Can We Measure Corneal Biomechanical Constants in a Clinical Setting?

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Objectives

First considerations:

- Why measure biomechanics?

*What will we do with the measurements?*

How do we measure?

- Emerging techniques
- Promising cross-discipline technologies
“Central Dogma” of Corneal Biomechanics

- Anatomy + Material Properties =>
- Biomechanical behavior =>
- Shape =>
- Optical outcome/vision

- Biomechanics links anatomy and any structural perturbation, instantaneous or delayed, to vision
- Exquisite measurement capabilities: the perfect tissue for studying biomechanics

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Corneal Biomechanics: 3 Impact Areas

- Refractive surgery
  - Improved predictability with true biomechanical customization
- Keratectasia
  - Determining the biomechanical phenotype of keratoconus/PMD/Ehlers Danlos
  - Preventing iatrogenic ectasia (preclinical diagnosis)
- Glaucoma/OHT
  - Accurate transcorneal IOP measurement

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Area #1: Refractive Surgery Outcomes

Do good outcomes argue against a biomechanical contribution to refractive outcome?

- True custom treatment is:
  - Deterministic
  - Individual
  - Prospective
  - Predictable results in patients who don’t represent the mean

- Algorithm design is:
  - Probabilistic
  - Populational
  - Retrospective
  - Iterative

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A conceptual biomechanical model of central keratectomy

- Central keratectomy causes *peripheral lamellar relaxation*
- Peripheral fluid imbibation & stromal *thickening*
- Crosslinks couple peripheral volume increase to *central flattening*
- *Stress* contributes to early flattening, late viscoelastic relaxation

Paired Control Donor Eye Study

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Central Flattening and Peripheral Stromal Thickening

Dupps WJ, Roberts C (JRS 2001)

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Custom Finite Element Modeling

- Macrostructural geometry
  - Topography, elevation, pan-corneal pachymetry
- Substructural meshing
  - Viscoelastic material constants
- Load
- Stress/strain/geometric solutions
- Treatment
- Refine
- Comparison to empirical data

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Area #2: Keratectasia

- First reported after LASIK in 1998 (Seiler et al, JRS)
- Incidence:
  - Pallikaris 2001: 19 of 2873 eyes, mean 14.65 D
  - Rare after hyperopic LASIK, PRK
- Onset often delayed:
  - Mean 16 months, range 1 to 45 (Randleman et al, 2003)
  - Long-term concern
Characterizing the Phenotype of Ectasia

Before any clinical, topographic or wavefront signs of ectasia, there is a *biomechanical abnormality*

Targeting this abnormality may facilitate:
- Sensitive and specific screening of at-risk patients
- Better clinical definition of KCN for understanding pathogenesis, early detection, linkage analysis, and development of tissue/animal models

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Area #3: Glaucoma

- Major cause of preventable blindness
- Again, biomechanical risk factor precedes injury
- IOP measurement still elusive
  - Imbert-Fick principle: $P = \text{Force/Area}$
    - Applanation force is dependent on corneal resistance
  - Over-estimated in thick corneas, scar
  - Underestimated in corneal edema, thin corneas (post refractive surgery, ectasia)

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Which properties should we measure?

- Application dependent:
  - Refractive surgery:
    - SHAPE changes are starting point
    - Conceptual models
    - Material properties that drive the shape change
  - Ectasia
    - Discriminating mechanical predictors (elastic & shear strength, Poisson’s ratio)
  - IOP
    - Stiffness analogues (E, K)

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A Biomechanical Survey of the Cornea: Assumptions and Challenges

- Stroma predominates response
- Elasticity, plasticity, nonlinearity
- Viscoelasticity
  - Time-dependent
  - Biological modulation
- Anisotropy & inhomogeneity with respect to:
  - Meridian
  - Radius
  - Depth
- But most material property measurements involve a bulk measurement

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Can We Measure Material Constants?

- Can *measure* strain, wave propagation speed, etc.
- Material constants *calculated* from a given model of the tissue (e.g., Hooke’s Law)
- Constitutive properties are highly dependent on input parameters
  - if disease involves a different range of stress, strain and model geometry, the same model may not suffice

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Thomas Young (b. 1773)

- English physicist, physician, Egyptologist
  - Expert on mechanics, hemodynamics
  - Young-Helmholtz trichromatic theory
  - Principle of interference
  - Described astigmatism
  - Helped decode the Rosetta stone
Young’s Modulus (E)

- Measured many times, in many ways in cornea
- Units of force/area (N/m\(^2\) = Pa)
- Stiffer materials have higher modulus
- Increases with age, crosslinking, IOP
Young’s Modulus

Generalized Hooke’s Law

\[ \sigma_{ij} = \sum_{kl} C_{ijkl} \cdot \varepsilon_{kl} \]

\[ F = kx \]

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Young’s Modulus

- Extensiometry remains the gold standard, but
- Problems with destructive tissue testing
  - Hydration
  - Age/status of donor tissue
  - Composite behavior compromised
Young’s Modulus

- Relevance
  - Instantaneous elastic response to surgery (photoablation, incisional)
  - Post-LASIK “pre-ectasia” (Guirao, JRS March/Apr 2005)
  - Elastic strength decreased in keratoconus specimens
    - Edmund, Acta Ophth 1989
    - Foster & Yamamoto, AJO 1978

- Trans-corneal IOP

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Ocular Rigidity Coefficient (K)

- Friedenwald (AJO 1937)
  - Slope of pressure/volume relationship
  - Postmortem eyes

- Pallikaris (IOVS 2005)
  - In vivo $K = 0.0126$ mm Hg/ uL
  - Linear (in 10 – 35 mm Hg range)
  - Increased with age ($r = 0.27$, $p = 0.02$)

- Equivalent to bulk modulus (K)

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Shear Modulus (G) & Interlamellar Relationships

- Modeling shear (*sliding, bending*)
  - Crosslinking greatest in anterior and peripheral stroma (Komai & Ushiki, 1993)—lowest in postero-central stroma
  - Lower interlamellar cohesion infero-centrally (Smolek 93)

- Provides mechanism for transfer of tensile loads between lamellae (PTK response)
- Ectasia: Relative shear weakness, esp. in posterior stroma, keratocyte dysfunction may exacerbate (Achilles’ heel?)

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Poisson’s Ratio ($\nu$)

- Relates out-of-axis strain to axial strain

- Corneal estimates 0.3 to 0.49
  - 0.5 for incompressible material (rubber vs. cork)
  - Can be calculated or measured directly by geometry

- Relationship to elastic modulus:
  - $\varepsilon_{xx} = \frac{1}{E} \{\theta_{xx} - \nu \theta_{yy} - \nu \theta_{zz}\}$

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Poisson’s Ratio

- Viscoelastic domain
  - Time and strain-rate dependent
  - Transverse response may be out of phase
  - Leads to creep and stress relaxation
- Relevance in refractive surgery
  - May account for residual stromal thickness thinner at time of enhancement (Chavala et al, ARVO 2003)
Nondestructive Corneal Elastometry: Mechanical Techniques

- Indentation/suction techniques (Dermatology)
- Holographic interferometry (Kasprzak et al 1993, Smolek 1994)
  - Apical displacement measured with submicron resolution and sensitive to <<1mmHg IOP change
  - Simple thin shell analysis
  - Both give only a bulk measure

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Nondestructive Corneal Elastometry: Mechanical Techniques

- Surface wave propagation
  - Established dermatologic stiffness analogue
  - Sonic Eye ® (PriaVision, Inc., Menlo Park CA)
    - 4.5 mm propagation distance
    - Rayleigh wave principle (long wavelength)
    - Reports time-of-flight or velocity
    - Simplified model: $E \propto \rho V^2$
    - Provides directional information

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Sonic Eye® output display

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Surface Wave Elastometry

- Porcine globe studies
  - To determine:
    - Repeatability
    - Effect of debridement
    - Effect of keratotomy depth
  - Methods
    - IOP by infusion (15)
    - Replicates at 10 “cardinal” positions
      - With epithelium
      - Without epithelium
      - 250 um deep central incision
      - Extension of same incision to 750 um

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Results

- Mean Velocities: 116 – 153 m/s
- No systematic change with epithelial removal (p > .05)
- Debridement reduced inter-subject SD (from 40 to 25 m/s)
- Pre-incision velocity: 130 ± 33 m/s
- Across 250 um incision: 79 ± 17 m/s (p = .001)
- Across 750 um incision: 66 ± 31 m/s (p = .24)

![Graphs showing wave velocity with and without epithelium before and after debridement.](image)
Conclusions in porcine tissue

- Epithelium does not contribute systematically to stiffness, but does contribute to inter-subject measurement variability.

- Stiffness is decreased across a partial-thickness wound but is unchanged along uncut fibrils.

- Sampling depth predominantly within anterior 250 um.

- Comparison of regional/directional values underway, modeling surface wave for calculation of Young’s modulus.

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Corneal Stiffness and Transcorneal IOP

Purpose: Demonstrate that transcorneal IOP is a function of corneal stiffness, independent of CCT

Methods:
- 2 debrided donor globes, intravitreal IOP maintained at 30
- Glutaraldehyde 4% for 45 minutes (each thinned slightly)

<table>
<thead>
<tr>
<th>Donor</th>
<th>Pneumo (mmHg)</th>
<th>Tonopen (mmHg)</th>
<th>Stiffness (m/s)</th>
<th>Pneumo (mmHg)</th>
<th>Tonopen (mmHg)</th>
<th>Stiffness (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.5</td>
<td>35</td>
<td>80 ± 3</td>
<td>71</td>
<td>87</td>
<td>145 ± 5</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>36</td>
<td>79 ± 4</td>
<td>79.5</td>
<td>89</td>
<td>147 ± 5</td>
</tr>
</tbody>
</table>

After crosslinking

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Surface Wave Elastometry

Potential limitations:
- Indentation
- Visit-to-visit positional repeatability
- Dependence on surface hydration
- Modest IOP increase during measurement
- Effective sampling depth
Optical Elastography

Optical approaches

Potential advantages:

- Non-invasive to non-contact (no indentation artifact)
- Mapping of moduli, optical registration
- High resolution, detects low-contrast moduli
- Non-invasive technique may allow longer viscoelastic measurements for relaxation moduli
- Internal strains detectable, depth analysis feasible
Optical Elastography

- Speckle-shift elastography (Kirkpatrick, Duncan)
  - Coherent light produces speckled images
  - Speckle patterns tracked with applied stress
  - Elastic modulus mapped in 2-D (skin)
  - Acoustic (low freq) or laser modulation possible

Duncan & Kirkpatrick, 2002
Optical Elastography

- OCT elastography (Schmitt 1998)
  - Micron-resolution strain mapping to 1mm depth, calculation of elastic modulus
  - Recent application to arterial wall stiffness measurements with pulsatile stimulus
Conclusion

Global view:
- Inadequate models are the rate-limiting step

View from the ground:
- We need individual, repeatable, practical, & minimally-invasive biomechanical measurements to predict surgical response, risk of ectasia, IOP
- Simple regression models can serve as predictive/screening tools as we explore relationships between constitutive properties and shape change

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Peripheral Stromal Thickening: Paired human donor eye study

- 100-um broad beam PTK ablations
- Paired controls received sham ablation
- Optical section photography
- 6.3 ± 3.2 D hyperopic shift (p = .002)

Max ablation depth determines hyperopic response

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An Integrated Approach to Measurement, Modeling and Clinical Implementation

- Clinical & tissue-oriented laboratory investigation
  - *In vivo* measurement of biomechanical properties
    - Characterization of corneal shape changes with various surgical stimuli using robust biometry, correlation with mechanical predictors
- Integrated optical and biomechanical modeling
  - Incorporation of prospective biomechanical predictors
    - Test models against empirical data
    - Develop custom ablation routines, refine with optical analyses
- Account for/modify wound healing
Problem: Who will develop ectasia?
Peripheral lamellar relaxation

Photo courtesy of J. Marshall, Ph.D
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