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A computational study of circulating large tumor cells traversing microvessels

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Abstract: Circulating tumor cells (CTCs) are known to be a harbinger of cancer metastasis. The CTCs are known to circulate as individual cells or as a group of interconnected cells called CTC clusters. Since both single CTCs and CTC clusters have been detected in venous blood samples of cancer patients, they needed to traverse at least one capillary bed when crossing from arterial to venous circulation. The diameter of a typical capillary is about 7 μm, whereas the size of an individual CTC or CTC clusters can be greater than 20 μm and thus size exclusion is believed to be an important factor in the capillary arrest of CTCs – a key early event in metastasis. To examine the biophysical conditions needed for capillary arrest, we have developed a custom-built viscoelastic solid–fluid 3D computational model that enables us to calculate, under physiological conditions, the maximal CTC diameter that will pass through the capillary. We show that large CTCs and CTC clusters can successfully cross capillaries if their stiffness is relatively small. Specifically, under physiological conditions, a 13 μm diameter CTC passes through a 7 μm capillary only if its stiffness is less than 500 Pa and conversely, for a stiffness of 10 Pa the maximal passing diameter can be as high as 140 μm, such as for a cluster of CTCs. By exploring the parameter space, a relationship between the capillary blood pressure gradient and the CTC mechanical properties (size and stiffness) was determined. The presented computational platform and the resulting pressure–size–stiffness relationship can be employed as a tool to help study the biomechanical conditions needed for capillary arrest of CTCs and CTC clusters, provide predictive capabilities in disease progression based on biophysical CTC parameters, and aid in the rational design of size-based CTC isolation technologies where CTCs can experience large deformations due to high pressure gradients.

1. Introduction

The presence of circulating tumor cells (CTCs) indicates that the process of blood-borne cancer metastasis has already been initiated [1,2]. Numerous technologies [3] (e.g. microfluidic devices [4,5]) have been employed to isolate the rare CTCs from blood samples of cancer patients, usually obtained from venous blood draws. Several studies have also shown that the presence of CTC clusters in the circulation potentially plays an important role in metastasis [6–9]. CTCs or larger CTC clusters generally need to traverse: (1) venous drainage of the tumor leading to the right side of the heart followed by passage through the pulmonary capillaries leading back to the heart; (2) then from the left heart to the distal small arteries in the hand followed by passage through the distal hand capillary bed leading to venous side of the arm. This implies that not one, but two capillary beds may need to be crossed by the CTCs and CTC clusters. The typical diameter of a capillary is around 7 microns (although the range can be from 5–10 microns) [10,11], whereas an individual CTCs can be as large as ~20 μm and the CTC clusters can be much larger, on the order of 100 μm [4,5,12]. Based on this considerable size difference, it has been postulated that the larger size of CTCs prevents them from passing through capillaries [13], implying that size restriction plays an important role in cancer metastasis [13,14]. The arrest of CTCs in capillaries is believed to be a key part of the metastatic process, as the step prior to their extravasation and subsequent growth in the surrounding tissues [14,15]. Additionally, in certain blood cancers, such as acute leukemia, a very large number of cancer blood cells can exist in blood due to uncontrolled proliferation of myeloid or lymphoid lineage cells. This situation can then precipitate the onset of leukostasis – a poorly understood condition where cancer cells aggregate within the vasculature and cause

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grave clinical symptoms [16–18]. In the above cases, the arrest of the CTCs or CTC clusters as well as large leukemic cells in capillaries is mainly dictated by two mechanisms: (1) the interaction of the cells with the vasculature, which we term as the biochemical component and (2) the size and mechanical properties of the cells coupled to the local fluid conditions, termed the biophysical component. Although there has been considerable focus on the former [14,15], the effect of the latter, biophysical component, is not well understood.

We here present a custom-built computational platform that allows us to determine how a large visco-elastic solid (CTC) deforms and passes through a smaller-sized narrowing (microvessel). The platform is finite-element based, and we introduce a strong-coupling method that enables direct coupling of the solid properties (e.g. stiffness) to the fluid conditions (e.g. pressure) in order to solve for the resulting deformations. With this customized approach we examine the biophysical conditions needed to allow large-diameter CTCs to pass through a typical 7 μm capillary. The computational model reveals a simple relationship between the three key biophysical parameters: (1) CTC diameter, (2) CTC stiffness, and (3) fluid (blood) pressure gradient across the capillary. Our analysis spans several orders of magnitude for cell diameter and stiffness, and offers predictive capability about what kind of CTC (e.g. size) may be arrested in the microvasculature under physiological conditions. The pressure–size–stiffness relationship reveals that, for a given pressure, cell stiffness strongly affects the maximal cell size that can pass into the capillary. We have found that, under physiological conditions, even a very large cell or a cluster of cells (~100 μm diameter) can pass only if its stiffness is very small (~10 Pa), and conversely a CTC whose stiffness is 1000 Pa will be arrested in the capillary if its diameter is greater than 12 μm. Taken together, the computational results and derived biophysical relationship provide a tool to better understand how large CTCs go through smaller-sized capillaries; this is central not only for cancer metastasis but also for size-based CTC isolation technologies where CTCs can experience large pressure gradients [19].

2. Methods

In order to develop a computational model of an incompressible solid (cell) going through a smaller-sized narrowing (capillary) we had to address the following two challenging issues: (1) to model solid–fluid interaction with motion of the deformable solid within the fluid, and (2) to model solid–solid interaction with large relative displacements of the interacting surfaces as well as to model large deformations of the incompressible solid. We here summarize the basic relations and steps involved in addressing these issues.

2.1. Fundamental relations

For the fluid, we have the basic equations of balance of linear momentum, known as the Navier–Stokes equations:

$$\rho_f\left(\frac{\partial v_i}{\partial t}+\frac{\partial v_i}{\partial x_k}v_k\right)=-\frac{\partial p_f}{\partial x_i}+\mu\frac{\partial^2 v_i}{\partial x_k\partial x_k}+f_i^{fV},\quad i=1,\ 2,\ 3;\quad \text{sum on } k,$$
$$k:\ \ k=1,\ 2,\ 3 \tag{1}$$

where ρ_f and p_f are density and pressure of the fluid, respectively, μ is the viscosity, f_i^{fV} are the volumetric forces, and v_i are fluid velocities. We consider an incompressible fluid (water), hence, the continuity equation is expressed as

$$div(\mathbf{v})=\partial v_i/\partial x_i=0 \tag{2}$$

Using a standard Galerkin procedure [20], Eqs.(1) and (2) can be transformed into the finite element (FE) incremental-iterative algebraic equations (corresponding to one FE):

$$\begin{bmatrix}\frac{1}{\Delta t}\mathbf{M}_f+\mathbf{K}_{vv}{}^{(i-1)} & \mathbf{K}_{vp}\\ \mathbf{K}_{vp}^T & 0\end{bmatrix}\begin{Bmatrix}\Delta\mathbf{V}^{(i)}\\ \Delta P_f^{(i)}\end{Bmatrix}=\begin{Bmatrix}\mathbf{F}_f^{ext}\\ 0\end{Bmatrix}$$
$$-\begin{bmatrix}\frac{1}{\Delta t}\mathbf{M}_f+\mathbf{K}_{vv}{}^{(i-1)} & \mathbf{K}_{vp}\\ \mathbf{K}_{vp}^T & 0\end{bmatrix}\begin{Bmatrix}\mathbf{V}_f^{(i-1)}\\ P_f^{(i-1)}\end{Bmatrix}+\begin{Bmatrix}\frac{1}{\Delta t}\mathbf{M}_f\mathbf{V}_f^t\\ 0\end{Bmatrix} \tag{3}$$

where $\mathbf{V}_f$ are velocities of FE nodes ($\mathbf{V}_f^t$ is the velocity at the start of the time step), P_f is the pressure of the element (we use a constant pressure assμmption for the element), and $\mathbf{F}_f^{ext}$ are external nodal forces, which include actions of other elements; Δt is the time step size, and 'i' is the equilibrium iteration counter. The explicit expressions for the element matrices $\mathbf{M}_f$, $\mathbf{K}_{vv}$ and $\mathbf{K}_{vp}$ can be found elsewhere [20].

For the solid, treated as incompressible, we adopt the approach analogous to the one generally used for modeling incompressible elastic or inelastic material deformation [21,22]. The stress tensor σ_{ij} can be decomposed into the deviatoric stress σ'_{ij} and the mean stress p,

$$\sigma_{ij}=\sigma'_{ij}+p \tag{4}$$

$$p=(\sigma_{11}+\sigma_{22}+\sigma_{33})/3 \tag{5}$$

Then, differential equations of balance of linear momentum can be written in the form:

$$-\rho_s\frac{\partial^2 u_i}{\partial t^2}+\frac{\partial\sigma'_{ij}}{\partial x_j}+\frac{\partial p}{\partial x_i}+f_i^{sV}=0,\quad \text{sum on } j \tag{6}$$

where ρ_s is the solid density, u_i are displacements, and f_i^{sV} are volumetric forces. Further, we use deviatoric strains e'_{ij},

$$e'_{ij}=e_{ij}-\delta_{ij}e_v/3 \tag{7}$$

where $e_v=e_{11}+e_{22}+e_{33}$ is the volumetric strain, and δ_{ij} is the Kronecker delta symbol. Elastic constitutive relations can be written as

$$\sigma'_{ij}E=2Ge'_{ij} \tag{8}$$

where $\sigma'_{ij}E$ are elastic deviatoric stresses, and G is the shear modulus. In order to treat the solid as viscoelastic, we employ linear viscoelastic relations,

$$\sigma_{ij}^{vE}=D\frac{\partial e_{ij}}{\partial t} \tag{9}$$

where σ_{ij}^{vE} are viscoelastic stresses, and D is the damping coefficient. The incompressibility condition has the same form as for the fluid (Eq. (2)).

Using the principle of virtual work, the above fundamental equations for the solid can be transformed into equations of balance for a solid finite element:

$$\begin{bmatrix}\frac{1}{\Delta t}\mathbf{M}_s+\Delta t\mathbf{K}_{uu}^{(i-1)} & \mathbf{K}_{vp}\\ \mathbf{K}_{vp}^T & 0\end{bmatrix}\begin{Bmatrix}\Delta\mathbf{V}_s^{(i)}\\ \Delta P_s^{(i)}\end{Bmatrix}=\begin{Bmatrix}\mathbf{F}_{ext}-\mathbf{F}^{\mathrm{int}(i-1)}\\ 0\end{Bmatrix}$$
$$-\begin{bmatrix}\frac{1}{\Delta t}\mathbf{M}_s & \mathbf{K}vp\\ \mathbf{K}_{vp}^T & 0\end{bmatrix}\begin{Bmatrix}\mathbf{V}_s^{(i-1)}\\ P_s^{(i-1)}\end{Bmatrix}+\begin{Bmatrix}\frac{1}{\Delta t}\mathbf{M}_s\mathbf{V}_s^t\\ 0\end{Bmatrix} \tag{10}$$

where $\mathbf{V}_s^{(i)}$ are nodal velocities, P_s is the mean stress of the element (assumed constant over the element, as for the fluid), and $\mathbf{F}^{int}$ are the internal element forces, corresponding to stresses. Details about element matrices and derivations of this equation can be found in [20,23].