

Computational Study of Collective Cell Migration By Meshfree Method

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Abstract: The collective cell migration behavior on a substrate was studied using RKPM meshfree method. The cells were modeled as nematic liquid crystal with hyperelastic cell nucleus. The cell-substrate and cell-cell interactions were modeled by coarse-grained potential forces. Through this study, the pulling and pushing phenomenon during collective cell migration process was observed and it was found that the individual cell mobility significantly influenced the collective cell migratory behavior. More self-propelled cells are in the system along the same direction, the faster the collective group migrates toward coordinated direction. The parametric study on cell-cell adhesion strength indicated that as the adhesion strength increases, the collective cell migration speed increases. It also showed that the mechanical stress in leader cell is higher than stress in follower cells.

Keywords: Cell-cell interaction, cell-substrate interaction, collective cell migration, meshfree method, numerical simulation.

1 Introduction

Cell migration plays a significant role in many biological processes at different stages throughout the entire life of creatures [Frascoli, Hughes, Zaman et al. (2013); Li and Sun (2014); Hwang, Jung, Lee et al. (2015)]. Many biological activities require the coordinated cell movement toward a certain direction in a collective manner. Collective cell migration happens during tumor metastasis, wound healing process, morphogenesis of different organs or tissues, immune response, etc. For instance, during the inflammatory response, the leukocytes will move through the endothelial borders toward the site of infection in a highly coordinated manner in animal immune system [Simon and Green (2005); Muller (2013); Orellana, García-Solares, Donnez et al. (2017)].

Migratory behavior of cell group could be influenced by the interaction between neighboring cells and the interaction between cell and the extracellular matrix. In order to study cell motions in a collective manner and to investigate their roles in fundamental biological process, a number of studies have been conducted. The specific genes and key modules that influence cell migration and cell adhesion now can be identified by the high-throughput genomic methods [Simpson, Selfors, Bui et al. (2008); Vitorino and Meyer (2008); Wu, Siadaty, Berens et al. (2008)]. These studies showed that different genes or proteins regulate collective cell behavior in different ways. Several studies found that the

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adhesion of cell-cell junction which results from the intercellular transmission of mechanical forces would turn the highly random and uncoordinated cell motion into a coordinated collective motion [Vitorino and Meyer (2008); Vedula, Leong, Lai et al. (2012)]. Tambe et al. [Tambe, Hardin, Angelini et al. (2011)] found that cell-cell interaction forces govern the collective migration, directing cells moving along the orientations of minimal intercellular shear stress.

Meanwhile, a lot of recent studies have been focused on theoretical modeling of the collective cell migratory processes. Some discrete mathematical models such as vertex models [Honda and Eguchi (1980)] and cellular potts models [Graner and Glazier (1992)] have been developed and extensively used in the numerical simulation for cell migration and many other biological processes. These models take into account some features such as cell elasticity, contractility and cell-cell adhesion, and identify that intercellular forces regulate the cell shape [Farhadifar, Röper, Aigouy et al. (2007); Fletcher, Osterfield, Baker et al. (2014)]. By employing a vertex model, Bi et al. [Bi, Lopez, Schwarz et al. (2015)] found a new type of liquid-to-solid transition in confluent tissues. Continuum models have also been used to study the collective cell migration processes, where the cell sheet is considered as active continuous media. Chen et al. [Chen and Brodland (2000)] and Brodland et al. [Brodland, Viens and Veldhuis (2007)] proposed cell-based finite element models to study the stretching of cell sheet. A finite element method incorporating cell-cell interfacial interaction was used to study the collective epithelial migration [Lin and Zeng (2018)]. It was found that normal cell-cell adhesion regulates the coordinated epithelial movements.

Although the collective cell migratory behaviors and their roles in various physiological and pathological processes have been extensively studied, the mechanisms of coordination among cells are still not well understood due to the lack of advanced computational tools. How the mechanical clues will influence the collective cell migration behavior is not very clear. To elucidate how individual cell mobility and cell-cell interaction will affect the collective migratory behavior, we model the cell aggregates containing three monocytes to study the collective cell migration. In this study, we use liquid crystal and hyperelastic material models to model major cell components. A coarse-grained potential force was used to represent the cell-cell/substrate interactions. The RKPM meshfree method was employed to study the collective cell migratory behavior.

2 Computational algorithms

The numerical simulations were conducted by using the Reproducing Kernel Particle Methods (RKPM) [Liu, Li and Belytschko (1997); Li and Liu (2002)]. A total Lagrangian meshfree formulation was developed under finite deformation and a related Galerkin weak formulation was derived for numerical computation [Lin and Zeng (2017)]:

$$\int_{\Omega_0} \rho_0 \ddot{u} \delta u d\Omega = \int_{\Omega_0} \rho_0 \mathbf{B} \delta u d\Omega + \int_{\Gamma_t} \mathbf{f}^{c-s} \delta u dS + \int_{\Gamma_t} \mathbf{f}^{c-c} \delta u dS + \int_{\Gamma_t} \bar{\mathbf{T}} \delta u dS - \int_{\Omega_0} \mathbf{P} \delta \mathbf{F} d\Omega \quad (1)$$

where Ω_0 , ρ_0 represent the volume and material density in the reference configuration respectively; Γ_t is external traction boundary; \mathbf{P} is the first Piola-Kirchhoff stress tensor; \mathbf{F} is the deformation gradient; \mathbf{B} is the body force density; $\bar{\mathbf{T}}$ defines the external driving traction

vector; f^{c-s} and f^{c-c} are the cell-substrate and cell-cell interaction forces. The discrete equations of motion can be derived following the standard meshfree discretization procedure:

$$M\ddot{\mathbf{u}} = \mathbf{F}^b + \mathbf{F}^{c-s} + \mathbf{F}^{c-c} + \mathbf{F}^d - \mathbf{F}^{int} \quad (2)$$

where \mathbf{u} is the displacement; \mathbf{F}^b is the body force; \mathbf{F}^{c-s} is the cell-substrate interaction force; \mathbf{F}^{c-c} is the cell-cell interaction force; \mathbf{F}^d is the external driving force (e.g., protrusion force applied at the cell leading edge); \mathbf{F}^{int} denotes internal force array arising from the current state of stress. The detailed expression of the forces can be found in Lin et al. [Lin and Zeng (2017)].

3 Model description

In this study, three monocytes were placed on a ligand-coated substrate surface with the right cell defined as Cell-1, the middle cell defined as Cell-2, and the left cell defined as Cell-3. The cell protrusion force will drive cell moving on the substrate. A schematic diagram of collective cell migration on the substrate is shown in Fig. 1 below.

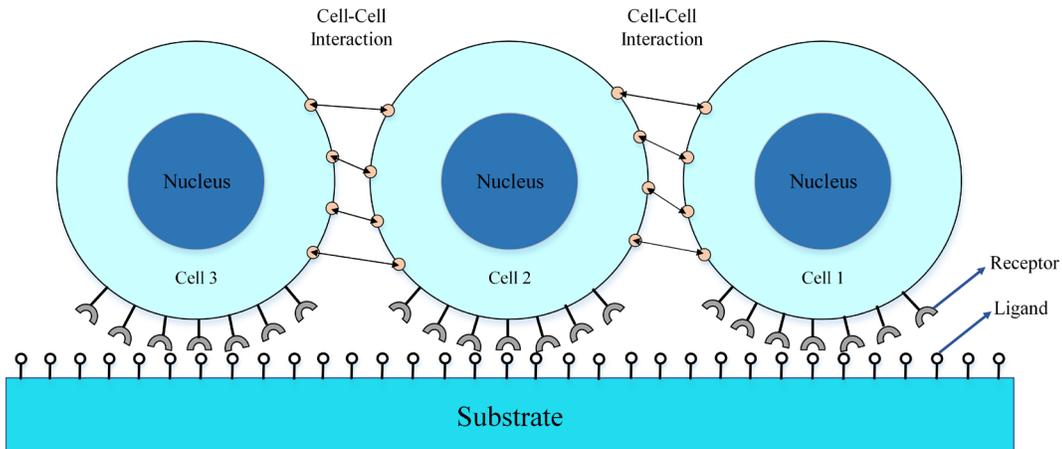


Figure 1: Schematic diagram of collective cell migration on a substrate

3.1 Cell-substrate interaction

At the beginning of the cell migration process, the cells will adhere to the substrate surface by forming the interaction bonds with the substrate. After that, the cells will spread over the substrate and finally move along the substrate collectively. Many theoretical models have been developed and used in order to capture the ligand-receptor interaction behavior [Zhu (2000); Zhu, Bao and Wang (2000); Liu, Zhang, Cheng et al. (2007); Sauer and Li (2007); Farsad and Vernerey (2012); Ruiz-Herrero, Estrada, Guantes et al. (2013); Fan and Li (2015)]. Here in this paper, a two-parameter potential given by Seifert [Seifert (1991)] was used to represent the cell-substrate interaction. Roy et al. [Roy and Qi (2010)] used this potential to study the cell crawling phenomenon. This adhesive potential shown in Eq. (3) was also used by Lin et al. [Lin and Zeng (2017)] to study the cell rolling behavior in a flow channel:

$$U(r) = \sigma \left[\left(\frac{\varepsilon}{r} \right)^4 - 2 \left(\frac{\varepsilon}{r} \right)^2 \right] \quad (3)$$

where σ is the energy depth; r represents the distance between the cell surface and the ECM substrate. Thus, the adhesive force vector can be derived by taking the negative gradient of the potential function:

$$\mathbf{F}(r) = -\frac{\partial U}{\partial r} = \frac{4\sigma}{\varepsilon} \left[\left(\frac{\varepsilon}{r} \right)^5 - \left(\frac{\varepsilon}{r} \right)^3 \right] \frac{\mathbf{r}}{r} \quad (4)$$

Taken into account the ligand-receptor bond density, the cell-substrate adhesive force can be derived as in Eq. (5) below. Here N_{c-s} is the surface bond density between the cell and substrate.

$$\mathbf{f}^{c-s}(r) = N_{c-s} \mathbf{F}(r) = N_{c-s} \frac{4\sigma}{\varepsilon} \left[\left(\frac{\varepsilon}{r} \right)^5 - \left(\frac{\varepsilon}{r} \right)^3 \right] \frac{\mathbf{r}}{r} \quad (5)$$

3.2 Cell-cell interaction model

Unlike the single cell moving on the substrate, collective cell migration is a more complicated process which include how cells interact with the substrate, also how a cell will interact with its neighbors. Here in this work, the cell-cell interaction was also represented by an adhesive potential function, which is similar to the cell-substrate interaction described in Eq. (5). The cell-cell interaction force may be calculated as in Eq. (6) below. Here N_{c-c} is the surface bond density between two neighboring cells.

$$\mathbf{f}^{c-c}(r, x) = N_{c-c} \mathbf{F}(r) = N_{c-c} \frac{4\sigma}{\varepsilon} \left[\left(\frac{\varepsilon}{r} \right)^5 - \left(\frac{\varepsilon}{r} \right)^3 \right] \frac{\mathbf{r}}{r} \quad (6)$$

3.3 Soft matter cell model

Different types of cells have different structures, and the mechanical properties of cells is a continuing topic of debate in the field of biophysics. Many experimental techniques such as atomic force microscopy (AFM) [Haase and Pelling (2015)], shearing and compression tests [Thoumine, Ott, Cardoso et al. (1999)], magnetic tweezers [Sleep, Wilson, Simmons et al. (1999); Dao, Lim and Suresh (2003)], optical dynamic light scattering and diffusing [Peetermans, Matthews, Nishio et al. (1987)] have been used to help probing the cell mechanics. Local viscoelasticity can be observed at different regions of cell with different stiffness. Recent studies found that cells can undergo a phase transition between fluid-like and solid-like states [Munder, Midtvedt, Franzmann et al. (2016); Mongera, Rowghanian, Gustafson et al. (2018)]. In the meantime, the theoretical modeling of cytoskeleton medium has been conducted using a variety of material models such as hyperelastic models [McGarry, Murphy and McHugh (2005); Mihai, Wyatt and Goriely (2017)], viscoelastic models [Karcher, Lammerding, Huang et al. (2003); Ragazzon, Gravidahl and Vagia (2018)], liquid crystal models [Helfrich (1973); Rey (2010); Zeng and Li (2011)], active gel models [Kruse, Joanny, Jülicher et al. (2005); Prost, Jülicher and Joanny (2015)], and multiphasic models [Vernerey and Farsad (2011); Zeng and Li (2012)].

Cell nucleus plays a pivotal role in sensing external conditions and force transfer. Experimental measurements have shown that the nucleus stiffness is nearly 10 times greater than the stiffness of cytoplasm [Thoumine and Ott (1997); Caille, Thoumine, Tardy

et al. (2002)]. Thus, in this work, we use a soft matter cell model developed by Zeng and Li [Zeng and Li (2012)] to study the collective cell migratory behavior. The cytoplasm and cytoskeleton network was modeled as nematic liquid crystal material which was represented by a simplified version of Ericksen-Leslie theory [Lin and Liu (2000)]. The Cauchy stress is described in Zeng et al. [Zeng and Li (2012)] as below:

$$\sigma_{ij} = -p\delta_{ij} + 2\mu d_{ij} - \eta h_{k,i} h_{k,j} - \zeta h_i h_j \quad (7)$$

where p is the hydrostatic pressure, μ is viscosity, d_{ij} is rate of deformation tensor, η is a coupling coefficient, $\zeta h_i h_j$ is the active stress term. The active stress represents the dipolar force generated by the individual particles, as a function of the director field. The sign of ζ determines whether the dipolar field generated by the particle is extensile ($\zeta > 0$) or contractile ($\zeta < 0$) [Edwards and Yeomans (2009)].

The cell nucleus was modeled as a hyperelastic material which was represented by a modified Mooney-Rivlin hyperelastic material model [Fried and Johnson (1988)]. The strain energy density function W for this model is described [Zeng and Li (2011); Zeng and Li (2013); Lin and Zeng (2017)] as below:

$$W = C_1 \left(I_1 - 3I_3^{1/3} \right) + C_2 \left(I_2 - 3I_3^{2/3} \right) + \frac{1}{2} \lambda (\ln I_3)^2 \quad (8)$$

where C_1, C_2 and λ are material constants which determine the elastic properties of cell; I_1, I_2, I_3 are the invariants of the right Cauchy-Green tensor. Therefore, the second Piola-Kirchhoff stress \mathbf{S} can be expressed correspondingly as below [Lin and Zeng (2017)]:

$$\mathbf{S} = 2 \left[(C_1 + C_2 I_1) \mathbf{I} - C_2 \mathbf{C} - \left(C_1 I_3^{1/3} + 2C_2 I_3^{2/3} - \lambda \ln I_3 \right) \mathbf{C}^{-1} \right] \quad (9)$$

Here $\mathbf{C} = \mathbf{F}^T \mathbf{F}$ is the right Cauchy-Green deformation tensor. \mathbf{P} is the first Piola-Kirchhoff stress tensor which can be derived from the second Piola-Kirchhoff stress: $\mathbf{P} = \mathbf{S} \cdot \mathbf{F}^T$. In order to calculate the internal nodal force, \mathbf{P} is substituted into the meshfree Galerkin formulation.

4 Numerical simulation

4.1 Simulation model

The cell diameter was assumed as $10 \mu\text{m}$ based on experimental observations [Fedosov and Gompper (2014); Palmer, Briggs, McFadden et al. (2015)]. The volume ratio of nucleus to cell is around 6 – 8% based on literature data [Huber and Gerace (2007); Jorgensen, Edgington, Schneider et al. (2007)]. Then, we assumed the radius ratio of nucleus to cell as 0.283. A total of 4,455 particles were used in discretization of cell in the meshfree computation. The meshfree dilation parameters are selected as $\rho_x = 2.2\Delta_x, \rho_y = 2.2\Delta_y$. The initial cell density is set to be $1.0 \times 10^3 \text{ kg/m}^3$. The material constants of the hyperelastic material model for cell nucleus were set as $C_1 = 2.126 \text{ KPa}$, $C_2 = 0.17 \text{ KPa}$, $\lambda = 170 \text{ KPa}$ [Zeng and Li (2011); Ravetto, Wyss, Anderson et al. (2014); Lin and Zeng (2017)]. For cell plasma parameter, the viscosity is $\mu = 0.001 \text{ kg/(ms)}$ and the bulk modulus was set as $k = 2.2 \times 10^6 \text{ KPa}$, the coupling coefficient is $\eta = 5.0 \times 10^{-8}$. The active term was ignored in this work. The cell-cell adhesion bond density was set as $N_{c-c} = 1000 (1/\mu\text{m}^2)$ and the energy depth is selected as $\sigma = 0.024 (pN \cdot \mu\text{m})$ for cell-cell

adhesion, and the equilibrium position is $\varepsilon = 10 \text{ nm}$ [Roy and Qi (2010)]. The cell-substrate ligand-receptor bond density was set as $N_{c-s} = 8,000 (1/\mu\text{m}^2)$ and the energy depth is $\sigma = 0.03 (pN \cdot \mu\text{m})$ for cell-substrate interaction. These parameter values are selected from published literature and they are in the suggested value range.

4.2 Simulation results

First, simulation was carried out when the protrusion force is generated at the leading edges of all three monocyte cells. The protrusion force was applied on the cell front half surface in contact with the substrate. The applied protrusion was proportional to the cell-substrate adhesion and we used a random number generator to adjust the value by multiplying it with a random number $\alpha = [0 \sim 1]$ at different locations. So the protrusion force is not constant at different locations. From this simulation, it can be observed that the cells are spreading over the substrate as shown in Fig. 2. We output the cell shape and effective stress of each cell at different time during the migration process, one may find that the contact area between cells and the substrate surface increased due to the cell-substrate adhesion (Figs. 2(a) & 2(b)). After initial spreading, cells started to move over the substrate driven by protrusion force applied at the leading edges (Figs. 2(b) & 2(c)). It can be seen that the contact areas between adjacent cells increased with time, which indicated that cells might exert lateral pushing on neighboring cells due to cell-cell interaction, resulting in cell displacement and movement [Haeger, Wolf, Zegers et al. (2015)].

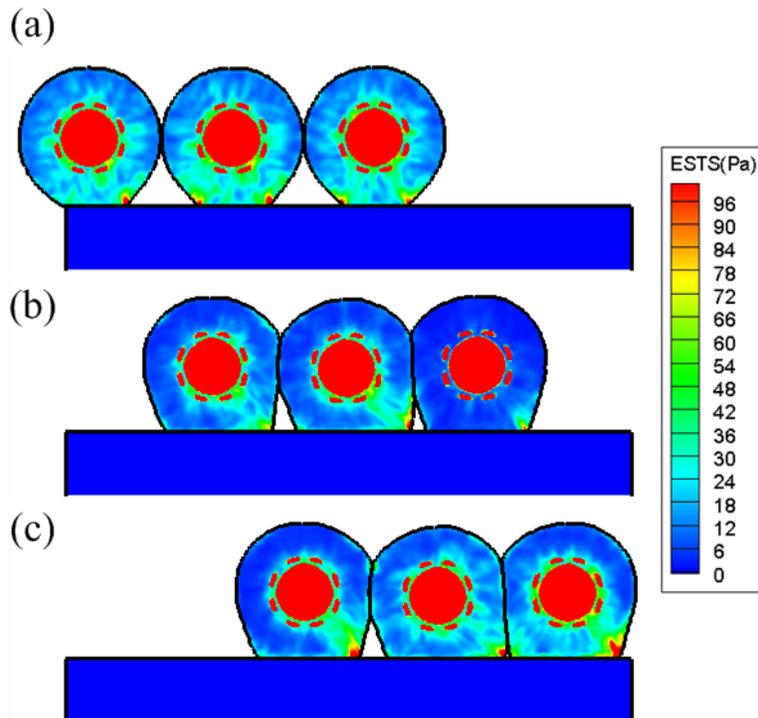


Figure 2: Snapshots of effective stress contour in cells (protrusion force applied to all cells) during collective cell migration: (a) $t = 20 \mu\text{s}$, (b) $t = 204 \mu\text{s}$, (c) $t = 268 \mu\text{s}$

We plotted the stress σ_{11} at the lower center point of the middle cell during cell migration as shown in Fig. 3. One may observe that the stress in cell migratory direction oscillates. Such stress profile implies that pushing and pulling may be imposed by neighboring cells which is highly important during collective cell migratory process [Vedula, Leong, Lai et al. (2012)].

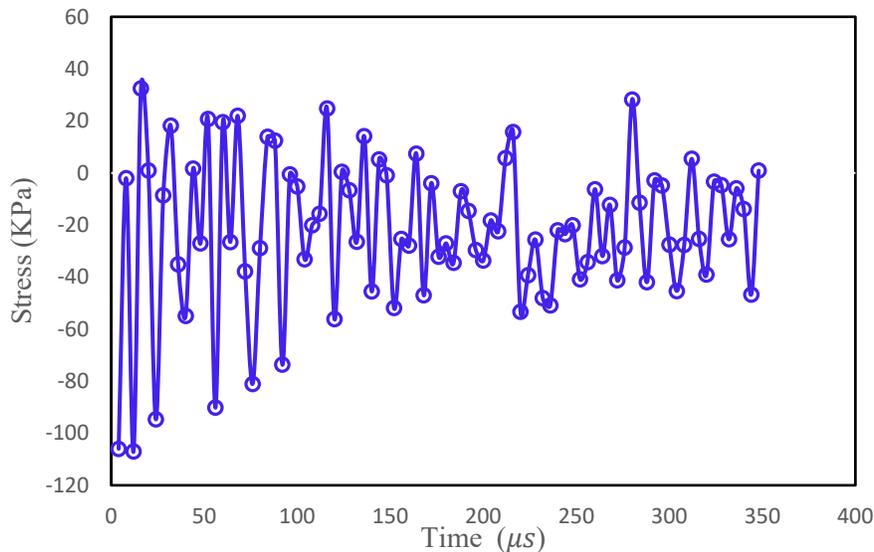


Figure 3: Stress status of the middle cell (Cell-2) during collective cell migration

In order to study how individual cells will affect collective migration behavior of the whole cell aggregate, three more cases were generated through applying protrusion force at the front edge of different number of monocyte cells. We output the average displacement of the three-cell aggregate for all four cases as shown in Fig. 4. The results show that the migratory displacement is smallest when the protrusion force is only applied at the leading edge of Cell-3, while the displacement is largest when the protrusion forces are applied at the leading edges of all three cells. This might indicate that the number of leader cells in the cell aggregate plays a role in the collective migratory behavior. In addition, it can be observed that the displacement of the cell aggregate for the case in which Cell-1 and Cell-3 are self-propelled is smaller than that for the case in which Cell-2 and Cell-3 are self-propelled. The possible reason for the smaller displacement is that at the very beginning of the migration, Cell-2 and Cell-1 were separated so that it inhibits the communication between the two leader cells (Cell-1 & Cell-3) as shown in Fig. 5(a). The results above shows that cell-cell interaction and communication between adjacent cells are very important and may regulate the collective cell migratory behavior [Khalil and Friedl (2010); Friedl and Mayor (2017)]. From the contour of effective stress shown in Fig. 5, one can find that the stress in Cell-2 is lower than the two self-propelled cells (Cell-1 & Cell-3). This implies that the stress in the leader cell may be higher than the stress in the follower cell, which is in agreement with a recent study [Vishwakarma, Di Russo, Probst et al. (2018)].

We also performed parametric studies in cell-cell adhesion strength. We found out that as the cell-cell adhesion strength increases, the collective cell migration speed increases as shown in Fig. 6. A parametric study in protrusion force indicated that the migration speed increases as the averaged cell protrusion increases.

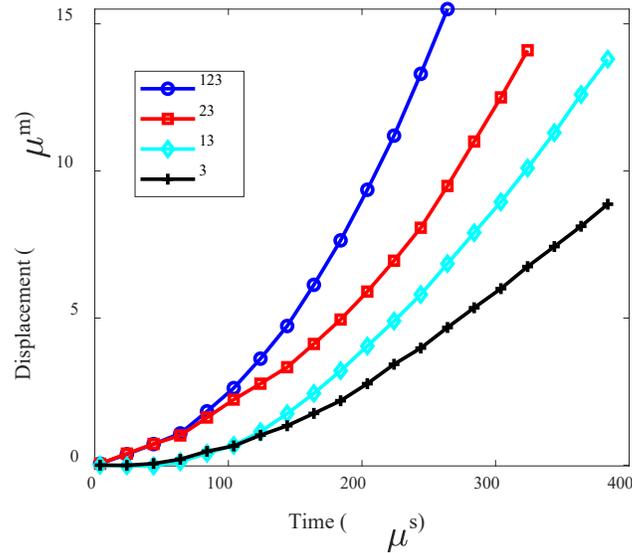


Figure 4: Average displacement of the cell aggregate during the collective cell migration (the number indicates which cell has protrusion force applied)

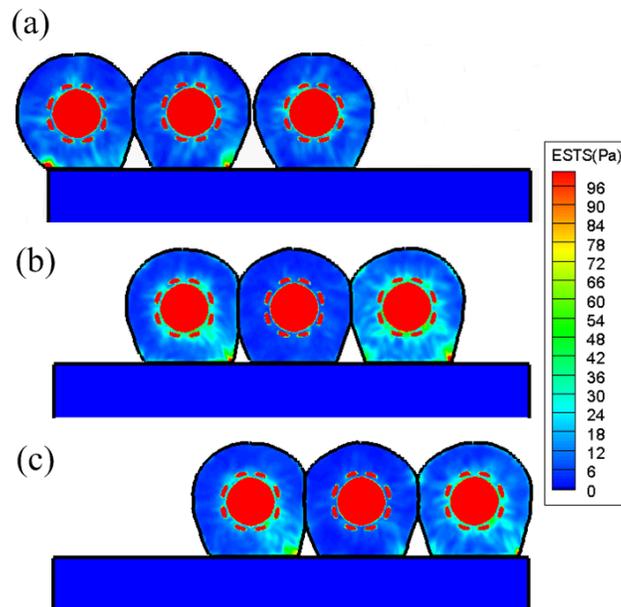


Figure 5: Snapshots of effective stress contour in cells during collective cell migration when Cell-1 & Cell-3 generate protrusion force: (a) $t = 24 \mu\text{s}$, (b) $t = 292 \mu\text{s}$, (c) $t = 388 \mu\text{s}$

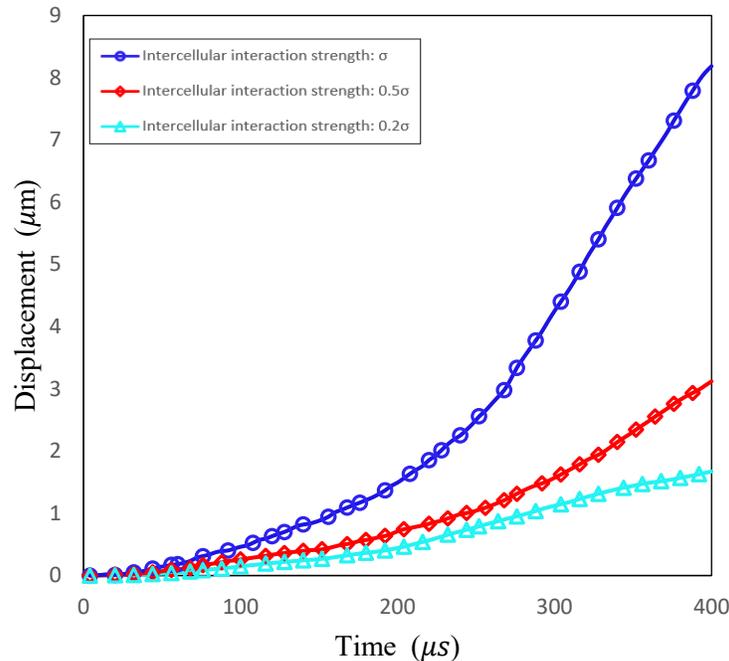


Figure 6: Average displacement of the cell aggregate with different magnitudes of cell-cell adhesion strength

5 Discussions and conclusions

To develop continuum physics-based cell model system that is capable of explaining the coordinated cell motion is a complex and challenging task. In this work, the cell was modeled as nematic liquid crystal with hyperelastic cell nucleus. A coarse-grained potential force was proposed to model the cell-substrate and cell-cell interactions. The collective cell migration behavior on a substrate was studied by using RKPM meshfree method. Through this study, the pulling and pushing phenomenon can be observed during collective cell migration process. It was found that the number of self-propelled cells in the system significantly influenced the collective cell migratory behavior. The more self-propelled cells are in the system, the faster the collective cell migration is toward the coordinated direction. The model-based study may provide possible explanations and insights on coordinated cell motion at the cellular level.

It should be noted that the collective cell migration is a very complex biological process. The proposed model is only intended to model the mechanical interactions of cells at mesoscale level, which cannot explain the molecular mechanisms of cellular processes. The computational model presented in this work is a primitive 2D model without consideration of “chemotaxis” or “durotaxis” in migrating cells, so the protrusion force applied may not be realistic in real situation. In our future work, we plan to build 3D models. The current study may provide computational model and simulation tool for our future work and may open a door for the study of coordinated cell motion in more realistic settings.

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