Tissue self-organization through mechanical feedback

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Summary

1. Problem and related works
2. Individual-based model
3. Results
4. Macroscopic model
5. Healing / regeneration
6. Conclusion

1. Problem and related works

The problem

Goal:

Explore possible mechanisms of tissue self-organization and homeostasis

Motivations:

Tissue regeneration

Tissue engineering

Tissue homeostasis disorders (fibrosis, inflammation, etc)

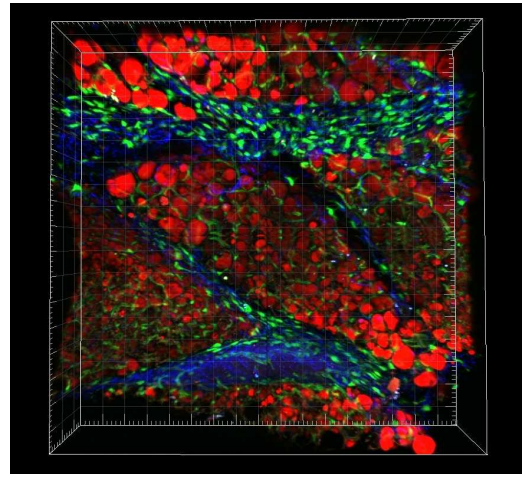
Adipose tissue

Adipose tisue as a model

- easy access
- health issues (obesity)
- plasticity (can undergo dramatic expansion/contraction)
- representative of the organization of many tissues

Morphology

- Groupment of adipocytes: lobules
- Separated by collagen fiber septa
- First noted by Wasserman (1965)



Problem

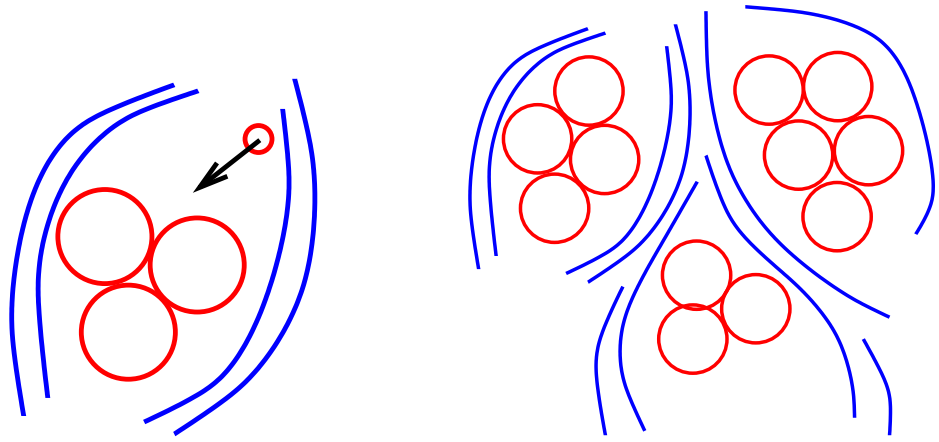
Investigate mechanisms by which the lobular organization takes place or is maintained

Our hypothesis

Simple mechanical cues could explain this morphology

Scenario:

- Collagen fibers resist bending and exert pressure on adipocytes
- New adipocytes formed by pre-adipocyte differentiation are forced to regroup into clusters
- Adipocyte clusters force the merging of fibers into a well-organized network



Achieved:

1. Individual based model for cells and fiber elements
2. Continuum model for fibers alone
3. Application of IBM to healing vs regeneration

Planned:

3. Coupling continuum fiber model with discrete cell model
4. Coupling continuum fiber and cell models

Literature

Cell-based models

Fiber-based models

Coupled cell-fiber models

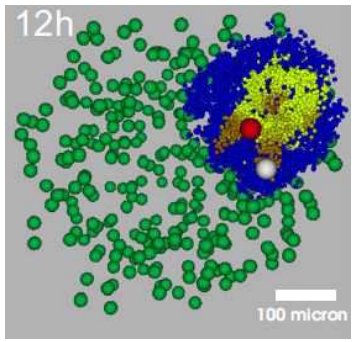
Literature: cell-based models

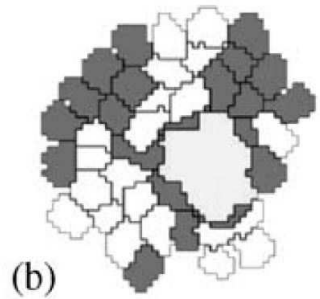
Cells modelled as simple objects (spheres)

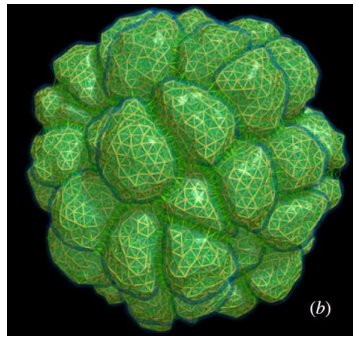
- Non-overlapping $\equiv$ repulsion force
- Off-lattice models: [Drasdo et al], [Beyer et al]

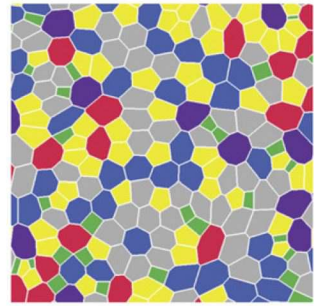
Cells modelled as complex objects

- Lattice-based: cellular Potts models [Merks Glazier], [Alber etal]
- Off-lattice: subcellular element model [Newman et al]
- Vertex model [Farhadifar, Jülicher, ...], [Fletcher et al], ...









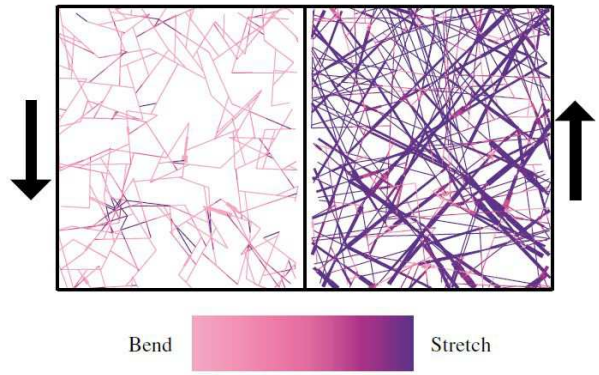
Literature: fiber-based models

Cross-linked fibers or lattice spring models

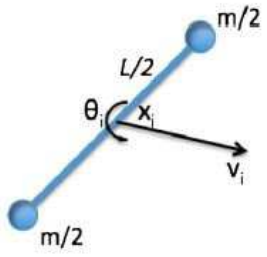
Stretching / Bending / Torsion

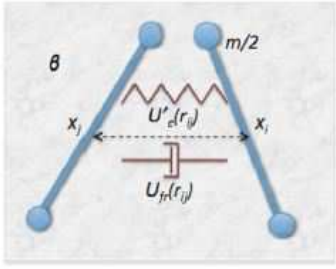
[Astrom et al], [Broedersz et al],
[Head et al], [Buxton & Clarke], ...

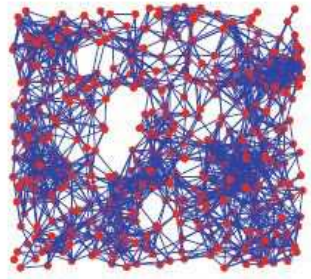
Bending to stretching phase transition

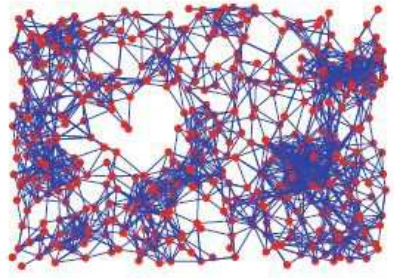


Fiber "flocking" model [Alonso et al]





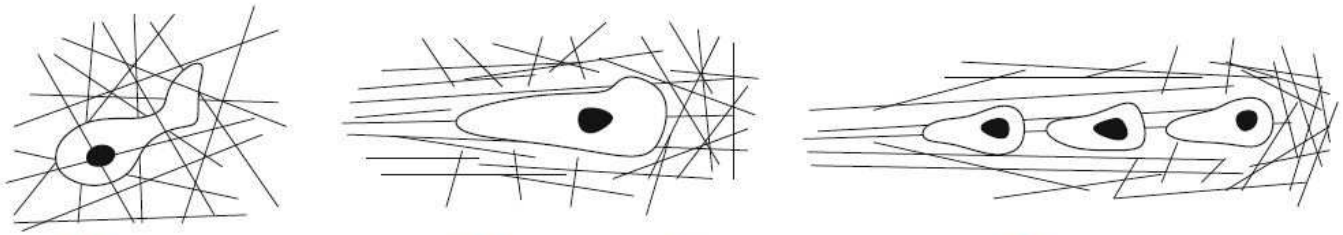




Literature: coupled cell-fiber models

Contact guidance

- Extra-cellular matrix (ECM) = network of collagen fibers
- Cells "crawl" along fibers
- Cells remodel ECM by proteolytic enzimes
- Chemical feedback of cells to ECM [Hillen], [Painter], ...



Present work: mechanical feedback

- Fiber resistance to bending
- Cell resistance to compression

Literature: cell-fiber mechanical feedback

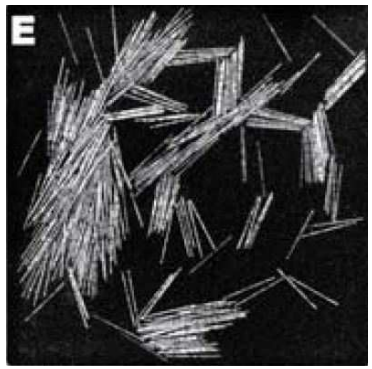
Few models (in particular for adipose tissue)

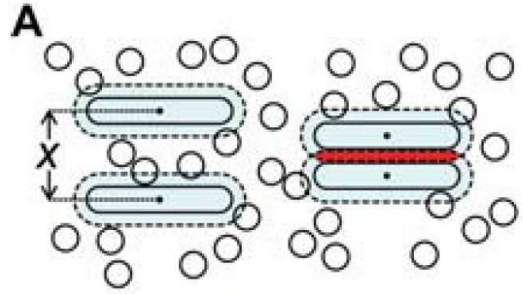
Mixing isotropic and elongated particles

- F-actin filaments and PEG beads [Hosek & Tang, PRE 04]
- Steel rods and hard spheres [Galanis et al, Soft Matter 10]
- Simulations [Jungblut et al, J Chem Phys 07]

Observed: nematic alignment of elongated particles

- Interpretation in terms of depletion force



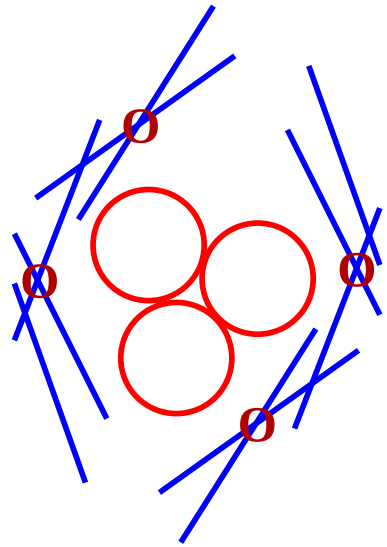


Here: also anisotropic effects on cell clusters !

Conclusion of literature review

In literature: detailed modelling of the biology

- Pro: good quantitative agreement
- Con:
  - difficult to disentangle influences of $\neq$ phenomena
  - difficult to derive a macro model from rigorous cross-graining



Our approach: look for "minimal model"

- with as few agents as possible
  - Cells: rigid spheres
  - Fibers: assembly of cross-linked rigid rods
- and as few phenomena as possible
  - Cells: non-overlapping constraints
  - Fibers: cross linking / unlinking & resistance to bending
  - Cell-fibers: mutual repulsion
- Allowing for coarse-graining to macro model

2. Individual-based model

Reference

Simple mechanical cues could explain adipose tissue morphology,

J. Theoret. Biol., 429 (2017), pp. 61-81

Joint work with

Diane Peurichard (INRIA Paris), Fanny Delebecque (Math, Toulouse)

Louis Casteilla, Anne Lorsignol, Corinne Barreau (Stromalab, Toulouse)

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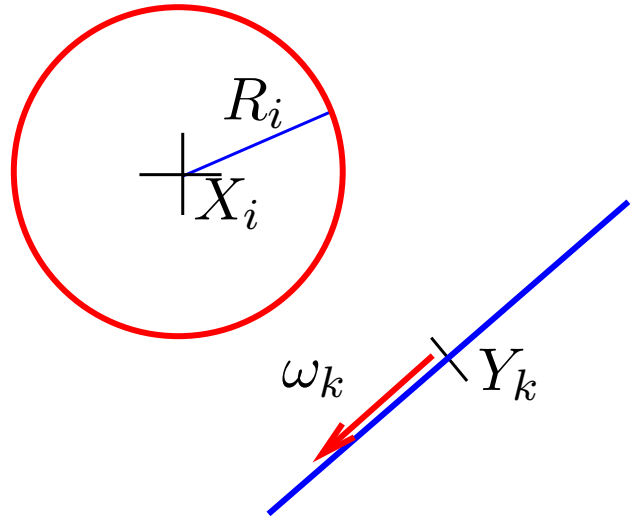
Agents

2-dimensional model



Cells

Disks: center X_i, radius R_i

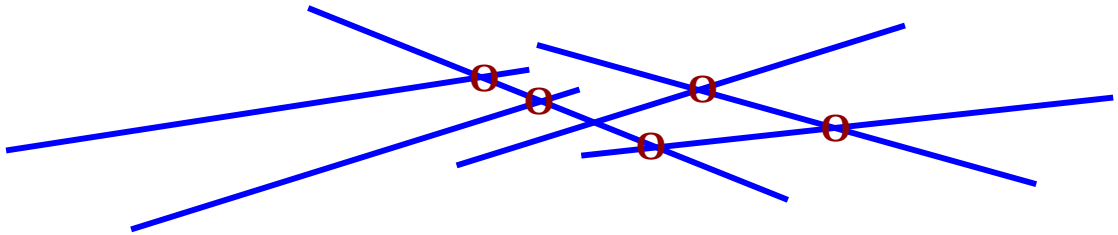
Fiber elements

Unit fiber element = line segment of fixed length L

centered at Y_k and directed along ω_k ($|\omega_k| = 1$)

Fiber

Set of connected fiber elements



Flowchart

Time t:

cells and fibers are in mechanical equilibrium

$$t \to t + \Delta t$$

Equilibrium disrupted

by biological phenomena

Time $t + \Delta t$

restoration of mechanical equilibrium

by minimizing energy functional

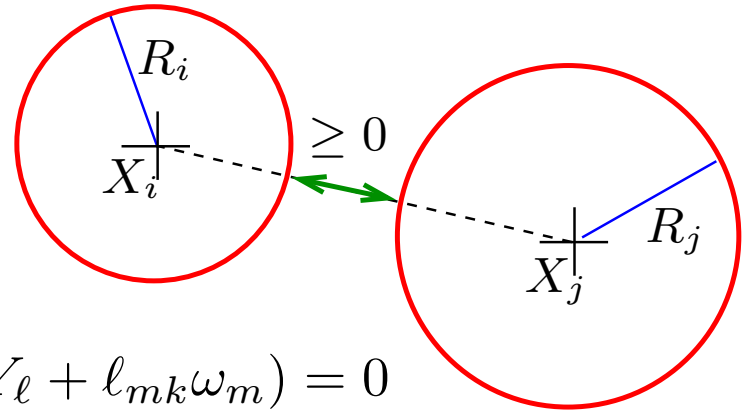
subject to constraints

Constraints

Cell-cell volume exclusion

Incompressible sphere approximates adipocyte shape

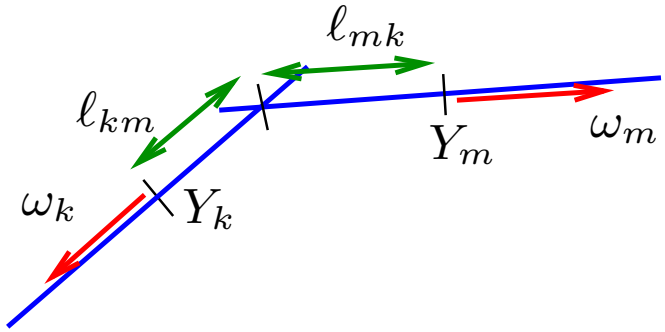
$$\Phi_{ij}(X_i, X_j) := (R_i + R_j)^2 - |X_i - X_j|^2 \leq 0$$

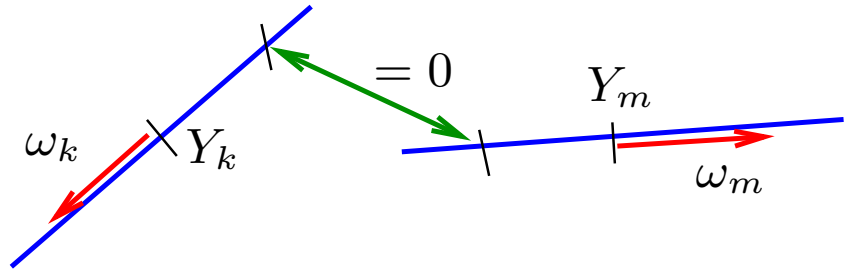


Maintenance of fiber links

Resistance to fiber breakage

$$\Psi_{km}(Y_k, \omega_k, Y_m, \omega_m) := (Y_k + \ell_{km}\omega_k) - (Y_\ell + \ell_{mk}\omega_m) = 0$$



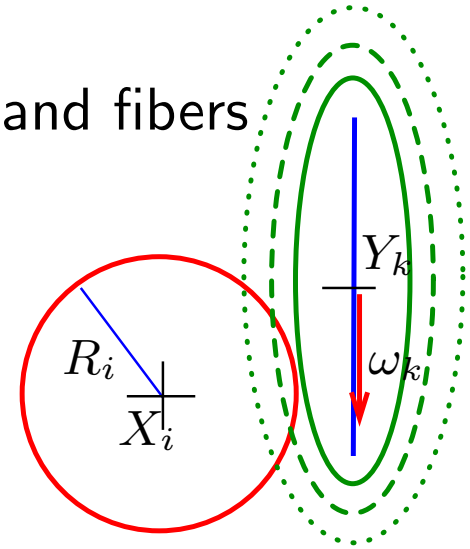


Mechanical energy

Cell-fiber repulsion potential

Models contact interaction between cells and fibers

$$W_{ik} = W_{ik}^{\mathsf{rep}}(X_i, Y_k, \omega_k)$$

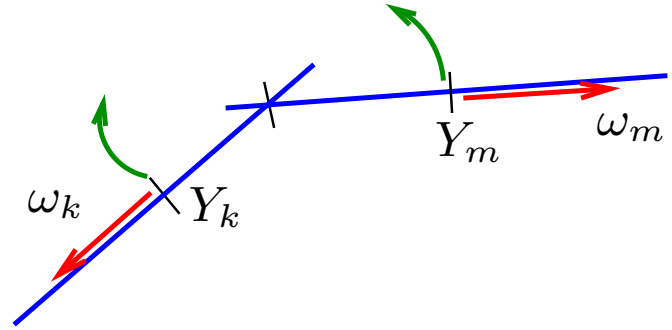


Fiber resistance to bending

Two connected fiber elements subject to alignment torque

$$\begin{aligned} W_{km} &= W_{km}^{\mathsf{al}}(Y_k, \omega_k, Y_m, \omega_m) \\ &= c_1 \sin^2(\theta_k - \theta_m) \end{aligned}$$

$c_1 \sim$ flexural modulus



Mechanical equilibrium

Total mechanical energy

$$W\left(\{X_i\}_{i=1}^{N_a}, \{(Y_k, \omega_k)\}_{k=1}^{N_f}\right) = \sum_{\text{cells } i, \text{fibers } k} W_{ik}^{\text{rep}} + \frac{1}{2} \sum_{\text{connected fibers } (k,m)} W_{km}^{\text{al}}$$

Minimization under constraints

Find $\{X_i\}_{i=1}^{N_a}$, $\{(Y_k, \omega_k)\}_{k=1}^{N_f}$ a solution of

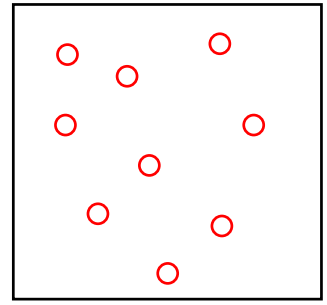
$$\min \Big\{ W \,|\, \Phi_{ij} \leq 0, \ \forall \text{ cell pairs } (i,j), \\ \Psi_{km} = 0, \ \forall \text{ connected fiber pairs } (k,m) \Big\}$$

Solved by Uzawa-Arrow-Hurwicz algorithm

Acceleration using [P. Degond, M. A. Ferreira, S. Motsch, Damped Arrow-Hurwicz algorithm for sphere packing, J. Comput. Phys., 332 (2017), pp. 47-65

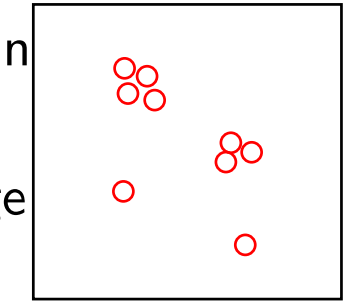
Biological phenomena 1

1. Pre-adipocyte differentiation
   - Immature cells not described
   - Differentiation into adipocyte $\Leftrightarrow$ birth of a new cell



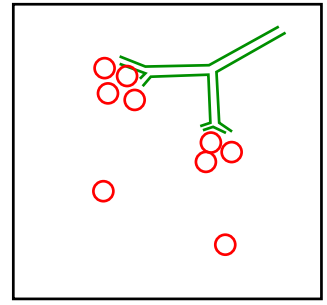
Two strategies for creating new cells (insemination)

- Strategy 1: random insemination
  - Random location with uniform probability over the domain
- Strategy 2: biased insemination
  - Higher probability where cell concentration is already large



Biased insemination $\Leftrightarrow$ influence of vasculature

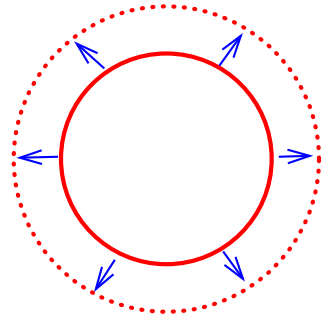
- Capillary network ensures nutrient supply
  - Adipocytes appear and grow where capillaries are present
  - Correlates appearance of new adipocytes
    to large concentrations of existing adipocytes



2. Adipocyte growth

   Constant volumic rate + random variation

   When maximal size is reached, growth is stopped



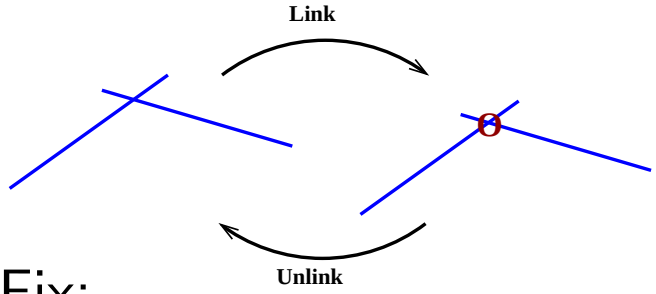
3. Fiber elongation or shortening

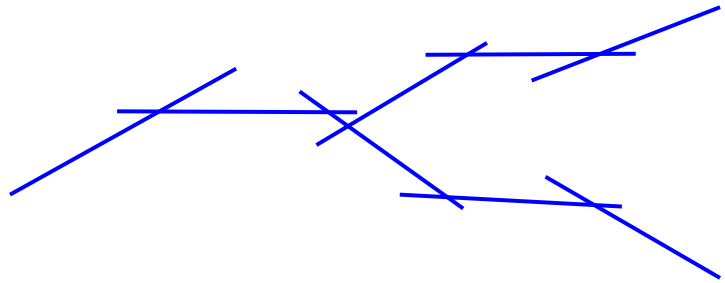
   By cross-linking or unlinking of fiber elements

   Models fiber polymerization, cross-linking or proteolysis

   Linking at rate ν_ℓ. Unlinking at rate ν_d

   Possibility of making long fibers with fiber branching





Fix:

$$\chi_\ell = \frac{\nu_\ell}{\nu_\ell + \nu_d} = \text{proportion of cross-linked fiber elements}$$

$\nu_d \approx$ ECM remodelling rate

Flowchart revisited

Time t:
cells and fibers are in mechanical equilibrium

$$t \to t + \Delta t$$

Equilibrium disrupted by biological phenomena:

1. Adipocyte insemination
2. Adipocyte growth
3. Fiber element cross-linking or unlinking

Time $t + \Delta t$
Restoration of mechanical equilibrium

$\to$ Minimizing energy functional

a. Cell-fiber repulsion
b. Fiber resistance to bending

$\to$ subject to constraints

(i) Cell-cell non-overlapping
(ii) Maintenance of fiber cross-links

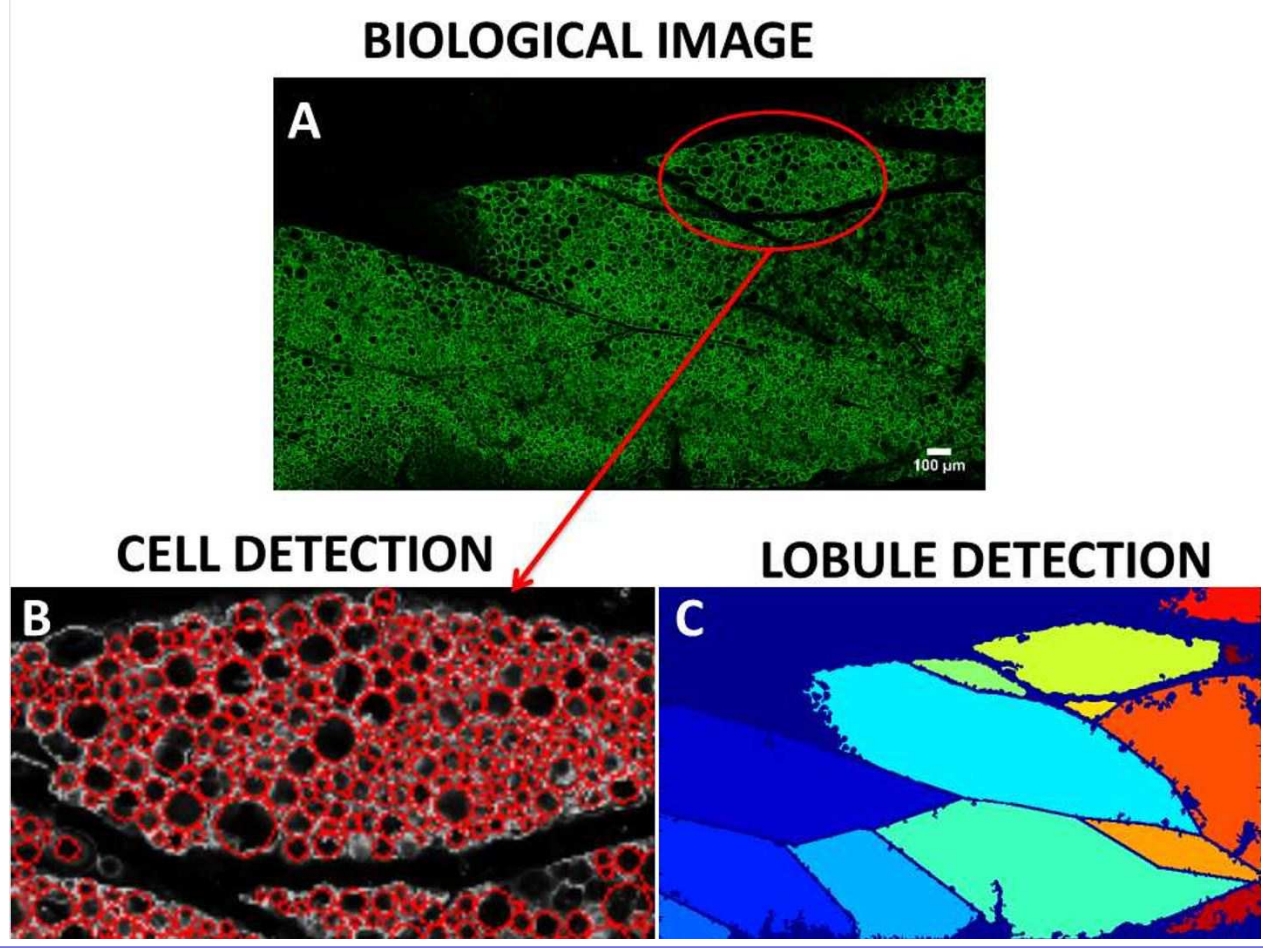
3. Results

Data procesing

Fixed mouse adipose tissue

Immuno-staining of perilipin (green)

protein that surrounds the lipid droplets

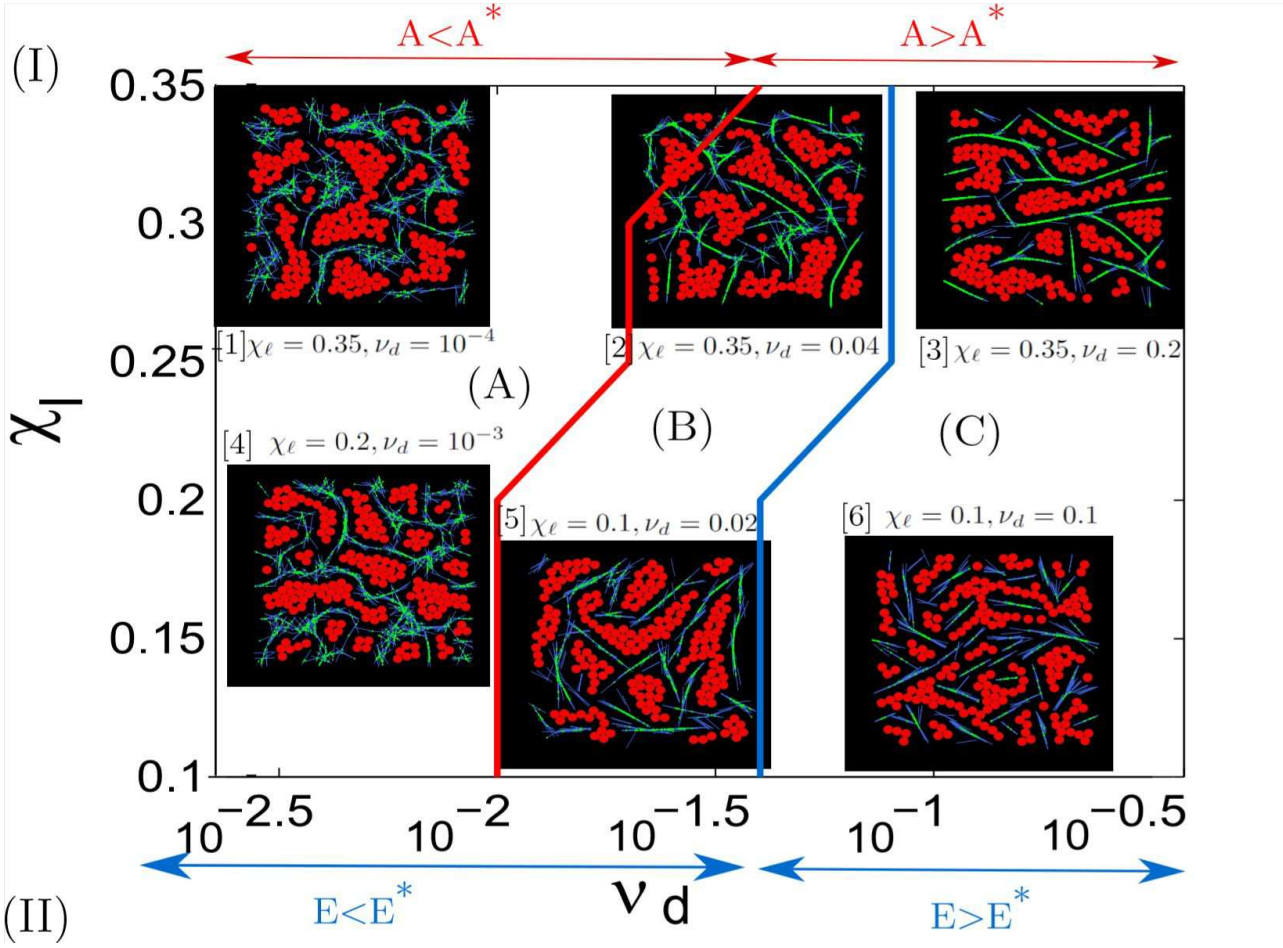


Influence of fiber linking-unlinking dynamics

Parameters varied:

Fraction of linked fiber pairs χ_ℓ: tunes rigidity of ECM

ECM remodelling rate ν_d: tunes fluid behavior of ECM



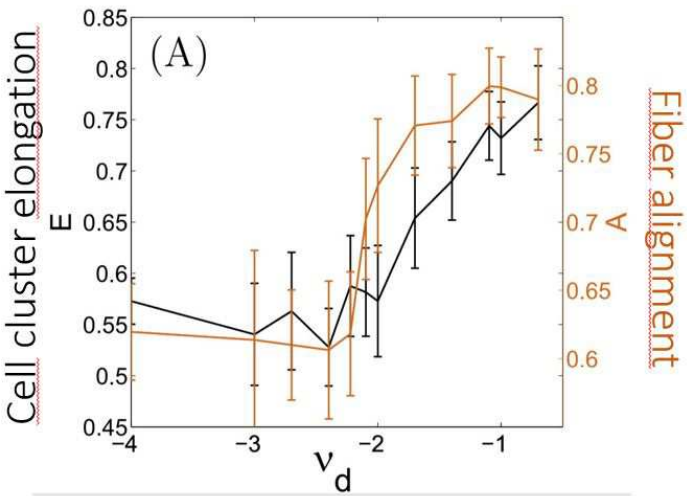
Identification of phases

Three "phases" as ECM remodelling rate ν_d increases:

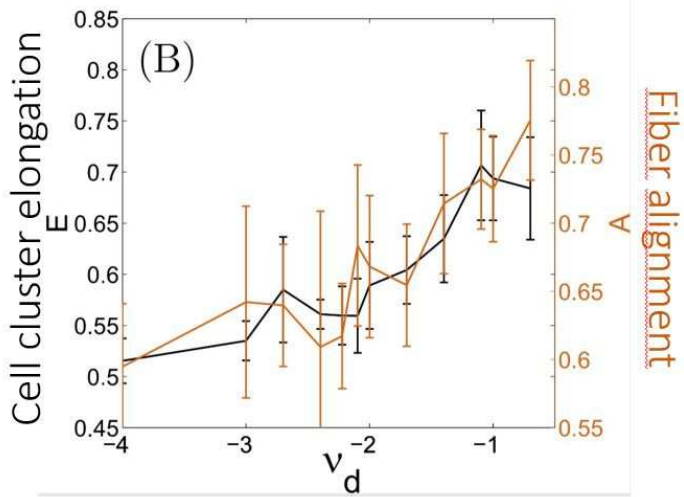
- Small ν_d: Compact cell clusters. Disorganized fiber clusters
- Medium ν_d: Compact cell clusters. Aligned fiber clusters
- Large ν_d: Elongated cell clusters. Aligned fiber clusters

Correspond to biologically relevant morphologies

- Depends on the location in the tissue
- On the status of the subject (age, health, . . .)

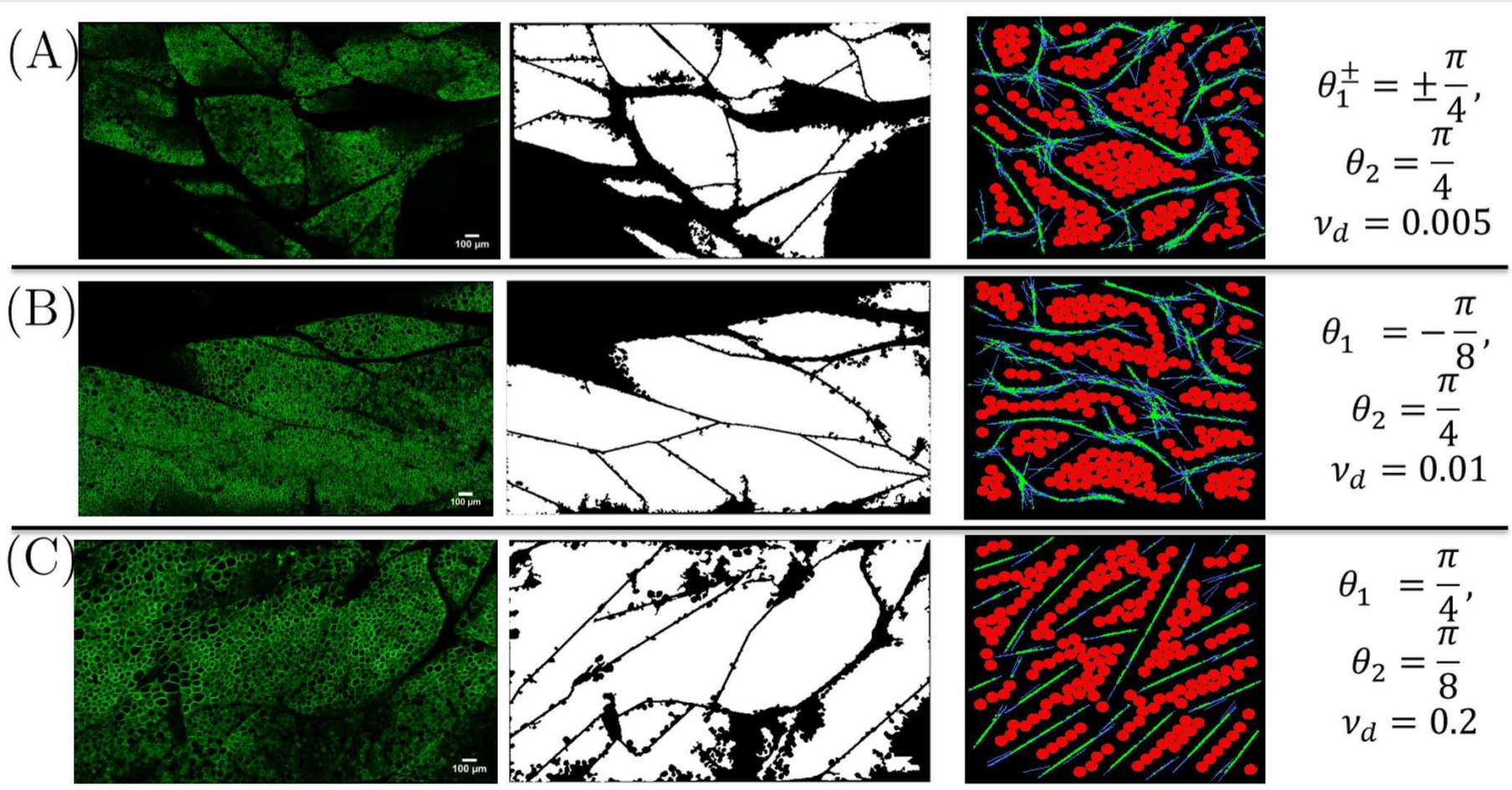


χ_d=0.1 : soft ECM



χ_d=0.35 : stiff ECM

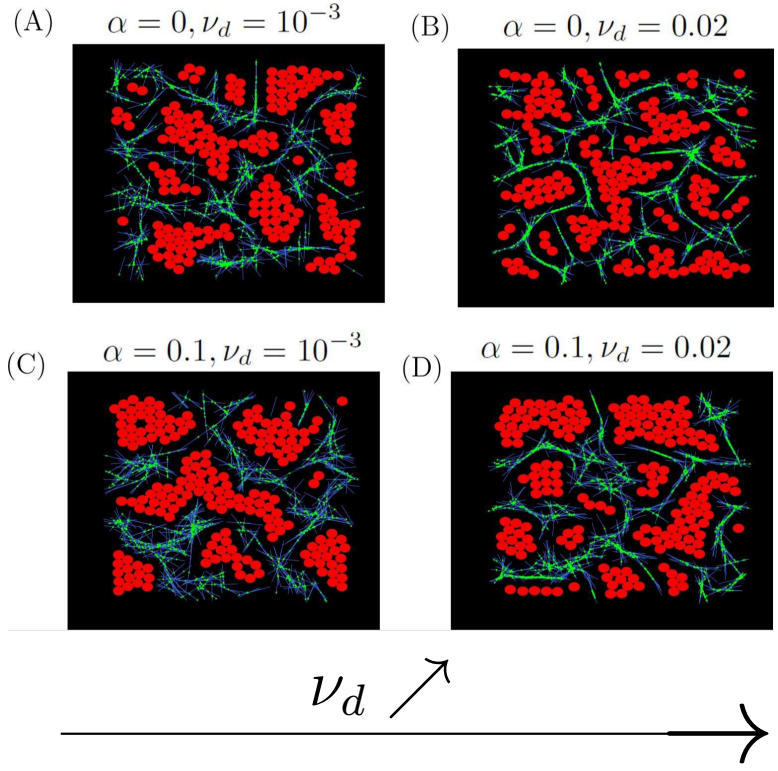
Comparison with data



Influence of biased insemination

Random

Biased



Biased insemination has little influence

- Vasculature not needed to explain the formation of lobules
- Mechanical cues alone can explain tissue morphology

4. Macroscopic model

PD, D. Peurichard, F. Delebecque

Continuum model for linked fibers with alignment interactions,

Math. Models Methods Appl. Sci, 26 (2016), pp. 269-318

D. Peurichard

Macroscopic model for linked fibers with alignment interactions:

existence theory and numerical simulations,

Mult. Model. Simul., 14 (2016), pp. 1175-1210

Macroscopic model for the ECM

Rigorous derivation from the Individual-based model

- Under scaling assumptions:
  - Very fast ECM remodelling rate
  - Strong fiber alignment force
  - Strong angular noise intensity
  - Small fiber length

In this limit, fiber angular distribution function:

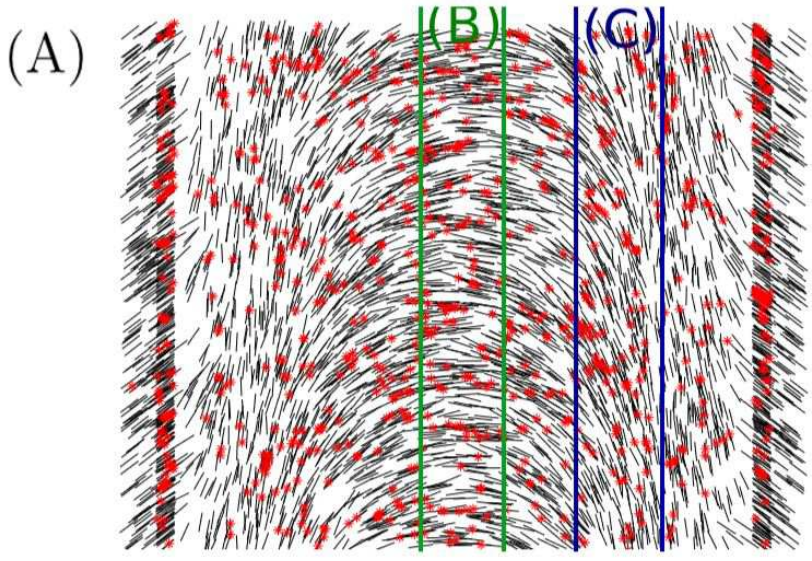
- has preferred direction θ
- solving a nonlinear parabolic equation of the form

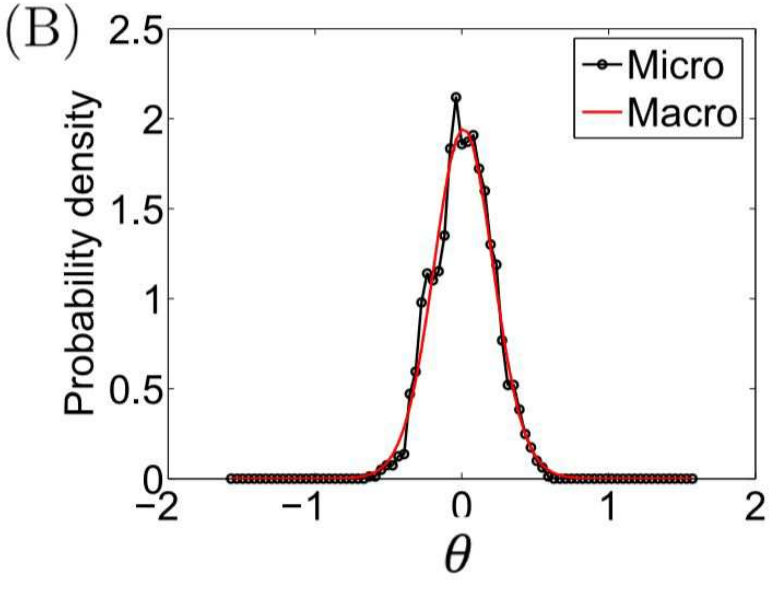
$$\partial_t \theta - \nabla \cdot (A(\theta) \nabla \theta) + h(\theta) = 0, \qquad A(\theta) = \begin{pmatrix} c_2 - c_3 \cos 2\theta & -c_3 \sin 2\theta \\ -c_3 \sin 2\theta & c_2 + c_3 \cos 2\theta \end{pmatrix}$$

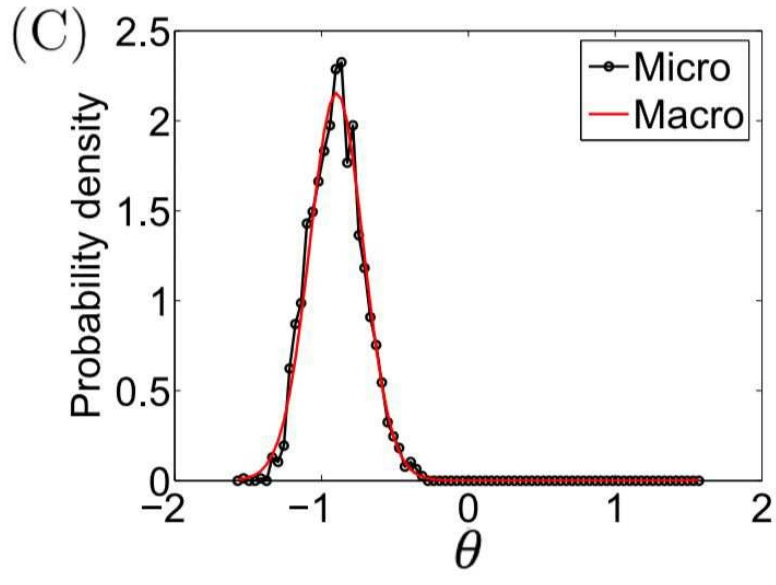
Derivation from mean-field kinetic version of IBM

- Difficulty: no physical conservations
- Methodology: use generalized collision invariant theory

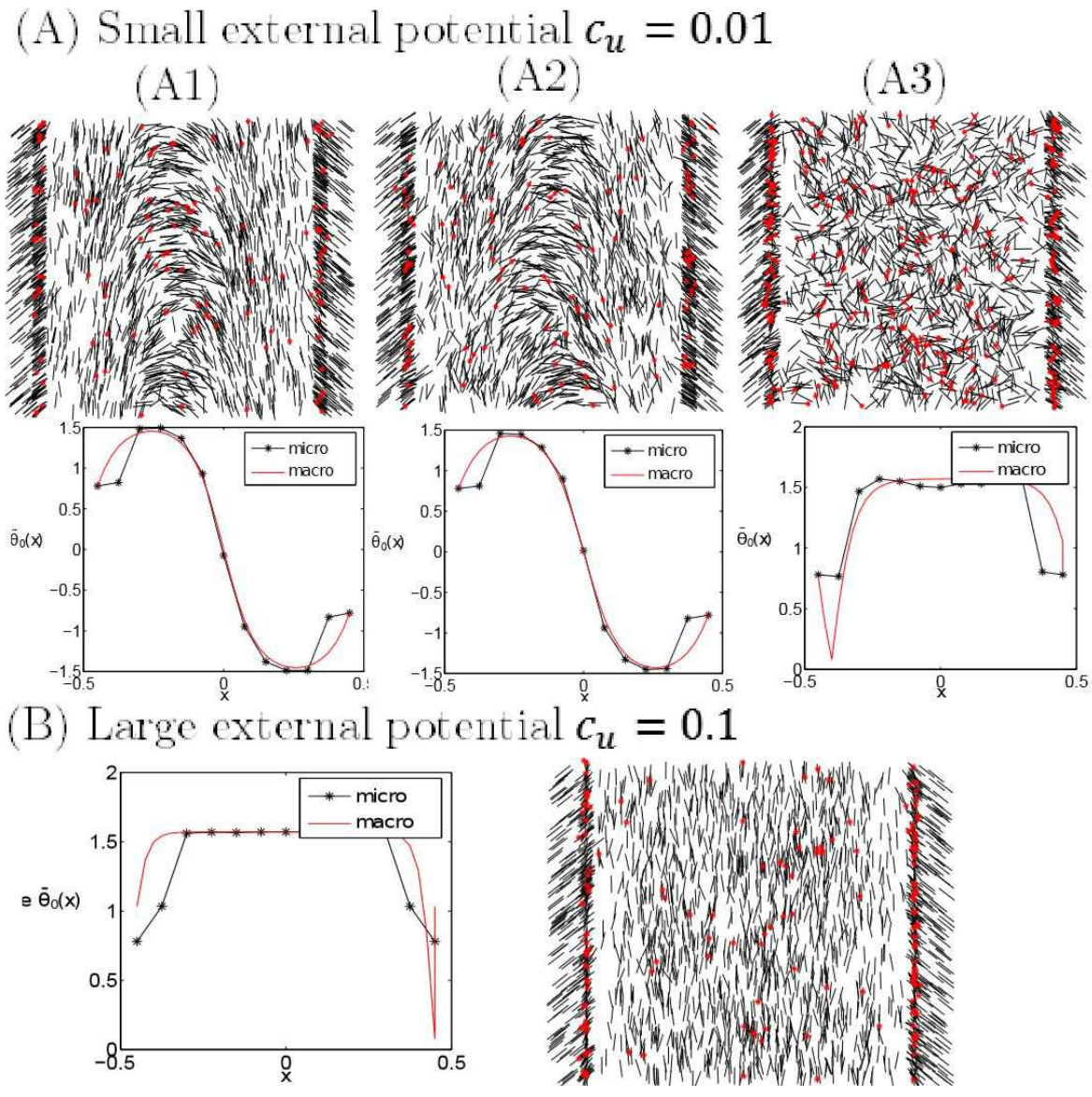
Comparison: angle distribution







Comparison: mean angle profile



5. Healing / regeneration

Reference

ECM rigidity may dictate the fate of injury outcome ,

in preparation

Joint work with

Diane Peurichard (INRIA Paris), Benjamin Aymard (INRIA, Nice)

Louis Casteilla, Anne Lorsignol, Marielle Ousset (Stromalab, Toulouse)

Scenario

Observations

- After injury, fibers repopulate wound
- Healing: excess of fibers compared with cells: $\rightarrow$ scar
- Regeneration: identical reconstruction of tissue

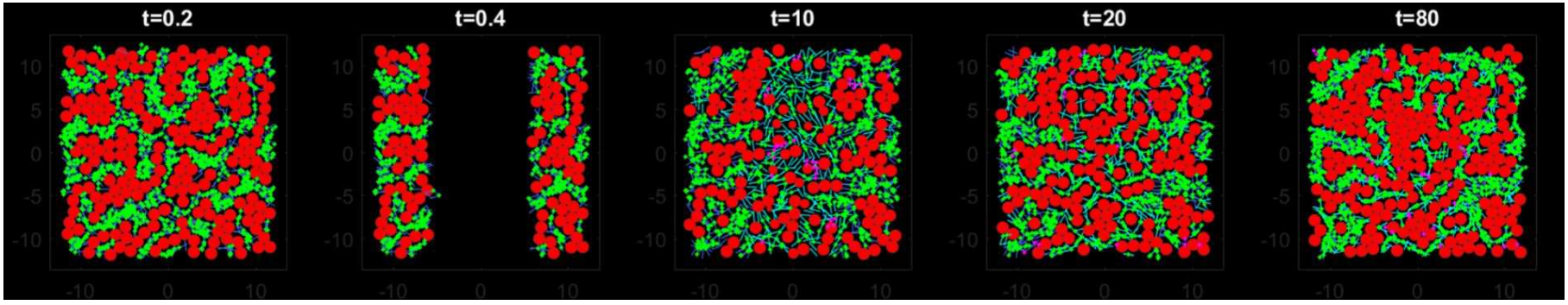
Scenario

- Following injury, part of the tissue is removed
  - Triggers repopulation of wound by fibers
  - Chemicals produced by injury diffuse along ECM
  - Inhibate repopulation by cells
  - Once chemicals have died, repopulation by cells starts
  - Ability of cells to differentiate depends on matrix stiffness

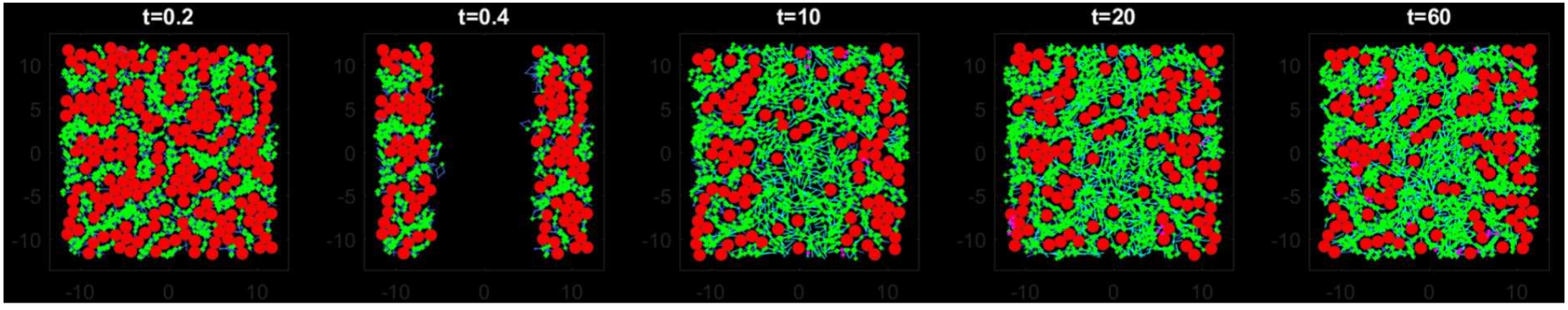
Result: influence of stiffness of new ECM

Critical parameter

Initial Fraction of linked fiber pairs in new ECM



New ECM initially soft: regeneration



New ECM initially stiff: scar formation

6. Conclusion

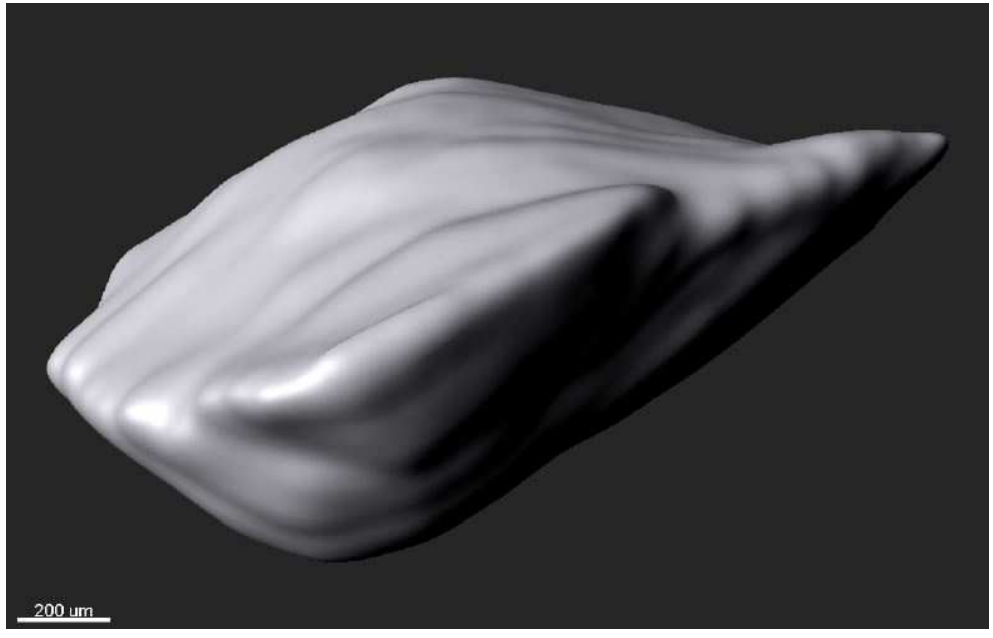
Summary and perspectives

Hypothesis: emerges from purely mechnical interactions
- Cell-cell non ovelapping
- Cell-fiber repulsion
- Fiber resistance to bending

Model shows that this is possible
- accounts for different types of morphologies
- proposes scenarios of healing vs regeneration

Macroscopic models has been derived
- and validated agains the microscopic one

Future work
- macroscopic model with cell/fiber phases
- hybrid models (e.g. continuous fibers vs discrete cells)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