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Functional verification of pulse frequency modulation-based image sensor for retinal prosthesis by in vitro electrophysiological experiments using frog retina

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Abstract

The functioning of a 16 × 16 pixel pulse frequency modulation (PFM) image sensor for retinal prosthesis is verified through in vitro electrophysiological experiments using detached frog retinas. This image sensor is a prototype for demonstrating the application to in vitro electrophysiological experiments. Each pixel of the image sensor consists of a pulse generator (PFM photosensor), a stimulus circuit, and a stimulus electrode (Al bonding pad). The image sensor is fabricated using standard 0.6 μm CMOS technology. For in vitro electrophysiological experiments, a Pt/Au stacked electrode is formed on the Al bonding pad of each pixel and the entire sensor is fixed in epoxy resin. The PFM image sensor is confirmed experimentally to provide electrical stimulus to the retinal cells in a detached frog retina.

Keywords: Subretinal prosthesis; CMOS image sensor; Pulse frequency modulation; Packaging; In vitro electrophysiological experiment; Frog retina

1. Introduction

Retinal degenerative diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD) have resulted in various degrees of irreversible vision loss in tens of millions of people worldwide. Electrical stimulation of retinal cells by an implanted device has been reported to be an effective approach that allows partial recovery of visual sensation in blind patients. One such approach is to implant a subretinal prosthesis that replaces the function of damaged photoreceptor cells with optical-to-electrical converting devices (i.e. photosensors) in the subretinal space (Zrenner et al., 1997, 1999; Chow et al., 2001; Margalit et al., 2002; Zrenner, 2002). The subretinal prostheses reported to date are based on a micro photodiode array (MPDA) operating passively without a power supply in "solar cell" mode. Our group, however, has proposed an active device to provide more adequate stimulation of retinal cells (Ohta et al., 2002). Although an active device requires a power supply, it has the advantage that it can inject sufficient charge into the retinal cells and allows more effectively and adaptive control of the stimulus pulse parameters, such as height, width, and frequency. Other research groups working on subretinal prostheses have recently developed similar active photosensors (Ziegler et al., 2004; Zrenner, 2002).

In vitro and in vivo experiments are essential for the development of retinal prostheses, and such experiments have been carried out by many groups (Humayun et al., 1999; Grumet et al., 2000; Stett et al., 2000; Schanze et al., 2002; Humayun et al., 2003; Jensen et al., 2003; Li et al., 2005). These experiments, however, have been conducted for epiretinal prostheses. To the best of the authors' knowledge, there have been no reports on experiments involving active subretinal prostheses.

In general, epiretinal prostheses involve the implantation of a single planar electrode array in the epiretinal space (Humayun et al., 1994; Wyatt and Rizzo, 1996; Eckmiller, 1997; Margalit et al., 2002; Schanze et al., 2002; Deguchi et

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al., 2004). For subretinal prostheses, however, it is necessary to implant both a photosensor and an electrode array in the subretinal space.

We have proposed a pulse frequency modulation (PFM) photosensor with an integrated electrode as an active subretinal prosthesis (Ohta et al., 2002). The device is implanted between the retina and the retinal pigment epithelium (subretinal space). The PFM photosensor converts incident light into a digital pulse stream (Yang, 1994; Andoh et al., 2000). This pulse stream is suitable for direct stimulation of retinal cells. Other features of the PFM photosensor include robustness against noise, compatibility with logic circuits, wide dynamic range, and low-voltage operation, all of which are useful features for implanted devices. The characteristics of the PFM photosensors have subsequently been improve in order to stimulate retinal cells more effectively (Kagawa et al., 2003, 2004).

To apply this PFM photosensor in electrophysiological experiments, the sensor must be packaged in such as way to ensure biocompatibility, durability, and circuit protection. This packaging requirement also necessitates the integration of the stimulus electrodes with the PFM photosensor. The present report describes the fabrication of a 16×16 pixel PFM image sensor for use in in vitro electrophysiological experiments, and experimental verification of the prototype using detached frog retina.

This study is organized as follows. The fabrication, specifications and operation of the prototype prosthesis are presented in Section 2, and the packaging process and setup for in vitro experiments are described in Section 3. The ability of the PFM photosensor to stimulate retinal cells is confirmed through control the firing rate of retinal ganglion cell (RGC) spikes based on analysis of the dependence of the stimulus current amplitude and the frequency in the RGC response. Light-controlled stimulation using the PFM photosensor is also demonstrated. The experimental results are presented in Section 4 and discussed in Section 5, and the paper is finally summarized in Section 6.

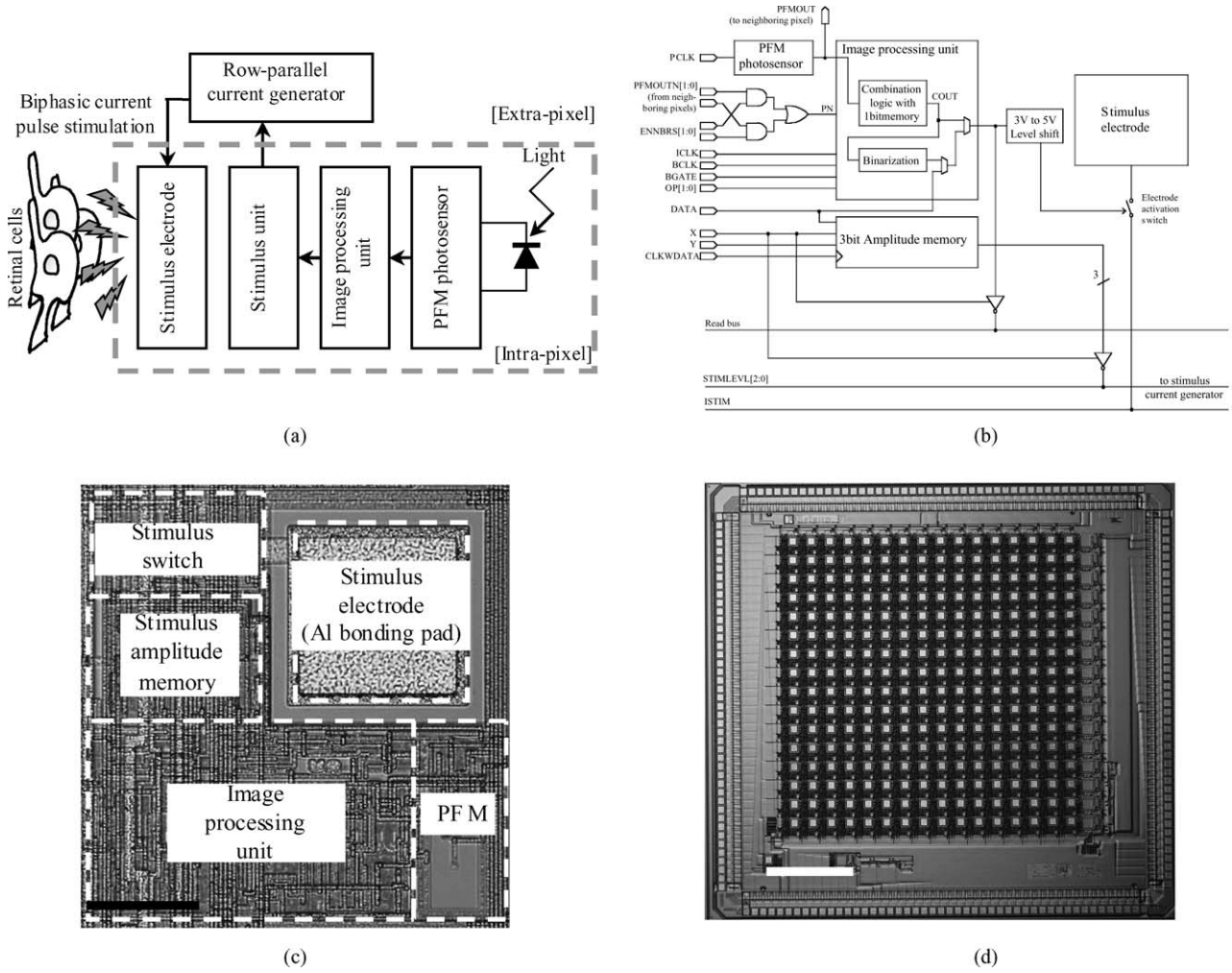

Fig. 1. (a) Block diagram of sensor architecture. (b) Simplified schematic. (c) Photomicrograph of image sensor pixel (scale bar: 80 μm). (d) Photomicrograph of image sensor (scale bar: 1 mm).