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A unified term for directed and undirected motility in collective cell invasion

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ABSTRACT

In this paper, we develop mathematical models for collective cell motility. Initially we develop a model using a linear diffusion–advection type equation and fit the parameters to data from cell motility assays. This approach is helpful in classifying the results of certain cell motility assay experiments. In particular, this model can determine degrees of directed versus undirected collective cell motility. Next we develop a model using a nonlinear diffusion term that is able to capture in a unified way directed and undirected collective cell motility. One goal of this work is to demonstrate that the forms of collective cell motility seen in the scratch assays and possibly other systems of interest need not reference external and more complicated migratory signals such as chemotaxis, but rather could be based on quorum sensing alone, collectively represented as density-dependent diffusivity. As an application we apply the nonlinear diffusion approach to a problem in tumor cell invasion, noting that neither chemotaxis or haptotaxis are present in the system under consideration in this article.

1. Introduction

A basic characteristic of many organisms is their capability for active movement known as motility. Cell motility is fundamental in many important and interesting biological phenomena such as morphogenesis, wound healing, and tumor invasion and metastasis [1–3]. The association of cell motility with diseases, and in particular cancer, makes it a topic of interest not just for basic science but also medical research.

Much of the experimental research into cell motility focuses on molecular or mechanical details and is carried out in such a way that it is difficult to form a unified picture of cell motion [1]. To complicate matters further, both individual cell motion and collective cell motility are important in many phenomena. For example, the conventional view of tumor metastasis is that individual cells detach from a primary tumor and migrate to other areas [2]. However, now it is known that sheets or clusters of cells that maintain cell–cell contacts and migrate collectively also influence tumor invasion and metastasis [2,3]. Spurred by experimental work and the surrounding difficulties, researchers have begun to develop mathematical and computational models of cell motility (see [4,1,5] and references therein). Such models can aid experimentalists in hypothesis testing, experiment design, and the creation of a unified picture of cell motility. It would also be valuable if such models could be used to provide insight into systems of interest in the biomedical sciences such as tumor invasion.

Mathematical models of individual cell motion such as in [5,6] are able to incorporate much of the mechanical details of migration and model the migration of cells in tissue in which motion in some directions may be restricted. For example, in [5], Hillen derives mathematical models for three dimensional cell motion through temporally varying tissue networks

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using kinetic transport equations. In this case, the motion in certain directions is limited by the orientation of tissue or extra cellular matrix. This type of motion is often referred to as mesenchymal motion, and direction of motility is influenced by external factors not the intrinsic behavior of the cell population. Two cases are studied in [5], cell motion at the individual cell level and at the population level. Hillen begins with a transport equation model for individual cell mesenchymal motion and then uses scaling arguments to derive a model for motion of a population of cells.

In this work, we consider the development of models of collective cell motility that can be applied to the case of a group of cells that undergo collective migration where the degree of directed motility is determined by the intrinsic behavior of the cell population. More precisely, we consider the epithelial–mesenchymal transition (EMT) which is characterized by the loss of cell–cell adhesion and the resulting effects on motility [2,7,8]. The work presented in this paper is motivated in part by experiments of the Stipp lab [9–12] and in part by the possibility of applying the results to simple but useful models of tumor invasion such as in [13–15]. We note that the cell motility scratch assays by the Stipp lab include neither chemotaxis since no chemoattractant is introduced into the scratch. Likewise, for the models in [13–15] of spherical *in vitro* tumors no chemotaxis or haptotaxis since no chemoattractants or macromolecules exist outside the boundary of the tumor. In particular, the model of Stein et al. [13] is developed for glioblastoma tumor spheroid in a three-dimensional *in vitro* experiment.

2. Preliminaries

Cell adhesion, is the result of the interactions of certain cell receptors with adhesion molecules. For example, proteins known as cadherins have been shown to influence cell–cell adhesion of cancer cells [2]. In particular, epithelial cells express the protein E-cadherin which is responsible for the tight junctions between cells that is characteristic of the epithelium. Collective cell migration depends on cell–cell adhesion, while migration of individual cells is often associated with the loss of cell–cell adhesion. Such a loss of cell–cell adhesion may be an effect of an epithelial–mesenchymal transition (EMT). It is thought that in (epithelial) cancers an EMT is essential for invasion and metastasis.

The Stipp lab has performed experiments known as scratch assays in order to study the effects of an EMT on collective motility properties of cells [10]. In a scratch assay, cells are cultured on a surface and then a scratch is made to create a gap between some of the cells. Cells are then filmed migrating to "fill in the gap". The purpose of these experiments is to study the difference in motility properties between two cell types known as PC-3 and TEM4-18, the primary distinction being how the cell–cell adhesion properties of the two cell types affects their respective motility behaviors. In particular, the TEM4-18 cells are a subline of the PC-3 cells that show stronger cell–cell contacts and enhanced ability to traverse an endothelial cell layer. For a detailed discussion of these cell types see [12]. Software (NIH Image J 1.63 software) can then be used to track some number of the cells in order to generate data from which cell velocities can be determined [10]. That is, the experiments provide data about the individual random walks of the cells. For more details on the scratch assay experiments see [16] and references contained therein. By applying standard statistical techniques to this data, one can compute diffusion and drift coefficients that offer a potential method for characterizing the results of such scratch assays. In particular, by computing the drift and diffusion coefficients we may be able to characterize the degree of cell–cell contact in a given assay. This is based on the observation that cell–cell contact influences motility properties (i.e. how quickly a population of cells migrates to fill in the gap). Using the mathematical models described below the motility properties can be characterized by corresponding values of the parameters with the cell–cell adhesion properties that influence the motility behavior of interest in the experiments.

3. Main result

Using the data from the scratch assays, we have developed mathematical representations of collective motility. One such representation simply makes use of the diffusion and drift coefficients by input into a linear equation of the form

$$\partial_t u = \nabla \cdot (D\nabla u - \mathbf{v}u), \tag{1}$$

where $u(x, t)$ represents the cell density at a given position x and time t, D is the diffusion coefficient, and $\mathbf{v}$ is the drift velocity. An alternative approach developed in [17] uses a discrete modeling method to build cell motility models based on individual cell random walk data.

Fig. 1(a) shows the results typical of using (1) to track the front propagation in a scratch assay. Here we have used a scaling to have unit maximum cell population density. The spatial domain for the computation is the interval $[-15, 1]$, with a non-dimensional length scale. On the left boundary we take $u(-15, t) = 1$ for all t, a so-called far-field condition. This is justified, since in a typical scratch assay the scratch is small compared with the area containing cells. We employ a no-flux condition on the right boundary. We take as the initial condition

$$u(x, 0) = \begin{cases} 1, & \text{if } x \leq \dfrac{3}{5}, \\ 0, & \text{otherwise.} \end{cases} \tag{2}$$

This represents the assay at the time of the scratch. The scratch creates a front between a region with cells and a region without cells, which moves as the cells migrate to fill in the gap. Fig. 1(a) shows a right-moving cell population that

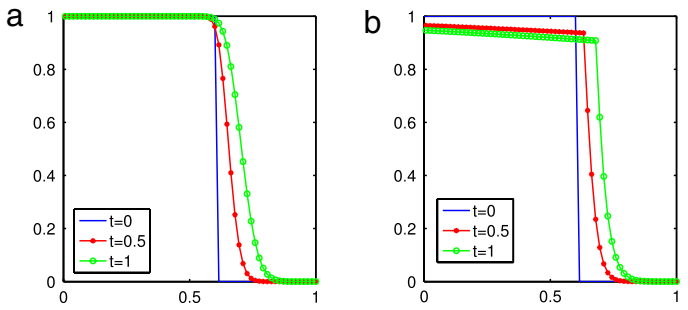


Fig. 1. The front propagation of invading cells using (1) and (3).

corresponds to the motion of the front in the scratch assays. From the computations we can approximate the front speed by dividing the distance between fronts by the corresponding time interval and compare it with experimental results. In the case shown in Fig. 1(a) the parameter values are chosen to correspond to a scratch assay with epithelial (PC-3) cells. When compared with experimental results smaller diffusion coefficients and larger drift coefficients match the motility behavior of TEM4-18 cells while larger diffusion coefficients and smaller drift coefficients match the motility behavior of PC-3 cells. This provides a method for characterizing the motility properties, and possibly the degree of cell–cell adhesion, in such assays. All simulations are based on computations performed using both the software BuGS [18] and the MATLAB `pdepe` parabolic equations solver with each giving the same results.

In [19], Aronson describes the role of diffusion equations in modeling dispersing populations. In particular, [19] covers how the behavior of a dispersing population is related to the form of the diffusion operator appearing in the equations modeling the spatial dynamics of a population. It is pointed out that it can be useful to consider nonlinear diffusion terms. In [4] the authors present a discrete model of cell motility that incorporates cell–cell adhesion. This discrete model has as its continuum limit a nonlinear diffusion equation of the form

$$\partial_t u = \nabla \cdot (D(u)\nabla u). \tag{3}$$

Due to the occurrence of cell–cell adhesion, in [4], the diffusivity is described by a function of the form

$$D(u) = a\,(u-b)^2 + c, \tag{4}$$

where a, b, c are constants related to the adhesion properties of cells. Under the influence of [4,19] we seek an alternative to (1) by considering nonlinear diffusion equations of the form (3).

Fig. 1(b) shows the results of using a nonlinear diffusion model of the form (3) to represent cell motility as observed in the scratch assays discussed above. In order to get a qualitative match with the results, such as in Fig. 1(a), using (1) we have taken the nonlinear diffusivity to have the form

$$D(u) = a \cdot \max(0, u-b)u + c, \tag{5}$$

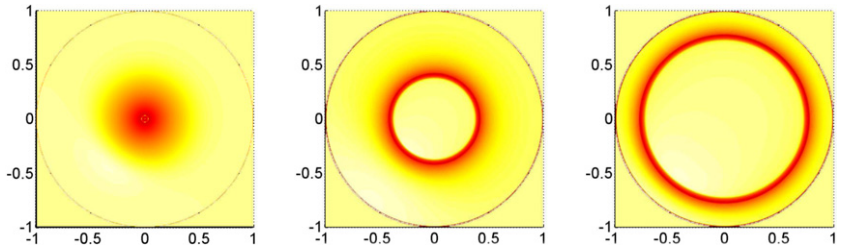
which is similar to (4). The boundary and initial conditions are the same as above. Fig. 1(b) again simulates a right-moving cell population (epithelial (PC-3) cells) that corresponds to the motion of the front in the scratch assays. The advantage of using a nonlinear diffusion model is that the effects of the degree of cell–cell adhesion on motility, of interest in the study of the EMT, can be explicitly represented. Note that by making the constant a smaller or the constant b larger in (5) the diffusion becomes closer to linear, that is we get closer to purely random motility.

In [14,15] Swanson et al. apply simple but useful mathematical models of tumor invasion. In particular, the authors use a reaction–diffusion equation of the form

$$\partial_t u = \nabla \cdot (D\nabla u) + gu\left(1 - \frac{u}{u_{\max}}\right) \tag{6}$$

to model the invasion of a spherically symmetric glioblastoma tumor. The use of a reaction–diffusion equation is based on the assumption that the net dispersal of tumor cells is captured by a random walk which translates mathematically into diffusion. In the case of [14,15] diffusion is assumed to be linear. The term $gu(1 - \frac{u}{u_{\max}})$ describes the proliferation of cells. Based on invasion assays of tumor cells, Stein et al. [13] suggest that there is a need to consider not only random motility of invasive cells but also directed motility. In particular, the authors of [13] conclude that while diffusion alone is sufficient for describing cell motility of cells making up the central core of the tumor, cells at the invasive rim of the tumor have different motility properties that include both random and directed motility. By modifying (6) the authors of [13] arrive at the following model for the invasion of tumor cells

$$\partial_t u = \nabla \cdot (D\nabla u - \mathbf{v}u) + s\delta(x - x_0 - \mathbf{v}t) + gu\left(1 - \frac{u}{u_{\max}}\right). \tag{7}$$



(a) $t = 0$. (b) $t = 5$ days. (c) $t = 10$.

Fig. 2. Simulation of tumor invasion with nonlinear model (8).

Here $\delta(\cdot)$ is the Dirac delta function. In the above model the $s\delta(x - x_0 - \mathbf{v}t)$ term represents the shedding of invasive cells from the invasive rim.

Based on the scratch assay experiments and the nonlinear model for cell motility presented above we modify the model of Stein et al. (7) to have the form

$$\partial_t u = \nabla \cdot (D(u)\nabla u) + s\delta(x - x_0 - \mathbf{v}t) + gu\left(1 - \frac{u}{u_{\max}}\right), \tag{8}$$

where the motility is described by a nonlinear diffusion term of the general form $\nabla \cdot (D(u)\nabla u)$. We interpret this as having the motility dependent on the population density. This is of particular interest in the case where there is cell-to-cell adhesion but no chemotaxis. Fig. 2 shows simulations using the model (8) of a spherically symmetric tumor. Our results are similar to those of [13–15]; see [16] for a detailed comparison. We note the qualitative similarity of the behavior of the invasive rim with the results in [13].

In conclusion, based on the data from the scratch assays performed in the Stipp Lab we are able to obtain information on the random walks of individual cells. From the individual random walks we are able to classify the results of the experiments in terms of the diffusion and drift coefficients. Using these coefficients we can represent the motility of cells by a linear drift-diffusion model. This model is capable of providing a qualitative match to experimental observations of the scratch assays. However, a linear drift-diffusion model does not provide a mechanism, in this case cell–cell adhesion, that accounts for the difference in the motility properties of the two cell types (PC-3 and TEM4-18) used in the scratch assay experiments. On the other hand, by using a nonlinear diffusion model, we can represent the motility of cells such that we again obtain a qualitative match to experimental observations but provide a mechanism that accounts for the difference in the motility properties observed between the PC-3 and TEM4-18 cell types. Since the difference in the motility behavior between the PC-3 and TEM4-18 cell types is not due to external migratory signals but quorum sensing alone, the ability of the nonlinear model to represent collective cell motility as observed in the scratch assays demonstrates that the forms of collective cell motility seen in the scratch assays and possibly other systems of interest need not reference external and more complicated migratory signals such as chemotaxis, but rather could be based on quorum sensing alone. Moreover, for certain other applications such as tumor invasion, the nonlinear model may be appropriate for this same reason, since as discussed in [3] cell–cell adhesion and hence population density dependent migration occurs. The models developed here provide an alternative for capturing directed cell motility in cases where mechanisms such as chemotaxis, haptotaxis, etc. are not dominant, and when there are no external factors such as anisotropic tissue to influence the direction of cell motion.

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