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Disposable MEMS optrode array integrated with single LED for neurostimulation

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ABSTRACT

We present an LED-waveguide-based neural probe array with the highest total light power delivery from a single commercial LED. A separable configuration between the LED and the waveguide has been proposed and verified experimentally for a disposable probe tip. The system comprises of a disposable MEMS optrode array and a reusable unit. The optrode array consists of a 4 × 4 array of 6 mm-long optical fibers assembled with thermally reflowed square-shaped glass microlenses. The reusable unit includes a domed top LED and driving circuitry. Measured light delivery efficiency of the optrode array and the total power efficiency of the probe were −10.6 dB and −21.6 dB, respectively.

1. Introduction

Recently, optogenetics has gained increasing research interest due to the unique characteristics of cell-type selectivity and the high spatial and temporal resolution for neural stimulation and probing. In optogenetics, activities of the neural cells can be controlled by photostimulation of genetically modified neurons with a specific wavelength [1]. Researches have been carried out in mainly two representative branches, which are the development of opsin genes to modify the neurons and the development of control interface, which includes light sources and waveguides for light delivery to targeted neurons. Up to the present, various types of light delivery probes with enhanced performance and extended functionality have been reported. Examples include silicon-based μLED (micro Light Emitting Diode) [2], polymer waveguides [3,4], glass optrode array [5], and fiber-optic probes [6,7].

Fiber-optic probes were the principal drivers of the light delivery experiment in early-stage development. A bare optical fiber with tapered tip has been directly utilized as a light delivery probe. Direct illumination via optical fiber inherits the advantages of conventional fiber-optic systems such as coherence with narrow bandwidth and low light loss. Availability of various peripheral tools equipped with mature technologies is another advantage. Compared with other type of approaches, the fiber-based configuration provides superior scalability in probe length, which can be critical in some applications approaching deep brain regions. In terms of biocompatibility, many researchers have already experimentally validated the safety of fiber insertion into a living body and direct contact with neural cells. Nevertheless, direct insertion of μLED into brain still needs utmost care on both localized heat dissipation and electrical leakage. Most polymers are not fully validated in terms of biocompatibility and long-term stability, which are significant issues in chronical applications [8,9].

Despite the various advantages mentioned above, conventional fiber-based configuration still has several fundamental limitations [6,7]. First, it is difficult to implement an untethered and wirelessly controlled system due to the need for an external light source and resulting mechanical robustness issue of the fiber. The problem becomes even more complicated when a bundle of fibers is used or when the fibers are integrated along with additional electrodes for read out. Difficulties with forming an array and relatively low spatial resolution of the fiber are also challenging issues. Several approaches have been proposed as the solutions to these issues while maintaining the advantages of the fiber-based configuration [10–12]. These probes are implemented through the integration of segmented optical fibers and μLEDs. Direct integration of a two-dimensional (2D) array of μLEDs and fibers have been demonstrated and the feasibility of a wirelessly controllable system have been tested [8,9]. Wireless illumination of a single ferruled fiber has been demonstrated successfully [12]. These approaches are based

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on monolithic integration of the fiber and the light source, namely the butting method [13]. It is well known that direct butting of a fiber to a Lambertian light source maximizes the coupling efficiency when the areal ratio of the fiber cross-section to the luminous surface of the LED is less than unity, as demonstrated in above devices.

For the optical neural probes used in optogenetics, delivery of sufficient amount of light is critical. As the maximum power of light is predetermined by the performance of the LED, effective delivery of light becomes more crucial for a wirelessly controlled system operated by a limited amount of stored energy. A breakthrough technology to overcome the limitations of conventional butting method would be required, as the method still wastes a considerable amount of light even at the ideal maximum efficiency condition. For in vitro stimulation with a blue light source, light intensity required to activate the light-sensitive opsin is in the range of 1–5 mW/mm^2 [14,15]. However, in practice, the experiment involves a couple of undesirable optical phenomena, which are absorption and scattering in the brain tissue. Previous experiments showed that the intensity decreases to below 10% of the value at the tissue surface within only a few hundreds of micrometers [16,17]. Moreover, considering the misalignment between the targeted neurons and the probe tip after insertion, in vivo neurostimulation would require a much higher optical power at the probe tip compared to the previously reported in vitro test requirements. This is indirectly supported by the fact that the average maximum instantaneous optical power used in several animal experiments reported so far exceeds 0.9 mW [3,8,9,18–23], which corresponds to the light intensity of 28.6 mW/mm^2 when the light is delivered via a single 200 μm-diameter optical fiber.

Moreover, cost issue in the conventional LED-waveguide-based probes cannot be overcome with the systems based on monolithic integration of μLEDs and waveguides because a substantial portion of the system including LED and waveguides has to be disposed of after biological experimentation. The issue becomes even more challenging when the port count of the fibers and μLEDs increases or additional structures are integrated for advanced functionalities. Although it might be possible to use the probe repeatedly for another animal experiments after appropriate cleaning and sterilization, the potential risk of contamination and infection cannot be fully avoided.

In this paper, we present a new type of light delivery probe array system for optogenetic neurostimulation, where the total light power delivered at the probe tip from a single commercial LED has been substantially improved via a MEMS (Micro-Electro-Mechanical System) optrode array (MOA). Moreover, the MOA can be fully separated from the LED circuitry. The MOA consists of a 4×4 array of square-shaped glass microlens monolithically integrated with silicon guiding structure and assembled with high numerical aperture (*NA*) optical fibers. By utilizing the MEMS fabrication technology, we have fabricated disposable optrode array while improving the total light power delivery. The proposed approach can potentially lead to a new alternative for the design and fabrication of wireless fiber-optic neural probe for in vivo optogenetic applications.

2. Design

2.1. Overall design

Fig. 1 shows the schematic diagram of the proposed light delivery probe in cross-sectional view. The probe comprises two mechanically separable parts, which are the reusable LED driver unit and the disposable MOA. Both parts are packaged with customized polycarbonate housings and a set of latch structures is utilized for non-permanent assembly of two parts. During animal experiments, probes are inserted into the brain and the housing of the disposable MOA is fixed to the skull. The upper part of the housing, which contains LED and control circuitry, can be separated and reused after the experiment. In addition to the reusability for minimization of the wasted part, the device can be equipped with added functionalities, which were impossible to be implemented in previous configurations. By replacing the reusable unit, light source with different wavelength can be used without having to replace the inserted probes.

The reusable top unit consists of a domed top LED and its driver circuitry. The disposable bottom unit with an MOA consists of a 4×4 array of high *NA* optical fibers and matching array of square-shaped glass microlenses. The microlens array is formed on a silicon substrate and the optical path is secured via hole formed through the substrate. The via hole works as a fiber guide structure which provides both lateral and vertical alignment of the fiber to the microlens and substrate. Although only 4×4 array has been demonstrated in this work, proposed fabrication approach can be advantages in terms of the scalability of the probe array size, as the fibers are passively assembled with silicon substrate with integrated glass microlens array. Probe array with large port count can enhance the total output power and potentially be advantageous in researches on large area neural systems or applications targeted for larger mammals such as non-human primates [24,25].

Maximum achievable efficiency in coupling of an optical fiber with light source having Lambertian emission pattern is known to be proportional to the square of the fiber *NA* and the areal ratio of the fiber cross-section to the LED luminous surface, while unaffected by additional collimating optics when the areal ratio is less than unity [13]. In order to improve the light coupling efficiency above this limitation, we have utilized an LED whose luminous area is smaller than the total light receiving area of the fiber array. The method is analogous to the well-known approaches of enhancing light coupling efficiency by either coupling the bulb-ended fiber to planar LED [26] or deploying a spherical microlens between the fiber and the domed top LED [27]. Proposed method enlarges the light receiving area rather than reducing the size of the LED to less than a single fiber cross-section by adopting microlens array. This method has the advantage of simple fabrication process by utilizing commercially available LEDs with necessary requirements.

For the proof-of-concept, light delivery probe consisting of sixteen high *NA* optical fibers (FP200URT, Thorlabs, Inc.) with core diameter of 200 μm and *NA* of 0.5 has been proposed. The fibers are arranged in a square 4×4 array configuration with fiber pitch and a gap of 320 μm and 95 μm in both directions, respectively. Although it is true that relatively large diameter of the optical fiber and narrow gap between the optical fibers may cause damage to the tissue during the deep insertion, all the geometric parameters can be modified if required, at the cost of modification of optics design.

In contrast to bare LEDs, domed top LEDs generally have narrower viewing angle down to a few degrees and higher luminous intensity in the region of interest due to integrated converging microlens. Domed top LED (XZFBB78W, SunLED Electronic Co., Ltd.) with p-n junction size of approximately $200 \times 200\ \mu m^2$ has been selected considering the total light receiving area of the fiber array which is 0.50 mm^2. In reference to [13], calculated achievable maximum efficiency is over unity which indicates that ideal collimating optics could theoretically achieve light delivery from LED to fiber distal end without any loss.

The diameter of the dome and viewing angle are 1.8 mm and $\pm 10^\circ$, respectively. As the selected LED has relatively low viewing angle, emission from the source has been assumed to be a plane wave for design simplification. In this case, the area ratio of the light receiving region of the microlens array to the light transmitting region of the LED indicates the coupling efficiency between the LED and the MOA. Microlenses are arranged in order to maximize