Viscoelastic gel-strip model for the simulation of migrating cells

by

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Abstract

Migrating tumor cells can exhibit both mesenchymal-type and amoeboid-type behaviors. Recent studies have shown that both cellular and extracellular structural and mechanical variables control the transition of tumor cells from one mode to the other and provide them with morphological plasticity. The mesenchymal-mode migration is characterized by strong adhesion and proteolytic machinery to navigate through complex extracellular matrices. The amoeboid-mode migration is characterized by little or no adhesion and strong actomyosin contraction to squeeze through the matrices. While adhesion dependent migration has been computationally and experimentally studied in both 2D and 3D environments, quantitative models of amoeboid motion in native environments are lacking. In order to address this major gap in our understanding and to probe the mesenchymal to amoeboid transitions quantitatively and comprehensively, we have developed an axisymmetric viscoelastic gel-strip model of a single cell to investigate a cell migrating in native-like environments. In this model, cell migration and morphology are governed by internal stresses as well as external forces. The internal stresses are controlled by F-actin density distribution, protrusion strength, and contraction strength. The external forces are controlled by adhesion strength and steric resistance from the extracellular matrix. Our model predicts that the transition of the cell migration mode from mesenchymal- to amoeboid-type, and vice versa, is closely related to the loss of adhesion as well as increased contraction strength of the cells. Our results indicate that amoeboid migration is more suited for low-resistance environment while mesenchymal migration is preferred in high-resistance environment, which would explain the versatile behaviors of tumor cells in complex environments.

1 Introduction

Tumor metastasis, the process by which cancer spreads from one part of the body to another, is responsible for nearly all cancer related deaths. The metastatic process is complex and multistep
involving Epithelial-to-Mesenchymal Transition (EMT), invasion, and migration, to name a few. Invasion by tumor cells involves coordinated processes such as adhesion, proteolytic interaction with the extracellular matrix (ECM), responsible for degrading and remodeling the tissue barriers, and migration through dense ECM environments [15]. While cell migration has been studied for decades, only recently have we started to appreciate the complexity and plasticity of cell migration in native-like environments, especially in three-dimensional domains. Cells in 3D environments exhibit dynamic changes in their morphology in order to crawl through matrix gaps [47] while cells in 2D environments exhibit flattened morphology and slowly migrate on substrates in the absence of matrix resistance or complex proteolytic interactions. Recent studies have suggested that the morphology and migration behavior of a tumor cell in 3D environments are controlled by the balance of multiscale factors such as ECM density, ECM orientation, ECM stiffness, cell-ECM adhesion, Rho and Rac signaling, all influencing the cell protrusion and contraction strengths as well as proteolytic activities [11]. For example, inhibition of the cell-ECM adhesion and proteolytic activities results in a transition from mesenchymal-like to amoeboid-like morphology in an individually migrating cell [35, 37, 47, 49]. Mesenchymal migration is characterized by a spindle-shaped morphology of the cell with strong adhesion to the ECM while amoeboid migration is characterized by protrusion into preexisting matrix gaps and formation of constriction rings with high actomyosin contractility. While the biochemical factors regulating these transitions are starting to be uncovered, little is known about the biomechanical factors contributing to this transition. A detailed and quantitative investigation of key biomechanical factors regulating tumor cell motility, as well as cell migration transition, would help improve our understanding of tumor cell migration in native environments, see e.g. [8, 9, 12, 47, 48].

In recent years, various mathematical and computational models have been developed to study motility processes of cells in general and of tumor cells in particular. These models include reaction-diffusion-type models that describe kinetics and reactions [14, 21], ordinary differential equation models for various signaling pathways [38], molecular dynamics models to account for the molecular motors and molecules at the cell-matrix interface [26, 44], continuum mechanics models to describe the force generation and dissipation in various positions in migrating cells [4, 27, 34], or probabilistic multiscale models for tumor growth and invasion [2, 18], or for cell-matrix interactions [51, 52, 53]. These approaches have been extremely useful in providing quantitative frameworks for existing experimental data, for resolving contradictions in experimental literature, for making a priori predictions, and for suggesting a series of new experiments to develop a richer understanding of processes underlying cell migration at various length and time scales. However, models describing migration of a whole cell in native environments are lacking [31], due to the lack of experimental data to support or validate the models. A new generation of detailed migration models are crucially needed to better understand migration processes of cells in their actual environments.

In order to understand the complexity of cell migration in native environments and develop a tractable and scalable approach, we have constructed a viscoelastic gel-strip model for the simulation of cells migrating through three-dimensional environments. The model has a length scale of 1 to 10 µm and time scale of 10 to 100 minutes, which correspond to the length and time scales of actual cell migration processes. The model reduces, in the case of axisymmetric cells, to a set of one-dimensional differential equations that can be approximated by the finite element method. In our model, we have focused on the biophysical and biomechanical features of cell migration and have accounted for biochemical factors implicitly. The results of our model qualitatively agree with
experimental observations [19, 47] and provide a new scalable framework for analyzing the relation between physical properties of cells and their migration pattern and morphology.

2 Cell Model

Our goal is to develop a realistic viscoelastic model for cell migration that is capable of capturing the migration behaviors of both mesenchymal- and amoeboid-type cells as well as the transition from one type to the other. We are particularly interested in the long-term average behaviors of cells. Thus, rather than considering a structurally changing ECM environment, we assume that a given cell migrates through a continuum from which it continuously receives uniform external excitations. This assumption enables us to use continuum mechanics models to simulate a cell along with its external environment. We assume that the migration of a cell can be described by an axisymmetric model. Since the goal of our study is to compare behaviors and environmental regulation of motility, this assumption, while simplistic, should allow us to predict the essential (large-scale) features of cell motion.

We thus consider an axisymmetric cell with length $L = L(t)$ and cross-area $A = A(x, t)$, whose initial configuration is shown in Fig 1. Here, $x$ denotes the position of a material point on the cell axis and $t$ an instant of time. Moreover, we assume that the cell can be modeled as a homogeneous continuum mixture (small-scale phenomena are neglected) and that momentum exchanges in the radial direction are negligible compared to those in the axial direction due to the axisymmetric assumptions. We only consider the normal stress due to the fact that a migrating cell exhibits a polarized actin cytoskeleton that grows into the direction of migration [11, 25]. We also assume that all material properties remain constant along each cross-section. We denote by $\Omega(t)$ the interval occupied by the cell centerline as time evolves and suppose that the initial domain is given by $\Omega_0 = (-L_0/2, L_0/2)$ (i.e. the center of gravity of the cell is located at the origin at $t = 0$), where $L_0 = L(0)$ represents the initial length. The displacement $u = u(x, t)$ with respect to the position $x$ in the reference configuration $\Omega_0$ is obtained as $u(x, t) = \varphi(x, t) - x$, where $\varphi(x, t)$ provides the evolution of the material point $x$. The velocity $v = v(x, t)$ can then be determined as $v(x, t) = \partial \varphi / \partial t(x, t) = \partial u / \partial t(x, t)$. Based on these assumptions, deformation and migration of the cell are governed by the balance of momentum equation:

$$\frac{-\partial A(x, t)\sigma(x, t)}{\partial x} = f_{\text{ext}}(x, t), \quad \text{for } x \in \Omega_0$$

and are subjected to the initial conditions:

$$\begin{cases}
  u(x, 0) = 0 \\
  v(x, 0) = 0 \\
  A(x, 0) = A_0(x)
\end{cases} \quad \text{for } x \in \Omega_0$$

where $f_{\text{ext}}$ includes the $x$-component of all external body force densities per unit length exerted by the ECM on the cell. Inertial effects are neglected due to the very small values of the velocity (typically in the range 0.1–1 µm/min). The cell being axisymmetric and assumed incompressible, the cell shape is determined in terms of the cross-sectional area, equivalently the radius $r = r(x, t) = \sqrt{A(x, t)/\pi}$, and updated at each time from the previous area/radius and strain
\( \epsilon(x,t) = \partial u/\partial x(x,t) \) as:

\[
A(x, t + dt) = \frac{A(x, t)}{1 + \epsilon(x,t)} \quad \text{or} \quad r(x, t + dt) = \frac{r(x, t)}{\sqrt{1 + \epsilon(x,t)}} \tag{3}
\]

The cytoplasm of the cell is characterized as a viscoelastic material [20, 40]. A number of studies actually suggest that the viscoelastic characteristics of cells can be described by the Kelvin-Voight model for short time scales [30]. Hence, in this case, the cell can be viewed as a gel-like linear viscoelastic material giving rise to a passive stress. We note that passive stresses are not responsible for moving the cell forward but can promote the deformation of the cell. The constitutive equation can therefore be described as:

\[
\sigma(x,t) = E(x,t) \epsilon(x,t) + \mu(x,t) \frac{\partial \epsilon}{\partial t} + \Gamma(x,t) \tag{4}
\]

where \( E = E(x,t) \) is the elastic modulus, \( \mu = \mu(x,t) \) is the viscosity, and \( \Gamma = \Gamma(x,t) \) the contractile stress (described below). The balance equation (1) and constitutive equation (4) are complemented by the boundary conditions,

\[
A(-L_0/2, t) \sigma(-L_0/2, t) = 0 \quad \text{(at the trailing edge)} \tag{5}
\]

\[
A(+L_0/2, t) \sigma(+L_0/2, t) = 0 \quad \text{(at the leading edge)} \tag{6}
\]

The cell only comes into contact with the ECM along the membrane. Therefore, no forces are exerted on the leading edge and trailing edge. Traction applied to the cell surfaces are actually converted into body forces per unit length thanks to the axisymmetric assumptions.

### 2.1 Modeling of internal stresses

Actin network is the primary component of the cell cytoskeleton. Its polymerization generates the protrusive force at the leading edge and its contraction due to binding of myosin generates the contractile stress in the rear of the cell [25]. Therefore, the actin cytoskeleton should be considered as one of the most important mechanical structures during migration. It has been observed (see e.g. [23]) that the cell stiffness profile is comparable to the F-actin density profile in the sense that the elastic modulus of a cell may increase two to ten-fold from the rear of a lamellipod to its front. Here, the elastic modulus is assumed proportional to the F-actin density,

\[
E(x,t) = E_0 a(x,t) \tag{7}
\]

where \( E_0 \) is a characteristic modulus of elasticity. We indeed assume that the cell follows a linearly elastic behavior. The initial cytoskeletal actin density is modeled as,

\[
a(x,0) = a_{\text{max}} \left( \frac{1 - \exp((1/2 + x/L_0)/\theta)}{1 - \exp(1/\theta)} \right) + a_{\text{min}} \left( \frac{\exp((1/2 + x/L_0)/\theta) - \exp(1/\theta)}{1 - \exp(1/\theta)} \right) \tag{8}
\]

We chose here to normalize the F-actin density by its minimum value at the trailing edge. In other words, \( a(x,0) \) varies from \( a_{\text{min}} \) at the trailing edge to \( a_{\text{max}} \) at the leading edge with an exponential profile controlled by parameter \( \theta \). We chose \( \theta \) as 0.05 to mimic the actual actin density profile observed in experiments [23] and to incorporate the fact that actin polymerization mainly occurs
at the leading edge while depolymerization mainly takes place at the rear of the cell [39]. The F-actin density \( a(x,t) \) is modeled in time based on the following conservation law:

\[
a(x,t + dt) = a(x,t) + \frac{A(x,t)}{A(x,t + dt)} \tag{9}
\]

Moreover, the viscosity of the cell is assumed uniform, \( \mu(x,t) = \mu_0 \), where the value of the parameter \( \mu_0 \) is taken from [3, 7]. We also incorporate in the model the effects of actomyosin motors that are responsible for the contraction of the cell [20, 22]. The mechanical details of the myosin-based contraction process has yet to be fully elucidated. Here, we assume that the formation of actomyosin network activates the actomyosin motors, which makes the cell stiffer [25, 24]. In our model, the contractile stress is given by the elastic stress controlled by the concentration of bound myosin density \( m_b \) onto the actin network in a cell. The contraction strength is proportional to the elongation rate (strain) at each point. The contractile stress is thus modeled as

\[
\Gamma(x,t) = \gamma_0 m_b(x,t) \epsilon(x,t) \tag{10}
\]

where \( \gamma_0 \) is a characteristic myosin stress parameter. Binding of myosin to F-actin is at equilibrium at every time step and diffusion of free myosin is an instantaneous process. The concentration of myosin can thus be assumed constant in the cell. These assumptions are actually justified by the fact that cell migration is a very slow process so that the diffusion of free myosin and association/dissociation of myosin molecules to F-actin occur rather instantaneously. The kinetic reaction for myosin is given by:

\[
m_f + a \xrightarrow{k^+} m_b \xrightarrow{k^-} m_f \tag{11}
\]

\( m_f \) being the concentration of free myosin. Observation in keratocytes suggests that the actomyosin contractility activity is concentrated in the cell body, after the lamellipodial region [39]. We mathematically modeled this actomyosin contractility profile through the myosin binding rate. The binding rate \( k^+_m(x,t) \) reaches a maximum value, denoted by \( \psi_k(t) = \max_x k^+_m(x,t) \), at the center of the cell and zero at the boundaries while the dissociation rate \( k^-_m \) is constant throughout the cell. We also assume that the total number \( N_m \) of myosin molecules is conserved over time and that the maximum binding rate does not change over time (\( \psi_k(t) = \psi_k \)). Based on these assumptions, we derive the following equations,

\[
m_b(x,t) = \frac{k^+_m(x,t)}{k^-_m} a(x,t) m_f(t) \tag{12}
\]

\[
k^+_m(x,t) = 4\psi_k \frac{[\varphi(L_0/2,t) - \varphi(x,t)] [\varphi(x,t) - \varphi(-L_0/2,t)]}{[\varphi(L_0/2,t) - \varphi(-L_0/2,t)]^2} \tag{13}
\]

\[
N_m = \int_{-L_0/2}^{+L_0/2} (m_f(t) + m_b(x,t)) A(x,t) \, dx
\]

\[
= m_f(t) \int_{-L_0/2}^{+L_0/2} \left( 1 + \frac{k^+_m(x,t)}{k^-_m} a(x,t) \right) A(x,t) \, dx \tag{14}
\]
Using these equations, we can compute $m_f$ and $m_b$ at each point and at every time. Also, note that the contraction strength is controlled by the “contractility” parameter, which we define here as $\Gamma_c = \gamma_0 N_m$, and that $k_m^+(x,t)$ is scaled by $k_m^-$ in equation (12) and (14). We choose the value of $k_m^-$ to be equal to unity, without loss of generality, so that the ratio $k_m^+/k_m^-$ can be controlled by the parameter $\psi_k$. The contractility parameter is chosen so that for the average bond myosin density and average strain, the contractile stress is of the order of 100 Pa [13, 28].

2.2 Modeling of external forces

Using our viscoelastic gel strip model, we are also able to study the effect of external forces on the cell. External forces acting on a cell are modeled by force densities and can be divided into three contributions, namely a viscous adhesion force density, a resistance force density from the ECM, and a protrusive force density:

$$f_{\text{ext}}(x,t) = f_{\text{adh}}(x,t) + f_{\text{res}}(x,t) + f_{\text{pro}}(x,t)$$ (15)

Note that all external forces are exerted on the cell surface. The exact mechanisms of adhesion between the cell surface and substrates are yet to be elucidated through experiments. Here, we simply suppose that the adhesion force can be represented as a viscous force,

$$f_{\text{adh}}(x,t) = -\beta(x,t) \frac{\partial u}{\partial t}(x,t) t_x$$ (16)

$$t_x(x,t) = \frac{1}{\sqrt{1 + \left(\frac{\partial r}{\partial x}\right)^2}}$$ (17)

where $\beta = \beta(x,t)$ is the effective adhesion drag coefficient of the cell-ECM interaction and $t_x$ is the $x$-component of the unit tangent vector on the cell surface. The tangent vector which is directed towards the direction of migration is chosen here. See Fig. 1. Note that the assumption that the adhesion drag force can be described as a viscous force has already been used in a number of other models for cell motility [14, 21, 33]. We assume further that the adhesion strength at a point depends linearly on the concentration of integrin complexes attached to the ligands on the ECM surface. Thus, we can model the adhesion strength as $\beta(x,t) = \beta_0 n_b(x,t)$, where $\beta_0$ is a characteristic adhesion strength parameter and $n_b(x,t)$ the pointwise concentration of the bounded integrin complexes. Again, we assume that the diffusion of free integrin and association/dissociation of integrins to/from the ligands can be considered as instantaneous processes when compared to the cell migration time scale, so that:

$$n_f + n_s \xrightarrow{k_f} k_{r_0} g_{r_0}(x,t) n_b$$ (18)

where $n_f$ and $n_s$ are the concentrations of the free integrins and of the surface ligands, respectively. The formation rate $k_f$ is taken constant and the dissociation rate $k_{r_0} g_{r_0}(x,t)$ is supposed to depend on the position in the cell. Since diffusion of free integrin is considered an instantaneous process, $n_f^0$ is constant. Also, we assume that there exists a saturating number of ligands on the ECM. Thus, assuming the ligand density $n_s^0$ to be constant and the depletion of ligands to be negligible,
one then has:

\[ n_s(x, t) = n_s^0 \times 2\pi r(x, t) \] (19)

\[ n_f(x, t) = n_f^0(t) \times 2\pi r(x, t) \] (20)

The concentration of the complexes, \( n_b \), can then be determined as

\[ n_b(x, t) = \frac{k_f}{k_r n_s^0} n_s(x, t) n_f(x, t) \] (21)

Recent studies suggest that the complexes form mainly in the protrusive region while they rapidly dissociate away from the protrusive region [5, 46]. It is also observed that the traction stress is concentrated in the same region [42]. In order to mathematically model the cell adhesion dynamics, we assume that the dissociation rate increases from the front to the rear of the cell, being unity at \( x = L_0/2 \) and \( \psi_r \) at \( x = -L_0/2 \), \( \psi_r \geq 1 \), i.e.

\[ g_{r0}(x, t) = \psi_r + (1 - \psi_r) \frac{\varphi(x, t) - \varphi(-L_0/2, t)}{\varphi(L_0/2, t) - \varphi(-L_0/2, t)} \] (22)

where \( \psi_r \) is a given parameter of the model. If the total number \( N_c \) of integrins in a cell remains constant with time, then we can determine \( n_f^0 \) using the relationship:

\[ N_c = \int_{-L_0/2}^{+L_0/2} n_b(x, t) \, dx + n_f(x, t) \, dx \]

\[ = n_f^0(t) \left( \frac{k_f}{k_r n_s^0} \int_{-L_0/2}^{+L_0/2} r^2(x, t) \, dx + 2\pi \int_{-L_0/2}^{+L_0/2} r(x, t) \, dx \right) \] (23)

Here, we can see that the larger the value of \( \psi_r \), the more asymmetric the adhesion is. The total number of integrins \( N_c \) is chosen as that given in [14] and the characteristic adhesion strength parameter \( \beta_0 \) is identified from the data provided in [1, 42], where the average traction stress is in the range 10–100 Pa. We also introduce a new parameter, \( B_c = 4\pi^2 \beta_0 n_s^0 / k_r \), that we shall refer to as adhesivity in the remainder of the paper

\[ \beta(x, t) = 4\pi^2 \beta_0 \frac{n_s^0}{k_r} k_f r^2(x, t) n_f^0(t) = B_c k_f r^2(x, t) n_f^0(t) \] (24)

In order for a cell to crawl through the ECM in 3D environments, it has to overcome the steric resistance force from the ECM [20]. The resistance force depends on the shape of the cell as well as on the density, porosity, and modulus of elasticity of the ECM. Here, we assume that the ECM is a continuum that does not have any variations in its material parameters. In an elastic solid, the force necessary to deform the matrix depends on the rate of deformation, and hence, the velocity, and its direction is normal to the cell surface. Therefore, the resistance force density is modeled here as:

\[ f_{\text{res}}(x, t) = -A(x, t) f_{\text{res}}^0 \frac{\partial u}{\partial t}(x, t) n_x \] (25)

\[ n_x(x, t) = \frac{-\frac{\partial r}{\partial x}}{\sqrt{1 + \left(\frac{\partial r}{\partial x}\right)^2}} \] (26)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$L_0$</td>
<td>Characteristic length of cell</td>
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<td>µm</td>
<td>[47]</td>
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<td>$E_0$</td>
<td>Basal modulus of elasticity</td>
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<td>pN/µm$^2$</td>
<td>[23]</td>
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<tr>
<td>$\mu$</td>
<td>Viscosity</td>
<td>$2 \times 10^4$</td>
<td>pNs/µm$^2$</td>
<td>[3, 7]</td>
</tr>
<tr>
<td>$a_{\text{max}}$</td>
<td>Maximum F-actin density</td>
<td>2</td>
<td></td>
<td>[23]</td>
</tr>
<tr>
<td>$f_{\text{pro}}^0$</td>
<td>Protrusion force coefficient per complex</td>
<td>$2.4 \times 10^{-9}$</td>
<td>N/m</td>
<td>estimated from [1, 45]</td>
</tr>
<tr>
<td>$\Gamma_c$</td>
<td>Contractility</td>
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<td>N/m$^2$</td>
<td>estimated from [13, 28]</td>
</tr>
<tr>
<td>$\psi_r$</td>
<td>Integrin dissociation increase</td>
<td>$1 - 10^{10}$</td>
<td>N/m$^2$</td>
<td>estimated from [5, 42, 46]</td>
</tr>
<tr>
<td>$\psi_k$</td>
<td>Maximum rate of myosin binding</td>
<td>$1 - 10^5$</td>
<td></td>
<td>estimated from [39]</td>
</tr>
<tr>
<td>$k_f$</td>
<td>Rate of formation of adhesion complexes</td>
<td>$10^{-18} - 10^{-5}$</td>
<td></td>
<td>estimated in this paper</td>
</tr>
<tr>
<td>$N_c$</td>
<td>Total number of complexes in a cell</td>
<td>$10^3$</td>
<td>( \text{N/m}^2 )</td>
<td>[14]</td>
</tr>
<tr>
<td>$B_c$</td>
<td>Adhesivity</td>
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<td>N s/m$^3$</td>
<td>estimated from [1, 42]</td>
</tr>
<tr>
<td>$f_{\text{res}}^0$</td>
<td>Steric resistance coefficient</td>
<td>$0 - 10^{20}$</td>
<td>N s m$^4$</td>
<td>estimated in this paper</td>
</tr>
</tbody>
</table>

Table 1: Model parameters.

where \( f_{\text{res}}^0 \) is the steric resistance coefficient exerted by the ECM which depends on the density, porosity, and elasticity of the ECM, and \( n_x \) is the \( x \)-component of the unit outward normal vector on the cell surface, which is shown in Fig. 1. Since a value of \( f_{\text{res}}^0 \) is not available in the literature, we choose to make it a parameter that we vary in order to study its influence: from the value 0, for which there is no resistance, to the value $10^{20}$, for which the cell is completely stationary.

In the protrusive region, the cell elongates due to F-actin polymerization, which pushes the cell membrane outward [20, 22]. The process is modeled here by a force density (per unit length) acting mainly on the protrusive region that drives the cell forward. The magnitude of the protrusion force density \( f_{\text{pro}} \) should depend on the polymerization rate of the F-actin fiber and adhesion strength. Clearly, if the polymerization cannot overcome the membrane resistance, the cell cannot elongate, and thus, there is no protrusion. Also, if there is no adhesion at the leading edge, the cell cannot generate any traction force to pull itself forward. Therefore, the protrusive force can be modeled as

\[
f_{\text{pro}}(x, t) = f_{\text{pro}}^0 \left( a(x, t) - a(-L_0/2, t) \right) n_b(x, t) n_x
\]

where \( f_{\text{pro}}^0 \) is a given parameter, which is arbitrarily chosen so that the force produced by a cell is within the range provided in [1, 45] ($\sim 1000$ nN), and \( n_x \) is the \( x \)-component of the unit normal vector on the cell surface described in (26). The strength of the protrusion is governed by the pointwise polymerization intensity, which is proportional to the increase of actin density from its base value, \( a(-L_0/2, t) \). The protrusion force also directly relates to the bound integrin complex density \( n_b(x, t) \) because a cell has to attach its membrane onto the ECM in order to generate the force that pulls itself forward. Thus, the more adhesion complexes a cell can produce at its leading edge, the stronger the protrusive force it can generate.

As a summary, all model parameters introduced in above equations are collected in Table 1 and are assigned values relevant to the conditions of interest.

### 2.3 Numerical implementation of axisymmetric model

The problem consisting of the ordinary differential equation (1), along with the constitutive equation (4), the initial conditions (2) and boundary conditions (5), is discretized in space using the
finite element method and in time using a second-order Runge-Kutta method (midpoint rule) for the approximation of the displacement $u(x, t)$. We assume that the external force and boundary conditions remain constant within each time step whenever the time step is kept sufficiently small. It follows that $f_{\text{ext}}$ can be explicitly computed using the solution on the initial configuration. In addition, the cross-sectional area $A$ and F-actin density $a$ are updated at each time step using the current solution state. Convergence of the algorithm has been numerically observed when sufficiently small time steps $\Delta t$ and mesh sizes $h$ are used.

3 Results

In this model, we consider a cell whose initial shape is given by an ellipsoid, as shown in Fig. 1, and whose centroid is located at $x = 0$.

3.1 Cell migration

We first investigate the evolution of shape and velocity of the cell as well as other output quantities, to confirm whether the proposed model is able to realistically reproduce the cell behavior. Figure 2 shows snapshots of a cell migrating in a given ECM at times $t = 0$ s, 100 s, 200 s, and 600 s. The initial length is set to $L_0 = 30 \, \mu m$. The evolution of the cell leading edge and trailing edge is plotted in Fig. 3. We observe in this case that the cell starts from a spherical shape, quickly elongates at first, and later moves forward with a constant length and a steady velocity. Time scales of cell deformation and cell acceleration are in qualitative agreement with the ones observed in experiments [47]. Note that the evolution of the cell depends naturally on the modeling parameters. For example, a stiffer cell tends to form a protrusive region more quickly.

Figure 4 shows the cell displacement, the adhesion strength, and modulus of actin elasticity ($E_0 a$) and contractile elasticity ($\gamma_0 m_b(x, t)$) at $t = 600$ s obtained on the same cell as the one described in Fig. 2. Figure 4(a) shows that the cell elongates more towards its front, forming a protrusive region. In Fig. 4(b), we note that the adhesion drag coefficient $\beta$ reaches a maximal value in the protrusive region, which is consistent with the observations in [42]. The bounded integrin complexes form more rapidly towards the front, and the cell has the largest circumference in the middle region. Consequently, the adhesion strength decreases significantly in the trailing and leading regions. Due to this strong adhesion in the protrusive region, the cell is able to generate enough force to pull its back. Figure 4(c) shows that the moduli of actin elasticity and contractile elasticity. Note that we use the terminology “contractile elasticity” because the contractile stress produced in the cell is proportional to the value of $\gamma_0 m_b(x, t)$ and strain. The modulus of contractile elasticity reaches a maximum in the middle part of the cell and is responsible for generating the force that can pull the cell body forward. The simulation result is consistent with the observation that actomyosin contractility activity is concentrated in the cell body, right after the protrusive region [39]. Overall, our model is able to simulate the adhesion and contraction behaviors of a cell during migration and is consistent with existing cell migration studies.

3.2 Effect of adhesion

In tumor cells, particularly during the mesenchymal to amoeboid transition, cell adhesion plays a central role in cell migration [20]. In this section, we vary the adhesion parameters and investigate
their influence on cell migration behaviors.

**Asymmetry of adhesion**

Recent studies have suggested that the adhesion strength has to be stronger in the front region of the cell so that the cell can attach onto the ECM and pull its body forward while it has to be weaker in the back so that the contraction can overcome the attachment \([20, 22]\). Consistent with these observations, we hypothesized that asymmetry of adhesion correlates with higher cell speeds and enhanced migration. The relation between the asymmetry of cell adhesion and the velocity is illustrated in Fig. 5. Here, velocity refers to the velocity of the centroid of a cell after it reaches the steady state, typically after 20 minutes. Asymmetry is controlled by increasing the dissociation rate parameter \(\psi_r\). Larger dissociation rates towards the rear are responsible for stronger adhesion at the front of the cell and weaker adhesion at the rear, a phenomenon that makes the adhesion strength asymmetric. Figure 5 shows that the more asymmetric the adhesion, the faster the cell migrates. This is due to the fact that stronger adhesion at the front allows for stronger protrusion, which in turn drives the cell faster, and that weaker adhesion at the rear weakly holds the cell back, which again makes the cell move faster. This result is consistent with the previous observations for cell migrations in 2D environment, which suggest that asymmetry of the adhesion pattern is important \([52]\).

**Strength of adhesion**

Some research works suggest that the adhesion strength affects the cell migration behavior, see e.g. \([11, 20]\). Figures 6(a) and 6(b) show the dependence of cell migration velocity and cell length on adhesion strength. The adhesion strength of a cell can be controlled in our model by increasing the rate of integrin complex formation \(k_f\). The higher the rate of formation, the more complexes form on the cell surface, which in turn should result in stronger adhesion throughout the cell. We also vary here the steric resistance in order to investigate its effect. Figure 6(a) clearly shows that there exists an optimal value for \(k_f\) that yields the fastest migration. The cell tends to migrate at slower speeds when adhesion is stronger since the protrusion force exerted at the front will fail to overcome the adhesion forces exerted at the rear of the cell. In the same way, the cell moves at slower velocities when adhesion is weak since in this case the protrusion force would become too weak for the cell to move forward. Figure 6(b) shows that the cell length increases as adhesion becomes stronger up to a maximum value. Since strong adhesion generates a large protrusion force, but also more resistance in the back, the frontal region of the cell can extend more while the rear does not move much. It follows that in the case of strong adhesion, the cell moves at slower speeds but can significantly elongate. Note that at large values of \(k_f\), the rate of formation of adhesion complexes reaches a maximum. Therefore, after a certain point, increasing \(k_f\) does not have any particular effect on cell adhesion, and the velocity and length of the cell eventually reach terminal values. It is notable that in Fig. 6(a), the maximum velocity moves closer to the right as the resistance increases. It indicates that if a cell is subjected to significant steric resistance forces, it would still be able to migrate if adhesion is also strong, due to the fact that a cell with enough adhesion can overcome the steric resistance by its strong protrusion force. In other words, strong adhesion and large protrusion forces are required to drive a cell forward in an environment with large resistance. We also observe that the length of the cell may slightly decrease when the resistance is set small (data not shown). It is due to the fact that the protrusion force is used
to extend the cell rather than driving the cell forward. Therefore, even though a cell moves very slowly in the case of significant resistance, it is still advantageous for a cell to have strong adhesion because it can extend more, spreading further into the ECM.

### 3.3 Effect of contraction due to actomyosin activity

Contraction of the cytoskeleton has the effect of pulling the back of the cell towards the front. It follows that contraction should influence the migration velocity and morphology of cells [20]. In this section, we investigate in particular the sensitivity of the contraction parameter on cell migration and morphology. Here, we vary the contraction strength by varying the maximum rate of myosin binding, $\psi_k$. Large values of $\psi_k$ correspond to higher activities of actomyosin, which lead to stronger contraction. Figures 7(a) and 7(b) show the dependence of cell migration velocity and cell length on contraction strength. In the case of significant contraction, the velocity of the cell approaches its maximal value and its length tends to its minimal value. Once again, we can observe two distinct modes of migration from the results of these figures. On one hand, a cell with weak contraction can elongate more, exhibiting mesenchymal-like morphology, as it can reach further in the ECM. However, it will migrate at a slower pace than cells characterized by large moduli of elasticity since its protrusion strength is weaker due to less F-actin polymerization at its front. On the other hand, a cell with strong contraction elongates less, exhibiting amoeba-like behavior, and can migrate faster due to stronger protrusion. Finally, we can see in these figures that steric resistance has little effects on cell length. Therefore, under significant resistance conditions, cells will not be able to migrate, but mesenchymal cells can at least elongate and extend further into the ECM, and are thus more suited for dense ECM environments.

### 4 Discussion

We have constructed a one-dimensional viscoelastic gel strip model for the simulation of migrating cells in three-dimensional environments. Simulations of migration were performed for various values of key parameters appearing in the models for protrusion, adhesion, contraction, or steric resistance. Our approach is different from those proposed in previous works in the sense that we have considered here migration in axisymmetric 3D environments rather than on 2D surfaces. Therefore, the proposed model allows one to study not only the migration velocity of a cell but also the evolution of its morphology during migration. The results provided by the model are consistent with previous computational models, such as those described in [14, 52], but give also additional insights on behaviors that could not be simulated with the other models, such as the transition from mesenchymal to amoeboid migration modes upon loss of adhesion. Here, amoeboid-type migration is characterized by spherical, relatively undeformed morphologies with fast migration speeds, while mesenchymal-type migration is described by elongated morphologies with slow migration speeds. We were able to reproduce the two types of cell behavior using the same mathematical model with different values of the model parameters. Differences in these two types of migration are illustrated in Fig. 8.

Our results allow us to substantiate our hypothesis that cell adhesion strength and asymmetry play a critical role in cell migration and morphology in native-like environments. First, we have put in evidence a biphasic behavior for the cell velocity when varying the cell adhesion strength to the ECM. The biphasic behavior suggests that the maximum velocity is obtained for intermediate...
values of the adhesion parameter and that the velocity becomes negligible for extreme values of the parameter. The biphasic behavior is observed in the computational works by [14, 52] as well as in experimental results obtained using various cell types, see e.g. [29, 41, 43, 54]. Second, we have observed that the spatial asymmetry of adhesion strength is important for cell migration, as suggested by other research works [20, 22]. A cell can protrude and pull the back due to stronger adhesion at the front and weaker adhesion at the rear. However, if adhesion at the front is too weak, the cell cannot generate enough force to protrude, and if the adhesion at the rear is too strong, the cell cannot pull its back forward. We also observe this behavior in our results. This result is consistent with the computational work described in [6]. Also, it is reinforced by observations that the cell has the largest integrin concentration in the protrusive region and that traction stresses are concentrated in the same region [5, 32, 46]. Third, we observed that when the resistance from the ECM is strong, cells with stronger adhesion can migrate faster. A cell with significant adhesion has stronger protrusion at its front so that it can overcome the resistance. In contrast, a cell with weak adhesion can only migrate well in weak-resistance condition. Also, a cell exhibits elongated morphology with stronger adhesion. The resistance from the ECM has only a small effect on the elongation length of the cells. These results are clearly in agreement with the observations that mesenchymal migration is characterized by elongated morphology with strong adhesion accompanied by slow path-generating processes while amoeboid migration is characterized by roundish morphology with weak adhesion and relatively fast path-finding processes [10, 47]. In our model, we did not incorporate the proteolytic activity of a cell. However, changes in adhesion strength are sufficient to observe a transition of the migration pattern.

We also note that contraction has an important role in the transition from mesenchymal to amoeboid modes of migration. This is particularly important since very little modeling effort has been devoted to study mesenchymal to amoeboid transition of individually migrating tumor cells. We first confirmed that the results of our simulation are consistent with the experimental observations that a cell exhibits the largest contractile forces after the protrusive region due to more myosin II activities [25, 39]. Secondly, we investigated how the contractile strength affects the cell migration pattern by varying the actomyosin activities. It is clear from our results that the cells that are more elastic and less contracting exhibit an elongated, mesenchymal morphology. A cell exhibiting mesenchymal morphology migrates at a slower speed because it has less F-actin polymerization at its front due to elongation, and the ECM slows it down more due to steric resistance and adhesive traction. In contrast, a stiffer, more contractile cell shows spherical, amoeboid morphology, with a larger migrating velocity. In fact, strong actomyosin activities and contraction are observed in migrating amoeboid cells [17, 20]. Moreover, some studies also suggest that reducing the actomyosin activities in amoeboid cells can generate mesenchymal migration [36], which is consistent with our results. Our results primarily indicate that an amoeboid cell is better suited for migration. However, when a cell lies in an ECM with high steric resistance, a mesenchymal cell can elongate and reach further, finding a path. Thus, amoeboid cells have an advantage under weak-resistance condition while mesenchymal cells have an advantage under strong-resistance condition. Friedl and Wolf [11] suggest that the ECM density and stiffness affect the cell migration modes in which a cell tends to exhibit mesenchymal-type migration in stiffer and denser environments while it tends to exhibit amoeboid-type migration in less stiff and less dense environments. They argue that soft ECM does not facilitate the adhesion and cytoskeletal contraction, resulting in cell rounding. Our present study indicates that changes in cell internal kinetics are capable of modifying the migration mode of cells. We can therefore hypothesize that variations in the ECM...
properties may affect the internal kinetics, which may in turn induce the transition from one migration mode to the other. Our results also indicate that for the same adhesion and contraction strengths, the resistance strength has little or no effect on the length of the cells under the range provided in Table 1. However, we have confirmed that the stronger the resistance, the slower the elongation process becomes (data not shown). The steric resistance force is considered as viscous force, which is proportional to the velocity of a cell. Therefore, for sufficiently long time periods, the cell eventually reaches its steady-state shape independently of the value of the resistance. This can be compared to the situation where the denser and stiffer the ECM is, the harder it is for the cell to find empty space and quickly elongate.

Although the proposed model is a simple 1D line model for cell migration, it can be employed to investigate a number of 3D characteristics of a migrating cell. Even if the model can deliver results that are in reasonable qualitative agreement with experiments for cellular migration in complex environments, the model has admittedly a limited range of applicability. First, the model gives no information about the radial motion, assumed to be only controlled by the strain at each point. Thus, the present model does not account for the radial momentum and radial force in the cell. Second, our model only considers the cell motion along one single direction. The cell can only move forward or backward while in reality, cells can move in all directions in 3D environments. Third, we assume that the 3D ECM around the cell is a smoothed continuum free of small-scale changes and incorporated the ECM density, stiffness, and porosity into one lumped parameter, “resistance”. Thus, we cannot capture specific interactions between a cell and the ECM, such as matrix remodeling and cell rounding in denser ECM [16], or contractile ring formation of a cell crawling through a pore. The model would need to be expanded to include the effects of randomness and inhomogeneities of the ECM environment. Finally, we do not explicitly incorporate the underlying signaling pathways regulating cell migration. While they are critically important in cell migration processes, they are beyond the scope of the present study, as we focused on the underlying biomechanical and structural components. Thus, in order to be able to use the model for processes like angiogenic sprouting, which involves complex spatio-temporal regulation in signaling pathways [50], the model would need to be expanded to incorporate cell signaling phenomena. That said, some pathways are actually included implicitly within the model by varying parameters associated with the bound integrin concentration or bound myosin II concentration. We are aware of the limitations of these simplifications, and that much larger number of molecules may be associated with the cell adhesion and contraction functions. Moreover, the usefulness of the proposed model lies in the fact that it can provide a basic understanding of the migration process in order to construct a more detailed model that can integrate both biochemical and biomechanical features in more complex 3D environments.

In this paper, we have mainly focused on the migration of amoeboid and mesenchymal cells and on their transition from one migrating mode to the other. The model has been used so far to provide qualitative results. However, with recent advances in high resolution microscopy, both in vitro and in vivo, that could provide data from tumor cells, the model could be fine tuned to study individual cancer types in a number of complex environments, and elucidate mechanisms for cell migration as well as processes involved in the transition from mesenchymal to amoeboid behaviors. We hope that information obtained from our computational model will be useful to predict different types of cell behaviors and to design new experiments to investigate the cell migration for improved understanding of metastasis and drug discovery.
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References


Figure 1: Schematic of an axisymmetric cell shown at the initial time. The initial shape of the cell at each cross-section is given by the radius $r_0(x)$, or equivalently, by the area $A_0(x) = \pi r_0^2(x)$. The centroid of the cell at the initial time is located at $x = 0$. 
Figure 2: Cell migration transition from $t = 0$ s to $t = 1000$ s. The elongation of the cell occurs rather quickly in the early stage of migration. After the cell fully elongates, it migrates with a steady velocity and shape.
Figure 3: Evolution of the cell leading edge and trailing edge positions from $t = 0$ s to $t = 1000$ s. The cell elongation occurs rather quickly from its initial configuration and its length remains constant once the cell is fully elongated. The elongation of a cell corresponds to the formation of the protrusive region. Once the cell fully elongates, it starts to move forward at a steady velocity.
Figure 4: Cell displacement, adhesion, and elasticities plots at $t = 1000$ s. $x$-coordinates in the plots represent the current positions of the cell. Figure 4(a) shows the displacement, which increases significantly towards the front, creating an elongated protrusive region. Figure 4(b) shows the adhesion strength ($\beta$) of the cell. The adhesion increases significantly towards the front, reaching its maximum in the protrusive region. It generates a protrusive force and helps form an elongated region in the cell front. Figure 4(c) shows the actin elasticity and contractile elasticity of the cell. The actin elasticity is proportional to the actin density, which exponentially increases from the back to the front of the cell. The contractile elasticity reaches its maximum value in the cell body after the protrusive region. The elastic behavior of a cell is controlled by these two types of elasticity and is responsible for generating the contractile force that pulls the rear of the cell toward the front.
Figure 5: Effect of the asymmetry of adhesion on cell velocity. Increasing the dissociation rate parameter $\psi_r$ makes the cell adhesion more asymmetric, i.e. adhesion is stronger at the front and weaker at the back. The cell migrates much faster with more asymmetric adhesion.

Figure 6: Effect of adhesion strength on cell velocity. Increasing the value $k_f$ increases the adhesion strength of the cell. Also, increasing the value $f_0^{\text{res}}$ increases the steric resistance. Figure 6(a) shows that the cell has optimal adhesion strength at which it migrates fastest. Also, this optimum adhesion strength depends on the resistance. The weaker the resistance, the larger the range of the optimum adhesion strength. Thus cell with weak adhesion can still migrate as fast as the one with strong adhesion for the case of small resistance. Figure 6(b) shows that the cell elongates more significantly with stronger adhesion. In this case, the cell protrudes more and adheres more on the ECM, which in turn pulls the cell backwards. Also steric resistance does not have any effect on the cell length.
Figure 7: Effect of the contraction strength on cell velocity and length. The contraction strength is controlled by the maximum rate of myosin binding, $\psi_k$. Figure 7(a) shows that the stronger the contraction is, the faster the cell migrates due to stronger protrusive forces. Figure 7(b) shows that the stronger the contraction, the shorter the cell becomes because contraction pulls the cell body to the front. The steric resistance has little effect on the cell length.
Figure 8: Evolution of the morphologies of cells in either an amoeboid-type migration (left) or a mesenchymal-type migration (right). An amoeboid cell exhibits spherical morphology with a faster migration speed while a mesenchymal cell exhibits elongated morphology with a slower migration speed.