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Abstr	8
ECM degrading enzymes can degrade some used to enhance gene transfection or penet to evaluate the effect of an injection of ECM of a biological tissue.	tra
 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 an ECM degrading enzyme 	
Mathematic	
Assumptions : saturated medium, incompressolid phase, negligible inertia	;S
Mass balance on fluid Volume fraction (Porosity)	
Interstitial pressure (2) Mass balance law on ECM Volume fraction of	of E
Mass balance law on cells Volume fraction of	of c

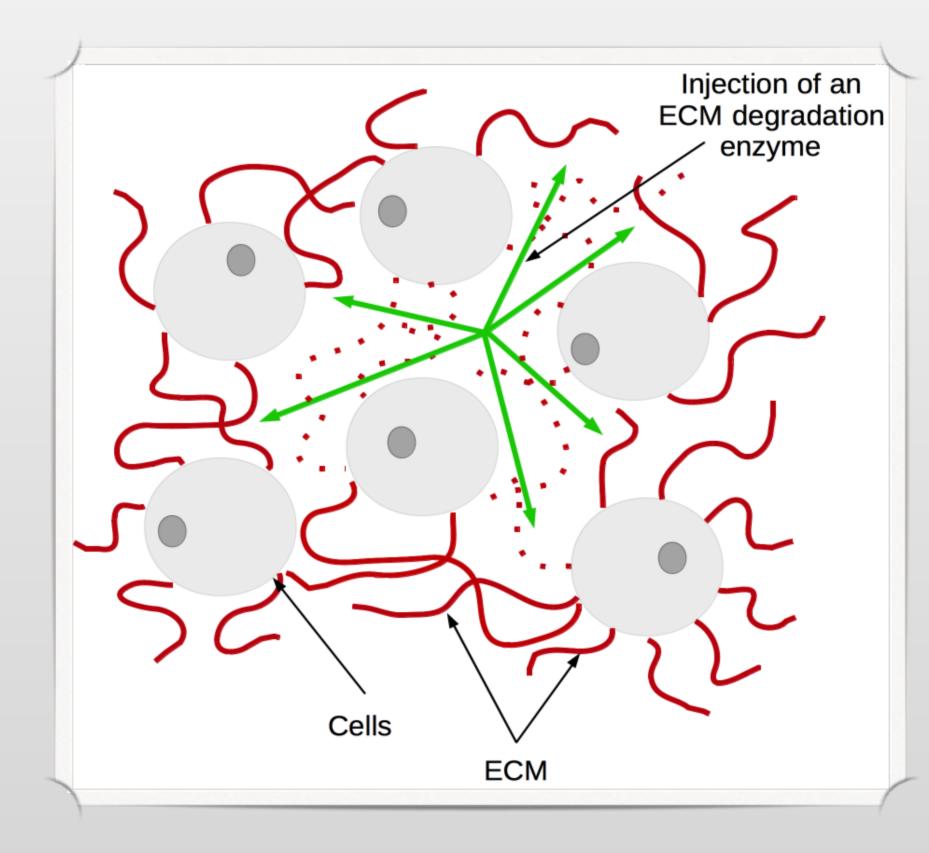
Momentum balance law on fluid phase **Displacement (1)** Momentum balance law or solid phase Mass balance law on Enzyme's concentration (4) enzyme's concentration Mass balance law on Therapeutic agent's therapeutic agent's concentration (7) concentration **Constitutive Relations** Darcy, Hooke, Starling

A continuum mechanics model of enzyme-based tissue degradation in cancer therapies

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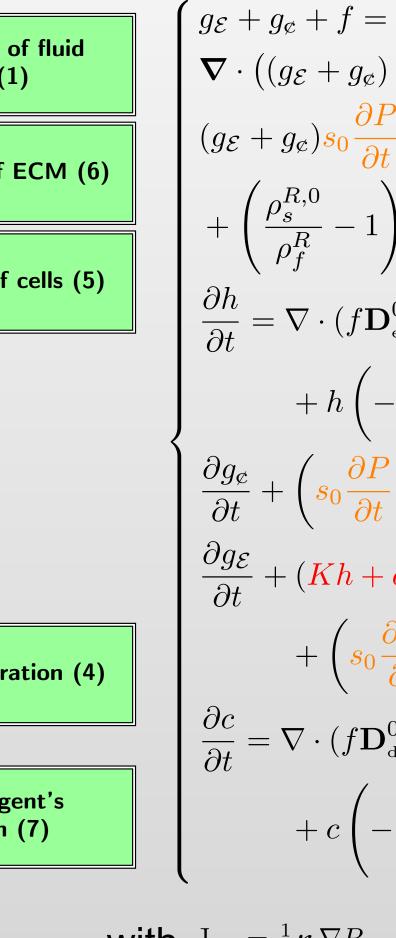
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constituents of the **ECM**. They are ration of drugs into tumors. Our goal is degrading enzymes on the porosity



al Model

ssible liquid phase, slightly compressible



$$\nabla \cdot \left((g_{\mathcal{E}} + g_{\varepsilon}) \left(\lambda (\nabla \cdot \mathbf{u}) I + \mu (\nabla \mathbf{u} + \nabla \mathbf{u}^{T}) \right) \right) = \nabla P \qquad (2)$$

$$(g_{\mathcal{E}} + g_{\varepsilon}) s_{0} \frac{\partial P}{\partial t} - \nabla \cdot (\kappa \nabla P) = Q_{\text{inj}}^{\text{tot}} + \gamma (P_{v} - P)$$

$$+ \left(\frac{\rho_{s}^{R,0}}{\rho_{f}^{R}} - 1 \right) g_{\mathcal{E}} (Kh + a_{r} (f(0, \mathbf{x}) - f)) - \nabla \cdot \left(\frac{\partial \mathbf{u}}{\partial t} \right)^{(3)}$$

$$\frac{\partial h}{\partial t} = \nabla \cdot (f \mathbf{D}_{\text{enz}}^{0} \nabla h + h J_{\text{enz}})$$

$$(4)$$

$$+h\left(-\frac{k_{\rm enz}^{\rm o}}{f}-\nabla\cdot\left(\frac{\partial\mathbf{u}}{\partial t}\right)\right)+\mathcal{S}_{\rm enz}$$

$$\frac{g_{\mathcal{C}}}{\partial t}+\left(s_{0}\frac{\partial P}{\partial t}+\nabla\cdot\left(\frac{\partial\mathbf{u}}{\partial t}\right)\right)g_{\mathcal{C}}=0$$
(6)

$$\frac{\partial g_{\mathcal{E}}}{\partial t} + \left(\frac{s_0}{\partial t} + \nabla \cdot \left(\frac{\partial u}{\partial t}\right)\right) g_{\mathcal{E}} = 0$$

$$\frac{\partial g_{\mathcal{E}}}{\partial t} + \left(Kh + a_r(f(0, \mathbf{x}) - f)\right) g_{\mathcal{E}}$$
(5)

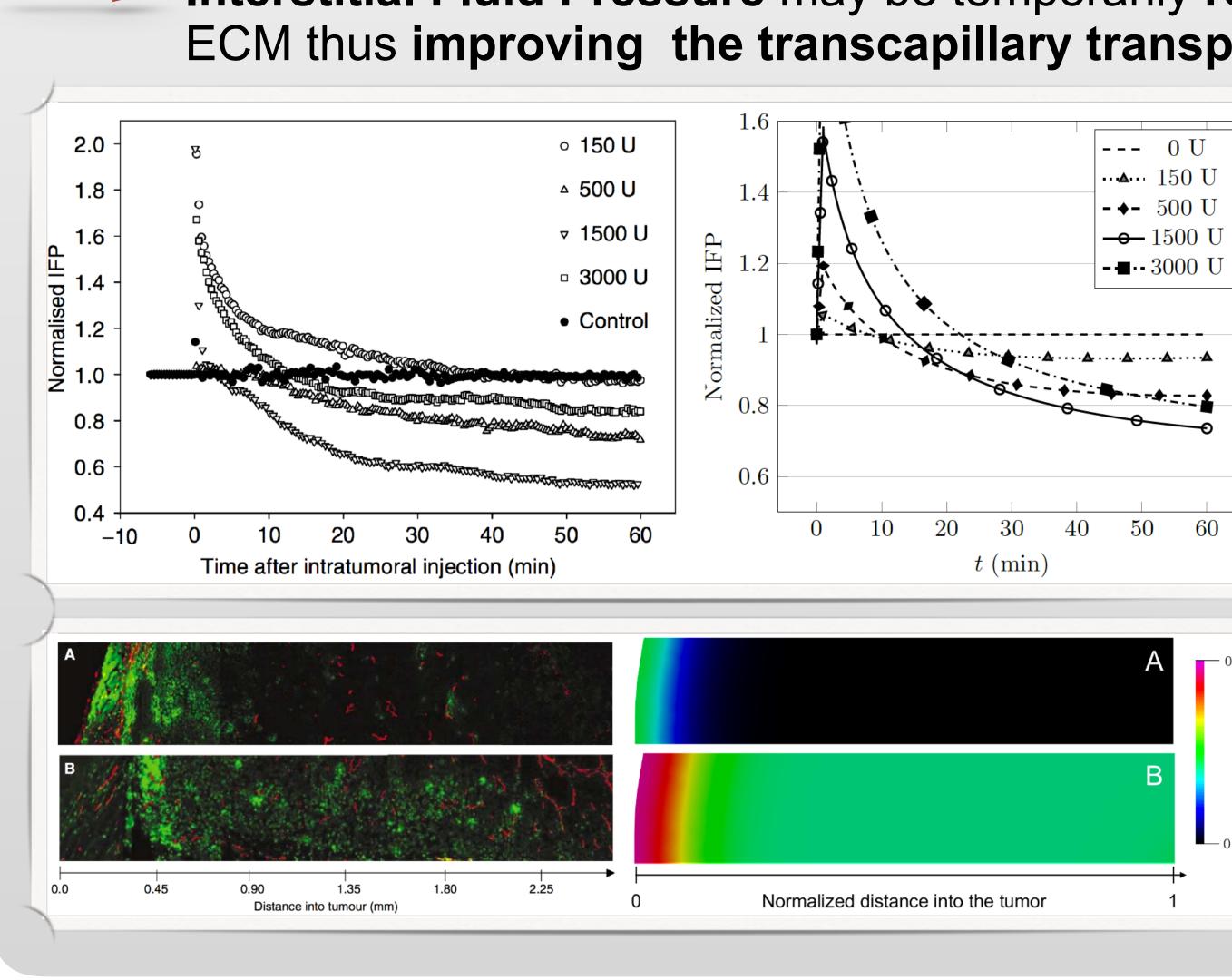
$$+\left(\frac{s_0}{\partial t}\frac{\partial P}{\partial t} + \nabla \cdot \left(\frac{\partial \mathbf{u}}{\partial t}\right)\right)g_{\mathcal{E}} = 0$$
(6)

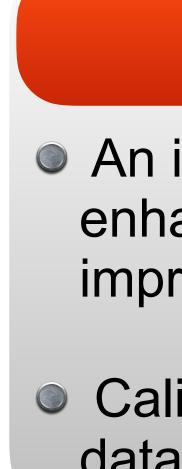
$$\frac{\partial c}{\partial t} = \nabla \cdot \left(f \mathbf{D}_{drug}^{0} \nabla c + c J_{drug} \right) + c \left(-\frac{k_{drug}^{d}}{f} - \nabla \cdot \left(\frac{\partial \mathbf{u}}{\partial t} \right) \right) + \mathcal{S}_{drug}$$
(7)

with $J_{enz} = \frac{1}{f} \kappa \nabla P - \mathbf{D}_{enz}^0 \nabla f$ and $J_{drug} = \frac{1}{f} \kappa \nabla P - \mathbf{D}_{drug}^0 \nabla f$

The **distribution** of therapeutic agents is into an ECM degrading enzyme, thereby process.

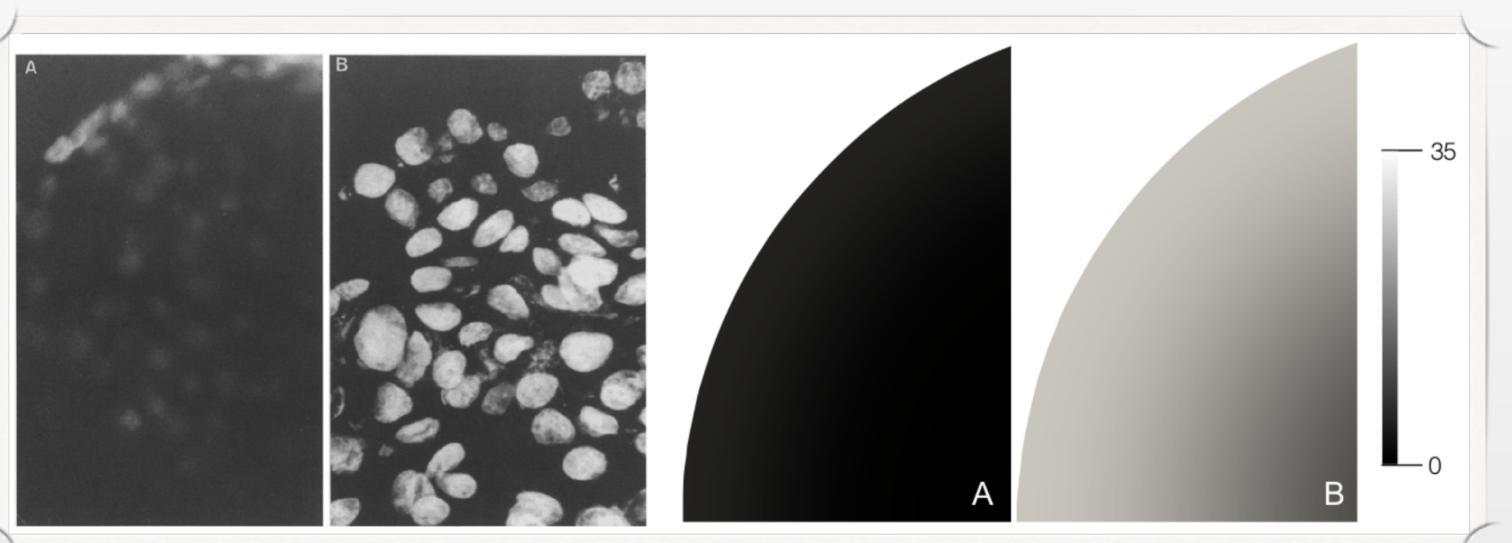
wider when the spheroid was previously incubated improving the diffusion





Drug penetration in tumors

An injection of matrix degrading enzymes **removes diffusive hindrance** to the penetration of therapeutic molecules



Interstitial Fluid Pressure may be temporarily reduced by degrading the tumor ECM thus improving the transcapillary transport of therapeutic agents

Conclusion

An injection of ECM degrading enzyme enhances the distribution of drugs by improving both diffusion and convection

Calibration with additional experimental data is needed



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IFP is reduced in a dosedependent manner up to a maximum reduction. Increasing the dose further, IFP is reduced to a lesser extent.

Without pretreatment, the drugs stay at the **periphery**. An enzyme pretreatment permits to obtain a **wider** distribution.

References

Hyaluronidase induces a transcapillary pressure gradient and improves the distribution and uptake of liposomal doxorubicin (Caelyx) in human osteosarcoma xenografts, Eikenes, Tari, Tufto, Bruland and De Lange Davis (2010)

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