OptoFlex: A Flexible, Broadband Parylene Photonic Platform with Integrated Micro-Mirrors for Optical Biointerfaces

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ABSTRACT
Targeted light delivery into biological tissue is needed in applications such as optogenetic stimulation of the brain, and in vivo functional or structural imaging of tissue. These applications require very compact, soft, and flexible implants that minimize damage to tissue. Here, we demonstrate a novel implantable photonic platform based on a high-density, flexible array of ultracompact (30 μm x 5 μm), low-loss (3.2 dB/cm at λ = 680 nm, 4.1 dB/cm at λ = 633 nm, 4.9 dB/cm at λ = 532 nm, 6.1 dB/cm at λ = 450 nm) optical waveguides made of biocompatible polymers Parylene C and PDMS. This photonic platform features unique embedded input/output micro-mirrors that redirect light from the waveguides perpendicularly to the surface of the array for localized, patterned illumination in tissue. This architecture enables the design of a fully flexible, compact integrated photonic system for applications such as in vivo chronic optogenetic stimulation of brain activity.

INTRODUCTION
From biological science to clinical practice, optical methods for imaging1–3 and manipulation4–9 of tissue are the gold-standard for non-invasive interaction. However, scattering and absorption of light in tissue pose fundamental limitations to the achievable resolution and depth of penetration. Depending on the type of tissue and wavelength of light, non-invasive optical microscopy techniques are typically limited to the superficial layers of tissue due to scattering and absorption of light, especially in the visible range of the optical spectrum10. Multiphoton techniques, which utilize simultaneous absorption of longer wavelength photons to activate visible-range optical agents, achieve deeper penetration into tissue due to reduced attenuation of near-infrared and infrared light. Even using advanced multiphoton techniques, optical access is still limited to a couple of millimeters of depth into the tissue11. In the context of brain imaging and manipulation, accessing deeper regions is required to study the neural mechanisms of disorders such as Parkinson’s disease that involve malfunction of circuits in deep structures, namely, the basal ganglia nuclei. The issue of penetration depth is even more limiting for studying larger brains of non-human primates and humans. Implantable devices that enable targeted light delivery deep into the tissue are therefore needed to advance scientific understanding of biological mechanisms and to aid clinical intervention.

Optical imaging and manipulation in free-roaming animal subjects require miniaturized technologies that are much smaller than traditional bulky microscopes. Recently-demonstrated miniaturized microscopes and miniscopes, powered by electrical and fiber optic tethers, can be carried by a mouse during ambulatory experiments12. Moreover, compact optical implants, such as light emitting diodes, optical fibers, and integrated photonic waveguides, have been used to deliver or collect photons deep within tissue to record and stimulate disparate regions simultaneously13–20. Unlike their external counterparts, these techniques require a physical device to be implanted into the tissue. Therefore, compact and flexible devices are highly desired to minimize damage to tissue, while still benefiting from the power of optical techniques deep in tissue.

Among different biomedical applications, neurophotonics is an emerging field that demands minimally-invasive and highly flexible optical implants for light delivery into the brain with high spatial resolution for optogenetic stimulation and functional imaging of brain activity. To study and understand the distributed and dynamic neural circuits in the brain, we need methods to monitor and manipulate neuronal activity at single-cell resolution over different areas of the brain during naturalistic behavior.
The brain tissue is especially vulnerable to damage from rigid implants. It has been shown that the performance of neural implants gradually degrades over time due to the foreign body response (FBR)\textsuperscript{21}. This biological tissue response, which involves inflammation and astro-glial scarring, is believed to be triggered, in part, by the mismatch between the mechanical properties of the implanted device and neural tissue\textsuperscript{22}. The buildup of scar tissue around the implantation site degrades recording signal-to-noise ratio and stimulation efficiency, limiting the lifetime of such implants. For electrical recording, flexible polymer devices have been shown to reduce damage to the brain tissue, and thus enable longer term neural recording\textsuperscript{23}. An equivalent flexible optical platform is desired to enable optical interrogation of neural circuits.

Most existing integrated photonic waveguides are made of rigid dielectrics and semiconductor materials such as silicon, silicon dioxide, and silicon nitride (SiN)\textsuperscript{24}. These integrated photonic platforms are mainly designed for optical communications and not necessarily optimized for implantable or wearable biophotonics. In addition to microfabricated integrated photonic devices, comparatively large single-channel light guides, including optical fibers and polymer silicone light guides\textsuperscript{25,26}, have been used for light delivery into tissue. Polymers such as SU-8, have also been incorporated into integrated photonic devices\textsuperscript{15,27,28}.

The overall stiffness of a device is determined by the geometry and the Young’s (elastic) modulus. Chronic tissue response is also a function of the shape of the probe cross-section. Typically, neural probe architectures are fabricated in long, high aspect ratio shapes that minimize cross-sectional area to reduce acute tissue damage during implantation\textsuperscript{29}. The probe mechanics in this shape are well-characterized by the cantilever stiffness, which scales linearly with the Young’s modulus of the material\textsuperscript{21}. Compared to other commonly-used materials for photonic waveguides, Parylene C and polydimethylsiloxane (PDMS) exhibit orders of magnitude lower Young’s moduli, closer to most biological tissues (Table 1), suggesting that this architecture will be less damaging to surrounding tissue after implantation. Although polymer materials are still many orders of magnitude stiffer than the surrounding tissue, histology studies have shown that polymer probes cause reduced foreign body response compared to more rigid silicon probes\textsuperscript{30}.

| Material       | Young’s Modulus, E (GPa) |
|----------------|--------------------------|
| Silicon        | 130 – 170                |
| Silicon Nitride| 280 – 290                |
| Parylene C     | 1.5 – 4                  |
| PDMS           | $1.32 \times 10^{-3}$    |
| Brain Tissue   | $(1.389 -1.895) \times 10^{-6}$ |
| Skin           | $(6 – 222) \times 10^{-6}$ |
| Muscle         | $(2 – 12) \times 10^{-6}$ |

Here, we demonstrate an integrated photonic platform to realize compact, biocompatible, and fully-flexible polymer-based optical waveguide arrays that can deliver light efficiently into tissue.
in a minimally invasive way. Our architecture, OptoFlex, is realized entirely in a flexible, biocompatible material platform composed of Parylene C and PDMS polymers. PDMS is optically transparent in the visible range and is resistant to degradation from prolonged exposure to a biological environment\textsuperscript{37,38}. Both polymers are used in FDA-approved medical implants\textsuperscript{39,40}, and are also widely used in research as well as clinical applications\textsuperscript{41}. With a proven track record of biosafety in humans, Parylene C and PDMS form a compelling photonic platform for biointerface development with the translational potential for medical applications.

**DEVICE DESIGN AND ARCHITECTURE**

**Compact Parylene photonic waveguides confine and guide light**

Our flexible photonic platform, OptoFlex, utilizes a dense array of waveguides in the shape of an implantable probe to deliver light from external light sources deep into tissue (Fig. 1a). Light is coupled to each waveguide from light sources located at the backend of the probe, which remains outside of the tissue. These light sources can be either integrated laser diodes, or a fiber tether connecting to an external laser source. The probe has a long flexible shank that is implanted into the tissue to deliver light at the target depth. Here, we have demonstrated 5 cm long waveguides. To minimize damage to surrounding tissue, the shank is designed to be very thin (7 µm total thickness) and narrow (60 µm waveguide pitch). The total shank width is determined by the number of waveguide channels and the size of individual waveguides.

Our waveguide core is made of Parylene C, a high refractive index biocompatible polymer (n = 1.639), which is transparent throughout the visible range of the optical spectrum\textsuperscript{42}. PDMS is used as the waveguide cladding due to its lower refractive index compared to Parylene C (n = 1.4). The material choice of Parylene C and PDMS provide a large index contrast (Δn = 0.239) amongst biocompatible polymers to confine an optical mode. A large index contrast improves mode confinement and results in a small bend loss. However, it can exacerbate the scattering losses due to sidewall roughness, which can be alleviated by smoothening the waveguide sidewalls. A cross-sectional schematic of the waveguide structure on the wafer is shown in Fig. 1b.

**Embedded micro-mirrors enable vertical input/output coupling**

A unique feature of our OptoFlex design is the monolithic integration of embedded 45-degree micro-mirrors at the input and output ports, which enables broadband input/output coupling of light. The mirror topography is first precisely defined in a silicon mold (Fig. 1c) and then transferred to the flexible polymer device via deposition of Parylene C and PDMS onto the Si mold. These monolithically embedded micro-mirror structures are capable of 90-degree out-of-plane input/output light coupling (Fig. 1d).

As output ports, these micro-mirrors enable out-of-plane illumination normal to the surface of the implantable probe. Traditional optical waveguides and fibers operate in an end-firing configuration (Fig. 1e), in which light is emitted from the end facet. End-firing waveguides result in an in-plane beam profile which is oriented along the axis of the probe, causing a large portion of the probe surface area to be illuminated and limiting the number of non-overlapping output ports that can be arranged on the surface. To enable a high spatial resolution illumination pattern along the probe shank, an out-of-plane scheme is preferred (Fig. 1f). Additionally, in the context of neural probes, where electrical recording sites are patterned on the surface of the shank, an out-of-plane beam profile avoids direct illumination of recording electrode sites, reducing the severity of photoelectric artifacts\textsuperscript{43}. A comparison of in-plane and out-of-plane illumination profiles is presented in Figure 1e, f. In-plane mirrors have also been used for side-
firing waveguides in order to increase optical probe spatial resolution\textsuperscript{44}, but out-of-plane mirrors can be collocated with surface electrode arrays on the same probe shank.

Output ports may be lithographically defined in the desired arrangement along the probe shank to suit the purpose of the intended experiment. Although OptoFlex can be broadly used in any biomedical application, here we focus on a device design in the context of neural stimulation using optogenetics. For example, output ports may be spaced along the length of the probe shank to stimulate different regions of tissue (i.e., layers of cortex) or placed in a dense grid for interrogation of neural circuits in the same region.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{a) Schematic diagram of Parylene C/PDMS optical waveguide neural probe. The inset image shows the integrated device capable of out-of-plane light delivery. b) Schematic of waveguide cross-section on the wafer. c) Scanning electron micrograph (SEM) of Si trench etched via KOH with \{110\} plane indicated, which acts as the mold for the micro-mirror port as shown in the cross-sectional schematic diagram. d) Out-of-plane input coupling from an optical fiber into Parylene C waveguide using 45-degree micro-mirror at the input port. Adjacent waveguides appear bright due to brightfield illumination and reflections from the bright beam spot of the input fiber. Only a single waveguide is excited, as seen by the bright line of outscattered light in the center of the array. Fiber alignment is performed using a precision micromanipulator (\textit{PatchStar, Scientifica, UK}) e) Schematic of the traditional in-plane illumination from an end-firing waveguide, where waveguide illumination is along the probe shank, limiting spatial resolution. f) Schematic of the out-of-plane illumination in our design, where waveguide output is oriented perpendicular to the probe shank, allowing for higher spatial resolution.}
\end{figure}
Packaging with optical fibers
Packaging of microfabricated optical waveguides with light sources is a uniquely stringent requirement for implantable applications. The device backend must be compact and robust in order to enable implantation. A unique feature of our integrated photonic waveguide platform is the embedded micro-mirror input ports that facilitate coupling of light from the surface.

Optical fibers can be aligned to the waveguide input facet using a 3D-printed V-groove (Fig. 2a) and directly bonded to the waveguide array with optical epoxy as shown in Fig. 2b, (Materials and Methods). Due to the compact size of optical fibers (3.0 μm core diameter, 125 μm cladding diameter), many fibers may be bonded to the probe backend, allowing independent light coupling to multiple waveguides in the array. The chosen optical fiber (S405-XP, Thorlabs Inc, USA) operates as a single mode fiber over wavelengths of 400 nm - 680 nm, covering the entire visible spectrum, relevant for most optical reporters and commonly used opsins for optogenetic stimulation. Packaging optical fibers at the backend of our implantable optical waveguide arrays has the advantage of enabling operation at different wavelengths using different external laser sources.

Bonding laser diode chips
It is highly desired that implantable photonic waveguide probes are realized such that the prohibitive tether connections to the backend are either eliminated or at least reduced in size to enable chronic experiments on free-roaming animals. Utilizing the micro-mirrors for input coupling, compact vertical cavity surface emitting laser chips (VCSELs) may be directly bonded to the input facet using a thin layer of Anisotropic conductive film (ACF) using a method described in Material and Methods section. The resulting probe is shown in in Fig. 2c. The diode chips (λ=680nm, Vixar Inc, USA) emit at a wavelength of λ = 680 nm and are both compact (220 μm x 220 μm) and lightweight (0.5 mg). ACF provides mechanical and electrical connections to the VCSELs without significantly attenuating the light. We measured an optical transmission of more than 67% through ACF across the visible range of optical wavelengths. Direct integration of light sources precludes the use of an external fiber-coupled laser sources. Thus, our optical probe requires only an external electrical connection of a pair of small wires which can be much less cumbersome and restrictive than a stiff, delicate fiber connection.

Design of cladding thickness to enable integration of functional electrical layers
In the context of neural interfaces, electrical recording as well as optical stimulation capabilities are desired in order to enable simultaneous electrophysiology recording and optogenetic stimulation experiments in the brain. Recording electrodes are usually formed via exposed
metal sites connected by traces embedded in polymer insulation\textsuperscript{45,46}. A conceptual schematic diagram of an additional planar layer of recording electrodes on OptoFlex is shown in Fig. 3a.

One concern of combining electrical and optical functionalities on the same platform is the interaction of the optical waveguide modes with electrical traces which will decrease the delivered optical power due to absorption losses in the metal. Commonly used metals such as Au, Pt, Ti, and Al exhibit large absorption coefficients in the visible range of the optical spectrum\textsuperscript{47}. In our OptoFlex platform, electrical traces can be routed along the length of the device, parallel to the optical waveguides. Therefore, any significant interaction between the guided optical mode and metal traces would cause significant attenuation of light. This interaction can be minimized if the electrical traces are routed through a separate layer, vertically spaced from the photonic layer by the PDMS cladding (Fig. 3b). To study the optical propagation loss due to the electrical traces, we performed rigorous finite difference eigenmode (FDE) simulations of the OptoFlex waveguide geometry (30 μm x 5 μm) with a thin sheet of metal (200 nm of Pt) situated over the cladding.

The OptoFlex waveguide with dimensions of 30 μm x 5 μm is multimode in the visible range. Therefore, different modes experience different levels of attenuation due to the existence of the metal sheet since each mode profile has a different spread outside and around the waveguide core. However, when such a multimode waveguide is excited by an external light source (i.e., a laser), optical power is preferentially coupled to lower order modes, due to the larger overlap between the typical Gaussian mode profile of the light source and the optical mode profiles of the lower order modes. Optical losses caused by the interactions with the Pt layer were modeled for the lowest 30 modes and were found to be less than $3 \times 10^{-10}$ dB/cm for the fundamental mode, and less than $5 \times 10^{-8}$ dB/cm for each of the remaining simulated modes (Fig. 3c). These results demonstrate that 1 μm of PDMS cladding is sufficiently thick to insulate the waveguide modes from interaction with additional metal layers.
RESULTS

Parylene photonic waveguides guide light with low propagation loss
OptoFlex operates over a wide range of wavelengths, especially in the visible range that is relevant for optogenetic stimulation of neural activity. The input/output mirrors are broadband and enable coupling of light at different wavelengths (Fig. 4a). The propagation losses were measured at different wavelengths of interest for optogenetic stimulation including at 450 nm (ChR2), 532 nm (Arch), and 633 nm, 680 nm (red-shifted opsins, e.g., Chrimson)\(^\text{48}\). Table 2 lists the measured propagation losses in comparison with other waveguide technologies at different wavelengths. Measurement uncertainty is reported for waveguide-to-waveguide measurement variation. These results show that the propagation losses of our Parylene C waveguides are comparable to those measured in silicon nitride waveguides used in neural probes (Table 2). Our previous work showed that the primarily source of optical loss is the waveguide sidewall roughness as a results of etching the outline of the waveguide core\(^\text{49}\). OptoFlex exhibits low-losses across the entire visible range of the spectrum (450 – 680 nm) and the input/output coupling is broadband. Therefore, OptoFlex can operate over a wide range of wavelengths.

Table 2: Comparison of Neural Probe Waveguide Material Platforms and Losses\(^\text{1}\)

\(^1\) Measurement uncertainty is reported as ±1 standard deviation.
Flexible Parylene waveguides can guide light with low bend loss

OptoFlex is designed as a flexible photonic architecture that can freely flex with the tissue to avoid exerting strain on tissue (Fig. 4b). To operate reliably in vivo, the bends induced by tissue motion should not significantly impact the delivered optical power at the output port. However, bending of optical waveguides results in radiation of confined optical modes before light reaches the output facet. To characterize the overall bend loss, we experimentally measured the bend loss at different radii of curvature using a custom-designed jig (Fig. 4c). This jig has two parts. The first part is a 3D printed V-groove to hold the input fiber in place, and the second part is a precisely machined cylindrical rod to form the bend geometry. We used a series of different rods with different diameters to study the effect of bend loss at different bend radii.

The experimental bend loss measurement results are presented in Fig. 4d, showing negligible bend losses for millimeter-scale bends, i.e., more than 95% of maximum output intensity even at a bend radius of 1.5 mm. For bend radii smaller than 1 mm, the variance in measurements is larger compared to the measurements at larger radii of curvature. This is caused by experimental challenges in wrapping the probe smoothly around rods at such small radii. We suspect that loops or creases formed in the probe shank during these tight bends reduce the measurement accuracy. Therefore, the presented flexible waveguides preserve their performance through millimeter-scale bends in the probe shank. Bends of this size (1.5 mm – 5 mm) are likely to occur during implantation and routing of the flexible shank in the body. Our bend loss measurement results suggest that the output optical power will be minimally affected by flexing in the tissue after implantation.

| Work          | Material Platform | Wavelength λ (nm) | Propagation Loss α (dB/cm) | N (number of waveguides measured) |
|---------------|-------------------|-------------------|----------------------------|----------------------------------|
| OptoFlex      | Parylene C        | 450               | 6.1 ± 1.4                  | 3                                |
| Zorzos 2010   | SiN               | 473               | 3.2                        |                                  |
| OptoFlex      | Parylene C        | 532               | 4.9 ± 1.2                  | 12                               |
| OptoFlex      | Parylene C        | 633               | 4.1 ± 0.8                  | 14                               |
| Kampasi 2016  | SiN               | 635               | 5.0                        |                                  |
| OptoFlex      | Parylene C        | 680               | 3.2 ± 1.7                  | 5                                |
Figure 4: a) Outscattered light along the length of the waveguide is imaged at three different optical wavelengths in the visible range to show the trajectory of guided light. The waveguides were imaged from the side to avoid direct illumination from the output port, and the input power from the laser was increased so that the outscattered light along the waveguide path is clearly visible. b) Micrograph of released Parylene C/PDMS waveguide array. c) The flexible waveguide array bent over a custom jig to measure the bend loss (radius = 1.49 mm). d) Waveguide bend loss measurements of relative output intensity (normalized to the output intensity from a straight waveguide) through a 90-degree bend of various radii. Low waveguide bend losses demonstrated with high intensity ratio (more than 95%) at millimeter-scale bends. The number of measurements for each datapoint was N = 4. Error bars denote standard deviation.

Embedded micro-mirrors enable out-of-plane illumination with localized beam profiles
In addition to enabling a broadband vertical input coupling, the 45-degree output micro-mirrors are capable of localized broadband illumination normal to the probe surface. To characterize the output beam profile, a CCD camera was aligned to the output port of a Parylene waveguide in an array and input coupling was adjusted to maximize the light intensity at the output port (Fig. 5a). Subsequently, to image the beam profile, a block of fluorescent tissue phantom (Agar 0.6% mixed with 10 ppm AlexaFluor 532) was aligned above the output port with a micromanipulator and imaged from the side (Fig. 5b). The resulting fluorescent emission profile is shown in Fig. 5c, with iso-intensity contours superimposed on the image to show the spatial decay of light intensity.

The output beam profile reflected by the micro-mirror was quantitatively measured by imaging the output light intensity at multiple different angles (Fig. 5d). Characterization of a 30 μm x 5 μm micro-mirror output port at λ = 532 nm shows a narrow beam profile (1/e² beam width is 13.0°) orthogonal to the surface of the probe (Fig. 5e, f). This localized illumination profile allows for multiple output ports to be independently spaced along the probe surface for targeted light delivery. The light intensity directly reflected from the output micro-mirror port was measured via a CCD camera to be > 36 dB more intense than the outscattered light from the waveguide.
Figure 5: a) A brightfield image of waveguide array (top view) featuring an illuminated output port. b) Schematic illustration of fluorescent beam imaging experiment setup. c) Out-of-plane beam profile imaged in fluorescent tissue phantom with labeled iso-intensity contours. d) Schematic of beam profile characterization system. e) Radial beam profile, showing peak intensity at 90 degrees, with rapid off-axis decay. f) Gaussian curve fit to the radial beam profile, showing a beam divergence of 13.0 degrees, 1/e² beam width.

DISCUSSION
The embedded micromirror input/output port is a unique feature of the OptoFlex platform. The micromirrors are broadband, unlike traditional out-of-plane illumination mechanisms such as grating couplers, which are highly wavelength dependent. Using the micro-mirrors, light at multiple wavelengths can be coupled to the waveguides. In the context of neural probes, different optogenetic wavelengths can be used to switch between stimulation and inhibition, or to perform cell-type specific targeting. This biophotonic platform is the first to enable such high-resolution, broadband, out-of-plane light delivery in a fully compliant and biocompatible platform.

The waveguide output power can be controlled by changing the input optical power. Since the extinction between output port light intensity and the outscattered background light from the probe shank near the output port is >36 dB, off-target illumination is minimal. If the input power is very high, outscattered light along the probe shank can be further reduced by using additional optical shielding layers. For biological experiments, the input power must be carefully chosen to achieve an output power that is higher than the threshold of activation or detection of the
desired optical agent, while also remaining lower than the threshold of photothermal damage to the tissue at the wavelength of operation.

The OptoFlex platform utilizes flexible polymer materials to reduce the tissue response after implantation. However, the overall device stiffness depends on the shape of the probe cross-section in addition to the material platform. For example, wide and thin probes are highly compliant when bent along the probe length but have higher stiffness along the width of the probe, resulting in a greater tissue response along the probe edges\(^{52}\). Therefore, a neural probe design with a compact footprint (i.e., thin and narrow), in addition to a soft material platform, is necessary to minimize damage to the tissue. When designing a specific implant with the OptoFlex platform, the number and size of optical channels must be chosen such that the overall width of the probe is minimized.

Here, we report relatively large waveguides (30 \(\mu m \times 5 \mu m\)) for proof-of-principle demonstration. However, optical mode simulations suggest that the refractive index contrast between Parylene C and PDMS is sufficiently large to realize ultracompact optical waveguides that have well-confined modes even for small cross-sectional dimensions of 1 \(\mu m \times 1 \mu m\). At this small size, the mode exposure to the sidewall is increased, which necessitates process optimization to fabricate these devices with smooth sidewalls and reduce scattering losses. In a dense array configuration (1 \(\mu m\) gap), such waveguides exhibit negligible crosstalk of less than -30 dB over 5 cm length (Supplementary Material, Appendix I). These simulations suggest that under ideal conditions, the presented platform can be used to realize waveguide arrays even with an extremely dense pitch of only 2 \(\mu m\).

Another factor that limits the size and density of a multichannel OptoFlex device is the density of light source coupling at the device input. Here, we have demonstrated bonding of a single fiber to the waveguide input facet. Although the fiber core and cladding are small (125 \(\mu m\) diameter), serial bonding of individual fibers must take into account the prohibitive size of the fiber ferrule and its sleeve, which is typically 2.5 mm. Scaling the bonding process to many channels will require matching the waveguide spacing to the pitch of commercially available photonic chip coupler arrays which are now available at channel pitches from 127 \(\mu m\) to 20 \(\mu m\) pitch (PLC Connections, USA).

In addition to coupling light from benchtop laser sources with a fiber tether, we leverage the versatility of the embedded micro-mirror input ports for direct out-of-plane coupling of light to the polymer waveguides from laser diode chips. The low weight of the VCSEL sources (0.5 mg/diode) is important in the context of chronic experiments on freely-moving subjects, where the weight budget is typically 10% of the weight of the animal (2 – 3 g, headstage weight limit for mice\(^{53}\)). This integrated laser diode platform may be directly modulated via electrical power supplies integrated into a headstage or used for tetherless experiments with the addition of a battery and wireless communications. Due to the relatively large output facet (65 \(\mu m\)) of the bare chip VCSEL sources used here, a large input port is required to achieve efficient coupling into the waveguide. In future designs, the waveguide could be tapered to achieve high coupling efficiency while routing compact waveguides in the probe shank or more compact laser diodes can be used.

The fabrication process outlined in this paper to realize OptoFlex is compatible with commonly-used microfabrication techniques. During the fabrication process, harsh chemicals such as hydrofluoric acid (HF) are employed as an efficient way to remove oxide hardmask and sacrificial layers, necessitating careful rinsing in deionized water to avoid contamination of tissue. Other hardmask and sacrificial release layers, such as germanium\(^{54}\) (Ge) that can be
removed using biosafe solvents such as 1% hydrogen peroxide, could be used as viable alternatives. Our scalable microfabrication process enables monolithic integration of additional planar structures prior to release. Thus, using this platform, additional photonic layers can be stacked to increase device density, or electrical layers can be added to create a multimodal flexible device platform.

Although flexible devices are less damaging during chronic experiments, they are difficult to implant as they lack the structural rigidity to penetrate tissue. To address this need, implantation cannulas and bioresorbable stiffeners have been developed to temporarily increase the stiffness of neural probes for implantation. Bioresorbable materials such as polyethylene glycol (PEG), silk, callogen/Gelatin, and PLGA have demonstrated tunable properties for both stiffness and dissolution rate, which may be explored in combination with OptoFlex55. The required insertion force can be reduced via shaping the bioresorbable stiffener into a sharp tip using controlled dip coating56 or a molding process57. Additionally, external braces may be added to change the cantilever properties of the probe at the tissue interface to increase the buckling force of the probe58. These parameters require additional optimization for the OptoFlex architecture, but compatibility with existing techniques allows future OptoFlex implementations to benefit from the rich literature on implantation techniques for flexible neural probes.

CONCLUSION
OptoFlex shows great promise as a chronically implantable biointerface due to its compliance, which can reduce the foreign body response in tissue. The out-of-plane, broadband input/output ports enabled by embedded micro-mirrors allow OptoFlex to create patterns of localized illumination beams normal to the surface for collocated integration with recording electrodes and enable direct packaging with light sources on the probe backend. This photonic device platform is broadband and allows operation throughout a wide range of wavelengths with unprecedented flexibility in choosing the desired wavelength of light for opsins and optical reporters. While in this paper, we discussed packaging and implantation considerations to show feasibility of using this platform to realize optical neural probes, the OptoFlex platform can be used in a gamut of biomedical applications where a flexible, biocompatible optical device is desired.

MATERIALS AND METHODS
Fabrication process
Preparing the silicon mold: To implement Parylene C photonic waveguides and integrated micro-mirrors, fabrication was performed on 4-inch silicon wafers (n {100}) with 1 μm thermal oxide. The waveguide fabrication process flow is shown in Fig. 6 (additional process details in Table 2). The thermal oxide layer serves as a hardmask for deep etching of silicon. Oxide was patterned using optical lithography and anisotropic reactive ion etching (RIE) (Step 1 in Table 3). Then, 45-degree Si sidewalls were formed using wet etching in potassium hydroxide (KOH) mixed with Triton X-100 Surfactant59 (Step 2 in Table 3) to reach the desired trench depth of 6 microns (Fig. 6a). The oxide hardmask is subsequently stripped via wet etching in 49% HF. Careful design of the mask orientation with features at 45 degrees to the (100) plane, indicated by the wafer main flat, is required to expose the (110) crystal plane and define the micro-mirror surface59. The patterned Si surface serves as a mold for subsequent polymer layers, defining the 3D shape of the micro-mirrors. Subsequently, 300 nm of conformal oxide was deposited on the patterned Si surface using a plasma enhanced chemical vapor deposition (PECVD) process (Step 3 in Table 3) as a sacrificial layer to enable device release from the Si mold (Fig. 6b).

Spin-coating PDMS substrate: To form the substrate for the waveguide structure, a 1 μm PDMS layer was spin-coated on the silicon mold. Due to the high viscosity of PDMS, such a thin
layer requires dilution with Hexane prior to spin-coating. The PDMS (Sylgard 184, Dow Corning Corp, USA) was diluted to 1:10 PDMS:Hexane by volume, thoroughly mixed, and filtered through a 0.2 μm membrane filter to remove any particulates. The PDMS solution was degassed in vacuum (1 Torr) for 4 minutes to remove air bubbles. The solution was spin-coated for 60s at 2000 rpm, then degassed again in 400 mTorr vacuum for 4 minutes. Finally, wafers were oven baked for 45 minutes at 100 °C to cure the thin film and remove the solvent. To verify the thickness of PDMS to be 1 μm, the thin-film was measured using surface profilometer (P-15 Stylus Profiler, KLA Tencor, USA), wherein PDMS was mechanically removed from a portion of the wafer to measure the step height. The PDMS spin-coating process is not perfectly conformal and is affected by the waveguide trench topography. The spin-coating parameters and size of the trench must be optimized to achieve the desired thickness at the bottom of the trench. Multiple waveguides can be routed through a wide common trench.

Metal micro-mirrors: Due to the low surface energy of PDMS, photoresist cannot be directly spin-coated on its surface for lithography. To overcome this issue, we developed and optimized a fabrication process, in which a very thin (300 nm) layer of Parylene C film was deposited on PDMS to serve as an adhesion layer for the photoresist and enable optical lithography (Fig. 6c, Step 4 in Table 3). Direct chemical vapor deposition (CVD) of Parylene C on PDMS provides strong adhesion, making Parylene an ideal material. Embedded metal micro-mirrors were patterned using a lift-off process composed of lithography (AZ 4210) and evaporation of 5 nm Pt and 100 nm Al films (Steps 5,6 in Table 3). Pt serves as a strong adhesion layer to Parylene C, while Al is chosen as the mirror surface for its high reflectance across the visible spectrum. Lift-off was performed via acetone soaking, followed by pulsed (5-10 s) sonication (Fig. 6d). The root mean square surface roughness of the Al micromirrors was measured via optical profilometer (Zygo NV7000, AMETEK, USA) to be 49.3 nm with a standard deviation of 3.7 nm from mirror to mirror (N = 10).

Waveguide core etching and smoothing: In the next step, the waveguide core was realized in a subsequent layer of Parylene C. We designed multimode Parylene photonic waveguides with a core thickness of 3.5 μm. Parylene C was therefore deposited to a thickness of 3.5 μm using the CVD process described earlier. To define the outlines of individual waveguides, Parylene C was removed from the surrounding regions (Fig. 6e) using an anisotropic oxygen plasma etching process. We used a 40-nm sputtered chromium (Cr) hard mask (Step 7 in Table 3) to achieve a high selectivity for etching Parylene C. The waveguide patterns were aligned to the mirrors using a contact lithography process (AZ 5214E) and the hard mask was patterned by wet etching of Cr (Cr 1020 Etchant, Microchem GmbH, DE). The patterns were then transferred to Parylene C via oxygen plasma RIE (Step 8 in Table 3). PDMS acts as an etch stop layer, since PDMS is not effectively etched by oxygen plasma alone. After Parylene C has been etched (verified via reflectometer), the Cr hardmask is stripped with Cr etchant. The etched sidewall roughness results in optical scattering and significant propagation loss, thus rendering the optical waveguide not practical for efficient guiding of light. To alleviate this issue, we use our previously reported technique of depositing an additional 1.3 μm conformal layer of Parylene C over the etched sidewalls to reduce the sidewall roughness and the associated propagation loss. We use this technique here to smoothen the etched sidewalls and reduce the propagation loss of the implantable waveguides. The three sequential Parylene C layers, i.e., the thin layer on PDMS substrate, the waveguide layer, and the conformal coating on the top form the waveguide core with a total thickness of approximately 5 μm (Fig. 1b).
**Device release:** After the upper cladding of 1 μm PDMS was spin-coated (Fig. 6f), a 1 μm aluminum (Al) hardmask was sputtered to define outline of the entire waveguide array (Step 9 in Table 3). The Al hardmask was lithographically patterned (AZ 4210), and wet etched (*Al Etchant Type-A, Microchem GmbH, DE*). PDMS cladding was etched and arrays were singulated using RIE (Step 10 in Table 3). Finally, the Al hardmask was stripped. To release the devices, the silicon substrate was first thinned down to 100 μm using backside etching in SF₆ (Step 11 in Table 3), and then the thinned Si wafer was completely etched in a subsequent etching step in XeF₂ (Xactix e2). The sacrificial oxide layer serves to protect the backside of the waveguide array. Once Si was removed, the sacrificial layer was stripped in Buffered Hydrofluoric acid (BHF), resulting in a released, flexible waveguide array (Fig. 6g). Devices are thoroughly rinsed in deionized water after release to avoid contamination of biological tissues by process chemicals.

![Diagram](image)

**Figure 6:** Process flow diagram for waveguide fabrication

**Table 3: Fabrication Process Parameters**

| Process Step       | Tool                        | Parameters                                      | Rate          |
|--------------------|-----------------------------|-------------------------------------------------|---------------|
| 1) Thermal Oxide Etch | PlasmaTherm 790 RIE         | Gas: 22.5 SCCMs CHF₃ Gas: 16 SCCMs O₂ Pressure: 100 mTorr Power: 200W | 55 nm/min     |
| 2) Anisotropic Si Etch | Wet Bench                  | Concentration : 2M KOH Concentration : 60 ppm Triton X-100 Surfactant Temperature: 90 °C Agitation: 210 rpm stirring | 280 nm/min    |
| 3) PECVD Oxide Deposition | Trion Orion II PECVD       | Temperature: 375 °C Pressure: 900 mTorr Gas: 75 SCCMs N₂O Gas: 70 SCCMs SiH₄ | 60 nm/min     |
| 4) Parylene Deposition | SCS Labcoter-2             | Furnace Temperature: 690 °C Chamber Gauge Temperature: 135 °C Vaporizer Temperature: 175 °C Pressure: 35 mTorr | 1g -> 300 nm 2g -> 1.3 μm 6.9 g -> 3.5 μm |
| 5) Pt Evaporation   | Kurt J. Lesker PVD 75 Electron Beam Evaporator | Pressure: 3 x 10⁻⁷ Torr | 3 Å/s         |
### Experimental Methods

**Fiber optic bonding:** First, a drop of optical quality epoxy (EPO-TEK 301, Epoxy Technology Inc, USA) is placed on the waveguide array backend. An optical fiber is fixed to a custom-designed 3D printed fixture with a V-groove and aligned to the input micromirror using a precision micromanipulator (PatchStar, Scientifica Inc, UK). After maximizing input coupling efficiency, the epoxy is thermally cured (60 °C, 2H) to provide a stable mechanical connection between the fiber and the waveguide array.

**VCSEL light source bonding:** ACF film (CP34531-18AK, Dexerials Corporation, Tokyo, Japan) is placed over the input micromirror. The VCSEL chip is then aligned to the input facet using a commercial flip-chip bonding tool (M9A, BE Semiconductor Industries N.V. (Besi), The Netherlands). Once aligned, the ACF is cured (120 °C, 15 minutes) to fix the VCSEL in place. The p-contact and n-contact of the diode are electrically connected to an external PCB using an Al wirebond (Model 7476D, West Bond, Anaheim, CA).

**Characterization of propagation loss:** To characterize the device performance, a single mode fiber (S405-XP, Thorlabs Inc, USA) or a laser diode (PL 450B, OSRAM GmbH, Germany) was aligned to the input facet of the waveguide, while imaging the output port onto a CCD camera. The input coupling was optimized by adjusting the position of the light source using a precision micromanipulator (PatchStar, Scientifica Inc, UK) to maximize the light emission from the output port. Propagation losses in the waveguide were characterized by measuring the decay in the intensity of out-scattered light along the length of the optical waveguide. Traditionally, the modified cutback method is used to measure waveguide loss, which involves recording the output light intensity from multiple waveguides of different lengths and interpolating the loss as a function of length. However, our method based on extracting the propagation loss from the out-scattered light allows for measurements of individual waveguide performance in one shot, and thus eliminates the errors inherent to the cutback method due to waveguide-to-waveguide variations or changes in input coupling efficiency from one waveguide to another.

**Characterization of bend loss:** A single OptoFlex probe was sequentially wrapped around rods of different radii (0.3 mm – 5 mm) to measure the bend loss. In all cases, the bend angle
was 90 degrees. The transmitted output power was measured by imaging the output port onto a CCD camera. To minimize errors due to variations in input coupling conditions, we optimized and maximized the coupling from the input optical fiber by measuring the transmission of the straight waveguide and then permanently affixed the fiber to the input facet using an epoxy to maintain a consistent input coupling. We repeated the experiments four times, each time sweeping the range of bend radii, to ensure the repeatability of the results and characterize the measurement error at different radii.

**Characterization of micro-mirror output beam profile:** The optical properties of the waveguide platform were characterized to demonstrate broadband, localized, out-of-plane illumination capabilities. A single mode optical fiber (S405 XP, Thorlabs Inc, USA) was aligned vertically to the input mirror for input coupling to the waveguide.

Input coupling efficiency was optimized by adjusting the fiber position using a precision micromanipulator (PatchStar, Scientifica Inc., UK) while monitoring the peak intensity from the output port in the CCD camera (EO-5012M, Edmund Optics, USA).

Output port beam profiles were imaged by rotating the imaging platform in fixed increments about the axis of the waveguide and imaging the output port light intensity. To increase the dynamic range of the system, the imaging exposure time was scaled for each sample to avoid individual pixel saturation, and the pixel intensity values were then scaled by the exposure time.

**Agar phantom preparation:** Powdered bacteriological agar (A5306, Sigma-Aldrich, USA) was mixed by weight with 200 mL of deionized water in a 500 mL beaker and stirred at 600rpm while heating on a hotplate. The top of the beaker is covered with a quartz watch glass to prevent evaporation. Once the solution is boiling, the hotplate is switched off and the temperature is monitored via a thermocouple, until the temperature has dropped to 60 °C. For fluorescent samples, 10 ppm of AlexaFluor 532 is added to the solution and mixed for an additional 5 minutes. The solution is then poured into a mold and cooled in a refrigerator at 6 °C for 30 minutes before use.

**Simulation method**

Optical simulations were performed using commercial FEM software (Lumerical MODE Solutions 2018b, Lumerical Inc., USA). The waveguide mode profiles were solved in 2 dimensions (2D), by taking a cross-section of the device geometry along the axis of propagation (z-axis). The finite difference eigenmode method was used to solve Maxwell’s equations in 2D to find the electric and magnetic field profiles for each mode, as well as the complex propagation constant, $\beta$. Mode profiles are visualized by plotting the normalized electric field intensity, $|E|^2$. A perfectly matched layer (PML) boundary condition was used around the simulation domain. In all simulations, a background index of 1.0 was used. Simulations were performed at a wavelength of $\lambda = 450$ nm.

Parylene waveguides were simulated with dimensions (1 μm x 1 μm) and (30 μm x 5 μm).

To simulate the waveguide structure, Parylene C is defined as a dielectric with refractive index ($n = 1.639$), and PDMS is defined as a refractive index ($n = 1.4$). Platinum optical properties were taken from the E. Palik.65

**Supplementary Material**

**Appendix I: Crosstalk Simulation**
Parylene C and PDMS are excellent candidate materials for a biophotonic platform due to their biocompatibility, flexibility, transparency in the visible range, and ease of processing using traditional microfabrication techniques. Additionally, Parylene C has a high refractive index amongst polymer materials (n = 1.639), whereas PDMS has a low refractive index (n = 1.4), allowing for high index contrast devices. Compared to dielectric materials such as silicon nitride (n = 2.05 at λ = 450 nm)\(^6\), however, Parylene C provides much less index contrast. A simulation is performed in order to show that the index contrast in Parylene C/PDMS is sufficient for a high-density photonic platform. A concern of densely integrated waveguide arrays is the crosstalk between adjacent channels due to evanescent field coupling between the channels. As waveguides become smaller, the modes become less confined and more optical power propagates in the cladding. As a result, this optical power can be coupled into adjacent channels.

The simulation is performed using a bidirectional eigenmode expansion (EME) solver (*Lumerical MODE Solutions 2018b, Lumerical Inc., USA*). The simulated waveguide has a cross section of 1 µm x 1 µm (Fig. S1a). Two parallel waveguides with 1 µm spacing are simulated over a propagation length of 5 cm (Fig. S1b). Input optical power in the “input waveguide” is normalized to 1 and the proportion of optical power in the adjacent “probe waveguide” is measured. Over the 5 cm propagation length, increasing power is observed in the probe waveguide due to evanescent field coupling (Fig. S1c,d). Over a 5 cm length, a total crosstalk of -32.86 dB is observed.

**Figure S1:** a) 1 µm x 1 µm waveguide cross section showing fundamental mode profile (at λ = 450 nm) b) Schematic of the geometry for crosstalk analysis. The input waveguide (left) is powered while the probe waveguide (right) is...
monitored over a propagation length of 5 cm. c) Electric field profile of a parallel waveguide structure over 5 cm propagation distance. Light coupling into the probe waveguide can be observed. d) Plot of crosstalk in the probe waveguide vs propagation length in decibels (dB). At 5 cm, a crosstalk of -32.86 dB is observed.

References

1. Yang, W. & Yuste, R. In vivo imaging of neural activity. *Nat. Methods* **14**, 349–359 (2017).
2. Wu, D. et al. Fluorescent chemosensors: the past, present and future. *Chem. Soc. Rev.* **46**, 7105–7123 (2017).
3. Carrasco-Zevallos, O. M. et al. Review of intraoperative optical coherence tomography: technology and applications [Invited]. *Biomed. Opt. Express* **8**, 1607 (2017).
4. Riley, R. S. & Day, E. S. Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment. *Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology* **9**, e1449 (2017).
5. Kim, J., Kim, J., Jeong, C. & Kim, W. J. Synergistic nanomedicine by combined gene and photothermal therapy. *Adv. Drug Deliv. Rev.* **98**, 99–112 (2016).
6. Li, Z. et al. Small gold nanorods laden macrophages for enhanced tumor coverage in photothermal therapy. *Biomaterials* **74**, 144–154 (2016).
7. Thompson, A. C., Stoddart, P. R. & Jansen, E. D. Optical Stimulation of Neurons. *Curr. Mol. Imaging* **3**, 162–177 (2014).
8. Fenno, L., Yizhar, O. & Deisseroth, K. The Development and Application of Optogenetics. *Annu. Rev. Neurosci.* **34**, 389–412 (2011).
9. de Freitas, L. F. & Hamblin, M. R. Proposed Mechanisms of Photobiomodulation or Low-Level Light Therapy. *IEEE J. Sel. Top. Quantum Electron.* **22**, 348–364 (2016).
10. Ntziachristos, V. Going deeper than microscopy: the optical imaging frontier in biology. *Nat. Methods* **7**, 603–614 (2010).
11. Deng, X. & Gu, M. Penetration depth of single-, two-, and three-photon fluorescence microscopic imaging through human cortex structures: Monte Carlo simulation. *Appl. Opt.* **42**, 3321 (2003).
12. Ziv, Y. & Ghosh, K. K. Miniature microscopes for large-scale imaging of neuronal activity in freely behaving rodents. *Curr. Opin. Neurobiol.* **32**, 141–147 (2015).
13. Wu, F. et al. An implantable neural probe with monolithically integrated dielectric waveguide and recording electrodes for optogenetics applications. *J. Neural Eng.* **10**, 056012 (2013).
14. Hoffman, L. et al. High-density optrode-electrode neural probe using SixNy photonics for in vivo optogenetics. in *2015 IEEE International Electron Devices Meeting (IEDM)* 29.5.1-29.5.4 (IEEE, 2015). doi:10.1109/IEDM.2015.7409795.
15. Schwaerzle, M., Paul, O. & Ruther, P. Compact silicon-based optrode with integrated laser diode chips, SU-8 waveguides and platinum electrodes for optogenetic applications. *J. Micromechanics Microengineering* **27**, 065004 (2017).
16. Oh, G., Chung, E. & Yun, S. H. Optical fibers for high-resolution in vivo microendoscopic fluorescence imaging. *Opt. Fiber Technol.* **19**, 760–771 (2013).
17. Guo, Q. et al. Multi-channel fiber photometry for population neuronal activity recording. *Biomed. Opt. Express* **6**, 3919 (2015).
18. Reddy, J. W., Kimukin, I., Ahmed, Z., Towe, E. & Chamanzar, M. High density, double-sided, flexible optoelectrical neural probes with embedded micro-LEDs. *Front. Neurosci.* **13**, 572 (2019).
19. Chamanzar, M., Denman, D. J., Blanche, T. J. & Maharbiz, M. M. Ultracompact optoflex neural probes for high-resolution electrophysiology and optogenetic stimulation. in *2015
20. Klein, E., Gossler, C., Paul, O. & Ruther, P. High-Density μLED-Based Optical Cochlear Implant With Improved Thermomechanical Behavior. Front. Neurosci. 12, 659 (2018).
21. Kozai, T. D. Y., Jaquins-Gerstl, A. S., Vazquez, A. L., Michael, A. C. & Cui, X. T. Brain Tissue Responses to Neural Implants Impact Signal Sensitivity and Intervention Strategies. ACS Chem. Neurosci. 6, 48–67 (2015).
22. Moshayedi, P. et al. The relationship between glial cell mechanosensitivity and foreign body reactions in the central nervous system. Biomaterials 35, 3919–3925 (2014).
23. Weltman, A. et al. Flexible, Penetrating Brain Probes Enabled by Advances in Polymer Microfabrication. Micromachines 7, 180 (2016).
24. Thomson, D. et al. Roadmap on silicon photonics. J. Opt. 18, 073003 (2016).
25. Ersen, A. & Sahin, M. Polydimethylsiloxane-based optical waveguides for tetherless powering of floating microstimulators. J. Biomed. Opt. 22, 055005 (2017).
26. Rehberger, F. et al. Lichtwellenleiter aus PDMS für biomedizinische Anwendungen. Biomed. Eng. Tech. 59, S1068–S1071 (2014).
27. Kwon, K. Y., Lee, H.-M., Ghovanloo, M., Weber, A. & Li, W. Design, fabrication, and packaging of an integrated, wirelessly-powered optrode array for optogenetics application. Front. Syst. Neurosci. 9, 1–12 (2015).
28. Son, Y. et al. In vivo optical modulation of neural signals using monolithically integrated two-dimensional neural probe arrays. Sci. Rep. 5, 15466 (2015).
29. Szarowski, D. H. et al. Brain responses to micro-machined silicon devices. Brain Res. 983, 23–35 (2003).
30. Lee, H. C. et al. Histological evaluation of flexible neural implants; Flexibility limit for reducing the tissue response? J. Neural Eng. 14, (2017).
31. Hopcroft, M. A., Nix, W. D. & Kenny, T. W. What is the Young’s Modulus of Silicon? J. Microelectromechanical Syst. 19, 229–238 (2010).
32. Khan, A., Philip, J. & Hess, P. Young’s modulus of silicon nitride used in scanning force microscope cantilevers. J. Appl. Phys. 95, 1667–1672 (2004).
33. Hassler, C., von Metzen, R. P., Ruther, P. & Stieglitz, T. Characterization of parylene C as an encapsulation material for implanted neural prostheses. J. Biomed. Mater. Res. Part B Appl. Biomater. 9999B, NA-NA (2010).
34. Johnston, I. D., McCluskey, D. K., Tan, C. K. L. & Tracey, M. C. Mechanical characterization of bulk Sylgard 184 for microfluidics and microengineering. J. Micromechanics Microengineering 24, 035017 (2014).
35. Budday, S. et al. Mechanical properties of gray and white matter brain tissue by indentation. J. Mech. Behav. Biomed. Mater. 46, 318–330 (2015).
36. McKee, C. T., Last, J. A., Russell, P. & Murphy, C. J. Indentation versus tensile measurements of Young’s modulus for soft biological tissues. Tissue Eng. Part B. Rev. 17, 155–64 (2011).
37. Heo, C. et al. A soft, transparent, freely accessible cranial window for chronic imaging and electrophysiology. Sci. Rep. 6, (2016).
38. Minev, I. R. et al. Electronic dura mater for long-term multimodal neural interfaces. Science (80-. ). 347, 159–163 (2015).
39. FDA. 21CFR878.3540. (FDA Code of Federal Regulations, Title 21, 2018).
40. Stark, N. Literature Review: Biological Safety of Parylene C. Med. Plast. Biomater. (1996).
41. Marjanović-Balaban, Ž. & Jelić, D. Polymeric Biomaterials in Clinical Practice. in Biomaterials in Clinical Practice 101–117 (Springer International Publishing, 2018). doi:10.1007/978-3-319-68025-5_4.
42. Jeong, Y. S., Ratier, B., Moliton, A. & Guyard, L. UV-visible and infrared characterization
of poly(p-xylylene) films for waveguide applications and OLED encapsulation. in *Synthetic Metals* vol. 127 189–193 (2002).

43. Libbrecht, S. *et al.* Proximal and distal modulation of neural activity by spatially confined optogenetic activation with an integrated high-density optoelectrode. *J. Neurophysiol.* **120**, 149–161 (2018).

44. Zorzos, A. N., Scholvin, J., Boyden, E. S. & Fonstad, C. G. Three-dimensional multiwaveguide probe array for light delivery to distributed brain circuits. *Opt. Lett. 37*, 4841 (2012).

45. Ahmed, Z., Reddy, J. W., Teichert, T. & Chamanzar, M. High-density Steeltrodes: A Novel Platform for High Resolution Recording in Primates . in *2019 9th International IEEE/EMBS Conference on Neural Engineering (NER)* 835–838 (IEEE, 2019). doi:10.1109/NER.2019.8716921.

46. Ahmed, Z. *et al.* Flexible Ultra-resolution Subdermal EEG Probes. in *2018 IEEE Biomedical Circuits and Systems Conference, BioCAS 2018 - Proceedings* (Institute of Electrical and Electronics Engineers Inc., 2018). doi:10.1109/BIOCAS.2018.8584672.

47. Rakić, A. D., Djurišić, A. B., Elazar, J. M. & Majewski, M. L. Optical properties of metallic films for vertical-cavity optoelectronic devices. *Appl. Opt. 37*, 5271 (1998).

48. Klapek, N. C. *et al.* Independent optical excitation of distinct neural populations. *Nat. Methods 11*, 338–346 (2014).

49. Reddy, J. W. & Chamanzar, M. Low-loss flexible Parylene photonic waveguides for optical implants. *Opt. Lett. 43*, 4112 (2018).

50. Zorzos, A. N., Boyden, E. S. & Fonstad, C. G. Multiwaveguide implantable probe for light delivery to sets of distributed brain targets. *Opt. Lett. 35*, 4133 (2010).

51. Kampasi, K. *et al.* Fiberless multicolor neural optoelectrode for in vivo circuit analysis. *Sci. Rep. 6*, 30961 (2016).

52. Nguyen, J. K. *et al.* Mechanically-compliant intracortical implants reduce the neuroinflammatory response. *J. Neural Eng.* **11**, 056014 (2014).

53. Mendrela, A. E. *et al.* A High-Resolution Opto-Electrophysiology System With a Miniature Integrated Headstage. *IEEE Trans. Biomed. Circuits Syst.* **12**, 1065–1075 (2018).

54. Kalmykov, A. *et al.* Organ-on-chip: Three-dimensional self-rolled biosensor array for electrical interrogations of human electrogenic spheroids. *Sci. Adv. 5*, (2019).

55. Lecomte, A., Descamps, E. & Bergaud, C. A review on mechanical considerations for chronically-implanted neural probes. *J. Neural Eng.* **15**, 031001 (2018).

56. Xiang, Z. *et al.* Ultra-thin flexible polyimide neural probe embedded in a dissolvable maltose-coated microneedle. *J. Micromechanics Microengineering 24*, 065015 (2014).

57. Pas, J. *et al.* A bilayered PVA/PLGA-bioresorbable shuttle to improve the implantation of flexible neural probes. *J. Neural Eng. 15*, 065001 (2018).

58. Shoffstall, A. J. *et al.* A Mosquito Inspired Strategy to Implant Microprobes into the Brain. *Sci. Rep. 8*, 122 (2018).

59. Rola, K. P. & Zubel, I. Triton Surfactant as an Additive to KOH Silicon Etchant. *J. Microelectromechanical Syst. 22*, 1373–1382 (2013).

60. Chen, W., Lam, R. H. W. & Fu, J. Photolithographic surface micromachining of polydimethylsiloxane (PDMS). *Lab Chip 12*, 391–5 (2012).

61. Lim, A. E.-J. *et al.* Review of Silicon Photonics Foundry Efforts. *IEEE J. Sel. Top. Quantum Electron. 20*, 405–416 (2014).

62. Kuo, J. T. W. *et al.* Novel flexible Parylene neural probe with 3D sheath structure for enhancing tissue integration. *Lab Chip 13*, 554–561 (2013).

63. Hass, G. & Waylonis, J. E. Optical Constants and Reflectance and Transmittance of Evaporated Aluminum in the Visible and Ultraviolet*. *J. Opt. Soc. Am. 51*, 719 (1961).

64. Garra, J. *et al.* Dry etching of polydimethylsiloxane for microfluidic systems. *J. Vac. Sci. Technol. A Vacuum, Surfaces, Film. 20*, 975–982 (2002).
65. Palik, E. D. *Handbook of optical constants of solids. III.* (Academic Press, 1998).
66. Philipp, H. R. Optical Properties of Silicon Nitride. *J. Electrochem. Soc.* 120, 295 (1973).