Maximum velocity of self-propulsion for an active segment

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Abstract
The motor part of a crawling eukaryotic cell can be represented schematically as an active continuum layer. The main active processes in this layer are protrusion, originating from non-equilibrium polymerization of actin fibers, contraction, induced by myosin molecular motors, and attachment due to active bonding of trans-membrane proteins to a substrate. All three active mechanisms are regulated by complex signaling pathways involving chemical and mechanical feedback loops whose microscopic functioning is still poorly understood. In this situation, it is instructive to consider the problem of finding the spatial organization of standard active elements inside a crawling layer ensuring an optimal cost-performance trade-off. If we assume that (in the range of interest) the energetic cost of self-propulsion is velocity independent, we obtain, as an optimality criterion, the maximization of the overall velocity. We choose a prototypical setting, formulate the corresponding variational problem and obtain a set of bounds suggesting that radically different spatial distributions of adhesive complexes would be optimal depending on the domineering active mechanism of self-propulsion. Thus, for contraction-dominated motility, adhesion has to cooperate with ‘pullers’ which localize at the trailing edge of the cell, while for protrusion-dominated motility it must conspire with ‘pushers’ concentrating at the leading edge of the cell. Both types of crawling mechanisms have been observed experimentally.

Keywords
Cell motility, crawling, optimization, active gels, pushers, pullers, adhesion, contraction, protrusion

I. Introduction
Eukaryotic cells are spatially extended active bodies that can steadily self-propel in viscous environments at low Reynolds numbers [1, 2]. It has been understood that in these conditions a combination of stationarity and linearity of friction leads to kinematic reversibility and that a symmetric (under time reversal) stroke cannot produce self-propulsion [3–5]. For Stokes swimmers, a variety of non-symmetric motility strategies have been proposed and optimized using various efficiency criteria [6–12]; similar models for crawlers advancing on a frictional background have been considered as well [13–15]. Most of the proposed mechanisms of self-propulsion are kinematic in the sense that the time dependence of the shape of a swimmer or crawler is prescribed which implies that appropriately chosen actuators can always...
perform the required internal movements. In cells the role of such actuators is played by active agents whose redistribution must respect the fundamental balances of mass and momentum.

In the context of eukaryotic cells, a prototypical scheme of self-propulsion includes protrusion through polymerization of actin filaments which is accompanied by dynamic assembly of focal adhesions; myosin-driven contraction of the actin network which allows the motor part to advance a cargo, and, finally, detachment of adhesive contacts with a simultaneous depolymerization of actin fibers [16]. It is usually assumed that active polymerization ensuring protrusion can be described as the work of spatially distributed pushers, generating positive force couples, while active contraction can be viewed as an outcome of the mechanical action of distributed pullers, responsible for negative force couples [17–21]. The nature of reversible adhesion patches (focal adhesions) is understood rather poorly and individual focal adhesions are usually treated as passive viscous binders whose spatial distribution is regulated actively [22].

Since we do not know the mechanism controlling the transport and the intensity of active agents performing protrusion, contraction and adhesion, here we adopt a kinematic (reverse engineering) framework and treat the corresponding distributions as functional control parameters constrained by the fundamental mechanical balances. We then pose a variational problem of finding the optimal temporal and spatial distributions of these parameters inside a crawling continuum body, while anticipating that our optimal solutions will be eventually backed by an appropriate constitutive theory [23].

While the real organisms are expected to optimize some measure of a trade-off between the velocity of self-propulsion and the corresponding energy expenditure, in this paper we make a simplifying assumption that the energetic cost of self-propulsion is fixed and use as optimality criterion the maximization of the overall velocity. We are interested in steady translocation and assume that the internal distribution of mechanical parameters is compatible with the traveling wave ansatz. This simplifying assumption allows us to replace the optimization of the crawling stroke in space and time by a purely spatial optimization of the internal distribution of active elements in the co-moving coordinate system.

In the interest of analytic transparency we use the simplest one-dimensional model of actively contracting continuum subjected to viscous frictional forces that has been used repeatedly in the cell motility studies [16, 24–31]. In this setting, a study of the dependence of cell velocity on the distribution of active stresses on one side and adhesion properties on the other, was initiated in [18] where both contraction and protrusion were modeled by active couples. Given that protrusion is usually localized at the leading edge of the cell, we model the effect of active polymerization differently by using Stefan type boundary conditions on the edges of a crawling segment that fix the influx and the outflow of actin, see [21, 32, 33]. For the given strength of protrusion, we prescribe the average level of contractile activity, and then search for the optimal internal distribution of contractile and adhesive agents.

Our analysis of the ensuing variational problem demonstrates that radically different distributions of focal adhesions are optimal depending on the domineering active mechanism of self-propulsion. Thus, for contraction-dominated motility, focal adhesions have to cooperate with pullers which end up localizing at the trailing edge of the cell while for protrusion-dominated motility they must conspire with pushers which concentrate in our model at the leading edge of the cell. Both types of crawling mechanisms have been observed experimentally.

The paper is organized as follows. In Section 2 we formulate the model. A simple analytically tractable case of contraction-dominated motility is treated in Section 3. In Section 4 we obtain upper and lower bounds for the self-propulsion velocity in the general case and present some evidence that our lower bound coincides with the optimal solution. Finally Section 5 contains the discussion of our results.

2. The model
Following [29, 32], we consider a one-dimensional segment of viscous active gel representing the cell lamellipodium on a frictional substrate. The segment has two free boundaries which we identify as the trailing edge \( l_-(t) \) and the leading edge \( l_+(t) \). The force balance can be written in the form

\[
\partial_t \sigma = \xi \nu
\]  
(1)
where $\sigma$ is the stress and $v$ is the velocity. We assume that the frictional coefficient mimicking the distribution of focal adhesions [32–37] is space and time dependent $\xi(x, t) \geq 0$. The constitutive behavior of the gel is modeled by the equation [29, 32]

$$\sigma = \eta \partial_x v + \chi$$

(2)

where the active pre-stress $\chi(x, t) \geq 0$ accounting for the presence of myosin molecular motors [38–42] is also assumed to be a function of space and time. For simplicity we assume that the bulk viscosity coefficient $\eta > 0$ is constant. The assumption of infinite compressibility in equation (2) allows us to decouple the transport of (actin) density $\rho(x, t)$, from force balance making the mechanical problem ‘statically determinate’. The mass balance equation $\partial_t \rho + \partial_x (\rho v) = 0$ can then be solved independently after the velocity field is determined.

We further assume that some internal mechanism (stiffness of the cell cortex [43–48], osmotic pressure actively controlled by the channels and pumps on the cell membrane [49, 50], etc.) maintains a given size $L_0 = l_+ - l_-$ of the cell. Therefore the stress at the edges must be the same $\sigma(l_-(t), t) = \sigma(l_+(t), t) = \sigma_0$, where $\sigma_0(t)$ is an unknown function. To model active protrusion we impose two kinematic Stefan type boundary conditions characterizing the rate of actin polymerization $v_+ > 0$ and depolymerization $v_- > 0$ [29, 32–34]

$$\dot{l}_\pm = v_\pm + v(l_+(t), t)$$

(3)

For consistency, the overall mass balance must also be respected on the moving boundaries $\rho(l_-(t), t) v_- = \rho(l_+(t), t) v_+$, which implies an instantaneous recycling of depolymerized actin from the trailing edge to the leading edge, see [21, 51] for more detail. While there is considerable experimental evidence that active polymerization is indeed localized at the leading edge of a crawling cell, the de-polymerization edge to the leading edge, see [21, 51] for more detail. While there is considerable experimental evidence that active polymerization is indeed localized at the leading edge of a crawling cell, the de-polymerization is spread along the length of the lamellipodium [32, 33], however for our purposes such spreading can be ignored [21].

The two functions $\chi$ and $\xi$ will be considered as infinite-dimensional control parameters and found through an optimization procedure. In the absence of a detailed microscopic model governing the rearrangement of these agents we subject them to integral constraints prescribing the average number of adhesion complexes [42]

$$\frac{1}{L_0} \int_{l(t)} l_-(t) \xi(x, t) dx = \xi^*$$

(4)

where $\xi^* > 0$ is the given constant average number of motors [52] and

$$\frac{1}{L_0} \int_{l(t)} l_-(t) \chi(x, t) dx = \chi^*$$

(5)

where $\chi^* > 0$ is another given constant. It is clear from equations (4) and (5) that since we prescribe the density of active agents, the output of the self-propulsion machinery will be proportional to the length of the active segment.

To simplify the analysis we further assume that the motion of the active segment is steady with unknown velocity $V = l_+ - l_-$ and that the unknown functions $\sigma$, $\nu$ and the controls $\xi$, $\chi$ depend exclusively on the appropriately chosen co-moving coordinate $u = (x - x_0 - Vt)/L_0 \in [-1/2, 1/2]$ [32, 33]. Then in dimensionless variables $\sigma = \sigma/\chi^*, x = x/\sqrt{\eta/\xi^*}, t = t/(\eta/\chi^*), \xi = \xi/\xi^*$ and $\chi_0 = \chi/\chi^*$ we obtain the force balance equation

$$-\frac{1}{L^2} \partial_u \left( \frac{\partial_x \sigma(u)}{g_1(u)} \right) + \sigma = g_2(u)$$

(6)

where $L = L_0/\sqrt{\eta/\xi^*}$ and the new control functions

$$g_1(u) = \xi(Lu) \geq 0, g_2(u) = \chi(Lu) \geq 0$$
must satisfy the constraints
\[ \int_{-1/2}^{1/2} g_1(u) \, du = \int_{-1/2}^{1/2} g_2(u) \, du = 1 \]  
(7)

The boundary conditions take the form
\[ \left\{ \begin{align*}
    \sigma(-1/2) &= \sigma(1/2) \\
    \frac{1}{L^2} \left( \frac{\partial_u \sigma(1/2)}{g_1(1/2)} - \frac{\partial_u \sigma(-1/2)}{g_1(-1/2)} \right) &= -\Delta V
\end{align*} \right. \]  
(8)

where
\[ \Delta V = \frac{\eta(v_+ - v_-)}{\chi^2 L_0} \]

The dimensionless velocity of the segment per length \( \bar{V} = V/L \) can be found from the formula
\[ \bar{V} = \bar{V}_m + \frac{1}{2L^2} \left( \frac{\partial_u \sigma(1/2)}{g_1(1/2)} + \frac{\partial_u \sigma(-1/2)}{g_1(-1/2)} \right) \]  
(9)

where
\[ \bar{V}_m = \frac{\eta(v_+ + v_-)}{2\chi^2 L_0} \]

Now, if we assume that the two parameters \((\bar{V}_m, \Delta V)\) characterizing actin treadmilling are fixed we can pose the optimization problem of finding the controls \((g_1(u), g_2(u))\) ensuring the maximization of the velocity \( \bar{V} \). This problem is nontrivial because the functional \( \bar{V}(g_1, g_2) \) is prescribed implicitly through the unknown solution of the boundary value problem, equations (6) and (8). To our advantage though this linear elliptic problem is well studied, e.g. \([53]\).

We observe that the parameter \( \bar{V}_m \) enters the expression for the velocity, equation (9), in the additive way and does not affect the solution of the optimization problem. The reason for this is that \( \bar{V}_m \) characterizes a propulsion mode associated with simple accretion of the material at the front and its simultaneous removal at the rear; when \( \bar{V}_m \neq 0 \) a priori polarity is imposed and the problem of motility initiation disappears. In view of the additive decoupling of this mode, known as Listeria propulsion mode, from our control problem, we assume without loss of generality in the rest of the paper that \( \bar{V}_m = 0 \). Instead, the second parameter \( \Delta V \), also characterizing the protrusion strength, does not induce polarity and the dependence of the crawling velocity on \( \Delta V \) is more subtle.

3. Pushers and pullers

To show that the parameter \( \Delta V \) characterizes the activity of ‘pushers’ in our setting consider the global balance of couples in the co-moving coordinate system
\[ L \int_{-1/2}^{1/2} g_1(u)v(u)u \, du = -\Delta V + \int_{-1/2}^{1/2} g_2(u) \, du + \sigma_0 \]  
(10)

Here the term on the left-hand side gives the frictional moment due to external forces. The first term on the right-hand side
\[ T = \Delta V \]
is due to active protrusion while the second term \( \int_{-1/2}^{1/2} g_2(u) \, du = 1 \) is due to active contraction. The last term \( \sigma_0 \) corresponds to passive reaction forces resulting from the prescription of the length of the segment.
Our assumption that \( \Delta V > 0 \) means that the protrusion couple has a negative sign showing that the corresponding force dipoles act on the surrounding medium by pushing outward and creating negative stress. Instead, the contraction couple has a positive sign because the contractile forces pull inward and the induced stresses are positive. We can therefore associate protrusion with the presence of pushers and contraction with the activity of pullers [18, 21]. We can also (tentatively) argue that motility is protrusion dominated when \( T > 1 \) and it is contraction dominated when \( 0 < T < 1 \). This assertion will be confirmed later on by rigorous analysis.

To illustrate the different roles played in our motility mechanism by pushers and pullers, we present below an analysis of a toy model which anticipates the main conclusions of the paper. We temporarily set \( \Delta V = 0 \) and instead, following [18] describe the distribution of pushers and pullers by the same function \( g_2(u) \) allowing it to be both positive and negative. Our goal is to show that for protrusion-dominated motility driven by pullers it is the trailing edge that should have the strongest adhesion.

Consider a special choices of control functions,

\[
g_1(u) = q\delta(u - u_1) + (1 - q)\delta(u - u_2), \quad g_2(u) = p\delta(u - u_3) - (1 - p)\delta(u - u_4)
\]  

(11)

where \( \delta \) is the Dirac distribution, \( 0 \leq q, p \leq 1 \) and \(-1/2 \leq u_1, u_2, u_3, u_4 \leq 1/2 \). The control function \( g_1(u) \) represents two adhesion sites \( u = u_1 \) and \( u = u_2 \) whose locations must be optimized in relation to the prescribed positions of single puller placed at \( u = u_3 \) and a single pusher located at \( u = u_4 \). The two locations are characterized by a positive dipole moment \( p \) and a negative dipole moment \( p - 1 \), correspondingly. The parameter \( p \) measures the relative importance of contraction versus protrusion.

Suppose that \( u_3 < u_1 \) and \( u_2 < u_4 \) which ensures that our active segment moves from left to right and that in the segment the adhesion sites are outside while the active agents are inside. By using equation (11) we can express the velocity of the segment as

\[
\dot{V} = \frac{1}{2} \left( 1 - \frac{(1 - 2p)(u_2 - u_1)c}{u_1 - u_2 + 1 + (u_2 - u_1)a} \right)
\]

where,

\[
a = \frac{1}{1 + q(1 - q)(u_2 - u_1)L^2} \quad \text{and} \quad c = \frac{1 - 2q}{1 + q(1 - q)(u_2 - u_1)L^2}
\]

Suppose for simplicity that our two adhesive complexes are placed symmetrically with respect to the center of the segment and denote \( \Delta u = u_1 + 1/2 = 1/2 - u_2 \). Then we obtain,

\[
\dot{V} = \frac{1}{2} \left( 1 + \frac{(1 - 2p)(1 - 2q)}{1 + 2\Delta u q(1 - q)L^2 + \frac{2\Delta u}{1 - 2\Delta u}} \right)
\]

At \( \Delta u = 0 \), when adhesive complexes localize at the edges of the segment, the velocity reaches its maximum value

\[
\dot{V} = \frac{1}{2} [1 + (1 - 2p)(1 - 2q)]
\]

(12)

Because of the inequalities, in this configuration we necessarily have \( u_3 = -1/2 \) and \( u_4 = 1/2 \) meaning that pushers and pullers are also localized at the edges. Note however that the inequalities \( u_3 < u_1 \) and \( u_2 < u_4 \) are necessary for formula (12) to hold, so the limits \( u_3 = -1/2 \) and \( u_4 = 1/2 \) are an abuse of notation. In a theory where pushers, pullers and adhesion complexes have a characteristic size, the adhesion cluster would be slightly ahead of the pullers and slightly behind of the pushers so that the active agents take advantage of the firm attachment to either push or pull.
One can see that if the pullers dominate \((p > 1/2)\) the optimal way to tune adhesion is to set \(q = 1\) and concentrate the adhesive complexes at the trailing edge of the moving segment with velocity \(\bar{V} = 1\) for the optimal \(p = 1\). In this way the focal adhesions would conspire with pullers. If, instead, pushers dominate \((p < 1/2)\), the optimal way to tune adhesion is to set \(q = 0\) and concentrate adhesive complexes at the leading edge to obtain \(\bar{V} = 1\) now for the optimal \(p = 0\). In this way focal adhesions maximally reinforce the pushers. In other words, to be effective, pullers have to concentrate on the trailing edge and ensure strong adhesion on the leading edge. In this way pullers can inflict contraction that displaces the trailing edge which due to the length constraint also propels the leading edge. In contrast, pushers can take advantage of the firm attachment at the trailing edge to push against it and propel the leading edge which in turn pulls the trailing edge due to the length constraint.

4. Contraction driven motility

We now return to the study of the optimization problem in the original formulation. The simplest analytically transparent case is when the protrusion is disabled \((\Delta \bar{V} = 0)\) and motility is fully contraction-driven.

Suppose first that \(g_1 = 1\) and the adhesion complexes are distributed uniformly. Then the velocity of the active segment can be expressed as a quadrature

\[
\bar{V} = -\frac{1}{2 \sinh(\frac{u}{2})} \int_{-1/2}^{1/2} \sinh(Lu)g_2(u) \, du
\]

One can see that if the function \(g_2(u)\) is even, then \(\bar{V} = 0\). This result can be interpreted as an analogue of Purcell’s theorem [2, 4]. If the distribution \(g_3(u)\) is biased and, for instance, more motors are placed at the rear of the segment, the velocity will become positive. Using the fact that \(g_2(u) \geq 0\) we obtain \(\bar{V} \leq 1/2\). This upper bound is reached when all of the motors are fully localized at the rear and \(g_3(u) = \delta(u + 1/2)\).

Now, consider the general case when the focal adhesions are distributed inhomogeneously. We first observe that equation (6) is a Sturm–Liouville problem whose solution can be written as

\[
\sigma(u) = \sigma_0 - \int_{-1/2}^{1/2} G(u, s)[g_2(s) - \sigma_0] \, ds
\]

The Green’s function \(G(u, s)\) can be expressed in the form

\[
G(u, s) = \frac{1}{C} \left[ h(u)f(s)\mathbb{1}_{[s < u]} + h(s)f(u)\mathbb{1}_{[u < s]} \right]
\]

where \(\mathbb{1}\) denotes the indicator function and \(C = (hf' - fh')/g_1\) is a constant involving the Wronskian of the two auxiliary functions \(h(u)\) and \(f(u)\) which solve the following boundary value problems [53]:

\[
\begin{cases}
\left( \frac{1}{g_1} h' \right)' = L^2 h \\
L( -1/2) = 1, h(1/2) = 1 \\
\end{cases}
\quad \begin{cases}
\left( \frac{1}{g_1} f' \right)' = L^2 f \\
f( -1/2) = 1, f(1/2) = 1 \\
\end{cases}
\]

We obtain from equation (8)

\[
\bar{V} = \frac{1}{2} \int_{-1/2}^{1/2} f(u) (g_2(u) - \hat{g}_2) \, du
\]

where we introduced a new measure of inhomogeneity of contraction:

\[
\hat{g}_2 = \frac{\int_{-1/2}^{1/2} h(y)g_2(u) \, du}{\int_{-1/2}^{1/2} h(u) \, du}
\]
If both functions $g_{1,2}(u)$ are even, then $f(u)$ is odd and, since the integral of the product of an odd function and an even function is equal to zero, we get $\mathcal{V} = 0$. The same result follows if we assume that contraction is homogeneous $g_2(u) = g_2(u) = 1$ while the adhesion distribution $g_1(u)$ is arbitrary. Therefore, to ensure motility at $\Delta \mathcal{V} = 0$, contraction must be inhomogeneous while adhesion may still be uniform (provided the contraction is not even).

To find the optimal distributions $(g_1(u), g_2(u))$ we proceed in two steps. We first show that $\mathcal{V} \leq 1$ and then find a configuration of controls allowing the cell to reach this bound.

Notice that we can rewrite equation (16) in the form

$$\mathcal{V} = \frac{1}{2} \left( \int_{S_+} f(u)(g_2(u) - \hat{g}_2) \, du + \int_{S_-} f(u)(g_2(u) - \hat{g}_2) \, du \right)$$

where we defined the domains $S_- = \{u/g_2(u) \leq \hat{g}_2\}$ and $S_+ = \{u/g_2(u) > \hat{g}_2\}$. Applying the maximum principle to equation (15) we obtain $1 \geq h(u) \geq 0$ and $h(u) \geq f(u) \geq -h(u)$. Using the bounds on $f$, we can write

$$\mathcal{V} \leq \frac{1}{2} \left( \int_{S_+} h(u)g_2(u) \, du + \hat{g}_2 \int_{S_-} h(u) \, du \right)$$

Since the integrands are positive and $h(u) \leq 1$ it finally follows that

$$\mathcal{V} \leq \int_{-1/2}^{1/2} h(u)g_2(u) \, du \leq \int_{-1/2}^{1/2} g_2(u) \, du = 1$$

(17)

Below we show that this bound can be attained. Observe that in the case of a homogeneous distribution of adhesive clusters, the system can reach only one half of the maximal value of the velocity.

To find the internal configuration corresponding to $\mathcal{V} = 1$ we recall that the motor distribution maximizing the velocity at homogeneous friction is singular. We now show that the maximal velocity can be reached if both controls $g_1(u)$ and $g_2(u)$ are fully localized. Take $\theta > 0$ and consider a sequence

$$g_1(u; \theta) = \frac{1}{\pi \theta^2} \frac{\theta}{(u - u_1)^2}$$

with the property that $\lim_{\theta \to 0} g_1(u; \theta) = \delta(u - u_1)$. For this choice of $g_1$ the auxiliary functions $h(u)$ and $f(u)$ can be written explicitly in term of Legendre polynomials. In the limit $\theta \to 0$ we have

$$h(u) = 1 \quad \text{and} \quad f(u) = \begin{cases} 1 & \text{if } u \leq u_1 \\ -1 & \text{if } u > u_1 \end{cases}$$

By using these test functions we obtain from equation (16):

$$\mathcal{V} = \frac{1}{2} \left[ \int_{-1/2}^{u_1} g_2(u) \, du - \int_{u_1}^{1/2} g_2(u) \, du - 2u_1 \right]$$

(18)

We may now additionally suppose that $g_2(u) = \delta(u - u_2)$ is a Dirac distribution peaked at $u_2$. Then equation (18) reduces to

$$\mathcal{V} = \frac{1}{2} \begin{cases} 1 - 2u_1 & \text{if } u_2 < u_1 \\ -2u_1 & \text{if } u_2 = u_1 \\ -1 - 2u_1 & \text{if } u_2 > u_1 \end{cases}$$

This expression reaches its maximal value as $u_1 \to -1/2$ while $u_2 < u_1$. We can then formally write $u_2 = u_1 = -1/2$ and obtain the controls $g_2(u) = g_1(u) = \delta(u + 1/2)$ saturating the bound $\mathcal{V} = 1$. Note, however, that if we assume directly that $u_1 = u_2 \to -1/2$ in equation (18), we obtain $\mathcal{V} = 1/2$. This is in agreement with the physical intuition that the anchorage point must be located to the right of the pulling.
force dipole; in this case the pulling forces advance the rear edge of the segment with minimal slipping. Mathematically, we encounter here the case of non-commutation of the limiting procedures \( u_2 \to -1/2 \) and \( u_1 \to -1/2 \) giving \( V = 1 \) only if the limits are taken in the above order.

To summarize, the optimization of the distribution of focal adhesions allows the contraction-dominated mechanism of cell motility to reach a value of the velocity which is twice as large as when the adhesion is uniform. This means that in order to improve performance the adhesion machinery must conspire with the contraction machinery to make sure that both the motors and the adhesive centers are localized at the trailing edge. Interestingly, exactly this type of correlation between the stresses created by contraction and the distribution of focal adhesions has been observed in experiments and numerical simulations [22, 54–58]. The localization of adhesion complexes close to cell edges where contraction is the strongest has been also reported outside the motility context [59–61].

**5. Upper and lower bounds for velocity in the general case**

We now turn to the general case when both contraction and protrusion are active and, in particular, \( \Delta V = T > 0 \). We can then write

\[
\bar{V} = \frac{1}{2} \left[ \int_{-1/2}^{1/2} f(u) \, du + \int_{-1/2}^{1/2} h(u) \, du \right] = V_p + V_c
\]

As we see, the first term on the right-hand side \( V_p \) is associated with protrusion-based or filament-driven [62] motility while, as we have already seen, the second term, \( V_c \), is behind the contraction-based or motor-driven [62] motility. We note that if \( g_1(u) \) is even, then \( f(u) \) is odd and \( h(u) \) is even, leading to \( V_p = 0 \). If \( g_2(u) \) is also even, then \( V_c = 0 \). In this case the velocity of the segment is fully controlled by the accretion mechanism characterized by the parameter \( V_m \).

Consider first the case of protrusion-driven motility by assuming that contraction is homogeneous \( g_2(u) = 1 \) and therefore does not contribute to the overall velocity. By using again the maximum principle we obtain the inequalities

\[
-1 \leq \frac{\int_{-1/2}^{1/2} f(u) \, du}{\int_{-1/2}^{1/2} h(u) \, du} \leq 1
\]

leading to the upper bound

\[
\bar{V} = V_p \leq \frac{T}{2}
\]

The maximum of \( V_p \) is reached when \( g_1(u) = \delta (u - 1/2) \), because in this case \( h = 1 \) and \( f = 1 \) almost everywhere. Observe, that the optimal solution for \( g_1(u) \) in the case of protrusion-driven motility is in some sense *opposite* to the solution \( g_1(u) = \delta (u + 1/2) \) obtained in the case of the contraction-driven motility. One can then argue, based on equations (17) and (20), that in the case when both treadmilling and contraction are present, an upper bound for the velocity is

\[
\bar{V} \leq \frac{T}{2} + 1
\]

however, in view of the above contradiction, this bound cannot be reached. The optimal strategy for focal adhesions would instead involve a non-trivial compromise between the necessity to localize adhesion at the trailing edge in order to assist the contraction mechanism and the competing trend to localize adhesion at the leading edge in order to improve the protrusion power of the cell.

To obtain a lower bound for \( \bar{V} \) we can consider a particular test function representing a weighted sum of our competing optimal controls, \( g_1(u) = q \delta (u + 1/2) + (1 - q) \delta (u - 1/2) \). We also chose \( g_2(u) = \delta (u - u_0) \), where \( q \in [0, 1] \) and \( u_0 \in [-1/2, 1/2] \) are two parameters to be optimized. Then, by solving equation (15) we obtain,
Figure 1. The solid lines represent the lower bounds on the optimal velocity of the self-propulsion $\bar{V}$ as a function of the measure of the protrusive strength $\Delta V$. The optimal strategy depends on whether contraction (for $T < 1$) or protrusion (for $T > 1$) dominates. The dashed line represents the upper bound obtained by formally summing the upper bounds for the protrusion and contraction based strategies. The dotted line represents a sub-optimal strategy obtained under the assumption that adhesion is homogeneous. Insets schematically illustrate the associated configurations of controls $g_1(u)$ and $g_2(u)$.

\[ f(u) = \begin{cases} 
1 & \text{if } u = -\frac{1}{2} \\
\frac{1-2q}{1+q(1-q)L_2} & \text{if } u \in ]-\frac{1}{2}, \frac{1}{2}[, \\
-1 & \text{if } u = \frac{1}{2}
\end{cases} \]

and,

\[ h(u) = \begin{cases} 
1 & \text{if } u = -\frac{1}{2} \\
\frac{1}{1+q(1-q)L_2} & \text{if } u \in ]-\frac{1}{2}, \frac{1}{2}[, \\
1 & \text{if } u = \frac{1}{2}
\end{cases} \]

which leads to the expression

\[ \bar{V} = \frac{T}{2} (1 - 2q) + \frac{1}{2} (f(u_0) - (1 - 2q)h(u_0)) \]

The optimization with respect to $u_0$ gives $u_0 = -1/2$ and

\[ \bar{V} = \frac{T}{2} - q(T - 1) \]

Finally, optimizing in $q$ we obtain that if $T < 1$, we need to take $q = 0$ and if $T > 1$, we get $q = 1$. This result, illustrated in Figure 1, suggests that there is a switch at $T = 1$ between a contraction-centered optimization strategy ($q = 0$) and protrusion-centered optimization strategy ($q = 1$). Note that the switch takes place exactly where the negative protrusion generated couple $T$ becomes equal to the positive contractile couple (that is equal to one). In particular, at $T = 1$, the two active mechanisms neutralize each other and activity become invisible in the overall balance of dipole moments, see equation (10).
6. Numerical solution of the optimization problem

To show that the low bound obtained in the previous section is rather close to being optimal, here we solve the optimization problem numerically. A finite-dimensional reduction of the original variational problem is constructed by selecting \( N + 2 \) points \( u_i = i/(N + 1) - 1/2 \) that subdivide the segment \([-1/2, 1/2]\). We then localize adhesion and contraction in these points by choosing our control functions in the form

\[
g_1(u) = \sum_{i=1}^{N} g_i^1 \delta(u - u_i), \quad g_2(u) = \sum_{i=0}^{N+1} g_{2i} \delta(u - u_i)
\]

where \( \sum_{i=0}^{N+1} g_{2i}^1 = \sum_{i=1}^{N} g_i^1 = 1 \) and \( g_i^1 \geq 0, \ g_{2i}^1 \geq 0 \). In this way we also mimic the discrete nature of real adhesive clusters and real myosin motors so the discrete problem may be even more realistic than the continuum one. We however neglect here their characteristic size which may play a role.

By solving our auxiliary linear elliptic problems for this choice of controls we obtain that the functions \( h(u) \) and \( f(u) \) are piece wise constant \( h(u) = \sum_{i=0}^{N} A_i \mathbb{1}_{[u_i, u_{i+1})}(u) \) and \( f(u) = \sum_{i=0}^{N} C_i \mathbb{1}_{[u_i, u_{i+1})}(u) \). The coefficients with \( i \in [2, N] \) satisfy the equations

\[
g_i^1(A_{i-1} - A_{i-2}) + g_i^1 g_i^{-1} A_{i-1} L^2(u_i - u_{i-1}) = g_i^{-1}(A_i - A_{i-1})
\]

\[
g_i^1(C_{i-1} - C_{i-2}) + g_i^1 g_i^{-1} C_{i-1} L^2(u_i - u_{i-1}) = g_i^{-1}(C_i - C_{i-1})
\]

The boundary conditions give

\[ A_0 = 1, \quad A_N = 1, \quad C_0 = 1, \quad C_N = -1 \]

By using the conventions \( A_{-1} = A_0, A_{N+1} = A_N, C_{-1} = C_0 \) and \( C_{N+1} = C_N \), we can express the velocity of the segment, in the form

\[
\bar{V} = \frac{1}{2} \left( T - \sum_{i=0}^{N+1} g_{2i} A_i + A_{i-1} \right) \frac{1}{2} \sum_{i=0}^{N} C_i(u_{i+1} - u_i) + \frac{1}{2} \sum_{i=0}^{N+1} g_{2i} C_i + C_{i-1}
\]

The function (21) was optimized numerically with respect to parameters \( g_i^1 \) and \( g_{2i}^1 \) and subjected to the appropriate equality and inequality type constraints. To find the global minimum we used the method of simulated annealing with initial guesses corresponding to homogeneous configurations. In Figure 2 illustrating our results for \( N = 100 \), one can see that for \( T < 1 \) both optimal functions \( g_1(u) \) and \( g_2(u) \) are localized at the trailing edge. Instead, for \( T > 1 \) we observe that \( g_1(u) \) localizes at the leading edge while \( g_2(u) \) localizes at the trailing edge. This is in full agreement with the structure of the test functions delivering the lower bound for the velocity, \( \bar{V} \), which suggests that this bound may be (nearly) sharp. The resulting values of the velocity obtained numerically the same as the one obtained analytically up to an error proportional to the mesh size.

In agreement with our conclusion in Section 4 that optimally spaced adhesion points must be slightly shifted from the locations of force dipoles, we observe here that our numerical solution contains such shift at a mesh size \( L/(N + 2) \). Thus, the solution of the numerical (regularized) problem in the contraction-dominated regime (with \( T = 0.9 \)), shown in Figure 2, clearly distinguishes the optimal functions \( g_1(u) \) and \( g_2(u) \) that are both localized at the size of the mesh. More precisely, the function \( g_1(u) \) remains different from zero at one mesh size beyond the point where we already have \( g_2(u) = 0 \) (for positive velocity). In the protrusion-dominated regime (at \( T = 1.1 \)) shown in Figure 2, the mesh size again prevents localization of the function \( g_1(u) \) exactly at the leading edge while \( g_2 \) again localizes exactly at the trailing edge though it contributes in a negligible (but maximal) way to velocity.

7. Local stability analysis

In this section we use a perturbation analysis to provide additional evidence that our lower bounds are close to being optimal.
In what follows we use the superscript $^\circ$ to indicate the unperturbed state and superscript $^\star$ to mark parameters characterizing the perturbed configuration. We assume that for all functions $f(u)$ the following expansion holds in the first order

$$f(u) = f^\circ(u) + \epsilon f^\star(u)$$

where $\epsilon$ is a small parameter. Keeping only the first-order term in the expression for $\bar{V}$, we obtain

$$\bar{V}^\star = \frac{1}{2} \left[ \int_{-1/2}^{1/2} g_2^\circ f^\star + f\circ g_2^\star - \frac{\int_{-1/2}^{1/2} f\circ}{\int_{-1/2}^{1/2} h\circ} \left( \int_{-1/2}^{1/2} g_2 h^\star + h\circ g_2^\circ \right) \right]$$

$$+ \frac{T - \int_{-1/2}^{1/2} h\circ g_2^\circ}{\int_{-1/2}^{1/2} h\circ} \left( \int_{-1/2}^{1/2} f^\star - \frac{\int_{-1/2}^{1/2} h^\star}{\int_{-1/2}^{1/2} h\circ} \int_{-1/2}^{1/2} f\circ \right)$$

where $h^\star = H^\star$, $f^\star = F^\star$, and

$${H^\star}'' - L^2 g_1^\circ H^\star = L^2 h\circ g_1^\star$$

$${H^\star}'(-1/2) = H^\star'(1/2) = 0$$

$${F^\star}'' - L^2 g_1^\circ F^\star = L^2 f\circ g_1^\star$$

$${F^\star}'(-1/2) = F^\star'(1/2) = 0$$

(22)

In view of the saturation of the constraints by the unperturbed solution $\int_{-1/2}^{1/2} g_2^\circ = \int_{-1/2}^{1/2} g_1^\star = 1$, we must have

$$\int_{-1/2}^{1/2} g_2^\star = \int_{-1/2}^{1/2} g_1^\star = 0$$

Suppose now that we perturb the ‘optimal’ controls $g_1^\circ(u) = g_2^\circ(u) = \delta(u + 1/2)$ delivering the lower bound for velocity at $T < 1$. With some abuse of notation we can then set

$$h^\circ(u) = 1 \quad \text{and} \quad f^\circ(u) = \begin{cases} 1 & \text{if } u = -1/2 \\ -1 & \text{if } u > -1/2 \end{cases}$$

while remembering that the localization point for adhesion must be shifted with respect to the point of localization of active elements. The perturbation of velocity can be written as

\[ T = 0.9 < 1 \quad \text{and} \quad T = 1.1 > 1 \]
\[ V^* = \frac{1}{2} \left[ \int_{-1/2}^{1/2} (f^*(u) + h^*(u)) g_2^*(u) \, du + (T - 1) \int_{-1/2}^{1/2} (f^*(u) + h^*(u)) \, du \right] \]

A rather general class of perturbed controls can be represented in the form

\[
\begin{align*}
  g_1^*(u) &= -q\delta(u + 1/2) + r(u) \text{ with } \int_{-1/2}^{1/2} r(u) \, du = q \\
  g_2^*(u) &= -p\delta(u + 1/2) + l(u) \text{ with } \int_{-1/2}^{1/2} l(u) \, du = p
\end{align*}
\]  

(23)

Since \( g_1 \geq 0 \) and \( g_2 \geq 0 \) we demand that \( r(u) \geq 0 \) and \( l(u) \geq 0 \) and therefore also \( q \geq 0 \) and \( p \geq 0 \). We obtain

\[ V^* = -p + (T - 1) \int_{-1/2}^{1/2} r(u)(u + 1/2) \, du \]  

(24)

From equation (24) we see that if \( T \leq 1 \), a perturbation of the controls \( g_1^*(u) = g_2^*(u) = \delta(u + 1/2) \) leads to the decrease of the velocity, \( V^* \leq 0 \). Instead, if \( T > 1 \), by choosing \( r(u) \) such that,

\[ \int_{-1/2}^{1/2} r(u)(u + 1/2) \, du > \frac{p}{T - 1} \]

one can construct a perturbation with \( V^* > 0 \). These observations suggest that beyond the threshold \( T = 1 \) the control function \( g_1(u) \) should be no longer localized at the trailing edge. We also see that the most ‘efficient’ way to make the velocity larger at \( T > 1 \) is to localize the function \( r(u) \) at the leading edge of the segment (at \( u = 1/2 \)).

Consider now a perturbation of the set of controls \( g_1^*(u) = \delta(u - 1/2) \) and \( g_2^*(u) = \delta(u + 1/2) \) delivering our lower bound for \( T > 1 \). With the same abuse of notations as before we can write that

\[ h^*(u) = 1 \text{ and } f^*(u) = \begin{cases} 
  1 & \text{if } u < 1/2 \\
  -1 & \text{if } u = 1/2
\end{cases} \]

We represent the perturbations in the form

\[
\begin{align*}
  g_1^*(u) &= -q\delta(u - 1/2) + r(u) \text{ with } \int_{-1/2}^{1/2} r(u) \, du = q \\
  g_2^*(u) &= -p\delta(u + 1/2) + l(u) \text{ with } \int_{-1/2}^{1/2} l(u) \, du = p
\end{align*}
\]  

(25)

where again \( r(u) \geq 0 \) and \( l(u) \geq 0 \) and therefore also \( q \geq 0 \) and \( p \geq 0 \). The ensuing perturbation of velocity is

\[ V^* = \frac{1}{2} \left[ \int_{-1/2}^{1/2} (f^*(u) - h^*(u)) g_2^*(u) \, du + (T - 1) \int_{-1/2}^{1/2} (f^*(u) - h^*(u)) \, du \right] \\
= -(T - 1) \int_{-1/2}^{1/2} \left( \frac{1}{2} - u \right) r(u) \, du \]

It is now clear that if \( T \geq 1 \), then \( V^* \leq 0 \), showing that the perturbations of controls are sub-optimal. This gives additional evidence that the test function providing the lower bound for velocity at \( T \geq 1 \) are, at least, close to being optimal.

Based on this analysis we conjecture that the function \( V(T) \), representing the optimal velocity, is piece-wise linear with a kink at \( T = 1 \). The presence of a threshold indicates a switch from contraction-dominated motility pattern to protrusion-dominated motility pattern. As the relative power of protrusion epitomized by \( T \) increases beyond this threshold, the focal adhesions, maintaining the optimality of the self-propulsion velocity, must migrate from the trailing to the leading edge of the active segment. The dynamic migration of adhesion proteins to the edges has been observed in experiments [59]. In real
cells, however, both edges are usually populated by adhesion complexes and in this way cells can adjust smoothly to transitions from one driving mode to another.

8. Discussion

In this paper we used a simple analytically tractable model of cell motility to study the optimal strategies which allow cells to move faster by actively coordinating spatial distributions of contractile and adhesive agents. We made specific predictions regarding the advantageous correlations between these distributions and showed a possibility of a non-monotone dependence of the maximal velocity of self-propulsion on the relative strengths of active contraction and protrusion. In particular, our model predicts that a limited activation of protrusion will inevitably lower the maximal velocity achieved in a purely contractile mode of self-propulsion; however, as the protrusion strength increases, protrusion can overtake contraction and the velocity of self-propulsion will increase beyond the level achieved in the contraction-dominated case. More generally, our study reveals that if adhesion complexes can detect the dominating mechanism of self-propulsion, they can self-organize to ensure the best performance.

Previously we have shown that a contraction-dominated motility mechanism may be used for cell polarization, motility initiation, motility arrest and the symmetrization of a cell preparing for the mitosis [31, 63]. From the analysis presented in this paper it becomes evident that, if the speed of self-propulsion is an issue, cells should mostly rely on protrusion. Therefore, to maximize its velocity performance after motility initiation a cell must switch from a contraction-dominated to a protrusion-dominated motility mechanism by increasing the protrusive power and appropriately rearranging the distribution of adhesive complexes. Similar transitions between contraction and protrusion dominating mechanisms may be used by a cell to accommodate various types of cargo [51].

To compare our predictions with experiments we can use numerical values of the parameters available in the literature. For instance, taking the data for keratocyte fragments from [29, 32, 34], we obtain the following rough estimates: $\chi^* = 10^3 \text{ Pa}$, $\xi^* = 3 \times 10^{16} \text{ Pa} \cdot \text{m}^{-2} \cdot \text{s}$, $\eta = 3 \times 10^4 \text{ Pa} \cdot \text{s}$, $L_0 = 10 \mu\text{m}$, $V_m = 8 \mu\text{m} \cdot \text{min}^{-1}$ and $\Delta V = 0.6 \mu\text{m} \cdot \text{min}^{-1}$. Our first quantitative prediction concerns the case when active treadmilling of actin is knocked down and adhesion is homogeneous. As we have shown, the largest velocity in this case is reached when all myosin motors are localized at the trailing edge as observed in most eukaryotic cells [64–67]. In dimensional form, the predicted maximal velocity is $V = \frac{L_0 \chi^*}{2 \eta} \approx 10 \mu\text{m} \cdot \text{min}^{-1}$, which is low in view of the data on keratocyte fragments suggesting that velocity should be in the interval 30–40 $\mu\text{m} \cdot \text{min}^{-1}$ (see [68]); however, according to our results, only half of the total amount of motors are “used” in this case which implies that adhesion homogeneity is highly sub-optimal.

If the adhesion inhomogeneity is allowed, the configuration becomes optimal when both myosins and integrins are localized at the trailing edge. Such highly correlated distributions have been observed in both experiments and the microscale-based numerical models [55–61, 69]. As a result of the cooperative response a cell can be more efficient achieving the velocity that is two times larger than in the case of homogeneous adhesion: $V = \frac{L_0 \chi^*}{\eta} \approx 20 \mu\text{m} \cdot \text{min}^{-1}$. To be even more realistic we need to take active treadmilling into consideration and our estimates suggest that $T \approx 0.1 \ll 1$. This means that we are in the contraction-dominated motility regime for which our velocity bound gives a much more realistic value $V = V_m + \frac{L_0 \chi^*}{\eta} \approx 28 \mu\text{m} \cdot \text{min}^{-1}$. Note, however, that reducing the value $\chi^*$ by one order of magnitude, which is within the existing error bounds, we may easily reach the regime where $T > 1$ where it would become more beneficial for adhesion clusters to localize at the leading edge conspiring with protrusive elements. A spatial correlation of this type between adhesion and protrusion has been recorded in both experiments and comprehensive numerical models of cell motility (e.g. [70, 71] for nematode spermatozoa).

The proposed model can be also tested indirectly. For instance, we know that the location of adhesion complexes in a moving cell can be identified by measuring the distribution of traction forces in the elastic environment [72, 73]. If the adhesive complexes are shifted towards the leading edge, we would argue that the cell relies for its advance mostly on actin treadmilling. If instead the adhesive complexes are preferentially positioned at the trailing edge, our model suggests that motility is mostly driven by contraction. Both predictions can be tested by independent measurements.
An interesting possibility is when a cell alternates the location of maximum adhesion between the trailing edge and the leading edge in response to oscillations in the level of activity of pullers and pushers. The evidence of such switching may be that both locations are populated with adhesive complexes. We may also recall that the classical mechanism of crawling for eukaryotic cells involves two phases [24, 26, 74, 75]. One of them is associated with the creation of protrusions that push at the front while relying on the stabilization of the trailing edge. Another phase involves pulling of the rear (of the cargo) which requires fixation at the front. The switching between these two phases takes place almost periodically and the associated reorganization of adhesion clusters from the leading to the trailing edge has been well documented [72, 76]. To capture this non-steady motility pattern our simplifying traveling wave assumption would have to be replaced by a more complex ansatz.

In conclusion, we point out that our interpretations are based on the study of a variational problem whose complete solution has not been attempted in this exploratory study. Still, even a partial analysis of this problem revealed some interesting correlations between the spatial arrangement of adhesion and contraction agents and has led us to quantitative predictions that are in agreement with experiments. The prototypical nature of the proposed model, however, conceals the considerable complexity of the actual cell motility phenomenon which involves intricate bio-chemical feedback loops, geometrically complex mechanical flows and highly nontrivial rheological behavior. In particular, the singular nature of the obtained solutions can be at least partially linked to the fact that treadmilling is modeled schematically with polymerization and depolymerization processes localized at the edges; at least one additional control function describing the distribution of pushers is needed to regularize the problem in this respect. The situation is complicated further by the fact that the dominant trade-off controlling the self-organization of active agents is still unknown, notwithstanding some recent results in this direction [23]; however, even in the absence of the definitive optimization criterion and with minimal assumptions about the inner working of the motility machinery, our study reveals that depending on the task and the available resources a cell may have to modify its mode of operation rather drastically to ensure the best possible performance at every condition.

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Conflict of interest

None declared.

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References

[1] Childress, S. Mechanics of swimming and flying. vol. 2. Cambridge University Press; 1981.
[2] Lauga, E, and Powers, TR. The hydrodynamics of swimming microorganisms. Rep Prog Phys 2009; 72(9): 096601. DOI:10.1088/0034-4885/72/9/096601
[3] Taylor, G. Analysis of the swimming of microscopic organisms. Proc R Soc of Lond A 1951; 209(1099): 447–461.
[4] Purcell, EM. Life at low Reynolds number. Am J Phys 1977; 45(1): 3–11.
[5] DeSimone, A, Alouges, F, and Lefebvre, A. Biological fluid dynamics: swimming at low Reynolds numbers. SISSA 2008; 21: 1–13.
[6] Shapere, A, and Wilczek, F. Self-propulsion at low Reynolds number. Phys Rev Lett 1987; 58: 2051–2054.
[7] Najafi, A, and Golestanian, R. Simple swimmer at low Reynolds number: Three linked spheres. Phys Rev 2004; 69: 062901.
[8] Leshansky, AM, Kenneth, O, Gat, O, et al. A frictionless microswimmer. New J Phys 2007; 9(5): 145.
[9] Alouges, F, DeSimone, A, and Lefebvre, A. Optimal strokes for axisymmetric microswimmers. Eur Phys J E Soft Matter 2009; 28: 279–284.
[10] Alouges, F, DeSimone, A, and Heltai, L. Numerical strategies for stroke optimization of axisymmetric microswimmers. Math Mod Meth Appl S 2011; 21(2): 361–387.
[11] Osterman, N, and Vilfan, A. Finding the ciliary beating pattern with optimal efficiency. *Proc Natl Acad Sci USA* 2011; 108(38): 15,727–15,732.

[12] Michelin, S, and Lauga, E. Unsteady feeding and optimal strokes of model ciliates. Preprint (2012). Available from: http://arxiv.org/pdf/1210.1331.pdf.

[13] DeSimone, A, and Tatone, A. Crawling motility through the analysis of model locomotors: Two case studies. *Eur Phys J E Soft Matter* 2012; 35: 1–8.

[14] Noselli, G, Tatone, A, and DeSimone, A. Discrete one-dimensional crawlers on viscous substrates: Achievable net displacements and their energy cost. *Mech Res Commun* 2011; 38(1): 57–63.

[15] Gidoni, P, Noselli, G, and DeSimone, A. Crawling on directional surfaces. *Int J Nonlinear Mech* 2012; 47(2): 140–146.

[16] Mogilner, A. Mathematics of cell motility: have we got its number? *J Math Biol* 2009; 59(1–2): 105–134.

[17] Simha, R, and Ramaswamy, S. Hydrodynamic fluctuations and instabilities in ordered suspensions of self-propelled particles. *Phys Rev Lett* 2002; 89(5): 058101.

[18] Carlsson, AE. Mechanisms of cell propulsion by active stresses. *New J Phys* 2011; 13: 073009. DOI:10.1088/1367-2630/13/7/073009.

[19] Saintillan, D, and Shelley, MJ. Emergence of coherent structures and large-scale flows in motile suspensions. *J R Stat Soc* 2012; 9(68): 571–585.

[20] Marchetti, MC, Joanny, JF, Ramaswamy, S, et al. Soft active matter. Preprint (2012). Available from: http://arxiv.org/abs/1207.2929.

[21] Recho, P, Putelat, T, and Truskinovsky, L. Contraction-driven cell motility. *Phys Rev Lett* 2013; 111: 108102.

[22] Gao, H, Qian, J, and Chen, B. Probing mechanical principles of focal contacts in cell-matrix adhesion with a coupled stochastic-elastic modelling framework. *J R Soc Interface* 2011; 8(62): 1217–1232.

[23] Recho, P, Joanny, JF, and Truskinovsky, L. Optimality of contraction-driven crawling. *Phys Rev Lett* 2014; 112(21): 218101.

[24] Abercrombie, M. Croonian lecture, 1978 – Crawling movement of metazoan cells. *Proc R Soc Lond B* 1980; 207(1167): 129.

[25] DiMilla, P, Barbee, K, and Lauffenburger, D. Mathematical-model for the effects of adhesion and mechanics on cell-migration speed. *Biophys J* 1991; 60(1): 15–37.

[26] Stossel, T. On the crawling of animal-cells. *Science* 1993; 260(5111): 1086–1094.

[27] Ridley, AJ, Schwartz, MA, Burridge, K, et al. Cell migration: Integrating signals from front to back. *Science* 2003; 302(5651): 1704–1709.

[28] Vicente-Manzanares, M, Webb, D, and Horwitz, A. Cell migration at a glance. *J Cell Sci* 2005; 118(21): 4917–4919.

[29] Kruse, K, Joanny, JF, Julicher, F, et al. Contractility and retrograde flow in lamellipodium motion. *Phys Rev Lett* 2006; 97(7): 1853–1863.

[30] Shao, D, Rappel, WJ, and Levine, H. Computational model for cell morphodynamics. *Phys Rev Lett* 2010; 105(10): 108104.

[31] Doubrovinski, K, and Kruse, K. Cell motility resulting from spontaneous polymerization waves. *Phys Rev Lett* 2011; 107: 258103.

[32] Hawkins, RJ, Poincloux, R, Benichou, O, et al. Spontaneous contractility-mediated cortical flow generates cell migration in three-dimensional environments. *Biophys J* 2011; 101(5): 1041–1045.

[33] Salbreux, G, Joanny, JF, Prost, J, et al. Shape oscillations of non-adhering fibroblast cells. *Phys Biol* 2007; 4(4): 268.

[34] Bois, JS, Julicher, F, and Grill, SW. Pattern formation in active fluids. *Phys Rev Lett* 2011; 106: 028103.

[35] George, U, Stéphanou, A, and Madzvamuse, A. Mathematical modelling and numerical simulations of actin dynamics in the eukaryotic cell. *J Math Biol* 2013; 66: 547–593.

[36] Wolgemuth, CW, Stajic, J, and Mogilner, A. Redundant mechanisms for stable cell locomotion revealed by minimal models. *Biophys J* 2011; 101(3): 545–553.

[37] Barnhart, EL, Lee, KC, Keren, K, et al. An adhesion-dependent switch between mechanisms that determine motile cell shape. *PLoS Biol* 2011 05; 9(5): e1001059.

[38] Boal, D. *Mechanics of the Cell*. Cambridge: Cambridge University Press, 2002.
[45] Prost, J, Barbetta, C, and Joanny, JF. Dynamical control of the shape and size of stereocilia and microvilli. *Biophys J* 2007; 93(4): 1124–1133.

[46] Barnhart, EL, Allen, GM, Julicher, F, et al. Bipedal locomotion in crawling cells. *Biophys J* 2010; 98(6): 933–942.

[47] Du, X, Doubrovinski, K, and Osterfield, M. Self-organized cell motility from motor–filament interactions. *Biophys J* 2012; 102(8): 1738–1745.

[48] Loosley, AJ, and Tang, JX. Stick-slip motion and elastic coupling in crawling cells. *Phys Rev E* 2012; 86(3): 031908.

[49] Jiang, H, and Sun, SX. Cellular pressure and volume regulation and implications for cell mechanics. *Biophys J* 2013; 105(3): 609–619.

[50] Stroka, KM, Jiang, H, Chen, SH, et al. Water permeation drives tumor cell migration in confined microenvironments. *Cell* 2014; 157(3): 611–623.

[51] Recho, P, and Truskinovsky, L. Asymmetry between pushing and pulling for crawling cells. *Phys Rev E* 2013; 87: 022720.

[52] Thoresen, T, Lenz, M, and Gardel, M. Reconstitution of contractile actomyosin bundles. *Biophys J* 2011; 100(11): 2698–2705.

[53] Mikhlin, SG. *Linear Integral Equations*. Hindustan publishing corp., 1960.

[54] Wang, Y, Botvinick, E, Zhao, Y, et al. Visualizing the mechanical activation of Src. *Nature* 2005; 434(7036): 1040–1045.

[55] Bershadsky, A, Kozlov, M, and Geiger, B. Adhesion-mediated mechanosensitivity: A time to experiment, and a time to theorize. *Curr Opin Cell Biol* 2006; 18(5): 472–481.

[56] Wolfenson, H, Henis, YI, Geiger, B, et al. The heel and toe of the cell’s foot: A multifaceted approach for understanding the structure and dynamics of focal adhesions. *Cell Motil Cytoskeleton* 2009; 66(11): 1017–1029.

[57] Shutova, M, Yang, C, Vasileiev, JM, et al. Functions of nonmuscle myosin II in assembly of the cellular contractile system. *PLoS One* 2012; 7(7): e40814–e40814.

[58] Novak, IL, Slepchenko, BM, Mogilner, A, et al. Cooperativity between cell contractility and adhesion. *Phys Rev Lett* 2004; 93(26): 268109.

[59] Deshpande, VS, Mrksich, M, McMeeking, RM, et al. A bio-mechanical model for coupling cell contractility with focal adhesion formation. *J Mech Phys Solids* 2008; 56(4): 1484–1510.

[60] Risler, T. Mechanics of motility initiation and motility arrest in active gels. Preprint (2011). Available from: http://arxiv.org/abs/1501.07185.

[61] Zajac, M, Dacanay, B, Mohler, WA, et al. Depolymerization-driven flow in nematode spermatozoa relates crawling speed to size and shape. *Biophys J* 2008; 94(10): 3810–3823.

[62] Fourrier, MF, Sauser, R, Ambrosi, D, et al. Force transmission in migrating cells. *J Cell Biol* 2010; 188(2): 287–297.

[63] Peschetola, V, Laurent, VM, Dupray, A, et al. Time-dependent traction force microscopy for cancer cells as a measure of invasiveness. *Cytoskeleton* 2013; 70(4): 201–214.

[64] Fournier, MF, Sauser, R, Ambrosi, D, et al. Force transmission in migrating cells. *J Cell Biol* 2010; 188(2): 287–297.

[65] Peschetola, V, Laurent, VM, Dupray, A, et al. Time-dependent traction force microscopy for cancer cells as a measure of invasiveness. *Cytoskeleton* 2013; 70(4): 201–214.

[66] Bellairs, R. Michael Abercrombie (1912-1979). *Int J Dev Biol* 2000; 44(1): 23–28.

[67] Alberts, B, Johnson, A, Lewis, J, et al. *Molecular biology of the cell*. 4th ed. Garland Science Taylor & Francis Group, 2002.

[68] Ambrosi, D, Dupray, A, Peschetola, V, et al. Traction patterns of tumor cells. *J Math Biol* 2009; 58(1–2): 163–181.