Model-Based Prediction of Crosslinking Outcomes

William J. Dupps, Jr., MD, PhD
Ophthalmology, Biomedical Eng. & Transplant
Cole Eye Institute & Lerner Research Institute
December 3, 2016

Disclosures: Intellectual property in biomechanical measurement & modeling (Cleveland Clinic/OptoQuest), Avedro (research), Ziemer (consultant), Zeiss (research)
Clinical Nomograms for Corneal Surgery Planning

All share mechanistic pathways mediated by biomechanics;
Yet there is no unifying clinical decision pathway
The Cornea: An Ideal Target for Simulation-Based Medicine

- Exquisite structure-function relationship
- Accessible for measurement
- Clinical applications that appeal directly to structural mechanics
Macro-effects of CXL: Computational Modeling Analyses

Geometry

Material properties

FE Mesh

Simulation

Load

Stress/strain/shape & optical solutions
Displacements after myopic LASIK with different corneal material properties

High stiffness => overcorrection

Low stiffness => undercorrection (± ectasia)

Sinha Roy and Dupps, JRS 2009
Modified treatment approaches for customization and optimization

Sinha Roy & Dupps, IOVS 2011

**Figure 7.** Tangential curvature maps of a cornea with a central cone after simulated CXL to a maximum depth of 300 μm in (A) a standard broad-beam stiffening protocol, (B) a variable-intensity broad-beam protocol, and (C) a cone-localized, variable-intensity protocol. (D–F) The corresponding tangential curvature difference maps.
Response to modified treatment approach

Standard 9mm  Graded 9mm  Cone-localized

Figure 8. Tangential curvature maps of a cornea with a more eccentric cone after simulated CXL to a maximum depth of 200 μm in (A) a standard broad-beam stiffening protocol, (B) a variable-intensity broad-beam protocol, and (C) a cone-localized, variable-intensity protocol. (D-F) The corresponding tangential curvature difference maps.

Sinha Roy & Dupps, IOVS 2011
Virtual trials of novel non-ablative refractive treatments

Myopia

Hyperopia

Astigmatism
Effect of stiffening factor with linear bowtie CXL pattern for astigmatism

Preop

Higher-Order Aberrations

Seven et al, JCRS 2015
**2x stiffening**

- Postop $k=2$
- Higher-Order Aberrations
4x stiffening

- Postop k=4
- Higher-Order Aberrations
6x stiffening

- Postop k=6
- Higher-Order Aberrations
Virtual clinical trial in 10 patients

<table>
<thead>
<tr>
<th>Patient</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.99</td>
<td>-0.92</td>
<td>-0.48</td>
<td>-1.1</td>
</tr>
<tr>
<td>2</td>
<td>-1.1</td>
<td>-1.04</td>
<td>-0.57</td>
<td>-1.12</td>
</tr>
<tr>
<td>3</td>
<td>-1.01</td>
<td>-0.99</td>
<td>-0.53</td>
<td>-1.12</td>
</tr>
<tr>
<td>4</td>
<td>-1.05</td>
<td>-1.02</td>
<td>-0.55</td>
<td>-1.1</td>
</tr>
<tr>
<td>6</td>
<td>-0.43</td>
<td>0.81</td>
<td>0.37</td>
<td>-1.09</td>
</tr>
<tr>
<td>7</td>
<td>-0.1</td>
<td>0.69</td>
<td>0.24</td>
<td>-0.74</td>
</tr>
<tr>
<td>8</td>
<td>-1.13</td>
<td>-1.07</td>
<td>-0.58</td>
<td>-1.15</td>
</tr>
<tr>
<td>9</td>
<td>-0.79</td>
<td>-0.78</td>
<td>-0.45</td>
<td>-1.1</td>
</tr>
<tr>
<td>10</td>
<td>-0.32</td>
<td>-0.29</td>
<td>-0.34</td>
<td>-1.2</td>
</tr>
</tbody>
</table>

Seven et al, JCRS 2014
Combined astigmatic keratotomy/CXL

Seven & Dupps, J Med Devices, 2014
Masked Comparison of Simulated & Actual Central CXL Treatment Outcomes

Axial Curvature

Actual post-treatment curvature

Simulated post-treatment curvature

Simulated - actual curvature
Personalized CXL pattern design and pre-clinical simulation-based verification

Pre-op tomography

UV delivery plan

SpecifEye™ client

FEA-predicted outcome
Conclusions

• **Computational modeling:**
  
  • Addresses a need for rational treatment design in crosslinking treatment planning
  
  • Leverages full 3D corneal datasets and treatment specs in patient-specific structural simulations
  
  • Shows high potential for translational implementation with short solution times
Acknowledgments

- **Ocular Biomechanics & Imaging Lab**
  - Ibrahim Seven, Ph.D.
  - Ali Vahdati, Ph.D.
  - Abhijit Sinha Roy, Ph.D.
  - Matthew Ford, Ph.D.
  - Donn Hardy, M.S.
  - Brent Hughes, M.S.
  - Josh Lloyd, M.S.
  - Ben Cowen, M.S.
  - Vinicius Silbiger De Stefano, M.D.

- **Support**
  - NIH R01 EY023381
  - Ohio Third Frontier Innovation Platform Award TECH-013
  - RPB Career Development Award
  - NIH/NCRR K12/ KL2RR024990
  - National Keratoconus Foundation
  - Cleveland Clinic Innovations Product Development Fund
  - Avedro, Inc.
  - The Pender Ophthalmic Research Fund
An “n of 1” virtual trial example

<table>
<thead>
<tr>
<th>Patient Name:</th>
<th>6624</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td>Female</td>
</tr>
<tr>
<td>DOB:</td>
<td></td>
</tr>
<tr>
<td>Laterality:</td>
<td>OD (Right)</td>
</tr>
<tr>
<td>Imaging Device:</td>
<td>Pentacam 1.20r29</td>
</tr>
<tr>
<td>QS:</td>
<td>OK</td>
</tr>
<tr>
<td>RMS Fit Error:</td>
<td>6.44 μm</td>
</tr>
<tr>
<td>IOP:</td>
<td>15.0 mmHg</td>
</tr>
<tr>
<td>Tonometer:</td>
<td>ORA</td>
</tr>
<tr>
<td>Estimated AEL:</td>
<td>21.29 mm</td>
</tr>
<tr>
<td>UDVA/CDVA:</td>
<td>20/20/20</td>
</tr>
<tr>
<td>MRx:</td>
<td>0.00 + 0.00 X 180</td>
</tr>
<tr>
<td>Surgeon:</td>
<td>William Dupps</td>
</tr>
</tbody>
</table>

| Treatment:     | Crosslinking |
| Treatment Device: | AvedroKxl |
| Epithelium:    | Off |
| Riboflavin:    | VibexXtra |
| Soak Time:     | 30 Minutes : 0 s |
| Illumination Type: | Continuous |

Pre-Treatment Clinical

Pre-Treatment Model
9mm CXL vs. elevation-centered spot
LASIK validation trial: prediction error in refractive change from FEA (n = 20)

\[ y = 0.98x + 0.16 \]

\[ R^2 = 0.97237 \]

Seven et al, IOVS 2016
LASIK + adjunctive CXL

**Rationale**
- reducing risk of post-refractive surgery ectasia
- prevention of postoperative refractive regression

**Clinical Evidence**
- results suggest early refractive outcomes similar to LASIK alone  *(Tomita et al, JCRS 2014)*
- less regression in hyperopic LASIK treatments  *(Kanellopoulos & Kahn, JRS 2012)*
- No direct data on benefit to ectasia risk
LASIK + adjunctive CXL

- Simulate LASIK and LASIK + CXL in 4 patient-specific models
- Mean correction -3.93 ± 0.56 D
- CXL stiffening factor = 1.5x^{1,2}
- Anisotropic material properties^{3,4}
- Preferred fiber orientations assigned to each element

<table>
<thead>
<tr>
<th></th>
<th>Preop error (verification)</th>
<th>Postop error (validation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kmean (D)</td>
<td>0.08 ± 0.20</td>
<td>0.26 ± 0.14</td>
</tr>
</tbody>
</table>

1) Roy et al, Exp. Eye Res 2013
2) Seifert et al, Plos One 2014
3) Wollensak et al., JCRS 2003
4) Hoeltzel et al, J Biomech Eng 1992
5) Meek et al, Prog Ret Res 2009
Keratometric and residual stromal displacement results: LASIK vs. LASIK + CXL

<table>
<thead>
<tr>
<th></th>
<th>LASIK IOP 15</th>
<th>LASIK + CXL IOP 15</th>
<th>LASIK IOP 30</th>
<th>LASIK + CXL IOP 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>194</td>
<td>183</td>
<td>393</td>
<td>371</td>
</tr>
<tr>
<td>2</td>
<td>206</td>
<td>195</td>
<td>419</td>
<td>396</td>
</tr>
<tr>
<td>3</td>
<td>205</td>
<td>194</td>
<td>416</td>
<td>394</td>
</tr>
<tr>
<td>4</td>
<td>270</td>
<td>254</td>
<td>547</td>
<td>516</td>
</tr>
</tbody>
</table>

Difference in Kmean (D) \(-0.19 \pm 0.08\) \((p>0.05)\)

Seven et al, ARVO 2014