Three Dimensional Mathematical Model of Extracellular Matrix in Breast Cancer

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***Short Abstract* — Breast cancer is the most common cause of cancer in women. Dense breast tissue is a strong and frequent risk factor for the development of invasive breast cancer and is associated with excess collagen deposition. Transgenic mouse tumor studies indicate that excess collagen does promote both tumor formation and invasiveness. However, the underlying mechanisms are 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 possible depending on the density, alignment, polymerization, and crosslinking. Because of the complex and multivariate nature of cell-matrix, matrix-matrix, and cell-cell interactions, a mathematical modeling approach is ideal to integrate variables and predict emergent features, such as tumor growth and invasion. We therefore combine data integration with mathematical modeling to determine the specific mechanisms by which tissue density and fibrosis promote breast cancer aggressiveness.**

***Keywords* — extracellular matrix, tumor invasion, breast cancer, collagen, mathematical model**

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]. Based on these *in vitro* and *in vivo* studies, extracellular matrix (ECM) significantly influences on tumor growth and invasion [1-4].

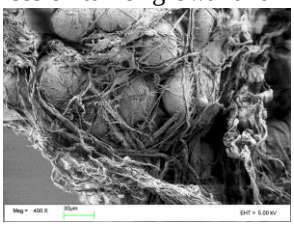

Figure 1: SEM images collagen fibers in breast [5].

The scanning electron microscopy (SEM) image in figure 1 shows the heterogeneous structure of type-I collagen fibers, one of the main components in ECM of the mammary tissue. A mathematical model to quantitatively examine how the density of collagen, the number of crosslinkers, tensile modulus of a fiber, and bending modulus of a fiber affect the stiffness of the ECM fiber network, is a crucial first step to better understand the detailed mechanism of tumor invasion. Moreover, how the mechanical force generated by tumor cells affects the alignment of the fiber network is another important and challenging problem in the tumor growth and invasion.

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We have developed both experimental models and computational models for collagen gels. We use 3D type-I collagen matrixes to measure structural and mechanical parameter values, including density and packing of collagen fibers, crosslinker densities, and bulk stress-strain and rheological response for systematically varying different matrix parameters (e.g. treatment of glutaraldehyde for increasing crosslinkers). These experimental data are used to build and validate our computational model. The current mathematical models treat collagen fibers as bead-and-spring fibers with stretch and bending elasticity, crosslinkers as fixed covalent bonds. We use Langevin dynamics to calculate the force balance on each point [6].

II. Conclusion and Discussion

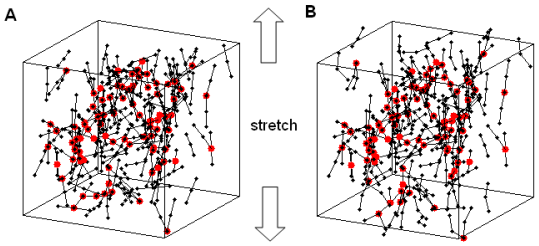

Figure 2: Simulation snapshots for 200 fibers and 100 crosslinkers, stretched force applied on top and bottom of 1nN. (A) 10μs (B) 3.8ms. The simulation box is $(500\mu m)^3$. The length of a fiber is 100μm and the diameter of a fiber is 0.3μm.

Figure 2 shows our fiber network models at a beginning state (A) and an intermediate state (B) after continuing stretched force applied to up and down of the box. The network structure of fibers is changed by applied mechanical force, partially showing an alignment on the direction of the force applied. We perform bulk tensile loading as well as shearing simulations, as a function of crosslinker densities and fiber geometry and mechanical properties. Preliminary tensile stretching test for the collagen gel (4mg/ml) shows the linear two-fold increment of stress in the low to medium range of stretch, up to 25% stretched case. Over 25% stretch, the matrix response is nonlinear, i.e. strain stiffening. Integrating this fiber model with a multiscale cellular tumor growth model [7] will provide more realistic and comprehensive model for investigating the effects of tissue rigidity in breast tumor invasion.

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