Review Article

Adaptive Optics in Ophthalmology

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Abstract

Backgraound: Adaptive Optics (AO) has emerged as a powerful imaging tool in ophthalmology, enabling high-resolution visualization of retinal structures in vivo. This technology, initially inspired by astronomy, has opened new avenues for diagnosis, monitoring, and treatment of various eye diseases. This paper aims to provide a comprehensive overview of AO in ophthalmology, highlighting its principles, different types of AO systems, and their clinical applications.
Material and Methods: A thorough review of the literature was conducted to gather information on the principles, components, and advancements in AO technology. Clinical studies and research articles involving the use of AO in ophthalmology were analyzed to identify its diverse applications.
Results: AO utilizes wavefront sensing and correction techniques to compensate for aberrations in the eye, enabling detailed imaging of the retina at a cellular level. Different AO modalities, including AO scanning laser ophthalmoscopy (AO-SLO) and AO optical coherence tomography (AO-OCT), offer unique capabilities in visualizing cellular structures, tracking disease progression, and evaluating treatment efficacy. Clinical applications of AO span a wide range of eye diseases, including age-related macular degeneration, diabetic retinopathy, glaucoma, and inherited retinal dystrophies.
Conclusions: AO has significantly contributed to our understanding of retinal diseases by providing unprecedented insights into cellular-level changes. It holds immense potential for advancing clinical management, personalized treatment strategies, and improving patient outcomes. Further advancements in AO technology, standardization of imaging protocols, and larger-scale clinical studies are crucial for its widespread adoption in routine clinical practice.

Keywords: Optics; Adaptive Optics; OCT; AO-OCT.

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Introduction

Adaptive optics (AO) is a technology initially developed by astronomers that revolutionizes the field of visual imaging and finds applications beyond astronomy. The main motivation for the development of AO in astronomy is to overcome the blinding of the Earth's atmosphere (known as atmospheric turbulence), which severely limits the resolution of ground-based telescopes. By correcting atmospheric aberrations in real time, astronomers can obtain better images than observatories in space. AO's entry into astronomy can be attributed to the pioneering work of Babcock (1953) and Labeyrie (1970) who recognized its ability to correct atmospheric aberrations to achieve high quality images of celestial objects [1, 2].

Babcock (1953) demonstrated the concept of adaptive optics by using a wavefront sensor to measure atmospheric distortions in real-time. It has been suggested to use deformable glass to prevent these effects and to gain clarity in astronomical images [1]. On this basis, Labeyrie (1970) introduced the concept of speckle interferometry, which involves combining multiple short-exposure images to reconstruct a diffraction-limited image [2]. This pioneering work laid the foundation for the development and use of AO in astronomy [3].

In addition to having a major impact on astronomy, AO has also found applications in ophthalmology, where its principles are used to improve visual imaging and diagnostics. The ophthalmic AO field was developed from the principles established by astronomers, but focused on the human eye. AO has revolutionized the field of ophthalmology by accurately measuring and treating the more defining aspects of the eye, enabling early detection, accurate diagnosis and personalized treatment of many ocular diseases [4, 5].

By incorporating AO into ophthalmic instruments, clinicians can obtain precise measurements of higher-order aberrations in the eye, including spherical aberration, coma, trefoil, and other irregularities that affect the quality of vision [6]. We note that AO is a non-invasive retinal imaging procedure. With adaptive optics, detailed maps of the aberrations can be generated, allowing for a personalized approach to vision correction and treatment [6].

AO-based imaging techniques, such as AO fundus camera (AO-FC) [7], AO scanning laser ophthalmoscopy (AO-SLO) [8, 9] and AO optical coherence tomography (AO-OCT) [10, 11], have enabled clinicians and researchers to visualize microscopic features of the retina, track disease progression, and assess treatment efficacy [6].

Throughout this paper, we will delve into the principles of AO and its applications in ophthalmology. We will explore how adaptive optics has revolutionized visual imaging, contributed to early diagnosis, and paved the way for improved treatments in ophthalmic disorders. We then outline the clinical applications of AO, covering various ophthalmic conditions. These applications include diabetic retinopathy, age-related macular degeneration, glaucoma, and inherited retinal dystrophies. We also discuss future directions, such as larger clinical trials, standardized protocols, normative databases, and integration with other imaging modalities.

Necessity, Historical Evolution, and Principles of AO in Ophthalmologys

The introduction of adaptive optics in ophthalmology can be traced back to the pioneering work of Liang et al. (1994) who implemented adaptive optics for the first time in the measurement of wavefront aberrations in human eyes [7]. By using a Hartmann-Shack wavefront sensor a deformable mirror, Liang et al. (1994) were able to precisely measure the wavefront distortions caused by the eye's optics and identify the specific aberrations present. This marked the beginning of a new era in ophthalmic diagnostics and personalized vision correction.

In the year 2000, a significant advancement occurred in the field of ophthalmology with the first clinical application of AO for evaluating cone-rod dystrophy, a retinal disorder characterized by the degeneration of cone and rod cells [12].

The essential components of the human eye are the corena, the anterior chamber, the lens, the vitreous body. Among these structures, the retina as a vital layer located on the inner surface of the eye, characterized by its intricate architecture and sensitivity to light. The retina plays a crucial role in visual perception and signal transduction. In fact, visual imaging relies on the ability of the eye to accurately focus light onto the retina, where the formation of a clear and sharp image occurs.

However, every optical system, including the human eye, inherently encounters specific limitations that can be attributed to the fundamental properties of light. When light rays enter the human eye, they inevitably result in chromatic and monochromatic aberrations. These wavefront aberrations impose a limit on the resolution of human vision, typically around 10-15 micrometers. In contrast, the diffraction limit equation provides a theoretical resolution of approximately 2 micrometers [13].

Achieving high-resolution imaging necessitates the assessment of the reflected light from the fundus. In an ideal eye, the reflected light from the fundus experiences minimal distortion, resulting in a flat wavefront. However, aberrations present in a typical eye cause the reflected light from the fundus to produce a distorted wavefront. As a consequence, the resolution attainable with conventional fundus imaging techniques becomes limited. Adaptive optics represents an intriguing approach to overcome this limitation and obtain high-resolution images. To demonstrate the effectiveness of AO, Figure 1 presents two images, (a) and (b), showcasing a cross-sectional view of the foveal region and representing the first documented visualizations of cones[7]. Panel (a) illustrates the view without the utilization of AO, while panel (b) exhibits the same region captured with AO technology[7]. This comparison underscores the remarkable impact of AO in enhancing image quality and enabling the visualization of cones with greater detail and accuracy.

In both astronomy and ophthalmology, the primary goal of AO is to measure and correct wavefront distortions caused by the optics of the system, be it the Earth's atmosphere in astronomy or the eye's optics in ophthalmology. By using a wavefront sensor and a deformable mirror, AO systems in both fields can measure the wavefront aberrations and subsequently apply corrective adjustments to improve the quality of the acquired images.

While the principles and objectives of AO are similar, there are notable differences in the application of this technology between astronomy and ophthalmology. In astronomy, the adaptive optics system compensates for the distortions introduced by the Earth's atmosphere, enabling astronomers to obtain sharper and clearer images of celestial objects. The adaptive optics systems used in astronomy often require large-scale and complex setups, including high-powered lasers to create artificial guide stars for wavefront sensing and precise control of deformable mirrors to correct for atmospheric turbulence.

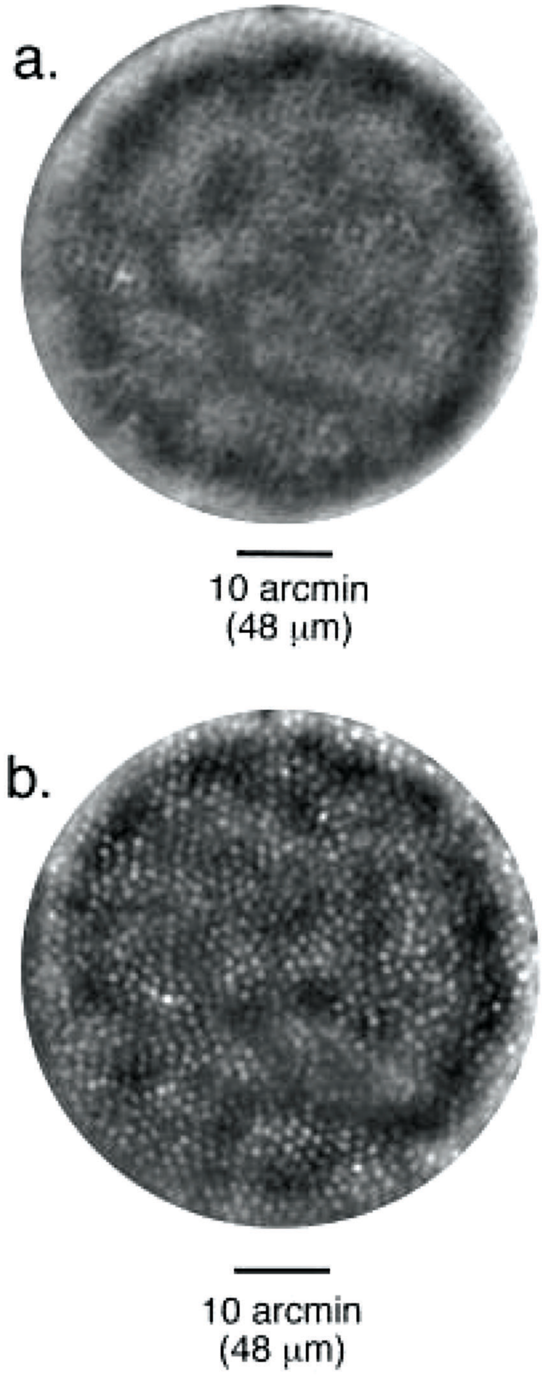

Figure 1: The presented images (a) and (b) exhibit a cross-sectional view of the foveal region, providing one of the earliest documented depictions of cones. Panel (a) displays the view without adaptive optics (AO), while panel (b) represents the same region captured with AO technology, highlighting its significance in enhancing image quality and visualizing cones with greater precision. *(Liang et al., 1997)*

On the other hand, in ophthalmology, adaptive optics is used to assess and correct the aberrations specific to each individual's eyes. AO imaging systems for the human eye are typically smaller in scale and designed to be non-invasive, making them suitable for clinical settings. They employ different wavefront sensing techniques, such as Hartmann-Shack or scanning laser ophthalmoscopy, to measure the aberrations in real-time and precisely correct them using deformable mirrors or other AO elements.

Here, we provide an overview of the fundamental principles underlying AO systems, with a focus on the core concepts. An AO system typically consists of two main components: a wavefront sensor and a wavefront corrector. The wavefront sensor records the ocular wave aberrations, while the wavefront corrector precisely controls and corrects these aberrations. The AO controller, typically a computer, interprets the wavefront sensor image and calculates the appropriate drive signals for the wavefront corrector. Most AO systems operate in a closed-loop configuration, where the sensor is strategically positioned to continuously assess the effectiveness of the wavefront correction.

Figure 2, adapted from Roorda 2011, depicts the process in which a properly contoured mirror generates a flat wavefront, which is subsequently recorded by the wavefront sensor[5]. The provided schematic encompasses both imaging and stimulus delivery aspects. Notably, a noteworthy feature of the system is its capability to use the same correction for light entering and emerging from the eye. The figure depicts how the beam entering the eye is intentionally pre-aberrated to precisely counterbalance the eye's aberrations, resulting in a pure spherical shape of the wavefront upon refraction.

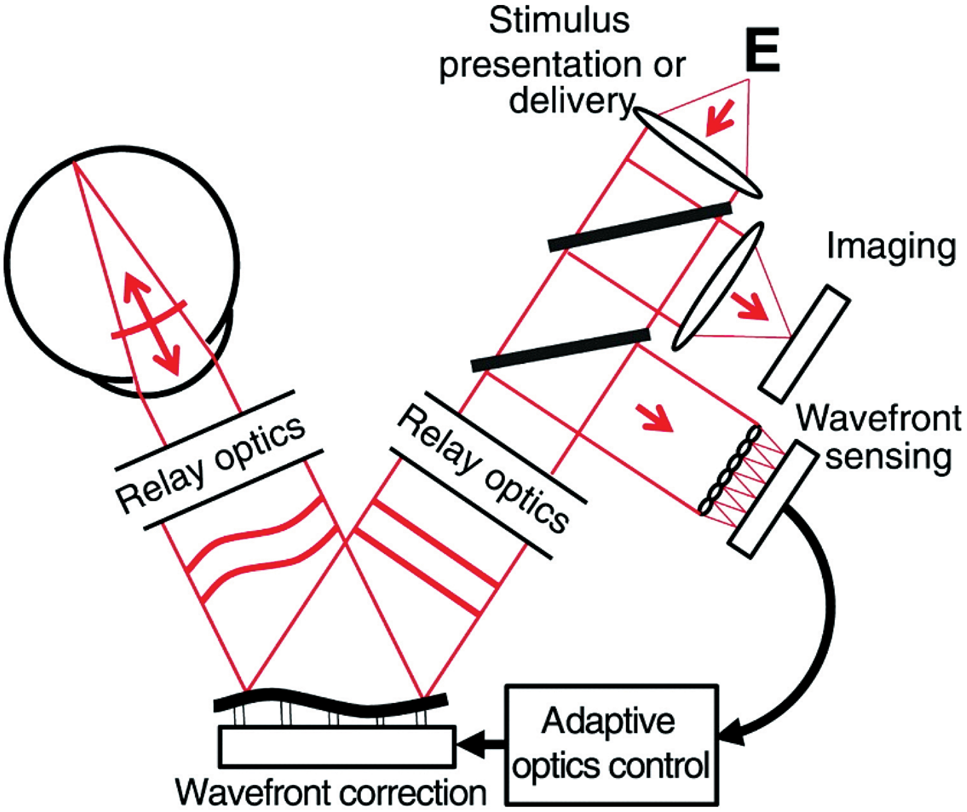

Figure 2: Basic Layout of an AO system for imaging and vision testing (Adopted from Roorda 2011 [5])

Varieties of AO Utilized in Ophthalmology

Following the initial implementation of AO in ophthalmology, researchers have explored various research and application directions to leverage the potential of this technology. One significant direction has been the development of advanced imaging techniques for high-resolution retinal imaging. As previously discussed, the primary objective of AO is to enhance imaging resolution to the level of individual cells or even subcellular structures. The versatility of AO allows for its integration with a wide range of ophthalmic imaging modalities, enabling substantial improvements in visualization and detail capture. The application of adaptive optics technology in ophthalmology has been realized through various imaging modalities, including adaptive optics flood illumination ophthalmoscopy (AO-FIO) [7], scanning laser ophthalmoscopy (AO-SLO) [14], and optical coherence tomography (AO-OCT) [10].

Adaptive Optics Flood Illumination Ophthalmoscopy

Merging adaptive optics with a fundus camera emerged as one of the initial strategies for employing AO in ophthalmology [7]. AO-FIO system provides a wide field of view and uniform illumination, ensuring comprehensive coverage and consistent lighting across the retinal surface. This approach offers a significant advantage in acquiring images within a relatively short timeframe, mitigating the potential impact of eye movement. This capability ensures enhanced image stability and reduces the risk of motion artifacts, enabling clinicians and researchers to obtain high-quality, precise retinal images for accurate diagnosis and comprehensive assessment of ocular conditions. The application of AO-FIO system has been instrumental in the examination of parafoveal cone photoreceptors and retinal vasculature in both healthy individuals and individuals affected by various eye diseases [15, 16].

Adaptive optics Scanning Laser Ophthalmoscopy

The invention and development of AO-SLO can be attributed to Webb et al. in the 1980s, and it has since gained widespread recognition as an exceptional modality for clinical imaging due to its remarkable contrast and resolution capabilities [8, 9, 14]. Differing from AO-FIO systems, AO_SLO employs a focused single-spot light beam that systematically scans the retina in a raster pattern. In SLO imaging, the intensity of each pixel is meticulously captured utilizing highly sensitive detectors, such as photomultiplier tubes, enabling precise measurement of the light intensity at various points on the retina. Additionally, the spatial coordinates of each pixel are determined by analyzing the outputs generated by the scanning mirrors, facilitating accurate mapping of the retinal structures in the captured image [17, 18].

Figure 3 illustrates the key components and fundamental configuration of an AO-SLO system. This schematic diagram, adapted from Liu et al. (2022) [13], provides an overview of the system's setup and highlights its main elements. The light emitted by the laser source in the AO-SLO system is directed towards the eye. To project patterns onto the retina, an acousto-optic modulator is implemented to modulate the laser beam. After traversing through the confocal pinhole, the scattered light emanating from the retina is captured by a photomultiplier tube. The achievable resolution in imaging is influenced by various factors, including the size of the pupil and the wavelength utilized. Enhanced resolution can be attained by increasing the size of the pupil or reducing the wavelength.

Adaptive Optics Optical Coherence Tomography

Optical Coherence Tomography (OCT) is a non-invasive imaging technique that provides high-resolution cross-sectional images of biological tissues. The first demonstration of OCT as a non-invasive imaging tool for the retina took place in 1991 [19]. It utilizes low-coherence interferometry to measure the echo time delay and magnitude of backscattered light from the tissue. By analyzing the interference pattern between the reference and sample beams, OCT generates depth-resolved images with micrometer-scale resolution. This imaging modality has revolutionized ophthalmology, allowing for the visualization and assessment of retinal layers, as well as the diagnosis and monitoring of various ocular diseases.

Early attempts to incorporate AO correction into OCT imaging were documented by Zhang et al. [10] and Zawadzki et al. [11], highlighting the potential for significant improvements in lateral resolution and speckle reduction. These instruments demonstrated the capability to achieve high lateral and axial resolutions of up to 3 μm and 2~3 μm, respectively, within the eye. Such remarkable resolution enabled cellular-level measurements and detailed imaging of ocular structures.

Clinical Utilization of AO in Practice

AO has demonstrated significant potential in the clinical assessment and management of various eye diseases. In healthy eyes, AO helps

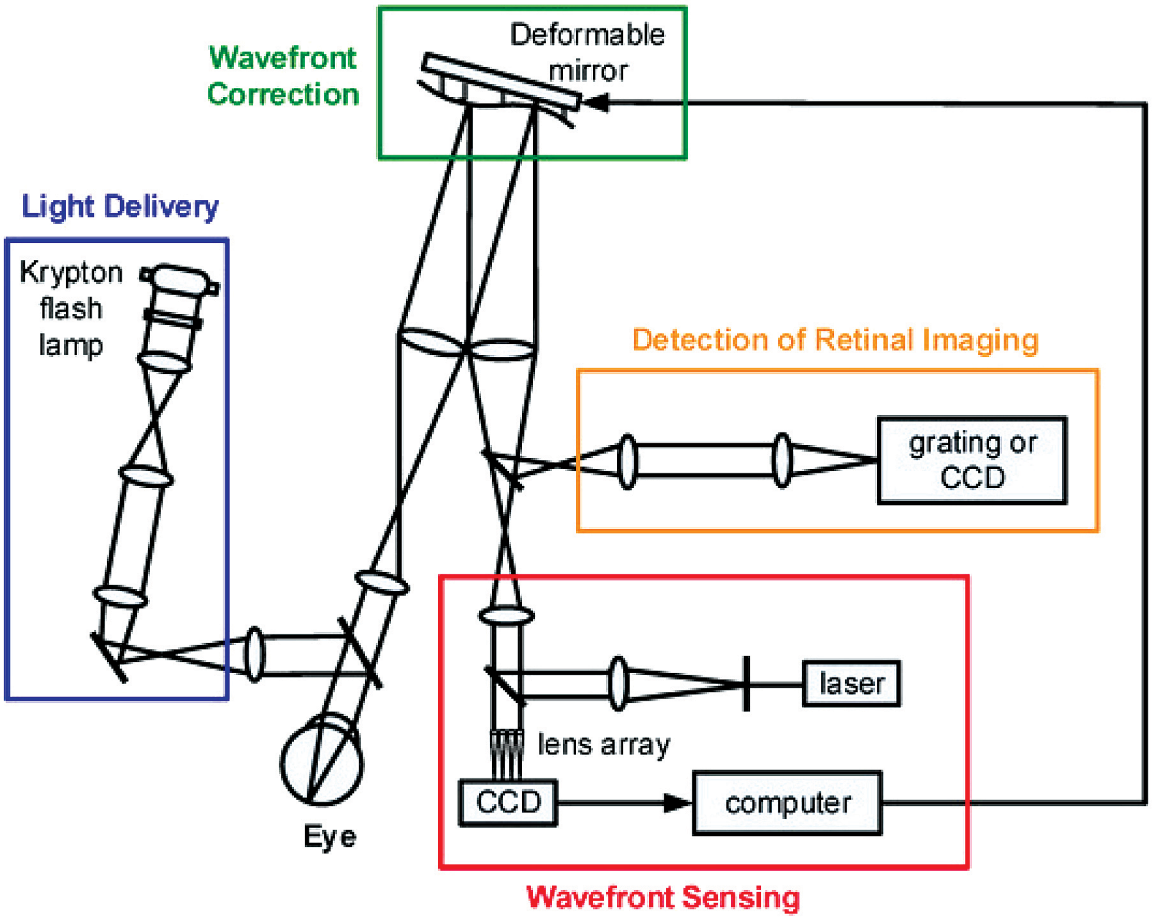

Figure 3: The diagram presented here depicts a simplified schematic of an AO-SLO optical system, which has been adopted from the work of Liu et al. (2022) [13]

establish normative databases and enables the identification of deviations from normal [16, 20]. In diabetic retinopathy, AO allows for the early detection of retinal changes, such as reduced cone density and alterations in blood vessels, providing valuable insights beyond conventional imaging techniques [21, 22]. AO has also been instrumental in assessing central serous chorioretinopathy, monitoring patients post-resolution, and revealing cone density changes and mosaic pattern abnormalities [23, 24]. Furthermore, AO aids in monitoring age-related macular degeneration, identifying early stages, and tracking disease progression [25, 26]. It has also proven valuable in studying inherited retinal dystrophies [27], glaucoma-related changes [28], and providing additional insights into various other eye diseases. Table 1 summarizes the clinical applications of AO in various eye diseases.

Prospective Developments in AO

Ongoing research and advancements in adaptive optics for ophthalmological applications continue to push the boundaries of this technology, aiming to further improve diagnosis, treatment, and patient outcomes. Researchers and scientists are actively exploring various areas to expand the capabilities and effectiveness of adaptive optics. Here are some key areas of ongoing research:

Table 1: Clinical applications of AO in eye diseases

Disease	Summary
Healthy eyes	AO analysis of healthy eyes helps in developing normative databases and assessing patients for deviations from normal.
Diabetic retinopathy	AO can identify early retinal changes in patients with diabetes, such as reduced cone density, alterations in blood vessels, and microaneurysms.
Central serous chorioretinopathy	AO can assess and monitor patients with resolved central serous chorioretinopathy, revealing cone density changes and mosaic pattern abnormalities.
Age-related macular degeneration	AO aids in monitoring retinal changes, such as drusen, pigmentations, and atrophy, and helps identify early stages and disease progression.
Inherited retinal dystrophies	AO provides valuable information about various types of inherited retinal dystrophies and their microscopic changes.
Glaucoma	AO studies have examined glaucoma-related changes in the lamina cribrosa and cone density, offering insights into the disease.

Image Processing and Analysis: Advanced image processing techniques are being developed to enhance the quality and interpretability of AO images. These techniques involve noise reduction, image reconstruction, and segmentation algorithms that improve the visualization and quantification of subtle retinal structures and abnormalities [29].

Wide Field of View Imaging: Traditional AO systems have a limited field of view, which restricts their applicability for imaging larger areas of the retina. Ongoing research focuses on expanding the field of view of AO systems to capture wide-area retinal images, enabling the examination of peripheral retina and facilitating the detection and management of peripheral retinal diseases [30].

Real-Time Imaging and Tracking: Real-time imaging and tracking systems are being developed to compensate for eye movements during image acquisition. By actively adjusting the deformable mirror in response to eye movements, AO can provide stable and high-resolution images in real-time, making it more practical for clinical applications.

Artificial Intelligence and Machine Learning: Integration of adaptive optics with artificial intelligence and machine learning techniques is being explored to automate image analysis, enhance diagnosis accuracy, and facilitate the development of predictive models for disease progression and treatment outcomes.

While facing technical challenges, the growing utilization of AO promises to revolutionize our understanding of retinal diseases and improve clinical outcomes. As the technology continues to evolve and becomes more accessible, AO is set to transform the landscape of ophthalmology, enabling more precise diagnostics, personalized treatments, and enhanced patient care.

Conclusions

Advancements in AO technology have greatly facilitated the precise measurement and correction of higher-order aberrations in visual imaging. AO systems, incorporating wavefront sensors and deformable mirrors, enable real-time monitoring and adjustment of the optical system to compensate for aberrations.

This review article provides a comprehensive overview of AO and its application in ophthalmology. Initially, the article explores the principles of AO, drawing inspiration from its origins in astronomy. The various types of AO systems are then discussed, highlighting their key components and operational mechanisms. Subsequently, the article delves into the extensive clinical applications of AO in the field of ophthalmology, shedding light on its role in disease diagnosis, monitoring, and treatment.

Looking ahead, the future of AO in ophthalmology appears bright. As technology continues to advance, we can expect further improvements in AO imaging systems, making them more compact, user-friendly, and cost-effective. This will facilitate broader integration of AO into routine clinical practice, allowing ophthalmologists to harness its potential for enhanced diagnostics and personalized management of eye conditions.

Additionally, ongoing research and collaborations are needed to expand the repertoire of AO applications in ocular diseases. Further investigations into the normative values and variations in AO parameters across different populations will be crucial for establishing standardized protocols and reference databases. Furthermore, longitudinal studies utilizing AO imaging can help unravel the natural history of retinal diseases, identify early biomarkers of progression, and assess the efficacy of novel therapies.

In conclusion, AO represents a transformative technology that has revolutionized our understanding of the retina and its associated pathologies. With its ability to visualize the intricate cellular architecture of the eye, AO has the potential to drive significant advancements in diagnosis, monitoring, and treatment of ocular diseases. As we continue to explore and refine the capabilities of AO, it is evident that this cutting-edge imaging modality will play a vital role in shaping the future of ophthalmology, leading to improved outcomes and better visual health for patients worldwide.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.