DRIVEN *Workshop*

Luxembourg, 11-12 September 2019

Constitutive modelling of healthy & pathologic biological tissues

An emerging physics-based theory and the automatic data assimilation perspective for predictive patient-specific numerical simulations

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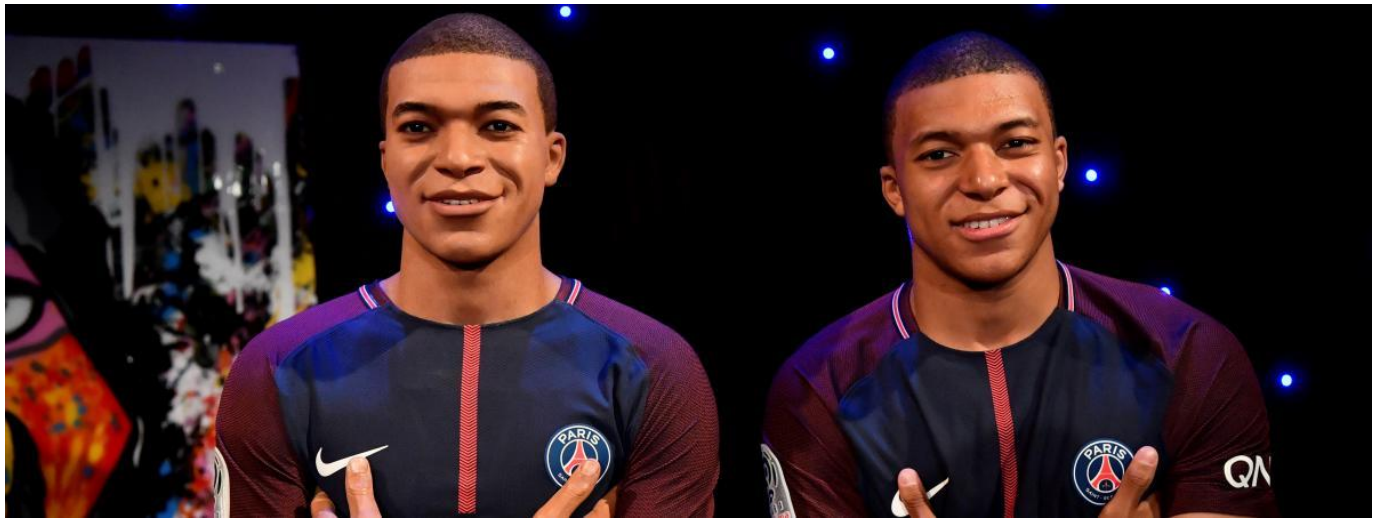
«Digital Twin: Simple, but detailed» (C. O'Connor, IBM – source *YOUTUBE*)



The Digital Twin is not like a wax statue!

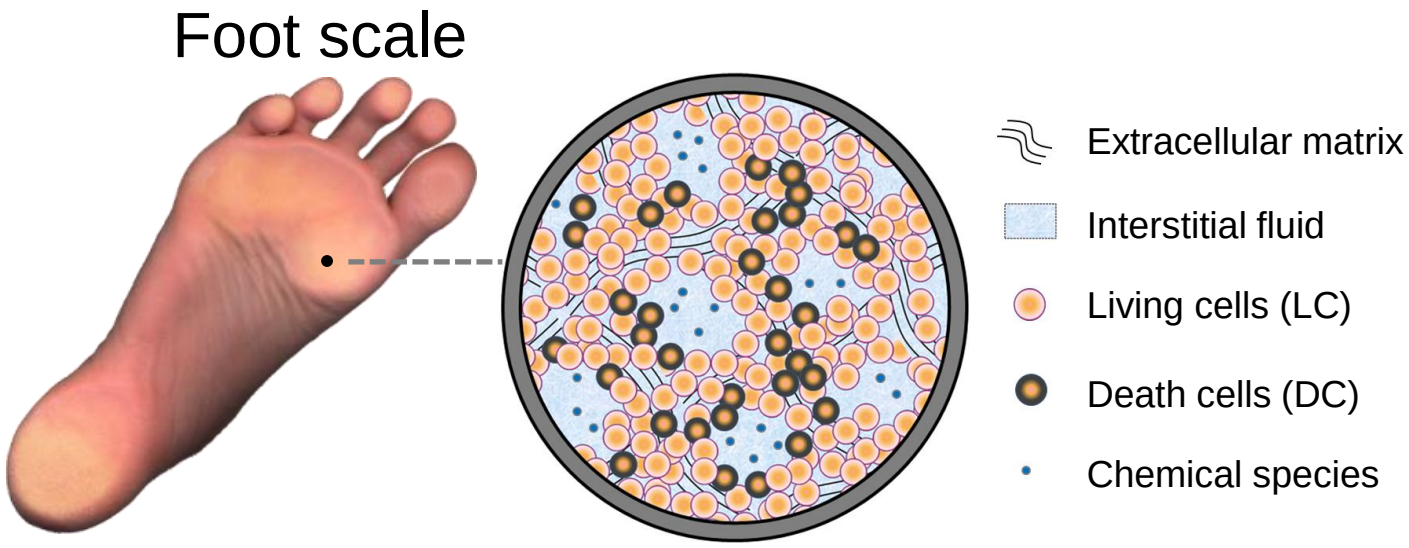
DT must:

1) look like the original system …but also
2) **behave like the original system**

2) is a very challenging task in **biological tissues mechanics** due to **multiscale & multiphase nature of tissues** and **coupling between biology and mechanics**

Healthy & Pathologic biological tissues

Multiphase Modeling: plantar tissue case



$$\varepsilon^f + \varepsilon^s = 1$$

Interstitial fluid

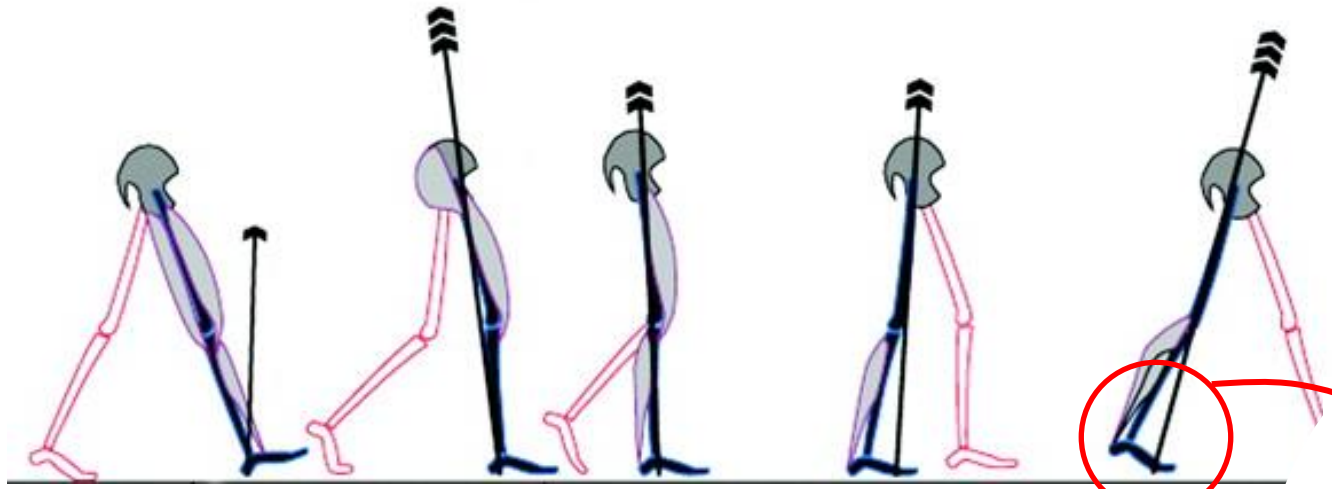
Tissue cells* and associate ECM

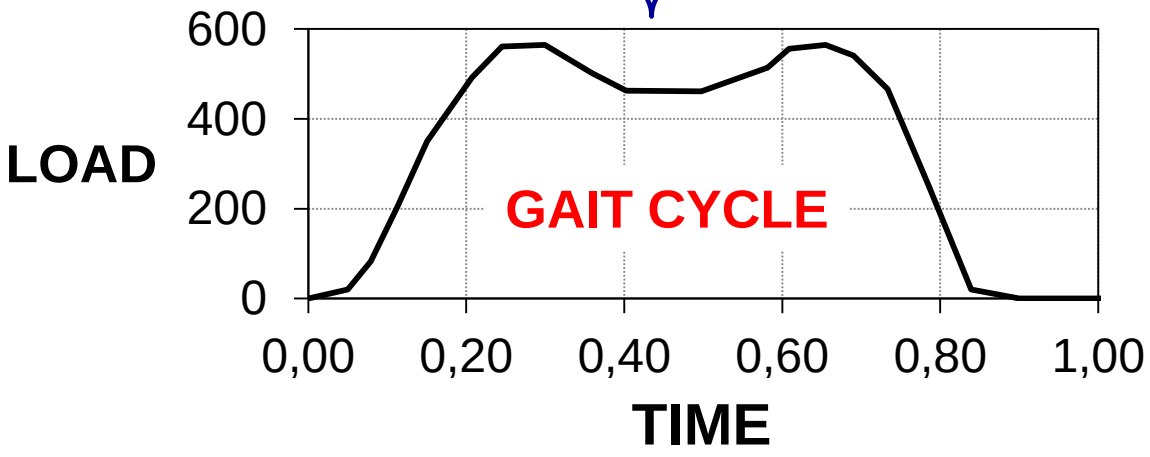
*healthy and death ones

A two-phase model of plantar tissue: a step toward prediction of diabetic foot ulceration
Sciumè *et al.* (2014) – *INT J NUMER METH BIO*

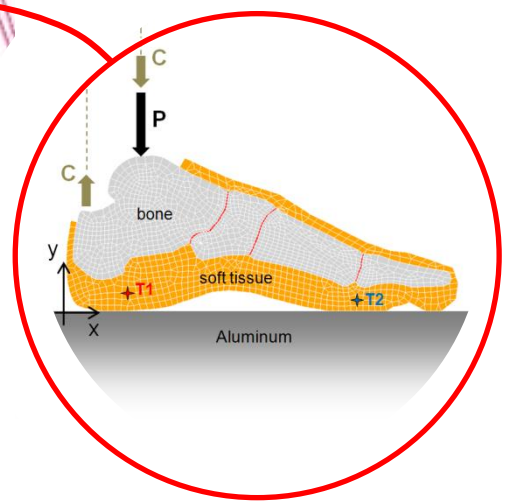
Time-dependent simulation of 4 gait cycles

Numerical simulation **from the beginning to the end of the mid-stance phase**

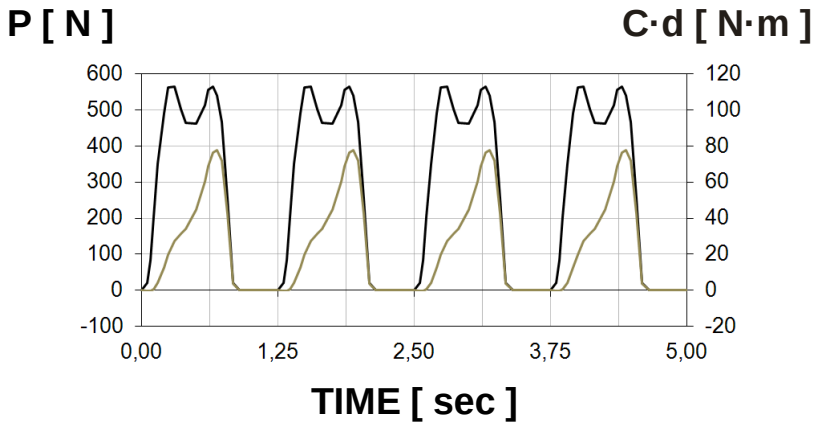


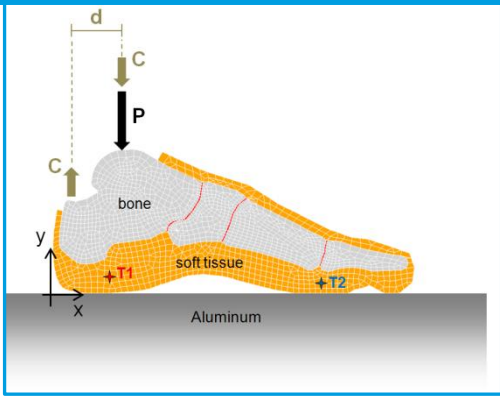


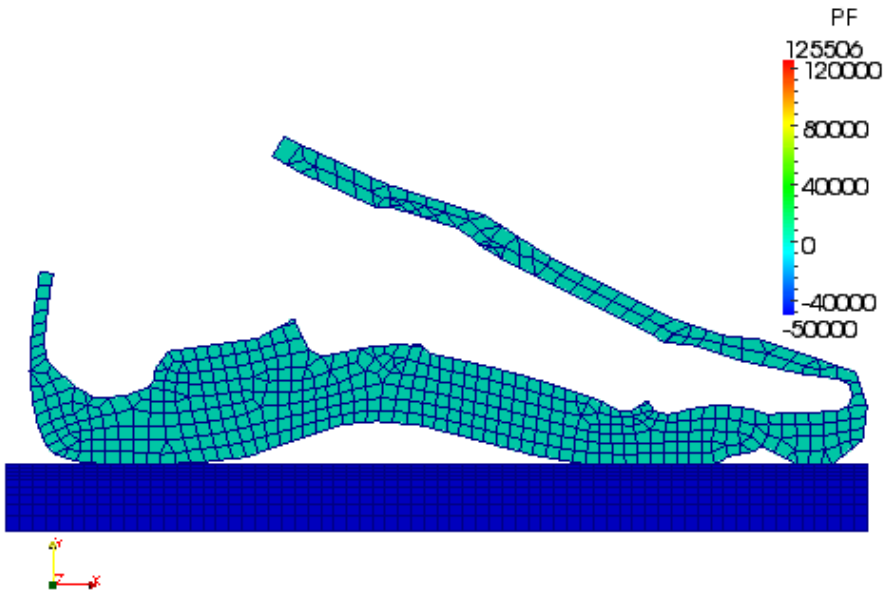
Time dependent load applied to the foot

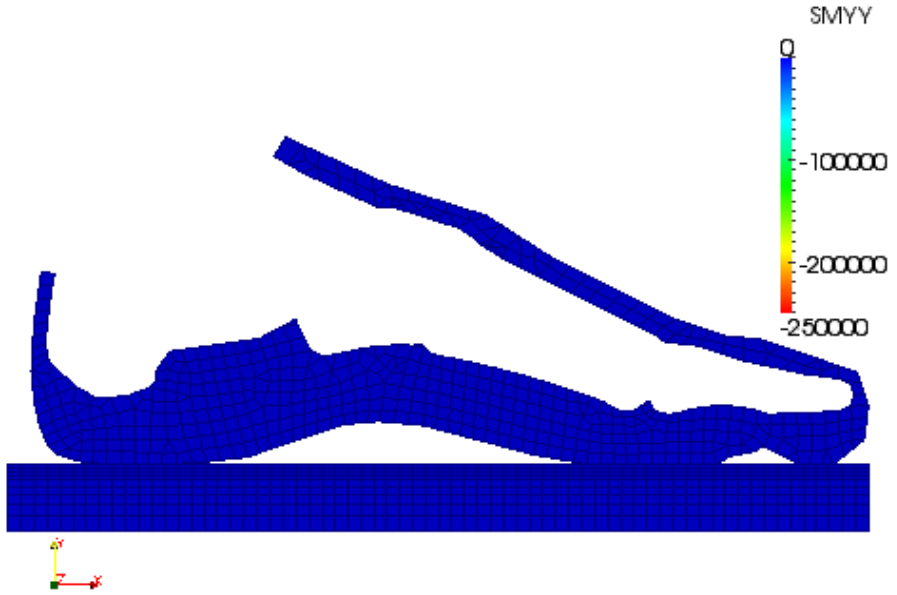


Time-dependent simulation of 4 gait cycles







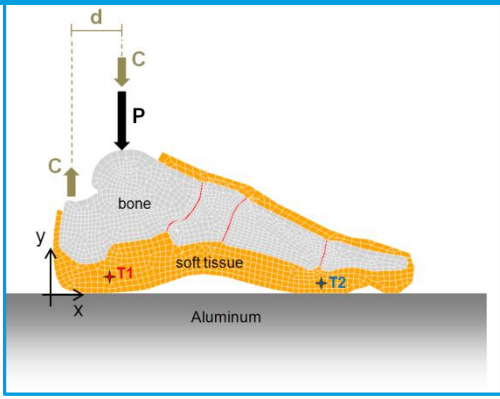


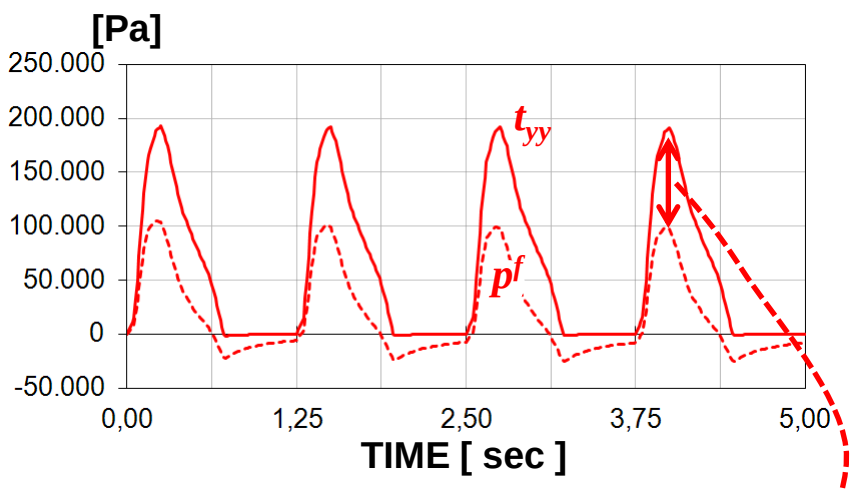
Cast3M

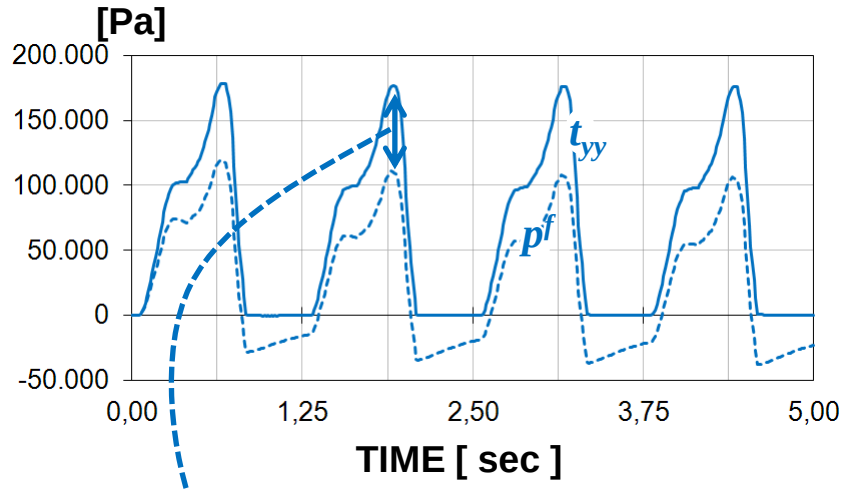
www-cast3m.cea.fr

Time-dependent simulation of 4 gait cycles

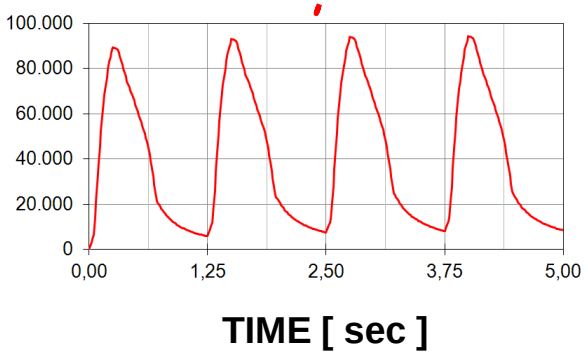
Evolution with time of the total stress t_{yy} and of the interstitial fluid pressure p^f in the points **T1** and **T2** represented in the insert.

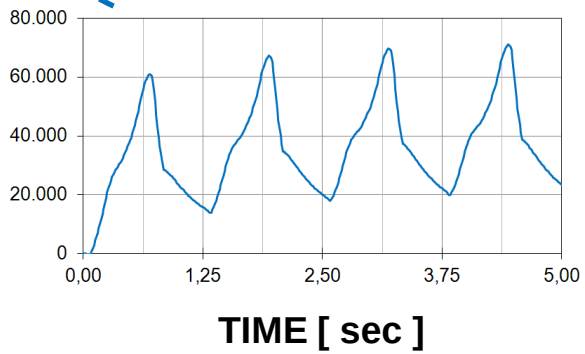






"Effective stress"



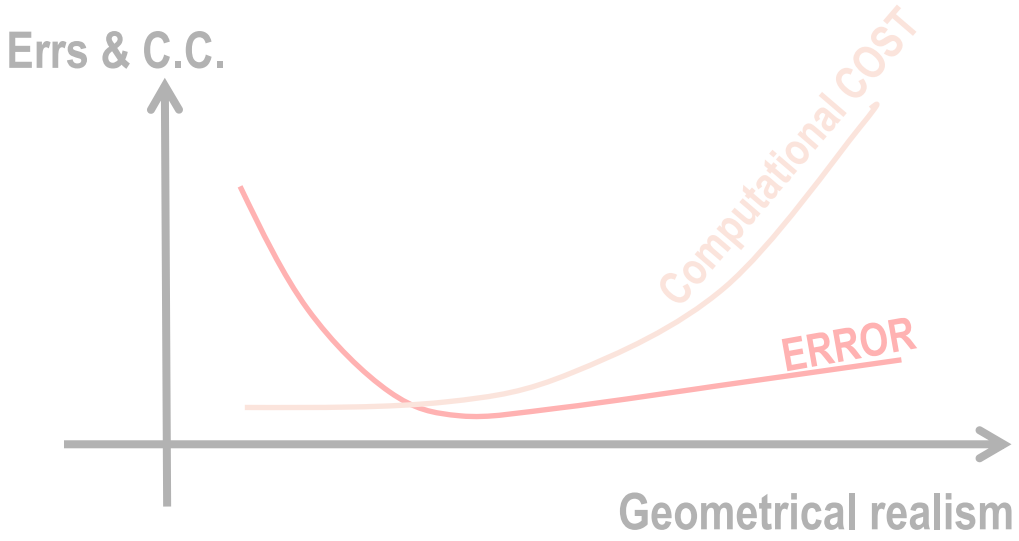


- Load is transferred from the IF to the solid scaffold
- Shock absorption capability comes from fluid-solid interaction

Plantar tissue modeling strategies

1. Improve geometrical realism ("look like")

The increase of model realism is not fully repaid by a corresponding increase in the prediction capability.



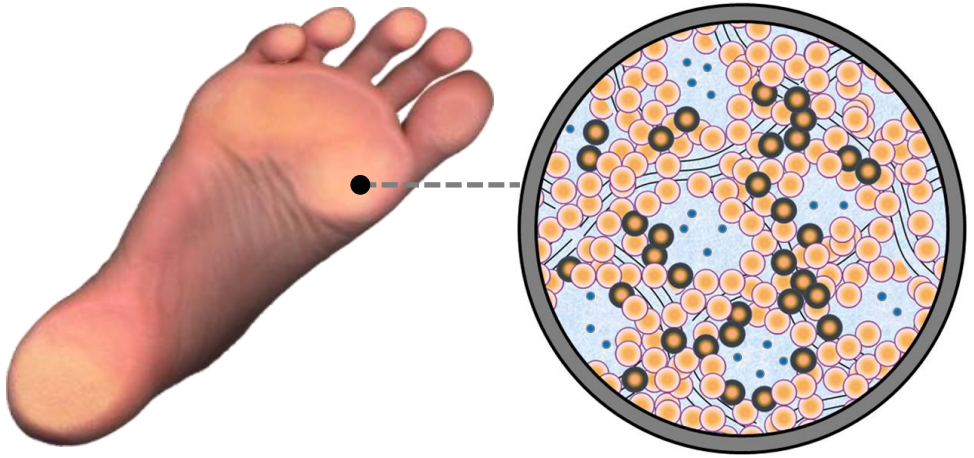
Models commonly assume an **hyperelastic behavior**

TIME becomes a dummy variable:

Modeling a gait cycle of 1 second or 1 year provides exactly the same results!

2. Improve behavior realism ("behave like")

Tissue modeled as a bi-phasic system (solid+ fluid).
This formulation allows to model the experimentally observed tissue viscoelastic behavior



TIME (*e.g.* duration of the gait cycle) **impacts tissue stress and strain!**

Porous Media Mechanics

Introduction and general theoretical concepts

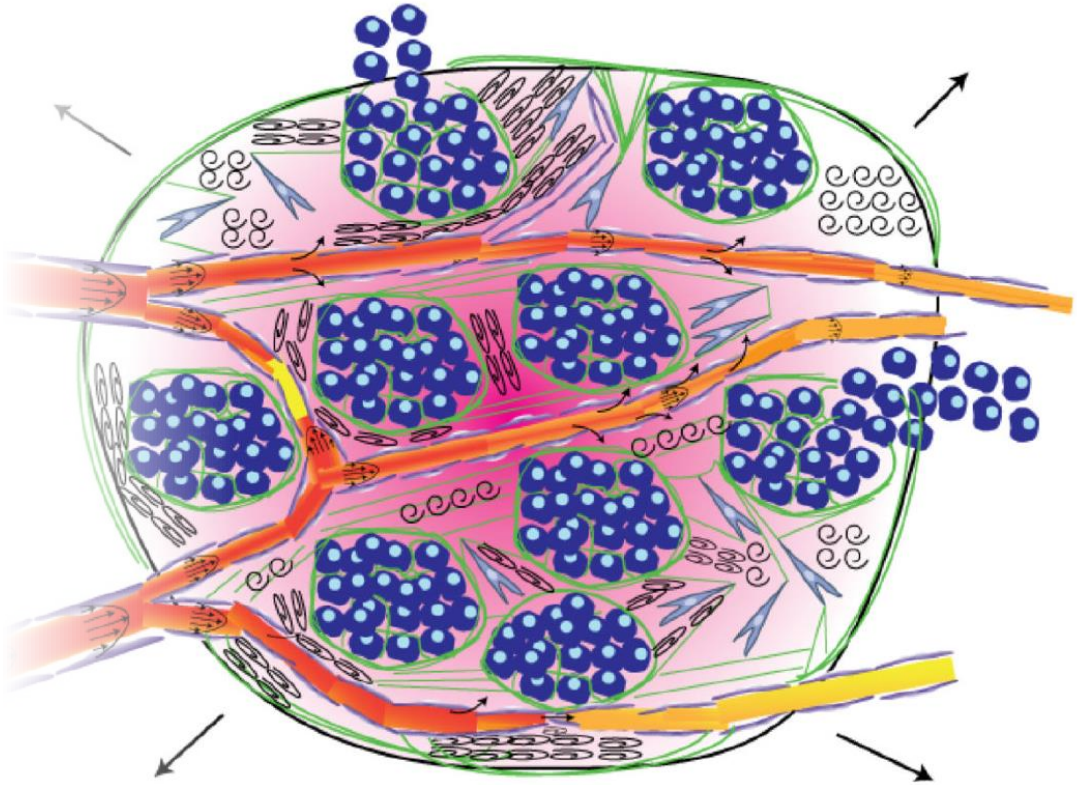
Porous Medium Systems

Some examples

wood, gravel, concrete, biological tissues, etc..

Main features

- **Multiphase systems** (phases may consist of several species);
- **Interactions between phases** (mechanical, chemical, etc.);
- **Multiphase flow** coupled with temperature;
- **Mass exchanges** between phases and/or between species;
- **Micro-scale physics** impacts strongly macroscopic behavior.



"The role of mechanical forces in tumor growth and therapy"
Jain, Martin, Stylianopoulos – Annu Rev Biomed Eng. 2014

Tumor growth modeling

A hierarchical multi-compartment porous medium model for vascularized tumors

Phases definition & preliminary hypotheses

$$\varepsilon^s + \varepsilon^b + \varepsilon^t + \varepsilon^h + \varepsilon^l = 1$$

Vascular porosity

ε: Extra-vascular porosity

- Vascular porosity ε^b **is always saturated by blood;**
- **Saturation degree is defined for extra-vascular porosity only** as: $S^\beta = \varepsilon^\beta / \varepsilon \qquad (\beta = t, h, l)$

Porosity, and saturation constraint:

$$\varepsilon = 1 - \varepsilon^b - \varepsilon^s$$

$$S^l + S^t + S^h = 1$$

Solid scaffold:

- ECM fibers (dominant species with structural function);
- Vessel walls (they assure immiscibility between blood and other fluid phases).

Multiphase System

5 PHASES ARE CONSIDERED

1 SOLID EXTRA-CELLULAR MATRIX, (s)

Permeated by

4 IMMISCIBLE FLUID PHASES:

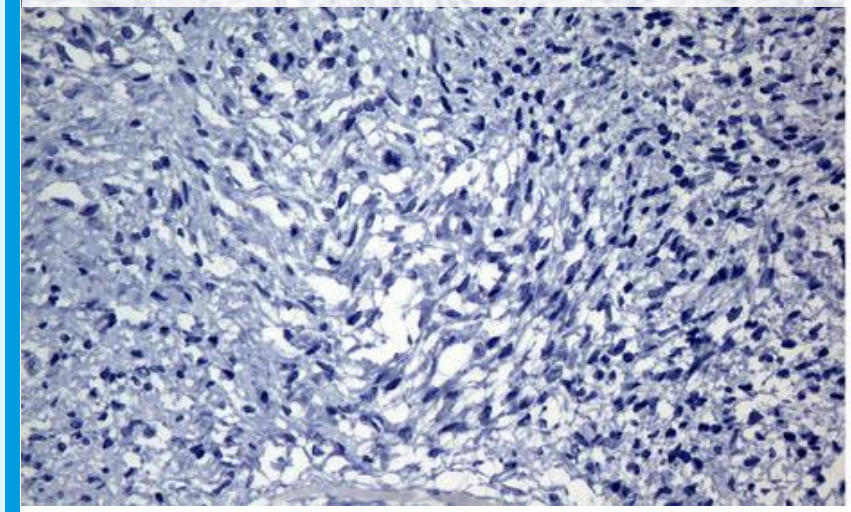
- Tumor cells, (t), (tN + tL)
- Host cells, (h)
- Interstitial fluid, (l)
- Blood (b)

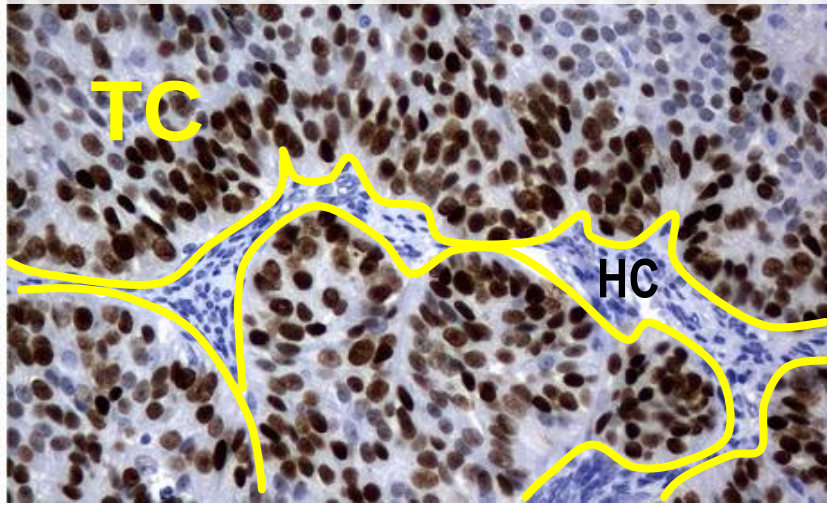
$$\varepsilon^s + \varepsilon^b + \varepsilon^t + \varepsilon^h + \varepsilon^l = 1$$

ε: Extra-vascular porosity

ε^b : vascular porosity

Taken from ORIGENE.com – Immunohistochemical staining of paraffin-embedded Human **normal ovary tissue (left)** and **ovary cancer tissue (rigth)**





Mass conservation eqs of S, TC, HC, IF, B:

(introducing mat. derivatives with respect of the moving solid phase)

TCs growth

ECh production

Vessels formation

$$\frac{D^s}{Dt}\left(\rho^s\varepsilon^s\right)+\rho^s\varepsilon^s\nabla\cdot\mathbf{v}^{\bar{s}} = \underset{ang}{M}^{ECh\to s} \qquad [ma.s]$$

$$\frac{D^s}{Dt}\left(\rho^t\varepsilon S^t\right)+\nabla\cdot\left(\rho^t\varepsilon S^t\mathbf{v}^{\overline{ts}}\right)+\rho^t\varepsilon S^t\nabla\cdot\mathbf{v}^{\bar{s}} = \underset{growth}{M}^{l\to t} \qquad [ma.t]$$

$$\frac{D^s}{Dt}\left(\rho^h\varepsilon S^h\right)+\nabla\cdot\left(\rho^h\varepsilon S^h\mathbf{v}^{\overline{hs}}\right)+\rho^h\varepsilon S^h\nabla\cdot\mathbf{v}^{\bar{s}} = M^{l\to ECh} - \underset{ang}{M}^{ECh\to s} \qquad [ma.h]$$

$$\frac{D^s}{Dt}\left(\rho^l\varepsilon S^l\right)+\nabla\cdot\left(\rho^l\varepsilon S^l\mathbf{v}^{\overline{ls}}\right)+\rho^l\varepsilon S^l\nabla\cdot\mathbf{v}^{\bar{s}} = -\underset{growth}{M}^{l\to t} - M^{l\to ECh} \qquad [ma.l]$$

$$\frac{D^s}{Dt}\left(\rho^b\varepsilon^b\right)+\nabla\cdot\left(\rho^b\varepsilon^b\mathbf{v}^{\overline{bs}}\right)+\rho^b\varepsilon^b\nabla\cdot\mathbf{v}^{\bar{s}} = 0 \qquad [ma.b]$$

Mass c. eqs of species in TC, HC & IF (5 scalar independent eqs)

Mass c. eqs for necrotic TC and ω^{it} constraint (2 scalar independent eqs)

$$\frac{\mathrm{D}^s\left(\rho^t \varepsilon S^t \omega^{\overline{Nt}}\right)}{\mathrm{D}t} + \nabla\cdot\left(\rho^t \varepsilon S^t \omega^{\overline{Nt}} \mathbf{v}^{\overline{ts}}\right) + \rho^t \varepsilon S^t \omega^{\overline{Nt}} \nabla\cdot\mathbf{v}^{\overline{s}} - \varepsilon^t r^{Nt} = 0 \qquad \omega^{\overline{Lt}} = 1 - \omega^{\overline{Nt}}$$

Mass c. eqs of EC species in HC (1 scalar independent eqn)

$$\frac{\mathrm{D}^s\left(\rho^h \varepsilon^h \omega^{\overline{ECh}}\right)}{\mathrm{D}t} + \nabla\cdot\left(\rho^h \varepsilon^h \omega^{\overline{ECh}} \mathbf{u}^{\overline{\overline{ECh}}}\right) + \nabla\cdot\left(\rho^h \varepsilon^h \omega^{\overline{ECh}} \mathbf{v}^{\overline{hs}}\right) + \rho^h \varepsilon^h \omega^{\overline{ECh}} \nabla\cdot\mathbf{v}^{\overline{s}} = \overset{l\to ECh}{M} - \underset{ang}{\overset{ECh\to s}{M}}$$

Mass c. eqs OXY and TAF species in IF (2 scalar independent eqs)

$$\frac{\mathrm{D}^s\left(\rho^l \varepsilon^l \omega^{\overline{OXYl}}\right)}{\mathrm{D}t} + \nabla\cdot\left(\rho^l \varepsilon^l \omega^{\overline{OXYl}} \mathbf{v}^{\overline{ls}}\right) + \nabla\cdot\left(\rho^l \varepsilon^l \omega^{\overline{OXYl}} \mathbf{u}^{\overline{\overline{OXYl}}}\right) + \rho^l \varepsilon^l \omega^{\overline{OXYl}} \nabla\cdot\mathbf{v}^{\overline{s}} = \overset{b\to OXYl}{M} - \overset{OXYl\to t}{M}$$

$$\frac{\mathrm{D}^s\left(\rho^l \varepsilon^l \omega^{\overline{TAFl}}\right)}{\mathrm{D}t} + \nabla\cdot\left(\rho^l \varepsilon^l \omega^{\overline{TAFl}} \mathbf{v}^{\overline{ls}}\right) + \nabla\cdot\left(\rho^l \varepsilon^l \omega^{\overline{TAFl}} \mathbf{u}^{\overline{\overline{OXYl}}}\right) + \rho^l \varepsilon^l \omega^{\overline{TAFl}} \nabla\cdot\mathbf{v}^{\overline{s}} = \overset{t\to TAFl}{M}$$

Momentum c. eqs for phases (15 scalar independent eqs)

Mom. c. eqn multiphase system (3 scalar independent eqs)

Summing **[mo.α]** over all phases gives the momentum equation of the whole multiphase system as (Summation allows eliminating momentum transfer terms $\overset{\kappa\to\alpha}{\mathbf{T}}$) :

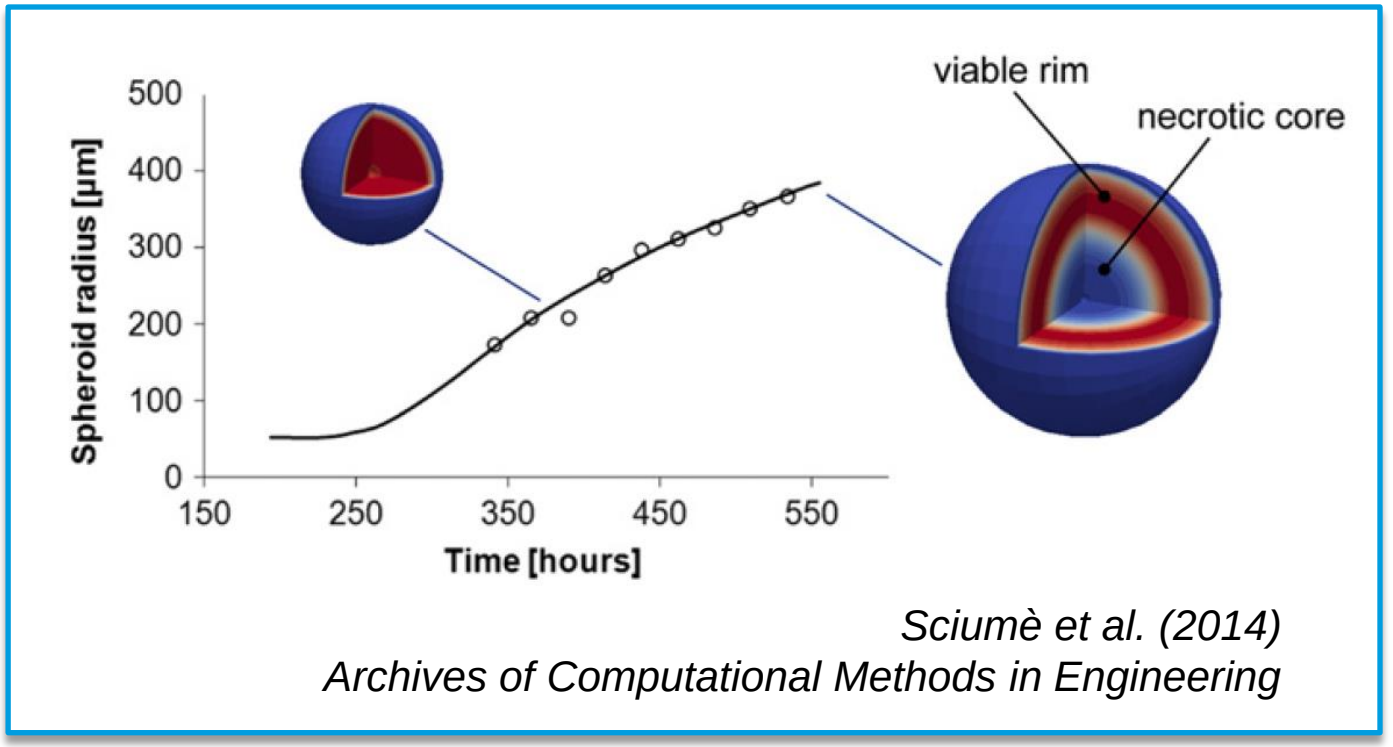
$$\nabla \cdot \bar{\bar{\mathbf{t}}}^{\mathrm{T}} = 0 \qquad [\mathrm{mo}.system]$$

where $\bar{\bar{\mathbf{t}}}^{\mathrm{T}}$ is the total stress tensor: $\bar{\bar{\mathbf{t}}}^{\mathrm{T}} = \varepsilon^s \bar{\bar{\mathbf{t}}}^s - \sum_{f=t,h,l,b} \varepsilon^f p^f \mathbf{1}$

Mom. c. eqs for fluid phases (12 scalar independent eqs)

$$\varepsilon^f \nabla p^f + \mathbf{R}^f \cdot (\bar{\mathbf{v}}^f - \bar{\mathbf{v}}^s) = 0 \qquad \text{with} \quad f = t, h, l, b \qquad [\mathrm{mo\text{-}a}.f]$$

Resistance tensor



Sciumè et al. (2014)
Archives of Computational Methods in Engineering

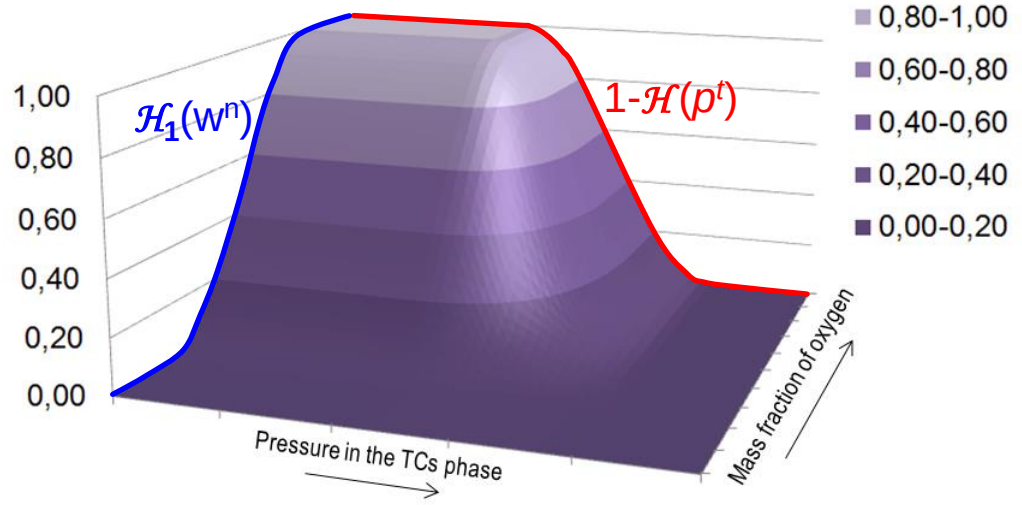
Avascular tumor growth

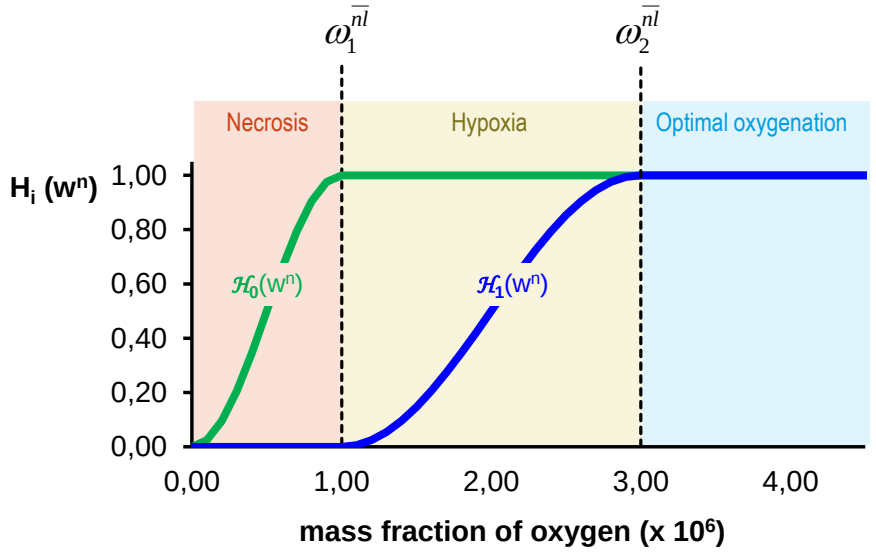
- **Multicellular tumor spheroid *in vitro***
- **Tumor growth in proximity of two blood vessels**

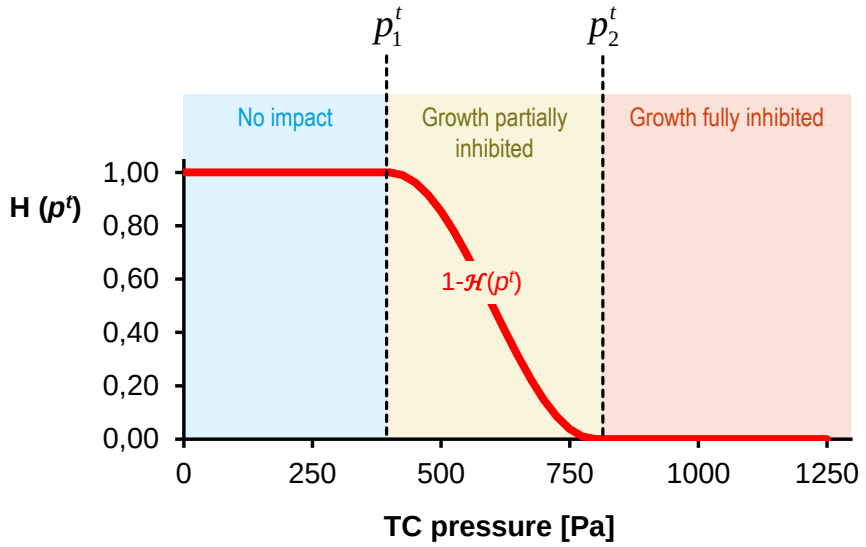
Growth mass exchange term

$$\frac{\mathrm{D}^s}{\mathrm{D}t}\left(\rho^t \varepsilon S^t\right) + \nabla\cdot\left(\rho^t \varepsilon S^t \mathbf{v}^{\bar{ts}}\right) + \rho^t \varepsilon S^t \nabla\cdot\mathbf{v}^{\bar{s}} = \underset{\text{TC growth}}{\overset{l\to t}{M}}$$

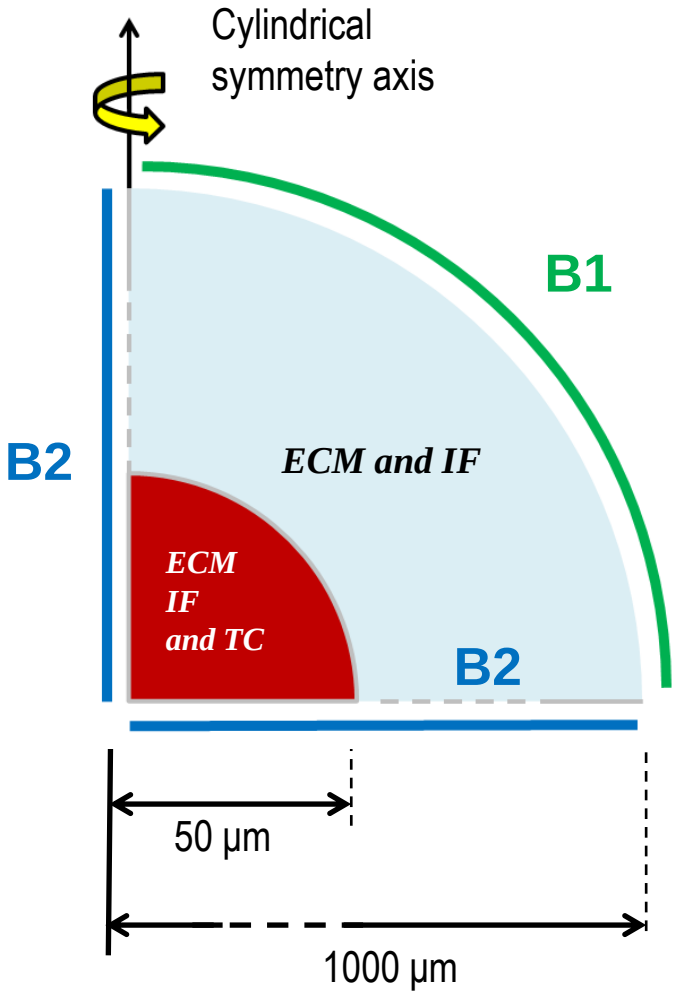
$$\underset{\text{TC growth}}{\overset{l\to t}{M}} = \gamma_g^t \mathcal{H}_1\left(\omega^{\bar{nl}}\right)\left[1-\mathcal{H}\left(p^t\right)\right](1-\omega^{N\bar{t}})\varepsilon^t$$







Multicellular Tumor Spheroid (MTS) *in vitro*



Boundary 1

Type: Imposed values

$\omega^{\overline{nl}} = \omega^{\overline{nl}}_{env} = 7.0 \cdot 10^{-6}$ $\quad \varepsilon^{s} = 1 - \varepsilon = 0.05$

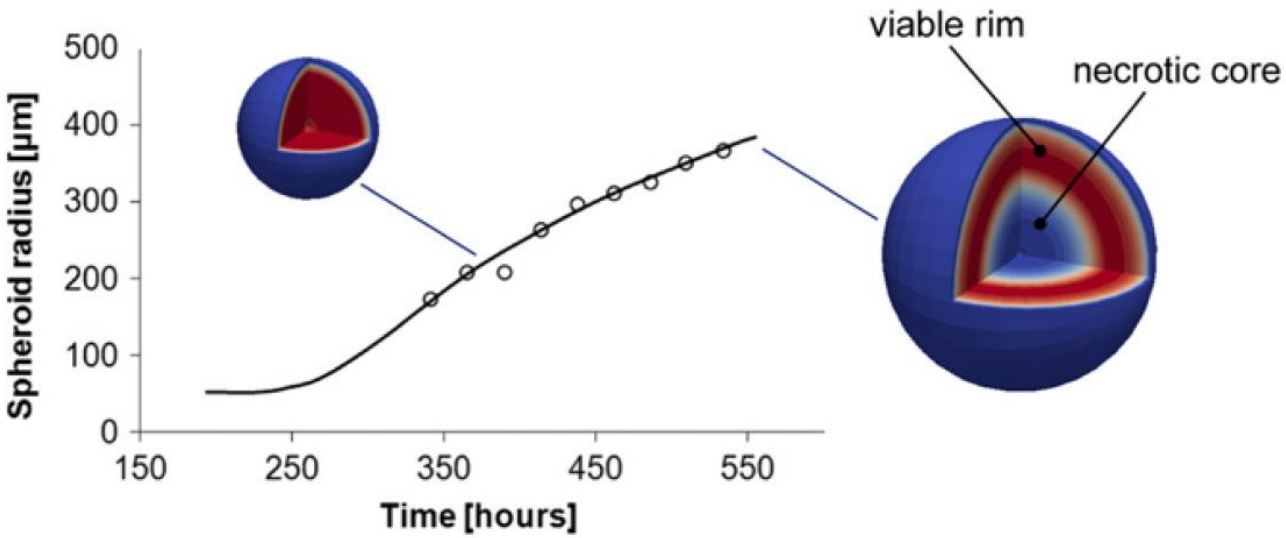
$\varepsilon^{h} = \varepsilon S^{h} = 0.00$ $\quad \varepsilon^{t} = \varepsilon S^{t} = 0.00$

$p^{l} = 0 \ \ mmHg$

Boundary 2

Type: Imposed fluxes

Due to the symmetry of the problem there are no normal fluxes.



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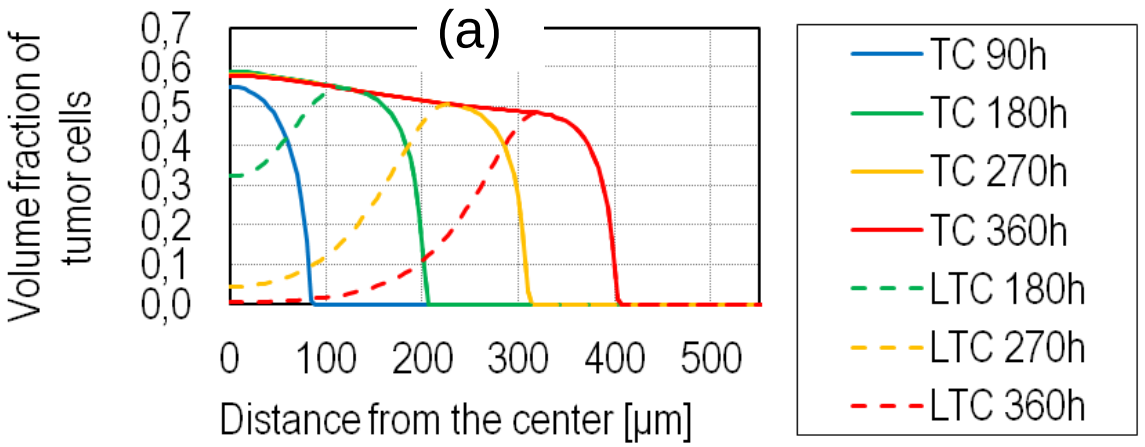
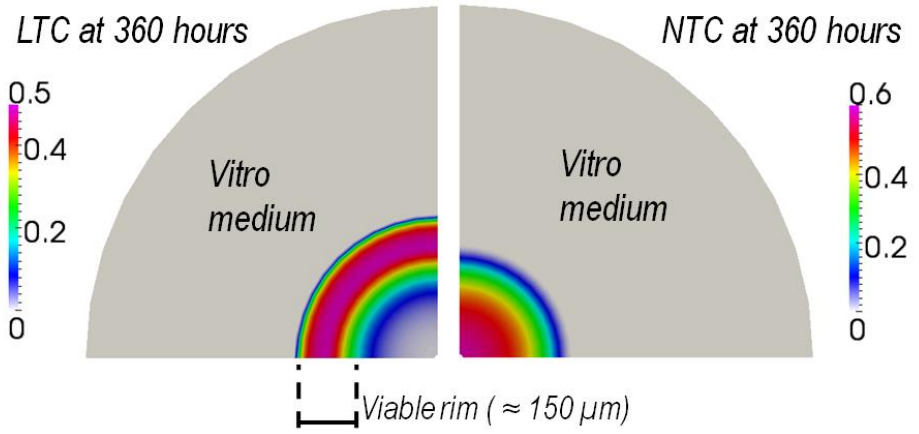
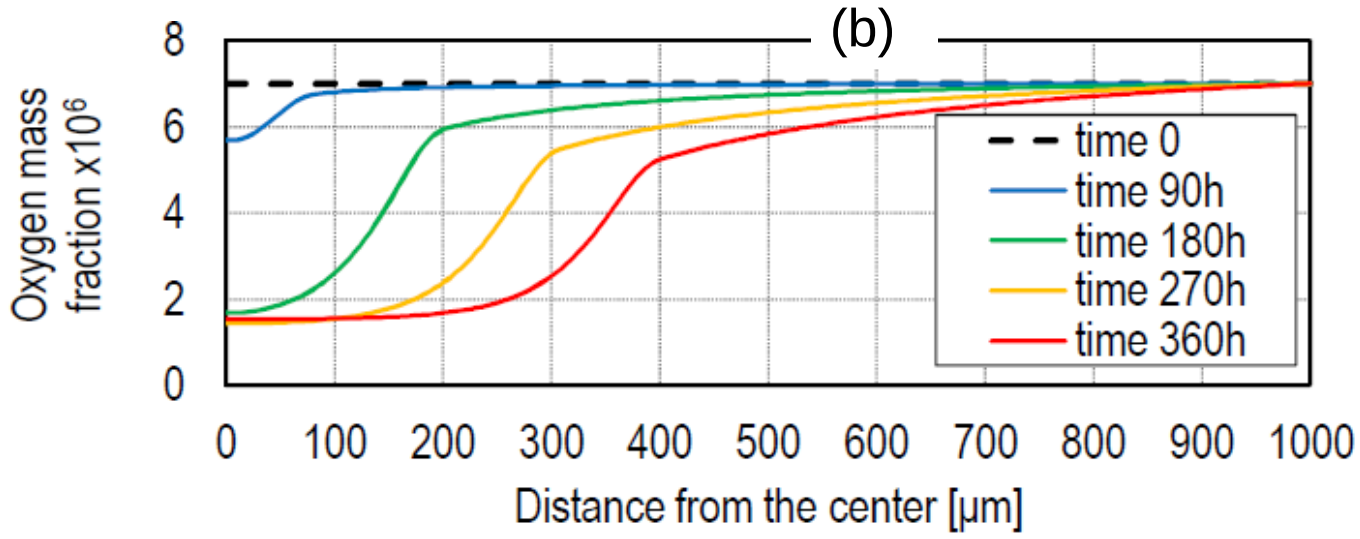
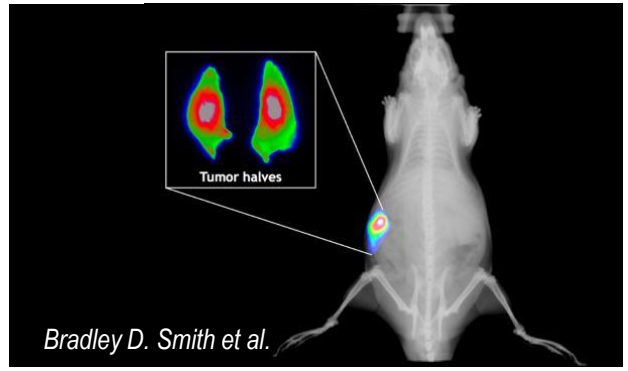




Living tumor cells (LTC) and necrotic tumor cells (NTC) at 360 hours.

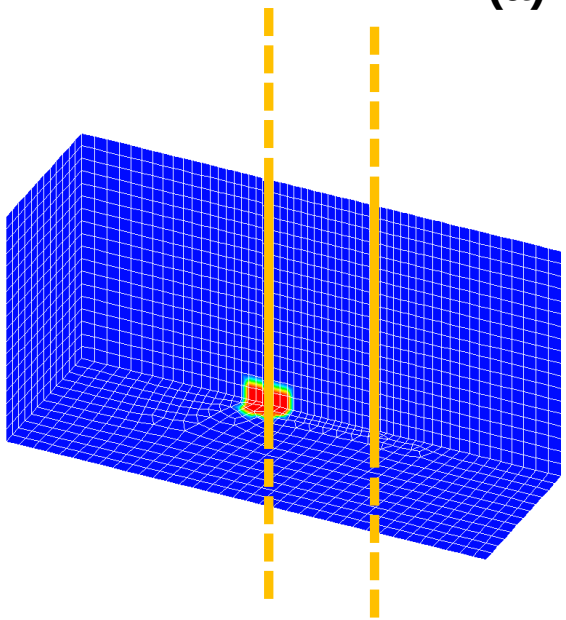




Optical Imaging of Prostate Tumor in Rat Model: the Fluorescent near-infrared probe (PSS-794) targets the necrotic core of the tumor

Tumor growth in proximity of two blood vessels

(a)



Blu zone:

$\omega^{\overline{nl}} = \omega^{\overline{nl}}_{env} = 4.2 \cdot 10^{-6}$

$\varepsilon^s = 1 - \varepsilon = 0.10 \qquad \varepsilon^t = \varepsilon S^t = 0.00$

$\varepsilon^h = \varepsilon S^h = 0.40 \qquad p^l = 0 \ mmHg$

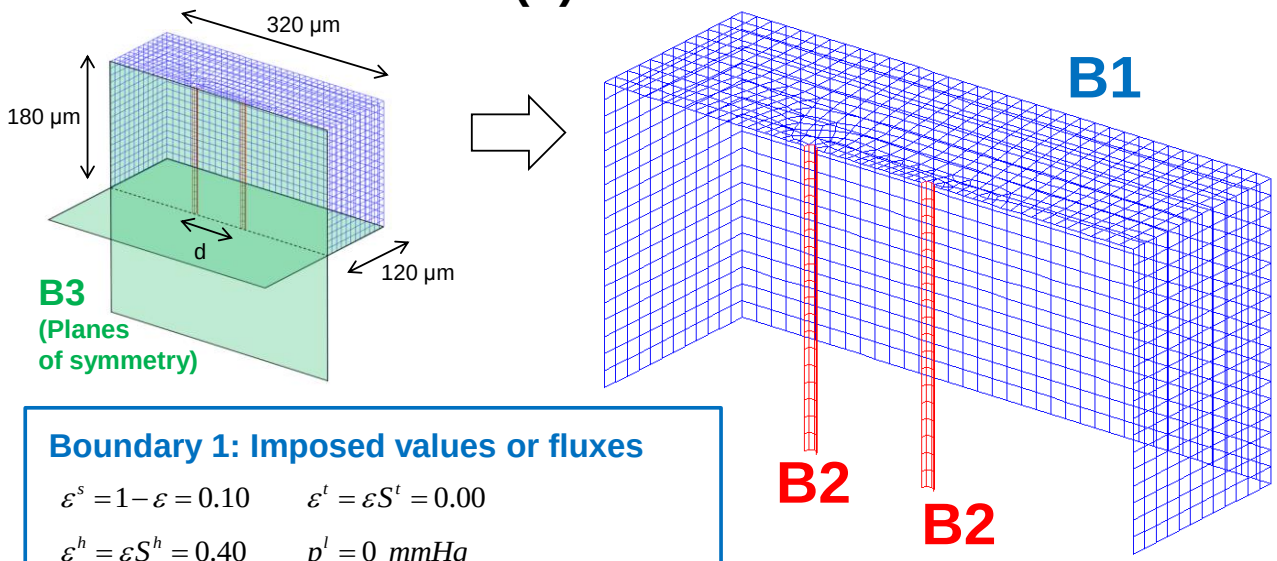
Red zone:

$\omega^{\overline{nl}} = \omega^{\overline{nl}}_{env} = 4.2 \cdot 10^{-6}$

$\varepsilon^s = 1 - \varepsilon = 0.10 \qquad \varepsilon^t = \varepsilon S^t = 0.40$

$\varepsilon^h = \varepsilon S^h = 0.00 \qquad p^l = 0 \ mmHg$

(b)



Boundary 1: Imposed values or fluxes

$\varepsilon^s = 1 - \varepsilon = 0.10 \qquad \varepsilon^t = \varepsilon S^t = 0.00$

$\varepsilon^h = \varepsilon S^h = 0.40 \qquad p^l = 0 \ mmHg$

Normal flux of oxygen equal to 0

Boundary 2: Imposed values or fluxes

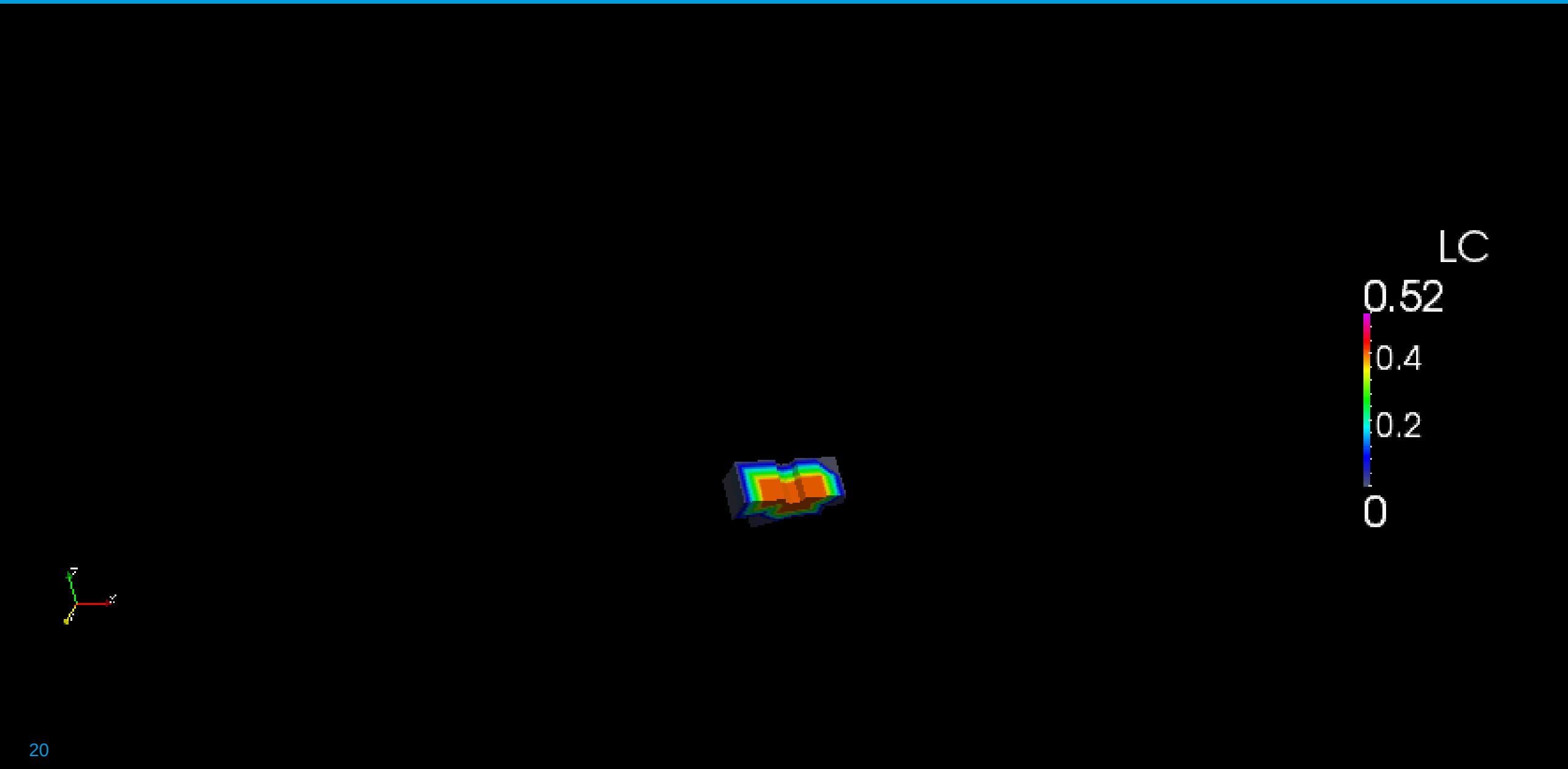
$\omega^{\overline{nl}} = \omega^{\overline{nl}}_{env} = 4.2 \cdot 10^{-6}$

Normal flux of *t*, *h*, and *l* equal to 0

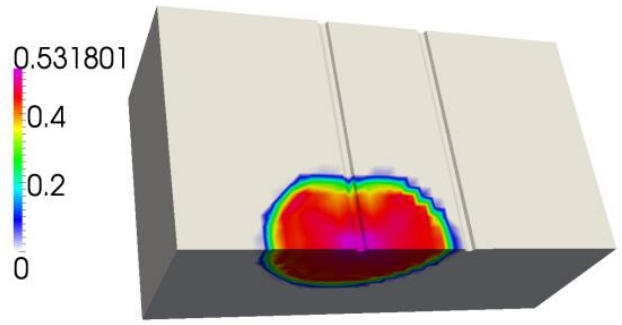
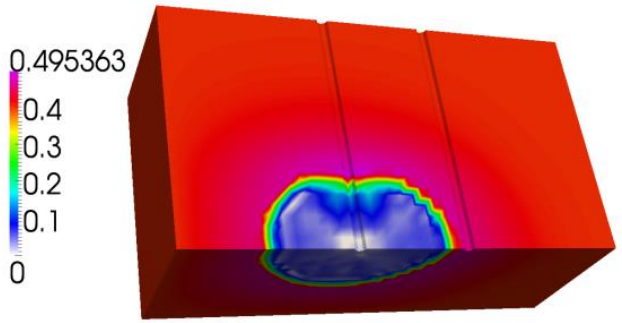
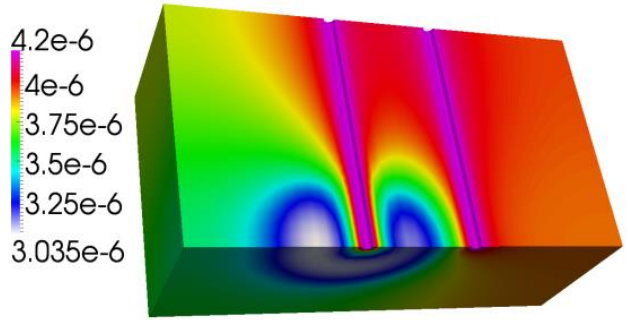
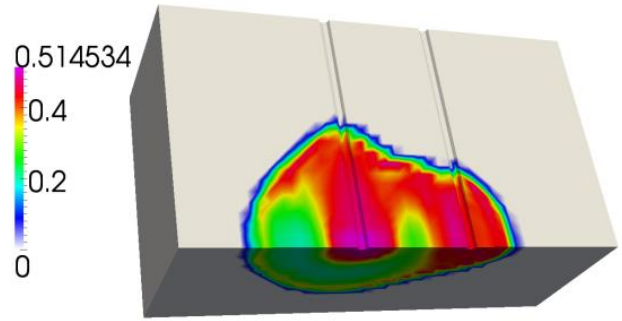
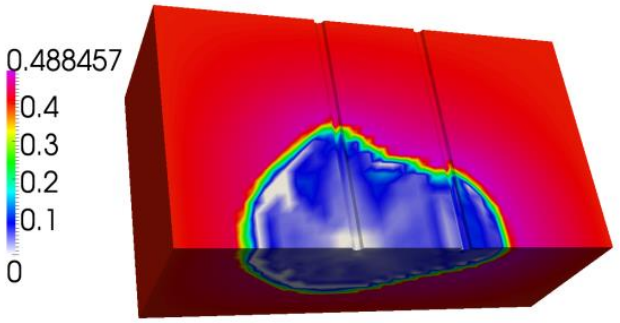
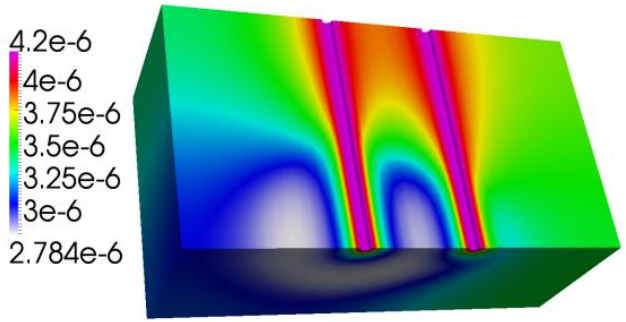
Boundary 3: Imposed fluxes

Due to the symmetry of the problem there are no normal fluxes.

Tumor growth in proximity of two blood vessels



Tumor growth in proximity of two blood vessels

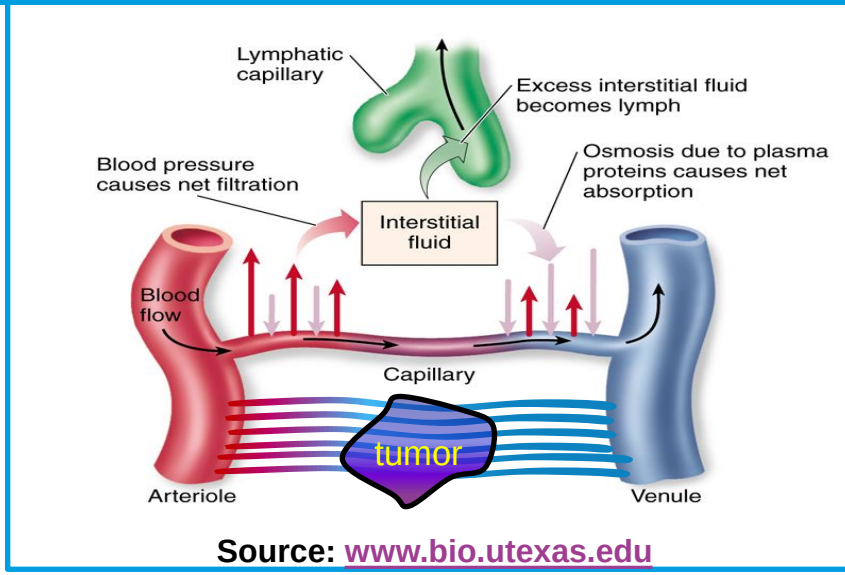
	Living tumor cells (LTC)	Host cells (HC)	Oxygen mass fraction
168 hours			
360 hours			

Volume fractions of the living tumor cells (first column) of the healthy cells (second column) and mass fraction of oxygen (third column) for the case S1.

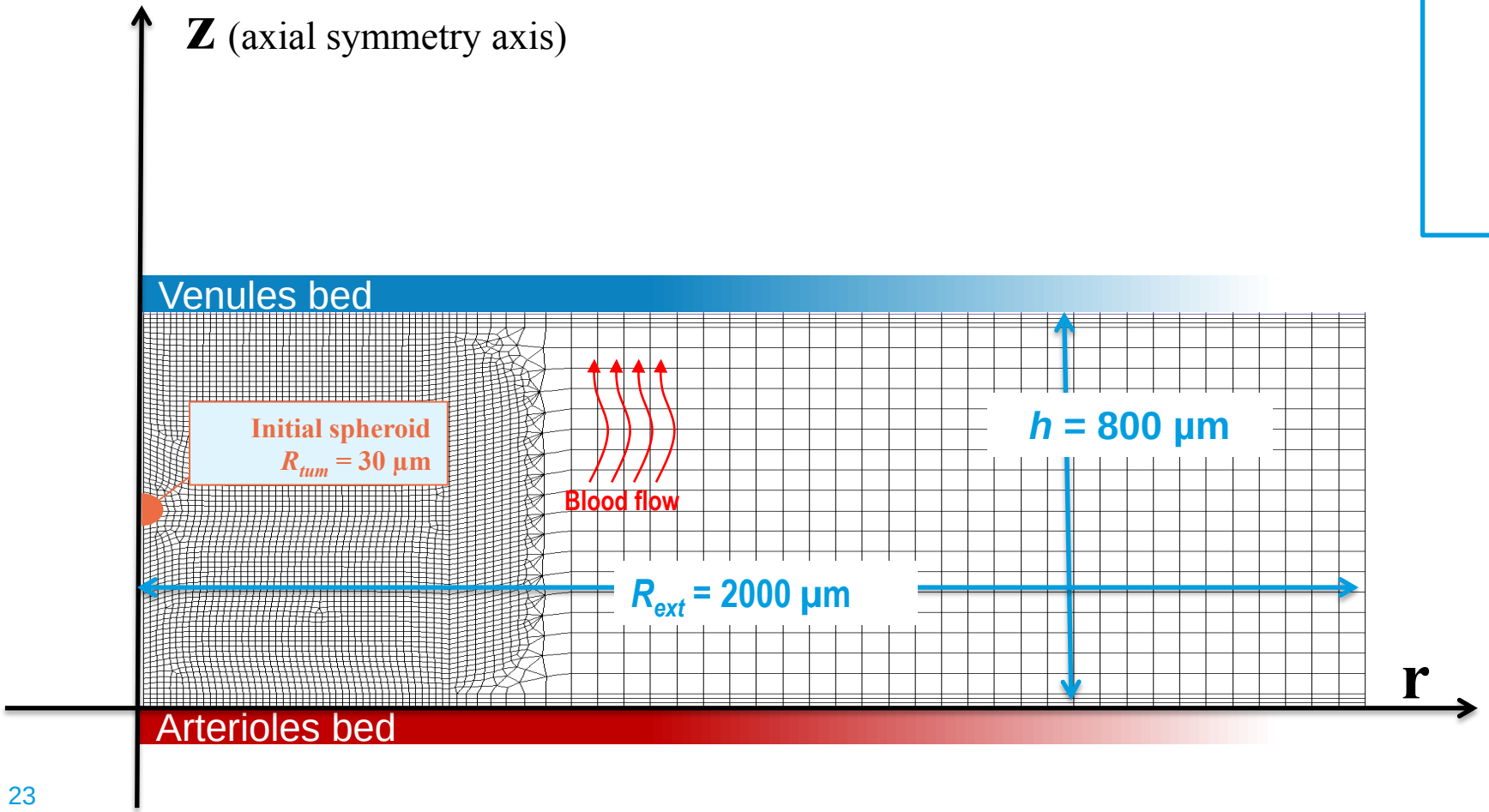
Angiogenesis

Reaction terms and interphase exchanges of mass

Angiogenesis: TAF release → ECh production → vessel formation dΓ



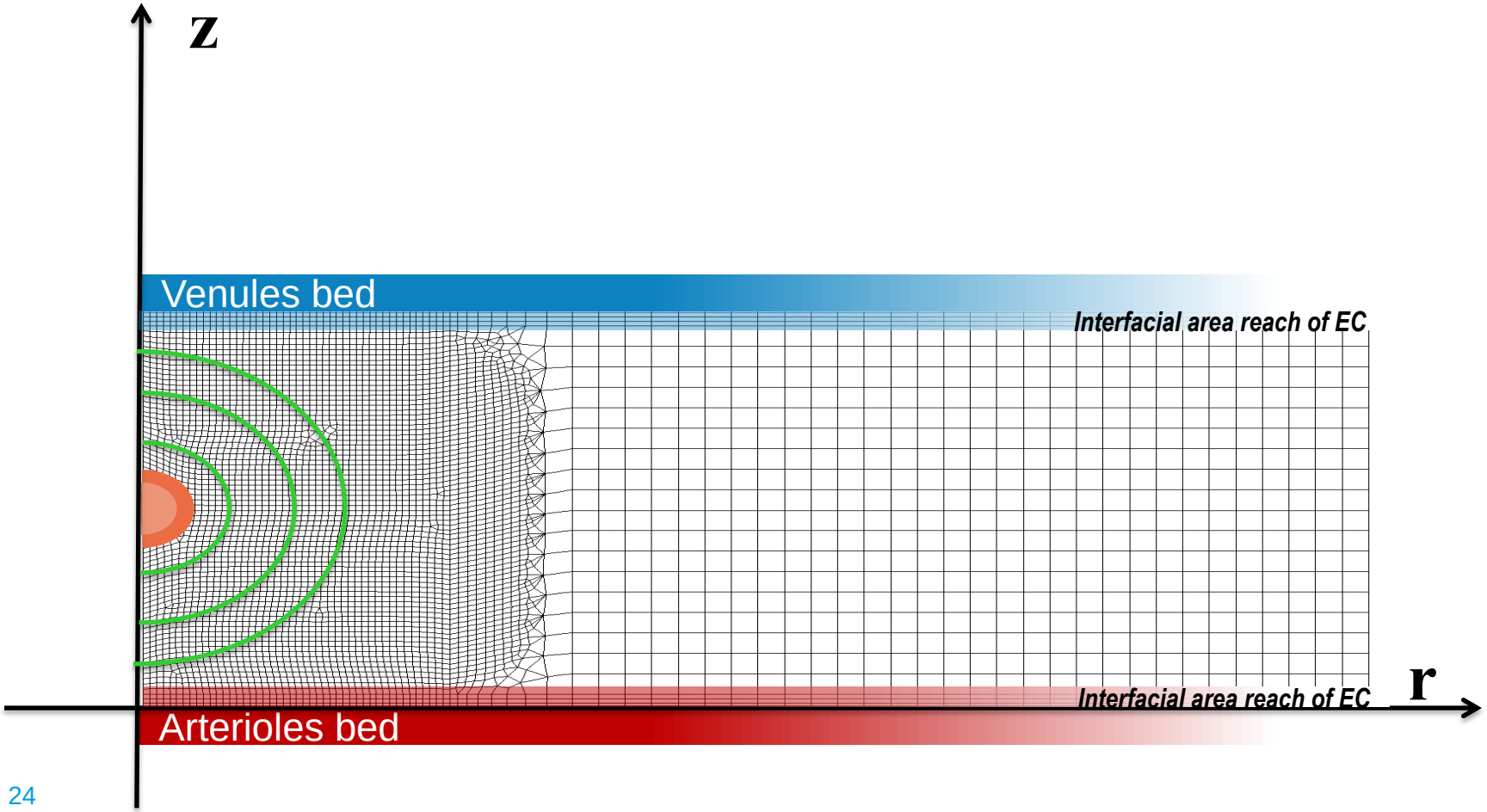
Source: www.bio.utexas.edu



Angiogenesis: TAF release → ECh production → vessel formation dΓ

TAF release

$$\frac{\mathrm{D}^{s}\left(\rho^{l}\varepsilon^{l}\omega^{\overline{TAFl}}\right)}{\mathrm{D}t}+\nabla\cdot\left(\rho^{l}\varepsilon^{l}\omega^{\overline{TAFl}}\mathbf{v}^{\overline{ls}}\right)+\nabla\cdot\left(\rho^{l}\varepsilon^{l}\omega^{\overline{TAFl}}\mathbf{u}^{\overline{\overline{OXYl}}}\right)+\rho^{l}\varepsilon^{l}\omega^{\overline{TAFl}}\nabla\cdot\mathbf{v}^{\overline{s}}=\overset{t\to TAFl}{M}$$



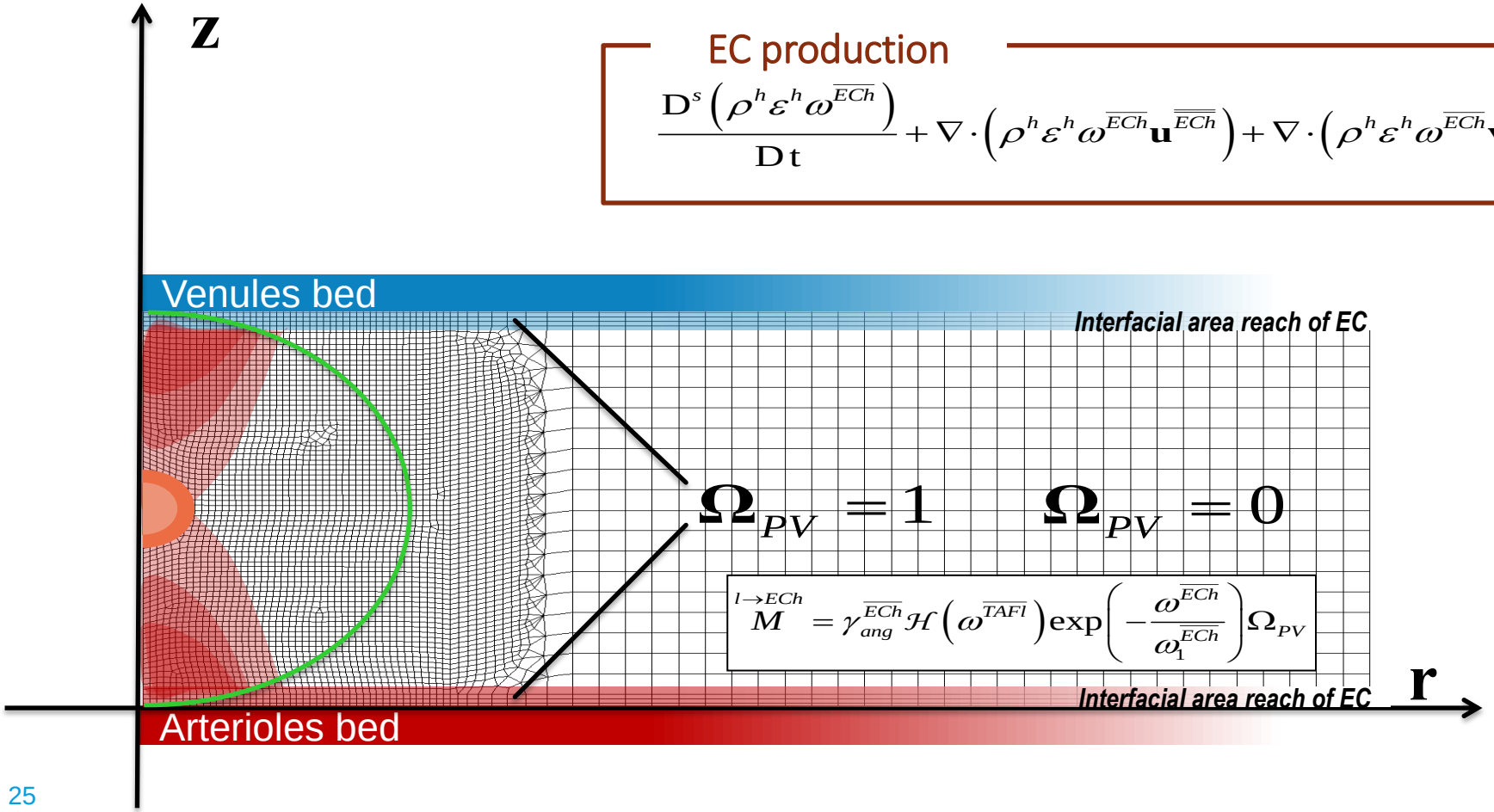
Angiogenesis: TAF release → ECh production → vessel formation dΓ

TAF release

$$\frac{\mathrm{D}^s\left(\rho^l\varepsilon^l\omega^{\overline{TAFl}}\right)}{\mathrm{D}t}+\nabla\cdot\left(\rho^l\varepsilon^l\omega^{\overline{TAFl}}\mathbf{v}^{\overline{ls}}\right)+\nabla\cdot\left(\rho^l\varepsilon^l\omega^{\overline{TAFl}}\mathbf{u}^{\overline{\overline{OXYl}}}\right)+\rho^l\varepsilon^l\omega^{\overline{TAFl}}\nabla\cdot\mathbf{v}^{\bar{s}}=\overset{t\to TAFl}{M}$$

EC production

$$\frac{\mathrm{D}^s\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\right)}{\mathrm{D}t}+\nabla\cdot\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\mathbf{u}^{\overline{\overline{ECh}}}\right)+\nabla\cdot\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\mathbf{v}^{\overline{hs}}\right)+\rho^h\varepsilon^h\omega^{\overline{ECh}}\nabla\cdot\mathbf{v}^{\bar{s}}=\overset{l\to ECh}{M}-\underset{ang}{\overset{ECh\to s}{M}}$$



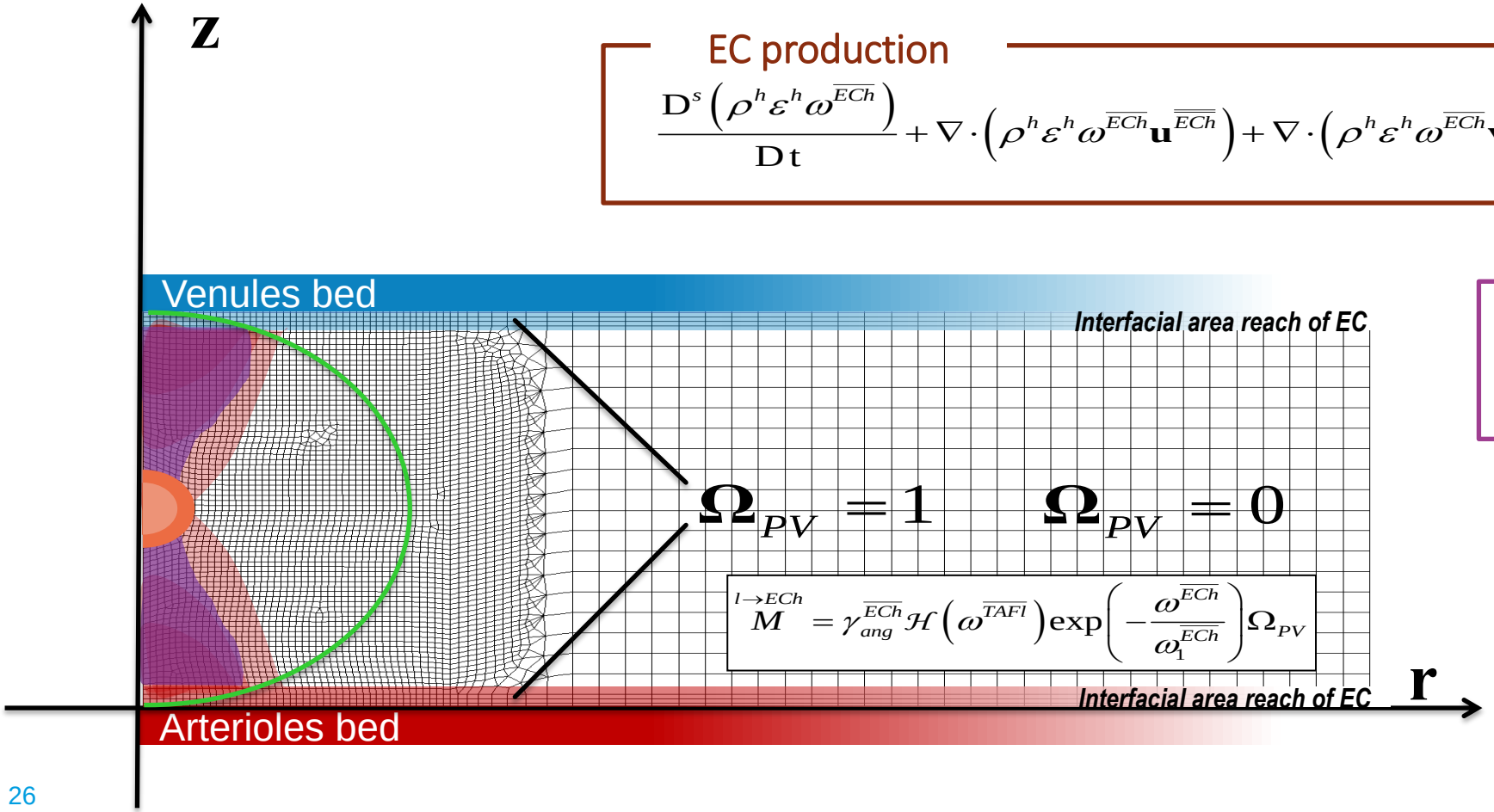
Angiogenesis: TAF release → ECh production → vessel formation dΓ

TAF release

$$\frac{\mathrm{D}^s\left(\rho^l\varepsilon^l\omega^{\overline{TAFl}}\right)}{\mathrm{D}t}+\nabla\cdot\left(\rho^l\varepsilon^l\omega^{\overline{TAFl}}\mathbf{v}^{\overline{ls}}\right)+\nabla\cdot\left(\rho^l\varepsilon^l\omega^{\overline{TAFl}}\mathbf{u}^{\overline{\overline{OXYl}}}\right)+\rho^l\varepsilon^l\omega^{\overline{TAFl}}\nabla\cdot\mathbf{v}^{\overline{s}}=\overset{t\to TAFl}{M}$$

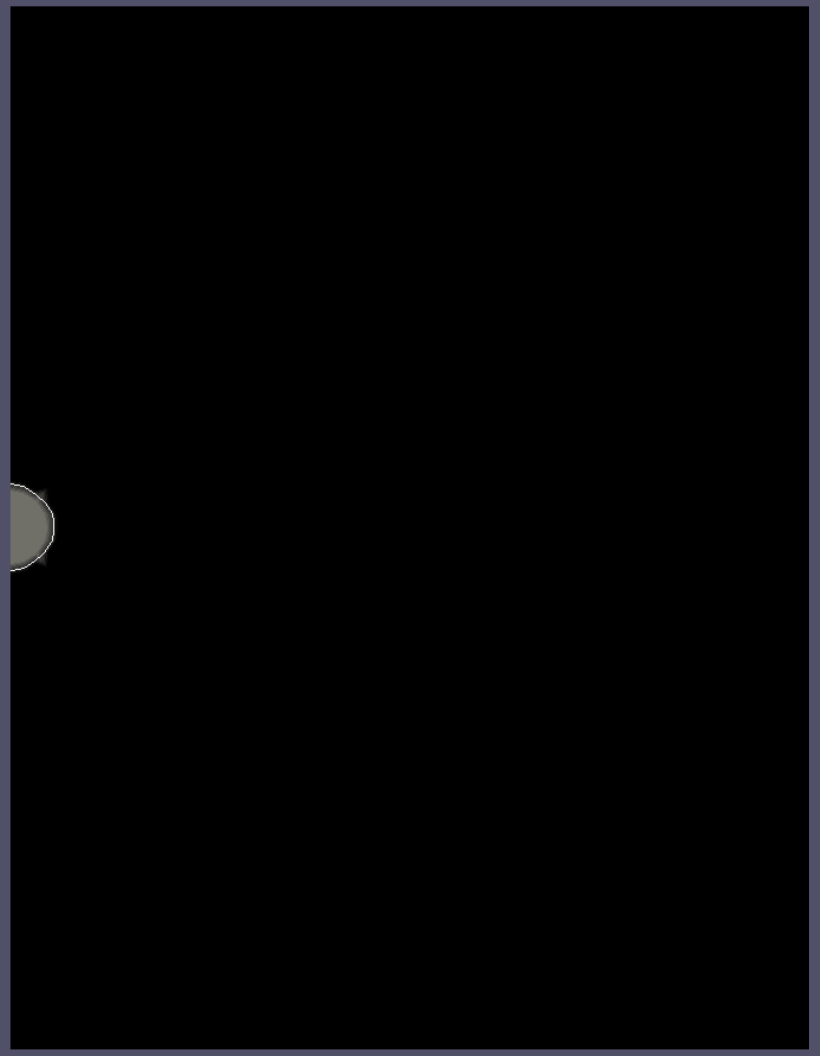
EC production

$$\frac{\mathrm{D}^s\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\right)}{\mathrm{D}t}+\nabla\cdot\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\mathbf{u}^{\overline{\overline{ECh}}}\right)+\nabla\cdot\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\mathbf{v}^{\overline{hs}}\right)+\rho^h\varepsilon^h\omega^{\overline{ECh}}\nabla\cdot\mathbf{v}^{\overline{s}}=\overset{l\to ECh}{M}-\underset{ang}{\overset{ECh\to s}{M}}$$



Vessel maturation

$$\frac{\mathrm{D}^s\Gamma}{\mathrm{D}t}=A(\Gamma)\mathcal{H}\left(\varepsilon^h\omega^{\overline{ECh}}\right)$$


Y
Z
X
DEPLA Magnitude
0.000e+00 1.9e-7 3.7e-7 5.6e-7 7.427e-07
TC
0.000e+00 0.044 0.087 0.13 1.743e-01


ECH
3.757e-02
0.028178
0.018786
0.0093928
0.000e+00
Y
Z
X


EPSB
2.293e-02
0.020764
0.018593
0.016421
1.425e-02
Y
Z
X

…Very nice mathematical framework… but:

- Have you exhaustively validated it? **….NO ☹**
- Is it useful today for oncologic research? **….NO ☹**
- Could be useful, when validated, to disclose still obscure mechanisms characterizing tumor behavior (invasion for instance)?

  YES ☺ and this motivated our research in this direction

THE MATHEMATICAL MODEL

Stephane Urcun

PhD Thesis (codirected with S. Bordas)

***REAL LIFE* BIOPHYSICAL & CLINICAL DIMENSIONS OF CANCER**

collaboration with
Dr. V. Lubrano et T. Duval
CHU de Toulouse