

Introduction

Emerging imaging developments in experimental vision sciences and ophthalmology

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Keywords: Biomedical, biophotonics, eye, imaging, ophthalmology, visual science

Experimental Biology and Medicine 2021; 246: 2137–2139. DOI: 10.1177/15353702211038891

With delicate anterior and posterior structures, the eye works as a robust optical imager to capture visual information, which is essential for sensing the beauty of the world and effective communication. The anterior segment of the eye, particularly the cornea and the crystalline lens, functions as an optical lens to project the target image into the fundus.¹ Located at the posterior of the eye, the retina is a complex neural network responsible for capturing light photons, converting light energy to bioelectronic activities, and initiating the visual information processing.² Because different diseases can target different parts of the eye, clinical examination of both anterior and posterior segments is important for eye disease detection and treatment assessment. As one part of the central nerve system (CNS), retinal neurovascular system is also frequently affected by neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD).³ In order to provide intuitive information for identifying ocular pathologies or neurodegenerations through the eye, different imaging approaches have been established for ophthalmic examination. Developments of quantitative imaging are also important for advancing the study of the nature of visual system.

Optical imaging methods, such as slit lamp biomicroscopy^{4–6} and fundus photography,^{7,8} have played an indispensable role for the eye examination. In traditional fundus cameras, a white light source is typically used for color fundus imaging. It is known that the short wavelength, such as blue or green, light is predominantly sensitive to the retinal morphology, while long wavelength, such as red and near infrared (NIR), light provides enhanced penetration through the retina to reveal choroidal structure. Therefore, multiple-spectral imaging can be used to selectively evaluate the retinal and choroidal layers.^{9–12} With the confocal configuration to reject out-of-focus light, scanning laser ophthalmoscopy (SLO) provides a feasible strategy to enhance the resolution and contrast of chorioretinal

imaging.^{13,14} Adaptive optics (AO) can be incorporated to compensate for optical aberrations of the eye to further enhance the fundus image resolution and contrast.^{15–17} Super-resolution ophthalmoscopy has been recently explored through virtually structured detection^{18,19} and optically reassigned SLO.²⁰ By coherent gating of the light from different depths, optical coherence tomography (OCT) enables three-dimensional (3D) imaging of ocular structures at micrometer level resolution.^{21,22} While most of the ophthalmic imaging modalities are based on the recording of backward scattered light from the ocular tissues, photoacoustic imaging has been demonstrated to map absorption properties of the anterior²³ and posterior^{24,25} segments of animal eyes. Moreover, ultrasound biomicroscopy have been also developed for evaluating the anterior^{26,27} and posterior^{28–30} segments.

In addition to morphological imaging assessment, there are active efforts to expand the imaging capabilities for functional assessment of physiological condition of the eye. For example, as a special OCT modality, OCT angiography (OCTA) can provide high-contrast imaging of the vasculatures with active blood flow at capillary-level resolution.^{31,32} In coordination with visible stimulation, functional OCT has been demonstrated for objective optoretinography of stimulus evoked intrinsic optical signal changes in animal^{33,34} and human^{35–37} retinas. Functional OCT has been also validated for depth-resolved rhodopsin molecular contrast imaging in retinal photoreceptors.³⁸ OCT^{39,40} and ultrasound^{41,42} elastography have been explored for imaging biomechanical property of ocular tissues.

Moreover, quantitative feature analysis and disease classification are being explored on fundus photos, OCT, and OCTA using computer-aided methods.^{43–46} Recently, extensive efforts have been made on implementing artificial

intelligence (AI) tools to improve analytical reliabilities, with machine learning and deep learning algorithms.^{47–50}

Four mini-reviews in this thematic issue focus on newly emerging developments of imaging technology and data analysis in experimental vision sciences and ophthalmology. Yao *et al.* summarize the interpretations of anatomic correlates of outer retinal bands in OCT and discusses potential differences of clinical OCT and AO-OCT.⁵¹ Berkowitz *et al.* spotlight one OCT biomarker, i.e. subretinal space change due to light-dark transition imaging, for monitoring mitochondrial respiration of rod photoreceptors.⁵² Hollak *et al.* emphasize the AI-aided OCT biomarkers in monitoring the progression of age-related macular degeneration.⁵³ Le *et al.* summarize the latest progresses in quantitative OCT angiography assisted by machine learning methods.⁵⁴

Eight original research articles in this thematic issue cover ultrasound-related and optical imaging-based experimental study and/or data analysis. Liu *et al.* report an ultrasound elastography study of corneal stromal deformation.⁵⁵ Gaffney *et al.* demonstrate AO-SLO to investigate cone photoreceptor reflectance variation in the northern tree shrew and 13-lined ground squirrel.⁵⁶ Ansari *et al.* illustrate polarized infrared retinal imaging of pathognomonic macular ripples in patients with foveal hypoplasia.⁵⁷ Jiao *et al.* highlight a comparative study of OCT angiography algorithms for rodent retinal imaging.⁵⁸ Tan *et al.* describe the potential effectiveness of using OCT for eye disease screening compared to clinical examination.⁵⁹ Zhou *et al.* validated 3D OCT segmentation and visualization of choroidal anatomy including topographical features of individual vessels.⁶⁰ Liu *et al.* performed normative perfusion measurements in the temporal retina using wide-field OCT angiography.⁶¹ Wang *et al.* developed a multiple subdivision-based algorithm for quantitative assessment of retinal vascular tortuosity in fundus photography.⁶²

In summary, this thematic issue provides a small snapshot of the various emerging imaging modalities in experimental vision and eye research as well as to encourage future submissions to *Experimental Biology and Medicine* that incorporate ophthalmic imaging approaches and experimental results into their articles.




DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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REFERENCES

1. Artal P. Optics of the eye and its impact in vision: a tutorial. *Adv Opt Photon* 2014;**6**:340–67
2. Masland RH. Processing and encoding of visual information in the retina. *Curr Opin Neurobiol* 1996;**6**:467–74
3. Cheung CY, Ikram MK, Chen C, Wong TY. Imaging retina to study dementia and stroke. *Progr Retinal Eye Res* 2017;**57**:89–107
4. Coakes RL. Slit-lamp fluorophotometry of the anterior segment. *Trans Ophthalmol Soc U K* 1981;**101**:149–51
5. Kercheval DB, Terry JE. Essentials of slit lamp biomicroscopy. *J Am Optom Assoc* 1977;**48**:1383–9
6. Schneider HL. Measuring the depth of the anterior chamber with the slit lamp. *Klin Monbl Augenheilkd Augenarztl Fortbild* 1951;**119**:192–3
7. Orr HC. Fundus photography in colour. *Proc R Soc Med* 1948;**41**:721
8. Rosen E. Fluorescein fundus photography. *Manch Med Gaz* 1968;**47**:22–40
9. Delori FC, Gragoudas ES, Francisco R, Pruett RC. Monochromatic ophthalmoscopy and fundus photography. The normal fundus. *Arch Ophthalmol* 1977;**95**:861–8
10. Zimmer C, Kahn D, Clayton R, Dugel P, Freund K. Innovation in diagnostic retinal imaging: multispectral imaging. *Retina Today* 2014;**9**:94–9
11. Everdell NL, Styles IB, Calcagni A, Gibson J, Hebden J, Claridge E. Multispectral imaging of the ocular fundus using light emitting diode illumination. *Rev Sci Instrum* 2010;**81**:093706
12. Toslak D, Son T, Erol MK, Kim H, Kim TH, Chan RVP, Yao X. Portable ultra-widefield fundus camera for multispectral imaging of the retina and choroid. *Biomed Opt Express* 2020;**11**:6281–92
13. Webb RH, Hughes GW. Scanning laser ophthalmoscope. *IEEE Trans Biomed Eng* 1981;**28**:488–92
14. Terasaki H, Sonoda S, Tomita M, Sakamoto T. Recent advances and clinical application of color scanning laser ophthalmoscope. *J Clin Med* 2021;**10**: 718
15. Roorda A, Romero-Borja F, Donnelly W III, Queener H, Hebert T, Campbell M. Adaptive optics scanning laser ophthalmoscopy. *Opt Express* 2002;**10**:405–12
16. Merino D, Loza-Alvarez P. Adaptive optics scanning laser ophthalmoscope imaging: technology update. *Clin Ophthalmol* 2016;**10**:743–55
17. Liang J, Williams DR, Miller DT. Supernormal vision and high-resolution retinal imaging through adaptive optics. *J Opt Soc Am A Opt Image Sci Vis* 1997;**14**:2884–92
18. Yao X, Lu R, Wang B, Lu Y, Kim TH. Super-resolution ophthalmoscopy: virtually structured detection for resolution improvement in retinal imaging. *Exp Biol Med (Maywood)* 2021;**246**:249–59
19. Lu Y, Son T, Kim TH, Le D, Yao X. Virtually structured detection enables super-resolution ophthalmoscopy of rod and cone photoreceptors in human retina. *Quant Imaging Med Surg* 2021;**11**:1060–9
20. DuBose TB, LaRocca F, Farsiu S, Izatt JA. Super-resolution retinal imaging using optically reassigned scanning laser ophthalmoscopy. *Nat Photonics* 2019;**13**:257–62
21. Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA. Optical coherence tomography. *Science* 1991;**254**:1178–81
22. Minakaran N, de Carvalho ER, Petzold A, Wong SH. Optical coherence tomography (OCT) in neuro-ophthalmology. *Eye (Lond)* 2021;**35**:17–32
23. Zhao H, Wang G, Lin R, Gong X, Song L, Li T, Wang W, Zhang K, Qian X, Zhang H, Li L, Liu Z, Liu C. Three-dimensional hessian matrix-based quantitative vascular imaging of rat iris with optical-resolution photoacoustic microscopy in vivo. *J Biomed Opt* 2018;**23**:1–11
24. Zhang X, Zhang HF, Puliafito CA, Jiao S. Simultaneous in vivo imaging of melanin and lipofuscin in the retina with photoacoustic ophthalmoscopy and autofluorescence imaging. *J Biomed Opt* 2011;**16**:080504
25. Liu X, Liu T, Wen R, Li Y, Puliafito CA, Zhang HF, Jiao S. Optical coherence photoacoustic microscopy for in vivo multimodal retinal imaging. *Opt Lett* 2015;**40**:1370–3

26. Liebmann JM, Ritch R. Ultrasound biomicroscopy of the anterior segment. *J Am Optom Assoc* 1996;**67**:469–79
27. Pavlin CJ, Harasiewicz K, Sherar MD, Foster FS. Clinical use of ultrasound biomicroscopy. *Ophthalmology* 1991;**98**:287–95
28. Arzabe CW, Akiba J, Jalkh AE, Quiroz MA, Trempe CL, McMeel JW, Celorio JM. Comparative study of vitreoretinal relationships using biomicroscopy and ultrasound. *Graefes Arch Clin Exp Ophthalmol* 1991;**29**:66–8
29. Gentile RC, Berinstein DM, Liebmann J, Rosen R, Stegman Z, Tello C, Walsh JB, Ritch R. High-resolution ultrasound biomicroscopy of the pars plana and peripheral retina. *Ophthalmology* 1998;**105**:478–84
30. Vasquez LM, Giuliani GP, Halliday W, Pavlin CJ, Gallie BL, Heon E. Ultrasound biomicroscopy in the management of retinoblastoma. *Eye (Lond)* 2011;**25**:141–7
31. Chen CL, Wang RK. Optical coherence tomography based angiography [invited]. *Biomed Opt Express* 2017;**8**:1056–82
32. Gao SS, Jia Y, Zhang M, Su JP, Liu G, Hwang TS, Bailey ST, Huang D. Optical coherence tomography angiography. *Invest Ophthalmol Vis Sci* 2016;**57**:OCT27–36
33. Yao X, Son T, Kim TH, Lu Y. Functional optical coherence tomography of retinal photoreceptors. *Exp Biol Med (Maywood)* 2018;**243**:1256–64
34. Ma G, Son T, Kim TH, Yao X. In vivo optoretinography of phototransduction activation and energy metabolism in retinal photoreceptors. *J Biophotonics* 2021;**14**:e202000462
35. Ma G, Son T, Kim T-H, Yao X. Functional optoretinography: concurrent OCT monitoring of intrinsic signal amplitude and phase dynamics in human photoreceptors. *Biomed Opt Exp* 2021;**12**:2661–9
36. Cooper RF, Brainard DH, Morgan JIW. Optoretinography of individual human cone photoreceptors. *Opt Express* 2020;**28**:39326–39
37. Azimipour M, Valente D, Vienola KV, Werner JS, Zawadzki RJ, Jonnal RS. Optoretinogram: optical measurement of human cone and rod photoreceptor responses to light. *Opt Lett* 2020;**45**:4658–61
38. Liu T, Wen R, Lam BL, Puliafito CA, Jiao S. Depth-resolved rhodopsin molecular contrast imaging for functional assessment of photoreceptors. *Sci Rep* 2015;**5**:13992
39. Wang S, Larin KV. Shear wave imaging optical coherence tomography (SWI-OCT) for ocular tissue biomechanics. *Opt Lett* 2014;**39**:41–4
40. Pitre JJ Jr, Kirby MA, Li DS, Shen TT, Wang RK, O'Donnell M, Pelivanov I. Nearly-incompressible transverse isotropy (NITI) of cornea elasticity: model and experiments with acoustic micro-tapping OCE. *Sci Rep* 2020;**10**:12983
41. Zhao L, Lin H, Hu Y, Chen X, Chen S, Zhang X. Corneal lamb wave imaging for quantitative assessment of collagen cross-linking treatment based on comb-push ultrasound shear elastography. *Ultrasonics* 2021;**116**:106478
42. Pavlatos E, Chen H, Clayson K, Pan X, Liu J. Imaging corneal biomechanical responses to ocular pulse using High-Frequency ultrasound. *IEEE Trans Med Imaging* 2018;**37**:663–70
43. Du J, Zou B, Chen C, Xu Z, Liu Q. Automatic microaneurysm detection in fundus image based on local cross-section transformation and multi-feature fusion. *Comput Methods Programs Biomed* 2020;**196**:105687
44. Alam M, Le D, Lim JI, Yao X. Vascular complexity analysis in optical coherence tomography angiography of diabetic retinopathy. *Retina* 2021;**41**:538–45
45. Yao X, Alam MN, Le D, Toslak D. Quantitative optical coherence tomography angiography: a review. *Exp Biol Med (Maywood)* 2020;**245**:301–12
46. Hwang TS, Hagag AM, Wang J, Zhang M, Smith A, Wilson DJ, Huang D, Jia Y. Automated quantification of nonperfusion areas in 3 vascular plexuses with optical coherence tomography angiography in eyes of patients with diabetes. *JAMA Ophthalmol* 2018;**136**:929–36
47. Wang Z, Camino A, Hagag AM, Wang J, Weleber RG, Yang P, Pennesi ME, Huang D, Li D, Jia Y. Automated detection of preserved photoreceptor on optical coherence tomography in choroideremia based on machine learning. *J Biophotonics* 2018;**11**:e201700313
48. Le D, Alam M, Yao CK, Lim JI, Hsieh YT, Chan RVP, Toslak D, Yao X. Transfer learning for automated OCTA detection of diabetic retinopathy. *Transl Vis Sci Technol* 2020;**9**:35
49. Shin J, Kim S, Kim J, Park K. Visual field inference from optical coherence tomography using deep learning algorithms: a comparison between devices. *Trans Vis Sci Tech* 2021;**10**:4
50. Hormel TT, Hwang TS, Bailey ST, Wilson DJ, Huang D, Jia Y. Artificial intelligence in OCT angiography. *Prog Retin Eye Res* 2021;100965. DOI: 10.1016/j.preteyeres.2021.100965
51. Yao X, Son T, Kim TH, Le D. Interpretation of anatomic correlates of outer retinal bands in optical coherence tomography. *Exp Biol Med (Maywood)* 2021;15353702211022674. DOI: 10.1177/15353702211022674
52. Berkowitz BA, Qian H. OCT imaging of rod mitochondrial respiration in vivo. *Exp Biol Med (Maywood)* 2021;15353702211013799. DOI: 10.1177/15353702211013799
53. Romond K, Alam M, Kravets S, Sisternes LD, Leng T, Lim JI, Rubin D, Hallak JA. Imaging and artificial intelligence for progression of age-related macular degeneration. *Exp Biol Med (Maywood)* 2021;
54. Le D, Son T, Yao X. Machine learning in optical coherence tomography angiography. *Exp Biol Med (Maywood)* 2021;15353702211026581. DOI: 10.1177/15353702211026581
55. Kwok S, Hazen N, Clayson K, Pan X, Liu J. Regional variation of corneal stromal deformation measured by high-frequency ultrasound elastography. *Exp Biol Med (Maywood)* 2021. DOI: 10.1177/15353702211029283
56. Gaffney M, Cooper RF, Cava JA, Follett HM, Salmon AE, Freling S, Yu CT, Merriman DK, Carroll J. Cone photoreceptor reflectance variation in the Northern tree shrew and thirteen-lined ground squirrel. *Exp Biol Med (Maywood)* 2021. DOI: 10.1177/15353702211029582
57. Ansari D, Borkar PP, Davis PL, Collision FT, Wynne N, Zangler N, Fishman GA, Carroll J, Yao X, Grassi MA. Pathognomonic macular ripples are revealed by polarized infrared retinal imaging. *Exp Biol Med (Maywood)* 2021;15353702211021089. DOI: 10.1177/15353702211021089
58. Dadkhah A, Paudel D, Jiao S. Comparative study of optical coherence tomography angiography algorithms for rodent retinal imaging. *Exp Biol Med (Maywood)* 2021;15353702211024572. DOI: 10.1177/15353702211024572
59. Tan O, Chen A, Li Y, Bailey S, Hwang TS, Lauer AK, Chiang MF, Huang D. Prospective evaluation of OCT for disease detection in the Casey mobile eye clinic. *Exp Biol Med (Maywood)* 2021;
60. Zhou H, Bacci T, Freund KB, Wang RK. Three-dimensional segmentation and depth-encoded visualization of choroidal vasculature using swept-source optical coherence tomography. *Exp Biol Med (Maywood)* 2021;15353702211028540. DOI: 10.1177/15353702211028540
61. Liu K, Guo Y, You Q, Hormel T, Hwang TS, Jia Y. Normative perfusion measurements in the temporal retina assessed by wide-field OCT angiography. *Exp Biol Med (Maywood)* 2021;
62. Wang G, Li M, Yun Z, Duan Z, Ma K, Luo Z, Xiao P, Yuan J. A novel multiple subdivision-based algorithm for quantitative assessment of retinal vascular tortuosity. *Exp Biol Med (Maywood)* 2021. DOI: 10.1177/15353702211032898