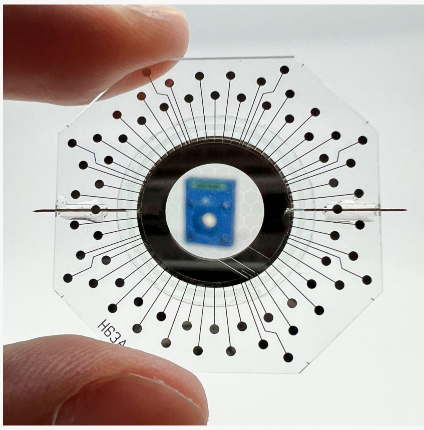
Refractive Adaptive Optics for Ophthalmoscopy

Phaseform develops refractive Adaptive Optics (AO) systems based on innovative hardware and software components. At the heart of our approach to AO is a novel optofluidic microsystem technology, Deformable Phase Plates (DPP). Their unique features combine the advantages of deformable mirrors and transmissive liquid crystal spatial light modulators in a compact form, thus paving the way for a new class of ultra-compact, high-efficiency, transmissive AO systems. In this white paper, we discuss how DPP technology can transform the burgeoning field of AO-ophthalmology.



The human visual system is a remarkable and complex system that has evolved to its current state over long periods of time. It is not only its intricate inner workings that make it fascinating, but also certain quirks that point to a seemingly incidental arrangement. One notable example is the structure of the retina, a multilayer at the posterior part of the eyeball that contains photoreceptor cells responsible for initiating nerve impulses that are propagated through interneurons to the optic nerve and finally to the brain, where they are further processed to form visual images. Interestingly, in order for light to reach the retina, it must first pass through several transparent layers of cells before reaching the photoreceptors. This arrangement provides us with a unique opportunity: Using advanced optical instruments, it is possible to look through the pupil and observe how these intricate structures work. Many diseases of the human visual system manifest themselves early on as subtle changes in these retinal layers. Because of its complexity, the eye is not only a window to the world, it can also be a window to our health.

Ophthalmoscopy is the technique of using high magnification optical imaging to visualize the retina, optic nerve, blood vessels, and macula. There are several advanced microscopy techniques adapted for ophthalmoscopy, each with its own advantages and disadvantages. Fundus photography (FP) [1] provides high-quality, single-frame retinal images at a high frame rate, but is limited in resolution and contrast. Scanning laser ophthalmoscopy (SLO) [2] improves resolution and contrast and provides some axial sectioning capability, but sacrifices imaging speed. Optical coherence tomography (OCT) [3] further improves axial sectioning and uniquely provides a cross-sectional view of the entire retina.

Unlike microscopy, where the optical performance, such as maximum resolution, is determined by the objective and the immersion medium, ophthalmoscopy is different. Here, the patient's eye itself defines the aperture size (e.g. the pupil) and the focal length (e.g. the lens). A fully dilated human pupil, about 7-8 mm in diameter, offers a theoretical resolution of about 2 µm at visible wavelengths, which would be sufficient to resolve cellular and even subcellular features such as cones and rods, retinal ganglion cells, and minute blood capillaries. However, the human eye, unlike a high-quality microscope objective, is not a "perfect" imaging device and is often subject to imperfections that cause optical aberrations. The effects of these aberrations increase as the pupil size increases. Beyond 2 mm, the image quality of an ophthalmoscope actually deteriorates with pupil dilation. As a result, traditional ophthalmoscopes struggle to resolve retinal features at the cellular level. This is a significant drawback because recent studies show that many major eye diseases such as, macular degeneration, diabetic retinopathy or glaucoma, can be detected at an early stage by observing microscopic changes in the retina. Thus, the "imperfect eye" limits the effectiveness of conventional ophthalmoscopic *in vivo* diagnostics.

Enter Adaptive Optics

Ocular aberrations are both patient-specific ("every human eye is different") as well as static or slow to change. Thus, nearly three decades ago, correction elements routinely used in astronomical telescopes to compensate for atmospheric turbulence were first implemented in ophthalmoscopy [6]. This groundbreaking "technology transfer" from one field to another signaled the beginning of a new era in ophthalmic research, giving researchers the ability to observe cellular and even subcellular structures of the retina *in vivo* for the first time. Since then, persistent research and development efforts have successfully integrated AO into virtually all types of ophthalmoscopes. This progress has provided answers to a wide range of scientific questions about the morphology and function of retinal structures, leading to the identification of definitive biomarkers for the early diagnosis of major eye diseases.

Conventional approach to AO Ophthalmoscopy

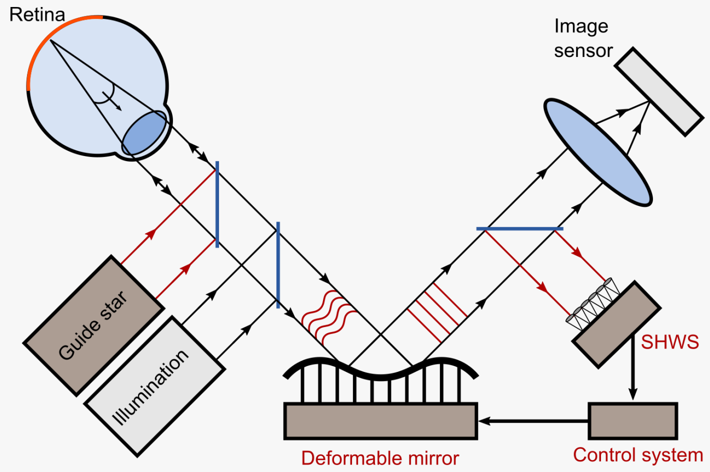


Figure 1: Conventional adaptive optics ophthalmoscope: Eye aberrations are measured with a wavefront sensor, which in closed-loop controls a deformable mirror placed at the conjugate plane of the pupil. This schematic omits the details of the varying illumination and detection optics, as these specifics can change significantly based on the microscopy method used by the instrument.

Figure 1 shows a simplified representation of a standard adaptive optics (AO) design for ophthalmology. To incorporate AO, the system must include a wavefront modulator, usually a *reflective* deformable mirror (DM), a Shack-Hartmann wavefront sensor (SHWS), and a laser guide star. The SHWS measures the distorted wavefront emanating from a known point on the retina created by the guide star laser. A control system then computes a series of drive signals from the measured distortion that instruct the DM to physically approximate the inverse of the wavefront error. Closed-loop operation allows the ideal correction for the best image quality to be identified after several iterations. Both the DM and the SHWS must be conjugated to the pupil plane of the eye, requiring additional relay and beam-folding optics. Such a setup requires numerous precisely aligned components, making the system very complex, large and costly. Due to this complexity, clinical adoption of AO has unfortunately been very slow, and AO ophthalmoscopes are often limited to large optical tables in research institutes and remain mostly out of reach for practical clinical use, with no way to easily retrofit existing clinical ophthalmoscopes.

Phaseform's *refractive* AO solutions offer a revolutionary way forward. These solutions aim not only to reduce the cost of new systems, but also to add AO capability to existing ophthalmoscope infrastructure, opening up unprecedented opportunities in ophthalmology.

Phaseform's Approach to AO Ophthalmoscopy

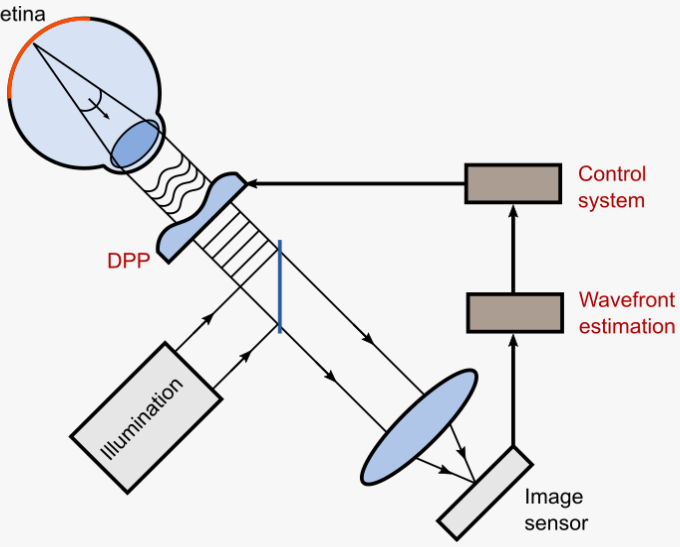


Figure 2: Phaseform's approach to AO ophthalmology. A Deformable Phase Plate (DPP) is placed in close proximity to the eye's pupil. This approach does not require relay or beam folding optics and the SHWS can be omitted by using a wavefront estimation technique.

Figure 2 illustrates Phaseform's approach to implementing AO correction in ophthalmoscopes, enabled by its unique Deformable Phase Plate (DPP) technology. DPPs are the transmissive counterparts to conventional continuous surface deformable mirrors. The clear aperture diameter of 10 mm covers the maximum human pupil diameter of 7-8 mm. As a result, it can be placed close to the pupil without the need for complex modification of existing elements and/or the addition of relay optics. This removes the complexity and space requirements of the beam folding of conventional AO ophthalmoscopy. The SHWS can also be eliminated by using wavefront estimation techniques that rely directly on the captured images. They algorithmically estimate the optimal set of control signals to be applied to the DPP to maximize the quality of the captured signals. One of the main requirements for the implementation of such sensorless wavefront estimation algorithms is the hysteresis-free and deterministic behavior of the adaptive element used, which is fulfilled by the characteristics of the DPP.

This approach allows a much more compact and easier integration of AO into ophthalmoscopes and even for the first time enables the possibility of retrofitting AO capability into existing ophthalmoscopes.

A CASE STUDY: Full-field OCT ophthalmoscope with *Truly Plug & Play* AO

In a recent landmark study, in collaboration with renowned vision scientists at the Institut Langevin, Quinze-Vingts National Ophthalmology Hospital, and Vision Institute (all in Paris), we retrofitted an existing research-grade ophthalmoscope with a DPP-enabled AO system. The specific system used in these experiments was a multimodal full-field OCT ophthalmoscope, which offers unprecedented imaging speed and field of view in retinal imaging [7,8]. It is a state-of-the-art instrument developed by expert optical engineers, but due to the inherent aberrations of the individual eye as discussed above, images acquired with this instrument without AO did not reach the quality that would be theoretically possible. For this reason, Dr. Pedro Mecê and his colleagues, Dr. Kate Grieve and Dr. Maxime Bertrand, were eager to add AO capability to their instrument. Since their goal was to build the most compact and cost-effective system possible, a conventional AO system based on deformable mirrors was out of the question. So they agreed to try Phaseform's refractive AO approach.

Figure 3: Retrofitting Phaseform's refractive AO system to an existing full-field OCT ophthalmoscope at the Institut Langevin. The only hardware change that was necessary for the AO upgrade was to introduce a DPP after the last lens in the system that is placed in front of the patient's eye (left). By feeding the instrument's image data into Phaseform's AO sensorless wavefront estimation algorithm, the integration was complete. The imaging workflow after AO integration remained mostly intact, the only exception being the aberration estimation step, which took about 3 seconds. The rest of the retinal image acquisition procedure proceeded as usual.

Figure 3 (left) shows how we upgraded the OCT ophthalmoscope at the Institut Langevin with Phaseform's DPP without any additional hardware changes to the original system. Following the scheme shown in Figure 2, all we had to do was insert our wavefront modulator between the imaging aperture and the patient's eye. Because its housing is compatible with standard optical laboratory equipment, this upgrade was literally completed in minutes. What took a few moments longer was the software integration to enable wavefront sensorless aberration measurement of the eye. For this, we used our implementation of a modal decomposition-based aberration estimation algorithm. Since our control routine is independent of the imaging modality used, it only needs the actual measurement signal feed from the native instrument, here the spectral domain OCT signal. As a result, such a procedure works in any case, and this step was completed in half a day. The workflow during the actual imaging session also remained largely intact, with the exception of the additional aberration estimation step that preceded the OCT image acquisition. Otherwise, the patient simply sat in front of the instrument as usual (Figure 3, right), and the imaging process proceeded as usual, with the crucial difference that ocular aberrations could now be actively compensated for by the DPP.

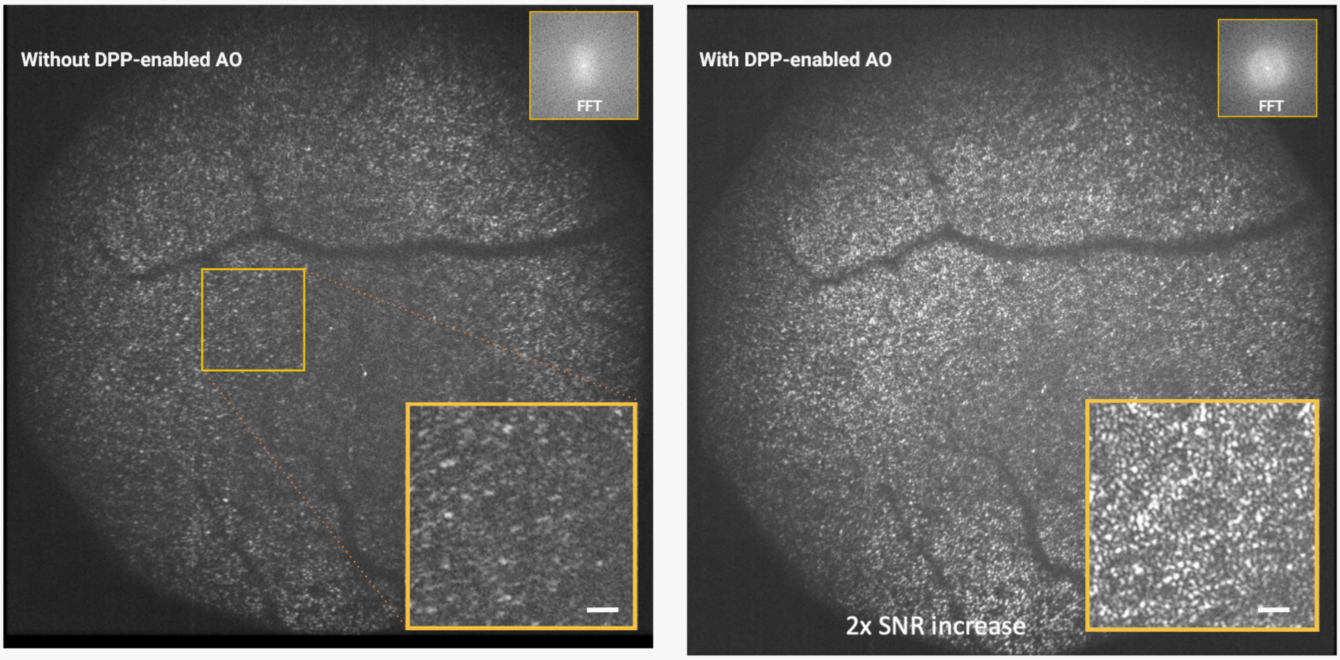


Figure 4: Retinal imaging results acquired by Institut Langevin without (left) and with (right) Phaseform's AO correction. Without AO, even though the pupil of the volunteer was dilated to enable cellular level resolution, individual cone and rod cells could not be resolved. With AO, image quality has improved substantially across the entire FoV, and the individual photoreceptors could be observed with this instrument after less than one day of full hardware and software integration of Phaseform's AO system. The SNR was also doubled as well. The scale bars on the insets correspond to 15 µm.

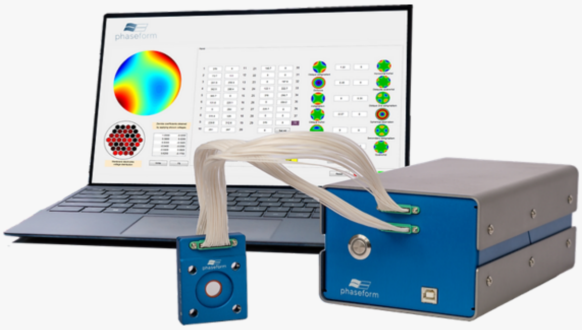
After the hardware and software integration, which took less than a day, the team proceeded with the actual *in vivo* ophthalmoscopy experiments, which were acquired from a healthy volunteer. First, inserting the DPP into the system in a vertical orientation, even when it was turned off, had no detrimental effect on the instrument's image quality. This is largely due to the fact that the DPP is gravity-optimized. An example of the actual retinal images is shown in Figure 4. This image pair shows a portion of the retina near the fovea with a dense mosaic of photoreceptors. Although the ophthalmoscope was more than capable of providing resolution at the cellular level, individual photoreceptors could not be resolved without AO. After a 3-second aberration estimation step, the image quality was completely transformed. Cellular-level resolution was available, revealing individual photoreceptors. In addition, the signal-to-noise ratio was improved by a factor of two. Comparison of the Fourier transforms of the acquired images shows that the spatial frequency content of the photoreceptor mosaic (the so-called Yellot's ring) is only visible after AO correction.

Implication

Phaseform's refractive AO technology significantly lowers the barriers to entry for AO ophthalmology, such as cost and system complexity. It also uniquely enables existing clinical and research ophthalmoscopy infrastructure to be retrofitted with the transformative capabilities of AO. It can thus provide more accurate insights into the morphology and functionality of the human visual system. Phaseform is committed to paving the way for novel, compact and low-cost AO ophthalmoscopes (possibly even for portable or home use) - bringing us one step closer to a future where high-quality, affordable retinal imaging is universally available.

DPP as a General-Use Wavefront Modulator

The first implementation of a DPP in a commercial product is the Phaseform Delta 7 Transmissive Wavefront Modulator. It is a continuous-sheet, refractive, optofluidic device featuring a 63-electrode Deformable Phase Plate capable of replicating Zernike modes up to the 7th radial order. It has an aperture diameter of 10 mm, is compatible with 30 mm optical cage systems, and comes with dedicated drive electronics, control software, and a simulation package. The Delta 7 can be used in the fields of Vision Science and Ophthalmology, Life Science & Microscopy, Material Science & Semiconductor Inspection, 3D Micro and Nano Printing and AR/VR.



Delta 7 (specifications subject to change)

About the company

Phaseform marks a leap forward in the capabilities of optical components. We enable dynamic correction of light distortions inherent in all optical systems. Phaseform's products enable novel, efficient, and high-performance optical products that open new frontiers in life-science imaging, medical diagnostics, optical inspection and -manufacturing. Phaseform GmbH is a spin-off from the Department of Microsystems Engineering (IMTEK) of the University of Freiburg in Germany.

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