Mechanisms of cell propulsion by active stresses

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Abstract. The mechanisms by which cytoskeletal flows and cell–substrate interactions interact to generate cell motion are explored by using a simplified model of the cytoskeleton as a viscous gel containing active stresses. This model yields explicit general results relating cell speed and traction forces to the distributions of active stress and cell–substrate friction. It is found that (i) the cell velocity is given by a function that quantifies the asymmetry of the active-stress distribution, (ii) gradients in cell–substrate friction can induce motion even when the active stresses are symmetrically distributed, (iii) the traction-force dipole is enhanced by protrusive stresses near the cell edges or contractile stresses near the center of the cell and (iv) the cell velocity depends biphasically on the cell–substrate adhesion strength if active stress is enhanced by adhesion. Specific experimental tests of the calculated dependences are proposed.

Online supplementary data available from stacks.iop.org/NJP/13/073009/mmedia
1. Introduction

Directed motion of eukaryotic cells is often achieved by a combination of protrusion at the front of the cell, contraction farther back and adhesion between the cytoskeleton and the cell’s environment. This mechanism encompasses a broad range of observed types of cell motion. For example, in actin-based motility, actin polymerization at the front of the cell causes protrusion, actomyosin-induced contraction occurs farther back, and coupling of the actin cytoskeleton to the cell’s environment via transmembrane proteins such as integrins pushes the cell forward. On the other hand, in nematode sperm, protrusion caused by polymerization and bundling of major sperm protein (MSP) at the front of the cell and contraction mediated by MSP depolymerization close to the rear appear to generate motion [1]. Studies of diverse cell types have suggested a continuum of different types of cell motion corresponding to different relative weights of protrusion, contraction and adhesive interactions with the environment. A large body of mathematical modeling work has treated these effects individually and in combination [3–17]. By simulation of detailed models, it has been possible to reproduce migration behaviors that are compatible with experimental observations, including the distribution of internal gel flows and the dependence of cell velocity on adhesion strength. However, there are as yet no clear, explicit relationships giving the velocity and traction forces of a moving cell in terms of the spatial distribution of key driving forces such as protrusion, contraction and adhesive interactions with the environment. This paper seeks to develop such relationships.

The fact that similar mechanisms are implemented by diverse sets of proteins suggests that a general theory of cell propulsion could encompass many of the known phenomena. I propose such a general theory based on the concept of ‘active stresses’ introduced by Kruse et al [18]. Active stresses lead to the flow of cytoskeletal gels, driven by nonequilibrium chemistry, even in the absence of externally applied stresses. They should be distinguished from traction forces. Active stresses are internal to the gel; traction forces act at the interface between the gel and the substrate, and result from the active stresses. The effects of active stresses on cell properties have been explored in a series of papers reviewed in [19]. They can be either protrusive, as would result from polymerization of cytoskeletal filaments, or contractile, as would result from...
depolymerization or actomyosin contraction. I develop explicit relationships between the cell velocity and traction forces on the one hand, and active stresses and adhesion on the other hand, by solving a simplified mathematical model. This model differs from current models of actin-based motility in that it treats actin polymerization and actomyosin contraction on an equal footing, via protrusive and contractile active stresses, respectively. By treating the effects of active stresses within a general framework, it gives results that are independent of the specific mechanisms creating the stresses. The simplicity of the present model has several advantages. Firstly, it establishes the ‘bare bones’ of cell migration, which furthers basic understanding and aids the development of biomimetic systems for studying cell migration. This makes it possible to correlate a large body of experimental data within one physically transparent mathematical framework. Secondly, it allows the ready exploration of a multidimensional parameter space, which may allow the discovery of new propulsion modes. Finally, it provides an easily interpretable ‘prequel’ to the more complex simulations, whose results can be difficult to understand.

This paper does not explicitly treat the mechanisms generating active stresses, which may include chemotactic signaling circuits and/or spontaneous cell polarization mechanisms. Rather I focus on the mechanisms by which a given distribution of active stress and friction generates cell motion and on evaluating the dependence of cell motion and traction forces on key parameters such as the adhesion strength. I focus on two key properties, the cell velocity \( V \) and the traction-force dipole moment \( P \), defined by

\[
P = \int \vec{r} \cdot \vec{f}_{\text{trac}}(\vec{r}) \, dA,
\]

where \( f_{\text{trac}} \) is the traction-force density (the force density exerted by the cell on the substrate), and the integral is performed over the two-dimensional (2D) contact area between the cell and the substrate [20]. Since the integrated traction force must vanish or nearly vanish [21], \( P \) is the most basic measure of the strength and orientation of the traction forces. \( P \) is negative (as in most cells) when traction forces at the front point backward and those at the rear point forward. The key results of the paper are the formulae for \( V \) and \( P \) given in equations (7), (10) and (13), respectively.

2. Model

2.1. Physical picture

The conceptual foundation of the model is shown in figure 1. A cell contains protrusive active stresses at the front and the contractile active stresses at the rear. Because accepted convention [22] assigns to stress the opposite sign of pressure, the stress in the protrusive region (positive pressure) is negative, and that in the contractile region is positive. The protrusive stresses lead to expansion of the cytoskeletal gel. Because this expansion is constrained by the front cell membrane, the gel flows backward relative to the cell. A similar mechanism for contraction near the rear of the cell, constrained by the rear cell membrane, also causes backward flow there. When the backward gel flow is coupled to the external environment, forward motion of the cell results, much in the same way that backwards motion of the bottom of a paddlewheel propels a riverboat forward. This picture encompasses the actin–myosin mechanism and the MSP mechanisms discussed above. It also has some overlap with currently held theories of apicomplexan motility, in which backward flows of actin relative to the cell body couple to a
Figure 1. Schematic representation of the forward cell motion resulting from the interaction of internal flows with the environment. Protrusion is indicated by ‘−’ sign and contraction by ‘+’ sign, in accordance with the accepted convention regarding the sign of stress.

substrate and thus cause forward motion [23]. However, in this case the flows appear to arise by a different mechanism, in which myosin A inside the cell forms a scaffold fixed relative to the cell, and polarized actin filaments are pushed backwards by their interaction with the myosin. The flows are caused not by protrusive and contractile active stresses, but rather by the fixed myosin scaffold and the polarization of the actin filaments.

Several previous works have treated viscous flow of the cytoskeletal gel in cells [3–8, 12, 14, 24, 25]. The current approach is mostly closely related to those of [24] and [12], which treated gel flow generated by active myosin stresses and actin polymerization. The approaches differ in that I treat actin polymerization as an active stress on an equal footing with myosin contraction and that the formulae derived for the velocity and traction-force dipole treat spatially varying active stresses.

To define a mathematical model embodying the mechanism of figure 1, I make the following assumptions:

- The gel flows may be convergent or divergent. Here, ‘divergent’ means dV/dx > 0 and ‘convergent’ means dV/dx < 0, where V(x) is the gel flow velocity and x is the direction of motion. Such flow behaviors are clearly demonstrated by speckle-microscopy studies of actin gels [26]. For example, near the leading edge of epithelial cells, the actin retrograde (negative) flow velocity rapidly decreases going into the cell [27], indicating convergent flow. Pronounced variations in flow velocity are also seen in speckle-microscopy studies of keratocytes [28, 29].

- Inhomogeneity in the gel flow leads to internal stresses. A uniform flow field causes no relative motion and requires no internal stresses for its maintenance. Therefore a natural baseline assumption is that the stress required for maintaining the flow is proportional to the gradient of the flow velocity. Such gradients could originate from either (a) variations in the height of the cell or (b) processes occurring at constant cell height. In the case (a), the flow naturally slows or accelerates going into the cell if the gel volume is conserved, and the stress arises from the shear viscosity of the gel as it deforms going into the cell. In the case (b), convergent or divergent flows in steady state must be accompanied
by gel disassembly or assembly, to avoid the buildup or depletion of the gel. Then the stress required for maintaining convergent or divergent flows is related to the dynamics of gel assembly or disassembly. Existing evidence supports the case (b). In keratocytes, the lamellipodium profile is quite flat for distances up to 10 µm into the cell [30]; in addition, speckle microscopy studies of epithelial cells have revealed correlations between convergent gel flow and depolymerization [31].

- The static elasticity of the actin cytoskeleton is ignored. This assumption is justified by experiments that show that cell-surface-attached beads subjected to constant forces eventually settle down to a constant nonzero velocity of motion [32], which cannot occur with finite zero-frequency elastic moduli. Such a description of the gel stresses is not quantitatively accurate, but I believe that for the slow processes that characterize cell migration, it will correctly identify the crucial effects.

- Propulsion is dominated by the isotropic component of the active stress. This assumption differs from that made in a previous study of lamellipodial flow [24], which emphasized the shear components. I focus on the isotropic component because of its clear relationship to cell propulsion.

- The force exerted by the substrate on the gel is assumed to be proportional to the gel velocity. This assumption has been found to be reasonably accurate by simultaneous measurements of force and velocity in keratocytes [33].

- The gel flows are assumed to be parallel or antiparallel to the direction of motion. The flows, and the profile of the cell, are also assumed to be independent of the position transverse to the direction of motion. These assumptions are made for mathematical simplicity and because the parallel/antiparallel components of the flows should dominate cell motion. The formalism for more general geometries is given in the supporting material (available from stacks.iop.org/NJP/13/073009/mmedia).

- The force required for detaching the rear of the cell from the substrate is independent of velocity. This assumption is based on previous analyses [34] that have indicated only a weak dependence of rupture forces on velocity.

2.2. Mathematical formulation of the model

The model shown in figure 2 embodies these assumptions. The cell has length $L$ in the direction of motion (the $x$-direction) and width $W$ in the transverse direction. It moves at constant velocity on a flat substrate and its dimensions remain constant. The equations of motion treat the actin gel immediately above the substrate, so that the vertical coordinate does not appear. Because the velocities and cell profile are assumed to be independent of the coordinate transverse to the direction of motion, I treat a 1D geometry, keeping in mind that it is a slice of the 2D cell. The active stresses $\sigma_{\text{act}}$, which are 2D (having units of force per length), are related to the 3D stresses by a factor of the cell height. As discussed above, gradients in the gel flow velocity $V(x)$ cause internal stresses. Thus, the internal force density, which is proportional to the gradient of the stress, is proportional to the second derivative of the velocity; the coefficient of proportionality $\nu$ acts as an effective viscosity. The interaction between the gel and the substrate is described by a friction coefficient per unit area $\xi(x)$. To simplify the mathematics, I assume that $\sigma_{\text{act}}$ vanishes very near the cell boundaries; this assumption can be relaxed at the expense of making the boundary conditions more complex.
Because the velocities of flow in the cell are very small, the inertia terms, and thus the net force acting on any element of the gel, are also small. Therefore I assume that the force density acting on the gel vanishes everywhere. The contributions to this force density are

- the force density $\sigma_{\text{act}}/dx$ resulting from the active stresses;
- the force density $\nu d^2 V/dx^2$ resulting from flow gradients;
- the frictional force density $-\xi(x)V(x)$ resulting from the interactions between the actin gel and the substrate;
- the force density $-F_{\text{det}}$ (per unit of transverse width) required for detaching the rear of the cell from the substrate (where $F_{\text{det}} > 0$). This force acts at the rear of the cell. However, it may act not directly on the actin gel, but rather on the membrane. The membrane may thus be pulled backwards in such a way that it exerts a force on the actin gel at the front of the cell—in other words, the membrane elastically transfers the force from the substrate at the rear of the cell to the actin gel at the front. I thus assume that $F_{\text{det}}$ acts on the gel at $x = L/2$. The results below on the dependence of cell velocity on $F_{\text{det}}$ are independent of the position where $F_{\text{det}}$ is exerted, so this is not a limiting assumption.

The resulting force balance for the cytoskeletal gel takes the form (see table 1 for a list of parameters and their units)

$$\frac{d^2 V}{dx^2} + \frac{d\sigma_{\text{act}}}{dx} - \xi(x)V(x) - F_{\text{det}}\delta(x - L/2) = 0.$$ (2)

Two boundary conditions apply to equation (2):

- The velocities at the front and the back of the cell must be equal for the cell to maintain a steady-state size, so
  $$V(L/2) = V(-L/2) = V_{\text{cell}}.$$ (3)

  Note that $V_{\text{cell}}$ is not known a priori but will rather emerge from the solution of the equations of motion.
- The total external force exerted by the substrate and cell membrane on the cytoskeletal gel must vanish, since the gel moves at a constant velocity. This zero-force condition has the form
  $$\int_{-L/2}^{L/2} \xi(x)V(x)\,dx + F_{\text{det}} = 0.$$ (4)
Table 1. Definitions and units of model quantities and parameters. F denotes force, T denotes time, and L denotes length.

| Parameter | Definition | Units |
|-----------|------------|-------|
| $V_{\text{cell}}$ | Cell velocity | L/T |
| $V(x)$ | Gel velocity | L/T |
| $\sigma_{\text{act}}(x)$ | Active stress density | F/L |
| $\nu$ | Effective gel viscosity | FT/L |
| $\xi(x)$ | Cell-substrate friction coefficient | FT/L |
| $\xi_0$ | Crossover friction coefficient | FT/L |
| $P$ | Traction-force dipole moment | FL |
| $F_{\text{det}}$ | Cell-rear detachment force density | F/L |
| $\alpha$ | $F_{\text{det}}/\xi$ | L^2/T |

This implies a boundary condition on $dV/dx$. Integrating equation (2) from $-L/2$ to a point $(L/2)_{-}$ just inside $L/2$ yields (recall that $\sigma_{\text{act}}$ vanishes just inside $\pm L/2$) and, using equation (4), gives

$$\nu \left[ \frac{dV}{dx} \bigg|_{(L/2)_{-}} - \frac{dV}{dx} \bigg|_{-L/2} \right] = \int_{-L/2}^{L/2} \xi(x) V(x) dx$$

$$= - F_{\text{det}}.$$ (5)

Because of equation (5), I will treat equation (2) on the interval $[-L/2, (L/2)_{-}]$, where only $\xi(x) V(x)$ contributes to the substrate force density. On this interval the simplified equation

$$\nu \frac{d^2 V}{dx^2} = -\frac{d\sigma_{\text{act}}}{dx} + \xi(x) V(x)$$ (6)

holds, with the effects of $F_{\text{det}}$ included via the boundary conditions.

2.3. The solutions of particular cases

Here, I summarize the solutions of equation (6) for some representative cases; for details see the supporting material (available from stacks.iop.org/NJP/13/073009/mmedia).

2.3.1. Cell velocity. Constant friction: I first obtain a solution for $V(x)$ in the special case of a stress localized at a point and then write the general solution as the sum of such solutions. The result is

$$V_{\text{cell}} = -\frac{1}{\nu} \int_{-L/2}^{L/2} \frac{\sigma_{\text{act}}(x) \sinh(\kappa x) \sinh(\kappa L/2) \sinh(\kappa L/2)}{2 \sinh(\kappa L/2)} dx - \frac{F_{\text{det}}}{2\nu \kappa \tanh(\kappa L/2)},$$ (7)

where

$$\kappa = \sqrt{\frac{\xi}{\nu}}$$ (8)

is a decay rate describing how quickly the flow generated by a point stress source decays away from the stress. A quantity very similar to $\kappa$ was defined in [24] but using the shear viscosity rather than the effective viscosity defined here. Thus $V_{\text{cell}}$ contains contributions from different...
parts of the cell, with those near the cell edges weighted more strongly because of the sinh term. The opposing force $F_{\text{det}}$ slows motion at a rate depending on both $\xi$ and $\nu$. Weakly varying friction, $F_{\text{det}} = 0$: I take the frictional term in equation (6) to have the form
\[
\xi(x) = \bar{\xi} + \Delta \xi(x),
\]
where $\bar{\xi}$ is constant and $\Delta \xi \ll \bar{\xi}$ is a small variation. By solving equation (6) to first order in $\Delta \xi$, one obtains the following correction to $V_{\text{cell}}$:
\[
\Delta V_{\text{cell}} = -\frac{\kappa^2}{2} \int_{-L/2}^{L/2} \frac{\cosh(\bar{\kappa}x) \bar{V}(x) \Delta \xi(x)}{\sinh(\bar{\kappa}L/2)} d\xi,
\]
where $\bar{V}(x)$ is the value of $V(x)$ in the absence of $\Delta \xi$ and $\bar{\kappa} = \sqrt{\bar{\xi}/\nu}$. Thus, a locally increased friction coefficient ($\Delta \xi(x) > 0$) increases the speed of the cell if it occurs in a region of backward flow ($\bar{V}(x) < 0$).

2.3.2. Traction-force dipole. I assume constant friction to keep the calculation tractable. The traction force consists of friction terms between the gel and the substrate, and the detachment force $F_{\text{det}}$. The traction-force dipole moment (1) is
\[
P = W \int_{-L/2}^{L/2} x f_{\text{trac}}(x) \, dx,
\]
where
\[
f_{\text{trac}} = \xi(x) V(x) + F_{\text{det}} \delta(x + L/2)
\]
is the force density exerted by the cell on the substrate, and I have assumed that $F_{\text{det}}$ acts on the substrate at the rear of the cell. In the supporting material (available from stacks.iop.org/NJP/13/073009/mmedia), it is shown that
\[
P = -W \left[ \int_{-L/2}^{L/2} \left[ 1 - \frac{(\kappa L/2) \cosh \kappa x}{\sinh \kappa L/2} \right] \sigma_{\text{act}}(x) \, dx + LF_{\text{det}}/2 \right].
\]
This expression generalizes a limiting case in which the second term in the integral can be ignored, derived for constant active stresses in lamellipodia [24].

3. Biophysical implications of the model results

The main results of the model analysis are equations (7), (10) and (13). Here, I use them in order to classify possible mechanisms of cell propulsion, to assess the dependence of $V_{\text{cell}}$ on substrate binding strength and to relate the traction-force dipole to other measures of actomyosin contractile stress. Because the model assumes that both the front and the back move at a constant velocity, it does not directly address ameboid-type motion associated with protrusion cycling and variations in cell length. However, in this case the main factor determining cell velocity will be the average distribution of active stress as a function of distance from the leading and trailing edges. If one were to identify the active stress in the model with these average stresses, the present results should be applicable to ameboid motion as well.
3.1. Cell propulsion mechanisms

Asymmetric active-stress mechanism: Equation (7) implies that active protrusive stresses near
the front of the cell and contractile stresses near the back of the cell enhance cell motion. This
occurs because a protrusive stress near the front of the cell generates a diverging flow field
that pushes the front membrane of the cell forward; a contractile stress near the rear of the cell
causes a converging flow field that pulls the rear membrane forward. Figure 3 shows the spatial
dependence of the cell velocity induced by a point negative (protrusive) stress as a function
of the point of application (essentially the sinh factor multiplying $\sigma_{\text{act}}$ in equation (7)). For
contractile (positive) stress the velocity has the opposite sign. For weak friction, $V_{\text{cell}}$ is seen
to depend linearly on the point of application of the stress. This occurs because weak friction
implies that $\kappa$ is small (cf equation (8)); in this limit, equation (7) reduces to
\begin{equation}
V_{\text{cell}} = \frac{1}{vL} \int_{-L/2}^{L/2} x \sigma_{\text{act}}(x) \, dx - \frac{F_{\text{det}}}{\xi L} .
\end{equation}

Thus, the factor multiplying $\sigma_{\text{act}}$ is proportional to $x$, and the driving force for cell motion
is simply the dipole moment of the active stress. The opposing force slows motion at a rate
inversely proportional to $\xi$. When the friction is stronger, $\kappa$ in equation (7) increases. This
occurs because the frictional coupling to the substrate reduces flows more effectively, limiting
the distance over which they can propagate in the cell. Therefore the effect of an active stress
near the center of the cell cannot propagate to the edge of the cell. This renders the contributions
from near the cell edges even more dominant, as seen in figure 3.

Figure 4(a) illustrates this propulsion mechanism for a hypothetical active-stress
distribution in which protrusive stress is concentrated in a narrow region near the front of the cell
(to the right), and contractile stress is concentrated farther back. Even though the total amount
of contractile stress exceeds the protrusive stress and the contractile stress is positioned to cause
backward motion of the cell, the protrusive stress outweighs the contractile stress because it is
closer to the front of the cell.
Figure 4. Examples of asymmetric-stress propulsion mechanism (a) and asymmetric-friction mechanism (b). The dashed line denotes results for $\Delta \xi = 0$. In (a) parameters satisfy $L^2 \xi = 8 \nu$, contractile active stress has magnitude 0.2 (arbitrary units) and extends from 0 to 0.2$L$, and protrusive active stress has magnitude $-1.0$ and extends from 0.48$L$ to 0.5$L$. In (b) parameters satisfy $L^2 \xi_{\text{min}} = \nu$, so $L^2 \xi_{\text{max}} = 8 \nu$, contractile stress has magnitude 1.0 and extends from $-0.2L$ to 0.2$L$, and $\xi$ switches from $\xi_{\text{min}}$ to $\xi_{\text{max}}$ at 0.3$L$. Remaining parameter choices affect only vertical scaling.

These predictions are consistent with known or inferred distributions of active stresses in cells. In the actin–myosin and MSP systems, polymerization of actin or MSP occurs near the front of the cell and contractile activity due to myosin activity or MSP depolymerization occurs in the middle or rear of the cell. Measured distributions of actin and myosin in cell fragments [35] also show actin at the front and myosin at the rear. The reduced impact of active stresses near the middle of the cell, shown in figure 3, might explain the observation that in some cell types myosin inhibition has a limited impact on cell velocity [36].

Equation (7) can be tested directly by localized stimulation of protrusion or contraction. Localized application of calyculin, which enhances myosin-induced contraction, causes keratocytes to move in the opposite direction from the point of application [28], consistent with

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equation (7) and figure 3 (with the sign changed to account for contractile stress). Better spatial resolution could be obtained by localized photoactivation of agents acting upstream of actin polymerization, such as Rho GTPases. By moving the photoactivated spot forward through the cell and simultaneously measuring $V_{\text{cell}}$, one could obtain a plot of $V_{\text{cell}}$ against position. Such a plot should reflect the main features of figure 3. Photoactivation of actomyosin contraction would have similar effects, but with a sign change.

It is instructive to relate the asymmetric-stress mechanism to a limiting case based on a fixed actin polymerization velocity localized at the front of the cell ($x = L/2$), independent of $v$ and $\xi$. This limit can be treated within the present approach as follows. The polymerization velocity $V_p$ is related to the strain rate: $V_p = \int_0^{L/2} (dV/dx) \, dx$, where it is assumed that $V(0) = 0$ —the flow velocity at the center of the cell—vanishes because of the substrate friction. If $v$ increases, then $\sigma_{\text{act}}(x)$ must increase proportionally to $v$ in order to maintain a constant strain rate, so the ratio $\sigma_{\text{act}}(x)/v$ in equation (7) will approach a constant. On the other hand, if the velocity (and thus the protrusive active stress) are localized at $x = L/2$, the first integral in equation (7) becomes independent of $\kappa$. There the cell velocity becomes independent of both $v$ and $\xi$, as expected for the limit of a fixed actin polymerization velocity.

Results having some similarities to equation (7) have been derived for the portion of the actin gel in the lamellipodium at the leading edge of a cell [24, 37]. Both of these treatments used a force balance similar to equation (2), with $\sigma_{\text{act}}$ taken positive (contractile) and constant, $\xi$ taken constant, different boundary conditions corresponding to the front and rear of the lamellipodial region and a varying height. It was found that, as in equation (7), the lamellipodium edge velocity depends linearly on the active stress. However, the present treatment, in the absence of an external force, would give zero cell velocity for a constant active stress; in [24, 37], the velocity is nonzero because of the asymmetric boundary conditions and the height variation. Kruse et al [24] found a linear dependence of velocity on the opposing force, as in equation (7). However, Zimmermann et al [37] found a nonlinear dependence because of the coupling between the external force and the crosslinking properties of the gel.

Asymmetric friction mechanism: Equation (10) shows that spatial variations in the friction coefficient can cause motion even when the active-stress distribution is symmetric. Motion will occur in the direction opposite to the gel flow in the region of enhanced friction. In the limit of weak friction (small $\kappa$), the effect of asymmetric friction on $V_{\text{cell}}$ takes the simple form

$$\Delta V_{\text{cell}} = -\frac{1}{L} \int_{-L/2}^{L/2} \tilde{V}(x) \left[ \frac{\Delta \xi(x)}{\xi} \right] \, dx. \quad (15)$$

Thus $V_{\text{cell}}$ is a weighted average involving $\tilde{V}(x)$ and the fractional change in the friction coefficient. When the friction is stronger, the contributions in equation (10) are more weighted toward the ends of the cell, and the contributions from the middle become relatively insignificant. The asymmetric-friction mechanism may be understood as an additional force acting on the gel: if the gel flow is backward where the friction is increased, this force points forwards. In the example of figure 4(b), the cell contains only symmetrically distributed contractile active stresses, which give no motion by themselves. However, they cause inwards gel flow from the cell edges (dashed line in the velocity plot). Because this flow is backwards near the front of the cell where the friction is enhanced, the cell moves forward, at the velocity indicated in the figure. Here the fractional change in $\xi$ is large, but the numerically obtained results for this case are nevertheless consistent with the predictions of equation (10).
The relationship between $V_{\text{cell}}$ and the distribution of adhesion strength given by equation (10) is consistent with existing data on the distribution of adhesion strength in cells. Since the gel at the front of a cell usually flows backwards, enhanced friction near the front of a cell enhances forward motion. Several observations indicate that cells may use such a mechanism to improve the efficiency of motion. For example, combined force and velocity measurements on migrating keratocytes [33] showed a friction coefficient approximately three times larger at the front of the cell than at the back. This work also demonstrated a strong dynamic correlation between the asymmetry of the friction coefficient and the direction of cell motion, as would be expected if friction asymmetry enhances motion. A correlation between asymmetry of cell–substrate interactions and cell motion was also found in a micropatterning study in which cells were found to protrude preferentially in the direction of newly formed adhesions [38]. Finally, measurements of actin speckle flow in keratocytes [28] revealed a reduction in $V_{\text{cell}}$ with increasing slippage at the front of the cell, as equation (10) would predict if the frictional coupling at the front were decreased. Motion induced by asymmetric friction is also a possible explanation of the observation that lifting one edge of keratocyte fragments, which should cause a reduction of adhesion at that end, causes motion in the opposite direction [35].

Quantitative tests of equation (10) could be accomplished by methods similar to those outlined above for $V_{\text{cell}}$, including localized photoactivation of key proteins acting upstream of adhesion. Moving the focus of adhesion from the front to the back should cause a gradual transition from acceleration to deceleration of cell motion as the direction of flow changes from retrograde to anterograde; the induced velocity change should mirror the retrograde flow rate.

3.2. Variation of $V_{\text{cell}}$ with substrate binding strength

Manipulation of cell–substrate adhesion by several different methods [39, 40] has shown that $V_{\text{cell}}$ first grows with increasing adhesion, reaches a maximum and then drops. To address this biphasic behavior, I assume that $\xi$ is proportional to the substrate binding strength. Because the binding strength varied in [39] and [40] refers to detachment forces rather than frictional sliding forces, this assumption needs to be tested. Such tests could be performed, for example, by combined measurements of gel flow and substrate forces, as in [33]. I also assume that $F_{\text{det}}$ in equation (7) is proportional to $\xi : F_{\text{det}} = \alpha \xi$, where $\alpha$ is a constant. Finally, I assume that propulsion is dominated by protrusion near the front of the cell. Then equation (7) gives a monotonic drop in $V_{\text{cell}}$ with increasing $\xi$, rather than biphasic behavior. This indicates that a crucial ingredient is missing from the model. Several explanations have been proposed for the biphasic behavior [3, 11, 15]. Recent experiments in epithelial cells [41], showing that increased substrate adhesion accelerates retrograde flow, shed light on this issue. If $\sigma_{\text{act}}$ were independent of adhesion or dropped with increasing adhesion, adhesion would instead slow retrograde flow. Therefore I assume that substrate adhesion enhances $\sigma_{\text{act}}$. This assumption is consistent with the signaling of adhesions to the actin cytoskeleton [42] and with the autocatalytic branching theory in which actin polymerization is enhanced by the opposing force [43]. To model the feedback of adhesion onto active-stress generation, I take $\sigma_{\text{act}}$ to have the simple mathematical form

$$
\sigma_{\text{act}}(x) = \begin{cases} 
\sigma_{\text{max}} \xi / (\xi + \xi_0), & L/2 - \Delta L < x < L/2, \\
0, & x \leq L/2 - \Delta L,
\end{cases}
$$

\[16\]
Figure 5. Cell velocity as function of $\xi$. Solid and dashed curves exemplify behaviors generated by equation (7), with active stress determined by equation (16), using $\Delta L = 0.2L$. $V_{\text{max}}$ and $\xi_{\text{max}}$ are values of $V_{\text{cell}}$ and $\xi$ at maximum velocity. Parameter values are such that $L^2 \xi_0 = \nu$. For solid line, $\sigma_{\text{max}}/\alpha \xi_0 = 2.95$, for dashed line $\sigma_{\text{max}}/\alpha \xi_0 = 5.5$. Remaining parameter values affect only vertical and horizontal scaling of plot. Solid squares are data taken from figure 4(a) of [40].

where $\sigma_{\text{max}}$ is the magnitude of the saturation value of $\sigma_{\text{act}}$, $\xi_0$ is the crossover value of $\xi$ and $\Delta L$ is the width of the region where the active stress is exerted. This corresponds to propulsion dominated by protrusion near the front of the cell, enhanced by $\xi$.

Evaluation of equation (7) using (16), over a broad range of model parameters, reveals that in some parameter ranges $V_{\text{cell}}$ is always zero. But for a sufficiently large $\sigma_{\text{max}}/\alpha \xi_0$, $V_{\text{cell}}$ has biphasic behavior as a function of $\xi$. The possible velocity behaviors are summarized by the solid and dashed curves in figure 5. I have fitted the solid curve to the data points of [40]. A reasonably close fit to the data is obtained, indicating that positive feedback of adhesion on active-stress generation is a possible origin of biphasic adhesion–velocity curves.

Other possible mechanisms causing a biphasic $V_{\text{cell}}$-adhesion curve include drag terms that are independent of $\xi$ but proportional to $V$. Such terms could come from the viscous drag of the medium (if it is much more viscous than water), the drag-resisting motion of the cell membrane over the substrate or the drag resulting from internal deformation of the cell if it rolls over the substrate. I have implemented such terms by taking $\xi_0 = 0$ (no positive feedback of adhesion onto active stress) and adding a second opposing-force term in equation (7) proportional to $V_{\text{cell}}$. The resulting equation is straightforwardly solved. In this case, the $\xi-V_{\text{cell}}$ curve always emerges linearly from the origin, and the descending branch is broader than the ascending branch. This yields curves that are broader than the experimental data shown in figure 5.

3.3. Factors favoring negative traction-force dipole

Traction forces usually point backwards at the front of the cell and forwards at the back, so $P < 0$. Equation (13) shows that protrusive (negative) stresses near the cell edges, and
contractile stresses near the center of the cell, produce negative values of \( P \). This dependence can be interpreted as follows. A focus of contractile stress near the center of the cell will produce a converging flow field, which exerts a backwards force on the substrate ahead of the point of application and a forwards force behind it. This leads to \( P < 0 \). On the other hand, a center of protrusive stress near the front of the cell will produce mainly retrograde flow, which would lead to forwards traction forces and thus to \( P > 0 \). But a center of contractile stress very near the cell rear would produce mainly backwards flow, which would lead to backwards forces near the front of the cell and thus again leads to \( P < 0 \). Therefore, I assume that the traction forces in myosin-active cells are caused by the myosin contribution \( \sigma_{\text{myo}} \) to \( \sigma_{\text{act}} \) and modify equation (13) as follows:

\[
P = -W \int_{-L/2}^{L/2} \left[ 1 - \frac{(\kappa L/2) \cosh \kappa x}{\sinh \kappa L/2} \right] \sigma_{\text{myo}}(x) \, dx.
\]  

(17)

Since \( P < 0 \) and \( \sigma_{\text{myo}} > 0 \) (because the myosin stress is contractile), the second term in the integral can only reduce the magnitude of \( P \); hence,

\[
|P| < W \int_{-L/2}^{L/2} |\sigma_{\text{myo}}(x)| \, dx = A|\bar{\sigma}_{\text{myo}}| = V|\bar{\sigma}_{\text{myo}}^3|,
\]  

(18)

where \( A \) and \( V \) are the area and volume of the cell, the overbars denote spatial averaging and \( \bar{\sigma}_{\text{myo}}^3 \) is the 3D active myosin stress. Thus \( |P| \) cannot exceed the volume-integrated active stress. Equality holds in equation (18) when the second term inside the integral in equation (17) can be ignored; this will be valid when \( \kappa L \) is large and \( \sigma_{\text{myo}}(x) \) is mainly concentrated away from the edges of the cell. In this case, the estimate of [24] for lamellipodia is reproduced.

In figure 6(a) of [47], for Dictyostelium during early spreading, one finds \( |f_{\text{trac}}| \simeq 40 \text{ Pa} \) and a cell area of about \( 700 \mu m^2 \). Dividing the measured traction forces into forwards and backwards components and taking these components to act at points \( \pm 8 \mu m \) from the center of the cell (a distance estimated from the figure), one finds that \( P = -40 \text{ Pa} \times 700 \mu m^2 \times 8 \mu m \simeq -2 \times 10^{-13} \text{ J} \). Furthermore, Robinson et al [48] found a cell volume of about \( 600 \mu m^3 \). Thus a lower bound on \( \bar{\sigma}_{\text{myo}}^3 \) is obtained:

\[
|\bar{\sigma}_{\text{myo}}^3| > |P|/V \simeq 2 \times 10^{-13} \text{ J per } 600 \mu m^3 \simeq 300 \text{ Pa}.
\]  

(19)

Is this bound consistent with known properties of myosin force generation? There are no direct measurements of the magnitude of \( \sigma_{\text{myo}}^3 \). However, measurements of cytokinesis in

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Dictyostelium [48] provide an estimate of myosin contraction forces. The force required for inward motion of a contractile ring of volume $20 \mu m^3$ and diameter about $3 \mu m$ was estimated to be $7 \text{nN}$. If the contractile ring is a torus, its cross-sectional area is about $20 \mu m^3/3\pi \mu m \simeq 2 \mu m^2$. Then $\sigma_{\text{myo}}^{3d} \simeq 7 \text{nN per } 2 \mu m^2 = 3500 \text{Pa}$. It is reasonable to assume that the active-stress generation capacity is proportional to the myosin concentration $c_{\text{myo}}$. The bulk myosin concentration was about six times smaller than that in the contractile ring, suggesting a bulk active-stress generation capacity of about $3500 \text{Pa}/6 \simeq 600 \text{Pa}$. This is consistent with the present lower bound of $300 \text{Pa}$.

4. Conclusion

This work has treated a simple mathematical model of cell propulsion incorporating active stresses and adhesion in a minimal fashion. It has shown that the cell velocity and a measure of the traction forces are given by very simple formulae based on the spatial distributions of active stress and the adhesion strength. The spatial distributions of protrusive/contractile active stress and adhesion observed in real cells are consistent with those which, according to the model, provide efficient propulsion and negative traction-force dipoles. It is hoped that the fundamental understanding gained from this model analysis can be useful in the design of biomimetic systems for moving cells. Biomimetic systems for *Listeria*, in which active stresses due to actin polymerization are generated externally (outside the moving object), have shed much light not only on *Listeria* motility, but also on force generation by actin polymerization at the leading edge of cells. A biomimetic system in which actin polymerization occurs internally, and contractile forces are included, would be a much closer analogue of cell migration. The results of this paper suggest that such a system could be obtained if a spatial gradient of active stresses in a gel, combined with a frictional coupling of the gel to the external medium, can be created. The efficiency of such a system would be enhanced if the frictional couplings could be focused at the front of the cell.

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