Can We Measure Corneal Biomechanical Constants in a Clinical Setting?

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February 12, 2005
6th Wavefront Congress, Athens

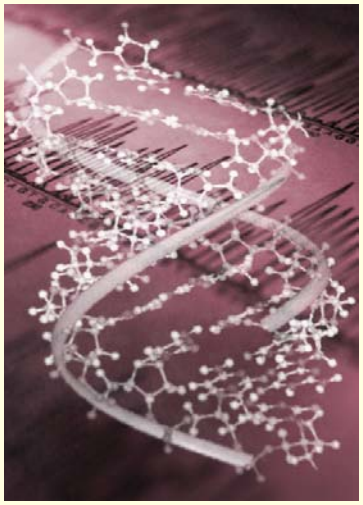
THE CLEVELAND CLINIC

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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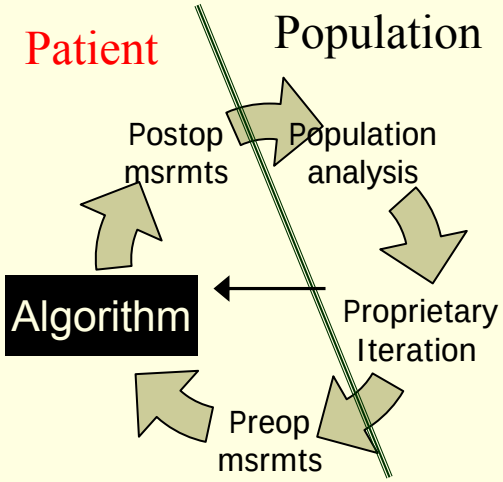
Area #1: Refractive Surgery Outcomes

- 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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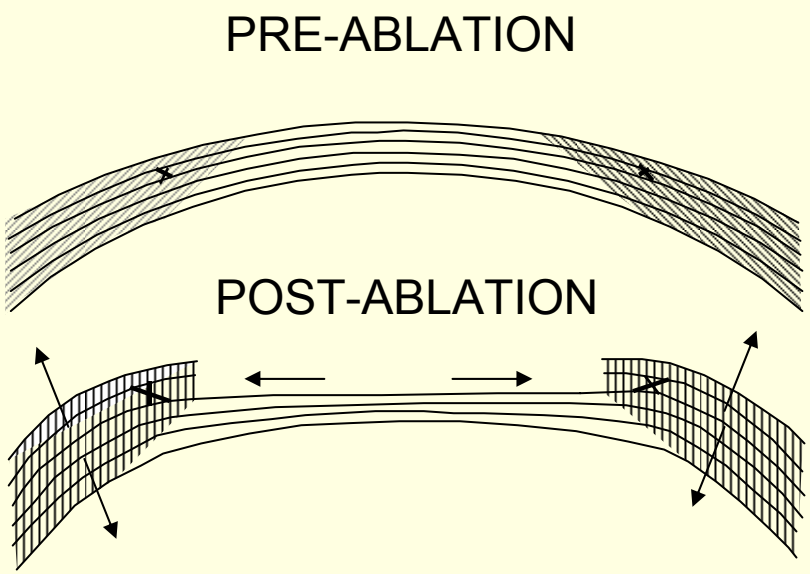
A conceptual biomechanical model of central keratectomy



Dupps WJ, Roberts C, Schoessler JP (ARVO 1995)

- 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

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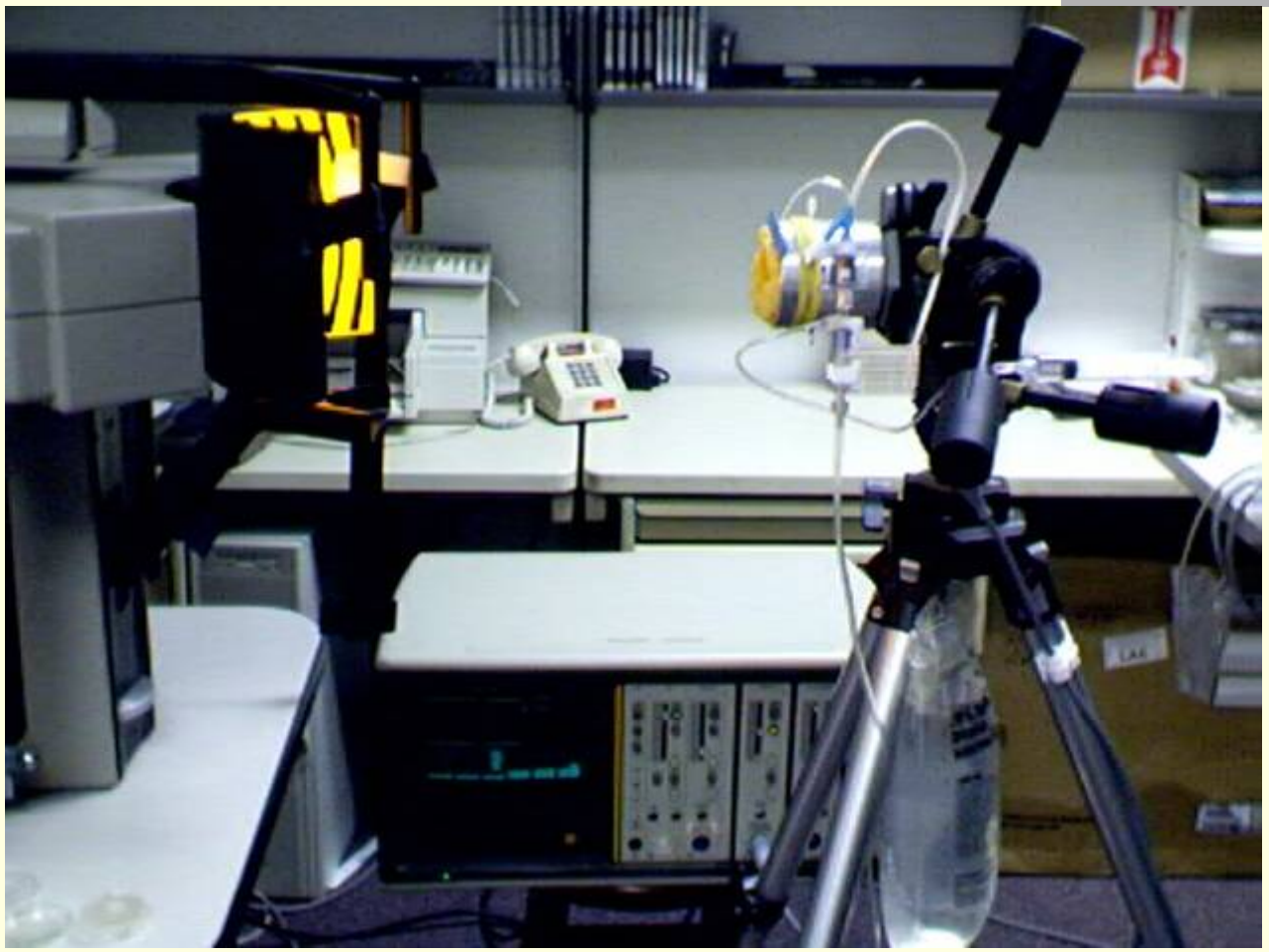
Paired Control Donor Eye Study



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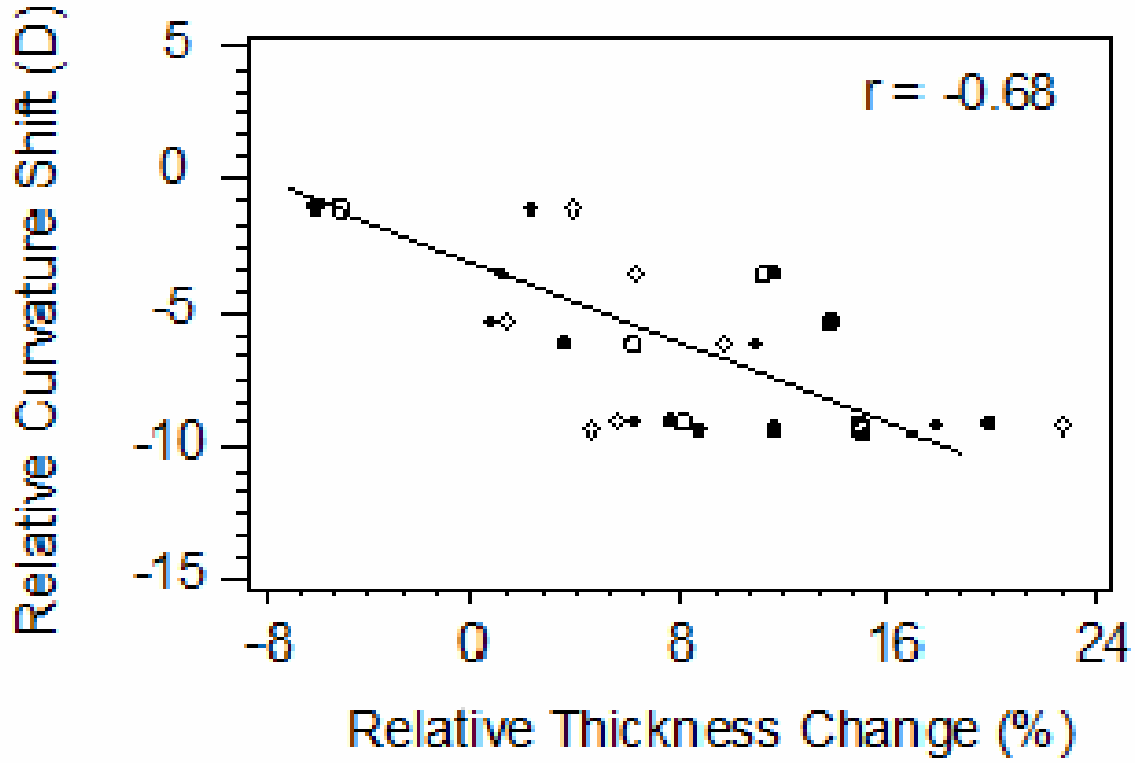
Central Flattening and Peripheral Stromal Thickening



Dupps WJ, Roberts C (JRS 2001)

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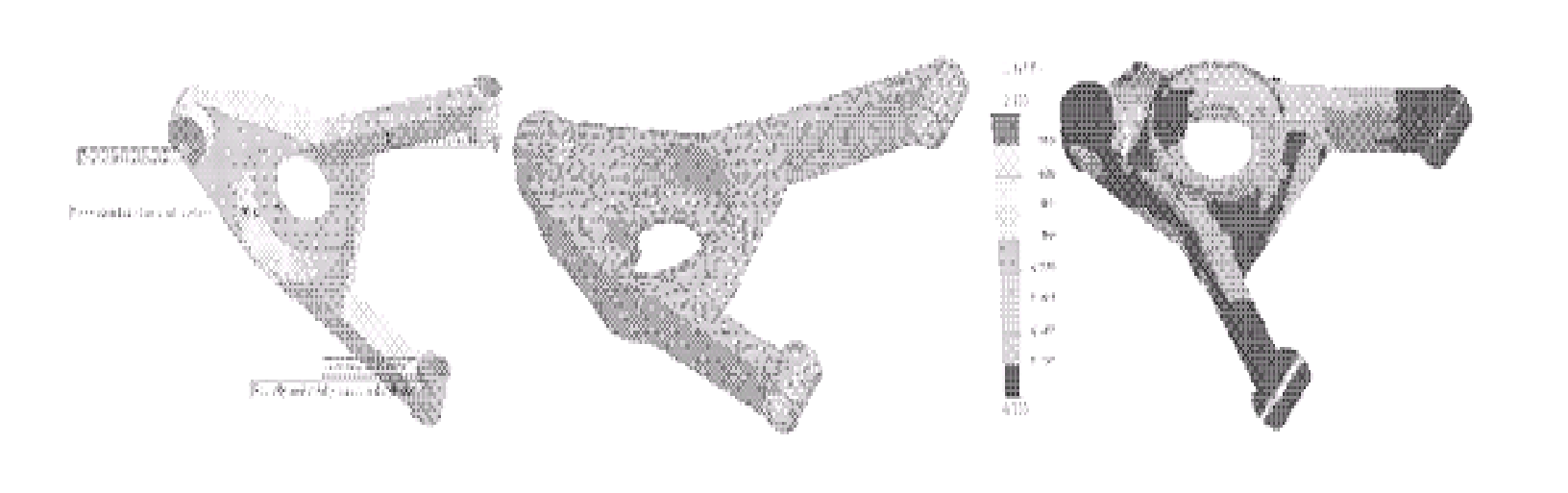
Custom Finite Element Modeling



Macrostructural geometry

Substructural meshing

Load

Stress/strain/ geometric solutions

Treatment

Topography, elevation, pan-corneal pachymetry

Viscoelastic material constants

2

1

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 = 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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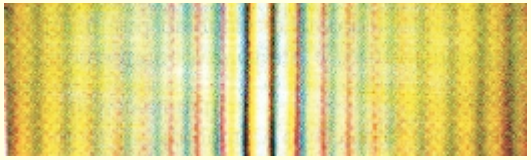
Can We Measure Material Constants?

- Can *measure* strain, wave propagation speed, etc.
- Material constants *calculated* from a given model of the tissue (eg., 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

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

Thomas Young
(1773-1829)



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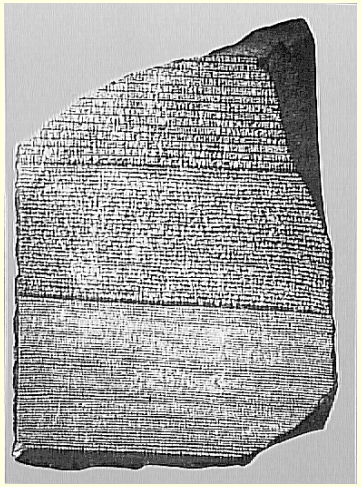
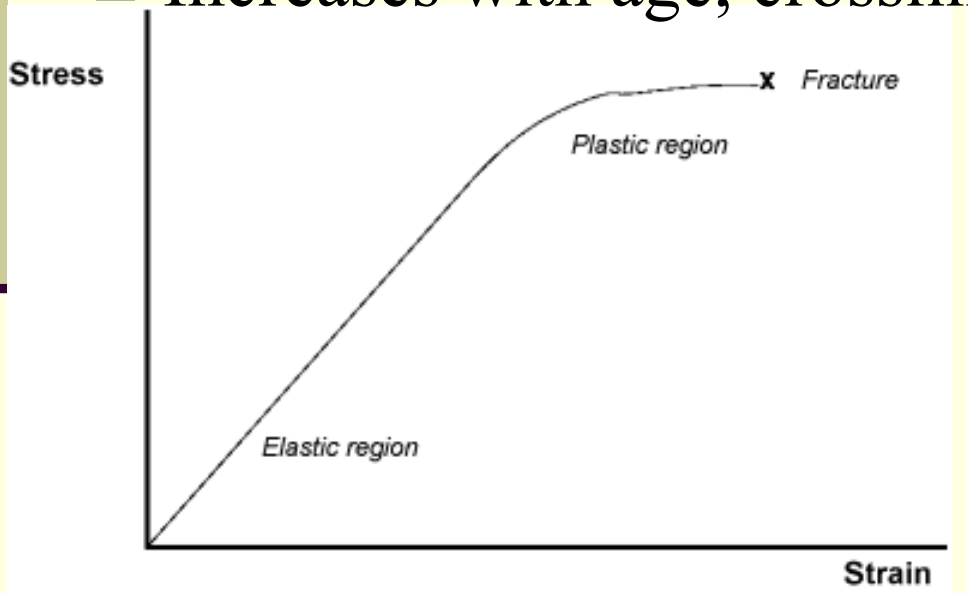
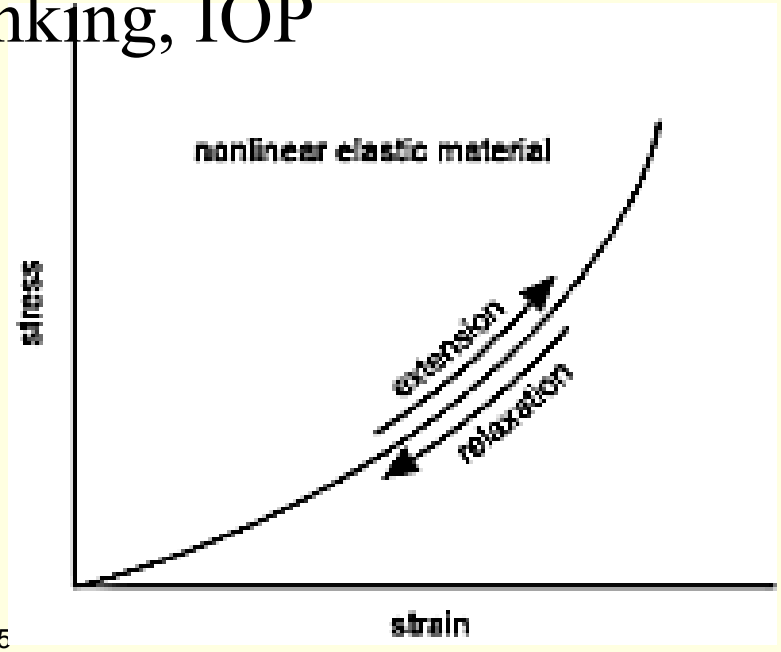


Young's Modulus (E)

- 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





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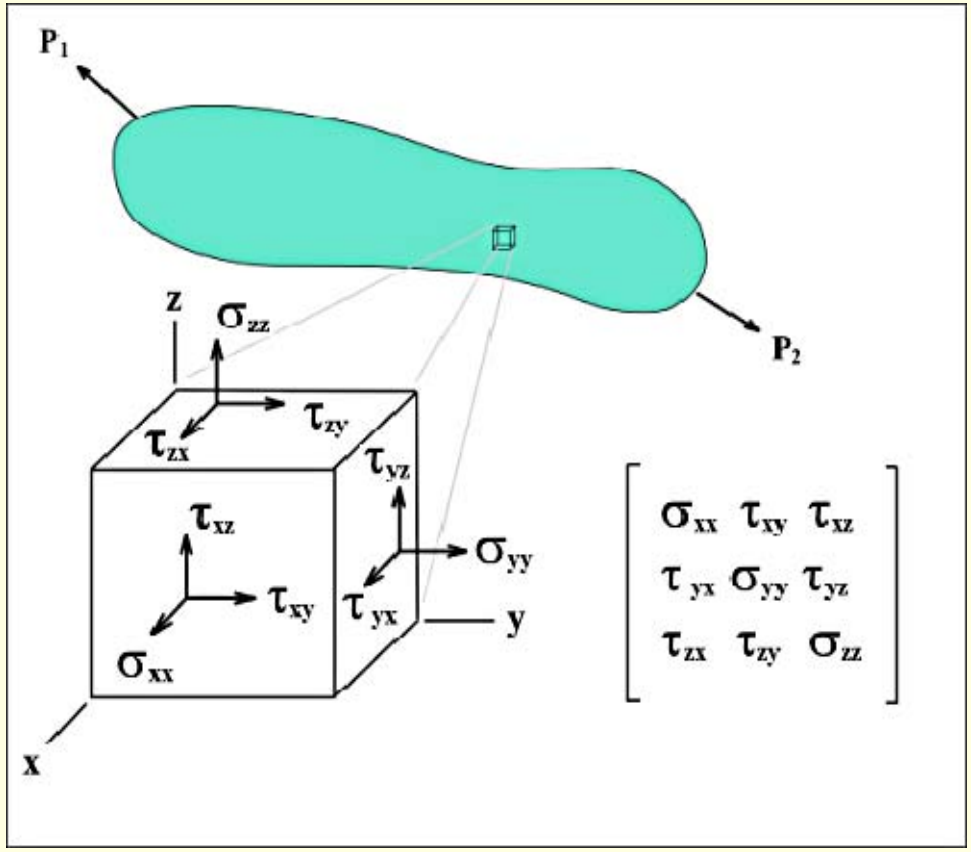
Young's Modulus

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

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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
    - Nash et al, Exp Eye Res 1982
    - Andreassen et al, Exp Eye Res 1980
    - Foster & Yamamoto, AJO 1978
  - Trans-corneal IOP

Ocular Rigidity Coefficient (K)

- Friedenwald (AJO 1937)
  - Slope of pressure/volume relationship
  - Postmortem eyes
- Pallikaris (IOVS 2005)
  - In vivo K = 0.0126 mm H/ uL
  - Linear (in 10 – 35 mm Hg range)
  - Increased with age ($r = 0.27$, $p = .02$)
- Equivalent to bulk modulus (K)

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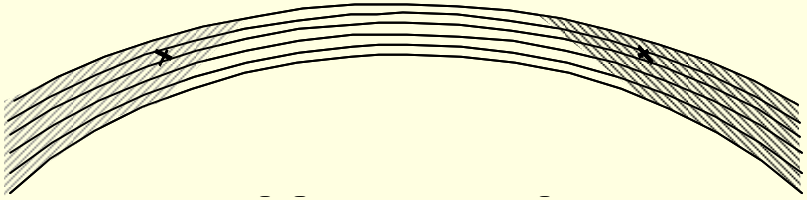
Shear Modulus (G) & Interlamellar Relationships

- 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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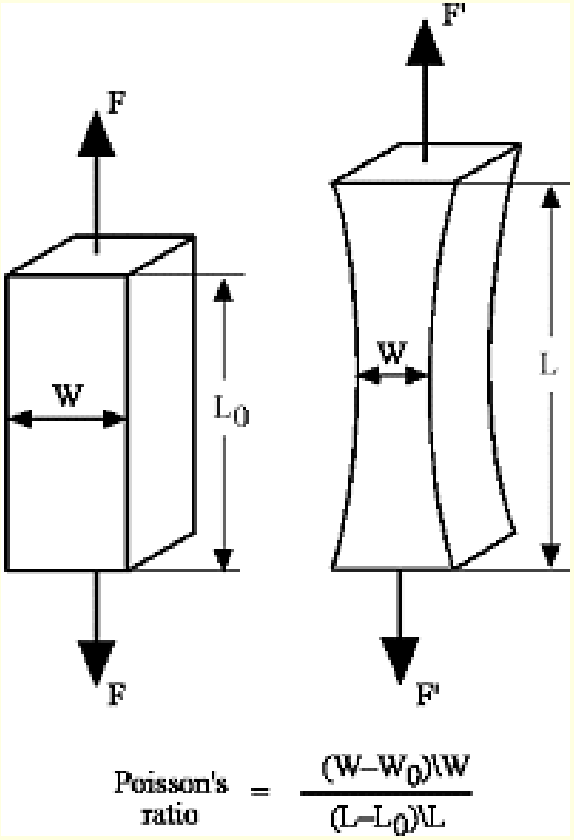
Poisson's Ratio (ν)

- 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:
  - $\varepsilon_{xx} = (1/E)\ \{\theta_{xx} - \nu\ \theta_{yy} - \nu\ \theta_{zz}\}$



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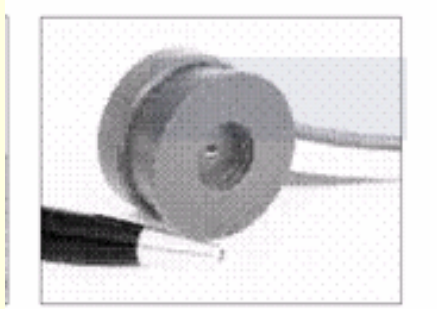
Poisson's Ratio

- 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



Suction cup elasticity probe

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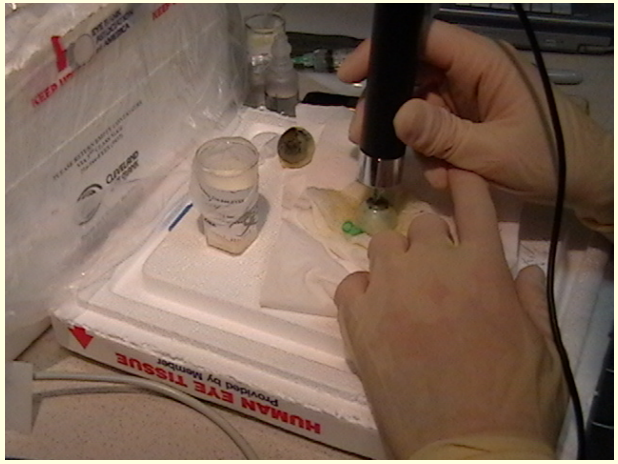
Nondestructive Corneal Elastometry: Mechanical Techniques

- 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: $E \alpha \rho V^2$
    - Provides directional information



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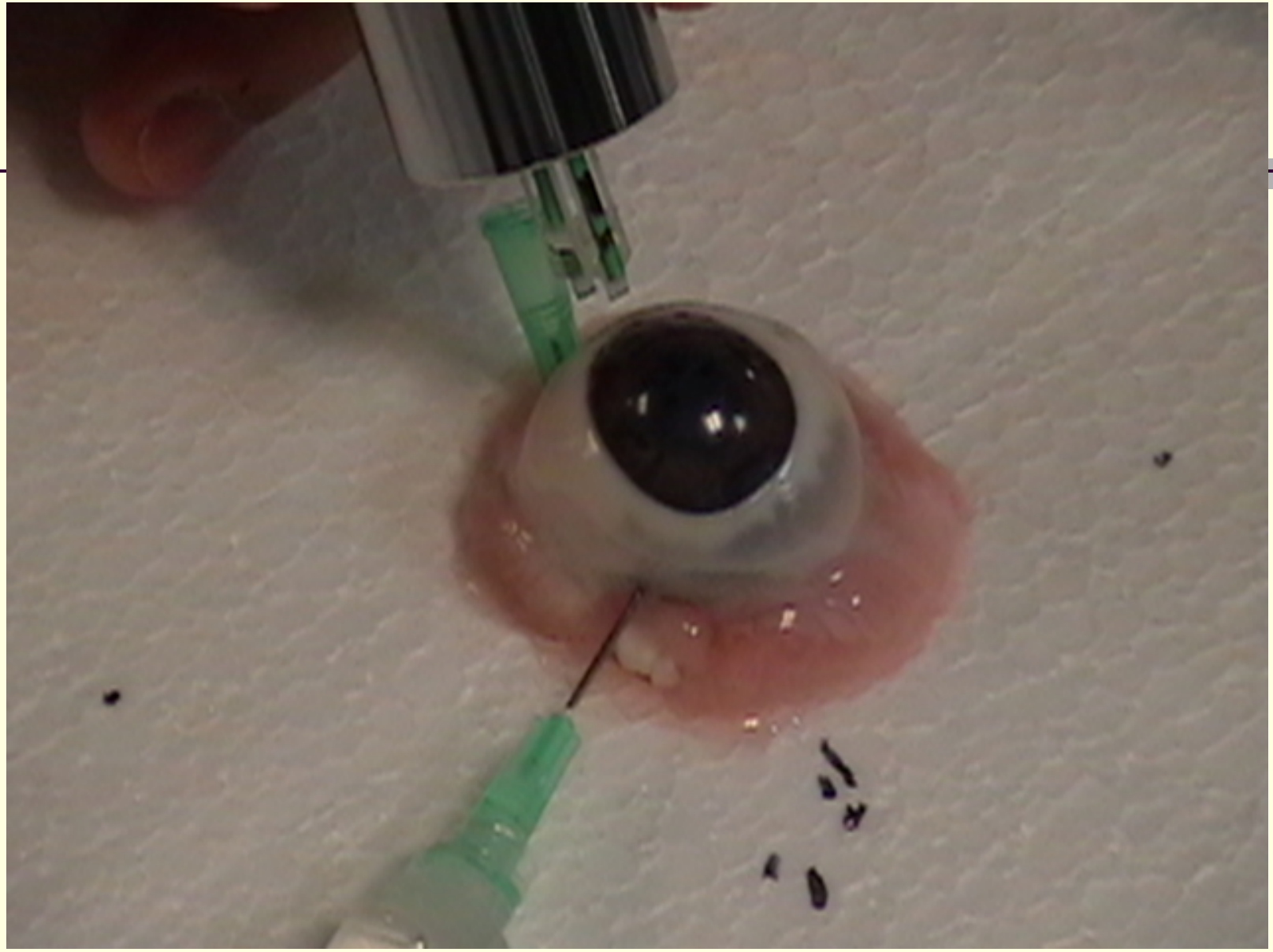

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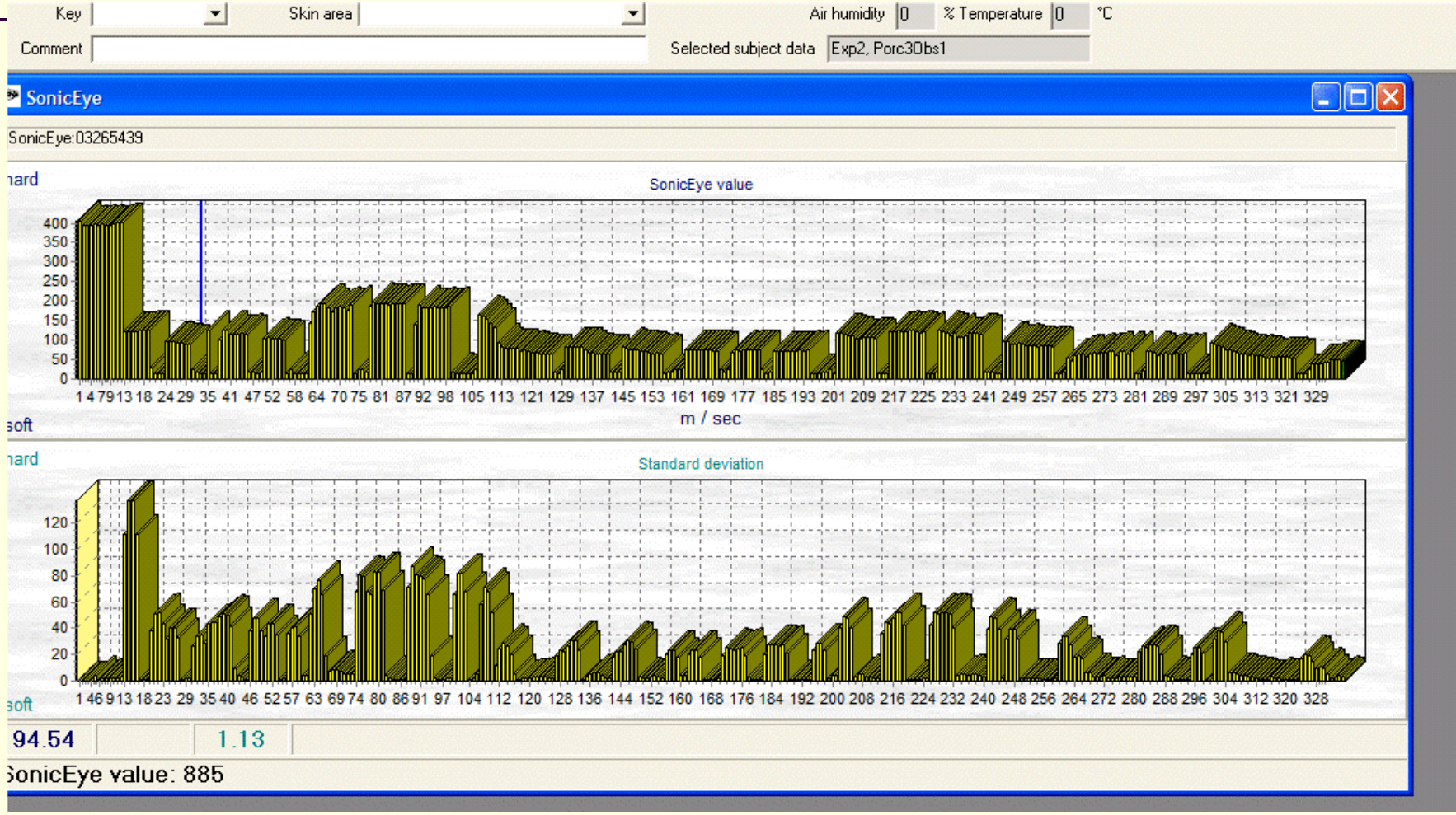
Sonic Eye® output display



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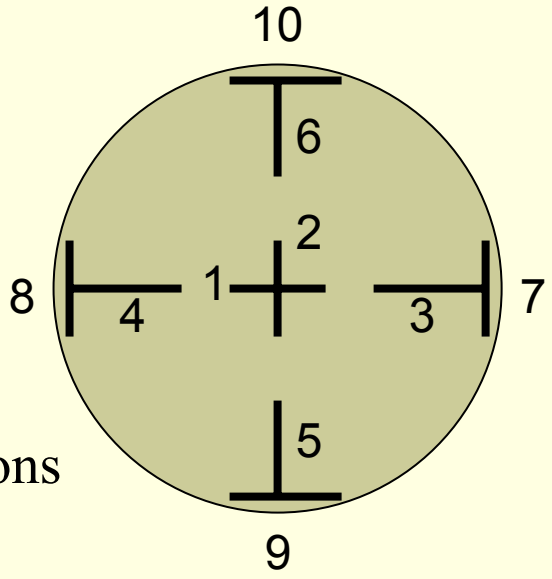
Surface Wave Elastometry

- 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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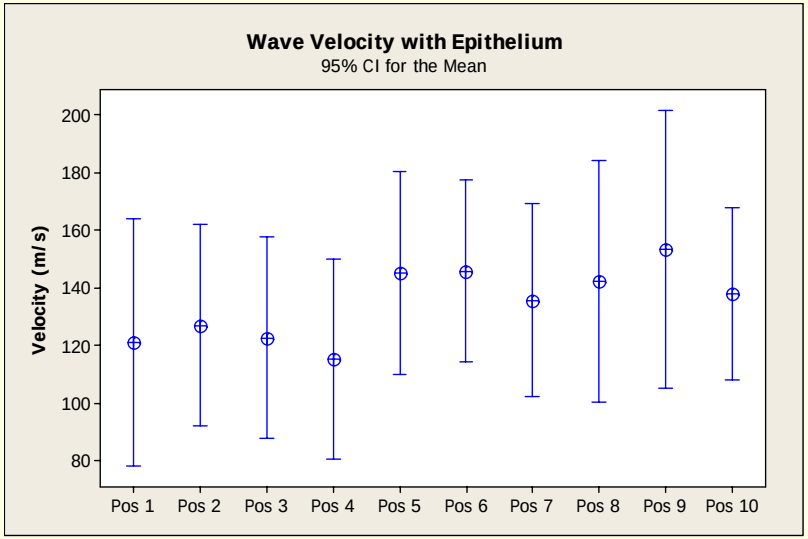
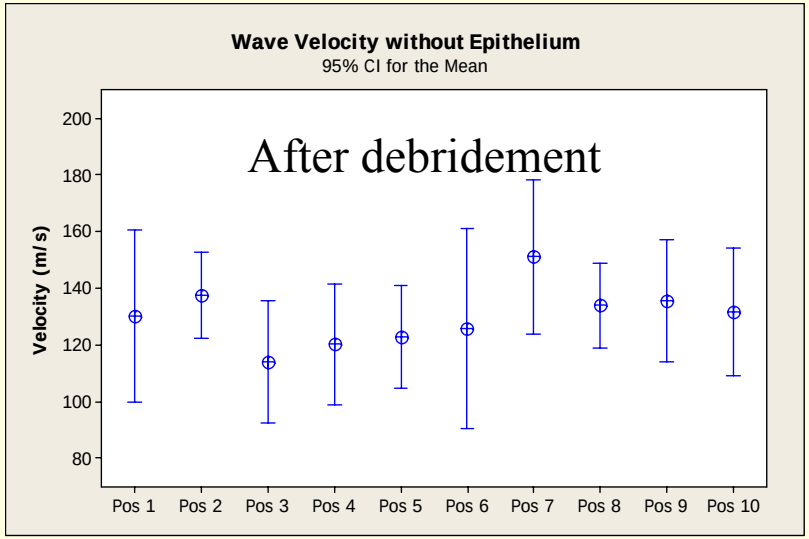
Results

- 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 ($p = .24$)





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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)

Donor	Pneumo (mmHg)	Tonopen (mmHg)	Stiffness (m/s)	Pneumo (mmHg)	Tonopen (mmHg)	Stiffness (m/s)
1	33.5	35	80 ± 3	71	87	145 ± 5
2	31	36	79 ± 4	79.5	89	147 ± 5

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↑ After crosslinking

Surface Wave Elastometry

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

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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

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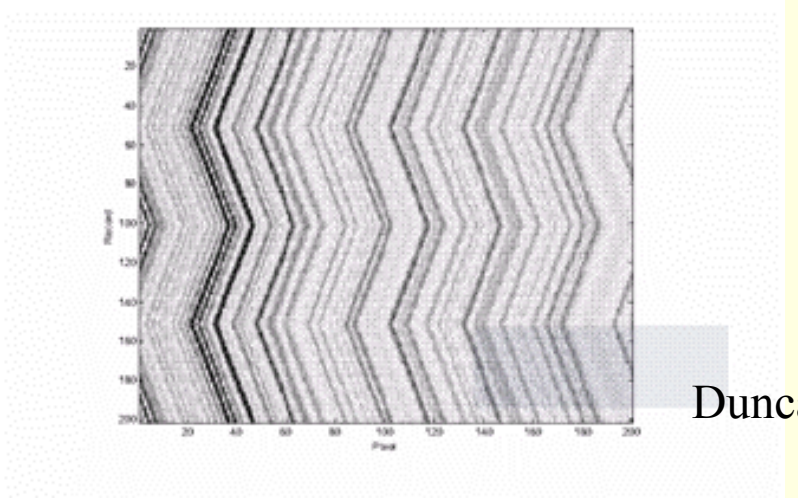
Optical Elastography

- 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

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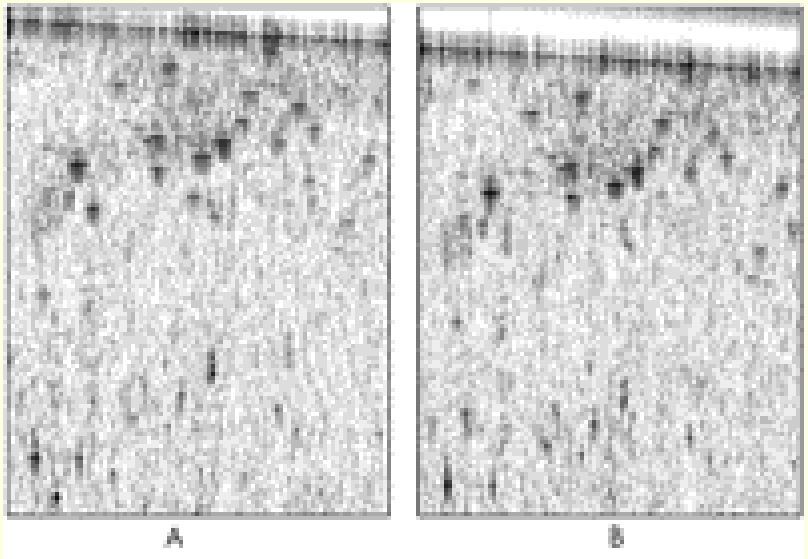
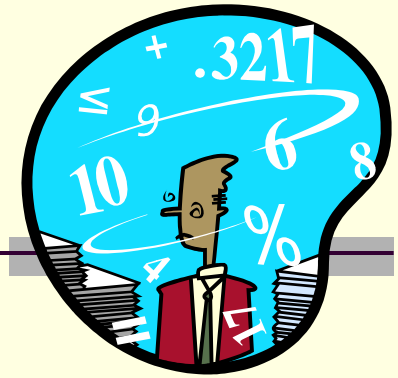
Optical Elastography

- 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



Rogowska, Heart 2004

Conclusion



- Global view:
  - Inadequate models are the rate-limiting step
- View from the ground:
  - We need <u>individual</u>, <u>repeatable</u>, <u>practical</u>, & 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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Acknowledgments

- Ronald R. Krueger, M.D., M.S.E., Cole Eye Inst.
- Marcelo V. Netto, M.D., Cole Eye Institute
- Cindy Roberts, Ph.D., Ohio State Univ.
- Steven E. Wilson, M.D., Cole Eye Institute
- Satish Herakar, M.S.E.E, PriaVision, Inc.

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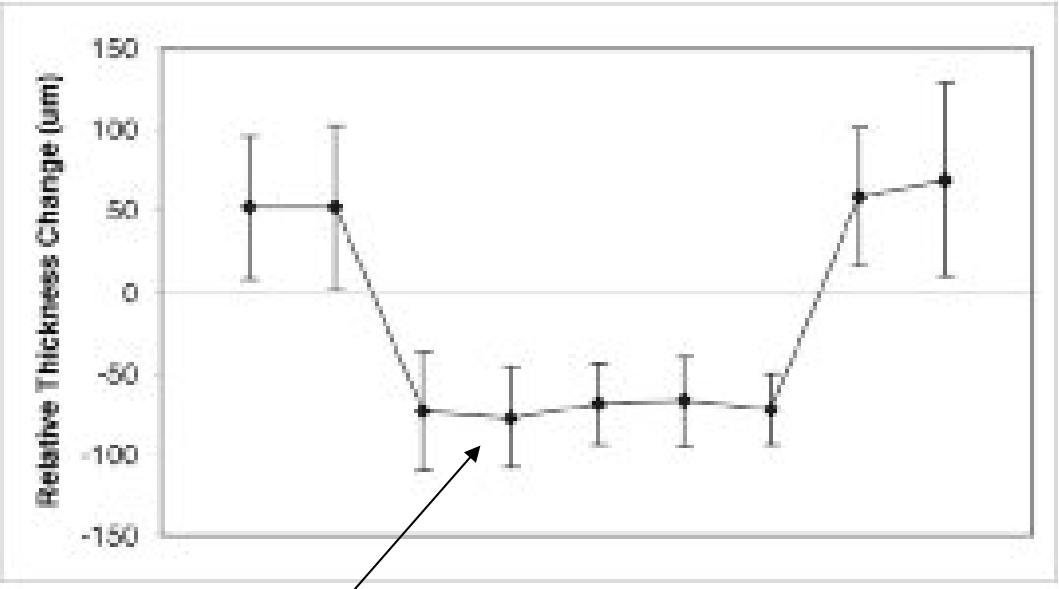
Peripheral Stromal Thickening: Paired human donor eye study



Dupps WJ, Roberts C (JRS 2001)

Max ablation depth determines hyperopic response

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

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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

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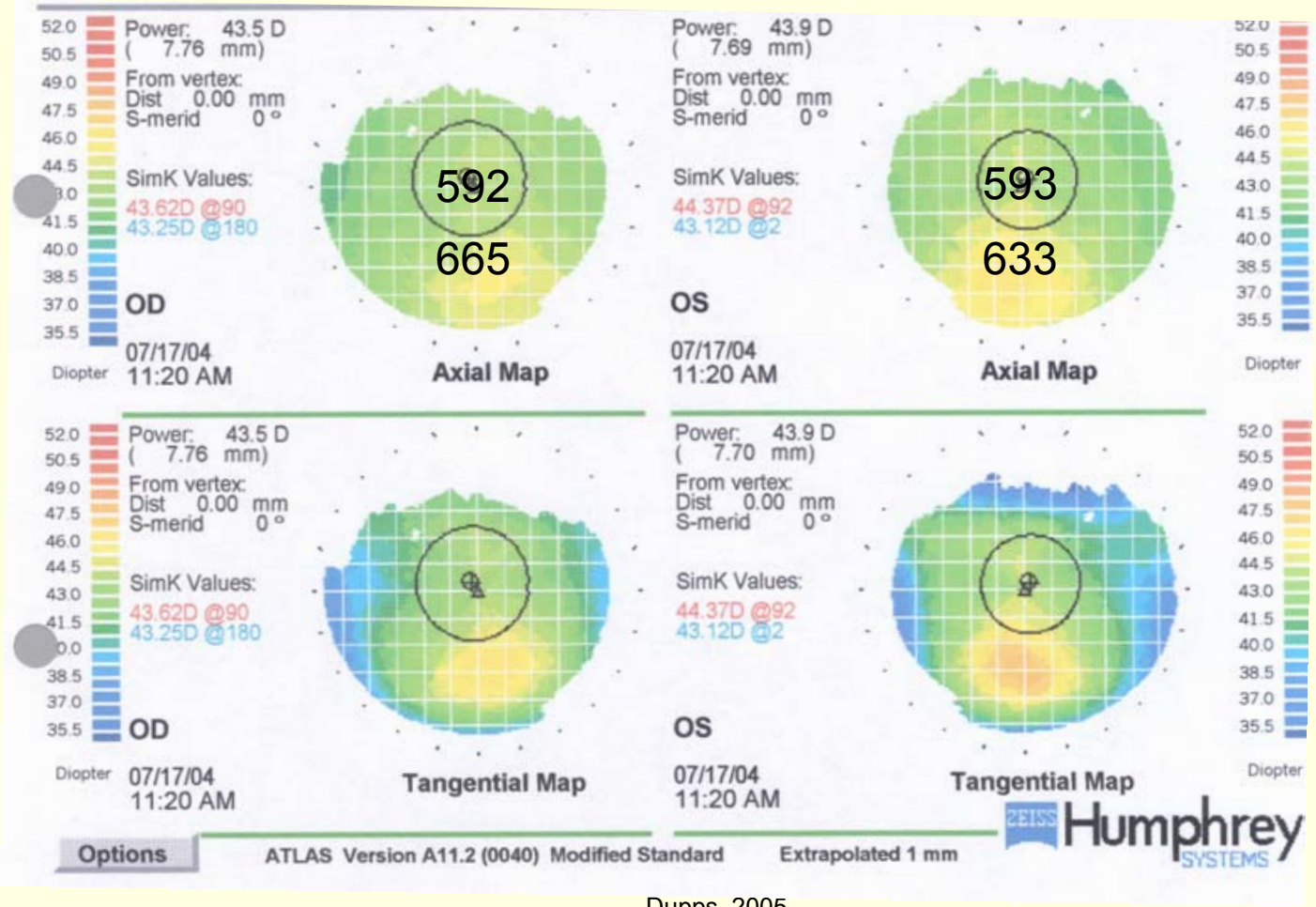
Problem: Who will develop ectasia?



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Peripheral lamellar relaxation

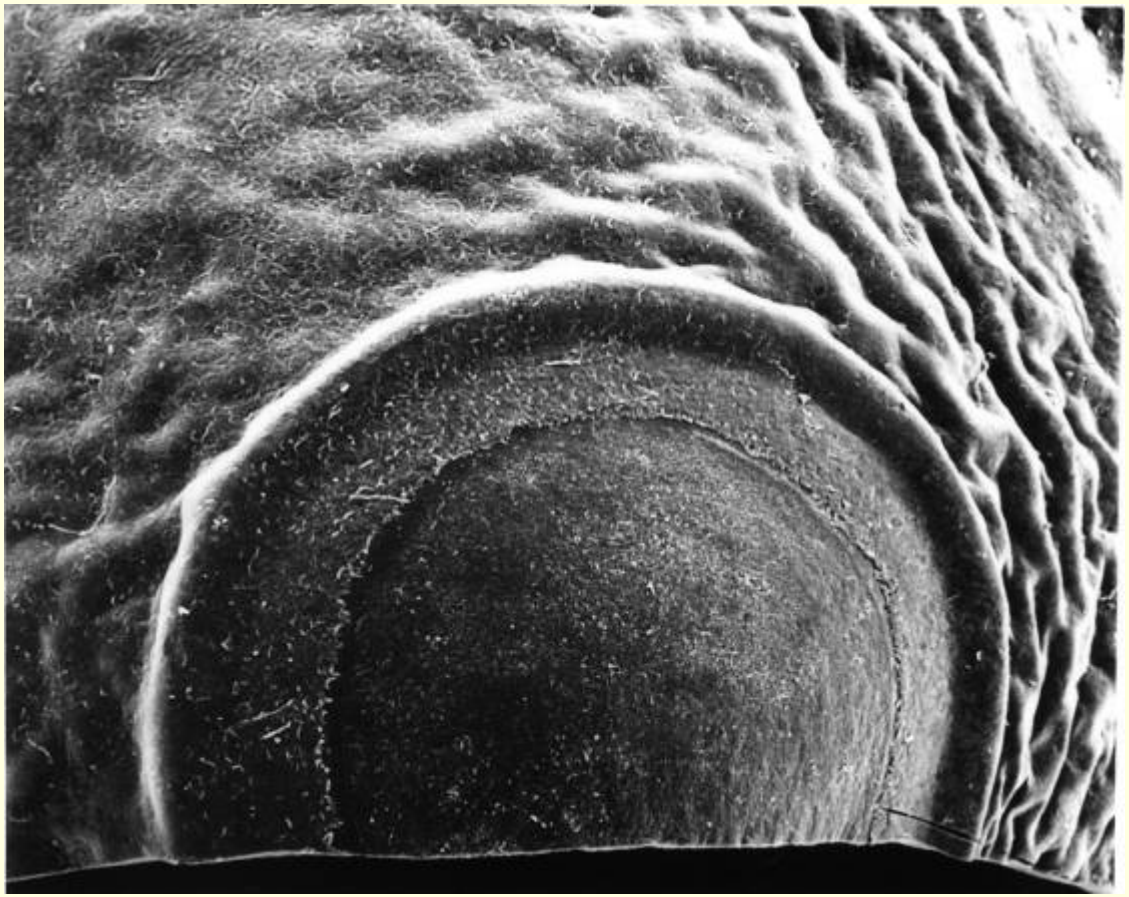

Photo courtesy of J. Marshall, Ph.D

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