Excerpt from the Proceedings of the 2011 COMSOL Conference in Tokyo

Computer simulation of drug release kinetics of Mauran-Chitosan Nanoparticle in COMSOL

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Abstract

- **Bionanotechnology is a stream of modern science that deals with the study of biotechnology & nanotechnology applications.**

- **Drug delivery applications as a key area of research attains more critical approaches where the role of nanoparticles are inevitable.**

- **Biocompatible, non-cytotoxic hybrid mauran- chitosan nanoparticles has been synthesized and the drug release kinetics were performed using computer simulation.**

- **Computer simulation of drug release from these nanoparticles were performed using COMSOL4.2a version**

Introduction

- Extremophilic bacteria- *Halomonas maura*, moderately halophilic bacterium producing mauran, sulfated polysaccharides used for the studies.
- Mauran- Chitosan nanoparticles can be used for various biomedical applications including drug delivery purposes, since they are found to be biologically compatible.

Fig.1: *Halomonas maura* showing mauran release.

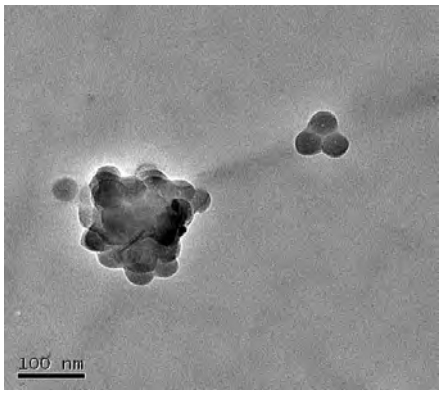


Fig.2: Mauran– Chitosan nanoparticles.

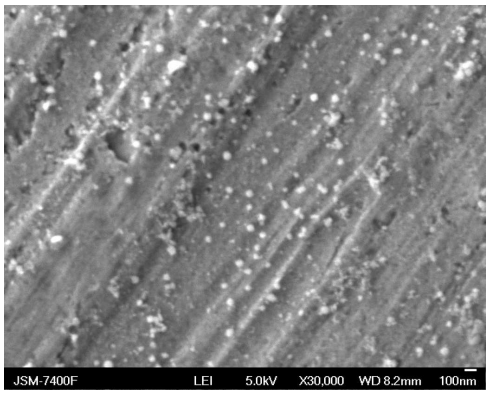


Fig.3: 5–Fluorouracil loaded Mauran– Chitosan nanoparticles.

Drug Release Kinetics

- Drug loaded nanoparticles on *invivo* delivery will reach the blood. The release of the drug from the nanoparticles can be either sustained or burst release., which is defined by kinetics.
- *Invitro* studies can be performed by mimicking the *invivo* setup, in which the drug loaded nanoparticles will be dispersed in a dissolution medium and the drug released were quantified using spectrophotometry.
- The release pattern can be plotted using drug concentration (%w/v) & time(hrs) period of release within 24hrs.
- This will help to conclude the release is sustained or not.

Physico-Chemical properties

- MR/CH nanoparticles formed are of size 30-200nm; spherical to quasispherical in shape.
- It can with stand acidic pH and hence suitable for oral drug delivery.
- Nanoparticles remain Stable for a minimum 8 weeks of time, with out degradation.
- Posses a Positive zeta potential of 27.5±5mV
- Hence can bind negatively charged peptides, drugs or small biomolecules.
- Since the raw material- mauran and chitosan is found to be biodegradable and biocompatible with less cytotoxicity, the nanoparticles can be an excellent molecule for biomedical applications.

Simulation in COMSOL

- Here we describe the release of the encapsulated drug from the nanoparticle of size 105nm, by assuming as a biomaterial matrix carrying drug to a target cell.

- With this simulation it is easy to investigate & design the parameters governing the rate of drug release such as:

  - Drug-to-biomaterial affinity
  - Biomaterial degradation
  - Drug loading
  - The influence of geometry and composition of the biomaterial matrix.

Model definition

- In this model a drug is released into a targeted region containing cancer cells or damaged tissues.
- The biomaterial i.e Mauran- chitosan nanoparticle holding the drug has a spherical shape and can serve various purposes depending on the target and application:

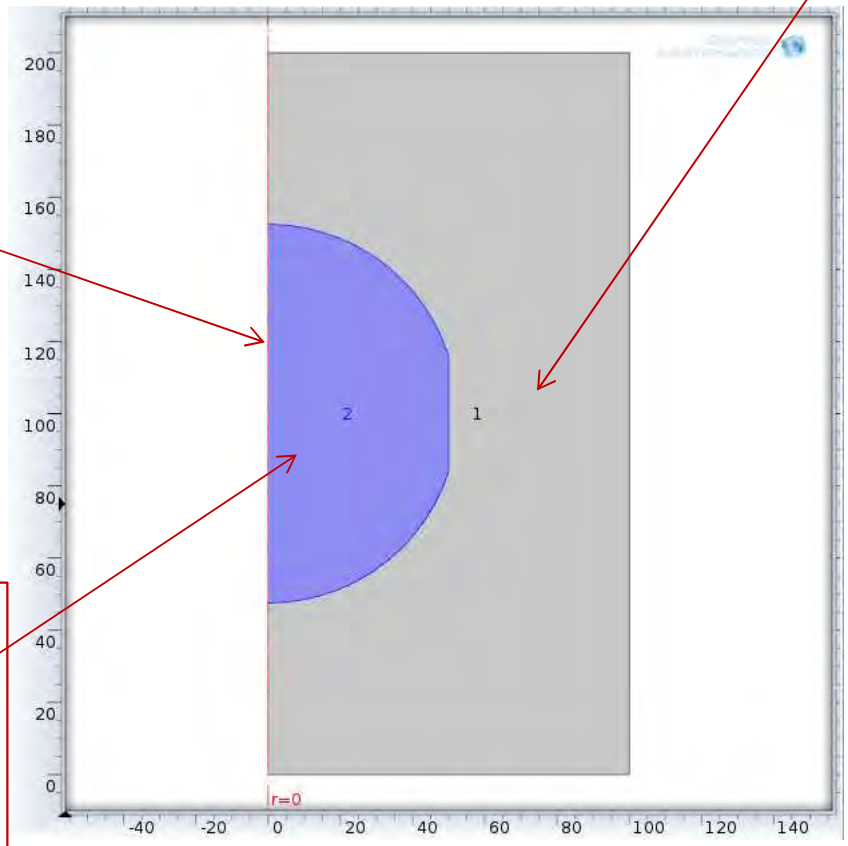
- Drug can act as a guide to help regeneration of damaged tissues
- Stimulates the healing process through targeted drug release.
- Kill cancer cells or etiological agent via targeted drug release

The model simulates Chemical species transport – Transport of Diluted Species module in a 2D geometry with axial symmetry.

Model Description

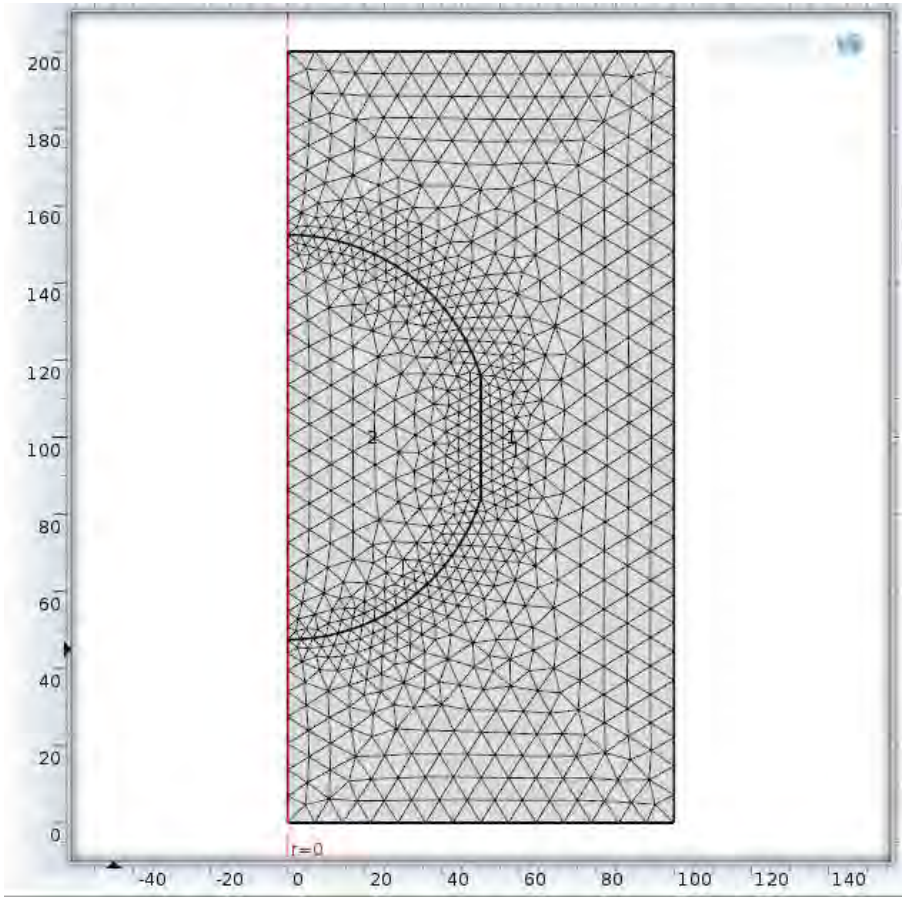
Human Tissue
100nm X 200nm

Axis symmetry

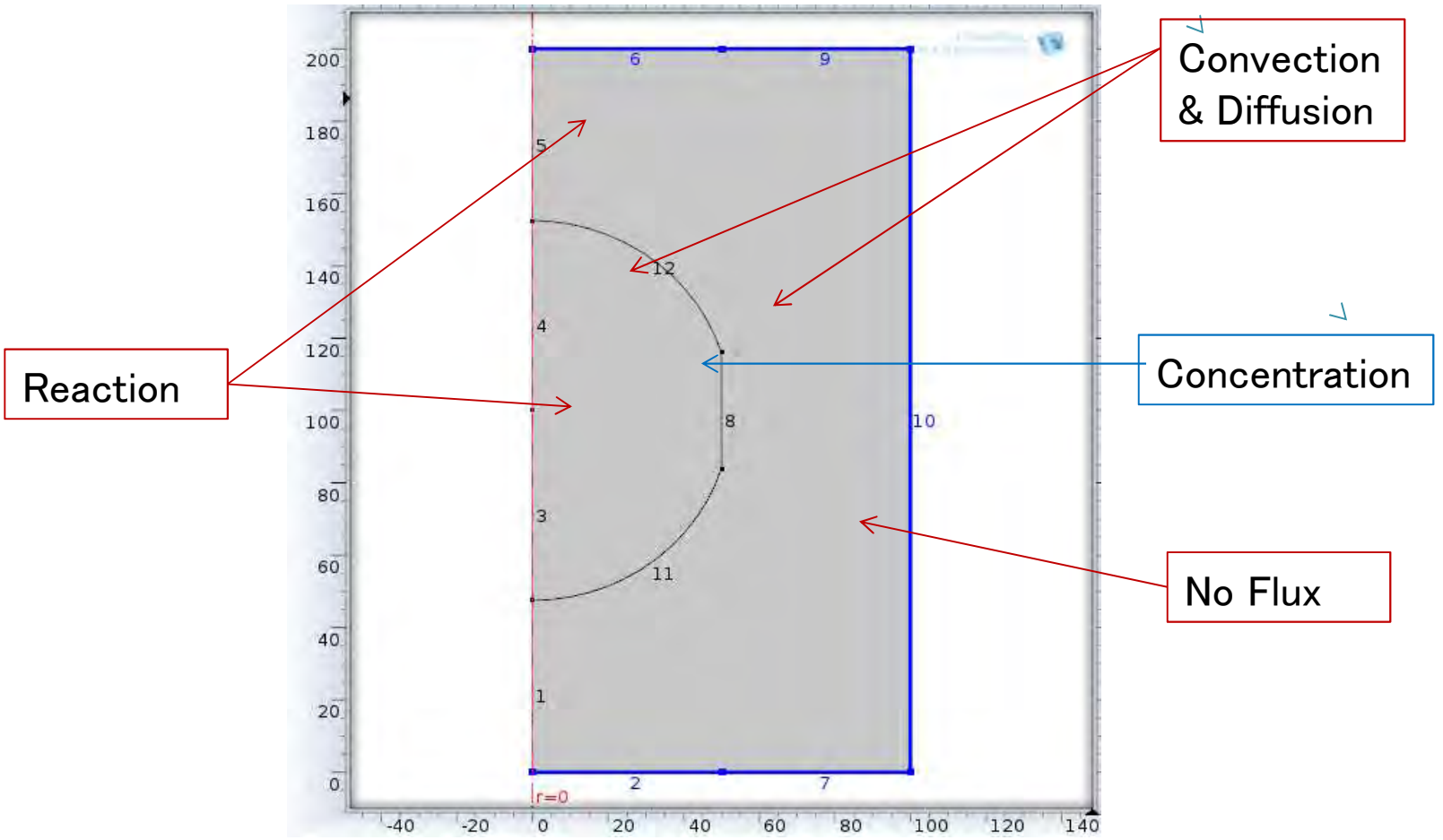


Drug within
Mauran-Chitosan
Nanoparticle
(sphere shape with
105nm diameter)

Mesh


200
180
160
140
120
100
80
60
40
20
0
-40
-20
0
20
40
60
80
100
120
140
r=0
2
1

Loads and Boundary conditions

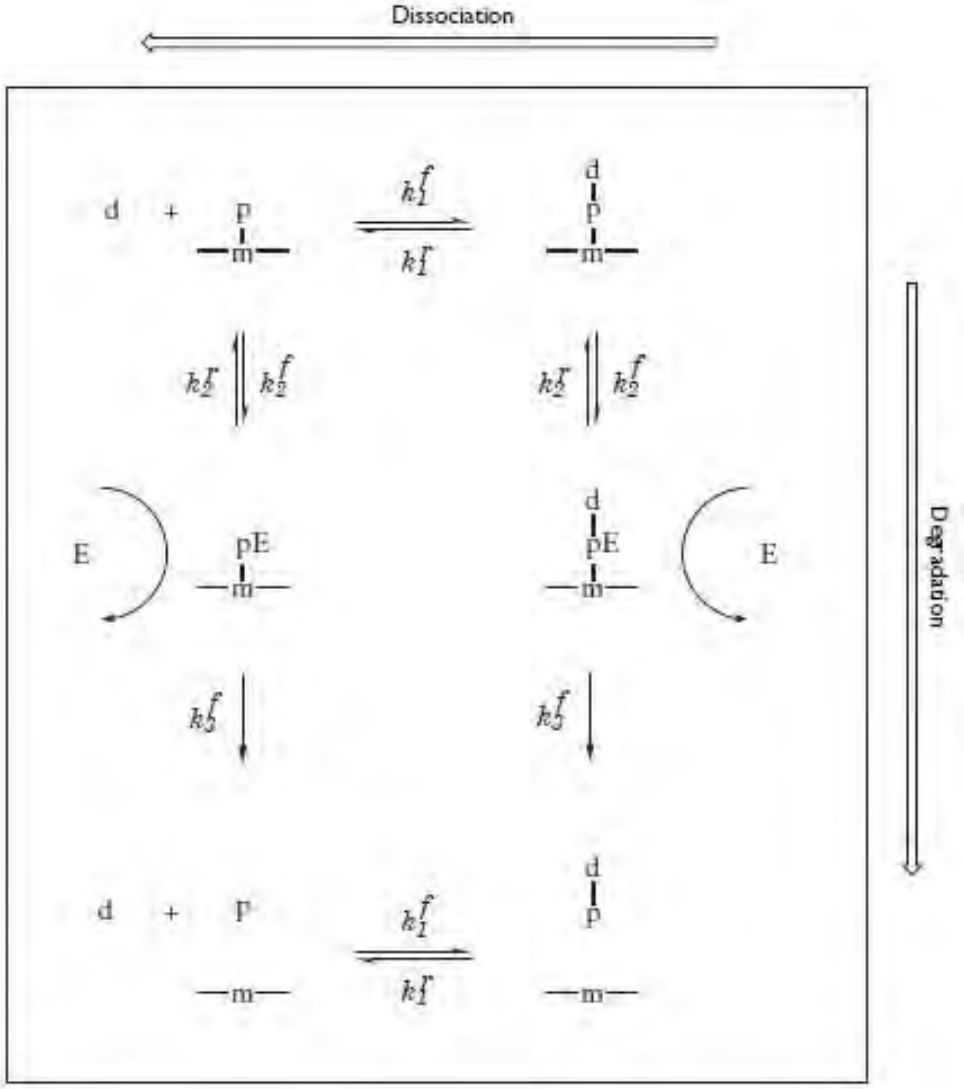


Model definition

- In the biomaterial matrix, a drug molecule, ***d***, binds to a polysaccharide, ***p***, which in turn is anchored to the matrix, ***m***. Matrix-bound species are labeled ***mpd*** and ***mp***, respectively, the latter referring to a species where no drug is bound to the polysaccharide. Species ***mpd*** and ***mp*** are active only in subdomain ***Ω2***.
- Two mechanisms release the drug from the matrix:

- The drug can simply dissociate from the matrix site ***mp***.
- Matrix degradation by an enzyme, ***e***, originating from the cell-tissue domain, leads to release of the drug-polysaccharide species, ***pd***, from which the drug subsequently dissociates. The unbound species ***p, d, pd***, and ***e*** are active in the entire model domain. Next Figure illustrates the complete reaction scheme.

Model definition



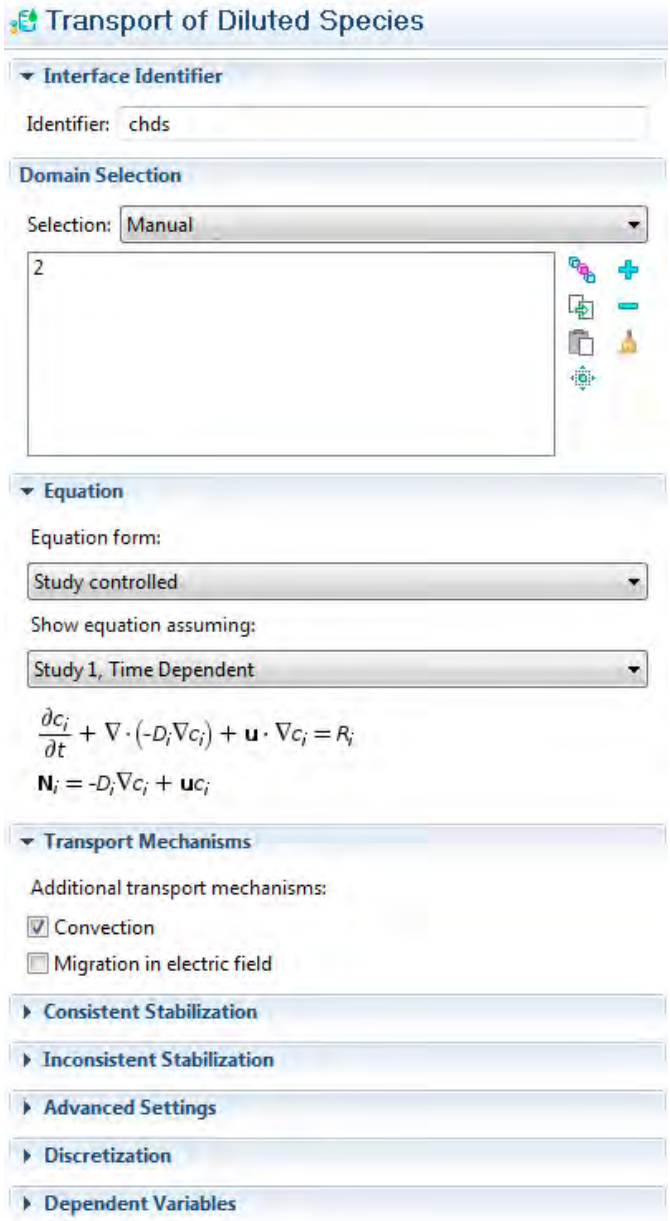
Reaction scheme describing drug dissociation/association reactions (horizontal) and matrix-degradation reactions (vertical).

Model definition

The simulation makes use of two diffusion application modes in the Chemical Engineering Module. The time-dependent mass balance per species is described by

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (-D_{ik} \nabla c_i) = R_{ik}$$

where *Dικ(m2/s) is the diffusion coefficient for species i in the medium of drug. Further, Rικ(mol/(m3·s)) is the rate expression for species i in the medium. In the matrix, all the reactions described in Figure above are possible, leading to the following rate expressions:*



Model definition

$$R_{d2} = -k_1^f c_d (c_{mp} + c_p) + k_1^r (c_{mpd} + c_{pd})$$

$$R_{p2} = -k_1^f c_d c_p + k_1^r c_{pd} + R_{MMmp}$$

$$R_{pd2} = k_1^f c_d c_p - k_1^r c_{pd} + R_{MMmpd}$$

$$R_{mp2} = -k_1^f c_d c_{mp} + k_1^r c_{mpd} - R_{MMmp}$$

$$R_{mpd2} = k_1^f c_d c_{mp} - k_1^r c_{mpd} - R_{MMmpd}$$

a= Variables

Variables

Name	Expression	Unit	Description
k3f	7.336e-3		
kM	0.01		
k1f	k1f_input		
k2f	k1f		
k1r	k1r_input		
k2r	k1r		

a= Variables

Geometric Entity Selection

Geometric entity level: Domain

Selection: Manual

2

Variables

Name	Expression	Unit
Rc_d	-k1f*c_d*(c_mp+c_p)+k1r*(c_mpd+c_pd)	
Rc_mp	-r_1-R_mm_mp	
Rc_mpd	r_1-R_mm_mpd	
Rc_p	-r_2+R_mm_mp	
Rc_pd	r_2+R_mm_mpd	
Rc_e	0	

Model definition

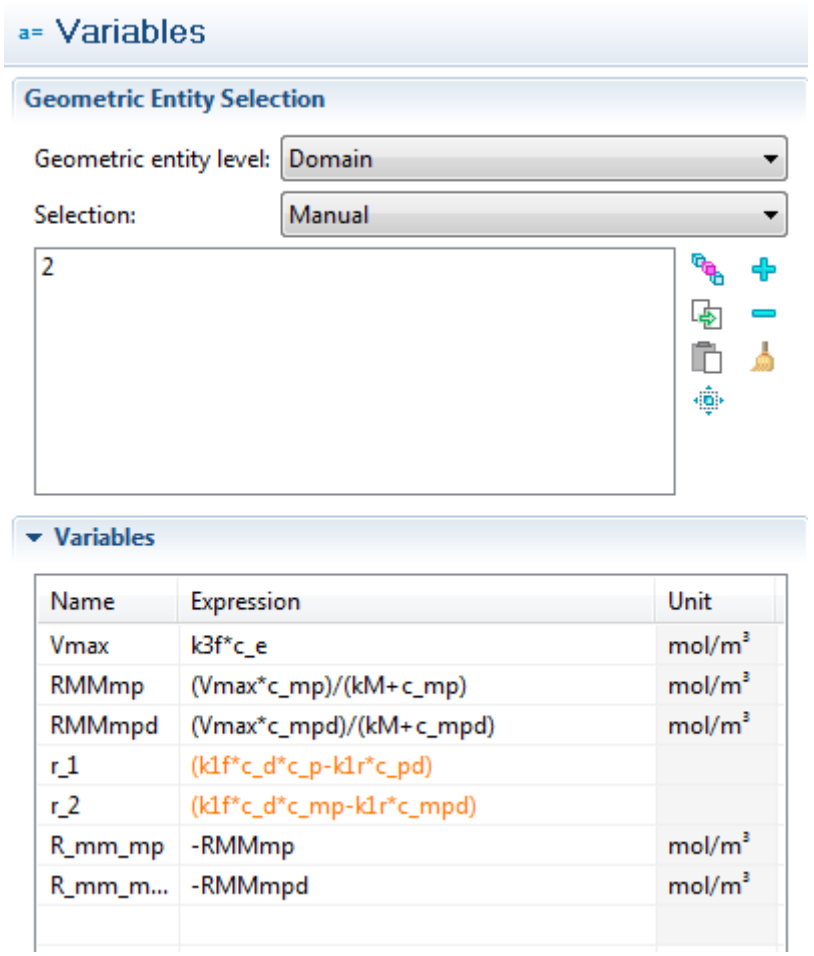
The rate terms *RMMmp and RMMmpd refer to the* ***Michaelis-Menten kinetics*** *describing the enzyme catalyzed degradation of the matrix:*

$$R_{MMmp} = \frac{V_{\max} c_{mp}}{K_M + c_{mp}}$$

$$R_{MMmpd} = \frac{V_{\max} c_{mpd}}{K_M + c_{mpd}}$$

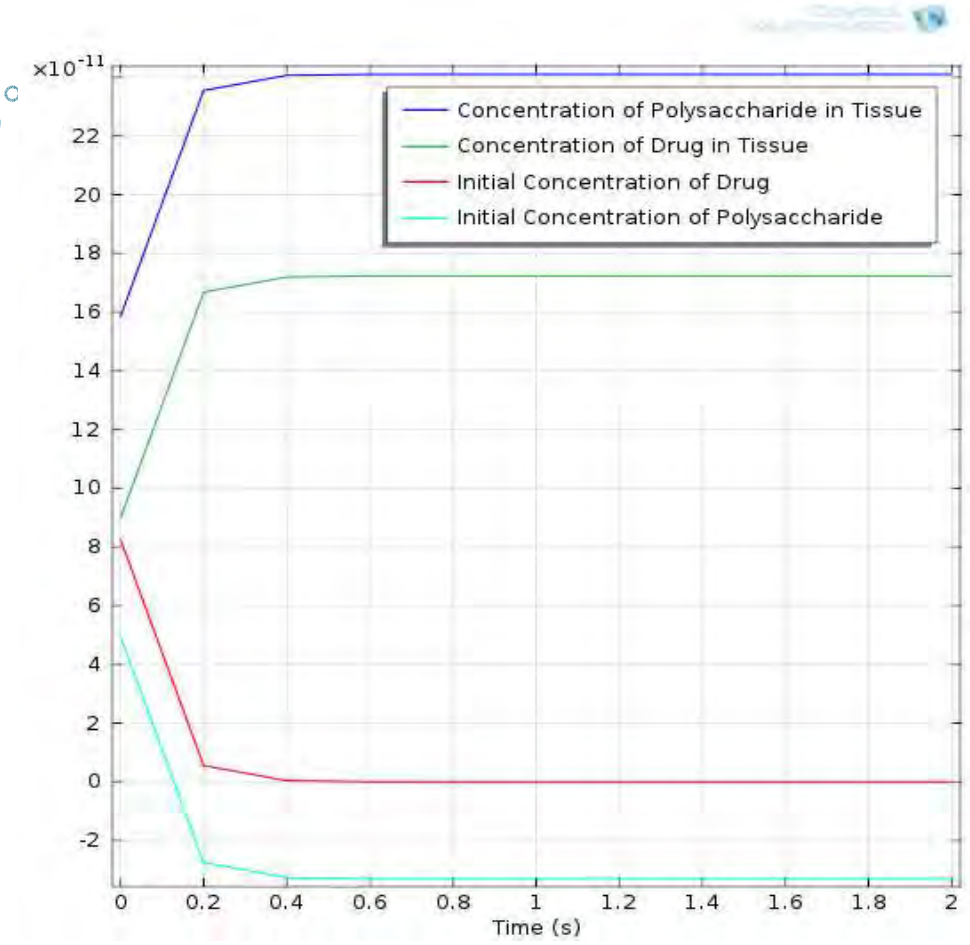
$$V_{\max} = k_3^f c_e$$

$$K_M = \frac{k_3^f + k_2^r}{k_2^f}$$



Name	Expression	Unit
Vmax	k3f*c_e	mol/m³
RMMmp	(Vmax*c_mp)/(kM+c_mp)	mol/m³
RMMmpd	(Vmax*c_mpd)/(kM+c_mpd)	mol/m³
r_1	(k1f*c_d*c_p-k1r*c_pd)	
r_2	(k1f*c_d*c_mp-k1r*c_mpd)	
R_mm_mp	-RMMmp	mol/m³
R_mm_m...	-RMMmpd	mol/m³

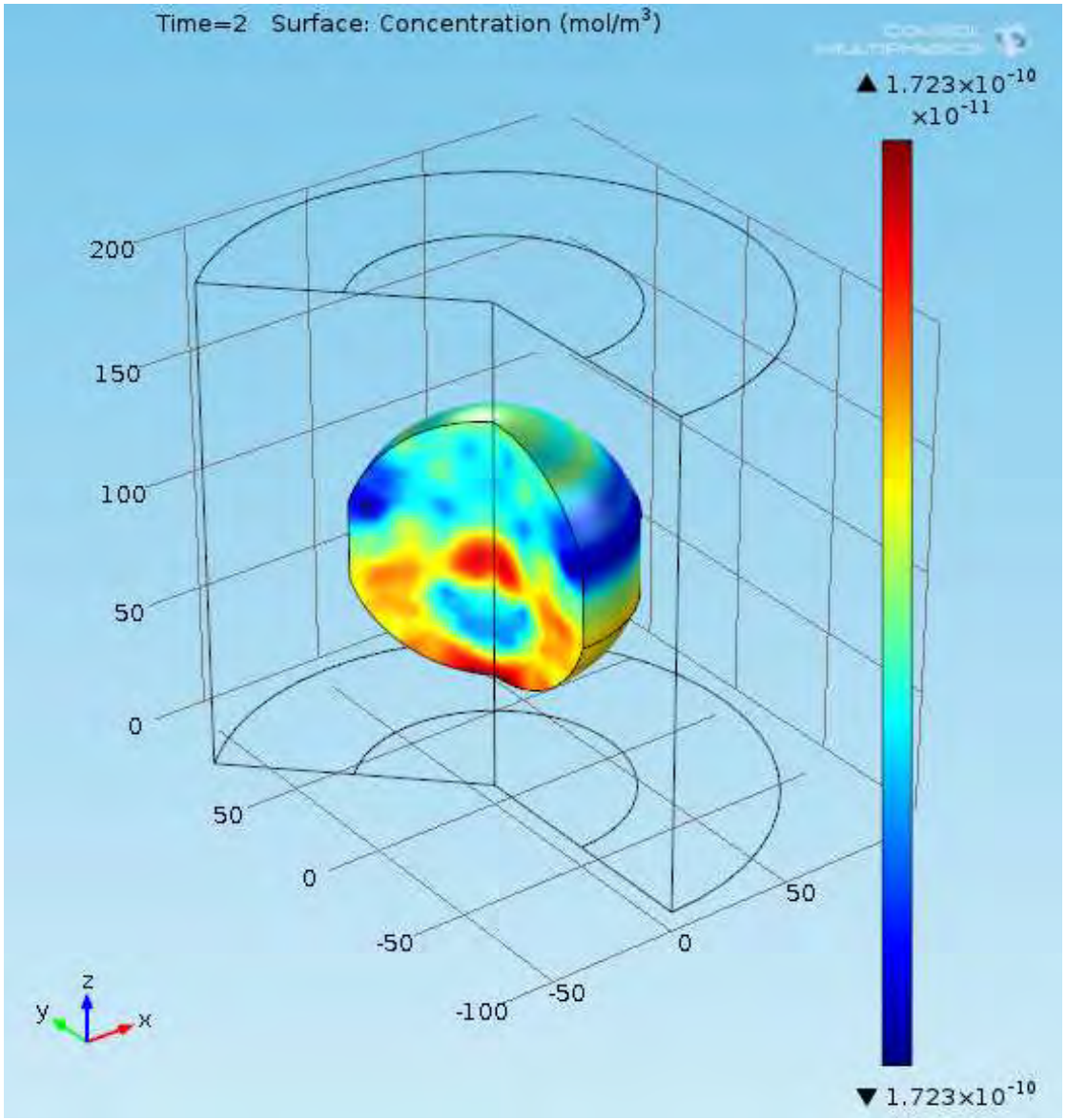
Results



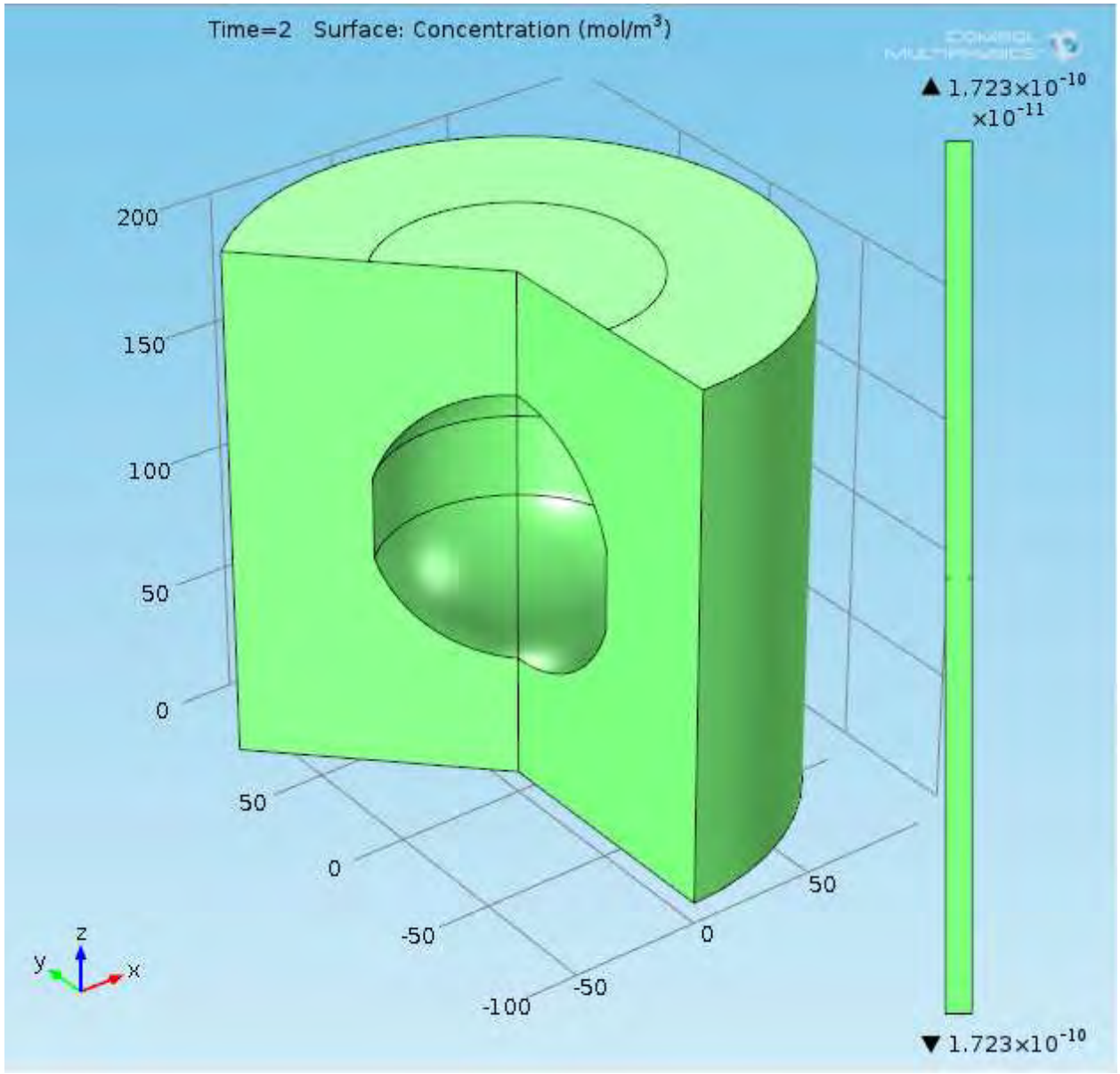
The effect of enzyme degradation is visible with matrix bound Initial concentration of drug, and Polysaccharide is decreasing with time.

Concentrations of the reacting species (mol/m3) as functions of time (s)

Results


Time=2 Surface: Concentration (mol/m3)
▲ 1.723×10-10
×10-11
200
150
100
50
0
50
0
-50
-100
-50
0
50
z
y
x
▼ 1.723×10-10

Results


Time=2 Surface: Concentration (mol/m³)
▲ 1.723×10⁻¹⁰
×10⁻¹¹
200
150
100
50
0
50
0
-50
-100
-50
0
50
z
y
x
▼ 1.723×10⁻¹⁰

Conclusion

- A 2D axisymmetric model of the Mauran-Chotosan nano particle is modelled in Comsol Multiphysics.
- Diffusion Matrix was defined.
- Concentration and Reactions simulated.
- Time dependent analysis study the process done.
- Simulation of the Drug delivery is done with COMSOL Multiphysics 4.2a
- Visualization of the Diffusion, Surface concentration, output could be done with COMSOL Multiphysics 4.2a.
- The above study can help research to move at a faster pace and in a cost effective manner with increased accuracy.
- Above study could be modified by simulation of actual chemical reaction in the elements and degradation of the drug chemical to human cells.

Thank you