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EN.585.743.81.SP25 Modeling Approaches to Cell and Tissue Engineering
Modeling Project
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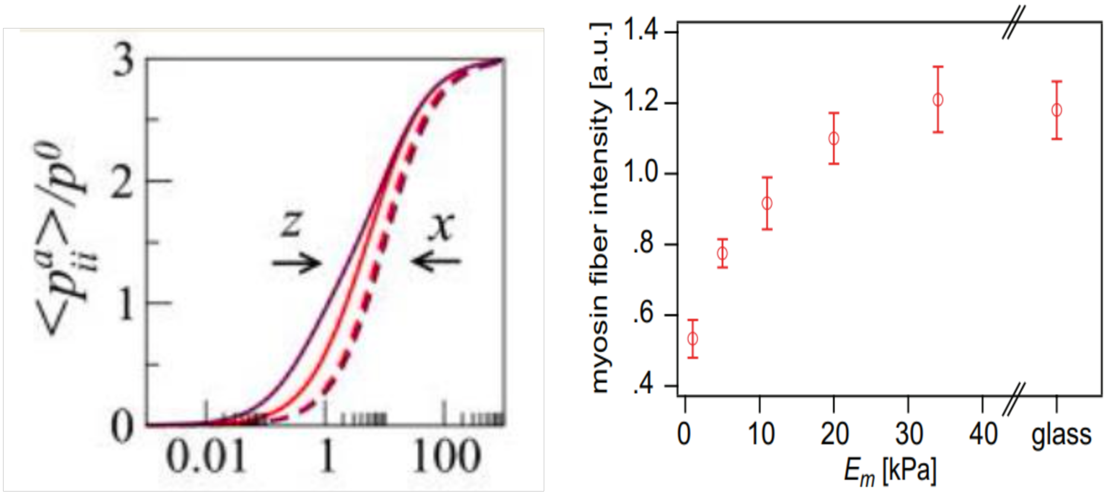
Introduction

In Lecture 12, the polarization of the stem cell cytoskeleton as a function of the stiffness of ECM is considered. A number of characteristics of cell/ECM interaction, such as the modeling-predicted order parameter [1] (Figure 1(a)) or experiment-estimated myosin fiber intensity [1] (Figure 1(b)) demonstrate an increase–saturation pattern as functions of ECM stiffness. Use the 1-D model where the cell and ECM are presented by the active and elastic springs, respectively [1] (Figure 2) and show that the active force generated by the cell, f_a, as a function of the ECM stiffness, has the same increase saturation pattern of behavior.



(a) Normalized order parameter vs. $\frac{E_m}{E_c}$.

(b) Myosin fibre intensity vs. E_m.

Figure 1: (a) Order–parameter saturation. (b) Actomyosin-intensity saturation.

Derivation

We want to show, using the 1D two-spring model of cell and matrix (Figure 2), that the cell's active force f_a satisfies the equation:

$$\frac{f^a}{f^0} = \alpha \, \frac{k_m}{\tilde{k}_c + k_m}$$

At equilibrium:

$$k_c(l_c - l_c^R) = k_m(l_m - l_m^R) \tag{1}$$
$$l_c + l_m = l_c^0 + l_m^R \tag{2}$$

From (2),

$$l_m = (l_c^0 + l_m^R) - l_c \tag{3}$$

Substitute (3) into the force-balance (1):

$$\begin{aligned} k_c(l_c - l_c^R) &= k_m\big(l_m - l_m^R\big) \\ &= k_m\big((l_c^0 + l_m^R) - l_c - l_m^R\big) \\ &= k_m(l_c^0 - l_c)\,. \end{aligned}$$

Rearrange to solve for l_c:

$$\begin{aligned} k_c\, l_c - k_c\, l_c^R &= k_m\, l_c^0 - k_m\, l_c \\ k_c\, l_c + k_m\, l_c &= k_m\, l_c^0 + k_c\, l_c^R \\ (k_c + k_m)\, l_c &= k_m\, l_c^0 + k_c\, l_c^R \\ l_c &= \frac{k_m\, l_c^0 + k_c\, l_c^R}{k_c + k_m} \end{aligned}$$

We have

$$l_c^R = l_c^0 + \Delta l_c^0,$$

then

$$\begin{aligned} l_c &= \frac{k_m\, l_c^0 + k_c\,(l_c^0 + \Delta l_c^0)}{k_c + k_m} \\ &= \frac{(k_m + k_c)\, l_c^0 + k_c\, \Delta l_c^0}{k_c + k_m} \\ &= l_c^0 + \frac{k_c}{k_c + k_m}\, \Delta l_c^0\,, \end{aligned}$$

so

$$\Delta l_c \;=\; l_c - l_c^0 \;=\; \frac{k_c}{k_c + k_m}\, \Delta l_c^0$$

Introducing myosin polarization of the cytoskeleton fibers within the cell, with

$$\tilde{k}_c \;=\; (1+\alpha)\, k_c \quad (\alpha > 0)$$

the cellular strain satisfies the equation

$$\frac{\Delta l_c}{l_c^0} = \frac{\tilde{k}_c}{\tilde{k}_c + k_m}\, \frac{\Delta l_c^0}{l_c^0}$$

The active force is modeled as:

$$f^a = -\,\alpha\, k_c\, (l_c - l_c^R)$$

from

$$\Delta l_c \;=\; l_c - l_c^0 \;=\; \frac{\tilde{k}_c}{\tilde{k}_c + k_m}\, \Delta l_c^0$$

Thus:

$$\begin{aligned} l_c^R - l_c &= (l_c^R - l_c^0) + (l_c^0 - l_c) \\ &= \Delta l_c^0 - \frac{\tilde{k}_c}{\tilde{k}_c + k_m} \Delta l_c^0 \\ &= \left(1 - \frac{\tilde{k}_c}{\tilde{k}_c + k_m}\right) \Delta l_c^0 \\ &= \frac{k_m}{\tilde{k}_c + k_m} \Delta l_c^0 \end{aligned}$$

Substituting back into the active force:

$$f^a = -\alpha k_c (l_c - l_c^R) = \alpha k_c \left(\frac{k_m}{\tilde{k}_c + k_m} \Delta l_c^0 \right)$$

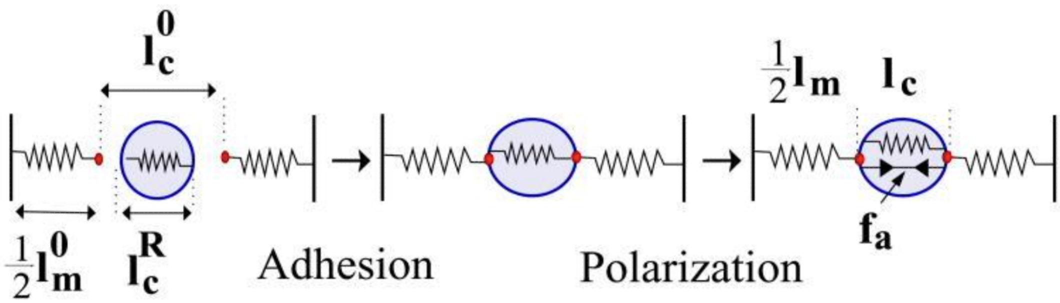
Since the baseline force f^0 is proportional to $k_c \Delta l_c^0$:

$$f^0 = k_c \Delta l_c^0$$

Thus, we have:

$$\boxed{\frac{f^a}{f^0} = \alpha\, \frac{k_m}{\tilde{k}_c + k_m}}$$

Figure 3



(Zemel et al., 2010 and Lecture 12)

Figure 2: 1D model: active cell spring (stiffness k_c) in series with ECM spring (stiffness k_m).

Interpretation

The formal form of anisotropic polarized actomyosin force is:

$$\frac{f^a}{f^0} = \alpha \, \frac{k_m}{\tilde{k}_c + k_m}$$

- α: polarizability factor
- $\tilde{k}_c = (1 + \alpha)\, k_c$: effective stiffness of the cell
- k_m: matrix rigidity
- For very soft matrices ($k_m \ll \tilde{k}_c$):

$$\frac{f^a}{f^0} = \alpha \, \frac{k_m}{\tilde{k}_c + k_m} \quad \longrightarrow \quad 0 \quad \text{as } k_m \to 0.$$

  If $k_m \ll \tilde{k}_c$, then $\tilde{k}_c + k_m \approx \tilde{k}_c$ and

$$\frac{f^a}{f^0} \approx \alpha \, \frac{k_m}{\tilde{k}_c} \approx \alpha^* \, k_m \quad \longrightarrow \quad 0 \quad \text{as } k_m \to 0.$$

- For very stiff matrices ($k_m \gg \tilde{k}_c$):

$$\frac{f^a}{f^0} = \alpha \, \frac{k_m}{\tilde{k}_c + k_m} \approx \alpha \, \frac{k_m}{k_m} \quad \longrightarrow \quad \alpha$$

Thus, the active force grows with matrix stiffness and saturates at a maximum value proportional to α.

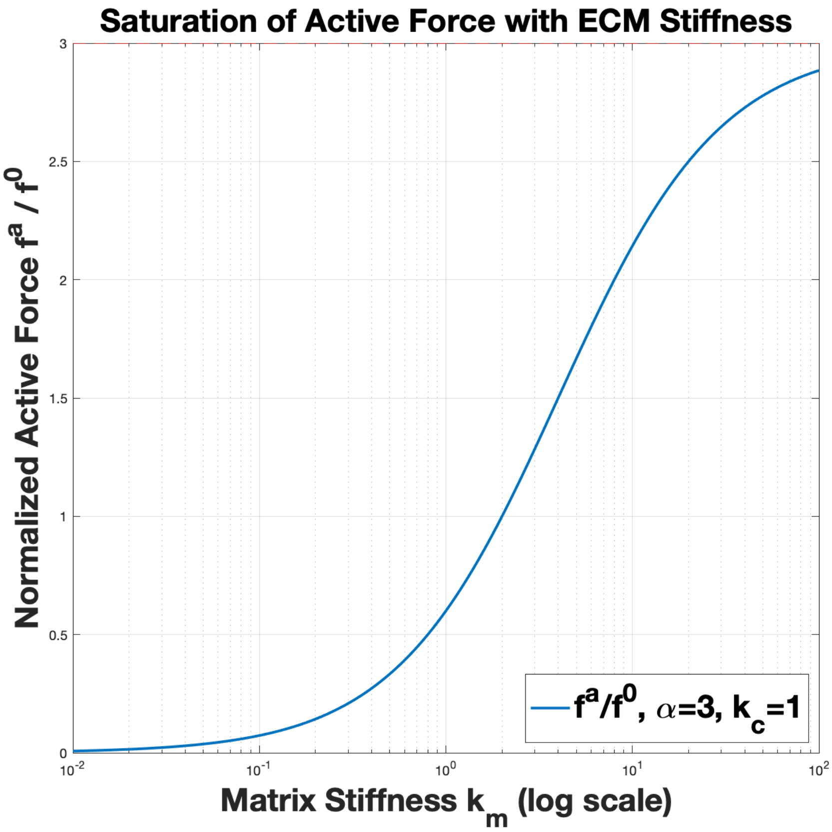


Figure 3: Active Force vs. Matrix stiffness.

References

[1] Assaf Zemel, Florian Rehfeldt, Alexander E.X. Brown, Dennis E. Discher, and Samuel A. Safran. Optimal matrix rigidity for stress-fibre polarization in stem cells. *Nature Physics*, 6(6):468–473, 2010.