

Effect of mechanical stimulations on an *in vitro* model of cartilage growth

Noémie Petitjean

GDR MecaBio - 28/11/2018



Context



Source : atlas.centralx.fr

Articular cartilage

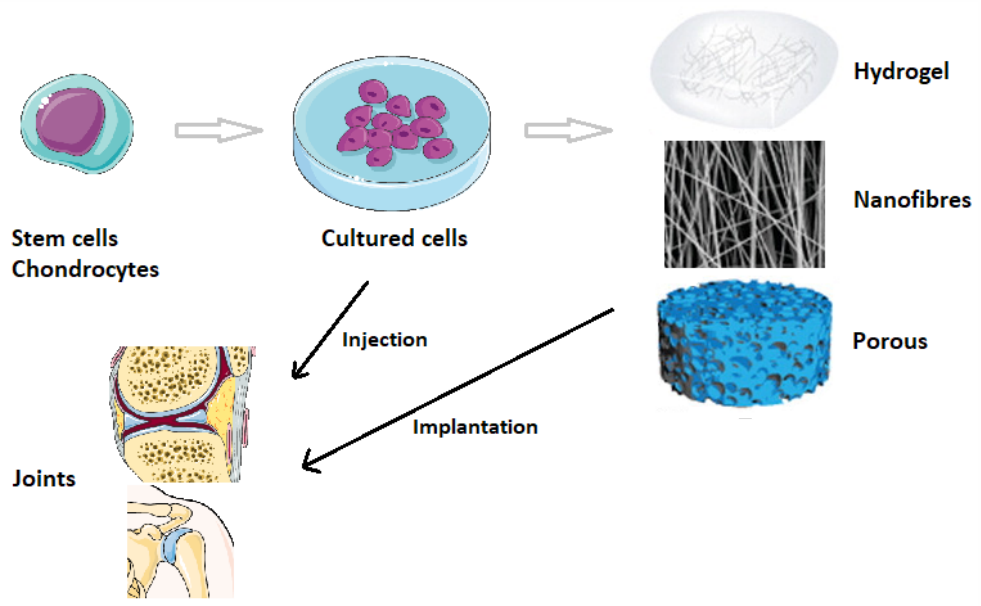
- Highly specialised connective tissue
- Smooth, lubricated surface for joint movements
- Damping and transmission of loads

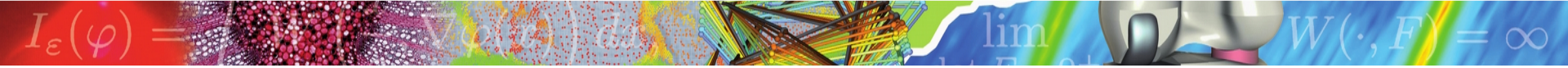
Issues :

- Function and structure of cartilage are altered by trauma or aging
- Capacity for intrinsic healing and repair are limited
- No treatment

Context

- Solutions :
 - Mesenchymal stem cells
 - Cell therapy : paracrine protective action
 - Tissue engineering : tissue repair





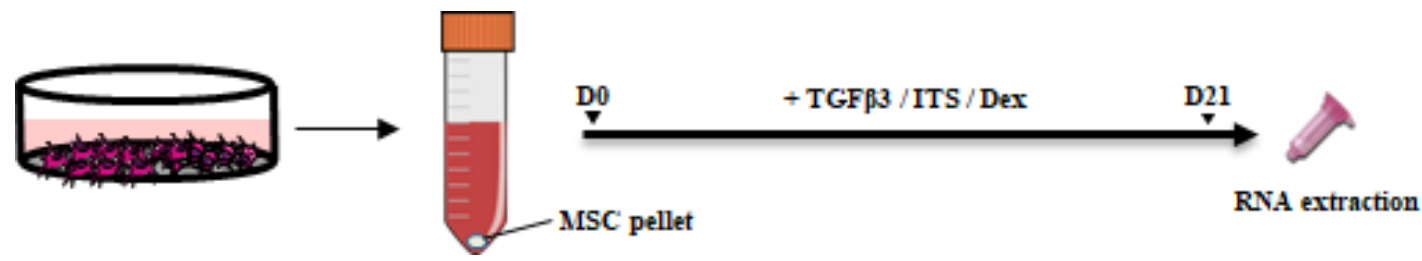
Objective

Principal objective : How mechanical stresses influence the development of an *in vitro* model of articular cartilage ?

- 1 - Create a device to stimulate the differentiation of MSC and the growth of cartilage
- 2 - Characterise the differentiation and the growth of cartilage in a mechanical and biological way
- 3 - Create a numerical growth model of cartilage

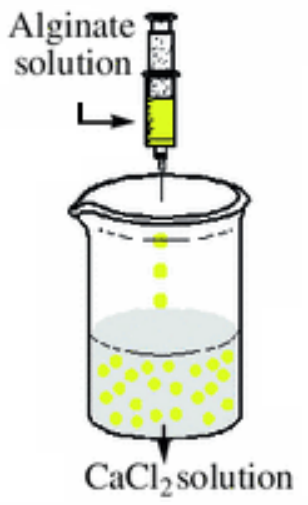
Growth model of articular cartilage

- Micropellets :



Micropellets of MSC or chondrocytes for stimulation tests

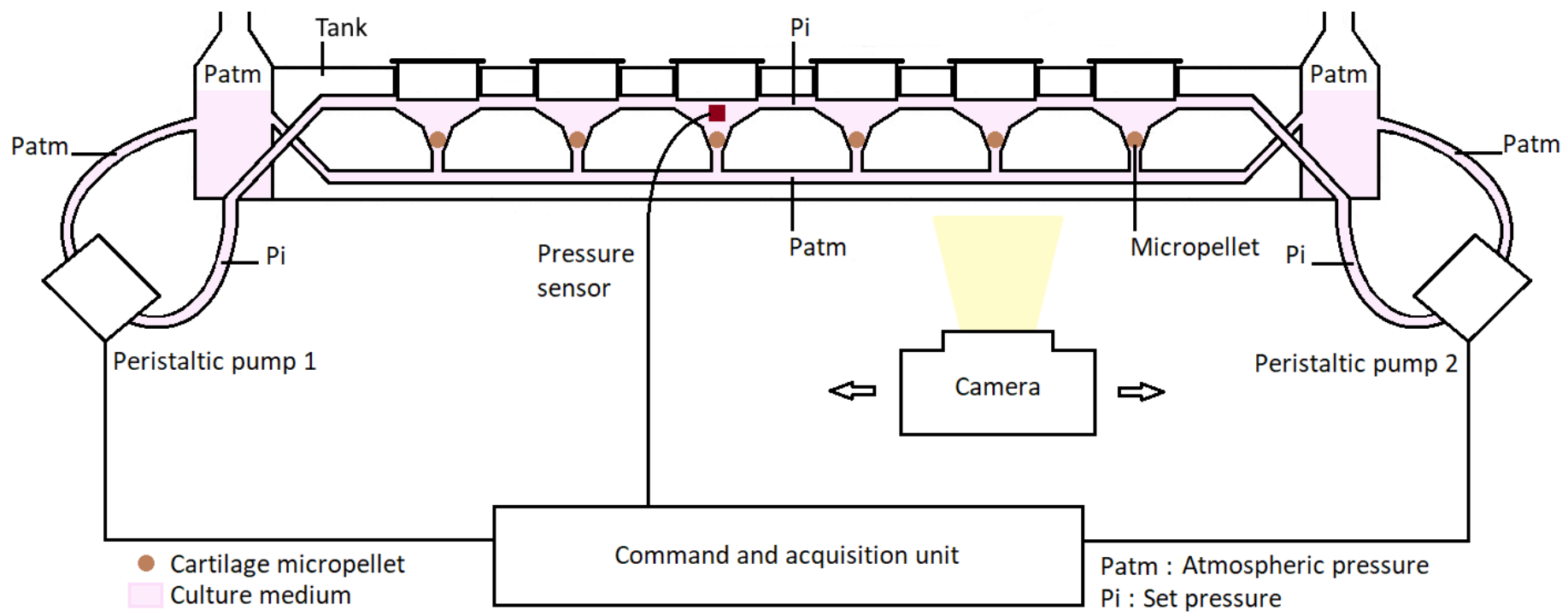
- Alginate beads :



Cell-free alginate beads to test the solicitation device

1) Micropellets stimulations

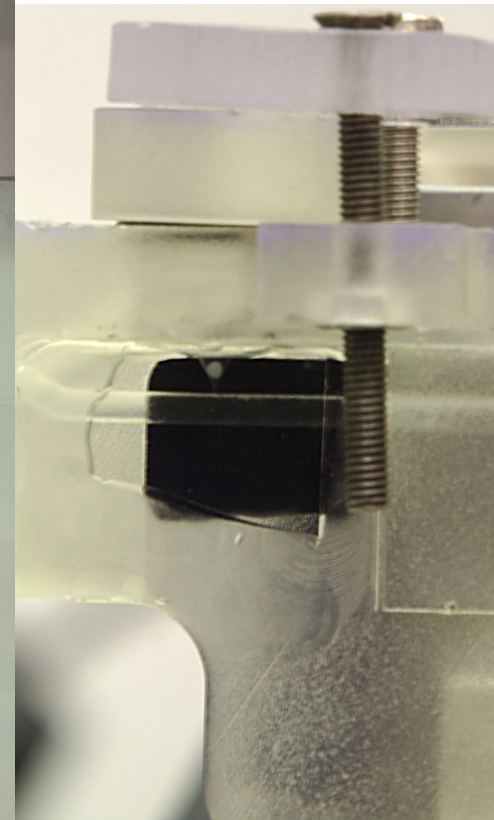
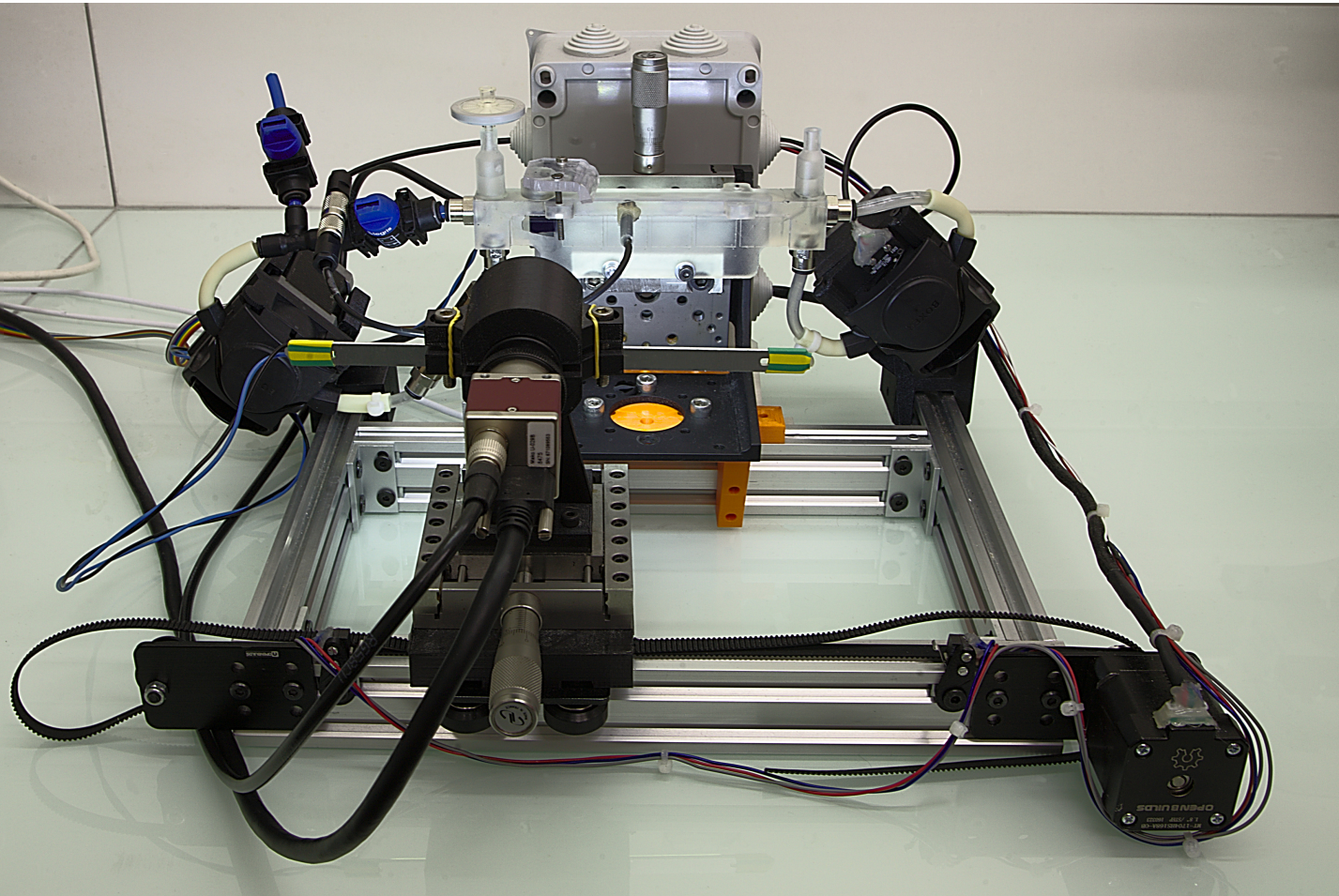
Scheme of the solicitation device :



Pressure are applied above micropellets

Micropellets are stressed by their insertion into the cone

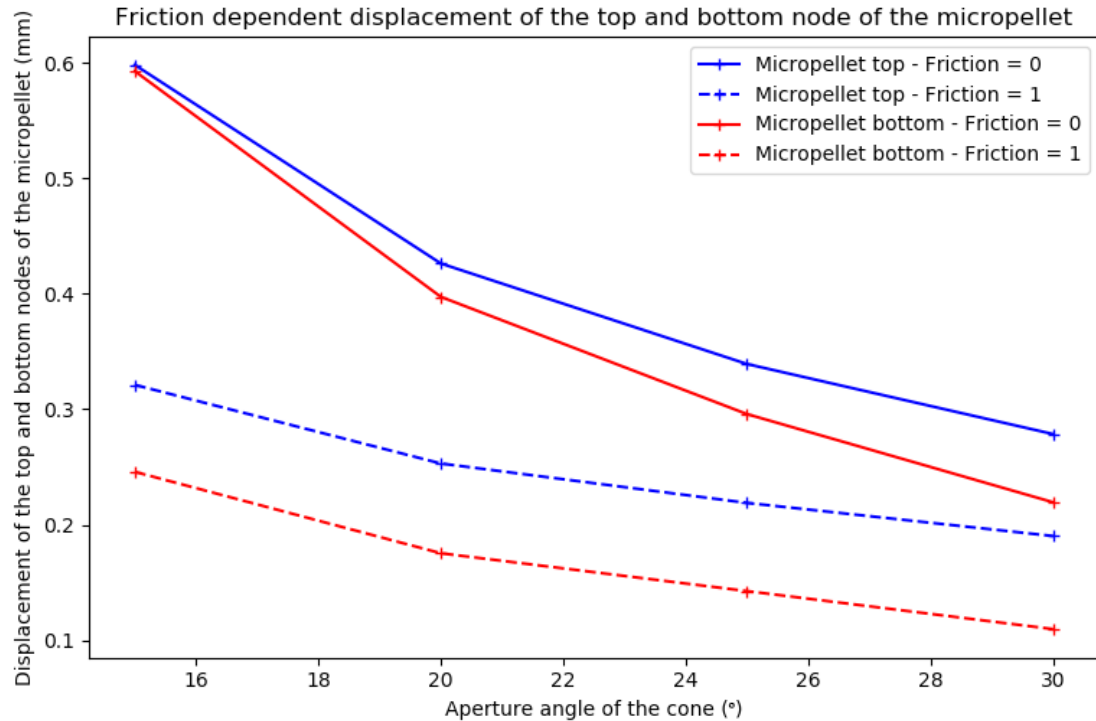
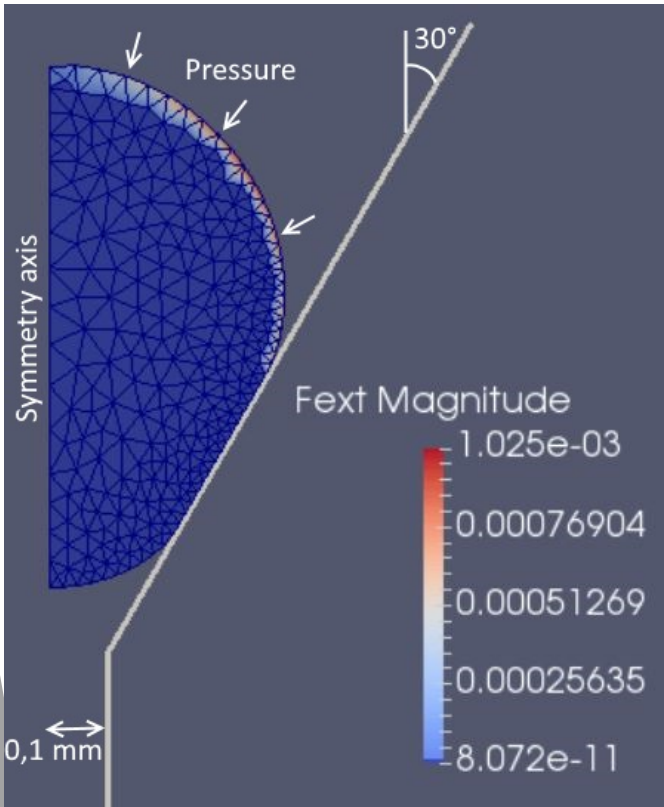
1) Micropellets stimulations

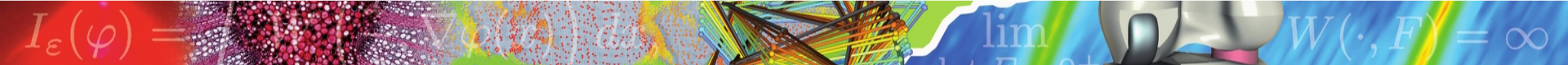


1) Micropellets stimulations

How to limit friction forces during micropellet sollicitations ?

- By modifying the aperture angle of the cone
- Measuring the frictions (pellet VS cone) and displacements (pellet)
- Validating the cone angle by numerical simulations



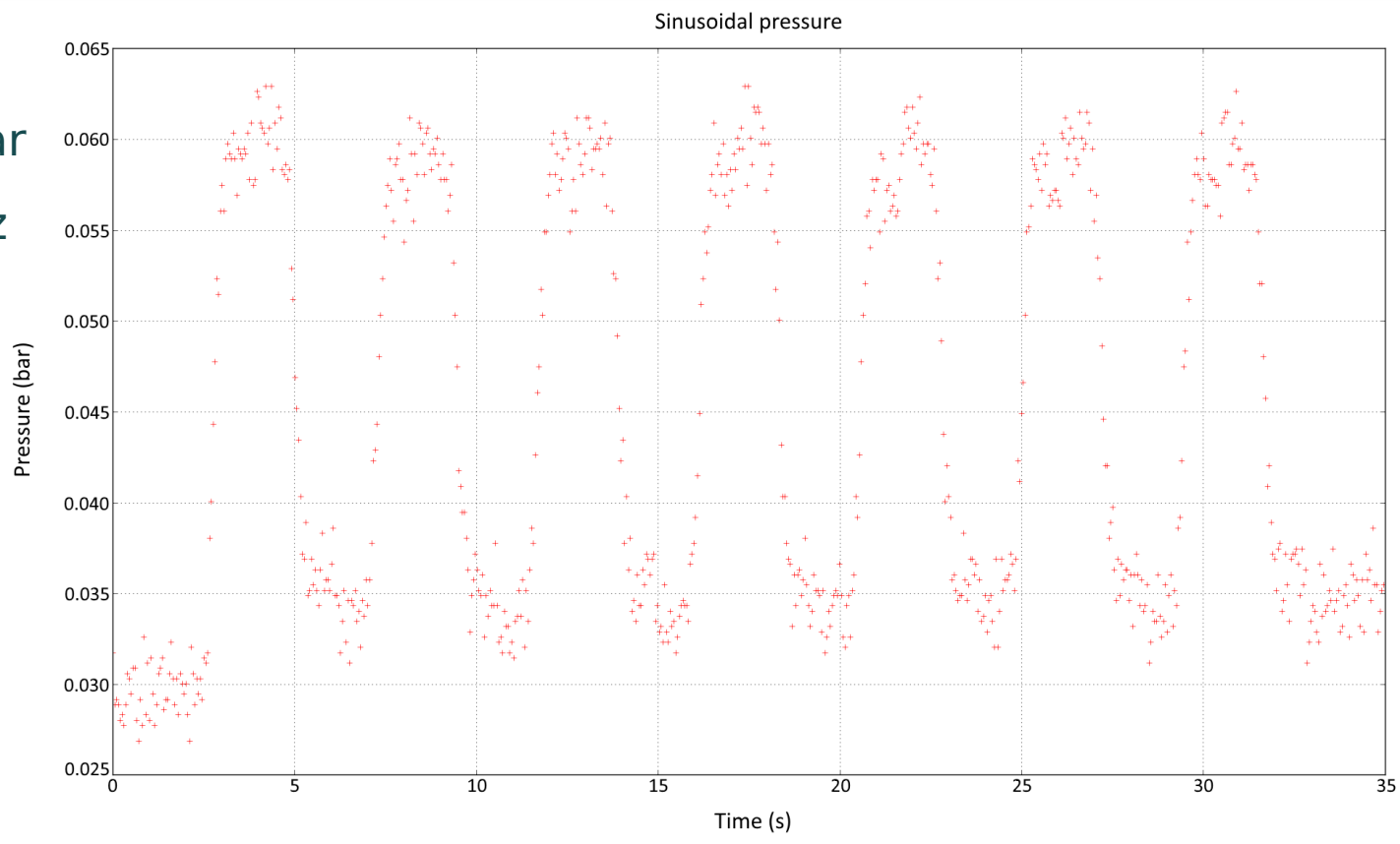


1) Micropellets stimulations

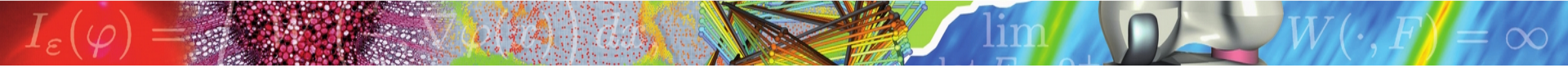
How stimulate the differentiation of MSC and growth of cartilage ?

- Cyclic :
amplitude = 0.03 bar
frequency = 0.25 Hz

- Ramps :
preloading for cyclic solicitations



- Devices for pressure managing :
Peristaltic pumps, check valve, pressure sensor, arduino card, python



1) Micropellets stimulations

Impact of mechanical loads :

Question 1 : Optimisation of solicitation parameters at day 0

amplitude : 0,03 ; 0,07 ; 0,1 bar

frequency : 0,3 ; 1 ; 3 Hz

duration : 15 min, 1h, 4h

number : 1, 2 or 3 times

delay between solicitations and evaluation of gene

expression : 24 ; 48 ; 96 h

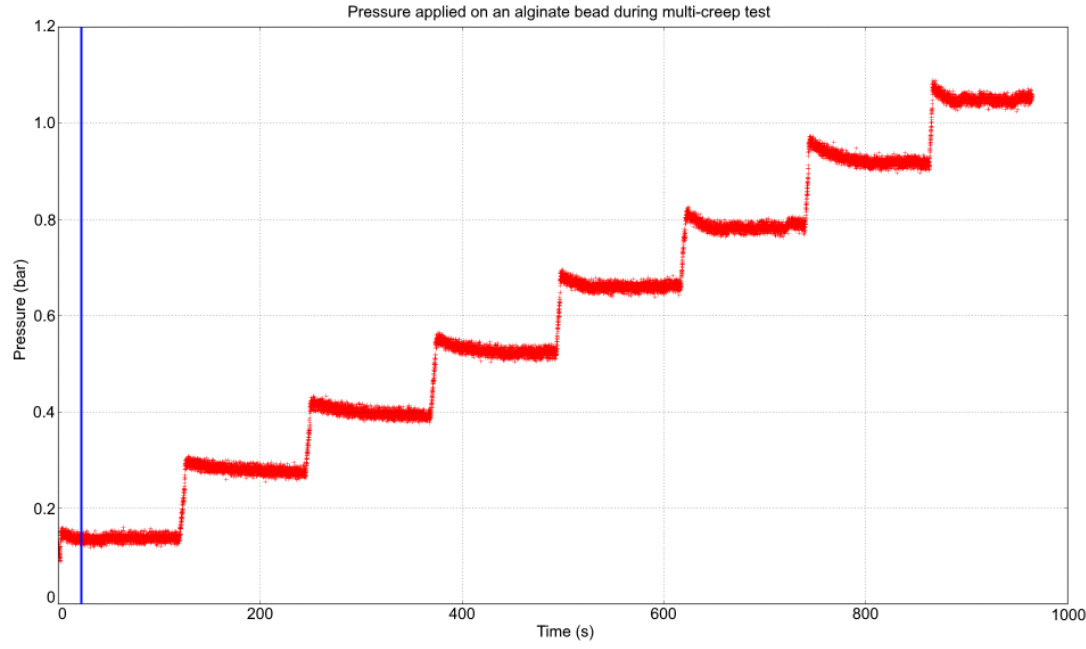
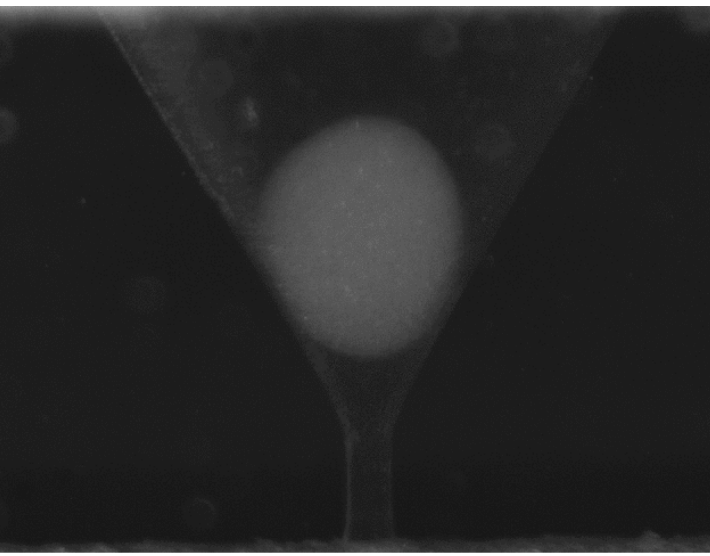
Question 2 : Evaluation of solicitation repetitions on gene expression and mechanical properties

weekly frequency : 1, 2 or 3 times per week

Question 3 : Mechanotransduction signals

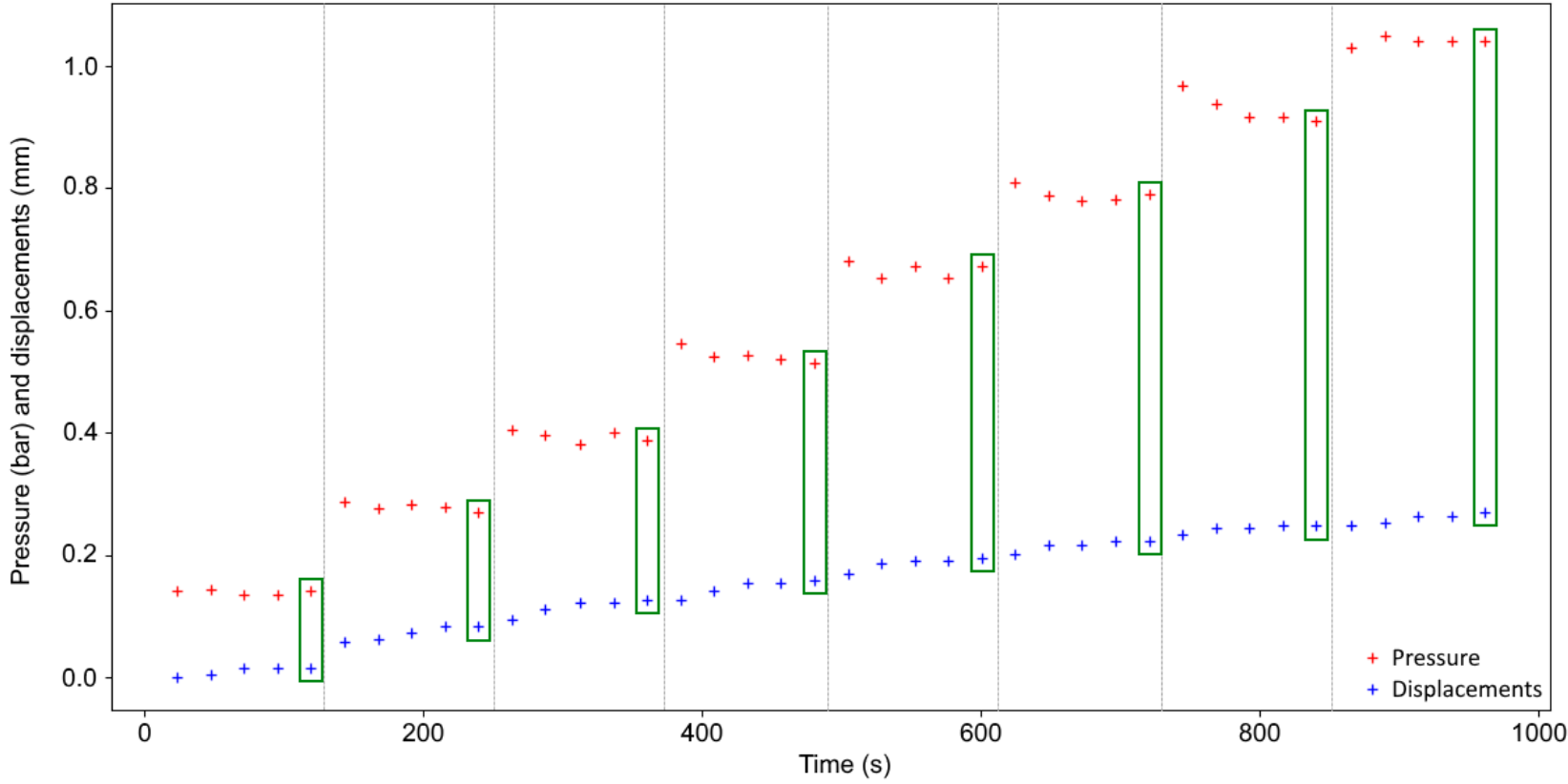
2) Measurement of mechanical properties

- Multi-creep test in the soliciation device to assess mechanical properties of micropellets



2) Measurement of mechanical properties

Pressure applied and displacement of the bottom of an alginate bead during a multi-creep test

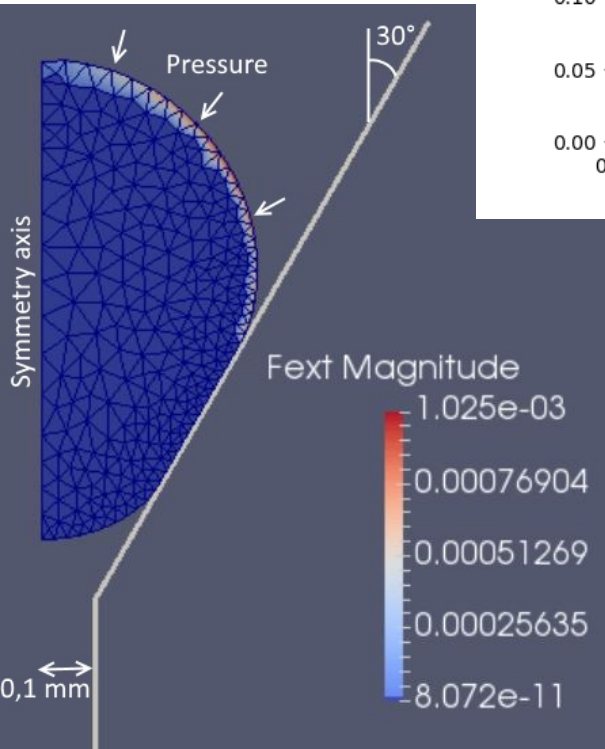
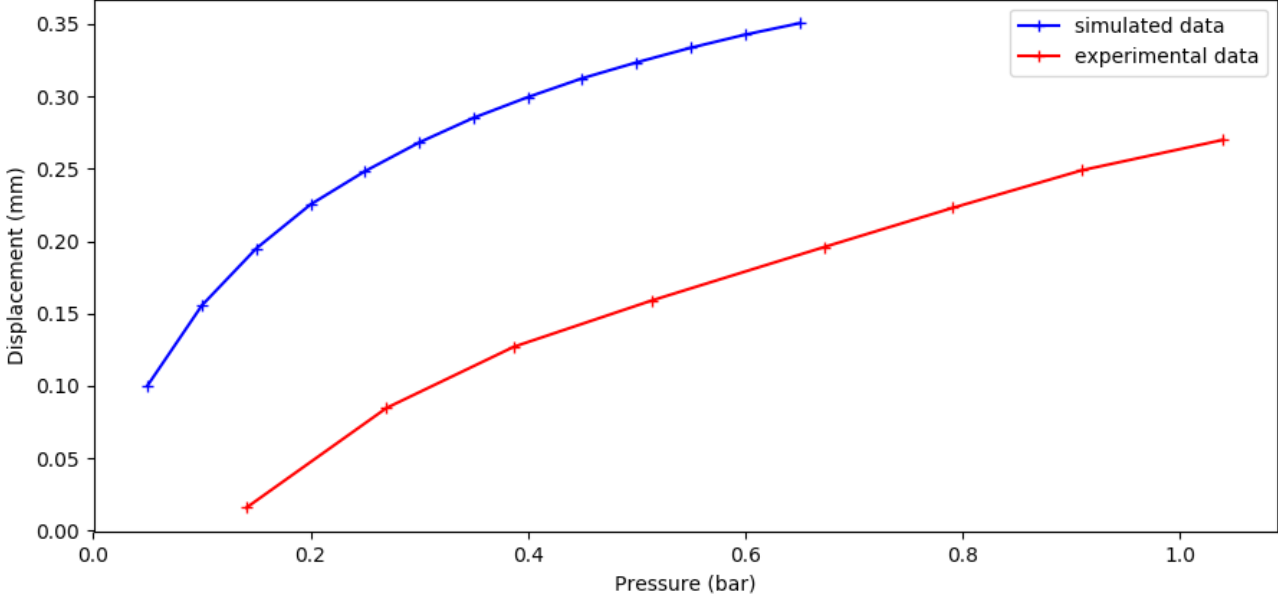


2) Measurement of mechanical properties

Inverse analysis

What global elasticity modulus ?

Comparison of the experimental and simulated displacement of an alginate bead as a function of the pressure applied

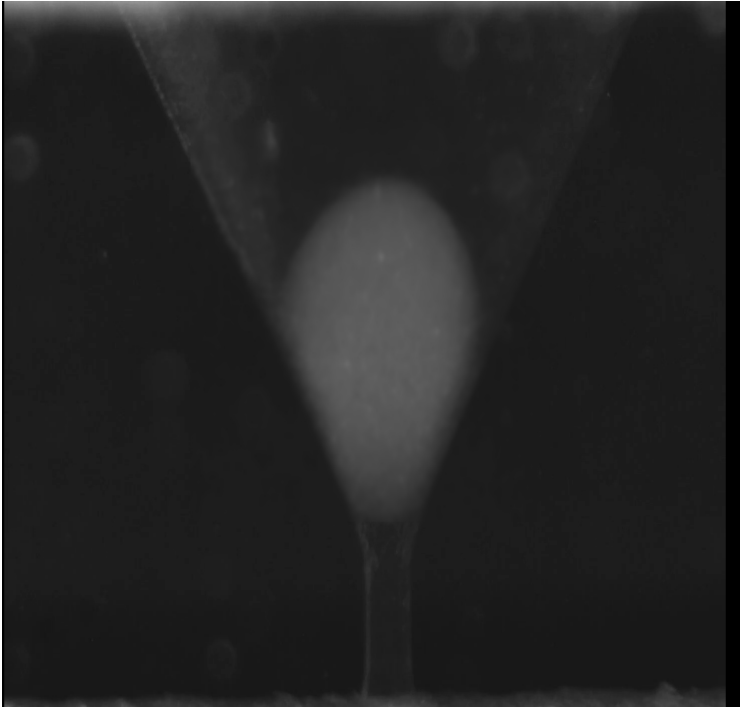
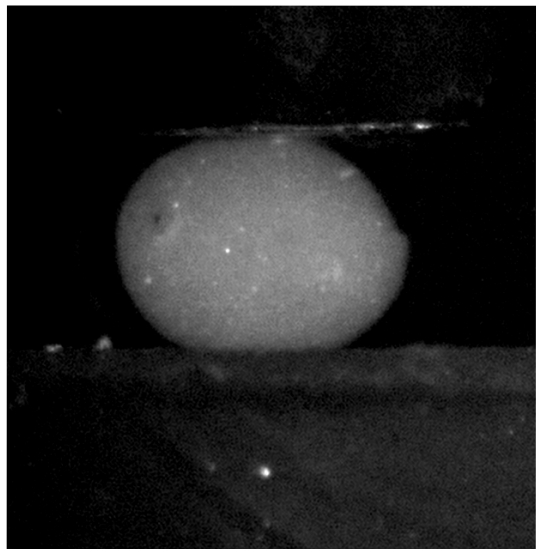


- FEM software LMG90
- Triangle elements T3
- Compressible neo-hookean material (MATLIB material)
- Axi-symmetric simulation
- Least square method

2) Measurement of mechanical properties

Validation of the sollicitation device : is it suitable to evaluate mechanical properties of micropellets during their development ?

Comparison with a brazilian test.

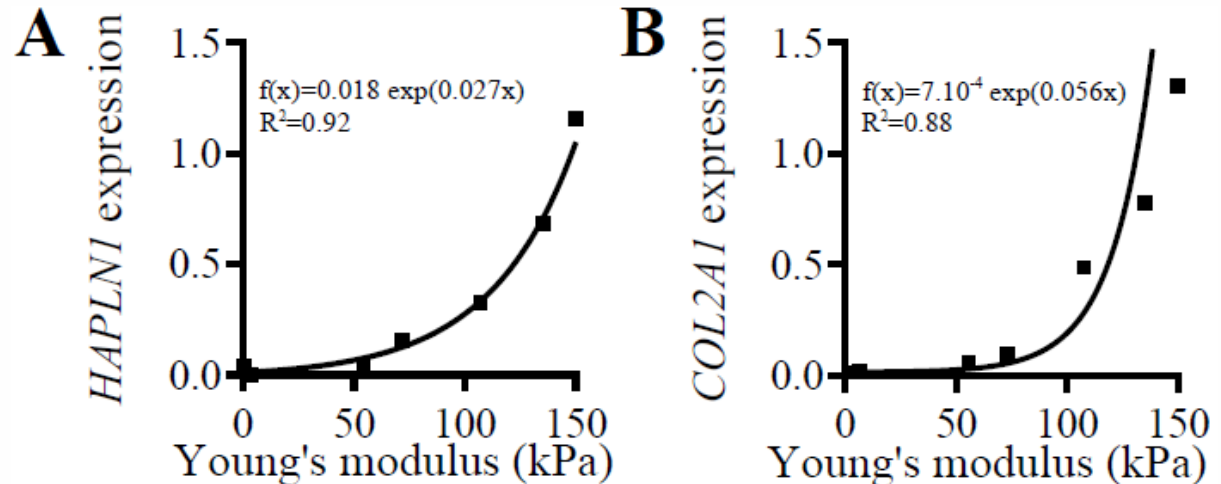


Multi-relaxation test (left) and multi-creep test (right)

3) Numerical growth model

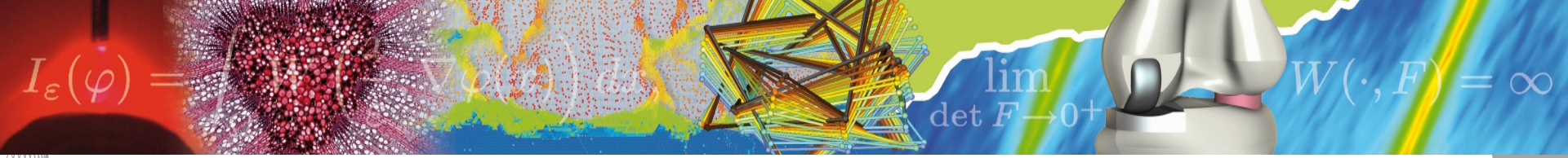
How can we predict the development of articular cartilage ?

- With correlations between environment parameters and micropellet properties.



Marie Maumus, Gilles Dusfour – submitted paper

- With theoretical model of growth

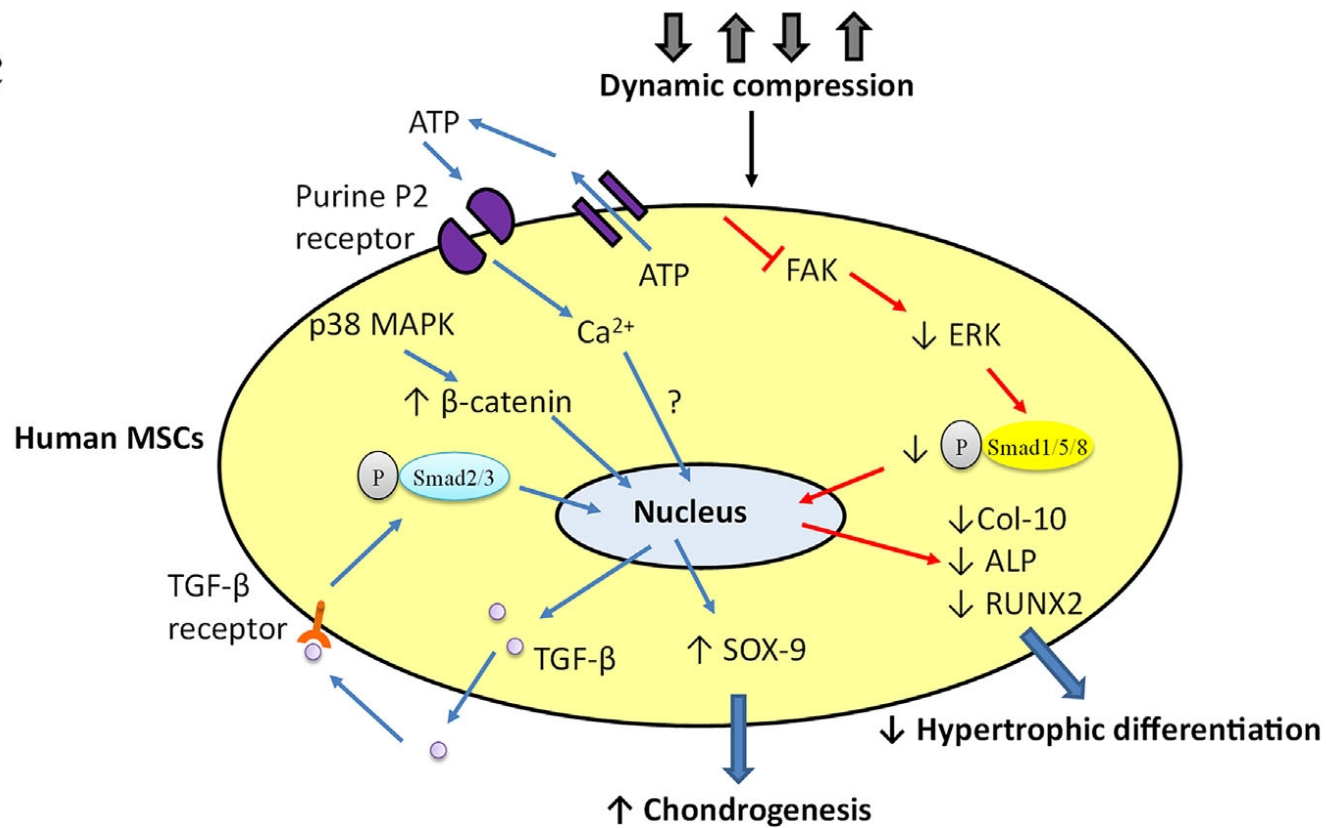


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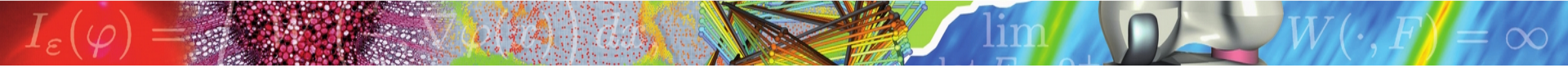
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Signaling pathways induced upon mechanical loading on hMSC



Neo-hookean law

Strain energy density function:

$$W = C_1 (\bar{I}_1 - 3) + D_1 (J - 1)^2 ; \quad J = \det(\mathbf{F}) = \lambda_1 \lambda_2 \lambda_3$$

$$\bar{I}_1 = J^{-2/3} I_1$$