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LATERAL MIGRATION OF CANCER CELLS IN A MICROCHANNEL

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ABSTRACT

This work presents the development of a novel approach to model cancer cell dynamics in microcirculation. The proposed numerical model is based on a hybrid continuum-particle approach. The cancer cell model includes the cell membrane, nucleus, cytoplasm and the cytoskeleton. The Dissipative Particle Dynamics method was employed to simulate the mechanical components. The blood plasma is modeled as a Newtonian incompressible fluid. A Fluid-Structure Interaction coupling, leveraging the Immersed Boundary Method is developed to simulate the cell's response to flow dynamics. The model is applied to resolve the transport of cancer cells with realistic morphologies in microcirculatory flows. Our results suggest that the controlling of oscillatory flows can be utilized to induce specific morphological shapes and the surrounding fluid patterns, allowing full manipulation and control of the cell. Furthermore, the intracellular and extracellular dynamics response of the cancer cell is intrinsically linked to their shape, in which certain morphologies displayed strong resistance to the fluid-induced forces and the ability to migrate in various directions. Our computational framework provides new capabilities for designing bioengineering devices for cell manipulation and separation.

Keywords: Continuum-Particle Method, Cancer cells, simulations.

NOMENCLATURE

CFL	Computational Fluid Dynamics
DPD	Dissipative Particle Dynamics
FSI	Fluid-Solid Interaction
GMRES	Generalized Minimal Residual
RBC	Red Blood Cell

1. INTRODUCTION

Cancer metastasis leads to the transport and widespread of malignant cells from the primary tumor to other parts of the body by exploiting body fluids (lymphatic fluid, bloodstream, and interstitial fluid) [1]. The metastasis process consists a series of successive actions beginning by: *(i)* invasion of tissues at the primary tumor; *(ii)* intravasation into the surrounding vasculature or lymphatic system; and *(iii)* survival in the circulation (cell fragmentation and death); and *(iv)* arrest at the new location. Finally, the cancer cell extravases and colonizes to the secondary tumor site [2]. While this process has been known in general, the detailed mechanism of cancer metastasis is not known, especially the impact of hydrodynamic force. In this work, we address this knowledge gap by investigating the migration process of cancer cells in a micro-channel.

Numerical simulations have been used to test and formulate key hypotheses on cancer mechanics such as deformability, adhesion, and extravasation dynamics of cancer cells [3,4]. 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 the literature rely only on particle-based methods to simulate cell and plasma dynamics, which do not report the extracellular flow patterns [2, 3, 4], as well as 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 [5]

will be reported to elucidate the history of cell deformation in flow.

2. MATERIALS AND METHODS

2.1 Cell Modeling Method

A biomechanical model of realistic breast cancer cells has been developed to investigate how these cells deform in shape during transport in microchannels. The model is based on extending our previous hybrid continuum-particle framework we developed for the transport of red blood cells [5]. The model incorporates the primary mechanical components found in eukaryotic cells, comprising the cell membrane, nucleus, cytoskeleton, and cytoplasm.

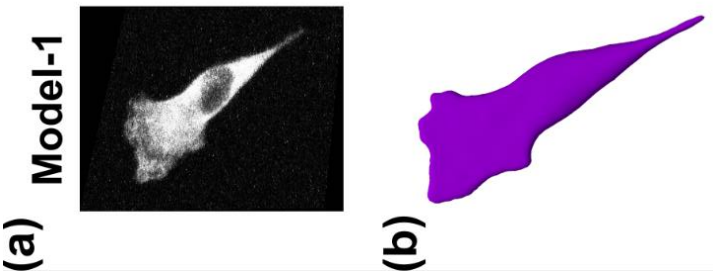

FIGURE 1. GEOMETRIES OF CANCER CELLS. (A) MICROSCOPIC IMAGES. AND (B) THE RECONSTRUCTED GEOMETRY

2.2 Cell geometries

Breast cancer cells (MDA-MB-231) were cultured on glass coverslips overnight in standard growth media as shown in Figure 1a (Model-1 and Model-2). They were then fixed with 4% paraformaldehyde and stained for focal adhesion protein paxillin. Individual cells were then imaged in full using a Leica Stellaris confocal microscope at 0.5 µm step size.

The 3D surface meshes were generated based on the confocal scans of the cancer cells. The images (TIFF files) were processed using the open-source imaging software 3D Slicer to generate the 3D mesh of the cell membrane by a sequence of thresholding. The final surface is exported to a triangular surface. The open-source software Meshmixer was used to manipulate the triangular mesh to control the mesh resolution while preserving the exact shape of the cell as shown in Figure 1b. Because the nucleus is inherently rigid, we represented it as a sphere and positioned it inside the interior volume of the cancer cell. The geometry of the cancer cell membrane and nuclear envelope are discretized using a triangulated mesh.

2.3 Flow Solver and Coupling Method

A network of non-linear springs is used to model the elasticity of the cancer cell (membrane and nucleus), in which each edge models the dynamics of the spectrin links [5]. At each vertex *i*, the dynamics of the membrane and nuclear envelop are derived from the nodal force, which is linked to Helmholtz's free energy at the same vertex *i*.

We use the three-dimensional, unsteady incompressible continuity and Navier-Stokes equations to govern the external plasma. To couple the CFD and DPD methods, we employ a two-way coupling approach with the curvilinear immersed boundary (CURVIB) method [6]. The discrete equations are integrated over time using a fractional step method. For solving the momentum equations, we use a Newton-Krylov solver in the momentum step, and a GMRES solver with a multigrid pre-conditioner is used for the Poisson equation.

2.4 FSI Simulation Setup

For each of the 3D surface meshes reconstructed based on the confocal scans shown in Figure 1, the cell membrane is released from the glass surface of the Petrie's disk suddenly to allow a relaxation toward the equilibrium condition as shown in Figure 2. These equilibrium shapes will be then used for all the subsequent Fluid-Structure Interaction simulations explained in below.

FIGURE 2. THE RELAXED SHAPE OF THE CANCER CELL

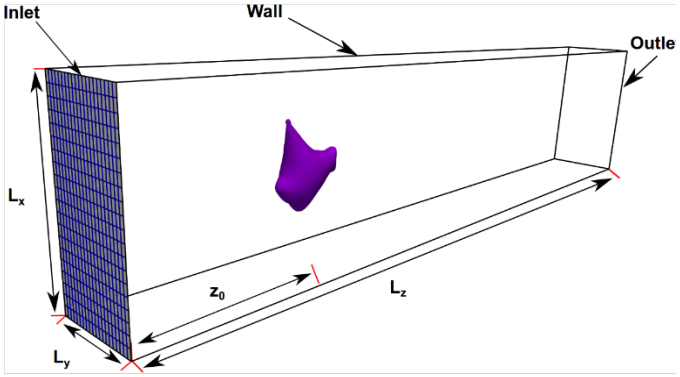

FIGURE 3. THE COMPUTATIONA DOMAIN

The computation domain is defined as a rectangular channel containing a single breast cancer cell as shown in Figure 3. The

dimensions of the domain along the x,y, and z directions are L_x (width), L_y (height), and L_z (length), respectively. The computational domain is discretized as a structured grid of size N_i x N_j x N_k with the spatial resolution in three directions (i,j,k) are $ Δx x Δy x Δz, respectively. The cancer cell is initially (t = 0) located at a distance z_0 from the channel's inlet as seen in Figure 3. An uniform flow is prescribed at the inlet with the magnitude U= 1mm/s.

3. RESULTS

3.1 Relaxation of cellular membrane

In Figure 2, we examined the response of the cancer cell models by performing a series of shape relaxation tests, aimed at reaching an equilibrium shape for each model. Our results pointed to a consistent behavior across all models of our cancer cells, as they all experienced a transient phase. Afterwards, the cell underwent a minimal deformation reaching the equilibrium state.

3.2 Deformation of the cancer cell under shear flow

The various time instances illustrate the shape deformation and highlight the significant influence of the flow across all cellular shapes, inducing substantial deformations characterized by pronounced stretching and compression of the cell membrane as shown in Figure 4.

The cell produces intricate and convoluted streamlines downstream of the cell in the extracellular fluid as shown in Figure 5. Additionally, the size and location of the vortex ring structure appeared to adapt in response to the morphological transitions of the cancer cells.

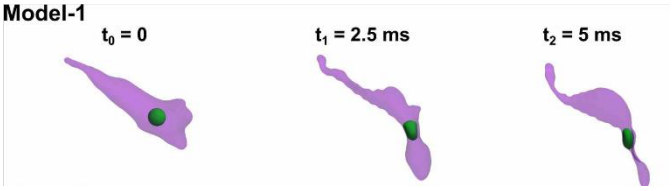

FIGURE 4. DEFORMATION OF CANCER CELL IN SHEAR FLOW

Notably, certain cancer cell models exhibit remarkable resistance to the predominant flow direction, demonstrating the capability to move in alternative orientations. It reorients and deviates from the streamwise flow direction, as it actively migrates towards the microchannel walls, instead of following the flow's axial velocity direction. Furthermore, the nucleus's behavior within the cell varies with shape. In instances where the cell adopts an elongated form, the nucleus showed a tendency to be confined within the membrane (Figure 4), with both elements maintaining close proximity. The nucleus exhibits a greater degree of mobility. It effectively retains its overall shape, experiencing compression only when approaching the cell membrane, where membrane-nucleus interactions are significant.

4. DISCUSSION

Extensive research efforts have been made to develop computational models, employing diverse numerical methods, to investigate various aspects of cancer cell transport in fluid flow. The ultimate aim is to uncover critical insights that can enhance our understanding of the intricate metastasis cascade. The Dissipative Particle Method (DPD) has been the popular choice for simulating various aspects of cellular dynamics. Xiao et al. (2023) [7] utilized the DPD method to explore the movement of tumor cells through symmetric bifurcated microvessels. Their findings underscored the significant influence of the initial position of circulating tumor cells (CTCs) on their flow trajectory. Cui et al. (2021) [8] employed the DPD method to investigate the adhesion behavior of CTCs within curved microvessels. Their results revealed that, in comparison to straight channels, CTCs exhibited a higher tendency to adhere to curved vessels. This phenomenon was attributed to the centrifugal force, which deviated CTC motion from the vessel axis and fostered CTC-wall interactions. Wang et al. (2023) [9] established a computational model for analyzing the transit of cancer cells through constricted microchannels using the finite element method. Their primary objective was to ascertain the minimum set of mechanical attributes necessary for quantitatively predicting the transient deformation of suspended cancer cells passing through narrow channels. Their findings highlighted that the hyper-elastic cell membrane model could accurately predict steady-state deformations in straight channels. However, to achieve excellent agreement with experimental results in transient cell dynamics, it was imperative to properly account for membrane viscoelasticity. While each of the aforementioned studies has provided invaluable insights, it's noteworthy that they all assumed an idealized spherical geometry for cancer cells.

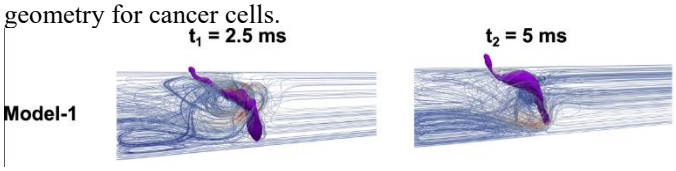

FIGURE 5. FLOW STREAMLINES INDICATE PATTERNS OUTSIDE OF THE CELLULAR MEMBRANE

5. CONCLUSION

In this study, we applied our novel framework, previously developed [5], which utilized a continuum-particle approach, to simulate the transport of realistic breast cancer cells within microchannels. These cell models were reconstructed from confocal scans of cancer cells on a flat glass substrate. An idealized spherical nucleus was placed inside each cell model. The cytoskeleton and cytoplasm, which describe the physical interaction between the membrane and nucleus modeled with a repulsive potential. Our findings demonstrate the exceptional efficiency of the hybrid numerical model in computing the

deformation of irregular tumor cell shapes and resolving the intricate flow field near the cell membrane. Furthermore, our results suggest that the response of cancer cells to fluid flow is primarily shape-dependent, with certain morphologies providing the cell with the ability to resist the predominant flow direction. Additionally, the mobility of the cell's nucleus was shown to be constrained by the shape of the cell's membrane.

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