DATA-INTEGRATED MULTISCALE MODELLING OF FIBROUS EXTRACELLULAR MATRIX

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BACKGROUND

Cellular processes constitute a fundamental system of complex cascades of intracellular signalling pathways and biomechanical interactions between cells and their surrounding microenvironment, whose major component is the **extracellular matrix (ECM)**: a convoluted network of **fibrous proteins** , e.g. collagen, which interact directly with cells and provide the means of **intercellular communication** through biomechanical signals. In particular, cells exert pulling forces to ECM fibers, inducing deformations localized within **tether-like bands**. These bands are characterized by enhanced **fiber alignment** and **high density**:

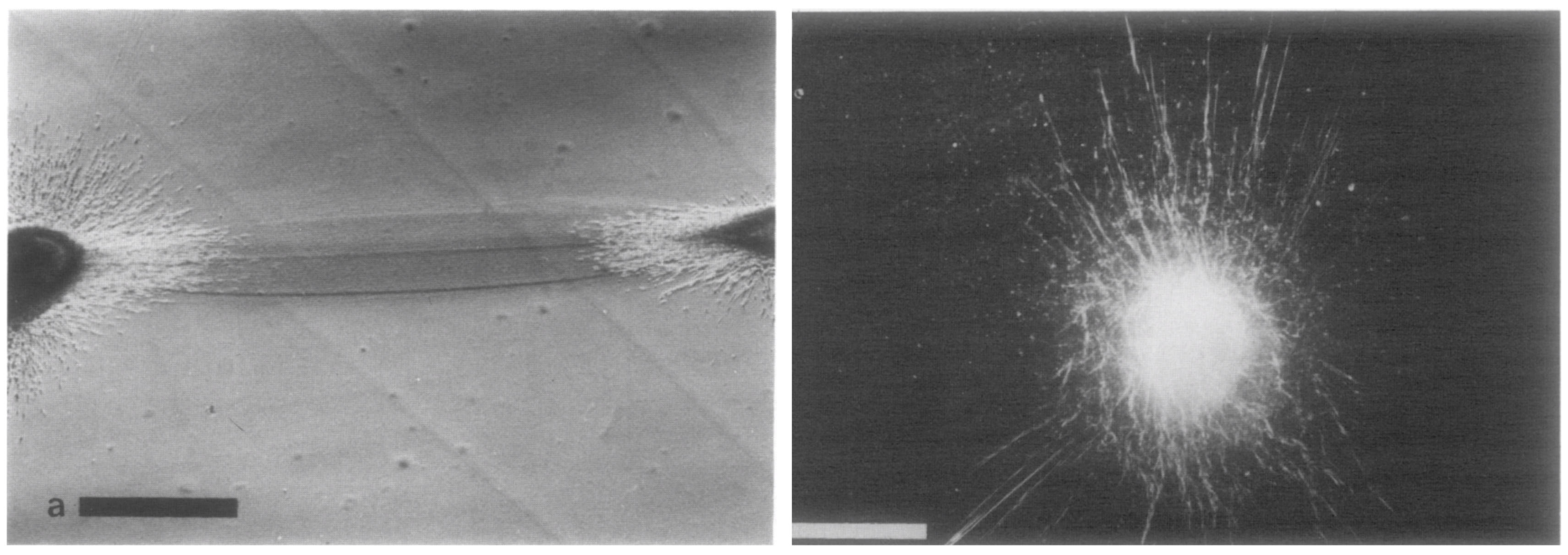

Fig.1: (Left) Collagen fibers realigned parallel to the axis connecting the two cluster of cells. Cells leave their cluster and move along this densified path towards the other cluster. (Right) A cluster of cells in the center, while the bright wavy lines surrounding it are wrinkles. Those wrinkles which radiate several millimeters outwards from the main cluster are tension wrinkles, while compression wrinkles form a more complex pattern which surrounds the ganglion circumferentially. Scale bar equals 1 mm. Reproduced from [1]

In addition to intercellular communication, cell migration [2] and stem cell differentiation [3] are also functions driven by collagen alignment. These examples illustrate the importance of understanding and optimizing the mechanical state of ECM with applications to stem cell therapy and regenerative medicine.

We consider the following:

- The mechanical behavior of natural ECMs is attributed to the mechanical behavior of individual fibers, which is **nonlinear.**
- Individual Fibers: they stiffen as they are being stretched **(strain stiffening)** while show low resistance to bending under compression **(buckling)**

METHODOLOGY

- In order to explore cell-induced deformations and how the mechanical properties of ECM contribute to the formation of tether bands that enable cells to interact, we implemented a 2D computational discrete model of the fibrous matrix (Fig.2). Based on fiber natural intrinsic behavior, we established and explored various constitutive models which describe the force-stretch relation.

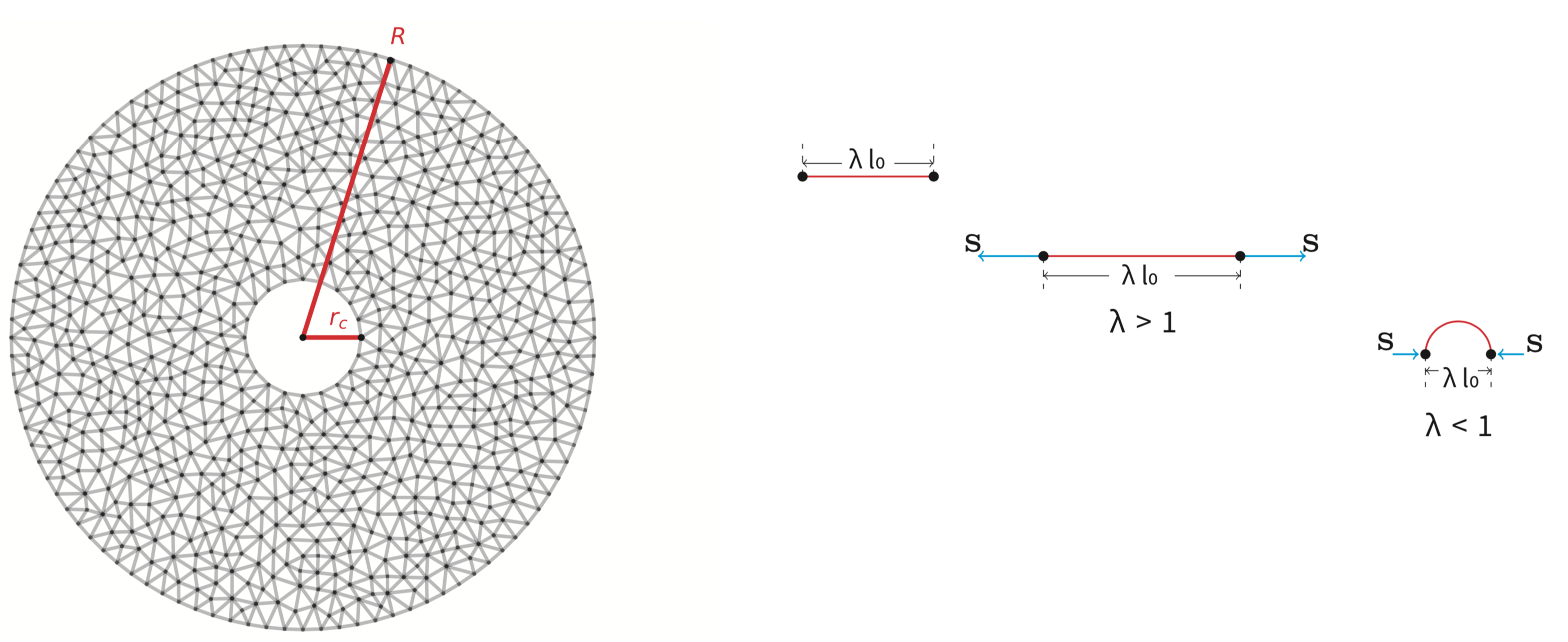

Fig.2: (Left) Example of a 2D discrete fiber network. Each edge corresponds to an individual fiber. The empty cavity represents a cell with r_c reference radius. (b) Effective stretch λ of a single fiber. λ is defined as the ratio of deformed to reference (l_0) distance of fiber's endpoints. From left to right: we have a relaxed fiber with l_0 length, a fiber under tension ($\lambda > 1$) and a buckled fiber under compression ($\lambda < 1$). The cyan arrows represent the applied loads on fiber's endpoints.

- We thoroughly studied the parameter space of the models (such as computational domain size, cell(s) contraction level, cell-cell distance, decay of displacements, fiber orientation, network density) for each one of the constitutive relations.

RESULTS

- Matrix response to cell(s) contraction is explored for each one of these constitutive models. Starting with simulations of a single contracting cell, our analysis then extends to pairs of contractile cells in order to explore the long-range intercellular mechanical interaction.

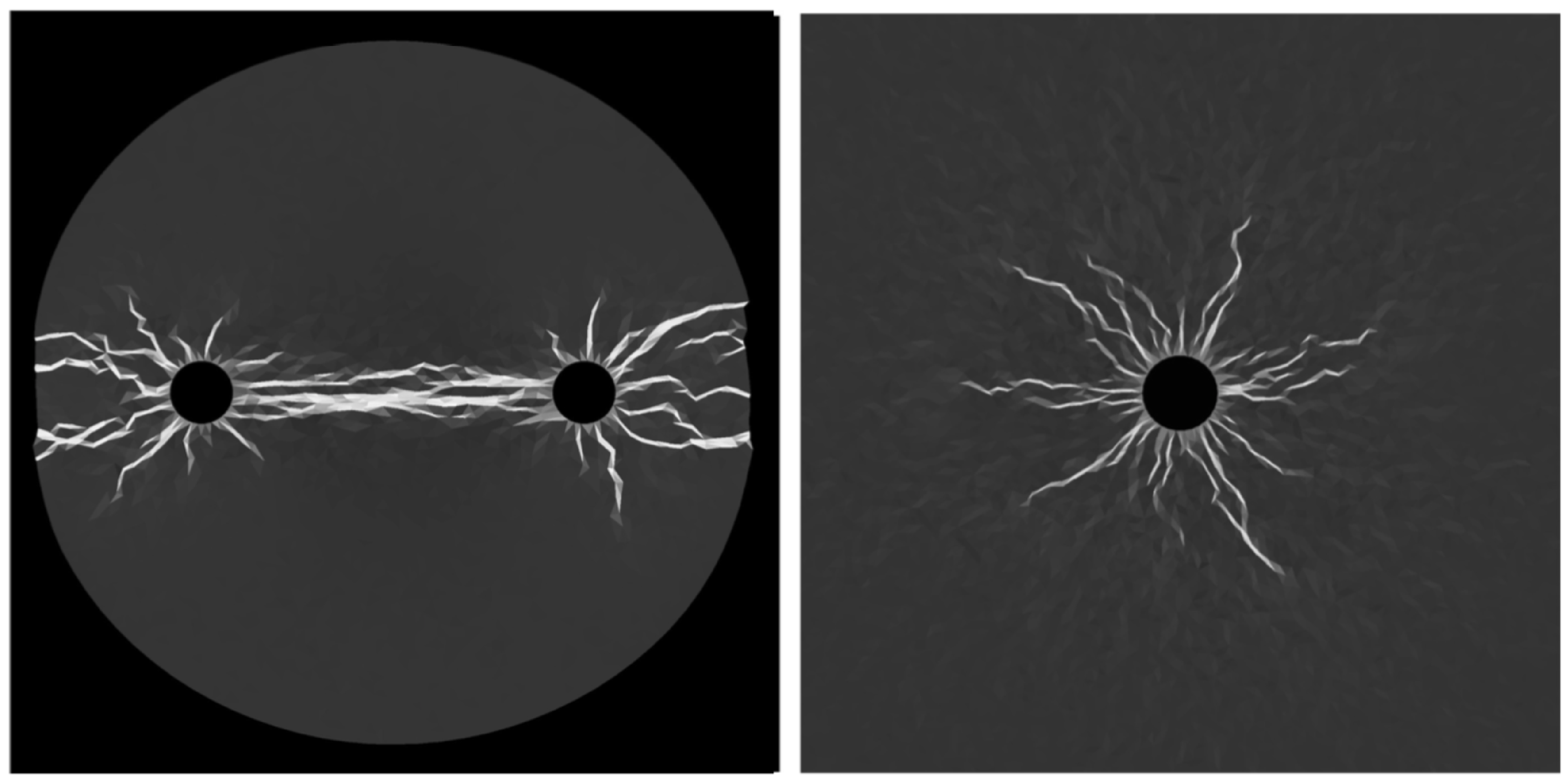

Fig.3: Predictions with one of the studied models. (Left) two cells separated by $4r_c$, r_c cell reference radius, contract by 50%. We observe a solid tether connecting the two cells, while wrinkles emanate radially from each cell. (Right) single cell contracting. Wrinkles emanate around the cell and extend into the matrix. Both wrinkles & tether are highly densified zones, where area density is 3 times higher than the rest of the matrix.

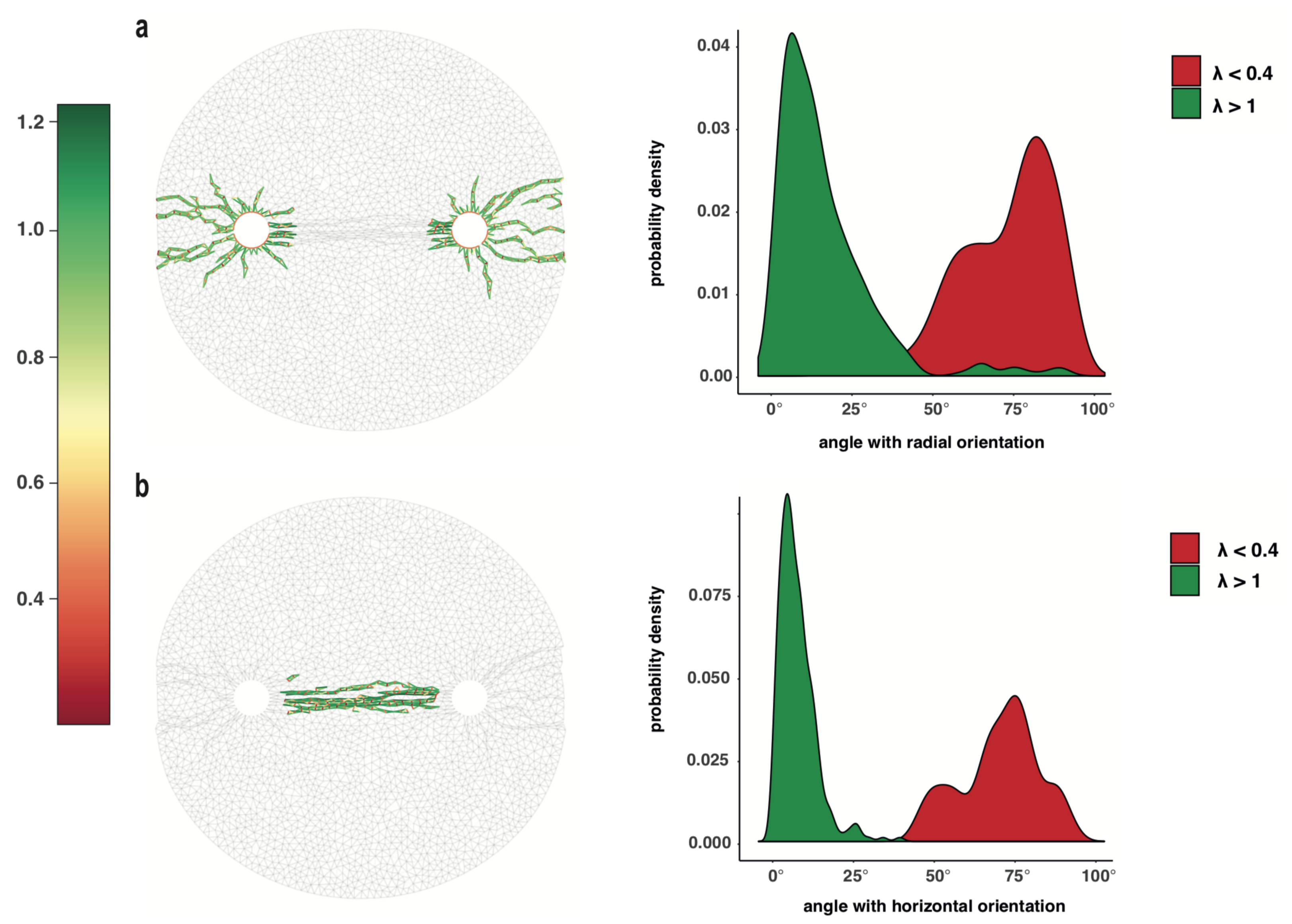

Fig.4: Fiber orientation within the tether (a) Highlighted triangles of the wrinkles emanating from each cell (Fig.3) and the distribution of fibers' radial orientation, in degrees, within these triangles with respect to each cell centre accordingly. Fibers under tension (green) are aligned with the radial direction while the compressed ones (red) are roughly perpendicular to them. Mean of each distribution $\sim$15° ($\lambda > 1$) and $\sim$70° ($\lambda < 0.4$) (b) Highlighted triangles of the tether connecting the two cells and their orientation with the horizontal direction in degrees. Tensed fibers (green) are aligned with the horizontal direction passing through the cells' and domain's centres, with the compressed to be oriented perpendicular to them. Mean values of the distributions are $\sim$7°($\lambda > 1$) and 70°($\lambda < 0.4$).

ACKNOWLEDGEMENTS

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