Research Summary

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1 Extracellular Matrix (ECM)

For an extensive overview, see [6].

- The ECM constitutes the non-cellular parts of all tissues.
- It consists of:
  - Fibrous proteins, most importantly collagen, elastin and fibronectin.
  - Up to 30% collagen. Forms fibrils and fibers of different sizes which can "stick together" to make up networks. There are a bunch of different collagen types.
  - Proteoglycans, which fill the interstitial space in the form of a hydrated gel.
- Cells move through and remodel their ECM, which in turn changes their behavior.
  $\Longrightarrow$ *in silico* models need to take this into account.
- Different tissues have different ECMs.

1.1 Properties of the Extracellular Matrix

Our approach takes a macroscopic view of the ECM. Individual fibrils/fibers should not be modeled. Nevertheless we include some microscopic properties.

- **Stiffness**: Matrix stiffness has an effect on tumor gowth, e.g. [12]. Measured using Young's modulus/elastic modulus E which is given in GPa.
- **Viscoelasticity**: Creep, Stress relaxation (see below), E, η
- **Pore size**
- **Density**

1.2 Viscoelasticity

Generally modeled using differential equations involving the elastic modulus E, viscosity η, stress σ and strain ϵ. [17] mentions these constitutive models:

What is viscoelasticity? Show some graphs and “oral” explanation

- Maxwell: Viscous flow on the long timescale, but additional elastic resistance to fast deformations (e.g. silly putty, warm tar). Does not describe creep or recovery.
- Kelvin-Voigt: Does not describe stress relaxation.
- Zener/Standard linear solid: Models creep and stress relexation.

The Lethersich and Jeffreys models are models for viscoelasticity that specifically model fluids.

1.3 Rheology and Materials Science of the ECM

[6] mentions Matrigel and collagen type I gels, so we will focus on these.

Great review with great figures: [5].

- [20] lists the elastic modulus of collagen structures at different scales, see Figure 1.
- [15] defines a model for the viscoelasticity of collagen. expand, give actual values
- [22] discusses properties of Corning® Matrigel®.
  - Lists elastic moduli for different concentrations and mixtures involving collagen type I around 10^1 to 10^3 Pa. This seems very low; investigate sources
  - This paper shows the viscous component in the graphs but doesn't really go into it.
- [2] discusses alternatives to Corning® Matrigel®.
- [21] experimentally investigate the elastic and viscous moduli of collagen gels. They find that the Kelvin-Voigt model can be used to model their viscoelastic behavior.

Since viscoelastic behavior is inherently time-dependent, it will be a challenge to choose a sensible time step resolution for the model.

2 Cellular Potts Model (CPM)

cites

- The CPM is a grid-based Monte-Carlo simulation for cells.
- Each cell consists of many voxels. These voxels contain its cell ID.
- In each Monte-Carlo Step (MCS), a random voxel copies the cell ID of its neighbor.
- The hamiltonian H gives the energy of a generation. It depends on the volume and surface of cells and their reciprocal adhesion.
- A MCS is always accepted if it reduces H. If it does not reduce H, it is accepted probabilistically.

Table 1 – Comparison of Young's modulus of collagen at multiple hierarchical levels.

Molecular	
Single molecule stretching, atomistic modeling (Lorenzo and Caffarena, 2005)	4.8 GPa
Single molecule stretching, reactive atomistic modeling (Buehler, 2006)	7 GPa
Single molecule stretching, atomistic modeling (Vesentini et al., 2005)	2.4 GPa
Coarse grain modeling (Gautieri et al., 2010)	4 GPa
Atomistic modeling (Gautieri et al., 2009)	4 GPa
Atomistic modeling (Pradhan et al., 2011)	4.5–6.2 GPa (long, short molecule)
X-ray diffraction (Sasaki and Odajima, 1996)	3 GPa
Brillouin light scattering (Harley et al., 1977)	9 GPa
Brillouin light scattering (Cusack and Miller, 1979)	5.1 GPa
Estimate from persistent length (Hofmann et al., 1984)	3 GPa
Estimate from persistent length (Nestler et al., 1983)	4.1 GPa
Estimate from persistent length (Sun et al., 2002)	0.35–12 GPa
Microfibril and Fibril	
MEMS stretching (Eppell et al., 2006)	0.4–0.5 GPa low strain, 12 GPa high strain
MEMS stretching (Shen et al., 2008)	0.86 GPa low strain
X-ray diffraction (Gupta et al., 2004)	1 GPa
X-ray diffraction (Sasaki and Odajima, 1996)	0.43 GPa
AFM testing (van der Rijt et al., 2006)	0.2–0.8 GPa aqueous, 2–7 GPa ambient,
Bead and string based mesoscale modeling (Buehler, 2006, 2008)	4.4 GPa low strain, 38 GPa high strain
Atomistic modeling (Gautieri et al., 2011)	0.3 GPa small strain, 1.2 GPa high strain
Fiber	
Crosslinked rat tail tendon (Gentleman et al., 2003)	1.10 GPa
Non-crosslinked rat tail tendon (Gentleman et al., 2003)	50–250 MPa
Extruded, crosslinked fiber (Gentleman et al., 2003)	260–560 MPa
Rat tail tendon (Haut 1986)	960–1570 MPa
Rat tail tendon (Kato et al., 1989)	480–540 MPa
Extruded, crosslinked fiber (Kato et al., 1989)	170–550 MPa
Rabbit patellar tendon (Miyazaki and Hayashi, 1999)	30–80 MPa
Tissue	
Skin (Yang et al., 2015)	0–50 MPa
Tendon (Rigby et al., 1959)	1 GPa
Cornea (Orssengo and Pye, 1999)	0.2–1.0 MPa
Mitral valve (Freed and Doehring, 2005)	0–50 MPa

Figure 1: Comparison of Young's modulus of collagen at multiple hierarchical levels. From [20].
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3 NAStJA & CiS

- Neoteric Autonomous Stencil code for Jolly Algorithms (NAStJA) is a massively parallel stencil code solver based on OpenMPI [3].
- Cells in Silico (CiS) is an implementation of the CPM in NAStJA [4, 9].

4 Lattice Models of Viscoelastic Materials

4.1 Lattice Boltzmann Model (LBM)

- A general-purpose model of hydrodynamics discrete in time and space.
- Discretisation in space makes it possible to calculate LBM time steps using stencil codes.
- Extensive literature exists including implementation details, e.g. [11]
- Can be used to model viscoelasticity, e.g. [7, 14, 10]
- Probably not that simple to model matrix porosity. Elaborate

5 ECM Models in the CPM

Reviews: [13, 8]

Elaborate a bit

5.1 ECM as a Cell

- Simple idea: Model ECM as a special cell, i.e. a set of voxels.
- Set properties of the ECM "cell" such that the model makes sense.
- Can model simple interactions such as matrix decomposition and deposition
- Can't really model matrix strains and deformation

E.g. [18, 19, 9]

5.2 Substrate Strain FEM

[16]

5.3 Discrete Fiber Networks

expand

See papers cited in [8], e.g. [1].

5.4 Molecular Dynamics Bead-Chain Model

[23]

6 Glossary

Acronyms

CiS Cells in Silico. 3

CPM Cellular Potts Model. 2–4

ECM Extracellular Matrix. 1, 2, 4

FEM Finite Element Method. 4

LBM Lattice Boltzmann Model. 3

MCS Monte-Carlo Step. 2

NAStJA Neoteric Autonomous Stencil code for Jolly Algorithms. 3

References

[1] Abhilash, A. S., Baker, B. M., Trappmann, B., Chen, C. S., and Shenoy, V. B. Remodeling of fibrous extracellular matrices by contractile cells: Predictions from discrete fiber network simulations. *Biophysical Journal 107* (10 2014), 1829–1840. Focuses on "pulling" effects.

[2] Aisenbrey, E. A., and Murphy, W. L. Synthetic alternatives to matrigel. *Nature reviews. Materials 5* (7 2020), 539.

[3] Berghoff, M., Kondov, I., and Hotzer, J. Massively parallel stencil code solver with autonomous adaptive block distribution. *IEEE Transactions on Parallel and Distributed Systems 29* (10 2018), 2282–2296.

[4] Berghoff, M., Rosenbauer, J., Hoffmann, F., and Schug, A. Cells in silico-introducing a high-performance framework for large-scale tissue modeling. *BMC Bioinformatics 21* (10 2020).

[5] Chaudhuri, O., Cooper-White, J., Janmey, P. A., Mooney, D. J., and Shenoy, V. B. Effects of extracellular matrix viscoelasticity on cellular behaviour. *Nature 2020 584:7822 584* (8 2020), 535–546.

[6] Frantz, C., Stewart, K. M., and Weaver, V. M. The extracellular matrix at a glance, 12 2010.

[7] Giraud, L., D'Humières, D., and Lallemand, P. A lattice boltzmann model for jeffreys viscoelastic fluid. *Europhysics Letters 42* (6 1998), 625.

[8] Guo, Y., Mofrad, M. R. K., and Tepole, A. B. On modeling the multiscale mechanobiology of soft tissues: Challenges and progress. *Biophysics Reviews 3* (9 2022), 031303. Another review containing a bunch of nice references. Kind of hard to pull apart though since its very dense in information.

[9] Herold, J., Behle, E., Rosenbauer, J., Ferruzzi, J., and Schug, A. Development of a scoring function for comparing simulated and experimental tumor spheroids. *PLoS Computational Biology 19* (3 2023).

[10] Ispolatov, I., and Grant, M. Lattice boltzmann method for viscoelastic fluids. *Physical Review E 65* (5 2002), 056704.

[11] Krüger, T., Kusumaatmaja, H., Kuzmin, A., Shardt, O., Silva, G., and Viggen, E. M. The lattice boltzmann method. *Springer International Publishing 10* (2017). https://github.com/lbm-principles-practice.

[12] Levental, K. R., Yu, H., Kass, L., Lakins, J. N., Egeblad, M., Erler, J. T., Fong, S. F., Csiszar, K., Giaccia, A., Weninger, W., Yamauchi, M., Gasser, D. L., and Weaver, V. M. Matrix crosslinking forces tumor progression by enhancing integrin signaling. *Cell 139* (11 2009), 891–906.

[13] Liedekerke, P. V., Palm, M. M., Jagiella, N., and Drasdo, D. Simulating tissue mechanics with agent-based models: concepts, perspectives and some novel results. *Comp. Part. Mech 2* (2015), 401–444. Overview over ECM models.

[14] Malaspinas, O., Fiétier, N., and Deville, M. Lattice boltzmann method for the simulation of viscoelastic fluid flows. *Journal of Non-Newtonian Fluid Mechanics 165* (12 2010), 1637–1653.

[15] Puxkandl, R., Zizak, I., Paris, O., Keckes, J., Tesch, W., Bernstorff, S., Purslow, P., and Fratzl, P. Viscoelastic properties of collagen: synchrotron radiation investigations and structural model. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 357* (2 2002), 191–197.

[16] Rens, E. G., and Merks, R. M. Cell contractility facilitates alignment of cells and tissues to static uniaxial stretch. *Biophysical Journal 112* (2 2017), 755–766.

[17] Roylance, D. Engineering viscoelasticity. *Department of Materials Science and Engineering–Massachusetts Institute of Technology, Cambridge MA 2139* (2001), 1–37.

[18] Rubenstein, B. M., and Kaufman, L. J. The role of extracellular matrix in glioma invasion: A cellular potts model approach. *Biophysical Journal 95* (12 2008), 5661–5680. 1 Type for Stroma, 1 Type for Collagen¡br/¿¡br/¿Initial experiments: Static ECM¡br/¿¡br/¿Then: ECM dissolution/deposition¡br/¿Not aligned with in vivo results¡br/¿Posits idea: Simulate more than two types of matrix.

[19] Scianna, M., Preziosi, L., and Wolf, K. A cellular potts model simulating cell migration on and in matrix environments. vol. 10, pp. 235–261.

[20] Sherman, V. R., Yang, W., and Meyers, M. A. The materials science of collagen. *Journal of the Mechanical Behavior of Biomedical Materials 52* (12 2015), 22–50.

[21] Sheu, M. T., Huang, J. C., Yeh, G. C., and Ho, H. O. Characterization of collagen gel solutions and collagen matrices for cell culture. *Biomaterials 22* (7 2001), 1713–1719.

[22] Slater, K., Partridge, J., and Nandivada, H. Tuning the elastic moduli of corning ® matrigel ® and collagen i 3d matrices by varying the protein concentration application note, 2017.

[23] Tsingos, E., Bakker, B. H., Keijzer, K. A., Hupkes, H. J., and Merks, R. M. Modelling the mechanical cross-talk between cells and fibrous extracellular matrix using hybrid cellular potts and molecular dynamics methods. *bioRxiv* (7 2022), 2022.06.10.495667.