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Implantable optoelectronic devices for biomedical applications

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Abstract—Recently, fluorescence imaging using GCaMP has become a necessary tool in life sciences. Its measurement is carried out mainly by fiber photometry and head-mountable microscope devices. In addition, optogenetics has emerged as a necessary tool. For optical stimulation, optical fibers and planar waveguide devices are used. We have proposed and demonstrated completely different approaches using active devices implanted in rodent brains to measure and control biological functions with light. In this review, I introduce the development of recent devices for fluorescence imaging and optogenetics, focusing mainly on implantable micro imaging devices we have developed.

1. Introduction

Behavioral experiments are important for memory and learning. In electrophysiology, a small implantable device, usually a silicon probe, has made it possible to measure nerve activity in the brain of small laboratory animals such as mice while they are roaming freely. Electrical stimulation is also possible in conjunction with free-roaming behavior. Several types of silicon probes have been developed for behavioral experimentation with rodents [1], [2]; thus, electrical methods have been widely used in behavioral experiments.

Recently, along with the development of optical measurement and stimulation technologies that make full use of genetic engineering, such as GCaMP [3] and channel rhodopsin-2 (ChR2) [4], devices capable of optical measurement and stimulation under free-roaming behavior are being developed. This paper reviews recent developments in optical measurement and control of biological functions of freely-moving rodents for behavioral experiments. Firstly, the development of recent optical devices that can be applied to freely-moving rodents are reviewed. Then, comparison among the latest devices is demonstrated. Among these technologies, implantable micro-optoelectronic devices, which we have been developing, are highlighted. Device structure and performance are described in detail. Finally, a conclusion is given.

2. Optical and electrical methods for measurement and control of biological functions

For optical measurement, GCaMP is widely used. GCaMP is a calcium sensor protein that can indicate cell activity with fluorescence under the illumination of blue excitation light [3]. Because it is a protein, it can be introduced into a gene, and in combination with a tissue- or cell-specific promoter, specific calcium imaging, can be achieved.

ChR2 is a photosensitive anion channel protein that activates cell activity in response to blue light illumination [4]. While ChR2 is used to excite cells through blue light illumination, halorhodopsin is a photosensitive chloride ion pump protein that inhibits cellular activity in response to yellow light illumination [4]. Such optical stimulation technology is called optogenetics [4]. Like GCaMPs, these ion channel proteins are expressed in specific cells. These optical technologies combined with gene technology can be used to measure and control specific cells, as shown in Fig. 1.

Alternatively, electrical methods use an electrode to measure and control electrical potential (voltage) through interstitial fluid, so these methods are not tissue- or cell-specific, as shown in Fig. 1. Thus, it is very important to introduce optical methods in behavioral experiments. In the next section, optical methods that can achieve measurement and control of biological functions *in vivo* are introduced.

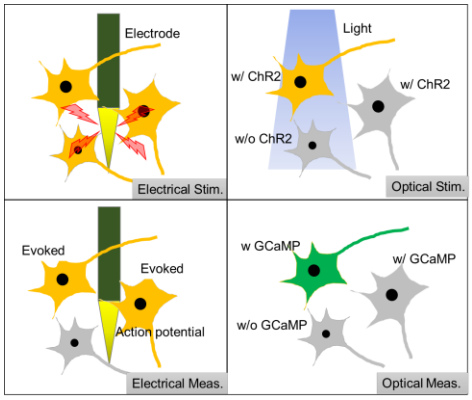

Fig. 1 Comparison of electrical and optical methods for measuring and stimulating cells

3. Optical methods for measurement and control of biological functions under free-roaming conditions

For fluorescence imaging, two main methods have been developed and are widely used: fiber photometry [5] and a head-mountable microscope device [6], as shown in Fig. 2. In fiber photometry (Fig. 2(a)), an optical fiber is used to deliver excitation light to the brain, as well as to transmit a fluorescent image outside the brain. The fiber is connected to an optical emitting device, such as a laser or optical detector. The configuration of fiber photometry is also applicable to optogenetics as such. One of the most important advantages is that this method can use conventional instruments for optical microscopy.

The head-mountable microscope device, as shown in Fig.

2(b), is usually composed of a miniaturized fluorescence microscope module and an optical rod lens that is inserted into the brain. The difference between the two methods is the cabling outside the body of the animal. In fiber photometry, optical fibers are connected to external instruments, and thus the movement of the animal is hindered to a greater degree than with head-mountable microscope devices, because electrical cables are more flexible than optical fibers. The other advantage is that it is possible to introduce wireless operation in head-mountable microscope devices, while it is difficult to do this with fiber photometry.

The third method is employing a device with an optical waveguide to deliver light into the body, as shown in Fig. 2(d) [7]. This method is mainly used for optical stimulation. Compared with an optical fiber device, multi-point emission can be implemented with this device, such as a Si probe with a number of electrodes for multi-point electrical stimulation.

We have been developing a fourth method that embodies a concept completely different from the others [8]. In the next section, the structure and performance of the device are described in detail.

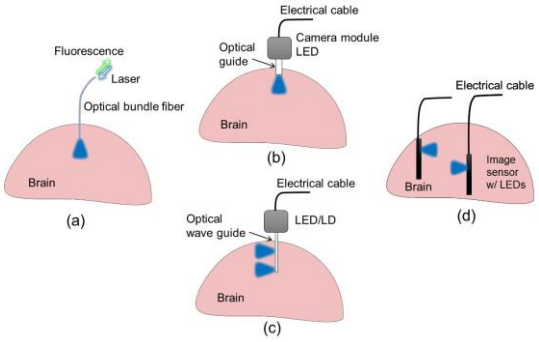

Fig. 2 Optical methods to measure and stimulate neural cells in the brain. (a) optical fiber or fiber photometry, (b) head-mountable microscope device, (c) optical waveguide device, and (d) micro-optoelectronic device. Adapted from ref. [8] with the permission of IEEE.

4. Implantable micro-optoelectronic devices

The implantable micro-optoelectronic device is based on a dedicated CMOS image sensor fabricated using standard CMOS technology [8]. In this setup, only objects in the vicinity of the sensor can be clearly observed because the device has no imaging optics. The device is compactly packaged in a polyamide substrate with LEDs and an excitation light filter for fluorescent imaging and improved biocompatibility. The color filter on the image sensor blocks the excitation light, allowing only fluorescent emission to reach the image sensor. LEDs are also implemented on the polyamide substrate.

Figure 3 shows examples of two types of this device. One example, the planar type, is used for implantation on the surface of the brain, whereas the other example, the needle type, is used for implantation into the deep brain. These devices are of different sizes.

Based on the planar type device, we have developed an optical stimulation device with imaging functions. Figure 4 shows the fabricated device [9]. It integrates a blue LED array to stimulate neural cells, and green LEDs to illuminate cells/tissues for the image sensor. Using an LED array enables us to stimulate cells in certain areas. This device can turn on arbitrary LEDs in the array, so it is suitable for patterned optical stimulation. It is difficult to achieve such patterned stimulation using optical fibers.

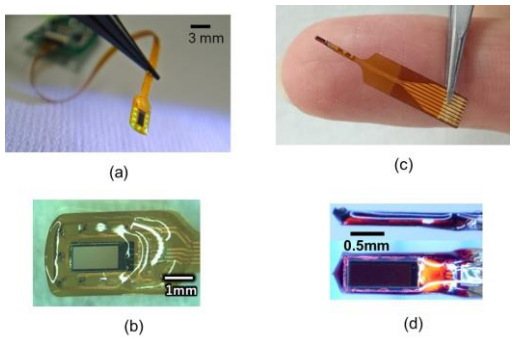

Fig. 3 Micro-optoelectronic devices. Whole and close-up photos of the planar type device (a) and (b), and the needle type device (c) and (d). Adapted from ref. [8] with the permission of IEEE.

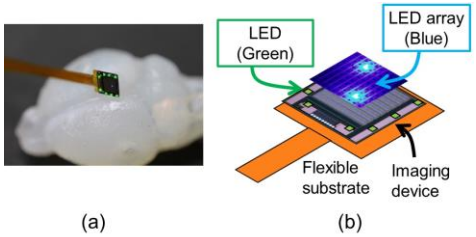

Fig. 4 Integrated device with patterned optical stimulation and imaging. (a) whole device view and (b) illustration of the device. Adapted from ref. [9] with the permission of IOP.

5. Conclusions

Optical technology for measuring and controlling biological functions are reviewed. Along with the advancement in genetic technology, this kind of optical technology is expected to become increasingly important in the future.

Acknowledgements

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