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Dual *in vitro-in silico* modeling of cell aggregates: from tumor growth to tissue engineering

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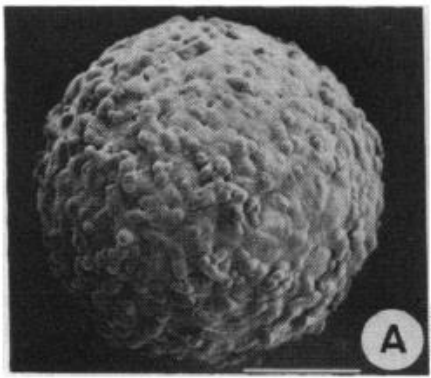
SIN-SMR day, 17 November 2023



In vitro 3D model of a tumor

The Multicell Spheroid Model

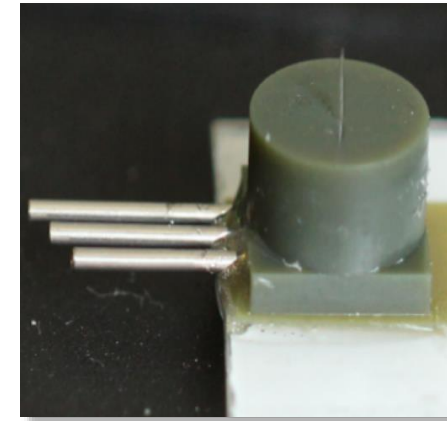
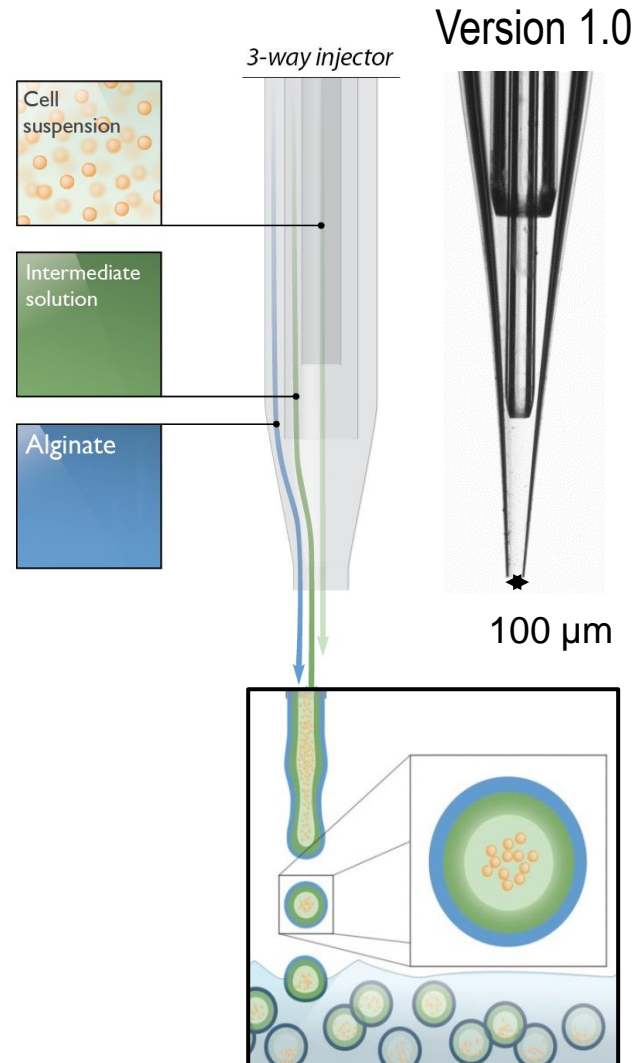
ROBERT M. SUTHERLAND 8 APRIL 1988



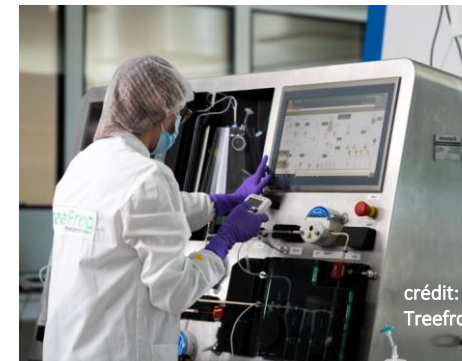
more relevant than
2D cultures



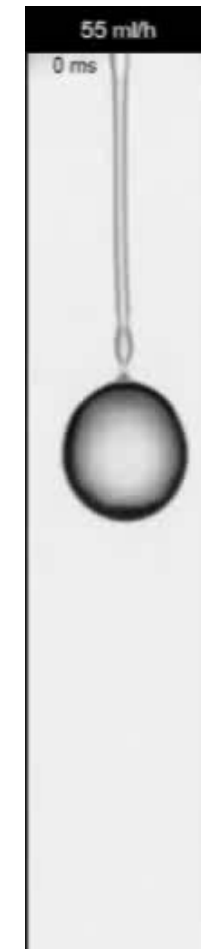
A microfluidic technology



Version 2.0



Version 18.0

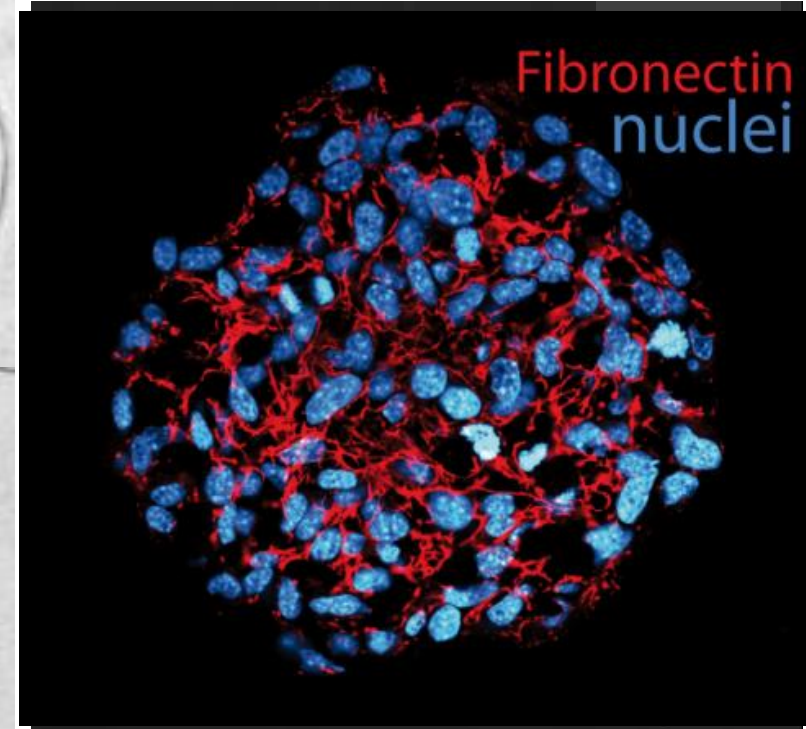
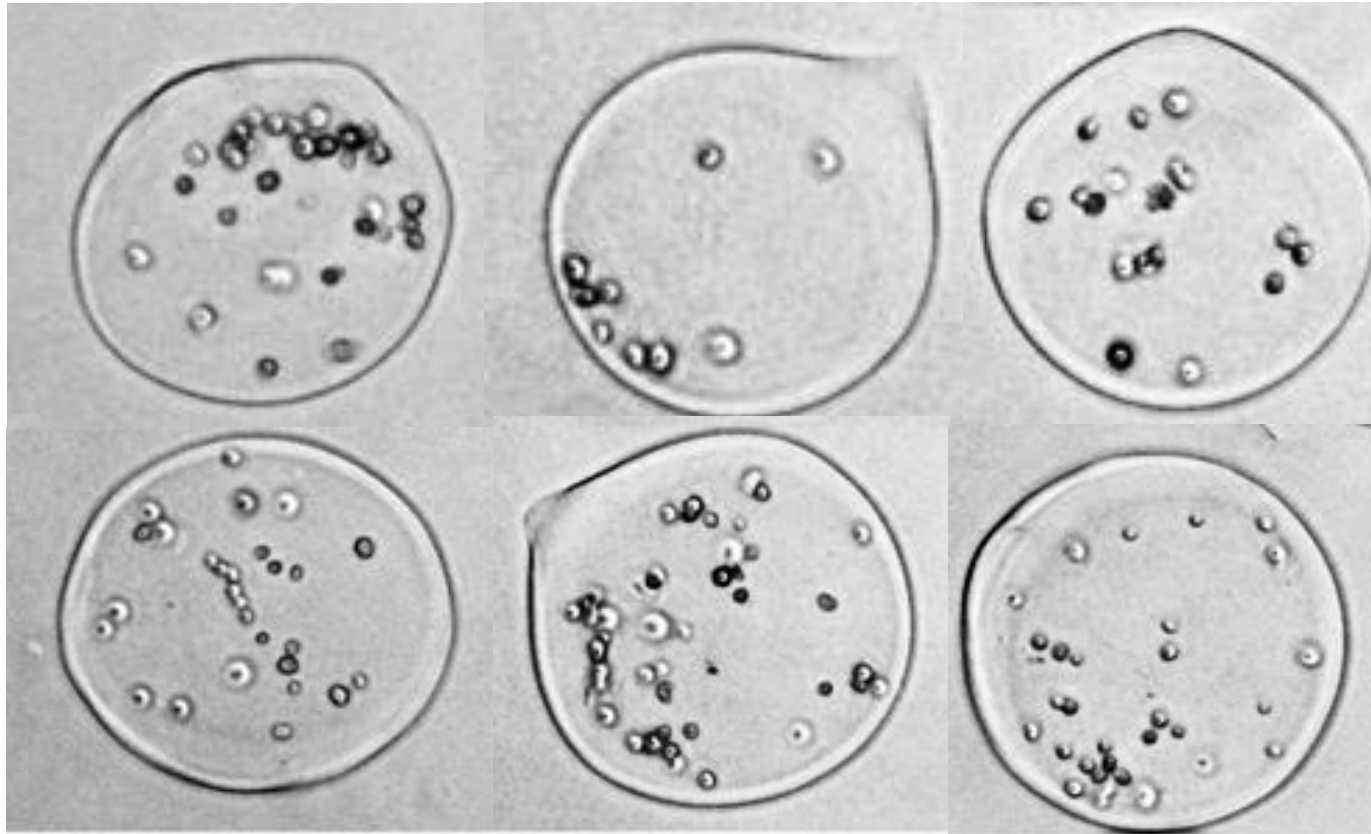
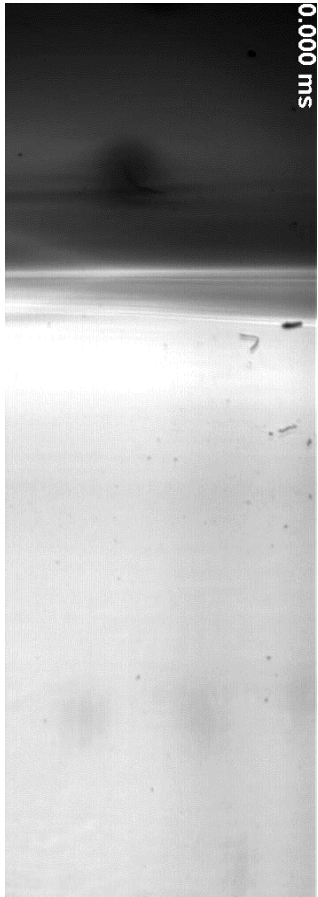


Dripping



Jetting
Rayleigh
instability

Cellular capsules



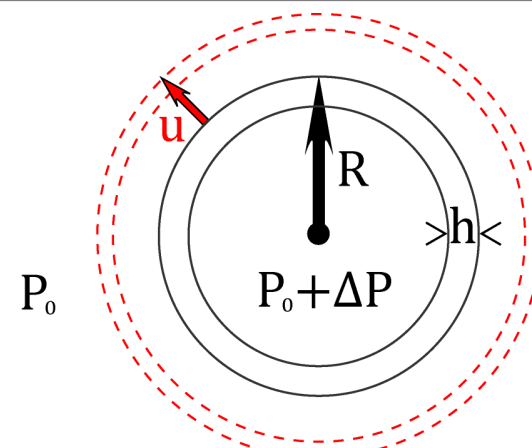
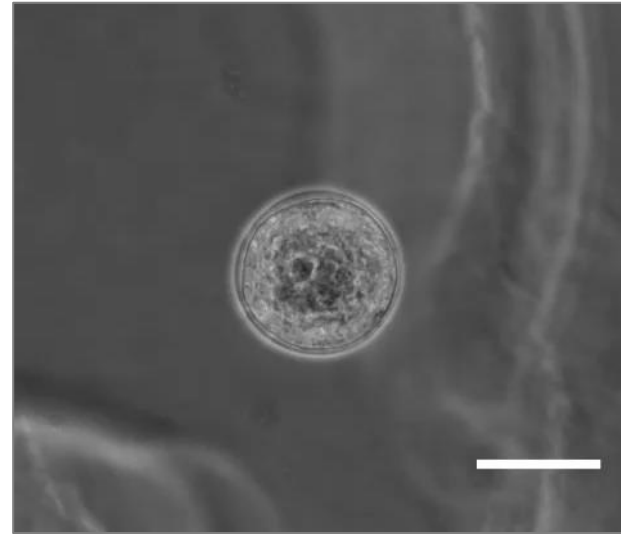
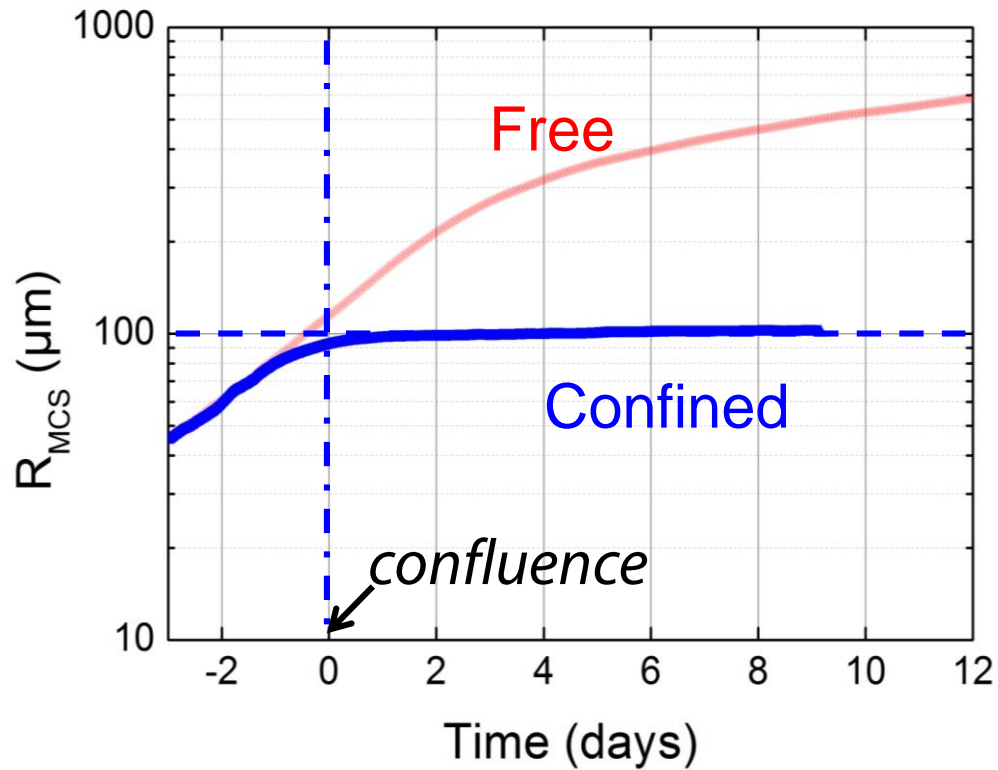
Fall

After encapsulation

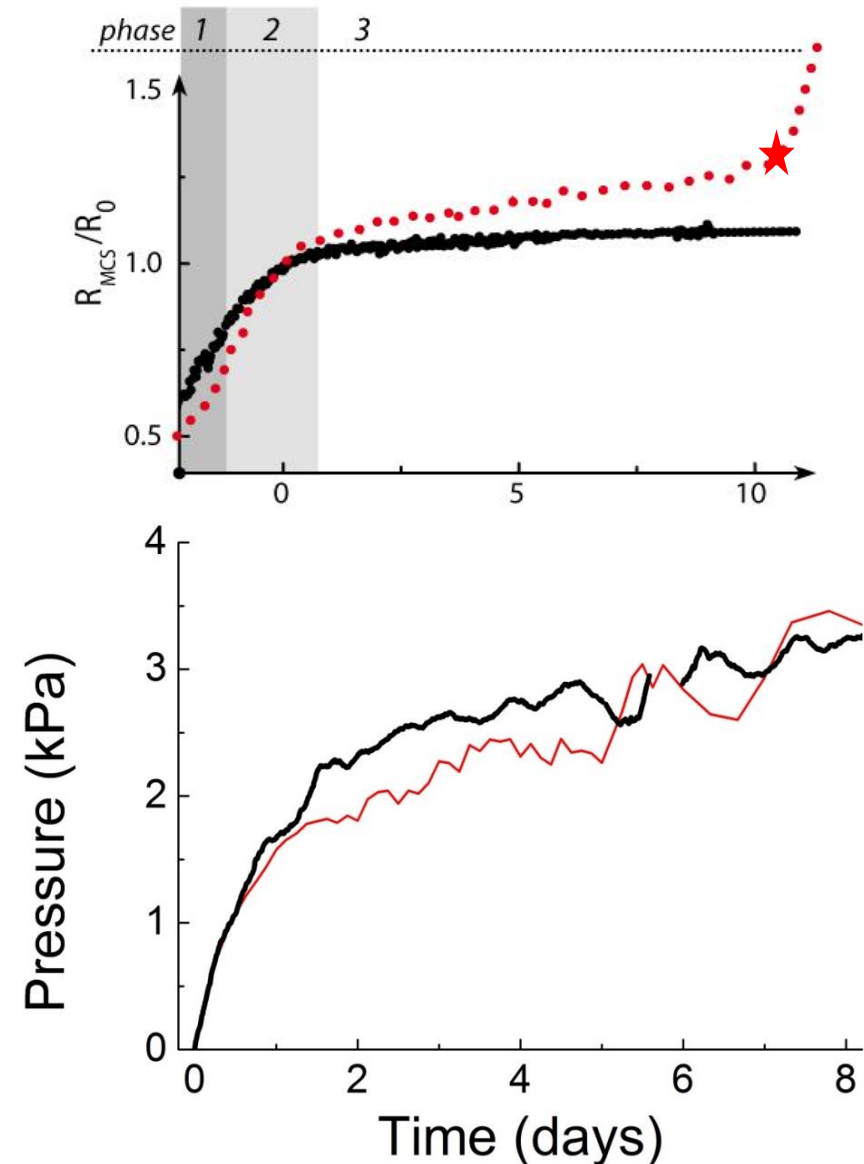
Confined growth

Role of confinement-induced mechanical stress ?

Growth kinetics



$$\Delta P = \frac{2E}{(1-\sigma)} \frac{h}{R} \frac{u}{R}$$

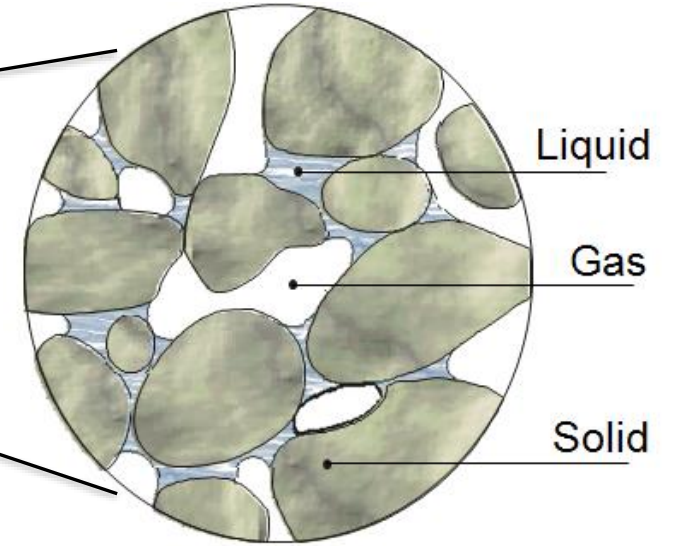


Can we provide a comprehensive mathematical model for the CCT experiment mimicking a tumor surrounded by host tissues?

Key issues:

- Link between parameters of the *in silico* and *in vitro* models
- Reduction of the complexity of the *in silico* model
- Assessment of parameters' sensitivity
- Predictive model (extrapolation and not interpolation)

Porous medium analogy (reactive and deformable)



Representative Elementary Volume (REV)

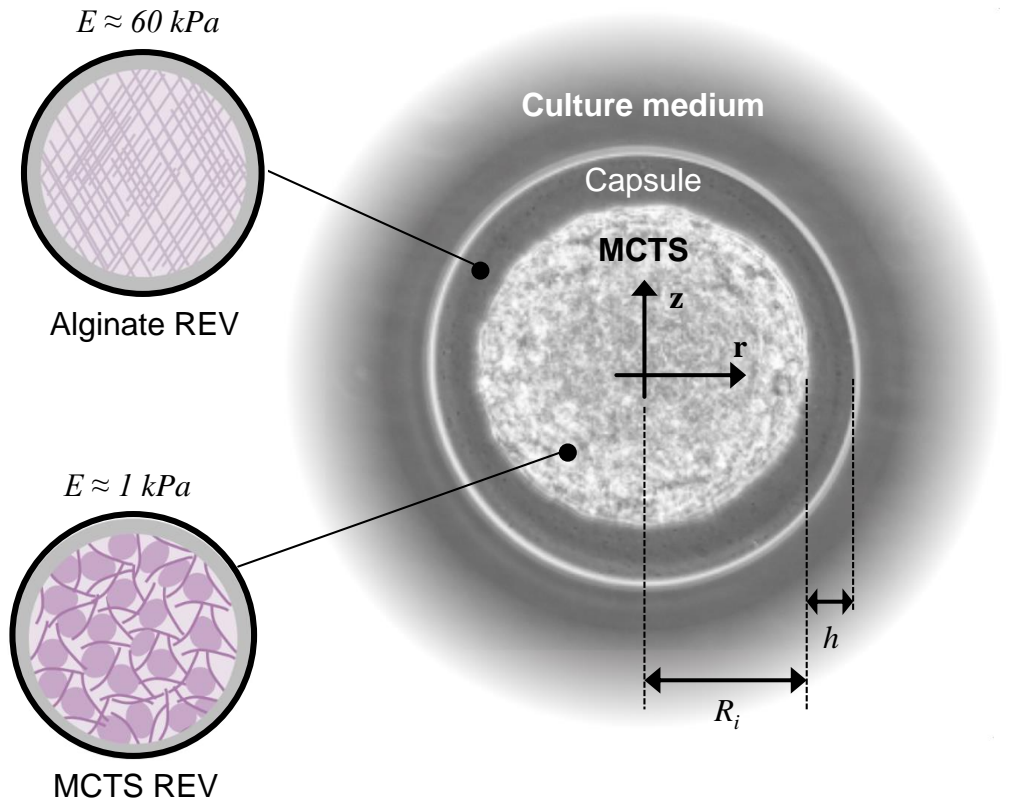
The behavior governed by :

- Conservation equations of mass
- Conservation equations of momentum
- Conservation equations of energy

+

Chemical reaction equations

Digital-twinning of the CTT: the role of stress



Volume fraction constraint: $\varepsilon^s + \varepsilon^t + \varepsilon^l = 1$

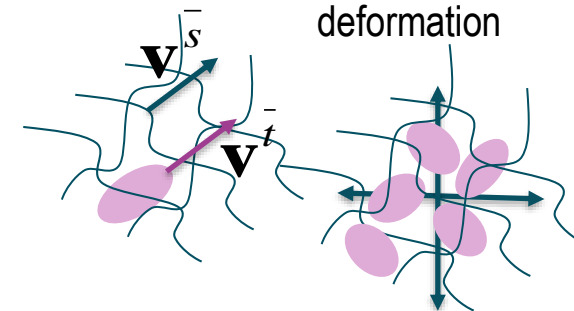
Mass conservation eqs of S, TC, IF:

$$\frac{D^s}{Dt}(\rho^s \varepsilon^s) + \rho^s \varepsilon^s \nabla \cdot \mathbf{v}^s = 0$$

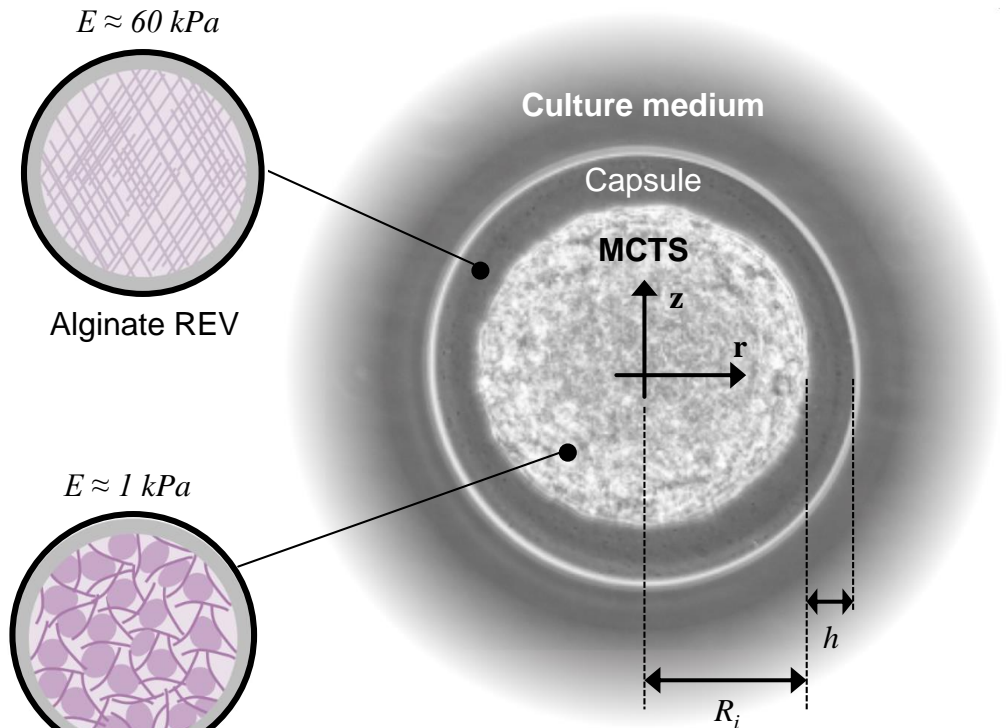
$$\frac{D^s}{Dt}(\rho^l \varepsilon S^l) + \nabla \cdot (\rho^l \varepsilon S^l \mathbf{v}^{ls}) + \rho^l \varepsilon S^l \nabla \cdot \mathbf{v}^s = - \overset{l \rightarrow t}{M}_{growth}$$

$$\frac{D^s}{Dt}(\rho^t \varepsilon S^t) + \nabla \cdot (\rho^t \varepsilon S^t \mathbf{v}^{ts}) + \rho^t \varepsilon S^t \nabla \cdot \mathbf{v}^s = \overset{l \rightarrow t}{M}_{growth}$$

Accumulation rate Infiltration ECM deformation



Digital-twinning of the CTT: the role of stress



- Medium/Interstitial fluid
- Tumor cells
- Extracellular matrix
- Alginate matrix

Urcun S, et al. (2021) PLOS ONE

Volume fraction constraint: $\varepsilon^s + \varepsilon^t + \varepsilon^l = 1$

Mass conservation eqs of S, TC, IF:

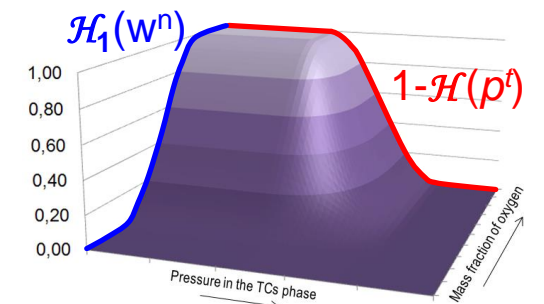
$$\frac{D^s}{Dt}(\rho^s \varepsilon^s) + \rho^s \varepsilon^s \nabla \cdot \mathbf{v}^s = 0$$

$$\frac{D^s}{Dt}(\rho^l \varepsilon^l) + \nabla \cdot (\rho^l \varepsilon^l \mathbf{v}^l) + \rho^l \varepsilon^l \nabla \cdot \mathbf{v}^s = - \overset{l \rightarrow t}{M}_{growth}$$

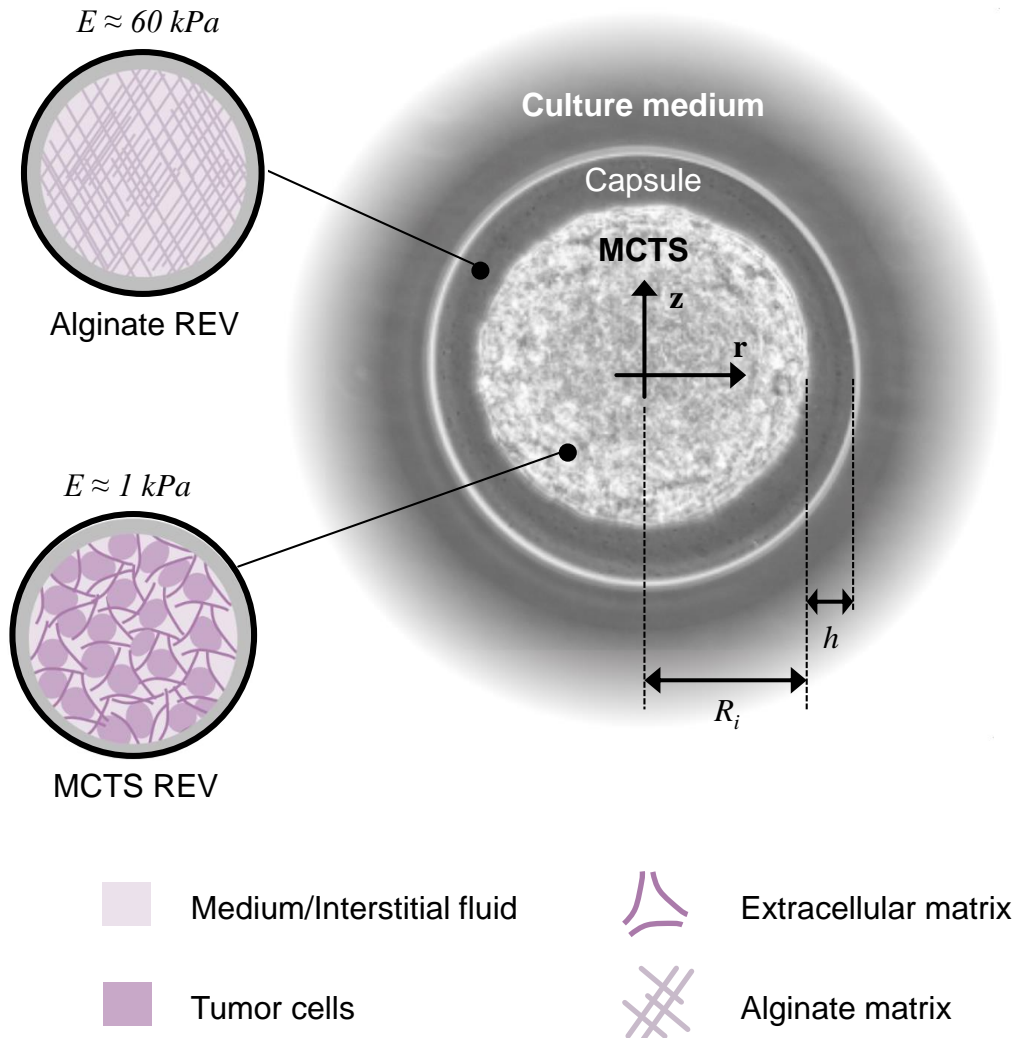
$$\frac{D^s}{Dt}(\rho^t \varepsilon^t) + \nabla \cdot (\rho^t \varepsilon^t \mathbf{v}^t) + \rho^t \varepsilon^t \nabla \cdot \mathbf{v}^s = \overset{l \rightarrow t}{M}_{growth}$$

Cell division

$$\overset{l \rightarrow t}{M}_{TC\ growth} = \gamma_g^t \mathcal{H}_1(\omega^{\bar{n}}) [1 - \mathcal{H}(p^t)] (1 - \omega^{N^t}) \varepsilon^t$$



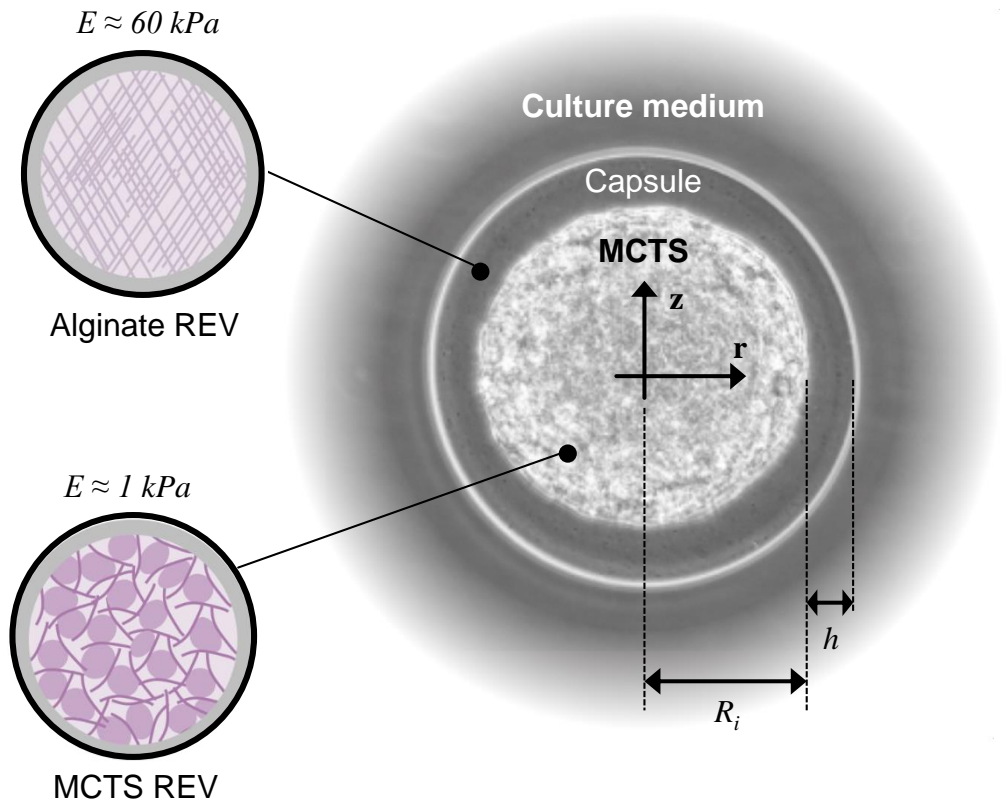
Digital-twinning of the CTT: the role of stress



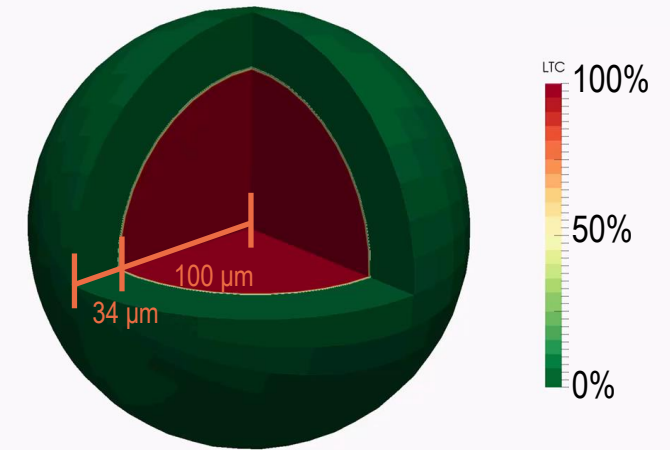
Constitutive equations :

- Generalized Darcy's law for cell and interstitial fluid velocities;
- Capillary pressure-saturation relationship;
- Biot's effective stress with a poroelastic behavior of the ECM scaffold;
- Fick's law for oxygen diffusion.

Digital-twinning of the CTT: the role of stress

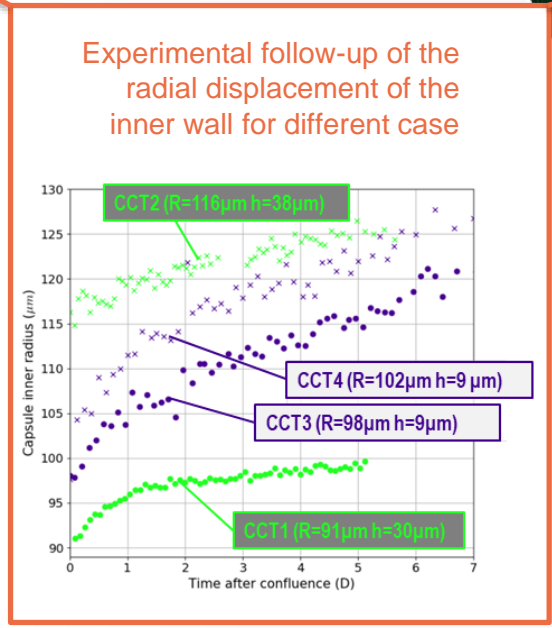
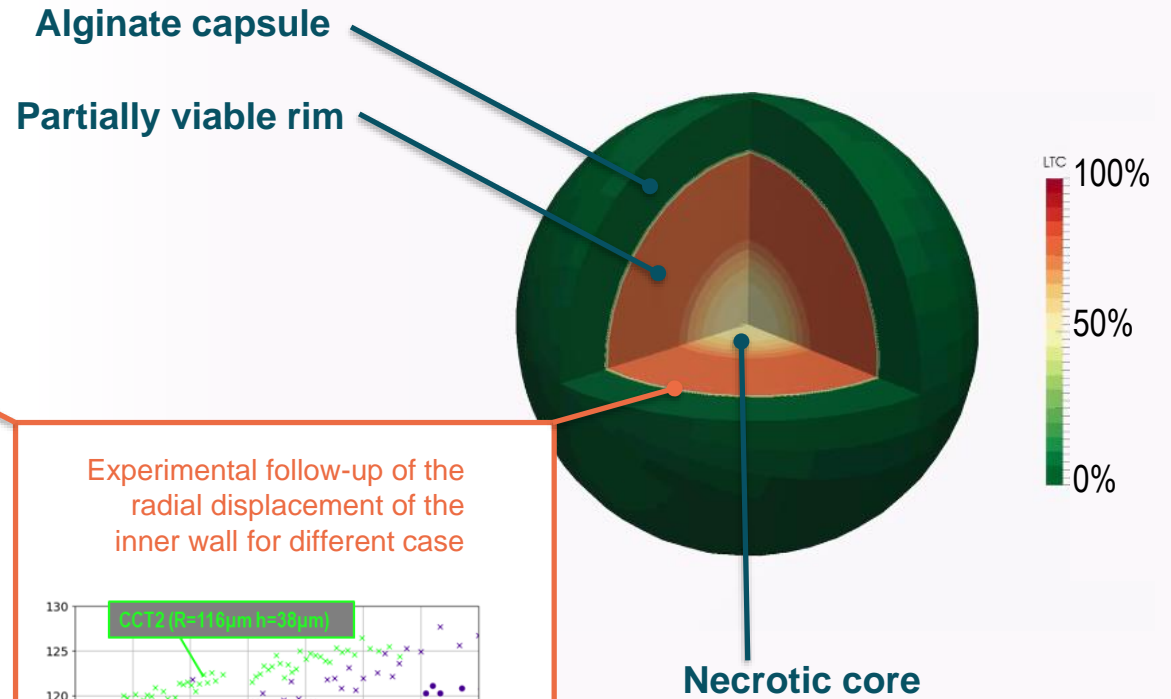
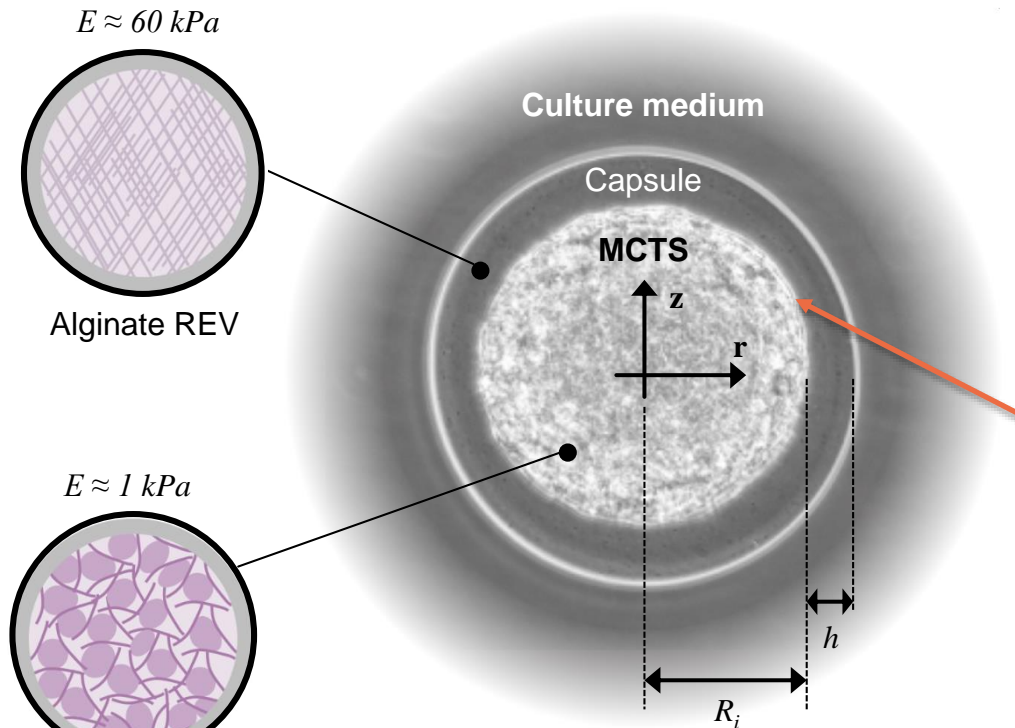


t_0 is the confluence instant



- Medium/Interstitial fluid
- Extracellular matrix
- Tumor cells
- Alginate matrix

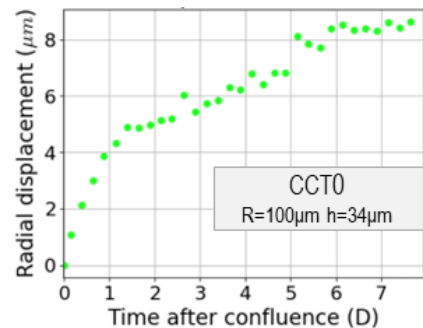
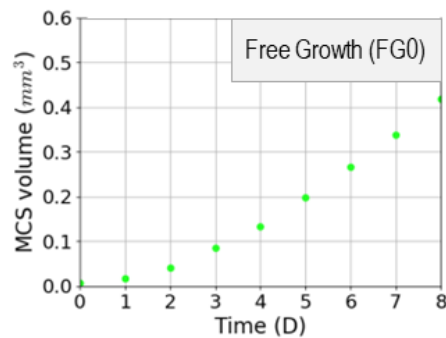
Digital-twinning of the CTT: the role of stress



Urcun S, et al. (2021) PLOS ONE

Digital-twinning of the CTT: the role of stress

Training dataset



Inverse modeling

Input parameters

Growth rate

TC viscosity

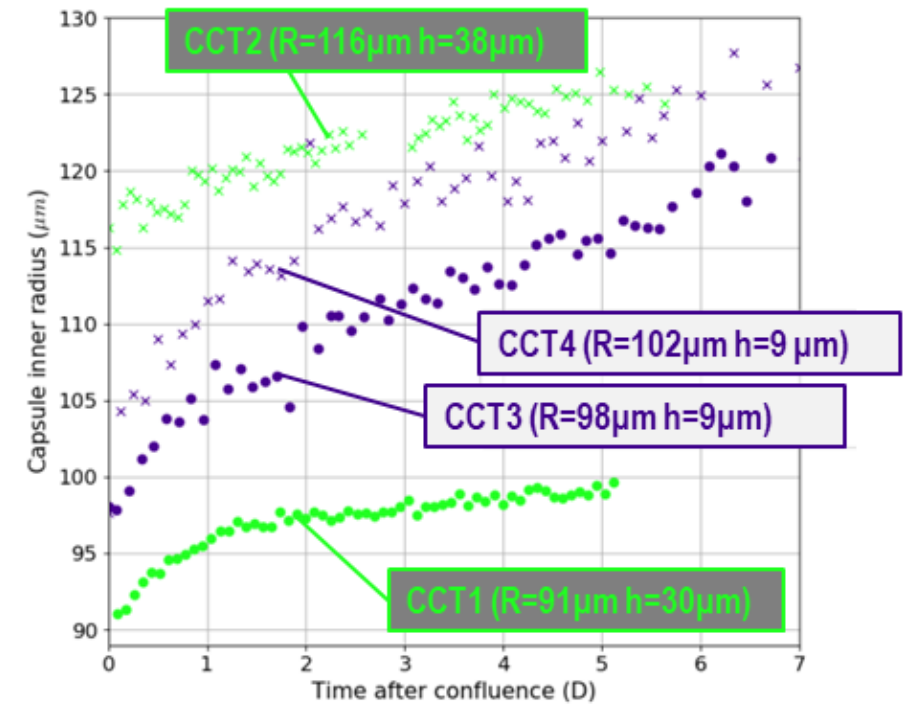
Oxygen consumption rate

Surface tension

Inhibition pressure

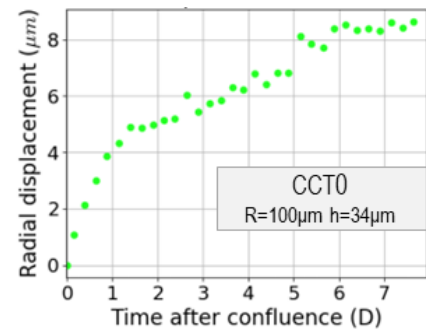
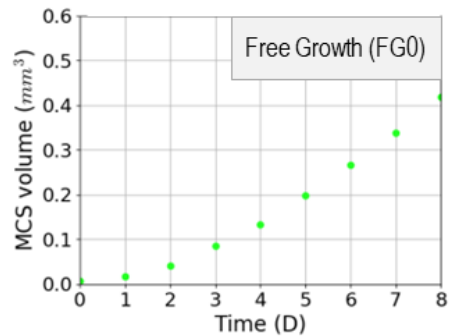
Direct modeling

Validation dataset



Digital-twinning of the CTT: the role of stress

Training dataset



Inverse modeling

Inverse modeling

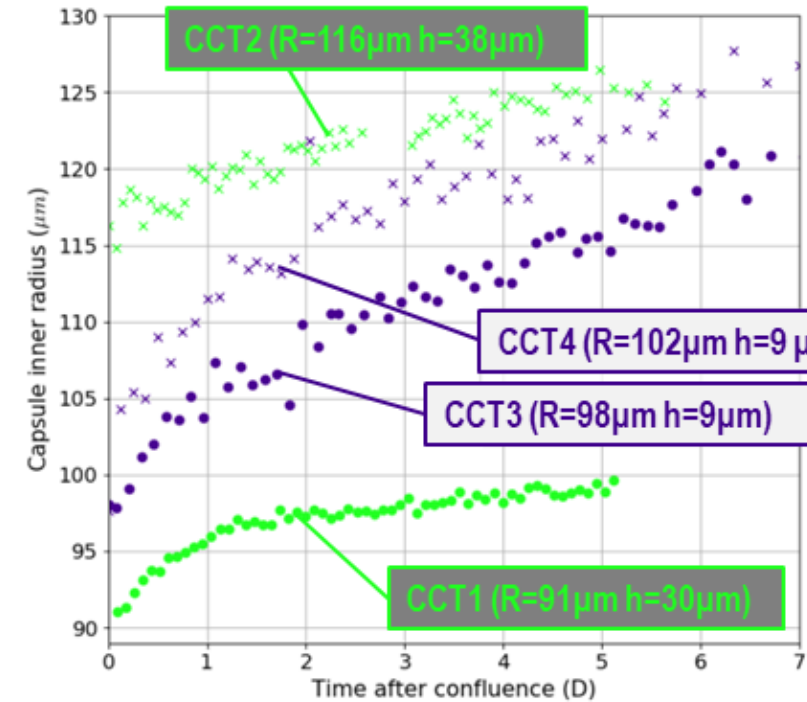
Input parameters

Growth rate
TC viscosity
Oxygen consumption rate

Surface tension
Inhibition pressure

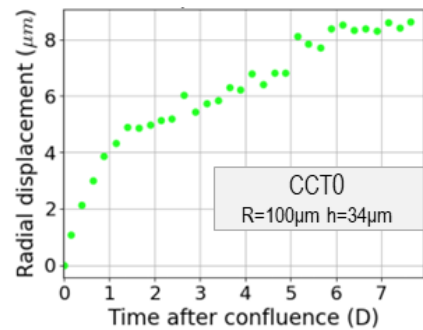
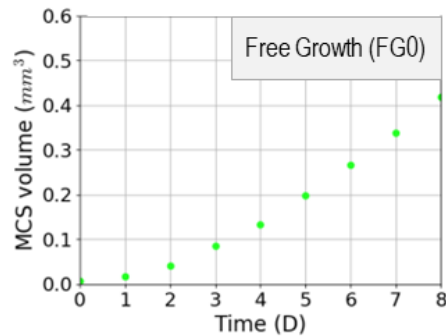
Direct modeling

Validation dataset



Digital-twinning of the CTT: the role of stress

Training dataset



Inverse modeling

Inverse modeling

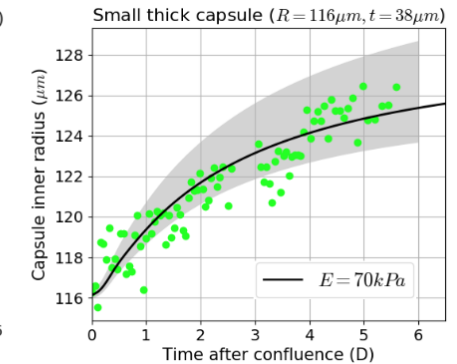
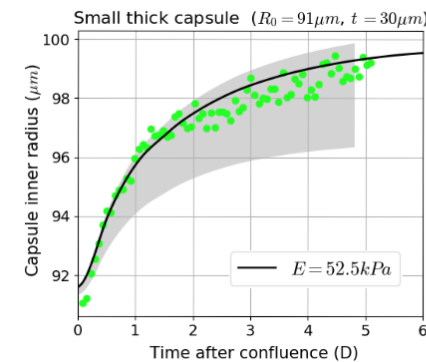
Input parameters

Growth rate
TC viscosity
Oxygen consumption rate

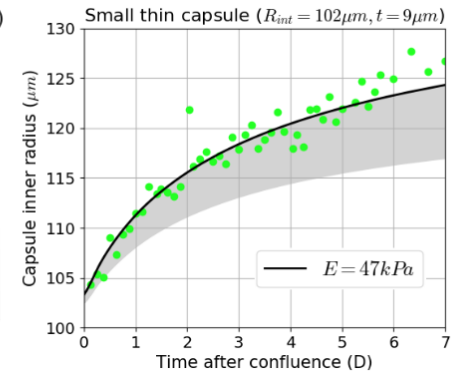
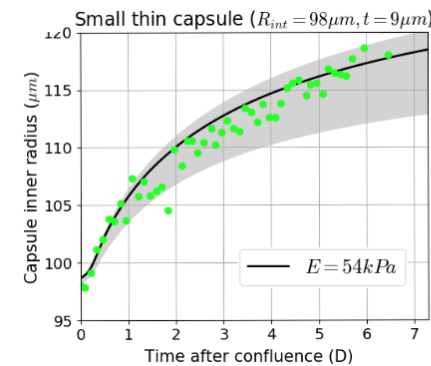
Surface tension
Inhibition pressure

Direct modeling

Validation dataset

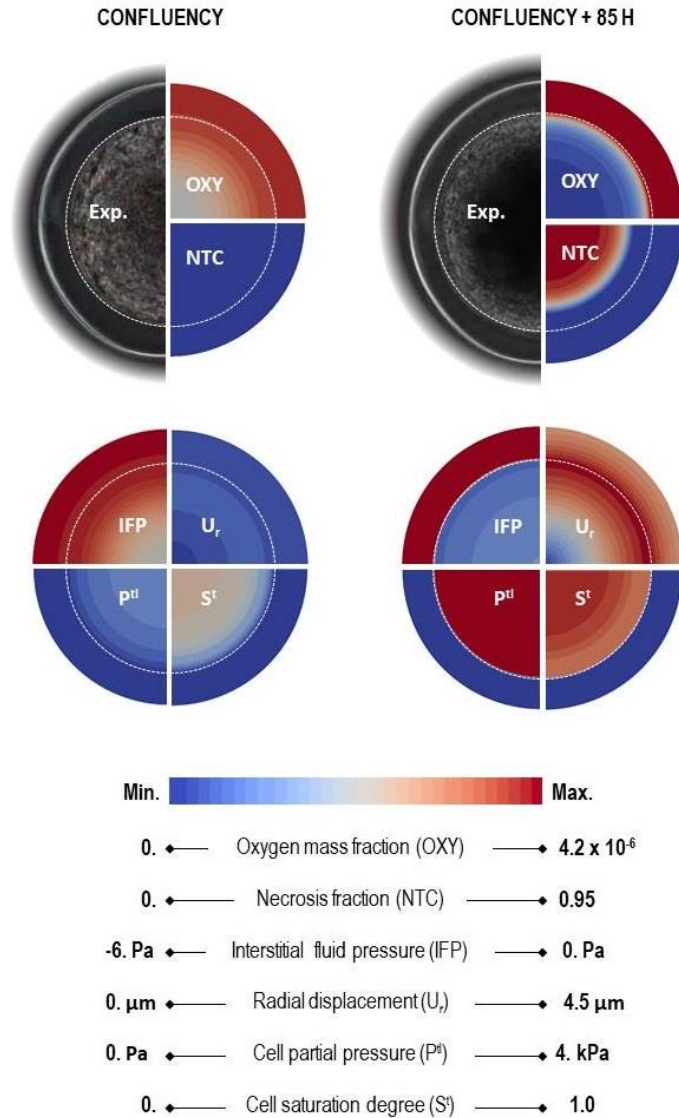


2 thick capsules

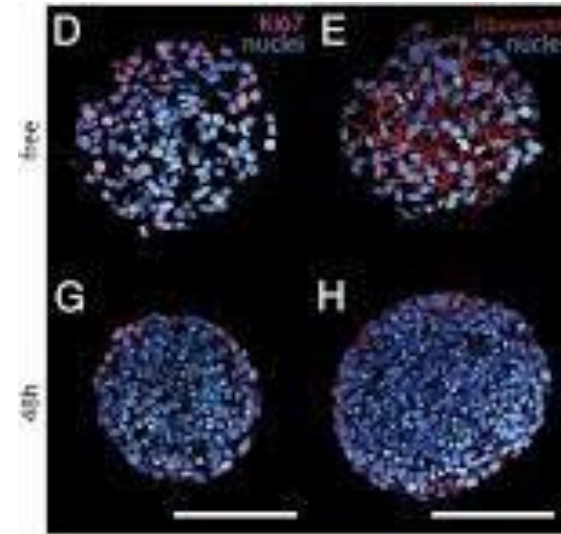


2 thin capsules

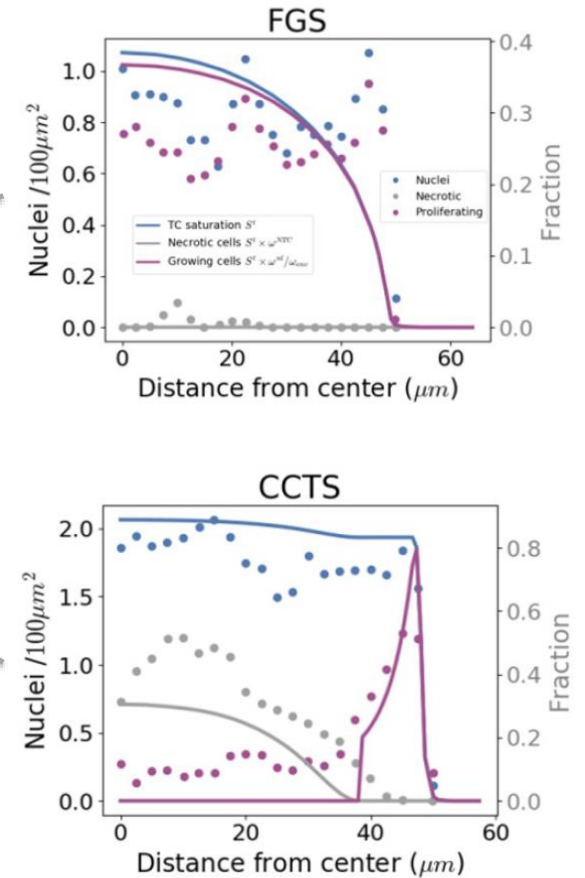
Digital-twinning of the CTT: the role of stress



Necrotic core and living rim



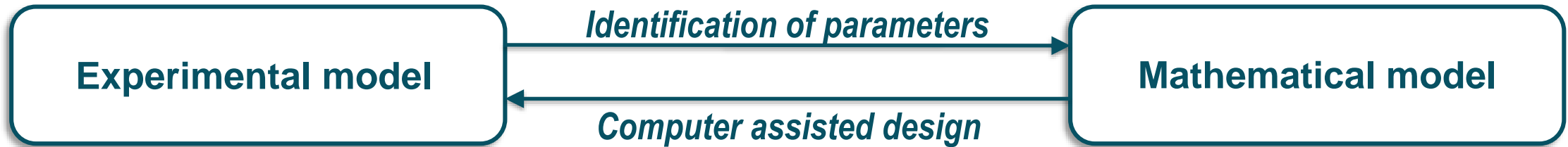
Confocal images of free (D and E) and confined (G and H) spheroids after cryosection and immunolabeling for DAPI (blue), KI67 (magenta), and fibronectin (red).



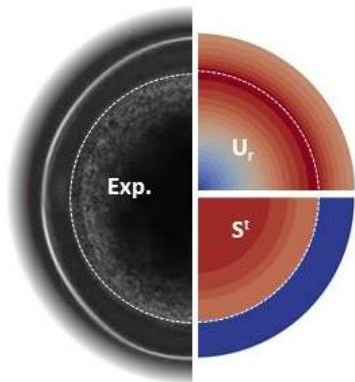
Digital-twinning of the CTT

Utility of the achieved *in vitro-in silico* synergy

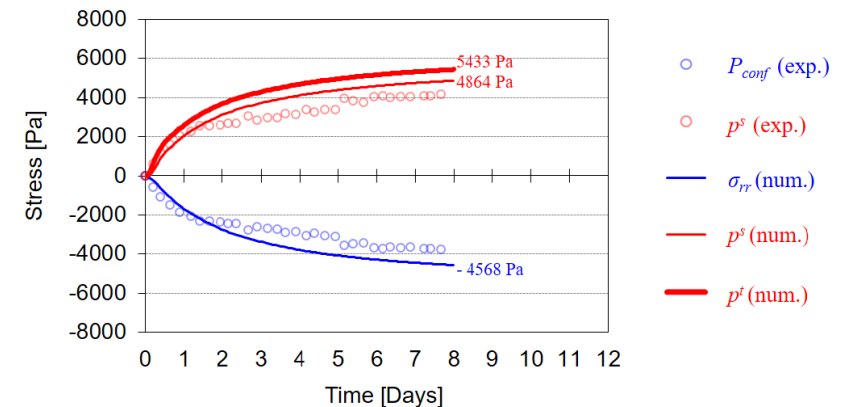
- Virtual testing



- Sensitivity analyses to identify dominant phenomena in a specific experiment
- Better interpretation of experimental results



The cells deform the ECM and the capsule so the stress retrieved from the capsule deformation is not a direct representation of the TC pressure



Can we provide comprehensive mathematical model for the CCT experiment accounting for alginate deformability ?

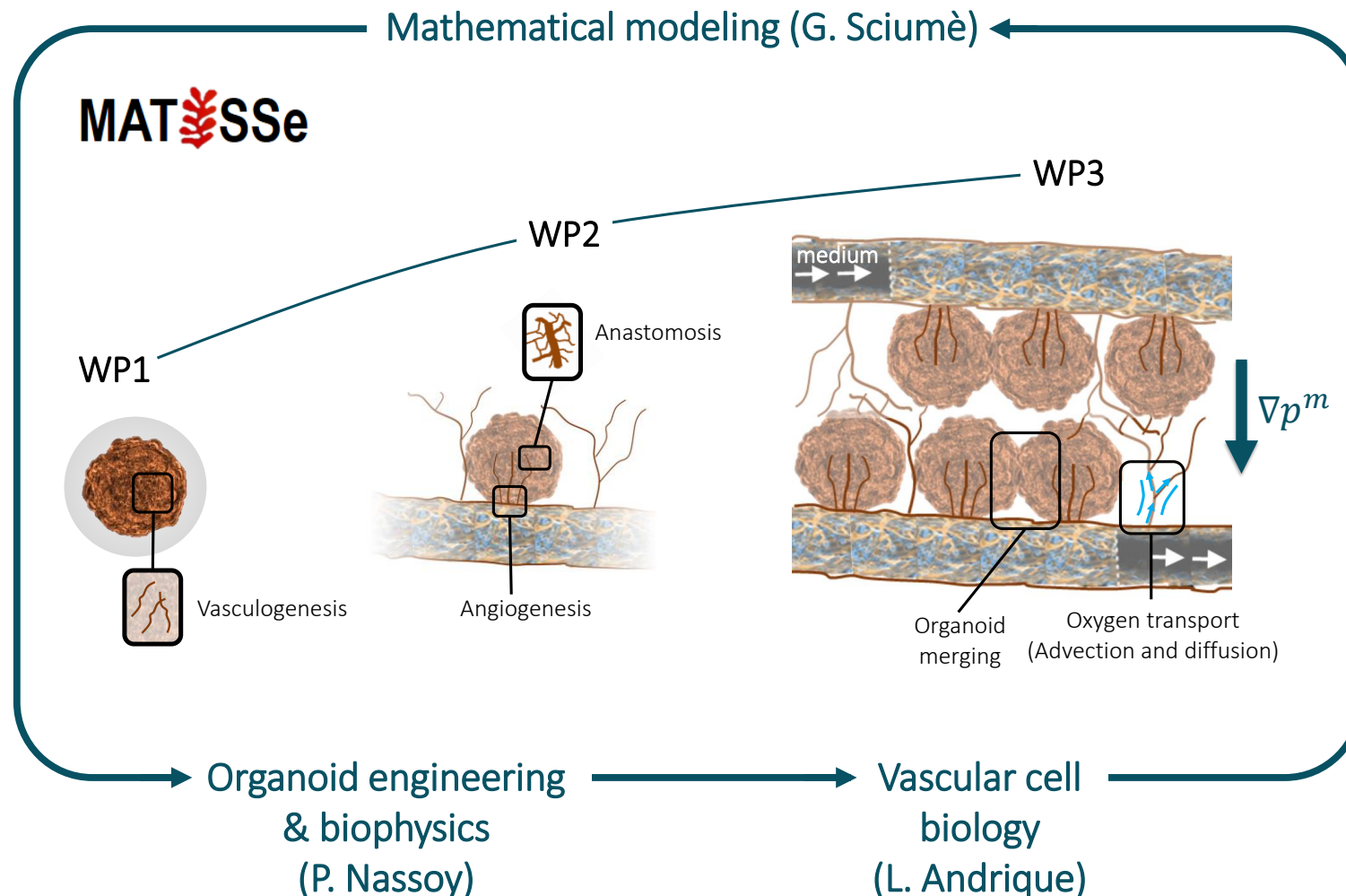
The answer is **YES**

Opportunities:

- Obtain a digital twin of cellular capsules that can be used reliably for further experiment-free testing of drugs.
- Extend this digital twinning approach to healthy tissues (or assemblies of organoids) for engineered design of tissues (vascularized) at the centimeter scale (*ANR MATISse*)

Project: Engineered design of vascularized tissues (MATISSe)

Mathematical **T**ISSues: an *in vitro-in silico* approach for engineering design and production of a new generation of vascularized organoid-based tissues



Thank you for your attention !

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Wafa Skalli (Professor at the *Institut de Biomécanique Humaine*, ENSAM)

Stéphane Bordas (Professor at University of Luxembourg)

BiOf lab (<https://biof-lab.org/>)