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Dynamics of Stress Fibers Turnover in Contractile Cells

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Abstract

Numerous experiments have shown that contractile cells like fibroblasts adapt their internal structure to their microenvironment by generating and orienting a network of stress fibers (SFs). This phenomenon has been modeled in previous studies with stability analysis through calculation of the fiber's potential or strain energy, where SFs are assigned a constant elasticity. Recent experiments have shown that the elasticity in SFs is rate dependent, resulting in a different stress fiber organization under constant or cyclic stretching. Here, a thermodynamical model that describes the anisotropic polymerization of the contractile units into SFs via the calculation of the mechanochemical potential of the two constituents is proposed. The stretch-dependent part of the SF potential is made of two terms that describe the passive and active behavior of the SF. In this paper, it is shown that the contributions of these two terms vary widely under constant or cyclic stretching as the SFs exhibit a rate-dependent elasticity and lead to two very different anisotropic SF organizations. It is further demonstrated that the substrate stiffness as well as its Poisson's ratio and anisotropy play a crucial role in the formation and organization of the SFs, consistent with what has been observed in various experiments.

Keywords

Mechanobiology; Tissue engineering; Stress fiber; Contractile cells; Cyclic stretch; Thermodynamics; Biophysics

CE Database subject headings

Fibers; Stress; Cyclic strength; Thermodynamics

Introduction

A critical issue in biology is to understand the mechanisms by which biological tissues are able to adaptively change their properties and structure in response to external stimuli. Indeed, these mechanisms are at the origin of important phenomena such as morphogenesis (Harris et al. 1981), remodeling and growth (Sawhney and Howard 2002), wound healing

(Martin 1997), and cancer dynamics (Paszek et al. 2005; Makale 2007; Butcher et al. 2009). Various studies have shown that tissue adaptation is driven by the ability of contractile cells to apply forces and deform or degrade their surrounding extracellular matrix (Vernerey et al. 2012). Cells acquire these abilities through the polymerization of actin and myosin monomers into a network of contractile fibers called stress fibers (SFs). These SFs connect the cells to their surrounding extracellular matrix (ECM) via focal adhesions (FAs) (multimolecular complexes localized on cell membranes) and allow them to sense stimuli conveyed by their ECM and respond accordingly by changing their internal stiffness and contractility. Studies have shown that SF organization is strongly influenced by the nature of the mechanical environment of cells (such as stiffness, deformation, and loading frequency) (Vernerey et al. 2011; Vernerey and Farsad 2011). When tissues are not stretched it has been shown that cell contractility and SF density are strongly dependent on substrate stiffness; i.e., the stiffer the substrate, the stronger is the contraction. Furthermore, in the presence of stretch SFs have been shown to align in the direction of maximum stretch for static loading and perpendicular to the direction of stretch for cyclic loading. Mathematical models have been proposed to describe the latter. For instance, the mathematical model proposed by Wang (2000) describes the SF orientation in a cell subjected to cyclic uniaxial stretch. Assuming that the perturbations in the SF strain energy cause their disassembly, the model predicts that the SFs are generated at 60° and 90° angles from the direction of stretch, respectively, for Poisson's ratios of 0.35 and 0, consistent with the experiments. Stamenovi et al. (2009) used the Maxwell stability criteria on the global mechanochemical energy of the SF-FA complex to find their orientation and densities in a cell subjected to uniaxial stretch. While these models are able to capture the alignment of SFs with respect to stretch, they do not describe how cell contractility depends on substrate stiffness or the time dependency of the SF.

To address this gap, this paper proposes a mathematical model based on thermodynamics to predict the orientation and contractile stress in SFs in response to uniaxial constant or cyclic stretch or changes in the substrate properties (such as the stiffness, Poisson's ratio, and anisotropy). The model is based on the three following assumptions backed up by experimental studies:

1. Contractile stress stabilizes and promotes the SFs self-assembly and the elastic energy of a SF causes its disassembly.
2. SFs exhibit a viscoelastic behavior.
3. The cell contractility and stiffness increase proportionally with the SF density in given directions.

Using the mechanochemical potential of the contractile units and SFs to find the angular volume fraction of the SFs when the system reaches chemical equilibrium, the model shows the effects of the substrate stiffness on the SF organization and can capture the behavior of a cell under both constant and cyclic stretch with great consistency from the experimental observations.

Model Formulation

Model

The capacity of contractile cells like fibroblasts to exert tensional forces and change their internal stiffness is principally a result of the existence of a network of SFs that generates tension through actomyosin across bridge dynamics. In vitro experiments have shown that SFs are generated by self-assembly when the cell is subjected to a stiff substrate or to constant or cyclic stretch, each case showing various SF organization patterns (Simpson et al. 1999; Yeung et al. 2005; Ghibaudo et al. 2008; Saez et al. 2007).

To capture these various SF organizations, a model was constructed in which cells were deposited on a substrate of stiffness E_s with maximum confluence. Each cell maintains a pool of contractile units that can be recruited to be polymerized into the SF (Fig. 1). This polymerization reaction is viewed as a thermodynamic phenomenon dependent on the difference of the mechanochemical potential between the monomers and polymers and on the angle from the direction of stretch. The final distribution of the SF is obtained when both mechanical and chemical equilibria are reached for all $\alpha \in [0, \pi]$.

Mechanical Equilibrium—A cell at mechanical equilibrium in direction α is subjected to the two following stresses (Fig. 2): a stress σ from the deformation of the substrate to which it is attached, and a stress σ^{SF} from the passive deformation and active contraction of the SFs of the cell. This yields the following equilibrium:

$$\sum_{\beta=s, \text{SF}} \sigma^{\beta} = \bar{\sigma} \quad (1)$$

where $\bar{\sigma}$ = externally applied stress.

Chemical Equilibrium—The polymerization of contractile units (CU) into SFs driving the self-assembly of SFs is described using the chemical potential of monomers μ^{CU} and polymers μ_{α}^{SF} . The chemical equilibrium is obtained when minimizing the Gibbs free energy (Atkins 1985) as follows:

$$\frac{\partial G}{\partial \xi} = \sum_{\beta=\text{CU}, \text{SF}} (\nu^{\beta} \mu^{\beta}) = \mu_{\alpha}^{\text{SF}} - \mu^{\text{CU}}, \quad \forall \alpha \in [0, \pi] \quad (2)$$

where ξ = extent of the reaction and ν_i and μ_i = stoichiometric coefficients and chemical potentials (here, μ_{α}^{SF} and μ^{CU}) of the various constituents involved in the reaction, respectively. If $\mu_{\alpha}^{\text{SF}} > \mu^{\text{CU}}$, the SFs are disassembled into CUs, if $\mu_{\alpha}^{\text{SF}} < \mu^{\text{CU}}$ the CUs are polymerized into SFs, and the state of equilibrium is reached when the potentials of the CUs and SFs are equal for all α .

Constitutive Equations—Here, a simple mathematical model is derived that can capture many features of SF organization and contraction based on the following three ideas.

Contractile Stress Stabilizes and Promotes the Self-Assembly of the SFs, and the Elastic Energy of a SF Causes Its Disassembly: Indeed, it has been shown that together with the RhoA enzyme, the contractility of the cell promotes the formation of the SF (Chrzanowska-Wodnicka and Burridge 1996); the activation of RhoA drives the myosin filament assembly and its interaction with actin, and the contractile tension allows the alignment and consolidation of the various components (Walcott and Sun 2010). Furthermore, myofibrils, which are close in structure to the SF, start fragmenting as their strain (i.e., their elastic energy) increases (Simpson et al. 1999). The same behavior has been observed for SFs (Lee et al. 2010). The chemical potentials μ^{CU} and μ_{α}^{SF} of the SF building unit can now be constructed. It consists of the classical formulation of the chemical potential plus the mechanochemical potential of the SF (Pathak et al. 2008; Shemesh et al. 2005)

$$\mu^{\text{CU}} = \mu_0^{\text{CU}} + k\Theta \ln \phi^{\text{CU}} \quad (3)$$

$$\mu_{\alpha}^{\text{SF}} = \mu_0^{\text{SF}} + k\Theta \left[\ln \phi_{\alpha}^{\text{SF}} + a_{\mu} \left(\frac{\phi_{\alpha}^{\text{SF}}}{\phi^*} \right)^{5/4} \right] + \mu_{\alpha}^{\text{SF, mech}} \quad (4)$$

where ϕ^{CU} and $\phi_{\alpha}^{\text{SF}}$ = volume fractions of contractile units and SFs, k = Boltzmann constant, Θ = absolute temperature, and a_{μ} = chemical potential of a SF oriented in the α direction. In Eqs. (3) and (4), the first term denotes the reference chemical potential and the second term represents the entropy of the configuration. The term a_{μ} is a correction of the entropy of the configuration for the case of semidilute polymers; however, this has not been determined for actin polymers. It is chosen to be zero in this study because this does not impact the results. The volumic mechanical contribution $\mu_{\alpha}^{\text{SF, mech}}$ to the chemical potential of the polymer on one stretching period T is constructed as follows based on Assumption 1:

$$\mu_{\alpha}^{\text{SF, mech}} = \frac{V_{\text{CU}}}{T} \int_0^T \left(\frac{1}{2} E_{\text{SF}}(t) \varepsilon_{\alpha}^2 - \sigma^* \varepsilon_{\alpha} \right) dt \quad (5)$$

where V_{CU} = volume of a contractile unit. The angular strain ε_{α} is assumed to be of the following sinusoidal form: $\varepsilon_{\alpha} = \bar{\varepsilon}_{\alpha} + \tilde{\varepsilon}_{\alpha} \cos(2\pi t/T)$. The elastic energy term $(1/2) E_{\text{SF}}(t) \varepsilon_{\alpha}^2$ will increase the chemical potential of the polymer, contributing to the disassembly of SFs, and the contractile work term $\sigma^* \varepsilon_{\alpha}$ will decrease it, inducing a stabilization of the SFs.

SFs Exhibit a Viscoelastic Behavior: It has been reported that SFs behave like a viscoelastic cable, made tense by the action of actomyosin motors (Kumar et al. 2006) [Fig. 1(c)]. Therefore, the time-dependent elasticity of a SF is constructed as follows, based on Assumption 2:

$$E_{\text{SF}}(t) = E_t + E_v \exp(-t/\tau) \quad (6)$$

where E_t and $E_v \exp(-t/\tau)$ = SF linear elasticity and time-dependent elasticity, respectively; t = relaxation time; and τ = relaxation time constant for a SF.

Cell Contractility and Stiffness Increase Proportionally with SF Density in Given

Directions: Further assuming that both the cell and substrate behave in a linear elastic fashion, the mechanical constitutive equations and the resulting equilibrium equation are as follows:

$$\sigma_{ij}^s = E/(1+\nu)\varepsilon_{ij} + E\nu/[(1+\nu)(1-2\nu)]\delta_{ij}\varepsilon_{kk} \quad (7)$$

$$\sigma_{\alpha}^{\text{SF}} = \phi_{\alpha}^{\text{SF}} [\sigma^* + E_{\text{SF}}(t)\varepsilon_{\alpha}] \quad (8)$$

where E and ν = stiffness and the Poisson's ratio of the substrate, respectively; ε_{α} = strain in direction α ; σ^* = stress produced by one SF; and

$\phi_{\alpha}^{\text{SF}}$ = volume fraction of the SFs in direction α .

Solution

First to be solved is the mechanical equilibrium for either stress-free or displacement control boundary conditions to get the angular strain ε_{α} . This allows calculating the average mechanical contribution to the potential $\mu_{\alpha}^{\text{SF, mech}}$ of the polymer and, subsequently, solving the chemical equilibrium as follows:

$$\mu_0^{\text{CU}} + k\Theta \ln \phi^{\text{CU}} = \mu_{\alpha}^{\text{SF}} + k\Theta \ln \phi_{\alpha}^{\text{SF}} + \mu_{\alpha}^{\text{SF, mech}} \quad (9)$$

Using the conservation of mass of the polymers and monomers $\phi_{\alpha}^{\text{CU}} + \phi_{\alpha}^{\text{SF}} = \phi$, Eq. (9) for the angular volume fraction of the polymers can be solved as follows:

$$\phi_{\alpha}^{\text{SF}} = \left(\phi - \phi_{\alpha}^{\text{SF}} \right) \exp \left(- \frac{\mu_0^{\text{SF}} - \mu_0^{\text{CU}} + \mu_{\alpha}^{\text{SF, mech}}(\varepsilon_{\alpha})}{k\Theta} \right) \quad (10)$$

$$\phi^{\text{CU}} = \phi - \frac{1}{\pi} \int_0^{\pi} \phi_{\alpha}^{\text{SF}} d\alpha \quad (11)$$

This system of equations is then to be solved using a nonlinear equation solver on the discretized region $[0, \pi]$.

Model Prediction of SF Distribution

The model's predictions were analyzed for the following three different stimuli: change in the substrate's stiffness, constant stretch, and cyclic stretch. The various parameters were chosen to match commonly accepted values. For all the various cases tested, the temperature was 310 K and the SF stiffness (E_f and E_v) was 100 kPa. The contractile stress generated by a SF, $\sigma^* = 10$ kPa, was extracted from the values found in Jeon et al. (2011) and Ghibaudo et al. (2008). The actin filament considered for the SF contractile unit was of the same length as a SF sarcomere (1 μm), and of the diameter 10 nm. The difference in the reference chemical potential $\mu_0^p - \mu_0^m = 4k\Theta$ was chosen such that the contractile stress of the cell, $\sigma^c = \phi^{\text{SF}} \sigma^*$, on a very stiff substrate matched the one extracted from Ghibaudo et al. (2008); i.e., 100 Pa.

Effect of Substrate Stiffness

The first case analyzed was the stress free boundary condition ($\bar{\sigma} = 0$). The cells and substrate of thickness h_s were at equilibrium; thus, the angular strain ε_α was found by considering the projection of the mechanical equilibrium Eq. (1) in the α direction

$$\varepsilon_\alpha = \frac{-\phi_\alpha^{\text{SF}} \sigma^* h_{\text{SF}}}{E h_s / [(1+\nu)(1-2\nu)] + \phi_\alpha^{\text{SF}} E_{\text{SF}}(t) h_{\text{SF}}} \quad (12)$$

The SFs angular volume fraction ϕ_α^{SF} was calculated for a sub strate stiffness ranging from 0 to a couple of hundred times the cytoskeleton stiffness. Consistent with the observations (Yeung et al. 2005; Ghibaudo et al. 2008) the model predicted a fast generation of SFs with the substrate stiffening that converged to an asymptotic total volume fraction of 1%. Indeed, increasing the substrate stiffness will decrease the compressive strain $-\varepsilon_\alpha$, further lowering the mechanochemical potential $\mu_\alpha^{\text{SF, mech}}$ [Fig. 3(a)] and stabilizing the SFs.

Fig. 3(b) shows the contractile stress $\sigma^c = \phi^{\text{SF}} \sigma^*$ is generated by the cell. The asymptotic value (for very stiff substrates) of $\sigma^c = 100$ Pa matched what is found in the literature (Ghibaudo et al. 2008) [Fig. 3(c)]. The anisotropy in the substrate stiffness is also known to affect the orientation of the SFs: the density of the SFs is higher in the direction of maximal substrate stiffness (Saez et al. 2007). To simulate a simplified anisotropic substrate, a fibrous material of Poisson's ratio $\nu = 0$ oriented in the direction $\alpha = 0^\circ$ was considered. The anisotropy was measured by the ratio r of stiffnesses at $\alpha = 0$ and 90° . Fig. 4 shows how the model captures this phenomenon; the SF angular distribution reflects the stiffness anisotropy.

Effect of Constant Stretch

The effects of constant stretch were investigated. When subjected to constant uniaxial stretch, SFs and myofibrils (which are very similar in behavior to SFs) were generated and oriented in the direction of stretch and started disassembling when the stretch exceeded a value that was, typically, around 10–20% (Simpson et al. 1999; Lu et al. 2008). To simulate

constant stretch, a state of uniaxial strain $\bar{\varepsilon}_{11}$ was applied such that the cellular angular strain is written as

$$\varepsilon_\alpha = \bar{\varepsilon}_\alpha = \bar{\varepsilon}_{11} [(1+\nu)\cos^2(\alpha) - \nu] \quad (13)$$

where ν = Poisson's ratio and α = angle from the direction of applied stretch. This expression was then substituted in Eq. (10) to solve for the angular volume fraction. In the case of constant stretch SF elasticity remained low; therefore, for small strains the stabilizing term $-\sigma^* \varepsilon_\alpha$ was dominant and the SFs were generated in the direction of the stretch. When the strain reached the critical value $\varepsilon_{\alpha\text{crit}} = \sigma^* / E_b \mu_\alpha^{\text{SF, mech}}$ was minimized, the disassembling term $1/2 E_l \varepsilon_\alpha^2$ became dominant and induced a drop in the SF volume fractions in the direction of the stretch (Fig. 5).

The model prediction presented in [Fig. 6(a)] shows how SFs are initially generated in the direction of stretch then disassemble when the strain reaches its critical value, which is consistent with the experimental observations [Fig. 6(b)].

Effect of Cyclic Stretch

Finally, the effects of dynamic stretching were investigated. The angular strain in the cell may now be written as $\varepsilon_\alpha = \bar{\varepsilon}_\alpha + \tilde{\varepsilon}_\alpha \cos(2\pi t/T)$ with

$$\tilde{\varepsilon}_\alpha = \tilde{\varepsilon}_{11} [(1+\nu)\cos^2(\alpha) - \nu] \quad (14)$$

and the stretching period T is chosen such that $T/\tau = 1$. When stretched cyclically, SFs have been experimentally observed to align perpendicularly ($\alpha = 90^\circ$) to the direction of stretch for $\nu = 0$ and in the $\alpha = 60^\circ$ direction for $\nu = 0.5$ (Kaunas et al. 2005; Takemasa et al. 1997). In the cyclic case, $E(t)$ is much larger than in the constant stretch case because of the SF stiffness time dependency (see Fig. 7). As a result, the disassembling term $1/2 [E_1 + E_2 \exp(-T/\tau)] \varepsilon_\alpha^2$ in the mechanochemical potential becomes dominant in the direction of stretch and null where $\varepsilon_\alpha = 0$; i.e., in the principal direction (which depends on the Poisson's ratio ν). Therefore, the SFs can only be generated at around 90° from the direction of stretch for $\nu = 0$, then they are generated at lower angles as the Poisson's ratio ν increases, until it reaches a 60° angle for $\nu = 0.5$. The predicted SF distributions in the case of cyclic stretching for Poisson's ratios of 0 and 0.5 [Fig. 8(a)] show great consistency with the experimental images of Kaunas et al. (2005) and Takemasa et al. (1997) [Figs. 8(b and c)]. These results demonstrate how the time dependency of the stiffnesses of the SFs and the Poisson's ratio of the substrate lead to radically different SF organizations for constant or cyclic stretching.

Conclusion

In this paper, a simple mathematical model that describes the formation and distribution of SFs when subjected to various external stimuli as a thermodynamic phenomenon, which

includes the SF mechanical contribution to the chemical potential, was developed. This approach reveals the importance of a viscoelastic description of SFs to accurately describe their rate-dependent behavior under constant or cyclic stretching as well as the effect of the Poisson's ratio of the substrate on the orientations of the SFs. It also shows that, while choosing commonly accepted physiological parameters, the results based on the hypotheses by which SFs are stabilized by contractile stress and disassembled by their elastic energy are proven consistent with numerous experimental observations.

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Fig. 1.

(a) System modeled: cells with maximum confluence on a substrate subjected to various stimuli; (b) stimuli induce a production of SF in the cell; and (c) SF exhibit contractile capability (σ^*), linear elasticity (E_l), and stress relaxation (E_v) at long time scales

Fig. 2.

(a) General view of the system; (b) corresponding to the slice at angle α defined in (a) (σ^s is the stress generated by the deformation of the substrate and σ^{sf} is the active and passive stress of SFs)

Fig. 3.

- (a) Effect of substrate stiffness on the mechanochemical potential $\mu_{\alpha}^{SF, mech}$ (shaded area);
 (b) contractile stress generated by the cell as a function of the substrate's stiffness; and (c)
 experimental results from Ghibaudo et al. (2008)

Fig. 4.

Polar plot of the angular volume fraction $\phi_{\alpha}^{\text{SF}}$ showing the effect of the anisotropic substrate on the orientation of SFs; ratio r of the stiffnesses in the directions $\alpha = 0$ and 90° represents the substrate anisotropy

Fig. 5.

General trend for $\mu_{\alpha}^{\text{SF, mech}}$ as a function of strain for constant stretch (shaded area)

Fig. 6.

(a) Effect of constant stretch on the total volume fraction of SF ϕ^{sf} ; (b) reproduction of the experimental results (Simpson et al. 1999) with the arrows representing the stretch direction

Fig. 7.

General trend of the mechanochemical potential $\mu_{\alpha}^{SF, mech}$ in the case of cyclic stretching

Fig. 8.

(a) Effect of cyclic stretching for ν ranging from 0; (b) reproduction of experimental result from Kaunas et al. (2005) to 0.5; (c) reproduction of experimental result from Takemasa et al. (1997)