Multiscale Mechanics of Human Skin

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Skin: our largest organ

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)
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
Several constitutive models proposed

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

\[ \psi = c_1 (I_1 - 3) - c_2 (I_2 - 3) + f(I_3) \]

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

\[ \psi = \sum_{i=1}^{N} 2 \mu_i \left( \lambda_1^{\alpha_i} + \lambda_2^{\alpha_i} + \lambda_3^{\alpha_i} - 3 \right) \]

\[ \psi = (1 - \psi_c - \psi_e) \frac{\mu}{2} (I_1 - 3) + \sum_{k} \psi_k \sum_{\alpha} R_k (\theta) \frac{K_k}{2} (\lambda - 1)^2 \]

\[ \psi = \psi^v(J) + \sum_{i=1}^{2} \left[ \psi_i^I (\lambda_i) + \psi_i^I (\alpha_i^1) + \psi_i^I (\alpha_i^2, \lambda_i) \right] \]

\[ \psi = \frac{\mu}{2} (I_1 - 3) + \sum_{i=1}^{2} \frac{k_{i1}}{k_{i2}} \left( \exp \left[ k_{i2}[H_i : C - 1]^2 \right] - 1 \right) \]

\[ \rho_0 \psi = \frac{\mu_0}{2q} \left[ \exp(qg) - 1 \right] \]

\[ g_1 = 2m_1 \left[ (J - 1) - 1n(J) \right], \quad g_2 = (1 - \omega)m_2(\beta - 3), \]

\[ g_3 = 0, \quad g_4 = \chi - 3, \]

Veronda-Westmann
Mooney-Rivlin
Polynomial
Ogden
Lanir
Gasser-Holzapfel-Ogden
Limbert
Rubin-Bodner

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...

For each application:
Model assumptions and simplifications might be adequate, or not!
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
Skin stretch influences biological processes (physiology and pathology).

Keoloids correlate with skin tension

Tension shielding reduce scarring

How does skin stretch change the physical environment of cells?
Some insights on deformation behavior of soft collagenous tissues

\[ t = \frac{F}{\lambda_2 W_0} \]

significant volume change!

\[ \lambda_3 = \frac{f}{f_0} \]

DIC

modified from Mauri et al. (2015JB)

modified from Ehret et al. (2017NC)

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.
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.
Consequences for fracture behavior

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

Collagen (from SHG)  Nuclei (nuclei Hoechst/DAPI stain)  NAR =$\frac{a}{b}$

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)


- Neglects possible **relative motion** between solid and fluid phases


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**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
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
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 \( \text{grad}(\mu = p - \pi) \)
- 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

- Bi-phasic matrix as homogenized continuum
  - solid volume fraction \( \phi_s = \frac{v_s}{v} \)
  - fluid volume fraction \( \phi_f = \frac{v_f}{v} \)
  - saturation condition \( \phi_s + \phi_f = 1 \)

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

  Various degrees of coupling considered

  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),
  \( \rightarrow \) free energy depends on deformation gradient and fluid molar concentration

Hong, Liu, Suo, Int. J. Solids and Structures, 46, 2009
Model implementation, specific for present case
(saturation condition, solid and liquid phases as incompressible)

free energy: \( \psi(\underline{E}) \rightarrow \psi(\underline{E}, C) \)

\[ C: \text{Nr of moles of liquid per referential volume; } C = \frac{n M}{V} \]

\[ P \cdot \dot{\underline{E}} + \dot{P}_F - \dot{\psi} \geq 0 \]

\( P_F: \text{fluid power} \)

\[ \text{chemical potential per mole} \]

\[ \text{liquid flux (nr of moles per unit time)} \]

\[ P_F = - \int_{\partial \Omega_R} \bar{\mu} Q \cdot N dA = - \int_{\Omega_R} \text{Div}(\bar{\mu} Q) dV \quad \rightarrow \quad \dot{P}_F = -\bar{\mu} \text{Div}(\underline{Q}) - \underline{Q} \text{Grad}(\bar{\mu}) \]

\[ \dot{C} = -\text{Div}(\underline{Q}) \quad \leftrightarrow \quad \text{continuity equation} \]

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

\[ \dot{C} = \frac{\partial C}{\partial J} \frac{\partial J}{\partial \underline{E}} \cdot \dot{\underline{E}} \]

\( Q: \text{volumetric flux} = \underline{Q} \cdot V_M \)

\( \mu: \text{chemical potential per volume of liquid} = \frac{\bar{\mu}}{V_M} \)

\[ P \cdot \dot{\underline{E}} + \mu J \underline{E}^{-T} \cdot \dot{\underline{E}} - Q \text{Grad}(\mu) - \dot{\psi}(\underline{E}, C(J)) \geq 0 \]
Model implementation, specific for present case
(saturation condition, solid and liquid phases as incompressible)

\[
\psi = \psi_s(F) + \psi_{osm}(J)
\]

\[
\psi_s = \left(\psi_{Matrix} + \psi_{Fibers}\right) \cdot \Phi_s^{ref}
\]

\[
\dot{\psi} = \frac{\partial \psi_s}{\partial F} \cdot \dot{F} = \left(\frac{\partial \psi_s}{\partial J} \cdot JF^{-T}\right) \cdot \dot{F}
\]

\[
\rightarrow \left(P + \mu JF^{-T} - \frac{\partial \psi_s}{\partial F} - \frac{\partial \psi_{osm}}{\partial J} JF^{-T}\right) \cdot \dot{F} - QGrad(\mu) \geq 0
\]

\[
\rightarrow P = \frac{\partial \psi_s}{\partial F} - (\pi + \mu) JF^{-T} \quad \pi + \mu = p \quad \text{(Fluid hydrostatic pressure)}
\]

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

with \( Q = -KGrad(\mu) \) \( \rightarrow \) \(-QGrad(\mu) = K(Grad(\mu))^2 \geq 0 \) dissipation satisfied

Flow depends on Grad of \( \mu = p - \pi \)

\[
J = \Phi_s^{ref} + V_M C \quad \rightarrow \quad \dot{J} = V_M \dot{C} = -Div(Q) \quad \rightarrow \quad \dot{J} = Div(KGrad(\mu)) \quad \text{Rate of change of volume} \leftrightarrow \text{flow}
\]

Hydraulic conductivity \( \frac{K}{k_0} = \frac{J - \phi_{s}^{ref}}{1 - \phi_{s}^{ref}} \left[ \frac{k_1}{k_2} (J^2 - 1) \right] e^{k_2 (J^2 - 1)} \)

\( k_2 \sim 10^{-14} \text{ m}^4/\text{N/s}, \quad [\text{Holmes&Mow} 1990] \)
The model can rationalize experimental data

Macroscopic response:

Relaxation with change of bath

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
Osmotic pressure term

\[ \pi(J) = -\frac{R \Theta}{V_M} \left[ \ln \left( \frac{J - \phi_s^{\text{ref}}}{J} \right) + \frac{\phi_s^{\text{ref}}}{J} + \frac{\chi_{FH} (\phi_s^{\text{ref}})^2}{J^2} \right] \]

Based on Flory-Huggins potential

\[ \pi = R \Theta \left( \sqrt{c_F^2 + 4c_{\text{ext}}^2} - 2c_{\text{ext}} \right) \quad c_F(J) = c_F^{\text{ref}} \frac{1 - \phi_s^{\text{ref}}}{J \phi_s^{\text{ref}}} = c_F^{\text{ref}} \frac{1 - \phi_s^{\text{ref}}}{J - \phi_s^{\text{ref}}} \]

Based on Donnan equilibrium

\[ \pi = a_0 \left( \frac{1 - \phi_s^{\text{ref}}}{J - \phi_s^{\text{ref}}} \right)^{2a_1} + \pi_0 \]

Based on measurements (fit an empiric relation)

Confined compression

Relaxation with change of bath

Microindentation with change of bath

Experiment vs. Model

\[ \sigma_s = \phi_s^{\text{ref}} C_0 C_1 e^{g g_m J^{-1}} \bar{F} \bar{F}^T - \pi \]
Corresponding continuum model (i.e. without discrete fibers)

Fibers considered in strain energy formulation
Rubin-Bodner type strain energy function

\[ \tilde{\Psi}_s(F, \lambda_{e,1}, \lambda_{e,2}, ..., \lambda_{e,N}) = \phi^\text{ref}_s \frac{C_0}{2q} \left[ e^q(g_m + g_{fe}) - 1 \right] \]

\[ g_m = c_1 \left[ \text{tr}(F^TF) - 3 \right] \]

\[ g_{fe} = \frac{c_2}{c_3} \frac{1}{N} \sum_{i=1}^{N} (\lambda_{e,i} - 1)^{2c_3} \]

[Rubin&Bodner 2002]

\[ \lambda_i = |FM_i|, \langle \bullet \rangle - \text{Macauley brackets} \]

quasi in-plane isotropy

solid stress \( \sigma_s \)

\[ \frac{\dot{\lambda}_{e,i}}{\lambda_{e,i}} = \frac{\dot{\lambda}_i}{\lambda_i} - \phi^\text{ref}_s c_0 e^q(g_m + g_{fe}) \frac{c_2}{\nu_F} \lambda_{e,i} (\lambda_{e,i} - 1)^{2c_3} - 1 \]


...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
Cells biophysical environment in stretched skin

Model based prediction of stretch induced local changes

Tension leads to changes in local cell environment.


Stracuzzi, ETH dissertation, 2021; Wahlsten, ETH dissertation, 2022
Stracuzzi, ETH dissertation, 2021
Cells biophysical environment in stretched skin

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Stracuzzi, ETH dissertation, 2021
Cells biophysical environment in stretched skin

Model based prediction of stretch induced local changes

Tension leads to changes in local cell environment.

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
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


Wahlsten A. et al, Biomaterials, 2021

Ki67 mRNA expression (RT-qPCR)
Mechanical factors influencing wound healing

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

Evolution of mechanical properties contrary to expectations from histology.


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
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


Characterization based on suction measurements

Advantages of new suction device

Displacement controlled measurement

Influence of pre-force

Diagnosis based on biomechanical measurements

Early detection of scleroderma (collaboration with University Hospital Zurich)


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).

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<thead>
<tr>
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<th>HEALTHY</th>
<th>SCAR</th>
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<tbody>
<tr>
<td></td>
<td>Nimble</td>
<td>Cutometer*</td>
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<tr>
<td>ICC(2,1)</td>
<td>0.88</td>
<td>0.56</td>
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<tr>
<td>ICC(2,k)</td>
<td>0.95</td>
<td>0.79</td>
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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.

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