Physiologically Based Pharmacokinetic Models

PSCI-518, Spring 2024

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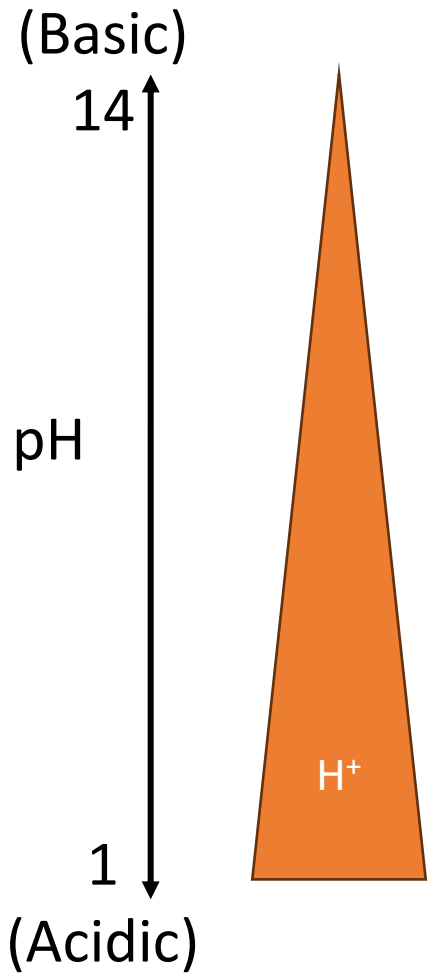
pKa Review



Acidic Group

Deprotonated | Protonated

Negative | Neutral

pKa

$^{-}O—$ / $HO—$

$^{-}O—$ / $HO—$

$^{-}O—$ / $HO—$

Basic Group

Deprotonated | Protonated

Neutral | Positive

pKa

$H_3N—$ / $^{+}H_4N—$

$H_3N—$ / $^{+}H_4N—$

$H_3N—$ / $^{+}H_4N—$

Physiologically Based Pharmacokinetic Models:

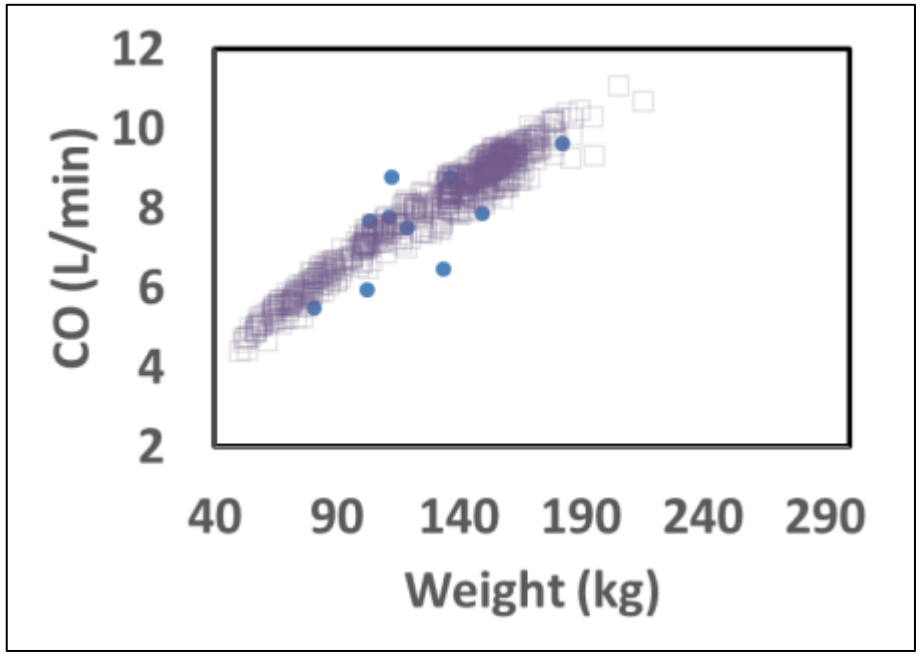
Two Components:

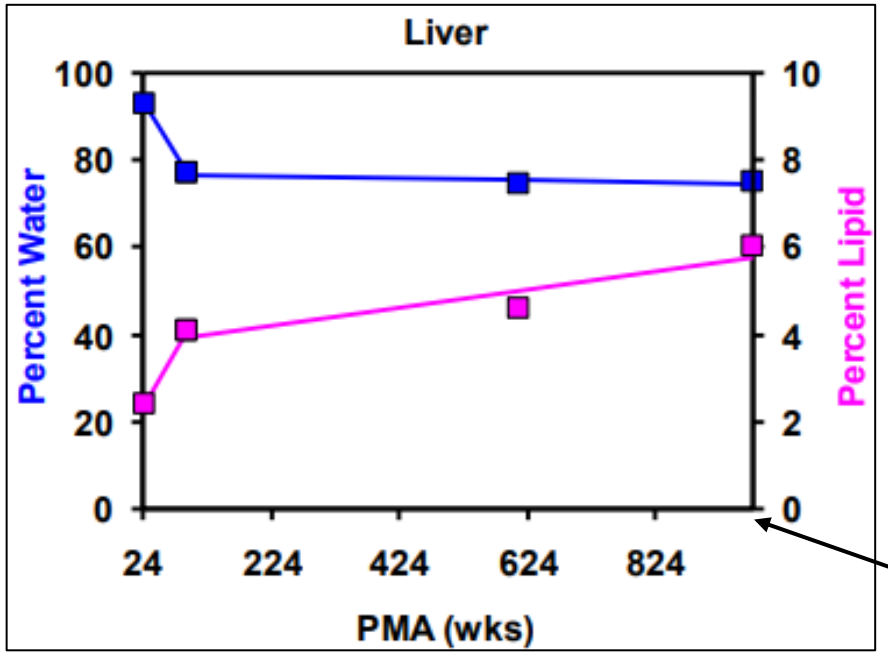
- Physiology
  - Detailed setup of the body tissues, each with individual size, composition, protein expression, and blood flow
- Pharmacokinetics
  - How each of those tissues interacts with the drug, based on both tissue and drug properties

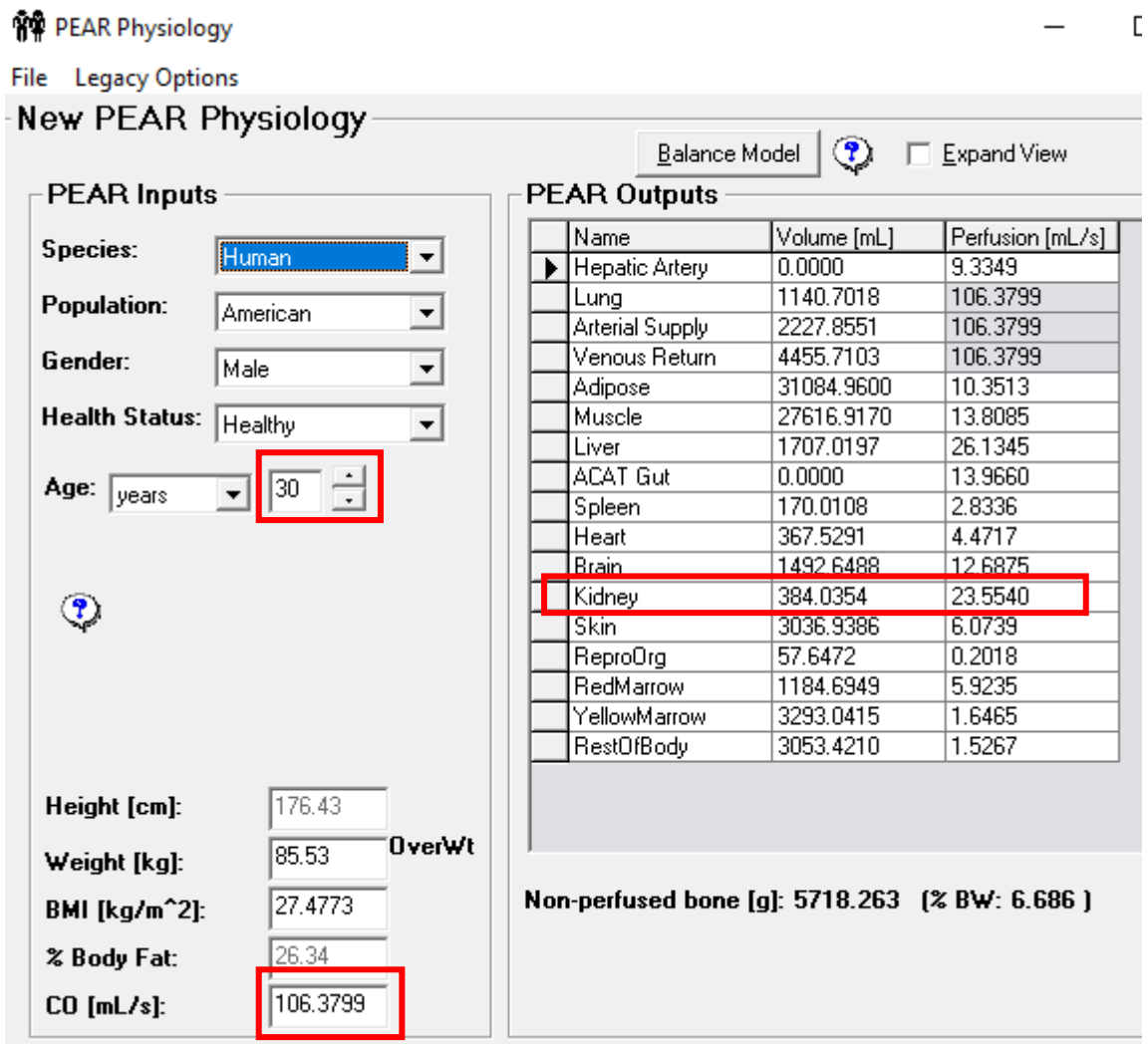
Physiologies in GastroPlus

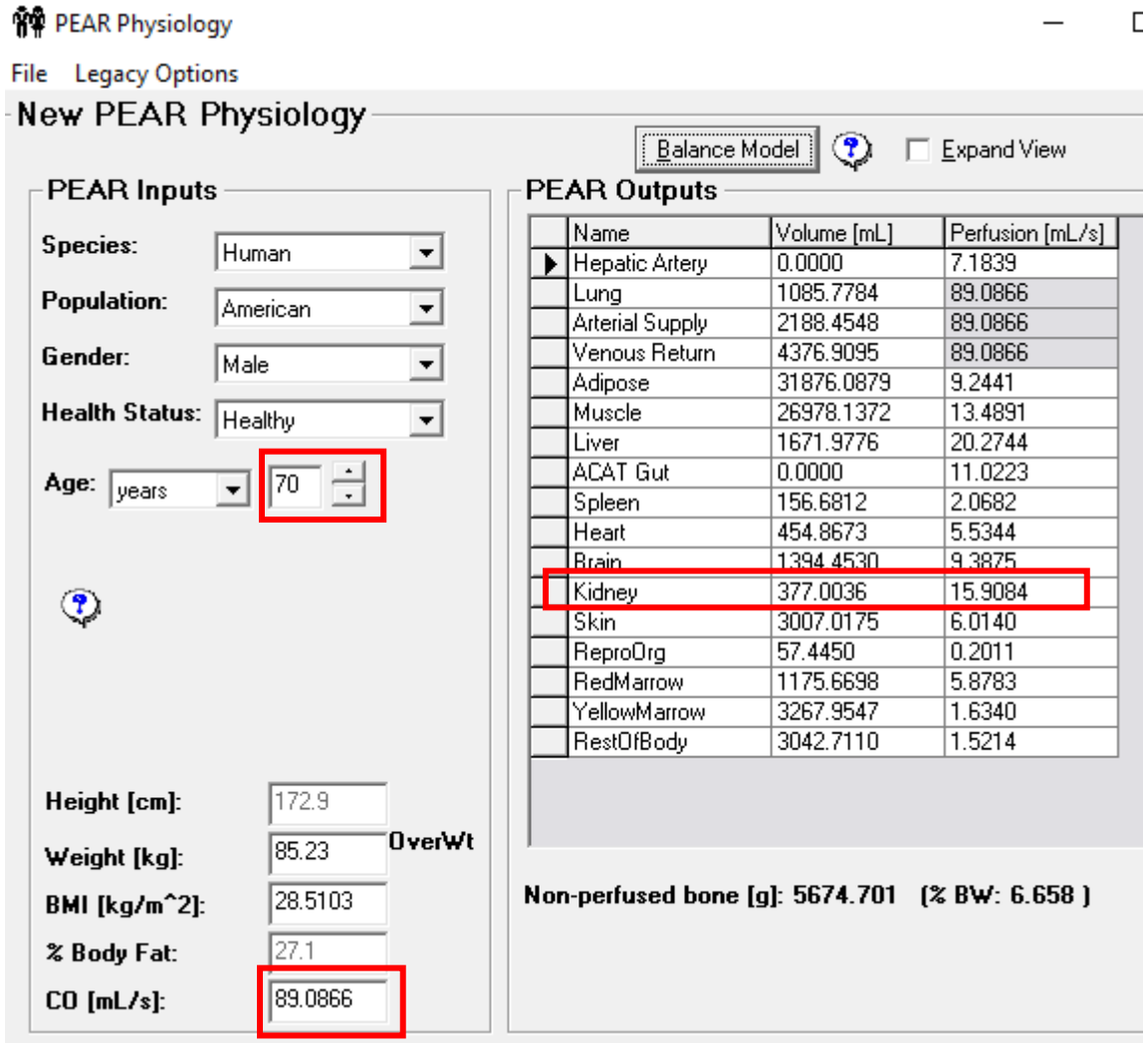
PEAR = Population Estimates for Age-Related Physiology

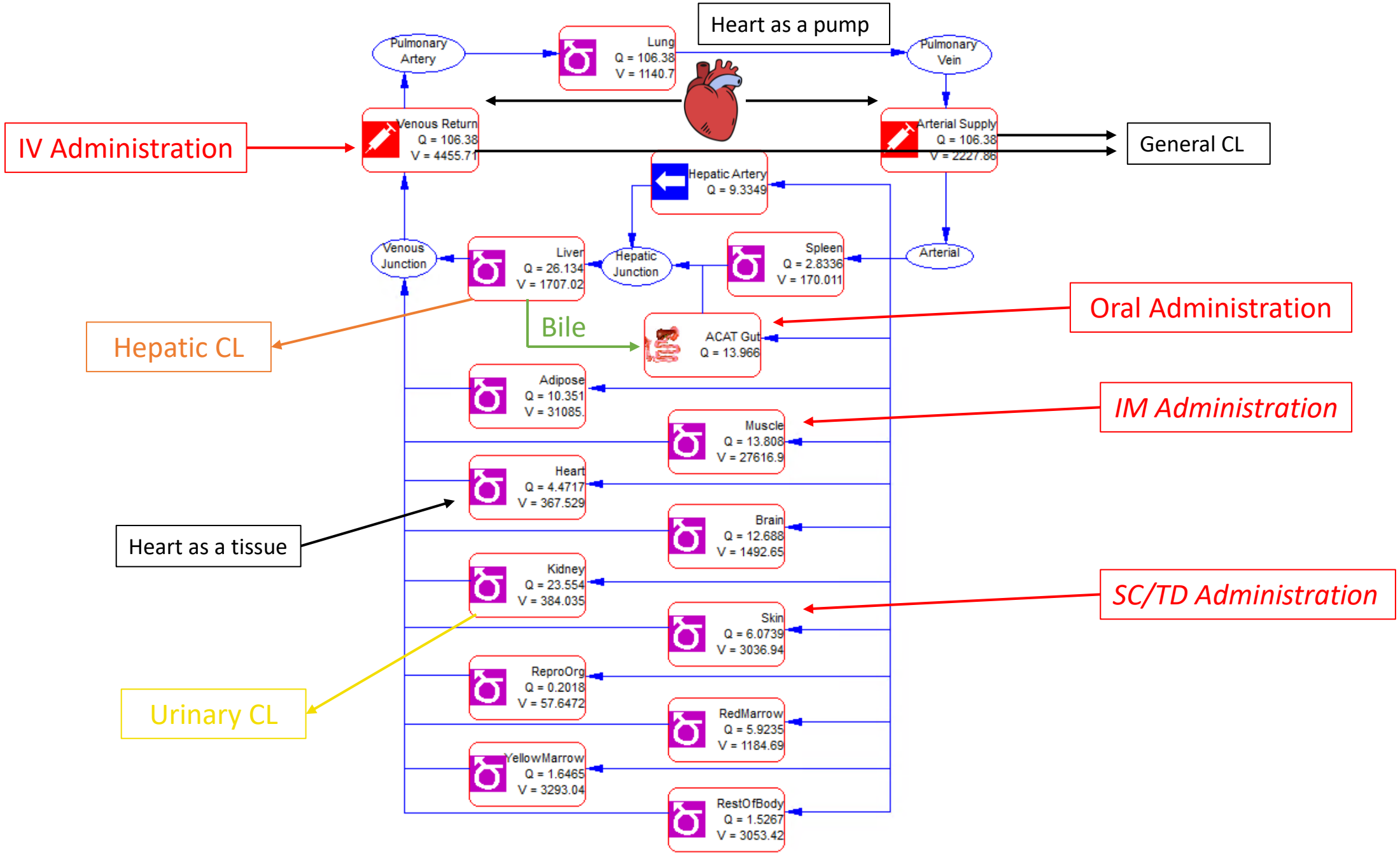
- Tissue size and composition based on age, sex, weight, BMI, and ethnicity
- Whole body parameters include cardiac output, body fat %, and health status

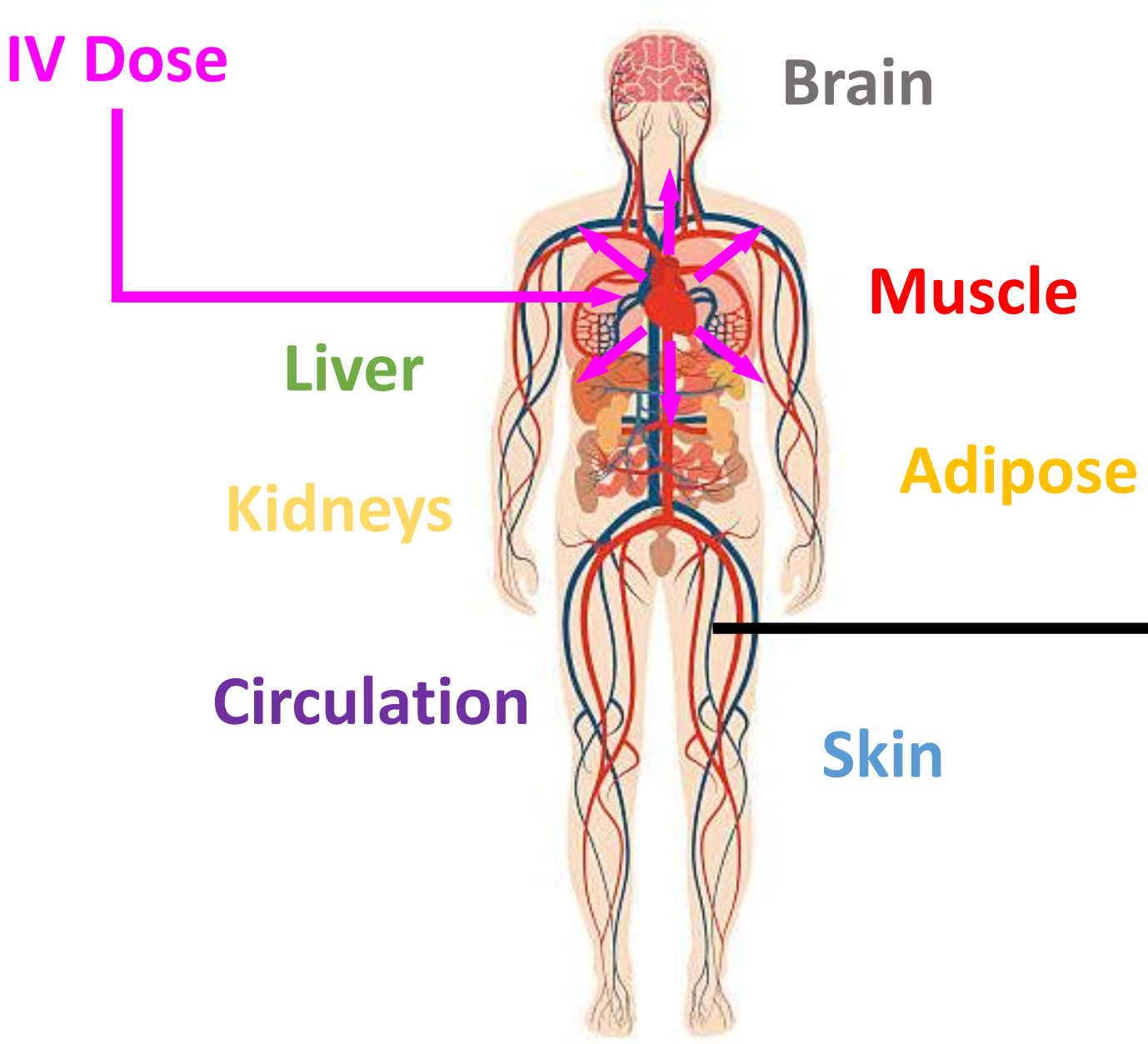





PEAR Physiology
File
Legacy Options
New PEAR Physiology
Balance Model
Expand View
PEAR Inputs
Species: Human
Population: American
Gender: Male
Health Status: Healthy
Age: years 30
Height [cm]: 176.43
Weight [kg]: 85.53 OverWt
BMI [kg/m^2]: 27.4773
% Body Fat: 26.34
CO [mL/s]: 106.3799
PEAR Outputs
Name | Volume [mL] | Perfusion [mL/s]
Hepatic Artery | 0.0000 | 9.3349
Lung | 1140.7018 | 106.3799
Arterial Supply | 2227.8551 | 106.3799
Venous Return | 4455.7103 | 106.3799
Adipose | 31084.9600 | 10.3513
Muscle | 27616.9170 | 13.8085
Liver | 1707.0197 | 26.1345
ACAT Gut | 0.0000 | 13.9660
Spleen | 170.0108 | 2.8336
Heart | 367.5291 | 4.4717
Brain | 1492.6488 | 12.6875
Kidney | 384.0354 | 23.5540
Skin | 3036.9386 | 6.0739
ReproOrg | 57.6472 | 0.2018
RedMarrow | 1184.6949 | 5.9235
YellowMarrow | 3293.0415 | 1.6465
RestOfBody | 3053.4210 | 1.5267
Non-perfused bone [g]: 5718.263 (% BW: 6.686)


PEAR Physiology
File
Legacy Options
New PEAR Physiology
Balance Model
Expand View
PEAR Inputs
Species: Human
Population: American
Gender: Male
Health Status: Healthy
Age: years 70
Height [cm]: 172.9
Weight [kg]: 85.23 OverWt
BMI [kg/m^2]: 28.5103
% Body Fat: 27.1
CO [mL/s]: 89.0866
PEAR Outputs
Name | Volume [mL] | Perfusion [mL/s]
Hepatic Artery | 0.0000 | 7.1839
Lung | 1085.7784 | 89.0866
Arterial Supply | 2188.4548 | 89.0866
Venous Return | 4376.9095 | 89.0866
Adipose | 31876.0879 | 9.2441
Muscle | 26978.1372 | 13.4891
Liver | 1671.9776 | 20.2744
ACAT Gut | 0.0000 | 11.0223
Spleen | 156.6812 | 2.0682
Heart | 454.8673 | 5.5344
Brain | 1394.4530 | 9.3875
Kidney | 377.0036 | 15.9084
Skin | 3007.0175 | 6.0140
ReproOrg | 57.4450 | 0.2011
RedMarrow | 1175.6698 | 5.8783
YellowMarrow | 3267.9547 | 1.6340
RestOfBody | 3042.7110 | 1.5214
Non-perfused bone [g]: 5674.701 (% BW: 6.658)

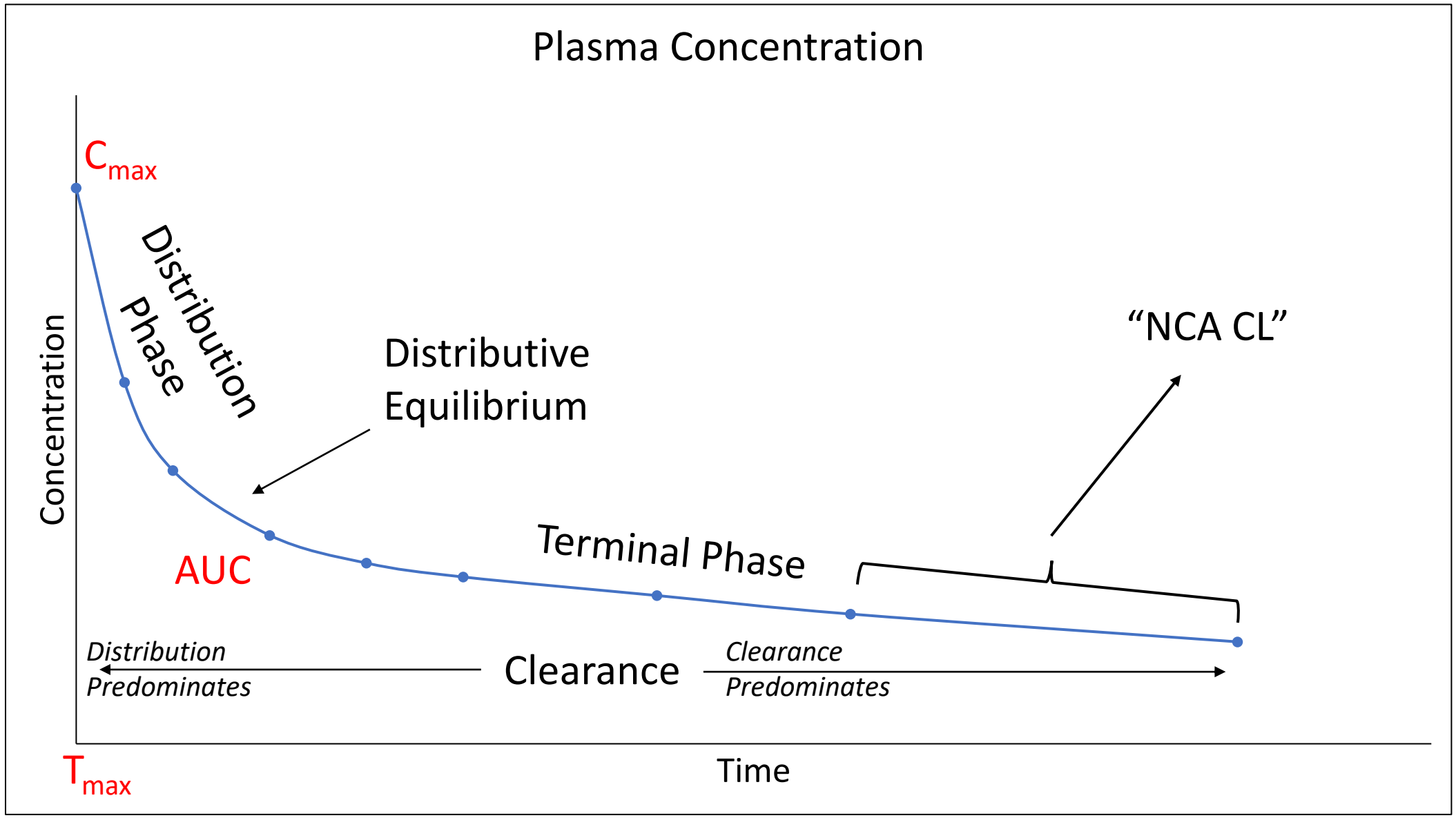

Heart as a pump
Pulmonary Artery
Lung
Q = 106.38
V = 1140.7
Pulmonary Vein
IV Administration
Venous Return
Q = 106.38
V = 4455.71
Arterial Supply
Q = 106.38
V = 2227.86
General CL
Hepatic Artery
Q = 9.3349
Venous Junction
Liver
Q = 26.134
V = 1707.02
Hepatic Junction
Spleen
Q = 2.8336
V = 170.011
Arterial
Oral Administration
Hepatic CL
Bile
ACAT Gut
Q = 13.966
Adipose
Q = 10.351
V = 31085.
IM Administration
Muscle
Q = 13.808
V = 27616.9
Heart
Q = 4.4717
V = 367.529
Heart as a tissue
Brain
Q = 12.688
V = 1492.65
Kidney
Q = 23.554
V = 384.035
SC/TD Administration
Skin
Q = 6.0739
V = 3036.94
ReproOrg
Q = 0.2018
V = 57.6472
Urinary CL
RedMarrow
Q = 5.9235
V = 1184.69
YellowMarrow
Q = 1.6465
V = 3293.04
RestOfBody
Q = 1.5267
V = 3053.42



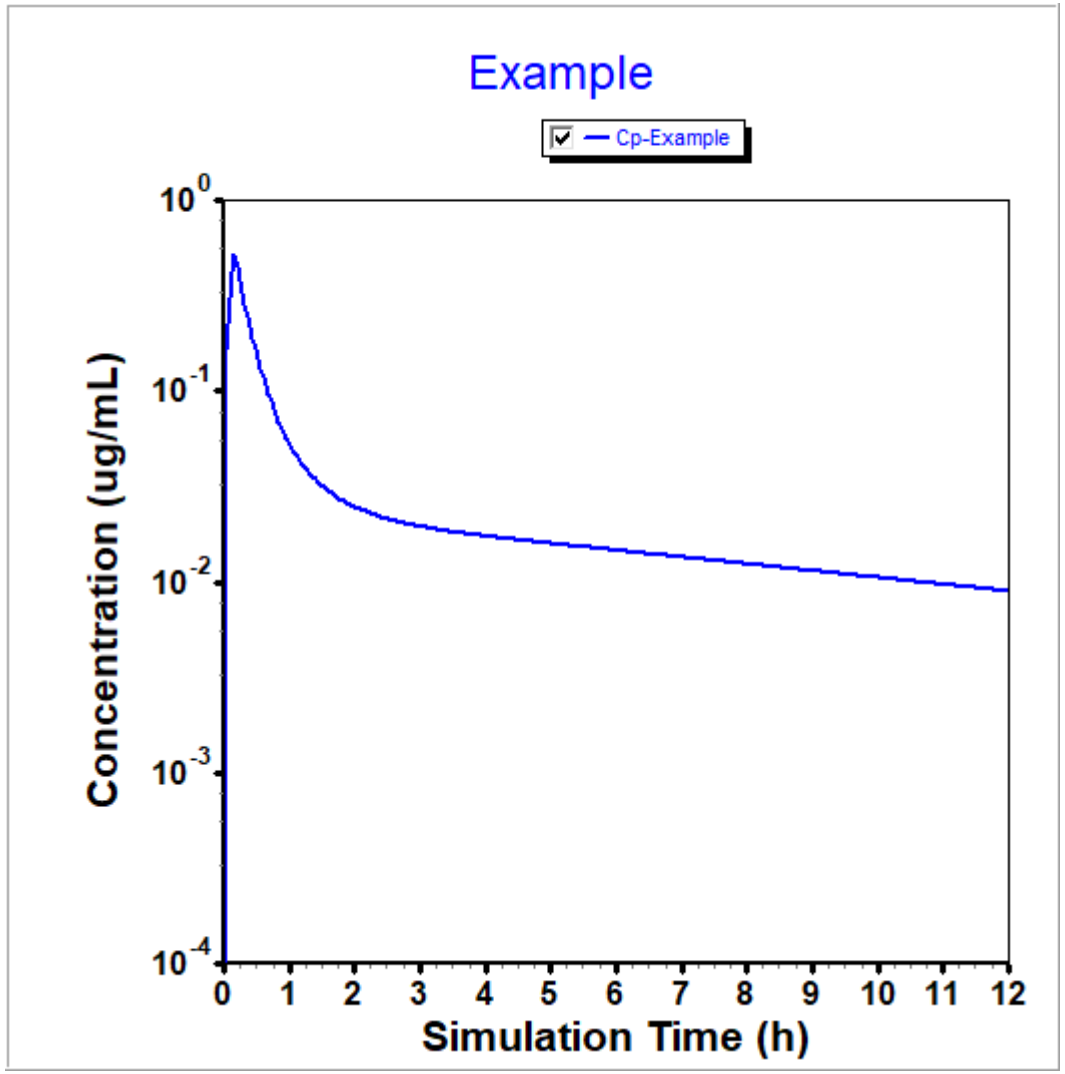
$$Kp = \frac{[Tissue]}{[Plasma]}$$

Kps define equilibrium concentrations between plasma and tissue, each tissue will have its own Kp for each drug

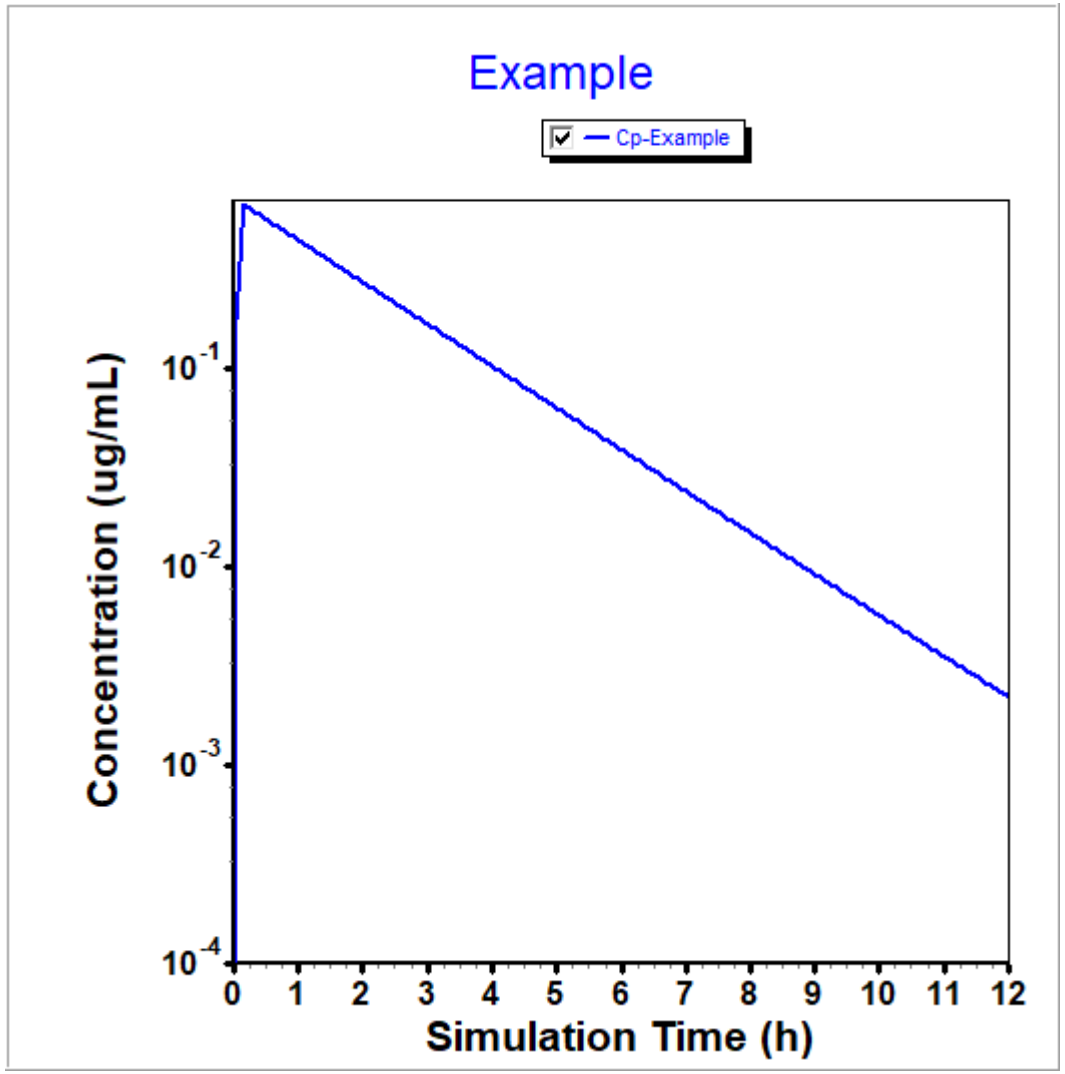
Having a fixed, known CL from observed data will allow us to focus on modeling distribution (solve for one variable at a time)


Plasma Concentration
C_{max}
Distribution Phase
Distributive Equilibrium
"NCA CL"
Concentration
AUC
Terminal Phase
Distribution Predominates
Clearance
Clearance Predominates
T_{max}
Time

100 mg IV / 10 min

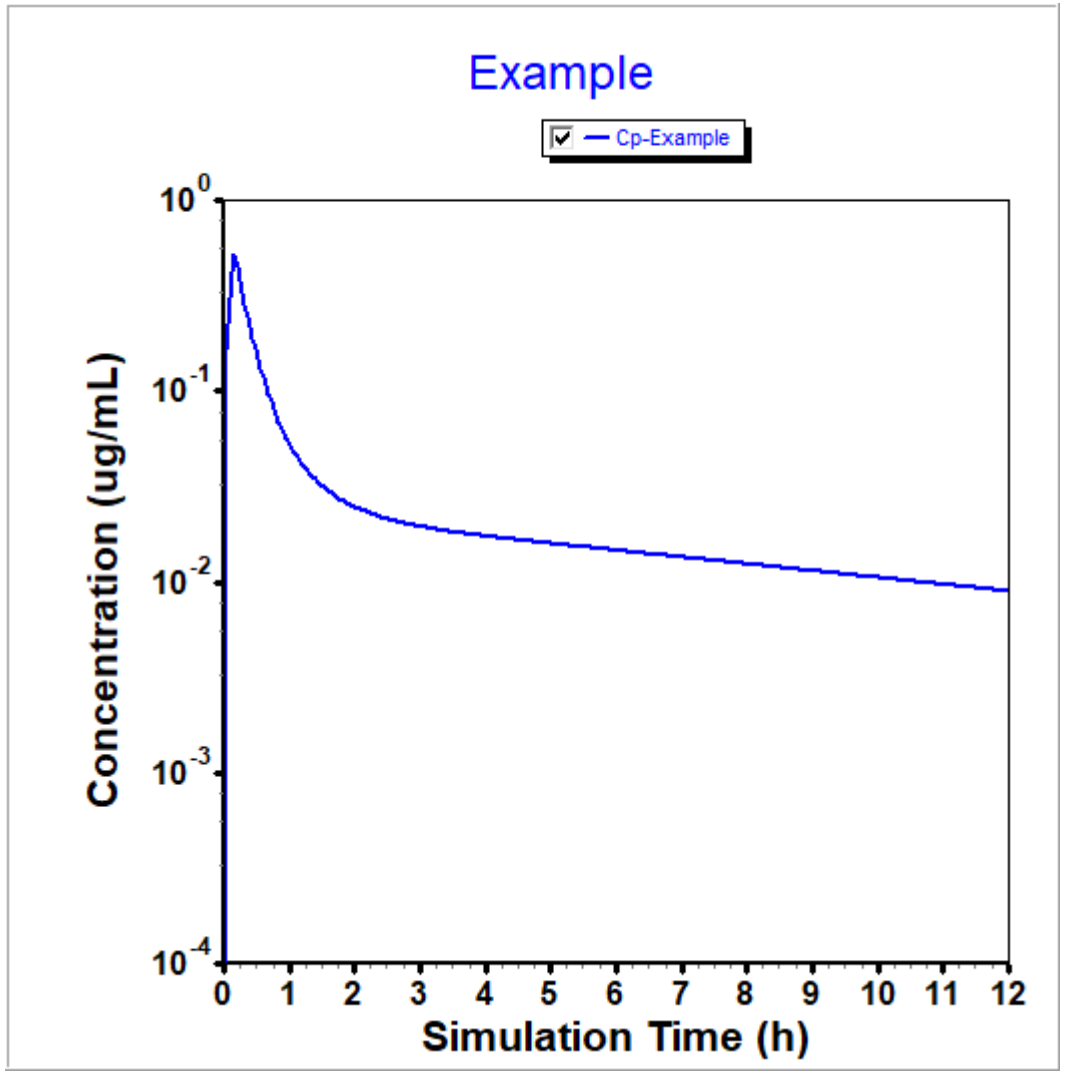


Distribution > CL



CL > Distribution

100 mg IV / 10 min



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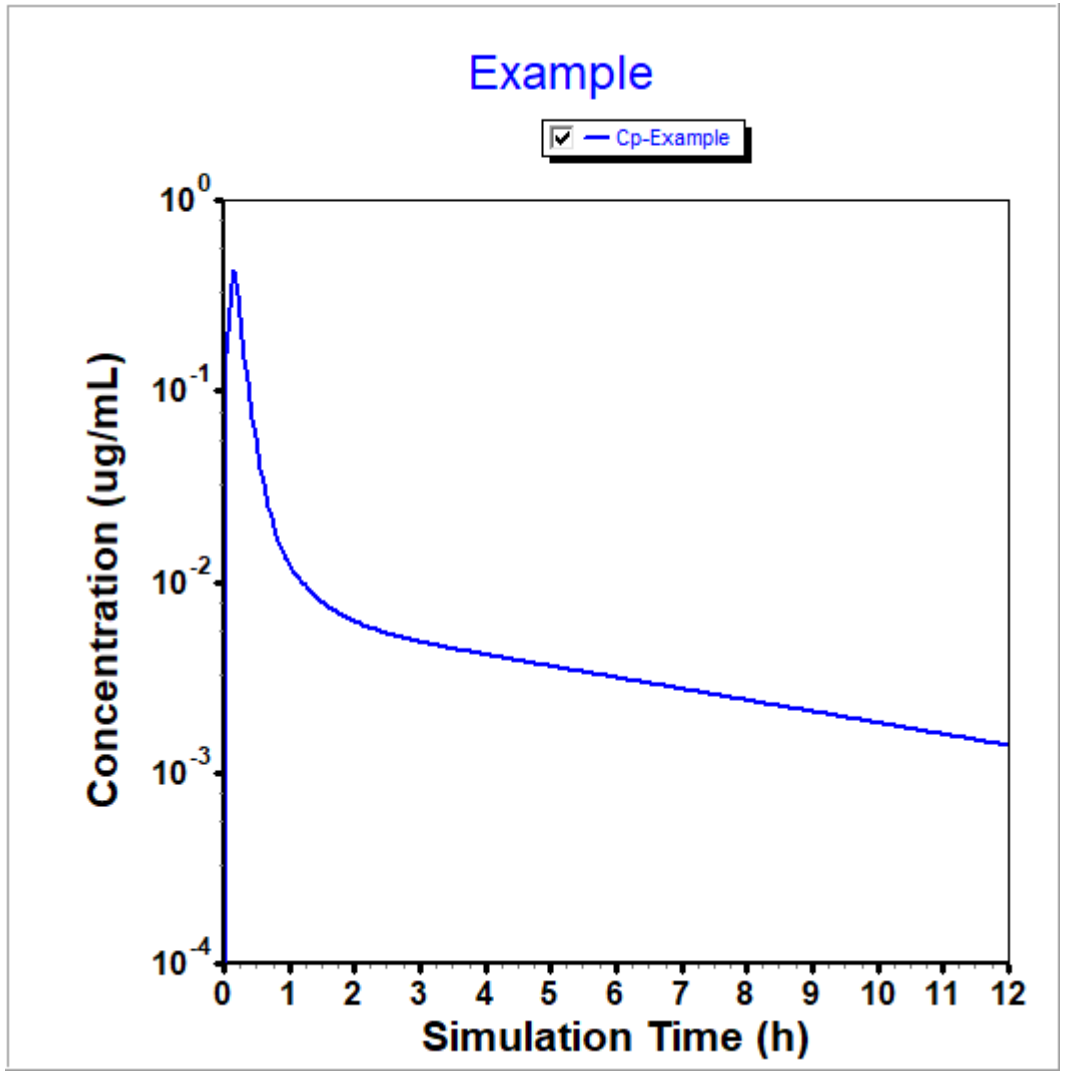
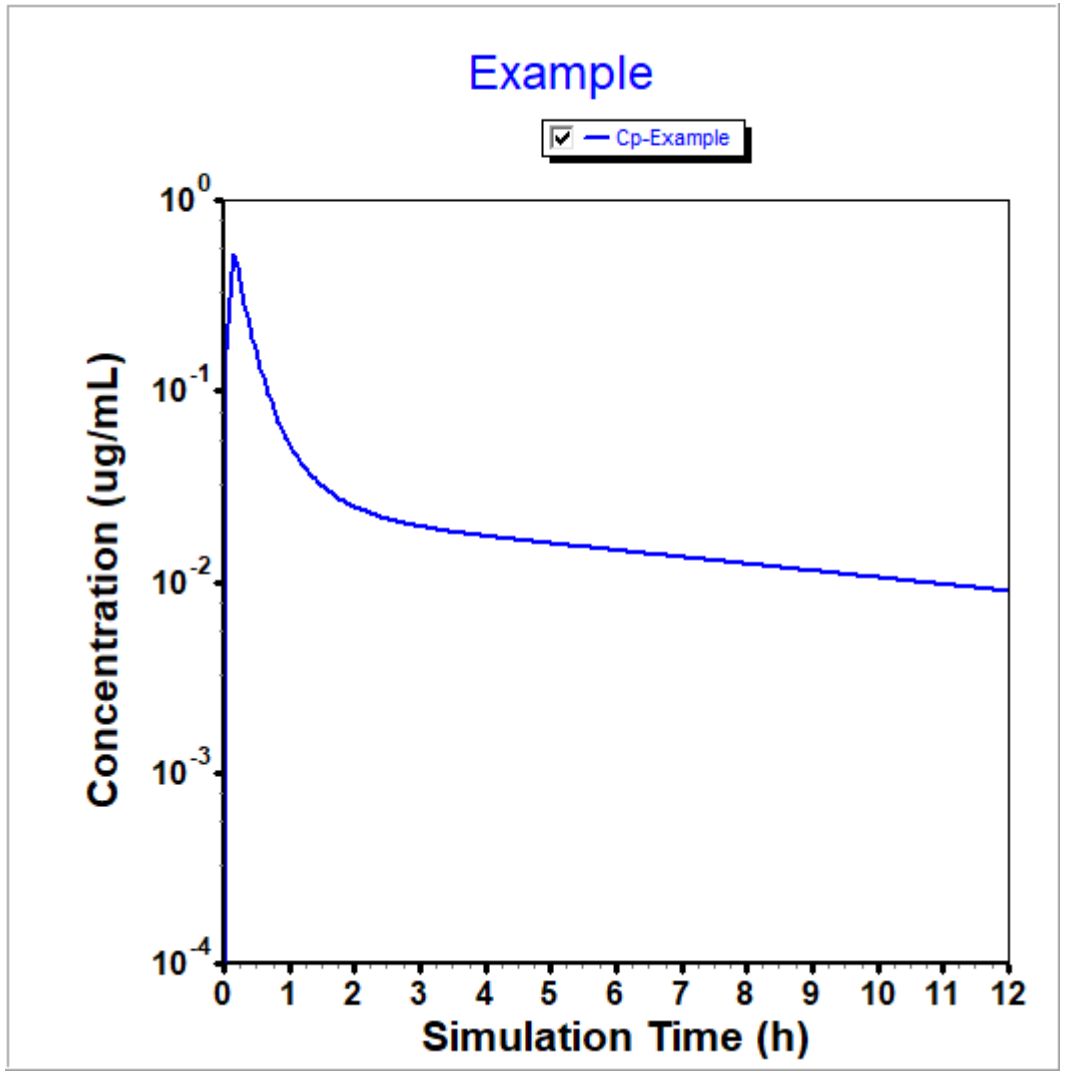


New

100 mg IV / 10 min



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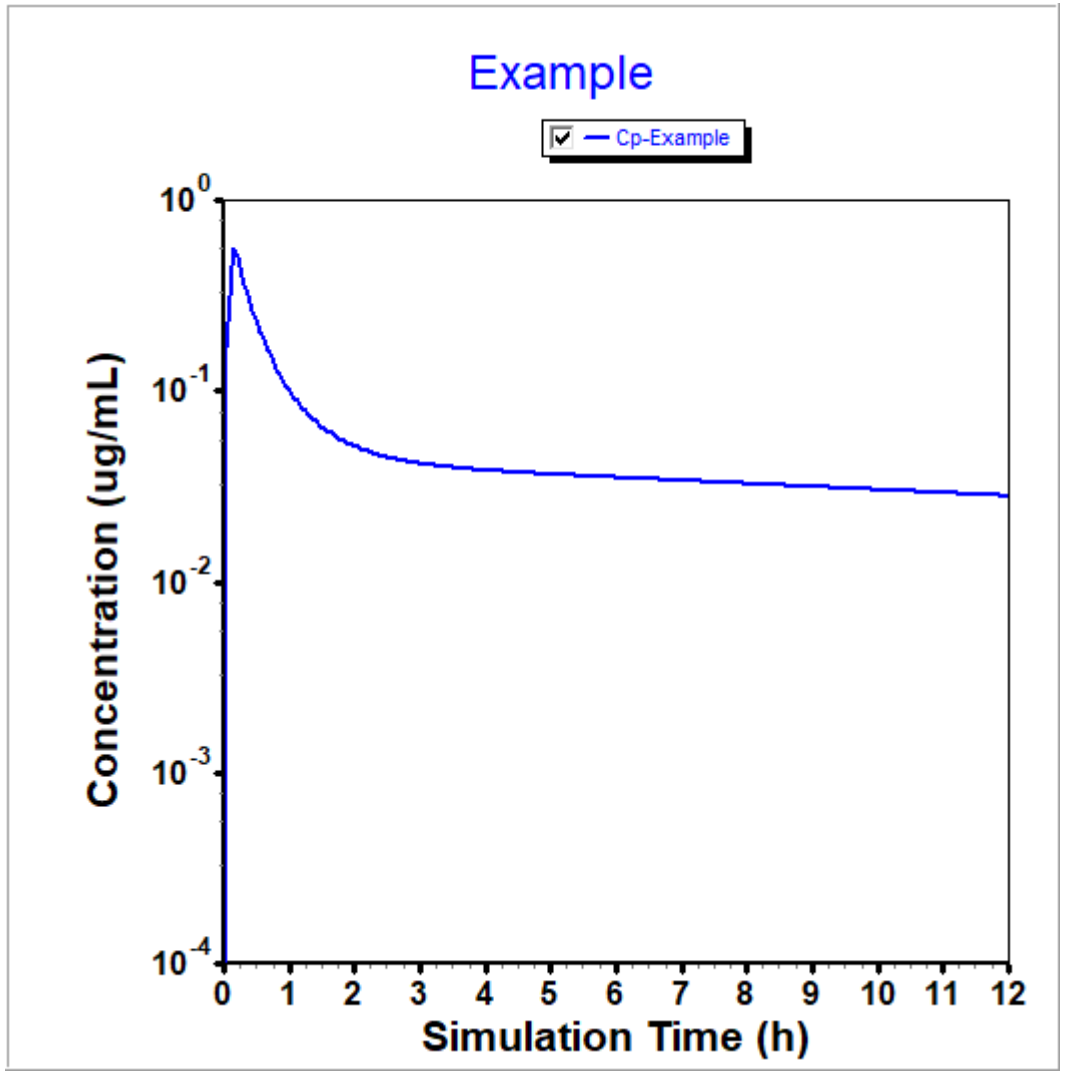
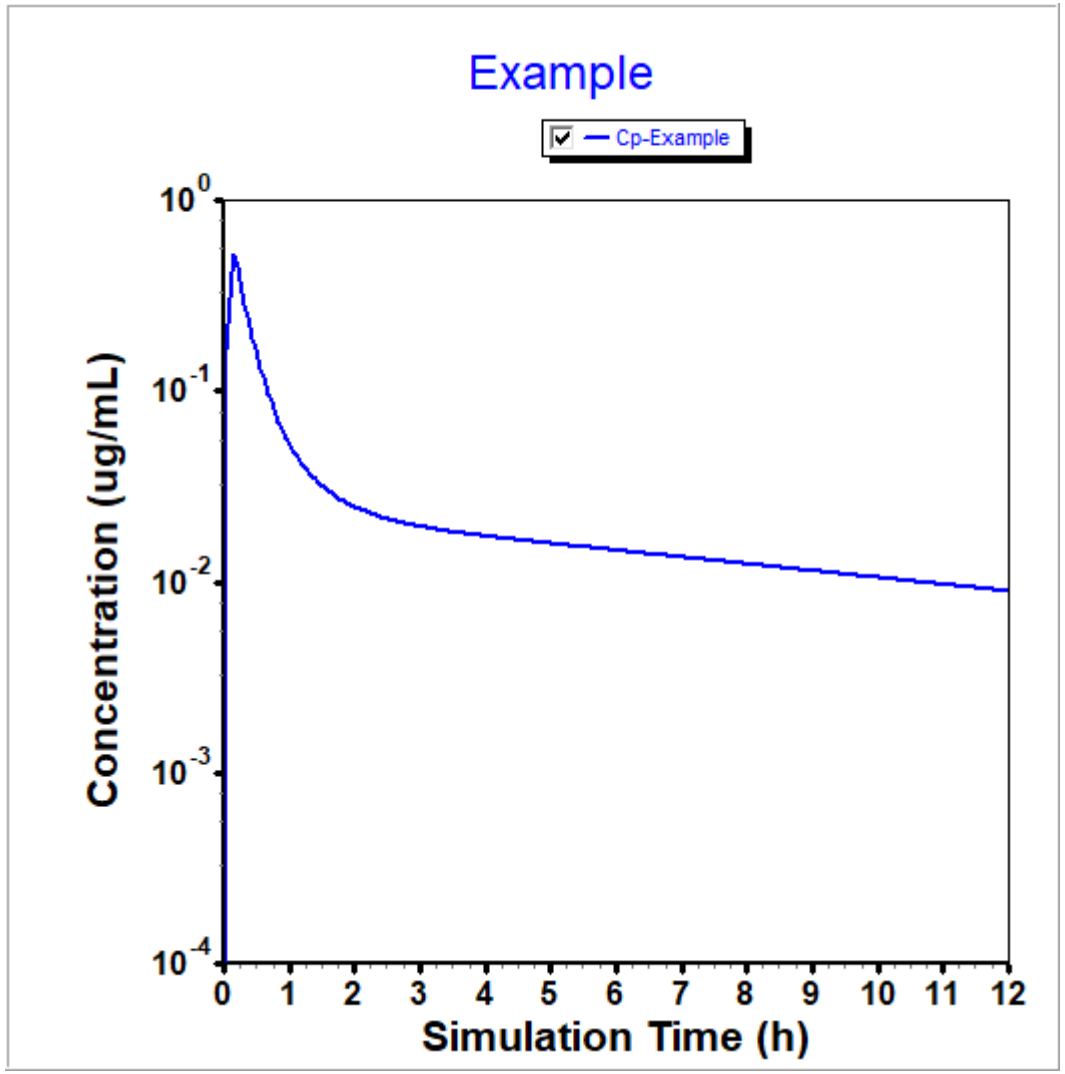


New

100 mg IV / 10 min



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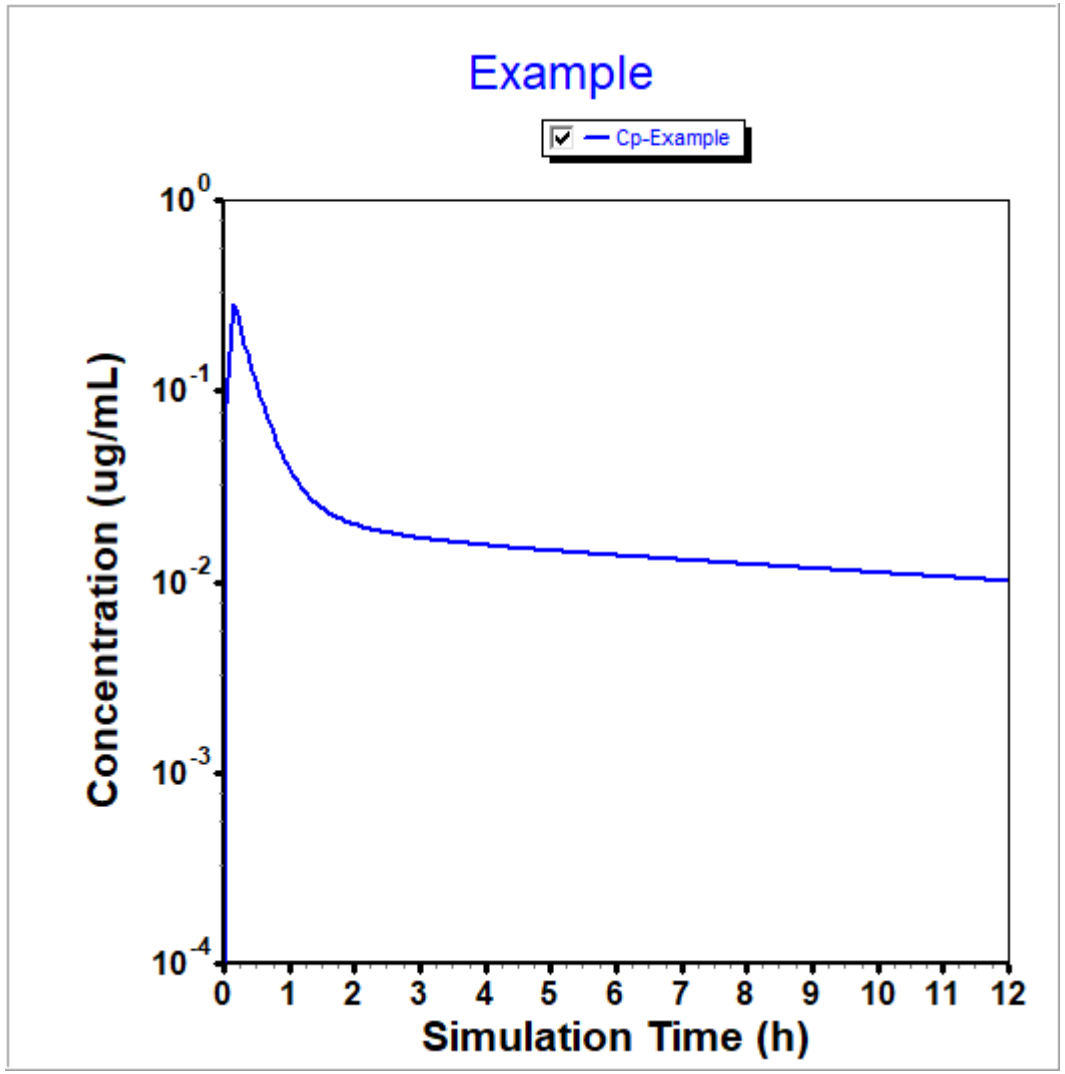
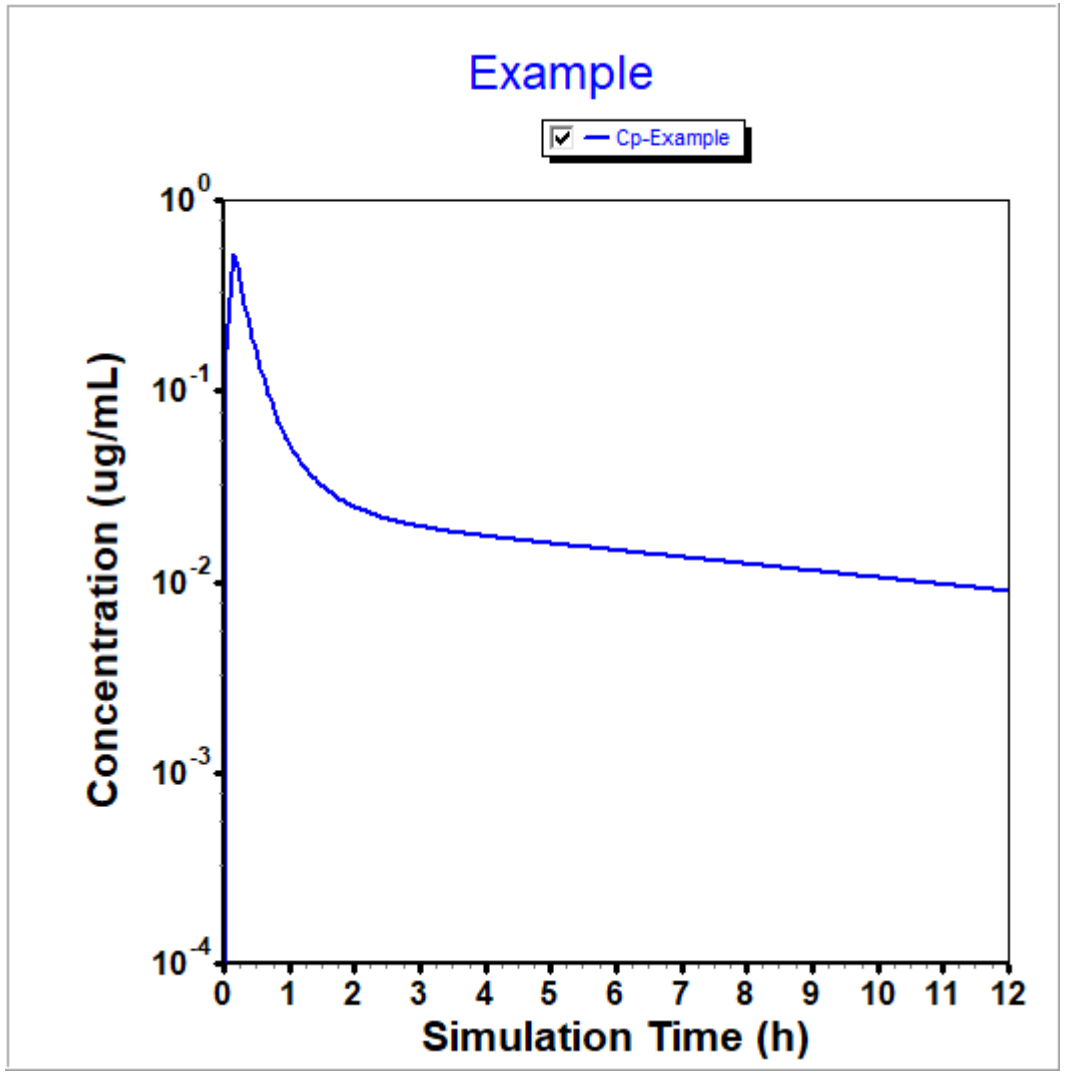


New

100 mg IV / 10 min



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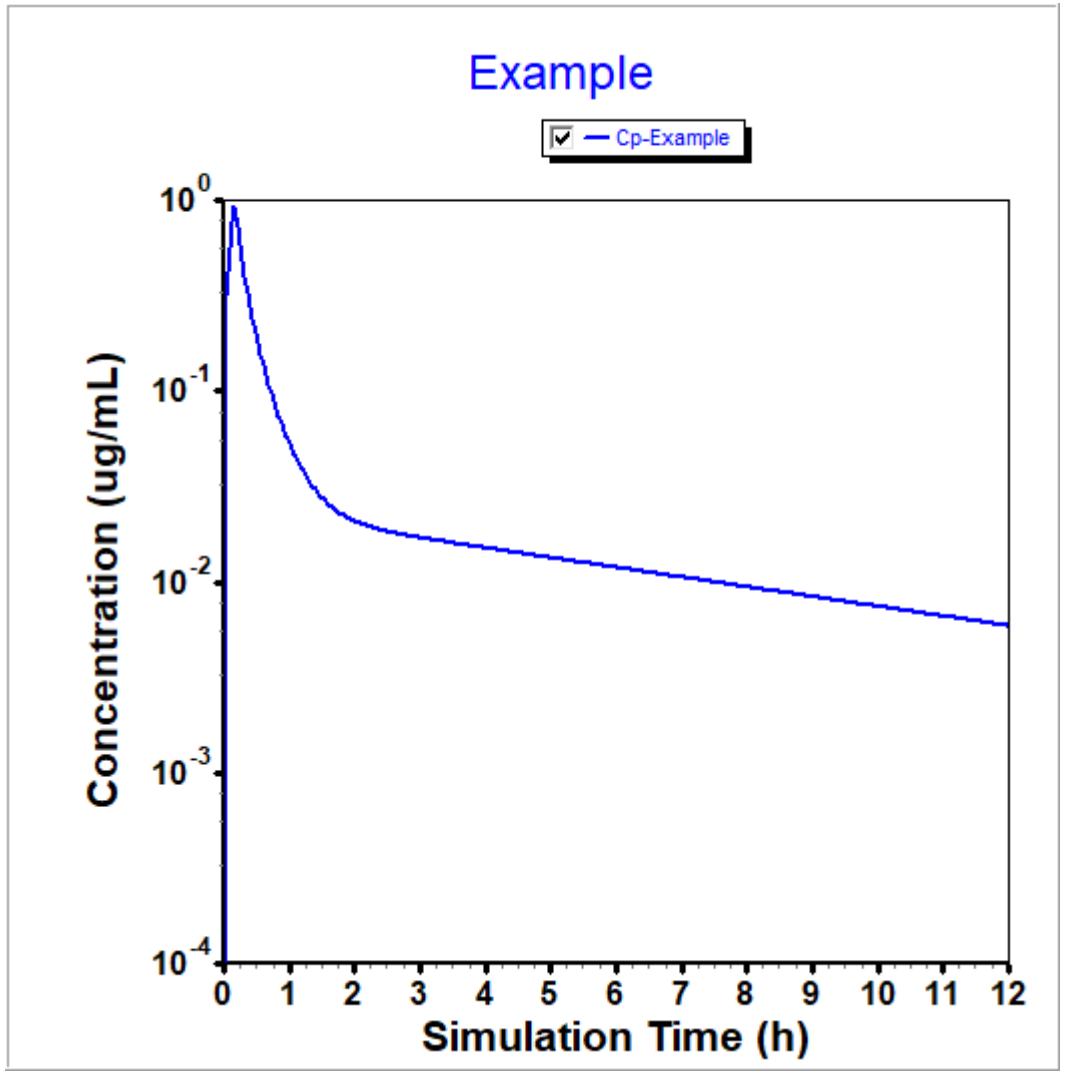
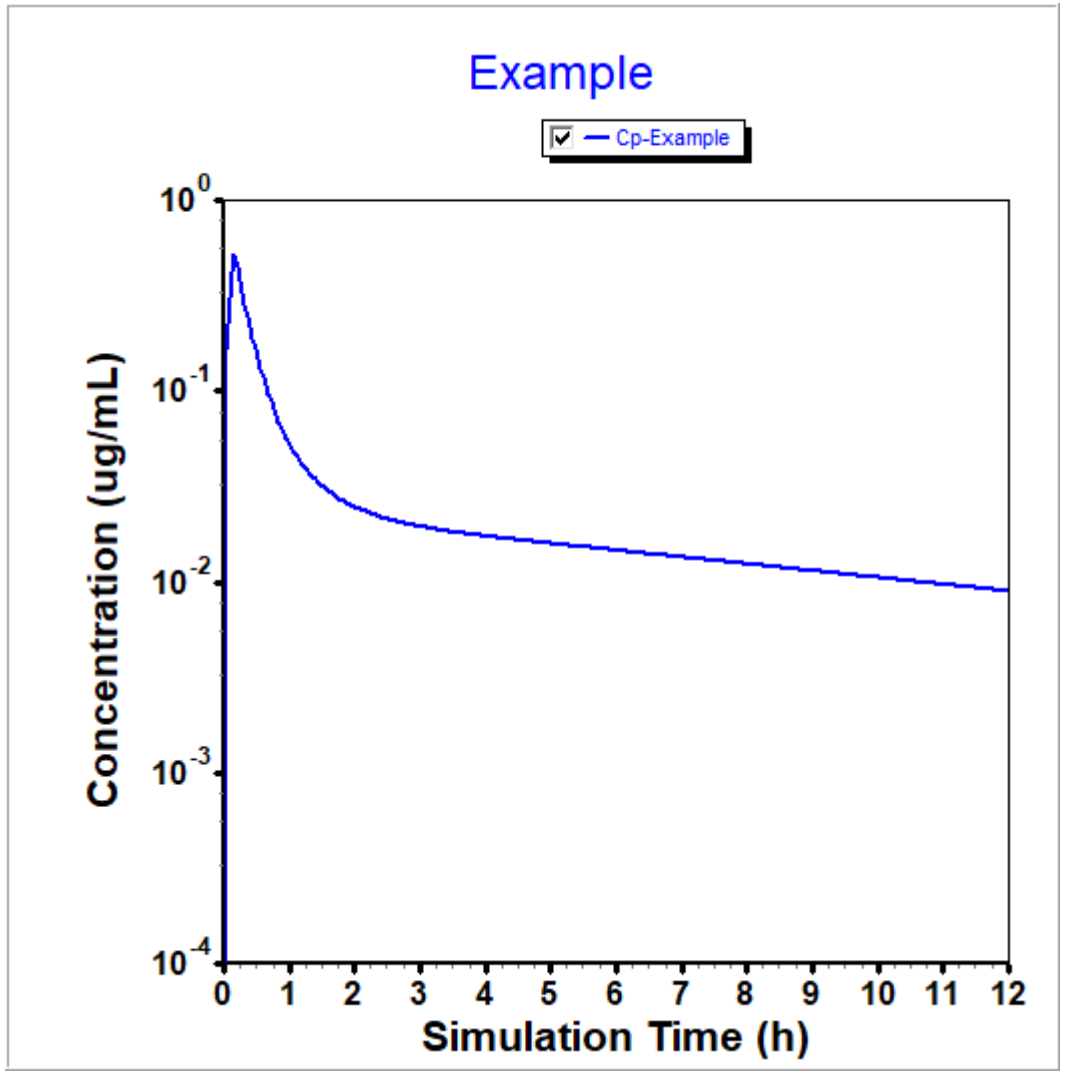


New

100 mg IV / 10 min



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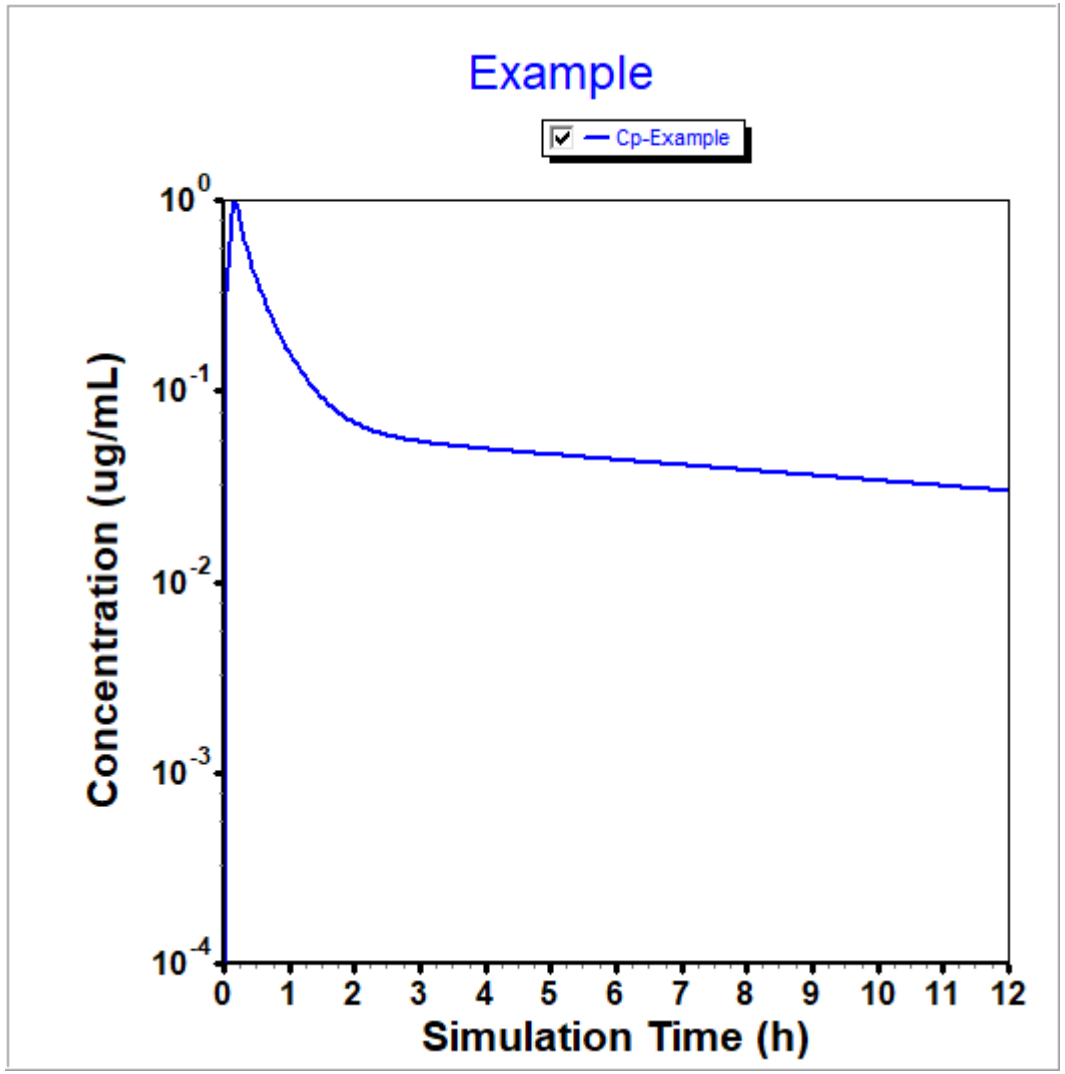
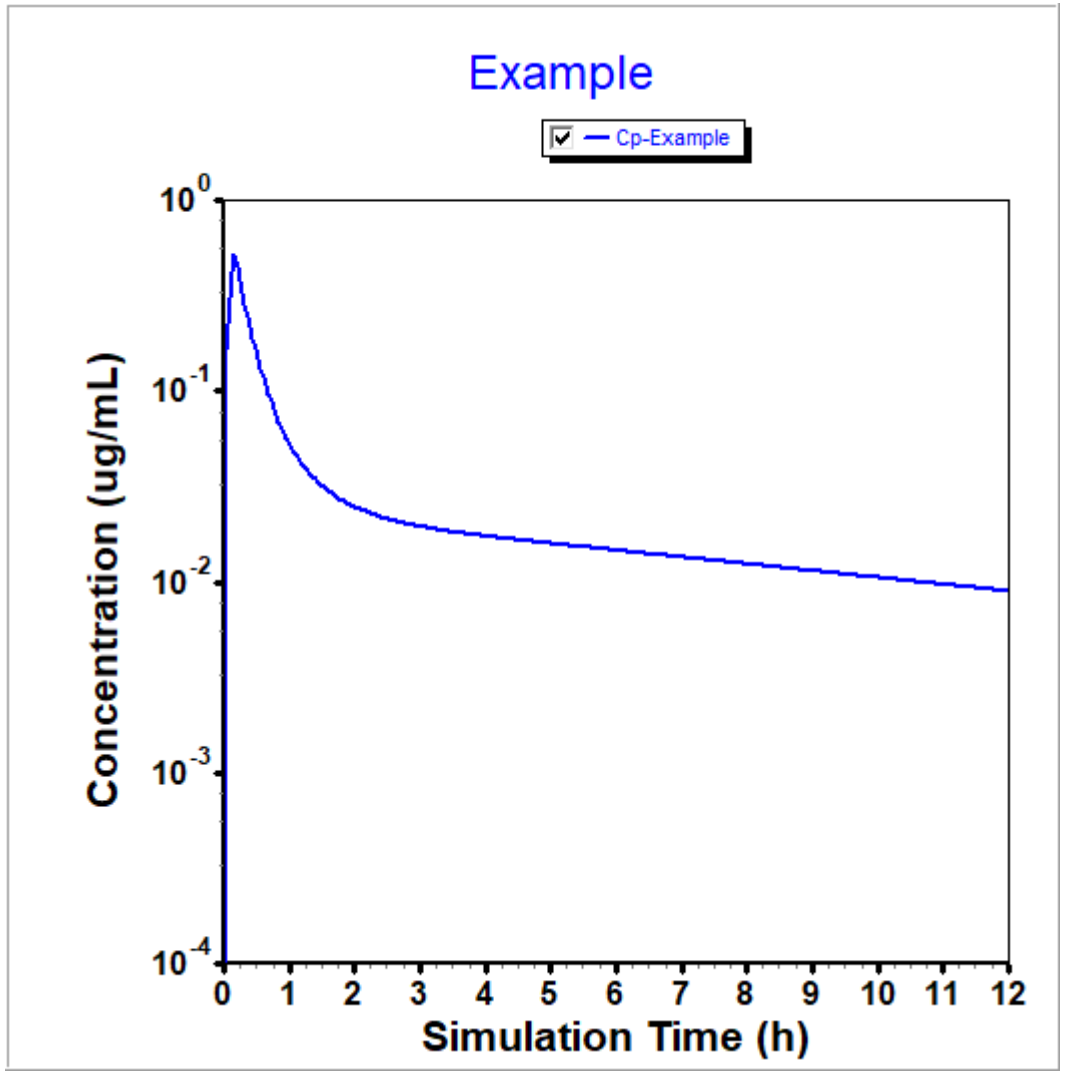


New

100 mg IV / 10 min



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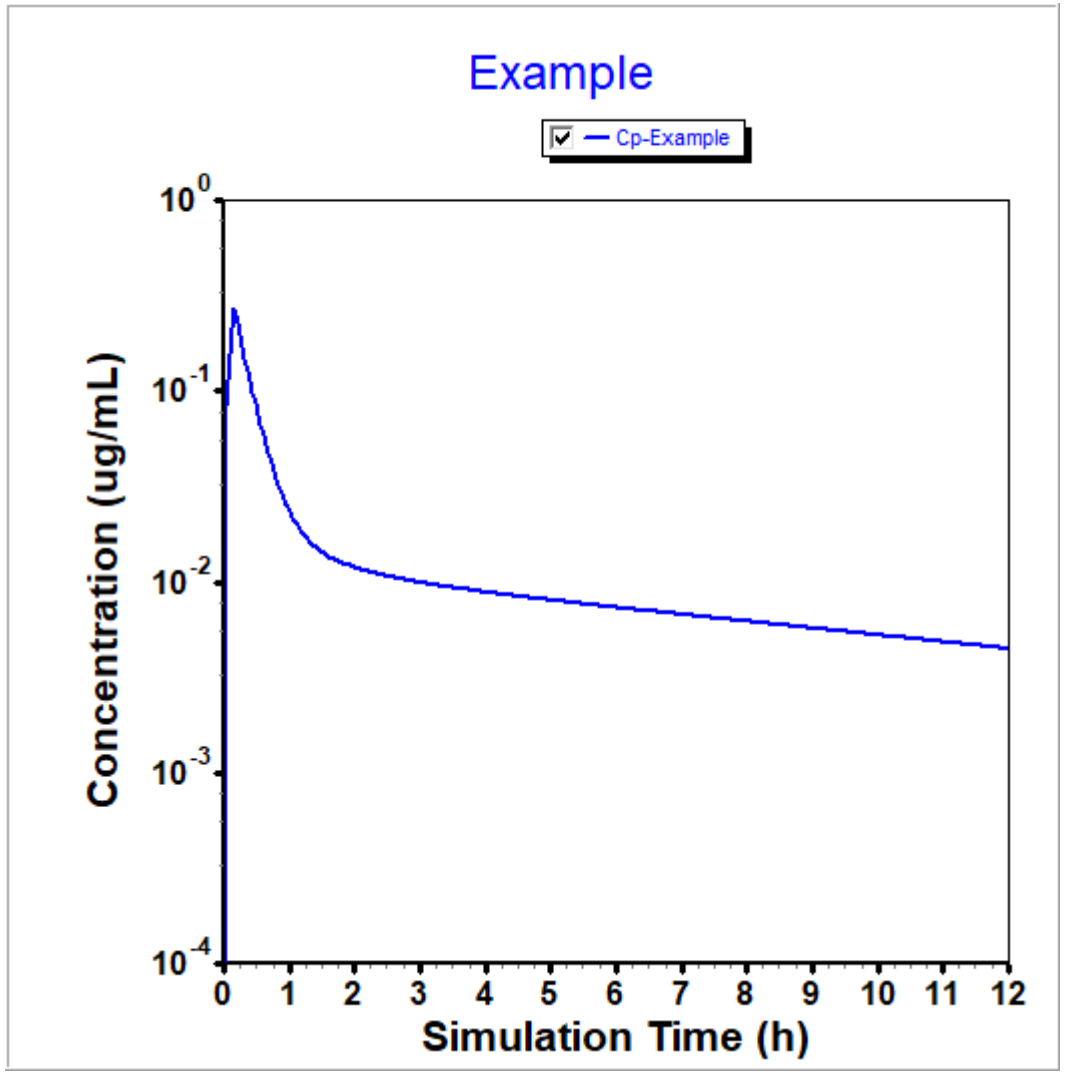
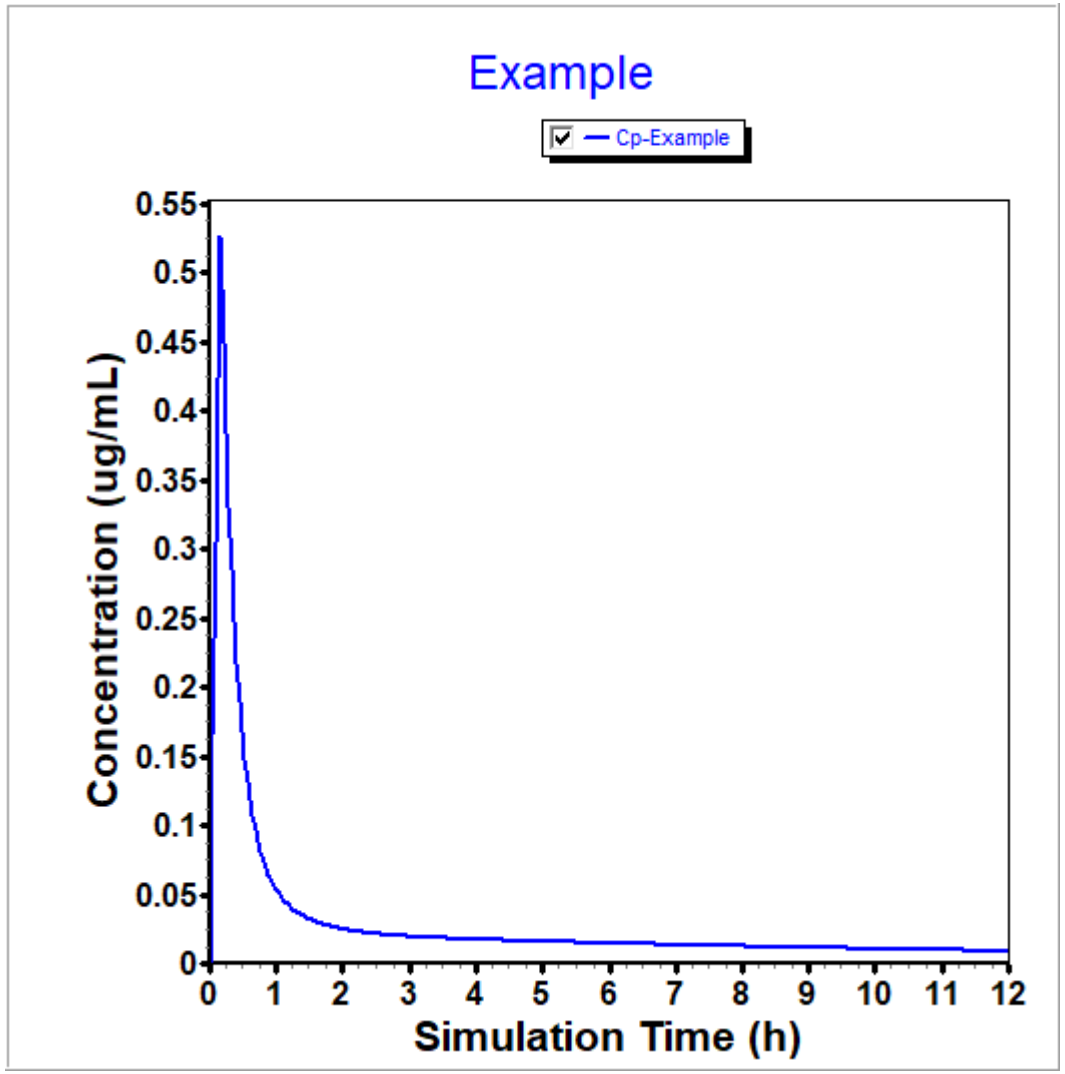
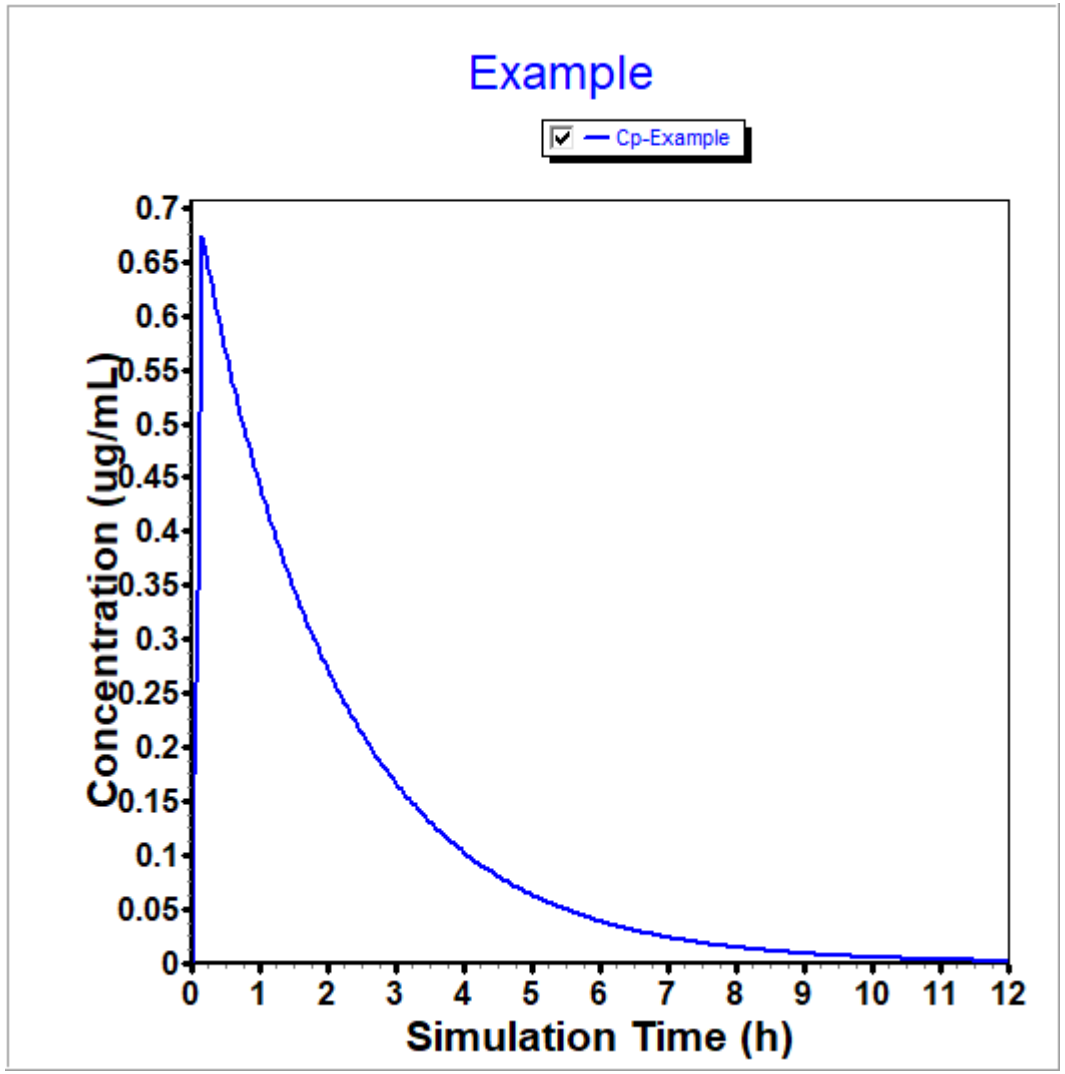


New

100 mg IV / 10 min





Some General Equations

$$K_{el} = \frac{CL}{Vd}$$

$$C_{max} \sim \frac{F \times Dose}{Volume}$$

$$CL = K_{el} \times Vd$$

$$AUC = \frac{F \times Dose}{CL}$$

$$C_2 = C_1 e^{-Kelt}$$

$$T½ = \frac{0.693 \times Vd}{CL}$$

$$CL = \frac{F \times Dose}{AUC}$$

GastroPlus Activities

- Create PEAR Physiology/PBPK model based on clinical demographics
- Use PKPlus to perform noncompartmental analysis (NCA)
- Add Linear/NCA CL to systemic circulation
  - Sum of Arterial Supply + Venous Return = NCA CL
  - Keeping observed CL as a single, fixed param allows us to focus on modeling distribution