POLITECNICO DI TORINO

Modelling cell re-orientation under stretch

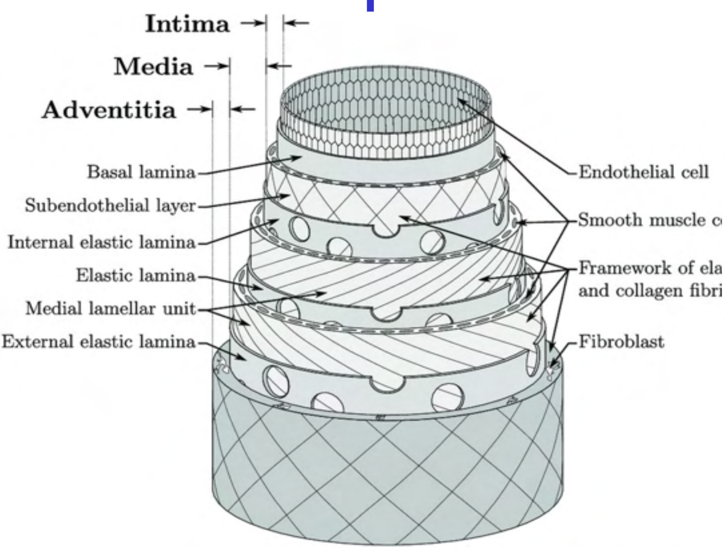
Luigi Preziosi

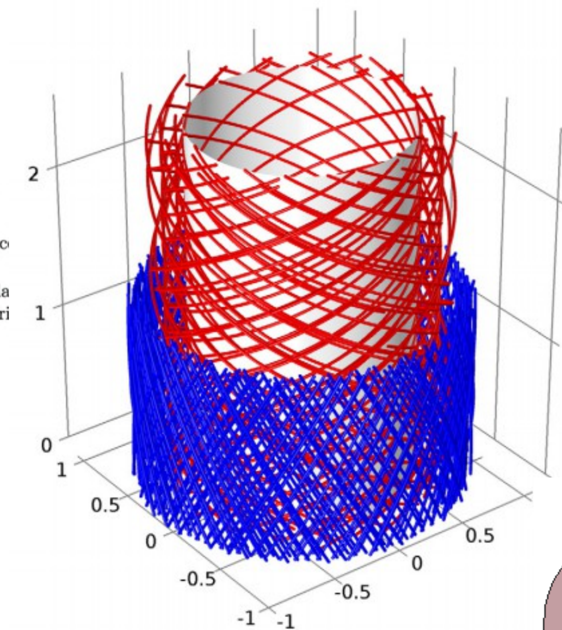
Cell re-orientation under stretch: The effect of substratum elasticity and randomness

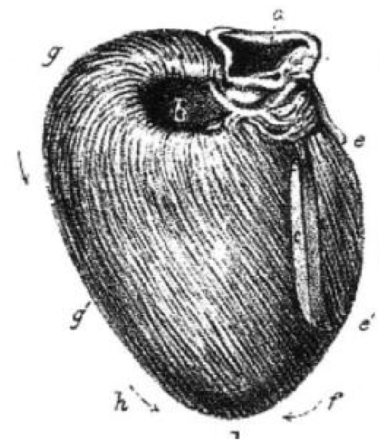
Luigi Preziosi

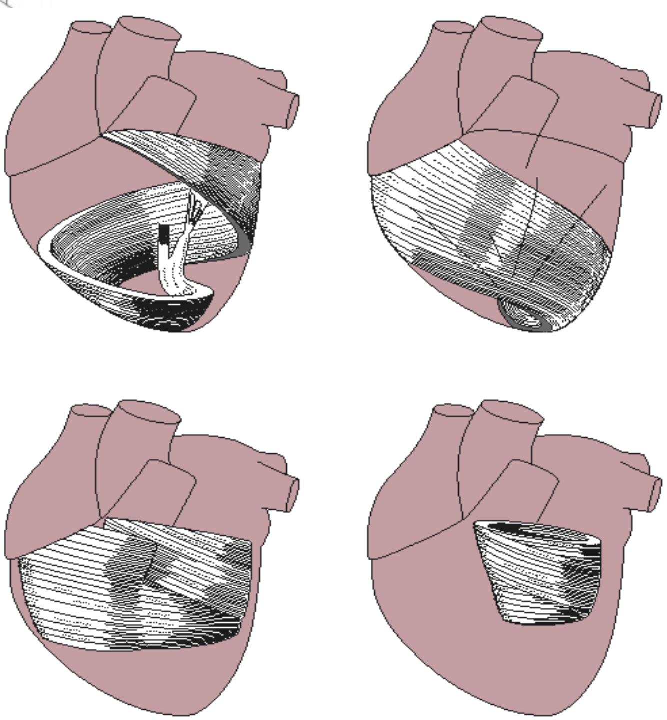
POLITECNICO DI TORINO

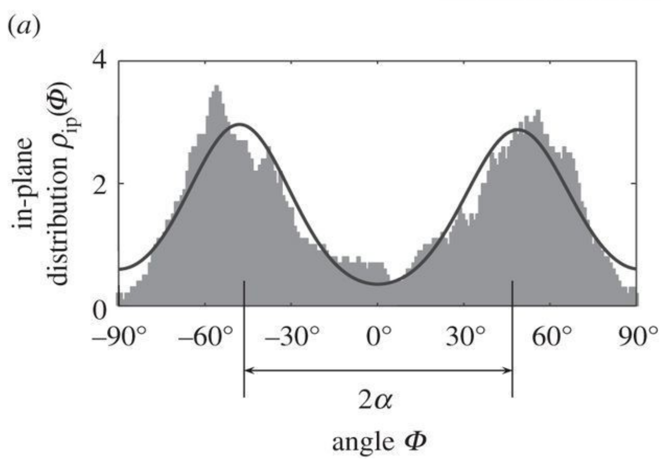
Cell orientation in tissues





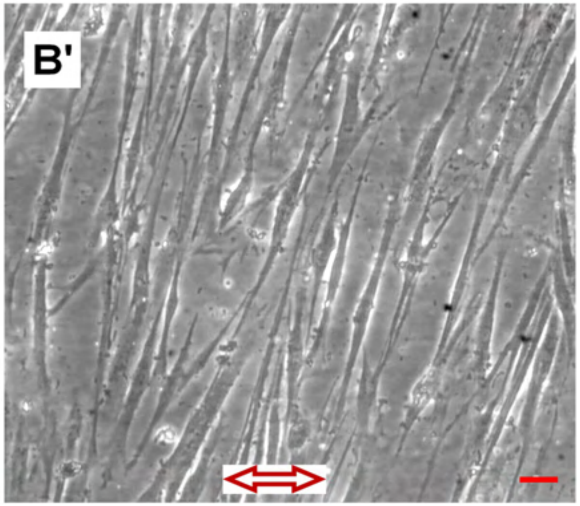




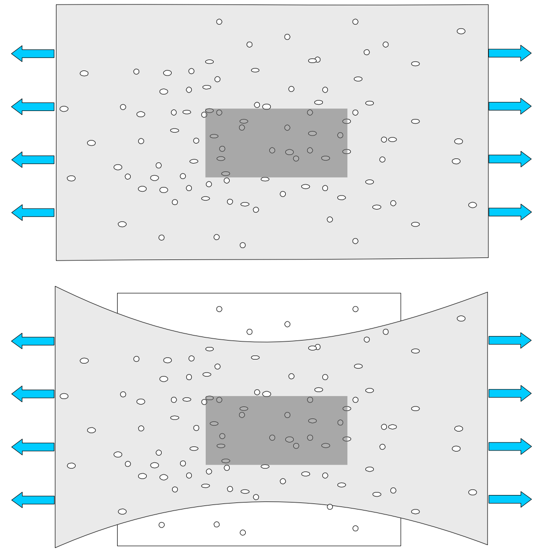


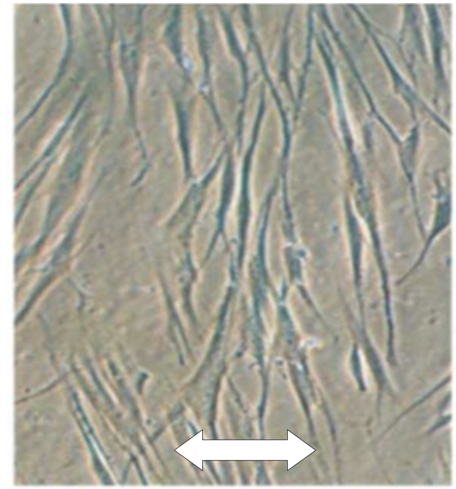
Holzapfel (2015)

Cell orientation on stretched substrates

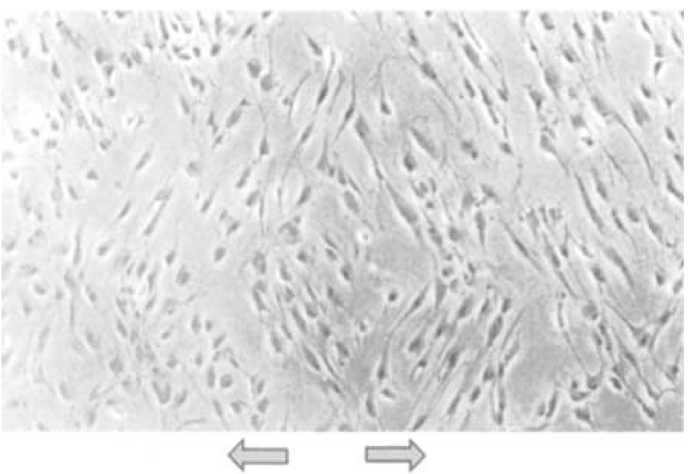


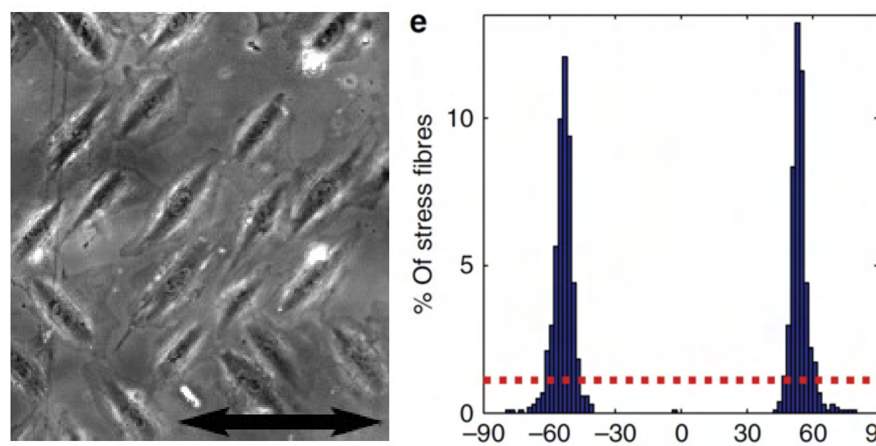
Wang (2000)





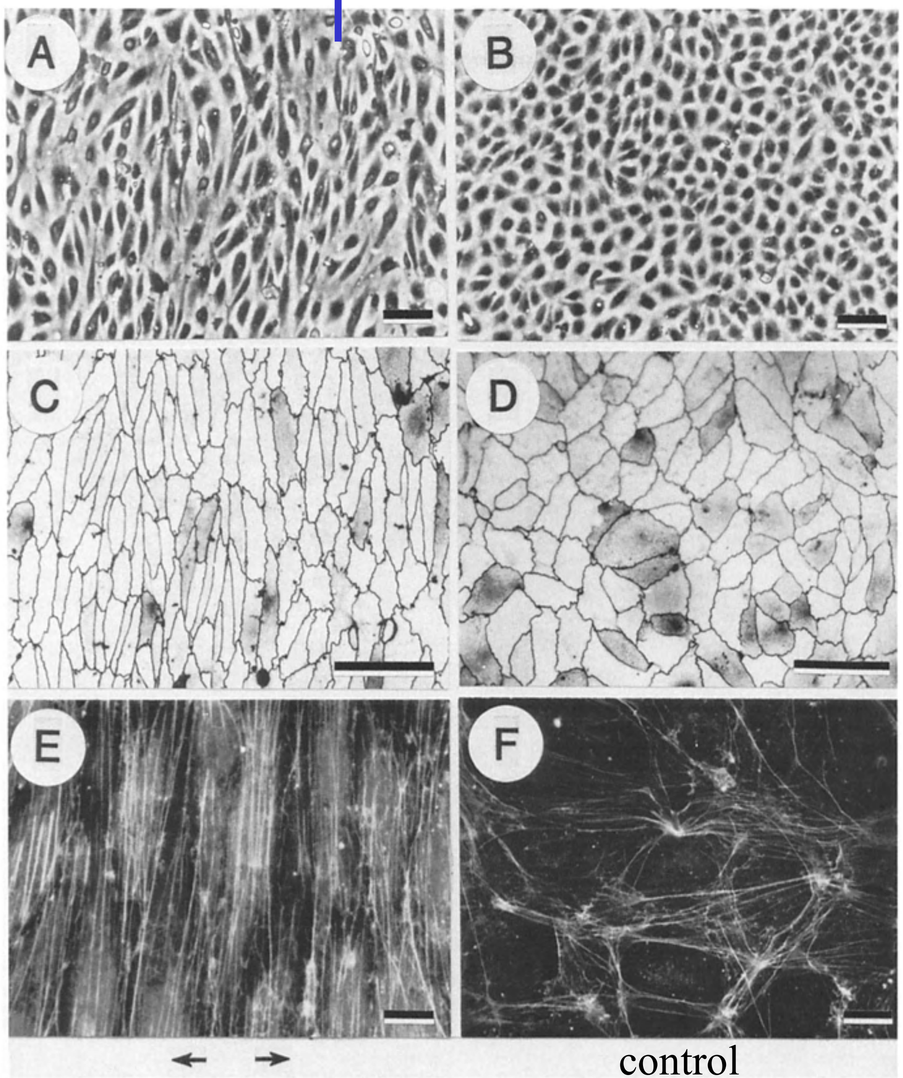
Morioka (2011)





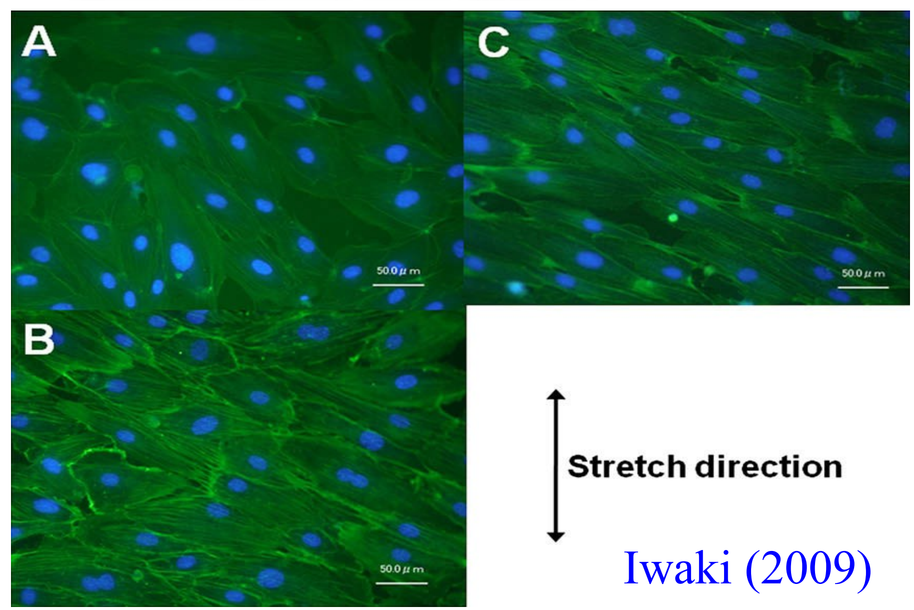
Livne (2014)

Distribution in confluent conditions



Shirinsky (1989)


Takemasa (1998)

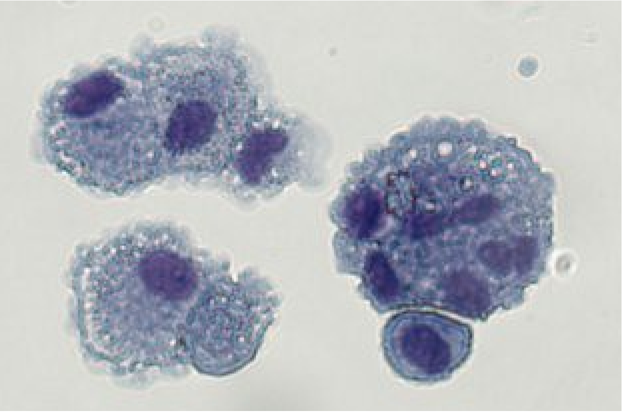


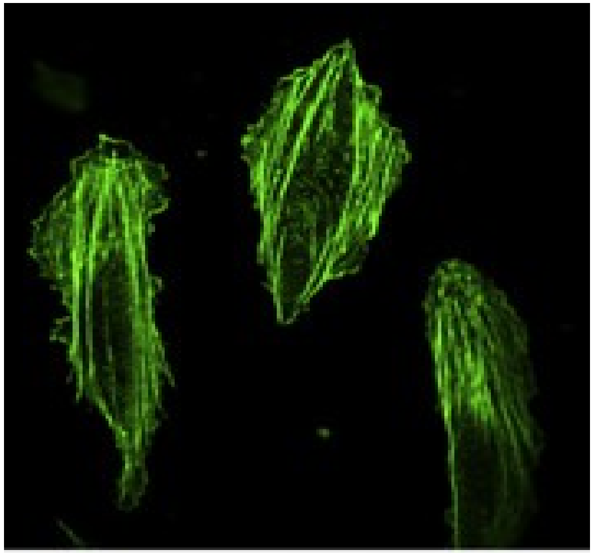
Iwaki (2009)

Cell types

- Endothelial cells
- Epithelial cells
- Fibroblasts
- Smooth muscle cells
- Myocytes
- Osteoblasts
- Melanocytes
- Mesenchymal stem cells
- Multipotent stromal cells

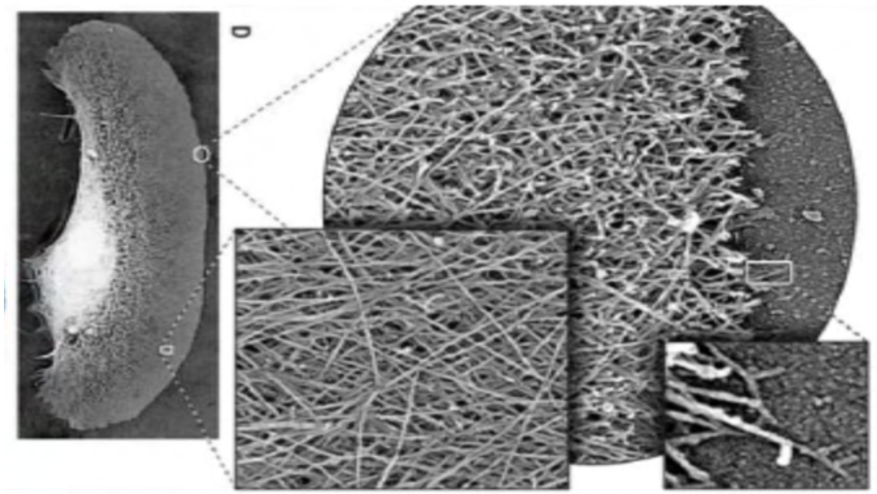
Not macrophages

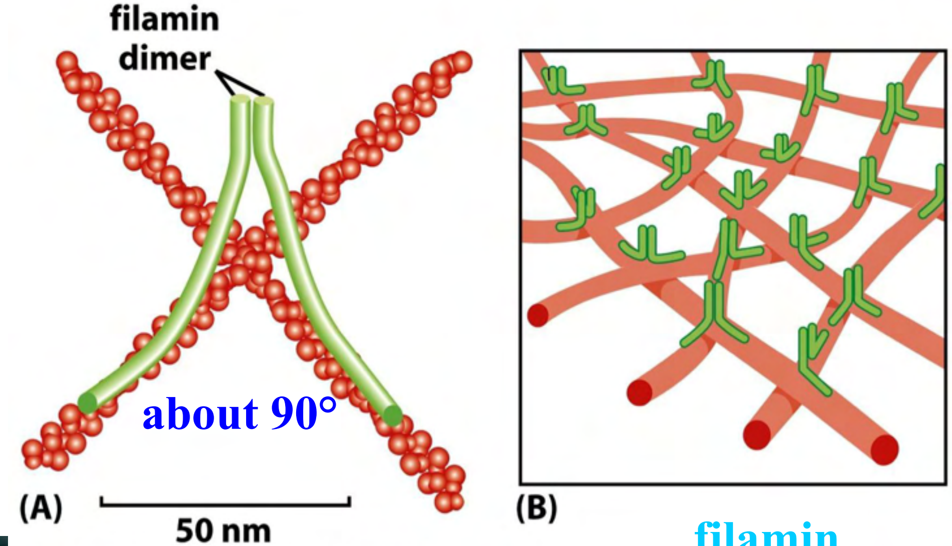




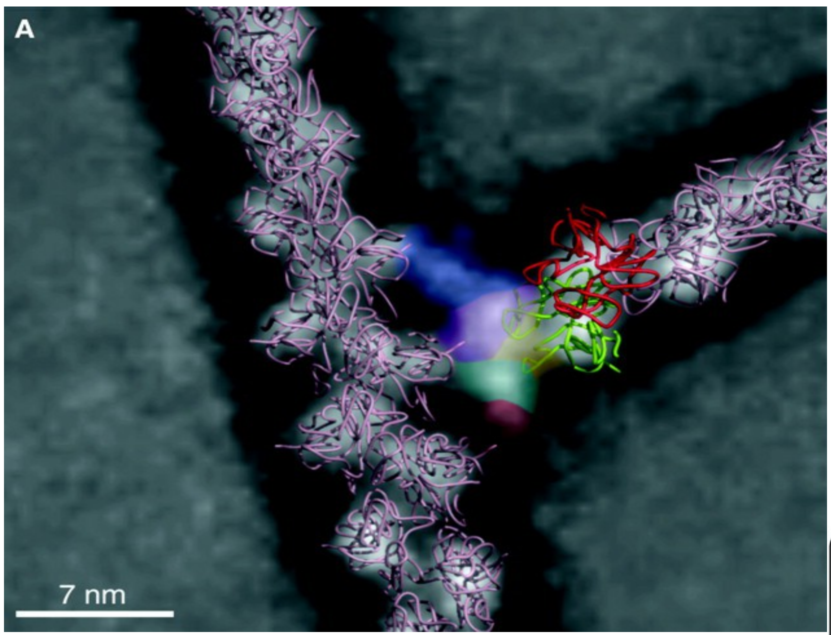
Osteosarcoma cells
Tondon et al. (2012)

Movie of an endothelial cell
from Greiner et al. (2015)

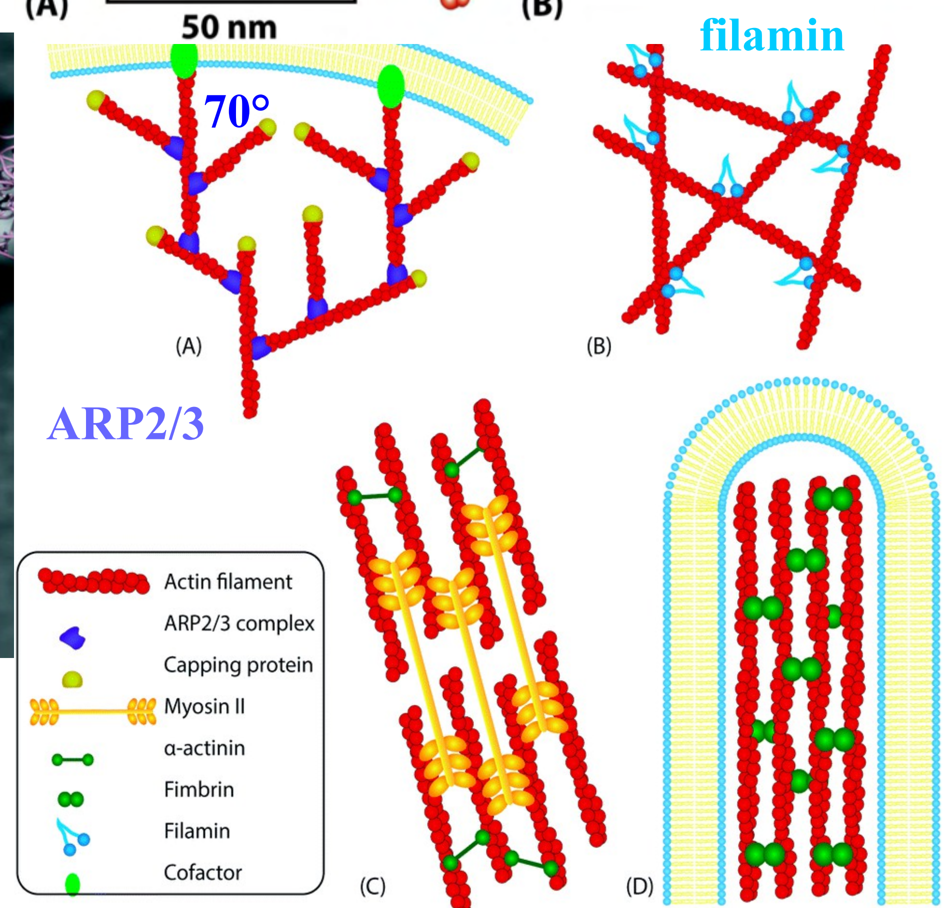




filamin
dimer
about 90°
(A)
50 nm
(B)



A
7 nm

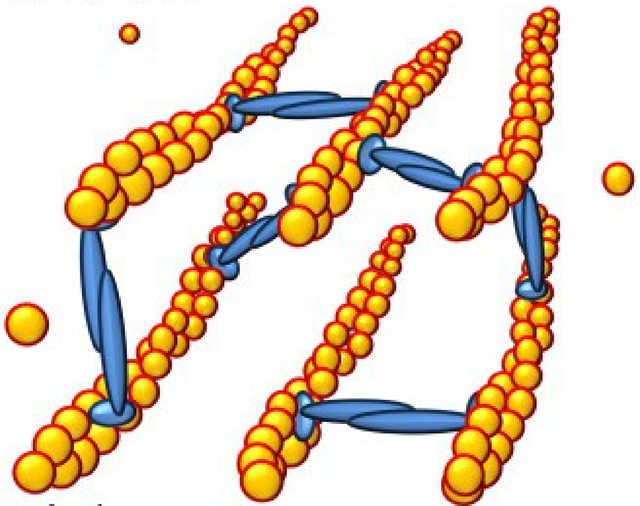


filamin
70°
(A)
(B)
ARP2/3
Actin filament
ARP2/3 complex
Capping protein
Myosin II
α-actinin
Fimbrin
Filamin
Cofactor
(C)
(D)

POLITECNICO DI TORINO

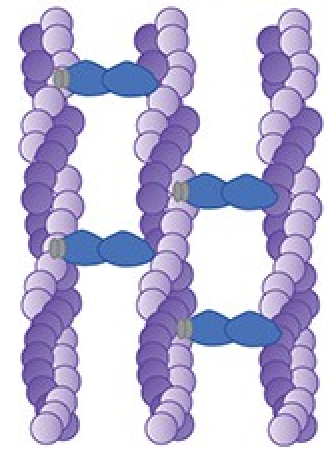
Cross-linking molecules

alpha-actinin and actin

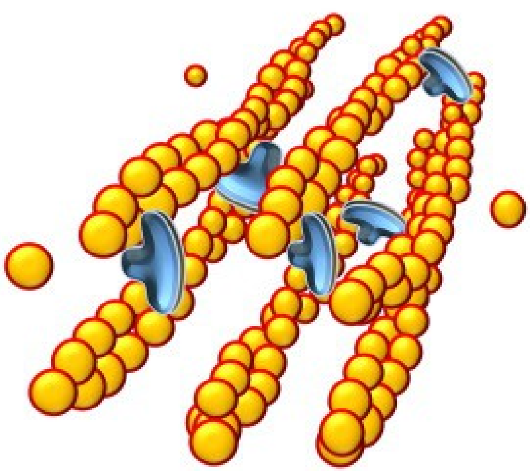


α-actinin

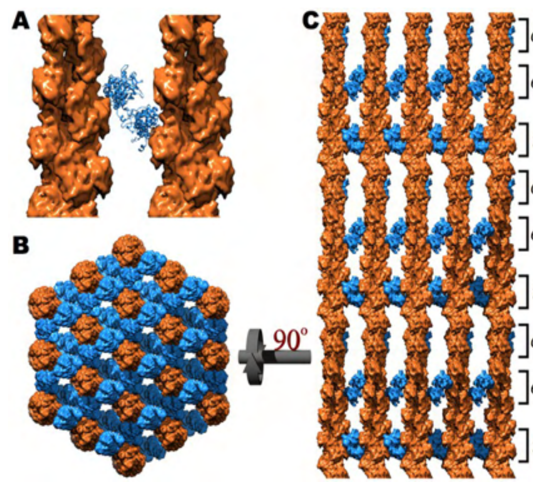
fimbrin

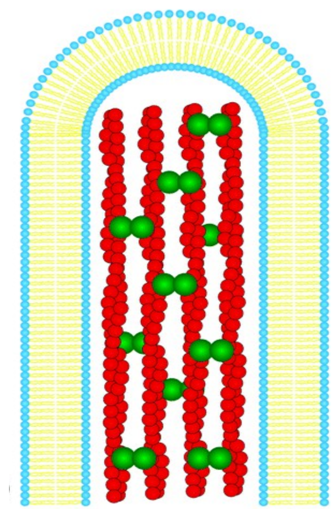


fascin and actin



fascin





Ranges of observation

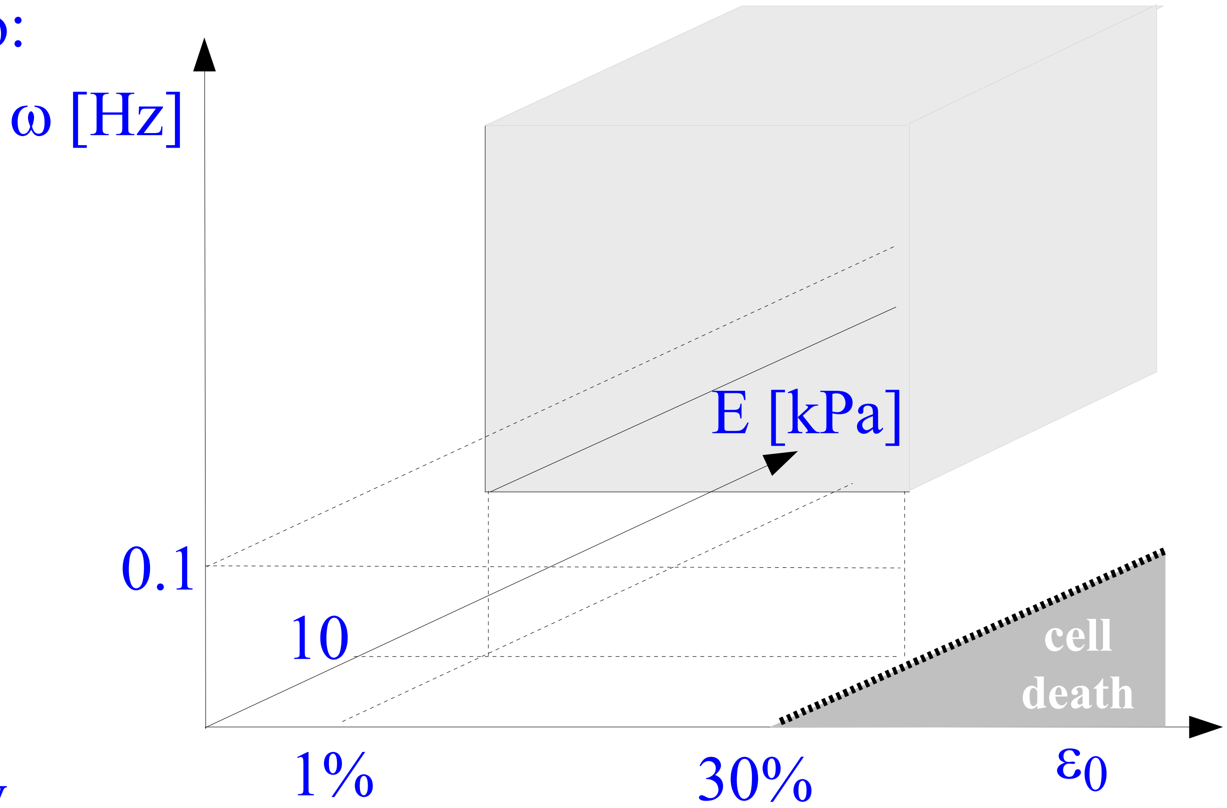
Robust with respect to:

- Cell type

- Substratum
  (stiffness > 10 kPa)

- Strain amplitude
  (> 1-2%)

- Stretching frequency
  (> 0.1 Hz)



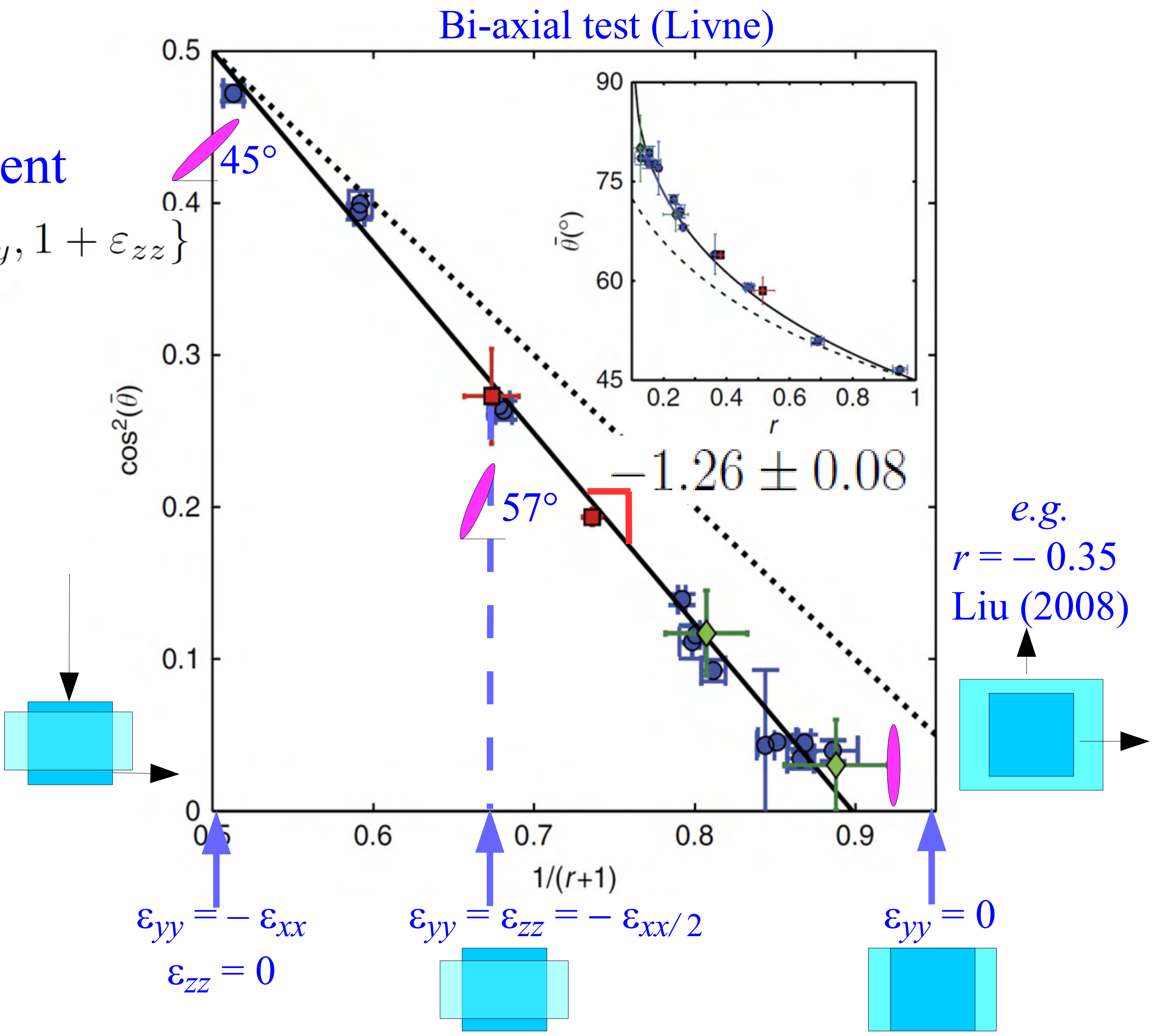
The continuum mechanics model

Deformation gradient

$$\mathbb{F} := \mathrm{diag}\{1+\varepsilon_{xx}, 1+\varepsilon_{yy}, 1+\varepsilon_{zz}\}$$

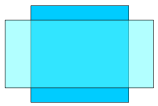
$$\varepsilon_{yy} = -r\varepsilon_{xx}$$

bi-axiality ratio



POLITECNICO DI TORINO

Elastic model



Deformation gradient

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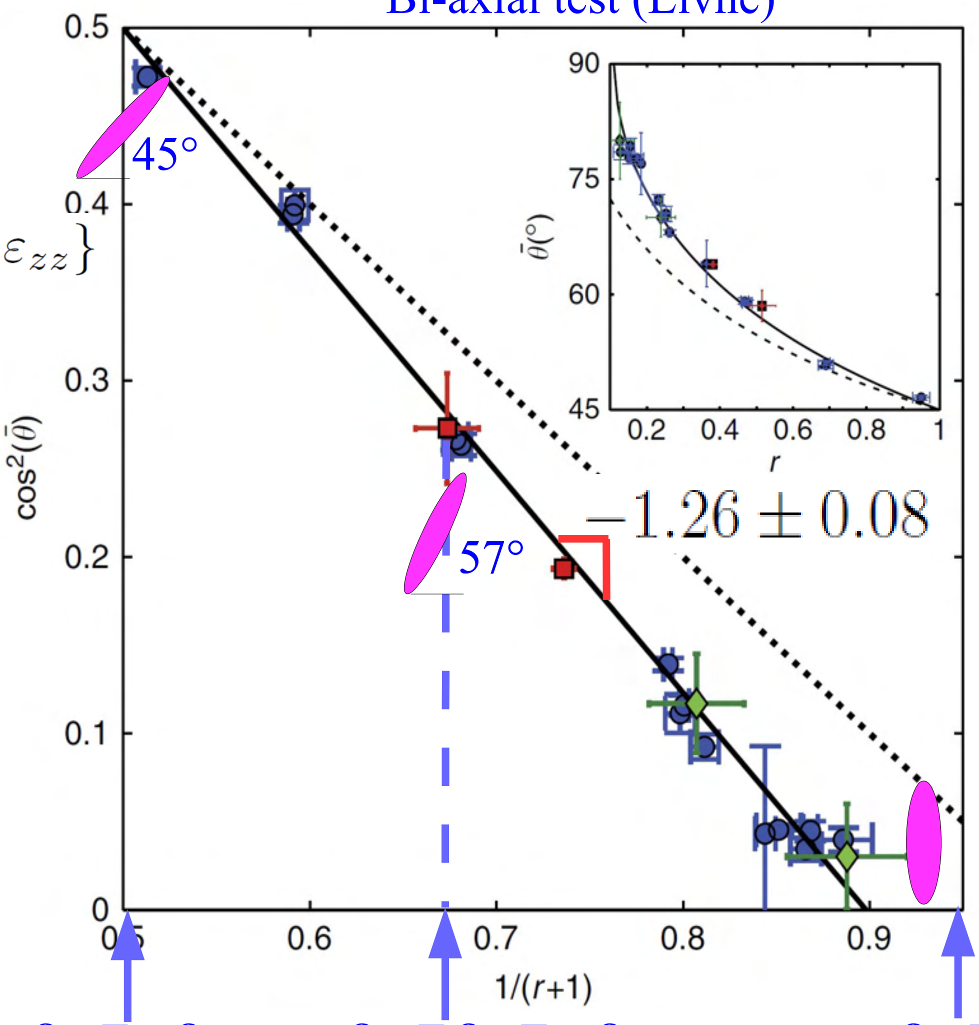
$$\varepsilon_{yy} = -r\varepsilon_{xx}$$

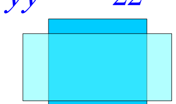
bi-axiality ratio

Bi-axial test (Livne)

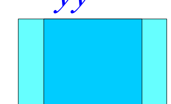


$\varepsilon_{yy} = -\varepsilon_{xx}$
$\varepsilon_{zz} = 0$

$\varepsilon_{yy} = \varepsilon_{zz} = -\varepsilon_{xx}/2$



$\varepsilon_{yy} = 0$



The continuum mechanics model

G. Lucci & L.P., Biomech. Model. Mechanobiol. (2021)

$$\hat{\mathcal{U}} = \mathcal{U}(\mathbf{I}) + \mathcal{V}$$

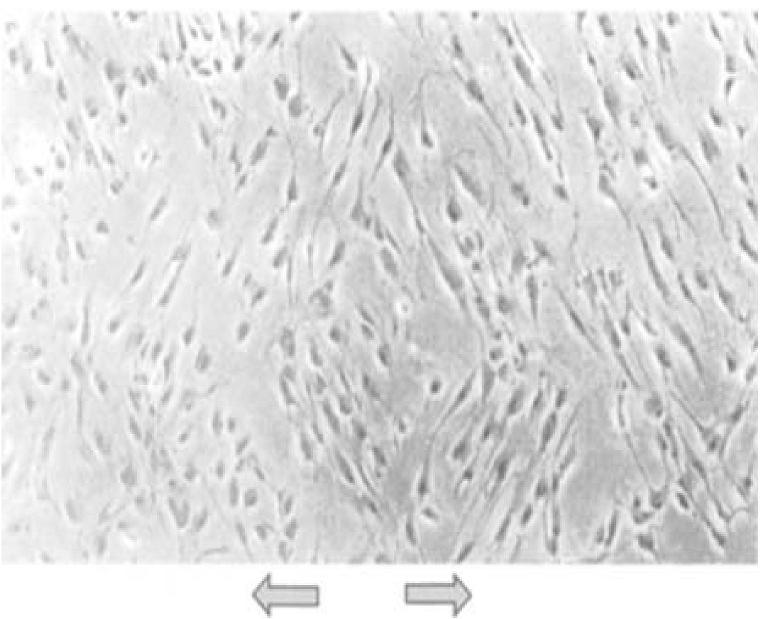
Isotropic part

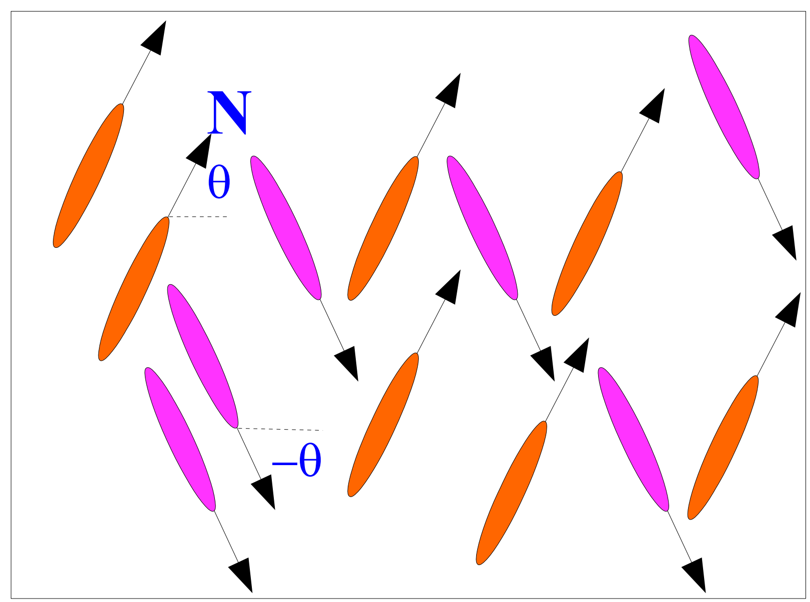
$$\mathbf{I} := \left(\hat{\mathrm{I}}_4, \hat{\mathrm{I}}_5, \hat{\mathrm{I}}_6, \hat{\mathrm{I}}_7, \mathrm{I}_8\right)$$

$$\begin{cases} \hat{\mathrm{I}}_4 = \mathbf{N}\cdot\mathbb{C}\mathbf{N} - 1 = |\mathbb{F}\mathbf{N}|^2 - 1 = (\lambda_x - \lambda_y)\cos^2\theta + \lambda_y\,, \\ \hat{\mathrm{I}}_5 = \mathbf{N}\cdot\mathbb{C}^2\mathbf{N} - 1 = |\mathbb{C}\mathbf{N}|^2 - 1 = (\lambda_x^2 - \lambda_y^2)\cos^2\theta + \lambda_y^2\,, \end{cases}$$

Cauchy-Green strain tensor

$$\mathbb{C} := \mathbb{F}^T\mathbb{F} = \mathrm{diag}\{\lambda_x, \lambda_y, \lambda_z\}$$





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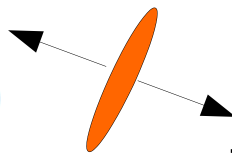

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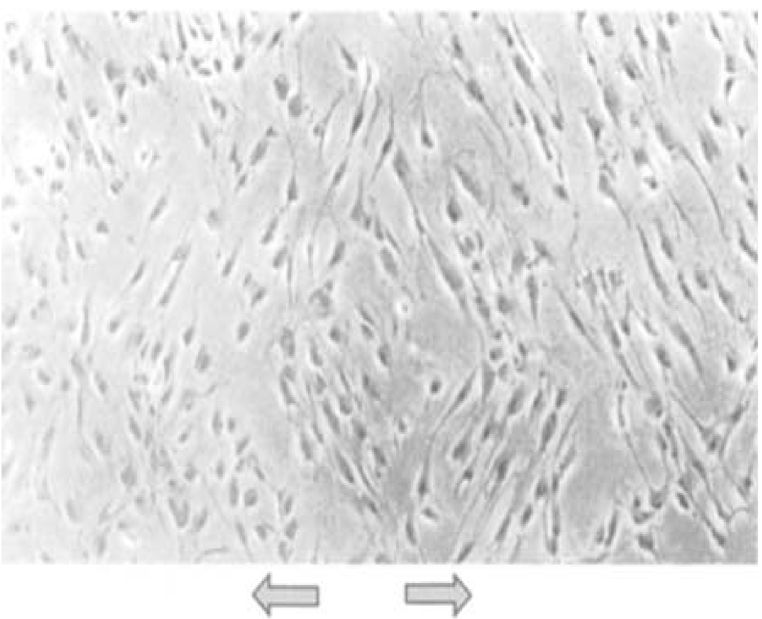

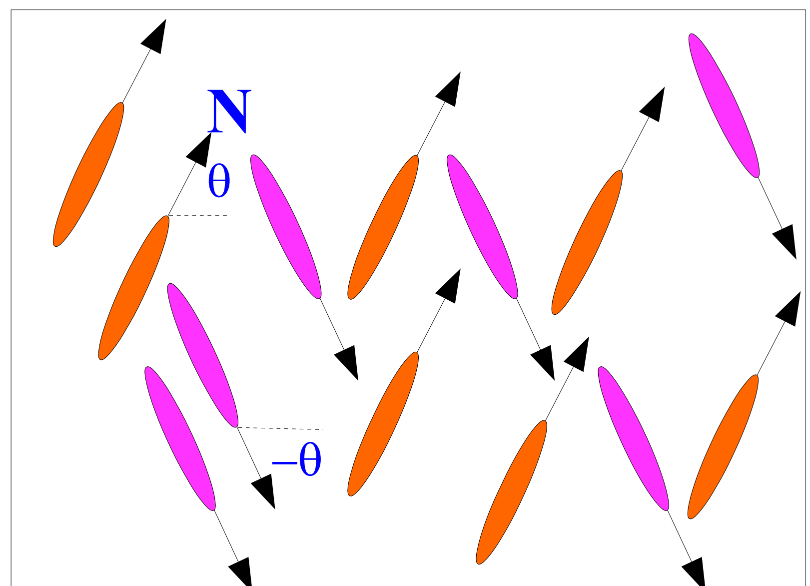

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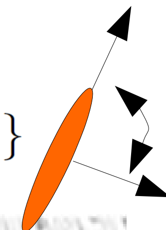

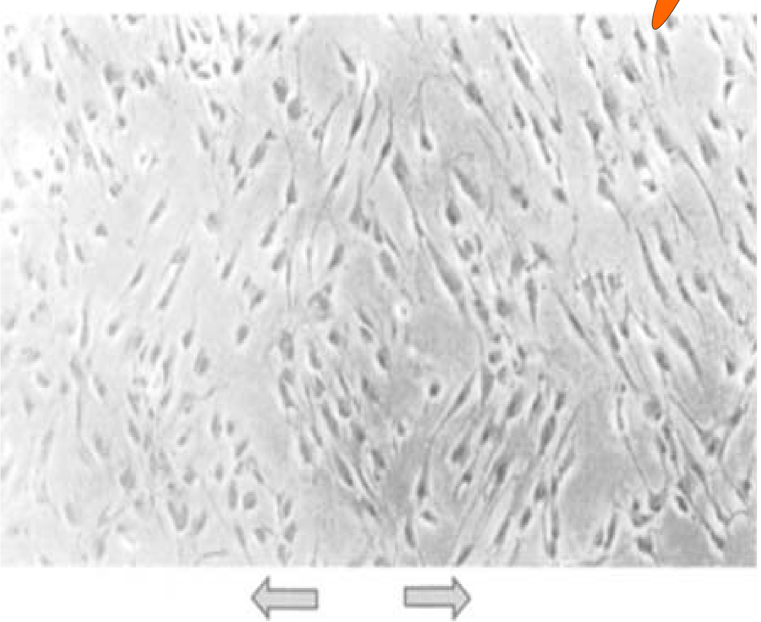

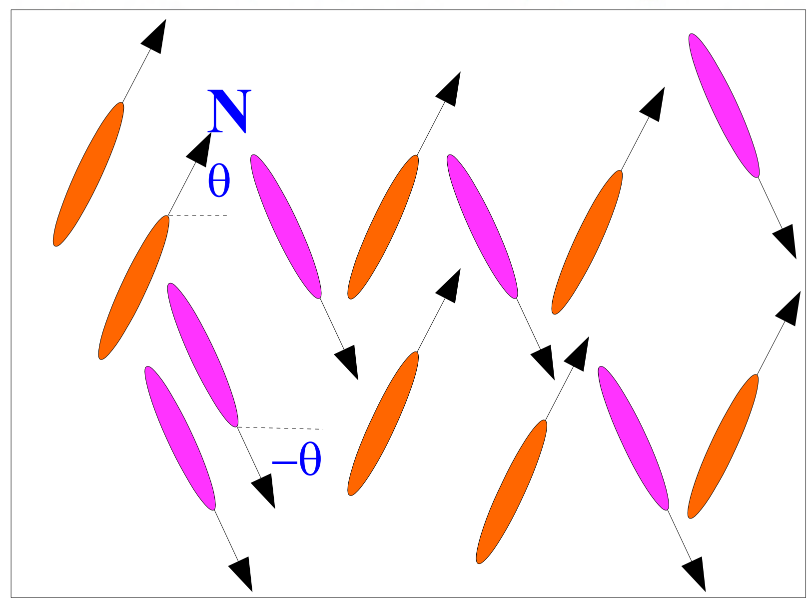

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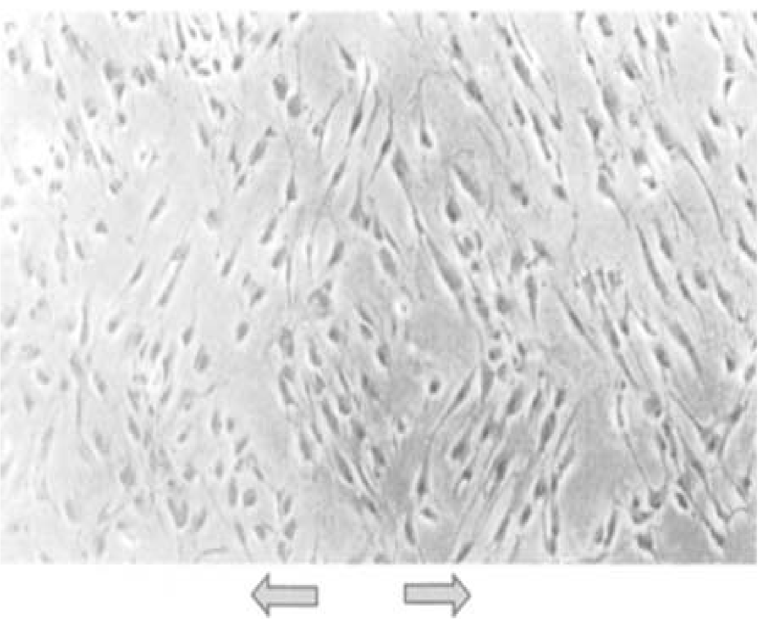

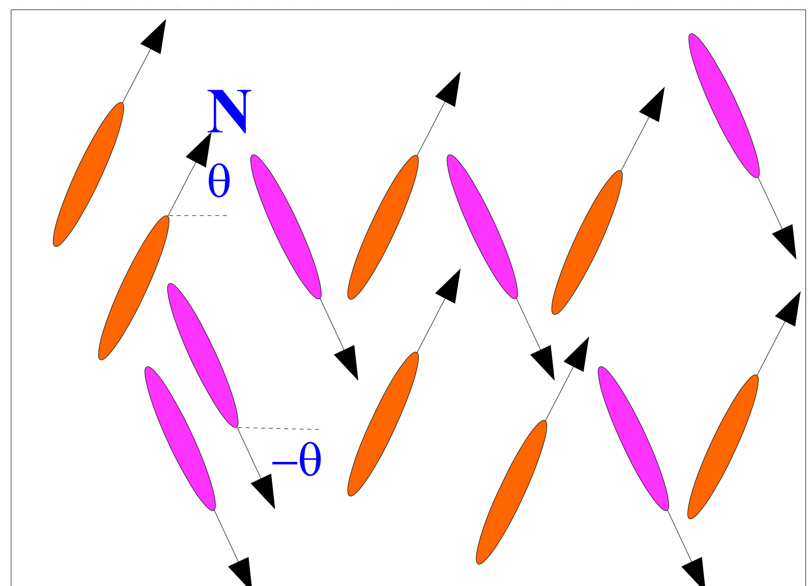

The continuum mechanics model

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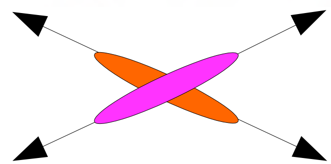
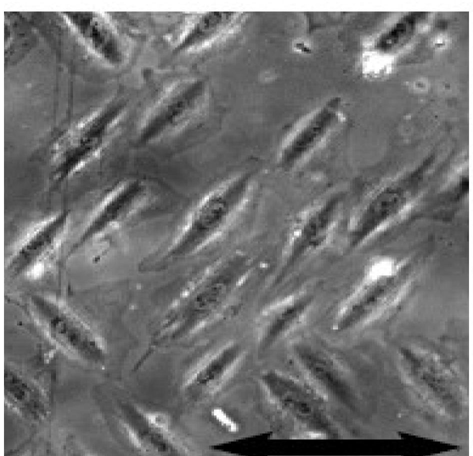


Symmetry

Energy even in I_8



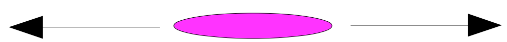
$$\mathcal{U}(\mathrm{I}_1, \mathrm{I}_2, \mathrm{I}_3, \mathrm{I}_4(\theta), \mathrm{I}_5(\theta), \mathrm{I}_6(\theta), \mathrm{I}_7(\theta), \mathrm{I}_8(\theta)) = U(\cos^2\theta)$$

Equilibrium orientations

$$\mathcal{U}(\mathrm{I}_1, \mathrm{I}_2, \mathrm{I}_3, \mathrm{I}_4(\theta), \mathrm{I}_5(\theta), \mathrm{I}_6(\theta), \mathrm{I}_7(\theta), \mathrm{I}_8(\theta)) = U(\cos^2\theta)$$

Equilibria when $U'(\cos^2\theta)\sin\theta\cos\theta = 0$

$$\theta_{eq} = 0$$



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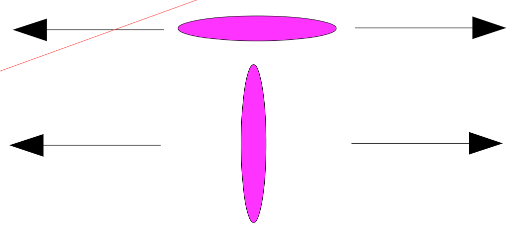
$\theta_{eq} = 0$

$\theta_{eq} = \frac{\pi}{2}$



Equilibrium orientations

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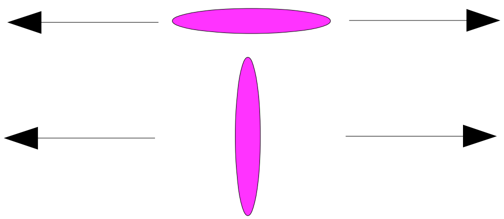
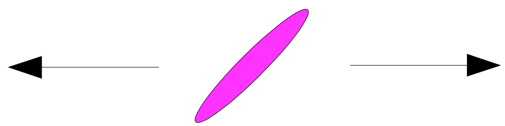


Equilibrium orientations

Quadratic elastic energy $\mathcal{U}(\mathbf{I}) = \frac{1}{2}\mathbf{I} \cdot \mathbb{K}\mathbf{I} + \mathcal{V}$

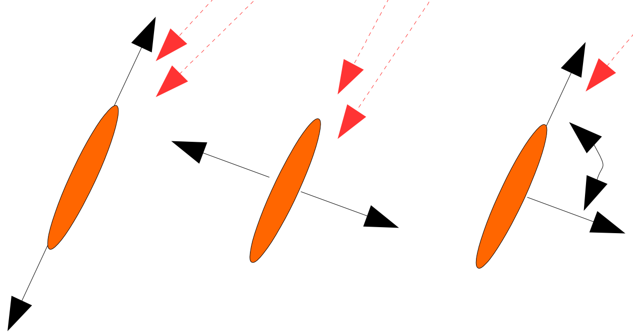
Generalized Fung's energy $\mathcal{U}_F = C\left[\exp\left(\frac{\mathcal{U}}{\mathcal{U}_0} - 1\right) - 1\right]$

$$\cos^2\theta_{eq} = \frac{1}{2} + \frac{k_{44} - k_{66}}{k_{44} + k_{66} - 2k_{46} - k_{88}}\left(\frac{1}{2} - \frac{\lambda_x - 1}{\lambda_x - \lambda_y}\right)$$



$$\|$$

$$\Lambda$$



Linear regime

$$\cos^2\theta_{eq} = \frac{1}{2} + \frac{1}{\alpha}\left(\frac{1}{2} - \frac{1}{1+r}\right)$$

POLITECNICO DI TORINO

Equilibrium orientations

I think that the first part must be rewritten using the **Vianello point of view. Indeed, this is more general and elegant that the present one.** It is clear that I am not claiming that the result presented by the authors is empty. Indeed, in their application they find the additional extrema that are not ensured by the application of the extreme value theorem.

POLITECNICO DI TORINO

Equilibrium orientations

Journal of Elasticity **44**: 193–202, 1996. 193

Optimization of the Stored Energy and Coaxiality of Strain and Stress in Finite Elasticity

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Received 5 December 1995

THEOREM 1. *A rotation* $\mathbf{Q}$ *is critical for* Σ *if and only if the strain tensor* $\mathbf{C}^*$ *and the corresponding stress* $\mathbf{S}^*$ *are coaxial.*

THEOREM 2. *There are at least two rotations such that* $\mathbf{C}^*$ *and* $\mathbf{S}^*$ *are coaxial.*

$$\mathbb{C}^* := \mathbb{Q}\mathbb{C}\mathbb{Q}^{\mathrm{T}}$$

Mathematics and Mechanics of Solids
http://mms.sagepub.com/

A Universal Relation Characterizing Transversely Hemitropic Hyperelastic Materials

Giuseppe Saccomandi and Maurizio Vianello

Mathematics and Mechanics of Solids 1997 2: 181
DOI: 10.1177/108128659700200205

The online version of this article can be found at:
http://mms.sagepub.com/content/2/2/181

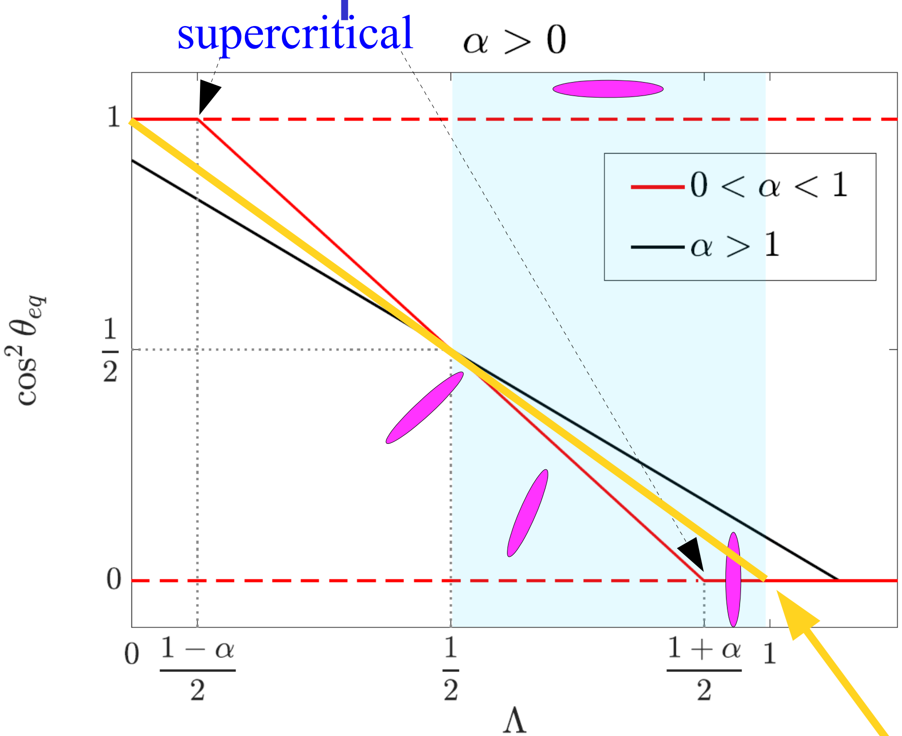
Journal of Elasticity **47**: 217–224, 1997. 217

Rotations which Make Strain and Stress Coaxial*

CARLO SGARRA and MAURIZIO VIANELLO
Dipartimento di Matematica, Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milano, Italy

Received 22 November 1996

Bifurcation diagram



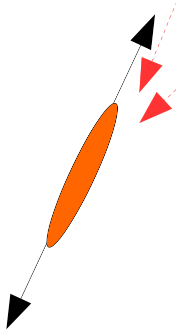
$$\cos^2\theta_{eq} = \frac{1}{2} + \frac{1}{\alpha}\left(\frac{1}{2} - \frac{1}{1+r}\right)$$

$$\Lambda := \frac{\lambda_x - 1}{\lambda_x - \lambda_y} \approx \frac{1}{1+r}$$

$$r = -\frac{\varepsilon_{yy}}{\varepsilon_{xx}}$$

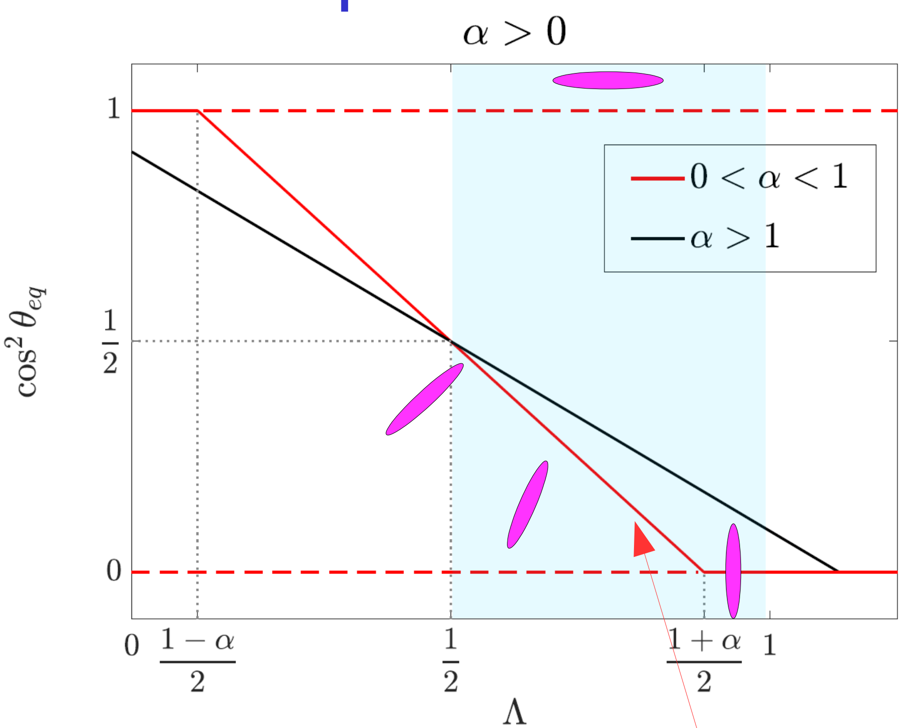
Depends on the ratio (not on stretch amplitude!)

$$\alpha := \frac{k_{44} + \sout{k_{66} - 2k_{46} - k_{88}}}{k_{44} - \sout{k_{66}}}$$



If $k_{66} = k_{46} = k_{88} = 0$ ⇒ $\alpha = 1$

Bifurcation diagram



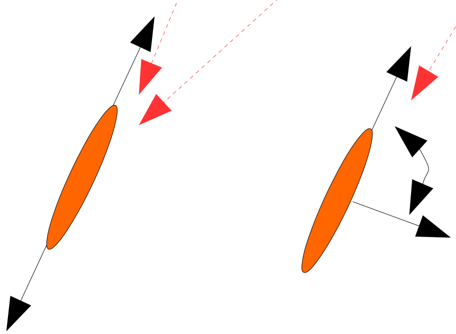
$$\cos^2\theta_{eq} = \frac{1}{2} + \frac{1}{\alpha}\left(\frac{1}{2} - \frac{1}{1+r}\right)$$

$$\Lambda := \frac{\lambda_x - 1}{\lambda_x - \lambda_y} \approx \frac{1}{1+r}$$

$$r = -\frac{\varepsilon_{yy}}{\varepsilon_{xx}}$$

$$\alpha := \frac{k_{44} + k_{66} - 2k_{46} - k_{88}}{k_{44} - k_{66}} \approx 0.794$$

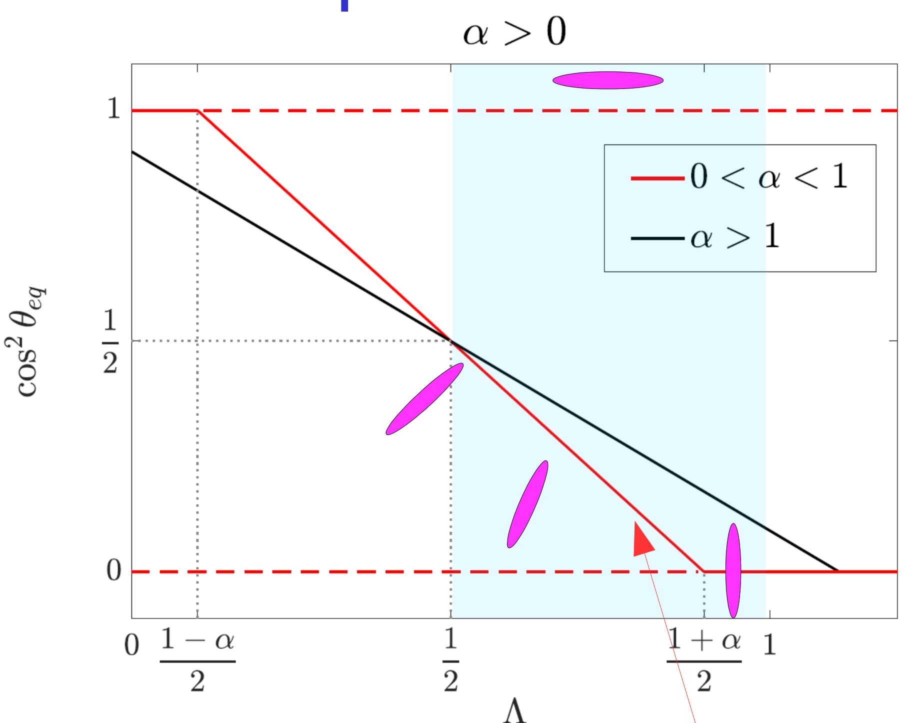
(Livne)



$\alpha < 1 \Longrightarrow k_{46} + k_{88}/2 > k_{66}$

$k_{88} = 0.206\, k_{44}$

Bifurcation diagram



$$\cos^2\theta_{eq} = \frac{1}{2} + \frac{1}{\alpha}\left(\frac{1}{2} - \frac{1}{1+r}\right)$$

$$\Lambda := \frac{\lambda_x - 1}{\lambda_x - \lambda_y} \approx \frac{1}{1+r}$$

$$r = -\frac{\varepsilon_{yy}}{\varepsilon_{xx}}$$

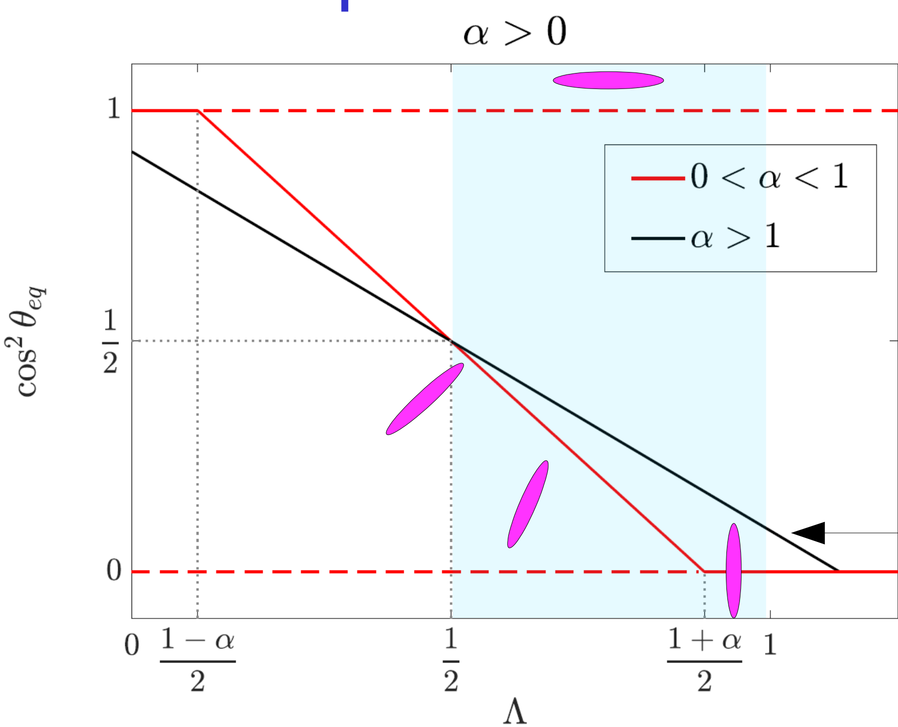
$$\alpha := \frac{k_{44} + k_{66} - 2k_{46} - k_{88}}{k_{44} - k_{66} + 4k_{14} - 4k_{16}} \approx 0.794$$

(Livne)

$$U = U_\ell\left(\hat{\mathrm{I}}_1, \hat{\mathrm{I}}_4, \hat{\mathrm{I}}_6\right) + U_q(\mathrm{I}_4, \mathrm{I}_5, \mathrm{I}_6, \mathrm{I}_7, \mathrm{I}_8)$$

$\alpha < 1$ ⟹ $k_{14} = 0.065\, k_{44}$

Bifurcation diagram

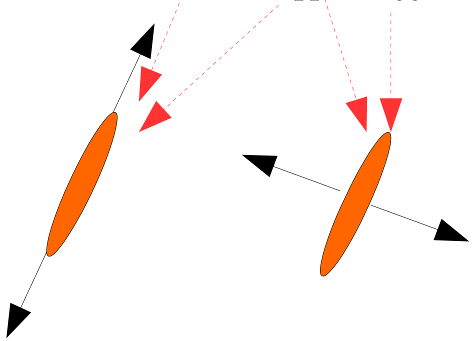


$$\cos^2 \theta_{eq} = \frac{1}{2} + \frac{1}{\alpha}\left(\frac{1}{2} - \frac{1}{1+r}\right)$$

$$\Lambda := \frac{\lambda_x - 1}{\lambda_x - \lambda_y} \approx \frac{1}{1+r}$$

$$r = -\frac{\varepsilon_{yy}}{\varepsilon_{xx}}$$

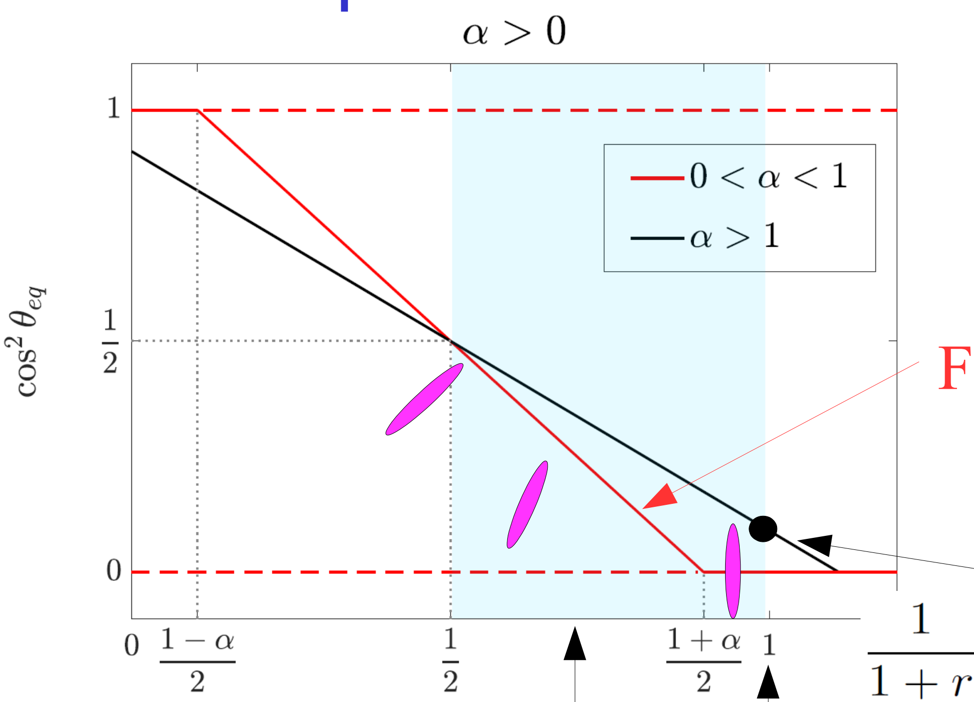
$$\alpha := \frac{k_{44} + k_{66} \sout{- 2k_{46} - k_{88}}}{k_{44} - k_{66}}$$

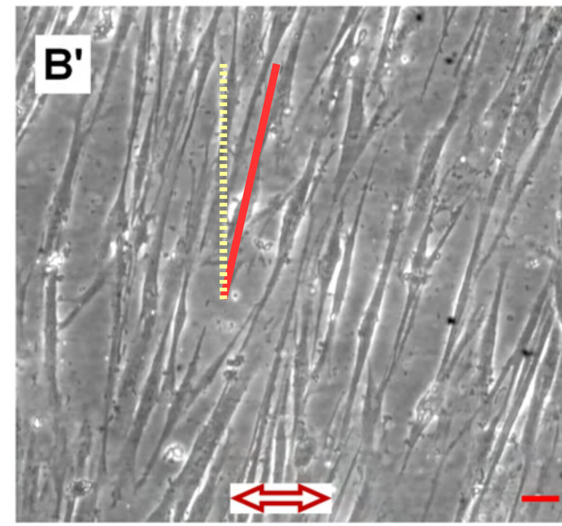


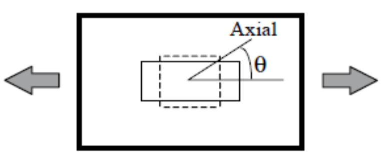
If $k_{46} = k_{88} = 0 \Longrightarrow \alpha > 1$

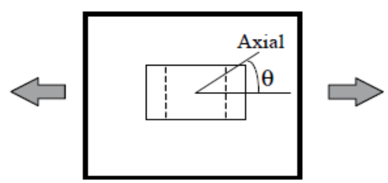
Can the slope change?

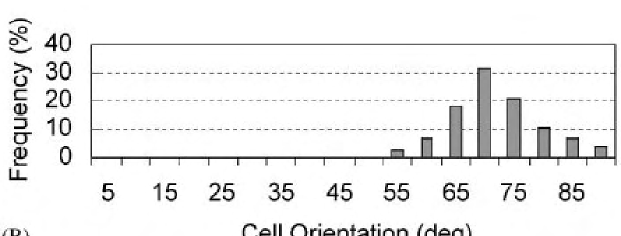
Is $\alpha = 0.794 \pm 0.08$ universal?

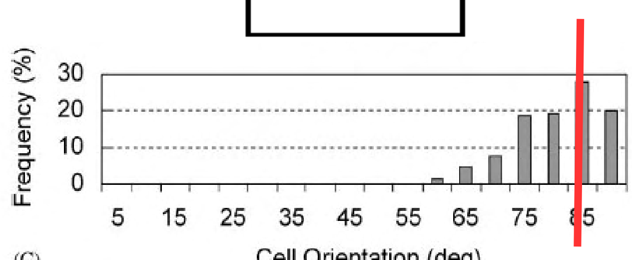








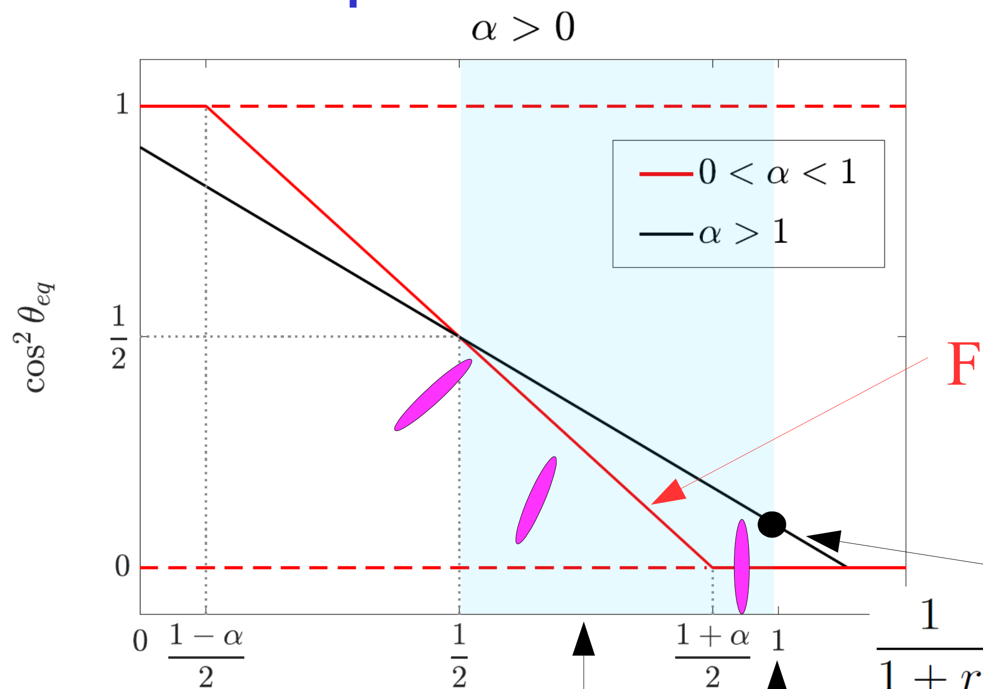


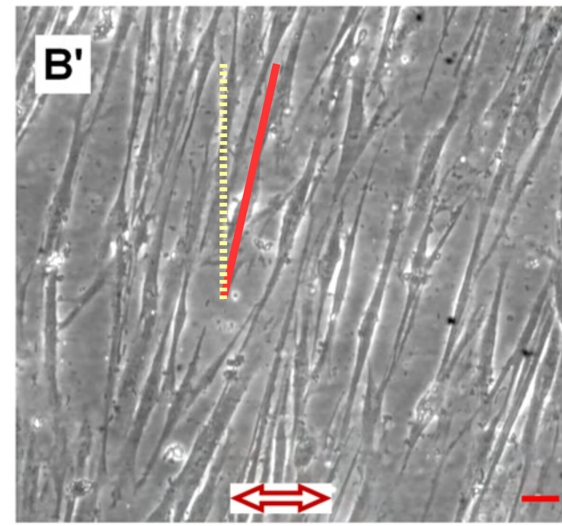


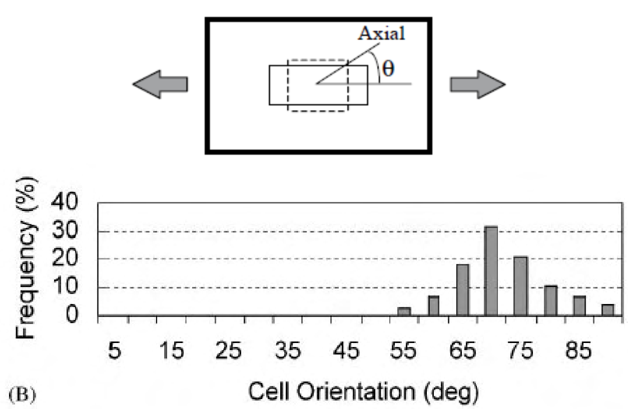
Endothelial cells seem to have a non negligible k_{66}

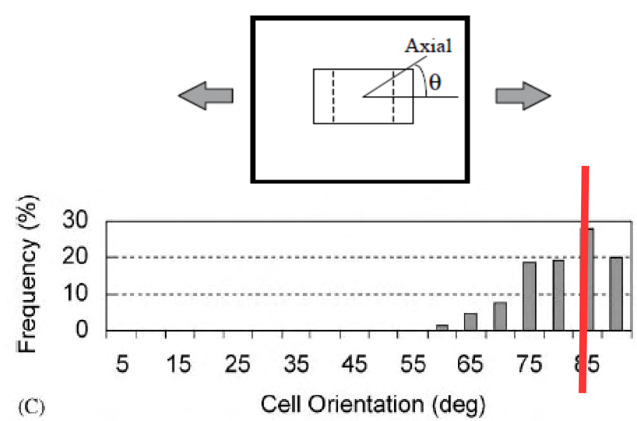
Can the slope change?

Is $\alpha = 0.794 \pm 0.08$ universal?





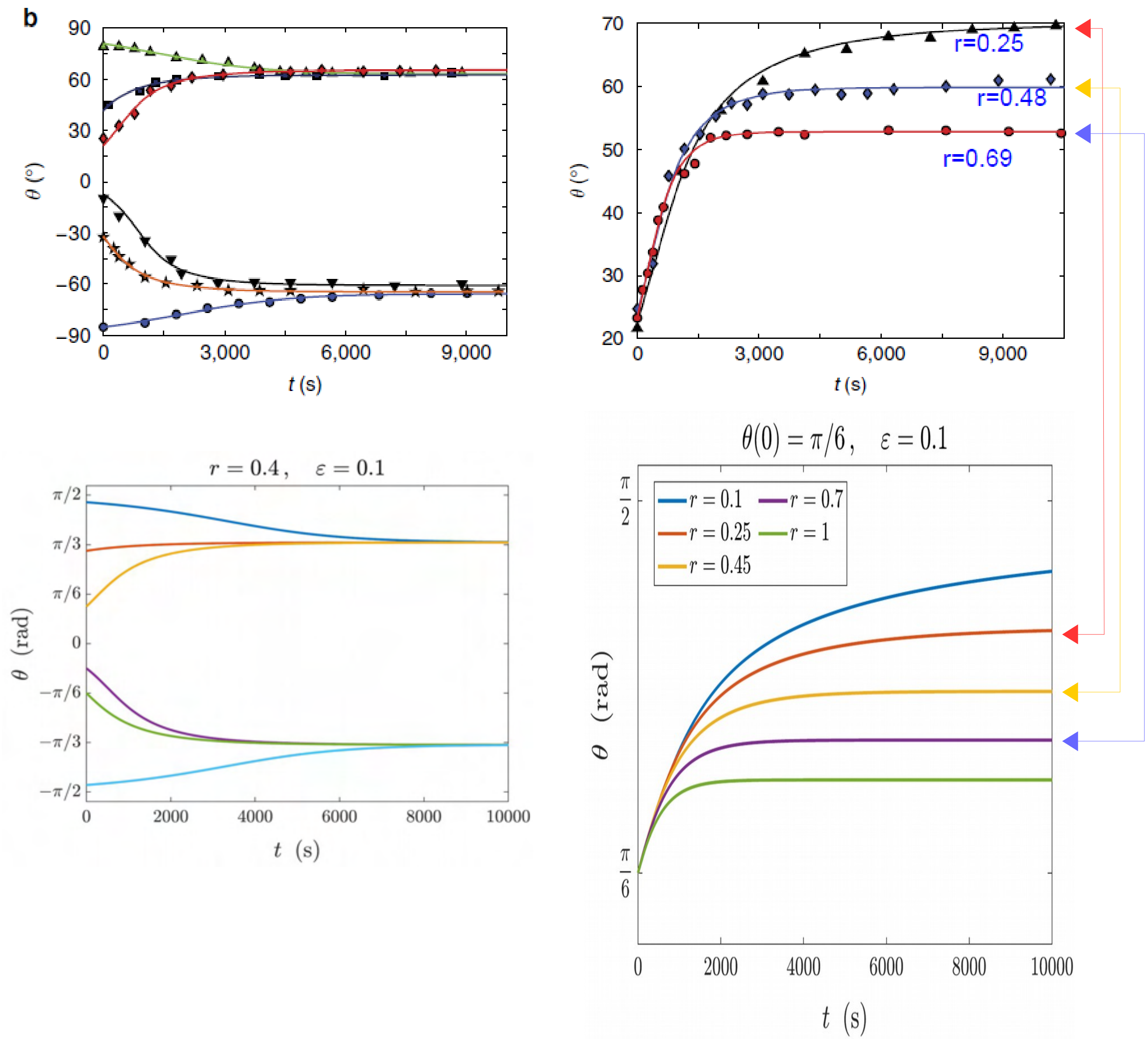




POLITECNICO DI TORINO

Temporal evolution

$$\frac{d\theta}{dt} = -\frac{1}{\eta}\frac{\partial U}{\partial \theta}$$



Dependence from strain amplitude

$$\frac{d\theta}{dt} = -\frac{1}{\eta}\frac{\partial U}{\partial \theta} = \frac{(\lambda_x - \lambda_y)^2}{\tau_\theta} f(\theta;\Lambda)$$

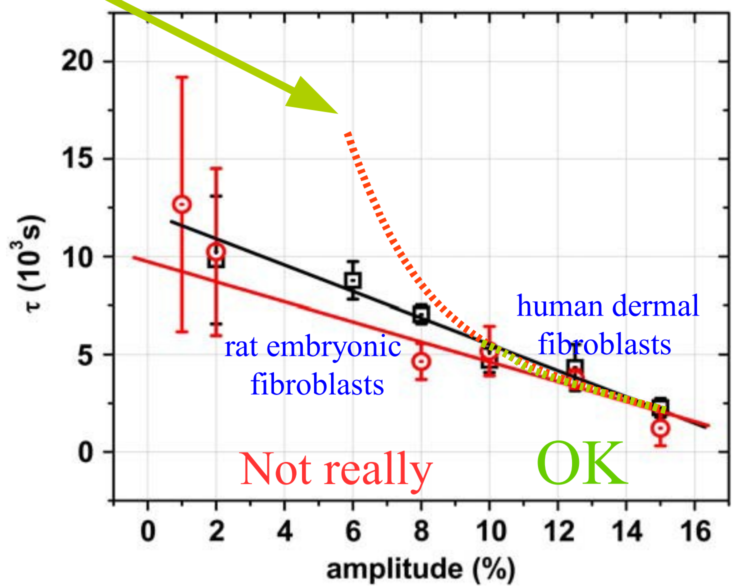
$\propto (1+r)^2\,\varepsilon_{xx}^2$

Re-orientation time decreases increasing the strain amplitude

Human lung epithelial cells

Strain (%)		Cyclic stretch (CS) Cell body	Post-CS release Cell body
5	94.6	58.7 min	36.9 min
10	23.6	22.2 min	72.7 min
15		10.5 min	87.8 min

Roshadeh et al. (2020)



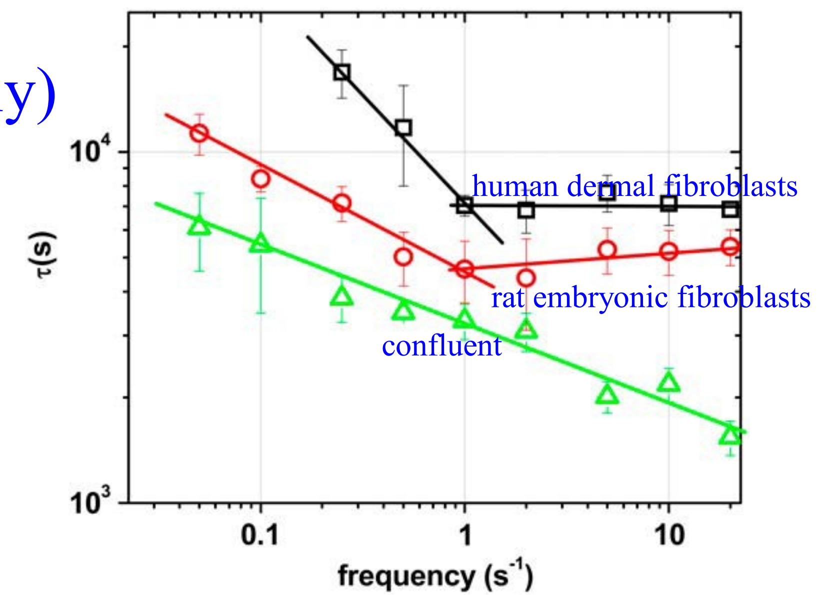
Jungbauer et al (2008)

Dependency from stretch frequency

$$\frac{d\theta}{dt} = -\frac{1}{\eta}\frac{\partial U}{\partial \theta} = \frac{(\lambda_x - \lambda_y)^2}{\tau_\theta} f(\theta;\Lambda)$$

Not good enough
We need an intrinsic time

Re-orientation time decreases
increasing the frequency (asymptotically)

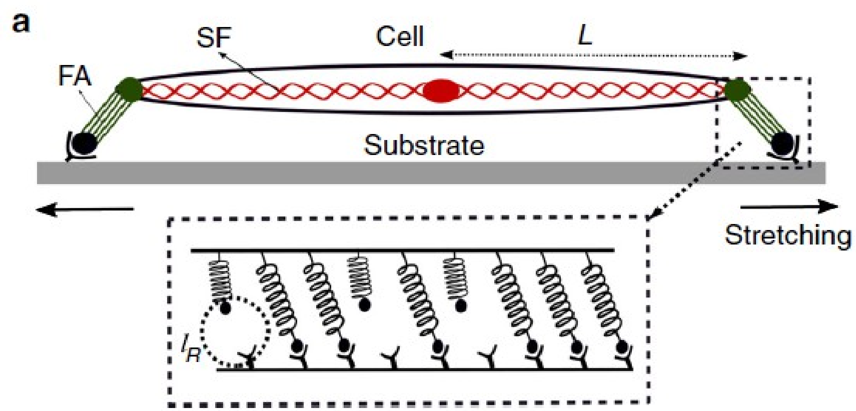


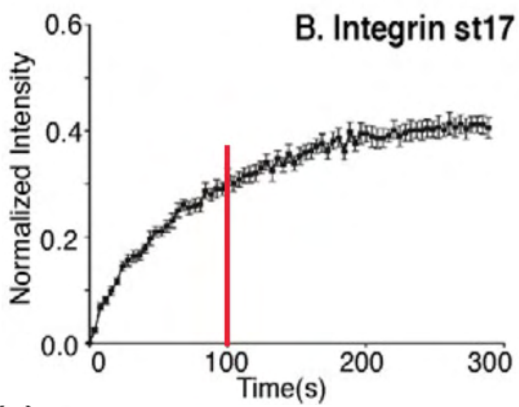
Jungbauer et al (2008)

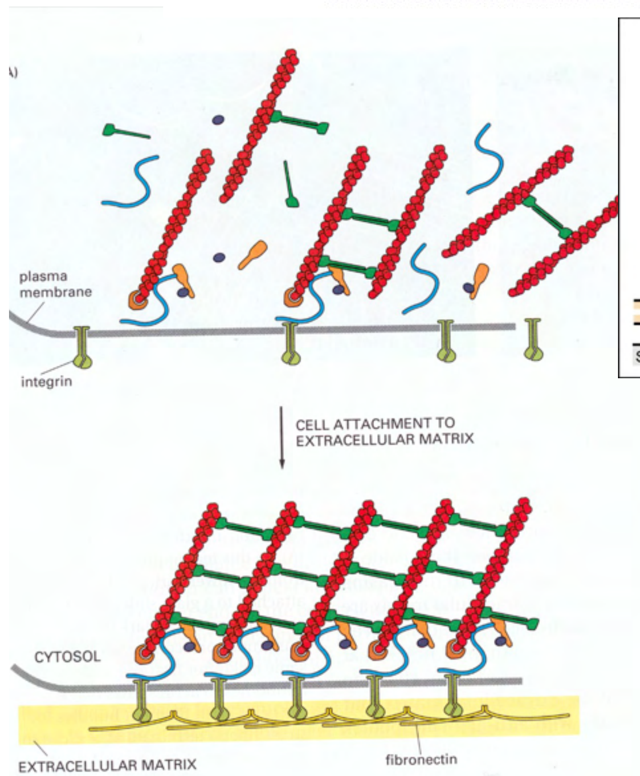
Intrinsic times and viscoelastic effects

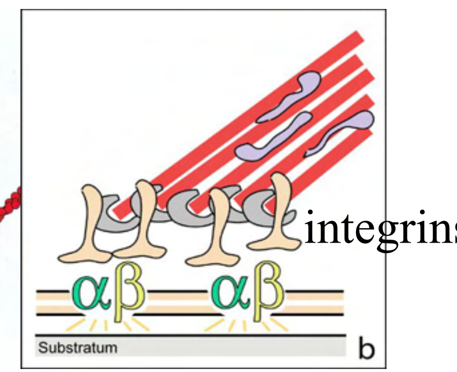
Possible causes of viscoelasticity

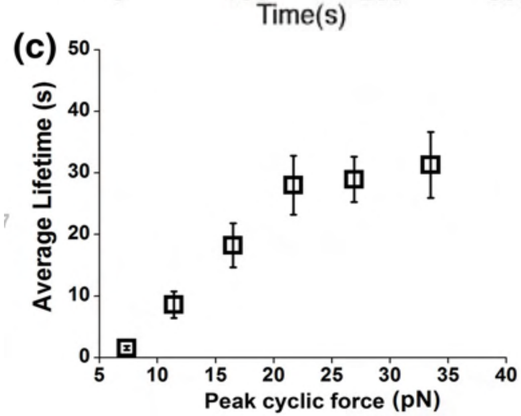
- Cytosol
- Actin cytoskeleton
- Adhesion bond turnover











Linear viscoelastic model

Relaxation kernel — Past elasticity tensor — Strain tensors

$$\mathbb{T}(t|\theta) = \int_{-\infty}^{t} \frac{1}{\lambda} e^{-(t-\tau)/\lambda} \mathbf{C}_0(\theta(\tau))[\mathbb{E}(t) - \mathbb{E}(\tau)]\, d\tau$$

$$\begin{cases} \dfrac{d\theta}{dt}(t) = -\dfrac{1}{K\lambda_\theta} \dfrac{\partial \mathbb{T}}{\partial \theta}(t|\theta) : \mathbb{E}(t) \\ \lambda \dfrac{d\mathbb{T}}{dt}(t|\theta) + \mathbb{T}(t|\theta) = \not{\mathbb{C}}_0(t|\theta) \dfrac{d\mathbb{E}}{dt}(t)\,, \end{cases}$$

$$\not{\mathbb{C}}_0(t|\theta) := \int_{-\infty}^{t} e^{-(t-\tau)/\lambda} \mathbf{C}_0(\theta(\tau))\, d\tau = \int_0^{+\infty} \lambda e^{-s} \mathbf{C}_0(\theta(t-\lambda s))\, ds$$

G. Lucci, C. Giverso & L.P., *Math. Biosci.* **337**, 108630 (2021)

Linear viscoelastic model

$$\mathbb{T}(t|\theta) = \int_{-\infty}^{t} \frac{1}{\lambda} e^{-(t-\tau)/\lambda} \mathbb{C}_0(\theta(\tau))[\mathbb{E}(t) - \mathbb{E}(\tau)]\, d\tau$$

High frequency regime

$$\mathbb{T}(t|\theta) = \mathbb{C}_0(\theta(t))\mathbb{E}_0 e^{i\omega t} + \left[\frac{\lambda}{K\lambda_\theta}\int_0^{+\infty} e^{-s}\frac{\partial \mathbb{C}_0}{\partial \theta}(\theta(t-\lambda s))\frac{\partial \mathbb{T}}{\partial \theta}(t-\lambda s|\theta) : \mathbb{E}_0 e^{-i\lambda\omega s}\, ds\right]\mathbb{E}_0 e^{i2\omega t}$$

$$\frac{d\theta}{dt} = -\frac{1}{\eta}\left[\frac{\partial \mathbb{C}_0}{\partial \theta}\mathbb{E}\right] : \mathbb{E} = -\frac{2}{K\lambda_\theta}\frac{\partial U}{\partial \theta} \qquad U(t,\theta) := \frac{1}{2}\mathbb{E}(t) : \mathbb{C}_0(\theta)\mathbb{E}(t)$$

Linear viscoelastic model

$$\mathbb{T}(t|\theta) = \int_{-\infty}^{t} \frac{1}{\lambda} e^{-(t-\tau)/\lambda} \mathbb{C}_0(\theta(\tau)) [\mathbb{E}(t) - \mathbb{E}(\tau)] \, d\tau$$

Low frequency regime

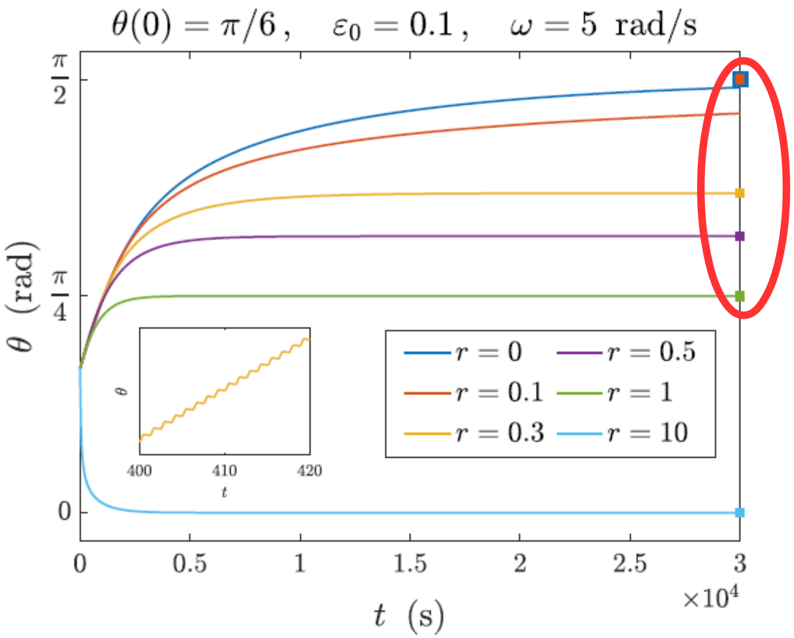
$$\mathbb{T}(t|\theta) \approx i\lambda\omega \left[\int_{0}^{+\infty} s e^{-s} \mathbb{C}_0(\theta(t - \lambda s)) \, ds \right] \mathbb{E}_0 e^{i\omega t}$$

$$\mathbb{T}(t|\theta) \approx \lambda \overline{\mathbb{C}}_0(t|\theta) \frac{d\mathbb{E}}{dt}(t)$$

Dependence from stretch frequency

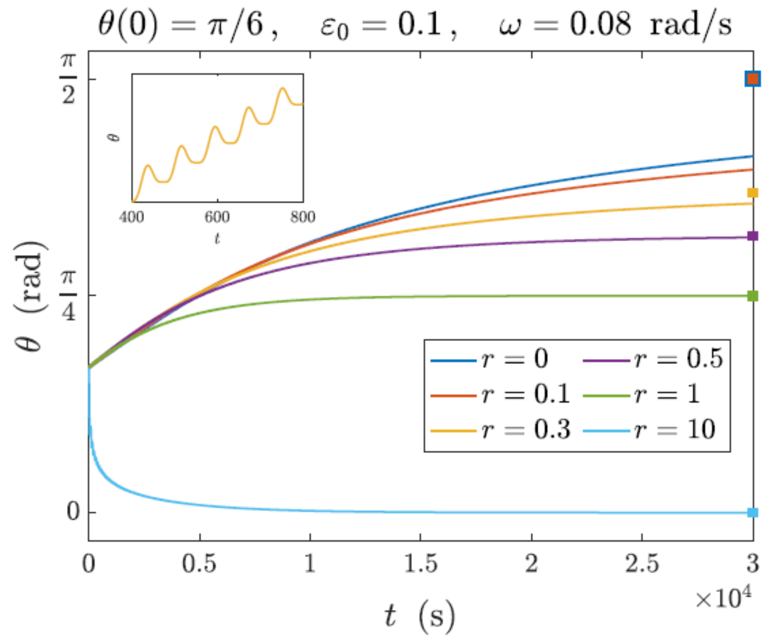
Varying stretch ratio *r*

Higher frequencies



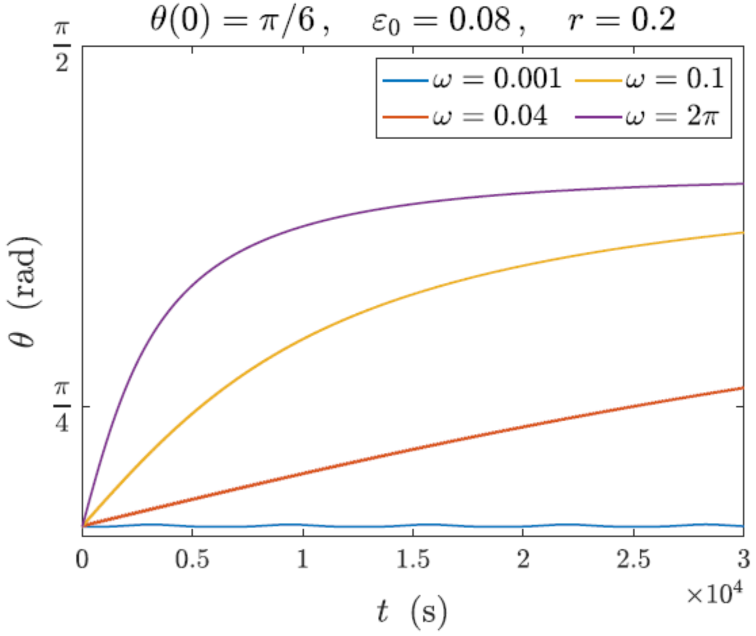
equilibrium values

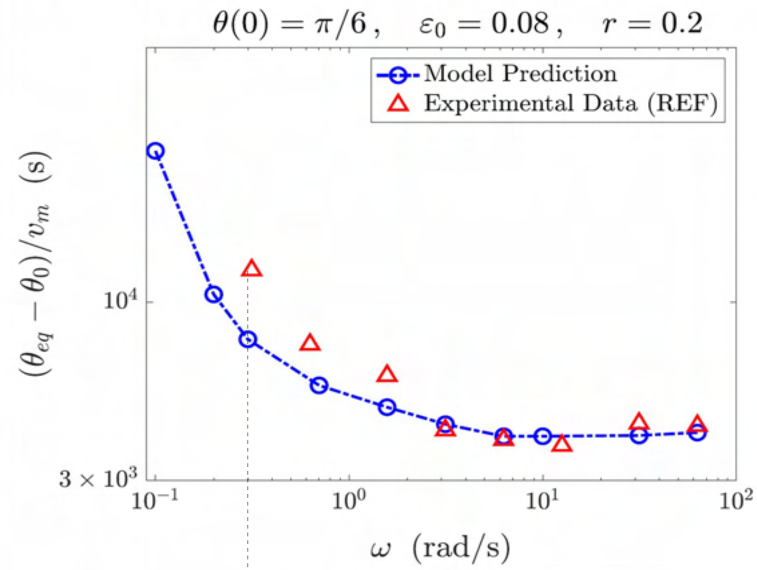
Lower frequencies

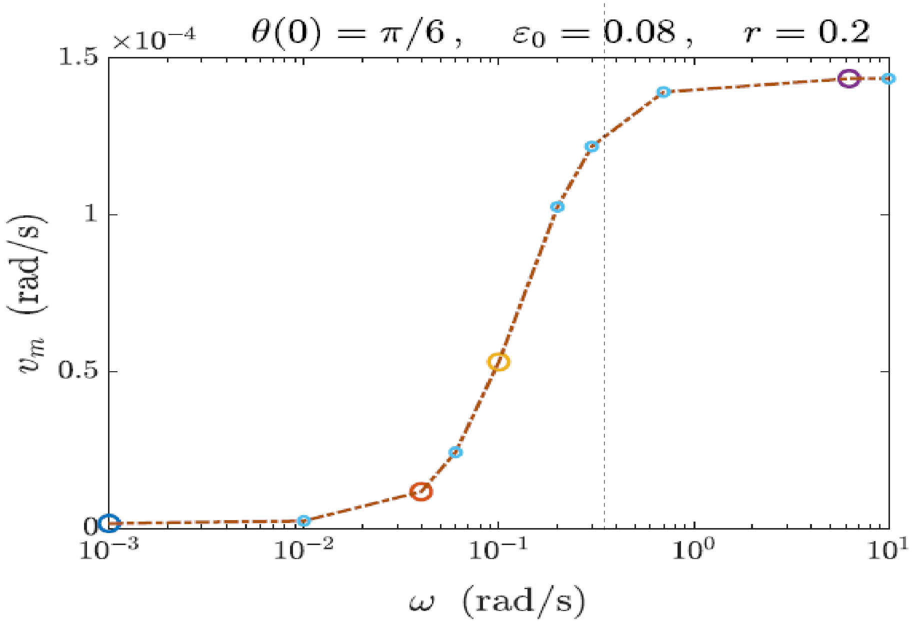


Dependence from stretch frequency

Varying frequencies

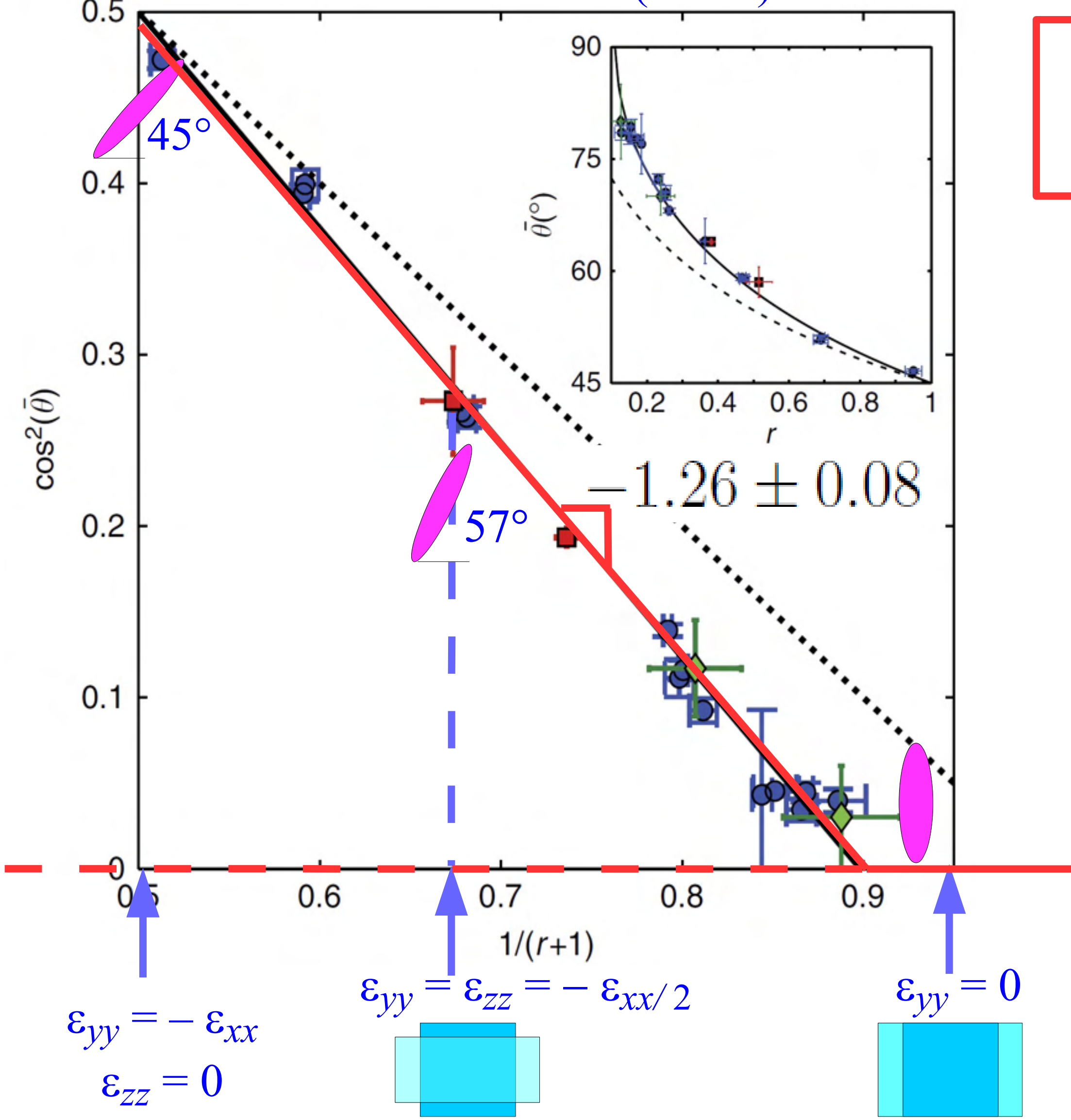






Summary: Elastic model

Bi-axial test (Livne)

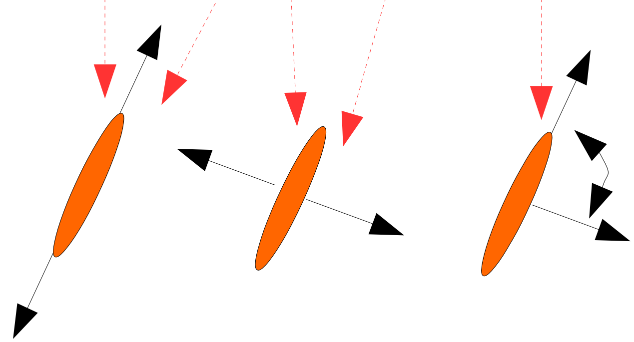


$$\cos^2\theta_{eq} = \frac{1}{2} + \frac{1}{K}\left(\frac{1}{2} - \Lambda\right)$$

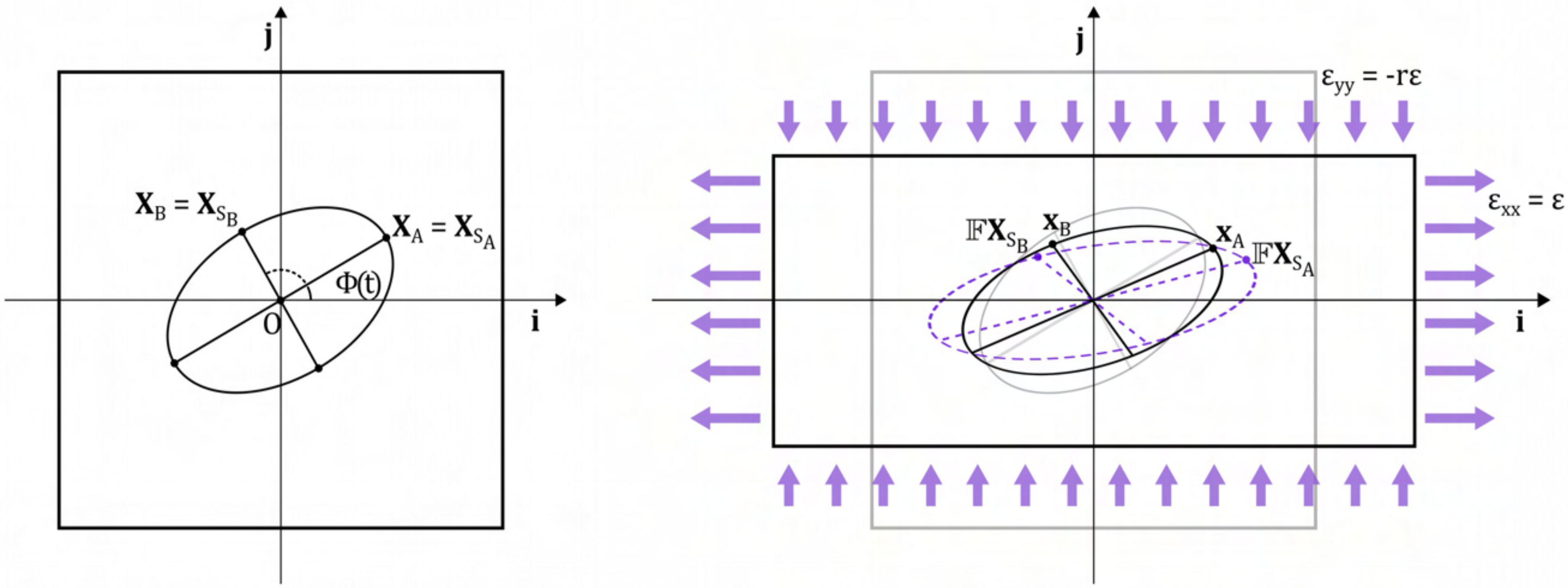
$$\Lambda := \frac{\lambda_x - 1}{\lambda_x - \lambda_y} \approx \frac{1}{1+r}$$

$$r = -\frac{\varepsilon_{yy}}{\varepsilon_{xx}}$$

$$K := \frac{k_{44} + k_{66} - 2k_{46} - k_{88}}{k_{44} - k_{66}}$$



Effect of substratum elasticity



Stress fiber remodel to minimize the "internal" energy $U_{\text{in}} = -\frac{1}{2}k_a\bar{\xi}_a^2 - \frac{1}{2}k_b\bar{\xi}_b^2 - \frac{1}{2}k_\theta\bar{\theta}_{ab}^2$

$$h\,\frac{d\Phi}{dt}(t) = 2\varepsilon^2(t)k_s^2(1+r)\left\{\frac{k_a L_a^2}{(k_a+k_s)^2}\left[(1+r)\cos^2\Phi(t) - r\right] + \frac{k_b L_b^2}{(k_b+k_s)^2}\left[(1+r)\cos^2\Phi(t) - 1\right] - \frac{2k_\theta}{\left[\left(\frac{1}{L_a^2}+\frac{1}{L_b^2}\right)k_\theta + k_s\right]^2}(1+r)\left[2\cos^2\Phi(t) - 1\right]\right\}\sin\Phi\cos\Phi$$

POLITECNICO DI TORINO

Effect of substratum elasticity

$$\frac{d\Phi}{d\hat{t}} = \frac{2\hat{k}_s^2}{(1+\hat{k}_s)^2}\,\varepsilon^2(t)\,(1+r)^2(\alpha\cos^2\Phi-\beta)\sin\Phi\cos\Phi$$

$$\frac{|\alpha\cos^2\Phi(\hat{t})-\beta|^{\alpha/(\beta\gamma)}}{[\cos^2\Phi(\hat{t})]^{1/\beta}[\sin^2\Phi(\hat{t})]^{1/\gamma}} = C\exp\left[-\frac{4\hat{k}_s^2}{(1+\hat{k}_s)^2}(1+r)^2\int_0^{\hat{t}}\varepsilon^2(\hat{\tau})\,d\hat{\tau}\right]$$

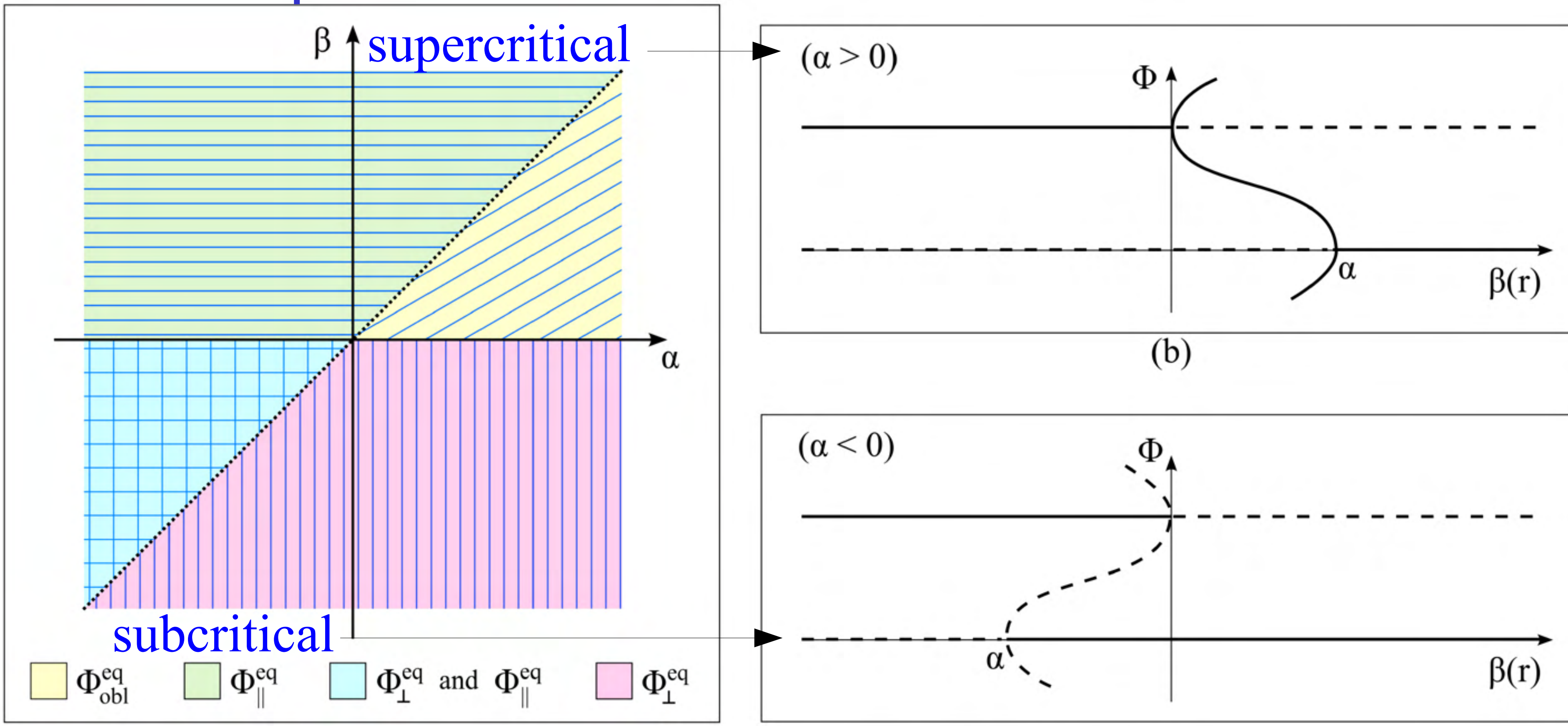
$$\alpha = 1+\lambda\hat{k}_b\left(\frac{1+\hat{k}_s}{\hat{k}_b+\hat{k}_s}\right)^2 - 2\hat{k}_\theta\left(\frac{1+\hat{k}_s}{\frac{\lambda+1}{2\lambda}\hat{k}_\theta+\hat{k}_s}\right)^2,$$

$$\beta = \frac{r}{1+r}+\frac{\lambda\hat{k}_b}{1+r}\left(\frac{1+\hat{k}_s}{\hat{k}_b+\hat{k}_s}\right)^2 - \hat{k}_\theta\left(\frac{1+\hat{k}_s}{\frac{\lambda+1}{2\lambda}\hat{k}_\theta+\hat{k}_s}\right)^2$$

$$\hat{k}_b = \frac{k_b}{k_a},\qquad \hat{k}_s = \frac{k_s}{k_a},\qquad \hat{k}_\theta = \frac{2k_\theta}{k_a L_a^2},\qquad \lambda = \frac{L_b^2}{L_a^2},$$

$$\gamma = \alpha - \beta$$

Effect of substratum elasticity

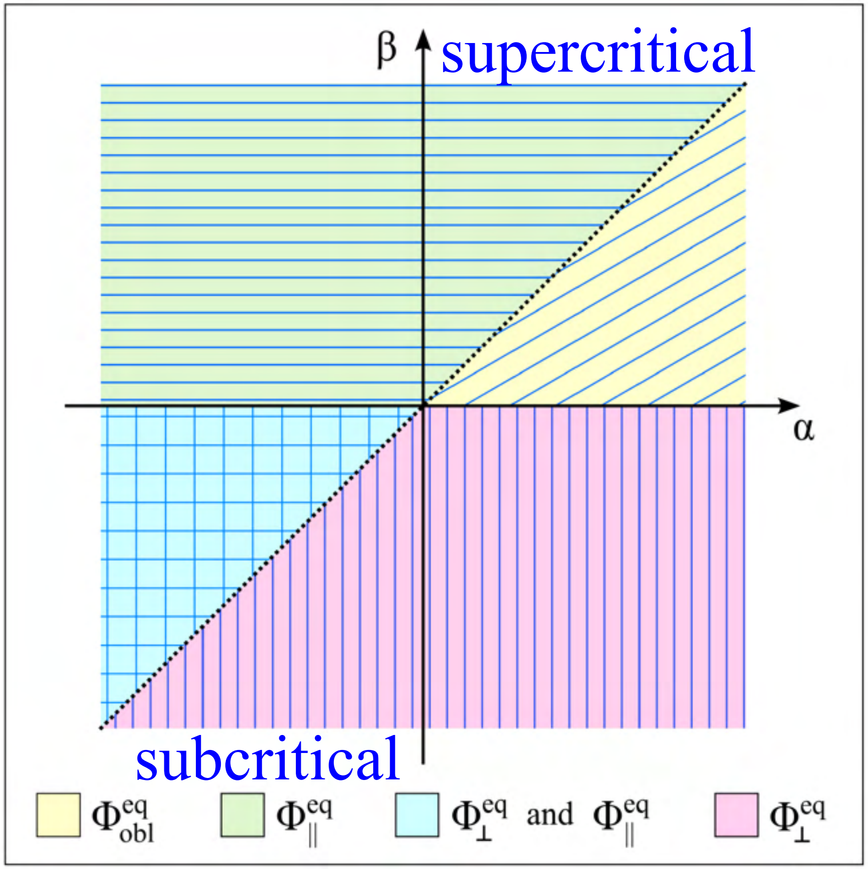


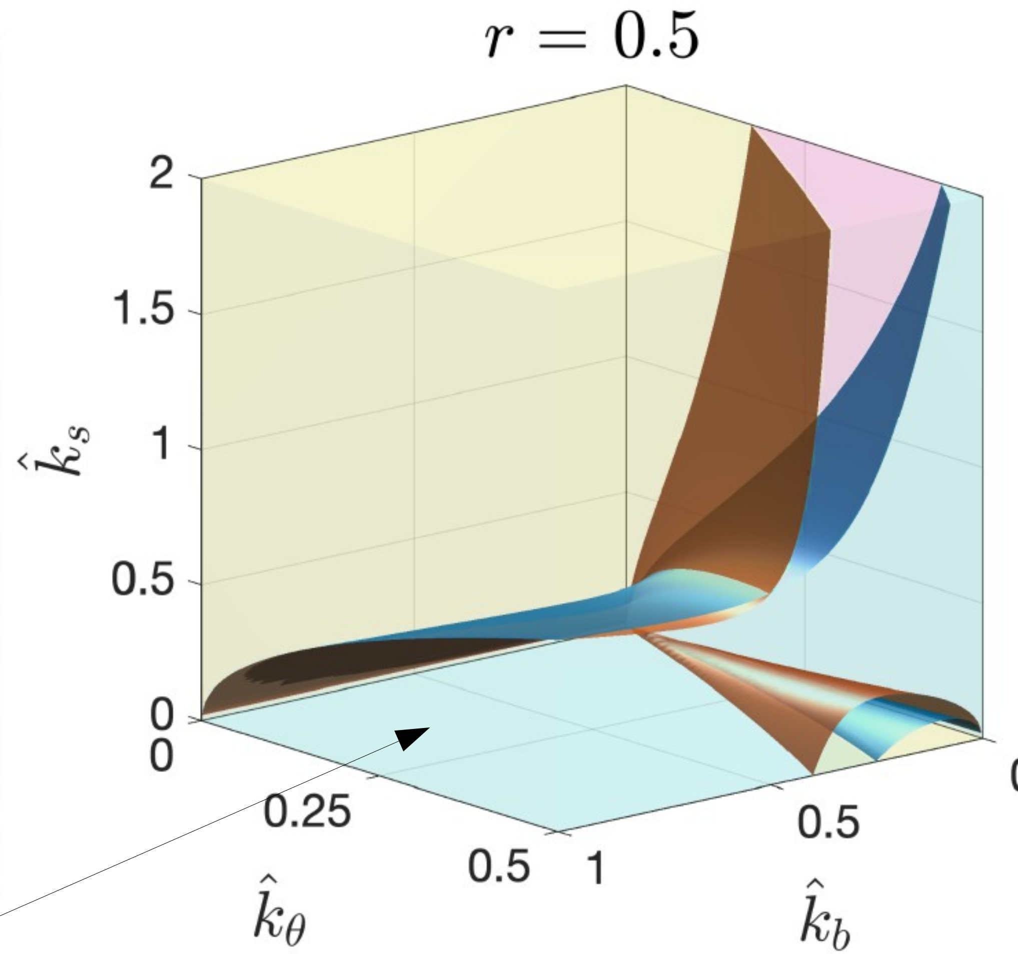
$$
\begin{aligned}
\alpha &= 1+\lambda\hat{k}_{\mathrm{b}}\left(\frac{1+\hat{k}_{\mathrm{s}}}{\hat{k}_{\mathrm{b}}+\hat{k}_{\mathrm{s}}}\right)^2-2\hat{k}_\theta\left(\frac{1+\hat{k}_{\mathrm{s}}}{\frac{\lambda+1}{2\lambda}\hat{k}_\theta+\hat{k}_{\mathrm{s}}}\right)^2, \\
\beta &= \frac{r}{1+r}+\frac{\lambda\hat{k}_{\mathrm{b}}}{1+r}\left(\frac{1+\hat{k}_{\mathrm{s}}}{\hat{k}_{\mathrm{b}}+\hat{k}_{\mathrm{s}}}\right)^2-\hat{k}_\theta\left(\frac{1+\hat{k}_{\mathrm{s}}}{\frac{\lambda+1}{2\lambda}\hat{k}_\theta+\hat{k}_{\mathrm{s}}}\right)^2
\end{aligned}
$$

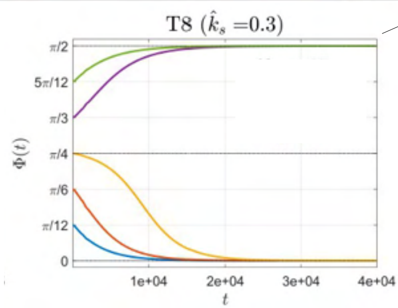
$$
\hat{k}_{\mathrm{b}}=\frac{k_{\mathrm{b}}}{k_{\mathrm{a}}}, \qquad \hat{k}_{\mathrm{s}}=\frac{k_{\mathrm{s}}}{k_{\mathrm{a}}}, \qquad \hat{k}_\theta=\frac{2k_\theta}{k_{\mathrm{a}}L_{\mathrm{a}}^2}, \qquad \lambda=\frac{L_{\mathrm{b}}^2}{L_{\mathrm{a}}^2},
$$

$$
\gamma=\alpha-\beta
$$

Effect of substratum elasticity

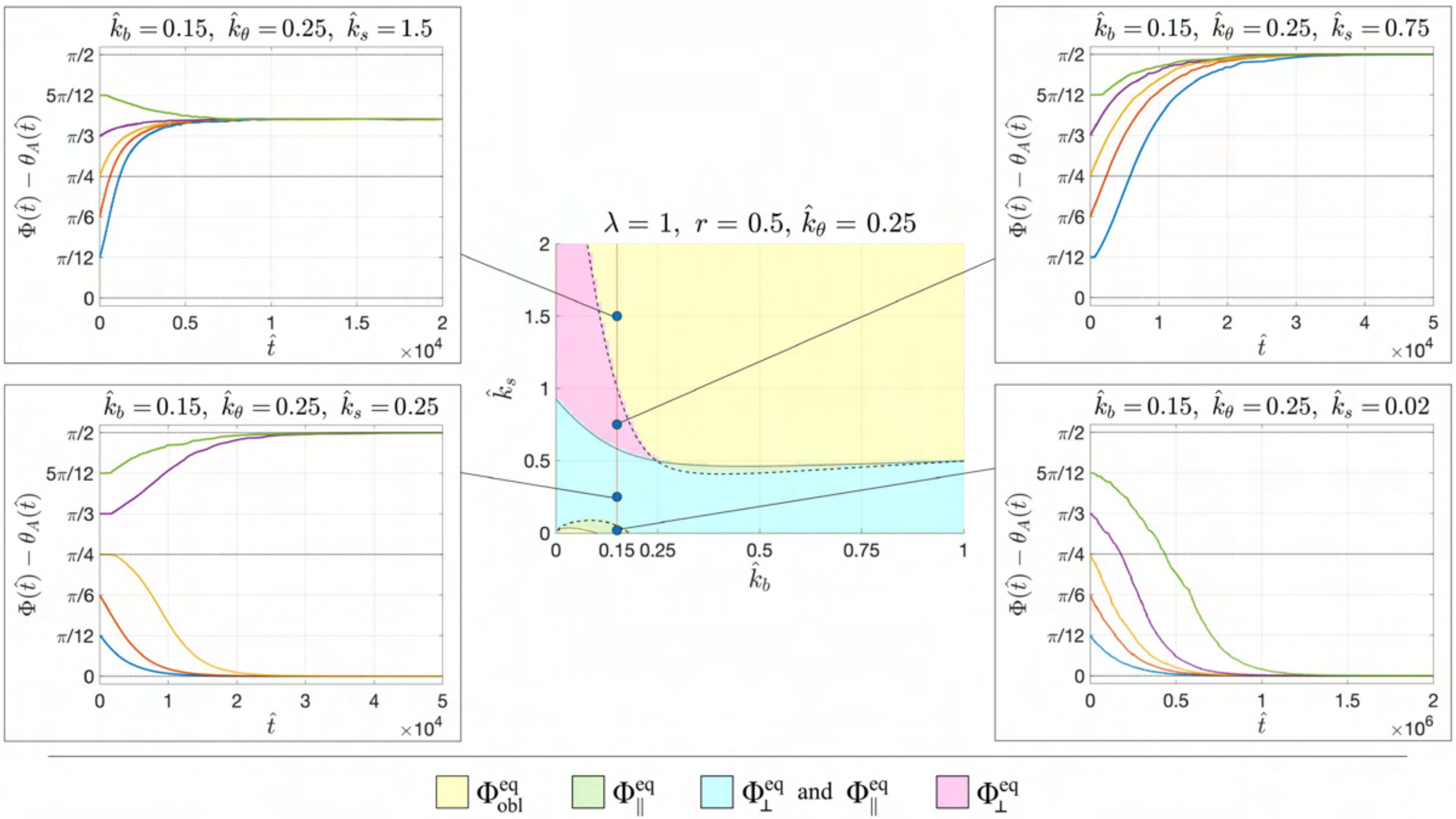






$$\hat{k}_\mathrm{b} = \frac{k_\mathrm{b}}{k_\mathrm{a}}\,, \qquad \hat{k}_\mathrm{s} = \frac{k_\mathrm{s}}{k_\mathrm{a}}\,, \qquad \hat{k}_\theta = \frac{2k_\theta}{k_\mathrm{a}L_\mathrm{a}^2}\,, \qquad \lambda = \frac{L_\mathrm{b}^2}{L_\mathrm{a}^2}\,,$$

Effect of substratum elasticity



$$\hat{k}_b = \frac{k_b}{k_a}, \qquad \hat{k}_s = \frac{k_s}{k_a}, \qquad \hat{k}_\theta = \frac{2k_\theta}{k_a L_a^2}, \qquad \lambda = \frac{L_b^2}{L_a^2},$$

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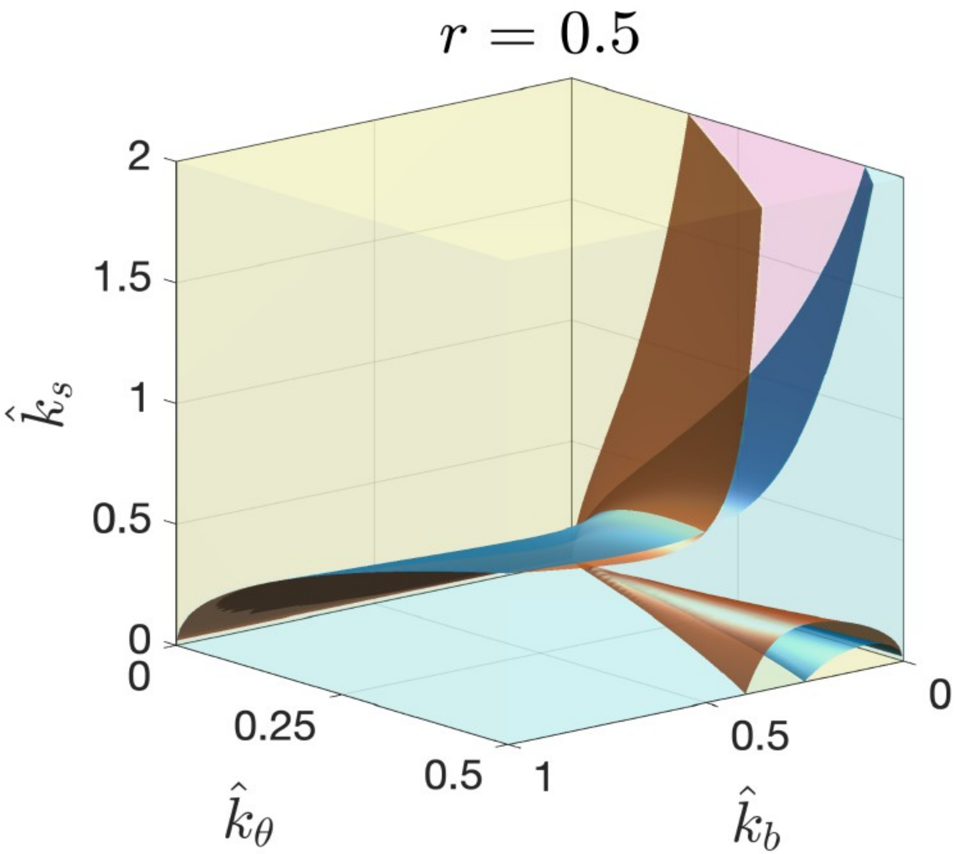
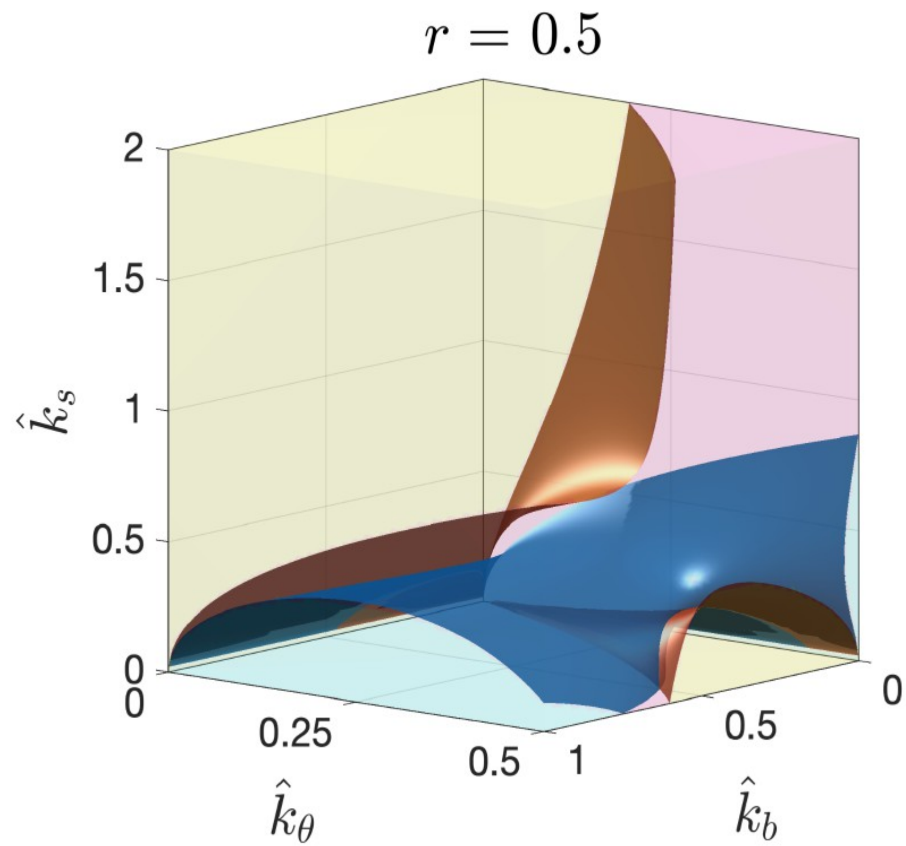
Effect of cell elongation

round cell

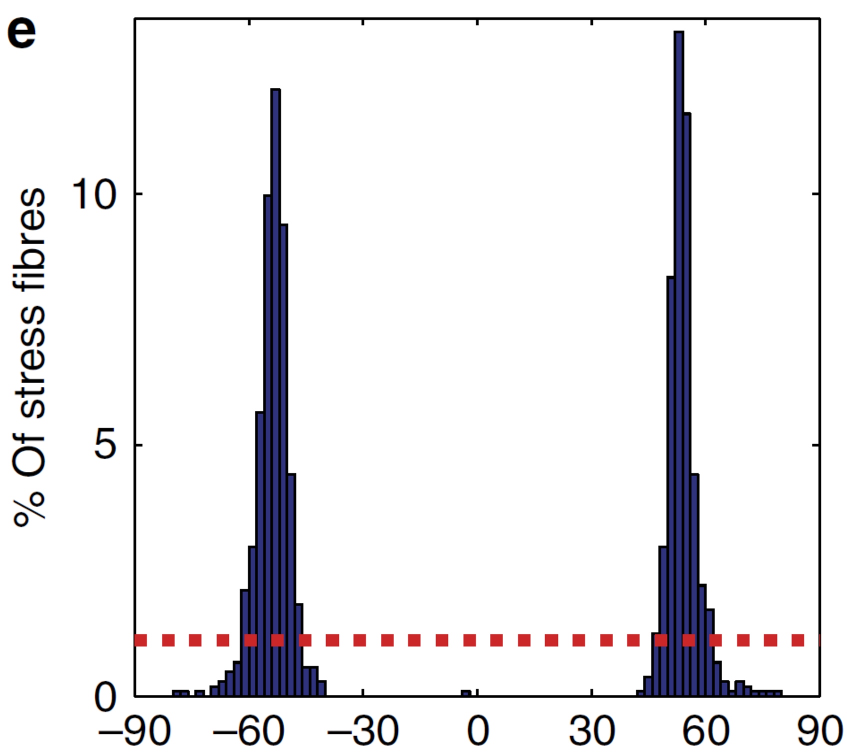


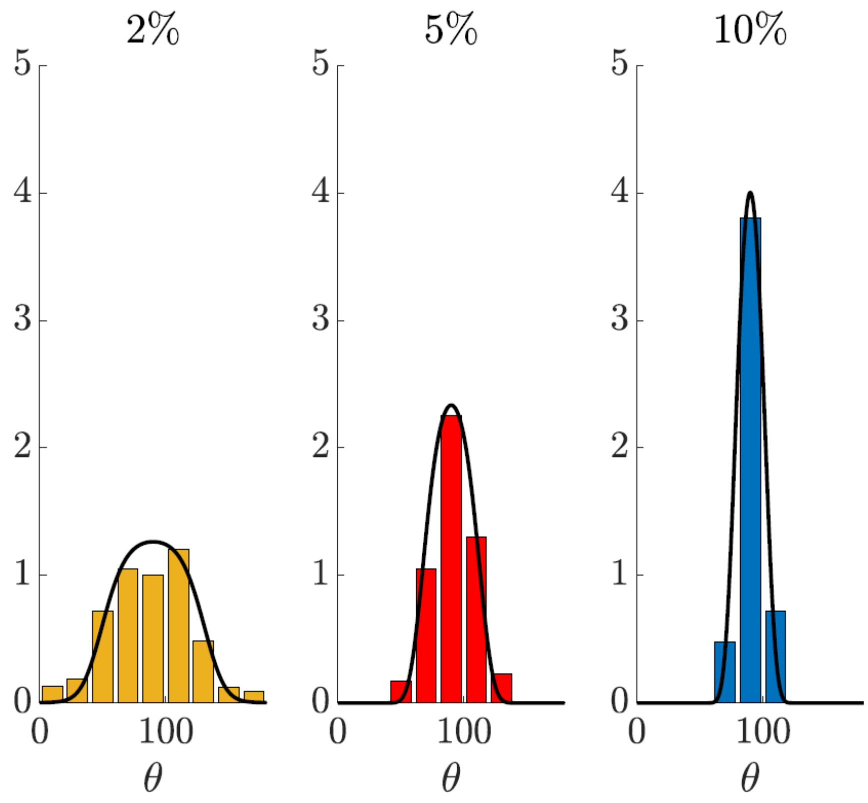
elongated cell $\lambda = 0.5$



Φ^{eq}_{obl} $\Phi^{eq}_{||}$ $\Phi^{eq}_{\perp}$ and $\Phi^{eq}_{||}$ $\Phi^{eq}_{\perp}$

A kinetic approach





A kinetic approach

π–periodic probability density $f(t,\theta) \ : \quad f(t,\pi-\theta) = f(t,\theta)$

Ito process: $$d\theta = -\frac{\varepsilon^2}{\lambda_\theta}\frac{\partial \bar{\mathcal{U}}}{\partial \theta}dt + \sqrt{\frac{\sigma^2}{\lambda_\theta}}\,dW_t$$

$$\mathcal{U} = k_{44}\varepsilon^2\bar{\mathcal{U}}$$

$$\lambda_\theta = \frac{\eta}{k_{44}}$$

$$\frac{\partial}{\partial t}f(t,\theta) = \frac{\varepsilon^2}{\lambda_\theta}\frac{\partial}{\partial \theta}\left(\frac{\partial \bar{\mathcal{U}}}{\partial \theta}(\theta) f(t,\theta)\right) + \frac{1}{2\lambda_\theta}\frac{\partial^2}{\partial \theta^2}\left(\sigma^2 f(\theta,t)\right)$$

N. Loy & L.P., *Arxiv .org/pdf/2108.00894.pdf*

A kinetic approach

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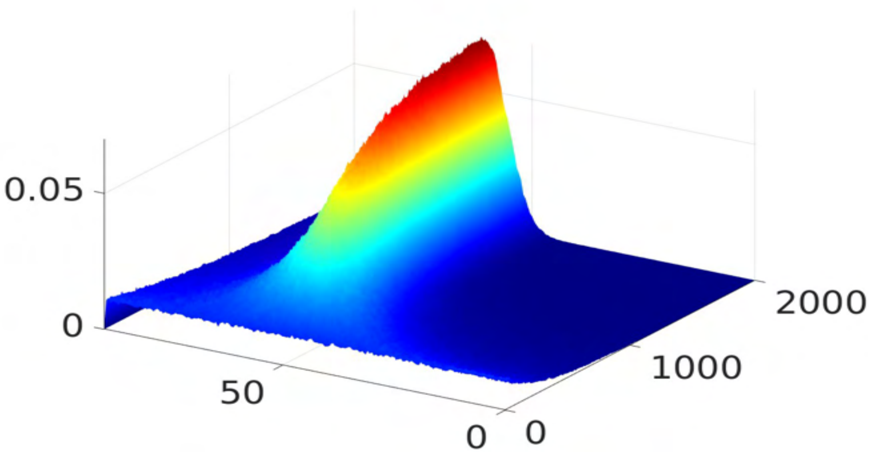
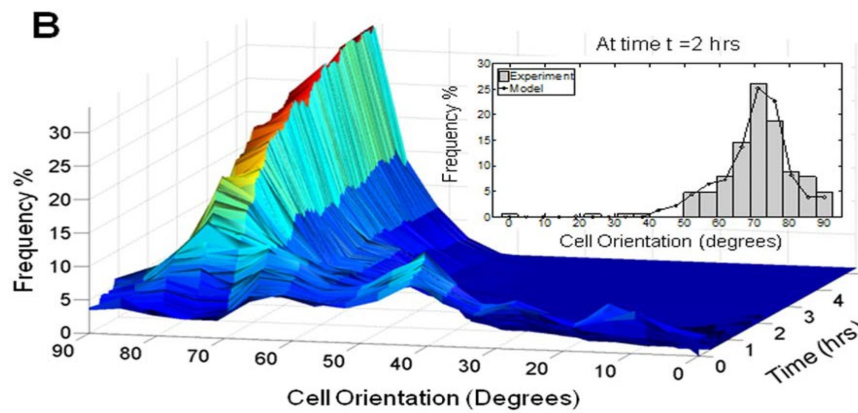




N. Loy & L.P., *Arxiv.org/pdf/2108.00894.pdf*

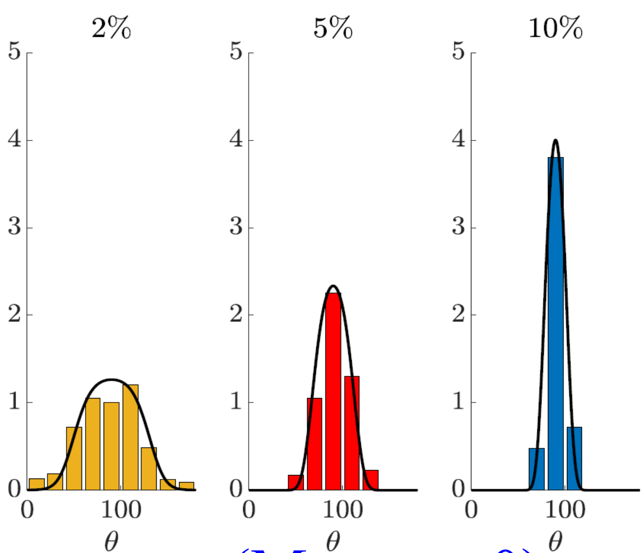
(Morioka)

A kinetic approach

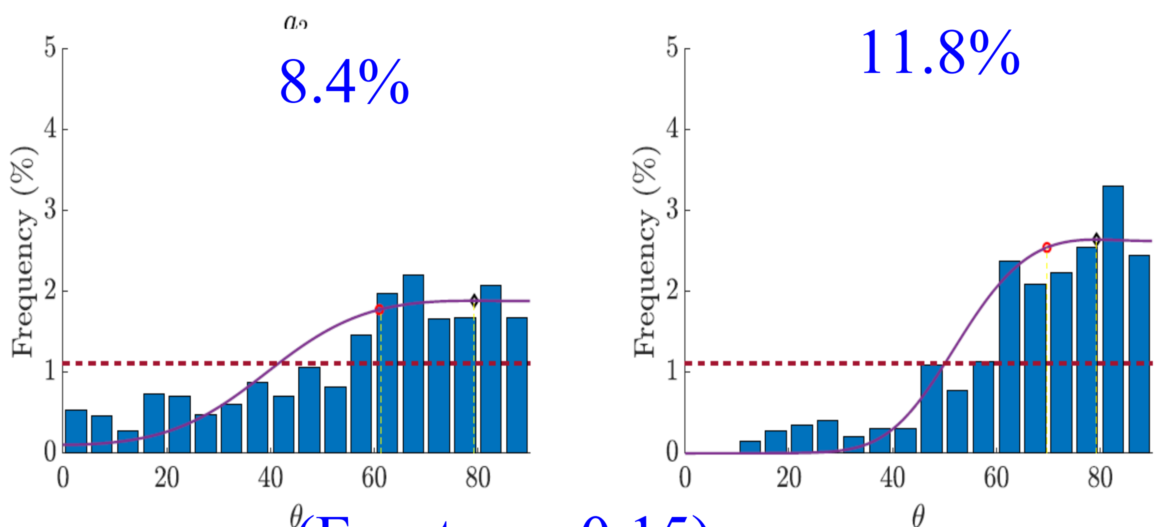
$$\frac{\partial}{\partial t} f(t,\theta) = \frac{\varepsilon^2}{\lambda_\theta} \frac{\partial}{\partial \theta} \left(\frac{\partial \bar{\mathcal{U}}}{\partial \theta}(\theta) f(t,\theta) \right) + \frac{1}{2\lambda_\theta} \frac{\partial^2}{\partial \theta^2} \left(\sigma^2 f(\theta,t) \right)$$

Equilibrium distribution $$f^\infty(\theta) = C \exp\left(-\frac{\bar{\mathcal{U}}(\theta)}{\bar{\sigma}^2} \right)$$

$$\bar{\sigma}^2 = \frac{\sigma^2}{2\varepsilon^2}$$



(Mao, r = 0)



(Faust, $r = 0.15$)

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Cell reorientation as a control problem

$$\theta' = \theta + \nu\psi_{opt}, \quad \psi_{opt} = \mathrm{argmin}_{\psi}\mathcal{J}(\psi),$$

$$\mathcal{J}(\psi) = \nu\frac{\psi^2}{2} + \langle g(\theta')\rangle$$

$$\psi_{opt} + \left\langle \frac{dg}{d\theta'}(\theta')\Big|_{\theta'=\theta+\nu\psi_{opt}} \right\rangle = 0$$

$$g = \varepsilon^2\bar{\mathcal{U}} \quad \Longrightarrow \quad \frac{\partial}{\partial t}f(t,\theta) = \frac{\varepsilon^2(t)}{\lambda_\theta}\frac{\partial}{\partial\theta}\left(\frac{\partial\bar{\mathcal{U}}}{\partial\theta}(\theta)f(t,\theta)\right) + \frac{1}{2\lambda_\theta}\frac{\partial^2}{\partial\theta^2}\left(\sigma^2 f(\theta,t)\right)$$

Cell reorientation as a control problem

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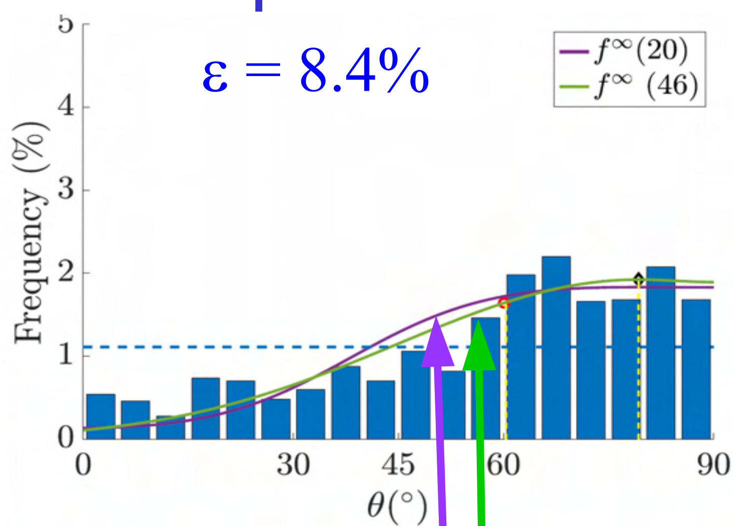
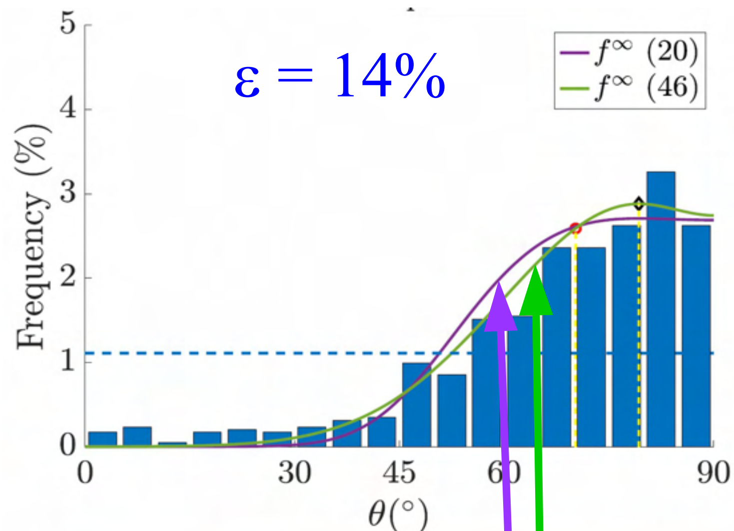
$$\psi_{opt} + \left\langle \frac{dg}{d\theta'}(\theta')\Big|_{\theta'=\theta+\nu\psi_{opt}} \right\rangle = 0$$

$$g(\theta') = \frac{\varepsilon^2}{2}[\theta' - \hat{\theta}(\theta)]^2 \Rightarrow \psi_{opt} = -\frac{\varepsilon^2}{1+\nu\varepsilon^2}(\theta - \hat{\theta})$$

$$\Rightarrow \frac{\partial}{\partial\tau}f(\tau,\theta) = -\frac{\varepsilon^2}{\lambda_\theta}\frac{\partial}{\partial\theta}\left[(\hat{\theta}(\theta) - \theta)f(\tau,\theta)\right] + \frac{1}{2\lambda_\theta}\frac{\partial^2}{\partial\theta^2}\left[\sigma_c^2 f(\tau,\theta)\right]$$

Cell reorientation as a control problem





$$g = \varepsilon^2 \bar{\mathcal{U}} \quad \Rightarrow \quad \frac{\partial}{\partial t} f(t,\theta) = \frac{\varepsilon^2(t)}{\lambda_\theta}\frac{\partial}{\partial\theta}\left(\frac{\partial\bar{\mathcal{U}}}{\partial\theta}(\theta) f(t,\theta)\right) + \frac{1}{2\lambda_\theta}\frac{\partial^2}{\partial\theta^2}\left(\sigma^2 f(\theta,t)\right)$$

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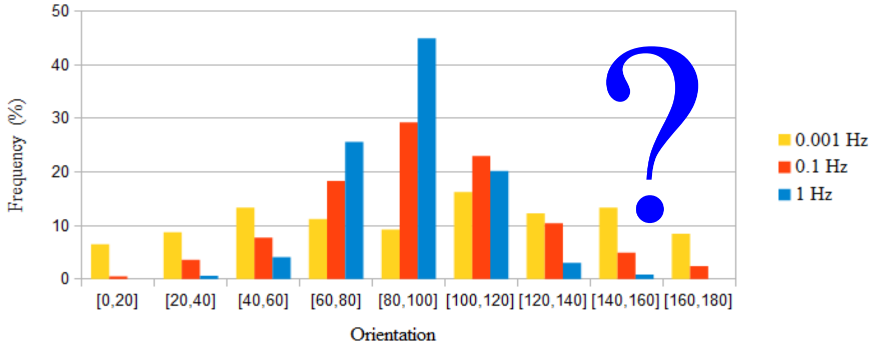
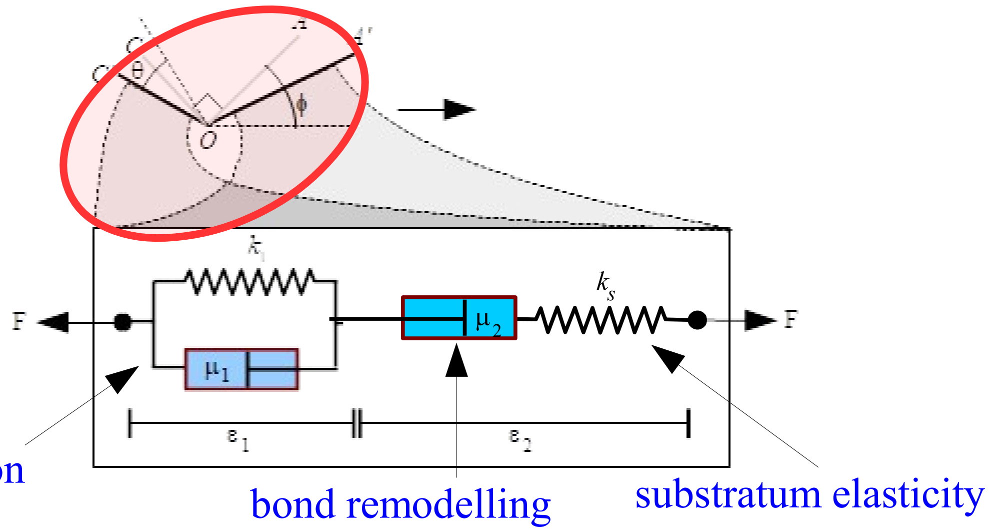
What's next

- Viscoelastic effects in kinetic and discrete models





- Building (on demand) heterogeneous and anisotropic tissues by non-homogeneous deformations

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(Effect of substratum elasticity)
- A. Colombi, L.P., M. Scianna, *Bull. Math. Biol.* **85**, 79 (2023)

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(Review)
- C. Giverso, N. Loy, G. Lucci, L.P., *J. Theor. Biol.* **572**, 111564 (2023)