EuroHPC
Joint Undertaking

Data driven Computational Mechanics at EXascale

DCoMEX

Data driven Computational Mechanics at EXascale

Work program topic: EuroHPC-01-2019
Type of action: Research and Innovation Action (RIA)

DCOMEX-BIO PROTOTYPE (Theory Manual)

DELIVERABLE D7.2

Version No 1

http://www.dcomex.eu/
This project has received funding from the European High-Performance Computing Joint Undertaking Joint Undertaking ('the JU'), under Grant Agreement No 956201

DOCUMENT SUMMARY INFORMATION

Project Title	Data driven Computational Mechanics at EXascale
Project Acronym	DCoMEX
Project No:	956201
Call Identifier:	EuroHPC-01-2019
Project Start Date	01/04/2021
Related work package	WP 7
Related task(s)	Task 7.1
Lead Organisation	UCY
Submission date	18/02/2024
Re-submission date	
Dissemination Level	PU

Quality Control:

	Who	Affiliation	Date
Checked by internal reviewer	George Stavroulakis	NTUA	31/09/2021
Checked by WP Leader	T. Stylianopoulos	NTUA	31/09/2021
Checked by Project Coordinator	Vissarion Papadopoulos	NTUA	31/09/2021

Document Change History:

Version	Date	Author (s)	Affiliation	Comment

Contents

1. Description

Deliverable 7.1 is associated to WP7 “XXX YYY” of the DCoMEX project, and it provides a comprehensive report on the theoretical description, and the computational solution of a coupled system of ordinary and partial differential equations that represent the growth, transport and reaction phenomena occurring in the microenvironment of a biphasic tumor (TME). The outline of the deliverable is the following: Section 2 illustrates the mathematical model of the TME, presenting all the equations and all the involved variables while Section 3 provides the aspects of the numerical solution in MSolve as well as the obtained numerical results. In Section 4 an illustration of the MSolve Coupled problem solver is given.

2. Mathematical Model of the Tumor Micro-Environment TME

2.1 Problem setup

The tumor tissue is modeled as an eighth of a sphere ($r = 5E-4m$) embedded in a cube ($\alpha = 1E-1m$) representing the healthy tissue. Both tissue types are biphasic, consisting of a solid and a fluid phase with heterogenous material properties, indicating the interstitial fluid flow through the solid matrix. Due to this type of solid-fluid interaction the medium is considered porous. Healthy and tumor tissues are known to be heterogeneous, leading to variations in mechanical properties, which cause non-uniform flows between regions. By applying proper mathematical formulations, the model accounts for the porous medium mechanics and the developed stresses as well as the transport of oxygen and cancer cells and the effect of the tumor growth on the resulting deformation state.

2.2 Fluid Phase

The pressure field p_i of the interstitial fluid affects the stress state of the tissues by adding hydrostatic components to the stress tensor. Darcy's law for porous media describes the fluid velocity vector $\boldsymbol{v_f}$ as a function of the gradient of interstitial fluid pressure p_i, the hydraulic conductivity k_{th}, of the interstitial space and the velocity of the solid phase $\boldsymbol{v_s}$ and is expressed as follows:

$$\boldsymbol{u_f} = -k_{th}\nabla p_i + \boldsymbol{v_s}$$

The differential form of the continuity equation is given as:

$$\boldsymbol{\nabla \cdot u_f} = L_p S_v(p_v - p_i) - L_{pl} S_{vl}(p_i - p_l)$$

The source term denotes the flux entering from the blood vessels into the tissue minus the fluid flux exiting through lymphatic vessels and accounts for the contribution of the divergence of the solid velocity vector field. By combining the above equations, the steady-state fluid transport equation is yielded:

$$-k_{th}\nabla^2 p_i = L_p S_v(p_v - p_i) - L_{pl} S_{vl}(p_i - p_l) - \nabla \cdot (v_s)$$

The above equation describes the flow of the interstitial fluid as a result of the occurring pressure gradients, the divergence of the solid phase velocity and the pressure differences between the interstitial fluid and the vascular and blood vessels.

Variable/ Constant	Description	Unit
p_i	Fluid Phase Pressure	kPa
v_s	Solid Phase Velocity	m/s
k_{th}	Hydraulic Conductivity	$m^2/(kPas)$
L_p	Blood Vessel Walls Hydraulic Conductivity	$m/(kPas)$
S_v	Vascular Density	$1\ /\ m$
p_v	Vascular Pressure	kPa
p_l	Lymphatic Pressure	kPa
$L_{pl}S_{vl}$	Lymphatic Vessel Permeability	$1/(kPas)$

Table 1: Fluid Phase Parameters and Coefficients

2.3 Solid Phase

The solid matrix of the tissues is subjected to deformations due to the pressure of the interstitial fluid and the internal strain developed during the tumor growth. The deformation gradient tensor F, is calculated as a function of the initial and final position vectors x and X:

$$\boldsymbol{F} = \frac{\boldsymbol{\partial x(X,t)}}{\boldsymbol{\partial X}}$$

And is decomposed multiplicatively as

$$\boldsymbol{F} = \boldsymbol{F_e F_g}$$

where $\boldsymbol{F_g}$ is the growth component, that accounts for the growth of the tumor :

$$\boldsymbol{F_g} = \lambda_g \boldsymbol{I}$$

And $\boldsymbol{F_e}$ the elastic component that accounts for mechanical interactions of the tumor with the surrounding normal tissue, calculated as

$$\boldsymbol{F_e} = \boldsymbol{F F_g^{-1}}$$

The equation of motion describing a solid tumor can be expressed as follows:

$$\boldsymbol{\nabla \cdot \sigma = 0}$$

The isotropic hydrostatic fluid pressure components act on the solid stress tensor, producing an equal force in all normal directions and contributes directly to the total stress state of the solid phase:

$$\boldsymbol{\nabla \cdot \left(\sigma^s - \sigma^f\right) = \nabla \cdot (\sigma^s - p_i I) = 0}$$

The mechanical behavior of the tissue is simulated with a hyper-elastic, Neo-Hookean material while the Cauchy stress tensor $\boldsymbol{\sigma^s}$ is:

$$\boldsymbol{\sigma^s} = J_e^{-1} \boldsymbol{F_e} \frac{\partial W}{\partial \boldsymbol{F_e^T}}$$

where $J_e = \det F_e$ and W is the modified neo-Hookean strain energy density function for a nearly incompressible hyper-elastic material:

$$W = \frac{1}{2}\mu(-3 + \bar{I}_1) - p(J_e - 1) - \frac{p}{2k}$$

with μ, k being the shear and bulk moduli of the material, $\bar{I}_1 = I_1 J_e^{-2/3}$, $I_1 = trC^e$ the first and second invariants of the elastic Cauchy-Green deformation tensor while p_i is a Lagrange multiplier enforcing material constraints.

.

2.4 Oxygen Transport

Oxygen transport phenomena are paramount in the TME. Impaired blood perfusion in the tumor region limits the delivery of drugs, immune cells, and oxygen. Reduced oxygen concentration, known as hypoxia, is considered a hallmark of the abnormal tumor micro-environment, inducing immunosuppression. Conversely, high oxygen supply can fuel tumor growth and proliferation.

The mathematical modeling of oxygen concentration is achieved by the transient convection-diffusion-reaction equation. Oxygen is transported due to a diffusive flow through the pores of the medium and a convective flow due to the bulk motion of the interstitial fluid. The consumption of oxygen due to cancer cell proliferation is localized to the tumor region. Both tumor and host regions utilize a shared source term to describe the exchange of oxygen between blood vessels and tissues, encapsulating the process of oxygen delivery and leakage from the vasculature to the interstitial space, which is influenced by both the permeability of vessel walls and vascular density. The equations that describe the aforementioned phenomena in the tumor and host regions are:

$$\frac{\partial c_{ox}}{\partial t} + \nabla \cdot \left(c_{ox}\boldsymbol{v_f}\right) = D_{ox}\nabla^2 c_{ox} - \frac{A_{ox}c_{ox}}{c_{ox}+k_{ox}}T_{CC} + P_{er}S_v(c_{iox} - c_{ox})$$

$$\frac{\partial c_{ox}}{\partial t} + \nabla \cdot \left(c_{ox}v_f\right) = D_{ox}\nabla^2 c_{ox} + P_{er}S_v(c_{iox} - c_{ox})$$

Variable/ Constant	Description	Unit
c_{ox}	Oxygen Concentration	mol/m^3
T_{cc}	Cancer Cell Population	1
$\boldsymbol{v}_f$	Fluid Phase Velocity	m/s
D_{ox}	Diffusion Coefficient	m^2/s
A_{ox}	Maximal Oxygen Uptake	$mol/m^3 s$
P_{er}	Permeability of tumor vessel walls	m/s
S_v	Vascular Density	m^2/s
c_{iox}	Initial Oxygen Concentration	mol/m^3
k_1	Growth Rate Parameter	$1/s$
k_2	Growth Rate Parameter	mol/m^3

Table 2 Oxygen Concentration Parameters and Coefficients

2.5 Cancer Cell Population

Proliferation of cancer cells tends to decrease vessel diameter due to the compression of tumor vessels, thereby not only physically modifying the TME but also impacting nutrient and oxygen supply, which subsequently influences further tumor development. The population balance of Cancer Cells T_{cc} is intricately linked to tumor growth and oxygenation, augmenting with an elevation in the oxygen level as well as the convective flow due to the divergence of the solid phase velocity field. The mathematical modeling of cancer cell proliferation is expressible through a Partial Differential Equation (PDE), exemplified below:

$$\frac{\partial T_{CC}}{\partial t} + \nabla \cdot (T_{CC}\boldsymbol{v_s}) = \frac{k_1 c_{ox}}{k_2 + c_{ox}} T_{CC}\lambda_g$$

Variable/ Constant	Description	Unit
T_{cc}	Cancer Cell Population	1
c_{ox}	Oxygen Concentration	mol/m^3

λ_g	Growth Stretch Ratio	1
v_s	Solid Phase Velocity	m/s
k_1	Growth Rate Parameter	$1/s$
k_2	Growth Rate Parameter	mol/m^3

Table 3Cancer Cell Population Parameters and Coefficients

2.6 Growth Stretch Ratio

In the study of tumor progression, the volumetric growth stretch ratio λ_g, represents the relative change in the tumor volume over time by considering the oxygen concentration and the proliferation of cancer cells. The effect of λ_g in the deformation of the solid matrix is apparent as it appears in the diagonal of the elastic non-stress- deformation gradient tensor $\boldsymbol{F_g}$ adding external strains. The mathematical formulation for λ_g is:

$$\frac{d\lambda_g}{dt} = \frac{1}{3}\frac{k_1 c_{ox}}{k_2 + c_{ox}} T_{CC}$$

Variable/ Constant	Description	Unit
λ_g	Growth Stretch Ratio	1
c_{ox}	Oxygen Concentration	mol/m^3
T_{cc}	Cancer Cell Population	1
k_1	Growth Rate Parameter	$1/s$
k_2	Growth Rate Parameter	mol/m^3

Table 4Tumor growth evolution equation parameters and coefficients

2.7 Mathematical Model Summary

The mathematical model described in the previous sections has strong coupling connections between the 5 differential equations, which can be described as follows : The interstitial fluid pressure is affected by the divergence of the solid phase velocity field and affects the solid phase by adding hydrostatic components to the stress state. The divergence of the velocity fields of the solid and fluid phases are responsible for the convective flows of cancer cells and oxygen correspondingly. Cancer cell transport is included in the growth stretch ratio equation and the non-linear source term of oxygen transport, while oxygen supply plays a major role in the genesis of cancer cells since it is included in the source. The effect of oxygen is also very important in the growth stretch ratio of the solid phase, which affects the elastic deformation gradient tensor **F**.

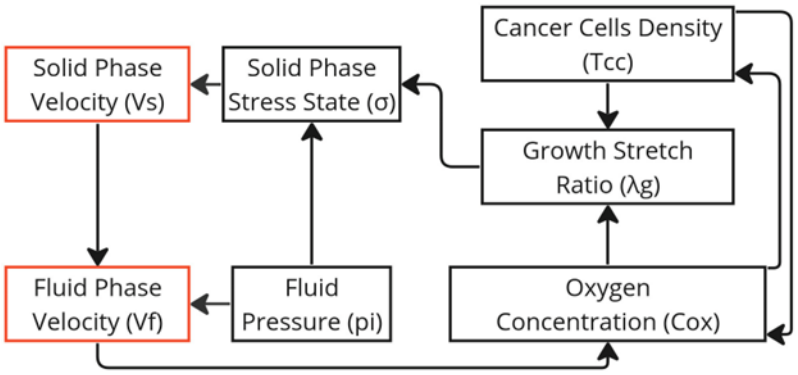

Figure 1 Equation coupling flowchart: Black frame denotes an equation and a red frame denotes an exchanged secondary variable

2.8 Coupling scheme

In general two solution approaches exist for the coupled solution of multi-physics problems: the monolithic approach that dictates that the set of the coupled equations should be solved simultaneously and the Seggregated solver approach that considers a partition of the coupled equations, solves each one of them separately and iteratively corrects their solution until all of the equations are satisfied simultaneously. The coupled solution scheme implemented in MSolve can be regarded mainly as a Staggered (segregated) solver as it employs a partition of the system of equations, but combines the stability and robustness of the monolithic solver as the such a scheme is employed for the solution of the fluid/solid phase interaction. The details of the staggered analyzer solution steps are given in the following flowchart:

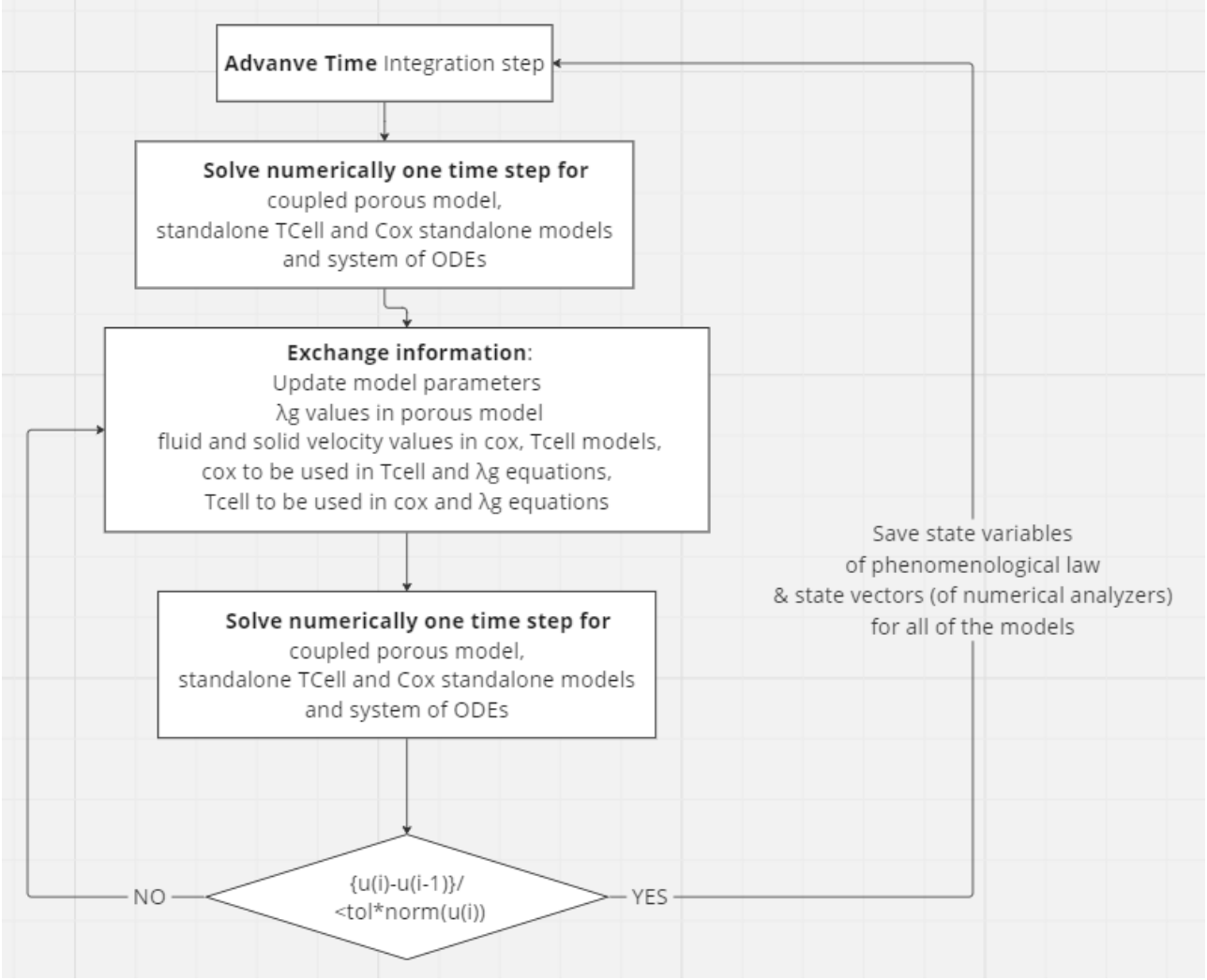

Figure 2 FlowChart of the partitioned solution procedure for the coupled TME model of MSolve for one time integration step

3. Computational Solution and Validation in MSolve software

The spatiotemporal response of the equations described in the previous section are solved with MSolve and are validated meticulously with COMSOL, as standalone equations and as coupled systems of equations. The aim of this validation process is to ensure that all the building blocks perform correctly and the corresponding code can be found in https://github.com/mgroupntua/DrugDeliveryModel.Tests. In particular, the C# classes Finitestrain5eqCoupledModelSolution.cs, Smallstrain5eqCoupledModelSolution.cs, PorousHyperelasticNonLinearRealisticMesh.cs, PorousRealisticAndRealisticMesh.cs, CoxEquationStandaloneSolution.cs, TCellStandaloneSolution.cs
perform the numerical solution of:
A) the fully coupled 5 equation model, as presented in section 2, for 2 solid model configurations (i-finite deformations with hyperelastic material ii- small strains elastic material) ,
B) the porous only model for the same 2 solid phase configurations and

C) the oxygen transport and cancer cell transport equations as standalone models.

3.1 Coupled 5-equation Model Validation

This section presents the results produced from the validation of the coupled system of differential equations, presented in Subsections 2.2-2.6 under different solid phase configurations that allow for small and finite strains as well as linear elastic or hyperelastic material law respectively.

Tumor Geometry Type	1/8 Sphere
Tumor Radius	5E-4 [m]
Host Geometry Type	Cube
Host Edge	1E-1 [m]
Number of Nodes	733
Finite Element Type	Tetrahedra
Number of Finite Elements	2815

Table 5 Discrete Computational Domain Parameters

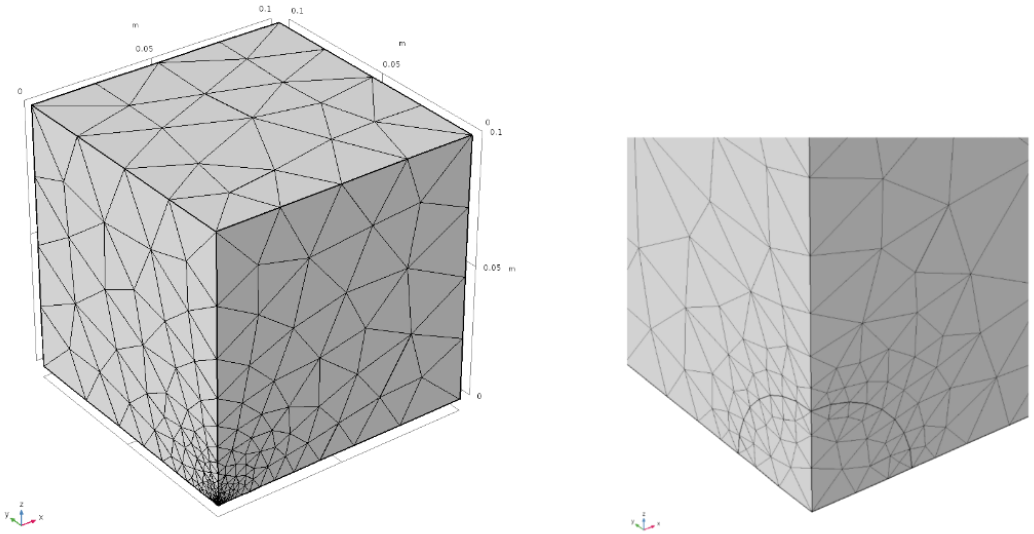

Figure 3:Finite element discretization of the studied examples

Parameter	Tumor Domain Value	Host Domain Value	Units [SI]
μ	22.44	5	kPa
k	216.7	6.667	kPa
k_{th}	7.55E-11	7.55E-13	$m^2/kPas$
S_v	7E3	7E3	m^{-1}
c_{iox}	0.2	0.2	mol/m^3
D_{ox}	1.79E-9	1.79E-9	m^3/s
P_{er}	3.55E-4	3.55E-4	m/s
A_{ox}	2.55E-2	-	mol/m^3s
k_{ox}	4.64E-3	-	mol/m^3s
k_1	1.74E-6	-	
k_2	8.3E-3	-	mol/m^3
p_v	4	4	kPa
p_l	0	0	kPa
Lp	2.794E-9	2.794E-9	$m^2/kPa\ s$
$L_{pl}S_{vl}$	3.75E-1	3.75E-1	$1\ /\ kPa\ s$

Table 6 Computational Model Constants

3.2.1 Fully Coupled 5 equation model - Large Deformation/Hyper-elastic Solid Skeleton

In this subsection the solid phase of the TME is described by a non-linear, hyperelastic, neo-Hookean material that allows large displacement fields and large strain states. The effect of the growth is included in the calculations of F tensor. The results presented are the solid displacement in the z-direction, the pressure of the interstitial fluid, the concentrations of oxygen and cancer cells as well as the growth stretch ratio.

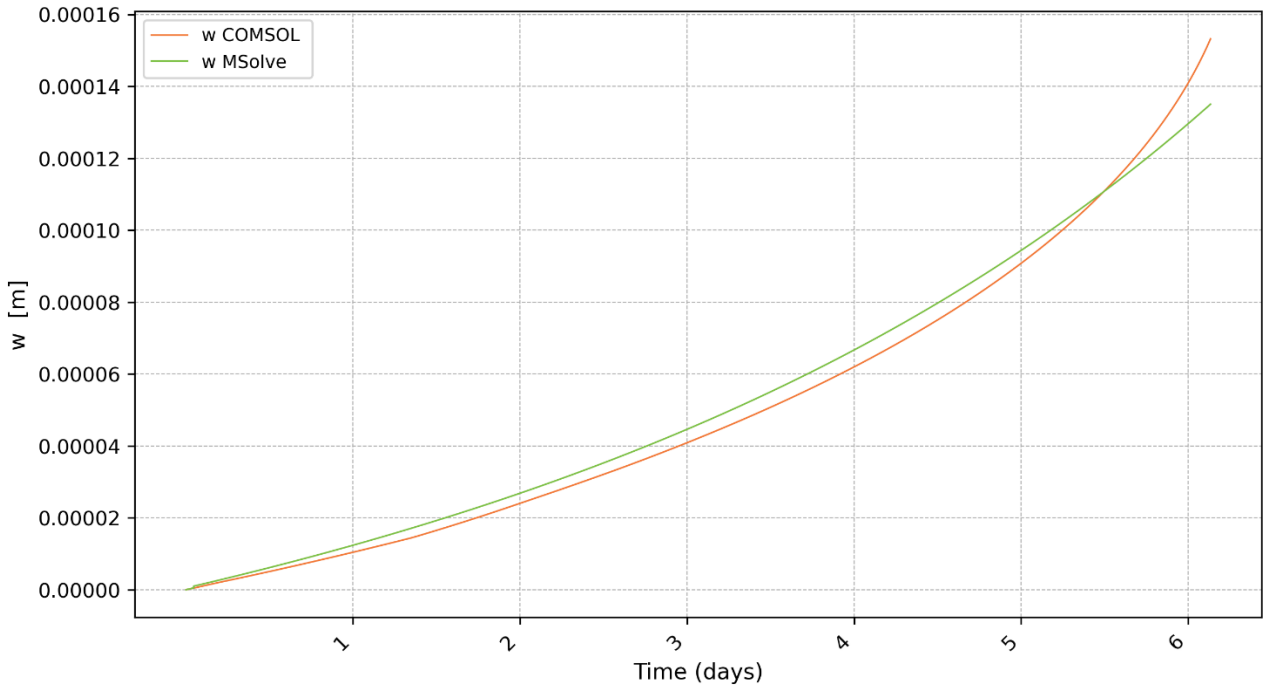

Figure 4:Solid Displacement at z-Direction at (x,y,z)=(2.8E-4,2.8E-4,2.8E-4)

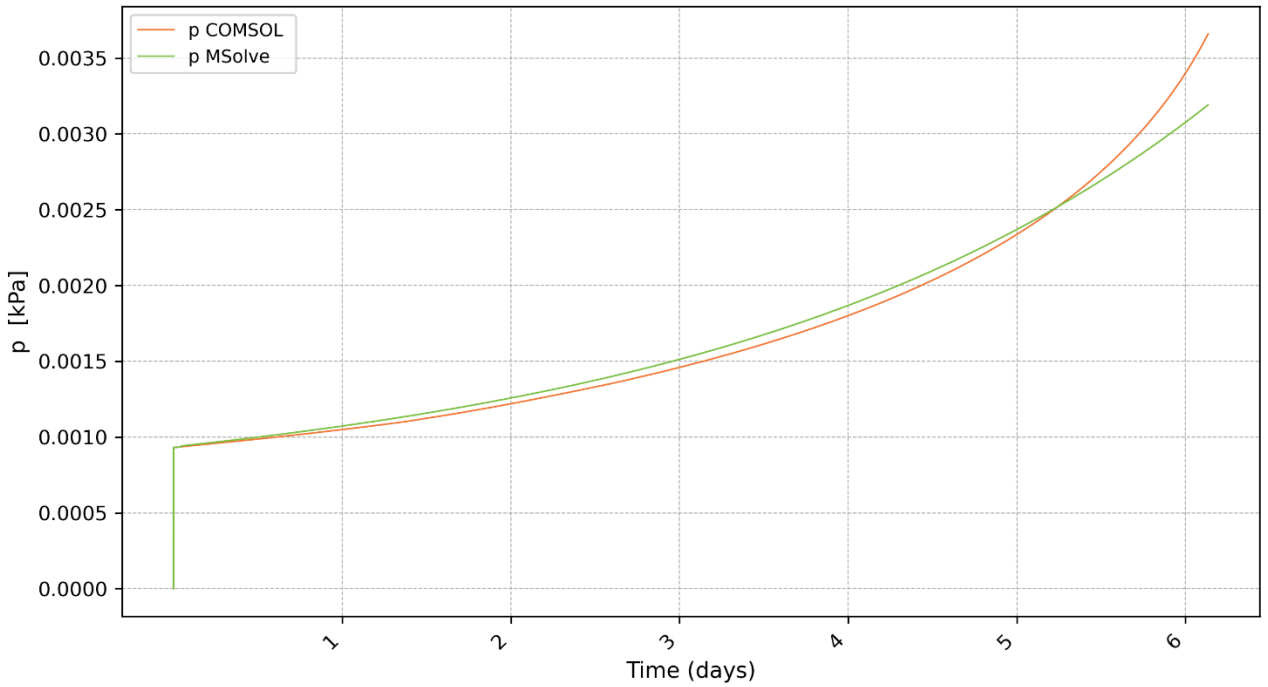

Figure 5Fluid phase pressure at (x,y,z)=2.8E-4,2.8E-4,2.8E-4

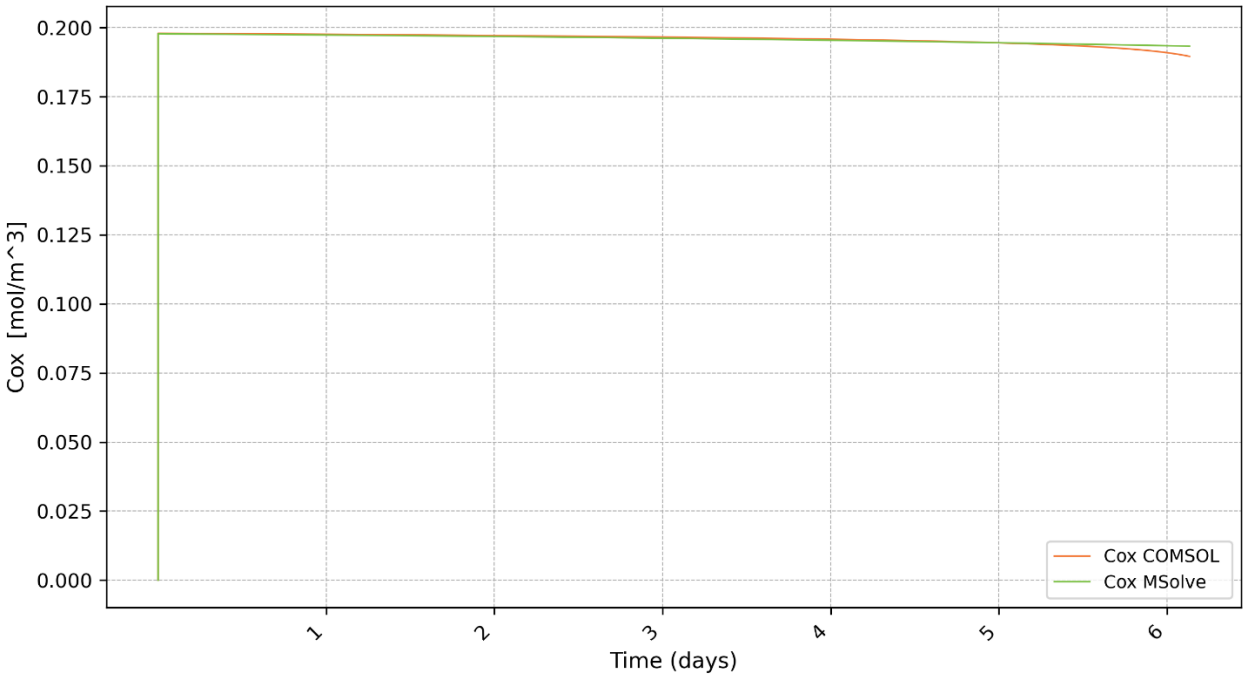

Figure 6: Oxygen Concentration at x,y,z=2.8E-4,2.8E-4,2.8E-4

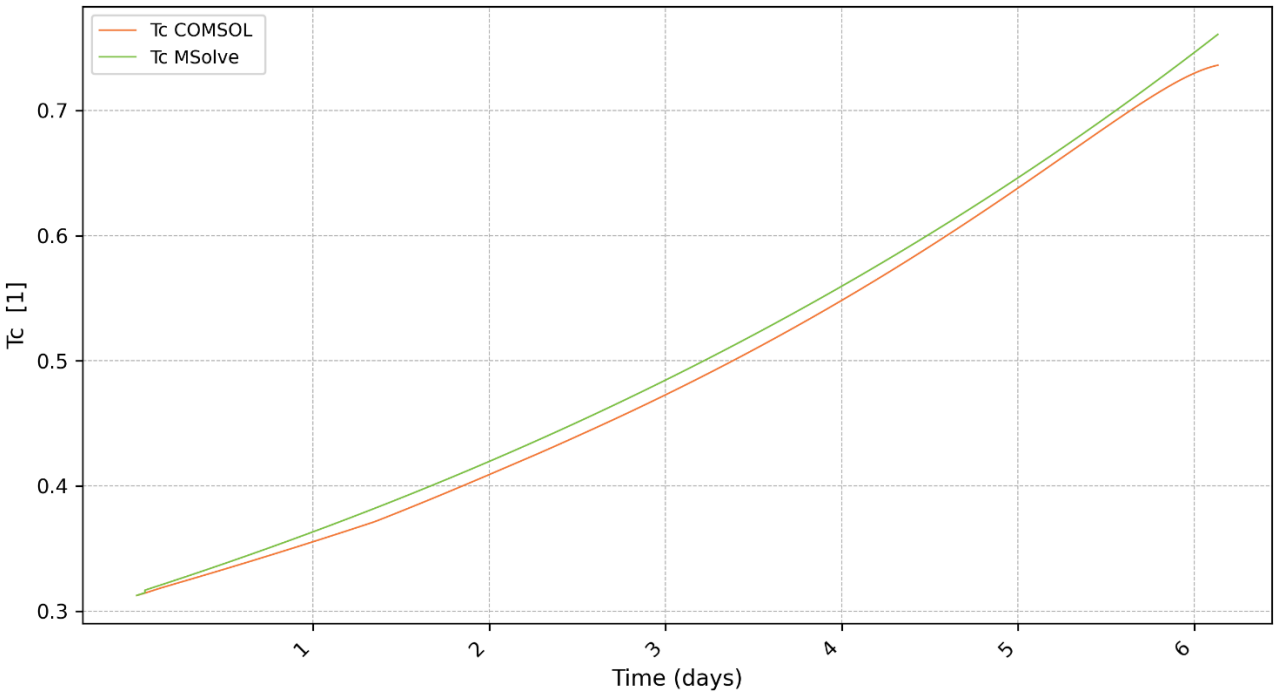

Figure 7 Cancer Cell population at x,y,z=2.8E-4,2.8E-4,2.8E-4

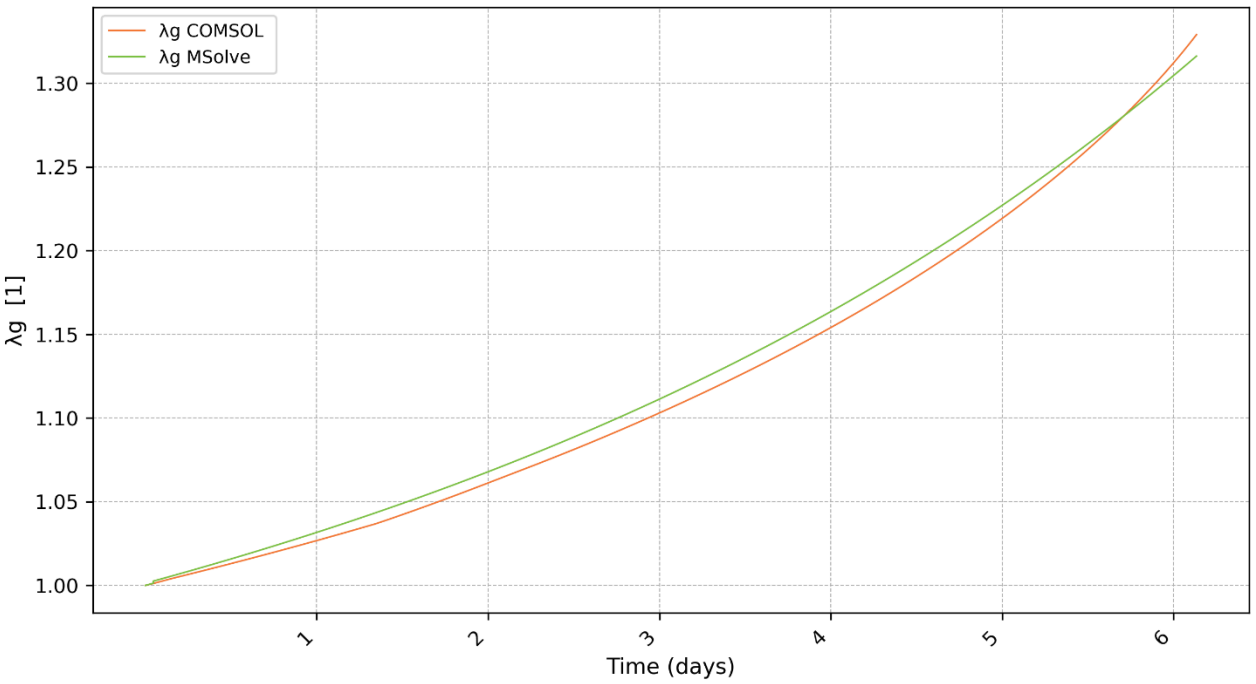

Figure 8: Growth Stretch Ratio t x,y,z=2.8E-4,2.8E-4,2.8E-4

The comparison of the results between MSolve and COMSOL are in good agreement. Solid displacements, fluid phase pressure, cancer cell population and growth stretch ratio have an exponential temporal response for the selected node. The effect of the volumetric growth rate is apparent in the response of the solid phase displacement, since it is the most dominant strain producing mechanism. In addition to that the increase of the fluid phase pressure leads to increased solid stresses in the tumor region. Oxygen concentration is reduced as it is consumed by the increasing population of cancer cells.

3.2.2 Fully Coupled Model / Small Strain – Elastic Solid Skeleton

In this subsection the solid phase of the TME is described by a linear and elastic material that allows small displacements and small strains. The effect of the growth is neglected in the calculations of small strain tensor. The results presented are the solid displacement in the z-direction, the pressure of the interstitial fluid, the concentrations of oxygen and cancer cells as well as the growth stretch ratio.

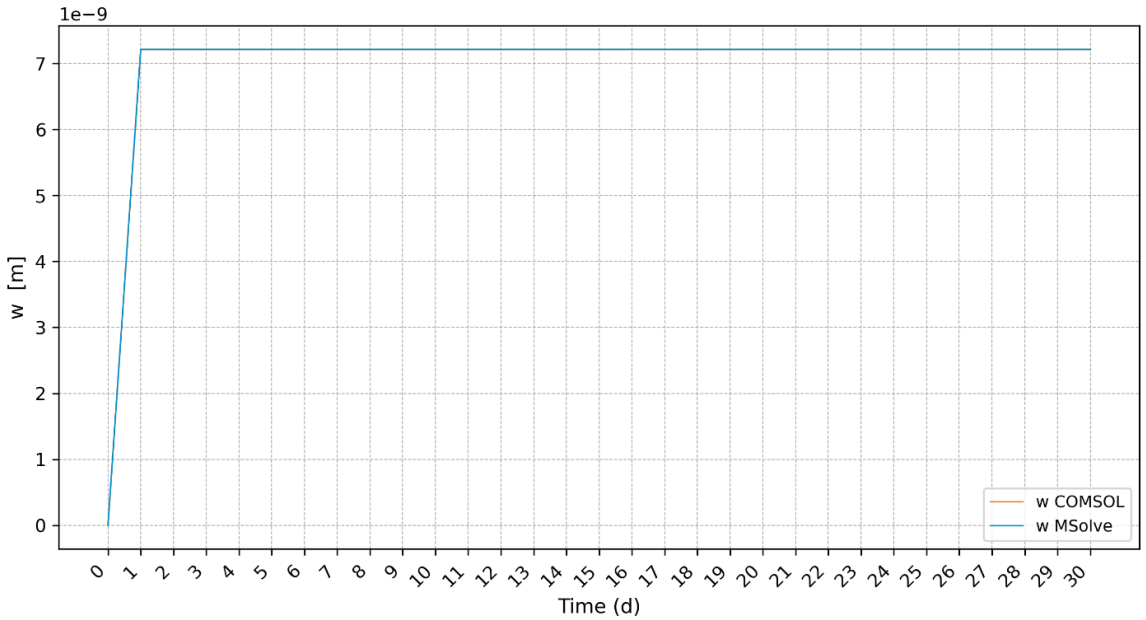

Figure 9:Solid Displacement at z-Direction at x,y,z=2.8E-4,2.8E-4,2.8E-4

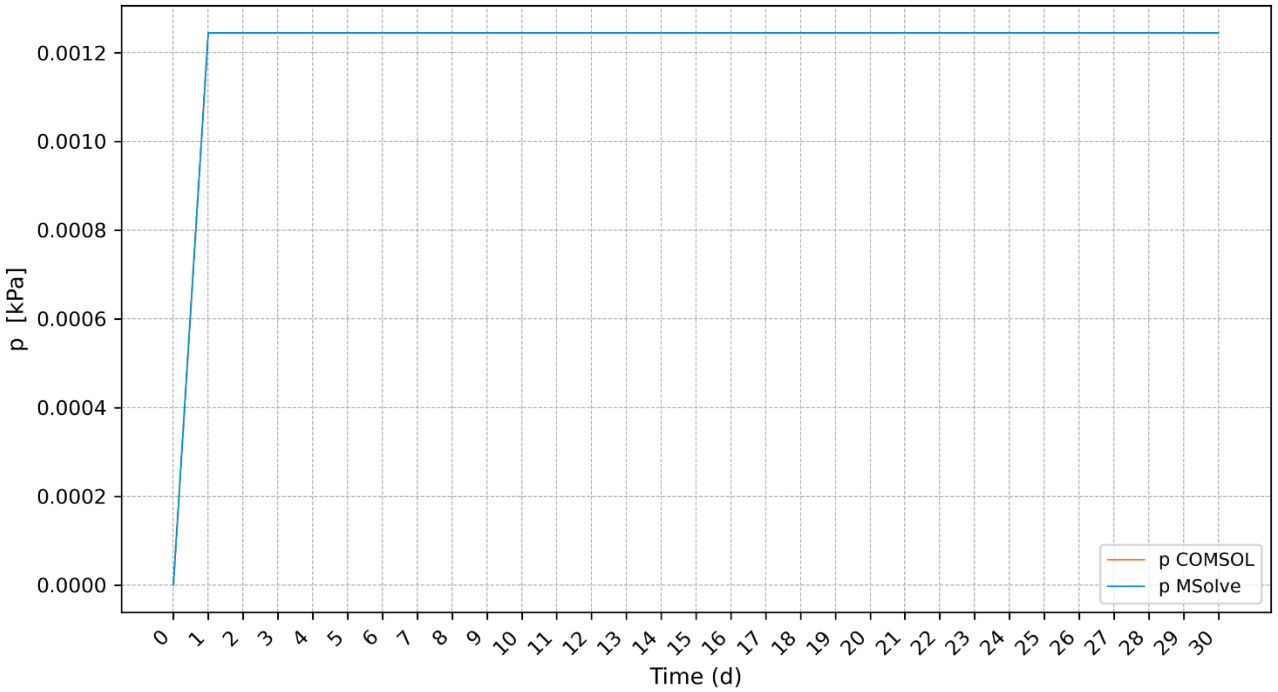

Figure 10: Fluid phase pressure at x,y,z=2.8E-4,2.8E-4,2.8E-4

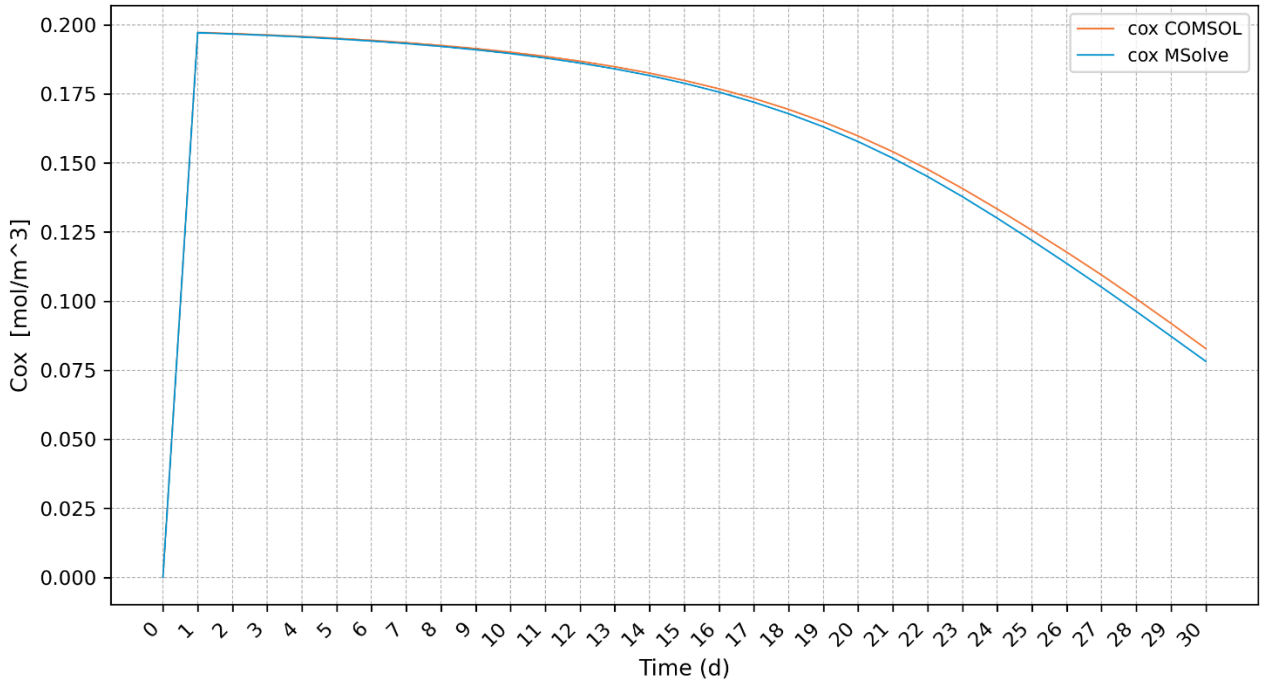

Figure 11: Oxygen Concentration at x,y,z=2.8E-4,2.8E-4,2.8E-4

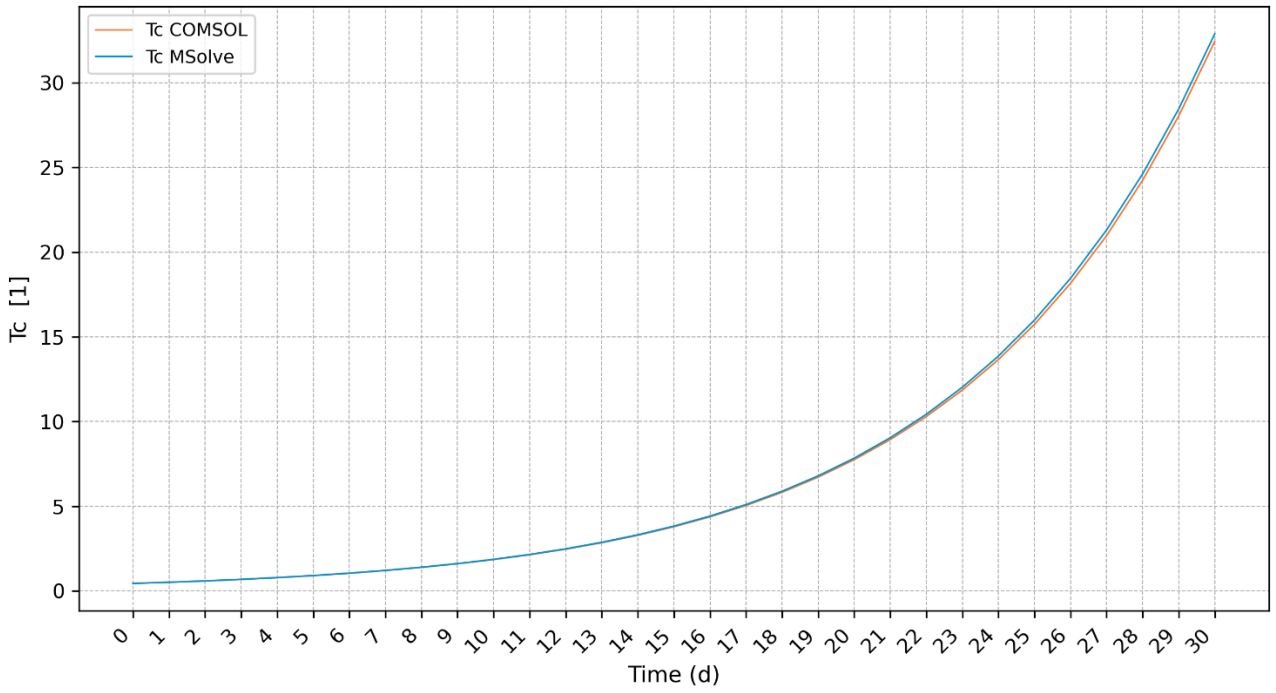

Figure 12: Cancer Cell population at x,y,z=2.8E-4,2.8E-4,2.8E-4

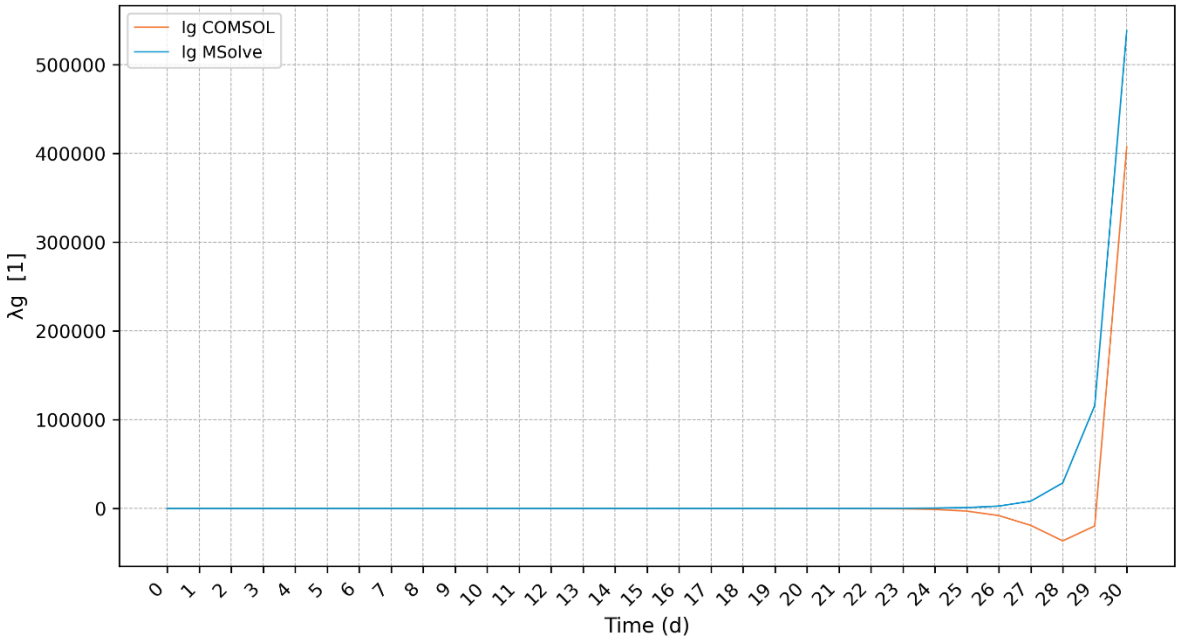

Figure 13: Growth Stretch Ratio t x,y,z=2.8E-4,2.8E-4,2.8E-4

The comparison of the MSolve and COMSOL results are in perfect agreement in almost all variables. Cancer cell population and growth stretch ratio have an exponential temporal response for the selected node while the fluid phase pressure field and the solid displacements reach steady state in the first seconds of the analysis. The latter occurs due to the fact of the growth stretch ratio in the calculation of the elastic stain tensor is neglected, leading to non-temporally-varying displacement and pressure fields. Since the duration of this analysis is 30 days the intricate relationship between the oxygen concentration and the genesis of cancer cells is obvious. A steep increase in the population of the cancer cells is accompanied by a steep decrease in the oxygen concentration. The calculated response of the growth stretch ratio is in good agreement with the corresponding COMSOL solution, though the values have no physical meaning.

3.3 Porous Medium Validation

In this subsection the coupled, transient response of the solid and fluid phases is validated. The interactions between these two phases are dictated by the laws of porous media and the corresponding numerical solution is obtained by a single, non-symmetric linear system. The solid phase of the TME is described by a non-linear, hyper-elastic, neo-Hookean material that allows large displacement fields and large strain states and a elastic-linear material that allows finite strains. The effect of the growth is included in the calculations of F tensor. The results presented are the solid displacement in the z-direction and the pressure of the interstitial fluid.

Tumor Geometry Type	1/8 Sphere
Tumor Radius	4E-2 [m]
Host Geometry Type	Cube
Host Edge	1E-1 [m]
Number of Finite Elements	2815

Table 7Discrete Computational Domain Parameters

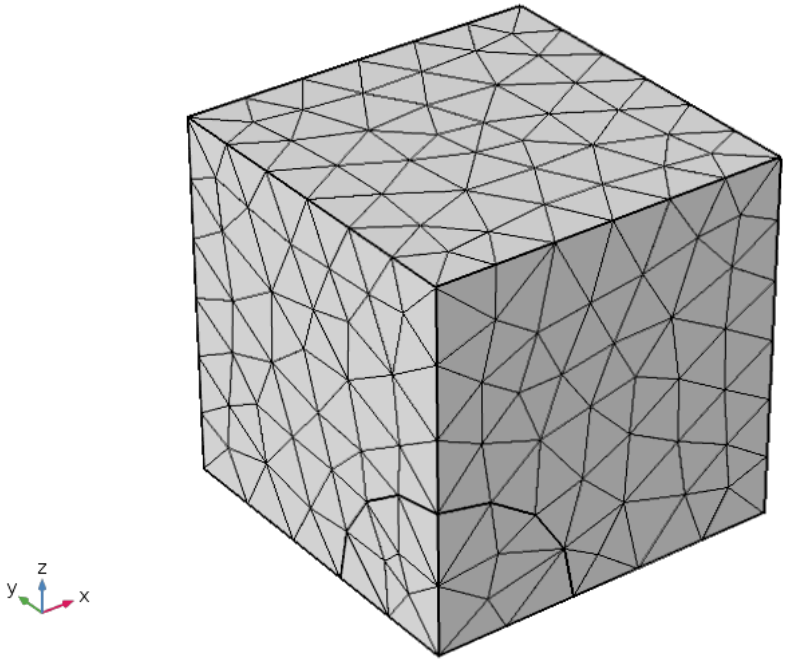

Figure 14:Finite element discretization mesh

Parameter	Tumor Domain Value	Host Domain Value	Units [SI]
μ	22.44	5	kPa
k	216.7	6.667	kPa
k_{th}	7.55E-11	7.55E-13	$m^2/kPas$
S_v	7E3	7E3	m^{-1}
p_v	4	4	kPa
p_l	0	0	kPa
Lp	2.794E-9	2.794E-9	$m^2/kPa\ s$
$L_{pl}S_{vl}$	3.75E-1	3.75E-1	$1\ /\ kPa\ s$

Figure 15: Computational Model Constants

3.3.1 Hyper-elastic Solid Phase

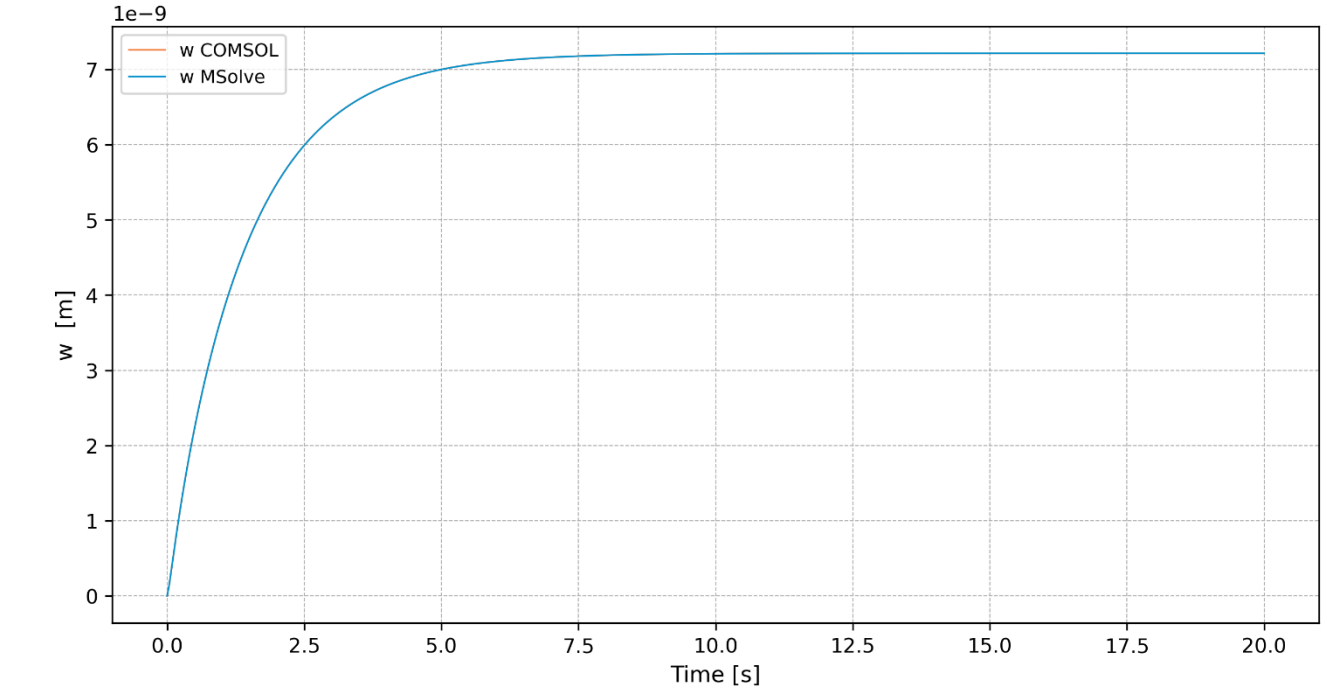

Figure 16: Solid Displacement at z-Direction at x,y,z=2.5E-2,2.5E-2,2.5E-2

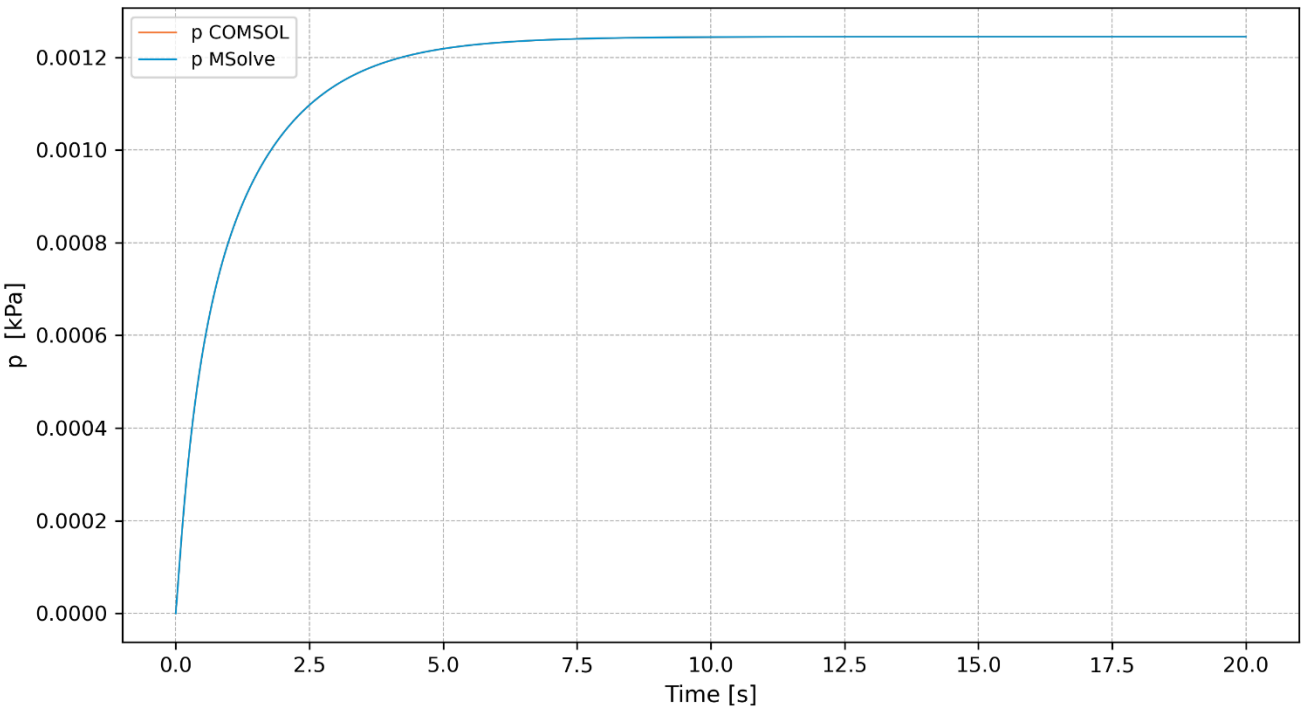

Figure 17: Solid Displacement at z-Direction at x,y,z=2.5E-2,2.5E-2,2.5E-2

The MSolve results for the coupled porous medium equation with hyperelastic solid phase material law are in perfect agreement with COMSOL. Since there is no external strains from the growth stretch ratio the two equations reach at a steady state response during the first 10 seconds of the analysis. The transient response occurs due to the contribution of the fluid phase pressure in the solid phase stress state and the contribution of the divergence of the solid phase velocity as a source in the pressure equation.

3.3.2 Small Strain Solid Phase

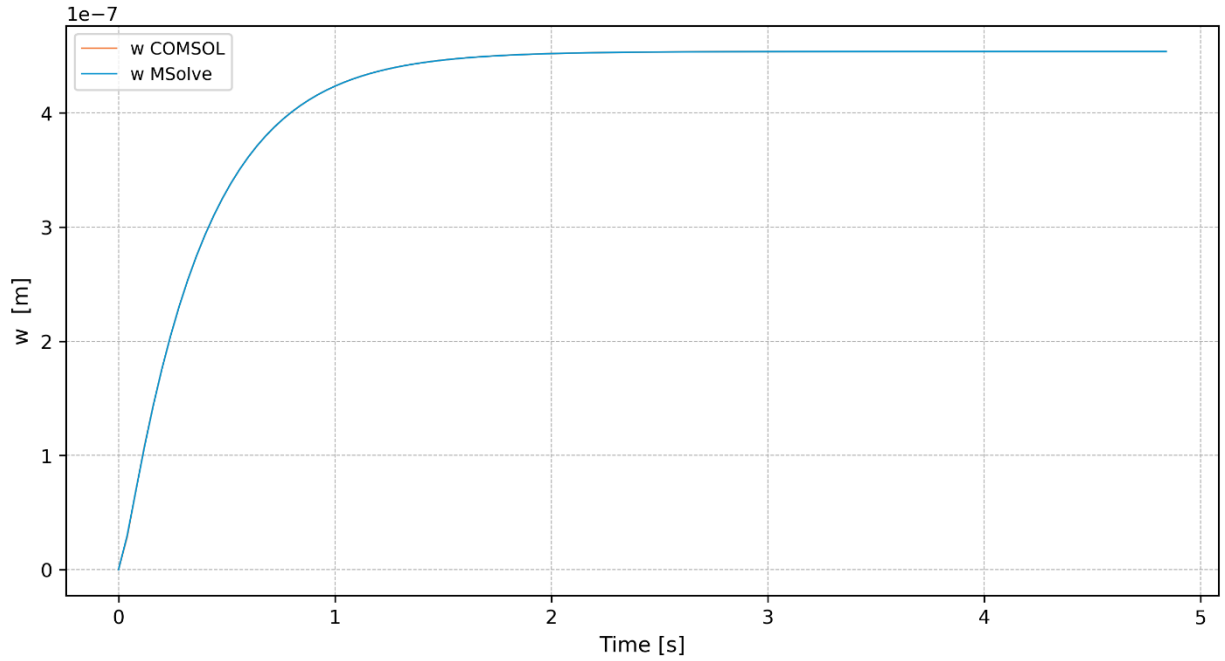

Figure 18: Solid Displacement at z-Direction at x,y,z=2.5E-2,2.5E-2,2.5E-2

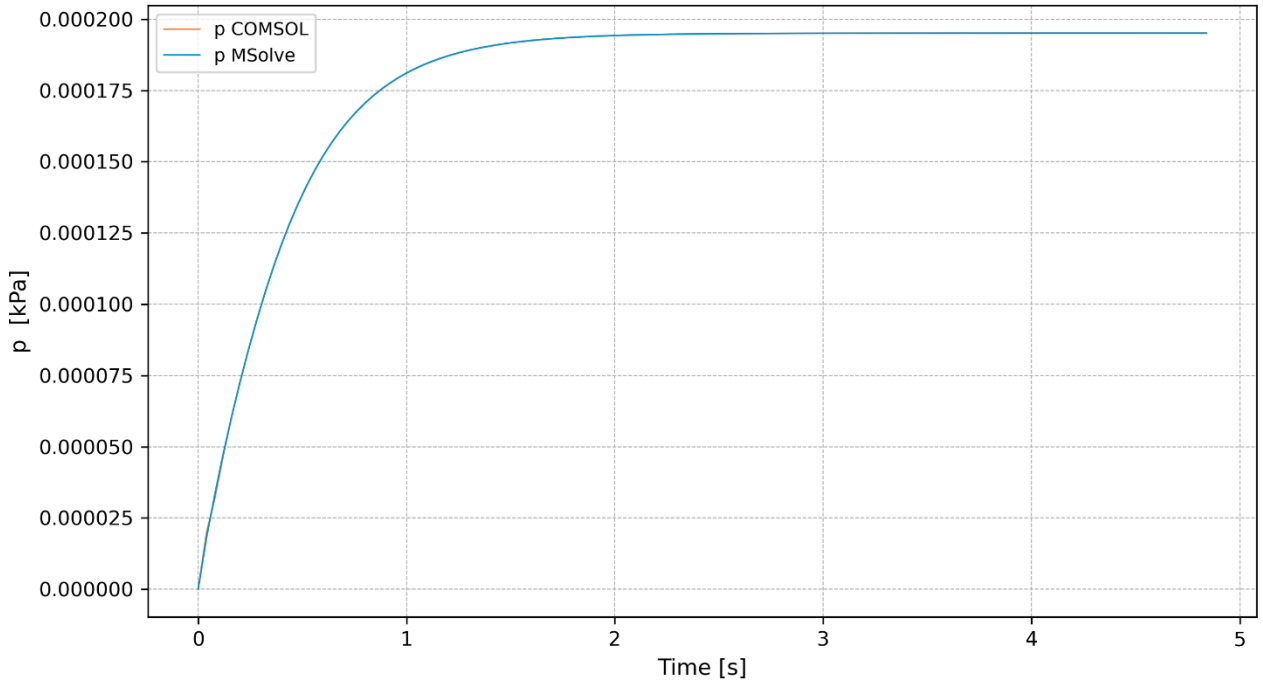

Figure 19: Fluid phase pressure at x,y,z=2.5E-2,2.5E-2,2.5E-2

The MSolve results for the coupled porous medium equation with linear and elastic solid phase constitutive law are in perfect agreement with the corresponding COMSOL solution. The contribution of the the growth stretch ratio is neglected the two equations reach at a steady state response during the first 2 seconds of the analysis. The transient response occurs due to the contribution of the fluid phase pressure in the solid phase stress state and the contribution of the divergence of the solid phase velocity as a source in the pressure equation.

3.4 Oxygen Concentration Equation Validation

In this subsection the response of the oxygen concentration in the tumor region is presented. For validation purposes the diffusivity and the convective stream velocity are fluctuated by some orders of magnitude. The source of the tumor region is non-linear and the cases considered are with initial conditions equal to 0 and 0.2.

Tumor Geometry Type	Cube
Tumor Edge	1E-1 [m]
Number of Nodes	490
Finite Element Type	Tetrahedra
Number of Finite Elements	2185

Table 8Discrete Computational Domain Parameters

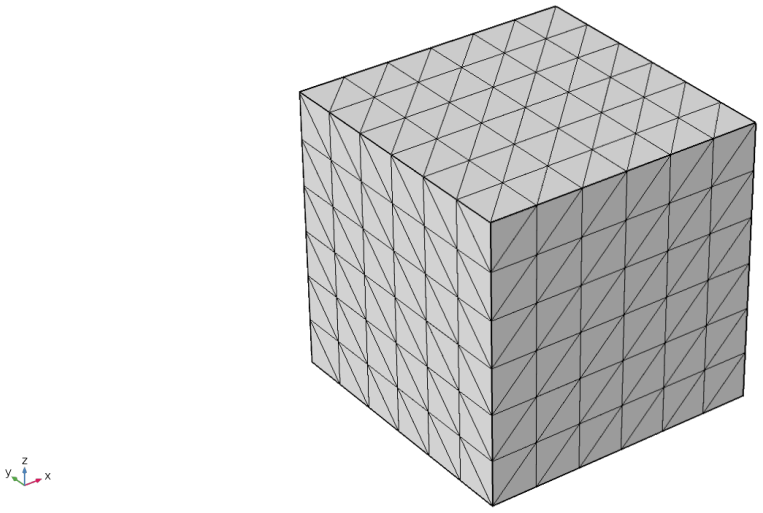

Figure 20: Finite element discretization mesh

Parameter	Tumor Domain Value	Units [SI]
S_v	7E3	m^{-1}
c_{iox}	0.2	mol/m^3
D_{ox}	1.79E-4	m^3/s
P_{er}	3.55E-4	m/s
A_{ox}	2.55E-2	$mol/m^3 s$
k_{ox}	4.64E-3	$mol/m^3 s$
k_1	1.74E-6	
k_2	8.3E-3	mol/m^3
$\boldsymbol{v_f}$	2.32	m/s

Table 9:Computational Model Constants

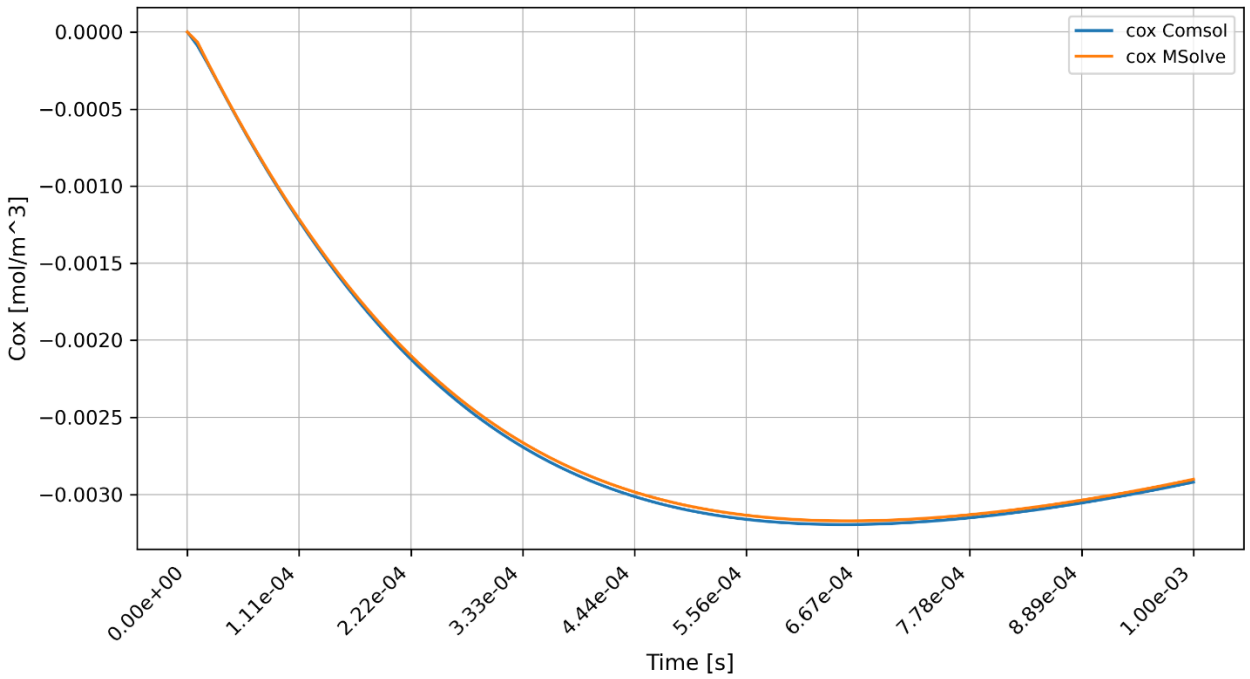

Figure 21:Oxygen Concentration with c_ox^0=0 at x,y,z=2.8E-4,2.8E-4,2.8E-4

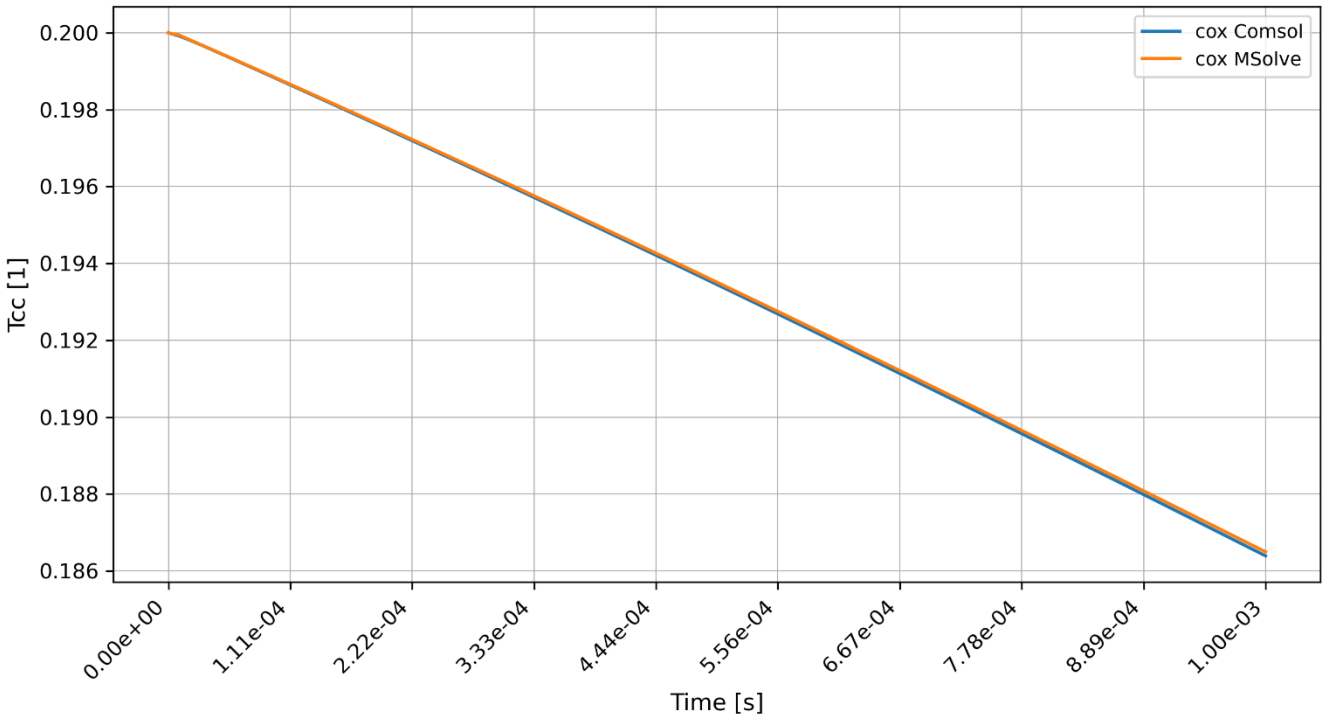

Figure 22:Oxygen Concentration with c_ox^0=0.2 at x,y,z=2.8E-4,2.8E-4,2.8E-4

The MSolve results of the oxygen concentration equation of the tumor region, for both initial conditions are in perfect agreement with COMSOL. The response for zero initial conditions has a non-linear decline while the response for initial conditions equal to 0.2 declines in a linear fashion.

3.5 Cancer Cell Population Validation

In this subsection the population of cancer cells in the tumor region is examined. For validation purposes the the source term is ignored and the problem is deduced to a transient convective flow.

Tumor Geometry Type	Cube
Tumor Edge	1E-1 [m]
Number of Nodes	490
Finite Element Type	Tetrahedra
Number of Finite Elements	2185

Table 10: : Discrete Computational Domain Parameters

Parameter	Tumor Domain Value	Units [SI]
k_1	0	-
k_2	8.3E-3	mol/m^3
v_s	-5E3 t x	m/s

Table 11: Computational Model Constants

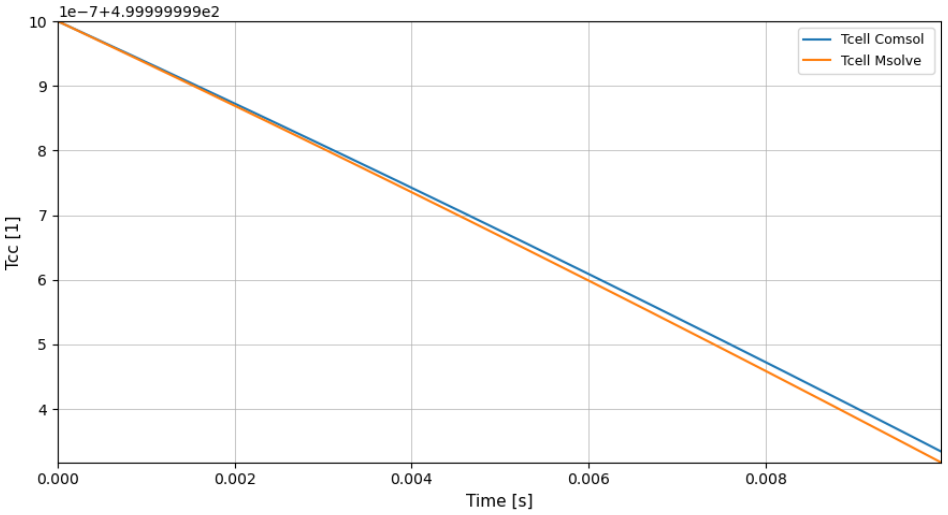

Figure 23 Cancer Cell Population at $\{x, y, z\} = \{0,\ 7.12e-02,\ 7.12e-02\}$

The comparison of the MSolve and COMSOL results for the cancer cell population are in perfect agreement. It should be noted that the standalone equation is solved for validation purposes and the applied velocity field as well as the results have no physical meaning.

4. Algorithmic implementation in the MSolve software

The implementation of the coupled Multiphysics Solver in MSolve software resulting to the DCOMEX-BIO protptype consists of 4 main building blocks that are described in detail in the DCOMEX-BIO prototype software module report in D7.1.