HHS Public Access

Author manuscript

*Curr Opin Biotechnol*. Author manuscript; available in PMC 2022 December 11.

Published in final edited form as:

*Curr Opin Biotechnol*. 2021 December ; 72: 121–130. doi:10.1016/j.copbio.2021.11.001.

# Flexible optoelectric neural interfaces

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## Abstract

Understanding the neural basis of brain function and dysfunction and designing effective therapeutics require high resolution targeted stimulation and recording of neural activity. Optical methods have been recently developed for neural stimulation as well as functional and structural imaging. These methods call for implantable devices to deliver light into the neural tissue at depth with high spatiotemporal resolution. To address this need, rigid and flexible neurophotonic implants have been recently designed. This article reviews the state-of-the-art flexible passive and active penetrating optical neural probes developed for light delivery with minimal damage to the tissue. Passive and active flexible neurophotonic implants are compared and insights about future directions are provided.

## Introduction

Optical neuromodulation based on optogenetics has enabled stimulation of specific cell types using light at different wavelengths [1,2]. Functional optical imaging is also possible using calcium indicators and voltage-sensitive dyes [3,4]. Moreover, monitoring hemodynamic response as a proxy to neural activity is another method in which light can measure neural function without any optical tags [5]. A challenge for these light-based methods is the limited optical access to deep neural tissue with high spatial resolution, mainly because of the absorption and scattering of light in tissue.

To address this problem, implantable optical devices have been designed to enable efficient light delivery and collection within deep tissue. In recent years, different neural implants



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Conflict of interest statement

Nothing declared.

have been designed that include photonic structures. Some of these designs involve surface arrays that project light from the surface of tissue [6,7]. Other designs include penetrating probes that are implanted into the neural tissue. To realize such devices, integrated photonic design concepts are borrowed from telecommunications to realize optical waveguides, mostly based on rigid materials such as Silicon, Silicon Nitride or Silicon Dioxide [8–11]. However, it has been shown that rigid penetrating neural implants can cause more severe damage to the neural tissue [12–14]. The glial scarring and tissue response depend on the size, material density, and stiffness of the neural implants [15,16•]. The significant mechanical mismatch between rigid neural implants and soft neural tissue causes damage to the tissue [17]. Moreover, brain micromotions arising from sources like cardiac rhythm, fluctuations in respiratory pressure, and head movements [18–20] exacerbate tissue damage, especially when the implanted neural probe is anchored to the skull [18,21]. Flexible neural implants, by contrast, have been shown to reduce damage to the brain tissue [22].

In this review article, we focus on penetrating flexible neurophotonic implants in two categories of passive and active optical neural probes. Passive neurophotonic implants route light into the tissue from light sources located outside the tissue. These light sources can be either benchtop lasers or laser diodes and LEDs, integrated to the backend of the neural probes, that emit light in the visible range of the spectrum (380 nm–700 nm) matching the absorption band of light-sensitive proteins such as opsins (e.g., 450 nm (ChR2/H134) — 632 nm (Jaws)) [1,23]. In both cases, the light sources are located outside the tissue, thus minimizing the risk of thermal damage to the tissue due to the limited efficiency of light sources. On the other hand, active neurophotonic implants are devices that generate light directly inside the tissue by converting electricity to light. Three general designs of photonic neural implants are shown in Figure 1. The first one is an implantable Michigan-style microarray neural probe (indicated as ①) that consists of an array of active light sources or optical waveguides on the probe shank. Implantation of these probes would require a small craniotomy and multiple layers of the cortical laminae can be targeted along the shank. The second one (②) is an array of individual shanks, each acting as an independent optical waveguide (Utah-array-style) and the third one is a fiber-based design (③). In both of these designs, only the neural tissue near the tip of the shanks can be stimulated. Implantation of the Utah-array-style neural probes requires a large craniotomy. Electrical recording electrodes can be integrated with these different designs to realize optoelectric neural probes with both optical and electrical functionality.

It should be noted that flexibility is not only determined by the bulk material properties, but also depends on the geometry of the implant [16•]. Assuming a simple cantilever model for a neural probe that can represent any of the three designs discussed in Figure 1, the stiffness is determined by the dimensions of the neural probe as well as the bulk elastic modulus of the material (Young's modulus), listed in Figure 2a for the commonly used flexible materials [13]. Here, we are assuming that the probe is anchored to the skull on one side and is floating in the brain (Figure 2b), The smaller the cross section of the neural probe, the more compliant it is (i.e., lower stiffness as indicated by $k_x$ and $k_y$). Therefore, even for materials with high elastic modulus (e.g., Silicon), it is still possible to reduce the stiffness to some extent by designing devices with smaller cross sections. On the other hand, devices made of materials with relatively low Young's moduli can retain low stiffness at

larger dimensions. Overall, a neural probe made of a soft material with small cross-sectional dimensions exhibits a lower level of stiffness. Luan *et al.* have demonstrated glial scar-free neuronal recording with ultra-flexible SU-8-based neural probes with a very small cross section of 10 μm × 1.5 μm [24]. In addition to reducing cross sectional dimensions and using a low elastic modulus material, meandering wiring in neural probes has also been utilized to reduce the stiffness of neural implants [25]. Highly flexible neural probes may lack enough rigidity to penetrate brain tissue. For successful implantation, the neural probe must not buckle under the insertion force [16•]. Therefore, there is a trade-off between the need for stiffness to facilitate implantation and the need for compliance to minimize damage to the tissue once the device is implanted. Much like the stiffness of neural probe, the buckling force for a rectangular shank also depends on the elastic modulus and the geometrical parameters (Figure 2b).

Various techniques have been developed to stiffen flexible neural probes during implantation including using insertion shuttles [24], external insertion guides [26], bioresorbable stiffeners [27,28], mechanically adaptive polymer nanocomposites [29], thermally softening polymers [30], hydration-dependent stiffness modulated hydrogel matrix [31], liquid crystal polymers [32], liquid metal integrated microfluidic channels [33], pressurized fluidic channels [34], a PEG brace [35] or a dissolvable silk-based scaffold to reduce the effective length [36]. Some of these techniques have been developed for implantation of flexible electrical neural probes, but they can also be adopted for flexible optoelectric neural implants.

In the following sections, we provide a review of the state-of-the-art passive and active flexible neurophotonic implants.

## Passive flexible neurophotonic implants

Flexible neural probes based on passive integrated photonic waveguides have been designed to deliver light from outside into the brain tissue. The essence of an optical waveguide is a high refractive index core surrounded by a lower refractive index cladding. Therefore, two flexible and biocompatible materials with a refractive index contrast are needed to form flexible optical waveguides that can be integrated into neural implants. One method to realize passive flexible photonic implants is to use a fiber drawing process using polymer materials [38]. Microfabrication techniques using different polymers such as Polycarbonate, SU-8, Parylene C and N, PDMS, Ormocers, EpoCore, and Cytop have also been used to construct integrated photonic waveguides. In some of these designs, the polymer waveguides are fabricated on rigid substrates, thus rendering such neural implants rigid [39,40]. It was only recently that fully flexible integrated photonic platforms, which utilize flexible core and cladding materials not attached to a rigid substrate were demonstrated. These designs include Polymeric Opto-Electro-Mechanical Systems (POEMS) [41••], flexible multifunctional fibers [31,42], and Parylene photonics [43•,44••,45•,46•]. POEMS is designed based on Cytop as the cladding and Ormocers or EpoCore as the material to form the waveguide core. Flexible multifunctional fibers are fabricated through a thermal drawing process using Polycarbonate Polymer as the optical fiber core and Cyclic Olefin Copolymer (COC) as the cladding [31,42]. To implement Parylene photonic waveguides,

Parylene N is used as the core and Parylene C as the cladding to form a flexible photonic waveguide [43•,46•]. Parylene C has also been used as the material for waveguide core with PDMS as the cladding [44••,45•]. The much higher refractive index contrast between PDMS and Parylene C results in highly confined optical modes.

The design of input and output ports in these passive flexible neural probes is critical. The input port to each optical waveguide must be designed to enable efficient coupling of light from external light sources at the backend (Figure 1). Moreover, the backend packaging should be compact and minimally cumbersome. Optimization of the input/output coupling has not been explored much for fully flexible neurophotonic implants. However, some of the design concepts for input/output coupling to rigid waveguides can translate to fully flexible optical neural probes. For example, input coupling from optical fibers has been achieved via butt-coupling from the edge [39] or using grating couplers from the surface of the waveguide [8]. The grating couplers are usually designed for specific wavelengths and are narrowband. Scaling up the number of channels would require packaging many input fibers at the backend. An alternative technique is to use a single fiber bundle combined with a digital micromirror device or a scanning mirror galvanometer to direct light to multiple input facets without the complexity of aligning and bonding individual fibers [9]. However, all these methods require a rigid tethered fiber connection to the external light sources, which can be cumbersome. To address this issue, compact light sources have been directly bonded to the input ports, including packaged laser diodes [10] and flip-chip bonded bare laser diodes using direct butt-coupling [47] or through a GRIN lens to boost the coupling efficiency [11]. In this case, light sources (e.g., laser diodes or LEDs) are integrated with the neural probe backend, obviating the need for having a tether fiber connection to a benchtop external light source, but still stay outside the brain tissue. While these techniques are mainly developed for rigid neurophotonic implants, they can still be adopted for light coupling to flexible optical waveguides. For example, butt-coupling from optical fibers to flexible polymer waveguides has been used [42,46•,48,49]. More recently, coupling to such waveguides from integrated light sources such as micro-LEDs [50] or edge-emitting laser (EEL) diodes [41••] or through 3D printed flexible optical wirebonds [41••] have been demonstrated. Also, embedded micromirrors have been used for out-of-plane input coupling into fully flexible Parylene photonic waveguides [44••].

The design of output waveguide ports is also crucial to illuminate localized volumes of the brain tissue. In one design variant, light leaves the output facet along the length of the waveguide in the so-called end-firing waveguides. This design has been used in Utah-array-style neural implants, where a 2D array of individual waveguide shanks have been realized by a variety of methods, including bonding an array of optical fibers to light sources [51,52], micromachining glass substrates [53], or patterning photodefinable polymer shanks [54]. To increase spatial resolution by incorporating multiple output ports on a single shank, and to collocate the electrical recording and optical stimulation volumes, an out-of-plane illumination scheme is desired. Out-of-plane output coupling also prevents direct illumination of recording electrodes, reducing the photoelectric artifact [55]. Out-of-plane output coupling has been demonstrated using grating couplers [55,56] in rigid neurophotonic implants as well as broadband micromirrors in fully flexible Parylene photonic implants [44••].

Table 1 summarizes recent designs of passive photonic neural implants based on optical waveguides made of flexible polymers, including the materials, their refractive index values, waveguide propagation loss, input coupling mechanism and output light illumination arrangement, the method of fabrication, as well as the implantation site.

## Active flexible neurophotonic implants

To deliver light deep into the tissue with high spatial resolution, active light sources can be directly implanted into the neural tissue. These light sources include light emitting diodes (LEDs) or lasers that emit light when powered by electricity. Implants have been recently demonstrated with an array of such light sources integrated on a flexible substrate (Table 2). For example, Gallium Nitride (GaN) LEDs have been used to design active photonic neural implants that generate blue light in the wavelength range that overlaps with the absorption band of Channelrhodopsin (ChR2), one of the most widely used opsins in optogenetics, as well as fluorescent tags used for structural and functional imaging of the brain. GaN is usually grown on sapphire as the substrate. Epitaxial growth of GaN on Silicon has also been demonstrated recently for designing implantable Silicon neural probes with photonic functionality [64]. Off-the-shelf LEDs also have been packaged with flexible neural probes. In this scheme, metal traces and bondpads are lithographically defined on a polymer substrate and then the LED chips are flip-chip bonded onto the polymer shank. This method has the advantage that LEDs emitting light at different wavelengths can be integrated on the same probe shank to stimulate different opsins. These LEDs can be bonded on the surface of the neural probe in any arbitrary arrangement. Existing off-the-shelf LED chips are usually large and thick (220 μm × 270 μm × 50 μm) [65••], thus limiting the density of these neurophotonic probes. Such devices have also been used in cochlear implants [66]. To address the size and density limitations, smaller LED chips have been custom-designed and fabricated. In this method, first, an array of micro-LEDs are fabricated on a sapphire substrate and the flexible probe shanks are fabricated on a separate substrate and then the micro-LEDs with dimensions as small as 50 μm × 50 μm × 6.45 μm are transferred to the polymer substrate using a laser liftoff (LLO) process, where an excimer laser is used to detach GaN from sapphire [67,68,69••]. The flip-chip bonding process requires precise alignment and is usually serial, which would limit the scalability and throughput of the packaging process. To increase the packaging throughput and scale up the density of active photonic neural probes, a transfer process has been developed for cochlear implants to directly transfer an array of micro-LEDs to flexible substrates at the wafer scale [70,71]. A monolithic fabrication process has also been recently demonstrated to directly fabricate flexible micro-LED neural probes on a Silicon wafer with epitaxially grown GaN layers [72••]. In this scheme, the Silicon handle layer is etched to fully release the flexible devices. This method provides a high degree of customizability. Any size and arrangement of micro-LEDs can be lithographically defined on the neural probe collocated with recording electrodes. Moreover, the fabrication process is scalable and potentially high throughput. The efficiency of micro-LEDs fabricated on Silicon (~6%) is usually lower than the efficiency of GaN micro-LEDs fabricated on sapphire (~17%) [73].

## Comparison of flexible active and passive neurophotonic implants and the future outlook

Research on developing passive and active flexible neurophotonic implants has produced interesting results recently. Each technology platform offers certain advantages and has some limitations, based on which it can be adopted for specific applications. Here, we provide a comparison between the state of the art passive and active flexible photonic technology platforms, with the understanding that each of these two technologies are evolving fast to address the shortcomings and offer more effective solutions. The active neurophotonic implants based on micro-LEDs can potentially be realized with a very high density of light sources. To power these active light sources, we would only need electrical traces that can be made very small and densely routed even with very sharp in-plane bends. The passive photonic waveguides on the other hand, must be routed all the way from the backend to the probe shank and cannot be defined over trajectories with sudden sharp bends. Moreover, we do not necessarily have to use two independent metal traces to power each active light source. In fact, one metal trace can be used in common for all of them (e.g., to connect to the p-contacts) and the n-contacts can be addressed individually. This way, to address $N$ number of LEDs, we would only need $N$+1 metal traces. Moreover, it has been shown that a dense 2D array of $N$ micro-LEDs can be controlled using a matrix grid of $2\sqrt{N}$ metal interconnects by indexing individual micro-LEDs via the row and column in the array [72••]. Therefore, active photonic neural probes can be potentially realized with a much higher density of optical output ports compared to passive photonic waveguide neural implants. However, the lower efficiency of micro-LEDs contributes to heat generation and dissipation in the probe shank. It is important to minimize the heat conduction to the brain tissue. The safe operation condition is considered to be temperature change of less than 1°C in tissue [74], although the effect also depends on the exposure time [75]. To minimize heat dissipation to the brain tissue, a heat-sinking layer can be implemented [76]. Moreover, active light sources can be pulsed to prevent accumulation of heat [64]. In addition to improving the epitaxial structure of the micro-LEDs, integrated planar [77] and hemispherical mirrors [78] have also been explored in rigid optrodes to improve the efficiency and enhance the optical stimulation. Further research is needed to improve the efficiency of active photonic light sources and mitigate heat generation and dissipation into the tissue. On the other hand, passive flexible optical waveguides route light from external light sources, thus minimizing the conduction of heat generated by these light sources to the brain tissue. Most of the passive flexible neurophotonic implantable probes demonstrated so far are based on one or just a few optical channels. Currently available flexible polymers used as core materials in flexible optical waveguide neural probes have lower refractive indices compared to rigid materials such as Silicon Nitride, which puts constraints on miniaturization of waveguide core dimensions and reduction of the pitch between adjacent waveguides (due to crosstalk) for dense routing of passive waveguides. Therefore, development of novel biocompatible flexible polymers with higher index contrasts can enable higher density of optical channels in passive photonic neural probes. Moreover, like multilayer metal traces used in electrical neural probes, multilevel photonic waveguides can also be realized to increase the density of optical channels. In addition, similar to what has been demonstrated in Silicon Nitride neural probes, wavelength-domain multiplexing

can be used to route multiple wavelengths of light from one input waveguide to achieve illumination with individual spectral components at multiple waveguides terminating at different spatial locations along the probe shank [56]. These design concepts need to be optimized to realize high-density neurophotonic implantable probes.

Overall, existing active flexible photonic neural probes are best suited for acute experiments, in which high-density light illumination is highly desired. On the other hand, passive flexible neural probes have the potential to serve the purpose of chronic long-term neural interfacing. Of course, with the ongoing research in the field, we expect to see future work address the shortcomings of both technology platforms, which would enable their use in a broader range of acute and chronic experiments.

## Acknowledgements

This material is based upon work supported in part by the National Science Foundation under Grant No. 1926804 and also by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Numbers RF1NS113303 and R01NS116464.

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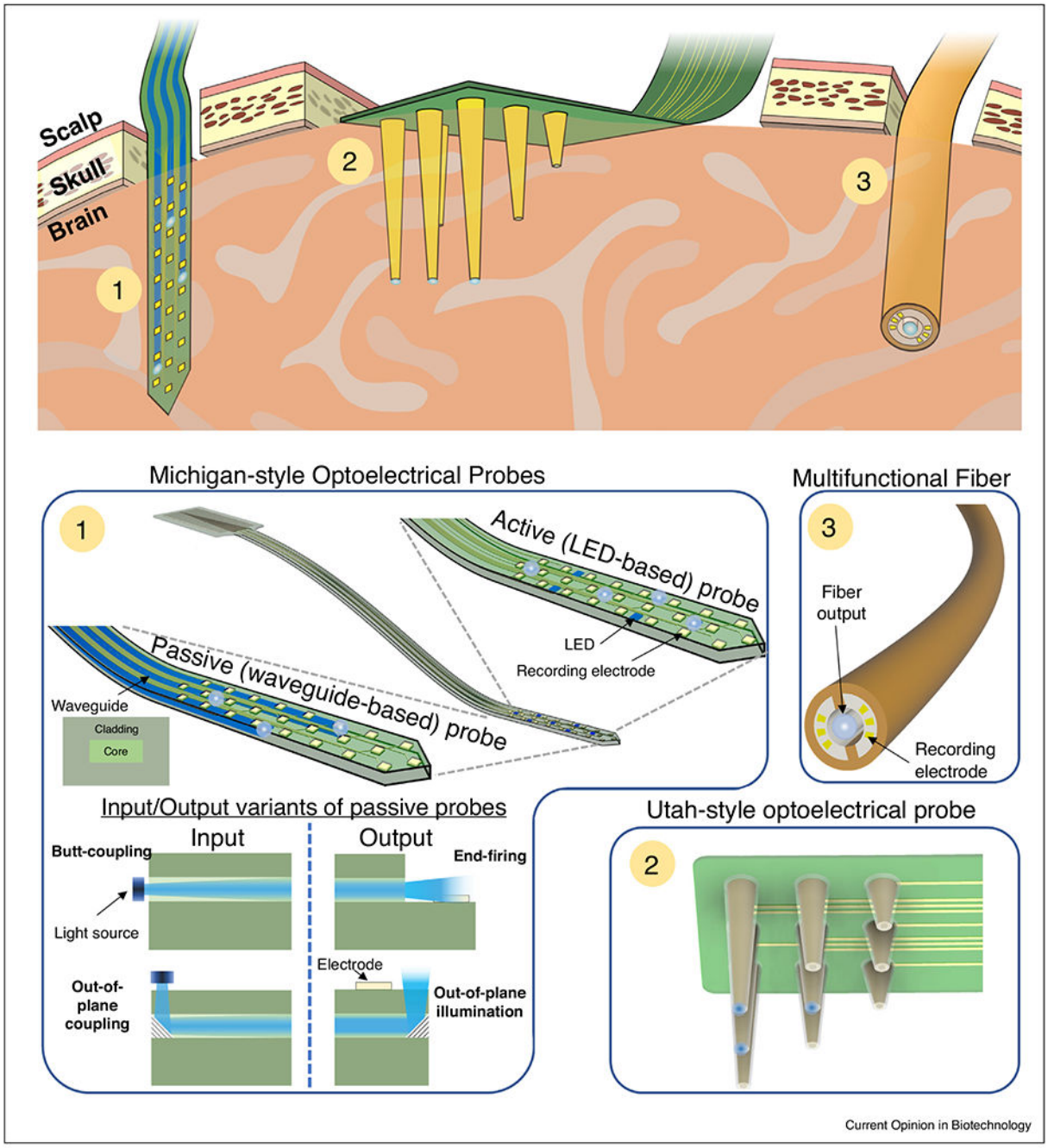


**Figure 1.**

Taxonomy of flexible optoelectric neural probe designs discussed in this paper. Three different designs are shown: (1) an implantable microarray neural probe (Michigan-style) with an array of active light sources or optical waveguides, (2) an array of individual optoelectric shanks (Utah-array-style) and (3) a fiber-based design. Active neurophotonic probes consist of an array of light sources (LEDs), while passive neurophotonic probes consist of an array of optical waveguides, each consisting of a high refractive index core

surrounded by low-index cladding. The input/output coupling mechanisms are illustrated for the optical waveguides.

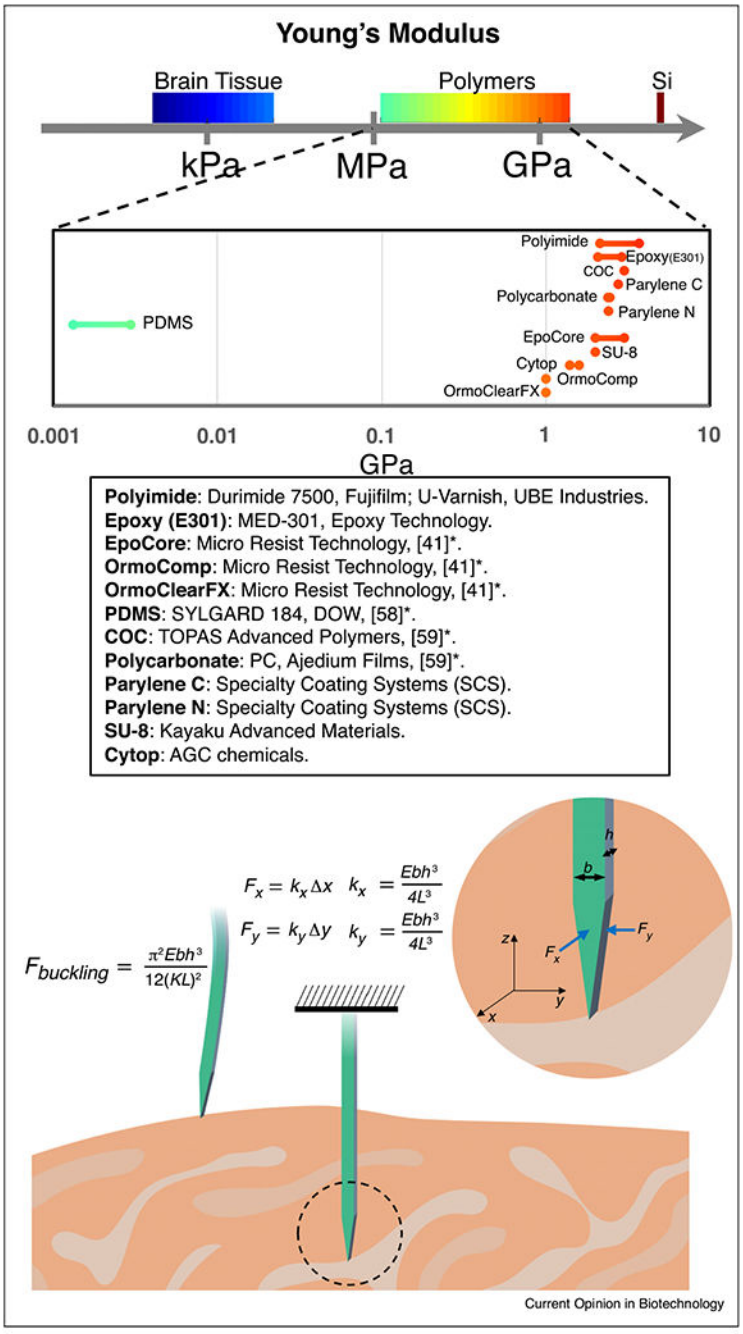


**Figure 2.**

**(a)** The Young's modulus for polymers commonly used to realize neurophotonic probes in comparison with the elasticity of brain tissue and Silicon as a representative stiff material that is used to design neural probes. **(b)** Implantation of flexible neural probes may fail if the required insertion force is larger than the buckling force that the device can endure [16•,37]. Buckling force is a function of the material elastic modulus ($E$) and its geometry (length: $L$, width: $b$, and thickness: $h$). $K$ is the effective length factor, which depends on the boundary conditions at two ends of the neural probe and is in the range of ($K$ = 0.5 to 2) [35]. The

expressions for the bending stiffness along $x$ and $y$ directions are provided as a function of the bulk elastic (Young's) modulus ($E$) and the geometrical parameters.

* The value of the Young's modulus is reported in the indicated reference.

**Table 1**

Different designs of passive flexible neurophotonic waveguide-based neural implants

| Ref. | Core (Refractive index) | Clad (Refractive index) | Young's modulus, E (GPa) (Core, Clad) | Core size (μm) | Propagation loss (dB/cm) | Input | Output | Fabrication method | Implantation site[d] |
|---|---|---|---|---|---|---|---|---|---|
| Kampasi *et al.* [41••] | OrmoClearFX (1.555) | Cytop (1.37) | <1, 1.4–1.6 | 10 × 10 | 4.9–7.8 @(405–635 nm) | EEL[b] Diode | End-firing | Microfab | CNS (Proposed) |
| | EpoCore (1.58) | Cytop (1.37) | 2–3, 1.4–1.6 | 10 × 10 | 7.6–11.2 @(405–635 nm) | EEL Diode | End-firing | Microfab | CNS (Proposed) |
| Reddy *et al.* [44••] | Parylene C (1.64) | PDMS (1.4) | 2.75, (1.32–2.97) × $10^{-3}$ [58] | 5 × 30 | 3.2–6.1 @(450–680 nm) | VCSEL[c], Optical Fiber | Out-of-plane | Microfab | CNS (Proposed) |
| Park *et al.* [42] | Polycarbonate (1.586) | Cyclic Olefin Copolymer (COC) (1.53) | 2.40–2.45, 3 [59] | 50–80 (Diameter) | 1.32 @473 nm | Optical Fiber | End-firing | Thermal Drawing | CNS (Brain) |
| Kwon *et al.* [50] | SU-8 (1.58) | Indium tin oxide (N/A) | 2.0, 116 [61] | 30–300 (Diameter) | N/A[a] | micro-LED | End-firing | Microfab | CNS (Brain) |
| Yamagiwa *et al.* [46•] | Parylene N (1.661) | Parylene C (1.639) | 2.4, 2.75 [57] | 6 × 70 | N/A | Optical Fiber | End-firing | Microfab | CNS (Proposed) |
| Rehberger *et al.* [48] | MED-6020 (1.4378) | MED-1000 (1.4136) | N/A | 130 × 120 | 0.038 @473 nm | Optical Fiber | End-firing | Microfab | N/A |
| Rubehn *et al.* [49] | SU-8 (1.58) | Gold & Tungsten–Titanium (N/A) | 2.0 [60], 79 [62] and 110 [63] | 105 × 150 | 1.5–6.4 @(473–593 nm) | Optical Fiber | End-firing | Microfab | CNS (Proposed) |

[a]N/A: Not Available.

[b]EEL: Edge emitting laser.

[c]VCSEL: Vertical-cavity surface-emitting laser.

[d]The proposed or demonstrated implantation site.

CNS: Central Nervous system.

**Table 2**

Different designs of flexible active neurophotonic implants

| Ref. | LED Qty. | LED size (μm) | Wavelength (nm) | Power/Intensity[a] | Shank material | LED integration method | Implantation site[b] |
|---|---|---|---|---|---|---|---|
| Liu *et al.* [67] | 1 | 180 × 125 | 470 | 10 mW/mm$^2$ at 1 mA | SU-8, Polyimide, PDMS | Monolithic microfab | CNS (Brain) |
| Keppeler *et al.* [66] | 10 | 220 × 270 | 457 | 14 mW 236 mW/mm$^2$ at 30 mA | Polyimide, Cytop, Silicone | Flip-chip bonding | PNS (Cochlear) |
| Reddy *et al.* [72••] | 32 | 22 × 22 | 445 | 200 μW at 2 mA | Parylene C | Monolithic microfab | CNS (Proposed) |
| Ji *et al.* [65••] | 16 | 220 × 270 | 460 | 11 mW<br>225 mW/mm$^2$ at 20 mA | SU-8, PKM12C-1 Epoxy, Polyimide | Manual assembly | CNS, PNS (Proposed) |
| Klein *et al.* [70], Dieter *et al.* [71] | 144 | 60 × 60 | 462 | 407 mW/mm$^2$ at 10 mA | E301 Epoxy, Polyimide | Monolithic microfab | PNS (Cochlear) [71] |

[a]For some designs the power was reported and in some other references the measured intensity was reported.

[b]The proposed or demonstrated implantation site;

CNS: Central Nervous system, PNS: Peripheral nervous system.