Lattice-free descriptions of collective motion with crowding and adhesion

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Cell-to-cell adhesion is an important aspect of malignant spreading that is often observed in images from the experimental cell biology literature. Since cell-to-cell adhesion plays an important role in controlling the movement of individual malignant cells, it is likely that cell-to-cell adhesion also influences the spatial spreading of populations of such cells. Therefore, it is important for us to develop biologically realistic simulation tools that can mimic the key features of such collective spreading processes to improve our understanding of how cell-to-cell adhesion influences the spreading of cell populations. Previous models of collective cell spreading with adhesion have used lattice-based random walk frameworks which may lead to unrealistic results, since the agents in the random walk simulations always move across an artificial underlying lattice structure. This is particularly problematic in high-density regions where it is clear that agents in the random walk align along the underlying lattice, whereas no such regular alignment is ever observed experimentally. To address these limitations, we present a lattice-free model of collective cell migration that explicitly incorporates crowding and adhesion. We derive a partial differential equation description of the discrete process and show that averaged simulation results compare very well with numerical solutions of the partial differential equation.

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I. INTRODUCTION

Cell-to-cell adhesion is an important aspect of malignant spreading [1,2], and the impact of cell-to-cell adhesion is often observed in images from the experimental cancer cell biology literature. For example, the image in Fig. 1(a) shows a population of ovarian cancer cells in which individual cells show a tendency to adhere to others within the population [3]. The image in Fig. 1(b) depicts a population of breast cancer cells which show similar behavior [4]. Given that cell-to-cell adhesion plays a key role in influencing the behavior of individual malignant cells, it is reasonable to assume that cell-to-cell adhesion will also play a role in controlling the spatial spreading of populations of these cells [5,6]. Therefore, it is relevant for us to develop biologically realistic simulation tools that mimic the essential features of such collective spreading processes and that we are able to analyze such simulation tools to provide more general insight into the description of adhesive collective motion.

Previous approaches to simulating and analyzing collective migration of adhesive cells have used a lattice-based random walk framework where the lattice spacing is taken to be equivalent to the cell diameter. For example, Khain et al. [8] proposed a lattice-based model of collective cell migration, where the movement of individual agents in the random walk was affected by the ability of those agents to adhere to others in the population. This model was implemented on a square lattice, and it explicitly included crowding effects since each lattice site could be occupied by no more than one agent [8,9]. Since this model was first proposed, it has been adapted by others and used to interpret experimental data describing the collective migration of breast cancer cells [10], glioma cells [11], as well as addressing other theoretical questions related to modeling cell biology experiments [12]. A similar lattice-based model, implemented on a hexagonal lattice, was introduced by Deroulers and co-workers [13]. This particular model was inspired by in vitro observations of glioma cell migration, and the model also included crowding effects by allowing, at most, one agent to occupy each lattice site. Deroulers showed that the averaged behavior of their model could be accurately described by a nonlinear diffusion equation, provided that the strength of adhesion was not too large [13].

Taking a more theoretical approach, Fernando and co-workers [14] presented a suite of random walk models describing collective migration with adhesion on a range of regular lattices. Inspired by Deroulers’ work, which linked the discrete process to a nonlinear diffusion equation, Fernando considered 13 different regular lattices and three different ways that agent-to-agent contact effects, including adhesion, could be incorporated into the discrete model [14]. Fernando’s analysis showed that each of the very different adhesive collective migration mechanisms gave rise to a nonlinear diffusion equation, and they presented an extensive list of the different nonlinear diffusivity functions for each discrete mechanism [14]. Since these initial investigations, others have also considered different aspects of modeling adhesive collective migration processes in a lattice-based framework [15–18].

These previous kinds of models of collective migration of adhesive cells rely on a lattice-based framework. This implies that the movements of individual agents are restricted in the sense that they only ever move on a predefined lattice structure. The limitations of a lattice-based framework become obvious when considering regions of space where the agent density is relatively high [19]. In such situations it is visually obvious that the agents align along the underlying lattice, which is never observed in experimental images, such as those shown in Fig. 1. One way to overcome this would be to use a more finely spaced lattice, rather than making the usual assumption that the lattice spacing is equal to one cell diameter. However,
this would be nontrivial, as it would no longer be possible
to implement crowding effects simply via the restriction that
no more than one agent can simultaneously occupy the same
lattice site. Instead, we address this limitation by developing
a lattice-free model for the collective migration of adhesive
cells.

Previous lattice-free random walk models applied to biolog-
ical problems have typically neglected crowding effects [20]
and allowed individual agents in the random walk to step on
top of, or to move across, other agents in the system [21].
More recent biologically inspired lattice-free models have
incorporated crowding effects by ensuring that individual
agents in the model cannot occupy the same location, and
cannot step across other agents in the system. These previous
studies have investigated collective motion in one- and
two-dimensional geometries [22–24], combined motility and
proliferation mechanisms [19], as well as considering the
collective motion of different subpopulations of agents within
a multispecies framework [25]. We note that none of these
previous lattice-free models of collective cell motion have
incorporated any kind of adhesion mechanism.

In summary, the aim of this work is to present, and
analyze, a lattice-free model of collective cell migration with
crowding and adhesion effects. As we have already described,
several investigators have previously presented and analyzed
lattice-based models of collective cell migration with crowding
and adhesion. In contrast, others have considered lattice-free
models of collective cell migration without crowding or
adhesion. Therefore, we aim to extend these previous studies
by analyzing a lattice-free model that includes crowding
effects and adhesion. We focus our simulations and analysis
on a typical scratch assay, shown in Fig. 1(c), where an
initially uniform layer of cells is scratched to reveal a sharp
front that separates the occupied region from the vacant
region. The assay proceeds by measuring the spreading of
the population into the initially vacant region. Although the
domain of such experiments is two-dimensional, the initial
condition and boundary conditions reduce the description of
the process to a one-dimensional problem [15,19]. In Sec. II
we describe the discrete mechanism and present simulation data
showing how varying the parameters in the discrete model
influences the collective behavior of a population of agents. In
Sec. III we derive an approximate conservation argument that
leads to a nonlinear diffusion equation, while in Sec. IV we
compare numerical solutions of the partial differential equation
description to averaged simulation data. Finally, in Sec. V, we
summarize and discuss the outcomes of our work.

II. RANDOM WALK MODEL

We consider agents in the discrete model to be uniformly
sized disks of diameter $\Delta$. Each agent is permitted to occupy
any point in the two-dimensional plane provided that there is
sufficient space available to accommodate that agent without
overlapping any other agent. The position of the center of
the $i$th agent is denoted $(x_i, y_i)$ for $i = 1, 2, 3, \ldots, Q$. Simulations
are performed using a random sequential update method [26]
where, during each time step of duration $\tau$, $Q$ agents are
selected independently, at random, one at a time, and given the
opportunity to undergo a motility event. Each potential motility
event involves an agent attempting to move a distance $d$, along
a straight line, in a randomly chosen direction $\theta \in [0, 2\pi)$, as
illustrated in Fig. 2(a).

Before we describe the details of how the discrete mecha-
nism is implemented, we will first explain how data from the
discrete model will be presented and analyzed. In addition to
presenting visual results showing the arrangement of agents
after a single realization of the discrete model, we also present
averaged agent density profiles which are measured in the
following way. At the conclusion of each simulation we
discretize the domain into uniformly spaced vertical strips,
each of width $\Delta$, and count the number of agents whose
center lies within each strip $N$ [19]. This number is converted
into an estimate of agent density by assuming that each
strip, of width $\Delta$ and height $Y\Delta$, can be occupied by
$Y$ agents, giving $C(x_i, t) = N/Y$ for the $i$th strip. This data
can be averaged over $M$ identically prepared realizations to give
\[\psi(x, t) = \frac{1}{M} \sum_{m=1}^{M} C^m(x, t),\]
where $C^m(x, t)$ is the agent density of the $i$th vertical strip during
the $m$th identically prepared realization. It is important for us to note that if a
strip of width $\Delta$ and height $Y\Delta$ was occupied by $Y$ agents,
perfectly aligned along the centerline of the strip, these agents
would occupy an area of $Y\pi \Delta^2/4$ out of a total strip area of
$Y\Delta^2$, meaning that $C(x, t) = 1$ corresponds to $\pi/4 \approx 78.5\%$
area coverage. We note that a more accurate estimate of the
column density would be to exactly compute the proportion of

FIG. 1. (Color online) (a)–(b) Images of OV-90 ovarian cancer cells [3] and MCF-7 breast cancer cells [4], respectively, showing the
tendency of individual cells to adhere together. The images in (a) and (c) are reproduced with permission from Neoplasia and PNAS,
respectively. (c) Image of a typical scratch assay, in this case using U87 glioma cells [7]. To perform such a scratch assay, a uniform layer
of cells is scratched to form an initial sharp front as indicated by the red (dashed) line. The subsequent motion of the population, in the direction
indicated by the arrow, is observed and measured. The scratch assay in (c) can be quantified by dividing the domain into uniformly spaced
strips as indicated in (d), and converting the number of cells per strip into a cell density profile [7]. The images in (c)–(d) are reproduced with
permission from the American Physical Society.
FIG. 2. (Color online) (a) Schematic of the discrete mechanism showing a potential motility event. To assess the potential movement event, the number of agents occupying some region, such as the light gray annulus around the agent, are counted and the function \( f(C) \) is used to quantify the effect of adhesion on that particular motility event. The motility event takes place with probability \( P_m f(C) \) and, if successful, the agent will attempt to step a distance \( d \) along a straight line path at some randomly chosen angle \( \theta \in [0,2\pi) \). For the potential motility event to be successful, the path between the initial location and the final location needs to be vacant. This means that there is no other agent overlapping with the dark gray area. (b) Schematic illustration of how we define the agent density by dividing the domain into strips with width \( \Delta \). In the potential motility event depicted, the agent will attempt to move from column \( i-3 \) to column \( i \).

Each agent that overlapped each column. This approach would be very computationally intensive, whereas our approach of associating each agent with the column that contains the center of that agent is far simpler to implement in a practical setting.

To ensure that our discrete model produces biologically realistic results, we incorporate crowding effects since real biological cells cannot occupy the same location in space and cannot leapfrog across other cells in the population. To achieve this we implement a path-based, lattice-free, exclusion mechanism which ensures that potential motility events only take place if there is sufficient room to do so. To enforce this we check that any motility event in which the agent’s attempted path

\[
(x_i, y_i) + s \Delta (\cos \theta, \sin \theta) \quad \text{where} \quad s \in [0,1] \tag{1}
\]

passes within a distance \( \Delta \) of any other agent is aborted and the agent in question remains at the original location \((x_i, y_i)\). Such a path is illustrated by the dark shaded straight line path in Fig. 2(a). This discrete mechanism is related to the mechanism described and implemented previously by Plank and Simpson [19], except that here we introduce the generalization that the step length \( d \) is arbitrary.

The second important feature of our model is that it incorporates an adhesion mechanism to mimic the way that biological cells tend to adhere to each other. To do this we estimate the local density of agents in some region \( R \) about the location of the particular agent for which we are assessing a possible motility event. In this work we consider \( R \) to be an annulus of thickness \( \Delta \), centered at \((x_i, y_i)\), such as the light gray annulus in Fig. 2(a). We note, however, that our algorithm can be applied to consider any other reasonable definition of \( R \) if necessary. For each potential motility event we count the number of agents \( N \) whose center lies within \( R \). We convert this into a density by assuming that under an optimal, hexagonal arrangement of agents, the number of agents in \( R \) would be six. We therefore define a measure of the density in \( R \) to be \( C_R = N/6 \), where the subscript \( R \) refers to the fact that we are measuring the density of agents in \( R \). To connect our estimate of \( C_R \) with our previous definition of the column-based density, we note that \( C_R = 1 \) implies that an area of \( 6\pi \Delta^2/4 \) out of the total area of the annulus \( 9\pi \Delta^2/4 - \pi \Delta^2/4 = 8\pi \Delta^2/4 \) is occupied, so that \( C_R = 1 \) corresponds to \( 3/4 \approx 75\% \) of the total area covered by agents. Therefore our estimate of \( C_R \) can be converted into an equivalent estimate of \( C(x,t) \) by \( C(x,t) = C_R \times 3/\pi \). With our estimate of \( C \), we introduce an adhesion effect by reducing the motility of individual agents in the discrete mechanism by a factor that decreases with \( C \), meaning that an agent will attempt to undergo a motility event with probability \( P_m f(C) \) during a time step of duration \( \tau \). We choose a relatively straightforward model for the adhesion mechanism, which is given by

\[
f(C) = \max[0,1 - \alpha C], \tag{2}
\]

where the parameter \( \alpha \) controls the strength of adhesion. Setting \( \alpha = 0 \) implies that agents have no tendency to adhere to each other, whereas increasing the value of \( \alpha \) reduces the probability that a particular agent of interest will undergo a motility event. We interpret this decrease in motility as being the result of that agent adhering to other agents within \( R \). Since we are interpreting \( f(C) \) as a factor that reduces the probability that an agent will attempt to undergo a motility event, we must restrict \( f(C) \) to be non-negative in Eq. (2). The majority of results presented in this work, given in Secs. II and III, focus on simulations with sufficiently small values of \( \alpha \) that \( f(C) \) is smooth for all values of \( C \) considered. In addition, we briefly present and discuss some results in Sec. V for larger values of \( \alpha \) where \( f(C) \) is not smooth.

We note that Eq. (2) is very similar to the discrete adhesion mechanism proposed by Anguige and Schmeiser [18], which has since been studied by others [14,17]. The previous work by Anguige and Schmeiser focused on a lattice-based model, and here we aim to investigate how this description can be applied in a lattice-free framework. Although we restrict our focus to this particular form of \( f(C) \), we note that our discrete simulations and the corresponding analysis, presented in Sec. IV, also applies to other forms of \( f(C) \).

A. Discrete simulations

To demonstrate the key features of this model we present a suite of results in Fig. 3. To mimic a scratch assay geometry [such as Fig. 1(c)], we consider a two-dimensional, long and narrow domain with an initial distribution of agents that is, on average, independent of the vertical location [19,27]. Unlike the scratch assay in Fig. 1(c), where the initial population is adjacent to the left boundary and spreads in the positive \( x \) direction, we consider an initial population of cells in the center of the domain so that we observe spreading in both the positive and negative \( x \) direction [19]. To initiate our simulations, we place agents, at random, within the interval \( 130 \leq x \leq 170 \), subject to the condition that no two agents are permitted to overlap. Note that, since we initialize the agents randomly, we never observe a perfectly aligned initial distribution and it becomes increasingly difficult to initialize these simulations.
FIG. 3. (Color online) Results from the discrete model on a domain with $0 \leq x \leq 300$ and $0 \leq y \leq 10$. Reflecting boundary conditions are imposed at both ends of the finite domain $x = 0$ and $x = 300$, and periodic boundary conditions are imposed at $y = 0$ and $y = 10$. The initial condition for each simulation is a random nonoverlapping placement of 240 agents within a region where $130 \leq x \leq 170$. Simulations are performed with $P_m = \tau = 1$. Results correspond to (a) the step size is equal to the agent diameter with no adhesion, $d = 1$, and $\alpha = 0$; (b) the step size is twice the diameter of the agent with no adhesion, $d = 2$, and $\alpha = 0$; (c) the step size is equal to the agent diameter with some adhesion, $d = 1$, and $\alpha = 1.0$; and (d) the step size is equal to the agent diameter with stronger adhesion, $d = 1$, and $\alpha = 1.5$.

as the initial number of agents to be packed into this finite area increases [19]. For this reason all simulations in Fig. 3 begin with a random initial distribution of agents with $C(x,0) = 0.6$ in the region $130 \leq x \leq 170$. There are no agents placed outside of this region, which means that we have $C(x,0) = 0$ elsewhere in the domain [19,27].

Results in Fig. 3(a) show the observed spreading in one realization with $d = 1$ and $\alpha = 0$ so that we have no adhesion and the step length is equal to the agent diameter. In this case we observe that the population spreads symmetrically from the initial condition, as we might expect [19]. It is interesting to note that all images of the spreading process in Fig. 3(a) indicate that the agents in the simulations are distributed in two-dimensional continuous space, just like we observe in real experimental images such as Fig. 1(c). This is more realistic than an equivalent lattice-based random walk model where snapshots reveal that the agents align themselves on an underlying artificial lattice structure [19], which is particularly evident in high-density regions of the domain.

The simulation results in Fig. 3(b) show the observed spreading in one realization with $d = 2$, $\Delta = 1$, and $\alpha = 0$ so that we have no adhesion acting and the step length is twice the agent diameter. As a result of this difference, we see that the population in Fig. 3(b) spreads further during the same period of time than the population in Fig. 3(a). Results in Figs. 3(c)–3(d) show the spreading in one particular realization for adhesive motion with $d = 1$, $\Delta = 1$, with $\alpha = 1.0$, and $\alpha = 1.5$, respectively. Comparing the results in Figs. 3(a), 3(c), and 3(d) shows how the differences in $\alpha$ affect the collective spreading of the population, and we observe that...
Numerical solutions of Eq. (4) are superimposed in red (dashed). The numerical solutions were obtained using the same method outlined in the main text with an identically prepared stochastic model. Averaged agent density data correspond to a low cell-to-cell adhesion strength. These differences are associated with a high cell-to-cell adhesion strength, whereas those populations which exhibit enhanced spreading are associated with a low cell-to-cell adhesion strength.

The fact that our model captures these differences is relevant for a fixed value of \( M \) and varying \( \alpha > 0 \) and the averaged density profiles are constructed using \( M = 1000 \). Results in the top row of Fig. 5 show the collective spreading for fixed \( d \) and varying \( \alpha \) and profiles are given at \( t = 0.500 \), and 1000. Comparing these profiles confirms that the amount of spreading decreases with \( \alpha \). The results in the lower row of Fig. 5 show an equivalent set of averaged discrete results for the same values of \( \alpha \) as in the top row except that the step length is increased to \( d = 2 \). Comparing the average agent density profiles in the top and lower rows in Fig. 5 shows that for a fixed value of \( \alpha \), the rate of spreading increases with \( d \).

### III. PARTIAL DIFFERENTIAL EQUATION DESCRIPTION

We now derive an approximate partial differential equation description of our discrete model, since this will give us a more formal description of the discrete process that is more accurate for describing the spreading of agent densities.
the domain into vertical strips of width $\eta\Delta$ and denote the density of agents in the $i$th strip as $C_i$. Since we are dividing the domain into strips of width $\Delta$, we will consider the step length $d$ to be an integer multiple of the agent diameter so that we have $d = \eta\Delta$, where $\eta = 1, 2, 3, \ldots$. An approximate conservation statement, describing the net change in agent density within the $i$th strip during a time interval of duration $\tau$ can be developed with reference to the schematic diagram in Fig. 2(b) [15,19]. For our model, with a step length $d = \eta\Delta$ and an arbitrary adhesion function $f(C)$, we obtain

$$\delta C_i = \frac{P_m}{4} \left[ f(C_{i-\eta})C_{i-\eta} \prod_{k=0}^{\eta-1} P(C_{i-k}) + f(C_{i+\eta})C_{i+\eta} \prod_{k=0}^{\eta-1} P(C_{i+k}) \right]$$

$$- \frac{P_m}{4} \left[ f(C_i)C_i \prod_{k=1}^{\eta} P(C_{i-k}) + f(C_i)C_i \prod_{k=1}^{\eta} P(C_{i+k}) \right].$$

(3)

Positive terms on the right of Eq. (3) are associated with motility events that increase the occupancy of the $i$th strip, while negative terms are associated with motility events that decrease the occupancy of the $i$th strip. All four terms on the right of Eq. (3) are products of several factors that depend on the agent density within various strips along the domain. Since we are interpreting products of these densities as a net transition probability, we are making the standard assumption that the occupancies of different strips are independent [19]. This assumption amounts to the neglect of short-range correlations [19]. The adhesion effect is incorporated in Eq. (3) through the $f(C)$ function. The function $P(C_i)$ represents the probability that a particular motility event that attempts to place an agent in, or across, strip $i$ is successful. Therefore, the product terms on the right of Eq. (3) approximately describe the probability of success of motility events that would take an agent across multiple strips. We also note that all terms on the right of Eq. (3) are proportional to $1/\tau$, which reflects the fact that an isolated agent in the $i$th strip undergoing a motility event does not necessarily alter the occupancy of that strip. For example, a motility event for an isolated agent with $\theta = \pm \pi/2$ will not alter the occupancy of the strip containing that agent [19,27]. The factor of $1/\tau$ approximately incorporates the fact that only a proportion of events alter the occupancy of the $i$th strip depending on the random choice of $\theta$ [19,27].

To arrive at a partial differential equation description of this process, we divide both sides of Eq. (3) by $\tau$, and identify the averaged discrete density of the $i$th column with a continuous function $C(x,t)$ [19]. We expand all terms on the right of Eq. (3) in a truncated Taylor series, neglecting terms of $O(\Delta)^3$ and smaller, and consider the limit as $\Delta \to 0$ and $\tau \to 0$ with the ratio $\Delta^2/\tau$ held constant to arrive at

$$\frac{\partial C}{\partial t} = D_0 \frac{\partial}{\partial x} \left[ D(C) \frac{\partial C}{\partial x} \right],$$

where

$$D_0 = \lim_{\Delta, \tau \to 0} \frac{P_m(d\Delta)^2}{4\tau},$$

$$D(C) = (P(C))^\theta \left[ (Cf(C))' - Cf(C) \frac{P'(C)}{P(C)} \right].$$

(4)
where the prime represents an ordinary derivative with respect to $C$. We note that in the special case where $Cf(C) \equiv P(C)$ we have $D(C) \equiv 0$, and we discuss the implications of parameter combinations leading to $D(C) < 0$ and $D(C) > 0$ in Sec. V.

In summary, our approximate partial differential equation description takes the form of a nonlinear diffusion equation with a free-agent diffusivity $D_0$ and a nonlinear diffusivity function $D(C)$. To examine how this approximate description matches averaged data from our simulations, we will generate numerical solutions of Eq. (4) using a finite difference approximation on a uniformly discretized domain with step size $\delta x$ [32]. The corresponding system of nonlinear ordinary differential equations will be solved using a backward Euler method with constant time steps of duration $\delta t$ [32]. The nonlinear system is linearized using Picard iteration, with an absolute convergence tolerance of $\epsilon$. The resulting system of linear equations is solved using the Thomas algorithm [33].

To solve Eq. (4) we need to specify both the adhesion function $f(C)$ and the crowding function $P(C)$. In our formulation $P(C)$ represents the probability that an attempted motility event that would place an agent on a uniformly occupied strip of density $C$ is successful. Intuitively we expect that $P(0) = 1$ and that $P(C)$ will be a decreasing function of $C$. In an equivalent lattice-based framework the form of $P(C)$ is widely reported to be $P(C) = 1 - C^{\alpha}$ [10,13,14]. However, we expect that the crowding effects are different in a lattice-free description and we discuss the implications of this in Sec. V. The resulting system of linear equations is solved using the Thomas algorithm [33].

To explore this we solve Eq. (4) on $0 < x < L$, with $L$ chosen to match the domain used in the discrete simulations. No flux boundary conditions, $-D(C) \partial C/\partial x = 0$, are imposed at both ends of the finite domain $x = 0$ and $x = L$, and the initial condition, $C(x,0)$, was chosen to match the various initial conditions used in Figs. 4 and 5. The relevant numerical solutions of Eq. (4) are superimposed in Figs. 6(b) and 17. We now address the question of whether Eq. (4) can accurately predict the averaged density data in Figs. 4 and 5. To explore this we solve Eq. (4) on $0 < x < L$, with $L$ chosen to match the domain used in the discrete simulations. No flux boundary conditions, $-D(C) \partial C/\partial x = 0$, are imposed at both ends of the finite domain $x = 0$ and $x = L$, and the initial condition, $C(x,0)$, was chosen to match the various initial conditions used in Figs. 4 and 5. The relevant numerical solutions of Eq. (4) are superimposed in Figs. 4 and 5, which shows that, in general, we observe a high quality of match between the averaged discrete density profiles and the solution of Eq. (4).

![Figure 6](image)  

**Figure 6.** Comparison of $D_0D(C)$ for various parameter values. Results in (a) show $D_0D(C)$ for $\Delta = \tau = P_m = d = 1$ and various values of $\alpha$ for $C \in [0,0.6]$. Profiles are shown for $\alpha = 0.05, 1.0, 1.5, 1.10$, with the arrow showing the direction of increasing $\alpha$. Results in (b) show $D_0D(C)$ for $\Delta = \tau = P_m = 1, \alpha = 0$, and various values of $d$ for $C \in [0,0.6]$. Profiles are shown for $d = 1, 2, 3$, with the arrow showing the direction of decreasing $d$.  

IV. COMPARING SOLUTIONS OF THE PARTIAL DIFFERENTIAL EQUATION DESCRIPTION AND AVERAGED SIMULATION DATA

We now address the question of whether Eq. (4) can accurately predict the averaged density data in Figs. 4 and 5. To explore this we solve Eq. (4) on $0 < x < L$, with $L$ chosen to match the domain used in the discrete simulations. No flux boundary conditions, $-D(C) \partial C/\partial x = 0$, are imposed at both ends of the finite domain $x = 0$ and $x = L$, and the initial condition, $C(x,0)$, was chosen to match the various initial conditions used in Figs. 4 and 5. The relevant numerical solutions of Eq. (4) are superimposed in Figs. 4 and 5, which shows that, in general, we observe a high quality of match between the averaged discrete density profiles and the solution of Eq. (4).

Looking more closely at the results in Fig. 4, we observe a very good match between the averaged discrete density profiles and the solution of Eq. (4) for $d = 1$ and $d = 2$. However, we notice that the quality of the match decreases as $d$ increases, and we observe that Eq. (4) does not match the averaged discrete density profiles for $d = 3$ as well as it did for smaller $d$. We can attribute this decrease in the quality of match between the average discrete profiles and the solution of approximate partial differential equation to the failure of the independence assumptions that are inherent in Eq. (3) and Eq. (4) [17].
We note that as $d$ increases, the number of product terms in Eq. (3) increases. Therefore, we expect that the independence assumption underpinning Eq. (4) becomes less reliable as $d$ increases.

The comparison between the averaged discrete density profiles and the solution of Eq. (4) in Fig. 4 is made for various values of the step length $d$ at the same time points $t = 0.500,$ and 1000. This means that we observe an increasing amount of spreading as $d$ increases. We provide an additional comparison between the averaged discrete data and the solution of Eq. (4) for various step lengths $d$, where we stop the simulations after different time periods so that we keep the product $dt^2$ constant. We note that keeping $dt^2$ constant means that, on average, the mean squared displacement of an isolated agent would be equivalent at time $t$ when we compare results from different simulations with different $d$. This means that these additional comparisons, outlined in Appendix B, allow us to compare results in which we observe a similar amount of spreading at the leading edge of the various populations.

The results in Fig. 5 show the performance of Eq. (4) for adhesive motion with $\alpha > 0$, and we see that the solution of Eq. (4) accurately captures the reduced spreading as $\alpha$ increases. In general, we observe a high-quality match between the solution of Eq. (4) and the averaged discrete density profiles. Similar to the results with $\alpha = 0$, we also observe a slight decrease in the quality of the match between Eq. (4) and the averaged discrete data as $d$ increases; however, the overall quality of match between the averaged discrete simulation results and the solution of Eq. (4) is excellent.

V. DISCUSSION

Experimental observations indicate that some types of malignant cells have a tendency to adhere to other cells within a population [3,4], and it is well-known that certain cell types are more strongly affected by such cell-to-cell adhesion than others [28,29]. To describe this kind of behavior, previous modeling studies have proposed lattice-based random walk frameworks where individual motility events are affected by the presence of agent-to-agent attachments [8,10,13]. One of the key limitations of this kind of lattice-based random walk models is that the agents in the simulations are restricted in the sense that the agents can only occupy spatial locations that are associated with an artificial lattice, whereas experimental images show that real cells are aligned less regularly in continuous space. To overcome these limitations we have developed a lattice-free random walk model that includes realistic crowding effects and an agent-to-agent adhesive mechanism.

Previous studies that have developed lattice-free models of collective cell migration have focused on studying collective migration with crowding effects [24], collective motion of systems with distinct subpopulations [25], and populations of agents that are both motile and proliferative [19,27]. None of these previous lattice-free models have incorporated any kind of agent-to-agent adhesion mechanism. Here, we have developed a lattice-free model that incorporates both a crowding and an agent-to-agent adhesion mechanism, and our discrete simulations illustrate that the spreading of an initially confined population is reduced as the adhesion parameter $\alpha$ increases. To complement the discrete simulations, we also developed an approximate partial differential equation (PDE) description of the model and compared averaged simulation data to numerical solutions of the continuum description to explore whether it could accurately predict the average behavior of the discrete model. In all cases considered we found that the solutions of the partial differential equation provided a reasonable match to the averaged discrete data, which means that the continuum model can be used to study the averaged behavior of the system without the need for having to perform many repeated stochastic simulations.

The continuum model derived here is a nonlinear diffusion equation. Similar to lattice-based models of adhesion, we find that the nonlinear diffusivity is a decreasing function of the adhesion parameter $\alpha$. In particular, with $\tilde{d} = 1$, our nonlinear diffusivity function simplifies to $D(C) = -(a + b\alpha)C^2 - 2\alpha C + 1$. We note that in the low-density limit, as $C \to 0^+$, we have $D(C) = 1 - 2\alpha C + O(C)^2$ and that this expression is equivalent to the expression for the low-density limit of the nonlinear diffusivity function reported previously for a lattice-based adhesion model with an equivalent $f(C)$ function [17,18]. Therefore, when the agent density is low, adhesion has a similar effect on the population-level diffusivity in the lattice-free model as it does in a similar lattice-based model. However, when the density is high, the quadratic term in the $D(C)$ function means that the lattice-based and lattice-free diffusivity functions are different. This complements previous findings that lattice-free and lattice-based models behave similarly in low-density situations but can be quite different in high-density situations [27]. This makes sense intuitively, since the key difference between the lattice-based and lattice-free individual-based models is in the way that they handle crowding effects.

All results presented so far correspond to the case where $D(C) > 0$. We note, however, that increasing $\alpha$ leads to a nonlinear diffusivity function which can become negative for a range of $C$ and that similar behavior has been observed and analyzed previously for lattice-based models of adhesive motion [10,14,15,17,18,35]. For example, with $d = 1$, $a = 0.9078$, and $b = -2.1095$, our nonlinear diffusivity function becomes negative for a range of $C$ whenever $\alpha > 1.6$. We note that the solutions of nonlinear diffusion equations, where $D(C) < 0$ for a range of $C$, have been analyzed previously [36]. These solutions are of interest mathematically, since they do not necessarily obey the usual maximum principle [37,38] and can contain shock discontinuities [15,36].

Discrete simulations with a combination of parameters giving $D(C) < 0$ for a range of $C$ are associated with the formation of clusters of agents [15], which is similar to a phase transition [35]. To demonstrate this we provide a suite of simulations in Fig. 7. The results in the left column of Fig. 7 correspond to a sufficiently small value of $\alpha$ that we have $D(C) > 0$ for $0 \leq C \leq 0.6$. For this choice of parameters, we perform simulations starting from an initially uniform distribution of agents and reflecting boundary conditions are applied to all boundaries. Visual inspection of the simulations indicates that the agents appear to remain approximately evenly distributed for $0 \leq t \leq 1000$. Conversely, the results in the right column of Fig. 7 correspond to a sufficiently large value of $\alpha$ that we have $D(C) < 0$ for a range of $C$. 

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model to be applied to scratch assays, and we do not consider a
of [15]. We would like to reiterate that the primary aim of
whereas the same perturbation is unstable if
Clustering. Results in the left column correspond to
Simulation results in the right column of Fig. 7, with the same
particular, it is possible to show, using linear stability analysis,
clusters. These differences are consistent with previously
initial condition and boundary conditions as those in the left
column, indicates that the model leads to the formation of agent
Simulation results in the right column of Fig. 7, with the same
initial condition and boundary conditions as those in the left
column, indicates that the model leads to the formation of agent
clustering. These differences are consistent with previously
established results for analogous lattice-based models [15]. In
particular, it is possible to show, using linear stability analysis,
that a small perturbation to a spatially uniform steady solution
of a nonlinear diffusion equation is stable provided \( D(C) > 0 \),
whereas the same perturbation is unstable if \( D(C) < 0 \). The
details of this linear stability analysis are given in Sec. 5.2 of
[15]. We would like to reiterate that the primary aim of
this work is to demonstrate the potential for our lattice-free
model to be applied to scratch assays, and we do not consider a
detailed analysis of agent clustering. Therefore, when applying
our model to mimic a scratch assay, such as the results shown
in Figs. 4 and 5, we chose to focus on parameter choices
where \( a \) was sufficiently small that \( D(C) > 0 \) for all relevant
values of \( C \).
A potential limitation of our lattice-free models is the
increase in computational complexity of implementing the
crowding mechanism relative to standard-lattice-based
approaches. If each attempted movement path was checked for
potential collisions with every other agent in the system, the
required computation time would be \( O(Q^2) \) [19], where \( Q \)
is the total number of agents in the simulation. To avoid
this we implemented a modified algorithm that ordered the
agents by their \( x \) coordinate. This allowed us to efficiently
check for potential collisions by paying attention only to
those agents whose \( x \) coordinate was sufficiently close that
a collision could occur. We found that this modification
reduced the computation time to approximately \( O(YQ) \), where
\( Y \) is the vertical height of the domain. An alternative way
to overcome the computational limitations of lattice-free
models would be to implement a lattice-based model with a
very finely spaced lattice rather than making the usual
assumption that the lattice spacing is equal to the agent
diameter [8,10,13]. However, this approach would introduce
different computational complications, since it would no
longer be possible to implement crowding effects simply by
invoking the restriction that each lattice site can be occupied by,
at most, one agent [8,10,13]. Instead, the number of lattice sites
that would need to be checked for each potential movement
event would be \( O(\Delta^{-2}) \), leading to a computation time of
\( O(Q\Delta^{-2}) \).
Our lattice-free model of collective cell migration could be
extended in several ways with an obvious extension
to three dimensions so that it could be applied to

![Figure 7](image_url)

**FIG. 7.** (Color online) Discrete simulations illustrate the formation of agent clustering. Results in the left column correspond to \( \Delta = 1, d = 1, \) and \( \alpha = 1 \). The \( D_h D(C) \) function, given for \( 0 \leq C \leq 0.6 \), shows that the diffusivity is positive for all \( C \). Simulations on \( 0 \leq x \leq 50 \) and \( 0 \leq y \leq 50 \), with a spatially uniform initial condition, \( C = 0.3 \), and reflecting boundary conditions show that the agents remain approximately spatially uniform during the interval \( 0 \leq t \leq 1000 \). Results in the right column correspond to \( \Delta = 1, d = 1, \) and \( \alpha = 2.5 \). The \( D_h D(C) \) function, given for \( 0 \leq C \leq 0.6 \), shows that the diffusivity becomes negative for a range of \( C \). Equivalent simulations to those in the left column indicate that the agents cluster within the interval \( 0 \leq t \leq 1000 \).

![Figure 8](image_url)

**FIG. 8.** (Color online) Computationally derived estimate of \( P(C) \) (red squares) and the corresponding quadratic fit (solid green) are compared to the equivalent function \( P(C) = 1 - C \) for a lattice-based model (dashed black). Values of \( P(C) \) were obtained by populating a strip of width \( \Delta \) at some density \( C \in [0,0.6] \) and then attempting to place an additional agent on that strip at various locations. Using \( M = 1000 \) identically prepared realizations for each \( C \), we estimated the mean of \( P(C) \) at \( C = 0,0.05,0.1,0.15,\ldots,0.6 \) (red squares). The variability of our estimates are shown using error bars which correspond one standard deviation from the mean. This data was fitted to \( P(C) = ac^2 + bc + 1 \), and the least-squares estimates of the parameters are \( a = 0.907 \) and \( b = -2.109 \).
three-dimensional cell migration assays, such as Transwell assays and spheroid migration assays [39]. Additional details, such as investigating populations of adhesive agents with different subpopulations with differential adhesion [40,41] or agent proliferation [19,27], could also be incorporated into the discrete model. Another interesting extension is to consider the influence of changing the shape of the agents in the discrete simulation so that our lattice-free framework can be applied to cell populations where individual cells have different shapes and sizes, and to understand how these differences in agent shape lead to differences in the approximate partial differential equation description of the process [42,43]. We anticipate that a detailed analysis of how the present model could be extended to deal with these complications could be a subject of future consideration.

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APPENDIX A: COMPUTATIONAL ESTIMATE OF \( P(C) \)

To estimate \( P(C) \) we randomly populated a vertical strip, of width \( \Delta \) and height 1000\( \Delta \), at some density \( C \in [0,0.6] \). We then attempt to place a new agent at various locations along the centerline of that strip. By using \( M \) identically prepared realizations of this procedure, we estimated \( P(C) \) as the number of successful placement attempts divided by \( M \) to obtain the data points in Fig. 8. The uncertainty in our results is indicated by the error bars in Fig. 8, which represent one standard deviation from the mean. We also checked that our estimates of \( P(C) \) were independent of the height of the domain by repeating the procedure using domains of different height which showed that the data in Fig. 8 are independent of the height of the domain.

Given the mean data in Fig. 8, we used MATLAB’s \textsc{lsqnonlin} [34] to estimate \( a \) and \( b \) to describe this data using \( P(C) = ac^2 + bc + 1 \). This procedure gave \( a = 0.907 \) and \( b = -2.109 \).

We now derive an approximate estimate of \( P(C) \) using a geometric argument that is relevant in the dilute limit as \( C \rightarrow 0^+ \). To show this we consider a domain of height \( h \) and width \( \Delta \), that is populated by \( YC \) nonoverlapping agents, at density \( C \). In the dilute limit, as \( C \rightarrow 0^+ \), each agent will exactly exclude a vertical distance of \( 2\Delta \). Under these circumstances the probability of placing another agent on the strip is \( P_{\text{dilute}}(C) = 1 - (2\Delta \times YC)/(\Delta Y) = 1 - 2C \), which is approximately consistent with our computational results, which gave the coefficient of \( C \) as \(-2.1093\).

We note that although the low-density limit of \( P(C) \) is different for lattice-based \( \{P(C) = 1 - C\} \) and lattice-free \( \{P(C) = 1 - 2C\} \) models, the low-density limit of the nonlinear diffusivity function \( D(C) = 1 - 2\alpha C \) turns out to be the same for the lattice-based and lattice-free models, as we pointed out in Sec. V, since \( D(C) \) is independent of the coefficients in the \( P(C) \) polynomial.

APPENDIX B: COMPARING SOLUTIONS OF THE PARTIAL DIFFERENTIAL EQUATION DESCRIPTION AND AVERAGED SIMULATION DATA AT DIFFERENT TIME POINTS

All discrete and continuous results presented in Fig. 4 consider collective motion without adhesion, \( \alpha = 0 \), and compare results for varying step lengths, \( d = 1, 2, 3 \), at fixed inspection times, \( t = 500, 1000 \). These previous results illustrate that for a particular initial condition, larger \( d \) leads to more spreading at a fixed inspection time \( t \). In this Appendix we repeat the stochastic simulations that were presented in the top row of Fig. 4, but we now stop the simulations after different amounts of time so that we observe a similar amount of spreading for systems with different \( d \). Results in Fig. 9 compare averaged discrete density profiles, for \( d = 1, 2, 3 \), with the inspection time chosen to keep the product \( \Delta^2 t \) constant. These profiles illustrate two key results: first, the averaged discrete density profiles and the solution of Eq. (4) compares very well for all problems considered. Second, if we compare the location of the leading edge of the three simulations we see that, unlike the results in Fig. 4, here these three simulations all display a similar spatial extent of spreading. We note, however, that while the three profiles in Fig. 9 show a similar amount of...
spreading at the leading edge, where $C(x,t) \approx 0$, the shape of the density profile away from the leading edge is very different in each case. These differences are caused by the differences in the step length $d$ and our approximate partial differential equation description accurately captures these differences.