Modeling Extracellular Matrix in Breast Cancer

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***Short Abstract* — Breast cancer is a fatal disease, but the detailed mechanism of metastasis is unclear since extracellular matrix (ECM) affects many aspects of cellular behavior, including migration, invasion, and proliferation. Furthermore, the properties of ECM itself are also complex, with diverse topographies and mechanical properties depending on the density, alignment, polymerization, and crosslinking. We use *in vitro* and *in silico* ECM models to study how biophysical parameters of individual fibers affect the mechanical property of ECM network. The computational ECM model will be a key step toward simulating and investigating the invasive behavior of aggressive breast cancer cells.**

***Keywords* — extracellular matrix, breast cancer**

I. Introduction

TUMORS are usually stiffer and denser than normal tissue [1]. Increased collagen density and crosslinking increase mammary tumor formation and metastases [2, 3]. These *in vitro* and *in vivo* studies indicate that extracellular matrix (ECM) significantly influences on tumor growth and invasion [1-4].

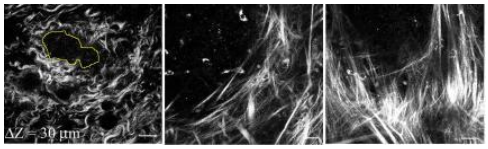

Figure 1: Tumor-associated collagen signatures (TACS) [5].

The second harmonic generation (SHG) images in Fig. 1 show three unique features of collagen, associated with growing and invading tumor [5]. Small size or pre-palpable tumors can be identified with denser collagen, shown in the left figure. Growing tumors make tangentially stretched collagen fibers, shown in the middle, and then invading tumors show normally stretched collagen fibers and thus cancer cells can invade out along radially aligned collagen fibers, shown in the right figure [5]. How these individual collagen fibers are deformed and realigned by growing and migrating cancer cells and how the applied force of a fiber propagates though the fiber network are fundamental questions to further examine the effect of TACS. As the first step to investigate the TACS effects on growing and invading tumors, we have developed both experimental models and computational models for collagen gels.

Our mathematical model of ECM treats collagen fibers as bead-and-springs with a Young's modulus and crosslinkers as non-covalent bonds between a pair of collagen fibers. We apply an energy minimization method to simulate the fiber network for efficiently reaching the quasi-equilibrium state.

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We use 3D type-I collagen matrixes of different densities, crosslinker densities (e.g. treatment of glutaraldehyde for increasing crosslinkers), and measure the bulk stress-strain and rheological response for systematically varying matrix parameters. These experimental data are used to build and validate our computational model. A mathematical model to quantitatively examine how collagen density, structure, and the number of crosslinkers, affect the stiffness of the ECM fiber network, is a crucial first step to better understand the detailed mechanism of tumor invasion.

II. Conclusion and Discussion

Simulation results of our random and pre-aligned ECM models for different crosslinker elastic moduli and crosslinker densities (Fig 2) are compared directly with experimental stress-strain data of 3D collagen gels. Bulk stress-strain measurements for pre-strained and un-strained collagen gels *in vitro* show that straining pre-aligns the fiber network is at least 10 fold stiffer than un-strained, randomly distributed fiber network. We determine quantitatively the relation between the unknown crosslinker strength and crosslinker density in the gel. This mechanical model of three-dimensional ECM is poised for a full integration with biomechanically-realistic cell migration models.

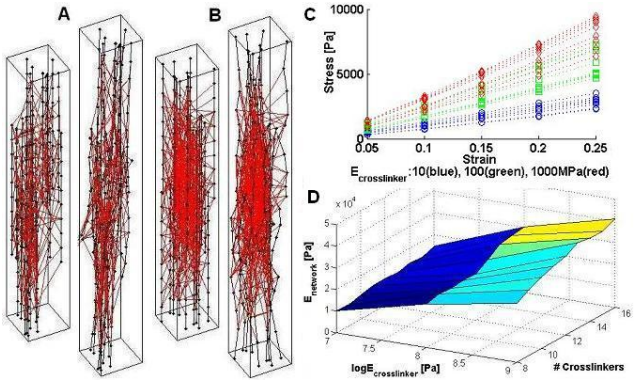

Figure 2: Simulation results: Fiber network snapshots (A and B), stress-strain curves (C), and fiber network modulus (D) for 1mg/ml collagen. Five different strains are applied to the fiber network, from 0.05 to 0.25 with an increment of 0.05. In (A) $E_{crosslinker}$ =10MPa, #Crosslinkers=8x, and (B) $E_{crosslinker}$ =1000MPa, #Crosslinkers=16x, each left figure is the initial state at 0% strain and the right figure is a quasi-equilibrium state at 25% strain. Three crosslinker strengths ($E_{crosslinker}$ =10, 100, 1000MPa) and nine crosslinker numbers (#Crosslinkers =8, 9, 10, 11, 12, 13, 14, 15, 16 x total fiber numbers) are plotted in (C) and (D).

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