Multiscale Mechanics of Human Skin

E. Mazza

A. E. Ehret, A. Wahlsten, A. Stracuzzi, D. Sachs, B. Müller, A. Martyts, H. Junker, C. Giampietro

Dept. of Mechanical and Process Engineering, ETH Zurich

Swiss Federal laboratories for Materials Research, Empa Dübendorf, Switzerland

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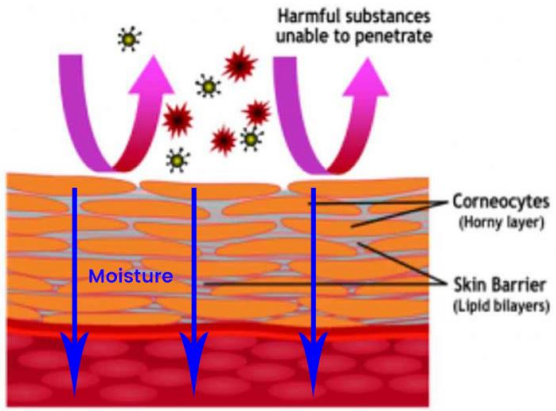
Skin: our largest organ

livescience.com

Mechanical properties of skin are relevant for its many functions, a.o.:

- Barrier (thermal, chemical, electromagnetic, mechanical insults)
- Energy transfer
- Haptics, sense of touch
- Biomechanical processes
- Reservoir for substances
- Visual appearance (influence of age, health status)



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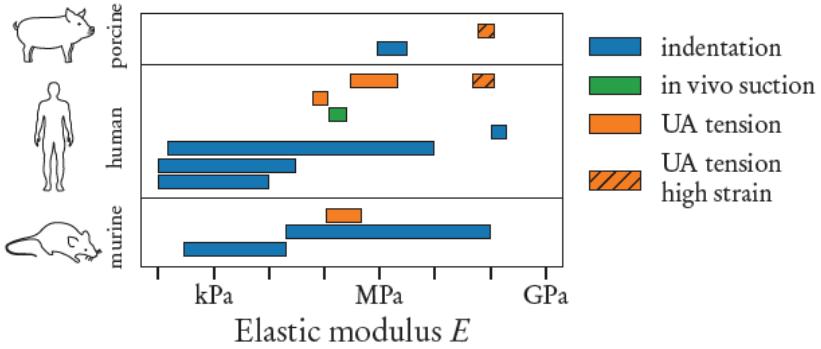
Skin: accessible for mechanical characterization

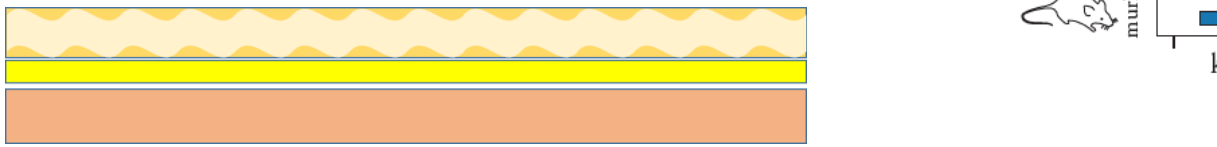
Although easily accessible:

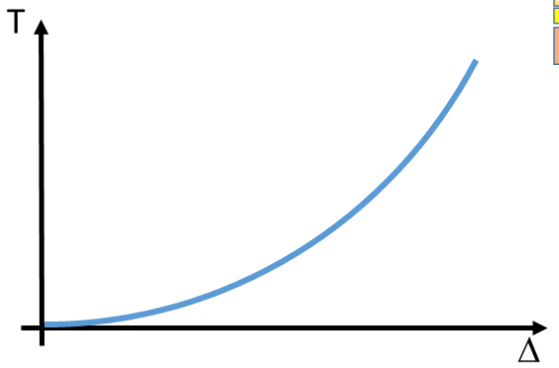
- Difficult to control boundary conditions for mechanical experiments
- Multilayer material, elastic fundament, in-vivo tension

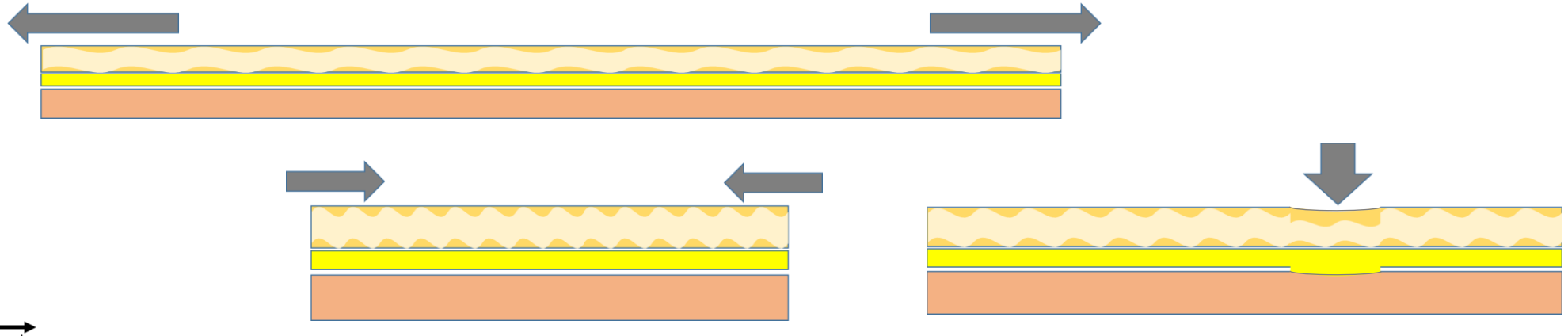
→ Wide range of properties reported in the literature



Wahlsten A., Diss. ETH, 2022







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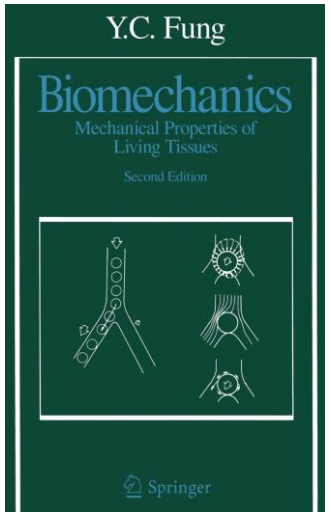
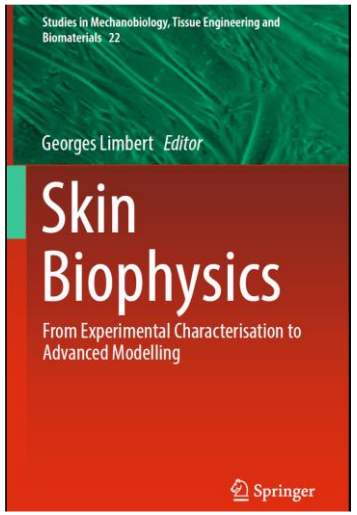
Several constitutive models proposed





Biaxial experiments on rabbit skin have been reported by Lanir and Fung (1974a,b) from whose data Tong and Fung (1976) gleaned the pseudo-strain-energy function for a loading process (increasing strain). The skin specimens

$$\rho_0 W^{(2)} = \tfrac{1}{2}(\alpha_1 E_1^2 + \alpha_2 E_2^2 + \alpha_3 E_{12}^2 + \alpha_3 E_{21}^2 + 2\alpha_4 E_1 E_2) + \tfrac{1}{2} c \exp(a_1 E_1^2 + a_2 E_2^2 + a_3 E_{12}^2 + a_3 E_{21}^2 + 2a_4 E_1 E_2 + \gamma_1 E_1^3 + \gamma_2 E_2^3 + \gamma_4 E_1^2 E_2 + \gamma_5 E_1 E_2^2),$$

$$\psi = c_1 \{\exp[c_2 (I_1 - 3)] - 1\} - \frac{c_1 c_2}{2}(I_2 - 3) + f(I_3)$$ Veronda-Westmann

$$\psi = c_1 (I_1 - 3) - c_2 (I_2 - 3) + f(I_3)$$ Mooney-Rivlin

$$\psi = \sum_{i+j=1}^{N} c_{ij} (I_1 - 3)^i (I_2 - 3)^j + f(I_3)$$ Polynomial

$$\psi = \sum_{i=1}^{n} 2\frac{\mu_i}{\alpha_i^2}\left(\lambda_1^{\alpha_i} + \lambda_2^{\alpha_i} + \lambda_3^{\alpha_i} - 3\right)$$ Ogden

$$\psi = (1 - \mathcal{V}_c - \mathcal{V}_e)\frac{\mu}{2}(I_1 - 3) + \sum_k \mathcal{V}_k \sum_\theta \mathcal{R}_k(\theta)\frac{K_k}{2}(\lambda - 1)^2$$ Lanir

$$\psi = \psi^v(J) + \sum_{i=1}^{2}\left[\psi_i^{\bar\lambda}(\bar\lambda_i) + \widehat{\psi}_i^1\left(\alpha_1^i\right) + \tilde{\psi}_i^2\left(\alpha_2^i, \bar\lambda_i\right)\right]$$ Gasser-Holzapfel-Ogden

$$\psi = \frac{\mu}{2}(I_1 - 3) + \sum_{i=1}^{2}\frac{k_{i1}}{k_{ki2}}\left(\exp\left\{k_{ki2}[\mathbf{H}_i : \mathbf{C} - 1]^2\right\} - 1\right)$$ Limbert

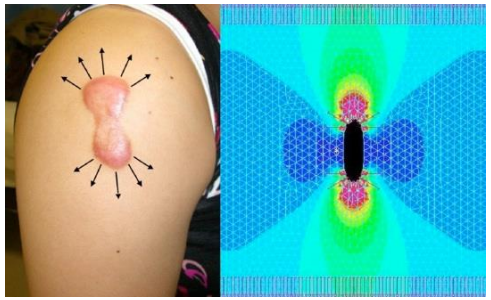
$$\rho_0 \psi = \frac{\mu_0}{2q}[\exp(qg) - 1]$$ Rubin-Bodner

$$g_1 = 2m_1\,[(J - 1) - \ln(J)],\ g_2 = (1 - \omega)m_2(\beta_1 - 3),$$
$$g_3 = 0,\ g_4 = \alpha_1 - 3,$$

Continuum models to describe:
nonlinear, anisotropic, viscoelastic, viscoplastic behavior of skin
Formulations proposed also for skin aging (Mazza, Rubin), skin growth and remodeling (Kuhl, Buganza-Tepole)

Analysis of skin mechanics: applications

Optimize surgery
Diagnosis
Wound healing and scarring
Aging - implications
Cosmetics
Autologous implants (expanders)
Mechanical biocompatibility of wearable devices
Skin tissue engineering
…



Rai Ogawa et al., 2011

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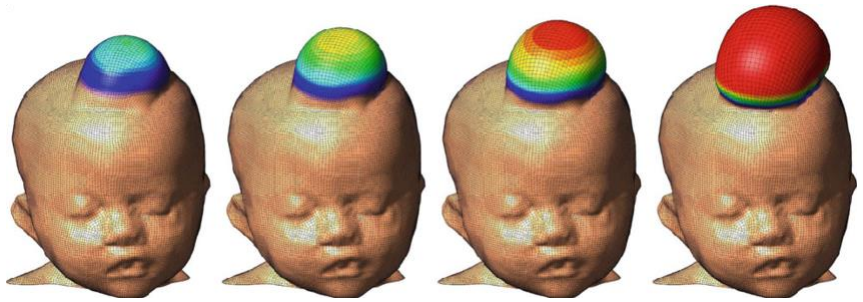
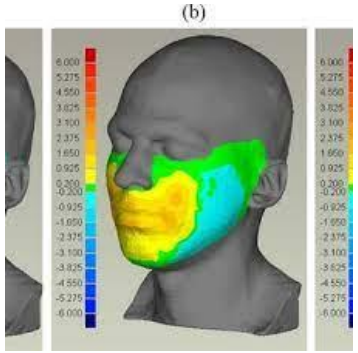


Zöllner et al., 2011



Barbarino et al., 2009

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For each application:
Model assumptions and simplifications might be adequate, or not!

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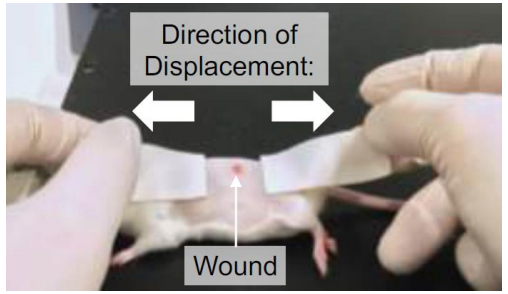
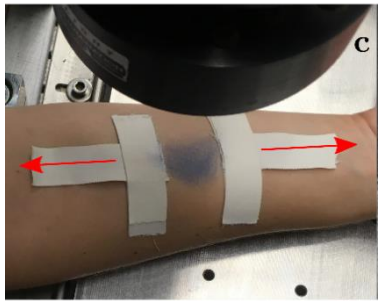
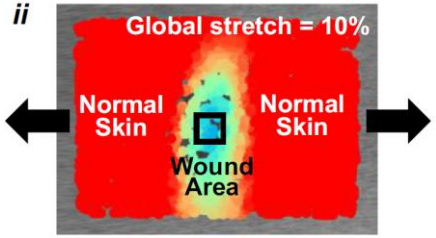
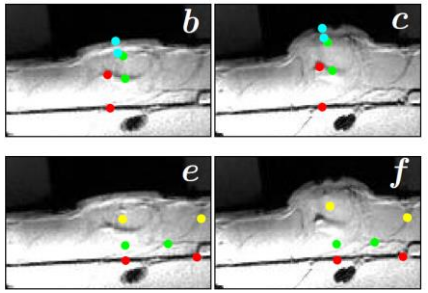
Experimental characterization of skin

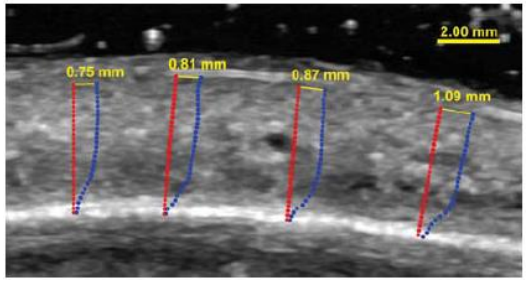
In vivo:



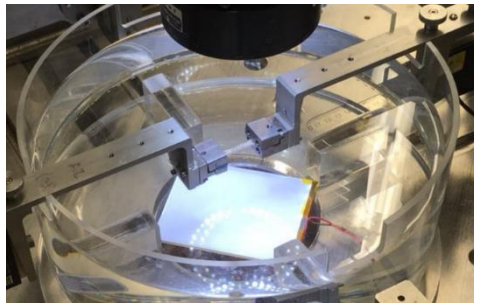


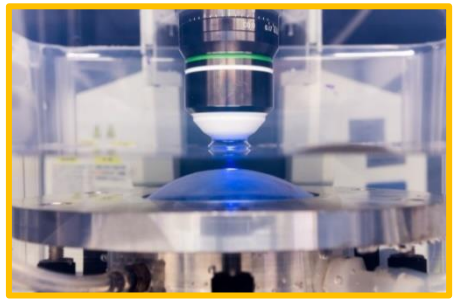


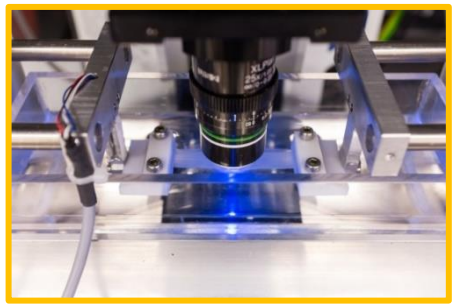


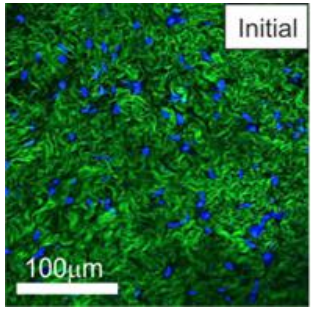


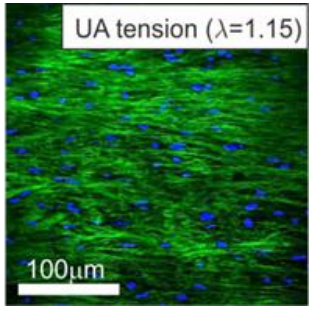
Ex vivo:

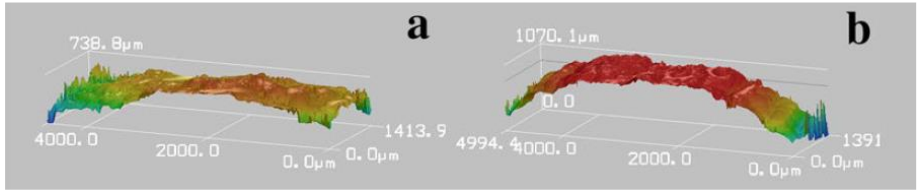




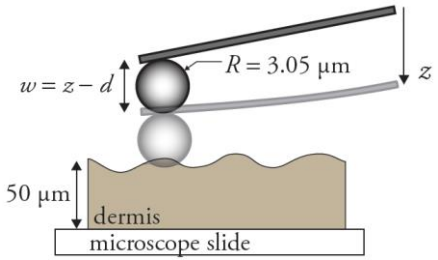


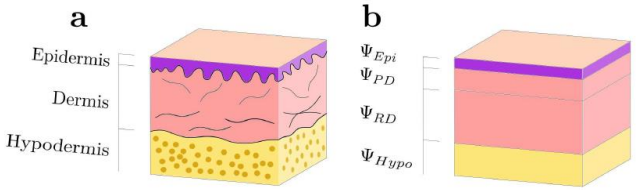






→ Experimental data used to inform multilayer bi-phasic model of skin, see later.





Sachs D. et al., Biomechanics and Modeling in Mechanobiology (2021) 20

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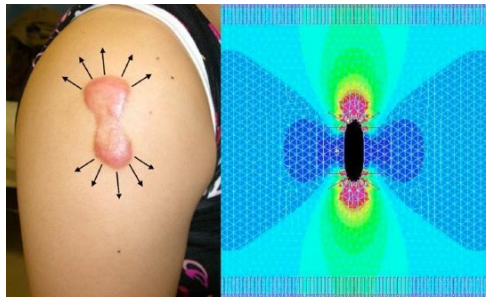
Mechanobiology: cells biophysical environment in stretched skin

Skin stretch influences biological processes (physiology and pathology).

Keoloids correlate with skin tension



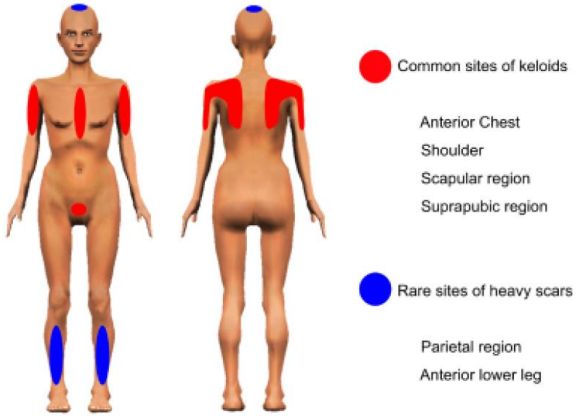
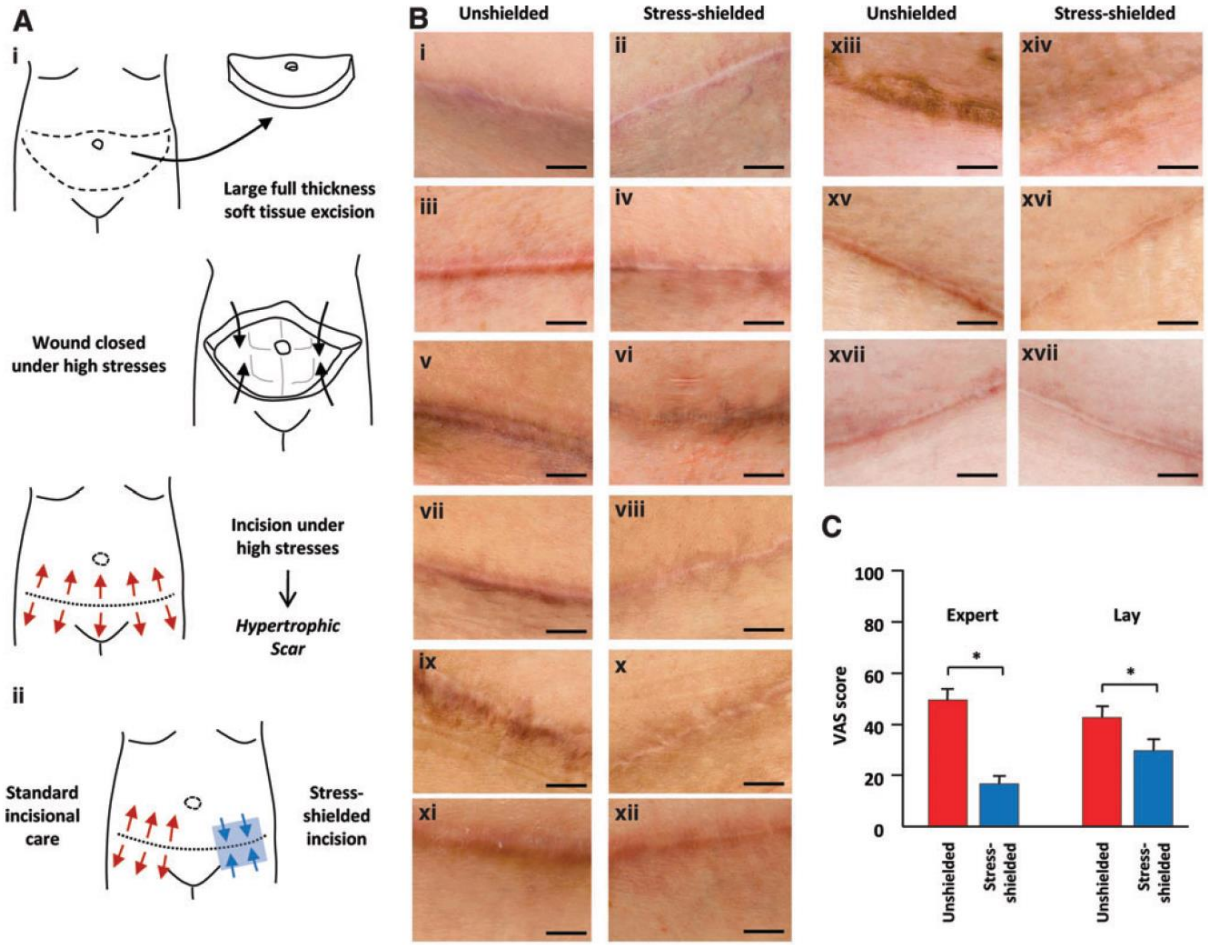


Figure 5. Site specificity of scars. Keloids tend to occur at specific sites, such as on the anterior chest, shoulder, scapula, and suprapubic region. All of these sites are constantly or frequently subjected to mechanical forces, including skin stretch-

Rai Ogawa et al.

Tension shielding reduce scarring



Geoffrey C Gurtner et al.

Skin expanders

How does skin stretch change the physical environment of cells?

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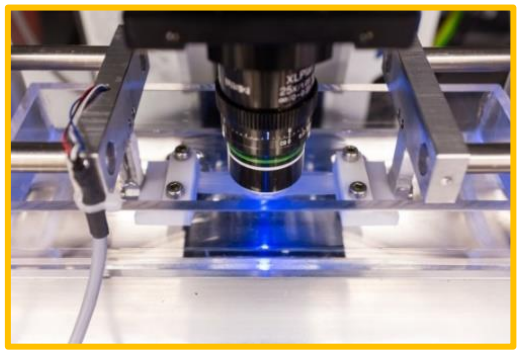
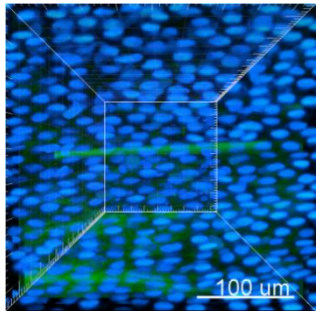
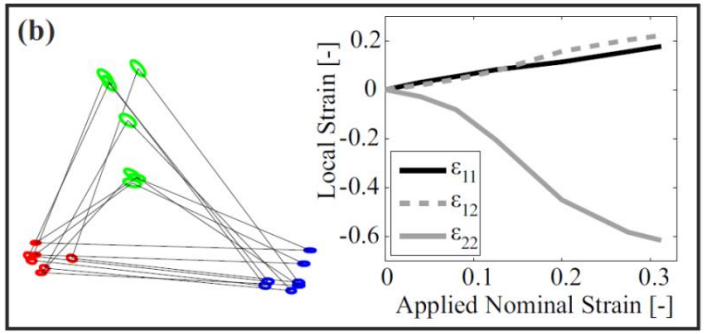
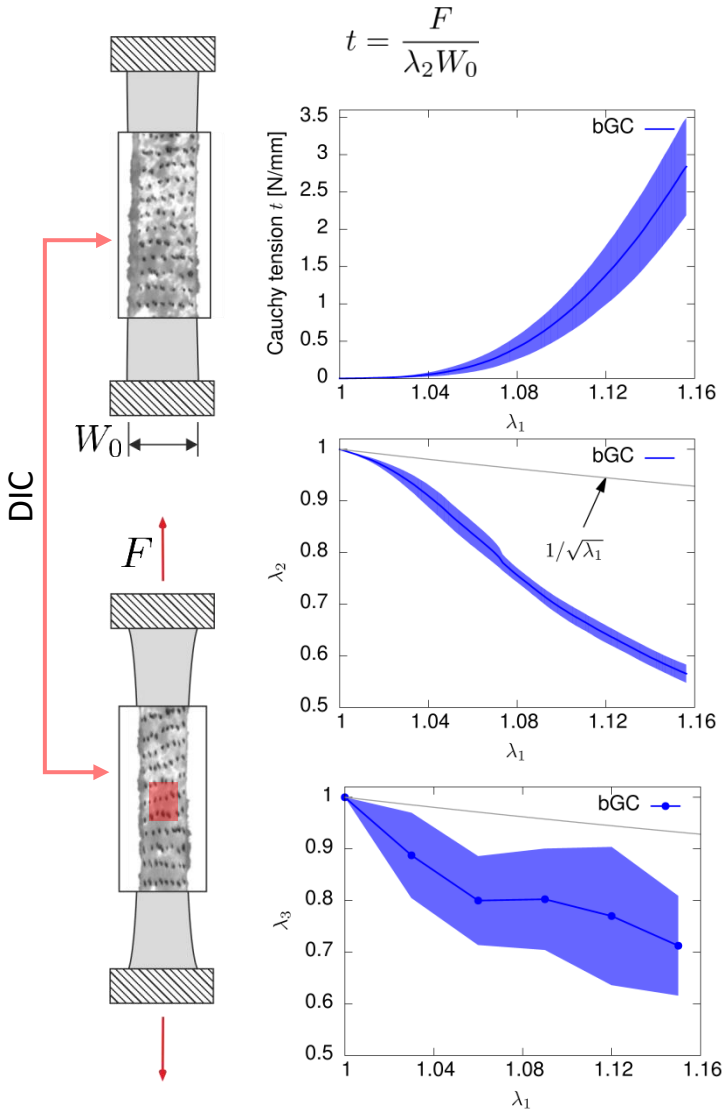
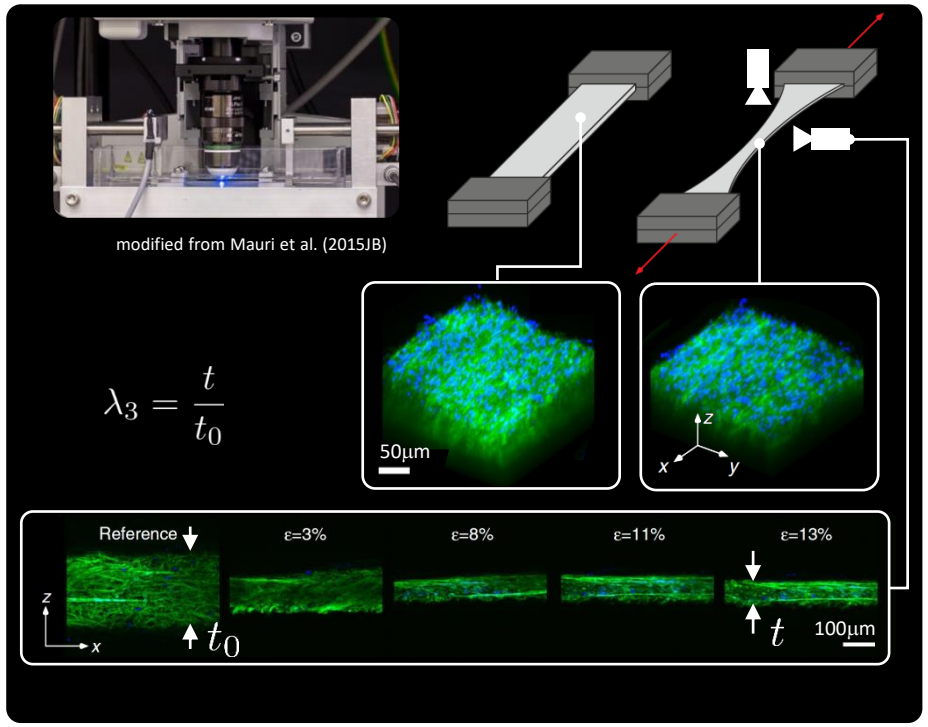
Some insights on deformation behavior of soft collagenous tissues

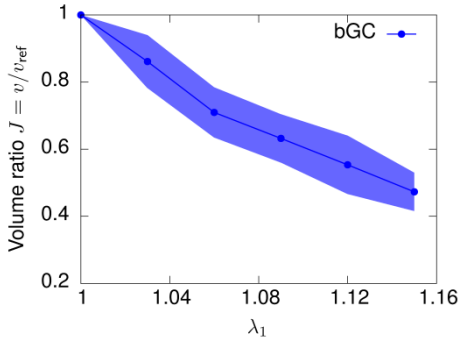












significant volume change!

Buerzle W., Mazza E., 2013, J. Biomechanics, 46; Mauri A. et al., 2013, Placenta, 34; Mauri et al., 2015, J. Biomechanics, 48

Ehret A. et al., 2017, *Nat. Commun.* **8**, 1002.

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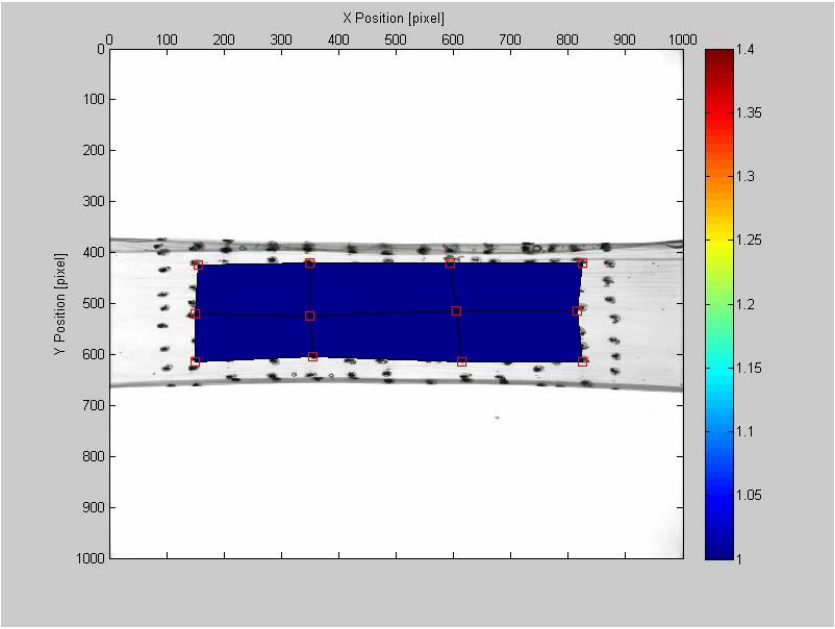
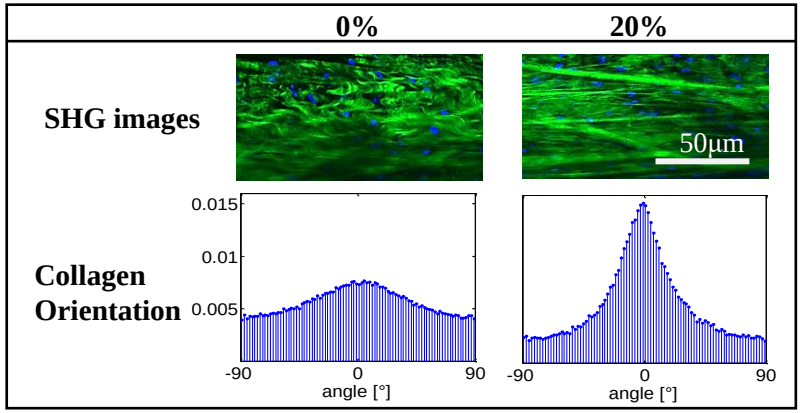
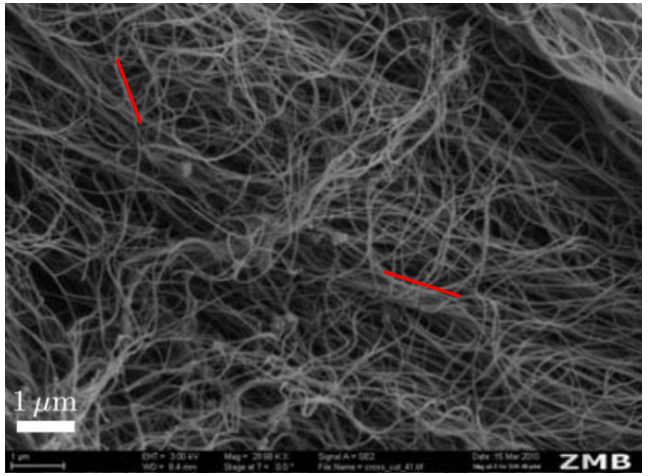
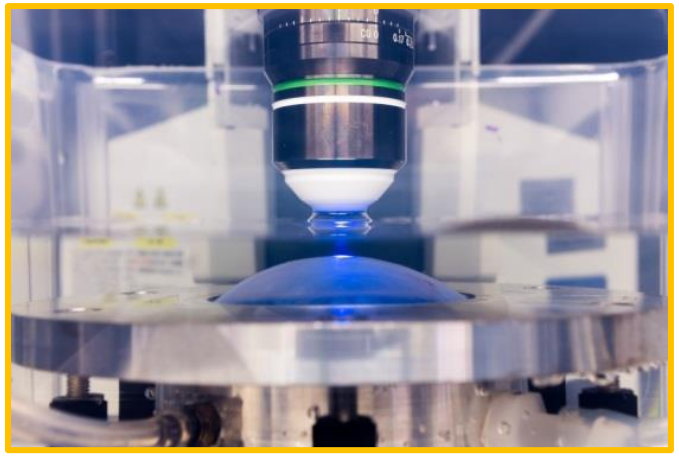
Some insights on deformation behavior of soft collagenous tissues

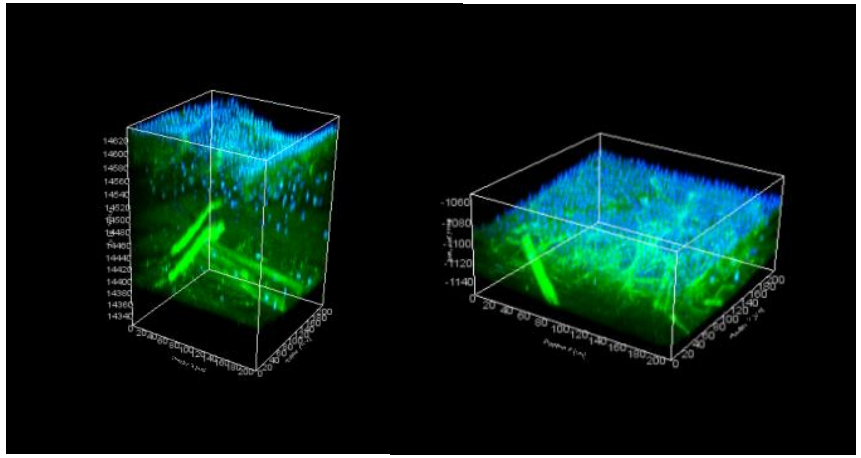




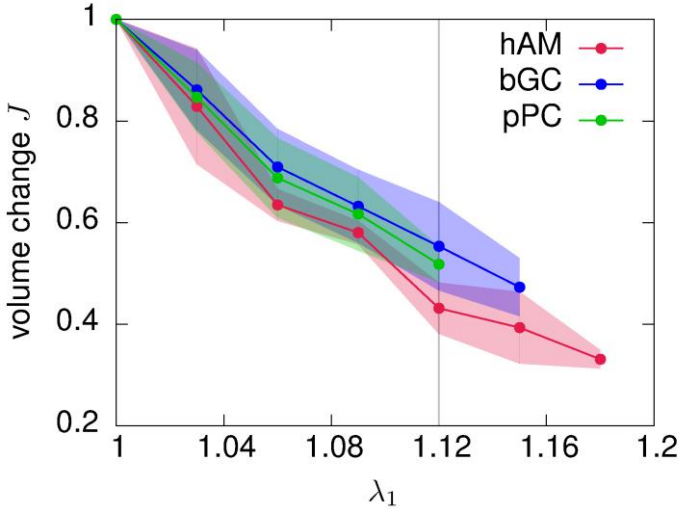
Network of athermal fibers: strong fibers orientation towards loading direction







Volume reduction, liquid retention due to PG



Buerzle W., Mazza E., 2013, J. Biomechanics, 46; Mauri A. et al., 2013, Placenta, 34; Mauri et al., 2015, J. Biomechanics, 48

Ehret A. et al., 2017, *Nat. Commun.* **8**, 1002.

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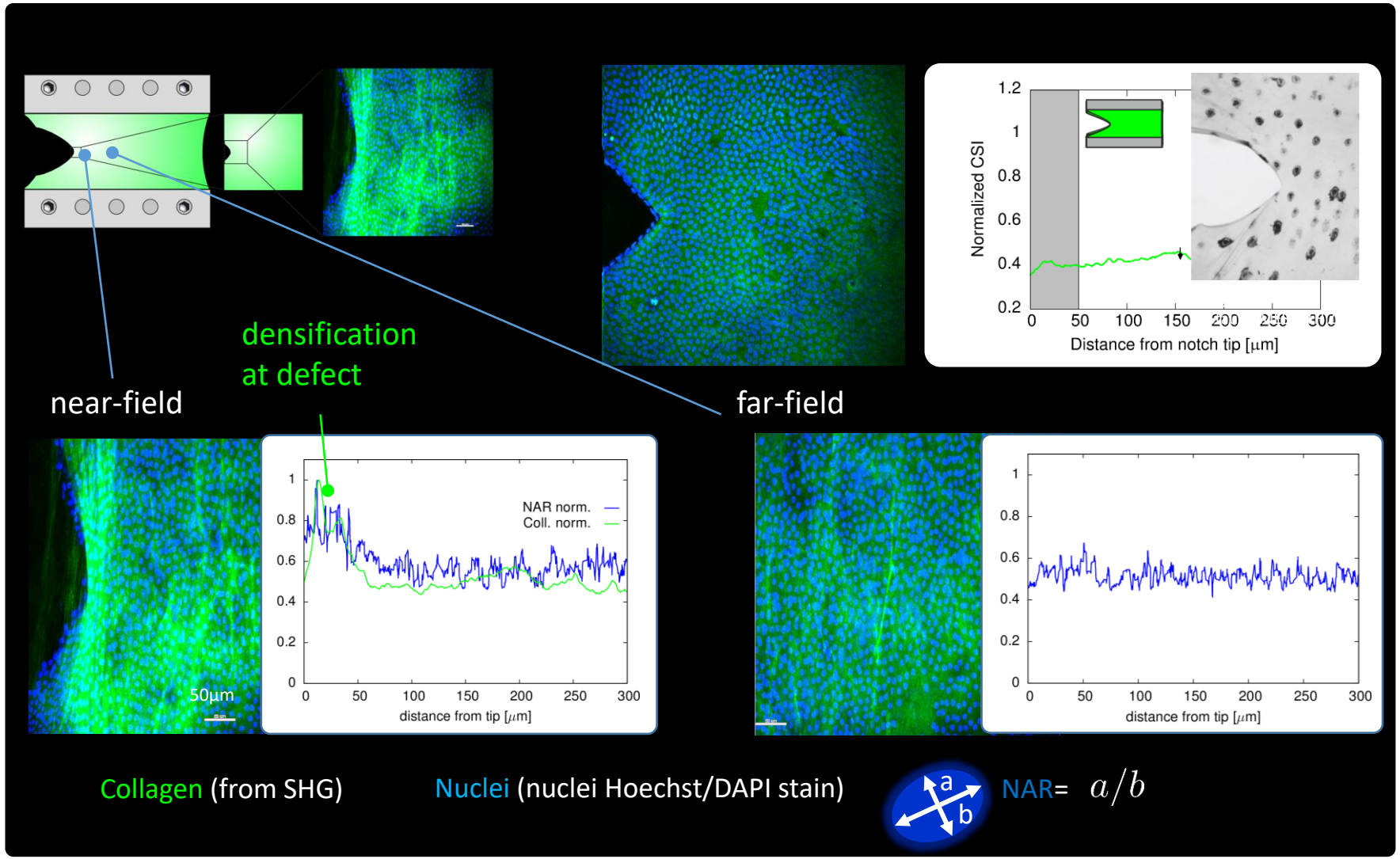
Consequences for fracture behavior

SCT have a small region of enhanced deformation due to compaction of collagen fibers at crack tip



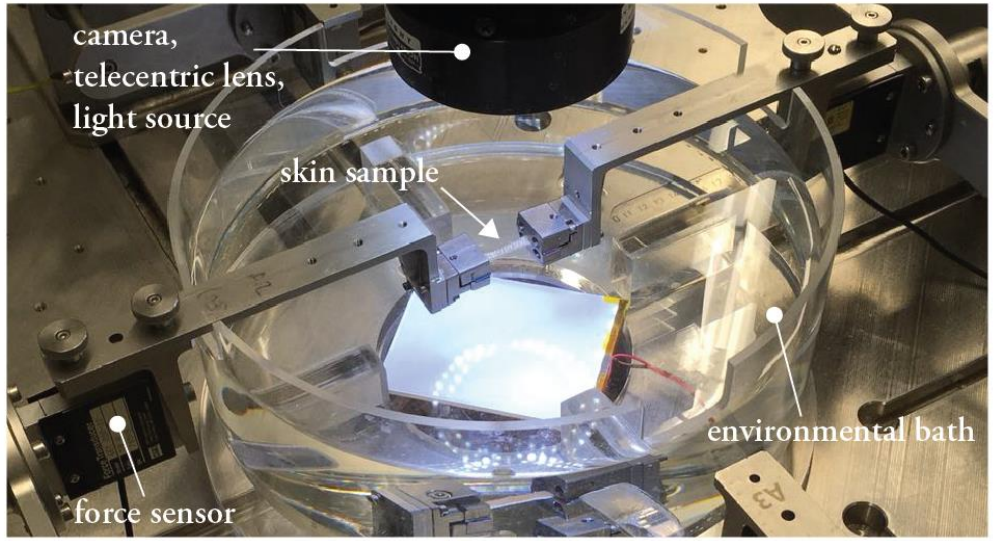
High defect tolerance!

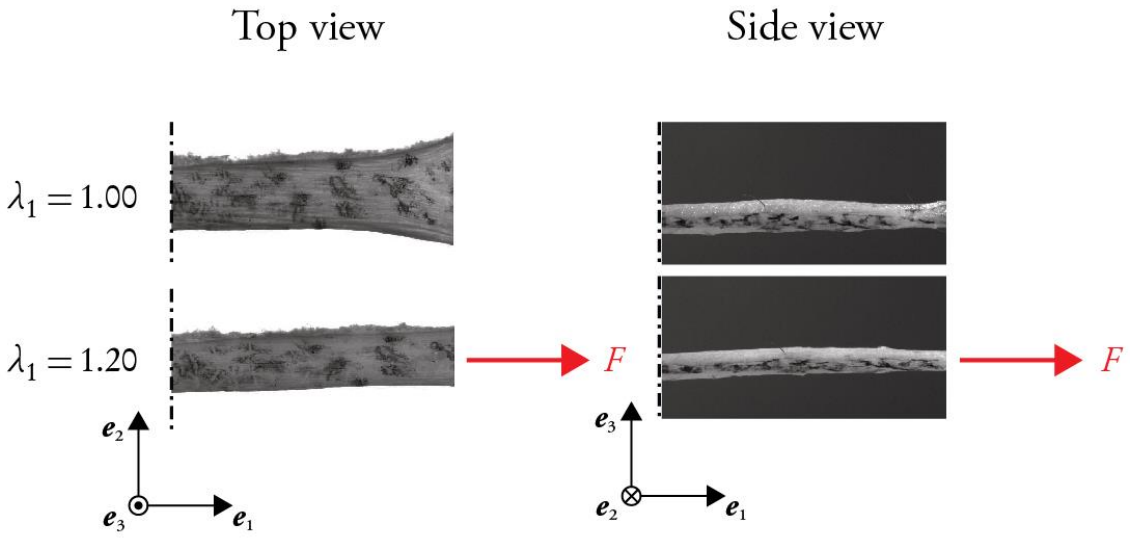
Bircher K et al, Nat Commun 10(2019):792

Skin compressibility and poroelasticity

- **Incompressibility assumption** based on **high bulk modulus of water** (~2.1 GPa) compared to typical **distortional stiffness** of tissues (kPa – MPa)
  [cf. Vossoughi & Vaishnav (1979) J. Biomech. 12:481; Ehret et al. (2017) Nat. Commun. 8:1002]
- Neglects possible **relative motion** between solid and fluid phases
  [e.g., Mow et al. (1980) J. Biomech. Eng. 102:73-84; Oomens et al. (1987) J. Biomech 20:877-885; Ehlers et al. (2009) BMMB 8:233-251]

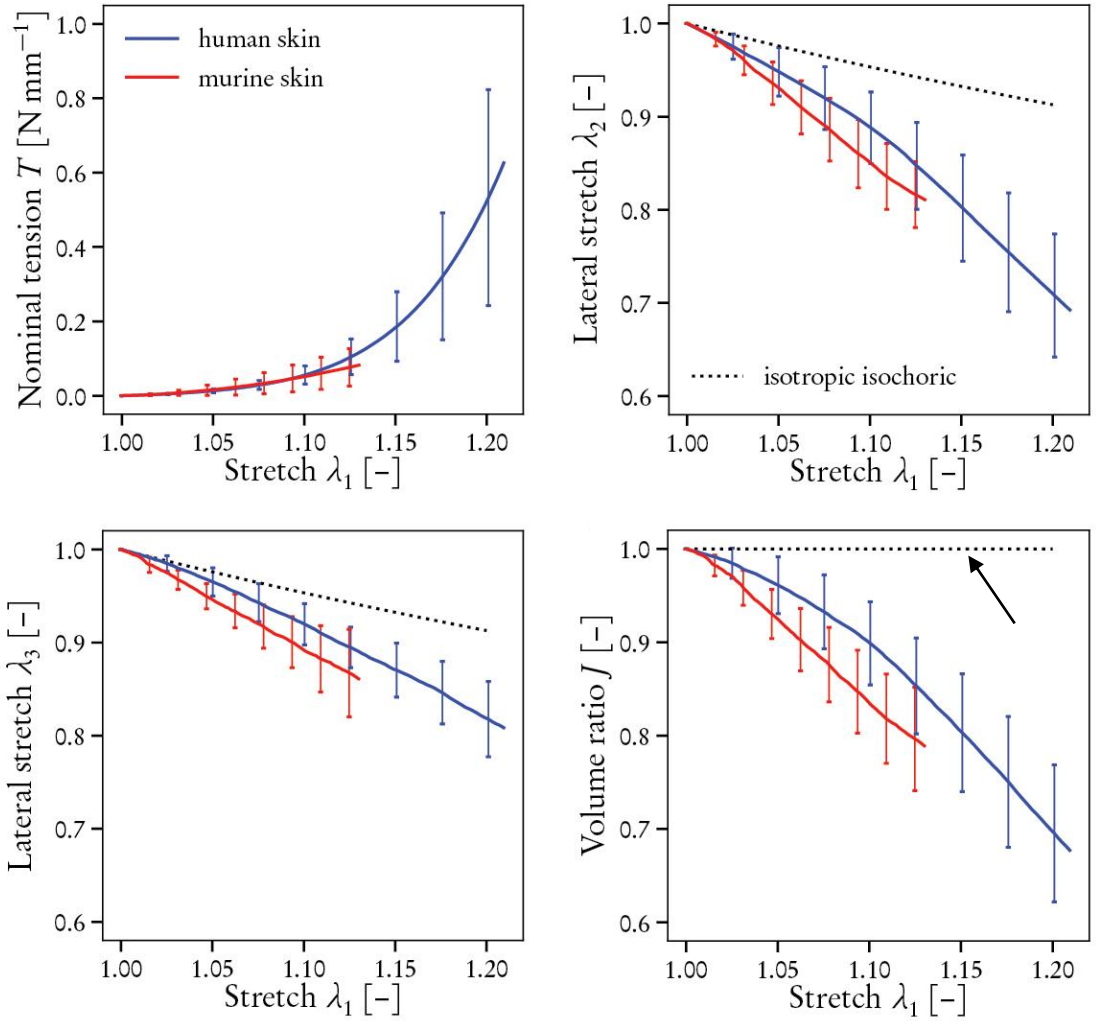
Macroscale uniaxial tension experiments with **three-dimensional optical deformation analysis**





Wahlsten A., Pensalfini M., Stracuzzi A., Restivo G., Hopf R., Mazza E., 2019, On the compressibility and poroelasticity of human and murine skin, Biomech.and Modeling in Mechanobiol., 18, 4, 10

Volume loss under uniaxial tension



Volume ratio $J = \lambda_1 \lambda_2 \lambda_3$

Wahlsten A., Pensalfini M., Stracuzzi A., Restivo G., Hopf R., Mazza E., 2019, On the compressibility and poroelasticity of human and murine skin, Biomech.and Modeling in Mechanobiol., 18, 4, 10

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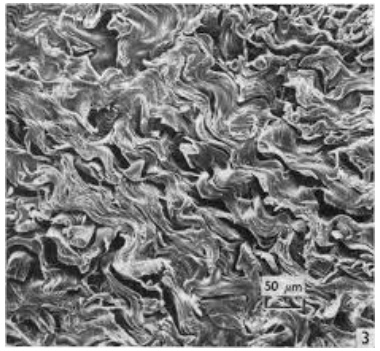
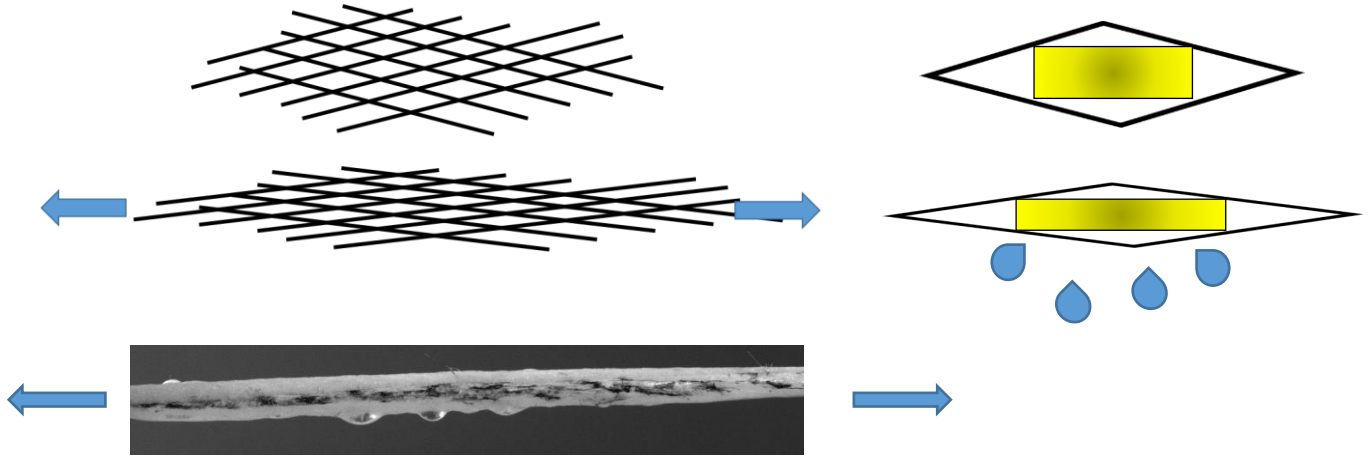
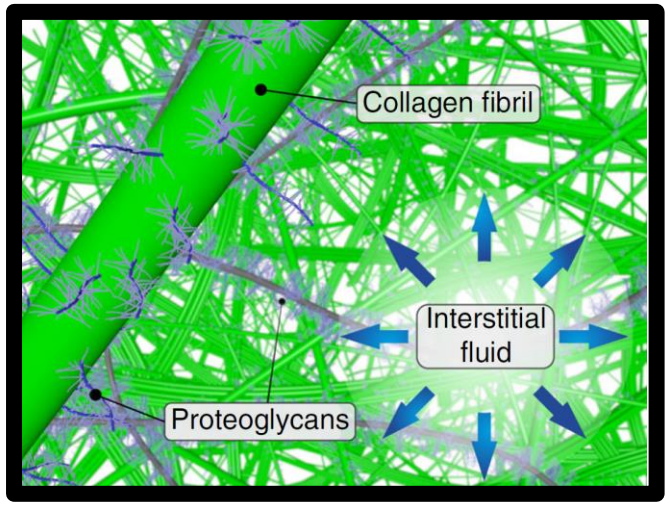
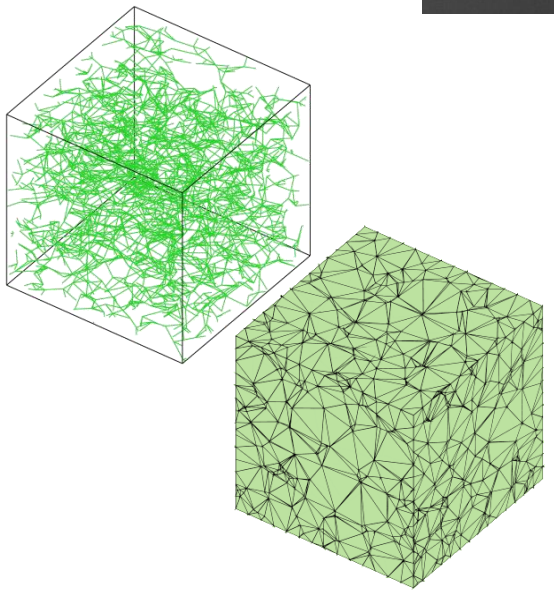
Mechanobiology: cells biophysical environment in stretched skin

Stretch of **dermis** leads to increased compression (hydrostatic pressure) and to fluid outflow:









Stretch leads to changes in:

- hydrostatic pressure and osmotic pressure of interstitial liquid
- porosity, permeability of ECM, interstitial fluid flow
- macroscopic and microscopic stiffness.

Wahlsten A., Pensalfini M., Stracuzzi A., Restivo G., Hopf R., Mazza E., 2019, On the compressibility and poroelasticity of human and murine skin, Biomech. and Modeling in Mechanobiol., 18, 4, 10

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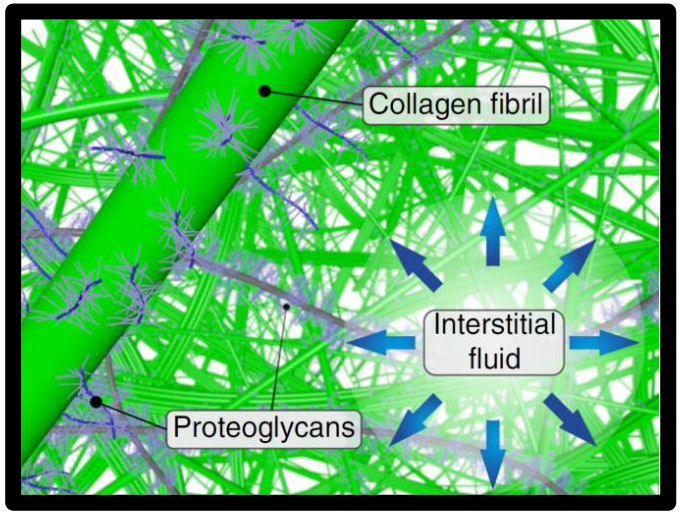
Soft collagenous tissues: a simplified view

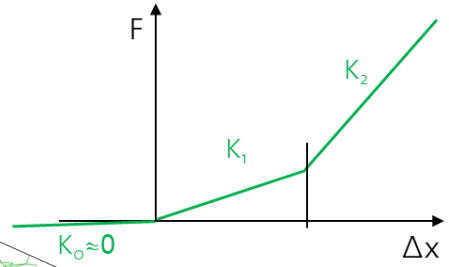


Fluid
Collagen fibers
Ground substance (with fixed charges – GAGs)

Model representation includes:

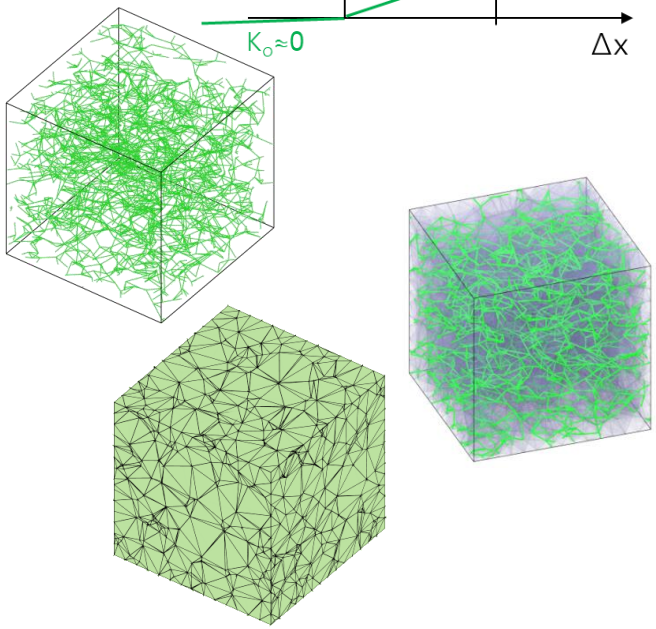
→ Poroelastic "matrix" (osmotically active)

→ Collagen fibers as slender beams
(μm-length scale)



These two elements determine the **main features** of the mechanical behavior

- Fibers as connectors with zero stiffness in compression (network of athermal fibers)
- Matrix with (low) distorsional stiffness. Volumetric response mainly depends on fluid motion, driven by grad($\mu = p - \pi$)
- Fibers kinematic as non affine (w.r.t. global deformation gradient, as well as local deformation of matrix)

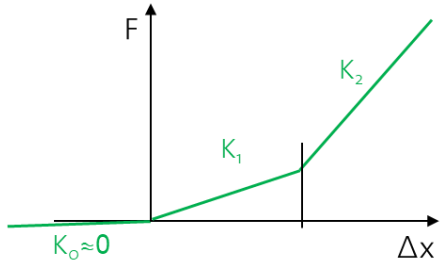


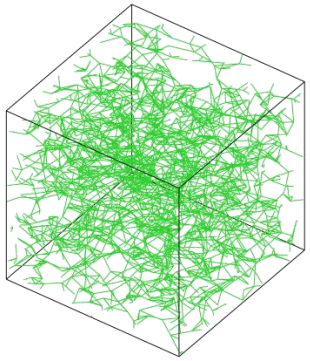
→ Model ground matrix as homogenized continuum and fibers as discrete elements

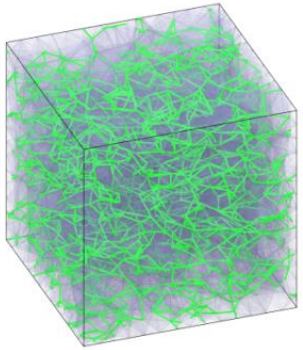
Discrete/continuum model representation (RVE) for dermis

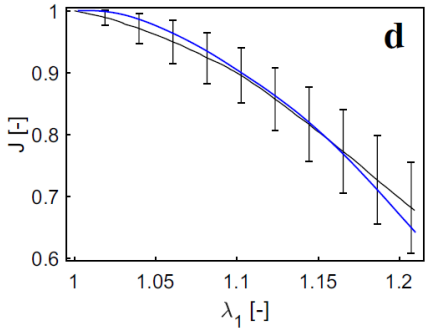
-Fiber network as non-linear connectors in 3D

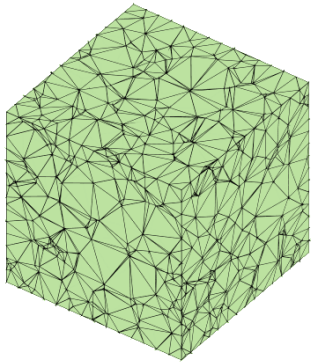
- connectivity
- stabilization, damping
- boundary conditions







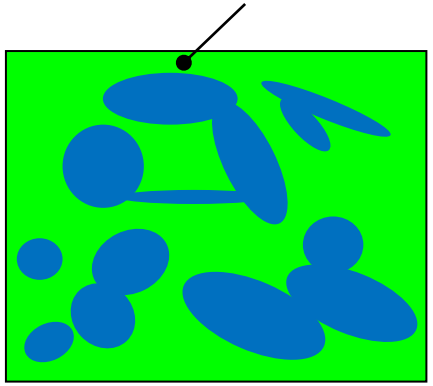




Various degrees of coupling considered

-Bi-phasic matrix as homogenized continuum

solid volume fraction $\phi_s = v_s/v$



fluid volume fraction

$$\phi_f = v_f/v$$

saturation condition

$$\phi_s + \phi_f = 1$$

[e.g. de Boer 2000, Ehlers, 2002]

Needed components:

solid constitutive law
fluid constitutive law (here inviscid)
hydraulic conductivity (~permeability, Darcy's law)
osmotic pressure–volume dependence

Representation as chemo-elastic solid (e.g. gels as polymeric networks swollen by a solvent),
→ free energy depends on deformation gradient and fluid molar concentration

Hong, Liu, Suo, Int. J. Solids and Structures, 46, 2009

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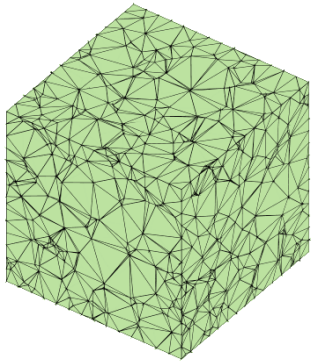
Model implementation, specific for present case

(saturation condition, solid and liquid phases as incompressible)



Osmoleasticity (Lanir 1987, Biorheology 24:173)
Hong, Liu, Suo, Int. J. Solids and Structures, 46, 2009
Stracuzzi et al., 2018, ZAMM

free energy: $\psi(\underline{\underline{F}}) \rightarrow \psi(\underline{\underline{F}}, C)$ $\quad C$: Nr of moles of liquid per referential volume; $\quad C = \dfrac{n_M}{V}$

$$\underline{\underline{P}} \cdot \dot{\underline{\underline{F}}} + \tilde{P}_F - \dot{\psi} \geq 0$$

P_F : fluid power

chemical potential per mole

liquid flux (nr of moles per unit time)

$$P_F = -\int_{\partial\Omega_R} \overline{\mu}\underline{\overline{Q}} \cdot \underline{N} dA = -\int_{\Omega_R} Div(\overline{\mu}\underline{\overline{Q}}) dV \quad \rightarrow \quad \tilde{P}_F = -\overline{\mu} Div(\underline{\overline{Q}}) - \underline{\overline{Q}} Grad(\overline{\mu})$$

$$\dot{C} = -Div(\underline{\overline{Q}}) \quad \leftarrow \quad \text{continuity equation}$$

$$\hookrightarrow \quad \underline{\underline{P}} \cdot \dot{\underline{\underline{F}}} + \overline{\mu}\dot{C} - \underline{\overline{Q}} Grad(\overline{\mu}) - \dot{\psi}(\underline{\underline{F}}, C) \geq 0$$

Incompressibility of each phase (solid and liquid): $\quad J = \Phi_s^{ref} + V_M \cdot C$

$$\dot{C} = \frac{\partial C}{\partial J}\frac{\partial J}{\partial \underline{\underline{F}}} \cdot \dot{\underline{\underline{F}}}$$

$\underline{Q}$: volumetric flux $= \underline{\overline{Q}} \cdot V_M$

μ: chemical potential per volume of liquid $= \overline{\mu}/V_M$

$$\hookrightarrow \quad \boxed{\underline{\underline{P}} \cdot \dot{\underline{\underline{F}}} + \mu J \underline{\underline{F}}^{-T} \cdot \dot{\underline{\underline{F}}} - \underline{Q} Grad(\mu) - \dot{\psi}(\underline{\underline{F}}, C(J)) \geq 0}$$

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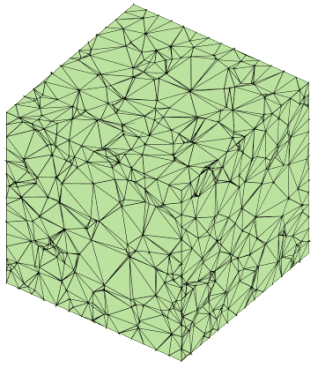
Model implementation, specific for present case

(saturation condition, solid and liquid phases as incompressible)



$$\psi = \psi_s(\underline{\underline{F}}) + \psi_{osm}(J)$$

$$\psi_s = (\psi_{Matrix} + \psi_{Fibers}) \cdot \Phi_s^{ref}$$

$$\dot{\psi} = \frac{\partial \psi}{\partial \underline{\underline{F}}} \cdot \dot{\underline{\underline{F}}} = \left(\frac{\partial \psi_s}{\partial \underline{\underline{F}}} + \frac{\partial \psi_{osm}}{\partial J} J \underline{\underline{F}}^{-T} \right) \cdot \dot{\underline{\underline{F}}}$$

$$\hookrightarrow \left(\underline{\underline{P}} + \mu J \underline{\underline{F}}^{-T} - \frac{\partial \psi_s}{\partial \underline{\underline{F}}} - \frac{\partial \psi_{osm}}{\partial J} J \underline{\underline{F}}^{-T} \right) \cdot \dot{\underline{\underline{F}}} - \underline{Q} Grad(\mu) \geq 0$$

$$\rightarrow \quad \underline{\underline{P}} = \frac{\partial \psi_s}{\partial \underline{\underline{F}}} - (\pi + \mu) J \underline{\underline{F}}^{-T} \qquad \pi + \mu = p \quad \text{(Fluid hydrostatic pressure)}$$

$$\pi = -\frac{\partial \psi_{osm}}{\partial J} \quad \text{osmotic pressure}$$

$$\text{with} \quad \underline{Q} = -\underline{\underline{K}} Grad(\mu) \quad \rightarrow \quad -\underline{Q} Grad(\mu) = \underline{\underline{K}} (Grad(\mu))^2 \geq 0 \qquad \text{dissipation satisfied}$$

Flow depends on Grad of $\mu = p - \pi$

$$J = \Phi_s^{ref} + V_M C \quad \rightarrow \quad \dot{J} = V_M \dot{C} = -Div(\underline{Q}) \quad \rightarrow \quad \dot{J} = Div(\underline{\underline{K}} Grad(\mu))$$ Rate of change of volume ↔ flow

Hydraulic conductivity $\underline{\underline{K}} = k_0 \left[\frac{J - \phi_s^{\text{ref}}}{1 - \phi_s^{\text{ref}}} \right]^{k_1} e^{\frac{k_2}{2}(J^2 - 1)} \mathbf{I}$ $k_0 \sim 10^{-14}\ m^4/N/s$,

[Holmes&Mow 1990]

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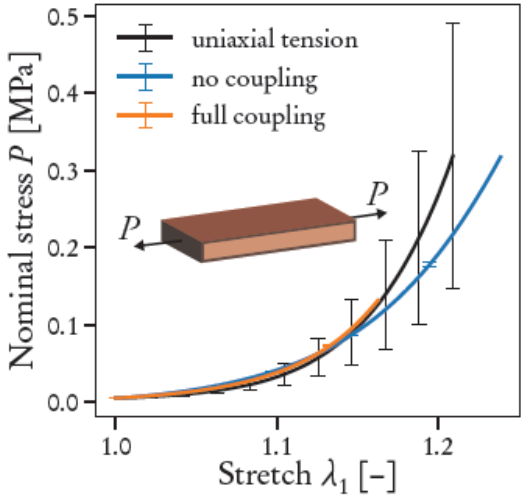
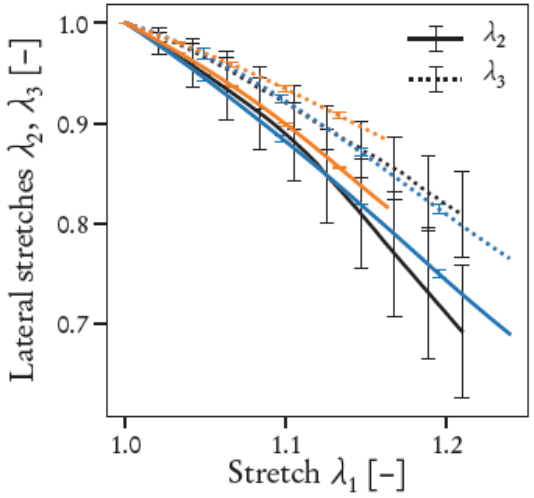
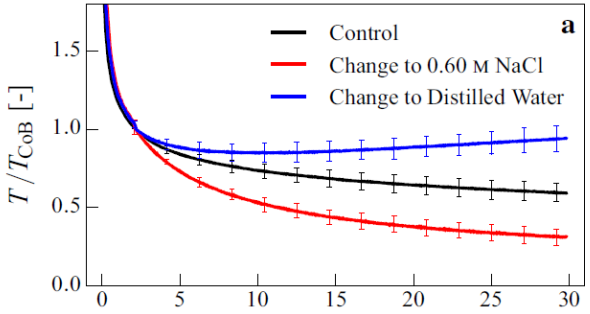
The model can rationalize experimental data

Macroscopic response:

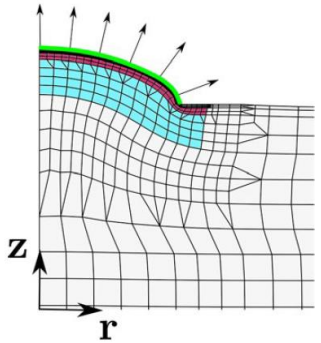


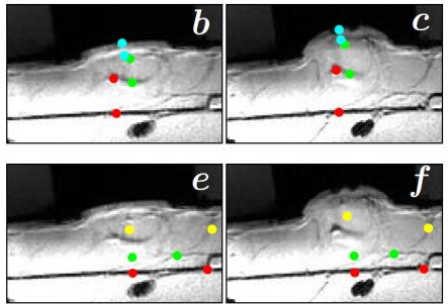


Relaxation with change of bath

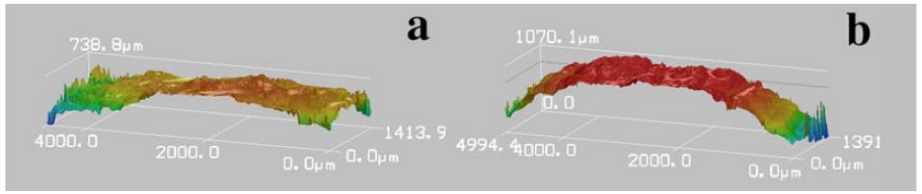


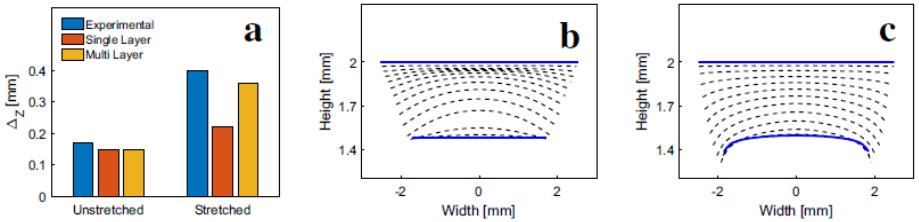
In vivo suction



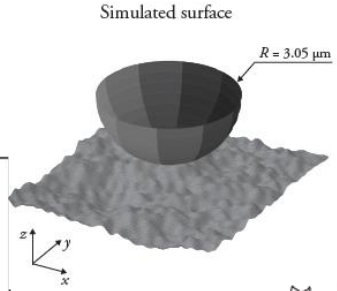


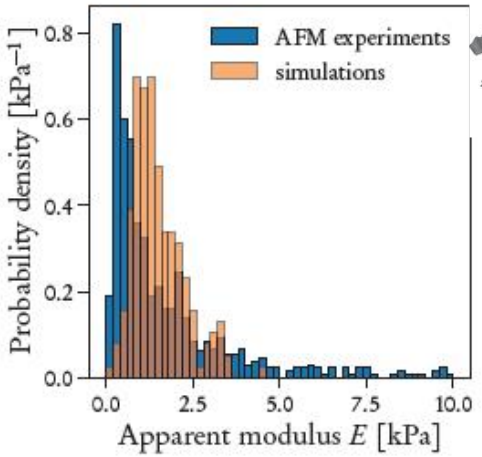
Out of plane kinematics

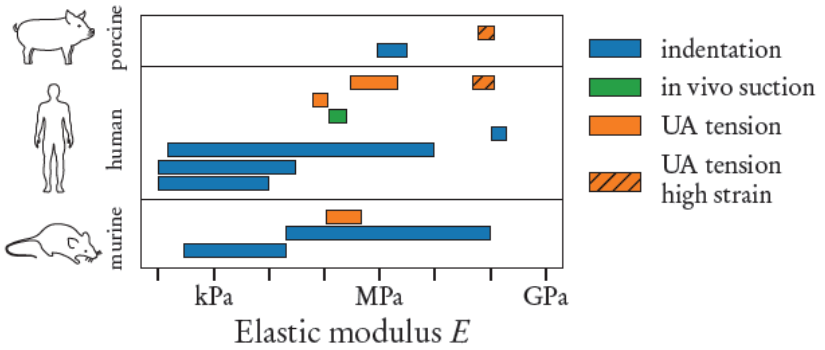




AFMIndentation







Sachs D. et al., Biomechanics and Modeling in Mechanobiology (2021) 20
Wahlsten et al., Biomechanics and Modeling in Mechanobiology (2019) 18; Wahlsten A., 2022

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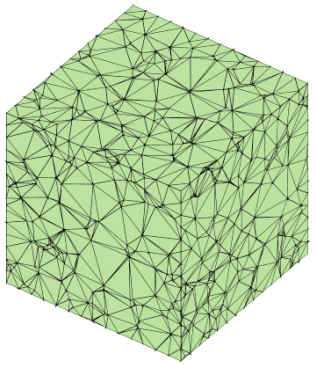
Osmotic pressure term

$$\pi = -\frac{\partial \hat{\Psi}_{\mathrm{x}}(J,\mu)}{\partial J}$$



$$\pi(J) = -\frac{\mathrm{R}\Theta}{V_{\mathrm{M}}}\left[\ln\left(\frac{J-\phi_{\mathrm{s}}^{\mathrm{ref}}}{J}\right)+\frac{\phi_{\mathrm{s}}^{\mathrm{ref}}}{J}+\frac{\chi_{\mathrm{FH}}\left(\phi_{\mathrm{s}}^{\mathrm{ref}}\right)^2}{J^2}\right]$$

Based on Flory-Huggins potential

$$\pi = \mathrm{R}\Theta\left(\sqrt{c_{\mathrm{F}}^2+4c_{\mathrm{ext}}^2}-2c_{\mathrm{ext}}\right) \qquad c_{\mathrm{F}}(J) = c_{\mathrm{F}}^{\mathrm{ref}}\frac{1-\phi_{\mathrm{s}}^{\mathrm{ref}}}{J\phi_{\ell}} = c_{\mathrm{F}}^{\mathrm{ref}}\frac{1-\phi_{\mathrm{s}}^{\mathrm{ref}}}{J-\phi_{\mathrm{s}}^{\mathrm{ref}}}$$

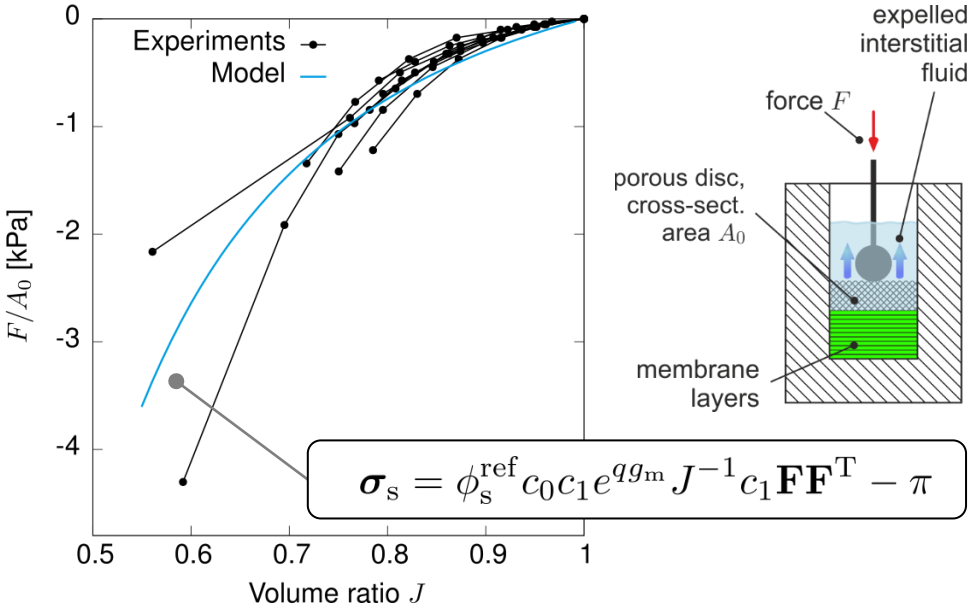
Based on Donnan equilibrium

[Donnan 1924, Kovach 1995]

$$\pi = a_0\left[\frac{1-\phi_{\mathrm{s}}^{\mathrm{ref}}}{J-\phi_{\mathrm{s}}^{\mathrm{ref}}}\right]^{2a_1}+\pi_0$$

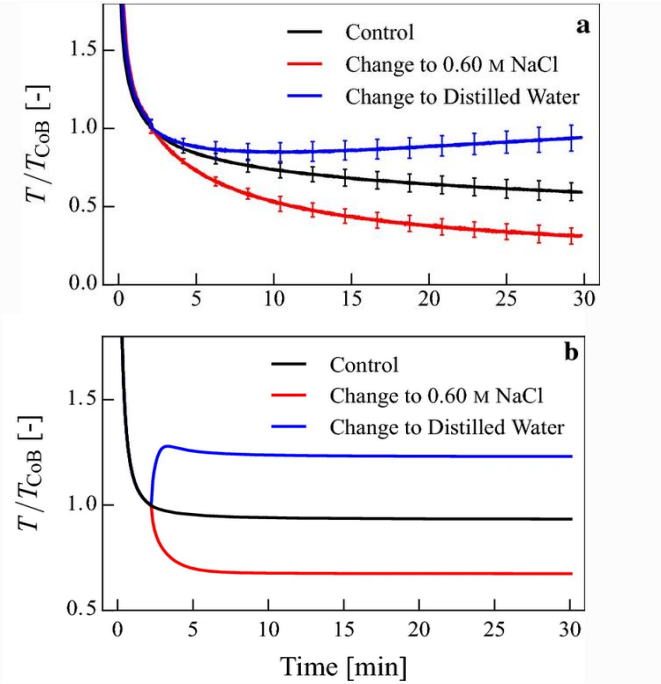
Based on measurements (fit an empiric relation)

Confined compression

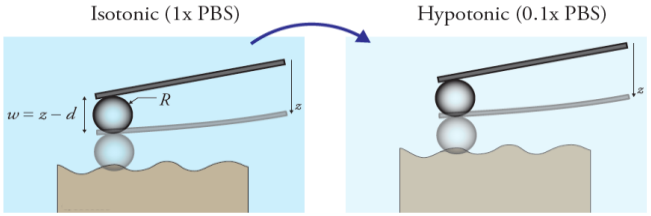


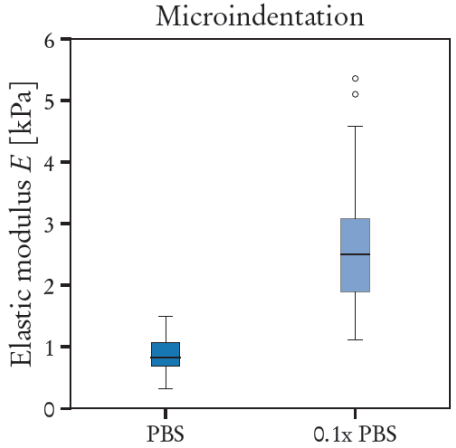
$$\boldsymbol{\sigma}_{\mathrm{s}} = \phi_{\mathrm{s}}^{\mathrm{ref}} c_0 c_1 e^{q g_{\mathrm{m}}} J^{-1} c_1 \mathbf{F}\mathbf{F}^{\mathrm{T}} - \pi$$

Relaxation with change of bath



Microindentation with change of bath





Corresponding continuum model (i.e. without discrete fibers)

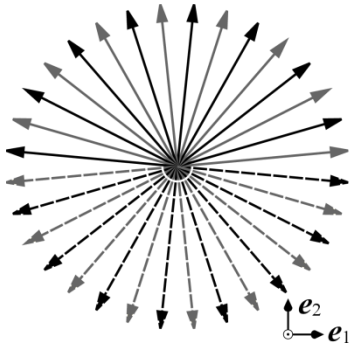
Fibers considered in strain energy formulation

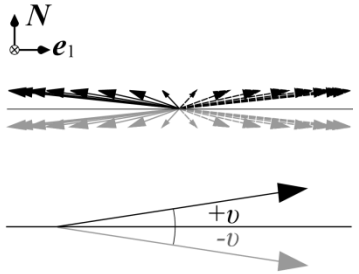
Rubin-Bodner type strain energy function

$$\hat{\Psi}_{\mathrm{s}}(\mathbf{F}, \lambda_{\mathrm{e},1}, \lambda_{\mathrm{e},2}, \ldots, \lambda_{\mathrm{e},N}) = \phi_{\mathrm{s}}^{\mathrm{ref}} \frac{c_0}{2q} \left[e^{q(g_{\mathrm{m}} + g_{\mathrm{fe}})} - 1 \right]$$

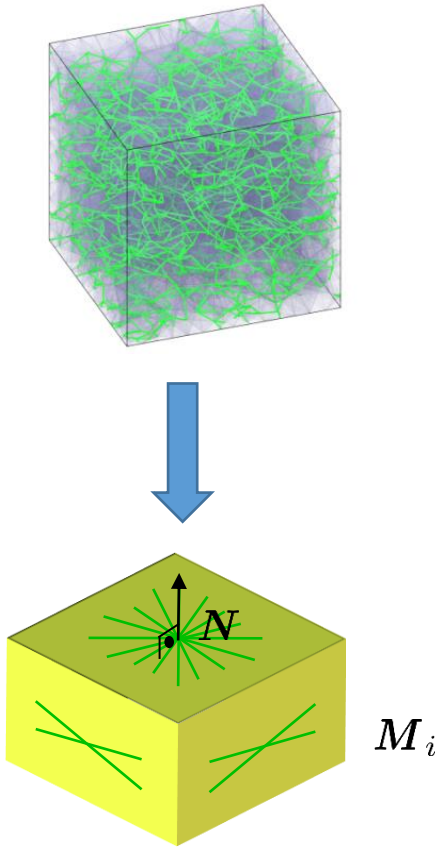
$$g_{\mathrm{m}} = c_1 \left[\mathrm{tr}(\mathbf{F}\mathbf{F}^{\mathrm{T}}) - 3 \right] \qquad g_{\mathrm{fe}} = \frac{c_2}{c_3} \frac{1}{N} \sum_{i=1}^{N} \langle \lambda_{\mathrm{e},i} - 1 \rangle^{2c_3}$$

[Rubin&Bodner 2002]





$\lambda_i = |\mathbf{F} M_i|$, $\langle \bullet \rangle$ – Macauley brackets



quasi in-plane isotropy

solid stress $\boldsymbol{\sigma}_{\mathrm{s}}$

Fibre creep responsible for long term time-dependent behaviour: evolution equations

$$\frac{\dot{\lambda}_{\mathrm{e},i}}{\lambda_{\mathrm{e},i}} = \frac{\dot{\lambda}_i}{\lambda_i} - \phi_{\mathrm{s}}^{\mathrm{ref}} c_0 e^{q(g_{\mathrm{m}} + g_{\mathrm{fe}})} \frac{c_2}{\nu_{\mathrm{F}}} \lambda_{\mathrm{e},i} \langle \lambda_{\mathrm{e},i} - 1 \rangle^{2c_3 - 1}$$

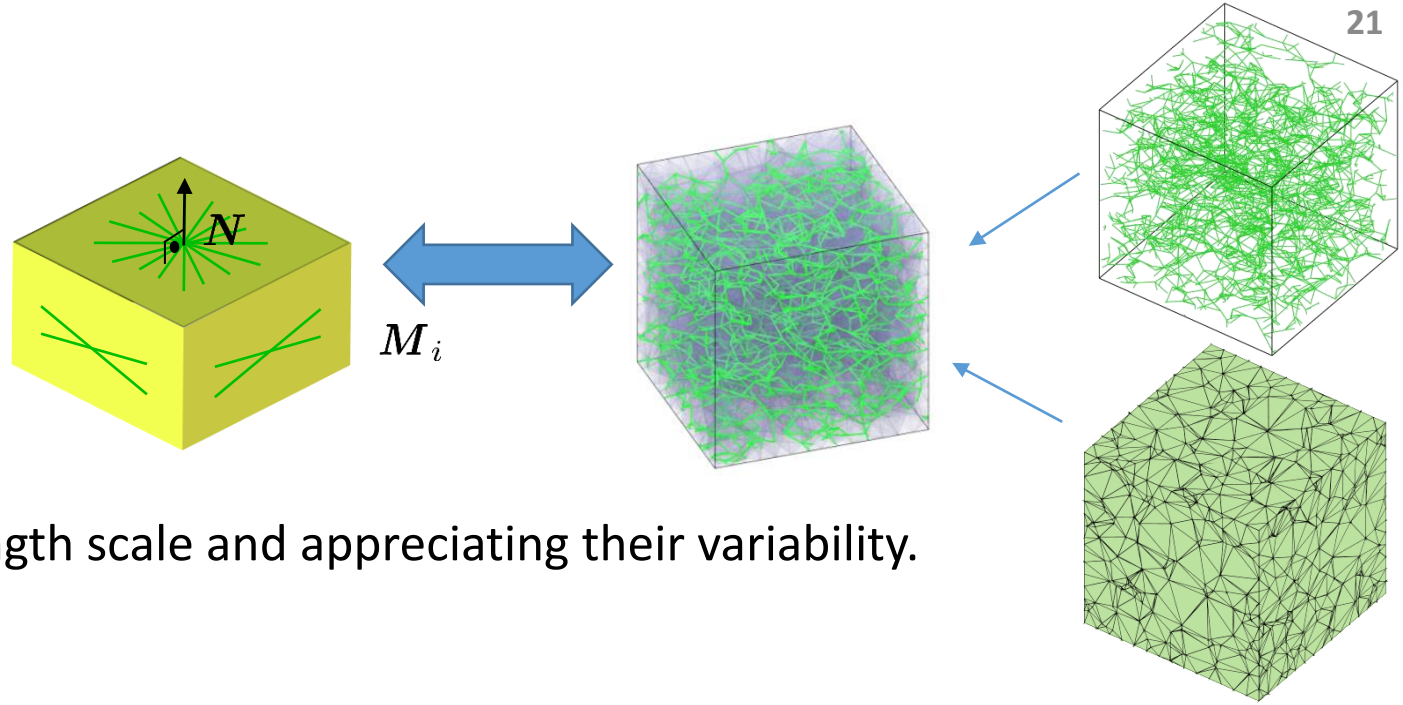
[Bürzle&Mazza,(2013),*J Biomech* 46:1777, Mauri et al.(2016) BMMB15;1005]

…but affine fibers kinematics, see:

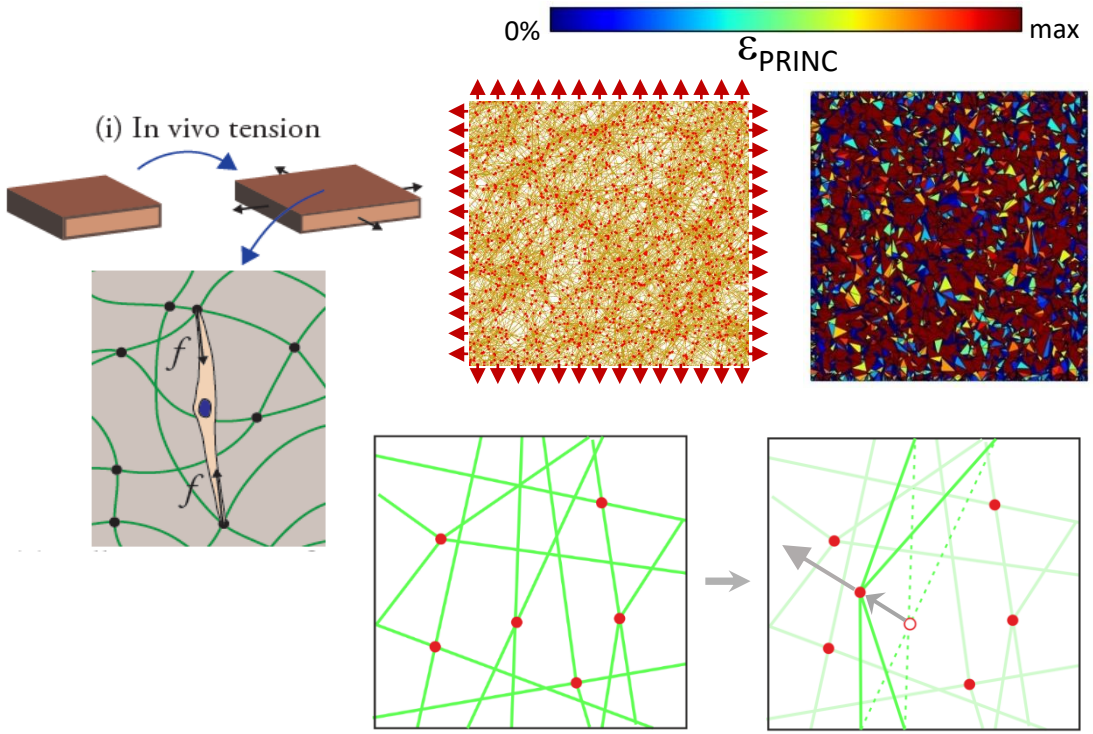
A. Stracuzzi, B. R. Britt, E. Mazza and A. E. Ehret, 2022, Risky interpretations across the length scales: continuum vs. discrete models for soft tissue mechanobiology, Biomech. and Model. in Mechanobiol., https://doi.org/10.1007/s10237-021-01543-4

Shift of length scale of homogenization:

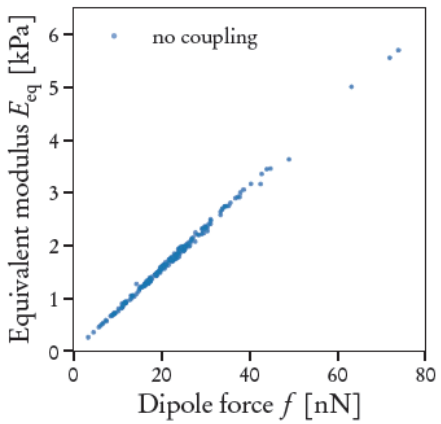
Explicit representation of collagen fibers network
Homogenized continuum for “rest of solid matrix”

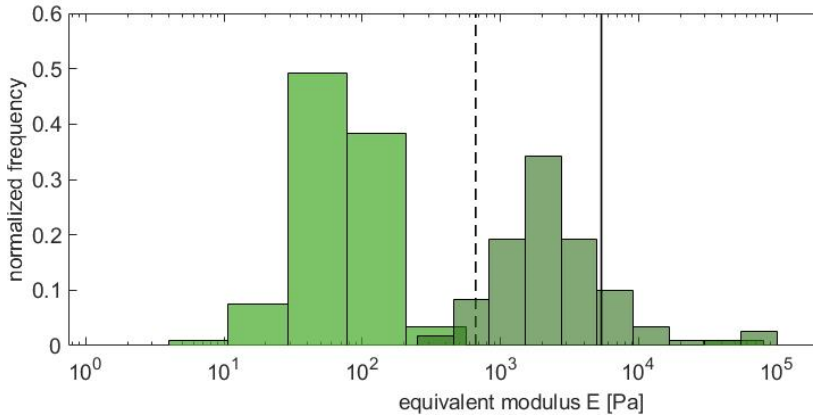


→ Allows quantifying mechanical signals at cell length scale and appreciating their variability.



→ Large scatter of perceived stiffness
→ Large scatter of local strain





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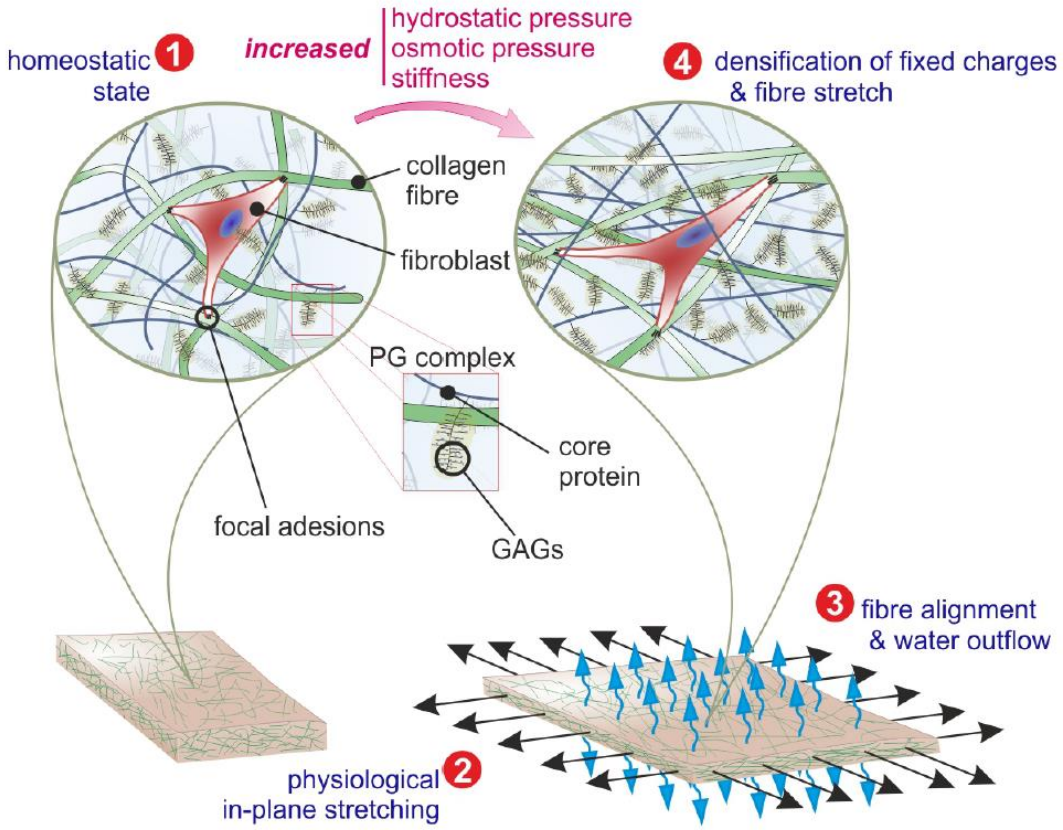
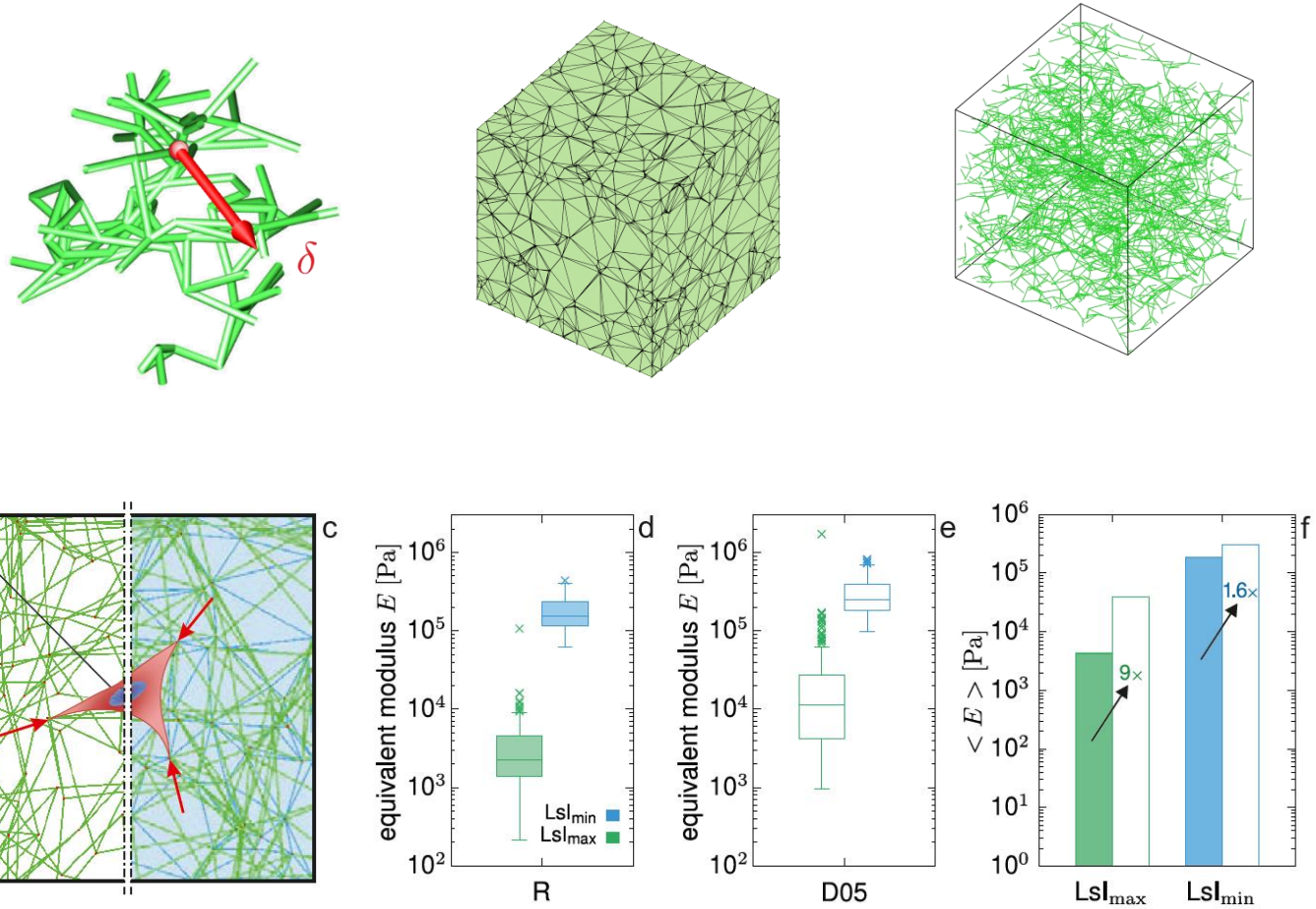
Cells biophysical environment in stretched skin

Model based prediction of stretch induced local changes

Tension leads to changes in local cell environment.





M. Zündel, A.E. Ehret, E. Mazza, 2019, The multiscale stiffness of electrospun substrates and aspects of their mechanical biocompatibility, *Acta biomaterialia,* 84, 146-158

Stracuzzi, ETH dissertation, 2021; Wahlsten, ETH dissertation, 2022

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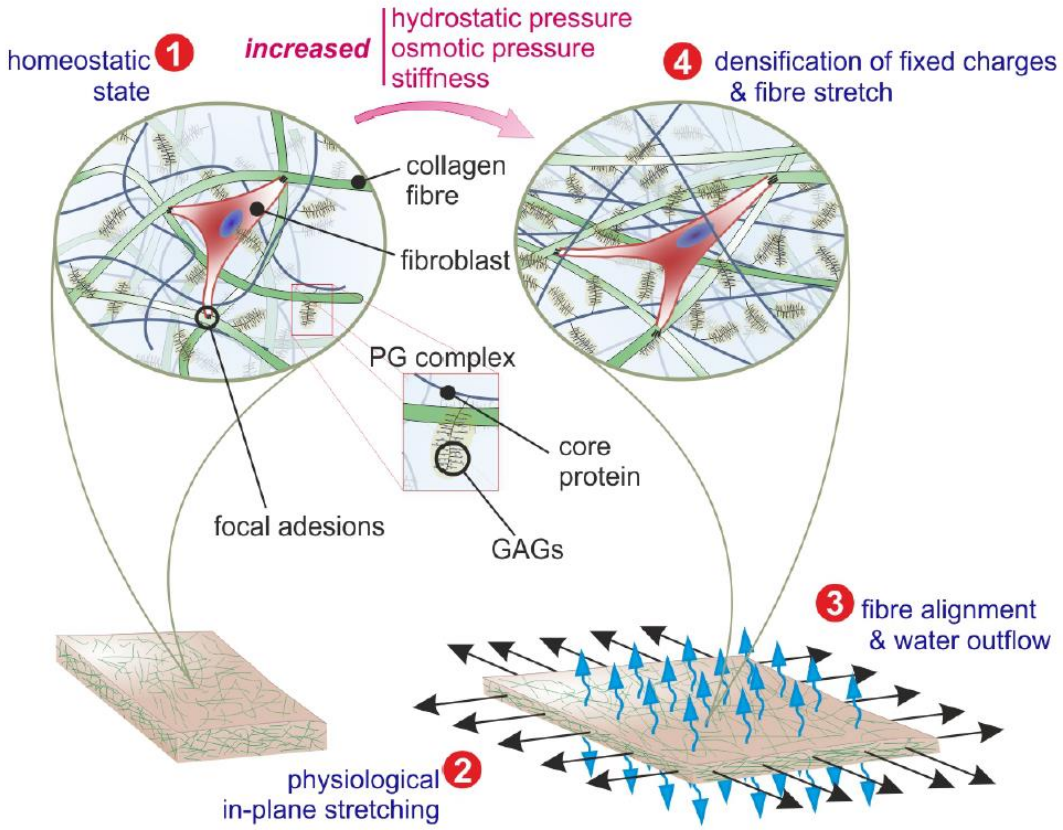

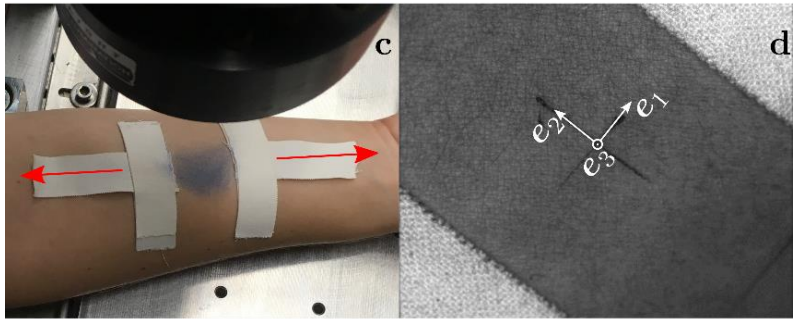

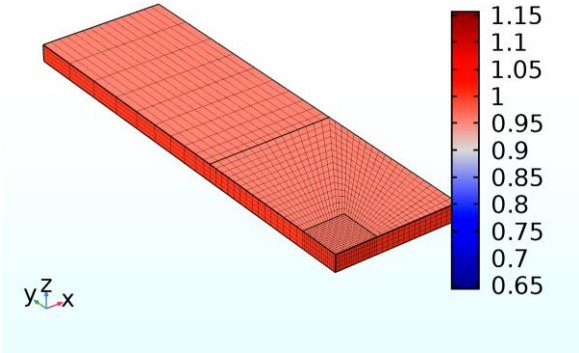

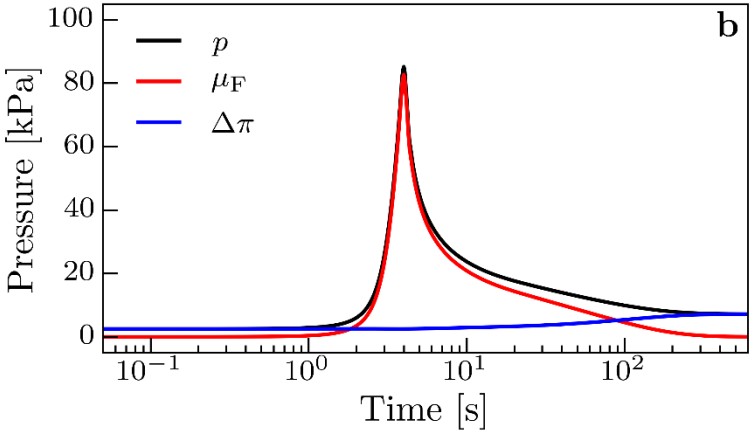

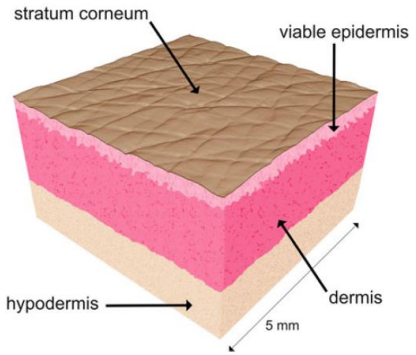

G. Limbert, Skin Biophysics

Stracuzzi, ETH dissertation, 2021

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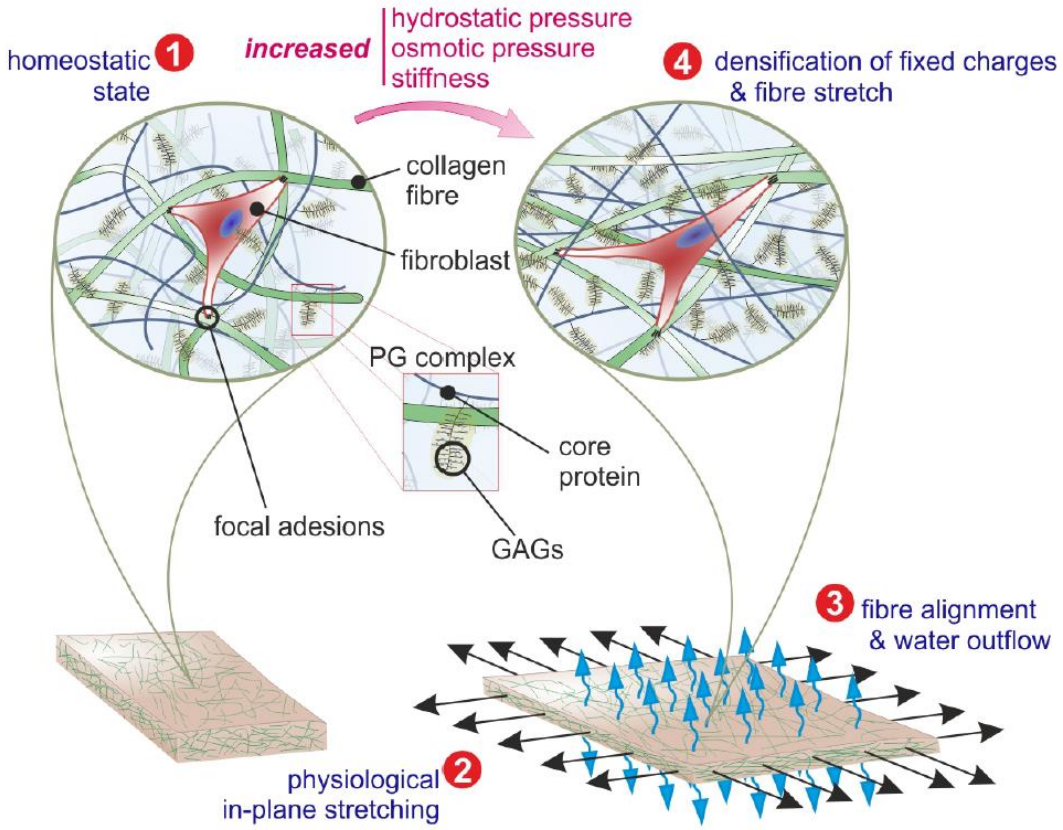
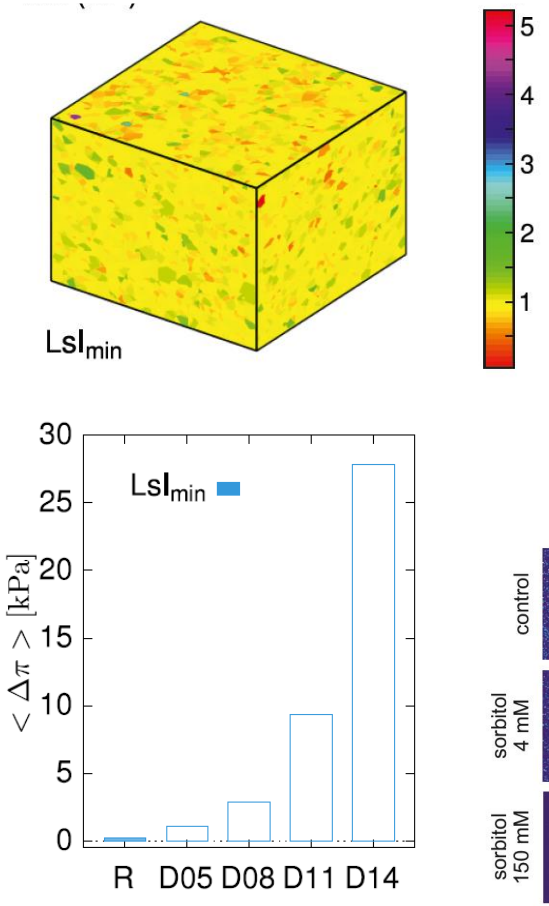
Cells biophysical environment in stretched skin

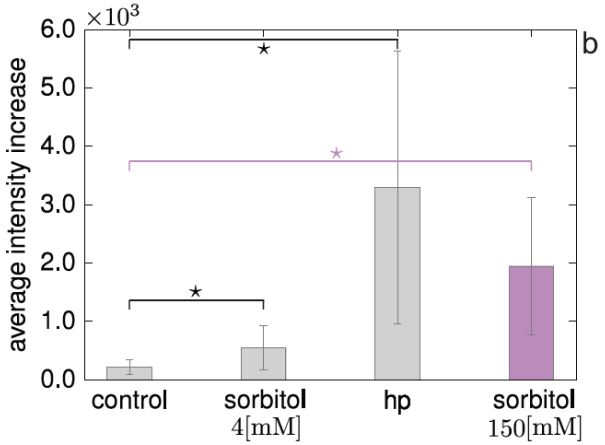
Model based prediction of stretch induced local changes

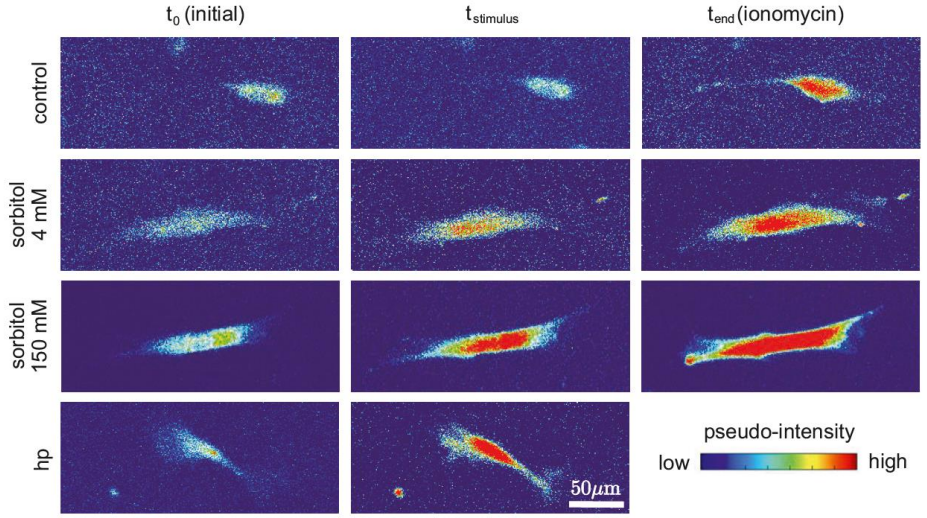
Tension leads to changes in local cell environment.





Calcium signaling in fibroblasts





Stracuzzi, ETH dissertation, 2021

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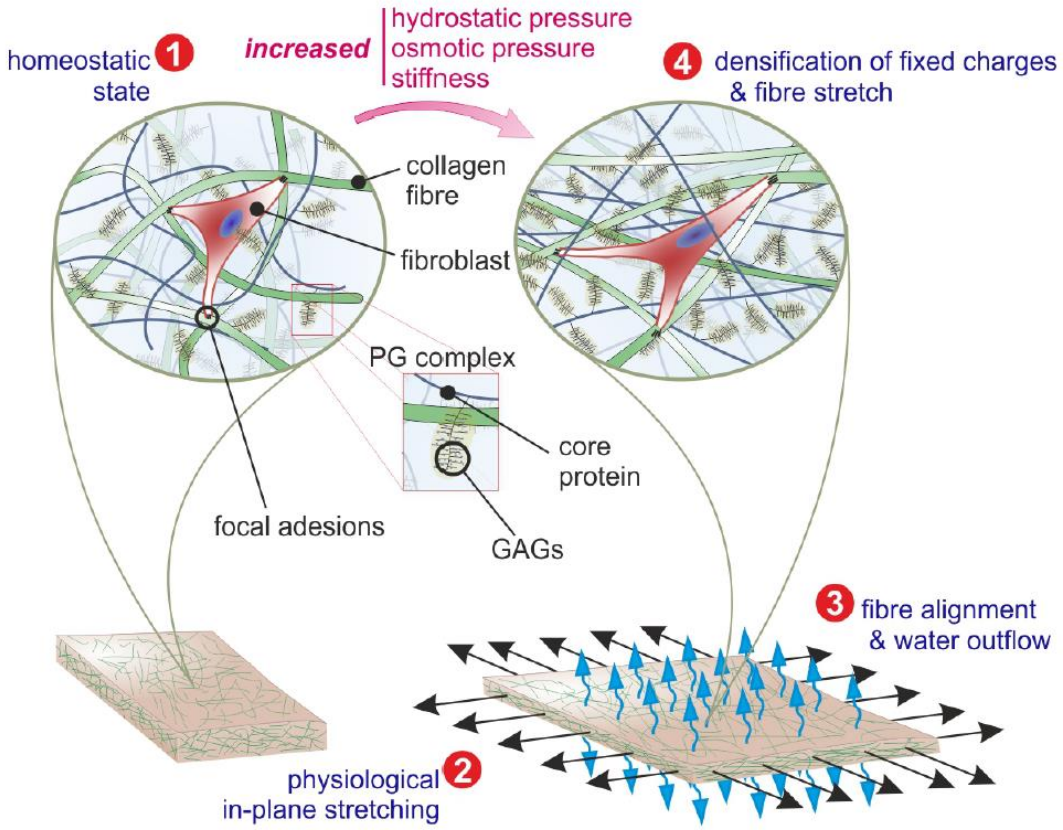

Mechanotransduction:

cell strain
change in perceived stiffness
change in hydrostatic pressure
change in osmolarity
change in interstitial fluid flow

→ Several components of the "***mechanome***"
→ Current investigations to identify dermal cell response (proteins and/or gene expression)

A. Martyts et al., in preparation

Stracuzzi, ETH dissertation, 2021

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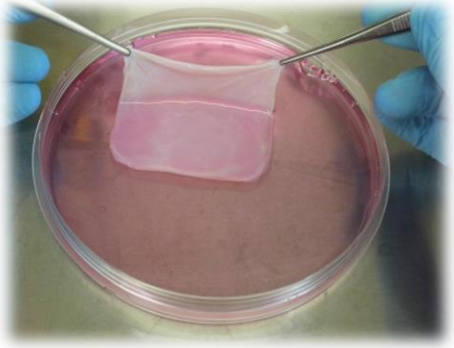
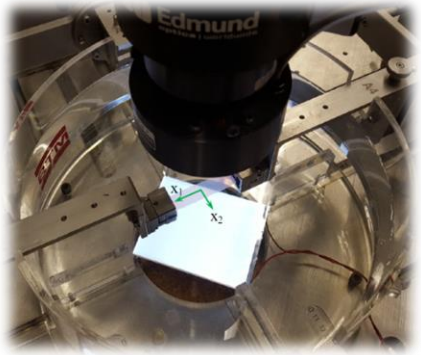
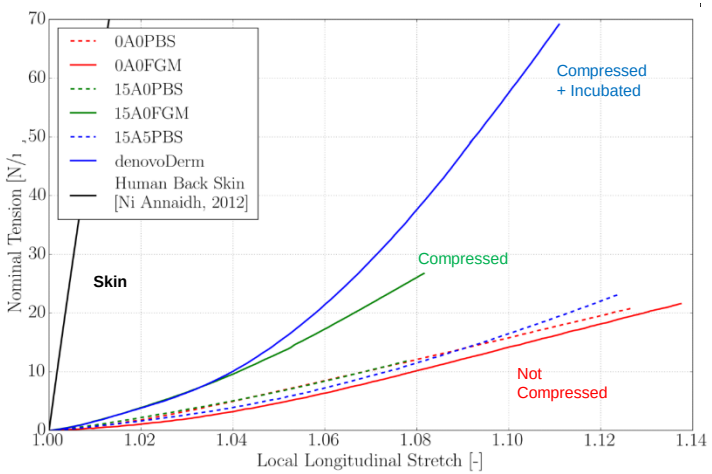
Skin tissue engineering

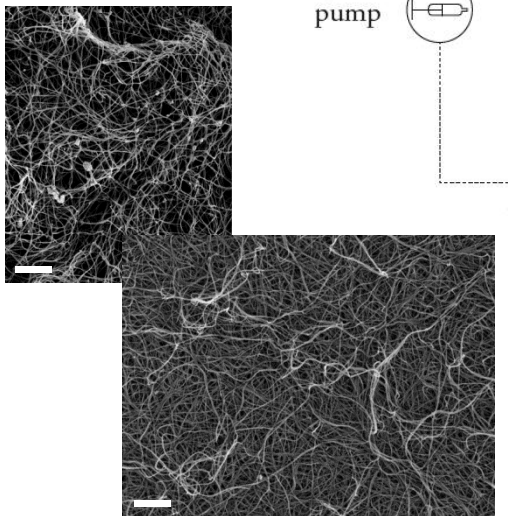
Accelerated maturation of skin substitutes (collaboration with Kinderspital Zurich)

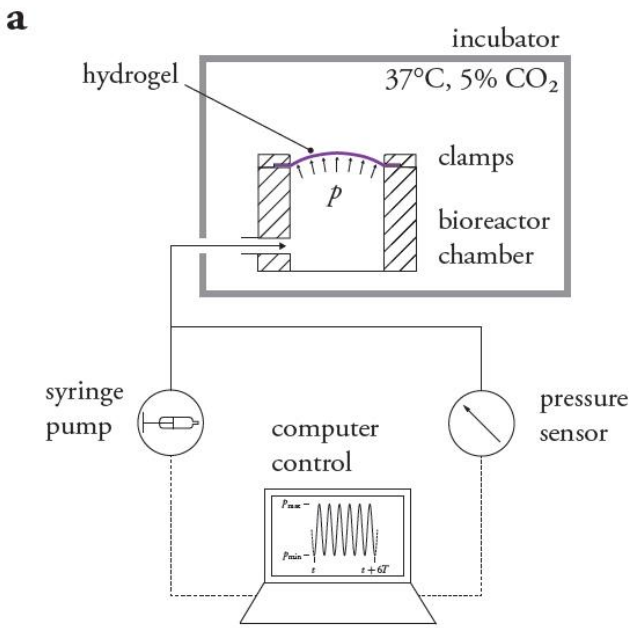
Hypothesis: optimization of (chemo-)mechanical properties of scaffolds (mimicking native tissue at cell length scale) and mechanical stimulation leads to faster maturation

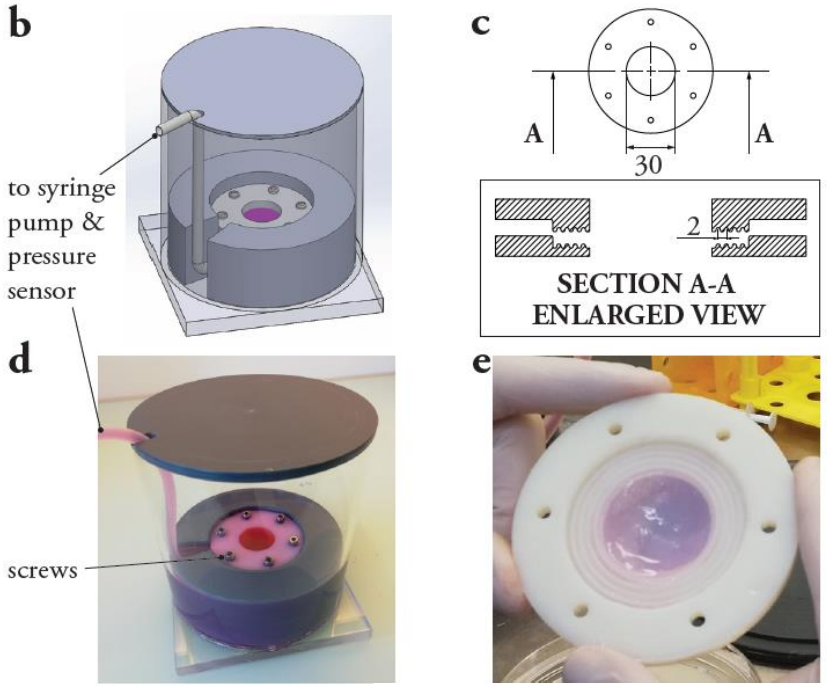


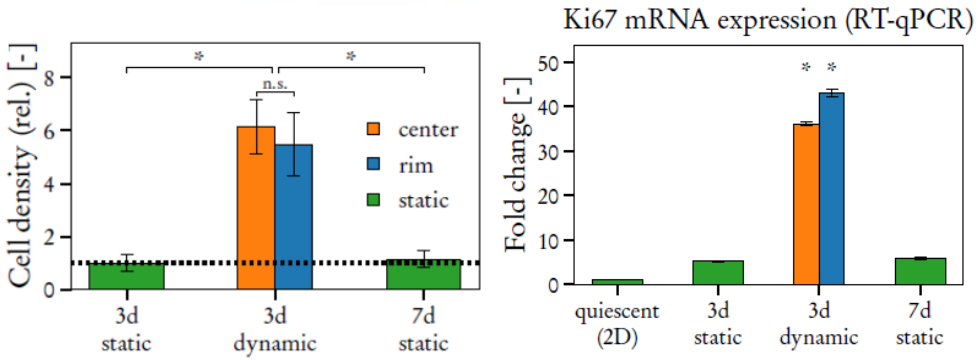












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Wahlsten A. et al, Biomaterials, 2021

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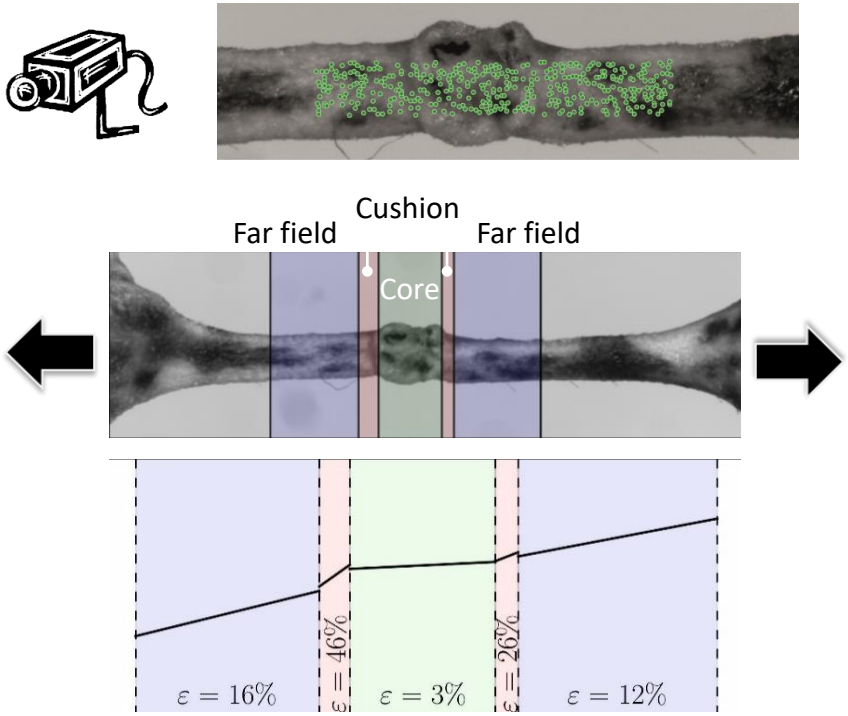
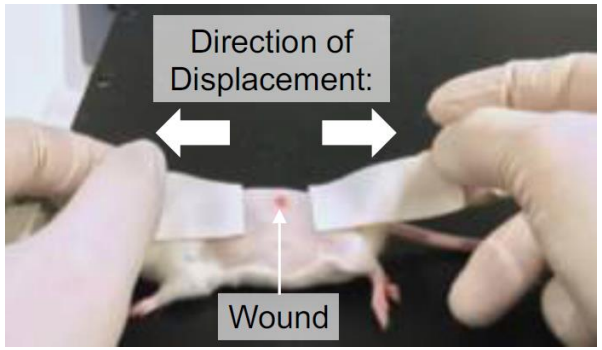
Mechanical factors influencing wound healing

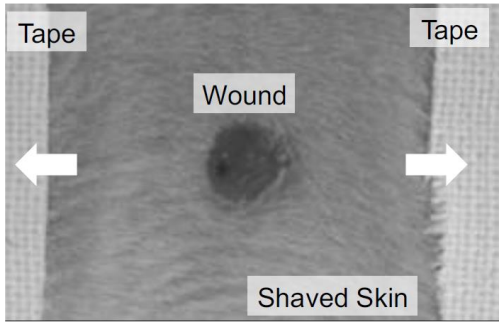
Understand wounds' biophysical environment (collaboration with S. Werner, ETH)

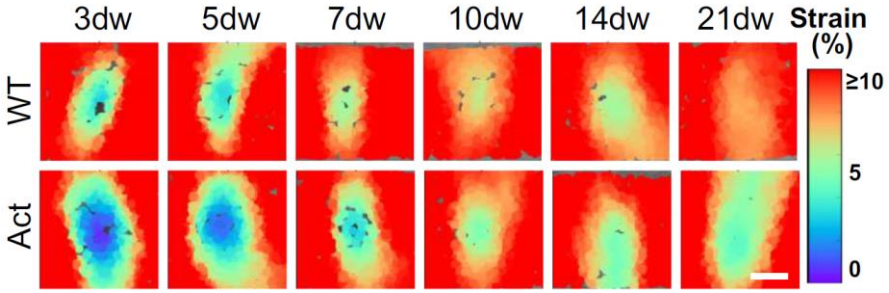
Evolution of mechanical properties contrary to expectations from histology.

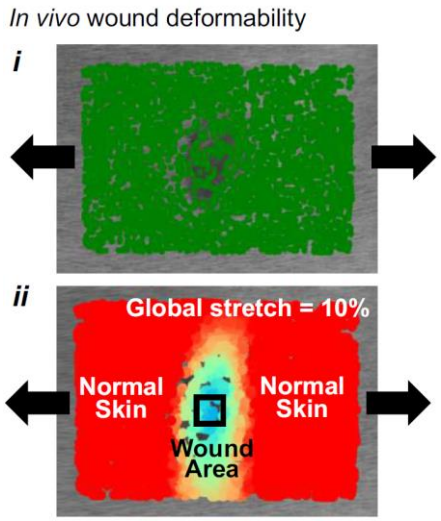


Ex-vivo









In-vivo

Pensalfini M. et al., 2017, The mechanical fingerprint of murine excisional wounds, Acta Biomaterialia, 65, 226 – 236

Wietecha, M. et al., 2020, Activin-mediated alterations of the fibroblast transcriptome and matrisome control the biomechanical properties of skin wounds, *Nature Communications*, 11, 2604

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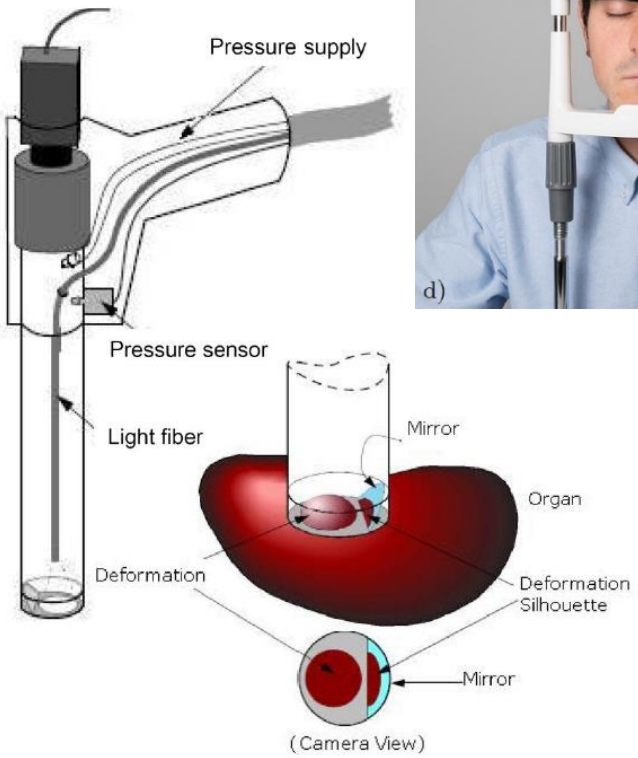
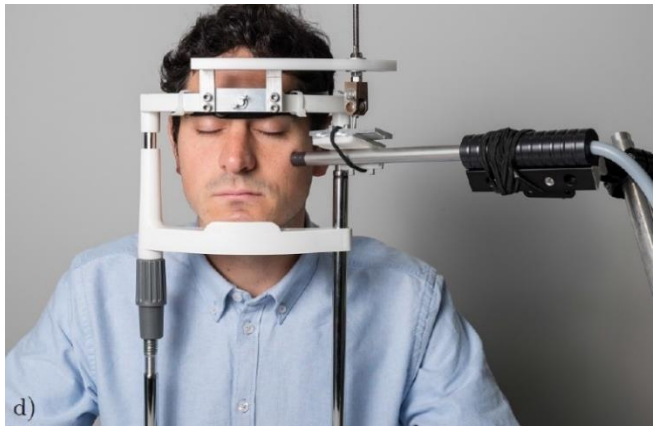
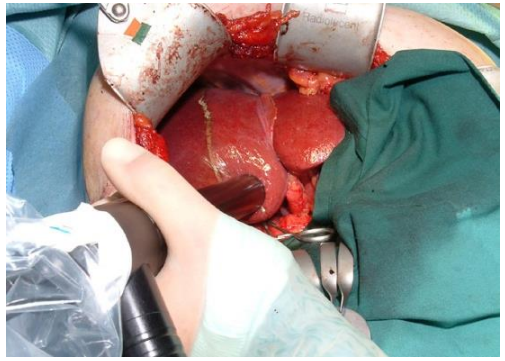
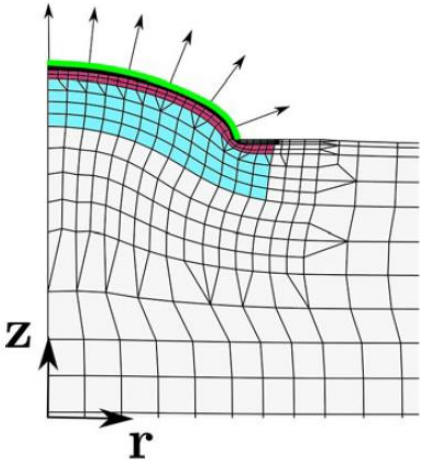
Characterization based on suction measurements

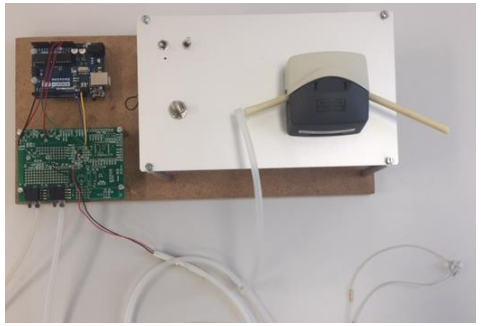
→ Optimization of suction method

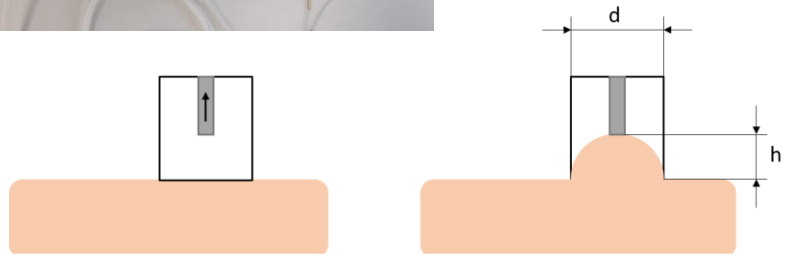


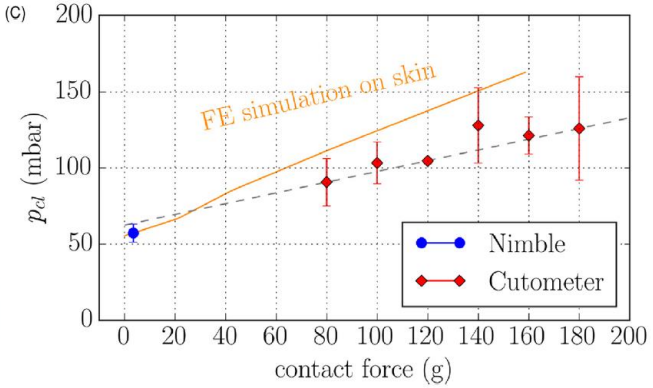












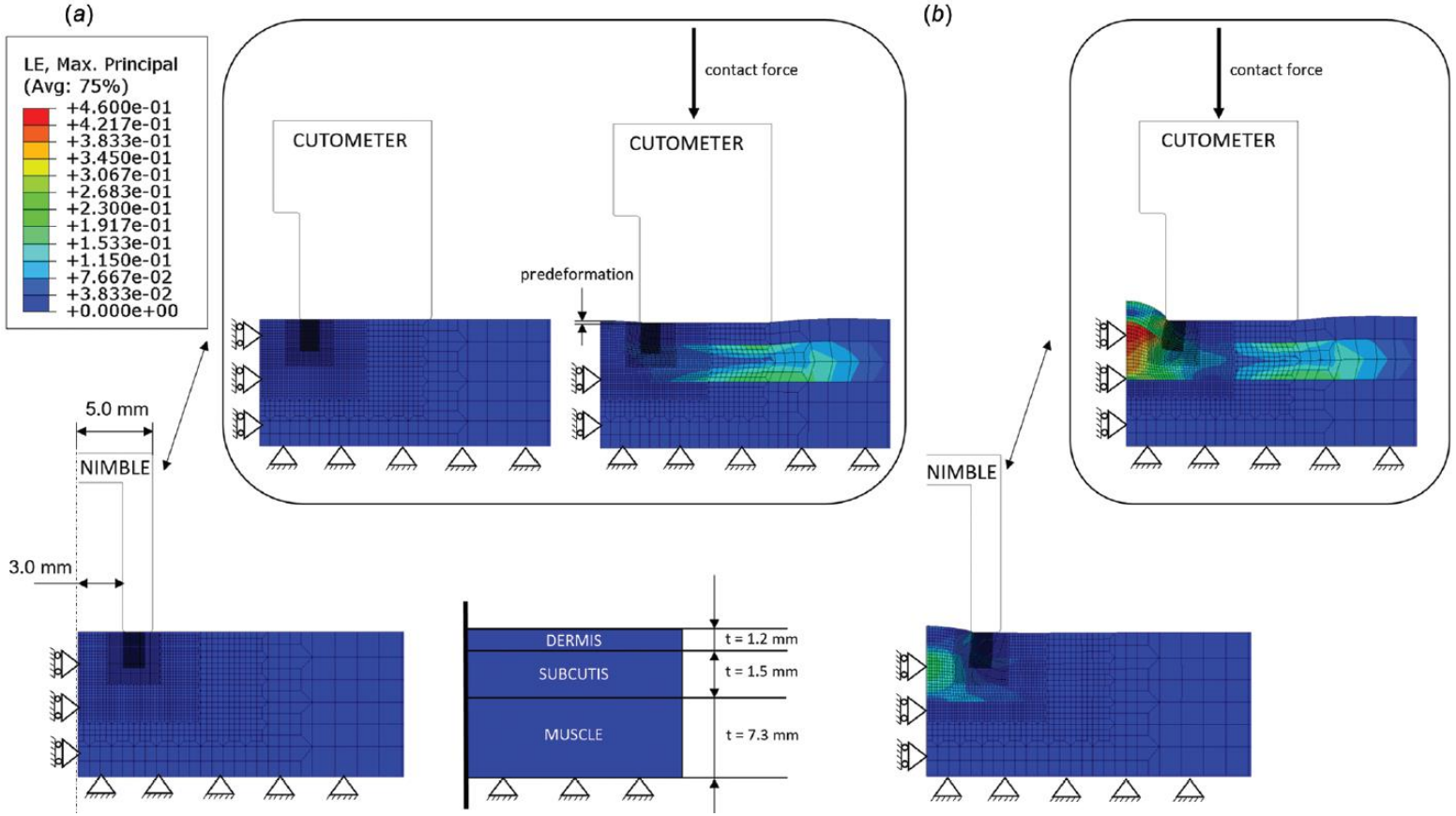
Barbarino G., Jabareen M. , Mazza E., 2011, Experimental and numerical study on the mechanical behavior of the superficial layers of the face, Skin research and Technology, 17, 4

Pensalfini M, Weickenmeier J, Rominger M, Santoprete R, Distler O, Mazza E. 2018, Location-specific mechanical response and morphology of facial soft tissues. Journal of the Mechanical Behavior of Biomedical Materials **78**: 108-115

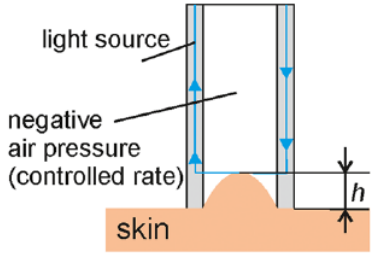
Müller B., Elrod J., Pensalfini M., Hopf R., Distler O., Schiestl C., Mazza E., 2018, A novel ultra-light suction device for mechanical characterization of skin, PLOS ONE, 13(8)

B. Mueller, J. Elrod, O. Distler, C. Schiestl and E. Mazza, 2020, On the Reliability of Suction Measurements for Skin Characterization. Journal of Biomechanical Engineering, vol. 143: no. 2

Characterization based on suction measurements



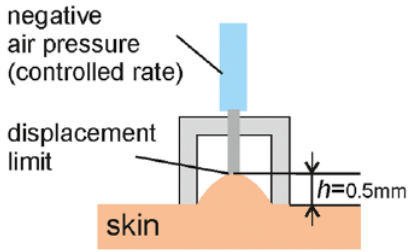
Load-controlled (Cutometer)



suction experiment with prescribed **maximum pressure**

extract elevation for a defined pressure

Displacement-controlled (Nimble)



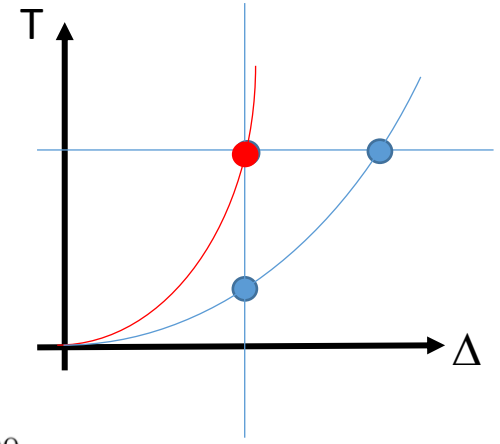
suction experiment with prescribed **maximum elevation**

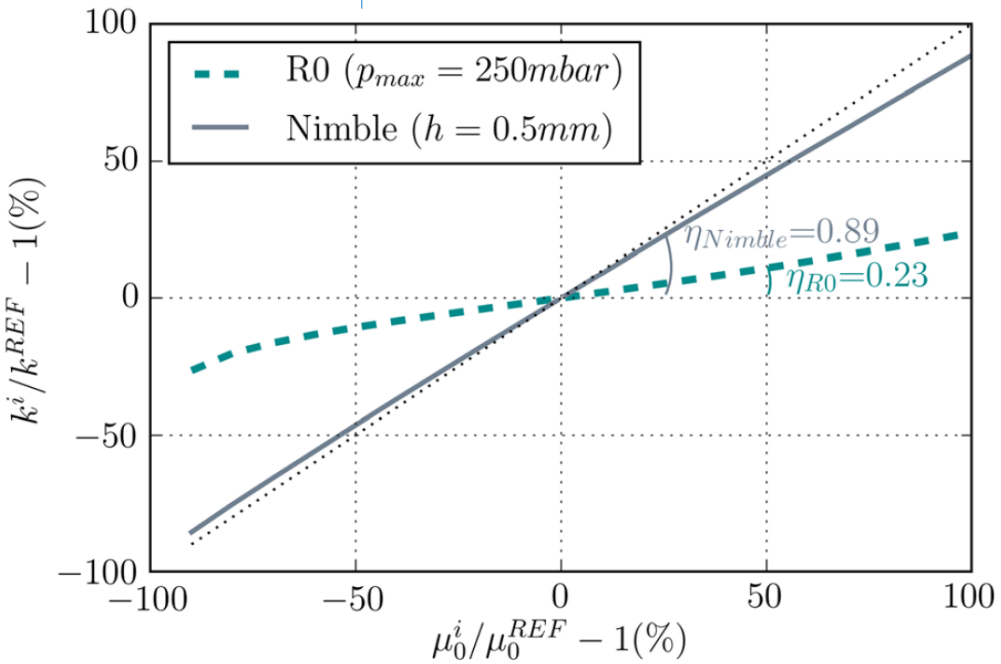
extract pressure for a defined elevation

B. Müller et al., 2021, On the Reliability of Suction Measurements for Skin Characterization, Journal of Biomechanical Engineering, Vol. 143

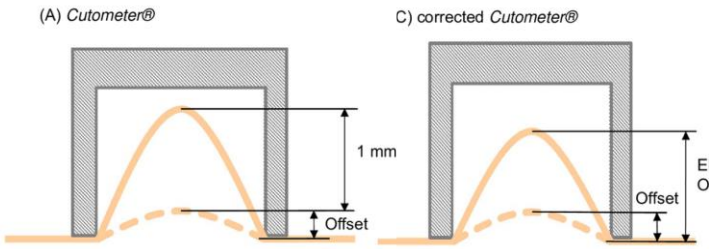
Advantages of new suction device

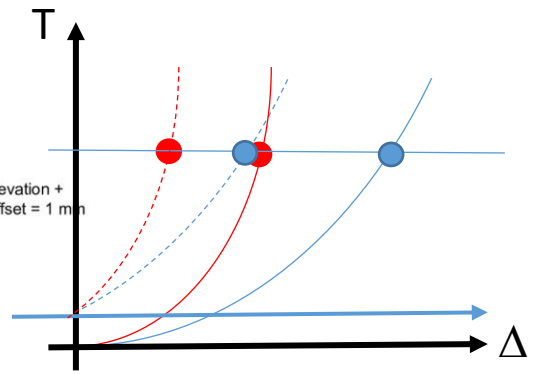
Displacement controlled measurement

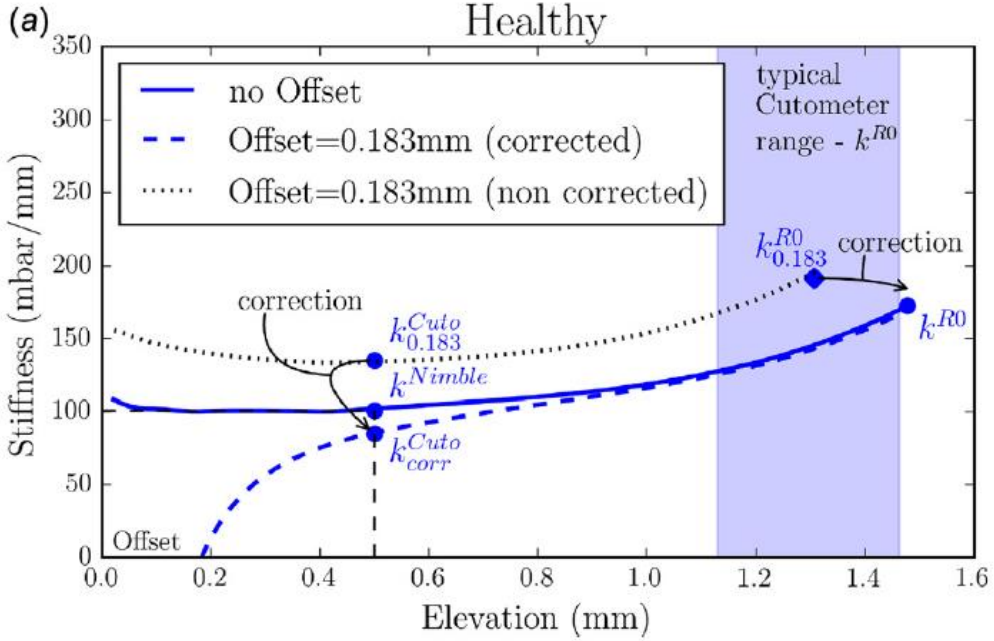




Influence of pre-force



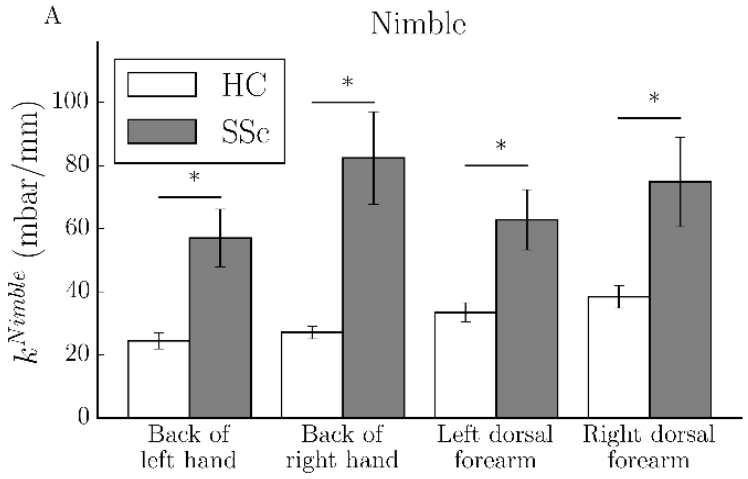


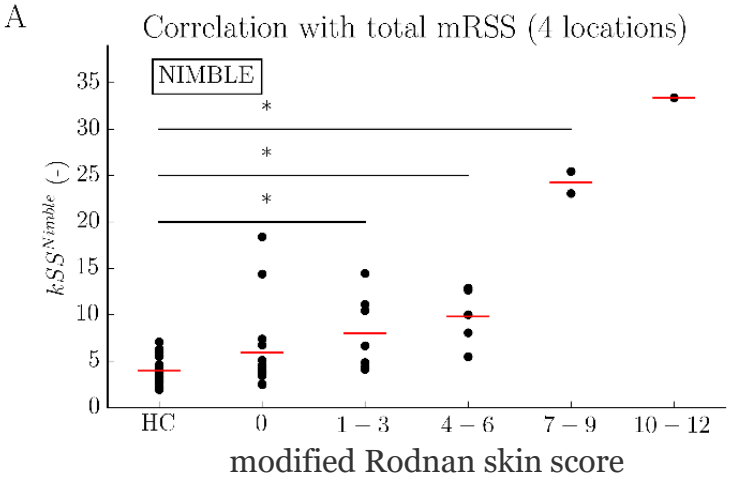


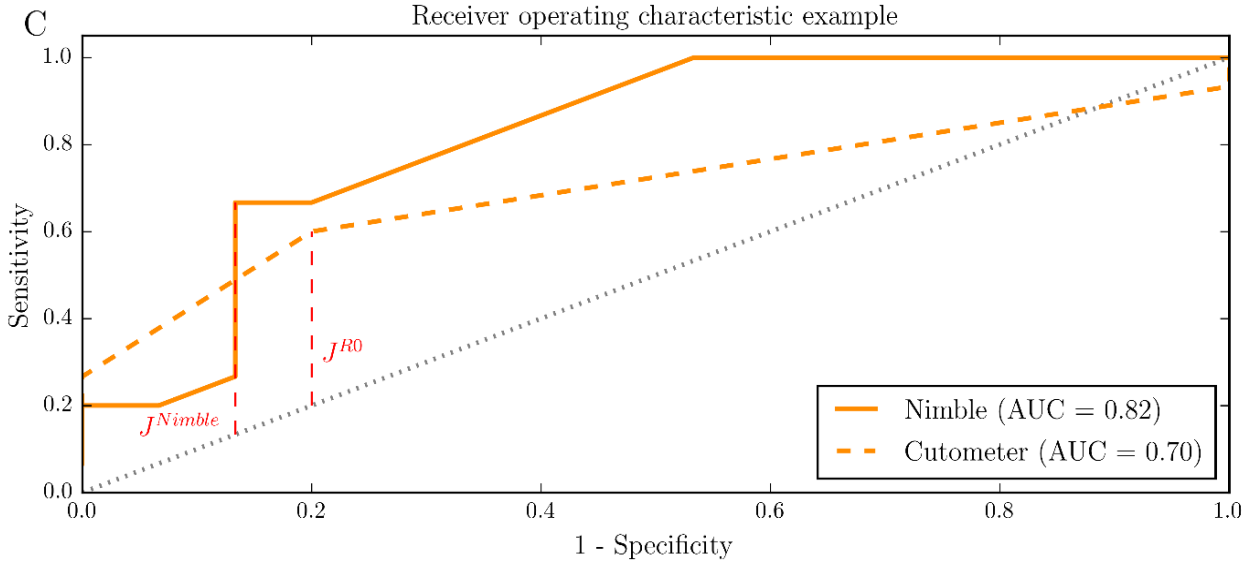
B. Müller et al., 2021, On the Reliability of Suction Measurements for Skin Characterization, Journal of Biomechanical Engineering, Vol. 143

Diagnosis based on biomechanical measurements

Early detection of scleroderma (collaboration with University Hospital Zurich)







Bettina Müller, Lisa Ruby, Suzana Jordan, Marga B. Rominger, Edoardo Mazza and Oliver Distler, 2020, Validation of the suction device Nimble for the assessment of skin fibrosis in systemic sclerosis. Arthritis Research & Therapy, vol. 22: no. 1,

Diagnosis based on biomechanical measurements

Scar monitoring (collaboration with Kinderspital Zurich)

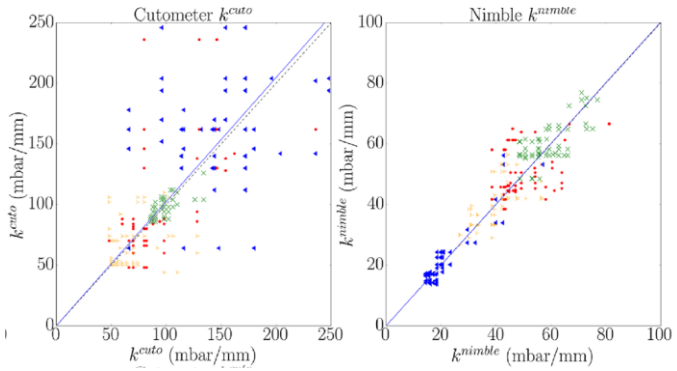
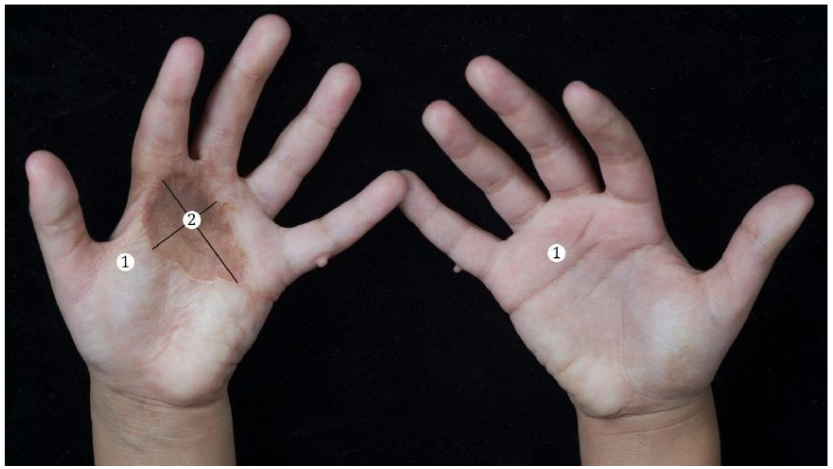
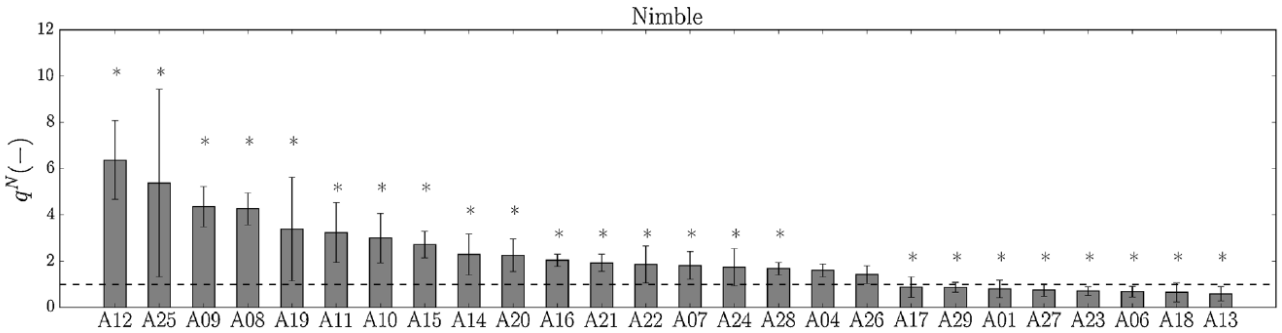


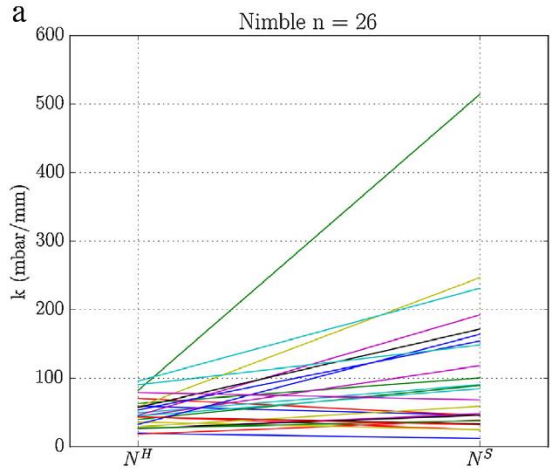
Table 2 – Interobserver variability assessed by means of ICC (2,1) and ICC (2,k).

Interobserver variability – ICC

	HEALTHY		SCAR	
	Nimble	Cutometer®	*Nimble*	Cutometer®
ICC(2,1)	0.88	0.56	0.87	0.75
ICC(2,k)	0.95	0.79	0.95	0.90







Julia Elrod, Bettina Müller, Christoph Mohr, Martin Meuli, Edoardo Mazza and Clemens Schiestl, 2020, An effective procedure for skin stiffness measurement to improve Paediatric Burn Care, Burns, vol. 45: no. 5

Conclusions

- Skin biomechanics and mechanobiology as an exciting playground for continuum mechanics, with important applications.
- Modeling approach depends on the specific question in each application, simplifications are needed and often well justified.
- Shift of length scale of homogenization is relevant for mechanobiological studies (to represent heterogeneity at cell length scale) → dermal mechanome!
- Understanding of skin biomechanics and mechanobiology relevant for clinical applications.

<u>Thanks to:</u>

FNSNF Fonds national suisse de la recherche scientifique

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Confédération suisse
Confederazione Svizzera
Confederaziun svizra

ETH zürich

SKINTEGRITY.CH


Dr. A. Wahlsten


D. Sachs


Dr. A. Stracuzzi


A. Martyts


Dr. B. Müller


H. Junker


Dr. C. Giampietro


Dr. A. Ehret