Crawling of a driven adherent membrane

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We discuss motions of an elastic N × M membrane model whose constituents can bind reversibly with strength ε to adhesive sites of a flat substrate. One of the edges of the membrane (“front”) is driven in one direction at rate constant p by N stochastically treadmilling short parallel lines (“cortex”). The main conclusions derived from Monte Carlo studies of this model are the following: (a) Since the polymerizing cortex pushes only the leading edge of the membrane, the major part of the membranes is dragged behind. Therefore, the locomotion of the membrane can be described by frictional sliding processes which are asymmetrically distributed between front and rear of the membrane. A signature of this asymmetry is the difference between the life times of adhesion bonds at front and rear, τ₁ and τₘ, respectively, where τ₁ ≫ τₘ. (b) There are four characteristic times for the membrane motion: The first time, T₀ ∼ τₘ ∼ ε⁻³², is the resting time where the displacement of the membrane is practically zero. The second time, Tₚ ∼ τ₁ ∼ M, is the friction time which characterizes the time between two consecutive ruptures of adhesion bonds at the front, and which signals the onset of drift (“protrusion”) at the leading edge. The third time, Tᵣ ∼ M⁻¹(γ > 1), characterizes the “retraction” of the trailing edge, which is the retarded response to the pulling leading edge. The fourth time, Tₐ ∼ M², is the growth time for fluctuation of the end-to-end distance. (c) The separation of time scales, Tₚ/Tₚ ∼ M⁻¹(γ) −¹, leads to stretched fluctuations of the end-to-end distance, which are considered as stochastic cycles of protrusion and retraction on the time scale of Tₐ. (d) The drift velocity v obeys anomalous scaling, v/p ∼ f(p¹/γ(ε)M), where f(z) ∼ const. for small drag pM ≪ 1, and f(z) ∼ z⁻¹(ε) for pM ≫ 1, which implies v ∼ M⁻¹(ε). These results may also turn out to be useful for the (more difficult) problem of understanding the protrusion-retraction cycle of crawling biological cells. We compare our model and our results to previous two-particle theories for membrane protrusion and to known stochastic friction models. © 2012 American Institute of Physics. [http://dx.doi.org/10.1063/1.4757664]

I. INTRODUCTION

The present study is motivated by the biological phenomena of crawling of a cell over flat adhesive substrates. The motility of adherent biological cells proceeds by cycles of edge protrusion, adhesion, and retraction.1–6 How these functions are coordinated by biochemical and/or mechanical processes is important to know in order to understand several biological phenomena related to cell migration in tissues and during self-organization of cells. The basic molecular mechanisms underlying the locomotion of adherent cells are thought to be shared by different cell types, including those that appear morphologically distinct. Such locomotion is usually regarded as a single complex phenomenon, which is the dynamic interplay of various processes such as cell-substratum adhesion, actin-driven extension of the leading cell edge, and retraction of the trailing cell edge. For continued locomotion extension and retraction must be regulated both spatially and temporally. Several attempts to model cell motility have been published.7,8 After the pioneering work of Oster and co-workers9–11 introducing the concept of Brownian ratchets to explain protrusive forces, models of networks of actin filaments,12,13 and of adhesive gels14,15 have been studied to elucidate the physical mechanism of cell locomotion. In other attempts, computer simulations have been used to study the crawling of a nematode sperm16,17 and the force-velocity relationship during cell crawling18 and Listeria propulsion.19

Inspired by these previous investigations, we consider in the present paper some specific aspects of a membrane sliding over an adhesive substrate, similar as in models of friction20,21 and earthquakes.22 In particular, we are interested in the effects of the size of the membrane and how the asymmetry between the driven leading edge and the trailing edge of the membrane dictates its velocity and its conformation. We employ a simple model system consisting of a two-dimensional elastic membrane and a discrete adhesive substrate, which are coupled to each other by breakable harmonic bonds. The leading edge of the membrane is driven in one direction by advancing short lines (“cortex”). The general predictions of the model as the M-dependency of velocity and membrane stretching may be related to certain types of biological cells8,23 and could be tested by experiments.

II. MODEL AND SIMULATION METHOD

A. Surface model

We consider an elastic surface in two dimensions described by N × M coordinates on a square lattice with lattice spacing a = 1, which scales all lengths in our model system.
The membrane has \( N \) columns labeled by \( 1 \leq i \leq N \) (in \( x \) direction) and \( M \) rows labeled by \( 1 \leq k \leq M \) (in \( y \) direction). Each of the constituents (“particles”) of the membrane can perform stochastic movements along the columns only. In this sense, the membrane model is an effective one-dimensional model. The movements of the membrane particles, located at \( x_{ik}^{(m)}, y_{ik}^{(m)} \), are restricted by four springs connecting a particle at \( (i, k) \) to its nearest neighbors \( (i \pm 1, k, k \pm 1) \). We used periodic boundary conditions in \( x \) direction for each row \( k \). The first row, \( k = 1 \), and the last row, \( k = M \), are called leading (LE) and trailing (TE) edge of the membrane, respectively. They are free boundaries in both \( y \) directions. If not otherwise stated, we restrict our studies (for the sake of saving computer time) to stripes of width \( N = 5 \); larger values do not change qualitatively the results. Since a membrane has a finite extensibility, we employed the harmonic-tether approximation, i.e., the membrane particles are connected by truncated harmonic springs

\[
U_m(\ell) = \frac{\kappa}{2}(\ell - b)^2, \quad \text{if} \quad \ell < \Delta b, \tag{2.1}
\]

where \( \ell^2 = (x_{ik}^{(m)} - x_{ik+1,k+1}^{(m)})^2 + (y_{ik}^{(m)} - y_{ik+1,k+1}^{(m)})^2 \) is the bond length, \( U_m(\ell) = \infty \) for \( \ell > \Delta b = 9 \), and \( \kappa \) is the elasticity constant in units of \( \text{energy/length}^2 \). If not otherwise stated, we used \( \kappa = 0.2 \) and the equilibrium bond length \( b = 3 \). Throughout the paper all energy constants are given in units of \( k_B T \), where \( k_B \) is the Boltzmann constant and \( T \) is the absolute temperature. We consider a “self-avoiding membrane” where double occupancy of lattice sites by membrane particles is excluded.

B. Adhesion

The adhesion of a cell to its environment is mediated by transmembrane receptors and corresponding adhesive proteins (ligands) of an extracellular matrix on a flat substratum. An important example of such transmembrane receptors is the integrin family which plays a key role in cell adhesion during assembly of multimolecular complexes that couple to the adhesive proteins and to the actin cytoskeleton.24–26

We consider the case where each membrane particle carries a molecule which can bind to one of the adhesive sites, \( y_{ij}^{(s)} \), of a substrate on the square lattice. In analogy to biological systems, we may use for these molecules the term “integrin” as a technical term. These “integrins” can be in either of the two states: bound (“occupied”) and unbound (“unoccupied”). We do not consider here the case where the number of integrins \( N_I \) is diluted, \( N_I < M \), where diffusion of integrins in the membrane plays an important role.27,28 Hence, we consider only the case \( N_I = M \). Each adhesion site of the substrate can be bound to only one integrin. Binding of one adhesion site to more than one integrin is excluded. The energy of an integrin bond is given by a truncated harmonic potential

\[
U_s(\ell) = \begin{cases} 
(k_s/2)\ell^2 : & \ell < b_s, \\
(k_s/2)b_s^2 + \varepsilon : & \ell = b_s, \\
0 : & \ell > b_s, 
\end{cases} \tag{2.2}
\]

where \( \ell = y_{ik}^{(m)} - y_{ij}^{(s)} \) is the bond length, \( b_s = 6 \) is the maximal bond length, and \( \kappa_s = 0.02 \) is the stiffness of the bond. The rupture of an occupied integrin bond may take place during a Monte Carlo step if the attempted move exceeds the energy \( U_s(b_s) \), where \( \varepsilon \) is the threshold energy. It would be of interest to calculate the local friction force which is proportional to the membrane’s local velocity. However, since from a computational point of view this quantity has large statistical uncertainties, we rather define a dimensionless quantity called the “local pinning force,” which characterizes the strain of the adhesion bonds between the membrane particle at \( y_{ik}^{(m)} \) and the substrate site at \( y_{ij}^{(s)} \). The average is taken over row \( k \) of the membrane

\[
F_k = -\frac{1}{\kappa_s b_s} \frac{dU_s}{d\ell} = \frac{1}{Nb_s} \sum_{i,j} \left[ y_{ik}^{(m)} - y_{ij}^{(s)} \right] \sigma_{ik,ij}, \tag{2.3}
\]

where \( \sigma_{ik,ij} \) is the “occupation variable”

\[
\sigma_{ik,ij} = \begin{cases} 
0 : & \text{integrin unoccupied}, \\
1 : & \text{integrin occupied}, 
\end{cases} \tag{2.4}
\]

where the substrate indices are \(-\infty < (i, j) < +\infty \). We also define the “occupation site” \( S_k \) of the substrate, which is the average site of the substrate to which the membrane particles in row \( k \) are bound

\[
S_k = \frac{1}{Nb_s} \sum_{i,j} y_{ij}^{(s)} \sigma_{ik,ij}. \tag{2.5}
\]

A typical snapshot of membrane and adhesion sites is depicted in Fig. 1. We consider also the special case of a “freely driven” membrane, i.e., without adhesion to a substrate (\( N_I = 0 \)). This situation is important both from theoretical and experimental point of view. It is well known that the force generated by the actin network growing below the leading edge of the plasma membrane simultaneously causes the membrane to protrude and pushes the cortex backwards. It was commonly thought this would lead to an annihilation of protrusive and backsliding movements and would yield zero average movement of the cell. Therefore, as a kind of paradigm, it was commonly assumed that adhesion sites at the lamellipodium are required to generate traction by transmitting the retrograde force of actin polymerization to a substrate.2 Recent experiments, however, have indicated that within confined environments integrin-mediated force coupling is dispensable for locomotion.29,30 and it was demonstrated that actin polymerization rate was adjusted such that the protrusion velocity remains constant when the cell changed from adhesive to non-adhesive substrates. These findings are also consistent with recent theoretical studies on driven boundaries31 and on a two-particle model.32

C. The cortex

Two actin networks – the lamellipodium and the lamella – occupy the front position of migrating cells.33–35 The lamellipodium is localized to a 1–3 \( \mu \text{m} \) band near the leading edge of the cell membrane. The lamella is a more stable network occupies a wider band (15 \( \mu \text{m} \)). Experiments30,36–38 indicate that the polymerization of actin filaments at their fast...
In most cases the actin filaments are organized as a branched network.\(^7,35\) But in various cell types it was also found\(^9\) that the actin filaments are organized as dense ensembles of unbranched actin filaments in the lamellipodium. Their packing near the leading edge is almost parallel and perpendicular oriented towards the membrane.\(^33,39\) Therefore, we assume a model where the filaments are placed in parallel on the square lattice and perpendicular to the leading edge, which is the first row of our membrane model, \(k = 1\).

Defining the \(y\)-coordinates of the “plus ends” of the filaments by \(y_{i1}^{(a)}\) (which is the green line in Fig. 1(b)), the interaction between the “plus ends” and the leading edge of the membrane is taken to be purely repulsive such that \(y_{i1}^{(a)} \leq y_{1,1}^{(m)}\) at all times.

Since in many cases the adenosine triphosphate (ATP)-mediated polymerization rate of actin filaments at their the “plus ends” is much larger than its depolymerization rate,\(^35\) we neglect depolymerization at the plus end. And vice versa, we neglect polymerization at the “minus end.” Assuming furthermore that association, \(p^+\), and dissociation, \(p^-\), at plus and minus ends, respectively, take place with the same rate 0 \(p \equiv p^+ = p^- \leq 1\), then we have the case of “treadmilling” filaments. Neglecting nucleation of actin filaments,\(^40,41\) we have to assume that the length \(N_F\) of each filament is always \(N_F \geq 2\). Since the successful attempts of association at the plus ends are limited by the repulsion of the membrane, which is in contrast to the minus end where depolymerization is not limited, the length of the filaments shrinks to an average size \(\langle N_F \rangle \approx 3\). Henceforth, we use the word “cortex” as a technical term for this simple model of a filament ensemble.

**D. Remarks and implications**

Without polymerization \((p = 0)\), the Monte Carlo (MC) method provides a force balance for the whole system, which can be monitored indirectly by various quantities, for example, by its symmetrical diffusional displacements as function of time. Of course, since Newton’s law is not employed during MC (in contrast to molecular dynamics simulations), a local force balance is not provided, and hence momentum is not conserved at the microscopic level. Instead, there is an energy balance of the elastic and “entropic” forces of the membrane, on one hand, and the polymerization force,\(^9\) on the other hand, which is related to the attempts of adding a particle at the filament’s front, thereby prohibiting subsequent backflow of the leading edge of the membrane. In this sense, the growing cortex \((p > 0)\) has to be considered as an “internal” force which is opposed and balanced by the fluctuating leading edge of the membrane. This is different from previous approaches\(^18,19\) where a fixed “external” load force on the lamellipod had to be imposed in order to balance the force from the filaments on the leading edge. As a consequence, the probability of successful polymerization attempts, \((p)\), is such that \((p)/p < 1\).

The adhering membrane advances by polymerization at the leading edge of the cortex. It should be emphasized that this is a special type of driven advancements, where only the flux balance can be dispensable in theoretical considerations of sliding effects of membranes on adhesive substrates.
leading edge of the membrane experiences the polymerization force, whereas the remaining part of the membrane is dragged in response to this force, thereby trying to reconcile membrane elasticity and membrane adhesion. At sufficiently large advancements the adhesion points undergo ruptures.

The polymerization is a far from equilibrium phenomenon which needs a supply of external energy, usually ATP. The free energy gain is the source of energy for the locomotion. The subsequent dissipation is repeatedly provided by the local membrane contractions followed after the rupture of adhesion bonds.

Since the MC method is based on the principle of “detailed balance,” it is of interest to know how far this principle is valid in a driven system. The latter case is similar to MC studies on quenched systems such binary alloys and others. For the present system it seems conceivable that as long as the typical time between successive polymerization steps at the front, $\Delta t \sim (\ell/k)^{-1}$, is large as compared to a typical time needed to relax at least a few steps from these perturbed states towards equilibrium, the detailed balance can be assumed to be valid. In contrast, considering the situation of a very large polymerization rate, $p = 1$, detailed balance is probably not valid, because after each fluctuation of the leading edge of the membrane away from the tip of the filament, an immediate subsequent polymerization step prohibits the membrane to relax symmetrically.

E. Simulation protocol

One Monte Carlo time step refers to updating all particles of membrane, integrins, and cortex in the model. In the case of a single column $N = 1$, we select at random from a string $M + N_I + N_F$, one of the particles from the ensemble of membrane, integrins, and filaments.

If one of the membrane particles is chosen, then it performs a random displacement where the energy difference $\Delta U_m = [U_m(l') - U_m(l)]$ of the new and the old membrane bonds, $l'$ and $l$, respectively, and, if this particle site carries an integrin, of the integrin-substrate bond, $\Delta U_s$, are used for the Metropolis criterion. The movement of the membrane is accepted by the standard Metropolis criterion employed in Monte Carlo simulations with probability $r = \exp\{-\Delta U_m - \Delta U_s\}$, where $0 < r < 1$ is a random number.

If one of the integrin particles is selected, then it is decided with probability $0 < q_I \leq 1$ whether the formation of a new integrin bond (if it does not exit yet) takes place at this site. In the present work, we employed $q_I = 1/2$.

If one of the cortex particles is selected, then, if one of the two ends of the filament is chosen, a polymerization at the front or depolymerization at the rear is attempted with probability $0 < p \leq 1$. A polymerization attempt is successful if the membrane-cortex condition $y^{(m)}_i < y^{(m)}_{i+1}$ is fulfilled.

III. RESULTS

A. Membrane stretching

We have tested the case of the non-adherent ($q_I = 0$), non-driven ($p = 0$) membranes in order to test the validity of the dynamics of the model. As expected the root mean square displacement of the center-of-mass of the $N \times M$ membrane exhibits regular diffusion, $y(t) \sim \sqrt{t/M}$, and the average end-to-end distance of the membrane is linear in $M$, $L \approx A_0 M$, where

$$L = \frac{1}{N b} \sum_{i=1}^{N} \left( y^{(m)}_{i} - y^{(m)}_{i+1} \right),$$

and the prefactor $A_0$ of $L$ depends on the elasticity constant $k$ (e.g., $A_0 = 1.146$ for $k = 0.2$).

If, however, one edge of the membrane is pushed constantly by the advancing cortex, then the membrane is asymmetrically stretched. The strain of membrane bonds between two successive rows, $k$ and $k+1$, in the direction of drift is given by

$$L_k = \frac{1}{N b} \sum_{i=1}^{N} \left| y^{(m)}_{i,k} - y^{(m)}_{i,k+1} \right|.$$  \hspace{1cm} (3.2)

The membrane is gradually stretched from its rear ($k/M = 1$) to its front ($k/M = 1/M$) (Fig. 2). Similarly, the local pinning force $F_k$ (Eq. (2.3)) shows that the integrin-substrate bonds are stretched as well near the front which is shown in Fig. 3.

The overall stretching of the membrane can be measured by the end-to-end distance $L$, which is characterized by a function $f(z)$ according to

$$L/M \sim f(p M),$$

which is shown in Figs. 4(a) and 4(b). The scaling variable $p M$ has the dimension of a velocity, because $a M$ and the polymerization rate $p$ have dimensions of length and frequency, respectively. Since the membrane is pushed only at its front at rate $p$, the whole rest of the membrane is “dragged” forward in the same direction. Therefore, the longer the membrane the larger the “drag velocity” $p M$.

For non-adherent membranes ($\varepsilon = 0$), the scaling function $f(z)$ shows a smooth sigmoidal transition to a constant value $L/M \approx 2.3$ (Fig. 4(a), red curve). The inflection point,
at about $pM \approx 1$, separates the two regimes of low and high drag, $pM \ll 1$ and $pM \gg 1$, respectively. The saturation $LM = \text{const.}$ for $pM \gg 1$ indicates that for fixed $p$ and increasing $M$, the conformation of the membrane separates into two regimes: a front part near the leading edge of the membrane which is strongly stretched by the polymerizing cortex, and a trailing part of the membrane, which is less stretched and is dragged behind (compare also Fig. 2). For the case $\epsilon = 0$, a good fit for the two regimes is given by the function
\begin{equation}
    f(z) \sim \begin{cases} 
        1.13 + 0.7z^{0.6}, & \quad z < 1 \\
        2.32(1 - 0.25z^{-0.75}), & \quad z > 1,
    \end{cases} \tag{3.4}
\end{equation}
which shows the nonlinearity of the deformation of a dragged elastic membrane.

For adherent membranes ($\epsilon > 0$) and $pM < 1$, the relation (3.3) remains valid for each $\epsilon$ and the inflection point is shifted towards smaller values of $pM$. For $pM \gg 1$, however, relation (3.3) becomes invalid. In the regime of high drag $pM$, the curves for each $\epsilon$ split off for different values of $p$ and exhibit maxima at different $pM$. Similar observation is obtained for $\epsilon = 4$ and for $\epsilon = 6$ which is shown in Fig. 4(b). The maxima of $LM$, which appears at high drag and for all adhesion strengths $\epsilon \geq 1$, is related to different internal stretching $L_k$ with increasing size $M$ of the membrane. The inset in Fig. 2 shows for the case $\epsilon = 1$, $p = 1.0$ that with increasing membrane size $M$, the stretching of $L_k$ becomes smaller, and hence, according to the relation $L = 1/(M - 1) \sum_{k=1}^{M-1} L_k$, $L$ becomes smaller with increasing $pM$. This explains the maxima in Fig. 4. The physical reason for the different behavior of $L_k$ with increasing $M$ could be the following. The membrane exhibits two different internal stretching regimes. At short distance from the leading edge, there is a strong response dominated by the polymerization processes, whereas with larger distances from the leading edge the response becomes weaker and the adhesion dominates. The two curves in Fig. 2 for $\epsilon = 6$, which show a slight transition between front and rear, seems to corroborate this explanation. However, it should be noted that from an experimental point of view the regime of high drag $pM \gg 1$ may not be accessible because real membranes have viscoelastic properties\textsuperscript{43} with fluid-like behavior, which probably prohibits this high limit of membrane stretching. But still, the phenomena of two conformational different regimes of the membrane, one near the leading edge and a second regime far away, is a typical signature of this driven-dragged system. Similar observations are made for the life times of membrane-substrate (“integrin”) bonds which is discussed in Sec. III B.

### B. Frictional sliding

The time-averaged root mean-square deviation (RMSD) of the coordinate $y(t)$,
\begin{equation}
    d y(t) = \sqrt{(y(t') - y(t' + t))^2} dt', \tag{3.5}
\end{equation}
describes the time-dependent displacements of the center-of-mass of the membrane (CM), the leading edge of the membrane (LE), and the trailing edge of the membrane (TE). This is shown in Fig. 5 for one set of parameters ($M = 160$, $\epsilon = 6$, $p = 0.001$).
$p = 0.1$). In addition, the figure contains the RMSD of the end-to-end distance $L/M$, Eq. (3.1), and the local pinning force $F_1$, Eq. (2.3), at the LE. It is observed that the center of mass exhibits a crossover between diffusion at very short times ($t < 100$) and a drift at large times, $t \gg T_p$, which is separated by extremely slow subdiffusion, the “resting regime,”

$$d_{\text{cm}}(t) \sim \begin{cases} \text{const.} & t < T_0 \\ \nu t & t \gg T_p. \end{cases}$$  

(3.6)

Similar to CM the RMSD of the trailing edge (TE) is almost constant in the first regime, but its magnitude is larger by a factor of 8. This is followed by a long crossover in the second and third regime before the TE starts to drift at a characteristic time $T_L$. The leading edge (LE) does not exhibit a plateau, but rather a long crossover until it starts to drift about the time $T_p$. The time $T_p$ is also the characteristic time for the local friction force $F_1$, Eq. (2.3). Its RMSD, $dF_1(t)$, increases approximately as $\sqrt{t}$ until a saturation at $t > T_p$ occurs. Since $F_1$ characterizes the stretching of the integrin bond at the LE, $T_p$ is the average time when ruptures of integrin bonds at the LE occur. This is discussed in more details below. $T_L$ is the time when the membrane needs to move a distance approximately of its own length $L$, $d_{\text{cm}}(T_L) \approx L$, and which is also the time for the fluctuation of the end-to-end distance of the membrane to grow until its saturation. This is discussed in Sec. III D.

It is instructive to estimate the average life time of integrin occupation and analyze the rupture events in more details. Figure 6 shows the time trajectories of occupation sites $S_k(t)$, Eq. (2.5), for three different membrane rows: LE ($k = 1$), TE ($k = M$), and the middle one ($k = M/2$). The occupation site is the average location of sites on the substrate to which the row $k$ of the membrane is bound. It is observed that $S_1(t)$ for the LE of the membrane advances after an average dwell time $\tau_1 (\approx 10^5$ in Fig. 6). In contrast, the $S_M(t)$ of the TE of the membrane performs random motions at short time with a bias towards the front. The corresponding average life time of these integrin bonds is much shorter, $\tau_M \ll \tau_1$.

The estimated average life times $\tau_k$ of integrin bonds for all rows $k$ and for different $M$ are shown in Fig. 7. At the front, the life time depends on the size of the membrane, $\tau_1 \sim M$, whereas at the rear the life time $\tau_M$ is independent of $M$. Both life times, $\tau_1$ and $\tau_M$, depends exponentially on the adhesion strength and are independent of $p$ (Fig. 8),

$$\tau_1 = A e^{\alpha M},$$

$$\tau_M = B e^{\alpha},$$

(3.7)

where $A$ is a constant and $B/A \approx 30$.

The explanation for $\tau_k$ is as follows. The bond fluctuations of the integrins are increasingly reduced towards the front by the filament-induced stretching of the membrane and the concomitant stretching of integrin bonds (compare Figs. 2 and 3). This implies that at the front the binding of the membrane by integrins to the substrate is more stable and hence their life times $\tau_k$ are longer than at the rear. Such a situation where locally reduced entropic fluctuation favors bound states is common in other physical phenomena. For example, a similar situation is encountered during aggregation of mobile adhesion bonds.\textsuperscript{27,44} when one integrin molecule adheres to the

FIG. 5. RMSD $d_y(t)$ of an adherent membrane ($M = 160, \varepsilon = 6, p = 0.1$).

FIG. 6. Location of integrin bonds, $S_k(t)$, at membrane site $k$ as function of time for $k = 1$ (LE), $k = M$ (TE), and $k = M/2$ (parameters: $M = 160, \varepsilon = 6, p = 0.1$).

FIG. 7. Average life time, $\tau_k$, of integrin bonds at membrane row $k$.  

FIG. 8. Average life time, $\tau_k$, of integrin bonds at membrane row $k$.
substrate, it suppresses locally membrane fluctuations; then this region acts as an attractor for other integrins; this process increases collectively the life time of such integrin patches, and hence \( \tau_1 \gg \tau_M \). Indeed, it can be shown that for low densities and for small diffusivity of integrins, the integrins aggregate near the front of the membrane (to be published).

In general, one can describe the different time scales \( \tau_k \) as the result of two antagonistic processes: the integrins, the agonists, which are characterized by the parameter \( \varepsilon \), make a resistance against rapid movements, whereas the cortex, the antagonist, which is characterized by the parameter \( k \), tries to enforce rapid movements. Since the antagonists are distributed very asymmetrically, namely, at one end of the agonist’s population, the result is a separation into two different dynamical behaviors of the membrane at its front and at its rear, which is reflected by the distribution of the time scales \( \tau_k \) (Fig. 7). This characterization of the system by a front and a rear part is in qualitative agreement with previous observations \(^{14}\) on an adhesive gel which exhibits an adhesive aggregate near the front of the membrane (to be published).

Since the life time \( \tau_1 \) of integrin-substrate bonds at the front depends linearly on \( M \), one may consider that \( \tau_1 \) is related to a “transport process.” Therefore, one may consider \( \tau_1 \) as the typical time required for \( M \) sequential rupture-occupation events which propagate along the membrane towards the front (compare Fig. 6) in order to induce the rupture needed for the advancement of the LE. Therefore, one may identify

\[
\tau_1 \sim \tau_1. \tag{3.8}
\]

The time \( \tau_M \) between ruptures at the TE is independent of \( M \) is related to the resting time \( T_0 \),

\[
T_0 \sim \tau_M, \tag{3.9}
\]

which depends exponentially on the adhesion strength \( \varepsilon \).

### C. Velocity

The time-dependent displacements of the center-of-mass of the membrane exhibit for sufficiently long time a drift with velocity \( v \) which depends on the drag \( pM \). For the non-adherent case (\( \varepsilon = 0 \), Fig. 9), the velocity obeys a scaling function

\[
vM \sim f_1(pM), \tag{3.10}
\]

in the whole range of \( pM \). The inset in Fig. 9 shows a semi-log plot of these data, which have an inflection point around \( pM \approx 1 \), similar as for \( L/M \) in Fig. 4, which indicates the separation in high and low drag regimes. The broken line in Fig. 9, which is \( vM = pM \), clearly shows that only in the limit \( pM \rightarrow 0 \) a linear relationship \( v \sim p \) is valid (compare also Appendix, Fig. 13(b)). In fact, for the special case \( M = 1 \) and \( p \ll 1 \) the velocity has a linear relationship \( v \sim p \), which is in variance with classical two-particles theories.\(^{9,10,32,45}\) The saturation of \( vM \approx 0.785 \) for \( \varepsilon = 0 \) and \( pM \gg 1 \) has a similar origin as the saturation of \( L/M \) (compare Fig. 4(a)): for large drag \( pM \gg 1 \) and large membranes \( M \gg 1 \), the cortex-driven front part near the leading edge of the membrane, which is short ranged, becomes less important as compared to the trailing part of the membrane, which is dragged behind. Therefore, in the limit of \( M \gg 1 \), the velocity becomes \( v \sim M^{-1} \).

For adherent membranes, \( \varepsilon > 0 \), however, we have to assume an anomalous scaling where \( \gamma(\varepsilon) \) is an effective exponent which depends on \( \varepsilon \), and where \( vM' = f_2(p^{1/\gamma}(M) \), \( f_2(z) \sim z' \) for \( z \ll 1 \), and \( f_2(z) = const. \) for \( z \gg 1 \), which implies \( v \sim M^{-\gamma(\varepsilon)} \). This is shown and discussed in the Appendix. The dependency of the velocity on the size of the membrane \( M \) and adhesion strength \( \varepsilon \) is a new prediction which is not included in previous works on cell crawling.\(^{14,17-19}\)

### D. Growth of end-to-end distance

In order to discuss the correlation time of the end-to-end distance, \( T_L \), which was introduced in Sec. III B, we consider the RMSD \( dL(t) \), which describes the average growth of \( L \) in time. This is shown in Fig. 10. It is known that a free harmonic chain (\( \varepsilon = 0, p = 0 \)) exhibits a certain finite-size scaling...
behavior \( dL(t) = M^\alpha f(t/M^2) \) with \( f(x) = \text{const.} \) for \( x \gg 1 \) and \( f(x) \sim x^{3/2} \) for \( x \ll 1 \), and the limiting cases

\[
dL(t) \sim \begin{cases} 
  t^{\alpha/2}: & t \ll T_L \sim M^2 \\
  M^\alpha: & t \gg T_L 
\end{cases} \tag{3.11}
\]

where the dynamical exponent is \( \alpha = 1/2 \). The dynamics of the center-of-mass and of both ends obey the scaling for classical diffusion: \( dy_d(t)/\sqrt{tM^{-1}} \sim f(t/M^2) \). It should be noted that similar crossover scaling as Eq. (3.11) is known for the cases of the free Rouse polymer chain \(^{46}\) and the growth of surfaces.\(^{47}\)

For weak perturbation, i.e., for weak adhesion \( 0 \leq \varepsilon < 1 \) and any rate \( p > 0 \), the crossover scaling (3.11) is essentially the same, which is demonstrated in Fig. 10 by the case \( \varepsilon = 0 \) and \( p = 0.1 \) where \( \alpha \approx 0.47 \). For strong adhesion (\( \varepsilon = 6 \)), however, although the characteristic time \( T_L \sim M^2 \) remains the same, the growth of \( L \) is a very slow crossover between the “resting state,” where \( dL(t) \approx \text{const.} \), and the saturation for \( t > T_L \), where \( dL(\infty) \sim M^{\gamma(\varepsilon)} \). The end of the resting state is signalized by the characteristic time \( T_p \sim M \), which is shown in the lower inset of Fig. 10 by the scaling plot \( dL(t) \) versus \( t/M \). Therefore, in the case of strong adhesion instead (3.11), we have

\[
dL(t) \sim \begin{cases} 
  \text{const.:} & t \ll T_p \sim M \\
  f(t/M): & T_p < t < T_L \sim M^2 \\
  M^{\gamma(\varepsilon)}: & t \gg T_L 
\end{cases} \tag{3.12}
\]

As a consequence, the saturation of fluctuations depends anomalously on \( \varepsilon \) (compare left upper inset of Fig. 10): \( \alpha(\varepsilon) \) decreases with increasing \( \varepsilon \). As an example the crossover scaling for the case \( \varepsilon = 6 \) is shown in Fig. 10 where \( \alpha(\varepsilon) \approx 0.2 \).

Since the front of the membrane is practically prohibited by the cortex to perform retrograde movements, and performs advancements after a dwell time \( T_p \sim \tau \sim M \), this implies that the opposite end of the membrane, the TE, must provide an explanation for the slow crossover between \( T_p \) and \( T_L \). Therefore, it is of interest to examine the RMSDs of the LE and the TE, which are shown in Fig. 11. The RMSD \( dy(t) \) is plotted normalized by the asymptotic behavior \( dy(t) = vt \), where the drift velocity is \( v \sim M^{-\gamma(\varepsilon)} \) (see the Appendix). It confirms the expected crossover scaling for the LE,

\[
dy_{LE}(t)/tM^{-\gamma(\varepsilon)} \sim f(t/T_p), \quad T_p \sim M, \tag{3.13}
\]

whereas the TE exhibits a “retarded” crossover to drift at the characteristic time \( T_r \sim M^{\gamma(\varepsilon)} \),

\[
dy_{TE}(t)/tM^{-\gamma(\varepsilon)} \sim f(t/T_r), \quad T_r \sim M^{\gamma(\varepsilon)}, \tag{3.14}
\]

where similar as for \( \alpha(\varepsilon) \) the exponent \( \gamma \) depends on \( \varepsilon \) (compare inset in Fig. 11). This means that the retardation increases with increasing \( \varepsilon \) and increasing \( M \). Assuming that the retardation factor \( T_r/T_p \) is inversely proportional to the decrease of the end-to-end fluctuation,

\[
\frac{T_r}{T_p} \sim \frac{M^{\gamma(\varepsilon)}}{M^{\alpha(\varepsilon)}}, \tag{3.15}
\]
which is verified by comparing the data for $\alpha(\varepsilon)$ and $\gamma(\varepsilon)$ shown in the insets of Figs. 10 and 11, respectively.

E. Protrusion-retraction cycles

The separation of the membrane’s dynamics according to different time scales, $T_p$ and $T_r$, has some consequences for the type of locomotion of the membrane. This is best evaluated by analyzing the dynamics of the end-to-end distance $L$. Typical examples of the time evolution of $L$ are shown in Fig. 12 for weak and strong adhesion, $\varepsilon = 1$ and $\varepsilon = 7$.

Comparing the two cases it is observed that $L$ performs fluctuations of different time scales: rapid fluctuations at short times which are similar for both $\varepsilon$, although their heights differ, which is in variance with $\alpha(\varepsilon)$. For strong adhesion ($\varepsilon = 7$), however, the end-to-end distance exhibits “large-time” or “retarded” fluctuation which are indicated by the solid black line. The latter fluctuation grows almost periodically on the time scale of $T_L$ such that the end-to-end distance exhibits extensions followed by contractions. It is noted that in both cases of $\varepsilon$ the rate $p$ and the size $M$ are the same. Therefore, this effect must be attributed to the influence of $\varepsilon$, and is reflected by the retardation exponent $\gamma(\varepsilon)$. The LE is advancing at average time $T_L \sim M$, whereas the movements of the pulled TE are retarded by the factor $T_p/T_L \sim M^{\gamma(\varepsilon)}$. This leads to a stretching of $L$ in time until its saturation $dL(\infty) \sim M^{\alpha(\varepsilon)}$ at time $T_L \sim M^2$ takes place. Since the extension-contraction cycles are not strictly periodic in size and separation, one may describe this type of fluctuation as “stochastic cycles of extensions and contractions.” Although the average magnitude of fluctuation is only about 5% of the end-to-end distance, the absolute magnitude for large $M$ is significant and should be visible.

FIG. 12. End-to-end distance, $L(t)$ of the membrane (parameters: $M = 160$, $p = 0.1$).

IV. DISCUSSIONS

A. The model: Limitations and comparisons

The analysis of the simulation data has raised some new physical aspects which could be tested by experiments. However, since the results are based on a specific model we have to address the question about the weaknesses of the model. (1) We have employed an elastic model for the membrane, but experiments have shown that the lipid bilayer membrane has viscoelastic properties.\(^{43}\) (2) Since the membrane model is strictly two-dimensional, entropic repulsion between membrane and substrate caused by membrane undulations are neglected. (3) The cortex model is a strong simplification. The actual polymerization of actin filaments is a much more complicated process.\(^{13, 48}\) (4) In the present study, we neglect the stochasticity of filament couplings to the substrate via the membrane, and we rather assume the filaments always to be strongly attached to the membrane and to be immobile. Therefore, retrograde movements of the filaments are neglected, and hence a flux balance of the polymerizing filament is not included. However, recent experiments have shown that actin coupling to substrates can be dispensable and protrusion still can take place.\(^{30}\) In variance, it can be shown by simulation (unpublished) that inclusion of filament retrograde flow will slow down the speed of locomotion, but not annihilate the directional movements. (5) The Monte Carlo method does not provide a microscopic force balance and hence momentum is not conserved. (6) In the limit of high drag velocities $pM \gg 1$ and high adhesion strength $\varepsilon$, the stretching of the membrane and the drift velocity become anomalous, which is indicated by the the maxima of $L/M$ (Fig. 4(b)) and of $vM$ (Fig. 9), respectively. This may be an artefact attributed to the finite elasticity of the model, because real membrane have viscoelastic properties\(^{43}\) with fluid-like behavior, which prohibits this high limit of membrane stretching. (7) The principle of detailed balance\(^{45}\) becomes invalid for large polymerization rates, $p \rightarrow 1$. This may also play a role for the anomalous behavior of the drift velocity at large drag velocities, $pM \gg 1$.

B. Comparisons to friction models

The present model of a driven adherent surface shares some similarities with known friction models. The Burridge-Knopoff (BK) model\(^{22}\) was proposed as a model to understand the critical event at an earthquake fault during sliding. More elaborated automata models had been studied by Rundle et al.\(^{49, 50}\) and by Olami et al.\(^{51}\) The Frenkel-Kontorova-Tomlinson (FKT) model\(^{20, 21}\) is to the BK model and was proposed to explain dry friction of an adsorbed monolayer on an atomically flat surface. The main difference between the BK and FKT models is the interaction with the lower body. Whereas in the BK model the interaction is replaced by a phenomenological dry friction law (a velocity-weakening law is chosen), in the FKT model the interaction is described by a spatially periodic potential, which defines the hard substrate. There are important differences between these friction models and the present one. (1) In friction models, all atoms of the driven surface are pulled with the same
velocity, whereas in the present crawling model only the front is pulled. (2) The present model membrane has a finite size \( M \) and no periodic boundary conditions are employed in direction of locomotion. Therefore, finite size effects for a driven membrane are significant. (3) Usually, in friction models of the FKT type the \( N \) atoms interact with a one-dimensional sinusoidal potential with a certain energy corrugation and a certain periodicity.\(^{52-54}\) In the present model, the interaction with the substrate is stochastic, which resembles the stretching and rupture of molecular bonds.

**C. Conjectures on cell crawling**

(1) Our current theoretical understanding of membrane protrusion is based on two-particle approximations,\(^9,10,31,32,45\) which do not take into account the size of the cell membrane. It is conceivable, however, that the mass \( M \) of the cell membrane must play a role. The whole membrane has to be pulled and dragged behind solely by the advancing leading edge. The two-particle theory and the theory of a locomoting adhesive gel\(^14\) predicts a linear relationship between the velocity and the polymerization rate, \( v \sim p \), which is consistent with our results for small drag \( pM \ll 1 \) or in the limit \( M \to 1 \). Equations (3.10) and (A3), which implies \( v \sim M^{-\gamma(\varepsilon)} \), are new results. It would be of interest to examine experimentally the dependency of the cell velocity on \( M \). (2) The reported power laws, where the exponents \( \alpha(\varepsilon) \) and \( \gamma(\varepsilon) \) depend on the adhesion strength \( \varepsilon \), can be considered as merely “effective” exponents, which may be replaced in a more accurate analytical formulation by certain functions. However, it may turn out that the various experimentally accessible quantities (\( v, L_k, \tau_k, dL(t) \)) may still be described to a good approximation by these exponents. (3) The reported protrusion-retraction cycle is generic as long as there exists a dynamic asymmetry between the leading and the trailing edge, which is manifested in the present model by the different time scales \( T_p \sim M \) and \( T_r \sim M^\gamma \). However, since in many cases the distribution of integrins at low concentrations is asymmetric with regard to front and rear, it would be of importance to examine whether such protrusion-retraction cycles still exist in this case. (4) It has been reported that the engaged “integrin-actin clutch” turns actin polymerization entirely into protrusion, whereas on disengagement actin undergoes slippage and retrograde flow.\(^30\) Furthermore, it was found that accelerated retrograde flow was balanced by an increased actin polymerization rate.\(^30\) In the present model, the clutch is always engaged. Therefore, actin polymerization is fully converted into protrusion. If the clutch would be “stochastically” engaged-disengaged, we would probably have a different scenario as compared to the present model.

**APPENDIX: ANOMALOUS SCALING FOR LARGE DRAG VELOCITIES**

As noticed in Sec. III C, the velocity obeys for very small drag velocities, \( pM \ll 1 \), a scaling \( vM^\gamma \sim f_1(pM) \). For high drag velocities, this scaling becomes poor. One possibility in order to obtain a reasonable overlap of the data can be achieved by assuming an effective exponent \( \gamma \), where

\[
vM^\gamma \sim f_2(p^{1/\gamma}M), \quad (\varepsilon > 0), \tag{A1}
\]

and

\[
f_2(z) \sim \begin{cases} z^\gamma : & z \ll 1 \\ const. : & z \gg 1, \end{cases} \tag{A2}
\]

where \( 1 \leq \gamma(\varepsilon) \leq 1.3 \) for various \( 0 \leq \varepsilon \leq 6 \). The corresponding scaling plot is shown in Fig. 13(a).

In the limit of very small drag, \( pM \to 0 \), the drift velocity is in variance with previous two-particle theories, \( v \sim p \). The deviation from linearity, however, with increasing drag is significant. Therefore, we have plotted \( v/p \) versus \( p^{1/\gamma}M \), which is shown in Fig. 13(b). The corresponding scaling function is

\[
v/p \sim f_3(p^{1/\gamma}M), \tag{A3}
\]

![Graph showing scaled drift velocity \( v \) of membranes as function of \( p^{1/\gamma}M \). Parameters: 0.001 \( \leq p \leq 1 \); 20 \( \leq M \leq 2560 \); \( \varepsilon = 0, 1, 2, 4, 6 \). The exponent \( \gamma \) used for each \( \varepsilon = 0, 1, 2, 4, 6 \) is \( \gamma = 1, 1.05, 1.15, 1.25, 1.3 \), respectively.](image)
where

\[
    f_3(z) \sim \begin{cases} 
        \text{const.} & : z \ll 1 \\
        z^{-\gamma} & : z \gg 1.
    \end{cases} \quad (A4)
\]

The latter relation (A4) implies that \( v \sim M^{-\gamma(v)} \).