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.
  $\implies$ *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

- **Creep**:

- **Stress relexation**:

What is viscoelasticity? Show some graphs and "oral" explanation

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

- 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.

- [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 paper shows the viscuous 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)

- 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.

[Margin notes: "expand, give actual values"; "This seems very low; investigate sources"; "cites"]

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 Models of Viscoelastic Materials

4.1 Chopard (Cellular Automaton)

4.2 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

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