POEMS (POLYMERIC OPTO-ELECTRO-MECHANICAL SYSTEMS) FOR ADVANCED NEURAL INTERFACES

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Abstract

There has been a growing interest in optical neural interfaces which is driven by the need for improvements in spatial precision, real-time monitoring, and reduced invasiveness. Here, we present unique microfabrication and packaging techniques to build implantable optoelectronics with high precision and spatial complexity. Material characterization of our hybrid polymers shows minimal in vitro degradation, greater flexibility, and lowest optical loss (4.04-4.4 dB/cm at 670 nm) among other polymers reported in prior studies. We use the developed methods to build Lawrence Livermore National Laboratory’s (LLNL’s) first ultra-compact, lightweight (0.38 g), scalable and minimally invasive thin-film optoelectronic neural implant that can be used for chronic studies of brain activities. The paper concludes by summarizing the progress to date and discussing future opportunities for flexible optoelectronic interfaces in next generation clinical applications.

Graphical Abstract

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INTRODUCTION

The long-term stability of an implantable device depends on the careful selection of interface materials, geometry and scale\(^1\). Implantable neural interfaces have undergone quite an evolution in their design, starting from millimeter-scale electrodes\(^2\) in early 20\(^{th}\) century to microfabricated probes\(^3\)-\(^6\) and multi-modal optoelectrodes of today’s age\(^7\)-\(^9\). Optical tools for neural manipulation and recording have recently allowed scientists to control, map and image brain circuits with cell-type specificity at high spatial and temporal precision\(^7\),\(^10\)-\(^12\). However, bidirectional optical communication between an implanted device and a tissue remains an implementation challenge. Light scatters randomly in inhomogeneous media like biological tissues, and light-guiding materials often suffer eventual degradation \textit{in vivo}. New materials and advanced engineering can help to mitigate these challenges and deliver stable optical interfaces for chronic use.

Light-guiding materials in an optical implant must have high transmissivity and transparency over the visible spectrum, this allows use of a wide range of wavelengths for cell stimulation or cell imaging. Traditional silicon-based semiconductor materials are optically clear and have well understood process techniques\(^4\),\(^13\),\(^14\) but may suffer from long-term biocompatibility issues due to their mechanical stiffness\(^15\). Carbon-based materials are flexible and biocompatible\(^15\),\(^16\) but relatively less understood in the context of optical propagation. Polymer materials such as polyimide\(^17\), Parylene-C\(^18\) and SU-8\(^19\) are flexible and may promote cell attachment thereby enhancing signal acquisition. However, major
drawbacks of polymers include lower optical transmittance and transparency, high moisture absorbability and reduced chemical and thermal stability which limits their application.

Recently, nano-hybridization of polymers with metallic or inorganic nanoparticles has been proposed as a promising technique to overcome optical polymers’ drawbacks without reducing their inherent advantages\textsuperscript{20}. These organic-inorganic hybrid polymers obtained via a sol-gel process\textsuperscript{21} are lightweight and flexible and enable a wide range of molecular designs. Unlike semiconductor material growth and deposition approaches which are carried out at higher temperatures, hybrid polymers can be spun at room temperature and cured at lower temperatures to achieve a wide range of thicknesses. Furthermore, with the aid of computational models, molecular formations can be synthesized to tune optimal physical properties like elasticity and strength. Ormocers\textsuperscript{22} (ORganically-MODified-CERamics) are an example of hybrid polymers which constitute characteristics useful for fabrication of flexible structures in a simple and cost-effective manner. Their UV-induced polymerization yields a cured thermosetting composite with no glass transition temperature, high chemical and thermal stability, and high optical transparency\textsuperscript{23}. Ormocers\textsuperscript{2} have attracted considerable attention for wafer-scale design of optical elements such as waveguides\textsuperscript{22} and Bragg gratings\textsuperscript{24} and as biocompatible tissue scaffolds\textsuperscript{25}. However, to the best of our knowledge, their use in biomedical optical implants has not yet been adopted.

Lawrence Livermore National Laboratory (LLNL) has developed a series of thin-film polymer implants for research and clinical applications\textsuperscript{26-29}, including the first FDA-cleared polyimide-based retinal prosthesis in the world\textsuperscript{26}. In this work, we present integration of LLNL’s thin-film polymer technology with hybrid polymers to enable Polymeric Opto-Electro-Mechanical Systems (POEMS). We characterize hybrid and non-hybrid polymers (Table 1) and then use the chosen materials and developed technologies to build LLNL’s first flexible optoelectrode that can deliver guided light for neural activation. The presented work demonstrates POEMS’s potential to allow selective sensing and actuation capabilities for biomedical applications.

**FLEXIBLE OPTOELECTRONICS: MATERIALS AND DESIGN**

**Material characterization**

The optical performance of a material depends on its transmission and scattering properties. If a film is non-absorbing, optically homogeneous and isotropic, the transmitted ray propagates without loss of intensity. However, realistically, the transmitted ray, \(T\), loses intensity during travel as the result of scattering from inhomogeneities within the material. The distribution of the scattered light can be represented in terms of reflected, \(R\), back-scattered, \(B\), and forward-scattered, \(F\), components of the total flux using equation \(1\)\textsuperscript{30}:

\[
I(dB) = T(dB) + R(dB) + F(dB) + B(dB) \tag{1}
\]

We measured \(T\) of 180 \(\mu\)m-thick polymerized films (Figure 1a) using a UV-Vis spectrophotometer (Perkin Elmer, Houston, Texas). \(R\), a fraction of the incident flux, \(I\), gets reflected from the surface at the point of incidence. Fresnel’s equation for normal incidence...
was used to determine the reflected component (equation 2), where, Refractive Index (RI) of air and polymer are denoted by $n_1$ and $n_2$, respectively. For example, at an air - polymer interface, 4-6% of the incident flux is reflected for polymers with $n_2$ ranging between 1.5 to 1.6 (Table 1).

$$R = \frac{(n_2 - n_1)^2}{(n_1 + n_2)^2}$$  \hspace{1cm} (2)

$F$ and $B$ form a very small fraction for smooth, transparent films and their summation can be calculated numerically using equations 1 and 2.

The optical transmission and appearance of the polymers can vary across the visible spectrum (Figure 1 a-b) owing to their thickness, homogeneity, and difference in light scattering processes. Ormocers® demonstrate enhanced optical transmission, transparency, and flexibility (Figure 1, Table 1). Whereas, EpoCore and IP-Dip absorb light in the near-UV spectrum and appear yellowish when viewed under white light; IP-Dip is also less flexible at the measured thickness of 180 μm, with visible cracks along the edges (Figure 1b).

Accelerated lifetime soak tests (Figure 1c) and photodamage tests (Figure 1d) were conducted to determine polymers’ transmission characteristics and longevity \textit{in vitro}. The accelerated lifetime soak provides an initial prediction of material degradation kinetics \textit{in vivo}. UV photo-exposure experiments quantify possible film degradation during waveguide operation, acknowledging the fact that polymers are damaged most by UV radiation which causes them to crack or disintegrate. The findings in Figure 1 suggest that hybrid polymers offer appreciable chemical and photo resistance with evidence of biocompatibility\textsuperscript{32}, and form promising materials for further study in preparation for long-term \textit{in vivo} implants\textsuperscript{33}. In comparison, both EpoCore and IP-Dip show lower optical transmissivity for lower visible wavelengths and have no record of biocompatibility in the literature.

### Patterning technologies

An in-depth study of polymer microfabrication has been presented extensively in the literature\textsuperscript{18,26,34}. In this work, we report microfabrication and additive manufacturing methods to pattern microscale polymer optical structures on different substrates while considering material properties and surface adhesion, which are critical for long-term device performance. We use microfabrication for wafer-scale design of continuous, millimeter-long planar waveguides and three-dimensional (3D) printing for design of micro-scale non-planar optical interconnects. When combined, these technologies offer solution to interconnect challenges at the Printed Circuit Board (PCB) and Multi-Chip-Module (MCM) level, potentially replacing typical electrical interconnects with high-performance, low-cost, compact polymer-based photonic alternatives. One such envisioned device schematic is shown in Figure 2a where constituent sub-assemblies use flexible optoelectronics at the off-and on-chip interconnect level.

**Planar microfabrication.**—Microfabrication methods of resist spin-coating, UV lithography, and curing were used to pattern photo-definable OrmoClearFX and EpoCore
planar waveguides on a polymer substrate called Cytop (AGC chemicals, Japan). OrmoClearFX is an Ormocer® whereas EpoCore is an SU8-like negative resist. Cytop is an amorphous fluoropolymer that was chosen as an optical cladding material because of its low RI (RI = 1.34), transparency, insulation properties, and very low moisture absorption compared to other polymers like polyimide and parylene. The fabricated waveguides had 10 μm-thick and 10 μm-wide core and 2.5 μm-thick Cytop cladding. A characteristic rounding of OrmoClearFX waveguide edges was observed due to oxygen inhibition (Figure 2b), a phenomenon whereby molecular oxygen at the surface inhibits free radical polymerization leaving uncured polymer on structure surfaces and interfaces. This can be advantageously utilized to round-off waveguide edges and corners to achieve diffused illumination profiles. On the other hand, EpoCore waveguides have straighter sidewalls and can be used for applications that demand rectangular waveguide cross-section (Figure 2c). Both OrmoClearFX and EpoCore waveguides exhibit high flexibility (Figure S1) and thus attract growing interest in microfabrication of flexible optoelectronics.

3D printing.—3D waveguides and optical interconnects were additively manufactured with two-photon resists, OrmoComp and IP-Dip, using a direct laser lithography system (Nanoscribe GT, Nanoscribe GmbH, Germany). OrmoComp is an Ormocer® and IP-Dip is a RI-matched negative resist specifically developed for two-photon polymerization (2PP/TPP) at 780 nm laser wavelength of the Nanoscribe. The Nanoscribe focuses ultrafast laser pulses into a volume of a photosensitive two-photon resist to initiate 2PP and a developer solution removes non-illuminated unpolymerized regions, leaving behind a 3D structure. A parametric study was conducted to capture the printable regime for OrmoComp and IP-Dip on different substrate types (Figure S2). All structures were printed using a bottom-up printing approach and were optimized for adhesion and alignment while printing within material’s thermal threshold. In addition to the commonly reported damage and writing threshold, we also characterized a 50%-dimensional tolerance threshold (±5 μm in X, Y, and Z axes) to further characterize the dimensional integrity of printed shapes as compared to their actual programmed dimensions. The results showed that IP-Dip’s damage threshold followed previously reported trends for opaque and reflective surfaces. OrmoComp exhibited wider printing windows with no boiling damage within the 50 mW-laser power and 10 mm/s writing speed on most substrate types. Power intensity in OrmoComp was also found to be lower than in IP-Dip for the same average beam power due to the RI mismatch between immersion objective (1.52) and OrmoComp (1.51) at 780 nm.

These printing methods were implemented to design 3D interconnects on polymers (Figure 2d-2e) and on VCSELs (SM67-3N001M, Optowell Co. Ltd., South Korea) and optical fibers (FG050LGA, Thorlabs) (Figure 2f-2g). The optical performance of printed interconnects depends on material’s degree of crosslinking which is optimized by increasing laser power and decreasing laser speed during print and using UV exposure post-print. Since 2PP printing must be carried out under carefully controlled conditions near polymerization threshold, post-print UV cure is recommended to saturate crosslinking, thus reducing structural and functional variability, i.e. adhesion, modulus, and RI, across all printed structures.
Optical loss measurements

The direct cut-back method was used to evaluate propagation loss per unit length of microfabricated and 2PP printed waveguides. The propagation losses in planar 10 μm x 10 μm waveguides measured as 4.9-7.8 dB/cm (OrmoClearFX) and 7.6-11.2 dB/cm (EpoCore) (Figure 3a). The high precision optical interconnects or “optical wirebonds” were shown to enhance optical coupling between on- and off-chip components. The propagation losses in printed 50 μm diameter OrmoComp waveguides measured between 4.08-4.4 dB/cm (Figure 3b) (Figure S3, S4). IP-Dip was excluded from optical waveguide characterization due to its low optical transmission and clarity (Figure 1), high Young’s modulus, and low glass transition temperature, making it unfit for design of flexible and optically clear waveguides.

TOWARDS A POEMS-BASED IMPLANTABLE NEURAL INTERFACE

Adoption of emerging flexible photonic technologies can greatly benefit the implantable device field, which has been arguably hindered by an almost singular dependence on electromagnetics. As the electrode size is reduced to attain smaller implants, electrical recording suffers from reduced detectable signals with increase in noise, further worsening the signal-to-noise ratio. The addition of optics not only reduces device footprint and inter-wire crosstalk, but also offers light as a more sensitive modality to manipulate and sense biological signals. Utilizing the materials and technologies discussed above, we developed an all-polymer POEMS neural optoelectrode that can deliver guided light for neural activation. At just 0.38 g, the volume and weight of the device (Figure 4) are almost an order of magnitude smaller than other state-of-art approaches. The fabrication process leverages LLNL’s thin-film polymer technology and additionally incorporates customizable waveguide fabrication and 635 nm Edge Emitting Laser (EEL) diode assembly onto a 15 μm-thick flexible neural probe (Movie S1). The waveguide core has a 10 μm-by-10 μm cross-section for optical stimulation. The 2.5 μm-thick Cytop cladding prevents optical scattering loss, prevents moisture absorption, and offers electrical, thermal, and chemical stability beyond the standard polyimide. The platinum/iridium (50 nm/50 nm, 20μm diameter) electrodes are arranged around the waveguide tip for electrical recording. An indium/gold eutectic bond pad for the flip-chipped EEL diode enables flux-less bonding at low bonding temperatures and no applied pressure. Flip-chipped connectors are assembled directly on thin-film probe to avoid use of bulky PCBs.

The electrodes measured average baseline peak-to-peak signal of 14.5 ± 2.4 μV (mean ± std. error) and average impedance of 407 ± 50.2 kΩ (mean ± std. error) at 1 kHz (n=15, 2 devices) during in vitro characterization in saline, recording good signal-to-noise ratio. The power measured at the output of the waveguides was 80-120 μW (800-1200 mW/mm² intensity) which is sufficiently more than 5-10 mW/mm² optical intensity required for the target applications. A heat transfer model was designed to study thermal behavior of the system during device operation (Figure S5). Implantable devices should be able to deliver light deep into the brain while not causing thermal damage to the tissue or to the device sub-components. Our model results showed that POEMS optoelectrodes (thermal conductivity ~0.2 W/m.K) allow for a much slower temperature increase in the tissue compared to silicon.
optoelectrodes (thermal conductivity ~130 W/m.K) while operating within temperature limits of the diode. The response was found similar to the previously demonstrated GRIN lens-based assembly solution, but with a significant reduction in device footprint, weight, and cost. This improvement is promising and will critically impact scaling up the number of shanks and diodes per shank to enable multi-color, multi-site optogenetic studies. Future assembly modifications will focus on further reducing optical coupling losses by 3D printing the last-micron connection between assembled EEL chips and fabricated waveguides, boosting power efficiency.

**DISCUSSION AND OUTLOOK**

The success of devices such as cochlear and retinal implants has encouraged interest in new applications of flexible interfaces, paving the way for incorporation of novel materials and new modalities such as optical. Thermal loading via pulsed, low-power infrared light alongside electrical stimulation has been shown to reduce electrical current thresholds in cochlear implants. Photomanipulation techniques, such as introduction of light-sensitive channels to retinal ganglion cells, may provide a functional cure for people with retinitis pigmentosa. Waveguides with integrated photodetectors can allow simultaneous perturbation and imaging of neural activity.

Most existing optical light delivery solutions in neurotechnology are realized using optical fibers which may restrict animal movement. More recently, light-emitting diodes (LEDs) and laser diodes (LDs) were integrated on silicon neural probes to provide fiber-free solutions with reduced electromagnetic interference and safer thermal design. The search for mechanically compliable materials than silicon and glass has fueled the ongoing development of softer and flexible polymer-based interfaces. State-of-art polymer neural optoelectrodes either offer partially-flexible solutions, use low optical transmission materials like SU-8 or are susceptible to artifacts and local heating. In this work, we report implementation of EEL-coupled waveguides on an all-polymer neural device which is fiber-free, flexible, compact, and lightweight. Use of optically clear materials like hybrid polymers and Cytop makes the devices suitable for delivering or collecting light from the surrounding and underlying tissue while maintaining good power efficiency. An all-polymer backbone can potentially facilitate better mitigation of electromagnetic, photochemical, or photoelectrical artifacts. High optical efficiency of hybrid polymers makes them particularly well-suited for micro-optics. The attenuation in a waveguide increases with a decrease in core diameter which makes micro-waveguides more susceptible to optical losses. The measured transmission losses for 10 μm-core microfabricated (4.9-7.8 dB/cm at 405-635 nm) and 50 μm-core 3D-printed (4.08-4.4 dB/cm at 670 nm) hybrid polymer waveguides are amongst the lowest reported for polymer waveguides in literature. Previous work on SU-8 waveguides reported 6.4 dB/cm optical loss at 473 nm for 150 μm waveguide core and 25 dB/cm optical loss at 473 nm for 25 μm waveguide core. More recent waveguide designs made from 80 μm core polycarbonate-cyclic olefin copolymer (PC-COC) core and 15 μm parylene core report 1.5 dB/cm loss at 473 nm and 5.5 dB/cm loss at 532 nm, respectively.
In summary, hybrid polymers-based POEMS show potential for high resolution and minimally invasive optical waveguiding and imaging. Further research and development can eventually enable their use in biomedical technologies such as optoelectronic brain-machine interfaces and wearables.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Novel hybrid polymers offer material advantages of both organic and inorganic materials.
- Hybrid polymer-based waveguides enable efficient microscale optical systems.
- Microfabricated waveguides allow minimally invasive optical waveguiding and imaging.
- 3D optical wirebonds can enhance optical coupling between on- and off-chip components.
- Optoelectronic implants fabricated from hybrid polymers are compact, low-weight and low-loss.
Figure 1:
Material characterization of fully polymerized, 180 μm-thick, hybrid and non-hybrid polymer films. a-b) Optical transmissivity plots show that hybrid polymers allow >90% transmissivity in 300-800 nm wavelength range while non-hybrid polymers absorb light in near-UV region, c) Change in polymer transmissivity post accelerated aging soak tests conducted for a period of one month in 1X PBS at 75 °C, equivalent to 12-month time at 37 °C in vivo. All polymers withstood soak tests with 2.92% (OrmoClearFX), 8.01% (OrmoComp), 14.07% (EpoCore), and 9.78% (IP-Dip) average drop in transmissivity over 300-800 nm wavelength range, d) Change in transmissivity post photo-exposure with a dose of 150 J/cm² from a 360 nm UV lamp at 17 mW/cm² light intensity. OrmoClearFX, OrmoComp and IP-Dip show less than 0.18% decrease in transmissivity as compared to 17.62% decrease for EpoCore, particularly in the 400-550 nm region.
Figure 2:
Modular POEMS for flexible optoelectronics. a) A conceptual schematic of a POEMS interface with integrated optoelectronic transmitter and receiver subassemblies. Individual modules can be independently fabricated using microfabrication and additive manufacturing techniques and then assembled using printable interconnects or optical wirebonds. SEM images show examples of independent planar and 3D structures, b-c) Microfabricated EpoCore and OrmoClearFX planar multimode waveguides on Cytop, d) 2PP-printed IP-Dip hollow waveguide on Cytop, e) 2PP-printed optical jumper on Cytop, f) 2PP-printed cylindrical vertical waveguide on top of a 670 nm VCSEL, g) 2PP-printed cylindrical horizontal interconnect between two flat-cleaved ends of an optical fiber, h) Process flow to fabricate structures shown in b) through g).
Figure 3:
Measurement cut-back method for optical loss calculation in microfabricated and additively manufactured waveguides. The measured output power for each waveguide length is plotted in a) and b) where the observed slope and y-intercept of the linear-fit corresponds to transmission loss and coupling loss, respectively. a) Optical transmission loss in 10 μm x 10 μm microfabricated OrmoClearFX and EpoCore waveguides measured 4.9-7.8 dB/cm and 7.6-11.2 dB/cm, respectively, at 406 nm and 638 nm wavelengths. Fibered bench-top laser source (LDC202C, Thorlabs) was used as the light source at 1 mW optical power, b) Optical transmission loss in 50 μm-diameter 2PP-printed waveguide on a 1 mW-optical power VCSEL measured 4.4 dB/cm at 670 nm wavelength. Zoomed-in view of the printed waveguide shows precise placement of waveguide at the coupling joint and smooth waveguide walls.
Figure 4:
POEMS implantable neural optoelectrode. a) Device schematic with design components, b) Fully assembled prototype, compared to a US dime in size, c) Optoelectrode’s flexible probe shank with waveguides and recording electrodes, d) Eutectic bond pad for EEL diode placement. Zoomed-in view shows eutectic bond pad positioned next to the distal waveguide tapered end to allow easy butt-coupling during assembly (right), e) Probe shank’s tip showing waveguide emission site and Pt/Ir recording electrodes. Magnified view of waveguide front end (right), f) EEL diode flip-chipped at the eutectic pad of the thin film optoelectrode. Inset shows active diode-waveguide interface at 635nm, g) Optical scattering along the waveguide length, without and with patterned cytop cladding around the core.
Table 1:

Properties of hybrid and non-hybrid polymerized polymers.

| Polymer                              | Refractive index at 600 nm, RI | Glass transition temperature, $T_g$ (°C) | Young's modulus, E (GPa) |
|--------------------------------------|-------------------------------|------------------------------------------|--------------------------|
| OrmoClearFX (Hybrid) (micro resist technology, Germany) | 1.555                         | N/A                                      | <1                       |
| OrmoComp (Hybrid) (micro resist technology, Germany)    | 1.52                          | N/A                                      | ~1                       |
| EpoCore (Non-hybrid) (micro resist technology, Germany) | 1.58                          | 145                                      | 2-3                      |
| IP-Dip (Non-hybrid) (Nanoscribe GmbH, Germany)          | 1.548                         | 103                                      | 2-5                      |