Open Systems Pharmacology Suite - 9 Installation Validation

user

July 22, 2020

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Chapter 1

Installation Validation Results

Overall Validation Result

Valid

1.1 Validation Summary

Run Duration

Start time: 2020-07-22 13:15 End time: 2020-07-22 13:46

Validation performed in 30m:35s:287ms

Input Configuration Folder

 $C: \label{lem:condition} C: \label{lem:condition} Paramacology \label{lem:condition} Inputs \label{lem:condition} BatchFiles$

Local Outputs Location

Application Versions

PK-Sim Version 9.1.2 MoBi Version 9.1.1

Computer Name

WIN-TSALD3O4R5J

Operating System

Windows 7 Ultimate - Service Pack 1 - Service Pack 1

Architecture

x64

Running on Virtual Machine

Yes

Running on Terminal Session

No

1.2 Comparison Results

Overall Comparison Result

Valid

Installation Folder

C:\ProgramData\Open Systems Pharmacology\InstallationValidator\9.1\Outputs\BatchFiles

Computed Folder

1.2.1 Valid Simulations (148/148)

Simulation: Beagle_SingleORAL_Dissolved-Beagle_SingleORAL_Dissolved

Result of the validation: Valid

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

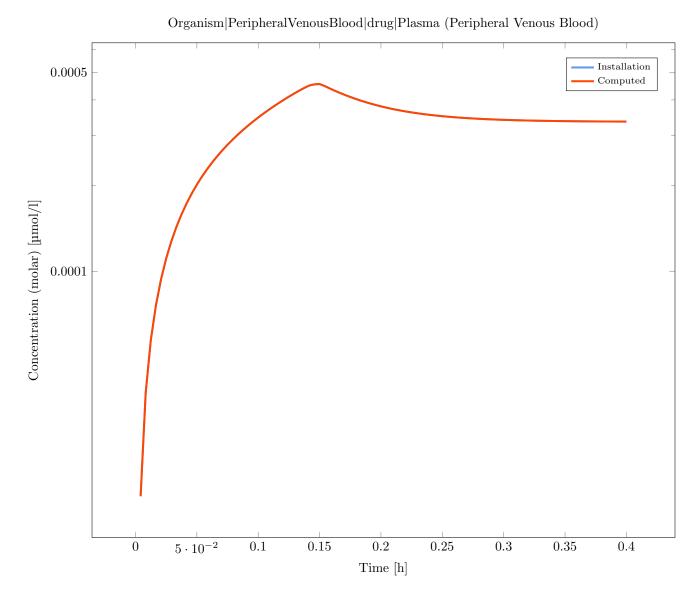


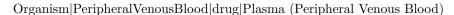
Figure 1.1

 $Simulation: Beagle_SingleORAL_Dissolved_Beagle_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_-$

Result of the validation: Valid

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

Deviation: 0



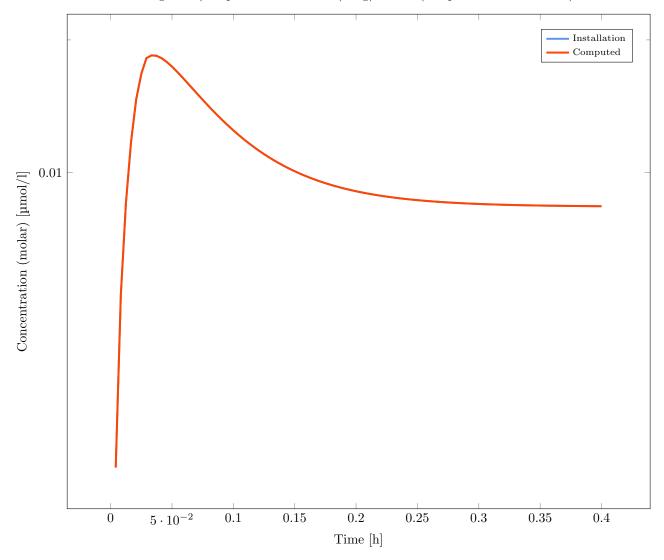


Figure 1.2

 $Simulation: Beagle_SingleORAL_Dissolved_Beagle_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_-5$

Result of the validation: Valid

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

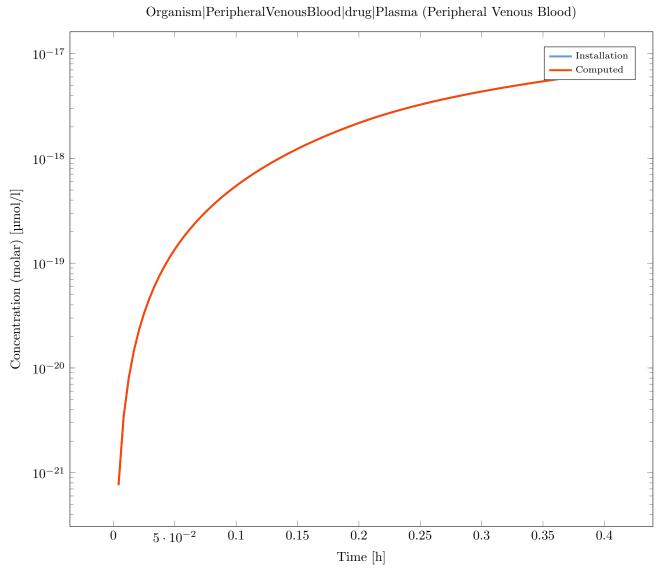
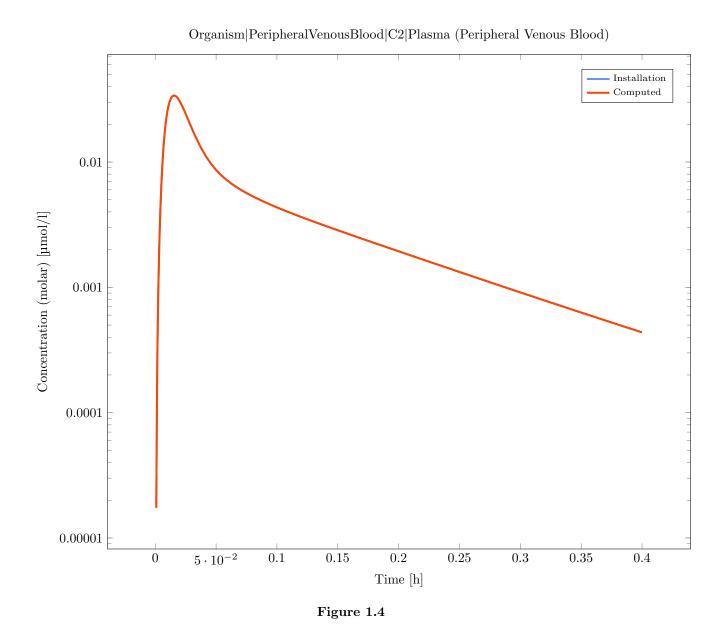


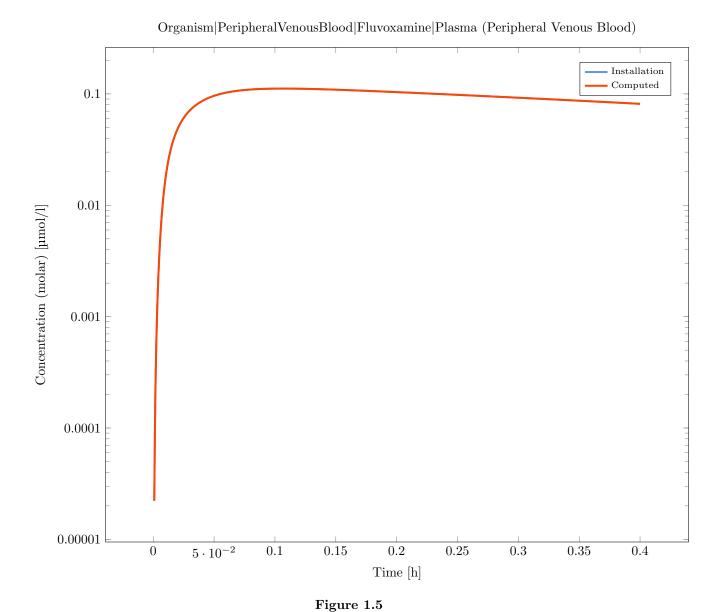
Figure 1.3

 ${\bf Simulation:\ DDI_Multiple Combinations-01_MM_Competitive_Competitive_Result\ of\ the\ validation:\ Valid}$

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



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



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

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

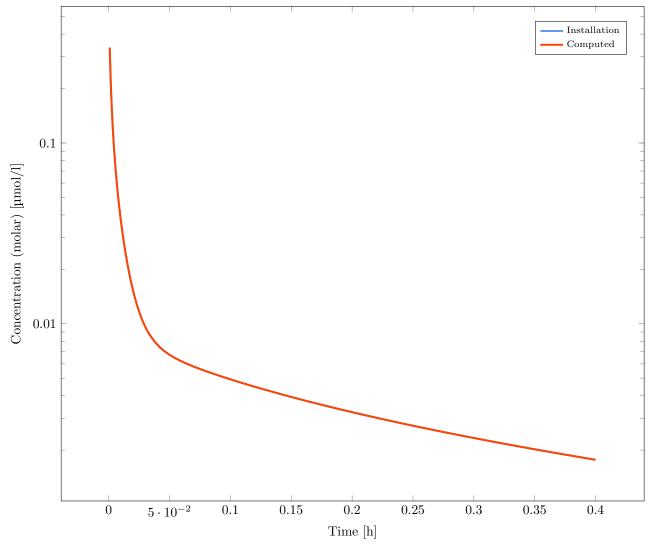
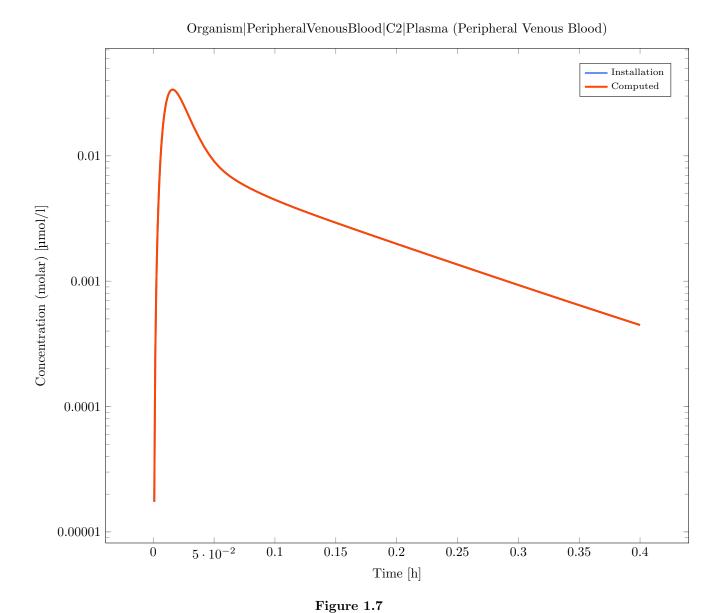


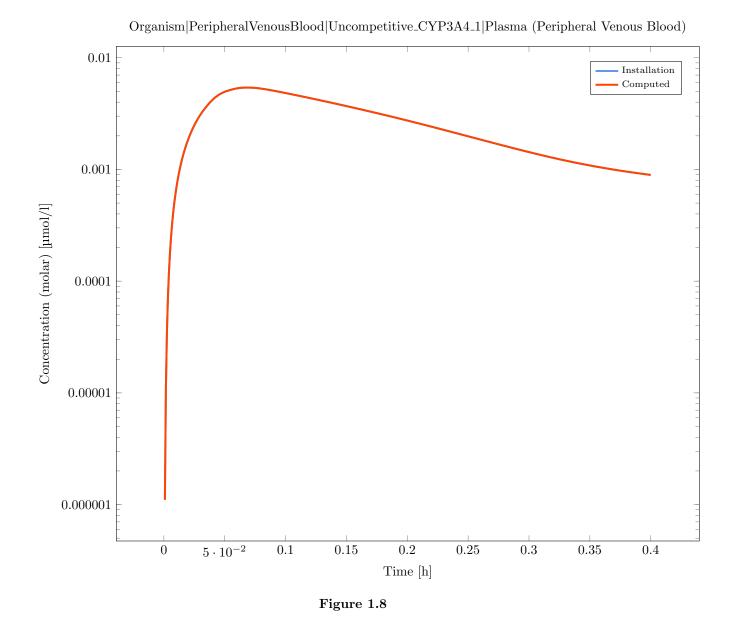
Figure 1.6

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

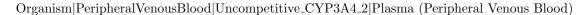
Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood) Deviation:
 $\mathbf 0$



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



Output Path: Organism |PeripheralVenousBlood |Uncompetitive_CYP3A4_2 |Plasma (Peripheral Venous Blood) | Deviation: 0



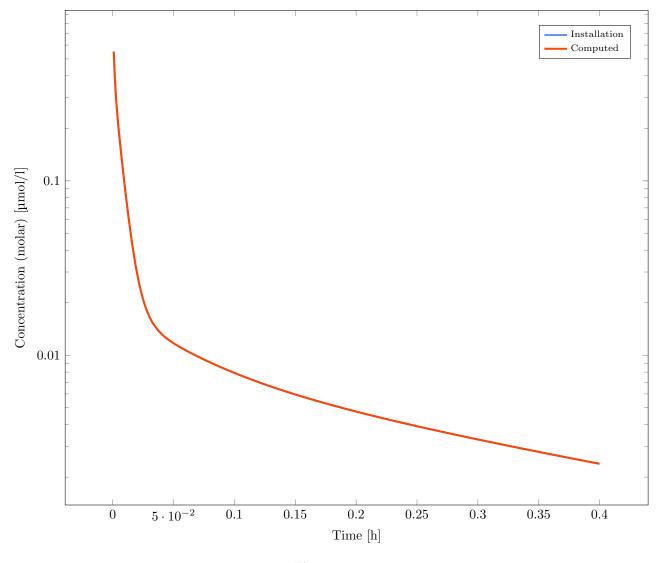


Figure 1.9

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

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

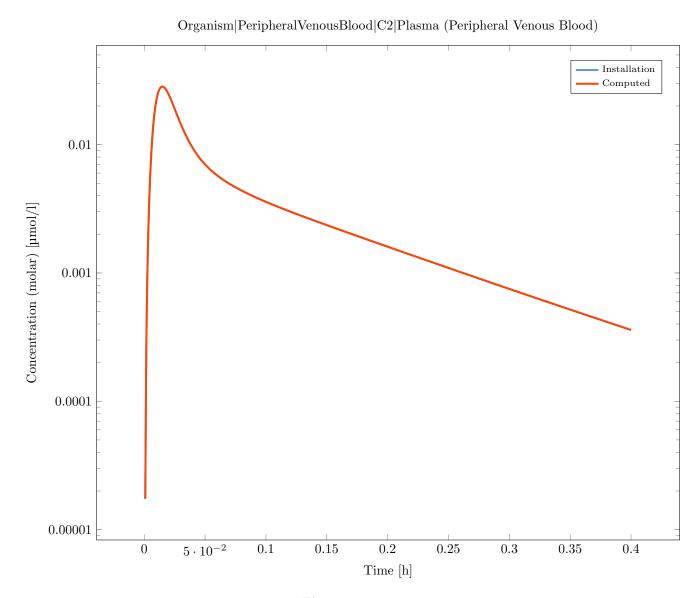


Figure 1.10

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

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

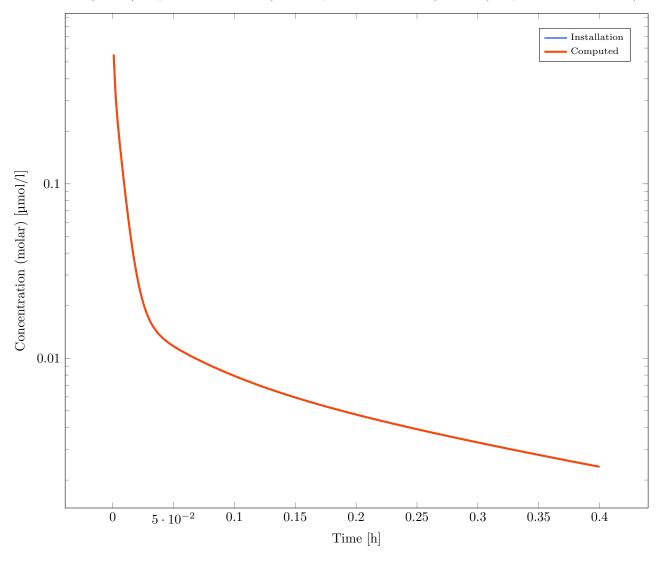


Figure 1.11

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

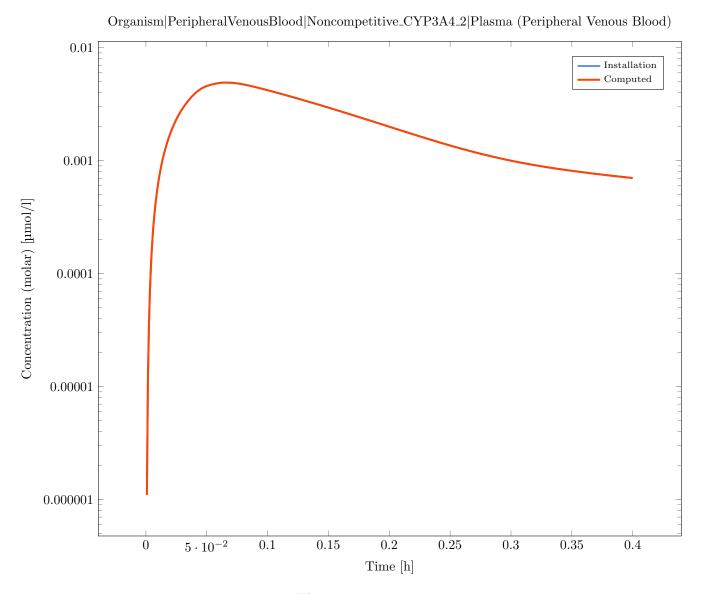
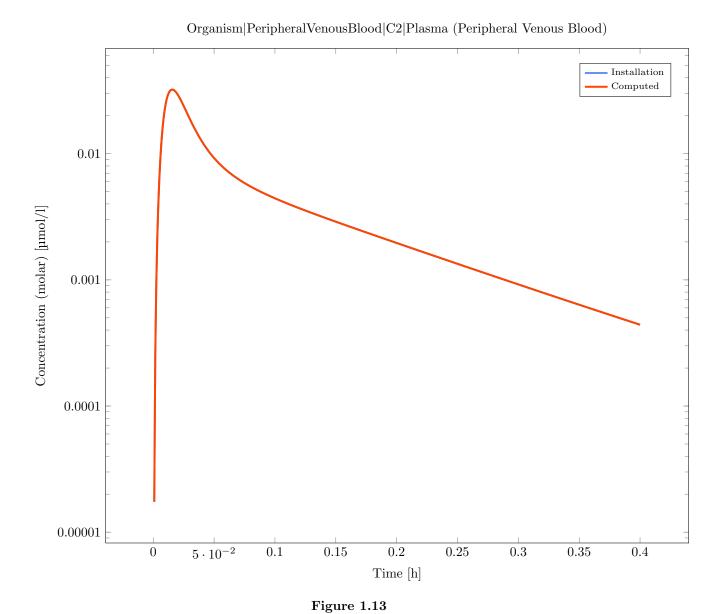


Figure 1.12

 $Simulation: DDI_MultipleCombinations-04_MM_Mixed_Mixed$

Result of the validation: Valid

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



Output Path: Organism |PeripheralVenousBlood |Mixed_CYP3A4_1 |Plasma (Peripheral VenousBlood)
 Deviation: 0

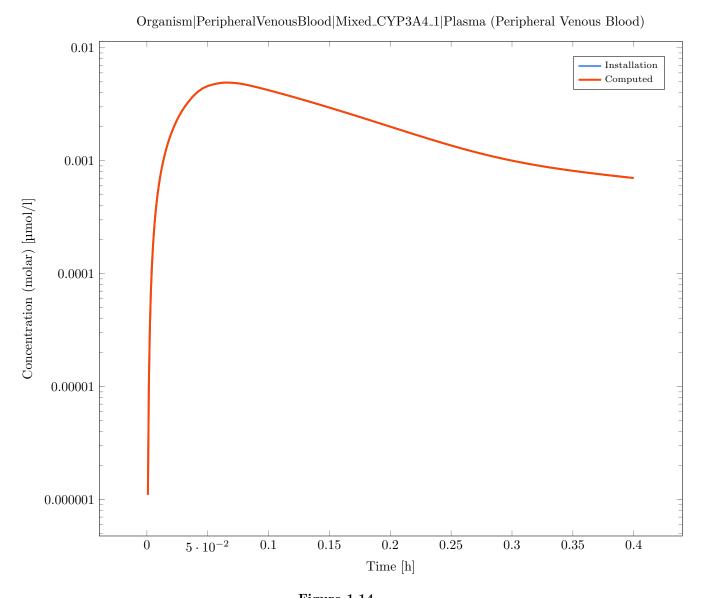
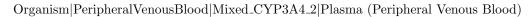


Figure 1.14

Output Path: Organism |PeripheralVenousBlood |Mixed_CYP3A4_2 |Plasma (Peripheral VenousBlood)
 Deviation: 0



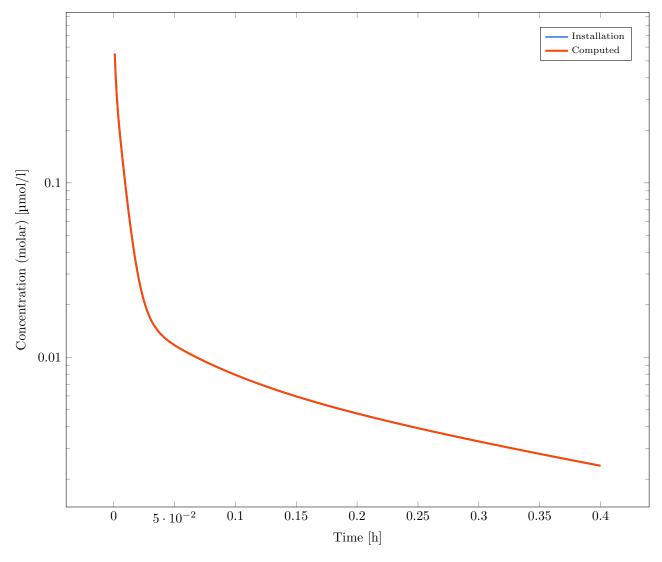
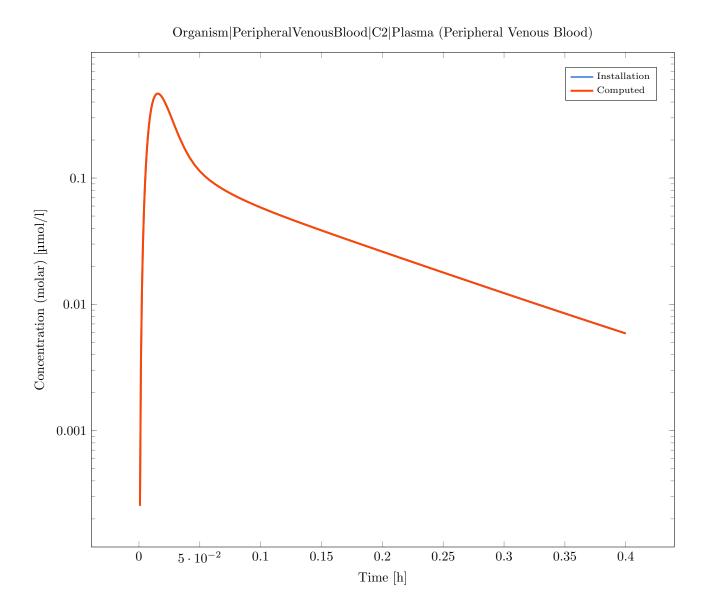


Figure 1.15

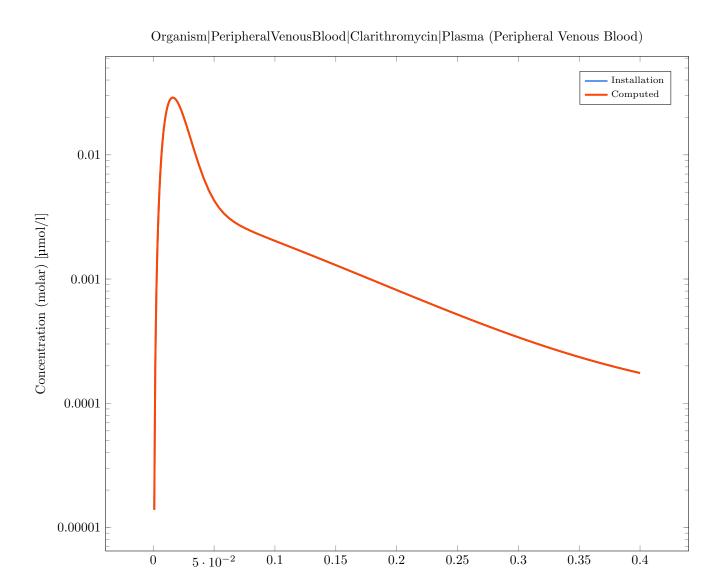
Simulation: DDI_MultipleCombinations-05_MM_Mechanismbased_Mechanismbased Result of the validation: Valid

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



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

Figure 1.16



Deviation: 0

Time [h]

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

Figure 1.17

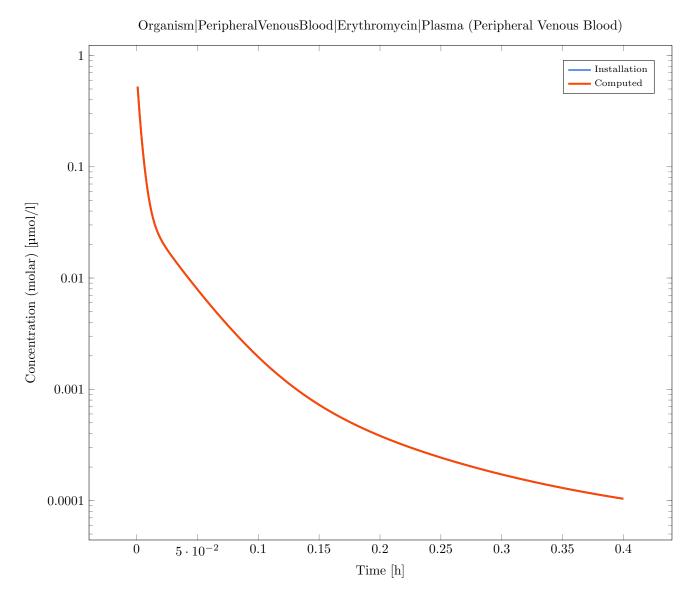
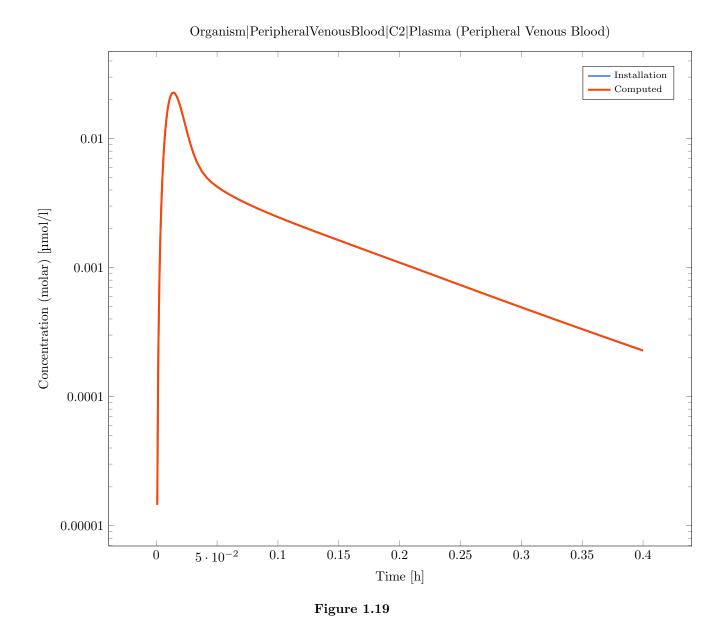


Figure 1.18

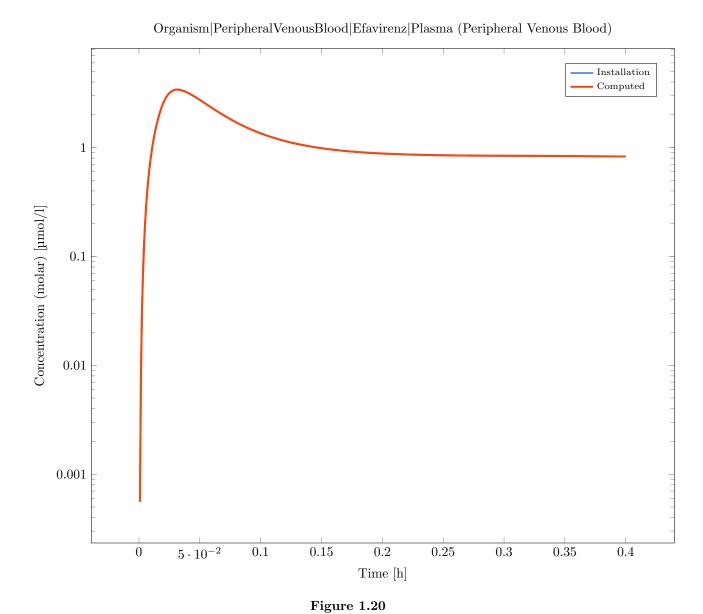
 ${\bf Simulation:\ DDI_Multiple Combinations-06_MM_Induction_Induction}$

Result of the validation: Valid

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



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



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

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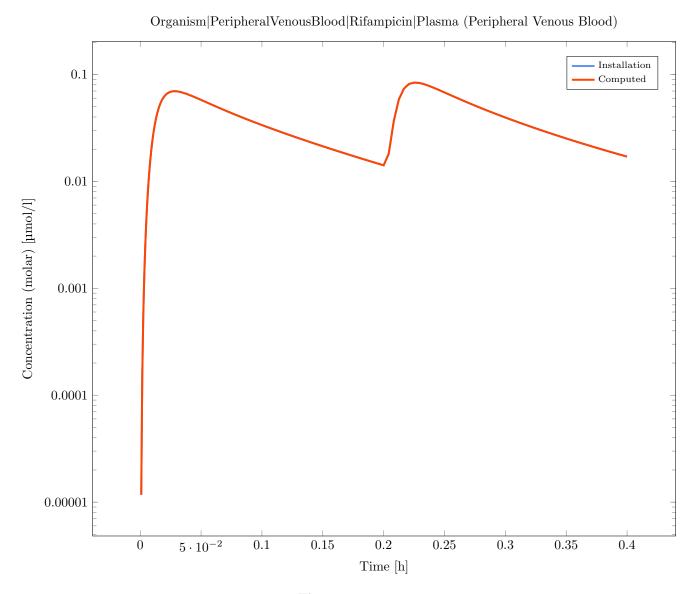
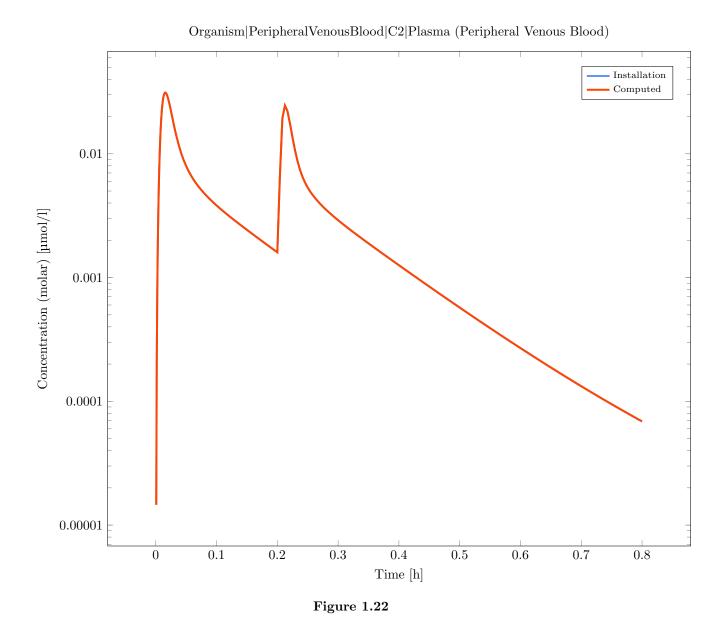


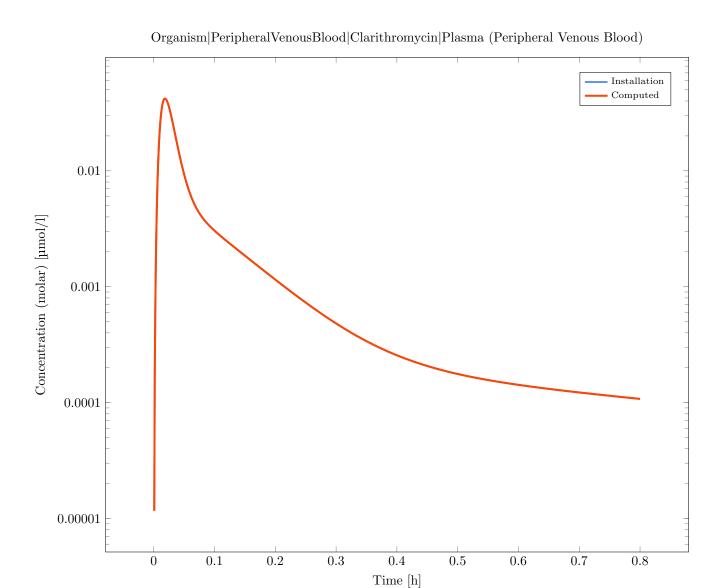
Figure 1.21

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: 0

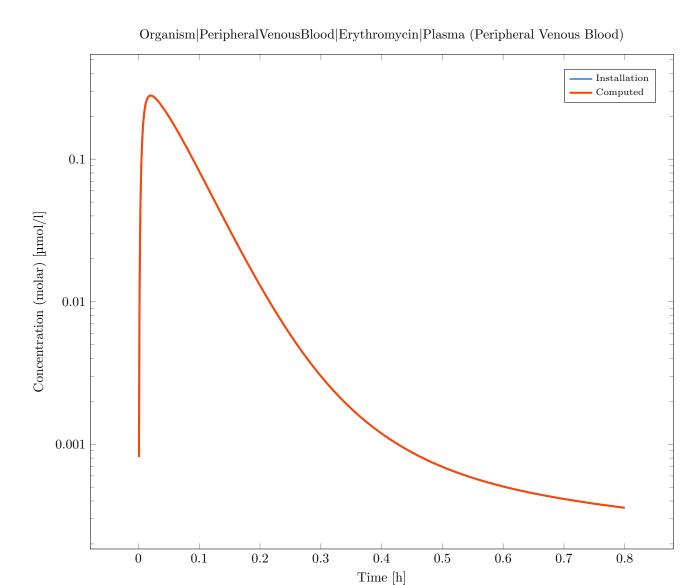


Output Path: Organism |Peripheral Venous
Blood |Clarithromycin |Plasma (Peripheral Venous Blood)
 Deviation: $\boldsymbol{0}$



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

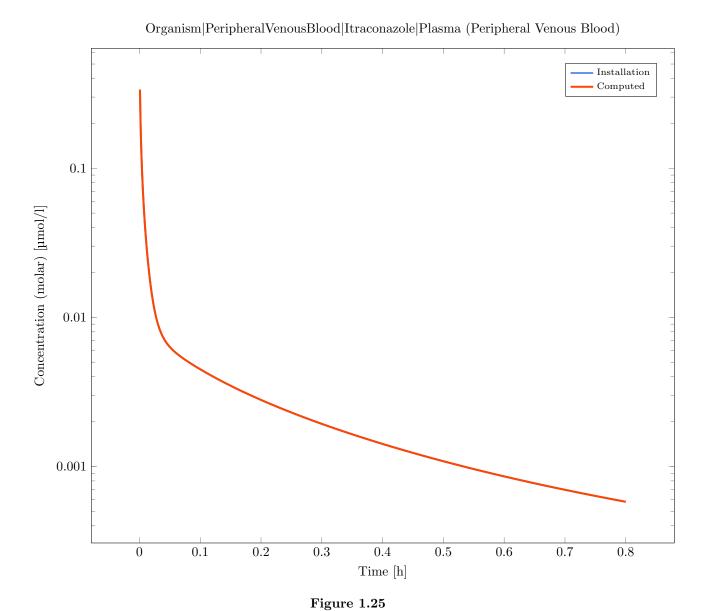
Figure 1.23



Deviation: 0

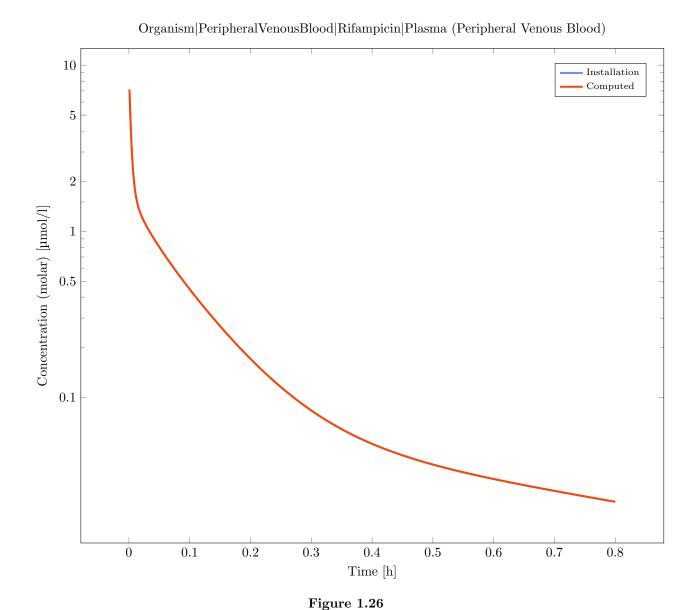
Figure 1.24

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



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

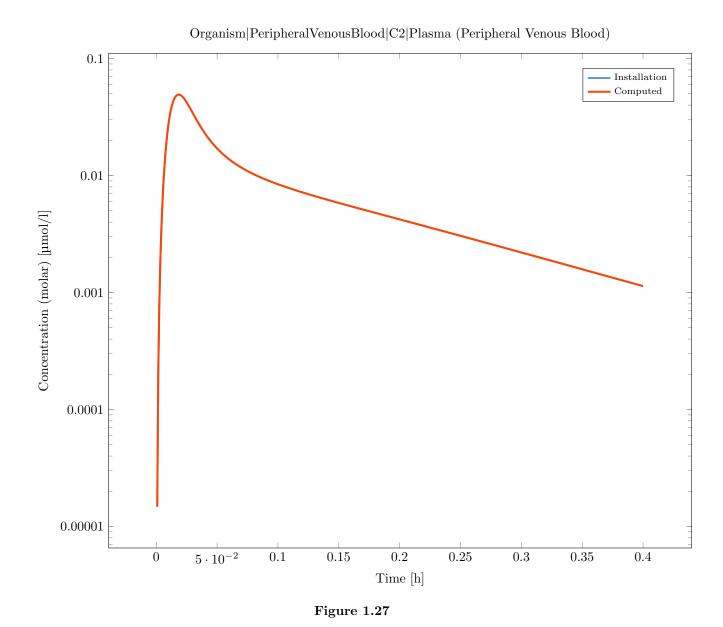
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 $Simulation: \ DDI_Multiple Combinations - 08_MM_Uncompetitive_Uncompetitive_Mechanism based_Mechanism based$

Result of the validation: Valid

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



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

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

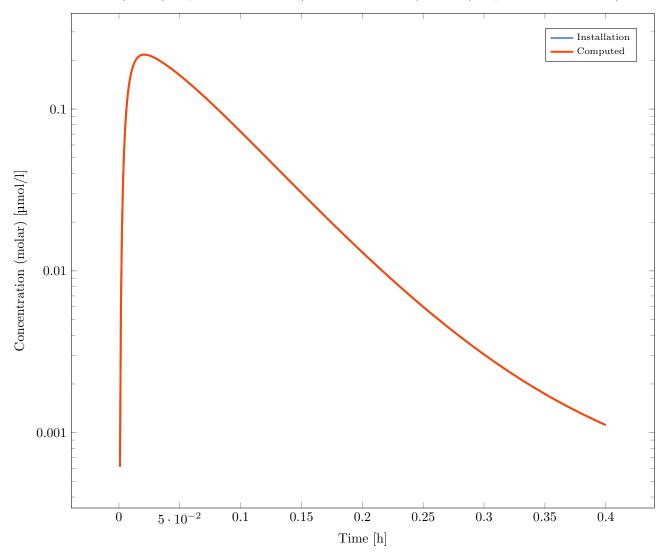
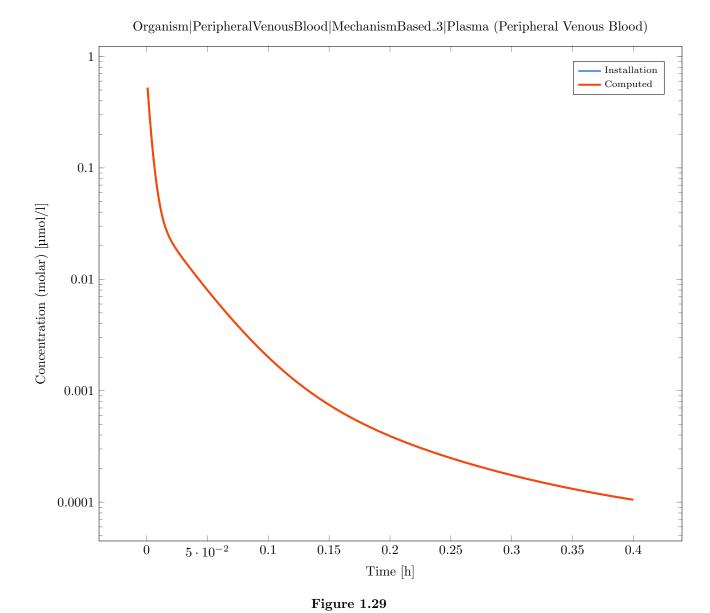
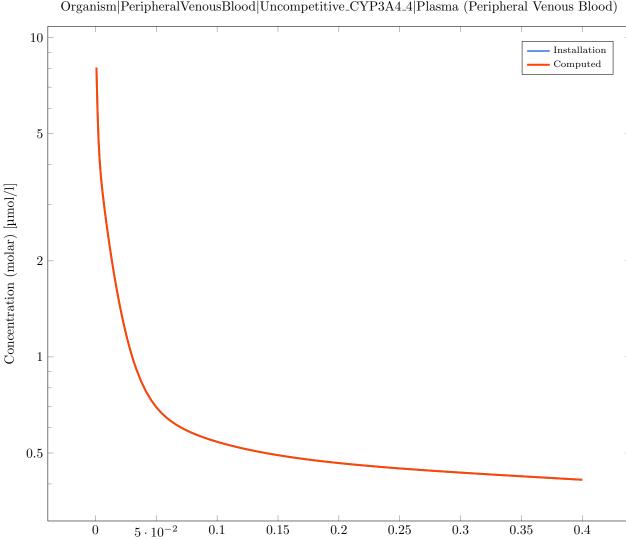


Figure 1.28

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



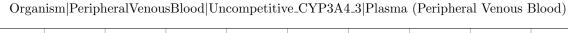


Organism|PeripheralVenousBlood|Uncompetitive_CYP3A4_4|Plasma (Peripheral Venous Blood)

Figure 1.30

Time [h]

 $Output\ Path:\ Organism | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Perip$ Venous Blood)



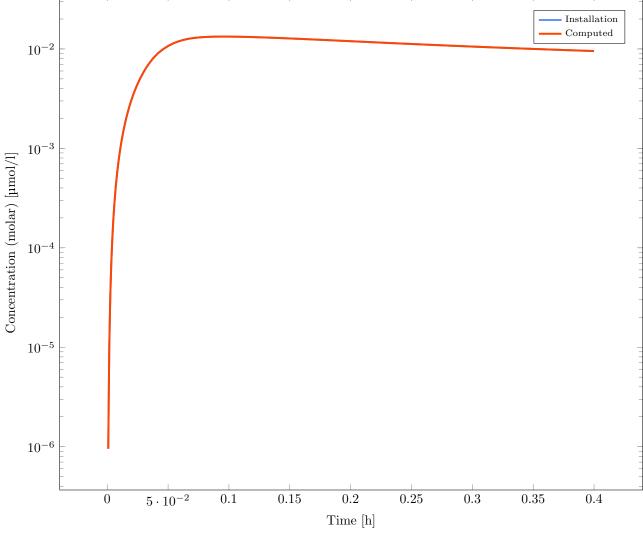
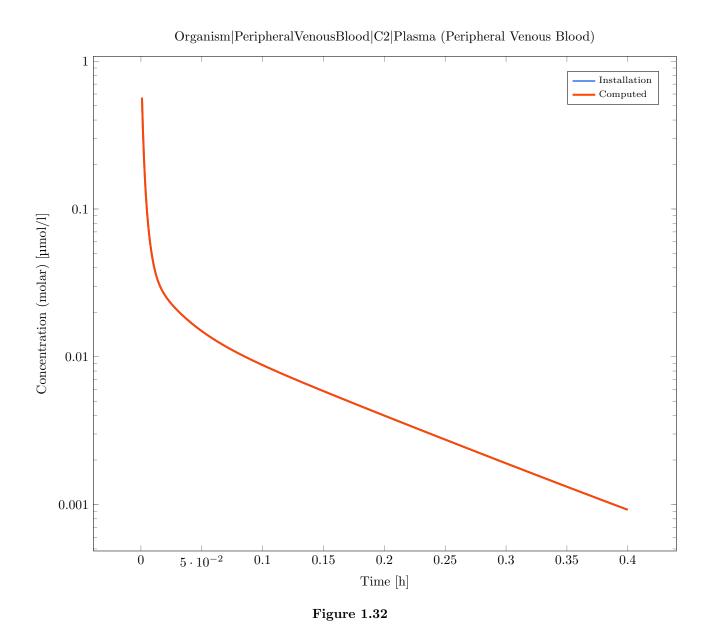


Figure 1.31

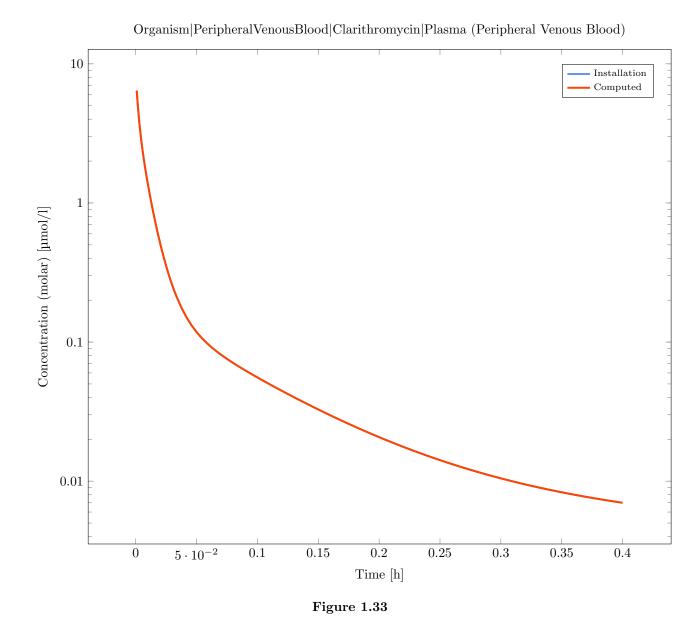
 $Simulation: \ DDI_Multiple Combinations - 09_MM_Noncompetitive_Noncompetitive_Mechanism based_Mechanism based$

Result of the validation: Valid

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



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



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

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

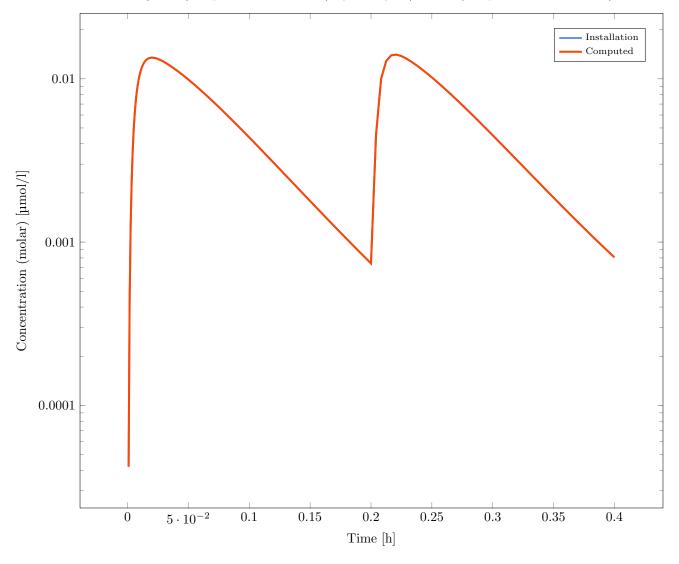


Figure 1.34

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

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

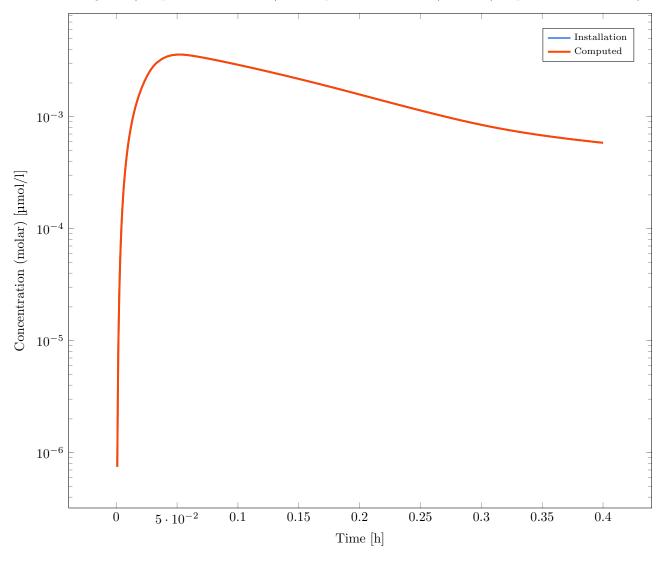


Figure 1.35

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

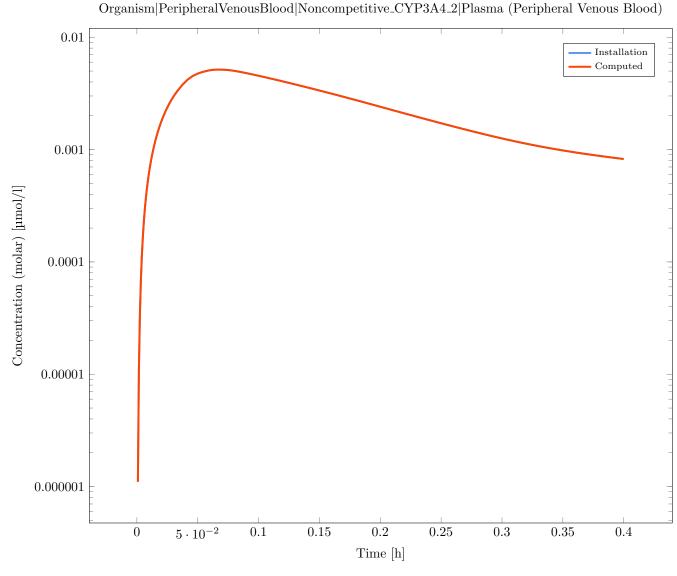
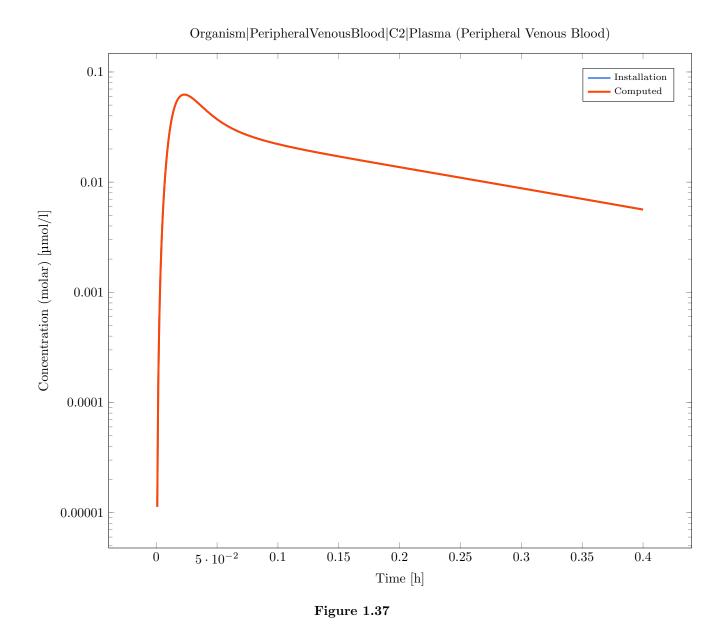


Figure 1.36

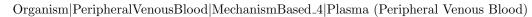
 ${\bf Simulation:\ DDI_Multiple Combinations-10_MM_Mixed_Mixed_Mechanismbased_Mech$

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



Output Path: Organism |PeripheralVenousBlood |MechanismBased_4 |Plasma (Peripheral VenousBlood)
 Deviation: 0

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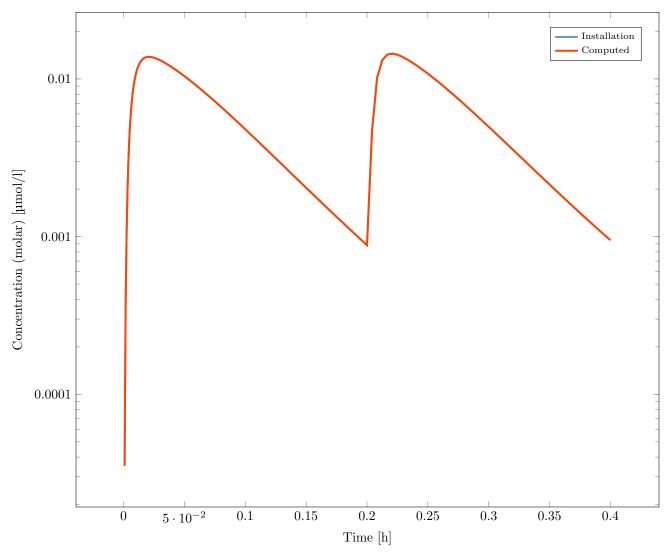


Figure 1.38

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

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

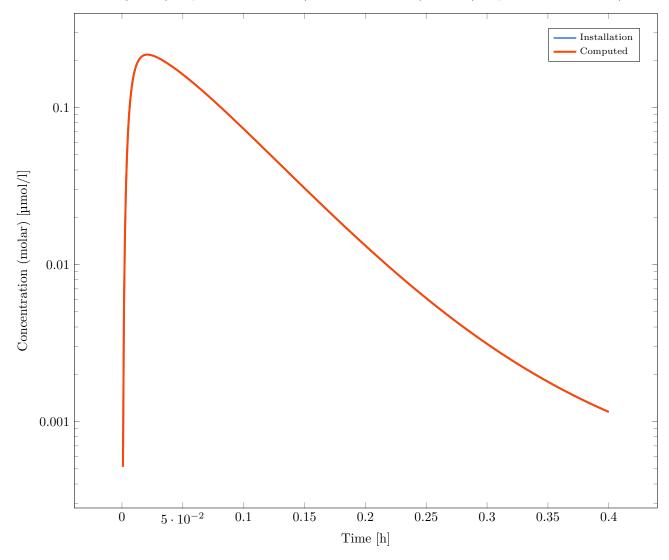
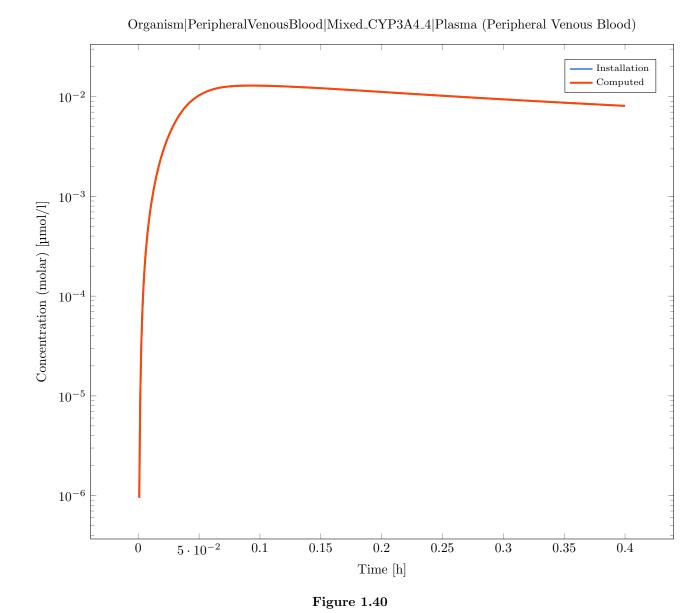


Figure 1.39

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



Output Path: Organism |PeripheralVenousBlood |Mixed_CYP3A4_3 |Plasma (Peripheral VenousBlood)
 Deviation: 0

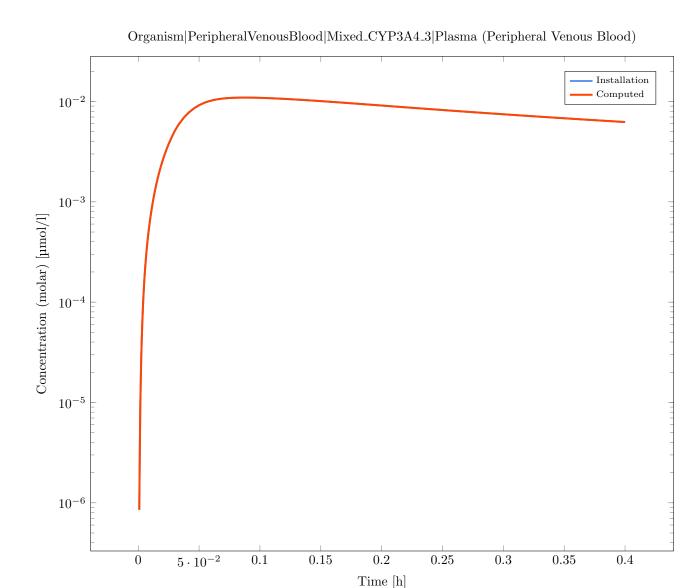
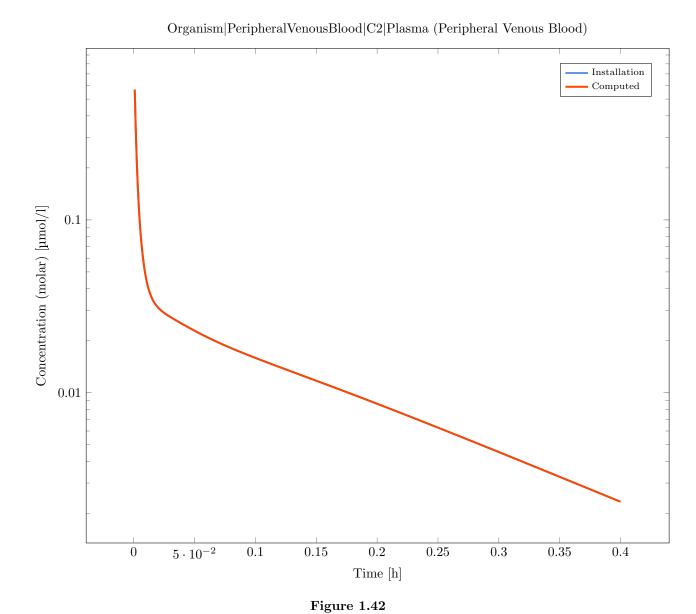


Figure 1.41

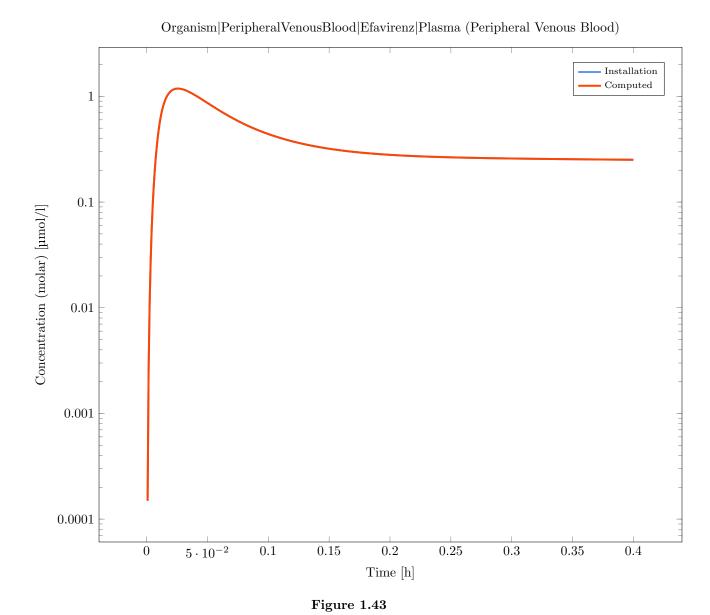
 $Simulation: \begin{tabular}{ll} DDI_Multiple Combinations-11_MM_Mechanism based_Mechanism based_Induction_Induction \end{tabular}$

Result of the validation: Valid

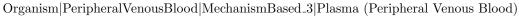
Output Path: Organism |PeripheralVenousBlood |C2|Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$



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



Output Path: Organism |PeripheralVenousBlood |MechanismBased_3 |Plasma (Peripheral VenousBlood)
 Deviation: 0



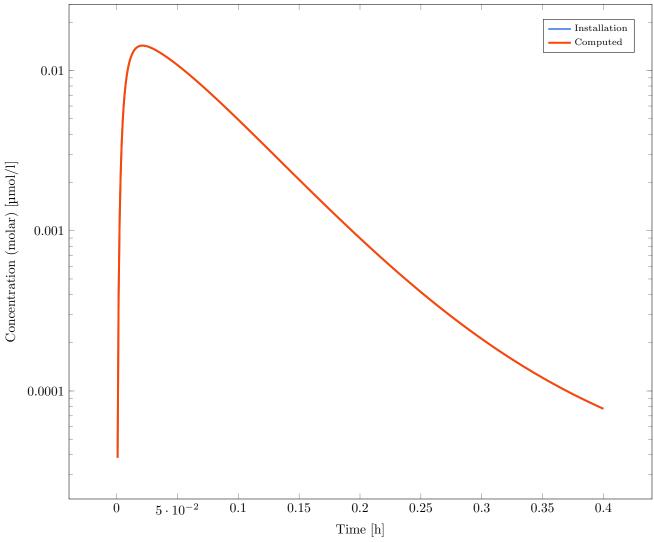


Figure 1.44

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



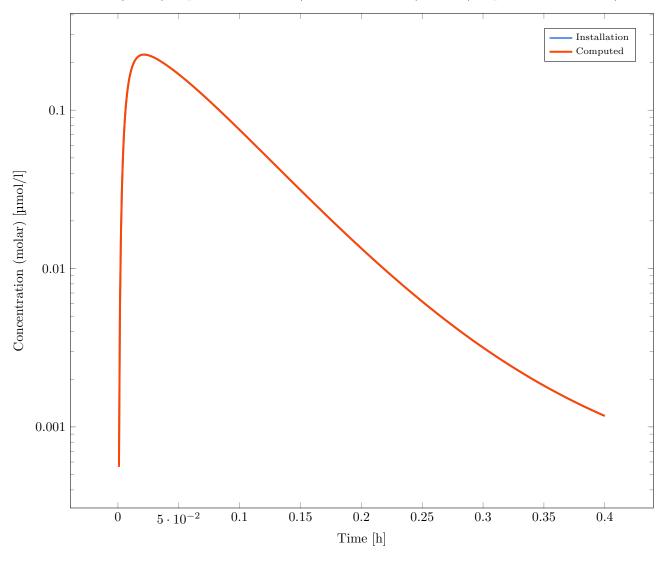


Figure 1.45

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

Organism|PeripheralVenousBlood|Rifampicin|Plasma (Peripheral Venous Blood) Installa Compt

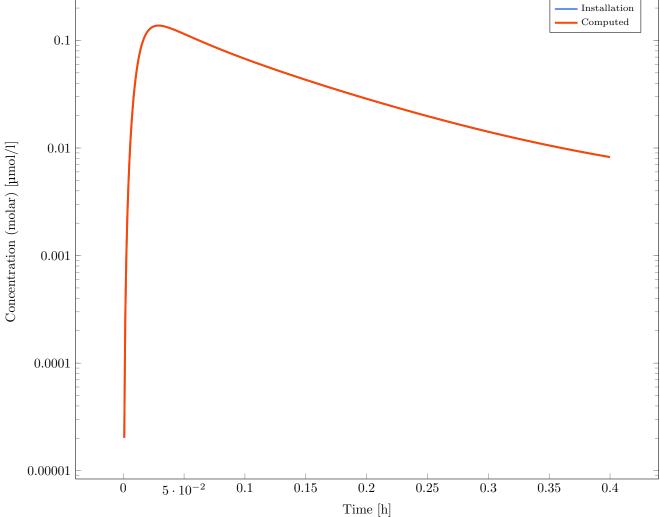
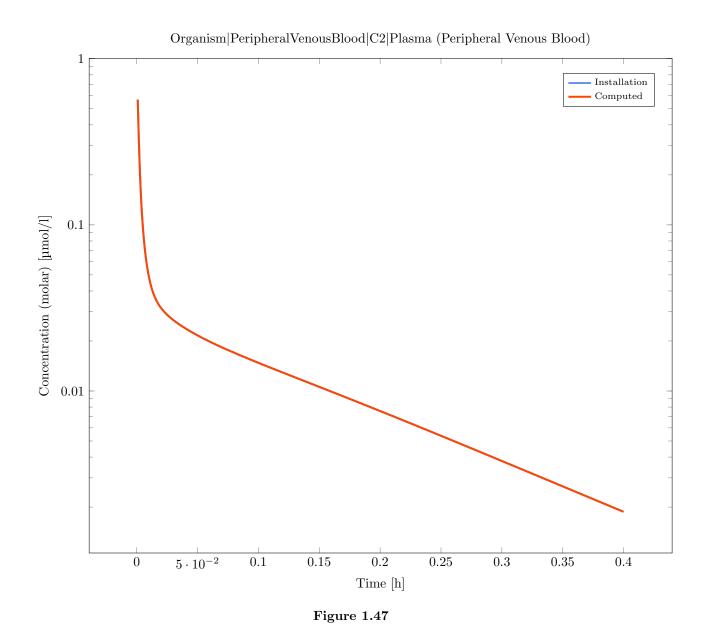


Figure 1.46

 $Simulation: \ DDI_MultipleCombinations-12_MM_All_DDI_Types$

Result of the validation: Valid

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



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

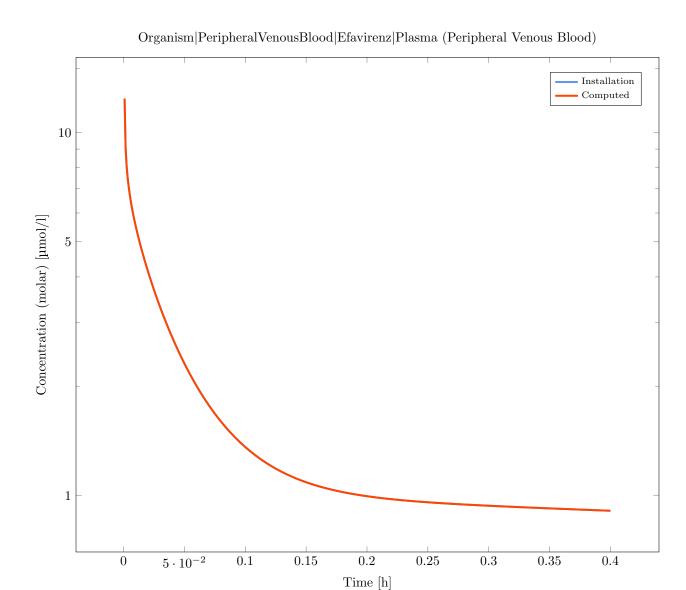
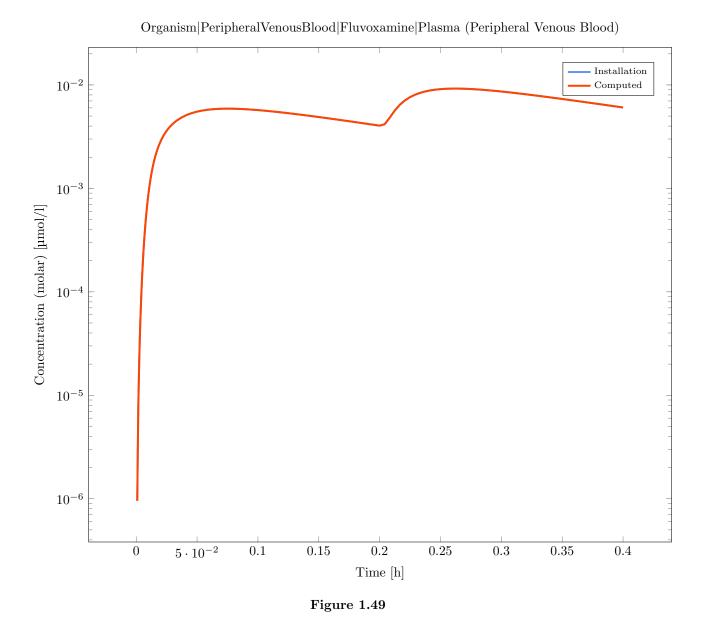
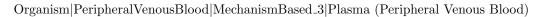


Figure 1.48

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



Output Path: Organism |PeripheralVenousBlood |MechanismBased_3 |Plasma (Peripheral VenousBlood)
 Deviation: 0



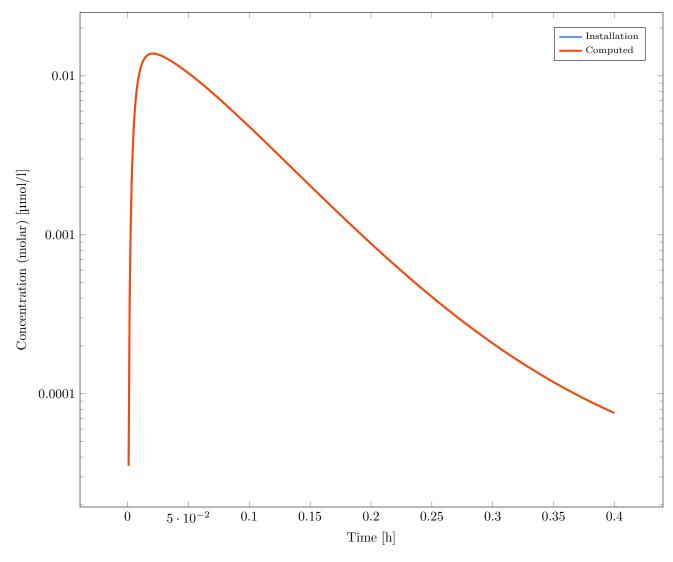


Figure 1.50

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

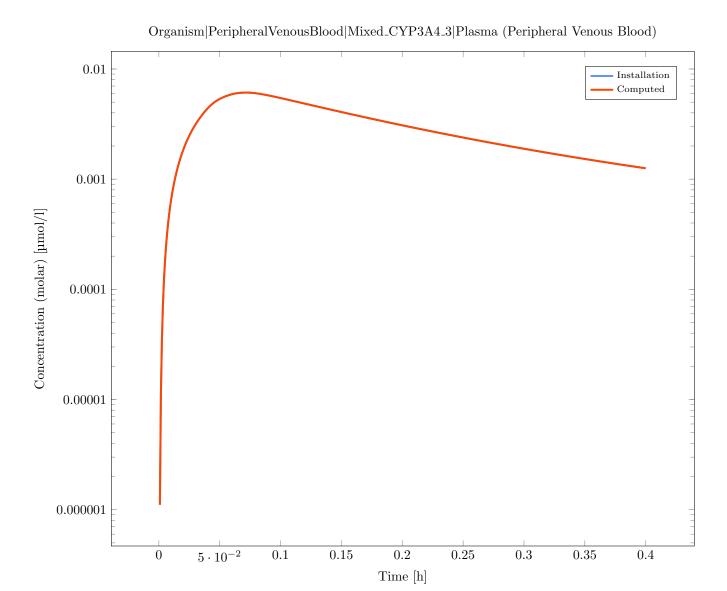
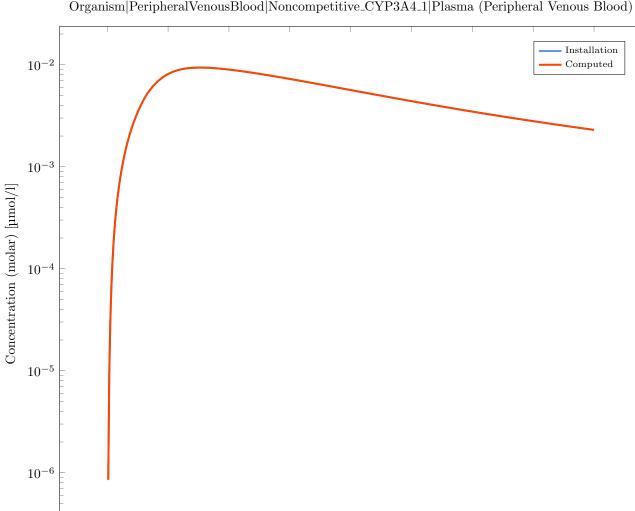


Figure 1.51

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



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

Figure 1.52

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

0.1

 $Output\ Path:\ Organism | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Perip$ Venous Blood)

Deviation: 0

0

 $5 \cdot 10^{-2}$

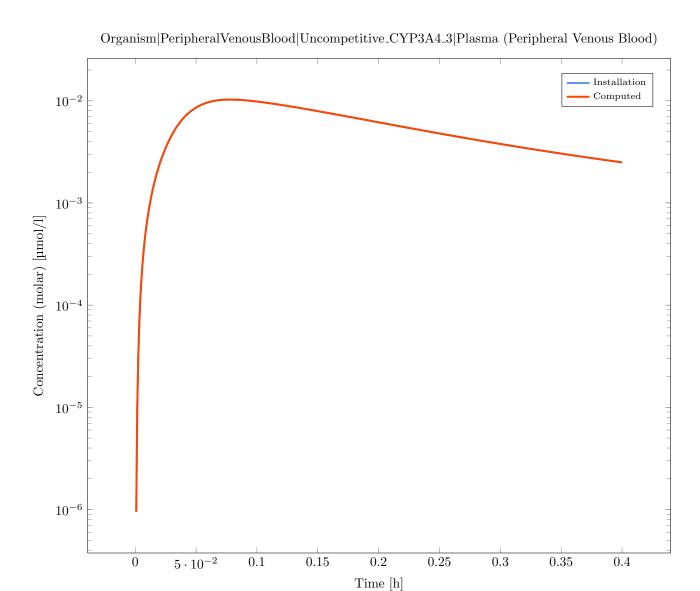
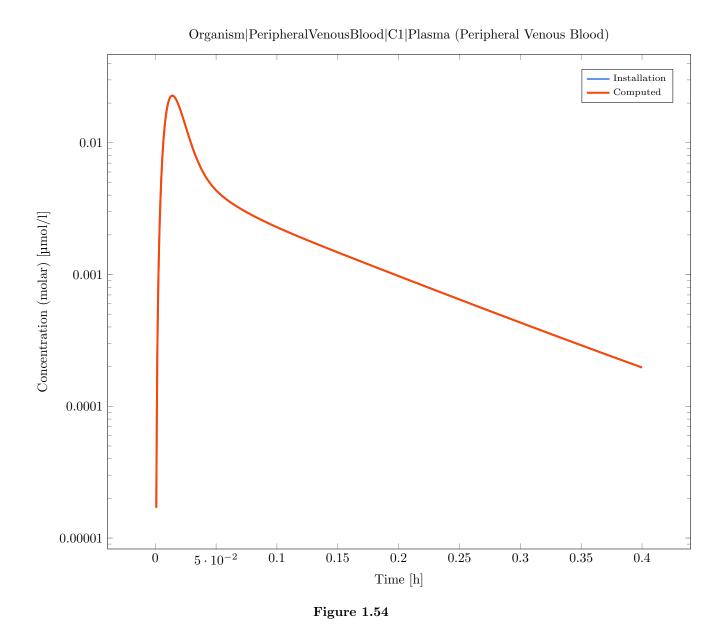


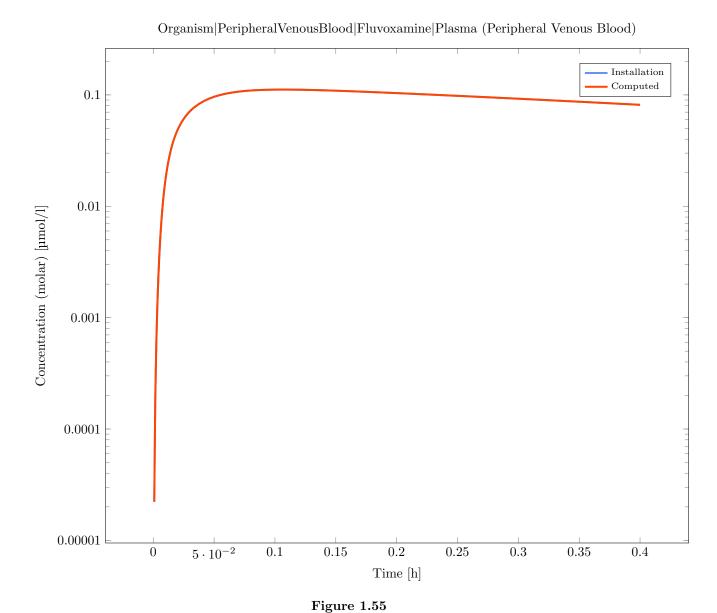
Figure 1.53

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

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



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



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

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: 0

0

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

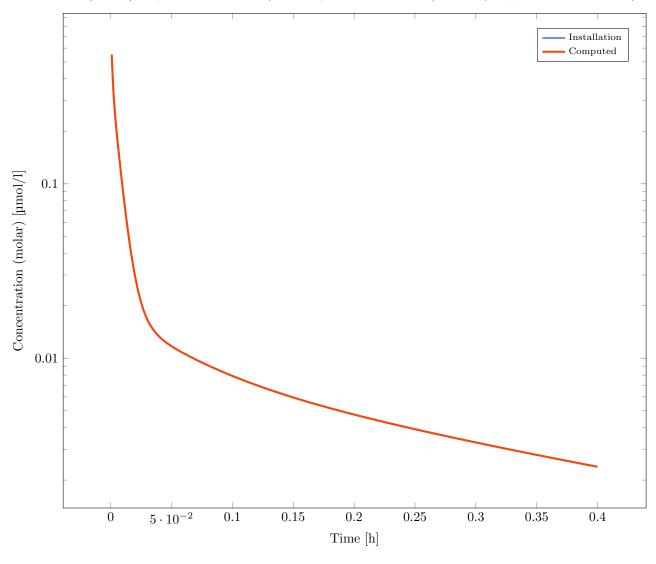
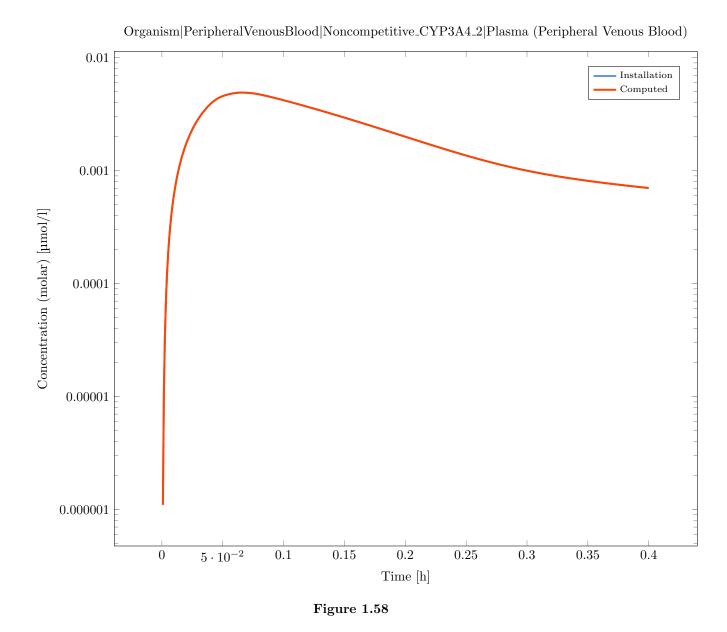


Figure 1.57

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



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

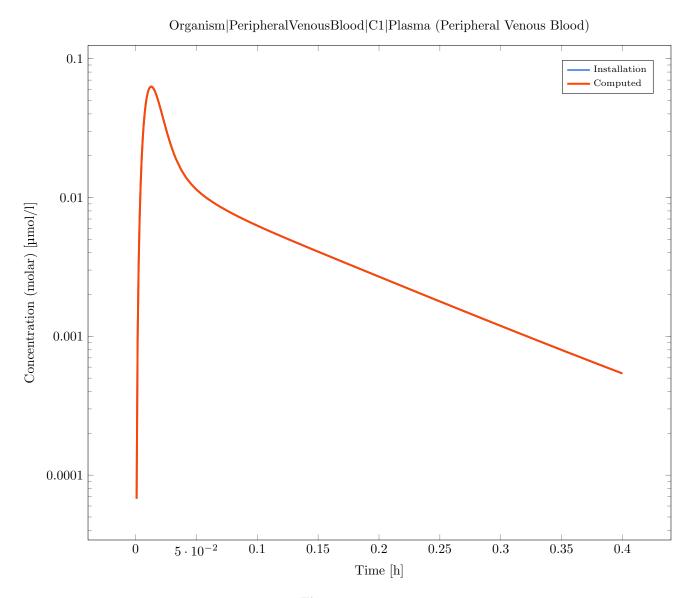
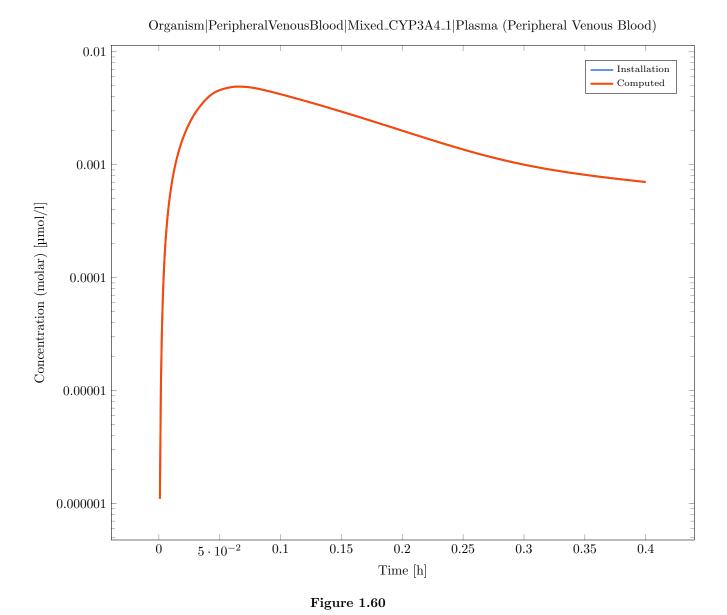


Figure 1.59

 $Simulation: \ DDI_MultipleCombinations \textbf{-} 24_1st_Mixed_Mixed$

Result of the validation: Valid

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



Output Path: Organism |PeripheralVenousBlood |Mixed_CYP3A4_2 |Plasma (Peripheral VenousBlood)
 Deviation: 0

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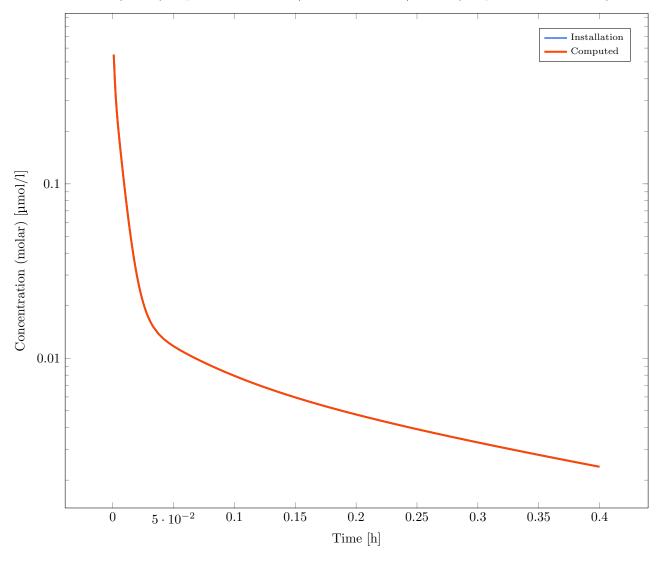
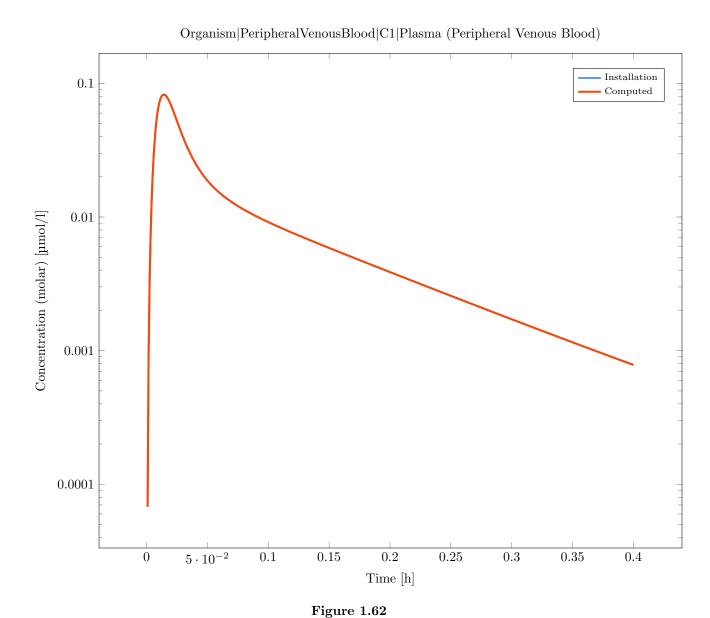


Figure 1.61

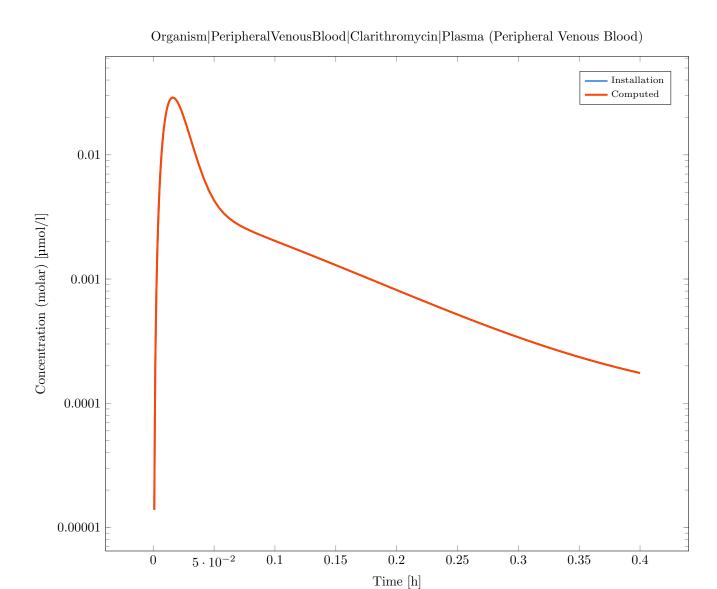
Output Path: Organism |PeripheralVenousBlood |C1|Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$



Simulation: DDI_MultipleCombinations-25_1st_Mechanismbased_Mechanismbased

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

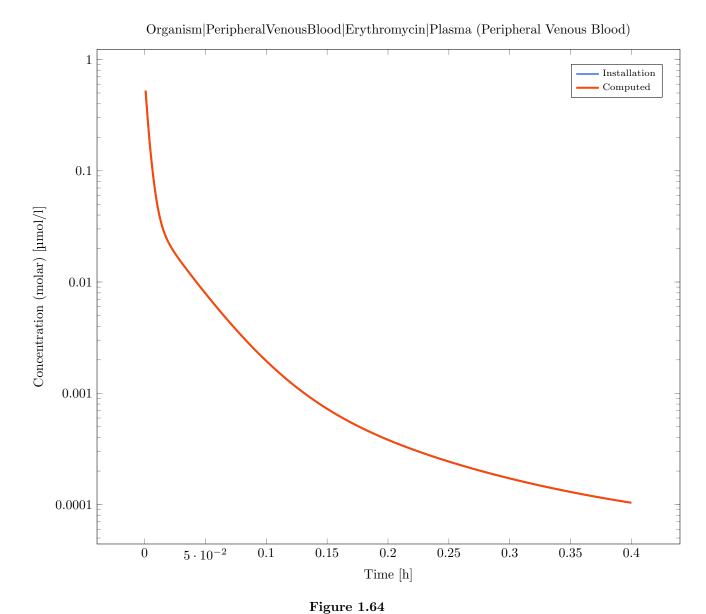
Result of the validation: Valid



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

Deviation: 0

Figure 1.63



Output Path: Organism |Peripheral Venous
Blood |C1 |Plasma (Peripheral Venous Blood) Deviation:
 0

Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood) O.1 O.001 O.001

Figure 1.65

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

 ${\bf Simulation: \ DDI_Multiple Combinations\hbox{--}26_1st_Induction_Induction}$

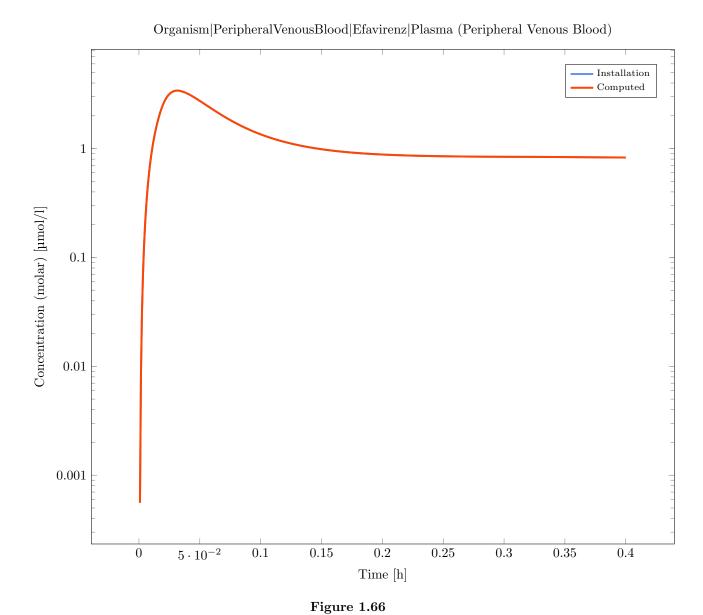
0.1

 $5 \cdot 10^{-2}$

Result of the validation: Valid

0

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



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

Deviation: 0

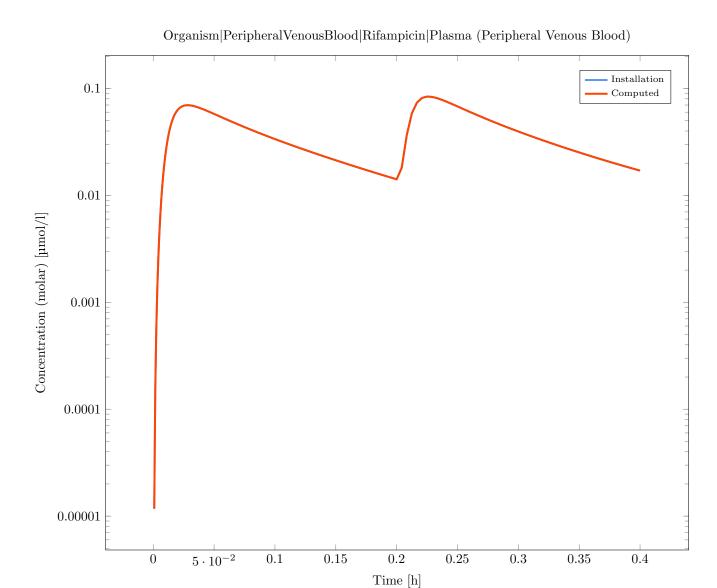
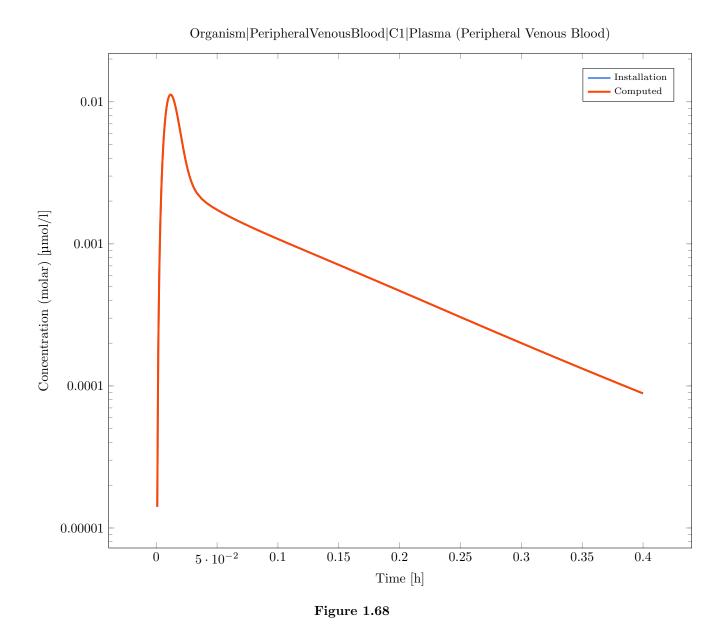


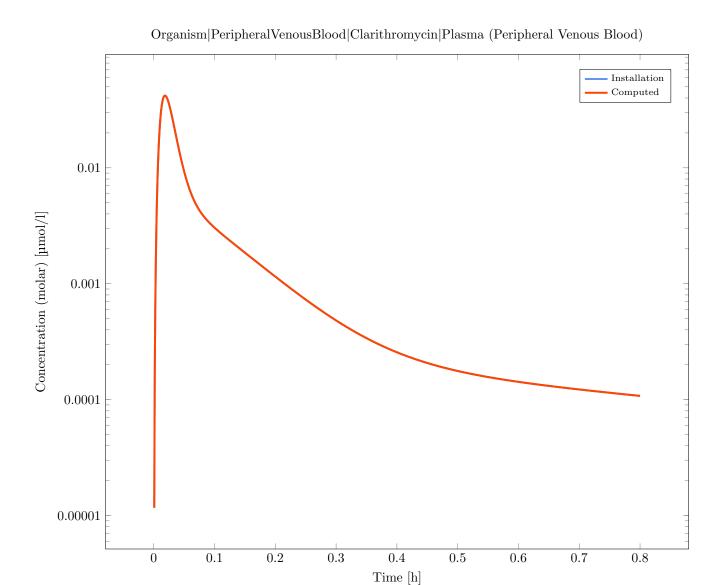
Figure 1.67

Output Path: Organism |PeripheralVenousBlood |C1|Plasma (Peripheral Venous Blood)
 Deviation: 0



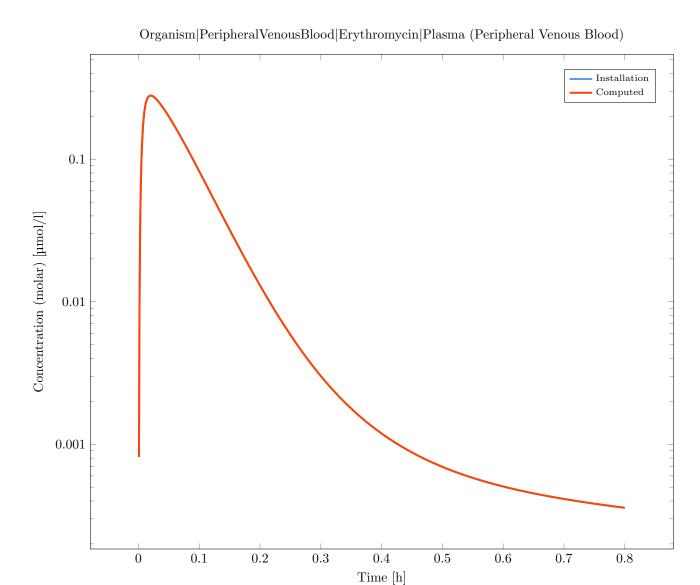
Simulation: DDI_MultipleCombinations-27_1st_Competitive_Competitive_Mechanismbased_Mechanismbased Result of the validation: Valid

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



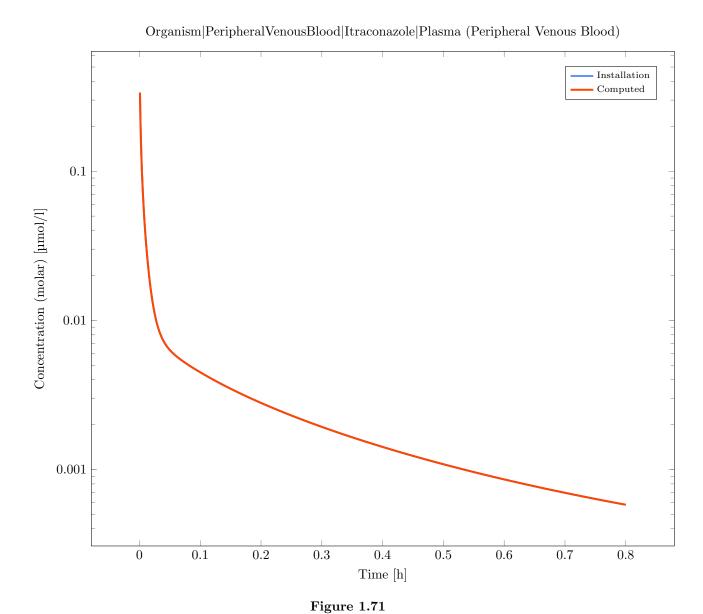
Output Path: Organism |Peripheral Venous
Blood |Erythromycin |Plasma (Peripheral Venous Blood)
 Deviation: $\boldsymbol{0}$

Figure 1.69

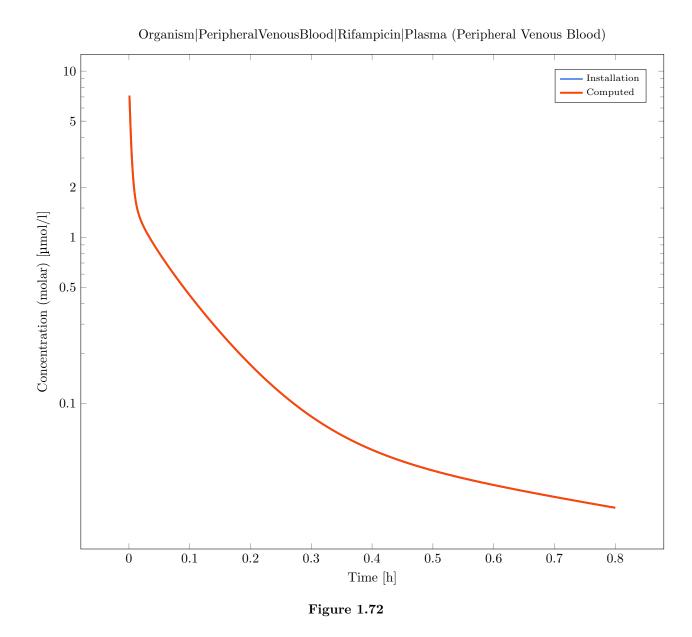


 $Output\ Path:\ Organism | Peripheral Venous Blood | Itraconazole | Plasma\ (Peripheral Venous\ Blood)$ Deviation: 0

Figure 1.70



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



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

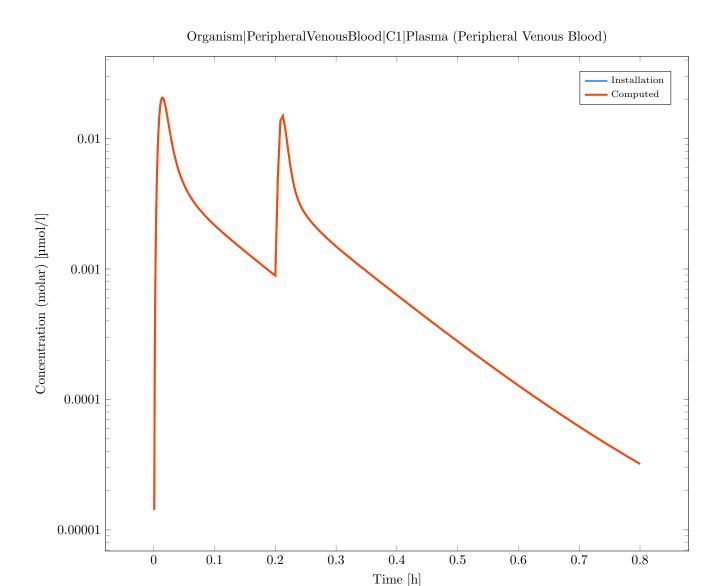


Figure 1.73

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

Result of the validation: Valid

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

$Organism | Peripheral Venous Blood | Mechanism Based_4 | Plasma \ (Peripheral Venous Blood)$

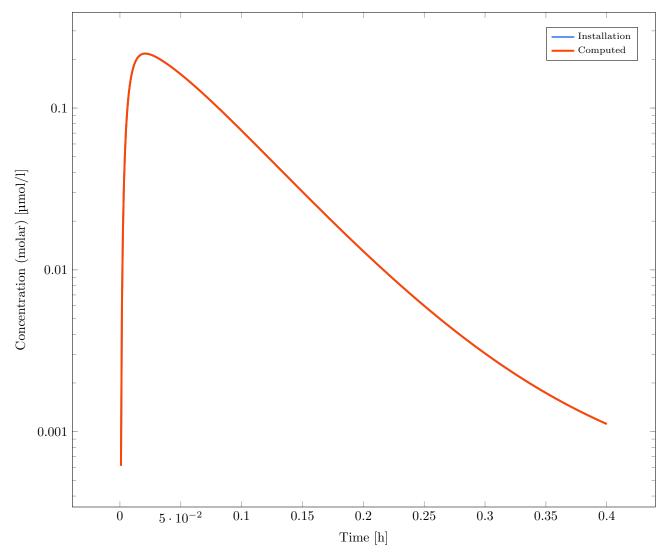
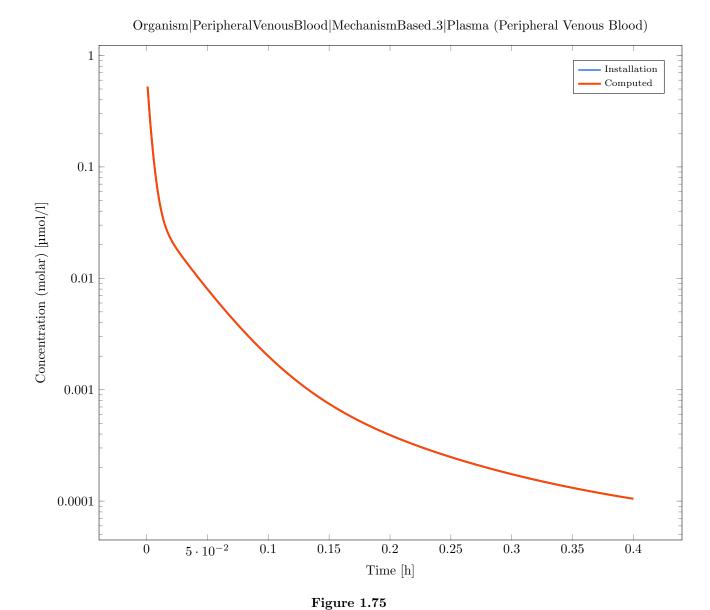
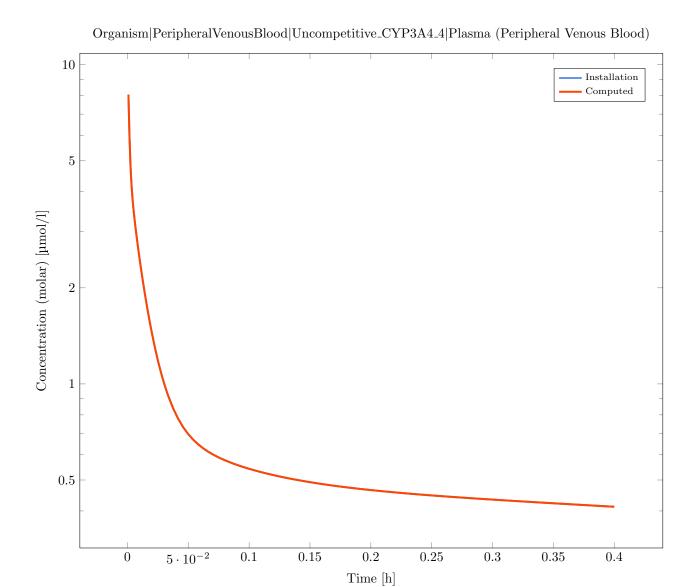


Figure 1.74

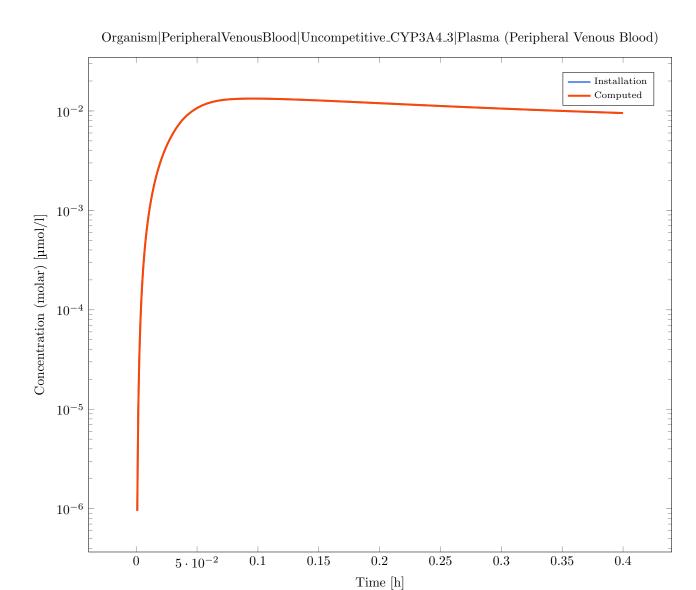
 $Output\ Path:\ Organism|PeripheralVenousBlood|MechanismBased_3|Plasma\ (Peripheral\ Venous\ Blood)$





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

Figure 1.76



Deviation: 0

Figure 1.77

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

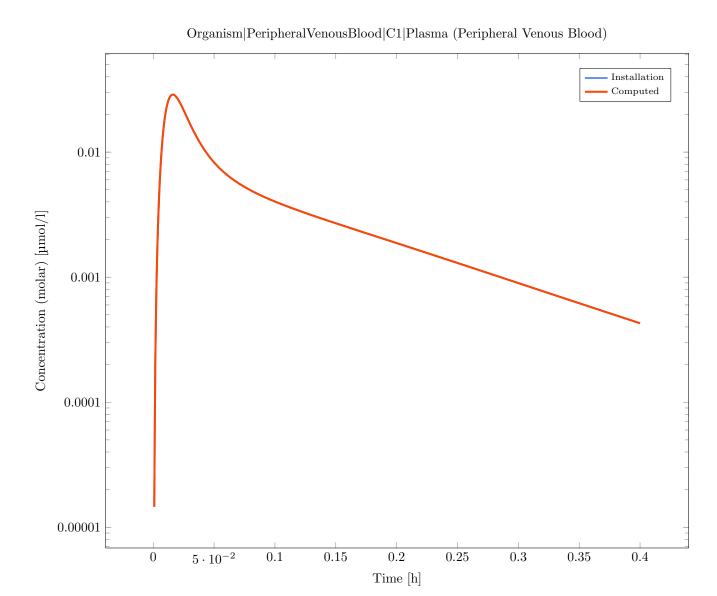
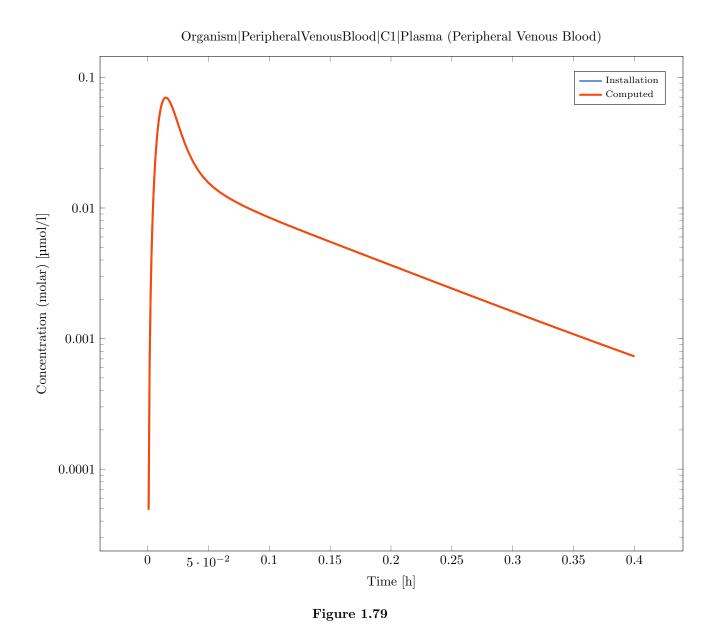


Figure 1.78

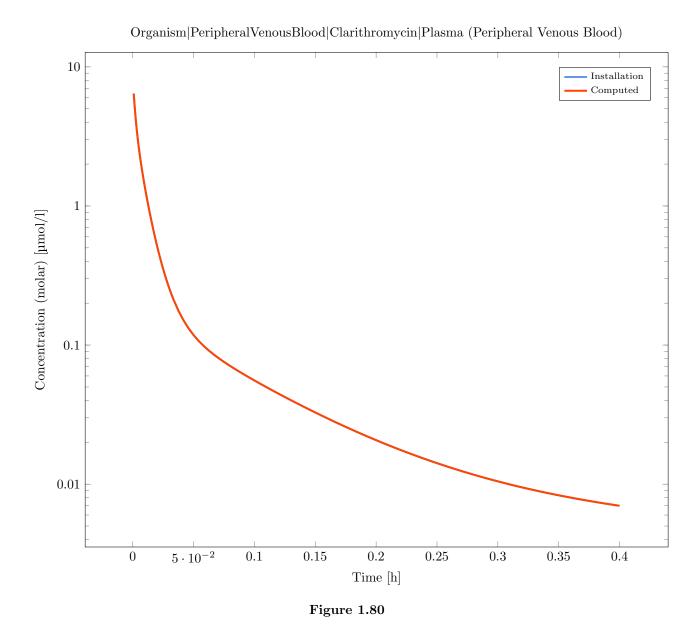
 $Simulation: \ DDI_Multiple Combinations \textbf{-} 29_1st_Noncompetitive_Noncompetitive_Mechanism based_Mechanism based$

Result of the validation: Valid

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



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



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

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

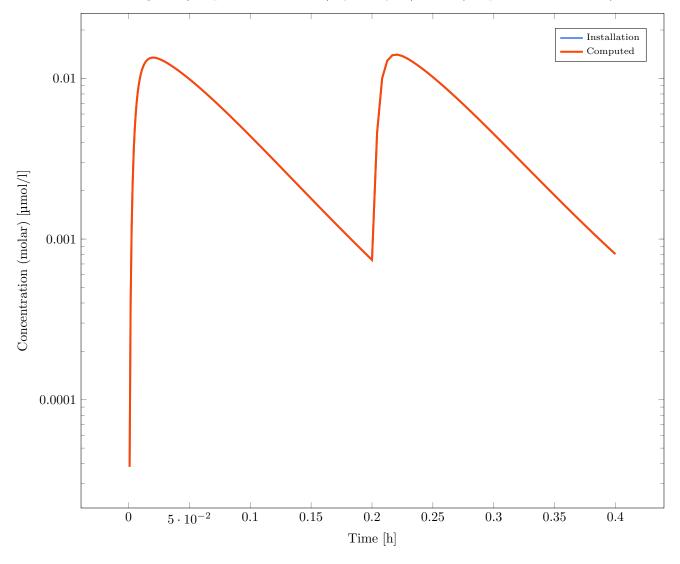


Figure 1.81

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

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

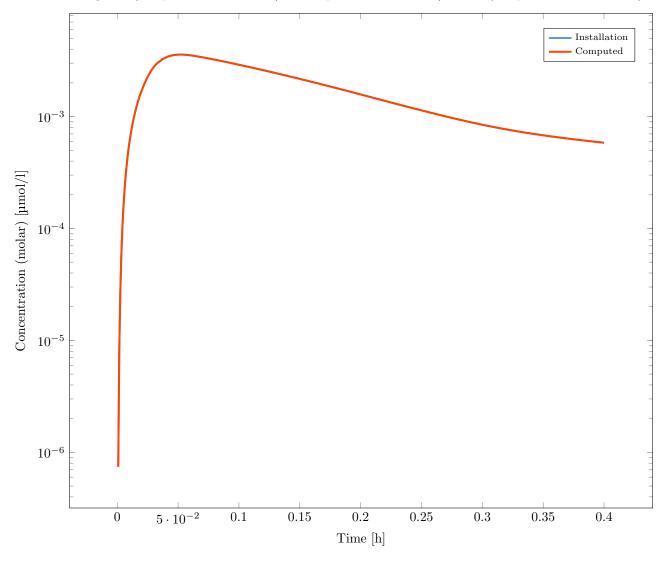


Figure 1.82

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

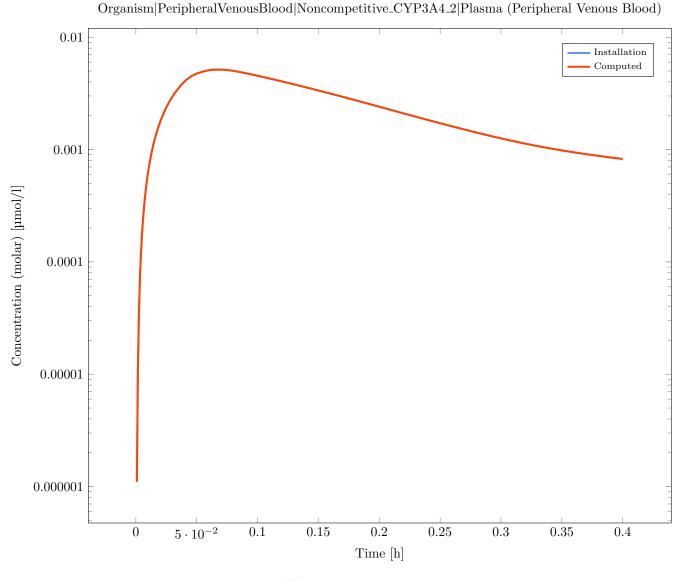


Figure 1.83

 ${\bf Simulation:\ DDI_Multiple Combinations-30_1st_Mixed_Mechanismbased_Mechanism$

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



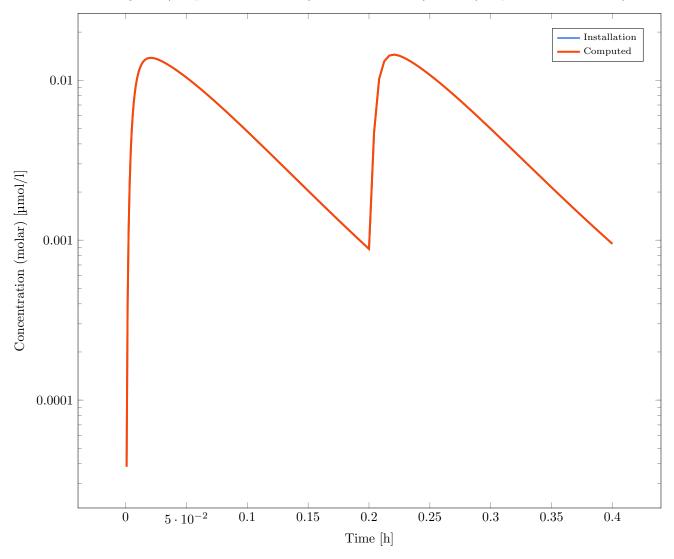


Figure 1.84

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

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

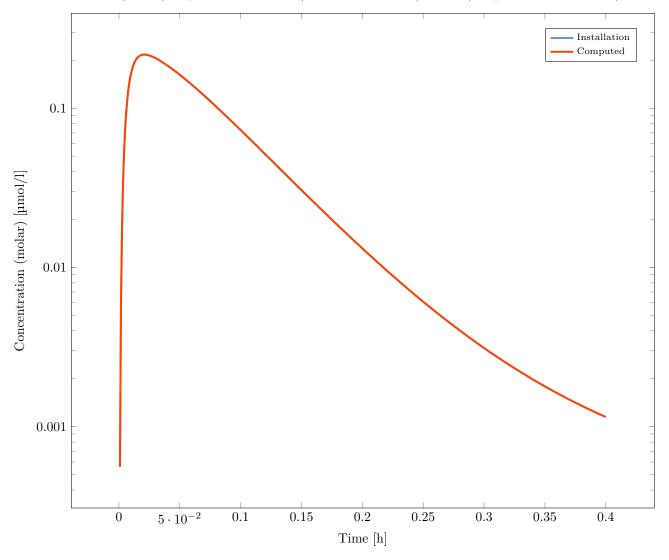
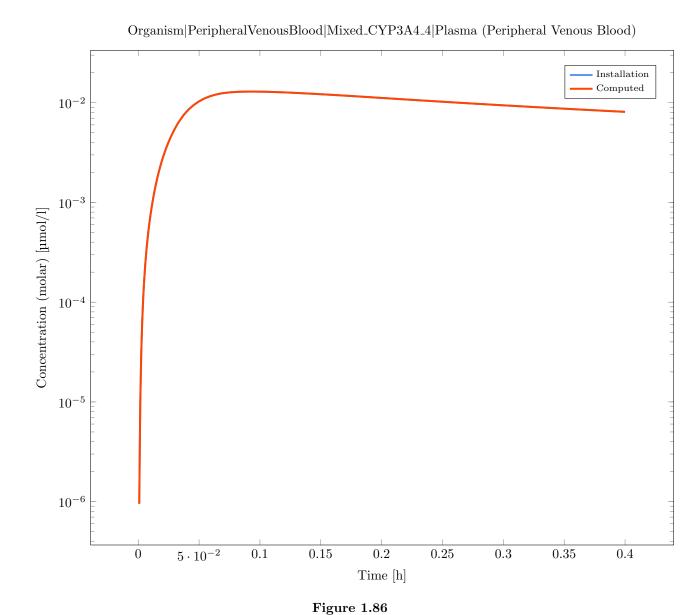
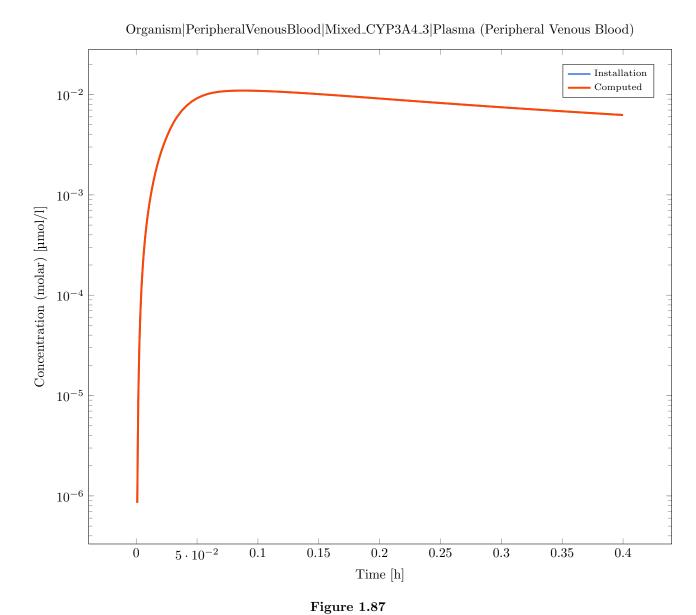


Figure 1.85

 $Output\ Path:\ Organism|Peripheral Venous Blood|Mixed_CYP3A4_4|Plasma\ (Peripheral\ Venous Blood)$



Output Path: Organism |PeripheralVenousBlood |Mixed_CYP3A4_3 |Plasma (Peripheral VenousBlood)
 Deviation: 0



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

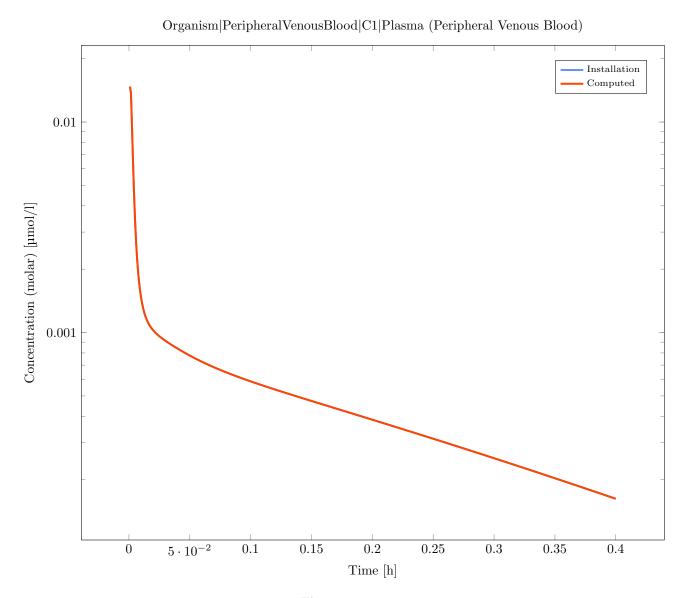
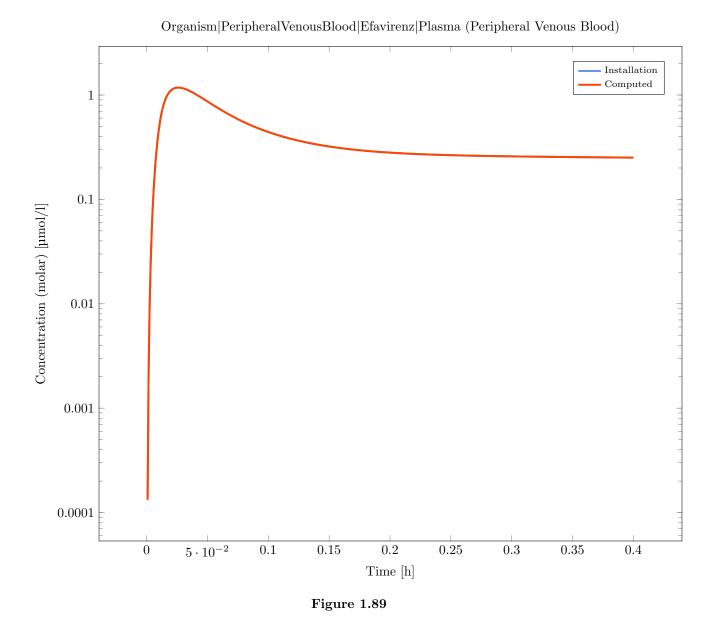


Figure 1.88

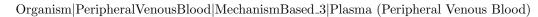
 ${\bf Simulation:\ DDI_Multiple Combinations\hbox{--}31_1st_Mechanismbased_Mechanismbased_Induction_Induction} \\ {\bf Result\ of\ the\ validation:\ Valid}$

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



Output Path: Organism |PeripheralVenousBlood |MechanismBased_3 |Plasma (Peripheral VenousBlood)
 Deviation: 0

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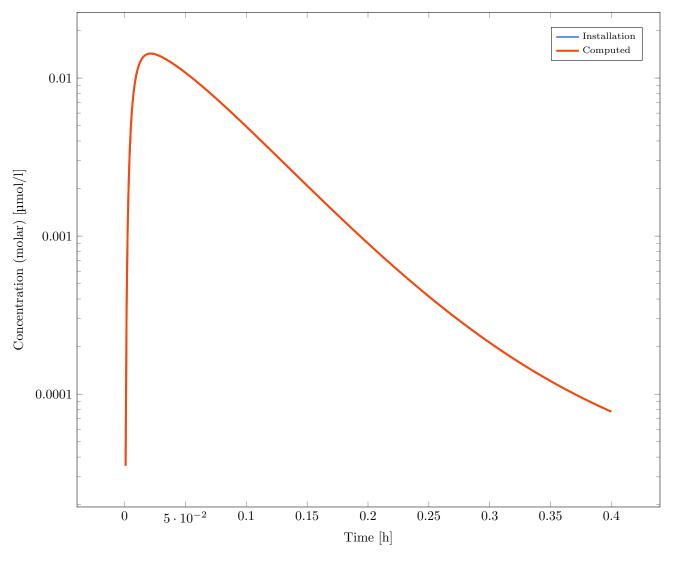
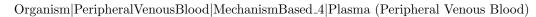


Figure 1.90

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



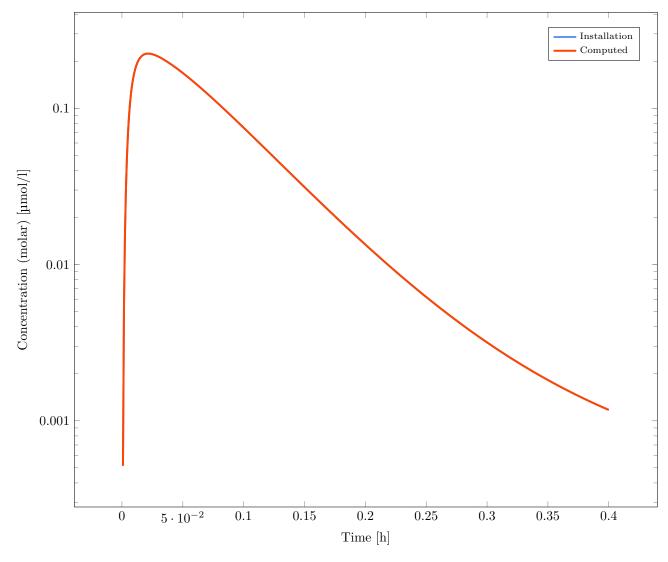


Figure 1.91

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

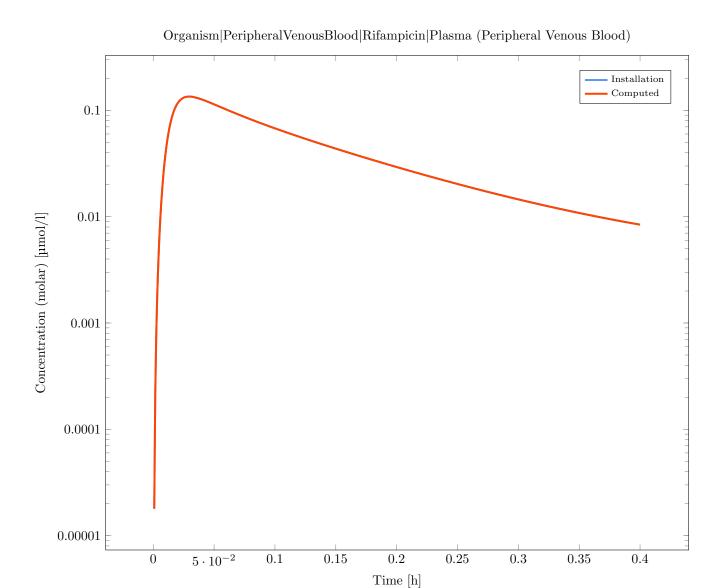


Figure 1.92

Output Path: Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood) Deviation: 0

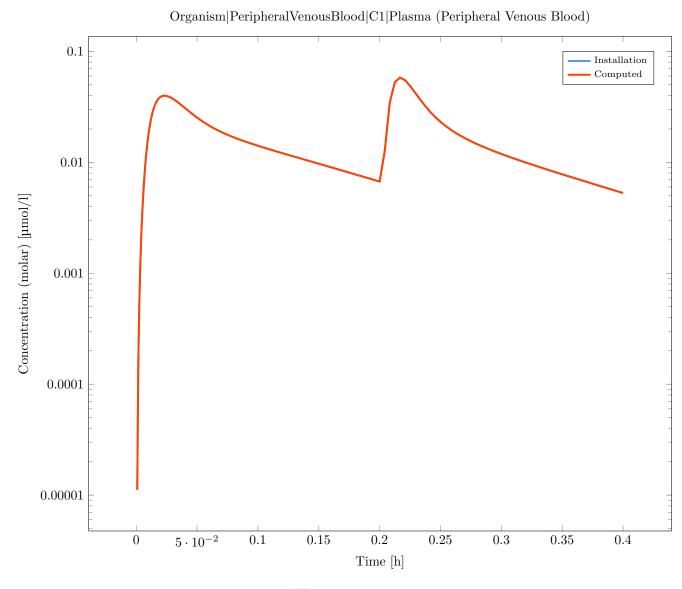
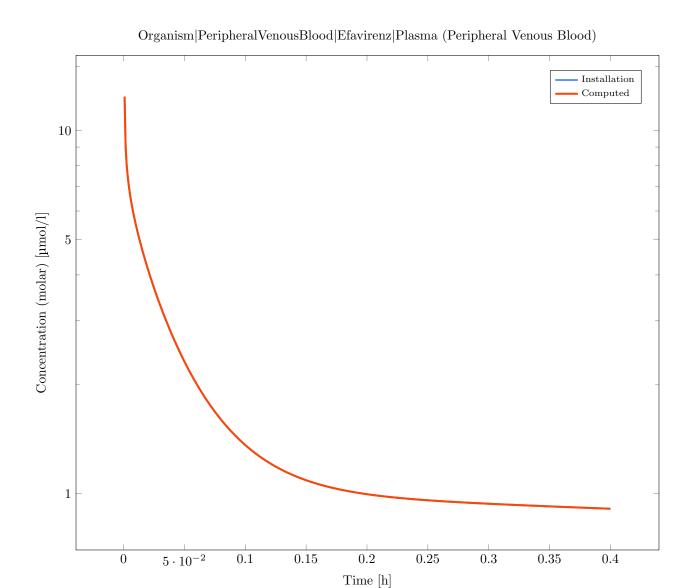


Figure 1.93

 $Simulation: \ DDI_Multiple Combinations \textbf{-32_1st_All_DDI_Types}$

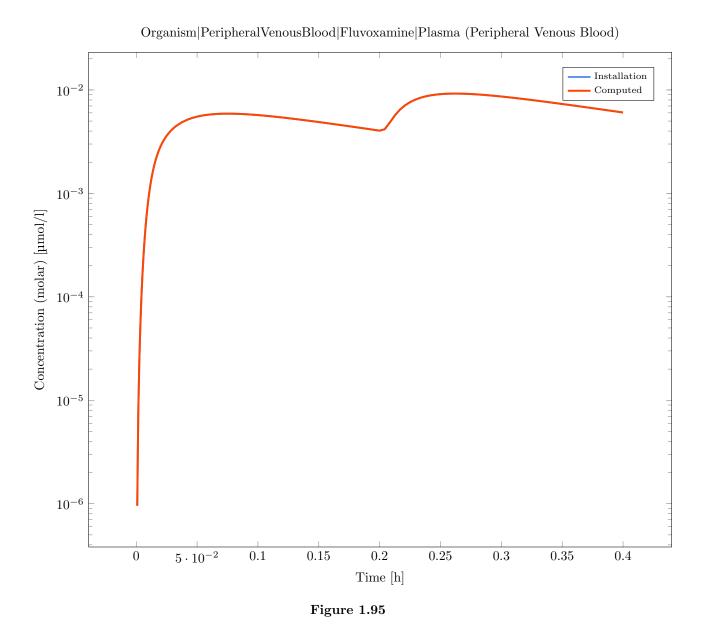
Result of the validation: Valid

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

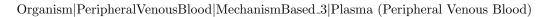


 $Output\ Path:\ Organism | Peripheral Venous Blood | Fluvoxamine | Plasma\ (Peripheral\ Venous\ Blood)$ Deviation: 0

Figure 1.94



Output Path: Organism |Peripheral VenousBlood |Mechanism
Based_3 |Plasma (Peripheral Venous Blood)
 Deviation: 0



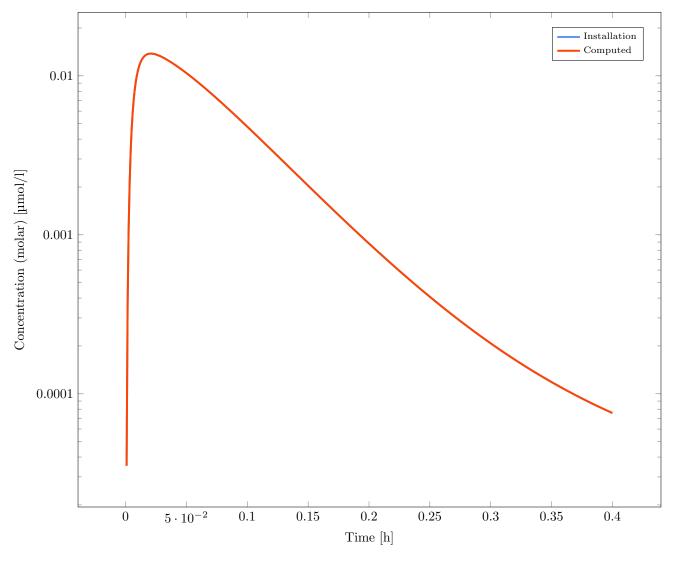


Figure 1.96

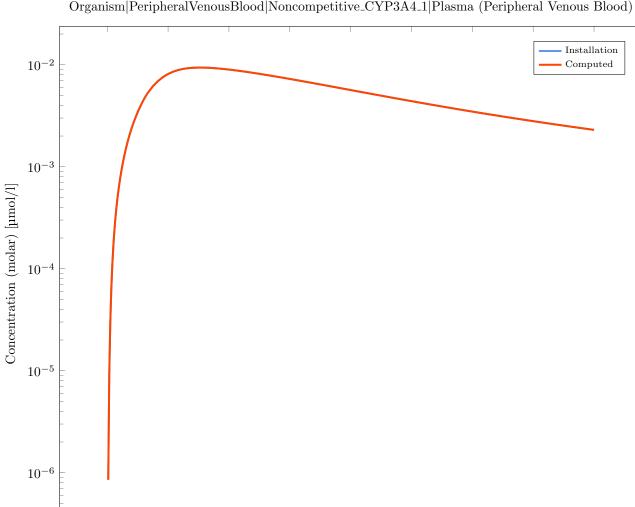
 $Output\ Path:\ Organism|PeripheralVenousBlood|Mixed_CYP3A4_3|Plasma\ (Peripheral\ VenousBlood)$

$Organism | Peripheral Venous Blood | Mixed_CYP3A4_3 | Plasma~(Peripheral Venous~Blood)$ 0.01Installation Computed 0.001 Concentration (molar) [µmol/1] 0.00010.000010.0000010 0.1 0.15 0.2 0.25 0.3 0.35 0.4 $5 \cdot 10^{-2}$

Figure 1.97

Time [h]

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



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

Figure 1.98

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

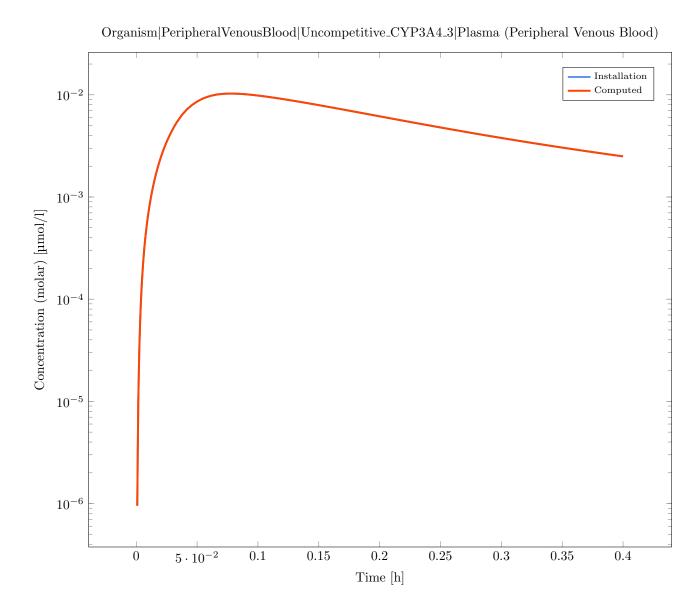
0.1

 $5\cdot 10^{-2}$

 $Output\ Path:\ Organism | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Uncompetitive_CYP3A4_3 | Plasma\ (Peripheral Venous Blood) | Peripheral Venous Blood | Perip$ Venous Blood)

Deviation: 0

0



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

Figure 1.99

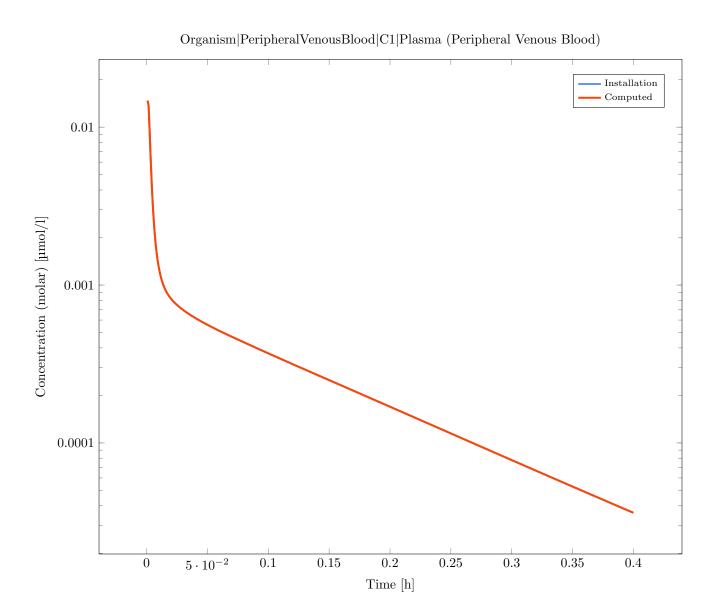


Figure 1.100

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

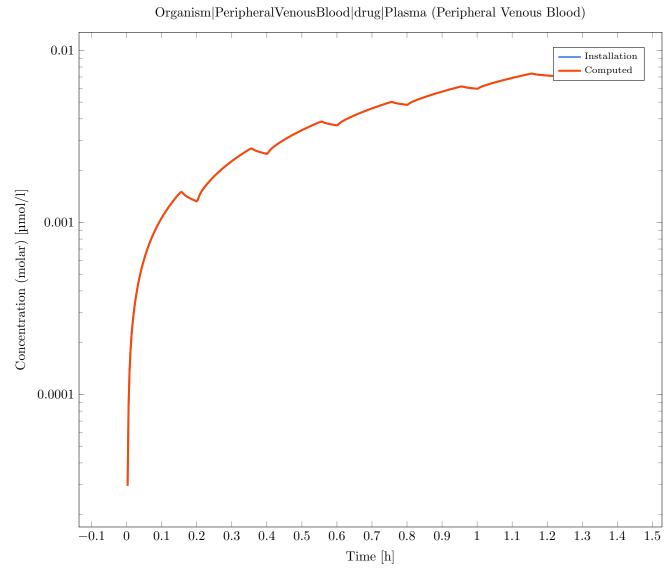


Figure 1.101

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

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

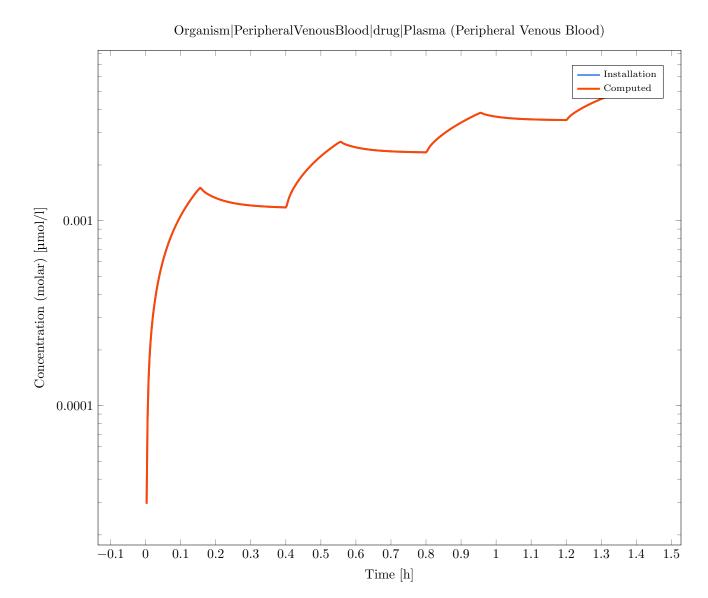
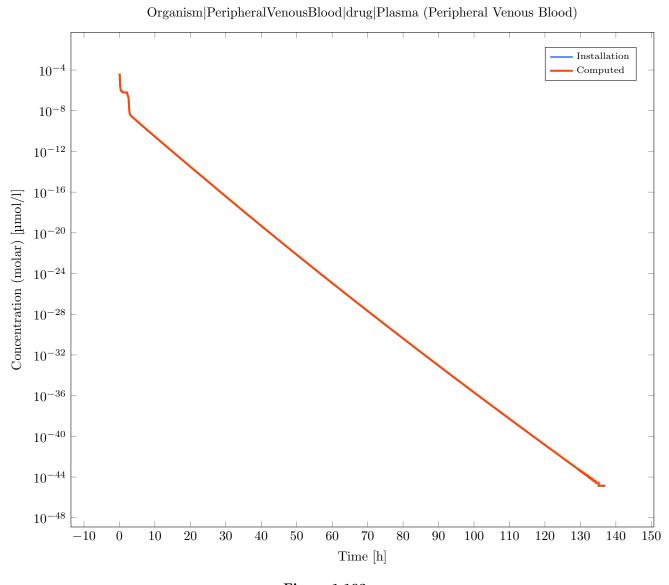


Figure 1.102

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

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



 ${\bf Figure~1.103}$

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

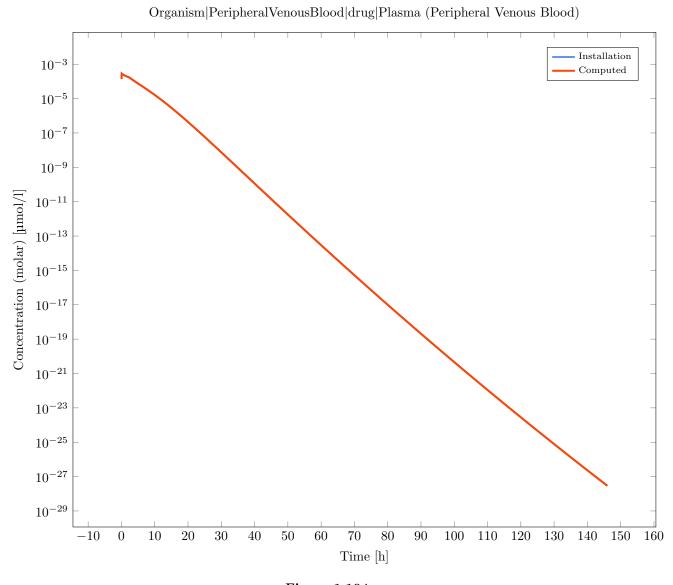
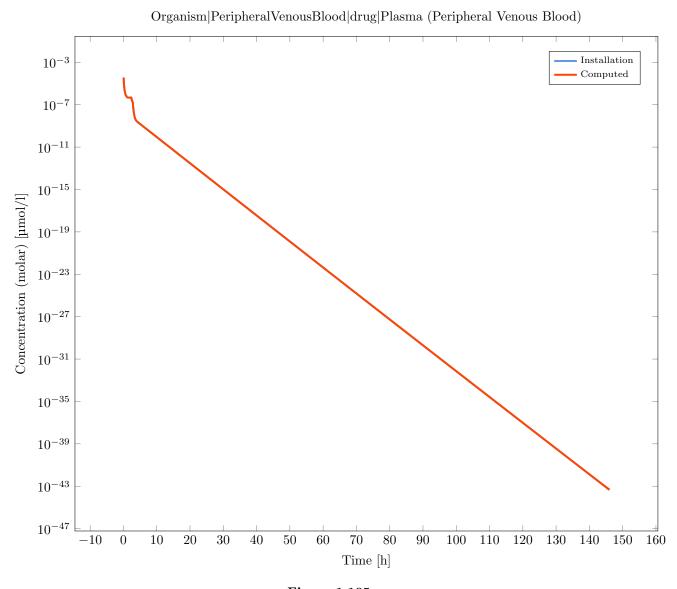


Figure 1.104

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

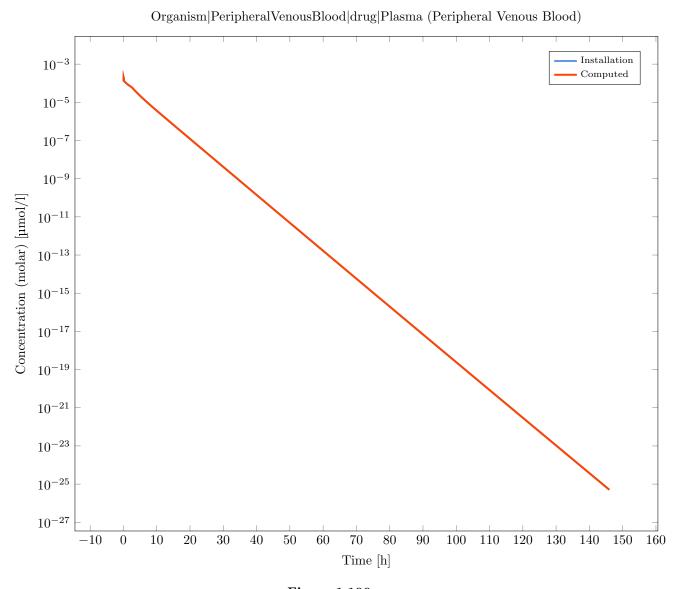
Output Path: Organism |Peripheral Venous
Blood |drug |Plasma (Peripheral Venous Blood)
 Deviation: 2.02E-6



 ${\bf Figure~1.105}$

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

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



 ${\bf Figure~1.106}$

Simulation: Human_CompetitiveInhibition-Human_CompetitiveInhibition

Result of the validation: Valid



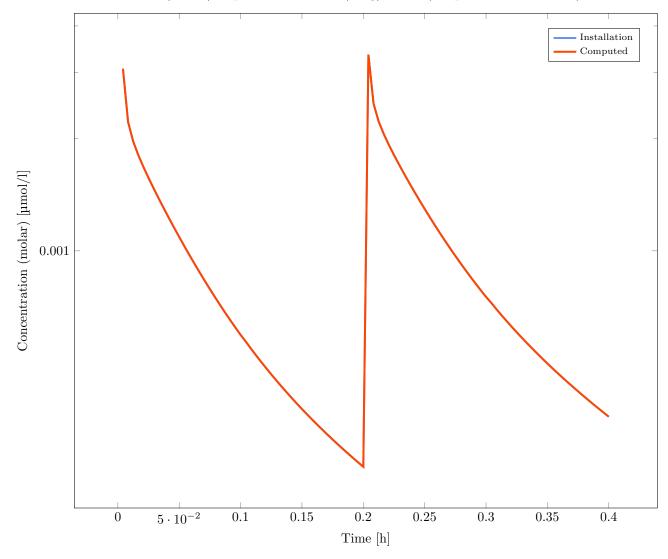


Figure 1.107

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

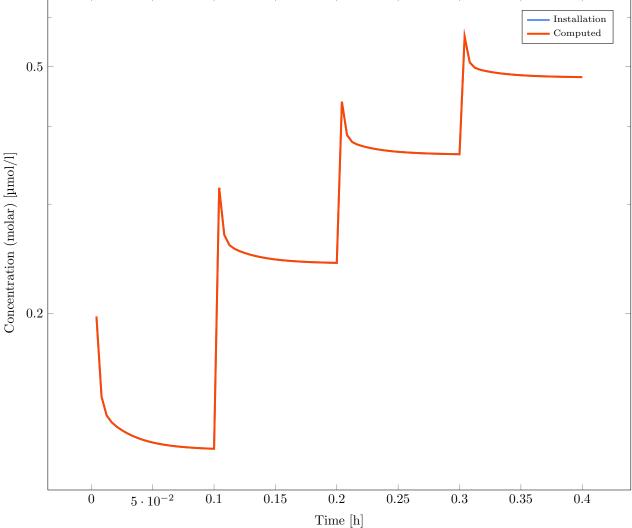


Figure 1.108

Simulation: Human_ICRP_AGP-01_ICRP_0y_Male

Result of the validation: Valid

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

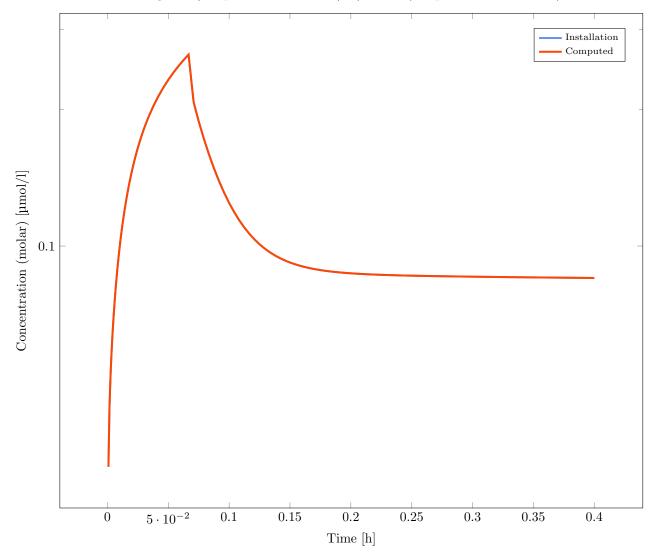


Figure 1.109

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

Result of the validation: Valid

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

Organism|PeripheralVenousBlood|C1|Plasma (Peripheral Venous Blood) O.5 Installation Computed One of the control of the cont

Figure 1.110

0.2

Time [h]

0.25

0.3

0.35

0.4

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

 $5\cdot 10^{-2}$

0.1

Result of the validation: Valid

0

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

0.15

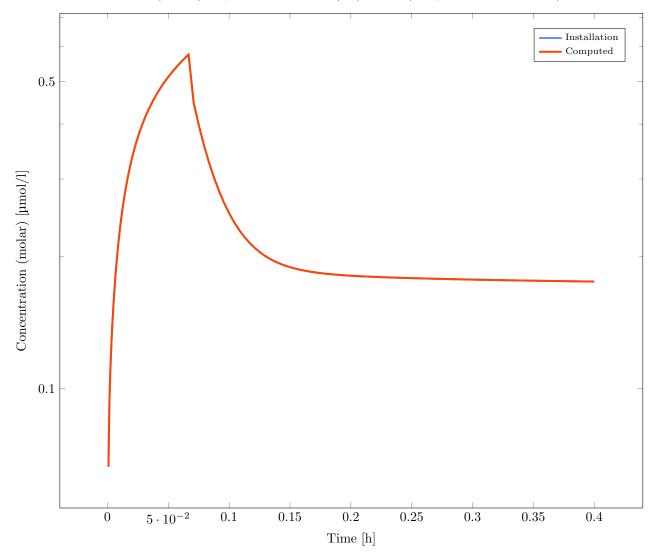


Figure 1.111

 $Simulation: \ Human_ICRP_AGP-04_ICRP_1y_Female$

Result of the validation: Valid

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

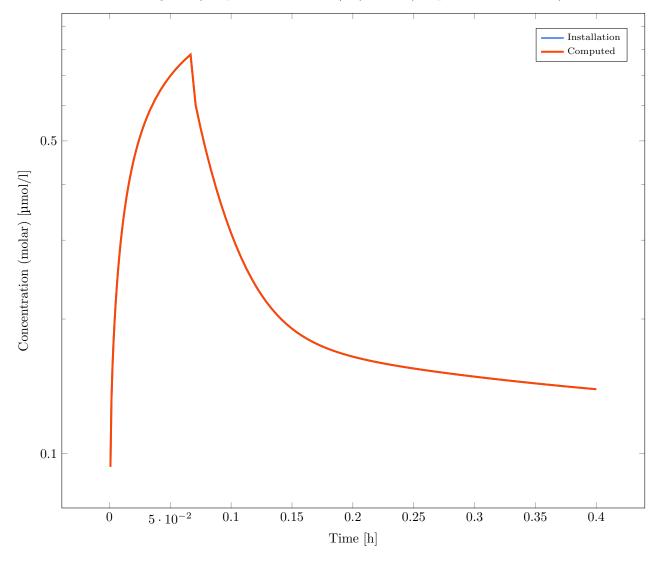


Figure 1.112

 $Simulation: \ Human_ICRP_AGP-05_ICRP_12y_Male$

Result of the validation: Valid

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

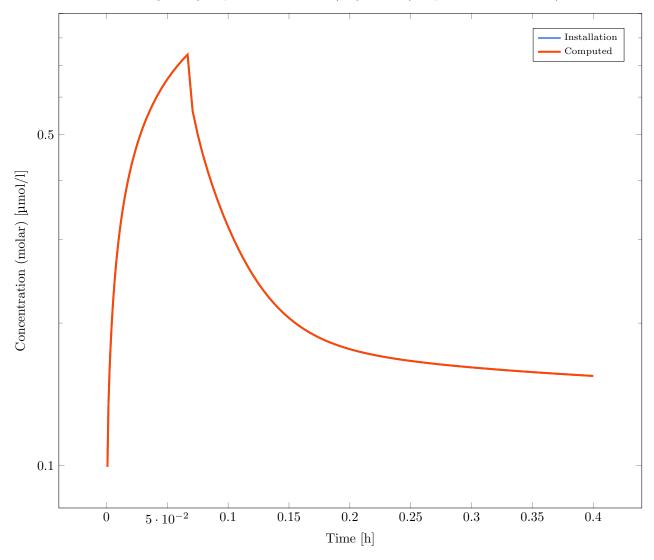


Figure 1.113

 $Simulation: \ Human_ICRP_AGP-06_ICRP_30y_Female$

Result of the validation: Valid

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



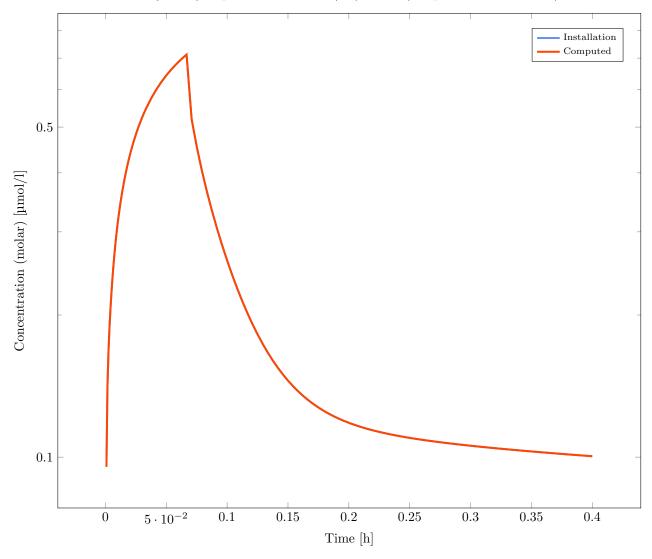


Figure 1.114

 $Simulation: \ Human_ICRP_AGP-07_ICRP_100y_Male$

Result of the validation: Valid

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

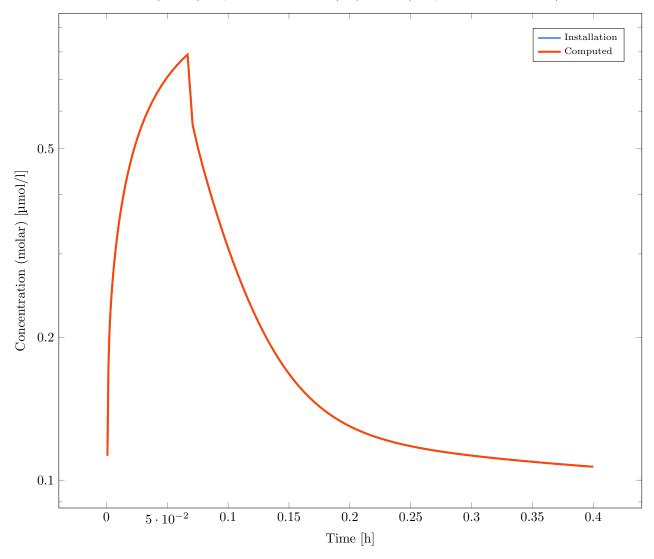
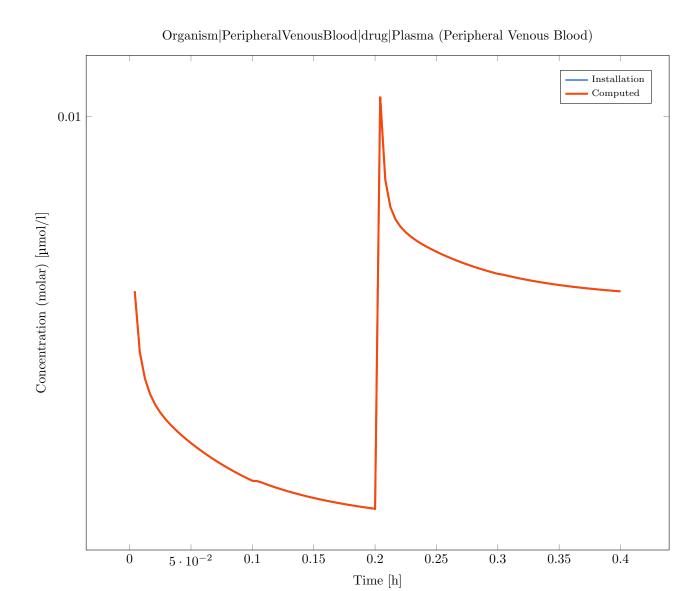


Figure 1.115

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

Result of the validation: Valid



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

 $Figure \ 1.116$

Organism|PeripheralVenousBlood|inhibitor|Plasma (Peripheral Venous Blood) | Installation | Computed | Compute

Figure 1.117

Time [h]

 $Simulation: \ Human_MixedInhibition-Human_MixedInhibition$

Result of the validation: Valid

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

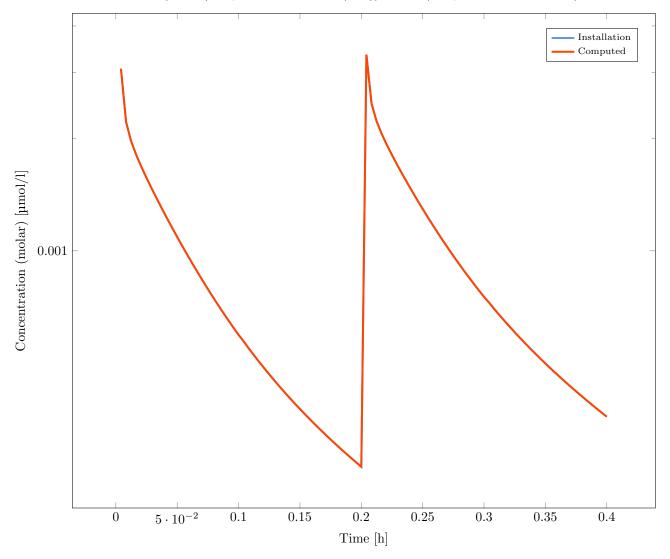


Figure 1.118

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

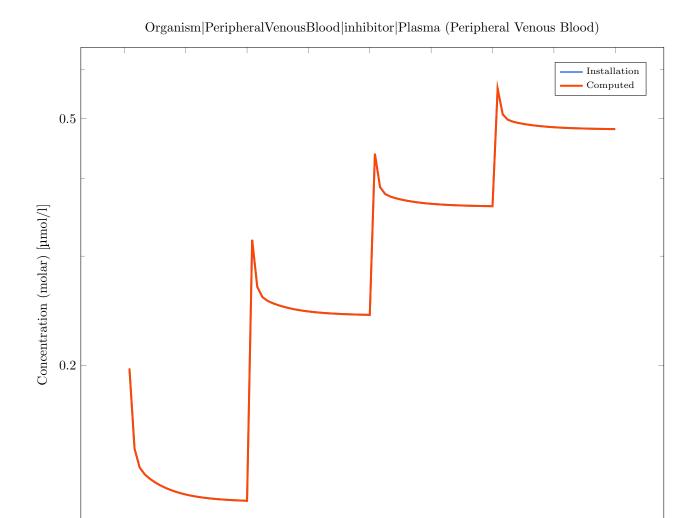


Figure 1.119

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



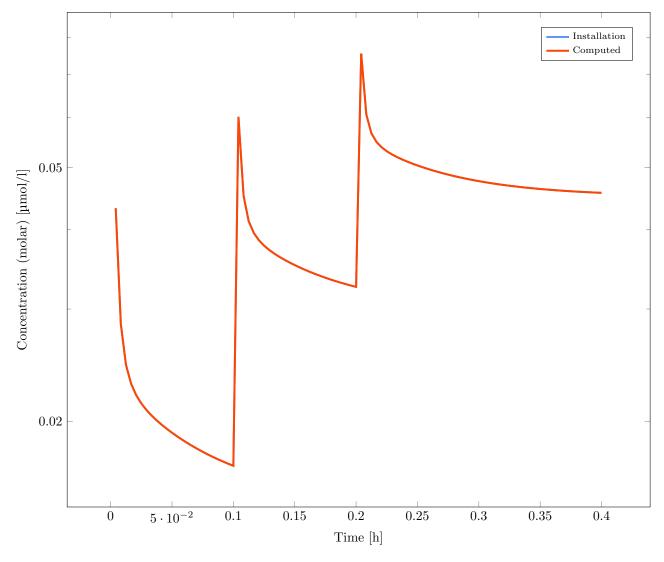


Figure 1.120

 $Simulation: \ Human_MultiORAL_6_12_12_Dissolved-Human_6_12_Dissolved-Human_6_12_$

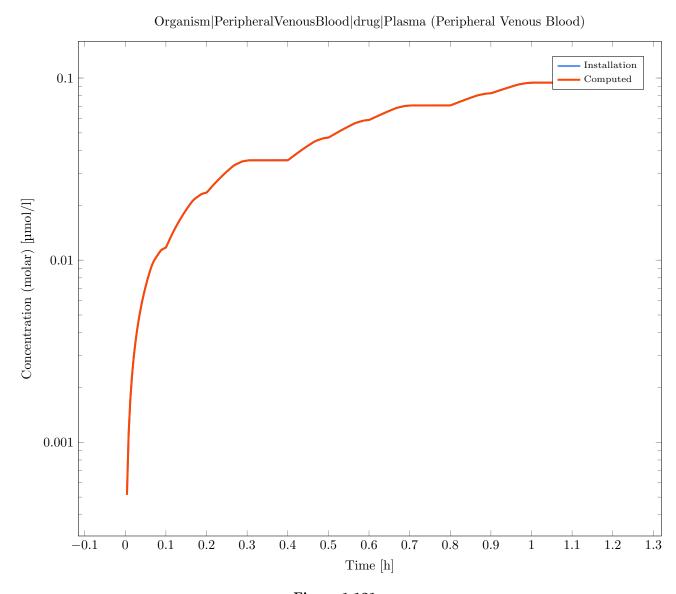
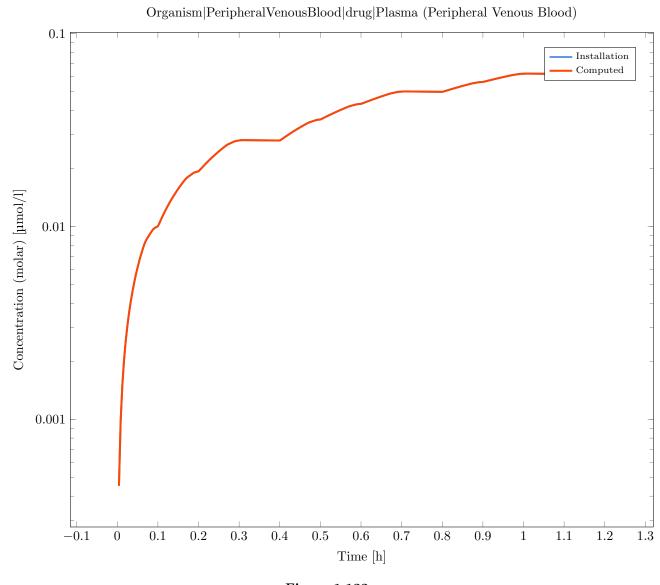


Figure 1.121

 $Simulation: Human_MultiORAL_6_12_12_Dissolved-Human_MultiORAL_6_12_12_Dissolved_absorption_sink_conditions$

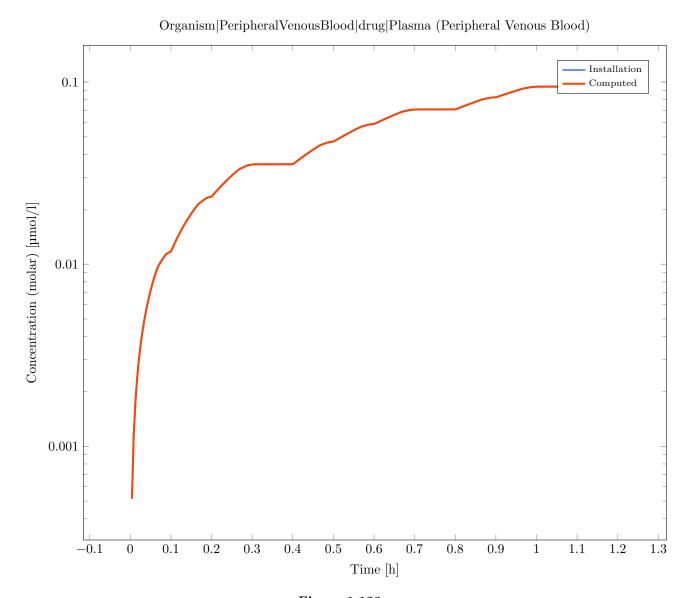
Result of the validation: Valid



 ${\bf Figure~1.122}$

 $Simulation: Human_MultiORAL_6_12_12_Dissolved-Human_MultiORAL_6_12_12_Dissolved_EHC_continuous_fraction_0.5$

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

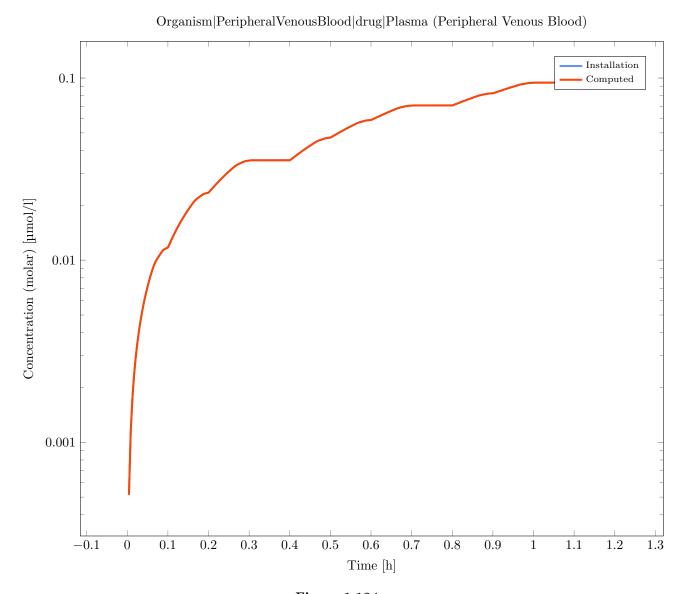
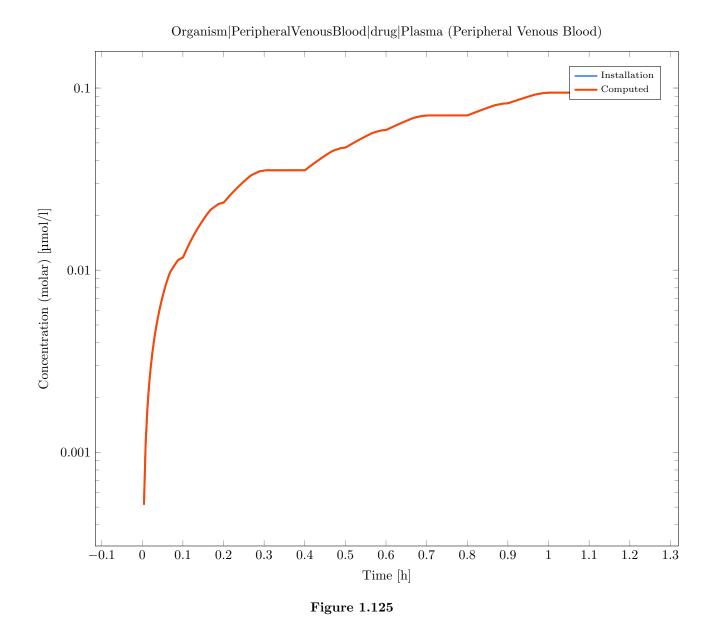
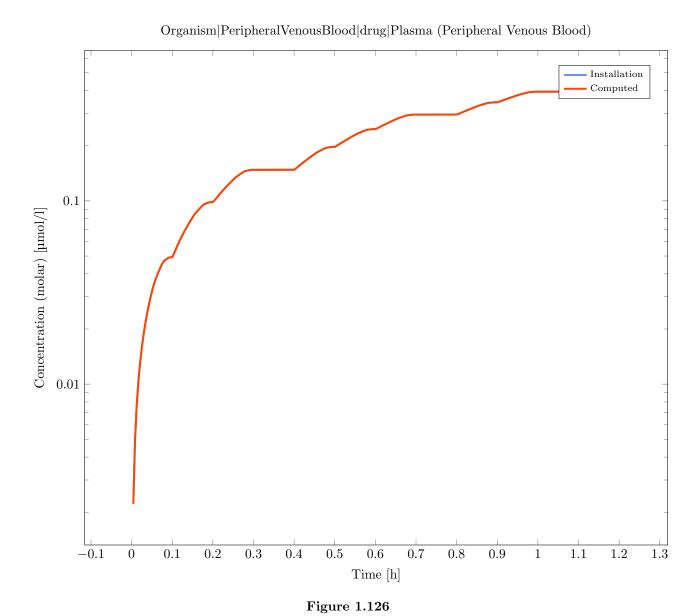


Figure 1.124

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



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



 ${\bf Simulation: \ Human_Multiple IV_All Active Processes-Human_Multiple IV_All Active Processes \ Result of the validation: \ Valid$

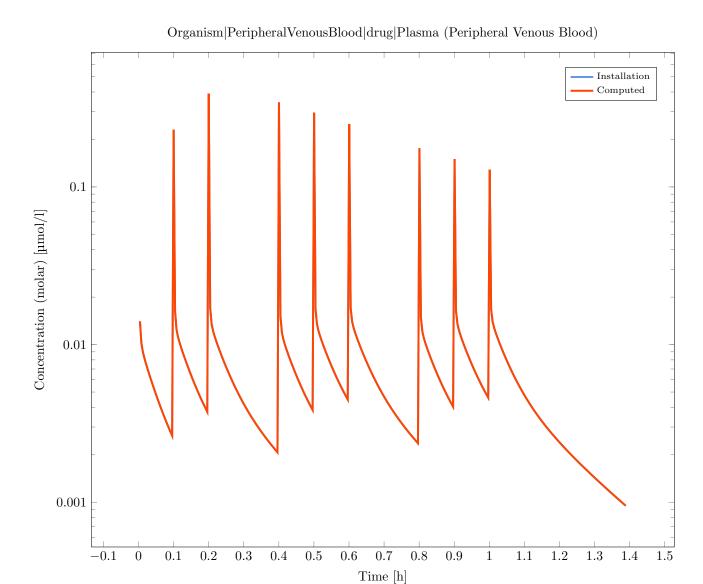


Figure 1.127

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

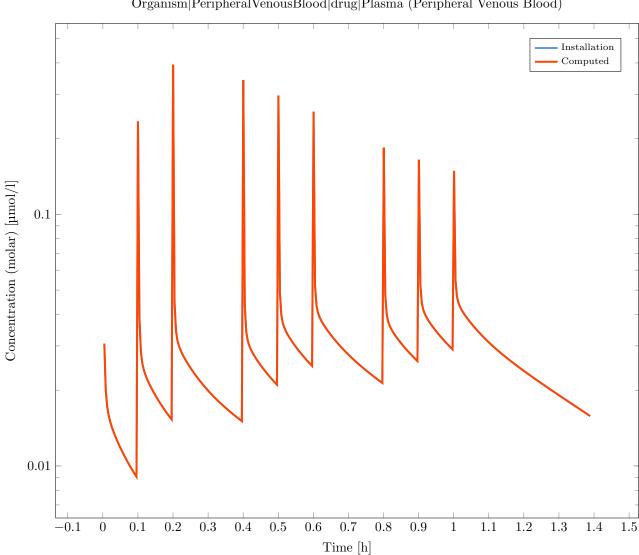
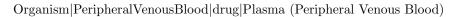
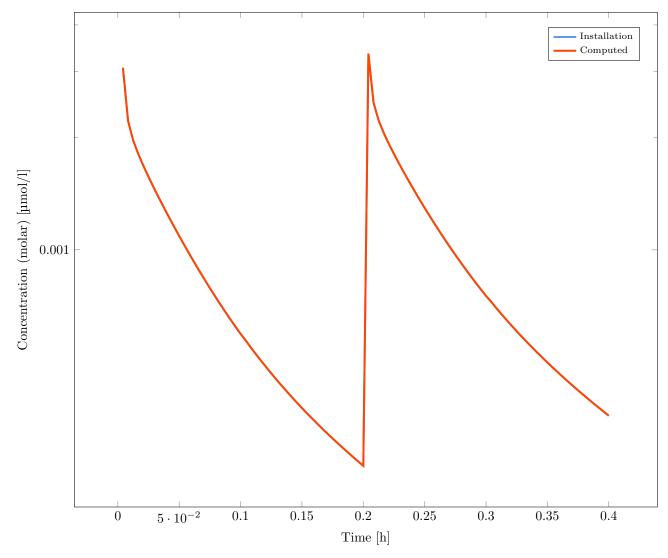


Figure 1.128

 $Simulation: \ Human_NonCompetitiveInhibition-Human_NonCompetitiveInhibition$ Result of the validation: Valid





 $Figure \ 1.129$

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

Organism|PeripheralVenousBlood|inhibitor|Plasma (Peripheral Venous Blood) Installation Computed 0.5 0.2

Figure 1.130

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: \ Human_Oral_BiDaily_Table Formulation-S1_suspension$

0.1

Result of the validation: Valid

0

 $5 \cdot 10^{-2}$

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

0.15

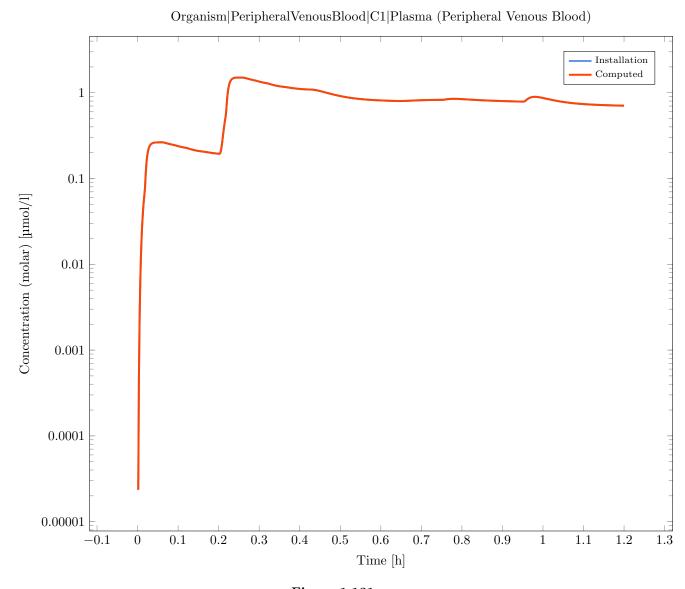
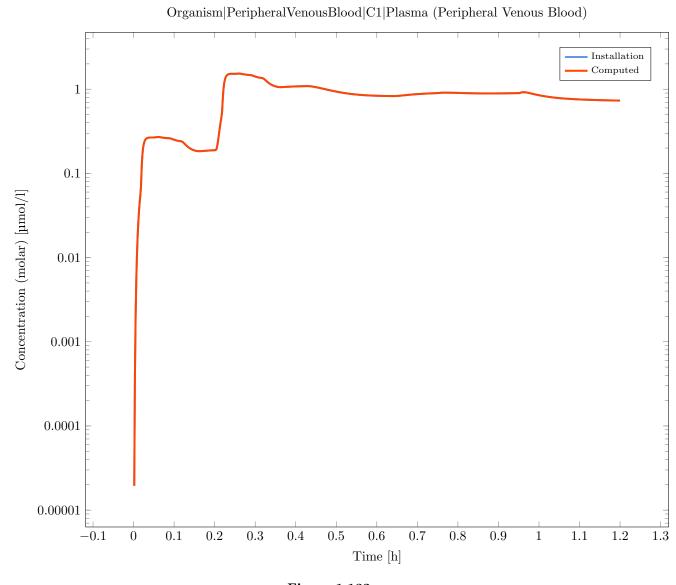


Figure 1.131

 ${\bf Simulation: Human_Oral_BiDaily_Table Formulation-S2_NoSuspension}$

Result of the validation: Valid

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



 ${\bf Figure~1.132}$

Simulation: Human_pH_SolubilityTable-S1_Table

Result of the validation: Valid

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

Deviation: 7.47E-6

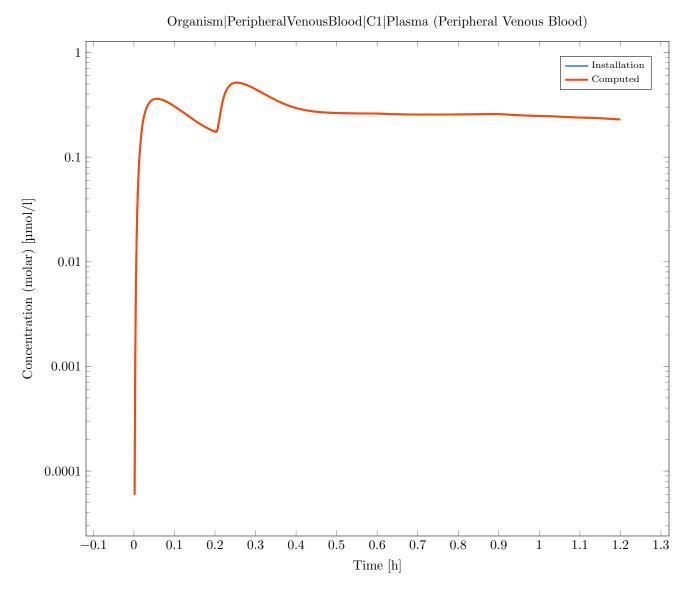


Figure 1.133

Simulation: Human_pH_SolubilityTable-S2_Measurement

Result of the validation: Valid

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

Deviation: 2.09E-6

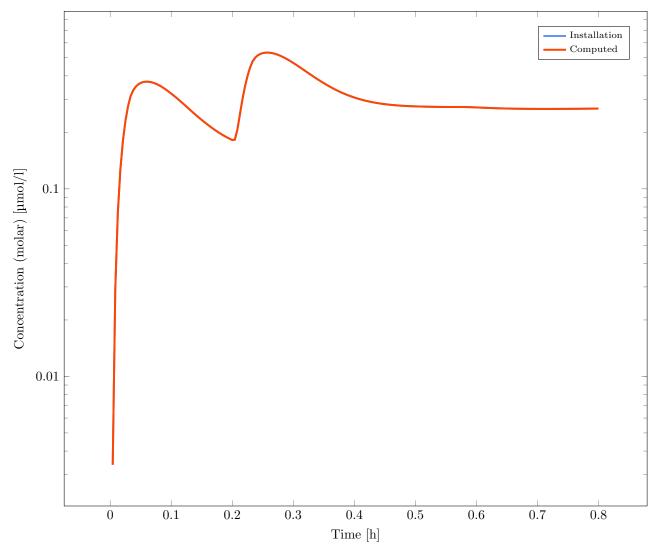


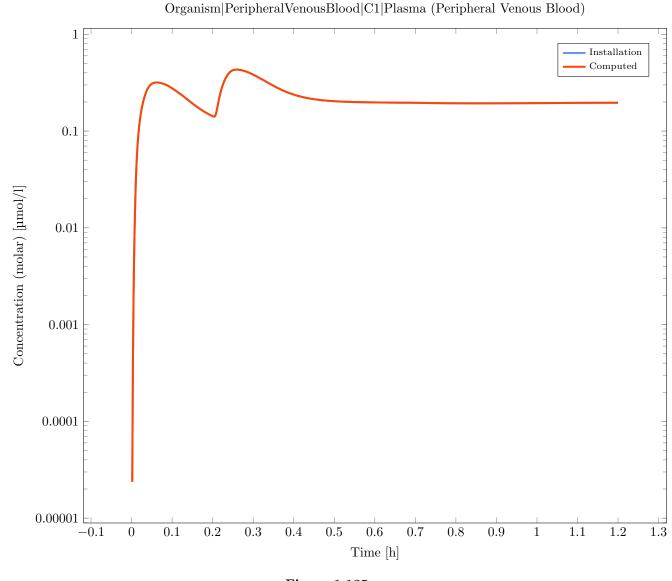
Figure 1.134

 $Simulation: \ Human_pH_SolubilityTable_SolubilityChanged$

Result of the validation: Valid

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

Deviation: 6.73E-6



 ${\bf Figure~1.135}$

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

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

Deviation: 6.13E-7

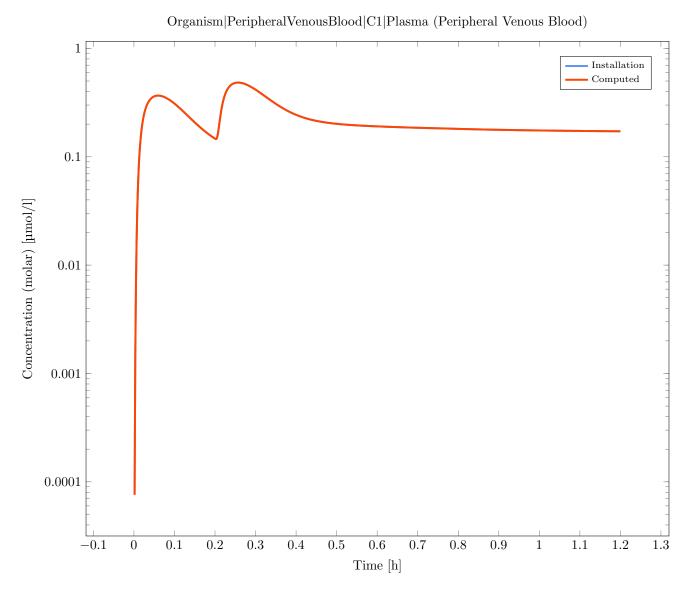


Figure 1.136

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

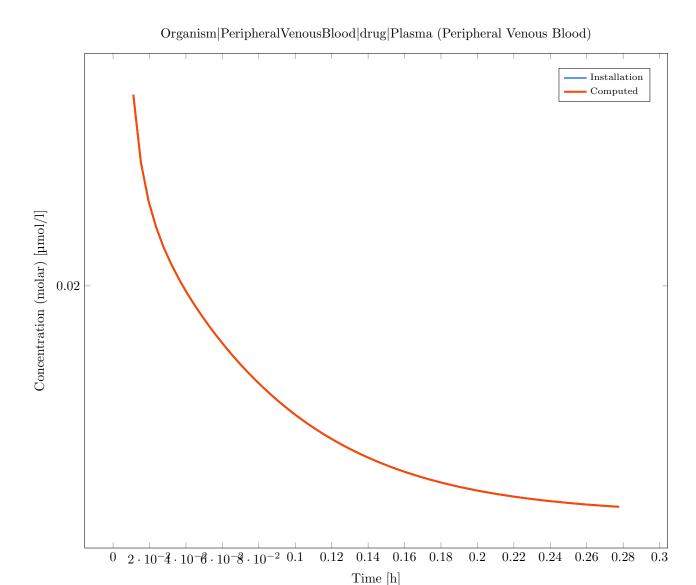


Figure 1.137

 $Simulation: \ Human_Single IV-Human_Single IV$

Result of the validation: Valid

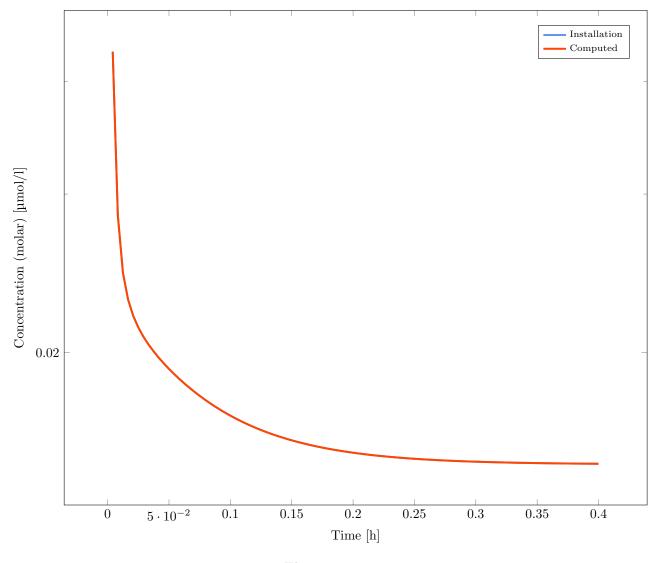


Figure 1.138

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

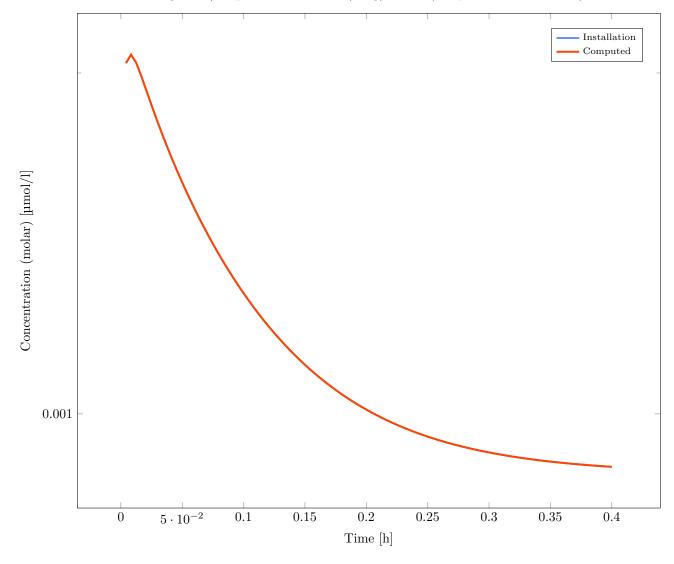


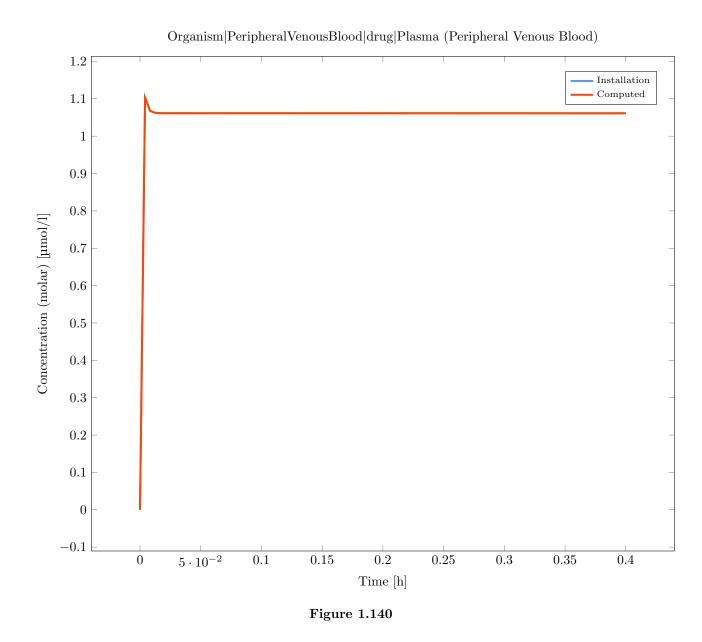
Figure 1.139

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

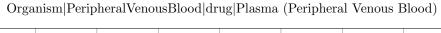
Result of the validation: Valid

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

Open Systems Pharmacology Suite - 9



Simulation: Human_SingleORAL_Dissolved_PlasmaClearance-Human_SingleO



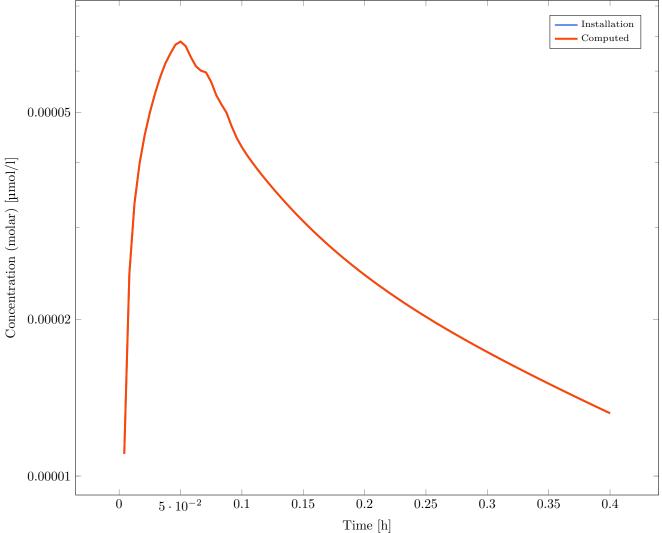
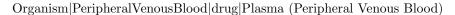


Figure 1.141

 $Simulation: Human_SingleORAL_Dissolved_PlasmaClearance-Human_Singl$

Result of the validation: Valid

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



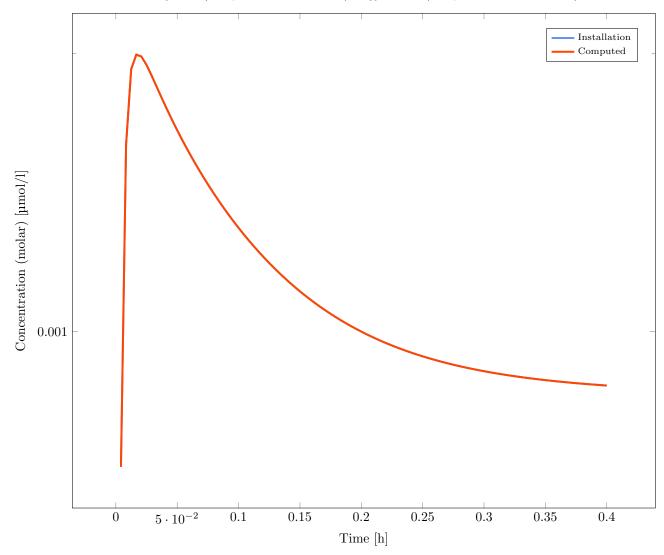


Figure 1.142

 $Simulation: Human_SingleORAL_Dissolved_PlasmaClearance-Human_Singl$

Result of the validation: Valid

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

Deviation: 0

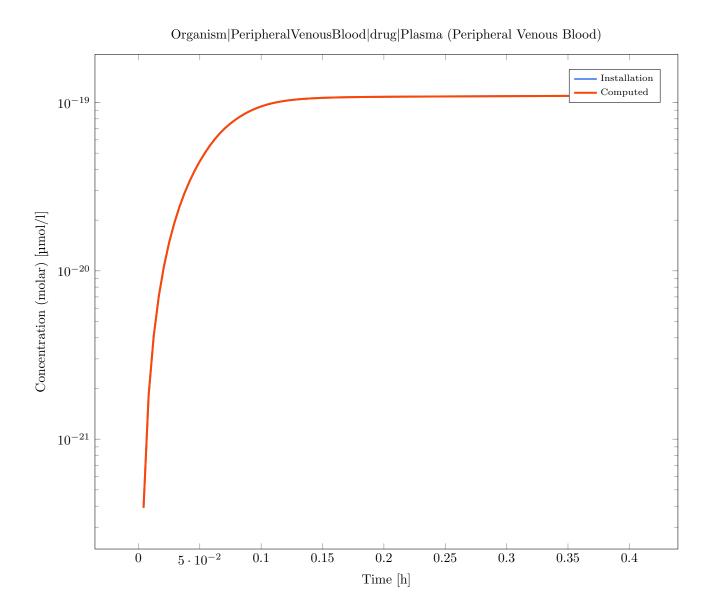


Figure 1.143

Simulation: Human_SingleORAL_Dissolved-Human_SingleORAL_Dissolved Result of the validation: Valid

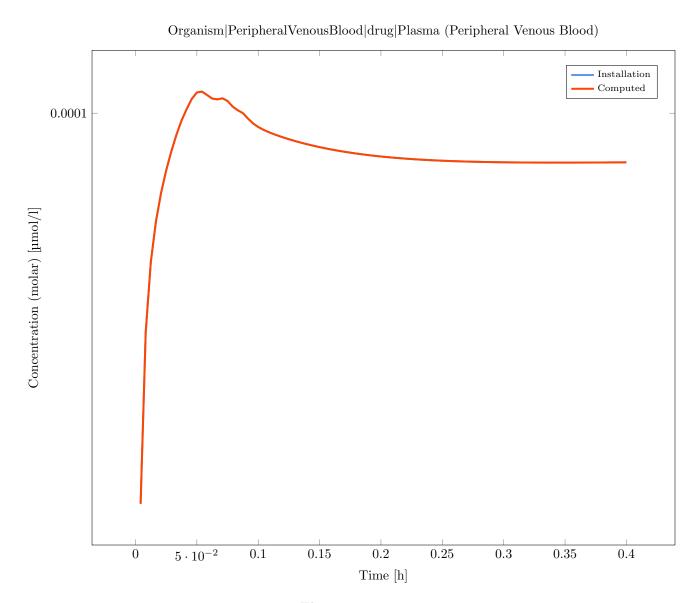


Figure 1.144

 $Simulation: \ Human_SingleORAL_Dissolved_Human_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5$

Result of the validation: Valid

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

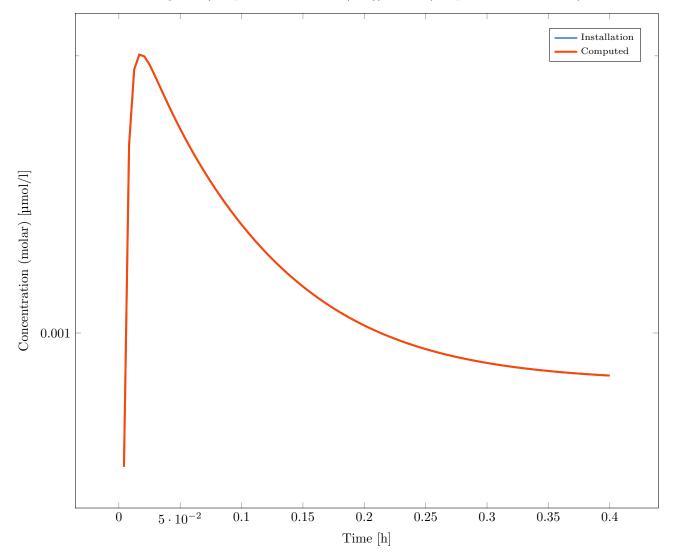
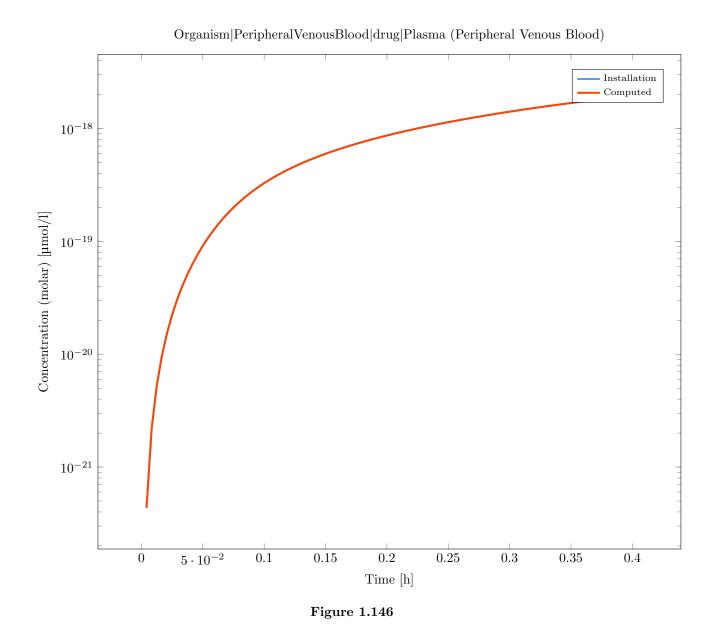


Figure 1.145

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



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

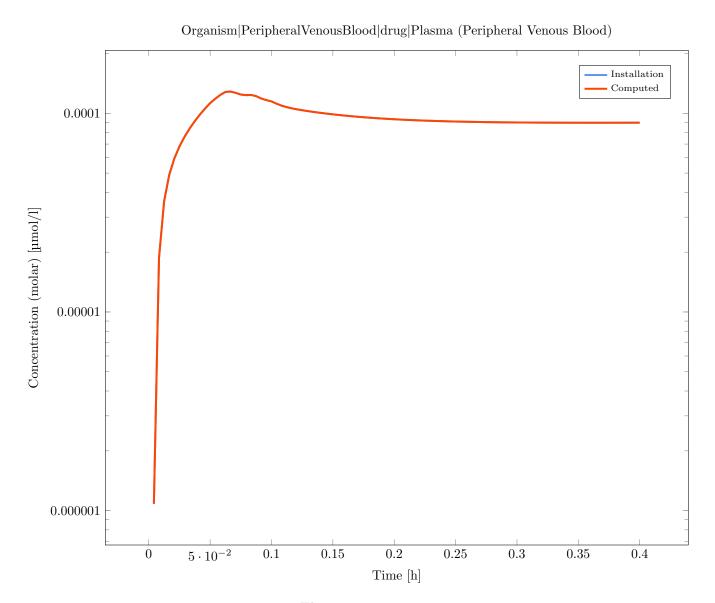


Figure 1.147

 $Simulation: \ Human_SingleORAL_Lint80-Human_SingleORAL_Lint80$

Result of the validation: Valid

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

Deviation: 0

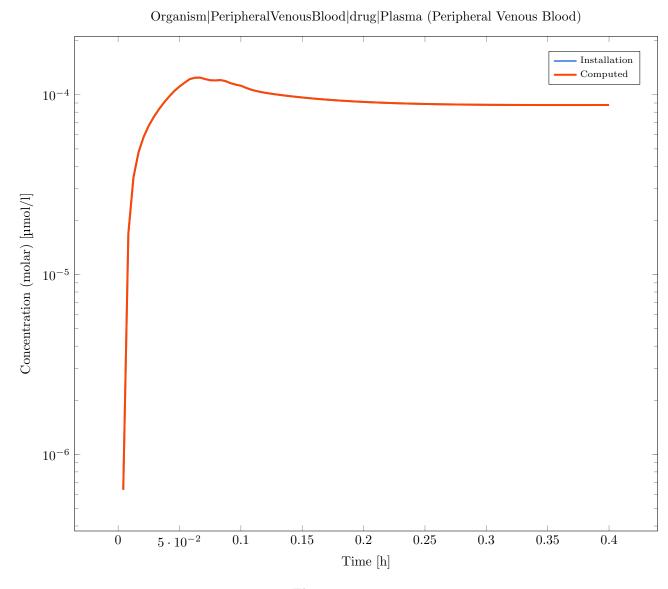


Figure 1.148

 $Simulation: Human_SingleORAL_MonoParticles_AsSuspention-Human_SingleORAL_MonoParticles_AsSuspention\\$

Result of the validation: Valid

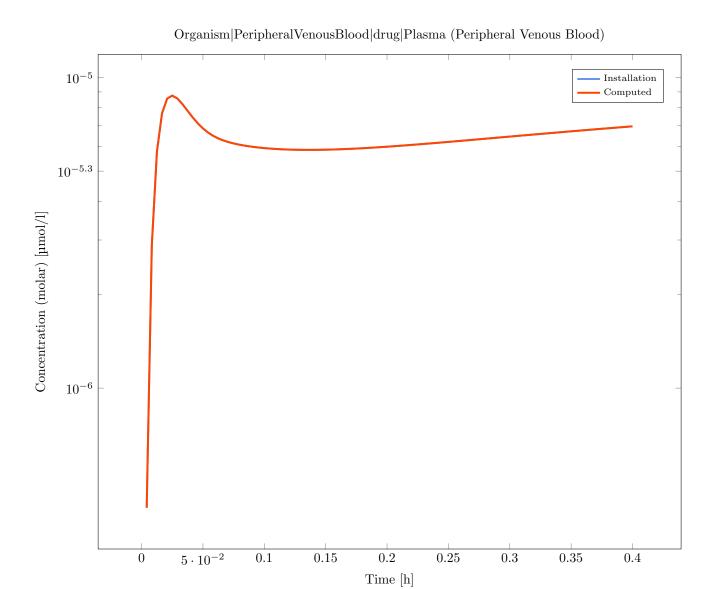
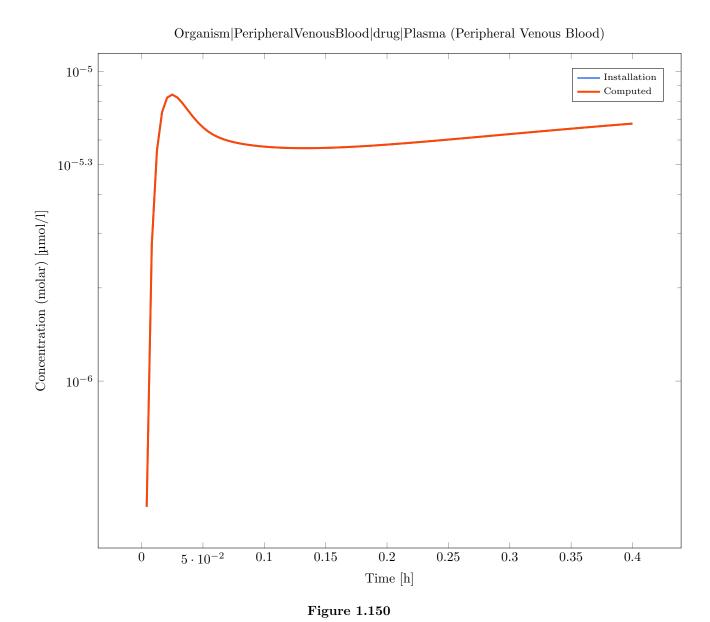


Figure 1.149

 $Simulation: \ Human_SingleORAL_PolyParticlesLogNormal_AsSuspention-Human_SingleORAL_PolyParticlesLogNormal_AsSuspention$

Result of the validation: Valid



 $Simulation: Human_SingleORAL_PolyParticlesNormal_AsSuspention-Human_SingleORAL_PolyParticlesNoAsSuspention\\$

Result of the validation: Valid

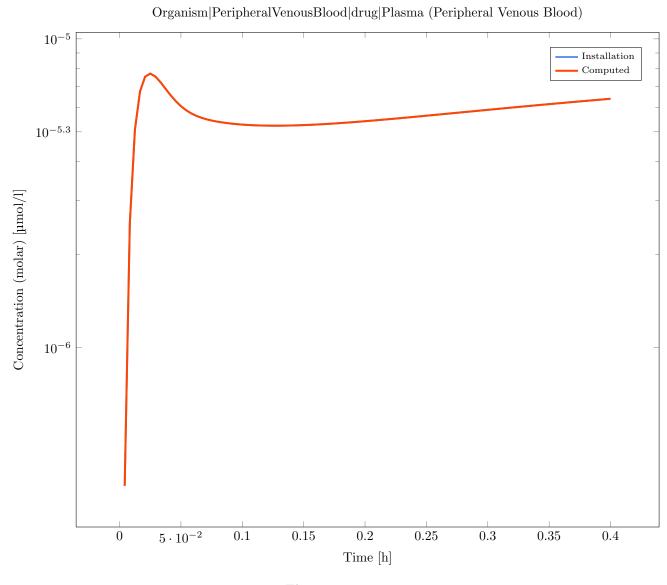


Figure 1.151

 $Simulation: Human_SingleORAL_PolyParticlesNormal_AsSuspention-Human_SingleORAL_PolyParticlesNormal_AsSuspention_dissolved_radius$

Result of the validation: Valid

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

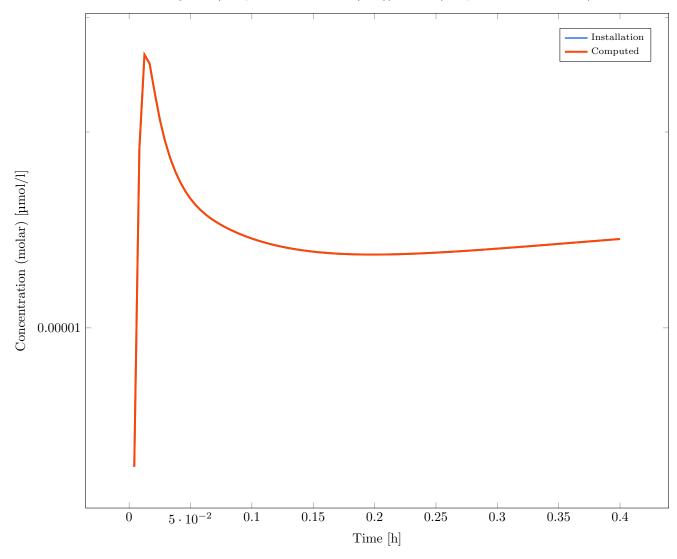


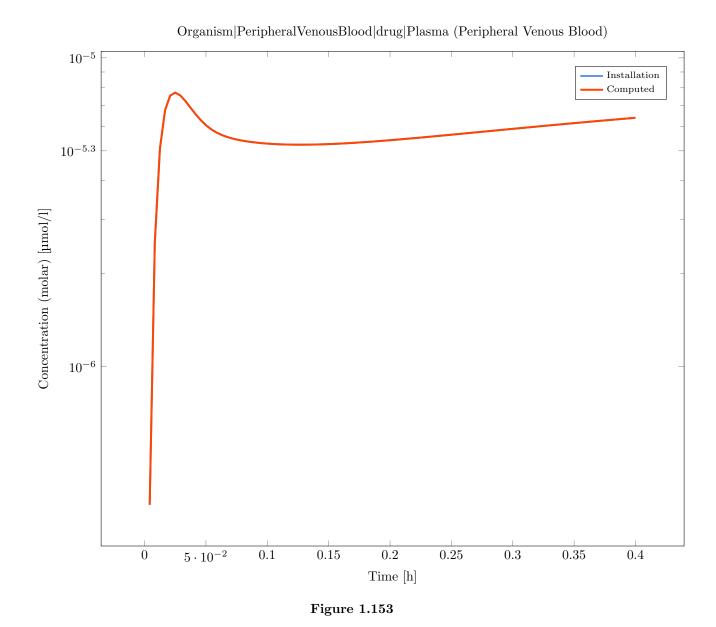
Figure 1.152

 $Simulation: Human_SingleORAL_PolyParticlesNormal_AsSuspention-Human_SingleORAL_PolyParticlesNormal_AsSuspention_treat_precipated_drug_as_soluble$

Result of the validation: Valid

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

Deviation: 0



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

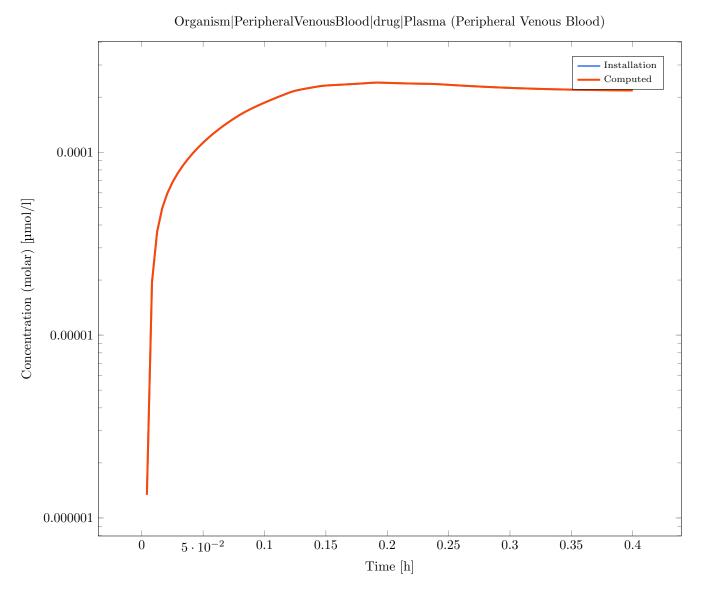


Figure 1.154

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

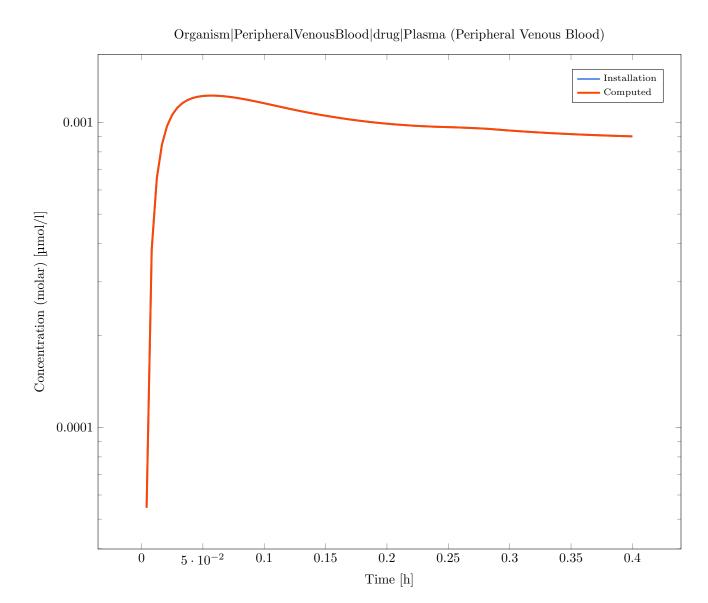
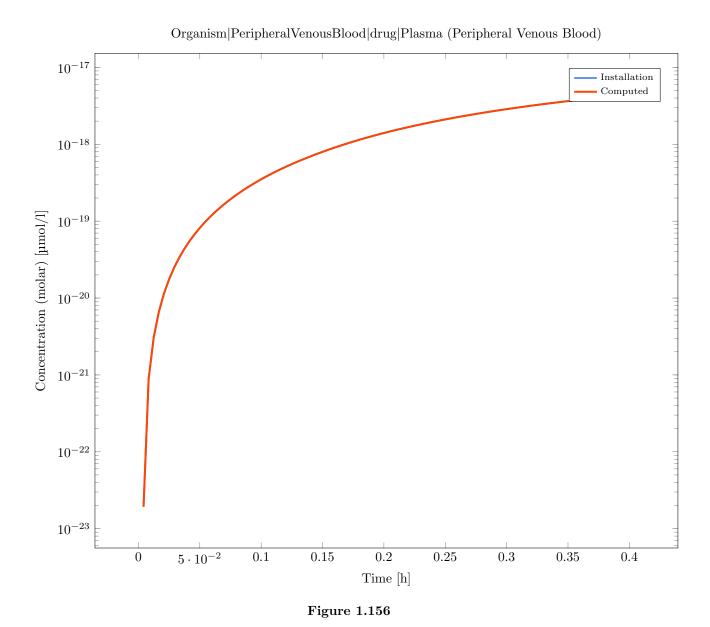
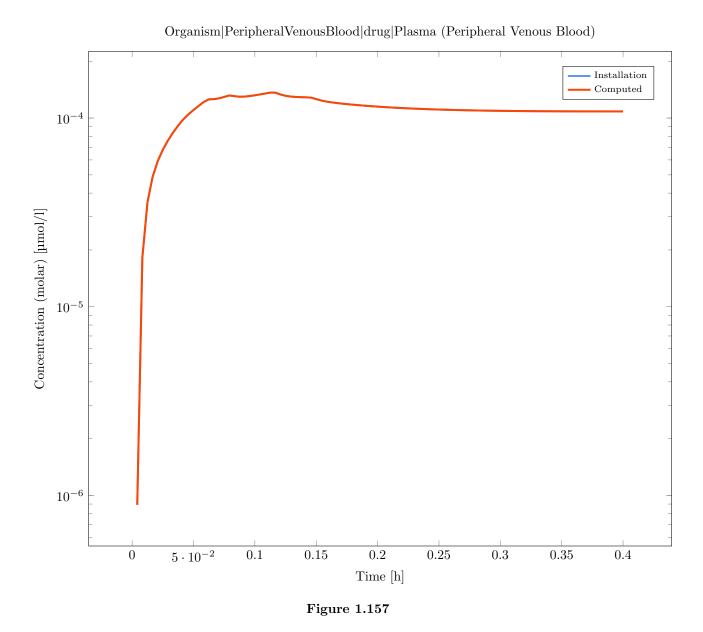


Figure 1.155

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



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



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

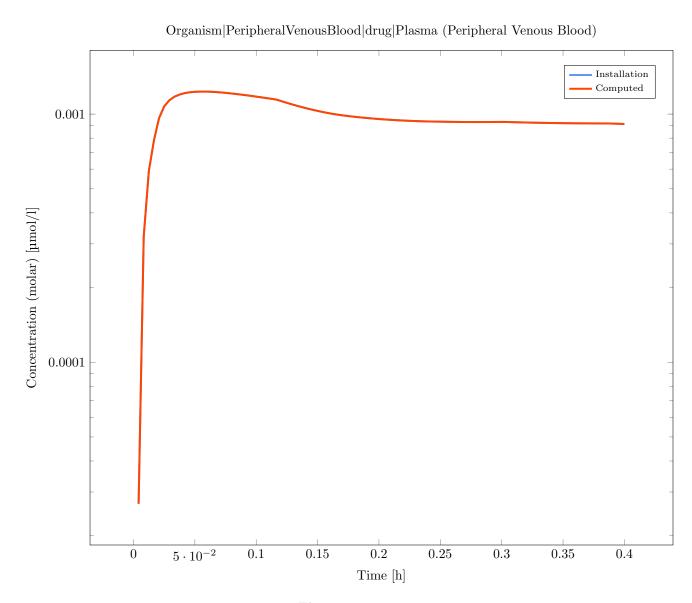


Figure 1.158

 $\label{lem:singleORAL_Weibull-Human_SingleORAL_Weibull_MW_800_fu_0.6_LogP_5 \\ Result of the validation: Valid$

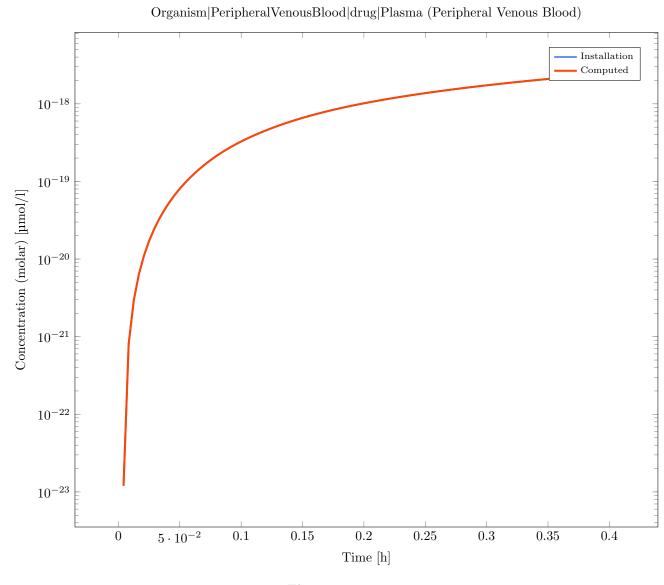


Figure 1.159

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

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

Figure 1.160

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

0.1

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

0

 $5 \cdot 10^{-2}$

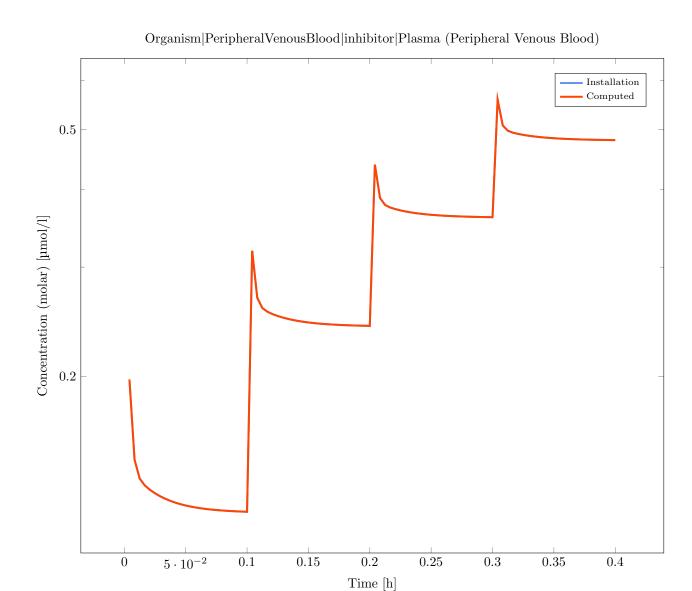
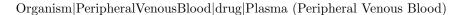


Figure 1.161

Simulation: Minipig_SingleORAL_Dissolved-Minipig_SingleORAL_Dissolved Result of the validation: Valid



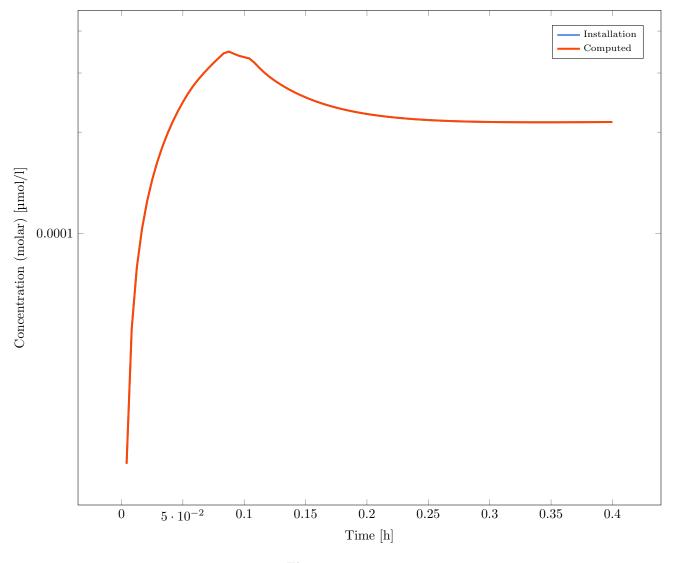


Figure 1.162

 $Simulation: Minipig_SingleORAL_Dissolved_Minipig_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5$

Result of the validation: Valid

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

Deviation: 0

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

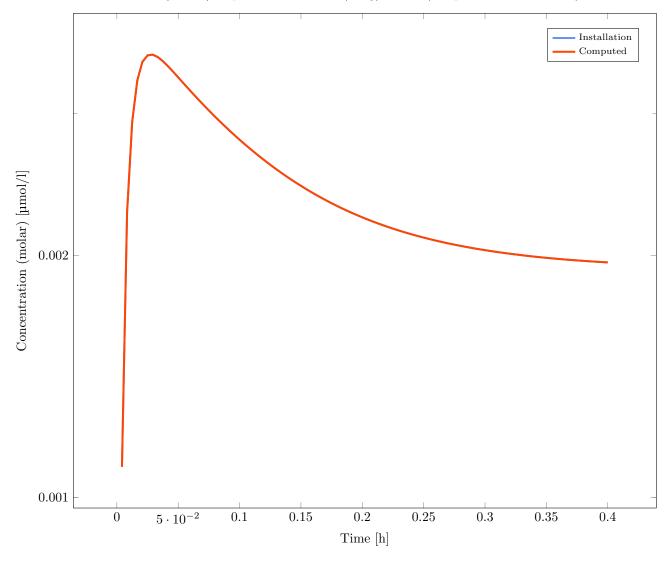


Figure 1.163

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

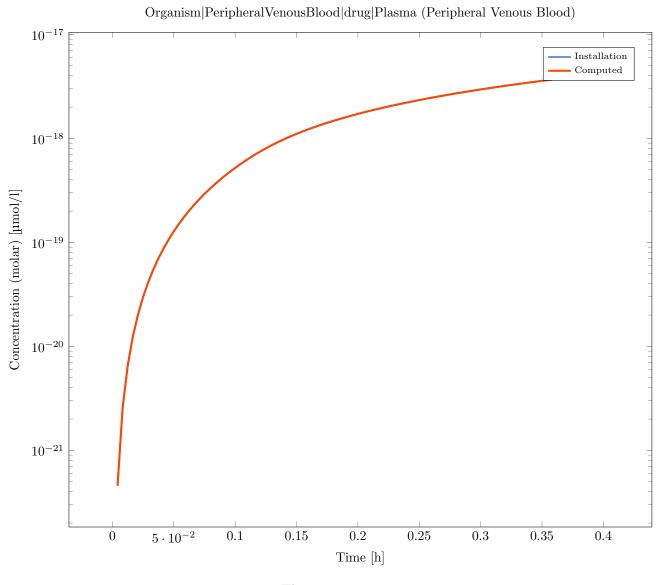


Figure 1.164

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

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

0.15 0.2

Time [h]

0.25

0.35

0.3

0.4

0.1

Figure 1.165

 $Simulation: Monkey_SingleORAL_Dissolved_Monkey_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5$

Result of the validation: Valid

0

 $5 \cdot 10^{-2}$

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

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

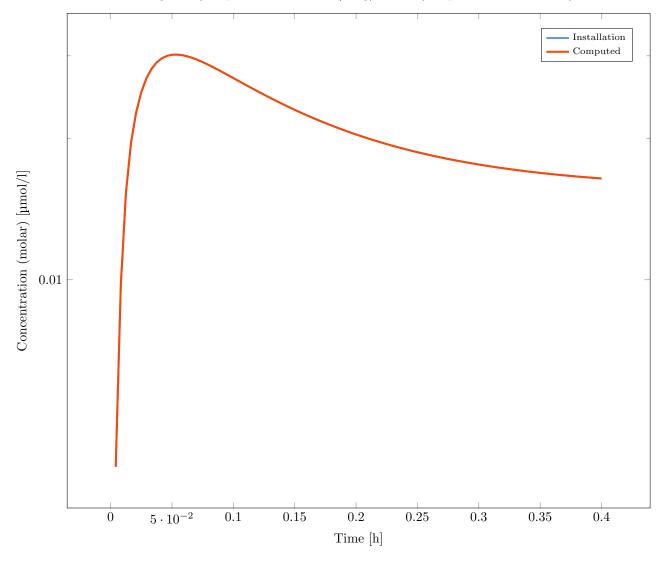


Figure 1.166

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

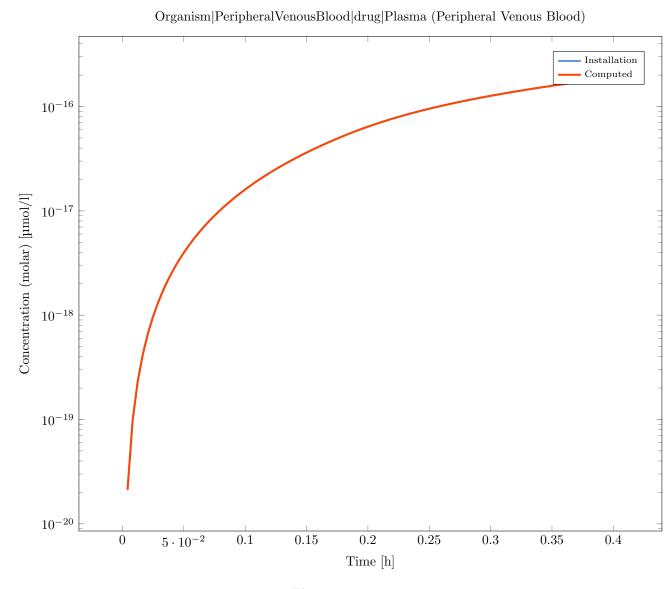


Figure 1.167

Simulation: Mouse_SingleORAL_Dissolved-Mouse_SingleORAL_Dissolved Result of the validation: Valid



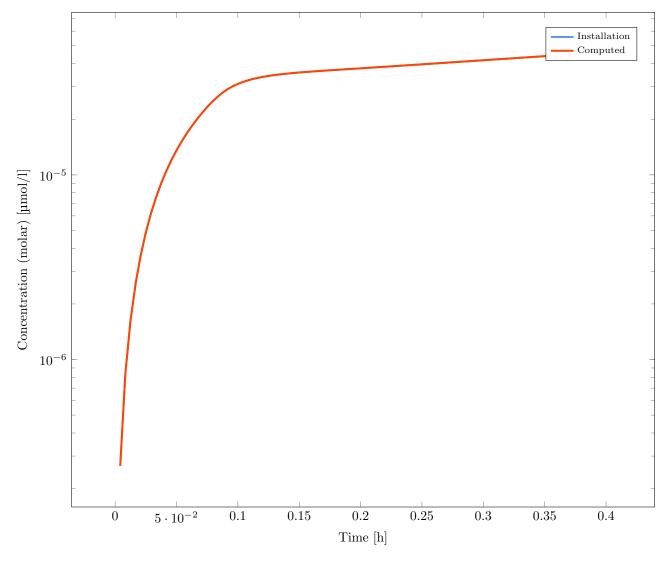


Figure 1.168

 $Simulation: Mouse_SingleORAL_Dissolved_MOUSe_SingleORAL_Dissolved_MW_200_fu_0.2_LogP_5$ Result of the validation: Valid

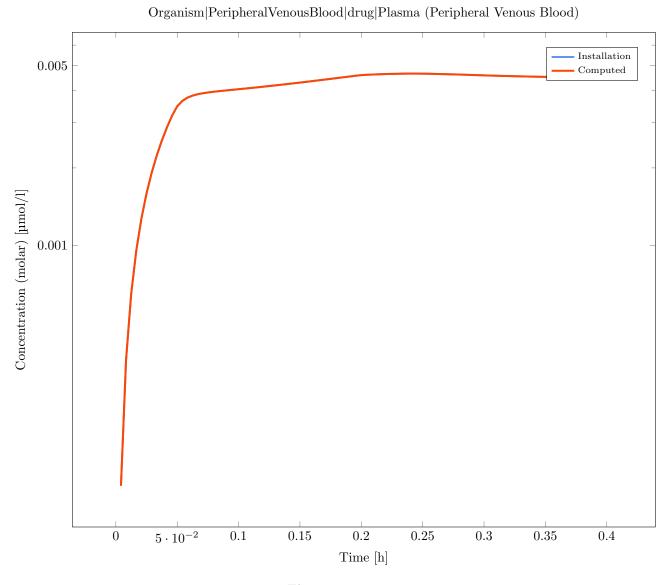
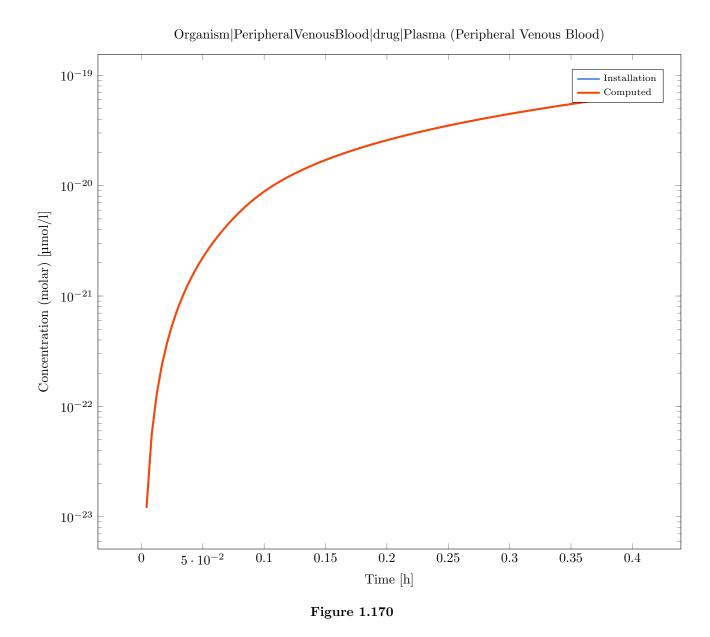
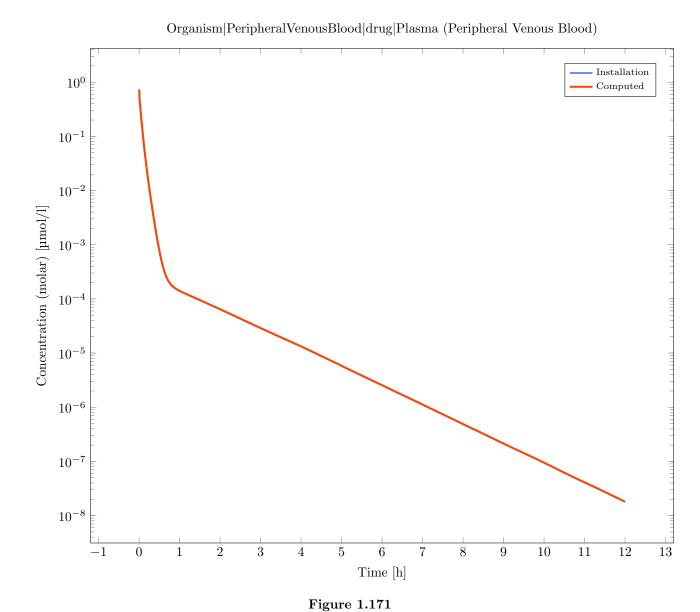
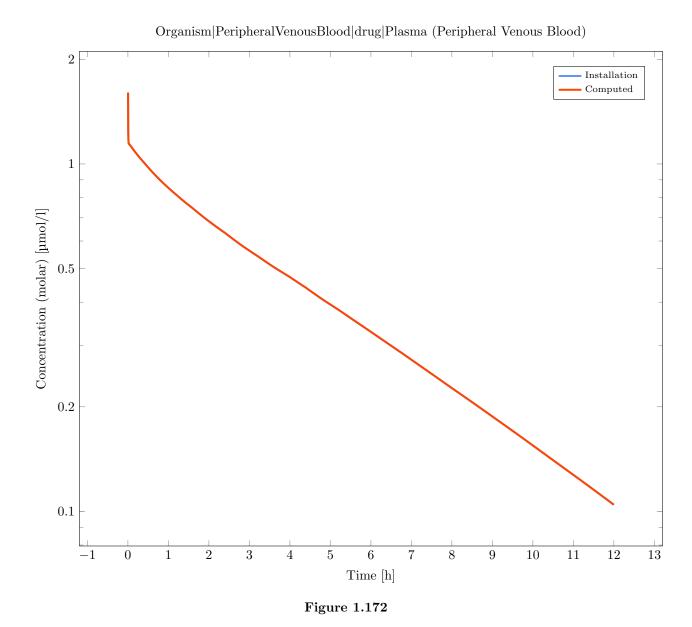


Figure 1.169

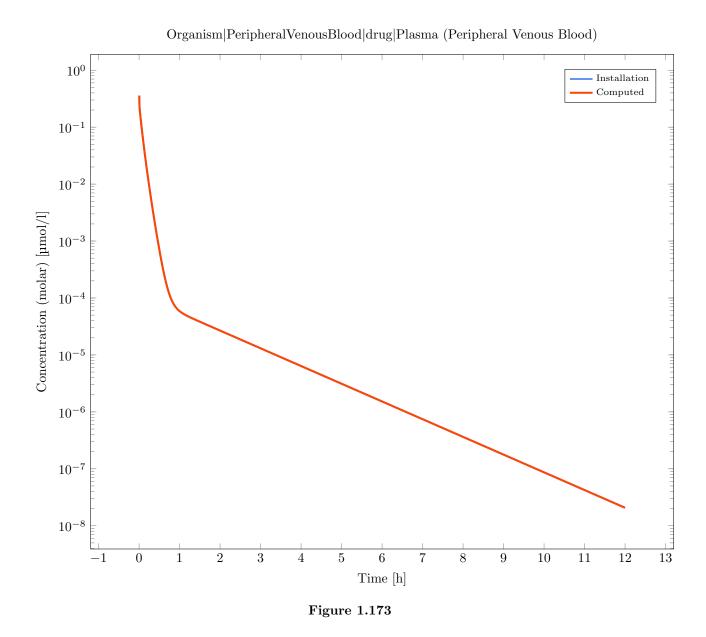
 $\label{local_simple_oral_bis} Simulation: Mouse_SingleORAL_Dissolved_MW_800_fu_0.6_LogP_-5 \\ Result of the validation: Valid$







 $\label{lem:condition:condition:preterm_SingleIV_Age_15_GA_32_CYP3A4-Preterm_SingleIV_Age_15_GA_25_CYP3A4-Preterm_SingleIV_Age_15_GA_25_CYP3A4-Preterm_SingleIV_Age_15_GA_25_CYP3A4-Preterm_SingleIV_Age_15_GA_25_CYP3A4-Preterm_SingleIV_Age_15_GA_25_CYP3A4-Preterm_SingleIV_Age_15_GA_25_CYP3A4-Preterm_SingleIV_Age_15_GA_25_CYP3A4-Preterm_SingleIV_Age_15_CYP3A4-Preterm_SingleIV_Age_$



 $\label{lem:simple_simple_simple_simple_simple} Simulation: \ Preterm_SingleIV_Age_15_GA_32_GFR-Preterm_Sin$

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood) Installation Computed Concentration (molar) $[\mu]$ 0.1 0.01 2 3 10 -10 4 5 6 11 12 13

Figure 1.174

Time [h]

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

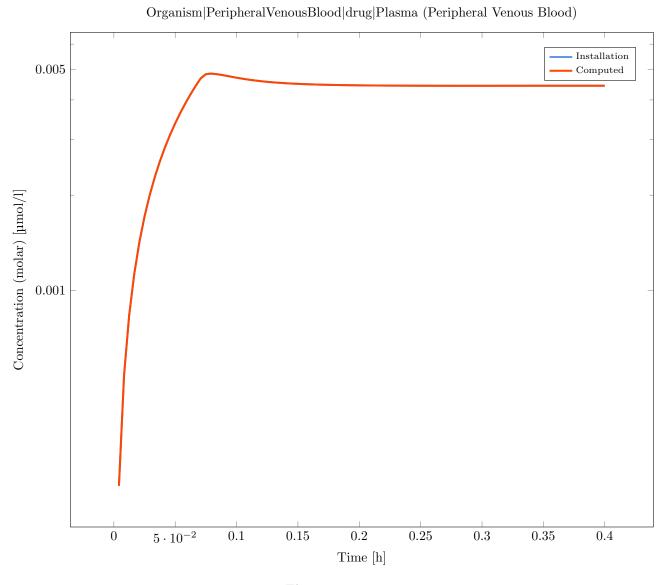


Figure 1.175

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

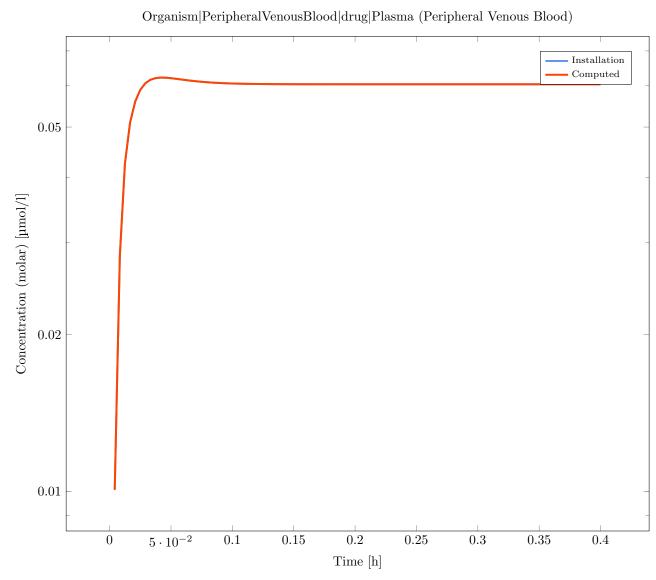


Figure 1.176

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

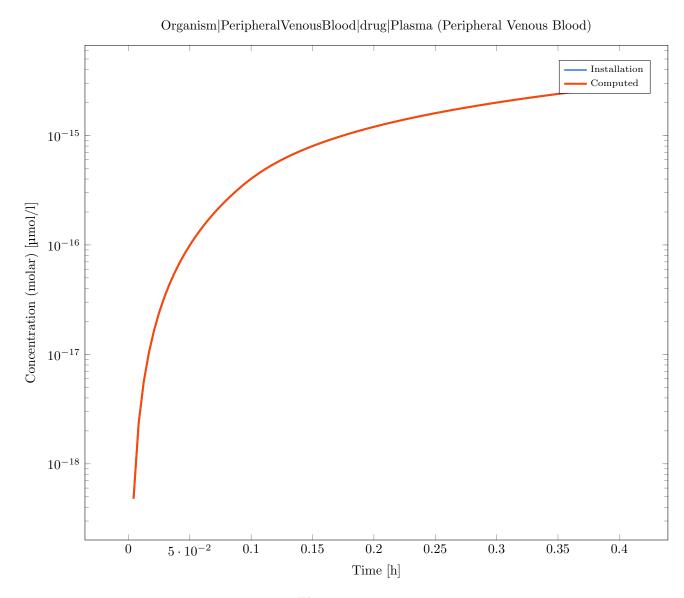
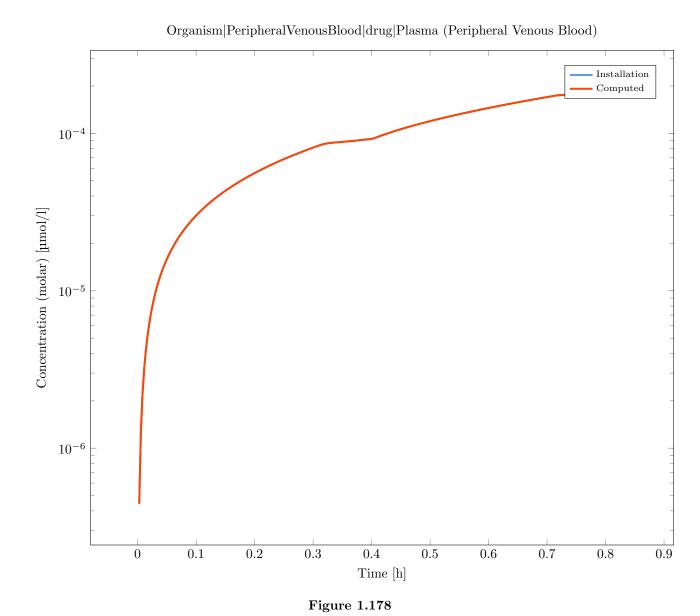


Figure 1.177

Simulation: Rat_MultiORAL_6_6_12_Dissolved-Rat_MultiORAL_6_6_12_Dissolved Result of the validation: Valid



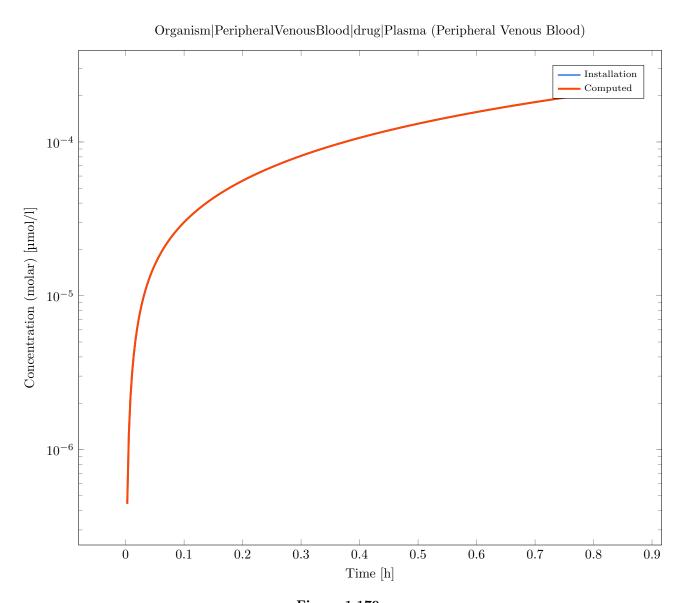


Figure 1.179

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

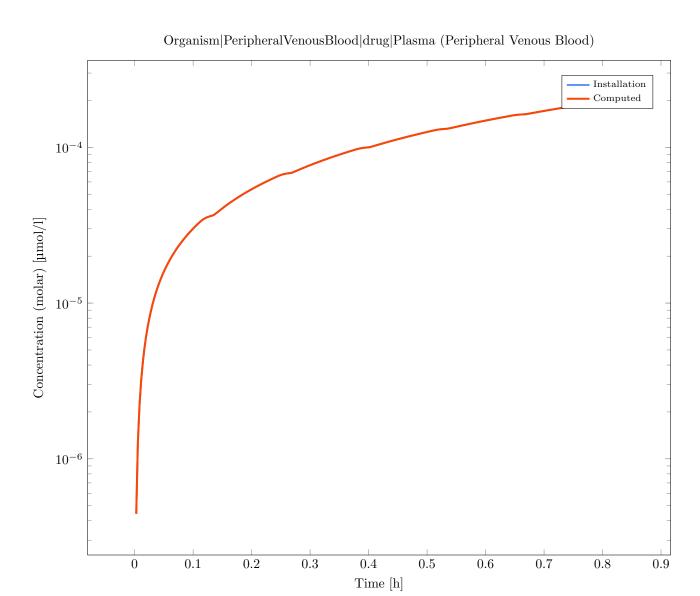


Figure 1.180

 $Simulation: Single IV_2 Pores_Human-Single IV_2 Pores_Human$

Result of the validation: Valid

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

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

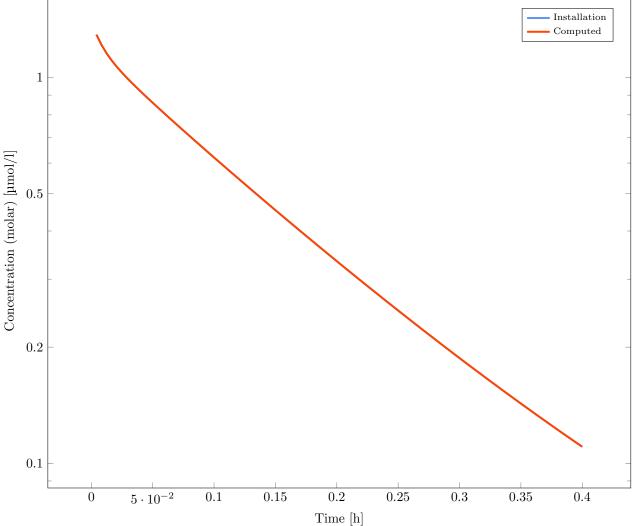


Figure 1.181

Simulation: SingleIV_2Pores_Human-SingleIV_2Pores_Human_SimulationC Result of the validation: Valid

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

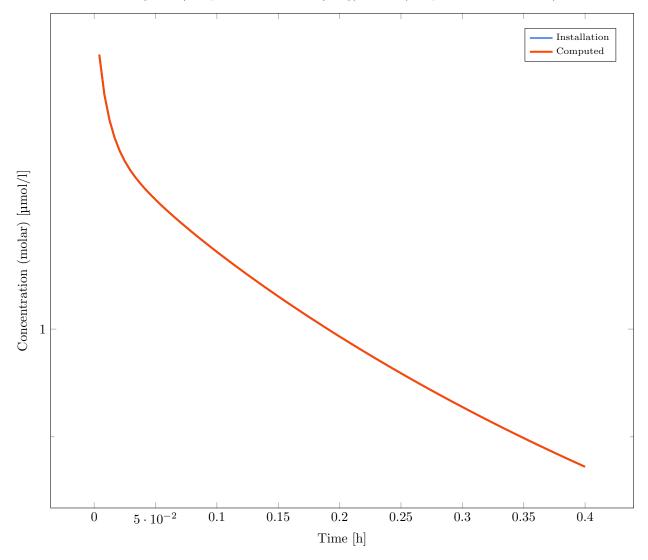


Figure 1.182

Simulation: SingleIV_2Pores_Human-SingleIV_2Pores_Human_SimulationD Result of the validation: Valid

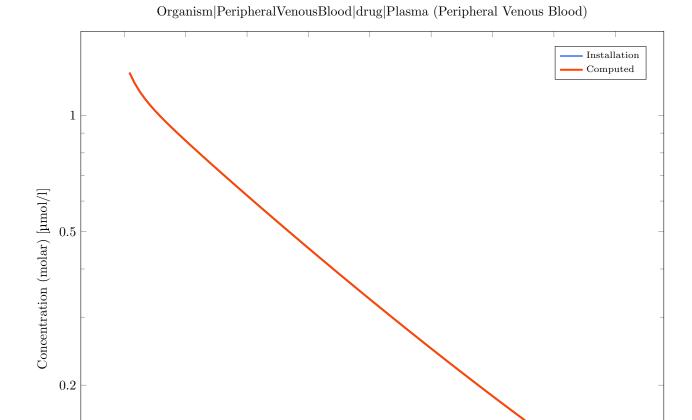


Figure 1.183

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)

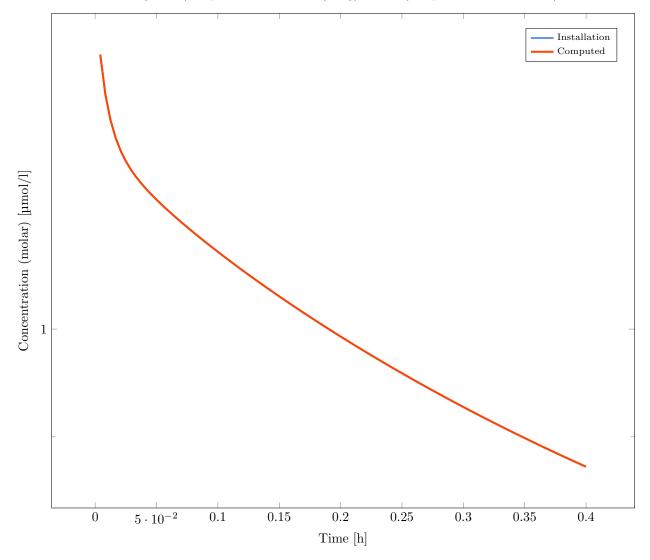


Figure 1.184

 $Simulation: Single IV_2 Pores_Monkey-Single IV_2 Pores_Monkey$

Result of the validation: Valid

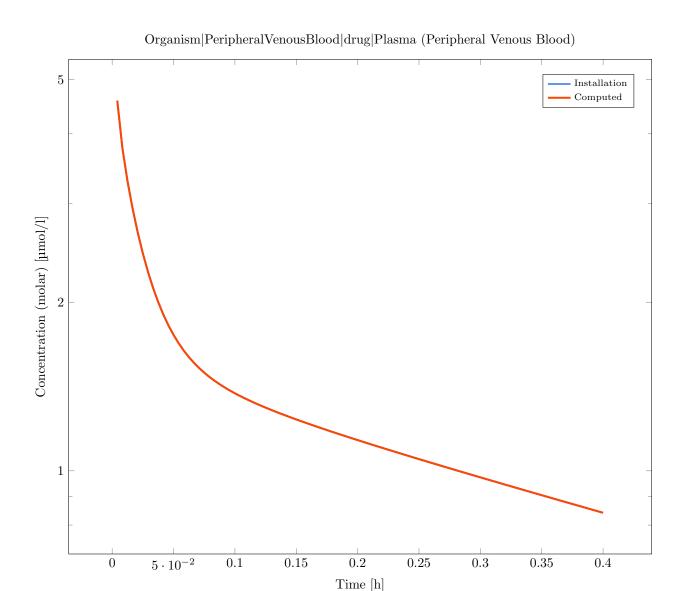


Figure 1.185

Simulation: SingleIV_2Pores_Monkey-SingleIV_2Pores_Monkey_SimulationG Result of the validation: Valid



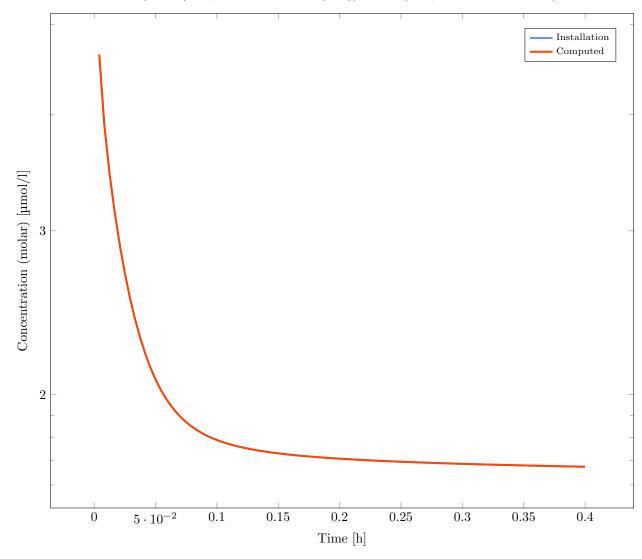


Figure 1.186

Simulation: SingleIV_2Pores_Monkey-SingleIV_2Pores_Monkey_SimulationH Result of the validation: Valid

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

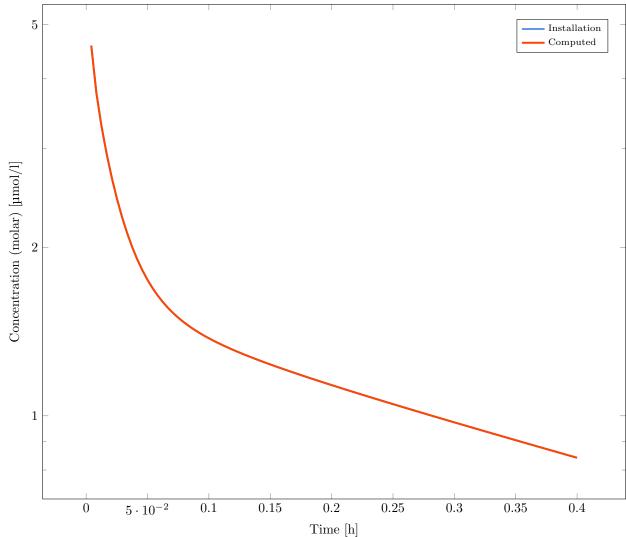


Figure 1.187

 $Simulation: Single IV_2 Pores_Mouse-Single IV_2 Pores_Mouse$

Result of the validation: Valid

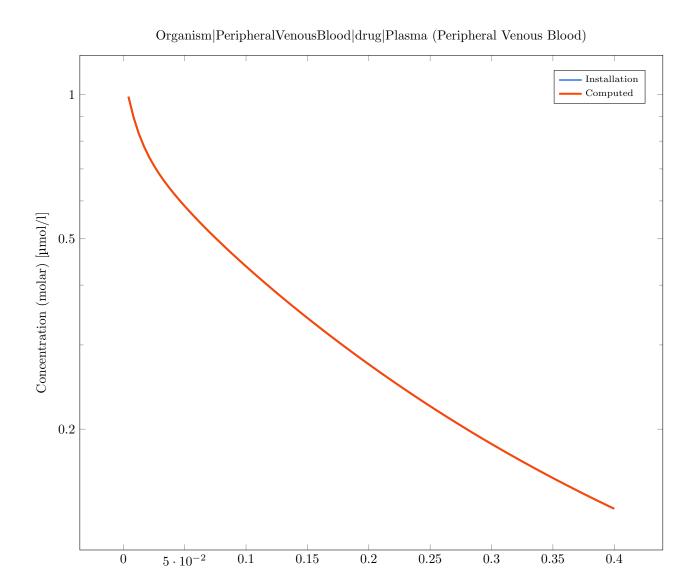


Figure 1.188

Time [h]

Simulation: SingleIV_2Pores_Mouse-SingleIV_2Pores_Mouse_SimulationA Result of the validation: Valid

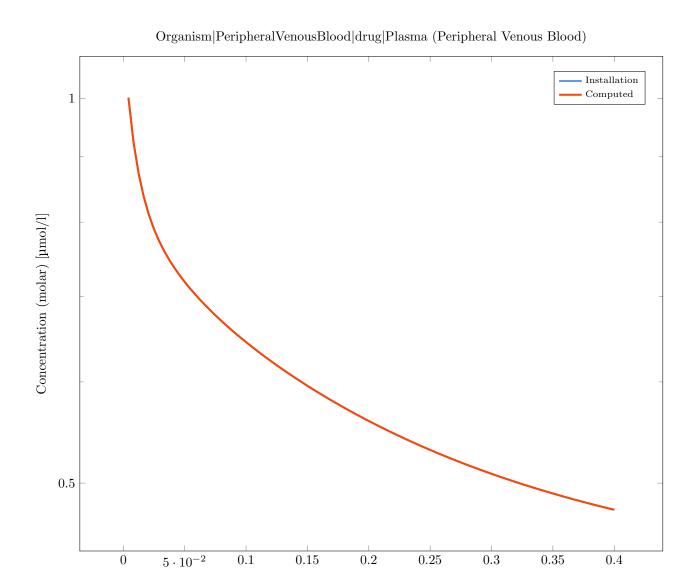


Figure 1.189

Time [h]

Simulation: SingleIV_2Pores_Mouse-SingleIV_2Pores_Mouse_SimulationB Result of the validation: Valid

Organism|PeripheralVenousBlood|drug|Plasma (Peripheral Venous Blood) Installation Computed O.5 O.2

Figure 1.190

0.2

Time [h]

0.25

0.3

0.35

0.4

0.15

Simulation: SingleIV_2Pores_Mouse-SingleIV_2Pores_Mouse_SimulationE Result of the validation: Valid

0.1

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

0

 $5\cdot 10^{-2}$

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

Figure 1.191

 $Simulation: Single IV_C1_4 Comp_standard_stand$

Time [h]

Result of the validation: Valid

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



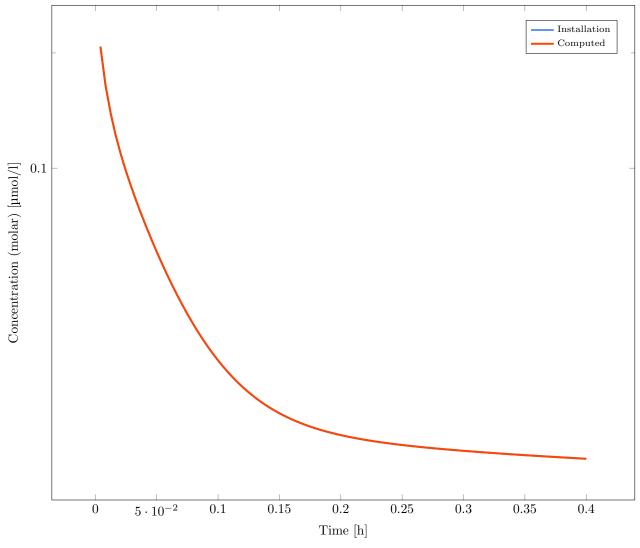


Figure 1.192

 $Simulation: Single IV_C2_4 Comp_PT_standard_st$

Organism|PeripheralVenousBlood|C2|Plasma (Peripheral Venous Blood)

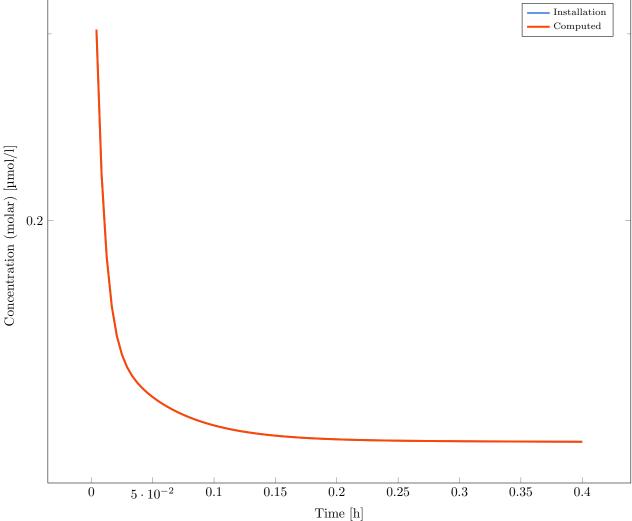


Figure 1.193

 $Simulation: Single IV_C2_4 Comp_RR_standard_st$

Output Path: Organism |Peripheral Venous
Blood |C2 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$ 1.2

Organism|PeripheralVenousBlood|C2|Plasma (Peripheral Venous Blood) — Installation — Computed

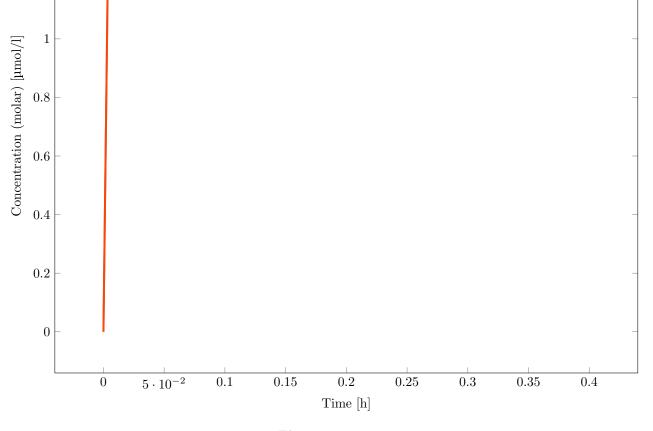


Figure 1.194

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

Result of the validation: Valid

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

Organism|PeripheralVenousBlood|C2|Plasma (Peripheral Venous Blood) Installation Computed Oorganism|Oorganism|PeripheralVenousBlood|C2|Plasma (Peripheral Venous Blood)

Figure 1.195

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: Single IV_C3_4 Comp_RR_schmitt_standard-Single IV_C3_schmitt_standard-Single IV_C3_schmitt$

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

0.15

0.1

0

 $5\cdot 10^{-2}$

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



Figure 1.196

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

Result of the validation: Valid

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

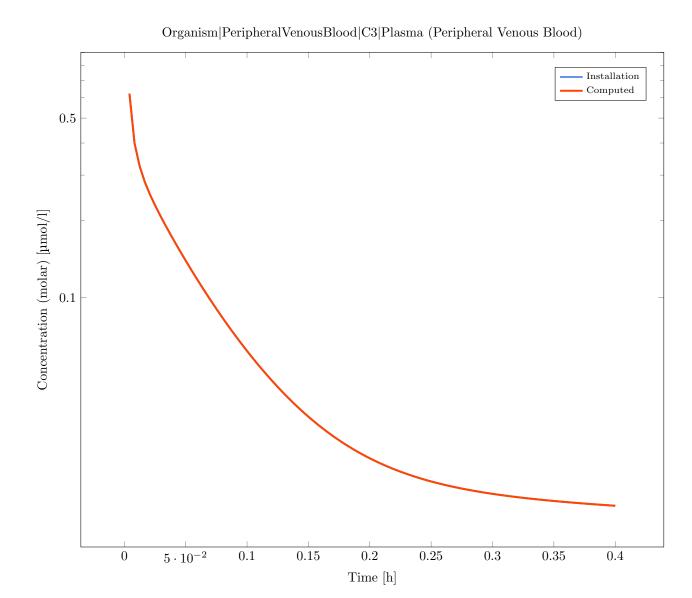


Figure 1.197

 $Simulation: Single IV_C4_2 Pores_RR_standard_s$

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

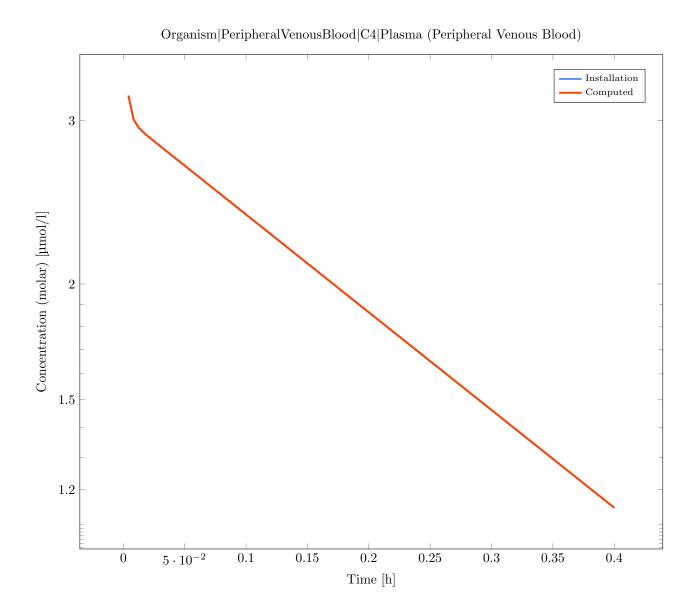


Figure 1.198

 $Simulation: Single IV_C4_4 Comp_Ber_standard_s$

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

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

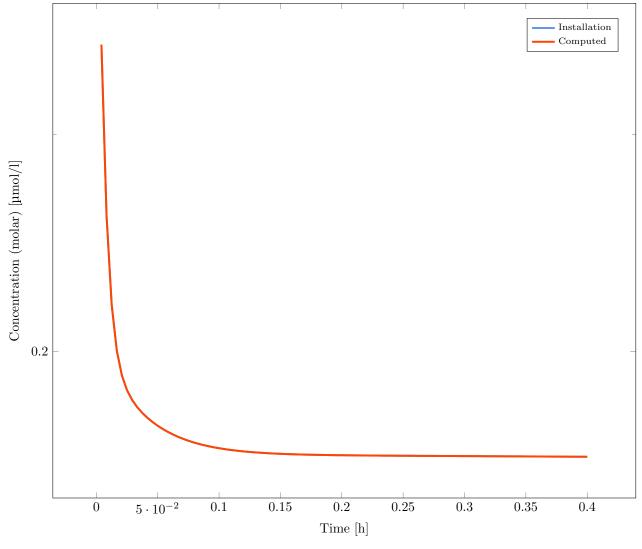
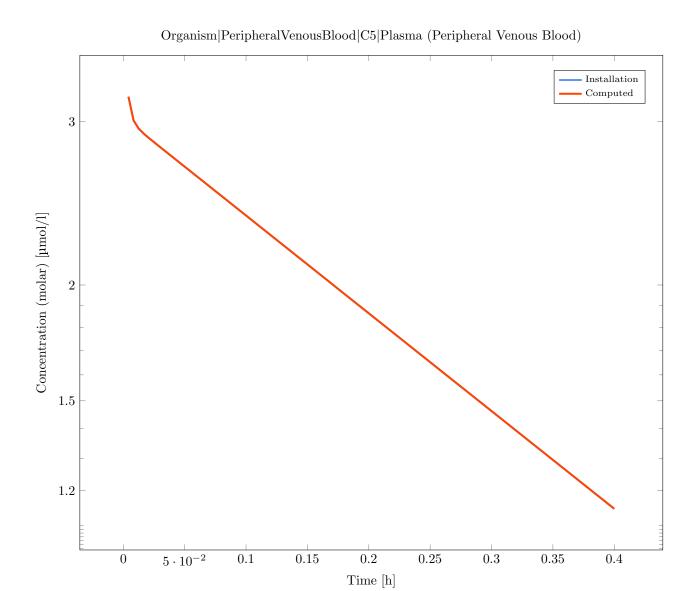


Figure 1.199

 $Simulation: Single IV_C5_2 Pores_Ber_standard_$



 $Simulation: Single IV_C5_2 Pores_PT_standard_s$

Figure 1.200

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

Result of the validation: Valid

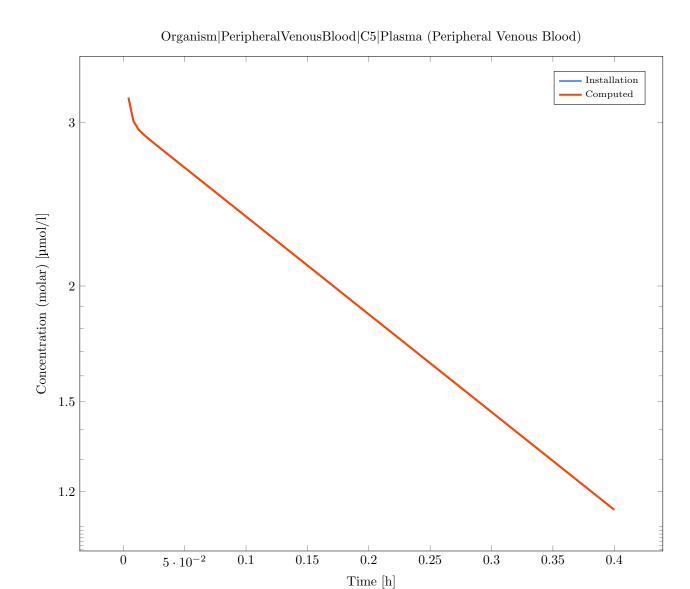


Figure 1.201

 $Simulation: SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_C5_2Pores_RR_schmitt_standard-SingleIV_schmitt$

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



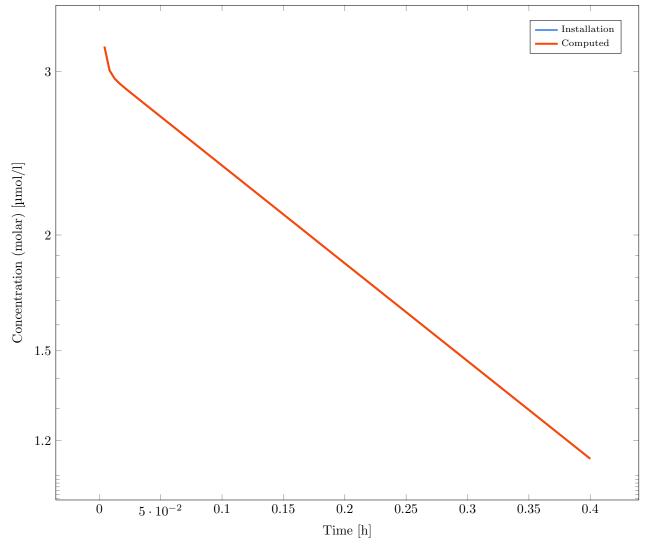


Figure 1.202

 $Simulation: Single IV_C6_2 Pores_standard_stan$

Result of the validation: Valid

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

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

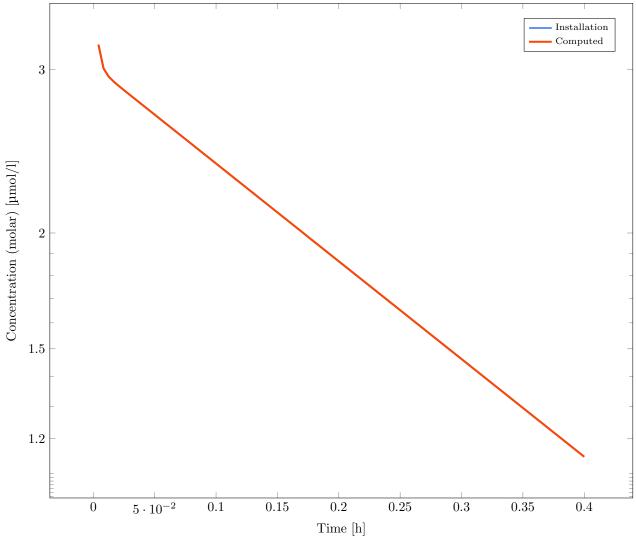


Figure 1.203

 $Simulation: Single IV_C7_2 Pores_standard_schmitt_standard_Single IV_C7_2 Pores_standard_schmitt_schmitt$

Result of the validation: Valid

 $Output\ Path:\ Organism|PeripheralVenousBlood|C7|Plasma\ (Peripheral\ Venous\ Blood)$

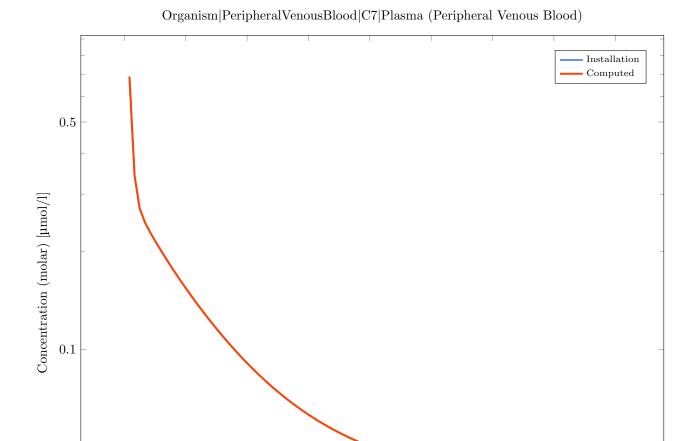


Figure 1.204

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

$Organism|Peripheral Venous Blood|C7|Plasma\ (Peripheral Venous Blood)$

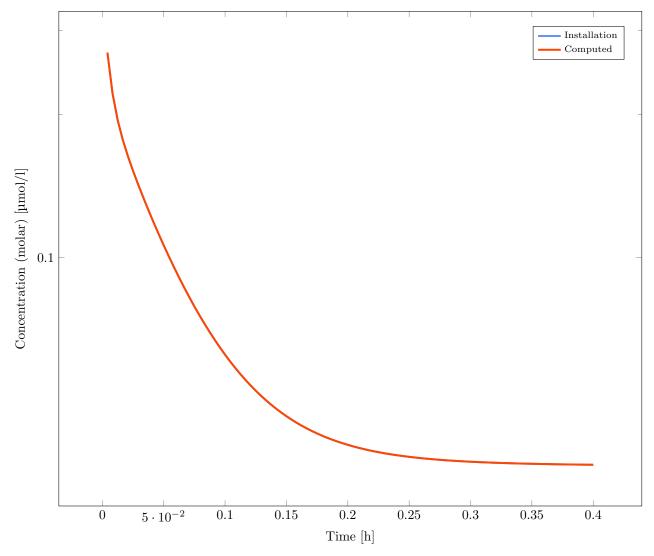
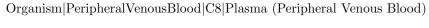


Figure 1.205

 $Simulation: Single IV_C8_2 Pores_standard_schmittnormalized_standard_Single IV_C8_2 Pores_standard_schmittnormalized_schmittnormalized_schmittnor$

Result of the validation: Valid

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



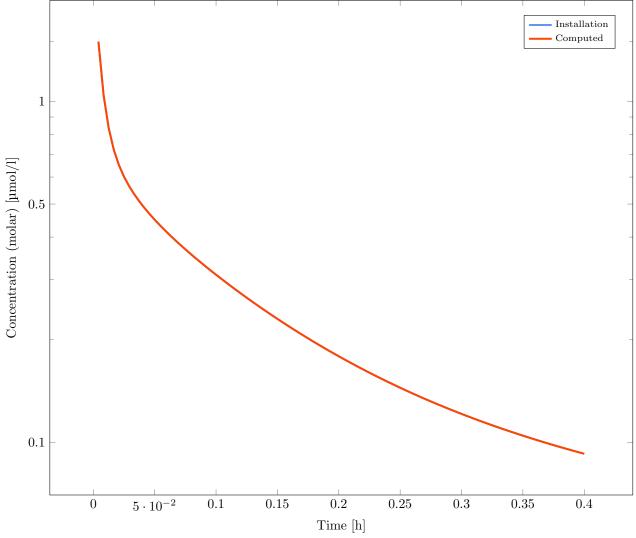


Figure 1.206

 $Simulation: Single IV_C9_2 Pores_schmitt_standard_standard_Single IV_C9_2 Pores_schmitt_standard_sta$

Result of the validation: Valid

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

Organism|PeripheralVenousBlood|C9|Plasma (Peripheral Venous Blood)

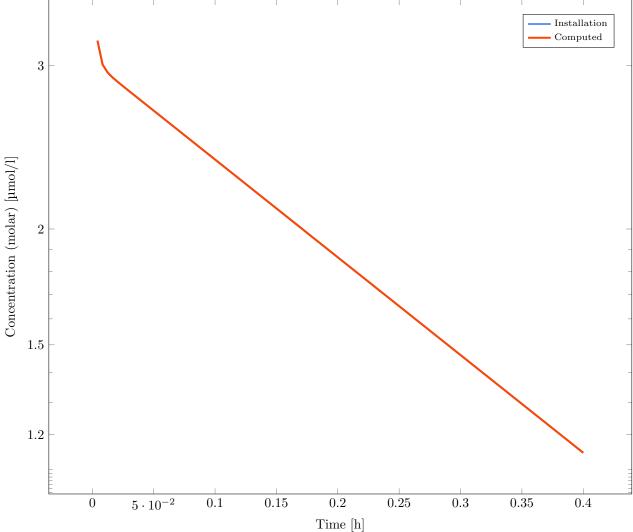


Figure 1.207

 $Simulation: Single ORAL_C10_4 Comp_PT_standard_standard_Single ORAL_C10_4 Comp_PT_standard_$

Result of the validation: Valid

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

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

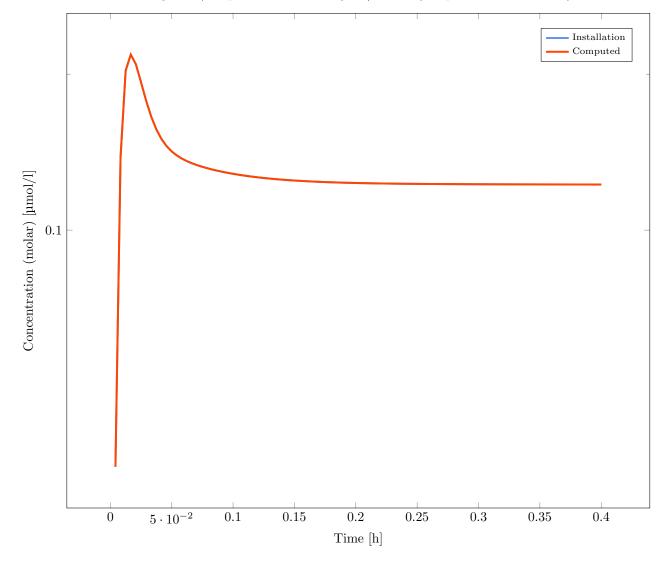


Figure 1.208

 $Simulation: Single ORAL_C11_4 Comp_schmitt_standard_standard_Single ORAL_C11_4 Comp_schmitt_standard$

Result of the validation: Valid

 $Output \ Path: \ Organism | Peripheral Venous Blood | C11 | Plasma \ (Peripheral \ Venous \ Blood)$

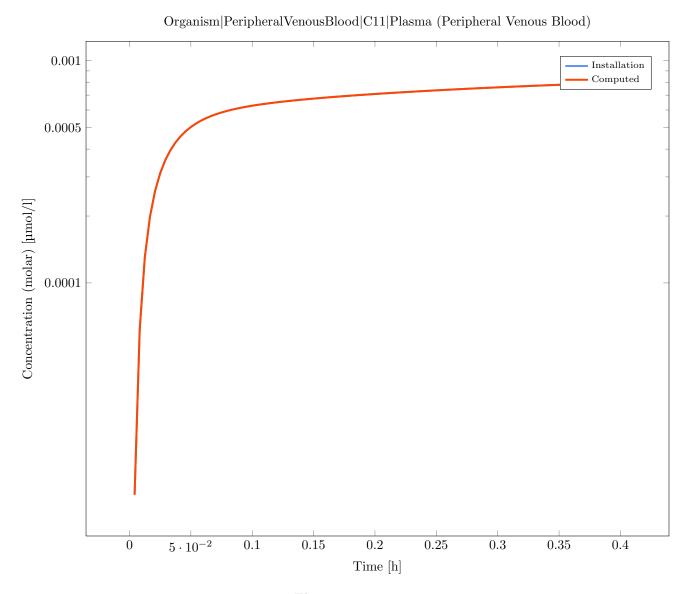


Figure 1.209

 $Simulation: Single ORAL_C11_4 Comp_standard_st$

Result of the validation: Valid

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

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

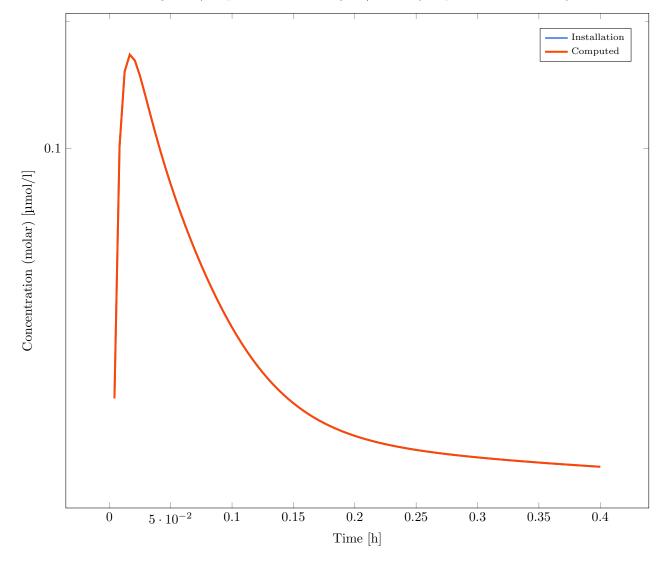


Figure 1.210

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

Result of the validation: Valid

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

Organism|PeripheralVenousBlood|C12|Plasma (Peripheral Venous Blood)

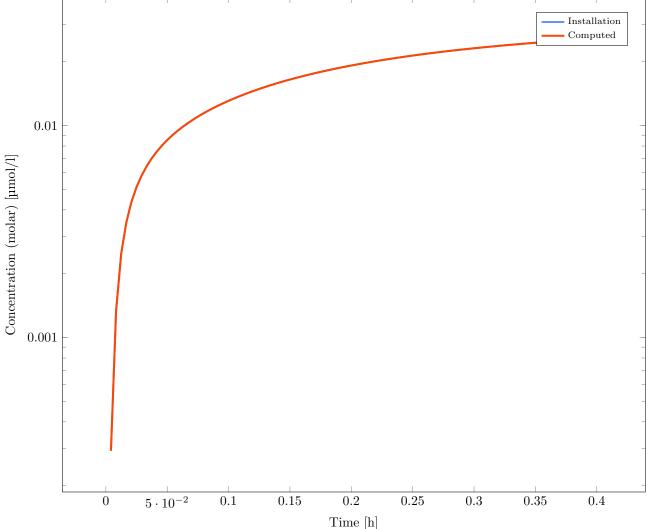
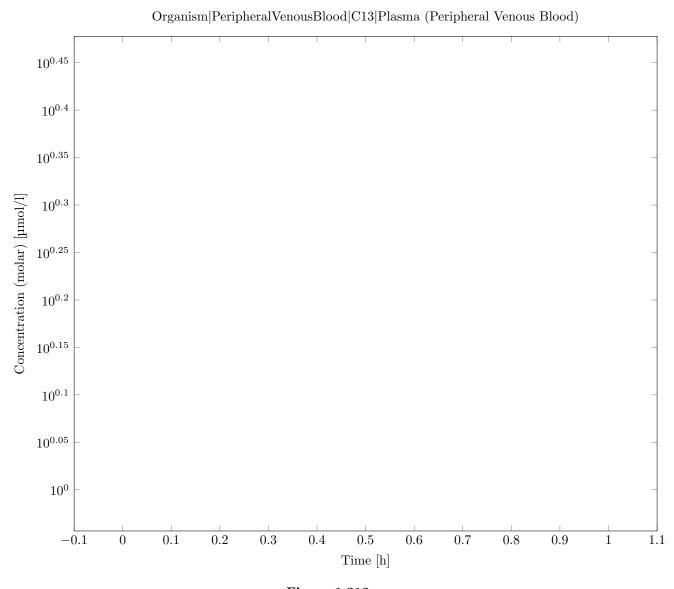


Figure 1.211

 $Simulation: Single ORAL_C13_2 Pores_schmitt_standard_st$

Result of the validation: Valid

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



 $\mathbf{Figure}\ \mathbf{1.212}$

 $Simulation: Single ORAL_C13_4 Comp_standard_schmittnormalized_schmittnormalized_sc$

Result of the validation: Valid

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

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

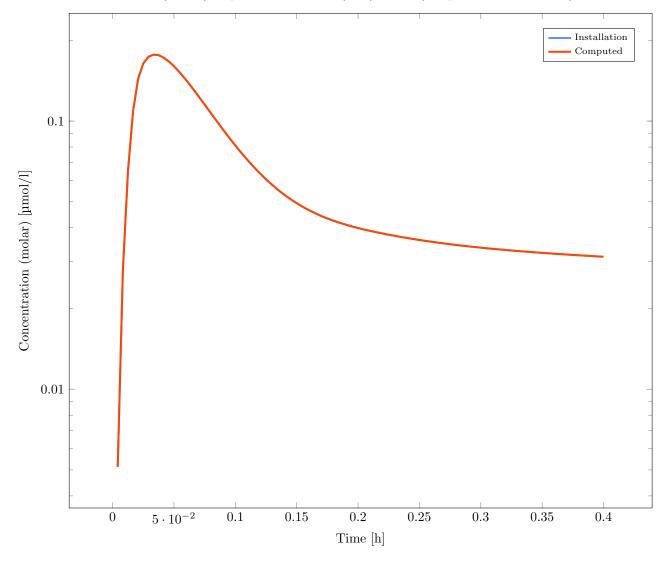


Figure 1.213

 $Simulation: Single ORAL_C14_2 Pores_PT_standard_standard_Single ORAL_C14_2 Pores_PT_standard_standar$ standard

Result of the validation: Valid

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

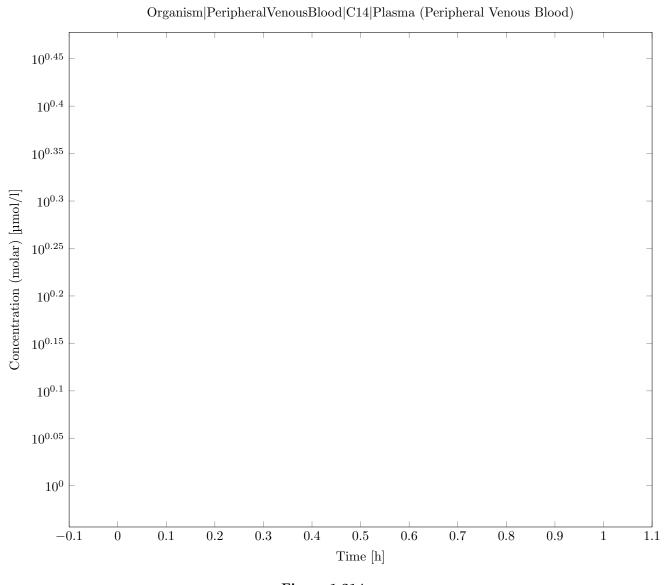
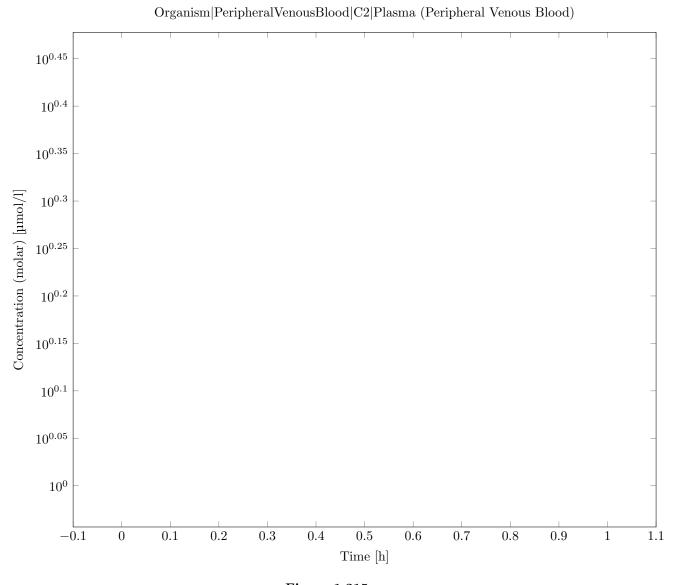


Figure 1.214

 $Simulation: Single ORAL_C2_2 Pores_standard_st$

Result of the validation: Valid

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



 ${\bf Figure~1.215}$

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

Result of the validation: Valid

Output Path: Organism |PeripheralVenousBlood |C3|Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

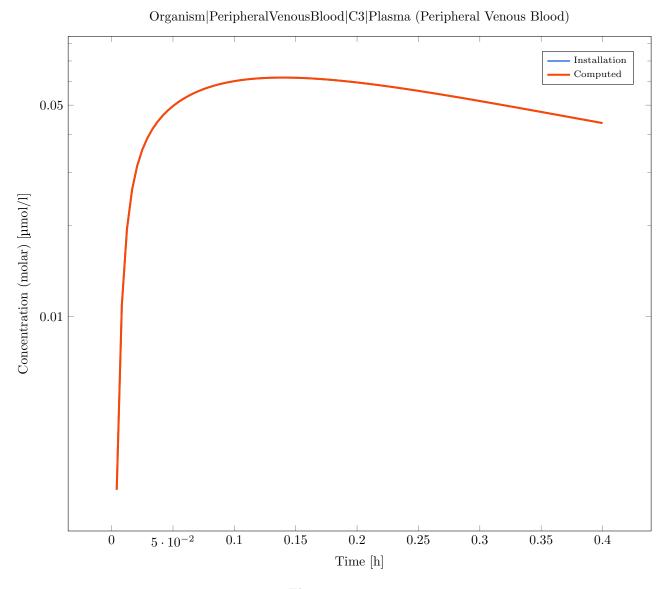


Figure 1.216

 $Simulation: Single ORAL_C4_2 Pores_standard_schmittnormalized_standard_Single ORAL_C4_2 Pores_standard_schmittnormalized_standard$

Result of the validation: Valid

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

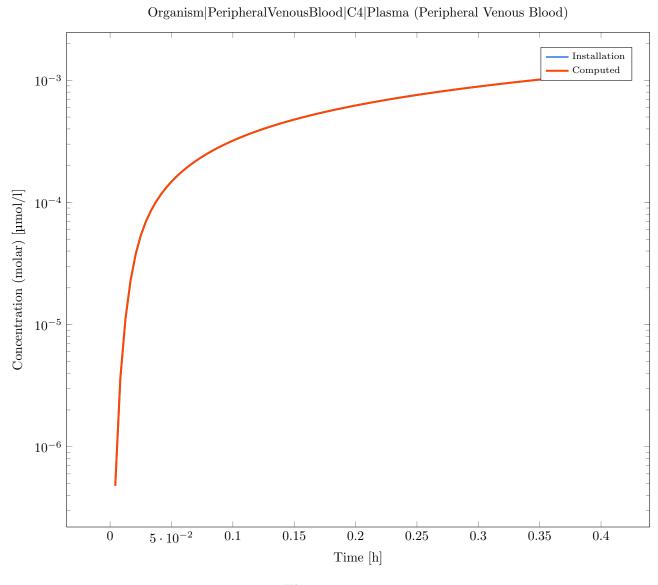


Figure 1.217

 $Simulation: Single ORAL_C6_4 Comp_Ber_standard_standard_Single ORAL_C6_4 Comp_Ber_standard_$

Result of the validation: Valid

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



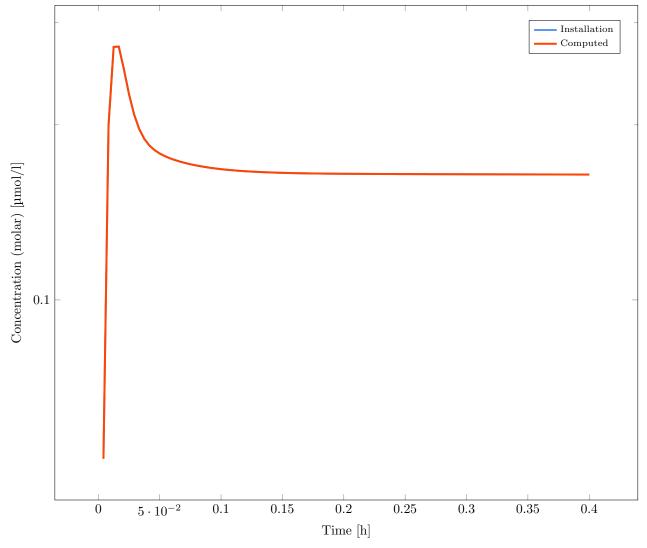


Figure 1.218

 $Simulation: Single ORAL_C6_4 Comp_RR_standard_standard_Single ORAL_C6_4 Comp_RR_standard_st$

Result of the validation: Valid

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

Organism|PeripheralVenousBlood|C6|Plasma (Peripheral Venous Blood) Installation Computed 0.05Concentration (molar) [µmol/1] 0.01

Figure 1.219

0.2

Time [h]

0.25

0.3

0.35

0.4

 $Simulation: Single ORAL_C7_2 Pores_Ber_standard_standard_Single ORAL_C7_2 Pores_Ber_standard_standar$ standard

Result of the validation: Valid

0

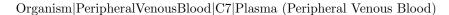
 $5\cdot 10^{-2}$

0.1

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

0.15

Deviation: 0



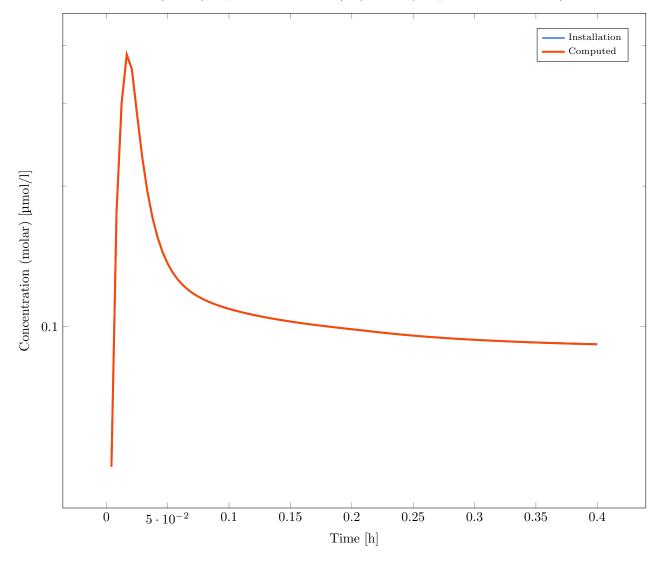


Figure 1.220

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

Result of the validation: Valid

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

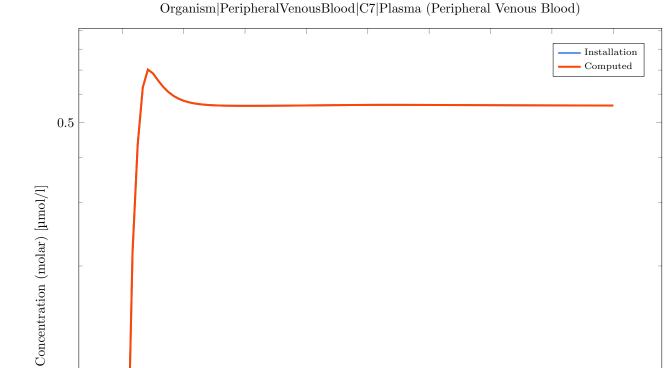


Figure 1.221

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

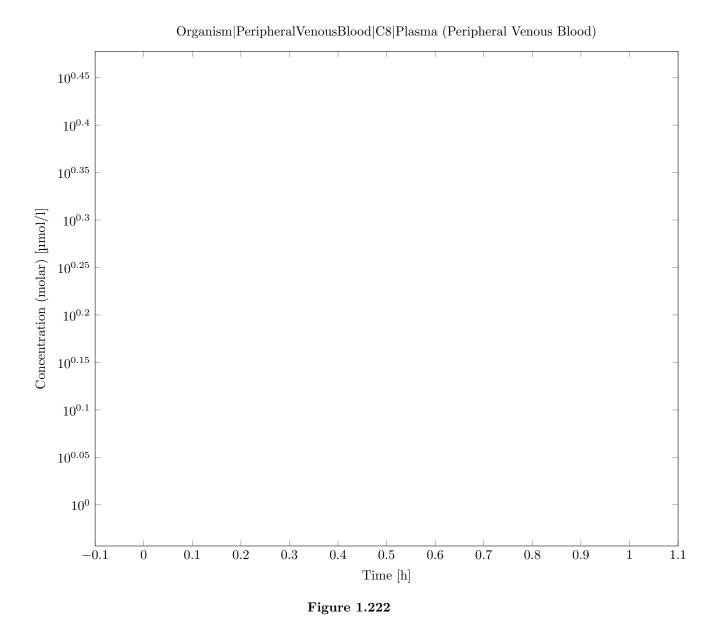
 $5\cdot 10^{-2}$

0.1

Output Path: Organism |Peripheral Venous
Blood |C8 |Plasma (Peripheral Venous Blood) Deviation:
 0

0.15

0.1



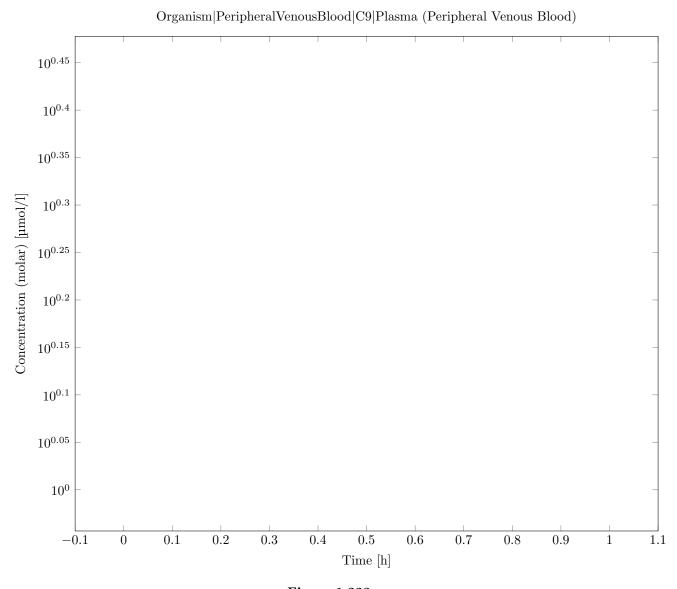
 $Simulation: Single ORAL_C9_2 Pores_RR_schmitt_standard-Single ORAL_S Pores_S Pore$

Result of the validation: Valid

standard

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

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 ${\bf Figure~1.223}$

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

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

Deviation: 0

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

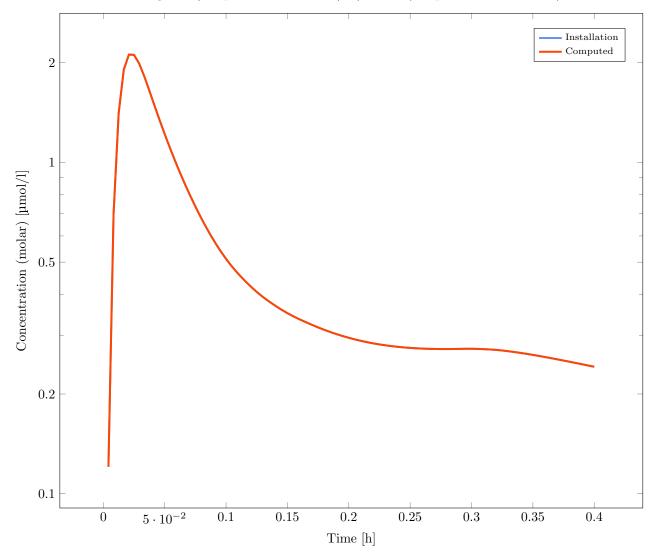
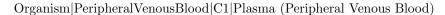


Figure 1.224

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: ${\bf 0}$



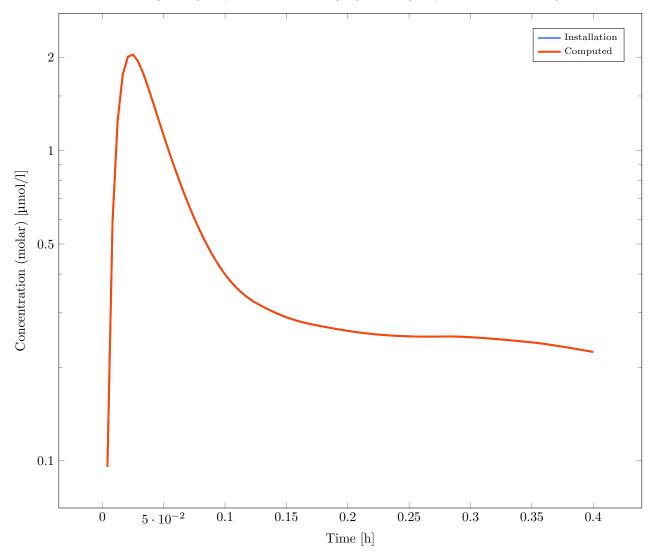


Figure 1.225

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) Deviation:
 0

Deviation. 0

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

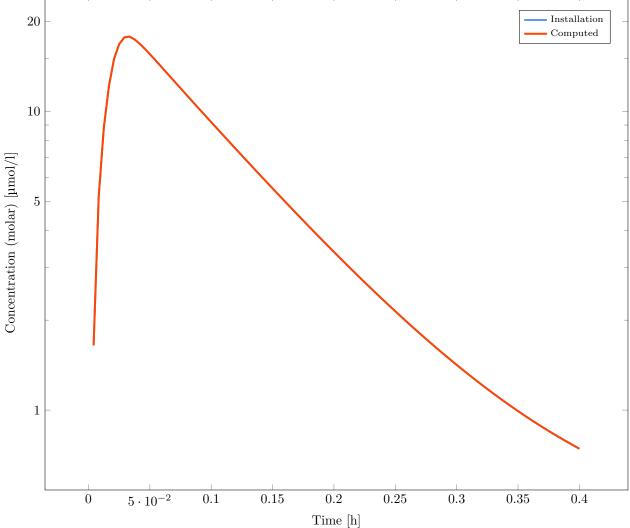


Figure 1.226

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

Output Path: Organism |Peripheral Venous
Blood |C3 |Plasma (Peripheral Venous Blood)
 Deviation: ${\bf 0}$

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

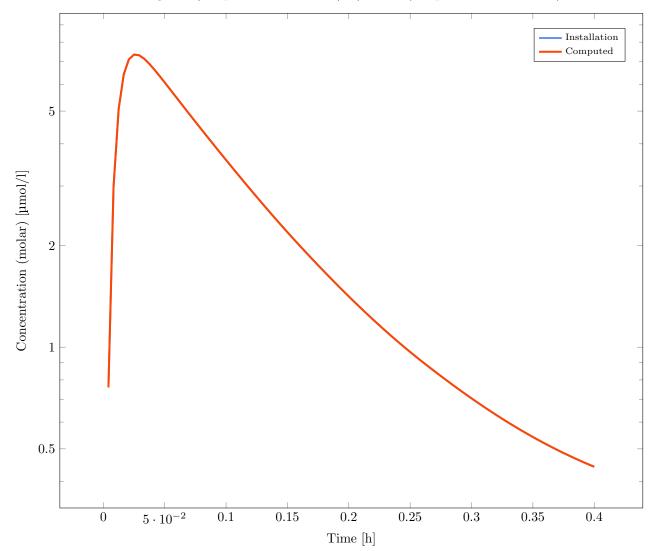


Figure 1.227