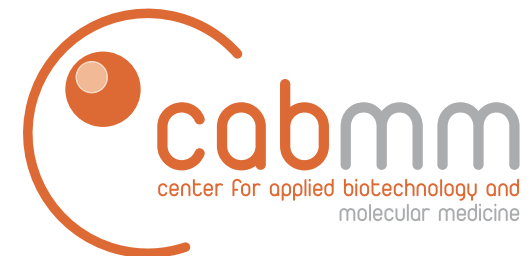


A model to predict the stiffening effect of CXL: theory

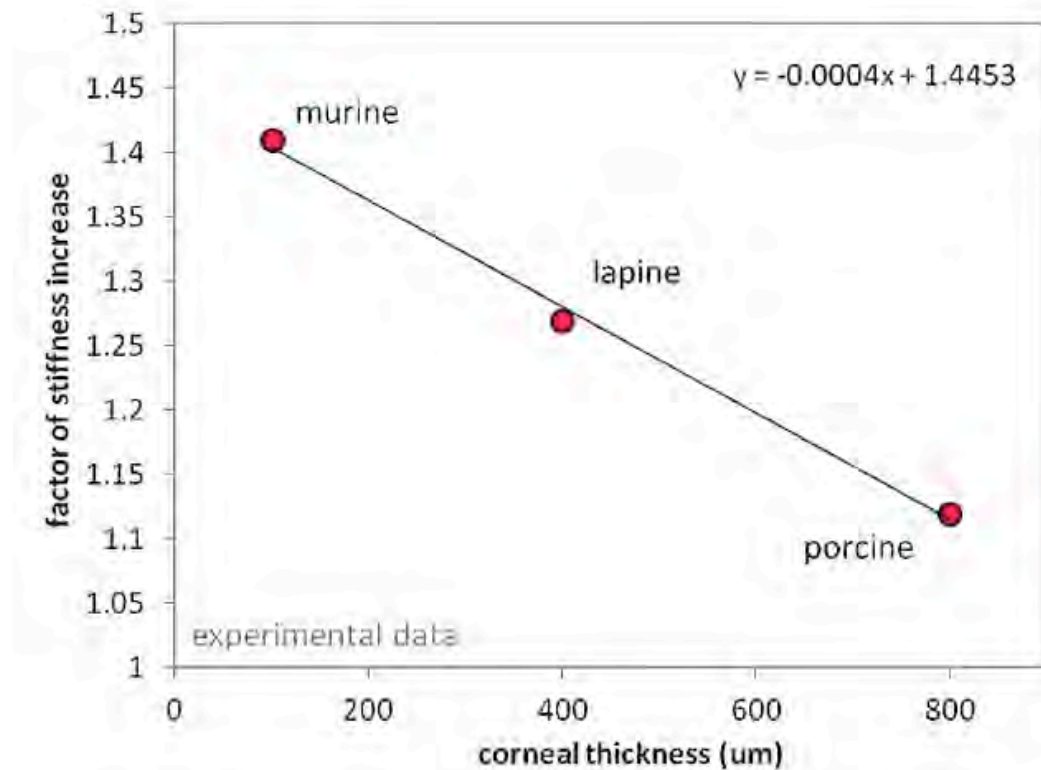
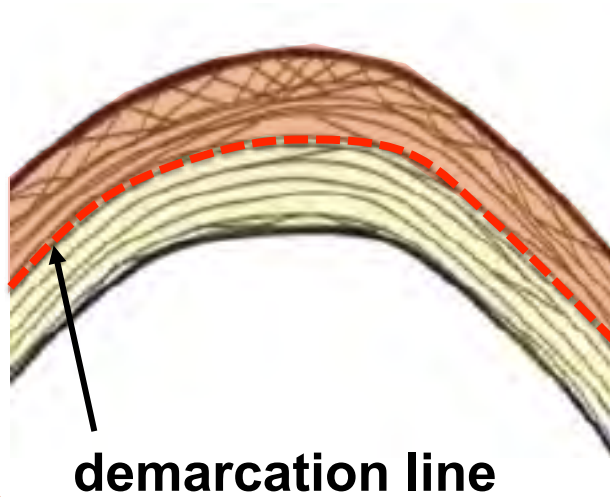
Sabine Kling, PhD, Farhad Hafezi, MD, PhD



Universität Zürich



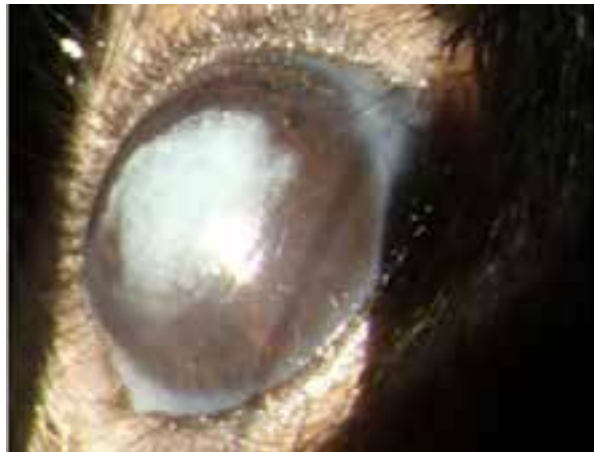
CXL efficacy as a function of corneal thickness



→ stronger CXL in thinner corneas

Complications of strong CXL

**100 μm murine cornea
treated with 5.4 J/cm²**



*REF. Kling S.
CXL congress (2014)*

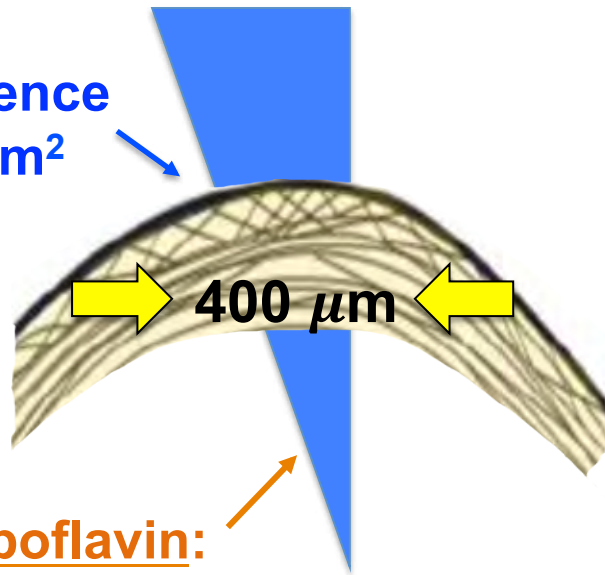
**404 μm human cornea
treated with 5.4 J/cm²**



*REF. Soeters N. J Pediatr
Ophthalmol Strabismus (2011)*

Safety of CXL treatment

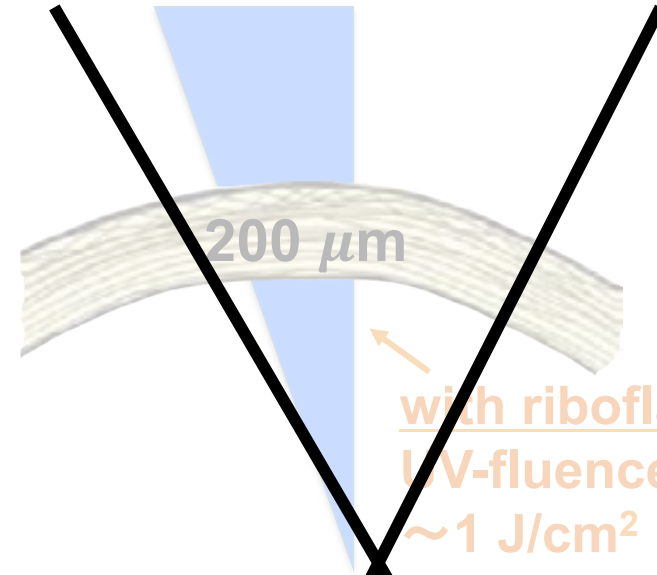
UV-fluence
5.4 J/cm²



with riboflavin:
UV-fluence
~0.18 J/cm²

Normal cornea:

- high UV absorption
→ protection of the endothelium and crystalline lens



with riboflavin:
UV-fluence
~1 J/cm²

Thin cornea:

- low UV absorption
- higher UV dose at the endothelium
→ risk of endothelial damage
→ risk of cataract

Thin corneas



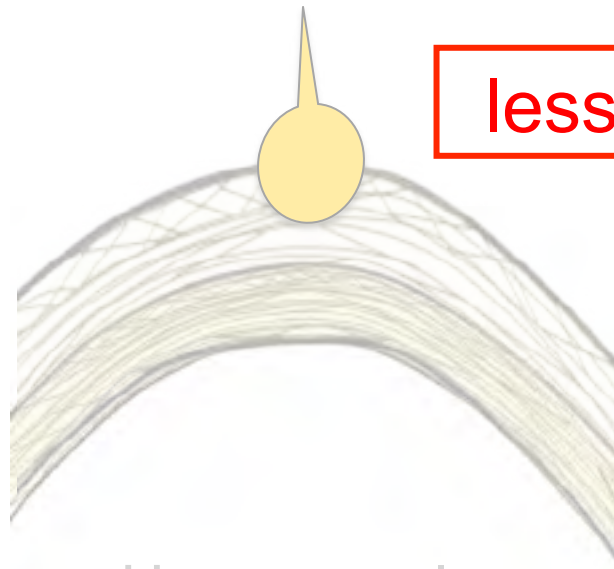
- **strongly require CXL treatment**

Treatment protocols for thin corneas

hypo-osmolar riboflavin
to swell the cornea

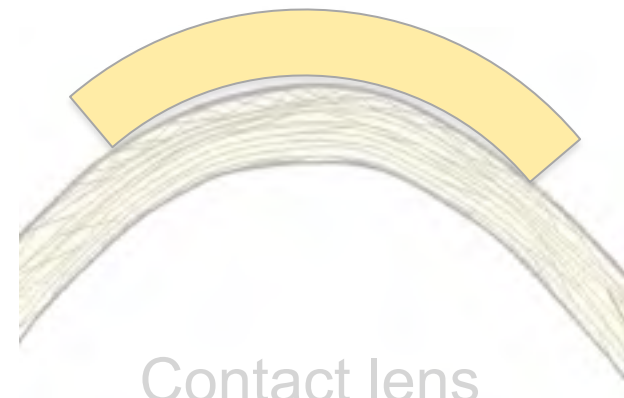
contact lens to partially
shield the UV light

less effective



Hypo-osmolar
CXL

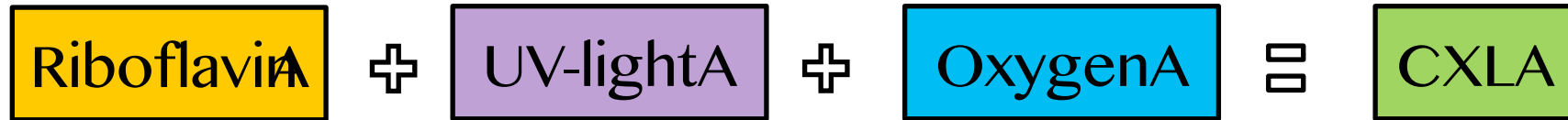
REF. Hafezi F. JCRS (2009)



Contact lens
assisted CXL

REF. Jacobs S. JRS (2014)

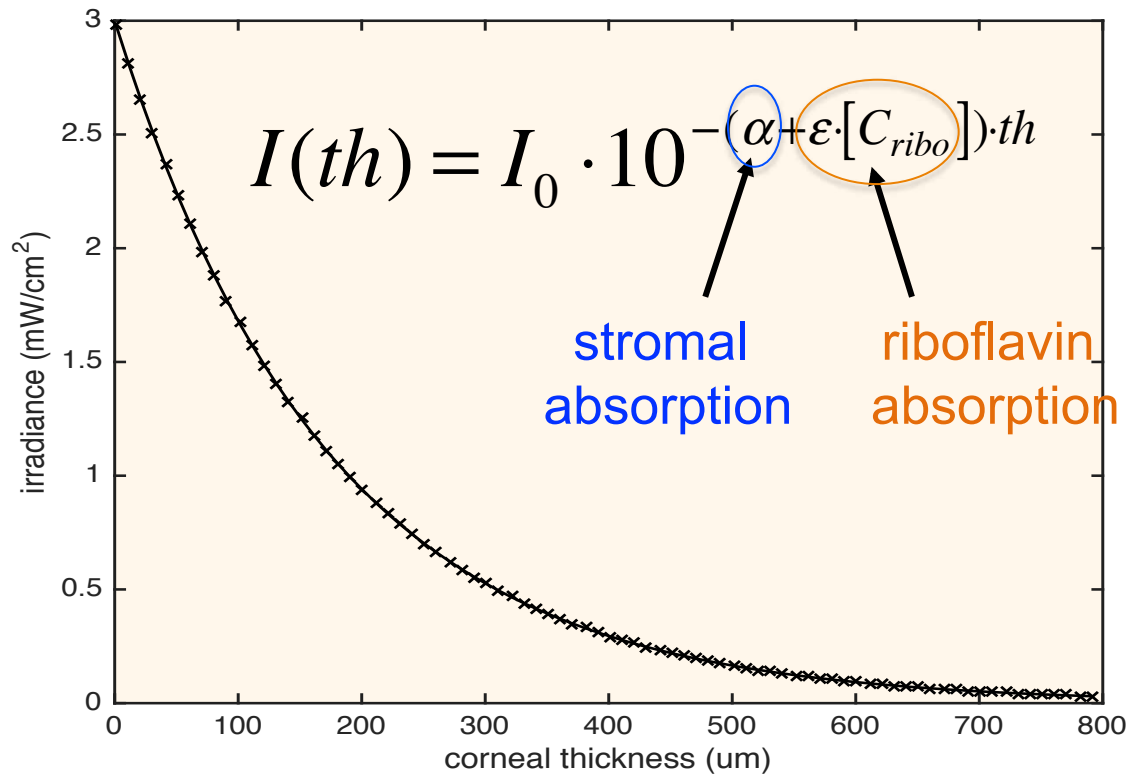
How to adapt CXL for thin corneas?



- **Increasing ~~“corneal”~~ thickness**
 - Increased collagen fibril spacing ↓
 - Reduced oxygen availability ↓
- **Decreasing UV irradiance**
- **Decreasing irradiation time**
- **Increasing riboflavin concentration**
- **Decreasing oxygen availability**

**Algorithm to predict the stiffening effect
and demarcation line as a function of
different CXL treatment parameters.**

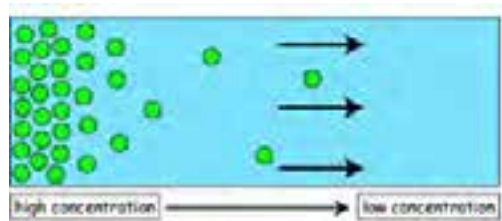
Lambert-Beer law of light absorption



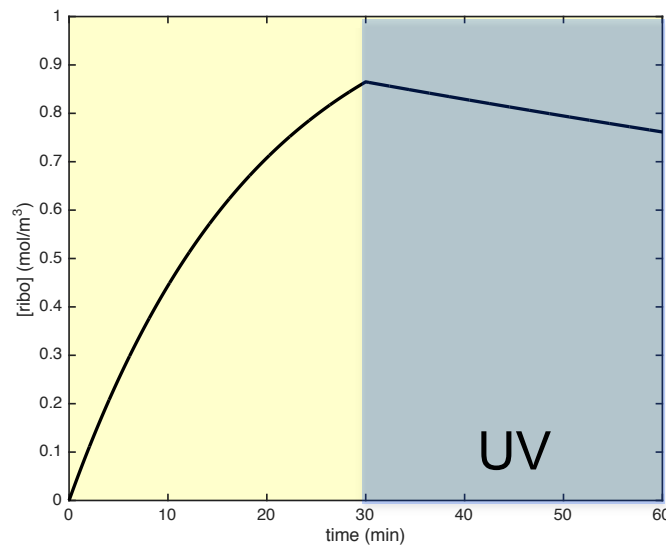
**UV-light
availability**

- **exponential decrease**
- **dependent on riboflavin concentration**

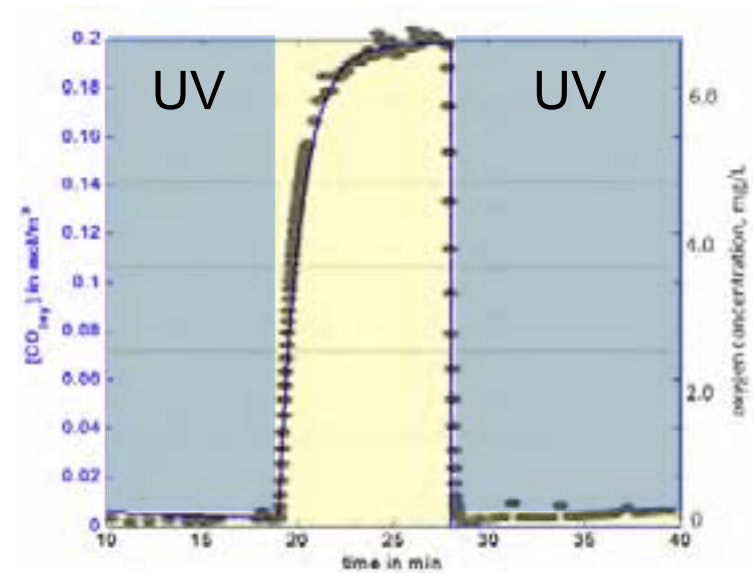
Fick's law of diffusion



Temporal diffusion of riboflavin and oxygen into the corneal stroma



Riboflavin availability below a 120 μm corneal flap

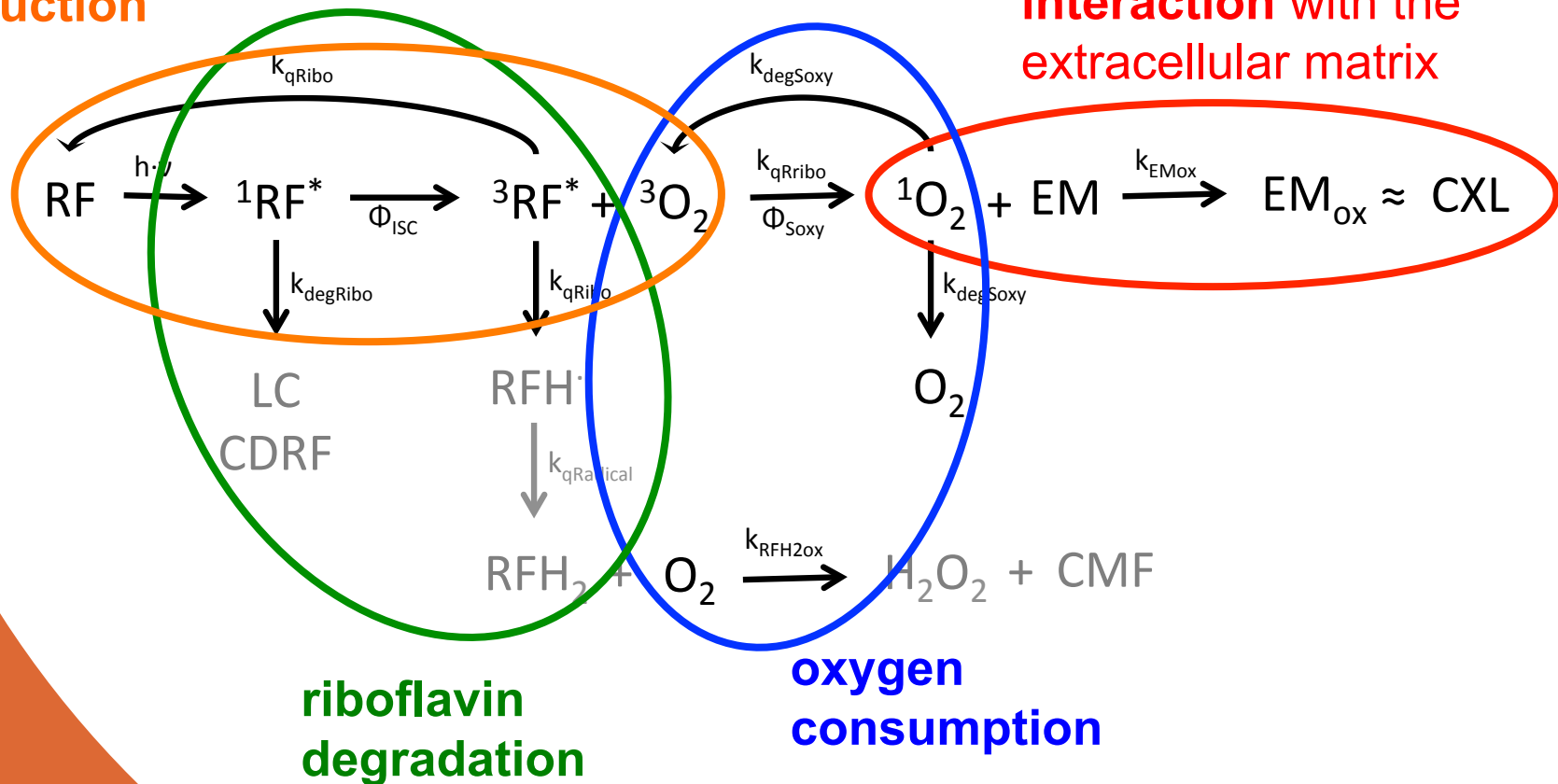


Oxygen availability below a 120 μm corneal flap

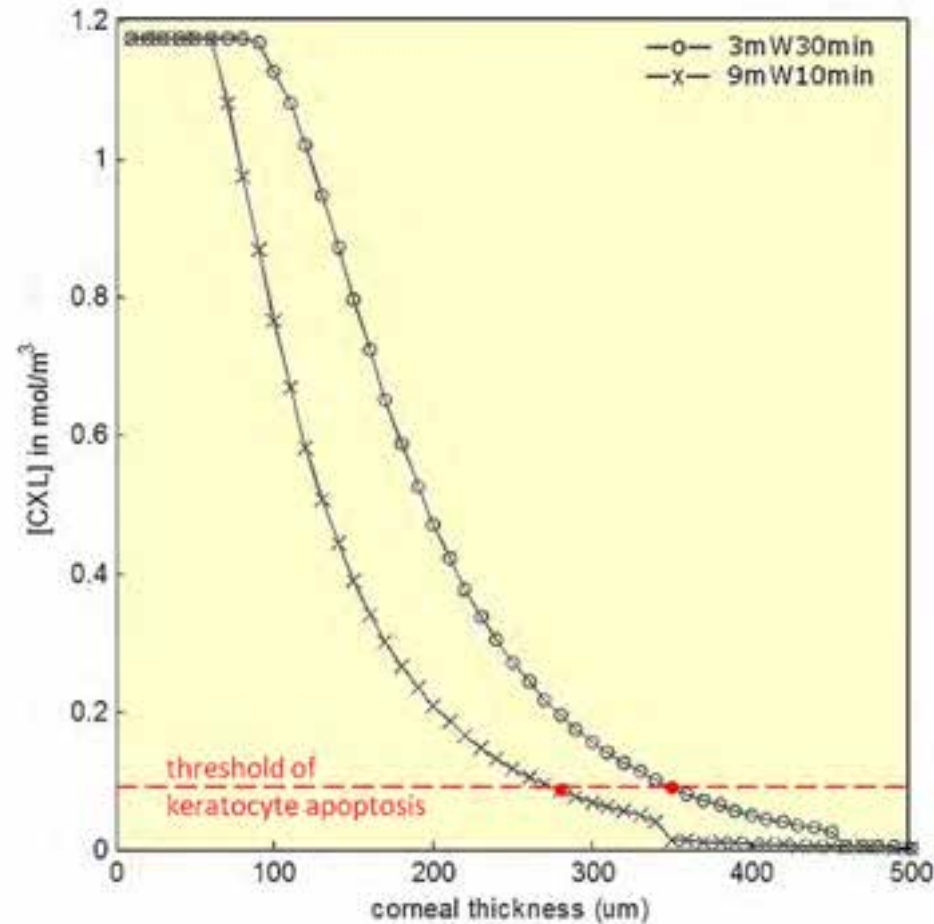
Chemical reaction scheme

Rate of photon and singlet oxygen production

Rate of singlet oxygen interaction with the extracellular matrix

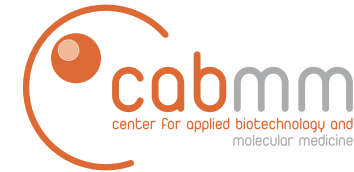


Demarcation line prediction



Accelerated CXL produced a more shallow demarcation line than standard CXL.

Studying different CXL protocols



Irradiances: 250 $\mu\text{W}/\text{cm}^2$ to 18 mW/cm^2

Irradiation times: 30s to 30 min

UV fluences: 0.09 J/cm^2 to 5.4 J/cm^2

UV source: pulsed / continuous

Corneal thickness:

- pig (~800 μm)
- rabbit (~400 μm)
- mouse (~100 μm)

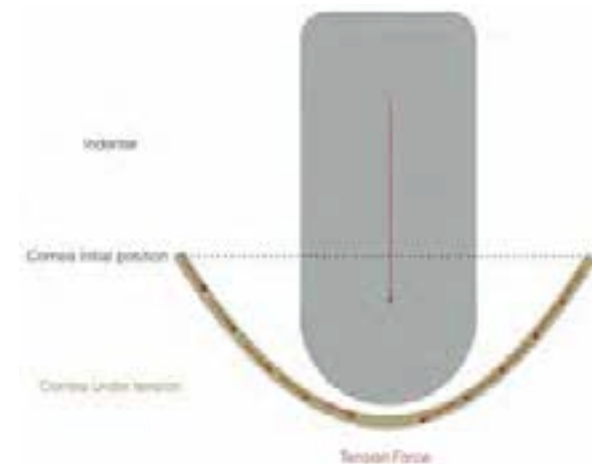


Experimental analysis

Experimental material testing:
stress-strain extensiometer (Zwicki-line)
+ customized 2D-holder

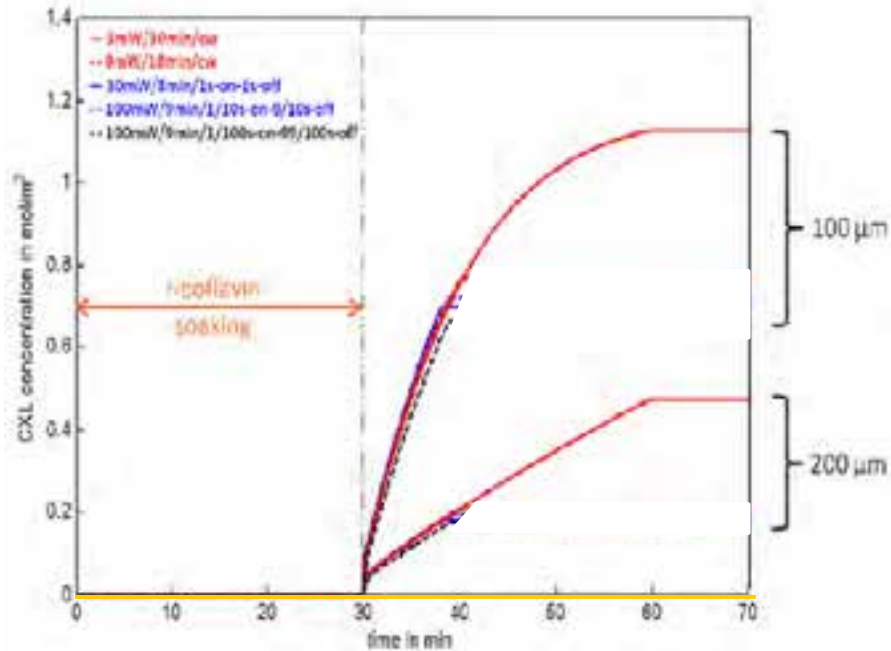
**Elastic + Viscoelastic
material properties:**

- Pre-conditioning
- Stress-relaxation
- Stress-strain curve

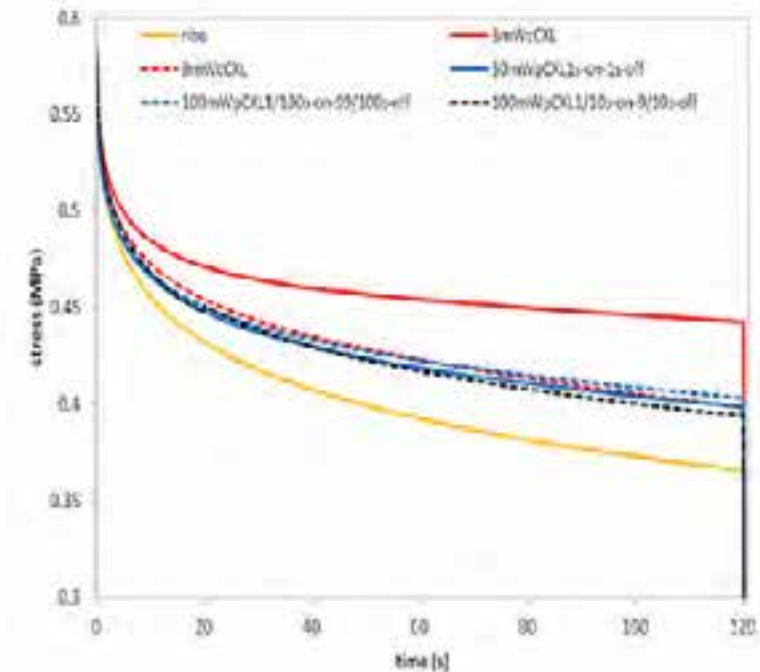


Comparing CXL efficacies

Theoretical:



Experimental:

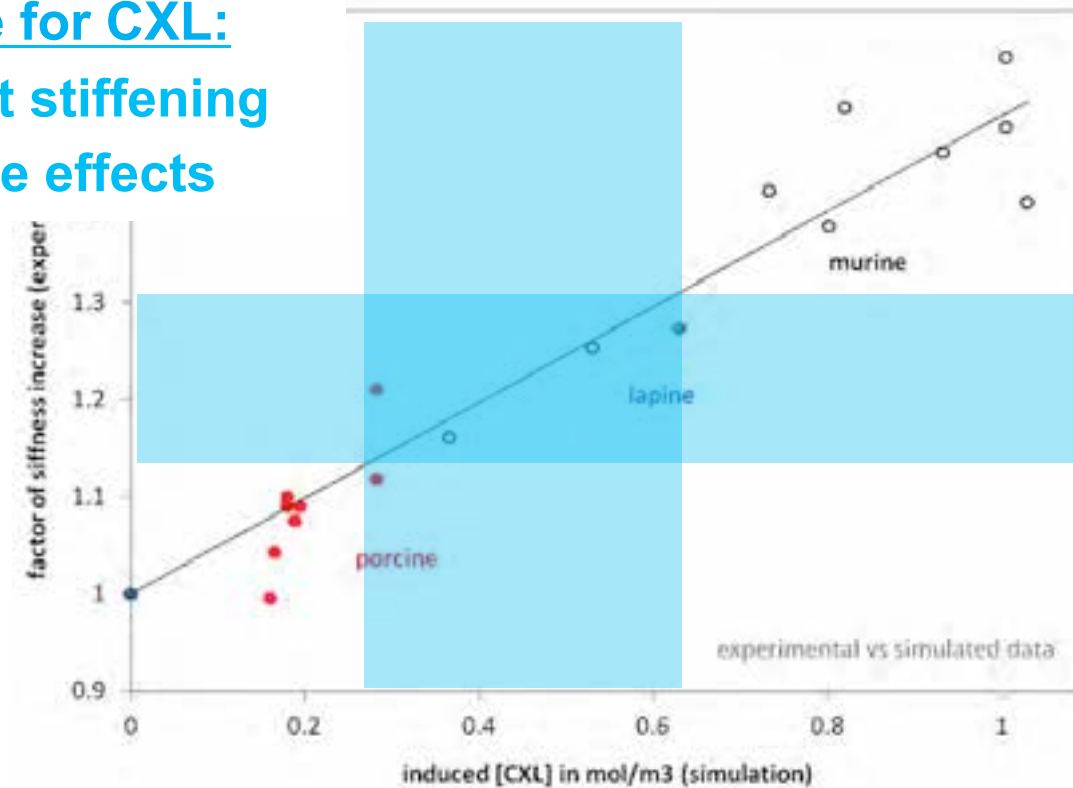


- Oxygen availability determines the speed of CXL: short-term irradiation is less effective
- Irradiate for a long time (with a low UV-irradiance) to reach the maximal stiffening effect.

Experimental stiffening versus theoretical number of cross-links

Best range for CXL:

- significant stiffening
- no adverse effects



REF. Kling S. in press at JRS

Linear relationship: CXL-density determines the amount of corneal stiffening.

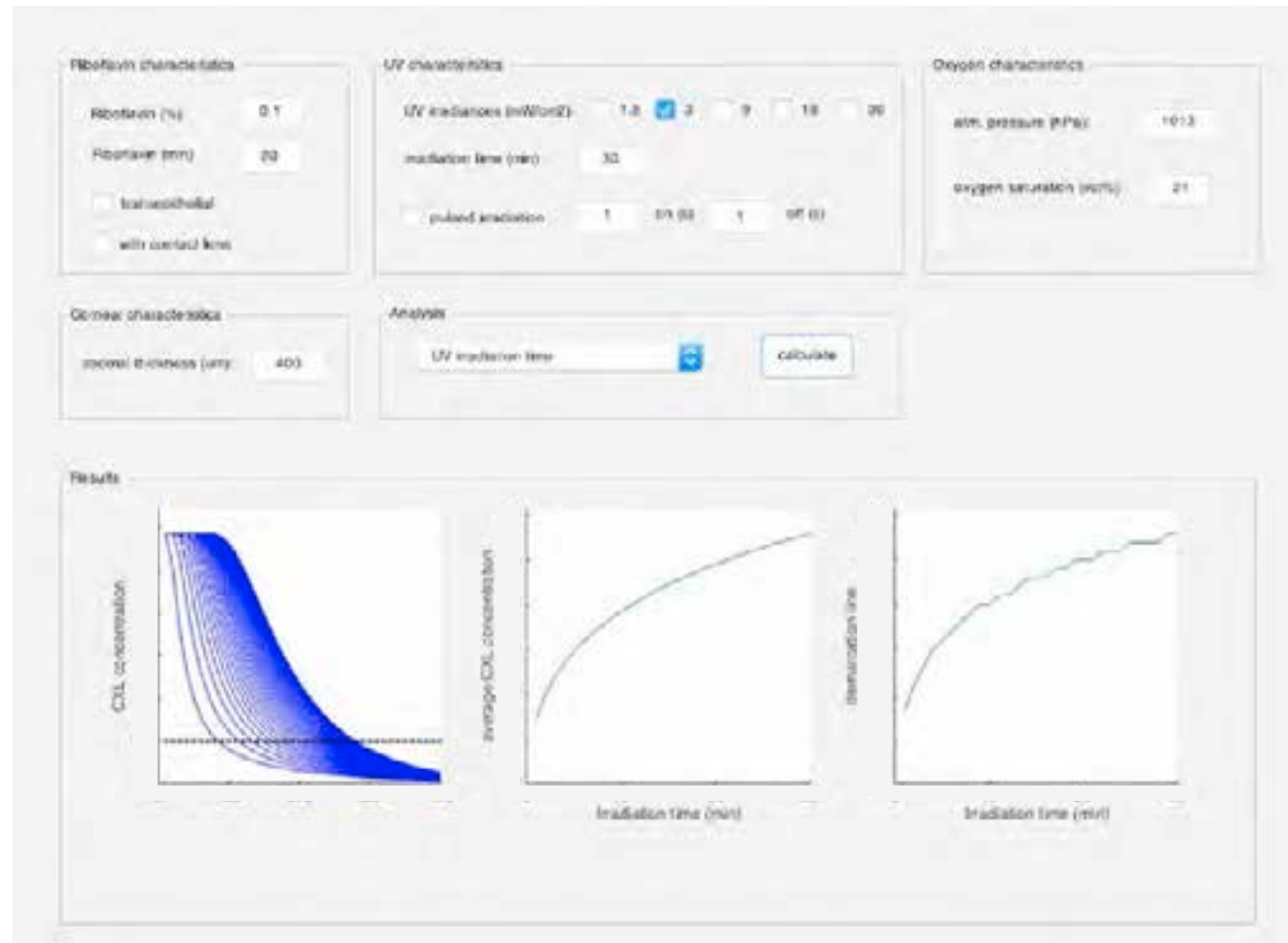
Adaptation of the CXL protocol for thin corneas

**AIM: Inducing a similar density of cross-links
like in thicker corneas.**

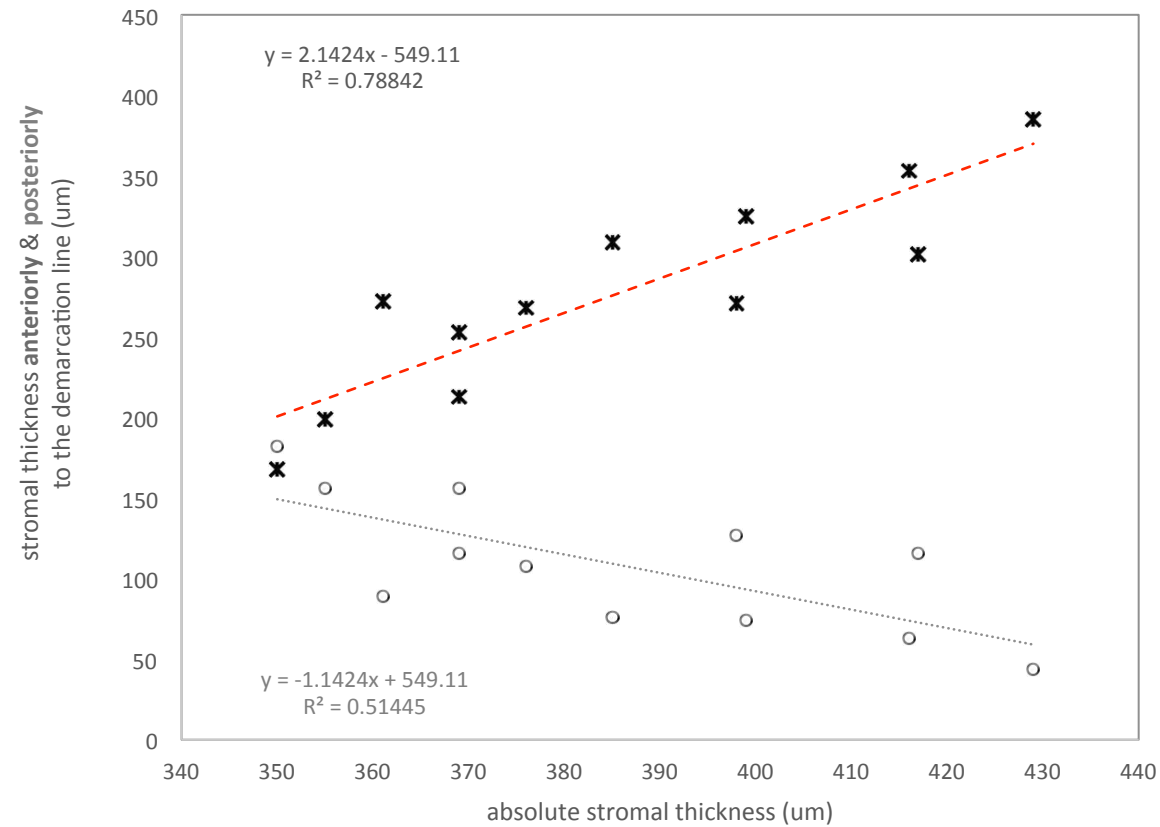
$$\frac{\text{number of cross-links}}{\text{corneal volume}} = 0.3-0.6 \text{ mol/m}^3$$

UV fluence at the endothelium $\leq 0.3 \text{ J/cm}^2$

Patient-specific parameter selection



Demarcation line as a function of corneal thickness



- **linear correlation relationship**

Conclusions

- **We have developed a theoretical model that predicts well the CXL efficacy for different corneal thicknesses.**
- **The density of theoretically induced cross-links is linearly related to the experimental increase in corneal stiffness.**
- **The model allows a patient-specific adaptation of treatment parameters and allows CXL treatment even in thicknesses $<400\mu\text{m}$.**

**Thank you
for your attention**