SBMC 2018 7th Conference on Systems Biology of Mammalian Cells
Bremen, July 4 – 6, 2018

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Quantifying Tissue Mechanics and Tissue Formation with High Resolution Models

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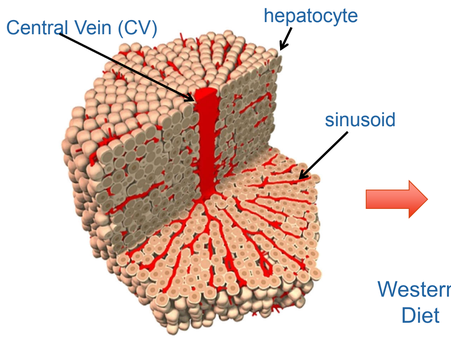
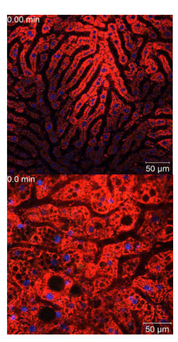
Situation and Objectives

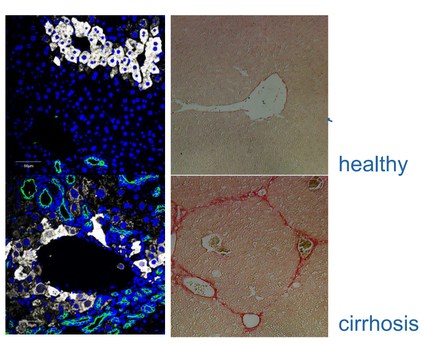
- In fatty liver disease, or late stage liver fibrosis or cirrhosis, contrary to healthy tissue, the tissue micro-architecture is largely disturbed and may exhibit largely heterogenous cell sizes, high degree of lobular disorder and cells obstructed by extracellular matrix.



Liver lobule structure

Western Diet





After Western Diet (Left) or repetitive CCL4 (right):
Distortion of architecture and / or heterogeneous cell shapes & sizes.

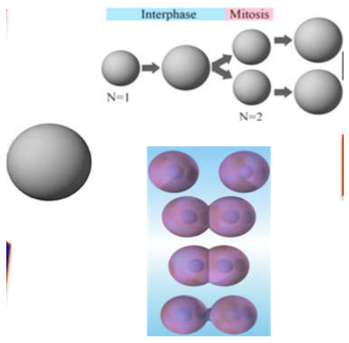
- Goals:
  - ➢ Develop a computational model permitting to study in how far regeneration of liver micro-architecture after pericentral drug damage might be influenced by cell shape and deformability.
  - ➢ Mid-term: modeling liver degeneration in disease

Mathematical Model: agent-based

- **Agent-based Models** are mathematical models representing each cell by physical object able to move, grow & divide. The model is parameterized by measurable biophysical and bio-kinetic parameters. The cells move and interact according to laws of physics.

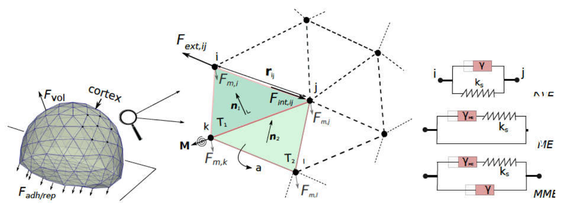
1. Center-based Models (CBM)

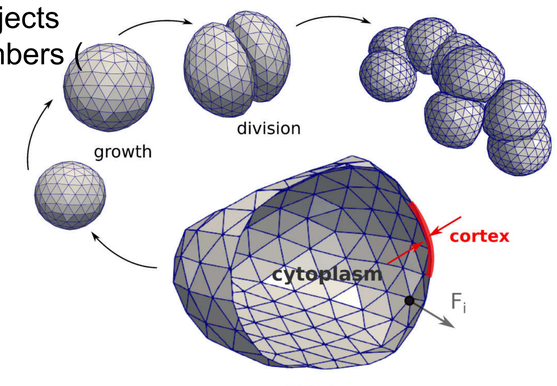
- Cells are represented by spheres
- Rigid shape !
- Forces between cells act between centers (Hertz theory) - NOT accurate for large cell densities!
- Simulations with large cell numbers possible



2. Deformable Cell Models (DCM)

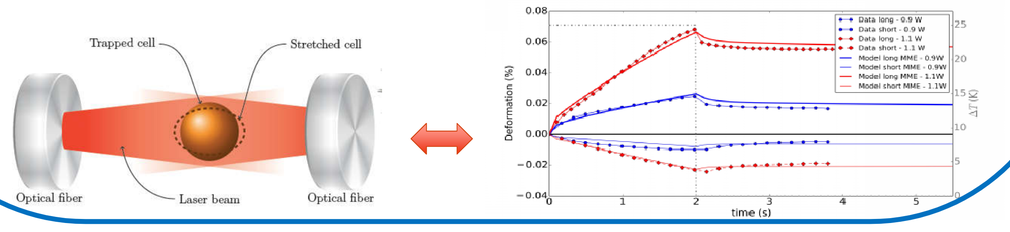
- Cells are represented by network of viscoelastic elements (scaffolding)[2]
- Accurate forces at cytoskeleton level
- Accurate shape representation
- Allows interactions with any other objects
- Simulations only with small cells numbers (~1000)





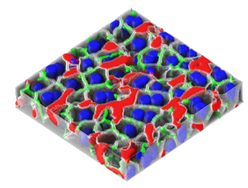
DCM

- **Parameter calibration**
  - We require that cells behave mechanically correct
  - We simulate single cell experiments (optical stretcher) and compare data (deformations) with simulations



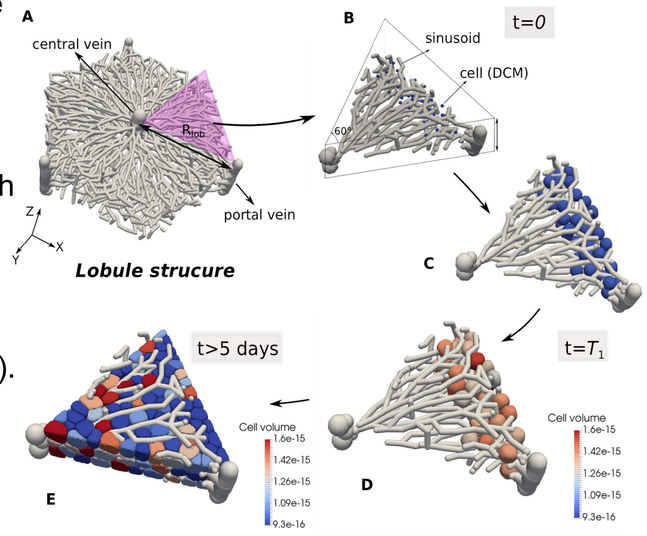
Simulations of regeneration

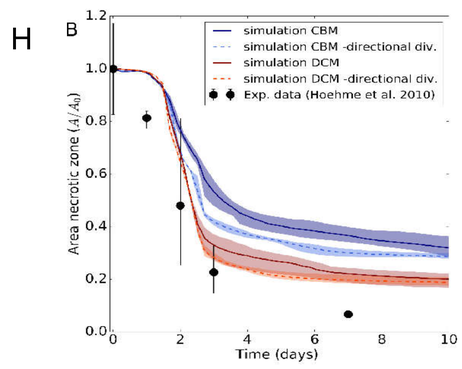
For comparison: tissue sample from confocal microscopy

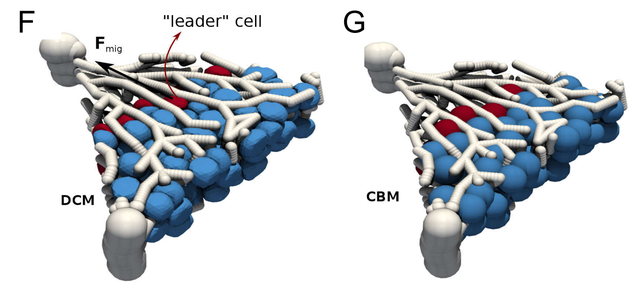


- Only part of lobule is simulated because of high computation time (Fig. A)
- During regeration, cells proliferate and move through the sinuoidal network toward CV (Fig. C-E)
  - Regeneration stops when lesion closed
- Simulation of closure of lesion compared with experimental data[1] (Figs. H, I)
- Random cell micromotility and pushing of cells as consequence of proliferation insuffisient to close the lesion in time (Fig. H).
- Directed migration (*DMF*) necessary to achieve agreement with experiment (Fig. I).
  - *DMF* of leader cells sufficient *(*Fig. F)

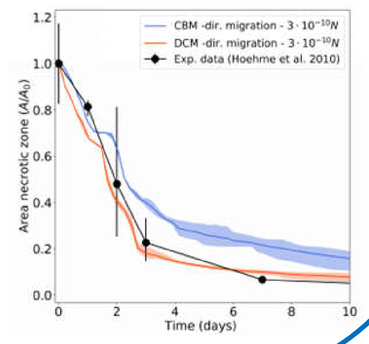
Fig. A-I: Model simulations







- Comparison DCM / CBM simulations (Fig. F-G)
  - CBM yields worse agreement with experiment in abscence of DMF as cells in CBM are too rigid to squeeze in between sinusoids easily
  - 10 times higher DMF is required compared to DCM
  - With DCM, cells can adapt their shape to pass obstacles



Conclusions

- We have developed a cell-based **Deformable Cell Model** that can **accurately simulate cell shape** and **quantify intracellular forces,** allowing simulations of tissue organisation processes in complex tissue architectures
- Center-based models becausee of rigid cell shapes partially unable to capture the complex interaction between cells and confined environment
- DCM is prime candidate to simulate cell mechanics & migration in dense tissues

References

1. Hoehme et al. (2010) Proceedings of the National Academy of Sciences 107 (23), 10371-10376
2. Van Liedekerke et al. (2015) Simulating tissue mechanics with agent-based models: concepts, perspectives and some novel results. Computational Particle Mechanics 2 (4), 401-444

Funding and Acknowledgements

LiSyM Liver Systems Medicine
virtual liver network
Federal Ministry of Education and Research
NOTOX
PhysCancer
iLite Innovation in Liver Tissue Engineering
Agence Nationale de la Recherche ANR

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