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TOPICAL REVIEW

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## Topical Review

# Single-channel opto-neurostimulators: a review

**Weiyang Yang, Wasif Khan, Jiajia Wu and Wen Li**

Electrical and Computer Engineering Department, Michigan State University, East Lansing, MI, United States of America

E-mail: wenli@egr.msu.edu

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**Abstract**

Optogenetics is a revolutionary neuromodulation technique to excite or inhibit the activity of the targeted neurons that express light-sensitive opsin proteins. Opto-neurostimulators as neural interface devices are significantly important for optogenetic applications in neuroscience and future clinical research. To date, a wide variety of optical stimulators have been developed and could be classified into two broad categories: single-channel and multi-channel stimulators. Although multi-channel opto-neurostimulators allow spatially controlled optical stimulation of cells, they require complicated fabrication procedures and might require specialized coupling strategies at the distal end of the optical source. As an alternative, single-channel opto-neurostimulators are gradually being prevalent in many applications for their simplicity, ease of use, and low cost. We have reviewed a variety of single-channel optogenetic neural stimulators that were developed in recent years, based on different light sources, material selection, and tethered or wireless systems. This paper accumulates and summarizes these single-channel opto-neurostimulators to provide a comprehensive outlook for the trend of this field.

Keywords: optogenetics, single-channel, optical neurostimulator

(Some figures may appear in colour only in the online journal)

## 1. Introduction

Optogenetics is a revolutionary neuromodulation technique that uses light to excite or inhibit the activity of the target neurons expressing light-sensitive opsins [1]. In contrast with electrical stimulation where there is a possibility to stimulate unwanted neurons, optogenetic stimulation is highly selective, thereby enabling analysis of specific neural circuit functions underlying various diseases [1–3]. Besides cell-type specificity, optogenetics allows for rapid excitation of neuronal populations with millisecond temporal precision and in a fully reversible manner [4], as well as less damage to tissue [5]. To date, a wide variety of optical stimulators have been reported and can be classified into two primary categories: single-channel and multi-channel stimulators. Different configurations of multi-channel opto-neurostimulators have previously been reported, which typically consist of individual optical fibers and waveguides separately coupled to different light sources [6], or an array of microscale light emitting diodes ($\mu$-LEDs) directly assembled on solid or flexible substrates [7–9]. Particularly, multi-channel LED-based neurostimulators have become prevalent because of their low power consumption, illumination stability, fast switching ability [10], and the possibility of miniaturization towards a fully implantable neural interface. The primary advantage of these multi-channel stimulators is to offer spatially controlled, optical stimulation with high spatial resolution. While they have moved the field forward, development of such multi-channel devices requires complex and expensive microfabrication and integration technologies [11].

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Single-channel opto-neurostimulators provide unique advantages over multi-channel devices, such as low power consumption, miniaturized dimensions, fabrication simplicity, and low cost. Over the last decade, great efforts have been made to develop various single-channel optoelectronic devices that are light-weight and compact. However, these devices are not yet commercially available for chronically reliable, optical stimulation in neuroscience and clinical research [12]. An ideal single-channel optical neurostimulator should enable precise manipulation of the target neurons with minimal power consumption. Miniaturization of the devices is imperative to reduce surgical invasiveness as well as tissue inflammation and damage. In addition, the device should ideally be constructed and packaged with biocompatible and mechanically flexible materials that ensure minimum tissue damage while simultaneously protecting the functioning electronics from the corrosive biological environments over the long term. For behavioral experiments particularly, an untethered device would be desired to enable free movement of the experimental subjects and prevent unwanted interference to the experimental outcomes. All these considerations place unique constraints on the light sources, materials, and system architecture of single-channel optical neurostimulators.

In this article, we reviewed the recent development of single-channel optogenetic neural stimulators in the past decade, in terms of different light sources, materials, and system implementation, with a motivation to accelerate the research on single-channel opto-neurostimulators and to provide a guideline on the appropriate design choices to assist future development of specific applications using these interfaces. The whole article is organized as follows. Section 2 discusses various single-channel optical stimulators based on different optical sources: lamp, laser, laser diode (LD) and LED [4, 13–16]. Material selection of the optical devices is critical to ensure their chronic biocompatibility, safety, and reliability, which will also be discussed in this section. Section 3 focuses on two approaches of system-level implementation, namely, tethered and wireless approaches. Two different wireless strategies, battery powering and electromagnetic (EM) coupling, will be reviewed and compared. Finally, a conclusion and outlook is provided, aiming to provide researchers with an insightful overview of the state-of-the-art devices, and put forward the future and potential in this field.

## 2. Single-channel optical devices for neuromodulation

### *2.1. Light sources*

Light sources are one of the key components of the optogenetic interface systems. Selection of proper optical devices for excitation or inhibition very much depends on different organisms or tissues where the device will be applied as well as experimental environments. Specifications under consideration may include but are not limited to, central wavelength, light intensity, physical dimensions, illumination volume size, long-term stability, and cost.

There are four major types of light sources commonly used in optogenetics: lamp, laser, LD, and LED. Early designs of the single-channel devices relied on a laser or LD coupled optical fiber [16, 17]. However, multi-mode optical fibers usually have a core diameter of 50–200 $\mu$m, which is too bulky to precisely control the light stimulation spot, and cannot be integrated with microelectrodes for applications that require simultaneous recording of optically-evoked neural activity [18]. Recently, several groups have developed microfabricated, LED-based stimulating devices [7–9] with integrated recording microelectrodes to achieve a precisely controlled, multi-modal interface with neurons. Single-channel optical systems based on other light sources have also been reported. The pros and cons of these light sources will be discussed in more details in the following subsections.

*2.1.1. Lamp.* Lamps provide continuous wavelength from ultraviolet (UV) to infrared (IR) spectrum with high radiant intensity. Different lamps, such as xenon lamps, mercury lamps, mercury–xenon lamps, and metal halide lamps have unique light profiles and spectral peaks, which should be carefully considered for target optogenetic opsins [4, 16, 19]. Among these, xenon lamps have the most uniform spectral output across the visible range, while the mercury-xenon lamps emit a board wavelength with sharp peaks in the UV and visible regions corresponding to mercury's spectral lines. To select the desired wavelength of the emitting lamp, interference filters or diffraction grating systems are typically incorporated [19, 20] to attenuate light at unwanted wavelengths. A filter wheel or a shutter (electronic, mechanical or acoustic) can also be added to control and adjust the light illumination [21–23]. However, the operating time of the shutter is typically longer than 3 ms, which is slower than the kinetics of most channelrhodopsin variants (typically in ~1.21 ms) [24]. Coupling a lamp into a submillimeter optic fiber also presents significant challenges, making it impractical for spatially defined stimulation. Other limitations of the lamp-based systems include the large housing size and the short lifespan that is typically less than 200 h for the mercury lamps and 2000 h for the metal halide lamps [25]. As such, whereas lamps are easily available in most laboratories [26], they have not been widely adopted in optogenetics studies due to the complex system assembly, limited spatial resolution, and lifetime.

*2.1.2. Laser/laser diode (LD).* The first optogenetics experiments were conducted by utilizing the lasers, which can be coupled efficiently with the submillimeter optical fiber because of their high intensity, highly directional output, and low divergence of light beams [27, 28]. For example, Ozden *et al* designed and tested a laser-coupled, single-channel coaxial optrode as a multi-modal probe for optogenetic studies in non-human primates [29]. Compared to lamps, lasers and LDs have a narrow spectral linewidth of 0.1 nm or better, which permits precise manipulation of a specific opsin without cross-talking while eliminating the need for additional filters [30]. Optical components, such as a free-space fiber launch system [31], can also be incorporated in the beam

path of a laser, to rapidly direct high-intensity light to the targeted region. As an attempt towards therapeutic optogenetic implants, Paralikar *et al* demonstrated a laser diode-coupled dual wavelength stimulator [32], which was able to generate 5.3 mW $mm^{-2}$ optical power density at 50 mA. This implant had specifications comparable to commercially available deep brain stimulation systems and was compatible with MRI/EMI.

Despite their many advantages, the major drawback of lasers and LDs is their limited options of wavelengths, which may not accommodate a wide variety of optogenetic opsins. The safety regulation for laser and LD operation is stricter than that of LEDs [33]. In addition, application of lasers and LDs in *in vivo* optogenetics requires tethering to optic fibers [34, 35] or polymer waveguides [36]. There are critical challenges concerning the negative impact of tethering on the subject's natural behavior [37], the limited optical power transmitted from the microscale fiber/waveguide to the target tissue, and light leakage at the laser-fiber junction [36].

*2.1.3. Light emitting diode (LED).* As an alternative light source, $\mu$-LEDs have been widely used in optoelectronic neural interfaces. Several $\mu$-LED-based single-channel neurostimulators have been developed and successfully validated both *in vitro* and *in vivo* [38–41]. Compared to other light sources, $\mu$-LEDs provide unique advantages for optogenetics applications. First, $\mu$-LED can be integrated with simple and miniaturized circuit architectures for easy installation on the animal's head [42]. $\mu$-LEDs can be driven by battery [43], inductive power telemetry [41], or ultrasonic powering interfaces [44] to achieve truly untethered optoelectronic systems for optogenetics studies in freely moving subjects [45, 46]. Furthermore, the light intensity of the LED can be controlled by tuning current or voltage amplitude, and the light pulses can be directly modulated at high speed with little distortion in pulse shape [47]. Besides direct amplitude modulation, pulse-width modulation of the intensity has also been demonstrated, which provides sufficient optical power with relatively low electrical power requirements and minimal heat generation [42]. LEDs are also cost-effective and have a long lifespan of about 10 000 h to 100 000 h [48].

Despite the aforementioned benefits, LEDs suffer from overheating when operated under high current intensity [49, 50]. Increase in local temperature may alter neural activity, change behavior outcomes, induce thermal artifacts, and result in irreversible cell damage and even cell death. To mitigate the overheating effect, the input power of LEDs needs to be carefully controlled, which, however, limits the effective illumination volume. Incorporating a heat sink with the light source is another potential solution to overheating [29, 51], but these extra components inevitably increase the overall geometry of the device. Also concerned is the diverged light beam profile of the LEDs, resulting in poor output light intensity when coupled with optic fibers or waveguides. Typically for a blue LED coupled fiber stimulator, 20–30 mW is the maximum achievable output at the fiber tip due to the low efficiency of the butt coupling [29]. To address this challenge, Khan *et al* proposed a reflector-coupled optical stimulator, where a spherical silicon cavity acts as a reflector to collect the backside illumination of a $\mu$-LED and to focus the diverged light beams [52]. With the reflector, the overall output light intensity could be improved by over 60% as compared to a bare $\mu$-LED [40].

### 2.2. Material selection

Development of single-channel optical stimulators requires careful consideration of a multitude of material's factors. These factors include, but are not limited to, mechanical flexibility, biocompatibility, biostability, dielectric strength, hermeticity, and optical properties of the materials involved. The combination of material properties chosen not only determines the device performance but also the extent to which the body reacts to the implanted devices [53]. With the rapid growth of microtechnology, many unconventional organic and inorganic materials have been applied to the fabrication of optoelectronic neural interfaces, including the interface materials with the neural tissues and the packaging materials for electronics protection.

Among various interface materials, silicon has been the most popular substrating and structural material for neural implants to achieve high-resolution microstructures using traditional integrated circuit fabrication techniques [54]. However, the opacity of silicon can cause significant attenuation in light intensity and non-uniform distribution of light delivery to neurons [55]. Glass core has also been utilized as the sharpened tip to reduce the thickness of a multi-mode optical fiber for improving spatial resolution and minimizing the tissue damage during device insertion [56]. In addition, inorganic waveguiding materials, such as oxynitride thin films, provide superior optical properties as well as low water absorption rate and hermeticity for applications in chronic implantation [57]. Despite their many advantages, the stiffness of these inorganic materials yields the mechanical property mismatch with the soft brain tissues [58]. As such, the small movement of the rigid implants may damage the neural cells and cause negative tissue responses, inflammation, or scarring [59–61].

In contrast, polymeric materials possess a unique combination of optical transparency, biocompatibility, mechanical flexibility, and chemical inertness. Therefore, various polymers, such as poly-(ethylene terephthalate) [62], SU-8 [36] and Parylene C [9], have been utilized extensively as interface materials for a substrate or waveguiding structures in optoelectronic neural interfaces. For example, SU-8 is commonly used as a waveguiding material because it has a high refractive index and can be easily patterned with UV lithography techniques [55]. However, SU-8 has high absorption loss near 473 nm wavelength, resulting in a significant decrease in the light guiding quality [63, 64]. SU-8 also suffers from high moisture permeation and absorption, and thus is not suitable for long-term implantation.

Polymers have also been widely used as packaging materials in optoelectronic neural interfaces, because of their aforementioned properties. However, polymer films have high porosity and hygroscopicity, which can reduce the long-term stability of device performance [65, 66]. To address this

challenge, hybrid inorganic–organic films have been explored to reduce the moisture permeability of polymers while maintaining their biocompatibility and flexibility. For example, there is evidence that metal-coated Parylene-C can keep the device intact inside the organisms for more than ten years [67]. Parylene combined with atomic-layer-deposited alumina has also been proven to be capable of protecting the Utah electrode array from corrosion during 200 d soaking test in phosphate-buffered saline at 37 °C [68, 69]. Besides moisture/gas permeation, heat generated from the light source is another main cause of the failure of the polymer package, since most polymers have low glass transition temperatures and poor thermal conductivity [70]. To reduce the thermally-induced device failure, materials with high thermal conductivity, such as diamond and sapphire, have been explored by several groups as a heat spreader to dissipate the heat rapidly to the surrounding tissues [71, 72]. However, the mechanical rigidity of such materials still remains unsolved.

## 3. System-level implementation

### 3.1. Tethered system

By definition, tethered integration for neural interfaces consists of physical wiring or connections of the stimulation devices with external power sources or data acquiring systems. Tethered single-channel optogenetic stimulators usually use thick optical fibers of a few hundred microns to deliver light from light sources to the nervous tissues [16]. Microscale waveguides made out of dielectric materials [57] or polymers [36, 73] can be coupled with optical fiber to enable optogenetic neuromodulation with improved spatial resolution and minimal power. SU-8 waveguides can sometimes be covered with oxide cladding that can enhance the efficiency of light delivery and prevent side leakage [57]. Besides waveguides and optical fibers, other optical elements have also been explored for light delivery to local neurons. For example, Park *et al* demonstrated a single-channel optical probe where a chemically etched silicon mirror was coupled with a LD to selectively guide the light beam to the target neurons [54]. A one-touch butt-coupling jig was designed to facilitate the alignment and assembly of the silicon mirror with the light source. Wire tethered, single-channel $\mu$-LED stimulators have also been implemented on polyimide substrates [74, 75], which showed advantages over fiber-coupled laser-based optrode, in terms of the closed-loop integration, single-implant compactness, and lower electrical power requirements.

Despite their simplicity and efficacy, single-modal optical stimulators lack the ability to directly detect the changes in neural activity resulted from the optical stimulation. As such, behavioral outcomes, imaging, or immunohistological analysis are normally used as indirect measures of the light-evoked neural responses. To facilitate *in situ* neural circuit analysis and bridge the gap between optogenetics and neurophysiology, dual-modal optrodes [29, 36, 57, 76, 77] have been developed by several groups, in which an optical fiber or waveguide enables single site stimulation optically while a single or multiple electrodes enable extracellular recording of light-evoked neural activity. The integrated electrodes are usually made out of noble metallic materials, such as gold [28], platinum [35], or iridium [73]. Unconventional materials, such as carbon monofilament [76] and polyethylene and 5% graphite [78], have also been utilized as electrode materials for neural recording with significantly reduced photoelectric artifacts. In addition to stimulation and recording modalities, microfluidic channels have also been integrated into the opto-electronic neural interfaces to enable drug delivery or gene transfection to local neurons with high precision and efficiency [36, 78, 79].

Apart from the central nervous systems, single-channel optogenetic stimulators have also been utilized in the peripheral nervous systems (PNS) and other excitable cells. For example, Nussinovitch *et al* [17] demonstrated an optical fiber coupled single-channel stimulator for cardiac pacing and re-synchronization of the heart at different beating frequencies with blue light illumination both *in vivo* and in isolated perfused hearts. For PNS stimulation, Michoud *et al* [80] utilized a single-channel tethered optical fiber to construct an optical cuff for stable stimulation of the axons of the sciatic nerve. The cuff was fabricated using a gold-coated, 150 $\mu$m-thick silicone spun on a polystyrene rod template, and the silicone cuff was perpendicularly coupled to a 150 $\mu$m inner diameter optical fiber.

Significant improvement in optogenetic interfaces, as well as results in neuroscience research, has been accomplished using these tethered optical stimulators. However, wire tethering significantly limits the mobility of the animal subjects and restrict the animals from entering small entrances or to follow complex routes, such as a maze. Tethered interfaces at some extent limit the natural social interaction among multiple animals. In addition, a tethered interface requires manual attach/detachment of the tethered coupling, which could cause discomfort or pain of the subject that might lead to unwanted deviation in the behavioral outcomes or artifacts in neural recordings [81–83]. The tethering may also increase the risk of tissue damage and inflammation [82].

### 3.2. Wireless system

Implementing a wirelessly controlled optical stimulator, along with wireless data telemetry, provides a practical approach towards a fully implantable neural interface to eliminate the aforementioned disadvantages of tethering. Recently, several attempts have been made to develop wireless single-channel opto-neurostimulators based on different powering mechanisms, battery and EM coupling, which will be reviewed separately in the following sub-sections.

*3.2.1. Battery-powered system.* A battery-powered optical stimulation system is normally configurated into a head-mounted headstage, consisting of a power module, a control module, and an optical module [43, 83–85]. The control module typically includes a microcontroller and its peripheral electronics assembled on a printed circuit board (PCB) to control the parameters of optical stimulation. For dual-modal stimulation/recording systems, the built-in Bluetooth interface of

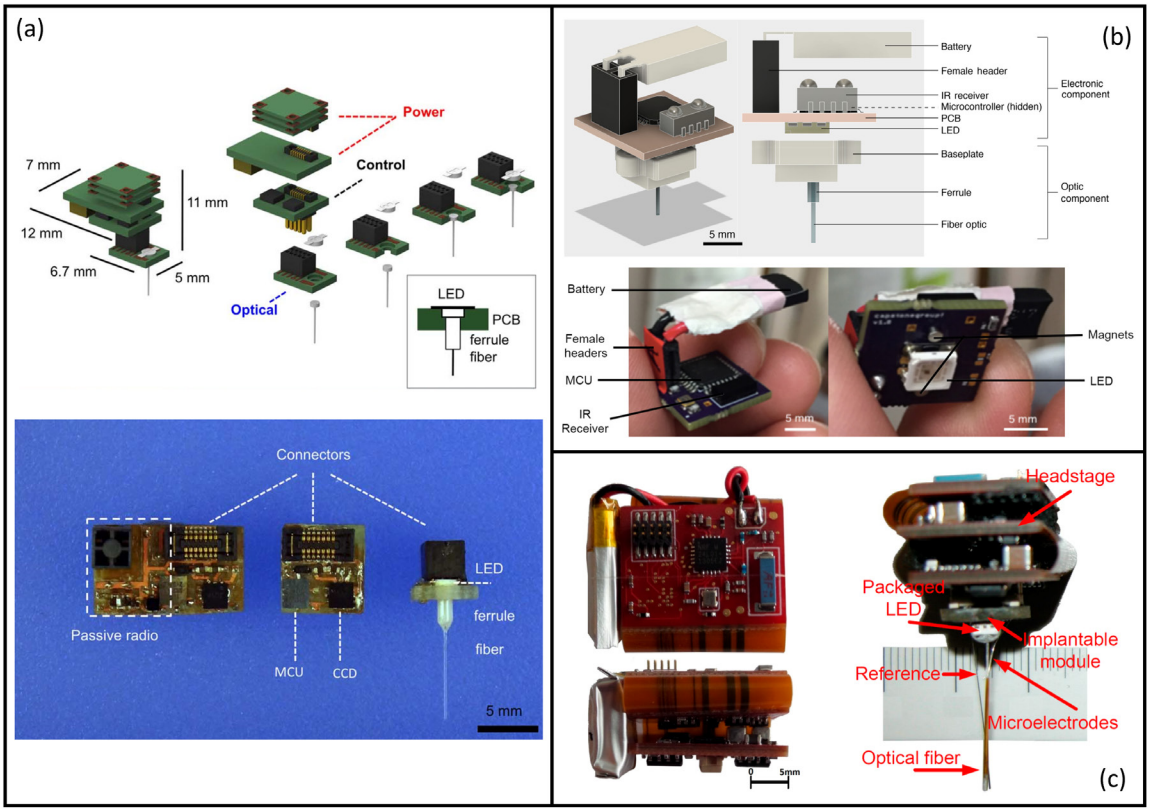


**Figure 1.** (a) A battery-powered, single-channel, modular optical stimulator with controllable stimulation parameters for achieving deep brain optical stimulation in freely behaving mice. Bottom image shows the fabricated control modules for wireless (left), internal triggering (middle), and the optical module (right) with a fiber-ferrule coupled with an LED. © 2015 IEEE. Reprinted, with permission, from [43]. (b) CerebraLux (battery-powered, 0.95 $cm^3$ dimension, single-channel, optogenetic probe) consisting of two magnects-aligned main components (electronic and optical component). Reproduced from [84]. CC BY 3.0. (c) A battery-powered, single-channel, optogenetic headstage capable of opto-stimulation and electrophysiological recording for experiments with small transgenic rodents. Reproduced from [85]. CC BY 4.0.

the microcontroller also enables wireless data transmission between the headstage and the external data storage and processing unit [85]. The optical module carries an LED light source, with or without an optical fiber, to deliver the light to the targeted neurons. The power stage mainly consists of batteries and associated voltage regulating circuitry to provide sufficient power for driving the control module and light source [43]. Various batteries, such as non-rechargeable lithium batteries as well as rechargeable solid-state batteries [83] and lithium polymer (LiPo) batteries [84], have been used in the single-channel optical stimulators. Since non-rechargeable batteries have a limited lifespan, rechargeable batteries in combination with energy storage capacitors are more desirable, which can be charged through inductive telemetry [43] or light [84]. Passive power supply filter network has also been incorporated after the regulating stage to improve the stability of the LED input and remove potential optical fluctuation [85]. For device applications in animal experiments, the optical fiber is usually implanted in the targeted brain region, while the LED and circuitry are cranially mounted and fixed to the skull using screws, dental cement [43, 84, 85] or fast-acting adhesive [83]. Custom designed interface connectors, such as magnets on the PCB, have been utilized to enable the easy attachment of the headstage while facilitating the correct alignment between the optic fiber and LED [84]. To reduce discomfort or interference with the subject's natural behavior, compact volumetric dimensions and light weight head-mounted systems are required. Current research prototypes typically have a volume size of 1 to 3 $cm^3$ and an overall weight of 1 to 7 g including the battery.

Figure 1 shows several examples of the battery-powered single-channel systems. A battery-powered, single-channel, modular optical stimulator with controllable stimulation parameters was reported by Lee *et al* for achieving deep brain optical stimulation in freely behaving mice [43] (figure 1(a)). This wireless stimulator consists of three connecting modules, including power, control, and optical modules. Two 50 $\mu$A-Hr batteries are stacked in parallel on top of the control module with optical module undersneath. Direct butt-coupling of the fiber to the LED ensures 27 mW $mm^{-2}$ illumination at 21.01 mA input current of LED. The stimulation has dimensions of $12 \times 7 \times 11\,mm^3$ ($L \times W \times H$) and a weight of less than 1.6 g. The temperature increase at the bottom of the optical modulus joint to the optical fiber is within 0.8 °C. As another example, Dagnew *et al* developed a battery-powered, CerebraLux system consisting of two magnect-aligned components (electronic and optical component) [84] (figure 1(b)). The electronic component includes a custom PCB, an IR receiver, a microcontroller, a 3.7 V, 20 mAh light-rechargeable lithium polymer (LiPo) battery, and a LED at the bottom

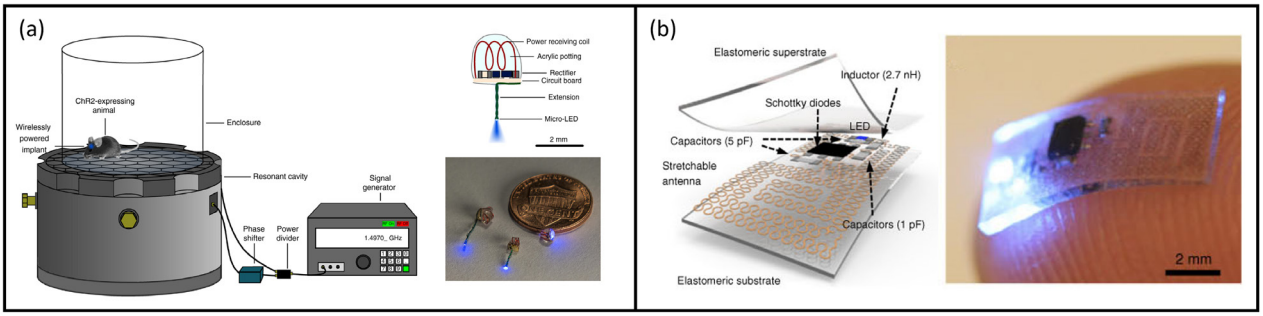


**Figure 2.** (a) An implantable, far-field wireless optogenetic device powered by a resonant cavity for brain, spinal cord or peripheral nerve ending stimulation. [39] Copyright © 2015, Springer Nature. With permission of Springer. (b) A far-field, single-channel, soft optoelectronic systems with stretchable wireless radio power and control systems for optogenetic modulation of spinal cord and peripheral nervous system. [46] Copyright © 2015, Springer Nature. With permission of Springer.

of PCB. Optical component includes a fiber optic-ferrule and a baseplate for holding the fiber in place. Total weight of the device is 2.8 g with 2.3 g for the electronic component and 0.5 g for the optic component, respectively. This device can produce $824 \pm 17$ $\mu$W power, leading to irradiance of $4.2 \pm 0.1$ mW mm$^{-2}$ when coupled with a 500 $\mu$m diameter fiber. Recently, Gagnon-Turcotte *et al* reported a dual-mode, battery-powered system for optical stimulation and neurophysiology recording in small transgenic rodents [85] (figure 1(c)). This system consists of an implantable module (LED-coupled optic fibers and microelectrodes) and a headstage that contains five blocks: an analog front-end, optical stimulation circuitry, a power management unit, a wireless transceiver, and a mixed-signal controller. The headstage is $25 \times 20 \times 15$ mm$^3$ and weighs 4.9 g. The lithium-ion battery is able to continously power the headstage for up to 3 h. The measured optical power density at the tip of the optic fiber is 70 mW mm$^{-2}$. The neural recordings are amplified and conditioned by the analog front end, and transmitted wirelessly to an external station by the transceiver at a maximum effective rate of 0.7 Mbps. A microcontroller FunkOS controls the parameters of stimulation with the context switching latency of about 35 $\mu$s at 8 MHz. Sleeping Task mode is implemented in this system, which enables 3.3 mW power saving when the sleeping task occupies 73% of the time duration.

While useful in many applications, these battery-powered systems suffer from the limited operational time between charges, mainly due to the low current capacity of the battery. Particularly, the instantaneous current required for driving LEDs may be prohibitively large in rodent experiments when high light intensity is required, e.g. for deep brain stimulation or behavioral studies. Previous studies have shown that the light intensity required to trigger changes in mouse behavior is 6–40 mW mm$^{-2}$ [39], much higher than the cellular level activation intensity of 1.2 mW mm$^{-2}$ for 406 nm wavelength or 2.3 mW mm$^{-2}$ for 589 nm wavelength [86]. In addition, the battery is much bulkier than the dimensions of electronics which sets the limit on further miniaturization of the system.

*3.2.2. Far-field EM coupling system.* Wireless power transfer based on EM coupling provides a truly untethered, battery-free solution to driving neural stimulation systems when periodic charging or replacement of batteries is impractical. The region of the EM wave can be classified into near-field and far-field, depending on the distance of wave travel, also known as the Fraunhofer's distance. The Fraunhofer's distance is defined as $d_f = 2D^2 f/\nu$, where $D$ is the diameter of the transmitter antenna, $f$ is the frequency of the transmitting wave, and $\nu$ is the wave velocity ($3 \times 10^8$ m s$^{-1}$ in air). Far-field EM coupling enables power transfer over a long distance, which is ideal for use in large animal models or freely moving animals. Several groups have already demonstrated wireless optogenetic stimulation approaches utilizing far-field EM coupling to drive LED light sources [26, 39, 87]. For example, Montgomery *et al* [39, 88] demonstrated a single-channel, easy-to-construct, optogenetic implant for optical stimulation of the brain, spinal cord, or peripheral nerve endings (figure 2(a)). The implant consists of the power receiving coil, rectifier circuit board, and a blue $\mu$-LED on the tip of an extended wire. The LED is powered by a 21 cm diameter, 15 cm height aluminum resonant cavity at a radio frequency (RF) of 1.5 GHz with 19% power transferring efficiency. This results in an optical power density of 1–20 mW mm$^{-2}$, suitable for optogentic stimulation. The overal dimension and weight of the implant are 10–25 mm$^3$ and 20–50 mg, respectively, depending on the target neural structure. While promising, the heating effect of the implant is significant, resulting in a local temperature change of over 1 °C when the duty cycle is around 40%. In the approach developed by Park *et al*, the LED light source is driven by a fully implantable, wireless radio power and control system, where a stretchable antenna acts as an RF harvesting unit to receive signals from a transmitter through capacitive coupling at 2.34 GHz or 2.7 GHz [46, 87] (figure 2(b)). The received power after transferring is reduced by 10%–20% corresponding to the 3%–6% decrease in optical output power as a result of 30% LED's conversion efficiency. The optical power density of this device is 10 mW mm$^{-2}$ with 40% duty cycle [46]. Encapsulated by silicon elastomer, the device is flexible and stretchable with dimensions of $0.7 \times 3.8 \times 6$ mm$^3$ and weight of only ~16 mg.

Compared to battery-powered systems, the far-field RF systems are much smaller (typically in the range of 10–25 mm$^3$) and lighter (20–50 mg), more suitable for small animal models, such as mice. However, due to the small device dimensions, the far-field EM coupling must be operated at relatively high frequencies between 420 MHz to 2.4 GHz [89], which may

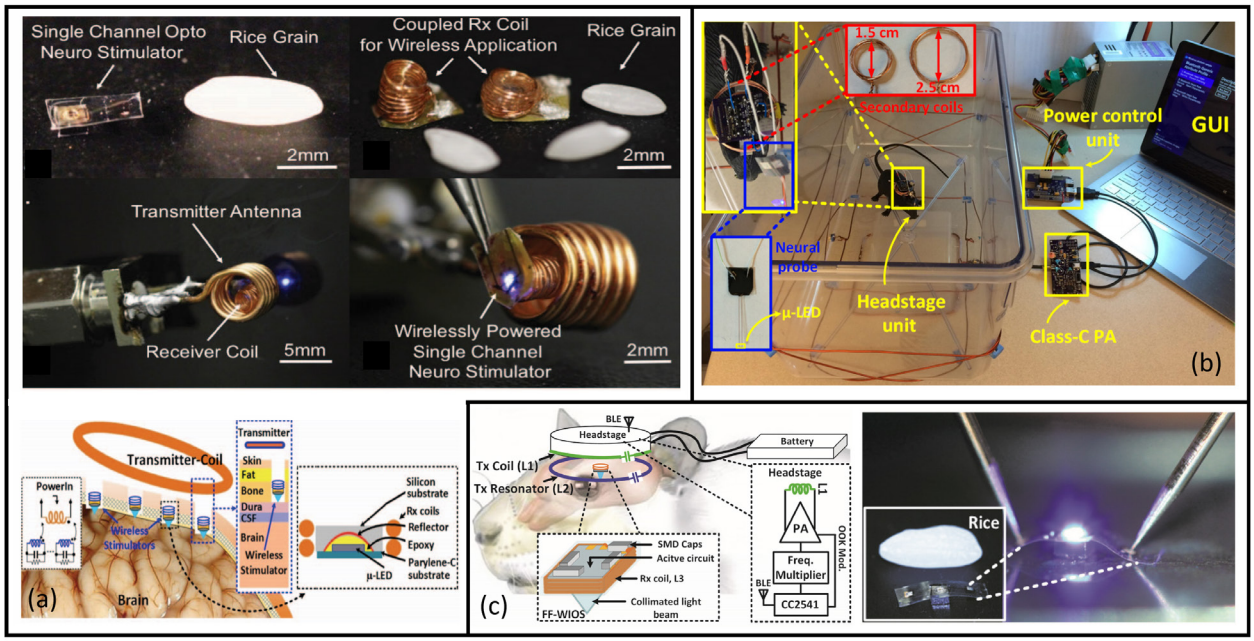


**Figure 3.** (a) A near-field, miniaturized, wireless single-channel stimulator powered by a two-coil telemetry link. © 2018 IEEE. Reprinted, with permission, from [40]. (b) A closed-loop wireless home-cage for optogenetic stimulation experiments with a wireless headstage. © 2015 IEEE. Reprinted, with permission, from [99]. (c) A near-field, mm-sized, single-channel, free-floating wireless optogenetic stimulating implant. © 2017 IEEE. Reprinted, with permission, from [91].

increase the risk of microwave-induced heating and over-exposure of the EM radiation of the stimulated tissues [90]. In addition, the far-field EM coupling systems are very sensitive to the size of the experimental subjects. As such, human subjects without surpassing the specific absorption rate (SAR) limit at a high frequency is challenging [91].

*3.2.3. Near-field EM coupling system.* Compared to far-field EM coupling, near-field EM power transfer relies on inductive coupling through pairs of antenna coils [40, 92] to sufficiently power the light sources at much lower frequencies (<135 MHz) [91] without surpassing the SAR limits. For example, Shin *et al* [93] developed a miniaturized, injectable optogenetic implant, which uses subdermal magnetic coil antennas to wirelessly power LEDs at 13.56 MHz. The coil telemetry is carefully designed to enable full wireless coverage across various cage types while having little sensitivity to physical obstructions and environmental interferences, such as metal components, water, and moisture. As another example, Khan *et al* reported a tiny wireless single-channel stimulator, which consists of a $3 \times 2\,\text{mm}^2$ reflector-coupled $\mu$-LED source and a 2 mm inner diameter and a nine-turn receiver coil [40] (figure 3(a)). The transmitter coil is constructed in a solenoid configuration with a 5 mm inner diameter and six turns. The two-coil inductive link is optimized with a maximum power transmission efficiency of 4% at a low resonant frequency of 96 MHz for wireless powering of $\mu$-LED. The light intensity of the stimulator exceeds the minimum required intensity of 1 mW $\text{mm}^{-2}$. The overall temperature rise of this reflector-couple stimulator is below 0.5 °C.

Since the total efficiency of the near-field power transfer mainly depends on the performance of the receiver circuitry [94], significant efforts have been made to design and develop high-performance receiver modules. Ammar Aldaoud *et al* [95] employed multiple coils in the receiver module to selectively turn on different color LEDs at different carrier frequencies of 5–25 MHz. This approach eliminates the power-hungry and area-consuming electronics, while having the ability to address and modulate individual light sources by shifting this complexity to the external wireless power transmitter. Recently, a very compact receiver module was designed by Biwas *et al* [96], which consists of a miniaturized $6 \times 6\,\text{mm}^2$ receiver antenna and a Schottky diode to efficiently deliver 200 mV DC voltage to a mini-LED at a low carrier frequency of 7.15 MHz and at a 5 mm distance.

Multi-coil telemetry configurations have also been utilized to further enhance the near-field EM coupling efficiency. For example, Jia *et al* [91] demonstrated a resonator-based three-coil inductive link to continuously power a free-floating, mm-sized $\mu$-LED implant at an optimal frequency of 60 MHz with 37% total efficiency [97] (figure 3(c)). The implant has a very low power consumption of around 170 $\mu$W. Building on this work, a wireless power transmission (WPT) home-cage was recently developed by the same group [98, 99], where a four-coil resonant link was used to wirelessly power an optogenetic headstage, a motion tracking system, and a base station (figure 3(b)). The headstage integrates a surface mounted LED with four recording microelectrodes in a compact ($1.7 \times 2 \times 1.6\,\text{cm}^3$) and lightweight (4.2 g) package. The home-cage is equipped with magnetic resonance-based WPT module to deliver 51 mW to the headstage up to the maximum elevation of 10 cm at 13.56 MHz, and a bluetooth low energy module for wireless data communication. The overall dimensions of the home-cage are $20 \times 40 \times 20\,\text{cm}^3$, specifically designed for rodent experiments. Similarly, the WPT home-cage designed by Maghsoudloo *et al* [100] featured a

**Table 1.** Comparison of representative single-channel optical stimulators based on different system configurations.

| Reference | Tethered or wireless | Light source | Power consumption | Output light intensity | Dimensions | Weight | Wearable or implantable | Increased temperature |
|---|---|---|---|---|---|---|---|---|
| [16] | Tethered | Lamp (*in vitro*); LD (*in vivo*) | 300 W; 380 mW mm$^{-2}$ | 20 mW; 10 mW mm$^{-2}$ | 200 $\mu$m diameter | — | Implantable | — |
| [17] | Tethered | $\mu$LED | — | 1.95–4.06 mW mm$^{-2}$ | 3.03 $\pm$ 0.53 mm | — | Implantable | — |
| [29] | Tethered | Laser | 16 mW | 1 mW mm$^{-2}$ | 310 $\mu$m diameter | — | Implantable | 0.018 (10 $\mu$m aperture); $6.6 \times 10^{-5}$ °C (200 $\mu$m) |
| [36] | Tethered | Laser | 35 mW | 88.9 mW mm$^{-2}$ | 150 $\times$ 150 $\mu$m$^2$; 7 mm length | — | Implantable | — |
| [57] | Tethered | Laser | 7 mW | 51 mW mm$^{-2}$ | 50 $\mu$m diameter; 5 mm length | — | Implantable | — |
| [75] | Tethered | $\mu$LED | — | 0.7 mW mm$^{-2}$ | 12 mm length; 900 $\mu$m wide | — | Implantable | — |
| [77] | Tethered | Laser | 150 $\mu$V | 500 $\mu$W–5 mW | 1 mm length | — | Implantable | — |
| [43] | Battery-powered wireless | LED | Two 50 $\mu$A-Hr batteries | 27 mW mm$^{-2}$ | 12 $\times$ 7 $\times$ 11 mm$^3$ | <1.6 g | Implantable | <0.8 °C |
| [83] | Battery-powered wireless | $\mu$LED | 5 V battery input | 5.5–7 mW | 7 $\times$ 7 $\times$ 5 mm$^3$ | 3.1 g | Implantable | — |
| [84] | Battery-powered wireless | LED | A 3.7 V, 20 mAh battery for 35 min | 4.2 $\pm$ 0.09 mW mm$^{-2}$ | 0.95 cm$^3$ | 2.8 g | Implantable | — |
| [85] | Battery-powered wireless | LED | 1 mA @ 3.0 V (3 mW) | 70 mW mm$^{-2}$ | 25 $\times$ 20 $\times$ 15 mm$^3$ | 7 g | Implantable | — |
| [39] | Far-field wireless | $\mu$LED | ~10 mW (19% efficiency) | 20 mW mm$^{-2}$ | 10–25 mm$^3$ | 20–50 mg | Implantable | >1 °C |
| [46] | Far-field wireless | LED | 2.7 V | 10 mW mm$^{-2}$ | 0.7 $\times$ 3.8 $\times$ 6 mm$^3$ | 16 mg | Implantable | No detectable change |
| [40] | Near-field wireless | $\mu$LED | — | <20 mW mm$^{-2}$ | 3 $\times$ 2 mm$^2$ | — | Implantable | <0.5 °C |
| [91] | Near-field wireless | $\mu$LED | 1.8 V, 95 $\mu$A | — | 1 $\times$ 1 mm$^2$ | — | Implantable | — |
| [93] | Near-field wireless | $\mu$-ILED | — | <50 mW mm$^{-2}$ | 9.8 mm diameter | ~30 mg | Implantable | <0.8 °C |
| [95] | Near-field wireless | LED | 10 W input power | <30 mW mm$^{-2}$ | 2 mm diameter; <5 mm length | <1 g | Implantable | <1.6 W kg$^{-1}$ SAR limit |
| [96] | Near-field wireless | $\mu$LED | 200 mW | — | 6 $\times$ 11.25 $\times$ 1.72 mm$^3$ | Antennas 20–25 mg | Implantable | — |
| [100] | Near-field wireless | LED | 74 mW PDL | 29.4% PTE | 1 cm diameter | — | Implantable | — |

hybrid power transmitter coil array and the segmented multi-coil resonators, while the receiver module contains a receiver coil and a resonator coil. At 13.56 MHz, the average power transfer efficiency from the home-cage to the receiver coil was 29.4% at a nominal distance of 7 cm.

*3.2.4. Other approaches to wireless power transmission.* Single-channel opto-stimulators have also been combined with other wireless powering technologies, such as ultrasound and IR light. For example, Weber *et al* [44] proposed the first ultrasonically powered optogenetic stimulator comprised of a single LED on each 15 $mm^2$ platform. The ultrasonic transmitter can be programmed thoroughly to control the implant utilizing pulsed transmission waveforms. Wirdatmadja *et al* [101] also demonstrated a highly miniaturized, wireless single-channel optogenetic neural 'dust' based on ultrasonic powering mechanism. In such 'dust', mechanical energy is generated by ultrasound-induced vibration of piezoelectric nanowires, converted to electrical energy through a transducer, and delivered to a LED light source for deep brain stimulation. For the IR light powered system, Tokuda *et al* [102] reported a complementary metal-oxide-semiconductor (CMOS)-controlled photovoltaic power-transfer platform for potential applications in implantable healthcare devices or distributed nodes for the Internet of things. In this work, a $1.25 \times 1.25\,mm^2$ CMOS power receiver chip that contains integrated photovoltaic (PV) cells is used to optically power an InGaN blue LED through IR light. Incorporation of the PV cells allows miniaturization of the power receiver platform, resulting in a total volume size of 1 $mm^3$.

### 3.3. Power management and control module

After the WPT stage, the power management and control stage is of significant importance within the optogenetic systems. As one of the key components, energy storage elements, typically a battery or a super-capacitor, are used to temporarily store energy harvested via wireless interfaces. Batteries are better at energy densities while super-capacitors provide high power densities [103]. Compared to super-capacitors, the battery systems have some disadvantages, such as slow charging rate, internal chemical leak, and finite charge-discharge cycles. The battery also adds a considerable amount of weight and dimension to the whole system. The driver stage of the control module for light sources typically consists of a rectifier to convert AC voltage or current to DC voltage or current as well as a voltage regulator to prevent overvoltage across the rectifier. Microcontroller may also be incorporated in the control module on the same PCB to enable precise control of stimulation parameters, such as pulse amplitude, duty cycle, and frequency. For example, Lee *et al* assembled passive radio part, microcontroller, constant current driver and power module connector on the PCB control module [43]. The external wireless trigger from the passive RF receiver can wake up the microcontroller from deep sleep to stimulation, which significantly reduces the power consumption of the system.

## 4. Conclusion and outlook

Table 1 summarizes the specifications of representative single-channel optical stimulators under different system configurations from head-mounted tethered systems to fully implantable, wireless systems. Wireless opto-stimulators using EM resonance based, near-field and far-field coupled WPT are more competitive than battery-powered devices for their longer operation duration, lighter weight, smaller dimensions, and less restriction of the subject's movement. On the other hand, the miniaturization of the wireless antennas presents significant challenges, mostly related to the low power transfer efficiency of the EM coupling or SAR limit at high operating frequencies. As such, future improvement in WPT interfaces is urgently needed to maximize power transfer efficiency, reduce power consumption, and minimize device geometries, which will require the development of new theories and hardware architectures. Besides engineering innovations, research in highly efficient, light-sensitive optogenetic opsins to enable stable gene expression under low light intensity [104] will play an essential role in developing the next generation of single-channel optogenetic stimulators.

In terms of light source selection, UV lamps are seldom utilized in the complete system-level implementation due to their low spatial resolution. Moreover, the large housing size of the lamps makes them inconvenient for practical experiments. At present, lasers, LDs, and LEDs are most commonly used in optogenetic stimulation systems. However, lasers and LDs require tethered optic fibers or waveguides for light delivery and have relatively high power consumption compared to LEDs. While LEDs provide many advantages such as compact size, low power consumption, and compatibility with WPT interfaces, LED-based stimulators usually suffer from overheating under high current density that may induce tissue damage as well as diverging light beam that limits the spatial resolution. As a bottom line, light sources need to be carefully selected according to the specific need of the experiments to achieve the expected outcomes.

Power storage, management, and control units are also critical for the development of single-channel optical stimulators. Low-power, microcontroller-based control circuits are usually used to enable precise control of stimulation pulse and duration, while maintaining a small volumetric size of the device. For applications that do not require *in situ* reconfiguration of stimulation parameters, rectifier circuits with capacitors, inductors, and diodes would be a simple and efficient solution for power management and delivery to the light sources. From the system perspectives, energy harvesting and storage components could be incorporated to enable high instantaneous power output and extend the operation duration. Novel stimulating mechanisms, such as a decaying exponential stimulus method [105], also has the potential to improve the overall energy efficiency of optogenetic stimulation, compared to conventional rectangular and ramp stimuli. In light of this new mechanism, Jiao *et al* [97] implemented a switched-capacitor based stimulation system,

which can efficiently charge storage capacitors directly from an inductive link and periodically discharge them into decaying exponential stimulus pulses for driving $\mu$-LEDs with high instantaneous power without loading the wireless link and dropping the system supply voltage.

It is of note that the majority of the devices surveyed in this article are still in the early stage of development, and mostly evaluated as success in short-term *in vivo* studies. For applications in chronic studies, there are major concerns about the long-term stability and safety of the devices with different choices of materials. Solid materials (e.g. glass) provide a hermetic seal of electronics but suffer from mechanical property mismatch with the soft tissues. While polymers are more advantageous than solid materials for their mechanical flexibility and biocompatibility, polymer-based package is not hermetic due to the porosity nature of polymer thin films. Engineered inorganic–organic thin films are promising hermetic barriers but their long-term packaging performance has not been fully understood. Besides packaging issues, the invasiveness of the implants is another concern, which might be alleviated by reducing device dimensions and improving material mechanical flexibility. However, the miniaturization and/or flexibility of the devices imposes challenges for their implantation into the nervous tissues. To resolve this issue, biodegradable or dissolvable materials, such as polyethylene glycol and silk fibrous [106, 107], can be applied to temporarily strengthen the soft implants during insertion. In addition, bioengineered materials, such as immune-suppressants [108] and enzymes [109], may be adapted to minimize immune responses caused by the device implantation. For example, Rennaker *et al* proved that the orally-administered minocycline to rats could improve the signal-to-noise ratio and longevity of chronic neural recordings, mainly due to reduced inflammation and decreased astrocyte [108]. Paralikar *et al* verified that collagenase treatment of the implant site could decrease the peak insertion force, therefore making it possible to implant more flexible and smaller devices [109].

Overall, there has been considerable progress in the development of single-channel optogenetic neurostimulation systems over the past decade. sTo realize the full potential of these optogenetics tools in behavioral neuroscience research, future improvements will require multidisciplinary efforts in overcoming the challenges of the current technologies. This will provide tremendous research opportunities not only in engineering but also in material science, biology, and neuroscience.

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## ORCID iDs

Weiyang Yang https://orcid.org/0000-0003-2502-3359
Jiajia Wu https://orcid.org/0000-0002-4321-9868
Wen Li https://orcid.org/0000-0002-6862-8561

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