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Control of actin-based motility through localized actin binding

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Abstract

A wide variety of cell biological and biomimetic systems use actin polymerization to drive motility. It has been suggested that an object such as a bacterium can propel itself by self-assembling a high concentration of actin behind it if it is repelled by actin. However, it is also known that it is essential for the moving object to bind actin. Therefore, a key question is how the actin tail can propel an object when it both binds and repels the object. We present a physically consistent Brownian dynamics model for actin-based motility that includes the minimal components of the dendritic nucleation model and allows for both attractive and repulsive interactions between actin and a moveable disk. We find that the concentration gradient of filamentous actin generated by polymerization is sufficient to propel the object, even with moderately strong binding interactions. Additionally, actin binding can act as a biophysical cap, and may directly control motility through modulation of network growth. Overall, this mechanism is robust in that it can drive motility against a load up to a stall pressure that depends on the Young's modulus of the actin network and can explain several aspects of actin-based motility.

Keywords

actin; motility; ActA; self-assembly; self-diffusiophoresis

1. Introduction

Actin-based motility is ubiquitous in cell biology [1], and drives processes such as lipodial protrusion during cell crawling [2, 3], motility by the infectious bacteria *Listeria monocytogenes* [4–6] and *Shigella exneri* [7, 8], transit of viruses through cells [9, 10], and trafficking of vesicles [11] and organelles [12]. In these examples, motility involves at least hundreds of actin filaments and requires a many-filament approach to understanding the physical mechanism underlying motility. Such a mechanism, known as the “self-diffusiophoretic” mechanism, has been suggested [13]. Through this mechanism, actin network growth leads to a concentration gradient, so that the actin concentration is higher behind the moving object than in front of it. This leads to motion of the object down the concentration gradient if the object is repelled by actin. However, it is known that actin binds to proteins on the moving object [8, 14, 15], leading to attractive interactions between the object and actin. The existence of attractions would appear to invalidate the self-diffusiophoretic mechanism. In this paper, we show that this is not the case, actin binding does not disrupt the self-diffusiophoretic mechanism at reasonable binding energies and

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densities. In addition, we find that if actin binding at the surface caps growing ends, it regulates motility by slowing network growth, rather than by resisting forward motion.

The biochemical components of actin-based motility have long been understood through the dendritic nucleation model [16, 17]. Although the full biochemistry of cell crawling by the dendritic nucleation model has many components, *in vitro* experiments have shown that only a few ingredients are essential to actin-based propulsion [18–21]. Actin polymerizes into filaments of F-actin by adding monomers of G-actin to the “barbed” ends of filaments. The protein Arp2/3 is activated near the object by actin-binding proteins such as ActA or WASP, and Arp2/3 in turn mediates branching of filamentous F-actin, creating additional growing barbed ends. Turnover is accelerated by cofilin, which severs actin filaments, generating additional barbed ends and enhancing disassembly. Further from the moving object, capping proteins halt barbed end growth and depolymerization occurs at the “pointed” ends of filaments. The result is a dynamic, branched actin network that polymerizes near the moving surface and disassembles at the trailing edge of the actin network (the end of the tail or rear of the lamellipodium). Altogether, these biochemical components lead to motion of the object [3, 16, 17]. The physical mechanism by which motion is generated is the subject of this paper.

Actin polymerization may occur within a moving object, such as during cell crawling, when it generates the lamellipodium, a branched actin network at the leading edge of the cell [3, 22]. Alternatively polymerization can occur outside the object, such as when *Listeria* grows a trailing actin network called the “comet tail” [4, 6, 23]. This has been demonstrated not only for biological objects such as the membrane at the leading edge of a crawling cell or a *Listeria* bacterium, but also for polystyrene beads [18, 21] and disks [24], oil droplets [25], and lipid vesicles [26, 27].

Many models have been proposed to explain actin-based motility, including the single-filament Brownian ratchet model [28–30], the continuum gel model [31, 32], and a variety of others [33–38]. Recently, it was suggested that the mechanism relies on the generation and maintenance of a steady-state F-actin concentration gradient [13]. Since polymerization activity is very high behind the moving surface and far lower elsewhere [17], there is a gradient of F-actin so that the actin concentration is higher behind the object than in front of it. A short-ranged repulsive interaction (for instance, due to excluded volume or screened Coulomb interactions) suffices to drive the object towards lower concentrations of F-actin, down the concentration gradient. According to this model, actin-based motility is an example of self-diffusiophoresis [13, 39], a phenomenon in which a particle generates around itself a concentration gradient that induces a steady-state, fluid flow which propels the particle [40–42].

However, the fact that F-actin not only repels the object but also locally attracts it at the sites of actin-binding proteins such as ActA or WASP [8, 14, 15] poses a major challenge to this model. Since the self-diffusiophoretic mechanism relies on repulsive interactions, these attractive interactions could, in principle, disrupt or destroy concentration-gradient-mediated propulsion. It is therefore important to investigate whether the many-filament model proposed in [13] is truly viable with actin-binding proteins such as ActA.

Here we extend the model of [13, 39] to include local binding interactions between the moving object (a disk) and actin. We find that binding interactions do not destroy the self-diffusiophoretic mechanism, and indeed, have little effect on motility up to reasonably large binding energies or binding site densities. In addition, binding interactions provide a novel mechanism for control of motility through the modulation of actin network growth. We show that the material properties of the F-actin network provide robustness against opposing

loads even in the presence of actin binding to the object, consistent with experiments. Our simulations demonstrate that self-diffusiophoresis must exist in actin-polymerization-driven systems even if other phenomena [28–38] might come into play.

2. Methods and Model

Our Brownian dynamics simulations are similar to those in [13, 39], but they have been adapted to effectively model actin-based motility with specific binding between a motile disk and F- and G-actin subunits. As in [13, 39], some of the model parameters differ from experiments (see Table 1 for details) so that simulations can be completed within a reasonable time. However, in contrast to other simulated models [43–47], our model is physically consistent in that it conserves mass. This is important because the violation of mass conservation can lead to motility as an artifact.

At the start of the simulations, a moveable disk of radius $10a$ and thickness a is placed at the center of the simulation box and actin subunits of diameter a are distributed randomly throughout the box. A small percentage of the actin subunits are initially joined together as dimers, whose barbed ends may polymerize to form F-actin filaments. Arp2/3 point particles are released from the back of the disk, facilitating additional network growth through side-on branching. Both the F-actin network and G-actin subunits interact with the disk through repulsive excluded volume interactions and short-ranged and localized attractive interactions with actin binding sites on the back of the disk. The binding sites attract actin to the disk, but unlike ActA and WASP in experimental systems [19, 48], do not enhance Arp2/3 or actin-polymerization activity. In order to simplify the analysis and obtain results for small system sizes, the disk is constrained to move only in the z -direction, as shown in figure 1(a)-(b). Relaxing this constraint should not alter conclusions about the viability of motility, which is the subject of this paper. However, we fully expect that if we were allow the disk to move freely in all directions, our model would lead to the complicated trajectories observed and studied previously [49, 50], due to spatial fluctuations in the distribution of binding sites. The simulation takes place in a $40a \times 40a \times 80a$ box with periodic boundary conditions on all sides.

2.1. Units

We convert simulation units into physical units by taking the actin subunit length to be $a = 5$ nm and the diffusion coefficient to be $D = 36.6 \mu\text{m}^2/\text{s}$. This gives a viscosity $\eta = 2.4$ cP, as measured experimentally in cell extracts [51], and a characteristic time scale $\tau = a^2/D = 0.68 \mu\text{s}$. Typically, we use time steps $\Delta t = 0.68$ ns and collect data for about 1 s.

2.2. Interactions

All actin subunits are diameter a spheres that interact with each other by a repulsive potential:

$$U_R(r_{ij}) = \begin{cases} \frac{1}{2} K_R (r_{ij} - a)^2 & \text{for } r_{ij} < a, \\ 0 & \text{for } r_{ij} \geq a, \end{cases} \quad (1)$$

where r_{ij} is the center-to-center distance between subunits i and j , and $K_R = 100k_B T/a^2$. A similar soft repulsion acts along the z -direction between actin subunits and the disk (except at the disk edge, where actin may be repelled in the x and y directions). F-actin subunits are bound to neighboring subunits through the bond potential:

$$U_B(r_{ij}) = \begin{cases} \frac{1}{2}K_B(r_{ij} - a)^2 & \text{for } r_{ij} < a, \\ 0 & \text{for } r_{ij} \geq a, \end{cases} \quad (2)$$

where $K_B = 100k_BT/a^2$. Thus, attractive bond forces are only felt for subunit separations of $r_{ij} > a$ and are zero for $r_{ij} < a$. Filaments and branches are given a stiffness by the bending potential [52]:

$$U_S(\theta_i) = \frac{1}{2}K_S(\cos\theta_i - \cos\theta_0)^2, \quad (3)$$

where $K_S = 100k_BT$, θ_i is an angle between the bond vectors $\vec{b}_{hi}$, connecting neighboring subunits h and i , and $\vec{b}_{ij}$ connecting neighboring subunits i and j , and θ_0 is the preferred bond vector angle. For filaments, bond vectors prefer to align, so $\theta_0 = 0^\circ$. For branches, the subunits form y-shaped structures with filaments [13], at these “y-junctions,” the bond vectors connect at an angle of $\theta_0 = 70^\circ$ as observed in experiments [16, 22, 23, 53].

2.2.1. Interactions between actin and disk—In addition to the above interactions from [13, 39], we include specific binding interactions between binding sites on the back of the disk and actin subunits. To do this, we introduce a polarization unit vector, $\hat{p}_i$, for each subunit, i , that points to the “plus” pole of the subunit, thus, each subunit has a preferred spot on its surface for actin-binding site attractive interactions. The polarization vectors tend to align along the direction of the filament bond unit vectors, $\vec{b}_{i-1,i} = \vec{b}_{i-1,i}/|\vec{b}_{i-1,i}|$ and $\vec{b}_{i,i+1} = \vec{b}_{i,i+1}/|\vec{b}_{i,i+1}|$, through the potential:

$$U_P(\hat{p}_i, \hat{b}_{i-1,i}, \hat{b}_{i,i+1}) = \frac{1}{2}K_P(\hat{p}_i \cdot \hat{b}_{i-1,i} - \cos\theta_P)^2 + \frac{1}{2}K_P(\hat{p}_i \cdot \hat{b}_{i,i+1} - \cos\theta_P)^2, \quad (4)$$

where $K_P = 50k_BT$ and $\theta_P = 0^\circ$. Actin binding sites are randomly distributed on back of the disk and all actin subunits with the sites through the short-ranged, specific binding potential:

$$U_A(r_{i\alpha}, \psi_{i\alpha}) = \begin{cases} \frac{\varepsilon}{C} \left(\frac{\sigma^{14}}{r_{i\alpha}^{14}} - \frac{\sigma^{12}}{r_{i\alpha}^{12}} \right) \cos^6 \psi_{i\alpha} & \text{for } \cos \psi_{i\alpha} > 0, a < r_{i\alpha} < 2a, \\ \frac{\varepsilon}{C} \cos^6 \psi_{i\alpha} & \text{for } \cos \psi_{i\alpha} > 0, r_{i\alpha} < a, \\ 0 & \text{otherwise,} \end{cases} \quad (5)$$

where $r_{i\alpha} = |\vec{r}_a - \vec{r}_i|$ is the center-to-center distance between the actin subunit i and binding site α . We vary the binding energy ε in our simulations. $C = (\sigma/a)^{12} - (\sigma/a)^{14}$ is a

normalization factor for the binding energy scale. The length $\sigma = a\sqrt{6/7}$ sets $r_{i\alpha} = a$ as the minimum of the binding potential. Binding site specificity is enforced through the angle, $\psi_{i\alpha}$, which is the angle between $\hat{p}_i$ and $\vec{r}_{i\alpha}$. The cutoff distance $2a$ for U_A is chosen so that the spatial discontinuity in the energy is small. For $r_{i\alpha} < a$, U_A only acts to adjust $\psi_{i\alpha}$. This is done in order to avoid extremely large repulsive forces that would otherwise exist for $r_{i\alpha} < a$. In addition, actin subunits necessarily overlap with the disk when $r_{i\alpha} < a$, and thus repel the disk through the potential in Eq. 1. Forces exerted on the binding sites are exerted on the motile disk.

2.3. Equations of motion

All actin subunits translate and rotate diffusively according to Brownian dynamics [54]. Thus, the evolution of the system is governed by coupled Langevin equations where each particle's instantaneous velocity is determined by forces exerted by other subunits and thermal forces, $\vec{F}$:

$$\zeta \dot{\vec{r}} = -\vec{\nabla}_r(U_R + U_B + U_S + U_P + U_A) + \vec{F}(t) \quad (6)$$

$$\langle \vec{F}(t) \rangle = 0, \langle \vec{F}(t) \cdot \vec{F}(t') \rangle = 6k_B T \zeta \delta(t - t') \quad (7)$$

and

$$\zeta_p \dot{\vec{p}} = -\nabla_p(U_P + U_A) + \vec{G}(t) \quad (8)$$

$$\langle \vec{G}(t) \rangle = 0, \langle \vec{G}(t) \cdot \vec{G}(t') \rangle = \frac{2a^2}{9} \langle \vec{F}(t) \cdot \vec{F}(t') \rangle = 4k_B T \zeta_p \delta(t - t'). \quad (9)$$

The translational drag is $\zeta = 3\pi\eta a$, and the rotational drag is $\zeta_p = \pi\eta a^3$, where η is the viscosity.

The disk is constrained to move only in the z direction. Thus, it undergoes translational diffusion and experiences forces due to interactions with actin through U_A and a repulsive potential analogous to U_R (Eq. 1). We take $D_{\text{disk}} = D/20$.

Arp2/3 molecules are modeled as point particles that diffuse with diffusion coefficient $D_{\text{Arp}} = D/20$, which is small in order to localize them to near the back of the disk. We note, however, that our results are insensitive to the precise value of D_{Arp} . Arp2/3 particles are reected by disk, but do not exert forces on either the disk or actin.

2.4. Biochemistry

We include the basic components of the dendritic nucleation model [16, 17], as described in [13, 39]. Precise numbers for rate constants are given in Table 1.

A G-actin monomer polymerizes at an F-actin filament or branch barbed end if the two subunits are in contact ($a - \delta r < r_{ij} < a$), the G-actin subunit is aligned with the rest of the filament ($|\cos \theta_i - \cos \theta_0| < \delta \theta_0$, $\theta_0 = 0^\circ$), and the G-actin polarization vector points along the filament ($|\hat{p}_i \cdot \hat{b}_{i-1,i} - \cos \theta_p| < \delta \theta_p$, $\theta_p = 0^\circ$). Similarly, G-actin nucleates a branch along the side of a filament if satisfying these conditions (with $\theta_0 = \theta_p = 70^\circ$) with an F-actin subunit that has been tagged with Arp2/3. Arp2/3 tagging occurs when an Arp2/3 molecule comes into contact with an untagged F-actin subunit.

Polymerization proceeds in this manner until it is halted by capping, which stochastically occurs at the barbed end at rate k_{C+} . To determine whether capping of a filament occurs at the current time step, we draw a random number, R , uniformly distributed over $[0, 1]$, if $R < k_{C+}\Delta t$, the filament is capped. Similarly, depolymerization (and debranching) occurs stochastically from the pointed end (or y-junction) at rate K_- (K_d). A depolymerized G-actin monomer no longer interacts through the bond potential and is thus free to diffuse around the simulation box.

We use $\delta r = 0.1a$, $\delta \theta_0 = 0.06$, and $\delta \theta_p = 0.1$ in our standard model, but the polymerization rate, K_+ , will depend on the precise choice of these parameters, especially $\delta \theta_0$ and $\delta \theta_p$, as described in [13]. The intrinsic diffusion-limited polymerization and branching rates, K_+ and K_b , respectively, are reduced by about a factor of 10 in our simulations as compared to [13, 39]. This is because we have introduced a polarization vector for each subunit and the polymerization rate depends on the tolerance, $\delta \theta_p$, for deviation of the polarization vector

direction. Thus, in order to obtain motility, we lowered the depolymerization, debranching, and capping rates (K_- , K_d , and k_{C+} , respectively) by a similar factor.

Finally, we note that actin dynamics in the bulk system (without a disk) agrees well with the mean field theory in [55]. Our results are therefore insensitive to the precise choice of constants K_R , K_B , K_S , and K_P , except for details described in [13].

3. Results

3.1. Specific binding does not inherently disrupt motility

The release of Arp2/3 from the back of the disk breaks the symmetry of the system and leads to the production of a branched network of F-actin behind the disk (figure 1(a)). We found motility over a broad range of binding site strengths, ϵ , and densities, ρ_{ActA} (figures 1–2). The range of ρ_{ActA} used in our simulations is wide enough to cover the physiological regime [56, 57] and to allow us to investigate the crossover behavior of our model. The values of these simulation parameters, as well as the values of other relevant physical variables, are listed in Table 1.

We find that the overall physical mechanism of motility is preserved in the presence of actin-binding sites on the disk. Each binding site is small and short-ranged, and can strongly bind an F-actin filament only when the filament's barbed end is aligned properly (Eq. 5). However, in general, this is not sufficient to overcome the repulsive excluded volume interaction between F-actin and the disk, so the disk is propelled forward on average (figure 1(a)). As in [13, 39], there is a gradient of F-actin such that the F-actin concentration, ρ_F , behind the disk is higher than the concentration in front (figure 1(a)-(b)). Since F-actin continually polymerizes near the back of the disk, the F-actin concentration gradient translocates with the disk as it moves forward (figure 1(b)). This leads to a steady-state F-actin concentration profile in the reference frame of the disk, as shown in figure 1(c).

Compared to the system without actin binding, the steady-state concentration profile exhibits steeper gradients in the z -direction, normal to the disk. Due to tighter actin binding as the disk-actin binding energy, ϵ , increases, the concentration gradient spans a narrower spatial range and the F-actin profile behind the disk decays more sharply.

3.2. Strong binding affects motility by modulating actin network growth

The translocation velocity, v_{disk} , depends on binding energy, ϵ , and binding site density, ρ_{ActA} , in a surprising manner. Up to intermediate binding energies, ϵ , the translocation velocity, v_{disk} , is approximately constant. However, as shown in figure 2(a), for large ϵ , v_{disk} decreases with increasing ϵ . Additionally, as the binding site density, ρ_{ActA} , increases, v_{disk} becomes more sensitive to ϵ . For instance, v_{disk} begins to decrease at smaller ϵ for $\rho_{\text{ActA}} = 1.3$ sites per 100 nm^2 (squares in figure 2(a)) than for $\rho_{\text{ActA}} = 0.32$ or 0.64 sites per 100 nm^2 (triangles and circles, respectively, in figure 2(a)).

Similarly, v_{disk} is insensitive to ρ_{ActA} when either ρ_{ActA} or ϵ is small (figure 2(b)). For example, for $\epsilon = 2k_B T$, $v_{\text{disk}} \approx 10 \text{ } \mu\text{m/s}$ over the entire range of ρ_{ActA} studied (black circles in figure 2(b)). In contrast, for large ϵ and ρ_{ActA} , v_{disk} decreases as ρ_{ActA} increases. We note that in our model, the density of activated Arp2/3 is the same for all binding ϵ and ρ_{ActA} . Together, these results indicate that the translocation velocity is not determined by the total binding energy, $\epsilon_{\text{Tot}} = \epsilon \rho_{\text{ActA}} \pi R_{\text{disk}}^2$. Instead, v_{disk} is primarily dependent on the individual binding site binding energy, ϵ , and is a weaker function of ρ_{ActA} .

The dependence of v_{disk} on actin binding can be understood by considering F-actin polymerization kinetics behind the disk. In order to understand how polymerization is

affected by actin binding, we measured the detachment rate, ω_d , of barbed ends bound to the disk (figure 3(a)). ω_d is the rate at which a barbed end interacting with a binding site moves or rotates away from the site so that either $r_{ia} > 2a$ or $\cos\psi_{ia} < 0$ (see Eq. 5). In order to avoid artifacts from barbed ends that only weakly and transiently interact with the binding site for a few time steps, we only measure ω_d for barbed ends that experience an interaction energy $E > 0.1\epsilon$ at some time during the attachment. Although this choice of E is arbitrary, the measured ω_d is insensitive to E over the range $0.1\epsilon < E < 0.5\epsilon$, indicating that essentially all barbed ends that experience some significant attraction will eventually fully bind to the binding site before detaching.

As expected for thermally activated processes [58, 59], ω_d decays approximately exponentially with ϵ for large ϵ . Although the exact expression for ω_d in our system is unknown, detachment rates are typically of the form $\omega_0 e^{b\epsilon - c\epsilon/kBT}$, where ω_0 is an intrinsic detachment rate, and b and c are parameters [58, 59]. We fit this function to the data shown in figure 3(a) over the entire range of ϵ , and found the best fit with $\omega_0 = 4420 \text{ s}^{-1}$, $b = 0.532$, and $c = 0.535$.

These values roughly agree with the typical values of $b \approx 1$ and $c \approx 1$ found for escape processes along a single coordinate [58, 59]. The depressed value of the best-fit b may be due to local crowding of F-actin inhibiting the escape of barbed ends. The deviation of the best-fit value of c from $c \approx 1$ is probably due to the effective dimensionality of detachment processes in our system. In particular, instead of traversing along just one coordinate such as z displacement in order to unbind, barbed ends can also unbind through rotations of their polarization vectors, $\hat{p}_i$, away from their respective binding sites. Additionally, barbed ends can sometimes detach from the disk by moving laterally in the x and y directions. Collectively, these effects increase the dimensionality of the escape process, leading to a slower than expected decay of ω_d as a function of ϵ .

The decrease of the detachment rate ω_d with increasing binding energy ϵ has important implications for actin network growth. When a barbed end is attached to the disk, it is sterically inhibited from polymerizing at its plus end by the excluded volume interaction between G-actin subunits and the disk. Thus, an attached barbed end is effectively capped until it detaches from the disk. We therefore examined the effect of binding energy on the total rate of F-actin polymerization, α , which is known to be closely linked to the translocation velocity of actin-based motility [13, 60].

The F-actin production rate is given by $\alpha = K_+ \rho_b^* \rho_g$, where ρ_b^* is the concentration of detached barbed ends, which are free to polymerize actin, and ρ_g is the concentration of monomeric G-actin. As shown in figure 3(b) (solid circles), the first variable, ρ_b^* , depends on the attachment/detachment dynamics of barbed ends. These are governed by the kinetic rate equation

$$\partial_t \rho_b^* = -\omega_a \rho_b^* + \omega_d (\rho_b - \rho_b^*), \quad (10)$$

where ω_a is the attachment rate of free barbed ends and ρ_b is the total concentration of barbed ends (*i.e.*, the sum of attached and detached barbed end concentrations). In steady-state, $\partial_t \rho_b^* = 0$, and ρ_b^* is given by

$$\rho_b^* = \frac{\omega_d}{\omega_a + \omega_d} \rho_b. \quad (11)$$

figure 3(b) (solid line) shows the theoretical estimate for ρ_b^* from 11 using ω_d from figure 3(a), the simulated value of ρ_b at $\epsilon = 0$, and a best-fit for ω_d . Since barbed ends in our

simulation are generated through Arp2/3-mediated branching, the total concentration of barbed ends, ρ_b , is insensitive to ε (inset to figure 3(b)). The agreement between the theoretical estimate and the simulation indicates that the assumption of constant ω_d is reasonable, the rate at which barbed ends diffuse onto binding sites is insensitive to the strength with which they are bound. Thus, the decrease in ω_d explains the observed behavior of ρ_b^* as ε increases. When $\omega_d/\omega_a \gg 1$, ρ_b^* is unaffected by decreasing ω_d . But when ε is large enough that $\omega_d/\omega_a \lesssim 1$, further decreases in ω_d are manifested by a marked decrease in ρ_b^* , leaving fewer barbed ends free to polymerize new F-actin.

The inset to figure 3(c) shows the behavior of ρ_g , the other variable that determines α , the F-actin production rate. As ε increases, ρ_g increases because an increasing number of barbed ends are inhibited from polymerizing F-actin by attachment to the disk. However, since $\rho_b^* \ll \rho_g$, the F-actin production rate, α , is far more sensitive to variation in ρ_b^* than in ρ_g . Combining K^+ , ρ_b^* , and ρ_g , we determine α , as shown by the solid circles in figure 3(c). By overlaying the v_{disk} versus ε data (dashed line in figure 3(c)), we find a close correlation between α and v_{disk} , as expected [13, 60]. Thus, the entire dependence of v_{disk} on ε and ρ_{ActA} (figure 2) can be explained by changes in the F-actin production rate resulting from barbed end attachment/detachment dynamics (figure 3).

3.3. Pressure-velocity relation

To better understand how specific binding affects the robustness of actin-based motility, we introduced an external load pressure, P , on the disk. As shown in figure 4(a), the attractive interactions between actin and the disk do not eliminate the ability of the disk to move under an opposing load, for various ε (different colored points), $v_{\text{disk}} > 0$ over a wide range of P . Moreover, similar to experiments in [61–64] and simulations in [39], we find that v_{disk} is insensitive to P at small loads. At larger P , as P increases, v_{disk} decreases until it reaches zero and the disk stalls at P_{stall} . In the inset to figure 4(a), we scale v_{disk} by the zero load velocity, v_0 , and pressures by the pressure, $P_{1/2}$, when $v_{\text{disk}} = v_0/2$, as described in [39, 62]. While the pressure-velocity curves collapse for small ε (black and red symbols), the curve is not universal for large ε (blue and brown symbols).

As shown in figure 4(b), P_{stall} is insensitive to ε for $\varepsilon \lesssim 8 k_B T$. Above this binding energy, P_{stall} decreases, indicating that motility is less robust for very large binding energies ε . In our simulations, P_{stall} is of order $10^{-2} \text{ nN}/\mu\text{m}^2$, much smaller than the experimental value [62, 64–66] of $P_{\text{stall}}^{\text{expt}} \approx 1\text{--}10 \text{ nN}/\mu\text{m}^2$. Our stall pressure, P_{stall} , also differs from the value observed in earlier simulations with a higher polymerization rate without actin binding to the disk [39], $P'_{\text{stall}} \approx 0.1 \text{ nN}/\mu\text{m}^2$.

Both of these observations can be explained by the behavior of the Young's modulus, Y , of the F-actin network. Y has been argued to govern the pressure-velocity relation for actin-based motility [38, 39]. Specifically, the actin network can continue to grow as long as the opposing load does not exceed its elastic modulus, which is on the order of $1\text{--}10 \text{ nN}/\mu\text{m}^2$ [67] in experiments. In general, for a network of semiexible filaments,

$$Y = \frac{k_B T \ell_p^2}{\xi_m^5}, \quad (12)$$

where ℓ_p is the filament persistence length and ξ_m is the mesh size of the network [68, 69].

The mesh size depends on the concentration of F-actin, $\rho_f: \xi_m \sim 1/\sqrt{\rho_f}$ [68, 69]. In the inset to figure 4(b), we show that ρ_f is approximately constant for $\varepsilon \lesssim 8 k_B T$, and decreases dramatically above this binding energy. This is consistent with the dramatic decrease in the

concentration, ρ_b^* , of free barbed ends at large ε . Thus, the decrease in ρ_b^* and consequent decrease in ρ_f due to increased actin binding is sufficient to explain the qualitative behavior of P_{stall} as a function of ε .

Eq. 12 provides a quantitative explanation of the difference between the three values of stall pressure. Assuming $Y \approx P_{\text{stall}}$, we expect that the experimental stall pressure, $P_{\text{stall}}^{\text{expt}}$, should be related to the simulated P_{stall} through appropriate rescaling of the persistence length and F-actin concentration:

$$P_{\text{stall}}^{\text{expt}} \approx \left(\frac{\tilde{\ell}_p}{\ell_p} \right)^2 \left(\frac{\tilde{\rho}_f}{\rho_f} \right)^{5/2} P_{\text{stall}} \approx 10^2 \cdot 2^{5/2} \cdot 10^{-2} \text{nN}/\mu\text{m}^2 \approx 6 \text{nN}/\mu\text{m}^2. \quad (13)$$

This order of magnitude estimate is in good agreement with experiments [62, 64–66]. Moreover, it is clear that the agreement is not coincidental. Eq. 12 also predicts that our simulated P_{stall} should be lower than P_{stall}' in previous simulations [39] by about a factor of $(\rho_f'/\rho_f)^{5/2} \approx 10$ due to the difference between the F-actin concentration, ρ_f , in our simulations and the F-actin concentration, ρ_f' , in [39]. Consequently, it is clear that in simulations with stiffer filaments and higher F-actin concentration in the tail, we would measure the experimentally observed value of stall pressure, as suggested in [39]. Simulations with higher stiffnesses and F-actin concentrations are too timeconsuming at current computational speeds, but nonetheless, with the parameters used in our simulations, we capture the underlying physics of actin-based motility.

4. Discussion

We have presented physically consistent simulations of actin-based motility in which self-assembly of an F-actin network stimulated by an object (a disk) propels that object forward through the creation of a steady-state actin gradient. In the case of a purely repulsive interaction between actin and the disk, the disk moves towards lower actin concentration, and continues to do so as it stimulates further F-actin polymerization through activation/release of Arp2/3 [13, 39] via the self-diffusiophoretic mechanism [40, 41], discussed further below. Here we have shown that this mechanism is viable even when actin binds to specific sites on the object. Note that in contrast to some other models [33, 35, 37] we do not require that the binding sites simultaneously allow for binding and polymerization. Indeed, our model assumes that the opposite is true - if a barbed end is bound, it cannot grow.

This assumption has consequences for the behavior as a function of binding energy, ε , and density of binding sites, ρ_{ActA} . If either of these quantities is sufficiently low, then specific binding of actin to the disk has little effect on the velocity or stall pressure of the disk. However, if both are high enough, a large number of barbed ends remain bound to the disk, inhibiting polymerization. This decreases the network growth rate, $\alpha = K_{+\rho_b^* \rho_g}$, and thus the rate of forward motility, v_{disk} . Sufficient binding of barbed ends to the disk also decreases the concentration, ρ_f , of F-actin behind the disk, leading to a smaller Young's modulus, Y , and consequently, a depressed stall pressure, P_{stall} .

4.1. The self-diffusiophoretic mechanism is robust to specific binding of actin to the moving object

Based on Brownian dynamics simulations it was suggested that proteins such as ActA or WASP activate Arp2/3 and together catalyze polymerization of F-actin leading to the formation of a concentration gradient and that the repulsive interactions between F-actin and

the disk therefore propel the disk forward, down the gradient [13, 39]. A major objection to this model is that it relies explicitly on repulsive interactions between F-actin and the disk, despite the fact that there are also significant attractive interactions due to actin-binding proteins like ActA or WASP [8, 14, 15, 25–27]. However, we have found that a concentration gradient can propel the disk forward even when actin binds to the disk. Such attractions do not disrupt the F-actin-gradient-driven mechanism of motility (figure 2). Furthermore, the observation of a steady-state F-actin concentration gradient in simulations agrees with several experiments [22, 61, 70, 71] showing an actin uorescence profile qualitatively similar to those shown in figure 1(b)-(c).

In a fluid environment, actin-gradient-driven motion could occur via self-diffusiophoresis [40–42]. Although we do not explicitly include fluid flow in our simulations, recent analyses demonstrate they can nonetheless accurately describe concentration-gradient-driven motility [72, 73]. A catalyst (Arp2/3) activated by an object (colloid/bacterium covered with ActA or WASP) stimulates the production of a chemical species (F-actin) near the surface of the object. Since this reaction only occurs locally, the concentration of this chemical species is non-uniform, so that it is higher behind the the object than it is elsewhere. This generates a steady-state fluid flow, whose precise nature is governed by the interaction of the chemical species with the object [40–42, 73, 74]. Since the catalyst is continually activated by the object, this concentration gradient persists in steady state, so that the object continues to move in this manner.

Our simulations show that this self-diffusiophoretic actin-based motility should not be disrupted by ActA- or WASP-mediated disk-actin attractions. However, in contrast to the prediction in [13], but in agreement with calculations in [75], we do not observe backwards motility when the strength (or density) of the attractive interactions is large. In both our Brownian dynamics simulations and the fluid dynamics calculation, polymerized actin cannot simultaneously pull the disk and move out of its way, so backwards motility cannot occur.

4.2. Novel mechanism of actin cytoskeleton control

Our results suggest a biophysical mechanism for control of actin-based motility. We find that at high enough concentrations or binding energies, actin-binding proteins can sterically inhibit polymerization. Specifically, in our model, actin-binding proteins on the disk directly attach to the barbed ends of F-actin filaments, preventing actin growth. If binding is weak, the attachment is transient, and thus its effect is limited by rapid F-actin detachment from the disk. On the other hand, if binding is strong, attachment is long-lived and detachment occurs infrequently, leading to stalled actin growth. This is consistent with the work of Co *et al.* [76], in which the authors studied beads coated with weak actin-binding N-WASP mutants. As in our model, the bead in their experiments moves more rapidly for weak-actin-binding N-WASP mutants.

The actin-binding protein cortactin, which also binds WASP and Arp2/3, has been shown to enhance the detachment of nucleated actin branches from surface-bound WASP. In turn, the branching rate, and thus overall rate of actin network growth is enhanced by cortactin up to a few tens of nanomolar concentrations [77, 78]. As a result, the speed of actin-based motility increases [78]. These effects can be explained in our model by supposing that cortactin decreases the actin-WASP binding energy, ϵ . This would lead to enhanced detachment of actin branches from the surface. By decreasing the duration of growing end attachments, cortactin should increase the concentration, ρ_b^* , of free growing ends. The decrease in branching and motility at higher cortactin densities may be explained by the interplay between capping and branching [13, 55, 61, 79, 80], as follows. Since at high cortactin concentrations, barbed ends are released from N-WASP (thus “uncapping” the barbed ends),

network growth is focused at filament ends rather than new branches, decreasing the amount of branching. This morphological change could decrease motility so that direct branch inhibition effects by cortactin, proposed in [78], may not be necessary. This idea could be tested experimentally by investigating systems with higher concentrations of capping protein. In these systems the concentration of cortactin required to inhibit branching should be higher than in the experiments in [78].

The primary difference between our model and the cortactin experiments is that cortactin, WASP, and actin bind with Arp2/3 at nascent branches, not at barbed ends. However, it has been shown that self-diffusiophoretic propulsion is insensitive to whether the disk interacts with the tips or sides of filaments [13]. Therefore, the experiments of [78] demonstrate that actin growth may be directly and physically regulated by actinbinding, consistent with our predictions.

Experiments such as those in [18, 51] that vary ActA surface density are more difficult to compare to our model because increasing ρ_{ActA} stimulates additional actin polymerization in experiments. We have not included this detail in our model. As a result, our simulations do not capture the slight increase in velocity with increasing ρ_{ActA} observed in the experiments. It would be straightforward to extend our model to capture this effect.

Several other models have considered competition between propulsive forces of actin polymerization and resistive forces due to binding interactions [26, 27, 30–32, 38, 44, 67, 81]. According to this idea, filaments that are not bound to the surface can grow and exert protrusive forces, while filaments that are bound to the surface exert a resistive force backwards. This competition has been suggested to lead to the intermittent velocity observed in actin-based motility of *Listeria* [14], beads [82], and vesicles [26, 27].

In contrast, we find that the actin-binding strength, ϵ , and concentration, ρ_{ActA} , of actin-binding sites influence motility (figure 2) by controlling the polymerization rate (figure 3), rather than exerting resistive pulling forces. We do observe an increase in internal stresses within the actin tail as ϵ increases (supplementary figure 1), but it is clear from figure 3 that polymerization rate is the primary control for velocity. In other words, we find that the direct effect on motility of actin binding by regulating the growth of the network (figure 3(b)-(c)) is more important than the indirect effect arising from tensile stress in the tail. However, while our tail is a branched network that can support some tensile stress, we have not included cross linking in our simulations, it is possible that once the elastic modulus of the tail is large enough, stresses in the tail could dominate the physics as predicted by the elastic gel model [31, 32, 67].

Our predictions for the effect of binding energy on propulsion speed can be tested directly in an experiment proposed in [13]. The idea is to coat polystyrene beads not only with actin nucleators such as ActA and N-WASP but also with an actin-binding protein that does not promote branching. In this way, instead of varying surface concentration of ActA or N-WASP [18, 51, 61, 76] to study the effects of actin binding, one could vary the concentration of the second binding protein. This would directly test how actin binding influences motility without the complication of simultaneously varying the rate of actin nucleation [13]. Our model's prediction for this experiment is shown by the data in figure 2(b).

4.3. Pressure-velocity relation

Our simulations demonstrate that the Young's modulus, Y , of the F-actin network is the most important factor in determining the stall pressure, P_{stall} . The Young's modulus is important because the self-diffusiophoretic mechanism propels the object forward until the

concentration gradient required for motility is significantly deformed [39]. A significant deformation to the profile will only occur if the load pressure is greater than the strength of the F-actin network. This is consistent with previous work estimating both Y and P_{stall} to both be of order $1\text{--}10\text{ nN}\cdot\mu\text{m}^2$ in experiments [38, 39, 62, 64–67].

In our simulations, the stall pressure is approximately two orders of magnitude smaller than it is in experiments, but this is due the short persistence length ℓ_p and the relatively low concentration, ρ_f , of F-actin filaments (which increases the mesh size, ξ_m). Together, these factors reduce Y below the experimentally observed value (Eqs. 12 and 13). Clearly, direct strengthening of the network through cross-linking should decrease ξ_m and increase P_{stall} [39, 68]. Additionally, our simulations reveal an alternative mechanism to control the robustness of actin-based motility. By increasing actin binding, the concentration of F-actin is decreased (figure 2), which in turn leads to a decrease in P_{stall} (figure 4(b)).

The overall pressure-velocity curve is in good agreement with several experiments that show a concave-down pressure-velocity curve [62–64]. Similarly, our model agrees with experiments showing that actin-based motility is insensitive to small opposing pressures [61–64]. In contrast to experiments in [62] and simulations in [39], the pressure-velocity curves at high binding energies in our simulations do not collapse onto a single curve when rescaled (inset to figure 4(a)). This is unsurprising because the F-actin network has fundamentally different material properties for different binding energies due to the change in ρ_f induced by varying ε and ρ_{ActA} . By similar reasoning, we would expect that in AFM-based pressure-velocity experiments similar to those in [62], but with varying concentrations of cross-linking proteins (such as α -actinin [17]) would lead to several different pressure-velocity curves that do not collapse across different cross-linker concentrations (but would collapse when comparing experiments at the same cross-linker concentration).

4.4. Self-diffusiophoresis in filopodia

We propose that cofilin-driven filopodial retraction may constitute another biological realization of self-diffusiophoresis. It has been known for over a decade that the speed of filopodial protrusion and retraction are highly correlated with actin polymerization and myosin-driven retrograde flow [83]. More recently, cofilin, an actin disassembling protein has been implicated in filopodial retraction [84]. In particular, as the filopodium retracts, actin is depolymerized by cofilin at the tip of the filopodium. This is similar to the situation in bacterial chromosome segregation recently studied in [85]. Specifically, actin-like ParA filaments in the bacterial cytoskeleton can pull a chromosome by depolymerization of ParA subunits from the tips of filaments because chromosome-associated proteins are attracted to ParA. This works by a self-diffusiophoretic mechanism, depolymerization creates a ParA gradient, and the chromosome tends to move up this concentration gradient. Similarly, actin is thought to bind proteins at the tip of the filopodium [84], giving rise to an attractive interaction between actin and the filopodium tip. In this case, depolymerization of actin by cofilin could create the gradient necessary to drive filopodia tip retraction.

This idea could be tested by covering a polystyrene bead with actin-binding proteins from the filopodium tip complex and placing it in an F-actin solution. It is thought that proteins in this complex may enhance cofilin-mediated actin disassembly by phosphate release from ATP-F-actin [84] and thus could disassemble actin near the bead. Ideally, one would use Janus beads with one half covered with actin-binding proteins from the filopodium tip complex to eliminate the need for symmetry breaking. If actin and cofilin coordinate to drive filopodium retraction through self-diffusiophoresis, the bead should begin to move, and there should be a corresponding F-actin gradient of increasing concentration with distance from the bead.

4.5. Comparison of proposed mechanisms of actin-based motility

Many models have been proposed for motility, most notably Brownian elastic ratchet models [28–30], the elastic gel model [31, 32, 38] and an entropic model [86]. It is quite possible that barbed ends of individual filaments actuate away from the surface and grow, as studied by Brownian ratchet models [28–30]. However, it was shown that the Brownian elastic ratchet mechanism does not predict the filament stiffness dependence of motility that is seen in Brownian dynamics simulations [13]. This is not surprising, since a single-filament picture is unlikely to capture motility, which is an emergent, collective phenomenon in the many-filament system.

One requirement for the self-diffusiophoretic mechanism to apply is that the actin filament density in the tail should be high compared to the average actin concentration in solution. If the actin filament density is sufficiently low, self-diffusiophoresis could be a weak effect and propulsion may be dominated by entropic effects [36, 86].

The elastic gel model is fully consistent with and complementary to the self-diffusiophoretic mechanism. In the case of a disk, the elastic gel model assumes that the propulsion speed is given by the polymerization speed, or the rate of production of F-actin. But the model does not explain why this is the case. In fact, this is true because of the self-diffusiophoretic mechanism. The elastic gel model focuses on a different issue - how stresses can build up in the tail to alter motility. We have not explored the motion of curved objects when actin tails are cross linked, but we would expect our mesoscopic model to capture the type of saltatory motion predicted by the macroscopic elastic gel model in that case [31, 32].

In addition to the above-mentioned models, many simulation models have been proposed and studied [43–47]. While these simulations have been instructive in many respects, it is crucial to note that none of them can yield any insight into the origin of motility. The models underlying these simulations [43–47] share the common property that single actin monomers cannot exert forces but actin filaments can. Such models are unphysical in that they violate mass conservation. Since the growing ends of filaments are concentrated behind the moving object, mass is created behind the moving object, thus *unphysically creating new forces from nothing*. These forces clearly lead to motility, so the violation of mass conservation has the serious consequence of generating motility as an artifact. Mechanisms underlying motility in real systems are much more subtle. Since concentration-gradient-driven motility emerges from our model, which conserves mass, it is a viable candidate for the mechanism of motility in real systems.

Self-diffusiophoresis is not only a viable candidate for the mechanism of motility, but also, it must exist in real systems. When an object is in the presence of a concentration gradient in a low Reynolds number fluid, diffusiophoresis necessarily occurs [42, 74]. In the case of actin-driven motility, it is obvious that a concentration gradient exists - the concentration in the actin comet tail is several orders of magnitude higher than the average concentration of actin in the system, so the concentration behind the moving object is substantially higher than the concentration in front [22, 61, 70, 71]. As a result, self-diffusiophoresis must occur.

Just because self-diffusiophoresis must occur, however, does not mean that it is necessarily the dominant mechanism underlying actin-driven motility. In order for self-diffusiophoretic motility to be dominant, it must lead to fluid flows that are not too slow compared to the scale of the velocity that is observed in experiments. An earlier estimate using Darcy's law [13] found that this is indeed the case. For the expected solute-generated pressure gradient, actin network permeability, and fluid viscosity, the F-actin concentration gradient could generate a fluid flow of up to 1 $\mu\text{m/s}$ [13]. This is not too much larger than the 1 – 10 $\mu\text{m/min}$ range of actin-based motility of *Listeria* [5, 14, 20, 50, 51, 67], viruses [9, 10], and

ActA- or N-WASP-coated polystyrene beads [18, 21, 51, 61, 82], lipid vesicles [26, 27], and oil droplets [25].

Altogether, it is possible that a variety of physical phenomena may occur in real systems that are propelled by actin polymerization. The many models that have been proposed explore different facets of these phenomena. We reiterate, however, that statistical mechanical and hydrodynamic principles dictate that self-diffusiophoresis *must* occur [42, 74]. Mass-conserving, steady-state simulations here and in previous work [13, 39] suggest that self-diffusiophoresis is indeed the mechanism for actin-based motility. Moreover, a back-of-the-envelope calculation [13] suggests that it is a significant effect, of the right order of magnitude to explain motility. One would have to argue that self-diffusiophoretic flow is negligible in order to argue that another mechanism is instead responsible for actin-polymerization-driven motility.

5. Conclusion

We have found that self-diffusiophoresis, whereby an object generates and sustains a steady-state F-actin concentration gradient that propels it, can robustly provide actin-based propulsion, even in the presence of localized actin-binding sites. Actin-binding sites provide an additional mechanism of control, which could be used for diverse purposes ranging from transient physical capping to filopodial retraction. The self-diffusiophoretic mechanism is robust and stalls only against pressures exceeding the Young's modulus of the network. Since there is a steady-state actin concentration gradient, self-diffusiophoresis must occur.

Moreover, self-diffusiophoresis is potentially a mechanism for biological motility in other contexts because it is robust and relies on an ubiquitous feature of biological systems - the existence of concentration gradients. Recent experiments [87–89], have shown that diffusiophoresis can also provide precise spatiotemporal control. It has been suggested that chromosomal translocation in bacteria such as *Caulobacter crescentus* may rely on self-diffusiophoresis [85]. It remains to be seen whether filopodial retraction due to cofilin-driven actin depolymerization constitutes a similar example.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) F-actin (green) accumulates behind the disk (purple). Pointed ends are shown in blue, bases of actin branches are shown in red, and subunits attached to the disk are shown in orange. For clarity, G-actin is not displayed. The system shown has 50 $6 k_B T$ binding sites randomly distributed on the back of the disk ($\rho_{ActA} = 0.64$ per 100 nm^2). Axes and scale match those of panel (b), below. (b) The F-actin concentration profile along the z -direction is potted at times corresponding to the snapshots shown above in (a). As described in [13], Arp2/3-mediated F-actin polymerization generates a concentration gradient of F-actin behind the disk. As the disk moves forward, F-actin continues to polymerize behind the disk so that the concentration gradient moves forward as well, maintaining the mechanism of motility. (c) In the center of mass frame of the disk, which is located at $z = 0$, the concentration gradient has a well-defined steady-state average that depends on the binding energy.

Figure 2.

(a) The velocity of the disk, v_{disk} vs. binding energy, ϵ . At small ϵ , v_{disk} is insensitive to the binding energy, but at higher ϵ , v_{disk} decreases as ϵ increases. ρ_{ActA} is reported in number of binding sites per 100 nm^2 . (b) The dependence of v_{disk} on the density of binding sites, ρ_{ActA} , depends on binding energy. For small ϵ (e.g., $2 \text{ k}_B T$, black), v_{disk} is insensitive to ρ_{ActA} . At higher ϵ (e.g., $6 \text{ k}_B T$, $8 \text{ k}_B T$, and $14 \text{ k}_B T$, red, green, and blue, respectively), v_{disk} decreases as ρ_{ActA} increases.

Figure 3.

a) Detachment rate, ω_d (solid circles), decreases approximately as $\omega_0 \epsilon^b e^{-c\epsilon/k_B T}$ (solid line) as the binding energy, ϵ , increases, where $\omega_0 = 4420 \text{ s}^{-1}$, $b = 0.532$, and $c = 0.535$. (b) The concentration, ρ_b^* , of uncapped barbed ends not attached to the disk is approximately constant at small binding energies and decreases at larger binding energies. This mirrors the theoretical steady-state concentration of free barbed ends, $\rho_b^* = \rho_b \omega_d / (\omega_a + \omega_d)$, where ρ_b is the total (attached and unattached) uncapped barbed end concentration and ω_a is the rate at which uncapped barbed ends attach to the disk. This theoretical estimate for ρ_b^* is indicated by the solid line. $\omega_a = 60 \text{ s}^{-1}$ is a fitting parameter. *Inset*: Plot of the total barbed end

concentration, ρ_b , which is insensitive to ε , remaining close to its $\varepsilon = 0$ value until large ε . (c) The measured velocity of the simulated disk, v_{disk} (dashed line), is correlated with the total production rate of F-actin, which is given by $K_{+\rho_b^* \rho_g}$, where ρ_g is the steady-state G-actin concentration. *Inset*: ρ_g is insensitive to ε at small ε , but increases as ε and ρ_b^* (and thus F-actin concentration, ρ_f) decrease.

Figure 4.

(a) Velocity versus load pressure P . At small pressures, P , the disk velocity, $v_{\text{disk}} \approx v_0$, where v_0 is the zero load velocity. As P increases, v_{disk} drops until the disk stalls ($v_{\text{disk}} = 0$) at the stall pressure, P_{stall} . Above P_{stall} , the disk is pushed backwards into the F-actin tail. Data is shown for disks with $\rho_{\text{ActA}} = 0.64$ per 100 nm^2 and binding energy $\epsilon = 0$ (black), $2 \text{ k}_B T$ (red), $8 \text{ k}_B T$ (blue), and $11 \text{ k}_B T$ (brown). *Inset:* We rescale the v_{disk} by v_0 and P by the pressure, $P_{1/2}$, at which $v_{\text{disk}} = v_0/2$, as in [39, 62]. For small ϵ , we obtain the expected rescaling. For large ϵ , we see the same qualitative pressure-velocity relation, but rescaling by $P_{1/2}$ and v_0 does not produce the same curves. (b) At small ϵ , P_{stall} is insensitive to ϵ .

However, at larger ε , P_{stall} decreases as ε increases. *Inset:* F-actin concentration, ρ_f , vs. binding energy ε . At higher binding energies, ρ_f decreases with increasing ε .

Table 1

Values of the parameters used in the simulations compared to those in experiments. All values listed are taken from *in vitro* experiments except for the ones marked with (*). All simulated parameters except for K_+ ; K_- ; k_{C+} ; K_d ; and ρ_{ActA} were chosen to match those of previous studies [13, 39]. K_+ was set by the additional polymerization constraint of aligning subunit polarization vectors (see Methods and Model); we decreased K_- and k_{C+} to compensate for the reduced polymerization rate. ρ_{ActA} was chosen to cover the experimental range of ActA densities, and also to explore the full range of behaviors of our model. ε was estimated from [81] which estimates 10–40 active binding sites per bacterium and a total bacterium binding energy of 10 kcal/mol (order $10 k_B T$ per bacterium).

Parameter	<i>in vitro</i> Exp. [ref]	Simulated
ℓ_p	0.5–17.7 μM [90–94]	0.1 μm
l_{ave}	0.1–1 μm [95, 96]*	0.1 μm
typical bead diameter	0.2–2 μm [51]	0.1 μm
viscosity (η)	2.4 cP [51]	2.4 cP
$D = k_B T / 3\pi\eta a$	36.6 $\mu\text{m}^2/\text{s}$	36.6 $\mu\text{m}^2/\text{s}$
K_+	11.6 $\mu\text{M}^{-1}\text{s}^{-1}$ [17, 97]	50 $\mu\text{M}^{-1}\text{s}^{-1}$
K_-	0.3 s^{-1} [17, 97]	2860 s^{-1}
[G-Actin] (initial)	7 μM [20]	600 μM
[G-actin] (steady state)	8.5 μM [65]*	370 μM
$K_+[\text{G-Actin}]/K_-$ (initial)	270	11
K_a	? $\mu\text{M}^{-1}\text{s}^{-1}$	$\sim K_+$
K_d	0.002 s^{-1} [98]	2860 s^{-1}
[Arp2/3]	0.1 μM [20]	2.1 μM
$K_a[\text{Arp2/3}]/K_d$	N/A	0.037
K_{C+}	8 $\mu\text{M}^{-1}\text{s}^{-1}$ [79]	—
K_{C-}	4 $\cdot 10^{-4}$ s^{-1} [79, 99]	0 s^{-1}
[Cap]	0.1 μM [20]	—
$k_{C+} = K_{C+}[\text{Cap}]$	0.8 s^{-1}	1570 s^{-1}
ρ_{ActA}	0.3–2.1 per 100 nm^2 [56, 57]	0–2.6 per 100 nm^2
ε	Few $k_B T$ [81]*	0–16 $k_B T$