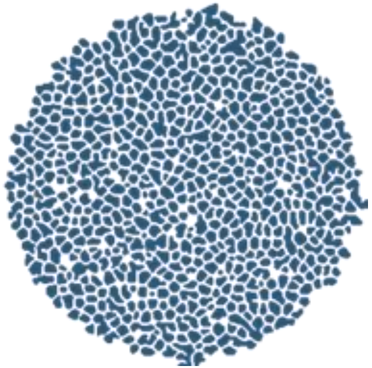
Establishing the Fractal Nature of Corneal Epithelial Cell Boundaries



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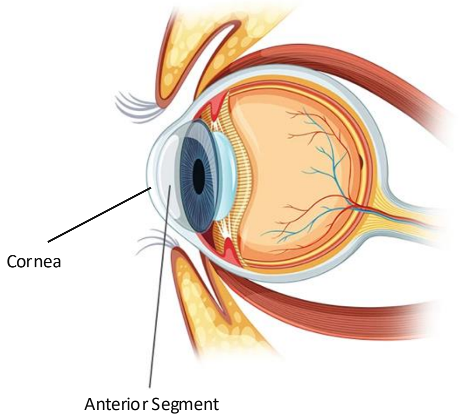
CONTENTS

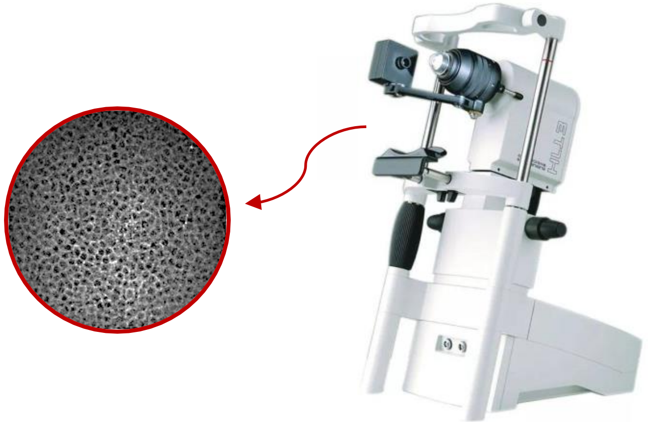
Newcastle University

CONTEXT

- ## The Cornea
  - Clear front part of the eye; protects the eye and focuses light.
  - Outermost layer: epithelium, a sheet of cells that renews and protects the surface of the cornea.
  - Cell-cell junctions form a network; their shape and pattern may matter for function and healing.

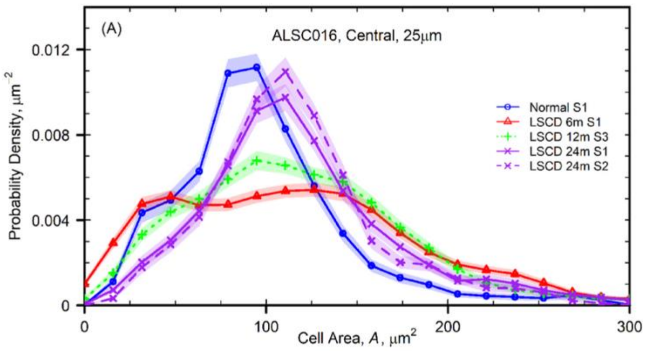


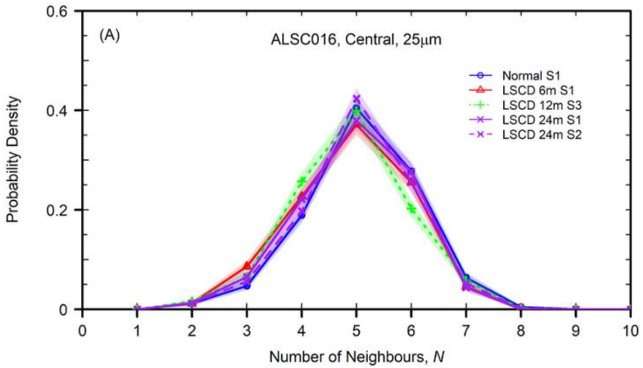
- ## IVCM: In Vivo Confocal Microscopy
  - IVCM is one of many ways to image the ocular surface.
  - We image the living cornea without removing tissue.
  - High resolution: we see single cells and their boundaries.
  - We can follow the same patient over time (e.g. before and after surgery).



CONTEXT

- **Biomarkers Studied by our IVCM Group**
  - **Cell-area PDF**: By 24 months after surgery, the initially broad post-operative cell area PDFs narrow and overlap with the sharp healthy reference distribution.
  - **Area vs Imaging Depth**: Linear trend; fit is patient-specific (no universal “standard cornea”).
  - **Neighbour Counts**: The most common number of neighbors is actually five (pentagonal) at all depths and regions.
  - **Exploring a New Biomarker**: Fractal boundary scaling: next slide.



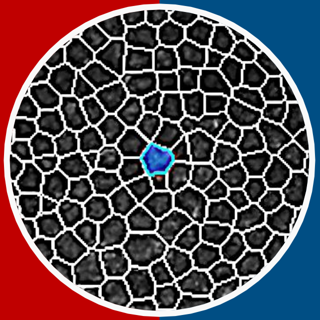


Newcastle University: Parkinson et al., Ocular Surface 2025 (DOI: 10.1016/j.jtos.2025.08.005)

CONTEXT

- **Why Look at Boundary Complexity?**
  - Standard metrics: cell area, cell density depend on scale.
  - Cell-cell junctions form a complex network; shape may matter for nutrients and healing.
  - We ask: can we describe this complexity in a scale-invariant way?
  - Idea: Treat boundaries as fractal curves → one number (fractal dimension D) captures complexity.

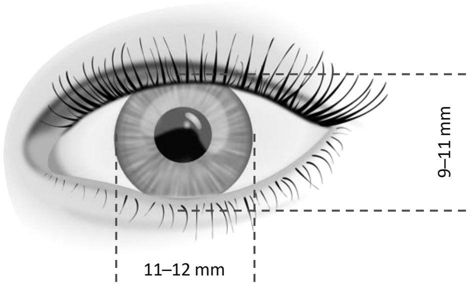
- **Traditional Morphometry**
  - Mean cell area
  - Cell density (cells/mm^2)
  - Simple shape indices

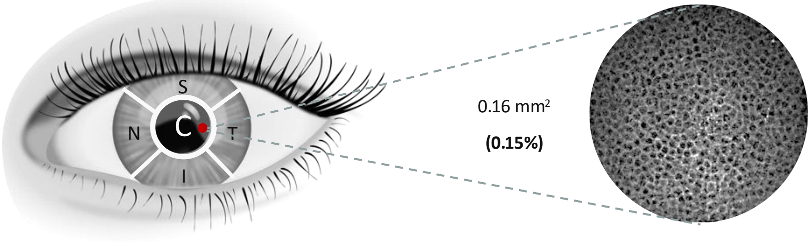


- **Fractal Analysis**
  - Treat cell boundaries as fractal curves
  - Use fractal dimension D from perimeter–area scaling

DATA & METHODS

- **How Do We Get Cell Boundaries?**
  - Dataset: 10 patients · limbal stem cell transplantation (LSCT) · IVCM
  - Regions: Central, temporal, nasal, superior, inferior (5 regions of the cornea)
  - Time: Baseline → 6, 12, 18, 24, 36 months after surgery
  - Segmentation: Bespoke MATLAB watershed algorithm, tuned for IVCM, preserves fine detail at junctions
  - Note: Other algorithms (e.g. Cellpose 3) are being compared; they can smooth boundaries and change D.

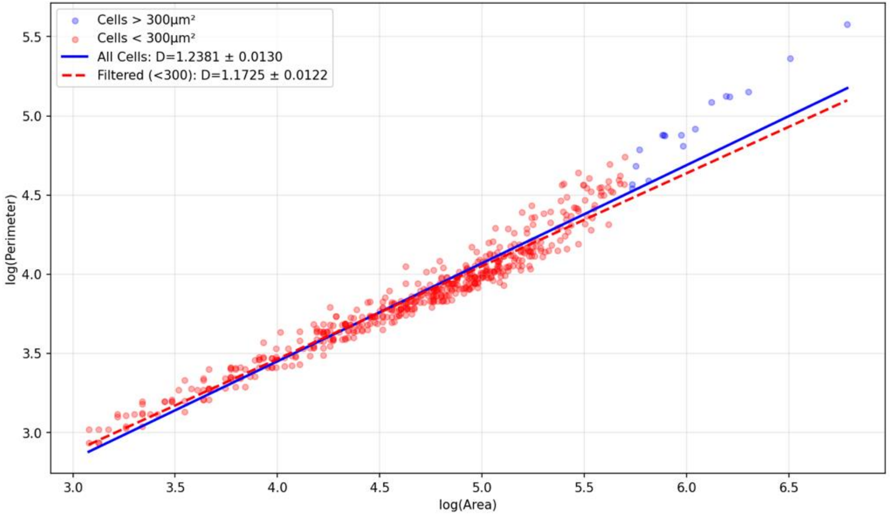




DATA & METHODS

- **The Fractal Framework: Perimeter–Area Scaling**
  - For fractal boundaries: $P \propto A^{(D/2)}$ (Mandelbrot–Lovejoy)
  - In log space: $\log P = (D/2) \times \log A + \text{constant}$ → straight line
  - Slope of the line → $D = 2 \times \text{slope}$
  - We fit this with standard regression (OLS); we check fit quality (R^2) and that D is between 1 and 2.

Log (P) vs Log (A)

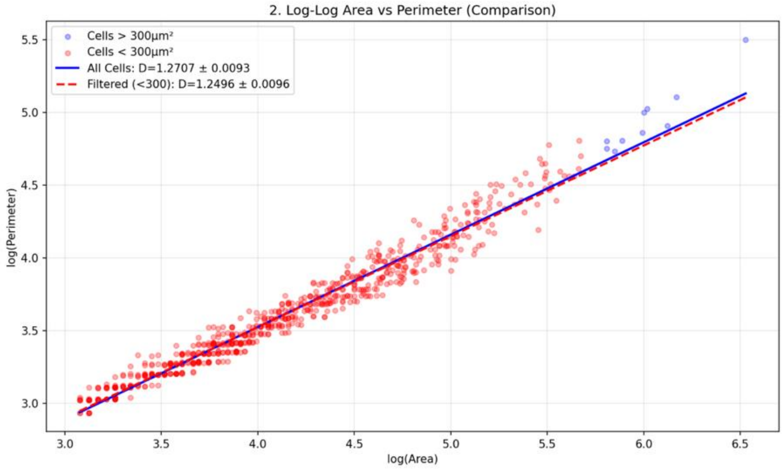


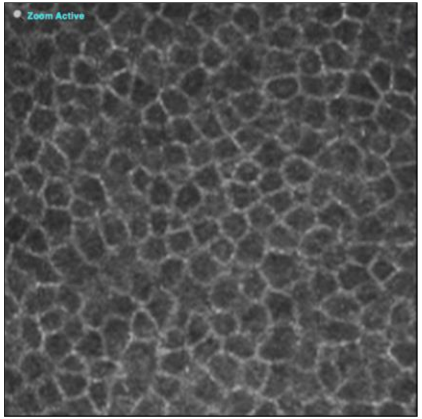
Note: Slope of blue line → Fractal Dimension (D)

D ≈ 1: smooth; D ≈ 1.5: moderate; D → 2: very rough

RESULTS

- **Boundaries Follow a Power Law**
  - Across 1,114 images, mean fractal dimension D = 1.246 (±0.011)
  - Log–log fits are good (high R^2) → supports fractal scaling
  - Caveat: This value uses our bespoke MATLAB watershed; D can change with another segmentation algorithm.





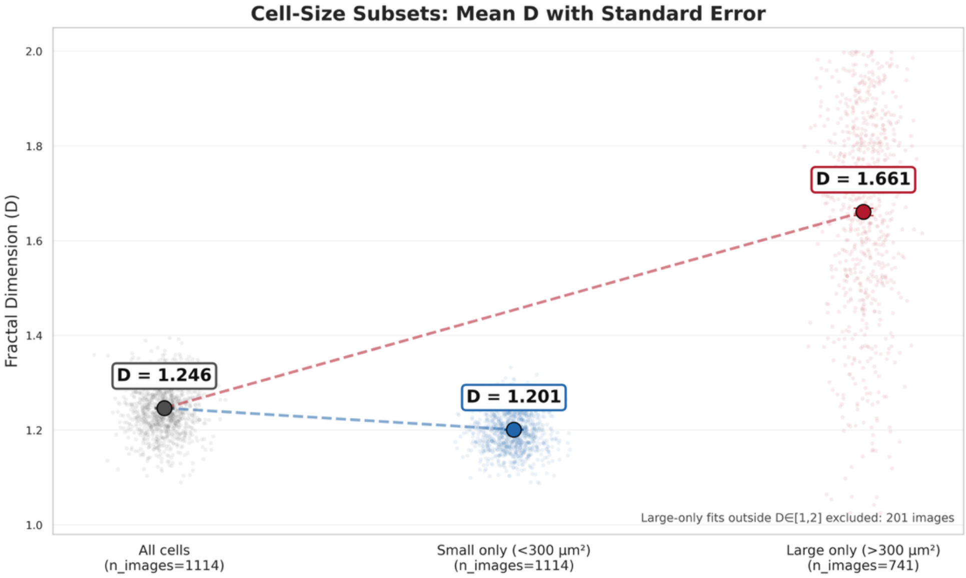
1.24

Mean D = 1.246 ± 0.011 · n = 1,114 images

Power-law behaviour

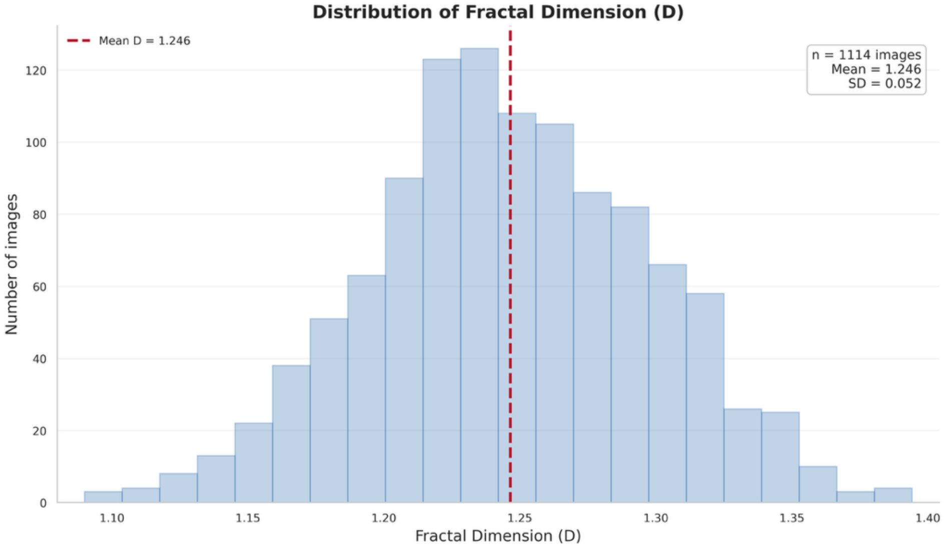
RESULTS

- **Does D Depend on Cell Size?**
  - We estimated D in three subsets per image: all cells, small cells (<300 μm²), and large cells (>300 μm²).
  - Mean values (current figure): All cells D = 1.263 (n=1,114), small-only D = 1.208 (n=1,114), large-only D = 1.661 (n=741 valid fits).
  - Interpretation: Small-cell filtering lowers D relative to all cells. Large-cell-only fits are higher but less stable.
  - Take-home: Fractal behaviour remains clear, but subset choice and segmentation context must be reported.



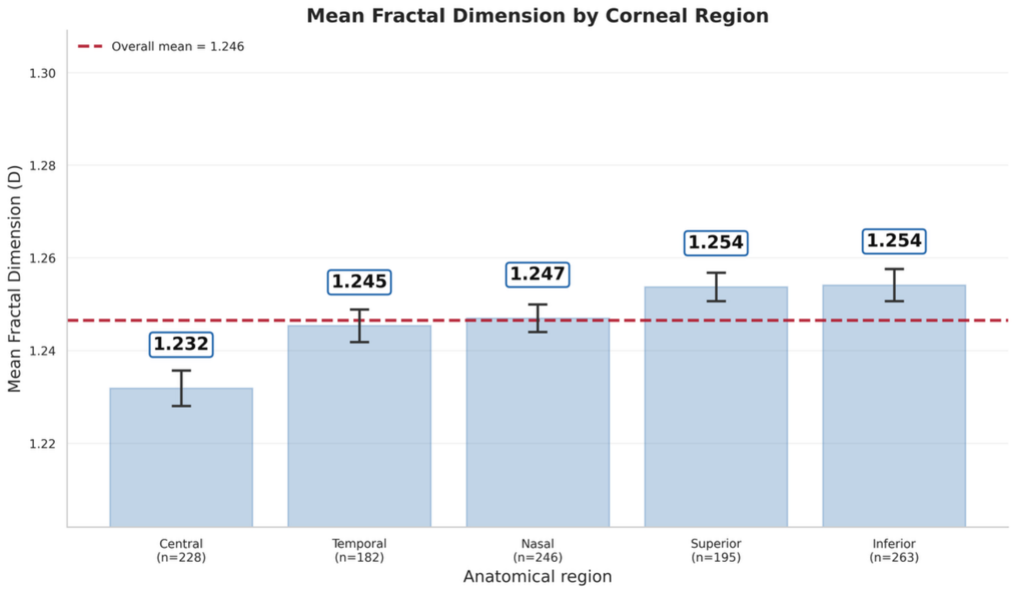
RESULTS

- **Distribution of Fractal Dimension D**
  - n = 1,114 images
  - Mean D = 1.246 (std ≈ 0.05)
  - Distribution is unimodal and roughly symmetric around the mean (SD ≈ 0.05) → D behaves as a stable summary across images.



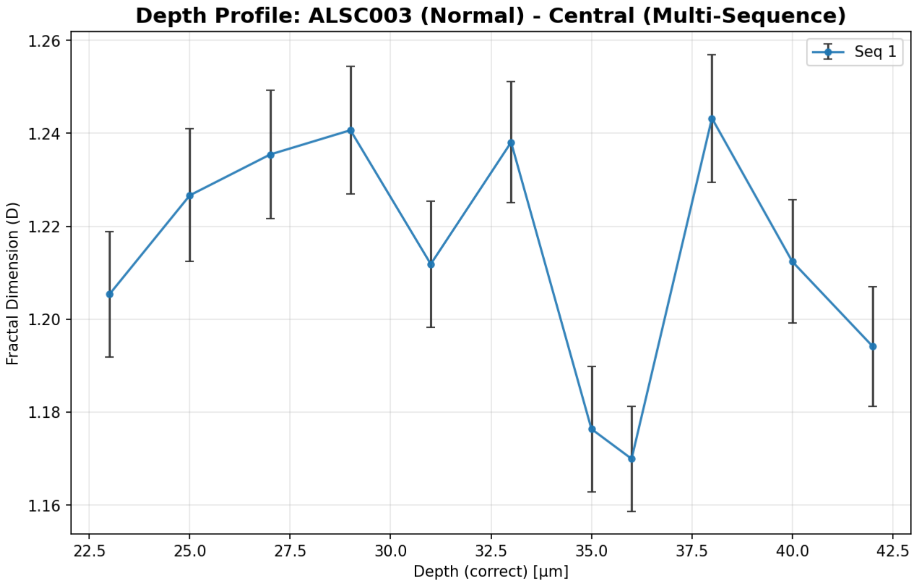
RESULTS

- **D Across the Five Anatomical Regions**
  - n = 1,114 images
  - Central ~1.23; Inferior, Nasal, Superior, Temporal ~1.25.
  - Message: Mean D is similar everywhere → fractal complexity looks like a general property of the epithelium, not only one region.



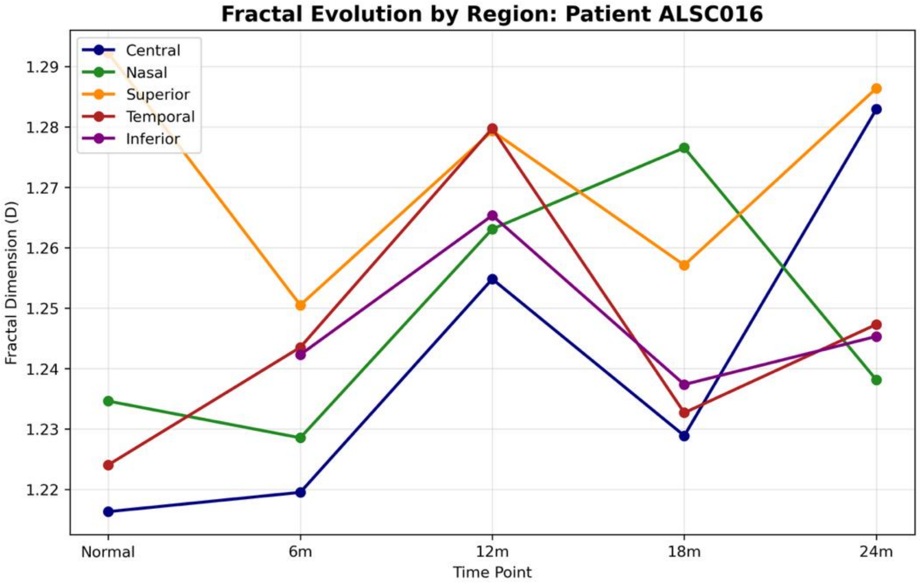
RESULTS

- **D is Stable Across Depth**
  - We computed D at different depths (different layers within the epithelium).
  - Example: One patient, central region → D does not depend strongly on depth.
  - So the power-law behaviour holds across the tissue, not only at one depth.



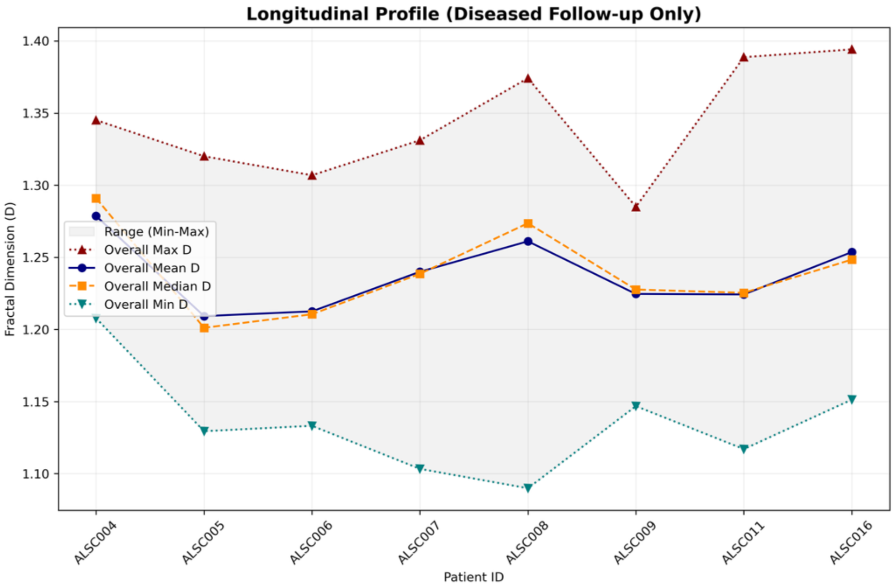
RESULTS

- **D Across the Recovery 36-month Timeline**
  - Timepoints: Baseline (Normal), 6, 12, 18, 24, 36 months
  - Example: One patient → D by timepoint and region (lines with markers).
  - Work in progress: We are linking D to clinical outcome (healing, recovery).



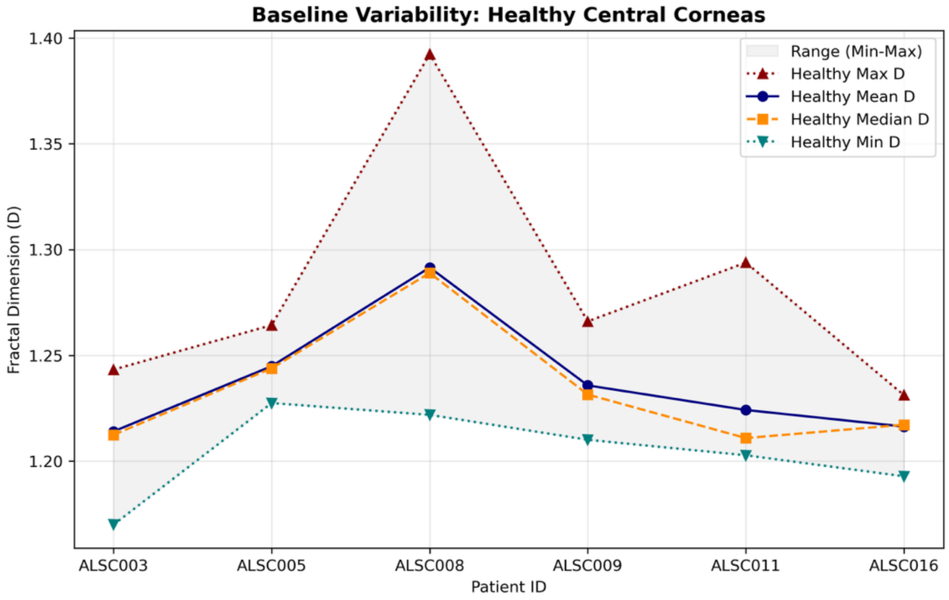
RESULTS

- **Between-patient Variability in D**
  - Each patient has a range of D (mean, median, min, max across their images).
  - Patient-level mean D falls in ~1.21–1.28 (diseased follow-up only; Normal baseline excluded) → supports comparison across patients.



RESULTS

- ## Healthy Baseline
  - D in healthy **central cornea** at baseline, one value per patient.
  - Establishes a reference for comparing before and after surgery and across time.

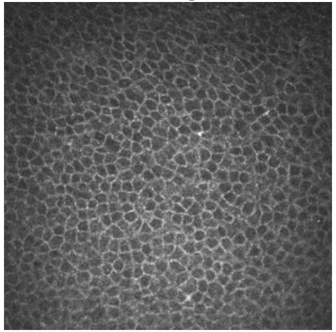


Algorithm Sensitivity

- **D Depends on the Segmentation Algorithm**
  - Same image, different boundaries: segmentation method changes contour detail.
  - Bespoke MATLAB watershed (example frame): D = 1.257, n = 547 cells.
  - Cellpose output: typically smoother contours on the same frame: D = 1.127, n = 534 cells.
  - Message: reported D must always be interpreted with the segmentation method.

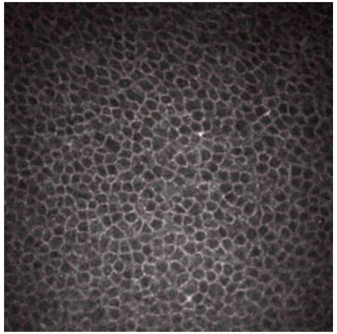
Raw Image

Before Processing



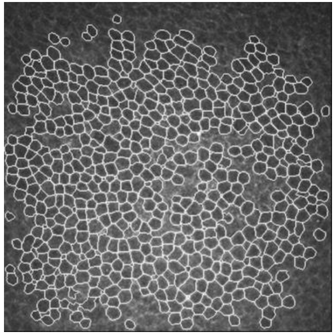
Watershed

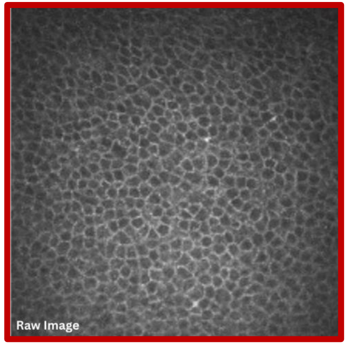
D = 1.257, n = 547 cells



Cellpose

D = 1.127, n = 534 cells





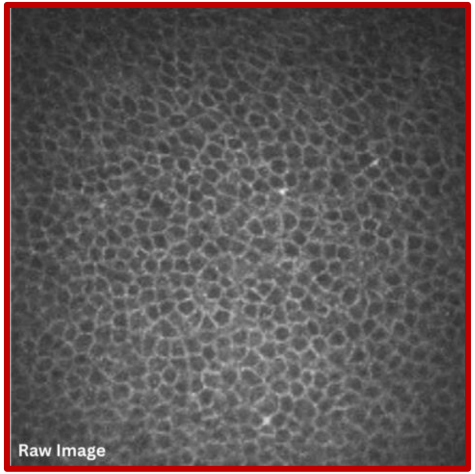
Accessibility note: this slide's GIF alternates between light and dark frames and may be distracting.

Future Work

1. **Quantify Algorithm Sensitivity (ongoing)**
   - Same-frame comparisons are now in place (Raw vs MATLAB vs Cellpose).
   - Next: run this systematically across patients/regions/timepoints and report ΔD, uncertainty, and stability.

2. **Test Clinical Sensitivity (next phase)**
   - Link D to health and recovery after LSCT across the 36-month follow-up.
   - Ask whether D can act as a practical biomarker of epithelial recovery.

3. **Principle:** Keep one baseline method (bespoke MATLAB watershed) for primary reporting and treat alternatives as sensitivity analyses.



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CONCLUSIONS

Fractal Nature of Corneal Epithelium

- **Beyond Averages:** Mean area and density alone do not capture junction complexity.
- **Scale-Invariant Descriptor:** Perimeter-area analysis supports fractal behaviour of epithelial boundaries.
- **Baseline Finding:** Mean $D = 1.246 \pm 0.011$ across n=1,114 images, with stable behaviour across region/depth checks.
- **Key Caveat:** D depends on segmentation method; interpretation must be method-specific.
- **Clinical Direction:** D is a promising quantitative candidate biomarker for epithelial recovery after LSCT.
- Fractal dimensions appear across nature and biology; corneal epithelium fits into this continuum.

D=1.35

D=1.63

D=1.3

D=1.24

Thank You!

Questions & Discussion

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Supervisors: Francisco Figueiredo, Majlinda Lako, Anvar Shukurov, Laura Wadkin

INTRODUCTION

- **LIMBAL STEM CELL DEFICIENCY (LSCD)**
  - **Etiology**: Loss of LSCs (e.g., via chemical burns) compromises the limbal barrier.
  - **Conjunctivalization**: Opaque conjunctival epithelial cells migrate into the cornea, causing chronic inflammation, scarring, and severe vision loss.
  - **Gold-Standard Treatment**: Cultivated autologous limbal epithelial transplantation (auto-CLET) for unilateral LSCD.
  - **Mechanism**: Ex-vivo expanded LSCs from the patient's healthy contralateral eye are transplanted following a superficial keratectomy to clear scarred tissue.