Self-Organization of Honeycombing in an Agent-Based Model of Lung Fibrosis

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Introduction

- Pulmonary fibrosis is a rapidly progressing and incurable disease involving abnormal interactions between fibroblasts and the extracellular matrix they normally regulate.
- Our goal was to investigate how characteristic macroscale structures such as lung "honeycombing" emerge from pathological microscale cell-ECM interactions.

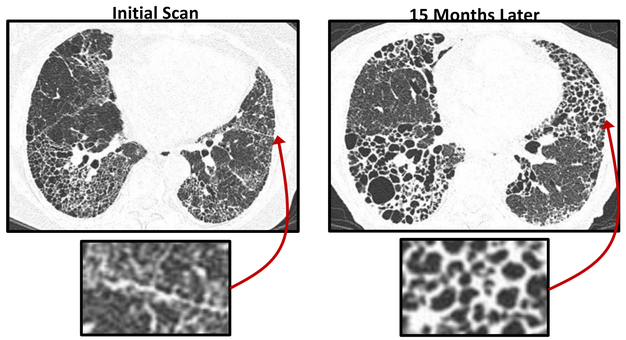


Figure 1. Example CT images of fibrotic lung, initially and 15 months later, illustrating the rapid progression of fibrosis and characteristic honeycombing pattern **[1]**.

Agent Model

Figure 2. Fibroblasts regulation of lung parenchymal stiffness was modeled as two competing processes of collagen fiber degradation and repair.

$$\dot{N} = R - D\sqrt{N}$$

N: Number of fibrils in fiber cross-section

D: Rate of degradation (enzymatic fibril digestion around exposed fiber perimeter)

$\dot{N}$: Rate of change in N

R: Rate of repair (new fibril deposition)

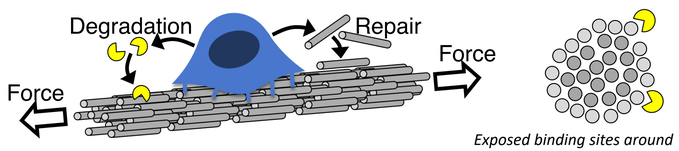


Figure 3. Degradation rate was assumed to depend on fiber strain ε according to tissue strip experiments **[2]**:

$$D(\varepsilon) = D_{\text{bas}} e^{-\beta_1 \varepsilon} + D_{\text{sat}} \frac{1}{1 + e^{-\beta_2(\varepsilon - \varepsilon^*)}}$$

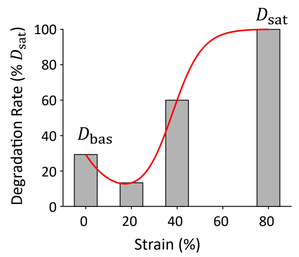
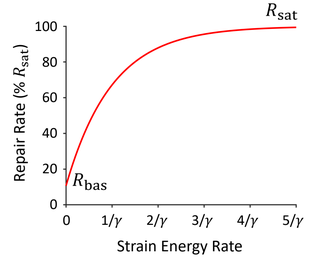


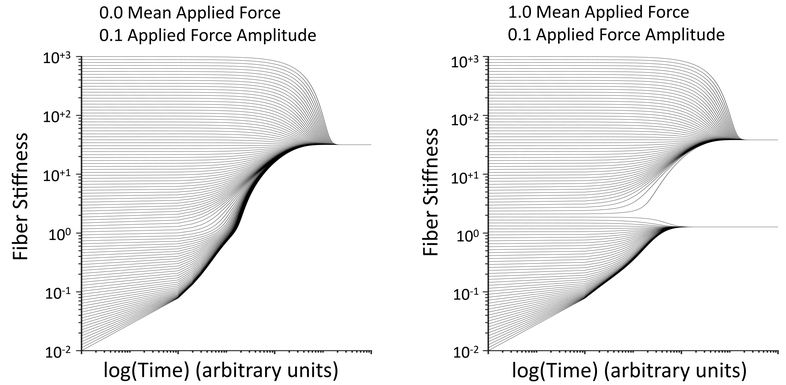
Figure 4. Repair rate (or production of new fibrils) was assumed to depend on fiber strain energy rate ($\dot{E}$) **[3]**:

$$R(\dot{E}) = R_{\text{bas}} + (R_{\text{sat}} - R_{\text{bas}})(1 - e^{-\gamma_1 \dot{E}})$$



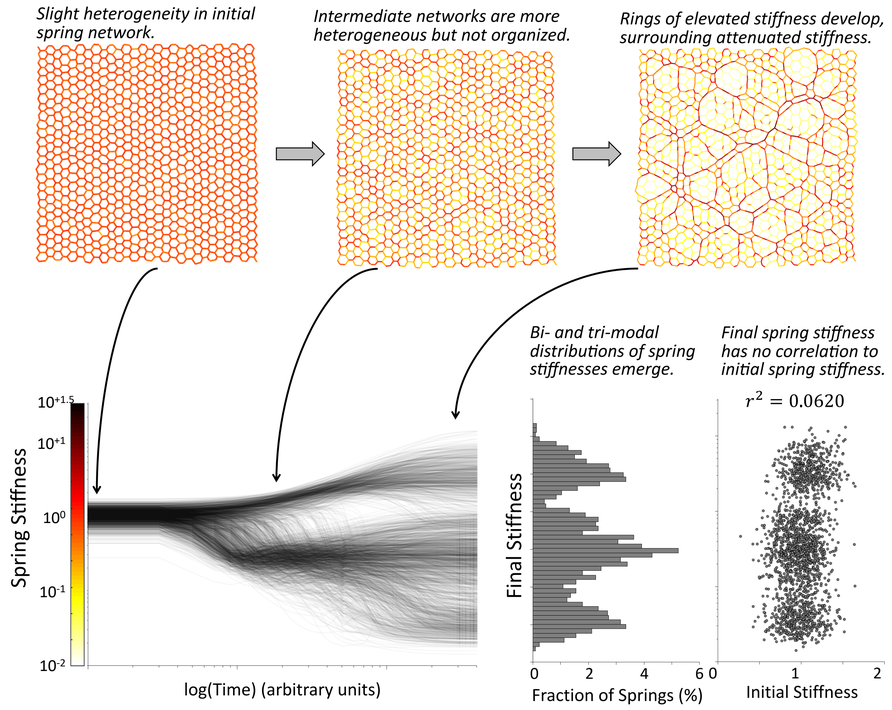
Results – Microscale Single Fiber Model

Figure 5. Mechanical forces can produce a bifurcation in the dynamics of fiber maintenance. Collagen fiber stiffness (assumed proportional to N) modified over time by fibroblast-mediated repair and degradation, during sinusoidal force oscillations applied to the fiber starting from different initial values of Y. Either one or two distinct steady state values of fiber stiffness are observed, depending on applied forces.



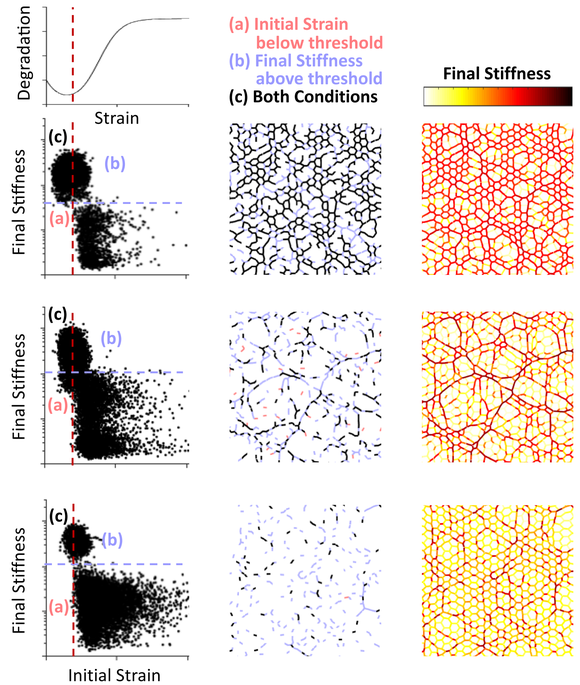
Results – Macroscale Spring Network Model

Figure 6. Network models exhibit trimodal stiffness distributions and self-organized honeycomb patterns. Every spring in a hexagonal network was assigned a random stiffness and rest length (0.2 coefficient of variation). At each time step, equilibrium network configurations were solved for two different applied forces directed outwards from the boundaries (representing tidal pressure changes during breathing). Strain energy rate and average strain were computed for each spring, and used to determine agent regulation of spring stiffness.



Results – Mechanism

Figure 7. Tri-modal stiffness and honeycombing emerge from initial strain and from mechanical interactions. Three quadrants of the *final stiffness* vs. *initial strain* maps were used to color springs, revealing the formation of "bridges" connecting initially sub-threshold springs, resulting in honeycomb-like cells. Increasing the mean applied force alters the distribution of mean strain and degradation rate, ultimately eliminating the pattern.



Low mean force:

Many springs exhibit low initial strain, in the bottom of the "U" degradation-strain curve, and become stiffer **(c)**.

Springs between them are induced into a similar state (b).

Increasing force:

Some springs are below the strain threshold initially: (a) and **(c)**.

Gaps between them are bridged (b), forming honeycomb cells.

Isolated springs inside cells (surrounded by stiffer springs) receive little strain energy rate and become heavily degraded (a).

High mean force:

Springs with low initial strain are few and sparse **(c)**.

Honeycomb cells are more difficult to form (b).

Conclusions

- **A 2D spring network model describing fibroblast-mediated maintenance of alveolar wall stiffness exhibited tri-modal distributions of stiffness—in contrast to the bi-modal prediction given by the same agent rules in a 1D single fiber model.**
- **Self-organizing ring-like structures emerge, resembling honeycombing patterns that develop in pulmonary fibrosis and other lung diseases.**
- **Although speculative, this model suggests that abnormal fibroblast behavior, or even normal fibroblast behavior under abnormal applied forces, may naturally develop honeycombing patterns due to complex network interactions and biomechanical feedback.**

Acknowledgment

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References

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[2] E. Yi, S. Sato, A. Takahashi, H. Parameswaran, T.A. Blute, E. Bartolák-Suki, B. Suki. **Mechanical forces accelerate collagen digestion by bacterial collagenase in lung tissue strips**. *Frontiers in Physiology*, 7(287), 2016.

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