Coupling an Agent-Based Model of Scar Formation to a Finite-Element Model of Tissue Mechanics

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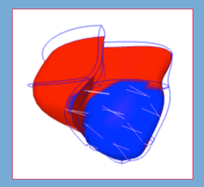
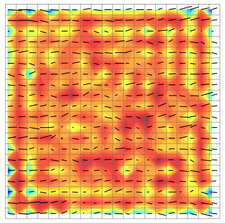


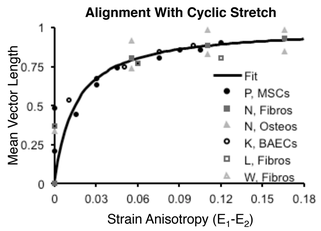
Introduction

- We recently developed an agent-based (ABM) model of scar formation following infarction in the heart.[1]
- Reflecting experimental evidence,[2] strain is an important determinant of local cell and collagen alignment in the ABM; early versions of the model simply prescribed strains throughout healing as an input.
- In this study, we aimed to couple the ABM to a finite-element model, so that strains were determined throughout simulated healing by prescribed loading and evolving material properties.

Agent-Based Model (ABM)

- In the ABM, fibroblasts migrate, proliferate, apoptose, deposit collagen aligned with the cell axis, re-orient collagen towards the cell axis, and degrade collagen; activity depends on local chemokine concentration.
- Fibroblast alignment is selected at each time step from a probability distribution determined by the vector average of individual orientation cues: mechanical, chemical, and structural.





$$\mathbf{v}_m = \frac{(E_1 - E_2)}{k_m + (E_1 - E_2)}\mathbf{M}_1 \quad , \quad \mathbf{v}_c = \frac{1}{2\pi}\int_{-\pi}^{\pi} c\,\mathbf{n}\,d\theta \quad , \quad \mathbf{v}_s = MVL * \begin{bmatrix} \cos(MA) \\ \sin(MA) \end{bmatrix}$$

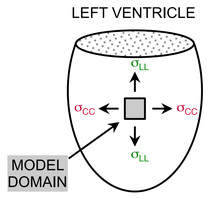
where E_1, E_2 are principal strains, $\mathbf{M}_1$ indicates 1st principal direction, MVL = mean vector length, MA = mean angle of local collagen fibers

$$\mathbf{r} = \frac{w_s\mathbf{v}_s + w_c\mathbf{v}_c + w_m\mathbf{v}_m}{w_s + w_c + w_m + \alpha} \quad , \quad \varphi(\theta,\mathbf{r}) = \frac{1}{\sigma\sqrt{2\pi}}\sum_{k=-\infty}^{\infty} e^{-(\theta-\theta(\mathbf{r})+2\pi k)^2/2\sigma^2} \quad , \quad \sigma^2 = -2\ln\|\mathbf{r}\|$$

Figure 1: Key features of agent-based model. **Left Panel:** ABM of 20x20 element grid showing collagen density (red = more dense) and alignment (dash indicates mean vector). **Center Panel:** Fitted cell orientation as a function of difference in applied principal strains across a range of published cyclic stretching experiments (see Rouillard and Holmes[3] for details). **Right Panel:** Key equations for defining and integrating mechanical, chemical, and structural cue vectors.

Finite-Element Model (FEM)

- The FEM was created in FEBio v1.5 (Musculoskeletal Research Lab, University of Utah).
- A single layer of 400 elements was employed to represent a thin midwall section of a healing rat infarct parallel to the epicardial surface; model was defined and modified by writing standard XML (.feb) files.
- Prescribed stresses were applied perpendicular to the edges of the mesh to reproduce measured strains.



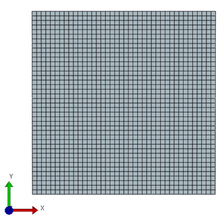


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Figure 2: Key features of finite-element model. **Left Panel:** FE model simulated a small region of a healing myocardial infarct in a rat heart. **Center Panel:** FE mesh consisted of a single layer of 400 elements in the circumferential-longitudinal plane. **Right Panels:** Excerpts from XML (.feb) file used to define FEBio model showing header with solver settings and an example of the material definition for one of the elements.

References & Acknowledgments

1. Rouillard AD, Holmes JW. *J Physiol* 590(18):4585-4602, 2012.
2. Fomovsky GM, Rouillard AD, Holmes JW. *J Mol Cell Cardiol* 52:1083-1090, 2012.
3. Rouillard AD, Holmes JW. *Prog Biophys Mol Biol* 115(2-3):235-243, 2014.
4. Costa KD, Holmes JW, McCulloch AD. *Phil Trans Royal Soc Lond A* 359:1233-1250, 2001.

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ABM-FEM Coupling

- Because scar formation and remodeling occur on a much longer time scale than a single heart beat, the overall strategy was: 1) simulate a single beat in the FEM; 2) pass regional strains to the ABM and simulate a growth & remodeling step; 3) then update the FEM constitutive properties to reflect the new scar structure and repeat.
- The key challenge in this approach is translating ABM-predicted scar structure into tissue constitutive properties. We utilized a previously published approach for modeling scar based on the density and orientation of large collagen fibers.[4]
- We treated scar as isotropic, hyperelastic, and composed of collagen fibers embedded in an isotropic background matrix; assuming collagen fibers can only bear tension along their axes and summing over the ABM-predicted fiber distribution yields an expression for coefficients in the exponential strain-energy function (SEF) that depend only on global strains and fiber orientations in the reference state:

$$W = C_{nh}\left(I_c - 3\right) + \frac{1}{2}C_{fung}\left(e^Q - 1\right) + \frac{1}{2}K\left(\ln J\right)^2 \quad , \quad I_c = tr(\mathbf{F}^T\mathbf{F}) \quad , \quad J = \det(\mathbf{F})$$

$$Q = C_{fiber}\left(C_1E_{11}^2 + C_2E_{22}^2 + C_3\left(E_{11}E_{22} + 4E_{12}^2\right) + C_4\left(4E_{11}E_{12}\right) + C_5\left(4E_{22}E_{12}\right)\right)$$

$$E_\alpha = \begin{bmatrix} \cos\alpha & \sin\alpha & 0 \end{bmatrix}\begin{bmatrix} E_{11} & E_{12} & E_{13} \\ E_{12} & E_{22} & E_{23} \\ E_{13} & E_{23} & E_{33} \end{bmatrix}\begin{bmatrix} \cos\alpha \\ \sin\alpha \\ 0 \end{bmatrix}$$

$$\Rightarrow \quad C_1 = \frac{AF}{k}\sum_{j=1}^{k}\cos^4\alpha_j \;,\; C_2 = \frac{AF}{k}\sum_{j=1}^{k}\sin^4\alpha_j \;,\; C_3 = \frac{AF}{k}\sum_{j=1}^{k}\cos^2\alpha_j\sin^2\alpha_j \;,\; C_4 = \frac{AF}{k}\sum_{j=1}^{k}\cos^3\alpha_j\sin\alpha_j \;,\; C_5 = \frac{AF}{k}\sum_{j=1}^{k}\cos\alpha_j\sin^3\alpha_j$$

- *note: AF = collagen area fraction, terms in red not available in FEBio Fung orthotropic SEF.*

Results and Discussion

- Collagen deposition and degradation rates were chosen to match collagen accumulation data from healing rat infarcts (Figure 3); initial collagen content was 0.03%, with strong circumferential alignment.
- Reproducing measured acute strains ($E_{LL} > E_{CC}$) in the model led to early deposition of collagen fibers in the longitudinal direction, reducing mean vector length to near zero, in agreement with data (Figure 3).
- When applied stresses were held constant over the entire time course of healing, strains dropped rapidly as the infarct stiffened; gradually increasing stresses were required to maintain strains in measured range. *In vivo*, infarct thinning and cavity dilation do increase stresses during healing, though probably not 5-fold.

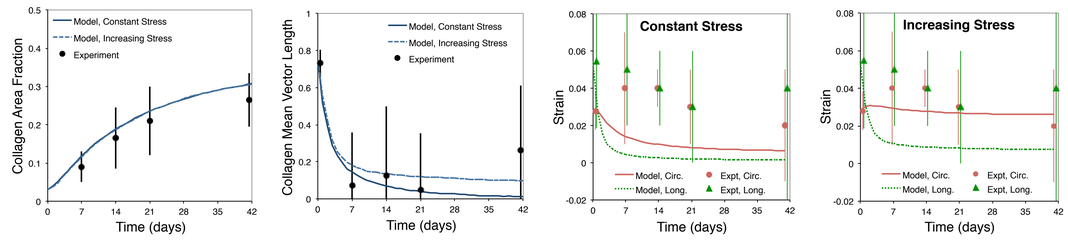

Figure 3: Results of coupled simulations. **Left Panels:** Collagen content and alignment fell within 1 SD of experimental measurements from healing rat infarcts regardless of assumptions about applied stress. **Right Panels:** When applied stress was constant across entire time course of healing, increase in stiffness due to collagen accumulation rapidly dropped strains below experimentally measured levels; gradually increasing applied stresses 5-fold to simulate infarct thinning and cavity dilation maintained strains closer to measured levels.

- Overall, when stretch determines collagen alignment, the coupled system opposes perturbations: stretch anisotropy > collagen alignment in direction of highest stretch > more equal stretches. By contrast, when contact guidance determines collagen alignment, the coupled system amplifies perturbations: increased local collagen alignment > greater cell alignment > further increases in collagen alignment.