Corneal Biomechanics: A Primer for Understanding Ectasia and CXL

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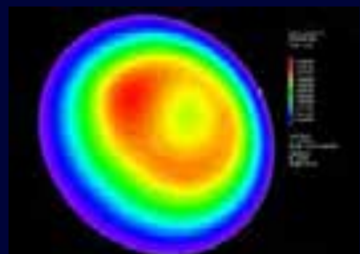
Disclosures: Intellectual property in biomechanical measurement & modeling (Cleveland Clinic/OptoQuest), Avedro (research), Ziemer (consultant), Zeiss (research)

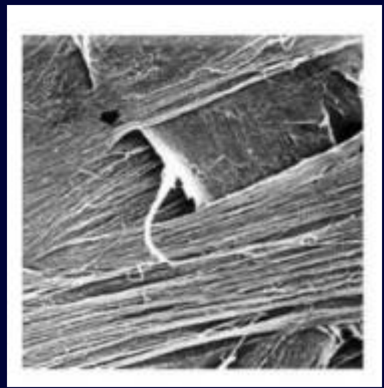
“Central Dogma” of Corneal Biomechanics

- Microstructure
  - Biomechanical behavior
    - Macrostructure
      - Optical function

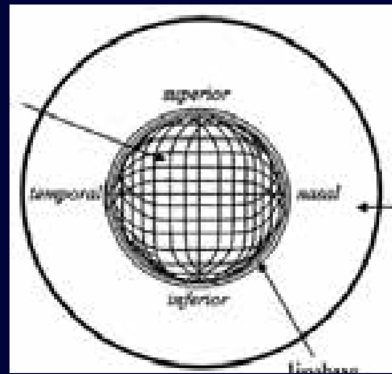


Corneal biomechanics is the intersection at which genetics, microstructure, collagen/matrix homeostasis and repair and related diseases interact with physics to drive curvature change, thus ***linking these process to refractive function***

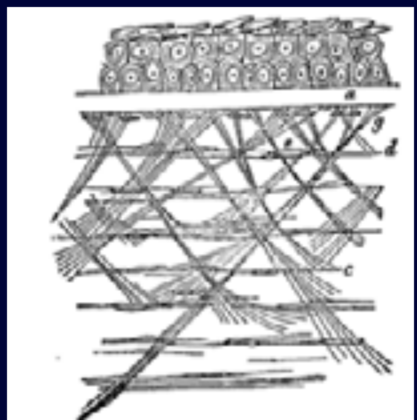
Normal corneal structure



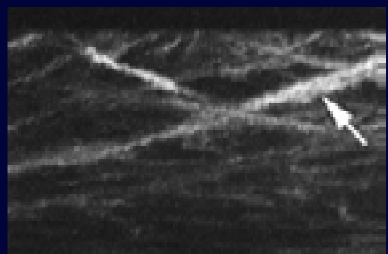
Meek et al, IOVS 2005



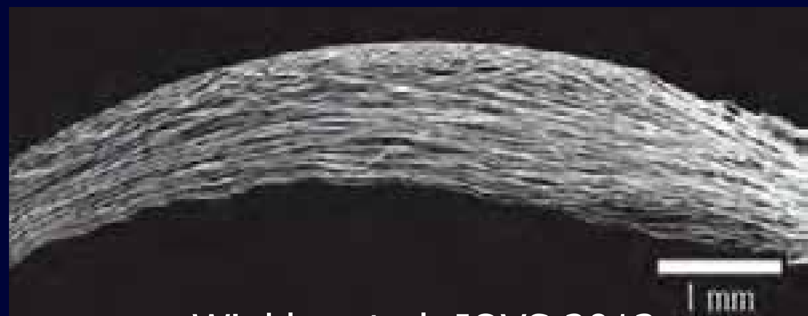
Boote et al, J Struct Biol 2005



William Bowman, 1847

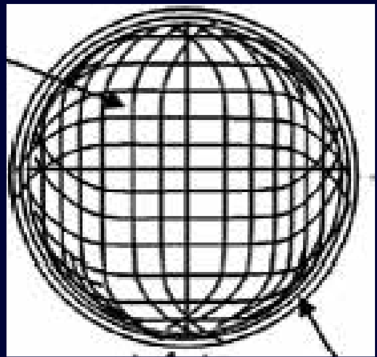


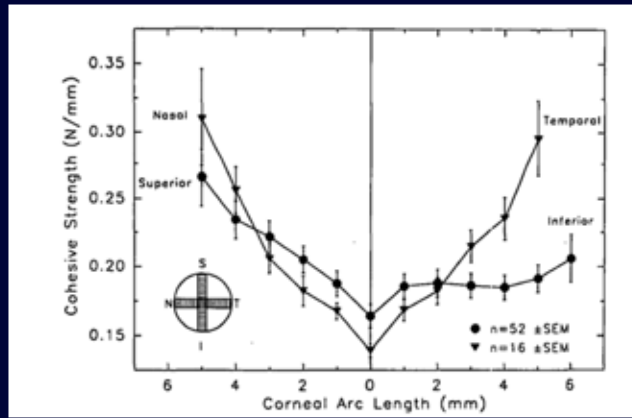
Morishige et al, JCRS 2007



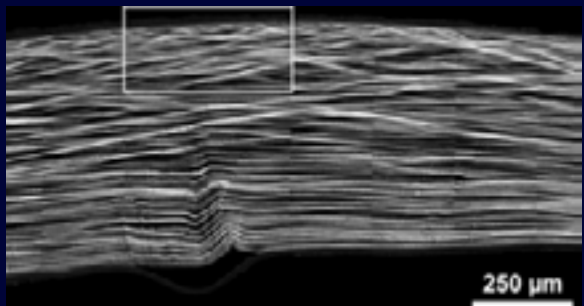
Winkler et al, IOVS 2013

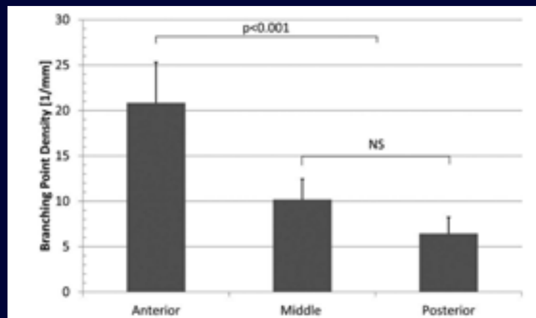
Spatial corneal property variation

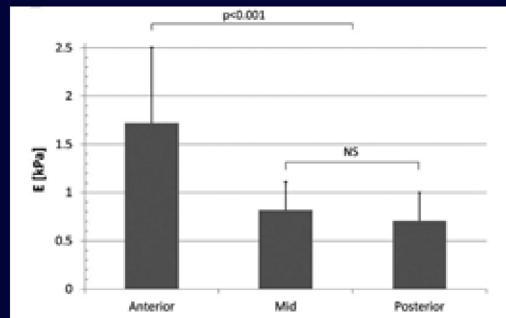




Smolek, IOVS 1990, 1993

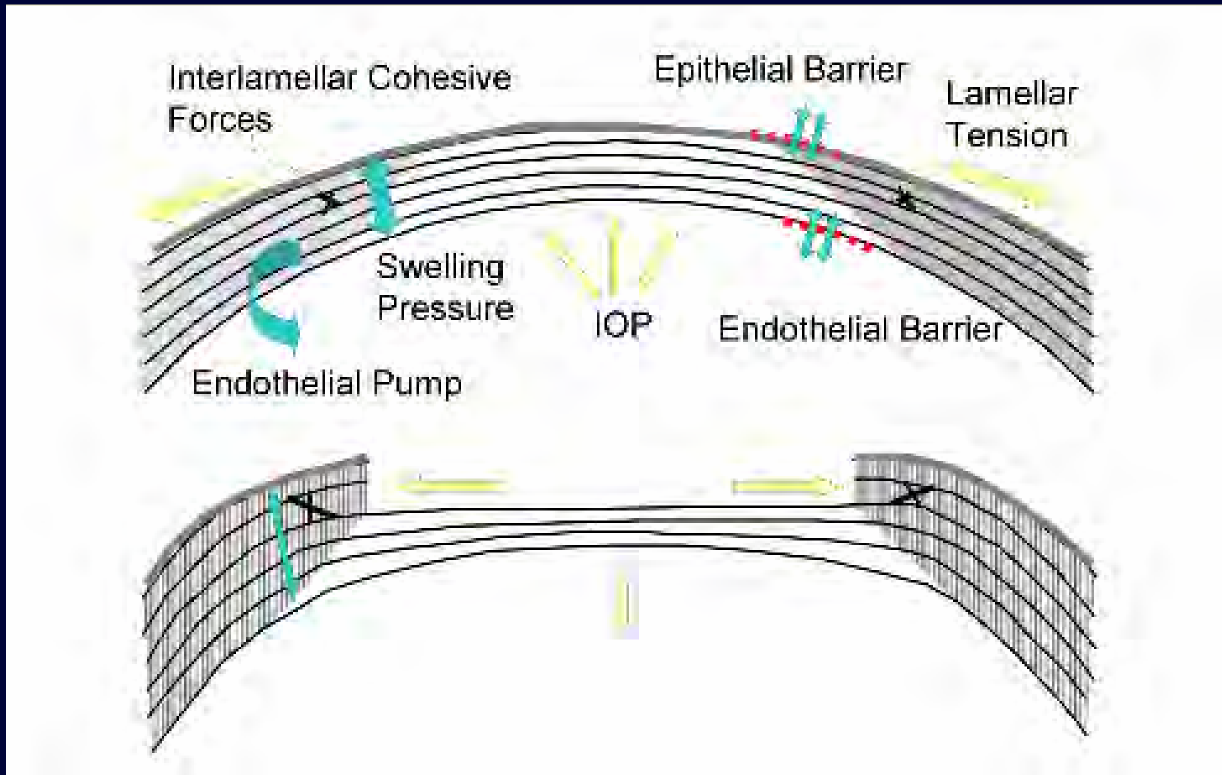






Winkler et al, IOVS 2011

The mechanical steady state is *dynamic*



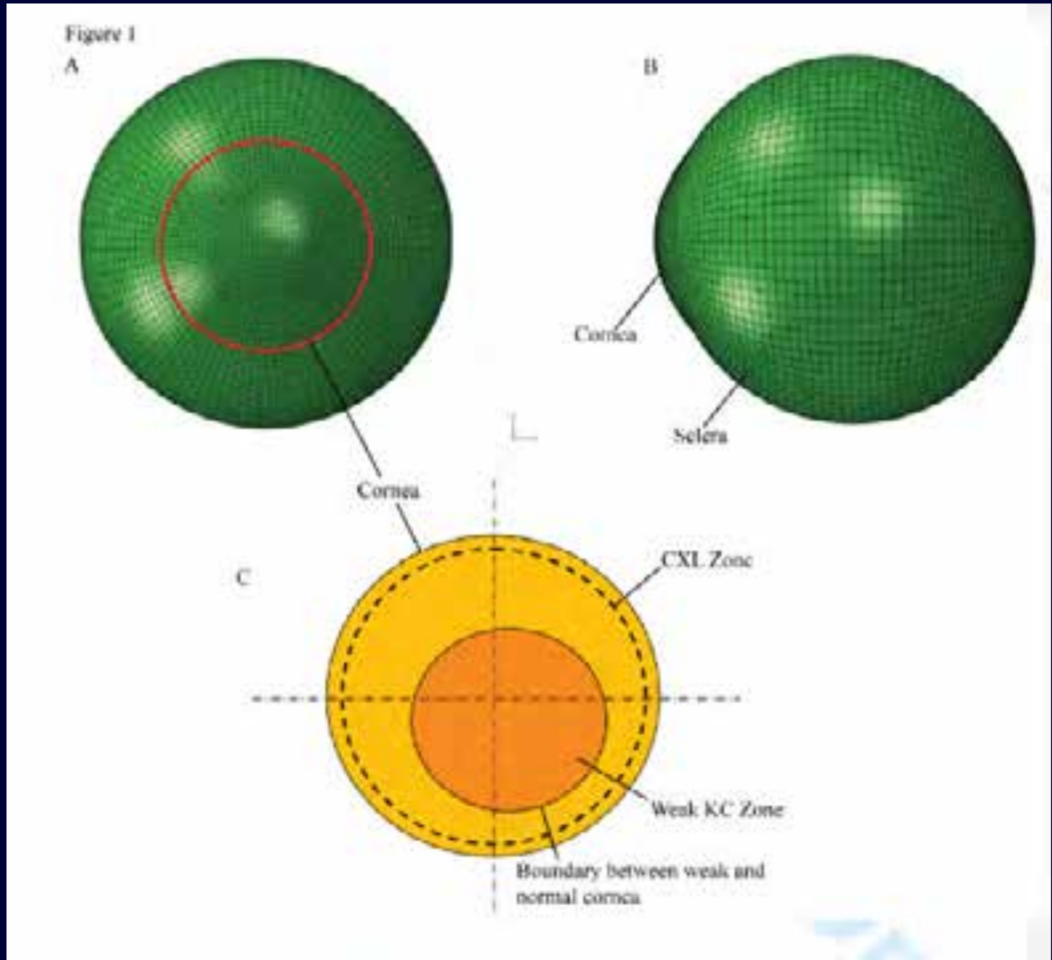
Dupps & Roberts, 1995, JRS 2001

The biomechanics of keratoconus

- What we know:
  - Structural abnormalities & loss of interlacing fibrils at Bowman layer (including Morishige 2007)
  - Elastic modulus is low (Andreassen 1980)
  - The response to an air puff indicates less elastic resistance and other abnormalities (Luce 2005)

- Questions of clinical interest:
  - What is the relationship between biomechanical properties and topographic features?
  - How does this inform our approach to treatments such as collagen crosslinking (CXL)?
  - How does corneal geometry influence disease propensity in refractive surgery?

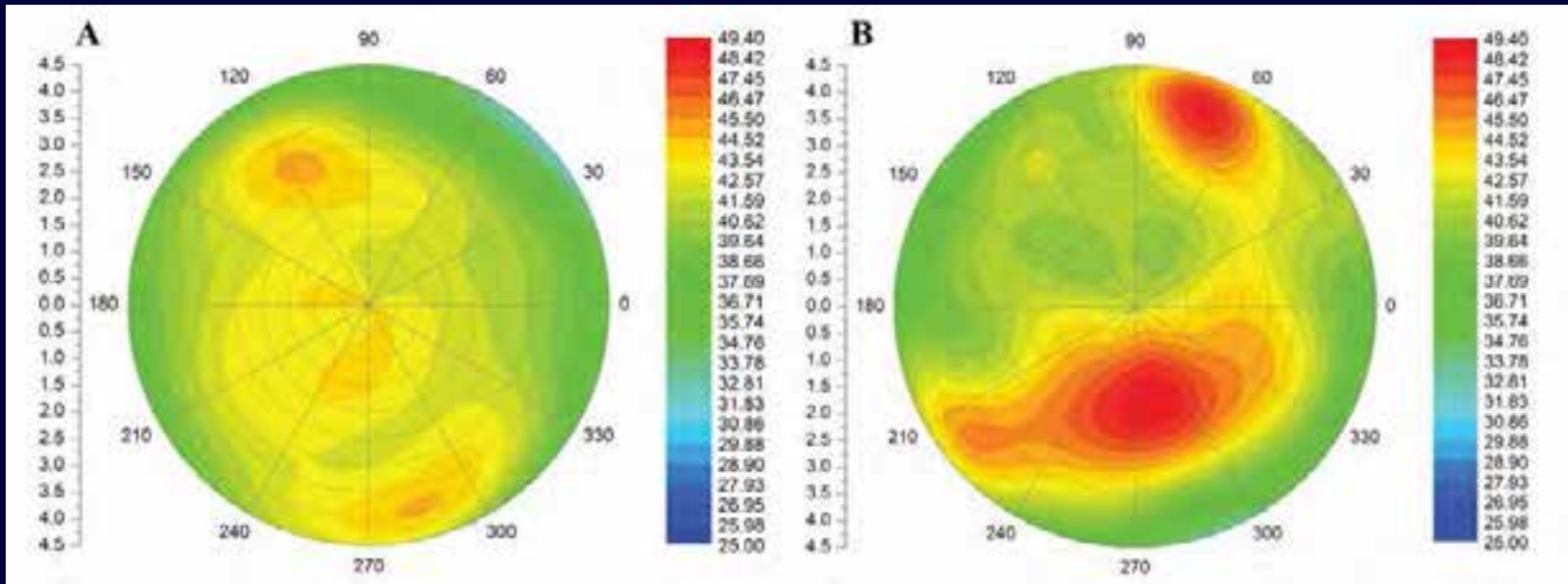
Mechanical-shape associations and hypothesis testing in KC



Sinha Roy & Dupps, IOVS 2011

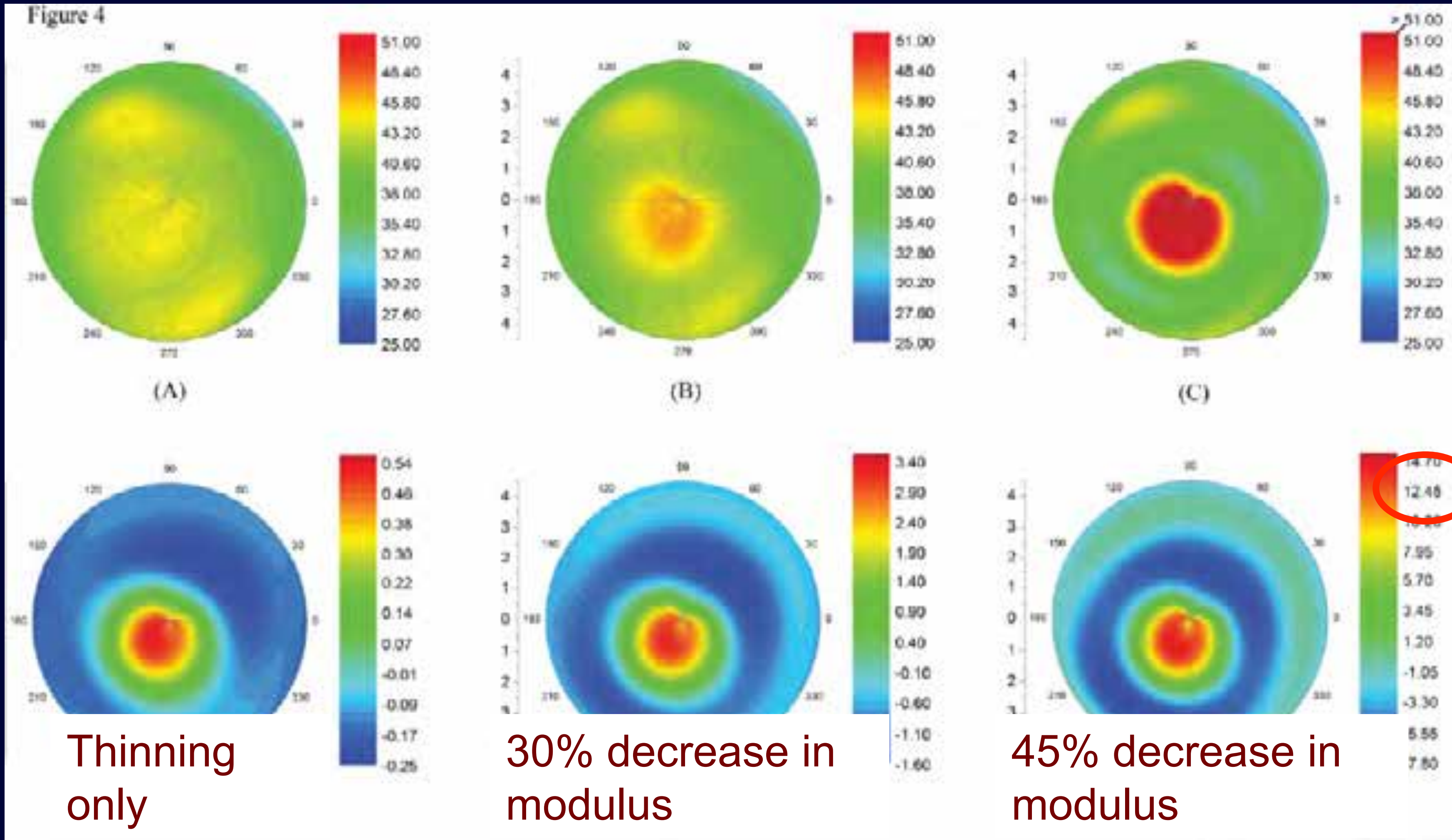
Experimental computational model of KC progression

OD OS



Sinha Roy & Dupps, IOVS 2011

Reducing elastic modulus simulates KC progression



Sinha Roy & Dupps, IOVS 2011

Steepening driven by elastic weakening

Table 2. Simulation of KC Progression

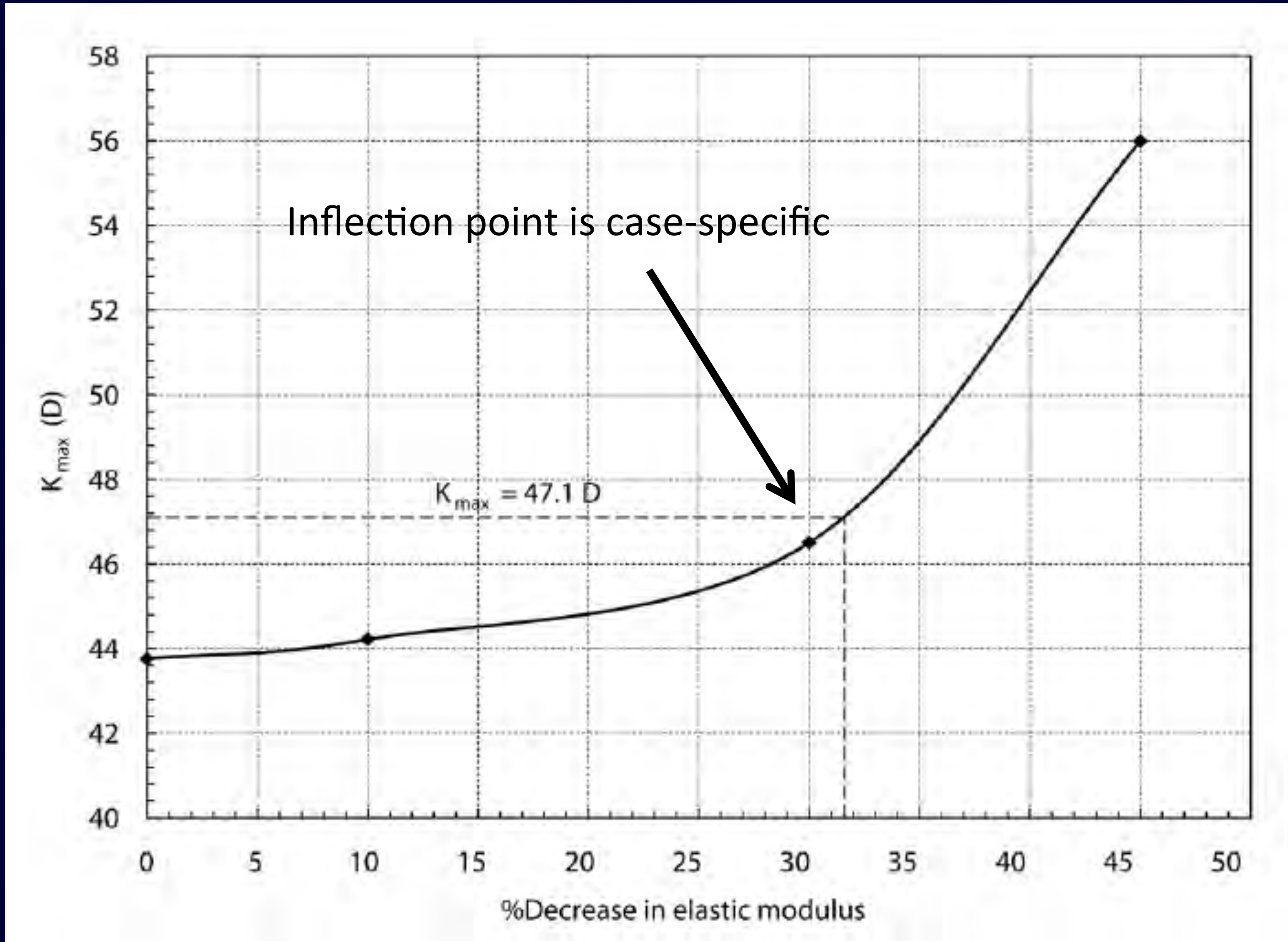
Reduction in Elastic Modulus (%)	SimK (D)	K_{max} (D)	LO RMS (μm)	HO RMS (μm)	Defocus $C_{2,0}$	Coma $C_{3,-1}$	Coma $C_{3,1}$	Spherical $C_{4,0}$	Surface Area (mm²)
Case 1: Reduced Thickness by 27 μm and Reduced Elastic Modulus									
Right Eye	42.79/43.38@156°	43.76	0.69	0.29	0.457	−0.111	−0.129	0.128	89.186
10	43.08/43.71@156°	44.22	0.63	0.32	0.337	−0.165	−0.161	0.100	89.228
30	44.36/45.24@159°	46.50	0.75	0.64	−0.305	−0.500	−0.338	−0.042	89.369
45	48.35/50.68@159°	55.99	3.51	2.57	−3.023	−2.132	−1.129	−0.647	89.705
Case 2: Reduced Elastic Modulus Only									
10	43.10/43.61@162°	44.01	0.69	0.34	0.826	−0.122	−0.157	0.177	89.227
30	44.27/45.05@162°	46.02	0.73	0.58	0.273	−0.430	−0.313	0.052	89.365
45	47.91/50.00@162°	54.38	2.64	2.23	−2.038	−1.869	−0.998	−0.468	89.684

Changes in topographic and optical characteristics such as SimK, K_{max}, lower and higher order aberrations, and surface area of the anterior corneal surface with progressive hyperelastic weakening of the cornea.

- 3 key observations:
  - Thinning was additive to progression but not required
  - Steepening was nonlinear as a function of modulus degeneration
  - Corneal surface area is minimally changed even at 12D Kmax increase

Sinha Roy & Dupps, IOVS 2011

Steepening driven by elastic weakening



Sinha Roy & Dupps, IOVS 2011

Collagenase-mediated tissue model of ectasia

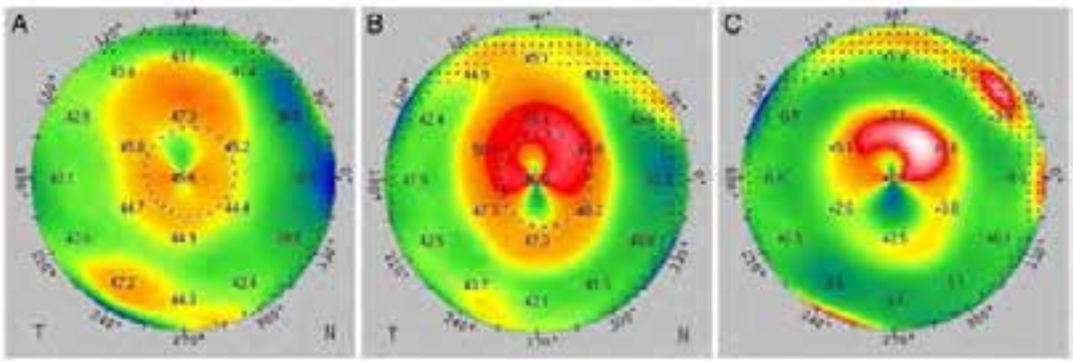


Figure 2. Axial curvature maps of anterior cornea surface before (A) and after collagenase exposure (B). (C) Subtraction map.

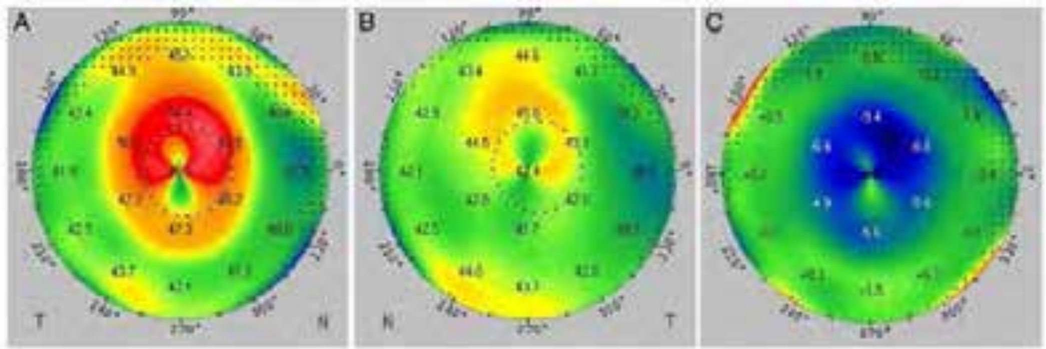


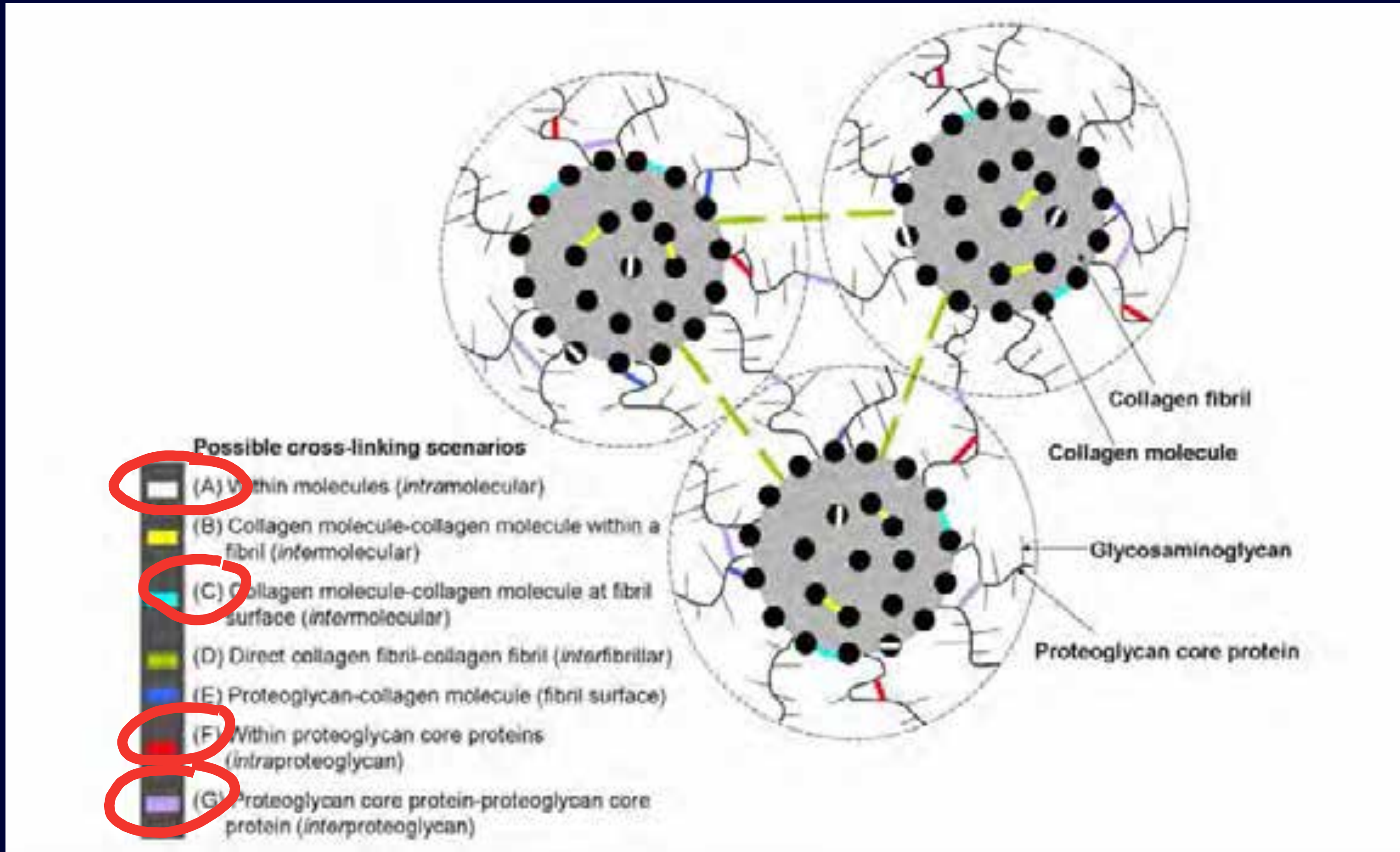
Figure 4. Axial curvature maps of anterior cornea surface after collagenase exposure before crosslinking (A) and after crosslinking (B). (C) Difference map.

Hong et al, IOVS 2012

Overview of the Crosslinked Cornea

- Caveat: CXL encompasses various approaches
- Common final effect is stromal *stiffening*
  - Increased elastic modulus
  - Decreased rates of enzymatic digestion
  - Reduced corneal permeability
  - Resistance to swelling*
  - Increased autofluorescence
  - Collagen fibril diameter increased 12%*
  - No increase in separation between adjacent collagen molecules

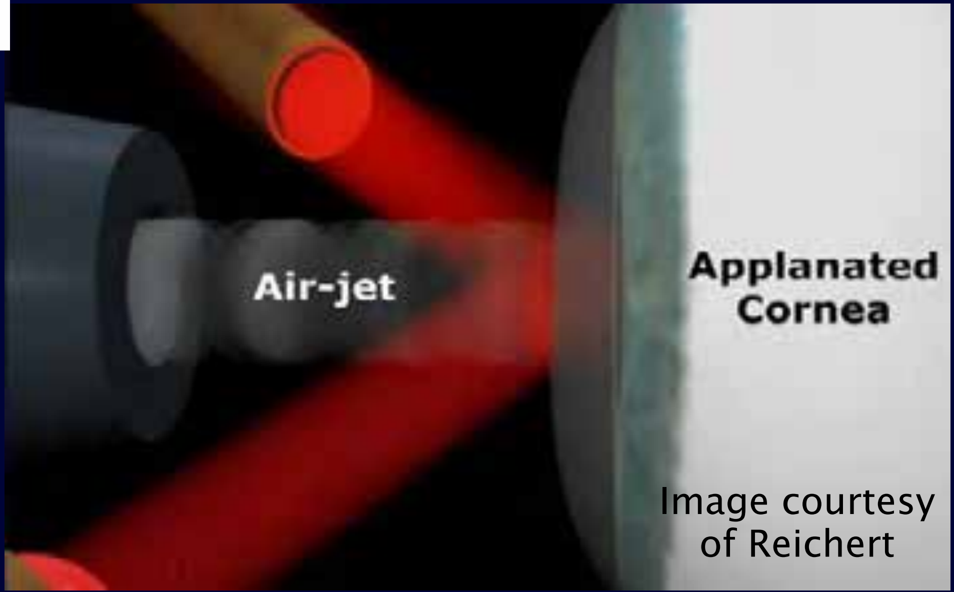
Microstructural Effects of CXL



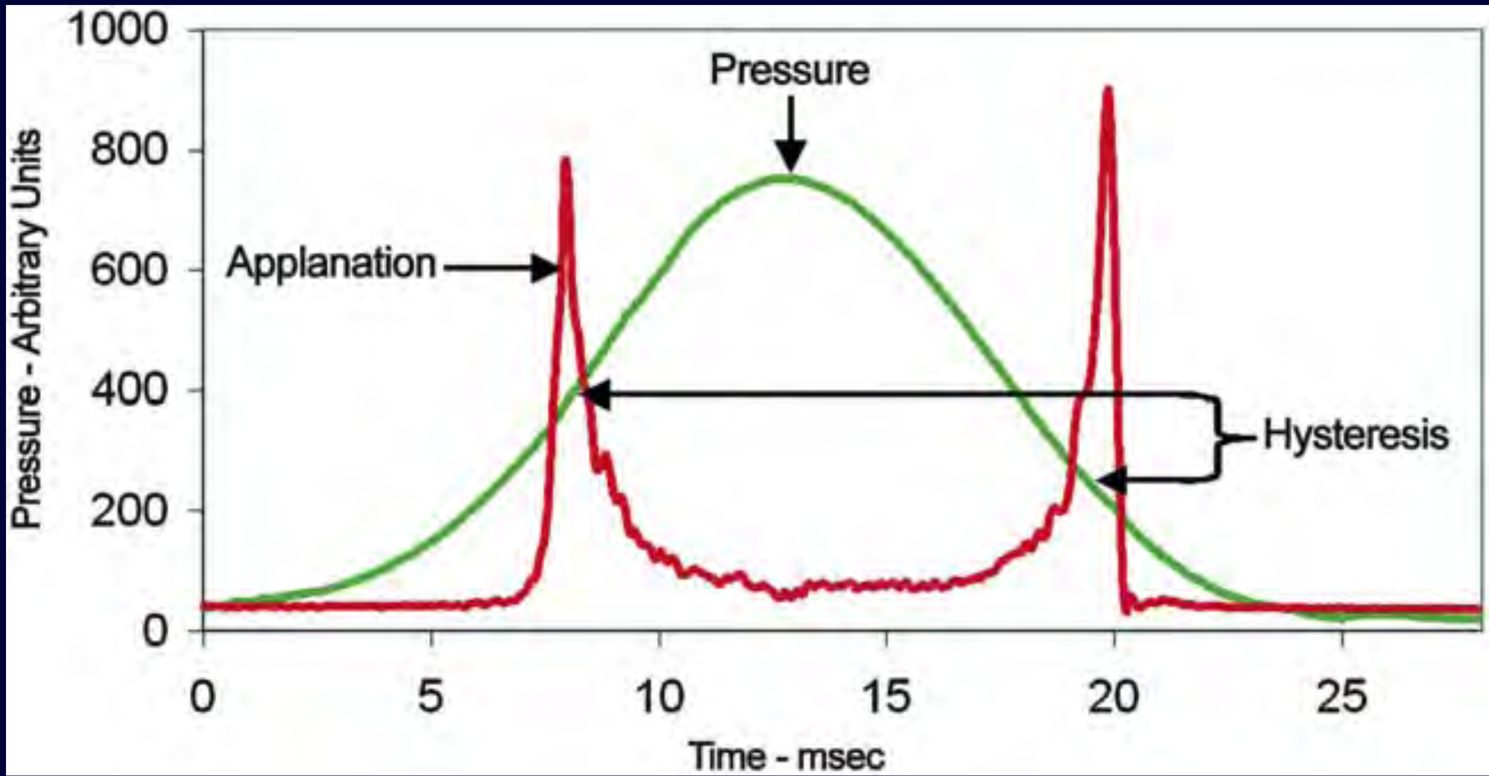
Hayes et al, PLOS One 2013

Biomechanical Measurement and Characterization of CXL Effect

Ocular Response Analyzer®: a high-speed measure of the corneal bending response

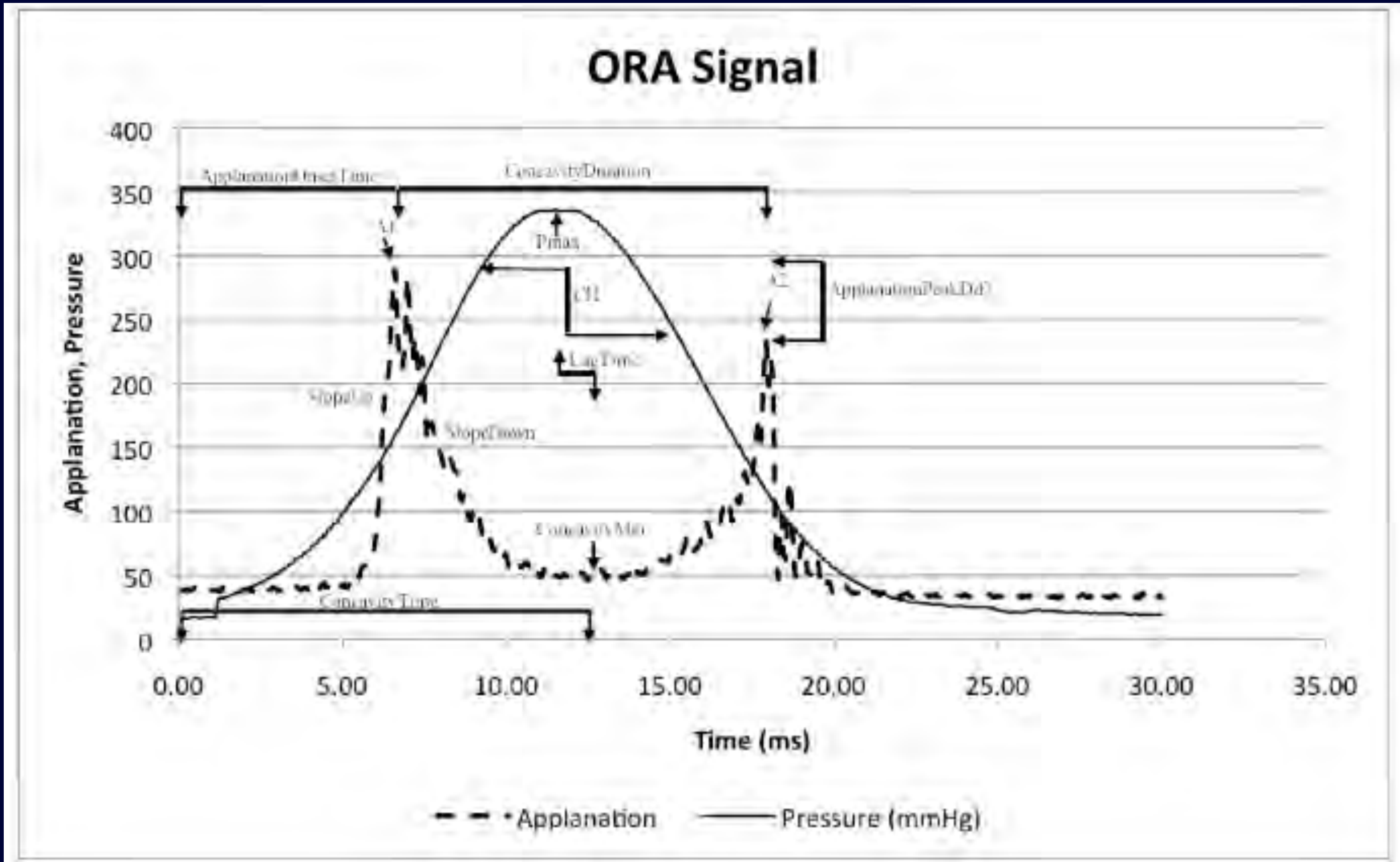


ORA signal and corneal hysteresis (CH)



Luce, JCRS 2005

Custom derived variables



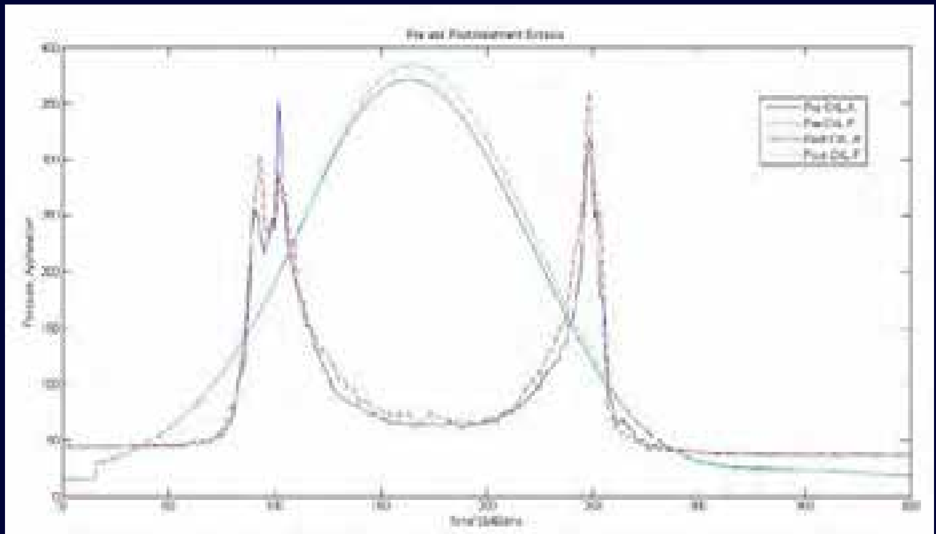
Hallahan et al, Ophth 2014

Does CH increase after crosslinking?

- NO
  - Goldich et al, Cornea 2012
  - Greenstein et al, Cornea 2012
  - Asri et al, JCRS 2011
  - Spoerl et al, JRS 2011
  - Segeghadt et al, JCRS 2010
  - Vinciguerra et al, JRS 2010
  - Goldich et al, Cornea 2009
- 37 custom variables: area under peak 2 increased 35% in KC patients after CXL (Spoerl et al, 2011)

ORA changes with CXL: post-LASIK ectasia

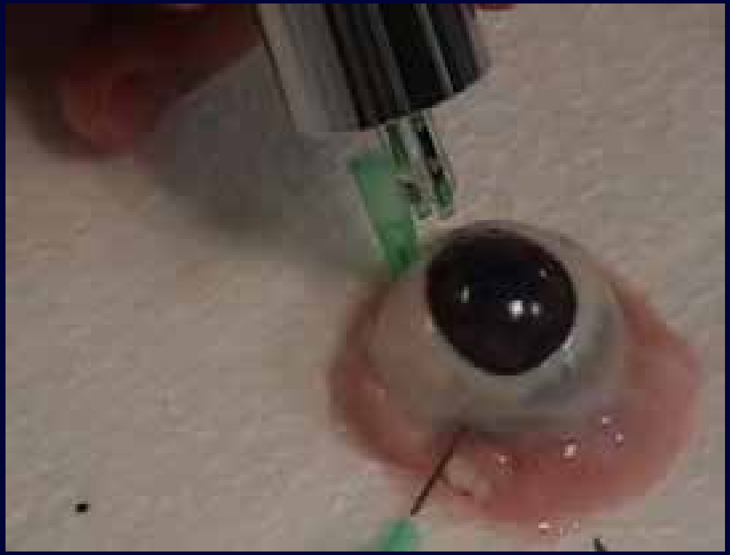
- 31 eyes, before and 3 months after epi-off CXL
- No changes in CH, CRF
  - Peak 1 onset time higher (p=.002)
  - Concavity time shorter (p=.04)
  - Higher applanation pressures (p<.004)



Hallahan et al, ECL 2014

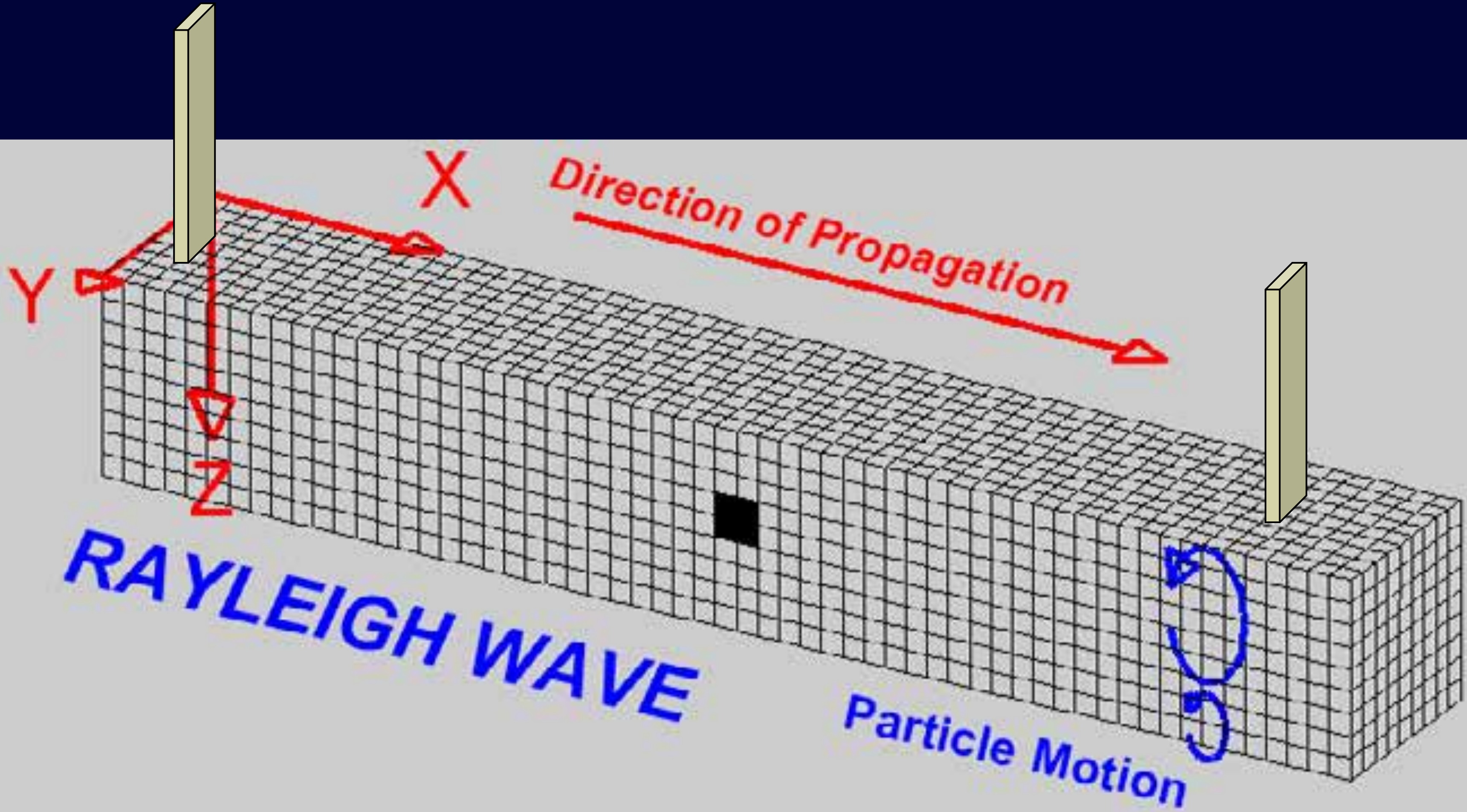
Surface wave elastometry

- Sonic Eye® (PriaVision, Menlo Park CA)
  - Measures time-of-flight of low frequency wave over 4.5 mm distance
  - Elastic modulus related to ρV^2



Dupps et al, JRS 2007

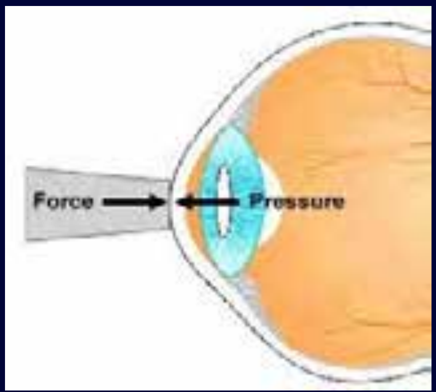
Sonic corneal stiffness interrogation



Wave animation courtesy of Professor Larry Braile, Purdue U.

Corneal stiffening and IOP measurement

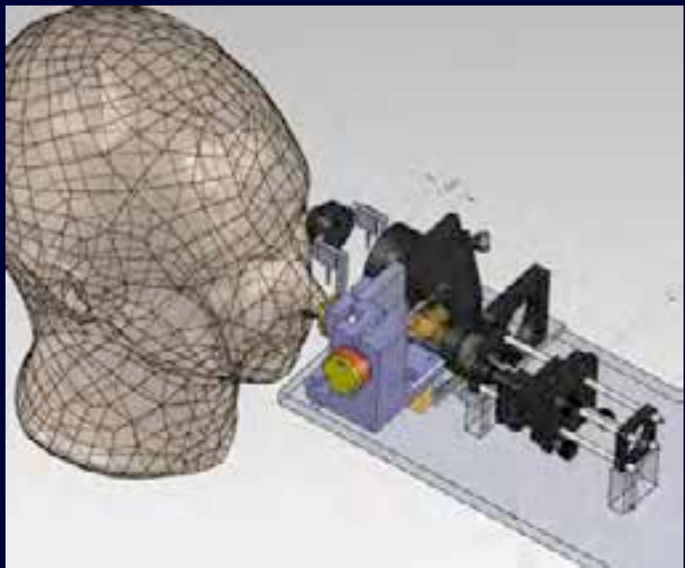
- 2 human globes
  - Intra-vitreal IOP **maintained at 30 mmHg**
  - Crosslinking with glutaraldehyde 4%, 45 min.

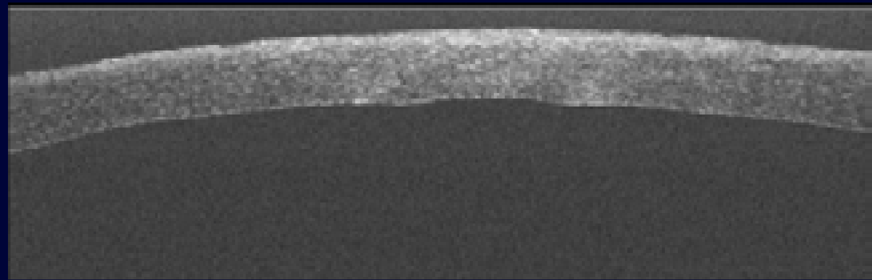


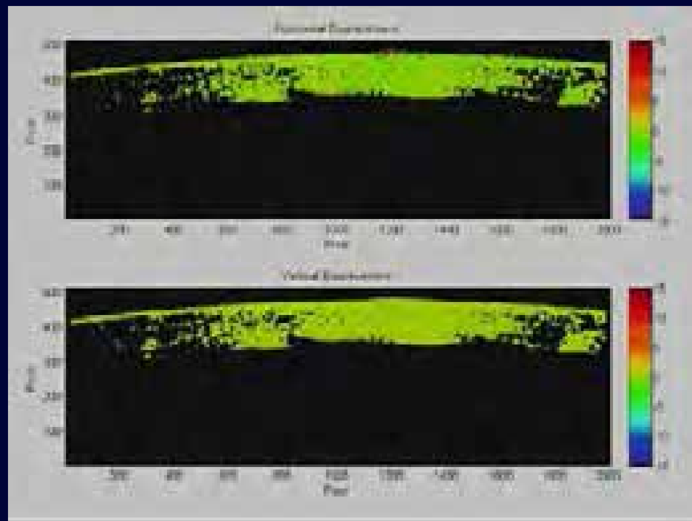
	Before CXL	After CXL
Central Wave Velocity (m/s)	80 ± 3 79 ± 4	145 ± 5 147 ± 5
Pneumo (mmHg)	33.5 31	71 79.5
Tonopen (mmHg)	35 36	87 89

Dupps et al, JRS 2007

3D OCT-based elasticity imaging

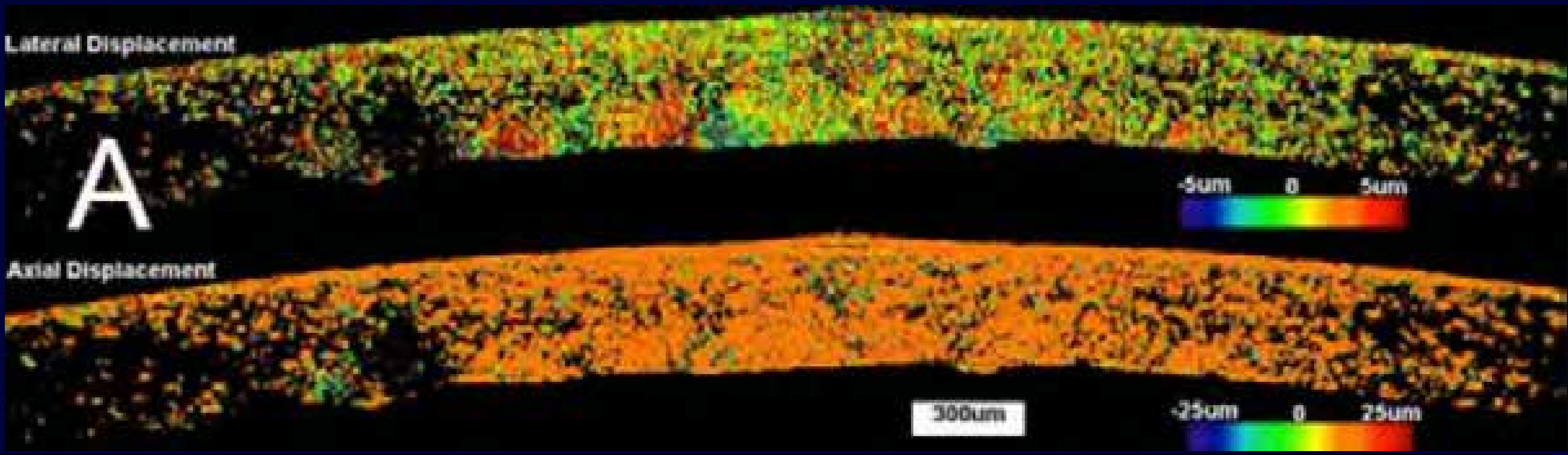


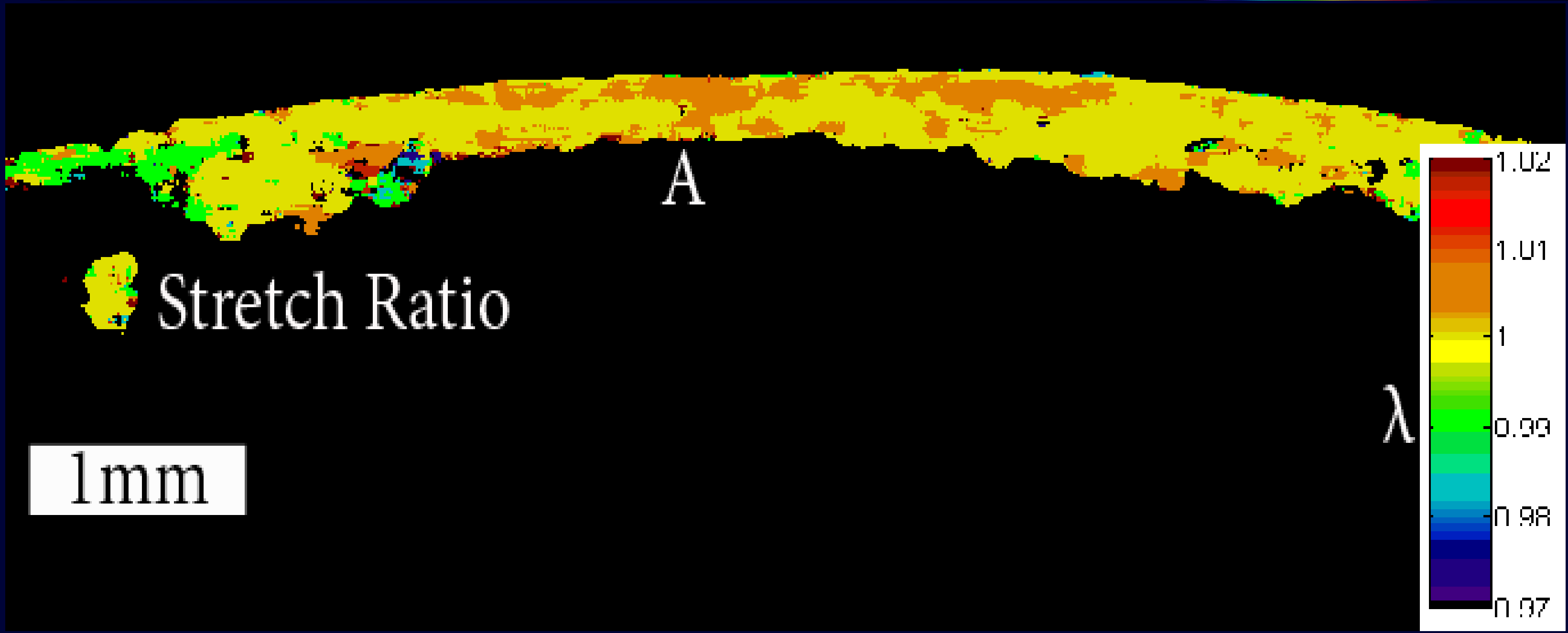




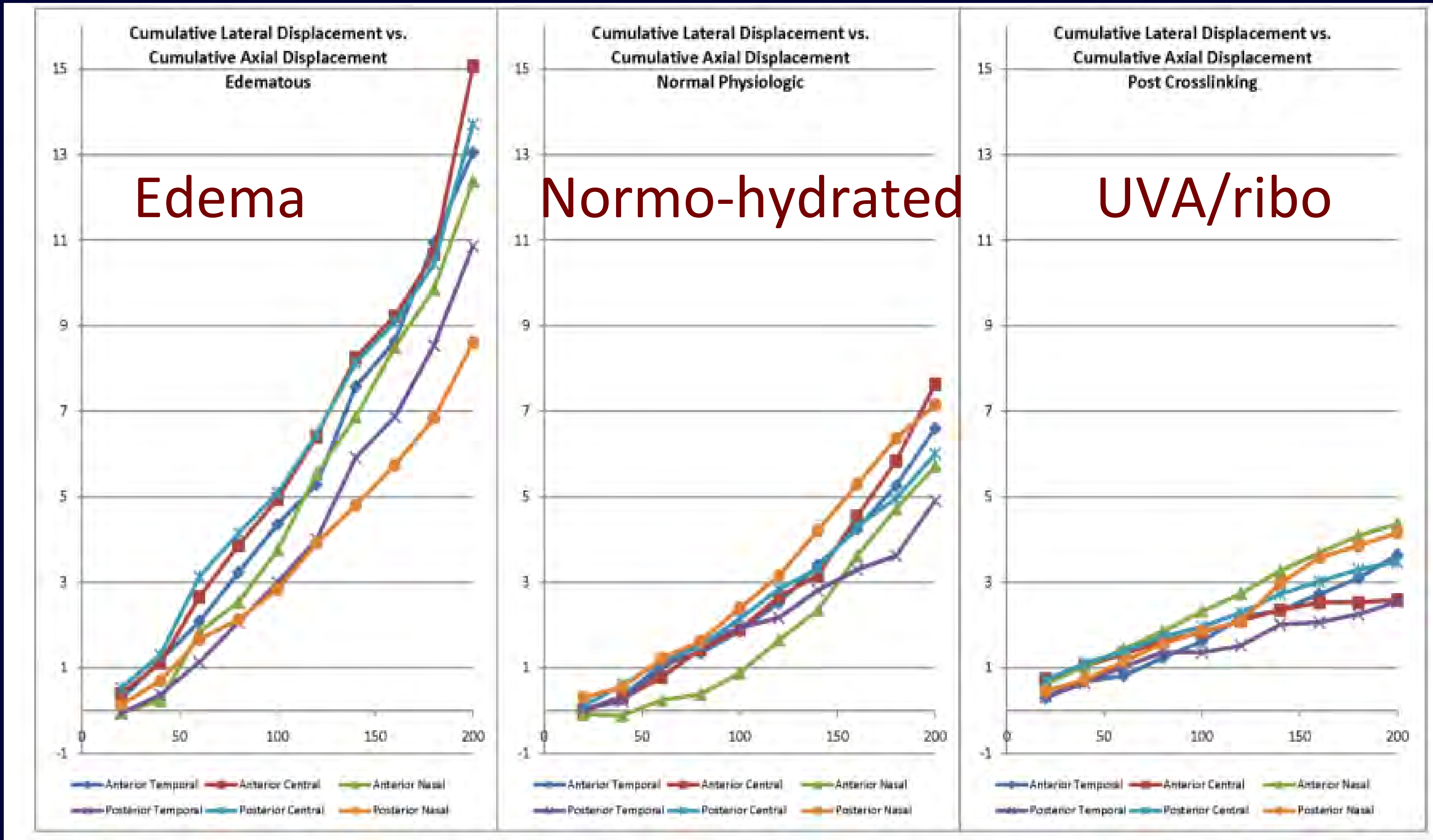
Ford et al, J Biomed Opt 2011

OCT elastography: Normal & KC



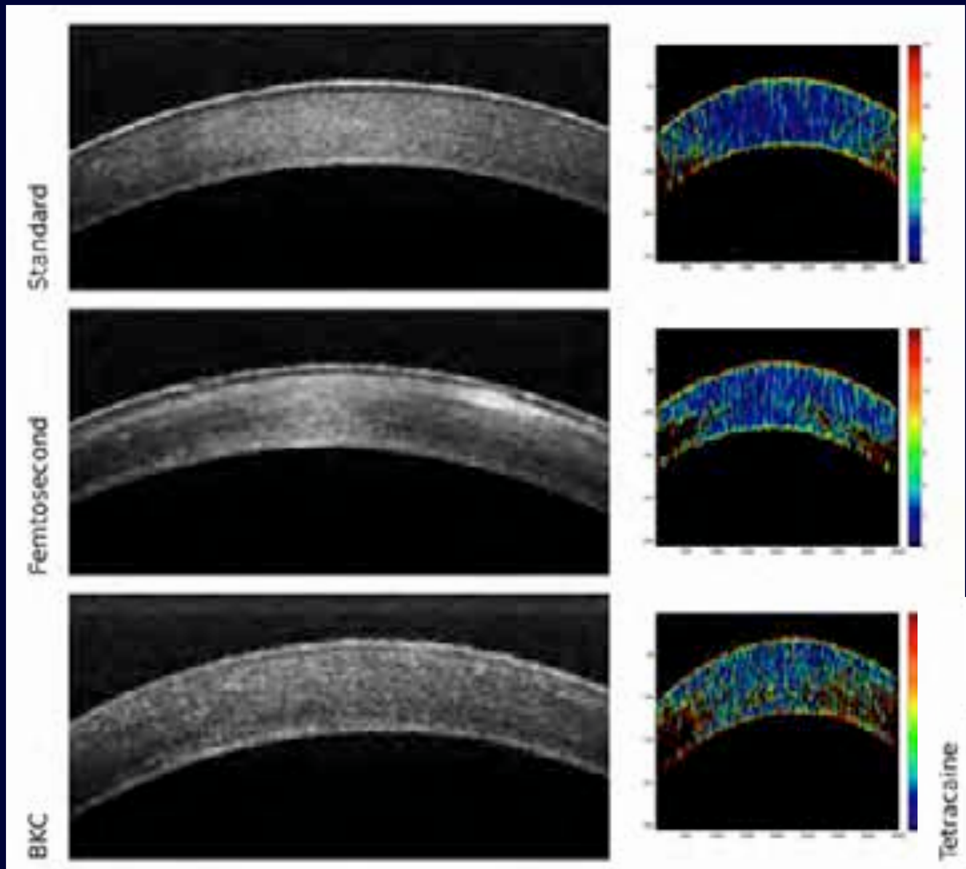


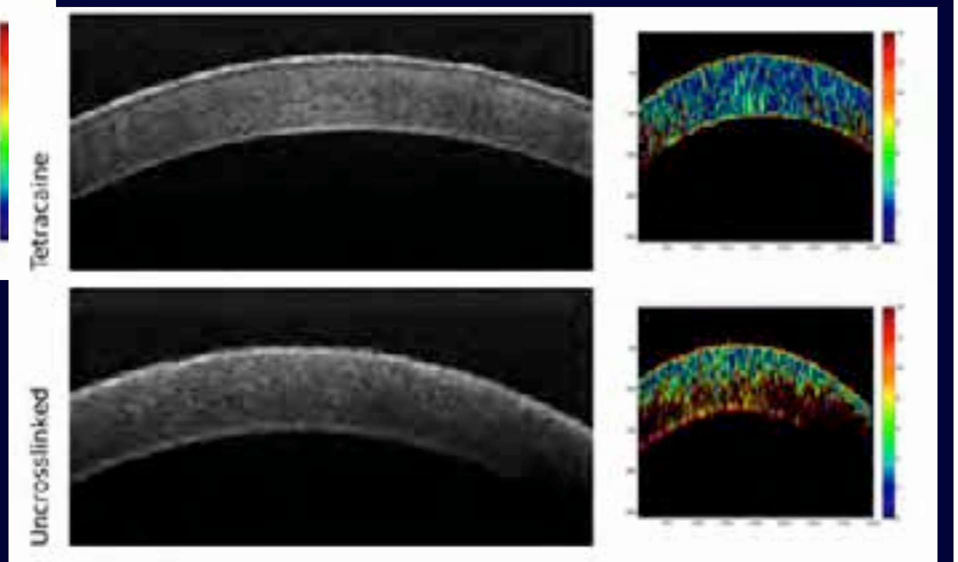
OCT elastography in human donor globes



Ford et al, JCRS 2014

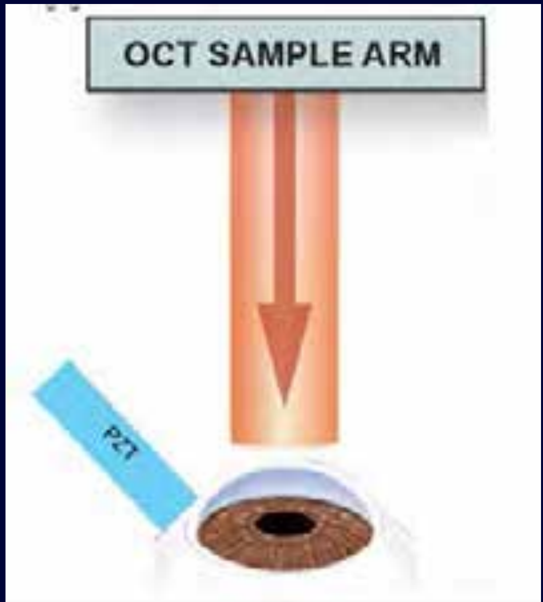
OCE comparison of CXL effect

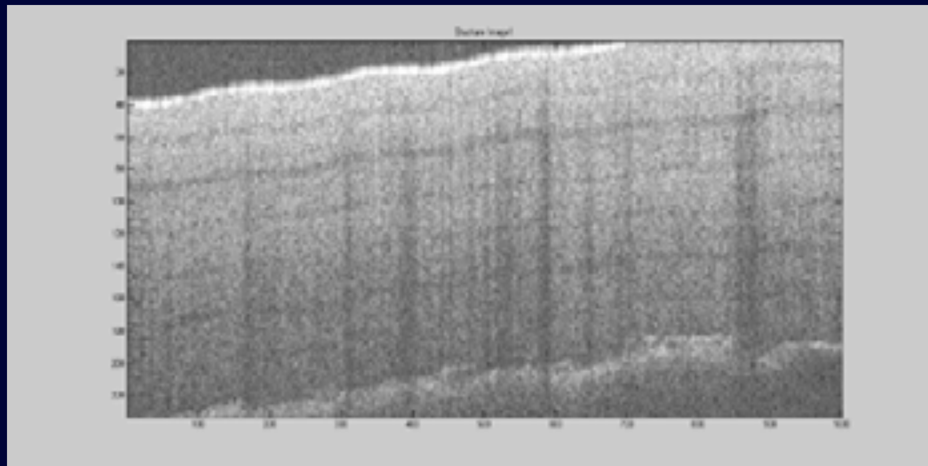




Armstrong & Lin et al, JRS 2013

Non-contact *in vivo* Doppler OCE



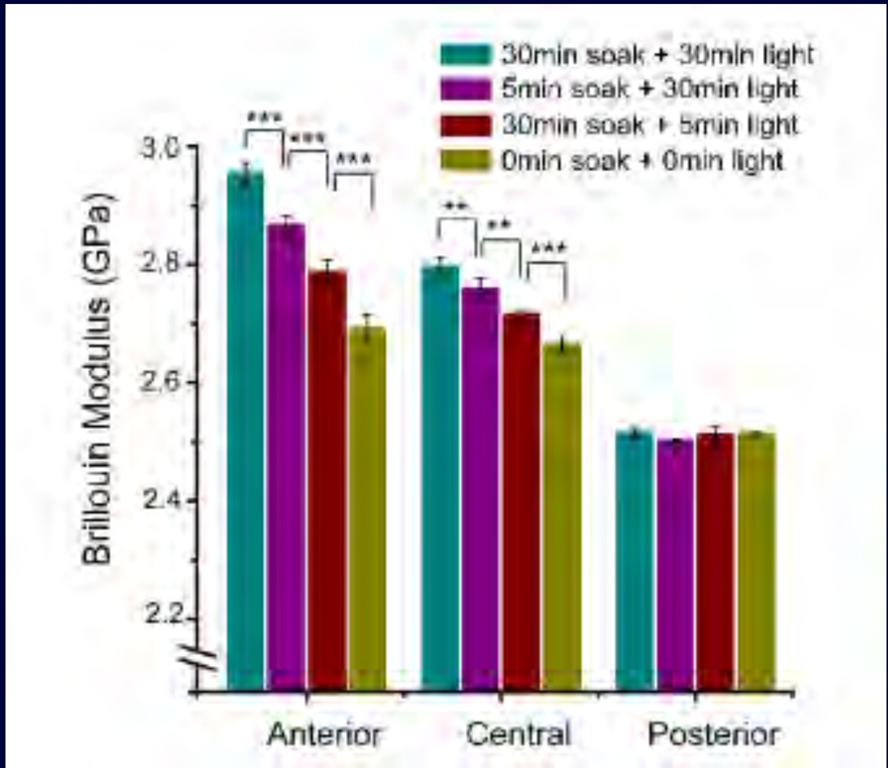


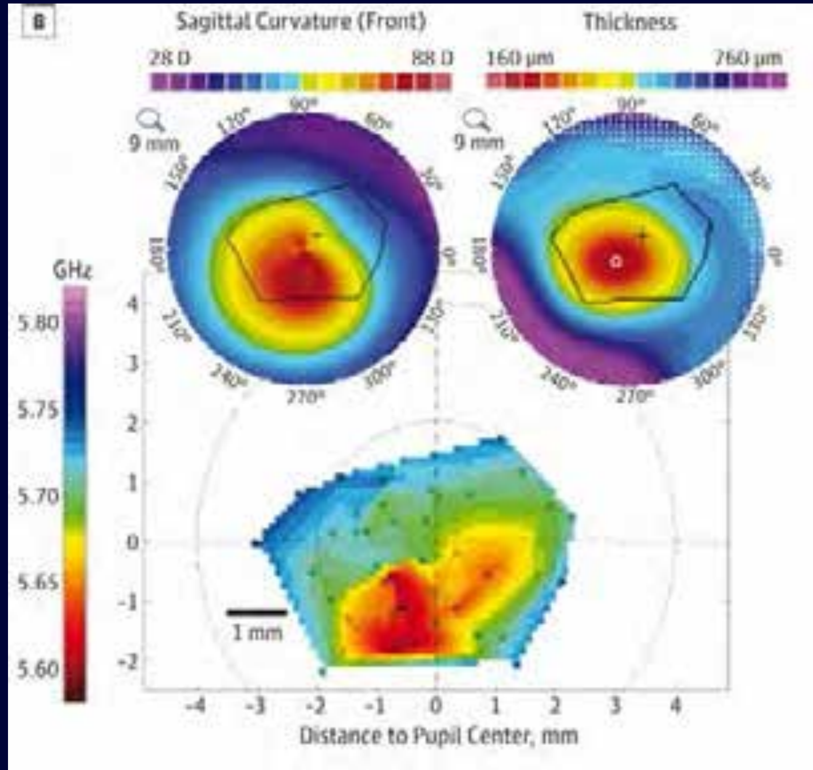
Shear Modulus = 177kPa
Young's Modulus = 530kPa

Ford et al, ARVO 2014

Brillouin scattering

Relates to elastic modulus (M′): $M' = \rho\lambda^2\Omega^2/4n^2$



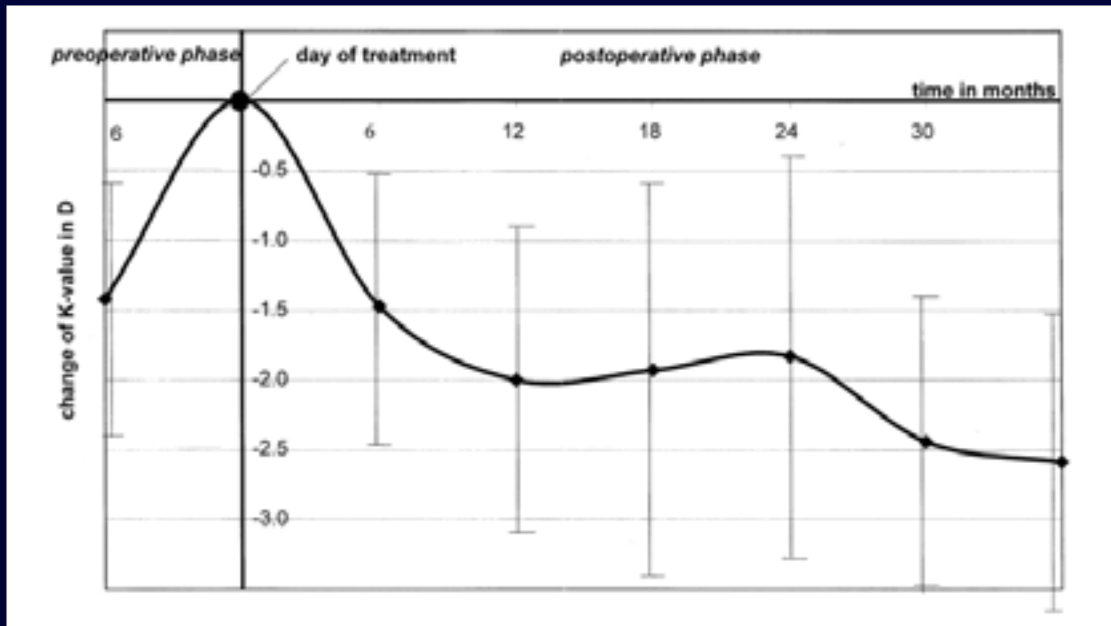


Scarcelli et al, IOVS 2013, AJO 2015

Macro-structural Effects of CXL

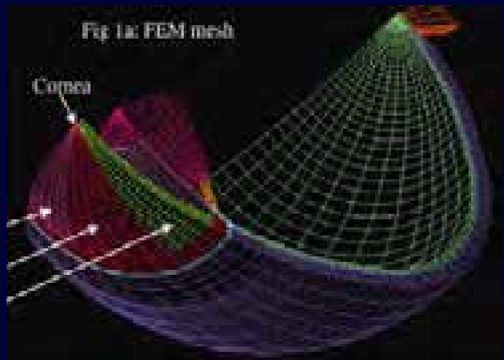
Corneal collagen crosslinking for KC

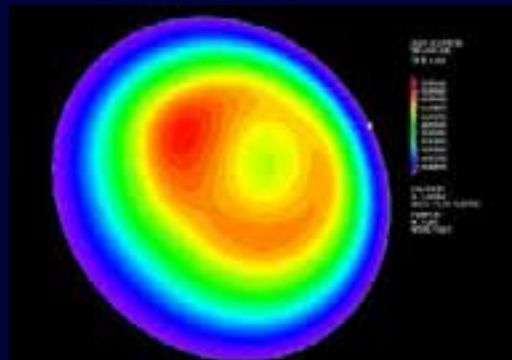
- 23 eyes, progression halted, 70% regressed
  - UVA/riboflavin, broad pattern approach



Wollensak et al, AJO 2003

Macro-effects of CXL: Computational Modeling Analyses





Geometry

Material properties

FE Mesh

Simulation

Load

Stress/strain/shape & optical solutions

Comparison to actual/desired outcome

Refine surgical algorithm

Acknowledgments

- Ocular Biomechanics & Imaging Lab
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