

FINITE ELEMENT ANALYSIS OF PLATELET ACTIVATION AND CELL MECHANICS IN CIRCULATING TUMOR CELL ARREST

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1. Introduction

The progression of cancer from a localized tumor to a widespread metastatic disease is a complex and multifaceted process, making it cancer patients' leading cause of death [1]. The driving force behind this process is the presence of the Circulating Tumor Cells (CTCs), which break from the primary tumor site and spread through the bloodstream to colonize other organs (Fig. 1). The presence of CTCs in the blood is a strong indicator of the metastatic potential of a tumor [2-4].

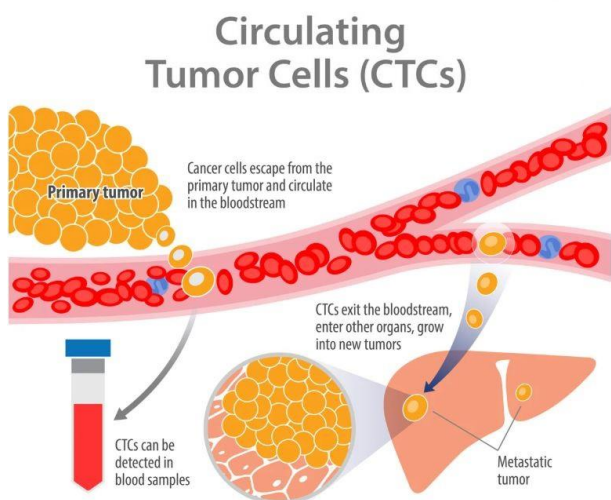


Fig. 1. Human metastasis disease progression process.

Despite their heterogeneity—since only a fraction can initiate secondary tumors—CTCs that persist in the bloodstream and evade immune surveillance are pivotal to metastatic progression. Metastasizing cancer cells can activate platelets at the primary site, increasing the local concentration of platelet microparticles (PMPs) [5], that consequently can target CTCs regarding their number or affecting their metastatic potential presents a promising strategy for managing and preventing metastatic disease. Over the past decades, extensive research has explored the interaction between CTCs and platelets in the context of metastasis. Activated platelets play a crucial role in protecting CTCs from immune surveillance and hemodynamic shear forces, thereby enhancing their survival during circulation [6].

Although the role of platelets in cancer metastasis is increasingly acknowledged, the exact mechanisms that initiate and sustain CTC–platelet interactions remain only partly understood. A deeper understanding of the molecular dynamics underlying CTC–platelet and CTC–vessel wall interactions is crucial for developing targeted strategies to disrupt these processes selectively, without compromising normal hemostasis or inflammatory responses and stiffness), the platelet size and stiffness, the ligand–receptor interaction intensity, on one side; and time in contact between

the CTCs and platelet, conditions for the cell arrest, on the other side.

This study applies a 2D computational model to investigate CTC dynamics in plasma flow through a parametric analysis of platelet adhesion, CTC size and stiffness, and ligand–receptor bond stiffness. Using a strong coupling method, solid–fluid interactions are solved simultaneously, supported by dynamic remeshing for stability. Ligand–receptor bonds are represented by 1D rope elements and experimentally measured adhesive forces with non-activated and thrombin-activated platelets are incorporated. This framework enables systematic evaluation of how geometrical and material properties, as well as platelet activation, influence CTC arrest and adhesion in circulation.

2. Materials and methods

In our previous work [7], we have considered the motion of cells and platelets within the systemic circulation as the motion of the deformable solid bodies within the fluid. Therefore, as it is mentioned above, we used a strong coupling concept with a remeshing procedure, and furthermore, introduced a simple concept for modeling the contact problems between the moving deformable solids, by using 1D solid elements that represent the contact conditions. Complete review of the basic and governing equations for modeling the fluid and solid part, as well as the solid-fluid interaction are given in [7].

2.1 Process of the experimentally determined CTC-platelets adhesion forces

This procedure is inspired by a method for measuring cell adhesion force [8]. To quantify CTC–platelet adhesion forces, mouse platelets were incubated in 96-well plates for 1 h to form a platelet-coated substrate, after which non-adherent platelets were removed by gentle washing. Fluorescently labeled 4T1 clone 17 cancer cells were then added, centrifuged at $10 \times g$ for 5 min to ensure platelet contact, and overlaid with RPMI medium. Wells were sealed with microplate tape and centrifuged upside down at forces ranging from $10 \times$ to $750 \times g$. Images of identical regions were acquired before and after each centrifugation step, and adherent cell counts were quantified using ImageJ.

2.2 Governing equations for the correction of platelet-cell adhesion forces

Here, we will focus on the explanation of the platelet-cell adhesion forces correction, according to previously mentioned experimental results and to describe the computational concept for the

correction of platelet-cell adhesion forces according to we use schematics shown in Fig. 2.

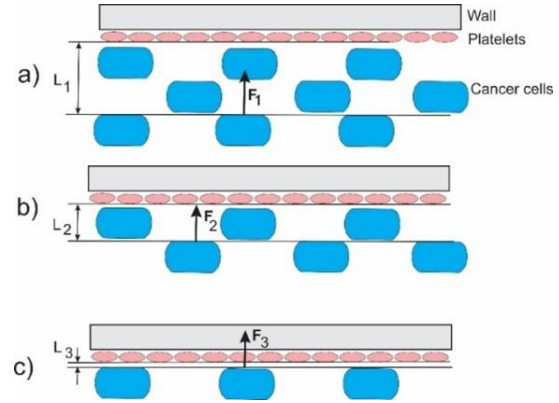


Fig. 2. Schematics of detachment of cells from the wall. a)-c) Cell distances L_1 , L_2 , L_3 from the wall covered by platelets, and the detachment adhesive forces F_1 , F_2 , and F_3 , respectively. (According to [10])

As the brief explanation of the process is given above, the detachment begins when the smallest centrifugal force is acting on cells (smallest angular velocity of the device) and starts with cells at the largest distance from the wall. This is possible when the distance is $L = L_{\max}$ ($L_{\max}$ is essentially the size of the wall-cell interaction domain), the interaction force is equal to zero, so we can write for $L = L_{\max}$:

$$L / L_{\max} = 1, \quad p_{\max} = 100, \quad F = 0. \quad (1)$$

$p_{\max}$ represents the maximum percentage of adhered cells, and F is the adhesion force. We can represent the $p_{\max}$ as

$$p_{\max} = \frac{\rho_A L_{\max}}{\rho_A H} = \frac{L_{\max}}{H} = 100 \quad (2)$$

where ρ_A is the area density of cells, and H is the device height. Regarding Fig. 2a, displayed are cells with the detachment distance L_1 so that the percentage p_1 of adhered cells is

$$p_1 = \frac{\rho_A L_1}{\rho_A H} = 100 \frac{L_1}{L_{\max}} \quad (3)$$

From the above equation (3), the percentage of the adhered cells is proportional to the distance L_1 , which can be considered the thickness of the adhered cell layer. Further, the detachment continues with the cells corresponding to distances L_2 and L_3 (Fig. 2b, and 2c) with the percentages- p_2 and p_3 , respectively. This leads to the conclusion that related to the distance L , we have a percentage p ,

$$p = 100 \frac{L}{L_{\max}} \quad (4)$$

Considering our FE model, we can state that for a distance L between corresponding nodes at a platelet and a cell, cell and wall, or platelet and wall (length of our 1D element), we have that the value (modulus) of the adhesion force is

$$F = K(L_{\max} - L), \quad F_a = K_a(L_{\max} - L) \quad (5)$$

3. Results and discussion

A simple benchmark example of the 2D axisymmetric capillary with a CTC and platelets attached is considered (Fig. 3). At first, we examine the CTC flow through a capillary without flowing platelets, leading to the cases with one up to four platelets. We have considered a case where adhesion is present in the case of non-activated platelets, as well as the adhesion forces between all the solid bodies (cells and platelets) and walls are always present.

As is described above, we consider a 2D problem of the motion of the cell and platelets caused by fluid flow within a capillary. Adhesion forces are present between cell and platelets, and cell and platelets with the wall (Fig.3a). Regarding the modeling process and generation of the computational model (Fig.3b), we have established a procedure for executing the FE simulations, which consists of three steps: pre-processing, execution of FE simulation, and post-processing. Pre-processing and model generation, ready to be executed using the FE code PAK, is achieved using our CAD FiS (Fields and Solids) software [9] (Figure 3).

The model generation process begins with the selection of appropriate options within the CAD environment, including the choice of the CAD module, definition of model geometry, specification of material models, and assignment of time-stepping parameters. Dedicated dialog interfaces are provided to define the geometrical characteristics of individual solid components (e.g., capillary channels, circulating tumor cells, and platelets), fluid flow parameters and their associated

boundary conditions, mesh configuration, and the material properties of solid structures.

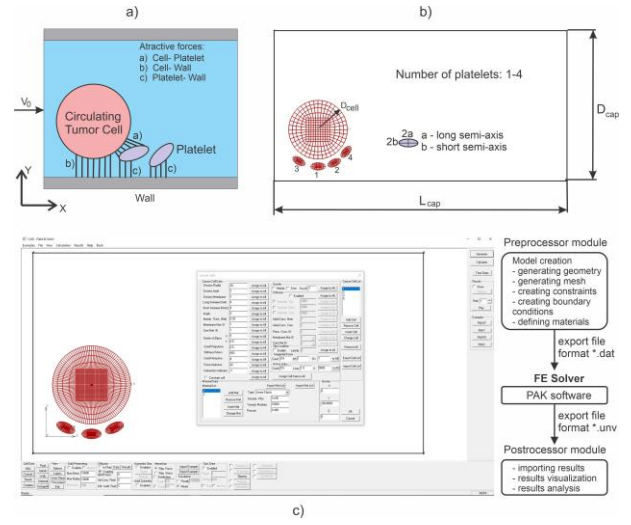


Fig. 3. Schematics of deformable cell motion in a capillary with platelet and wall interactions: a) adhesion forces between cell, platelets, and wall; b) initial platelet positions relative to the cell (1–4 platelets); c) CAD FiS pre-/post-processing interface showing CTC and platelet generation with data flow for input/output.

We examine the effects of the number of flowing platelets on the CTC stoppage time and axial position within the capillary channel. Solutions are shown in Figs. 4a and 4b, assuming cases: without platelets, 1-4 platelets, and for cell diameters $D=8$ and $11 \mu\text{m}$. The left panels represent the axial velocity V_x (of the cell center, normalized to the entering velocity V_0) vs. Time; while on the right panels are the graphs of velocity V_x vs. axial position of the CTC center. Value for the ligand-receptor bond stiffness is constant- $K=350 \text{ [kPa } \mu\text{m}]$ as well as the Young modulus of the cell- $E_{\text{cell}}= 30 \text{ [kPa]}$.

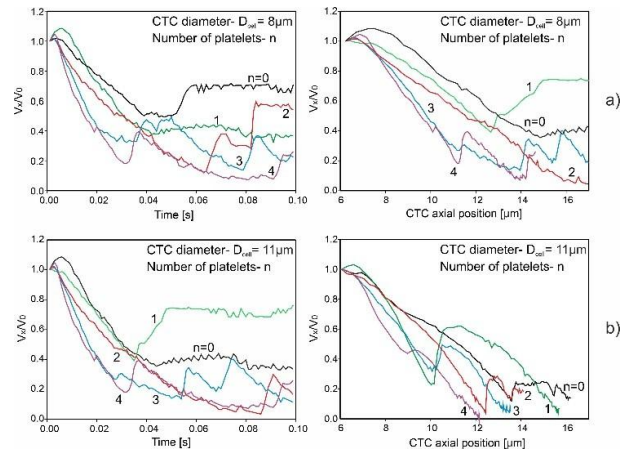


Fig. 4. Effects of number of platelets for 2 different cell diameters. Axial Velocity–Time graphs (left) and Velocity–Axial Position graphs

(right) of the cell center, for 2 cell diameters $D[\mu\text{m}]$ of CTC: a) $D=8$, b) $D=11$ (According to [10])

It is notable, from Fig.4a, that only CTC without attached platelets ($n=0$ line on diagrams) can overcome the ligand-receptor bond forces of the capillary wall and continue its motion through the channel. Ultimately, for the cell diameter of $11\mu\text{m}$ (Fig.5b), the cell continues its motion even for a maximum number of platelets. Hence, an increase in the number of attached platelets enhances the attachment to the wall (enhances metastasis, right panel of the Fig. 5b). This can be explained because of fluid flow changes and instabilities, but also due to an overall increase of adhesive bonds per unit surface of the cell.

4. Conclusion

This study analyzed CTC transport within capillaries, focusing on fluid flow, platelet interactions, and vessel wall adhesion. Using a finite element solid-fluid interaction framework, we showed that CTC arrest is strongly influenced by platelet activation and by key parameters including platelet number, CTC size, stiffness, and ligand-receptor bond properties. Experimental data further confirmed the role of platelet activation in enhancing CTC adhesion, underscoring its importance in metastasis.

Acknowledgments

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References

- [1] Ganesh, K. & Massagué, J. Targeting metastatic cancer. *Nat. Med.* 27, 34–44 (2021).
- [2] Chen J, Luo Y, Xi X, Li H, Li S, Zheng L, Yang D, Cai Z. Circulating tumor cell associated white blood cell cluster as a biomarker for metastasis and recurrence in hepatocellular carcinoma. *Front Oncol.* 2022 Nov 17;12:931140. <https://doi.org/10.3389/fonc.2022.931140>
- [3] Ju S, Chen C, Zhang J, Xu L, Zhang X, Li Z, Chen Y, Zhou J, Ji F, Wang L. Detection of circulating tumor cells: opportunities and challenges. *Biomark*

- Res.* 2022 Aug 13;10(1):58. <https://doi.org/10.1186/s40364-022-00403-2>
- [4] Lin D, Shen L, Luo M, Zhang K, Li J, Yang Q, Zhu F, Zhou D, Zheng S, Chen Y, Zhou J. Circulating tumor cells: biology and clinical significance. *Signal Transduct Target Ther.* 2021 Nov 22;6(1):404. <https://doi.org/10.1038/s41392-021-00817-8>
- [5] Lou XL, Sun J, Gong SQ, Yu XF, Gong R, Deng H. Interaction between circulating cancer cells and platelets: clinical implication. *Chin J Cancer Res.* 2015 Oct;27(5):450-60. <https://doi.org/10.3978/j.issn.1000-9604.2015.04.10>
- [6] Yu L, Guo Y, Chang Z, Zhang D, Zhang S, Pei H, Pang J, Zhao ZJ, Chen Y. Bidirectional Interaction Between Cancer Cells and Platelets Provides Potential Strategies for Cancer Therapies. *Front Oncol.* 2021 Oct 14;11:764119. <https://doi.org/10.3389/fonc.2021.764119>
- [7] Milosevic M, Simic V, Nikolic A, Shao N, Kawamura Hashimoto C, Godin B, Leonard F, Liu X, Kojic M. Modeling critical interaction for metastasis between circulating tumor cells (CTCs) and platelets adhered to the capillary wall. *Comput Methods Programs Biomed.* 2023 Dec;242:107810. <https://doi.org/10.1016/j.cmpb.2023.107810>
- [8] McClay D R, Hertzler P L. Quantitative measurement of cell adhesion using centrifugal force[J]. *Current Protocols in Cell Biology*, 1998 (1): 9.2.1-9.2.10.
- [9] Milosevic M. (2020). CAD Solid and Field - software for biomedical engineering research and accompanied software for the book: "Computational Models in Biomedical Engineering - Finite Element Models Based on Smeared Physical Fields: Theory, Solutions, and Software". <https://github.com/miljanmilos/CAD-Solid-Field>
- [10] Simic V, Nikolic A, Ning S, Milosevic M, Leonard F, Liu X, Kojic M. A parametric study of motion and attachment to capillary walls of circulating tumor cells (CTCs) interacting with non-activated and activated platelets. *Comput Methods Programs Biomed.* 2025 Jun;264:108699. <https://10.1016/j.cmpb.2025.108699>