

Substrate properties and actin polymerization speed dictate universal modes of cell migration: Gripping, slipping, and stick-slip

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Understanding how cells sense mechanical cues and regulate migration is crucial in the development, fibrosis, and oncogenesis processes. However, a comprehensive physical picture of cell migration remains lacking, given the diverse environmental properties and cell physiologies. Here, we generalize the motor-clutch model to the whole-cell level and systematically investigate the effects of substrate stiffness, friction, and actin polymerization speed on cell migration. We unveil three distinct migration modes: gripping, slipping, and stick-slip. Notably, stiffness sensing occurs exclusively in the stick-slip mode, which requires a low substrate stiffness and a minimum actin polymerization speed as necessary conditions. Intriguingly, the optimal substrate stiffness that maximizes the migration speed is inversely proportional to the actin polymerization speed. Moreover, the maximal speed only depends on the nature of the clutch molecules, independent of substrate properties. We reveal the boundary criteria among the three migration modes and demonstrate that fast- and slow-migrating cells can coexist in an isogenic cell population without the need for biochemical feedback loops.

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I. INTRODUCTION

Cellular behaviors such as migration [1–3], spreading [4], and differentiation [5,6] are sensitive to cell-matrix interactions and crucial for developmental processes, tumorigenesis [7], and wound healing [8]. During cell migration, force transmission begins with adaptor proteins linked to actin and proceeds through integrins that bind to ligands on the extracellular matrix (ECM) [9,10]. Polymerization of filamentous actin (F-actin) at the leading edge leads to retrograde actin flow, which can be converted to cell migration relative to the substrate through focal adhesions [11–13]. In the meantime, myosin II localized at the cell rear disassembles the actin network together with actin-depolymerizing factor (ADF)/cofilins, which allows the recycling of actin monomers [14,15].

Multiple mathematical models have been proposed to understand cell migration from different perspectives [16]. Among them, the motor-clutch model is one of the most illuminating ones [17–25]. The model was first proposed to explain how substrate stiffness affects filopodia traction dynamics, in which molecular clutches link F-actin to the substrate and mechanically resist the retrograde flow [26]. As our understanding of mechanosensing improves, the motor-clutch model has been extended to study the effects of integrin subtypes [27], substrate stiffness gradients [28], ECM

viscoelasticity [29–33], adhesion growth [34], spatial sensing of ligands [35], effects of force loading rate [36], etc. Despite the vast applications of the motor-clutch model in various experimental conditions, several key issues remain.

First, cellular physiologies, e.g., the actin polymerization speed, can vary significantly across different cell types; indeed, migration speed varies from less than 1 $\mu\text{m}/\text{min}$ for fibroblasts to 15 $\mu\text{m}/\text{min}$ for keratocytes [37]. Second, substrate properties, e.g., the stiffness, can vary by orders of magnitude across different experiments [28]. Third, even for an isogenic population in the same environment, experimental observations of freely migrating cells have revealed significant cell-to-cell variability, including a slow-moving subpopulation [38,39]. However, most theoretical studies of the motor-clutch model are computational and/or involve a dozen variables, in which parameter values are chosen for a particular cell type and experimental setup; therefore, the universality and generalizability of their conclusions are unclear [23]. Thus, an analytically treatable model connecting cell migration to cellular physiologies (e.g., actin polymerization speed) and environmental properties (e.g., substrate stiffness) and capturing phenotypic variability is fundamentally essential, which is presented in this work.

Here, we study the motor-clutch model at the whole-cell level, which allows us to explicitly relate the migration speed to the actin polymerization speed, the substrate stiffness, and the substrate friction. Using a mean-field approximation, we significantly simplify the model to a system with two degrees of freedom: the engagement probability of clutches (P_b) and the traction force (F). We obtain the phase diagram of cell migration and reveal three distinct migration modes: gripping, slipping, and stick-slip. The transition mechanisms between different modes are rich, including saddle-node bifurcation, and discontinuous and continuous Hopf bifurcation [40].

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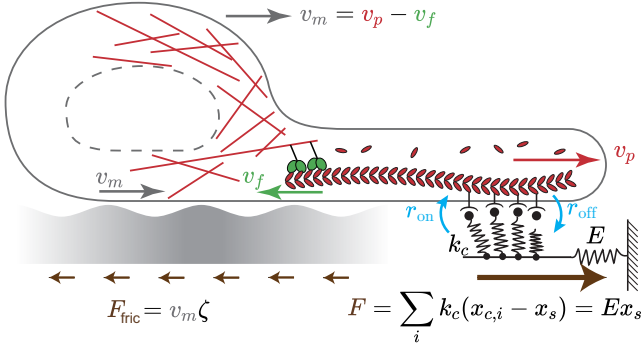


FIG. 1. A schematic of the cell migration model. We consider a cell migrating toward the right side with migration speed v_m , related to the actin polymerization speed v_p and the retrograde speed of F-actin v_f . The clutches can engage with F-actin and resist its retrograde flow, and they are modeled as springs with spring constant k_c . The substrate is modeled as a spring with a spring constant E . The traction force is the sum of the forces on all clutches, which also sets the substrate displacement x_s . Furthermore, the traction force is also proportional to the migration speed as $F = v_m \zeta$, where ζ is the friction coefficient of the substrate.

We highlight several key insights gained from our model: (1) stiffness sensing only occurs in the stick-slip mode of cell migration where the optimal substrate stiffness maximizing migration speed is inversely proportional to the actin polymerization speed, but the maximal migration speed only depends on the properties of molecular clutches; (2) the migration speed and traction force show a biphasic dependence on the actin polymerization speed; (3) the period of the stick-slip mode is proportional to the clutch number, the inverse of substrate stiffness, and the inverse of actin polymerization speed; and (4) different migration modes, e.g., fast- and slow-moving cells, can coexist in an isogenic population without relying on biochemical feedback loops.

II. MODEL DESCRIPTION

We introduce a modified motor-clutch model to study a migrating cell moving in a fixed direction, which we denote as the cell migration model in the following (Fig. 1). F-actin polymerizes at the leading edge with a constant speed v_p . Meanwhile, the speed of the retrograde actin flow relative to the substrate is v_f , and the engagement of molecular clutches to the F-actin resists the retrograde flow [41]. The engagement of clutch i with F-actin is characterized by a constant association rate r_{on} and an unbinding rate, which increases exponentially with force F_i exerted on clutch i : $r_{off,i} = r_{off}^0 \exp(F_i/F_b)$, where F_b is a characteristic force for clutch breakage [42].

The force on each engaged clutch is proportional to its elongation, $F_i = k_c(x_{c,i} - x_s)$, where k_c is the spring constant of the clutch and $x_{c,i}$ is the displacement of the clutch's end bound to the F-actin. The substrate displacement, denoted by x_s , is set by the traction force exerted by the migrating cell: $F = E x_s = \sum_i F_i$, where $F_i = 0$ for unengaged clutches. Here, we neglect the contribution of the globally distributed friction force to x_s , since the localized traction force produces a logarithmically enhanced substrate displacement at the lead-

ing edge compared to the distributed friction (Sec. A of the Supplemental Material [43] for a detailed derivation). The spring constant k_c should be regarded as the overall spring constant of the series of the ligand, integrin, and other proteins involved in the force transmission through a single clutch [44].

By exerting backward traction force on the substrate, the cell migrates forward with a migration speed $v_m = F/\zeta$, where ζ is the friction coefficient between the cell and substrate, characterizing the general membrane-substrate friction (Sec. A of the Supplemental Material [43] for an estimate of ζ). Specifically, the traction force F is generated by molecular clutches and acts specifically at the leading edge. In contrast, passive friction is presumably distributed over the entire cell-substrate contact area (Fig. 1). Consequently, substrate displacement at the leading edge is primarily driven by the localized traction force F , which constitutes the dominant mechanical load in this region. Our model is consistent with the observation that traction force is localized at the cell front, while the cell's back moves passively against the substrate [45]. The retrograde flow speed v_f is related to the migration speed v_m and the actin polymerization speed v_p through $v_f = v_p - v_m$. If the cell moves without relative displacement between the F-actin and substrate, $v_f = 0$ and $v_m = v_p$, it moves at its highest possible speed [15]. We provide estimates of the typical parameter values in Table S1 of the Supplemental Material [43].

In steady-state migration, the total force exerted by the cell on the environment must sum to zero. This includes the traction force F and the external friction force $F_{fric} = \zeta v_m$, which determines the migration speed. The cell does not accelerate because the driving force from the actin-clutch system is exactly balanced by the resistive friction. It is important to note that internal forces, such as the friction between the membrane and the actin meshwork, do not affect the force balance of the cell as a whole.

III. MEAN-FIELD MODEL

We introduce P_b as the fraction of engaged clutches, $P_b = \sum_i s_i/N$, where N is the total number of clutches, $s_i = 1$ for engaged clutches, and $s_i = 0$ for unengaged ones. The time derivative of P_b is $\dot{P}_b = r_{on}(1 - P_b) - \langle r_{off,i} \rangle P_b$, where $\langle r_{off,i} \rangle = \sum_i s_i r_{off,i}^0 \exp(F_i/F_b) / \sum_i s_i$. In the mean-field model, the force fluctuation among clutches is neglected, and $\langle r_{off,i} \rangle_s$ is replaced by $r_{off} \equiv r_{off}^0 \exp(\frac{F}{N P_b F_b})$. Using the same approximation, the mean-field equation of the traction force becomes $\dot{F} = N P_b k_c v_f - \frac{N P_b k_c}{E} \dot{F} - r_{off} F$, where we have used the fact that a newly engaged clutch bears zero force, i.e., $x_{c,i} = x_s$ right after engagement (Sec. A of the Supplemental Material for a detailed derivation from the full stochastic model [43]). In the following, we analyze the dimensionless equations of the mean-field model:

$$\frac{dP_b}{d\tilde{t}} = \alpha(1 - P_b) - P_b \exp(\tilde{F}/P_b), \quad (1)$$

$$(1 + P_b/\tilde{E}) \frac{d\tilde{F}}{d\tilde{t}} = P_b(\tilde{v}_p - \tilde{F}/\tilde{\zeta}) - \tilde{F} \exp(\tilde{F}/P_b). \quad (2)$$

Here, $\alpha = r_{on}/r_{off}^0$. We take $\tilde{t} = 1/r_{off}^0$ as the time unit, $\tilde{F} = N F_b$ as the force unit, and $\tilde{E} = N k_c$ as the stiffness unit.

Therefore, the dimensionless actin polymerization speed becomes $\tilde{v}_p = v_p k_c / r_{\text{off}}^0 F_b$ and the dimensionless friction coefficient becomes $\tilde{\zeta} = \zeta r_{\text{off}}^0 / N k_c$. The dimensionless equations unify the behaviors of different cell types and experimental conditions.

We set the time derivatives of Eqs. (1) and (2) as zero to analyze the steady-state properties and obtain

$$\tilde{v}_p = \frac{\alpha}{\tilde{\zeta}} \frac{x}{\alpha + \exp(x)} + x \exp(x). \quad (3)$$

Here, $x = \tilde{F}/P_b$ defines the averaged force on a single clutch, with the steady-state binding probability given by $P_b = \alpha/[\alpha + \exp(x)]$. In steady states, Eq. (3) means that $\tilde{v}_p = \tilde{v}_m + \tilde{v}_f$, as $\tilde{v}_m = \tilde{F}/\tilde{\zeta}$ corresponding to the first term on the right-hand side; thus, the retrograde flow speed is $\tilde{v}_f = x \exp(x)$. We highlight two key features of Eq. (3). First, a critical substrate friction $\tilde{\zeta}_c$ exists below which the left side of Eq. (3) is nonmonotonic, and three solutions may exist in which the middle solution must be unstable (Fig. 2(b); Sec. B and Fig. S1(A) of the Supplemental Material [43]). Second, the solutions of Eq. (3) are independent of the substrate stiffness $\tilde{E}$, but $\tilde{E}$ influences the stability of these solutions, as we show later.

IV. MODES OF CELL MIGRATION

To gain a global view of the migration behavior, we first present the phase diagram of cell migration, in terms of the migration modes, as a function of the actin polymerization speed $\tilde{v}_p$, the substrate stiffness $\tilde{E}$, and the friction coefficient $\tilde{\zeta}$ [Fig. 2(a)]. Our analysis reveals two distinct stable migration modes: gripping (fast moving) and slipping (slow moving), in agreement with previous experiments [38,39]. Our model further predicts an oscillatory stick-slip mode, which has also been reported experimentally [26].

In the gripping mode, most clutches are engaged: $P_b \approx 1$, leading to a vanishing retrograde flow and a migration speed close to $\tilde{v}_p$ in the steady states [Fig. 2(d)]. Conversely, in the slipping mode, only a tiny fraction of clutches is engaged, resulting in significant sliding of F-actin and a low migration speed [Fig. 2(e)], corresponding to the “frictional slippage” regime in the agent-based simulations of Ref. [26]. In the limit of low substrate friction ($\tilde{\zeta} \ll 1$), we prove that P_b has a lower bound in the gripping mode and is of order one. In contrast, P_b has an upper bound in the slipping mode that is approximately $(\alpha \tilde{\zeta})^{1/2}$ (Sec. B of the Supplemental Material [43]).

In the stick-slip mode [e.g., the red-curve region in Fig. 2(c)], the cell migrates in a stick-slip behavior: Clutches gradually bind to the F-actin, followed by a collective rupture, producing a serrated traction force [Fig. 2(f)]. The area of the stick-slip mode in the parameter space given a fixed substrate stiffness increases as the substrate stiffness decreases (see slices of the phase diagram in Fig. 2(a) at different $\tilde{E}$ and in Fig. S5 of the Supplemental Material [43]). We compare direct simulations of the full stochastic model (Fig. 1) and numerical calculations of the mean-field model [Eqs. (1) and (2)] and find they agree well, validating our mean-field assumptions [Figs. 2(d) and 2(f)]. We include the details of stochastic simulations and numerical calculations in Sec. A of the Supplemental Material [43].

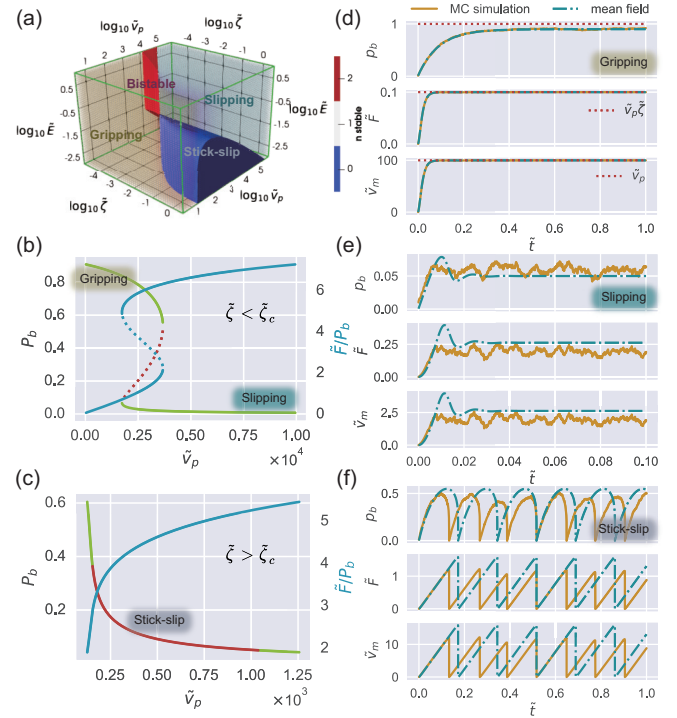


FIG. 2. Modes of cell migration. (a) Phase diagram of migration modes as a function of $\tilde{v}_p$, $\tilde{E}$, and $\tilde{\zeta}$. The red area denotes the bistable phase, where slipping and gripping modes coexist. The solid blue area identifies the stick-slip mode. The remaining monostable region comprises two stable modes: the gripping mode (yellow) and the slipping mode (light blue), with a continuous transition between them. (b) The fraction of engaged clutches P_b (green line) and the force per clutch $\tilde{F}/P_b$ (blue line) vs $\tilde{v}_p$ according to Eq. (3) under the condition $\tilde{\zeta} < \tilde{\zeta}_c$ such that three solutions may exist at most. The change of $\tilde{v}_p$ can be considered as moving along the red rod in panel (a). The dotted lines represent the unstable middle solution. (c) The same as panel (b) but for $\tilde{\zeta} > \tilde{\zeta}_c$ in which only one solution exists for Eq. (3), which is unstable in the red regime. The change of $\tilde{v}_p$ can be considered as moving along the blue rod in panel (a). (d)–(f) A comparison of direct simulations of the full stochastic model (solid yellow curve) and numerical calculations of the mean-field model (blue dot-dashed line) for the three modes.

In the following section, we show that the stick-slip mode can be further subdivided into grippinglike and slippinglike submodes. Moreover, besides the coexistence of gripping and slipping modes within the bistable phase [Fig. 2(b)], the oscillatory stick-slip mode can also coexist with either stable mode near phase boundaries, which we discuss in a later section. Therefore, an isogenic population of cells in the same environment may exhibit subpopulations of cells, such as fast- and slow-migrating cells, in agreement with experiments of freely migrating keratocytes [39].

V. MIGRATION SPEEDS OF DIFFERENT MODES

As shown in the phase diagram [Fig. 2(a)], the gripping mode typically occurs at low polymerization speeds. Taking the limits $\tilde{v}_p \ll 1$ in Eq. (3) reveals that migration speed $\tilde{v}_m$ is

proportional to polymerization speed $\tilde{v}_p$ in the gripping mode:

$$\tilde{v}_m = \begin{cases} \frac{\alpha \tilde{v}_p}{\alpha + (\alpha + 1)\tilde{\zeta}} & \text{gripping: } \tilde{v}_p \ll 1, \\ \frac{\alpha \ln^2(\tilde{v}_p)}{\tilde{\zeta} \tilde{v}_p} & \text{slipping: } \tilde{v}_p \gg 1. \end{cases} \quad (4)$$

In particular, in the limit of low substrate friction $\tilde{\zeta} \ll 1$, $\tilde{v}_m = \tilde{v}_p$: The cell migrates at its highest possible speed, independent of $\tilde{\zeta}$, in agreement with the numerical calculations of the mean-field model [lower left panel of Fig. 3(b)].

In the slipping mode, Eq. (3) is simplified as $x \exp(x) = \tilde{v}_p$ in the limit of $\tilde{v}_p \gg 1$, which means that $\tilde{v}_f \approx \tilde{v}_p$ and $x = W(\tilde{v}_p)$, where $W(z)$ is the root of the equation $z = x \exp(x)$, i.e., the Lambert W function. Therefore, $\tilde{F} = \alpha x / \exp(x) \approx \alpha \ln^2(\tilde{v}_p) / \tilde{v}_p$, leading to the migration speed for the slipping mode in Eq. (4). Here, we use the approximation $W(x) \approx \ln(x)$ for $x \gg 1$ [46]. Surprisingly, the migration speed is inversely proportional to the actin polymerization speed $\tilde{v}_p$ up to a logarithmic correction in the slipping mode, in agreement with numerical simulations [lower right panel of Fig. 3(b)]. The distinct behaviors of the migration speed in the $\tilde{v}_p \ll 1$ and $\tilde{v}_p \gg 1$ regimes suggest that the migration speed must be a nonmonotonic function of the actin polymerization speed [Figs. 3(a) and 3(b)]. This prediction aligns with the biphasic relationship between traction force (proportional to migration speed in our model) and actin retrograde speed observed experimentally [47] (Fig. S6 of the Supplemental Material [43]).

For the stick-slip mode, we analyze the migration speed averaged over one cycle, $\langle \tilde{v}_m \rangle$. As $\tilde{v}_p$ increases inside the stick-slip mode, $\langle \tilde{v}_m \rangle$ exhibits a peak, followed by a sharp but continuous decline before transitions to the slipping mode [Figs. 3(a) and 3(b)]. Intriguingly, the stick-slip mode can be divided into two distinct submodes: slippinglike and grippinglike. In the slippinglike submode, the system has negligible clutch engagement ($P_b \ll 1$), and the system oscillates around the unstable solution of the slipping mode given by Eq. (3) [Figs. 3(a) and 3(d)]. This behavior reflects a continuous Hopf bifurcation driving the transition from the slipping mode to the slippinglike stick-slip submode (see the next section), accompanied by a continuous change in $\langle \tilde{v}_m \rangle$ [Fig. 3(b)].

In the grippinglike submode, corresponding to the “load-and-fail” dynamics in the agent-based simulations of Ref. [26], the system is characterized by significant clutch engagement [$P_b \sim 1$, Fig. 3(c)], and the ridge of maximum $\langle \tilde{v}_m \rangle$ also locates in this region [Fig. 3(a)]. Interestingly, the transition from the gripping mode to the grippinglike stick-slip submode is a discontinuous Hopf bifurcation (see the next section), with a discontinuous change in $\langle \tilde{v}_m \rangle$ [Fig. 3(b)].

To gain analytical insights into the stick-slip loops for the grippinglike submode, we consider the limiting case where $\tilde{E} \ll 1$ while keeping $\tilde{E} \tilde{v}_p$ as a constant. In this case, $\tilde{v}_m \ll \tilde{v}_p$ [Fig. 3(a)], and Eq. (2) is simplified as

$$\frac{d\tilde{F}}{d\tilde{t}} \approx \tilde{E} \tilde{v}_p - \tilde{E}(\tilde{F}/P_b) \exp(\tilde{F}/P_b). \quad (5)$$

Since $\tilde{E}$ is small, the second term on the right-hand side of Eq. (5) becomes significant only when $P_b \rightarrow 0$, where collective rupture occurs. Therefore, the clutch dynamics described

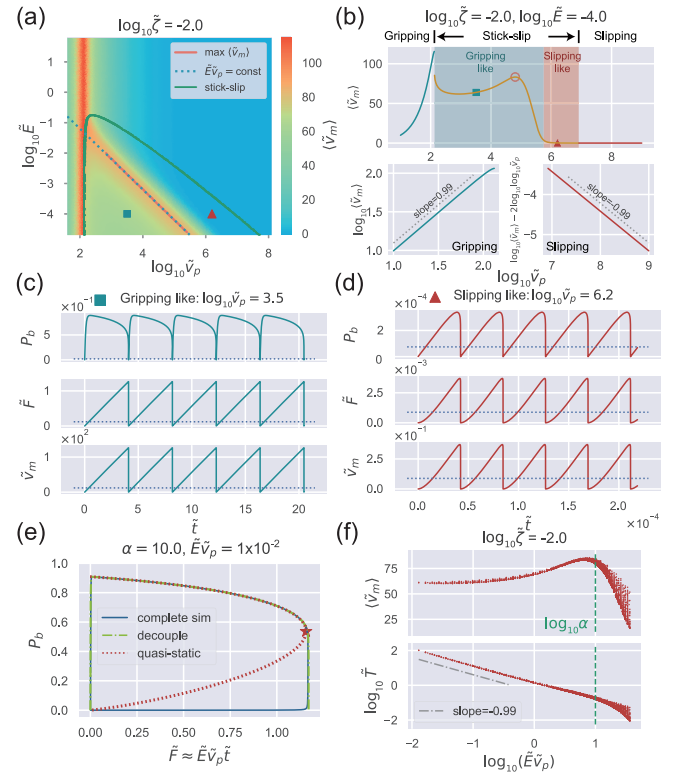


FIG. 3. Migration speeds of different modes. (a) Heatmap of the migration speed. Averaged values during one cycle are shown for the stick-slip mode, and the green line marks the boundary of the stick-slip mode. In the stick-slip mode, the red line marks the maximum $\langle \tilde{v}_m \rangle$. The blue dotted line is a fit to the position of maximum $\langle \tilde{v}_m \rangle$ with a constant $\tilde{E} \tilde{v}_p$. (b) A slice of the heatmap [panel (a)] along $\log_{10} \tilde{E} = -4$. Lines of different colors denote different modes. In the stick-slip mode, the orange circle marks the maximum $\langle \tilde{v}_m \rangle$. The bottom panels show the scaling relationship between $\tilde{v}_m$ and $\tilde{v}_p$ in the gripping and slipping modes, respectively. (c) A typical grippinglike stick-slip loop whose position in the parameter space is marked by the blue squares in panels (a) and (b). The dashed line represents the unstable fixed point of Eqs. (1) and (2). (d) A typical slippinglike stick-slip loop, which corresponds to the red triangle in panels (a) and (b). The dashed line represents the unstable fixed point of Eqs. (1) and (2) (there is only one fixed point here because $\log_{10} \tilde{\zeta} > \log_{10} \tilde{\zeta}_c = -2.35$). (e) The blue solid line is a direct simulation of Eqs. (1) and (2). The green dot-dashed line is the same as the blue solid line but employs the decoupled dynamics approximation to Eq. (2) in the grippinglike submode. The red dotted line represents the quasistatic approximation [Eq. (7)]. The star marks $\tilde{F}_*$ beyond which no solutions of Eq. (7) exist. (f) Parameters within the stick-slip mode of panel (a) are randomly sampled to examine the dependence of the stick-slip period $\tilde{T}$ and averaged migration speed $\langle \tilde{v}_m \rangle$ on $\tilde{E} \tilde{v}_p$. The vertical dashed line marks when $\tilde{E} \tilde{v}_p = \alpha$. In the bottom panel, the gray dot-dashed line is a linear regression of the data for $\tilde{E} \tilde{v}_p \ll \alpha$.

by Eq. (5) is decoupled into two stages: a linear accumulation in the traction force $d\tilde{F}/d\tilde{t} \approx \tilde{E} \tilde{v}_p$, followed by a sudden rupture in all clutches when the total force reaches a threshold $\tilde{F}_*(\alpha, \tilde{E} \tilde{v}_p)$, in agreement with numerical calculations of the mean-field model [Fig. 3(c)]. Given this decoupled dynamics, the average migration speed and the period of the stick-slip

loop become

$$\langle \tilde{v}_m \rangle = \frac{\tilde{F}_*(\alpha, \tilde{E} \tilde{v}_p)}{2\tilde{\zeta}}, \quad \tilde{T} = \frac{\tilde{F}_*(\alpha, \tilde{E} \tilde{v}_p)}{\tilde{E} \tilde{v}_p}. \quad (6)$$

We remark that $\tilde{E} \tilde{v}_p$ appears as an entirety in Eq. (6), which explains why the maximum $\langle \tilde{v}_m \rangle$ sits on the ridge of a constant $\tilde{E} \tilde{v}_p$ [Fig. 3(a)].

To further verify the dependence on the product $\tilde{E} \tilde{v}_p$, we randomly sample the values of $\tilde{E}$ and $\tilde{v}_p$ within the grippinglike stick-slip submode. We confirm that $\tilde{T}$ and $\langle \tilde{v}_m \rangle$ are similar as long as the product $\tilde{E} \tilde{v}_p$ is the same [Fig. 3(f)]. Such dependence breaks down quickly as the accumulation rate of the traction force, which is $\tilde{E} \tilde{v}_p$, exceeds the changing rate of the binding probability, which is α , leading to the maximal $\langle \tilde{v}_m \rangle$ when $\tilde{E} \tilde{v}_p \approx \alpha$. In particular, in the limit $\tilde{E} \tilde{v}_p \ll \alpha$, $\tilde{F}_*(\alpha, \tilde{E} \tilde{v}_p)$ is independent of $\tilde{E} \tilde{v}_p$; therefore, $\tilde{T} \sim 1/\tilde{E} \tilde{v}_p$ and $\langle \tilde{v}_m \rangle$ is a constant.

We highlight several intriguing predictions after translating Eq. (6) to physical units. First, the maximum migration speed in the stick-slip mode scales as $\langle v_m^{\max} \rangle \sim NF_b/\zeta$ and is independent of actin polymerization speed. Second, the optimal stiffness maximizing $\langle v_m \rangle$ scales as $E^* \sim NF_b r_{\text{on}}/v_p$ using the condition $\tilde{E}^* \tilde{v}_p \sim \alpha$ [Fig. 3(f)]. Third, the period of the stick-slip mode scales as $T \sim NF_b/(E v_p)$. We note that some of these scaling relationships were previously identified empirically in computational studies [18,26]. Our work provides a unifying mechanistic explanation and offers new predictions.

We seek the analytical expression of $\tilde{F}_*(\alpha, \tilde{E} \tilde{v}_p \rightarrow 0)$. Because of the separation of the timescales that govern the dynamics of P_b [α in Eq. (1)] and the dynamics of $\tilde{F}$ [$\tilde{E} \tilde{v}_p$ in Eq. (5)], P_b is always approximately at the steady-state value given the instantaneous $\tilde{F}$:

$$\tilde{F} = P_b \ln \left[\frac{\alpha(1 - P_b)}{P_b} \right]. \quad (7)$$

Here, P_b is a multivalued function of $\tilde{F}$. $\tilde{F}_*(\alpha, \tilde{E} \tilde{v}_p \rightarrow 0)$ is precisely the threshold force beyond which no solutions of P_b exist, which is $\frac{\alpha[1+W(\alpha/e)]}{\alpha+\exp[1+W(\alpha/e)]}$ corresponding to the overall rupture in Fig. 3(e). To validate the quasistatic approximation, we compute the relationship between P_b and $\tilde{F}$ by the direct simulation of Eqs. (1) and (2), a reduced simulation using Eq. (1) and the decoupled dynamics approximation $\tilde{F} = \tilde{E} \tilde{v}_p \tilde{t}$, and the quasistatic results given by Eq. (7). Indeed, these three results match very well [Fig. 3(e)].

VI. BOUNDARIES BETWEEN MODES

The Jacobian matrix $A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$ of the dynamical system [Eqs. (1) and (2)] around a fixed point is

$$A = \begin{bmatrix} -\alpha + e^x(x-1) & -e^x \\ \frac{y}{y+1}(x+1)xe^x & -\frac{y}{(1+y)z}[e^x(1+x)z+1] \end{bmatrix}, \quad (8)$$

where $x = \tilde{F}/P_b$, $y = \tilde{E}/P_b$, and $z = \tilde{\zeta}/P_b$ to simplify the notation. Together with the fixed point equation [Eq. (3)], we remark that, as $\tilde{E} \rightarrow +\infty$, neither the fixed point location nor the Jacobian depends on the substrate stiffness $\tilde{E}$. Hence, in this regime, the system dynamics is entirely independent

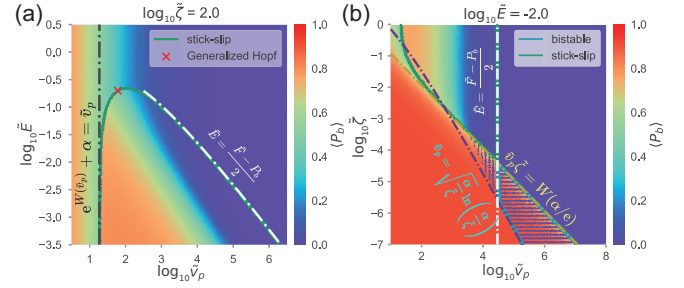


FIG. 4. Boundaries between different migration modes. (a) Heatmap of the binding probability P_b at a fixed $\tilde{\zeta} \gg 1$. The average value over one cycle is shown for the stick-slip mode, whose boundary is marked by the green line. The black dot-dashed line represents the predicted gripping boundary [Eq. (9)]. The white line represents the predicted slipping boundary [Eq. (10)]. The red cross marks the generalized Hopf bifurcation point at which discontinuous Hopf bifurcation transitions to a continuous one. The same heatmap at a small friction coefficient $\tilde{\zeta} < \tilde{\zeta}_c$ is shown in Fig. S7 of the Supplemental Material [43]. (b) The same as panel (a) but at a fixed $\tilde{E}$. The green and blue solid lines represent the boundaries of the stick-slip mode and the bistable phase. Within the bistable phase, horizontal stripes indicate $\langle P_b \rangle$ values for both stable modes. In the coexistence region of slippinglike stick-slip mode and gripping mode, $\langle P_b \rangle$ is displayed as vertical stripes. The yellow dot-dashed line represents the predicted gripping boundary [Eq. (9)]. The yellow dashed line marks the saddle-node bifurcation of the slipping mode, while the vertical white line corresponds to the Hopf bifurcation, where the slipping mode becomes unstable. A heatmap as a function of $\tilde{E}$ and $\tilde{\zeta}$ is shown in Fig. S8 of the Supplemental Material [43].

of $\tilde{E}$, consistent with the phase diagram shown in Fig. 2(a). Furthermore, we find that the stick-slip mode is also absent for $\tilde{E} \gg 1$ [Fig. 2(a)].

Given $P_b \sim O(1)$ for the gripping mode, we find that the unstable condition for a gripping solution is $a_{11} = -\alpha + e^x(x-1) > 0$ in the limit of weak substrate stiffness $\tilde{E} \ll 1$ (Sec. C of the Supplemental Material [43]), which can be written as $x > 1 + W(\alpha/e)$, where $W(z)$ is the Lambert W function. To translate the unstable condition determined by the average force per clutch x to the actin polymerization speed $\tilde{v}_p$, we consider two asymptotic regimes of $\tilde{\zeta}$. In the limit $\tilde{\zeta} \gg 1$, Eq. (3) is reduced to $x \exp(x) = \tilde{v}_f \approx \tilde{v}_p$; in the limit $\tilde{\zeta} \ll 1$, Eq. (3) is reduced to $\frac{x}{\tilde{\zeta} \alpha + \exp(x)} = \tilde{v}_m \approx \tilde{v}_p$. Thus, we obtain the boundary of the gripping mode in the limit $\tilde{E} \ll 1$ (Sec. C of the Supplemental Material [43]):

$$\text{gripping boundary} \begin{cases} e^{W(\tilde{v}_p)} + \alpha = \tilde{v}_p & (\tilde{\zeta} \gg 1), \\ \tilde{v}_p \tilde{\zeta} = W(\alpha/e) & (\tilde{\zeta} \ll 1). \end{cases} \quad (9)$$

The gripping boundary at low substrate friction $\tilde{\zeta} \ll 1$, i.e., the right boundary of the bistable phase in Fig. 4(b), is induced by a saddle-node bifurcation. Therefore, we can get the same boundary by requiring the existence of a gripping solution in Eq. (3) without requiring the condition $E \ll 1$ (Sec. B of the Supplemental Material [43]). The boundary condition in physical units, $v_p \zeta / NF_b \sim O(1)$, has a clear physical meaning: For gripping migration, the cell must apply a traction force close to $v_p \zeta$ to overcome the substrate friction since $v_m \approx v_p$ according to Eq. (4); nevertheless, the maximum traction force

has to be smaller than NF_b , which is the maximum force all the clutches can hold.

Since the stability of the gripping mode is dominated by a_{11} in the limit of $\tilde{E} \ll 1$, fixing $\tilde{F}$ and applying a small perturbation δP_b is most likely to trigger instability, suggesting that the destabilization mechanism of gripping mode resembles the rupture observed in the loops of the grippinglike stick-slip submode. When the steady-state traction force $\tilde{F}$ exceeds a threshold value $\tilde{F}_*$, no solution of P_b exists. Indeed, employing $\tilde{F} = \alpha x / [\alpha + \exp(x)] = \tilde{F}_*(\alpha, \tilde{E} \tilde{v}_p \rightarrow 0) = \frac{\alpha(1+W(\alpha/e))}{\alpha + \exp(1+W(\alpha/e))}$ from the quasistatic approximation of the grippinglike stick-slip submode, we recover the boundary criterion for the gripping mode: $x = 1 + W(\alpha/e)$.

The slipping mode has two boundaries. The first is the boundary where stable slipping migration turns into slippinglike stick-slip, corresponding to the white dot-dashed line in Fig. 4(a) and the vertical white dot-dashed line near $\log_{10} \tilde{v}_p = 4$ in Fig. 4(b). This boundary marks the instability of the slipping mode. Since clutches are barely engaged $P_b \ll 1$ for slipping solution, we have $z = \tilde{\zeta}/P_b \gg 1$. In this scenario, $a_{22} \approx -y(1+x)e^x/(1+y)$. We prove that the unstable condition of the slipping mode must be governed by a Hopf bifurcation (Sec. C and Fig. S2(A) of the Supplemental Material [43]); therefore, the boundary of the slipping mode is $\text{tr}(A) = 0$, i.e., $y + 1 = (x + 1)/(2 + \alpha e^{-x})$, which is simplified as $y = (x - 1)/2$ using $\alpha e^{-x} \ll 1$ (recall that $P_b = \alpha/(\alpha + e^x) \ll 1$). Consequently, the unstable condition becomes $\tilde{E} = (\tilde{F} - P_b)/2 \approx \tilde{F}/2$ or $F/E \sim F_b/k_c$ in physical units, which has a clear physical meaning: A significant substrate deformation relative to the maximal clutch elongation leads to stick-slip motion.

Another boundary of the slipping mode appears at the bistable phase at low substrate friction $\tilde{\zeta}$, corresponding to the purple dot-dashed line shown in Fig. 4(b). This boundary can be derived by requiring the existence of a slipping solution in Eq. (3) when $\tilde{\zeta} \ll 1$, which means a saddle-node bifurcation. Specifically, it corresponds to the minimal $\tilde{v}_p$ that guarantees three fixed points in Eq. (3) (Sec. B of the Supplemental Material [43]). In summary, the boundary of the slipping mode is defined by the onset of either the instability condition or the existence condition, depending on which one is encountered first as $\tilde{v}_p$ decreases from a large value:

$$\text{slipping boundary} \begin{cases} \tilde{E} = \frac{\tilde{F} - P_b}{2} \approx \frac{\tilde{F}}{2}, \\ \tilde{v}_p = \sqrt{\frac{\alpha}{\tilde{\zeta}}} \ln\left(\frac{\alpha}{\tilde{\zeta}}\right) \quad (\tilde{\zeta} \ll 1). \end{cases} \quad (10)$$

We summarize Eqs. (9) and (10) in Fig. 4, and leave a comprehensive discussion on the transition mechanisms between modes in Sec. C and Table S2 of the Supplemental Material [43]. We remark that at high substrate friction [Fig. 4(a)], the entire boundary of the stick-slip mode is governed by Hopf bifurcation (Fig. S2(A) of the Supplemental Material [43]), on which both discontinuous and continuous Hopf bifurcations occur, separated by a generalized Hopf bifurcation point [40] [the red cross in Fig. 4(a)]. A discontinuous Hopf bifurcation induces the transition between the gripping mode and the stick-slip mode: Crossing the boundary between the gripping and stick-slip modes—for instance, by increasing $\tilde{E}$ —transforms the unstable gripping solution into a stable

fixed point and generates an unstable limit cycle nearby (Fig. S3(A) of the Supplemental Material [43]). The global limit cycle, corresponding to the macro stick-slip loop in the grippinglike submode, persists until it collides with the unstable limit cycle, resulting in a hysteresis loop in the migration modes (Fig. S3(A) of the Supplemental Material [43]). Thus, even when the system exhibits only one fixed point for $\tilde{\zeta} > \tilde{\zeta}_c$, the gripping mode and the stick-slip model can still coexist near the phase boundary.

When the slipping mode becomes unstable, it undergoes a continuous Hopf bifurcation, producing a stable micro limit cycle corresponding to the slippinglike submode (Figs. S3(B) and S4(B) of the Supplemental Material [43]). If a stable gripping mode also exists, the two modes coexist, as illustrated by the vertically striped region in Fig. 4(b). However, the limit cycle generated by the continuous Hopf bifurcation does not persist indefinitely. As $\tilde{v}_p$ gradually decreases, it eventually collides with the middle solution of Eq. (3)—a saddle point—leading to a homoclinic bifurcation (Fig. S4(B) of the Supplemental Material [43]), after which only the stable gripping mode remains. Consequently, this coexistence region does not extend to the saddle-node boundary of the slipping mode when $\tilde{\zeta} \ll 1$ [Eq. (10)]. We remark that the slippinglike submode cannot persist if the saddle point is close to the slipping solution of Eq. (3) or if $\tilde{E} \tilde{v}_p \sim \alpha$, where the micro stick-slip loop gradually expands to the macro loop (see the transition between the slippinglike and grippinglike submodes in Figs. 3(b) and S4(A) of the Supplemental Material [43]).

VII. DISCUSSION

By generalizing the motor-clutch model to the whole-cell level and using a mean-field approximation, we systematically investigate how actin polymerization speed, substrate stiffness, and friction govern cell migration. Compared with previous mean-field descriptions of the motor-clutch model [17,24,25,31,32], we take account of the dissipation of the traction force during the clutch dissociation process, i.e., the $\tilde{F} \exp(\tilde{F}/P_b)$ term in Eq. (2). Despite its minimal nature, our model provides key insights into the physical mechanisms of distinct migration modes, substrate stiffness sensing, and cell-to-cell variability during migration.

We identify three distinct migration modes [Fig. 2(a)]. In the gripping mode, strong clutch engagement ensures efficient traction force transmission, and the migration speed increases monotonically with the actin polymerization speed [Eq. (4)]. Conversely, the slipping mode converts actin polymerization speed primarily into retrograde flow rather than cell migration, and the migration speed decreases as the actin polymerization speed increases [Eq. (4)]. Notably, these two stable migration modes can coexist at low substrate friction but transition continuously at high friction. Our model also predicts a biphasic relationship between the migration speed and the actin retrograde speed, in agreement with previous experiments [47].

Remarkably, the migration speed in the two stable modes is independent of substrate stiffness, which means that the cell can only sense substrate stiffness in the stick-slip mode. Importantly, the stick-slip mode can be classified into two submodes: the grippinglike submode, characterized by macro stick-slip loops with substantial clutch engagement and fast

cell migration, and the slippinglike submode, involving small loops with negligible clutch engagement and slow migration. In between, an optimal substrate stiffness maximizes the migration speed and the traction force in the stick-slip mode. Therefore, on a substrate with a stiffness gradient, cells preferentially migrate toward this optimal stiffness, which serves as the critical threshold separating durotaxis from negative durotaxis [48]. Interestingly, the optimal stiffness scales as $E^* v_p \sim N F_b r_{on}$, with the maximal migration speed $\langle v_m^{\max} \rangle \sim N F_b / \zeta$, independent of the actin polymerization speed. When the substrate stiffness is significantly lower than the optimal value, the timescale of clutch binding and dissociation is much faster than that of traction force accumulation, making the grippinglike stick-slip loop a quasistatic process. In this case, the maximum traction force triggering overall rupture equals the maximal traction force achievable in the gripping mode (F_*), leading to a constant average migration speed [Fig. 3(f)].

These theoretical predictions find support in experimental observations of neutrophil migration on substrates of varying stiffness [49]. Specifically, the biphasic relationship between migration speed and substrate stiffness predicted by our model is in qualitative agreement with the findings of Ref. [49]. Moreover, our model predicts that the maximal migration speed in the stick-slip regime scales with the total number of available clutches as $\langle v_m^{\max} \rangle \sim N F_b / \zeta$. This is consistent with the experimental results of Ref. [49], which demonstrated that a lower fibronectin concentration, corresponding to a reduced number of available clutches (N), leads to a significant decrease in the maximal track speed. However, Ref. [49] also observed that the optimal stiffness for migration increases as the fibronectin concentration decreases, which seemingly contradicts our model's scaling relation $E^* \sim N$. This discrepancy may arise from a biological compensatory mechanism: A low-density environment of adhesion ligands might trigger intracellular signaling pathways that upregulate the clutch association rate (r_{on}), leading to an increase in the optimal stiffness $E^* \sim N F_b r_{on} / v_p$ that could potentially overcompensate the decrease in N . Such complex biological regulations are beyond the scope of our current minimal model but present an exciting avenue for future research.

Beyond experimental validation, it is instructive to compare our approach with other theoretical frameworks. Our model is complementary to the one-dimensional (1D) model of stick-slip dynamics by Ron *et al.* [50]. While both models investigate the transition between smooth and stick-slip motion, they focus on different core mechanisms. Ron *et al.*'s model emphasizes an internal biological feedback loop, where the cell's length dynamically regulates protrusion speed via a universal cytoskeletal polarity mechanism on a rigid substrate. In their framework, stick-slip dynamics are driven by the avalanchelike detachment of clutches at the cell rear. In contrast, our model focuses on the role of external mechanics, explicitly incorporating substrate elasticity as a key parameter that couples with clutch dynamics to govern the migration mode.

Our model predicts that an isogenic population of cells can exhibit multiple migration modes in the same mechanical environment. First, the stable gripping and slipping modes can

coexist in the bistable region under low substrate friction [see the horizontal-stripe region in Fig. 4(b)]. Moreover, since the slipping mode is destabilized through a continuous Hopf bifurcation, the slippinglike stick-slip submode can coexist with the gripping mode [see the vertical-stripe region in Fig. 4(b)]. In contrast, the transition from the gripping mode to the grippinglike stick-slip submode must follow a discontinuous Hopf bifurcation under high substrate friction, leading to a hysteresis loop such that the grippinglike submode can coexist with the gripping mode (Fig. S3(A) of the Supplemental Material [43]).

Regarding molecular motors, our model treats myosin II contractility as an internal force that does not directly contribute to net propulsion. This view is consistent with simplified systems where actin polymerization alone can drive motility, such as actin lamellar fragments [51] or *Listeria* propulsion [52]. This perspective rationalizes observations that myosin activity does not always affect migration speed [15,53–55] and that cell migration can be powered by actin assembly alone [45]. However, we acknowledge the crucial and complex role of myosin II in the migration of many cell types. Myosin II plays significant indirect roles, such as maintaining cell polarity, regulating adhesion maturation, and generating intracellular tension. For example, myosin IIB is vital for stabilizing polarity in fibroblasts [56], while myosin IIA facilitates rear adhesion detachment in migrating T cells [57] and is required for adhesion maturation in restrictive environments [58]. Moreover, myosin-generated tension can pull the cell body forward during neuronal migration [59]. Consequently, the effect of myosin II on migration speed is highly context dependent. While its inhibition can slow migration in some contexts [60,61], its depletion can also increase migration speed in others, potentially by shifting the balance between cytoskeletal systems [62]. Therefore, perturbations in myosin II activity can induce complex physiological changes that affect multiple parameters in our model, leading to diverse and sometimes contradictory effects on migration speed observed experimentally.

In the future, it will be exciting to incorporate more complex biological effects into the cell migration model in future work, such as focal adhesion reinforcement [27,34], biochemical feedback loops on cytoskeletal activity—including Rac- and Rho-GTPase signaling [63,64], the roles of membrane tension [21], contractility-driven cell motility [65], and periodic force dipoles in driving spontaneous polarization [66].

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DATA AVAILABILITY

The data that support the findings of this article are not publicly available. The data are available from the authors upon reasonable request.

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