Club Cast3M 2017 – Paris, 24 November 2017

A two-compartment hierarchical porous medium system for vascular tumor growth: theory and implementation in Cast3M

Giuseppe Sciumè

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PHYSICS & CANCER

➔ What does physics have to do with cancer?

Franziska Michor et al. – NATURE REVIEWS | CANCER VOLUME 11 | SEPTEMBER 2011 | 657

- ➔ Transport OncoPhysics: multiscale modelling of cancer growth and multiparameter response to therapy; multiscale imaging; and multiscale probes

➔ Getting physical

Jennie Dushek – NATURE | VOL 491 | 22 NOVEMBER 2012 | S50

- ➔ Physics, maths and evolutionary biology are among the scientific disciplines providing cancer research with fresh perspective and therapeutic approaches.

"As biology begins to confront the limits of the molecular approach — which has yielded vast amounts of data but not always clear understanding — some scientists have returned to a more biomechanical view of life, and their research is starting to bear fruit."

MECHANICS & CANCER

➔ **The forces of cancer**

Erica Jonietz - NATURE | VOL 491 | 22 NOVEMBER 2012 | S56

➔ The way cells mechanically interact with each other and their environment could help researchers understand the invasion and metastasis of solid tumors.

The aim is here to exploit **porous media mechanics and multiphase flow dynamics** to better understand some paradigms of **tumor growth mechanobiology**

Multiphase System

5 PHASES ARE CONSIDERED

1 SOLID SCAFFOLD, (s)

Permeated by

4 IMMISCIBLE FLUID PHASES:

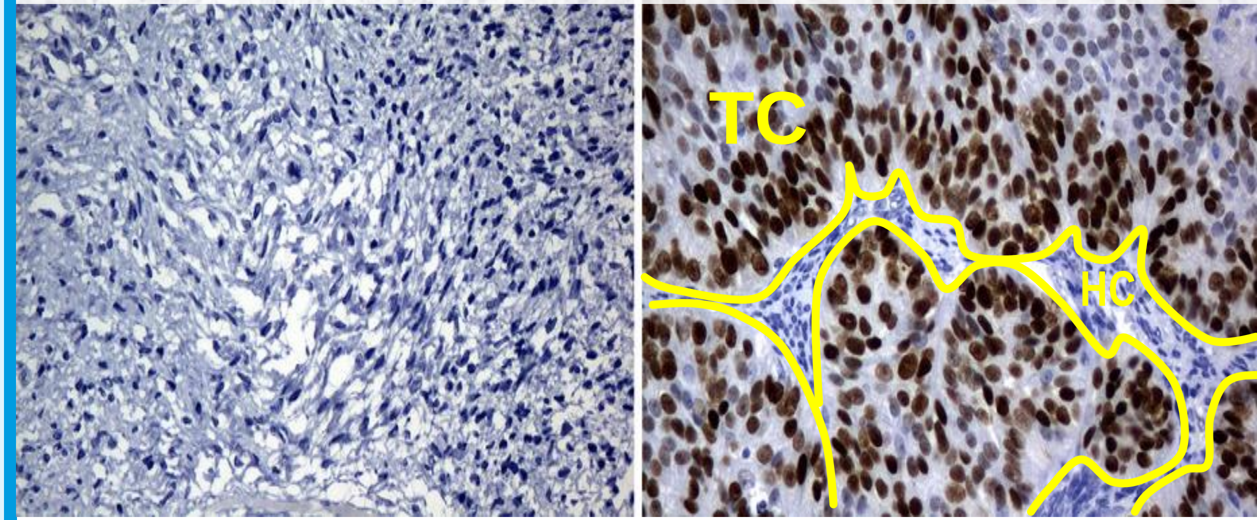
- Tumor cells, (t), (tN + tL)
- Host cells, (h)
- Interstitial fluid, (l)
- Blood (b)

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

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)**



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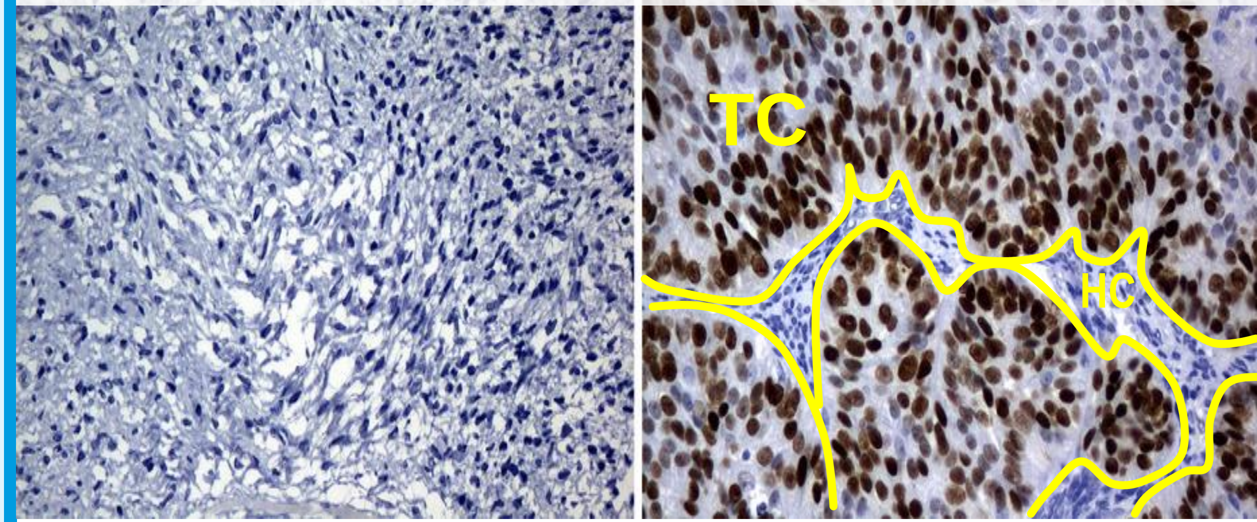

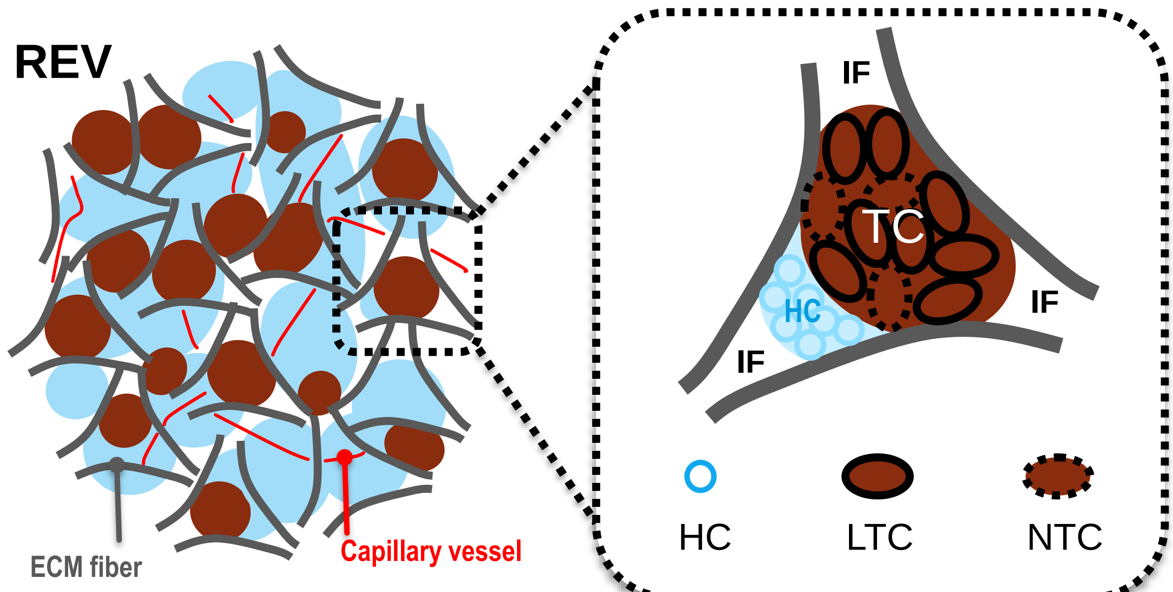

Phases definition & preliminary hypotheses

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

Vascular porosity (ε^b)

$\boldsymbol{\varepsilon}$: Extra-vascular porosity ($\varepsilon^t + \varepsilon^h + \varepsilon^l$)

- Vascular porosity ε^b **is always saturated by blood;**
- **<u>Saturation degree is defined for extra-vascular porosity only</u>** 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).**

Mass c. eqs of phases (7 scalar independent eqs)

Definition of porosity and saturation constraint:

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

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

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

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

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

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

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

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

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)

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

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

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

$$\omega^{\overline{ECh}}\mathbf{u}^{\overline{\overline{ECh}}}=-\mathbf{D}^{ECh}\nabla\omega^{\overline{ECh}}+\mathbf{D}^{ECh}\frac{C\omega^{\overline{ECh}}}{1-C\omega^{\overline{TAFl}}}\nabla\omega^{\overline{TAFl}}$$

Derived from the SEI (TCAT: paper 5 – W. G. Gray, C. T. Miller)

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)

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

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

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

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

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

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

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 $\overset{\kappa\to\alpha}{\mathbf{T}}$)

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

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)

$$\varepsilon^f \nabla p^f + \mathbf{R}^f \cdot (\bar{\mathbf{v}}^f - \bar{\mathbf{v}}^s) = 0 \qquad [\text{mo-a.}f]$$

Resistance tensor

with $f = t, h, l, b$

Model closure

Summary of model conservation eqs

- Mass c. eqs of phases .... 7 scalar independent eqs
- Mass c. eqs of TC species .... 2 scalar independent eqn
- Mass c. eqs of HC species .... 1 scalar independent eqn
- Mass c. eqs of IF species .... 2 scalar independent eqs
- Mom. c. eqs multiphase system .... 3 scalar independent eqs
- Mom. c. eqs for fluid phases .... 12 scalar independent eqs

Total : 27 scalar independent eqs

Summary of model independent variables

Phase	Phase indicator	Species	Associated variables	N. equivalent scalar variables
Solid	s	-	$\varepsilon^s, \varepsilon, \rho^s, \mathbf{t}^{\bar{\bar{\mathrm{T}}}}, \mathbf{v}^{\bar{s}}$	12
Tumor cells	t	Lt, Nt	$S^t, \rho^t, p^t, \mathbf{v}^{\bar{t}}, \omega^{\overline{Lt}}, \omega^{\overline{Nt}}$	8
Host cells	h	ECh	$S^h, \rho^h, p^h, \mathbf{v}^{\bar{h}}, \omega^{\overline{ECh}}, \mathbf{u}^{\overline{\overline{ECh}}}$	10
Interstitial fluid	l	$OXYl$, $TAFl$	$S^l, \rho^l, p^l, \mathbf{v}^{\bar{l}}, \omega^{\overline{OXYl}}, \omega^{\overline{TAFl}}, \mathbf{u}^{\overline{\overline{OXYl}}}, \mathbf{u}^{\overline{\overline{TAFl}}}$	14
Blood vessels	b	-	$\rho^b, p^b, \varepsilon^b \mathbf{v}^{\bar{b}}$	6
			Total of scalar unknowns	**50**

23 Constitutive/state eqs are needed for model closure

Model closure / assuming phases incompressibility*

Summary of model conservation eqs

- Mass c. eqs of phases .... 7 scalar independent eqs
- Mass c. eqs of TC species .... 2 scalar independent eqn
- Mass c. eqs of HC species .... 1 scalar independent eqn
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Total : 27 scalar independent eqs

Summary of model independent variables

Phase	Phase indicator	Species	Associated variables	N. equivalent scalar variables
Solid	s	-	$\varepsilon^s, \varepsilon, \cancel{\rho}^s, \mathbf{t}^{\overline{\overline{\mathrm{T}}}}, \mathbf{v}^{\bar{s}}$	12
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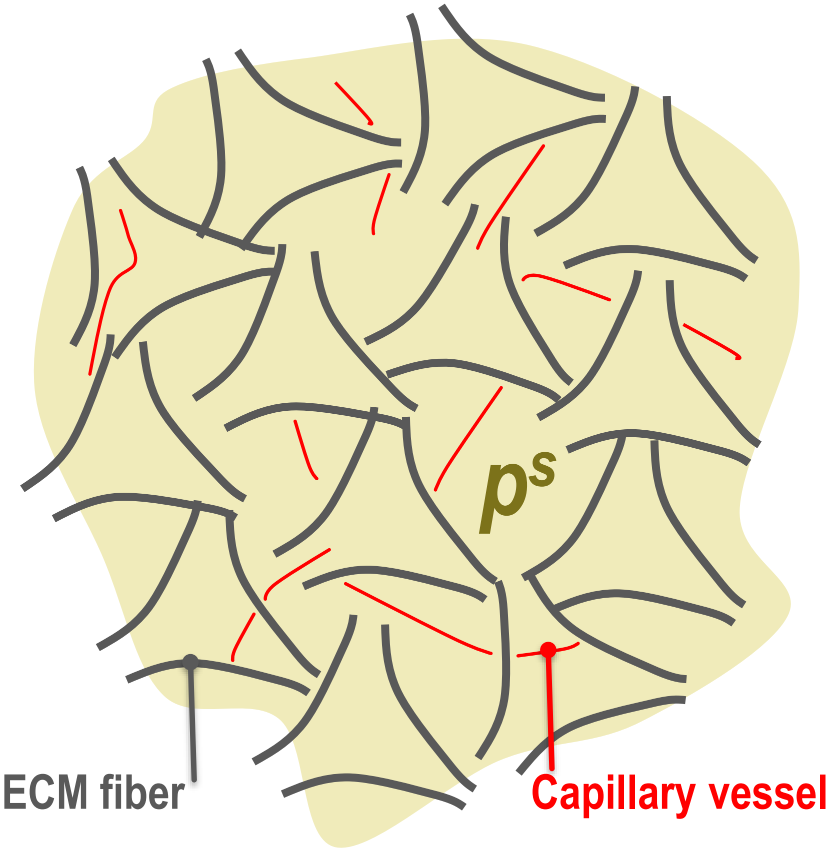
Host cells	h	ECh	$S^h, \cancel{\rho}^h, p^h, \mathbf{v}^{\bar{h}}, \omega^{\overline{ECh}}, \mathbf{u}^{\overline{\overline{ECh}}}$	10
Interstitial fluid	l	$OXYl$, $TAFl$	$S^l, \cancel{\rho}^l, p^l, \mathbf{v}^{\bar{l}}, \omega^{\overline{OXYl}}, \omega^{\overline{TAFl}}, \mathbf{u}^{\overline{\overline{OXYl}}}, \mathbf{u}^{\overline{\overline{TAFl}}}$	14
Blood vessels	b	-	$\cancel{\rho}^b, p^b, \varepsilon^b \mathbf{v}^{\bar{b}}$	6
			Total of scalar unknowns	**45**

18 Constitutive/state eqs are needed for model closure

*this does not mean that the overall ECM scaffold is incompressible because porosity is inside.

Constitutive laws (18 scalar equations)

- State equation for ε^b 1 eqn
- Mechanical constitutive model 6 eqs
- Two pressure-saturation eqs 2 eqs
- Fick's law for species diffusion 9 eqs



Effective Stress Tensor

A non-conventional form accounting for hierarchy of porous compartments

Effective Stress Tensor: a non-conventional form

Stress tensor solid phase

$$\overline{\overline{\mathbf{t}}}^{s} = \overline{\overline{\boldsymbol{\tau}}}^{s} - p^{s}\mathbf{1}$$

effective solid phase stress tensor

solid phase pressure

Stress for fluid phases

$$\overline{\overline{\mathbf{t}}}^{f} = -p^{f}\mathbf{1} \quad (f = t,h,l,b)$$

Pressure in the fluid phase (positive if the fluid is in compression)

Summing of phase tensors weighed by their own volume fraction gives the **total stress tensor** as

$$\overline{\overline{\mathbf{t}}}^{\mathrm{T}} = \sum_{\alpha=s,t,h,l,b} \varepsilon^{\alpha}\overline{\overline{\mathbf{t}}}^{\alpha} = \varepsilon^{s}\left(\overline{\overline{\boldsymbol{\tau}}}^{s} - p^{s}\mathbf{1}\right) - \sum_{f=t,h,l,b} \varepsilon^{f} p^{f}\mathbf{1}$$

Effective Stress Tensor: a non-conventional form

$$\mathbf{t}^{\overline{\overline{\mathrm{T}}}} = \sum_{\alpha=s,t,h,l,b} \varepsilon^{\alpha} \mathbf{t}^{\overline{\overline{\alpha}}} = \varepsilon^{s}\left(\boldsymbol{\tau}^{\overline{\overline{s}}} - p^{s}\mathbf{1}\right) - \sum_{f=t,h,l,b} \varepsilon^{f} p^{f} \mathbf{1}$$

Hypothesis 1: **blood vessels** are mostly surrounded by extra-vascular fluids (*TC*, *HC* and *IF*), hence they **have no relevant mechanical interaction with "structural" ECM fibers**

Hypothesis 2: the **solid pressure, p^s, is assumed being related with pressures of extra-vascular fluids (*TC*, *HC* and *IF*) only:**

$$p^{s} = \sum_{\beta=t,h,l} S^{\beta} p^{\beta} = S^{t} p^{t} + S^{h} p^{h} + S^{l} p^{l}$$

$$\mathbf{t}^{\overline{\overline{\mathrm{E}}}} = \underbrace{\varepsilon^{s} \boldsymbol{\tau}^{\overline{\overline{s}}}}_{\text{EFFECTIVE STRESS TENSOR (EST)}} = \mathbf{t}^{\overline{\overline{\mathrm{T}}}} + p^{s}\mathbf{1} - \varepsilon^{b}\left(p^{s} - p^{b}\right)\mathbf{1}$$

EFFECTIVE STRESS TENSOR (EST)

Effective Stress Tensor: $\mathbf{t}^{E} = \mathbf{t}^{T} + p^{s}\mathbf{1} - \varepsilon^{b}(p^{s} - p^{b})\mathbf{1}$

Material objective time derivative of the effective stress tensor :

$$\overset{=}{\dot{\mathbf{t}}}^{E} = \overset{=}{\dot{\mathbf{t}}}^{T} + \left(1-\varepsilon^{b}\right)\dot{p}^{s}\mathbf{1} + \varepsilon^{b}\dot{p}^{b}\mathbf{1} - \left(p^{s} - p^{b}\right)\dot{\varepsilon}^{b}\mathbf{1}$$

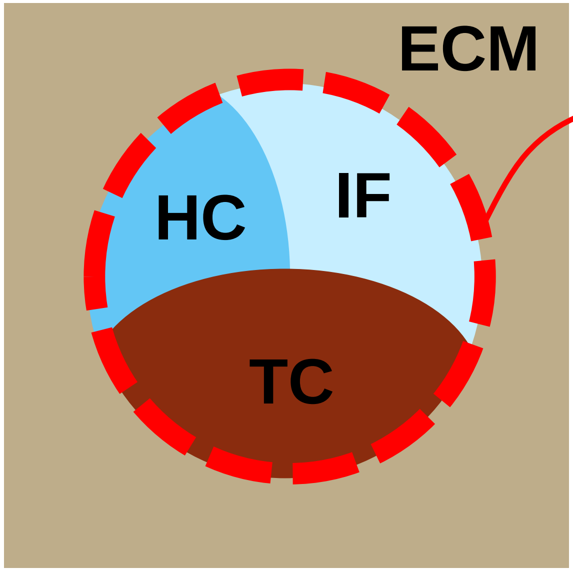
EST induces all deformations of ECM scaffold: $\overset{=}{\dot{\mathbf{t}}}^{E} = \mathbf{C}_{ECM} : \mathbf{d}$

Introducing this constitutive relationship in the previous eqn gives:

$$\overset{=}{\dot{\mathbf{t}}}^{T} = \mathbf{C}_{ECM} : \left(\mathbf{d} - \mathbf{d}_{sw}\right)$$

$$\mathbf{d}_{sw} = d_{sw}\mathbf{1} = \left(\frac{\left(1-\varepsilon^{b}\right)}{3K}\dot{p}^{s} + \frac{\varepsilon^{b}}{3K}\dot{p}^{b} - \frac{\left(p^{s} - p^{b}\right)}{3K}\dot{\varepsilon}^{b}\right)\mathbf{1}$$

State eqn for volume fraction of blood vessels

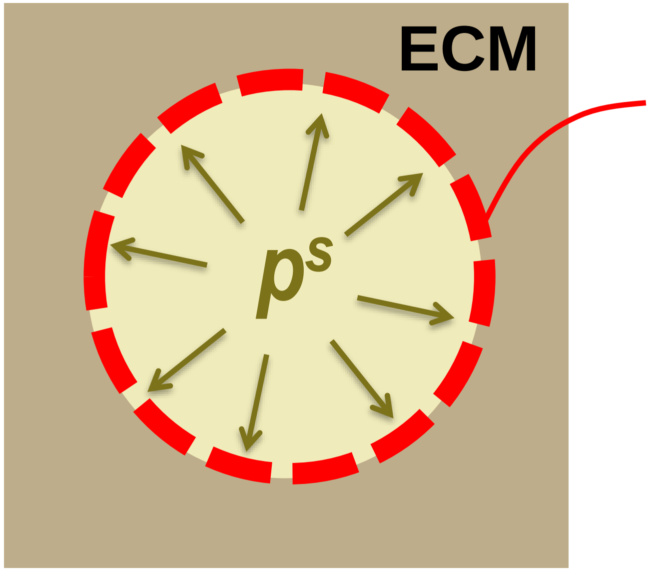


Ω_{fs}(fs interface)

$$p^s = \sum_{\beta=t,h,l} S^\beta p^\beta = S^t p^t + S^h p^h + S^l p^l$$

S^β are Bishop's parameters

State eqn for volume fraction of blood vessels

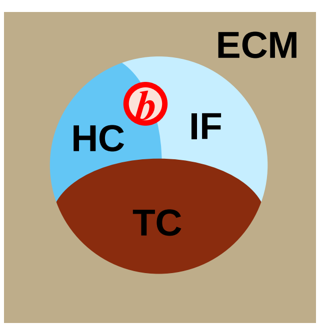


Ω_{fs}(fs interface)

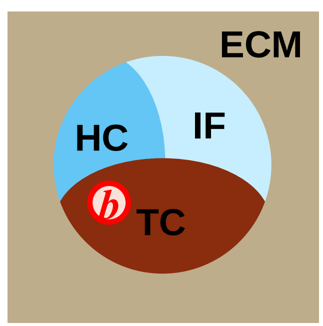
$$p^s = \sum_{\beta=t,h,l} S^\beta p^\beta = S^t p^t + S^h p^h + S^l p^l$$

S^β **are Bishop's parameters**

Vascular model (ε^b depends on (p^b - $p^{extra\text{-}vascular}$)):

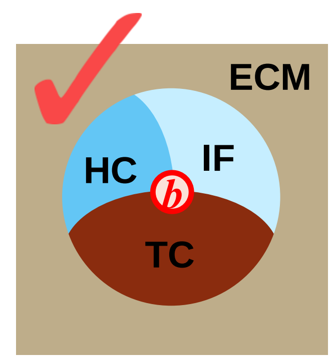


$$p^{ext} = \chi^h p^h + (1-\chi^h) p^l$$



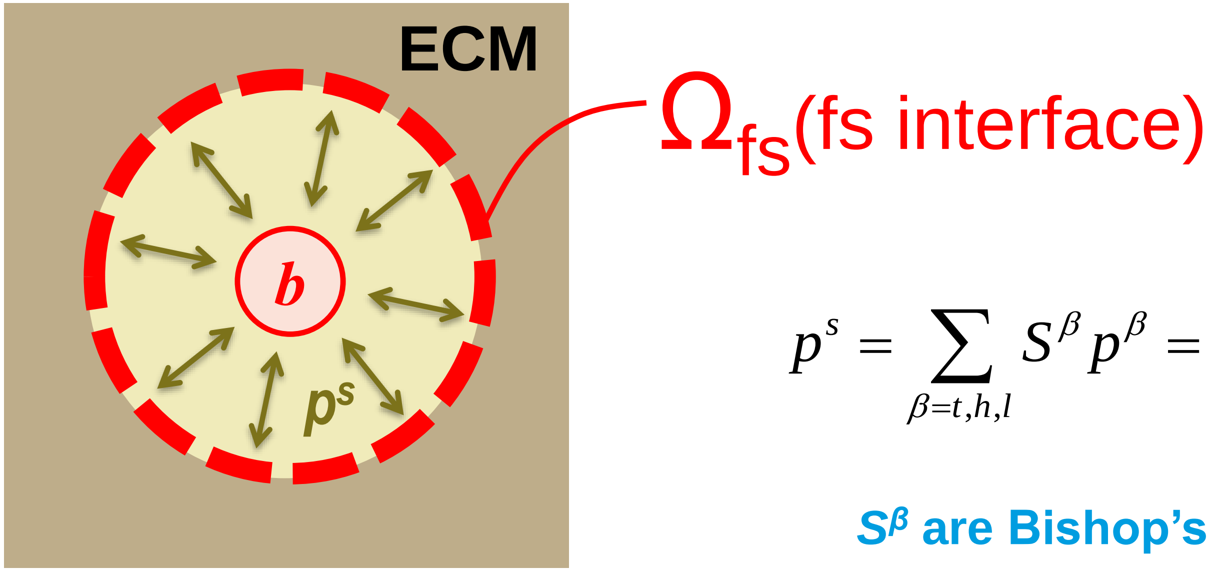
$$p^{ext} = p^t$$

… or ….



$$p^{ext} = S^t p^t + S^h p^h + S^l p^l = p^s$$

State eqn for volume fraction of blood vessels



$$p^s = \sum_{\beta=t,h,l} S^\beta p^\beta = S^t p^t + S^h p^h + S^l p^l$$

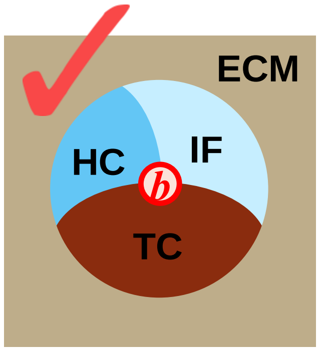
S^β are Bishop's parameters

Vascular model (ε^b depends on **(p^b - $p^{extra\text{-}vascular}$)):**

$$\varepsilon^b\left(p^b, p^s, \Gamma\right) = \varepsilon_0^b\left(1+\alpha\Gamma\right)\left(1-\frac{p^s-p^b}{K^{vess}}\right)$$

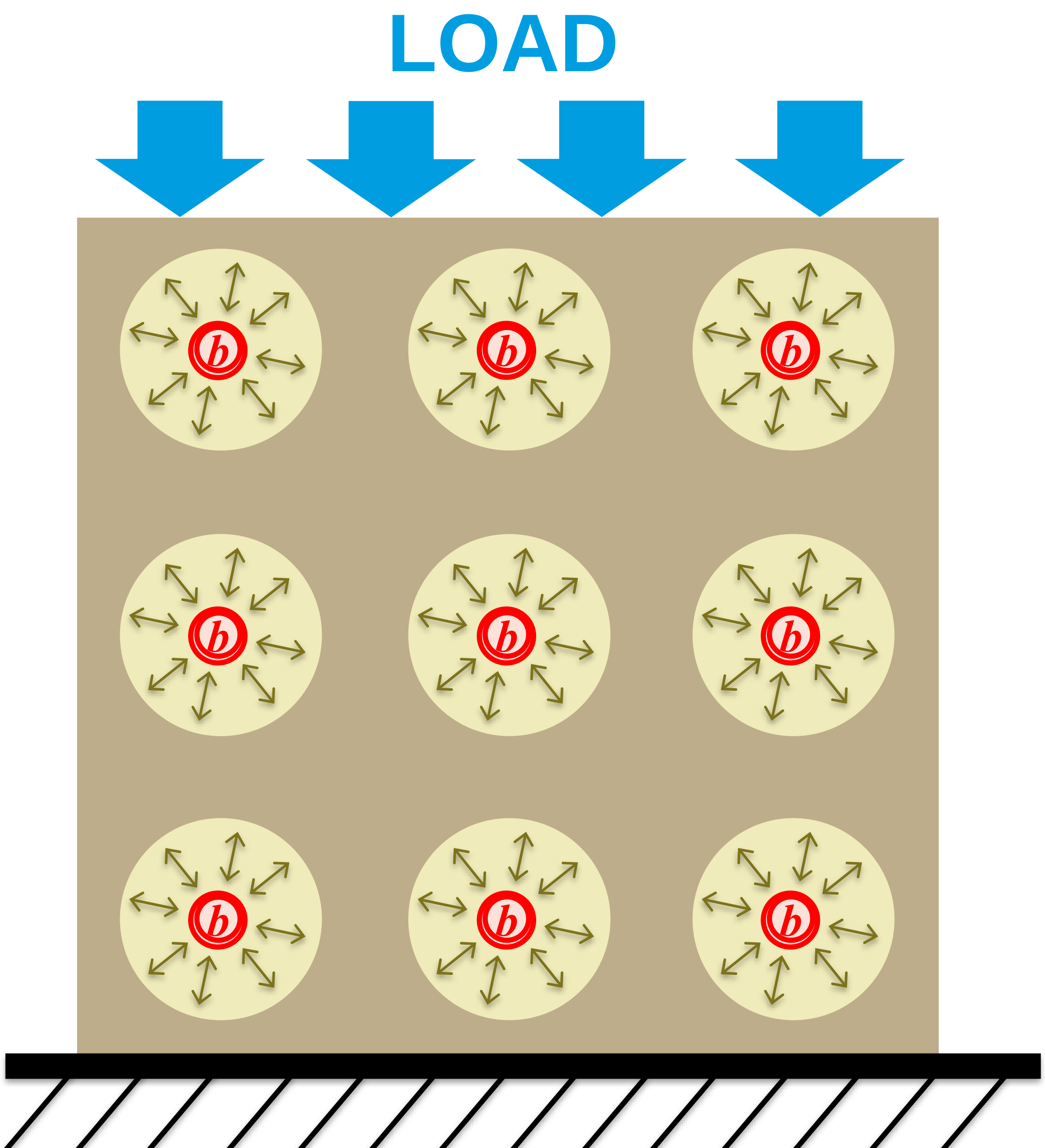
Internal variable describing **angiogenesis**

(no angiogenesis) $0 \le \Gamma \le 1$ (angiogenesis fully developed)



$$p^{ext} = S^t p^t + S^h p^h + S^l p^l = p^s$$

State eqn for volume fraction of blood vessels

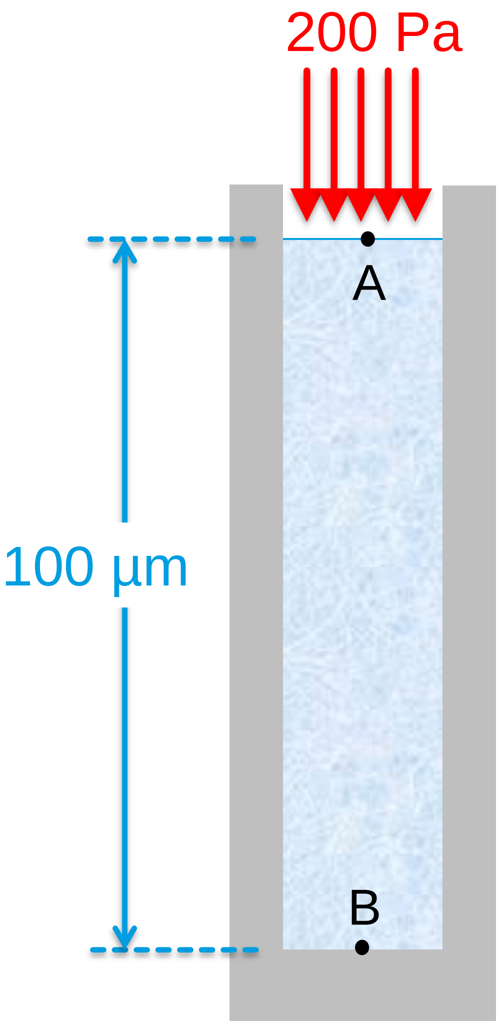


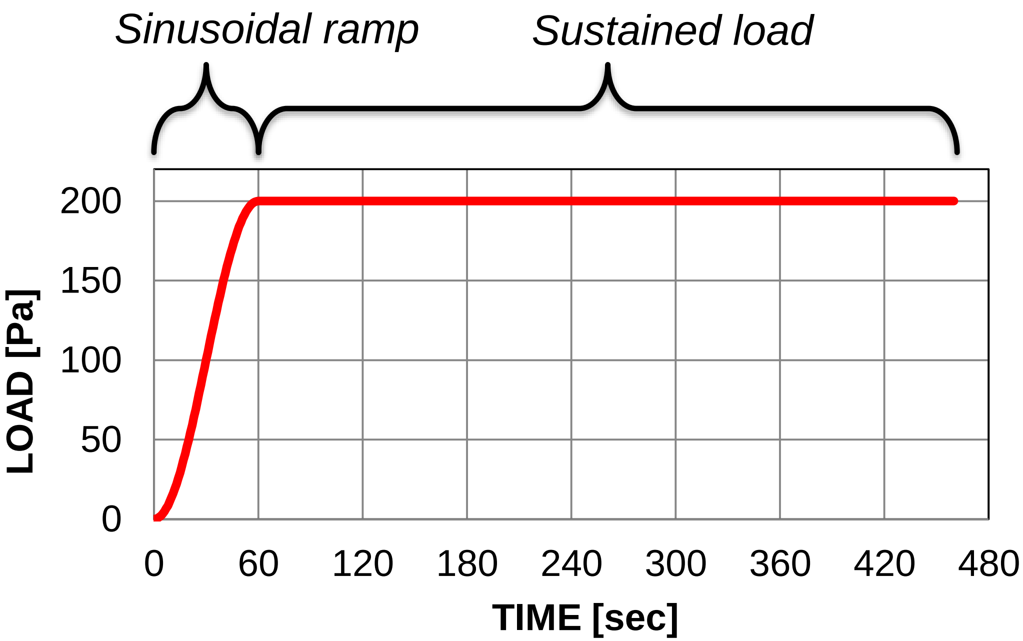
“ How does it work ? ”

ECM interacts with **blood vessel** *via* extravascular fluids

Comment: This is a reasonable assumption for the considered system and simplifies importantly the mathematical formulation.

1D bio-consolidation with and without vessels

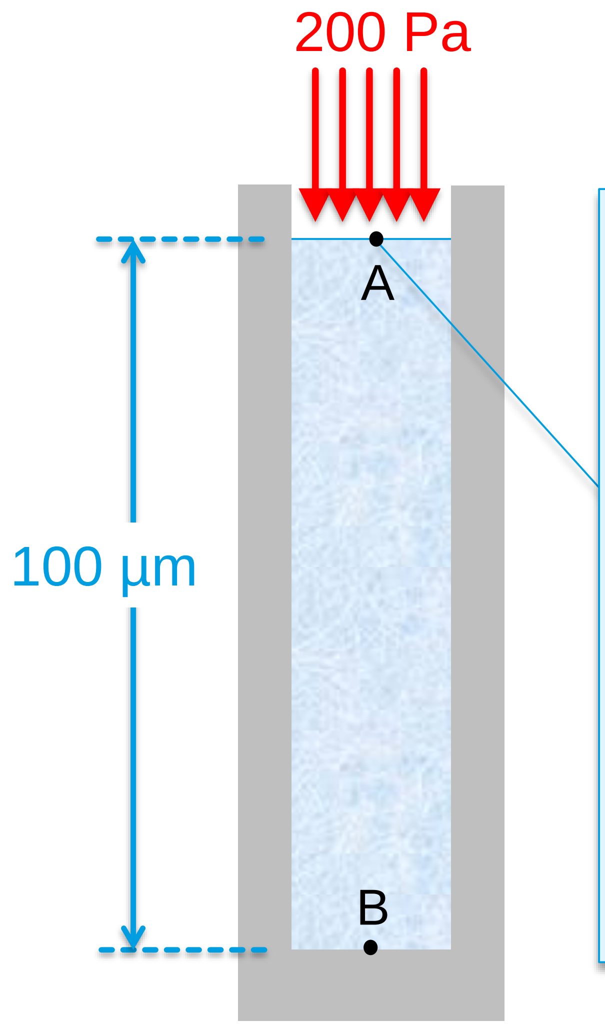




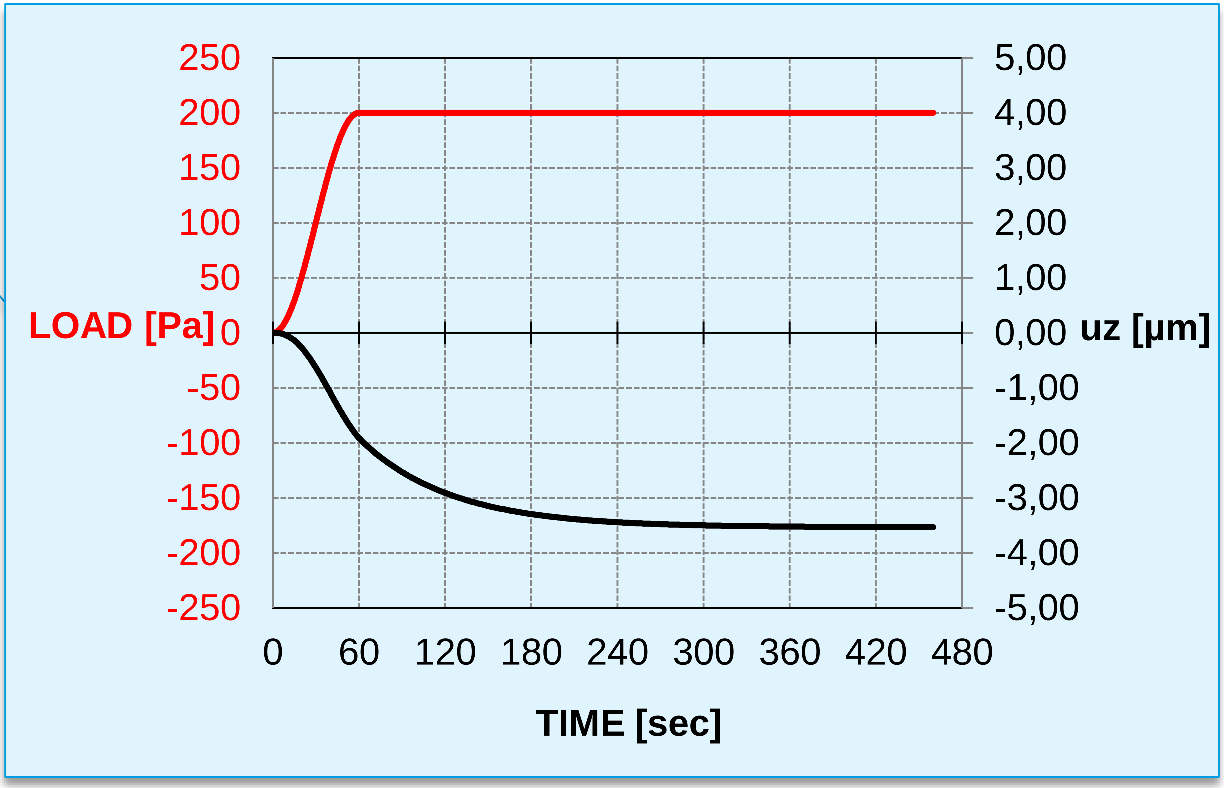
Material data

E	ν	ε	k_ε	μ_f	ε_{b0}	K_{vess}	k_{vess}	μ_b
5000	0.2	0.5	1.10^{-14}	1	0.1	5000	1.10^{-15}	0.02
Extra-vascular porosity data					Vascular porosity data			

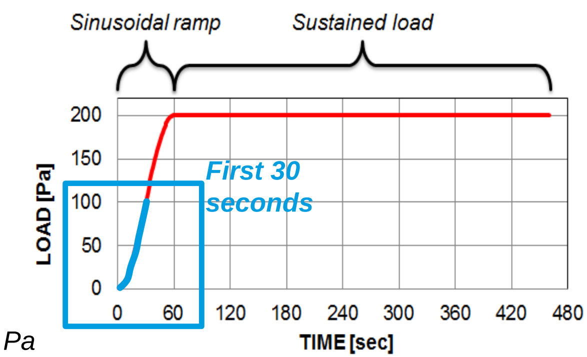
1D bio-consolidation with and without vessels

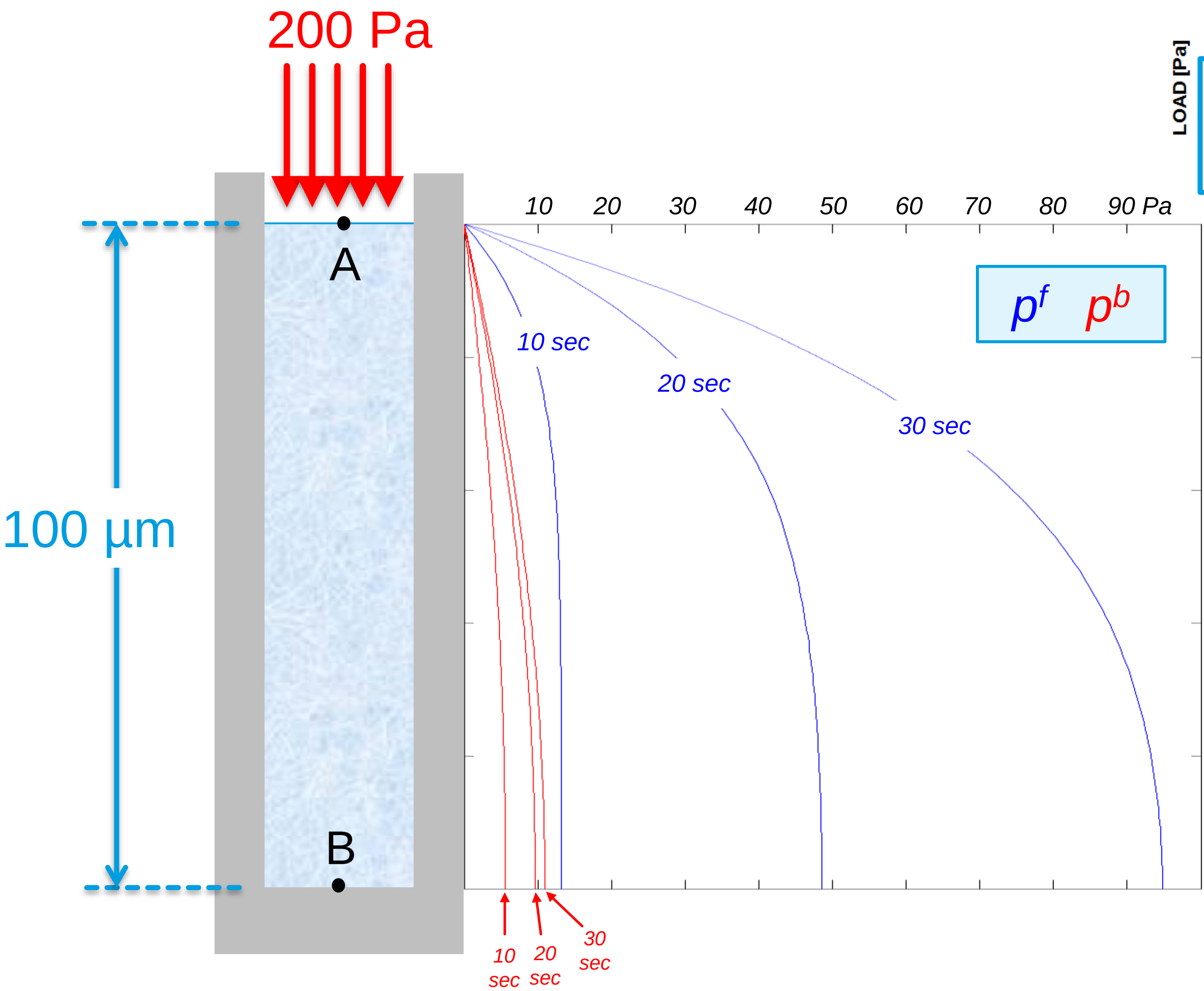


Point A – Load & vertical displacement with time



1D bio-consolidation with and without vessels



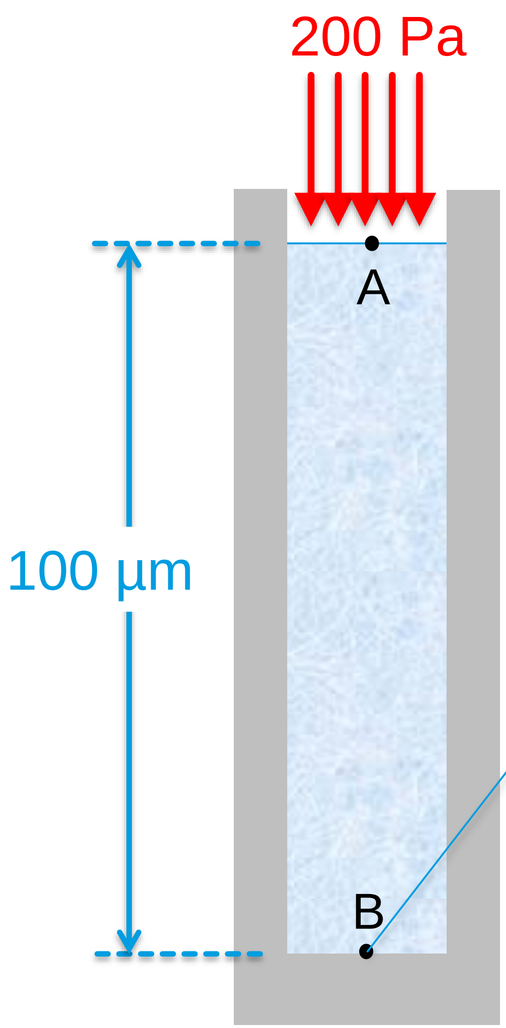


Coupling:

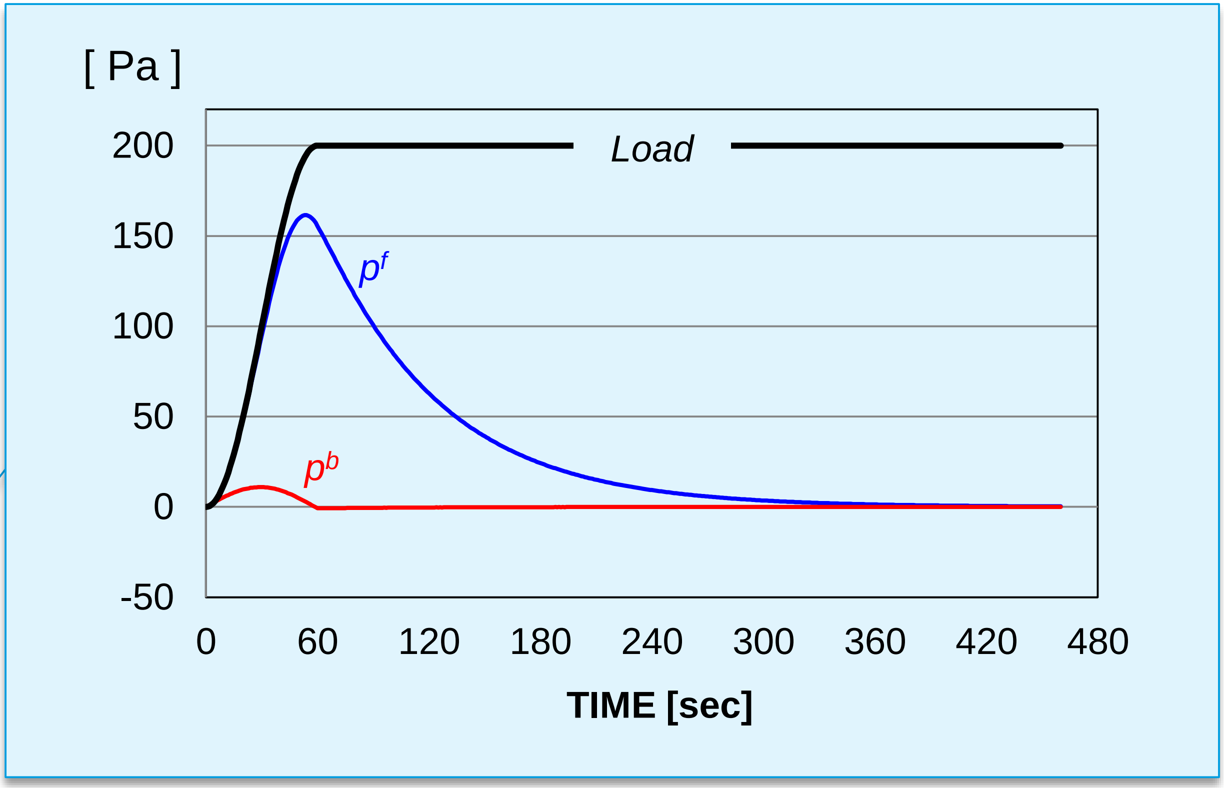
Flow is induced in the interstitial fluid phase as well as in the blood phase.

Dynamics is however very different; this will be shown in the following slides …

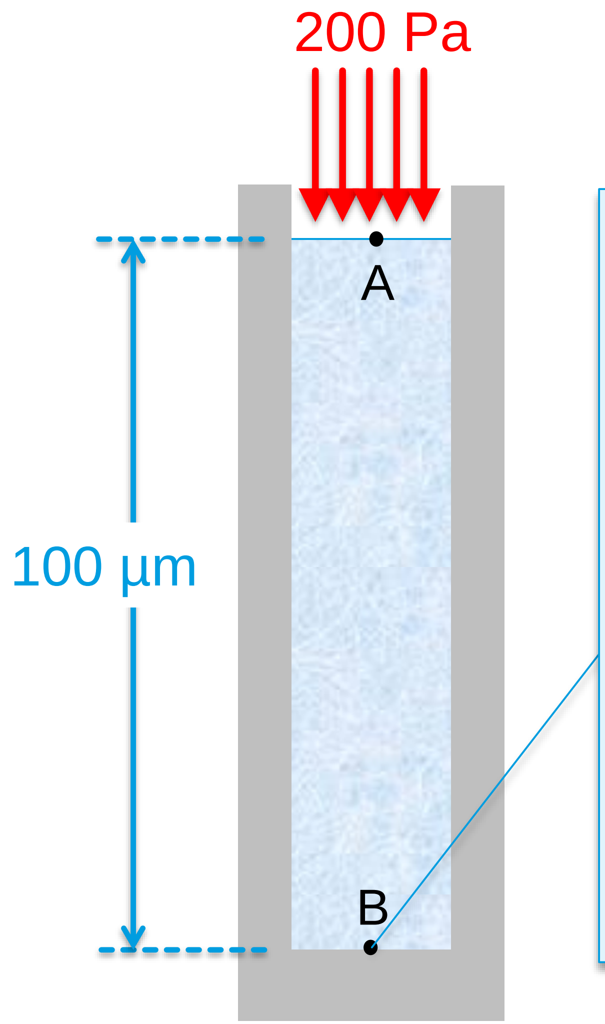
1D bio-consolidation with and without vessels



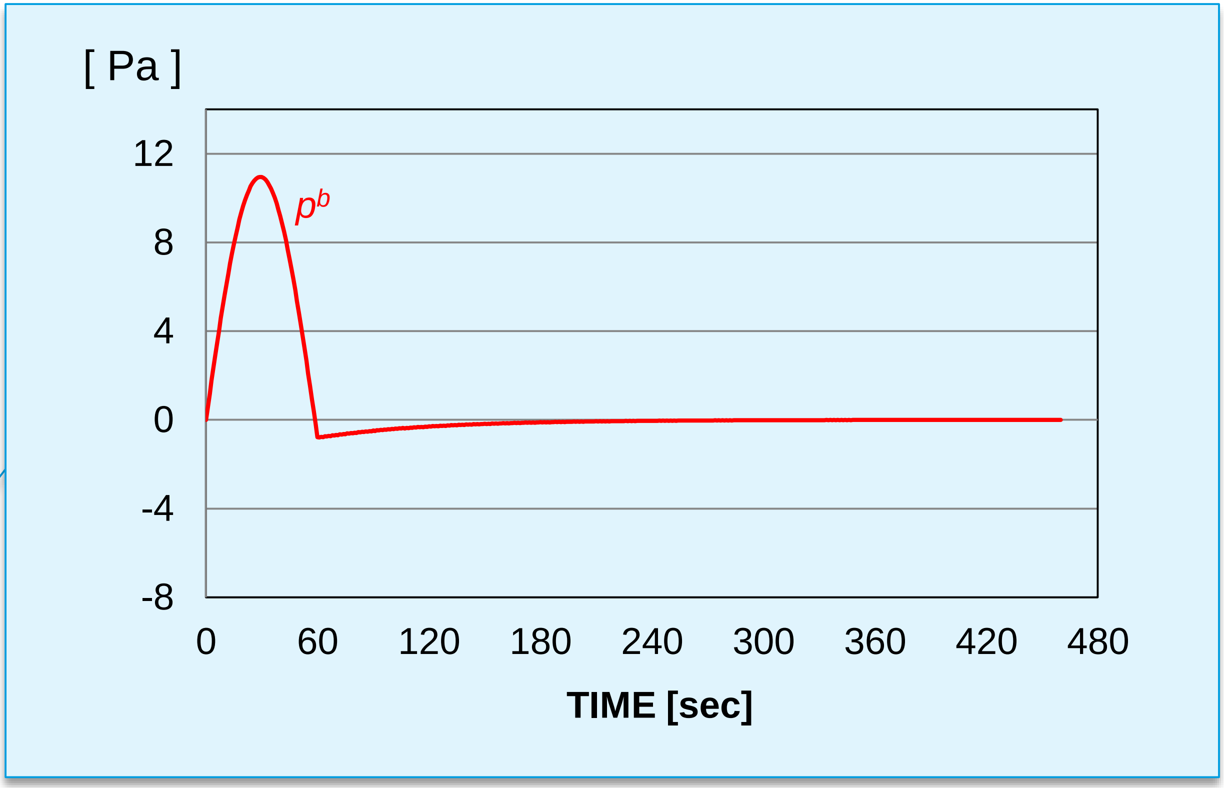
POINT B – p^f AND p^b *VERSUS* TIME



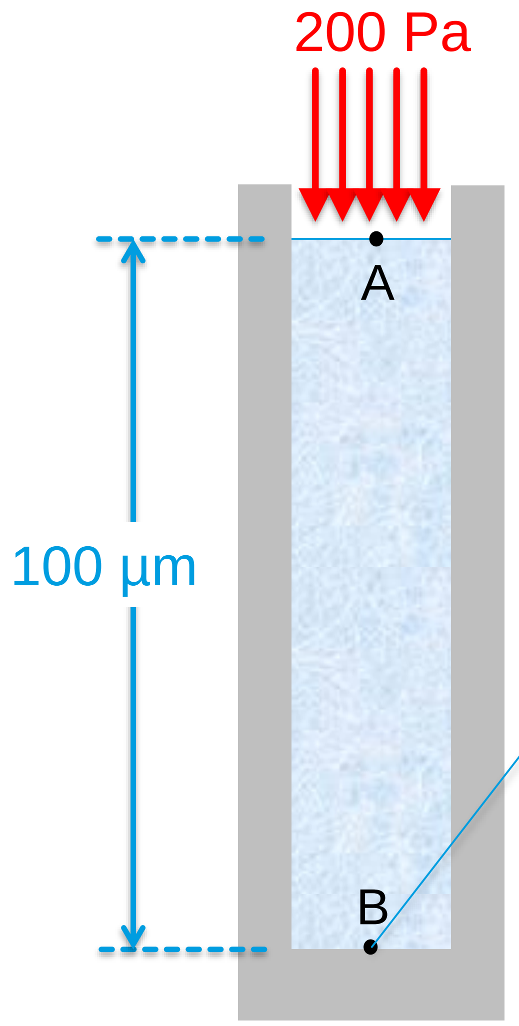
1D bio-consolidation with and without vessels



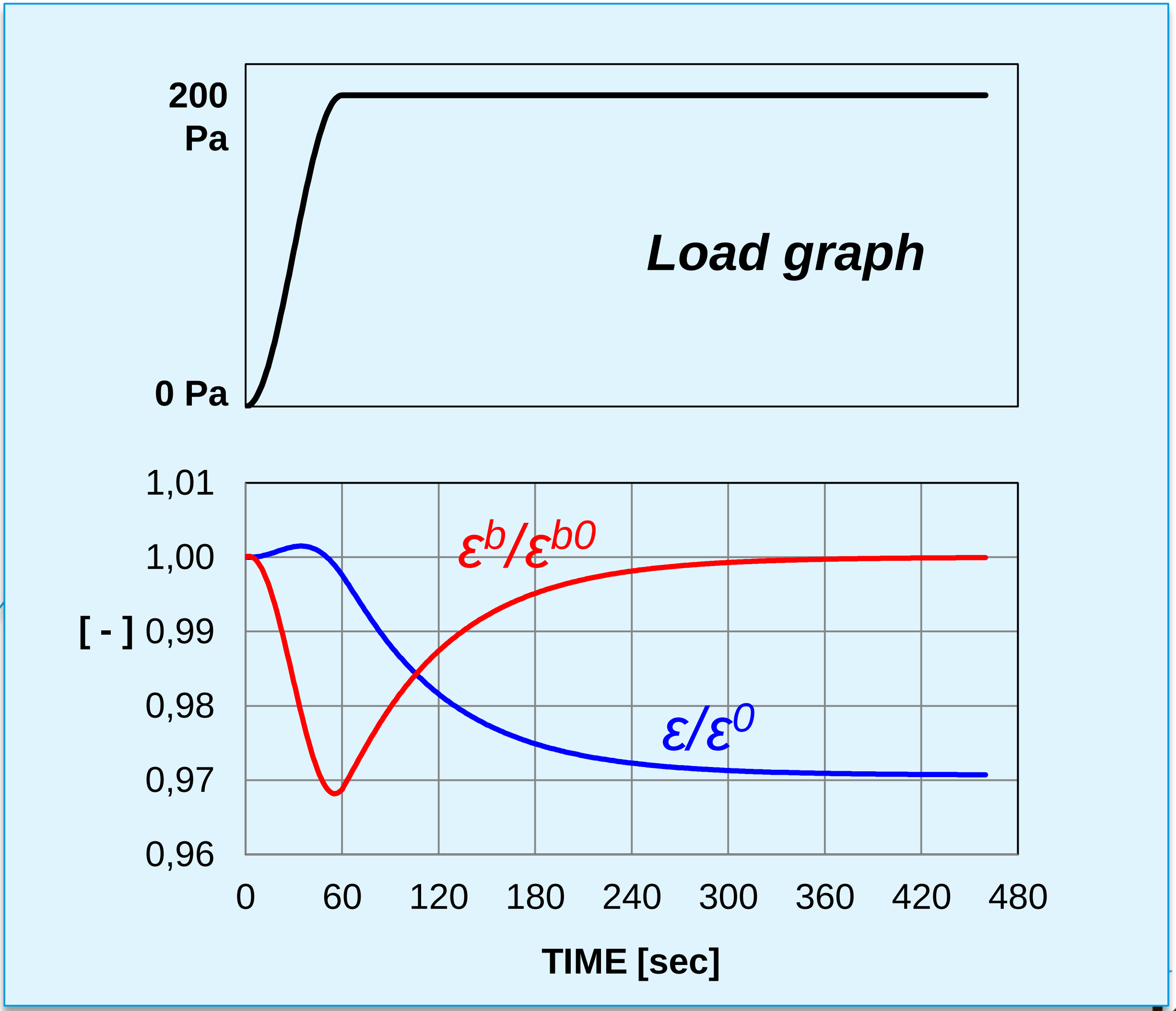
POINT B – zoom p^b *VERSUS* TIME



1D bio-consolidation with and without vessels



POINT B – NORMALIZED POROSITIES *VERSUS* TIME



Mechanical model for the solid scaffold

Hence **the stress-strain constitutive law reads**

$$\dot{\mathbf{t}}^{\overline{\overline{\mathrm{T}}}} = \mathbf{C}_{ECM} : \left(\mathbf{d} - \mathbf{d}_{sw}\right)$$

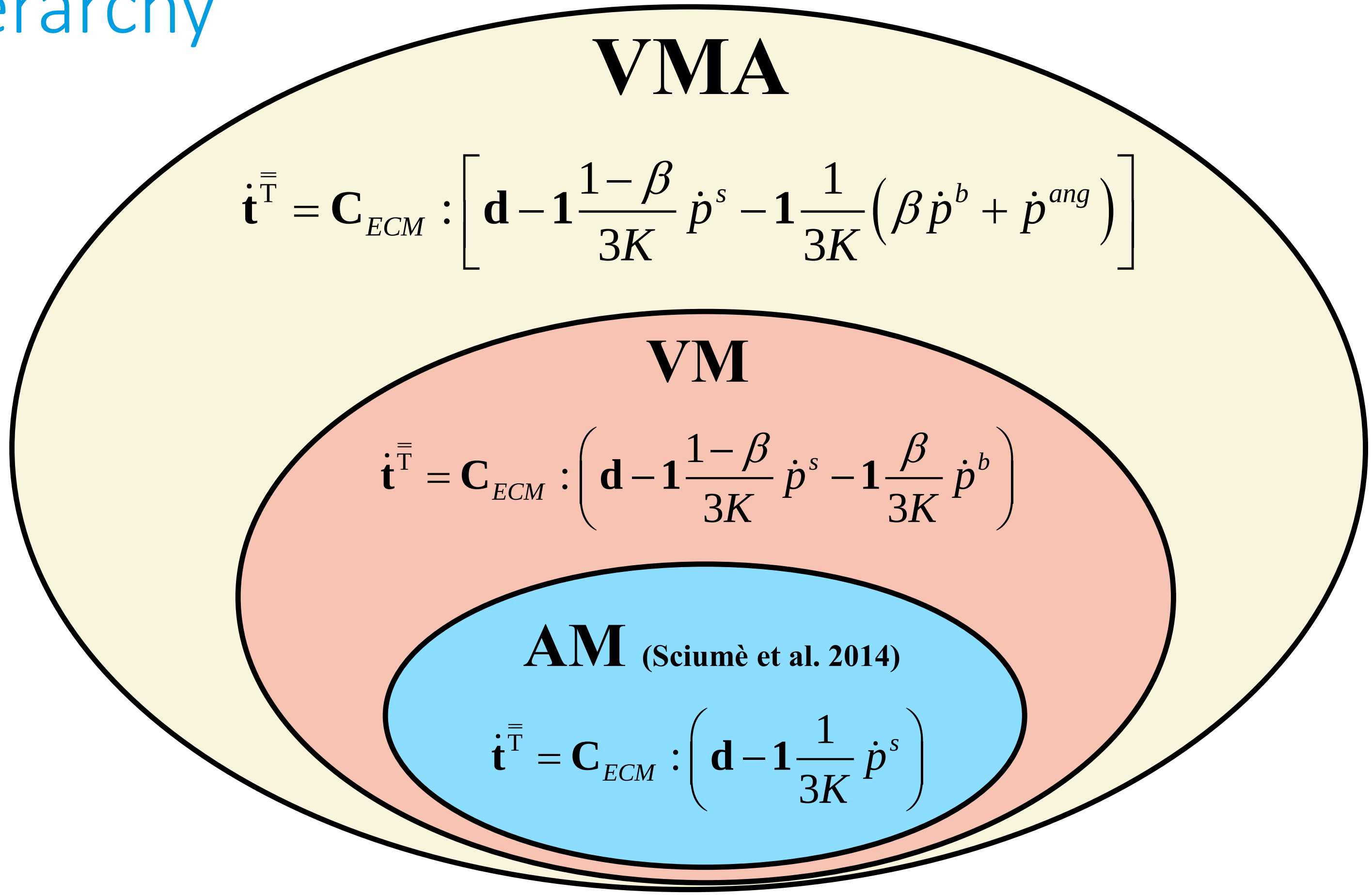
$$\beta = \varepsilon_0^b \left(1 + \alpha\Gamma\right)\left(1 - 2\frac{p^s - p^b}{K^{vess}}\right)$$

$$\dot{p}^{ang} = -\varepsilon_0^b \alpha \left(p^s - p^b\right)\left(1 - \frac{p^s - p^b}{K^{vess}}\right)\dot{\Gamma}$$

with: $$\mathbf{d}_{sw} = \mathbf{1}\frac{1-\beta}{3K}\dot{p}^s + \frac{1}{3K}\mathbf{1}\left(\beta\dot{p}^b + \dot{p}^{ang}\right)$$

<u>Vascular model with angiogenesis (VMA)</u>

Models hierarchy



Reduced models:

- **Vascular model without angiogenesis (VM):** $\beta = \varepsilon_0^b\left(1 - 2\frac{p^s - p^b}{K^{vess}}\right)$ $\quad \dot{p}^{ang} = 0$
- **Avascular model (AM):** $\beta = 0 \quad \dot{p}^{ang} = 0$

Final system of eqs

Primary variables:

$p^{th} \quad p^{hl} \quad p^{l} \quad p^{b} \quad \omega^{\overline{nl}} \quad \omega^{\overline{TAFl}} \quad \omega^{\overline{ECh}} \quad \mathbf{u}_s$

Numerical solution

Computational procedure

- ❖ Mass conservation equation of …
- ❖ Mass conservation equation o…
- ❖ Mass conservation equation o…
- ❖ Mass conservation equation of TUMOR CELLS
- …ation of HOST CELLS
- …ation of ε-fluids (TC…
- …ation of BLOOD

Primary variables:

$p^{th} \quad p^{hl} \quad p^{l} \quad p^{b} \quad \omega^{\overline{nl}} \quad \omega^{\overline{TAFl}} \quad \omega^{\overline{ECh}} \quad \mathbf{u}_s$

Discretization:
FE in space and FD in time

Mathematical model implemented in
Cast3M (FE code of the CEA)

- ❖ Linear momentum equation of the multiphase system (rate form)

MODULE 1
Capillary pressures, interstitial fluid pressure, blood pressure and mass fractions of considered species

MODULE 2
Displacement vector
(solid phase)

Staggered procedure

Residuals controls
Global convergence check

No

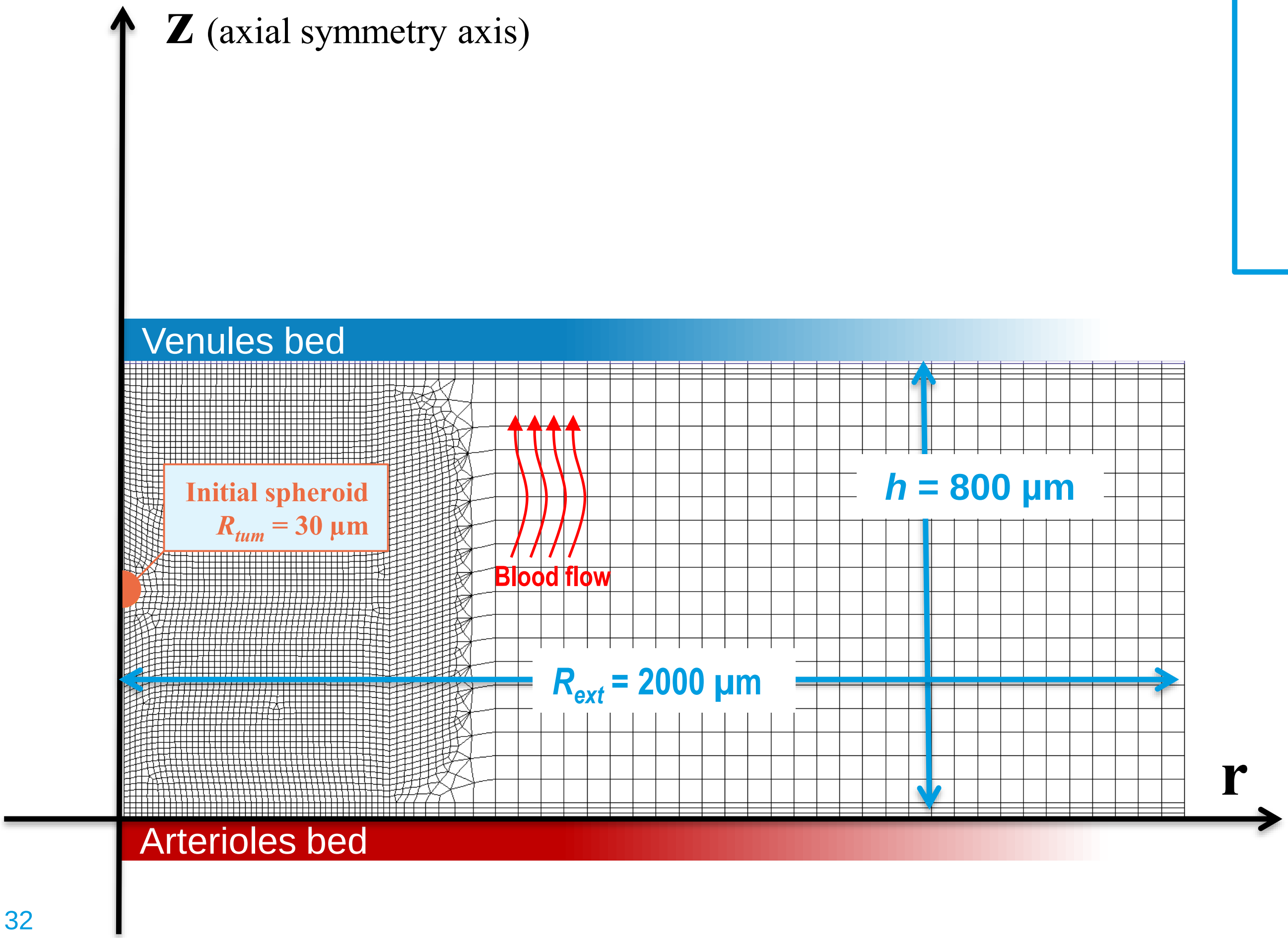
Yes

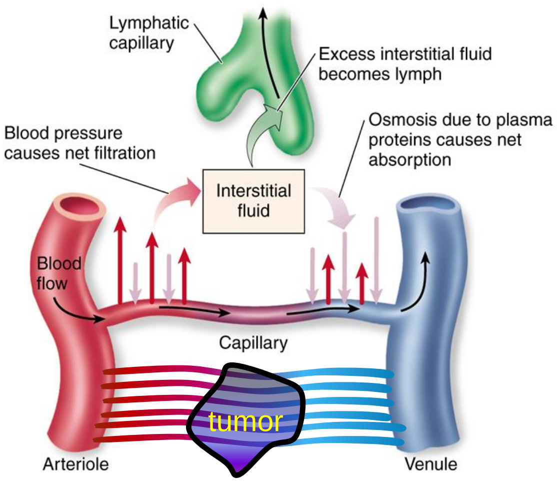
Next step

Angiogenesis

- Modeled phenomena and numerical results

Angiogenesis: TAF release → ECh production → vessel formation dΓ



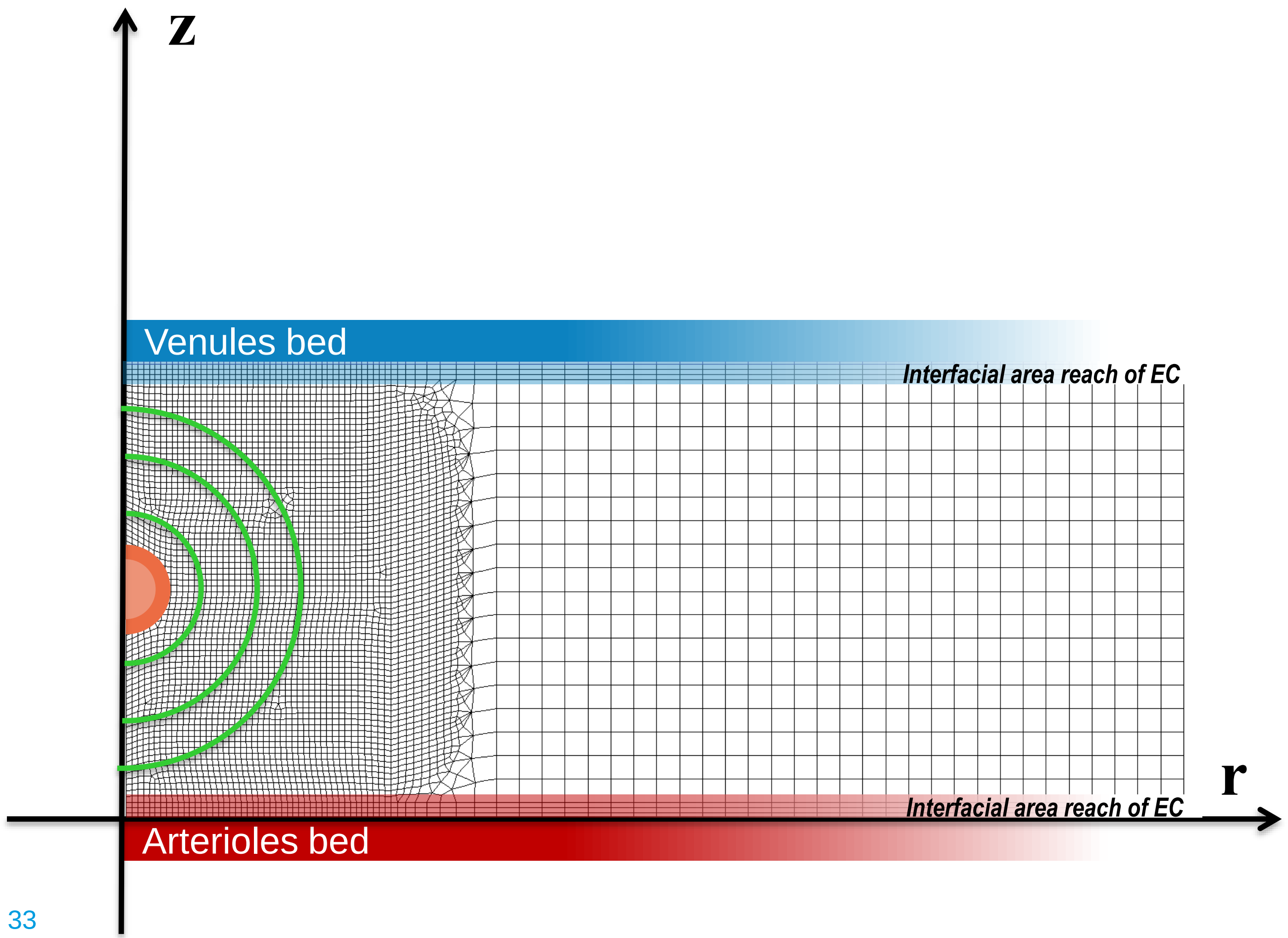


Source: www.bio.utexas.edu

Angiogenesis: TAF release → ECh production → vessel formation dΓ

TAF release

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



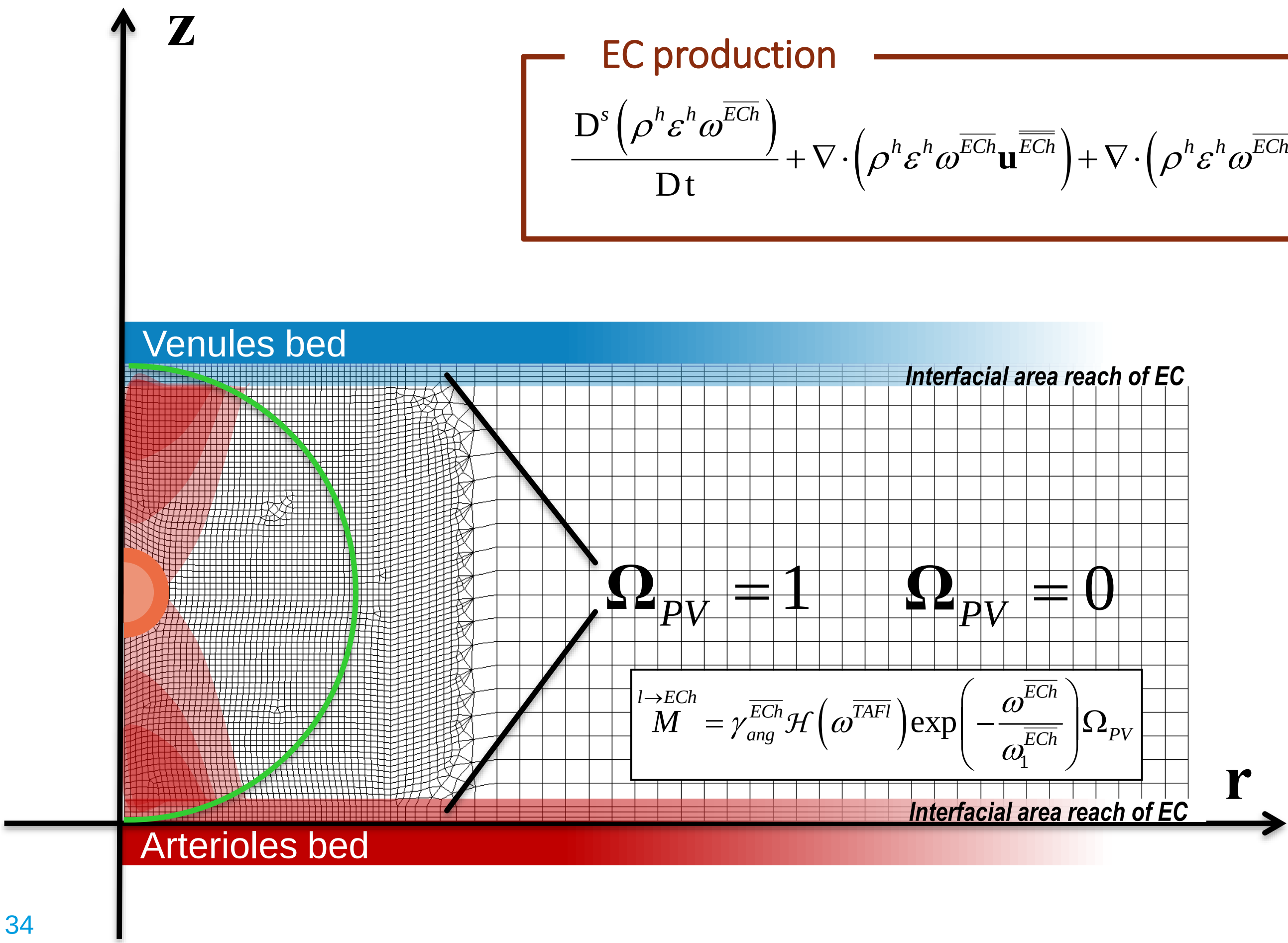
Angiogenesis: TAF release → ECh production → vessel formation dΓ

TAF release

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

EC production

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



$$\overset{l\to ECh}{M} = \gamma_{ang}^{\overline{ECh}}\,\mathcal{H}\left(\overline{\omega^{TAFl}}\right)\exp\left(-\frac{\overline{\omega^{ECh}}}{\overline{\omega_1^{ECh}}}\right)\Omega_{PV}$$

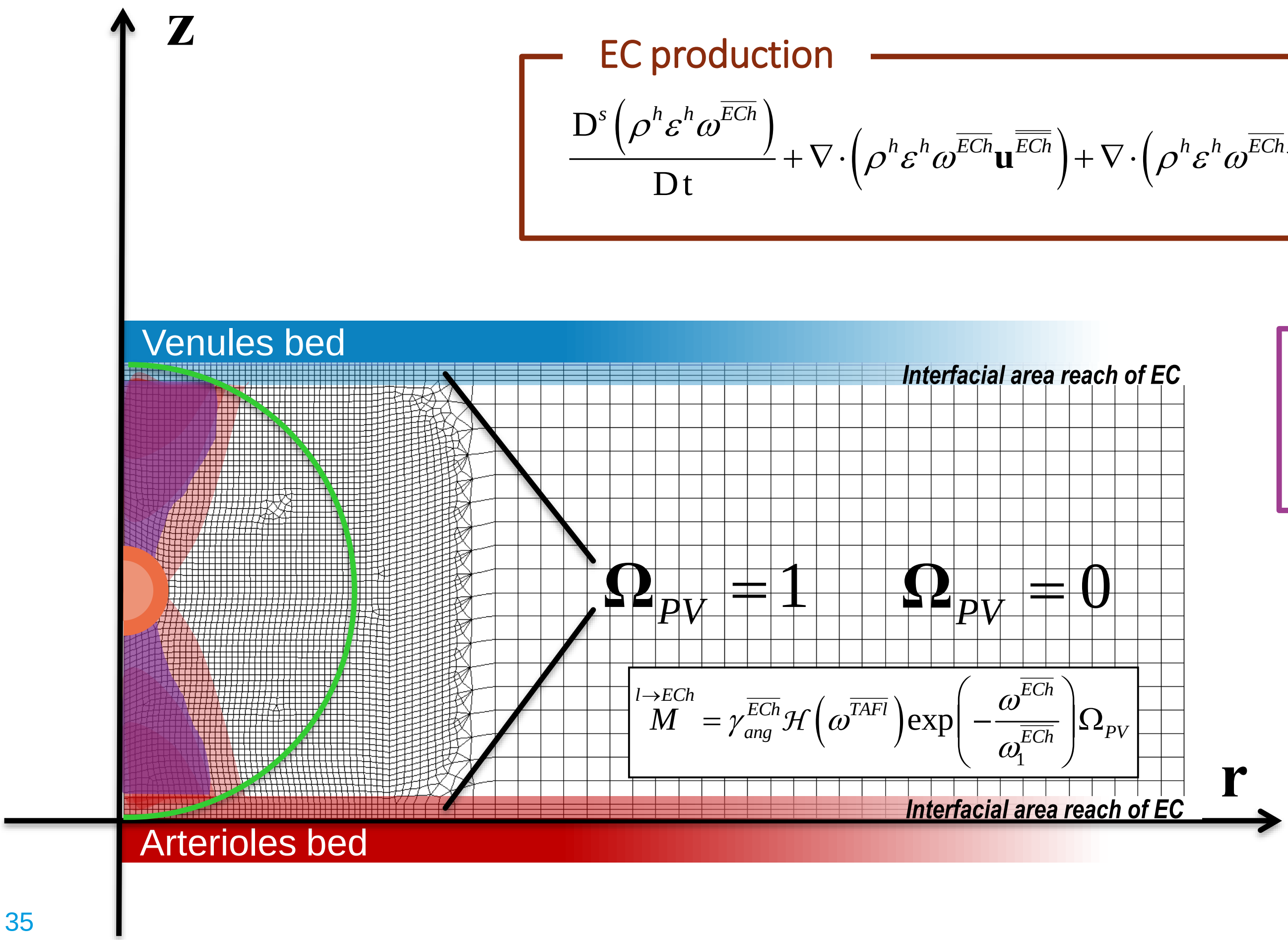
Angiogenesis: TAF release → ECh production → vessel formation dΓ

TAF release

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

EC production

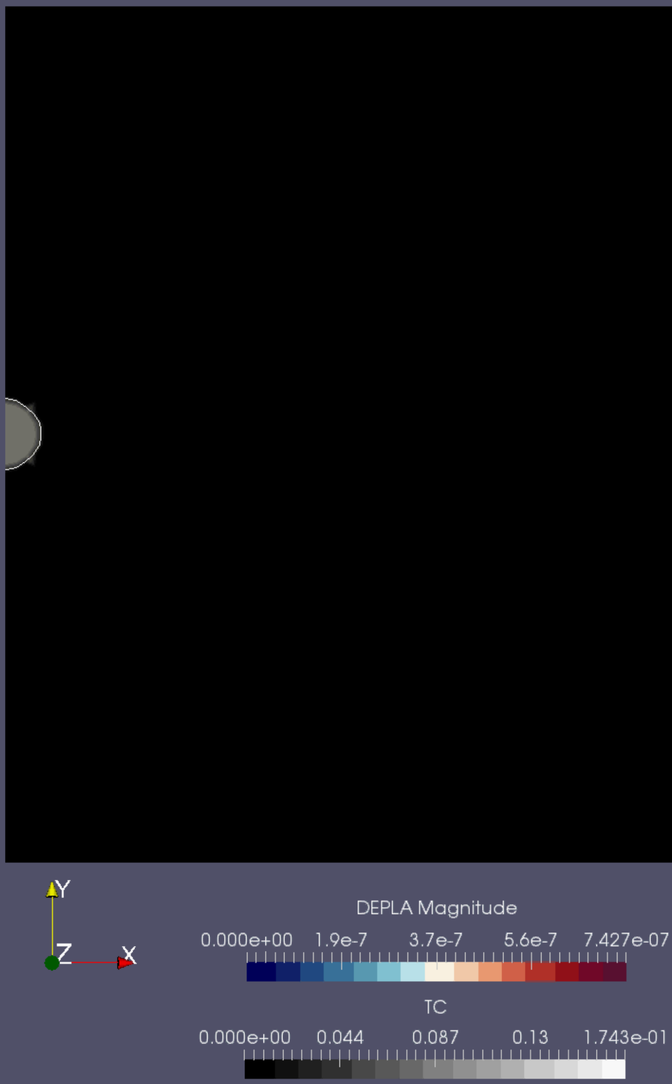
$$\frac{D^s\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\right)}{Dt} + \nabla\cdot\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\mathbf{u}^{\overline{\overline{ECh}}}\right) + \nabla\cdot\left(\rho^h\varepsilon^h\omega^{\overline{ECh}}\mathbf{v}^{\overline{hs}}\right) + \rho^h\varepsilon^h\omega^{\overline{ECh}}\nabla\cdot\mathbf{v}^{\bar{s}}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



Vessel maturation

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

Angiogenesis: TAF release → ECh production → vessel formation dΓ



Computational Algorithm

1st level procedure (called in .dgibi)

$$$$ PASAPAS (ORIGINAL V2016)

```
'DEBPROC' PASAPAS  PRECED*'TABLE';
[…]
Line 132:  'REPETER' BEXTERN; (boucle sur pas de temps)
[…]
Line 197:     'REPETER' BO_BOTH; (boucle couplage)
[…]
                 # CALCUL THERMIQUE
Line 238:           CHTER = TRANSNON PRECED;
Line 269:           REEV_THE PRECED  1 ;
[…]
                 # CALCUL MECANIQUE
Line 310:           TT = UNPAS PRECED;
Line 354:           REEV_MEC PRECED 1;
[…]
                 # Test de la convergence méca-thermique !
[…]
Line 411:     'FIN' BO_BOTH ;
[…]
              PRECED.'PERSO1_APPEL' = 2 ;
              PERSO1 PRECED;
[…]
Line 703:  'FIN'  BEXTERN;
[…]
'FINPROC' PRECED ;
```

2nd level procedure (called by pasaps)

$$$$ TRANSNON (ORIGINAL V2016)

- CALL **@MATETHM** (update necrosis, ε, ε^b, $\mathbf{d}_{sw}$, K_{ij}, C_{ij} and f_i)
- COMPUTE SOLUTION FOR PRESSURE AND MASS FRACTIONS

$$$$ REEV_THE (PERSONAL PROCEDURE)

- CALL **@MATETHM** (update necrosis, ε, ε^b, $\mathbf{d}_{sw}$, K_{ij}, C_{ij} and f_i)
- UPDATE of **PRECED . 'ETAT2'**
- PROVIDES SWELLING STRAIN RATE, $\mathbf{d}_{sw}$, to the mechanical part

$$$$ UNPAS (ORIGINAL V2016)

COMPUTING OF THE DIPLACEMENT VECTOR $\mathbf{u}^s$

$$$$ REEV_MEC (PERSONAL PROCEDURE)

COMPUTING OF **div**($\mathbf{v}^s$), THIS TERM IS NEEDED BY TRANSNON

$$$$ PERSO1 (PERSONAL PROCEDURE)

- **UPDATE THE STATE VARIABLE VECTOR**
- PREPARE THE NEXT TIME STEP: **PRECED.ETAT1 = PRECED.ETAT2;**

Computational Algorithm: @MATETHM

3rd level procedure

$$$$ @MATETHM (PERSONAL PROCEDURE)

```
'DEBPROC' @MATETHM  MOD_THM*'MMODEL' THPC_W*'CHPOINT';
[…]
     'REPETER' BZ_THM nzone; (boucle THM-zones)
[…]
        Call of material parameters
        Call of primary variables
        Computing of dependent variables
[…]
        (1) Update of angiogenesis;

        (2) Update of porosity;

        (3) Update of necrosis;

        (4) Update THERMOHYDRIQUE material;
           (3.a) computing of swelling strain d_sw
           (3.b) computing of K_ij, C_ij, f_i for phases' flow

        (5) Update DIFFUSION material;
          (4.a) K_ij, C_ij, f_i for oxygen advection-diffusion
          (4.b) K_ij, C_ij, f_i for TAF advection-diffusion
          (4.c) K_ij, C_ij, f_i for EC advection-diffusion
          (4.d) K_ij, for the blood flow model
[…]
     'FIN' BZ_THM;
[…]
'FINP'  MAT1 F0;
```

2nd level procedure (called by pasaps)

$$$$ TRANSNON (ORIGINAL V2016)

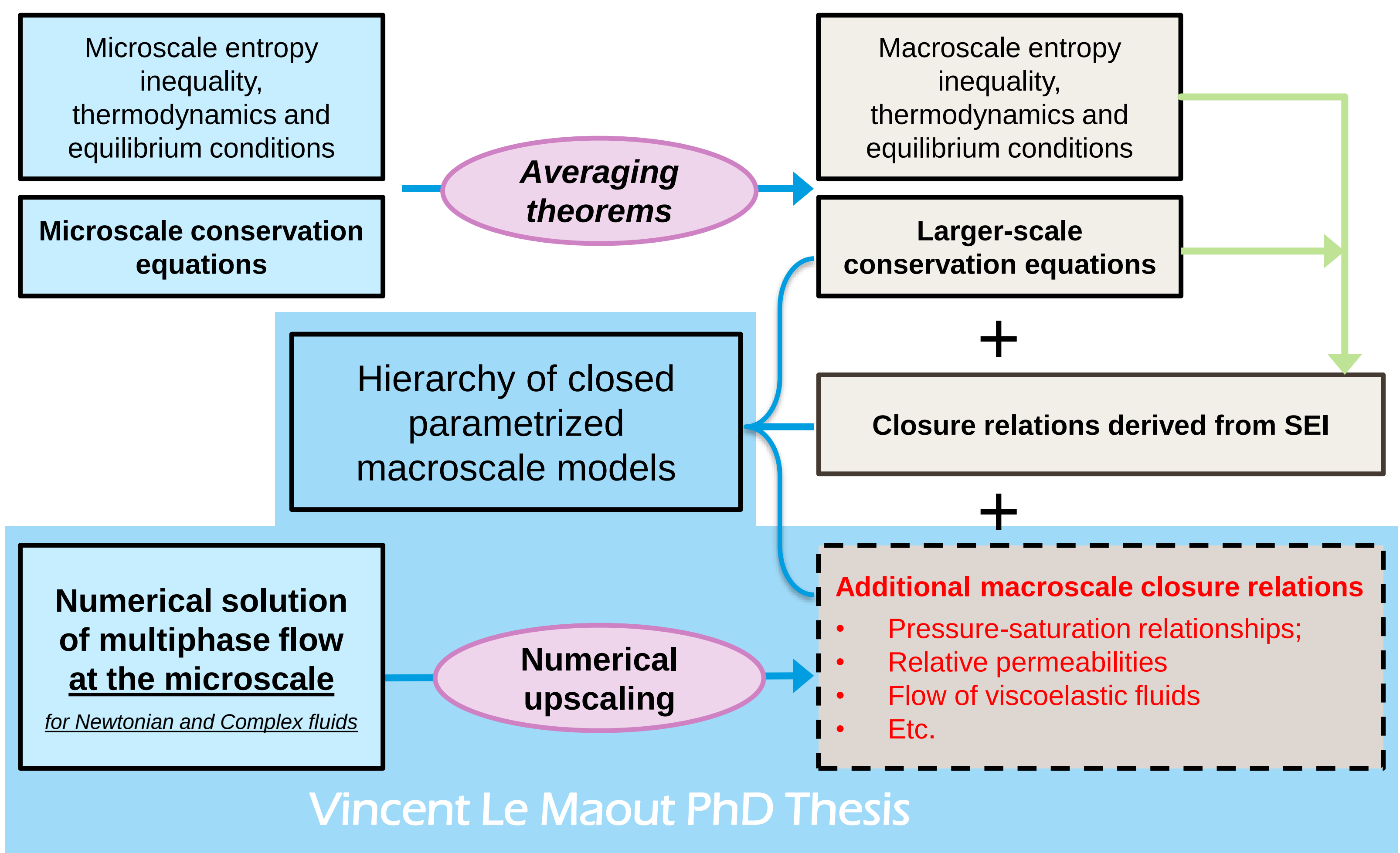
- CALL **@MATETHM** (update necrosis, ε, ε^b, $\mathbf{d}_{sw}$, K_{ij}, C_{ij} and f_i)
- COMPUTE SOLUTION FOR PRESSURE AND MASS FRACTIONS

$$$$ REEV_THE (PERSONAL PROCEDURE)

- CALL **@MATETHM** (update necrosis, ε, ε^b, $\mathbf{d}_{sw}$, K_{ij}, C_{ij} and f_i)
- UPDATE of **PRECED . 'ETAT2'**
- PROVIDES SWELLING STRAIN RATE, $\mathbf{d}_{sw}$, to the mechanical part

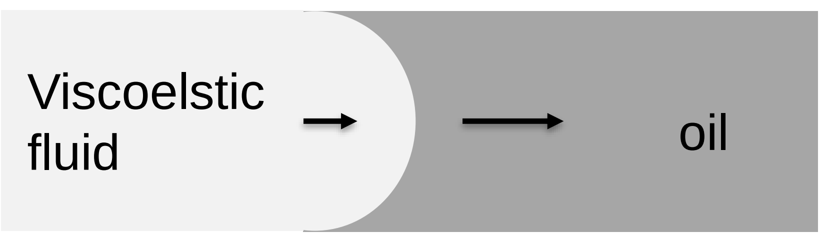
Micro- Macro- Description in Averaging Theories

Thermodynamically Constrained Averaging Theory (TCAT)

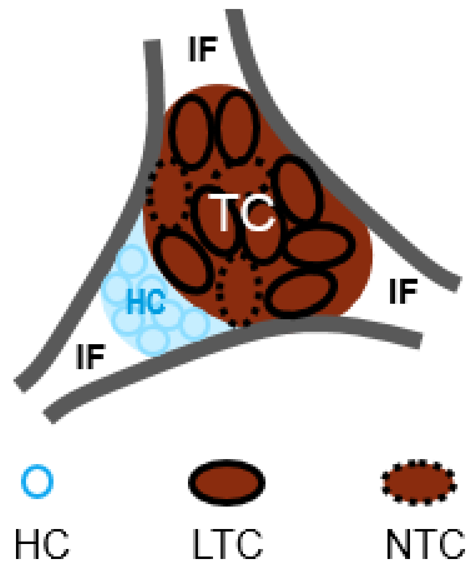


Aim of the research project

Simulate **microscale multiphase flows** in **porous media** in order to provide **closure relation** to macroscale model or **micro-relevant equations** for volume-averaging method. The target applications deal with the fields of **petroleum engineering** and **biomechanics area**.



Pore-scale flow for enhanced oil recovery simulation



Micro model for biological multiphase flow
Source Giuseppe Sciume ALERT Workshop

Diffuse interface model

The **description** of the interface's motion is taken into account by the **Cahn-Hilliard** model [1].

$$\frac{\partial C}{\partial t} + \mathbf{u} \cdot \nabla C - \frac{1}{\mathrm{Pe}} \nabla \cdot \left(M \nabla \psi \right) = 0$$

$$\psi = -\lambda \Delta C + \beta \phi'\left(c\right)$$

The **Phase-Field model** ensures the **continuity** of the fluid properties through the interface. The interface thickness is controlled by the parameter ε

$$\varepsilon = \sqrt{\frac{\lambda}{\beta}}$$

[1] Faruk O. Alpak, Beatrice Riviere and Florian Frank. *A phase-field method for direct simulation of two-phase flows in pore-scale media using a non-equilibrium wetting boundary condition*. Comput. Geosci 2016

Multiphasic Flow Simulation

Flow dynamic model in a single pore

The **Cahn-Hilliard system** is coupled with the **Navier-Stokes equation** :

$$\bar{\rho}\frac{d\mathbf{u}}{dt}+(\mathbf{u}\cdot\nabla)\mathbf{u}=-\nabla p+\frac{1}{\mathrm{Re}}\nabla\cdot\left[\bar{\mu}\left(\nabla\mathbf{u}+\nabla^{t}\mathbf{u}\right)\right]+\bar{f}$$

$$\nabla\cdot\mathbf{u}=0$$

coupling term

$\bar{f}$ accounts for the **capillarity forces** between the phases [1]

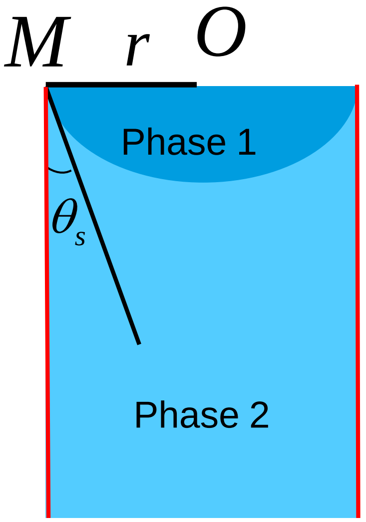
$$\bar{f}=\frac{\psi\nabla C}{\mathrm{Ca}\,\mathrm{Re}}$$

Dynamic boundary conditions for the interface

No flux conditions do not take into account the **wettability** of the solid scaffold. On solid walls, conditions are imposed such as it corresponds to **realistic interface behavior**

$$\frac{\partial \mu}{\partial n} = 0 \text{ sur } \partial\Omega$$

$$\vec{n} \cdot \nabla C = -\tan\left(\frac{\pi}{2} - \theta_s\right)\left|\vec{t} \cdot \nabla C\right| + \kappa \frac{\partial C}{\partial t} \text{ sur } \partial\Omega$$

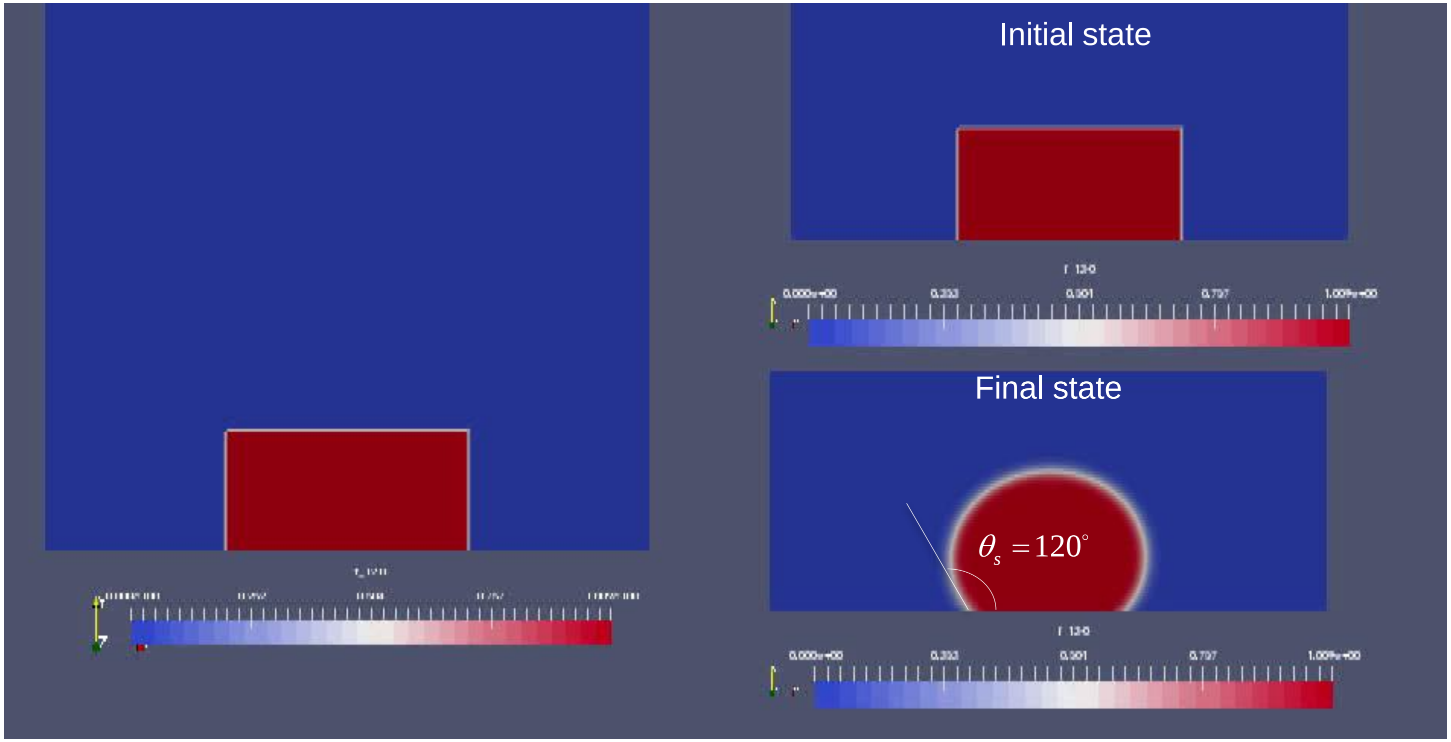


Static angle equilibrium condition at common point

Multiphasic Flow Simulation

Numerical results

Even if the full-coupled Cahn-Hilliard/Navier-Stokes model is **not completely validated** yet, **some interesting results has been obtained** with the Fenics Software:



Conclusion

- The Cahn-Hilliard model has been successfully implemented, either with no flux or dynamic angle boundary conditions;
- The Navier-Stokes/Cahn-Hilliard system is implemented and is being validated;

Next steps

- Migrate the code currently under fenics to Castem for compatibility;
- Compute and test upscaling methods for macroscale model ;
- More complex geometry will be tested in order to study the robustness of the NSCH system;