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Recovery of 3D Tractions Exerted by Cells on Fibrous Extracellular Matrices

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Abstract: Tractions exerted by cells on the extracellular matrix (ECM) are critical in many important physiological and pathological processes such as embryonic morphogenesis, cell migration, wound healing, and cancer metastasis. Traction Force Microscopy (TFM) is a robust tool to quantify cellular tractions during cell-matrix interactions. It works by measuring the motion of fiducial markers inside the ECM in response to cellular tractions and using this information to infer the traction field. Most applications of this technique have heretofore assumed that the ECM is homogeneous and isotropic [1], although the native ECM is typically composed of fibrous networks, and thus heterogeneous and anisotropic.

In this work, we present a novel nonlinear TFM approach to recover 3D tractions exerted by cells fully encapsulated in fibrous hydrogels that mimic the *in-vivo* cellular environment. We pose the problem as an inverse hyperelasticity problem, with the objective of determining the traction field that is consistent with the measured displacement field in the ECM. We formulate the inverse problem as a constrained minimization problem and develop an efficient adjoint-based minimization technique to solve it [2]. In particular, we account for the fibrous character of the ECM by employing a microstructure-based homogenization model that links the microscopic features of the fibrous gels to the macroscopic response.

We apply our TFM approach to *in-silico* problems with realistic geometric models of NIH 3T3 and microglial cells. We find that the proposed algorithm is able to accurately recover the traction fields. By comparison with results obtained using isotropic models (e.g., Neo-Hookean model and Blatz model), we find that the error introduced by neglecting the fibrous nature of the ECM is significant. These results suggest that it is crucial to account for the microstructure of the ECM to accurately quantify cellular forces in physiologically relevant settings. In light of this, our algorithm represents a step toward more accurate, broadly-applicable 3D TFM.

Keywords: Cell traction force microscopy; inverse problem; adjoint method; fibrous model

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