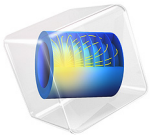

Model created in COMSOL Multiphysics 6.4

Drug Release from a Biomaterial Matrix

Introduction

Biomaterial matrices for drug release are useful for *in vivo* tissue regeneration. The following example describes the release of a drug from a biomaterial matrix into damaged cell tissue. Specifically, a nerve guide delivers a regenerating drug to damaged nerve ends.

This model examines detailed drug-release kinetics, with rate expressions handling drug dissociation/association reactions as well as matrix degradation by enzyme catalysis. The enzyme reaction is described by Michaelis–Menten kinetics. The model enables investigation of design parameters governing the rate of drug release such as drug-to-biomaterial affinity, biomaterial degradation, drug loading, and the influence of geometry and composition of the biomaterial matrix.

Model Definition

The model consists of two parts. The first part uses the batch reactor type in the Reaction Engineering interface. This reactor type specifies the reacting system in a perfectly mixed environment, that is, no space dependency is assumed. The purpose of this part is to study the reaction kinetics. The second part includes a space dependent component generated from the Reaction Engineering interface. It utilizes the Transport of Diluted Species in Porous Catalysts interface and serves to investigate the drug transport from the biomaterial into a region with damaged nerve ends.

Figure 1 shows the full 3D geometry as well as the 2D modeling domain, reduced by axial symmetry and a mirror plane, for the space-dependent model. The biomaterial holding the drug is assumed to have a strictly cylindrical shape. The three distinct areas (domains) are:

- Nerve-cell tissue
- Porous biomaterial
- Surrounding medium

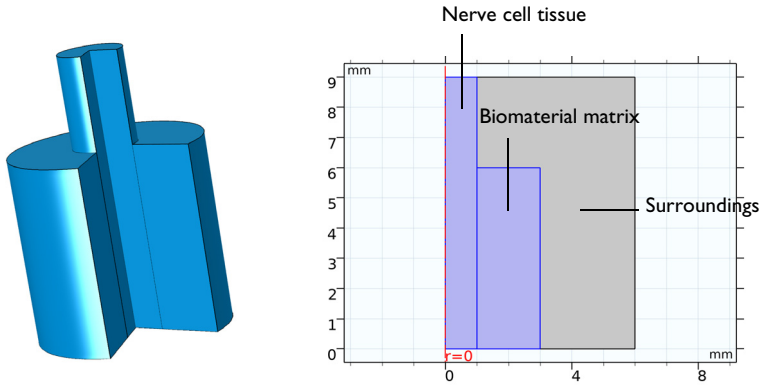

Figure 1: The full 3D geometry (left) and the equivalent modeling domains reduced to 2D by axial symmetry (right). The regions are: the nerve-cell tissue, the biomaterial matrix, and the surrounding medium.

In the biomaterial, a drug molecule, d, binds to a peptide, p, which in turn is anchored to the matrix, *m*. Matrix-bound species are labeled mpd and mp, respectively, the latter referring to a species where no drug is bound to the peptide. The species mpd and mp are modeled as surface species attached to the matrix surface, and are only present in the biomaterial.

Two mechanisms release the drug from the matrix. First, the drug can simply dissociate from the matrix site mp. Second, matrix degradation by an enzyme, e, originating from the cell-tissue domain, leads to release of the drug-peptide species, pd, from which the drug subsequently dissociates. The unbound species p, d, pd, and e are free bulk species and present in the entire model geometry. Figure 2 illustrates the complete reaction scheme.

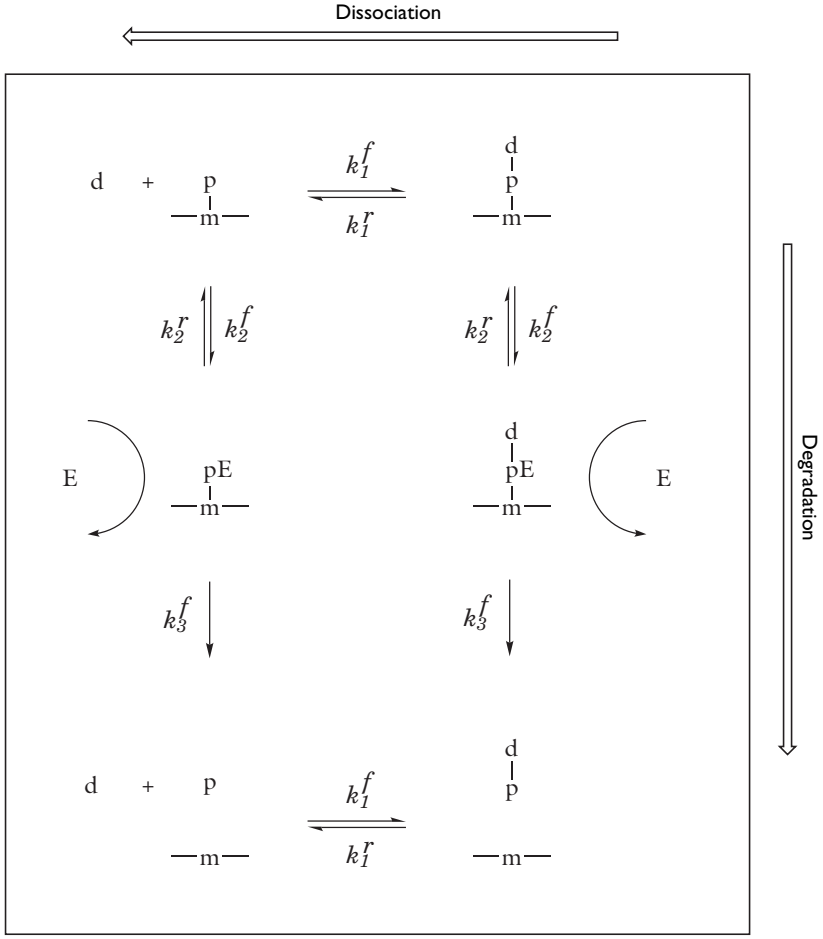

Figure 2: Reaction scheme describing drug dissociation/association reactions (horizontal) and matrix-degradation reactions (vertical).

The time-dependent mass balance per species is described by

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (-D_{ik} \nabla c_i) = R_{ik} + R_{\mathrm{s},i} S_{\mathrm{sa}} \tag{1}$$

where D_{ik} (SI unit: m^2/s) is the diffusion coefficient for species i in the respective medium k. In the right-hand side R_{ik} (SI unit: $\mathrm{mol}/(\mathrm{m}^3 \cdot \mathrm{s})$) is the rate expression for volumetric reactions, involving bulk species only, of species i in domain k. The second term on the

right-hand side results from surface reactions involving matrix-bound species (mpd and mp) in the biomaterial. $R_{s,i}$ is the surface reaction rate (SI unit: mol/(m^2·s)) and S_{sa} the specific surface area of the biomaterial (SI unit: 1/m).

In the biomaterial (index $k = 2$), all the reactions described in Figure 2 are possible, leading to the following rate expressions:

$$R_{\mathrm{d}2} = -k_1^f c_{\mathrm{d}} (c_{\mathrm{mp}} S_{\mathrm{sa}} + c_{\mathrm{p}}) + k_1^r (c_{\mathrm{mpd}} S_{\mathrm{sa}} + c_{\mathrm{pd}})$$

$$R_{\mathrm{p}2} = -k_1^f c_{\mathrm{d}} c_{\mathrm{p}} + k_1^r c_{\mathrm{pd}} + R_{\mathrm{MMmp}}$$

$$R_{\mathrm{pd}2} = k_1^f c_{\mathrm{d}} c_{\mathrm{p}} - k_1^r c_{\mathrm{pd}} + R_{\mathrm{MMmpd}}$$

$$R_{\mathrm{mp}2} = -k_1^f c_{\mathrm{d}} c_{\mathrm{mp}} + k_1^r c_{\mathrm{mpd}} - R_{\mathrm{MMmp}}$$

$$R_{\mathrm{mpd}2} = k_1^f c_{\mathrm{d}} c_{\mathrm{mp}} - k_1^r c_{\mathrm{mpd}} - R_{\mathrm{MMmpd}}$$

The rate terms R_{MMmp} and R_{MMmpd} refer to the Michaelis–Menten kinetics describing the enzyme catalyzed degradation of the matrix:

$$R_{\mathrm{MMmp}} = \frac{V_{\max} c_{\mathrm{mp}}}{K_{\mathrm{M}} + c_{\mathrm{mp}} S_{\mathrm{sa}}}$$

$$R_{\mathrm{MMmpd}} = \frac{V_{\max} c_{\mathrm{mpd}}}{K_{\mathrm{M}} + c_{\mathrm{mpd}} S_{\mathrm{sa}}}$$

with

$$V_{\max} = k_3^f c_{\mathrm{e}}$$

$$K_{\mathrm{M}} = \frac{k_3^f + k_2^r}{k_2^f}$$

R_{MMmp} describes the disappearance of mp sites and the production of p species. R_{MMmpd} describes the disappearance of mpd sites and the production of pd species. $V_{\max}$ is the maximum rate and K_{M} the Michaelis–Menten constant. In the cell region (index $k = 1$) and in the surrounding medium (index $k = 3$) only dissociation/association reactions occur, leading to the rate expressions

$$R_{d1} = R_{d3} = R_{p1} = R_{p3} = -k_1^f c_d c_p + k_1^r c_{pd}$$

$$R_{pd1} = R_{pd3} = k_1^f c_d c_p - k_1^r c_{pd}$$

The boundary condition is axial symmetry along the rotational axis and insulation/symmetry elsewhere. Values for diffusion coefficients and rate constants come from the literature (Ref. 1).

Results and Discussion

Figure 3 shows the concentration transients of the reacting species in a perfectly mixed (space-independent) system.

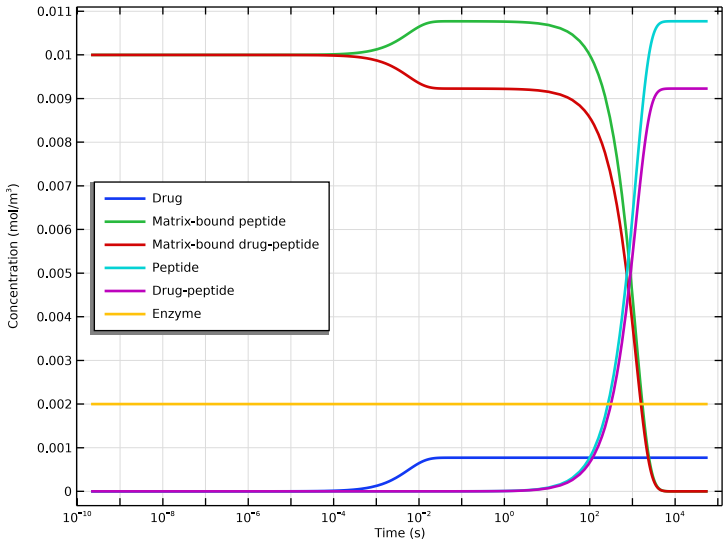

Figure 3: Concentrations of all reacting species (mol/m^3) as functions of time (s).

The effect of enzyme degradation is clearly visible, with matrix-bound peptide species (mp and mpd) decreasing and free peptide species (p and pd) increasing with time. The matrix is completely degraded after approximately 5000 seconds. As the drug and peptide species have the same association/dissociation kinetics, no matter the peptide is free or matrix-bound, the steady-state concentration of drug is constant during the degradation process.

Solving the space-dependent mass balances of Equation 1 results in concentration distributions of all participating species as functions of time. Figure 4 shows the concentration of all bulk species.

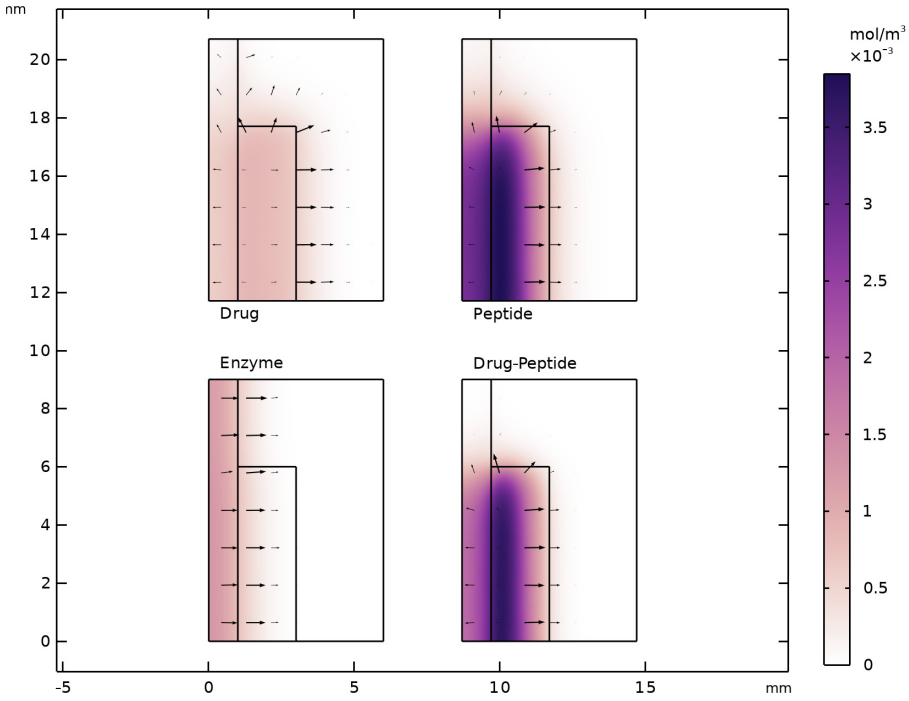

Figure 4: Bulk species concentrations after 1.5 h.

As mentioned earlier, the enzyme originates from the nerve-cell tissue. From Figure 5, where the total drug release is shown, it is clear that matrix degradation has a directing effect on the drug release toward the damaged cell region.

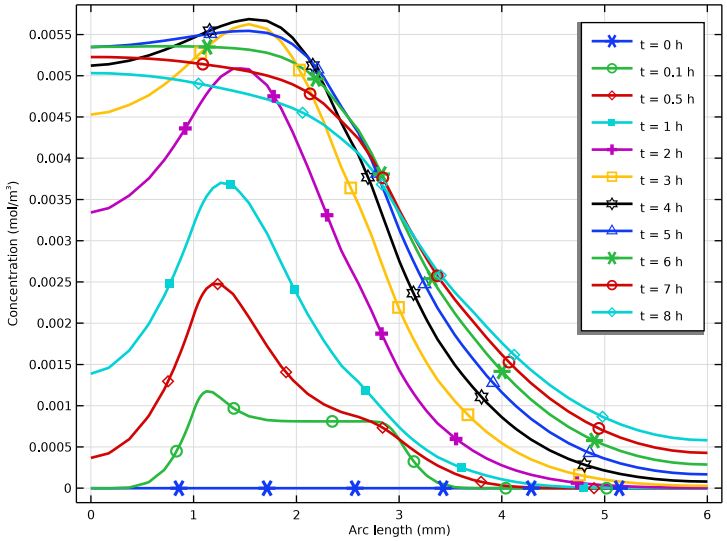

Figure 5: Concentration profiles describing the total drug concentration ($c_d + c_{pd}$) across the modeling domain.

Figure 6 visualizes the biomaterial matrix degradation. The plotted total matrix site concentrations ($c_{mp} + c_{mpd}$) shows how the degradation front passes through the biomaterial geometry.

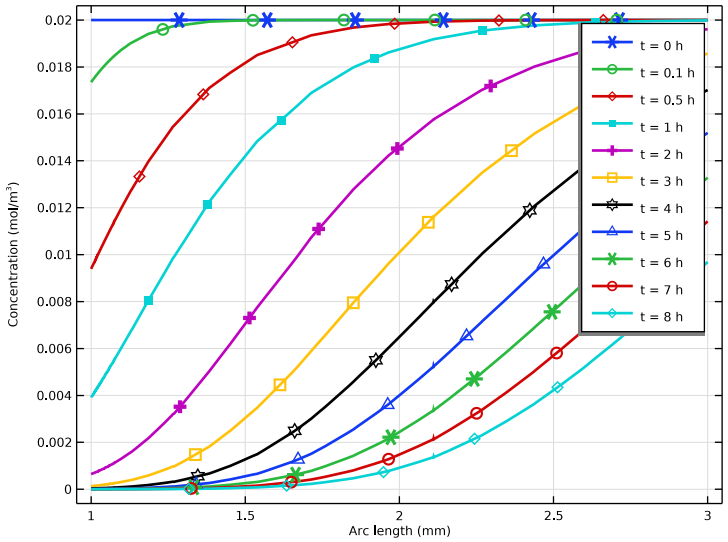

Figure 6: Concentration profiles describing the total matrix site concentration ($c_{mp} + c_{mpd}$).

Figure 7 shows how the drug distribution in the different domains vary during the simulation. It can be noted that the drug level in the biomaterial reaches a maximum after about 5 hours. The same is true for the drug level in the nerve.

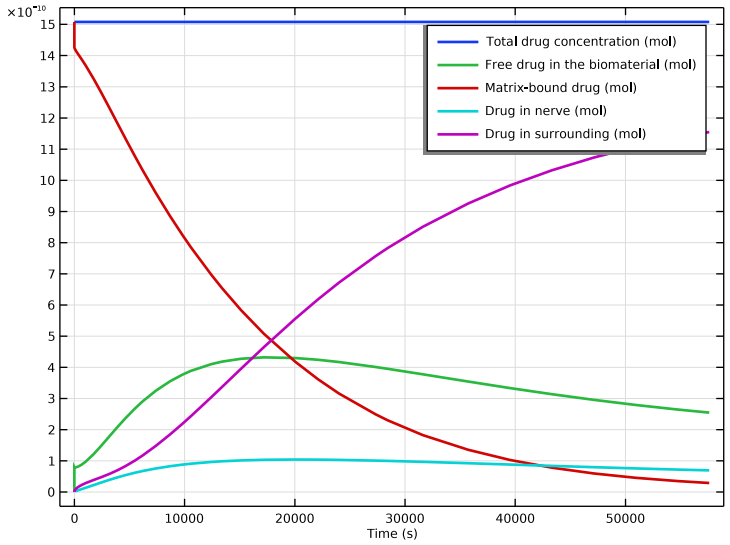

Figure 7: Drug distribution among the different domains.

The detailed reaction/transport description in this model allows for the investigation of many design parameters relevant to bioengineering. This case presents the effect of matrix degradation on drug release as a function of time and geometry. Furthermore, it is straightforward to study the influence of the drug/peptide affinity by varying the rate constants $k^f{}_1$ and $k^r{}_1$, or the influence of drug loading by varying the $c_{\mathrm{mp}}:c_{\mathrm{mpd}}$ ratio. The ability to examine alternative geometries and mixed biomaterial domains gives even more design flexibility.

Reference

1. D.J. Maxwell and others, "Development of Rationally Designed Affinity-Based Drug Delivery Systems," *Acta Biomat.*, vol. 1, no. 1, pp. 101–113, 2005.

Application Library path: `Chemical_Reaction_Engineering_Module/Reactors_with_Mass_Transfer/drug_release`

From the **File** menu, choose **New**.

NEW

In the **New** window, click **Model Wizard**.

MODEL WIZARD

1 In the **Model Wizard** window, click **0D**.

2 In the **Select Physics** tree, select **Chemical Species Transport** > **Reaction Engineering (re)**.

3 Click **Add**.

4 Click **Study**.

5 In the **Select Study** tree, select **General Studies** > **Time Dependent**.

6 Click **Done**.

REACTION ENGINEERING (RE)

Read global parameters from a text file.

GLOBAL DEFINITIONS

Parameters 1

1 In the **Model Builder** window, under **Global Definitions** click **Parameters 1**.

2 In the **Settings** window for **Parameters**, locate the **Parameters** section.

3 Click **Load from File**.

4 Browse to the model's Application Libraries folder and double-click the file `drug_release_parameters.txt`.

REACTION ENGINEERING (RE)

First, model the reaction behavior of drug release from the biomaterial matrix, regarding the material as a perfectly mixed batch reactor.

1 In the **Model Builder** window, under **Component 1 (comp1)** click **Reaction Engineering (re)**.

2 In the **Settings** window for **Reaction Engineering**, locate the **Mixture Properties** section.

3 From the **Phase** list, choose **Liquid**.

Reaction 1

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `d+mp(ads)<=>mpd(ads)`.

4 Click **Apply**.

5 Locate the **Rate Constants** section. In the k^{f} text field, type `kf_d`.

6 In the k^{r} text field, type `kr_d`.

Species: d (drug)

1 In the **Model Builder** window, click **Species: d**.

2 In the **Settings** window for **Species**, type `Species: d (drug)` in the **Label** text field.

Species: mp(ads) (matrix-peptide)

1 In the **Model Builder** window, under **Component 1 (comp1)** > **Reaction Engineering (re)** click **Surface species: mp(ads)**.

2 In the **Settings** window for **Species**, type `Species: mp(ads) (matrix-peptide)` in the **Label** text field.

Species: mpd(ads) (matrix-peptide-drug)

1 In the **Model Builder** window, under **Component 1 (comp1)** > **Reaction Engineering (re)** click **Surface species: mpd(ads)**.

2 In the **Settings** window for **Species**, type `Species: mpd(ads) (matrix-peptide-drug)` in the **Label** text field.

Reaction 2

1 In the **Reaction Engineering** toolbar, click  **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `d+p<=>pd`.

4 Click **Apply**.

5 Locate the **Rate Constants** section. In the k^{f} text field, type `kf_d`.

6 In the k^{r} text field, type `kr_d`.

Species: p (peptide)

1 In the **Model Builder** window, click **Species: p**.

2 In the **Settings** window for **Species**, type `Species: p (peptide)` in the **Label** text field.

Species: pd (peptide-drug)

1 In the **Model Builder** window, click **Species: pd**.

2 In the **Settings** window for **Species**, type `Species: pd (peptide-drug)` in the **Label** text field.

Reaction 3

1 In the **Reaction Engineering** toolbar, click **Reaction**.

Add the reactions describing the enzyme catalyzed degradation of the matrix. mp and mpd sites are consumed while producing free p and d species.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `mp(ads)+e=>p+e`.

4 Click **Apply**.

5 Locate the **Reaction Rate** section. From the list, choose **User defined**.

6 In the r_j text field, type `kf_mm*re.c_e*re.csurf_mp_surf/(Km+re.csurf_mp_surf*Ssa)`.

Species: e (enzyme)

1 In the **Model Builder** window, click **Species: e**.

2 In the **Settings** window for **Species**, type `Species: e (enzyme)` in the **Label** text field.

Reaction 4

1 In the **Reaction Engineering** toolbar, click **Reaction**.

2 In the **Settings** window for **Reaction**, locate the **Reaction Formula** section.

3 In the **Formula** text field, type `mpd(ads)+e=>pd+e`.

4 Click **Apply**.

5 Locate the **Reaction Rate** section. From the list, choose **User defined**.

6 In the r_j text field, type `kf_mm*re.c_e*re.csurf_mpd_surf/(Km+re.csurf_mpd_surf*Ssa)`.

Species 1

1 In the **Reaction Engineering** toolbar, click **Species**.

2 In the **Settings** window for **Species**, locate the **Name** section.

3 In the text field, type `H2O`.

4 Locate the **Type** section. From the list, choose **Solvent**.

5 In the **Model Builder** window, click **Reaction Engineering (re)**.

6 In the **Settings** window for **Reaction Engineering**, locate the **Reactor** section.

7 Find the **Surface reaction area** subsection. Click the **Surface area to volume ratio** button.

8 In the a_s text field, type `Ssa`.

Initial Values 1

1 In the **Model Builder** window, click **Initial Values 1**.

2 In the **Settings** window for **Initial Values**, locate the **Volumetric Species Initial Values** section.

3 In the table, enter the following settings:

Species	Concentration (mol/m^3)
H2O	c_solv
e	c_e_init

4 Locate the **Surface Species Initial Values** section. In the table, enter the following settings:

Species	Surface concentration (mol/m^2)	Site occupancy number (1)
mp(ads)	c_mp_init	1
mpd(ads)	c_mpd_init	1

5 In the Γ_s text field, type `(c_mp_init+c_mpd_init)`.

STUDY 1

Step 1: Time Dependent

1 In the **Model Builder** window, under **Study 1** click **Step 1: Time Dependent**.

2 In the **Settings** window for **Time Dependent**, locate the **Study Settings** section.

3 From the **Time unit** list, choose **h**.

4 In the **Output times** text field, type `range(0,0.1,16)`.

5 In the **Study** toolbar, click **Compute**.

RESULTS

Biomaterial Concentrations, 0D model

Follow these steps to create Figure 3.

1 In the **Settings** window for **1D Plot Group**, type `Biomaterial Concentrations, 0D model` in the **Label** text field.

2 Click the **x-Axis Log Scale** button in the **Graphics** toolbar.

Global 1

1 In the **Model Builder** window, expand the **Biomaterial Concentrations, 0D model** node, then click **Global 1**.

2 In the **Settings** window for **Global**, locate the **y-Axis Data** section.

3 In the table, enter the following settings:

Expression	Unit	Description
re.csurf_mp_surf*Ssa	mol/m^3	
re.csurf_mpd_surf*Ssa	mol/m^3	

4 Locate the **x-Axis Data** section. From the **Unit** list, choose **s**.

5 Click to expand the **Coloring and Style** section. From the **Width** list, choose **2**.

6 In the **Biomaterial Concentrations, 0D model** toolbar, click **Plot**.

7 Click to expand the **Legends** section. From the **Legends** list, choose **Manual**.

8 In the table, enter the following settings:

Legends
Drug
Matrix-bound peptide
Matrix-bound drug-peptide
Peptide
Drug-peptide
Enzyme

9 In the **Biomaterial Concentrations, 0D model** toolbar, click **Plot**.

10 Click the **Zoom Extents** button in the **Graphics** toolbar.

Biomaterial Concentrations, 0D model

1 In the **Model Builder** window, click **Biomaterial Concentrations, 0D model**.

2 In the **Settings** window for **1D Plot Group**, click to expand the **Title** section.

3 From the **Title type** list, choose **None**.

4 Locate the **Plot Settings** section.

5 Select the **y-axis label** checkbox. In the associated text field, type `Concentration (mol/m<sup>3</sup>)`.

6 Locate the **Legend** section. From the **Position** list, choose **Middle left**.

Start setting up the space-dependent model by exporting the settings of the **Reaction Engineering** interface with the **Generate Space-Dependent Model** feature.

REACTION ENGINEERING (RE)

Generate Space-Dependent Model 1

1 In the **Reaction Engineering** toolbar, click **Generate Space-Dependent Model**.

2 In the **Settings** window for **Generate Space-Dependent Model**, locate the **Component Settings** section.

3 From the **Component to use** list, choose **2Daxi: New**.

4 Locate the **Physics Interfaces** section. Find the **Chemical species transport** subsection. From the list, choose **Reacting Flow in Porous Media: New**.

5 From the list, choose **Porous Catalyst**.

6 Locate the **Study Type** section. From the **Study type** list, choose **Time dependent**.

7 Locate the **Space-Dependent Model Generation** section. Click **Create/Refresh**.

COMPONENT 2 (COMP2)

In the **Model Builder** window, expand the **Component 2 (comp2)** node.

GEOMETRY 1 (2DAXI)

1 In the **Model Builder** window, expand the **Component 2 (comp2)** > **Geometry 1 (2Daxi)** node, then click **Geometry 1 (2Daxi)**.

2 In the **Settings** window for **Geometry**, locate the **Units** section.

3 From the **Length unit** list, choose **mm**.

Rectangle 1 (r1)

1 In the **Geometry** toolbar, click **Rectangle**.

2 In the **Settings** window for **Rectangle**, locate the **Size and Shape** section.

3 In the **Width** text field, type 6.

4 In the **Height** text field, type 9.

Rectangle 2 (r2)

1 Right-click **Rectangle 1 (r1)** and choose **Duplicate**.

2 In the **Settings** window for **Rectangle**, locate the **Size and Shape** section.

3 In the **Width** text field, type 1.

Rectangle 3 (r3)

1 Right-click **Rectangle 2 (r2)** and choose **Duplicate**.

2 In the **Settings** window for **Rectangle**, locate the **Size and Shape** section.

3 In the **Width** text field, type 2.

4 In the **Height** text field, type `6`.

5 Locate the **Position** section. In the **r** text field, type `1`.

6 Click **Build All Objects**.

In this model, the fluid flow is not taken into account so you can delete the **Porous Material**, **Brinkman Equations** and **Reacting Flow, Diluted Species** nodes.

MATERIALS

Porous Material 1 (pmat1)

1 In the **Model Builder** window, expand the **Component 2 (comp2)** > **Materials** node.

2 Right-click **Component 2 (comp2)** > **Materials** > **Porous Material 1 (pmat1)** and choose **Delete**.

BRINKMAN EQUATIONS (BR)

In the **Model Builder** window, under **Component 2 (comp2)** right-click **Brinkman Equations (br)** and choose **Delete**.

MULTIPHYSICS

Reacting Flow, Diluted Species 1 (rfd1)

1 In the **Model Builder** window, expand the **Multiphysics** node.

2 Right-click **Component 2 (comp2)** > **Multiphysics** > **Reacting Flow, Diluted Species 1 (rfd1)** and choose **Delete**.

CHEMISTRY (CHEM)

Species matching is used to assign concentration variables to the species in the **Chemistry** interface. The species solved for by the **Porous Catalyst** feature (bulk species and surface species) have already been matched by the **Generate Space-Dependent Model** node. This can be verified by selecting the **Chemistry 1** node and inspecting the **Species Matching** section.

Also define the molar masses. These makes it is possible to compute several transport properties outside the scope of this example.

Species: d

1 In the **Model Builder** window, expand the **Component 2 (comp2)** > **Chemistry (chem)** node, then click **Species: d**.

2 In the **Settings** window for **Species**, locate the **Chemical Formula** section.

3 In the M text field, type `M_d`.

Surface species: mp(ads)

1 In the **Model Builder** window, click **Surface species: mp(ads)**.

2 In the **Settings** window for **Species**, locate the **Chemical Formula** section.

3 In the M text field, type `M_p`.

Surface species: mpd(ads)

1 In the **Model Builder** window, click **Surface species: mpd(ads)**.

2 In the **Settings** window for **Species**, locate the **Chemical Formula** section.

3 In the M text field, type `M_pd`.

Species: p

1 In the **Model Builder** window, click **Species: p**.

2 In the **Settings** window for **Species**, locate the **Chemical Formula** section.

3 In the M text field, type `M_p`.

Species: pd

1 In the **Model Builder** window, click **Species: pd**.

2 In the **Settings** window for **Species**, locate the **Chemical Formula** section.

3 In the M text field, type `M_pd`.

Species: e

1 In the **Model Builder** window, click **Species: e**.

2 In the **Settings** window for **Species**, locate the **Chemical Formula** section.

3 In the M text field, type `M_e`.

TRANSPORT OF DILUTED SPECIES IN POROUS CATALYSTS (TDS)

1 In the **Model Builder** window, expand the **Component 2 (comp2)** > **Transport of Diluted Species in Porous Catalysts (tds)** node, then click **Transport of Diluted Species in Porous Catalysts (tds)**.

2 In the **Settings** window for **Transport of Diluted Species in Porous Catalysts**, locate the **Transport Mechanisms** section.

3 Clear the **Convection** checkbox.

Porous Catalyst - Biomaterial

In this model the adsorption process is not considered to be at equilibrium. The built in adsorption functionality is based on the assumption of equilibrium. Therefore, omit this functionality by clearing the checkbox **Adsorption/Desorption of bulk species**.

1 In the **Model Builder** window, under **Component 2 (comp2)** > **Transport of Diluted Species in Porous Catalysts (tds)** click **Porous Catalyst 1**.

2 In the **Settings** window for **Porous Catalyst**, locate the **Adsorbed Species** section.

3 Clear the **Adsorption/Desorption of bulk species** checkbox.

4 Click to collapse the **Adsorbed Species** section. Locate the **Surface Species** section. In the table, enter the following settings:

Surface species	Initial values (mol/m^2)
mp	c_mp_init
mpd	c_mpd_init

5 In the **Label** text field, type `Porous Catalyst - Biomaterial`.

Continue setting the mass transport properties in the biomaterial matrix in the **Transport of Diluted Species** interface.

Fluid 1

1 In the **Model Builder** window, click **Fluid 1**.

2 In the **Settings** window for **Fluid**, locate the **Diffusion** section.

3 In the D_{cd} text field, type `D_d`.

4 In the D_{ce} text field, type `D_e`.

5 In the D_{cp} text field, type `D_p`.

6 In the D_{cpd} text field, type `D_pd`.

7 From the **Effective diffusivity model** list, choose **No correction**.

Porous Matrix 1

1 In the **Model Builder** window, click **Porous Matrix 1**.

2 In the **Settings** window for **Porous Matrix**, locate the **Matrix Properties** section.

3 From the ε_p list, choose **User defined**. In the associated text field, type `epsBio`.

Fluid - Surroundings

1 In the **Physics** toolbar, click **Domains** and choose **Fluid**.

2 Select Domain 3 only.

3 In the **Settings** window for **Fluid**, type `Fluid - Surroundings` in the **Label** text field.

4 Locate the **Diffusion** section. In the D_{cd} text field, type `D_d_s`.

5 In the D_{ce} text field, type `D_e_s`.

6 In the D_{cp} text field, type `D_p_s`.

7 In the D_{cpd} text field, type `D_pd_s`.

Fluid - Nerve

1 Right-click **Fluid - Surroundings** and choose **Duplicate**.

2 Select Domain 1 only.

3 In the **Settings** window for **Fluid**, type `Fluid - Nerve` in the **Label** text field.

4 Locate the **Diffusion** section. In the D_{cd} text field, type `D_d_n`.

5 In the D_{ce} text field, type `D_e_n`.

6 In the D_{cp} text field, type `D_p_n`.

7 In the D_{cpd} text field, type `D_pd_n`.

Reactions 1

1 In the **Physics** toolbar, click **Domains** and choose **Reactions**.

2 Select Domains 1 and 3 only.

3 In the **Settings** window for **Reactions**, locate the **Reaction Rates** section.

4 From the R_{cd} list, choose **Reaction rate for species d (chem)**.

5 From the R_{ce} list, choose **Reaction rate for species e (chem)**.

6 From the R_{cp} list, choose **Reaction rate for species p (chem)**.

7 From the R_{cpd} list, choose **Reaction rate for species pd (chem)**.

8 Click to expand the **Reacting Volume** section.

Reactions 2

1 Right-click **Reactions 1** and choose **Duplicate**.

2 Select Domain 2 only.

3 In the **Settings** window for **Reactions**, locate the **Reacting Volume** section.

4 From the list, choose **Pore volume**.

Initial Values 2

1 In the **Physics** toolbar, click **Domains** and choose **Initial Values**.

2 Select Domains 2 and 3 only.

MESH 1

Set up the mesh. Refine the mesh at the interfaces where the different domains types meet. Sharp gradients will develop here at the start of the simulation due to the initial conditions.

1 In the **Model Builder** window, under **Component 2 (comp2)** click **Mesh 1**.

2 In the **Settings** window for **Mesh**, locate the **Sequence Type** section.

3 From the list, choose **User-controlled mesh**.

Size

1 In the **Model Builder** window, under **Component 2 (comp2)** > **Mesh 1** click **Size**.

2 In the **Settings** window for **Size**, locate the **Element Size** section.

3 From the **Calibrate for** list, choose **Fluid dynamics**.

4 From the **Predefined** list, choose **Fine**.

5 Click **Build Selected**.

Size 1

1 In the **Model Builder** window, right-click **Mesh 1** and choose **Size**.

2 In the **Settings** window for **Size**, locate the **Geometric Entity Selection** section.

3 From the **Geometric entity level** list, choose **Boundary**.

4 Select Boundaries 4, 7, and 9 only.

5 Locate the **Element Size** section. Click the **Custom** button.

6 Locate the **Element Size Parameters** section.

7 Select the **Maximum element size** checkbox. In the associated text field, type `0.1`.

Free Triangular 1

In the **Model Builder** window, right-click **Free Triangular 1** and choose **Build Selected**.

Boundary Layers 1

In the **Mesh** toolbar, click **Boundary Layers**.

Boundary Layer Properties

1 In the **Model Builder** window, click **Boundary Layer Properties**.

2 Select Boundaries 4, 6, 7, and 9 only.

3 In the **Settings** window for **Boundary Layer Properties**, click **Build All**.

In order to compare concentrations, define volumetric concentration variables for the matrix-bound species residing in the biomaterial.

DEFINITIONS (COMP2)

Biomaterial Concentrations

1 In the **Model Builder** window, under **Component 2 (comp2)** right-click **Definitions** and choose **Variables**.

2 In the **Settings** window for **Variables**, locate the **Geometric Entity Selection** section.

3 From the **Geometric entity level** list, choose **Domain**.

4 Select Domain 2 only.

5 Locate the **Variables** section. In the table, enter the following settings:

Name	Expression	Unit	Description
cmp	tds.csurf_mp*Ssa	mol/m³	Matrix-bound peptide, volumetric concentration
cmpd	tds.csurf_mpd*Ssa	mol/m³	Matrix-bound peptide-drug, volumetric concentration

6 In the **Label** text field, type `Biomaterial Concentrations`.

STUDY 2

1 In the **Model Builder** window, click **Study 2**.

2 In the **Settings** window for **Study**, locate the **Study Settings** section.

3 Clear the **Generate default plots** checkbox.

The results from the space independent model show that the initial drug release is complete after approximately 0.01s. Simulate this process by using a manual initial time step less than this initial transient. By using the option **Steps taken by solver** for setting **Times to store**, it is also possible to post process the transient.

Solution 2 (sol2)

1 In the **Study** toolbar, click **Show Default Solver**.

2 In the **Model Builder** window, expand the **Solution 2 (sol2)** node, then click **Time-Dependent Solver 1**.

3 In the **Settings** window for **Time-Dependent Solver**, locate the **General** section.

4 From the **Times to store** list, choose **Steps taken by solver**.

5 In the **Store every Nth step** text field, type `6`.

6 Click to expand the **Time Stepping** section.

7 Select the **Initial step** checkbox. In the associated text field, type `1e-6`.

Step 1: Time Dependent

1 In the **Model Builder** window, under **Study 2** click **Step 1: Time Dependent**.

2 In the **Settings** window for **Time Dependent**, locate the **Study Settings** section.

3 In the **Output times** text field, type `0 16 [h]`.

4 In the **Study** toolbar, click **Compute**.

Use the **Result Templates** to visualize all the bulk species concentrations in one array plot.

RESULT TEMPLATES

1 In the **Home** toolbar, click **Result Templates** to open the **Result Templates** window.

2 Go to the **Result Templates** window.

3 In the tree, select **Study 2/Solution 2 (3) (sol2)** > **Transport of Diluted Species in Porous Catalysts** > **Plot array: Concentrations, d, e, p, pd (tds)**.

4 Click the **Add Result Template** button in the window toolbar.

5 In the **Home** toolbar, click **Result Templates** to close the **Result Templates** window.

RESULTS

Bulk Concentrations

Follow these steps to set up Figure 4.

1 In the **Settings** window for **2D Plot Group**, type `Bulk Concentrations` in the **Label** text field.

2 Locate the **Data** section. From the **Time (s)** list, choose **Interpolation**.

3 In the **Time** text field, type `1.5[h]`.

4 Locate the **Color Legend** section. Clear the **Show titles** checkbox.

5 Click to expand the **Plot Array** section.

Surface, d

1 In the **Model Builder** window, expand the **Bulk Concentrations** node, then click **Surface, d**.

2 In the **Settings** window for **Surface**, locate the **Coloring and Style** section.

3 From the **Color table** list, choose **Cerinthe**.

d

1 In the **Model Builder** window, click **d**.

2 In the **Settings** window for **Annotation**, locate the **Annotation** section.

3 In the **Text** text field, type `Drug`.

Surface, e

1 In the **Model Builder** window, click **Surface, e**.

2 In the **Settings** window for **Surface**, click to expand the **Inherit Style** section.

3 From the **Plot** list, choose **Surface, d**.

e

1 In the **Model Builder** window, click **e**.

2 In the **Settings** window for **Annotation**, locate the **Annotation** section.

3 In the **Text** text field, type `Enzyme`.

4 Locate the **Position** section. In the **Z** text field, type `10`.

Surface, p

1 In the **Model Builder** window, click **Surface, p**.

2 In the **Settings** window for **Surface**, locate the **Inherit Style** section.

3 From the **Plot** list, choose **Surface, d**.

p

1 In the **Model Builder** window, click **p**.

2 In the **Settings** window for **Annotation**, locate the **Annotation** section.

3 In the **Text** text field, type `Peptide`.

Surface, pd

1 In the **Model Builder** window, click **Surface, pd**.

2 In the **Settings** window for **Surface**, locate the **Inherit Style** section.

3 From the **Plot** list, choose **Surface, d**.

pd

1 In the **Model Builder** window, click **pd**.

2 In the **Settings** window for **Annotation**, locate the **Annotation** section.

3 In the **Text** text field, type `Drug-Peptide`.

4 Locate the **Position** section. In the **Z** text field, type `10`.

Bulk Concentrations

1 In the **Model Builder** window, click **Bulk Concentrations**.

2 In the **Settings** window for **2D Plot Group**, click to expand the **Title** section.

3 From the **Title type** list, choose **None**.

Set up a plot for the matrix-bound species concentrations.

Matrix-Bound Species Concentrations

1 Right-click **Bulk Concentrations** and choose **Duplicate**.

2 In the **Model Builder** window, click **Bulk Concentrations 1**.

3 In the **Settings** window for **2D Plot Group**, type `Matrix-Bound Species Concentrations` in the **Label** text field.

Surface, e, Surface, pd, Total Flux, e, Total Flux, pd, e, pd

1 In the **Model Builder** window, under **Results** > **Matrix-Bound Species Concentrations**, Ctrl-click to select **Surface, e**, **Total Flux, e**, **e**, **Surface, pd**, **Total Flux, pd**, and **pd**.

2 Right-click and choose **Delete**.

Surface, mp

1 In the **Model Builder** window, under **Results** > **Matrix-Bound Species Concentrations** click **Surface, d**.

2 In the **Settings** window for **Surface**, type `Surface, mp` in the **Label** text field.

3 Locate the **Expression** section. In the **Expression** text field, type `cmp`.

4 Locate the **Coloring and Style** section. From the **Color table** list, choose **Arctium**.

Total Flux, d

In the **Model Builder** window, right-click **Total Flux, d** and choose **Delete**.

Total Flux, p

In the **Model Builder** window, right-click **Total Flux, p** and choose **Delete**.

mp

1 In the **Model Builder** window, under **Results** > **Matrix-Bound Species Concentrations** click **d**.

2 In the **Settings** window for **Annotation**, type `mp` in the **Label** text field.

3 Locate the **Annotation** section. In the **Text** text field, type `Matrix-Bound Peptide`.

Surface, mpd

1 In the **Model Builder** window, under **Results** > **Matrix-Bound Species Concentrations** click **Surface, p**.

2 In the **Settings** window for **Surface**, type `Surface, mpd` in the **Label** text field.

3 Locate the **Expression** section. In the **Expression** text field, type `cmpd`.

mpd

1 In the **Model Builder** window, under **Results** > **Matrix-Bound Species Concentrations** click **p**.

2 In the **Settings** window for **Annotation**, type `mpd` in the **Label** text field.

3 Locate the **Annotation** section. In the **Text** text field, type `Matrix-Bound Peptide-Drug`.

Matrix-Bound Species Concentrations

Click the **Zoom Extents** button in the **Graphics** toolbar.

The concentration profiles across parts of the modeling domains, as in Figure 5 and Figure 6, require cut line datasets.

Cut Line 2D 1

1. In the **Results** toolbar, click **Cut Line 2D**.
2. In the **Settings** window for **Cut Line 2D**, locate the **Line Data** section.
3. In row **Point 1**, set **Z** to 3.
4. In row **Point 2**, set **R** to 6.
5. In row **Point 2**, set **Z** to 3.
6. Click **Plot**.

1D Plot Group 4

1. In the **Results** toolbar, click **1D Plot Group**.
2. In the **Settings** window for **1D Plot Group**, locate the **Data** section.
3. From the **Dataset** list, choose **Cut Line 2D 1**.

Line Graph 1

1. Right-click **1D Plot Group 4** and choose **Line Graph**.

   Create Figure 5 following these steps.
2. In the **Settings** window for **Line Graph**, locate the **y-Axis Data** section.
3. In the **Expression** text field, type `cpd+cd`.
4. Click to expand the **Coloring and Style** section. From the **Width** list, choose **2**.
5. Find the **Line markers** subsection. From the **Marker** list, choose **Cycle**.
6. From the **Positioning** list, choose **Interpolated**.
7. In the **Number** text field, type 6.

Total Drug Concentration

1. In the **Model Builder** window, under **Results** click **1D Plot Group 4**.
2. In the **Settings** window for **1D Plot Group**, type `Total Drug Concentration` in the **Label** text field.
3. Locate the **Data** section. From the **Time selection** list, choose **Interpolated**.
4. In the **Times (s)** text field, type `0 0.1[h] 0.5[h] range(1,1,8)[h]`.
5. Locate the **Title** section. From the **Title type** list, choose **Manual**.

6 In the **Title** text area, type `c<sub>drug</sub> + c<sub>peptide-drug</sub>`.

7 Locate the **Plot Settings** section.

8 Select the **y-axis label** checkbox. In the associated text field, type `Concentration (mol/m<sup>3</sup>)`.

9 In the **Total Drug Concentration** toolbar, click **Plot**.

Line Graph 1

1 In the **Model Builder** window, click **Line Graph 1**.

2 In the **Settings** window for **Line Graph**, click to expand the **Legends** section.

3 From the **Legends** list, choose **Evaluated**.

4 In the **Legend** text field, type `t = eval(t/3600) h`.

5 In the **Total Drug Concentration** toolbar, click **Plot**.

6 Select the **Show legends** checkbox.

Total Drug Concentration

Create Figure 6 following these steps.

Total Drug Concentration 1

In the **Model Builder** window, right-click **Total Drug Concentration** and choose **Duplicate**.

Line Graph 1

1 In the **Model Builder** window, expand the **Total Drug Concentration 1** node, then click **Line Graph 1**.

2 In the **Settings** window for **Line Graph**, locate the **y-Axis Data** section.

3 In the **Expression** text field, type `cmp+cmpd`.

Total Matrix Concentration

1 In the **Model Builder** window, under **Results** click **Total Drug Concentration 1**.

2 In the **Settings** window for **1D Plot Group**, type `Total Matrix Concentration` in the **Label** text field.

3 Locate the **Title** section. In the **Title** text area, type `c<sub>mp</sub> + c<sub>mpd</sub>`.

4 In the **Total Matrix Concentration** toolbar, click **Plot**.

Now use an **Evaluation Group** to compute how the drug is distributed among the domains.

Evaluation Group 1

1 In the **Results** toolbar, click  **Evaluation Group**.

Create multiple **Surface Integration** nodes to visualize the concentration in each part of the domain. Note that the free species in the biomaterial needs to be multiplied by the porosity.

2 In the **Settings** window for **Evaluation Group**, locate the **Data** section.

3 From the **Dataset** list, choose **Study 2/Solution 2 (3) (sol2)**.

Surface Integration 1

1 Right-click **Evaluation Group 1** and choose **Integration** > **Surface Integration**.

2 Select Domain 2 only.

3 In the **Settings** window for **Surface Integration**, locate the **Expressions** section.

4 In the table, enter the following settings:

Expression	Unit	Description
(cd+cpd)*epsBio	mol	Free drug in the biomaterial

Surface Integration 2

1 Right-click **Surface Integration 1** and choose **Duplicate**.

2 In the **Settings** window for **Surface Integration**, locate the **Expressions** section.

3 In the table, enter the following settings:

Expression	Unit	Description
cmpd	mol	Matrix-bound drug

Surface Integration 3

1 In the **Model Builder** window, right-click **Evaluation Group 1** and choose **Integration** > **Surface Integration**.

2 Select Domain 1 only.

3 In the **Settings** window for **Surface Integration**, locate the **Expressions** section.

4 In the table, enter the following settings:

Expression	Unit	Description
cd+cpd	mol	Drug in nerve

Surface Integration 4

1 Right-click **Evaluation Group 1** and choose **Integration** > **Surface Integration**.

2 Select Domain 3 only.

3 In the **Settings** window for **Surface Integration**, locate the **Expressions** section.

4 In the table, enter the following settings:

Expression	Unit	Description
cd+cpd	mol	Drug in surrounding

Evaluation Group 1

1 In the **Model Builder** window, click **Evaluation Group 1**.

2 In the **Settings** window for **Evaluation Group**, locate the **Transformation** section.

3 From the **Transformation type** list, choose **General**.

4 In the **Column header** text field, type `Total drug concentration`.

5 In the **Evaluation Group 1** toolbar, click **Evaluate**.

6 Select the **Keep child nodes** checkbox.

7 In the **Evaluation Group 1** toolbar, click **Evaluate**.

EVALUATION GROUP 1

1 Go to the **Evaluation Group 1** window.

2 Click the **Table Graph** button in the window toolbar.

RESULTS

Table Graph 1

1 In the **Settings** window for **Table Graph**, locate the **Coloring and Style** section.

2 From the **Width** list, choose **2**.

3 Click to expand the **Legends** section. Select the **Show legends** checkbox.

Drug Distribution

1 In the **Model Builder** window, click **1D Plot Group 6**.

2 In the **Settings** window for **1D Plot Group**, locate the **Legend** section.

3 From the **Position** list, choose **Middle right**.

4 In the **Label** text field, type `Drug Distribution`.

5 In the **Drug Distribution** toolbar, click **Plot**.

The following steps show how you can set up animations of your model results.

Animation - Bulk Concentrations

1 In the **Results** toolbar, click **Animation** and choose **Player**.

2 In the **Settings** window for **Animation**, type `Animation - Bulk Concentrations` in the **Label** text field.

3 Locate the **Scene** section. From the **Subject** list, choose **Bulk Concentrations**.

4 Locate the **Animation Editing** section. From the **Time selection** list, choose **Interpolated**.

5 In the **Times (s)** text field, type `range(0,0.5,16)[h]`.

6 Locate the **Frames** section. From the **Frame selection** list, choose **All**.

7 Click the **Play** button in the **Graphics** toolbar.

Animation - Matrix Concentrations

1 Right-click **Animation - Bulk Concentrations** and choose **Duplicate**.

2 In the **Settings** window for **Animation**, type `Animation - Matrix Concentrations` in the **Label** text field.

3 Locate the **Scene** section. From the **Subject** list, choose **Matrix-Bound Species Concentrations**.

4 Click the **Play** button in the **Graphics** toolbar.