Chemical and mechanical signaling in epithelial spreading

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Abstract

We propose a minimal mathematical model to explain long-range coordination of dynamics of multiple cells in epithelial spreading, which may be induced, under different conditions, by a chemical signal, or mechanically induced strain, or both. The model is based on chemo-mechanical interactions including a chemical effect of strain, chemically induced polarization and active traction, and interaction between polarized cells. The results, showing kinase concentration distribution and cell displacement, velocity, and stress fields, allow us to reproduce qualitatively available experimental data and distinguish between distinct dynamical patterns observed under conditions of injury or unconstraining.

1. Introduction

Controlled spreading and deformation of epithelial layers, two-dimensional sheets of cells that tightly adhere to one another, is a key process in adult and developing tissues. During embryogenesis, spreading and folding of epithelia plays a central role in gastrulation, an event that initiates the formation of three-dimensional structures of tissues and organs, as well as in subsequent dorsal closure. In adult tissues, epithelial migration is important for wound healing; far-reaching analogies exist between embryogenesis and wound healing [1]. Mechanisms of collective cell migration are a subject of intensive research [2, 3]. It is generally believed that epithelial spreading involves polarization of the cell cohort propagating from ‘leading’ cells to the ‘followers’. The process is mediated by the intracellular actin machinery and proteins of adherens junctions and is regulated by complicated chemical pathways, which remain as yet largely unexplored.

Wounding generates both free area for spreading cells and an active species emitted as a result of injury that initiates the spreading process. Spreading also occurs, however, albeit at a slower speed, in the absence of injury, being initiated by a purely mechanical action following unconstraining of the epithelial layer [4, 5], i.e. providing it a space to spread without injuring. Matsubayashi \textit{et al} [6] proposed that collective cell migration during wound healing is caused by an activation (phosphorylation) wave of mitogen activated protein kinase (MAPK) and detected a notable correlation between its level and cell motility. The experiments of Nicolic \textit{et al} [4] followed up on this by tracing both spreading dynamics and distribution of activated kinase levels under different boundary conditions. In the case of spreading initiated by injury, two waves of MAPK activation were observed [4, 6]. The first, fast, wave is excited by the signal emitted at the wounded edge; consequently, it rapidly decays and is followed by a slow wave gradually spreading into the interior of the epithelial layer. Based on the earlier evidence of MAPK activation induced by stretching, Matsubayashi \textit{et al} [6] speculated that the mechanical action may cause the second slow wave. In the absence of injury, only the slow wave is present [4]; its form and spreading speed are similar to those in injured epithelium, indicating that the same mechanical signal may be operating in both cases. The experiments also confirmed the crucial role of MAPK, proved by suppression of spreading in the presence of a MAPK inhibitor [4].

Further studies provided detailed information on velocity fields in a spreading epithelium (excluding direct chemical effect of wounding) [5, 7], which turned out to be highly intermittent, with local bursts separated by quiescent periods. Trepat \textit{et al} [8] and Saez \textit{et al} [9] reported direct measurements...
of cell traction and stress in a spreading epithelial layer (in the absence of injury), which proved that traction is not restricted to a proximity of the leading edge, as has been commonly believed, but remains substantial deep inside the layer. This implies an effective mechanism of propagation of active traction within the tissue. Thus, mechanical and/or chemical signals at the wound edge can coordinate shape changes and movements of multiple cells deep within the epithelium. These experiments gave evidence for the importance of chemomechanical interactions, whereby directional cell migration is maintained by a positive feedback loop between cell deformation and intracellular signal transduction.

Early models of epidermal wound healing [10], adopted also in some later publications, were based on reaction–diffusion equations describing cell motion and proliferation in response to a diffusive chemical signal secreted by the wound. This approach turned out to be inadequate for the description of spreading epithelia, as it could not explain proliferation in the absence of injury and many above-mentioned features, like edge roughness and intermittent velocity, observed in later experiments. A very recent one-dimensional model [11] including chemical interactions and diffusive ligands has roughly reproduced a double-wave structure by fitting a large number of parameters in a complicated model possessing multiple steady states but acknowledged in the conclusion that a more realistic approach should involve the modeling of the forces transmitted by adjoining cells. It is clear that introducing mechanical interactions is necessary for this purpose, and a one-dimensional model can neither account for such interactions nor explain inhomogeneities of cell velocity distribution and instabilities of the leading edge observed in the experiments. Other recent modeling studies have reproduced fingering instabilities in spreading epithelia but have not considered explicit chemical mechanisms and their mechanical effects. Ouaknin et al [12] have developed a discrete Monte Carlo model involving chemotactic square cells moving to minimize the combined chemical and adhesion energy. Mark et al [13] have concentrated on the advancing edge of the tissue treating it as a continuous one-dimensional elastic contour pushed outward by the internal force due to the cellular motility, without describing internal processes in the tissue.

In this paper, we propose that directional collective cell migration is maintained by a positive feedback loop between cell deformation and intracellular signal transduction. Our aim is to develop and test a minimal phenomenological model taking into account the effect of both chemical and mechanical factors on collective cell motion and compatible with available observations. While chemical pathways and chemo-mechanical interactions are still unknown (and are certainly far more complex than the rough model to be described), there are a few well-pronounced experimental features that need to be explained: (a) faster advance in the presence of injury, especially at the leading edge [4], (b) activation of MAPK in the absence of injury and similarity of the emerging MAPK wave with the second wave in the presence of injury [4], (c) strong internal traction, large internal stress [8] and weak decay of the speed of advance with depth [4] in uninjured epithelia and (d) patchiness of velocity distribution.

2. The model

2.1. Mechanical properties

In order to arrive at a realistic description allowing one to reproduce irregular stress and velocity distributions, we will work with a cell-based (rather than continuous) model combining basic mechanical and reaction–diffusion processes. The epithelium is represented by an elastic 2D array of polygonal cells. We take as the initial configuration a regular hexagonal lattice. In the course of spreading, it becomes distorted and incorporates also polygons with a different number of vertices due to cell division and proliferation. We define the elastic potential energy $E$ of the tissue by summing up the contributions of the perimeter $L$ and the area $A$ of each cell [14]:

$$E = \frac{1}{2} \sum_{\text{cells}} \left[ \mu L^2 + \nu (A - A_0)^2 \right],$$

where $\mu$ is attributed to the action of active contractile forces within the cell cortex, $\nu$ is an elastic constant that reflects resistance to stretching or compressing the cell vertically when its area decreases or increases at conserved volume and $A_0$ is the reference cell area. This area should be larger than the initial cell area $\bar{A}_0$ to prevent shrinkage under the action of the perimeter force.

The tissue is evolved by moving the cell junctions (nodes). The mechanical force acting on any $j$th node is defined as the derivative of the potential energy with respect to the node position $\mathbf{x}_j$:

$$\mathbf{F}_\text{mech}^j = -\partial E/\partial \mathbf{x}_j.$$  

In addition, we impose an external wetting force with the force density $F_w$ per unit length that acts along the normal $\mathbf{n}$ to the leading edge of the spreading tissue. This force, responsible for the tendency of an unconstrained layer to spread into available space, may be weak but plays nevertheless an essential role by triggering the tissue advance in the absence of an injury signal.

The crucial ingredient of the model is the active force. For any $j$th cell, the active force is directed along the polarization vector $\mathbf{p}_j$ and is dependent on the local MAPK concentration $m_j$. We assume that the cells polarize under the influence of both the active force exerted by adjacent cells (which reflects cell interaction through adherens junctions and ensures coherence of motion) and the wetting force (which initiates polarization at the leading edge). Accordingly, the active force $\mathbf{F}_\text{act}^j$ is computed as the average over adjacent cells:

$$\mathbf{F}_\text{act}^j = \langle m_k \mathbf{p}_k \rangle_{k \text{adj}(j)},$$

The wetting force is present only for the edge cells and is computed by summing over their free edges with the respective lengths $l_{jk}$ and normals $\mathbf{n}_{jk}$:

$$\mathbf{F}_\text{wett}^j = \sum_k F_w l_{jk} \mathbf{n}_{jk}.$$
Accounting also for a linear polarization decay with the coefficient \( \beta_p \) and an uncorrelated zero-mean stochastic input \( \mathbf{F} \), we write the dynamic equation of the polarization vector as

\[
\partial_t \mathbf{p}_j = D[\kappa \mathbf{F}_\text{act} + \mathbf{F}_\text{wett}] - \beta_p \mathbf{p}_j, \tag{5}
\]

where \( D \) is the polarization mobility coefficient and the parameter \( \kappa \) plays a role of polarization diffusivity. Equations (3) and (5) combine to a discretized diffusion-decay equation with the wetting force as a boundary source term and an additional random noise. The inverse of \( D \) characterizes the time scale of the polarization rotation, whereas the inverse decay parameter \( \beta_p \) estimates the time scale of the polarization decay in the absence of driving forces. The ratio \( \sqrt{D \kappa / \beta_p} \) characterizes the polarization penetration length measured in the number of cells.

Since the motion is strongly overdamped, the appropriate equation governing the displacement velocities \( \mathbf{v}_j \) should be based on Aristotelean rather than Newtonian dynamics, having the form similar to the Darcy law with the mobility coefficient (inverse friction factor) \( K \). We also introduce a threshold force \( F_0 \) below which the node remains immobile:

\[
\mathbf{F}^\prime = \mathbf{F}_\text{mech} + \mathbf{F}_\text{act} + \mathbf{F}_\text{wett},
\]

\[
\mathbf{v}_j = \mathbf{x}_j / \partial t = K H(\mathbf{F}_j - F_0) \mathbf{F}_j^\prime,
\tag{6}
\]

where \( H(\cdot) \) is the Heaviside step function: \( H(x) = 1 \) at \( x > 0 \), \( H(x) = 0 \) at \( x \leq 0 \). Although the mobility should be generally anisotropic in a polarizable medium [15], we assume \( K \), as well other coefficients defining mechanical properties as above, to be scalars, both for simplicity and due to the lack of data. Since \( \mathbf{F}_\text{act} \) and \( \mathbf{F}_\text{wett} \) in Equations (3) and (4) are defined on cells, the interpolation between the adjacent cells is applied to calculate the forces in Equations (6) that are defined on nodes.

### 2.2. Chemical signaling

MAPK activation, caused by either chemical or mechanical signaling, plays a crucial role in cell spreading, as indicated by suppression of spreading by MAPK inhibition [4]. Although the mechanism of MAPK action remains so far unclear, it is reasonable to assume that it enables active traction, as implied in equation (3). The experiment suggests that MAPK can be activated both chemically and mechanically.

A chemical signal is emitted at the leading edge if the tissue spreading follows the injury rather than mere unconstraining. We assume that the signaling species is transported diffusively from one cell to the other, whereas its flux \( J_{ij} \) does not depend on the distance between the two cells but is proportional to the boundary length \( l_{ij} \); this implies that the transport is limited by the transfer through cell membranes. Allowing for a linear decay with the coefficient \( \beta_c \), we write the equation for the signal concentration in a \( j \)th cell as

\[
\partial_t c_j = \sum_{i: \text{adj}(j)} J_{ij} - \beta_c c_j, \quad J_{ij} = \alpha h_{ij}(c_i - c_j), \tag{7}
\]

where \( \alpha \) is the transfer coefficient and the fluxes are summed over the adjacent cells. The signal is supplied at the free edge where the boundary condition is given by

\[
J_{ij}^{(0)} = \Gamma e^{-|l_{ij}|/(c_0 - c_j)}, \tag{8}
\]

This implies that the signal decays exponentially following the injury with the characteristic time \( T_c \).

We assume that the MAPK level is driven by both the injury signal \( c \) and strain \( \sigma = A/A_0 - 1 \), defined as the change of the cell area relative to the reference value \( A_0 \). The dynamic equation of the activated MAPK concentration is written as

\[
\tau \partial_t m = c + \frac{aH(\sigma)\sigma}{1 + b\sigma} - \beta_m m. \tag{9}
\]

The chemical interactions here include the MAPK activation linear in the signal concentration and the linear decay with the constant \( \beta_m \); \( \tau \) is the capacity constant. The mechanically induced activation is supposed to occur under extension only; this is accounted for by the Heaviside step function \( H(\sigma) \). To prevent the runaway instability, we have chosen the strain dependence of a saturating type implying the maximum mechanical activation rate \( a/\beta_m \) and, respectively, the maximum strain-induced MAPK level \( m_{\text{max}} = a/(\beta_m b) \).

### 2.3. Cell proliferation and intercalation

Due to the elastic constraining of the cell area, persistent spreading is possible only if cell division takes place. When a cell division event occurs, the longest edge and the corresponding opposite edge are divided as in figure 1(a). Since each cell division leads to creation of a pair of penta-hepta defects, it causes the original hexagonal lattice to become strongly disordered [14]. In order to restrict (though not to eliminate) the disordering tendency, we assume the probability of cell division \( p \) to be dependent on the number of nodes \( n_j \):

\[
p = p_0 q^{-n}, \tag{10}
\]

where \( p_0 \) is a scaling factor. For \( q > 1 \), division of cells with a larger number of nodes is facilitated, thereby preventing strong deviations from the standard value \( n = 6 \).

An additional feature enhancing the tissue liquidity and preventing weird shapes of individual cells is intercalation. It is enabled by collapsing a link when its length falls below a minimal value \( l_0 \) and replacing it by a link of a slightly larger length in the normal direction. This leads to restructuring of the cell neighborhood as shown in figure 1(b). Intercalation is known to be important in many tissue reshaping processes [16, 17].

### 2.4. Summary of model parameters

The model equations contain a large number of parameters; their values are mostly not known from independent measurements but only their relative values are essential. In our computations, we adopt the values in the ranges making the simulation results qualitatively compatible with the experimental observations. The typical values of the parameters are given in table 1.

### 3. Simulation results

#### 3.1. Qualitative description: disorder and spreading speed

The simulations have been carried out in the geometry similar to that of the experiments of the group of Silberzan [5, 7, 9] with
Table 1. Typical simulation parameters.

| Parameter | Value |
|-----------|-------|
| $\mu_1$ | 1.0 |
| $\nu_1$ | 1.0 |
| $K$ | 1.0 |
| $F_0$ | 0.02 |
| $A_0$ | $\frac{3}{2} \sqrt{3}$ |
| $A_0 + 4\sqrt{3} \mu / \nu$ | |
| $F_W$ | 0.01 |
| $D$ | 0.4 |
| $|\tilde{F}|$ | $10^{-5}$ |
| $\kappa$ | 0.1 |
| $\beta_p$ | Variable |
| $c_0$ | 0 |
| $\beta_c$ | 0.1 |
| $\Gamma$ | 0 |
| $T_c$ | 0.01 |
| $\beta_m$ | 1.0 |
| $\tau_m$ | 0.1 |
| $a$ | 500 |
| $b$ | 0.05 |
| $\rho_0$ | $2 \times 10^{-4}$ |
| $q$ | 1.4 |
| $l_0$ | |

the tissue having originally the form of a stripe with two free edges allowing it to spread out. The only difference is in the periodic boundary conditions imposed in the direction normal to the free edges of the tissue. The cell polarization has initially a very small absolute value and a random direction. Figure 2(a) shows the shape of the tissue after a typical simulation run. One can see both the developing disorder in cell arrangement and roughening of the free edges, as well as a relative increase of the cell area near the edges, although not as pronounced as in the experiments. The size of the cells is distributed over a wide range, including a fraction of small cells just following a division event.

In accordance with the experiment [7], the velocity field, is highly intermittent but in the course of simulations, the largest velocities, roughly normal to the outer boundary, become typically confined to the leading edges. Accordingly, the displacement is generally more pronounced for cells or nodes at the edges than those in the bulk of the tissue, as shown in figure 2(b), which compares well with the experimental measurements (see figure 5 in [4]). Simulation movies can be requested from the authors.

3.2. Spreading with no injury: effect of active force

The active force directed along the polarization vector is the main factor driving the tissue spreading. Therefore, the results strongly depend on the parameter $\beta_p$ determining...
the polarization decay. Other parameters have been fixed at the values detailed in table 1 with the signal concentration set to zero in the runs simulating spreading with no injury. Figure 3(a) shows the boundary positions at a fixed time for runs with different values of $\beta_p$. With growing $\beta_p$, both the mean spreading length and the visible roughness decrease.

The evolution of roughness with time is characterized quantitatively in figure 3(b). The roughness is computed as

$$R^2(t) = \frac{1}{n_0} \sum_j \sum_{i(j)} (x_{ij} - \langle x \rangle_j)^2,$$  \hspace{1cm} (11)

where $n_0$ is the number of nodes in both edges ($j = 1, 2$) with positions $x_{ij}$ along the spreading direction. The curves for individual runs are quite noisy, especially at low values of $\beta_p$, but the curves averaged over ten runs in figure 3(b) show clear tendency of increased roughness (as well as the spreading speed) with decreasing $\beta_p$. At all values of $\beta_p$, except the lowest one, the roughness passes a maximum close to the onset of spreading but keeps increasing almost linearly at a slower pace as time progresses. The long-time behavior is therefore equivalent to a random drift with the effective diffusivity about $3 \times 10^{-4}$ squared cell lengths per time unit, almost independent of $\beta_p$ and increasing only at very small polarization decay rates.

Both the active and the elastic forces in the spreading layer transmit momentum from the cell tissue to the substrate. We calculate the averaged stress in a cross-section $x$ as

$$S(x; t) = \left( \int_{-\infty}^{x} dx' F_x(x', y, t) \right),$$ \hspace{1cm} (12)

where the angular brackets denote averaging along the axis $y$ normal to the spreading direction $x$, and $F_x$ is the $x$-component of the total force $F$ defined in equation (6). The negative stress at the different values of $\beta_p$ is plotted as a function of $x$ in figure 4. One can see that the force driving the cells is restricted to a narrow area close to the wound edges. This is consistent with recent findings [18] indicating a finite limit to the number of mobilized rows of cells, as well as with measured increase of stress with depth [8]. The stress increases with the decreasing decay parameter. The curves are noisy near the edges due to the roughness effects. Since polarization breaks the momentum conservation of the system, we may find an asymmetry of both the forces and tissue displacement. This asymmetry is again stronger at smaller values of $\beta_p$.

The temporal intermittency of the velocity field can be characterized quantitatively by the correlation function

$$C(s) = \langle v_i(t) v_i(t+s) \rangle,$$ \hspace{1cm} (13)

where the angular brackets denote averaging over all nodes $i$. For convenience, we have taken into account only the nodes that had already existed at $t = 0$. The correlation function for the velocity component in the spreading direction is shown in figure 5 against the product $\beta_p t$. We see that the functional dependence falls close to a universal curve when time is scaled by the polarization decay rate. We could not construct a meaningful spatial correlation function since our discretization scale is comparable with the scale of the correlation decay. The correlation appears to decay faster than in the reported experiments [7]. This may be caused by the presence of a threshold force in equation (6): apparently, the nodes overcome their motion thresholds individually at separated time steps rather than simultaneously in groups even though their connection is always retained.

**Figure 3.** (a) The form of the tissue edge for the indicated values of $\beta_p$. The shaded area corresponds to the initial stripe. (b) Evolution of roughness with time. The curves are averaged over ten runs for the indicated values of $\beta_p$.

**Figure 4.** Negative stress at $t = 2000$ (averaged in the lateral direction) as a function of the distance $x - \langle x \rangle$ from the center of the tissue for the indicated values of $\beta_p$. 

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**Figure 5.** Correlation function $C(s)$ as a function of the product $\beta_p t$.
3.3. Injury signal: double wave

The injury signal causes the MAPK concentration to grow rapidly at the outset; following this, as the evanescent signal decays, the MAPK concentration decreases and is restored again under the action of strain, proceeding as in the absence of injury [4]. This gives rise to a characteristic double MAPK wave (see figure 3 in [4]). There are, of course, no self-similar wave solutions propagating with a definite speed in this system, and the MAPK ‘front’ propagating into the tissue has to be defined in a particular way. To define the MAPK front position, we, first of all, average the MAPK concentration over the tissue cross-section to obtain $m(x, t) = \langle m(x, y; t) \rangle$. The maximum $m_{\text{max}}(t) = \text{Max}(\langle m(y, t) \rangle)$ is taken as a reference value, and the front position is defined as the cross-section $x$ satisfying $m(x, t) = 0.1m_{\text{max}}$. The evolution of the front position with time is shown in figure 6. The double wave seen here is qualitatively similar to that described in [4]. As in the experiment, the mechanical action causes deeper but slower penetration of the MAPK wave into the tissue. The insets showing spatial distribution of the MAPK level near both maxima are very dissimilar: the chemically induced distribution decays more steeply, while that induced mechanically is far more noisy, as it is influenced by polarization fluctuations.

4. Discussion

The model that we have described allows us to analyze systematically the effects of empty space, signaling, tissue polarization and growth on wound healing. We find that all peculiar features of our results, such as spontaneous edge undulations and spatio-temporal intermittency of the velocity field, are the consequence of an intrinsic instability of the chemo-mechanical feedback loop at the core of our model. This loop is maintained by polarization correlation among neighboring cells and is weakened when polarization decays. Many details of this model need experimental verification, as direct identification of the mechanisms involved in this feedback loop is not yet available. We anticipate that the minimal model that we have presented, built under conditions of uncertainty, will encourage further quantitative studies on chemo-mechanical interactions in spreading tissues and will, in its turn, be adjusted and modified as more data become available.

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