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EXTRACELLULAR FLOW PATTERNS SURROUNDING A BREAST CANCER CELL DURING TRANSPORT IN A MICROCHANNEL

Lahcen Akerkouch
Department of Civil and Environmental Engineering
North Dakota State University,
Fargo, North Dakota

Trung Bao Le
Department of Civil and Environmental Engineering
North Dakota State University,
Fargo, North Dakota

Amanda Haage
Department of Biomedical Sciences
School of Medicine & Health Sciences
University of North Dakota
Grand Forks, North Dakota

Aaron Vanyo
Department of Biomedical Sciences
School of Medicine & Health Sciences
University of North Dakota
Grand Forks, North Dakota

ABSTRACT

We performed the transport of a breast cancer cell (MB231-TGFb) in a microvessel using high-resolution simulations. Using open-source imaging software Slicer3D and Meshmixer, the 3D surface mesh forming the cell membrane was reconstructed from confocal microscopic images. The Dissipative Particle Dynamics method is used to model the cell membrane. The extracellular fluid flow is modeled with the Immersed Boundary Method to solve the governing equations of the blood plasma. The unsteady flow is applied at the inlet of the microchannel with an oscillatory pattern. Our results showed that the extracellular flow patterns are highly dependent on the waveform profile. The oscillatory flow showed the creation of vortices that influence the cellular deformations in the microchannel. These results could have implications on the destination of the cancer cells during transport in physiological flows.

Keywords: Extracellular flows, Cancer Cell, Transport

NOMENCLATURE

CFD	Computational Fluid Dynamics
FSI	Fluid-Structure Interaction

1. INTRODUCTION

Cancer metastasis leads to the transport and widespread of malignant cancer cells to other parts of the body by exploiting body fluids (lymphatic fluid, bloodstream, and interstitial fluid) [1]. In particular, the actual metastasis process is simplified to a series of successive actions beginning by (i) invasion of tissues at the primary tumor; (ii) intravasation into the surrounding vasculature or lymphatic system; (iii) survival in the circulation (cell fragmentation and death); (iv) arrest at the new location, and followed by extravasation and colonization to a secondary tumor [2]. While this process has been known in general, the detailed mechanism of cancer metastasis in micro-vessels is not known.

In this work, we address this knowledge gap by investigating the deformed shapes of cancer cells during fluid transport. Most previous studies assume that cancer cells have spherical shape, which is not necessarily realistic. For example, Byrd et al. [3] generated three-dimensional tumor models based on MRI images obtained from various breast cancer patients. Their results showed that breast cancers were categorized into four

main distinct tumor shapes: discoidal, segmental, spherical and irregular. These shapes are important as they are the building blocks for the creation of 3D tumors in microvasculature environments. While numerical simulations have been used to test and formulate key hypotheses on cancer mechanics such as deformability, adhesion, and extravasation dynamics of cancer cells [4-5]. However, due to the irregular shapes of the cancer cells, previous numerical models typically consider cancer cells as idealized spheres [2]. Furthermore, previous models in literature rely only on particle-based methods to simulate cell and plasma dynamics, which do not report the extracellular flow patterns [2, 4-5] as well the loading condition on the cellular membrane. In this project, we investigate the deformation of a breast cancer cell during its detachment from the primary tumor in micro-circulation. The intracellular and extracellular flow dynamics [6] will be reported to elucidate the history of cell deformation in flows.

2. MATERIALS AND METHODS

The 3D surface mesh was generated based on the confocal scans of breast cancer cell type MDA-MB-231 as seen in Figure 1a. Briefly, cells were cultured on glass coverslips overnight in standard growth media. They were then fixed with 4% paraformaldehyde and stained for focal adhesion protein paxillin as previously described [7]. Individual cells were then imaged in full using a Leica Stellaris confocal microscope at 0.5 µm step size. The images (TIFF files) were processed using the open-source imaging software Slicer3D to generate the 3D mesh of the cell membrane by a sequence of thresholding. The open-source software Meshmixer to manipulate the triangular mesh to control the mesh resolution while preserving the exact shape of the cell as shown in Figure 1b.

The cancer cell membrane is modeled using the Dissipative Particle Dynamics (DPD) method. The DPD particles are connected using a triangulated mesh of non-linear springs based on the coarse-graining procedure [6] as shown in Figure 1b. The model incorporates the physical properties of the lipid bilayer, in-plane stretching, bending stiffness, the area contains and volume conservation as well as plasma viscosity [6]. Furthermore, the governing equations for the external plasma are the three-dimensional, unsteady incompressible continuity and Navier-Stokes equations with density and dynamic viscosity of 1000 kg/m^3 and 1.2 mPa s, respectively. The continuity and Navier-Stokes equations are solved using the curvilinear immersed boundary (CURVIB) method [8]. The discrete equations are integrated in time using a fractional step method. A Newton-Krylov solver is used to solve the momentum equations in the momentum step and a GMRES solver with a multigrid pre-conditioner is employed for the Poisson equation. The coupling between the cellular dynamics and the extracellular flow field is established using the FSI methodology [6].

Two types of inflow waveforms (steady and oscillatory profiles) were carried out with a bulk inflow velocity of $U_0 = 10\ mm/s$. with the length scale of $L_s = 1\ \mu m$, the corresponding Reynolds number is $R_e = 8.33 \times 10^{-3}$. The computational domain was defined as a rectangular box and discretized using a structured grid of size 61x61x81.

A uniform flow profile is applied at the inlet of the computational domain. Fully-developed flow is assigned at the domain's outlet. On the surface of the cellular membrane and the microchannel wall, the no-slip boundary condition is applied for the fluid plasma.

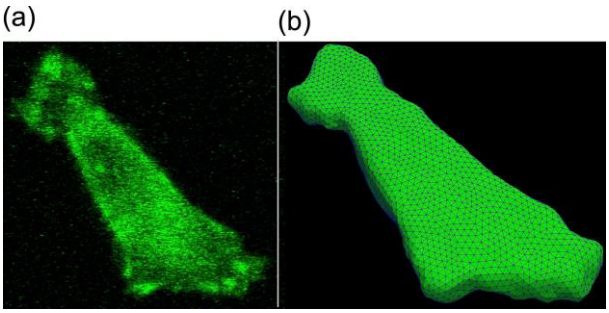

FIGURE 1: (a) Confocal scan of breast cancer cell type MDA-MB-231 placed on a flat substrate. (b) Constructed 3D triangulated surface mesh.

3. RESULTS AND DISCUSSION

The results of two simulations with steady and oscillatory flow profiles are shown in Figure 2.

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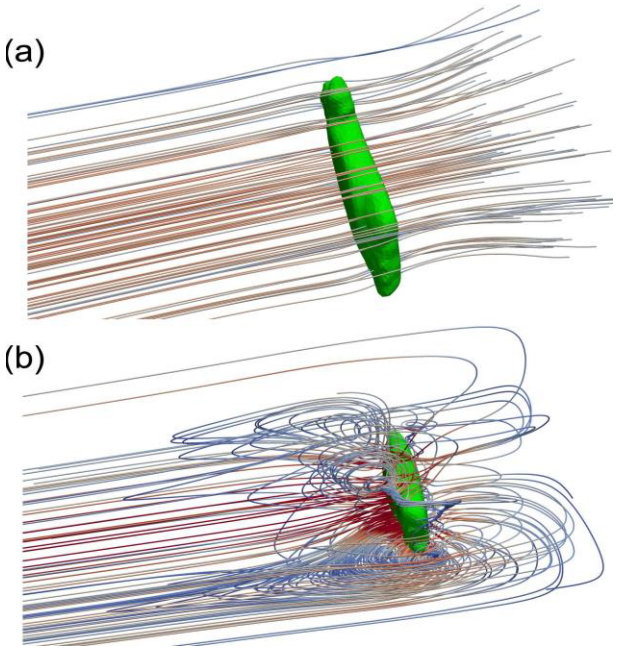

FIGURE 2: 3D extracellular flow streamlines induced by the cellular dynamics of the cancer cell and the (a) steady flow and (b) oscillatory flow.

At first, the cell is allowed to relax in the first period of the simulation. This period provides the cytoskeleton DPD

particles on the cellular membrane to reach the equilibrium condition (no loading). The fluid-structure interaction is activated only when the cell has reached the equilibrium state.

There exists a drastic difference between the dynamics of the steady and oscillatory flows. In the case of the steady flow, the streamlines were observed to follow a laminar trend due to low flow velocity and the minimal deformation induced by the cell membrane on the plasma (Figure 2a). The cell propagates along the microchannel in a straight trajectory, which is defined by the flow streamline. However, the oscillatory flow streamlines were observed to be fully chaotic and forming multiple fully closed vortex rings (Figure 2b). The cell responds to the change in the flow rate. The interaction between these vortex rings with the microchannel wall is significant as the cell propagates toward the outlet. Our results suggest that the cell exhibits very different history on mechanical loading in the oscillatory flow from the steady flow. This effect might play a role in the malignance of the cancer cells [1].

4. CONCLUSION

In this work, we performed CFD simulations on a realistic/irregular geometry of the breast cancer cell type MDA-*MB-231* considering only the outer membrane envelope. The 3D surface mesh of the cancer cell was reconstructed based on the confocal scans. The results revealed that our current formulation can simulate the cellular dynamics of the complex irregular shape of the cancer cell as well as capture the detailed extracellular flow field induced by various flow profiles. Future works will aim to incorporate the cytoskeleton into the current model to study its internal impact for instance on the deformation and adhesion of the cell.

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