ARIES: Alconfocal Rapid Image Evaluation System of Corneal Microstructure

#1748

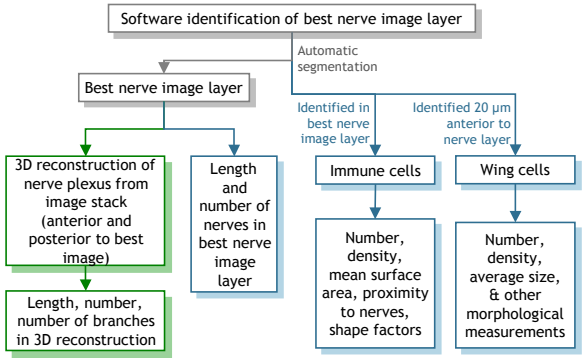
Christine W. Sindt, OD, FAAO; Ophthalmology, University of Iowa, Iowa City, IA — Bruno Lay, PhD; ADCIS, Herouville Saint-Clair, France
Jami R. Kern, PhD; Global Medical Affairs, Alcon Research Ltd, Fort Worth, TX

BACKGROUND AND PURPOSE

In vivo confocal microscopy has been used clinically to characterize various parameters of corneal health and disease.[1] However, the images contain a massive amount of data that is difficult to analyze and interpret consistently and quickly. This project was designed to develop robust and rapid image processing techniques to objectively evaluate confocal microscopy images to quantify corneal changes.

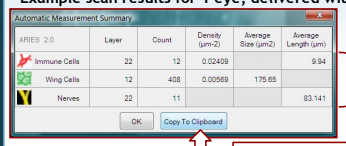
METHODS

- **Confocal Microscope**
  - Heidelberg Retina Tomograph Rostock Cornea Module (HRT/RCM; Heidelberg Engineering GmbH)
  - Light source = 670 nm diode laser (Class 1) with 1 m resolution
  - Area of each captured image = 400 m by 400 m
  - Digital image size = 384 by 384 pixels
  - Each volume scan = 40 images through 80 m depth in 2- m increments
- **Subjects: From an image database of healthy subjects who had consented to HRT scans, the investigators selected**
  - 10 representative central corneal scans to develop ARIES, and
  - an additional >390 scans were used for software validation.
- **Software Development**
  - ARIES 2D (blue and gray boxes below) was designed to automatically identify, quantify, and characterize wing cells, dendritic immune cells, and the nerves in the single best nerve image layer
  - ARIES 3D (green and gray boxes below) was designed to reconstruct and analyze nerves in 3D



RESULTS: 2D MEASUREMENT SUMMARY

Example scan results for 1 eye, delivered within 15 seconds:



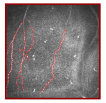
The user can accept the initial results, or can enter into post-processing modes, refine the recognition parameters, and then repeat the measurement summary

Summary can be exported for analysis (eg, averaging results from multiple subjects)

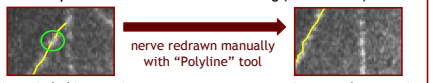
RESULTS: 2D ANALYSIS OF BEST NERVE IMAGE

- The software automatically detects the best nerve image layer and calculates the length and number of nerves and branches
- If the nerve detection is not optimal, the user can enter "nerve post-processing mode" and use the tools to delete undesired objects, add new objects, and fill in gaps in nerves

Representative Best Nerve Image Layer (red outlines show nerves detected by software)

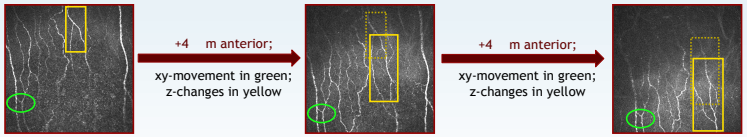


Representative Nerve Post-Processing (Detail/Zoom)



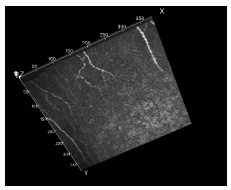
RESULTS: 3D NERVE REGISTRATION AND RECONSTRUCTION

- Between depth layers, nerve features can change (real changes in z-direction) while eye movements can complicate tracking (artifactual changes in x-direction and y-direction):

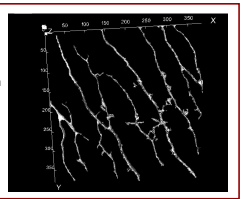


- The software was capable of recognizing the best nerve image layer, then registering features through images anterior and posterior(within 4 seconds); user can change registration manually if desired
- The software was capable of building images into a stack in the 3D space in less than1 second
  - Default mode builds a stack from best nerve image layer, plus 5 images anterior and 5 images posterior to that layer; users can manually add more images to the stack if desired
  - Stack can be freely rotated in the 3D space, as shown in the "composite mode" image below
  - Other display modes include "isosurface mode" (shown below) and "slice mode" (not shown); both modes are freely rotatable in the 3D space

3D Stack Reconstruction in Composite Mode



3D Nerve Reconstruction in Isosurface Mode

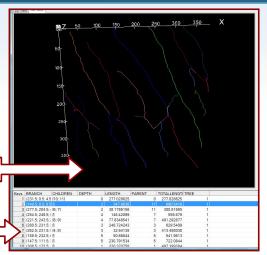


- Video of rotation in composite mode or isosurface mode can be exported as .avi file, which can be imported into presentations

RESULTS: 3D NERVE MORPHOMETRY

After reconstructing the nerves, the ARIES 3D software in "3D skeletonization mode" (see right) was capable of:

- segmenting the nerves by processing voxels,
- identifying and quantifying the number of branches and parents in the nerve structure,
- quantifying the lengths of branches, parents, and total nerves
- calculating the tortuosity of each branch

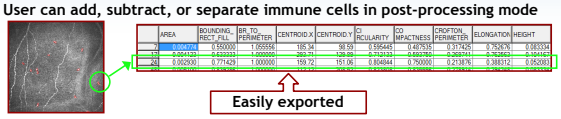


Each branch is displayed in a different color

These morphometric data can be easily exported for statistical analysis

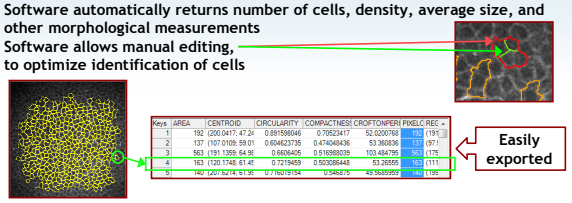
RESULTS: 2D IMMUNE CELL ANALYSIS

- Software automatically analyzes number of cells, density, mean surface area, proximity to nerves, and shape factors
- User can add, subtract, or separate immune cells in post-processing mode



RESULTS: 2D WING CELL ANALYSIS

- Software automatically returns number of cells, density, average size, and other morphological measurements
- Software allows manual editing, to optimize identification of cells



RESULTS: ATTRIBUTE HISTOGRAMS

Within the software, an attribute of all cells or all nerves in one image (such as circularity, shown here) can be plotted as a histogram:

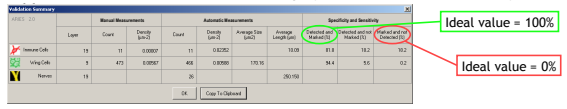
RESULTS: VALIDATION MODE

- The validation mode allows the user to manually annotate an image, and then compare manual and automatic counts:

Wing Cells: Automatic detection (green outlines) versus manual annotation (violet centers)

Immune Cells: Automatic detection (red outlines) versus manual annotation (blue centers)

- Manual versus automatic results are displayed in a validation summary



DISCUSSION

The software will facilitate the analysis of phenomena such as

- Immune cell response in the corneas of contact lens wearers versus nonwearers,[2] of contact lens wearers using different types of lens care solutions,[3] and of patients with keratitis or infectious disease[1]
- Wing cell changes in the corneas of patients with bullous keratopathy,[4] of patients treated with eye drops that contain preservatives,[5] and of patients with progressive epithelial corneal dystrophies[1]
- Corneal nerve changes in patients after corneal refractive surgery[6] or in patients with dry eye syndrome[7]

1. Niederer RL, McGhee CNJ. Prog Retin Eye Res 2010;29:30-58. 2. Zhivov A, et al. Cornea 2007;26:47-54. 3. Sindt C, et al. J Am Optom Assoc. 2009:80;287. 4. Glasgow BJ, et al. Invest Ophthalmol Vis Sci 2009;50:4060-4064. 5. Edman P. Biopharmaceutics of ocular drug delivery. Informa Healthcare; 1993. 6. Bohnke M, et al. Br J Ophthalmol 1998;82:1393-400. 7. Benitez Del Castillo JM, et al. Invest Ophthalmol Vis Sci 2004;45:3891.

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