Modeling Porosity Changes induced by Hyaluronidase Injection into Biological Tissue

M. Deville*, R. Natalini°, C. Poignard*

*Inria Sud-Ouest, MONC team

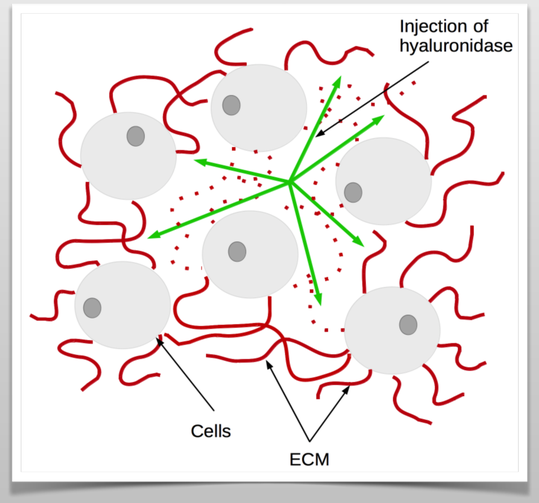
°IAC, Rome, Italy

Abstract

- The hyaluronidase is an enzyme that **degrades** hyaluronic acid, a constituent of the **ECM**. It is used to enhance gene transfection. Our goal is to evaluate the **effect of an injection of hyaluronidase on the porosity** of a biological tissue.

- We developed a **poroelastic macroscopic model** of biological tissue based on :
  - Balance laws
  - Constitutive relations

- We consider that the **changes of porosity** are due to :
  - the **elasticity** of the medium
  - the fact that cells are **slightly compressible**
  - the **effect of hyaluronidase**



Mathematical Model

- **Assumptions** : saturated medium, incompressible liquid phase, slightly compressible solid phase, negligible inertia

$$\begin{cases} \nabla.\left(\left(g\varepsilon_{cm}+g\mathcal{C}_{ells}\right)\left(\lambda(\nabla.\mathbf{u})I+\mu(\nabla\mathbf{u}+\nabla\mathbf{u}^T)\right)\right)=\nabla P \\ (g\varepsilon_{cm}+g\mathcal{C}_{ells})s_0\dfrac{\partial P}{\partial t}-\nabla.(\boldsymbol{\kappa}\nabla P)=fQ_{inj}+\left(\dfrac{\rho_s^{R,0}}{\rho_f^R}-1\right)g\varepsilon_{cm}(Kh+a_r(f(0,\mathbf{x})-f))-\nabla.\left(\dfrac{\partial\mathbf{u}}{\partial t}\right) \end{cases}$$

$$\begin{cases} \dfrac{\partial H}{\partial t}=\nabla.(\mathbf{D}^0\nabla H)+\nabla H.(\dfrac{1}{f}\boldsymbol{\kappa}\nabla P-\dfrac{1}{f}\mathbf{D}^0\nabla f)+H\left(-\dfrac{k_d}{f}-\nabla.\left(\dfrac{\partial\mathbf{u}}{\partial t}\right)+\nabla.\left(\dfrac{1}{f}\boldsymbol{\kappa}\nabla P-\dfrac{1}{f}\mathbf{D}^0\nabla f\right)\right)+\mathcal{S}_{inj} \\ \dfrac{\partial g\mathcal{C}_{ells}}{\partial t}+\left(s_0\dfrac{\partial P}{\partial t}+\nabla.\left(\dfrac{\partial\mathbf{u}}{\partial t}\right)\right)g\mathcal{C}_{ells}=0 \\ \dfrac{\partial g\varepsilon_{cm}}{\partial t}+\left(KH+a_r(f(0,\mathbf{x})-f)+s_0\dfrac{\partial P}{\partial t}+\nabla.\left(\dfrac{\partial\mathbf{u}}{\partial t}\right)\right)g\varepsilon_{cm}=0 \\ g\varepsilon_{cm}+g\mathcal{C}_{ells}+f=1 \end{cases}$$

→ The **final model** contains equations on :

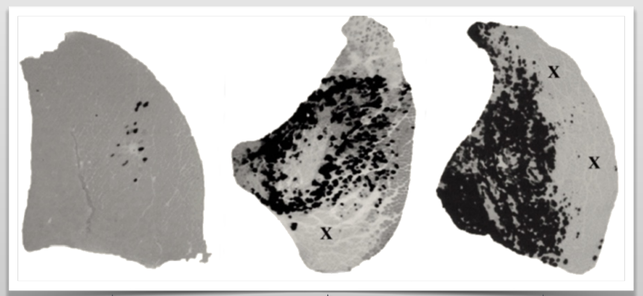
- *displacement*
- *pressure*
- *enzyme concentration*
- *volume fraction of cells*
- *volume fraction of ECM*
- *porosity*

→ **Boundary conditions** :

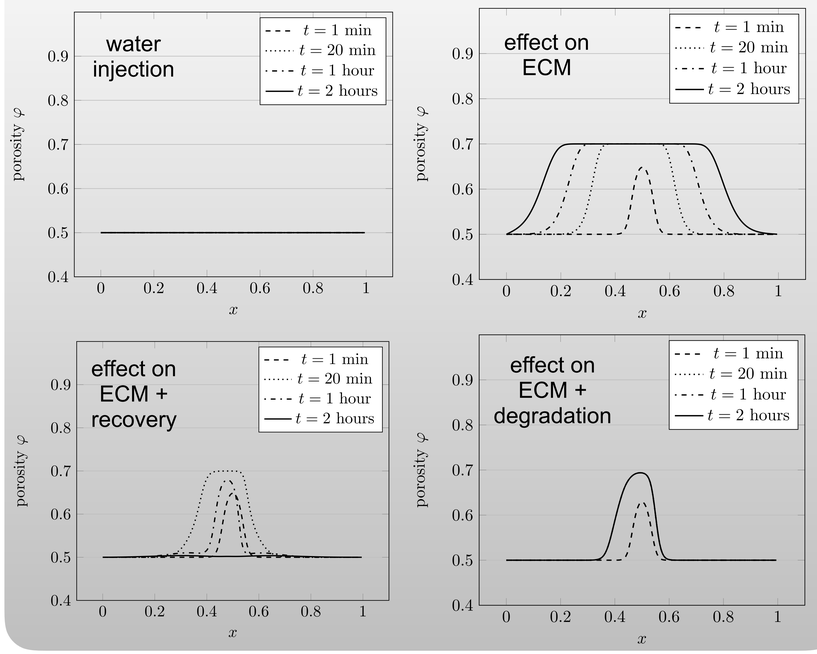
- Free boundary on Γ_1 : $\boldsymbol{\sigma}(\mathbf{u})\,n=0,\ \nabla P\,.\,n=0,\ H=0$
- Fixed boundary on Γ_2 : $\mathbf{u}=0,\ P=0,\ H=0$

Motivation

Pretreatment of skeletal muscle with hyaluronidase followed by electrotransfer of plasmid DNA **improves gene expression**

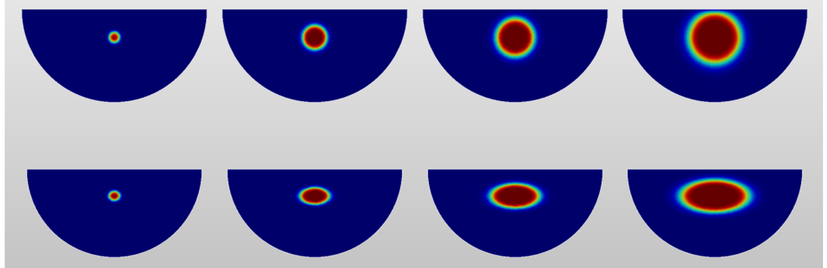


1D numerical simulations



2D numerical simulations

Isotropic medium vs transverse isotropic medium



References

1. **Optimisation of electrotransfer of plasmid into skeletal muscle by pretreatment with hyaluronidase - increased expression with reduced muscle damage,** E. Signori, KE. Wells, VM. Fazio, and DJ. Wells
2. **Mathematical Modeling of a Solid–Liquid Mixture with Mass Exchange Between Constituents,** L. Fusi, A. Farina, D. Ambrosi