Model created in COMSOL Multiphysics 6.4

Modeling an LFA Rapid Detection Test

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Introduction

The COVID-19 pandemic has made the world painfully aware of the importance of contact tracing. Knowing who is infected, as well as when and where that person was infected, is required in order to be able to contain an outbreak of a virus infection. The lack of this knowledge has forced most of the countries in the world to implement restrictions and lockdowns, which have led to severe social disruptions and a global economic recession.

The development of rapid detection test devices has allowed for contact tracing in the areas of society that are critical and cannot shut down, such as healthcare and food supply. Access to inexpensive tests has also allowed for people to self-diagnose and then self-isolate, if infected. This has also helped in slowing down the spreading of the virus. South Korea and Germany have successfully used testing to slow down the pandemic on a broader scale, in all areas of society (Ref. 1).

One possible rapid detection test for COVID-19 is based on lateral flow assay (LFA), also called lateral flow immunoassay (LFIA) or immunochromatographic tests. The standard pregnancy test that can be bought at supermarkets is probably the most familiar application of LFA. LFA offers an inexpensive, relatively reliable, robust, and easy-to-use test for many diseases and conditions (Ref. 2).

The test consists of the following parts (shown in Figure 1): The sample pad, the conjugation pad, the membrane, and the absorption pad, also called a wick pad. The assembly of the different components (pads and membrane) is often referred to as the test strip. The test strip is protected by a plastic housing (Ref. 3).

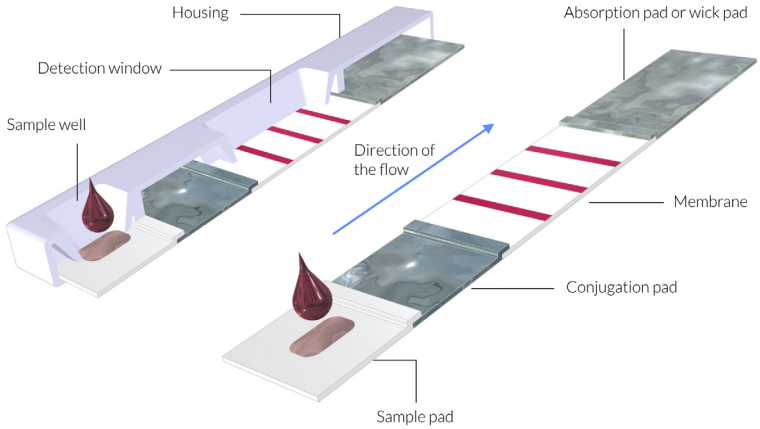

Figure 1: Schematic drawing of a rapid detection test device. Here, the thickness of the membranes and pads is exaggerated by a factor of 5 in order to show the structure. The assembly of the pads and the membrane can be referred to as a test strip.

Test Functionality

When the body is infected with the coronavirus, SARS-CoV-2, the immune system quickly reacts by forming antibodies. Dendritic cells may present virus antigens to allow recognition by T-cells. T-cells may activate B-cells to secrete antibodies that target the antigen (Ref. 1). Among the first to form are the so-called IgM antibodies. These antibodies attach to the surface of so-called antigens on the virus particles as soon as they come close. In the case of the coronavirus, the antigens can be the spike proteins at the surface of the virus (S antigen). Once attached to the antigens, the antibodies block the spike proteins of the virus, impeding them to attach and infect human cells. This neutralizes the virus, since it is not able to replicate outside of an infected cell. There are a number of different antibodies that may target different antigens. Note that there are also other mechanisms for fighting the infection. In addition, T-cells that recognize the virus may also target infected cells directly. They can instruct the cells to self-destruct or they may kill the infected cells, thus also neutralizing the virus.

The IgM antibodies manufactured by the immune system attach, for example, to the spike antigen (S antigen) of the SARS-CoV-2 virus particle, thus neutralizing the particle. The neutralized virus cannot enter a human cell and therefore cannot replicate. The virus particle is destroyed.

The IgM antibodies patrol the body in groups of five, forming small particles (or large molecules), attaching to every virus particle they encounter. Later in the infection, the immune system also forms other antibodies, for example, IgG, that patrol the body on their own and fasten to every virus particle they see. The IgG antibodies take longer to manufacture by the body, but they also last longer and grant immunity as long as they are present.

Some of the LFA rapid detection tests for COVID-19 are based on the detection of both IgM and IgG antibodies. These are the tests that are investigated in the model featured here.

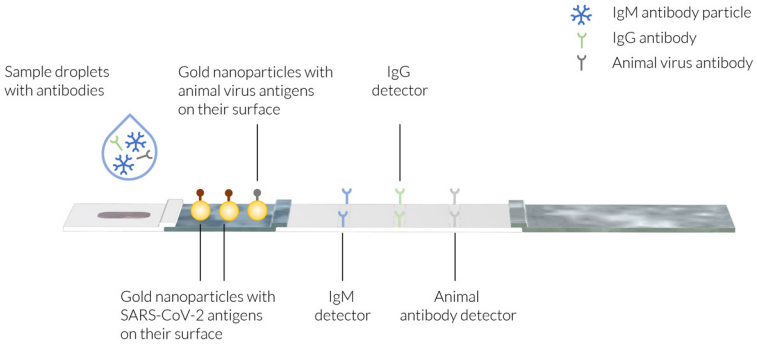

Figure 2: Schematic drawing of a rapid detection test device. The sample contains the human antibodies IgM and IgG, created due to COVID-19 infection. An animal antibody (AA) is also added to the sample liquid with the buffer solution. The test lines have immobilized antibody detectors on the three different areas. Note that the test lines are not yet visible.

The patient's blood (or saliva) may be applied to the sample well followed by an application of the buffer, by dripping a couple of droplets of buffer in the sample well. The buffer contains an animal antibody AA to test whether the test is working correctly.

The sample is transported by the capillary forces to the conjugate pad. Here, the IgM and IgG antibodies attach to a conjugate label. A conjugate label may be a gold nanoparticle that has SARS-CoV-2 antigens on its surface. Two different complexes are then formed: IgM with the conjugate (=IgM-C) and IgG with the conjugate (=IgG-C). Also, the animal virus antibody picks up its respective particle (AA-C). These complexes are dissolved in the sample liquid.

The sample is then transported to the membrane by the capillary forces. In the first test line, IgM detectors are immobilized at the surface of the membrane during the

manufacturing of the membrane. These IgM detectors capture the IgM-C complex and keep these complexes stationary in the area of this test line. The nanoparticles accumulate and reveal the presence of the complex on the test line by coloring the test line red.

In the same way, the IgG-C complex and the AA-C complex react with immobilized detectors in the other test lines. The coloring of the control test line reveals that the sample has passed the membrane area.

The flow continues to the absorption pad (wick pad). The pore volume of this pad determines the sample volume that can flow through the test strip. Once the absorption path is full, the flow in the test strip stops. The only possibility to restart the flow is to evaporate some of the sample liquid in the absorption pad.

Model Definition

It could be shown that once passed the sample pad, the sample fluid flow quickly forms a flat velocity profile (Ref. 4). This means that it flows uniformly along the width of the test strip. This implies that a 2D model is enough to understand the challenges and functionality of the rapid detection test device, as long as the sample pad does its job in distributing the flow uniformly. We therefore used 2D models to investigate the transport and reactions in the test strip. The 2D models allow us to use a higher resolution of the mesh along both the length and thickness of the test strip.

The model combines the Richards' Equation interface for porous media flow and the Transport of Diluted Species in Porous Medium interface in COMSOL Multiphysics.

Here, the model was simplified assuming that the reaction sites are spread all across the thickness of the conjugate pad and, for the test line, across the membrane thickness. Therefore, the reactants do not have to be transported to the surface of the test strip and the reaction between the conjugate label and the antibodies are maximized. In this way, the conjugate label picks up as much antibodies as possible.

The reactions that form the IgM-C, IgG-C, and AA-C complex species are defined by the Domain ODEs and DAEs interface.

FLUID FLOW

Richards' equation describes the unsaturated–saturated flow of water in porous media. In this problem, Richards' equation can only be used for the water since the air in the test strip is supposed to be at atmospheric pressure. The governing equation for the model is

$$\rho\left[\frac{C}{\rho g} + S_e S_p\right]\frac{\partial p}{\partial t} + \nabla \cdot \rho\left[-\frac{\kappa_s \kappa_r}{\mu}\nabla p\right] = Q_m \tag{1}$$

The pressure, p, is the dependent variable, C denotes the specific moisture capacity (m^{-1}), S_e is the effective saturation, S_p is a storage coefficient (m^{-1}), t is time, κ_s denotes the permeability at saturation (m^2), and κ_r is the relative permeability, which is calculated, after Brooks and Corey, as

$$\kappa_r = S_e^{\frac{2}{n}+l+2}$$

$$S_e \begin{cases} \dfrac{1}{|\alpha\rho g p|^n} & p < -\dfrac{1}{\rho g \alpha} \\ 1 & -\dfrac{1}{\rho g \alpha} \le p \end{cases} \tag{2}$$

The material properties are assumed to be constant within the whole domain, regardless of the different pads or membranes used in the test.

CHEMICAL REACTIONS

On the conjugate pad, two processes take place. First, IgM and IgG antibodies from the saliva sample bind to gold nanoparticles SCoAu, creating complexes IgMC and IgGC.

$$\text{IgM} + \text{SCoAu} \rightarrow \text{IgMC}$$
$$\text{IgG} + \text{SCoAu} \rightarrow \text{IgGC}$$

Second, animal antibodies are released into the liquid.

$$\text{AA} + \text{AAu(ads)} \rightarrow \text{AAC}$$

On the first test line, the IgMC complex reacts with the adsorbed IgMd detector protein to form the adsorbed IgMPos surface species. The formation of the immobilized IgMPos gives the first test line its detection color.

$$\text{IgMC+IgMd(ads)} \rightarrow \text{IgMPos(ads)}$$

Analogously to above, in the second test line the IgGC complex reacts with the adsorbed IgGd detector protein. The adsorbed species IgGPos gives the second test line its red color.

$$\text{IgGC+IgGd(ads)} \rightarrow \text{IgGPos(ads)}$$

On the third test the antigen complex AAC binds to immobile detector molecules AAd. The adsorbed species AAPos gives the control test line its red color.

$$\mathrm{AAC} + \mathrm{AAd(ads)} \rightarrow \mathrm{AAPos(ads)}$$

In this homogenized version, the chemical reactions are provided in the Domain ODEs and DAEs interface which can be imported from an external file using the **Insert Physics** option.

TRANSPORT OF ANTIBODIES

The species transport is simulated using the Transport of Diluted Species in Porous Media interface. The values used for diffusion and reaction rates are listed in Table 1.

TABLE 1: TRANSPORT PROPERTIES.

Name	Value	Description
D1	$3 \cdot 10^{-11}$ m^2/s	Diffusion coefficient within all domains
k1	10 $m^3/(s \cdot mol)$	Rate constant, conjugate pad
k2	1 $m^3/(s \cdot mol)$	Rate constant, test line
c0	$2.3 \cdot 10^{-4}$ mol/m^3	Inlet antibody concentration
c0ads	$5 \cdot 10^{-7}$ mol/m^2	Adsorbed species surface concentration,conjugate pad

Results and Discussion

Figure 3 and Figure 4 show how the pressure front and the effective saturation front proceed with time. At about 260 s of simulated time the test strip is fully saturated.

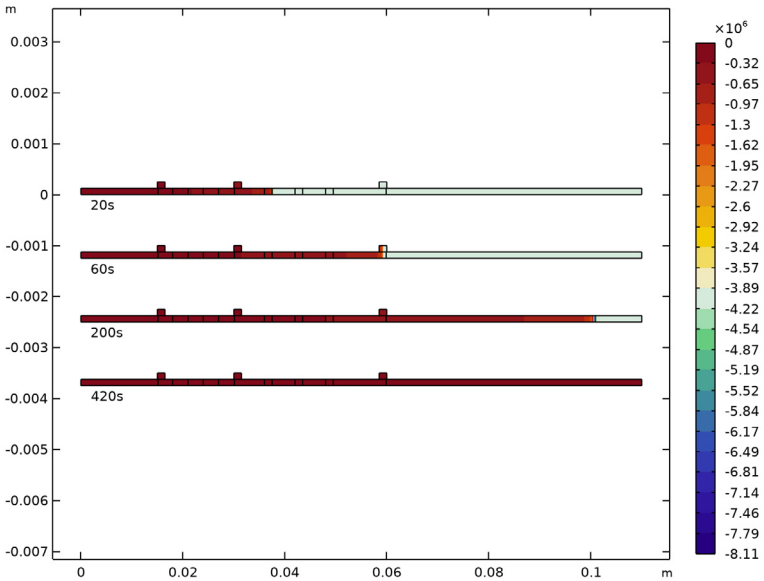

Figure 3: Pressure distribution at different output times (t = 20 s, t = 60 s, t = 210 s, t = 280 s, and t = 410 s).

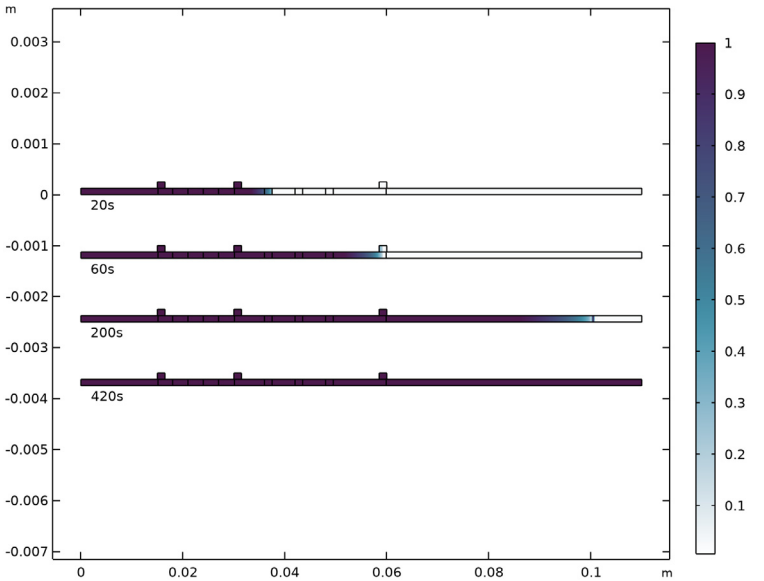

Figure 4: Effective saturation in the test strip at 20 s, 60 s, 210 s, 280 s, and 410 s (from top to bottom).

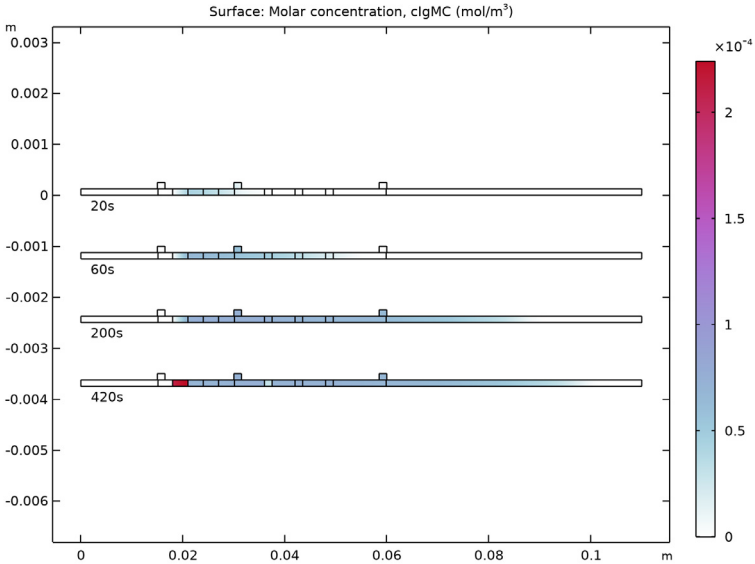

Figure 5: Concentration field of IgMC after 20 s (top), 60 s, 210 s, 280 s, and 410 s (bottom).

Figure 5, Figure 6, and Figure 7 illustrate the concentration fields of IgM-C, IgG-C, and AA-C complex species at different simulation times. After 410 s, there is no longer any flow through the test strip. We get a zone with high concentrations in the conjugate pad and a zone with low concentrations below the test line for the corresponding antibody.

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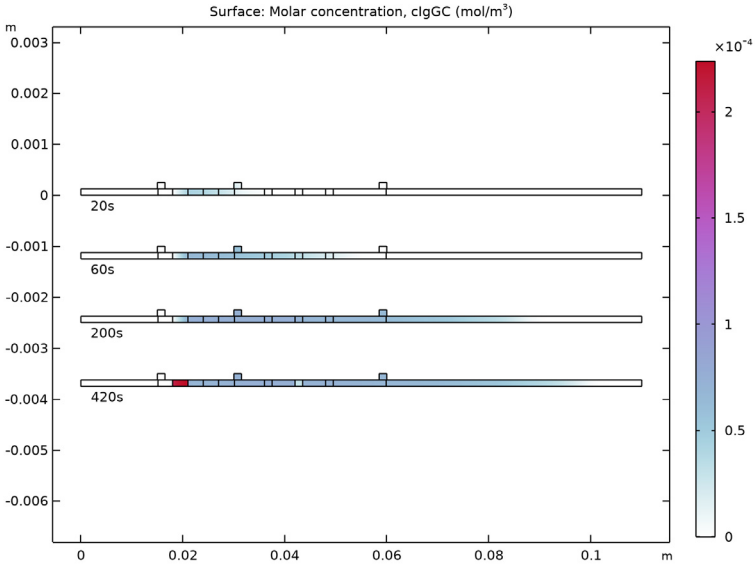


Figure 6: Concentration field of IgGC after 20 s (top), 60 s, 210 s, 280 s, and 410 s (bottom).

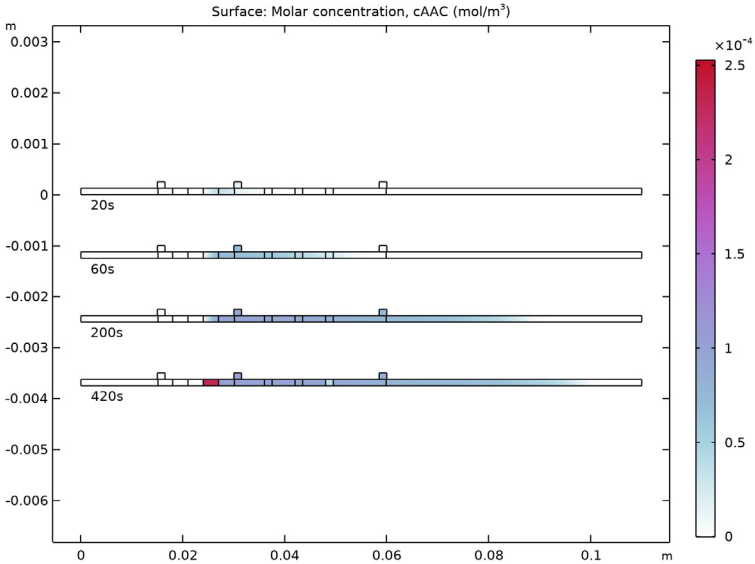


Figure 7: Concentration field of AAC after 20 s (top), 60 s, 210 s, 280 s, and 410 s (bottom).

The impact of the flow is clear if we plot the particle concentration of the detection species IgMPos, IgGPos, and AAPos at their respective test line area (Figure 8). The increase in particle concentrations starts with a delay given by when flow reaches the respective test line. The concentration grows almost linearly as IgMC is adsorbed at the test line area and the detector species IgMPos is formed. IgMPos and IgGPos compete for the same conjugate label and therefore AAPos grows slightly faster. The linear increase means a constant adsorption rate. When the flow stops, due to the saturation of the absorption pad, the rate of formation of IgMPos continues about the same rate. This implies that, in this case, the formation of IgMPos is determined by the adsorption kinetics; that is, it is determined by the adsorption rate of the gold nanoparticles in IgMC to the adsorption site. If it was mass transport controlled, we would see a change of the slope of the curve and the grow would be slowed down when the flow stops. This could, of course, change if we change the rate constant for the adsorption kinetics. The visibility of the test lines starts at about 1×10^8 particles/mm^2.

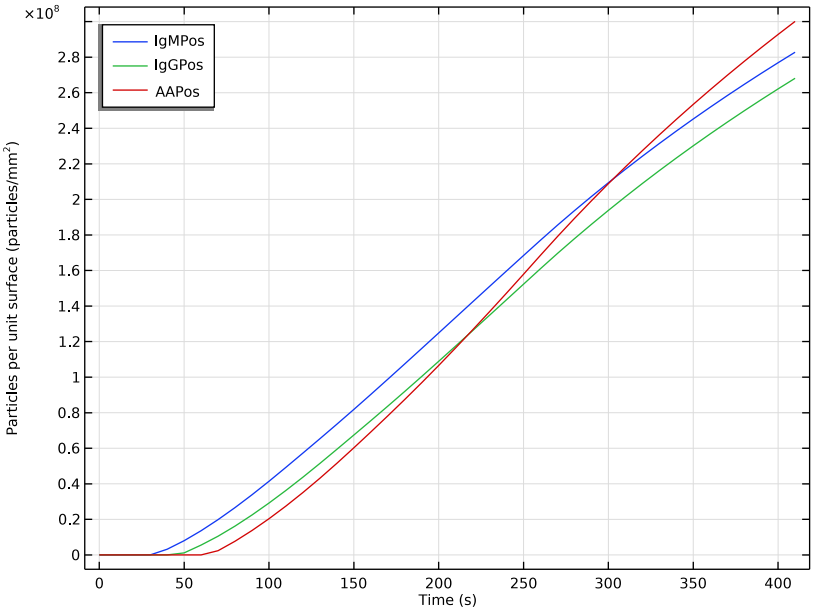


Figure 8: Particles per unit surface (t = 20 s, t = 60 s, t = 210 s, t = 280 s, and t = 410 s).

References

1. T. Kilic, R. Weissleder, and H. Lee, "Molecular and Immunological Diagnostic Tests of COVID-19: Current Status and Challenges," *iScience*, vol. 23, no. 8, 101406, 2020; doi.org/10.1016/j.isci.2020.101406.

2. B.G. Andryukov, "Six decades of lateral flow immunoassay: from determining metabolic markers to diagnosing COVID-19," *AIMS Microbiology*, vol. 6, no. 3, pp. 280–304, 2020; pubmed.ncbi.nlm.nih.gov/33134745/.

3. "Rapid Lateral Flow Test Strips, Considerations for Product Development," *Merck Millipore*, 2013 EMD Millipore Corporation, Billerica, MA, USA.

4. www.comsol.com/blogs/modeling-a-rapid-detection-test-in-comsol-multiphysics/

Application Library path: `Porous_Media_Flow_Module/Solute_Transport/rapid_detection_test_2d`

Modeling Instructions

Start setting up the physics for flow in unsaturated porous media using the Richards' Equation interface. The physics for the chemical reactions and the transport mechanisms are added later.

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

NEW

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

MODEL WIZARD

1. In the **Model Wizard** window, click **2D**.
2. In the **Select Physics** tree, select **Fluid Flow** > **Porous Media and Subsurface Flow** > **Richards' Equation (dl)**.
3. Click **Add**.
4. Click **Study**.
5. In the **Select Study** tree, select **General Studies** > **Time Dependent**.
6. Click **Done**.

GEOMETRY 1

Import the geometry sequence from a separate file.

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 `rapid_detection_test_2d_geom_sequence.mph`.

3 In the **Geometry** toolbar, click **Build All**.

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

DEFINITIONS

As the geometry is long and very flat, the view is scaled in the y direction to make it easier to select different domains within the geometry.

View 1

In the **Model Builder** window, expand the **Component 1 (comp1)** > **Definitions** node.

Axis

1 In the **Model Builder** window, expand the **View 1** node, then click **Axis**.

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

3 From the **View scale** list, choose **Manual**.

4 In the **y scale** text field, type `10`.

5 Click **Update**.

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

GLOBAL DEFINITIONS

The geometry has been set up using parameters. Add more parameters relevant for the material, chemistry and operation conditions. For convenience, all these parameters can be imported from external files.

Parameters: Geometry

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

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

Parameters: Material

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 `rapid_detection_test_2d_parameters_material.txt`.

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

Parameters: Operating Conditions

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 `rapid_detection_test_2d_parameters_operating_conditions.txt`.

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

RICHARDS' EQUATION (DL)

Next, set up the physics for unsaturated porous media flow.

1 In the **Model Builder** window, under **Component 1 (comp1)** click **Richards' Equation (dl)**.

2 In the **Settings** window for **Richards' Equation**, locate the **Gravity Effects** section.

3 Clear the **Include gravity** checkbox as the geometry is so flat that gravity does not take any effect.

To improve the convergence of the model, set the shape function to linear.

4 Click to expand the **Discretization** section. From the **Pressure** list, choose **Linear**.

Unsaturated Porous Medium 1

1 In the **Model Builder** window, under **Component 1 (comp1)** > **Richards' Equation (dl)** click **Unsaturated Porous Medium 1**.

2 In the **Settings** window for **Unsaturated Porous Medium**, locate the **Porous Medium** section.

3 From the **Storage model** list, choose **From retention model**.

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 **Permeability model** list, choose **Kozeny–Carman**.

4 In the d_p text field, type `d_p`.

5 Locate the **Retention Model** section. From the **Retention model** list, choose **Brooks and Corey**.

6 In the α text field, type `alpha`.

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

Initial Values 1

1 In the **Model Builder** window, under **Component 1 (comp1)** > **Richards' Equation (dl)** click **Initial Values 1**.

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

3 In the *p* text field, type `p0`.

MATERIALS

Now add the materials needed.

Fluid

1 In the **Model Builder** window, under **Component 1 (comp1)** right-click **Materials** and choose **Blank Material**.

2 In the **Settings** window for **Material**, type `Fluid` in the **Label** text field.

3 Locate the **Material Contents** section. In the table, enter the following settings:

Property	Variable	Value	Unit	Property group
Density	rho	`rho_l`	kg/m³	Basic
Dynamic viscosity	mu	`mu_l`	Pa·s	Basic

Porous Material 1 (pmat1)

1 Right-click **Materials** and choose **More Materials** > **Porous Material**.

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

3 From the **Selection** list, choose **All domains**.

4 Locate the **Porosity** section. In the ε_p text field, type `por`.

5 Locate the **Phase-Specific Properties** section. Click **Add Required Phase Nodes**.

Fluid 1 (pmat1.fluid1)

1 In the **Model Builder** window, click **Fluid 1 (pmat1.fluid1)**.

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

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

GLOBAL DEFINITIONS

A pressure boundary condition is prescribed at the inlet. To improve stability, the inlet pressure is ramped up smoothly over a short initial time interval rather than being applied instantaneously. Therefore, create a step function first.

Step 1 (step1)

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

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

3 In the **Location** text field, type `0.5[s]`.

4 Click to expand the **Smoothing** section. In the **Size of transition zone** text field, type `1`.

RICHARDS' EQUATION (DL)

Pressure 1

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

2 Select Boundary 4 only.

3 In the **Settings** window for **Pressure**, locate the **Pressure** section.

4 In the p_0 text field, type `p0+(pw-p0)*step1(t)`.

MESH 1

To capture the saturation front correctly, a high mesh resolution is needed. In this case, a mapped mesh is chosen as this combines efficiency and good resolution.

1 In the **Model Builder** window, under **Component 1 (comp1)** click **Mesh 1**.

2 In the **Settings** window for **Mesh**, locate the **Physics-Controlled Mesh** section.

3 From the **Element size** list, choose **Extremely fine**.

Mapped 1

In the **Mesh** toolbar, click **Mapped**.

Size

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

2 In the **Settings** window for **Size**, click to expand the **Element Size Parameters** section.

3 In the **Maximum element size** text field, type `1e-4`.

Mapped 1

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

2 In the **Settings** window for **Mapped**, click to expand the **Reduce Element Skewness** section.

3 Select the **Adjust edge mesh** checkbox.

Size 1

1 Right-click **Mapped 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 **Domain**.

4 Select Domain 1 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 `3e-5`.

Distribution 1

1 Right-click **Mapped 1** and choose **Distribution**.

2 Select Boundary 66 only.

3 In the **Settings** window for **Distribution**, locate the **Distribution** section.

4 In the **Number of elements** text field, type `3`.

Distribution 2

1 Right-click **Mapped 1** and choose **Distribution**.

2 Select Boundaries 54 and 56 only.

3 In the **Settings** window for **Distribution**, locate the **Distribution** section.

4 From the **Distribution type** list, choose **Predefined**.

5 In the **Number of elements** text field, type `200`.

6 In the **Element ratio** text field, type `5`.

7 Select the **Reverse direction** checkbox.

This expression creates a gradually increasing mesh size, so the elements become larger toward the right end.

Distribution 3

1 Right-click **Mapped 1** and choose **Distribution**.

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

3 Click **Paste Selection**.

4 In the **Paste Selection** dialog, type `6, 8, 25, 27, 53, 55` in the **Selection** text field.

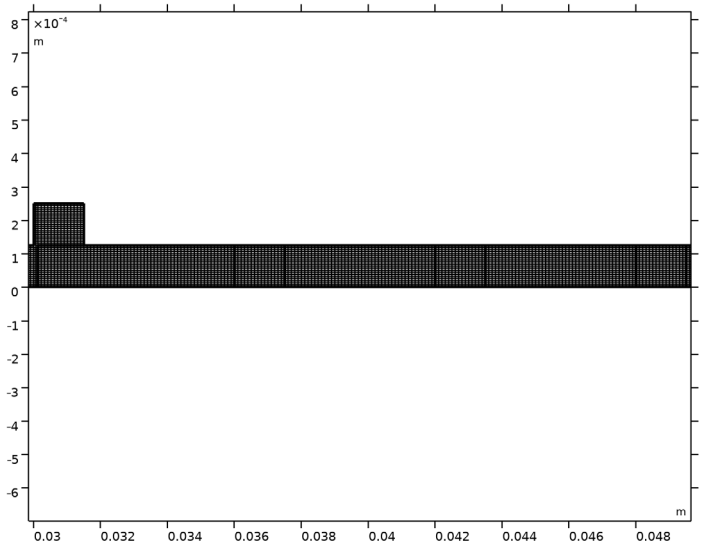
5 Click **OK**.

6 In the **Settings** window for **Distribution**, locate the **Distribution** section.

7 In the **Number of elements** text field, type `20`.

8 Click **Build All**.

Zoom in and make sure the mesh size corresponds to that in the image below.



DEFINITIONS (COMP1)

Next, set up the study. As the wetting front advances and the strip approaches full saturation, capillary suction decreases and no longer provides a stabilizing gradient, which may cause the solver to have convergence issues. To prevent this, use an **Implicit Event** that reinitializes the pressure to be in equilibrium with the applied pressure when the strip is almost fully saturated, i.e., when the effective saturation exceeds 0.8 at position 0.105 m. After that, the pressure remains constant and the Darcy velocity becomes zero.

Domain Point Probe 1

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 In row **Coordinates**, set **x** to `0.105`.

4 In row **Coordinates**, set **y** to `th/2`.

Point Probe Expression 1 (ppb1)

1 In the **Model Builder** window, expand the **Domain Point Probe 1** 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 `dl.Se`.

ADD PHYSICS

1 In the **Home** toolbar, click **Windows** and choose **Add Physics**.

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

3 In the tree, select **Mathematics** > **ODE and DAE Interfaces** > **Events (ev)**.

4 Click the **Add to Component 1** button in the window toolbar.

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

EVENTS (EV)

Indicator States 1

1 In the **Physics** toolbar, click **Global** and choose **Indicator States**.

2 In the **Settings** window for **Indicator States**, locate the **Indicator Variables** section.

3 In the table, enter the following settings:

Name	g(v,vt,vtt,t)	Initial value (u0)	Description
`saturated`	`ppb1-0.8`	`0`	

Implicit Event 1

1 In the **Physics** toolbar, click **Global** and choose **Implicit Event**.

2 In the **Settings** window for **Implicit Event**, locate the **Event Conditions** section.

3 In the **Condition** text field, type `saturated>0` as the event is triggered when the condition changes sign.

4 Locate the **Reinitialization** section. In the table, enter the following settings:

	Expression
p	pw

5 Locate the **Event Conditions** section. Clear the **Use consistent initialization** checkbox.

STUDY 1

This is a highly nonlinear problem, so solver settings need some adjustments. At the start, changes happen quickly, so choose time steps that capture the moving liquid front accurately. Use a stable damped Newton method to manage the nonlinearity. While convergence is the top priority, settings should also keep computation time reasonable. For more details of each setting, see the manual.

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 In the **Output times** text field, type `5*(exp(range(0,1/19,1)*4)-1)/(exp(4)-1) range(10,5,420)`.

The first five seconds are divided into 20 time steps, which gradually increase in size. Keep in mind that the software uses extra time steps if needed for convergence.

4 Click to expand the **Results While Solving** section. From the **Probes** list, choose **None**.

Solution 1 (sol1)

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

2 In the **Model Builder** window, expand the **Solution 1 (sol1)** node, then click **Time-Dependent Solver 1**.

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

4 From the **Steps taken by solver** list, choose **Strict**.

5 Find the **Algebraic variable settings** subsection. From the **Consistent initialization** list, choose **Off**.

6 From the **Error estimation** list, choose **Exclude algebraic**.

7 In the **Model Builder** window, expand the **Study 1** > **Solver Configurations** > **Solution 1 (sol1)** > **Time-Dependent Solver 1** node, then click **Fully Coupled 1**.

8 In the **Settings** window for **Fully Coupled**, click to expand the **Method and Termination** section.

9 In the **Damping factor** text field, type `0.6`.

10 In the **Maximum number of iterations** text field, type 30.

11 In the **Model Builder** window, under **Study 1** > **Solver Configurations** > **Solution 1 (sol1)** > **Time-Dependent Solver 1** click **Direct, pressure (dl) (Merged)**.

12 In the **Settings** window for **Direct**, locate the **General** section.

13 From the **Solver** list, choose **PARDISO**.

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

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

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

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

RESULTS

A pressure plot and a plot of the effective saturation can be loaded from the **Result Templates** menu. Follow the steps below to reproduce Figure 3 and Figure 4.

RESULT TEMPLATES

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

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

3 In the tree, select **Study 1/Solution 1 (sol1)** > **Richards' Equation** > **Pressure (dl)** and **Study 1/Solution 1 (sol1)** > **Richards' Equation** > **Effective Saturation (dl)**.

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

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

RESULTS

Pressure (dl)

1 In the **Model Builder** window, expand the **Results** > **Pressure (dl)** node, then click **Pressure (dl)**.

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

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

4 Click to expand the **Plot Array** section. From the **Array type** list, choose **Linear**.

5 From the **Array axis** list, choose **y**.

6 From the **Displacement** list, choose **Absolute**.

7 In the **Cell displacement** text field, type `-1.25e-3`.

Solution Array 1

1 In the **Model Builder** window, right-click **Surface** and choose **Solution Array**.

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

3 From the **Time selection** list, choose **Interpolated**.

4 In the **Times (s)** text field, type `20 60 200 420`.

5 In the **Pressure (dl)** toolbar, click **Plot**.

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

Pressure (dl)

In the **Pressure (dl)** toolbar, click **More Plots** and choose **Table Annotation**.

Table Annotation 1

1 In the **Settings** window for **Table Annotation**, locate the **Data** section.

2 From the **Source** list, choose **Local table**.

3 In the table, enter the following settings:

x-coordinate	y-coordinate	Annotation
0	0	20s
0	-1.25e-3	60s
0	-2.5e-3	200s
0	-3.75e-3	420s

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

Pressure (dl)

1 In the **Model Builder** window, click **Pressure (dl)**.

2 In the **Pressure (dl)** toolbar, click **Plot**.

Effective Saturation (dl)

1 In the **Model Builder** window, expand the **Results** > **Effective Saturation (dl)** node, then click **Effective Saturation (dl)**.

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

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

4 Locate the **Plot Array** section. From the **Array type** list, choose **Linear**.

5 From the **Array axis** list, choose **y**.

6 From the **Displacement** list, choose **Absolute**.

7 In the **Cell displacement** text field, type `-1.25e-3`.

Solution Array 1

1 In the **Model Builder** window, right-click **Surface 1** and choose **Solution Array**.

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

3 From the **Time selection** list, choose **Interpolated**.

4 In the **Times (s)** text field, type `20 60 200 420`.

Table Annotation 1

In the **Model Builder** window, under **Results** > **Pressure (dl)** right-click **Table Annotation 1** and choose **Copy**.

Table Annotation 1

1 In the **Model Builder** window, right-click **Effective Saturation (dl)** and choose **Paste Table Annotation**.

2 In the **Effective Saturation (dl)** toolbar, click **Plot**.

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

COMPONENT 1 (COMP1)

Next, set up the chemical reactions together with mass transport. If available in your license, the **Chemistry** interface provides a convenient way to define reactions. In this model, the **Domain, ODEs and DAEs** interface is used. For convenience, a fully set-up interface is imported from an external file.

1 In the **Home** toolbar, click **Insert Physics** and choose **Insert Physics**.

2 In the **Insert Physics** dialog, click **Browse**.

3 Browse to the model's Application Libraries folder and double-click the file `rapid_detection_test_2d_geom_sequence.mph`.

4 Click **OK**.

Inspect the **Reactions** node (the Domain ODEs and DAEs interface). Eight species and hence eight dependent variables are defined. For each section of the detection test, a domain feature specifies the reactions described in Chemical Reactions. Some variables are still undefined at this stage, namely the species that are transported. These will be introduced in the next step, when setting up the transport interface.

ADD PHYSICS

1 In the **Home** toolbar, click **Windows** and choose **Add Physics**.

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

3 In the tree, select **Chemical Species Transport** > **Transport of Diluted Species in Porous Media (tds)**.

4 Find the **Physics interfaces in study** subsection. In the table, clear the **Solve** checkbox for **Study 1** as the chemical reactions and transport variables will be solved for in a different study.

5 Click the **Add to Component 1** button in the window toolbar.

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

TRANSPORT OF DILUTED SPECIES IN POROUS MEDIA (TDS)

1 In the **Settings** window for **Transport of Diluted Species in Porous Media**, click to expand the **Discretization** section.

2 From the **Concentration** list, choose **Quadratic**.

3 Click to expand the **Dependent Variables** section. In the **Number of species** text field, type `6`.

4 In the **Concentrations (mol/m³)** table, enter the following settings:

`cIgM`
`cIgMC`
`cIgG`
`cIgGC`
`cAA`
`cAAC`

Fluid 1

1 In the **Model Builder** window, under **Component 1 (comp1)** > **Transport of Diluted Species in Porous Media (tds)** > **Porous Medium 1** click **Fluid 1**.

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

3 From the $\mathbf{u}$ list, choose **Total Darcy velocity field (dl/usporous1)**.

4 Locate the **Diffusion** section. In the $D_{\mathrm{F,cIgM}}$ text field, type `D1`.

5 In the $D_{\mathrm{F,cIgMC}}$ text field, type `D1`.

6 In the $D_{\mathrm{F,cIgG}}$ text field, type `D1`.

7 In the $D_{\mathrm{F,cIgGC}}$ text field, type `D1`.

8 In the $D_{\mathrm{F,cAA}}$ text field, type `D1`.

9 In the $D_{\mathrm{F,cAAC}}$ text field, type `D1`.

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

Inflow 1

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

2 Select Boundary 4 only.

3 In the **Settings** window for **Inflow**, locate the **Concentration** section.

4 In the $c_{0,\mathrm{cIgM}}$ text field, type `c0*step1(t)`.

5 In the $c_{0,\mathrm{cIgG}}$ text field, type `c0*step1(t)`.

6 In the $c_{0,\mathrm{cAA}}$ text field, type `c0*step1(t)`.

DEFINITIONS (COMP1)

Add the reactions for the different conjugation pad areas and test lines. First, define the reaction variables.

Variables: Reaction Rates

1 In the **Model Builder** window, under **Component 1 (comp1)** right-click **Definitions** and choose **Variables**.

2 In the **Settings** window for **Variables**, type `Variables: Reaction Rates` in the **Label** text field.

3 Locate the **Variables** section. Click **Load from File**.

4 Browse to the model's Application Libraries folder and double-click the file `rapid_detection_test_2d_variables_reaction_rates.txt`.

TRANSPORT OF DILUTED SPECIES IN POROUS MEDIA (TDS)

Reactions: Antibody Binding

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

2 In the **Settings** window for **Reactions**, type `Reactions: Antibody Binding` in the **Label** text field.

3 Locate the **Domain Selection** section. From the **Selection** list, choose **Antibody Binding**.

4 Locate the **Reaction Rates** section. In the R_{cIgM} text field, type `-r_IgMC`.

5 In the R_{cIgMC} text field, type `r_IgMC`.

6 In the R_{cIgG} text field, type `-r_IgGC`.

7 In the R_{cIgGC} text field, type `r_IgGC`.

Reactions: Animal Antibodies

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

2 In the **Settings** window for **Reactions**, type `Reactions: Animal Antibodies` in the **Label** text field.

3 Locate the **Domain Selection** section. From the **Selection** list, choose **Animal Antibodies**.

4 Locate the **Reaction Rates** section. In the R_{cAA} text field, type `-r_AAC`.

5 In the R_{cAAC} text field, type `r_AAC`.

Reactions: IgM Detection

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

2 In the **Settings** window for **Reactions**, type `Reactions: IgM Detection` in the **Label** text field.

3 Locate the **Domain Selection** section. From the **Selection** list, choose **IgM Detection**.

4 Locate the **Reaction Rates** section. In the R_{cIgMC} text field, type `-r_IgMPos`.

Reactions: IgG Detection

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

2 In the **Settings** window for **Reactions**, type `Reactions: IgG Detection` in the **Label** text field.

3 Locate the **Domain Selection** section. From the **Selection** list, choose **IgG Detection**.

4 Locate the **Reaction Rates** section. In the R_{cIgGC} text field, type `-r_IgGPos`.

Reactions: Antigen Detection

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

2 In the **Settings** window for **Reactions**, type `Reactions: Antigen Detection` in the **Label** text field.

3 Locate the **Domain Selection** section. From the **Selection** list, choose **Antigen Detection**.

4 Locate the **Reaction Rates** section. In the R_{cAAC} text field, type `-r_AAPos`.

ADD STUDY

1 In the **Home** toolbar, click **Windows** and choose **Add Study**.

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

3 Find the **Physics interfaces in study** subsection. In the table, clear the **Solve** checkboxes for **Richards' Equation (dl)** and **Events (ev)**.

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

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

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

STUDY 2

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 `5*(exp(range(0,1/19,1)*4)-1)/(exp(4)-1) range(10,5,420)`.

3 Locate the **Results While Solving** section. From the **Probes** list, choose **None**.

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

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

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

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

8 In the **Settings** window for **Time Dependent**, click to expand the **Values of Dependent Variables** section.

9 Find the **Values of variables not solved for** subsection. From the **Settings** list, choose **User controlled**.

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

11 From the **Study** list, choose **Study 1, Time Dependent**.

12 From the **Time (s)** list, choose **Automatic (all solutions)**.

For each time step in the transport and reaction simulation, the corresponding solution from Richards' Equation is retrieved.

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 **Dependent Variables 1**.

3 In the **Settings** window for **Dependent Variables**, locate the **Scaling** section.

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

5 In the **Model Builder** window, under **Study 2** > **Solver Configurations** > **Solution 2 (sol2)** click **Time-Dependent Solver 1**.

6 In the **Settings** window for **Time-Dependent Solver**, locate the **Time Stepping** section.

7 From the **Steps taken by solver** list, choose **Strict**.

8 Find the **Algebraic variable settings** subsection. From the **Consistent initialization** list, choose **Off**.

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

STUDY 1

In case you want to rerun the first study, the reactions need to be deactivated there.

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 **Physics and Variables Selection** section.

3 In the **Solve for** column of the table, under **Component 1 (comp1)**, clear the checkbox for **Reactions (dode)**.

RESULTS

To plot the different antibody concentrations, follow the steps below.

IgMC Concentration

1 In the **Results** toolbar, click **2D Plot Group**.

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

Surface 1

Right-click **IgMC Concentration** and choose **Surface**.

IgMC Concentration

Locate the **Data** section. From the **Dataset** list, choose **Study 2/Solution 2 (sol2)**.

Surface 1

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

2 In the **Settings** window for **Surface**, click **Replace Expression** in the upper-right corner of the **Expression** section. From the menu, choose **Component 1 (comp1)** > **Transport of Diluted Species in Porous Media** > **Species cIgMC** > **cIgMC - Molar concentration, cIgMC - mol/m³**.

3 Locate the **Coloring and Style** section. From the **Color table** list, choose **Acanthaster**.

Solution Array 1

1 Right-click **Surface 1** and choose **Solution Array**.

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

3 From the **Time selection** list, choose **Interpolated**.

4 In the **Times (s)** text field, type `20 60 200 420`.

IgMC Concentration

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

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

3 From the **Array axis** list, choose **y**.

4 From the **Displacement** list, choose **Absolute**.

5 In the **Cell displacement** text field, type `-1.25e-3`.

Table Annotation 1

1 In the **IgMC Concentration** toolbar, click **More Plots** and choose **Table Annotation**.

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

3 From the **Source** list, choose **Local table**.

4 In the table, enter the following settings:

x-coordinate	y-coordinate	Annotation
0	0	20s
0	-1.25e-3	60s
0	-2.5e-3	200s
0	-3.75e-3	420s

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

IgMC Concentration

1 In the **Model Builder** window, click **IgMC Concentration**.

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

3 From the **Title type** list, choose **Custom**.

4 Find the **Solution** subsection. Clear the **Solution** checkbox.

5 In the **IgMC Concentration** toolbar, click **Plot**.

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

IgGC Concentration

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

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

3 In the **Settings** window for **2D Plot Group**, type `IgGC Concentration` 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 **Expression** section.

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

4 In the **IgGC Concentration** toolbar, click **Plot**.

AAC Concentration

1 In the **Model Builder** window, right-click **IgGC Concentration** and choose **Duplicate**.

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

3 In the **Settings** window for **2D Plot Group**, type `AAC Concentration` 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 **Expression** section.

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

4 In the **AAC Concentration** toolbar, click **Plot**.

Continue with plotting the number of particles per unit surface as in Figure 8 which indicates the visibility of the test line.

Evaluation Group: Test Line

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

2 In the **Settings** window for **Evaluation Group**, type `Evaluation Group: Test Line` in the **Label** text field.

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

Surface Average 1

1 Right-click **Evaluation Group: Test Line** and choose **Average** > **Surface Average**.

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

3 From the **Selection** list, choose **IgM Detection**.

4 Locate the **Expressions** section. Click **Clear Table**.

5 In the table, enter the following settings:

Expression	Unit	Description
`IgMPos*N_A_const*1e-5[m]/1e6`	`1/m^2`	`IgMPos particles`

Surface Average 2

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

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

3 In the table, enter the following settings:

Expression	Unit	Description
`IgGPos*N_A_const*1e-5[m]/1e6`	`1/m^2`	`IgGPos particles`

4 Locate the **Selection** section. From the **Selection** list, choose **IgG Detection**.

Surface Average 3

1 Right-click **Surface Average 2** and choose **Duplicate**.

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

3 From the **Selection** list, choose **Antigen Detection**.

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

Expression	Unit	Description
`AAPos*N_A_const*1e-5[m]/1e6`	`1/m^2`	`AAPos particles`

Evaluation Group: Test Line

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

2 In the **Evaluation Group: Test Line** toolbar, click **Evaluate**.

EVALUATION GROUP: TEST LINE

1 Go to the **Evaluation Group: Test Line** window.

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

RESULTS

Table Graph 1

1 In the **Settings** window for **Table Graph**, click to expand the **Legends** section.

2 Select the **Show legends** checkbox.

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

4 In the table, enter the following settings:

Legends
`IgMPos`
`IgGPos`
`AAcPos`

Concentration, IgMPos, IgGPos, AAPos

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 **Upper left**.

4 Locate the **Plot Settings** section.

5 Select the **y-axis label** checkbox. In the associated text field, type `Particles per unit surface (mm<sup>2</sup>)`.

6 Click to expand the **Title** section. From the **Title type** list, choose **Manual**.

7 In the **Label** text field, type `Concentration, IgMPos, IgGPos, AAPos`.

8 Locate the **Title** section. From the **Title type** list, choose **None**.

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

10 In the **Concentration, IgMPos, IgGPos, AAPos** toolbar, click **Plot**.