Computational Investigation of Role of Platelets In Cancer Metastasis

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Recent studies suggest that platelets have a significant role in improving the survival of circulating tumor cells and aggravating cancer metastasis. The main function of platelets, as a blood constituent, is to bind to the sites of the damaged vessels and stop bleeding. However, in cancer patients, activated platelets adhere to circulating cancer cells in the bloodstream and exacerbate the metastasis process in different ways. We hypothesize that: (1) platelets can protect circulating tumor cells from being destroyed by the blood flow due to large deformations and high shear stress; (2) platelets can form a protective layer around the circulating tumor cells that prevent the white blood cells from recognizing and destroying circulating tumor cells, increasing the survival rate of circulating tumor cells; (3) platelets enhance the extravasation of circulating tumor cells by increasing the number of adhesion bonds to the vessel wall and by secreting vascular endothelial growth factor that increases the permeability of vessels. These hypotheses have been stated several times in the literature, but the underlying mechanism of the platelet-cancer cell is still a mystery. Hence, in order to test these hypotheses and to find new therapeutic methods to reduce metastasis outcomes, we investigated the interactions between circulating tumor cells, blood flow, and platelets via computational modelling at the cellular scale. We used the Lattice Boltzmann method to simulate the plasma flow, the Discrete Element Method to model the deformation of the cells, and the Immersed Boundary Method to allow interactions between the plasma flow and deformable cells. We defined cell-cell and cell-vessel wall adhesion forces based on a stochastic adhesion model. Our highly detailed computational model helps us to understand and explain these phenomena and provides an effective tool to design and test new potential therapeutic methods based on platelet regulation.

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Finally, I wish to thank all the people whose assistance was a milestone in the completion of this project.

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Dedication

This dissertation is dedicated to my parents, Mahmoud Anvari Naeini and Farahnaz Mohammadi, who always encouraged me to pursue my dreams.

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Chapter 1
Introduction

Cancer is among the leading cause of death in the world and metastasis is responsible for 90% of cancer deaths (1). The global estimates for only 2018 were 18.1 million new cancer cases and 9.6 million cancer deaths (2). Our knowledge of cancer, its progression, and the metastasis cascade is far from complete. Better quantitative analysis methods can help to advance fundamental understanding of the processes involved in cancer and can facilitate the development of novel therapeutic and diagnostic methods.

Metastasis is a multi-phase process in which tumor cells detach from the primary tumor and travel through the body by means of blood circulatory system and lymphatic system and form a secondary tumor in distant parts of the body (3–5). This complex process is coordinated at the sub-cellular level by biochemical signals such as growth factors, chemokines, metabolites, and at the cellular and tissue level by biophysical properties of cells and force-interactions between cells, extracellular matrix (ECM), and interstitial fluid (6–9). Furthermore, solid tumors have increasingly been recognized as organs rather than only a collection of cancer cells (10–12). These have led researchers to investigate cancer at different levels of complexity(6). In addition to *in vitro* and *in vivo* studies (13), which have helped us to understand genetic underpinnings of cancer, we need methods to quantify mechanical, chemical, and biophysical factors affecting tumor cells that are responsible for the progression and spread of cancer (14). In this regard, computational methods may help us to predict disease progression (15) and to discover novel targeted therapies (16).

Developing mathematical and computational models to simulate cancer and metastasis cascade has been the subject of active research in recent years (17). Statistical models (e.g. Markov Chain Monte Carlo (18)), probabilistic models (e.g. models of tumor cell proliferation and apoptosis (19)), game theory models (e.g. model of invasive tumor (20)) and physics-based models are some popular types of mathematical models of cancer. Physics-based mathematical models emulate and quantify biological processes involved in cancer metastasis and can help us understand different steps of the metastasis cascade (21, 22), and interpret experimental and clinical observations (23). Furthermore, performing experiments could be extremely costly and time-consuming (8); computational models can be immensely helpful in reducing the number of experiments and also, provide a guidance for effective design of those experiments (23, 24). With the help of computational models, one can also test different hypothesis and measure related parameters in situations where physical experiments is not possible.

Recent advances in computer technologies have made it possible to develop more realistic models with more parameters (25). In this section, we focus on computational models of biophysical processes in cancer metastasis such as tumor-induced angiogenesis, diffusion of nutrients and chemicals in tumors, mechanical stresses applied on tumors due to tumor growth, mechanical stresses applied on tumors cell during intravasation and extravasation, and circulation of tumor cells in the circulatory system. The mathematical and computational models focusing on therapeutic methods, drug delivery, and the immune response of the body to cancer are not covered in this review. There exist some excellent reviews of computational models of tumor growth and angiogenesis and their underlying mathematics (23, 26–29), but here we cover computational models and frameworks for all steps of the metastasis process and we classify the models and frameworks based on their targeted step of metastasis cascade as depicted in Figure 1. Some of the reviewed frameworks are open-source tools that have been modified over time and their applications have been expanded to cover more than one process in the metastasis cascade.

The metastasis cascade is considered as a four-step process along with tumor growth and tumor-induced angiogenesis as a necessary primary step (30). The mathematical representations of biological processes involved in metastasis and the computational approaches to solve them are discussed in Section 1.1. In Section 1.2, the models and simulations on tumor growth and angiogenesis, as a necessary initial condition for cancer metastasis, are reviewed (0^{th} step of metastasis). The models based on the transformation of normal tumor cells to invasive cells, and their migration and intravasation to the blood circulatory system (1^{st} step) are discussed in Section 1.3 followed by the review of the models of the circulation and movement of tumor cells within the circulatory system (2^{nd} step) in Section 1.4. The models of tumor-cell arrest and extravasation out of the circulatory system (3^{rd} step) as well as the models which can predict the most probable secondary cancer-sites are reviewed in Section 1.5. The simulations and models of tumor-cell invasion in intravasation (1^{st} step) and extravasation (3^{rd} step), as well as the ones for metastatic colonization (4^{th} step) are presented in Section 1.6. Finally, we reviewed the existing literature on the role of platelets in cancer metastasis and the related works in this field that support the underlying idea of our computational investigation.

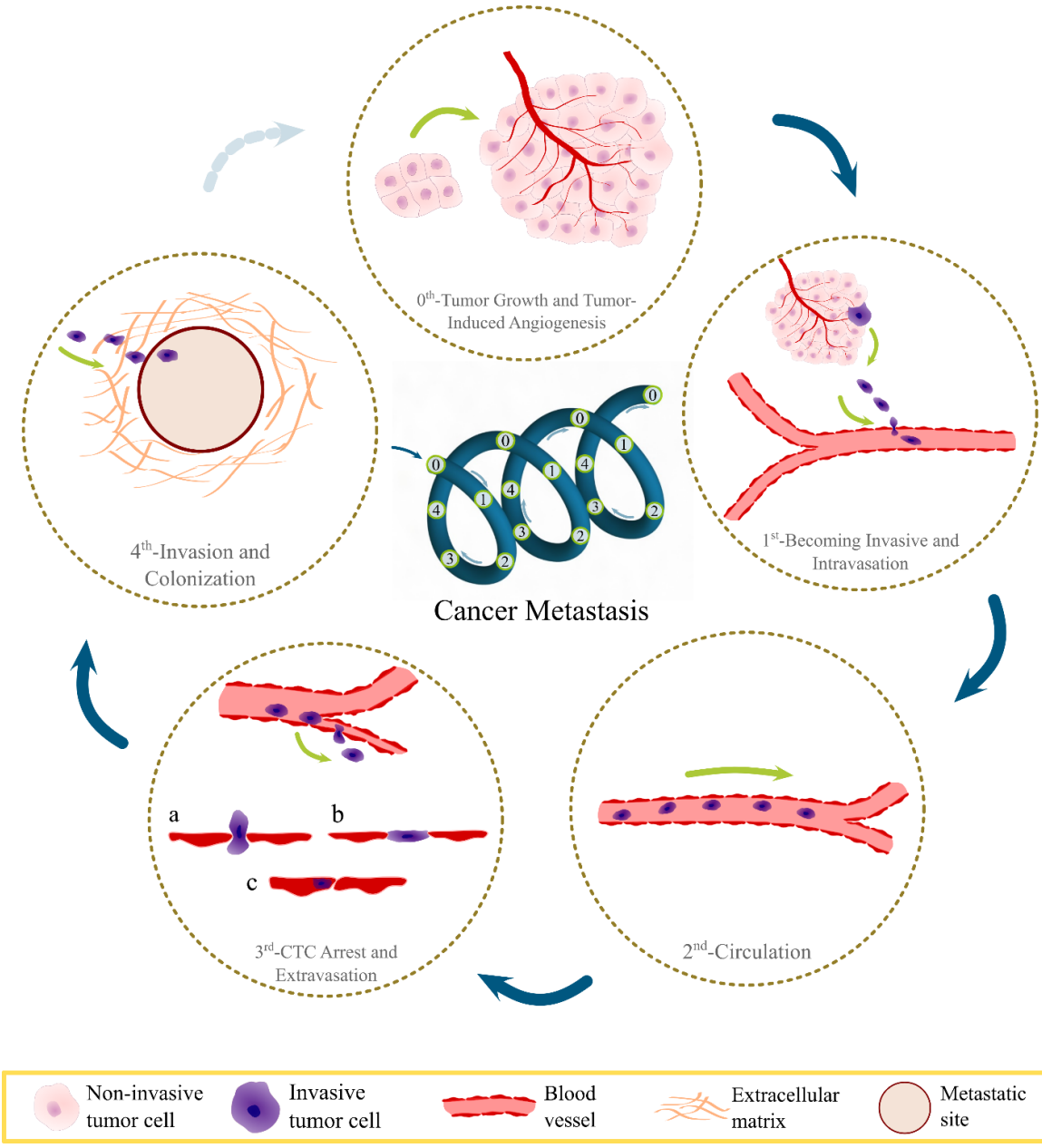

Figure 1- Metastasis Cascade: 0th step: Tumor growth and tumor-induced angiogenesis is the necessary step for initiation of metastasis. 1st step: Acquisition of invasive traits and intravasation into the circulatory system; 2nd step: Circulation of CTCs to travel to distant organs; 3rd step: Arrest of CTCs and extravasation out of the circulatory system (transmigration) by means of three different mechanisms: a) perivascular migration, b) mosaic process, and c) transcellular migration; 4th step: Invasion to the secondary cancer site, survival and proliferation to form a secondary tumor. The metastasis can progress by starting a new cascade from the secondary site and entering into a spiral of spreading (31). Concept of the illustration was partly adopted from (1, 7, 32).

1.1 Mathematical Basis of Computational Metastasis Models

Mathematical models represent physiological realities in terms of mathematical equations describing how physiological variables (e.g. hematocrit, the density of nutrients in a cell, or diffusion rate in tissues) vary as functions of time or space (Table 2) (33). Physics-based mathematical models can provide a means for obtaining quantitative understandings of cancer initiation, tumor growth, interactions between tumor and host tissue, and steps of metastasis. Numerous mathematical models analyzing different chemical, mechanical, and biological aspects of the metastasis cascade have been proposed in recent years. While some of these models focus on processes common in every step of metastasis like reaction-diffusion models (e.g. 34–37), others only focus on a specific phenomenon like the role of haptotaxis and chemotaxis in the invasion process (e.g. 38, 39). Excellent reviews solely focusing on different types of mathematical models, developed for cell-related processes, have been published (17, 40).

Biophysical processes can be modelled using discrete, continuum, and hybrid (multiscale) approaches, each of which has its advantages and disadvantages (41). Continuum mathematical models have been used to model the behaviour and evolutions of biophysical systems and with the advent of computers, scientists discretized these continuum models of systems and solved them numerically (25). This allowed numerical solution of some problems for which analytical solutions could not be derived. Owing to further advances in computers, computational models with discrete formulation principles (such as agent-based models), rather than discretized continuum models, were developed. Because such models directly deal with the discrete nature of systems, at the molecular level, they can be more accurate and closer to the reality than the continuum-based models (25). Table 1 summarizes important models in continuum and discrete categories as well as their advantages and disadvantages and their targeted metastatic steps and length scale. The computational cost of discrete models has restricted researchers from using them for complex systems (42) and has led to the emergence of hybrid discrete-continuum models.

1.1.1 **Continuum models** use systems of partial differential equations (PDEs) and ordinary differential equations (ODEs) to describe motions and changes in cell populations and chemical substances at the macroscale (43). Table 2 provides some common differential equations used in continuum models. PDEs describe spatially and temporally varying processes such as the reaction-diffusion process, representing the evolution of chemical concentrations or densities, while ordinary differential equations describe intracellular machinery in which only temporal variation matters and spatial variations are

ignored due to the confined infinitesimal intracellular space (43, 44). These models are computationally less expensive than discrete and hybrid models and they are suitable choices for investigating general behaviours of biological systems at the macroscale (such as cell volume fraction, ECM density, oxygen and nutrient concentrations (45)) where the properties of individual cells can be averaged over a group of cells of a given type and these properties are assumed to gradually change in space (6, 25). In addition to the crucial computational-cost advantage, continuum representations of biophysical processes are supported by fundamental physical principles. Therefore compared to the two other approaches, results are more reliable at the macroscale and they can be directly compared with experimental data (41). Because the continuum-based equations cannot be solved analytically in complex geometries typical to cancer problems, they should be discretized on the domain and then should be solved numerically. Therefore, as Table 1 shows, the computational approach for continuum models are solved using the finite-element, finite-difference and finite-volume methods (FEM, FDM and FVM).

1.1.2 Discrete individual-cell based models are suitable for simulations at the micro- and mesoscale (the length- and time-scales which bridge the gap between nanoscale and macroscale (44, 46)). In these models, each cell is considered as a separate entity with properties and variables (6) individually defined on a fixed lattice (e.g. CA method (47)), on an array of discrete fixed sites connected to each other with well-defined neighbors, or at discrete freely moving off-lattice particles (25). Since avascular tumors consist of tens to thousands of cells, discrete individual-cell based models are attractive for cancer modelling as they are particularly powerful for studying cell-cell and cell-matrix interactions. Table 2 shows some common mathematical formulations used in discrete models.

Lattice-based methods are commonly used in the simulation of biophysical phenomena, specifically for modelling deformations or rigid-body motions. One of the advantages of lattice-based methods is their perfect compatibility with rule-based models which can produce complex biologically mimicking patterns (48). Physical conservation laws and biological constraint have been used to create rules which govern the status of each computational mesh (19). Cellular Automata (CA) and Cellular Potts model (CPM) are the most common lattice-based methods which are used in simulation frameworks focusing on tumor growth and tumor deformation. These two methods connect the characteristics of the tumor directly to the properties of its constituting cells such as the physiological state of the cell (e.g. death, alive, dormant), cell deformation, and reactions to microenvironmental stimuli (25). In CA method, each lattice site represents one cell and the state and reaction of each cell are determined by governing rules based on the states of its neighboring cells (26, 47, 49). In contrast,

CPM uses several lattice sites to represent a biological cell to simulate the cell shape and its deformations with more resolution and accuracy (26). CPM uses governing equation, known as "effective energy", which should be minimized. This energy is a purely mathematical concept to model the behaviour of the cells and it has nothing to do with the real physical energy of the cells (6, 50). CA and CPM were designed for simulating a small biological entity, as a result, the computational cost can be prohibitive when simulating a complex biological system (50–52). On the contrary, off-lattice (i.e. particle-based) methods such as agent-based models and dissipative particle dynamics (DPD) models do not limit particles or cells to a fixed mesh at the cost of a greater computational complexity. In off-lattice methods (e.g. 53, 54) each cell is represented by individual non-overlapping points and the underlying mathematics is based on the potential energy of particles (6). DPD (55, 56) is an integration of Molecular Dynamics (MD) (42) method and Lattice-Gas Cellular Automata method (57) and is a good example of particle-based methods largely used for modelling isothermal systems at the mesoscale(58) (e.g. biological tissues(59)). Briefly, MD method studies physical movements of interacting particles (e.g. atoms and molecules) at the nanoscale by solving the equations of motion for all of the particles simultaneously (42) while Lattice-Gas Cellular Automata studies the physical interactions of groups of particles based on the conservation laws of mass and momentum (57). DPD considers the chemical bonds, steric repulsions, the viscosity of the medium and the size of the interacting particles (60, 61). DPD is faster than MD while more flexible than Lattice-Gas Cellular Automata.

1.1.3 Hybrid discrete-continuum models are classically defined as the coupling of a continuum approach with a discrete one. The advantages of discrete models are drawbacks of continuum models and vice versa (35). Hybrid modelling is widely used for complex phenomena due to their intrinsic multiscale nature (44). Both continuum and discrete approaches provide important insight into the cancer-related processes, however, to understand the relationship between cell-level and tissue-level phenomena at different length and time scales, we need multiscale (hybrid) approaches that use both continuum and discrete representations of tumor cells, tumor microenvironment and host tissue to couple the molecular and cellular scales to the tumor and tissue scales (19). Hybrid discrete-continuum modelling is capable of providing descriptions of microscopic mechanisms while efficiently simulating macroscopic characteristic (19). Irving et al. was first to develop the general theory of hybrid models to derive the continuum quantities in fluid mechanics as ensemble-averaged quantities of discrete particles using statistical mechanics (62). In biology, hybrid modelling is commonly used for

connecting continuum models including systems of partial differential equations and ordinary differential equations to discrete models such as CA and agent-based models.

As an example of hybrid modelling, Franssen et al. have recently proposed a novel hybrid framework which couples a discrete model of cell dynamics with a continuum model of abiotic factors discretized using FDM to describe all steps of the metastasis cascade (63). In this framework, a rule-based algorithm governed movement and proliferation of each alive cancer cell and survival of circulating tumor cells (CTCs) and CTC clusters in circulation was defined by probability functions. Although the framework did not consider several biophysical cell-related processes, it was an important step toward a comprehensive computational model of metastasis.

Table 1- Popular mathematical models in cancer research (6, 19, 26, 41, 48, 53, 55–58, 64, 65)

Model Type	Mathematical / Computational approach	Scale	Application in cancer research	Advantages	Disadvantage
discrete	Molecular Dynamics	nanoscale (atoms and molecules)	• cell mutation process • cell signalling • receptor-ligand interactions (1st and 3rd steps)	• high resolution • physics based down to the atomistic level	• Limited spatiotemporal domain size • High computational cost • tenuous connection with experiments
	Agent-based model (ABM)	mesoscopic and macroscopic large molecular complexes, extracellular networks, single and collective cells	• individual cell migration • tumor growth (1st, 3rd and 4th steps)	• simulation of interacting components at different scales • agents are meaningful entities allowing realistic simulations	• may not produce all biologically relevant phenomena at either small or large scales
	Cellular Automata (CA)	macroscopic tissue and tumor	• shape and structure of tumors and tissues • response to flow and forces (0th step)	• computationally efficient • suitable for modelling rule-based biological processes	• finite in space and cardinality • artificial constraints on arrangement and orientation of cells
	Cellular Potts model (CPM)	microscopic and mesoscopic single cells and small tissues	• morphology of individual cells • tumor growth and angiogenesis (0th step)	• cells modeled as deformable bodies • suitable for modelling rule-based biological processes	• finite in space and cardinality • high computational cost
	dissipative particle dynamics	mesoscopic scale	• complex fluids (fluid structure modelling) • blood flow modelling • biological membrane and tissues (2nd and 3rd steps)	• bridges the gap between nano (MD method) and macro (continuum methods) scales • continuous in space • large time and space scales	• hard to implement (equilibrium properties) • unable to model microscopic processes
	Lattice-Boltzmann (Based on LGCA)	mesoscopic and macroscopic scale	• blood flow modelling (2nd step)	• computationally efficient • easy treatment of complex geometries • large time and space scale • provides bridge to continuum methods	• large memory requirement
continuum	FEM FDM FVM	tissues and organs macroscopic scale	• evolution of chemical concentration in tumor • intracellular enzymatic and metabolic reactions • fluid-flow simulation (all steps)	• large physical domain size • underlying physical principles can be experimentally tested directly • supported by fundamental physical principals • computationally cost effective	• limited resolution for discrete biological entities

Table 2- Samples of mathematical representations of different biophysical phenomena

Physiological Process	Mathematical Representation	Description	model type	Targeted metastatic step (#)	Mathematical / Computational approach
change in extracellular matrix (ECM) density(35)	$\frac{\partial e}{\partial t} = -\alpha m e$	e: density of ECM α: ECM degradation rate by MDE m: density of MDE D_m: MDE diffusion coefficient β: MDE production rate by cells c: density of cells γ:MDE natural decay rate n: density of nutrient D_n:diffusion coefficient δ:production rate of nutrient φ: consumption rate of nutrient λ: nutrient natural decay rate	continuum	0, 4	Discretized by FDM or FEM
change in Matrix-Degrading Enzyme (MDE) density(35)	$\frac{\partial m}{\partial t} = D_m \nabla^2 m + \beta c - \gamma m$		continuum	0, 4	Discretized by FDM or FEM
diffusion of nutrients (oxygen)(35)	$\frac{\partial n}{\partial t} = D_n \nabla^2 n + \delta e - \varphi c - \lambda n$		continuum	0, 4	Discretized by FDM or FEM
cell invasion process(63)	$\frac{\partial c}{\partial t} = D\nabla^2 c - \phi \nabla .(c \nabla w)$	c: density of cells D: diffusion rate ϕ: constant haptotactic sensitivity coefficient w: ECM density Second term is related to haptotaxis	continuum	1, 3, 4	Discretized by FDM or FEM
cell migration (Langevin Dynamics)(35)	$m\frac{d\vec{v}_i(t)}{dt} = -\xi \vec{v}_i(\mathrm{t}) + \overrightarrow{f^R}_i(\mathrm{t}) + \overrightarrow{f^D}_i(\mathrm{t})$	$\vec{v}_i$(t) : Velocity ξ : effective friction coefficient $\overrightarrow{f^R}_i$: Random stochastic force $\overrightarrow{f^D}_i$: deterministic forces	discrete	4	particle-based methods
proliferation (probability)(19)	$\Pr(S(t+\Delta t) = \mathcal{P} \mid S(t) = \mathcal{Q}) = 1 - e^{-\alpha_p \Delta t} \approx \alpha_p \Delta t$ $\alpha_p = \alpha_p(S(t), \sigma, *, \blacksquare) = \begin{cases} \overline{\alpha_p}(*, \blacksquare)\frac{\sigma - \sigma_H}{1 - \sigma_H} & if\ S(t) = \mathcal{Q}, \\ 0 & otherwise, \end{cases}$	$\mathcal{Q}$: Quiescent state $\mathcal{P}$: Proliferative state $\mathcal{A}$: Apoptosis $S(t)$: the state of cell at time t σ: oxygen level σ_H: threshold oxygen leading to hypoxia $\overline{\alpha_p}(*, \blacksquare)$: cell's $\mathcal{Q}\to\mathcal{P}$ transition rate when σ=1 $\overline{\alpha_A}(*, \blacksquare)$: cell's $\mathcal{Q}\to\mathcal{A}$ transition rate $*$: cell's internal (genetic and proteomic) state $\blacksquare$: local microenvironmental conditions (except oxygen)	discrete (rule based)	0, 4	ABM, CA, CPM
apoptosis (probability)(19)	$\Pr(S(t+\Delta t) = \mathcal{A} \mid S(t) = \mathcal{Q}) = 1 - e^{-\alpha_A \Delta t}$ $\alpha_A = \alpha_A(S(t), *, \blacksquare) = \begin{cases} \overline{\alpha_A}(*, \blacksquare) & if\ S(t) = \mathcal{Q}, \\ 0 & otherwise, \end{cases}$		discrete (rule based)	0, 4	ABM, CA, CPM
cell adhesion (spring-based model)(66, 67)	$F(l^b) = k_s(l^b - l_0^b)$ $P_{on} = \begin{cases} 1 - e^{-k_{on}\Delta t} & l^b < d_{on} \\ 0 & l^b \geq d_{on} \end{cases}$ $P_{off} = \begin{cases} 1 - e^{-k_{off}\Delta t} & l^b < d_{off} \\ 0 & l^b \geq d_{off} \end{cases}$	k_s: spring constant l_0^b: equilibrium spring length l^b: distance between receptor and ligand $F(l^b)$: spring force (Hooke's law) P_{on}: probability of the formation of a new bond P_{off}: probability of the breakage of an existing bond k_{on}: association rate of forming a new bond k_{off}: association rate of rupturing an existing bond (see the reference for more information about k_{on} and k_{off})	discrete (rule based)	3	ABM, CA, CPM
blood flow(68)	$f_i(x + c_i\Delta t, t + \Delta t) - f_i(x,t) = -\frac{1}{\tau}\left[f_i(x,t) - f_i^{eq}(x,t)\right] + F_i\Delta t$	f_i: particle distribution function x: particle position c_i: particle velocity Δt: time-step size τ: nondimensional relaxation time f_i^{eq}: equilibrium distribution function F_i: external force term	discrete	2	Lattice-Boltzmann method

1.2 Tumor Growth and Angiogenesis (0th metastasis step)

Although tumor growth and angiogenesis (Figure 2-A) are not considered as steps of metastasis cascade, they are essential requirements (69). The chance of tumor cell entry into the circulatory system increases with tumor-induced angiogenesis especially considering the leaky and weak basement membranes of newly formed vessels that allow easier penetration of tumor cells into them (70, 71). Angiogenesis has a determinative role in cancer metastasis (72) and therefore prohibiting tumor-induced angiogenesis may have therapeutic values for metastasis (11, 73). In this section we discuss computational models and frameworks which were used for simulating tumor growth and angiogenesis. Numerous mathematical models have been proposed for different aspects of both avascular and vascular phases of the tumor growth (e.g. 74–77). Reaction-diffusion equations are the basis of continuum tumor models which describe the tumor cell density, the extracellular matrix, matrix-degrading enzymes, and concentrations of cell substrates (e.g. 78–80) and the related PDEs are usually discretized and solved using the finite difference method. Detailed reviews of mathematical models related to tumor growth and angiogenesis are available (81–83). In this section, we concentrate on more recent physics-based models and frameworks not covered in those reviews.

Non-uniform distribution of oxygen and nutrients along with diverse phenotypic responses of cells in interaction with host tissue, lead to heterogeneous growth of tumor (Figure 2-B) (74). Using a hybrid multi-parameter computational model of the heterogeneous proliferation of tumor cells across the three-dimensional tumor mass, it was shown that tumor growth can be portrayed as a predictable process which is dependent on cell velocity, adhesion forces, apoptosis, necrosis, and mutation (75). This study used a PDE derived from the law of conservation of mass assuming that cells are made up of only water while tumors are a mixture of dead and alive cells, interstitial fluid, and ECM (75). Through integrating mathematical models that described the status of oxygen and nutrients concentrations, a sophisticated 3-D multispecies model was proposed to investigate instability of tumor growth. This hybrid model focused on the role of tumor-induced angiogenesis and the effects of different parameters such as accessibility of oxygen on it (74, 84). Another hybrid computational model based on the laws of conservation of mass and momentum was used to study the interstitial fluid flow coupled with the blood flow inside a solid (85). In a more comprehensive study, tumor growth and angiogenesis were investigated in different spatiotemporal scales, using the CPM in a hybrid model, and the model was validated against *in vivo* experiments (Figure 2-C) (86).

Additionally, several studies based on the seminal works of Hanahan and Weinberg ("The Hallmarks of Cancer" (87) and "Hallmarks of Cancer: The Next Generation" (11)) have been done

using a combination of cellular automata for tumor growth and the Lattice Boltzmann method (LBM) for fluid flow in order to understand the role of different parameters in the tumor growth and angiogenesis (Figure 2-D). The final goal of these studies was to find the most significant hallmark (88) or a combination of them which could be knocked out to prevent tumor growth, angiogenesis, and invasiveness. Elimination of all of the hallmarks is costly and harmful due to the side-effects of the drugs so choosing the most effective hallmarks to knock out with the help of computational simulations is the best option (11, 87, 89).

Apart from the above individual simulations of tumor growth and tumor-induced angiogenesis, there are some computational frameworks which have been exclusively developed for this purpose. Tumorcode (continuum) is one of the frameworks designed specifically for simulating vascularized tumors. The lattice-based approach (90) employed in this framework makes it possible to generate the blood vessel networks and the tumor tissue at mesoscale and macroscale (Figure 2-E). Tumorcode simulates the vascular network and the bulk tissue of the tumor in the same space but in different lattices and then uses FDM and FEM to solve the equations related to tumor growth and the distribution of oxygen within the blood respectively. The framework can also model the fluid flow inside the vessels and the drug transport which are crucial in tumor-related studies. The vascularized tumor generated by this framework follows the topological, morphological, and hydrodynamic properties of real samples (91).

Cytowski et al (92) developed a novel large-scale hybrid computational framework named Timothy which allows 3-D simulations of cell colonies (like tumors) growing and interacting with a time-varying environment. Timothy's hybrid approach treats the cells as individuals located in a lattice-free space and the cellular environment as a continuum (Figure 2-F). Its high parallel scalability makes it possible to simulate systems consisting of 10^9 cells (93, 94). The discretization of the PDEs related to its continuum models was achieved by using an implicit in time finite-difference scheme. Furthermore, cell-cell interactions were modeled considering repulsive and adhesive forces and an algorithm was employed for rule-based cell-related processes (such as proliferation and apoptosis) to model discrete processes of individual cells (92, 93).

Additionally, because of the similarities between growth and angiogenesis in tumors and in other normal organs, general simulation frameworks developed for studying the growth and formation of normal organs, can be modified and used to investigate tumors. One of the popular computational frameworks for simulating the morphogenesis of a multicellular organism such as a tumor is CompuCell. This hybrid framework was developed based on three main elements: the CPM to model

the collective behaviour of cellular structures, a reaction-diffusion module to simulate the chemical interactions between cells and the ECM, and a set of differential equations to model gene regulations. CompuCell3D is the new version that can be used for 3-D simulation of tumor morphogenesis. Considering its remarkable ability to simulate cell-related biological processes such as cell-cell adhesion, cell growth, cell division and apoptosis, and chemotaxis and haptotaxis, the framework is suitable for simulating tumor growth and angiogenesis (Figure 2-G) (51, 95–97). Recently, another framework based on CPM has been developed which offers a user-friendly web-based graphical interface to adjust parameters of the cell-related processes and to visualize 2-D tumor growth (98).

CHASTE (Cancer, Heart and Soft Tissue Environment) is another general hybrid framework for simulating biological processes that can also be used for cancer. The framework is a C++ library that allows modelling different cell-related processes, mesh generation and solving general non-linear elasticity problems and ODEs and PDEs (Figure 2-H) (99). LBIBCell is another open-source simulation framework (hybrid) which employs both immersed boundary and LBM for modelling different phases and interactions in the tumor morphogenetic processes. In this framework, the cell membrane is modeled as a massless, purely elastic structure and the cytoplasm and ECM are modelled as viscous, Newtonian fluids (Figure 2-I) (100). The advantage of open-source frameworks (such as Tumorcode, Timothy, CompuCell, CHASTE, and LBIBCell) is their flexible application because they can be modified and improved for different objectives.

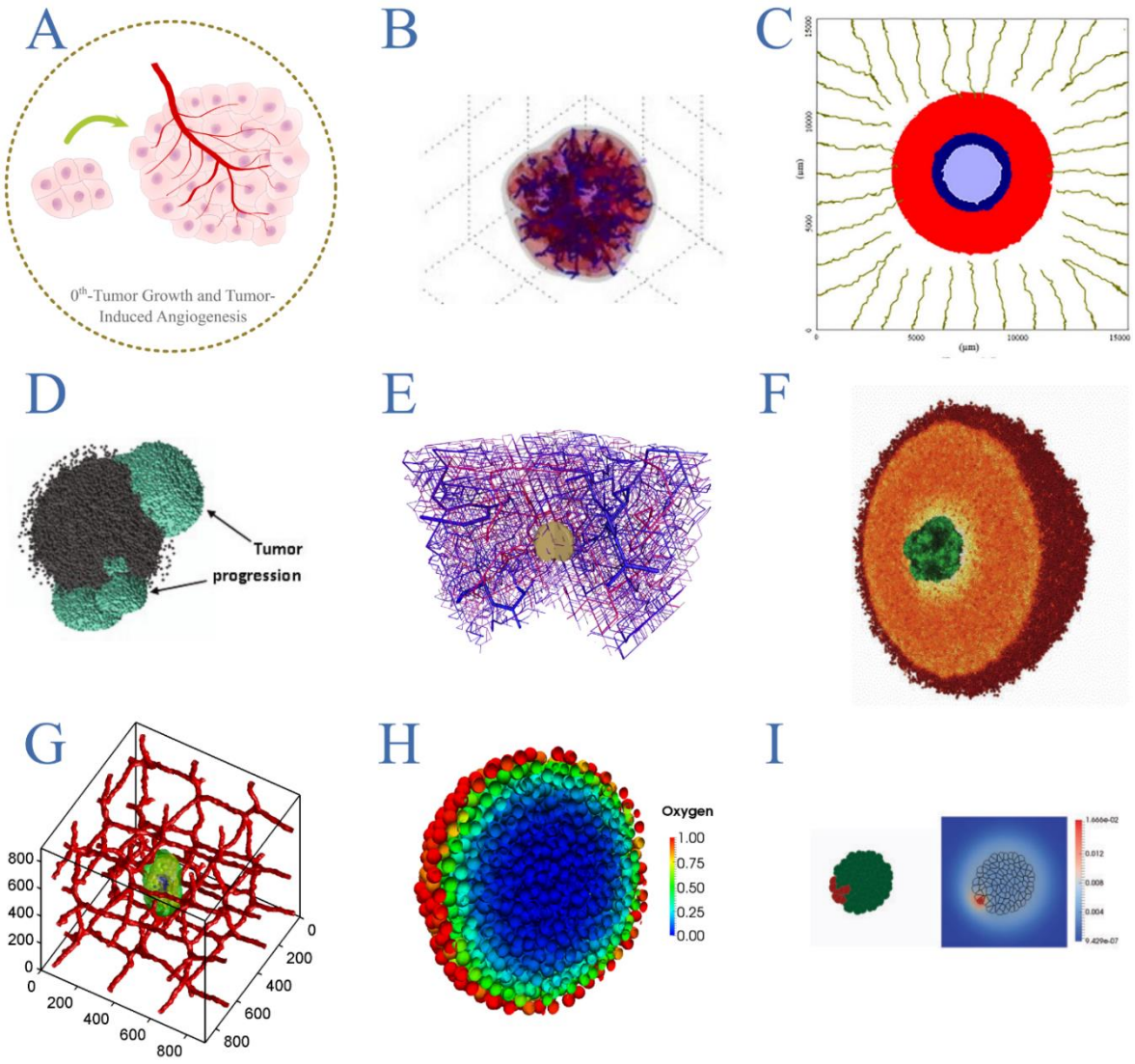

Figure 2- Computational models of tumor growth and angiogenesis: A) In the 0th step of metastasis tumor grows and vascularize; B) Simulation of heterogeneous growth of vascularized tumor with one viable cell species using a hybrid approach(74); C) Simulation of both avascular and vascular phases using CPM(86); D) Simulation of tumor progression using the CA method(88); E) Tumorcode can generate the blood vessel networks and the tumor tissue simultaneously (91); F) Simulation of growing solid tumor inside a healthy tissue using Timothy(94); G) Simulation of tumor growth and angiogenesis using CompuCell3D(97); H) Simulation of oxygen distribution in necrotic, dormant, and proliferating cell layers of tumor using CHASTE(99); I) Simulation of cell division and differentiation stimulated by mechanical and chemical signaling using LBIBCell(100)

1.3 Acquisition of Invasive Traits and Intravasation (1st metastasis step)

The metastasis cascade begins with the transformation of tumor cells from non-invasive cancer cells to cancer cells with extremely enhanced tumor-initiating potential (1). This transformation to invasive cancer cells significantly affects their mechanical properties (101). Invasive cancer cells have lower stiffness than benign ones and they are able to migrate and deform more efficiently (101–104). When a single tumor cell acquires an invasive phenotype and enhanced migration ability, it detaches from the primary tumor and initiates the metastasis cascade (72). Subsequently, these cells invade nearby tissues and intravasate into the circulatory or lymphatic system by entering the bloodstream and lymphatic vessels (Figure 3-A). Intravasation is the prerequisite of the 2nd metastasis step in which invasive tumor cells travel to distant organs of the body (1, 105).

We first review models and simulations related to phenotypic changes and genetic mutations at the molecular scale which happen during the development of the very first tumor cell and the development of invasive cancer cells. Then, we discuss the models of tumor cell detachment and intravasation into vessels from a mechanical standpoint that is chiefly investigated at the micro- and mesoscale.

To investigate phenotypic changes and genetic mutations of tumor cells, researchers investigated morphology and genetic properties of the cells at a subcellular level. IBCell is one of the computational frameworks which is able to simulate several steps of cancer metastasis (i.e., tumor growth (106), cancer mutations (107), and circulation of tumor cells in blood vessels (32)). It uses a continuum reaction-diffusion equation for simulating the density of nutrients in different locations and times. By considering cell proliferation, apoptosis, and adhesive forces between cells and ECM that control cell growth, IBCell can simulate phenotypic characteristics of cancer cells and the relationship between the histopathology of tumor cells and their underlying molecular defects (Figure 3-B) (107). Virtual Cell is another hybrid framework which considers the subcellular localization of the molecules in cell signaling and cell-related biochemical and electrophysiological processes. In addition to a graphical interface, Virtual Cell has a mathematical interface which allows direct mathematical model definitions and uses a web-based client-server system which makes it easy to use (108, 109).

Experimental studies showed that the concentration of epidermal and transforming growth factors can directly enhance the invasive traits of the cells (110, 111). Wang et al. conducted a multiscale agent-based simulation for investigating phenotypic changes due to epidermal and transforming growth factors at both molecular and multicellular levels (112, 113). Additionally, Lee et al (114) proposed a simplified 2-D continuum model of tumors for measuring biophysical alterations

(e.g. the migration rates of cells) during the transition of tumor from benign to metastatic (Figure 3-C). Although in reality tumor cells and ECM are separate from each other, in this model they were treated as a uniform continuum to be tractable with *in vitro* experiments.(114) Edelman et al. performed an excellent review on computational models of cancer initiation and progression process at the molecular level which included models of gene expression, cell signalling, and phenotypic responses (23).

In contrast to the mutation and phenotypic changes that should be investigated at the subcellular scale, the intravasation step should be studied at the mesoscale because of the larger spatial domain. There are two important processes involved in intravasation: cancer cell detachment from the primary tumor (Figure 3-D) and cancer cell penetration into the blood vessel (Figure 3-E). Both of these processes were modeled using cell-based FEM that not only simulated the movement of cancer cells but also predicted the mechanical forces required for tumor cell detachment and vessel penetration (115, 116). Using a forced-based multi-scale approach, cancer-cell penetration into the blood vessels can be investigated in more details. Ramis-Conde et al. proposed a hybrid computational model for trans-endothelial migration (Figure 3-F) (117). They considered three scales for investigating the intravasation process: the intra-cellular scale which included a system of ODEs for modelling the protein concentrations, the inter-cellular scale which used a modified Hertz theory to model cell-cell forces, and the extra-cellular scale which used the Langevin equation (Table 2) to model cell movement (Figure 3-F) (117). Comparing to other metastasis steps, fewer computational studies have been dedicated to tumor-cell intravasation (117). However, due to the similarities between tumor cell intravasation and extravasation, models proposed for extravasation can be minimal modified for intravasation (117).

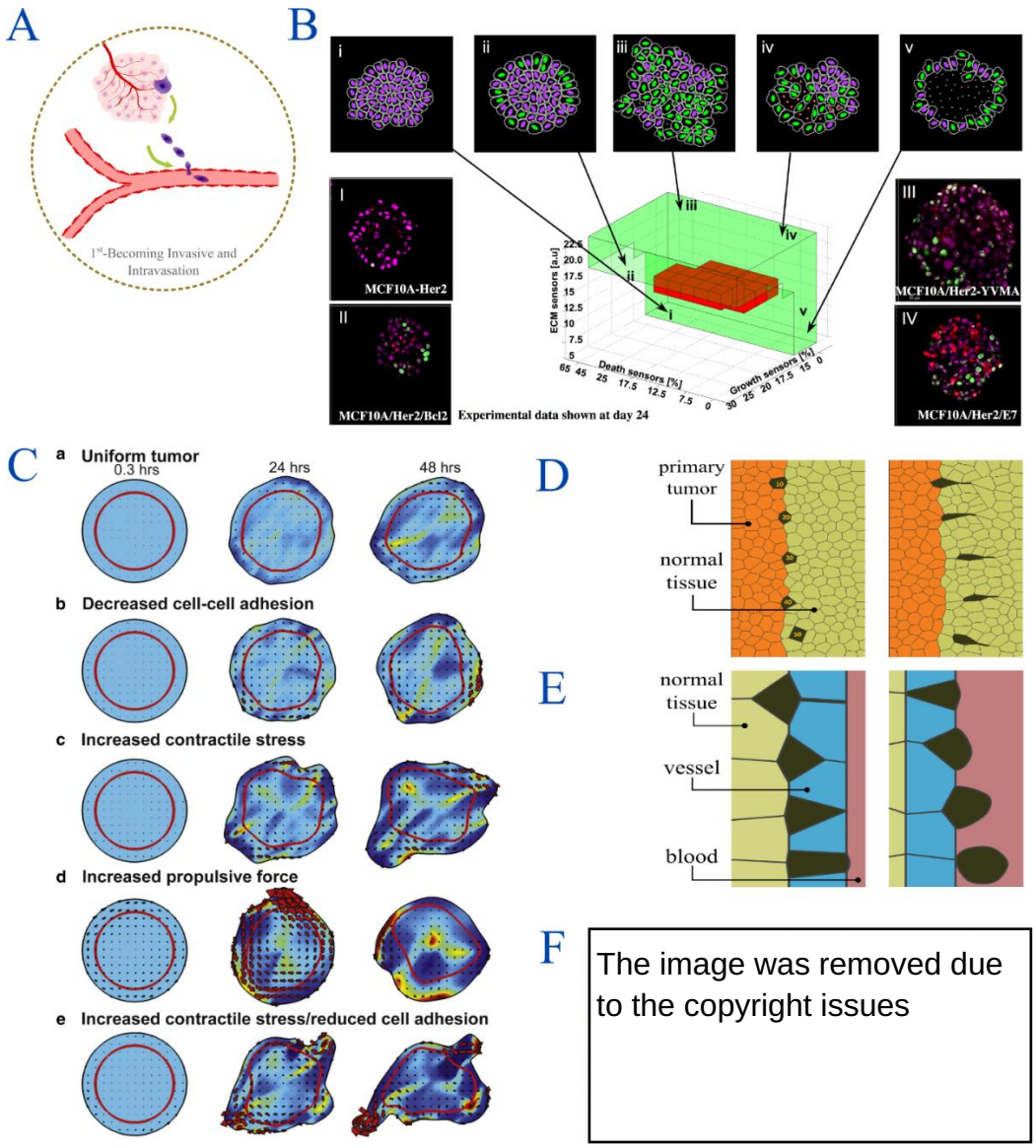

Figure 3- Computational models of invasive mutations and intravasation (1st step): A) In the 1st step of metastasis, cells of the vascularized tumor acquire invasive phenotype, invade nearby tissues and intravasate into the circulatory or lymphatic system; B) Simulation of invasive tumors based on the environmental factors and tumor-cell mutations using IBCell. Results of the computational model were comparable to the ones from experiments qualitatively(107); C) 2-D solid tumor model shows dynamics of the tumor as a result of genetic mutations of tumor cells(114); D) Simulation of tumor-cell detachment from a primary tumor and its migration through normal tissue using cell-based FEM(115); E) Simulation of intravasation process using cell-based FEM(115) F) Simulation of intravasation through trans-endothelial migration with focus on VE-cadherin bonds (green) and N-cadherin bonds (yellow)(117)

1.4 Circulation of Tumor Cells (2nd metastasis step)

Upon intravasation into the circulatory system, CTCs travel to different locations in the body in just a few seconds (Figure 4-A). Most of the CTCs could not make it to the microenvironment of the second organs as they do not survive during the travel in the circulatory system. CTCs die in the circulatory system maily because of the immune response, shear stresses applied by the plasma flow and other floating cells, and cell deformations (7). However, the small number of the CTCs which can attach to the vessel walls and extravasate out of the circulatory system (3rd metastasis step) are enough for initiating a secondary tumor. This makes the circulation phase a critical step in the metastasis cascade. Ideally, we should be able to study metastatic progress and predict the location of the secondary cancer site using simulations of the movement of the CTCs in the circulatory system, statistical models of metastasis or combinations of these two.

Metastasis steps and their models have overlaps and we classify and review them based on their main focuses, but the classification is not mutually exclusive. The models of adhesion are discussed in the extravasation step (3rd metastasis step) but because of the close relationships between the circulation and the adhesion processes, the frameworks which are covered in this section may include cell adhesion as one of the factors affecting the circulation. Mitchell et al (118) reviewed the computational models of effects of fluid shear stress on CTCs in the circulatory system including adhesion to the endothelium. King et al (119) used immersed finite-element method to simulate the blood flow and floating particles within it (Figure 4-B). They found that the CTCs, which had similar sizes and deformability properties to leukocytes, moved similarly to them in the blood vessels. Therefore, the models of the movements of the leukocytes can be considered as approximate models for movements of CTCs in the blood vessel and several authors used existing leukocytes models for studying CTC motion (e.g. 66). However, the properties of the CTCs are not the same in different types of cancer (72) and in some cases, the size of the CTCs are much larger than leukocytes (68). Takeishi et al (68) investigated the effects of the size of the CTCs on their motions in the vessels and the similarities and differences between their motions and those of leukocytes based on their sizes using a hybrid model which implement FEM for membrane mechanics, LBM for fluid mechanics, and IBM for coupling (Figure 4-C & D).

Furthermore, structural models of CTCs depend on the targeted metastasis step because mechanical properties of CTCs change dynamically in the metastasis cascade (120). In the circulation step, the CTCs can be simply modeled as linear-elastic materials (119) King et al (119) investigated the circulation of an individual tumor cell and a cluster of tumor cells (comprised of 2-5 cells) with computational simulation considering the collisions between the tumor cells and red blood cells (119).

Their hybrid physical model of circulation of tumor cells in the blood vessels included three components: tumor cells were modeled as a linear-elastic material (the Young's modulus of the cells was obtained using atomic force microscopy (121)), RBCs were modeled as a Mooney-Rivlin hyperelastic membrane (122) that contained cytoplasm which was modeled as a fluid with the same density as that of the blood plasma but with higher viscosity, and the blood plasma was modeled using the incompressible Navier-Stocks equation (119). The fluid-structure interaction between the blood plasma, RBCs, and CTCs was simulated using the immersed finite element method (123, 124) and for the RBC-RBC and RBC-CTC interactions, a Morse-type potential (125, 126) was assumed. In another hybrid study, circulation of the CTCs in the blood vessels was modeled using a combination of Lattice-Boltzmann method for simulating the blood flow in the vessels, deformable elastic spheres for simulating CTCs, and IBM for coupling the motion of the immersed objects such as RBCs and CTCs (127).

A comprehensive simulation framework should model blood-plasma flow, endothelium, RBC, leukocytes and CTC structures, and the interactions between them. IBCell (32) is one of the computational frameworks for modelling both circulation and adhesion process of the metastasis cascade. It uses a spring-based model for simulating the movements and deformations of CTCs and also the interactions between CTCs and the endothelial cells (Figure 4-E) (32). IBCell only considers the fluid phase of the blood (plasma) and does not include blood constituents such as RBCs, leukocytes or platelets and uses the IBM for modelling the interactions between the fluid and solid phases. It was employed to study different modes of cell movement such as rolling and crawling and to predict the required properties of CTCs to survive the circulation in the blood vessels (32, 120, 128).

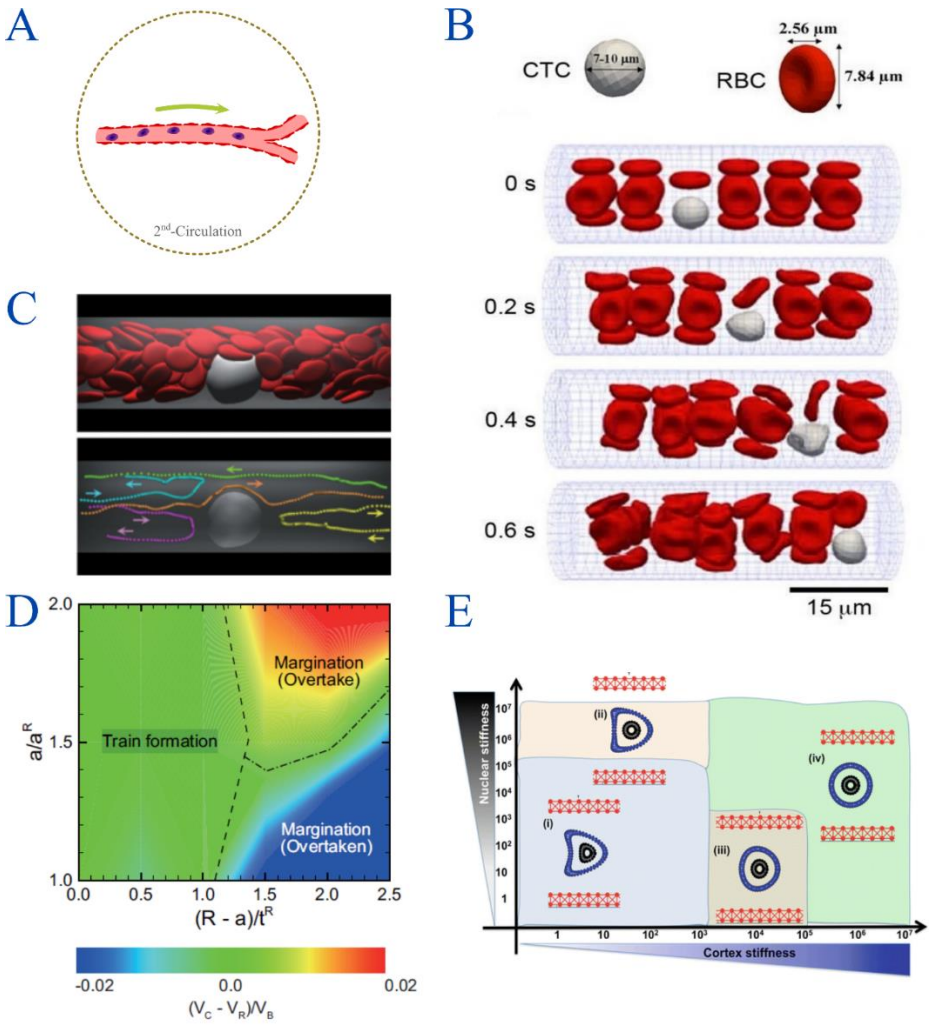

Figure 4- Computational models of CTCs circulation in the blood vessels (2nd step): A) CTCs intravasated into the blood vessels circulate in the body; B) Simulation of the motion and deformation of a CTC and RBCs within a microvessel using immersed FEM (119); C) Interactions between a CTC and RBCs in microvessels which leads to margination of the CTC(68) (simulations were done using FEM coupled to LBM via IBM); D) Using the same model as Panel C, three modes of CTC flow within the blood vessels including train formation: CTC velocity relative to the average velocity of the RBCs is almost zero, margination (overtake): CTC velocity relative to the average velocity of the RBCs is positive , and margination (overtaken): CTC velocity relative to the average velocity of the RBCs is negative . The modes depend on average velocity of RBCs [i.e., $(\boldsymbol{V_C - V_R})/\boldsymbol{V_B}$], hematocrit, and the size of CTCs [R is the radius of microvessel, $\boldsymbol{t^R}$is the thickness of RBCs, a is the radius of CTCs, $\boldsymbol{a^R}$is the radius of RBCs, $\boldsymbol{V_C}$ is the tumor-cell velocity, $\boldsymbol{V_R}$ is the average velocity of RBCs, $\boldsymbol{V_B}$ is the average velocity of blood] (68) E) Deformation of spring-based models of CTC with different cortex and nuclear stiffnesses under a steady blood flow using IBCell**(32)**.

1.5 Arrest of Circulating Tumor Cells and Extravasation (3rd metastasis step)

Adhesion to the vessel wall is the first step of tumor-cell extravasation out of the circulatory system (Figure 5-A) (129). This complex process depends on various mechanical, chemical and biological factors and it is hard to create a comprehensive computational model for it, partly due to the multitude of the parameters involved in the process. Adhesion of a circulating tumor cell determines whether and where the tumor cell will initiate a secondary tumor.

There are two main hypotheses explaining the patterns of metastasis progression and the location of the secondary tumor based on the most possible locations of tumor-cell arrest and the interactions with the microenvironment of the metastatic site. Paget (130) proposed the "seed and soil" hypothesis stating that a tumor cell (seed) metastasizes to an organ where the microenvironment (soil) is favourable. This hypothesis indicates that the metastasis outcome is not fortuitous, and the metastasis occurs only when the soil is perfectly compatible with the seed. On the other hand, Ewing (131) suggested that mechanical factors related to blood-flow patterns are solely responsible for metastasis and the number of metastatic tumors in a specific organ depends on the number of cancer cells reaching the organ and lodging in it (7, 132, 133). Experiments revealed that while the arrest of tumor cells in capillaries of distant metastatic sites can be ascribed to mechanical or anatomical factors, further reproduction and cancerous growth of tumor cells into distant organs depend on the organ microenvironment and adaptability of tumor cells (1, 3, 132, 134).

Almost all of the studies about tumor-cell adhesion to the vessel wall have used spring-based models with thermodynamics basis. Bell and coworkers proposed an initial simple mathematical model that described the adhesion process by employing a thermodynamic approach (135) focusing only on the rate of bond formations between cells (136). Their model considered a closed system containing two cells and introduced an equation to calculate the Gibbs free energy of this system in the adhesion process (137). Minimization of the free energy can determine the most probable state for cell adhesion in terms of the number of receptors on the cell, the contact area and the distance between the two cells. This approach indicates that if the distance between the cells is larger or smaller than the unstressed bond length, the bond is stretched or compressed which both lead to an increase in the internal energy which is similar to spring deformation energy (137). Later, the model evolved, was validated against experimental data and became more general encompassing other aspects of cell-cell adhesion such as the strength of the bonds (137). A more comprehensive mathematical model of the receptor-ligand adhesion was later proposed which simulated all of the phases of the adhesion process from the unencumbered motion of the cells to the firm adhesion. This model also considered the effects of

different parameters like the number of receptors, density of ligands and fluid-flow variables such as shear rate (67). The model has been commonly used (with some small modifications) for simulating receptor-ligand adhesion in different studies (e.g. 66, 138, 139).

The effects of wall shear stress and its gradient on the adhesion of CTCs in curved microvessels were studied using the LBM and Newton's laws of motion for simulating the flow and the movements of CTCs, respectively (138, 140). Also a modified adhesive-dynamics model which was based on the Bell's model and took into account the effects of sudden changes in the magnitude of the wall shear stress was presented for simulating tumor-cell adhesion (138, 140). Another hybrid study numerically examined the differences between the rolling motion and non-rolling bullet motion (motion in narrow capillaries with diameters comparable to the diameter of the tumor cell, Figure 5-B) using FEM, LBM, and IBM (141). The results of the numerical simulation suggested that in the bullet motion, the adhesion forces are equally distributed between bonds so that even for weak ligand-receptor bindings, bullet motion can lead to a strong adhesion to the vessel wall (141).

More recently, a hybrid modelling and *in vivo* and *in vitro* experimental study (142) was conducted to elucidate the effects of the blood flow on the arrest and extravasation of CTCs (Figure 5-C). Change in the endothelium structure during the extravasation process and the optimum conditions for a successful arrest and extravasation of CTCs were investigated in this study. They used AngioTK (143) for reconstructing vessels from medical images, modelled the blood flow using the incompressible Navier-Stokes equation and modelled the endothelium layer as a Saint Venant-Kirchhoff hyperelastic material (142).

In addition to individual CTCs, CTC clusters can exist in the bloodstream. CTC clusters are the result of either the detachment of a cluster of cells from the primary tumor and its migration into the bloodstream (144, 145) or the proliferation of tumor cells which are attached to the endothelium (145). In comparison with the same number of individual CTCs, a CTC cluster is more likely to survive in the blood vessels and to initiate a secondary tumor (32, 146, 147) because of its ability to protect innermost cells from immune responses (144) and shear stress, higher adhesion capability than individual CTCs (32), and possessing cancer cells of heterogeneous phenotypes (148). Rejniak et al (32) compared the adhesion probability and the effects of shear stress on individual CTCs and CTC clusters using IBCell (Figure 5-D). Anderson et al (145) studied the effects of the CTC cluster conformation and shape on its adhesion to vessel walls using the hydrodynamic feature of Multiparticle Adhesive Dynamics method. Phillips et al (149) developed a model for excessive blood coagulation induced by an individual CTC and a CTC cluster as a result of local thrombin generation. They used

the FEM to solve the incompressible Navier-Stokes equation coupled to a reaction-diffusion equation modelling thrombin generation. In this model, the individual CTC and CTC clusters were modeled as deformable entities inside the blood with surface tension at the interface.

Based on the experimental and numerical results of a study using commercial FV codes (150), the blood flow velocity, shear rate, and vessel shape are responsible for creating vorticity at the capillary intersections where tumor cell preferentially arrest. The study also highlighted the difference between mechanisms of adhesion of tumor cells and microbeads in capillaries which led to different favourable sites of the arrest (150). Arrest and distribution of micro and nanoparticles in the capillaries may have promising applications in drug delivery and therefore they were studied in detail employing commercial FV codes in order to find the effects of flow-dependent factors (151). However, to study the effects of more complicated properties of blood like hematocrit, open-source frameworks employing methods such as DPD (61, 152) integrated with a spring-based model for simulating the adhesion should be used. Such models were able to simulate two critical phenomena in the blood vessels: the aggregation of RBCs and margination of leukocytes (66). The models of margination of leukocytes can be adopted to simulate the migration of nanoparticles and CTCs (66, 153).

After anchoring to the endothelium, CTCs start to extravasate out the vessel through a drastic shape-changing process called transmigration (Figure 5-E). There are three types of CTCs transmigration through the endothelial vessel wall: perivascular migration (or paracellular trans-endothelial migration) (Figure 5-A-a), mosaic process (Figure 5-A-b), or the transcellular migration (Figure 5-A-c) (32). In the perivascular migration, which is the most common type of CTC transmigration (129), CTCs must withstand a large elastic deformation. Because the process happens at the microscale, DPD method was used to investigate the effects of cell elasticity, cell shape, and cell size during the cell passage (Figure 5-F) (139, 154). Additionally, Yingling et al (155) used NetLogo, an agent-based simulation (discrete) package, for investigating cellular behaviours during transmigration of CTCs. NetLogo is a web-based multi-agent programmable modelling environment which can be used for simulating biological phenomena.(156) Furthermore, the effects of cell adhesion on the transmigration of leukocytes and CTCs (54) and the thresholds for the rupture of nuclear envelopes in the plastic deformation of cells were investigated in two different studies using FEM (Figure 5-G) (157).

In addition to physics-based models, there are several statistical models which can be useful for predicting the location of the secondary tumor sites in the metastasis cascade. Markov chain Monte Carlo (MCMC) was used to apply the discrete Markov chain equations to autopsy datasets of cancer

patients and to calculate a transition matrix consisting of elements representing transition probability of the metastatic pathways between primary and secondary cancer sites. The important point regarding this method is that the algorithm did not converge to a solution unless a multi-directional (instead of unidirectional) connections for metastasis pathways from site to site was assumed (15, 18). On the other hand, a network-based modelling approach can be implemented to predict the primary cancer site employing the sequence of metastasis, multinomial logistic regression and an algorithm designed and trained with autopsy data (158).

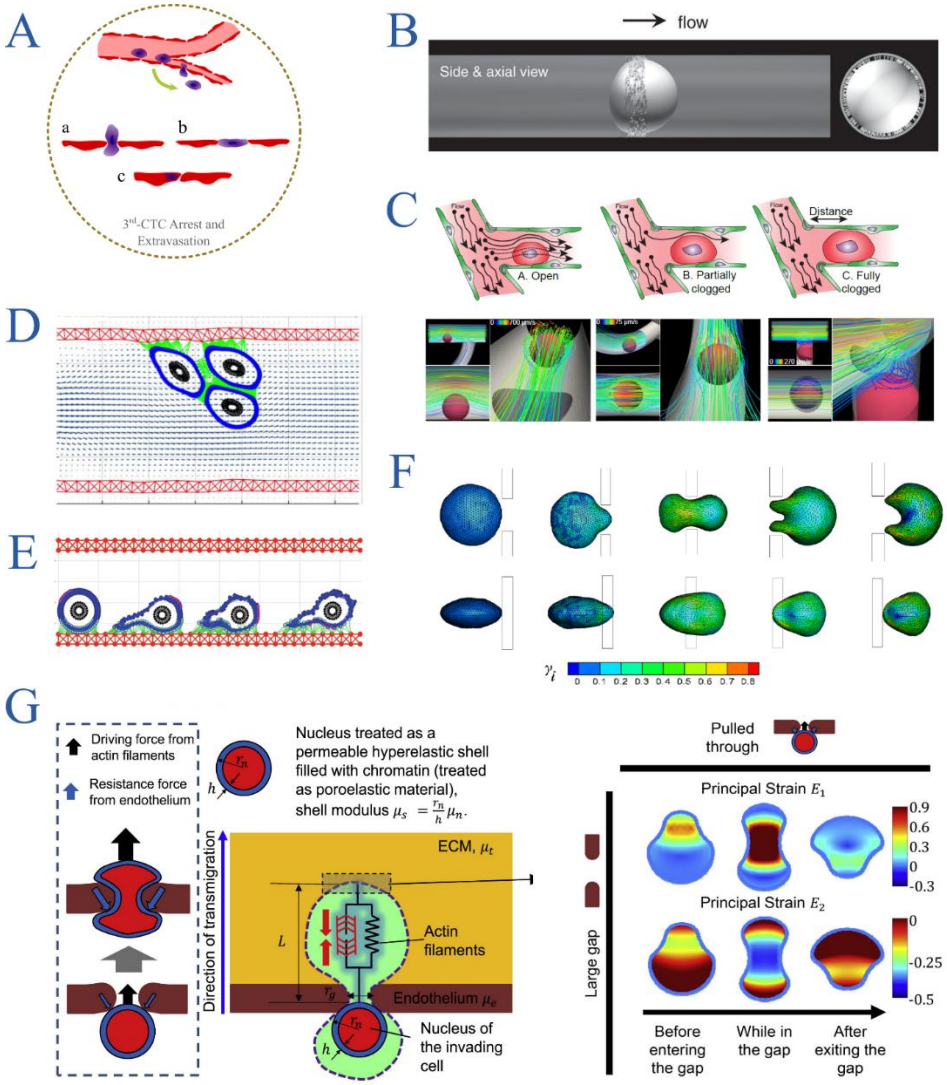

Figure 5- Computational models of arrest of CTCs and their extravasation out of the vessels (3rd step): A) Three mechanisms of extravasation: a) perivascular migration, b) mosaic process, and c) transcellular migration; B) Simulation of the bullet motion and arrest of a CTC in small capillary due to ligand-receptor binding(141); C) simulation of blood flow around an arrested CTC in three different clogging scenarios(142); D) Simulation of the arrest of a CTC cluster using IBCell**(32)** E) Simulation of a CTC crawling on the endothelium and its arrest using IBCell**(32)**; F) Cell deformation during migration through a narrow slit from front view (the upper row) and top view (the lower row)(154); G) Computational model for tumor-cell transmigration with a focus on deformation of the nucleus modeled as a permeable hyperelastic shell filled with poroelastic material ($\mathbf{E_1}$is in the direction of transmigration, $\mathbf{E_2}$ is aligned perpendicular to the transmigration direction)(157)

1.6 Invasion, Survival at Secondary Tumor Site, and Colonization (4th metastasis step)

Invasion occurs through several steps of metastasis: intravasation into the blood circulatory system, extravasation out of the vessels, and invasion of the microenvironment of the secondary cancer sites (Figure 6-A). We chose to discuss all models and simulations related to the invasion process in this section. Invasion process depends on several factors which are important in mathematical modelling: discharging the matrix-degrading enzymes, cell proliferation, cell-cell adhesion, and cell-matrix adhesion. A great number of mathematical models have been proposed for the invasion process investigating the effects of different factors such as chemotaxis, haptotaxis, ECM density and adhesion on the tumor-cell invasion (e.g. 34, 159, 160, 160, 161).

The invasion step of metastasis cascade can also be modeled using thermodynamics approaches. From a thermodynamics standpoint, every natural system (including biological systems) is an open system in thermodynamic interactions with the environment. These interactions are responsible for the formation, growth, and development of the system (162). Entropy generation approach was applied to describe the stationary state of tumors by focusing on cell proliferation and to describe transport processes and the interactions between cells and the surrounding microenvironment (163–165). Although the thermodynamic approaches were mainly used for studying and discovering new therapeutic methods(166), the thermodynamics equations could be integrated with other computational modelling approaches to develop more realistic models of invasion and tumor growth (e.g. 165).

In addition to mathematical models, there are some *in vitro* studies in conjunction with numerical simulation discussing the invasion process (a review of which was done by Y. Kam (167)) as well as different features and properties of the invasive cell. Fabry et al (168, 169) studied the magnitude and direction of the contractile forces exerted by invasive and non-invasive carcinoma cells during the invasion process in the simulated ECM. The study revealed that the direction of these forces is connected to cancer cell invasion, but the magnitude of the forces is not very important.

Because mathematical models of the invasion process include several ODEs and PDEs to be solved simultaneously, a proper invasion simulation framework must have a fast PDE and ODE solver. BioFVM (continuum) is a diffusive transport solver for biological problems which was used for modelling metastasis (170). An agent-based simulator (PhysiCell) based on BioFVM for modelling biochemical microenvironment and the interactions between the cells and the microenvironment was developed as well (171). A framework which connects gene perturbations and cell signalling to microenvironmental conditions and cell processes (e.g. migration and proliferation) has recently

become available as a combination of MaBoSS simulator (172, 173) (for intracellular signalling using Boolean modelling) and PhysiCell (for simulating the density of diffusing entities such as oxygen, glucose and growth factors as well as multicellular behaviour using an agent-based approach). This hybrid framework can simulate the invasion process properly and considering its ability to model the heterogeneous response to treatment and mutation effects, it seems to be the most complete framework for modelling cell invasion (Figure 6-B) (174).

Cell migration, the movement of the tumor cell through ECM and into and out of the vessel wall excluding the translocation of the cell by means of the circulatory system, is one of the fundamental phenomena in the metastasis cascade and specifically during the invasion process. It resembles the movement of leukocytes (175). The *in vitro* results of the mechanisms of cancer-cell migration through stromal ECM done by Carey et al (176) can be used to validate computational models. Like other cell-related processes, cell migration has been investigated in different length-scales and there have been several mathematical and computational approaches for studying it. Zaman et al (177) developed a hybrid computational 3-D model for cell migration using force-based dynamics. The model considered the force generation, polarity, and adhesion between ECM and cells and it calculated the total force on the centroid of the cell at discrete time steps (Figure 6-C & D). Some of the frameworks discussed in previous sections (e.g. CompuCell) model cell migration as well. For older studies (not covered here), refer to comprehensive reviews about different types of migration mechanisms and computational cell-migration models integrated with *in vitro* and *in vivo* measurements (178, 179).

The metastatic colonization process in a distant organ is similar to tumor growth and angiogenesis step and the mathematical models used for that step can be adopted for modelling colonization (180). However, because for the close metastatic sites the growth of metastatic tumors is affiliated with the primary tumor (181), we should consider these affiliations in simulations. Baratchart et al (181) proposed a group of continuum computational models for simulating the growth of secondary tumors. They simulated the global dynamics of metastasis development as interactions within and between the metastatic sites as well as with the primary tumor and were validated against experimental data (Figure 6-E).

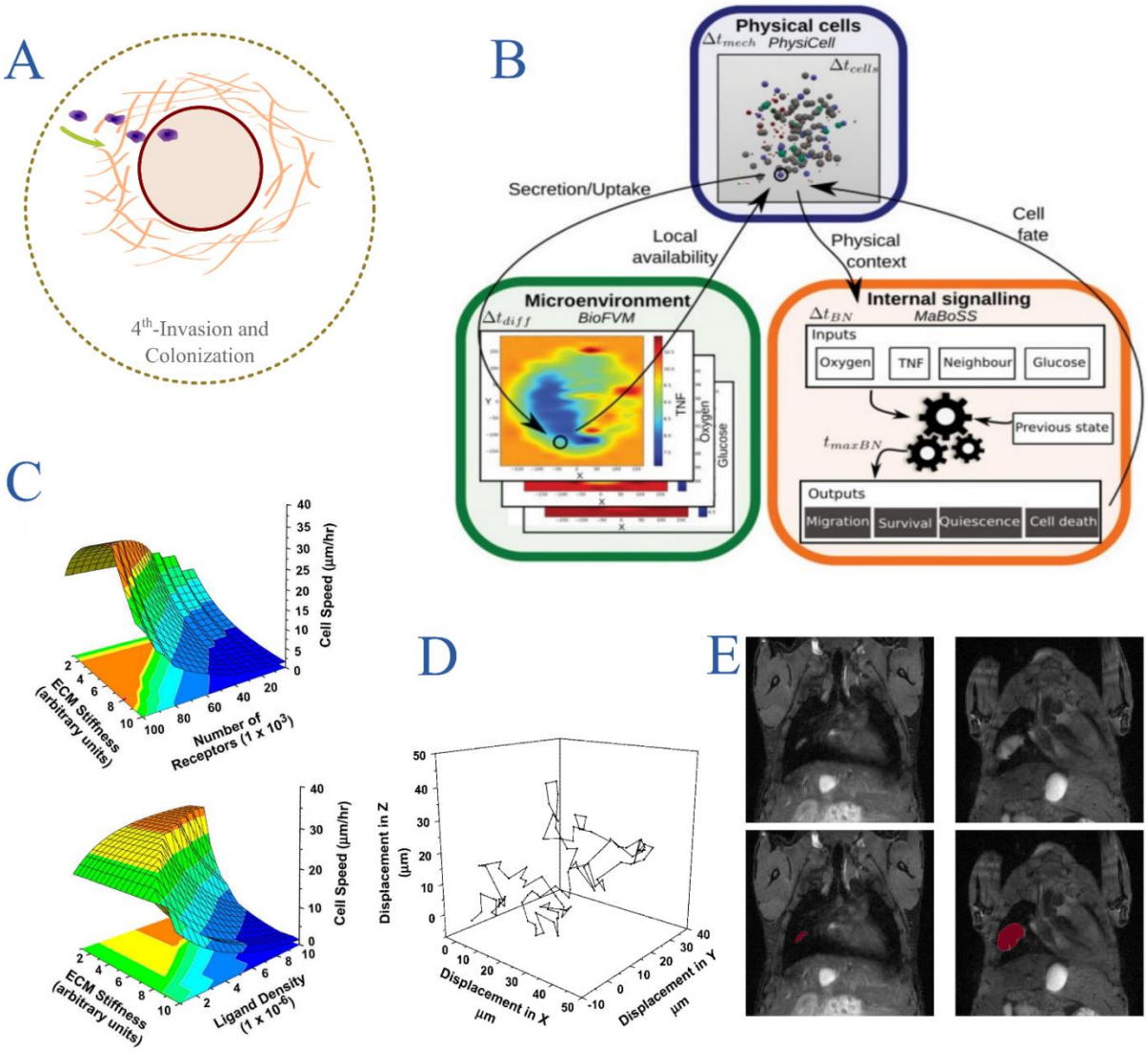

Figure 6- Computational models of invasion process and formation of secondary tumor (4th step): A) invasion of cancer cells to a distant organ and forming a secondary cancer site; B) Schematic representation of the relationship between the main components of PhysiBoSS framework: BioFVM, PhysiCell, and MaBoSS(174); C) Cell speed within the biological tissues is as an important characteristic of invasive cells and it is plotted as a function of ECM stiffness, number of available receptors (upper plot), and density of ligand (lower plot). The highest speeds occurred at higher number of receptors, intermediate ECM stiffness, and intermediate ligand concentration(177); D) Prediction of cell migration using a force-based dynamics *computational* model(177); E) Top: MRI data of the metastatic tumor growth in the lung. Bottom: Simulation of metastatic growth starting from the real shape of the tumor with a focus on spatial interactions of close metastatic sites(181)

1.7 Role of Platelets in Cancer Metastasis

Platelets are one of the blood components which contribute to the wound healing and hemostasis process by initiating a blood clot. Platelets have no nucleus, they have a round or oval shape, and their diameter is about two micrometers which is 2-3 times smaller than red blood cells (RBCs) (182). Platelets live around eight to ten days and the normal platelet count is between 150,000 to 450,000 platelets per microliter of blood which is approximately one-tenth of the number of RBCs (183). The main role of platelets is to stop bleeding when one of the blood vessels get damaged, by gathering together to form blood clots (184).

Trousseau established the link between the platelets and cancer for the first time in the nineteenth century (185). Trousseau observed excessive blood clotting in his patients who were diagnosed with cancer including himself (186). It is now well recognized that within the first stage of cancer (tumor growth), tumor secretes factors that stimulate and increase the production of platelets that leads to thrombocythemia (186). On the other hand, during the metastasis stage and chemotherapy, the platelet count decreases (186, 187). Both high platelet count and expression of coagulation factors by tumor cells are negative prognostic markers in different types of cancers (186, 188, 189). Platelets adhere to circulating tumor cells (CTCs) with receptor-ligand bonds and the attached platelets facilitate adhesion of the CTC to the vessel wall (186, 190). Furthermore, chemotherapy can suppress the number of circulating platelets by decreasing platelet production in the bone marrow (186, 191, 192). Consequently, the platelet count can be a useful biomarker to determine whether cancer is in the tumor growth, or the metastasis stage (187).

Cancer-related studies suggested the role of platelets in the metastasis cascade. When tumor cells detach from the primary tumor and intravasate into the blood vessels, there is a high probability that they are destroyed due to high shear stress exerted by the blood flow and the endothelium lining the blood vessels, or due to the immune response of the body (7, 118). However, it has been suggested that because the platelets adhere to CTCs with a receptor-ligand bond, immune cells cannot recognize CTCs and as a result, the survival rate of CTCs will increase (190, 193). Additionally, platelets can transfer the major histocompatibility complex to CTCs, which cause CTCs to mimic host cells and confound the immune cells (7). Nieswandt et al. (194) demonstrated that aggregation of platelets around CTCs inhibits the protective activity of immune cells. Therefore, minimizing the platelets-CTC microthrombi formation will lead to the attenuation of metastasis (193, 195). Additionally, even if leukocytes recognize CTCs by any chance, they do not have access to destroy them because platelets act as a barrier in front of them (190). In this respect, the platelet shield around CTCs has been proposed

to protect CTCs from shear stress by reducing the exerted force on the membrane of the CTC (196). Furthermore platelets are able to induce several factors (such as platelet-derived growth factors) which can stimulate and accelerate epithelial to mesenchymal transition in CTCs (197, 198). Thus, CTC-platelets interactions can lead to more efficient migration of the CTCs and the CTCs will extravasate out of the circulatory system easier (194, 195, 199).

Additionally, Burdick demonstrated that there is a higher probability that a CTC that is surrounded by platelets adheres to the vessel wall (200). Furthermore, the activation of the platelet endothelial cell adhesion molecule-1 (PECAM-1, CD31), that modulates the junctions between adjacent endothelial cells and regulates the transendothelial migration of CTC, is additional help for firm adhesion and extravasation of CTC (201–203). Stoletov et al. proposed that CTCs secrete vascular endothelial growth factor (VEGF) during intravasation which results in the permeabilization of microvessels which expand the space between two neighboring endothelial cells (204). Knowing that platelets can secrete VEGF as well, CTC-platelet interaction increases the possibility of successful extravasation of CTCs due to the higher permeability of microvessels (190). Altogether, the interactions between platelets and CTCs can lead to an increment in the survival rate of CTCs, enhancing the extravasation of CTCs, and raising the number of metastatic tumors. Therefore, because platelets have a major role in the cancer metastasis process, they can be targeted for developing novel therapeutic methods (205).

There is solid experimental evidence that thrombocytopenia caused by either platelet depletion with anti-platelet drugs or by defective platelet production significantly reduces the metastatic tumors. Borsig et al. (199, 206) showed with an experiment that heparin treatment attenuates cancer metastasis in mice by inhibiting selectin- and integrin-mediated interactions of platelets with carcinoma cell-surface ligands. By comparing two groups of mice, they proved that a single injection of heparin can impair CTC-platelet interactions and greatly reduce the metastasis outcome (206). Inhibiting CTC-platelet interaction was further studied experimentally using aspirin (207), prostacyclin (PGI_2) (208), dipyridamole (209), which led to reduced metastases. In addition to experimental studies, there are physics-based computational models designed to emulate and quantify biological processes involved in cancer metastasis. Lenarda et al. studied the mechanics of CTC's adhesion process and the effect of CTC stiffness on the adhesion with a computational model (210). Dabagh et al. employed a computational model to examine the underlying mechanisms of rolling motion and firm adhesion of CTCs in the microvasculature (211, 212). The interactions between CTCs, platelets, and endothelial cells mainly rely on the cell-cell adhesion bonds, and there exist several studies on modeling receptor-

ligand bonds with computational models. Almost all of the studies about CTC adhesion to the vessel wall have used spring-based models for simulating the adhesion forces. Bell and coworkers proposed an initial simple mathematical model that described the adhesion process by employing a thermodynamic approach (135) focusing only on the rate of bond formations between cells (136). Later, the model evolved and was validated against experimental data and became more general encompassing other aspects of cell-cell adhesion such as the strength of the bonds (137). A more comprehensive mathematical model of the receptor-ligand adhesion was later proposed which simulated all of the phases of the adhesion process from unencumbered motion of the cells to firm adhesion. This model also considered the effects of different parameters like the number of receptors, density of ligands, and fluid-flow variables such as shear rate (213). The model has been commonly used (with some small modifications) for simulating receptor-ligand adhesion in different studies (e.g. (66, 138, 139)). The effects of wall shear stress and its gradient on the adhesion of CTCs in curved microvessels were studied using the Lattice Boltzmann method and Newton's laws of motion for simulating the flow and the movements of CTCs, respectively (138, 140). Also, a modified adhesive-dynamic model which was based on Bell's model and took into account the effects of sudden changes in the magnitude of wall shear stress was presented for simulating CTC adhesion (138, 140).

Although the importance of the contribution of platelets in cancer metastasis has been in the center of focus in cancer research in recent years, the underlying mechanisms that initiate and support the interactions between CTCs and platelets are still unknown. Observing interactions between platelets, CTCs, and endothelium *in vivo* have not been possible experimentally so far and although there were suggestions of roles of platelets in metastasis, there has not been any quantitative study that could show the phenomena involved in the process. Computational models help us understand different steps of the metastasis cascade (22, 214) and interpret experimental and clinical observations (23). Furthermore, performing experiments could be extremely costly and time-consuming (8) and observing some phenomena at the sub-cellular scale is not feasible. Computational models can greatly help obtaining understanding and the discovery of new treatments by reducing the number of required experiments and by guiding the design of physiological experiments (23, 24).

In this work, we used a computational model to study the motions of platelets and CTCs in the plasma flow and their interactions with one another, RBCs, and the vessel wall. We used a modelling approach based on first principles and *a priori* knowledge to shed some light on these interactions and to our best knowledge, this is the first study that tries to quantitatively show the dynamics of interactions between platelets and CTCs. Our computational model considers blood plasma as an incompressible

fluid solved using the three-dimensional Lattice-Boltzmann Method (LBM) and considers cells as deformable bodies modelled using a coarse-grained spectrin link membrane approach. Coupling the fluid solver with the coarse-grained model was done using the Immersed Boundary Method (IBM) and enabled modelling of different biophysical interactions in mesoscale including the transport of CTCs in the microvasculature and receptor-ligand interactions between CTC, platelets, and endothelial cells. Details of the computational method and the underlying mathematical models that we used in the simulation are brought in Chapter 2. The results of our model that shows the effect of platelets in physiological cancer-related processes are brought in Chapter 3. We discussed our findings and we validated our model against several experiments on the platelet-aggregation inhibitor drugs that highlight the role of platelets in cancer metastasis and especially the arrest and extravasation process of CTCs in Chapter 4. The conclusion and the suggestions about the future works in this field are mentioned in Chapter 5.

Chapter 2

Materials and Methods

Because the aim of this study was to investigate the behaviour of individual cancer cells in microcirculation, we modelled the blood as suspension of deformable cells (RBCs, platelets, CTC) in a viscous plasma flow. Furthermore, in microcirculation, the rheology of blood is highly dependent on the behaviour of individual cells and their interactions in the flow (215). We modelled the plasma as an incompressible Newtonian fluid using the lattice Boltzmann method implemented in Palabos open-source code (Ver 2.0r0) (216). We modelled deformable cells (RBCs, platelets and CTCs) using solid Discrete Element Method (DEM) (216) in interaction with the plasma flow via the Immersed Boundary Method (IBM) (217) using the HemoCell open-source code (Ver 2.1) (183, 218–220) augmented in house to allow modelling of adhesion. Different modes of cell motions (such as parachute motion, aggregation of RBCs, and margination of platelets) in HemoCell were already validated against experimental data.

2.1 Plasma flow model using Lattice Boltzmann Method

The basis of the LBM formulation, we used in this study, was proposed by Bhatnagar, Gross, and Krook (BGK) (221) and revised by Chen and Doolen (222)

$$f_i\left(\vec{x}+\vec{e}_i\,,t+1\right)=f_i\left(\vec{x},t\right)+\frac{1}{\tau}\left(f_i^{eq}\left(\vec{x},t\right)-f_i\left(\vec{x},t\right)\right) \quad (1)$$

The *i* index indicates the discrete velocity direction, $\vec{x}$ is the position of the particle, t denotes the time, f_i^{eq} defines the equilibrium distribution function, $\vec{e}_i$ is the direction of the selected velocity, and τ is the relaxation time. Using the first two moments of the distribution function, the fluid density ρ and the macroscopic velocity $\vec{u}$ can be calculated at any site with the following equations:

$$\rho=\sum_i f_i \quad (2)$$

$$\vec{u}=\frac{1}{\rho}\sum_i f_i\vec{e}_i \quad (3)$$

The equilibrium distribution function was obtained from the Boltzmann distribution (223):

$$f_i^{eq}\left(\vec{x},t\right)=w_i\rho\left[1+3\left(\vec{e}_i.\vec{u}\right)+\frac{9}{2}\left(\vec{e}_i.\vec{u}\right)^2-\frac{3}{2}\vec{u}^2\right] \quad (4)$$

where the w_i indicates the grid dependent weight values. Based on Enskog-Chapman analysis (224) of the limit of long wavelengths, the above-defined system can be related to Navier-Stokes equation for incompressible flows with kinematic viscosity of $\nu = c_s^2\left(\tau - \frac{1}{2}\right)$ and an ideal equation of state: $p(\rho) = \rho\, c_s^2$ in which $p(\rho)$ stands for the pressure and c_s is the grid-dependent speed of sound with the assumed value of $\frac{1}{\sqrt{3}}$.

More information about the LBM implementation can be found elsewhere (225).

2.2 Cell deformation model using Discrete Element Method

The solid phase was modelled using a coarse-grained spectrin-link membrane model (220) modified from a model proposed by Fedosov et al. (226, 227). The advantages of this modelling approach have been discussed in the literature (226–228). In this approach the cell is modelled as a solid membrane discretized with triangular elements and its deformation is governed by reaction forces. Since the reaction forces originate from different features of the cells, the model assumes that for small deformations, the forces present a linear regime with different slopes. However, for large enough deformations, a quickly-diverging nonlinear term will come into effect (220). In the coarse-grained spectrin-link membrane model used in this work there are four types of forces each representing a specific mechanical behaviour.

1. The link force acts along the links and represents the reaction to stretching and compression of the underlying spectrin-network beneath the links. The formulation of the force presents a linear part corresponding to smaller deformations and a fast-diverging nonlinear part which represents the limits of the material as the stretch approaches the persistence-length.

   $$F_{link} = -\frac{k_l dL}{\varpi}\left[1 + \frac{1}{\tau_l^2 - dL^2}\right] \quad (5)$$

   In equation (5), $dL = \frac{L_i - L_0}{L_0}$ is the normal strain (relative deviation from the equilibrium length of the surface element (L_0)), ϖ is the persistence-length of a spectrin filament that equals to 7.5 nm (229), and $\tau_l = 3.0$ is the relative expansion ratio at which the spectrin-network reaches its persistence length (220).
2. The bending force acts between two adjacent cell surface elements and represents the membrane reaction force due to the underlying cytoskeleton and the non-zero thickness of the spectrin-network. On each surface, the bending force is in the direction normal to the surface (220).

$$F_{bend} = -\frac{k_b d\theta}{L_0}\left[1 + \frac{1}{\tau_b^2 - d\theta^2}\right] \quad (6)$$

In equation (6), $d\theta = \theta_i - \theta_0$, and $\tau_b = \frac{\pi}{6}$ is the limiting angle. Using the micropipette aspiration[4] images (230), τ_b was calibrated for this problem and it was chosen to prevents unrealistic sharp surface edges.

3. The local surface conservation force represents the reaction of the membrane and the spectrin-network to stretching and compression. The local surface conservation force acts locally on each surface element and is applied equally to each of the three vertices of cell surface triangles and points toward the centroid of the triangles (220). It should be noted that this force is tangent to the surface of the triangles.

$$F_{area} = -\frac{k_a dA}{L_0}\left[1 + \frac{1}{\tau_a^2 - dA^2}\right] \quad (7)$$

In equation (7), $dA = \frac{A_i - A_0}{A_0}$ is the relative deviation from the initial area and $\tau_a = 0.3$ is the limiting factor to prohibit surface area changes more than 30% (220). For dA near 30%, the area force gets large enough to stop further expansion of the surface area. Large changes in the surface area can lead to permanent damages to the cell membrane (231).

4. The volume conservation force acts globally on all nodes of the cell and is responsible to maintain the quasi-incompressibility of the cell. The volume conservation force is toward the normal of the surface of each surface triangle.

$$F_{volume} = -\frac{k_v dV}{L_0}\left[\frac{1}{\tau_v^2 - dV^2}\right] \quad (8)$$

In equation (8), $dV = \frac{V_i - V_0}{V_0}$ is the relative deviation from initial volume and $\tau_v = 0.01$ is the limiting factor to resist changes in the cell volume. The volume of the cell should be preserved because of the law of conservation of mass (220).

k_l, k_b, k_a, k_v in the above equations are the parameters chosen to satisfy the mechanical single-cell experimental results. The above constitutive model described by Equations (5) to (8) was validated for the RBC and the values for parameters were reported using optical tweezers experiment (232). This model was also used for platelets with rough estimates of the mechanical properties (220). In the present work, we refined the mechanical properties of the platelets based on the results of the work of Haga et al. (233).

[4] A technique to analyze the biomechanical properties of individual cells or a tissue without damaging the sample

We also modelled CTCs using the above constitutive equations with the parameter values provided in Table 3. The mechanical properties of cancer cells differ from one type of cancer to another and even for a specific type of cancer, properties of cancer cells are different in an individual patient depending on the malignancy of the cancerous cells (102, 234). Generally, metastatic tumor cells are softer than normal tumor cells enabling them to deform more efficiently (234). Softer CTCs can deform and as a result, the contact area between them and the vessel wall expands which favours firm adhesion. Fedosov et al. (228) studied the movement of white blood cells in microvessels using a coarse-grained spectrin-link membrane model, similar to one used in the present work, and considered white blood cells to be one order of magnitude stiffer than RBCs (228). Based on the similarities between the mechanical properties of white blood cells and CTCs (68, 118), and the work of Fedosov et al. (228) on white blood cells, we considered the stiffness of the CTCs in our model to be about 10 times of the stiffness of the RBCs. This is consistent with the stiffness that Lenarda et al. (210), used for CTCs. Additionally, we studied adhesion of the softer and stiffer CTCs and discussed the stiffness effects in the Results section (Chapter 3).

2.3 Plasma-cell interaction model using Immersed Boundary Method

Because the fluid nodes in the LBM are on a structured Eulerian grid, whereas solid cells use Lagrangian grids, the grid of a cell may not coincide with the Eulerian fluid grid. We coupled the fluid and solid domains and modelled their interactions using the immersed boundary method (IBM) (217) implemented and validated with an efficient parallel design in HemoCell open source code (235, 236). The fundamental assumption in IBM is the no-slip condition at the solid-fluid interface. The Lagrangian node of the cell surface $x_i(t)$ exerts the force $F_i(t)$ to the adjacent Eulerian node X of the fluid based on the following equation (235, 236):

$$f(X,t) = \sum_i F_i(t)\,\delta\big(X - x_i(t)\big) \tag{9}$$

where $\delta\big(X - x_i(t)\big)$ is the discrete Dirac delta function. Then, the position of the particle is updated according to the Eulerian scheme with the following formulation:

$$x_i(t + \Delta t) = x_i(t) + u_i(t + \Delta t)\Delta t \tag{10}$$

where

$$u_i(t + \Delta t) = \sum_i u(X, t + \Delta t)\,\delta\big(X - x_i(t)\big) \tag{11}$$

The 1-D interpolation of the kernel functions ϕ, provides $\delta(r)$ as: $\delta(r) = \phi(x)\phi(y)\phi(z)$. For the simplicity and compact support, the formulation of the kernel function considered in this work is:

$$\phi(r) = \begin{cases} 1 - |r| & |r| \leq 1 \\ 0 & |r| > 1 \end{cases} \quad (12)$$

More information about the IBM method used in this work is available in (235, 236).

2.4 Description of Adhesive-Dynamics Model

For simulating the adhesion forces between platelets, CTC, and endothelial cells, we implemented an adhesive-dynamics model proposed by Hammer and Apte (213). This model was originated from Bell's model of adhesion (136) and simulates all of the phases of the adhesion process from the unencumbered motion of the cells to firm adhesion and considers the effects of different parameters like the number of receptors, density of ligands, and fluid-flow variables such as shear rate (213). This model has been commonly used (with some small modifications) for simulating receptor-ligand adhesion in different studies [e.g. (66, 138, 139, 237)]. It employs a stochastic Monte Carlo method integrated with kinetics models to simulate the formation and rupture of receptor-ligand bonds. The kinetics of the models is based on the Dembo model (238) which formulates the rate constants as a function of distance. The forward and reverse rates for the receptor-ligand bond are calculated using the following equations:

$$k_f = k_f^0 exp\left[-\frac{\sigma_{ts}(l-l_0)^2}{2K_BT}\right] \quad (13)$$

$$k_r = k_r^0 exp\left[\frac{(\sigma_b-\sigma_{ts})(l-l_0)^2}{2K_BT}\right] \quad (14)$$

In the above equations, $k_f^0\ and\ k_r^0$ are the unstressed forward and reverse reaction rates, $l\ and\ l_0$ are the stretched and equilibrium bond lengths, σ_{ts} is the spring constant in the transition state, σ_b is the spring constant in the bonded state, K_B is the Boltzmann constant, and T is the absolute temperature. Because of the complexity and huge calculation cost, we skipped the tethering phase of adhesion and we focused on the adhesion process led by integrin molecules and we chose the values of the adhesive dynamics model based on that. We assumed a small value for σ_{ts} in this work indicating that forward reaction is possible with $k_f^0 = 1000\ s^{-1}$ for adhesive molecules with considerable distance (213). This assumption is valid because we ignored the initial phase of adhesion starting with the tethering process that is led by selectin molecules.

The force applied by the receptor-ligand bond is assumed to follow the Hookean spring model,

$$\vec{F}_{bond} = \sigma_b(l - l_0)\hat{e} \quad (15)$$

where σ_b is the spring constant and $\hat{e}$ is the direction of exerted adhesive force of each bond that depends on the position of the adhesive molecules (defined by nodes) on the surface of CTC, platelets,

or the endothelial cells. For example the time-varying vector of $\vec{e}_{f_{PLT-CTC}} = \vec{O}_{CTC} - \vec{O}_{PLT}$ determines the direction of the adhesive force between platelet and a CTC where $\vec{e}_{f_{PLT-CTC}}$ is the direction of the force exerted on a platelet by an adhesive bond between platelet and a CTC, $\vec{O}_{CTC}$ is the position of the adhesive molecule on the CTC, and $\vec{O}_{PLT}$ is the position of the adhesive molecule on the platelet.
The probability of the formation of a new bond (P_f) and rupture of an existing bond (P_r) during the time interval Δt is calculated using the following equations:

$$P_f = 1 - exp(-k_f \Delta t) \quad (16)$$

$$P_r = 1 - exp(-k_r \Delta t) \quad (17)$$

For reducing the computational cost, we used a new method in this study for applying the results of the probability function on the model. Since the time interval chosen for probability calculation is very small (0.1 μs) relative to the simulation time, we defined a new parameter, the "effective force", to integrate the force of each adhesion bond and the probability of formation and rupture of the bond. The effective force (F_{eff}) of each bond equals the product of the calculated force of the bond (F_{bond}) multiplied by the effective probability,

$$F_{eff} = P_{eff} \times F_{bond}. \quad (18)$$

Given the small time step for calculating the probability and force of each receptor-ligand bond, the variables of the probability function do not significantly change and we can assume that $P_{f_t} \cong P_{f_{t-1}}$ and $P_{r_t} \cong P_{r_{t-1}}$ for formation and rupture of the bonds respectively. Therefore, for each bond we have,

$$P_{eff} = P_f(1 - P_r). \quad (19)$$

After calculating the effective force using the effective probability function on each bond, probabilities P_f and P_r are updated at each time step. Compared to the original algorithm (213), in addition to reducing the computational cost, this approach also increases the stability of the simulation without changing the outcome by preventing abrupt appearance and disappearance of forces at each time step. In this work, we only focused on the receptor-ligand type of adhesion between CTC, platelets, and endothelial cells, therefore we considered the same adhesion properties for all of them.

2.5 Time step

There are three types of time steps in our model: 1. fluid field (LBM) 2. fluid-solid coupling (IBM) 3. cell model (DEM) which includes about 4000 equations per cell equivalent to the number of nodes in the mesh configuration of the cell (239). The DEM is the most computationally expensive one among the three. When the maximum force at each time step in the domain is below a lower limit set by the

simulation, the time step for updating DEM can be increased (239). When the maximum force is between the lower limit and upper limit, the time step should not be changed and finally, when the maximum force is above the upper limit of the maximum force generated within the system, the time step for updating the material model should be decreased for providing an accurate and stable outcome. These limits are fine-tuned based on the geometry of the problem to guarantee a balance between performance and numerical stability (239). With this approach, the performance of the computation can be optimized because the computation time is strategically spent on the specific time intervals of the simulation that need finer time steps to reach an accurate and stable solution (225). In general $dt_{LBM} < dt_{IBM} < dt_{DEM}$ but in this work, because of the relatively large deformations and strong adhesion forces, we set both time steps of updating the DEM model of cells and calculation of IBM equal to the time step of the LBM. The time step for the LBM was set to 0.1 μs which is a common value in similar works (237, 240). Each simulation ran for 2,000,000 time steps which is equal to 0.2 seconds. The length of the simulation time is in order of similar works on cell adhesion (240, 241) and was calibrated to provide enough time window for the CTC to adhere to the vessel wall and to reach a stable condition.

2.6 Geometry and Boundary Conditions

The computational domain was a cylindrical microvessel with a diameter of 20 μm and a length of 40 μm and periodic boundary conditions in the axial direction at the base faces of the cylinder. The microvessel wall was considered to be smooth and rigid, which are acceptable assumptions for small blood vessels, with no-slip boundary conditions imposed with the bounce-back algorithm (210, 242). Poiseuille flow with Reynolds number of 0.025 similar to (210), was considered for initializing the simulation and the physical volume of a lattice unit was equal to $0.5 \times 0.5 \times 0.5\ \mu m^3$.

We considered the CTC to be a sphere with a diameter of 8 μm (103) and generated the mesh for it with 1382 vertices using the Mefisto algorithm in SALOME 9.3.0.. We employed the same software and the same algorithm for refining the mesh of an existing platelet geometry to have 1148 vertices.

HemoCell (version 2.0) does not have any collision detector function for solids and all the solid-solid interactions (cell-cell or cell-wall) are handled with the IBM solver and by the means of the lubrication effect of the fluid flow and therefore there was no repulsive force in the peripheral boundaries and the cells went out of the computational domain. We added a collision detector function that works in the peripheral boundaries and applies a repulsive force proportional to the momentum of the cell impacting the endothelium. In our simulations, we assumed the vessel wall to be rigid and did

not model its deformation, however, and owing to the fact that the impact always involves energy loss (243) and little rebounding of particles happen in in plasma flow (244), we chose the value of 0 for the cell-wall coefficient of restitution.

The initial position of the cells in the simulation was generated randomly using the PackCells toolbox of HemoCell. We generated the initial positions for 1 CTC and 17 RBCs equivalent to a hematocrit of 12% which is a physiological value in microcirculation. Since the margination movement of the CTC is quite similar to the white blood cell and it is widely studied in the literature (68, 118, 228, 245), at the beginning of the simulation, we intentionally put platelets near the CTC and put the CTC-platelet complex near the vessel wall to decrease the simulation time and to focus on the effect of the platelets on the CTC adhesion to the vessel wall. Figure 7-a shows a snapshot of the computational domain at t=0 including the streamlines of the plasma flow, RBCs, and a CTC. Additionally, Figure 7-b shows the velocity profile obtained at t=0. The seeds of the streamlines were uniformly distributed on the line source located at (x, y, z) = (10, 0:20, 10). The velocity profiles in the Figure 7-c shows consistency between the Poiseuille flow generated with LBM method in this study and the classical Poiseuille parabolic profile which can be found in (246).

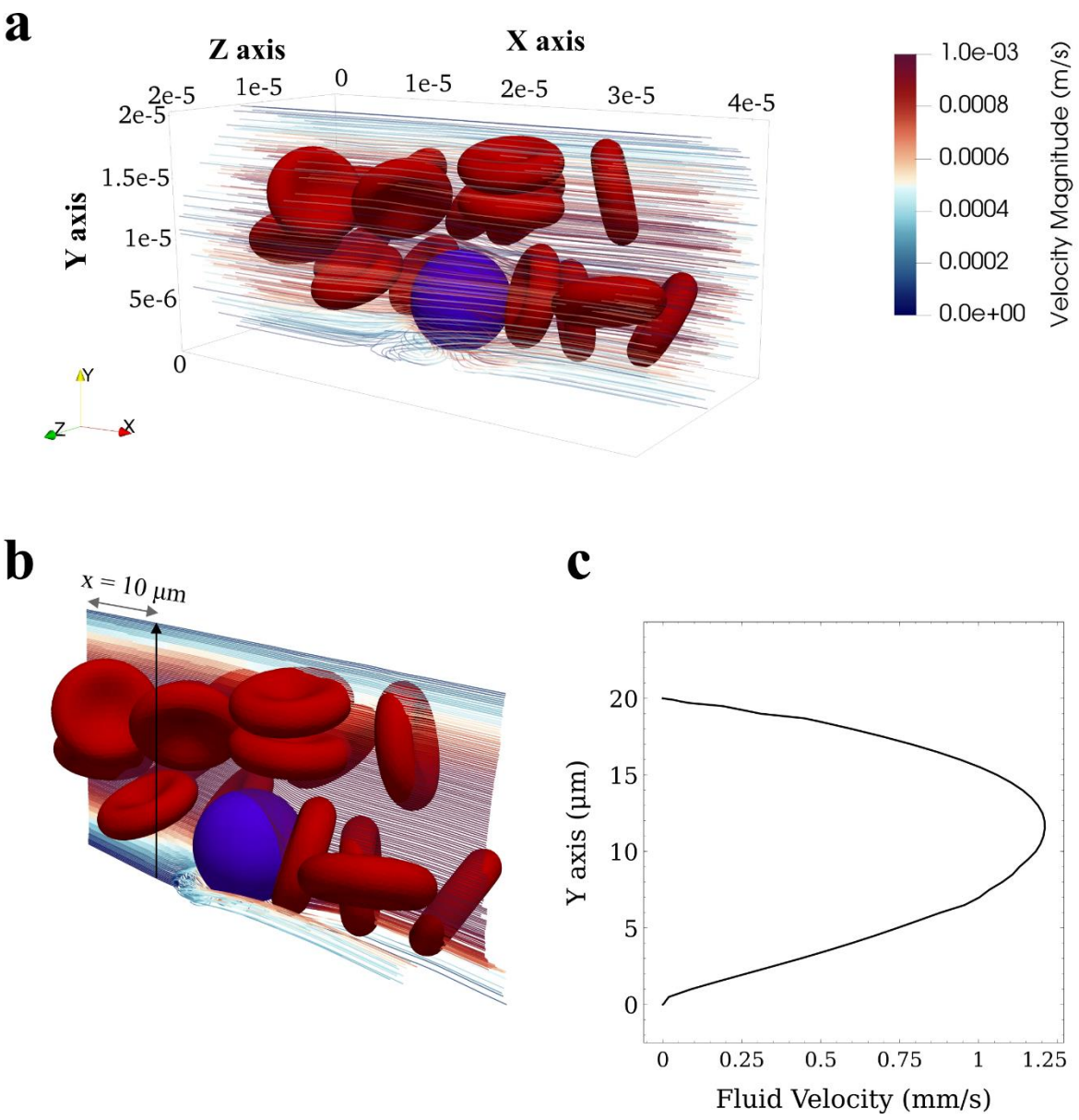

Figure 7- a) Snapshot of the computational domain including red blood cells (red), one circulating tumor cell (blue), and the plasma flow visualized by streamlines showing the velocity magnitude; b) Flow stream lines generated on the line source at x = 10 μm; c) The velocity profile of the plasma flow at x = 10 μm confirmed the accuracy of the generated flow

The simulations were done on the Niagara supercomputer at the SciNet HPC Consortium with Intel Skylake cores (2.4GHz, AVX512). We employed a total of 40 cores (that is the optimum number of cores considering the size of the domain) for each simulation parallelized using MPI. Each simulation took between 24 to 36 hours depending on the number of platelets in the simulation.

2.7 Sensitivity to simulation time span

To study the effect of the simulation time on our results and conclusions, we continued the simulations of two cases (0-platelets and 15-platelets around the CTC) for additional 2 million time steps to make sure our final results do not change after the simulation time. We observed that for 0-platelets around the CTC, the CTC continues its rolling motion without any significant changes in its velocity (stayed similar to the *Velocity-Time* graph of 0-platelets in Figure 10-a). For the case with 15-platelets around the CTC, the firm adhesion between the CTC and the vessel wall and the location of the CTC stayed unchanged. Additionally, the aspect ratio of the CTC in both cases increased less than 10%. Based on these results we can conclude that the final results of our model are stable and not sensitive to the simulation time span.

Table 3- Simulation parameters used in this study

Parameter	Definition	Physical value	Reference
T	Absolute temperature	$310\ K$	(247)
k_f^0	Unstressed forward reaction rate	$1000\ s^{-1}$	(248)
k_r^0	Unstressed reverse reaction rate	$1\ s^{-1}$	(249)
$k_{l_{CTC}}$	Link force coefficient	400	(210, 228)
$k_{b_{CTC}}$	Bending force modulus	800 $K_B T$	(210, 228)
$k_{a_{CTC}}$	Local area conservation coefficient	50	(210, 228)
$k_{v_{CTC}}$	Volume conservation coefficient	200	(210, 228)
σ_{ts}	Transition state spring constant	$10^{-9}\ {}^{N}/_{m}$	(213)
σ_b	Bond spring constant	$10^{-3}\ {}^{N}/_{m}$	(141, 238)
l_0	Equilibrium bond length in adhesive dynamics model	$20\ nm$	(247)
H_c	Cut-off length for bond formation	$100\ nm$	(210)
K_B	Boltzmann constant	$1.38 \times 10^{-23}\ J/K$	(250)
Δt	Time interval	$10^{-7}\ s$	(237, 240)
Re	Reynolds number	0.025	(210)
Δx	Fluid lattice resolution	$0.5\ \mu m$	(210)
D_{cp}	Microvessel diameter	$20\ \mu m$	(210)
L_{cp}	Microvessel Length	$40\ \mu m$	(210)
H_t	Hematocrit	12%	(251)
ν	Kinematic viscosity of plasma	$1.2 \times 10^{-6} \frac{m^2}{s}$	(210)
μ	Dynamic viscosity of plasma	$1.2\ mPa.s$	(211, 252)
r_{CTC}	CTC radius	$4\ \mu m$	(103)

Chapter 3

Results

3.1 Localized vortex formation upon rolling of circulating tumor cell initiates platelets

One of the unique phenomena elucidated by the results of our computational model was the formation of a localized vortex behind the CTC at the beginning of the rolling motion. Figure 8-a shows the plasma flow and deformation of CTC at four instances of the rolling motion. The closer look at the flow streamlines in the vicinity of CTC and vessel wall (Figure 8-b) shows a localized vortex behind the contact area of CTC and endothelial cells. Considering the Poiseuille flow profile expected for the plasma flow inside microvessels, the velocity of the fluid should be around 0 near the vessel wall (Figure 7-c) but, due to the presence of the vortex, the fluid velocity reaches to 2.57 mm/s that is twice the highest Poiseuille velocity magnitude in the microvessel (on the centerline). Thus, the localized vortex leads to a high shear rate around the CTC near the vessel wall and therefore may initiate the activation of adhesion molecules that attract platelets around the CTC. Karino et al demonstrated with an *in vitro* experiment that the localized vortex can activate the platelets and intensify the adhesion properties of the platelets (253, 254). Localized vortex can also force an outward migration of platelets that exist inside the vortex (255) and push them toward the CTC. In addition, the vortex causes a sudden flow reversal that is likely the basis for the increased permeability of the endothelium (as a result of shear forces in opposite directions applied to one point of endothelium) and increased adhesion and extravasation probability (256).

The vortex formed upon the onset of the rolling motion and the maximum vorticity magnitude of 4724.19 s^{-1} occurred at 2.2 μs after the onset of the rolling motion of CTC (Figure 8-a). Gou et al. used a computational model to show how localized vortex at the branching point of the microvessel can regulate cell-cell interactions and can result in increased CTC adhesion (150). Here we showed the vortex formation in the CTC rolling motion in a microvessel for the first time. The localized vortex can result in higher shear forces in that region and the stimulation of CTC-platelets interactions.

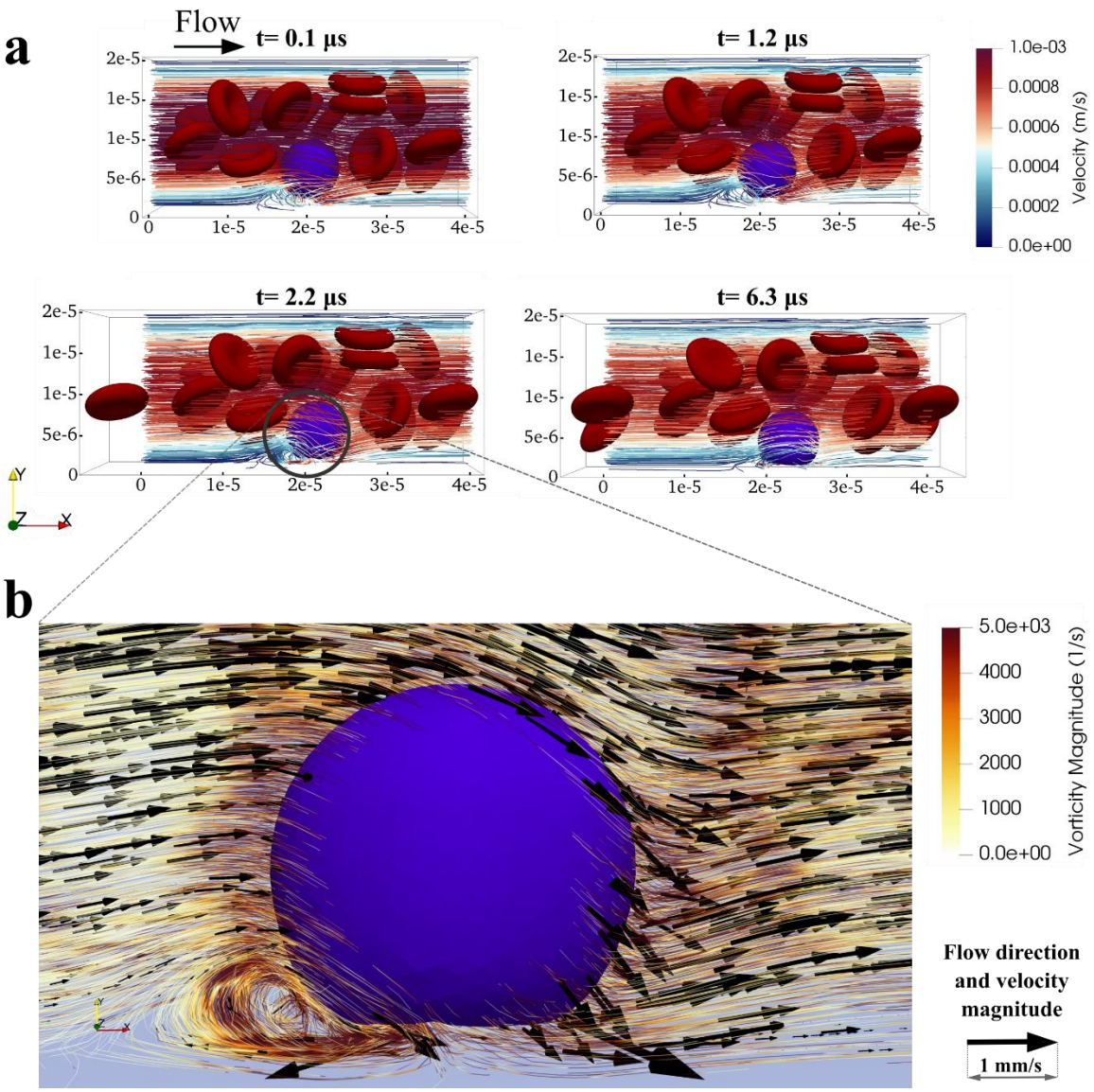

Figure 8- Rolling motion of the CTC in vicinity of the microvessel wall with a focus on the localized vortex that is formed upon the rolling motion. a) Rolling dynamics of the circulating tumor cell with no attached platelets at four initial instances of rolling. When CTC gets closer to the vessel wall, a localized vortex forms in the plasma flow behind the CTC. in the vicinity of the vessel wall; b) Closer look to the CTC and vortex at t = 2.2 µs with more quantitative details on the magnitude and direction of the velocity and the magnitude of the vorticity. Formation of the vortex upon rolling of the CTC causes a high shear rate in that region which can lead to the activation of adhesive molecules on platelets and endothelial cells around the circulating tumor cell

Figure 9 shows the vortex tube from different views. The maximum dimensions of the vortex tube reached to 6.32 µm in length and 2.26 µm in height. For visualizing the vortex tube in Figure 9, the seed points of the streamlines were distributed uniformly on a line source in the vicinity of the localized vortex. However, the streamlines were concentrated in the middle part of the vortex tube (Figure 9) which indicates the higher vorticity magnitude and higher shear rates in the region which can stimulate adhesion molecules on the platelets and activate the attached platelets (253).

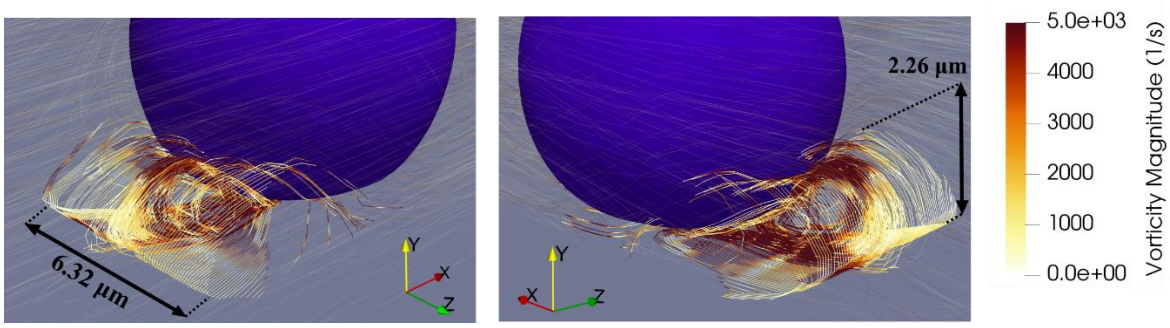

Figure 9- Visualization of the vortex tube in 3D view. The maximum length and maximum height of the vortex tube are indicated in the figure. Although the seed points of the streamlines are distributed uniformly along a line source, the streamlines are concentrated in the middle part of the vortex tube. Concentration of the streamlines in the middle part of the vortex tube indicates higher vorticity magnitude (as shown in the figure) and higher shear rates in that region which lead to activation of the adhesion molecules on attached platelets and initiation of CTC-platelets interactions.

3.2 Platelets reduce time and distance of circulation of circulating tumor cells by enhancing adhesion

To examine the effect of platelets on the adhesion and arrest of CTC, we simulated the movements of CTC in a microvessel as detailed in Materials and Methods. Considering the low abundance of CTCs in the blood, all the simulations were done using only one CTC to speed up the calculations. We studied the effect of platelets on the dynamics of CTC near the vessel wall by changing the number of platelets in the model from 0 to 15 (with a 5-platelet increment). The model included RBCs but other far less abundant blood cells, such as leukocytes, monocytes were not modeled. All simulations were carried out with the same initial and boundary conditions except for the number of platelets around the CTC. Because of the physical similarities between the CTCs and white blood cells (i.e. shape, size, and stiffness), the margination of CTC is quite similar to the margination of white blood cells (68, 118) as

experimental (257) and computational modelling (228, 245, 258) studies showed. Therefore, we skipped the margination movement to focus more on adhesion and arrest of the CTC by setting the initial position of the CTC near the vessel wall in all simulations to reduce the time required for the CTC to marginate to the vessel wall.

The results of the simulations show that upon margination, the CTC will immediately start a rolling motion due to the CTC-wall adhesion forces. As Figure 10 shows, when there was no platelet around the CTC (black line), the CTC continued its rolling motion without any remarkable changes in its velocity. This rolling motion continued as long as we continued the simulation. Increasing the number of attached platelets, slowed down the rolling motion of the CTC eventuating to a firm adhesion between the CTC and vessel wall. The velocity-time graph of Figure 10-a shows that increasing the number of attached platelets, decreased the duration of the rolling motion and caused the firm adhesion to happen faster. For the CTC with 5 attached platelets, the firm adhesion took almost 0.1 s to happen but when the number of attached platelets increased to 15, the adhesion time decreased by 0.06 s (a 40% decrease). Furthermore, the velocity-position graph of Figure 10-b shows the rolling distance until firm adhesion for the CTC 15 attached platelets was up to 8% shorter in comparison with that observed for a CTC with 5 attached platelets.

Another information that is provided by Figure 10-a and Figure 10-b is that the adhesion of CTC to the vessel wall with 10 attached platelets is similar to the adhesion of CTC with 15 attached platelets. Considering that only the platelets existing on the contact area between the CTC and the vessel wall can affect the adhesion dynamics, we can conclude that for an 8 μm-diameter CTC, 10 platelets can cover the entire contact area on the CTC. Although a higher number of attached platelets has no significant effect on the time and distance of the firm adhesion of CTC to the vessel wall, these platelets can shield CTC from external mechanical forces and preserve the integrity of the CTC. It should be noted that at the stage of firm adhesion, the velocity of CTCs still has small oscillations around 0 (Figure 10-a and Figure 10-b) because of the forces applied by the plasma flow and RBCs and the spring-like probabilistic adhesion bonds, but the change in the position of the CTC remains negligible (less than 5 micrometers).

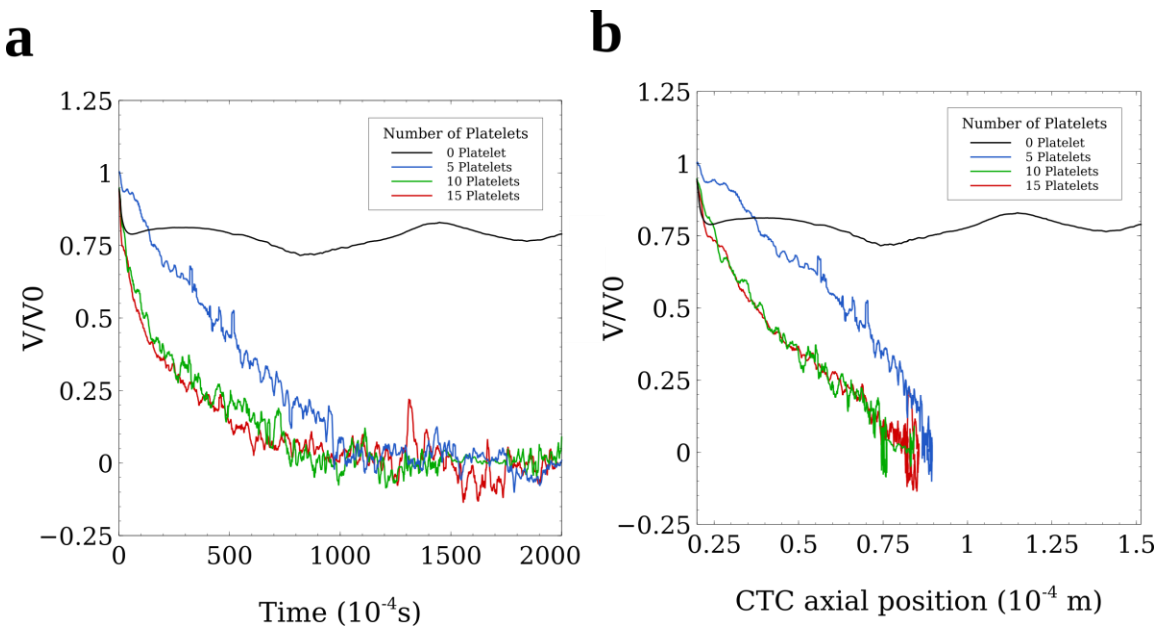

Figure 10- *Velocity-Time* and *Velocity-Axial Position* graphs showing that CTC-platelets interactions significantly enhance the probability of formation of the firm adhesion bonds between CTC and the endothelial cells stop the CTC from rolling. a) *Velocity-Time* graph showing the effect of the number of attached platelets on the adhesion of circulating tumor cells (CTCs). With increasing the number of platelets around the CTC, the velocity of the CTC decreases faster and the firm adhesion of the CTC to the vessel wall, as a prerequisite for extravasation, occurs in a shorter time. Lodging of the CTC to the vessel wall saves the CTC from further circulation in the vascular system, exposure to the high shear stress in larger vessels, and encountering immune cells. As a result, the faster the CTC adheres to the vessel wall, the higher survival chance it gets; b) *Velocity-Axial Position* of CTC graph showing the distance the CTC travels in the form of rolling and crawling in the microvessel until the firm adhesion occurs. Increasing the number of attached platelets reduces the rolling distance which leads to less shear forces exerted on the CTC by endothelial cells and as a result, higher chance of CTC survival and extravasation.

3.3 Platelets preserve the integrity of circulating tumor cells

We studied the effects of platelet shield on the CTC deformation and quantified these effects using Taylor's deformation parameter of aspect ratio (259) later adopted by Luo et al. (260, 261). Taylor's aspect ratio is a dimensionless quantity defined as $\varsigma = \frac{L-B}{L+B}$; where L and B are major and minor axes of the ellipsoid (CTC) with the same moment of inertia. ς is originally defined for small distortions from the spherical form that occur at small velocities of the flow such as plasma flow in microvessels. Taylor's aspect ratio is 0 for a perfect sphere. The highest aspect ratio in our model is 0.133 that belongs to the rolling CTC with no attached platelet and the experimental results show that the Taylor's

deformation parameter of aspect ratio is an accurate measure of deformation when the values of are less than 0.4 (259), which is the case in our simulation.

Figure 11 shows the evolution of the aspect ratio of a CTC with an increasing number of attached platelets up to 0.2 s after the onset of the rolling motion. The simulation time was specifically chosen to provide adequate time for the CTC to adhere to the vessel wall. We continued the simulations for an additional 0.2 s to guarantee the stability of the results (see time step). At the onset of the rolling motion, the aspect ratio of all CTCs was zero indicating spheres. During the rolling motion and after the firm adhesion instance (indicated in Figure 11 with ◆), the aspect ratio of all CTCs consistently increased with time. The slope of the increasing trend of the aspect ratio of CTCs, decreased with the number of attached platelets from 0.67 s^{-1} for the CTC with no platelet to 0.275 s^{-1} for the CTC with 15 platelets attached to it. At 0.2 s after the onset of the rolling motion, the CTC with no attached platelets was in rolling motion and its aspect ratio was 0.133 while a firm adhesion was formed between the vessel wall and the CTC with 5 attached platelets, and its aspect ratio decreased to 0.087. Increasing the number of attached platelets to 10 and 15 decreased the aspect ratio to 0.068 and 0.055 (at 0.2 s after the onset of the rolling motion) which are almost half and less than half of the aspect ratio of the CTC with no attached platelets, respectively. Our results demonstrate that increasing the number of platelets around the CTC (enlarging the platelet shield) reduces the deformation of the CTC in the adhesion process.

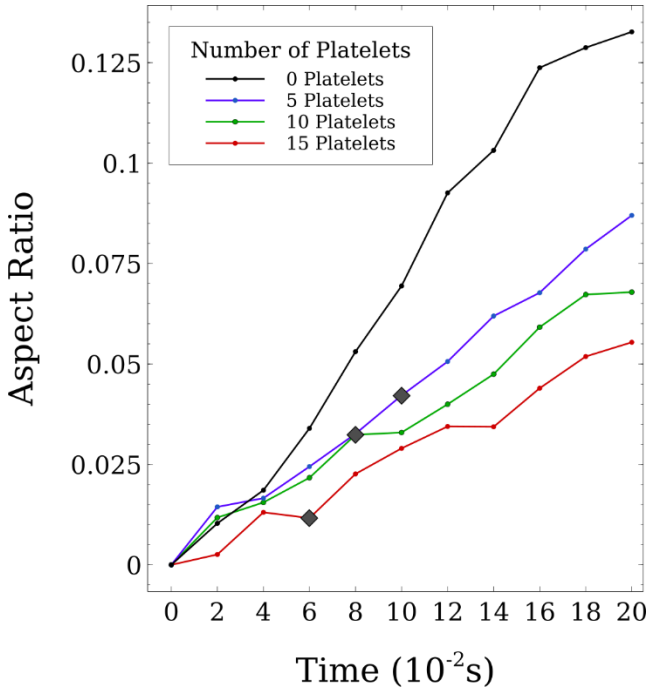

Figure 11- *Aspect Ratio-Time* graph showing the deformation of circulating tumor cells over the simulation time for different numbers of attached platelets. The aspect ratio is calculated by $\boldsymbol{\varsigma = \frac{L-B}{L+B}}$. Also, the firm adhesion instance is indicated with ◆ for the cases in which there are attached platelets and the firm adhesion occurs. The graph shows that the attached platelets can reduce the aspect ratio (i.e. deformations) of the CTC in the case with 0 attached platelet to less than half of its value when there are 15 platelets attached to the CTC. Attached platelets can preserve the integrity of the CTC and reduce the deformations of the CTC by making the force distribution on the CTC membrane homogeneous;

The total force distributions on the CTC membrane in the firm adhesion state (Figure 12) also confirm the protective role of platelets against external forces applied on the CTC. The force distributions in the firm adhesion state in these figures show that the maximum force applied to any individual node decreases as the number of attached platelets increases (from 328.7 pN with 5 platelets to 48.9 pN and 28.7 pN for 10 and 15 platelets, respectively). Also, the integral of the force magnitude over the entire CTC in the firm adhesion state decreased from 14.5 nN with 5 platelets attached to 10.58 nN and 7.55 nN for 10 and 15 platelets attached to the CTC respectively. Reduction in the detrimental force can be due to the wider contact area between the CTC and vessel wall as the results of attached platelets that

makes the distribution of force on the CTC membrane homogeneous. Mechanical experiments of the rupture of the cell membrane (262, 263) showed that external forces in the order of 10-30 nN are required to rupture the cell membrane. Our results suggest that attached platelets reduce the chance of CTC lysis due to external forces.

It should be noted that for the case where there is no platelet attached to the CTC, the firm adhesion bond did not form between the CTC and the endothelial cells as long as we could continue the simulation, and the CTC continued its rolling motion. Consequently, the forces applied on the CTC membrane (without attached platelets) in the rolling motion (with the maximum of 169.6 pN and the integral of 13.4 nN over the entire membrane) were not compared to the forces CTCs with attached platelets experienced with the firm adhesion bonds to the endothelial cells.

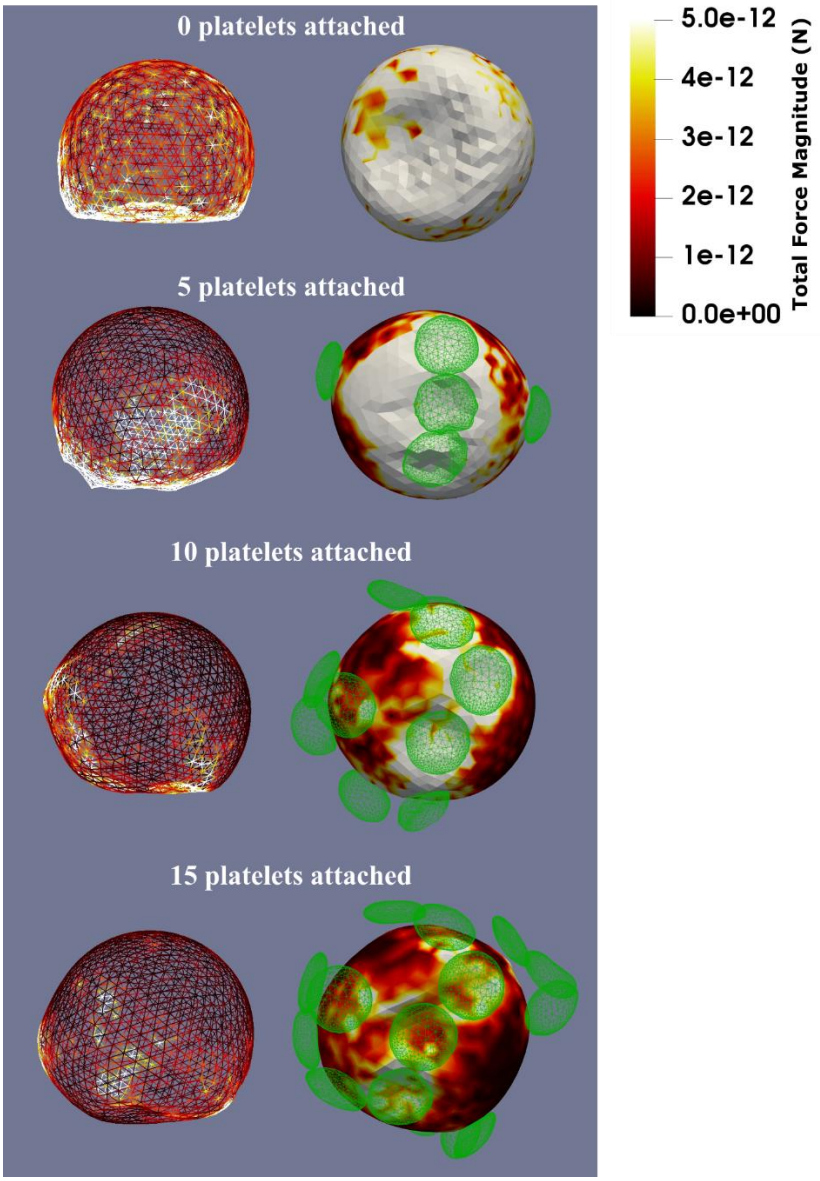

Figure 12- Front view (on the left side) and bottom view (on the right side) of the CTC showing its shape deformation in the rolling motion with 0 platelets and in firm adhesion state with 5, 10, and 15 attached platelets respectively. The membrane is colored with total force distribution on the CTC. External forces applied on small areas of CTC membrane can penetrate the CTC membrane and cause damage to the CTC during the adhesion process. Attached platelets reduce the maximum force applied to any node of the CTC by making the force distribution on CTC homogeneous.

3.4 Wall shear stress increases during adhesion and arrest of circulating tumor cells

The expression of VEGF is highly dependent on the wall shear stress (WSS) magnitude (264) and elevated VEGF can facilitate extravasation by expanding the space between two neighboring endothelial cells (200). Figure 13 shows that at t = 0.03 s when all CTCs (with any number of attached platelets) are in the rolling state, the endothelium experiences at least 200% higher WSS in a small area in the vicinity of CTC. The area of the elevated WSS expands with increasing the number of attached platelets which resulted in expanded contact area between CTC-platelets complex and the endothelium and is consistent with easier firm adhesion formation in terms of time and distance of travel as described above.

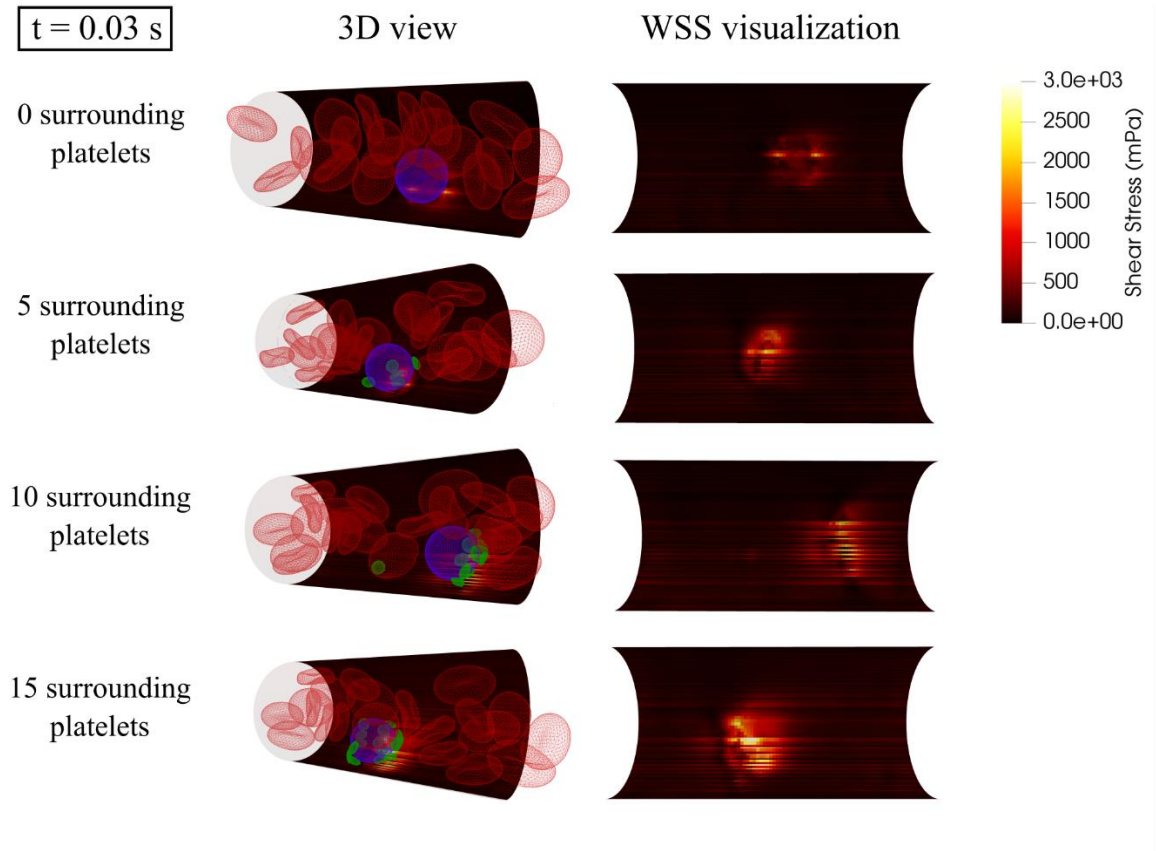

Figure 13- Illustration of WSS on the microvessel wall as a result of rolling motion of circulating tumor cells and the attached platelets near the vessel wall at t = 0.03. The area of elevated shear stress expands when more platelets are attached to the CTC. High shear stress on the endothelial cells initiates the adhesion molecules that is a necessary step before firm adhesion occurs

Figure 14 illustrates the WSS at t = 0.2 s, when the firm adhesion has occurred for all CTCs with attached platelets but the CTC with no attached platelet is still in the rolling motion phase. In the firm adhesion state of CTCs with attached platelets, the WSS increases substantially (more than 100%) in comparison with the rolling state of the same CTC. In contrast, since the CTC with zero attached platelets does not form firm adhesion with the endothelial cells and continues its rolling motion, the WSS at t = 0.2 s has the same value as it had at t = 0.03 s. Additionally, the area of the endothelium experiencing elevated WSS (greater than 1 Pa) also expanded as shown in Figure 14 from 1.25 μm^2 around CTC with no platelets to 17.25 μm^2, 52.75 μm^2, and 104.45 μm^2 with 5, 10 and 15 platelets, respectively.

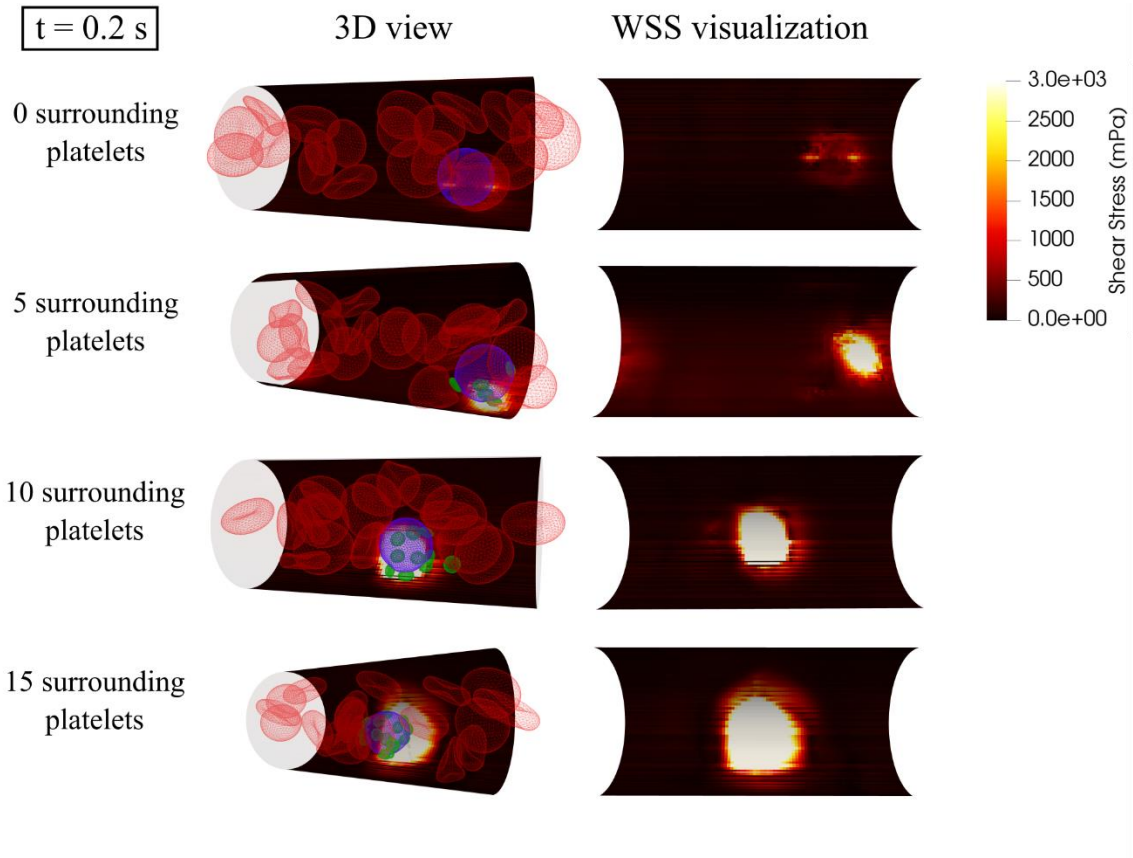

Figure 14- Illustration of the WSS on the microvessel wall for different numbers of platelets attached to the CTC at t = 0.2. When there is no platelet attached to the CTC, the CTC continues its rolling motion and the WSS is almost the same as t = 0.03 state. When there are platelets around the CTC, the firm adhesion occurs, and we observe that the WSS increases significantly in comparison with t = 0.03 state and reaches to its maximum magnitude. Additionally, the area of the elevated shear stress expands when more platelets are attached to the CTC, similar to the previous case.

Figure 15-a shows the maximum WSS occurred during the simulation. The maximum WSS of 2.378 Pa was observed in vicinity of the CTC in rolling motion with no attached platelets. In presence of 5 attached platelets, the maximum WSS reaches 14.116 Pa which is approximately 6 times its value for the rolling CTC with no platelet attached. Increasing the number of attached platelets around the CTC to 10 and 15, increases the maximum WSS to 24.359 and 26.880 Pa respectively. Consistently, the total shear force exerted on the endothelium by the CTC compound (obtained by integrating the WSS over

the contact area at t = 0.2 s) constantly increases by increasing the number of platelets as it is shown in Figure 15-b. Interestingly the total shear force plotted logarithmically in Figure 15-c shows the same increasing trend as the WSS in Figure 15-a. While a CTC in rolling motion with no platelets attached can cause a shear force of 1.38 μN on the adjacent endothelial cells, a CTC with 5 attached platelets in firm adhesion can cause a shear force of 70.73 μN on the adjacent endothelial cells and as Figure 15-b shows the applied shear force increased by increasing the number of attached platelets. The drastic jump in the shear force due to firm adhesion to the endothelial cells can boost the VEGF expression in that region and increase the chance of CTC extravasation.

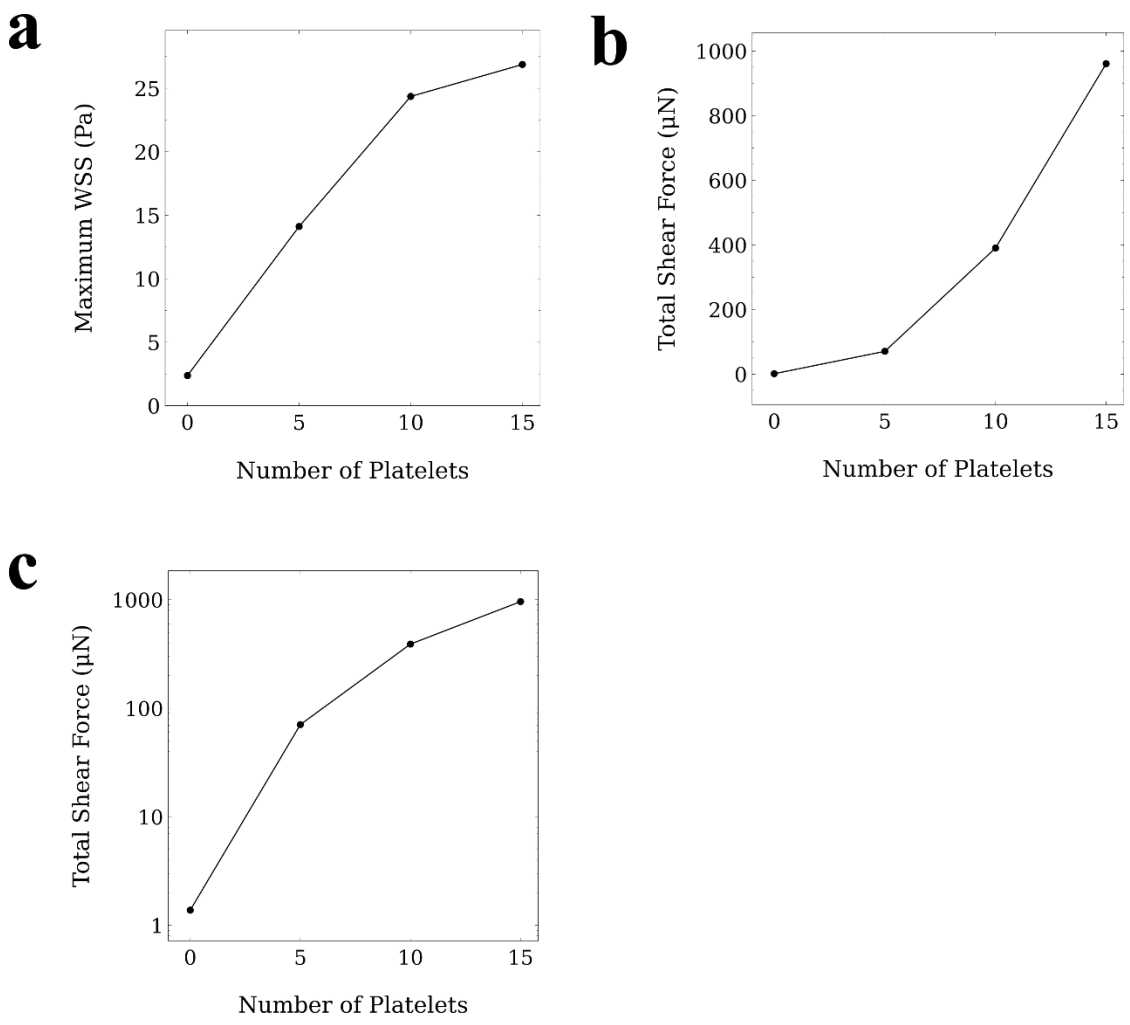

Figure 15- Maximum WSS and total shear forces applied to the endothelial cells based on different numbers of attached platelets. a) Maximum WSS applied to the endothelial cells because of the presence of the CTC and the attached platelets in vicinity of the vessel wall. The maximum WSS increases when more platelets are attached to the CTC. Because the contact area between platelets, and the endothelial cells reaches to its maximum value, the maximum WSS remains almost the same after a critical number of attached platelets (10 platelets); b) Total shear force applied to the endothelial cell in vicinity of the CTC and attached platelets. The total shear force applied to the endothelial cells is calculated by integrating the WSS over the contact area at t = 0.2 s. By increasing the number of attached platelets, the total shear force increases significantly which indicates a higher chance of VEGF expression and CTC extravasation; c) Total shear force plotted logarithmically that has the similar increasing rate as maximum WSS applied to the endothelium.

3.5 Softer and smaller CTCs adhere more effectively to the vessel wall

To study the effect of CTC stiffness on its adhesive properties, we repeated the simulation with 5 attached platelets. Katsantonis et al. suggested that the malignant transformation of tumor cells reduces F-actin in the cell cytoskeleton by ~30% and leads to higher deformability of the invasive cancer cells (234, 265). Thus, we studied the effects of increasing and decreasing the stiffness of CTCs by 30% through changing the spring constants related to each mechanical behavior of the CTC membrane explained in Materials and Methods. As Figure 16-a and Figure 16-b illustrate, softer CTCs adhered 0.05s faster (equivalent to 50% decrease in the adhesion time) to the vessel wall. We showed that invasive CTCs, that are known to be softer than normal tumor cells (103, 234, 265), deform and adhere to the vessel wall more efficiently (210). Our results also show that stiffer CTCs need 0.05s more time to adhere to the vessel wall that is 50% longer than the time that a baseline CTC takes. This phenomenon can be due to the smaller contact area between the stiffer CTC and the vessel wall.

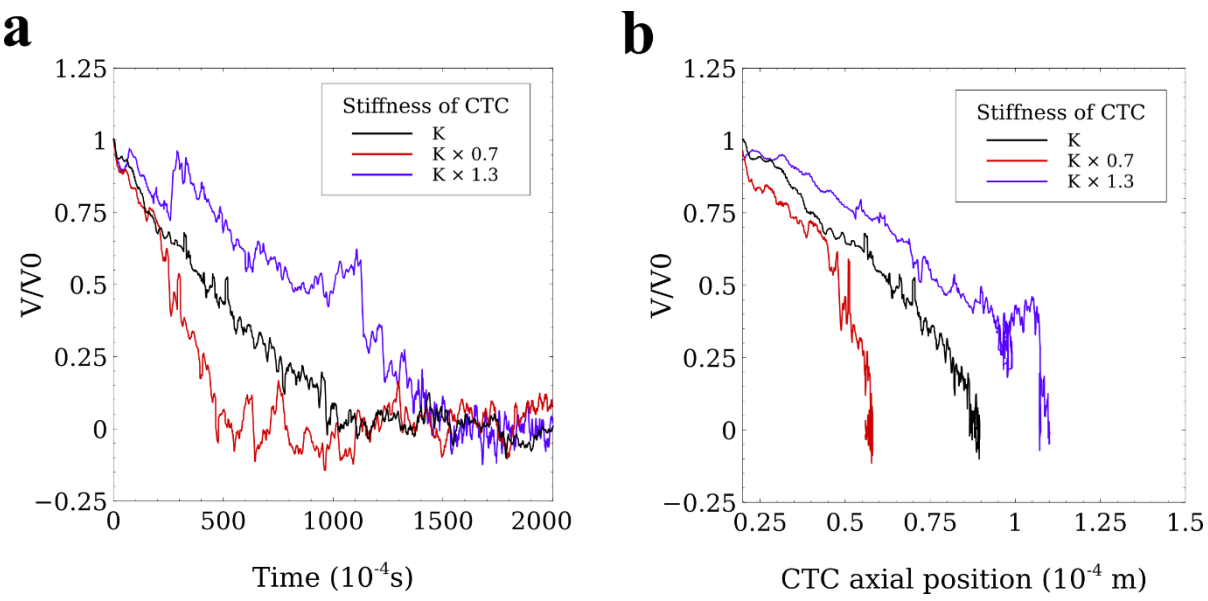

Figure 16- a) Softer CTCs adhere faster to the vessel wall than stiffer CTCs. Decreasing the stiffness of a CTC by 30% (red line) leads to 50% decrease in the adhesion time. Also increasing the stiffness of the CTC by 30% causes a 50% increase in the adhesion time of the CTC with attached platelets and the vessel wall. Faster adhesion of softer CTCs is mainly because of the expanded contact area between CTC and the vessel that leads to a higher number of adhesion bonds between CTC with attached platelets and endothelial cells; b) Softer CTCs travel shorter distances before firm adhesion mainly because they adhere faster than normal tumor cells;

Additionally, we performed the simulation with 30% stiffer and 30% softer platelets using the same approach described for CTCs. As Figure 17-a and Figure 17-b show, changing the mechanical properties of platelets does not have remarkable effects on the adhesion and arrest of the CTC. Thus, the results of the simulation are not sensitive to the mechanical properties of the platelets.

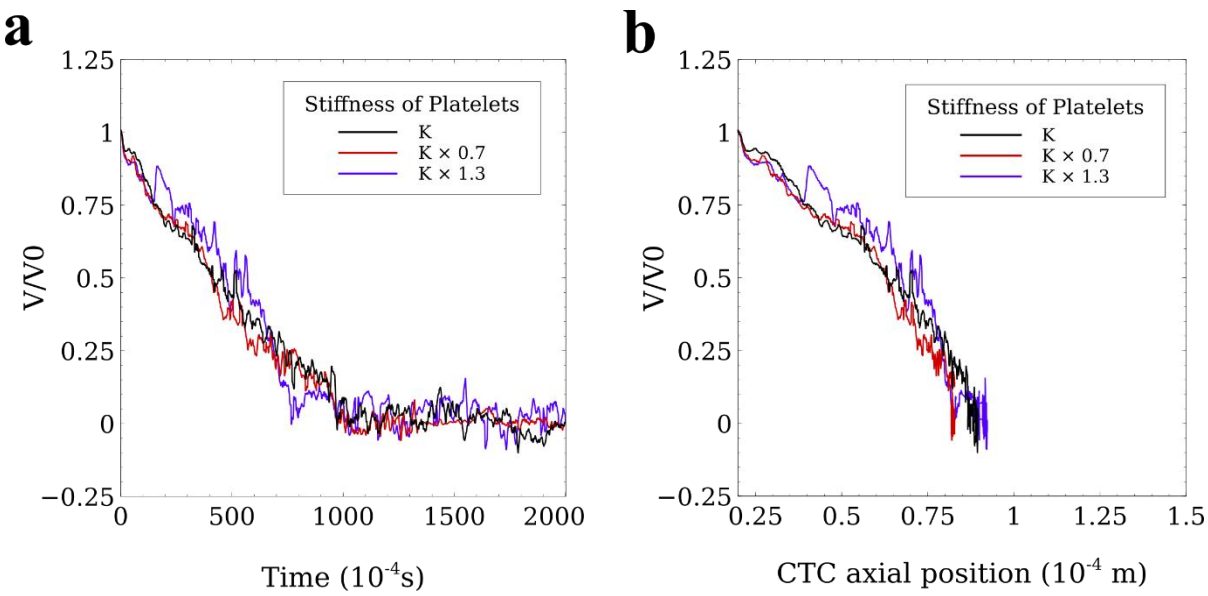

Figure 17- a) The adhesion time of the CTC with attached platelets with 30% softer and 30% stiffer mechanical properties were tested and the results of the simulation are presented. The results show that reducing or increasing the stiffness of the platelets by 30% does not have a significant effect on the adhesion time and the CTCs in all the three cases form the firm adhesion in the same time; b) Reducing the stiffness of the attached platelets by 30% can decrease the rolling distance of the CTC by 8% but the effect of increasing the stiffness of the attached platelets on the rolling distance of the CTC is less than CTC. Altogether, the stiffness of the CTC is a more determining factor in the adhesion and arrest of the CTC than the stiffness of the attached platelets.

Furthermore, we studied the effect of the diameter of CTCs on their adhesion to the vessel wall in the presence of platelets. We considered CTCs with diameters ranging from 8 to 12 μm that all had the same mesh configuration and adhesion-bond density to understand the effect of CTC size on metastasis in terms of cell deformation and adhesion. To investigate the effect of size of the cell on its deformation, we carried out a stretch test on CTCs of varying sizes similar to the tests performed both experimentally (232) and computationally (227) for RBCs. Because of the higher stiffness of CTC, the applied maximum tension force reaches 2000 pN which is 10-fold of its value in testing a RBC. The

results of the stretch test for different diameters are listed in Table 4. The results include the length of the major and minor axes of the CTC under stretching force from 0 to 2000 pN with 200 pN increment. The aspect ratio calculated for each state is also provided. These results can be implemented by other researchers as an alternative for optical tweezers experiments on CTC. Figure 18-a shows the force distribution on the 8-µm diameter CTC at the start (no applied force) and the end of the stretch test (with 2000 pN tension force). At the end of the tension test, the maximum force that the nodes of the cell locally bore was 20 pN and the major and minor axes lengths were 13.45 and 7.06 µm, respectively (aspect ratio of 0.31). Figure 18-b shows the evolution of the aspect ratio of the cells during the tension test for all cell sizes. As this figure shows, the maximum difference between the deformations of cells in terms of aspect ratio between the largest and smallest CTC is less than 10%.

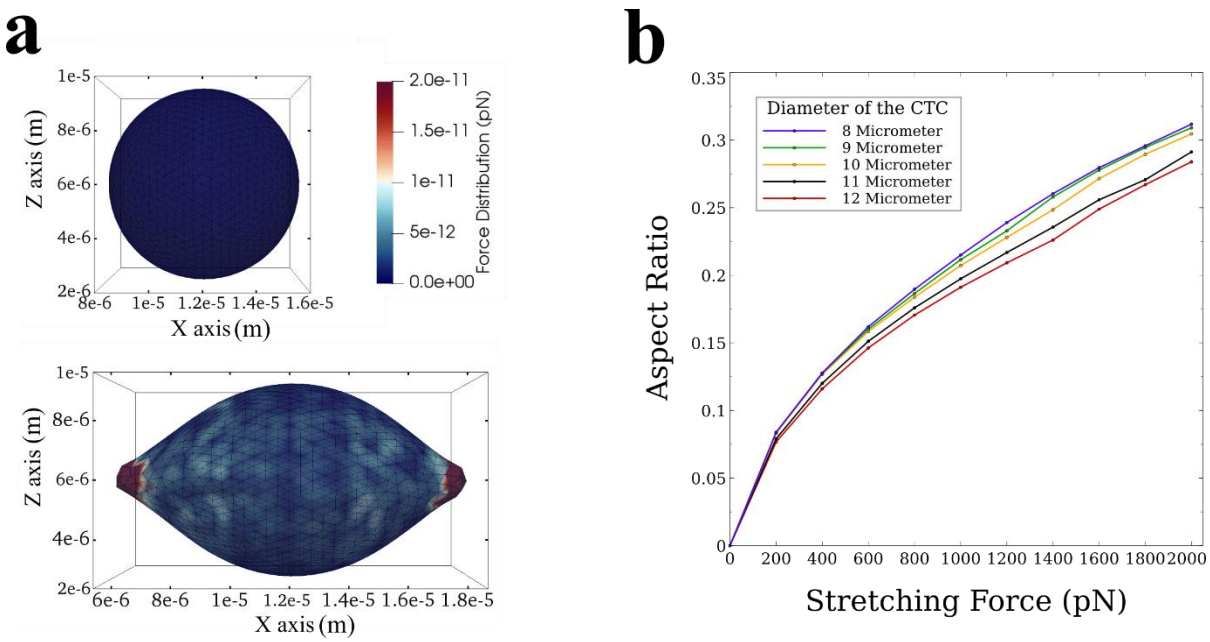

Figure 18- a) Stretch test simulation on circulating tumor cells with different diameters based on optical tweezers experiment. Top figure shows the CTC with no force applied on it and the bottom figure shows the CTC under tension force; b) Aspect Ratio-Stretching Force graph shows the difference in mechanical responses of the CTC with diameters ranging from 8-12 micrometer is under 10 percent that is negligible in our study

Table 4- Results of the stretch test of CTCs with different diameters

Stretch Test (Optical Tweezers)	Stretching Force (pN)											
	0	200	400	600	800	1000	1200	1400	1600	1800	2000
Largest Diameter of CTC (µm)	8	9.3138	10.0298	10.5997	11.0961	11.5154	11.9302	12.3572	12.7604	13.1022	13.4475
Smallest Diameter of CTC (µm)	8	7.8723	7.7569	7.64451	7.5586	7.4402	7.3278	7.2521	7.1838	7.1211	7.0552
Aspect Ratio ($\varsigma = (L-B)/(L+B)$)	0	0.08388	0.12779	0.16198	0.18963	0.21499	0.23899	0.26034	0.27961	0.29575	0.31178
Largest Diameter of CTC (µm)	9	10.4768	11.2823	11.9215	12.4779	12.9512	13.3618	13.8376	14.2867	14.6992	15.0649
Smallest Diameter of CTC (µm)	9	8.8586	8.7303	8.63	8.5547	8.4284	8.3136	8.1628	8.0743	8.0104	7.9514
Aspect Ratio ($\varsigma = (L-B)/(L+B)$)	0	0.08369	0.12752	0.16016	0.18653	0.21155	0.23290	0.25794	0.27782	0.29454	0.30906
Largest Diameter of CTC (µm)	10	11.6385	12.533	13.2388	13.8426	14.3672	14.8243	15.2825	15.8029	16.2769	16.6756
Smallest Diameter of CTC (µm)	10	9.8498	9.7132	9.6153	9.5434	9.4344	9.3185	9.1989	9.0538	8.9684	8.8886
Aspect Ratio ($\varsigma = (L-B)/(L+B)$)	0	0.08324	0.12675	0.15855	0.18384	0.20725	0.22805	0.24850	0.27152	0.28950	0.30461
Largest Diameter of CTC (µm)	11	12.786	13.7625	14.5371	15.1859	15.7539	16.259	16.7485	17.3173	17.7152	18.326
Smallest Diameter of CTC (µm)	11	10.9118	10.8112	10.7175	10.6417	10.5592	10.464	10.3608	10.2608	10.1676	10.0586
Aspect Ratio ($\varsigma = (L-B)/(L+B)$)	0	0.07909	0.12010	0.15124	0.17594	0.19742	0.21685	0.23563	0.25587	0.27069	0.29126
Largest Diameter of CTC (µm)	12	13.9341	14.9898	15.8304	16.535	17.1524	17.6997	18.2085	18.7859	19.3547	19.905
Smallest Diameter of CTC (µm)	12	11.9482	11.8724	11.7892	11.7163	11.6472	11.5745	11.4937	11.2975	11.1963	11.1018
Aspect Ratio ($\varsigma = (L-B)/(L+B)$)	0	0.07673	0.11605	0.14632	0.17057	0.19116	0.20924	0.22607	0.24892	0.26704	0.28391

The *Velocity-Time* graph (Figure 19-a) shows the firm adhesion state (zero velocity) happened for CTCs with 5 platelets attached with diameters of 8 µm (baseline) and 9 µm but for larger CTCs, i.e. diameters ranging from 10 to 12 µm, the CTC continues its rolling motion up to 0.2 s that was simulated. Since the number of platelets is the same (5 platelets) for all the simulations, we can conclude that as the diameter of CTC increases, the CTCs start rolling faster which is due to excessive forces applied by the flow of plasma and RBCs.

One of the interesting findings of the size analysis is that the adhesion of CTC with 9 µm diameter took place more effectively, i.e. faster and in the smaller rolling distance, than CTC with a diameter of 8 µm (Figure 19-b). This can be partially due to a specific ratio of vessel diameter to CTC diameter as investigated thoroughly by Takeishi et al. (68). The arrest of smaller cell clusters becomes more important when we consider their ability to extravasate easier through endothelial cells.

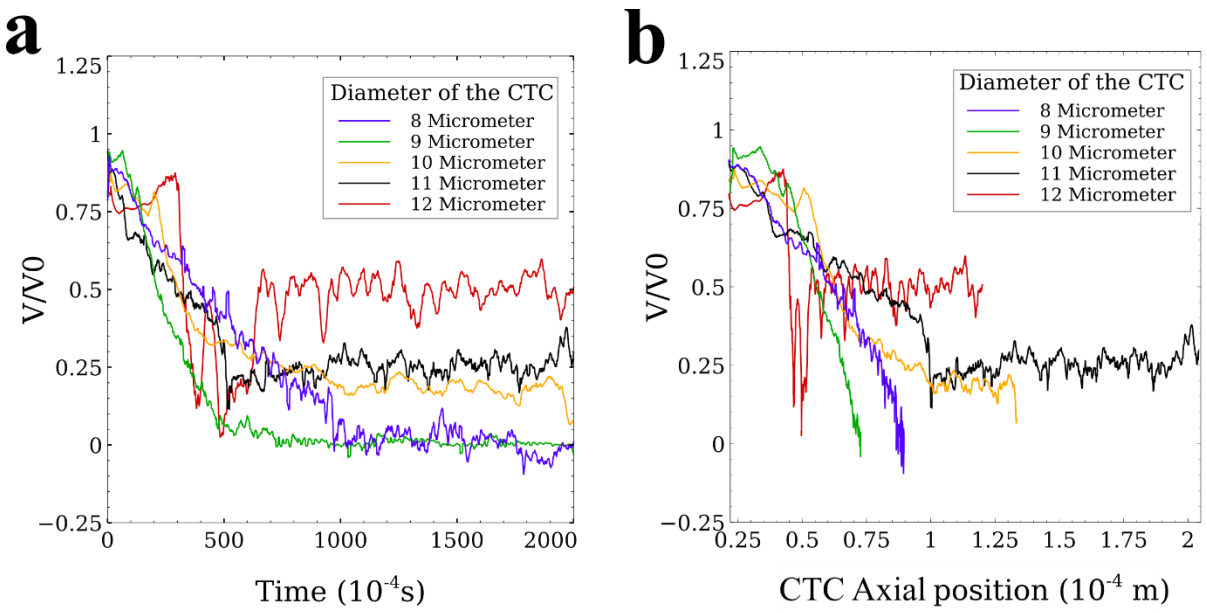

Figure 19- a) Velocity-Time graph showing the effect of size of the CTC with 5 platelets attached to it on its adhesion dynamics. CTCs with diameters equal or smaller than 9 micrometers form a firm adhesion with the vessel wall, but bigger CTCs continue their rolling motion in the microvessel. The velocity of the rolling CTC also increases when the CTC is bigger; b) Velocity- Axial Position graph of CTC showing the 9 micrometer CTC form the firm adhesion bond faster than 8 micrometer CTC that can be due to ratio of the CTC diameter to the diameter of the vessel. CTCs with diameters bigger than 9 micrometers do not stop rolling motion.

Chapter 4
Discussion

We showed that upon rolling of the CTC near the microvessel wall, a localized vortex is formed near the vessel wall. The velocity of the plasma flow near the vessel wall should be around zero but because of this localized vortex, the velocity of the plasma flow in vicinity of the CTC reaches to twice of the maximum flow velocity before vortex formation. As a result, the localized vortex leads to higher shear forces around the CTC that can activate the adhesion molecules on the attached platelets (253) and trigger the interactions between the CTC and the attached platelets. Attachment of the activated platelets to the CTC can enhance the CTC arrest and extravasation out of the vessel wall and aggravate the metastatic outcome.

Our result quantitatively showed that the adhesion of platelets to the CTC encourages the firm adhesion of the CTC to the vessel wall and increasing the number of platelets accelerates the adhesion to the vessel wall. In other words, the adhesion of the platelets to the CTC reduces the time of the exposure of the CTC to the shear stress induced by the plasma flow which is a critical factor for the viability of CTC as demonstrated *in vitro* (266) and it reduces the distance of the CTC rolling movement on endothelial cells which can harm the membrane of the CTC. Consequently, our results showed that CTCs greatly benefit from interacting with platelets.

Another aspect of the interactions between platelets and CTCs that we observed in the results of the simulation is the ability of the attached platelets to reduce large deformations resulting from collisions with RBCs and the hemodynamic shear forces applied by the plasma flow. The mechanical stresses induce apoptotic cell death in CTCs (267). Takamatsu et al. demonstrated that 55% increase of the strain on the cell surface that is induced by compressing the cell with two flat plates, decreases the viability of the cancer cells by 50% (268). Our results quantitatively showed the remarkable role of platelets in reducing the forces applied on the CTC, reducing its deformations and preserving the integrity of the CTC thus substantially increasing the durability of the CTC (190). Our results support the fact that the attached platelets around the CTC works as a shield against external forces and maintains the shape and integrity of the CTC by distributing the external force homogeneously on the CTC surface. As Figure 12-b illustrates, the total force exerted on the CTC membrane decreases when there is a layer of platelets around the CTC. Thus, platelets covering a CTC can significantly increase the survival rate of CTCs.

High shear stress has a critical role in the activation and adhesion of platelets to the endothelial cells. Savage et al. revealed that the elevated shear stress initiates and sustains platelet adhesion regulated by endothelial-derived von Willebrand factor expression (269, 270). Additionally, as suggested by Yan et al. the shear stress can modulate the interactions between the CTC and endothelial cells (140). The results of our simulation show that the area of elevated shear stress expands proportionally to the number of platelets around the CTC (Figure 13 and Figure 14). The expanded area of shear stress and the higher total shear force applied on the endothelial cells indicate higher chance of CTC arrest and extravasation. A comprehensive review of numerous studies about the effect of high shear stress on the activation and adhesion of platelets to the endothelial cells was done by Ruggeri (271). The endothelial-cell shear-stress response requires platelet endothelial cell adhesion molecule-1 (PECAM-1, CD31) which can sense exerted forces by blood flow and can lead to transactivation of endothelial VEGFR2. VEGFR2 triggers conformational activation of integrins leading to the firm platelet-endothelial adhesion (272). PECAM-1 expression is largely concentrated at junctions between adjacent cells and can regulate transendothelial migration of cells (205, 273, 274).

Furthermore, The integrity of the vascular endothelium within the microenvironment of the attached CTC may be directly, or indirectly, affected by growth factors released from platelet α-granules, including platelet-derived growth factor (PDGF), TGFβ, EGF, and VEGFA (186, 275). Therefore, the platelets can modulate the permeability of the vessel wall and facilitate CTC extravasation. This exemplifies another means by which interference with platelet activation can augment metastasis. Furthermore, since the immunosurveillance is primarily based on direct interaction of immune cells and CTCs, the platelets attached to the CTC may serve as a shield against immune assault (276). Our results also show that attachment of platelets to softer and smaller (8-9 micrometers in diameter) CTCs are more dangerous and provides even easier adhesion and arrest in comparison with attachment to other CTCs (Figure 16-a, Figure 16-b, Figure 19-a, and Figure 19-b). Since softer CTCs are able to deform efficiently and increase their contact area with the endothelial cells (210) and the platelets, they have a higher chance of formation of firm adhesion and extravasation. In addition, the ratio of the diameter of CTC to the diameter of the microvessel seems to have a considerable effect on the CTC adhesion (Figure 19-a and Figure 19-b). Based on our observations, there is a specific ratio for the diameter of the CTC to the diameter of the microvessel which results in the fastest arrest of the CTC. This is consistent with the suggestion made by Au et al. that larger clusters of CTCs in the microvessel tend to move faster than a single CTC (277) and it is unlikely that they form a firm adhesion with endothelial cells. Consistently, Takeishi et al. (68) also demonstrated that in the case of “train

formation" for bigger CTCs, the pushing force of the RBCs hinders the arrest of CTC in the microvessel and they proposed a mathematical function to determine the state of the CTC movement based on the CTC diameter, vessel diameter, and the hematocrit level of blood. Kumar et al. also presented a computational model to study realize the effect of size and rigidity of floating particles on their margination and they demonstrated that in suspensions of unequal-sized particles (e.g. blood), margination of the dilute component mainly depends on the size of the particle (278). Smaller cells tend to marginate while bigger cells tend to move toward the center of the vessel (278). It should be noted that in the presence of platelets, the CTC-vessel wall adhesion is mainly modulated by the platelets and because the number of the platelets around the CTC is considered similar in all of our tests, the adhesion forces cannot differ significantly, but in reality, larger CTCs may or may not acquire more platelets around themselves.

There exist several experimental studies that highlight the role of platelets in the metastasis process. Gastpar et al. (207) performed several experiments to observe the interaction between platelets and CTCs and also to test the effect of different platelet-aggregation inhibitors on the metastasis process. During the experiments on the mesentery of rats, the number of platelets was counted five minutes before and thirty minutes after CTC transplantation. They observed that the number of circulating platelets decreased drastically after CTC transplantation which is because of platelet adhesion to CTCs and attachment to the vessel wall (207, 279). Furthermore, it was reported that with the injection of platelets, the number of CTCs that adhere to the vessel wall which are observed with a fluorescent microscope (280) increased confirming the platelet-CTC interactions. Gastpar reported that with the use of platelet-aggregation inhibitor drugs (such as aspirin, heparin, and mopidamole RA 233), the probabilities of CTC arrest, CTC extravasation, and metastatic tumor formation were decreased because these drugs inhibit platelets from adhering to CTCs (207). Borsig et al. (206) undertook a detailed study focusing on heparin treatment. They showed that injecting heparin can inhibit interactions of platelets with carcinoma cell-surface ligands. Therefore, CTC-platelet interaction was impaired leading to a reduction of the metastatic spreading (206). Papa et al. suggested that using platelet decoys, modified platelets that lack aggregation and activation capacity, would inhibit the platelet-mediated pathogenic processes associated with cancer metastasis (281). In a nutshell, disturbing the interactions between platelets and CTCs may substantially reduce the cancer cell survival rate and metastatic outcome.

Chapter 5
Conclusion

Using a computational model consisting of the Lattice Boltzmann Method and Discrete Element Method that are integrated with the Immersed Boundary Method, the effect of attached platelets on CTC adhesion and movement was studied. For a better understanding of the cell-cell interactions in the metastasis process, the Adhesive Dynamics Model was employed. One of the advantages of our computational models is that it could provide the quantitative information about underlying physiological mechanisms including details of fluid motion, vortex formation, and WSS, that cannot be achieved in experiments easily and can advance our understanding of the adhesion process.

It has been demonstrated that the attached platelets can significantly boost the adhesion of the CTC to the vessel wall and decrease the time and the distance in which CTC is exposed to external forces and shear stress before extravasation out of the microvessel. In addition to the faster adhesion to the vessel wall, the attached platelets form a shield around the CTC, and by distributing the external forces homogeneously on the CTC membrane, they reduce the CTC deformation by more than 50% which notably increase the survival chance of the CTC during the adhesion process. Moreover, our results show that the attached platelets increase the WSS during the adhesion process. The amount of increase in the WSS has a relationship with the number of attached platelets and the area of the elevated WSS expands considerably with increasing the number of attached platelets. The WSS is a critical parameter for the activation of adhesion molecules on the CTC, platelets, and endothelial cells. Thus, by observing the results of our simulation, one can conclude that a CTC surrounded by platelets has a higher chance of forming firm adhesion with the endothelial cells.

We demonstrated that upon rolling of CTC on the vessel wall, a disturbance appears in the plasma flow behind the CTC that leads to the formation of a vortex in that region. The vortex formation upon rolling of the CTC gained importance when we analyzed the shear forces and the velocity of the flow in that region. Our findings show higher shear forces near the CTC as a result of this vortex and these shear forces can be one of the reasons for platelet activation near the CTC. To the best of our knowledge, this is the first study that reveals the formation of vortex upon the rolling of CTC.

Future works

- Analyzing the adhesion process of CTC in complicated geometries obtained from magnetic resonance angiograms to see the results in a more realistic conditions
- Adding the cell nucleus and design a more sophisticated model of CTC to improve the accuracy of the model
- Analyzing the effect of shear rate on the parameters of the adhesion model with the presented model
- Enhancing the mechanical properties of CTCs and platelets in the simulation using experimental data
- Considering the tethering phase of adhesion in the simulation
- Simulating the extravasation of CTC out of the microvessel
- Analyzing the robustness of he results to the numerical methods and computational parameters

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