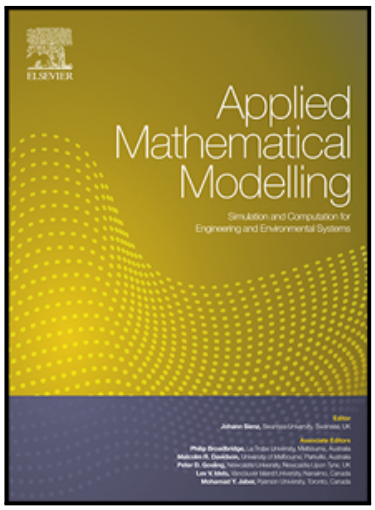


# 3D MECHANICAL ANALYSIS OF A SELF-CONTRACTILE CELL WITH STRESS FIBERS REORGANIZATION

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# Highlights

- The mechanical environment around a self-contractile cell is theoretical studied.
- The contractile stress analysis condiers the influence of the stress fibers reorganization in celss;
- The stress fibers reorganization can cause significant changes in the mechanical environment of cells.

# 3D MECHANICAL ANALYSIS OF A SELF-CONTRACTILE CELL WITH STRESS FIBERS REORGANIZATION

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**Abstract:** Contractile stress generated by a cell itself is crucial in sensing its surrounding microenvironment and regulating cell adhesion, differentiation and cytokinesis. However, the precise mechanisms underlying mechanotransduction remain unknown. In this paper, based on the Eshelby inclusion problem, we develop a theoretical model to characterize quantitatively the mechanical environment around a self-contractile cell experiencing stress fibers reorganization. We divide the contractile stress into two parts: the constant contractile stress and the perturbed contractile stress due to stress fibers reorganization, for internal stress fibers have enough time to reorganize actively during long-term deformation, leading to changes of contractile stress in both magnitude and direction. Obtained results suggest that stress fibers reorganization may cause significant changes in the mechanical environment of the cell, helpful for exploring the mechanisms behind cell mechanotransduction.

**Keywords:** self-contractile cell; constant contractile stress; perturbed contractile stress; stress fibers reorganization

## 1 Introduction

Cells like platelets, myoblast and cardiac myocytes have the ability to contract by themselves [1-4]. At the molecular level, this self-contractile stress is generated by internal myosin Ⅱ motors which continuously convert chemical energy of ATP hydrolysis to mechanical work and pull back the actin filaments [5-7]. Through local adhesions, cells transmit stress to the extracellular matrix (ECM) and

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receive the external feedback. Extensive experiments using soft hydrogel, an array of flexible micropillars and microdroplet techniques show that the magnitude of contractile stress is about 1kPa [8,9]. The activity of myosin motors controlled by electronic or chemical reagents severely affects cellular contractility [5,10,11]. Doss *et al*. [12] adhered fibroblasts to pillar arrays with different stiffness and found that the contractile stresses were significantly reduced with actin networks disorganized if cells were treated by high concentration of blebbistatin, while the contractile stress moderately decreased and the polarization of cytoskeleton was promoted on soft substrates if cells were treated by intermediate concentration of reagents. Moreover, it was reported that the maximum contractile stress for chick embryo fibroblasts could reach about 100kPa after treated by thrombin [13].

Mechanical stress, no matter applied externally or produced internally, can trigger a series of physiological responses, including structural changes in cytoskeleton and alterations in cell adhesion, differentiation and cytokinesis [14,15]. Li *et al*. [16] demonstrated that the microfilament network of eukaryotic cells experienced both strain hardening and softening during the stretching process. They also revealed that F-actin crosslinkers strengthend the bending stiffness and the buckling resistance of filopodial protrusion under the transverse and axial deformation, which had significant influences on the cell migration [17]. Besides, cell contraction induces mechanical stressing in the ECM, whose main microstructure is a network of cross-linked collagen fibers. When internal contractile stress spreads out, these fibers are aligned, densified and stretched, causing the stiffening of ECM [18-20]. Especially in the vicinity of cell, contractile stress provokes nonlinear response of ECM by buckling collagen filaments, causing even permanent plastic deformation [21-23]. As the survival of cell depends on the external environment, its behavior is inevitably influenced by the mechanical state of ECM [24-27]. For example, a stiffer matrix promotes a greater cell contraction and retards the attenuation of contractile stress, thus facilitating long-range interaction between individual cells [18].

Within the short time of mechanical action, internal stress fibers have no enough time to reorganize. The elasticity of cell and matrix dominates the mechanical response, which means that cell just acts as a passive inhomogeneity. But at the long time scale, stress fibers actively adapt to the overall mechanical state by changing their locations and orientations [28]. Trichet *et al*. [29] reported that when a cell was cultured on a soft micropillar substrate, the alignment of stress fibers were totally disordered, whereas the cell was fully polarized on a stiff substrate. Meanwhile, at every moment, new stress fibers are synthesized while old stress fibers are degraded. However, existing works of 3D (three-dimensional) mechanical analysis do not take into account the fact that, due to stress fibers reorganization, contractile stress changes in both magnitude and direction. Zemel *et al*. [30] developed a theoretical model to investigate the relationship between the alignment of intracellular stress fibers

and the stiffness of substrates. Combined with experiments which quantified the average orientation of stress fibers, it was demonstrated that the cellular contraction force increased monotonously with the increasing substrate stiffness and the alignment of stress fibers was a non-monotonic function of substrate stiffness. While the mechanical response of the matrix under the excitation of cell contraction was not given yet.

In the current study, we present a theoretical model to quantify the mechanical microenvironment around a single self-contractile cell, which is totally embedded in a 3D stress-free matrix, according the alignment of stress fibers after the contraction process is over. For simplicity, the influence of protein motors on the contractility of cell is not considered here It is assumed that the size of matrix is much larger than that of cell, so the problem can be treated as a self-contractile inhomogeneity contained in an infinite elastic matrix. Eshelby obtained the linear elastic field of an inclusion undergoing uniform eigenstrain in 1957 [31]. Then, researchers utilized these linear elastic solutions to analyze the contraction of human mesenchymal stem cells [30] and the cardiac myocytes [4,32]. Their theoretical predictions were in good agreement with experimental results, revealing that the linear elastic model is applicable to explore the small deformation of contractile cells. Based on these theoretical works as well as existing experimental results that cells exert a greater pulling stress to a stiffer matrix, we introduce a perturbed stress to describe the changes of contractile stress. Traditional cell-in-gel experiments measure the displacement of embedded micro-beads to characterize the whole displacement field. For a given gel stiffness, our model can give the mechanical state of any point in the system. To highlight general principles, a parameter study is carried out in the rest of this article.

## 2 Theoretical model

With reference to Fig. 1, the cell is modeled as an ellipsoidal inhomogeneity $\Omega_0$ embedded in an infinite matrix $\Omega$. It is assumed that both the cell and matrix are linearly elastic, isotropic and homogeneous, with their interface bonded perfectly to each other. The origin of a Cartesian frame $(x_1, x_2, x_3)$ is fixed at the center with the three base vectors parallel with the principle axes of cell. The semi-axes of the ellipsoidal cell along the three principal directions is $a_i (i = 1, 2, 3)$.

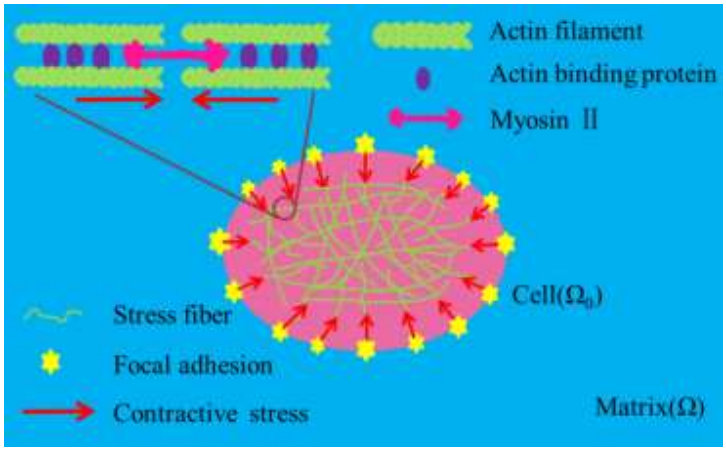


Fig. 1 A self-contractile cell $\Omega_0$ is embedded in an infinite elastic medium $\Omega$.

First, a reference state is defined, where the cell contracts itself uniformly by an initial stress $\sigma_{ij}^0$ but the matrix has not yet been deformed. During the deformation of the cell, stress fibers adjust their locations and orientations, and the contractile stress changes accordingly appearing to be dependent on the cell deformation. The contractile stress is assumed to be $\sigma_{ij}^{con}\left(\varepsilon_{ij}\right)=\sigma_{ij}^0+\alpha_{ijkl}\varepsilon_{kl}$, where $\sigma^p=\alpha_{ijkl}\varepsilon_{kl}$ is the perturbed stress due to reorganization of stress fibers and the fourth-rank susceptibility tensor $\alpha_{ijkl}$ describes the first-order approximation of perturbed stress on cell strain $\varepsilon_{kl}$ [28,30]. Here the introduction of the susceptibility tensor can be regarded as a phenomenological model to consider the stress change induced by the stress fiber reorganization. The complex relationship between the susceptibility tensor and the stress fiber reorganization is similar to the stiffness tensor of fiber composite and its fiber arrangement. Components of initial contractile stress $\sigma_{ij}^0$ and cell strain $\varepsilon_{kl}$ are negative. If components of susceptibility tensor $\alpha_{ijkl}$ are also set to be negative, then a smaller cell contraction within a stiffer matrix will correspond to a greater contractile stress. This is in agreement with related experiments that cell contractility increases as the elastic resistance becomes greater [1,2,9].

When the cell-matrix system reaches equilibrium, the elastic stress in the cell and matrix are:

$$\begin{aligned}\sigma_{ij}&=C_{ijkl}^c\varepsilon_{kl}-\left(\sigma_{ij}^0+\alpha_{ijkl}\varepsilon_{kl}\right) \quad \left(x_1,x_2,x_3\right)\in\Omega_0\\ \sigma_{ij}&=C_{ijkl}^m\varepsilon_{kl} \qquad\qquad\qquad\qquad \left(x_1,x_2,x_3\right)\in\Omega-\Omega_0\end{aligned} \tag{1}$$

where $C_{ijkl}^c$ and $C_{ijkl}^m$ are the stiffness tensor of cell and medium, respectively. Rearranging the above equation leads to:

$$\begin{aligned}\sigma_{ij} &= C_{ijkl}^{eff}\left(\varepsilon_{kl}-\varepsilon_{kl}^{eff}\right) \quad \left(x_1,x_2,x_3\right)\in\Omega_0\\ \sigma_{ij} &= C_{ijkl}^{m}\varepsilon_{kl} \qquad\qquad \left(x_1,x_2,x_3\right)\in\Omega-\Omega_0\end{aligned} \tag{2}$$

where $C_{ijkl}^{eff}=C_{ijkl}^{c}-\alpha_{ijkl}$ represents the effective stiffness tensor of cell, and the effective eigenstrain of cell $\varepsilon_{mn}^{eff}$ is defined by $C_{ijkl}^{eff}\varepsilon_{kl}^{eff}=\sigma_{ij}^{0}$. It is seen that the effective stiffness of cell covers both the passive elasticity and the active response of cell. The susceptibility tensor is related to the evolution of stress state via changing the stiffness of the cell.

According to the method of equivalent inclusion [31], the inhomogeneity problem can be simulated by a homogeneous inclusion problem with a fictitious eigenstrain $\varepsilon_{ij}^{*}$. The inclusion is contained in an infinitely homogeneous material, and the stiffness tensor for both the inclusion and the matrix are the same and denoted as $C_{ijkl}^{m}$. In this case, the elastic stress in the inclusion and matrix are:

$$\begin{aligned}\sigma_{ij} &= C_{ijkl}^{m}\left(\varepsilon_{kl}-\varepsilon_{kl}^{*}\right) \quad \left(x_1,x_2,x_3\right)\in\Omega_0\\ \sigma_{ij} &= C_{ijkl}^{m}\varepsilon_{kl} \qquad\qquad \left(x_1,x_2,x_3\right)\in\Omega-\Omega_0\end{aligned} \tag{3}$$

Stresses and strains in the above inhomogeneity and inclusion problems are equivalent as long as:

$$C_{ijkl}^{eff}\left(\varepsilon_{kl}-\varepsilon_{kl}^{eff}\right)=C_{ijkl}^{m}\left(\varepsilon_{kl}-\varepsilon_{kl}^{*}\right) \tag{4}$$

If the eigenstrain of inclusion is constant, the stress and strain fields are uniform for all internal points [31], as:

$$\varepsilon_{ij}=S_{ijkl}\varepsilon_{kl}^{*} \tag{5}$$

where $S_{ijkl}$ is the Eshelby tensor and its components are given in the Appendix. Substitution of Eq. (5) into Eq. (4) leads to:

$$C_{ijkl}^{eff}\left(S_{klmn}\varepsilon_{mn}^{*}-\varepsilon_{kl}^{eff}\right)=C_{ijkl}^{m}\left(S_{klmn}\varepsilon_{mn}^{*}-\varepsilon_{kl}^{*}\right) \tag{6}$$

The equivalent eigenstrain $\varepsilon_{ij}^{*}$ can thence be derived from:

$$\left[\left(C_{ijkl}^{eff}-C_{ijkl}^{m}\right)S_{klmn}+C_{ijmn}^{m}\right]\varepsilon_{mn}^{*}=\sigma_{ij}^{0} \tag{7}$$

Here in the small deformation case, though internal stress fibers actively reorganize, cell can still be assumed to remain isotropic with their mechanical properties almost unchanged during the deformation process, which has been proven to be feasible in Zemel *et al.*'s works [30].Thus, the susceptibility tensor $\alpha_{ijkl}$ should be a fourth-order isotropic tensor and can be defined as:

$$\alpha_{ijkl}=\alpha_v\delta_{ij}\delta_{kl}+\frac{\alpha_p-\alpha_v}{2}\left(\delta_{ik}\delta_{jl}+\delta_{il}\delta_{jk}\right) \tag{8}$$

Where $\delta_{ij}$ is Kronecker delta, $\alpha_p$ reflects a parallel response in which the contractile stress in a given direction changes with deformation in the corresponding direction, and $\alpha_v$ reflects a perpendicular response in which a given deformation affects the contractile stress of stress fibers in the perpendicular direction [30]. These two parameters describe different mechanisms by which stress fibers rearrange during cell deformation. As a phenomenological model, the key coefficients of the susceptibility tensor can be tested by experimental measurements [30].

For homogeneous materials, the stiffness tensor can be defined as:

$$\begin{aligned} C^c_{ijkl} &= \lambda_c \delta_{ij}\delta_{kl} + \mu_c \left(\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk}\right) \\ C^m_{ijkl} &= \lambda_m \delta_{ij}\delta_{kl} + \mu_m \left(\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk}\right) \end{aligned} \tag{9}$$

where $\lambda$ and $\mu$ are Lame's constants, related to Young's modulus $E$ and Poisson's ratio $\nu$ as:

$$\begin{aligned} \lambda_c &= \frac{\nu_c E_c}{(1-2\nu_c)(1+\nu_c)} \\ \mu_c &= \frac{E_c}{2(1+\nu_c)} \end{aligned} \tag{10}$$

$$\begin{aligned} \lambda_m &= \frac{\nu_m E_m}{(1-2\nu_m)(1+\nu_m)} \\ \mu_m &= \frac{E_m}{2(1+\nu_m)} \end{aligned} \tag{11}$$

and the corresponding subscripts *c* and *m* denoting the cell and the matrix, respectively.

We designate that cell experiences an isotropic contraction under its initial shape, as: $\sigma^0_{11} = \sigma^0_{22} = \sigma^0_{33} = -p$, where $p$ is the magnitude of contractile stress [30]. Then according to the rule of Voigt notation, rearrange Eq. (7) into matrix form, as:

$$\left(C_1 S + C_2\right)\begin{bmatrix} \varepsilon^*_{11} \\ \varepsilon^*_{22} \\ \varepsilon^*_{33} \end{bmatrix} = \begin{bmatrix} -p \\ -p \\ -p \end{bmatrix} \tag{12}$$

where the coefficient matrix $C_1$, $C_2$ and $S$ are given by:

$$C_1 = \begin{bmatrix} (\lambda_c + 2\mu_c) - (\lambda_m + 2\mu_m) - \alpha_p & \lambda_c - \lambda_m - \alpha_v & \lambda_c - \lambda_m - \alpha_v \\ \lambda_c - \lambda_m - \alpha_v & (\lambda_c + 2\mu_c) - (\lambda_m + 2\mu_m) - \alpha_p & \lambda_c - \lambda_m - \alpha_v \\ \lambda_c - \lambda_m - \alpha_v & \lambda_c - \lambda_m - \alpha_v & (\lambda_c + 2\mu_c) - (\lambda_m + 2\mu_m) - \alpha_p \end{bmatrix} \tag{13}$$

$$C_2 = \begin{bmatrix} \lambda_m + 2\mu_m & \lambda_m & \lambda_m \\ \lambda_m & \lambda_m + 2\mu_m & \lambda_m \\ \lambda_m & \lambda_m & \lambda_m + 2\mu_m \end{bmatrix} \tag{14}$$

$$S=\begin{bmatrix} S_{1111} & S_{1122} & S_{1133} \\ S_{1122} & S_{2222} & S_{2233} \\ S_{1133} & S_{2233} & S_{3333} \end{bmatrix} \tag{15}$$

The total displacement and elastic stress in the field are written as:

$$\begin{aligned} u_i &= B_{ijk}\varepsilon^*_{jk} \\ \sigma^t_{ij} &= C^c_{ijkl}S_{klmn}\varepsilon^*_{mn} \quad (x_1,x_2,x_3)\in\Omega_0 \\ \sigma^t_{ij} &= C^m_{ijkl}D_{klmn}\varepsilon^*_{mn} \quad (x_1,x_2,x_3)\in\Omega-\Omega_0 \end{aligned} \tag{16}$$

where $D_{klmn}$ and $B_{ijk}$ are presented in the Appendix. Cell volume change and stored deformation energy are:

$$\begin{aligned} \Delta V &= V\varepsilon_{ii} \\ U &= V\sigma^t_{ij}\varepsilon_{ij}/2 \end{aligned} \tag{17}$$

where $V=4\pi a_1a_2a_3/3$ is the volume of cell.

## 3 Results and discussion

The microscopic structure, composition, and mechanics properties of ECM provide biomechanical cues to mediate cell behavior. Extensive experimental evidence has indicated that ECM stiffness, besides cell self-contraction, is another factor influencing cell adhesion, migration and cytokinesis [24]. Thus, in the following mechanical analysis, we mainly analyze the influence of matrix stiffness on the whole mechanical field of a self-contractile cell. The susceptibility coefficients $\alpha_p$ and $\alpha_v$, related to stress fibers reorganization, can be deduced from the statistical deviation angle of stress fiber alignment [28,30]. According to previous works, the values of susceptibility coefficients can be taken as $\alpha_p=-0.5E_c$ and $\alpha_v=-0.1E_c$. As a comparison, the case that the cell exerts a constant contractile stress (i.e., $\alpha_p=0$ and $\alpha_v=0$) is also studied. Although great differences exist between cells, we typically set the three axial dimensions of cell as: $a_1=a$, $a_2=a_3=0.4a$, where *a* is the largest length of cell principal semi-axes. The Poisson ratios of cell and matrix are 0.4. For simplification, from here on it is convenient to denote the spatial coordinates as $(x_1,x_2,x_3)=(x,y,z)$.

Cells apply a contractile stress to the ECM by pulling back actin filaments. Thus, the density distribution and the orientations of actin filaments completely determine the magnitude and direction of the contractile stress. During the contraction process of cells within matrix of different stiffness, the internal stress fibers undergo corresponding reorganization, resulting in changes in the magnitude and direction of the contraction stress. Experiments have reported that when cell reaches the boundary

between the soft and stiff micropillar substrate, the cell is polarized with the reorganization of stress fibers and the contractile force increases rapidly, promoting the cell movement [29]. Mitrossilis *et al*. [2] measured the contraction of single myoblasts using two parallel fibrinogen-coated glass plates. One plate was fixed, the other was flexible. Single myoblast cells were placed between two plates, and once the cell began to contract, the flexible plate would be deflected. Based on the principle of elasticity, the contraction force could be derived according to the displacement of flexible plate. The results showed that myoblasts reached their maximum contraction in about 10 minutes. The contraction force was proportional to the stiffness of flexible plate when the stiffness did not exceed $60\,\mathrm{nN/\mu m}$. If the stiffness was higher, the contraction force reached the maximum value of about 300 nN.

In this work, the self-contractile cell is modeled as a three-dimensional (3D) inhomogeneous ellipsoid, and all the theoretical predictions are related to the 3D elastic field. While, the existing experiment is unidirectional measurement of contraction force [2], which cannot be directly compared with the present theoretical results. Figure 2 shows the contractile stress and internal total stress of cell when the cell and matrix finally reach equilibrium. Our theoretical results indicate that the cell exerts greater contraction stress on the stiffer matrix, which is consistent with the conclusion of the above experiment. The ability of cells to exert greater contractile stress on the stiffer matrix is crucial to the physiological behaviors of cells. For example, Jen and Mclntire [33] experimentally demonstrated that the contractile stress of platelets stiffened the fibrin polymers and enhanced the stiffness of clot. In turn, a stiffer matrix induced greater contractile stress of cell, as reported by Lam *et al*. [1]. This interaction between platelets and the fibrin polymers is helpful for the rapid formation of clot to stop bleeding. In contrast, the internal total stress decreases if the contractile cell is cultured within a stiffer matrix, for the elastic resistance exerted by the stiffer matrix gradually counteracts the self-contractile stress of cell. Moreover, after the influence of stress fiber reorganization is considered, both internal contractile stress and internal total stress become smaller. This indicates that the active regulation is an essential factor in characterising the overall mechanical environment of cell.

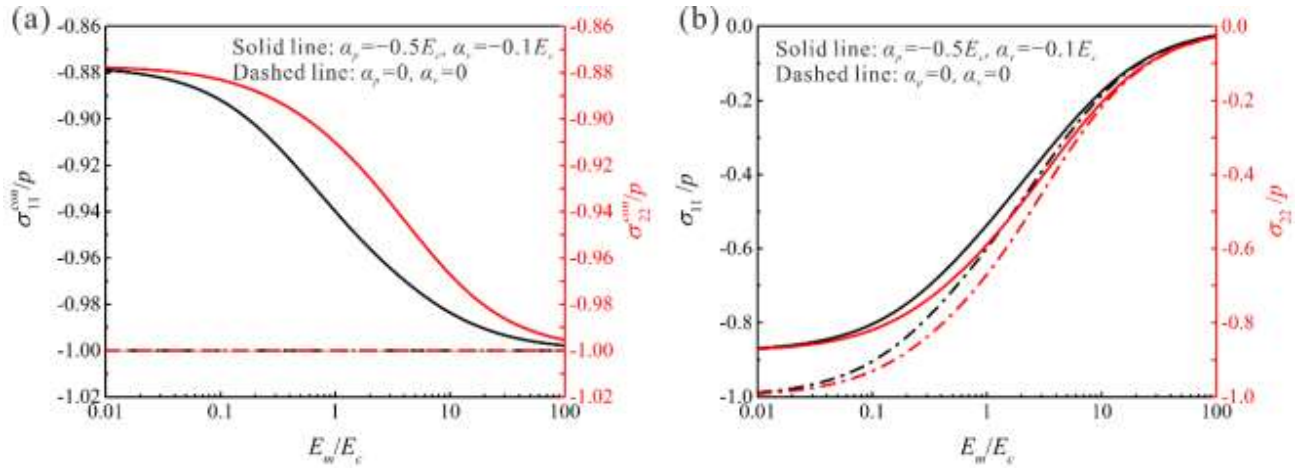


Fig. 2 Normalized contractile stress (a) and internal total stress (b) of cell vary with the increase of matrix modulus.

In Fig.3, the theoretical predictions of cell displacement in the *xy* plane are plotted. The ratio between the Young's modulus of the matrix to that of the cell is 0.2 in Fig. 3(a) and 3(b), increases to 1 in Fig. 3(c) and 3(d), and finally reaches 5 in Fig. 3(e) and 3(f). In all these cases, the ratio $p/E_c$ is set to 0.3. When the matrix is sufficiently soft, the maximum deformation of a contractile cell occurs at its apex. With the increase of matrix stiffness, the position of maximum deformation is gradually shifted to cell waist. Reorganization of stress fibers significantly affects cell deformation. Especially when the matrix modulus is close to cell modulus, stress fibers reorganization enables the deformation of each point on cell surface to be equivalent. Compared to the original morphology, cell still remains ellipsoidal but the size in all three principle axes decreases.

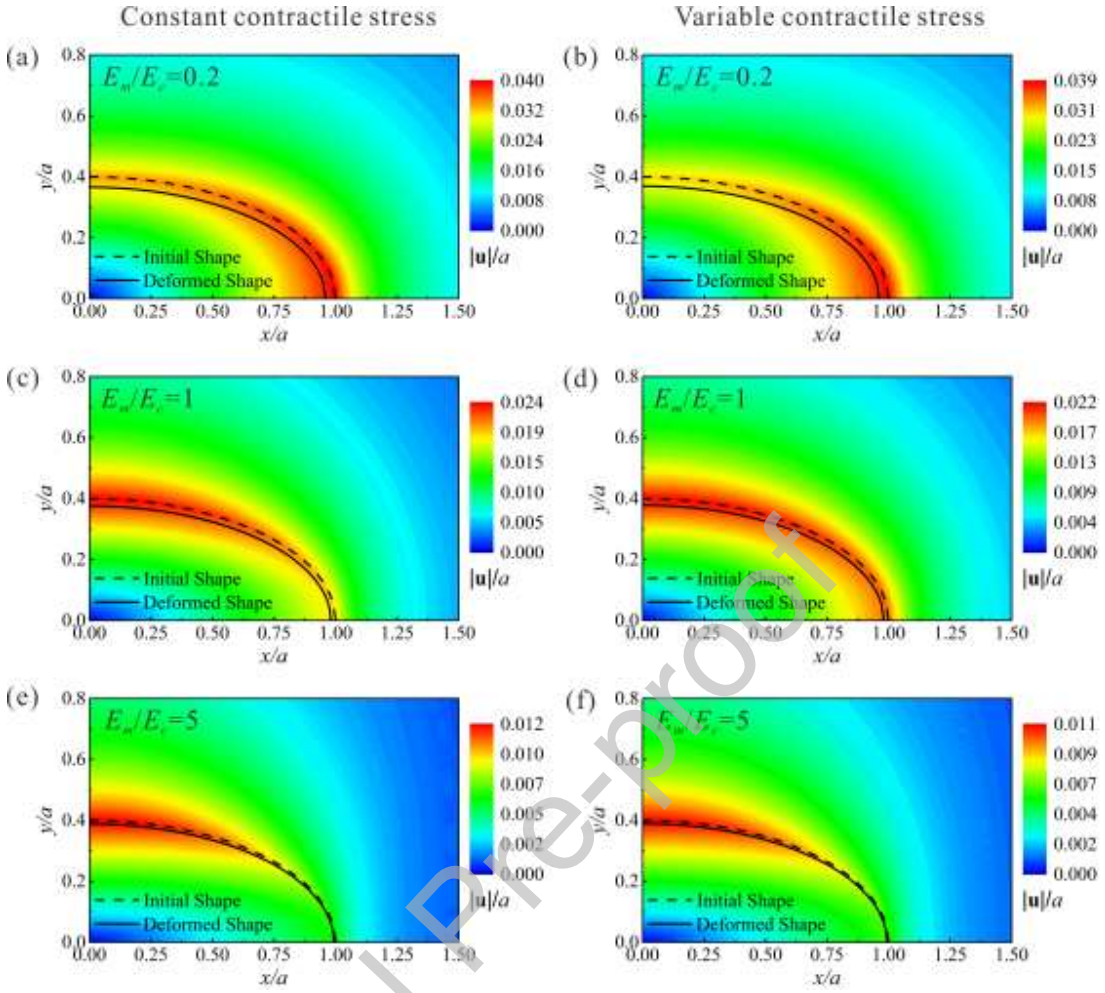


Fig. 3 Distribution of normalized displacement in *xy* plane for three selected values of matrix stiffness.

The cell volume change is of great importance to the behavior of living cells. For cardiac myocytes, Chiou *et al*. [4] proposed that the regulation mechanism of early embryonic heart beat is mechanical signal rather than electrical signal. When the volumetric strain of cardiomyocytes exceeds a threshold, they begin to contract and produce a mechanically propagated signal in the matrix to activate neighboring cells. In addition, physiological activities of cells convert the chemical energy to other forms of energy. When cardiomyocytes contract, part of the chemical energy consumed is stored as deformation energy. During the elongation period, deformation energy is released to promote ventricular relaxation. If the ability of myocardial cells to store deformation energy is impaired, it will inevitably affect the efficiency of cardiac congestion [34]. Figure 4 plots the normalized volume change $\Delta V/\left(pa^3E_c^{-1}\right)$ and the normalized deformation energy $U/\left(p^2a^3E_c^{-1}\right)$ of cell as functions of matrix stiffness. As the matrix stiffness is increased, it is difficult for cell to contract itself because it needs to overcome larger resistance. Consequently, both the cell deformation and the deformation

energy stored in the cell decrease. The reorganization of stress fibers results in less cell strain energy at each level of matrix stiffness.

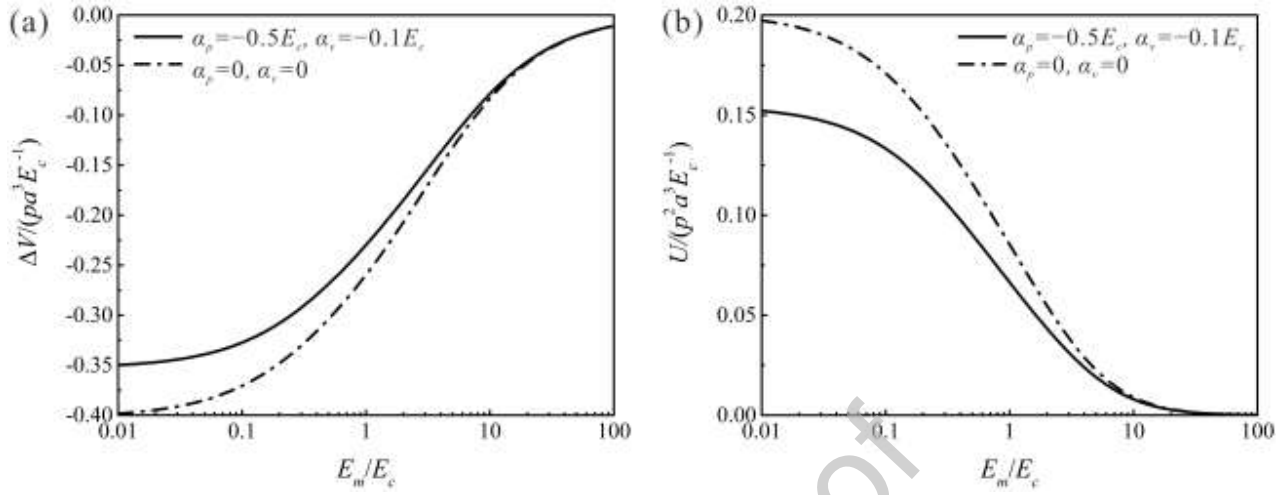


Fig. 4 Normalized volume change (a) and deformation energy (b) of cell plotted as functions of matrix stiffness.

## 4 Conclusions

Mechanical microenvironment has important influence on the physiological role of cells. Besides the stress or strain applied externally, the stimuli may also come from within the cell itself, such as self-contraction considered in the current study. During long-term deformation, internal stress fibers actively reorganize and thus alter the self-contractile force, which will significantly change the whole 3D mechanical field around a contractile cell. Built upon the classical Eshelby model of inclusion, we establish a theoretical model to quantitatively analyze the internal and external mechanical environment of a contractile cell cultured in matrix having varying stiffness. The contractile stress is divided into two parts: the constant contractile stress and the perturbed contractile stress due to reorganization of stress fibers. Obtained results imply that the reorganization of stress fibers may cause significant changes in cell mechanical environment, which are helpful for exploring the physical mechanisms underlying cell mechanotransduction.

## Appendix A

Given an ellipsoid with principle axes $a_1$, $a_2$ and $a_3$, the component of tensor $B_{ijk}$, $S_{ijkl}$ and $D_{ijkl}$ are expressed as:

$$B_{ijk}=\frac{1}{8\pi\left(1-\nu_m\right)}\left\{\begin{array}{l}2\nu_m\delta_{jk}x_iI_I\left(\lambda\right)+2\left(1-\nu\right)\left[\delta_{jk}x_kI_K\left(\lambda\right)+\delta_{ik}x_jI_J\left(\lambda\right)\right]\\-\left[\begin{array}{l}\left(\delta_{ik}x_j+\delta_{jk}x_i\right)\left(I_J\left(\lambda\right)-a_I^2I_{IJ}\left(\lambda\right)\right)+\delta_{ij}x_k\left(I_K\left(\lambda\right)-a_I^2I_{IK}\left(\lambda\right)\right)\\+x_ix_j\left[I_J\left(\lambda\right)-a_I^2I_{IJ}\left(\lambda\right)\right]_{,k}\end{array}\right]\end{array}\right\} \tag{A0}$$

$$S_{ijkl}\left(\lambda\right)=\frac{1}{8\pi\left(1-\nu_m\right)}\left\{\begin{array}{l}\delta_{ij}\delta_{kl}\left[2\nu_mI_I\left(\lambda\right)-I_K\left(\lambda\right)+a_I^2I_{KI}\left(\lambda\right)\right]\\+\left(\delta_{ik}\delta_{jl}+\delta_{jk}\delta_{il}\right)\left(a_I^2I_{IJ}\left(\lambda\right)-I_J\left(\lambda\right)\right)\\+\left(1-\nu\right)\left(\delta_{ik}\delta_{jl}+\delta_{jk}\delta_{il}\right)\left[I_K\left(\lambda\right)+I_L\left(\lambda\right)\right]\end{array}\right\} \tag{A0}$$

$$D_{ijkl}\left(\lambda\right)=\frac{1}{8\pi\left(1-\nu_m\right)}\left\{\begin{array}{l}8\left(1-\nu_m\right)S_{ijkl}\left(\lambda\right)+2\nu_m\delta_{kl}x_iI_{I,j}\left(\lambda\right)\\+\left(1-\nu\right)\left\{\delta_{il}x_kI_{K,j}\left(\lambda\right)+\delta_{jl}x_kI_{K,i}\left(\lambda\right)+\delta_{ik}x_lI_{K,j}\left(\lambda\right)+\delta_{jk}x_lI_{L,i}\left(\lambda\right)\right\}\\-\delta_{ij}x_k\left[I_K\left(\lambda\right)-a_I^2I_{IK}\left(\lambda\right)\right]_{,l}-\left(\delta_{ik}x_j+\delta_{jk}x_i\right)\left[I_J\left(\lambda\right)-a_I^2I_{IJ}\left(\lambda\right)\right]_{,l}\\-\left(\delta_{il}x_j+\delta_{jl}x_i\right)\left[I_J\left(\lambda\right)-a_I^2I_{IJ}\left(\lambda\right)\right]_{,l}-x_ix_j\left[I_J\left(\lambda\right)-a_I^2I_{IJ}\left(\lambda\right)\right]_{,lk}\end{array}\right\} \tag{A0}$$

where the integrals $I_i\left(\lambda\right)$ and $I_{ij}\left(\lambda\right)$ are defined as:

$$\begin{aligned}I_i\left(\lambda\right)&=2\pi a_1a_2a_3\int_\lambda^\infty\frac{ds}{\left(a_i^2+s\right)\Delta\left(s\right)}\\I_{ij}\left(\lambda\right)&=2\pi a_1a_2a_3\int_\lambda^\infty\frac{ds}{\left(a_i^2+s\right)\left(a_j^2+s\right)\Delta\left(s\right)}\\\Delta\left(s\right)&=\sqrt{\left(a_1^2+s\right)\left(a_2^2+s\right)\left(a_3^2+s\right)}\end{aligned} \tag{A0}$$

and the derivatives of $I_i\left(\lambda\right)$ and $I_{ij}\left(\lambda\right)$ are:

$$\begin{aligned}I_{i,j}\left(\lambda\right)&=\frac{-2\pi a_1a_2a_3}{\left(a_i^2+\lambda\right)\Delta\left(\lambda\right)}\lambda_{,j}\\I_{ij,k}\left(\lambda\right)&=\frac{-2\pi a_1a_2a_3}{\left(a_i^2+\lambda\right)\left(a_j^2+\lambda\right)\Delta\left(\lambda\right)}\lambda_{,k}\\I_{i,jk}\left(\lambda\right)&=\frac{-2\pi a_1a_2a_3}{\left(a_i^2+\lambda\right)\Delta\left(\lambda\right)}\left(\lambda_{,k}-\left(\frac{1}{a_i^2+\lambda}+\frac{1}{2}\sum_n\frac{1}{a_n^2+\lambda}\right)\lambda_{,j}\lambda_{,k}\right)\\I_{ij,kl}\left(\lambda\right)&=\frac{-2\pi a_1a_2a_3}{\left(a_i^2+\lambda\right)\left(a_j^2+\lambda\right)\Delta\left(\lambda\right)}\left(\lambda_{,kl}-\left(\frac{1}{a_i^2+\lambda}+\frac{1}{a_j^2+\lambda}+\frac{1}{2}\sum_n\frac{1}{a_n^2+\lambda}\right)\lambda_{,k}\lambda_{,l}\right)\end{aligned} \tag{A0}$$

For all internal points, $\lambda$ is equal to zero. When the point $\left(x_1,x_2,x_3\right)$ is located at the outside of the ellipsoid, $\lambda$ is the largest positive root of the equation:

$$\frac{x_1^2}{a_1^2+\lambda}+\frac{x_2^2}{a_2^2+\lambda}+\frac{x_3^2}{a_3^2+\lambda}=1 \tag{A0}$$

The corresponding derivatives $\lambda_{,i}$ and $\lambda_{,ij}$ can be deduced from Eq.(22), as:

$$\lambda_{,i} = \frac{x_i H}{a_i^2 + \lambda}$$
$$\lambda_{,ij} = \frac{\delta_{ij} H}{a_i^2 + \lambda} + \left( HG - \frac{1}{a_i^2 + \lambda} - \frac{1}{a_j^2 + \lambda} \right) \lambda_{,i} \lambda_{,j} \tag{A0}$$

where the intermediate parameters *H* and *G* are:

$$H = \frac{2\left(a_i^2 + \lambda\right)^2}{x_i x_i}$$
$$G = \frac{x_i x_i}{\left(a_i^2 + \lambda\right)^3} \tag{A0}$$

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