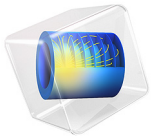

Model created in COMSOL Multiphysics 6.4

Production of Antibody–Drug Conjugates in a Stirred Tank Reactor

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Introduction

In oncology, antibody–drug conjugates (ADCs) are engineered proteins that carry a cytotoxic drug. They mimic human antibodies by binding selectively to specific antigen in the body in order to target the delivery of the drug to the malignant cells.

In this example, the conjugation process to produce an ADC in an isothermal, semi-batch, stirred tank reactor is modeled. The monoclonal antibody (mAb) used in this example has two linker molecules that serve to attach two drug molecules in a site-directed conjugation reaction. At the start of the conjugation process, the tank contains a dilute solution of mAb. The drug is fed into the tank through a dip-tube with an outlet into the tank close to the stirrer. The drug is fed at a controlled rate over a specified feed duration and once the feeding step is done, the reactions continue until the desired conversion is reached.

The desired outcome of the conjugation process is a homogeneous and stable antibody–drug conjugate without aggregation. The product quality of the ADC is highly dependent on the conjugation process conditions such as the initial antibody concentration, antibody-to-drug ratio, and mixing time. This model can be used to study the influence of these conditions, as well as broader process factors such as stirrer speed, feed rate, and reactor design.

The simulation gives the fluid flow and the concentration fields in the reactor. The space-dependent results are compared with the concentrations in a perfectly mixed system, described by the Reaction Engineering interface. The current model can be extended to study the influence of temperature by adding a heat transfer interface.

Model Definition

This model describes the coupled reaction kinetics, fluid flow, and mass transfer in the semi-batch stirred tank reactor. The temperature is assumed to be constant at 25°C.

MODEL GEOMETRY

The tank is cylindrical with a cone-shaped bottom. A stirrer with four blades is located on the slanted cone surface. The geometry is not axisymmetric so a full 3D geometry is needed. Figure 1 shows the tank geometry where half of the tank wall has been hidden in order to show the stirrer inside. The subdomain surrounding the stirrer marks the rotating domain. The dip-tube outlet is located close to the rotating domain, however the tube is not explicitly modeled. The total volume of the tank is 25 dm^3.

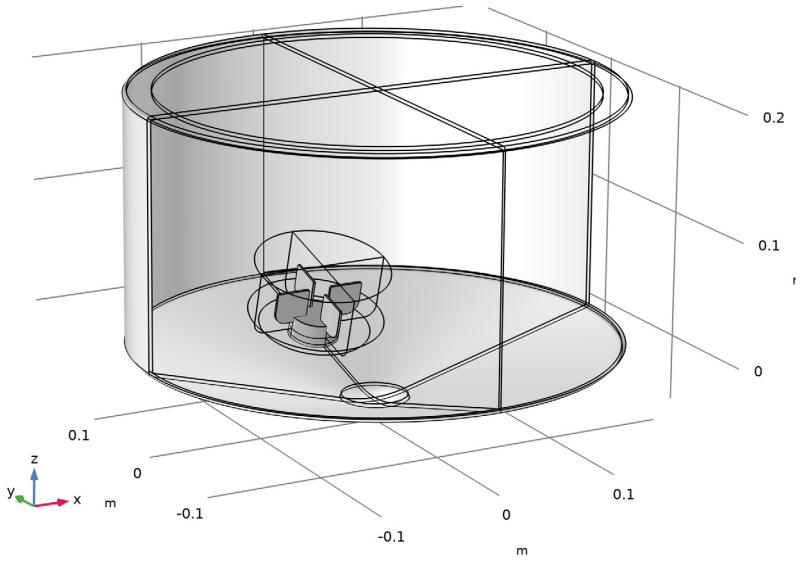

Figure 1: Model geometry. The edges around the stirrer show the rotating domain. The dip-tube is not included in the model.

REACTIONS

The modeled chemical system consists of two conjugation reactions to produce the ADC and one undesired side-reaction where the drug is consumed (Ref. 1):

- Conjugation step one:

$$\mathrm{mAb} + \mathrm{Drug} \rightarrow \mathrm{mAbDrug} \tag{1}$$

- Conjugation step two:

$$\mathrm{mAbDrug} + \mathrm{Drug} \rightarrow \mathrm{mAb(Drug)_2} \tag{2}$$

- Undesired side-reaction:

$$\mathrm{Drug} \rightarrow \mathrm{Sink} \tag{3}$$

The reactions are irreversible and the reaction rates are modeled according to the mass-action law. Since the system is isothermal, constant values are used for the reaction rate constants at the operating temperature.

FLUID FLOW

The Turbulent Flow, k–ε interface is used to describe the fluid flow. The flow is modeled as incompressible and the fluid material is water since the solution is dilute and the reactions are assumed to have little effect on the flow field. The rotational speed of the stirrer is 360 rpm and a flow continuity boundary condition is applied to the rotating domain boundaries which surround the stirrer.

MASS TRANSFER

The Transport of Diluted Species interface is used to describe the mass transfer in the fluid phase with water as the solvent. Initially, the tank contains a dilute concentration of the monoclonal antibody (mAb) reactant. A point mass source is used to feed the drug reactant into the tank since the dip tube outlet is not explicitly modeled. The feeding process is modeled using a step function which ramps up the feeding rate from zero during the first second, stays constant for two seconds, and then turns off. In an analogous manner to the fluid flow description, a continuity boundary condition for mass transfer is applied on the rotating domain boundaries that surround the stirrer.

COMPUTATION

The model contains four studies: one for the perfectly mixed system, and three for the space-dependent system.

1. A time-dependent study computes the concentration in a space-independent, ideal semi-batch reactor defined by the Reaction Engineering interface.
2. A stationary Frozen Rotor study solves only for the fluid flow in the tank. This study step uses an auxiliary sweep to increase the stirrer rate from 10 to 360 rpm.
3. A time-dependent study computes the flow field in the tank. The flow field solution from the previous stationary Frozen Rotor study step at 360 rpm is used as the initial flow field.
4. A time-dependent study solves all of the physics interfaces, including Chemistry, Transport of Diluted Species, Turbulent Flow, and the Reacting Flow multiphysics coupling. The flow field solution from the previous time-dependent study step is used as the initial flow field.

Figure 2 and Figure 3 compare the results from the perfectly mixed model and the space-dependent model. In Figure 2, the concentration of the monoclonal antibodies (mAb) as well as the conjugated antibodies (mAbDrug and mAb(Drug)$_2$) are shown.

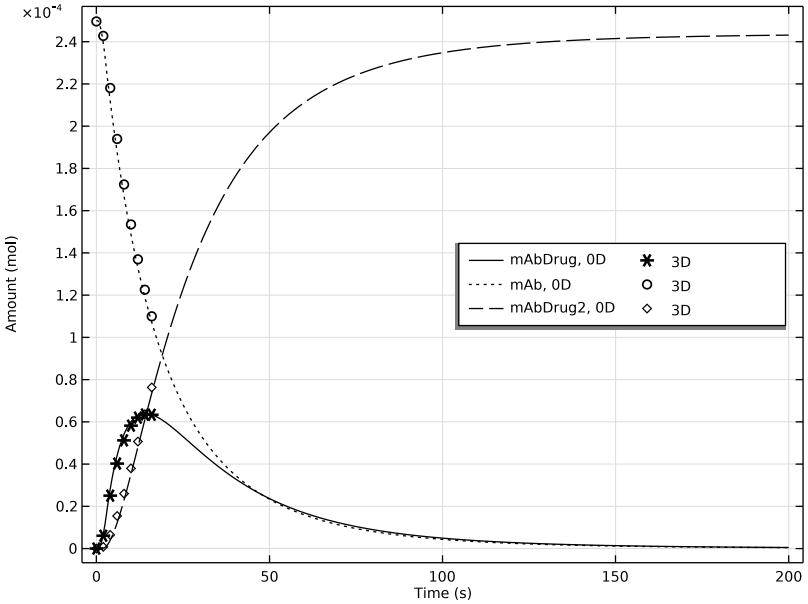

Figure 2: .The concentration of the nonconjugated antibody decreases as it reacts to form the conjugated species mAbDrug. This conjugated species is then converted into the final product.

Figure 3 shows the drug-to-antibody ratio (DAR) and the yield (Y) of the final product mAb(Drug)$_2$.

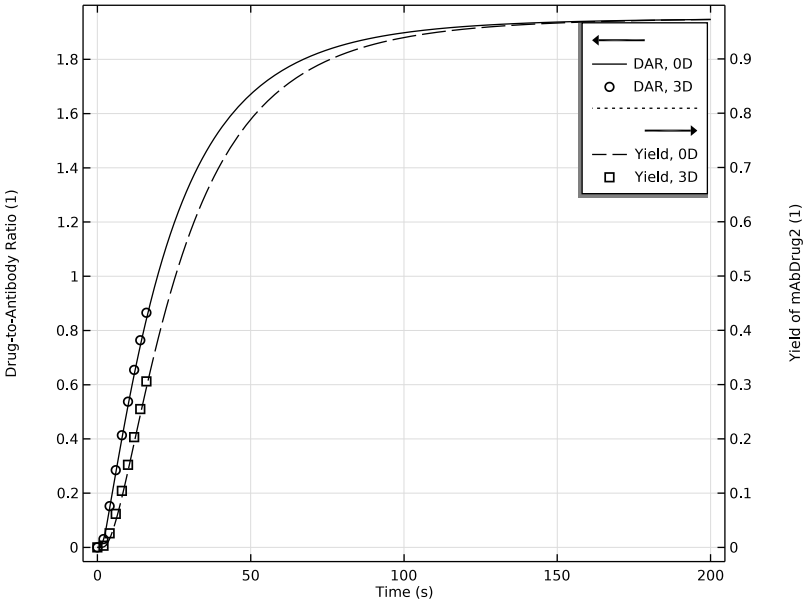

Figure 3: Drug-to-antibody ratio (DAR) and yield of final product for the perfectly stirred tank as well as for the space-dependent tank.

Figure 2 and Figure 3 clearly show that the results from the 3D model are consistent with those of the perfectly mixed system. This indicates that despite the concentration gradients in the space-dependent tank (see Figure 4 through Figure 15), the reactions are not limited by mass transfer at this mixing speed.

Figure 4 through Figure 7 show the concentration of Drug at 2, 4, 8, and 16 s. At time zero, there is no drug in the reactor yet. The feeding rate of the drug is ramped up during one second and reaches the maximum feed rate at 1 s. At 2 s, the feeding stops. At this time, the concentration gradients of the drug throughout the reactor are still high. At 8 s, the concentration gradients have decrease due to stirring and the reaction. At 16 s, the drug concentration is homogeneous in the tank.

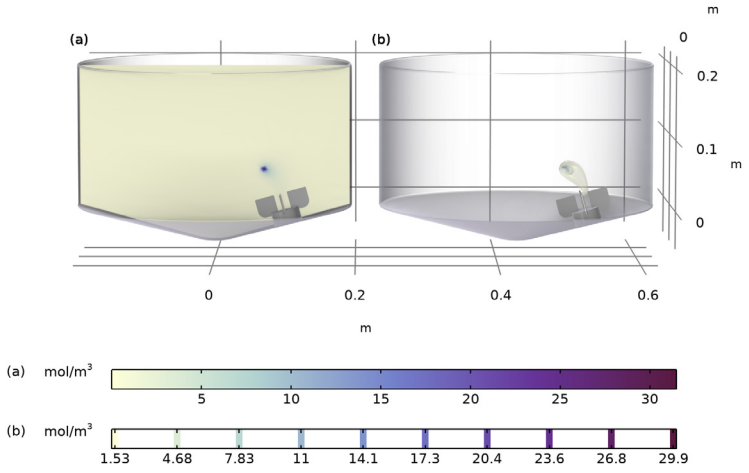

Figure 4: Concentration of Drug at 2 s.

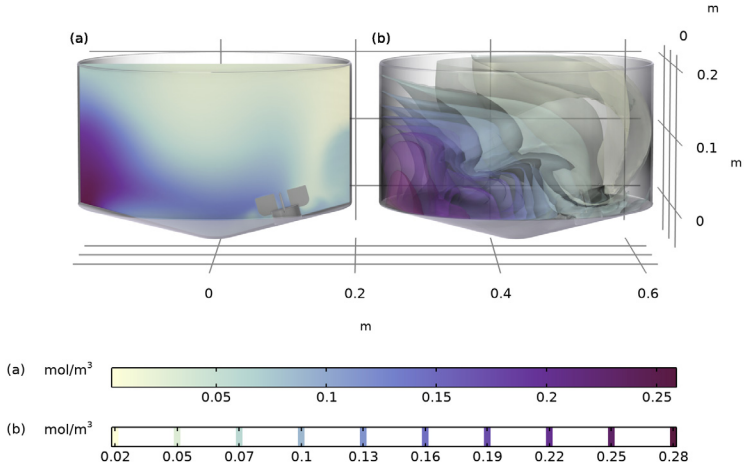

Figure 5: Concentration of Drug at 4 s.

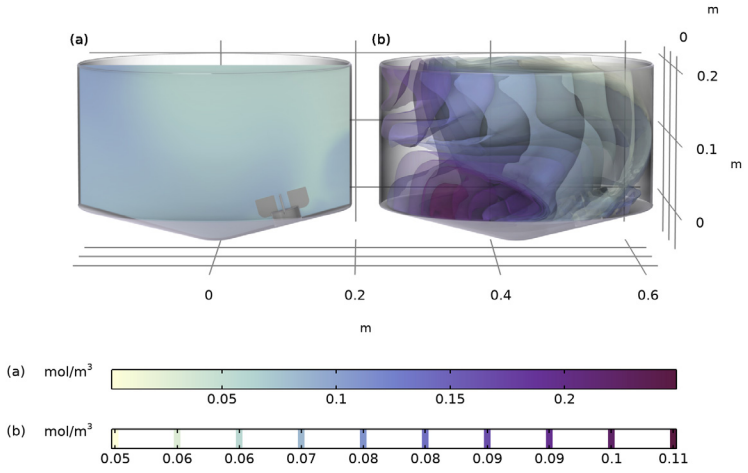

Figure 6: Concentration of Drug at 8 s.

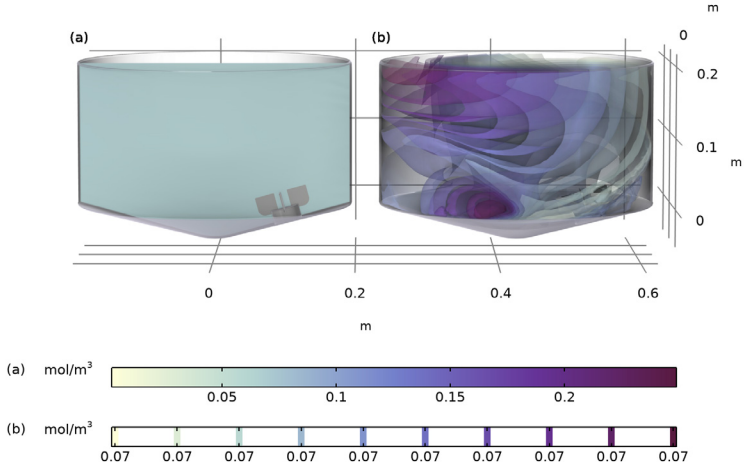

Figure 7: Concentration of Drug at 16 s.

Figure 8 through Figure 11 show the concentration of the mono-conjugated species, mAbDrug, at 2, 4, 8, and 16 s. The concentration of mAbDrug reaches a maximum before the stirring enables further reaction with Drug.

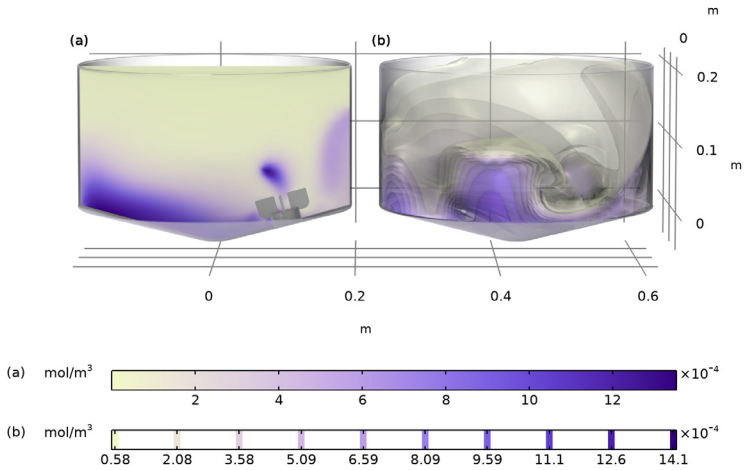

Figure 8: Concentration of mAbDrug at 2 s.

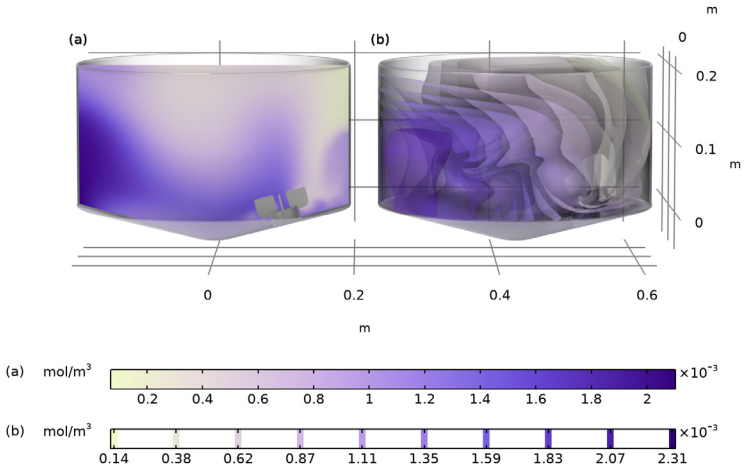

Figure 9: Concentration of mAbDrug at 4 s.

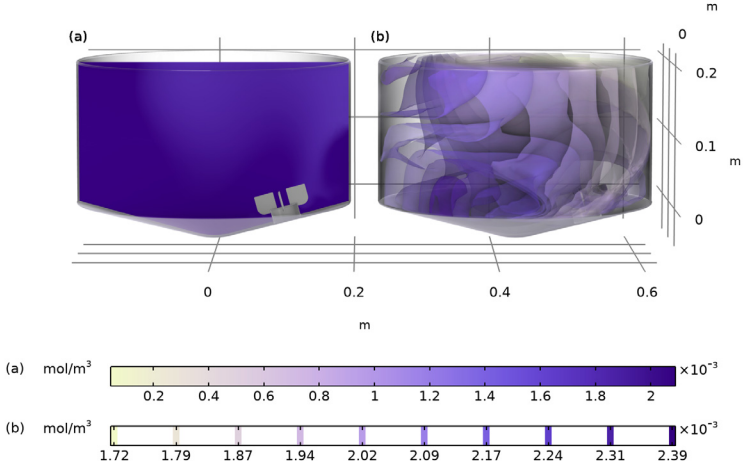

Figure 10: Concentration of mAbDrug at 8 s.

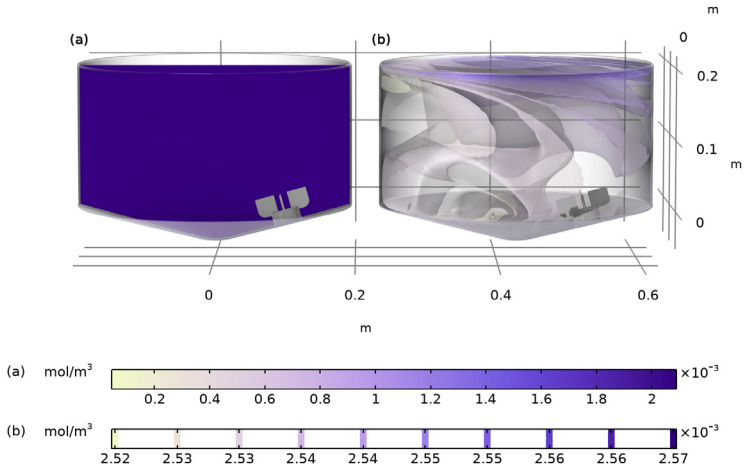

Figure 11: Concentration of mAbDrug at 16 s.

Figure 12 through Figure 15 show the concentration of the final product, mAb(Drug)$_2$, at 2, 4, 8, and 16 s. By 16 s the concentration is homogeneous in the tank reactor.

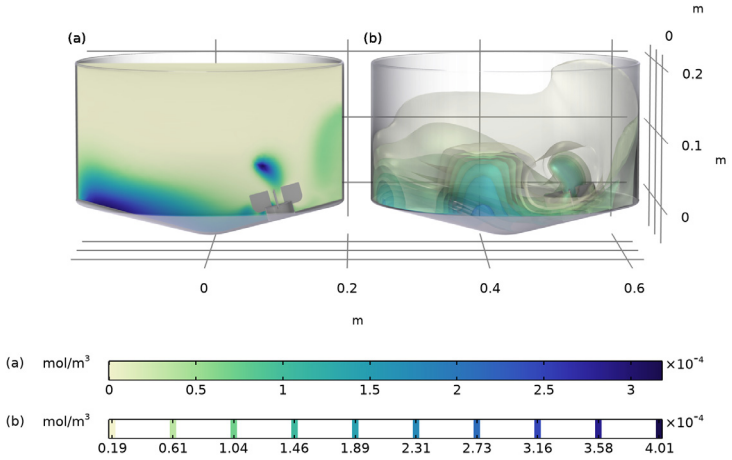

Figure 12: Concentration of mAb(Drug)$_2$ at 2 s.

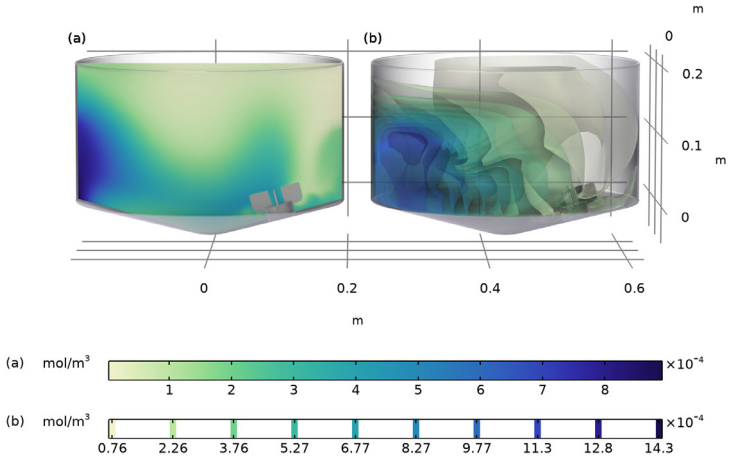

Figure 13: Concentration of mAb(Drug)$_2$ at 4 s.

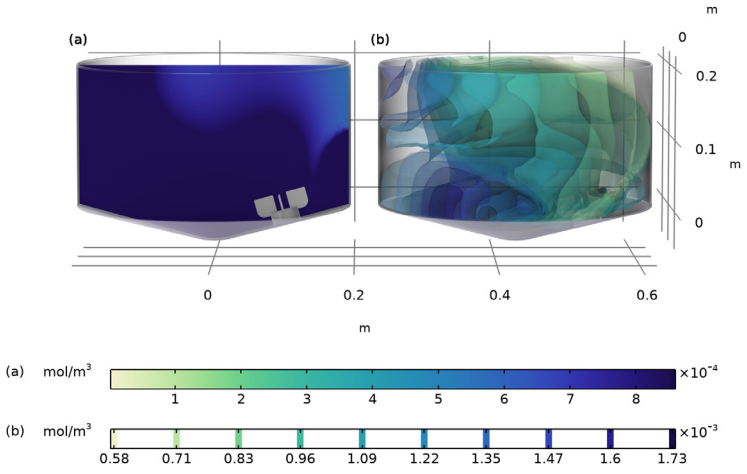

Figure 14: Concentration of mAb(Drug)$_2$ at 8 s.

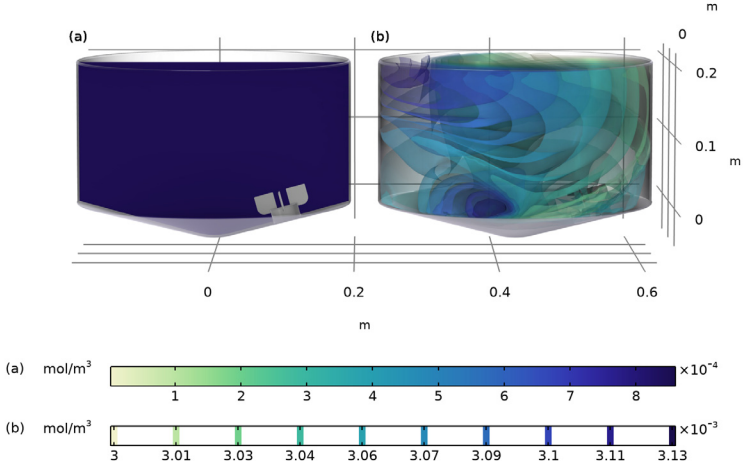

Figure 15: Concentration of mAb(Drug)$_2$ at 16 s.

Application Library path: `Chemical_Reaction_Engineering_Module/Reactors_with_Mass_Transfer/stirred_tank_adc_production`

Reference

1. J.T. Weggen, J. Seidel, R. Bean, M. Wendeler, and J. Hubbuch, "Kinetic studies and CFD-based reaction modeling for insights into the scalability of ADC conjugation reactions," *Front. Bioeng. Biotechnol.*, vol. 11, 2023; doi.org/10.3389/fbioe.2023.1123842.

Modeling Instructions

This space-dependent model describes a stirred semibatch tank reactor used for producing antibody-drug conjugates. When simulating a chemical reactor, it is often good practice to first study the reaction kinetics in an ideal tank reactor. The steps to set up such a space-independent system follows.

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

NEW

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

Import the model parameters from a text file. The imported parameters are for both the space-independent and the space-dependent models.

GLOBAL DEFINITIONS

Parameters: Process Conditions

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 `stirred_tank_adc_production_process_parameters.txt`.
5. In the **Label** text field, type `Parameters: Process Conditions`.

While at it, also import the parameters related to the tank geometry.

Parameters: Geometry

1 In the **Home** toolbar, click **Parameters** and choose **Add** > **Parameters**.

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 `stirred_tank_adc_production_geometry_parameters.txt`.

5 In the **Label** text field, type `Parameters: Geometry`.

Add the component for the ideal tank reactor system and give it a descriptive name.

ADD COMPONENT

In the **Home** toolbar, click **Add Component** and choose **0D**.

IDEAL SEMIBATCH REACTOR

In the **Settings** window for **Component**, type `Ideal Semibatch Reactor` in the **Label** text field.

ADD PHYSICS

1 In the **Home** toolbar, click **Add Physics** to open the **Add Physics** window.

2 Go to the **Add Physics** window.

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

4 Click the **Add to Ideal Semibatch Reactor** button in the window toolbar.

5 In the **Home** toolbar, click **Add Physics** to close the **Add Physics** window.

REACTION ENGINEERING (RE)

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

2 From the **Reactor type** list, choose **Semibatch**.

3 Locate the **Energy Balance** section. In the T text field, type `T_iso`.

4 Locate the **Mixture Properties** section. 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 `mAb + Drug => mAbDrug`.

4 Click **Apply**.

5 Locate the **Rate Constants** section. In the k^{f} text field, type `k1`.

Species: mAb

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

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

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

Species: Drug

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

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

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

Species: mAbDrug

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

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

3 In the M text field, type `M_mAb+M_Drug`.

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 `mAbDrug + Drug => mAb(Drug)2`.

4 Click **Apply**.

5 Locate the **Rate Constants** section. In the k^{f} text field, type `k2`.

Species: mAb(Drug)2

1 In the **Model Builder** window, click **Species: mAb(Drug)2**.

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

3 In the M text field, type `M_mAb+M_Drug*2`.

Reaction 3

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 `Drug => sink`.

4 Click **Apply**.

5 Locate the **Rate Constants** section. In the k^{f} text field, type `k3`.

Species: sink

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

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

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

Initial Values 1

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

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

3 In the V_{r0} text field, type `V_reactor`.

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

Species	Concentration (mol/m^3)
mAb	`c_init_mAb`

Add an **Analytic** function to specify the varying volumetric feed rate to the tank. For convenience, use the built-in **Step** function in the feed rate expression.

DEFINITIONS

Step 1 (step1)

1 In the **Definitions** toolbar, click f(x) **More Functions** and choose **Step**.

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

3 In the **Location** text field, type `t_transitionZone/2`.

4 Click to expand the **Smoothing** section. In the **Size of transition zone** text field, type `t_transitionZone`.

Click **Plot** if you want to see what the step function looks like.

Volumetric Feed Rate

1 In the **Home** toolbar, click f(x) **Functions** and choose **Local** > **Analytic**.

2 In the **Settings** window for **Analytic**, type `Volumetric Feed Rate` in the **Label** text field.

3 In the **Function name** text field, type `feedRate`.

4 Locate the **Definition** section. In the **Expression** text field, type `v_feed*(t<t_feed+t_transitionZone)*step1(t)`.

5 In the **Arguments** text field, type `t`.

6 Locate the **Units** section. In the **Function** text field, type `m^3/s`.

7 In the table, enter the following settings:

Argument	Unit
t	s

8 Locate the **Plot Parameters** section. In the table, enter the following settings:

Plot	Argument	Lower limit	Upper limit	Fixed value	Unit
√	t	0	t_run	0	s

Use the analytic function in a **Feed Inlet** feature.

REACTION ENGINEERING (RE)

Feed Inlet 1

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

2 In the **Settings** window for **Feed Inlet**, locate the **Feed Inlet Properties** section.

3 In the v_f text field, type `feedRate(t)`.

4 Locate the **Feed Inlet Concentration** section. In the table, enter the following settings:

Species	Concentration (mol/m^3)
Drug	c_feed_Drug

The perfectly mixed reactor system is now defined. Add a study to compute the solution.

ADD STUDY

1 In the **Study** toolbar, click **Add Study** to open the **Add Study** window.

2 Go to the **Add Study** window.

3 Find the **Studies** subsection. In the **Select Study** tree, select **General Studies** > **Time Dependent**.

4 Click the **Add Study** button in the window toolbar.

5 In the **Study** toolbar, click **Add Study** to close the **Add Study** window.

STUDY 1

Step 1: Time Dependent

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

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

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

4 In the **Settings** window for **Study**, type `Study 1: Ideal Semibatch Reactor` in the **Label** text field.

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

The **1D Plot Group** labeled Concentration shows the concentrations of the species in the ideal tank reactor.

In the next phase of this example, set up a space-dependent 3D model of the stirred tank reactor, including mass transport, reactions, and fluid flow.

REACTION ENGINEERING (RE)

The **Generate Space-Dependent Model** feature creates a link between the space-independent model and the space-dependent model. It allows you to transfer reaction kinetics, thermodynamics, and transport properties from the **Reaction Engineering** interface to the corresponding physics interfaces in the space-dependent model. For this example, we need physics that describe turbulent flow and mass transfer.

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 **Physics Interfaces** section.
3. Find the **Chemical species transport** subsection. From the list, choose **Reacting Flow: New**.
4. From the list, choose **Turbulent Flow, Diluted Species**.
5. Locate the **Study Type** section. From the **Study type** list, choose **None**.
6. Locate the **Space-Dependent Model Generation** section. Click **Create/Refresh**.

SPACE-DEPENDENT REACTOR

1. In the **Model Builder** window, click **Component 2 (comp2)**.
2. In the **Settings** window for **Component**, type `Space-Dependent Reactor` in the **Label** text field.

Begin by loading the geometry from a file.

GEOMETRY 1(3D)

1. In the **Geometry** toolbar, click **Insert Sequence** and choose **Insert Sequence**.
2. Browse to the model's Application Libraries folder and double-click the file `stirred_tank_adc_production_geom_sequence.mph`.
3. In the **Geometry** toolbar, click **Build All**.

Add **Selections** to the geometry. **Selections** are useful when setting up the physics interfaces, as well as the mesh and result nodes.

Explicit Selection 1: Symmetry Boundary (Physics)

1 In the **Geometry** toolbar, click **Selections** and choose **Explicit Selection**.

Add a Clip Plane to see inside the domain.

2 In the **Settings** window for **Explicit Selection**, in the **Graphics** window toolbar, click ▾ next to **Clipping**, then choose **Add Clip Plane**.

3 In the **Label** text field, type `Explicit Selection 1: Symmetry Boundary (Physics)`.

4 Locate the **Entities to Select** section. From the **Geometric entity level** list, choose **Boundary**.

5 On the object **fin**, select Boundaries 13, 14, 17, 18, 43, 45, 51, and 67 only.

Explicit Selection 2: Stirrer Edges (Results)

1 In the **Geometry** toolbar, click **Selections** and choose **Explicit Selection**.

2 In the **Settings** window for **Explicit Selection**, locate the **Entities to Select** section.

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

4 Click the **Select Box** button in the **Graphics** toolbar.

5 On the object **fin**, select Edges 150–153, 155, 156, 158, 159, 161, 162, 170, 173, 175, 176, 178, 179, 181, 182, 184, 186, 188, 193, 195, 198, 199, 201, 206, 208, 210, 212, 236–240, 243–248, 251–255, 257–260, 265, 266, 269, 272, 276, 277, 279, 280, 282, and 283 only.

6 In the **Label** text field, type `Explicit Selection 2: Stirrer Edges (Results)`.

Explicit Selection 3: Source (Mesh)

1 In the **Geometry** toolbar, click **Selections** and choose **Explicit Selection**.

2 In the **Settings** window for **Explicit Selection**, type `Explicit Selection 3: Source (Mesh)` in the **Label** text field.

3 Locate the **Entities to Select** section. From the **Geometric entity level** list, choose **Boundary**.

4 On the object **fin**, select Boundaries 73–80, 109–112, 114, and 116–118 only.

Explicit Selection 4: Destination (Mesh)

1 In the **Geometry** toolbar, click **Selections** and choose **Explicit Selection**.

2 In the **Settings** window for **Explicit Selection**, type `Explicit Selection 4: Destination (Mesh)` in the **Label** text field.

3 Locate the **Entities to Select** section. From the **Geometric entity level** list, choose **Boundary**.

4 On the object **fin**, select Boundaries 21–28, 55–58, 61, 63, 65, and 66 only.

Explicit Selection 5: Inside Glass Wall Boundary (Mesh)

1 In the **Geometry** toolbar, click **Selections** and choose **Explicit Selection**.

2 In the **Settings** window for **Explicit Selection**, type `Explicit Selection 5: Inside Glass Wall Boundary (Mesh)` in the **Label** text field.

3 Locate the **Entities to Select** section. From the **Geometric entity level** list, choose **Boundary**.

4 On the object **fin**, select Boundaries 9–12, 31, 32, 41, 42, 48, 50, 53, 56, and 69 only.

The steps left before we have defined our system are 1) add a material for the fluid phase, 2) add a moving mesh node, 3) set up all the physics interfaces, 4) build the mesh, and 5) add probes to evaluate the fluid flow field. The material that we will add for the fluid domains is water. After these steps, add studies to compute the solutions. Now, continue by adding the material.

ADD MATERIAL FROM LIBRARY

In the **Home** toolbar, click **Windows** and choose **Add Material from Library**.

ADD MATERIAL

1 Go to the **Add Material** window.

2 In the tree, select **Built-in** > **Water, liquid**.

3 Click the **Add to Component** button in the window toolbar.

4 In the **Home** toolbar, click **Add Material** to close the **Add Material** window.

MATERIALS

Water, liquid (mat1)

1 In the **Settings** window for **Material**, locate the **Geometric Entity Selection** section.

2 From the **Selection** list, choose **Fluid Domains**.

Now add the moving mesh node.

SPACE-DEPENDENT REACTOR (COMP2)

Rotating Domain 1

1 In the **Physics** toolbar, click **Moving Mesh** and choose **Rotating Domain**.

2 In the **Settings** window for **Rotating Domain**, locate the **Domain Selection** section.

3 From the **Selection** list, choose **Rotating Domain**.

4 Locate the **Rotation** section. From the **Rotation type** list, choose **Specified rotational velocity**.

5 From the **Rotational velocity expression** list, choose **Constant revolutions per time**.

6 In the *f* text field, type `rpm`.

Use the coordinated given by the **Centroid Measurement** nodes to define the rotational axis.

7 Locate the **Axis** section. Specify the $\mathbf{r}_{ax}$ vector as

`geom1.cm1.x`	X
`geom1.cm1.y`	Y
`geom1.cm1.z`	Z

8 Specify the $\mathbf{u}_{rot}$ vector as

`(geom1.cm1.x-geom1.cm2.x)/sqrt((geom1.cm1.x-geom1.cm2.x)^2+(geom1.cm1.y-geom1.cm2.y)^2+(geom1.cm1.z-geom1.cm2.z)^2)`	X
`(geom1.cm1.y-geom1.cm2.y)/sqrt((geom1.cm1.x-geom1.cm2.x)^2+(geom1.cm1.y-geom1.cm2.y)^2+(geom1.cm1.z-geom1.cm2.z)^2)`	Y
`(geom1.cm1.z-geom1.cm2.z)/sqrt((geom1.cm1.x-geom1.cm2.x)^2+(geom1.cm1.y-geom1.cm2.y)^2+(geom1.cm1.z-geom1.cm2.z)^2)`	Z

We have added the interfaces that we need. Now go through these and add the settings.

TRANSPORT OF DILUTED SPECIES (TDS)

Fluid 1

1 In the **Model Builder** window, expand the **Space-Dependent Reactor (comp2)** > **Transport of Diluted Species (tds)** node, then click **Fluid 1**.

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

3 From the **Material** list, choose **Water, liquid (mat1)**.

Inflow 1

In the **Model Builder** window, right-click **Inflow 1** and choose **Delete**.

Outflow 1

Right-click **Outflow 1** and choose **Delete**.

Point Mass Source 1

1 In the **Physics** toolbar, click **Points** and choose **Point Mass Source**.

2 In the **Settings** window for **Point Mass Source**, locate the **Point Selection** section.

3 From the **Selection** list, choose **Feed Point**.

4 Locate the **Species Source** section. In the [[dot]]$q_{p,cDrug}$ text field, type `comp1.feedRate(t)*c_feed_Drug`.

TURBULENT FLOW, K-ε (SPF)

1 In the **Model Builder** window, under **Space-Dependent Reactor (comp2)** click **Turbulent Flow, k-ε (spf)**.

2 In the **Settings** window for **Turbulent Flow, k-ε**, locate the **Domain Selection** section.

3 From the **Selection** list, choose **Fluid Domains**.

4 In the **Model Builder** window, expand the **Turbulent Flow, k-ε (spf)** node.

Fluid Properties 1

1 In the **Model Builder** window, expand the **Space-Dependent Reactor (comp2)** > **Turbulent Flow, k-ε** (spf) > **Fluid Properties 1** node, then click **Fluid Properties 1**.

2 In the **Settings** window for **Fluid Properties**, locate the **Model Input** section.

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

Inlet 1

In the **Model Builder** window, right-click **Inlet 1** and choose **Delete**.

Outlet 1

Right-click **Outlet 1** and choose **Delete**.

Pressure Point Constraint 1

1 In the **Physics** toolbar, click **Points** and choose **Pressure Point Constraint**.

2 Select Point 63 only.

Symmetry 1

1 In the **Physics** toolbar, click **Boundaries** and choose **Symmetry**.

2 In the **Settings** window for **Symmetry**, locate the **Boundary Selection** section.

3 From the **Selection** list, choose **Explicit Selection 1: Symmetry Boundary (Physics)**.

Time to build the mesh.

MESH 1

1 In the **Model Builder** window, under **Space-Dependent Reactor (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 **Space-Dependent Reactor (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 Click the **Custom** button.

5 Locate the **Element Size Parameters** section. In the **Maximum element size** text field, type `0.0206`.

6 In the **Minimum element size** text field, type `0.00289`.

Size 1

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

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

3 From the **Selection** list, choose **Rotating Domain**.

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

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

6 Select the **Maximum element size** checkbox. In the associated text field, type `2e-2`.

7 Select the **Minimum element size** checkbox. In the associated text field, type `1e-3`.

Size 2

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

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

3 From the **Selection** list, choose **Explicit Selection 1: Symmetry Boundary (Physics)**.

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

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

6 Select the **Minimum element size** checkbox. In the associated text field, type `0.00108`.

7 Select the **Maximum element size** checkbox. In the associated text field, type `0.0206`.

8 Select the **Maximum element growth rate** checkbox. In the associated text field, type `1.15`.

9 Select the **Curvature factor** checkbox. In the associated text field, type `0.6`.

10 Select the **Resolution of narrow regions** checkbox. In the associated text field, type `0.7`.

Size 3

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

2 Drag and drop **Size 3** below **Size 2**.

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

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

5 From the **Selection** list, choose **Explicit Selection 5: Inside Glass Wall Boundary (Mesh)**.

6 Locate the **Element Size** section. From the **Calibrate for** list, choose **Fluid dynamics**.

7 Click the **Custom** button.

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

9 Select the **Maximum element size** checkbox. In the associated text field, type `0.0114`.

10 Select the **Minimum element size** checkbox. In the associated text field, type `0.00108`.

11 Select the **Maximum element growth rate** checkbox. In the associated text field, type `1.1`.

12 Select the **Curvature factor** checkbox. In the associated text field, type `0.4`.

13 Select the **Resolution of narrow regions** checkbox. In the associated text field, type `0.9`.

Size 4

1 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 From the **Selection** list, choose **Explicit Selection 3: Source (Mesh)**.

5 Locate the **Element Size** section. From the **Calibrate for** list, choose **Fluid dynamics**.

6 Click the **Custom** button.

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

8 Select the **Maximum element size** checkbox. In the associated text field, type `0.004`.

9 Select the **Minimum element size** checkbox. In the associated text field, type `4.62E-4`.

10 Select the **Maximum element growth rate** checkbox. In the associated text field, type `1.08`.

11 Select the **Curvature factor** checkbox. In the associated text field, type `0.3`.

12 Select the **Resolution of narrow regions** checkbox. In the associated text field, type `0.95`.

Size 5

1 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 From the **Selection** list, choose **Stirrer Blade Short Surfaces (Straight Blade Bottom Fitted Impeller 1)**.

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 `0.001`.

Identical Mesh 1

1 In the **Model Builder** window, click **Identical Mesh 1**.

2 In the **Settings** window for **Identical Mesh**, locate the **First Entity Group** section.

3 From the **Selection** list, choose **Explicit Selection 3: Source (Mesh)**.

4 Locate the **Second Entity Group** section. From the **Selection** list, choose **Explicit Selection 4: Destination (Mesh)**.

Corner Refinement 1

1 In the **Model Builder** window, click **Corner Refinement 1**.

2 In the **Settings** window for **Corner Refinement**, locate the **Boundary Selection** section.

3 In the list box, select **33**.

4 Click to select the **Activate Selection** toggle button.

5 Select Boundaries 9–12, 31, 32, 41, 42, 48, 50, 53, and 69 only.

Free Tetrahedral 1

1 In the **Model Builder** window, click **Free Tetrahedral 1**.

2 In the **Settings** window for **Free Tetrahedral**, locate the **Domain Selection** section.

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

4 From the **Selection** list, choose **Fluid Domains**.

5 Click **Build Selected**.

Free Tetrahedral 2

In the **Mesh** toolbar, click **Free Tetrahedral**.

Boundary Layer Properties 1

1 In the **Model Builder** window, expand the **Boundary Layers 1** node, then click **Boundary Layer Properties 1**.

2 Select Boundaries 9–12, 31–34, 41, 42, 48, 50, 53, 59, 62, 64, 69, 81–108, 113, 115, and 119–129 only.

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

The mesh is finished. Now add probes. The probes will be used to monitor the fluid flow field in the tank at three points.

DEFINITIONS (COMP2)

Probe 1: Feed Point

1. In the **Definitions** toolbar, click  **Probes** and choose **Point Probe**.
2. In the **Settings** window for **Point Probe**, locate the **Source Selection** section.
3. Click  **Clear Selection**.
4. From the **Selection** list, choose **Feed Point**.
5. In the **Label** text field, type `Probe 1: Feed Point`.
6. Locate the **Expression** section. In the **Expression** text field, type `spf.U`.

Probe 2: Top of Tank Opposite Stirrer

1. Right-click **Probe 1: Feed Point** and choose **Duplicate**.
2. In the **Settings** window for **Point Probe**, type `Probe 2: Top of Tank Opposite Stirrer` in the **Label** text field.
3. Locate the **Source Selection** section. Click  **Clear Selection**.
4. Select Point 23 only.

Probe 3: Center of Tank Near Cone

1. In the **Definitions** toolbar, click  **Probes** and choose **Domain Point Probe**.
2. In the **Settings** window for **Domain Point Probe**, locate the **Point Selection** section.
3. From the **Line entry method** list, choose **None**.
4. In the **Label** text field, type `Probe 3: Center of Tank Near Cone`.

Point Probe Expression 1 (ppb1)

1. In the **Model Builder** window, expand the **Probe 3: Center of Tank Near Cone** node, then click **Point Probe Expression 1 (ppb1)**.
2. In the **Settings** window for **Point Probe Expression**, locate the **Expression** section.
3. In the **Expression** text field, type `spf.U`.

Probe 4: Between Wall and Rotary Domain

1. In the **Model Builder** window, right-click **Probe 3: Center of Tank Near Cone** and choose **Duplicate**.
2. In the **Settings** window for **Domain Point Probe**, type `Probe 4: Between Wall and Rotary Domain` in the **Label** text field.
3. Locate the **Point Selection** section. In row **Coordinates**, set **y** to `0.16`.

Add a **Frozen Rotor** study to find the initial conditions to be used in the time dependent simulation of the flow field. Use the **Auxiliary Sweep** functionality to ramp up the stirring speed to the desired one. This helps with convergence.

ADD STUDY

1 In the **Study** toolbar, click **Add Study** to open the **Add Study** window.

2 Go to the **Add Study** window.

3 Find the **Studies** subsection. In the **Select Study** tree, select **Preset Studies for Some Physics Interfaces** > **Frozen Rotor**.

4 Click the **Add Study** button in the window toolbar.

STUDY 2

Step 1: Frozen Rotor

1 In the **Settings** window for **Frozen Rotor**, locate the **Physics and Variables Selection** section.

2 In the **Solve for** column of the table, under **Space-Dependent Reactor (comp2)**, clear the checkboxes for **Chemistry (chem)** and **Transport of Diluted Species (tds)**.

3 In the **Solve for** column of the table, under **Space-Dependent Reactor (comp2)** > **Multiphysics**, clear the checkbox for **Reacting Flow, Diluted Species 1 (rfd1)**.

4 Click to expand the **Study Extensions** section. Select the **Auxiliary sweep** checkbox.

5 Click **Add**.

6 In the table, enter the following settings:

Parameter name	Parameter value list	Parameter unit
rpm (Revolutions per second)	`10 50 100 200 360`	`1/min`

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

8 In the **Settings** window for **Study**, type `Study 2: Frozen Rotor` in the **Label** text field.

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

Study and edit the default plots that were added.

RESULTS

Pressure (spf), Velocity (spf), Wall Resolution (spf)

Right-click and choose **Group**.

Frozen Rotor

In the **Settings** window for **Group**, type `Frozen Rotor` in the **Label** text field.

Frozen Rotor: Velocity (spf)

1. In the **Model Builder** window, expand the **Results** > **Frozen Rotor** > **Velocity (spf)** node, then click **Velocity (spf)**.
2. In the **Settings** window for **3D Plot Group**, type `Frozen Rotor: Velocity (spf)` in the **Label** text field.

Multislice 1

1. In the **Model Builder** window, click **Multislice 1**.
2. In the **Settings** window for **Multislice**, locate the **Coloring and Style** section.
3. From the **Color table** list, choose **Passiflora**.
4. From the **Color table type** list, choose **Discrete**.

Frozen Rotor: Pressure (spf)

1. In the **Model Builder** window, expand the **Results** > **Frozen Rotor** > **Pressure (spf)** node, then click **Pressure (spf)**.
2. In the **Settings** window for **3D Plot Group**, type `Frozen Rotor: Pressure (spf)` in the **Label** text field.

Surface

1. In the **Model Builder** window, click **Surface**.
2. In the **Settings** window for **Surface**, locate the **Coloring and Style** section.
3. From the **Scale** list, choose **Linear symmetric**.
4. From the **Color table type** list, choose **Continuous**.

Frozen Rotor: Wall Resolution (spf)

1. In the **Model Builder** window, expand the **Results** > **Frozen Rotor** > **Wall Resolution (spf)** node, then click **Wall Resolution (spf)**.
2. In the **Settings** window for **3D Plot Group**, type `Frozen Rotor: Wall Resolution (spf)` in the **Label** text field.

Surface 1

1. In the **Model Builder** window, click **Surface 1**.
2. In the **Settings** window for **Surface**, locate the **Coloring and Style** section.
3. From the **Color table** list, choose **Agama**.

Now use the solution for the highest stirrer rate as the initial value for a time dependent simulation of the fluid flow. Simulate two seconds, that is, 12 rotations for the stirrer. This time period should be sufficiently long to see if the flow field is varying significantly or not. The results from the time dependent study will be used to initiate the simulation of the complete system.

ADD STUDY

1 Go to the **Add Study** window.

2 Find the **Studies** subsection. In the **Select Study** tree, select **General Studies** > **Time Dependent**.

3 Click the **Add Study** button in the window toolbar.

4 In the **Home** toolbar, click **Add Study** to close the **Add Study** window.

STUDY 3

Step 1: Time Dependent

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

2 In the **Output times** text field, type `range(0,0.05,2)`.

3 Locate the **Physics and Variables Selection** section. In the **Solve for** column of the table, clear the checkbox for **Ideal Semibatch Reactor (comp1)**.

4 In the **Solve for** column of the table, under **Space-Dependent Reactor (comp2)**, clear the checkboxes for **Chemistry (chem)** and **Transport of Diluted Species (tds)**.

5 In the **Solve for** column of the table, under **Space-Dependent Reactor (comp2)** > **Multiphysics**, clear the checkbox for **Reacting Flow, Diluted Species 1 (rfd1)**.

6 Click to expand the **Values of Dependent Variables** section. Find the **Initial values of variables solved for** subsection. From the **Settings** list, choose **User controlled**.

7 From the **Method** list, choose **Solution**.

8 From the **Study** list, choose **Study 2: Frozen Rotor, Frozen Rotor**.

9 From the **Parameter value (rpm (1/min))** list, choose **360 1/min**.

10 In the **Model Builder** window, click **Study 3**.

11 In the **Settings** window for **Study**, type `Study 3: Time-Dependent Flow Field` in the **Label** text field.

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

Study the results in the added default plots and edit them if needed. Also study the probe plot.

RESULTS

Pressure (spf), Velocity (spf), Wall Resolution (spf)

Right-click and choose **Group**.

Time-Dependent Flow Field

In the **Settings** window for **Group**, type `Time-Dependent Flow Field` in the **Label** text field.

Multislice 1

1. In the **Model Builder** window, expand the **Velocity (spf)** node, then click **Multislice 1**.
2. In the **Settings** window for **Multislice**, locate the **Coloring and Style** section.
3. From the **Color table** list, choose **Passiflora**.
4. From the **Color table type** list, choose **Discrete**.

Surface

1. In the **Model Builder** window, expand the **Results** > **Time-Dependent Flow Field** > **Pressure (spf)** node, then click **Surface**.
2. In the **Settings** window for **Surface**, locate the **Coloring and Style** section.
3. From the **Color table type** list, choose **Continuous**.
4. From the **Scale** list, choose **Linear symmetric**.

Surface 1

1. In the **Model Builder** window, expand the **Wall Resolution (spf)** node, then click **Surface 1**.
2. In the **Settings** window for **Surface**, locate the **Coloring and Style** section.
3. From the **Color table** list, choose **Agama**.

Probe Plots

1. In the **Model Builder** window, under **Results** click **Probe Plot Group 2**.
2. In the **Settings** window for **1D Plot Group**, type `Probe Plots` in the **Label** text field.
3. Locate the **Legend** section. From the **Position** list, choose **Middle right**.
4. Drag and drop on **Time-Dependent Flow Field**.

Probe Table 1: Time-Dependent Flow Field

1. In the **Model Builder** window, expand the **Results** > **Tables** node, then click **Probe Table 1**.

2 In the **Settings** window for **Table**, type `Probe Table 1: Time-Dependent Flow Field` in the **Label** text field.

Time-Dependent Flow Field

1 In the **Model Builder** window, expand the **Probe Plots** node, then click **Probe Table Graph 1**.

2 In the **Settings** window for **Table Graph**, type `Time-Dependent Flow Field` in the **Label** text field.

Probe Plots

The probe plot suggests that although the field is not varying by orders of magnitude, it is not steady over time. In this system, neither the mass transfer or the addition of feed is assumed to influence the flow field, as the concentrations for the species are low, and the added total feed volume amounts to less than two percent of the total tank volume. Despite this, the probes indicate that the flow is not steady enough to be considered periodic. Therefore, add a time-dependent study step to perform the simulation of the complete system.

DEFINITIONS (COMP2)

Probe 1: Feed Point (point1)

1 In the **Model Builder** window, under **Space-Dependent Reactor (comp2)** > **Definitions** click **Probe 1: Feed Point (point1)**.

2 In the **Settings** window for **Point Probe**, click to expand the **Table and Window Settings** section.

3 Click + **Add Table**.

Probe 2: Top of Tank Opposite Stirrer (point2)

1 In the **Model Builder** window, click **Probe 2: Top of Tank Opposite Stirrer (point2)**.

2 In the **Settings** window for **Point Probe**, locate the **Table and Window Settings** section.

3 From the **Output table** list, choose **Table 2**.

Point Probe Expression 1 (ppb1)

1 In the **Model Builder** window, under **Space-Dependent Reactor (comp2)** > **Definitions** > **Probe 3: Center of Tank Near Cone** click **Point Probe Expression 1 (ppb1)**.

2 In the **Settings** window for **Point Probe Expression**, click to expand the **Table and Window Settings** section.

3 From the **Output table** list, choose **Table 2**.

Point Probe Expression 1 (ppb2)

1 In the **Model Builder** window, expand the **Space-Dependent Reactor (comp2)** > **Definitions** > **Probe 4: Between Wall and Rotary Domain** node, then click **Point Probe Expression 1 (ppb2)**.

2 In the **Settings** window for **Point Probe Expression**, locate the **Table and Window Settings** section.

3 From the **Output table** list, choose **Table 2**.

Add the fourth study that will be used to simulate the complete system.

ADD STUDY

1 In the **Study** toolbar, click **Add Study** to open the **Add Study** window.

2 Go to the **Add Study** window.

3 Find the **Studies** subsection. In the **Select Study** tree, select **General Studies** > **Time Dependent**.

4 Click the **Add Study** button in the window toolbar.

5 In the **Study** toolbar, click **Add Study** to close the **Add Study** window.

STUDY 4

Step 1: Time Dependent

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

2 In the **Output times** text field, type `range(0,2,16)`.

3 Locate the **Physics and Variables Selection** section. In the **Solve for** column of the table, clear the checkbox for **Ideal Semibatch Reactor (comp1)**.

4 Locate the **Values of Dependent Variables** section. Find the **Initial values of variables solved for** subsection. From the **Settings** list, choose **User controlled**.

5 From the **Method** list, choose **Solution**.

6 From the **Study** list, choose **Study 3: Time-Dependent Flow Field, Time Dependent**.

7 From the **Time (s)** list, choose **Last**.

Generate the solver nodes. This is needed since we want to edit them.

8 In the **Model Builder** window, click **Study 4**.

9 In the **Settings** window for **Study**, type `Study 4: Space-Dependent Semibatch Reactor` in the **Label** text field.

Solution 4 (sol4)

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

2 In the **Model Builder** window, expand the **Solution 4 (sol4)** node.

3 In the **Model Builder** window, expand the **Study 4: Space-Dependent Semibatch Reactor** > **Solver Configurations** > **Solution 4 (sol4)** > **Dependent Variables 1** node, then click **Concentration (comp2.cDrug)**.

4 In the **Settings** window for **Field**, locate the **Scaling** section.

5 From the **Method** list, choose **Manual**.

6 In the **Scale** text field, type `1e-2`.

7 In the **Model Builder** window, under **Study 4: Space-Dependent Semibatch Reactor** > **Solver Configurations** > **Solution 4 (sol4)** > **Dependent Variables 1** click **Concentration (comp2.cmAb)**.

8 In the **Settings** window for **Field**, locate the **Scaling** section.

9 From the **Method** list, choose **Manual**.

10 In the **Scale** text field, type `c_init_mAb`.

STUDY 4: SPACE-DEPENDENT SEMIBATCH REACTOR

1 In the **Model Builder** window, collapse the **Study 4: Space-Dependent Semibatch Reactor** > **Solver Configurations** > **Solution 4 (sol4)** > **Dependent Variables 1** node.

2 In the **Model Builder** window, under **Study 4: Space-Dependent Semibatch Reactor** > **Solver Configurations** > **Solution 4 (sol4)** click **Time-Dependent Solver 1**.

3 In the **Settings** window for **Time-Dependent Solver**, click to expand the **Time Stepping** section.

4 Select the **Initial step** checkbox. In the associated text field, type `t_rev/500`.

Compute the model. This will take something between one and three weeks, depending on your hardware.

5 In the **Model Builder** window, click **Study 4: Space-Dependent Semibatch Reactor**.

6 In the **Settings** window for **Study**, type `Study 4: Space-Dependent Semibatch Reactor` in the **Label** text field.

7 Locate the **Study Settings** section. Clear the **Generate default plots** checkbox.

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

Set up figures that illustrate how the concentrations of species vary.

Begin with the concentration of Drug.

RESULTS

2s

1. In the **Home** toolbar, click **Add Plot Group** and choose **3D Plot Group**.
2. In the **Settings** window for **3D Plot Group**, type `2s` in the **Label** text field.
3. Locate the **Data** section. From the **Dataset** list, choose **Study 4: Space-Dependent Semibatch Reactor/Solution 4 (8) (sol4)**.
4. From the **Time (s)** list, choose **2**.
5. Click to expand the **Selection** section. From the **Geometric entity level** list, choose **Domain**.
6. From the **Selection** list, choose **Fluid Domains**.
7. Click to expand the **Title** section. From the **Title type** list, choose **None**.
8. Locate the **Plot Settings** section. From the **View** list, choose **View 1**.
9. Clear the **Plot dataset edges** checkbox.
10. Locate the **Color Legend** section. Select the **Show titles** checkbox.
11. Select the **Show units** checkbox.
12. From the **Position** list, choose **Bottom**.
13. Click to expand the **Plot Array** section. From the **Array type** list, choose **Linear**.
14. From the **Array axis** list, choose **y**.
15. In the **Relative padding** text field, type `0.1`.

Slice 1

1. Right-click **2s** and choose **Slice**.
2. In the **Settings** window for **Slice**, locate the **Plane Data** section.
3. From the **Entry method** list, choose **Coordinates**.
4. Locate the **Coloring and Style** section. From the **Color table** list, choose **Excorticata**.
5. In the **Color legend title** text field, type `(a)`.
6. Click to expand the **Plot Array** section. Select the **Manual indexing** checkbox.

Surface 1: Tank

1. In the **Model Builder** window, right-click **2s** and choose **Surface**.
2. In the **Settings** window for **Surface**, type `Surface 1: Tank` in the **Label** text field.
3. Locate the **Expression** section. In the **Expression** text field, type `1`.
4. Click to expand the **Plot Array** section. Select the **Manual indexing** checkbox.

Material Appearance 1

1 Right-click **Surface 1: Tank** and choose **Material Appearance**.

2 In the **Settings** window for **Material Appearance**, locate the **Appearance** section.

3 From the **Appearance** list, choose **Custom**.

4 From the **Material type** list, choose **Glass**.

Selection 1

1 In the **Model Builder** window, right-click **Surface 1: Tank** and choose **Selection**.

2 Select Boundaries 1–10, 29, 30, 38–40, 47, 49, 54, 59, 62, 70, 71, 83, 84, 86, 90–92, 96, 99, 104, 113, 115, 119, 120, 124, 125, and 127–129 only.

Surface 2: Stirrer

1 In the **Model Builder** window, right-click **2s** and choose **Surface**.

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

3 Locate the **Expression** section. In the **Expression** text field, type `1`.

4 Locate the **Plot Array** section. Select the **Manual indexing** checkbox.

Material Appearance 1

1 Right-click **Surface 2: Stirrer** and choose **Material Appearance**.

2 In the **Settings** window for **Material Appearance**, locate the **Appearance** section.

3 From the **Appearance** list, choose **Custom**.

4 From the **Material type** list, choose **Car paint**.

Selection 1

1 In the **Model Builder** window, right-click **Surface 2: Stirrer** and choose **Selection**.

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

3 From the **Selection** list, choose **Stirrer with Socket**.

(a)

1 In the **Model Builder** window, right-click **2s** and choose **Annotation**.

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

3 Locate the **Annotation** section. In the **Text** text field, type `(a)`.

4 Locate the **Position** section. In the **y** text field, type `-d_tank/2`.

5 In the **z** text field, type `h_cyl*1.1`.

6 Locate the **Coloring and Style** section. Clear the **Show point** checkbox.

7 From the **Anchor point** list, choose **Lower middle**.

8 Click to expand the **Plot Array** section. Select the **Manual indexing** checkbox.

Isosurface 1

1 Right-click **2s** and choose **Isosurface**.

2 In the **Settings** window for **Isosurface**, locate the **Levels** section.

3 In the **Total levels** text field, type `10`.

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

5 In the **Color legend title** text field, type `(b)`.

6 Click to expand the **Plot Array** section. Select the **Manual indexing** checkbox.

7 In the **Index** text field, type `1`.

Transparency 1

1 Right-click **Isosurface 1** and choose **Transparency**.

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

3 Find the **Transparency** subsection. Set the **Transparency** value to **0.7**.

(a), Surface 1: Tank, Surface 2: Stirrer

1 In the **Model Builder** window, under **Results** > **2s**, Ctrl-click to select **Surface 1: Tank**, **Surface 2: Stirrer**, and **(a)**.

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

Surface 1: Tank 1

1 In the **Settings** window for **Surface**, locate the **Plot Array** section.

2 In the **Index** text field, type `1`.

Surface 2: Stirrer 1

1 In the **Model Builder** window, click **Surface 2: Stirrer 1**.

2 In the **Settings** window for **Surface**, locate the **Plot Array** section.

3 In the **Index** text field, type `1`.

(b)

1 In the **Model Builder** window, under **Results** > **2s** click **(a) 1**.

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

3 Locate the **Annotation** section. In the **Text** text field, type `(b)`.

4 Locate the **Plot Array** section. In the **Index** text field, type `1`.

2s

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

2 Click the **Zoom Box** button on the Graphics toolbar and then use the mouse to zoom in. Adjust the view according to your preferences.

Duplicate this plot group and edit the time for which the results are shown.

4s

1 Right-click **2s** and choose **Duplicate**.

2 In the **Settings** window for **3D Plot Group**, type `4s` in the **Label** text field.

3 Locate the **Data** section. From the **Time (s)** list, choose **4**.

8s

1 Right-click **4s** and choose **Duplicate**.

2 In the **Settings** window for **3D Plot Group**, type `8s` in the **Label** text field.

3 Locate the **Data** section. From the **Time (s)** list, choose **8**.

Slice 1

1 In the **Model Builder** window, expand the **8s** node, then click **Slice 1**.

2 In the **Settings** window for **Slice**, click to expand the **Range** section.

3 Select the **Manual color range** checkbox.

4 In the **Minimum** text field, type `0.00183`.

5 In the **Maximum** text field, type `0.24919`.

16s

1 In the **Model Builder** window, right-click **8s** and choose **Duplicate**.

2 In the **Settings** window for **3D Plot Group**, type `16s` in the **Label** text field.

3 Locate the **Data** section. From the **Time (s)** list, choose **16**.

16s, 2s, 4s, 8s

1 In the **Model Builder** window, under **Results**, Ctrl-click to select **2s**, **4s**, **8s**, and **16s**.

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

Concentration Drug

In the **Settings** window for **Group**, type `Concentration Drug` in the **Label** text field.

Set up similar plots for mAbDrug and mAbDrug2.

Concentration mAbDrug

1 Right-click **Concentration Drug** and choose **Duplicate**.

2 In the **Model Builder** window, click **Concentration Drug 1**.

3 In the **Settings** window for **Group**, type `Concentration mAbDrug` in the **Label** text field.

Slice 1

1 In the **Model Builder** window, expand the **Results** > **Concentration mAbDrug** > **2s 1** node, then click **Slice 1**.

2 In the **Settings** window for **Slice**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

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

Isosurface 1

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

2 In the **Settings** window for **Isosurface**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

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

Slice 1

1 In the **Model Builder** window, expand the **Results** > **Concentration mAbDrug** > **4s 1** node, then click **Slice 1**.

2 In the **Settings** window for **Slice**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

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

Isosurface 1

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

2 In the **Settings** window for **Isosurface**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

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

Slice 1

1 In the **Model Builder** window, expand the **Results** > **Concentration mAbDrug** > **8s 1** node, then click **Slice 1**.

2 In the **Settings** window for **Slice**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

4 Locate the **Range** section. In the **Minimum** text field, type `4.59966e-5`.

5 In the **Maximum** text field, type `0.00209`.

6 Locate the **Coloring and Style** section. From the **Color table** list, choose **Baptisia**.

Isosurface 1

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

2 In the **Settings** window for **Isosurface**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

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

Slice 1

1 In the **Model Builder** window, expand the **Results** > **Concentration mAbDrug** > **16s 1** node, then click **Slice 1**.

2 In the **Settings** window for **Slice**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

4 Locate the **Range** section. In the **Minimum** text field, type `4.59966e-5`.

5 In the **Maximum** text field, type `0.00209`.

6 Locate the **Coloring and Style** section. From the **Color table** list, choose **Baptisia**.

Isosurface 1

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

2 In the **Settings** window for **Isosurface**, locate the **Expression** section.

3 In the **Expression** text field, type `cmAbDrug`.

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

Perform the same steps for mAbDrug2. The steps are not shown in this modeling instruction.

Now look at the fluid flow in the model by setting up a velocity streamline 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 4: Space-Dependent Semibatch Reactor/Solution 4 (8) (sol4)** > **Turbulent Flow, k-ε** > **Velocity Streamlines (spf)**.

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

RESULTS

Streamline 1

1 In the **Model Builder** window, expand the **Velocity Streamlines (spf)** node, then click **Streamline 1**.

2 In the **Settings** window for **Streamline**, locate the **Streamline Positioning** section.

3 From the **Positioning** list, choose **Magnitude controlled**.

4 In the **Minimum density level** text field, type `0`.

5 In the **Maximum density level** text field, type `13.4`.

6 Locate the **Coloring and Style** section. Find the **Line style** subsection. From the **Type** list, choose **Tube**.

7 Find the **Point style** subsection. From the **Type** list, choose **Arrow**.

8 Select the **Number of arrows** checkbox. In the associated text field, type `80`.

9 From the **Arrow type** list, choose **Cone**.

10 Select the **Scale factor** checkbox. In the associated text field, type `0.1`.

Color Expression 1

1 In the **Model Builder** window, expand the **Streamline 1** node, then click **Color Expression 1**.

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

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

Surface 1: Tank, Surface 2: Stirrer

1 In the **Model Builder** window, under **Results** > **Concentration mAbDrug2** > **16s 1.1**, Ctrl-click to select **Surface 1: Tank** and **Surface 2: Stirrer**.

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

Velocity Streamlines (spf)

1 In the **Model Builder** window, under **Results** > **Concentration mAbDrug2** right-click **Velocity Streamlines (spf)** and choose **Paste Multiple Items**.

2 In the **Settings** window for **3D Plot Group**, locate the **Plot Settings** section.

3 Clear the **Plot dataset edges** checkbox.

4 Right-click **Velocity Streamlines (spf)** and choose **Move Out**.

Compare the results from the space-dependent model with those from the perfectly stirred tank model.

Evaluation Group 1

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

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

3 From the **Dataset** list, choose **Study 4: Space-Dependent Semibatch Reactor/ Solution 4 (7) (sol4)**.

Volume Integration 1

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

2 In the **Settings** window for **Volume Integration**, locate the **Data** section.

3 From the **Dataset** list, choose **Study 4: Space-Dependent Semibatch Reactor/ Solution 4 (8) (sol4)**.

4 Locate the **Selection** section. From the **Selection** list, choose **Fluid Domains**.

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

Expression	Unit	Description
cmAbDrug	mol	Molar concentration, cmAbDrug
cmAb	mol	Molar concentration, cmAb
cmAbDrug2	mol	Molar concentration, cmAbDrug2

6 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 Find the **Line style** subsection. From the **Line** list, choose **None**.

3 From the **Color** list, choose **Black**.

4 Find the **Line markers** subsection. From the **Marker** list, choose **Cycle**.

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

6 From the **Legends** list, choose **Manual**.

7 In the table, enter the following settings:

Legends
3D
3D
3D

Global 1

1 In the **Model Builder** window, right-click **1D Plot Group 22** and choose **Global**.

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

3 From the **Dataset** list, choose **Study 1: Ideal Semibatch Reactor/Solution 1 (sol1)**.

4 Locate the **y-Axis Data** section. Click **Clear Table**.

5 In the table, enter the following settings:

Expression	Unit	Description
comp1.re.c_mAbDrug*V_reactor	mol	
comp1.re.c_mAb*V_reactor	mol	
comp1.re.c_mAbDrug2*V_reactor	mol	

6 Click to expand the **Coloring and Style** section. Find the **Line style** subsection. From the **Line** list, choose **Cycle**.

7 From the **Color** list, choose **Black**.

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

9 In the table, enter the following settings:

Legends
mAbDrug, OD
mAb, OD
mAbDrug2, OD

Amount (mol)

1 In the **Model Builder** window, under **Results** click **1D Plot Group 22**.

2 In the **Settings** window for **1D Plot Group**, type `Amount (mol)` in the **Label** text field.

3 Locate the **Plot Settings** section.

4 Select the **y-axis label** checkbox. In the associated text field, type `Amount (mol)`.

5 Locate the **Legend** section. From the **Position** list, choose **Middle right**.

6 In the **Number of columns** text field, type 2.

Global 1

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

2 Drag and drop above **Table Graph 1**.

3 In the **Amount (mol)** toolbar, click **Plot**.

The final results to investigate in this model example is the drug-to- antibody ratio, and the product yield.

Volume Average 1

1 In the **Results** toolbar, click **More Derived Values** and choose **Average** > **Volume Average**.

2 In the **Settings** window for **Volume Average**, locate the **Data** section.

3 From the **Dataset** list, choose **Study 4: Space-Dependent Semibatch Reactor/ Solution 4 (8) (sol4)**.

4 Locate the **Selection** section. From the **Selection** list, choose **Fluid Domains**.

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

Expression	Unit	Description
`(cmAbDrug+2*cmAbDrug2)/c_init_mAb`	1	DAR
`cmAbDrug2/c_init_mAb`	1	`Yield`

6 Click ▼ next to = **Evaluate**, then choose **New Table**.

Drug-to-Antibody Ratio and Yield

1 In the **Results** toolbar, click ∿ **1D Plot Group**.

2 In the **Settings** window for **1D Plot Group**, type `Drug-to-Antibody Ratio and Yield` in the **Label** text field.

DAR, 0D

1 Right-click **Drug-to-Antibody Ratio and Yield** and choose **Global**.

2 In the **Settings** window for **Global**, type `DAR, 0D` in the **Label** text field.

3 Locate the **y-Axis Data** section. Click 🧹 **Clear Table**.

4 In the table, enter the following settings:

Expression	Unit	Description
`(re.c_mAbDrug+2* re.c_mAbDrug2)/c_init_mAb`	1	`Drug-to-Antibody ratio`

5 Locate the **Coloring and Style** section. From the **Color** list, choose **Black**.

6 Locate the **Legends** section. Find the **Include** subsection. Select the **Label** checkbox.

7 Clear the **Solution** checkbox.

8 Clear the **Expression** checkbox.

Yield, 0D

1 Right-click **DAR, 0D** and choose **Duplicate**.

2 In the **Settings** window for **Global**, type `Yield, 0D` in the **Label** text field.

3 Locate the **y-Axis Data** section. In the table, enter the following settings:

Expression	Unit	Description
re.c_mAbDrug2/c_init_mAb	1	Yield of mAbDrug2

4 Locate the **Coloring and Style** section. Find the **Line style** subsection. From the **Line** list, choose **Dashed**.

DAR, 3D

1 In the **Model Builder** window, right-click **Drug-to-Antibody Ratio and Yield** and choose **Table Graph**.

2 In the **Settings** window for **Table Graph**, type DAR, 3D in the **Label** text field.

3 Locate the **Data** section. From the **Table** list, choose **Table 3**.

4 From the **Plot columns** list, choose **Manual**.

5 In the **Columns** list box, select **DAR (1)**.

6 Locate the **Coloring and Style** section. Find the **Line style** subsection. From the **Line** list, choose **None**.

7 From the **Color** list, choose **Black**.

8 Find the **Line markers** subsection. From the **Marker** list, choose **Circle**.

9 Locate the **Legends** section. Select the **Show legends** checkbox.

10 From the **Legends** list, choose **Automatic**.

11 Find the **Include** subsection. Select the **Label** checkbox.

12 Clear the **Headers** checkbox.

Yield, 3D

1 Right-click **DAR, 3D** and choose **Duplicate**.

2 In the **Settings** window for **Table Graph**, type Yield, 3D in the **Label** text field.

3 Locate the **Data** section. In the **Columns** list box, select **Yield (1)**.

4 Locate the **Coloring and Style** section. Find the **Line markers** subsection. From the **Marker** list, choose **Square**.

Drug-to-Antibody Ratio and Yield

1 In the **Model Builder** window, click **Drug-to-Antibody Ratio and Yield**.

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

3 Select the **Two y-axes** checkbox.

4 In the table, select the **Plot on secondary y-axis** checkboxes for **Yield, 0D** and **Yield, 3D**.

5 Select the **y-axis label** checkbox. In the associated text field, type `Drug-to-Antibody Ratio (1)`.

6 Select the **Secondary y-axis label** checkbox.

7 Click to expand the **Title** section. From the **Title type** list, choose **None**.