**Int J Ophthalmol, Vol. 1, No. 3, Sept.18, 2008 www. IJO. cn**
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**·Review·**

# Epiretinal prosthesis for outer retinal degenerative diseases

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**Foundation item:** National Natural Science Foundation of China (No. 30470469)

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Received:2008-07-18 Accepted:2008-08-01

## Abstract

- Age-related macular degeneration (AMD) and retinitis pigmentosa (RP) are common outer retinal degenerative problems, and also the predominant causes of most blinding retinal diseases. Retinal prosthesis is a promising solution for such photoreceptor degeneration diseases. Most of current concepts for a retinal prosthesis are based on neuronal electrical stimulation. In the past twenty years, retinal prosthesis has been developed in two different directions: epiretinal prosthesis and subretinal prosthesis. Each prosthesis technique has its advantages and disadvantages. For epiretinal prosthesis, it is easier to be implanted and has the advantage of keeping most of the electronics in the vitreous cavity off the retinal surface, which greatly helps in dissipating the heat generated by the implant device. In this paper, a brief overview of retinal prostheses concepts is introduced. After that, several important aspects of epiretinal electrical stimulation will be discussed. Moreover, some practical epiretinal prosthesis devices developed by researchers in United States, Germany and Japan in the past have been reviewed. We hope that the devices will be used widely in the near future.

- KEYWORDS: outer retinal degeneration; retinal prosthesis; age-related macular degeneration; retinitis pigmentosa; epiretinal electrical stimulation; epiretinal prosthesis

Rao C, Yuan XH, Zhang SJ, Wang QL, Huang YS. Epiretinal prosthesis for outer retinal degenerative diseases. *Int J Ophthalmol* 2008;1(3):273-276

## INTRODUCTION

Degenerative retinal diseases result in death of photoreceptors: rod cells responsible for night vision at the periphery retina and cone cells responsible for color vision at the macula. Hereditary retinal degeneration and age-related macular degeneration (AMD) are two examples of blinding retinopathies, in which there are only a few ways to prevent or to halt the visual deterioration to legal blindness. Worldwidely, millions of people suffered from retinitis pigmentosa (RP), the leading cause of inherited retinal diseases. AMD is the major cause of vision loss in people at age of 65 or above, and the issue is becoming more critical as the population gets aged [1]. RP and AMD are the two most common outer retinal degenerative diseases. Currently, there is no effective treatment for most patients with RP and AMD. However, if one could bypass the photoreceptors and directly stimulate the inner retina with visual signals, one might be able to restore some degree of sight. The design of retinal prosthesis is based on the fundamental concept of replacing photoreceptor functions with an electronic device, which was initiated and has been developed further by de Juan *et al* [2]. The idea has attracted much attention and various artificial retina chips have been developed and some were implanted in patients' eyes for research purposes [3-5]. The different designs of visual prostheses are named according to their locations of implantation and action, such as cortical, optic nerve, subretinal, and epiretinal. For outer retinal pathologies, retinal prosthesis is a preferable choice because of the preserved physiological optics and retinotopic organization of the eye in addition to the natural processing ability along the proximal visual pathways. Epiretinal devices are easier for implantation compared to subretinal devices. This article will begin with a brief overview of retinal prostheses concepts and then concentrate on the epiretinal prostheses[6].

## CONCEPTS OF RETINAL PROSTHESIS

Light after entering the pupil, will be focused and inverted by the cornea and lens, and is then projected onto the back of the eye as an image. At the back of the eye lies the retina, a multilayer structure of alternating cells which convert the light signal into a neural signal. For better understanding of retinal prosthesis, let's follow the signal through the retina, as shown in Figure 1A and Figure 1B. Light enters the ganglion

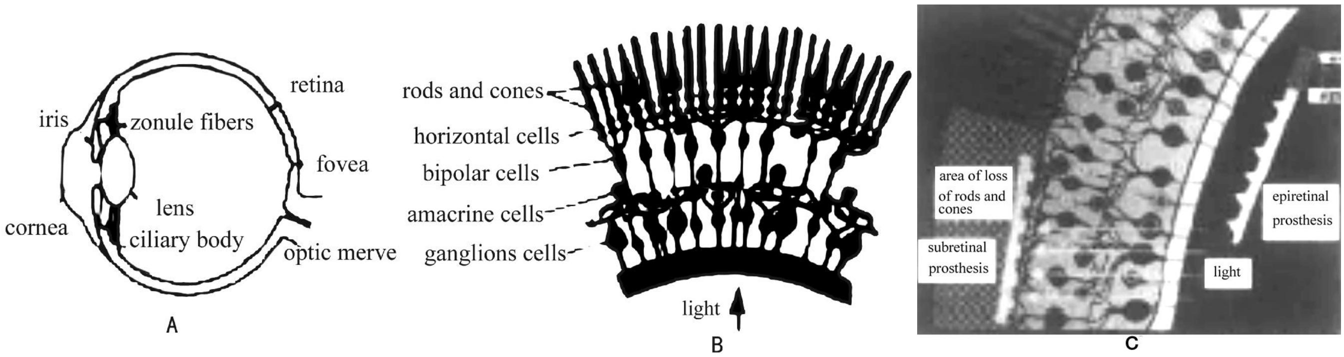

**Figure 1** A: Diagram of a human eye; B: The multilayer structure of retina and; C: The epiretinal and subretinal implantation concepts

cell layer first, and must penetrate all cell types before reaching the rods and cones. The outer segments of the rods and cones transduce the light and send the signal to their axons. The photoreceptor axons contact the dendrites of bipolar cells and horizontal cells. Horizontal cells are interneurons which aid in signal processing. The bipolar cells process input signals from photoreceptors and horizontal cells, and transmit the signals to their axons. Then the bipolar axons contact ganglion cell dendrites and amacrine cells. The ganglion cells send their axons through the optic fiber layer to the optic disc to make up the optic nerve and then to the brain in form of action potentials[7,8].

There are two types of retinal prosthesis, epiretinal prosthesis and subretinal prosthesis, and they work differently as shown in Figure 1C. The epiretinal implantation electrode array is implanted on the surface of the inner retina, while the subretinal implantation electrode array is installed at the subretinal space, at a level between sensory retina and the retinal pigment epithelium [3]. Both electrode arrays are generated and demonstrated without any additional necessary components such as the stimulating chip, receivers and photodiodes. According to the different implantation locations of the devices, the electrical stimulation meets the inner retina first in the epiretinal approach while for the subretinal approach, the electrical stimulation meets the outer retina initially[9]. Other than just for easier implantation, the epiretinal implantation has the advantage of keeping most of the electronics off the retinal surface, in the vitreous cavity, a naturally existing and fluid filled space, which greatly helps in dissipating the heat generated by the electronics[10].

## EPIRETINAL PROSTHESIS

### Epiretinal Electrical Stimulation

**Stimulated mode selection** When applying electrical stimulation, neural damage is a critical issue to be considered. Among the early studies, the histopathologic studies of long-term stimulation of neural tissue and the electro chemical studies of the electrode-electrolyte interface have had significant contribution and impact on this area. The relatively better safety level of biphasic charge balanced waveforms compared to monophasic waveforms has been demonstrated. Any net direct current (DC) can lead over time to irreversible electrolyte reactions [11]. A biphasic current waveform consisting of two consecutive pulses of equal charge but in opposite polarity. However, it does not generate any DC component. Whereas a simple monophasic waveform is unacceptable for neural stimulation because it delivers DC and creates irreversible faradic processes [9]. For retinal stimulation in blind patients it was determined, as shown in Figure 2, that the biphasic current pulse amplitude A should be 100-600μA, the current pulse duration B should be 0.1-2ms, and the period between biphasic pulses C should be 8-100ms, corresponding to a stimulating frequency of 10-125Hz[12].

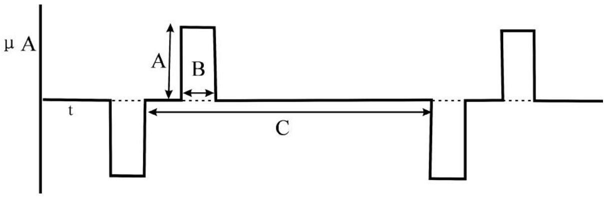

**Figure 2 Bipolar current pulse parameters for epiretinal stimulation**

**Threshold** Electrical stimulation elicits a neural response by opening the voltage-sensitive ion channels and bypassing the chemically gated channels in the stimulated cell. A number of factors can influence the efficacy of electrical stimulation. First, the threshold depends on the electrical properties and anatomy of the target neural elements, and which portion of the cell (dendrite, cell body, and axon) is going to be stimulated [13]. Second, the threshold is obviously affected by the distance from the electrodes to the target cell. Third, the threshold during bipolar stimulation is also affected by the pulse duration and current amplitude. Fourth, threshold can vary significantly due to the impedance of tissues and errors can be associated with the assumption that tissue electrical properties are the same in every stimulated compartment (homogenous and isotropic tissue properties) [14]. Another variable for threshold stimulation is the waveform. Two basic waveforms have been used frequently for neural stimulation: sinusoidal and square waveforms.

**Electrodes** The electrode array is in direct contact with the biologic tissue. Thus, it has the potential to damage the tissue mechanically, chemically, physically, and vice versa [15]. The electrodes' charge transfer efficiency will affect every subsystem of the prosthesis by influencing the power requirements and the electrode density. A stimulating electrode array must meet several requirements. These include a high number of densely packed electrodes to provide a high acuity image and individual electrodes that can safely inject a large amount of charge. The global shape of the array, the shape of each electrode, the way to insert and to attach it, and other factors depend on the anatomical location of stimulation.

**Some Epiretinal Prosthesis Solutions** Progress in the field of neural prostheses has converged with advances in retinal surgery to enable the development of an implantable retinal prosthesis. Several groups in the United States, Germany and Japan have proposed some versatile epiretinal prosthesis solutions.

**MARC system** Liu *et al* [12] have developed a multiple-unit artificial retina chipset (MARC) system to benefit the visually impaired. The rehabilitative device replaces the functionality of defective photoreceptors within patients suffering from RP and AMD [16-18]. The schematic representation of the MARC system is shown in Figure 3A and Figure 3B. The components of the MARC to be implanted consists of a secondary receiving coil mounted in close proximity to the cornea, a power and signal transceiver and processing chip, a stimulation-current driver, and a proposed electrode array fabricated on a material such as silicone rubber, thin silicon, or polyimide with ribbon cables connecting the devices. The biocompatibility of polyimide is being studied, and its thin, light weight consistency suggests it is possible to be used as a non-intrusive material for electrode array. Titanium tacks or cyanoacrylate glue may be used to hold the electrode array in place. The MARC system has several advantages over previous approaches: better heat dissipation, powering, diagnostic capability, physiological functionality, reduction of stress upon the retina, etc.

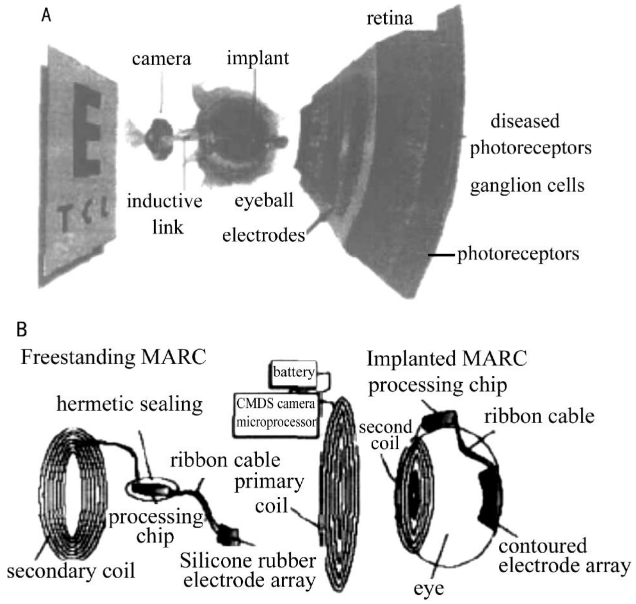

**Figure 3** A: The MARC system; B: RF coil configuration of the MARC system

**Schwarz's flexible microelectronic stimulators** Schwarz *et al* [19] have presented single chip CMOS imagers and a flexible microelectronic stimulator for realization of a retina implant system that will provide visual sensationsusing electrostimulation to patients suffering from photoreceptor degeneration. Its schematic architecture is shown in Figure 4. The external part of the retina implant system is the so-called retina encoder which provides image acquisition,computation of receptive-field functions of the degener ated retinal cell layers, and the wireless power and data transmission including telemetry and channel coding of the stimulus pattern sequences.

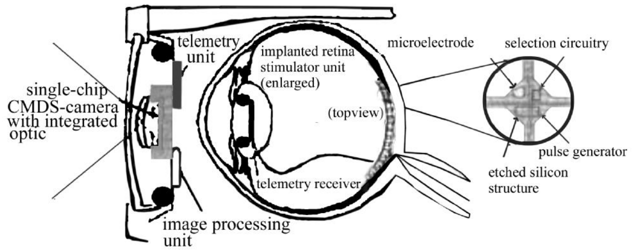

**Figure 4 Architecture of the retina implant system for epiretinal ganglion cell electrostimulation**

The sectional view of physical arrangement of the flexible silicon multielectrode electrostimulator is shown in Figure 5A and the block diagram is illustrated in Figure 5B. It consists of a telemetry receiver, stimulation electronics and the mechanical flexible active silicon multielectrode.

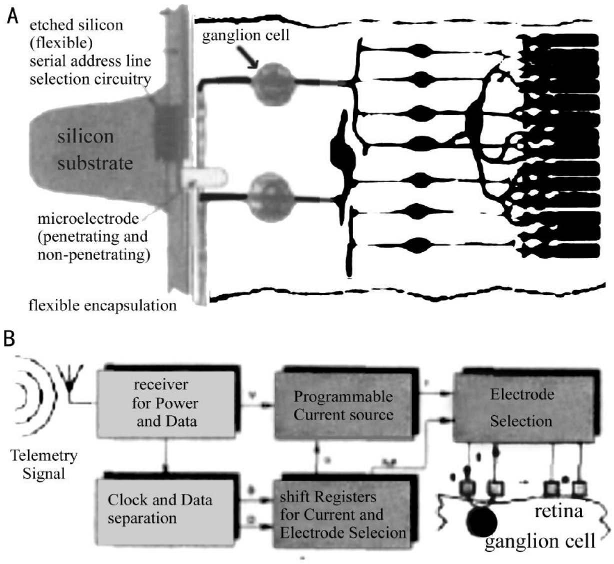

**Figure 5** A: Physical arrangement of the flexible silicon multi-electrode electrostimulator; B:Block diagram of the implantable simulator

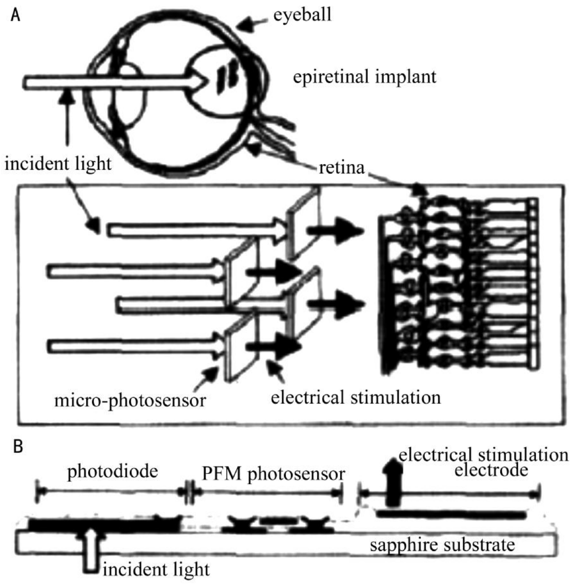

**Figure 6** A: Concept of implantation of epiretinal intraocular prosthesis device;B: Cross section of PFM photosensor

The stimulator electronics has been designed to generate pulses with a programmable pulse width (10-300$\mu$s), pulse polarity (including bipolar pulses), pulse current (10-100$\mu$A), and pulse rate (≤500Hz).

**Back-illuminated PFM photosensor** Uehara *et al*[20] have proposed an intraocular epiretinal prosthesis device using a back-illuminated photosensor. The photosensor, based on a pulse frequency modulation (PFM), was fabricated on a transparent sapphire substrate to detect the backside incident light [20]. Its conceptual drawing of the implantation of the intraocular epiretinal prosthesis device and cross section of PFM photosensor are shown in Figure 6A and Figure 6B.

There are some advantages for choosing PFM over other schemes, such as conventional active pixel sensors. First, PFM photosensors behave similarly to retinal ganglion cells, which is important because retinal ganglion cells are situated in the last layer of neural networks in the retina, and transmit visual data to the visual cortex. Secondly, pulsed stimulation is an effective way of exciting neurons electrically [16], which is achieved simply by PFM. Thirdly, the PFM photosensor is robust against power supply fluctuations and noise, which is a very important factor in implanted devices. Both the photocurrent and the output frequency of the PFM photosensor are proportionate to the incident light intensity over the dynamic range of 30dB of incident light.

In conclusion, to develop an effective epiretinal prosthesis device, the three levels of hierarchy in the sensory systems, namely the receptor organ, sensory pathways and perception, should be taken into account. Accordingly, artificial systems should include a transducer corresponding to the receptor organ, an encoder corresponding to the sensory processing system, and finally an interpreter corresponding to the perceptual functions. For the electrical stimulator device output, it should be characterized by the flexibility of several parameters such as amplitude, pulse width, repetition rate, pulse shape, and so on. As the development of microelectronics, micro- electronic mechanical system (MEMS), material science and electrophysiology, it is promising that such devices are widely used in the near future.

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