Modelling Cross-Linking in Collagen Fibrils

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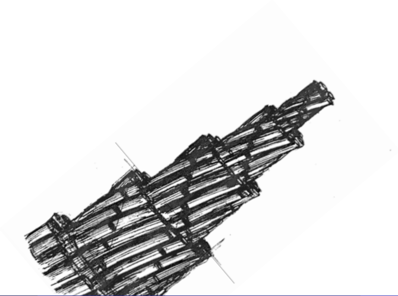


Collagen Fibrils

- Collagen fibrils are a principal structural component of many animal tissues such as tendons, bones, cartilage, and corneas.
- A fibril is a nematic liquid crystal composed of tropocollagen molecules oriented along a director field $\boldsymbol{n}$.

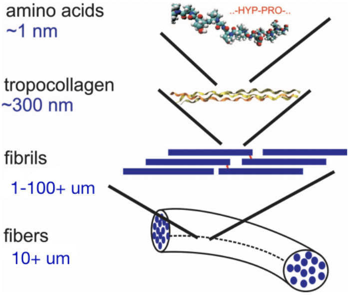
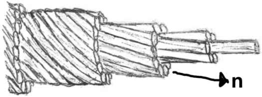


Figure: Adapted from Buehler *et al.* *PNAS*, (2006).



D-Band

Collagen fibrils are characterized by a periodic striation called a D-Band. Due to the arrangement of molecules within the fibril, a density modulation with a period of ≈ 67nm can be seen.

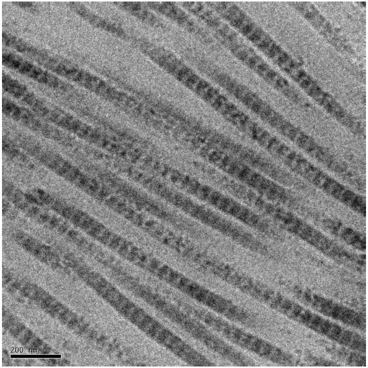


Figure: Sherman *et al.* *Acta Biomaterialia*, (2017).

Cross-linking

Collagen fibrils are held together by enzymatic cross-links (made by Lysyl Oxidase or LOX), spring-like molecules that connect two tropocollagen filaments at specific sites along their lengths.

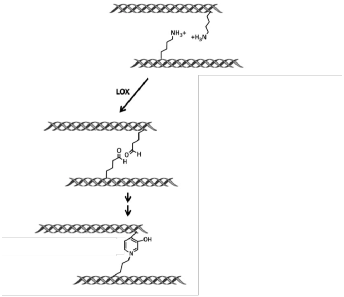


Figure: Perła-Kajan *et al.* *FASEB Journal*, (2016)

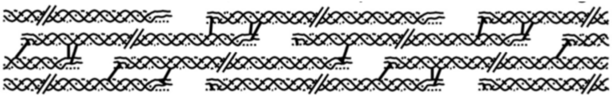


Figure: Kaku *et al.* *Journal of Prosthodontic Research*, (2014).

Questions:

- How does the structure of a cross-linked fibril determine its elastic properties?
- How does the structure of a cross-linked fibril change in response to mechanical strain?

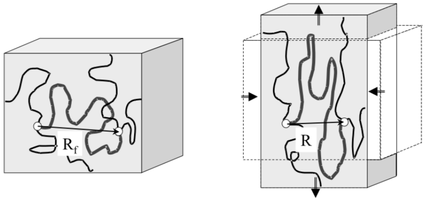
Cross-links Modelled as Gaussian Springs

We model cross-links as entropic springs with end-to-end distance $\boldsymbol{R}$:

$$P(\boldsymbol{R}) = \left[\left(\frac{3}{2\pi L}\right)^3 \frac{1}{\mathrm{Det}[\underline{\underline{\boldsymbol{\ell}}}_0]}\right]^{1/2} \exp\left(-\frac{3}{2L}\boldsymbol{R}^\top \underline{\underline{\boldsymbol{\ell}}}_{\boldsymbol{0}}^{\boldsymbol{-1}} \boldsymbol{R}\right). \tag{1}$$

Here $\underline{\underline{\boldsymbol{\ell}}}_0$ is a tensor describing the structure of the fibril and its cross-links. We define $\zeta = \ell_{||}/\ell_\perp$ to be the anisotropy ratio.

$$\underline{\underline{\boldsymbol{\ell}}}_0 = \underline{\underline{\boldsymbol{\delta}}} + [\zeta - 1]\boldsymbol{n_0} \otimes \boldsymbol{n_0}. \tag{2}$$



Warner and Terentjev, "Nematic elastomers – a new state of matter?" *Progress in Polymer Science* (1996).

Free Energy

The free energy density for a cross-linked liquid crystal elastomer subjected to a strain field $\underline{\underline{\boldsymbol{\lambda}}}$ is:

$$\boxed{f_{\text{Cross-Link}} = \frac{1}{2}\rho k_B T \ \mathrm{Tr}(\underline{\underline{\boldsymbol{\ell}}}_0 \underline{\underline{\boldsymbol{\lambda}}}^\top \underline{\underline{\boldsymbol{\ell}}}^{-1} \underline{\underline{\boldsymbol{\lambda}}}).} \tag{3}$$

Here ρ is the cross-linking density, and $\underline{\underline{\boldsymbol{\ell}}}$ is a tensor describing the post-strain fibril structure.

The volume averaged free energy density is:

$$E_{\text{Cross-Link}} = \frac{2}{R^2}\int_0^R f_{\text{Cross-Link}} r dr.$$

Free Energy

- Total Free Energy:

$$\begin{aligned} E_{\text{Total}} = & \, E^*_{\text{Surface}} \\ & + E_{\text{Frank}}(\underline{\underline{\boldsymbol{\ell}}})^* \\ & + E_{\text{D-Band}}(\delta, \eta, \underline{\underline{\boldsymbol{\ell}}}, \underline{\underline{\boldsymbol{\lambda}}})^* \\ & + E_{\text{Cross-Link}}(\mu, \zeta, \underline{\underline{\boldsymbol{\ell}}}_0, \underline{\underline{\boldsymbol{\ell}}}, \underline{\underline{\boldsymbol{\lambda}}}) \end{aligned}$$

- Procedure:

$$\text{Minimize } E_{\text{Total}} \underset{\text{Numerically}}{\Longrightarrow} \begin{cases} \text{Post-strain fibril structure } \underline{\underline{\boldsymbol{\ell}}} \\ \text{Stress field } \underline{\underline{\boldsymbol{\sigma}}} \ \left(\sigma_{ij} = \frac{\partial F}{\partial \lambda_{ij}}\right) \end{cases}$$

*Cameron, Kreplak, and Rutenberg. Submitted to *Physical Review Research*, 2019.

Double Twist Structure

Our ansatz:

$$\boldsymbol{n_0} = -\sin\psi(r)\hat{\boldsymbol{\phi}} + \cos\psi(r)\hat{\boldsymbol{z}}. \quad (4)$$

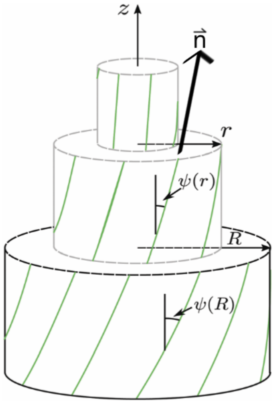


Figure: Cameron, Kreplak, and Rutenberg. *Soft Matter*, (2018).

Imposed Twist Phases

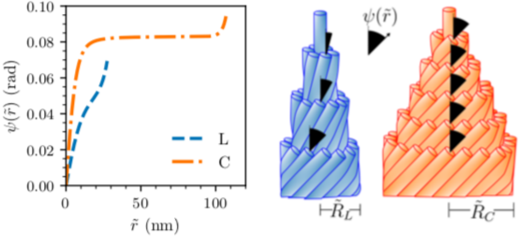


Figure: Cameron, Kreplak, and Rutenberg. *Unpublished,* (2019).

We consider two functional forms (phases) for $\psi(r)$:

- $\psi(r) = \alpha r$ (linear twist phase) (e.g. Tendon Fibrils),
- $\psi(r) = \beta \cdot \mathbb{1}_{[\frac{1}{10}R,R]}$ (constant twist phase) (e.g. Corneal Fibrils).

$\underline{\underline{\boldsymbol{\lambda}}}$: Strain Field

- We consider a longitudinal extension of the fibril by a factor of ϵ.

$$(L \to L \cdot \epsilon)$$

- We assume the fibril to be incompressible ($\mathrm{Det}(\underline{\underline{\boldsymbol{\lambda}}}) = 1$).

$$(R \to R/\sqrt{\epsilon})$$

- We assume the D-band strain is equal to the fibril strain.

$$(\eta \to \eta/\epsilon)$$

$\delta = 0$: Equilibrium Twist Angle

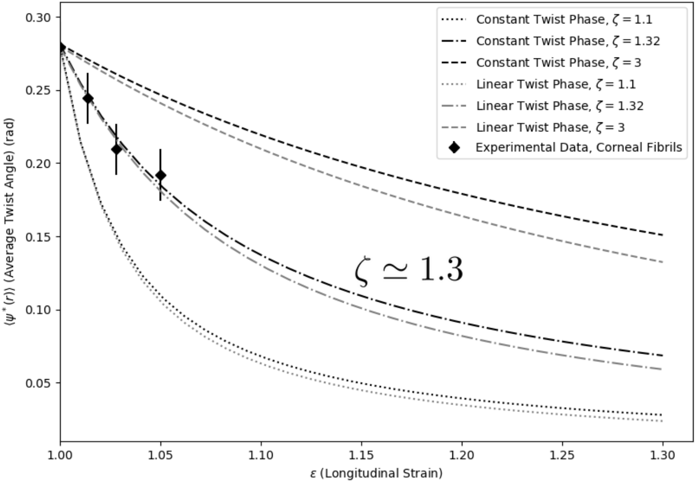


Figure: Data from Bell *et al.* *Acta Biomaterialia*, (2017).

$\delta = 0$: Stress-Strain Curves

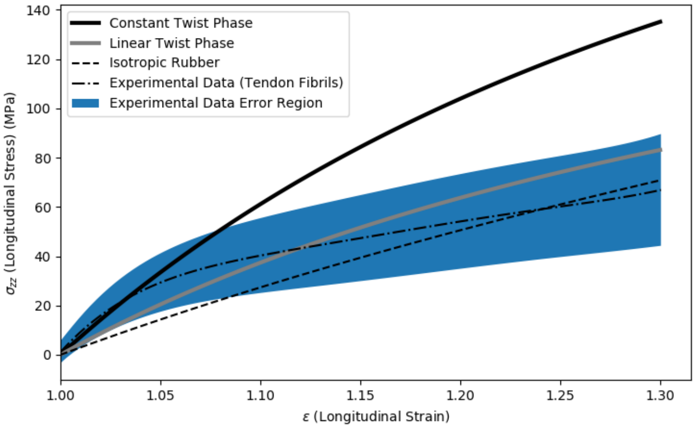


Figure: Data from Quigley, ..., and Kreplak. *Scientific Data,* (2018).

How does strain affect the D-band?

There is conflicting experimental evidence:

- Some experiments have found that the D-band amplitude remains constant with strain (**A**) ,
- Other experiments have seen the D-band disappear for strains beyond 4% (**B**).

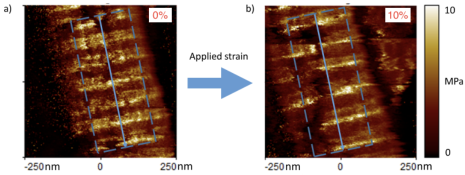


Figure: **A)** Peacock and Kreplak. *Nanoscale*, (2019).

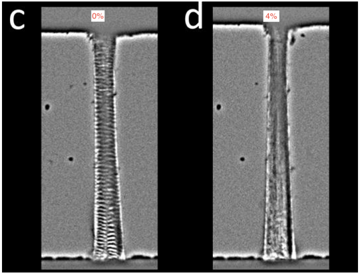


Figure: **B)** Buckley *et al. Journal of Biomechanics*, (2013).

D-Band Free Energy

The volume-averaged free energy density due to D-Band contributions is:

$$E_{\text{D-Band}} = \frac{\Lambda\delta^2}{2R^2}\int_0^R \left(\frac{4\pi^2}{d_{\|}^2} - \eta^2\cos^2\psi(r)\right)^2 r\,\mathrm{d}r + \frac{\omega\delta^2}{2}\left(\frac{3\delta^2}{4} - \delta_0^2\right).$$

Here $d_{\|}$ is the expected D-band period in the absence of molecular twist, Λ characterizes the D-band stiffness, and ω characterizes the energetics of D-band formation.

δ and η are the D-band amplitude and wavenumber, respectively.

D-Banded Fibrils: Molecular Twist Angle

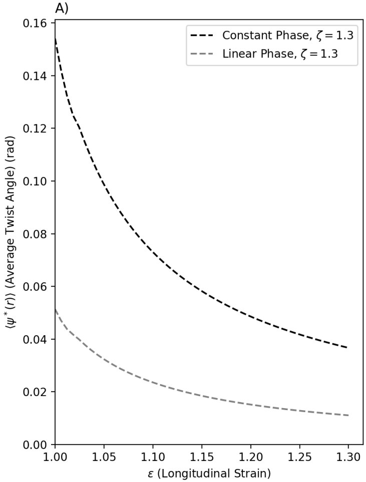


Figure: Variable δ

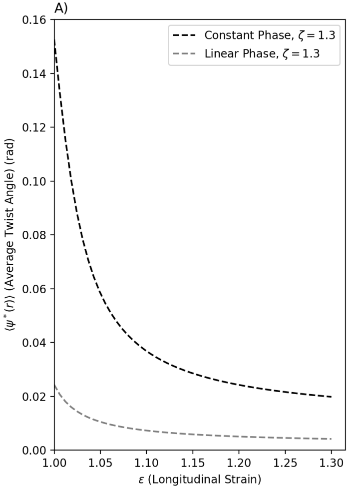


Figure: Constant δ

D-Banded Fibrils: Stress-Strain Curves

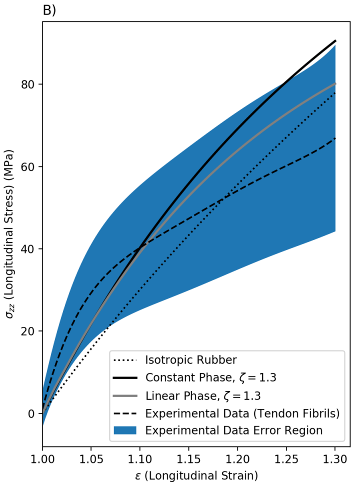


Figure: Variable δ

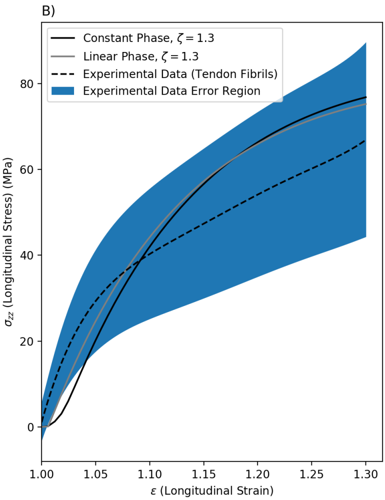


Figure: Constant δ

D-Banded Fibrils: D-Band Amplitude

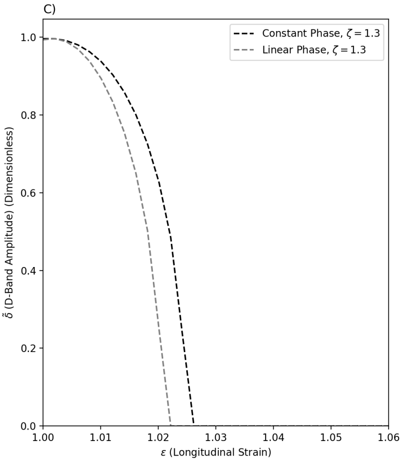


Figure: Variable δ

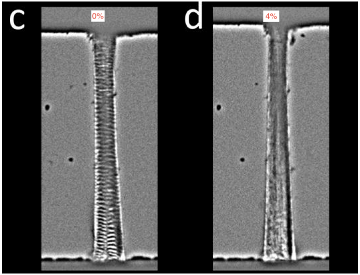


Figure: Buckley *et al. Journal of Biomechanics*, (2013).

Next Steps and Open Questions

Next Term:

- Consider a general twist angle function $\psi(r)$
- Better understand the interplay between the D-band and Cross-linking

Future work/Open questions:

- Consider non-constant cross-link density
- Consider finitely extensible cross-links

Thanks!

Form of the Anisotropy Tensor

$$\underline{\underline{\boldsymbol{\ell}}}_0 = \ell_\perp \underline{\underline{\boldsymbol{\delta}}} + [\ell_\parallel - \ell_\perp]\boldsymbol{n_0} \otimes \boldsymbol{n_0}$$
$$= \ell_\perp \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 + (\zeta - 1)\sin^2\psi & (1-\zeta)\sin\psi\cos\psi \\ 0 & (1-\zeta)\sin\psi\cos\psi & 1 + (\zeta - 1)\cos^2\psi \end{bmatrix},$$

where $\zeta = \ell_\parallel / \ell_\perp$. (5)

$$\underline{\underline{\boldsymbol{\ell}}}^{-1} = 1/\ell_\perp \underline{\underline{\boldsymbol{\delta}}} + [1/\ell_\parallel - 1/\ell_\perp]\boldsymbol{n} \otimes \boldsymbol{n}$$
$$= \ell_\perp^{-1} \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1+(\zeta^{-1}-1)\sin^2\psi^* & (1-\zeta^{-1})\sin\psi^*\cos\psi^* \\ 0 & (1-\zeta^{-1})\sin\psi^*\cos\psi^* & 1+(\zeta^{-1}-1)\cos^2\psi^* \end{bmatrix},$$

where ψ^* is the post-strain twist angle.

Frank Free Energy

The Frank free energy describes the energy contributions from the spatial arrangement of the tropocollagen filaments inside the fibril. For our double-twist director field $\boldsymbol{n}(\psi)$, the Frank free energy density is:

$$\begin{aligned} f_{\text{Frank}} = &\frac{1}{2}K_{22}\left(\frac{K_2}{K_{22}} - \psi' - \frac{\sin(2\psi)}{2r}\right)^2 \\ &+ \frac{1}{2}K_{33}\frac{\sin^4(\psi)}{r^2} \\ &- \frac{1}{2}(K_{22}+K_{24})\frac{1}{r}\frac{d}{dr}\left(\sin^2(\psi)\right). \end{aligned} \tag{6}$$

Here $K_2, K_{22}, K_{24}, K_{33}$ are the standard Frank elastic constants.

Experimental Data

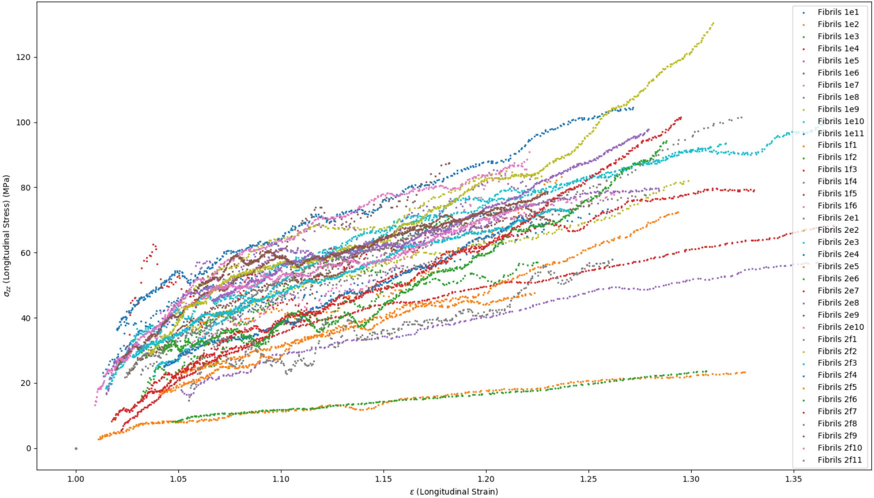


Figure: Data from Quigley, ..., and Kreplak. *Scientific Data,* (2018).