MEMS ENABLED TECHNOLOGIES FOR OCULAR MONITORING AND THERAPY

Ellis Meng[1], Eugene Yoon[1], and Christian Gutierrez[2]
[1]University of Southern California, Los Angeles, USA and
[2]Verily Life Sciences, South San Francisco, USA

ABSTRACT

The healthy human eye is an exquisite collection of different cell types that collectively form an intricate opto-electro-mechanical system that shapes the final input to the visual processing areas of the brain to achieve vision. A number of different diseases affecting the eye are amenable to engineering solutions enabled by MEMS technologies. The purpose of this paper is to examine different opportunities for MEMS technologies to impact ocular health and review examples of past and current research in this field. Commercial progress is also discussed.

KEYWORDS

Ocular microdevices, contact lens devices, glaucoma drainage devices, intraocular pressure, accommodative intraocular lens, retinal prostheses, retinal electrode arrays, *in vivo* force sensors

INTRODUCTION

In order to understand the device-related opportunities in the eye, it is first necessary to briefly review how visible light enters and is processed by the eye before it is transmitted by the optic nerve to different downstream processing centers in the brain (Fig. 1). Then, progress in MEMS-enabled technologies for the eye are reviewed including surgical tools, research devices, and monitoring or therapeutic devices categorized by the major ocular disease conditions they target.

Visible light is first refracted by the cornea, passes through the pupil, and is refracted once more by the lens into a small inverted image that is focused on the back retina. The lens is part of a mechanical system within the eye; the ciliary muscle acts on the lens via zonular fibers. Contraction and relaxation of the muscle causes increases in convexity or flattening which in turn allow the eye to focus on objects that are near or far, respectively.

Light exiting the lens then bypasses the outer layers of the 100-300 µm thick retina through several cell types and is projected onto the photoreceptor layer consisting of rod and cone cells (~130 million) which transduce the light stimulus into electrical pulses. Unlike other parts of the sensory system, a great deal of signal processing occurs in the retina outside of the brain. The electrical pulses are passed from photoreceptors to a cascade of different neuronal cell types (horizontal, bipolar, amacrine, and ganglion cells) that each contribute to visual processing. Action potentials are then transmitted by ~1.2 million ganglion cells through the optic nerve and on to the visual cortex and other parts of the brain.

The malfunction of or damage to any of these ocular components can result in vision impairment. As vision is a critical part of our sensory system, much attention has been devoted by researchers and industry to treat different ocular conditions. The following introduces MEMS technologies that have been developed for the eye by examining the needs of several ocular conditions.

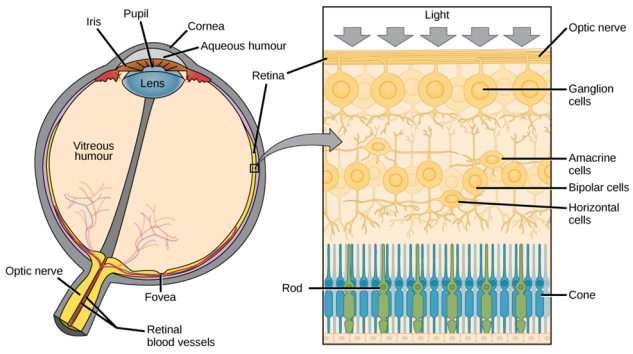

Figure 1: (left) Illustration of cross section of human eye detailing the configuration of major structures involved in vision. (right) Close-up view of the retina showing the layered arrangement of different neuronal cell types. Light bypasses the outer layers in contact with the vitreous humor and is converted into electrical pulses by the rods and cones in the photoreceptor layer. Image Source: OpenStax College, Vision. October 17, 2013, http://cnx.org/content/m44761/latest/Figure_36_05_02.png, OpenStax CNX under CC BY 3.0.

GLAUCOMA

Glaucoma is an incurable disease that affects millions worldwide. Vision loss occurs via damage to the optic nerve. Elevated intraocular pressure (IOP) is strongly implicated in the pathogenesis of glaucoma. Intraocular pressure is affected by the balance between production and outflow of aqueous humor. Glaucoma can be managed by implantation of drainage devices which lower IOP by improving the outflow of aqueous humor.

MEMS devices for the management of glaucoma include sensors to monitor IOP and glaucoma drainage devices that lower IOP by improving the outflow of aqueous humor [1]. Pressure sensors that are integrated into contact lenses or implanted have been proposed [2]. The Sensimed Triggerfish® is a contact lens sensor that uses a strain gauge to continuously monitor changes in IOP patterns by capturing circumferential changes in the corneoscleral area. The sensor transmits information wirelessly to an antenna adhered around the eye and stores data via Bluetooth to a portable recorder worn by the patient for later analysis. This system obtained US regulatory approval in 2016.

The contact lens format is also being explored for glucose sensing in tears in a joint effort between Verily and Novartis [3]. This was inspired by earlier research demonstrating L-lactate sensing in a MEMS contact lens device where platinum electrodes were evaporated onto poly(ethylene terephthalate) substrates, functionalized

with appropriate chemical additives, and coated with medical grade polyurethane. The amperometric sensor was capable of stable *in situ* monitoring of L-lactate in tear fluid at temperatures comparable to those at the surface of the eye [4].

Implantable IOP sensors are being pursued by a number of academic research groups [2]. Most utilize capacitive sensing methods which necessitates a wireless method for obtaining pressure data. A passive mechanical sensor was developed based on the Bourdon tube and allowed optical readout of pressure [5, 6].

To properly regulate IOP, MEMS glaucoma drainage shunts have been devised with micro check valves [7, 8] or magnetoelastic resonators micromachined from Metglas 2826MB ($Fe_{40}Ni_{38}Mo_4B_{18}$) for wireless actuation [9]. Drainage shunts that resist biofouling and minimize unwanted protein adhesion by using microfluidics composed of unique polyethylene glycol materials have also been described [10].

RETINITIS PIGMENTOSA

Diseases affecting the photoreceptor layer of the retina prevent the adjacent and otherwise intact layers from conducting visible light information to the brain. For example, retinitis pigmentosa is marked by degeneration of the photoreceptors and is incurable. The progressive loss of photoreceptors first results in compromised peripheral vision and eventually blindness. Although the photoreceptors in the outer retina are lost, the cells in the inner retinal layers are partially spared. Electrical stimulation of the inner retina has been shown to provide some level of useful light perception [11].

Dozens of research groups worldwide have thus pursued development of retinal prostheses including major efforts in the US, Germany, France, Japan, Korea, Australia, Taiwan, Israel, and China [12]. The approaches differ and can be categorized by the implant location within the eye and the mechanism by which electrical stimulation is applied to the ganglion cells of the inner retina. The Argus® II retinal prosthesis developed by Second Sight Medical Products includes an epiretinal microelectrode array designed to lay on top of the inner retina with the electrodes exposed to the ganglion cell layer. Visual information is acquired by an external camera mounted on eyeglass frames and that information is converted into an appropriate pattern of stimulus pulses by a processing unit. The Argus® II received US regulatory approval in 2013.

In addition to epiretinal placement, other ocular interface strategies to restore vision include subretinal, intrascleral, and suprachoroidal placement. Subretinal prostheses use electrode arrays or photodiodes inserted into the eye wall adjacent to the retina. Unlike microelectrodes which are used to send electrical impulses to tissue, photodiode arrays convert light stimulus into electrical current which is then converted into electrical stimulus. The advantage of the photodiodes is the elimination of the external camera and processor. The highest recovered visual acuity reported to date was obtained in a patient using the Alpha-IMS subretinal photodiode prosthesis developed by the University of Tübingen [13]. This device received regulatory approval in Europe in 2013. Intrascleral and suprachoroidal interfaces are positioned in the eye wall in layers outside of the retina.

The MEMS component in many of these efforts is the multielectrode retinal interface [14, 15]. Different flexible substrate materials including silicone rubber, Parylene C, polyimide, and liquid crystal polymer have been explored. Likewise, different electrode materials have been reported including platinum and sputtered iridium oxide films (SIROF).

Epiretinal prostheses typically include a rectangular multielectrode array attached to a multiwire cable. Electrode sites are ideally located within 100 µm of ganglion cells for effective electrical stimulation. The Argus® II uses a simple retinal tack to secure the electrode array in place. One challenge posed by this arrangement is the interfacial contact pressure imposed upon the delicate retina. A MEMS pressure sensor array (Fig. 2) was developed to study the magnitude of mechanical loading on the retina imposed by the contact of the array with the retina during surgical placement and tacking [16]. These Parylene C pressure sensing arrays were thermally shaped to match the curvature of the retina, a technique developed earlier for Parylene C epiretinal microelectrode arrays [17].

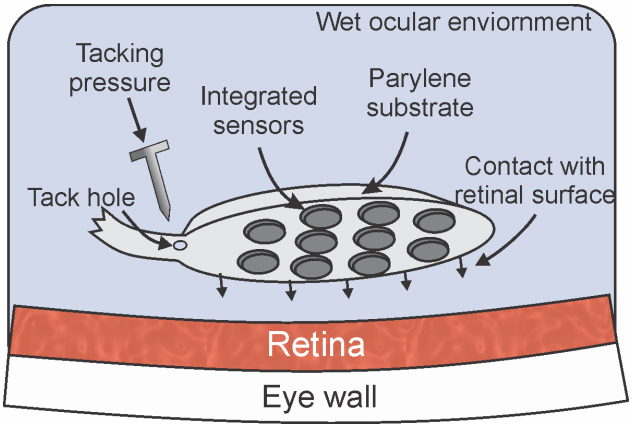

Figure 2: Illustration of Parylene-based pressure sensing array with discrete integrated sensors. The array was designed to operate in the wet ocular environment and mimic the shape and placement of an epiretinal electrode array. A tack hole allows the device to be secured to the retina.

Epiretinal arrays sized for research animals are also being pursued that will allow further understanding of electrical stimulation-based restoration of vision. Figure 3 shows a Parylene C epiretinal array having Pt stimulation electrodes of varying sizes with an integrated ribbon cable. The device has been thermally shaped to match the ocular anatomy of rats such that the electrode array is positioned on the retina and the ribbon cable bends around the eye wall. This arrangement allows the array to be sutured securely onto the sclera. The ribbon cable routes the contact pad array to head-mounted electronics. Optical coherence tomography and fundus images confirmed placement of the array within 100 µm of the retina in experiments performed with unpackaged arrays.

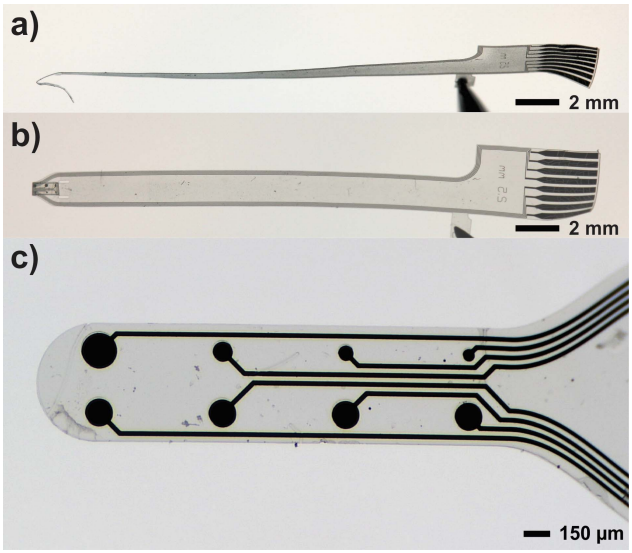

Figure 3: Prototype epiretinal array device sized for rat. a) Side view of device showing the thermally formed array and cable at the tip. The contact pad array is visible on the right. b) Top down view of device. Wires are placed on the cable periphery to minimize damage during surgical handling. c) Magnified view of the electrode array prior to thermal shaping. Electrode diameters are 210, 110, 80, and 60 µm in the top row and 160 µm in the bottom.

AGE-RELATED MACULAR DEGENERATION AND DIABETIC MACULAR EDEMA

Age-related macular degeneration (AMD) affects the macula located near the center of the retina and thus affects the quality of central vision. The disease is incurable and a common form of vision loss among the elderly. The wet form of AMD is associated with abnormal blood vessel growth. Diabetic macular edema (DME) follows from diabetic retinopathy and also results in loss of vision in the central field. The impairment is caused by fluid accumulation in the macula due to leaky blood vessels. Both conditions are treatable and a number of different interventions are available.

Pharmaceutical intervention typically entails drug injections via needles into the back of the eye. Drug is thus delivered to the vitreous humor, a jelly-like fluid filling the eye, and in close proximity to the retina. These drugs act to control the growth of blood vessels and slow their leaking. However, the need for frequent and repeated intraocular dosing to manage the progression of disease can lead to undesirable complications and further suffers from poor patient adherence.

An alternative to frequent intravitreal injections is the use of implantable drug delivery systems. Intraocular pumps have been developed using MEMS electrolysis pumps [18, 19]. In addition to replacing intravitreal injections, such pumps could also be used to deliver therapeutics to the front of the eye to manage, for example, glaucoma. In 2014, Replenish, Inc. reported the first-in-man safety study of their 60 µL payload MicroPump. A small group of 11 DME patients received the micropump, were administered microdoses into the vitreous cavity of the eye, and were followed for 90 days [20]. Further clinical studies are required before regulatory approval for such technology can be obtained.

Other MEMS approaches have been explored for ocular drug delivery beyond electrolysis pumps. MEMS transducers were developed for sonophoretic [21, 22] and iontophoretic [23] delivery. Delivery of defined doses of antiantiogenic drug targeting diabetic retinopathy was demonstrated using a magnetically activated drug reservoir [24, 25].

PRESBYOPIA

Presbyopia, a natural part of the aging process, is characterized by stiffening of the lens causing the eye to be fixed at a long-distance focus. In a healthy eye, the compliant lens is reshaped naturally as the zonular fibers respond to the activity of the ciliary muscle. As the muscle contracts, the lens increases in convexity which allows proper focus of light on the retina for close objects. As the muscle relaxes, the lens flattens allowing for focus of far objects. The process of changing optic power to enable focus is called accommodation.

Static corrective lenses in the form of glasses or contact lenses can provide vision correction but cannot restore accommodation. Novartis and Verily have partnered to achieve an autofocus contact lens to treat presbyopia which has yet to enter clinical trials.

It is also possible for the lens to be surgically replaced with intraocular lenses (IOLs). IOLs consist of a lens and haptics. First, the natural lens is removed, leaving an empty lens capsule. The IOL is positioned directly within the lens capsule and secured in place with the haptics to restore focusing power. Unlike conventional IOLs, the haptics in an accommodative IOL are flexible and interact with the ciliary muscle. Specifically, the microhinges enable the lens to vault forward and backward within the eye following the normal accommodation mechanism.

A recent example of an accommodative IOL uses a shape memory alloy ring actuator in combination with Parylene spring and shoes [26]. Alternatively, the lens shape can be directly manipulated by using an inflatable liquid-filled balloon with a self-sealing valve in place of the lens [27]. Commercially available accommodative IOLs include the Crystalens (approved in 2003) and Trulign Toric (approved in 2013) by Bausch + Lomb. Many other IOLs are being developed.

CONCLUSION

Many opportunities exist to treat chronic curable conditions that lead to vision loss. The anatomy and size of the eye are well matched to the strengths and features afforded by MEMS technology. Although several conditions are now addressed by recently approved medical devices incorporating MEMS technology, the performance achieved still lags behind that of a healthy ocular system. In addition to medical devices for monitoring and therapy, research devices also play an important role in informing new or improved interventions.

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CONTACT

*E. Meng, tel: +1-213-7406952; ellis.meng@usc.edu