Modeling 3D Cell Migration

X He[1*], K Riching[2*], B Lee[1], P Keeley[2], K Eliceri[3], A Weaver[4], Y Jiang[1]

***Short Abstract* — Cell migration is important for development, wound healing and cancer invasion. It is a complex process that involves multi-scale interactions between cells and the extracellular matrix (ECM). Empirical evidence of cell migration in 3D collagen gels showed that the stabilization of cell protrusion through cell-ECM interactions is a key mechanism to promote directional migration. How the biophysical and biomechanical properties of cell and ECM regulate cell morphology and control cell migration is still unclear. To understand this basic biomechanical motility machinery, we build a 3-D Cell-ECM model and perform experimentally parameterized simulations of 3D cell migration.**

***Keywords* — 3D cell migration, cell protrusion, cancer invasion, cell-ECM interaction.**

I. Introduction

Cell migration is a fundamental process that regulates numerous physiological functions of biological system [1]. Asymmetric morphology is the first step of cell motility cycle [2]. Cells define leading and trailing edges through random membrane extension and stabilization of cell protrusion. The formation of integrin-mediated adhesion is the beginning of cell migration, followed by generations of periodic interruptions of lamellipodial extension [3]. Contraction is the main part of the motility process during which the cells extend and encounter new ECM environment and determines the physical rigidity of the matrix through contractile forces. To characterize how the ECM guides and regulates cell migration and how the cell migration remodels the ECM, we develop a computational model of cell migration in 3D ECM, which reproduces the experimental measurements and provides new insights into the cell migration.

II. Approach

We have previously developed a collagen fiber network model [4]. We adopt the subcellular elements model [5] and integrate the cell and collagen models by specifying cell-ECM interactions. The model allows cell membrane elements to extend randomly, mimicking membrane fluctuation due to cytoskeletal activities. The key feature of the model is that the duration for the cell and ECM binding depends on the strength of the binding.

III. Results

With *In vitro* experiments of single cell migration in 3D collagen, we quantify the collagen alignment and rigidity as a function of density and alignment; we also quantify the preferential cell migration along the aligned and more rigid fibers. With our Cell-ECM model, we simulate cell protrusion as random short-range extensions of membrane elements, which allows the cell to probe the ECM environments and initiate binding between membrane element and collagen element. We find that the initial tension of the binding is a function of local rigidity of ECM. Stronger binding contributes to the formation and stabilization of cell protrusion. We model the periodical lamellipodial extension and rearward contraction through decaying of tension over time. We simulate the detailed morphology evolution and stress/strain distribution on the cell and in the ECM fiber network. We investigate the cell-ECM biomechanical interactions as a function of ECM properties, including density, stiffness, and 3D structure. In particular, we focus on studying the resulting ECM remodeling due to cell directed migration. The results resemble those observed in 3D cell traction experiments as well as 3D cell migration assays. With multiple cells migrating, the cell-cell interactions promote the population wise migration significantly.

IV. Conclusion

We have developed a biomechanical cell-matrix model. Integrated experimental and modeling study on ECM properties during cell migration show detailed dynamical changes within the neighborhood of cell-matrix binding sites. This model allows us to quantitatively and systematically investigate 3D cell migration through cell-matrix interactions and ECM remodeling as a result of cell migration.

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* Equal contribution

[1] Dept of Mathematics and Statistics, Georgia State University. E-mail: xhe9@student.gsu.edu

[2] Dept of Pharmacology and [3] Biomedical Engineering, University of Wisconsin-Madison.

[4] Dept of Cancer Biology, Vanderbilt University Medical Center.

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