T2: Nested Models in Biomedicine

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Kick-off del Gruppo di Fisica Matematica
14 marzo 2018
Politecnico di Torino

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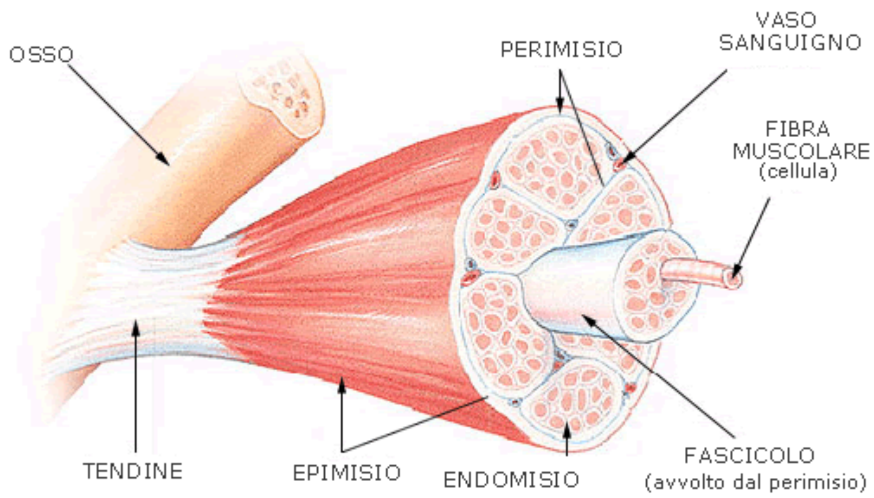
State of the art

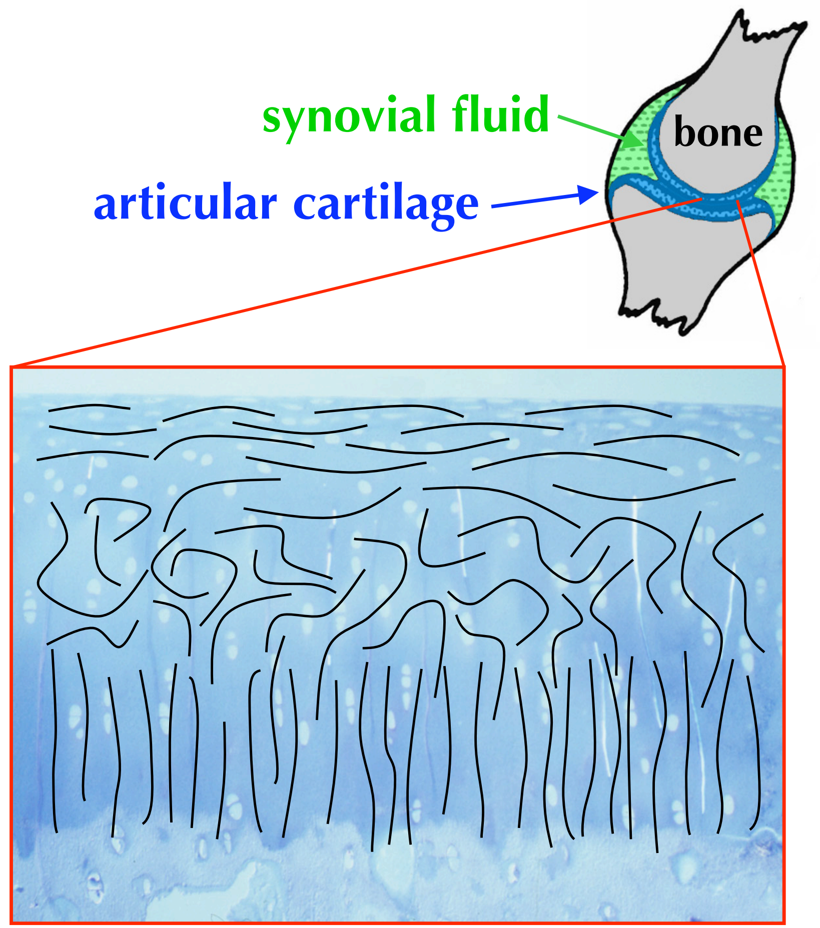
Biological tissues as *living* porous media

Muscle



https://www.google.it/search?q=muscoli...

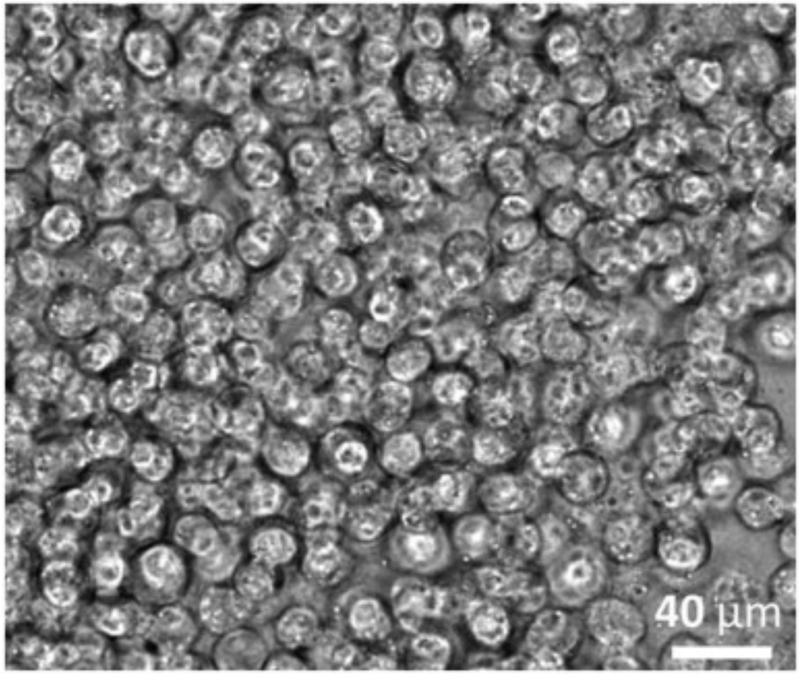
Articular cartilage



Federico, S., Grillo, A., La Rosa, G., Giaquinta, G., Herzog, W. (2005) *J. Biomech.*, **38**, 2008–2018.

Biological tissues as *living* porous media

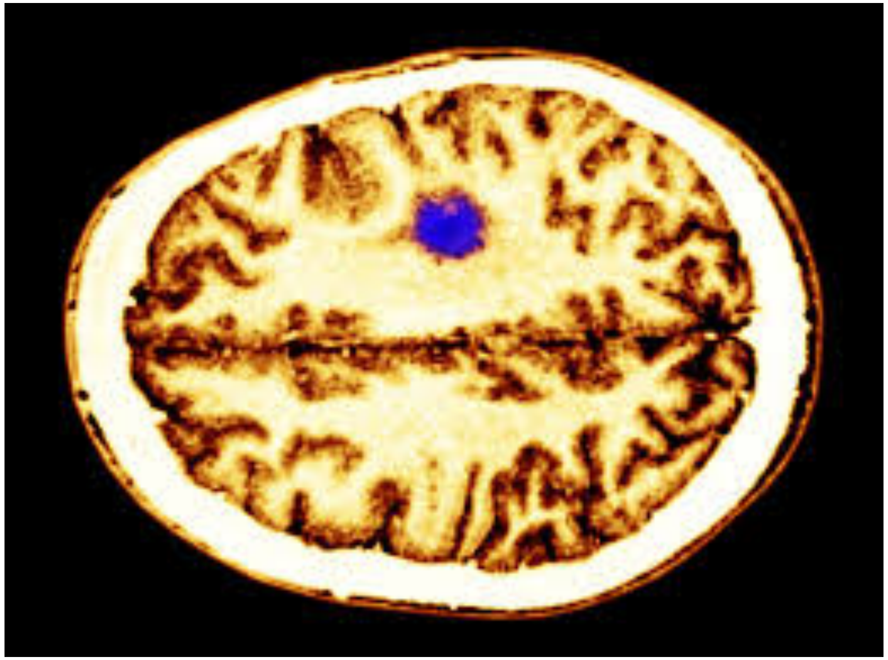
Cellular aggregates



"Photograph of CHO cell suspension"

Image taken from Preziosi, L., et al. (2010). *J. Theor. Biol.*, **262(1)**, 35–47

Tumour tissue



https://www.google.it/search?q=Brain&client...

Biological tissues are living matter

Remodelling:

Adaptation of the structure and of the material properties of a tissue in response to both internal and external stimuli.

Growth:

Gain or loss of mass of a tissue. It can be appositional (new material is either laid over or removed from the pre-existing one) or volumetric (it can be diverted either in a change of volume or in a change of density of the tissue).

Both phenomena are the result of complexes of processes that involve a variety of physical, chemical, and genetic processes, and several levels of observation (i.e., from the molecular to the macroscopic scale of the tissue).

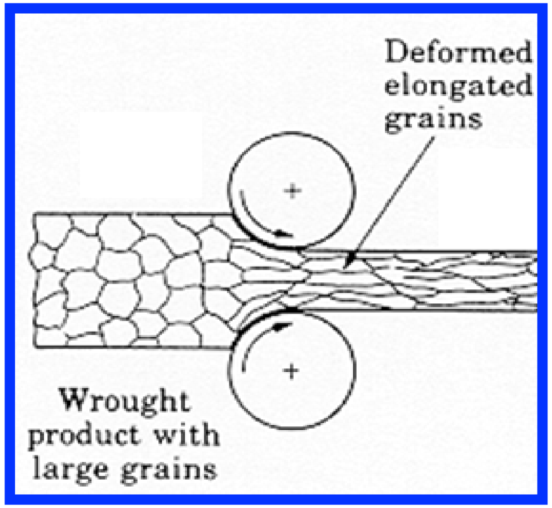
Taber, L.A. (1995). Biomechanics of growth, remodeling and morphogenesis. *ASME Appl. Mech. Rev.*, **48**, 487–545.

Cowin, S.C. (2000). How is a tissue built? *J. Biomech. Eng.*, **122**, 553–569.

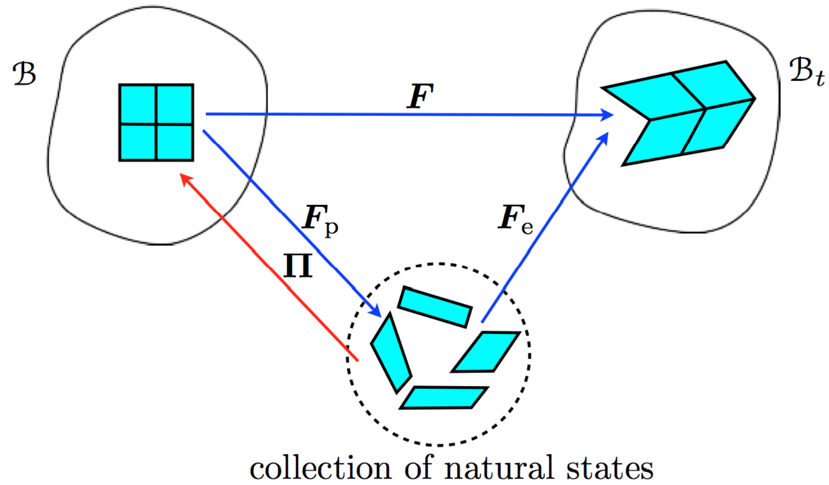
The role of mechanics

Inelasticity to describe growth and remodelling:

> ***The change of shape of a tissue is accompanied by a reorganisation of its internal structure, which manifests itself through plastic-like distortions, and leads to macroscopic variations of the mechanical properties of the material.***



Cold rolling (Source: The Internet)



Bilby-Kröner-Lee decomposition

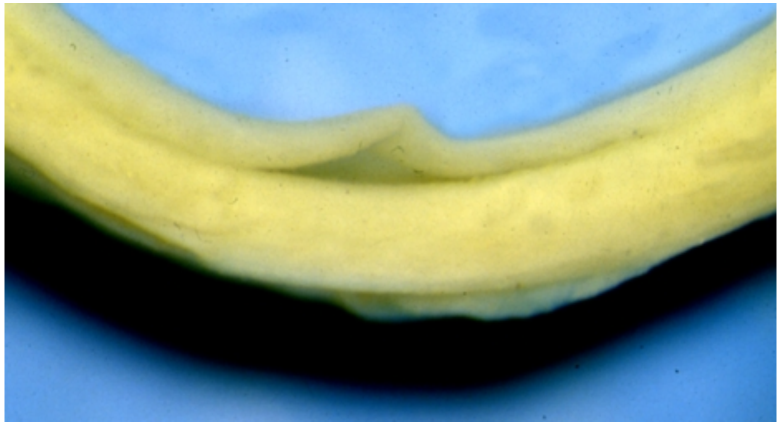
Rodriguez, E.K., et al. (1994). Stress-dependent finite growth in soft elastic tissues. *J. Biomech.*, **27**, 455–467.

Epstein, M., Maugin, G.A. (2000). Thermomechanics of volumetric growth in uniform bodies. *Int. J. Plasticity*, **16**, 951–978.

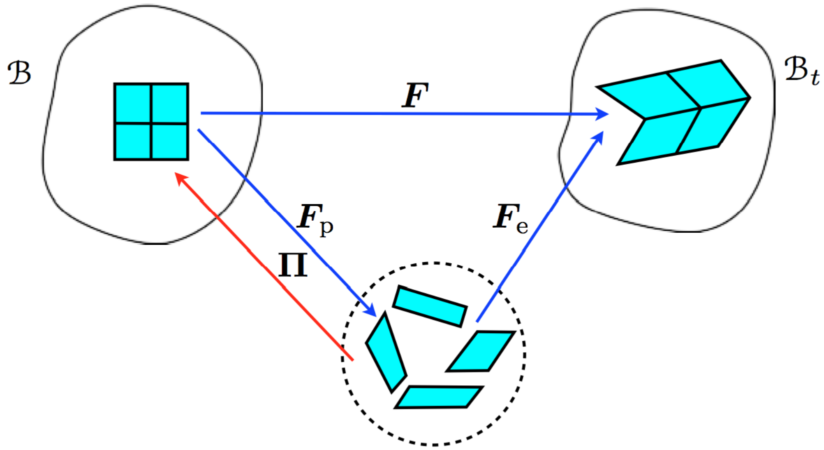
The role of mechanics

The issue of residual stresses

Growth can be thought of as the process that brings the tissue from a zero-stress state (i.e., the natural state) to a state in which residual stresses may be present also in the absence of external loading.



Delamination and buckling of a ring of a human iliac artery [Holzapfel&Ogden, 2010]



Bilby-Kröner-Lee decomposition

Rodriguez, E.K., et al. (1994). Stress-dependent finite growth in soft elastic tissues? *J. Biomech.*, **27**, 455–467.

Holzapfel, G.A., Ogden, R.W. (2010). Modelling the layer-specific three-dimensional residual stresses in arteries, with an application to the human aorta. *J. R. Soc. Interface*, **7(46)**, 787–799.

Mathematical description of soft tissues

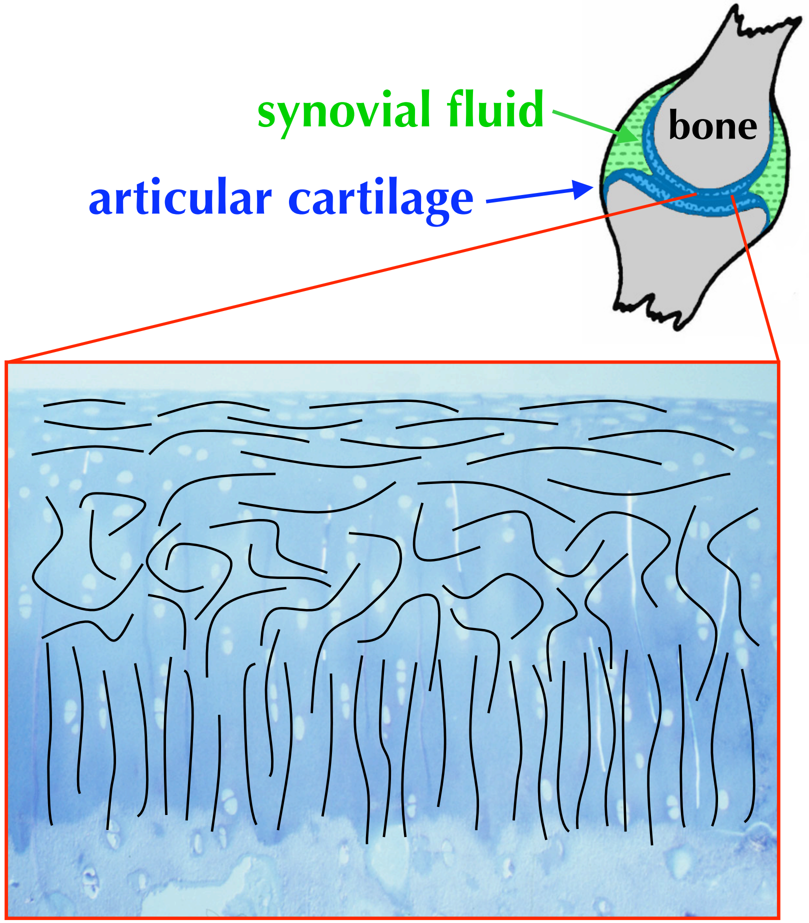
A tissue with a "rich" microstructure: Articular Cartilage

Soft connective tissue covering the continuous surfaces of bones in diarthrodial joints

Water: *«Approximately 70% to 85% of the weight of the whole tissue» [Mansour, 2003].*

Chondrocytes: *Cells that synthesise the ECM. They are "elongated" ellipsoids in the deep zone, spheres in the middle zone, and flat disks in the upper zone.*

Collages fibres: *Oriented statistically in inhomogeneous way; about the 60%-70% of the tissue's dry weight.*



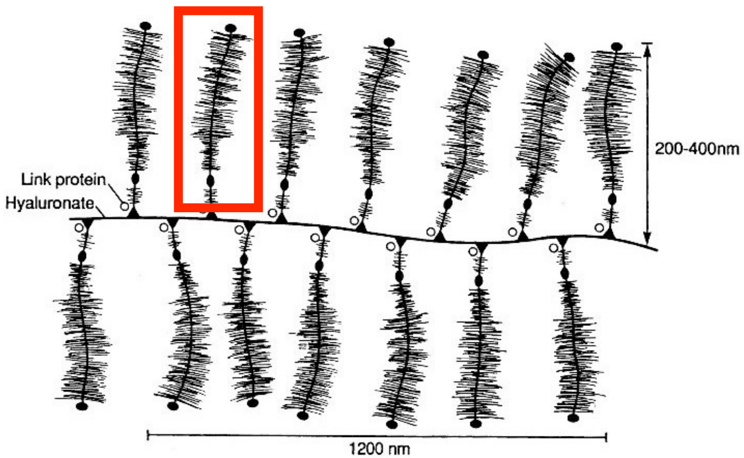
Federico, S., Grillo, A., La Rosa, G., Giaquinta, G., Herzog, W. (2005). A transversely isotropic, transversely homogeneous microstructural-statistical model of articular cartilage. *J. Biomech.*, **38**, 2008–2018.

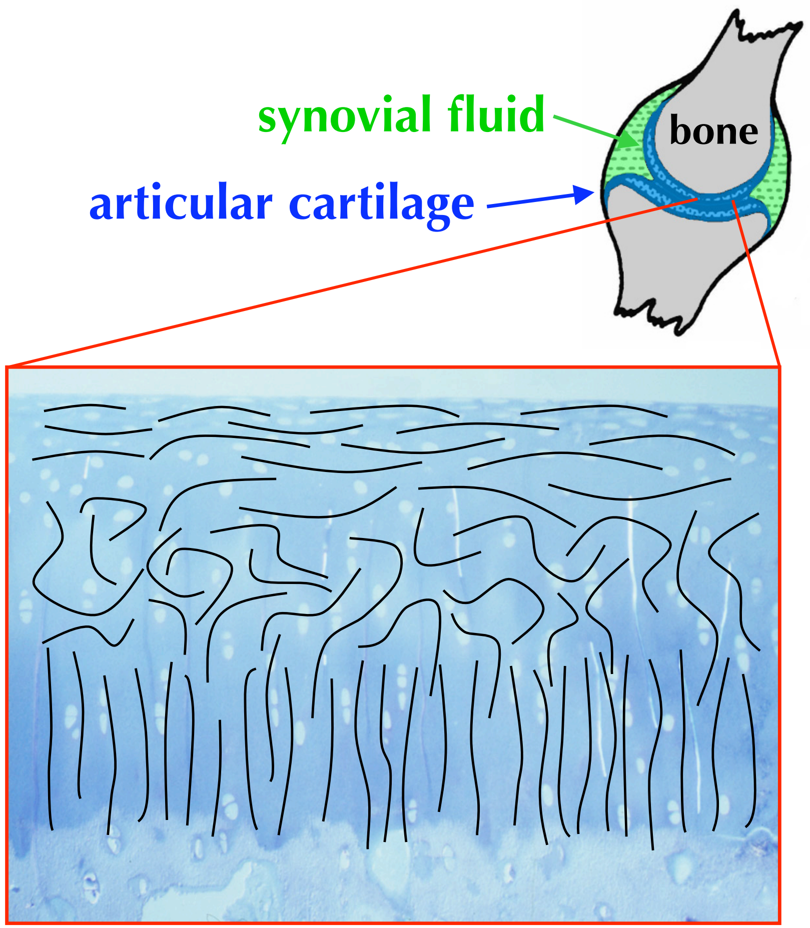
Mathematical description of soft tissues

A tissue with a "rich" microstructure: Articular Cartilage

Soft connective tissue covering the continuous surfaces of bones in diarthrodial joints

Proteoglycans: Bottlebrush structures to which chondroitin sulfate and keratan sulfate are attached.



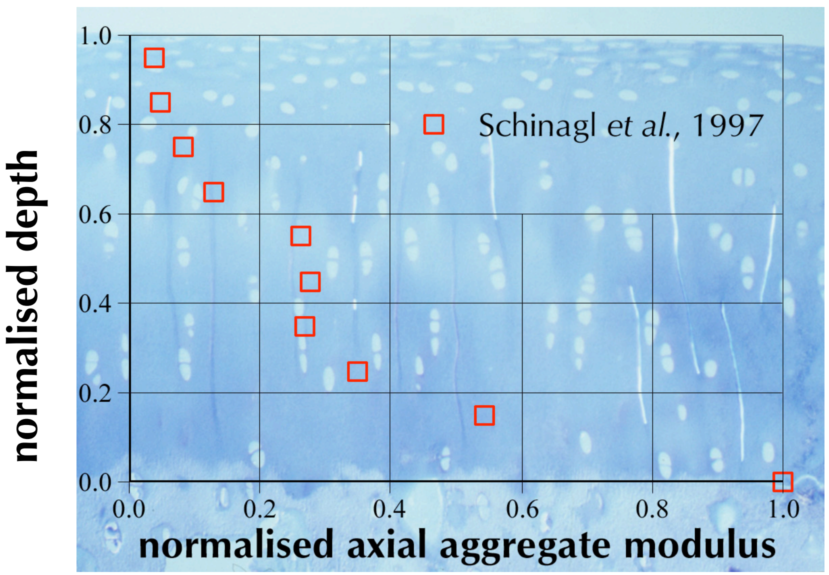


Federico, S., Grillo, A., La Rosa, G., Giaquinta, G., Herzog, W. (2005). A transversely isotropic, transversely homogeneous microstructural-statistical model of articular cartilage. *J. Biomech.*, **38**, 2008–2018.

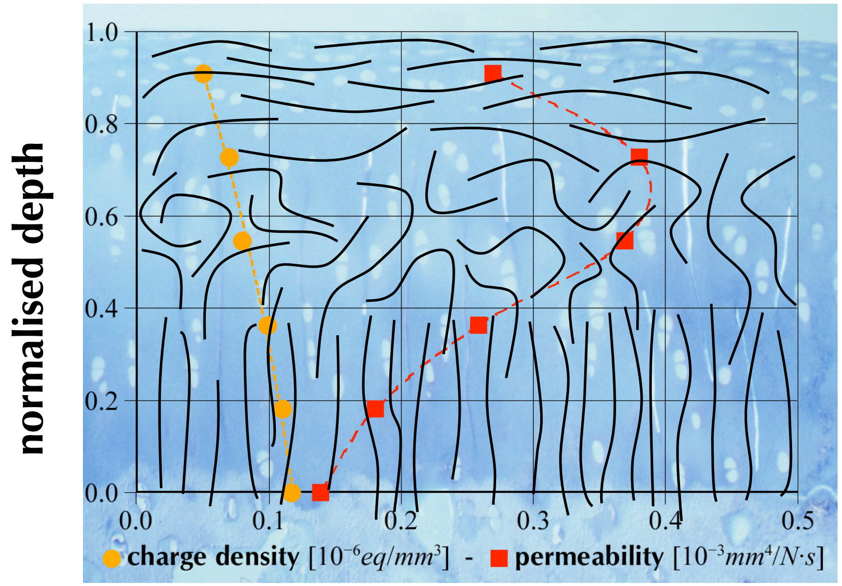
Elastic and hydraulic properties, and fibre orientation

Anisotropic and inhomogeneous tissue [analogy with fractures?]

Axial aggregate modulus: decreasing from the bottom to the top layers.



Permeability: influenced by water content and fibre concentration.



Maroudas, A., Bullogh, P. (1968). Permeability of articular cartilage. *Nature*, **219**, 1260–1261.

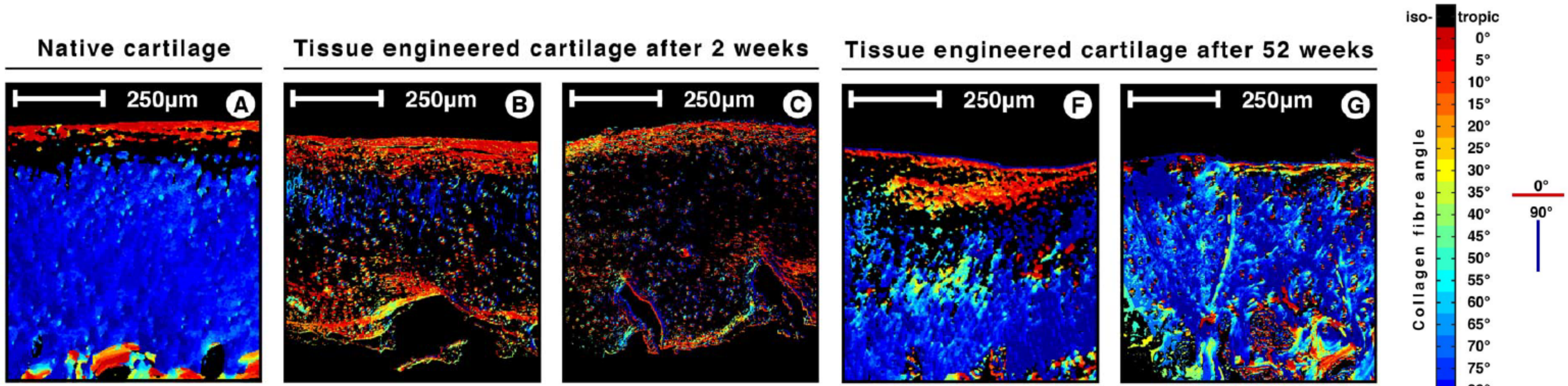
Schinagl, R.M., Gurskis, D., Chen, A.C., Sah, R.L. (1997). Depth dependent confined compression modulus of full-thickness bovine articular cartilage. *J. Orth. Research*, **15**, 499–506.

Motivations

Mathematical description of soft tissues

Towards engineered articular cartilage

«[...] it is possible to create tissue-engineered cartilage with sufficient proteoglycan content, but not to obtain sufficient amounts of collagen with an appropriate structural organization. As a result, the dynamic compressive properties and especially the tensile properties of tissue-engineered cartilage are inferior to native tissue.»



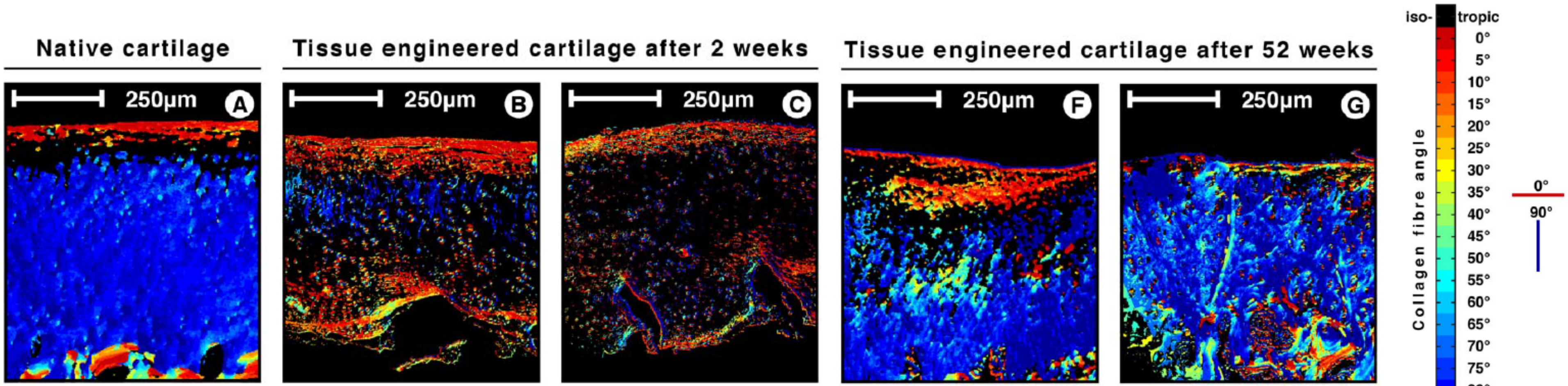
THE DEVELOPMENT OF THE COLLAGEN FIBRE NETWORK IN TISSUE-ENGINEERED CARTILAGE CONSTRUCTS IN VIVO. ENGINEERED CARTILAGE REORGANISES FIBRE NETWORK. [Paetzold et al.2012]

Wilson, W., Driessen, N.J.B., van Donkelaar, C.C., Ito, K. (2006). Prediction of collagen orientation in articular cartilage by a collagen remodelin algorithm. *Osteoarthritis and Cartilage*, **11**, 1196–1202.

Mathematical description of soft tissues

Towards engineered articular cartilage

«[…], the rules by which the spatial organisation of collagen fibres is related to mechanical and chemical stimuli are poorly understood. This makes it difficult to incorporate elements in tissue engineering strategies that stimulate engineered cartilage to develop the desired anisotropic organization.»



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Methods

Towards a non-standard mechanics, to comply with biology

- ***Re-interpret old equations***
- ***Invent new models***

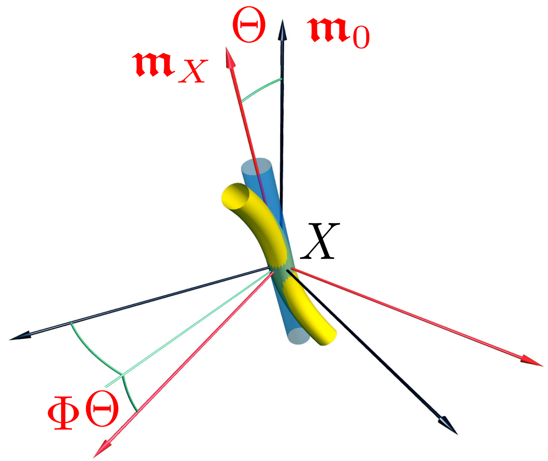
Anisotropy and statistical fibre-reinforcement

Directional averaging

$$\mathbb{S}^2_X\mathscr{B} = \{\mathfrak{m}_X \in T_X\mathscr{B} : \ \|\mathfrak{m}_X\| = 1\}$$

$$\mathfrak{F}_X(\boldsymbol{F}, \boldsymbol{F}_{\rm p}, \cdot\,) : \mathbb{S}^2_X\mathscr{B} \to \mathbb{R}, \quad \mathfrak{m}_X \ \mapsto \ \mathfrak{F}_X(\boldsymbol{F}, \boldsymbol{F}_{\rm p}, \mathfrak{m}_X),$$

$$\langle\!\langle \mathfrak{F}_X(\boldsymbol{F}, \boldsymbol{F}_{\rm p}, \mathfrak{m}_X) \rangle\!\rangle = \int_{\mathbb{S}^2_X\mathscr{B}} \mathfrak{F}_X(\boldsymbol{F}, \boldsymbol{F}_{\rm p}, \mathfrak{m}_X)\psi_X(\mathfrak{m}_X)$$



Main computational issue: *Spherical Design Algorithm*

Hardin, R., Sloane, N. (1996). McLaren's improved snub cube and other new spherical designs in three dimensions. *Discrete Comput. Geom.*, **15**, 429–441.

Mathematical description of soft tissues

The equations describing "pure" remodelling

$$(\det \boldsymbol{F})\operatorname{tr}[\dot{\boldsymbol{F}}\boldsymbol{F}^{-1}] = \operatorname{Div}\,[\boldsymbol{K}(\boldsymbol{F})\operatorname{Grad} p]\,,$$

Mass balance

$$\operatorname{Div}\left[-(\det \boldsymbol{F})\, p\, \boldsymbol{g}^{-1}\boldsymbol{F}^{-\mathrm{T}} + \boldsymbol{P}_{\mathrm{sc}}(\boldsymbol{F}, \boldsymbol{V})\right] = \boldsymbol{0},$$

Momentum balance

$$\Gamma\dot{\mathfrak{q}} = \operatorname{Div}\left[\Phi_{1\mathrm{s}\nu} D_0 \boldsymbol{V}^2 \operatorname{Grad}\mathfrak{q}\right] - \Phi_{1\mathrm{s}\nu}\frac{\partial(\hat{W}_{1\mathrm{a}} + \hat{W}_{\mathrm{str}})}{\partial\mathfrak{q}} - \operatorname{Div}\left[\Phi_{1\mathrm{s}\nu} D_0 \boldsymbol{V}^2 \operatorname{Grad}\mathfrak{q}_T\right] + \Phi_{1\mathrm{s}\nu}\left.\frac{\partial(\hat{W}_{1\mathrm{a}} + \hat{W}_{\mathrm{str}})}{\partial\mathfrak{q}}\right|_{\mathfrak{q}=\mathfrak{q}_T},$$

Fibre reorientation

$$\dot{\boldsymbol{V}} = -\operatorname{sym}\left(\frac{\lambda}{J}\,\frac{\boldsymbol{C}^{-1}[\operatorname{dev}\boldsymbol{\Sigma}_{\mathrm{eff}}(\boldsymbol{F},\boldsymbol{V})]\boldsymbol{C}}{\|\operatorname{dev}\boldsymbol{\Sigma}_{\mathrm{eff}}(\boldsymbol{F},\boldsymbol{V})\|_{\boldsymbol{C}}}\boldsymbol{V}\right)$$

Evolution of inelastic distortions

Giverso, C., Preziosi, L. (2012). Modelling the compression and reorganization of cell aggregates. *Math. Med. Biol.*, **29(2)**, 181–204.

Crevacore, E., Di Stefano, S., Grillo, A. (2018). Coupling among deformation, fluid flow, structural reorganisation and fibre reorientation in fibre-reinforced, transversely isotropic biological tissues. *Submitted*.

Mathematical description of soft tissues

The equations describing ”pure“ growth

$$(\det \boldsymbol{F})\mathrm{tr}[\dot{\boldsymbol{F}}\boldsymbol{F}^{-1}] = \mathrm{Div}\,[\boldsymbol{K}(\boldsymbol{F},\gamma)\mathrm{Grad}\,p]\,,$$

Mass balance

$$\mathrm{Div}\left[-(\det \boldsymbol{F})\,p\,\boldsymbol{g}^{-1}\boldsymbol{F}^{-\mathrm{T}} + \boldsymbol{P}_{\mathrm{sc}}(\boldsymbol{F},\gamma)\right] = \boldsymbol{0},$$

Momentum balance

$$f(\boldsymbol{F},\gamma)\dot{\omega} = \mathrm{Div}\,[\boldsymbol{D}(\boldsymbol{F},\gamma)\mathrm{Grad}\,\omega] - R(\gamma,\omega)\omega,$$

Mass balance of the nutrients

$$\frac{\dot{\gamma}}{\gamma} = \frac{\Gamma_0(\boldsymbol{F},\gamma)}{3}\left\langle\frac{\omega-\omega_{\mathrm{cr}}}{\omega_{\mathrm{env}}-\omega_{\mathrm{cr}}}\right\rangle_+\left[1-\frac{\delta_1\langle\bar{\sigma}\rangle_+}{\delta_2+\langle\bar{\sigma}\rangle_+}\right]$$

Growth

with $\bar{\sigma} = -\dfrac{1}{3\det\boldsymbol{F}}\mathrm{tr}\left[\boldsymbol{P}_{\mathrm{sc}}\boldsymbol{F}^{\mathrm{T}}\right]$ ***being the spherical part of the constitutive Cauchy stress tensor.***

Ambrosi, D., Mollica, F. (2002). On the mechanichs of a growing tumor. *Int. J. Eng. Sci.*, **40**, 1297–1316.

Giverso, C., Preziosi, L. (2012). Modelling the compression and reorganization of cell aggregates. *Math. Med. Biol.*, **29(2)**, 181–204.

Mascheroni, P., Carfagna, M., Grillo, A., Boso, D.P., Schrefler, B.A. (2017). An avascular tumor growth model based on porous media mechanics and evolving natural states. *Math. Mech. Solids*, In press.

Challenges

Paraphrasing Simon&Gerfunkel…

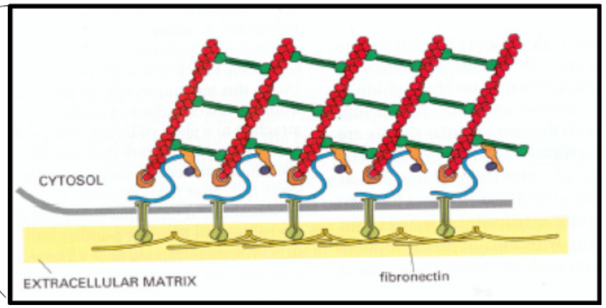
Building a "bridge over troubled"… scales

Nesting in continuum models: Growth

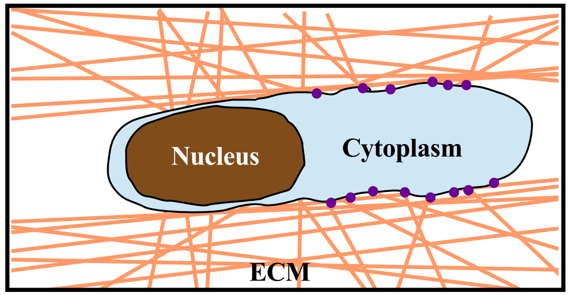
$$\partial_t \phi_\alpha + \mathrm{div}(\phi_\alpha \boldsymbol{v}_\alpha) = \Gamma_\alpha, \quad \alpha = \mathrm{c}, \mathrm{m},$$

$$\mathrm{div}\, \boldsymbol{\sigma}_{\mathrm{c}} + \boldsymbol{m}_{\mathrm{cm}} + \varrho \phi_{\mathrm{c}} \boldsymbol{b}_{\mathrm{c}} = \boldsymbol{0},$$

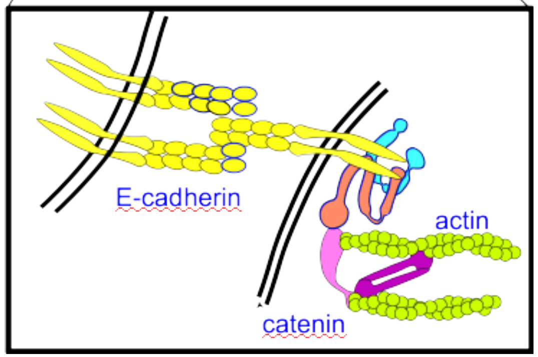
$$\mathrm{div}\, \boldsymbol{\sigma}_{\mathrm{m}} - \boldsymbol{m}_{\mathrm{cm}} = \boldsymbol{0}$$



Cell-ECM interaction



ECM microstructure and nucleus mechanical properties

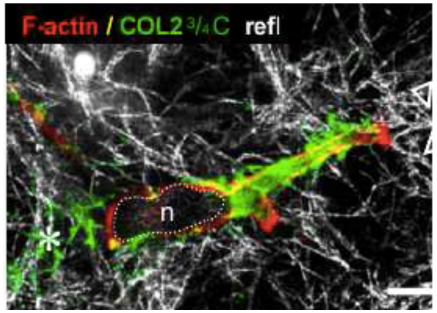


Cell-cell interactions

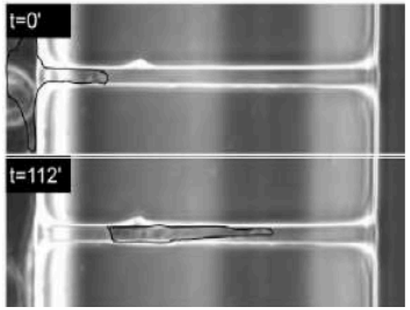
Giverso, C., Scianna, M., Grillo, A. (2015). Growing avascular tumours as elasto-plastic bodies by the theory of evolving natural configurations. *Mech. Res. Commun.*, **68**, 31–39.

Nucleus mechanical properties

Single cell migration

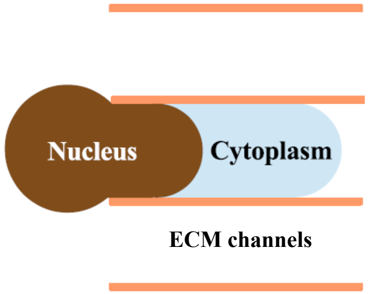


Friedl&Wolf (2009). *Canc. Met. Rev.*



Rolli et al. (2010). *Plos One*

Energy source for nucleus deformation: ***Active contraction of the cytoskeleton, thrust passively received from the fluid, and pressure from surrounding cells***



- ***Energy balance:***

  $$W_{\text{active}} + W_{\text{passive}} \geq W_{\text{def}}$$

- ***Elastic nucleus deformation:***

  $$W_{\text{def}} := W_{\text{def}}^S + W_{\text{def}}^V$$

- ***Active force model:***

  $$W_{\text{active}} := F_{\text{active}} \Delta L$$

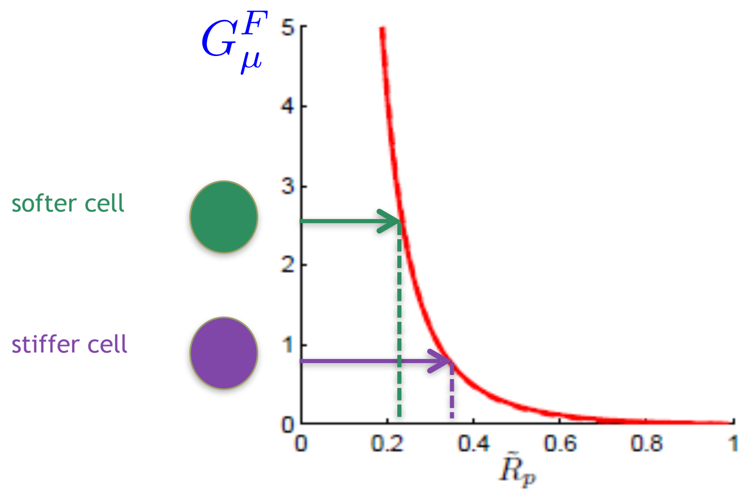
Giverso, C., Grillo, A., Preziosi, L. (2013). Influence of nucleus deformability on cell entry into cylindrical structures. *Biomech. Model. Mechanobiol.*, **13**, 481–502.

Criterium at the cell scale

Determination of the minimum pore size of the structure

Ratio between the adhesive/active properties of the cell and the mechanical properties of the nucleus:

$$G_\mu^F = \frac{\varrho_b \alpha_{ECM} F_b^M}{\mu}$$



Minimum size of the cross-section of a penetrable channel ("physical limit of cell migration")

Giverso, C., Grillo, A., Preziosi, L. (2013). Influence of nucleus deformability on cell entry into cylindrical structures. *Biomech. Model. Mechanobiol.*, **13**, 481–502.

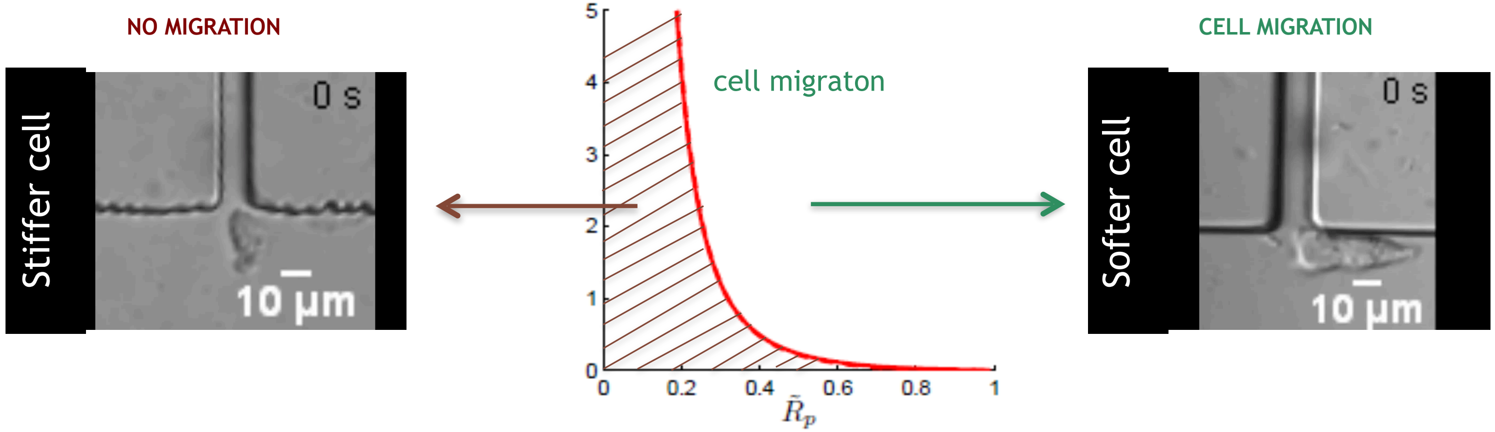
Cell-ECM interaction

Criterium at the cell scale

Determination of the minimum pore size of the structure

Definition of region in the space of parameters in which the cell migration is hindered.

Up-scale information to the Multicellular Aggregate Model.



Giverso, C., Grillo, A., Preziosi, L. (2013). Influence of nucleus deformability on cell entry into cylindrical structures. *Biomech. Model. Mechanobiol.*, **13**, 481–502.

Cell-ECM interaction

Upscale to the macroscopic model

Segregation vs invasion

The cytoplasm of cells at the border of multicellular aggregates extends inside the ECM, while their nuclei might remain trapped (tumour segregation) depending on:

- *Matrix-metalloproteinases secretion;*
- *Nuclear mechanical properties;*
- *ECM pore section*

Multiphase Model Equations

Evolution of the cellular volumetric fraction:

$$\partial_t \phi_\mathrm{c} + \mathrm{div}\left[\phi_\mathrm{c} \Sigma'(\psi) \boldsymbol{M} \nabla \psi\right] = \Gamma_\mathrm{c}$$
$$\psi = \phi_\mathrm{c} + \phi_\mathrm{m}$$

Motility tensor:

$$\boldsymbol{M} = \alpha \left[A_\mathrm{m}(\phi_\mathrm{m}) - A_0\right]_+ \boldsymbol{g}^{-1}$$

Critical pore cross-section A_0 determined by energetic inequality at the cell scale.

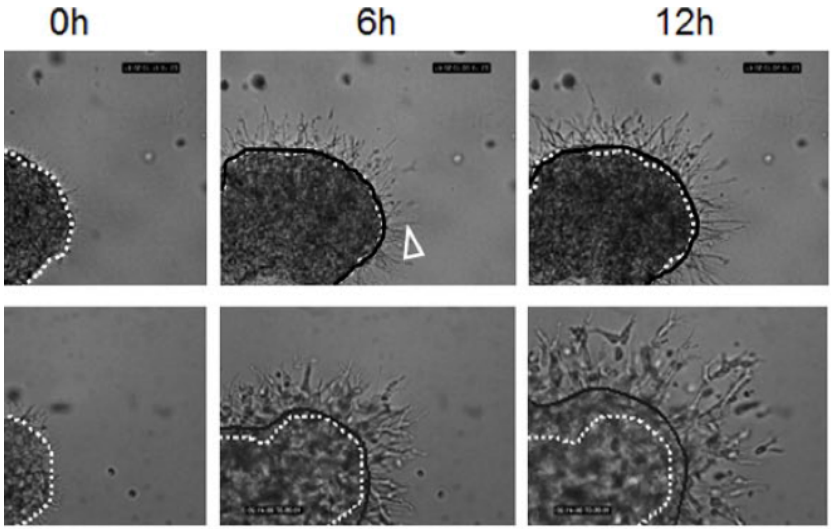
Giverso, C., Arduino, A., Preziosi, L. (2017). How Nucleus Mechanics and ECM Microstructure Influence the Invasion of Single Cells and Multicellular Aggregates. *Bull Math Biol.*, DOI:10.1007/s11538-017-0262-9

Cell-ECM interaction

Upscale to the macroscopic model

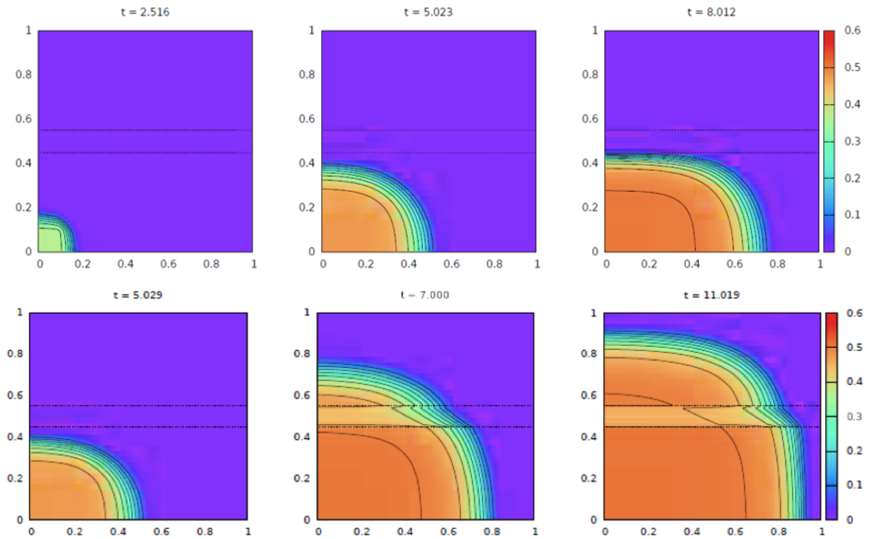
Segregation vs invasion

Formation of metastasis



Wolt et al. (2013). *J. Cell. Biol.*

Multiphase Model Equations



Arduino et al. (2018). *Ongoing work.*

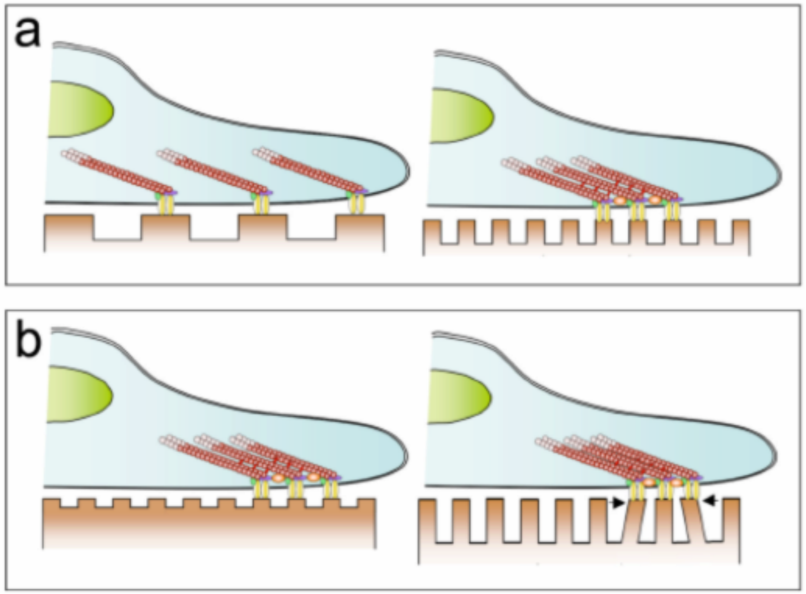
$$\partial_t \phi_c + \mathrm{div}\left[\phi_c \Sigma'(\psi) \boldsymbol{M} \nabla \psi\right] = \Gamma_c$$

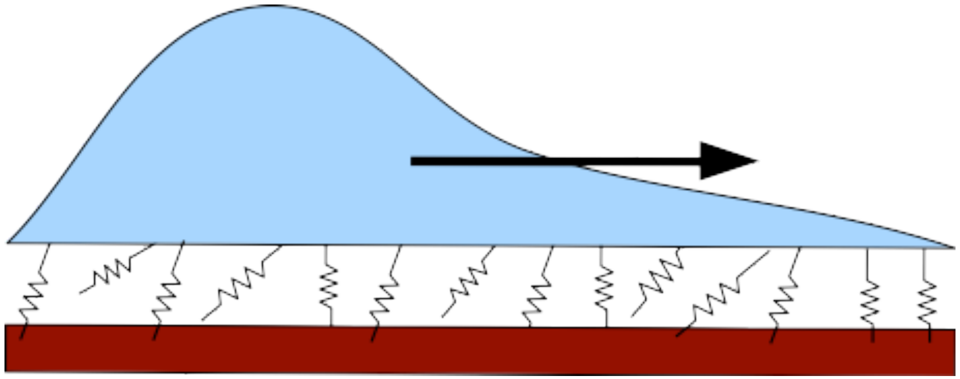
$$\boldsymbol{M} = \alpha \left[A_m(\phi_m) - A_0\right]_+ \boldsymbol{g}^{-1}$$

Cell-ECM interaction

Adhesion models

Forces exchanged between cell and ECM





$$\boldsymbol{m}_{\mathrm{cm}}^{\mathrm{ad}}(X_{\mathrm{c}}, t) = \int_{\mathcal{B}_{\mathrm{m}}} \boldsymbol{F}_{\mathrm{cm}}^{\mathrm{mic}}(X_{\mathrm{c}}, Y, t)\mathrm{d}Y$$

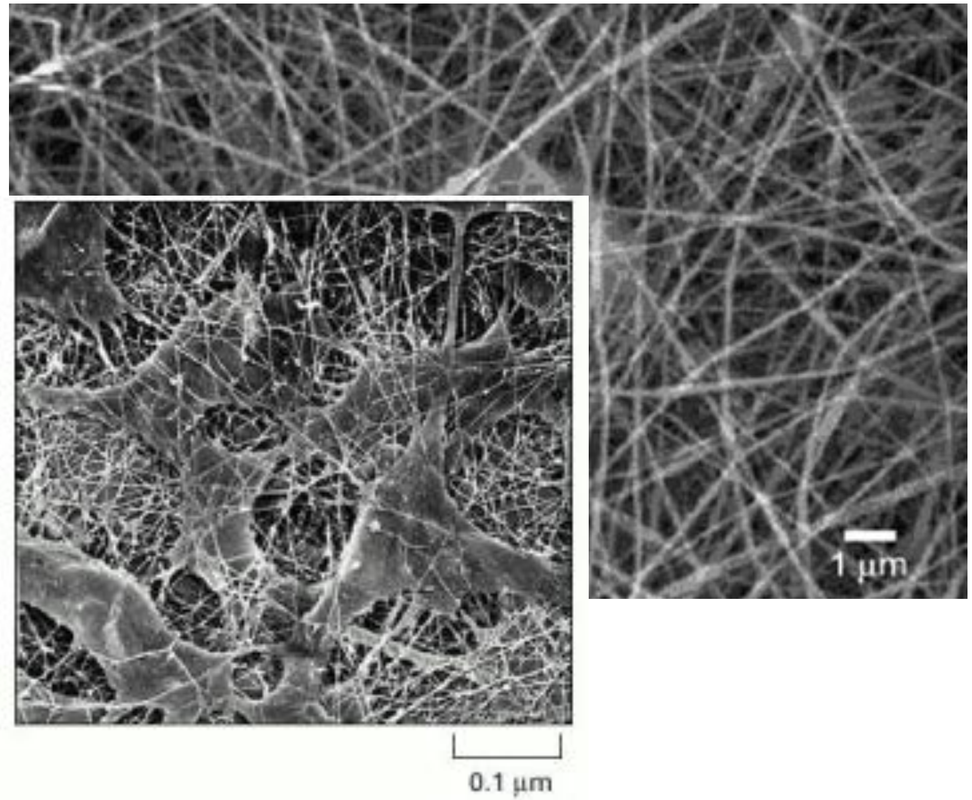
Preziosi, L., Vitale, G. (2011). A multiphase model of tumor and tissue growth including cell adhesion and plastic reorganization. *Math. Mod. Med. Appl. S.*, **21(9)**, 1901–1932.

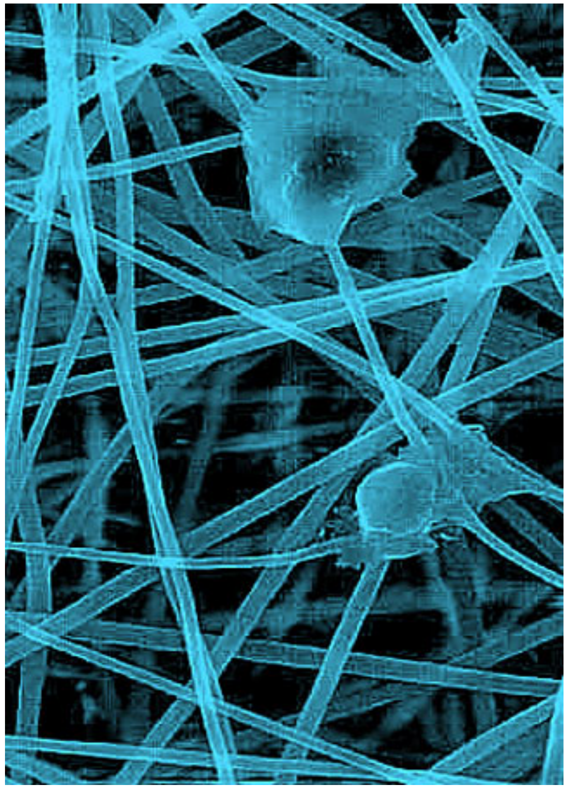
Théry … & Julicher (2007). Experimental and theoretical study of mitotic spindle orientation. *Nature*, **447**, 493–497.

Cell-ECM interaction

Again tissue engineering

Building a proper artificial ECM





Preziosi, L., Vitale, G. (2011). A multiphase model of tumor and tissue growth including cell adhesion and plastic reorganization. *Math. Mod. Med. Appl. S.*, **21(9)**, 1901–1932.

Again tissue engineering

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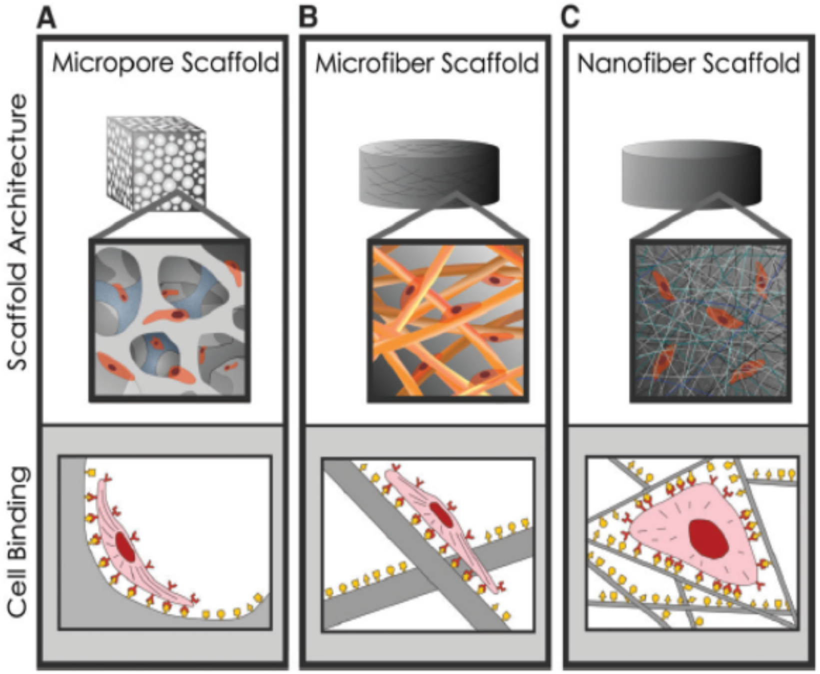
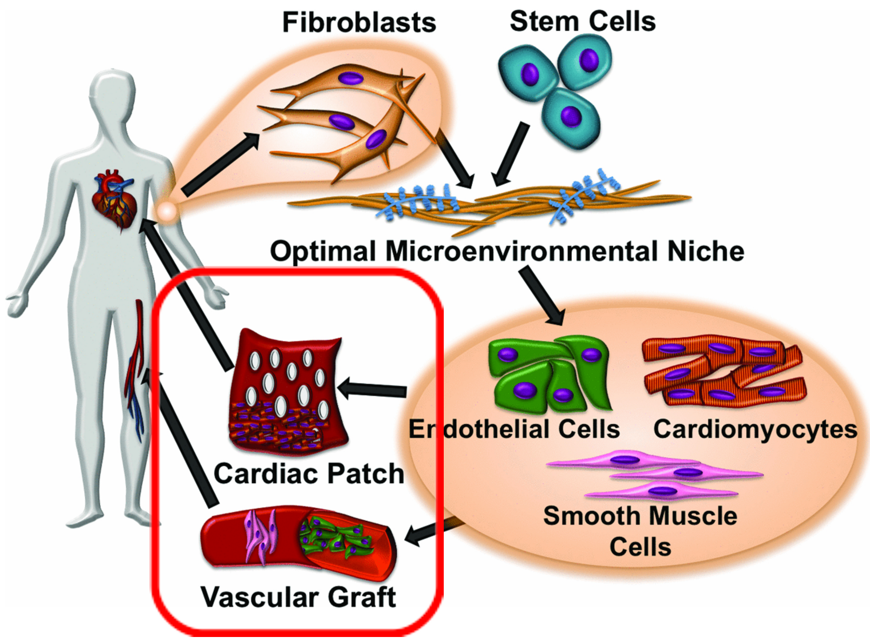
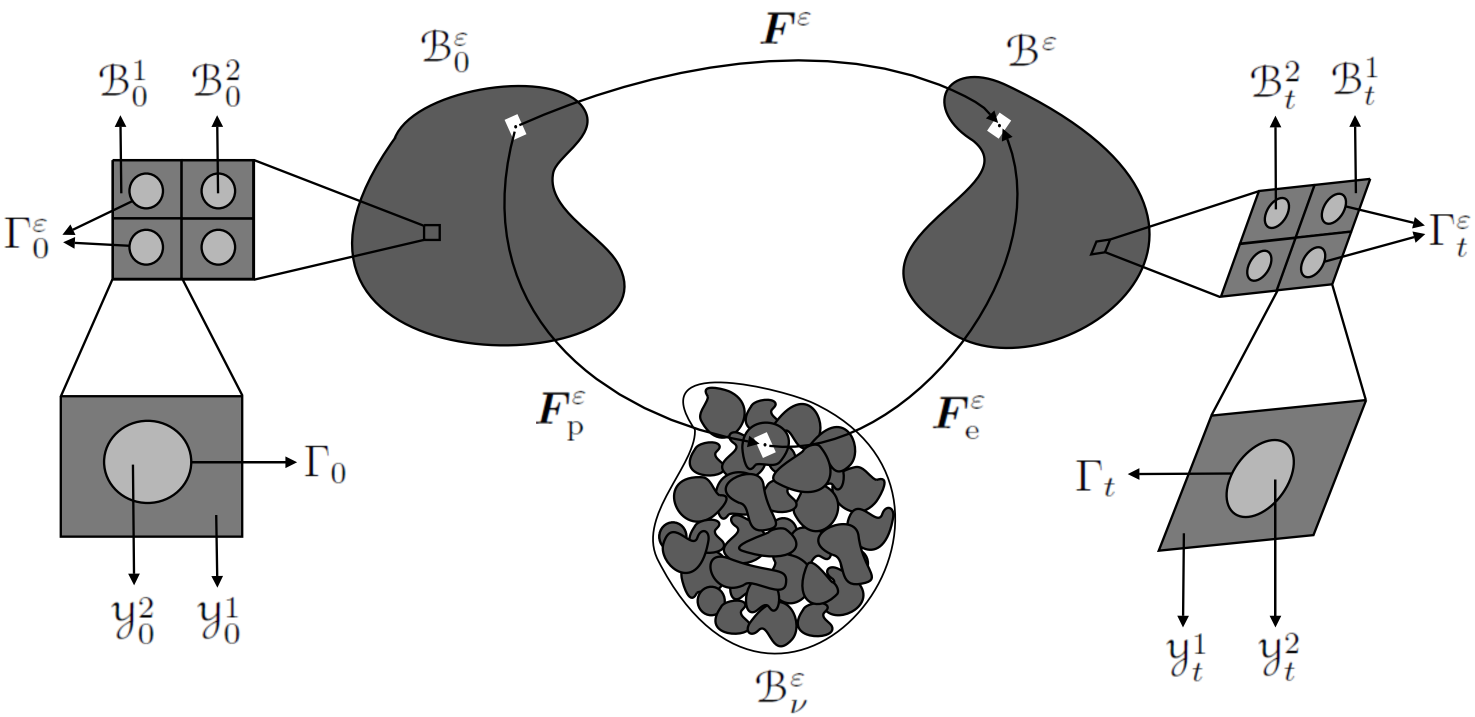


Fig. 2. Scaffold architecture affects cell binding and spreading. (A and B) Cells binding to scaffolds with microscale architectures flatten and spread as if cultured on flat surfaces. (C) Scaffolds with nanoscale architectures have larger surface areas to adsorb proteins, presenting many more binding sites to cell membrane receptors. The adsorbed proteins may also change conformation, exposing additional cryptic binding sites.



Stevens & George (2005). Exploring and engineering the cell surface interface. *Science*, **310**, 1135–1138.

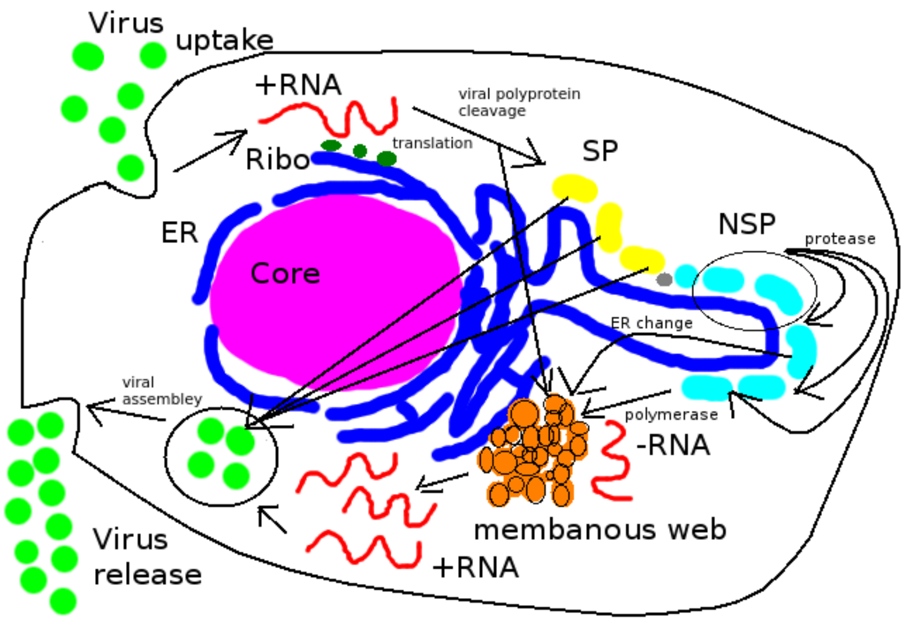
Homogenisation in the presence of structural evolution



- ***Highly non-linear and coupled cell problems; call for dedicated numerical schemes.***
- ***Breaking of the symmetry group of the material due to scale transfer.***

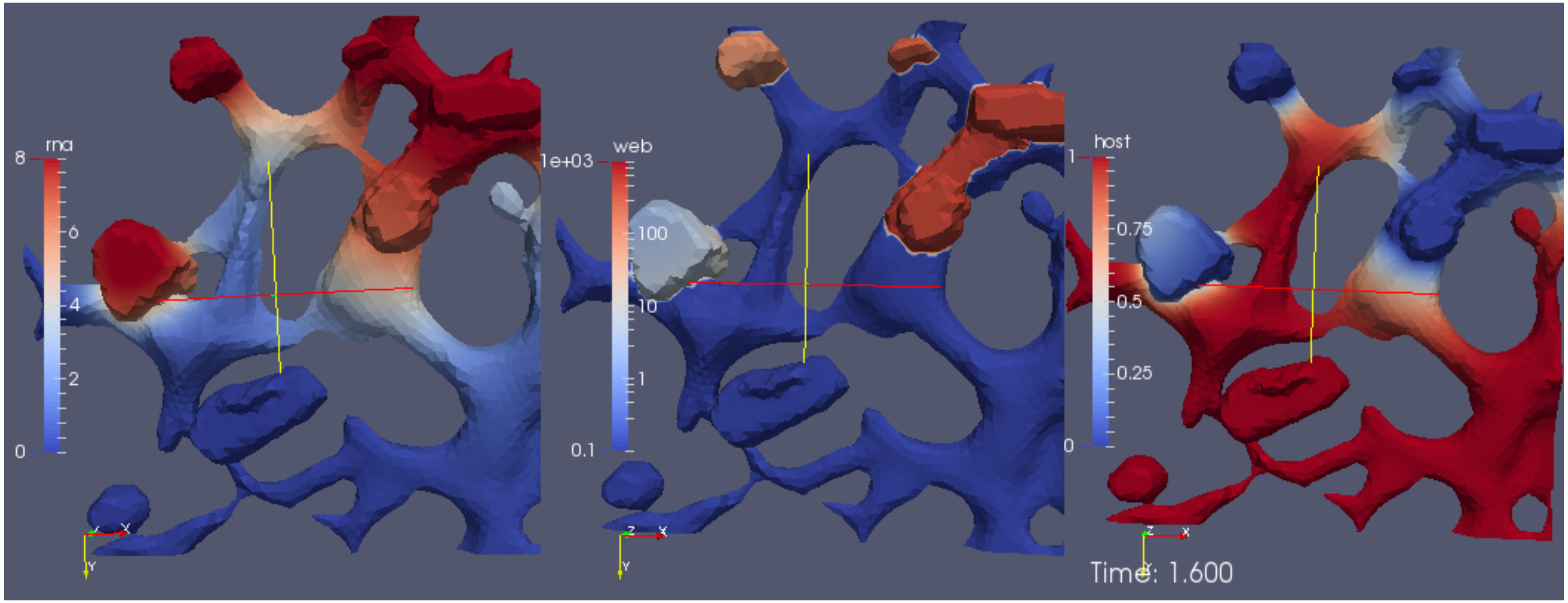
Ramírez-Torres, A., Di Stefano, S., Grillo, A., Rodríguez-Ramos, R., Merdio, J., Penta, R. (2018). An asymptotic homogenisation approach to the microstructural evolution of heterogeneous media. **Submitted**.

Replication cycle of the Hepatitis C viral genome



Knodel, M.M., Reiter, S., Targett-Adams, P., Grillo, A., Herrmann, E., Wittum, G. (2017). 3D Spatially resolved models of the intracellular dynamics of the hepatitis C genome replication cycle. *Viruses*, **9**, 282–318.

Replication cycle of the Hepatitis C viral genome



- ***Surface diffusion-reaction equations, with high nonlinear couplings***

Knodel, M.M., Reiter, S., Targett-Adams, P., Grillo, A., Herrmann, E., Wittum, G. (2017). 3D Spatially resolved models of the intracellular dynamics of the hepatitis C genome replication cycle. *Viruses*, **9**, 282–318.

Thank you very much …

… for your kind attention!!!

Eruption of Mt. Etna, Italy

$\xrightarrow{f}$

Turin, Italy

Source: The Internet