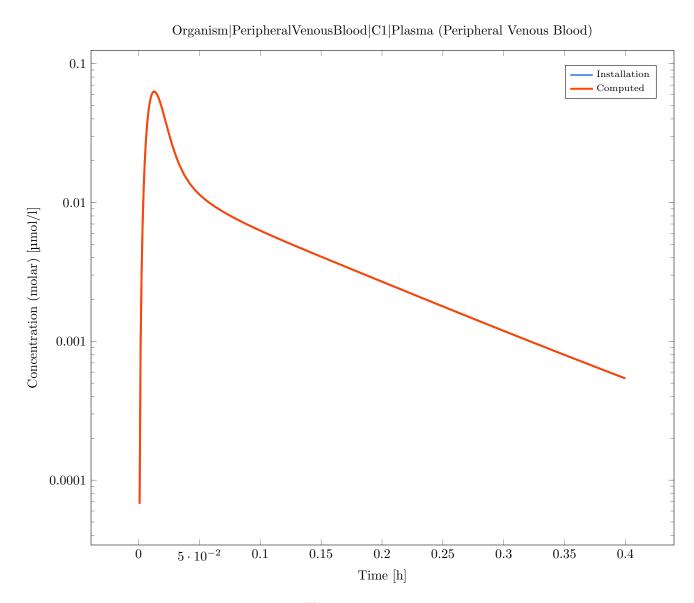


Figure 1.59

 $Simulation: \ DDI_MultipleCombinations-24_1st_Mixed_Mixed$

Result of the validation: Valid

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_1|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 3.11E-4

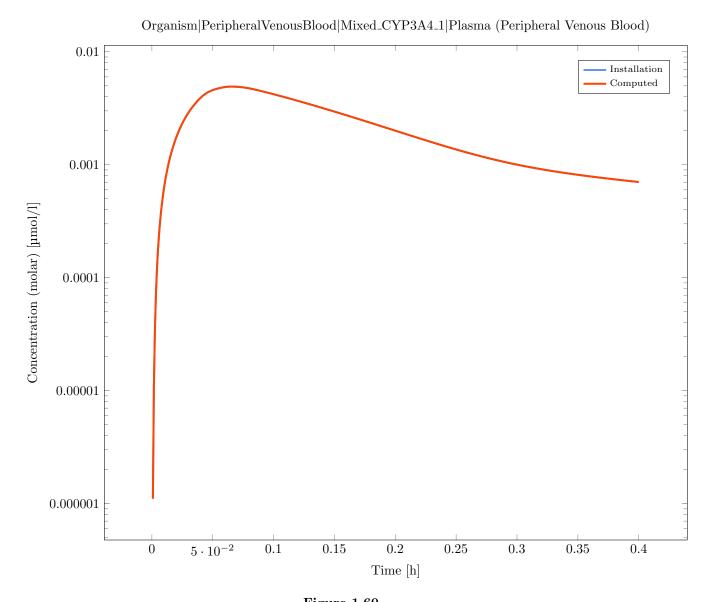


Figure 1.60

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_2|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 3.69E-4

$Organism | Peripheral Venous Blood | Mixed_CYP3A4_2 | Plasma~(Peripheral Venous~Blood)$

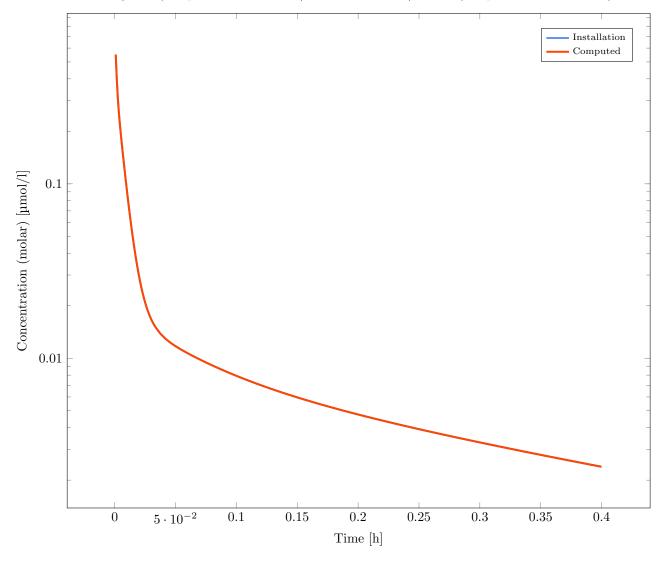


Figure 1.61

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 2.90E-4

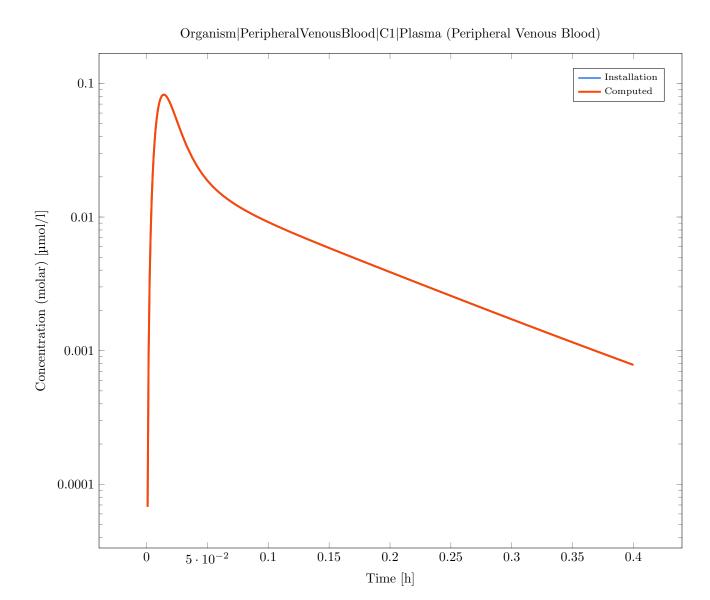
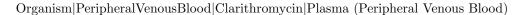


Figure 1.62

 ${\bf Simulation:\ DDI_Multiple Combinations\hbox{--}25_1st_Mechanismbased_Mechanismbased}. Result of the validation:\ Valid$

Output Path: Organism |Peripheral Venous
Blood |Clarithromycin |Plasma (Peripheral Venous Blood)
 Deviation: 2.03E-4



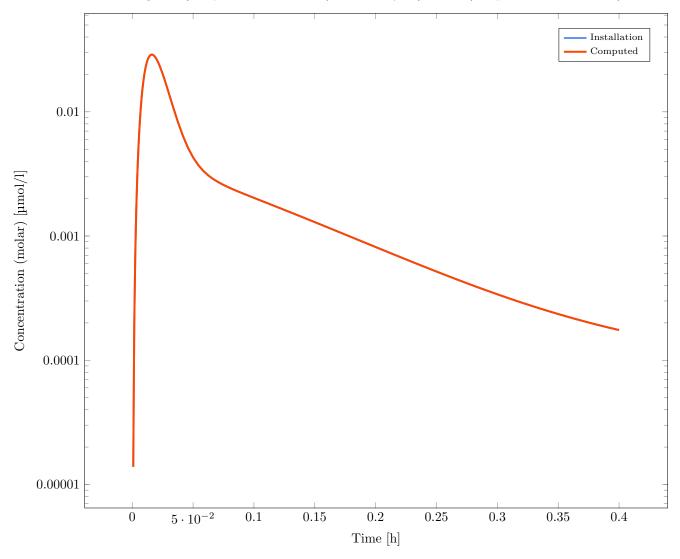
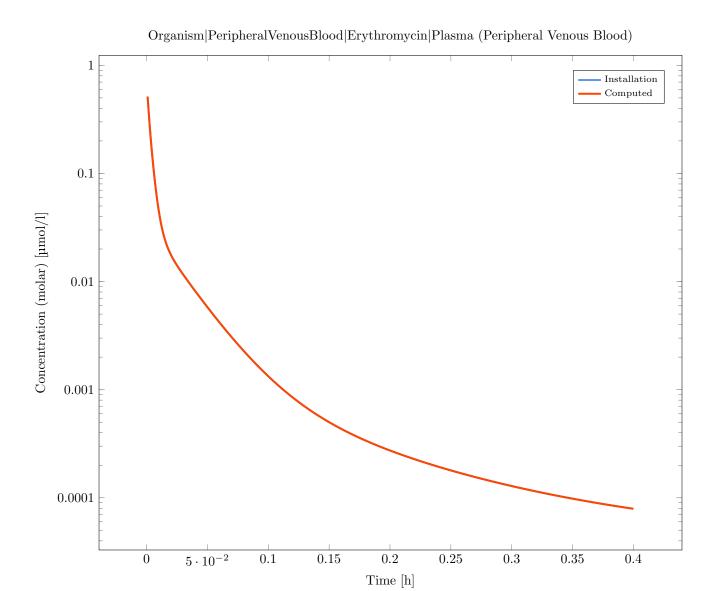


Figure 1.63

Output Path: Organism |PeripheralVenousBlood | Erythromycin |Plasma (Peripheral Venous Blood)
 Deviation: 3.61E-4



Output Path: Organism |Peripheral Venous
Blood |C1 |Plasma (Peripheral Venous Blood)
 Deviation: $2.67\hbox{E-}4$

Figure 1.64

Organism | Peripheral Venous Blood | C1 | Plasma (Peripheral Venous Blood) Installation Computed 0.1 0.01

Figure 1.65

0.15

0.2

Time [h]

0.25

0.3

0.35

0.4

Simulation: DDI_MultipleCombinations-26_1st_Induction_Induction

0.1

Result of the validation: Valid

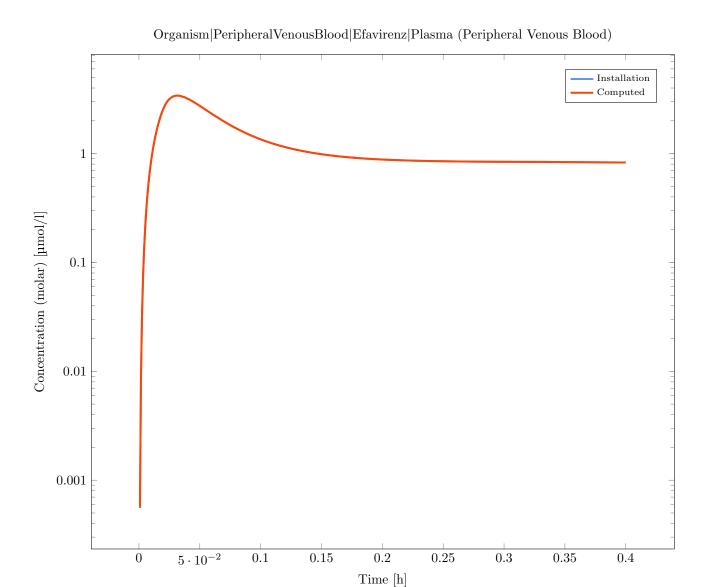
0

 $5\cdot 10^{-2}$

$Output\ Path:\ Organism | Peripheral Venous Blood | Efavirenz | Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 1.79E-4

0.001



Output Path: Organism|PeripheralVenousBlood|Rifampicin|Plasma (Peripheral Venous Blood)

Figure 1.66

Deviation: 3.68E-4

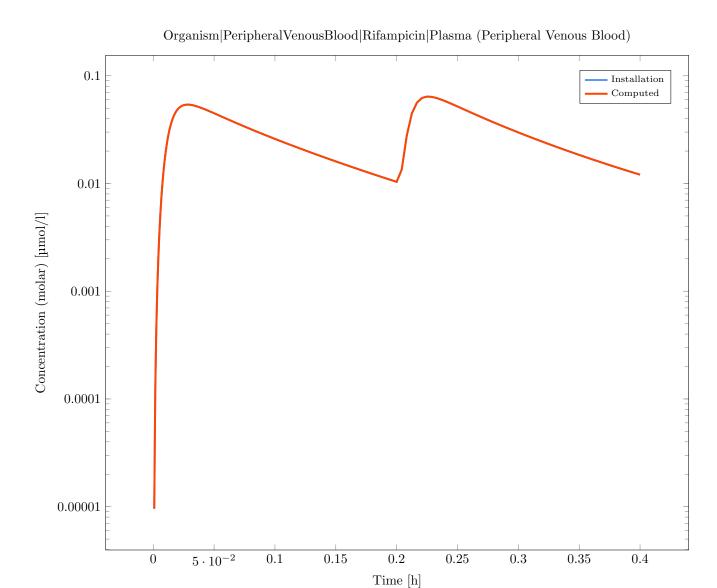
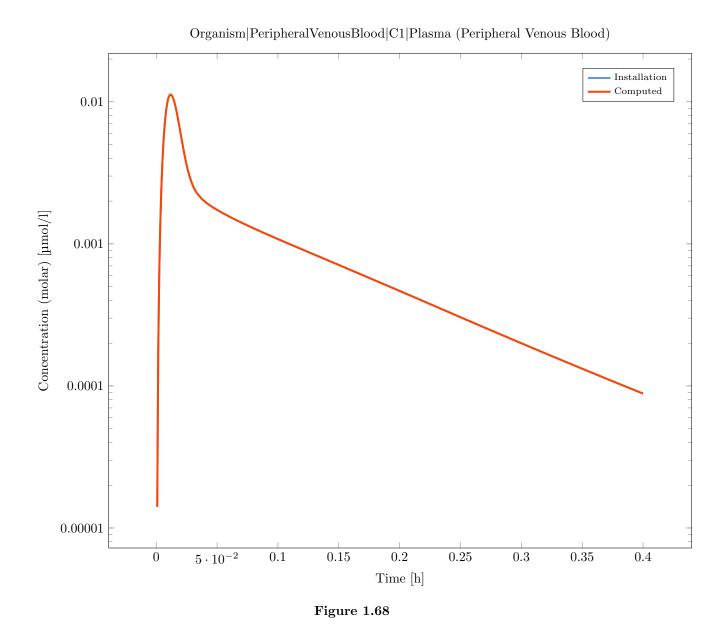


Figure 1.67

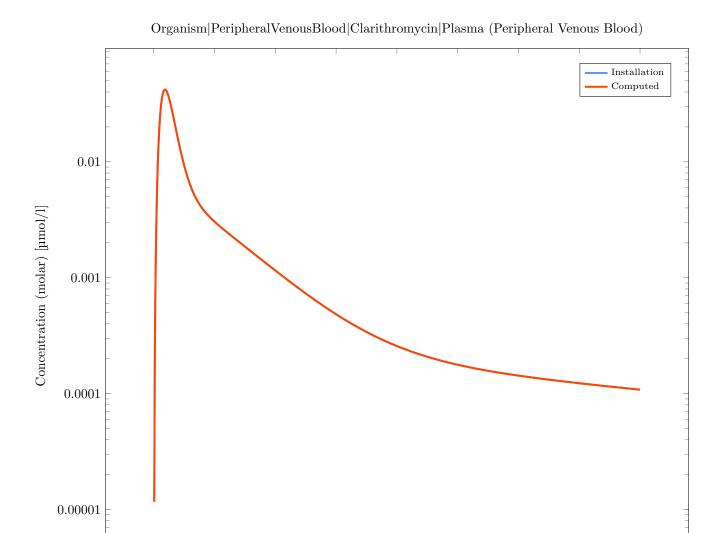
Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

Deviation: 2.59E-4



 $Simulation: \begin{tabular}{ll} DDI_MultipleCombinations-27_1st_Competitive_Competitive_Mechanismbased_Mechan$

Output Path: Organism |Peripheral Venous
Blood |Clarithromycin |Plasma (Peripheral Venous Blood)
 Deviation: 2.12E-4



Output Path: Organism |Peripheral Venous
Blood |Erythromycin |Plasma (Peripheral Venous Blood)
 Deviation: 6.19E-4

Figure 1.69

0.3

0.4

Time [h]

0.5

0.6

0.7

0.8

0

0.1

0.2

Organism|PeripheralVenousBlood|Erythromycin|Plasma (Peripheral Venous Blood)

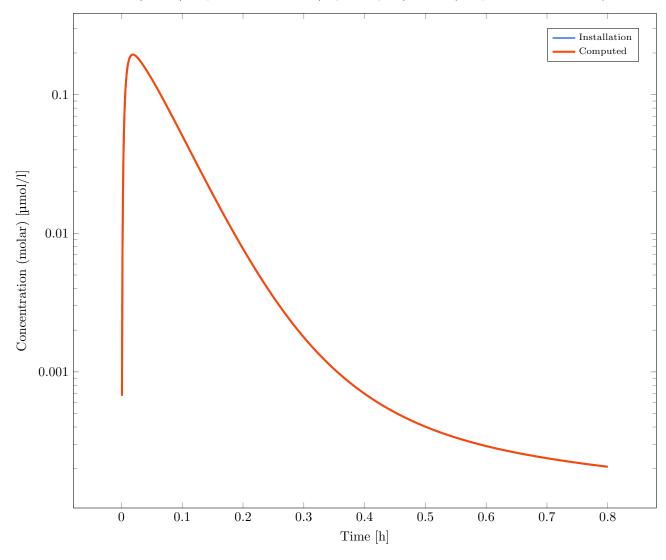


Figure 1.70

Output Path: Organism |Peripheral Venous
Blood |Itraconazole |Plasma (Peripheral Venous Blood)
 Deviation: 3.28E-4

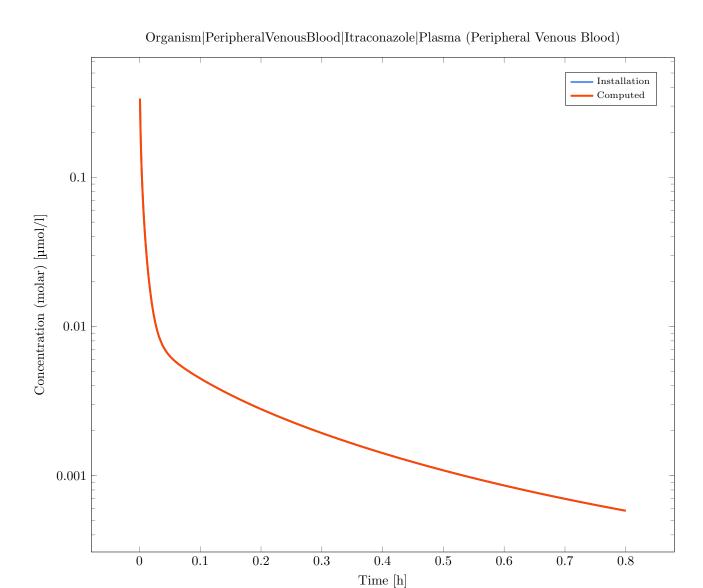
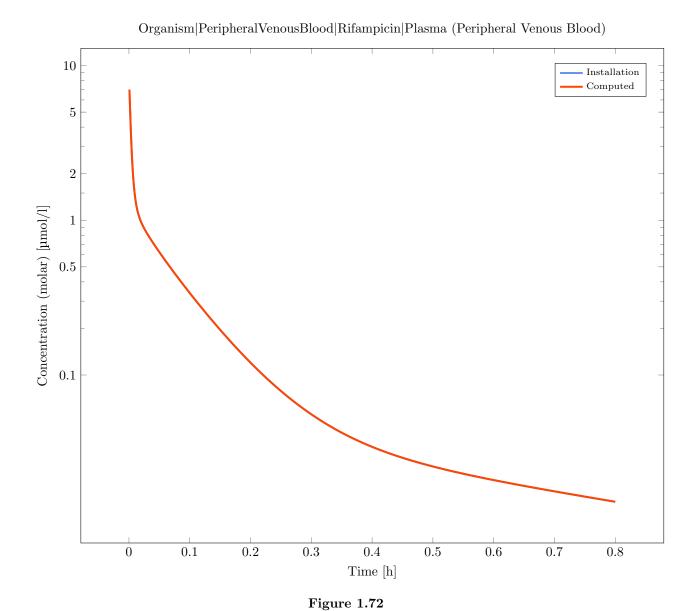


Figure 1.71

Output Path: Organism |Peripheral Venous
Blood |Rifampicin |Plasma (Peripheral Venous Blood)
 Deviation: $4.68 \hbox{E-}4$



Output Path: Organism |PeripheralVenousBlood |C1 |Plasma (Peripheral Venous Blood)
 Deviation: $2.84\hbox{E-}4$

Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood) O.01 O.0001 O.00001

Figure 1.73

0.4

Time [h]

0.5

0.6

0.7

0.8

0.3

 $Simulation: \ DDI_Multiple Combinations - 28_1 st_Uncompetitive_Uncompetitive_Mechanism based_Mechanism based$

Result of the validation: Valid

0

0.1

0.2

 $Output\ Path:\ Organism|Peripheral Venous Blood|MechanismBased_4|Plasma\ (Peripheral\ Venous Blood)$

Deviation: 5.98E-4

Organism|PeripheralVenousBlood|MechanismBased_4|Plasma (Peripheral Venous Blood)

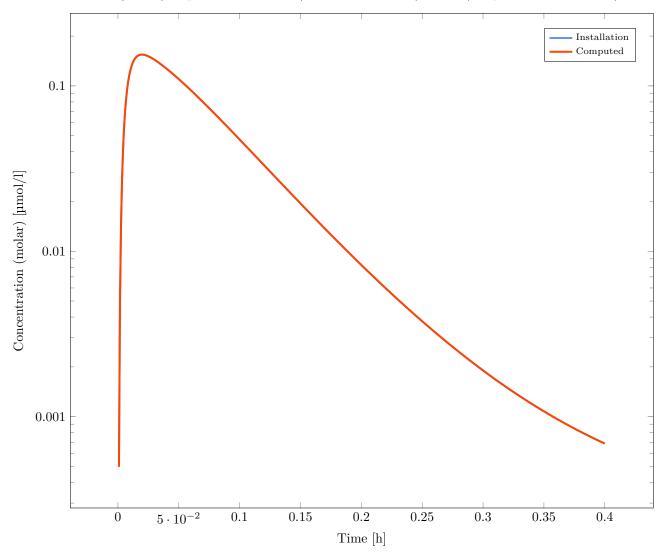
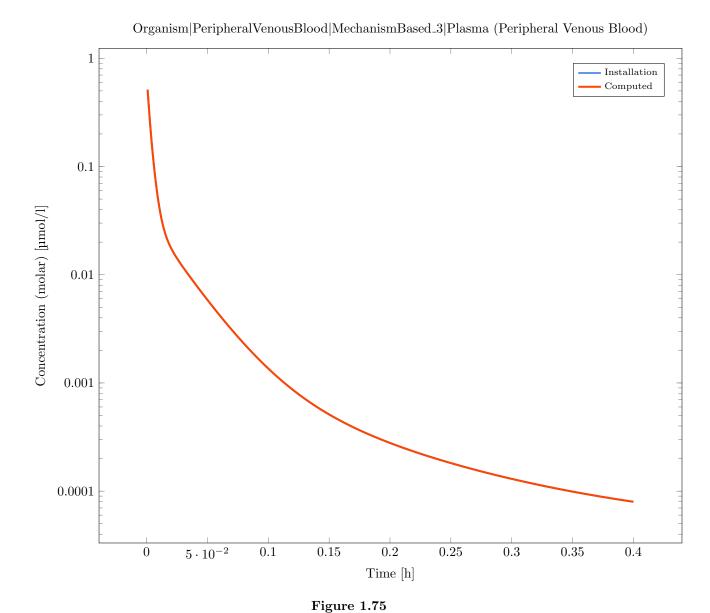


Figure 1.74

 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.67E-4



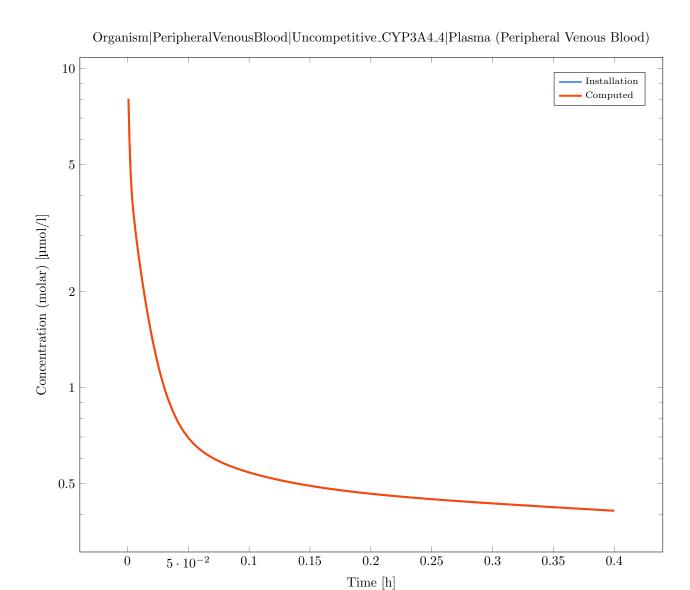
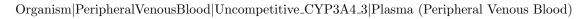


Figure 1.76

 $Output\ Path:\ Organism|PeripheralVenousBlood|Uncompetitive_CYP3A4_3|Plasma\ (PeripheralVenousBlood)\\ PeripheralVenousBlood)$

Deviation: 1.33E-4



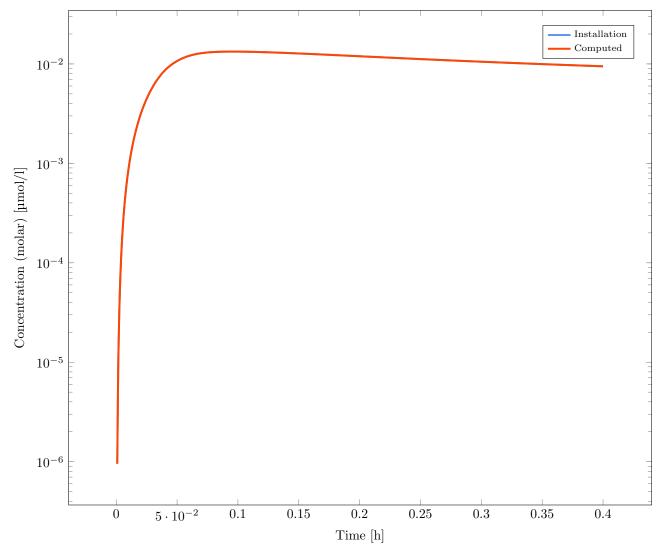


Figure 1.77

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 5.02E-4

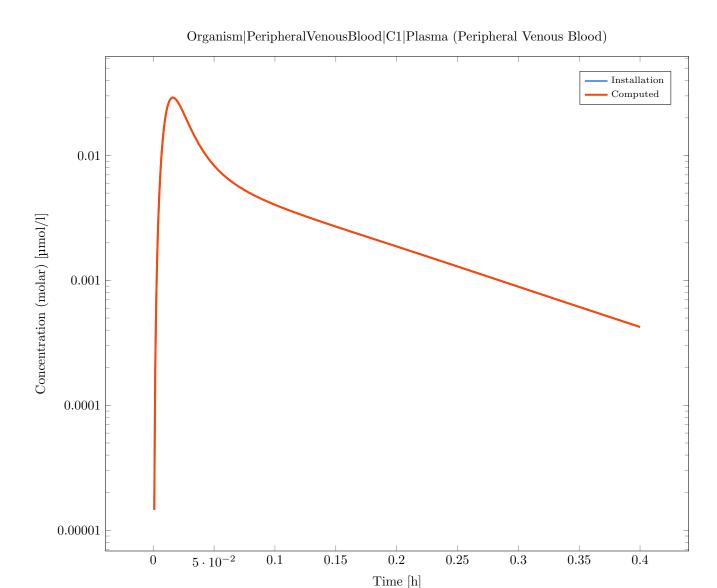


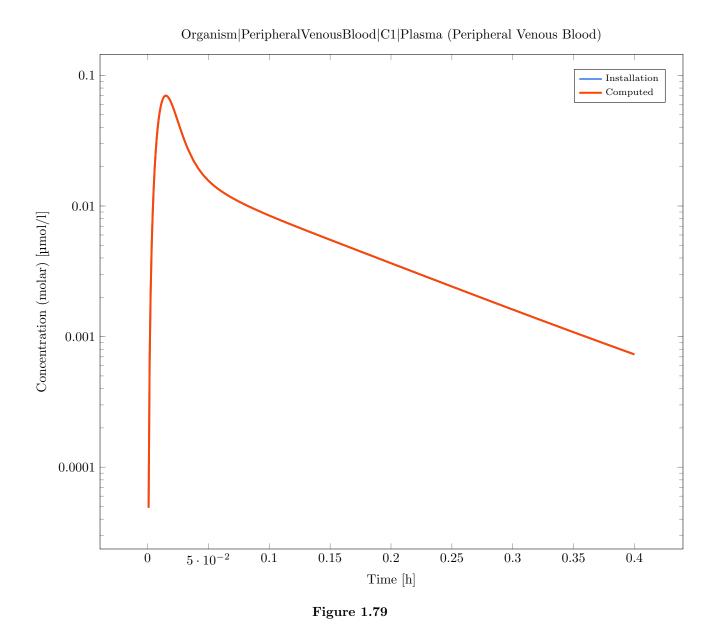
Figure 1.78

 $Simulation: \ DDI_Multiple Combinations \textbf{-} 29_1st_Noncompetitive_Noncompetitive_Mechanism based_Mechanism based$

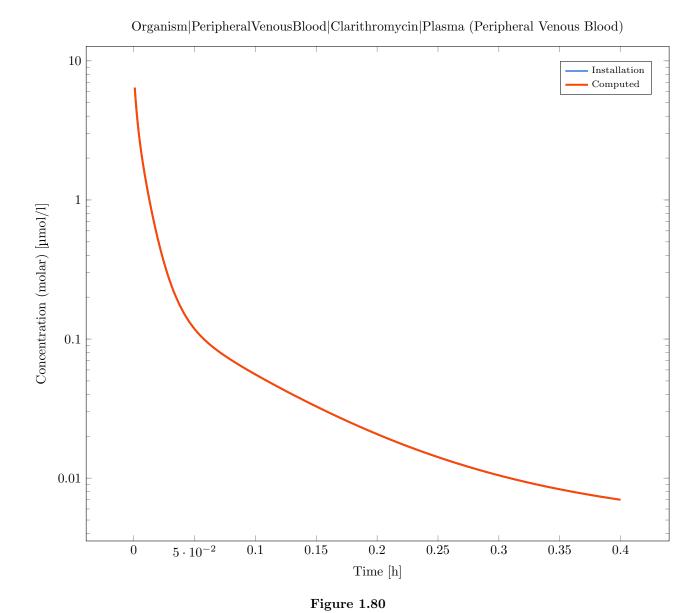
Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

Deviation: 2.88E-4



Output Path: Organism |Peripheral Venous
Blood |Clarithromycin |Plasma (Peripheral Venous Blood)
 Deviation: 2.49E-4



Output Path: Organism |Peripheral Venous
Blood |Erythromycin |Plasma (Peripheral Venous Blood)
 Deviation: 5.73E-4

Organism|PeripheralVenousBlood|Erythromycin|Plasma (Peripheral Venous Blood)

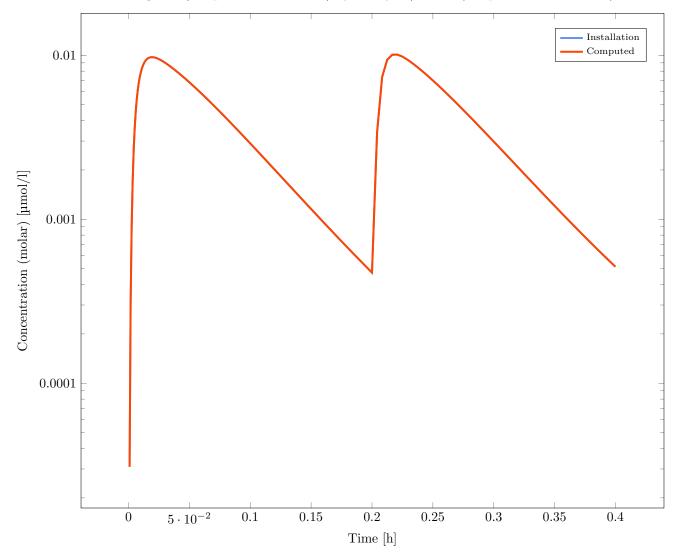


Figure 1.81

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.26E-4



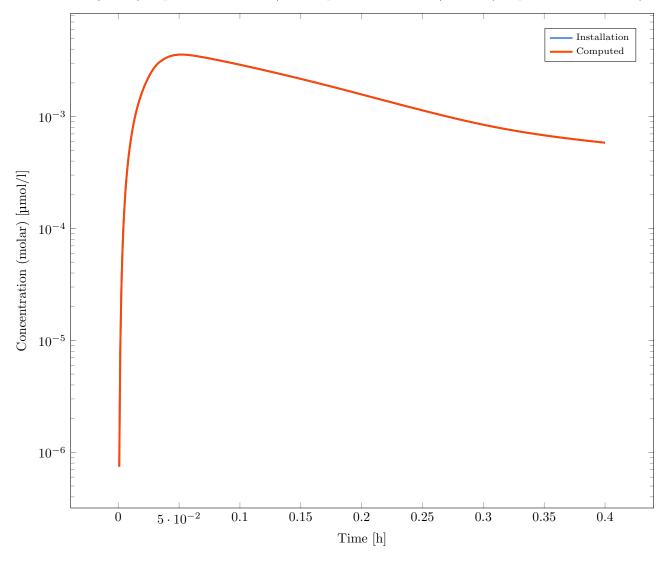
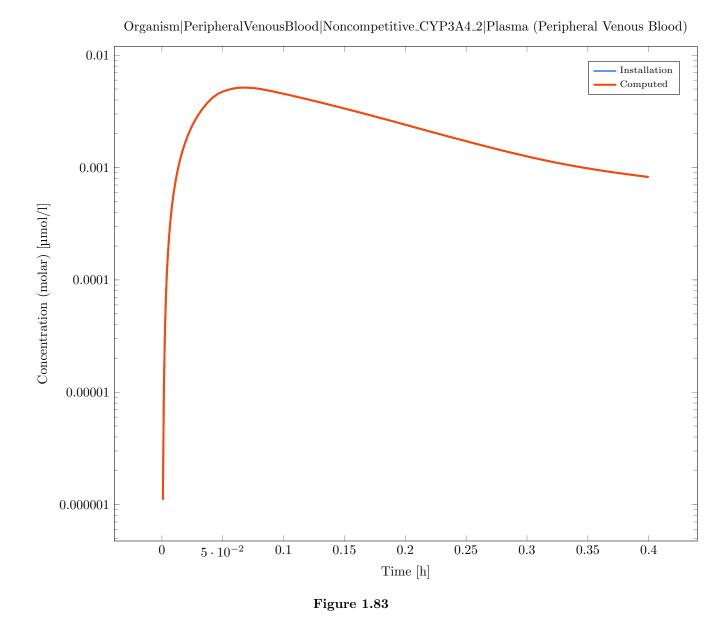


Figure 1.82

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_2|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 3.38E-4



 $Simulation: \begin{tabular}{ll} DDI_MultipleCombinations-30_1st_Mixed_Mechanismbased_Mechanism$

 $Output\ Path:\ Organism|Peripheral Venous Blood|MechanismBased_4|Plasma\ (Peripheral\ Venous Blood)$

Deviation: 5.77E-4

Organism|PeripheralVenousBlood|MechanismBased_4|Plasma (Peripheral Venous Blood)

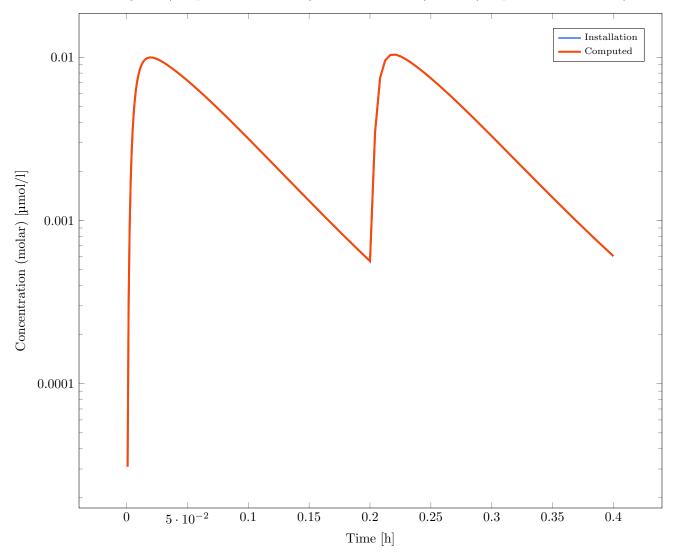


Figure 1.84

 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 6.10E-4

$Organism | Peripheral Venous Blood | Mechanism Based_3 | Plasma \ (Peripheral Venous Blood)$

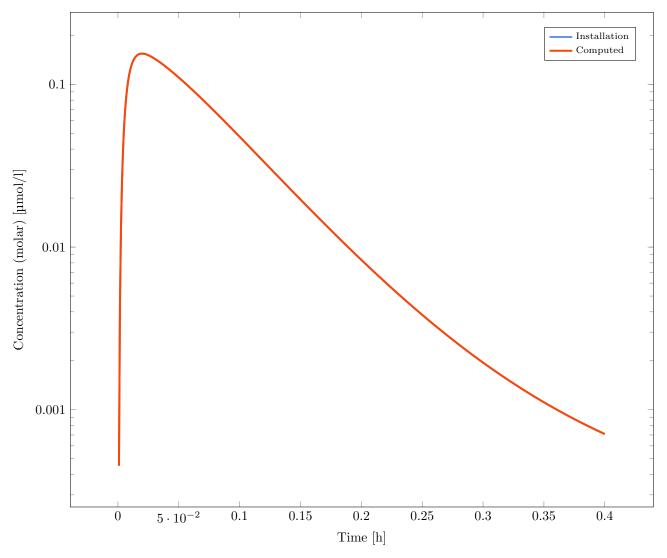
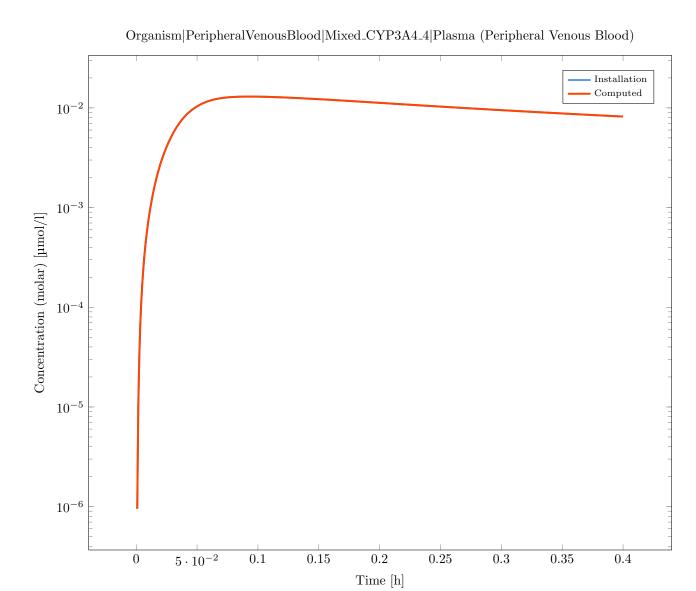


Figure 1.85

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_4|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 1.03E-4



 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_3|Plasma\ (Peripheral\ VenousBlood)$

Figure 1.86

Deviation: 1.65E-4

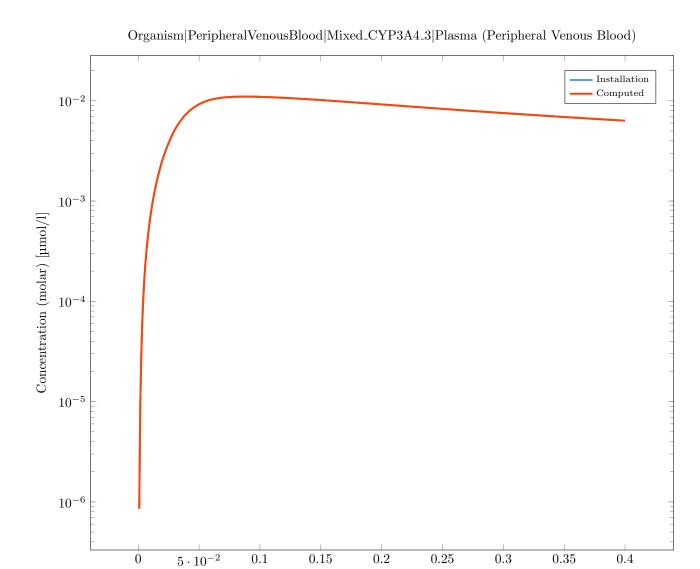


Figure 1.87

Time [h]

Output Path: Organism |PeripheralVenousBlood |C1 |Plasma (Peripheral Venous Blood)
 Deviation: $6.89\hbox{E-}4$

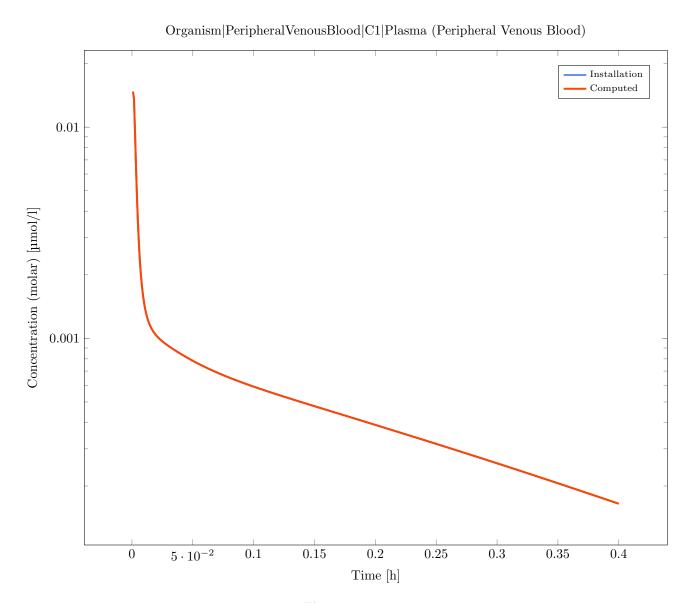
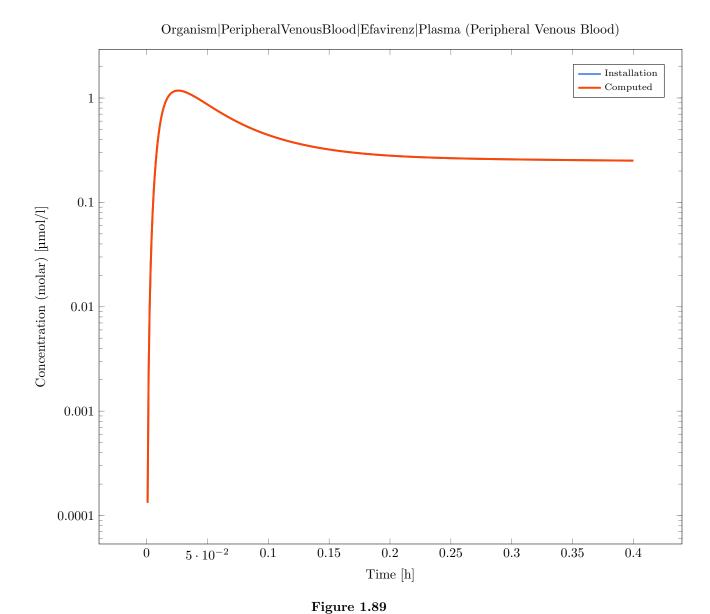


Figure 1.88

 ${\bf Simulation:\ DDI_Multiple Combinations\hbox{--}31_1st_Mechanismbased_Mechanismbased_Induction_Induction} \\ {\bf Result\ of\ the\ validation:\ Valid}$

Output Path: Organism |Peripheral Venous
Blood |Efavirenz |Plasma (Peripheral Venous Blood)
 Deviation: 1.73E-4



Output Path: Organism |PeripheralVenousBlood |MechanismBased_3 |Plasma (Peripheral Venous Blood)

Deviation: 6.11E-4

Organism|PeripheralVenousBlood|MechanismBased_3|Plasma (Peripheral Venous Blood)

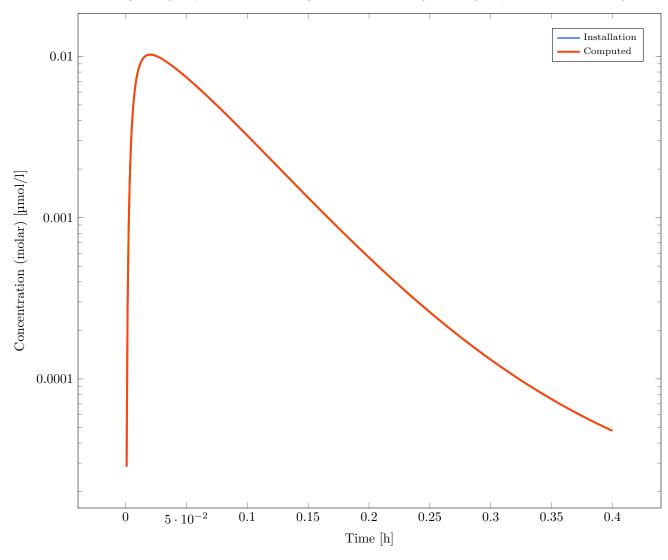


Figure 1.90

 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_4|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 6.12E-4

Organism|PeripheralVenousBlood|MechanismBased_4|Plasma (Peripheral Venous Blood)

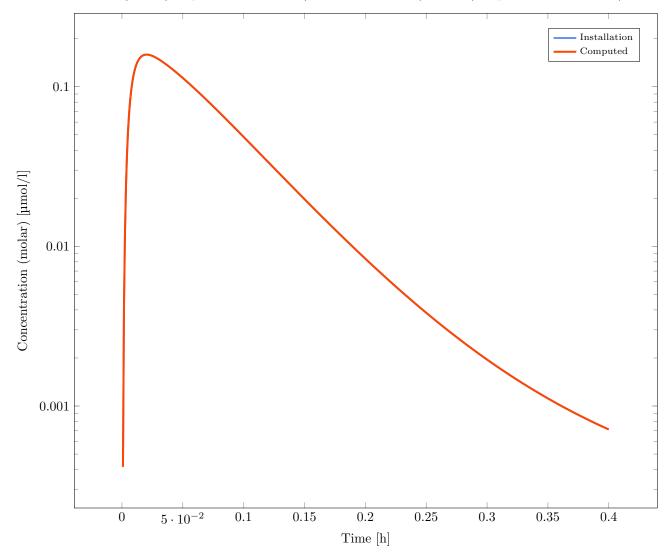
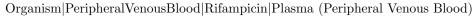


Figure 1.91

Output Path: Organism |Peripheral Venous
Blood |Rifampicin |Plasma (Peripheral Venous Blood)
 Deviation: $4.48\hbox{E-}4$



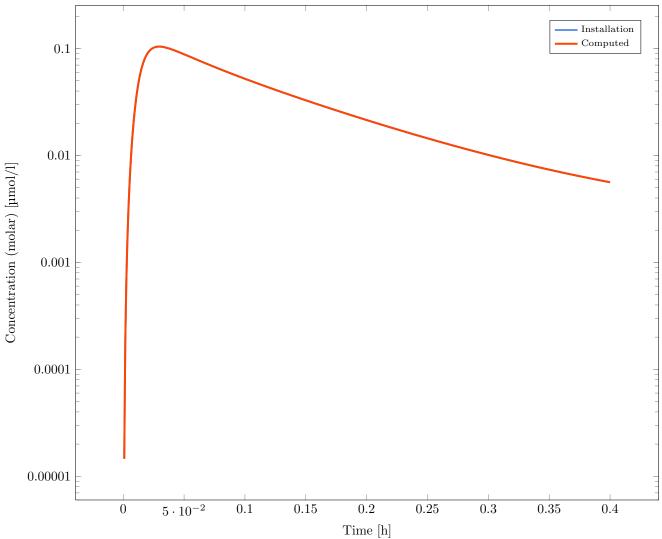


Figure 1.92

Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

Deviation: 5.56E-4

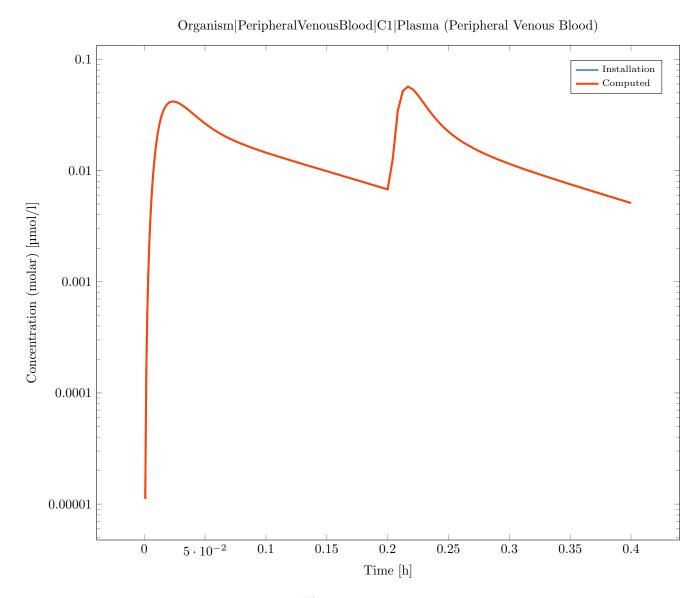


Figure 1.93

 $Simulation: \ DDI_MultipleCombinations-32_1st_All_DDI_Types$

Result of the validation: Valid

 $Output\ Path:\ Organism | Peripheral Venous Blood | Efavirenz | Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 1.92E-4

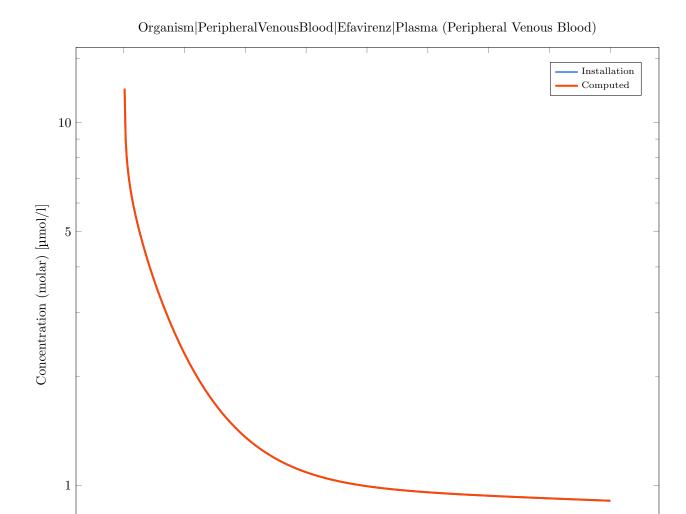


Figure 1.94

0.2

Time [h]

0.25

0.3

0.35

0.4

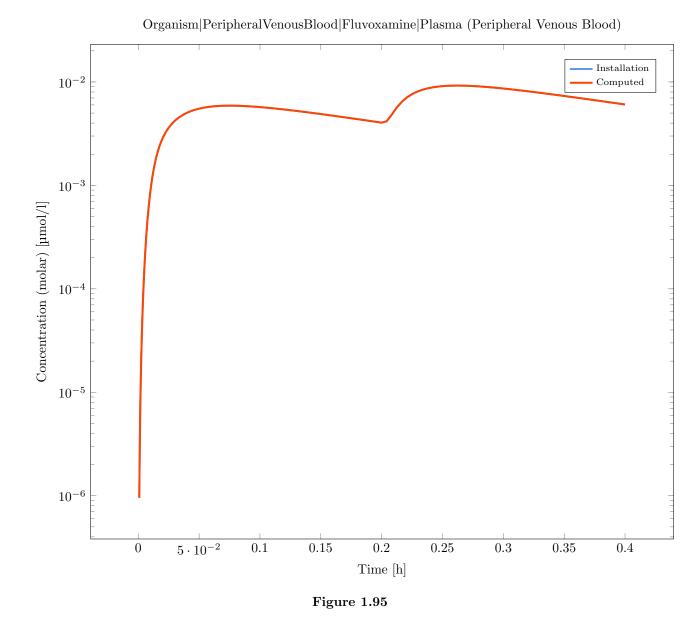
0.15

0.1

Output Path: Organism |Peripheral Venous
Blood |Fluvoxamine |Plasma (Peripheral Venous Blood)
 Deviation: 3.13E-4

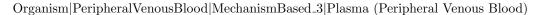
0

 $5\cdot 10^{-2}$



 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 6.04E-4



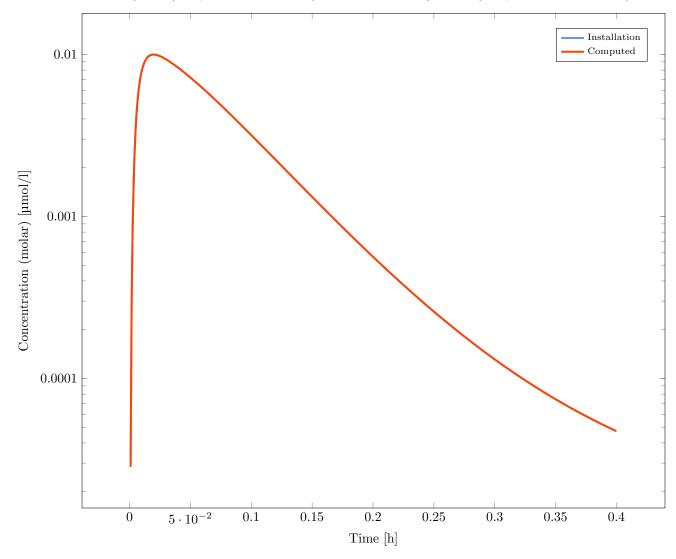


Figure 1.96

 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_3|Plasma\ (Peripheral\ VenousBlood)$

Deviation: 4.09E-4

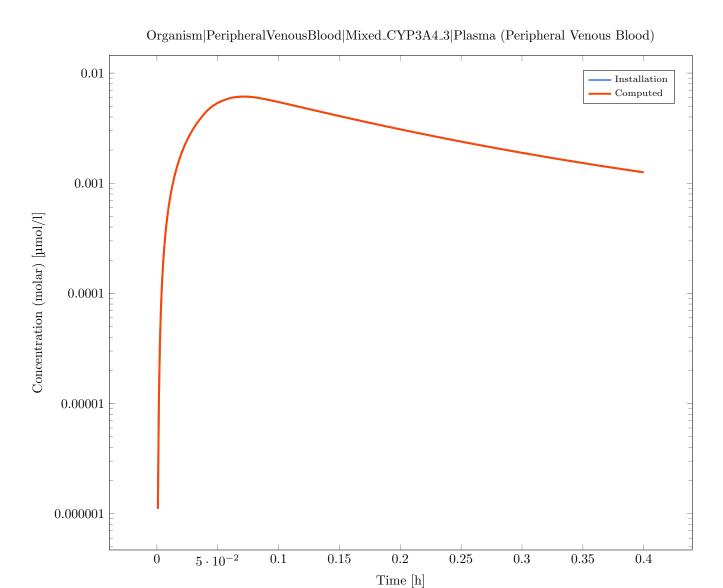
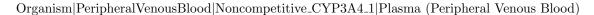


Figure 1.97

 $Output\ Path:\ Organism|Peripheral Venous Blood|Noncompetitive_CYP3A4_1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 5.14E-4



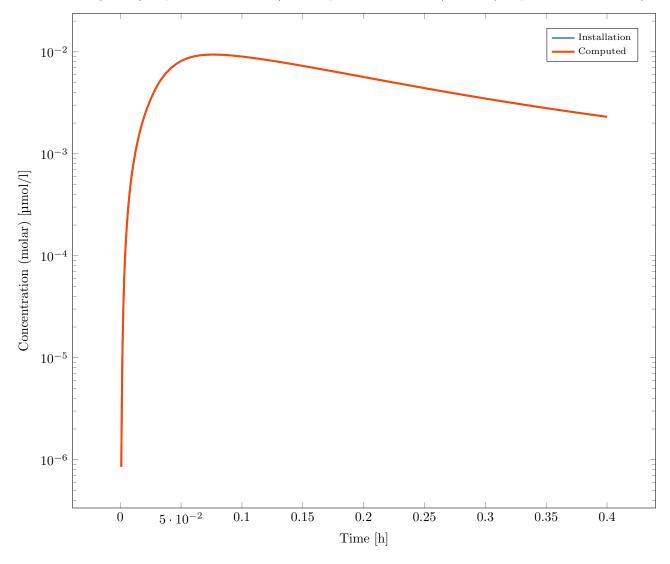
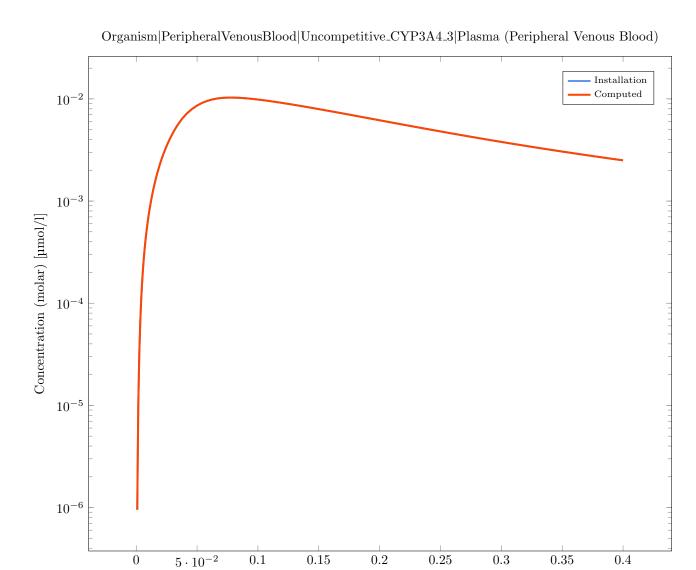


Figure 1.98

 $Output\ Path:\ Organism|PeripheralVenousBlood|Uncompetitive_CYP3A4_3|Plasma\ (PeripheralVenous\ Blood)$

Deviation: 5.21E-4



Output Path: Organism |Peripheral Venous
Blood |C1 |Plasma (Peripheral Venous Blood)
 Deviation: 6.80E-4

Time [h]

Figure 1.99

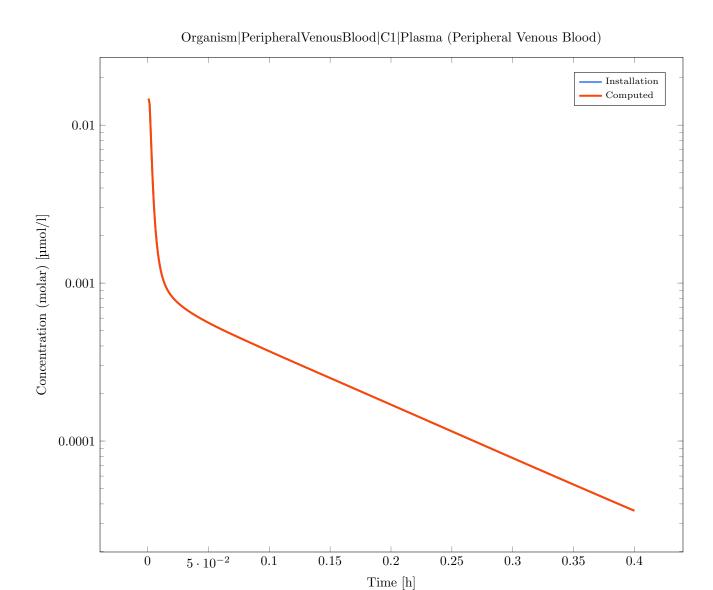


Figure 1.100

Simulation: Dog_MultiORAL_12_12_Dissolved-Dog_MultiORAL_12_12_Dissolved Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood) Deviation:
 0

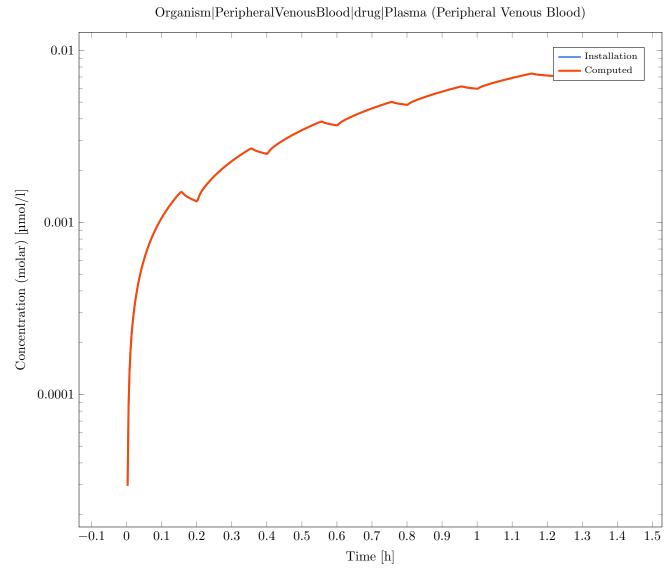


Figure 1.101

 $\begin{tabular}{ll} \bf Simulation: \begin{tabular}{ll} \bf Dog_MultiORAL_24_Dissolved-Dog_MultiORAL_24_$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood) Deviation:
 0

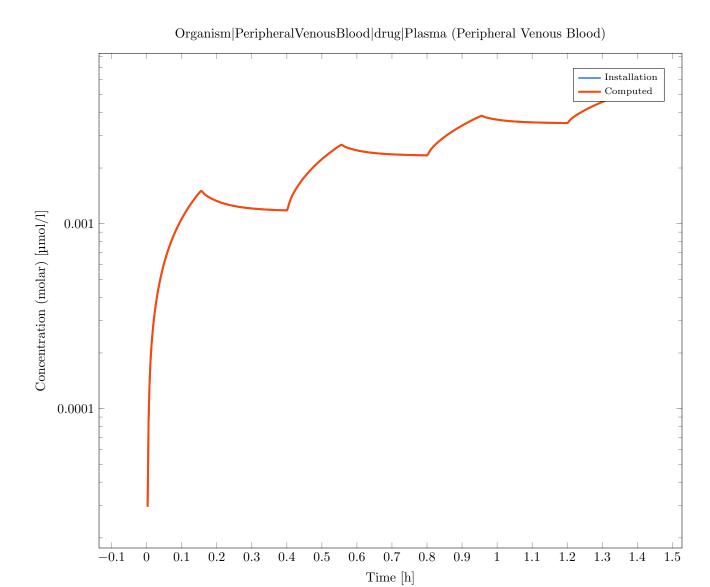
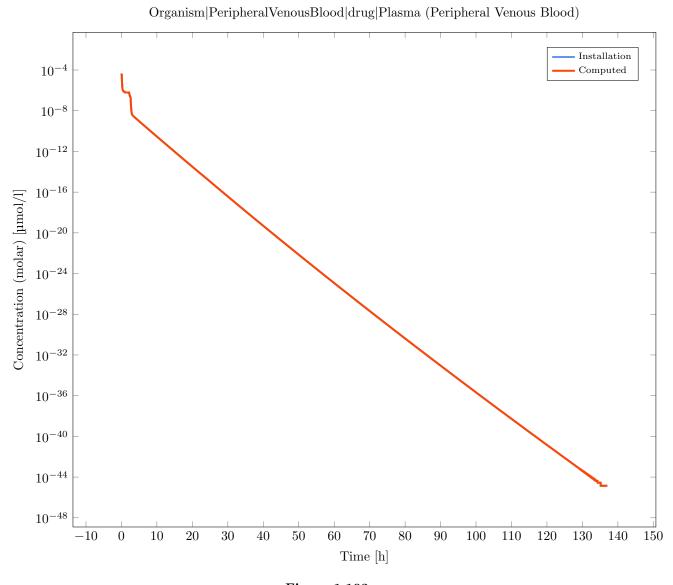


Figure 1.102

 $\begin{tabular}{ll} \bf Simulation: European_SingleORAL_Age_0_CYP3A4-European_SingleORAL_Age_0_CYP3$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 1.24E-5



 ${\bf Figure~1.103}$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: $8.28 \pm .5$

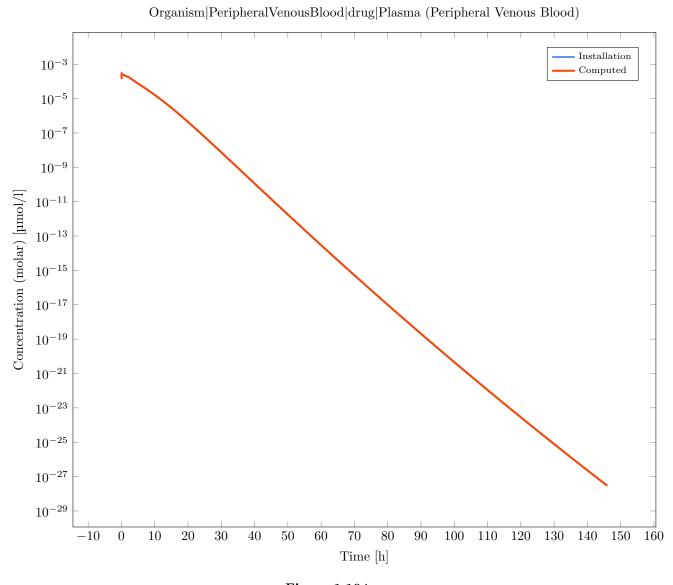
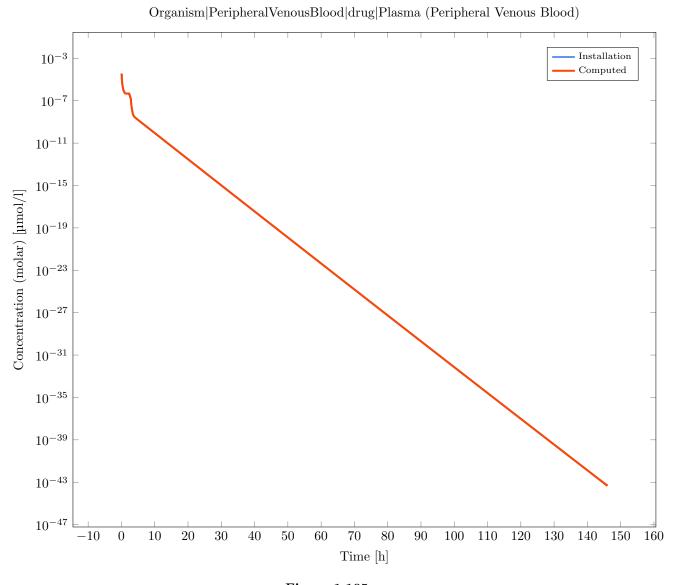


Figure 1.104

 $\begin{tabular}{ll} \bf Simulation: European_SingleORAL_Age_1_CYP3A4-European_SingleORAL_Age_1_CYP3$

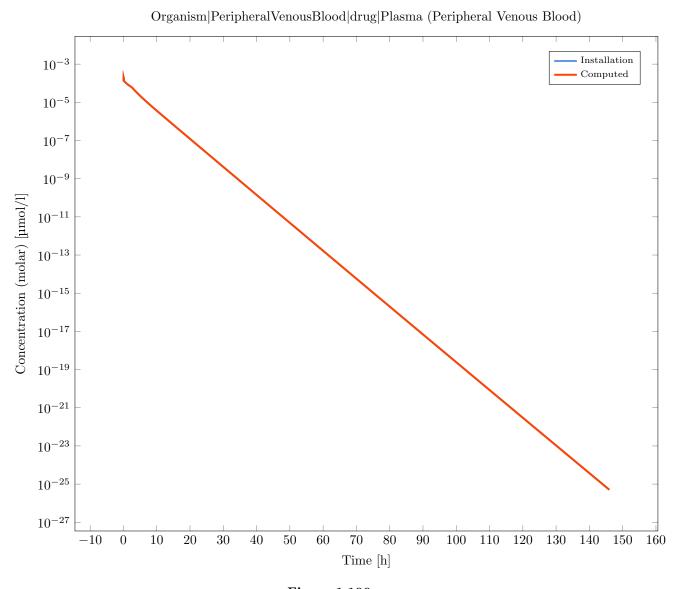
Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 1.68E-6



 ${\bf Figure~1.105}$

 ${\bf Simulation: European_SingleORAL_Age_1_GFR-European_SingleORAL_Age_1_GFR} \\ {\bf Result of the \ validation: \ Valid}$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 1.19E-7



 ${\bf Figure~1.106}$

 ${\bf Simulation: Human_Competitive Inhibition-Human_Competitive Inhibition}$

Result of the validation: Valid

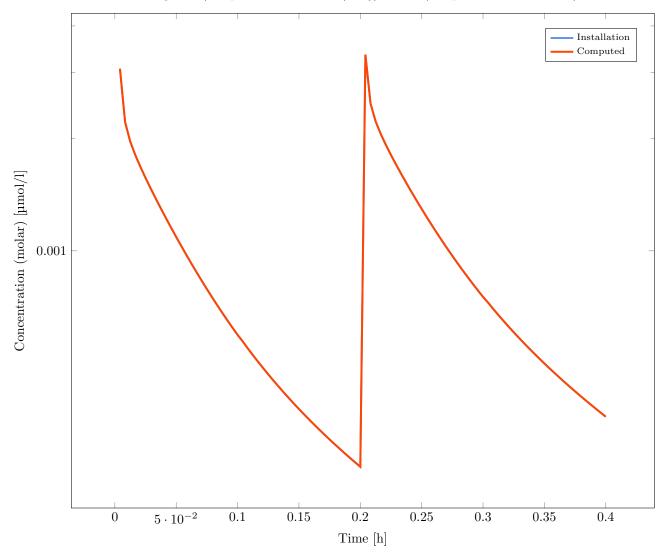


Figure 1.107

Output Path: Organism |PeripheralVenousBlood |
inhibitor |Plasma (Peripheral Venous Blood) | Deviation:
 0

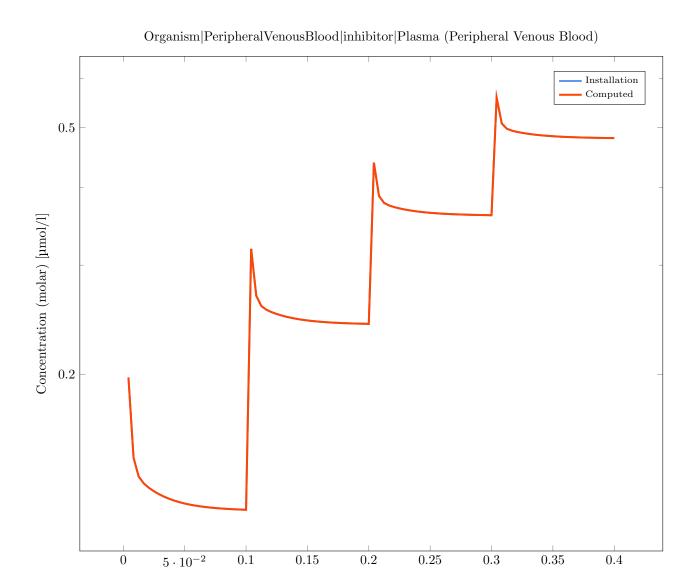


Figure 1.108

Time [h]

Simulation: Human_ICRP_AGP-01_ICRP_0y_Male

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

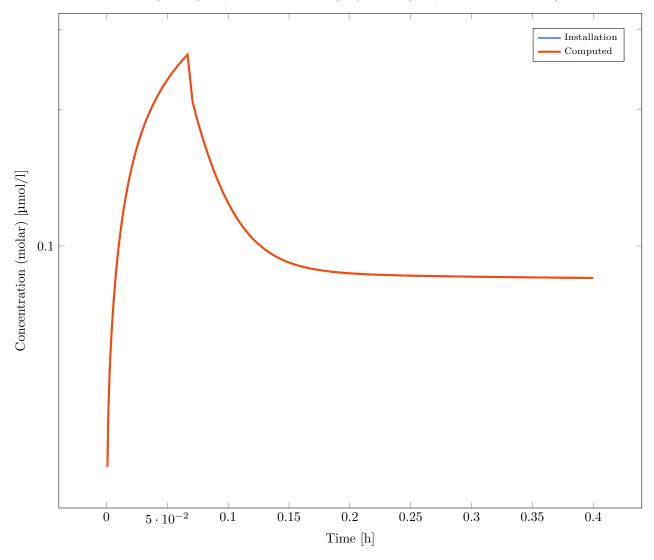
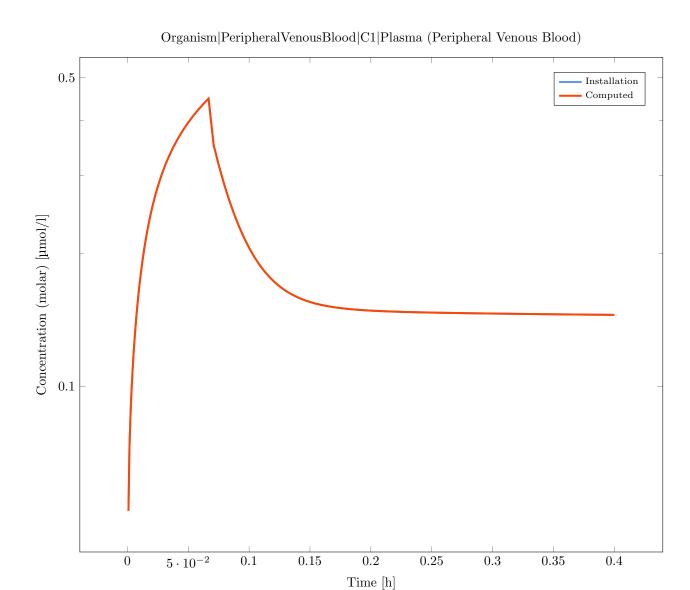


Figure 1.109

 $Simulation: \ Human_ICRP_AGP-02_ICRP_0.05y_Female$

Result of the validation: Valid

 ${\bf Output~Path:~Organism|Peripheral VenousBlood|C1|Plasma~(Peripheral~Venous~Blood)}$



 $Figure \ 1.110$

 $Simulation: \ Human_ICRP_AGP-03_ICRP_0.18y_Male$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$



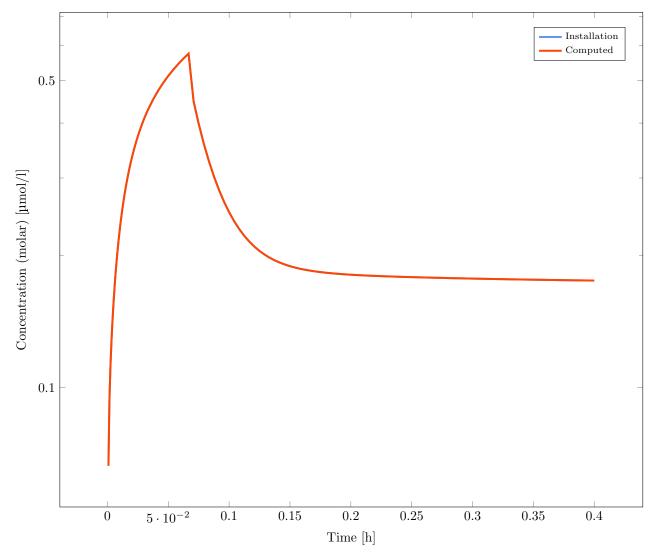


Figure 1.111

Simulation: Human_ICRP_AGP-04_ICRP_1y_Female

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

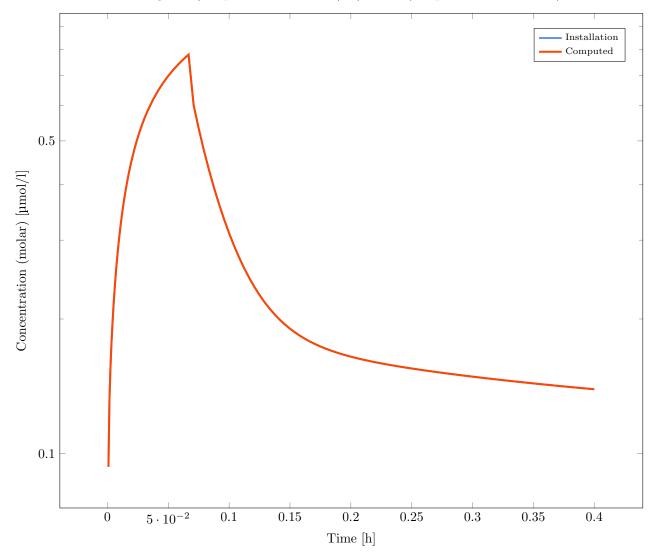


Figure 1.112

 $Simulation: \ Human_ICRP_AGP-05_ICRP_12y_Male$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 1.50E-4

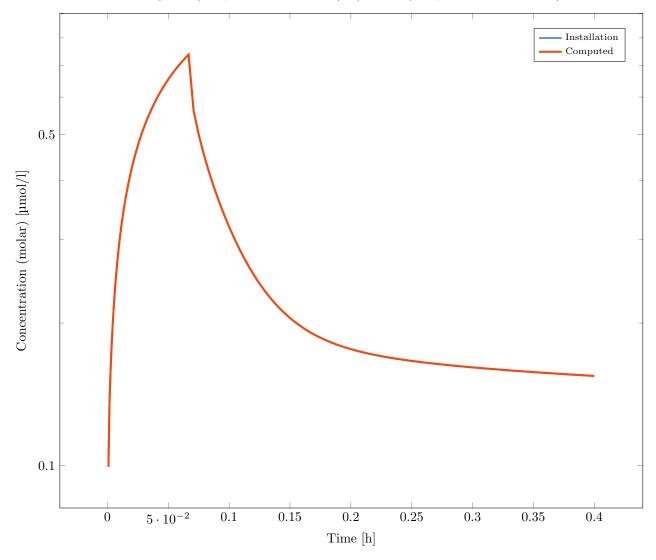


Figure 1.113

 $Simulation: \ Human_ICRP_AGP-06_ICRP_30y_Female$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

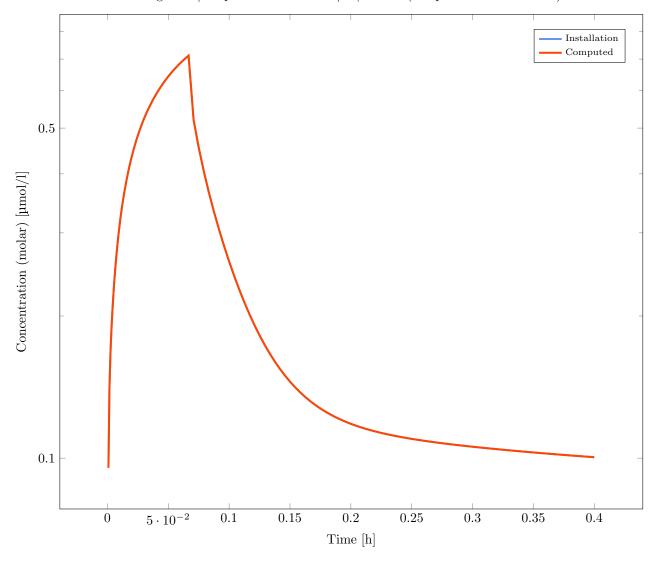
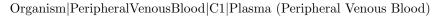


Figure 1.114

 $Simulation: \ Human_ICRP_AGP-07_ICRP_100y_Male$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$



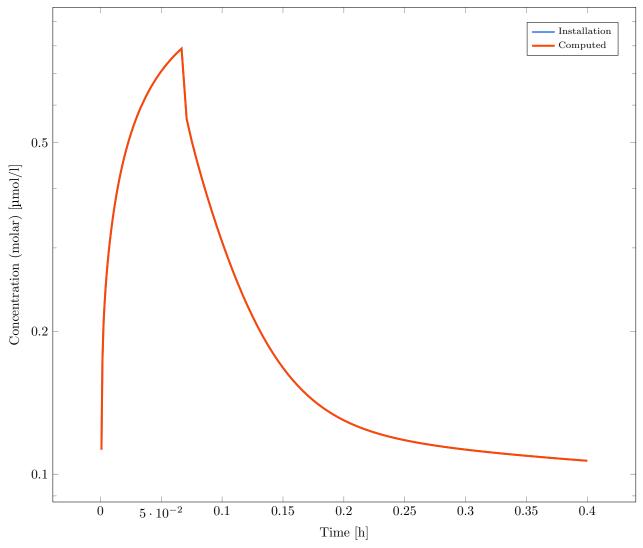
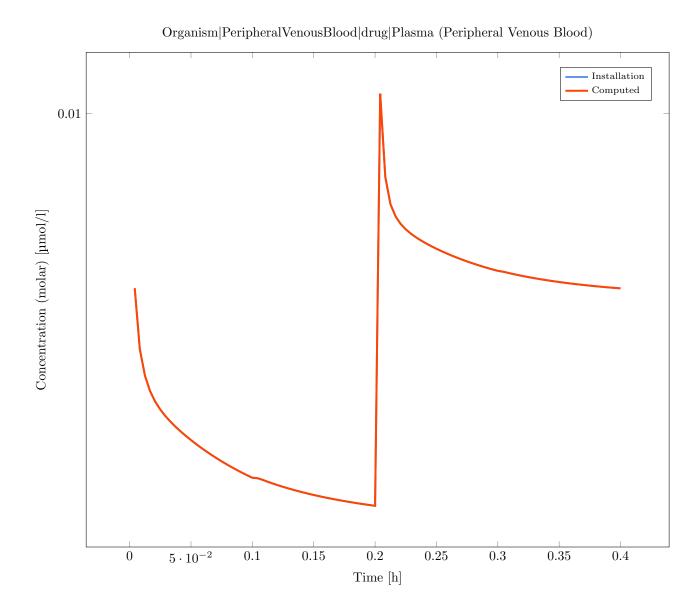


Figure 1.115

 ${\bf Simulation: \ Human_Irreversible Inhibition-Human_Irreversible Inhibition} \\ {\bf Result \ of \ the \ validation: \ Valid}$

Output Path: Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)



Output Path: Organism |PeripheralVenousBlood |
inhibitor |Plasma (Peripheral Venous Blood) | Deviation:
 0

 $Figure \ 1.116$

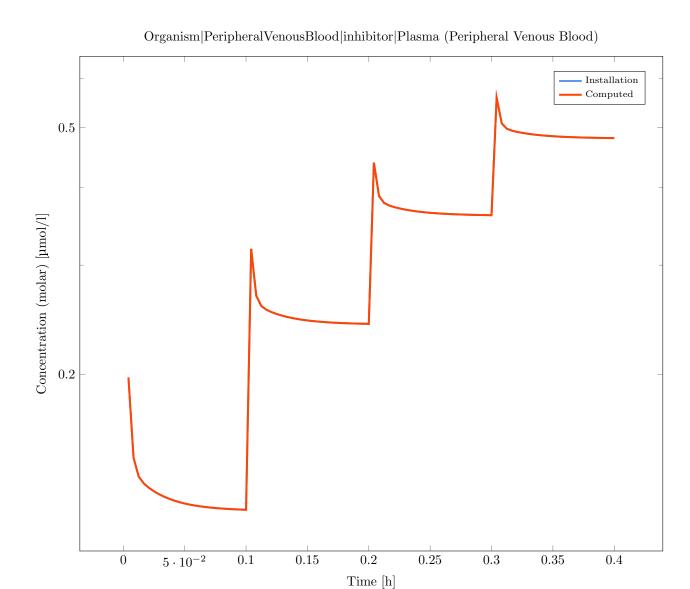


Figure 1.117

 $Simulation: \ Human_MixedInhibition-Human_MixedInhibition$

Result of the validation: Valid

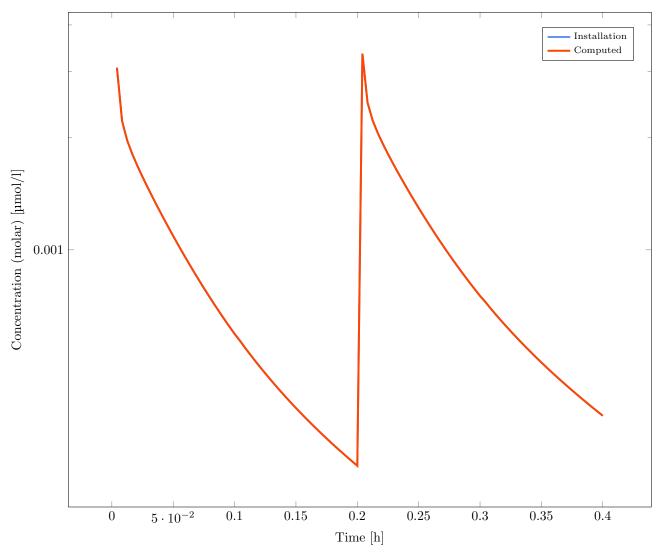


Figure 1.118

Output Path: Organism |PeripheralVenousBlood |
inhibitor |Plasma (Peripheral Venous Blood) | Deviation:
 0

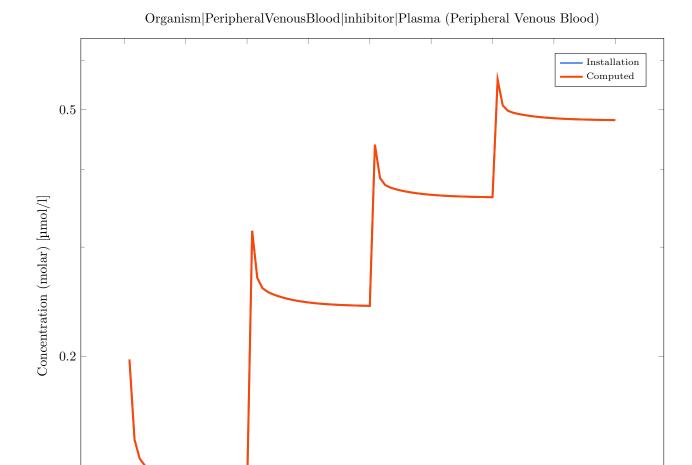


Figure 1.119

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: \ Human_MultiIV_6_6_12-Human_MultiIV_6_6_12$

0.1

Result of the validation: Valid

0

 $5 \cdot 10^{-2}$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood) Deviation:
 0

0.15

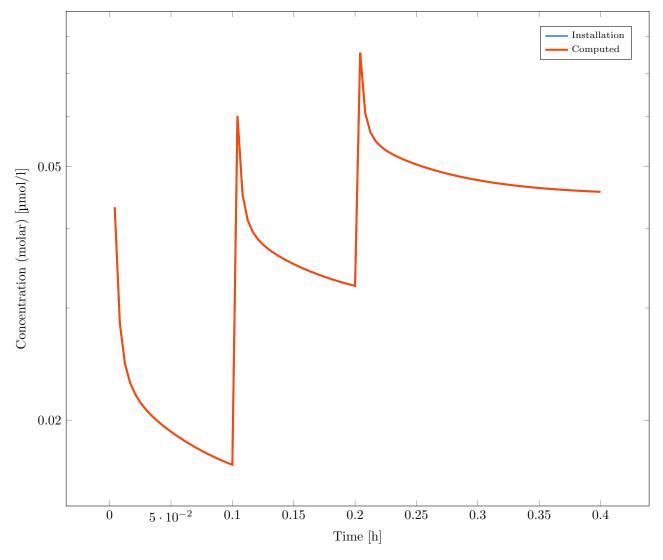


Figure 1.120

 $Simulation: \ Human_MultiORAL_6_12_12_Dissolved-Human_6_12_Dissolved-Human_6_12_$

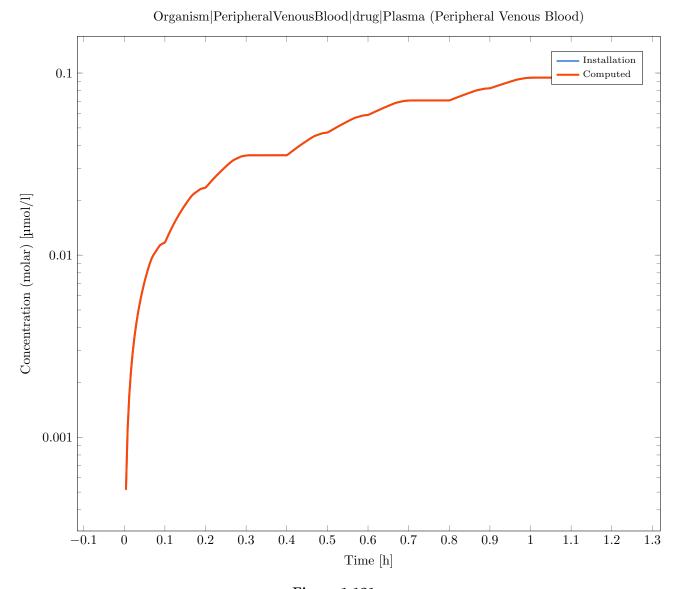
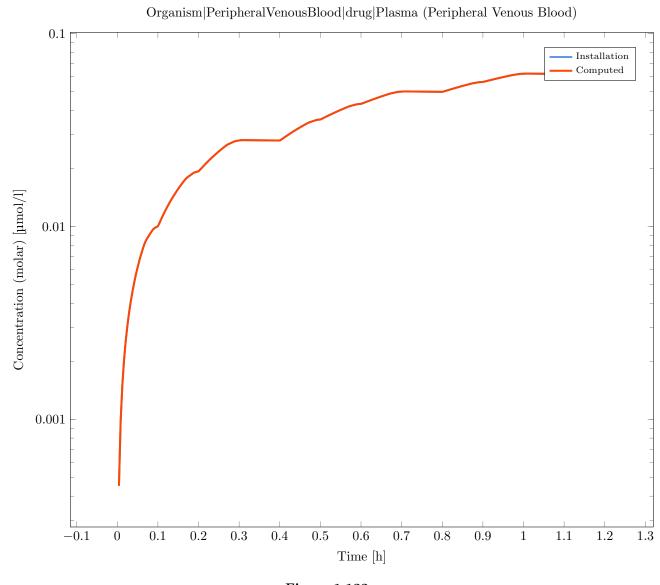


Figure 1.121

 $Simulation: Human_MultiORAL_6_12_12_Dissolved-Human_MultiORAL_6_12_12_Dissolved_absorption_sink_conditions$

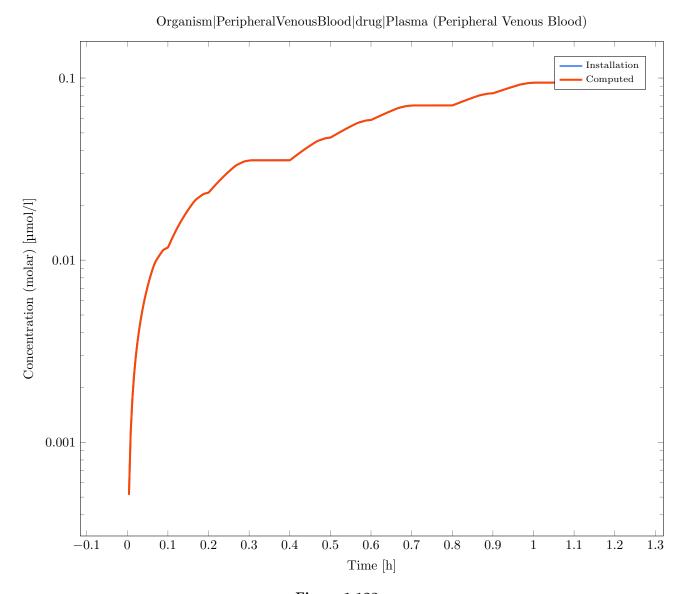
Result of the validation: Valid



 ${\bf Figure~1.122}$

 $Simulation: Human_MultiORAL_6_12_12_Dissolved-Human_MultiORAL_6_12_12_Dissolved_EHC_continuous_fraction_0.5$

Result of the validation: Valid



 ${\bf Figure~1.123}$

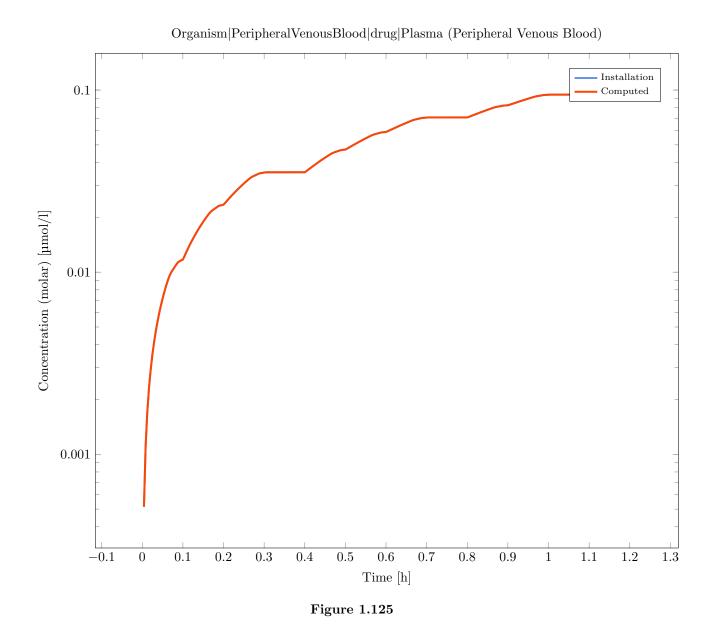
 $Simulation: Human_MultiORAL_6_12_12_Dissolved-Human_MultiORAL_6_12_12_Dissolved_EHC_continuous_fraction_1$

Result of the validation: Valid



Figure 1.124

Simulation: Human_MultiORAL_6_12_12_Dissolved-Human_MultiORAL_6_12_12_Dissolved_pKadependent penalty factor Result of the validation: Valid



 $Simulation: \ Human_MultiORAL_6_12_12_Dissolved-Human_MultiORAL_6_12_12_Dissolved_solubility \\ Result of the validation: \ Valid$

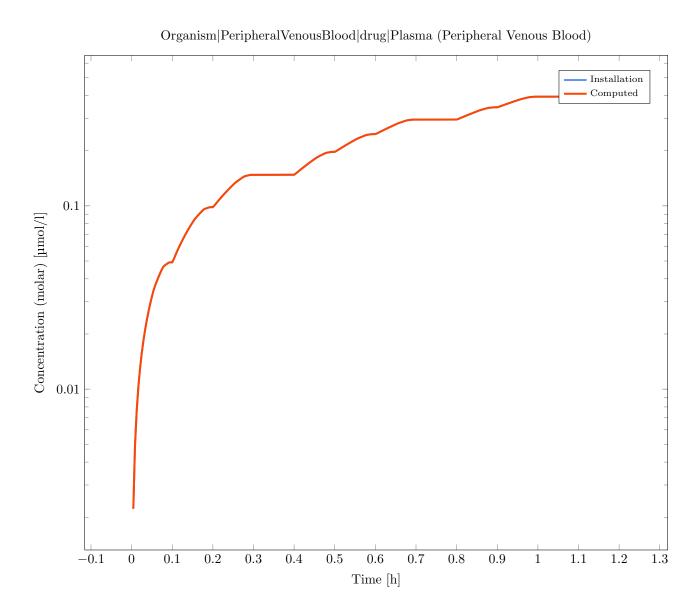


Figure 1.126

 $Simulation: \ Human_MultipleIV_Binding-Human_MultipleIV_Binding$

Result of the validation: Valid



Figure 1.127

 ${\bf Simulation: \ Human_Multiple IV_Efflux Basolateral-Human_Multiple IV_Efflux Basolateral-Result \ of the \ validation: \ Valid$

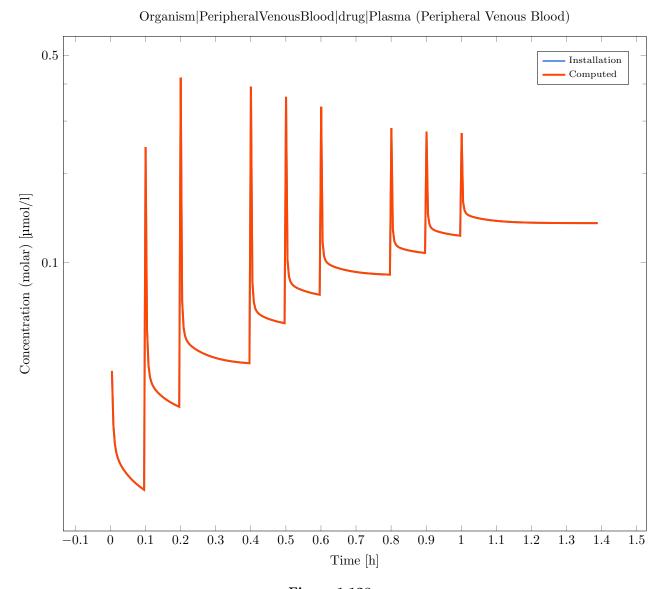


Figure 1.128

 $Simulation: \ Human_MultipleIV_Efflux-Human_MultipleIV_Efflux$

Result of the validation: Valid

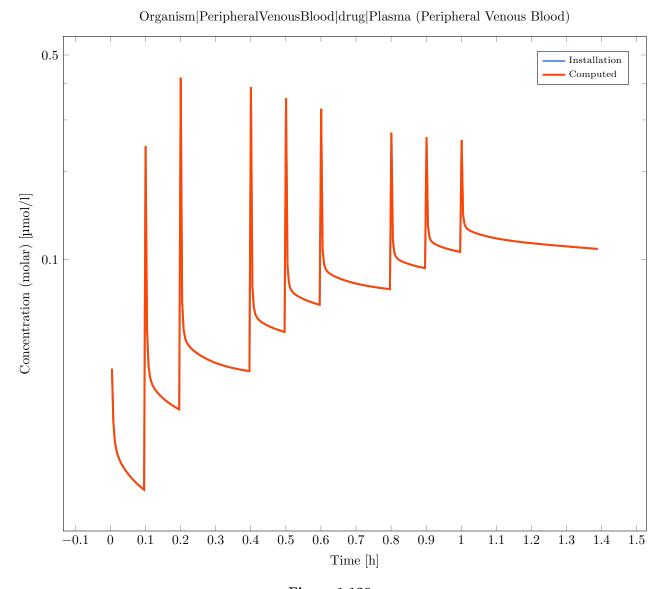
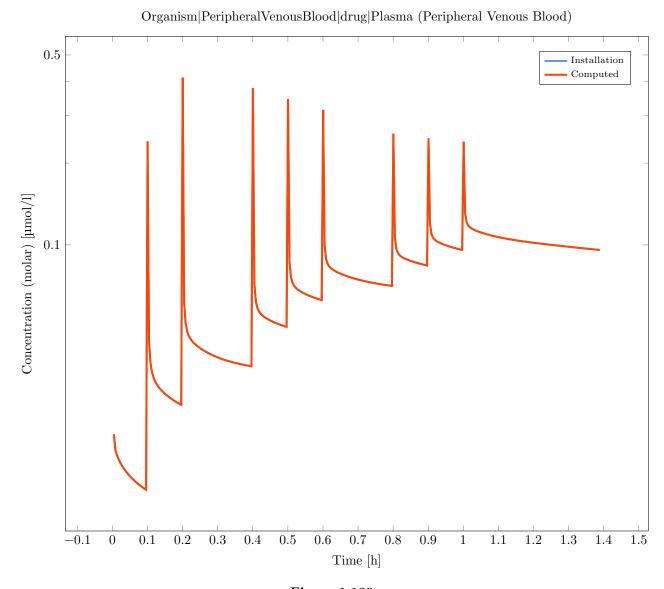


Figure 1.129

 ${\bf Simulation: \ Human_Multiple IV_Influx Basolateral-Human_Multiple IV_Influx Basolateral-Result \ of the \ validation: \ Valid$

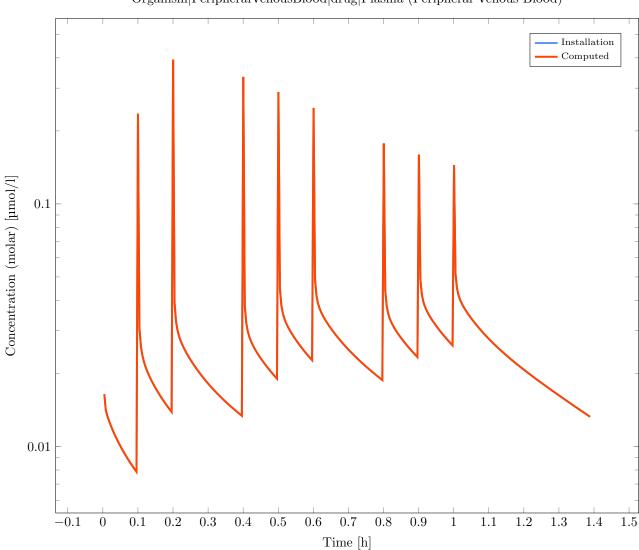
Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 1.81E-5



 ${\bf Figure~1.130}$

 $Simulation: \ Human_MultipleIV_Influx-Human_MultipleIV_ActiveInflux$

Result of the validation: Valid



Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

Figure 1.131

 ${\bf Simulation: \ Human_Multiple IV_Metabolizm Binding-Human_Multiple IV_Metabolizm Binding \ Result \ of \ the \ validation: \ Valid }$

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood) Installation Computed 0.1 Concentration (molar) $[\mu]$ 0.01 0.0010.2 0.3 0.7 0.8 0.9 1.1 1.2 -0.10 0.1 0.4 0.5 0.6 1.3 1.4 1.5

 ${\bf Figure~1.132}$

Time [h]

 ${\bf Simulation: \ Human_Multiple IV_Metabolizm-Human_Multiple IV_Metabolizm.} \\ {\bf Result \ of \ the \ validation: \ Valid}$

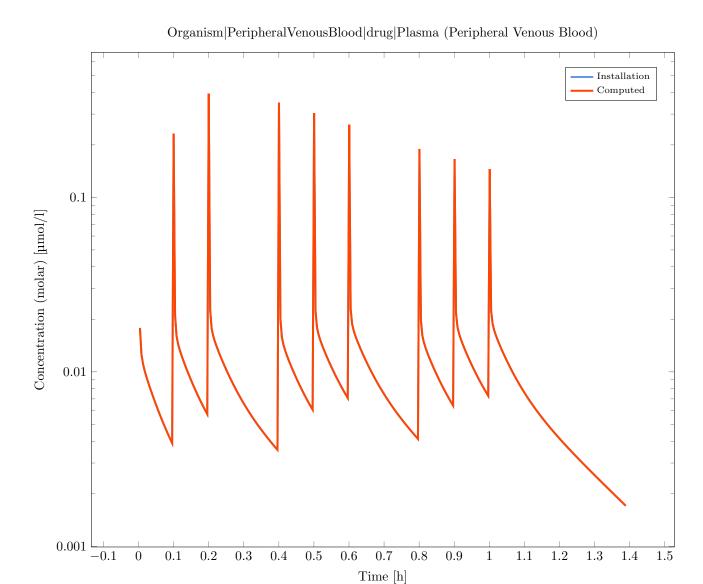


Figure 1.133

 ${\bf Simulation: \ Human_Multiple IV_PGPB a solateral-Human_Multiple IV_PGPB a solater$

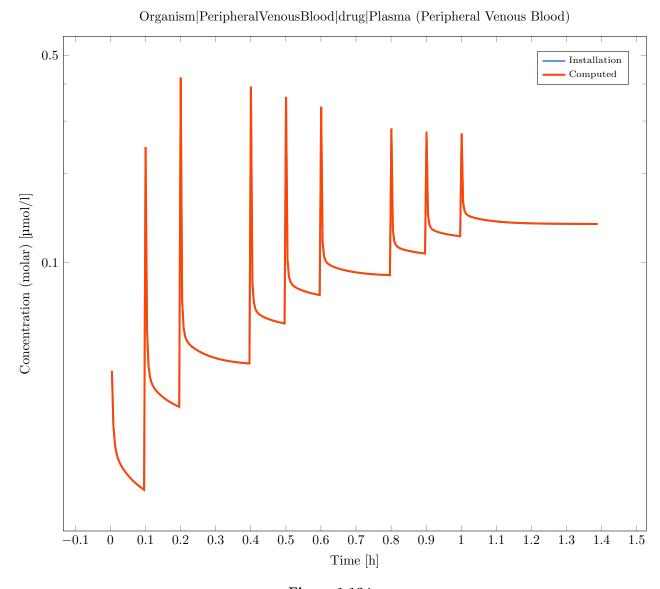


Figure 1.134

 $Simulation: \ Human_MultipleIV_PGP-Human_MultipleIV_PGP$

Result of the validation: Valid

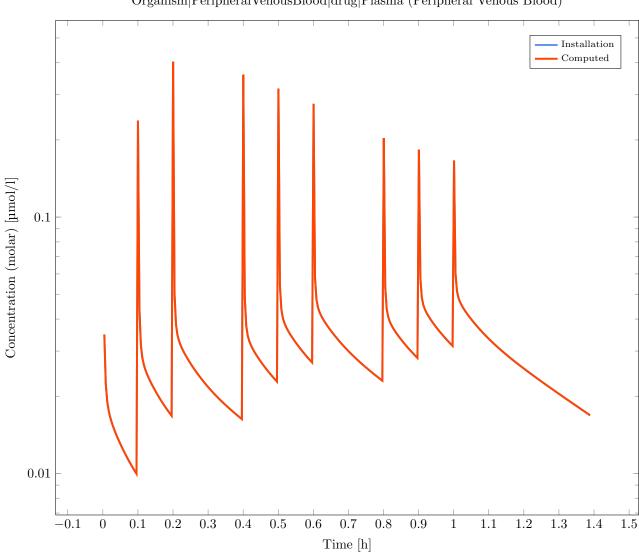
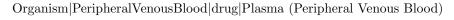
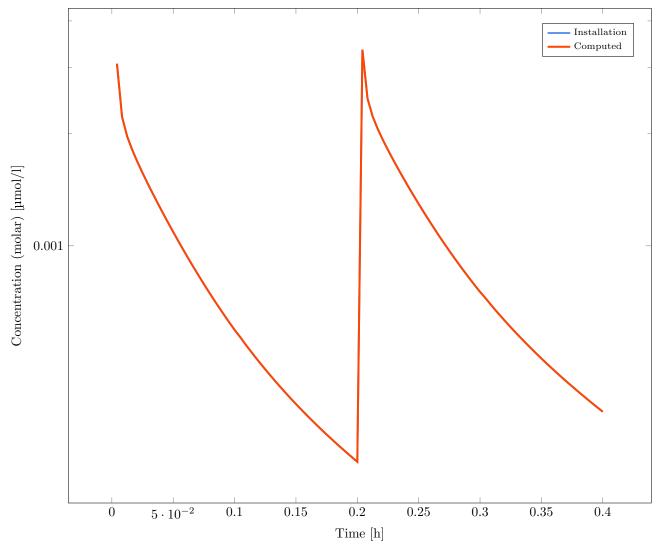


Figure 1.135

 ${\bf Simulation: \ Human_NonCompetitive Inhibition-Human_NonCompetitive Inhibition \ Result\ of\ the\ validation:\ Valid}$





 $Figure \ 1.136$

Output Path: Organism |PeripheralVenousBlood |
inhibitor |Plasma (Peripheral Venous Blood) | Deviation:
 0

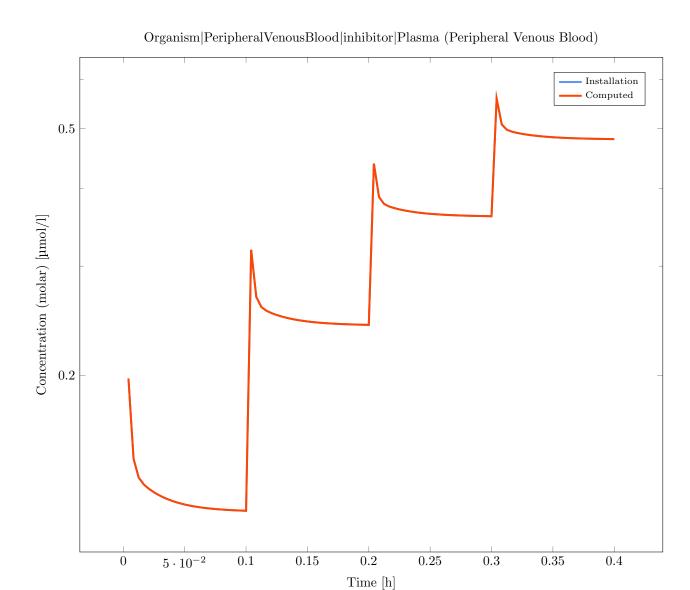
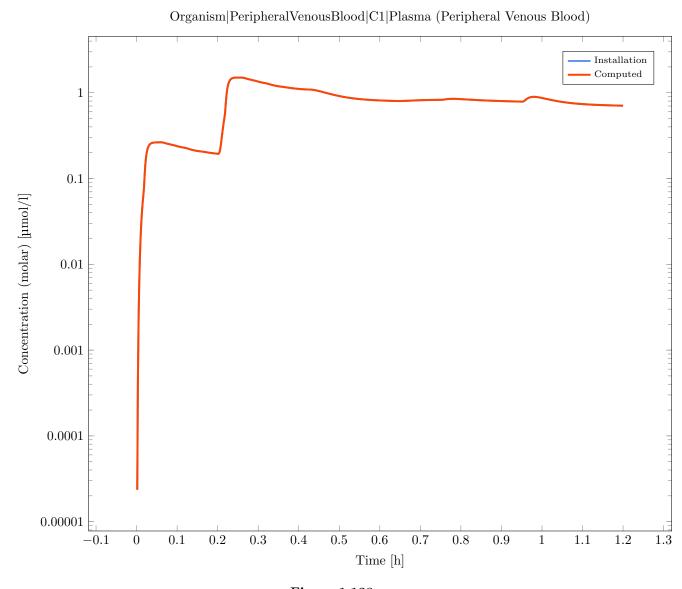


Figure 1.137

 $Simulation: \ Human_Oral_BiDaily_Table Formulation-S1_suspension$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$



 ${\bf Figure~1.138}$

 $Simulation: Human_Oral_BiDaily_TableFormulation-S2_NoSuspension$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

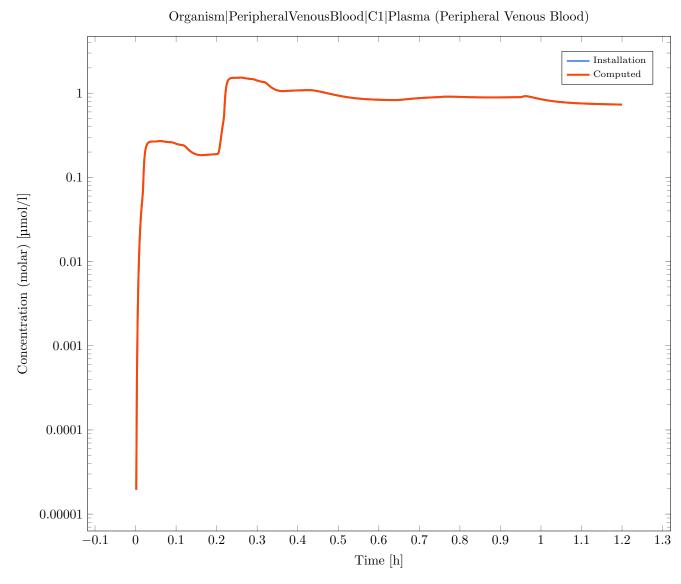


Figure 1.139

Simulation: Human_pH_SolubilityTable-S1_Table

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

Deviation: 4.04E-6

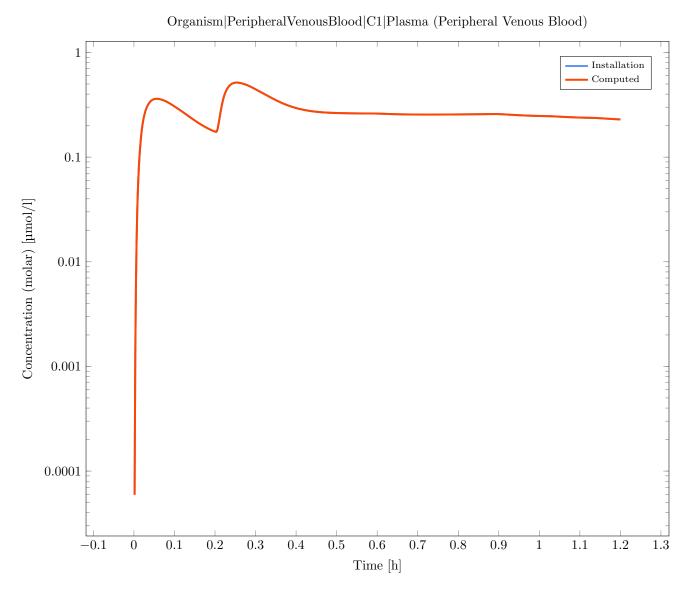


Figure 1.140

Simulation: Human_pH_SolubilityTable-S2_Measurement

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

Deviation: 3.61E-6

$Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral Venous Blood)$

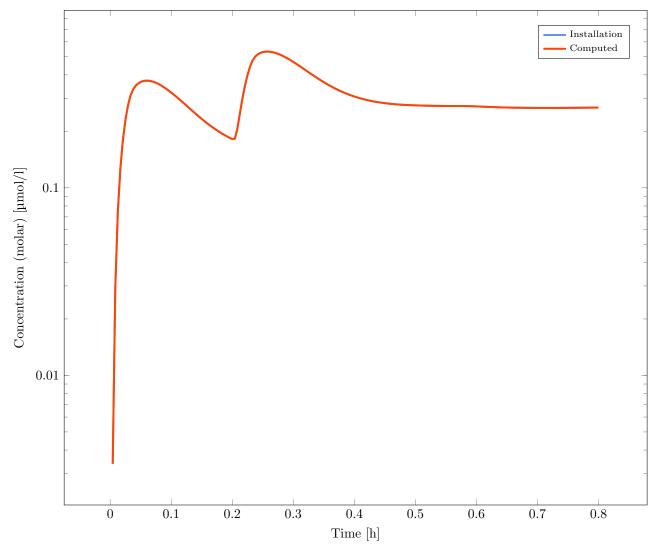


Figure 1.141

 $Simulation: \ Human_pH_SolubilityTable_SolubilityChanged$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 6.73E-6

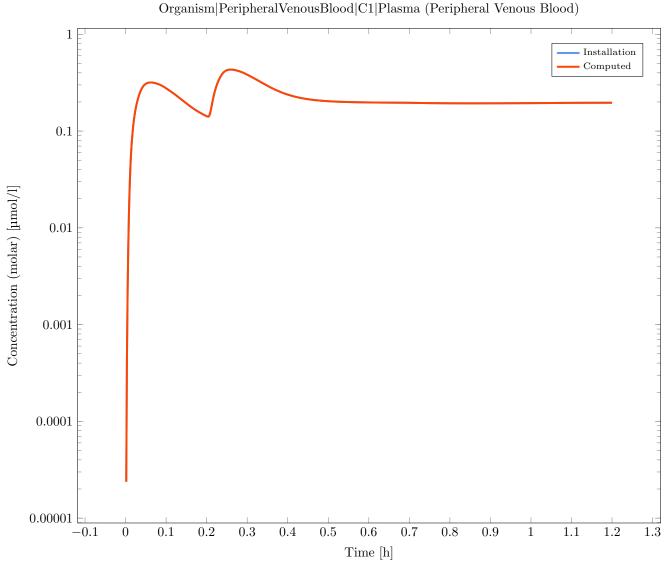


Figure 1.142

 ${\bf Simulation: \ Human_pH_SolubilityTable_S4_Table_SolubilityTableChanged \ Result\ of\ the\ validation:\ Valid}$

Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

Deviation: 6.13E-7

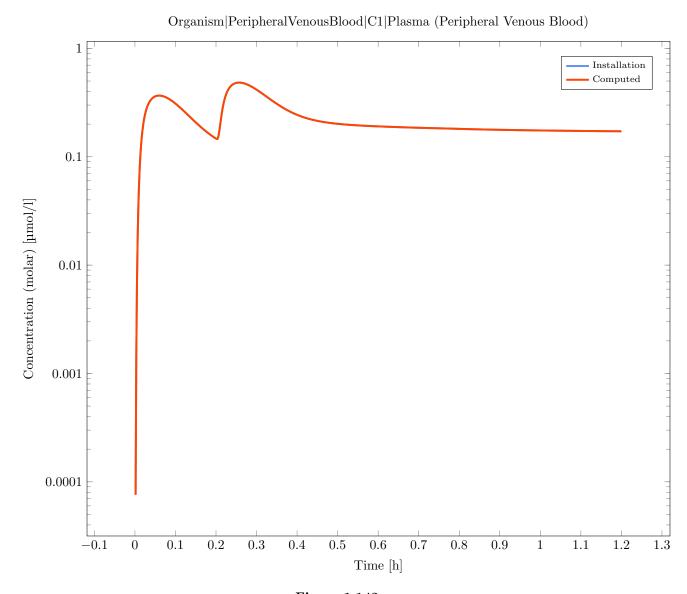
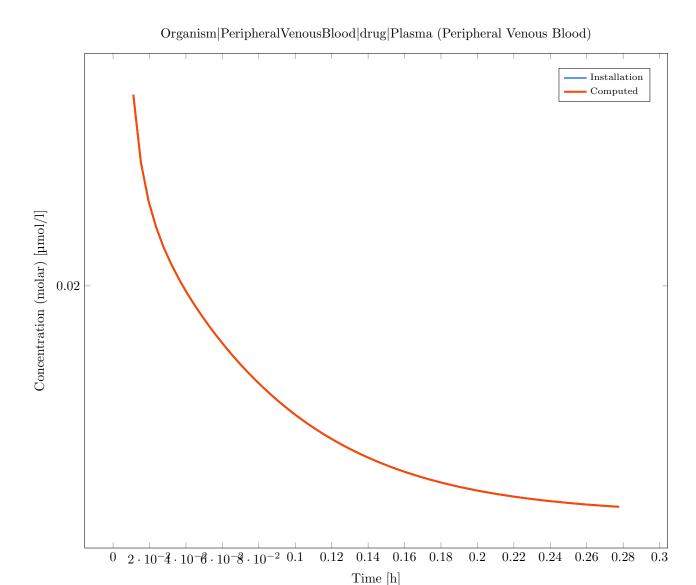


Figure 1.143

 ${\bf Simulation: \ Human_Single IV_Configuration-Human_Single IV_Configuration} \\ {\bf Result \ of \ the \ validation: \ Valid}$



Simulation: Human_SingleIV-Human_SingleIV

Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 0

Figure 1.144

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)



Figure 1.145

Simulation: Human_SingleIV-Human_SingleIV_MW_200_fu_0.2_LogP_5 Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

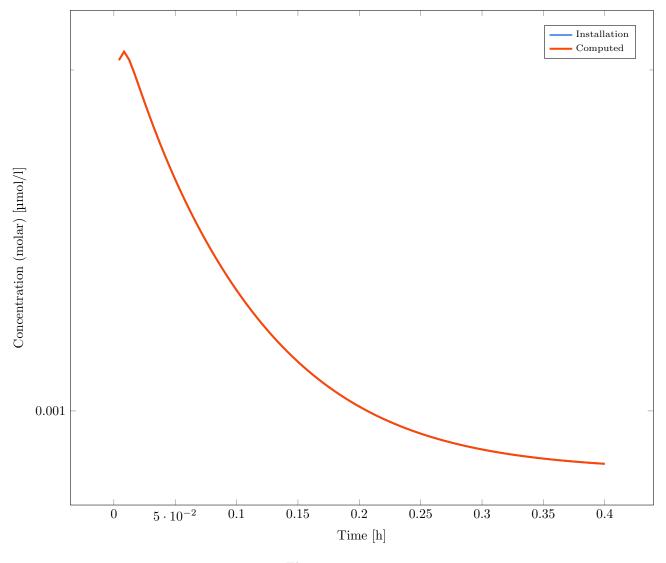
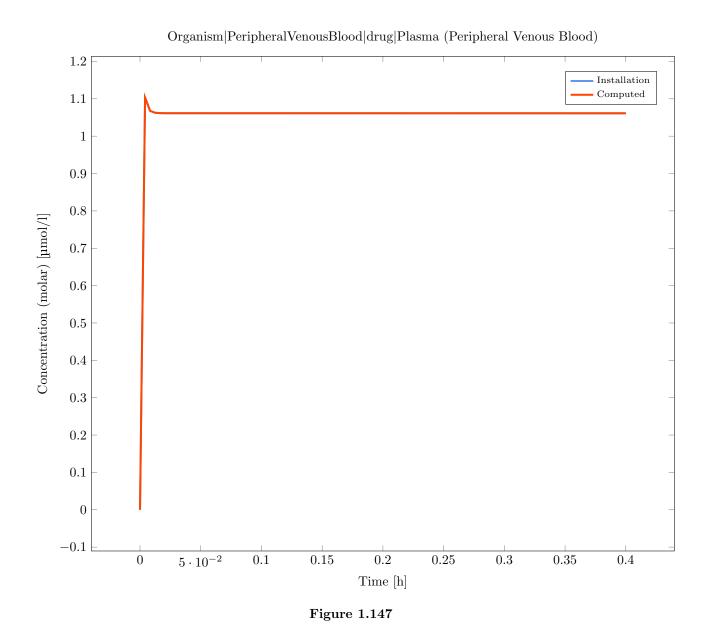


Figure 1.146

 $Simulation: \ Human_SingleIV-Human_SingleIV_MW_800_fu_0.6_LogP_-5$

Result of the validation: Valid



Simulation: Human_SingleORAL_Dissolved_PlasmaClearance-Human_SingleO

$\label{eq:constraint} Organism | Peripheral Venous Blood | drug | Plasma \; (Peripheral Venous Blood)$

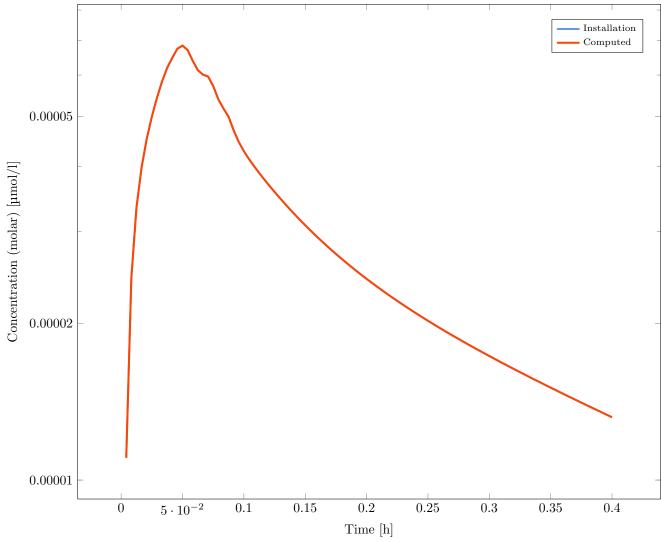


Figure 1.148

 $Simulation: Human_SingleORAL_Dissolved_PlasmaClearance-Human_Singl$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|drug|Plasma\ (Peripheral\ Venous\ Blood)$

Deviation: 0



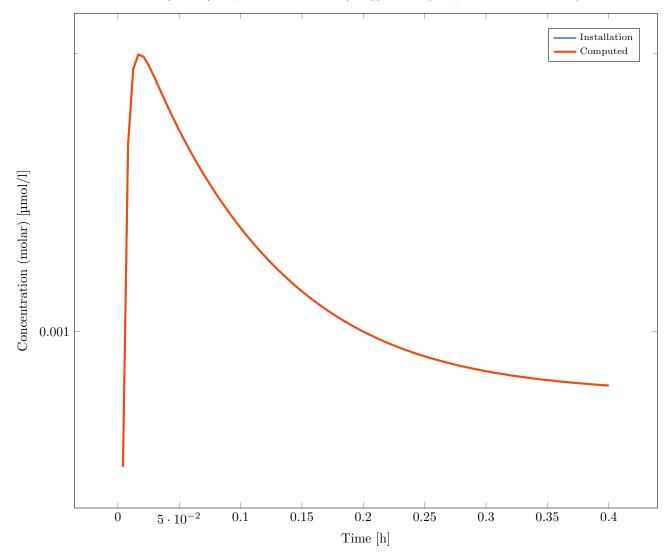


Figure 1.149

 $Simulation: Human_SingleORAL_Dissolved_PlasmaClearance-Human_Singl$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

Deviation: 0

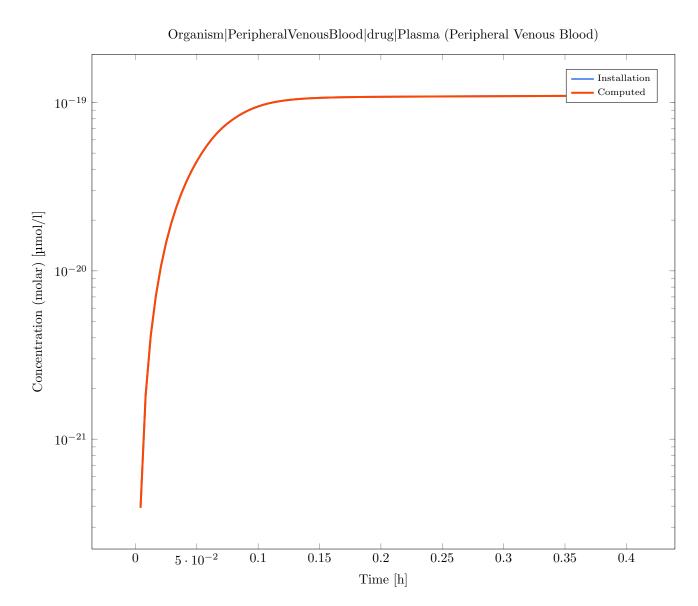


Figure 1.150

Simulation: Human_SingleORAL_Dissolved-Human_SingleORAL_Dissolved Result of the validation: Valid

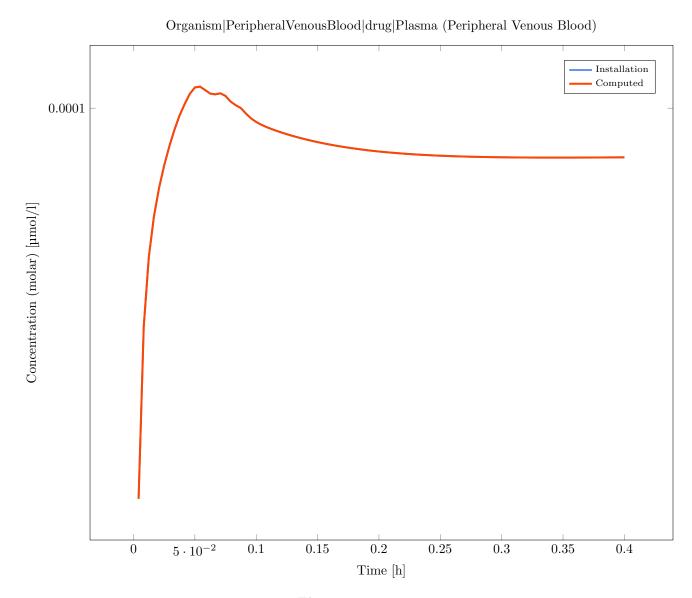


Figure 1.151

 $Simulation: Human_SingleORAL_Dissolved_Human_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5$ Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

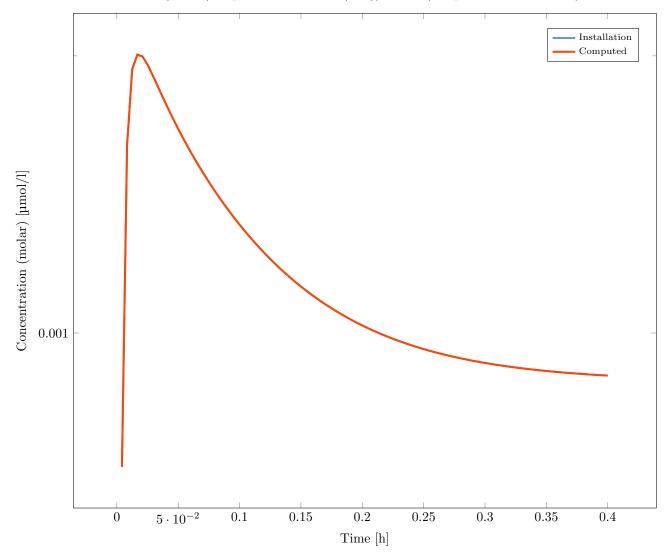
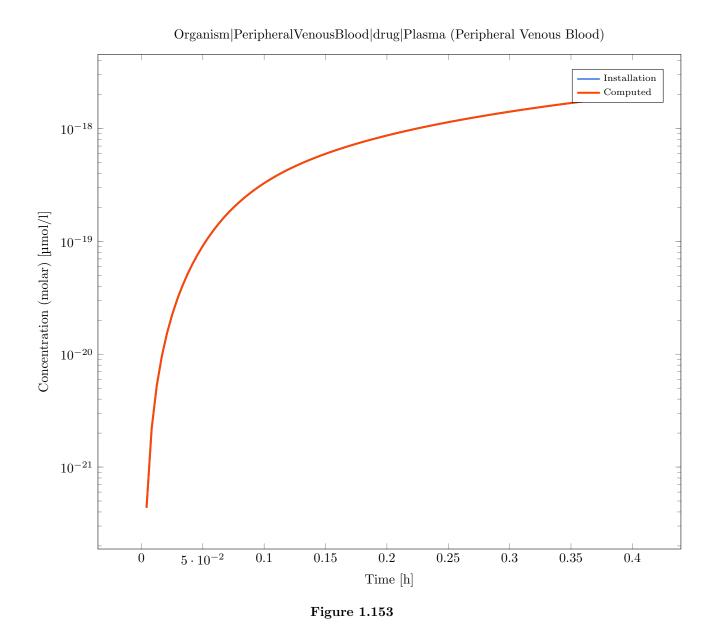


Figure 1.152

 $Simulation: Human_SingleORAL_Dissolved-Human_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_-5\\ Result of the validation: Valid$



 ${\bf Simulation: \ Human_SingleORAL_Lint80_AsSuspention-Human_SingleORAL_Lint80_AsSuspention.} \\ {\bf Result \ of \ the \ validation: \ Valid}$

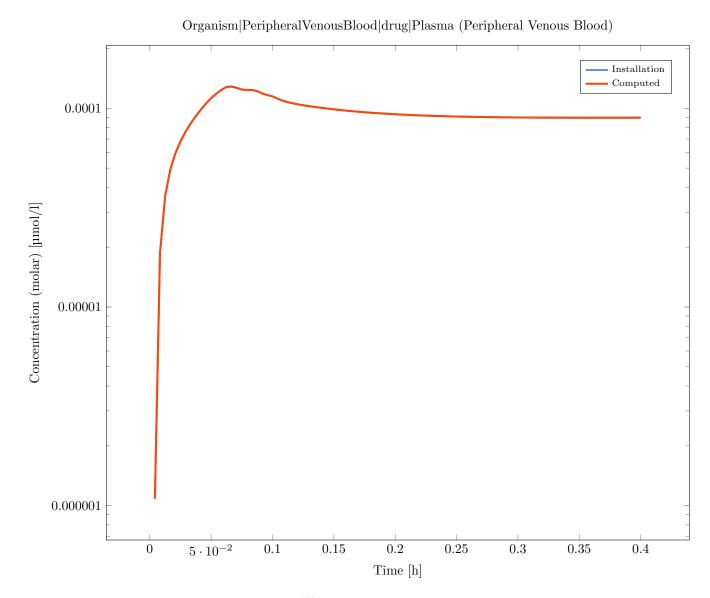
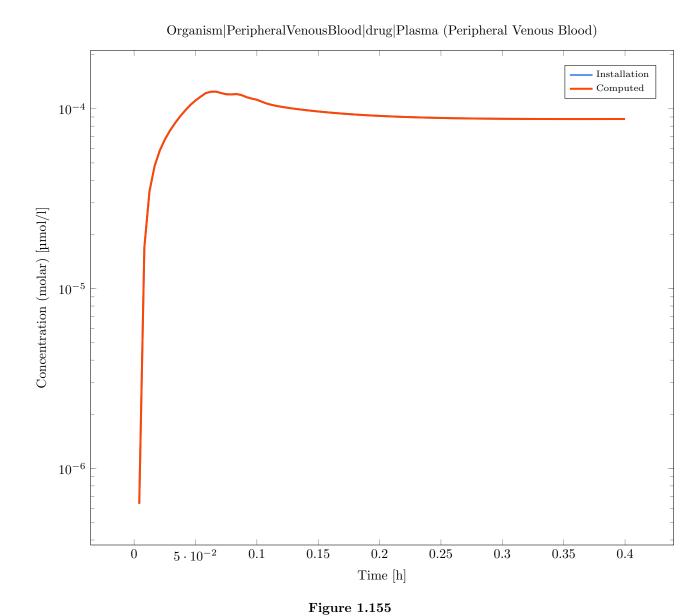


Figure 1.154

 $Simulation: \ Human_SingleORAL_Lint80-Human_SingleORAL_Lint80$

Result of the validation: Valid



 $Simulation: Human_SingleORAL_MonoParticles_AsSuspention-Human_SingleORAL_MonoParticles_AsSuspention\\$

Result of the validation: Valid

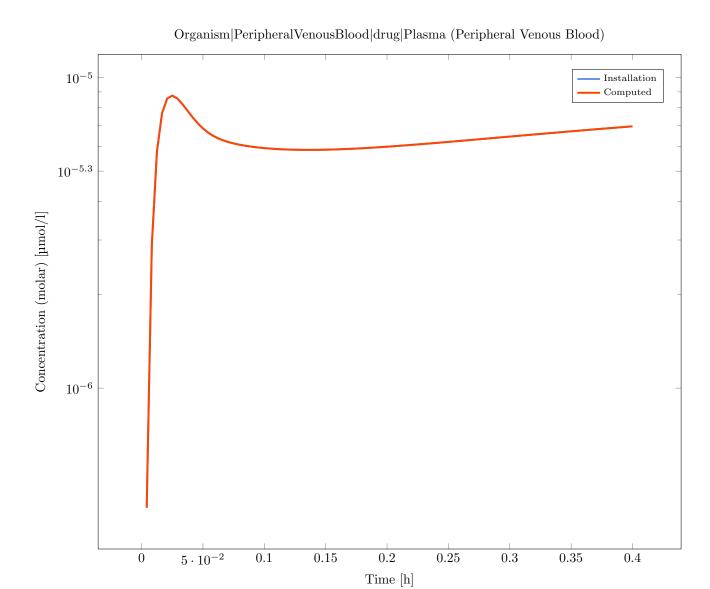


Figure 1.156

 $Simulation: \ Human_SingleORAL_PolyParticlesLogNormal_AsSuspention-Human_SingleORAL_PolyParticlesLogNormal_AsSuspention$

Result of the validation: Valid

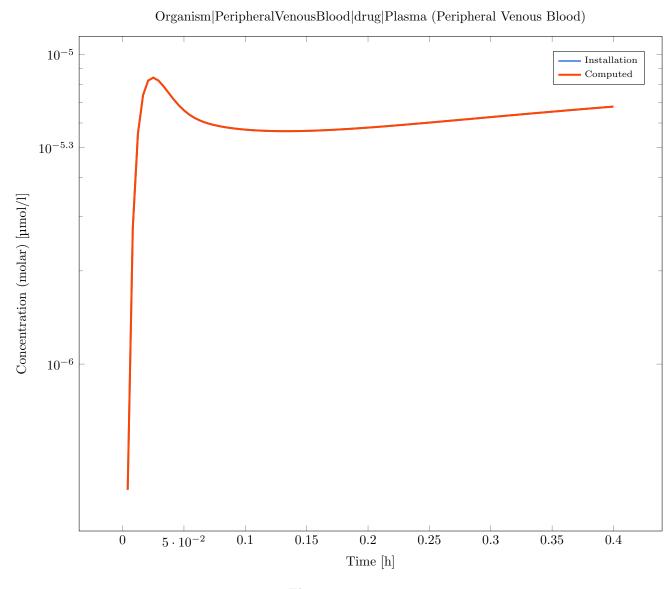


Figure 1.157

 $Simulation: Human_SingleORAL_PolyParticlesNormal_AsSuspention-Human_SingleORAL_PolyParticlesNormal_AsSuspention\\$

Result of the validation: Valid

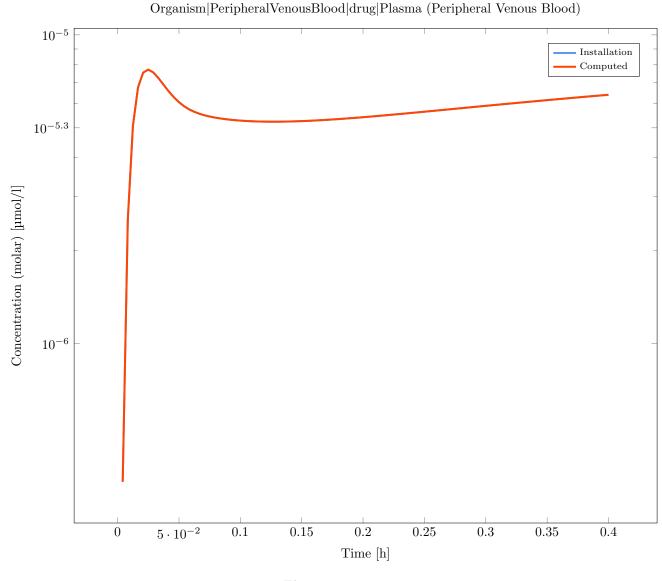


Figure 1.158

 $Simulation: Human_SingleORAL_PolyParticlesNormal_AsSuspention-Human_SingleORAL_PolyParticlesNormal_AsSuspention_dissolved_radius$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

Deviation: 6.85E-8

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

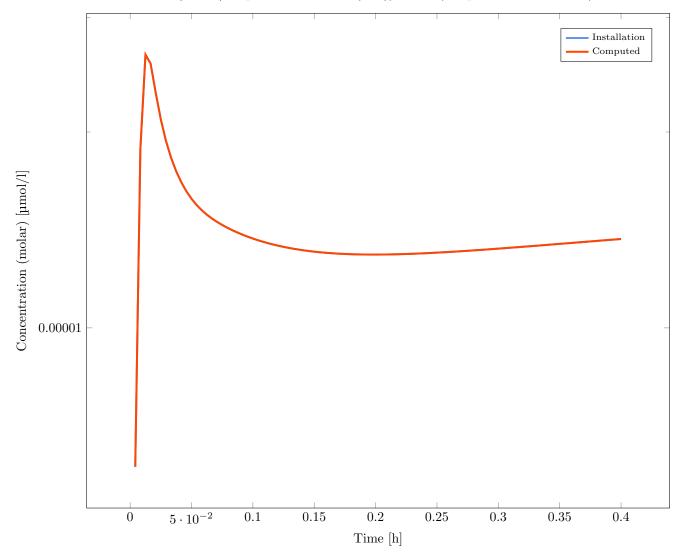


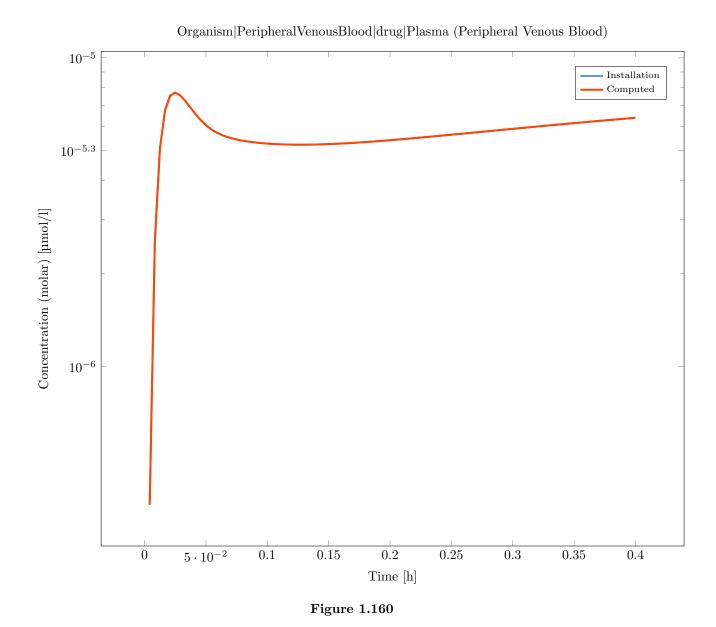
Figure 1.159

 $Simulation: Human_SingleORAL_PolyParticlesNormal_AsSuspention-Human_SingleORAL_PolyParticlesNormal_AsSuspention_treat_precipated_drug_as_soluble$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

Deviation: 0



 ${\bf Simulation: Human_SingleORAL_Weibull_AsSuspention-Human_SingleORAL_Weibull_AsSuspention}. \\ {\bf Result\ of\ the\ validation:\ Valid}$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 1.04E-5

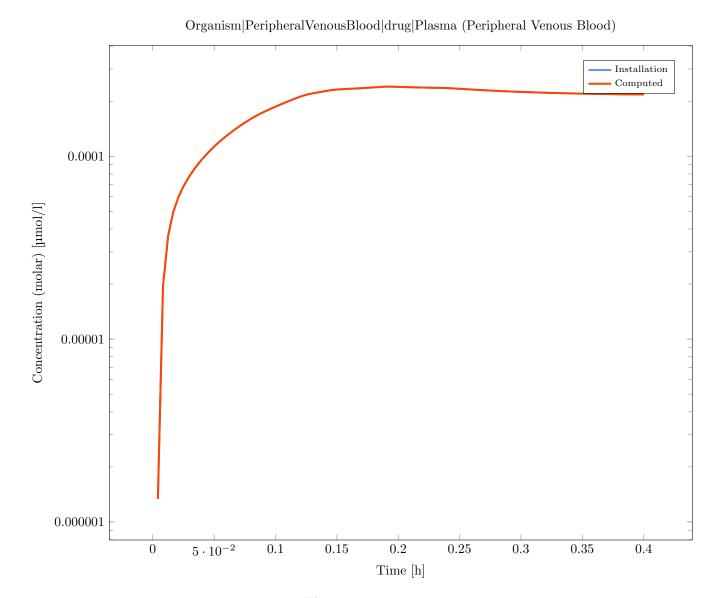


Figure 1.161

 $Simulation: Human_SingleORAL_Weibull_AsSuspention-Human_SingleORAL_Weibull_AsSuspention_MW_200_fu_0.2_LogP_5\\ Result of the validation: Valid$

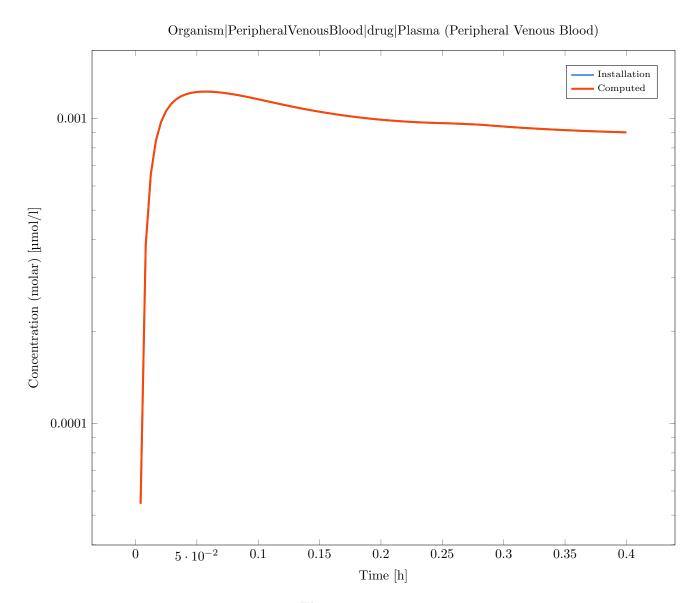
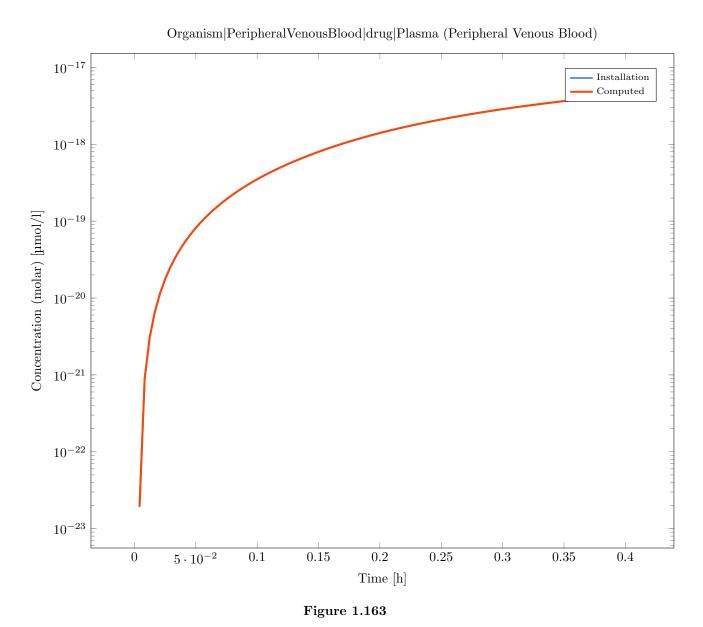


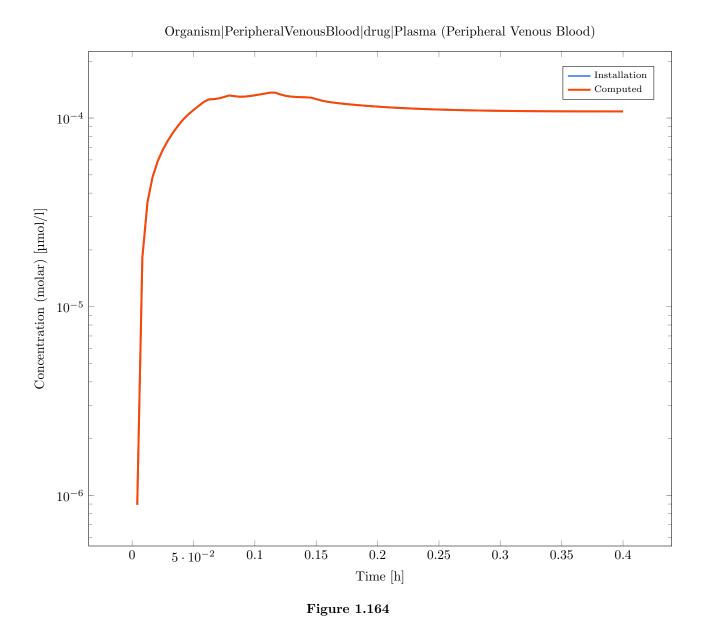
Figure 1.162

 $Simulation: Human_SingleORAL_Weibull_AsSuspention-Human_SingleORAL_Weibull_AsSuspention_MW_800_fu_0.6_LogP_-5\\ Result of the validation: Valid$



 ${\bf Simulation: \ Human_SingleORAL_Weibull-Human_SingleORAL_Weibull} \\ {\bf Result \ of \ the \ validation: \ Valid}$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 3.54E-5



 $Simulation: \ Human_SingleORAL_Weibull-Human_SingleORAL_Weibull_MW_200_fu_0.2_LogP_5 \\ Result of the validation: \ Valid$

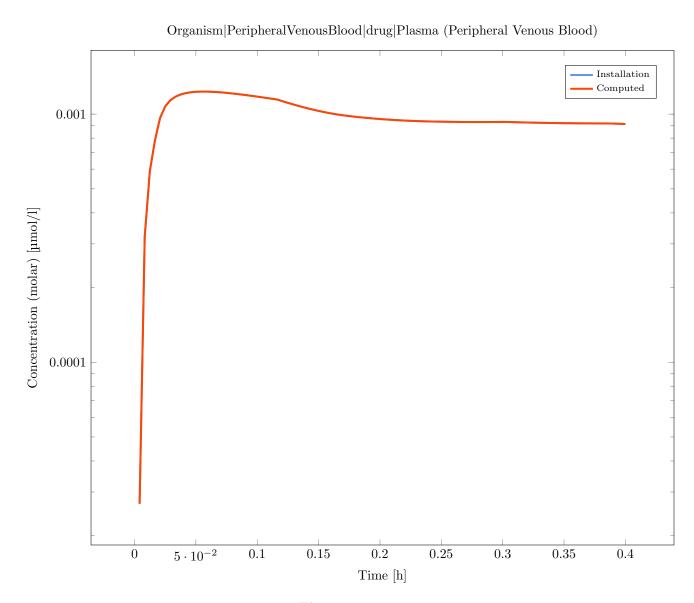


Figure 1.165

Simulation: Human_SingleORAL_Weibull-Human_SingleORAL_Weibull_MW_800_fu_0.6_LogP_5 Result of the validation: Valid

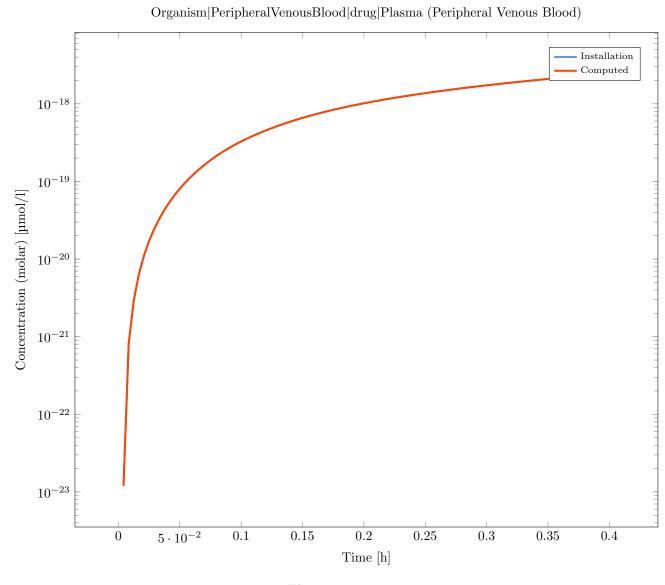
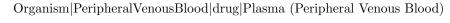


Figure 1.166

 ${\bf Simulation: Human_Uncompetitive Inhibition-Human_Uncompetitive Inhibition} \\ {\bf Result of the \ validation: \ Valid}$



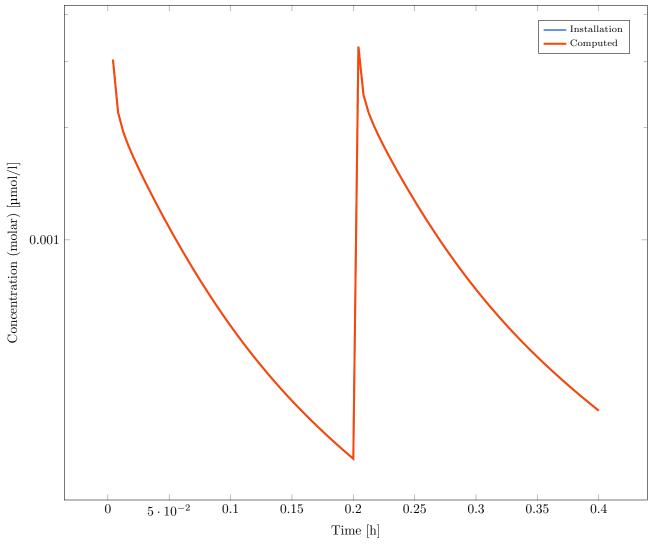


Figure 1.167

Output Path: Organism |PeripheralVenousBlood |
inhibitor |Plasma (Peripheral Venous Blood) | Deviation:
 0



 $\begin{array}{c} {\rm Time}\; [h] \\ \\ {\bf Figure}\; {\bf 1.168} \end{array}$

0.2

0.25

0.3

0.35

0.4

0.15

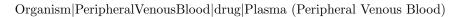
Simulation: Minipig_SingleORAL_Dissolved-Minipig_SingleORAL_Dissolved Result of the validation: Valid

0.1

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 1.18E-7

0

 $5 \cdot 10^{-2}$



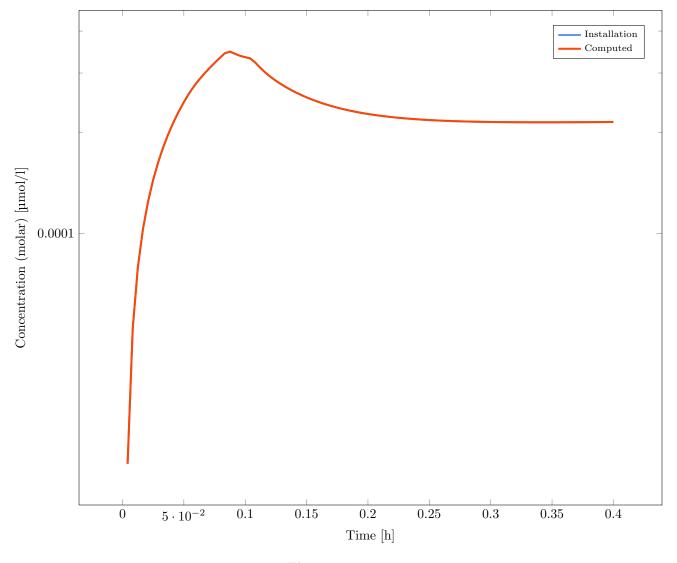


Figure 1.169

 $Simulation: \ Minipig_SingleORAL_Dissolved_Minipig_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5$ Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

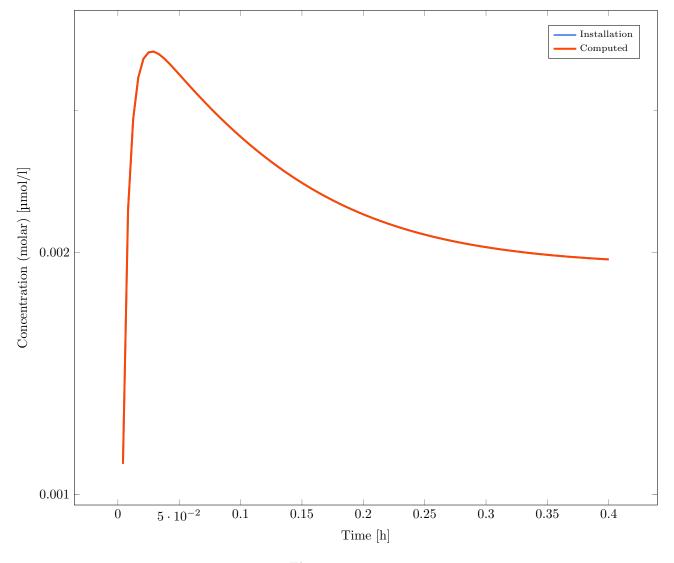


Figure 1.170

 $Simulation: \ Minipig_SingleORAL_Dissolved_Minipig_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_-5$ Result of the validation: Valid

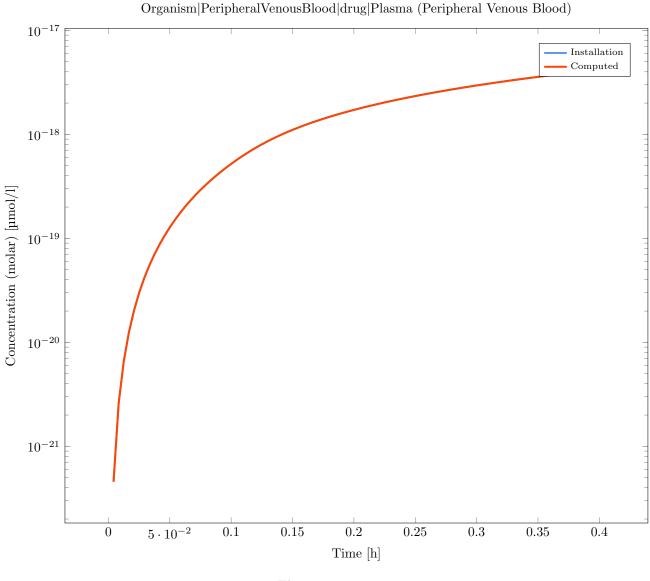


Figure 1.171

 ${\bf Simulation: \ Monkey_SingleORAL_Dissolved-Monkey_SingleORAL_Dissolved \ Result \ of \ the \ validation: \ Valid}$

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood) Installation Computed 0.001

Figure 1.172

0.2

Time [h]

0.25

0.35

0.3

0.4

0.15

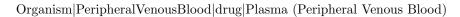
0.1

Simulation: Monkey_SingleORAL_Dissolved-Monkey_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5 Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |
drug |Plasma (Peripheral Venous Blood) Deviation: ${\bf 0}$

0

 $5 \cdot 10^{-2}$



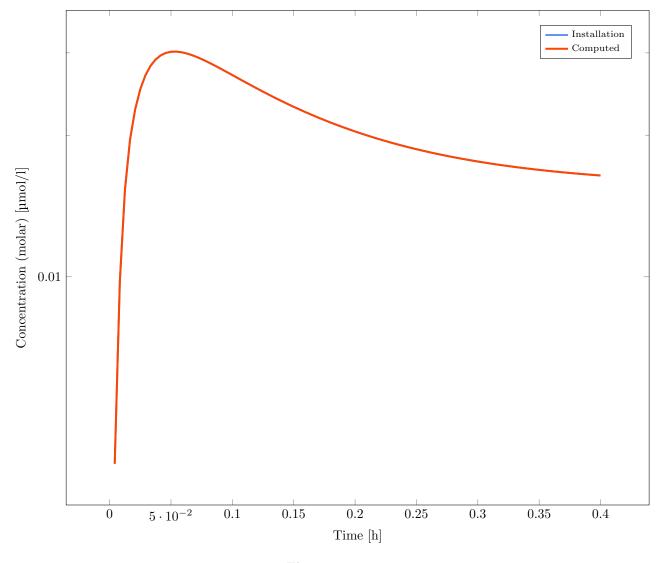


Figure 1.173

Simulation: Monkey_SingleORAL_Dissolved-Monkey_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_--5 Result of the validation: Valid

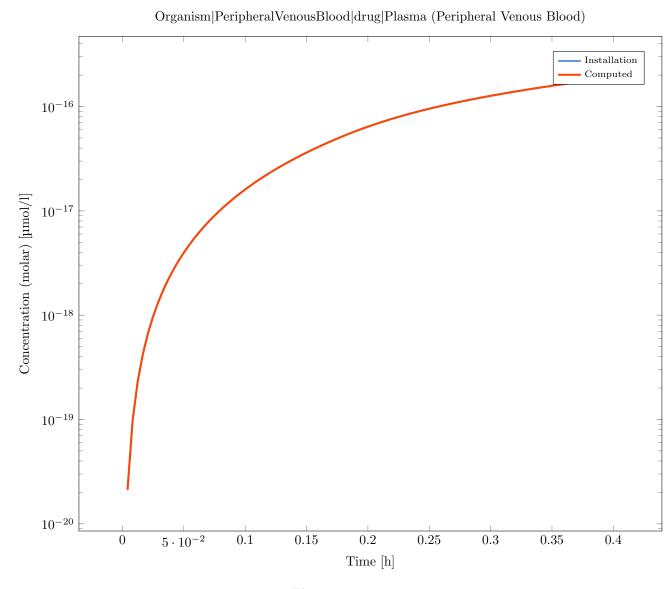


Figure 1.174

Simulation: Mouse_SingleORAL_Dissolved-Mouse_SingleORAL_Dissolved Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

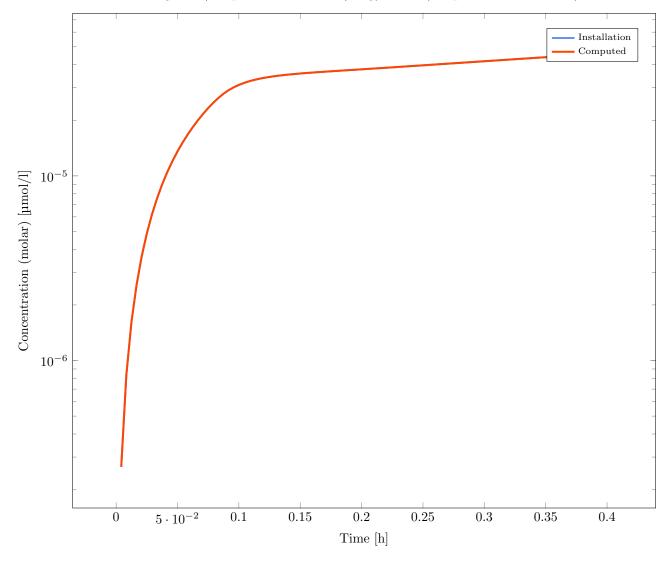


Figure 1.175

 $Simulation: Mouse_SingleORAL_Dissolved_MOUSe_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_-INFIGURE ALL_DISSOLVED ALL$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

Deviation: 1.04E-7

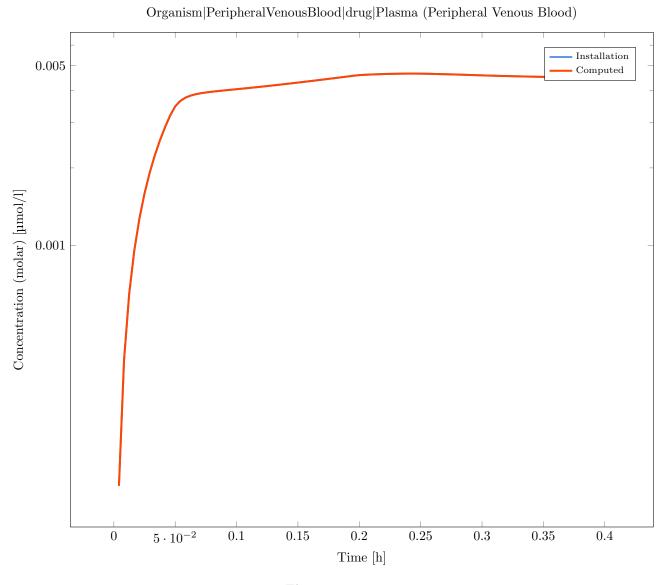


Figure 1.176

Simulation: Mouse_SingleORAL_Dissolved-Mouse_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_--5 Result of the validation: Valid

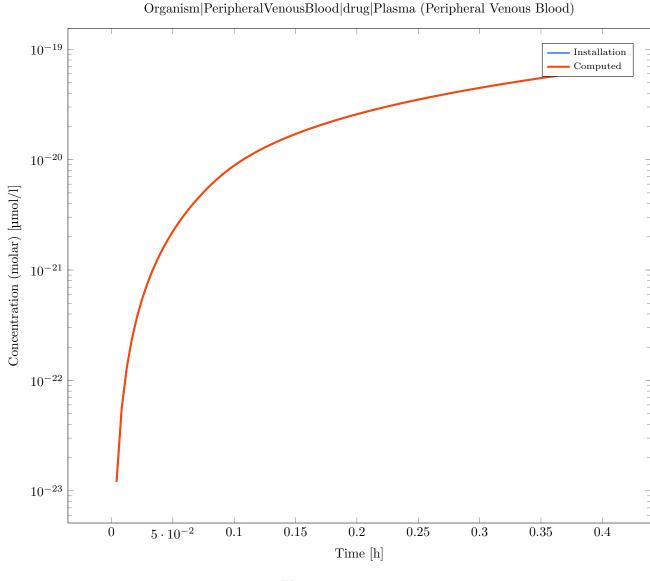
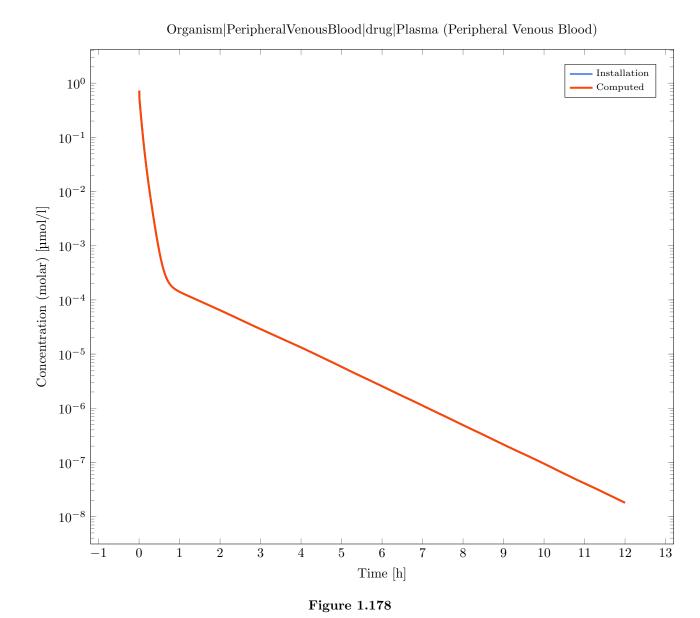


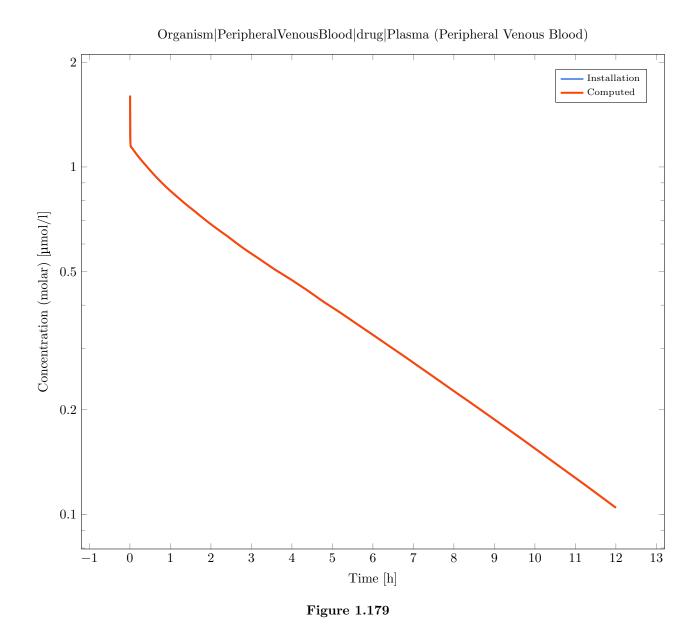
Figure 1.177

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 1.87E-4



 $Simulation: \ \, Preterm_SingleIV_Age_0_GA_32_GFR-Preterm_SingleIV_Age_0_GA_32_GFR \\ Result of the validation: \ \, Valid$

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 8.91E-5



 $Simulation: \ Preterm_SingleIV_Age_15_GA_32_CYP3A4-Preterm_SingleIV_Age_15_CYP3A4-Preterm_SingleIV_Age_1$



 $Simulation: \ \, Preterm_SingleIV_Age_15_GA_32_GFR-Preterm_SingleIV_Age_15_GA_32_GFR \\ Result of the validation: \ \, Valid$

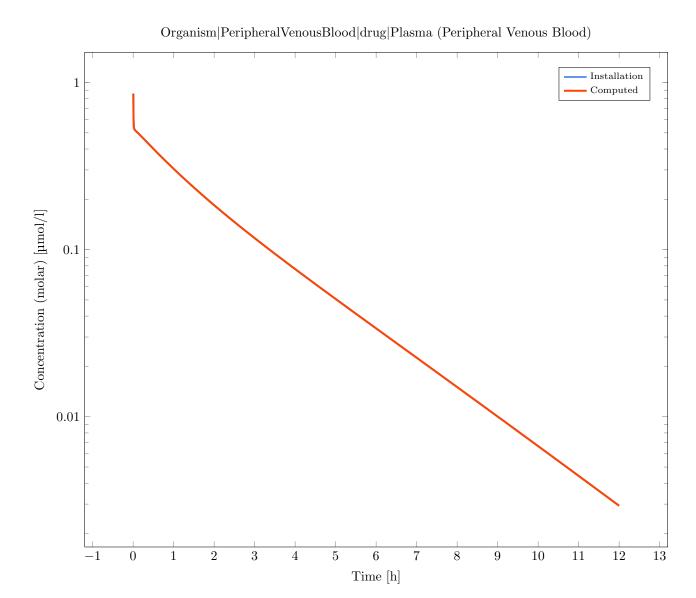


Figure 1.181

 ${\bf Simulation: Rabbit_SingleORAL_Dissolved-Rabbit_SingleORAL_Dissolved} \\ {\bf Result \ of \ the \ validation: \ Valid}$

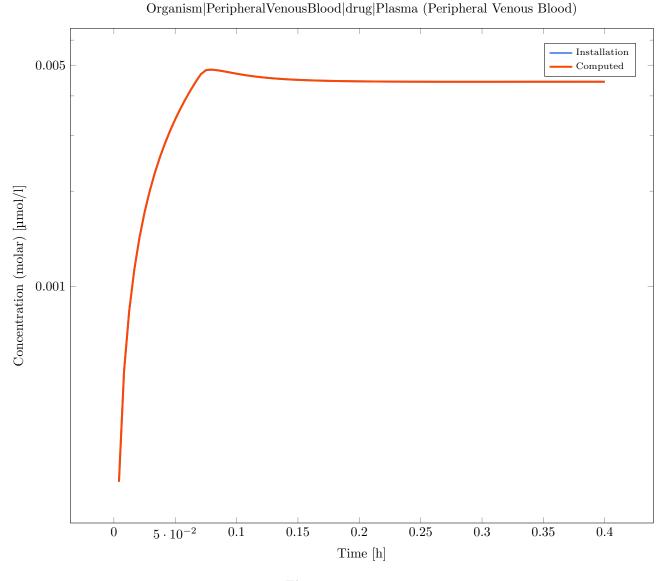


Figure 1.182

 $Simulation: Rabbit_SingleORAL_Dissolved_Rabbit_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5$ Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |
drug |Plasma (Peripheral Venous Blood) Deviation: ${\bf 0}$

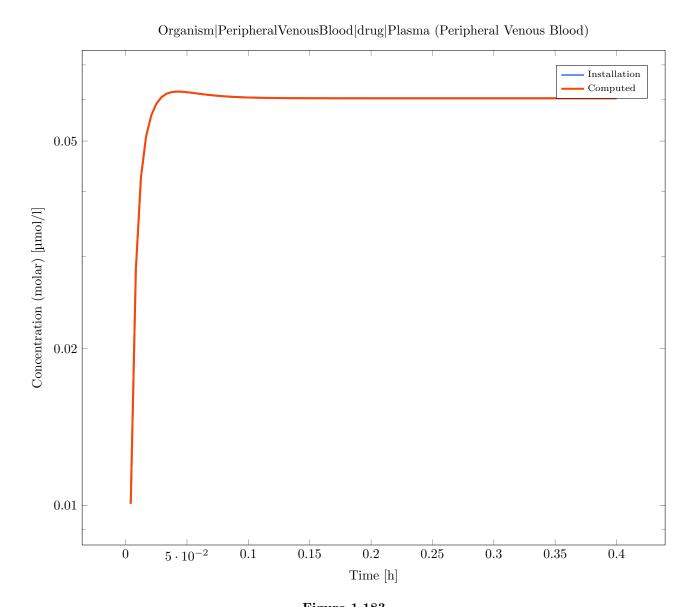


Figure 1.183

 $\label{local_simpleORAL_Dissolved_Rabbit_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_--5 \\ Result of the validation: Valid$

Output Path: Organism |PeripheralVenousBlood |
drug |Plasma (Peripheral Venous Blood) Deviation: ${\bf 0}$

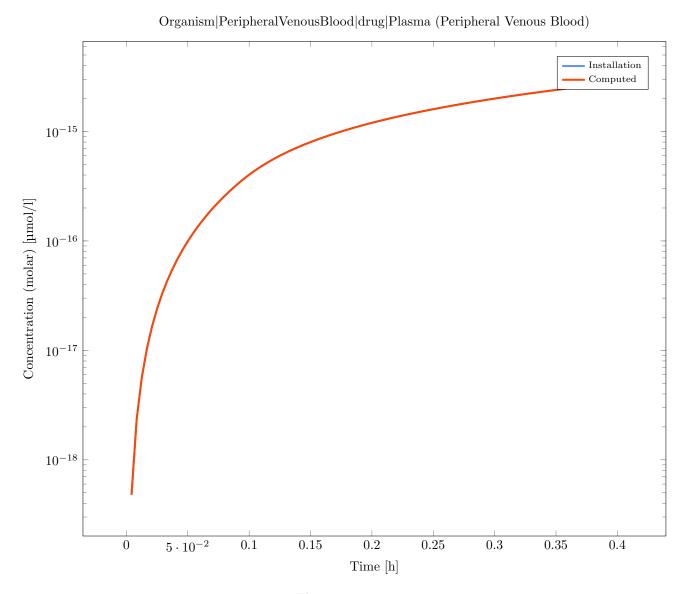
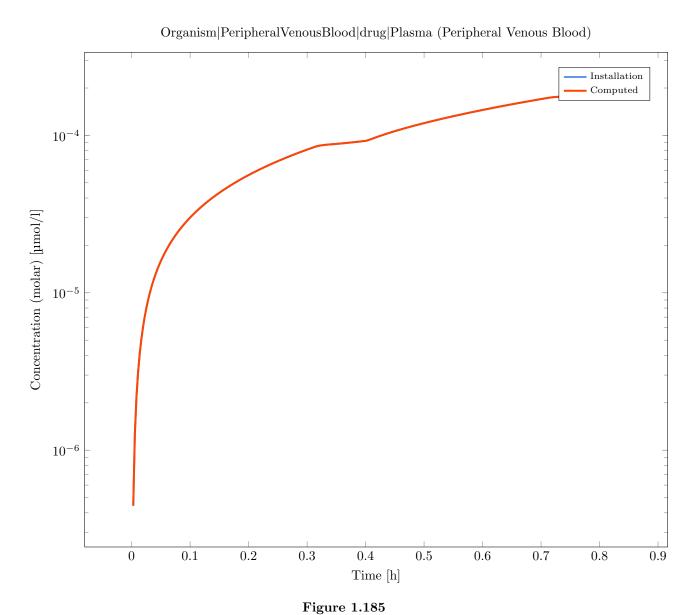


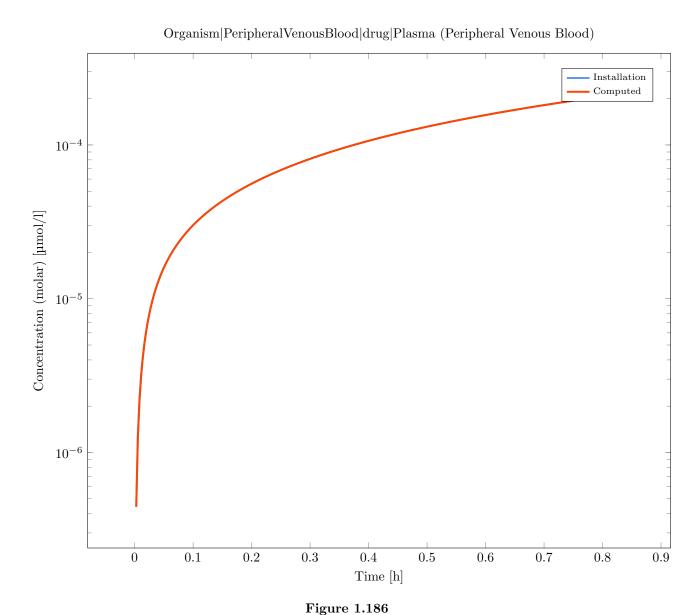
Figure 1.184

Simulation: Rat_MultiORAL_6_6_12_Dissolved-Rat_MultiORAL_6_6_12_Dissolved Result of the validation: Valid



 $\begin{tabular}{ll} \bf Simulation: & Rat_MultiORAL_6_6_6_6_6_0 \\ \bf Dissolved-Rat_MultiORAL_6_6_6_6_0 \\ \bf Dissolved-Rat_MultiORAL_6_6_6_0 \\ \bf Dissolved-Rat_MultiORAL_6_6_6_0 \\ \bf Dissolved-Rat_MultiORAL_6_6_6_0 \\ \bf Dissolved-Rat_MultiORAL_6_6_0 \\ \bf Dissolved-Rat_MultiORAL_6_0 \\ \bf Dissol$

Output Path: Organism |PeripheralVenousBlood |
drug |Plasma (Peripheral Venous Blood) Deviation: ${\bf 0}$



Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood) Installation Computed 10^{-4} Concentration (molar) $[\mu]$ 10^{-5} 10^{-6} 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

 ${\bf Figure~1.187}$

Time [h]

 $Simulation: Single IV_2 Pores_Human-Single IV_2 Pores_Human$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |
drug |Plasma (Peripheral Venous Blood) Deviation: ${\bf 0}$

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

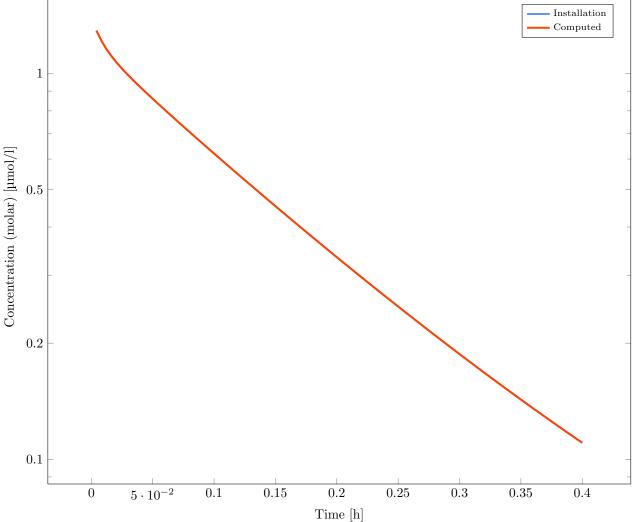


Figure 1.188

Simulation: SingleIV_2Pores_Human-SingleIV_2Pores_Human_SimulationC Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

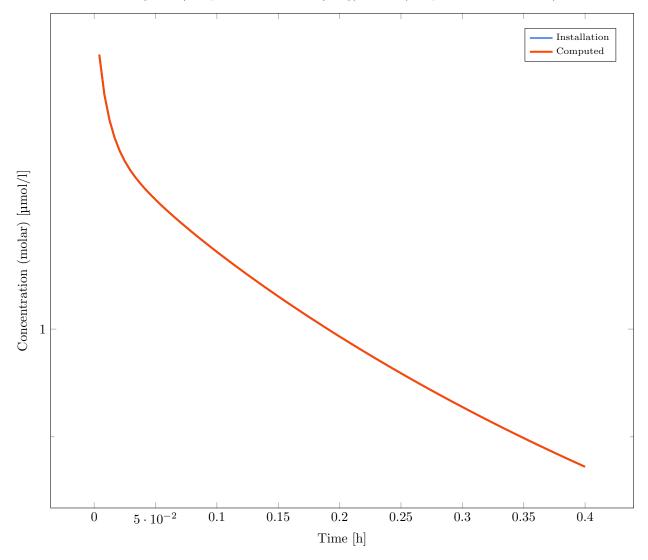


Figure 1.189

Simulation: SingleIV_2Pores_Human-SingleIV_2Pores_Human_SimulationD Result of the validation: Valid

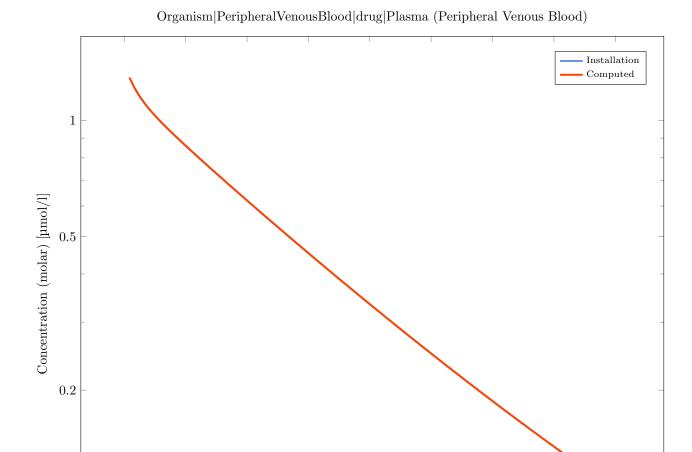


Figure 1.190

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

Simulation: SingleIV_2Pores_Human-SingleIV_2Pores_Human_SimulationF Result of the validation: Valid

0.1

Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood) Deviation:
 0

0.1

0

 $5\cdot 10^{-2}$

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood)

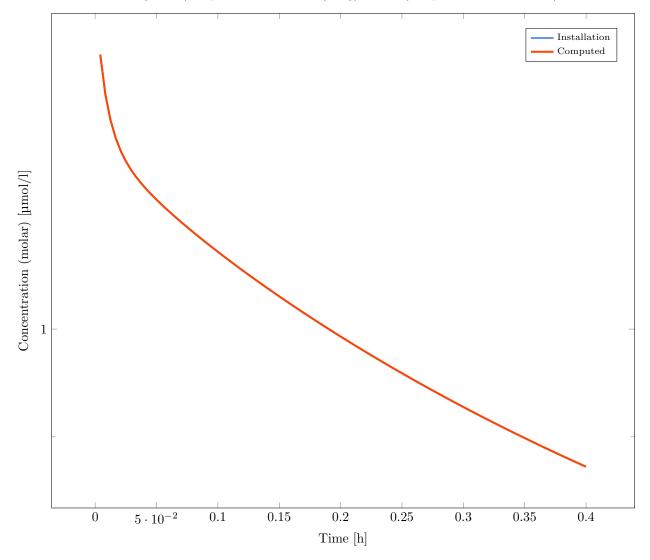


Figure 1.191

 $Simulation: Single IV_2 Pores_Monkey-Single IV_2 Pores_Monkey$

Result of the validation: Valid

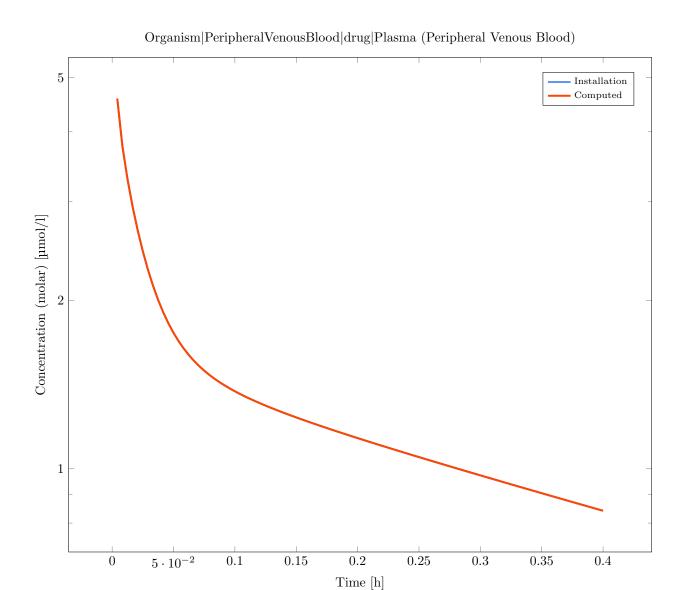


Figure 1.192

Simulation: SingleIV_2Pores_Monkey-SingleIV_2Pores_Monkey_SimulationG Result of the validation: Valid



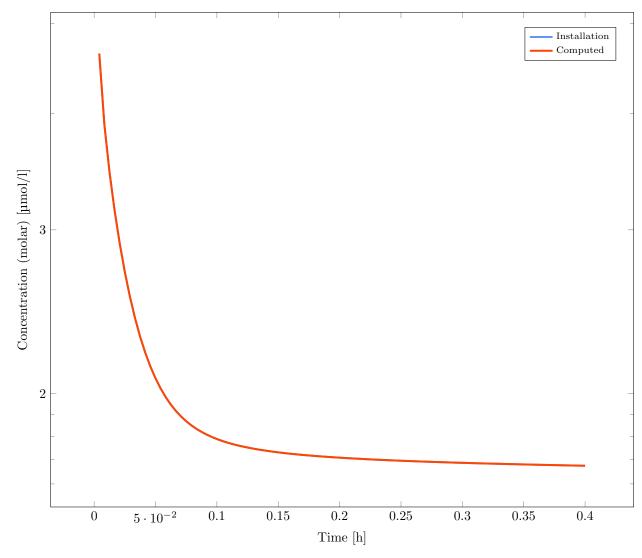


Figure 1.193

Simulation: SingleIV_2Pores_Monkey-SingleIV_2Pores_Monkey_SimulationH Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood) | Total Computed | To

Figure 1.194

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

 $Simulation: Single IV_2 Pores_Mouse-Single IV_2 Pores_Mouse$

0.1

 $5\cdot 10^{-2}$

Result of the validation: Valid

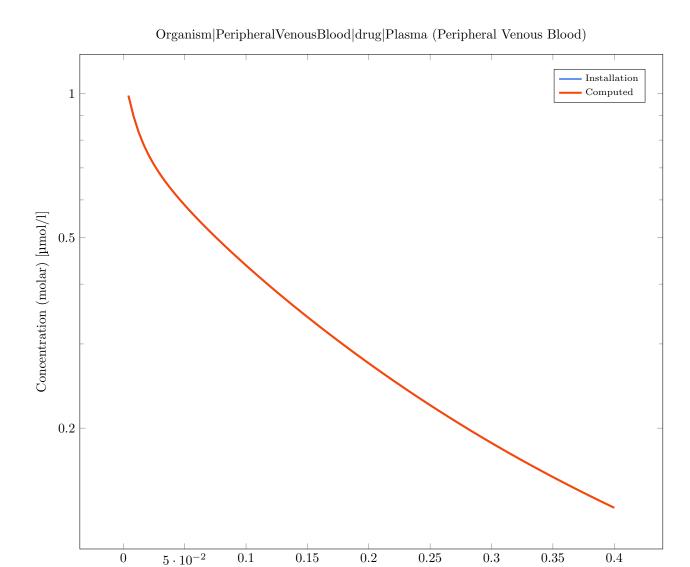


Figure 1.195

Time [h]

Simulation: SingleIV_2Pores_Mouse-SingleIV_2Pores_Mouse_SimulationA Result of the validation: Valid

Figure 1.196

Time [h]

Simulation: SingleIV_2Pores_Mouse-SingleIV_2Pores_Mouse_SimulationB Result of the validation: Valid

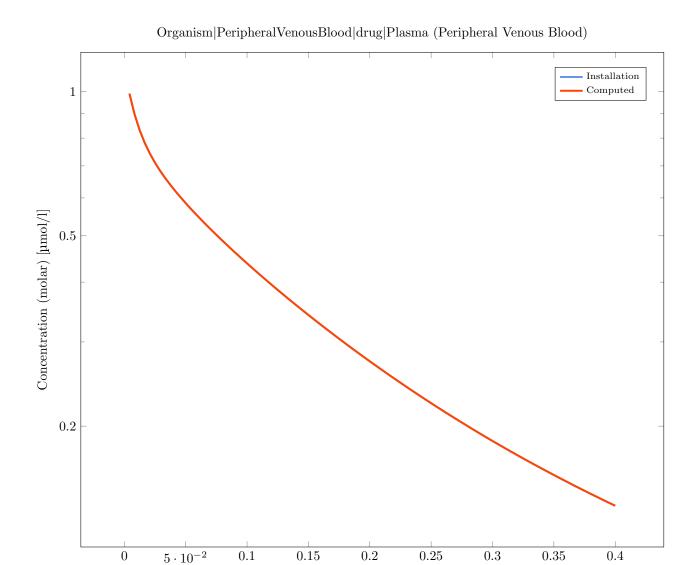


Figure 1.197

Time [h]

Simulation: SingleIV_2Pores_Mouse-SingleIV_2Pores_Mouse_SimulationE Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood) Installation Computed O.5 - 10⁻² 0.1 0.15 0.2 0.25 0.3 0.35 0.4

Figure 1.198

 $Simulation: Single IV_C1_4 Comp_standard_stand$

Time [h]

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C1|Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

$Organism|Peripheral Venous Blood|C1|Plasma\ (Peripheral Venous\ Blood)$

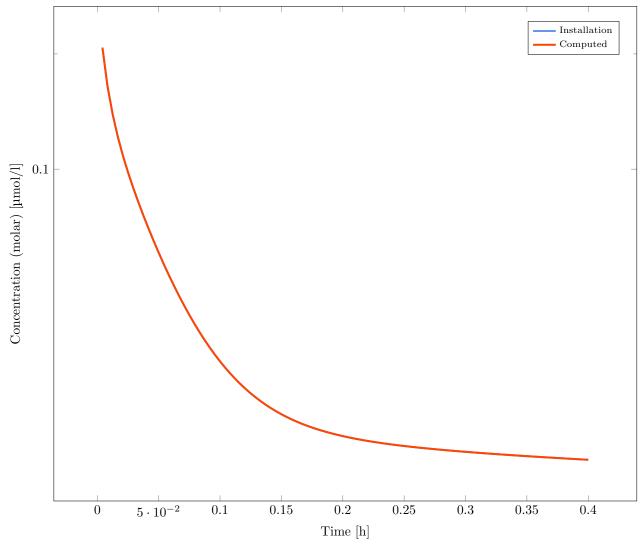


Figure 1.199

 $Simulation: Single IV_C2_4 Comp_PT_standard_st$

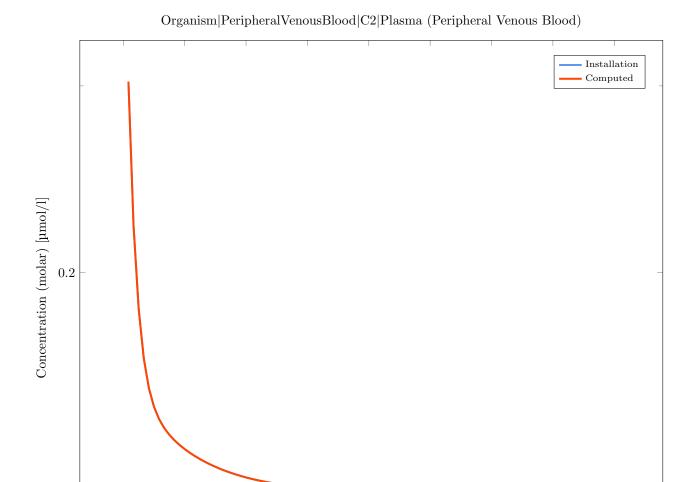


Figure 1.200

 $Simulation: Single IV_C2_4 Comp_RR_standard_st$

0.2

Time [h]

0.25

0.35

0.4

0.3

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

0.15

0.1

0

 $5\cdot 10^{-2}$

Figure 1.201

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: Single IV_C2_4 Comp_standard_schmitt_standard-Single IV_C2_4 Comp_standard_schmitt_standard\\$

Result of the validation: Valid

0

 $5\cdot 10^{-2}$

0

Output Path: Organism |PeripheralVenousBlood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

0.15

0.1

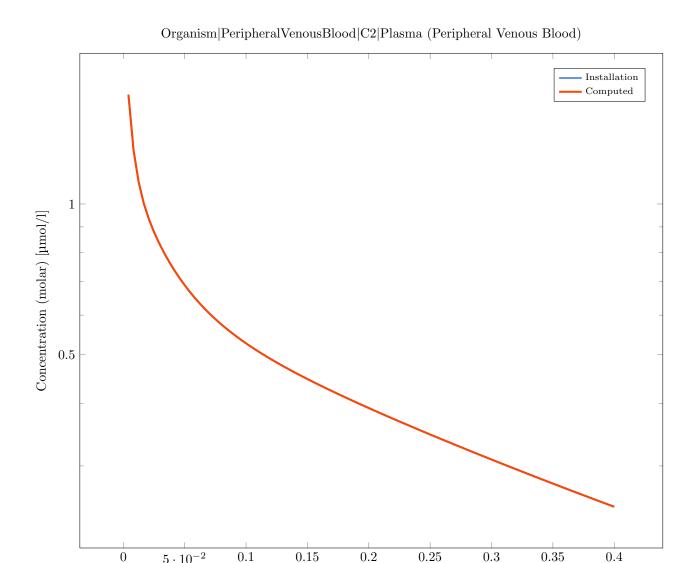


Figure 1.202

Time [h]

 $Simulation: Single IV_C3_4 Comp_RR_schmitt_standard-Single IV_C3_schmitt_standard-Single IV_C3_schmitt_s$ Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C3|Plasma (Peripheral Venous Blood) Deviation: 0

0

 $5\cdot 10^{-2}$

0.1

0.4

Organism|PeripheralVenousBlood|C3|Plasma (Peripheral Venous Blood)

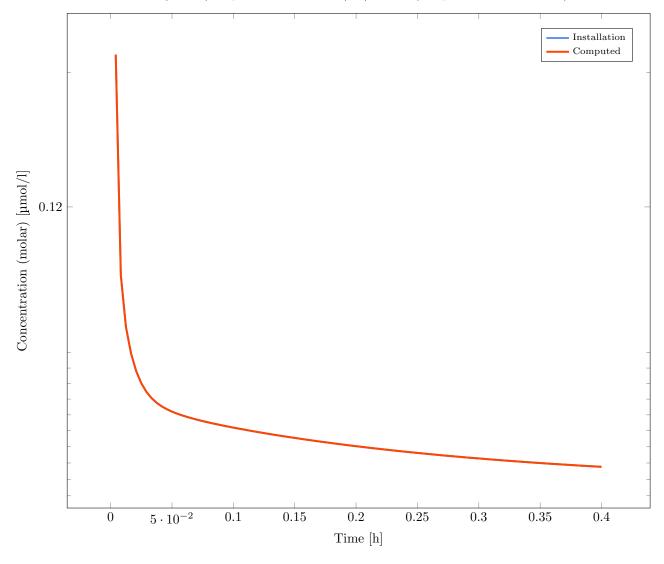


Figure 1.203

 $Simulation: Single IV_C3_4 Comp_standard_schmittnorm lized_standard-Single IV_C3_4 Comp_standard_schmittnorm lized_standard$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C3|Plasma (Peripheral Venous Blood)

Deviation: 0

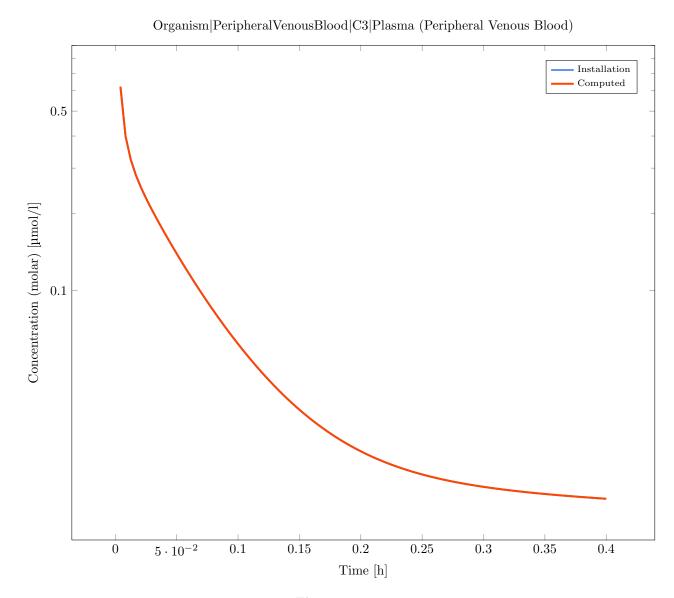


Figure 1.204

 $Simulation: Single IV_C4_2 Pores_RR_standard_s$

Output Path: Organism |Peripheral Venous
Blood |C4 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

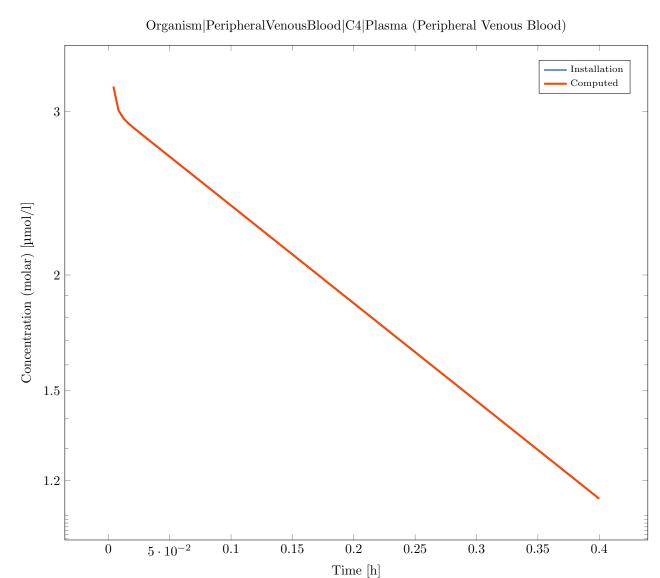


Figure 1.205

 $Simulation: Single IV_C4_4 Comp_Ber_standard_s$

Output Path: Organism |Peripheral Venous
Blood |C4 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

$Organism|Peripheral Venous Blood|C4|Plasma\ (Peripheral Venous\ Blood)$

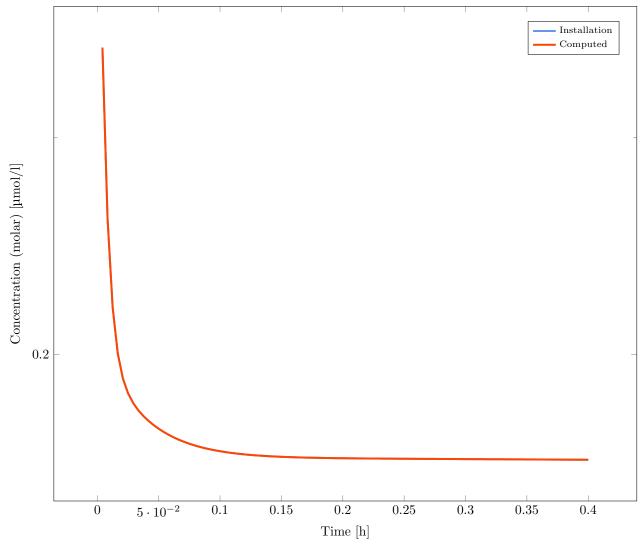


Figure 1.206

 $Simulation: Single IV_C5_2 Pores_Ber_standard_$

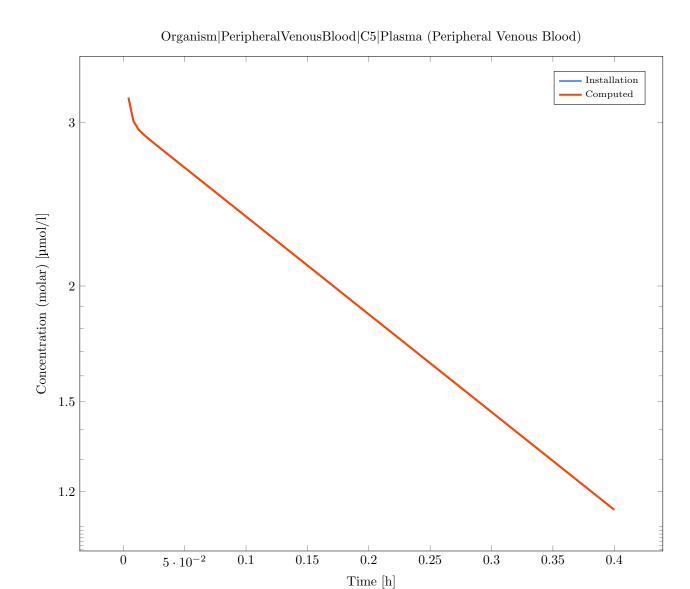


Figure 1.207

 $Simulation: Single IV_C5_2 Pores_PT_standard_s$

Output Path: Organism |Peripheral Venous
Blood |C5 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

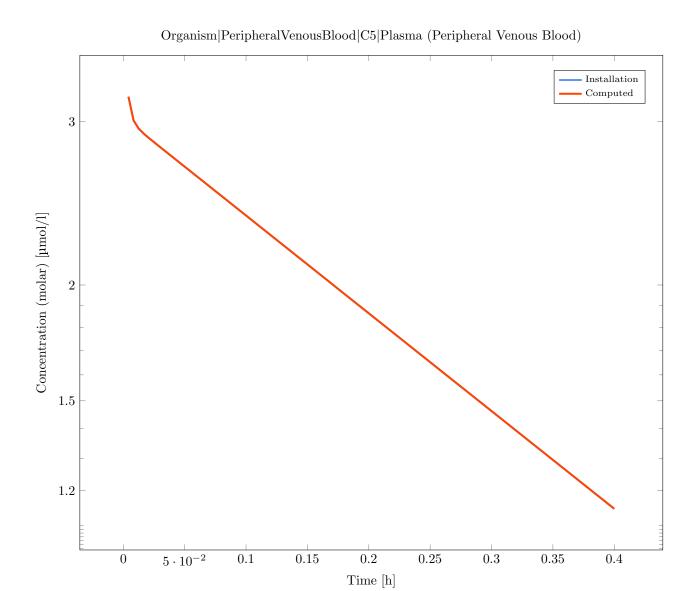


Figure 1.208

 $Simulation: SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_SingleI$

Output Path: Organism |Peripheral Venous
Blood |C5 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

Organism|Peripheral Venous Blood|C5|Plasma (Peripheral Venous Blood) Installation Computed Computed

Figure 1.209

 $Simulation: Single IV_C6_2 Pores_standard_stan$

0.2

Time [h]

0.25

0.3

0.35

0.4

Result of the validation: Valid

0

 $5\cdot 10^{-2}$

1.2

Output Path: Organism |PeripheralVenousBlood |C6 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

0.15

0.1

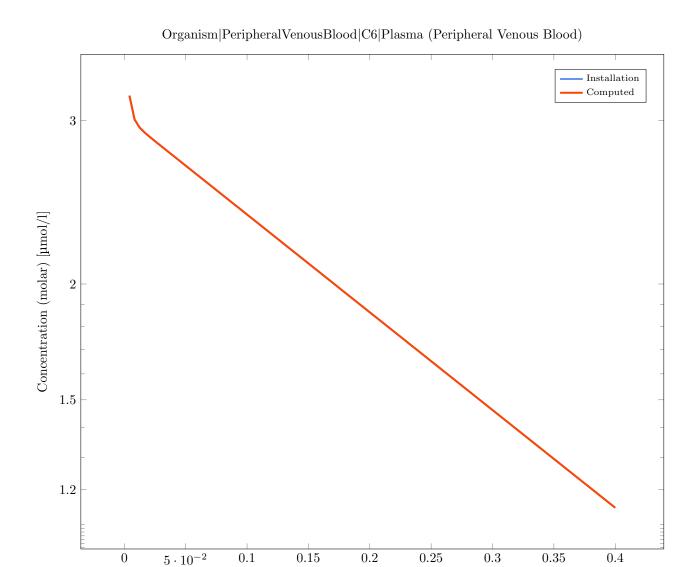


Figure 1.210

Time [h]

 $Simulation: Single IV_C7_2 Pores_standard_schmitt_standard_Single IV_C7_2 Pores_standard_schmitt_schmitt$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C7 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

Organism|PeripheralVenousBlood|C7|Plasma (Peripheral Venous Blood) Installation Computed 0.5 0.1

Figure 1.211

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: Single IV_C7_4 Comp_schmitt_standard_standa$

Result of the validation: Valid

0

 $5\cdot 10^{-2}$

Output Path: Organism |PeripheralVenousBlood |C7 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

0.15

0.1



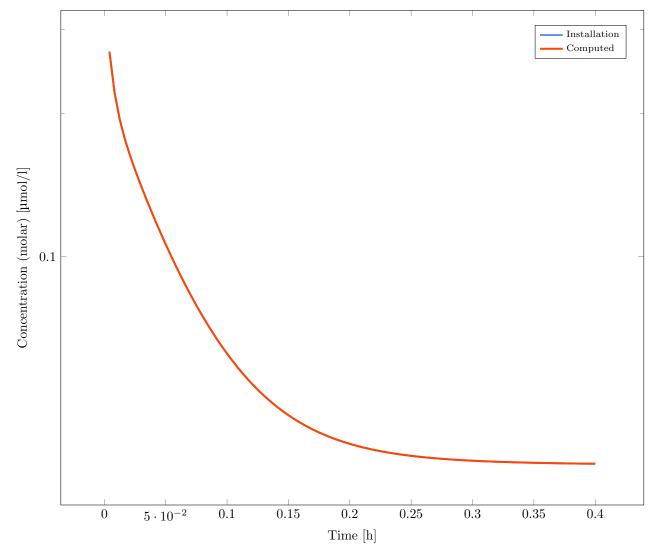


Figure 1.212

 $Simulation: Single IV_C8_2 Pores_standard_schmittnormalized_standard_Single IV_C8_2 Pores_standard_schmittnormalized_schmittnormalized_schmittnor$

Result of the validation: Valid

Output Path: Organism|PeripheralVenousBlood|C8|Plasma (Peripheral Venous Blood)

Deviation: 0

Organism|PeripheralVenousBlood|C8|Plasma (Peripheral Venous Blood)

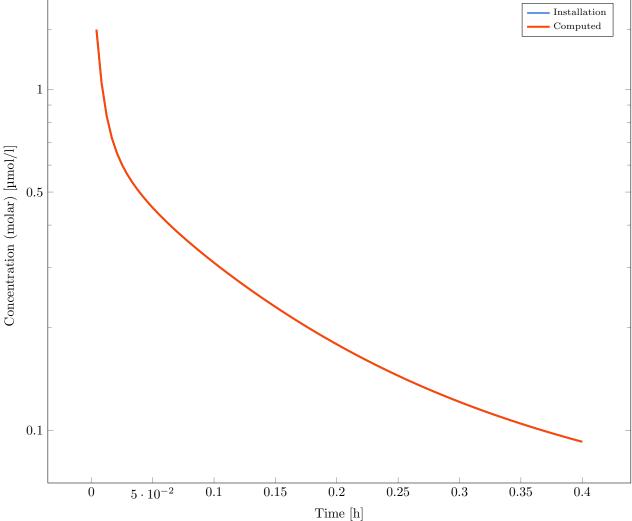
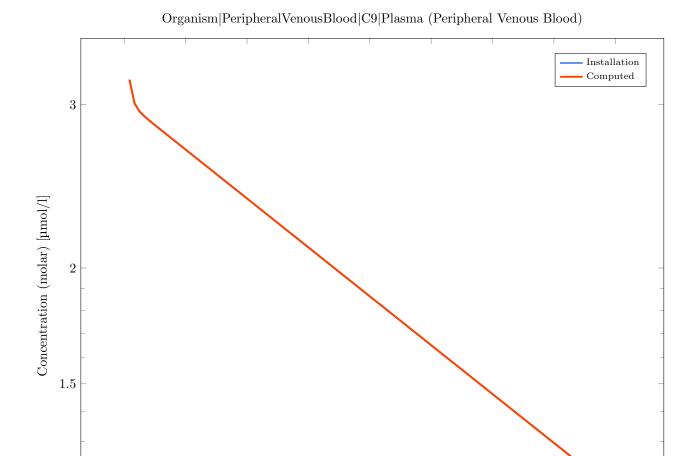


Figure 1.213

 $Simulation: Single IV_C9_2 Pores_schmitt_standard_standard_Single IV_C9_2 Pores_schmitt_standard_sta$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C9 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$



0.15 0.2

Time [h]

0.25

0.3

0.35

0.4

Figure 1.214

 $Simulation: Single ORAL_C10_4 Comp_PT_standard_standard_Single ORAL_C10_4 Comp_PT_standard_$

Result of the validation: Valid

0

 $5\cdot 10^{-2}$

0.1

 $Output \ Path: \ Organism | Peripheral Venous Blood | C10 | Plasma \ (Peripheral \ Venous \ Blood)$

Deviation: 0

1.2

Organism|PeripheralVenousBlood|C10|Plasma (Peripheral Venous Blood)

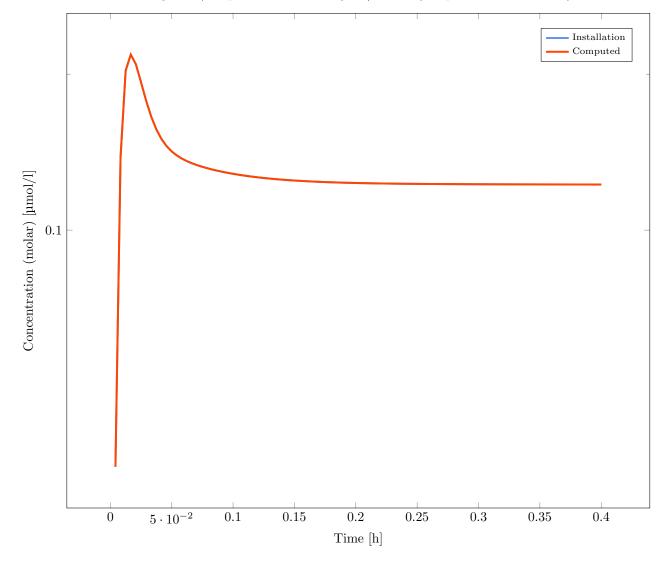


Figure 1.215

 $Simulation: Single ORAL_C11_4 Comp_schmitt_standard_standard_Single ORAL_C11_4 Comp_schmitt_standard$

Result of the validation: Valid

 ${\bf Output~Path:~Organism|Peripheral Venous Blood|C11|Plasma~(Peripheral~Venous~Blood)}$

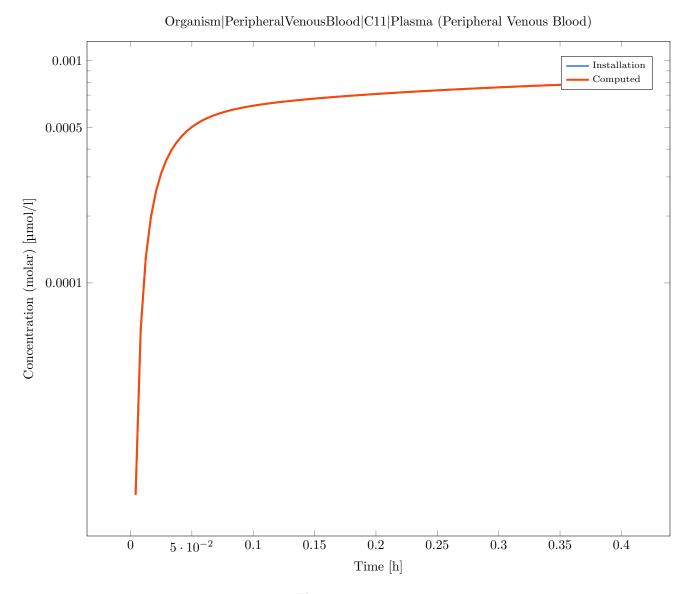


Figure 1.216

 $Simulation: Single ORAL_C11_4 Comp_standard_st$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C11 |Plasma (Peripheral Venous Blood)
 Deviation: 0

Organism|PeripheralVenousBlood|C11|Plasma (Peripheral Venous Blood)

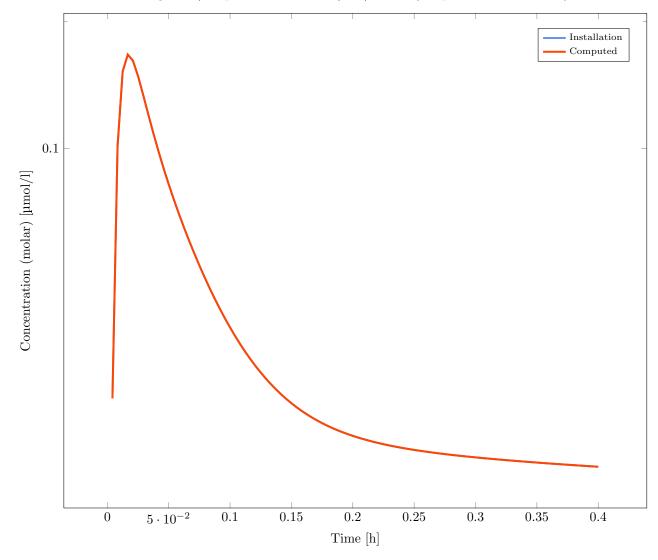


Figure 1.217

 $Simulation: Single ORAL_C12_4 Comp_standard_schmitt_standard-Single ORAL_C12_4 Comp_standard_schmitt_standard\\$

Result of the validation: Valid

 $Output \ Path: \ Organism | Peripheral Venous Blood | C12 | Plasma \ (Peripheral \ Venous \ Blood)$

Organism|PeripheralVenousBlood|C12|Plasma (Peripheral Venous Blood) Installation Computed O.01 O.001 O.001

Figure 1.218

0.15

0.2

Time [h]

0.25

0.35

0.3

0.4

0.1

 $Simulation: Single ORAL_C13_2 Pores_schmitt_standard_st$

Result of the validation: Valid

0

 $5\cdot 10^{-2}$

Output Path: Organism |PeripheralVenousBlood | C13 |Plasma (Peripheral Venous Blood)
 Deviation: 0

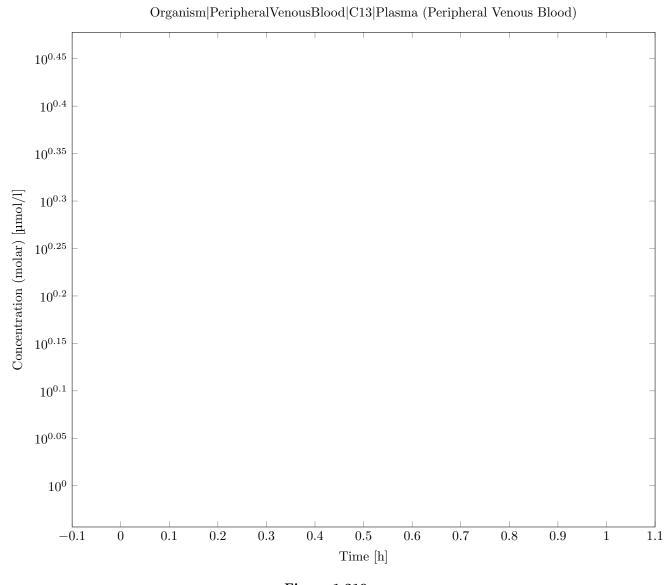


Figure 1.219

 $Simulation: Single ORAL_C13_4 Comp_standard_schmittnormalized_schmittnormalized_schmittnorm$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C13 |Plasma (Peripheral Venous Blood)
 Deviation: $\bf 0$

Organism|PeripheralVenousBlood|C13|Plasma (Peripheral Venous Blood)

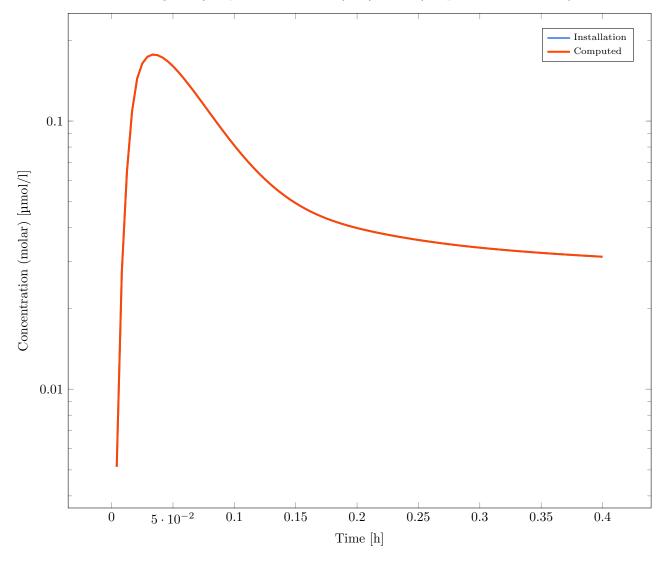


Figure 1.220

 $Simulation: Single ORAL_C14_2 Pores_PT_standard_standard_Single ORAL_C14_2 Pores_PT_standard_standar$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood | C14 |Plasma (Peripheral Venous Blood)

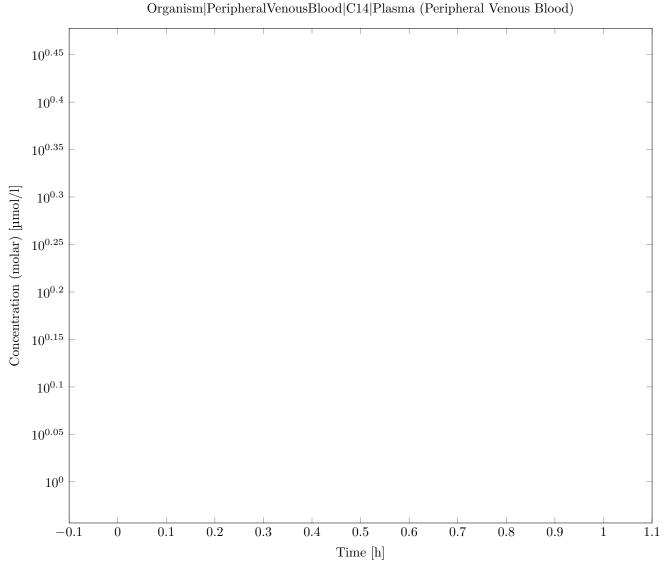
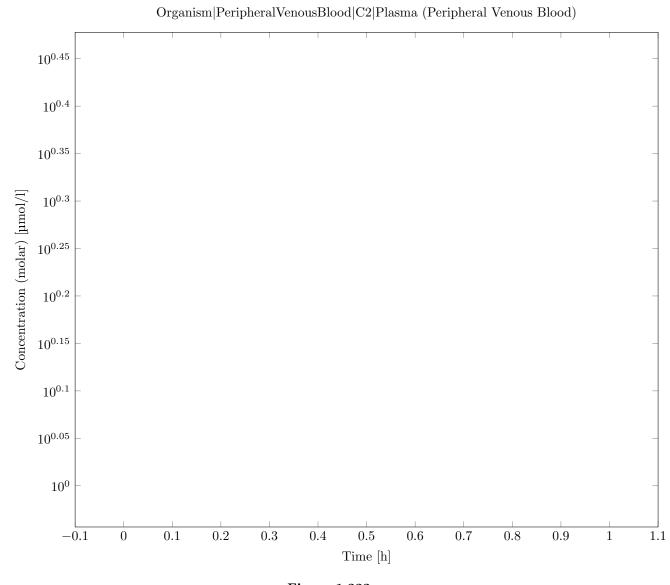


Figure 1.221

 $Simulation: Single ORAL_C2_2 Pores_standard_st$

Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood) Deviation:
 0



 ${\bf Figure~1.222}$

 $Simulation: Single ORAL_C3_2 Pores_standard_schmitt_standard-Single ORAL_C3_2 Pores_standard_schmitt_standard\\$

Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C3 |Plasma (Peripheral Venous Blood) Deviation:
 0

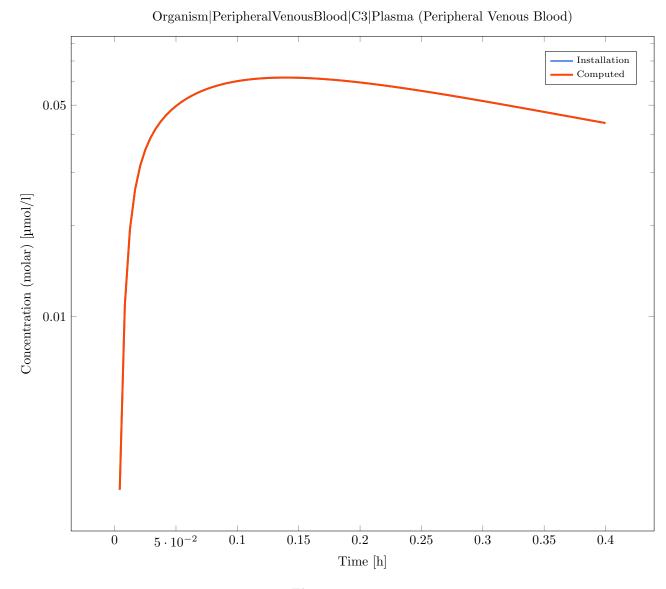


Figure 1.223

 $Simulation: Single ORAL_C4_2 Pores_standard_schmittnormalized_standard_Single ORAL_C4_2 Pores_standard_schmittnormalized_standard$

Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C4 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

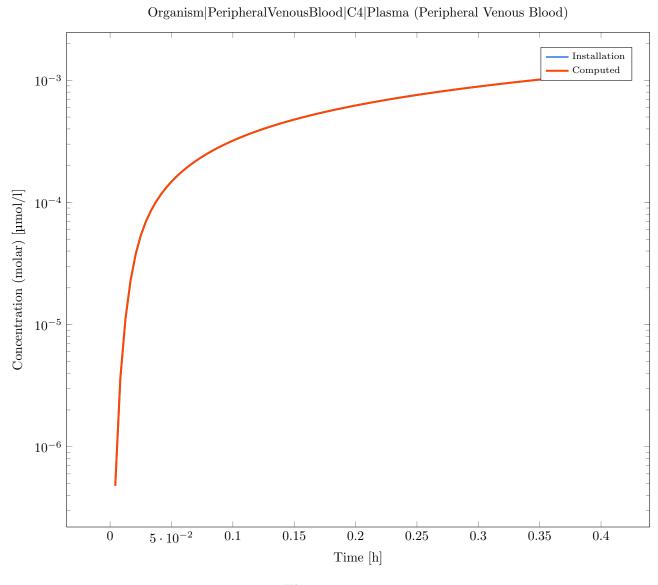


Figure 1.224

 $Simulation: Single ORAL_C6_4 Comp_Ber_standard_standard_Single ORAL_C6_4 Comp_Ber_standard_$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C6 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

$Organism|Peripheral Venous Blood|C6|Plasma\ (Peripheral Venous Blood)$

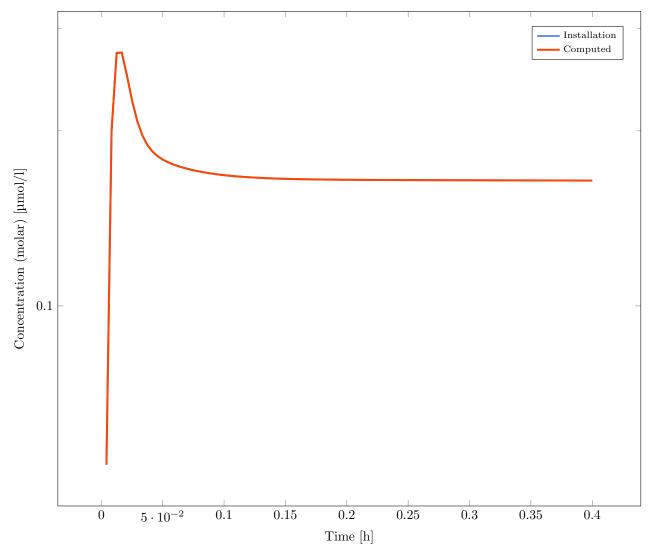


Figure 1.225

 $Simulation: Single ORAL_C6_4 Comp_RR_standard_standard_Single ORAL_C6_4 Comp_RR_standard_st$

Result of the validation: Valid

 $Output\ Path:\ Organism|PeripheralVenousBlood|C6|Plasma\ (Peripheral\ Venous\ Blood)$

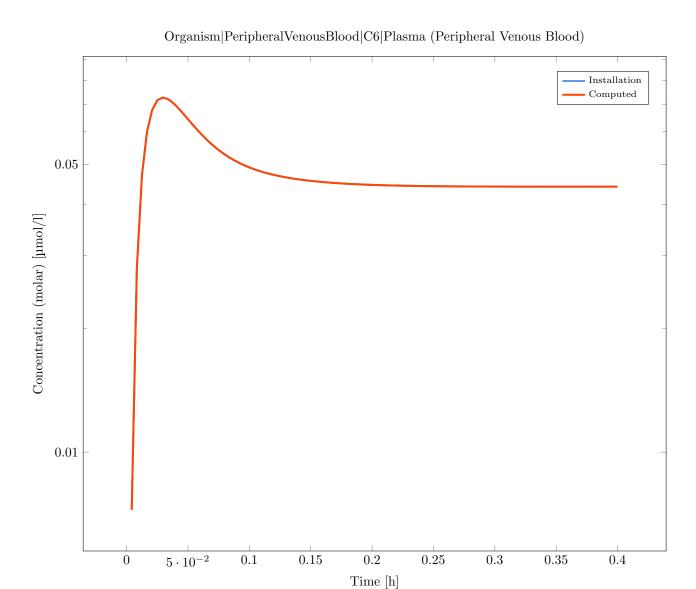


Figure 1.226

 $Simulation: Single ORAL_C7_2 Pores_Ber_standard_standard_Single ORAL_C7_2 Pores_Ber_standard_standar$

Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C7 |Plasma (Peripheral Venous Blood)
 Deviation: 0

Organism|PeripheralVenousBlood|C7|Plasma (Peripheral Venous Blood)

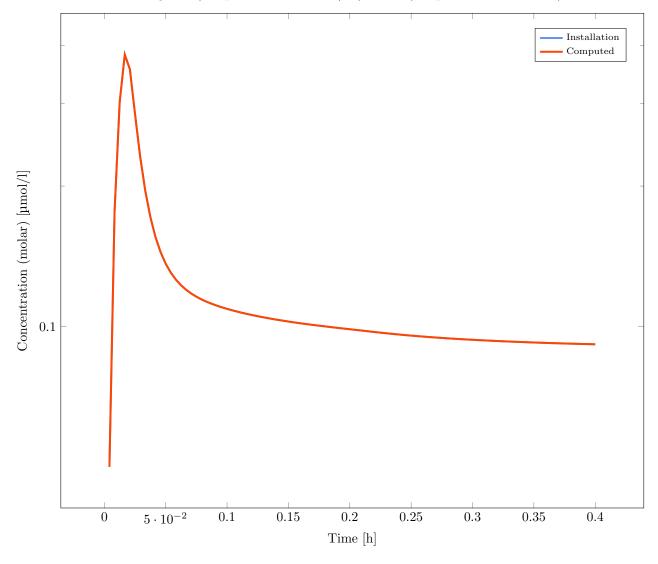


Figure 1.227

 $Simulation: Single ORAL_C7_4 Comp_RR_schmitt_standard-Single ORAL_C7_5 Comp_RR_schmitt_standard-Single ORAL_C7_5$

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C7 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

Organism|PeripheralVenousBlood|C7|Plasma (Peripheral Venous Blood) O.5 O.1 O.1 O.2 O.3 O.3 O.4 O.5 O.5 O.7 O.8 O.9 O.9 O.9 O.9 O.9 O.9 O.1 O.9 O.9

Figure 1.228

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: Single ORAL_C8_2 Pores_RR_standard_standard_Single ORAL_C8_2 Pores_RR_standard_$

Result of the validation: Valid

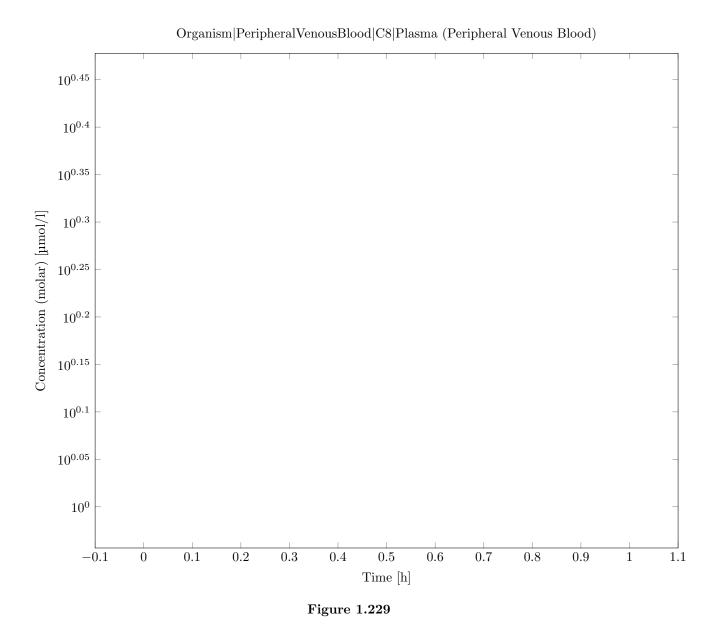
0

 $5\cdot 10^{-2}$

Output Path: Organism |PeripheralVenousBlood |C8 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

0.15

0.1



 $Simulation: Single ORAL_C9_2 Pores_RR_schmitt_standard-Single ORAL_SCHMitt_standard-Single ORAL_SCHMit$

Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C9 |Plasma (Peripheral Venous Blood) Deviation:
 $\mathbf 0$

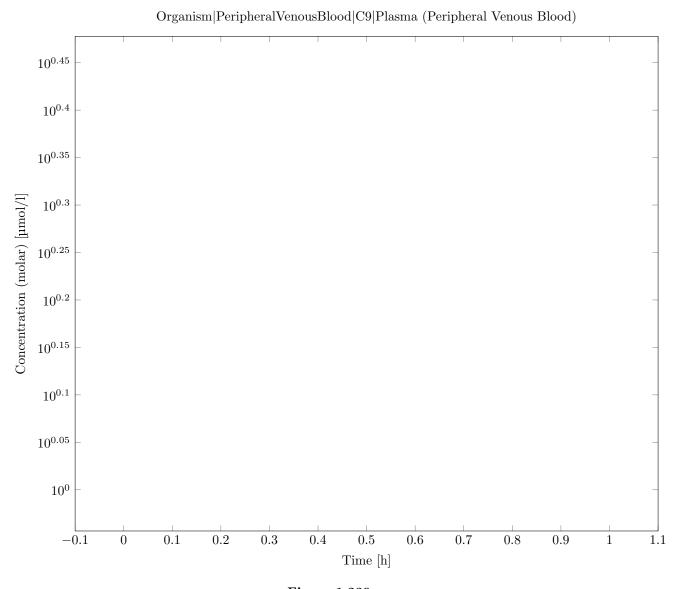


Figure 1.230

Simulation: Test 18.1_I1_C1_A1_Config1-Test 18.1_I1_C1_A1_Config1 Result of the validation: Valid

Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

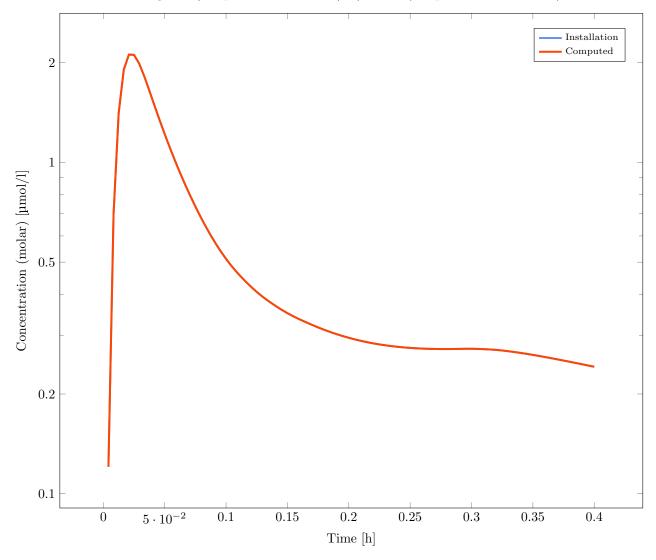


Figure 1.231

Simulation: Test $18.1_I2_C1_A1_Config2$ -Test $18.1_I2_C1_A1_Config2$ Result of the validation: Valid

Output Path: Organism |Peripheral Venous
Blood |C1 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood)

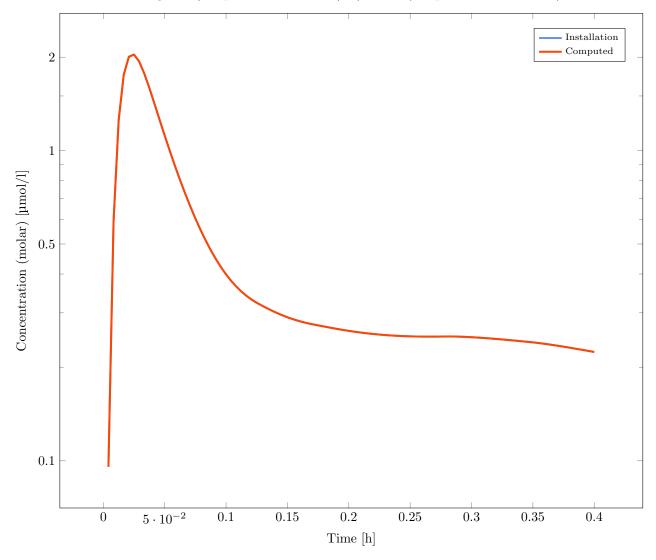


Figure 1.232

 $Simulation: \ Test\ 18.1_I2_C3_A1_Config2-Test\ 18.1_I2_C3_A1_Config2$

Result of the validation: Valid

 $Output\ Path:\ Organism|Peripheral Venous Blood|C3|Plasma\ (Peripheral\ Venous\ Blood)$

Organism|PeripheralVenousBlood|C3|Plasma (Peripheral Venous Blood) 10 - Installation Computed 10 - Installation Computed

Figure 1.233

0.2

Time [h]

0.25

0.3

0.35

0.4

Simulation: Test 18.1_I3_C3_A3_Config2-Test 18.1_I3_C3_A3_Config2 Result of the validation: Valid

0.1

Output Path: Organism |Peripheral Venous
Blood |C3 |Plasma (Peripheral Venous Blood)
 Deviation: 0

0.15

0

 $5\cdot 10^{-2}$

$Organism|Peripheral Venous Blood|C3|Plasma\ (Peripheral Venous Blood)$

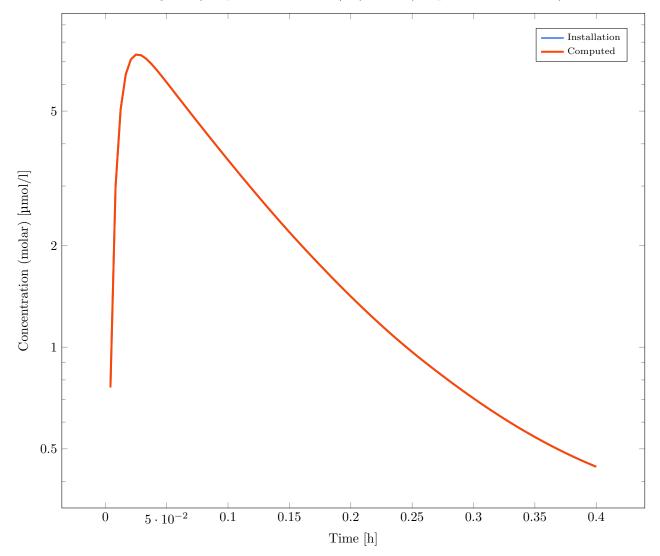


Figure 1.234