Sharp interface model for elastic motile cells

Yony Bresler a, Benoit Palmieri, and Martin Grant

Department of Physics, McGill University, 3600 University Montréal, Québec, H3A 2T8, Canada

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Abstract. In order to study the effect of cell elastic properties on the behavior of assemblies of motile cells, this paper describes an alternative to the cell phase field (CPF) we have previously proposed. The CPF is a multi-scale approach to simulating many cells which tracked individual cells and allowed for large deformations. Though results were largely in agreement with experiment that focus on the migration of a soft cancer cell in a confluent layer of normal cells, simulations required large computing resources, making a more detailed study unfeasible. In this work we derive a sharp interface limit of CPF, including all interactions and parameters. This new model scales linearly with both system and cell size, compared to our original CPF implementation, which is quadratic in cell size, this gives rise to a considerable speedup, which we discuss in the article. We demonstrate that this model captures a similar behavior and allows us to obtain new results that were previously intractable. We obtain the full velocity distribution for a large range of degrees of confluence, \( \rho \), and show regimes where its tail is heavier and lighter than a normal distribution. Furthermore, we fully characterize the velocity distribution with a single parameter, and its dependence on \( \rho \) is fully determined. Finally, cell motility is shown to linearly decrease with increasing \( \rho \), consistent with previous theoretical results.

1 Introduction

Cell monolayers have been used to study a variety of biological processes, such as cancer metastasis, wound healing, colony fronts, immunosurveillance and collective cell migration [1–3]. These can exhibit a complex behavior which can be studied at the intersection of in vivo, in vitro and in silico experiments. This paper is motivated by the metastasis pathway where a single cancer cell, having left the primary tumor, squeezes through the much stiffer endothelium in an attempt to reach a nearby blood vessel.

One method to simulate such cells which has been introduced in recent years is a phase-field approach [4–7], where each cell, labeled \( n \), is described by a field \( \phi_n(\mathbf{r}, t) \). These fields are defined at every point in space \( \mathbf{r} \) and time \( t \), and smoothly transitions from unity inside the cell to zero outside. In particular, the authors of this paper previously developed a multi-scale phase field for studying elasticity mismatch in cells [8]. That approach explicitly modeled each cell with tunable elasticity and allowed for large deformations. It was argued that these deformations play a key role in velocity “bursts”, as a highly deformed cell propagates to a more relaxed state with high velocity.

However, a major limitation of the model is the large computational resources required for large-scale, long-time simulations that are needed to obtain sufficient statistics. There are several methods known for improving the efficiency of phase field models. One approach is to replace the uniform mesh with an adaptive mesh [9]. While this reduces the number of mesh points required to perform a simulation, these methods still explicitly track details in both the interior and exterior the cell. Here we are only interested in the motion of the interface and simulating the bulk can be superfluous. Additionally, when the cell is highly deformed, the advantage of such an approach diminishes. Sometimes, in simple cases, it is possible to consider only the motion of the interface and simulate the bulk can be superfluous. Additionally, when the cell is highly deformed, the advantage of such an approach diminishes. Sometimes, in simple cases, it is possible to consider only the motion of the interface, and disregard the bulk evolution. See, for example [10], for a treatment of Ostwald ripening. Another approach is to represent all cells with a single field using a vacancy phase field crystal approach [11]. This allows efficient modeling of many cells but does not allow for large deformations.

A multitude of other models that have been used to study the motion of cells. These include the cellular Potts model approaches to the motion of cells, including their interaction with the extracellular matrix [12]; sub-cellular description using beads and springs models for cell rheology [13] and tissue growth [14]; and continuum models to model unconstrained spreading of epithelial layers [15], wound closure [16] or colony expansion using level-set

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a e-mail: yony.bresler@mail.mcgill.ca
method [17], See [18,19] for recent comprehensive reviews of various methods in collective cell motility. In recent years self-propelled Voronoi models have gained popularity [20–22] due to their relative simplicity and computational efficiency, though they are limited to systems at full confluence and offer limited cell deformation. Similarly, none of these methods both explicitly track each cell as well as allow for tunable elasticity and arbitrarily large deformations. Furthermore, many of these methods are limited to the study of perfectly confluent layers, whereas we wish to address any degree of confluence.

The model proposed in this paper bridges a gap between previous approaches. As a sharp-interface limit of the CPF, there is a significant numerical speedup over the standard CPF approach. Our method explicitly tracks each cell, allows for tunable elasticity, arbitrarily large deformations and permits any degree of confluence. It is similar in nature to treatments by Kopf [15] and more recently by Madhikar [23]. Here, the connection with CPF allows for a systematic way of deriving additional terms, as well as a hybrid sharp-interface/CPF method to simulate distinct parts of the system.

Since the 1950s, there has been extensive work on sharp interface models, including approaches to the Stefan problem [24], Ostwald ripening [25], and the Gibbs-Thomson effect [26]. The phase field model itself emerged to solve some of the morphological instabilities of sharp interfaces. A review of this evolution can be found here [27]. The model we propose does not suffer from those instabilities, as the number of cells is fixed, and cell volume is kept constant to good approximation. In the absence of growth, the sharp interface model is tractable and allows for a significant speedup over phase field models.

There has also been previous work using a sharp-interface approach to model or detect cell motion. Lee [28] used a sharp-interface mathematical model to track the motion of single Keratocytes cells. Their work has been extended to include details of the actin including nucleation [29] and cell polarization [30], and the Filament Based Lamellipodium Model [31]. These approaches provide a more detailed description of cells than the model we propose. By their nature, these models are more specialized to certain types of cells and may not be applicable to different cell lines. They have also been used to model single cells, but not multi-cell collective behavior.

The remainder of this paper is structured as follows: First, we derive our sharp interface model from the CPF including non-local terms, model parameters, as well as outline implementation details. Section 3 is the “Results” section, which includes reproducing “bursts” seen in the CPF, as well as a study of the effects of different concentrations and elasticities on cell motion which were not feasible with CPF. We conclude by summarizing our results and suggest future work.

2 Sharp interface model for cells

We begin with the CPF model, where the time evolution for the field of each cell (labeled $n$), $\phi_n$ is given in dimensionless units by

\[
\frac{d\phi_n}{dt} = -\mathbf{v}_n \cdot \nabla \phi_n + \gamma \nabla^2 \phi_n - \frac{30}{\lambda^2} \left[ \gamma \phi_n (1 - \phi_n) (1 - 2\phi_n) + 2\kappa \sum_{m \neq n} \phi_n \phi_m \right] - \frac{2\mu}{\pi R_0^2} \phi_n \left[ \int dx \int dy \phi_n^2 - \pi R_0^2 \right],
\]

(1)

where $\mathbf{v}_n$ is the velocity of each cell, $\gamma$ is the parameter that controls cell stiffness or elastic response, $\lambda$ is the width of the cell boundary interface, $\kappa$ sets the strength of neighbor-neighbor cell repulsion, and $\mu$ is a soft constraint to keep cells at their preferred size, $\pi R_0^2$. The interior of a cell is described where $\phi = 1$, smoothly decreasing across the interface, until reaching $\phi = 0$ at the cell exterior. This phase field model was shown to be successful, though it is computationally taxing. Although we choose to follow the CPF formulation, it is possible to adapt this sharp-interface approach to other phase-field models of cells. Hence, we set out to take the sharp interface limit of the phase field equations.

Consider a phase field with a free-energy function given by

\[
F = \int d^d r \left[ \frac{1}{2} C (\nabla \phi)^2 + f(\phi) \right],
\]

(2)

where $C$ is a constant, and $f(\phi)$ is the bulk free energy which has any double well structure. The connection between this continuous description and sharp-interface has been well studied, as early as van der Waals [32] and notably by Allen-Cahn [33]. When the thickness of the interface is much less than the radius of curvature of the interface, the local interface velocity $\mathbf{v}_{\text{interface}}$ can be approximated as

\[
\mathbf{v}_{\text{interface}} = \Gamma K \mathbf{n}.
\]

Here, $K = -\nabla \cdot \mathbf{n}$ denotes the local curvature, $\Gamma$ is a model dependent parameter, and $\mathbf{v}_{\text{interface}}$ points along the local normal $\mathbf{n} = \nabla u / |\nabla u|$ to the interface $u(r,t)$. $\Gamma$ has the same properties as surface tension, and for this simple model does not depend on exact form of the bulk free energy $f(\phi)$, although it may play a role in other models (for example, [34]). Now consider a system governed by a free energy of the form shown in eq. (2) and an interface initially given by $R(\theta, t = 0)$, where $R(\theta, t)$ describes the distance to the interface from the cell center for any angle $\theta$. We shall use this angular representation for simplicity, and though it precludes multi-valued radii, we will later generalize to remove this restriction. Its time evolution will be given by

\[
\left. \frac{\partial R(\theta, t)}{\partial t} \right|_{\text{Curvature}} = \mathbf{v}_{\text{interface}}(\theta, t) = \gamma K(\theta, t) \mathbf{n}(\theta, t),
\]

(3)

where in this model, $\Gamma = \gamma$. Evolving the system in time is thus reduced to computing the local curvature along the interface.
2.1 Approximating non-local terms

Although the sharp interface limit of eq. (2) does not depend on the details of the bulk free energy $f(\phi)$, the same does not hold for non-local terms. The CPF model had two such terms, the area conservation, and neighbor-neighbor interaction terms. Similar to the sharp interface approximation, we assume that $\lambda \ll K$ such that the radial component is in 1D equilibrium and obtain sharp-interface estimate of these terms by calculating the rate of change of the location of the interface. The long-time equilibrium solution of eq. (1) for a cell interface centered at $x = 0$ is given by

$$\phi_n^*(x) = \frac{1 + \tanh(\alpha x)}{2},$$  \hspace{1cm} (4)

with $\alpha = \sqrt{15 \pi}/\lambda$. We define the sharp interface to be at the point $x = 0$, where $\phi_n^*(x) = 0.5$ is halfway between the interior ($\phi = 1$) and exterior ($\phi = 0$) the cell.

Recall the evolution of the phase field model is restricted by the area conservation term

$$\frac{d\phi_n}{dt} \bigg|_{\text{Area}} = -\frac{2\mu}{\pi R^2} \phi_n \left[ \int dx \int d\phi \phi_n^2 - \pi R_0^2 \right].$$

Consider the interface $\phi_n$ to be at equilibrium at time $t_i$ but with a change $\Delta A$ from the equilibrium area $A_{eq} = \pi R_0^2$. Assuming all other terms remain at equilibrium, this will introduce a change to the field

$$\frac{d\phi_n}{dt} \bigg|_{\text{Area}} = -\frac{2\mu}{\pi R^2} \phi_n^* \left[ A_{eq} + \Delta A - A_{eq} \right] = -\frac{2\mu}{\pi R^2} \phi_n^* \Delta A.$$

Using the 1st-order (forward-Euler) approximation, we find that the solution at $t_{i+1}$ is

$$\phi_n(x, t_{i+1}) = \phi_n^*(x) + \Delta t \cdot (-\beta \phi_n^*(x)),$$

with $\beta = 2\mu \Delta A/\pi R^2$. Solving for the updated position of the interface, $\phi(x, t_{i+1}) = 0.5$, and using eq. (4), the updated position of the interface will be

$$0.5 = \phi_n^*(x) + \Delta t \cdot (-\beta \phi_n^*(x)),
\quad x = \frac{1}{\alpha} \arctan\left(\frac{\beta \Delta t}{\beta \Delta t - 1}\right).$$

We then take the limit

$$\lim_{\Delta t \to 0} \frac{x}{\Delta t} = \frac{\beta}{\alpha} = \sqrt{(8/15)} \lambda,$$

to obtain the rate at which a change in area $\Delta A$ moves the position of the interface. Thus, we obtain an approximation for the area conservation term in the sharp interface limit

$$\frac{\partial R(\theta, t)}{\partial t} \bigg|_{\text{Area}} = \mu' \left( A(R(\theta, t)) - \pi R_0^2 \right) \hat{n}(\theta, t),$$  \hspace{1cm} (5)

where we have defined $\mu' = \sqrt{\frac{8/15}{\pi R_0^2}} \mu$. Note that this derivation also assumed that the area of a cell at equilibrium is $\pi R_0^2$, for both the sharp interface and CPF models. This is a good approximation since $\int_{-\infty}^{d}(1 + \tan h(x))/2^2 dx \approx d - 0.5$.

To derive the neighbor-neighbor interactions, we follow a similar procedure, though the equations do not have a closed-form solution and will require some additional approximations. Note that the CPF repulsion term is second order, similarly to [7], while other phase-field methods may use a linear term. As the cells do not overlap during a simulation, we expect these changes to yield similar results with possible higher-order corrections such as the degree of confluence. We first consider the interface of cell $n$ centered at $x = 0$, and another cell with an interface in the opposite orientation centered at $x = -d$. We assume the cells to be at their unperturbed equilibrium, and now overlap. In actuality, this overlap would perturb the interface resulting in a smaller interface width and profile, though those corrections are unnecessary for our desired level of description. Assuming all other terms remain at equilibrium, this overlap leads to an updated interface location

$$\phi_n(x, t_{i+1}) = \phi_n^*(x) + \Delta t \left[ 1 - \frac{30}{\lambda^2} 2 \kappa \phi_n^*(x) \phi_n^*(x - d)^2 \right]$$

$$0.5 = \phi_n^*(x) \left[ 1 - \frac{30}{\lambda^2} 2 \kappa \phi_n^*(x - d)^2 \right]$$

$$0.5 = \kappa \left\{ -15 \Delta t + \lambda^2 + 30 \Delta t \tan h(\alpha d) \right\}$$

$$-15 \Delta t \tan h^2(\alpha d) + 15 \alpha \lambda^2 + \alpha \lambda^2$$

$$-45 \Delta t \tan h^2(\alpha d) + 30 \alpha \Delta t \tan h^3(\alpha d) \right\}$$

$$x = \frac{\alpha(15 \Delta t - 2 \Delta t \tan h(\alpha d) + 2 \Delta t \tan h^2(\alpha d))}{15(15 \Delta t + \lambda^2/\kappa - 45 \Delta t \tan h^2(\alpha d) + 30 \Delta t \tan h^3(\alpha d))},$$

where in the 3rd line we have taken the 1st-order series expansion around $x = 0$, so that the equation may be solved analytically. Taking the same limit as in the area term gives us an expression for the rate of change of the interface position due to the neighbor-neighbor term

$$\frac{\partial R_n(\theta, t)}{\partial t} \bigg|_{\text{Neigh}} = \frac{15 \kappa (\tan h(\alpha d_n, \theta) - 1)^2}{\alpha \lambda^2},$$

as a function of the distance $d$ between the two cell interfaces. Thus, the sharp interface limit of the interactions between cell $n$ and all other cells is given by

$$\frac{\partial R_n(\theta, t)}{\partial t} \bigg|_{\text{Neigh}} = \frac{15 \kappa (\tan h(\alpha d_n, \theta) - 1)^2}{\alpha \lambda} \hat{n}(\theta, t),$$  \hspace{1cm} (6)

where $d_{n, \theta}$ is understood to be the distance between $R_n(\theta, t)$ along $n_\theta$, to the nearest neighboring cell.

2.2 Cell velocity

Up to this point, our description of the sharp interface has not accounted for cell motility. We have already seen that a sharp interface cell $n$ will move with a velocity $v_n$ with the additional term

$$\frac{\partial R_n(\theta, t)}{\partial t} = v_n.$$
As in the CPF, each cell will have a single velocity which consists of both an active, and an inactive part,
\[ \mathbf{v}_n = \mathbf{v}_n^{\text{Active}} + \mathbf{v}_n^{\text{Inactive}}. \] (7)
The active velocity describes the cell’s net self-propulsion, and is driven by the cellular motors. This velocity can be applied directly to each cell. As before, we chose this active velocity to have a constant magnitude \( v_A \) and reoriented with probability \( P(\tau) = \frac{1}{2} e^{-\tau/\tau_e} \), where \( \tau \) is the mean time between reorientations. The inactive velocity of cell \( n \) is due to forces exerted by the other cells surrounding it. In CPF, the inactive velocity was given by
\[ \mathbf{v}_n^{\text{Inactive}} = \frac{60k}{\xi^2} \int dz \int dy \phi_n (\nabla \phi_n) \sum_{m \neq n} \phi_m^2, \]
where \( \xi \) is due to friction between the cells, the substrate, and the surrounding water. In a similar procedure to estimating the non-local terms, we will substitute the equilibrium solution \( \phi^*(x) \) for both cells \( n \) and \( m \), and evaluate the expression as a function of the distance \( d \) between the two interfaces. No approximations or simulated time step is needed, and the integral can be evaluated exactly to give
\[ \mathbf{v}_n^{\text{Inactive}} = \sum_{\varphi} \frac{30k}{(\varphi^2 d_n, \varphi^2 - 1)^4} \left[ 1 + e^{4\varphi d_n, \varphi^2} (4\varphi d_n, \varphi^2 - 5) 
+ e^{2\varphi d_n, \varphi^2} (4 + 8\varphi d_n, \varphi^2) \right] \mathbf{n}_\varphi. \] (8)
Since the calculation of \( d \) is the most computationally demanding portion of our model, we use the distance \( d_n, \varphi^2 \) computed for the neighbor-neighbor interaction, and assume that this value of \( \mathbf{v}_n^{\text{Inactive}} \) is constant over the interval \( \theta = \varphi \Delta \theta - \frac{\varphi + \varphi - 1}{2} \). Thus combining eqs. (3), (5), (6), (7) and (8) the complete evolution of each cell is given by
\[ \frac{\partial \mathbf{R}_n(\theta, t)}{\partial t} = \left[ \gamma K(\theta, t) + \mu(\theta = \pi R^2) \right. 
+ \frac{150 \tanh(\alpha d_n, \varphi - 1)}{\alpha \lambda} \mathbf{n}_\varphi 
+ \mathbf{v}_n^{\text{Inactive}} + \mathbf{v}_n^{\text{Active}}. \] (9)

2.3 Numerical implementation

To this point we have implicitly defined positions along the interface by a radial representation, \( R(\theta, t) \). While this is well suited to cells that are mostly spherical, this representation has several limitations, particularly for cells with large deformations. This representation is explicitly single valued and cannot account for overhangs. There are also challenges in the numerical implementation to the radial representation. For example, to have uniform spacing in \( \theta \), would require either that all tangential components \( \theta \) be discarded to preserve the uniform spacing; or alternatively that the points be redistributed to be uniform after every time step.

For our model system and parameter set, we found that a Cartesian coordinate representation was more convenient. Hence, we moved to represent each point \( P_i \) along the interface by its position in the \( x-y \) plane, as shown in fig. 1. This representation requires only infrequent redistribution of points. The curvature is computed as
\[ K(P_i) = \frac{P_i^y P_i^y - P_i^x P_i^x}{[(P_i^x)^2 + (P_i^y)^2]^{3/2}}, \]
and the area is given by \( A = \frac{1}{2} \int P_x P_y dP \), where \( P_x \) and \( P_y \) denote a partial derivative along \( x \) and \( y \). Since each point along the interface can move in any direction, they may move too closely together leading to numerical instability. Hence, we redistribute the points along the interface by use of spline interpolation when needed, using the centripetal Catmull-Rom spline [35], since it will not form closed loops or cusps within a curved section. We perform this redistribution whenever adjacent points \( \Delta P_i \) are either too close (\( \Delta P_i < 0.8 \Delta P \)) or too far apart (\( \Delta P_i > 1.5 \Delta P \)), as compared to \( \Delta P = 2\pi R/N \) which is the uniform spacing for a circle.

Another challenge is that cells can become too deformed and lead to instabilities. In particular, a soft cell that is pushed by two normal cells on opposite sides, may “pinch-off” a portion of the cell by bringing the two opposite interfaces of the soft cell to touch. This can be resolved in several ways. The first is to make the cells stiffer, however in our model system this would not allow for sufficient elastic mismatch between the soft and normal cells. A second option is to penalize pinching-off by adding a self repulsion term to the model. This would better represent the mechanical and chemical mechanisms that exist in real cells which prevent pinching-off from occurring. Another approach would be to add terms that account for pressure prorogation, as is done in cell blebbing [36], although
Table 1. Model parameters. Simulation parameters for our sharp interface model, and comparison with CPF.

|                | γ     | κ    | μ    | ξ    | τ    | v_A   |
|----------------|-------|------|------|------|------|-------|
| Sharp interface model | Soft: 0.45 | 5    | 0.5  | 10^3 | 10^4 | 10^{-2} |
|                | Normal: 1.25 |      |      |      |      |       |
| CPF            | Soft: 0.3  | 10   | 1    | 1.5 \cdot 10^3 | 10^4 | 10^{-2} |
|                | Normal: 1  |      |      |      |      |       |

Fig. 2. Simulation snapshot. Snapshot from a simulation with degree of confluence $\rho = 80\%$, showing the soft cell in green, and normal cells interfaces in blue.

Consisted of the first $t = 40000$. Following that, samples were taken every $t = 800$, for a total simulation time of $t = 2 \cdot 10^6$ for each run. Using these units, $t = 1$ corresponds to roughly 0.36 s in real time. Our sharp interface model was implemented using C++ and openMP, with use of the boost library [38]. Run on a Compute Canada cluster, a single $t = 2 \cdot 10^6$ simulations took approximately 8 hours of wall time using 16 cores. This constitutes a roughly 200 factor speedup over a traditional CPF implementation.

A more systematic comparison of the scaling of the two methods for simulating $n$ cells is as follows: in a phase-field implementation on a uniform grid, each cell requires $O(R^2)$ discrete points. Since each grid point is updated at each time-step $\Delta_{cpf}$, a simulation requires $O(R^2 \cdot n/\Delta_{cpf})$. In contrast, each cell in the sharp-interface model requires only points on the interface, and hence computing the curvature and area terms can be performed in $O(R)$. Finding the intersection point of the neighbor-neighbor interaction is the most computationally intensive portion of the method. We only include cells that are sufficiently close, and using simple geometric arguments, the number of comparisons can be limited to a handful of possible neighboring sites, and hence maintain linear scaling. Thus the overall scaling of the model is $O(R \cdot n/\Delta_{s-i})$. The linear scaling along with the larger time-step (here $\Delta_{s-i}/\Delta_{cpf} = 10$), yields, for our simulations, up to two to three orders of magnitude speedup compared to a phase-field implementation, in agreement with our numerical results.

3 Simulation results

Having derived a sharp interface model for cells with tunable elasticity, we present the results of our simulations. The model can be summed as solving eq. (9), using the natural curvature in eq. (10) and with the parameters shown in table 1. As in CPF, the model can be used at any degree of confluence, that is at any concentration, $\rho = N_{cells} \pi R_0^2 / L^2$.

This may significantly increase computation time due to the smaller length and time scales. We opted for a simple approach, which is to offset the curvature term

$$K_{natural}(P_i) = K(P_i) - \frac{1}{R_0},$$

by the natural curvature of a cell with radius $R_0$, analogous to Helfrich theory [37]. We found this was sufficient to prevent the cell from being pinched-off while still allowing large deformations needed for bursts.

Model parameters were estimated from experimental data, as was done in CPF. As shown in table 1 they remain similar, with some minor modifications, improving the stability of cells while also preserving the deformation needed to allow for bursts. Despite these minor changes, having derived our model directly from CPF, we think these models yields asymptotically the same results. A sample snapshot from a simulation is shown in fig. 2, where the soft cell is colored in green, and all other cells have normal stiffness and are shown in blue.

Simulations were performed with the same parameters shown above, unless otherwise mentioned, in a simulation box with periodic boundary conditions. 72 cells were used, each consisted of $N = 150$ points, and forward Euler integration was used with a time step $dt = 0.1$. The curvature was computed using a 2nd order (5 point) symmetric stencil. Simulations were initialized with the same random number seed and in a hexagonal lattice, and equilibration this may significantly increase computation time due to the smaller length and time scales. We opted for a simple approach, which is to offset the curvature term

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3.1 Burst behavior

Rare bursts of high cell velocity were observed in experiment [39] as well as by our previous CPF model and play...
The elasticity of all cells is changed, ranging from the all-uncorrelated with perimeter change as $\langle \rho \rangle$ formed at bursts, we look at the average change in perimeter $\langle \Delta L \rangle$, binned as a function of velocity magnitude $|v|$. Each symbol corresponds to different elasticity where all cells are adjusted, spanning $\gamma = 0.45$–1.25, and the active motor speed is 0.1. As elasticity is decreased, higher velocities become increasingly correlated with a negative $\langle \Delta L \rangle$, indicating that bursts are likely to occur when the cell has relaxed from a more deformed to a less deformed state.

### 3.2 Velocity distribution

We have shown that our sharp interface model can recover the main features of the CPF model, at a significant reduction in computation time. This speedup makes a broader study of parameter space feasible. We begin by studying the effect of system concentration. As before, a single soft cell with all other cells having normal elasticity are simulated at various concentrations, ranging from near confluent $\rho = 95\%$ to the very dilute $\rho = 25\%$.

Figure 5 shows the velocity probability distribution of an all-normal simulation in three regimes: (a) a very dense system, $\rho = 93\%$ (Movie #1 in the ESM), where the velocity probability distribution is highly non-Gaussian, but the overall velocity is limited by the presence of neighboring cells; (b) and (c) intermediate concentrations, $\rho = 81$ and $77\%$ (Movies #2 and #3 in the ESM), cells move faster but there are less bursts as the tail is nearly Gaussian; and finally (d) at a very dilute concentration, $\rho = 25\%$ (Movie #4 in the ESM), where the cells interact less frequently and the distribution resembles that of an isolated cell, which peaks at the motor active velocity $v_A = 0.01$. Each plot also shows several best fit lines. The solid lines are a Gaussian fit, obtained by including velocities $0 \leq v \leq v'$, where the cut-off $v'$ is chosen to minimizes the Chi squared of the fit. This was done since it is evident that the tail of the distribution is non-Gaussian and including it in the fit skews the low velocity behavior that

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**Fig. 3.** Sharp interface model recovers soft cell burst. Probability plot for instantaneous cell velocity of both soft-in-normal (green triangles) and all other normal cells (blue circles) of a $\rho = 83\%$ simulation. Plotted as quantile where Gaussian probability is a straight line, and showing best Gaussian fit for soft-in-normal (green dashed line) and all other normal cells (blue dashed line).

**Fig. 4.** Average change in perimeter as a function of velocity for different elasticities. The average change in perimeter, $\langle \Delta L \rangle$, binned as a function of velocity magnitude $|v|$. Each symbol corresponds to different elasticity where all cells are adjusted, spanning $\gamma = 0.45$–1.25, and the active motor speed is 0.1. As elasticity is decreased, higher velocities become increasingly correlated with a negative $\langle \Delta L \rangle$, indicating that bursts are likely to occur when the cell has relaxed from a more deformed to a less deformed state.
does appear to follow Gaussian statistics. The dashed red line is a student-t distribution fit for the entire velocity distribution.

The student-t distribution proved to be a fit for the velocity distribution in all but the most dilute of simulations. Given a set of Gaussian random numbers \(X_i\) with mean 0 and standard deviation \(\sigma\), sampling \(\sum_{i=1}^{n} X_i/S\sqrt{n}\) (where \(S\) is the sample variance) gives a student-t distribution with \(n-1\) degrees of freedom. \(X_i\) can be thought of as the cell motor sampled over the neighboring cells that it is interacting with. Here we use the 2-parameter student-t, where \(\sigma\) sets the scale of the distribution, and \(\beta = n - 1\) denotes the degrees of freedom [40]. Results of fitting the student-t \(\sigma\) parameter are plotted as a function of concentration at the top of fig. 6. This shows a clear relation where increased \(\rho\) leads to lower \(\sigma\), as crowding makes higher velocities increasingly unlikely. We found our results are well described by the one parameter fit

\[
\sigma(\rho) = a\sqrt{1 - \rho^2}, \tag{11}
\]

shown as a solid line. Therefore, we motivate this particular form by considering the symmetry around \(\rho = 1\). Although as plotted here \(\sigma\) is positive semi-definite, the complete \(v_\tau\) distribution is both positive and negative, and symmetric around zero. Similar to a Gaussian distribution, \(P(v = \pm \sigma)/P(v = 0) \approx 1/\sqrt{\pi}\) (given the relation for \(\sigma(\rho)\) and \(\beta(\rho)\), this is within 5% even at \(\rho = 1\)), and this form preserves this symmetry continuity. In the bottom of fig. 6, we plot the other fit-parameter of the student-t, \(\beta\). Rather than as a function of concentration, \(1/\beta\) as a function of the expected \(\sigma\) from eq. (11) shows that below a critical value of \(\sigma^*\), it follows

\[
\beta(\sigma)|_{\sigma < \sigma^*} = \frac{1}{b_1\sigma + b_0}. \tag{12}
\]

This reduces the two parameter student-t to a single fit parameter \(\sigma\) (or equivalently, \(\rho\)). As concentration is increased, cells are more confined and move with reduced velocity, yet the tail of the distribution becomes more pronounced as collective behavior leads to increased bursts. Note that fitting beyond \(\beta = 100\) proved difficult as it is numerically indistinguishable from a Gaussian distribution. There are, of course, many other possible distributions that resemble a Gaussian with fatter tail. In our previous analysis of the CPF results, we had shown that the heavier than Gaussian tail of the velocity distribution could be fitted in two ways: the student-t distribution, as well as a single parameter “caged cell” fit where the soft cell mostly behaves like a normal cell, with the exception of rare events where its motor supplements the Gaussian velocity given by the surrounding cells. Here we found the caged cell model was not a good fit, particularly for the all-normal cells.

To further illustrate the scaling of the velocity distribution with respect to concentration, fig. 7 shows the velocity probability distribution for all concentration in a quantitative plot \(T(v_\tau)\) such that a student-t distribution would form a straight line. Each concentration was rescaled by \(\sigma(\rho), \beta(\sigma)\) as given from eqs. (11), (12) respectively. The data largely collapses to the master curve showing that the student-t parameter relations as a function of \(\rho\), hence these are accurate in predicting the full velocity distribution at any concentration. The slight spread deep in the tail of the distribution is likely due to the small sampling of rare events, and propagation of error in determining \(\sigma\) and \(\beta\). The main exceptions are the two most dilute sim-

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**Fig. 5.** Velocity distribution. The instantaneous velocity probability distribution for all-normal cells at different concentrations (a) \(\rho = 93\%\), (b) \(\rho = 81\%\), (c) \(\rho = 77\%\), (d) \(\rho = 25\%\) plotted such that a Gaussian distribution is a straight line. Also plotted are Gaussian (black line) and student-t (red line) best fit lines. Simulation videos for each scenario can be found in the Electronic Supplementary Material (ESM).**

**Fig. 6.** Student-t parameter fits across concentrations. Student-t fit parameter of instantaneous velocity probability distribution, for all-normal cells at different concentrations. Top: \(\sigma\) as a function of concentration, with the solid line a single parameter best fit \(\sigma = a\sqrt{1 - \rho^2}\). Bottom: student-t fit parameter \(\beta\) as a function of \(\sigma\) according to the fit above (eq. (11)). The solid line is a linear fit for small \(\sigma\).
Data collapses onto the dashed line, with the exception of the $\sigma$ representing an ideal student-t distribution (for any $\sigma$ and $\beta$). The dashed line represents an ideal student-t distribution (for any $\sigma$ and $\beta$). Data collapses onto the dashed line, with the exception of the 2 most dilute simulations.

These more closely resemble the distribution of an isolated cell, with a peak at $v = v_A = 0.01$, as was seen in fig. 5(d). Here, the sharp fall off cannot be described by a normal or student-t distribution.

### 3.3 Cell motility

Having shown that softer cells experience more bursts, we now examine whether this leads to higher cell motility. There are various methods for calculating the motility. Here we chose to use the integral of the velocity auto-correlation (VACF), $D(t) = \frac{1}{2} \int_0^t \left( \mathbf{v}(t') \cdot \mathbf{v}(0) \right) dt'$, where taking $\lim_{t \to \infty} D(t)$ yields the diffusion constant [41,42]. We estimate this by averaging over $D(t)$ at late times. As shown in fig. 8, this allows for a good estimate of the VACF quickly converges to 0, and so a shorter time window can be used to accurately estimate $D(\infty)$ by averaging $D(t)$ after it stops rising. The solid line shows the final result of averaging. Since these simulations include 71 normal cells but only 1 soft cell, the latter has significantly more noise. The fluctuations of the average underestimate the systematic error since they are correlated. Instead we estimated systematic error as follows: performing 20 independent simulations, a diffusion constant was computed for each run. Fitting a normal distribution to these 20 results yields their standard deviation. We find that it is 3.2% for the normal cells, and 9.2% for the soft-in-normal cell. As such, it is difficult to evaluate the behavior of the soft-in-normal cell, beyond what we already demonstrated in fig. 3.

Examining the instantaneous velocity distribution, we showed competition between increasing burst frequency and an overall reduction in the mean velocity as $\rho$ increases. One may ask: how does this affect cell motility? Following the procedure outlined previously, fig. 9(a) shows the motility for different concentrations, as well as for different cell stiffness. Compared to the all-normal case, the error for the soft-in-normal is considerably higher, which makes it difficult to draw conclusions. Therefore, to study the effect of elasticity, it was varied for all cells in a given simulation ranging from the all-normal $\gamma = 1.25$ to the all-soft $\gamma = 0.45$. Also shown on the plot are our two previous CPF results, for both the soft-in-normal (green star) and normal-in-normal (blue star) simulations at $\rho = 90\%$, and the well-known result $D(\rho) = D_0 (1 - \rho)$, (13) derived for a discrete random walk where cells move to an adjacent site unless it is already occupied [43]. Overall, our results are consistent with these three results. The linear fit appears to describe general scaling, and diffusion is reduced with increased concentration. The inset shows the residuals between the $\gamma = 1.25$ all-normal simulation and the theoretical fit. Though the residuals are small, there appears to be some additional higher order behavior beyond linear scaling. We also see that at each concentration, lower elasticity leads to increased diffusion. To better illustrate this, in fig. 9(b) we plot $D(\gamma)$ for different concentrations. The best fit lines correspond well with data, indicating that at all concentrations, increased elasticity reduces cell diffusion, at a rate that is roughly constant within error. Hence, decreasing cell elasticity leads to increased cell motility, at all concentrations, consistent with results from CPF.

Finally, we examine the role of the cellular motor parameters on diffusion. For isolated cells, diffusion can be derived analytically. $D_{iso} = \frac{1}{2} v_A^2 \tau$. For non-isolated cells, that relation no longer holds for several reasons. As cells are interacting, the effective velocity is on average lower than the active velocity. As well, reorientation time due to collisions may be shorter and dominate over the motor reorientation time. To decouple these effects, fig. 10 shows the resulting diffusion constant when $\tau$ is varied while keeping $v_A$ constant, for a range of concentrations.

![Fig. 7. Instantaneous velocity probability distributions master curve.](image)

![Fig. 8. Estimating diffusion constant from velocity auto-correlation.](image)
magnitude of cellular diffusion, the qualitative behavior of higher \( \rho \) leading to slower diffusion remains consistent. It is also evident that the measured diffusion is non-linear with respect to \( \tau \), and the slope at \( \tau = \tau_0 \) is smaller than 1. At \( \tau / \tau_0 \ll 1 \), the active velocity oscillated rapidly, leading rapid decorrelation of the VACF and hence, a decreased diffusion constant [44]. Due to collisions with the surrounding cells, increasing \( \tau \) increases \( D \) but at a diminishing rate. This reduction is correlated with increased concentration, and diffusion appears to level off at a lower value of \( \tau / \tau_0 \) for denser systems.

4 Discussion

Our paper focused on a new, sharp interface model for the simulation of assemblies of motile cells with varying elasticities. The model was inspired by a previous phase field approach to this system. While successful in recreating velocity bursts, that method was very computationally demanding. By approximating the cell interface and ignoring all bulk behavior, we were able to dramatically speed up the simulation time by a factor of \( \sim 200 \). Model parameters allow to independently tune differing elasticities for each cell while keeping all other cell properties identical. These parameters were largely derived from the CPF model, using equilibrium approximations to determine the strength of the various terms. The sharp interface model is more susceptible than CPF to cell pinching, where opposite ends of the cell interface can overlap. In this study we circumvented this issue by making the cells slightly stiffer and adding a term which corresponds to a spontaneous curvature in the energy functional. Other solutions, such as adding an internal cell wall repulsion are feasible and may allow the simulations of softer cells. A comparison of these approaches may elucidate some of the observed difference between this sharp interface model and previous CPF results. Our model is also distinct from other sharp interface models of cells. Though some studies focused on the motion of individual cells in greater detail, we are able to simulate large systems efficiently, while maintaining description at the individual cell level. Conversely, most existing methods that do allow for much larger systems size do not allow for large deformations of individual cells, which we have shown to be key to velocity bursts.

We demonstrated that this model recovers behavior seen in experiment, as well as many but not all of the features of the full CPF model with respect to cell dynamics. As before, soft cells show an increased likelihood of high velocity burst events than stiffer cells. These bursts were described by performing a student-t fit to the velocity probability distribution, where a lower degree of freedom, \( \beta \) represents a “fatter” tail of the distribution. We have also shown that these bursts occur as a highly deformed cell relaxes to a more spherical configuration, qualitatively consistent with previous CPF results as well as with experiment. These bursts result in softer cells having higher motility (diffusion constant) than normal cells at the same concentration.
We also obtained several new results that were not feasible with the computationally slower CPF model. For a given elasticity, we have shown that both $\beta$ and $\sigma$ are consistent with a simple relation to $\rho$, and that these reduce the student-t to a single parameter fit. Below a cut-off concentration, $\beta$ is infinite suggesting the tail is Gaussian or below-Gaussian, as seen at very dilute simulations. Above this cut-off, $1/\beta$ is linearly correlated with concentration as more bursts are seen. On the other hand, $\sigma$ decreases with increased concentration, as cells lack free space to move to and overall mobility is reduced. This becomes clear when examining cell motility which appears to linear decrease with $\rho$, consistent with theory. Furthermore, this linear relation appears to hold across various cell elasticities. Finally, we have shown that at a given concentration, motility is also linearly related to cell elasticity. Although softer cells are more motile than stiffer cells, the quantitative difference between the two is less pronounced than that in the CPF model. Finally, we showed that varying our motor parameters does not affect these relations qualitatively.

There are several other prospects for application of this model. The first is to better understand some of the differences between CPF and this sharp interface model, though this will likely require considerable computational resources to perform comparable CPF simulations at various parameters and with sufficient statistics. Another avenue is to extend this model to other biologically relevant systems. In particular, future work will examine the additions of cell-cell adhesion, which can be different for cancer and healthy cells. It remains to be seen whether adhesion changes the burst behavior and in what way. Similarly, different cellular motor schemes could also lead to changes in bursts or motility.

Finally, we are also interested in applying the model to physics systems which may not be directly tied to biology. For example, as the concentration tends to 1 and $\sigma$ approaches zero, we are studying an apparent order-disordered phase transition, similar to those studied in other model systems.

In summary, we have developed a new model for simulating cells on a monolayer. This sharp interface model has similar advantages to CPF by explicitly tracking deformations of individual cells with tunable elasticity, yet it is 200 times faster. We recover previous results for velocity bursts, as well as demonstrate new description of the velocity distribution and cell motility as a function of concentration and cell elasticity.

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