Retinal Imaging and Vision at the Frontiers of Adaptive Optics

By compensating for the minor, as well as the major, defects in the eye's optics, we can look through the lens to observe retinal features the size of single cells.

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Vision is a most acute human sense, so it is rather surprising that the very first step in the visual process—the formation of an image on the retina—is often defective. One reason is that the human eye has significant optical defects, aberrations, that distort the passing optical wavefront, blur the retinal image, and degrade our visual experience. Diffraction, which is caused by the finite size of the eye's pupil, is the other reason for blurriness. Together, aberrations and diffraction limit not only what the eye sees looking out, but also determine the smallest internal structures that can be observed when looking into the eye with a microscope (see box 1 on page 33). Spectacles and contact lenses can correct the eye's major aberrations, but if all the aberrations could be quantified and corrected while, at the same time, minimizing diffraction, high-resolution retinal microscopy could become routinely feasible—and we might eventually achieve supernormal vision.

The low-order aberrations of defocus, astigmatism (cylinder), and prism (tilt, in which the eyes do not look in the same direction) are the only optical defects of the eye that are routinely corrected by the use of spectacles or contact lenses. Spectacles have been used to correct defocus since the 13th century (maybe earlier). They began to be used to correct astigmatism shortly after 1801, when Thomas Young discovered that condition in the human eye. But in the past two centuries, little progress has occurred in correcting additional, higher-order aberrations. There are three reasons for this lack of success.

First, the most significant and troublesome aberrations in the eye are defocus and astigmatism. Correcting these two usually improves vision to an acceptable level. Second, until recently, defocus and astigmatism were the only aberrations of the eye that could be easily measured. Third, even when higher-order aberrations could be measured by the cumbersome techniques that were available in the past, there was no simple or economical way to correct them. In 1961, for instance M. S. Smirnov of the USSR Academy of Sciences in Moscow measured many of the higher-order aberrations in the human eye for the first time.[1] But his psychophysical method unfortunately required 1–2 hours of measurements per eye, followed by an additional 10–12 hours of calculations. (Psychophysics is a branch of science that deals with the relationship between physical stimuli and sensory response—for example, using an eye chart to measure a patient's visual acuity.) On the strength of his results, Smirnov suggested that it would be possible to manufacture custom lenses to compensate for the higher-order aberrations of individual eyes. Now, nearly four decades later, no such lens has yet been made.

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Recent technological advances, notably in adaptive optics,[2] have provided solutions to the problems Smirnov encountered. The concept of adaptive optics was proposed in 1953 by astronomer Horace Babcock—then director of the Mount Wilson and Palomar Observatories—as a means of compensating for the wavefront distortion induced by atmospheric turbulence. (See Laird Thompson's article "Adaptive Optics in Astronomy" in Physics Today, December 1994, page 24.)

Transforming adaptive optics into a noninvasive vision tool fundamentally consists of measuring the aberrations of the eye and then compensating for them. But the technique has to be able to deal with the problem of variation of ocular and retinal tissue for a given person, as well as from person to person. And it must also take into account human safety. Despite the difficulties, adaptive optics has met those challenges. Furthermore, as described in this article, it has the potential for tackling a wide range of exciting clinical and scientific applications.

The mathematics of the eye's aberrations

In an eye without any aberrations whatsoever, the cone of rays emanating from a point source on the retina is refracted by the eye's optics to form parallel rays and a planar wavefront. But in a normal eye—even one belonging to someone with 20/20 vision—optical defects in the refractive surfaces skew the rays and distort the originally planar wavefront. The distortions blur the retinal image and diminish the eye's ability to see fine detail.

Mathematically speaking, the wave aberration of the eye, as in most optical systems, is usually described by a series of polynomials—a convenient approach in which an individual polynomial represents a particular type of aberration of known characteristics. For example, with Zernike polynomials, which are the preferred choice for the eye, the first-order polynomials represent tilt, the second-order correspond to defocus and astigmatism, the third-order are coma and comalike aberrations, the

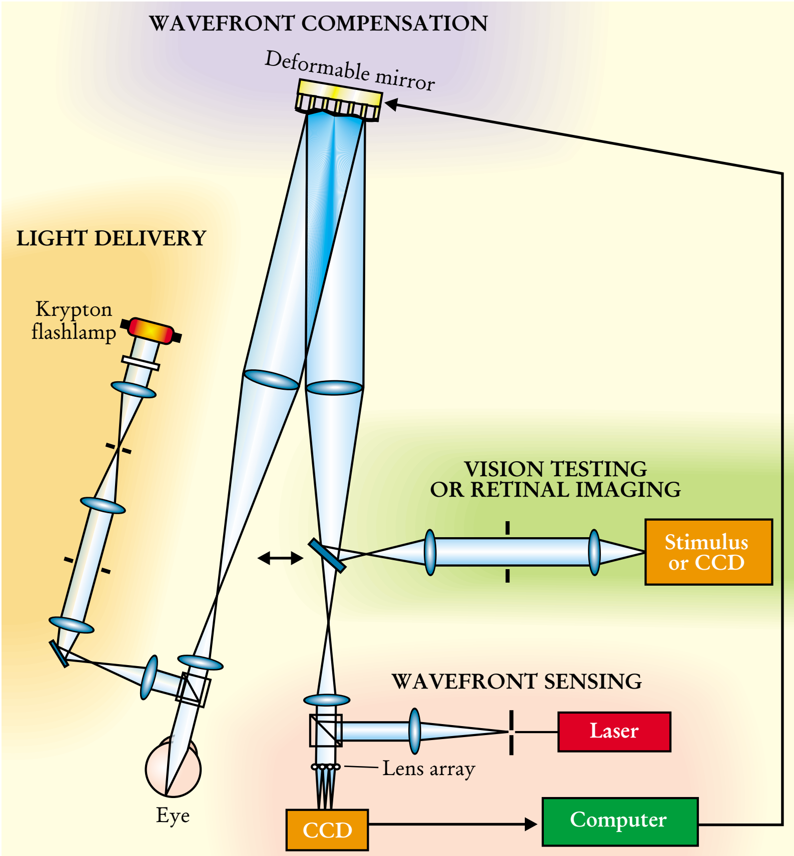


FIGURE 1. ADAPTIVE OPTICS RETINA CAMERA consisting of four components: wavefront sensing, wavefront compensation, light-delivery system, and vision testing and retinal imaging. The Hartmann–Shack wavefront sensor (HSWS) works by focusing a laser beam onto the subject's retina. The reflection from the retinal spot is distorted as it passes back through the refracting media of the eye. A two-dimensional lenslet array, placed conjugate with the eye's pupil, samples the exiting wavefront forming an array of images of the retinal spot. A CCD sensor records the displacement of the spots, from which first local wavefront slopes and then global wavefront shape are determined. Wavefront compensation is realized with a 37-actuator single-sheeted deformable mirror (made by Xinetics Inc). The mirror lies in a plane conjugate with the subject's pupil and the lenslet array of the HSWS. The light source was a Krypton flashlamp that illuminated a 1° patch of retina with 4 ms flashes. The flashlamp output is filtered to 10 nm, with a center wavelength typically between 550 nm and 630 nm to eliminate the chromatic aberrations of the eye. A scientific grade CCD camera was positioned conjugate to the retina to record the reflected aerial image of the retina.

fourth-order are spherical and spherical-like aberrations, and the higher orders are known collectively as irregular aberrations. Although the Zernike series represents the aberrations of the eye effectively, its popularity is undoubtedly due in part to its long use in astronomy for representing atmospheric turbulence. For the eye, other series could be as good, or even better.

Although we have just begun to accurately measure higher-order aberrations, their presence in the human eye has been recognized for some time.[1] They vary considerably among subjects. Many do not correspond to the classical aberrations of man-made optical systems. Indeed, Hermann von Helmholtz, commenting on the eye 150 years ago, put it as follows: "Now, it is not too much to say that if an optician wanted to sell me an instrument which had all these defects, I should think myself quite justified in blaming his carelessness in the strongest terms, and giving him back his instrument." [3]

The effect of diffraction and aberrations

Retinal blur is caused not only by ocular aberrations, but also by diffraction, which, for pupil diameters of less than about 3 mm, is actually the largest source of retinal image blur. A pupil about 3 mm in diameter—which is a typical pupil size under bright viewing conditions—generally provides the best optical performance in the range of spatial frequencies that are important for normal vision. Increasing the pupil size does increase the high-spatial-frequency cutoff, allowing finer details to be discerned, but at the high cost of increasing the deleterious effects of aberrations. Clearly, the very best optical performance would come from correcting all the eye's aberrations across the dilated pupil.

Quantitatively, the effects of diffraction and aberrations on corrected and uncorrected pupils of various diameters are best illustrated by the modulation transfer function (MTF). The figure in box 2 (on page 34) shows the MTF for normal pupils 3 and 7.3 mm in diameter and for a large corrected 8 mm pupil. The large corrected pupil has a higher optical cutoff frequency and an increase in contrast across all spatial frequencies. Peering inward through normal-sized pupils, only ganglion cell bodies and the largest photoreceptors and capillaries can be resolved with reasonable contrast. But with the corrected 8-mm pupil all structures except the smallest nerve fibers can be clearly discerned. Having a large corrected pupil is therefore critical for making use of the spatial frequencies that define single cells in the retina.

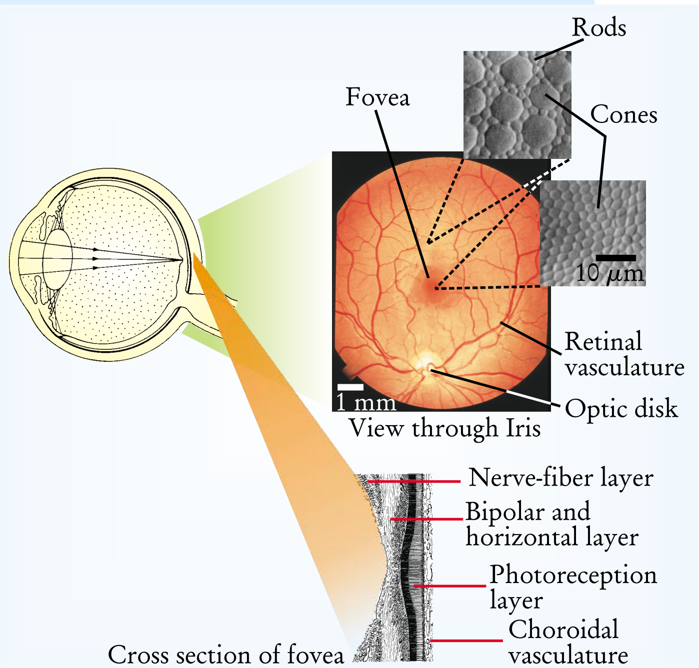
Many of the higher-order aberrations in the eye have been measured in research laboratories by means of a variety of psychophysical and objective methods.[1] But the optometric and ophthalmic professions have largely ignored such methods because they have not proven robust and efficient enough for practical use in a clinical setting.

To address these limitations, in 1994, Junzhong Liang, Bernhard Grimm, Stefan Goelz, and Josef Bille at the University of Heidelberg[4] developed an outstanding technique based on a Hartmann–Shack wavefront sensor (HSWS), an example of which is shown and described in figure 1. The technique is analogous to the artificial guide-star approach now being used to measure the wave aberration of atmospheric turbulence.[5]

The HSWS was a watershed. It provided—for the first time—a rapid, automated, noninvasive, and objective measure of the wave aberration of the eye. The method required no feedback from the patient; its measurements

Box 1. The Human Eye

The human eye is approximately 25 mm in diameter. The cornea and the ocular lens refract light to form an inverted image on the retina. The retina is a delicate 200 to 400 μm thick structure, made of highly organized layers of neurons, that is sandwiched between the retinal and choroidal vasculatures. A mosaic of light-sensitive single cells called rod and cone photoreceptors compose one of the retinal layers. The 5 million cones and 100 million rods in each eye sample the optical image at the retina, transducing the captured photons into an encoded neural image. Rods provide low-acuity monochrome vision at night. Cones provide high-acuity color vision during the day. The other retinal layers, as shown below in the cross section of the foveal part of the retina, contain a dense arrangement of neurons including bipolar, horizontal, and amacrine cells that pre-process the neural image. The nerve fiber layer transports the final retinal signal through the optics disk opening and to the brain.



could be collected in a fraction of a second; and its near-infrared illumination was less intrusive to the subject than earlier techniques had been. In 1997, Liang, with David Williams at the University of Rochester, developed the technique further and measured the first 10 radial orders (corresponding to the first 65 Zernike modes) to compile what is probably the most complete description to date of the eye's wave aberration.[6]

The left column of figure 2 displays surface plots of the point spread function (PSF), measured on two subjects by means of the Rochester HSWS. The PSF, defined as the light distribution in the image of a point source, can be obtained from the measured wave aberration by means of a Fourier transform. In the figure, the average Strehl ratio—defined in the figure caption—for the two (normal) subjects is 0.05. That number is substantially smaller than the diffraction limit of 0.8; it reflects the severity of the aberrations in the normal eye for large pupils.

Correcting the eye's aberrations

After the low- and higher-order aberrations have been measured, the next step is to correct them. Adaptive correction of the eye was first attempted in 1989 by Andreas Dreher, Bille, and Robert Weinreb at UC San Diego. They used a 13-actuator segmented mirror. Their attempt succeeded, but only to the extent that they could correct the astigmatism in one subject's eye by applying his conventional prescription for spectacles.

At the University of Rochester, in 1997, Liang, Williams, Michael Morris, and I constructed the adaptive optics camera shown in figure 1.[7] With a pupil 6 mm in diameter, the system substantially corrected aberrations up through the fourth Zernike order, where most of the significant aberrations in the eye reside. Thus, we demonstrated for the first time that adaptive optics allows coma, spherical aberration—and to a lesser extent, irregular aberrations—to be corrected in the eye. The right column of figure 2 shows the substantial improvement in retinal image quality that adaptive compensation can facilitate. For the two subjects, the Strehl ratio increased from an average value of 0.05 (uncompensated) to 0.4 (compensated).

Deformable mirrors, such as the one used in Rochester, are the technology of choice for wavefront correction in adaptive optics. Their expense and size, however, have prohibited many vision scientists from taking advantage of this technology and have also precluded the development of commercial ophthalmic instruments equipped with adaptive optics. Significant reduction in cost and size can be obtained with other corrector technologies, among them liquid crystal spatial light modulators, which are based on the same technology as LCD wrist watches,[1,8] microelectromechanical membranes,[9] and segmented micro-mirrors.[8]

Microscopic retinal imaging

Imaging the retina through the eye's intact optics dates back to Helmholtz, who devised the first ophthalmoscope. Although retina cameras have advanced substantially since the 19th century, only recently have they been able to observe retinal features with a size as small as a single cell. Optical blur had been a major factor in precluding retina camera observations, but other characteristics of the eye also impede high-resolution retinal imaging—namely, the factor-of-10^{-4} attenuation of light inside the eye, eye motion (with temporal fluctuations up to 100 Hz and spatial displacements of 2.3 arcminutes RMS, even in the fixating eye), a low damage threshold for light, severe ocular chromatic aberration (2 diopters across the visible spectrum), micro-fluctuations in ocular power (0.1-diopter RMS), and a light-sensitive iris that can change diameter from 1.5 mm to 8 mm.

During the last ten years, research groups in Canada,[10] the UK,[11] Spain,[12] and the US[7,13] have developed high-resolution retina cameras that address these imaging problems. The designs incorporate such methods as a dilated pupil, quasi-monochromatic illumination, short exposure times of a few milliseconds, and precise correction of defocus and astigmatism. Those retinal images, containing in some cases spatial frequencies well above 60 cycles/degree (normal vision makes use of spatial frequencies of 0–30 cycles/deg), have been good enough to give researchers a tantalizing first-ever glimpse of single cells in the retina of the living human eye. However, the microscopic structure revealed in the images typically has been of low contrast, while also being noisy and limited to

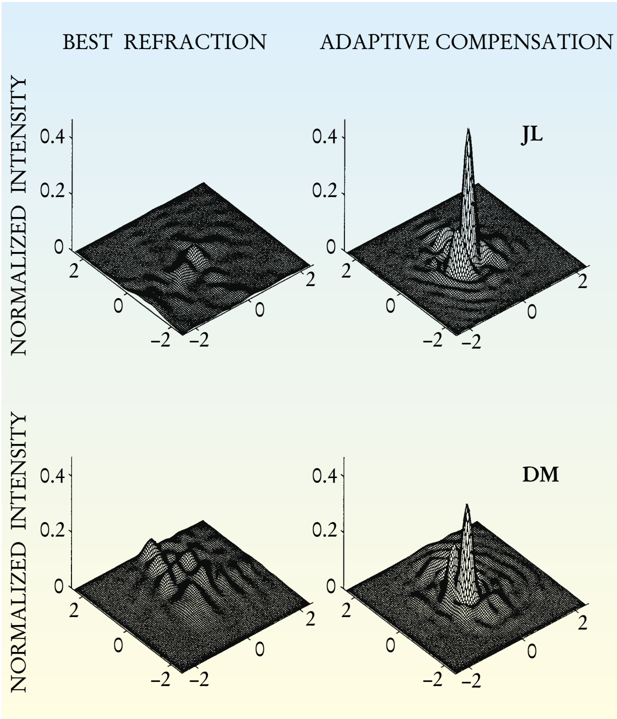


Figure 2. The point spread function of the eye for two normal subjects (JL and DM) without and with adaptive compensation. The subjects' pupils were 6 mm in diameter. The best refraction was obtained by means of trial lenses. The normalized-intensity ordinate corresponds to the Strehl ratio. (The Strehl ratio, which ranges from 0 to 1, is defined as the ratio of the maximum light intensity in the aberrated point spread function to that in the aberration-free PSF with the same pupil diameter.)

subjects with good optics. To achieve better imaging will require the correction of aberrations beyond defocus and astigmatism.

Using the adaptive optics camera in figure 1, my colleagues and I obtained the first images of the living retina with correction to the higher-order aberrations. Figure 3 shows three images, collected with the camera, of the same patch of retina both with and without adaptive correction. A regular array of small bright spots fills the images. Each bright spot corresponds to light exiting an individual cone photoreceptor after reflection from retinal tissue lying behind the receptor (compare it to the photoreceptor micrographs shown in box 1). The improvement in image clarity made possible by adaptive optics is striking.

Adaptive optics and supernormal vision

The correction of higher-order aberrations also offers the possibility of better vision. Because diffraction, which cannot be mitigated, is more deleterious for small pupils than aberrations are, the largest benefits will accrue when the pupil is large—under indoor lighting conditions, for example.

To illustrate what the retinal image would be like with supernormal optics, imagine yourself viewing the Statue of Liberty from a boat 3 km away in New York Harbor. Under optimal viewing conditions and with defocus and astigmatism removed, your retinal image of the statue with a normal 3 mm pupil would look like the image in figure 4a. If you viewed the statue through adaptive optics programmed to fully correct all ocular aberrations across your 3 mm pupil, the retinal image of the statue would look like the image in figure 4b. Notice the finer detail and higher contrast. The comparison illustrates that retinal image quality can be improved even for pupil sizes as small as 3 mm.

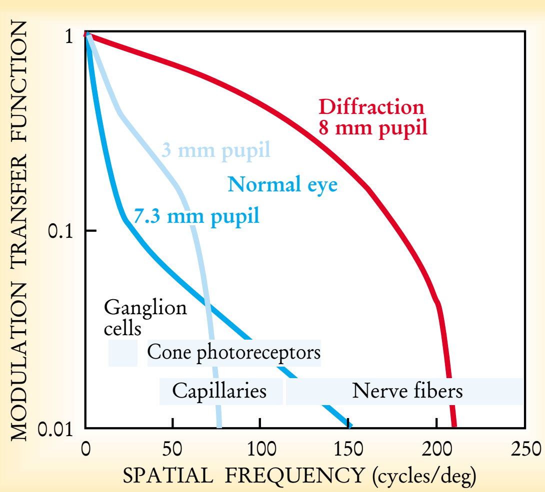
But the best retinal image quality is obtained with the largest physiological pupil diameter (8 mm) and with full correction of all ocular aberrations. This case is depicted in figure 4c, which shows that the theoretical maximum optical bandwidth that can be achieved with the human eye is substantially higher than what we are endowed with.

Improving the quality of the retinal image is an important step toward achieving supernormal vision. But it is only the first step. In an eye with perfect optics, visual performance becomes constrained by neural factors,

Box 2. The Modulation Transfer Function

The modulation transfer function (MTF) is a popular image-quality metric that reflects an optical system's amplitude response to sinusoidal patterns. In vision science, the sinusoids are described in terms of angular frequency and measured in cycles per degree. Using an angular, as opposed to a linear, measure avoids the need to measure the length of the eye, and the same frequency holds for both object and image space. For example, 1 cycle/deg corresponds to one period of a sinusoid located at the retina (or object plane) that subtends exactly 1° at about the eye's pupil. Most of the visual information we use occupies the range of 0–30 cycle/deg.

The accompanying figure shows the MTF of the eye under normal viewing, pupils that are 3 and 7.3 mm in diameters and with the best refraction achievable using trial lenses averaged across 14 eyes.[6,9] Also shown is the diffraction-limited MTF for the 8 mm pupil. The area between the normal and diffraction curves represents the range of contrast and spatial frequencies inaccessible with a normal eye, but reachable with adaptive optics. Also indicated is the range of fundamental frequencies defining various sized ganglion cell bodies, photoreceptors (within 2.5° of the foveal center), foveal capillaries, and nerve fibers.



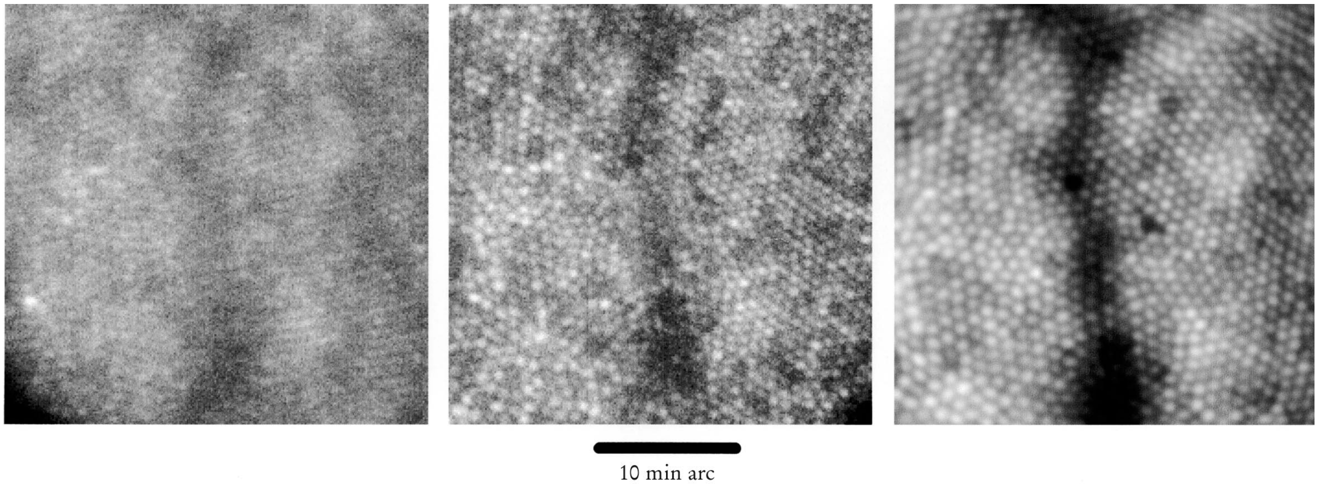


FIGURE 3. RETINAL IMAGES, before and after adaptive compensation. All three images are of the same 0.5° patch of retina, obtained with 550 nm light through a 6 mm pupil. The dark vertical band across each image is an out-of-focus shadow of a blood vessel. The leftmost image shows a single snapshot taken when only defocus and astigmatism had been corrected. The middle image shows additional aberrations having been corrected with adaptive optics. It also shows noticeably higher contrast and resolution, with individual photoreceptors more clearly defined. To reduce the effect of noise present in the images, the rightmost image demonstrates the benefit of registering and then averaging 61 images of a single retinal patch. (Images courtesy of Austin Roorda and David Williams, University of Rochester.)

specifically, the spacing between retinal photoreceptors, which represents a neural limitation to visual resolution that is only slightly higher than the normal optical limit. If the optical quality of the retinal image improves dramatically, the photoreceptor mosaic will appear relatively coarse by comparison, as shown in figure 4d. As a result of that mismatch, very fine spatial details in the retinal image will be smaller than the distance between neighboring cones, so those details will not be properly registered in the neural image—a problem known as aliasing. For everyday vision, however, the penalty of aliasing is likely to be outweighed by the reward of heightened contrast sensitivity and detection acuity. Indeed, laboratory observations indicate that stimuli seen through adaptive optics have the strikingly crisp appearance expected of an eye with supernormal optical quality.

It is unclear how well supernormal vision achieved under controlled conditions in the laboratory will transfer to everyday use. Nor is it clear just what the benefits of acquiring such vision will be. We can be fairly sure, however, that supernormal vision will not be realized with traditional spectacles, because the rotation of the eye in relation to the fixed spectacle lens severely limits the types of aberrations that can be corrected.

To counteract the effects of eye rotation, engineers could set out to devise a sophisticated visor (like the one worn by *Star Trek*'s Geordi LaForge) that dynamically adapts the correction to the wearer's focus and direction of gaze. Contact lenses, though, are a more realistic and inexpensive option. They move with the eye, and with current technology, they could be tailored to correct the higher-order aberrations in individual eyes. Another option is refractive surgery. The leading surgical technique today, laser-assisted *in situ* keratomileusis, corrects the refractive errors of both defocus and astigmatism by ablating corneal tissue with an excimer laser. That technology could be extended to compensate for the higher-order aberrations.

Adaptive optics has the potential to realize these corrective procedures by means of providing substantially faster and more sensitive measurements than previously possible. For example, measuring the eye's wave aberration before and after refractive surgery might help improve the surgery and optimize retinal image quality—perhaps making the surgical option superior to contact lenses and spectacles. The same approach may be applicable to improving other corrective procedures, such as the use of intracorneal polymer rings that are surgically implanted in the cornea to alter corneal shape. Wave-aberration measurements might also assist in the design and fitting of contact lenses. That application would be of particular benefit to patients with irregularly shaped corneas.

Medical and scientific applications

The medical and scientific benefits of adaptive optics—other than improving vision—are just beginning to be explored. Among the numerous potential applications are detection of local pathological changes and investigation of the functionality of the various retinal layers. A few specific examples are given below; more can be found in the literature.[7]

Glaucoma is a disease in which blindness ensues from the gradual loss of optic nerve fibers. With conventional techniques, it can be detected only after significant damage has occurred. By exploiting the greater sensitivity of adaptive optics, eye care specialists could make more accurate measurements of the thickness of the nerve fiber layer around the head of the optic nerve, and, conceivably, individual fibers or ganglion cell bodies could be monitored. Such detailed information would permit glaucoma to be detected earlier.

Diabetes, another disease that affects the retina, produces microaneurysms in the retinal vasculature that gradually grow larger and leak blood. Detection at a small size is critical for successful retinal surgery. With adaptive optics much smaller microaneurysms could be detected than can be now, possibly without the use of the invasive fluorescent dyes required by the current detection methods.

It is now possible to study the living retina at a micro-

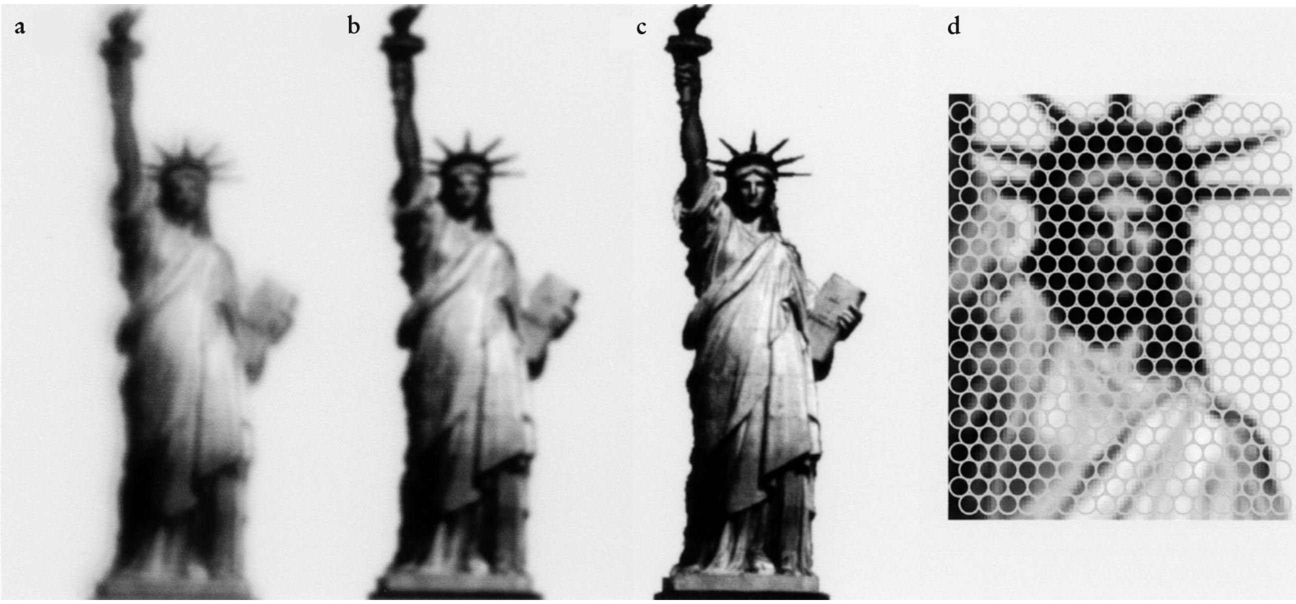


Figure 4. Predicted retinal image of the Statue of Liberty when viewed at a distance of 3 km with (**a**) normal optics and a 3 mm diameter pupil; (**b**) corrected optics, 3-mm pupil; and (**c**) corrected optics and an 8 mm pupil. The statue subtends almost 0.9°—about the same as a US quarter at a distance of 5 ft. A narrow-band chromatic filter is placed in front of the viewer's eye to prevent ocular chromatic aberrations. Optical microfluctuations in the eye are ignored. The wave aberration used in the simulation is that of the author's eye (he has normal vision with spectacle correction). **d:** An enlargement of the image of **c** is overlaid with a hexagonally packed mosaic of circles that represent the foveal cone mosaic. This neural mosaic is relatively coarse compared to the retinal image, a phenomenon that may introduce artifacts into the neural image and ultimately cause a kind of misperception called aliasing. (Wave aberration measurement courtesy of Xin Hong and Larry Thibos, Indiana University.)

scopic scale. Unfortunately, studies of the retina at the single-cell scale require removing the retina from the eye. That procedure has two great drawbacks: It drastically limits the types of experiment that can be conducted, and it irreversibly changes the tissue in ways that confound experiments.

It is now possible to collect whole temporal sequences in individual eyes to track retinal processes that vary over time at the microscopic spatial scale. Those data could be used, for example, to study both the development of the normal eye and the progression of retinal disease. Studying the retina at the single-cell level would improve our understanding not only of the light-collecting properties of the retina, but also of the spatial arrangement and relative numbers of the three types of cone photoreceptor that mediate color vision. Recently, Austin Roorda and Williams at Rochester used the adaptive optics camera shown in figure 1 as a retinal densitometer to obtain the first images showing the arrangement of the blue, green, and red cones in the living human eye (see the image on the cover).[14]

The realization of all these future applications will depend heavily on the continuing development of less expensive and smaller devices for adaptive optics. Such advances have traditionally excited the astronomy (and military) communities. Today, that excitement is also shared by those of us who conduct research in vision science.

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