**Spatial Scaling in Multiscale Models: A Method for Coupling Agent-based and Finite-element Models of Tissue Remodeling**

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Cellular activities, extracellular matrix (ECM) homeostasis and remodeling, and tissue mechanics form a mechanobiological feedback loop. We implemented a multi-scale model that couples agent-based modeling (ABM) to represent cell behaviors and finite-element modeling (FEM) to represent tissue mechanics to explore cell-ECM-mechanics interactions in healing myocardial infarcts. One of the challenges in coupling an ABM to an FEM is spatial scaling. ABMs typically require grid sizes on the micron scale to adequately represent cell migration, chemokine diffusion, and other relevant processes, while FEMs of tissue mechanics generally employ element sizes on the order of millimeters or centimeters, consistent with the assumptions of continuum mechanics. Thus, the present study aims to develop a general approach to ABM-FEM coupling that accounts for different spatial scaling in the two model components while allowing the user flexibility to adjust the mesh density of each component independently.

An ABM of cell migration and ECM remodeling was constructed in Repast Simphony based on a previous study of 42 days of infarct healing in the rat. Fibroblasts were modeled as agents that each occupy one discrete grid point (referred as a “GridPoint”), migrate and replicate without overlapping neighboring cells, deposit and degrade collagen, and apoptose after a specified lifetime within a 100-by-100 grid space. In the FEM, we simulated a thin slab of tissue as a neo-Hookean material and loaded in the x direction with a prescribed traction force in FEBio. The material properties of each element varied with local collagen fraction, which was obtained from the ABM. After every 7 days of ABM simulations, new material parameters were computed and FE simulations repeated, with strains passed back to the ABM. We established an ABM grid with GridPoints that are evenly spaced in physical coordinates; this simplifies calculations of cell migration, chemokine diffusion, and other processes that involve distances. To demonstrate the ability to establish spatial correspondence between an ABM and FEM with variable grid/mesh densities, we performed a mesh refinement study (from 2-by-2 to 50-by-50) in our simulated tissue slab while holding ABM grid density constant.

At all mesh densities, collagen fraction increased from 0.03 at 0 days to 0.28 at 42 days; as collagen accumulated, material stiffness increased, reducing mean strains from 0.08 to approximately 0.02. In the absence of feedback between local strain and collagen deposition and degradation rates, refinement of the FE mesh revealed the competing influence of two factors. FE mesh refinement typically reduces strain differences between adjacent elements. However, the fact that averaging over smaller and smaller regions of the ABM produced spatial heterogeneity in collagen content and material properties dominated the coupled problem, increasing strain differences between adjacent elements as the number of elements increased. We expect this heterogeneity to have significant nonlinear effects in our coupled model once strain is allowed to feed back on collagen deposition and degradation in the ABM. Thus, although the ABM and FEM literature provide methods for selecting grid or mesh densities when using either framework alone, new approaches for determining grid and mesh densities may be required for coupled models.

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