Case Study VII

VII Radioimmunotherapy of metastatic melanoma

Metastatic melanoma is the most dangerous form of skin cancer and causes 77% of all skin cancer-related deaths. New methods for its treatment are, therefore, urgently needed. The feasibility of radioimmunotherapy (RIT) in mice, which involves the binding of the antibody to a tumor-associated antigen to deliver a lethal dose of radiation to tumor cells, was established in a study by Dadachova *et al.* (2004). Another study (Schweitzer *et al.*, 2007) looked at the process of radioimmunotherapy in detail with the use of a computer model. In this particular example, we will follow this paper to develop a mathematical model of the process.

Problem formulation

Figure 6.11 shows the process of radioimmunotherapy. The process involves intravenous administration of a radio-labeled antibody in the patient's body which circulates in the plasma and is transported across capillary walls into the normal tissue. The shape of the tumor is assumed to be a sphere. The antibody then diffuses through normal tissue to the tumor to reach the antigen present inside the tumor and binds with it to form an antibody-antigen complex. Also, the antibody-antigen complex that is formed dissociates into free antibody and antigen. Some amount of the antibody in the normal tissue is removed by the lymphatic vessels and there is no significant binding of the antibody in the normal tissue.

Governing equations

The governing equations that describe the set of processes are given by:

(I) Antibody uptake from blood:

$$c_{\mathrm{Abp}}(t) = c_{\mathrm{Abo}} e^{-\lambda t} \tag{6.12}$$

where c_{Abo} is the initial plasma antibody concentration after intravenous administration, λ is the plasma kinetics constant and c_{Abp} is the antibody concentration in the plasma as a function of time.

(II) Transport, uptake and clearance of antibody in normal tissue:

$$\frac{\partial c_{\mathrm{Abt}}}{\partial t} = D_{\mathrm{tis}} \frac{1}{r^2} \frac{\partial}{\partial r}\left(r^2 \frac{\partial c_{\mathrm{Abt}}}{\partial r}\right) + k^{\mathrm{bl}} c_{\mathrm{Abp}} - k^{\mathrm{ly}} c_{\mathrm{Abt}} \tag{6.13}$$

where c_{Abt} is the antibody concentration in the normal tissue, D_{tis} is the diffusivity of antibody in the tissue, r is the radial distance from the tumor center, and k^{bl} and k^{ly} are the rate constants for uptake into and removal from tissue, respectively.

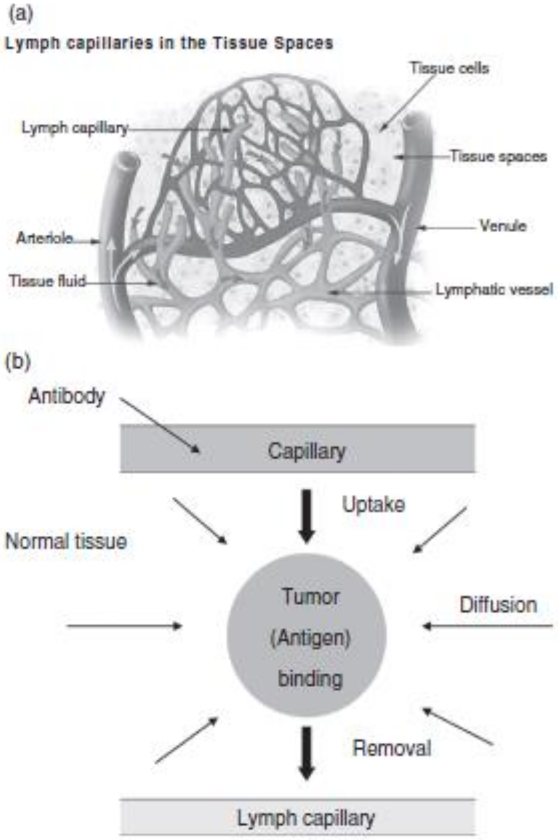


Figure 6.11

(a) The blood and lymph capillary system in the tissue. Figure from http://upload.wikimedia.org/wikipedia/commons/1/19/Illu_lymph_capillary.png; (b) physical description of radioimmunotherapy.

(III) Transport, complex formation and dissociation in tumor:

$$\frac{\partial c_{\mathrm{Ab}}}{\partial t} = D_{\mathrm{tum}} \frac{1}{r^2} \frac{\partial}{\partial r}\left(r^2 \frac{\partial c_{\mathrm{Ab}}}{\partial r}\right) - k_{+1} c_{\mathrm{Ab}} c_{\mathrm{Ag}} + k_{-1} c_{\mathrm{Ab-Ag}} \tag{6.14}$$

where c_{Ab} is the concentration of free antibody in the tumor, D_{tum} is the diffusivity of antibody in the tumor and k_{+1} and k_{-1} are the rates of the forward and backward reactions, respectively.

(IV) Antigen concentration due to complex formation and dissociation:

$$\frac{\partial c_{\mathrm{Ag}}}{\partial t} = n\left(-k_{+1} c_{\mathrm{Ab}} c_{\mathrm{Ag}} + k_{-1} c_{\mathrm{Ab-Ag}}\right) \tag{6.15}$$

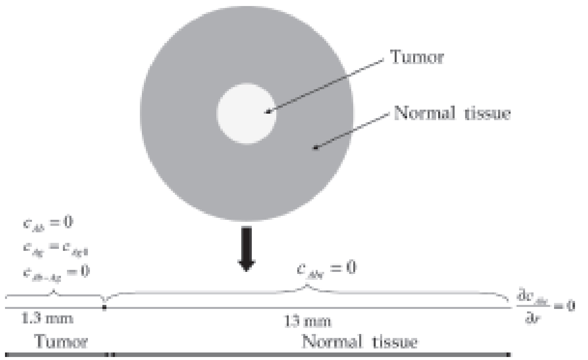


Figure 6.12

Schematic, boundary and initial conditions for the problem. The computations are done in 1D considering spherical symmetry (as discussed in the text).

Table 6.5 Input parameters (all values taken from Schweitzer *et al.*, 2007).

Input parameter	Value
Radius of tumor, r_{tum}	1.3 mm
Radius of tissue, r_{tis}	14.3 mm
Initial antibody concentration, c_{Ab0}	4.94 nM
Antigen concentration, c_{Ag0}	76 000 nM
Diffusivity of antibody in tumor, D_{tum}	4.16×10^{-7} cm^2 s^{-1}
Diffusivity of antibody in tissue, D_{tis}	2.0×10^{-7} cm^2 s^{-1}
Rate constant, λ	2.96×10^{-5} s^{-1}
Rate constant for transcapillary transport, k^{bl}	4.6×10^{-5} mL/(s*mL ECF)
Rate constant for lymphatic clearance, k^{ly}	1.78×10^{-5} mL/(s*mL ECF)
Forward binding rate constant, k_{+1}	5.0×10^{4} M^{-1}s^{-1}
Dissociation rate constant, k_{-1}	1.0×10^{-5} s^{-1}
Valence of antibody/antigen binding, n	5

where c_{Ag} is the antigen concentration and n is the valence of 6D2/melanin binding.

(V) Complex concentration due to formation and dissociation:

$$\frac{\partial c_{Ab-Ag}}{\partial t} = k_{+1} c_{Ab} c_{Ag} - k_{-1} c_{Ab-Ag} \tag{6.16}$$

where c_{Ab-Ag} is the complex concentration.

Boundary conditions The boundary conditions are shown in Figure 6.12. On the left tumor boundary, species flux for all species is zero due to symmetry. On the right normal tissue boundary, species flux is zero as the boundary is considered to be at a large distance. Initially, there is no antibody and complex in the domain. The tumor has an initial antigen concentration of 76 000 nM (Table 6.5).

Input parameters Input parameters are shown in Table 6.5.

References

Dadachova, E., Nosanchuk, J. D., Shi, L., *et al.* (2004). Dead cells in melanoma tumors provide abundant antigen for targeted delivery of ionizing radiation by a monoclonal antibody to melanin. *Proc Natl Acad Sci USA* 2004;**101**:14865–14870.

Schweitzer A. D., Rakesh V., Revskaya E., Datta A., Casadevall A., Dadachova E. (2007). Computational model predicts effective delivery of 188-Re-labeled melanin-binding antibody to the metastatic melanoma tumors with wide range of melanin concentrations. *Melanoma Research*, **17**(5):291–303.

Implementation in COMSOL

As discussed earlier, the shape of the tumor is a sphere. All the computations can, therefore, be done in the spherical coordinate system. Since the concentrations are dependent only on the radial distances, as can be seen in Equations 6.13 and 6.14, a simplified geometry consisting of a line can be used for the model (Figure 6.12). This reduces the amount of computational resources that would be required if we modeled the complete sphere. However, the governing equations need to be solved in the spherical coordinate system. COMSOL solves all the governing equations in the Cartesian system and hence, we need to modify the equations in COMSOL to implement the spherical coordinate system. We take the species transfer equation in the Cartesian (1D) and spherical (with radial dependence only) systems:

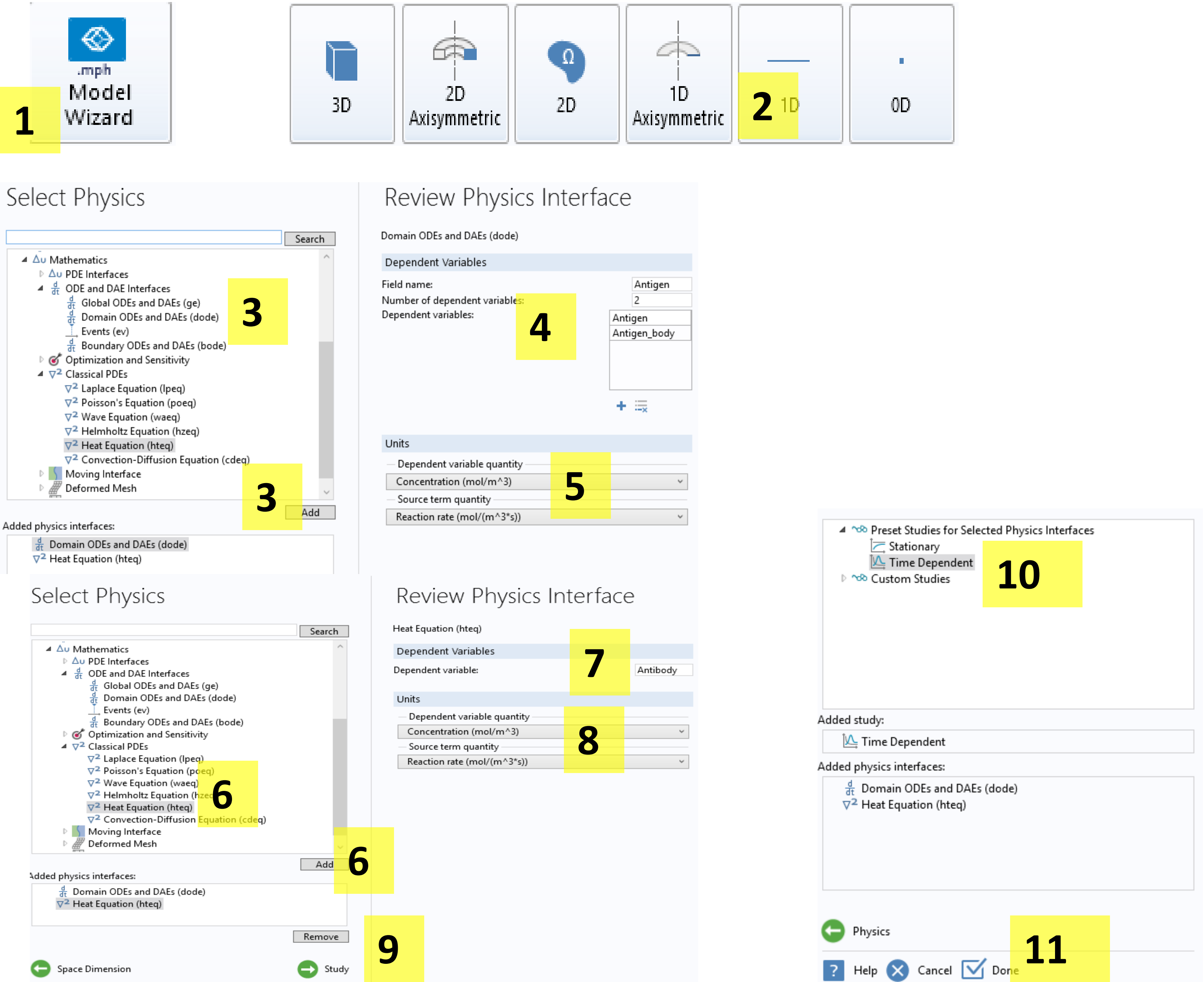
$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D_{cart}\frac{\partial c}{\partial x}\right) + R_{cart} \tag{6.17}$$

$$\frac{\partial c}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 D \frac{\partial c}{\partial r}\right) + R \tag{6.18}$$

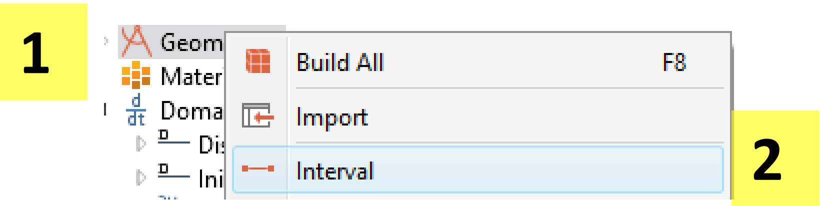
Equation 6.18 can be multiplied by r^2 on both sides giving:

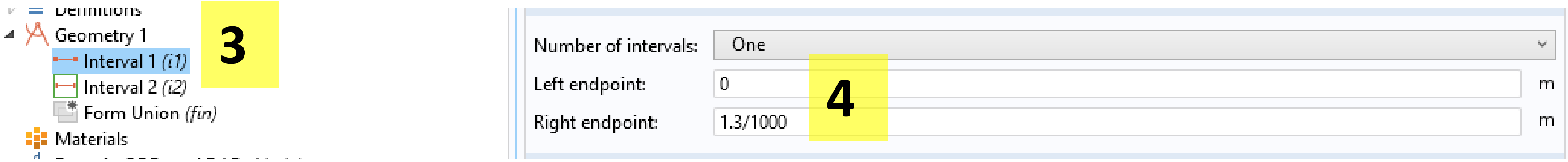
$$r^2\frac{\partial c}{\partial t} = \frac{\partial}{\partial r}\left(r^2 D \frac{\partial c}{\partial r}\right) + r^2 R \tag{6.19}$$

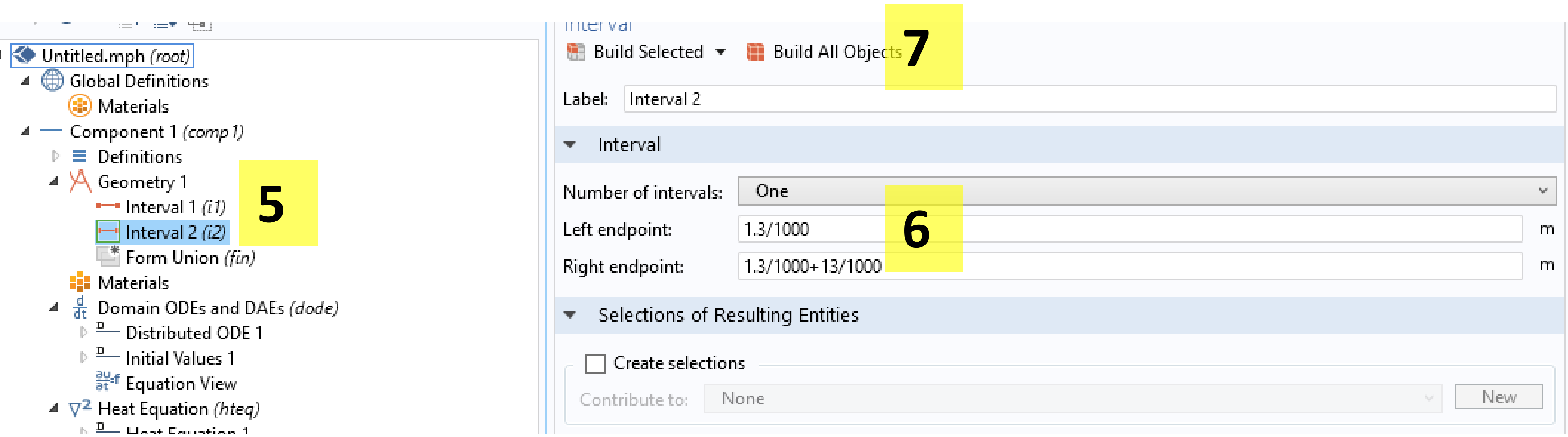
Equation 6.19 can be implemented in COMSOL as Equation 6.17 using the coefficient of $\partial c/\partial t$ as r^2, $D_{cart} = r^2 D$ and $R_{cart} = r^2 R$. The problem has been solved using this method for conversion to the spherical coordinate system in this example.



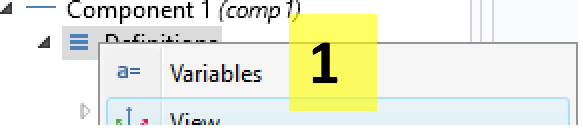
1) Select model wizard
2) Select 1D
3) Under mathematics>>ODE and DAE Interfaces, add ‘Domain ODEs and DAEs’
4) Rename the field name, number, and variable names as shown
5) Change quantity and source term
6) Under mathematics>>Classical PDEs, add ‘Heat equation’
7) Rename the variable names as shown
8) Change quantity and source term
9) Click study
10) Select time dependent
11) Click done





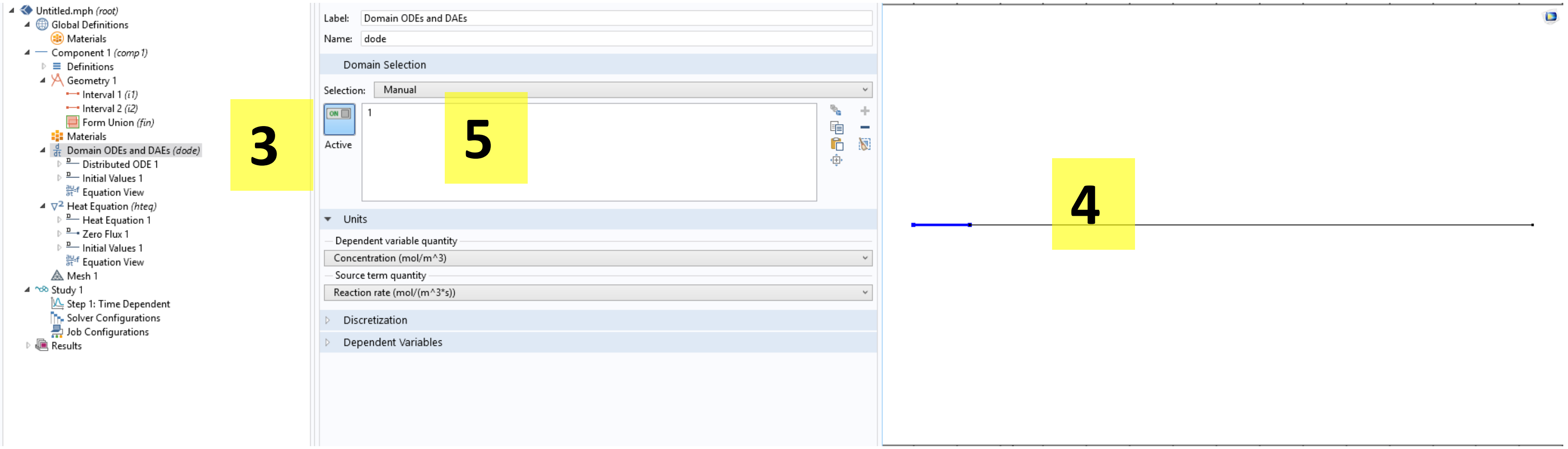


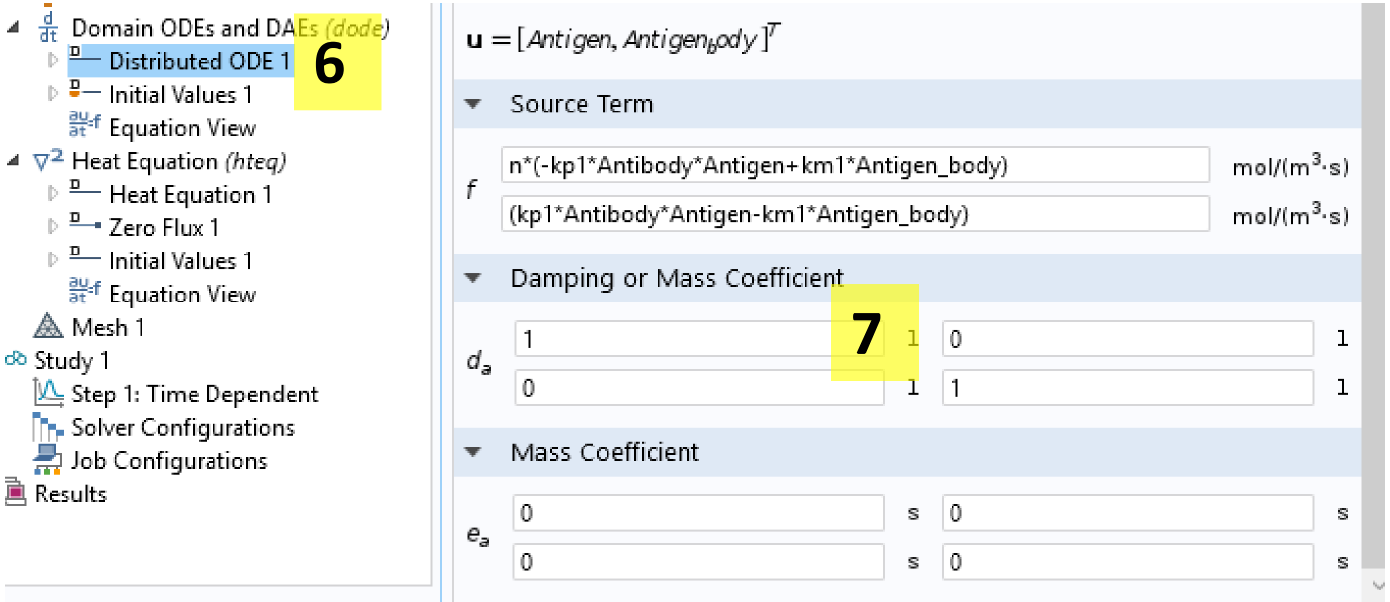
1) Right click geometry and select interval
2) Repeat step 1
3) Left click interval 1
4) Enter the dimensions
5) Left click interval 2
6) Enter the dimensions
7) Click Build all



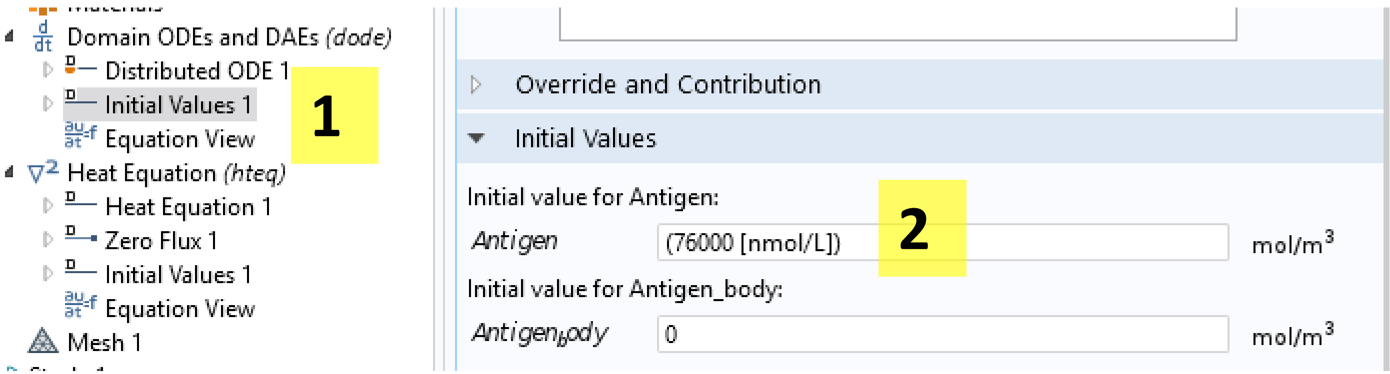
Name	Expression	Unit	Description
n	5		
kp1	(5e4) [L/(mol*s)]	m³/(s·m...	
km1	1e-5 [1/s]	1/s	
kbl	4.6e-5 [1/s]	1/s	
kly	1.78e-5 [1/s]	1/s	
lambda	2.96e-5 [1/s]	1/s	
D_tum	4.16e-7 [cm^2/s]	m²/s	
D_tis	2e-7 [cm^2/s]	m²/s	

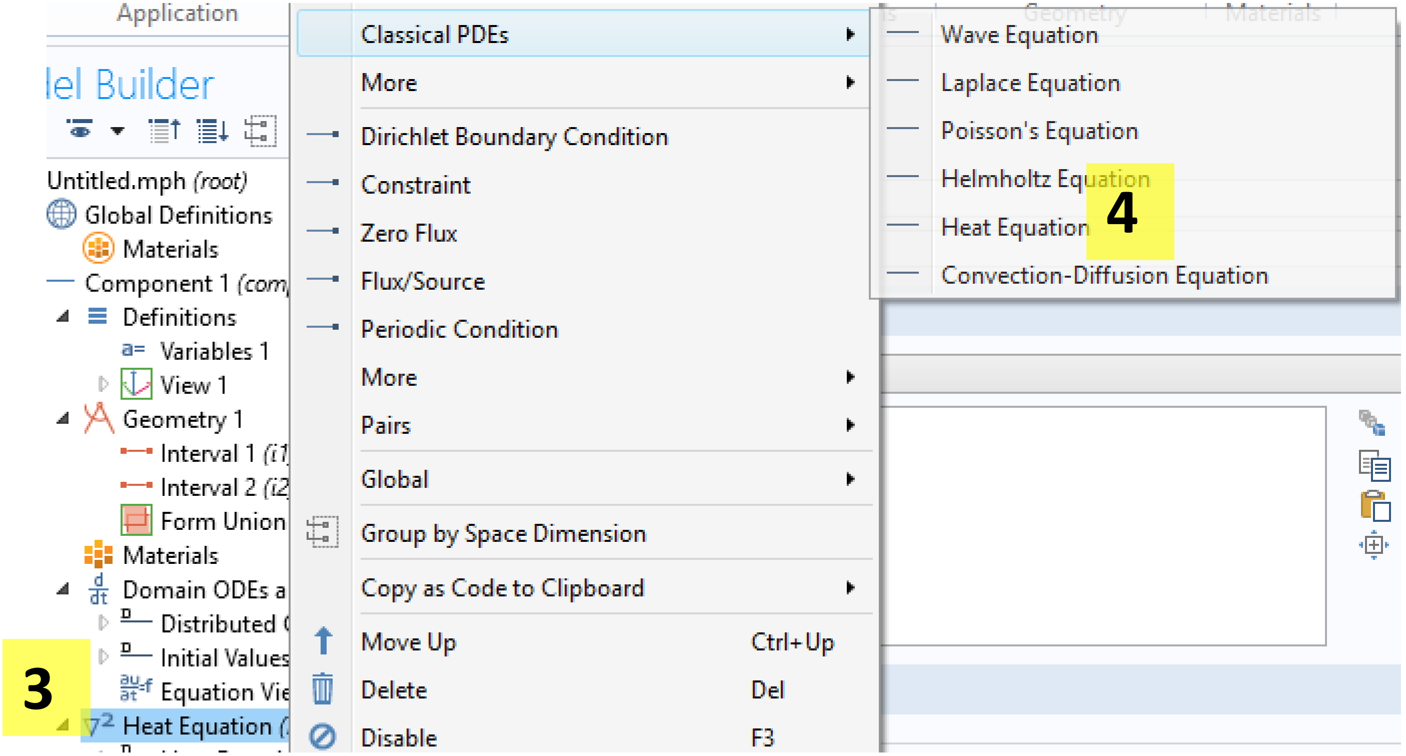
2



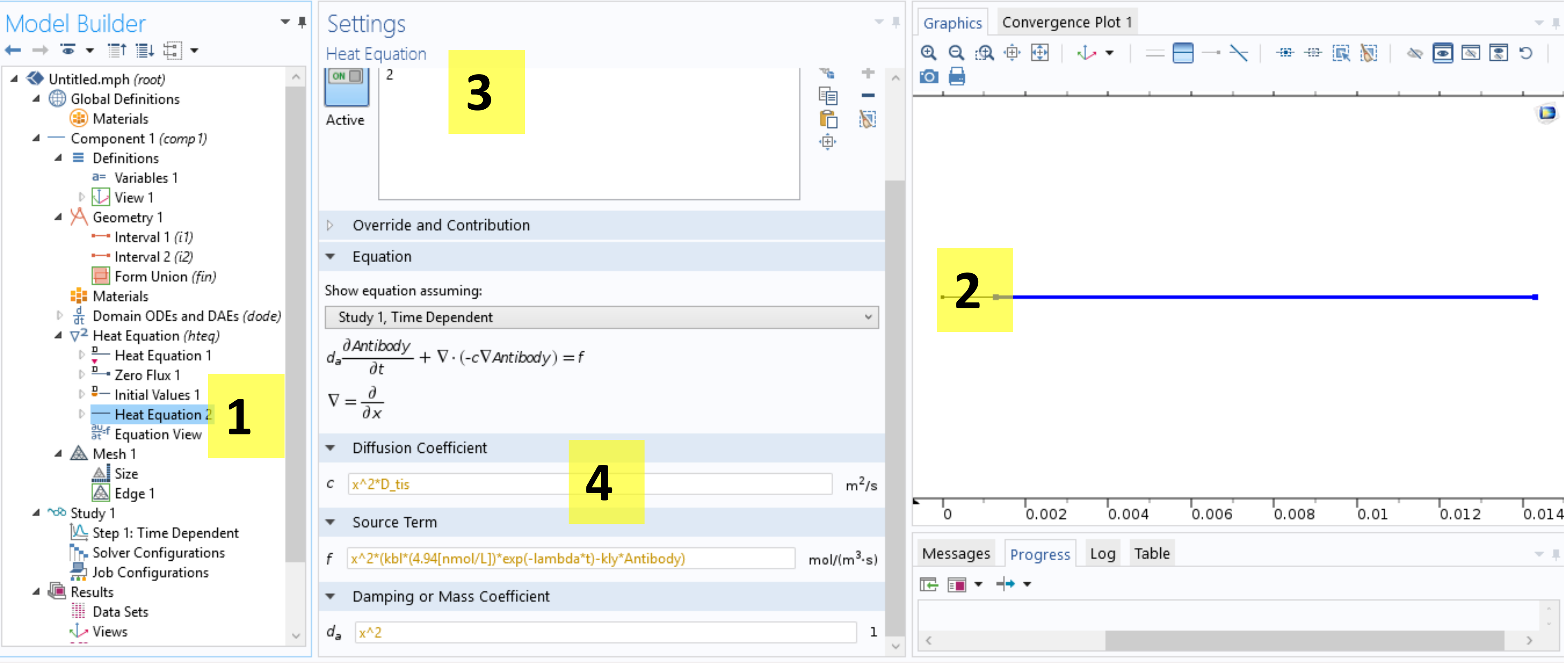


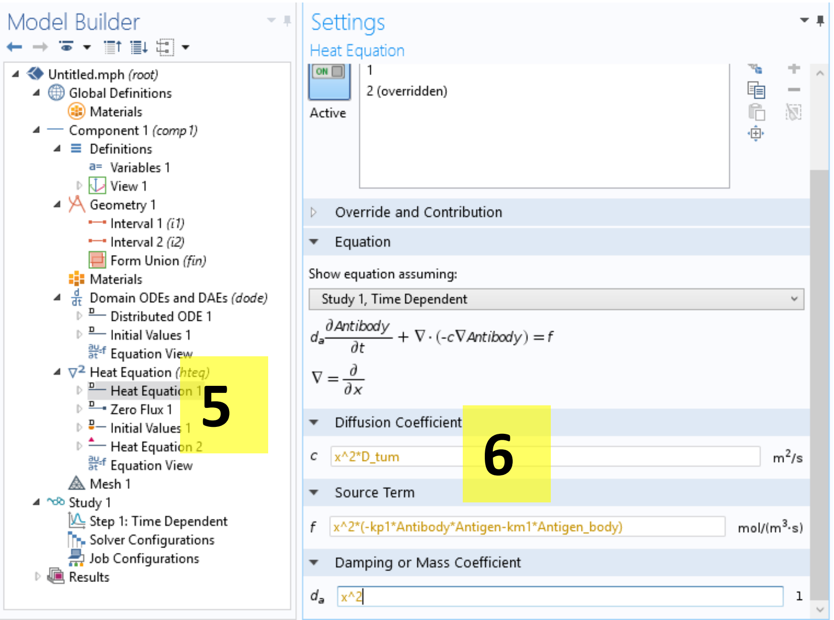
1) Click definitions and select variables
2) Enter the table
3) Click 'Domain ODEs and DAEs'
4) Left click domain 2
5) You should only see domain 1
6) Left click 'Distributed ODE 1'
7) Enter the following values



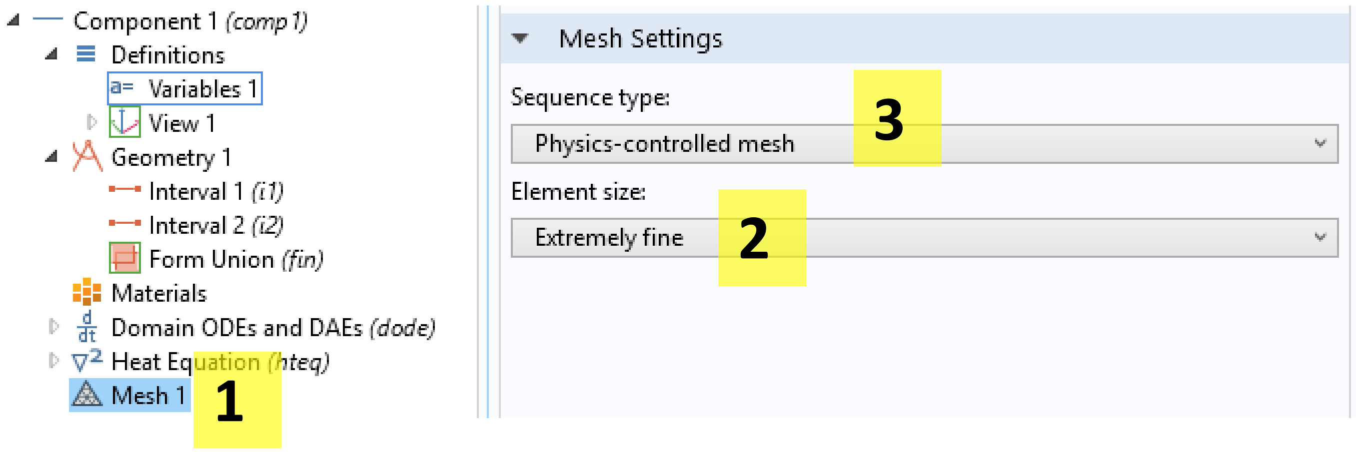


1) Left click 'Initial Values 1' under Domain ODEs
2) Enter the antigen concentration
3) Right click the Heat equation physics
4) Add another 'Heat equation'

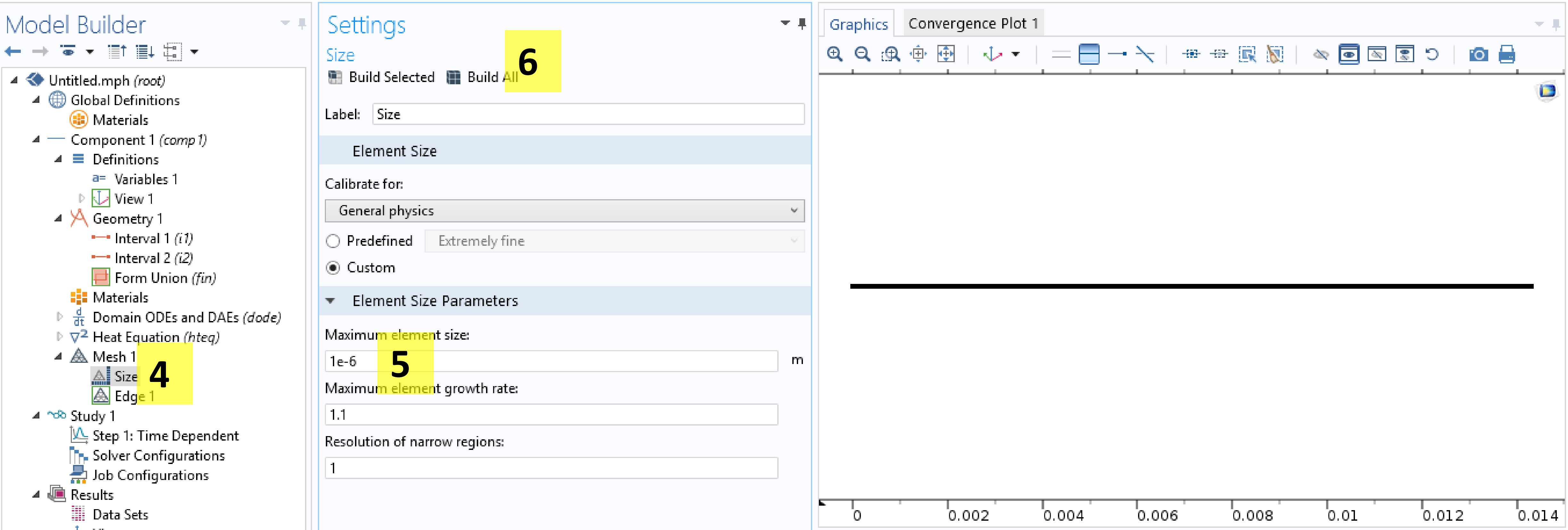




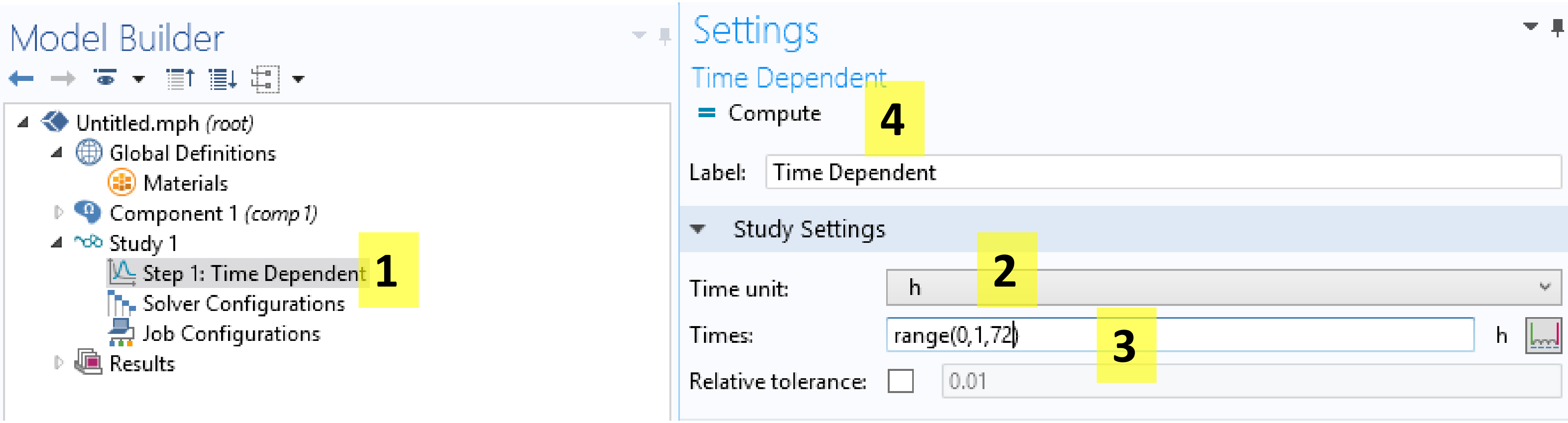
1) Left click 'Heat equation 2'
2) Left click the tumor domain (domain 1) deselecting it
3) You should only see domain 2
4) Enter the diffusivity and reaction rate
5) Left click 'Heat equation 1'
6) Enter the diffusivity and reaction rate

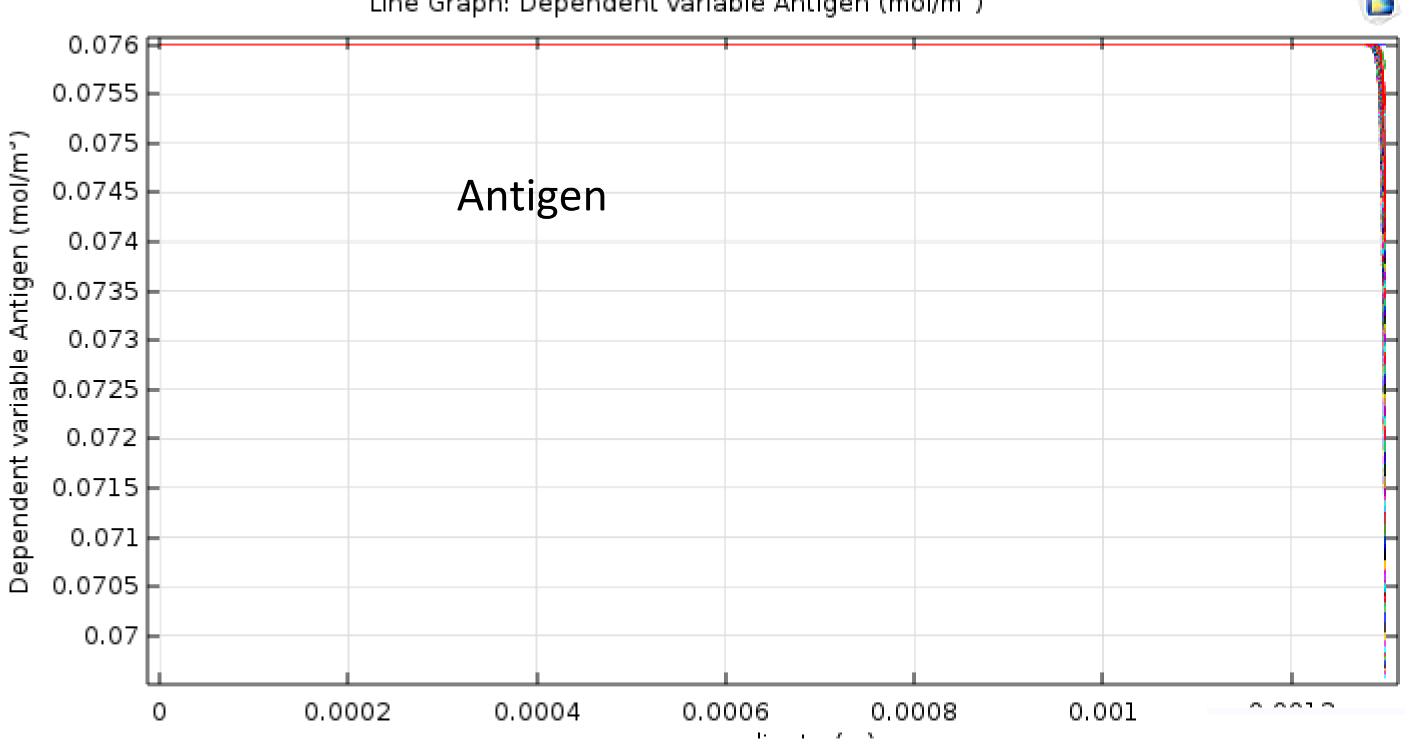


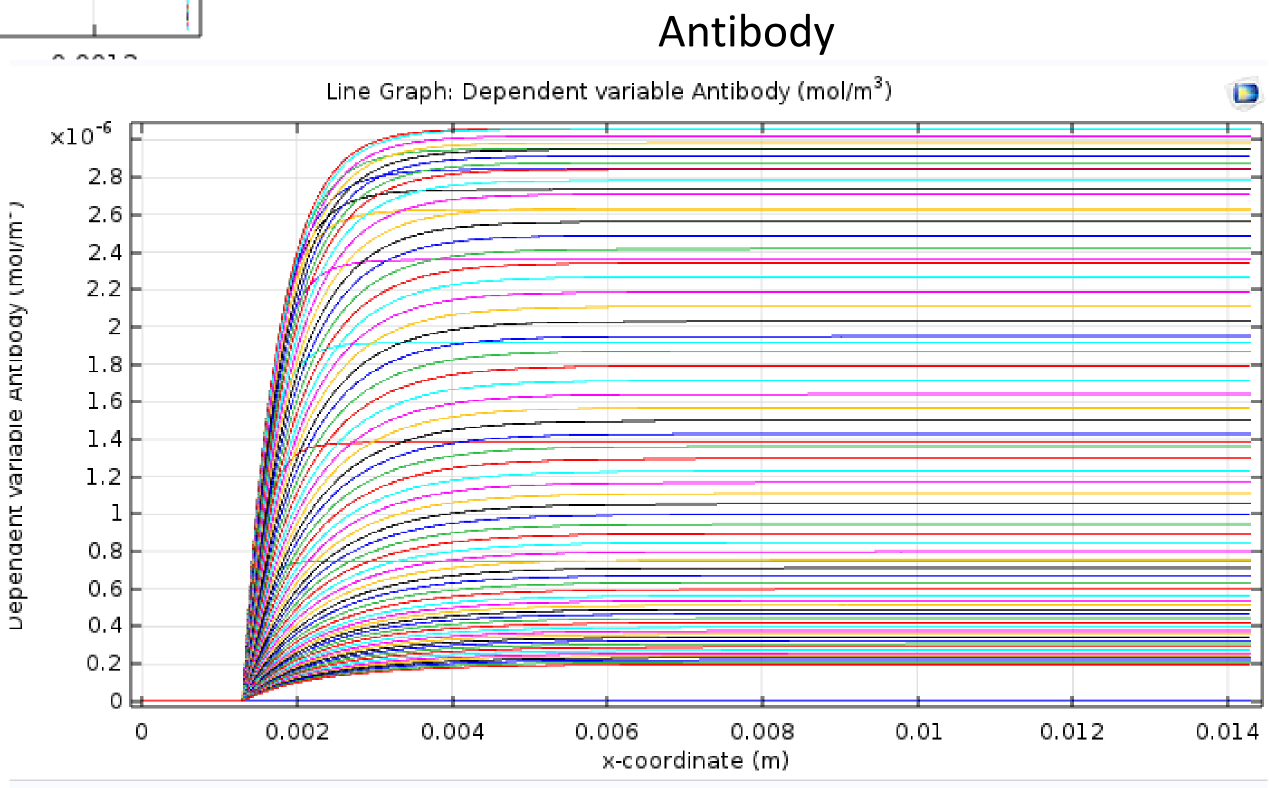
1) Left click mesh 1
2) Select extremely fine
3) Select 'User defined' from the dropdown
4) Left click size
5) Enter 1e-6
6) Click build all



1) Left click “Step 1: Time dependent’
2) Change time unit to hours
3) Enter range(0,1,72)
4) Click compute




Antigen
Dependent variable Antigen (mol/m³)
0.076
0.0755
0.075
0.0745
0.074
0.0735
0.073
0.0725
0.072
0.0715
0.071
0.0705
0.07
0
0.0002
0.0004
0.0006
0.0008
0.001


Antibody
Line Graph: Dependent variable Antibody (mol/m³)
x10⁻⁶
2.8
2.6
2.4
2.2
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
0.002
0.004
0.006
0.008
0.01
0.012
0.014
x-coordinate (m)

Case Study IX

IX Radiofrequency cardiac ablation

Arrhythmia is irregular beating of the heart which causes decreased blood flow and oxygen supply to the brain and body. Radiofrequency (RF) ablation (see Section 8.5) is the standard procedure for treating arrhythmias. In this example, we look at radiofrequency heating in a tissue using a partly modified and simplified version of this process modeled by Tungjitkusolmun *et al.* (2000).

Problem formulation

A cylindrical electrode is introduced into the middle of the tissue where RF ablation is needed. The problem is therefore axisymmetric and the schematic is shown in Figure 6.14. The properties of the tissue are homogenous. The tissue is heated by resistive heating due to Joule heat generation as there is a potential difference between the electrode tip and the outer edge of the tissue. The optimal goal of RF ablation is to increase the temperature of the tissue from 37 °C to more than 50 °C, when the desired myocardial injury takes place (Tungjitkusolmun *et al.*, 2000). However, the temperatures in the tissue should be kept below 100 °C to avoid unwanted phenomena such as boiling, charring etc.

Governing equations

The heat transfer in the tissue is governed by the bioheat equation:

$$\rho C_p \frac{\partial T}{\partial t} = \left[\frac{1}{r}\frac{\partial}{\partial r}\left(kr\frac{\partial T}{\partial r}\right) + \frac{\partial}{\partial z}\left(k\frac{\partial T}{\partial z}\right)\right] + \rho_b C_{p,b}\dot{V}_b^v(T_a - T) + Q \quad (6.22)$$

where $\rho_b C_{p,b}\dot{V}_b^v(T_a - T)$ is the blood perfusion term and Q is the heat generated during RF ablation.

The electric potential is given by:

$$\nabla \cdot (\sigma \nabla V) = 0 \quad (6.23)$$

The heat generated, Q, due to Joule heating is given by:

$$Q = \sigma\, |\nabla V|^2 \quad (6.24)$$

where V is the electric potential and σ is the electrical conductivity.

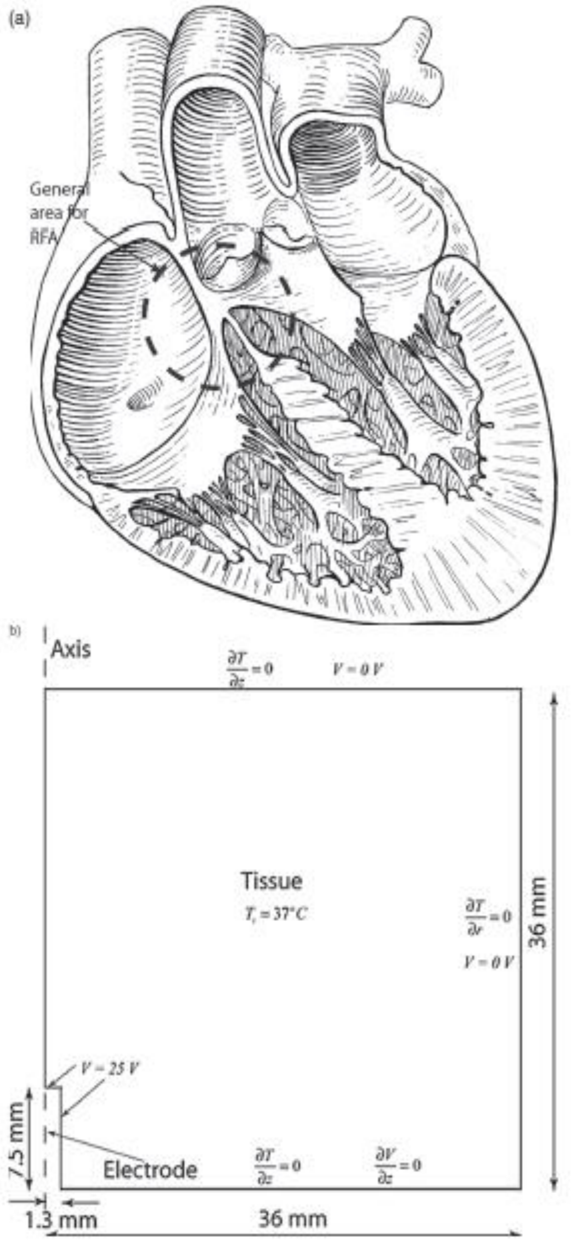


Figure 6.14

(a) Placement of the electrode for RF ablation in the heart; (b) the computational domain and initial conditions for the problem.

Table 6.7 Input parameters (all values taken from Tungjitkusolmun *et al.*, 2000).

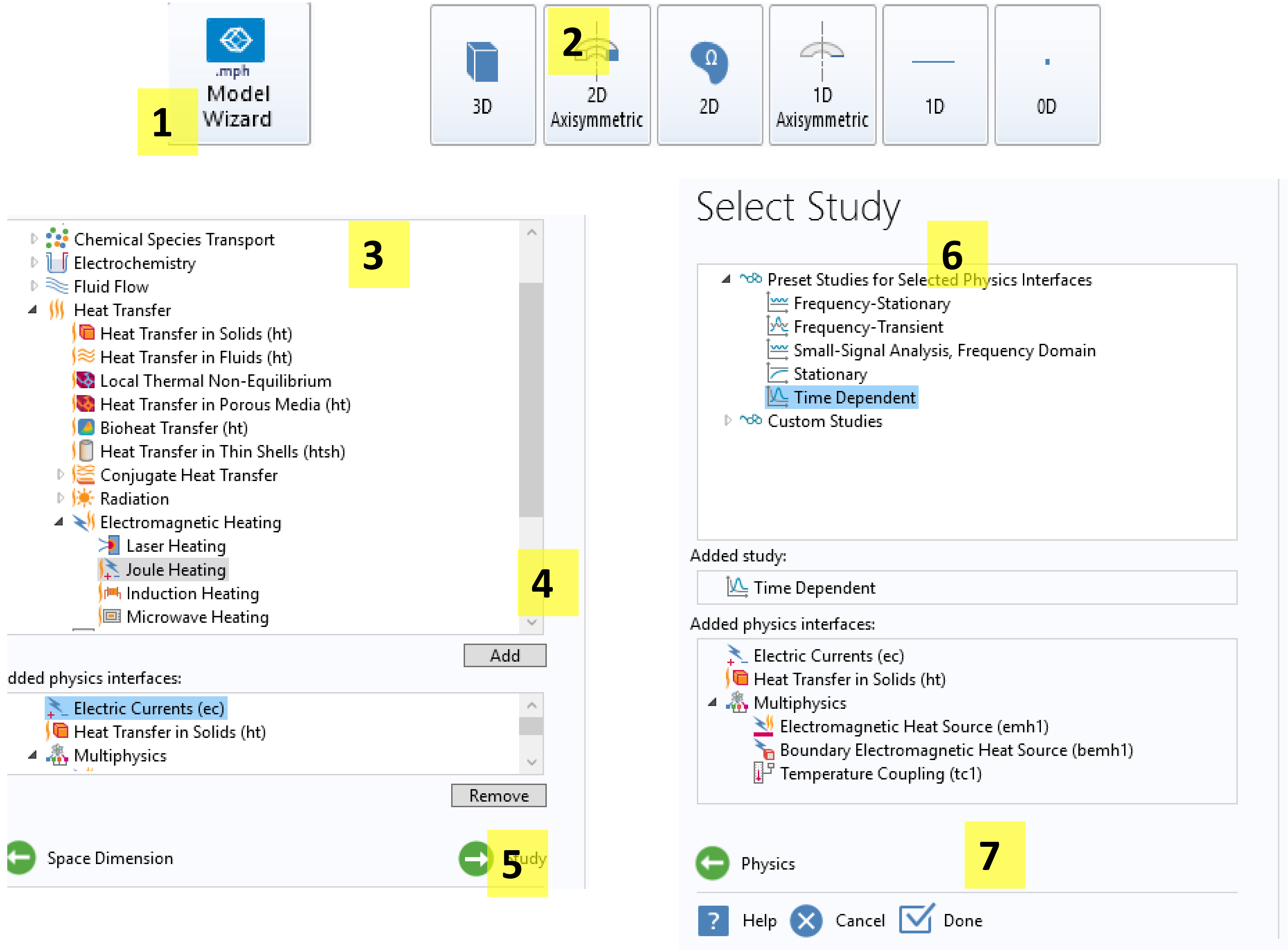
Parameter	Value
Thermal conductivity of the tissue, k	$0.4925+0.001\,195T$ $Wm^{-1}K^{-1}$
Specific heat of the tissue, C_p	3200 $Jkg^{-1}K^{-1}$
Density of the tissue, ρ	1200 kgm^{-3}
Duration of heating, t	60 s
Blood perfusion coefficient, $\rho_b C_{p,b} \dot{V}_b^v$	2000 $Wm^{-3}K^{-1}$
Electrical conductivity, σ	0.222 $S\,m^{-1}$
Arterial blood temperature, T_a	37 °C
Initial tissue temperature, T_i	37 °C
Electric potential at the electrode surface, V	25 V

Boundary conditions The boundary conditions and the schematic used for the model in COMSOL are shown in Figure 6.14. The geometry is modeled as axisymmetric as discussed earlier. The tissue is at a constant initial temperature of 37 °C. The electrode is not included in the geometry for simplicity and the electric potential to the surface of the electrode is implemented as a boundary condition. The heat fluxes at all surfaces are zero as the left surface is the axis and the other surfaces are assumed to be at a very far distance.

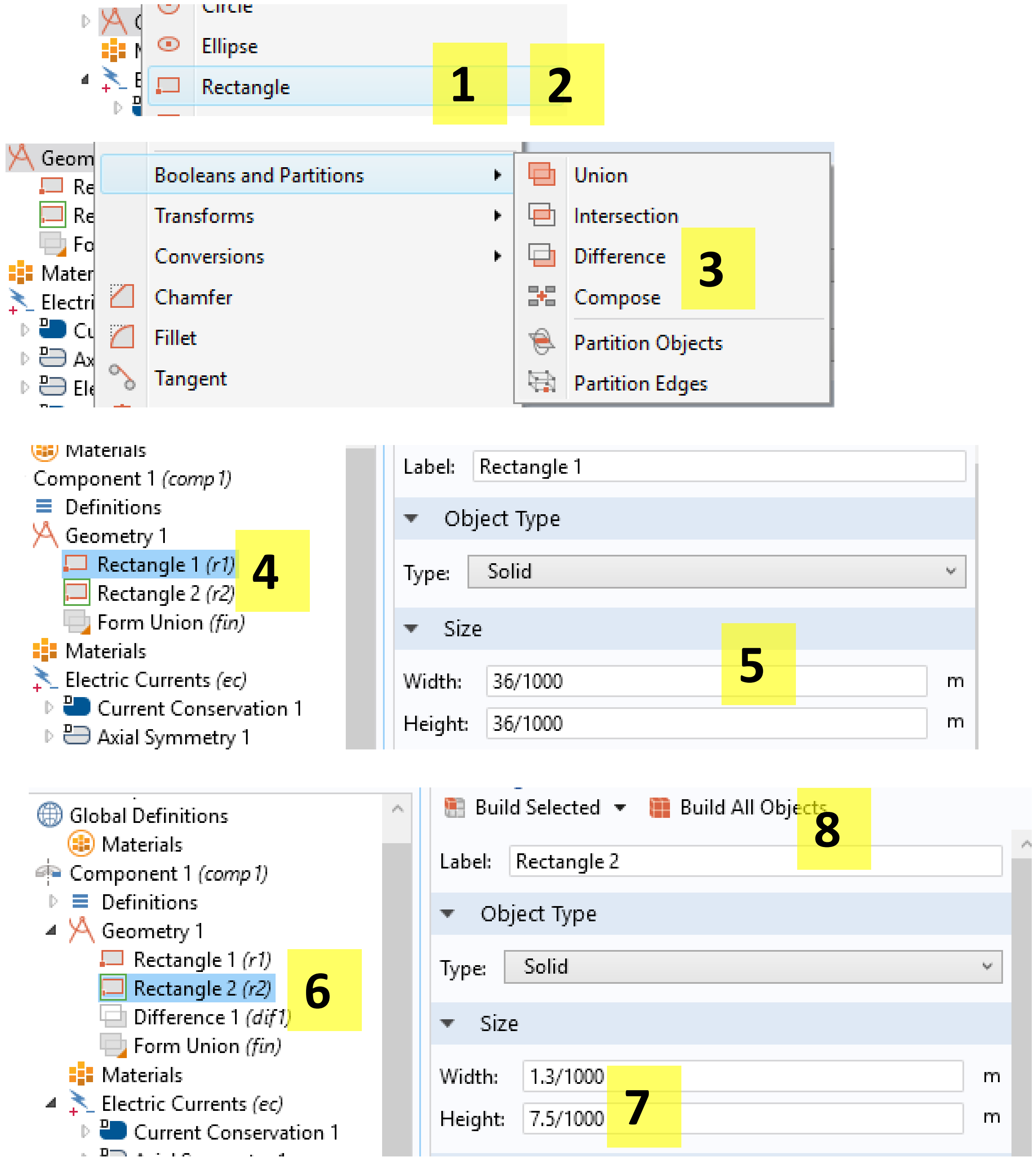
Input parameters Input parameters for the problem are listed in Table 6.7.

Reference

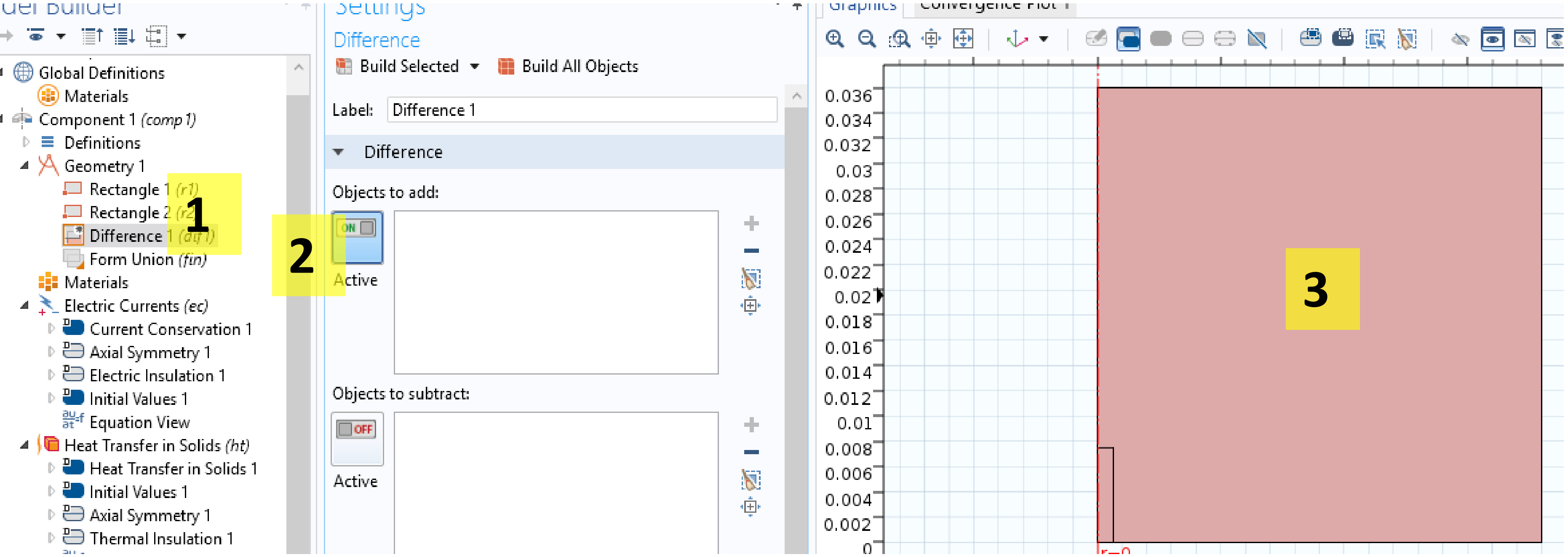
Tungjitkusolmun, S., Woo, E. J., Cao, H., Tsai, J. Z., Vorperian, V. R. and Webster, J. G. (2000). Finite element analyses of uniform current density electrodes for radio-frequency cardiac ablation. *IEEE Transactions on Biomedical Engineering*, **47**, pp. 32–40.



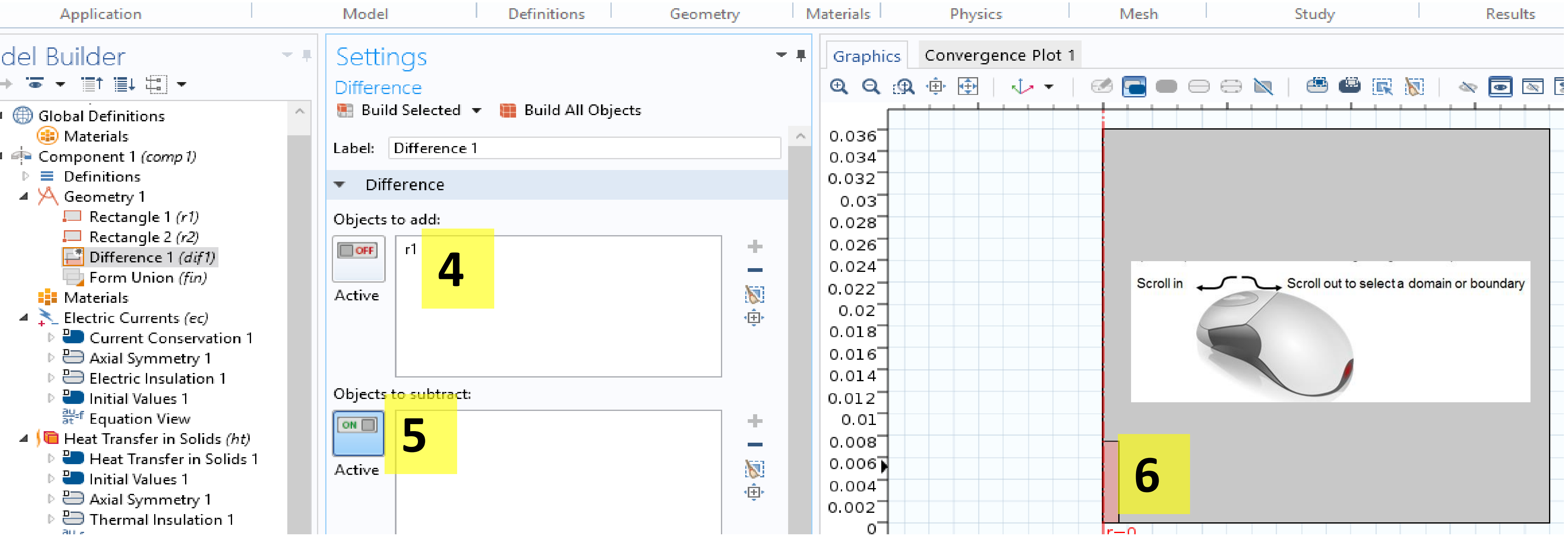
1) Select model wizard
2) Select 2D Axisymmetric
3) Select ‘Joule Heating’ under ‘Electromagnetic heating’
4) Click ‘Add’
5) Click ‘Study’
6) Click ‘Time Dependent’
7) Click ‘Done’

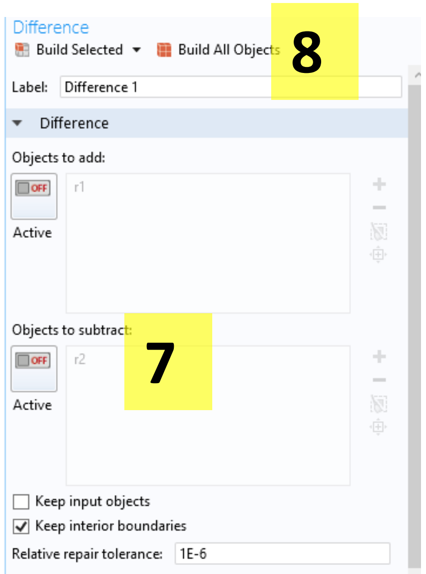


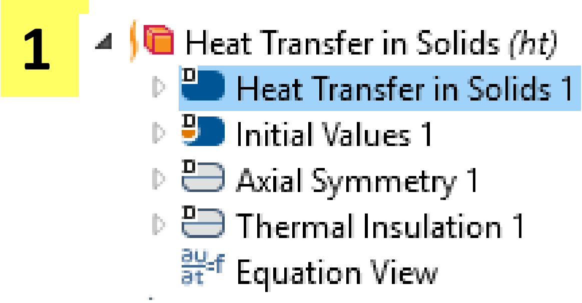
1) Right click geometry, select rectangle
2) Repeat 1
3) Right click geometry and add ‘Difference’
4) Left click rectangle
5) Input dimensions
6) Left click rectangle 2
7) Input dimensions
8) Build all



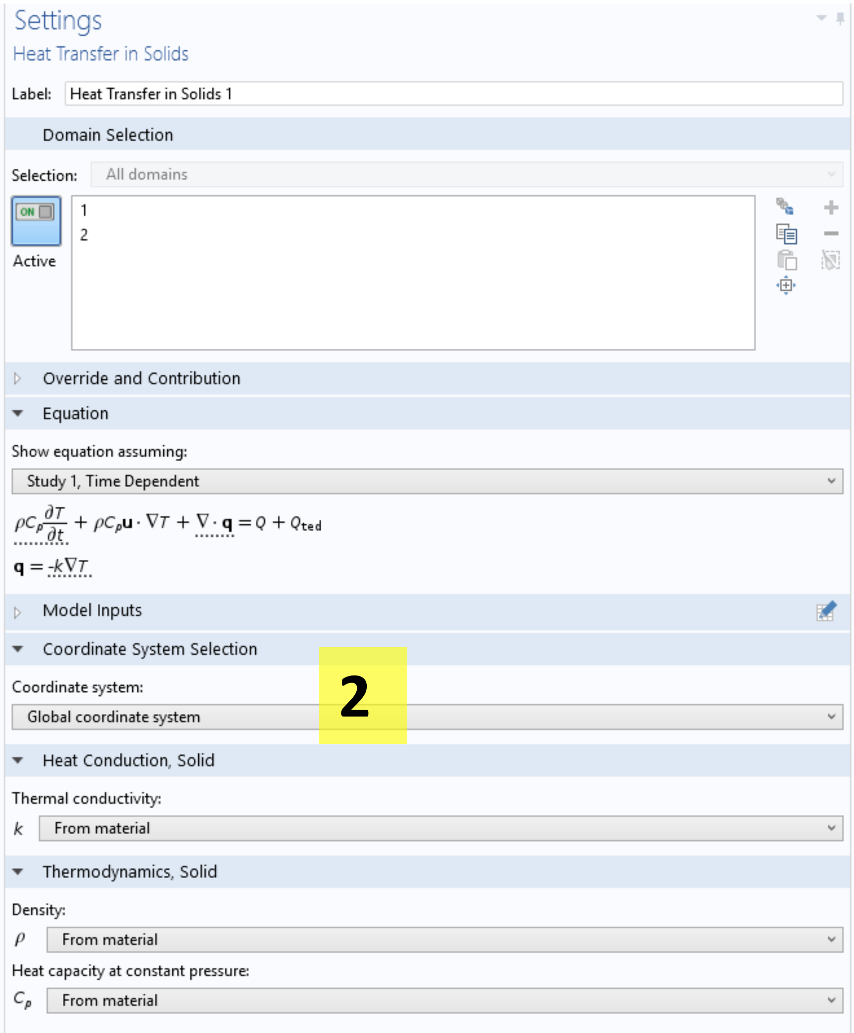
1) Left click difference 1
2) Make 'add' 'on'
3) Hover over the big domain, left click
4) R1 should appear
5) Make 'subtract' 'on'
6) Hover over the electrode domain, scroll with your mouse forward, and only the electrode domain should be red. Left click
7) R2 should appear
8) Build all

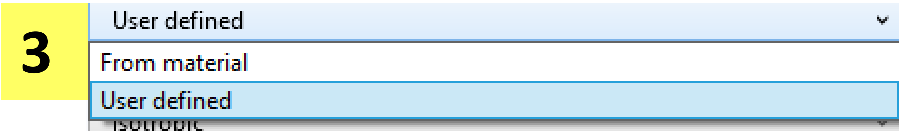


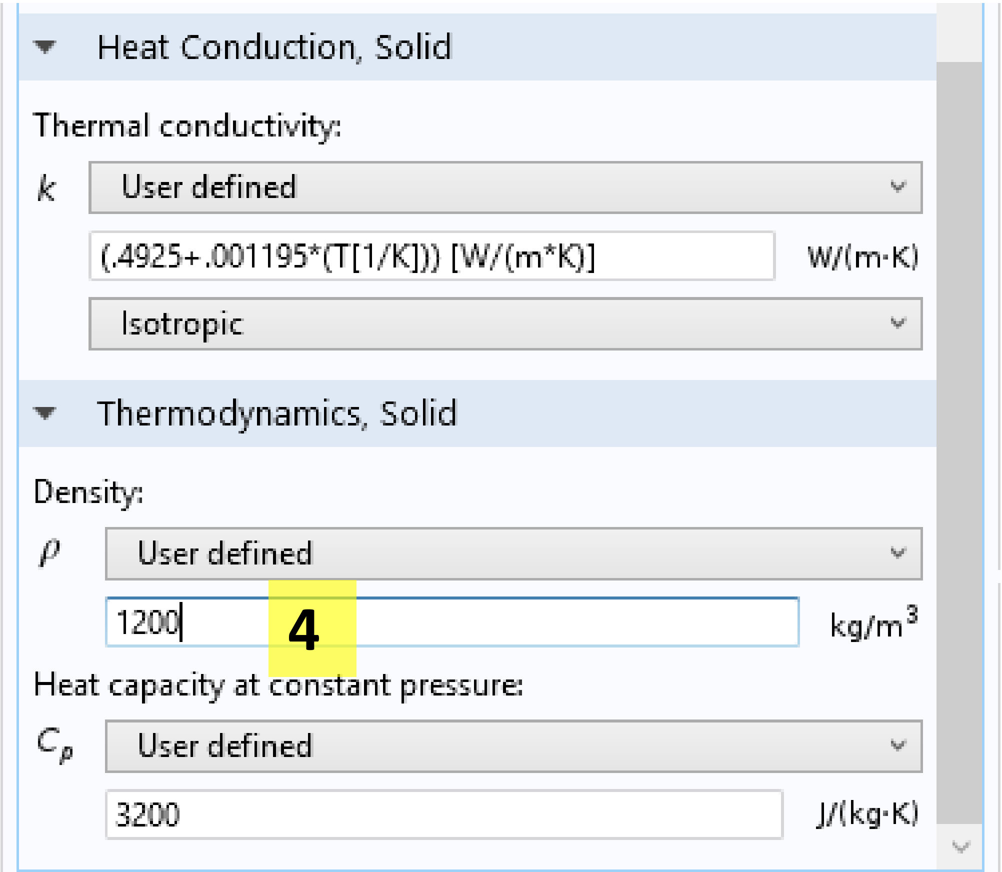


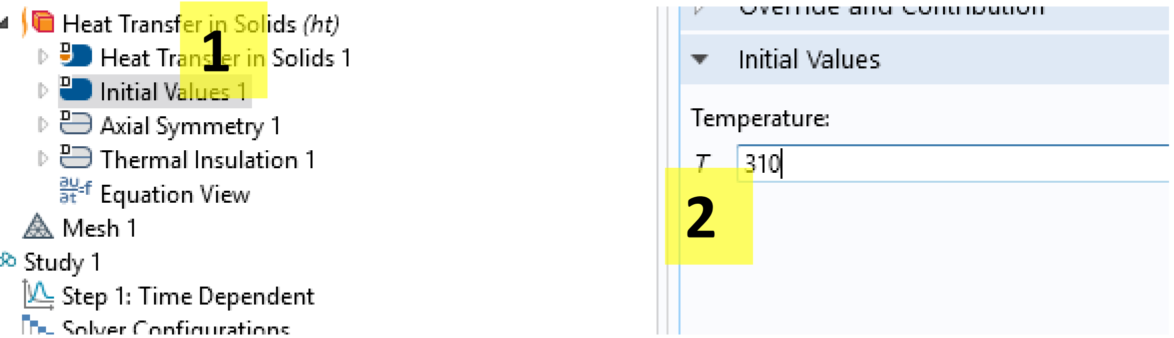


1) Go to ‘Heat transfer in solids’ >> ‘Heat transfer in solids 1’
2) In the middle panel, scroll down to k, ρ, and Cp
3) Select ‘user defined’ for all 3 properties
4) Input heat transfer properties as shown

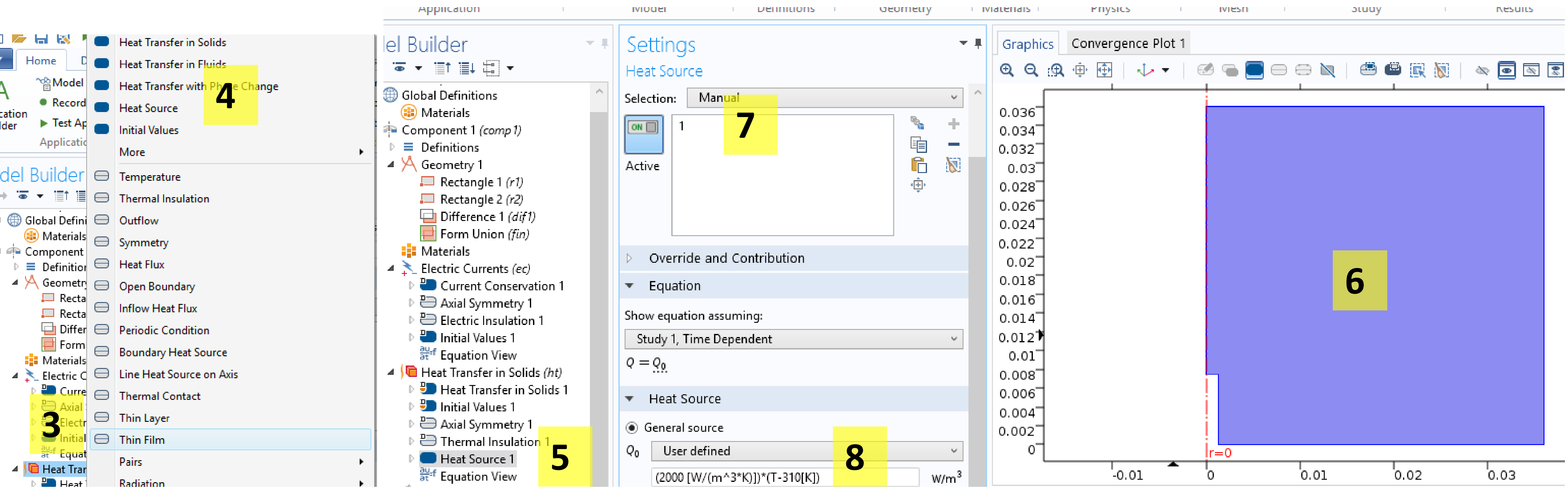


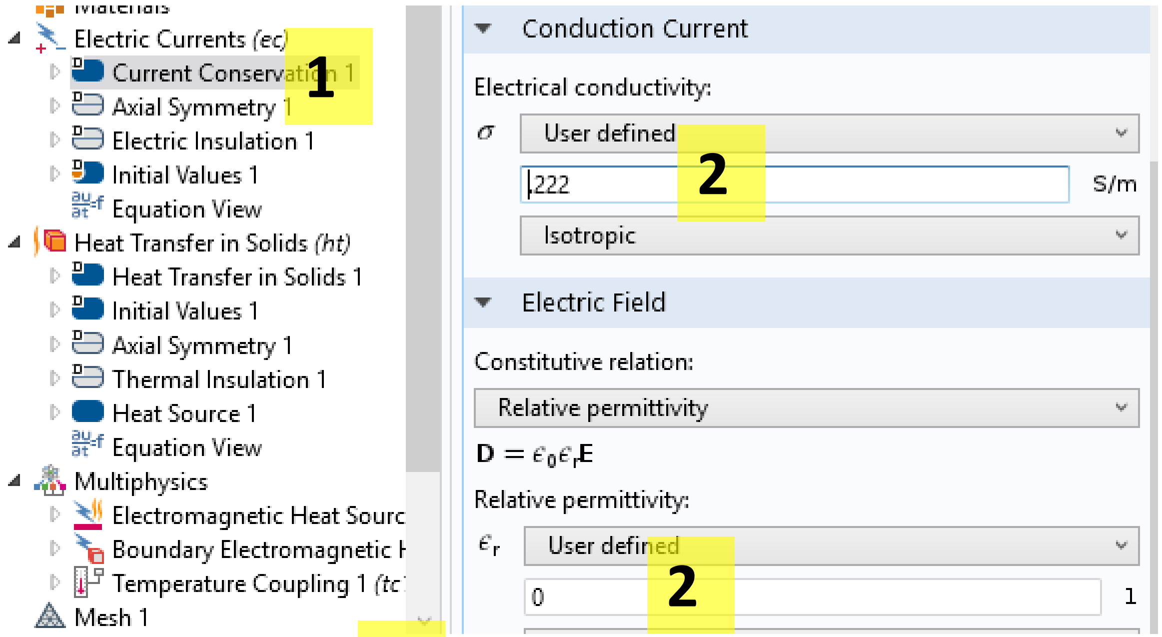




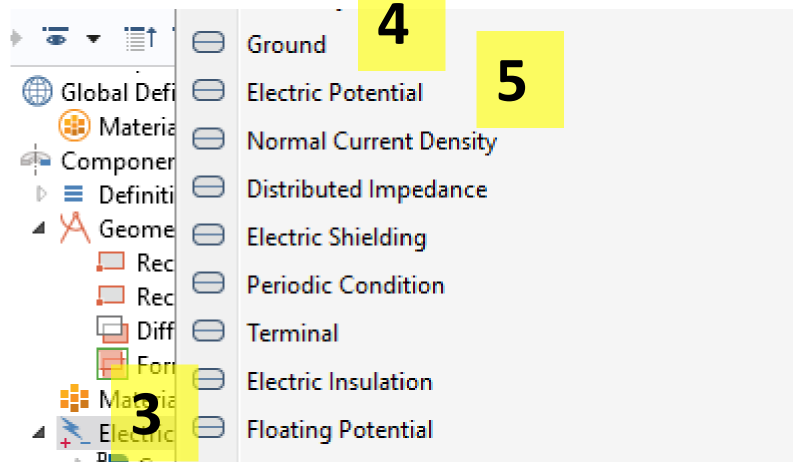


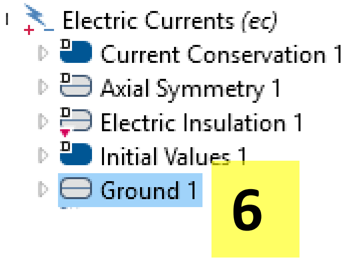
1) Left click 'Initial values 1'
2) Enter 310 K
3) Right click 'Heat transfer in solids'
4) Select heat source'
5) Left click on 'heat source 1'
6) Left click domain
7) 1 should appear
8) Enter heat source value shown

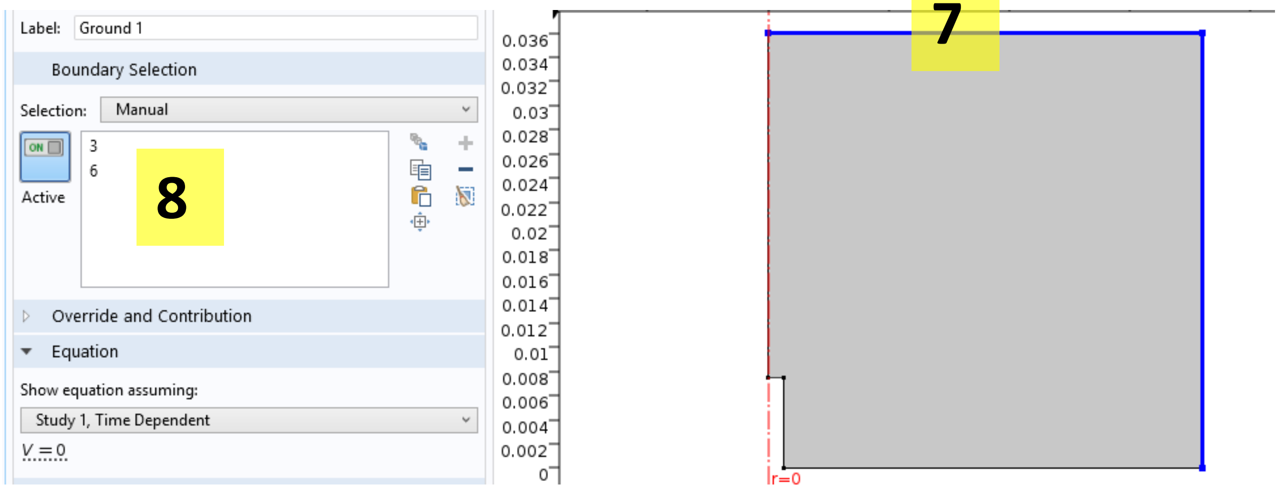




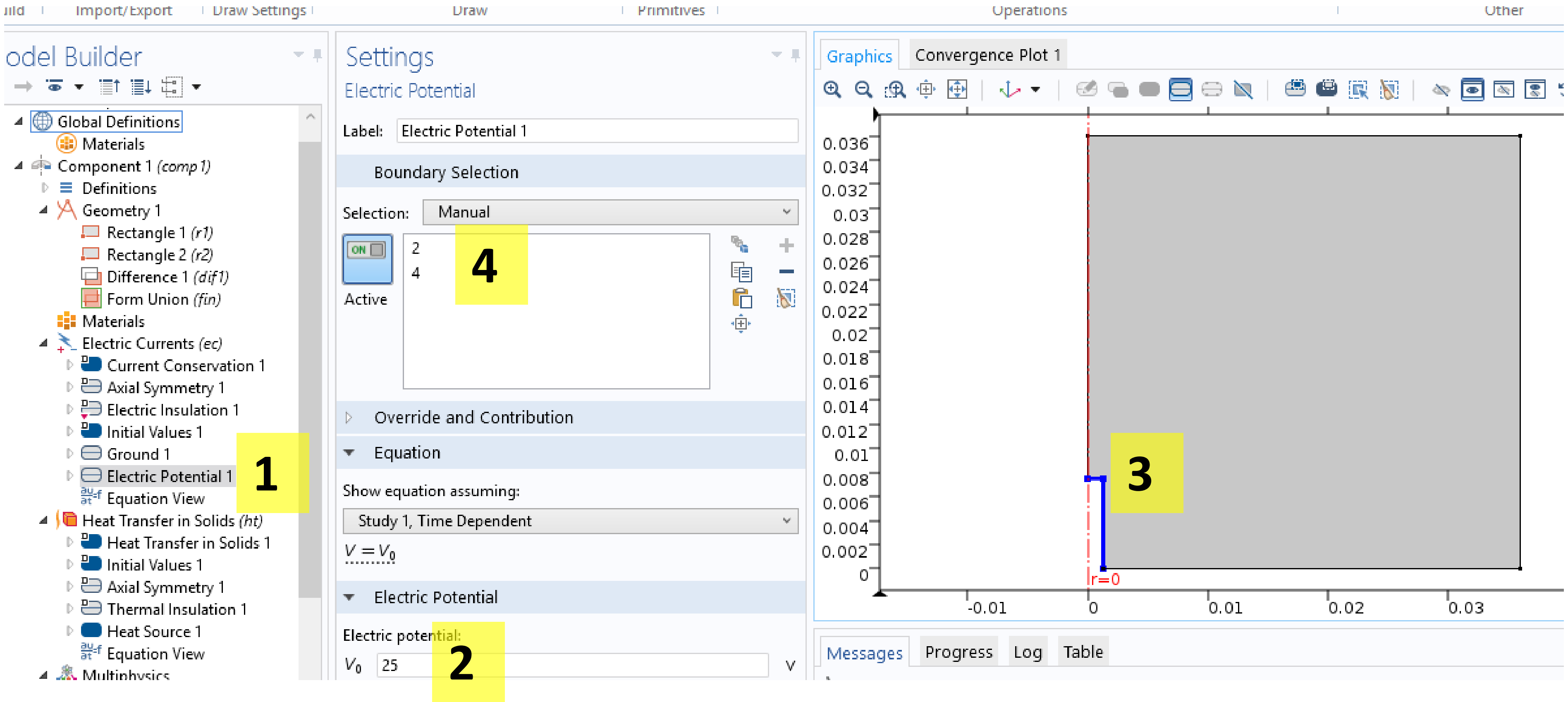
1) Left click Current conservation 1
2) Enter electrical conductivity and relative permittivity
3) Right click 'Electric currents'
4) Select 'Ground'
5) Repeat 3 and select electric potential
6) Left click on 'ground 1'
7) Select 2 boundaries in below
8) 3 and 6 should appear



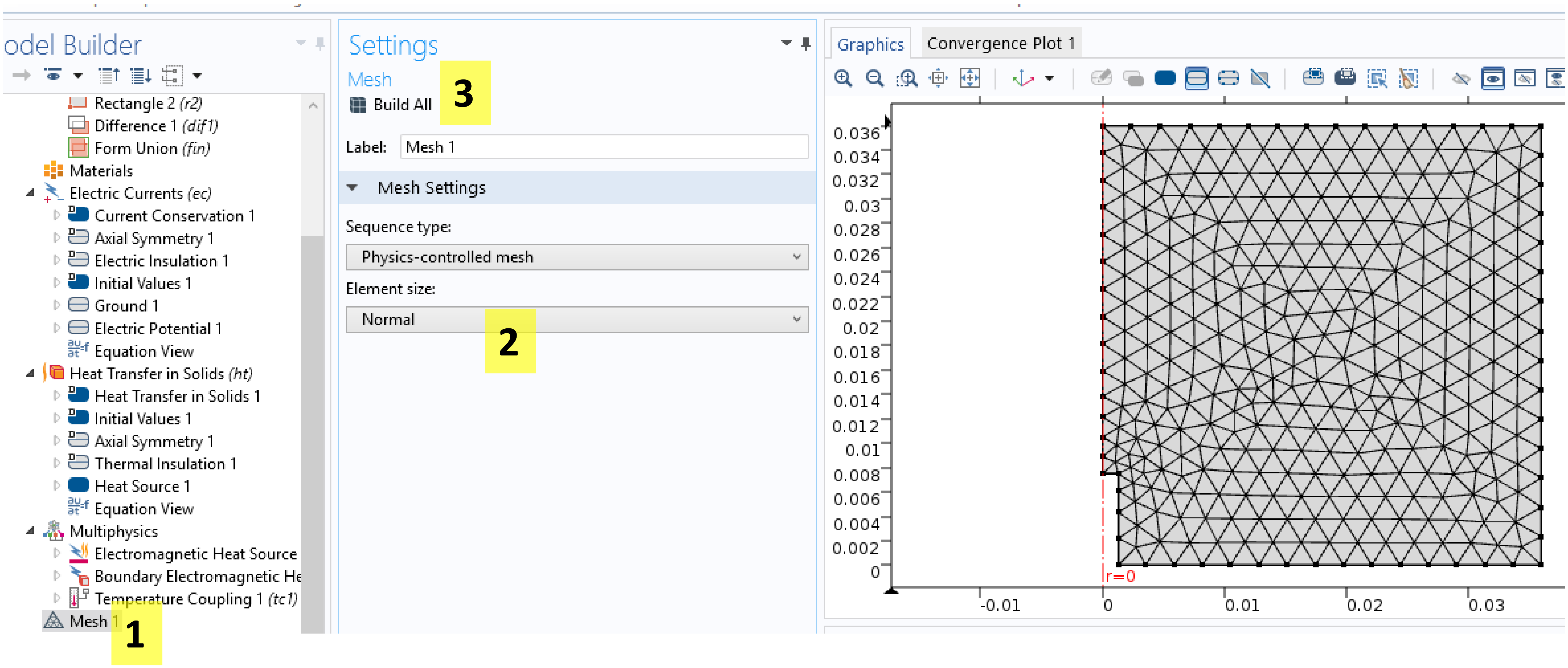


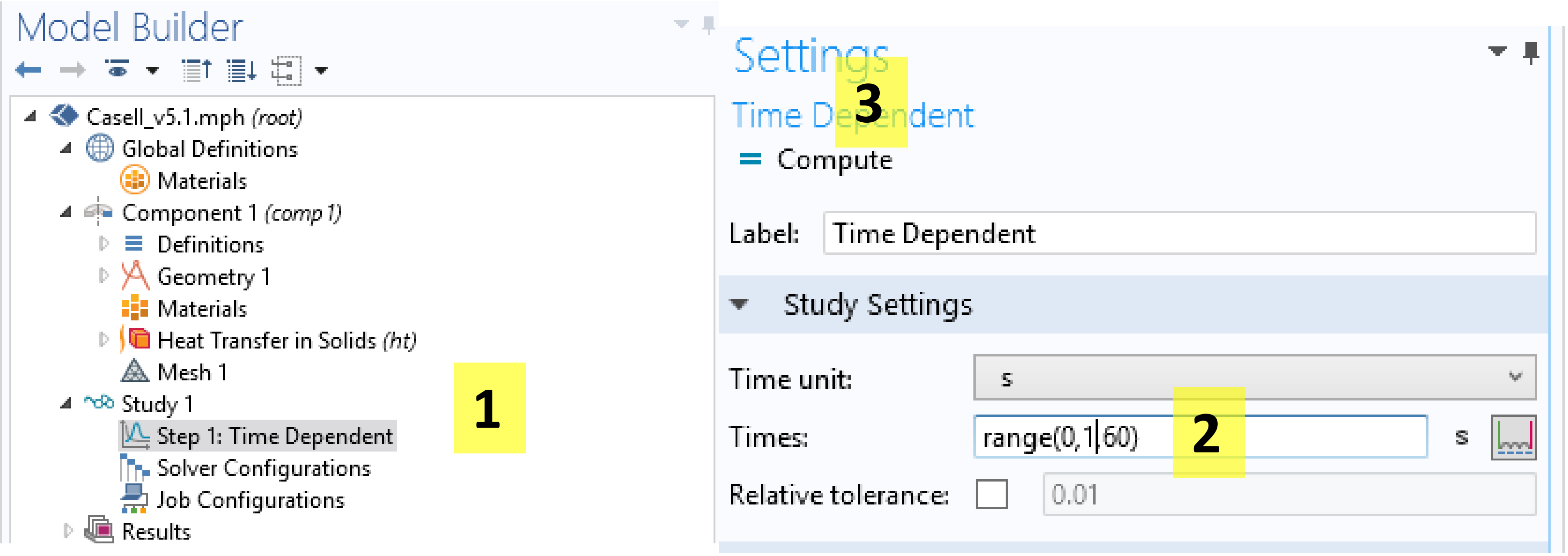


1) Select electric potential 1
2) Enter 25
3) Select 2 boundaries in blue
4) 2 and 4 should appear

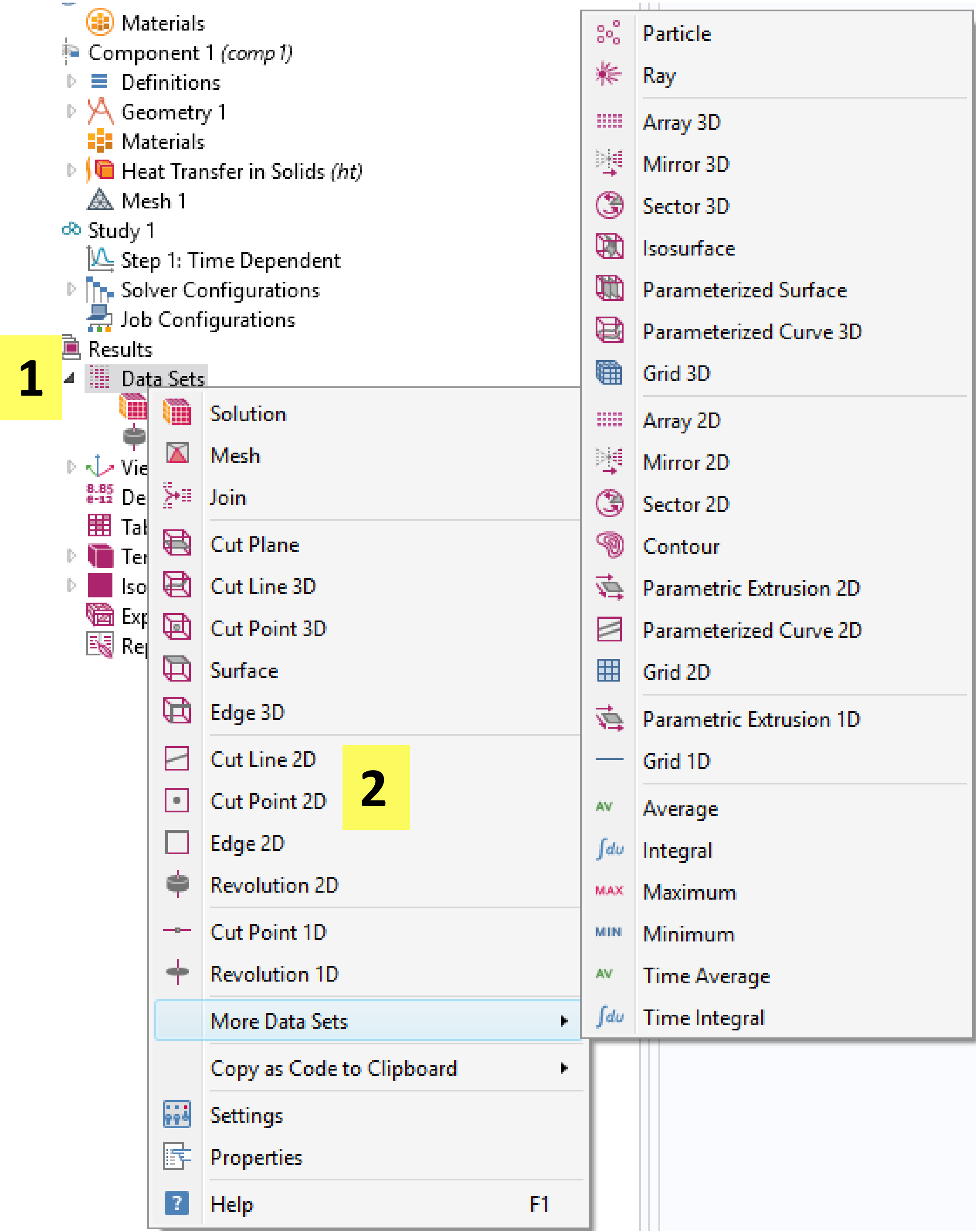


1) Left click mesh 1
2) Select 'normal'
3) Click build all

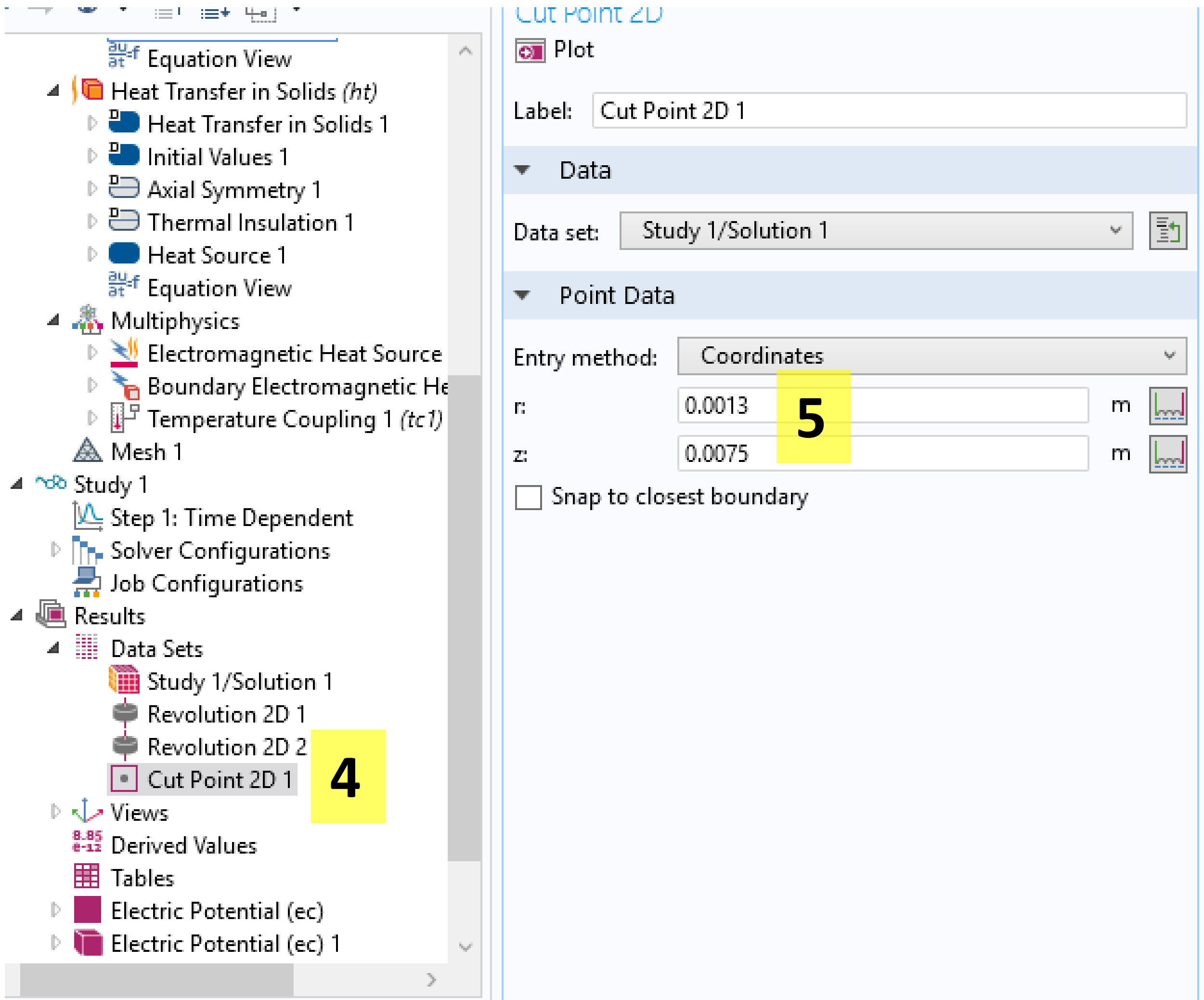


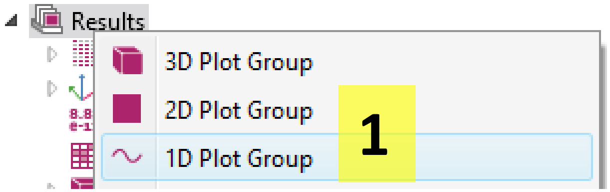


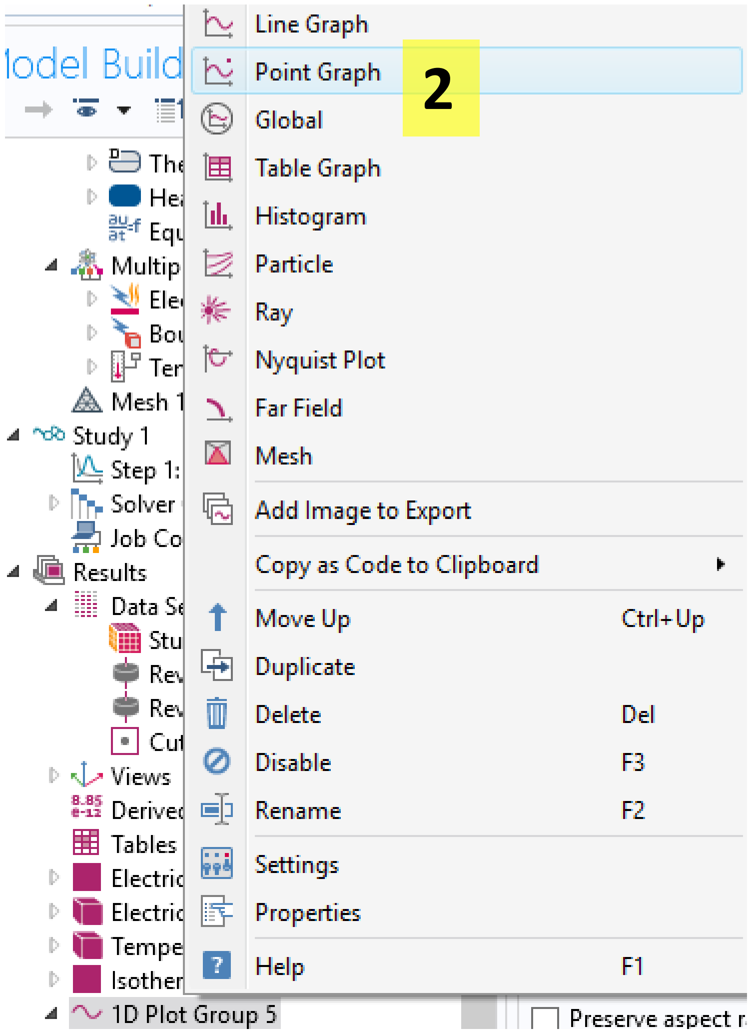
1) Left click “Step 1: Time dependent’
2) Enter range(0,1,60)
3) Click compute

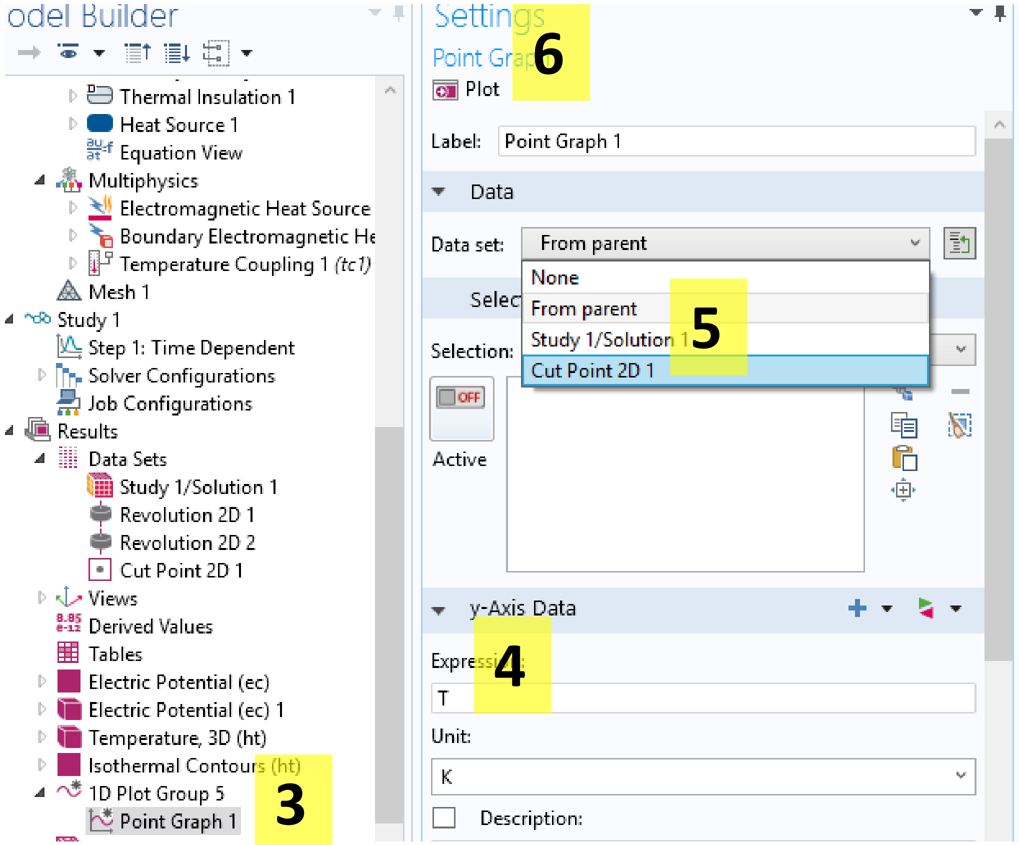


1) Right click data sets
2) Select ‘cut point 2d’
3) Do step 1 again and select ‘Average’
4) Left click ‘cut point 2D 1’
5) Enter r=0.0013 and z = 0.0075

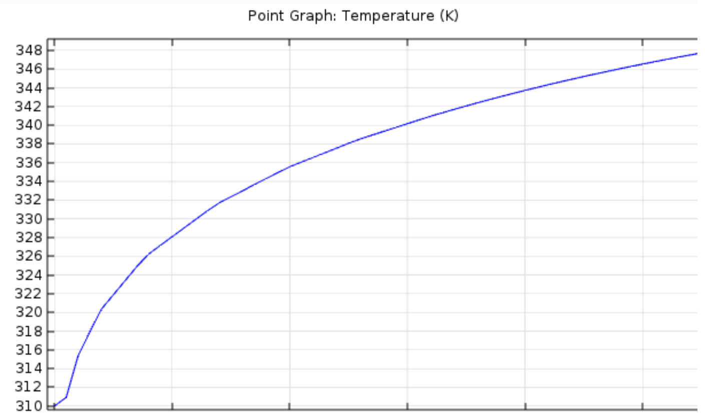




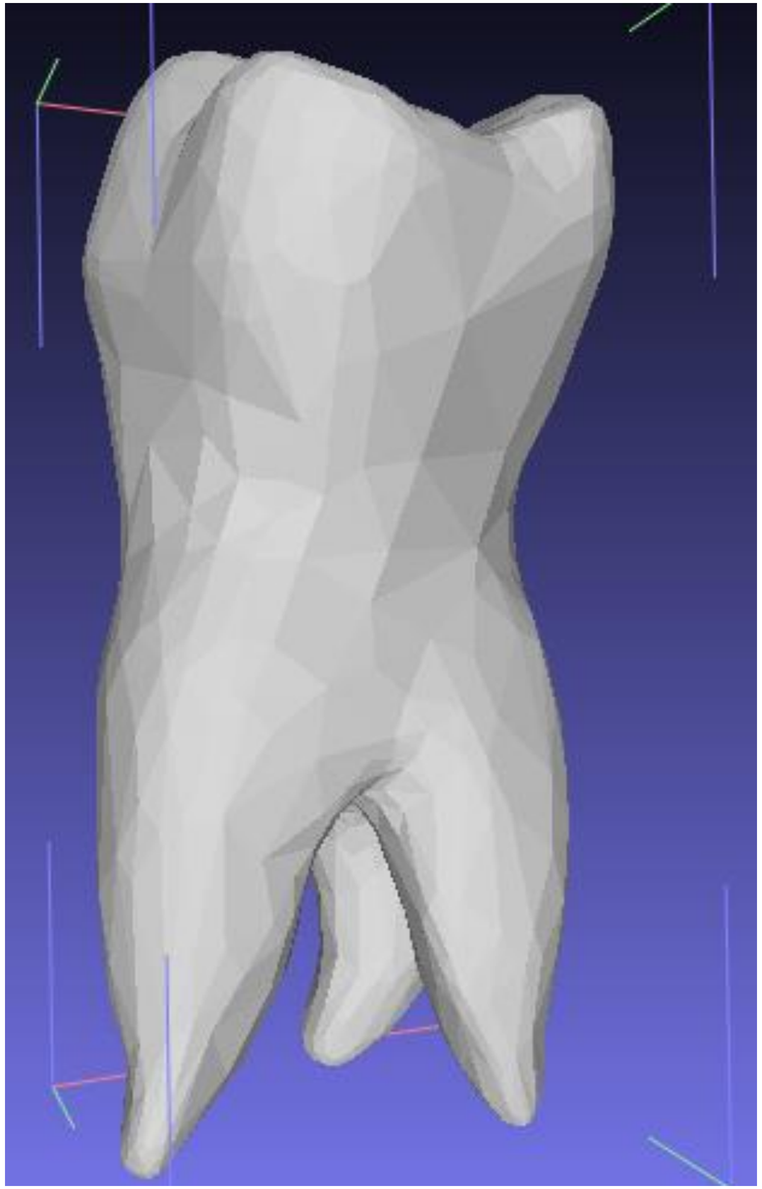




1) Right click ‘results’, Select ‘1D plot group’
2) Right click ‘1D plot group 5’ and add ‘point graph’
3) Left click ‘point graph 1’
4) Enter T
5) Select ‘Cut point 2D 1’
6) Click plot

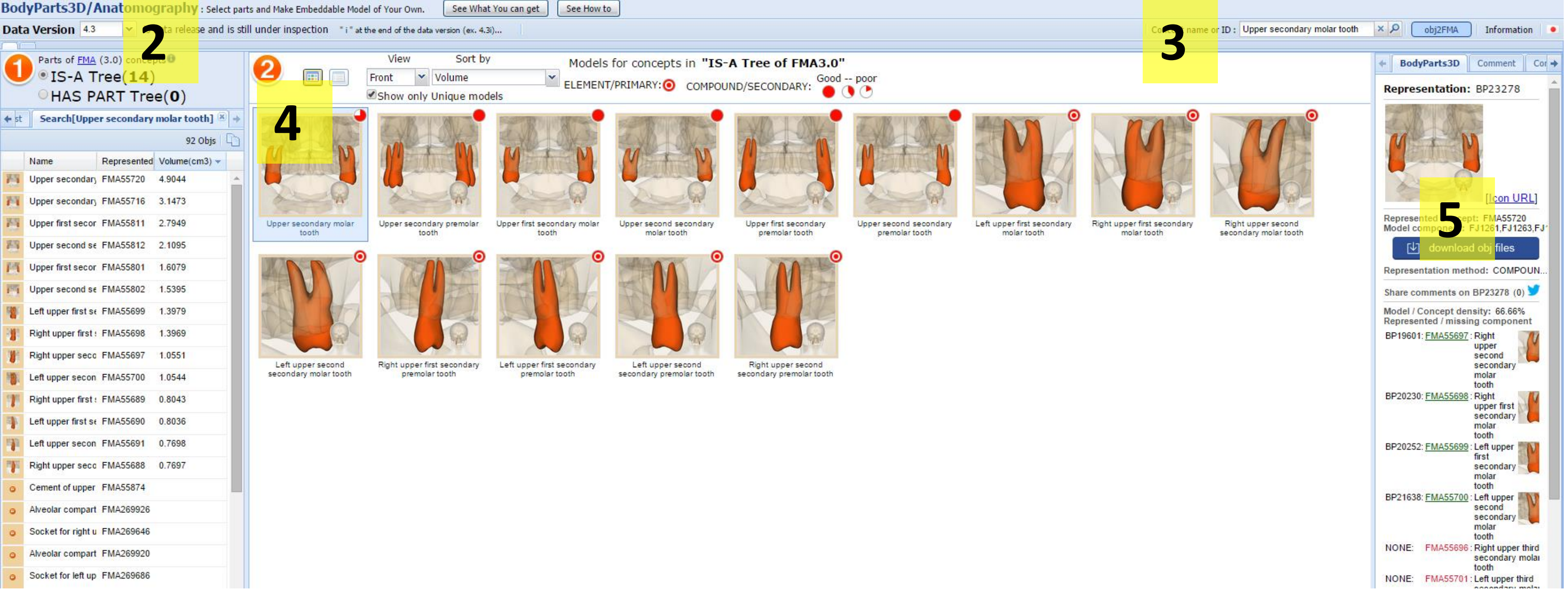


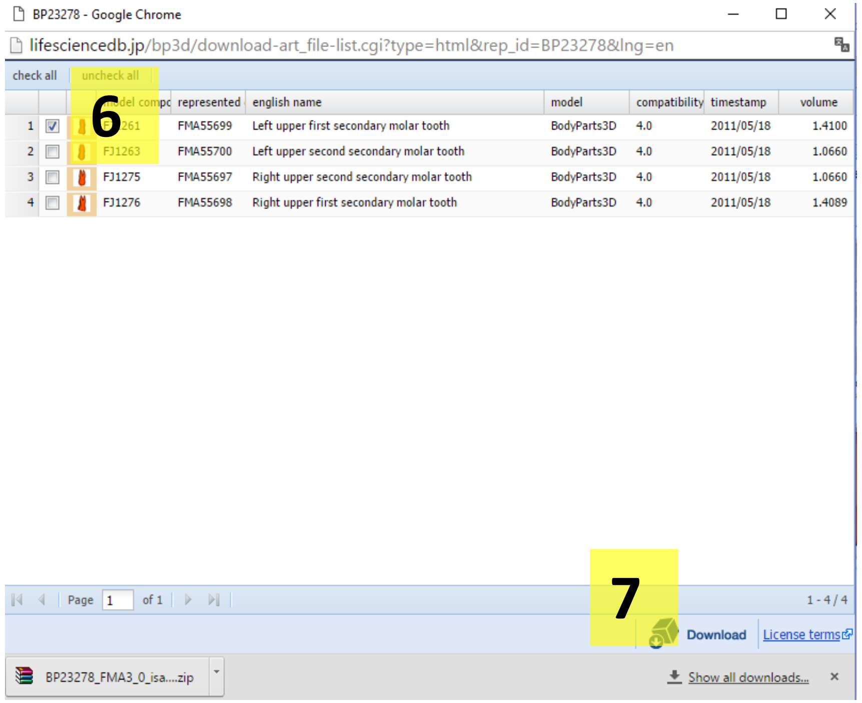
Tooth



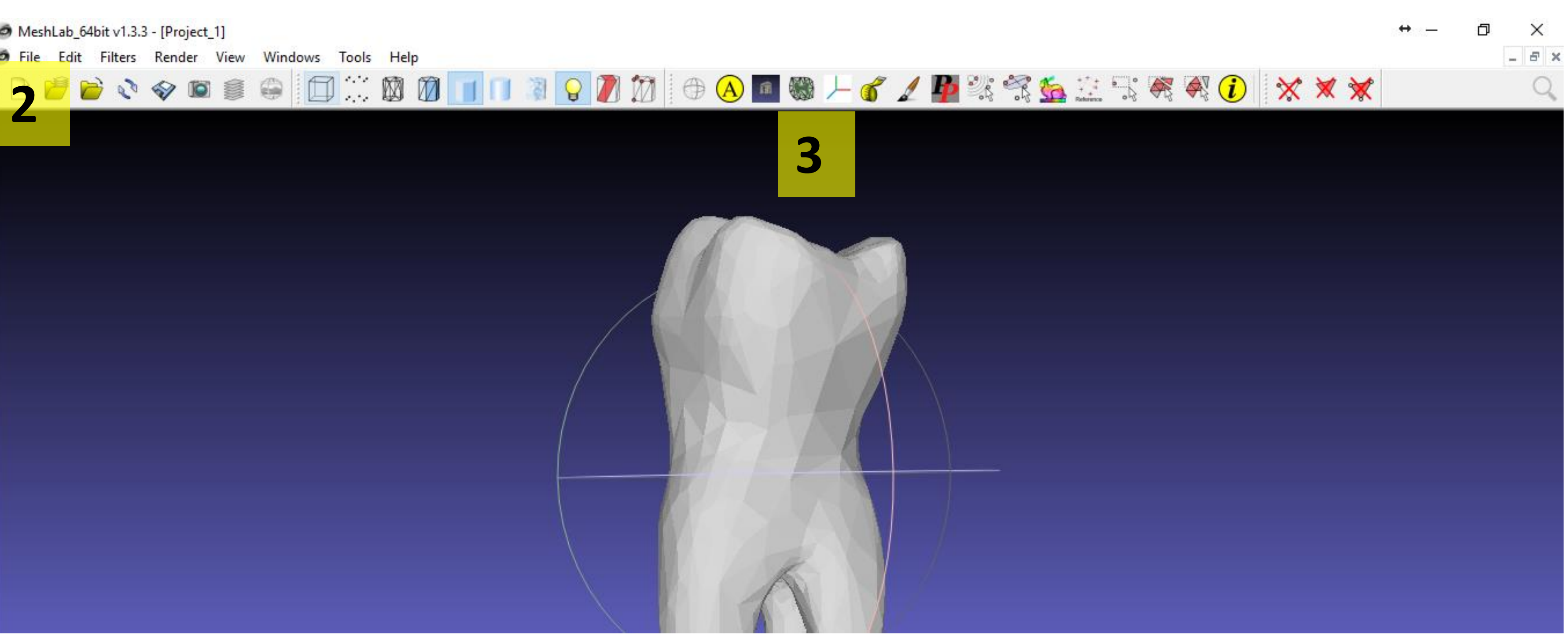
This homework assignment will teach the basics of doing simulations and actual geometries. The example here will be the heating of a tooth. The tooth was acquired from a full body MRI scan in the website listed herein. We will download the data from the scan just for the tooth. Clean the geometry by smoothing it, filling gaps in the surface, and decreasing the number of faces. Then, we will convert it to a solid object to simulate in COMSOL. Finally, we will solve a heat conduction problem.

The one major step we are not covering here is the geometry segregation step. This step involves taking raw MRI images and extracting the tooth geometry using imaging algorithms. Fortunately, the website here has done that step for us. We will focus on cleaning up the geometry such that it is capable of having a simulation run on it.

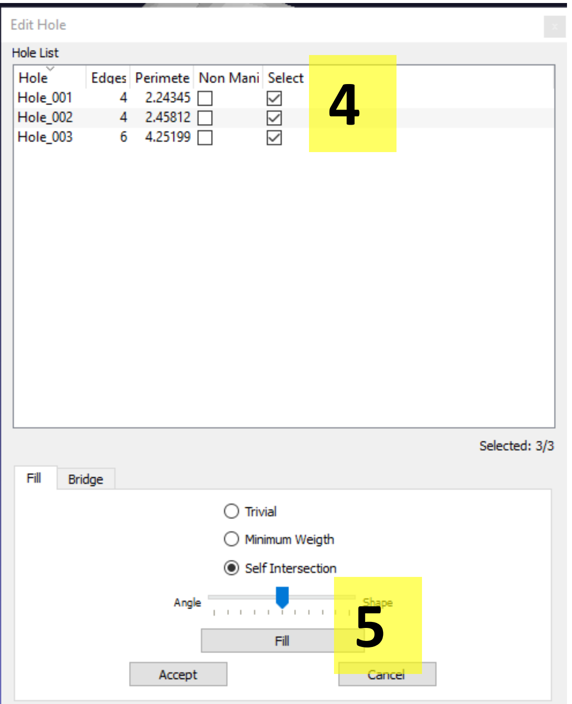


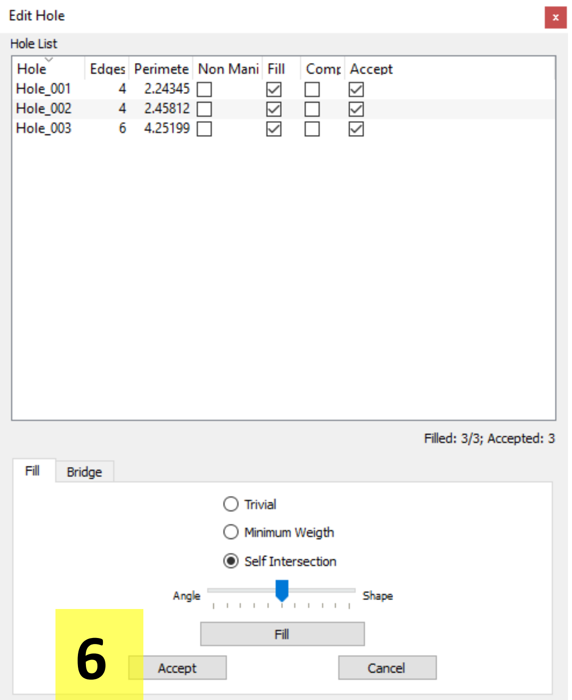


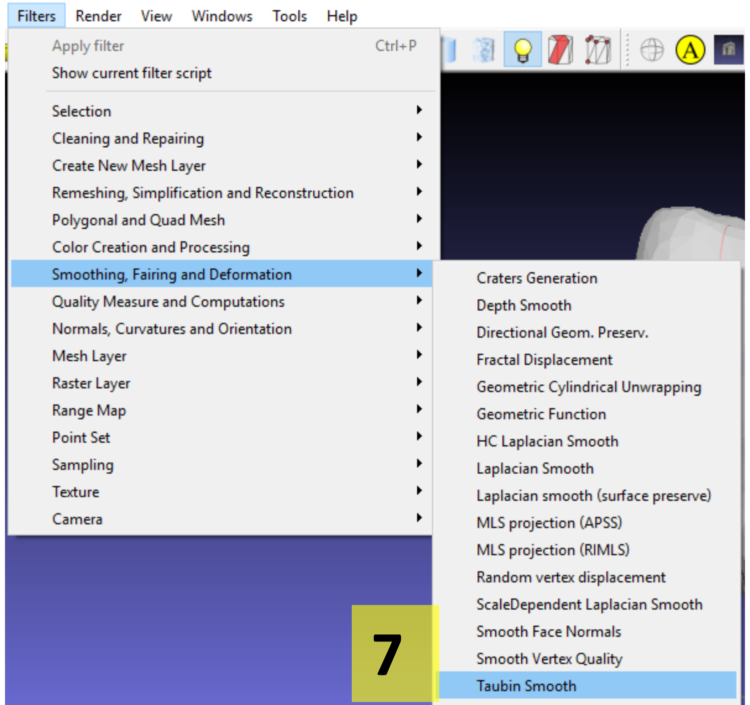
1) Go to: http://lifesciencedb.jp/bp3d/?lng=en
2) Select 4.3
3) Search for ‘Upper secondary molar tooth’
4) Click ‘Upper secondary molar tooth’
5) Click ‘download obj’
6) Select the first one ‘FJ1261’
7) Click download

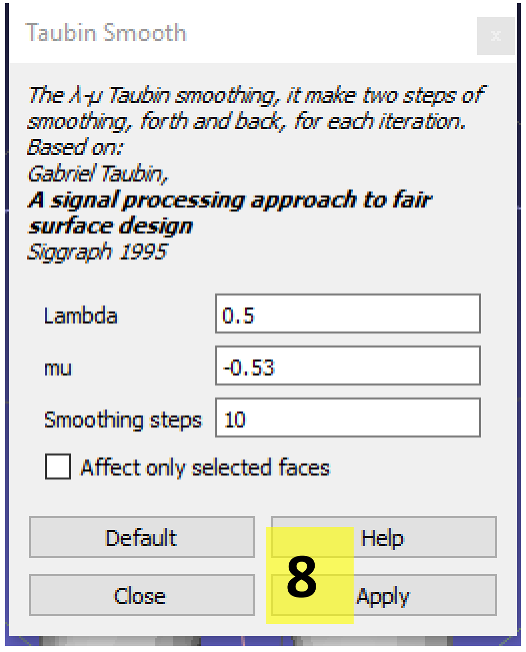


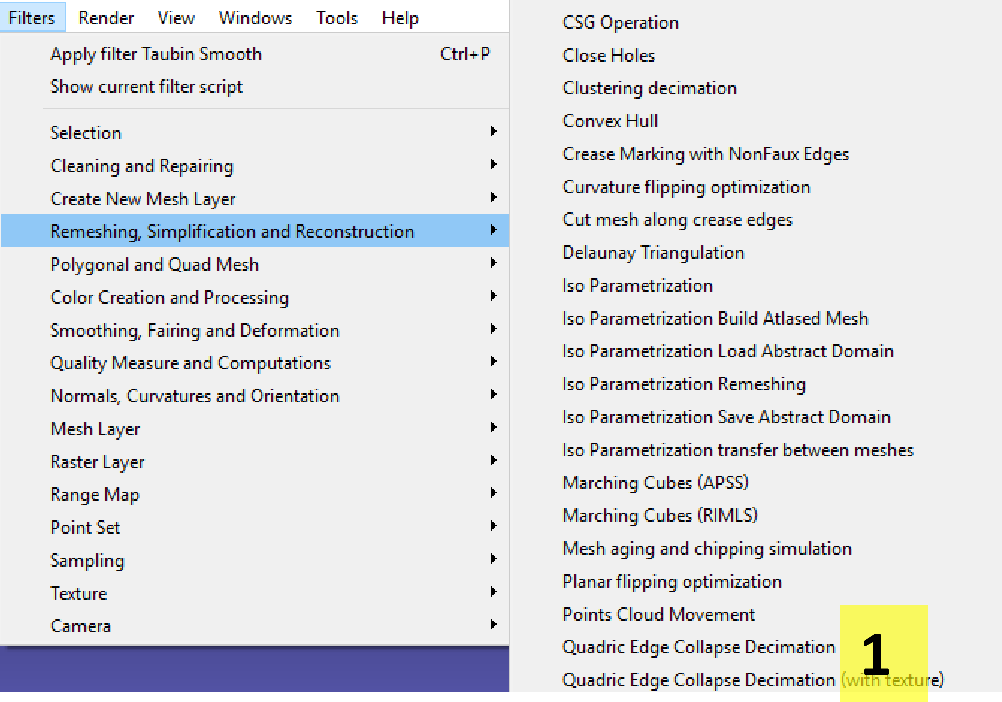
1) Open Meshlab or download from: http://meshlab.sourceforge.net/
2) In Meshlab, File>>import Mesh and select the obj file you downloaded
3) Click the 'fill hole' icon (you can hover over with the cursor to make sure which one it is)
4) Select all
5) Click 'Fill'
6) Click accept
7) Go to filters>>Smoothing, Fairing, and deformation>>Taubin smooth
8) Click apply
9) **<u>Repeat 3-6 again</u>**

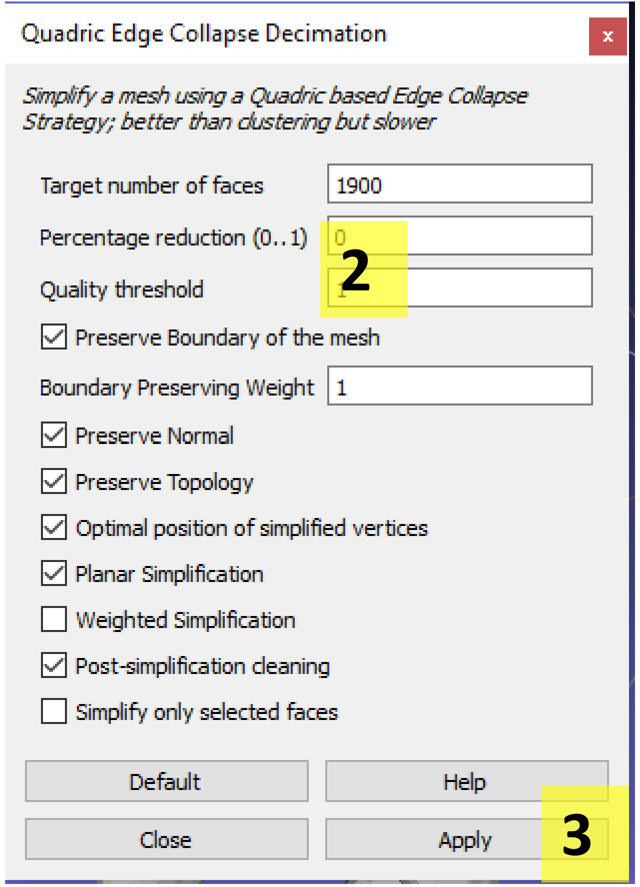


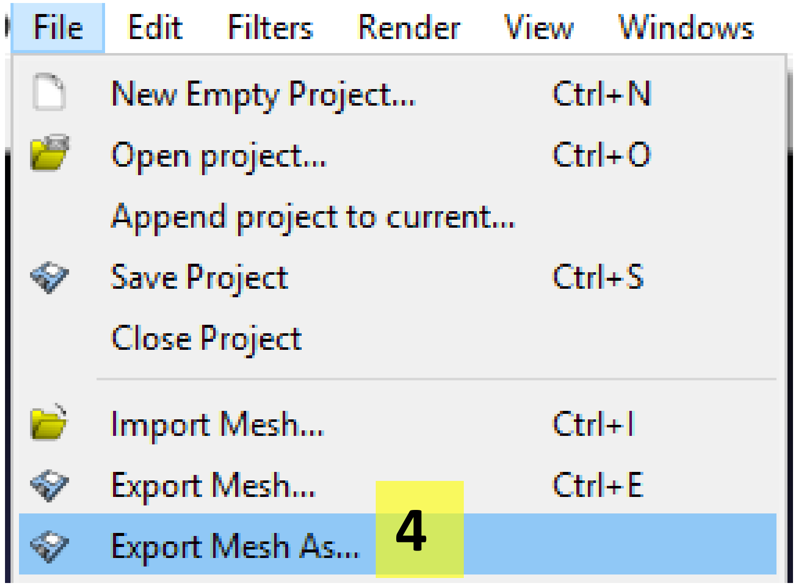




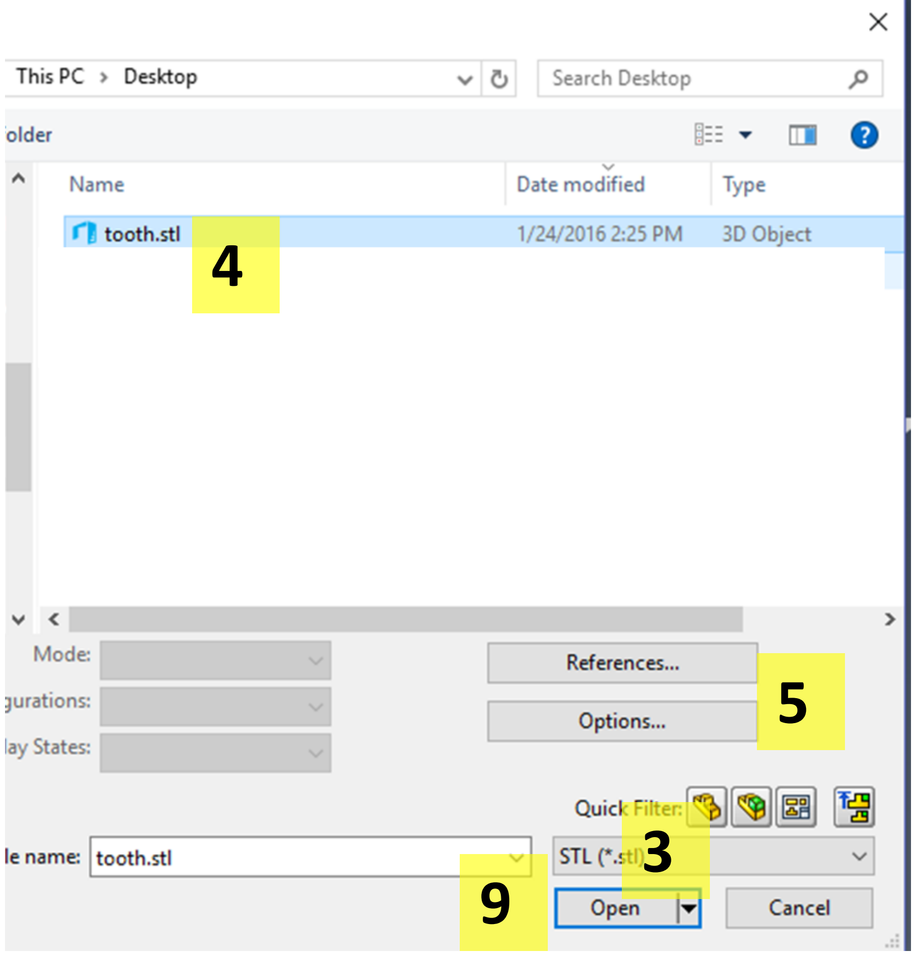


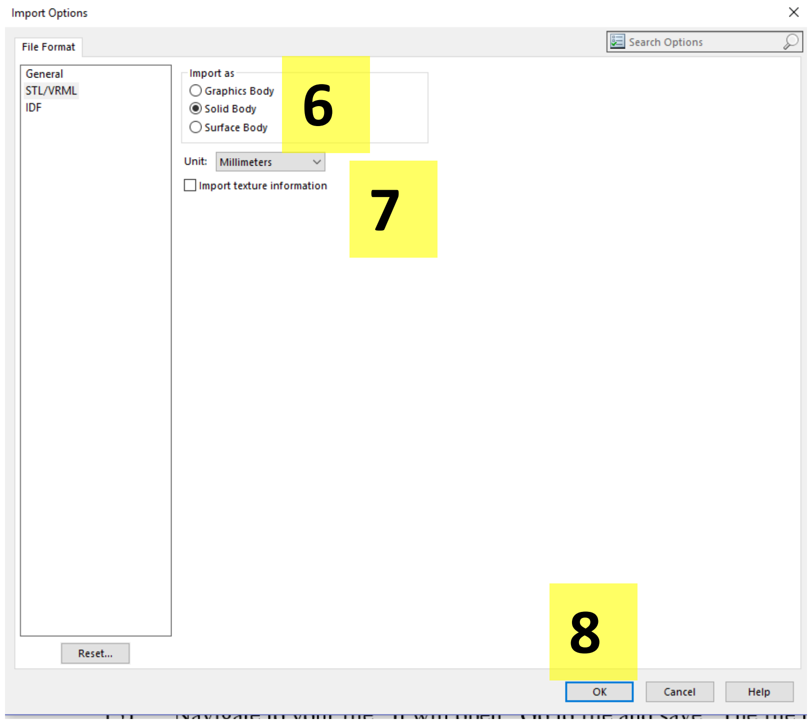


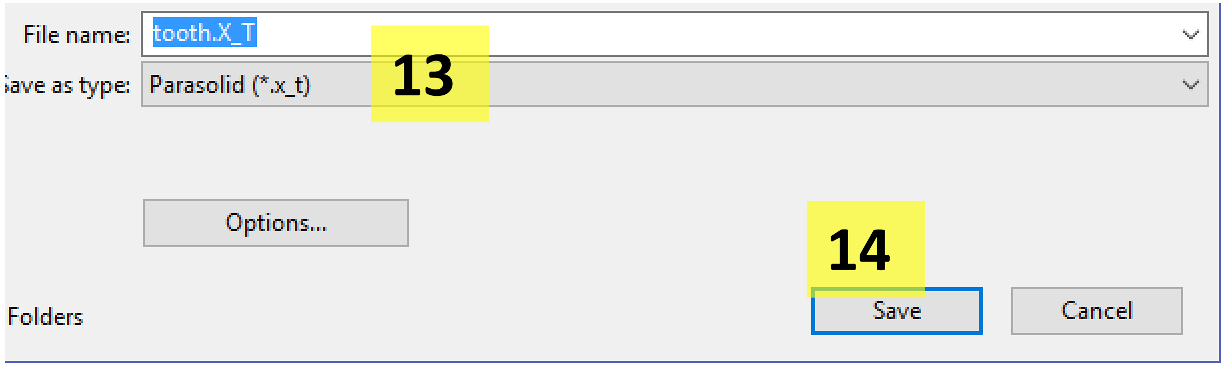




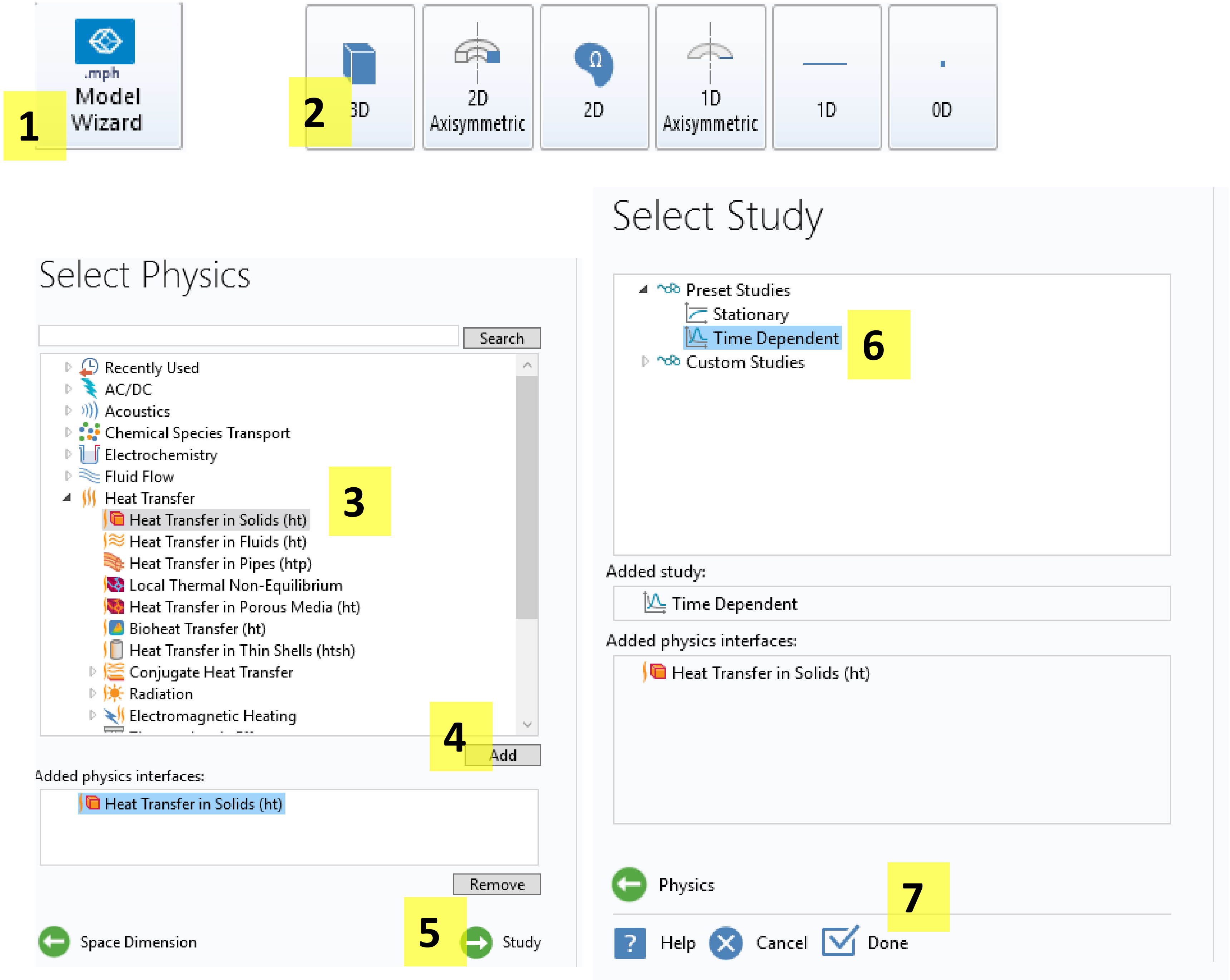
1) Go to filters>>Remeshing, simplifications, and reconstruction>>Quadratic edge collapse decimation
2) Enter the settings shown
3) Click apply
4) Go to file>>export mesh as…
5) **<u>Save the file as *.stl format and click ok to whatever boxes appear.</u>**



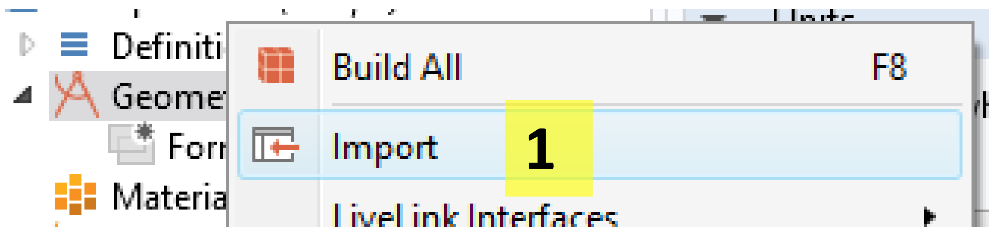


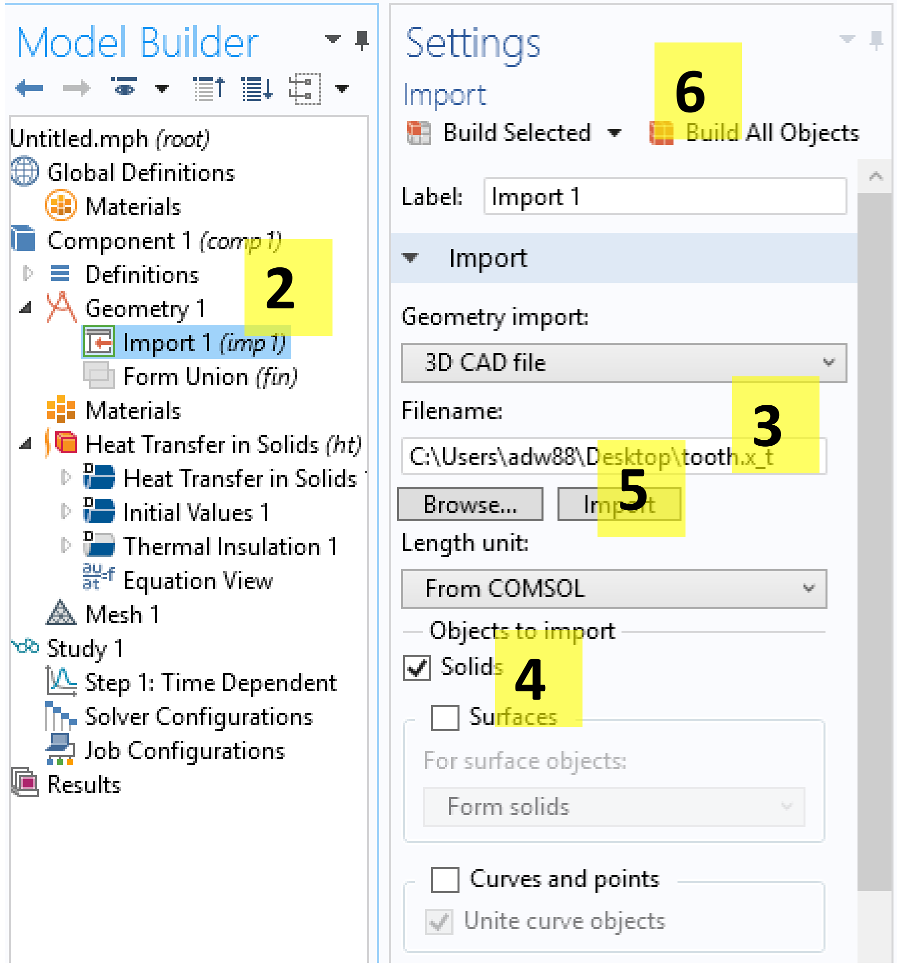


1) Open solidworks
2) Click the ‘open’ folder in the top left
3) Choose *.stl file
4) Click your file
5) Select ‘options’
6) Select solid body
7) Select millimeters
8) Click ok
9) Click open
10) Click ok to a message box about units
11) You do not need to run the diagnostics
12) Click save icon in top left
13) Save as a parasolid *.x_t
14) Click save



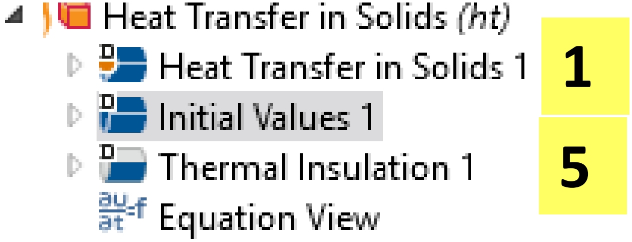
1) Select model wizard
2) Select 2D Axisymmetric
3) Select 'Heat transfer in solids'
4) Click 'Add'
5) Click 'Study'
6) Click 'Time Dependent'
7) Click 'Done'

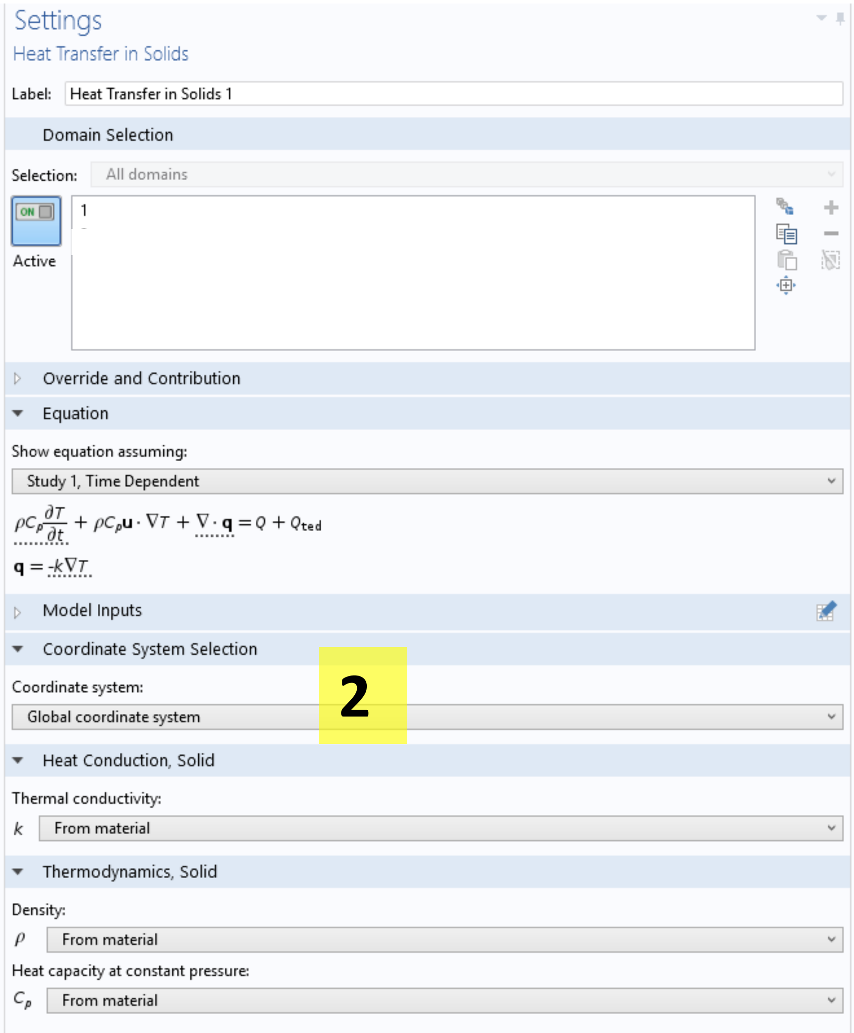


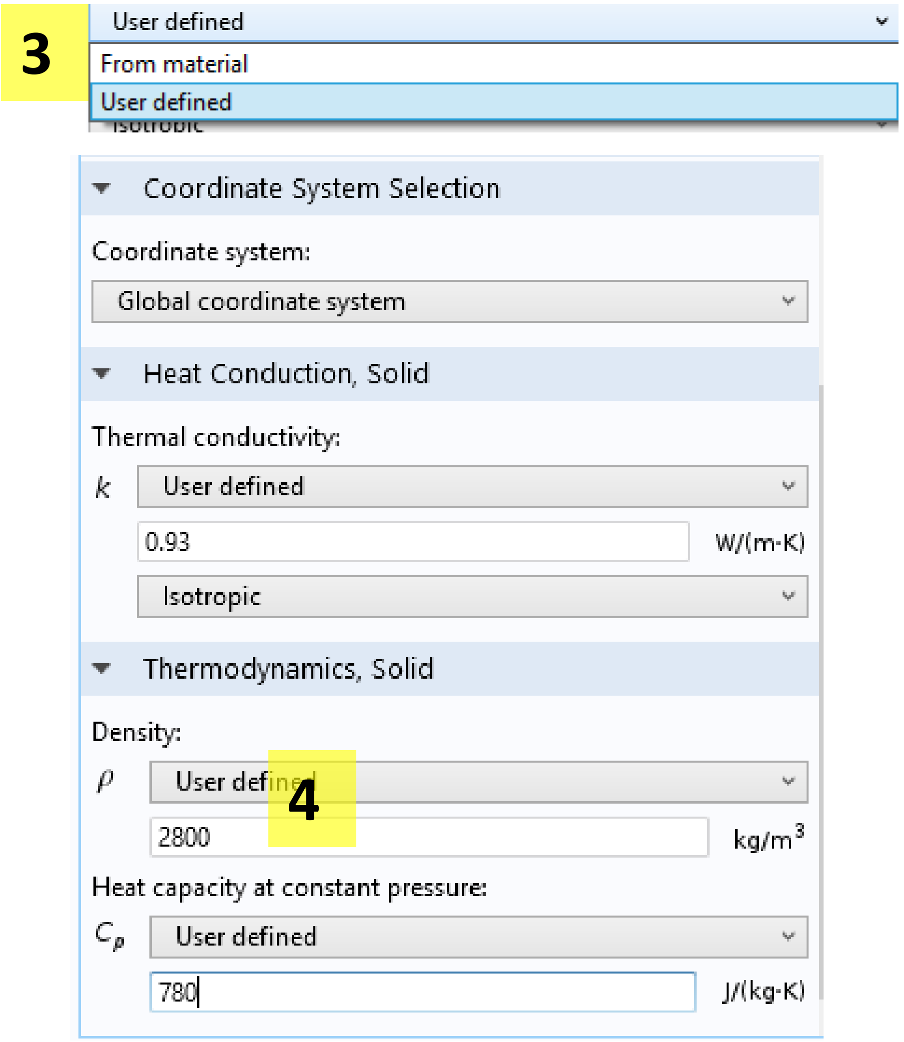


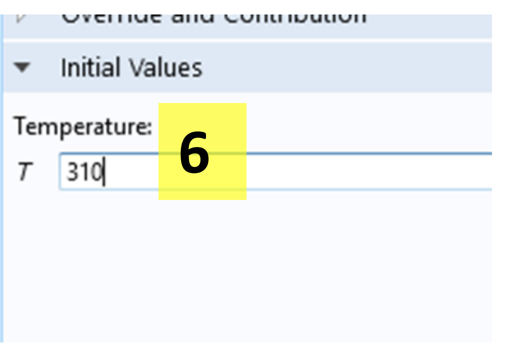
1) Right click geometry, select import
2) Left click import 1
3) Select your .x_t file
4) Only select solids
5) Click import
6) Build all

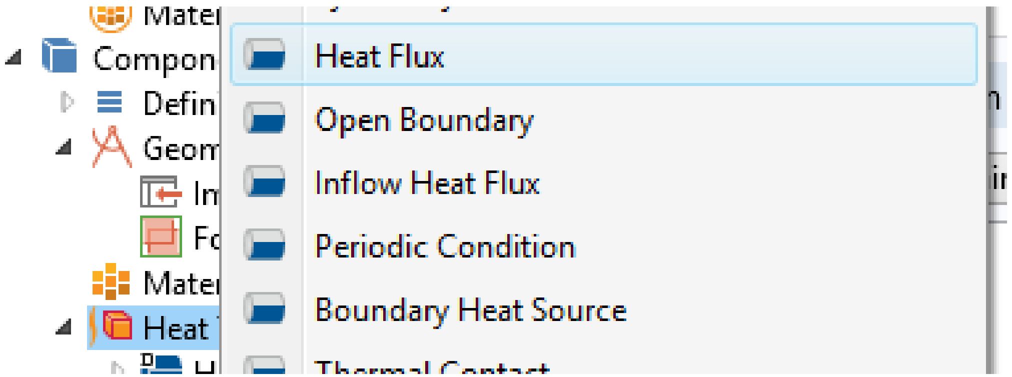
1) Go to ‘Heat transfer in solids’ >> ‘Heat transfer in solids 1’
2) In the middle panel, scroll down to k, ρ, and Cp
3) Select ‘user defined’ for all 3 properties
4) Input heat transfer properties as shown
5) Click initial values 1
6) Enter 310 K



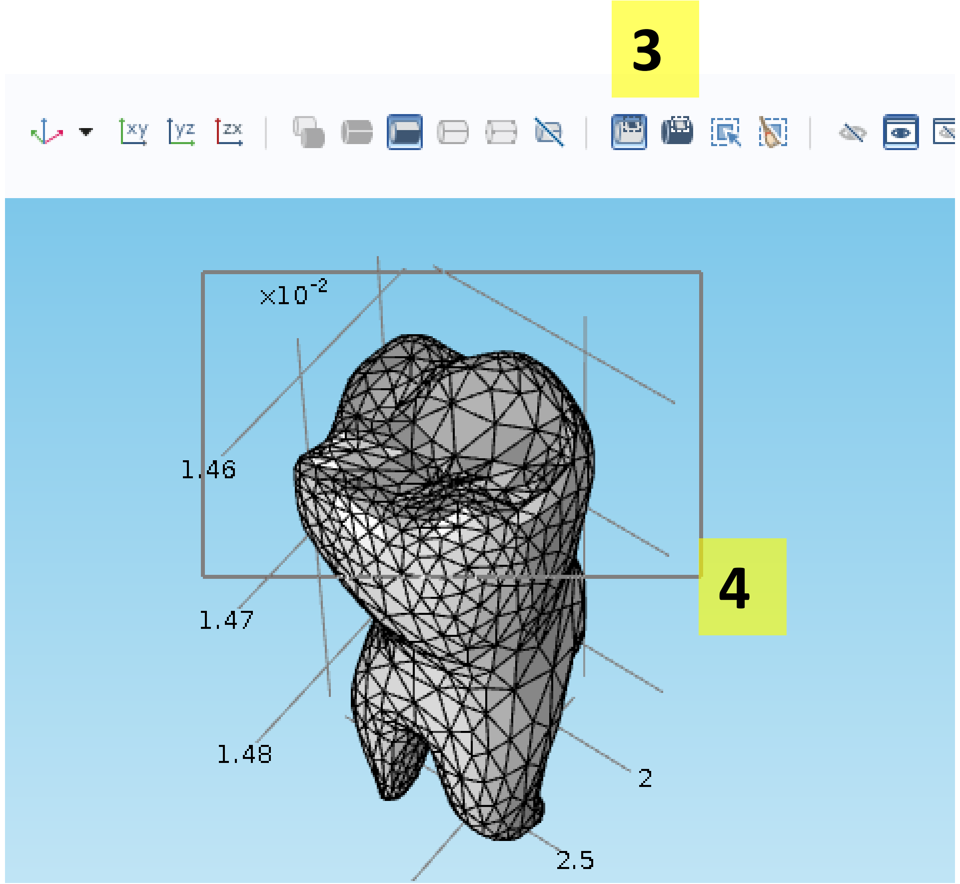


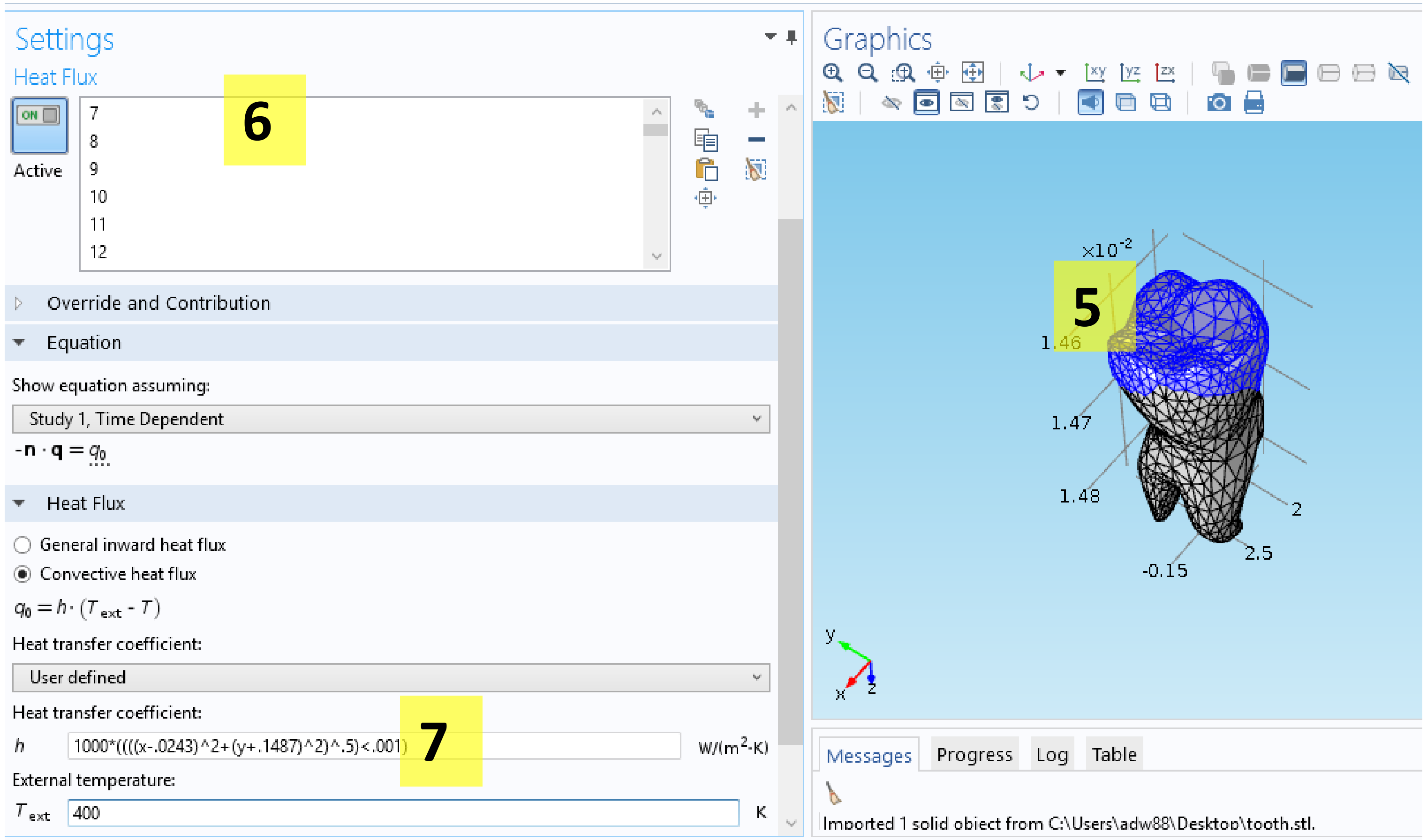




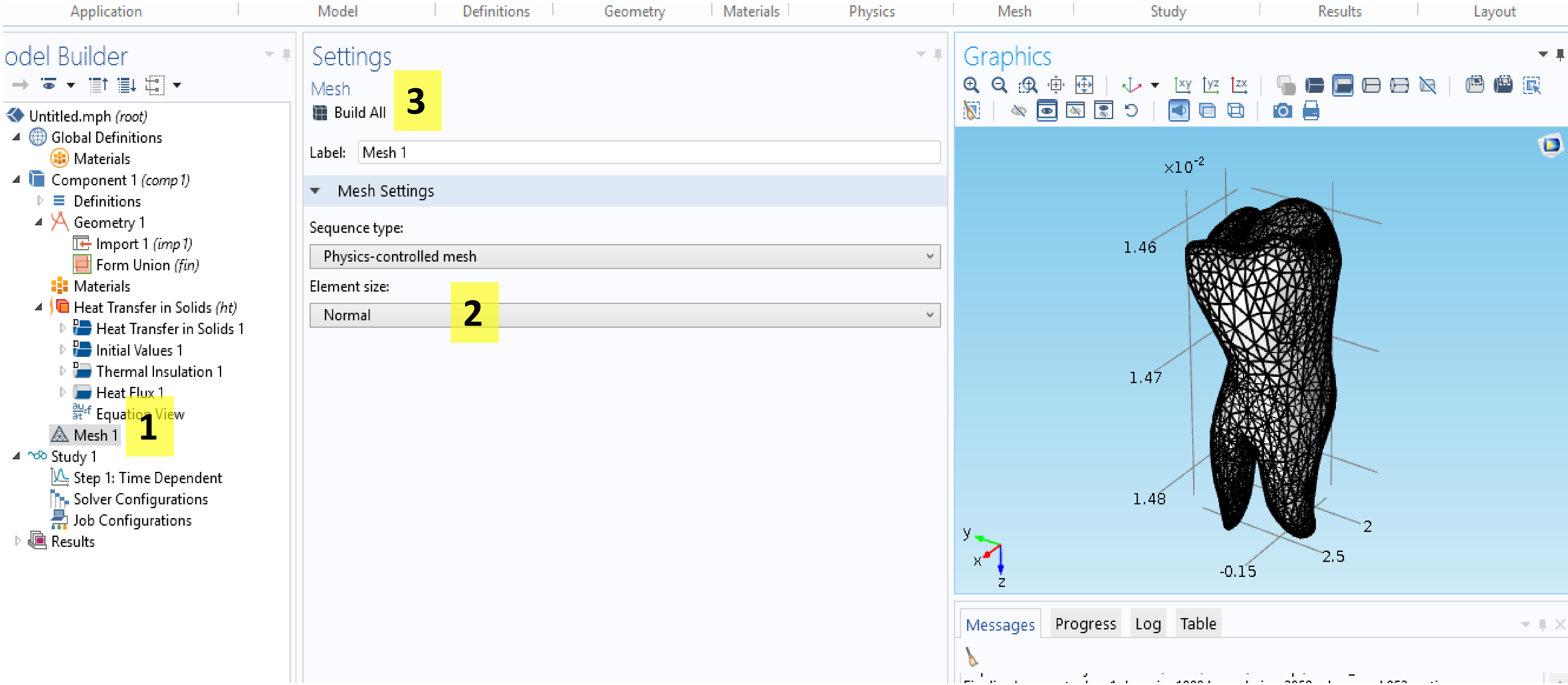


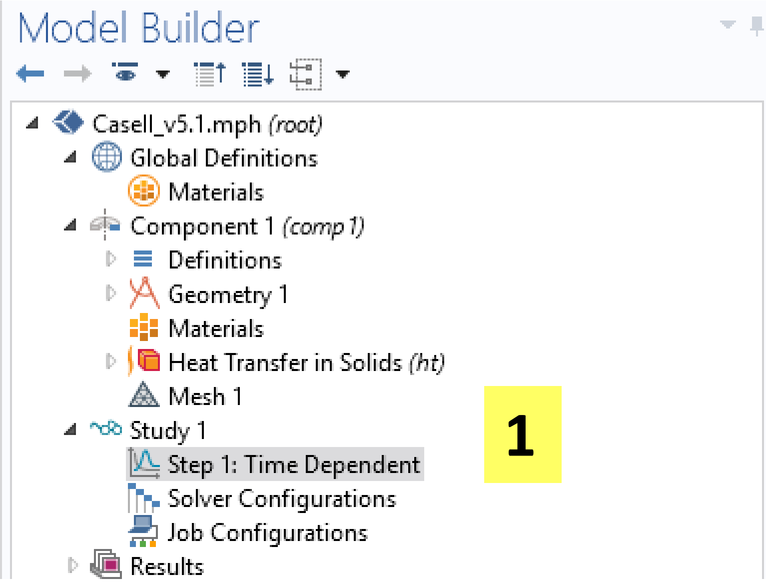
1) Right click 'Heat transfer in solids'
2) Select 'heat flux'
3) Select 'select box'
4) Draw a box as shown and let go
5) You should see the top turn blue
6) And boundaries appear
7) Enter the heat flux as shown

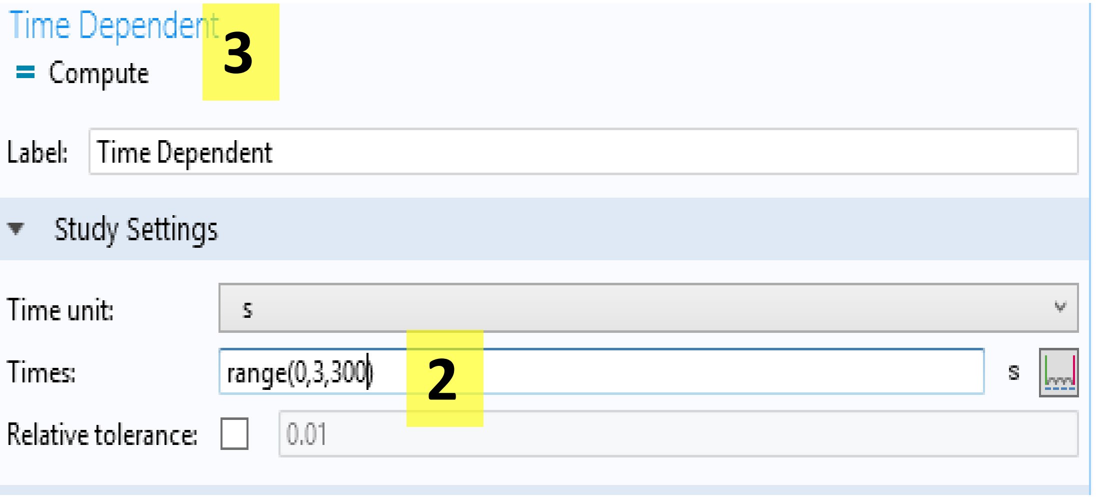




1) Left click mesh 1
2) Select 'normal'
3) Click build all







1) Left click “Step 1: Time dependent’
2) Enter range(0,3,300)
3) Click compute

Bee 4530/MAE 4530

Homework (Case studies VII and IX in text): Due Feb. 26, 2016 in class

Go through the case studies and submit materials asked for. Each student needs to submit this individually. **All plots must be properly labeled (title and axis names)**. There are tutorials on the course website to help you use the software, please check "Tutorials" before asking.

What to submit for Case study VII:

1) How many governing equations are you solving and for what variables?
2) What are the boundary conditions at the distance far away from the tumor and what is the reason for this? Can another boundary condition be used here?
3) When inputting the diffusivity and source variables, they are each multiplied by a factor of x*x. What is the reason for this?
4) Plot and describe the antigen concentration from r=0 to r=0.13 (tumor region only) after 3 days. Based on this, do you think that the antibody treatment worked? Why or why not?
5) Re-run the problem but this time use an antibody concentration of 3,000 nM instead of 4.94 nM. Submit the new plot of antigen concentration vs, r-position and compare with that obtained in 4.

What to submit for Case study IX:

1) Is there another way to solve the voltage equation (Eq. 6.23) using a different physics interface?
2) Why do you think that the domain size chosen is appropriate, i.e., large enough?
3) Obtain the Contour plot of temperature (in °C) for the entire geometry with user-specified labels after 60 s. The isotherms should be 38 40 45 50 55 60 70°C
4) Plot in EXCEL temperature vs. time for the point (.0013, .0075)
5) Run the same problem but with different blood perfusion terms (set Q_blood = 4000*(310.15-T), 2000*(310.15-T), 1000*(310.15-T), 500*(310.15-T),...,0). As before, you can use a parametric sweep for the coefficient term. Plot temperature vs. time for the point (.0013, .0075) on a different graph than part 4 (For this problem, you might want to consider doing a parametric sweep to run it quickly)
6) Discuss part 5

What to submit for the tooth assignment:

1) Turn in a multislice plot of temperature at 300s
2) On one plot, turn in a plot of the mean, maximum, minimum and standard deviation of temperature in the tooth versus time