Viscoelastic Matrix Mechanics in Hydrogels with Varying Cell-Matrix Interactions and Remodeling

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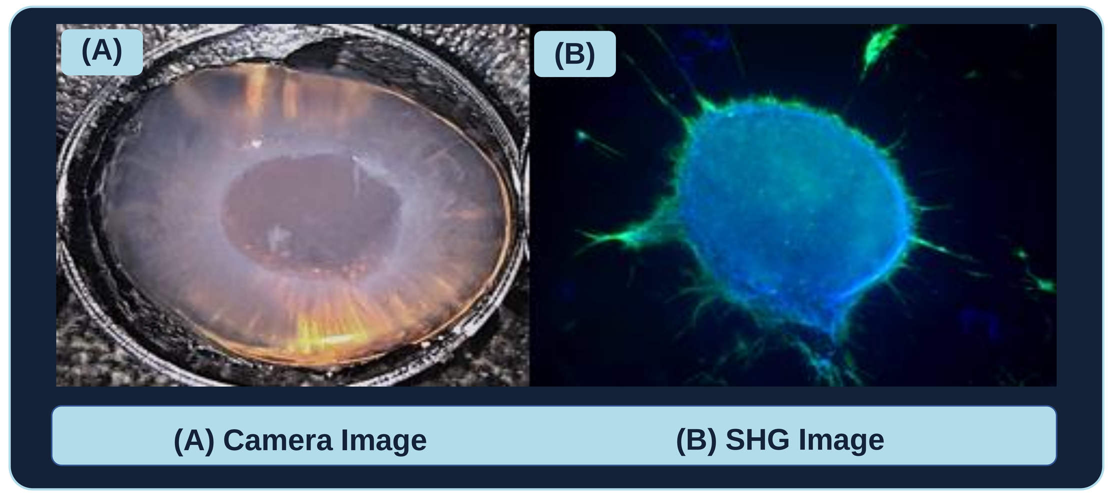
Introduction

Collagen Hydrogels
- Collagen is the most abundant extracellular matrix (ECM) protein in mammals
- Effective approach to simulating in vivo cell interactions ex vivo due to their versatility, biocompatibility, and widely tunable structure[1]

Mechanical Properties of the Extracellular Matrix
- Allows tissues to withstand physical stress
- Regulates numerous cellular functions such as spreading, migration, proliferation, and stem cell differentiation[1,2]
- Impacts many biological processes including
  - Embryonic development, adult tissue homeostasis, and pathogenesis of diseases such as fibrosis and cancer[2]

Toroid
Self-organizing tissue structure created by cells cultured on top of a hydrogel
- Cells migrate towards center through channels in the gel
- Collagen is remodeled through the unwinding of the triple helix during formation
- Cancer cell lines fail to form toroids but remain viable both on top of and inside matrices

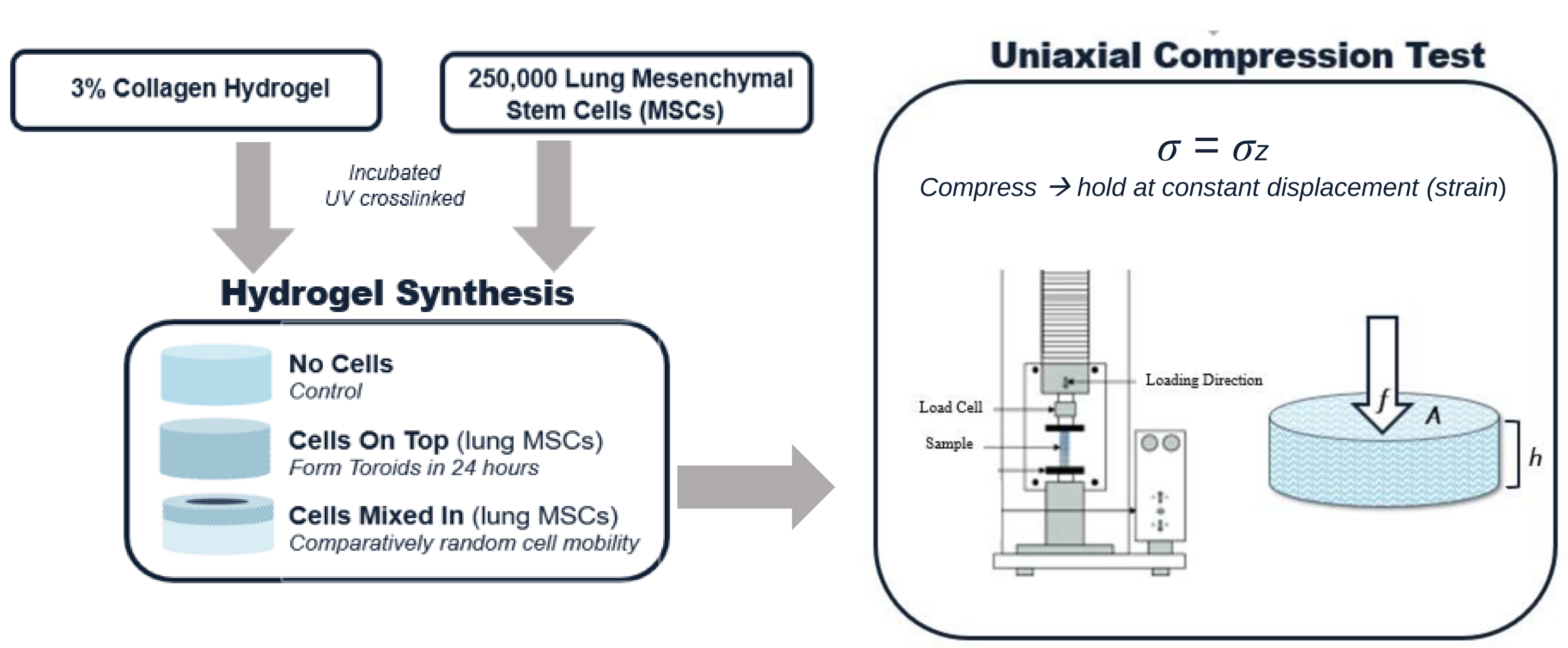


(A) Camera Image (B) SHG Image

Objectives

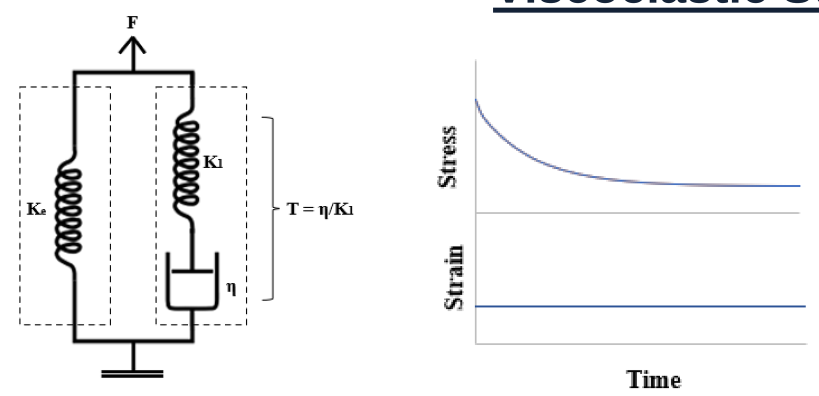
1) Characterize the mechanical response of collagen hydrogels with different cell seeding patterns under uniaxial compression test
2) Investigate the fit of the Standard Linear Solid (SLS) model to describe the viscoelastic mechanical response of collagen hydrogels

Methods



Methods

Viscoelastic Stress Response



Compressive Stress: $\sigma = f / A$ [Pa]

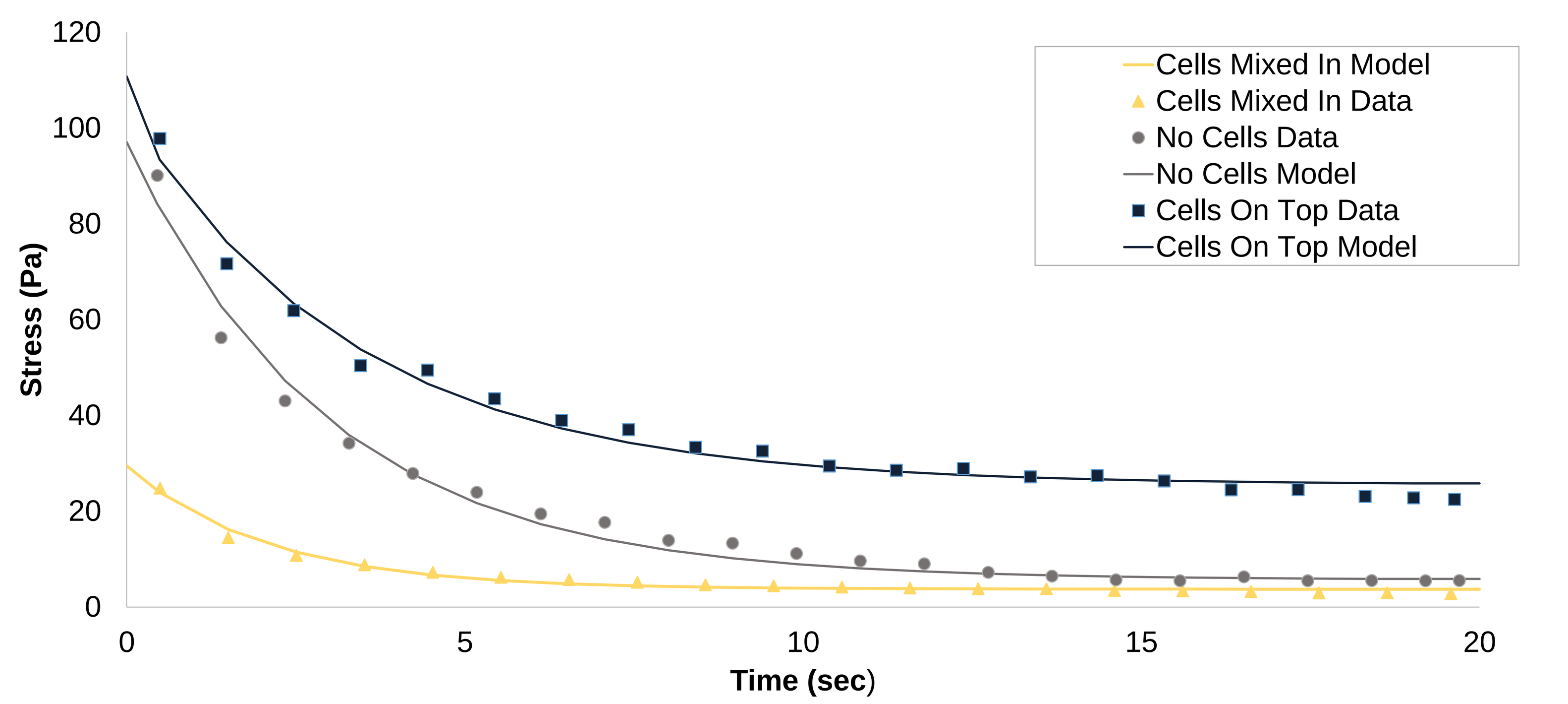
Constant Strain: $\varepsilon_0 = 0.2\text{-}0.25$

Standard Linear Solid (SLS) Model

$$\frac{d\sigma}{dt} + \frac{1}{\tau} = (K_e + K_1)\frac{d\varepsilon}{dt} + \frac{K_e}{\tau}\varepsilon \xrightarrow{(Constant\ \varepsilon_0)} \frac{\sigma(t)}{\varepsilon_0} = K_e + K_1\, e^{-t/\tau}$$

Equilibrium Stiffness, Ke [Pa]	Maxwell Stiffness, K1 [Pa]	Time constant, T [sec]
Represents constant equilibrium relaxation as time approaches infinity	Interpreted as how much the gel relaxes from the beginning of stress relaxation to the constant equilibrium relaxation	Describes kinematics of time-dependent viscoelastic stress relaxation

Results

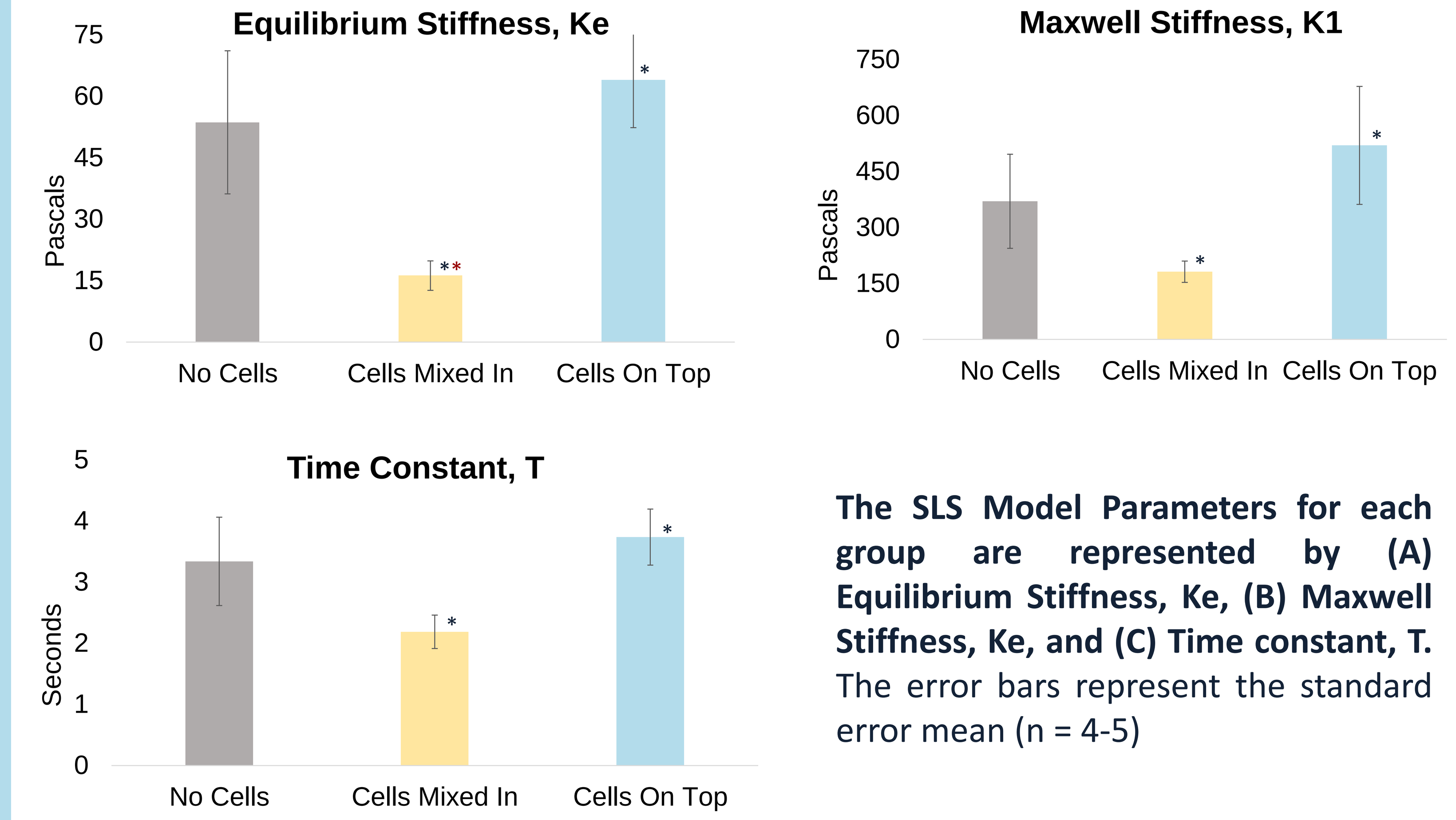


Representative data set for stress response and model for each group

	No Cells	Cells Mixed In	Cells On Top
Instantaneous Stress (Pa)	74.4 ± 18.5	40.4 ± 7.6**	121.1 ± 25.4*
Equilibrium Stress (Pa)	7.1 ± 2.6	2.1 ± 0.4*	9.0 ± 1.4*
Relaxed Stress (Pa)	84.9 ± 12.6	38.3 ± 7.7	112.1 ± 24.5
Relative Relaxation (%)	94.7 ± 1.6	93.8 ± 1.9	90.3 ± 2.2
Ke (Pa)	53.6 ± 17.5	16.2 ± 3.6**	64.0 ± 11.6*
K1 (Pa)	370.3 ± 126.0	181.7 ± 28.6*	520.1 ± 158.1*
T (sec)	3.3 ± 0.7	2.2 ± 0.3*	3.7 ± 0.5*

Stress relaxation data for each experimental group (n = 4-5, $R^2 > 0.98$)
**Significant difference versus no cells (control) group*
**Significant difference versus alternate experimental group*

Results



The SLS Model Parameters for each group are represented by (A) Equilibrium Stiffness, Ke, (B) Maxwell Stiffness, K1, and (C) Time constant, T. The error bars represent the standard error mean (n = 4-5)

Discussion

Mechanics of Varying Hydrogel Groups
- The SLS Model provided an optimal fit for the experimental groups
- Toroid gels demonstrated significantly greater stiffness and tensile strength than mixed in gels
- Mixed in gels responded with significantly less elasticity than both control and toroid gels, and to a lower equilibrium stress than the toroid gels
- Mixed in gels relaxed to equilibrium stress in a significantly shorter time period than the control and toroid gels

Implications
- Suggests that varying cell mobility and migration affects stress relaxation mechanics by remodeling/degradation of the collagen matrix
- Emphasizes importance of increasing understanding of the correlation between matrix mechanics and remodeling

Future Studies
- Quantitatively compare relationships between ECM biological parameters and the area of toroids with the mechanical response
- Expand experimental groups
  - Matrix Composition
  - Cell types
  - Single versus multi-cell environments
  - Varying time points in toroid formation

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References

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