

# Visual Prosthesis for Optic Nerve Stimulation

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**Abstract** The C-Sight visual prosthesis is based on optical nerve stimulation with a penetrating electrode array. A silicon-based microprobe by MEMS process techniques and Pt–Ir microwire arrays by electrochemical etching were fabricated in our project. Noise and impedance analyses were applied to optimize the electrode configuration. A multichannel microcurrent neural electrical stimulator and an implantable CMOS-based micro-camera were developed for neural stimulation and image acquisition, respectively, with a DSP-based system processing the captured image. Electrical evoked potentials (EEPs) from rabbit models were recorded using multichannel stainless-steel screws mounted on the primary visual cortex. The mean charge threshold density was  $20.99 \pm 5.52 \mu\text{C}/\text{cm}^2$  considering the exposed surface of the stimulating electrode. Current threshold decreased as the pulse duration of the stimulus increased while the corresponding charge threshold increased. The amplitude of P1 increased when the pulse duration increased from 0.4 to 1.0 ms while the latency of P1 changed little. Experiments also showed that different distribution maps of EEPs were elicited by different pairs of stimulating electrodes. The stimulating electrode pair along the axis of the optic nerve elicited cortical responses with much lower thresholds than that perpendicular to the axis of the optic nerve. The visual prosthesis with stimulating electrodes penetrating into the optic nerve has been validated in animal experiments.

## 1 Introduction

In the past several years, many approaches have been pursued to provide neural electrical stimulation at various positions along the visual pathway, such as the retina [1–4], suprachoroid [5], visual cortex [6, 7], or optic nerve

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[8, 9] to restore the vision of blind patients. One issue [10] with electrically stimulating the visual cortex or retina is that the visual field is represented over a relatively large area, making coverage of the entire visual field nearly impossible with current electrode array technologies. In the visual pathway, the optic nerve is one place where the entire visual field is represented in a relatively small area.

The ultimate goal of artificial vision systems, also known as vision prostheses [10], is to artificially produce visual perception in individuals with profound loss of vision due to disease or injury, that can be used to perform activities for which current assistive technologies have severe limitations. Such activities include reading text, recognizing faces, negotiating unfamiliar spaces, etc. Although the most significant difference between these approaches is the interface to the nervous system, all of them share a common set of components, such as a micro-camera, a visual information extraction and processing system, a power and information transmission system, a neural electrical simulator and electrode arrays [11].

The C-Sight (Chinese Project for Sight) is the first multidisciplinary research project on visual prosthesis in China funded by the Chinese Ministry of Science and Technology under the National Key Basic Research Program (973 Program, 2005CB724300) and by the Science and Technology Commission of Shanghai Municipality (STCSM). The C-Sight project aims at developing an implantable visual prosthesis for optic nerve stimulation by penetrating microelectrode arrays (MEAs) to restore helpful vision for RP (retinitis pigmentosa) and AMD (age-related macular degeneration) patients.

Visual information is transmitted via the optic nerve composed of millions of axons of ganglion cells. Visual phosphenes are created during optic nerve stimulation by cuff or penetrating microelectrode arrays. In 1998, Veraart et al. proved that electrical stimulation of the optic nerve in a 59-year-old volunteer with retinitis pigmentosa could elicit phosphenes. The contact spiral cuff electrode was used in their experiment. However, the spatial resolution of recovered vision was limited because surface stimulating electrodes were used. To improve spatial resolution, penetrating microelectrode arrays are invasively inserted into the optic nerve with endurable tissue trauma. Optic nerve visual restoration by penetrating microelectrode arrays has been verified in our animal experiments. With processing techniques advancing, the size of the microelectrode arrays can be minimized greatly, resulting in reduced optic nerve damage and high spatial resolution.

In the C-Sight project, we proposed specific penetrating microelectrode arrays as the neural interface to transmit the outside encoded electrical stimuli into the optic nerve bundles for visual recovery. Figure 1 shows the schematic diagram of the C-Sight approach and the details are presented in Fig. 2.

The total visual prosthesis was composed of two parts: outside the body and inside the body. In view of Fig. 2, the outer part included image capturing, processing, and transmitting. The surrounding images are captured by a

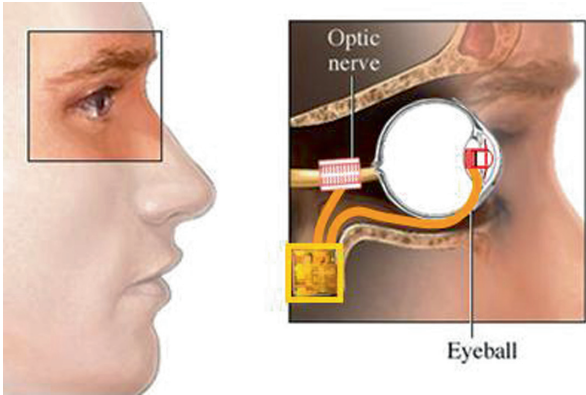


Fig. 1 Optic nerve visual prosthesis using penetrating microelectrode arrays

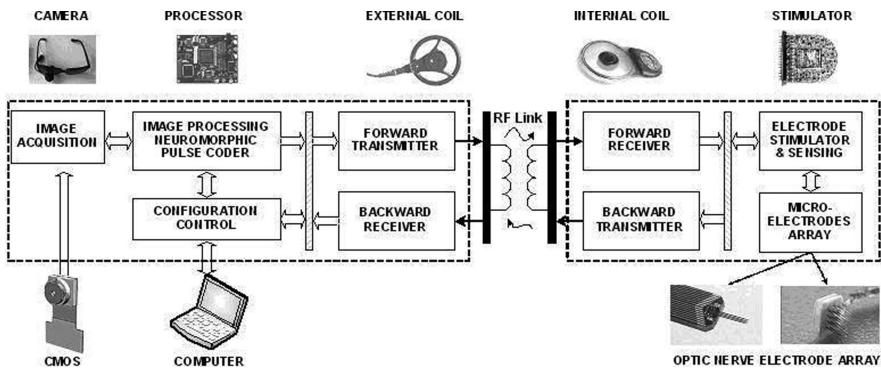


Fig. 2 Block diagram of optic nerve stimulation using penetrating microelectrode arrays

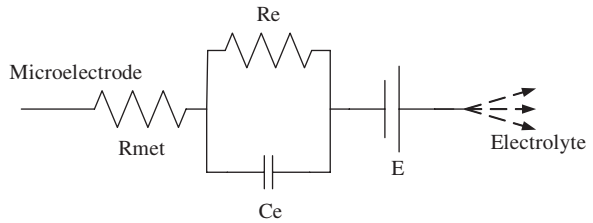
CMOS micro-camera implanted into the lens of the RP or AMD patients. This method will enhance the synchronization between outside images and visual phosphenes compared with the glasses-based image shot. Then, the key features of images are extracted from the original scenes by advanced image processing algorithms and encoded into trains of digital signals with a specific spatiotemporal stimulation pattern. These electrical pulses are forwarded by radio transmission. In the inner part, the internal coil transfers the received radio power and data to the implanted microcurrent stimulator which is electrically connected to the implanted microelectrode arrays. Considering these two parts, the outside images can be transformed into multichannel microcurrent pulses to stimulate the optic nerve where action potentials are generated and conveyed to the visual cortex.

## 2 Penetrating Microelectrode Arrays

The implantable microelectrodes are considered in different ways such as biocompatibility, tissue trauma, uniformity, low cost, and so on. Metal micro-wires and silicon microelectrode arrays are usually selected as the neural interface for neural recording and stimulation. Metal microwires made of stainless steel, tungsten, and platinum/iridium (Pt/Ir) alloy were prevalent in the early stage of neural prosthesis applications. With the development of MEMS (micro-electro-mechanical system) micromachining technique, silicon-based microelectrodes can be fabricated in batches and have satisfactory uniformity, high yield, and low cost. Several different types of MEAs were fabricated in our group.

### 2.1 Noise and Impedance Analyses

The in vivo neural recording or stimulating setup is unavoidably affected by main-frequency disturbance, background noise, and thermal (Johnson) noise of the microelectrode. Disturbance from the main frequency can be eliminated by a shielded cover, and the background noise results from respiration and excitation of thousands of neurons far from the exposed microelectrode sites and closely relates to the animal conditions, and so the thermal noise analysis is detailed here. After the microelectrode was implanted in vivo, the exposed metal sites were electrically related with the physiological saline solution. The equivalent circuit of metal–electrolyte interface [12] was illustrated in Fig. 3.  $R_{met}$  denotes the interconnecting metal wire resistance on the order of tens of ohms, and  $C_e$  and  $R_e$  denote the double-layer capacitance and resistance, respectively.  $E$  is the half-cell voltage at the metal–electrolyte interface.



**Fig. 3** Equivalent circuit of microelectrode–electrolyte interface

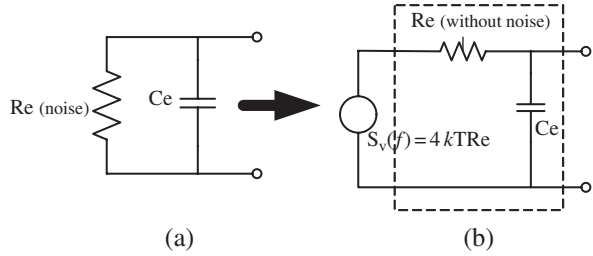
According to Fig. 3, thermal noise was dominated by  $R_{met}$ ,  $R_e$ – $C_e$  network.  $R_{met}$  and the resulted PSD (power spectral density) of thermal noise were shown in equations (1) and (2), respectively.

$$R_{met} = \rho \times \frac{L}{S} \quad (1)$$

$$S(f) = 4kTR_{met} \quad (2)$$

where  $k(= 1.38 \times 10^{-23} \text{ J/K})$  is the Boltzmann's constant,  $T$  is the absolute temperature with the unit of Kelvin,  $\rho$  is the metal resistivity,  $L$  is the connecting wire length of several millimeters, and  $S$  denotes the cross-section area. The thermal noise from the small-value metal resistance  $R_{met}$  is neglected. Therefore, the noise is mainly produced from Re–Ce network shown in Fig. 4.

Figure 4(a) shows the practical parallel network of resistor and capacitor,



**Fig. 4** Noise-analysis model of Re–Ce network

and Fig. 4(b) is the equivalent noise model of this network considering thermal noise from Re. The dashed-line block denotes the ideal network. PSD of Re and the transfer function  $h(f)$  are, respectively, expressed in equations (3) and (4), PSD of the output terminals  $S_{out}(f) = S_v(f)|h(f)|^2$  is shown in equation (5), and the total noise  $P_{n,out}$  within the total frequency range is shown in equation (6)

$$S_v(f) = 4kTRe \quad (3)$$

$$h(f) = \frac{1}{1 + j2\pi f Re Ce} \quad (4)$$

$$S_{out}(f) = \frac{4kTRe}{1 + 4\pi^2 Re^2 Ce^2 f^2} \quad (5)$$

$$P_{n,out} = \int_0^{\infty} S_{out}(f) df = \frac{kT}{Ce} \quad (6)$$

The unit of  $kT/Ce$  is  $V^2$ .  $(kT/Ce)^{1/2}$  is the equivalent noise voltage with units of Vrms. It was clear that the equivalent noise voltage of the Re–Ce network within the total frequency range was in inverse proportion to  $Ce$ . With settled temperature, increasing  $Ce$  can reduce thermal noise voltage, which means increasing the site area of the multichannel microelectrode with planar metal sites exposed. At body temperature of 310 K, the equivalent thermal noise voltage at the total frequency range was 65.4  $\mu\text{Vrms}$  with  $Ce$  of 1 pF.

Thermal noise analyses resulted in the size selection of the exposed planar site, and the impedance  $Z$  was mainly determined from  $\text{Re}$  and  $\text{Ce}$  in equation (7).

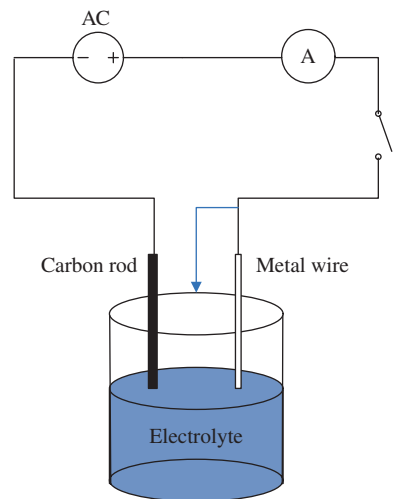
$$Z = \frac{\text{Re}}{1 + j2\pi f \text{ReCe}} \quad (7)$$

In view of equations (6) and (7), low thermal noise means large signal-to-noise ratio (SNR), large site size, low impedance, and low spatial resolution.

Microelectrodes for neural stimulation possessed satisfactory charge transmission ability and large double-layer capacitance resulting in low impedance of several to tens of  $\text{k}\Omega$ . Meanwhile the selectivity was affected, so the exposed site area must be compromised to satisfy the requirements of low thermal noise or high-sensitivity and high-spatial resolution or high selectivity.

## 2.2 The Tungsten Shafts

Tips of the implanted tungsten microwires were electrochemically etched with a tungsten probe as the working electrode (anode) and a carbon rod as the counter electrode (cathode). A 1 mol/l NaOH solution was used as the electrolyte. The experiment setup included a voltage power source, a switch, an ammeter, and an electrochemical cell with a pair of electrodes as shown in Fig. 5. The applied AC voltage was 50 Hz of frequency and 6 V of amplitude. After shaping a certain taper, the probe was insulated by Teflon and a 200  $\mu\text{m}$ -long tip was exposed. The impedance characteristics were measured by the Precision LRC Meter Agilent

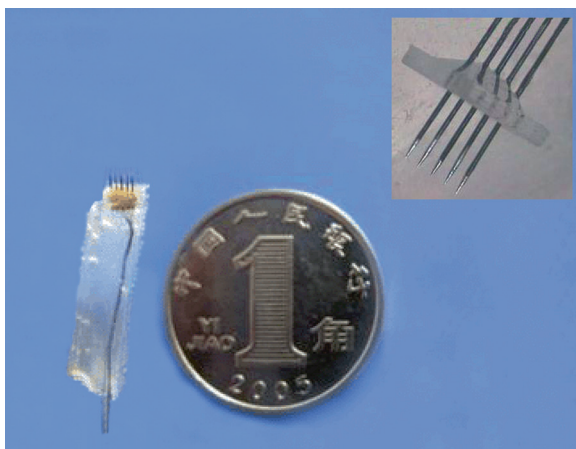


**Fig. 5** Electrochemical etching setup

E4980A with a three-electrode method at room temperature. The typical impedance at 1 kHz was 10 k $\Omega$ .

Five microelectrodes were mounted on a 0.4-mm-thick plastic pedestal. The size of the pedestal was 2.5 mm long and 1.5 mm wide with the electrodes spaced 275  $\mu\text{m}$  apart from the center. The shaft of the electrodes was 100  $\mu\text{m}$  in diameter with one end etched electrolytically to a penetrating cone-shaped tip with an included angle of 15° and the radius of curvature of 0.5–0.7  $\mu\text{m}$ . This microelectrode array had a height of 0.5  $\mu\text{m}$ . The electrode was insulated with Teflon with the tip exposed to yield a surface area of  $3155 \pm 100 \mu\text{m}^2$ . The lead cables were enameled wires and were connected to a 6-pin connector. The electrode array was encapsulated with medical grade silicon gel in an innovative designed mold, which was hemispheroidal with a 3-mm-wide and 2-mm-deep notch across the axis on the surface of the mold. The radius of the hemispheroid was 12 mm in accordance with the size of the human eye ball (Fig. 6). Due to the non-stable physical and chemical characteristics of tungsten material, the microelectrode array based on tungsten microwires was only for acute experiment purposes.

**Fig. 6** Five probes were mounted on the substrate with the enameled wire connected individually: the zoom-in penetrating microprobes were shown in the upper right corner



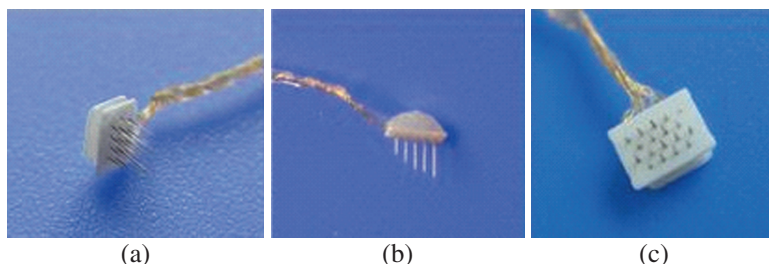
### 2.3 The Pt/Ir Alloy Shafts

In order to improve the biocompatibility and biostability of the implanted microelectrode array, noble metals platinum, and iridium were considered as the stimulating metal material. With the addition of iridium, hardness can be enhanced for optic nerve penetration. The Pt/Ir microelectrode arrays were also selected in our lab.

Different kinds of FMAs (floating multielectrode arrays) were customized by Micro-Probe Incorporated in the United States in the optic nerve stimulation



experiment. The lengths of microprobes ranged from 0.80 mm to 1.50 mm, and the impedance was 10 k $\Omega$  at 1 kHz shown in Fig. 7(a). Figure 7(b) shows the  $1 \times 5$  electrode array (100% Ir) with the probe lengths steeply increasing from 0.90 mm to 1.50 mm, and the exposed tip length of 100  $\mu\text{m}$ . Each shaft had an impedance of 10 k $\Omega$ . Figure 7(c) shows the 16-shaft FMA (70%Pt-30%Ir) with the shaft length of 0.2 mm and per-shaft impedance of 20 k $\Omega$ .



**Fig. 7** (a) Thirteen probes with length from 0.80 mm to 1.50 mm; (b) five probes with length from 0.90 mm to 1.50 mm; (c) sixteen probes with the same length of 0.2 mm

## 2.4 Silicon-Based Microelectrode Arrays

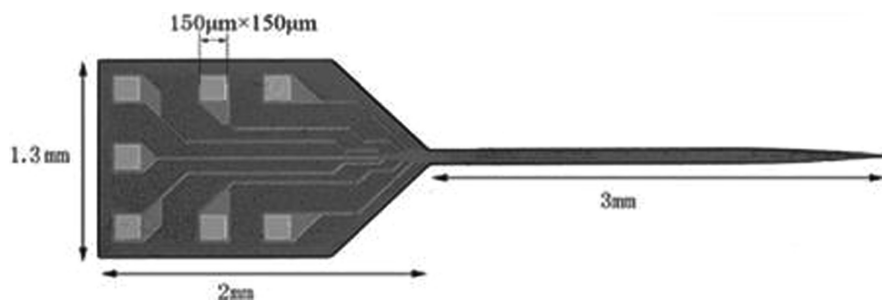
With the development of the MEMS (micro-electro-mechanical system) micro-machining technique, silicon-based microelectrodes can be fabricated in batches and have satisfactory uniformity, high yield, and low cost. The silicon microelectrodes bear relatively good flexibility and mechanical strength compared with silicon/silicon dioxide ones [13, 14]. Si (silicon), SiO<sub>2</sub> (silicon dioxide), and Si<sub>3</sub>N<sub>4</sub> (silicon nitride) are biocompatible with biological tissue and suitable for in vivo application [15]. As a result, silicon-based microelectrodes have attracted much interest in recent years. Two- or three-dimensional silicon microelectrodes have been fabricated [13–16] in Michigan and Utah. The silicon microelectrodes or microprobes can be fabricated based on a single-crystal silicon or SOI (silicon-on-insulator) wafer. Based on the single-crystal silicon substrate, a deep p<sup>++</sup> boron diffusion process is usually included to determine the outline of the silicon microelectrodes with higher concentration grades between the p<sup>++</sup> layer and the silicon substrate. This presents rigid requirements for the diffusion process. In contrast, based on the SOI wafer, the top silicon or silicon device layer determines the thickness of the silicon microelectrode with precisely controlled uniformity. Besides, the buried SiO<sub>2</sub> layer is an etch stop while releasing the microelectrode.

The original SOI wafer was manufactured by bonding a top silicon layer of 15  $\mu\text{m}$ , a buried silicon dioxide layer of 1  $\mu\text{m}$ , and a bottom silicon layer of 500  $\mu\text{m}$ . The fabrication process is detailed as follows: (a) Lower 3000  $\text{\AA}$  silicon nitride was deposited on the SOI wafer by plasma-enhanced chemical vapor deposition (PECVD) to electrically separate the top silicon from the SOI wafer and metal connecting wires; (b) Lower titanium/gold (Ti/Au) of 1000  $\text{\AA}$ /3000  $\text{\AA}$



was sputtered on the lower silicon dioxide and patterned as conductor traces by diluted buffered oxide etching (BOE) and gold corrosive, respectively. Then the probe was annealed at  $380^{\circ}\text{C}$  for 40 min; (c) Upper  $3000\text{\AA}$   $\text{SiO}_2$  was deposited by plasma-enhanced chemical vapor deposition to insulate the metal layer from the tissue solution. (d) The upper  $\text{SiO}_2$  layer was etched by BOE to open  $\Phi$ -6  $\mu\text{m}$  contact holes near the tip and bond pads at the rear. (e) According to step (b), seven  $\Phi$ -10- $\mu\text{m}$  circular recording sites were formed with the central space of 120  $\mu\text{m}$ . (f) Thick photoresist was used as the mask layer, and the horizontal architecture of the microelectrode was determined by an ICP (inductively coupled plasma) dry etching process technique. (g) The wafer was thinned to 200  $\mu\text{m}$  by physical ablation of the bottom silicon and adhered to a glass plate by black wax. Then the wafer could be further thinned to 50  $\mu\text{m}$  by BOE solution. (h) The wax was removed and the top side of wafer was protected and adhered to another silicon wafer by photoresist. The bottom silicon layer of the wafer was plasma dry etched using gas  $\text{SF}_6$ . Because of the low selectivity ratio between silicon and silicon dioxide, the buried silicon dioxide layer was removed at the same time. Consequently, the individual silicon microelectrodes were completed after performing photoresist-removing techniques using acetone.

Figure 8 shows the silicon microelectrode. The released microelectrode is shown in Fig. 9.



**Fig. 8** The top view of silicon-based MEAs after ICP etching: single probe with seven sites



**Fig. 9** The released SOI-based silicon microelectrodes

According to Figs. 8 and 9, seven bond pads corresponding to seven different recording sites are clearly shown with the lateral dimensions marked. The probe shank is 3 mm long and 100  $\mu\text{m}$  wide, and the seven recording sites are located in the center of the shank within the range of 1 mm from the tip. Since the shank is narrowed down like a sharp-edged sword near the tip, it is able to penetrate into the optic nerve with the tip angle of  $6^\circ$ .

### 3 Neural Electrical Stimulator

Some electrical stimulators for chronic pain treatment use battery power and rely on repeated surgery to replace the battery. Alternatively, it is possible to power implants without a physical connection by using an inductive link, in which current through a primary coil driven by a signal and energy source induces current in a secondary coil [16]. In this design, the external and internal parts exchange information by radio frequency (RF) telemetry.

The neural stimulator consists of three main parts: the communication unit, the processing and control unit, and the electrode driver unit. Figure 10 is the schematic architecture of the micro-stimulator.

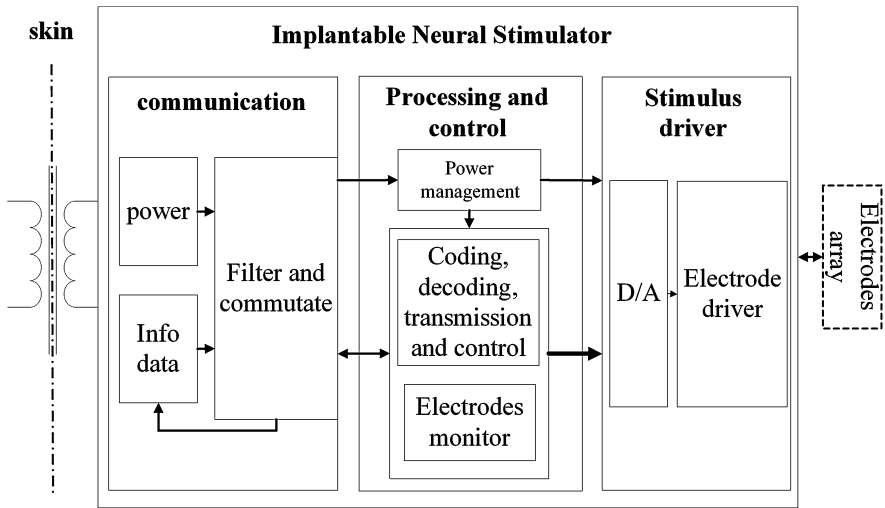


Fig. 10 Schematic architecture of the neural electrical stimulator

#### 3.1 Communication Unit

The communication unit receives power and data signal packets. Similarly, when the state information of electrode arrays is needed, the state packets are sent out by this unit too.

A high-efficiency Class-E amplifier is used to transmit power to the internal unit. The power is generated by the induced RF signal. The voltage swing of the

induced signal is as high as the need of the stimulator. Therefore, the signal must be rectified and regulated before it is delivered to the other parts of the stimulator.

The control data and stimulus information are provided by the external part. The valid packets in the system protocol include synchronization, start, data, and end packets. The basic format of each packet is: the start bit (1bit, 0), the information bits (8bits, include control and data information), the end bit (1bit, 1). The data packet format follows the format shown in Fig. 11.

|         |     |                    |          |             |   |                         |   |   |   |   |
|---------|-----|--------------------|----------|-------------|---|-------------------------|---|---|---|---|
| Sync1   | 0   | 1                  | 0        | 1           | 0 | 1                       | 0 | 1 | 0 | 1 |
| Sync2   | 0   | 1                  | 0        | 1           | 0 | 1                       | 0 | 1 | 0 | 1 |
| Start   | 0   | 1                  | 0        | 1           | 0 | 1                       | 0 | 0 | 1 | 1 |
| Data1_1 | 0   | SubBoard<br>Select | Continue | Reservation |   |                         |   |   |   | 1 |
| Data1_2 | 0   | DAC Select         |          |             |   | SubBoard Channel Select |   |   |   | 1 |
| Data1_3 | 0   | DATA               |          |             |   |                         |   |   |   | 1 |
| ...     | ... |                    |          |             |   |                         |   |   |   |   |
| End     | 0   | 0                  | 0        | 0           | 0 | 0                       | 0 | 0 | 0 | 1 |

**Fig. 11** Data packet format for the stimulator

As we all know, the information after image acquisition and processing is transferred from the external part to the internal stimulator according to the format of the frame. Each frame will consist of many data packets. If the continue bit is set to 1, it means the process of transmission needs transfer control and data information continuously. After finishing the transmission of information of one frame, the end packet will be added in the transmitting sequence. It shows the system has finished the transmission of one frame image. If we want to transfer the next frame, the synchronization packets should be sent over again.

### 3.2 Processing and Control Unit

The processing and control unit shown in Fig. 12 is responsible for managing power, coding, decoding data information, and monitoring the state of electrode array. Considering the feasibility of integration, the main function of the processing and control unit is implemented based on FPGA.

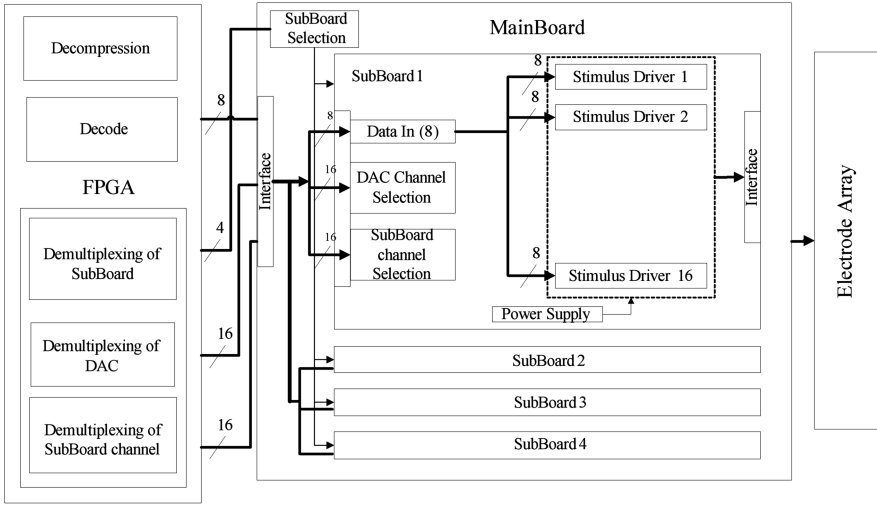


Fig. 12 Schematic of the main control circuit

The parameter collector also measures power supply voltage, electrode resistance, interference between electrodes, and other important internal parameters. These messages can be transmitted back to the outer controller by the reverse data transmission module. This part of the function is under research and development.

### 3.3 Electrode Driver Unit

The electrode driver unit converts digital signals into analog signals by a digital analog converter (DAC) and supplies biphasic current pulses of variable amplitudes and durations to the electrode array with penetrating electrodes.

Because the design style of the subboard and mainboard is used in the electrode driver unit, four subboards are plugged into four slots on the mainboard vertically. On each subboard, there is one DAC which has a 16-channel output and two octal SPST switches which are used to control which electrode is selected. Therefore, we need to design the circuit to control 64 electrodes aggregately. The schematic of the electrode driver unit is shown in Fig. 13.

To avoid stimulation current flowing to other electrodes freely, it is necessary that only two electrodes generate stimulation current every time. Besides, the accumulation of charge would induce a permanent injury in human tissues. According to the experiment results of Claude Veraart et al. [17, 18], stimulation based on the optic nerve needs biphasic current pulses. Therefore, two-phase pulse stimulation is adopted to balance the total charge. Fig. 14 shows the current stimulation pulses.

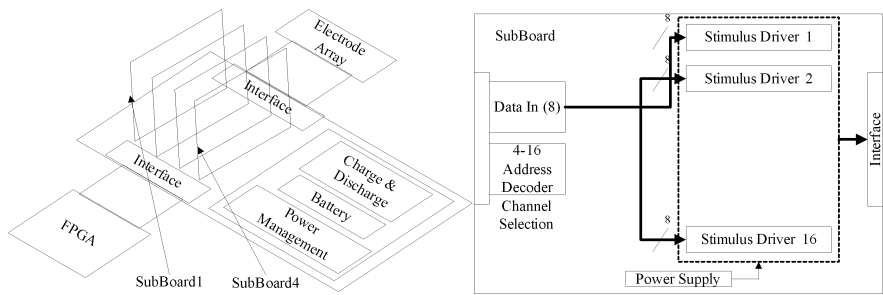


Fig. 13 Schematic of electrode driver unit

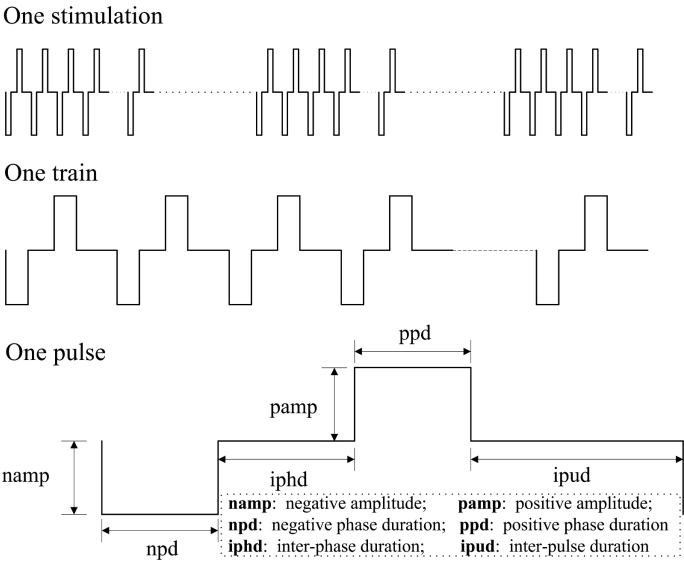


Fig. 14 Current stimulation pulses

The design is capable of controlling the electrode driver with the style of subboard and mainboard to generate biphasic current, from several  $\mu\text{A}$  up to several  $\text{mA}$  variable amplitudes, from tens of microseconds ( $\mu\text{s}$ ) up to hundreds of microseconds ( $\mu\text{s}$ ) in pulse duration and single or multiple pulses train. In the project, the main control unit uses FPGA to realize the decompression, coding, decoding, and demultiplexing control. In our design, it can offer single pulse or multiple pulse sequences which vary in range from  $10\ \mu\text{A}$  to  $4\ \text{mA}$  current amplitudes, from  $25$  to  $400\ \mu\text{s}$  duration, from  $40$  to  $350\ \text{Hz}$  frequency, etc. Due to the use of demultiplexing, we cannot give the  $64$  electrodes stimulus signal simultaneously. As in many imaging systems, for perceiving a continuous image, the retinal stimulation needs to be above a specific rate in order to

achieve flicker-free vision. The threshold stimulation rate above which the image appears continuous is between 40 and 50 Hz [19]. This parameter provides the opportunity to demultiplex one output from DAC to drive multiple stimulus drivers.

### 4 Image Acquisition and Processing

The visual information processing system is a very important portion of the application of the visual prosthesis. It is necessary to research and develop the hardware of the image processing system dedicated to visual prostheses as well as the image processing strategies applying to visual prostheses.

From Figs. 2 and 15, it is clear that the micro-camera and image processor are absolutely essential parts of visual prosthesis in our project.

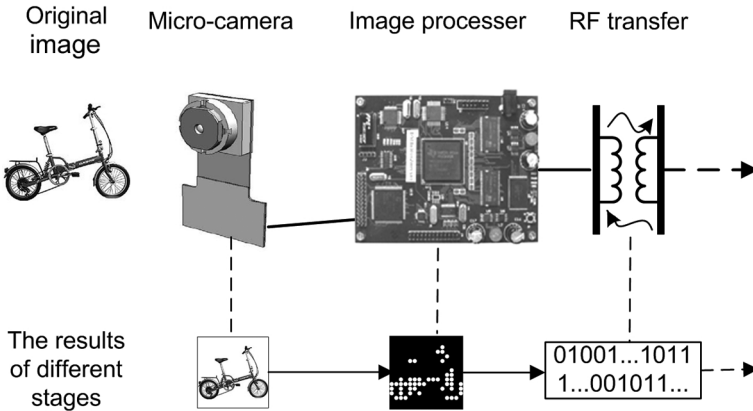


Fig. 15 Schematic of image acquisition and processing system

#### 4.1 Image Acquisition

As the prosthesis will be implanted into the human eye, all the components should be small in size with low weight and low power dissipation. A number of image acquisition devices or mini-cameras are available and suitable for this application, such as charge-coupled device (CCD) or complementary metal-oxide semiconductor (CMOS) cameras. Although a CMOS camera is more susceptible to noise and has lower light sensitivity than CCD, it is more suitable for implantable visual prosthesis applications with some crucial features, such as lower power dissipation, small size, and camera-on-a-chip integration. Based on such reasons, the OV6650FS (Omnivision Co.) was chosen as the photo-

sensor in our image acquisition system, for it is the smallest CMOS camera on the market and has relatively low power dissipation. As the former research mentioned, Stiles et al. have found that only 625 pixels are enough for object recognition by blind people [20]. Therefore, the resolution of CIF ( $352 \times 288$ ) of OV6650FS is enough for a visual prosthesis prototype.

4.2 DSP-Based Image Processing System

4.2.1 Hardware of Image Processing System

Image real-time processing is necessary in visual prostheses. The digital signal processor, due to strong operation capability and its special soft and hard structure, has been widely used in image processing. The computational complexity for the algorithms which can be applied to visual prostheses is very high, so our image processing system is based on TMS320DM642. It has a VLIW architecture which is a highly parallel architecture in which multiple instructions are executed per cycle, making it an excellent choice for visual image processing application.

Figure 16 shows our image processing system designed for visual prostheses, which consists of a digital signal processor (DSP), a synchronous dynamic random access memory (SDRAM), a FLASH, an advanced RISC machine (ARM), a special memory, an adjusting circuit, a data transmit interface, a data receive interface, and a power management.

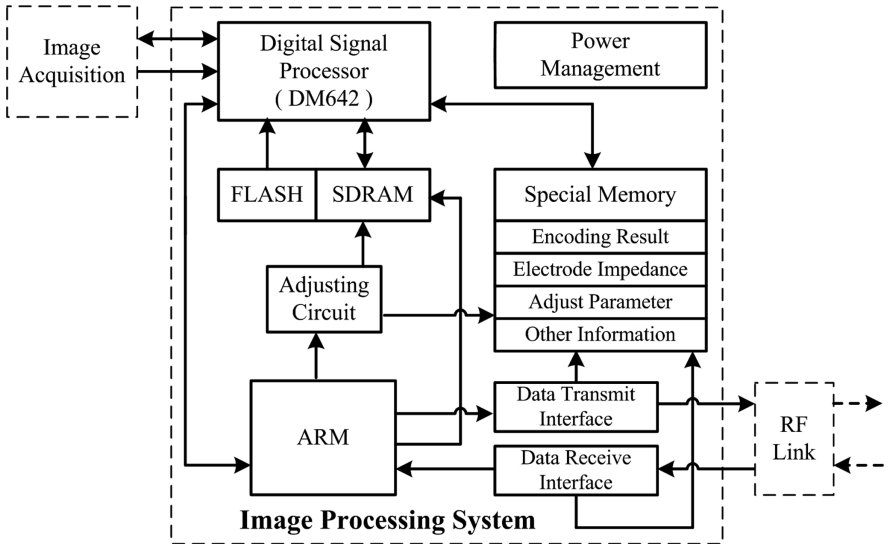


Fig. 16 Image processing system designed for visual prostheses



The DSP connects with the image acquisition system. It receives the image information from the image acquisition system and takes charge of the main functions of image processing, such as information reduction, extracting, encoding, and so on. The ARM connects with the DSP. It has a high ability of controlling the transmission of the information in the image processing system. SDRAM stores the image information with the specific format which was received from the image acquisition system. The special memory deposits the encoding results, electrode information, adjust information, as well as other information at the different addresses. The FLASH connects with the DSP. The program of the image processing strategies for the visual prostheses is stored in the FLASH. The adjusting circuit is used to emendate the image information deposited in the SDRAM and improve the image quality. The power management is in charge of offering the power supply to the whole image processing system.

4.2.2 Image Processing Strategies

The image processing strategies are the most important part of the software design in our system. These strategies are used in the flow of whole image processing. As Fig. 17 shows, the original images are acquired by the camera and sent to the DSP (digital signal processor) for the pre-processing. After that,

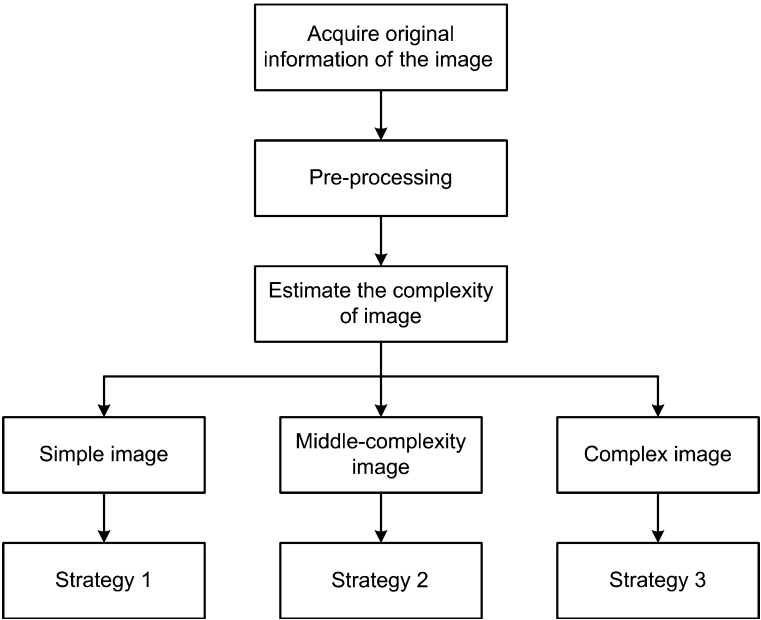
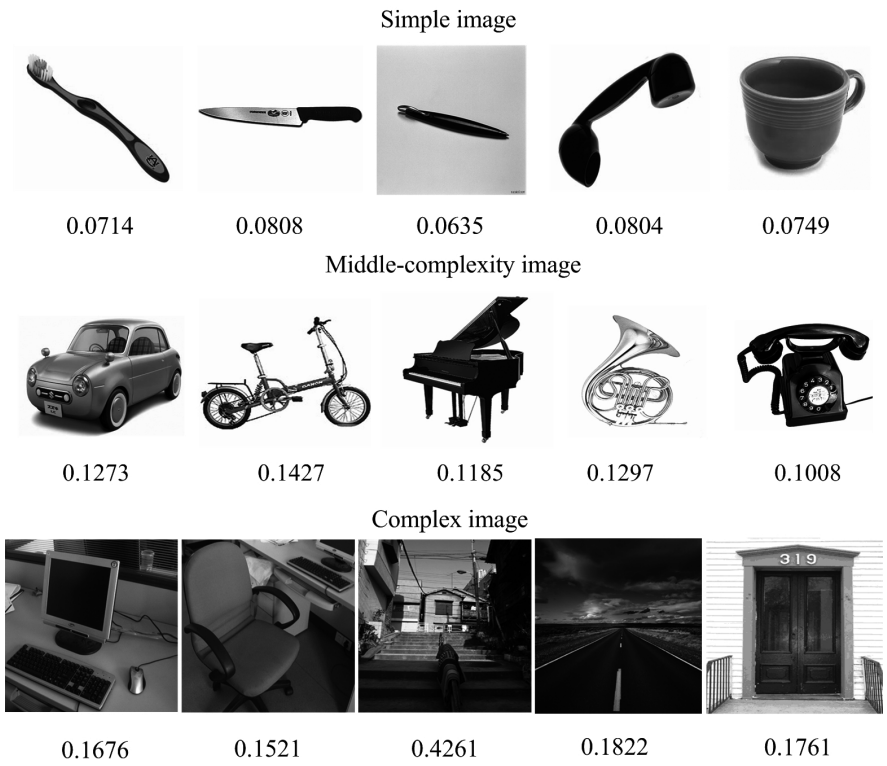


Fig. 17 Schematic of image processing strategies

the images will be classified according to complexity: simple images, middle-complexity images, and complex images.

Image Classification

The first key issue of image processing strategies is image classification. The approach is to use simple and effective mathematic methods to calculate and get an eigenvalue of image, then classify the different images according to this value. Based on former research, there are several methods to estimate the complexity of an image, such as local gray complexity [21], template [22], and two-dimensional C0 complexity [23], etc. Different measures can be adapted to process surrounding images in the daily life of blind patients. According to the analysis of comparative results, the method of two-dimensional C0 complexity gave the better distinction. Figure 18 shows the complexity of different object and scene images using the two-dimensional C0 complexity method.



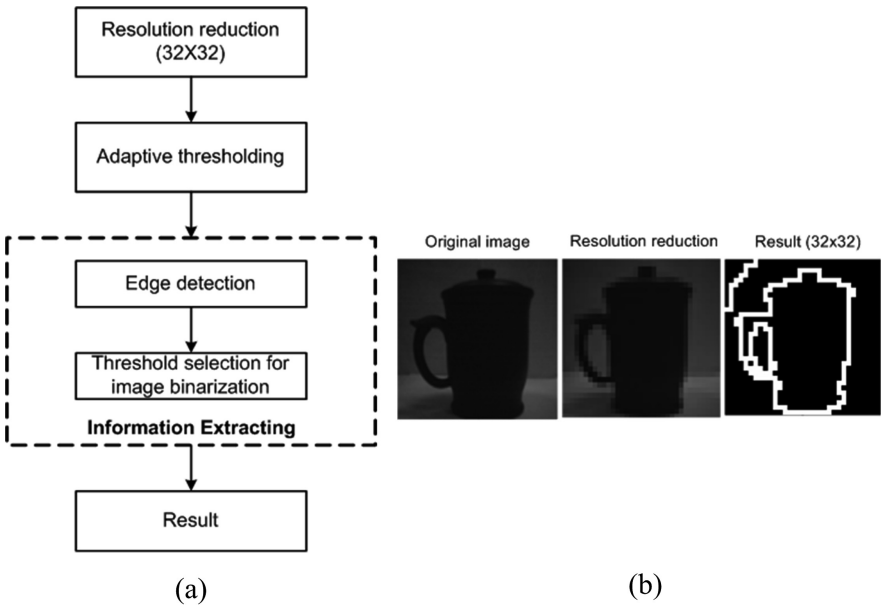
**Fig. 18** The complexity of different object and scene images using two-dimensional C0 complexity method

Different Image Processing Strategies According to Various Complexities

For different images, various image processing strategies are used to reduce the computation. If the simple strategy cannot get a better result, the image processing system will use a more complex processing strategy automatically.

(A) Strategy 1: Simple Image

Simple images include simple objects, characters, or words. As we can see in the Fig. 19, using the image reduction arithmetic reduced the original  $288 \times 288$  image to  $32 \times 32$  directly. The adaptive threshold binary method was applied to the simplified image. Then, four orientation kernels were used to extract the useful information. Finally the result ( $32 \times 32$  binary images) can be gotten after then edge detection process of the binary image.

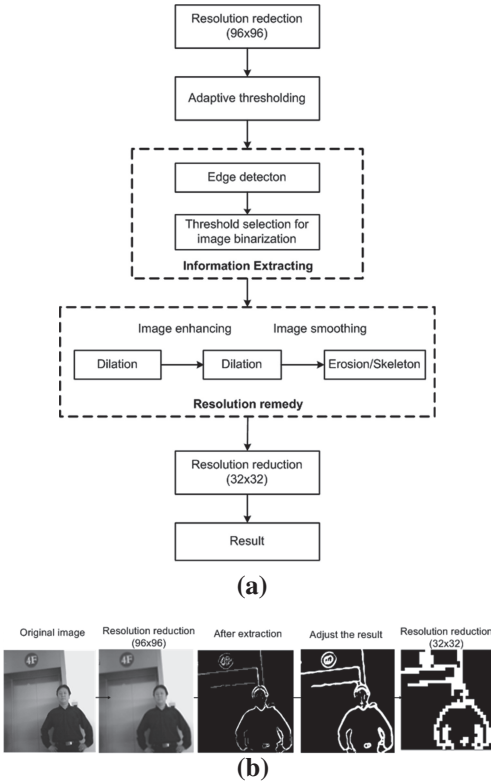


**Fig. 19** Strategy 1: (a) schematic of simple image processing strategy and (b) a series of results for different processing steps

(B) Strategy 2: Middle-Complexity Image

The middle-complexity images include more complex objects and simple scenes. Figure 20 shows the Strategy 2 for a middle-complexity image. After the estimation of complexity, the images ( $288 \times 288$ ) were reduced to  $96 \times 96$ . Then, the useful information was extracted from the pixelized image (using the method which was mentioned in Strategy 1). Some morphological operations like

**Fig. 20** Strategy 2:  
(a) schematic of middle-complexity image processing strategy and (b) a series of results of different processing steps

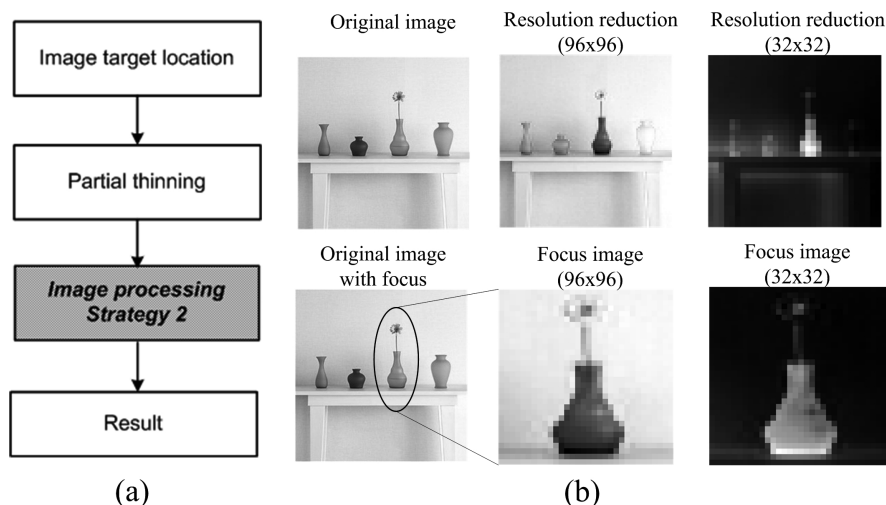


dilation, erosion, as well as a skeleton were used to enhance and mend the images. A process of erosion was executed which focuses on depressing the affection of noise and false contour. A skeleton was very useful in processing images of words. In the end, the results were regulated or reduced to  $32 \times 32$ .

(C) Strategy 3: Complex Image

Complex images will be the real objects and scenes we meet in daily life. It is hard to get satisfactory results when we use simple processing methods such as Strategy 1 and 2. Therefore, it is necessary to select the most important or interesting region (called focus of attention – FOA) as the focus. Then, Strategy 2 is used to process this region (focus image) to get satisfactory result. Figure 21 shows the schematic of Strategy 3.

To sum up, due to the limited electrode numbers and existing techniques, it will be difficult to increase the pixel number for the actual visual prosthesis, and only low-resolution image information can be transmitted to the brain. Therefore, currently the goal of visual prostheses is not to regenerate detailed vision, but to provide visual perception that is useful for blind individuals to perform common daily tasks such as text reading, facial recognition, and unfamiliar



**Fig. 21** Strategy 3: (a) schematic of complex image processing strategy and (b) a series of results for different processing steps and focus image

environment navigation. In the near future, with the development of technology and improvement of relative theories, the function of visual prostheses will be perfected to satisfy more requirements of blind people in their normal lives.

## 5 Psychophysical Study for Visual Prosthesis

The brain is able to function only if it is provided with sufficient information. Using visual prostheses, what the patients will see are pixelized images. Due to limited numbers of microelectrodes, the images are of low resolution which largely impairs the development of visual prostheses. To restore functional vision, we must know the minimum requirements that the brain needs.

Psychophysical experiments using simulated prosthetic vision can provide the minimum requirements of visual prostheses to realize certain tasks. These experiments simulate scenes of daily life in normal sighted people. Simulated experiments can control individual variables and experiments can be repeated on specific subjects. Many parameters could be adjusted in a large range. The psychophysical experiment on simulated prosthesis vision is an important way to study the minimum information requirement. The importance of simulated experiments has been proved by the success of multichannel cochlear implants.

Several groups all over the world have carried out such simulated experiments on different aspects as pixelized reading [24–26], human face recognition [27, 28], eye–hand coordination [27, 29], and movement [30].

Our team conducted some simulated experiments on normal sighted people to study the recognition of pixelized Chinese characters [31] and pixelized images in daily life. We also studied the positioning of simulated phosphenes based on psychophysical experiments [32].

## ***5.1 Recognition of Chinese Characters with a Limited Number of Pixels***

Visual prosthesis is based on point-to-point interconnection between stimulating microelectrode contacts and neural elements. The image captured by the camera is translated into electrical signals and then delivered by bypassing regions of the malfunctioned visual pathways. What the subjects “see” is a pixelized image, and a limited number of microelectrodes result in low resolution.

Most previous studies of pixelized reading focused on reading speed with Latin words as the experimental objects, while little attention has been paid to the reading and recognition of Chinese characters.

In order to acquire systematical knowledge about the optimal and economical recognition of pixelized Chinese characters with limited numbers of pixels, we conducted two phases of experiments.

### **5.1.1 Recognition Accuracy of Pixelized Chinese Characters Using Simulated Prosthetic Vision**

We used the first set of GB 2312-80 International Standard Code promulgated by the Standardization Administration of China as our experimental character set. A self-developed platform, HanziConvertor with digital image processing capacities was developed to convert original Chinese characters into pixelized optical stimulus.

Three experiments were carried out to study the discernible differences among the classes of pixel numbers, the character typefaces and stroke numbers in recognition of Chinese characters, respectively.

The subjects were asked to identify the pixelized images and wrote down the recognizable characters as quickly as they could. If the characters could not be identified, the subjects should write down “X”. The results were recorded and compared with the original characters saved in advance.

It was found that the pixel number is the crucial factor that determines the accuracy of recognition. The accuracy rises constantly with the array size. The accuracy of the pixel array size  $6 \times 6$  is nearly zero. Nearly all the characters sampled in size of  $6 \times 6$  were indecipherable except for several characters with very few strokes. In size of  $8 \times 8$  or  $10 \times 10$ , the recognition accuracy increases rapidly, and reached nearly 50%. When pixel number was  $12 \times 12$ , all the subjects could identify every character without error.

The four tested fonts were set as Fangsong Ti, Hei Ti, Kai Ti, and Song Ti, respectively. When Song Ti and Hei Ti were applied, the recognition accuracy was higher compared to the other two fonts, Kai Ti and Fangsong Ti. Especially in the pixel array size of  $10 \times 10$ , the disparity was obvious. It was mainly because Song Ti and Hei Ti occupy much more space than the other two fonts with the same pixel sizes.

We also found that the complexity of each character, measured by the number of strokes it contains, affected the recognition accuracy. Characters

with 1–4 strokes were identified correctly in all kinds of pixel array sizes, while satisfactory recognition accuracy of characters with 5–8 strokes could be achieved when pixel size was larger than  $8 \times 8$ . As for characters with more than nine strokes, only  $12 \times 12$  arrays were able to provide enough information for the subjects. When pixel size was lower than  $12 \times 12$ , the recognition accuracy decreased as the number of strokes increased.

### 5.1.2 Recognition of Chinese Characters with a Limited Number of Pixels Based on Complexity Analysis

All the information that the visual prosthesis translates and processes is based on the image captured by the camera. The stroke number of Chinese characters is not a clear conception for vision prosthesis. In view of the calculation speed and the applicability, the black pixel statistic algorithm was chosen in the study.

The 631 most commonly used Chinese characters were classified into six groups based on black pixel statistic algorithm complexity (0–0.16, 0.16–0.20, 0.20–0.24, 0.24–0.28, 0.28–0.32, and 0.32–0.36) as experimental characters set. Hei font was chosen in our experiment to minimize any unexpected confounding effects.

The experiment was performed in a quiet and dark room to shield from ambient light. The setup included a DSP-based embedded system, a head-mounted display (HMD) with an experimental software package developed by our team written in the C++ language. The pixelized images of Chinese characters with different resolutions ( $6 \times 6$ ,  $8 \times 8$ ,  $10 \times 10$ , and  $12 \times 12$ ) were rendered on a head-mounted display screen (Fig. 22).



**Fig. 22** The experimental scene of recognition of Chinese characters with a limited number of pixels: it was performed in a quiet and dark room to shield from ambient light. The pixelized images of Chinese characters with different resolutions ( $6 \times 6$ ,  $8 \times 8$ ,  $10 \times 10$ , and  $12 \times 12$ ) were rendered on head-mounted display screen

The complexity of the 631 most commonly used Chinese characters was evaluated by the black pixel statistic algorithm. The mean complexity and the number of Chinese characters with stroke numbers from 1 to 16 can be found in (Table 1). In general, Chinese characters with a high number of strokes will be more complicated than those with fewer strokes. Mean complexity increases gradually with the increase of the stroke number. The complexity rises rapidly when the stroke number is less than 4. From 4 to 16 strokes, the rate of rise slows down.

The mean recognition accuracy of Chinese characters is  $98.29 \pm 2.04\%$ ,  $91.98 \pm 7.56\%$ ,  $69.75 \pm 24.80\%$ , and  $28.40 \pm 27.97\%$  for  $12 \times 12$ ,  $10 \times 10$ ,  $8 \times 8$ , and  $6 \times 6$  pixels arrays, respectively, regardless the complexity of the characters.

The results indicate that the mean recognition accuracy increases with the increase of the pixel array number. The binary pixel arrays  $10 \times 10$  and  $12 \times 12$  are sufficient for recognition of Chinese characters, so that more than 90% of experimental samples can be identified correctly. A result of less than 30% of experimental samples identified correctly for  $6 \times 6$  pixel arrays indicates that  $6 \times 6$  pixel arrays are not suitable for recognition of Chinese characters. The pixel arrays  $8 \times 8$  are the threshold, with about 70% of characters identified correctly. As to our expectation, the mean recognition accuracy decreased with the increase of complexity for a given pixel array number. The more complicated a character is, the more difficult it is for a subject to identify.

## ***5.2 Image Processing Based Recognition of Images with a Limited Number of Pixels***

The purpose of this study was to investigate the primary factors in recognition of images of common objects and scenes and optimize the recognition rate on low resolution using image processing technologies. Two image processing methods (“threshold-binarization” images and “edge” images) and two kinds of pixel arrays (square pixel array and circular pixel array) were adopted in different image arrays, respectively ( $8 \times 8$ ,  $16 \times 16$ ,  $24 \times 24$ ,  $32 \times 32$ ,  $48 \times 48$ , and  $64 \times 64$ ).

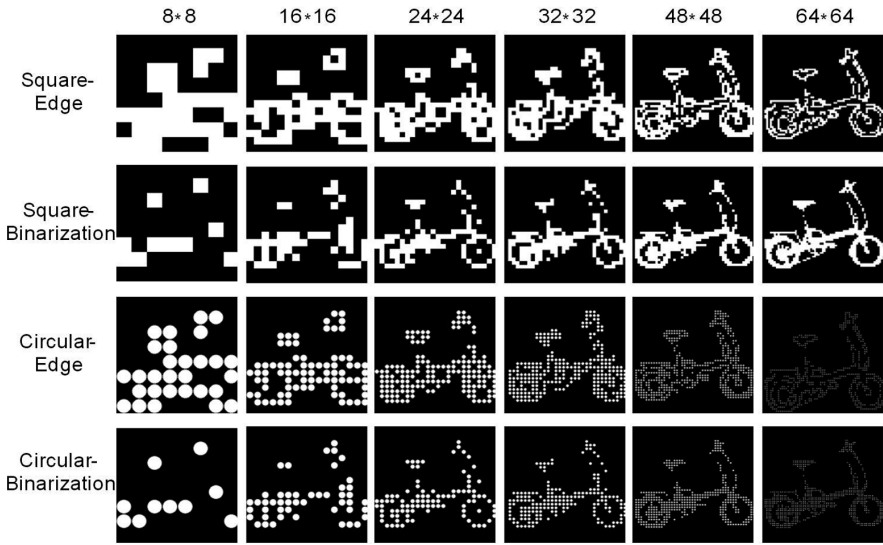
Twenty objects and five scene images were chosen from the databases which were familiar to almost everyone. The original images were captured using the mini CMOS image sensor which was a part of an embedded system based on DSP developed by ourselves.

The experiment was performed in a quiet and dark room to shield from ambient light. Setup was the same as mentioned above. The images were captured and processed by the embedded system, and then the results were transmitted to the computer through the USB device. The HMD was controlled by the computer (Fig. 23).



**Table 1** Mean complexity and number of Chinese characters with stroke number from 1 to 16

| Number of strokes    | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   | 12   | 13   | 14   | 15   | 16   |
|----------------------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Mean complexity      | 0.05 | 0.14 | 0.16 | 0.20 | 0.22 | 0.24 | 0.25 | 0.27 | 0.28 | 0.29 | 0.30 | 0.30 | 0.31 | 0.31 | 0.32 | 0.32 |
| Number of characters | 1    | 9    | 32   | 53   | 71   | 89   | 78   | 81   | 73   | 52   | 36   | 26   | 14   | 9    | 4    | 3    |



**Fig. 23** Sample images used in the experiment. Each column corresponds to a given number of pixels ( $6 \times 6$ ,  $8 \times 8$ ,  $10 \times 10$ , and  $12 \times 12$ ) and each row corresponds to a given processing method and shape of pixel. The image pixelized by white binary matrix pixels. Visual angle of each image was set in  $5^\circ$

The object recognition was close to zero in  $8 \times 8$  pixel arrays. When the pixel number increased to  $16 \times 16$  pixels, the recognition showed noticeable differences with two image processing strategies. Binarization showed better results than Edge strategy, the impact produced by the shape of pixels was relatively small. However, different pixel shapes with the same processing method produced no significant differences in image recognition. Furthermore, with the pixel number increased to  $24 \times 24$ , there was a great increase in recognition accuracy. The Circular-Binarization ( $69.57 \pm 9.42$ ) image was still the most easily identifiable, but the distinction was comparatively small. The fluctuant trend of recognition with higher pixel numbers demonstrated a relatively slow growth from the  $32 \times 32$  resolutions to  $64 \times 64$ . At the same time, the accuracy increased from 80% to nearly 100% (Fig. 24).

Scene images were very hard to identify without sufficient prior information when the resolution was lower than  $32 \times 32$ . With  $32 \times 32$  pixel arrays, there was a great diversity of recognition accuracy for two strategies and two pixel shapes from Square-Binarization ( $30.44 \pm 7.32$ ) to Square-Edge ( $9.57 \pm 8.60$ ). The diversity of recognition accuracy of different image modes became negligible at the resolution of  $48 \times 48$  pixels. Meanwhile, the mean recognition accuracy of different strategies and pixel shapes had an obvious growth (near 60%). For  $64 \times 64$  pixels, the mean recognition accuracy had reached near 80%. Binarization showed better results than Edge strategy in  $32 \times 32$  pixel arrays. However,

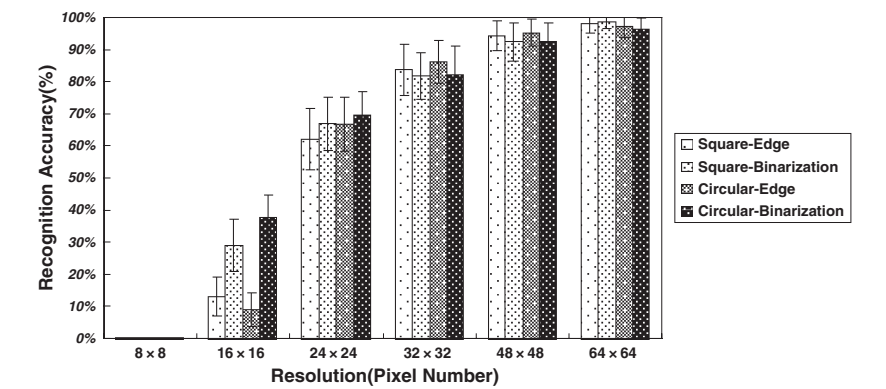


Fig. 24 Experiment results: the recognition accuracy of objects

with the number increasing to  $48 \times 48$ , the Edge got better results than the Binarization method. Different pixel shapes with the Edge method did not show distinct differences, while with the Binarization method, square pixels got better results than circular pixels when the pixel number increased to  $32 \times 32$ . “Circular-Edge” images were easier to recognize (Fig. 25).

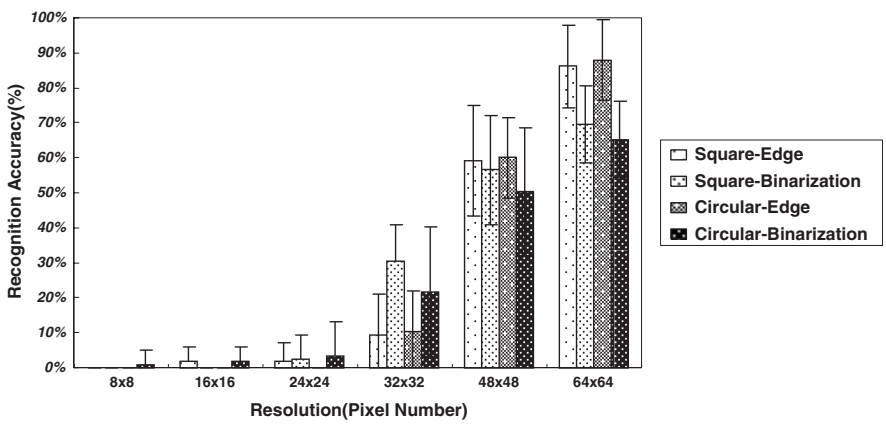


Fig. 25 Experiment results: the recognition accuracy of simple scenes

5.3 Dispersion and Accuracy of Simulated Phosphene Positioning

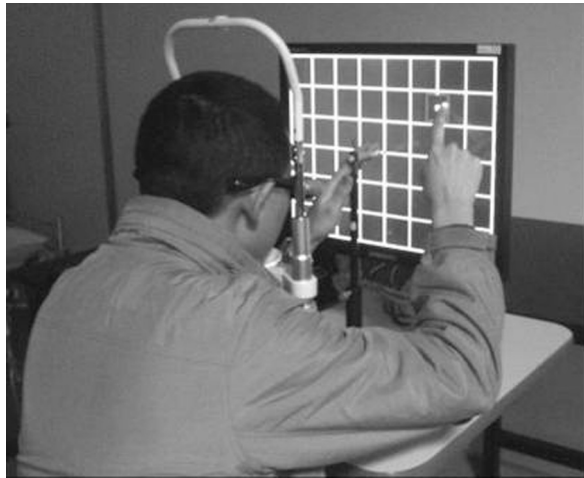
With the rapid development of prosthetic vision evaluating the characteristics of phosphenes after implantation of electrode arrays will become increasingly important in future research. Mapping phosphenes was of great importance after electrode array implantation of visual prostheses. Several methods have

been developed by our team to map phosphenes and evaluate their characteristics. Two phases of experiments were carried out in this regard.

### 5.3.1 Tactile Perception Based on Phosphene Positioning Using Simulated Prosthetic Vision

The setup included a head-mounted display, which was connected to the computer in order to generate simulated phosphenes, a 19-inch touch screen to record the subject's tactile position, a simple tactile guide that directs the subject to recognize the origin of the system, and an inverted "L" shaped short horizontal stick pointed toward the center of the touch screen. During the experiment, the subject's hands were placed at the tip of the short horizontal stick in order to help him/her realize where the center of the touch screen was. Moreover, the setup also included a chin rest placed 30 cm in front of the touch screen in order to hold the subject's head stable, and a Dell computer with a C++ experimental program to create the circular phosphene. The phosphene's size was  $16 \times 16$  mm (Fig. 26).

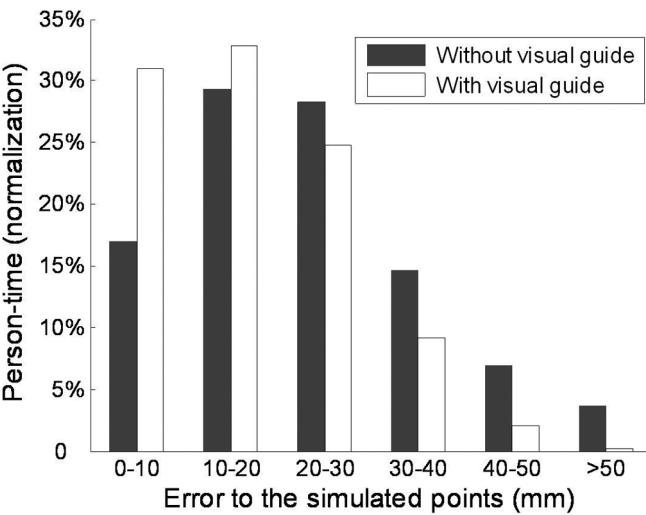
**Fig. 26** The setup of the simulated phosphene positioning system. It is totally dark in the HMD before the program is running. The image in the HMD is the same as that on the touch screen except for the resolution. The image also displays on the touch screen to help the experimenter track the experimental procedure. (From Chai et al., 2007b)



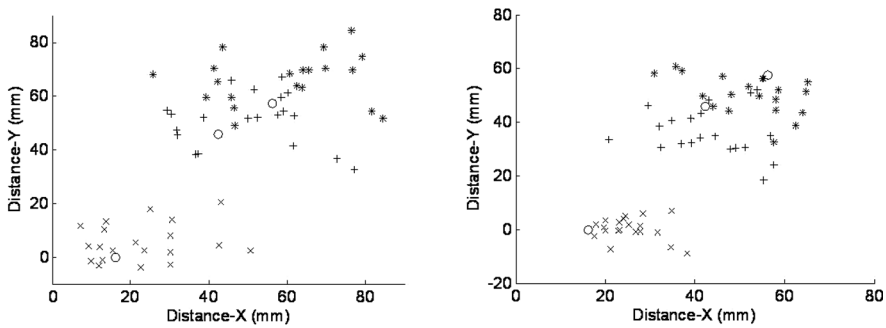
The experiment included two modes: without and with a visual guide. The visual guide was used to reduce the visual perception error. The equidistant horizontal and vertical lines divide the touch screen and the screen in the HMD into  $8 \times 6$  grids. In this situation, the visual perception error is reduced as the locations of simulated phosphenes are observed with more accuracy. Each mode included training and formal parts.

The visual guide increased the accuracy of tactile perception as the distribution was larger when the error was under 20 mm and became inverse as the error went above 20 mm.

Dispersion and response time have a significant relation to the distance to the origin. There are two main aspects that affect accuracy: the error of judgment and individual differences. The error of judgment can be explained using the visual guide, which obviously increases the accuracy as well as the other two parameters. The individual differences could be solved by systematic training (Figs. 27 and 28).



**Fig. 27** Contrast of tactile accuracy distribution in two modes (without and with visual guide). The statistics are based on three simulated points (the distance to the center of the touch screen is 16, 60, and 80 mm each) in 20 subjects. Each point is repeated 10 times. (From Chai et al., 2007b)

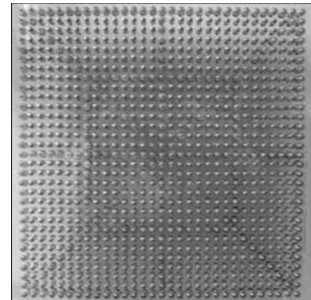


**Fig. 28** The scatter of simulated phosphenes and the mean values of the subject’s judged points in the mode without the visual guide (*left*). The scatter of simulated phosphenes and the mean values of the subject’s judged points in the mode with the visual guide (*right*). The *open circle* represents the three simulated phosphenes whose distances to the origin were 16, 60, and 80 mm, respectively. The *product sign*, *plus sign*, and *asterisk sign* represent the mean value of the subject’s judged points toward the 16, 60, and 80 mm simulated phosphenes, respectively. The 20 determinative signs toward each simulated phosphene represent the 20 subjects in the experiment. (From Chai et al., 2007b)

### 5.3.2 Dispersion and Accuracy of Simulated Phosphene Positioning Using Tactile Board

Three experiments were designed to evaluate the performance of phosphene positioning based on a tactile board using simulated prosthetic vision. They measured the effect of distance, the effect of quadrant, and the long-term effect.

The tactile board was a self-developed apparatus designed on Cartesian coordinates in order to reduce the tactile perception error. It consisted of a basic board, a pushbutton array, and adjustable retainers (Fig. 29).



**Fig. 29** The tactile board

The setup of the phosphene positioning system included a self-developed tactile board, a head-mounted display, a 19-inch touch screen, a personal computer with a self-developed experimental software system written in the C++ language (Fig. 30).



**Fig. 30** The setup of simulated phosphene positioning system

Each experiment included two processes: the training and the formal experiment. The procedures of the training part and the formal experiment were completed in a dark, quiet room so that the subjects could concentrate on the experiments.

The values of standard deviation (SD) were less than 6 mm. All of the values were in the range of 4–6 mm. The range of mean error was 4–9 mm. The response time for the distances of 56 mm, 79 mm, 113 mm, and 136 mm was from 24.5 to 28.3 seconds, while the response time for 11 mm distance was 17.7 seconds.

The dispersion based on the tactile board was significantly improved in evaluating simulated phosphenes in two aspects. One was that the dispersion of all judged points decreased in using the tactile board, while the other was that the differences of dispersion were small enough to be ignored as the distance to the origin increased.

The conclusion was that the tactile board increased accuracy. Using the tactile board not only decreased the mean error, but also reduced the accuracy's fluctuation as the distance to the origin changed.

Long-term experiments improved both dispersion and accuracy, and both SD and mean error were decreased in the long-term experiments, especially in the first two experiments.

## **6 Surgical Approach to Expose the Optic Nerve**

Anatomically, the retrobulbar segment of the optic nerve is located in the closed orbit. There is no way to access it except surgery. Therefore, a surgical approach should be selected and its efficiency and safety should be evaluated.

### ***6.1 Surgical Technique***

Anesthesia and sedation were introduced by intramuscular injections of ketamine hydrochloride and xylazine hydrochloride. Body temperature was maintained at a level of 39°C during the experiment and electrocardiogram was supervised so that the anesthesia could also be monitored. Atropine eye solution was administered into the conjunctival sac of the surgical eye to lessen the edema of the conjunctiva and the third eyelid.

Surgery was performed on right eyes only. After shaving the surgical area, povidone-iodine was used for disinfection and the surgical eye was routinely draped. A lateral canthotomy was performed and the conjunctiva was incised at the superior fornix. The superior rectus muscle was dissected with a thermal cauter; in order to avoid unnecessary bleeding, the vortex vein along the rectus muscle needed to be ligated. Then, the eye was rotated inferonasally. Care needed to be taken to avoid tearing or breaking the intraorbital venous sinuses. The soft tissue surrounding the posterior aspect of the globe was dissected superotemporally with care along the ciliary blood vessels on the sclera, until the optic nerve became visible. The outlet of the optic nerve was gently freed from the surrounding soft tissue and made ready for implanting the stimulation microelectrodes or electrode array.

6.2 Efficiency and Safety

Electrically evoked cortical responses generated by implanting the microelectrodes or electrode array into the retrobulbar segment of the optic nerve are shown in Fig. 31. In our investigation, the visual conduction function in terms of implicit time and amplitude in visually evoked potential recordings would be influenced transiently. However, these transient changes could be recovered naturally without any intervention about 1 month after surgery (Fig. 32). Moreover, the histological examination also provided no abnormal structural alterations at a level of light microscopy.

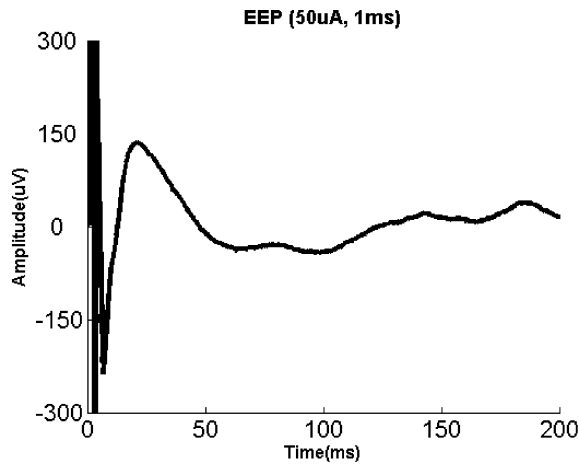


Fig. 31 EEP generated by current of 50  $\mu$ A with duration of 1 ms

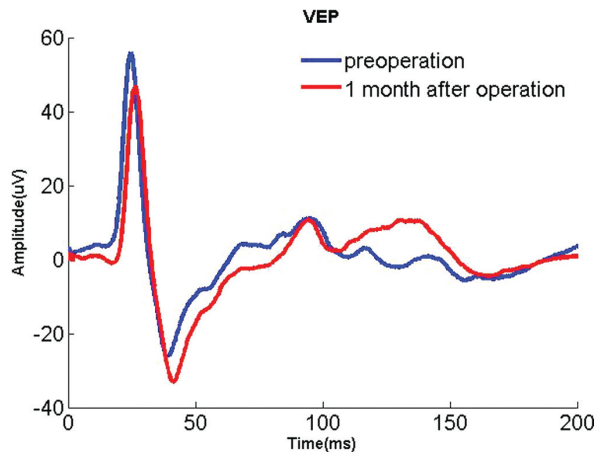


Fig. 32 A complete recovery of VEP in one month after surgery



As a whole, lateral canthotomy was a relatively safe and efficient surgical approach which served in the implementation of the visual prosthesis investigation.

## **7 In Vivo Electrophysiological Study**

By applying a penetrating electrode array in the optic nerve, the axons of the ganglion cells local to each electrode could be stimulated. This approach may potentially increase the spatial resolution of the visual prosthesis while lowering the thresholds of the stimulating current when compared with the surface cuff electrodes. To obtain the appropriate stimulating parameters and pattern, we investigated the feasibility and basic spatiotemporal properties of cortical responses evoked by optic nerve stimulation with penetrating electrodes in this study, using multichannel recording electrode arrays positioned at the visual cortex area in rabbits.

### **7.1 Subjects**

Thirty-six healthy adult Chinese albino rabbits, weighing about 2.0–3.0 kg, were used in this study. After intravenous anesthetization with 5% pentobarbital sodium, orbital surgery was performed to expose the intraorbital optic nerve of the rabbits. The temporal and spatial properties of electrically evoked potentials (EEP) evoked by optic nerve stimulation with penetrating electrodes were investigated, respectively.

### **7.2 Temporal Properties**

#### **7.2.1 Stimulations**

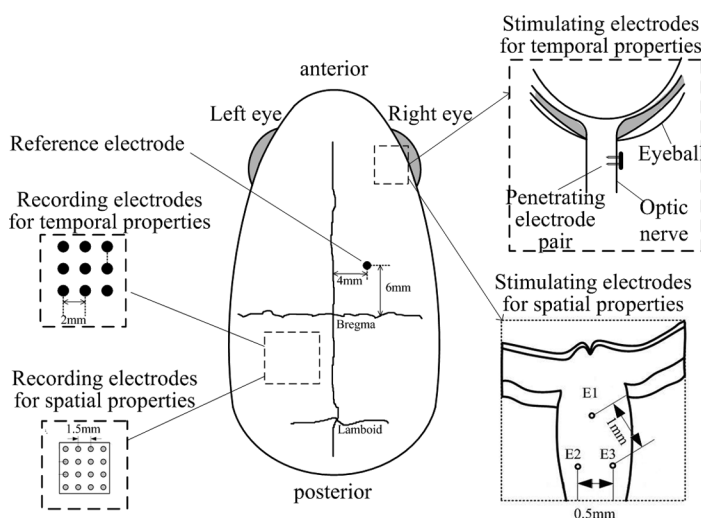
To investigate the temporal properties of EEP evoked by optic nerve stimulation with penetrating electrodes, two microelectrodes (each with 100  $\mu\text{m}$  diameter and 300  $\mu\text{m}$  tip exposure) were used to stimulate the optic nerve of rabbits. Each electrode was made of Teflon-insulated tungsten wire and the impedance of the electrode ranged from 2.5 to 3.5  $\text{k}\Omega$  at 1 kHz, 50 mV sinusoidal wave. The insertion site of the stimulating and return electrodes was about 1 mm and 2 mm, respectively, posterior to the eyeball (Fig. 1).

A single charge-balanced symmetrical cathode-first biphasic current pulse, generated by an isolated stimulator (MS16, Tucker-Davis Technologies, Alachua, FL, USA), was applied between the stimulating and return electrodes. When determining the charge threshold, a duration fixed current was used. The lowest current for eliciting reproducible EEP was found. Then the corresponding charge was calculated by multiplying current by duration.

Pulse amplitude and duration of the stimuli were varied to study their effects on EEP. The effects of stimulus pulse amplitude on EEP were investigated by using current intensity ranging from 40 to 120  $\mu\text{A}$  with fixed pulse duration of 0.5 ms. The effects of stimulus pulse duration on EEP were studied over a range of 0.4–1.2 ms with fixed pulse amplitude of 100  $\mu\text{A}$ . By fixing the charge as a constant value, the effects of varying pulse duration and pulse amplitude on EEP were examined. For the above experiments, the frequency of the pulses was 1 Hz. The influence of stimuli frequency on EEP was studied as well. The stimuli frequency was varied from 1 Hz to 10 Hz.

### 7.2.2 Recordings

In order to detect the maximal response of EEP, a nine-recording-electrode array was positioned over the contra-lateral visual cortex area of the stimulated eye. The skull was exposed through a skin incision at the top of the head along the midline, and nine stainless crew-type electrodes were drilled into the skull over the visual cortex (Fig. 33). The nine electrodes formed a  $3 \times 3$  array with 2 mm spacing. EEP from the visual cortex contra-lateral to the stimulated eye were recorded by a multichannel neurophysiology workstation (System 3, Tucker-Davis Technologies, Alachua, FL, USA). Signals from the nine recording electrodes were amplified and filtered with a band-pass of 3–2000 Hz. Fifty evoked responses were averaged.



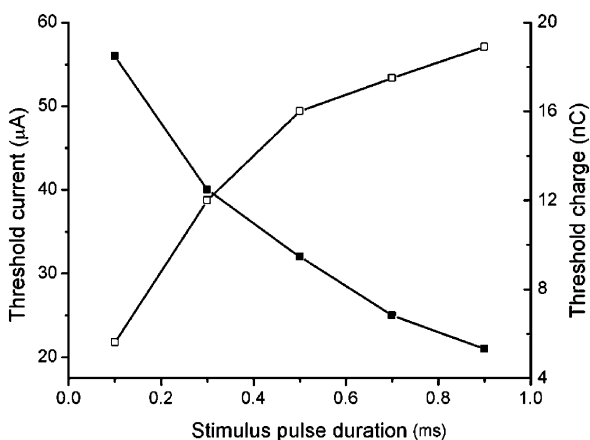
**Fig. 33** The strategy for electrical stimulation and cortical recording in rabbits

### 7.2.3 Temporal Properties of EEP

Electrical stimulation of the optic nerve evoked EEP in the visual cortex of all the rabbits. The waveform of the induced EEP was similar to that of VEP, while the latency of P1 of EEP was shorter compared with that of VEP.

The mean charge threshold for eliciting EEPs in the visual cortex was  $16.04 \pm 4.22$  nC (Mean  $\pm$  SD). Considering that the exposed surface of the stimulating electrode was about  $7.64 \times 10^{-4}$  cm<sup>2</sup>, the mean charge threshold density was  $20.99 \pm 5.52$   $\mu$ C/cm<sup>2</sup>.

The strength–duration curve was also investigated as displayed in Fig. 34. Current threshold decreased as the pulse duration of the stimulus increased (solid), while the corresponding charge threshold increased when increasing the pulse duration.



**Fig. 34** Current threshold and corresponding charge threshold as functions of stimulus pulse duration in one rabbit. *Solid*: current threshold and *hollow*: charge threshold. Unpublished data

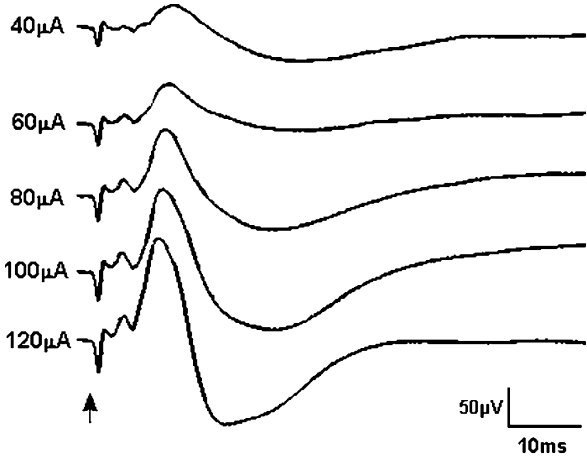
Figure 35 depicts the EEP waveforms to stimuli with varying pulse amplitude. The amplitude of P1 increased when increasing the stimulus pulse amplitude while the latency of P1 decreased.

The EEP waveforms to stimuli with the varying pulse duration are shown in Fig. 36. As can be seen, the amplitude of P1 increased when the pulse duration increased from 0.4 to 1.0 ms. But the latency of P1 changed little with increasing stimulus pulse duration.

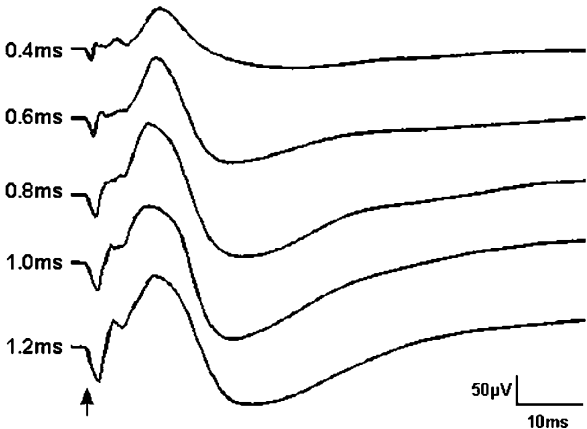
Figure 37 displays the typical EEP waveforms elicited by stimuli with a fixed pulse, but different pulse amplitude and pulse duration. The amplitude of P1 decreased and the latency increased when the pulse duration increased from 0.2 ms to 1.0 ms and the pulse amplitude decreased from 250  $\mu$ A to 50  $\mu$ A accordingly.

The influence of stimulation frequency on EEP was studied. For comparison, the influence of stimulation frequency on VEP was studied as well. Figure 38 shows the typical VEP and EEP responses as the stimulation

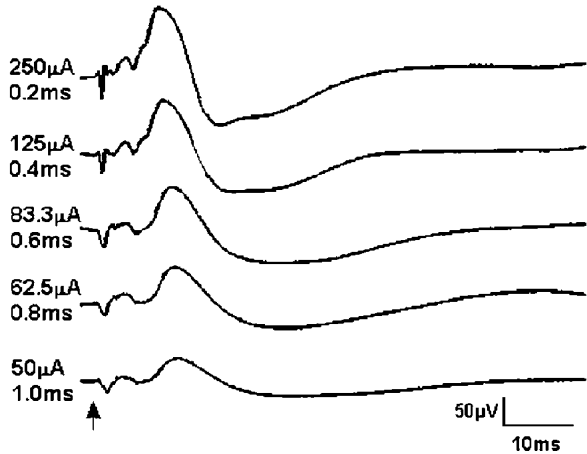
**Fig. 35** EEP waveforms to stimuli with varying pulse amplitude in one rabbit (pulse duration = 0.5 ms). *Arrow*: onset of the stimuli. Unpublished data



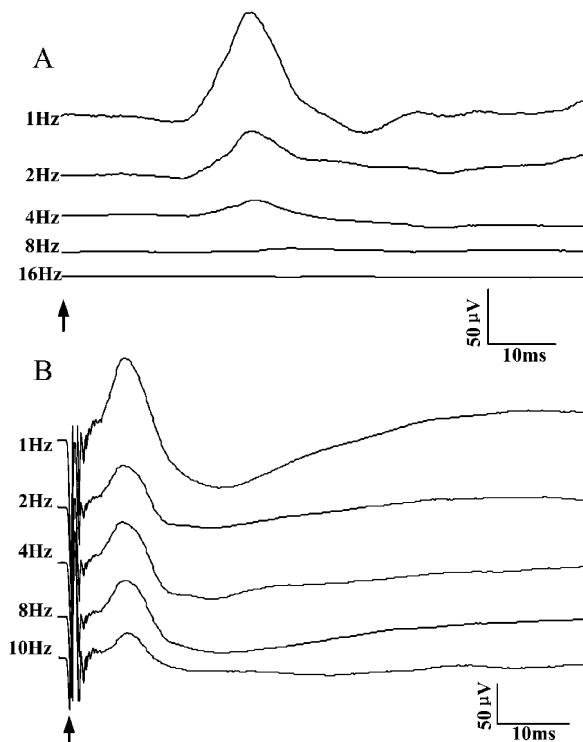
**Fig. 36** EEP waveforms to stimuli with varying pulse duration in one rabbit (pulse amplitude = 100  $\mu\text{A}$ ). *Arrow*: onset of the stimuli. Unpublished data



**Fig. 37** EEP waveforms to stimuli with fixed charge (50 nC) but different pulse amplitude and pulse duration in one rabbit. *Arrow*: onset of the stimuli. Unpublished data



**Fig. 38** (A) VEP waveforms to optic stimuli with different frequency; (B) EEP waveforms elicited by electrical stimuli with different frequency but fixed pulse amplitude and duration (100  $\mu$ A, 0.5 ms). Unpublished data



frequency was varied. As depicted in the figure, the amplitudes of both VEP and EEP decreased with the increase of stimulation frequency. But the VEP was depressed with lower stimulation frequency compared with EEP. This may be due to the direct electrical stimulation to the optic nerve, bypassing the retinal synaptic transmission, and therefore, the EEP could be elicited with a wider frequency range than VEP did.

## 7.3 Spatial Properties

### 7.3.1 Stimulations

To investigate the spatial properties of cortical responses elicited by optic nerve stimulation, three triangularly or linearly configured microelectrodes were inserted into the optic nerves of the rabbits (Fig. 33). The home-made needle-type electrodes were fabricated by micro-electric wires made of Platinum-Iridium alloy insulated by Teflon (80  $\mu$ m diameter, 100  $\mu$ m tip exposure). The uncoated area was about  $2.7 \times 10^{-4} \text{ cm}^2$  and the impedance was 5~12 k $\Omega$  at 1 kHz, 50 mV sinusoidal wave.

Electrical stimulation was applied to the different pairs of three stimulating electrodes. Biphasic charge-balanced rectangular stimuli with the cathode-first pulse were used. The pulse duration was fixed at 0.5 ms, while the pulse amplitude varied from 10  $\mu$ A to 100  $\mu$ A, with the frequency of 1 Hz.

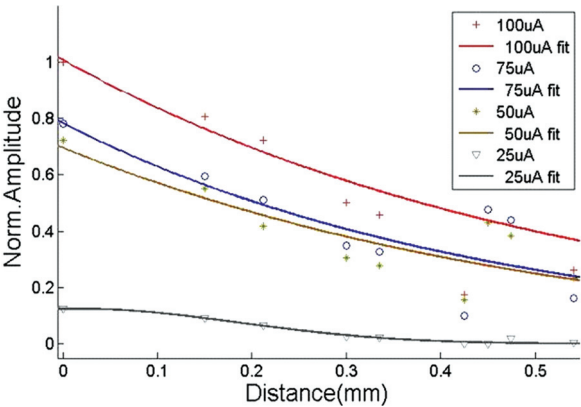
7.3.2 Recordings

The recording electrode array was made up of  $4 \times 4$  silver-ball electrodes with 0.3–0.4 mm in diameter. The silver wire (diameter = 0.2 mm) behind the silver ball was insulated by a glass tube. The 16 electrodes were fixed on a base plate in a matrix format, with the central distance of 1.5 mm between the two adjacent electrodes. One solid shaft was extended from the plate in order to be fixed onto a three-dimensional micromanipulator. The impedance of the silver-ball electrodes ranged from 500 to 800  $\Omega$  measured under 100  $\mu$ A, 1 kHz, AC stimulation.

The EEP responses of 16 channels at the contra-lateral visual cortex to the stimulated eye were recorded subdurally to investigate the spatial properties of EEPs (Fig. 33). The recording electrode array was moved within the cortex in order to cover the whole area of the visual cortex.

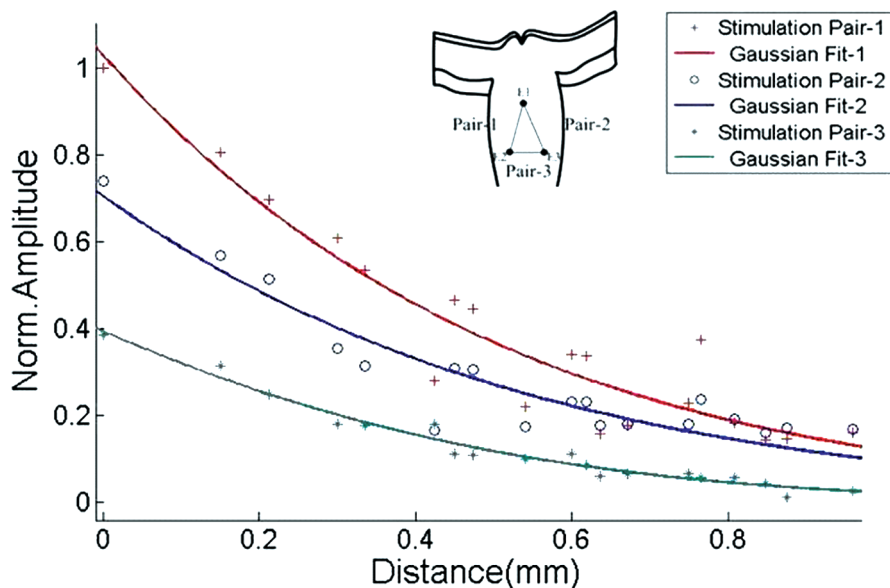
7.3.3 The Spatial Responses to the Optic Nerve Stimulation

Our experimental results showed that the extent of EEP increased as the stimulating intensity increased. Figure 39 illustrates normalized P1 amplitude of EEP as a function of recording distance from the response center (the maximal channel). The relation of normalized EEP amplitudes and recording distances was fitted by Gaussian function. As seen from the figure, the amplitude of P1 decreased when the recording distance from the response center increased, and the stimuli with larger amplitude evoked a larger response area in the visual cortex.



**Fig. 39** The normalized P1 amplitude of EEP as a function of recording distance from the channel with maximal response. The data was fitted by Gaussian function. The stimulus pulse duration was 0.5 ms. Unpublished data

We also investigated the spatial properties of EEP as the optic nerve was stimulated by different stimulating electrode pairs. Our experimental results showed that different distribution maps of EEP were elicited by different pairs of stimulating electrodes. The stimulating electrode pairs along the axis of the optic nerve elicited cortical responses with much lower thresholds than that perpendicular to the axis of the optic nerve. Figure 40 illustrates the spatial extension of EEP under the same stimulating parameters as the optic nerve was stimulated by different pairs of the stimulating electrodes in one rabbit. The horizontal axis represents the recording distance from the channel with the maximal response. The vertical axis represents the normalized P1 amplitude of EEP recorded by one channel. The relation of normalized amplitudes and distances was fitted by Gaussian function. As shown in Fig. 40, the spatial area of EEP elicited by the electrode pairs approximately parallel with the axis of the optic nerve (Pair-1 and Pair-2) were much larger than that elicited by the electrode pair perpendicular to the axis of the optic nerve (Pair-3). The attenuating speed under the same stimulating intensity by the electrode pairs approximately parallel with axis of the optic nerve was faster than that perpendicular to the axis of the optic nerve. When the optic nerve was stimulated by linearly arranged electrodes, larger EEPs were elicited by the electrode pair with a larger distance than the one with a smaller distance.



**Fig. 40** The spatial extension of EEP as the optic nerve was stimulated by different pairs of stimulating electrodes in one rabbit. Stimulating electrode pairs along the axis of the optic nerve elicited larger cortical responses than those perpendicular to the axis of the optic nerve. The stimulus pulse amplitude and pulse duration were 100  $\mu$ A and 0.5 ms, respectively. Unpublished data

## 7.4 Assessment of the Damage to the Optic Nerve

Electroretinograms (ERG) and visual evoked potentials (VEP) were monitored as a control at the different stages of all the experiments. Histological analysis of the optic nerve was performed after the experiments.

The experimental results showed that ERG did not vary significantly, but the P1 amplitude of VEP declined after the orbital surgery to expose the optic nerve. Histological analysis showed mild damage to the optic nerve tissue induced by electrical stimulation in acute experiments.

## 8 Conclusion

In the foregoing chapter, we have described an implantable visual prosthesis with a stimulating microelectrode array penetrating into the optic nerve, and animal experiments have validated the feasibility of this kind of visual restoration. The design of the microelectrode can be optimized from noise analyses. Two different types of penetrating electrode arrays were presented including a silicon-based microprobe produced by MEMS process techniques and *Pt-Ir* microwire arrays produced by electrochemical etching. Both of them are ideal candidates for optic nerve stimulation with the key difficulty in chronically in vivo fixing. As compared with cuff electrode arrays, penetrating ones can improve spatial resolution. In addition, our group accomplished a great achievement with the multichannel microcurrent stimulator. A commercial low-resolution CMOS micro-camera was adopted for image capturing, and a DSP processed these images in real time. Now our optic nerve visual prosthesis has been validated by animal experiments, and more such experiments will be conducted to optimize the penetrating microelectrode arrays.

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