

Supplementary Information

Early-time dynamics of acto-myosin polarization in cells of confined shape in elastic matrices

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I. GENERIC PROPERTIES OF THE DEFORMATION OF ELASTIC INCLUSIONS

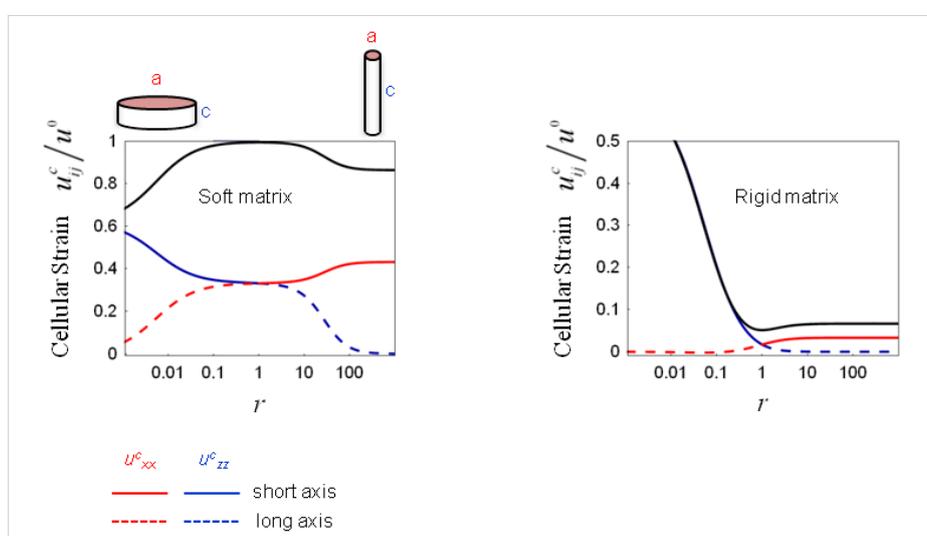


FIG. 1: The elastic deformation of the two principle axes of passive spheroidal inclusion in an infinitely extended homogeneous and isotropic 3D matrix. Left and right panels shows the behavior in soft and rigid matrices respectively. For the left panel we have $\mu_m/\mu_c = 0.01$, for the right panel $\mu_m/\mu_c = 30$. The cell and matrix Poisson's ratios are $\nu_c = \nu_m = 0.3$.

We examine here several generic properties of the deformation of elastic inclusions in solids in order to explain the origin of the behavior seen in Fig. 2. We consider the constrained deformation, u_{ij}^c , of a (passive) spheroidal inclusion comprising a uniform and isotropic eigen-strain [1], $u_{ij}^0 = \frac{1}{3}u^0\delta_{ij}$, embedded in an infinitely extended matrix. u_{ij}^0 is the strain the inclusion would spontaneously undergo in free space if released from the matrix. In the cellular system, u_{ij}^0 originates from the distribution of actomyosin dipoles in the cytoskeleton according to $p_{ij}^0 = \mathbf{C}_c u_{ij}^0$, where we associate p_{ij}^0 to the early-time stresses that the cell exerts into the matrix. According to Eshelby's theory, the strain in the inclusion is uniform and given by: $u_{ij}^c = \mathbf{A} \mathbf{S} \mathbf{C}_m^{-1} \mathbf{C}_c u_{ij}^0$ (cf. Eq. 1); the stress in the inclusion (cell) is given by, $\sigma_{ij} = \mathbf{C}_c (u_{ij}^c - u_{ij}^0)$ [1, 2]. Hence the larger the extent of the deformation, i.e., the ratio, u_{ij}^c/u_{ij}^0 , the smaller the stress resulting in the inclusion (cell). In our theory, the excess stress $\mathbf{C}_c (u_{ij}^c - u_{ij}^0)$ is the driving force for acto-myosin polarization (Eqs. 2, 4), hence understanding how a passive spheroidal inclusion deforms allows us to explain the behaviors predicted in Fig. 2.

The qualitatively different behaviors seen in Fig. 2 for cells in soft and rigid environments can be understood in terms of the deformations of the *short* and *long* axes of the spheroid. For oblate spheroids, the relative change in the long cell

axis is given by, $\delta a/a = u_{xx}^c = u_{yy}^c$, while the strain of the short axis is given by, $\delta c/c = u_{zz}^c$; for prolate spheroids the opposite is true. Fig. S1 plots the normalized strain components, u_{xx}^c/u^0 (in red), u_{zz}^c/u^0 (in blue) and the trace, u^c/u^0 (in black), as a function of the cell aspect ratio. The short axis of the spheroid is designated by solid lines, and the long axis by dashed lines. Few important conclusions can be drawn from this figure. (i) The matrix better resists deformations along the long axis of the cell. Indeed, the *long axis* of the spheroid is seen to *deform less* than the short axis (dashed lines are below the solid lines). (ii) The difference between the deformations of the short and long axes *increases* with the shape anisotropy of the spheroid – the more flattened or elongated the spheroid is, the smaller the deformation of the long axis (i.e., the dashed lines show a maximum for $r = 1$). Thus the long axis of the cell behaves effectively, as a more rigid direction, where internally generated stresses are better resisted along that direction. These conclusions explain the tendency of stress fibers to polarize parallel to the long axis of cells [3–5]. Along that direction there is higher resistance to the development of forces in the cell.

(iii) In a *soft matrix* the shape anisotropy of the spheroid adds to its overall mechanical stability. Indeed we see that the trace of the deformation tensor, u^c ($= \delta V/V =$ relative volume change), decreases with the shape anisotropy of the cell and is maximal for $r = 1$. That is, round inclusions undergo a larger deformation overall (i.e., larger volume change) compared to less symmetric structures. Thus, the apparently higher (effective) rigidity along the long axis is not only reflected in the anisotropy of the strains and stresses of the inclusion (i.e., the differences $u_{zz}^c - u_{xx}^c$ and $\sigma_{zz}^c - \sigma_{xx}^c$), but is also expressed in the *trace* of the strain and stress tensors. This is why in a soft environment, shape anisotropy is predicted to facilitate the generation of larger cellular forces, and why round cells are expected to exert least force, see green/blue curves in panel b. of Fig. 2. In contrast, (iv) as the matrix rigidity increases it may become rigid enough to suppress any deformation of the long axis, hence dashed lines in the right panel are close to zero. The major contribution to the non-monotonic behavior of the trace, u^c , is therefore the deformations of the *short axes*. We see that the *short axis* of an oblate spheroid (c) deforms more than those of a prolate spheroid (a), and both geometries are less stable (deform more) than a sphere. We thus find that a sphere is the most stable structure in a rigid matrix. This explains why cells embedded in a rigid matrix are predicted to exert largest forces if they are spherical. (v) The contrasting variations of the strain, along the long and short axes of the cell, with the cell aspect ratio, become equally important when the cell and matrix have similar rigidities. This explains why in the homogeneous system, the trace, u^c , (or the volume change of the inclusion) is *shape-independent*, as first noted by Eshelby [2]. It is also the reason why the trace of the dipole-tensor, p^{ss} , is shape-independent when the cell and matrix have comparable magnitude.

We note that our calculations for the passive inclusion, shown in Fig. S1 directly translate to predications for an *active* cellular inclusion, that possesses polarizable force-dipoles in its interior. This is because the elastic behavior of an active inclusion is determined, as we have shown, by the effective moduli, $\tilde{\mathbf{C}}_c = (\mathbf{I} + \boldsymbol{\chi})\mathbf{C}_c$, that incorporates cell activity via the susceptibility tensor, $\boldsymbol{\chi}$. Thus, our conclusions above about the relative stiffness of the matrix and cell pertain to the effective stiffness, $\tilde{\mu}_c = (1 + \chi_s)\mu_c$, rather than to μ_c . Hence the matrix rigidity, μ_m , should be regarded relative to, $\tilde{\mu}_c$, to validate these predictions.

II. QUANTITATIVE ANALYSIS OF THE POLARIZATION RESPONSE IN FEW SIMPLIFIED SITUATIONS

We examine here how the predicted behaviors seen in Fig. 3 follow from our equations. To this end we consider a simplified but still relevant situation where \mathbf{Z} is an isotropic tensor; this allows us to express the dynamics of the

polarization response as a simple sum of two exponents. Eq. 6 exhibits the polarization process as a generalized relaxation process $P_{ij}(t) = [\mathbf{I} - \mathbf{Exp}(-\tilde{\boldsymbol{\tau}}^{-1}t)] P_{ij}^{ss}$, where the characteristic time tensor is given by $\tilde{\boldsymbol{\tau}} = \mathbf{Z}\boldsymbol{\tau}$. In the special cases where \mathbf{Z} is an isotropic tensor, also $\tilde{\boldsymbol{\tau}}$ is an isotropic tensor, and similarly to $\boldsymbol{\tau}$ can be written in the form: $\tilde{\tau}_{ijkl} = \tilde{\tau}_v \cdot I_{ijkl}^v + \tilde{\tau}_s \cdot I_{ijkl}^s$, where $I_{ijkl}^v = \frac{1}{3} \delta_{ij} \delta_{kl}$ and $I_{ijkl}^s = I_{ijkl} - \frac{1}{3} \delta_{ij} \delta_{kl}$ are two orthonormal tensors [6]. Relevant cases where this applies are the case where the cell is a sphere, or when the matrix is infinitely soft or infinitely rigid; for these last two cases one finds, respectively, $\mathbf{Z} = [\mathbf{I} + \boldsymbol{\chi}]^{-1}$ and $\mathbf{Z} = \mathbf{I}$. When \mathbf{Z} is isotropic, P_{ij} can be broken into a sum of two exponents: $P_{ij} = (1 - e^{-t/\tilde{\tau}_v}) \mathbf{I}^v P_{ij}^{ss} + (1 - e^{-t/\tilde{\tau}_s}) \mathbf{I}^s P_{ij}^{ss}$; where the first term describes the time-variations of the trace of the polarization tensor, and the second term describes the development of the deviatoric part of the polarization tensor. The characteristic times, $\tilde{\tau}_v$ and $\tilde{\tau}_s$ are generally functions of the cell shape, elastic moduli, and the two susceptibility parameters. To obtain this simplified expression for $P_{ij}(t)$, one substitutes $(\mathbf{Z}\boldsymbol{\tau})^{-1}$ in the generalized tensorial exponent above, using $\mathbf{Exp}[\mathbf{Q}] = \sum_{n=0}^{\infty} \frac{1}{n!} \mathbf{Q}^n$, and then exploits the multiplication properties of the two orthogonal tensors, \mathbf{I}^v , and \mathbf{I}^s , namely: $(\mathbf{I}^v)^n = \mathbf{I}^v$, $(\mathbf{I}^s)^n = \mathbf{I}^s$, $\mathbf{I}^v \mathbf{I}^s = \mathbf{I}^s \mathbf{I}^v = 0$.

Next, to simplify our expression for $P_{ij}(t)$ even more, we note that for small values of $\boldsymbol{\chi}$, $\mathbf{Z} \rightarrow \mathbf{I}$, as can be verified from Eq.9. We thus expand $P_{ij}(t)$ to first order in powers of χ_v and χ_s , as well as in powers of the cell aspect ratio around the case of a sphere, $r = 1$, and we find :

$$\frac{P_{ij}(t)}{p^0} = \chi_v (1 - e^{-t/\tau_v}) g_{ij}^v + \chi_s (1 - e^{-t/\tau_s}) g_{ij}^s (r - 1)$$

with

$$(1)$$

$$g_{ij}^v = g_v \delta_{ij}$$

$$g_{ij}^s = g_v g_s (\delta_{ij} - 3\delta_{iz}\delta_{jz}) \quad \text{and} \quad Tr[g_{ij}^s] = 0$$

where g_v and g_s are functions of the elastic moduli and susceptibility parameters :

$$g_v = \frac{3E_m}{\alpha_1 E_c + E_m} \delta_{ij} \quad \text{and} \quad g_s = \frac{E_c}{\alpha_2 E_c + \alpha_3 E_m} \quad (2)$$

with $\alpha_1 = \frac{1+v_m}{2(1-2v_c)}$, $\alpha_2 = \frac{10v_m-8}{3(1-v_m)}$ and $\alpha_3 = \frac{(5v_m-7)(1+v_c)}{3(1-v_m^2)}$. These equations reflect many of the qualitative features described above of the polarization response.

(i) Because the trace of the second term in Eq. 1 is zero, the dipole magnitude, p , has no first order in r . Hence p shows an extremum at $r = 1$, irrespective of the matrix rigidity, this is nicely seen for the steady-state in panels b and d of Fig. 2 ; it also expresses the expected result that for spherical cells ($r = 1$) the polarization is isotropic hence the order parameter is zero, as seen in panels a and c of Fig. 2. These generic properties are independent of the underlying polarization mechanism.

(ii) For the *isotropic polarization* case, $\chi_s = 0$, thus only the first term in Eq. 1 governs the behavior; g_{ij}^v is an isotropic tensor hence $P_{xx}(t) = P_{zz}(t) \sim [1 - \exp(-t/\tau_v)]$. The trace, $P(t)$, follows similar dynamics, and the order parameter, $\mathbb{S}(t) = 0$. Note that no shape effect can be observed in this case, since the r -containing term in Eq. 1 is zero.

(iii) For the *orientational polarization* case, $\chi_v = 0$, and only the second term in Eq. 1 governs the behavior. This term is shape-dependent, and vanishes for $r = 1$. As can be verified from our expression for g_{ij}^s (Eq. 1), one has: $P_{zz}(t) = -2P_{xx}(t) \sim [1 - \exp(-t/\tau_s)]$; this corresponds to a net rotation of the force-dipoles from the $x - y$ plane to the z direction, or vice versa, as shown in panel II.a. Another way to see this is that the trace, $Tr[P_{ij}(t)] = P(t) = 0$, i.e., no change in the magnitude of the dipole is expected for an orientational response (panel II.b).

(iv) For an *axial-polarization*, one has $\chi_s = \chi_v$, and both terms of Eq. 1 contribute to the dynamics. For $\tau_v < \tau_s$, the first term dominates at early times, hence, an initial isotropic response is expected, with a characteristic time approximately, τ_v . This corresponds to an initial strengthening of the interaction between myosin and actin in response to the stresses that develop in the cell. At longer times, the response in one direction (z —for a prolate spheroids, $x - y$ —plane for oblate spheroids) takes over, and the cell gradually polarizes with a characteristic time, $\approx \tau_s$. This can be interpreted as a late orientational response. In contrast, when $\tau_s < \tau_v$, the second term in Eq. 1 dominates at early times, hence an initial orientation of the dipoles (from the z -direction to the $x - y$ plane, or vice versa) is expected, with a characteristic time, $\approx \tau_s$. At longer times, an isotropic response begins to dominate, hence the magnitude of the dipolar forces increases with equal rate (given approximately by τ_v) in all directions, as seen in panel III.a. These two phases in the response are nicely shown in the behavior of $p(t)$ and $S(t)$ (panels III.b and III.c). In the former case (red lines), the initial rise in $p(t)$ is dictated by τ_v . Hence τ_v may be interpreted as the characteristic time for the increase in the magnitude of the dipole tensor. In contrast, the initial rise of $S(t)$, is dictated by τ_s . Hence, τ_s , may be interpreted as the characteristic orientational-time.

This discussion for the simplified case where χ_s and χ_v are small, was helpful for interpreting the (physical) function of the four susceptibility parameters χ_s , χ_v , τ_s and τ_v in the polarization dynamics. Similar trends can be obtained for cells in infinitely rigid matrices or in perfect spheres. However, in the more general cases, $\tilde{\tau}_s$ and $\tilde{\tau}_v$ are shape and matrix rigidity dependent, as demonstrated and discussed in section 3.3.

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[6] When these tensors multiply a second-rank tensor, g_{ij} , they reveal its isotropic and deviatoric parts respectively, $I_{ijkl}^v g_{kl} = \frac{1}{3}g\delta_{ij}$ and $I_{ijkl}^s g_{kl} = {}'g_{ij}$, where ${}'g_{ij} + \frac{1}{3}g\delta_{ij} = g_{ij}$ and $g = Tr[g_{ij}]$.