Published in final edited form as:

Biomech Model Mechanobiol. 2018 April ; 17(2): 439–448. doi:10.1007/s10237-017-0970-y.

Numerical Investigation of the Role of Intercellular Interactions on Collective Epithelial Cell Migration

Liqiang Lin¹, Xiaowei Zeng¹

¹Department of Mechanical Engineering, University of Texas at San Antonio, TX 78249, USA

Abstract

During collective cell migration, the intercellular forces will significantly affect the collective migratory behaviors. However, the measurement of mechanical stresses exerted at cell-cell junctions is very challenging. A recent experimental observation indicated that the intercellular adhesion sites within a migrating monolayer are subjected to both normal stress exerted perpendicular to cell-cell junction surface and shear stress exerted tangent to cell-cell junction surface. In this study, an interfacial interaction model was proposed to model the intercellular interactions for the first time. The intercellular interaction model based study of collective epithelial migration revealed that the direction of cell migration velocity has better alignment with the orientation of local principal stress at higher maximum shear stress locations in an epithelial monolayer sheet. Parametric study of the effects of adhesion strength indicated that normal adhesion strength at the cell-cell junction surface has dominated effect on local alignment between the direction of cell velocity vector and the principal stress orientation while the shear adhesion strength has little effect, which provides compelling evidence to help explain the force transmission via cell-cell junctions between adjacent cells in collective cell motion and provides new insights into “adhesive belt” effects at cell-cell junction.

Keywords

Epithelial monolayer; Intercellular interactions; Cell migration; Normal traction; Shear traction; Finite element simulation

1 Introduction

All the stages of animal life, from its commencement to its end are associated with cell migration (Frascoli et al. 2013; Li and Sun 2014; Lin and Zeng 2017). When cells migrate in loosely or closely associated groups, it can be referred to as collective cell migration (Li and Sun 2014; Rørth 2009). A variety of fundamental processes in biological system, such as embryonic morphogenesis (Reig et al. 2014; Scarpa and Mayor 2016; Weijer 2009), wound healing (Anon et al. 2012; Shaw and Martin 2009) and tumor progression (Butcher et al. 2009; Levental et al. 2009), depend on the coordinated motion of cell groups. Although

Xiaowei Zeng xiaowei.zeng@utsa.edu.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

factors affecting migratory behavior of single cell are beginning to be understood, still little is known on directed migration when cells are in collective groups(Frascoli et al. 2013; Mogilner 2009).

Coordinated movement of cell group could be regulated through dynamic interaction with both neighboring cells and the extracellular matrix (ECM). To study the effects of different factors on coordinated cellular motions, a number of studies have been conducted. The high-throughput genomic approaches were employed to identify the categories of genes and molecular modules which influence cell migration and adhesion(Simpson et al. 2008; Vitorino and Meyer 2008), and it was found that different genes or proteins have different influences on collective behavior. The adhesion of cell-cell junction would regulate cell migration from random to collective migration(Vitorino and Meyer 2008). Friedl et al. (2004) demonstrated that the integrity of cell-cell junctions plays an important role on collective cell movement in morphogenesis, tissue repair and cancer. The cell-cell adhesion combined with contractility would largely determine the rearrangement of epithelial cell layers(Bertet et al. 2004; Montell 2008). In addition, a study on collective cell migration through cooperative intercellular forces indicated that the mechanical stresses exerted at cell-cell junctions will regulate the monolayer coordinated movements by navigating cells motion along orientation of minimal intercellular shear stress (Tambe et al. 2011).

On the other hand, a number of numerical models have been recently developed to investigate the collective cell behaviors. Sepúlveda et al. (2013) adopted a stochastic interacting particle model to describe the collective cell motion in an epithelial sheet and they demonstrated that leader cells invade free surface more easily than other cells and coordinate their motions with their followers. Bi et al. (2015) used a vertex model to describe the epithelial junctional network and studied the influence of cell-cell adhesion and cortical tension rigidity transition in biological tissues. It was found that the onset of rigidity transition from liquid to solid was governed by a model parameter in confluent tissues. Li and Sun (2014) studied coherent motions in confluent cell monolayer sheets by employing a passive force model to describe the mechanical force on the cell arising from cell deformation and cell-cell interaction. It showed that competition between the active persistent force and random polarization fluctuation is responsible for the robust rotation. Kabla (2012) used the membrane tension to account for interactions between cells and studied collective cell migration. It revealed that cell motility and cell-cell mechanical interactions are sufficient to navigate the collective cell migration. Brugués et al. (2014) adopted a cell-based FE model(Brodland et al. 2007; Chen and Brodland 2000) to study the wound healing process. In the cell-based FE model, the cell-cell adhesion mechanisms were resolved into an equivalent tension force tangent to each cell edge. Through simulation analysis, the study stated that the wound can close either through cell crawling or through purse-string contraction.

However, even with specific and detailed information in hand, the role of intercellular interaction on “ordered” collective cell behavior is still not fully revealed. In fact, the transmission of cooperative forces via cell-cell junctions plays a significant role on the guidance of collective cell migration(Trepat and Fredberg 2011). The adherence feature between cells would be the most specific to collective behaviors(Méhes and Vicsek 2014).

The heterogeneous physical force distribution across many cell bodies in a monolayer sheet indicated that the well-known mechanisms of chemotaxis, durotaxis, and haptotaxis are insufficient, which resulted in discovery of the plithotaxis mechanism (Tambe et al. 2011). The experimental observations provide evidence that the epithelial cells will migrate preferentially along the maximum principal stress direction. To elucidate how each individual factor at the cell-cell junction will influence the migration behavior, we are the first to propose an interfacial interaction model to directly investigate the role of intercellular interactions on collective cell migration motion. Via the proposed interfacial interaction model, we are able to describe different behaviors and properties of cell-cell interactions and evaluate their influences on close-packed collective cell migration. The simulation results revealed that the average normal stress was more heterogeneous and greater than the maximum shear stress in an epithelial monolayer sheet. The same trend of local alignment as shown in experiment between the direction of cell migration velocity and the orientation of local principal stress was observed. In addition, cumulative probability distribution was dependent on magnitude of local maximum shear stress. Furthermore, it was found that the intercellular strength in surface normal direction (i.e. perpendicular to cell-cell junction surface) has dominant effect on coordinated migration of epithelial monolayer sheet.

The paper is organized in four sections: in Section 2, materials and methods on collective epithelial cell migration was described; in Section 3, the simulation results were presented; in Section 4, the role of intercellular interaction strength in different directions on collective migration alignment was discussed and the conclusion was drawn.

2 Materials and methods

2.1 Protrusion force modeling at the cell edge

Generally, cell migration involves protrusion formation at the leading edge (Farooqui and Fenteany 2005; Gagliardi et al. 2015; Ponti et al. 2004). The formation of protrusion will exert protrusion forces on the free edge (Fig. 1) and this could lead to directional migration of the whole cell group (Mayor and Carmona-Fontaine 2010). According to the study of (Trepatt et al. 2009), each individual cell in an advancing epithelial cell sheet engaged in a global tug-of-war. Through measurement of dynamic traction forces exerted by epithelial cells on a substrate, Du Roure et al. (2005) presented that the traction forces on leading edge was in the range of $0.25\sim 3.0\text{ nN}$. Hence, in this study, the magnitude of the protrusion force on leading edge of leader cell was estimated as 2 nN and it was applied on the edge nodes in x direction (Fig. 1). The magnitude of protrusion forces applied on edges of all follower cells was randomly generated from $0\sim 0.3\text{ nN}$ and the direction of protrusion was also random.

2.2 Intercellular interaction modeling at the cell-cell junction surface

During collective cell migration process, the leader cells dragged a passive mass of follower cells and the forces were transmitted through the cell-cell junctions from the leader cells to the follower cells at the back (Vedula et al. 2013). Thus, the intercellular adhesion would exert tractions to support the integrity of cell groups, i.e. normal traction (T_n) which is perpendicular to cell-cell junction surface or shear traction (T_t) which is parallel to cell-cell

junction surface as shown in Fig. 2. Indeed, recent experiments indicated that the intercellular adhesion sites within a migrating monolayer are subjected to both normal stress and shear stress (Tambe et al. 2011; Trepap and Fredberg 2011). The normal stress, which could be compressive or tensile stress, is the stress exerted perpendicular to the cell-cell junction surface; on the other hand, the shear stress is exerted parallel to the cell-cell junction surface. In fact, the intercellular forces within a migrating monolayer are extremely heterogeneous in distribution (Vedula et al. 2013) and it is very challenging to measure these forces in a direct manner. From numerical simulation side, we are the first to propose an interfacial interaction model to model the intercellular interactions at the cell-cell junction surface.

To consider the overall effects of intercellular interactions and simplify the complex system, an interfacial interaction model was proposed to govern the mechanical intercellular interactions at cell-cell junction (Lin et al. 2017a) and it takes the following forms:

$$T_n = \begin{cases} \sigma_c \left(\frac{\Delta_n - \delta_0}{\delta_{dn} - \delta_0} \right) \left[e^{1 - \frac{\Delta_n - \delta_0}{\delta_{dn} - \delta_0}} \right]^{q_n} & \Delta_n \leq \delta_{dn} \\ \sigma_c \left(\frac{\delta_{fn} - \Delta_n}{\delta_{fn} - \delta_{dn}} \right)^{p_n} & \delta_{dn} < \Delta_n < \delta_{fn} \\ 0 & \Delta_n \geq \delta_{fn} \end{cases} \quad (1)$$

$$T_t = \begin{cases} \tau_c \left(\frac{\Delta_t}{\delta_{dt}} \right) \left[e^{\frac{1}{2} - \frac{\Delta_t^2}{2\delta_{dt}^2}} \right]^{q_t} & 0 \leq |\Delta_t| \leq \delta_{dt} \\ \tau_c \frac{\Delta_t}{|\Delta_t|} \left(\frac{\delta_{ft} - |\Delta_t|}{\delta_{ft} - \delta_{dt}} \right)^{p_t} & \delta_{dt} < |\Delta_t| < \delta_{ft} \\ 0 & |\Delta_t| \geq \delta_{ft} \end{cases} \quad (2)$$

In the proposed interfacial interaction model, there are six independent parameters (σ_c , δ_{dn} , δ_0 , δ_{fn} , q_n and p_n) in surface normal direction and five independent parameters (τ_c , δ_{dt} , δ_{ft} , q_t and p_t) in tangential direction to control different intercellular adhesion properties and behaviors (Fig. 3). Here, σ_c and τ_c are intercellular adhesion strength in surface normal and tangential direction, respectively; and the strength denotes the value of maximum intercellular interaction; δ_0 is the equilibrium distance of intercellular interaction and $e = 2.71828$; δ_{dn} and δ_{dt} are critical intercellular interaction distance in surface normal and tangential direction, beyond which the interaction intense at cell-cell junction surface

between two adjacent cells gradually decreases; the shape parameters (q_n, q_t) are introduced to describe different intercellular interactions before critical interaction distance and the shape parameters (p_n, p_t) are used to describe different intercellular interactions (e.g. linear, exponential) after critical interaction distance; δ_{fn} and δ_{ft} are normal and tangential intercellular interaction cutoff distance beyond which there is no interaction at cell-cell junction surface between two adjacent cells. The variables u_n and u_t are normal and tangential surface separations, respectively. This model can be used to describe different intercellular interactions through the selection of different model parameters.

2.3 Cell-substrate interaction modeling

Cell adhesion and motility are essentially dynamic interactions between cells and their environment (Zeng and Li 2012). The interactions between single cell and its environment (Fig. 1) involved a number of different cellular structures such as lamellipodia, filopodia, and podosomes (Sheetz et al. 1998; Vedula et al. 2013). To study the interactions of an individual cell over a substrate, there have been a lot of efforts on the modeling of cell-substrate interactions (Fan and Li 2015b; Farsad and Vernerey 2012; Liu et al. 2007; McGarry et al. 2005; Roy and Qi 2010; Vernerey and Farsad 2014; Zeng and Li 2011a). In McGarry et al.'s study (McGarry et al. 2005), an exponential cohesive zone model (Xu and Needleman 1994) was employed to model the cell-substrate interfacial behavior. According to the analysis of Trepats et al. (2009), the normal traction at the cell-substrate interface can be ignored. Thus, in this study, we simplified our previous proposed interfacial cohesive zone model (Lin et al. 2017b) to only consider the cell-substrate adhesive traction in xy plane. The cell-substrate interaction traction was expressed as:

$$\mathbf{T}^{C-S} = \begin{cases} \tau^{C-S} \left(\frac{\Delta u}{\delta_p} \right) e^{\frac{1}{2} - \frac{(\Delta u)^2}{2\delta_p^2}} & 0 \leq |\Delta u| \leq \delta_p \\ \tau^{C-S} \frac{\Delta u}{|\Delta u|} \left(\frac{\delta_f - |\Delta u|}{\delta_f - \delta_p} \right) & \delta_p < |\Delta u| \leq \delta_f \\ 0 & \text{other} \end{cases} \quad (3)$$

where τ^{C-S} is the maximum traction between cell and substrate. According to the experimental measurement (Trepats et al. 2009), the value of cell-substrate traction forces at different distances from the leading edge is different and the spatial average is typical in the order of $5Pa$. So in this study τ^{C-S} was estimated as $5Pa$. δ_p is critical interaction distance at which the cell-substrate traction reaches its maximum and the value was estimated as 25 (McGarry et al. 2005), δ_f is the detachment distance at which the cell-substrate traction decreased to zero and the value was estimated as $60nm$ based on the reported substrate deformation ($25nm \sim 291nm$) during cell migration (Saez et al. 2010; Saez et al. 2007; Schoen et al. 2010).

2.4 Geometric modeling of collective epithelial cell monolayer

Since the epithelial monolayer is a thin layer (5~10 μm) (Driessche et al. 1993), a 2D plane stress model of epithelial cell group was generated to mimic the monolayer sheet of epithelial cells (Das et al. 2015; Guillot and Lecuit 2013; Kim et al. 2013) for simplicity while ensuring reasonable accuracy. Briefly, polygon-shaped epithelial cells were first generated using the Centroidal Voronoi tessellation method in a 2D geometric model (Lin et al. 2017a; Lin et al. 2014). Then, an interfacial zone was created to represent the cell-cell junctions between the adjacent epithelial cells by recessing the edges of each cell in a parallel manner towards the centroid of the cell with a designated distance. In this study, one hundred and twenty four (124) epithelial cells of a close-patch group were created and the average cell size was set to be around 30 μm , which is in the size range (10 μm ~36 μm) of epithelial cells (De Paiva et al. 2006). The equilibrium position of intercellular interaction was set to be 10 nm throughout the model, which was estimated based on the data of intercellular interaction reported in literatures (Giepmans and van IJzendoorn 2009; Hernandez et al. 2007; Hunter et al. 2005).

2.5 Material property and model parameter determination

Since the main purpose of this study is to investigate the role of intercellular interaction on collective cell migratory behaviors, the epithelial cell was assumed as an isotropic elastic material and the Young's modulus was selected as $E = 20\text{KPa}$ and Poisson's ratio $\nu = 0.45$ according to the data reported in literatures (Berdyeva et al. 2004; Guz et al. 2014). The mass density of individual epithelial cell was estimated as $2 \times 10^{-3} \text{ng}/\mu\text{m}^3$ based on the data reported in literatures (Anaya-Hernández et al. 2015; Park et al. 2010; Patton et al. 2000).

The intercellular interaction distance is in the range of 1 μm to 10 μm according to data reported in the literatures (Hunter et al. 2005; Jacinto et al. 2000; Vasioukhin et al. 2000), so the critical intercellular interaction distance δ_{dn} (normal direction) and δ_{dt} (tangential direction) in our model were both estimated as 1.0 μm and the interaction cutoff distance δ_{fn} (normal direction) and δ_{ft} (tangential direction) were selected as 2.0 μm in this study. The intercellular adhesion strength σ_c (normal direction) and τ_c (tangential direction) were approximated as $2 \text{nN}/\mu\text{m}^2$ based on the value of cell-cell adhesive traction in a range of $1 \text{nN}/\mu\text{m}^2$ to $8 \text{nN}/\mu\text{m}^2$ measured by Liu et al. (2010). For simplicity of analyses without losing critical information, q_n and q_t were set to be unity in this study, which represents an exponential behavior in the normal and tangential direction, respectively. The p_n and p_t were also set to be unity in this study, which represents a linear detachment progression between neighboring cells when the intercellular separation (δ_n & δ_t) exceeds the initial cutoff distance (δ_{dn} & δ_{dt}) in the normal and tangential direction, respectively.

2.6 Finite element implementation

A displacement-based finite element (FE) formulation is derived from the principle of virtual work. During the deformation process, following standard procedures and neglecting the body force, a Galerkin weak formulation of cohesive zone model may be expressed as following:

$$\begin{aligned} \int_{\Omega_0} \rho \ddot{\mathbf{u}} \cdot \delta \mathbf{u} d\Omega &= \int_{S_{ed}} \mathbf{T}^p \cdot \delta \mathbf{u} dS + \int_{S_{int}} \mathbf{T}^{C-C} \cdot \delta \Delta dS \quad (4) \\ &+ \int_{S_{cell}} \mathbf{T}^{C-S} \cdot \delta \mathbf{u} dS - \int_{\Omega_0} \mathbf{P} : \delta \mathbf{F} d\Omega \end{aligned}$$

where $\mathbf{P} : \delta \mathbf{F} = P^{ij} \delta F_{ji}$, $\mathbf{P}$ is the non-symmetric first Piola-Kirchhoff stress tensor. $\mathbf{T}^p$ is the protrusive traction vector; $\mathbf{T}^{C-S}$ is the cell-substrate interaction traction vector and $\mathbf{T}^{C-C}$ is the intercellular interaction traction vector. Δ denotes the intercellular separation jump across the cell-cell junction. Ω_0 and S_{int} are the volume and cell-cell junction surface in the reference configuration, respectively. S_{ed} is the cell edge surface and S_{cell} is the cell monolayer surface. ρ is the cell material density in the reference configuration. To calculate the nodal displacements, the explicit time integration scheme is based on the Newmark β -method (Belytschko et al. 1976), with $\beta = 0$ and $\gamma = 0.5$.

Following the standard finite element discretization procedure, the following discrete equations of motion can be obtained:

$$\mathbf{M} \ddot{\mathbf{u}} = \mathbf{F}^{ext} - \mathbf{F}^{int} \quad (5)$$

$$\mathbf{F}^{ext} = \mathbf{F}^p + \mathbf{F}^{C-S} + \mathbf{F}^{C-C} \quad (6)$$

where $\mathbf{M}$ is mass matrix; $\mathbf{F}^{ext}$ is external force array including protrusion force $\mathbf{F}^p$, cell-substrate adhesion force $\mathbf{F}^{C-S}$ and cell-cell adhesion force $\mathbf{F}^{C-C}$; $\mathbf{F}^{int}$ denotes internal force array arising from the deformation of epithelial cell.

$$M_{IJ} = \int_{\Omega_0} \rho_0 N_I N_J d\Omega \quad (7)$$

$$F_I^p = \int_{S_{ed}} T_i^p N_I dS \quad (8)$$

$$F_I^{C-S} = \int_{S_{cell}} T_i^{C-S} N_I dS \quad (9)$$

$$F_I^{C-C} = \int_{S_{int}} T_i^{C-C} N_I dS \quad (10)$$

$$F_I^{int} = \int_{\Omega_0} P_{ij} N_{I,j} d\Omega \quad (11)$$

3 Results

3.1 Stress distribution in epithelial monolayer sheet

First, the distribution of average local normal stress and maximum shear stress was plotted. In the simulation model, the monolayer sheet was discretized into linear triangle elements. The element number and node number were 2,400 and 2,001, respectively. At every nodal point of the monolayer sheet, we can obtain the maximum and minimum principal stresses according to the standard relationship:

$$\sigma_{\max} = \frac{\sigma_{xx} - \sigma_{yy}}{2} + \sqrt{\left(\frac{\sigma_{xx} - \sigma_{yy}}{2}\right)^2 + \tau_{xy}^2} \quad (12)$$

$$\sigma_{\min} = \frac{\sigma_{xx} - \sigma_{yy}}{2} - \sqrt{\left(\frac{\sigma_{xx} - \sigma_{yy}}{2}\right)^2 + \tau_{xy}^2} \quad (13)$$

Then, the average local normal stress is defined as $\sigma_{ave} = (\sigma_{\max} + \sigma_{\min})/2$ and the maximum shear stress is defined as $\tau_{\max} = (\sigma_{\max} - \sigma_{\min})/2$.

As shown in Fig. 4, we observed that the distribution of average local normal stress is heterogeneous compared to the maximum shear stress. The fluctuations of average normal stress occur over the whole monolayer sheet. In addition, the value of average local normal stress is greater than that of the maximum shear stress. These observations were consistent to the experimental investigation (Tambe et al. 2011; Trepap and Fredberg 2011) that the average local normal stress is severely heterogeneous.

3.2 Alignment between the direction of local cellular migration velocity and the orientation of local principal stress

Here, we performed the analysis of cell migration velocity direction with respect to orientation of local principal stress. In this study, the angle of principal stress at each nodal point is defined as:

$$\tan(2\theta_p) = \frac{2\tau_{xy}}{\sigma_{xx} - \sigma_{yy}} \quad (14)$$

and the angle of velocity vector is defined as:

$$\sin(\theta_v) = \frac{u_y}{\sqrt{u_x^2 + u_y^2}} \quad (15)$$

Then, we can obtain the angle of principal stress as: $\theta_p = \frac{1}{2} \arctan\left(\frac{2\tau_{xy}}{\sigma_{xx} - \sigma_{yy}}\right)$ and the angle of velocity vector as: $\theta_v = \arcsin\left(\frac{u_y}{\sqrt{u_x^2 + u_y^2}}\right)$.

Thus, the alignment angle between the major axis of the principal stress and the direction of cell velocity vector is defined as $\phi = |\theta_p - \theta_v|$. After simulation calculation, we took the data (magnitude of maximum shear stress) and sort them in a descending order (the highest magnitude at the top and the lowest magnitude at the bottom). From the sorted data, the highest 20% is the top quintile, the middle 20% is the third quintile and the lowest 20% is the bottom quintile. For every quintile data, we calculated the probability frequency (p_ϕ) of alignment angle (ϕ) based on the angle distribution from 0° to 90° .

From the simulation results shown in Fig. 5(a)-(c), we observed that the greater the local maximum shear stress, the narrower is the distribution of alignment angle (ϕ) and the greater is the frequency at lower alignment angle (ϕ). The coincidence between the orientation of the principal stress versus the direction of the velocity vector is consistent with the phenomenon observed in experiments (Tambe et al. 2011; Treppe and Fredberg 2011). In addition, the cumulative probability frequency (P_ϕ) is defined as the summation of probability frequency (p_ϕ). The data of cumulative probability frequency (P_ϕ) shown in Fig. 5(d) indicated that cumulative probability distribution is dependent on magnitude of local maximum shear stress, which is consistent with experimental observation as well.

3.3 Contribution of the intercellular adhesion strength on the alignment (ϕ) between the orientation (θ_p) of maximum principal stress and the direction (θ_v) of cell migration velocity vector

The intercellular interactions have effects on collective cell migration behaviors, but little is known about how the cell-cell adhesion strength in normal direction (perpendicular to cell-cell junction surface) and shear direction (tangent to cell-cell junction surface) will affect the collective behaviors. To study the effects of the intercellular adhesion strength on collective migration behaviors in an epithelial monolayer, we considered two cases: (1) **case I**: different normal intercellular adhesion strength and keep the shear intercellular adhesion strength the same; (2) **case II**: different shear intercellular adhesion strength and keep the

same normal intercellular adhesion strength. The parameters of intercellular interaction model were listed in Table 1.

Through simulation analysis, we observed that when the normal intercellular adhesion strength was weakened, the alignment between the orientation of local principal stress and the direction of local cellular motion was lessened (Fig. 6(a)). However, the alignment between the orientation of local principal stress and the direction of local cellular motion was almost the same when the shear intercellular adhesion strength was weakened (Fig. 6(b)), which indicates that the shear intercellular adhesion strength has little effect on the migratory behavior. These results also demonstrated that the normal intercellular adhesion strength has significant effects on the cellular migratory behavior. Meanwhile, we conducted parametric studies on critical intercellular interaction distance and intercellular interaction cutoff distance and it was found that the interaction distance have none or very little effect on the local alignment between the direction of cell velocity vector and the principal stress orientation. Taken together, these observations indicated that transmission of mechanical stresses from cell to cell across many cells is mainly through normal adhesion connections, which provide evidence for the explanation of ‘plithotaxis’ mechanism.

4 Discussion

For a monolayer sheet to migrate cohesively, it has been indicated that each cell in the group will exert physical forces not only on extracellular matrix but also on its neighboring cells. The study on physical characterization of molecular environment within the monolayer suggested that the direct transmission of physical forces from cell to cell might play a major role to steer mechanically local cellular motions (Grainger et al. 1990; Trepap and Fredberg 2011). Through experimental observation, it showed that the cell-cell junction was the best candidate to transmit mechanical forces between neighboring cells (Lecaudey and Gilmour 2006). Through the study of the interplay between cell-cell adhesion proteins, intercellular forces and epithelial tissue dynamics, it revealed that different molecular modules play different mechanical roles on intercellular forces and cellular kinematics (Bazellières et al. 2015). For instance, E-cadherin predicts the rate of intercellular force formation, while P-cadherin influences force transmission throughout a monolayer (Bazellières et al. 2015; Collins and Nelson 2015). Other study indicated that E-cadherin clusters concentrate in the cell-cell junction region and form an “adhesive belt” to stitch cells together (Guillot and Lecuit 2013). Study on the influence of cooperative intercellular forces on cell group movement inferred that E-cadherin was engaged in regulating local intercellular forces throughout a monolayer (Tambe et al. 2011). In fact, from a mechanical point of view, the “adhesive belt” formed by the concentration of E-cadherin in the cell-cell junction will balance the intercellular interactions mainly in the direction perpendicular to the cell-cell junction surface. Trepap and Fredberg (2011) implied that the cell-cell junction and associated cytoskeletal structures are incapable to bear appreciable shear stress.

From our study, it showed that the normal intercellular adhesion strength has dominant effect on the coordinated movements of an epithelial monolayer sheet (Fig. 5). This finding provides new insights into “adhesive belt” effects at cell-cell junction. The cells sense the intercellular adhesion force from their neighboring cells and transmit appreciable

intercellular normal stress across the cell-cell junction due to the “adhesive belt” effect (Guillot and Lecuit 2013). Thus, the loading across the cell-cell junction will be mainly exerted in the surface normal direction, which implies that cell-cell junction may be unable to support shear stress. This connection will result in the local alignment between the orientation (θ_p) of the maximal principal stress and the cell-cell junction surface normal direction. This alignment may cause the average local normal stress more heterogeneous and greater than the maximum shear stress (Fig. 4). The cell will migrate (orientation of velocity vector θ_v) preferentially along surface normal direction since the forces transmitted across cell-cell junction are mainly in the surface normal direction. So, the alignment between θ_p and the surface normal direction will result in the alignment between θ_p and θ_v (Fig. 5), which may help explain the mechanism of ‘plithotaxis’ in collective cellular motion (Tambe et al. 2011; Treppe and Fredberg 2011) and force transmission via cell-cell junction.

On the other hand, when the normal adhesion strength was weakened, the function of force transmission through cell-cell junction will be weakened. Thus, the connection between cells will be decreased and cells tend to follow their own migration direction instead of cell-cell force transmission direction. This might cause the lessened alignment between θ_p and θ_v . Taken together, it may also help decipher the underlying mechanism of how the direct transmission of physical forces across cell-cell junction will steer mechanically local cellular motions.

There are several limitations associated with the current study. Firstly, a 2D plane stress model is used in this study, which may not be fully representative of 3D cases. Secondly, the current model does not consider the detailed cell microstructure, complex cell material properties, cell remodeling process and active force effect inside a cell. In our future work, we will consider using liquid crystal and liquid crystal elastomers to model major cell components (Zeng and Li 2011a; Zeng and Li 2011b; Zeng and Li 2012; Zeng and Li 2014) with prescribed active stress terms (Edwards and Yeomans 2009; Fan and Li 2015a). Thirdly, we are concentrating on the role of intercellular interactions on collective cell migration motions and did not consider other effects on the cell migration behavior, such as chemotaxis, durotaxis and haptotaxis. In addition, the intercellular properties of cell-cell junction are estimated based on the experimental observations and related information reported in the literatures, which could be used only for qualitative analysis. Nonetheless, the results of this study indicate that the proposed intercellular interaction model is still able to capture the migration behavior of epithelial monolayer sheet, which may give rise to new insights on how the intercellular interactions will regulate the coordinated movements of collective cells. In addition, the current study provides advanced computational models and simulation tools for study of more realistic cooperative intercellular forces guided collective cell migration motions.

Acknowledgements

This work is supported by a grant from National Institutes of Health (Grant No. SC2GM112575) and a grant from the University of Texas at San Antonio (UTSA), Office of the Vice President for Research. Valuable discussions with Professor Jean Jiang and Professor Bruce Nicholson at Biochemistry Department of University of Texas Health Science Center at San Antonio, Professor Xiaodu Wang at Mechanical Engineering of UTSA are gratefully acknowledged.

References

- Anaya-Hernández A, Rodríguez-Castelán J, Nicolás L, Martínez-Gómez M, Jiménez-Estrada I, Castelán F, Cuevas E (2015) Hypothyroidism affects differentially the cell size of epithelial cells among oviductal regions of rabbits. *Reproduction in Domestic Animals* 50:104–111 [PubMed: 25405800]
- Anon E, Serra-Picamal X, Hersen P, Gauthier NC, Sheetz MP, Treppe X, Ladoux B (2012) Cell crawling mediates collective cell migration to close undamaged epithelial gaps. *Proceedings of the National Academy of Sciences* 109:10891–10896
- Bazellières E et al. (2015) Control of cell–cell forces and collective cell dynamics by the intercellular adhesion. *Nature cell biology* 17:409–420 [PubMed: 25812522]
- Belytschko T, Chiapetta R, Bartel H (1976) Efficient large scale non-linear transient analysis by finite elements. *International Journal for Numerical Methods in Engineering* 10:579–596
- Berdyeva TK, Woodworth CD, Sokolov I (2004) Human epithelial cells increase their rigidity with ageing in vitro: direct measurements. *Physics in Medicine and Biology* 50:81
- Bertet C, Sulak L, Lecuit T (2004) Myosin-dependent junction remodelling controls planar cell intercalation and axis elongation. *Nature* 429:667–671 [PubMed: 15190355]
- Bi D, Lopez J, Schwarz J, Manning ML (2015) A density-independent glass transition in biological tissues. *Nature Physics* 11:1074–1079
- Brodland GW, Viens D, Veldhuis JH (2007) A new cell-based FE model for the mechanics of embryonic epithelia. *Computer methods in biomechanics and biomedical engineering* 10:121–128 [PubMed: 18651278]
- Brugués A et al. (2014) Forces driving epithelial wound healing. *Nature Physics* 10:683–690 [PubMed: 27340423]
- Butcher DT, Alliston T, Weaver VM (2009) A tense situation: forcing tumour progression. *Nature Reviews Cancer* 9:108–122 [PubMed: 19165226]
- Chen HH, Brodland GW (2000) Cell-level finite element studies of viscous cells in planar aggregates. *Journal of biomechanical engineering* 122:394–401 [PubMed: 11036563]
- Collins C, Nelson WJ (2015) Running with neighbors: coordinating cell migration and cell–cell adhesion. *Current opinion in cell biology* 36:62–70 [PubMed: 26201843]
- Das T, Safferling K, Rausch S, Grabe N, Boehm H, Spatz JP (2015) A molecular mechanotransduction pathway regulates collective migration of epithelial cells. *Nature cell biology* 17:276–287 [PubMed: 25706233]
- De Paiva CS, Pflugfelder SC, Li DQ (2006) Cell size correlates with phenotype and proliferative capacity in human corneal epithelial cells. *Stem Cells* 24:368–375 [PubMed: 16123387]
- Diessche W, Smet P, Raskin G (1993) An automatic monitoring system for epithelial cell height. *Pflügers Archiv European Journal of Physiology* 425:164–171 [PubMed: 8272373]
- Du Roure O, Saez A, Buguin A, Austin RH, Chavrier P, Siberzan P, Ladoux B (2005) Force mapping in epithelial cell migration. *Proceedings of the National Academy of Sciences of the United States of America* 102:2390–2395 [PubMed: 15695588]
- Edwards S, Yeomans J (2009) Spontaneous flow states in active nematics: a unified picture. *EPL (Europhysics Letters)* 85:18008
- Fan H, Li S (2015a) Modeling microtubule cytoskeleton via an active liquid crystal elastomer model. *Computational Materials Science* 96:559–566
- Fan H, Li S (2015b) Modeling universal dynamics of cell spreading on elastic substrates. *Biomechanics and modeling in mechanobiology* 14:1265–1280 [PubMed: 25850888]
- Farooqui R, Fenteany G (2005) Multiple rows of cells behind an epithelial wound edge extend cryptic lamellipodia to collectively drive cell-sheet movement. *Journal of cell science* 118:51–63 [PubMed: 15585576]
- Farsad M, Vernerey FJ (2012) An XFEM-based numerical strategy to model mechanical interactions between biological cells and a deformable substrate. *International Journal for Numerical Methods in Engineering* 92:238–267

- Frascoli F, Hughes BD, Zaman MH, Landman KA (2013) A computational model for collective cellular motion in three dimensions: general framework and case study for cell pair dynamics. *PloS one* 8:e59249 [PubMed: 23527148]
- Friedl P, Hegerfeldt Y, Tusch M (2004) Collective cell migration in morphogenesis and cancer. *International Journal of Developmental Biology* 48:441–449 [PubMed: 15349818]
- Gagliardi PA et al. (2015) Real-time monitoring of cell protrusion dynamics by impedance responses. *Scientific reports* 5:10206 [PubMed: 25976978]
- Giepmans BN, van IJzendoorn SC (2009) Epithelial cell–cell junctions and plasma membrane domains. *Biochimica et Biophysica Acta (BBA)-Biomembranes* 1788:820–831 [PubMed: 18706883]
- Grainger DW, Reichert A, Ringsdorf H, Salesse C, Davies DE, Lloyd JB (1990) Mixed monolayers of natural and polymeric phospholipids: structural characterization by physical and enzymatic methods. *Biochimica et Biophysica Acta (BBA)-Biomembranes* 1022:146–154 [PubMed: 2306452]
- Guillot C, Lecuit T (2013) Mechanics of epithelial tissue homeostasis and morphogenesis. *Science* 340:1185–1189 [PubMed: 23744939]
- Guz N, Dokukin M, Kalaparthi V, Sokolov I (2014) If cell mechanics can be described by elastic modulus: study of different models and probes used in indentation experiments. *Biophysical journal* 107:564–575 [PubMed: 25099796]
- Hernandez S, Munguia BC, Gonzalez-Mariscal L (2007) ZO-2 silencing in epithelial cells perturbs the gate and fence function of tight junctions and leads to an atypical monolayer architecture. *Experimental cell research* 313:1533–1547 [PubMed: 17374535]
- Hunter AW, Barker RJ, Zhu C, Gourdie RG (2005) Zonula occludens-1 alters connexin43 gap junction size and organization by influencing channel accretion. *Molecular biology of the cell* 16:5686–5698 [PubMed: 16195341]
- Jacinto A, Wood W, Balayo T, Turmaine M, Martinez-Arias A, Martin P (2000) Dynamic actin-based epithelial adhesion and cell matching during *Drosophila* dorsal closure. *Current Biology* 10:1420–1426 [PubMed: 11102803]
- Kabla AJ (2012) Collective cell migration: leadership, invasion and segregation. *Journal of The Royal Society Interface*:rsif20120448
- Kim JH et al. (2013) Propulsion and navigation within the advancing monolayer sheet. *Nature materials* 12:856–863 [PubMed: 23793160]
- Lecaudey V, Gilmour D (2006) Organizing moving groups during morphogenesis. *Current opinion in cell biology* 18:102–107 [PubMed: 16352429]
- Levental KR et al. (2009) Matrix crosslinking forces tumor progression by enhancing integrin signaling. *Cell* 139:891–906 [PubMed: 19931152]
- Li B, Sun SX (2014) Coherent Motions in Confluent Cell Monolayer Sheets. *Biophysical journal* 107:1532–1541 [PubMed: 25296305]
- Lin L, Samuel J, Zeng X, Wang X (2017a) Contribution of extrafibrillar matrix to the mechanical behavior of bone using a novel cohesive finite element model. *Journal of the Mechanical Behavior of Biomedical Materials* 65:224–235 [PubMed: 27592291]
- Lin L, Wang X, Zeng X (2014) Geometrical modeling of cell division and cell remodeling based on Voronoi tessellation method. *CMES: Computer Modeling in Engineering & Sciences* 98:203–220
- Lin L, Wang X, Zeng X (2017b) Computational modeling of interfacial behaviors in nanocomposite materials. *International Journal of Solids and Structures* 115:43–52 [PubMed: 28983123]
- Lin L, Zeng X (2017) Computational study of cell adhesion and rolling in flow channel by meshfree method. *Computer Methods in Biomechanics and Biomedical Engineering* 20:832–841 [PubMed: 28290214]
- Liu P, Zhang Y, Cheng Q, Lu C (2007) Simulations of the spreading of a vesicle on a substrate surface mediated by receptor–ligand binding. *Journal of the Mechanics and Physics of Solids* 55:1166–1181
- Liu Z et al. (2010) Mechanical tugging force regulates the size of cell–cell junctions. *Proceedings of the National Academy of Sciences* 107:9944–9949

- Mayor R, Carmona-Fontaine C (2010) Keeping in touch with contact inhibition of locomotion. *Trends in cell biology* 20:319–328 [PubMed: 20399659]
- McGarry J, Murphy B, McHugh P (2005) Computational mechanics modelling of cell–substrate contact during cyclic substrate deformation. *Journal of the Mechanics and Physics of Solids* 53:2597–2637
- Méhes E, Vicsek T (2014) Collective motion of cells: from experiments to models. *Integrative biology* 6:831–854 [PubMed: 25056221]
- Mogilner A (2009) Mathematics of cell motility: have we got its number? *Journal of mathematical biology* 58:105–134 [PubMed: 18461331]
- Montell DJ (2008) Morphogenetic cell movements: diversity from modular mechanical properties. *Science* 322:1502–1505 [PubMed: 19056976]
- Park K et al. (2010) Measurement of adherent cell mass and growth. *Proceedings of the National Academy of Sciences* 107:20691–20696
- Patton DL, Thwin SS, Meier A, Hooton TM, Stapleton AE, Eschenbach DA (2000) Epithelial cell layer thickness and immune cell populations in the normal human vagina at different stages of the menstrual cycle. *American journal of obstetrics and gynecology* 183:967–973 [PubMed: 11035348]
- Ponti A, Machacek M, Gupton SL, Waterman-Storer C, Danuser G (2004) Two distinct actin networks drive the protrusion of migrating cells. *Science* 305:1782–1786 [PubMed: 15375270]
- Reig G, Pulgar E, Concha ML (2014) Cell migration: from tissue culture to embryos. *Development* 141:1999–2013 [PubMed: 24803649]
- Rørth P (2009) Collective cell migration. *Annual Review of Cell and Developmental* 25:407–429
- Roy S, Qi HJ (2010) A computational biomimetic study of cell crawling. *Biomechanics and modeling in mechanobiology* 9:573–581 [PubMed: 20204447]
- Saez A et al. (2010) Traction forces exerted by epithelial cell sheets. *Journal of Physics: Condensed Matter* 22:194119 [PubMed: 21386442]
- Saez A, Ghibaudo M, Buguin A, Silberzan P, Ladoux B (2007) Rigidity-driven growth and migration of epithelial cells on microstructured anisotropic substrates. *Proceedings of the National Academy of Sciences* 104:8281–8286
- Scarpa E, Mayor R (2016) Collective cell migration in development. *The Journal of cell biology* 212:143–155 [PubMed: 26783298]
- Schoen I, Hu W, Klotzsch E, Vogel V (2010) Probing cellular traction forces by micropillar arrays: contribution of substrate warping to pillar deflection. *Nano letters* 10:1823–1830 [PubMed: 20387859]
- Sepúlveda N, Petitjean L, Cochet O, Grasland-Mongrain E, Silberzan P, Hakim V (2013) Collective cell motion in an epithelial sheet can be quantitatively described by a stochastic interacting particle model. *PLoS Comput Biol* 9:e1002944 [PubMed: 23505356]
- Shaw TJ, Martin P (2009) Wound repair at a glance. *Journal of cell science* 122:3209–3213 [PubMed: 19726630]
- Sheetz MP, Felsenfeld DP, Galbraith CG (1998) Cell migration: regulation of force on extracellular-matrix-integrin complexes. *Trends in cell biology* 8:51–54 [PubMed: 9695809]
- Simpson KJ, Selfors LM, Bui J, Reynolds A, Leake D, Khvorova A, Brugge JS (2008) Identification of genes that regulate epithelial cell migration using an siRNA screening approach. *Nature cell biology* 10:1027–1038 [PubMed: 19160483]
- Tambe DT et al. (2011) Collective cell guidance by cooperative intercellular forces. *Nature materials* 10:469–475 [PubMed: 21602808]
- Trepat X, Fredberg JJ (2011) Plithotaxis and emergent dynamics in collective cellular migration. *Trends in cell biology* 21:638–646 [PubMed: 21784638]
- Trepat X, Wasserman MR, Angelini TE, Millet E, Weitz DA, Butler JP, Fredberg JJ (2009) Physical forces during collective cell migration. *Nature physics* 5:426–430
- Vasioukhin V, Bauer C, Yin M, Fuchs E (2000) Directed actin polymerization is the driving force for epithelial cell–cell adhesion. *Cell* 100:209–219 [PubMed: 10660044]

- Vedula SRK, Rivasio A, Lim CT, Ladoux B (2013) Collective cell migration: a mechanistic perspective. *Physiology* 28:370–379 [PubMed: 24186932]
- Vernerey FJ, Farsad M (2014) A mathematical model of the coupled mechanisms of cell adhesion, contraction and spreading. *Journal of mathematical biology* 68:989–1022 [PubMed: 23463540]
- Vitorino P, Meyer T (2008) Modular control of endothelial sheet migration. *Genes & development* 22:3268–3281 [PubMed: 19056882]
- Weijer CJ (2009) Collective cell migration in development. *Journal of cell science* 122:3215–3223 [PubMed: 19726631]
- Xu X-P, Needleman A (1994) Numerical simulations of fast crack growth in brittle solids. *Journal of the Mechanics and Physics of Solids* 42:1397–1434
- Zeng X, Li S (2011a) Modelling and simulation of substrate elasticity sensing in stem cells. *Computer methods in biomechanics and biomedical engineering* 14:447–458 [PubMed: 21516529]
- Zeng X, Li S (2011b) Multiscale modeling and simulation of soft adhesion and contact of stem cells. *Journal of the mechanical behavior of biomedical materials* 4:180–189 [PubMed: 21262496]
- Zeng X, Li S (2012) A three dimensional soft matter cell model for mechanotransduction. *Soft Matter* 8:5765–5776
- Zeng X, Li S (2014) Biomechanical cell model by liquid-crystal elastomers. *Journal of Engineering Mechanics* 140:04013003

Fig. 1.
Mechanical interactions in an epithelial monolayer: (a) side view, (b) top view

Fig. 2. Schematic mechanical interaction forces at cell-cell junction: (a) monolayer of collective epithelial cells, (b) cell-cell junction

Fig. 3.
Traction-separation relations at cell-cell junction surface in: (a) normal direction, (b) tangential direction

Fig. 4.

Stress distribution in an epithelial monolayer sheet: (a-b) showed the average normal stress; (c-d) showed the maximum shear stress. It indicated that the distribution of the average local normal stress is heterogeneous compared to the maximum shear stress and the average normal stress σ_{ave} is greater than the maximum shear stress τ_{max} .

Fig. 5.

The alignment angle (ϕ) between the major axis of the principal stress and the direction of the velocity vector. (a) Highest 20% maximum shear stress, (b) Middle 20% maximum shear stress, (c) Lowest 20% maximum shear stress, (d) The cumulative probability distribution P_f was strongly dependent on magnitude of local maximum shear stress.

Fig. 6. Cumulative probability vs. Alignment angle(ϕ) for different intercellular adhesion strengths in: (a) cell-cell junction surface normal direction (b) cell-cell junction surface tangential direction

Table 1

Parameters in the cell-cell interaction model: (1) **Case I**: different normal adhesion strength (2) **Case II**: different shear adhesion strength

	Case I			Case II		
σ_c	$0.1nN/\mu m^2$	$0.5nN/\mu m^2$	$2nN/\mu m^2$	$2nN/\mu m^2$	$2nN/\mu m^2$	$2nN/\mu m^2$
δ_{dn}	$1\mu m$	$1\mu m$	$1\mu m$	$1\mu m$	$1\mu m$	$1\mu m$
q_n	1	1	1	1	1	1
δ_{fn}	$2\mu m$	$2\mu m$	$2\mu m$	$2\mu m$	$2\mu m$	$2\mu m$
p_n	1	1	1	1	1	1
δ_0	$10nm$	$10nm$	$10nm$	$10nm$	$10nm$	$10nm$
τ_c	$2nN/\mu m^2$	$2nN/\mu m^2$	$2nN/\mu m^2$	$0.1nN/\mu m^2$	$0.5nN/\mu m^2$	$2nN/\mu m^2$
δ_{dt}	$1\mu m$	$1\mu m$	$1\mu m$	$1\mu m$	$1\mu m$	$1\mu m$
q_t	1	1	1	1	1	1
δ_{ft}	$2\mu m$	$2\mu m$	$2\mu m$	$2\mu m$	$2\mu m$	$2\mu m$
p_t	1	1	1	1	1	1