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Flexible Photonic Probes for New-Generation Brain–Computer Interfaces

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1. INTRODUCTION

The brain-computer interface (BCI) refers to the direct connection created between human or animal brains and external devices to realize the information exchange between the brain and the device, which has developed rapidly in the past few decades in both regulating and recording neural activity. Neuroscientists are utilizing these interfaces to map and analyze the brain's neural network.¹ Since 2005, the emergence of optogenetics technology in neuroscience has made high spatial and cellular resolution stimulation possible, enabling neurons to be turned on and off with unprecedented precision.¹ This offers a great opportunity for clinical applications because it provides a way to activate or inactivate specific neurons and directly modulate the neural signal for external activities, bringing hope to patients with neurological disorders such as epilepsy,² Parkinson's disease,³ hearing impairment,⁴ and vision impairment.⁵ Therefore, it is highly desirable to develop implantable optogenetic devices with the capability of single-cell resolution stimulation and ultrafast neural signal recording that can be positioned at an arbitrary region and depth inside the brain.

Numerous attempts have been made to meet the needs mentioned above. Micrometer-scale light-emitting diodes (uLEDs) integrated with electrical probe arrays are one popular technique for multisite light delivery and signal recording. However, uLEDs have limited penetration depths and temporal resolution (<30 Hz).^{6,7} And the surface temperature of uLED at an implantation depth of 0.3 mm could increase by 10 °C under continuous 23.5 mW/mm² light power, which may cause irreparable tissue damage in the deep brain due to the accumulated heat.⁶ The optical phased array (OPA) is another adopted emerging technique, which could realize nanobeam scanning in 3D space, potentially stimulating specific neurals over a large area in the deep brain. Moreover, the temperature change produced by the thermal-optic switch could be further reduced.8 OPA technology has been successfully demonstrated in the near-infrared region for beam steering and high-resolution applications. However, the commonly used optogenetic proteins are primarily sensitive to visible light. Recently, a 64 channel OPA working in the blue wavelengths was demonstrated by Lipson,⁹ achieving a 50° field of view steering. Meanwhile, they also prepared a reconfigurable optical probe operating at 473 nm for neural stimulation.¹⁰ Although rigid probes witness this success in brain tissue,¹⁰ the damage to tissue caused by the physical rigidity of the hard probes and discomfort caused by prolonged wearing remains a concern. More importantly, the large elastic mismatch between photogenic nerve probes and brain tissues leads to unnecessary tissue reactions, such as glial scars and tissue encapsulation,¹¹ limiting the application of rigid OPA probes to further deep brain stimulation.

2. EMERGING TECHNOLOGY: TECHNICAL REQUIREMENTS AND CHALLENGES

To overcome the limits of existing techniques, we propose a flexible photonic probe consisting of arrays of light emitters based on OPA technology and electrodes for stimulating and recording neural activities dynamically. The ideal neurophotonic probe should be in the form of a minimally invasive and soft optical implant allowing multisite light delivery and neural recording. It should achieve not only single-cell resolution stimulation and fast signal recording, wide-angle beam steering in the deep brain but also high device stability and reliability for long-term use in the chronic treatment of neurological disorders and massive fabrication. As shown in Figure 1, creating such a flexible optogenetic platform relies on integrated efforts in materials selection, device design and fabrication.

First, the device materials must be mechanically flexible, biocompatible, and optically transparent. If the material platform is mechanically similar to neural tissues, it will allow the photonic probe to work as a soft and conformal implant in the deep brain with minimal damage to surrounding tissues. It would also reduce the possible foreign body response involving inflammation and glial scars after implantation.¹³ Second, hightemperature fabrication processes should be avoided to suppress the thermal stress that may lead to severe damage or unwanted cracks within the multilayer structures, degrading the performance of flexible photonic probes. Though polymers with intrinsic mechanical flexibility and low-processing compatibility exhibit advantages in device fabrication, it is beneficial to design compact and energy-efficient optical switches with high-refractive-index inorganic materials, which

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Figure 1. Four key considerations for the design and fabrication of flexible photonic probes. Reproduced with permission from ref 10. Copyright 2020 Springer Nature. Reproduced with permission from ref 12. Copyright 2015 Springer Nature.



Figure 2. Wishlist of future optical brain-computer interface. Reproduced with permission from ref 23. Copyright 2020 Elsevier. Reproduced with permission from ref 24. Copyright 2016 Springer Nature.

can reduce the mechanical and thermal damage to vulnerable biological tissues. Compared with polymers, the device size and device power consumption are smaller when using inorganic components, resulting in less damage to biological tissues. However, the large coefficients of thermal expansion (CTE) mismatch between flexible polymer substrates and inorganic materials would generate undesired cracks and degrade the device performance.^{12,14–16} While conventional semiconductor materials¹⁷ relying on transfer-printing techniques show excellent potential in flexible photonics, they also display limited yield and capability to integrate additional device functionalities. Therefore, new materials with high optical transparency, low-temperature fabrication capability, and biological compatibility are constantly being explored to design the novel photonic system in the visible light range.^{12,18} One such example is a monolithic technology based on amorphous glasses and biocompatible oxides, which allows room temperature fabrication of high-performance flexible photonic devices.^{12,14–16} And it is also worth stressing that this monolithic technique enables massive fabrication using mature nanofabrication technology. Third, the stability and mechanical flexibility of the neurophotonic probes must be taken into account for long-term use under extreme mechanical deformations. We have developed multineutral mechanical plane theory and meandering structures, which enable the devices to maintain optical performance upon thousands of cycles of bending and stretching.¹⁶ Last but not least, the optimization of flexible photonic probes based on OPA technology, including emitting grating couplers and optical switches, requires careful optical design and fabrication for wide-angle beam scanning with a high temporal and single-cell resolution.

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3. FUTURE PROSPECTS

This section outlines some perspectives concerning further developments in the future optical brain–computer interface based on flexible photonic probes (Figure 2).

There are different types of cells and neural connectivities in the brain circuits, and they are likely to respond differently to optical stimulation and recording. Moreover, each cell can perform distinct but complementary functions by interacting with other cells. Flexible photonic probes with single-cell resolution can help to differentiate such responses between different types of cells and more closely examine brain activities with higher precision.¹⁹ The monolithic fabrication technology enables the integration of photonic units with different functionalities on flexible substrates. Real-time 3D multisite light delivery, multiparameter sensing, and detection are anticipated to achieve based on the novel flexible photonic technology.

Current optogenetic devices generally operate in the visible wavelength range since optogenetic proteins are primarily sensitive to visible light. In 2018, Mager et al. demonstrated red-shifted channelrhodopsins (ChRs) for driving spiking of fast cerebral interneurons to the limit of their encoding range.⁴ Further red shift of the working wavelength of photosensitive proteins in the near-infrared (NIR) wavelength range can lead to epidermal probe technologies without device implantation thanks to the deeper penetration depth of NIR light.²⁰

The ultimate strategy for practical use should be a fully integrated device including the microscale light sources, multifunctional sensors, detectors based on the flexible platform. Moreover, wireless packaging for the flexible photonic probe is also required to ensure the portability and mobility of the brain–computer interface device. The wireless data transmission and wireless power supply by utilizing the current advanced wireless technology could finally achieve chronic disease treatment such as the pain management in Parkinson's disease²¹ and the prediction and intervention of epilepsy.²²

In the future, we could even consider using biodegradable materials to prepare transient neurophotonic probes in the deep brain that can harmlessly degrade within the brain tissues, thus eliminating the need for surgical removal. Recently, several polymers, such as silk fibers, lactide, poly(D,L-lactide-*co*-glycolide) (PLGA), and poly(L-lactic acid) (PLA), have been applied in implantable photonic devices, exhibiting advantageous properties for implantable optics and minimal systemic toxicity.²⁴

4. CONCLUSION

With the rapid development of integrated photonics and flexible device fabrication technology, neurophotonics based on reconfigurable flexible OPA technology has great potential in realizing rapid and high spatiotemporal resolution stimulation and recording of neural activities in the deep brain. While this new technical approach promises to break through the limitations of existing methods, consistent and concerted efforts in the fields of material science, photonics, electronics, and biology are highly desired to map and analyze the brain's neural network in the future.

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Notes

The authors declare no competing financial interest.

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Lan Li is currently the assistant professor of the School of Engineering at Westlake University. She obtained her B.S. degree from the University of Science and Technology of China (2010) and a Ph.D. degree from the University of Delaware (2016). Since then, she has been a postdoctoral associate at the Massachusetts Institute of Technology for three years. Her research interest focuses on nanophotonic materials and devices, integrated flexible photonic device fabrication, characterization, and application.

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