Statistical features of collective cell migration

Caterina A. M. La Porta and Stefano Zapperi

Abstract We discuss recent advances in interpreting the collective dynamics of cellular assemblies using ideas and tools coming from the statistical physics of materials. Experimental observations suggest analogies between the collective motion of cell monolayers and the jamming of soft materials. Granular media, emulsions and other soft materials display transitions between fluid-like and solid-like behavior as control parameters, such as temperature, density and stress, are changed. A similar jamming transition has been observed in the relaxation of epithelial cell monolayers. In this case, the associated unjamming transition, in which cells migrate collectively, is linked to a variety of biochemical and biophysical factors. In this framework, recent works show that wound healing induce monolayer fluidization with collective migration fronts moving in an avalanche-like behavior reminiscent of intermittent front propagation in materials such as domain walls in magnets, cracks in disordered media or flux lines in superconductors. Finally, we review the ability of discrete models of cell migration, from interacting active particles to vertex and Voronoi models, to simulate the statistical properties observed experimentally.

Keywords

jamming, bursts, particle image velocimetry, active particle models, wound healing

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1 Introduction

Collective cell migration is a fascinating topic of great biological relevance [23]. Cells in tissues often do not move independently, but interact closely and move together. This phenomenon is relevant for cancer metastasis [32], where group of cells have been observed to collectively invade neighboring tissues [52, 30, 25]. The biophysical aspects of collective cell migration can be discussed from the point of view of active matter [51]: Cell assemblies can be seen as peculiar type of out of equilibrium material that is able to convert internal biochemical energy into mechanical and kinetic energy. As for ordinary matter, active matter can display transitions into different states with characteristic macroscopic properties in terms of flow or spatial correlations. The main aspect that we wish to explore in this chapter is related to the fluctuations associated to these states.

Individual cells move in a very erratic manner, performing a persistent random walk with statistical properties accurately described by simple stochastic differential equations. The problem becomes more intriguing when the cell concentration is increased and cells respond due to their mutual interactions. When cells are crowded they slow down, up to a point where their motion becomes confined as in a glass [1, 48]. This can be quantified by cell mean-square displacements that grow in diffusive or ballistic fashion for isolated cells and becomes bounded in crowded conditions [40]. Cellular self-propulsion can counteract the caging effects due to crowding leading to a collectively flowing state. The most widespread interpretation of this phenomenon is in terms of the jamming/unjamming transition, widely observed in soft matter systems such as foams, colloids or granular media [39]. The main difference for cells lies in the presence of internal active forces driving the transition and thus creating a completely new playground.

Self-propulsion forces become important in particular conditions, for instance when cells are faced with an empty space to invade, as in the case of wound healing [13]. The intermittent dynamics of an invading cell front is reminiscent to other fronts studied in condensed matter systems, such as crack lines or magnetic domain walls. The analogy is not only qualitative, since the distribution of bursts in cell front invasion follow the same statistical distributions as in disordered elastic systems in condensed matter [12]. Here, we discuss analogies and differences between cell migration and the transitions to flow in ordinary matter, focusing on few relevant experiments and on computational models based on interacting cells, represented as active particle [62, 50, 28, 58, 66, 21, 6, 42, 63, 22, 38] or polygons in vertex models [7, 8].

2 Fluctuations in the migration of individual cells

Before discussing the fluctuations in the migration of collective assemblies of cells, it is useful to briefly recall here the stochastic behavior observed in individual cells as they migrate. It has been widely reported that cell trajectories *in vitro* display

random fluctuations similar to those observed in Brownian particles [16, 49]. Cells, however, are not just particles driven by the fluctuations in the fluid but involve internal active forces. As indeed shown by careful quantitative analysis, cells do not perform a simple random walk [61, 37, 17, 49, 69] but a persistent random walk (PRW), characterized by long periods of persistent directional motion in one direction separated by re-orientation event, as illustrated in Fig. 1a [37]. This process is well described by a persistent random walk, following a simple Langevin equation [61, 69]

$$\frac{d\mathbf{v}}{dt} = -\frac{\mathbf{v}}{\tau} + \sqrt{\frac{D}{\tau}}\eta(t), \tag{1}$$

where $\mathbf{v}$ is the cell velocity, τ is the persistence time, $\eta(t)$ is an uncorrelated Gaussian noise with zero mean and unit variance, and the noise strength is tuned by D. This linear stochastic model can be easily solved and yields a mean-square displacement

$$\langle(\mathbf{r}(t+t_0)-\mathbf{r}(t_0))^2\rangle = 2D\tau\left(\exp(-t/\tau) - \frac{t}{\tau} - 1\right). \tag{2}$$

Eq. 2 interpolates from an exponential increase at short times to a linear diffusive behavior at large times which agrees with experimental data for two dimensional motion as shown in Fig 1b [69].

An alternative model to explain the deviation from pure Brownian motion is provided by anomalous diffusion, where the mean square displacement scales as $t^2\alpha$, with $\alpha > 1/2$) [17]. Indeed, recent experiments tracked individual cells moving through a three dimensional collagen matrix (see Fig. 2) and showed clear deviations from the simple PRW model [69, 44]. In particular, the distribution of velocities is not Gaussian as assumed in the PRW [69]. The correct distribution can be obtained by modeling cell heterogeneity and substrate anisotropies [69] and introducing a superstatistical framework [44] where the motion is modeled by a PRW with parameters (e.g. τ and D) that are themselves random functions. The superstatistical model is in excellent agreement with experimental results for cell motion in two and three dimensions [44].

3 Avalanches and fluctuations in collective cell migration

Understanding collective cell migration, when cells move as a cohesive and coordinated group is important to shed light on key aspects of embryogenesis, wound repair and cancer metastasis [23]. While cellular and multicellular dynamics and motility is controlled by a complex network of biochemical pathways [29], it is becoming increasingly clear that a crucial role is also played by physical interactions among cells and between cells and their environment[65, 10, 26, 33, 31]. In particular, experiments revealed that collective cell migration depends on the composition and stiffness of the extracellular matrix (ECM) on which the cells move[65, 10, 26, 33, 31]. The ECM of animal tissues is composed by a random hierarchical assembly of collegen fibrils and fibers whose mechanical properties

have many advantages thanks to their characteristic non-linear strain stiffening, allowing for easy remodeling and high sensitivity at small deformations and higher rigidity against strong deformations [55]. Collective cell migration can be studied *in vitro* by wound healing assays [66, 62, 50, 58], where confluent cell layers are scratched and the ensuing migration is observed in time lapse microscopy. When those studies are performed on substrates covered with collagen [27] and other gels [46] or micro-patterned [56, 54], cell migration is found to crucially depend on the substrate structure and stiffness.

The statistical properties of collective cell migration do not only depend on the interaction between cells and substrate but also from the mutual interactions among cells. Experiments showed that cells are able to transfer mechanical stresses to their neighbors [65], producing long-ranged stress waves in the monolayer [59, 3]. This observation suggests an analogy with disordered elastic systems in materials, where the dynamics is ruled by the interplay of elastic interactions and the interaction with a quenched random field. In the case of collective cell migration, the elastic interactions are provided by intracellular adhesion, while the role of the random field is played by the substrate. Disordered elastic systems in materials, such as cracks lines [41, 64], imbibition fronts [15] or ferromagnetic domain walls [20], all share

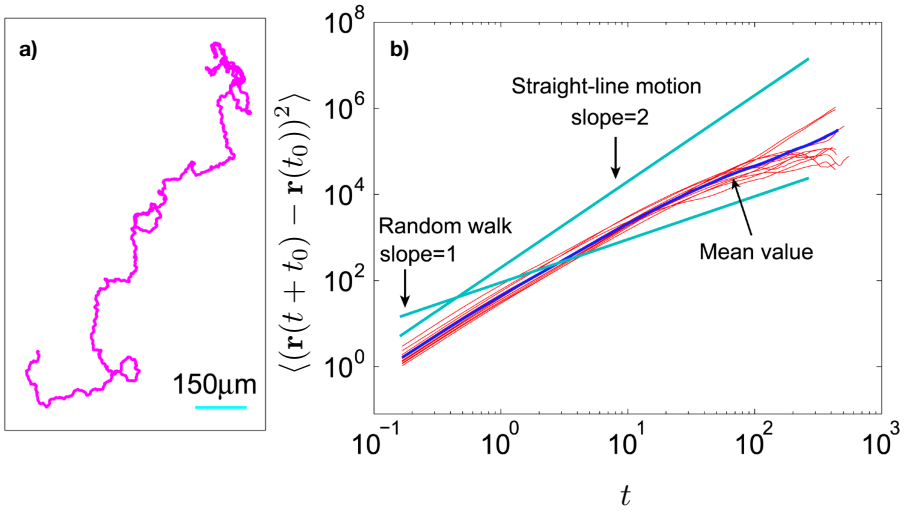

Fig. 1 a) A trajectory of a Dictyostelium cell lasting for 10 hours. b) The mean square displacements recorded of Dictyostelium cells follow the prediction of the persistent random walk model. Images adapted from Ref. [37] (Fig. 2a and 3b, CC licence).

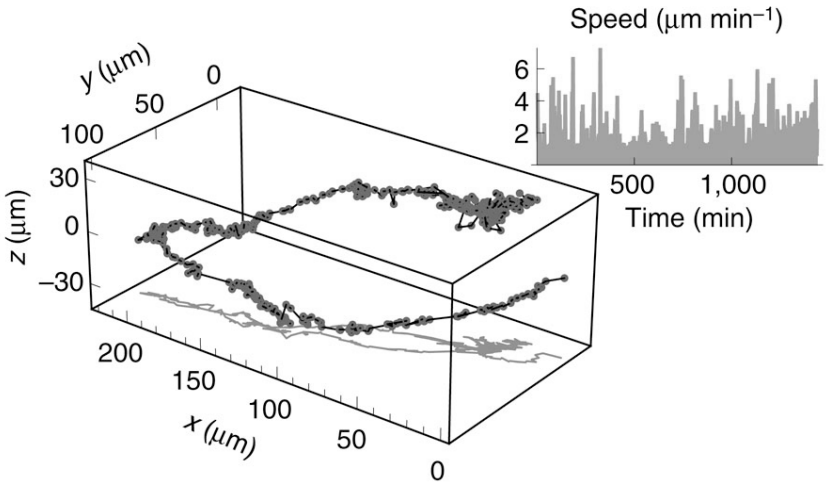

Fig. 2 A trajectory of a breast carcinoma cell migrating into a three dimensional collagen matrix . The inset shows the intermittent fluctuations of the cell velocity. Image from [44] CC licence

common features. When the driving force (e.g. the external load for cracks, the fluid pressure for imbibition and the magnetic field in ferromagnets) overcomes a threshold value the system flows while at low forces it is pinned by the disorder. The depinning threshold is associated with a non-equilibrium critical point characterized by scaling laws for the statistical properties of the dynamics, as revealed by numerical simulations [35, 53] and renormalization group theory [45, 35, 11, 34]. In particular close to the depinning threshold, the dynamic of the front is strongly fluctuating and intermittent, characterized by bursts of activity or avalanches. The statistics of these avalanche events follows a power law distribution with an exponent that is universal (i.e. it does not depend on the microscopic features of the system but only on the general symmetry of the interactions).

In a recent paper[12], we have shown by a careful analysis of time-lapse imaging during wound healing that a migrating cell front shares many similarities with moving front close to the depinning transition. The analysis has been performed on a variety of cell lines ((human cancer cells and epithelial cells, mouse endothelial cells) over different substrates (plastic, soluble and fibrillar collagen) and with varying experimental conditions (such as the tuning of intracellular adhesion by VE-cadherin knock down). An example of the evolution of the cell front in a monolayer of HeLa cell is reported in the bottom part of Fig. 3a. The fronts are rough and advance in bursts, as it is apparent by looking at activity map the top part of Fig. 3a, where the colored region corresponds to areas that move collectively, denoted

as clusters of activity. Activity maps were obtained using an algorithm devised to study avalanches in planar crack propagation [64] and imbibition [15]. As in the case of fracture or imbibition, the distribution of cluster areas S decays as a power law $P(S) \sim S^{-\tau}$ up to a cutoff length S^*, as illustrated in 3b for a variety of cell lines. It is interesting to remark that the value of the exponent $\tau \simeq 1.5$ is independent on the cell line [12] and is similar to the one observed in fracture [64].

In addition to the activity map, a useful technique to characterize the fluctuations in the dynamics of cell migration, both in confluent and in wound healing conditions, is provided by particle image velocimetry (PIV). PIV estimates local velocities by performing a digital image correlation analysis on the time-lapse sequence and allows to obtain a velocity map as the one reported in Fig. 3c for HeLa cells. The figure shows that cells move with significant fluctuations, also involving local motion that is opposite to the propagation direction of the front. The fluctuations can be captured by measuring velocity distributions as the ones reported in Fig. 3d. The distribution vary slightly for different cell lines, but the shape of the distribution is similar in all cases.

4 The jamming/unjamming transition in cell assemblies

The flow behavior of a wide class of soft matter systems, from colloidal suspensions [9] to emulsions [43], foams [19], gels [57] and pastes [14] is ruled by the presence of kinematic constraints, leading to jamming, a concept describing the suppression of temporal relaxation and the corresponding ability to explore the space of configurations [39]. These soft matter systems are typically composed randomly arranged particles, whose individual motion becomes constrained as the density increases. As a result of this, a jammed system responds like an elastic solid upon the application of low shear stresses. Under the action of externally applied shear stresses, however, these systems eventually yield and are able to flow like a viscous fluid. The yield stress depends also on the density, hindering the motion, and on the temperature that promotes flow. These observations can be summarized into a generic phase diagram for jamming systems that is reported in Fig. 4.

It has been argued that the collective dynamics of dense cellular assemblies, such as epithelial monolayers or cancer cell colonies, can bee described by the same framework employed for disordered soft matter. In particular, experiments show that cellular assemblies display slow glassy relaxation [2] leading to a jammed state, characterized by limited cellular motility [48]. Depending on the experimental conditions, cells can collectively flow like a fluid, but mutual crowding typically leads to slowing down and dynamic arrest in a way that is similar to the behavior observed in soft matter across the jamming transition [2, 48]. As in disordered solids, cell jamming can occur across different routes, but the potential ways are clearly more diverse in living systems than in soft matter. For instance, cell jamming can be triggered by an increase of cell density as in conventional soft matter, or by other cell specific mechanism such the reduction of the active forces responsible for

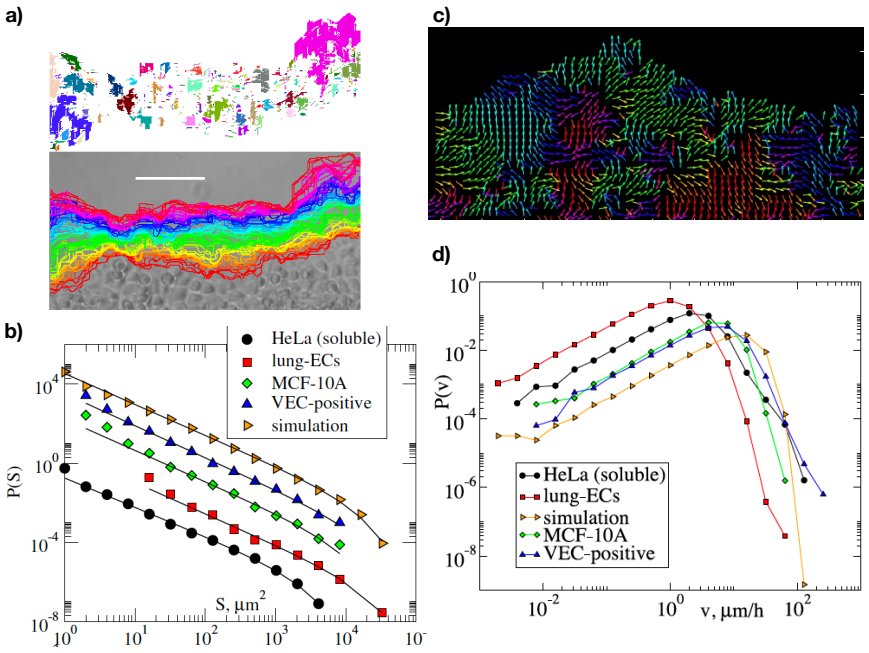

Fig. 3 Dynamic fluctuations in wound healing experiments. a) An example of cell a cell front and the activity maps reconstructed from the time evolution of the front in Hela cells moving on a collagen substrate. Regions marked by the same color in the activity map move collectively. The scale bar is 100μm. b) Distributions of the areas of activity clusters display power law scaling with a cutoff. The distributions for different cell types have been shifted for clarity. The slope obtained fitting the distributions is very similar for all cell types. c) Velocity map obtained from particle image velocimetry. The length of the arrows is proportional to the magnitude of the velocity. d) Distributions of velocity magnitudes for different cell types. Reprinted from [12] with permission.

cell motility [18], increased intracellular adhesion [24] or the expression level of some particular gene [40]. For instance, Malinverno et al. [40] showed that the overexpression of RAB5A, a master regulator of endocytosis, leads to rapid fluidization of a jammed epithelial layer. This unjamming is thought to arise due to the polarization of cell protrusion and increase in traction force. The role of cell-cell adhesion in affecting the properties of collective cell migration and the associated mechanical forces has been investigated extewnsively by knocking down more than twenty individual adhesion molecules [5]. The results show that P-cadherin is related to the strength of the adhesion forces, while E-cadherin controls the rate at which force grow.

Understanding cell jamming is important, not only for the intriguing analogies with soft matter systems but also for its possible functional biological role. Jamming could assist the development of tissue elasticity and the formation protective barriers in epithelial tissues, as well as suppressive mechanisms for the aberrant growth of

cancer cells. While experiments clearly show that jamming is a relevant concept to describe the behavior of cellular assemblies, it is difficult to fine tune parameters to carefully study the transition. This, however, can be done resorting to theoretical and computational models, as we discuss in the next section.

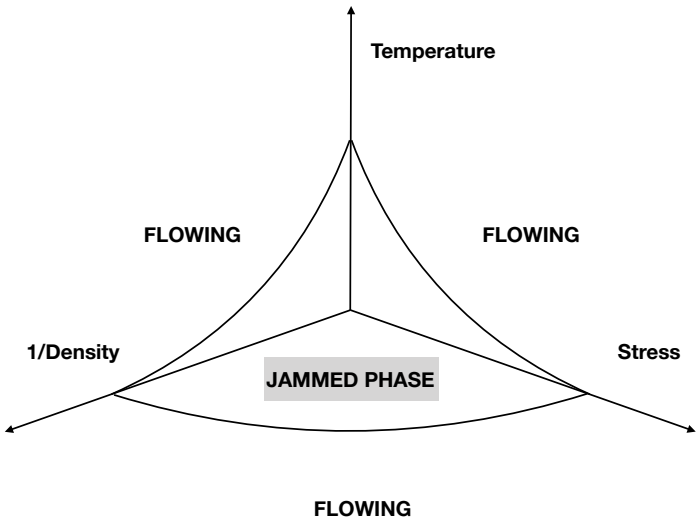

Fig. 4 A schematic jamming phase diagram in soft matter systems.

5 Discrete models for collective cell migration

To understand the statistical properties of collective cell migration it is useful to resort to theoretical and computational models. Models are interesting because they not only allow to reproduce with minimal ingredients the main features of the experiments, but mostly because they allow to identify the basic biophysical mechanisms ruling the observed behavior. Furthermore, simulations allow to explore the role of various biophysical parameters in determining the migration properties of the assembly and sometimes to reconstruct a possible phase diagram. The theoretical and computational literature on the subject is rather vast and here we restrict our attention to two main classes of discrete models, based on interacting active particles or Voronoi lattices. We refer the reader to chapter 4 for a detailed discussion of continuous models [60].

5.1 Interacting active particles

In active particle models [62, 50, 28, 58, 66, 21, 6, 42, 63, 22, 38], cells are modeled as a set of particles mutually interacting through an attractive force, due to intra-cellular adhesion, and hard core repulsion at short distances. Other important ingredients capture the tendency of active particle to align their velocities and self-propulsion forces driving the motion. Finally, the dynamics is affected by noise.

One of the first active particle models for cell migration [62] was constructed in analogy with flocking models originally devised to describe birds [67]. The model considers a two dimensional overdamped equation in which the velocity of each cell is driven by a combination of an active force and the interaction with neighboring cells [62]:

$$\frac{d\mathbf{r}_i}{dt} = \mathbf{n}_i(t)v_0 + \sum_j \mathbf{f}_{ij}, \tag{3}$$

where v_0 is proportional to the self-propulsion force and $\mathbf{f}_{ij}$ is the force between neighboring cells due to adhesion and repulsion. The cell orientation axis $\mathbf{n}_i$ evolves according to a stochastic differential equation, parametrized by an angle θ_i

$$\frac{d\theta_i}{dt} = \xi_i(t) + \frac{1}{\tau}\arcsin\left[\hat{z}\,(\mathbf{n}_i \cdot (\mathbf{v}_i/|\mathbf{v}_i)|)\right]. \tag{4}$$

Finally $\xi_i(t)$ is a random uncorrelated Guassian noise. The model was used to investigate the density dependence of the cell flow patterns and was found in good agreement with experiments on one keratocytes in vitro. In particular, the authors concluded that the transition to flocking in the model is in the same universality class as in the original flocking model [67].

A more refined active particle model for collective cell migration was designed to study wound healing in epithelial cells [58]. In this case, the equation of motion for each cell i was given by

$$\frac{d\mathbf{v}_i}{dt} = -\alpha\mathbf{v}_i + \sum_j \left[\frac{\beta}{N_i}(\mathbf{v}_j - \mathbf{v}_i) + \mathbf{f}_{ij}\right] + \sigma(\rho_i)\eta_i + \mathbf{F}_{\rm rf}(\mathbf{x}_i) \tag{5}$$

where the sum is restricted to the nearest neighbors of i, α is a damping parameter, β is the velocity coupling strength and $\mathbf{f}_{ij}$ is again the the interaction force. The equation of motion contains a stochastic self-propulsion force $\sigma(\rho_i)\eta_i$, where η_i follows an Ornstein-Uhlenbeck process with correlation time τ:

$$\tau\frac{d\eta_i}{dt} = -\eta_i + \xi_i, \tag{6}$$

ξ_i is a delta-correlated white noise $\langle\xi_i(t)\xi_j(t')\rangle = \delta_{ij}\delta(t-t')$. The amplitude of the noise term σ depends on the density of the neighboring cells ρ_i as

$$\sigma(\rho_i) = \sigma_0 + (\sigma_1 - \sigma_0)(1 - \rho_i/\rho_0), \tag{7}$$

where ρ_i and ρ_0 are the local and global particle densities, respectively. The neighbors of each cell i are found considering a circle of radius R surrounding the cell and then dividing it into 6 equal sectors. The neighbors are then defined as the cells that are closer to the cell i in each sector. The model as it is gives invasion fronts that are too diffusive when compared to the experiment. Therefore it was proposed to introduce a resistance of the medium to the invasion process [58]. To this end, one can consider a set of tightly packed surface particles, that are hindering cells to enter the empty space. The interaction between a surface particle and a cell is modeled by a simple repulsive potential. Prolonged contact between particles and cells leads to the damage of the latter, allowing cells to invade. Numerical simulations of the model allows to reproduce with great accuracy the experimentally observed dynamics in an epithelial wound healing assay (see Fig. 5).

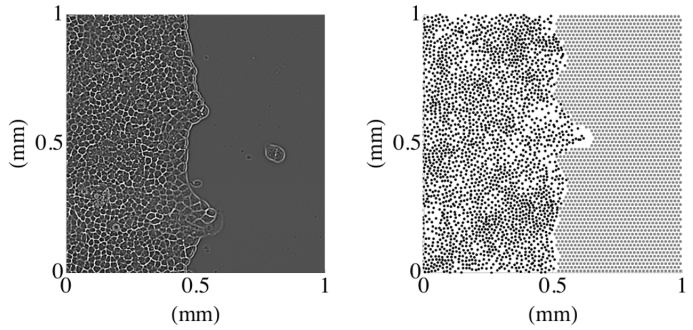

Fig. 5 Comparison between experiments on epithelial wound healing and simulations of an active particle model. Image from [58] (creative commons)

The model can also be used to simulate the role of leader cells [58], a subset of cells with a special phenotype that would allow them to drive the collective migration process by finding the best path and dragging the other cell with them [30]. In the context of the experiment illustrated in Fig. 5, leader cells would be associated to the formation of fingers in the front [58].

The same model was later used to study the statistical properties of front dynamics in wound healing experiments, focusing on the avalanche behavior discussed in section 3. Numerical results show that both the avalanche distributions and the velocity distributions measured in experiments, over a wide variety of cells are well described the model. This is illustrated in Fig. 3b and Fig. 3b where the result of the simulations is compared with the experimental curves obtain from different cell lines [12].

By fine tuning the parameters of Eq. 5 it is possible to fit quite accurately the not only the qualitative shape of velocity distributions (see 3d) but also the actual values velocity fluctuations and the correlation functions [13]. In some cases, however, a precise quantitative description can only be obtained by adding to Eq. 5 a self-propulsion term $F_0\hat{v}$ [13], similar to the one employed in Ref. [62]. Using this form of the model, it was possible to characterize experiments on epithelial cells where the induction of RAB5A leads to a dramatic fluidization of a jammed cellular monolayer [40]. The comparison between experiments in wound healing conditions and similar experiments performed in confluent conditions shows that the appearance of a wound is able to induce a fluidization transition by a change of the effective parameters in Eq. 5. This is a marked difference with respect to ordinary soft matter systems where changes in boundary conditions do not change the internal parameters. It is instead a peculiarity of living matter where cells can change their phenotype in response to external stimuli.

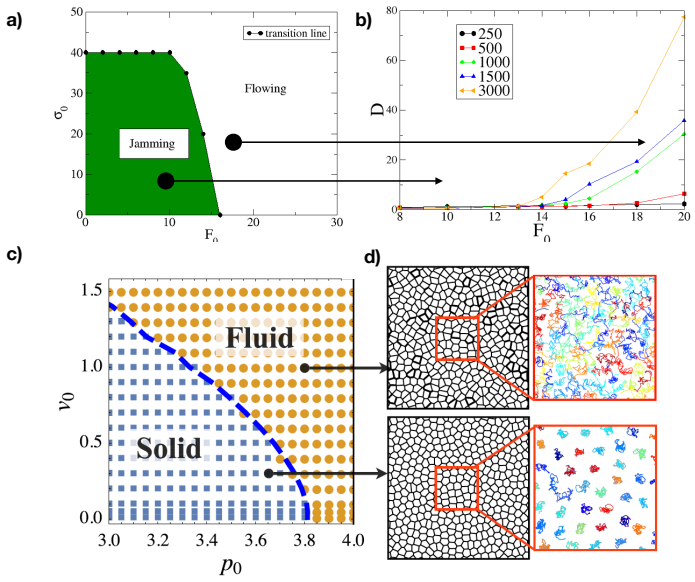

Fig. 6 A comparison of active particle and vertex models. a) The phase diagram obtained from simulations of the active particle model in terms of two parameters, the noise amplitude σ_0 and the self-propulsion F_0 [13]. b) In the jammed phase the particle self-diffusion is system size independent, while it depends on the system size for the flowing phase. c) A similar phase diagram can be obtained for the self-propelled Voronoi model in terms of the self-propulsion velocity v_0 and the anisotropy parameter p_0.

5.2 Vertex and Voronoi models

A different class of models of cell tissues is based on vertex models [7, 36, 8], originally developed to study foams rheology [68, 47]. In those models, cells are represented by polygons whose edges and vertices are shared by neighboring cells. This representation is well suited to describe a cell monolayer or an epithelial sheet where cells are in close contact and can form tight junctions. The dynamics of the sheet is captured by equation of motions for each vertex, possibly including rules for topological changes in the edges. There is a long tradition on the application of vertex models to study tissue growth and deformation as well as cell migration.

Here, we discuss a recent development of vertex models where the moving degrees of freedom are not the vertices but the centers of the polygons [8]. This case is defined as a Voronoi model, since the ensemble of polygons are part of a Voronoi tassellation of the plane. The elastic energy of each configuration composed by N polygons is similar to the one used in other vertex models and is given by

$$E = \sum_{i=1}^{N} \left[K_A (A(\mathbf{r}_i) - A_0)^2 + K_P (P(\mathbf{r}_i) - P_0)^2 \right]. \tag{8}$$

where $A(\mathbf{r}_i)$ and $P(\mathbf{r}_i)$ are area and perimeter of the cell i, respectively. The quadratic energy is designed to keep cell areas and perimeters close to their target values A_0 and P_0. One can thus characterize the energy by a dimensionless target shape $p_0 = P_0/\sqrt{A_0}$. Finally, K_A and K_P are the elastic moduli describing deformations of the area and the perimeter [8].

The equation of motion for each polygon is overdamped, so that the velocity is proportional to the sum of the forces given by the elastic interactions and self-propulsion

$$\frac{d\mathbf{r}_i}{dt} = \mu \mathbf{F}_i + v_0 \hat{n}_i, \tag{9}$$

where $\mathbf{F}_i$ is the elastic force derived from Eq. 8, v_0 is the self-propulsion velocity and the vector $\hat{n}_i$ indicates the polarity of the cell i. In analogy with the active particle model described in section 5.1, the polarity is parametrized by an angle θ_i evolving as

$$\frac{d\theta_i}{dt} = \xi_i(t) \tag{10}$$

where $\xi_i(t)$ is again an uncorrelated Gaussian white noise.

Simulations of the self-propelled Voronoi model allow to study the behavior as a function of a few key parameters, like the self-propulsion speed v_0 and the anisotropy p_0 [8]. The results are summarized in Fig. 6c showing the transition line between a solid-like and fluid-like phase. The phase is determined by looking at the trajectories of individual polygons. Those are confined for the solid phase and diffusive in the fluid phase. The results are similar to those discussed for the active particle models, although the system size dependence was not studied for the self-propelled Voronoi model.

While the description of the jamming transition is similar for vertex models and particle models, the latter seem more appropriate to study wound healing conditions which require particles to spread and possibly detach. Recent advances in vertex models have, however, overcome the limitations of periodic boundary conditions, allowing the study of front propagation also in this framework [4].

6 Conclusions

In this chapter, we have highlighted some similarities and differences between collective cell migration and the rheology of soft, but inanimate matter. Tools and ideas developed to study the physics of soft materials has been proven very useful in interpreting some properties of collective cell migration, with concept such as jamming and scaling that are being increasingly employed to describe cells. While the similarities are sometimes striking, one should always bear in mind the peculiarities of living cells that make them different from conventional soft matter and even active colloids. Cells can respond to external stimuli by changing their phenotype in a complex fashion, something that does not happen in materials. This leads to intriguing phenomena such as the boundary induced unjamming observed in confluent monolayers when a wound is produced [13]. These aspects may have important implications for critical biological and pathological processes such as development or tumor dissemination.

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References

1. Thomas E Angelini, Edouard Hannezo, Xavier Trepat, Jeffrey J Fredberg, and David A Weitz. Cell migration driven by cooperative substrate deformation patterns. *Phys Rev Lett*, 104(16):168104, Apr 2010.
2. Thomas E Angelini, Edouard Hannezo, Xavier Trepat, Manuel Marquez, Jeffrey J Fredberg, and David A Weitz. Glass-like dynamics of collective cell migration. *Proc Natl Acad Sci U S A*, 108(12):4714–9, Mar 2011.
3. Shiladitya Banerjee, Kazage J C Utuje, and M Cristina Marchetti. Propagating stress waves during epithelial expansion. *Phys Rev Lett*, 114(22):228101, Jun 2015.
4. Daniel L Barton, Silke Henkes, Cornelis J Weijer, and Rastko Sknepnek. Active vertex model for cell-resolution description of epithelial tissue mechanics. *PLoS Comput Biol*, 13(6):e1005569, Jun 2017.
5. Elsa Bazellières, Vito Conte, Alberto Elosegui-Artola, Xavier Serra-Picamal, María Bintanel-Morcillo, Pere Roca-Cusachs, José J Muñoz, Marta Sales-Pardo, Roger Guimerà, and Xavier Trepat. Control of cell-cell forces and collective cell dynamics by the intercellular adhesome. *Nat Cell Biol*, 17(4):409–20, Apr 2015.
6. Ludovic Berthier. Nonequilibrium glassy dynamics of self-propelled hard disks. *Phys. Rev. Lett.*, 112:220602, Jun 2014.

7. Dapeng Bi, J. H. Lopez, J. M. Schwarz, and M. Lisa Manning. A density-independent rigidity transition in biological tissues. *Nat. Phys.*, 11(12):1074–+, December 2015.
8. Dapeng Bi, Xingbo Yang, M. Cristina Marchetti, and M. Lisa Manning. Motility-driven glass and jamming transitions in biological tissues. *Phys. Rev. X*, 6:021011, Apr 2016.
9. Daniel Bonn, Sorin Tanase, Bérengère Abou, Hajime Tanaka, and Jacques Meunier. Laponite: aging and shear rejuvenation of a colloidal glass. *Phys Rev Lett*, 89(1):015701, Jul 2002.
10. Agusti Brugues, Ester Anon, Vito Conte, Jim H. Veldhuis, Mukund Gupta, Julien Colombelli, Jose J. Munoz, G. Wayne Brodland, Benoit Ladoux, and Xavier Trepat. Forces driving epithelial wound healing. *Nat Phys*, 10(9):683–690, 09 2014.
11. P. Chauve, P. Le Doussal, and K. J. Wiese. Renormalization of pinned elastic systems: how does it work beyond one loop. *Phys. Rev. Lett.*, 86:1785–1788, 2001.
12. Oleksandr Chepizhko, Costanza Giampietro, Eleonora Mastrapasqua, Mehdi Nourazar, Miriam Ascagni, Michela Sugni, Umberto Fascio, Livio Leggio, Chiara Malinverno, Giorgio Scita, Stéphane Santucci, Mikko J Alava, Stefano Zapperi, and Caterina A M La Porta. Bursts of activity in collective cell migration. *Proc Natl Acad Sci U S A*, 113(41):11408–11413, Oct 2016.
13. Oleksandr Chepizhko, Maria Chiara Lionetti, Chiara Malinverno, Costanza Giampietro, Giorgio Scita, Stefano Zapperi, and Caterina A M La Porta. From jamming to collective cell migration through a boundary induced transition. *Soft Matter*, 14(19):3774–3782, May 2018.
14. Michel Cloitre, Régis Borrega, Fabrice Monti, and Ludwik Leibler. Glassy dynamics and flow properties of soft colloidal pastes. *Phys Rev Lett*, 90(6):068303, Feb 2003.
15. Xavier Clotet, Jordi Ortín, and Stéphane Santucci. Disorder-induced capillary bursts control intermittency in slow imbibition. *Phys Rev Lett*, 113(7):074501, Aug 2014.
16. Edward A Codling, Michael J Plank, and Simon Benhamou. Random walk models in biology. *J R Soc Interface*, 5(25):813–34, Aug 2008.
17. Peter Dieterich, Rainer Klages, Roland Preuss, and Albrecht Schwab. Anomalous dynamics of cell migration. *Proc Natl Acad Sci U S A*, 105(2):459–63, Jan 2008.
18. Kevin Doxzen, Sri Ram Krishna Vedula, Man Chun Leong, Hiroaki Hirata, Nir S Gov, Alexandre J Kabla, Benoit Ladoux, and Chwee Teck Lim. Guidance of collective cell migration by substrate geometry. *Integr Biol (Camb)*, 5(8):1026–35, Aug 2013.
19. D J Durian, D A Weitz, and D J Pine. Multiple light-scattering probes of foam structure and dynamics. *Science*, 252(5006):686–8, May 1991.
20. G. Durin and S. Zapperi. Scaling exponents for Barkhausen avalanches in polycrystalline and amorphous ferromagnets. *Phys. Rev. Lett.*, 84:4075–4078, 2000.
21. Yaouen Fily, Silke Henkes, and M. Cristina Marchetti. Freezing and phase separation of self-propelled disks. *Soft Matter*, 10:2132–2140, 2014.
22. Elijah Flenner, Grzegorz Szamel, and Ludovic Berthier. The nonequilibrium glassy dynamics of self-propelled particles. *Soft Matter*, 12:7136–7149, 2016.
23. Peter Friedl and Darren Gilmour. Collective cell migration in morphogenesis, regeneration and cancer. *Nat Rev Mol Cell Biol*, 10(7):445–57, Jul 2009.
24. Simon Garcia, Edouard Hannezo, Jens Elgeti, Jean-François Joanny, Pascal Silberzan, and Nir S Gov. Physics of active jamming during collective cellular motion in a monolayer. *Proc Natl Acad Sci U S A*, 112(50):15314–9, Dec 2015.
25. N. S. Gov. *Cell and matrix mechanics*, pages 219–238. CRC Press, 2014.
26. Anna Haeger, Marina Krause, Katarina Wolf, and Peter Friedl. Cell jamming: collective invasion of mesenchymal tumor cells imposed by tissue confinement. *Biochim Biophys Acta*, 1840(8):2386–95, Aug 2014.
27. Hisashi Haga, Chikako Irahara, Ryo Kobayashi, Toshiyuki Nakagaki, and Kazushige Kawabata. Collective movement of epithelial cells on a collagen gel substrate. *Biophys J*, 88(3):2250–6, Mar 2005.
28. Silke Henkes, Yaouen Fily, and M. Cristina Marchetti. Active jamming: Self-propelled soft particles at high density. *Phys. Rev. E*, 84:040301, Oct 2011.
29. Olga Ilina and Peter Friedl. Mechanisms of collective cell migration at a glance. *J Cell Sci*, 122(Pt 18):3203–8, Sep 2009.

30. Antoine A Khalil and Peter Friedl. Determinants of leader cells in collective cell migration. *Integr Biol (Camb)*, 2(11-12):568–74, Nov 2010.
31. Thorsten M Koch, Stefan Münster, Navid Bonakdar, James P Butler, and Ben Fabry. 3d traction forces in cancer cell invasion. *PLoS One*, 7(3):e33476, 2012.
32. C. A. M. La Porta and S. Zapperi. *The Physics of Cancer*. Cambridge University Press, 2017.
33. Janina R Lange and Ben Fabry. Cell and tissue mechanics in cell migration. *Exp Cell Res*, 319(16):2418–23, Oct 2013.
34. Pierre Le Doussal and Kay Jörg Wiese. Size distributions of shocks and static avalanches from the functional renormalization group. *Phys. Rev. E*, 79:051106, May 2009.
35. H. Leschhorn, T. Nattermann, S. Stepanow, and L. H. Tang. Driven interface depinning in a disordered medium. *Ann. Physik*, 6:1–34, 1997.
36. Bo Li and Sean X Sun. Coherent motions in confluent cell monolayer sheets. *Biophys J*, 107(7):1532–41, Oct 2014.
37. Liang Li, Simon F Nørrelykke, and Edward C Cox. Persistent cell motion in the absence of external signals: a search strategy for eukaryotic cells. *PLoS One*, 3(5):e2093, May 2008.
38. Qinyi Liao and Ning Xu. Criticality of the zero-temperature jamming transition probed by self-propelled particles. *Soft Matter*, 14:853–860, 2018.
39. Andrea J. Liu, Sidney R. Nagel, and J. S. Langer. The jamming transition and the marginally jammed solid. *Annu. Rev. Condens. Matter Phys.*, 1:347–369, 2010.
40. Chiara Malinverno, Salvatore Corallino, Fabio Giavazzi, Martin Bergert, Qingsen Li, Marco Leoni, Andrea Disanza, Emanuela Frittoli, Amanda Oldani, Emanuele Martini, Tobias Lendenmann, Gianluca Deflorian, Galina V Beznoussenko, Dimos Poulikakos, Ong Kok Haur, Marina Uroz, Xavier Trepat, Dario Parazzoli, Paolo Maiuri, Weimiao Yu, Aldo Ferrari, Roberto Cerbino, and Giorgio Scita. Endocytic reawakening of motility in jammed epithelia. *Nat Mater*, 16(5):587–596, May 2017.
41. K. J. Maloy, S. Santucci, J. Schmittbuhl, and R. Toussaint. Local waiting time fluctuations along a randomly pinned crack front. *Phys. Rev. Lett.*, 96:045501, 2006.
42. Rituparno Mandal, Pranab Jyoti Bhuyan, Madan Rao, and Chandan Dasgupta. Active fluidization in dense glassy systems. *Soft Matter*, 12:6268–6276, 2016.
43. T.G. Mason, J. Bibette, and D.A. Weitz. Yielding and flow of monodisperse emulsions. *Journal of Colloid and Interface Science*, 179(2):439 – 448, 1996.
44. Claus Metzner, Christoph Mark, Julian Steinwachs, Lena Lautscham, Franz Stadler, and Ben Fabry. Superstatistical analysis and modelling of heterogeneous random walks. *Nat Commun*, 6:7516, 2015.
45. O. Narayan and D. S. Fisher. Critical behavior of sliding charge-density waves in 4- epsilon dimensions. *Phys. Rev. B*, 46:11520, 1992.
46. Mei Rosa Ng, Achim Besser, Gaudenz Danuser, and Joan S Brugge. Substrate stiffness regulates cadherin-dependent collective migration through myosin-ii contractility. *J Cell Biol*, 199(3):545–63, Oct 2012.
47. Tohru Okuzono and Kyozi Kawasaki. Intermittent flow behavior of random foams: A computer experiment on foam rheology. *Phys. Rev. E*, 51:1246–1253, Feb 1995.
48. Jin-Ah Park, Jae Hun Kim, Dapeng Bi, Jennifer A Mitchel, Nader Taheri Qazvini, Kelan Tantisira, Chan Young Park, Maureen McGill, Sae-Hoon Kim, Bomi Gweon, Jacob Notbohm, Robert Steward, Jr, Stephanie Burger, Scott H Randell, Alvin T Kho, Dhananjay T Tambe, Corey Hardin, Stephanie A Shore, Elliot Israel, David A Weitz, Daniel J Tschumperlin, Elizabeth P Henske, Scott T Weiss, M Lisa Manning, James P Butler, Jeffrey M Drazen, and Jeffrey J Fredberg. Unjamming and cell shape in the asthmatic airway epithelium. *Nat Mater*, 14:1040–1048, Aug 2015.
49. Alka A Potdar, Junhwan Jeon, Alissa M Weaver, Vito Quaranta, and Peter T Cummings. Human mammary epithelial cells exhibit a bimodal correlated random walk pattern. *PLoS One*, 5(3):e9636, 2010.
50. M Poujade, E Grasland-Mongrain, A Hertzog, J Jouanneau, P Chavrier, B Ladoux, A Buguin, and P Silberzan. Collective migration of an epithelial monolayer in response to a model wound. *Proc Natl Acad Sci U S A*, 104(41):15988–93, Oct 2007.

51. Sriram Ramaswamy. The mechanics and statistics of active matter. *Annual Review of Condensed Matter Physics*, 1(1):323–345, 2010.
52. Pernille Rørth. Collective cell migration. *Annu Rev Cell Dev Biol*, 25:407–29, 2009.
53. Alberto Rosso, Pierre Le Doussal, and Kay Jörg Wiese. Avalanche-size distribution at the depinning transition: A numerical test of the theory. *Phys. Rev. B*, 80:144204, Oct 2009.
54. Peter J F Röttgermann, Alicia Piera Alberola, and Joachim O Rädler. Cellular self-organization on micro-structured surfaces. *Soft Matter*, 10(14):2397–404, Apr 2014.
55. Michael S Sacks and Wei Sun. Multiaxial mechanical behavior of biological materials. *Annu Rev Biomed Eng*, 5:251–84, 2003.
56. Alexandre Saez, Marion Ghibaudo, Axel Buguin, Pascal Silberzan, and Benoît Ladoux. Rigidity-driven growth and migration of epithelial cells on microstructured anisotropic substrates. *Proc Natl Acad Sci U S A*, 104(20):8281–6, May 2007.
57. P N Segrè, V Prasad, A B Schofield, and D A Weitz. Glasslike kinetic arrest at the colloidal-gelation transition. *Phys Rev Lett*, 86(26 Pt 1):6042–5, Jun 2001.
58. Néstor Sepúlveda, Laurence Petitjean, Olivier Cochet, Erwan Grasland-Mongrain, Pascal Silberzan, and Vincent Hakim. Collective cell motion in an epithelial sheet can be quantitatively described by a stochastic interacting particle model. *PLoS Comput Biol*, 9(3):e1002944, 03 2013.
59. Xavier Serra-Picamal, Vito Conte, Romaric Vincent, Ester Anon, Dhananjay T. Tambe, Elsa Bazellieres, James P. Butler, Jeffrey J. Fredberg, and Xavier Trepat. Mechanical waves during tissue expansion. *Nat Phys*, 8(8):628–634, 08 2012.
60. M. Cristina Marchetti Shiladitya Banerjee. Continuum models of collective cell migration.
61. C L Stokes, D A Lauffenburger, and S K Williams. Migration of individual microvessel endothelial cells: stochastic model and parameter measurement. *J Cell Sci*, 99 (Pt 2):419–30, Jun 1991.
62. B. Szabó, G. J. Szöllösi, B. Gönci, Zs. Jurányi, D. Selmeczi, and Tamás Vicsek. Phase transition in the collective migration of tissue cells: Experiment and model. *Phys. Rev. E*, 74:061908, Dec 2006.
63. Grzegorz Szamel. Theory for the dynamics of dense systems of athermal self-propelled particles. *Phys. Rev. E*, 93:012603, Jan 2016.
64. Ken Tore Tallakstad, Renaud Toussaint, Stephane Santucci, Jean Schmittbuhl, and Knut Jorgen Maloy. Local dynamics of a randomly pinned crack front during creep and forced propagation: an experimental study. *Phys Rev E Stat Nonlin Soft Matter Phys*, 83(4 Pt 2):046108, Apr 2011.
65. Dhananjay T Tambe, C Corey Hardin, Thomas E Angelini, Kavitha Rajendran, Chan Young Park, Xavier Serra-Picamal, Enhua H Zhou, Muhammad H Zaman, James P Butler, David A Weitz, Jeffrey J Fredberg, and Xavier Trepat. Collective cell guidance by cooperative intercellular forces. *Nat Mater*, 10(6):469–75, Jun 2011.
66. Sri Ram Krishna Vedula, Andrea Ravasio, Chwee Teck Lim, and Benoit Ladoux. Collective cell migration: a mechanistic perspective. *Physiology (Bethesda)*, 28(6):370–9, Nov 2013.
67. Tamás Vicsek, András Czirók, Eshel Ben-Jacob, Inon Cohen, and Ofer Shochet. Novel type of phase transition in a system of self-driven particles. *Phys. Rev. Lett.*, 75:1226–1229, Aug 1995.
68. D. Weaire and J. P. Kermode. Computer simulation of a two-dimensional soap froth ii. analysis of results. *Philosophical Magazine B*, 50(3):379–395, 1984.
69. Pei-Hsun Wu, Anjil Giri, Sean X Sun, and Denis Wirtz. Three-dimensional cell migration does not follow a random walk. *Proc Natl Acad Sci U S A*, 111(11):3949–54, Mar 2014.