Mechanochemical model of cell migration on substrates of varying stiffness

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Cells propel themselves along a substrate by organizing structures at the leading edge called lamellipodia that contain the actin network, myosin, integrin, and other proteins. In this article, we describe a quantitative model that couples the response of stretch-sensitive proteins in the lamellipodia to the dynamics of the actin cytoskeleton, therefore allowing the cell to respond to different substrate stiffnesses. Using this model, we predict the various phases of dynamics possible, including continuous protrusion, unstable retractions leading to ruffling, and periodic protrusion-retraction cycles. We explain the necessary conditions for each type of migratory behavior to occur. In particular, we show that, for periodic protrusion-retraction cycles to occur, the stiffness of the substrate must be high, the myosin-dependent maturation rate of nascent to focal adhesions must be high, and the myosin-independent integrin activation rate must be low. In addition, we also predict the dynamics expected at a given substrate stiffness, leading to a quantitative explanation of experimental data that showed that periodic protrusion-retraction cycles disappear when cells are placed on soft substrates. We also suggest experiments with downregulating α actinin and/or talin and upregulating p130Cas and make predictions on what types of migratory dynamics will be observed.

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I. INTRODUCTION

Cells migrate to search for food and nutrients, seek out invading microorganisms, close wounds, form tissues and organs, etc. In recent years, biologists have begun to view the cell as a machine and have utilized physical principles to unravel the components and workings of the cell's machineries, such as during migration. In addition, computational models have become increasingly important in aiding researchers explore the mechanisms of cell migration. For example, cells have been modeled as compound liquid drops [1,2] and capsules [3,4] and their migratory behavior on an adhesive substrate investigated. Others have tried to incorporate the effects of cytoskeletal properties on the migratory behavior of cells as well as the nuclei [5,6].

A common feature in migrating cells is the presence of the lamellipodia, an actin-dense region located at the cell's periphery whose function is to adhere and anchor the cell to the substrate so that the rest of the cell can pull itself forward. Recent experiments have shown that the lamellipodium moves by periodic sequences of forward protrusions followed by backward retractions [7,8]. In addition, these retractions are only observed when the cell is placed on a sufficiently stiff substrate, suggesting the importance of the substrate stiffness in cell migration.

Earlier attempts have been made to represent the lamellipodium using mathematical and numerical methods. For example, Refs. [9,10] characterized the undulations of the cell membrane as a function of the bending and elastic moduli of the membrane, the intrinsic curvature of proteins either attached to or embedded in the membrane which therefore imposed curvatures on the membrane, the polymerization of actin, and the forces exerted on the membrane due to myosin. An analysis of the dispersion relation allowed a better understanding of the oscillatory behavior of lamellipodial motility. On the other hand, there are models that are based on the elastic Brownian ratchet model [11] that used a coarse-grained method to derive an average protrusion rate as a function of the free-energy change induced by the deformation of the membrane [12]. Another example is the model proposed in Refs. [13–15], where the cell membrane was deformed by forces exerted on it by both attached and nonattached actin filaments, the former tending to pull the membrane via myosin motors while the latter pushed the membrane. Depending on whether there were more attached or more nonattached filaments, the membrane would protrude or retract, leading to what was termed as oscillations in the membrane of the lamellipodium. Finally, a simpler model was proposed in Ref. [16], where actin activities such as polymerization, nucleation, and capping, coupled with the viscoelastic nature of the cytoplasm, led to protrusion of the membrane. While these models could explain all or some of the phenomena seen in lamellipodial protrusion—the previous two models suggested mechanisms behind the oscillatory behavior; the last model studied the retrograde flow and concentrations of actin as a function of distance from the membrane—none of them considered the influence of the substrate and hence cannot reproduce the experimental observation of the dependence of the occurrence of periodic protrusions and retractions on substrate stiffness.

There have been numerous experimental studies demonstrating the effect of changing the stiffness of the substrate upon which the cell is migrating on the cell migration velocity [7,17,18] and cell morphology [19,20]. This shows that the effect of substrate properties on cell migration cannot be ignored. Therefore, models must allow for the transmission of such information into the cell. There have been earlier modeling

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attempts to understand the effect of substrate stiffness on cell migration. An example is the work by Chan and Odde, in which the attachments of the actin network to the substrate are represented as molecular clutches that extend and fail upon high stresses [21]. Using the motor clutch mechanism, the authors were able to explain the generation of periodic motion in the filopodia. Their model has not been extended to the lamellipodia. In another work, Dokukina and Gracheva included the effects of substrate rigidity by introducing an additional viscositylike component that was proportional to the substrate stiffness, but they did not reproduce the periodic protrusions and retractions observed [22]. In a recent paper, Walcott and Sun [23] studied the effects of substrate rigidity on the alignment and formation of stress fibers and were able to explain the increase in stress fiber formation as a result of increased substrate stiffness but again did not consider the periodic protrusions and retractions observed in the lamellipodia.

While these models were able to predict the cell's response to substrate stiffness, the exact mechanism in which the cell receives information about the environment is still unknown. Experimentalists have found that the ability of the cell to respond to substrate stiffness can be regulated by certain stretch-sensitive proteins [24,25]. An example of one such protein is p130Cas, an adaptor protein at focal adhesions. Studies of the structure of p130Cas showed that the protein contains several Src phosphorylation sites which become exposed when the protein stretches, thus serving as a scaffold protein that enables the strengthening of the focal adhesion [26]. This can be achieved by the attachment of the cell to a sufficiently stiff substrate, which reduces the displacement of the focal adhesions when the actin network pulls on it during actomyosin contractility. Another example is talin, which similarly unfolds when it experiences stretch [27]. Therefore, we propose a mechanism where the cell can "sense" the substrate stiffness by means of nascent adhesions and stretch-sensitive proteins. Our objective is to develop a physical model of the interaction between the substrate and the lamellipodial actin machinery and use it to map out the types of dynamics possible and to quantitatively understand the origins and functions of the periodic protrusions and retractions on substrates of varying stiffness.

II. MODEL

A schematic of the components that make up the lamellipodium is shown in Fig. 1. The lamellipodium consists mainly of a dense actin network upon which myosin exerts contractile stress resisted by integrins that mediate adhesion between the cell and the substrate. In this manuscript, we focus on the dynamics of one radial segment of the actin network. As the attachment and detachment of the barbed ends of actin has been shown to occur very quickly [14], we will assume that the equilibrium separation between the actin network and the membrane is achieved almost immediately such that forces that the actin network and the membrane exert on each other can be neglected. Thus, we assume that the dynamics of the barbed end is equivalent to that of the cell's leading edge.

The position of the barbed end, denoted by b, can change in one of two manners. First, it can change by the growth/decay

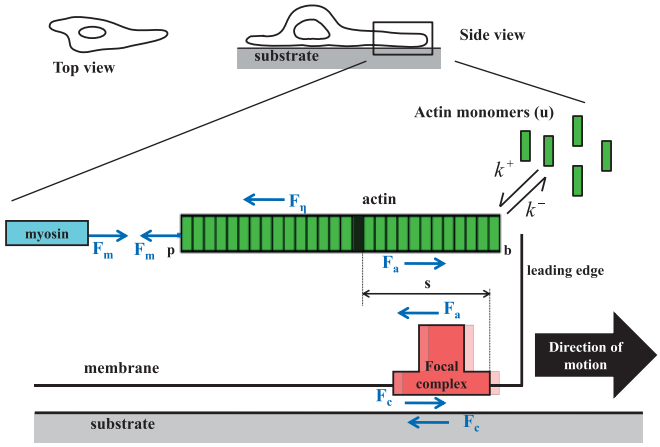

FIG. 1. (Color online) Schematic of the major components of the lamellipodium. Actin monomers are being added or deleted from the actin network at the barbed end (b). The viscous drag as the actin network grows or shrinks is F_η. Myosin pulls on the actin filament with a force F_m. Integrins in the focal complexes pull on the actin segment with a force F_a and experience a resistive force F_c due to its sliding on the substrate. The stretch s is the difference between the translation of the actin and the focal complex.

of the actin network. The dynamics of the actin network has been extensively modeled in the past. Researchers have studied in detail the factors governing the rate of network generation such as the role of capping proteins and branching rates using both stochastic and deterministic methods [28–31]. Here, we use a simple deterministic method to represent the dynamics of the position of the barbed end by the addition or deletion of actin monomers at rates k^+u and k^-, respectively, where u denotes the free actin monomer concentration at the barbed end. Second, b can change as a result of the contractile action of myosin motors, F_m, and the resistive action of integrins, F_a, on the actin segment. Force balance yields $F_a - F_m - F_\eta = 0$, where $F_\eta = \eta db/dt$ is the viscous drag. The actin network has been modeled as an incompressible material here to simplify the model. To account for the actin gel being suggested to be a viscoelastic material [32–35], the viscous effects can be incorporated into the model by choosing an appropriate drag coefficient η. Inertial forces are neglected. It is important to note that, in this model, as we are studying the growth of lamellipodium, stress fibers are not present in the lamellipodium and are therefore not responsible for the exertion of forces in the lamellipodium. As the amount of stress exerted on actin is likely to cause strains of less than 10% [36–38], we have assumed that the retraction of the barbed end is not significantly affected by stretching of the network.

In addition to the rapidly changing lamellipodial actin network, there is another region of the actin cytoskeleton known as the lamellum that has also been implicated in cell migration [39,40]. Anderson *et al.* suggested that the lamellipodium is carried into the lamellum by the retrograde flow of actin powered by myosin II [41]. However, the inhibition of myosin II did not hinder the generation of lamellipodium but instead blocked the replenishment of actomyosin bundles in the lamellum. Thus, it is likely that there is an overlapping continuous interface between the lamellipodium and the lamellum [42]. Therefore, in this paper, we will not

consider the lamellum and assume that the lamellipodium continuously transitions into the lamella. We therefore assume that F_m is proportional to the concentration of myosin $m(x,t)$, which is anchored to the less dynamic lamella, along the length x of the network at time t. F_a, however, is dependent on both the concentration of integrins $a(x,t)$ and the force exerted by myosin. This is because integrins serve to anchor the actin network and thus provide resistance to the motion of actin. Here, each integrin can exert a resistive force up to $f_a^{\max}$. When the total possible resistive force exerted by existing integrins exceeds the total force exerted by existing myosins, the actual total resistive force exerted by integrins is equal to that exerted by myosins. However, when the total force exerted by myosins is more than the amount of resistive force that the integrins can provide, the actual resistive force each integrin unit provides is $f_a^{\max}$. Therefore,

$$\frac{db}{dt} = \epsilon(k^+u - k^-) + \frac{1}{\eta}\left(f_a\int_p^b a\,dx - f_m\int_p^b m\,dx\right) \quad (1)$$

where

$$f_a = \begin{cases} f_m\frac{\int_p^b m\,dx}{\int_p^b a\,dx} & \text{if } f_m\int_p^b m\,dx < f_a^{\max}\int_p^b a\,dx. \\ f_a^{\max} & \text{otherwise} \end{cases}$$

Here, ϵ is the length of an actin monomer, f_m is the force exerted by a single myosin unit, and p denotes the position of the rear of the actin segment which we assume to be constant.

To solve this equation, we need to know how the concentrations of myosin, $m(x,t)$, and integrin, $a(x,t)$, change. Myosin activation is achieved by the phorphorylation of myosin light chains by the myosin light chain kinase. The myosin light chain kinase, in turn, can be activated by integrin mediated activation of Rho upon integrin binding to the substrate [43]. A similar signaling pathway was also used by Besser and Schwarz [44], where they studied the dynamics of stress fibers represented as a viscoelastic material with material properties that respond to chemical signals from the focal adhesions. In an extension of this work, the authors saw a delay in the myosin activation upon integrin activation [45]. Since the dynamics of the signaling pathway is not the focus of our study, we have replaced the integrin-myosin signaling pathway with a simple time delay. Therefore, myosin is activated at the rate α at a time delay ζ to account for the time taken for the chemical signal to be transduced down the signaling cascade after integrin activation:

$$\frac{\partial m}{\partial t} = \alpha a(x,t-\zeta). \quad (2)$$

The value used for the time delay ζ (see Table I) is consistent with the work of Besser and Schwarz [44,45].

Integrin concentration can change in one of two manners: myosin dependent and myosin independent. First, experiments have shown that contractile forces due to myosin can cause nascent adhesions (clusters of a small number of integrins) to mature into focal complexes (clusters of a large number of integrins) at the cell's leading edges [52,53]. Therefore, we expect the rate of change of integrin concentration of focal adhesions at the barbed end b to be proportional to F_m. Second, at all other locations, integrin concentration can change in a myosin-independent manner, where nascent adhesions can either disassemble or mature into focal adhesion complexes. Experiments have suggested that the presence of stretch-sensitive proteins that bind to the focal adhesions and the extent of their stretch determine either disassembly or maturation [27]. The hypothesis is that these stretch-sensitive proteins can expose phosphorylation sites when stretched, serving then as scaffold proteins to allow more proteins to assemble at and stabilize the focal adhesion complex. If the stretch is small, then the adhesions disassemble without maturing into larger focal complexes. This is supported by experiments that have shown that nascent adhesions can form along the leading edge of the lamellipodia and rapidly disassemble without maturing

TABLE I. Values of parameters used in the simulations.

Parameter	Symbol	Value	Reference
Drag coefficient	η	5 μkg s^{-1}	Estimated
Length of actin monomer	ϵ	2.7 nm	[46]
Concentration of G-actin at barbed end of actin	u	1 μM	[47]
Polymerization rate of barbed end of actin	k^+	10 μM^{-1} s^{-1}	[46]
Depolymerization rate of barbed end of actin	k^-	1.4 s^{-1}	[46]
Force generated by a single myosin unit	f_m	4 pN	[48]
Max. force generated by a unit focal complex	f_a^{max}	1 pN	[49]
Tensile strength of actin-actin bond	σ	100 pN	[50]
Young's modulus of substrate	Y	0.01–20 kPa	[51]
Poisson's ratio of substrate	ν	0.3	[51]
Substrate thickness	h	0.5 μm	[17]
Area of focal complex	A	0.05 μm^2	[52]
Activation rate of myosin	α	0.2 s^{-1}	Estimated
Time delay in integrin-myosin activation	ζ	20 s	[45]
Growth rate of focal complex due to the stretch-sensitive protein	γ^+	1.6 s^{-1}–1000 s^{-1}	Estimated
Rate of dissociation of focal complex	γ^-	-1.0 s^{-1}	Estimated
Critical stretch length of stretch-sensitive protein	s_0	5 nm	Estimated
Myosin-dependent activation rate of integrin	β	100 s^{-1}–1000 s^{-1}	Estimated

into stronger focal complexes [54]. On the other hand, if the stretch is large, then maturation occurs. Thus,

$$\frac{\partial a}{\partial t} = \beta\delta(x-b)\int_p^b m dx + [\gamma^- + (\gamma^+ - \gamma^-)H(s-s_0)]a. \tag{3}$$

In the first term of Eq. (3), β is a biochemical rate constant denoting the rate of integrin activation by myosin, and $\delta(x)$ is the Dirac delta function that is zero everywhere except at $x = 0$. This ensures integrin activation due to myosin only at the barbed end. The second term of the equation describes the activation rate of integrin due to the amount of stretch, denoted by s, created in the stretch-sensitive protein, which is activated when the stretch exceeds the stretch-threshold given by s_0. The Heaviside step function $H(x)$, where $H(x)$ is zero when x is negative and one when x is positive, is used to switch from a state of nascent adhesion disassembly, characterized by the disassembly rate γ^-, to a state of nascent adhesion maturation, characterized by the growth rate γ^+.

The amount of stretch s, is defined as the difference in the distance that the actin filament has moved (due to forces exerted on actin) and the distance that the integrins at the leading edge have moved (due to deformation of the substrate). In a time interval t, the actin filament will have moved a distance of $\int_0^t 1/\eta(F_a - F_m)dt$. Integrins, on the other hand, would have moved due to the stretching of the substrate. Using force balance on the integrins, the force exerted on the integrins by the substrate will be equivalent to the force exerted by the actin on the integrins, which will be equivalent to the force exerted by the integrin on actin, F_a (see Fig. 1 for schematic), i.e., $F_c - F_a = 0$. Since F_c is a result of the substrate deformation, it can be expressed as $F_c = -(GA/h)c$, where G is the substrate's shear modulus, A is the area on which the force acts (i.e., the area of adhesion), h is the thickness of the substrate, and c is the amount of stretch induced in the substrate, i.e., the distance moved by the integrins. For convenience, we rewrite F_c using the Young's modulus Y, namely, $F_c = -(YA)/[2(1+\nu)h]c$, where ν is substrate's Poisson ratio. This gives us the value of c as a function of F_a, namely, $c = 2(1+\nu)hF_a/(YA)$. Therefore,

$$s = \left| \int_0^t \frac{1}{\eta}\left(f_a\int_p^b a dx - f_m\int_p^b m dx\right)dt + \frac{2(1+\nu)hf_a}{YA}\int_p^b a dx \right|. \tag{4}$$

Equations (1)–(4) form a set of coupled integrodifferential equations in the variables $b(t)$, $m(x,t)$, $a(x,t)$, and $s(t)$. They are evolved until the tensile forces acting on the actin filament exceed the tensile strength σ of the actin segment, i.e., when $F_a > \sigma$ or $F_m > \sigma$. At this point, the actin segment breaks [7,8], and the process of actin polymerization and myosin and integrin pulling repeats from the fragment of actin left at the leading edge. We solve Eqs. (1)–(4) numerically using the explicit forward Euler method. Parameters used were obtained from literature as much as possible, as shown in Table I.

III. RESULTS AND DISCUSSION

A. Periodic protrusion-retraction cycles observed in simulations

By systematic parameter variations, we find that the parameters that have the most significant control on the dynamics of b are the time delay from integrin to myosin activation ζ, the rate of integrin activation by myosin β, the rate of focal complex maturation γ^+, and the substrate stiffness Y. By changing β, γ^+, and Y, we have found three types of migratory dynamics. First, b can protrude and retract periodically as illustrated in Fig. 2(a). This happens as protrusion due to actin polymerization at the barbed end is halted by the net effect of the forces exerted on actin. However, when the tension in the actin becomes too high, the actin strip severs, thereby initiating the next protrusion-retraction cycle. Thus, our model provides a quantitative understanding of the experimentally observed protrusion-retraction cycles [7,8], which are also seen in previous work by Falcke's group [13,14]. When we set $\beta = 200\ \mathrm{s}^{-1}$, $\gamma^+ = 1.6\ \mathrm{s}^{-1}$, $Y = 20$ kPa, and $\zeta = 20$ s, we were able to reproduce protrusion and retraction speeds of 39.4 and 45.2 nm/s, respectively, which fall in the range of protrusion and retraction speeds reported in Ref. [8].

B. Periodic protrusion-retraction requires a sufficiently stiff substrate

We observed that these periodic protrusion-retraction cycles persist over a wide range of parameter values. In particular, we found that a sufficiently stiff substrate is required for such

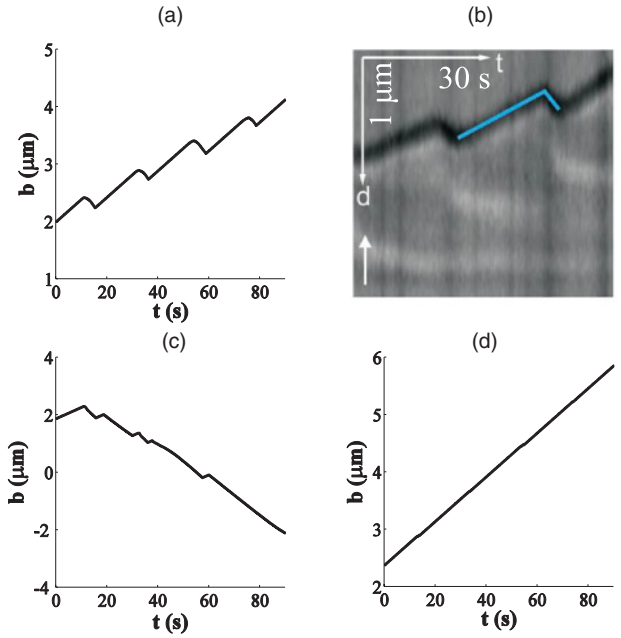

FIG. 2. (Color online) Three types of migratory dynamics are observed at $\zeta = 20$ s, as illustrated by "kymographs" showing the position of the barbed end $b(t)$ at time t (leading edge of the cell): (a) periodic protrusion-retraction observed at $\beta = 200\ \mathrm{s}^{-1}$, $\gamma^+ = 1.6\ \mathrm{s}^{-1}$, $Y = 20$ kPa; (b) periodic protrusion-retraction observed in experiments (figure adapted from Ref. [8]); (c) unstable retraction corresponding to ruffling observed at $\beta = 20\ \mathrm{s}^{-1}$, $\gamma^+ = 10\ \mathrm{s}^{-1}$, $Y = 20$ kPa; and (d) continuous protrusion observed at $\beta = 4000\ \mathrm{s}^{-1}$, $\gamma^+ = 4000\ \mathrm{s}^{-1}$, $Y = 20$ kPa.

cycles. If we keep $\beta = 200\ \mathrm{s}^{-1}$ and $\gamma^+ = 1.6\ \mathrm{s}^{-1}$, then we see these cycles as long as $Y \gtrsim 0.01$ kPa. Intuitively, this can be explained by sufficient myosin-independent activation of integrins due to the stretch-sensitive protein activation which occurs on sufficiently stiff substrates, therefore preventing the rapid retraction of actin when pulled on by myosin. Such a result is consistent with experiments in which periodic protrusion-retraction was seen on stiff substrates [7]. When the substrate was too soft, unstable retractions were observed instead, similar to that seen in Fig. 2(c). This is expected as a soft substrate would generate low stretch in the stretch-sensitive protein, reducing the myosin-independent activation rate of integrins and causing a decrease in the resistance to motion provided for by integrins. Physiologically, when retractions happen, the lamellipodium tends to fold backward as the large forces exerted by myosin cause the former to lose its adhesion to the substrate. This phenomenon is commonly described as ruffling [7,8]. We therefore associate unstable retractions as ruffling.

C. Periodic protrusion-retraction requires sufficient activation of integrins

Unstable retractions are also seen when there is insufficient activation of integrins. If we keep $\gamma^+ = 1.6\ \mathrm{s}^{-1}$ and $Y = 20$ kPa, then we see these cycles as long as $\beta \gtrsim 100\ \mathrm{s}^{-1}$. This suggests that a loss in the myosin-dependent activation rate of integrins can lead to loss of periodicity as well. When the rate of integrin activation by myosin is low, it results in low amounts of focal complex maturation from nascent adhesions at the front of the lamellipodium. The force exerted by myosin generated at the rear caused the actin network to retract rapidly due to lack of resistance by focal complexes. As long as β is small, no matter how fast the rate of focal adhesion growth γ^+ is, the barbed end always retracts, because there will always be insufficient focal complexes. However, when the substrate becomes less stiff, the crossover from periodic protrusion-retraction to unstable retraction occurs at a higher value of β. This is expected since a softer substrate would mean less myosin-independent activation of integrins, therefore requiring a higher amount of myosin-dependent activation of integrins for adequate integrin generation to resist the forces created by myosin.

D. Excessive activation of focal adhesions, coupled with stiff substrates, leads to continuous protrusion

If we keep $\beta = 200\ \mathrm{s}^{-1}$ and $Y = 20$ kPa, protrusion-retraction cycles were lost when $\gamma^+ \gtrsim 1000\ \mathrm{s}^{-1}$. Under such conditions, retraction was not observed and the barbed end protruded continuously, as shown in Fig. 2(d). This suggests that retraction is achieved only when the resistive forces exerted by integrins is not too high; i.e., the myosin-independent activation rate of integrins must be sufficiently low. Such a phenomenon is normally only observed at large β, i.e., when the rate of integrin activation by myosin is high, at large γ^+, i.e., when the rate of focal adhesion growth is high, and at large

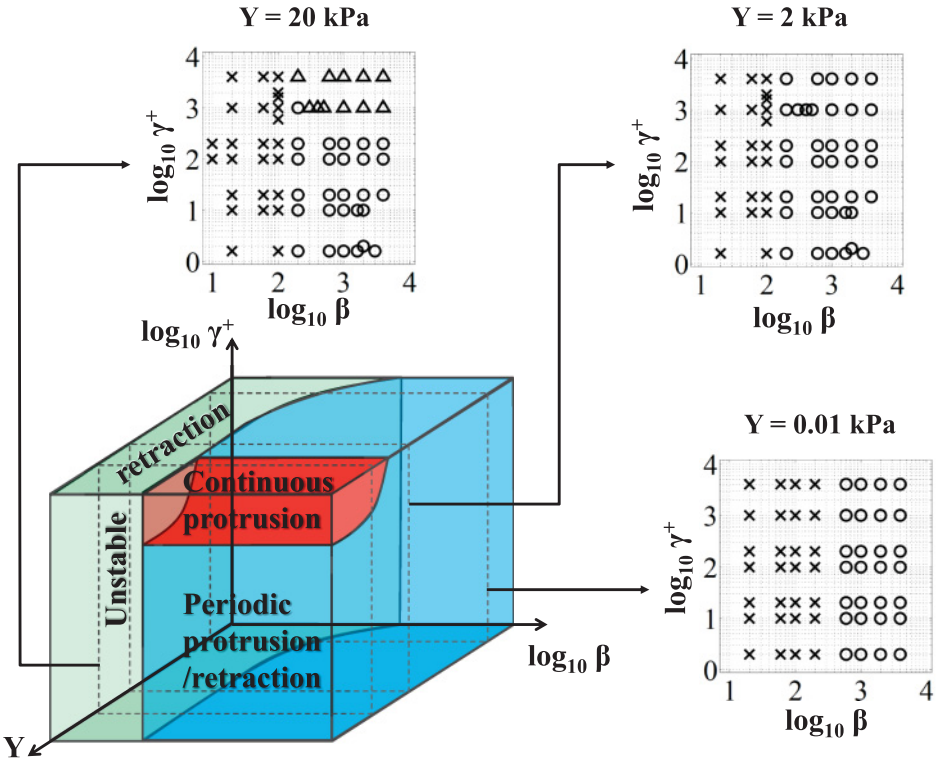

FIG. 3. (Color online) Phase diagram depicting the three types of migratory dynamics in this space spanned by the rate of integrin activation by myosin β, the rate of focal adhesion growth γ^+, and the substrate stiffness Y. Three frames in (β,γ^+) space at fixed Y of 0.01, 2, and 20 kPa are shown. The circles denote periodic protrusion-retraction, crosses denote unstable retraction, and triangles denote continuous protrusion.

Y, i.e., stiff substrates. Under these conditions, retraction due to myosin pulling at the rear was not possible due to the rapid growth of integrin at the focal complexes. Also, continuous protrusion was not observed on soft substrates because the high deformation of the substrate results in a reduction in the stretch induced in the stretch-sensitive protein, therefore rendering the stretch-sensitive protein less effective in inducing the growth of focal complexes.

E. Phase diagram and relation to experimental observations

The parameter regimes in which different types of migratory dynamics are exhibited are summarized in Fig. 3, which shows a phase diagram depicting the three types of migratory dynamics in the space spanned by the rate of integrin activation by myosin β, the rate of focal adhesion growth γ^+, and the substrate stiffness Y. Interestingly, experiments have found that during the initial phases of cell spreading before periodic protrusion-retraction cycles are observed, continuous protrusions are first observed [55]. From Fig. 3, the only way to transition from the continuous protrusion phase to the periodic protrusion/retraction phase is either to reduce Y or to reduce γ^+. Since the substrate is not changed, the only mechanism has to be a decrease in γ^+. Therefore, we postulate that, during cell spreading at the transition from the continuous protrusion phase to the periodic protrusion/retraction phase, there must be active signaling that results in a decrease in the rate of focal adhesion growth.

Next, we discuss how the parameters β and γ^+ can be changed biochemically. First, it has been suggested that the maturation of nascent adhesions into focal complexes requires the presence of talin [27] as well as α actinin, a protein involved in the binding of actin to the cell membrane [54]. Therefore, by downregulating α actinin and/or talin, β will have been decreased. In doing so, more unstable retractions should be observed in the lamellipodium. This will be more pronounced the higher the substrate stiffness. Second, it has been suggested that the rate of focal adhesion growth γ^+ can be increased by upregulating the stretch-sensitive protein p130Cas [56]. Therefore, on substrates that are sufficiently stiff, this upregulation will result in more continuous protrusions being observed.

F. Period of protrusion-retraction cycle is only affected by the time delay in signal propagation

The total period of each cycle was not affected by changing β, γ^+, and Y, but increased proportionately with the time delay ζ. This is shown in Fig. 4. This is to be expected since increasing the time delay would delay the onset of myosin force exertion which would cause retraction to occur later. However, when low time delays below the 20s were used, unstable retractions were seen instead, suggesting that an early onset of myosin activation could also lead to ruffling events often seen in experiments.

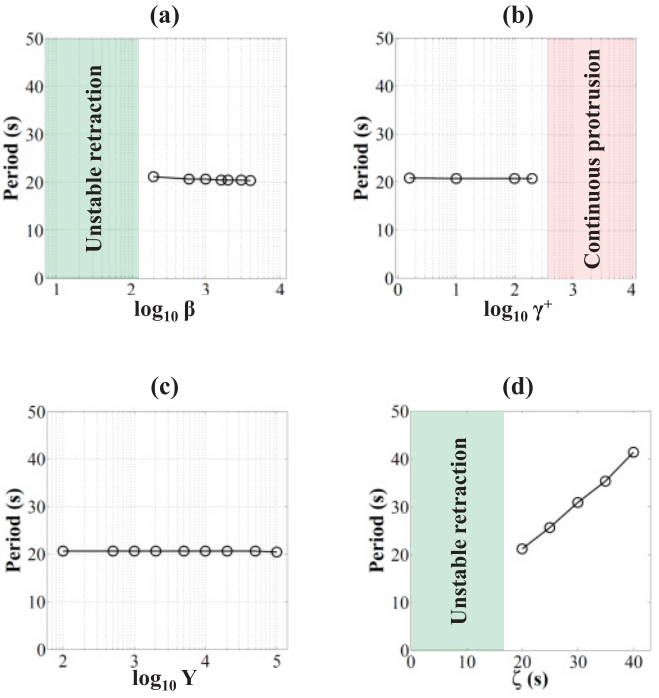

FIG. 4. (Color online) Variation of total period with (a) β at $\gamma^+ \leqslant 200\ \mathrm{s}^{-1}$, all values of Y, and $\zeta \geqslant 20$ s; (b) γ^+ at $\beta \geqslant 200\ \mathrm{s}^{-1}$, $Y > 2$ kPa, and $\zeta \geqslant 20$ s; (c) Y at $\beta \geqslant 200\ \mathrm{s}^{-1}$, $\gamma^+ \leqslant 200\ \mathrm{s}^{-1}$, and $\zeta \geqslant 20$ s; and (d) ζ at $\beta \geqslant 200\ \mathrm{s}^{-1}$, $\gamma^+ \leqslant 200\ \mathrm{s}^{-1}$, and $Y < 20$ kPa.

IV. CONCLUSION

We have shown that a mechanochemical model comprising interactions among actin, myosin, and integrin in the lamellipodium, as well as the substrate, allows us to explore and map out the types of migratory dynamics quantitatively. Our simulations show that there are three types of dynamics. In particular, we were able to explain when and why the periodic protrusion-retraction cycles occur, and make predictions on how they transition to unstable retractions and continuous protrusions that can be validated experimentally. Although different mechanisms were used, the phenomena of periodic protrusion-retraction cycles seen in our one-dimensional model are similar to the oscillations seen in the two-dimensional models proposed by Enculescu *et al.* [13] and Shlomovitz and Gov [9]. While this suggests that the cell is able to use a plethora of mechanisms to produce a particular phenomenon, the use of mechanosensitive proteins to obtain information about the substrate stiffness is a sufficient mechanism for the behavior observed in cells. Our model reinforces the importance of such mechanosensitive proteins in the cell, in the case the stretch-sensitive protein, to enable the cell to probe its external mechanical environment. This can play an important role in cell behavior such as cell migration [17,18] and determination of cell lineage [57,58]. In the future, we can enhance the model to study the effects of focal complex formation [59] and force loading on actin polymerization [14] and how it can affect leading-edge protrusion.

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