Monolithic and Scalable Au Nanorod Substrates Improve PEDOT–Metal Adhesion and Stability in Neural Electrodes

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1. Introduction

In the past decade, conducting polymers (CPs) have gained substantial attention as the direct interfacing material between biomedical devices and neural tissue due to their superior electrochemical properties compared to conventional metals such as Au, Pt, and Ir.[1] In particular, poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) has emerged as an outstanding material for neural interfaces and biomedical applications including recording and stimulating neural activity, neural regeneration, and therapeutic drug delivery.[1a,e,2] This is afforded with PEDOT:PSS due to several promising features such as low electrochemical impedance for high signal-to-noise ratio (SNR) recording, high charge injection capacity for safe and efficient stimulation, and compliant (soft) mechanical properties for conforming to biological tissue.

Despite the superior properties, exploiting the full capability of CP coatings in chronic biomedical applications has been limited due to their weak adhesion and mechanical stability driven by i) lack of strong covalent bonds between coated polymer layers and underlying noble metal conductors[3] and ii) the volumetric expansion and contraction of polymer coatings in physiological media.[4] As a result of the poor adhesion, cracks in the CP films or complete delamination from the underlying metal conductors are often observed during 1) in vitro aging experiments, 2) chronic implants, 3) prolonged charge injection, and 4) mechanical stresses driven by sterilization.[5] In vivo chronic implantation of PEDOT:PSS-coated electrodes resulted in a loss of conductivity/functionality of the device attributed to the mechanical failure of polymer coating.[5b,5b,6] Different groups have attempted to find a method of extending the operating lifetime of the polymer-based systems. Two approaches emerged to tackle this problem. The first approach is chemical in nature and utilizes an intermediate functionalized monolayer/organic molecule between PEDOT and the underlying metal conductor through formation of covalent bonds between the intermediate layer and both sides, PEDOT and the underlying metal conductor. One such approach involves electrografting amine-functionalized EDOT[7] to stabilize PEDOT on...
metallic conductors which was subjected to 1 h of ultrasonication without significant cracking or delamination, whereas untreated PEDOT delaminated within seconds. However, cyclic voltammetry (CV) stability tests affected the treated PEDOT coating and the electrochemical impedance showed a significant degradation after 300 CV cycles. The second approach is physical in nature and employs mechanical interlocking and more engaged surface area (roughened substrate) to anchor the coated CP to underlying metals. “Fuzzy gold” stabilization for polypyrrole (PPy) and laser-roughened Pt anchoring for PEDOT/p-toluenesulfonate (pTS) and PEDOT/ClO₄ are examples of the mechanical anchoring approach. When the latter was employed for PEDOT:PSS, severe delamination occurred upon biphasic pulsing (864 million pulses at 70 µC cm⁻²) or steam sterilization. Recently, Boehler et al. demonstrated sputtered iridium oxide film (SIROF) as an exceptional adhesion promoter layer for electrodeposited PEDOT coatings on macroscale electrodes (500 µm diameter), resulting in polymer survival for over 10 000 CV cycles and 110 days under accelerated aging conditions at 60 °C. The efficacy of this approach for microscale PEDOT-coated electrodes and for spin-cast PEDOT – used recently in recording for the surface of human cortex – is yet to be assessed for this technique.

Here, we report an alternative approach to improve the adhesion of the polymer on underlying metal conductors, using a gold nanorod (Au-nr) layer. We conducted different electrochemical tests including CV, electrochemical impedance spectroscopy (EIS) along with morphological characterizations (optical, focused-ion beam (FIB), and scanning electron microscopy (SEM)) to fully characterize the fabricated electrodes and examine the PEDOT:PSS/Au-nr surface/interface. The Au-nr structure was integrated on top of the conventional Au electrodes, using a dealloying technique, capable of enhancing the adhesion of spin-cast and electrodeposited PEDOT:PSS films. To benchmark the stability of modified PEDOT:PSS electrodes against conventional planar electrodes, we applied extensive CV stressing cycles (over 10 000) to validate the anchoring capability of the Au-nr layer. We hypothesize that the Au-nr interlocking layer prevents the delamination of PEDOT film under long-term reversible charge injections (cycling tests) where induced volumetric contraction/expansion of polymer film is possible as the result of electrostatic repulsions between fixed positive charges and exchange of cations, anions, and solvent molecules between the polymer and the solution. The Au-nr layer stabilized the PEDOT:PSS/Au-nr interface for over 10 000 stressing CV cycles, affording at least 20-fold more cycling of coated polymer compared to that of conventional spin-cast PEDOT:PSS on planar Au macroelectrodes with the same diameter of 500 µm for which delamination occurred only after only 500 cycles. Additionally, we investigated the efficacy of the Au-nr films on the stability of 50 µm diameter electrodes, important for high spatial resolution in recording and stimulating electrodes. Within microscale, a 50 µm PEDOT:PSS/Au-nr electrode passed 8000 CV cycles without significant morphological change or electroactivity loss, yielding a tenfold improvement given the only 800 cycles’ survival for PEDOT:PSS on planar Au. In addition, we observed a different degradation mechanism for spin-cast PEDOT:PSS compared to electrodeposited PEDOT:PSS film under cycling stress that is not discussed in earlier literature. We found that under CV stress experiments, the spin-cast PEDOT:PSS film tends to delaminate from the metal substrate, exhibiting stronger cohesive polymer film strength than that of the polymer/metal interface, whereas electrodeposited PEDOT film tends to leach out via surface decomposition and gradual thinning rather than delaminating from the substrate. To simulate a 6 month semi-chronic implant, accelerated aging tests (passive test) were performed to expose the electrodes to wetting environment over a long time (5 weeks) at 60 °C and longer survival of the coating was observed using the Au-nr structures. The adhesion-promoting effect of Au-nr layer was also validated in vivo where after 10 weeks chronic implant onto mouse barrel cortex, the PEDOT:PSS did not detach from the Au-nr substrate, in contrast to planar Au electrodes which were either partially or fully delaminated. In addition, the biocompatibility of PEDOT:PSS/Au-nr electrodes was verified through immunohistochemistry that showed no neuronal loss and minimal activation of astrocytes and microglia at the implant site.

2. Results

PEDOT:PSS electrodes were fabricated according to published procedures utilizing a thin film of Cr/Au layer with 15/100 nm thickness as metallic leads and conductors. The entire device is sandwiched in between 2 µm upper and 2 µm lower polystyrene C layers except where the PEDOT:PSS film is coated. The Au-nr layer was selectively patterned in regions where PEDOT:PSS was to be coated. To realize the Au-nr film, a dealloying process of the AuAg alloy and preferential etching of Ag was performed in a nitric acid solution, as detailed in the Supporting Information. To benchmark the electrochemical performance of Au-nr and planar Au (Au-pl) contacts, we prepared electrodes with 50 and 500 µm diameters, which we refer to as micro and macro hereafter. Figure 1a,b shows the optical images of the fabricated Au-nr and Au-pl macroelectrodes with their corresponding cross-sectional schematics, respectively. The darker color of Au-nr electrodes under optical imaging distinguishes them from Au-pl contacts due to light trapping in the nanoporous structure.

EIS was performed to characterize and understand the Au-nr and Au-pl electrochemical properties. Measured EIS within the frequency range of 1 Hz to 10 kHz is shown in Figure 1c,d which demonstrates lower magnitude for the electrochemical impedance of the Au-nr electrode for the whole frequency range compared to that of Au-pl contact. For Au-nr electrodes and at frequencies higher than 300 Hz, the impedance becomes limited with the series resistance Rₛ, as deduced from the negligible dependence on frequency beyond 300 Hz and a rapid increase of the phase from −90° to 0°. At these frequencies, the reactance due to the large double layer capacitance is lower than Rₛ. The lower capacitance and higher reactance of the Au-pl electrode delays such transition by one decade of frequency up to 3 kHz. CV is the standard practice to gain insights into the electrochemical reactions, presence...
Earlier works reported electrode models and are provided in Figure S2 (Supporting Information). Anisotropic conductive film (ACF) bonding was used to connect the device to commercial off the shelf ribbon cables that fit in the external characterization circuitry. The electrode arrays contain both macro- and microscaled electrodes which allowed us to investigate device stability for different diameters. In this stability study, only one macrosize (\(D = 500 \mu m\)) and microsize (\(D = 50 \mu m\)) electrodes were tested. The top view optical image of the patterned/dealloyed Au-nr film on 50 \(\mu m\) diameter electrode is shown in Figure 2c along with an SEM image of Au-nr structure. After deposition of the parylene C passivation layer, openings on top of electrode sites were realized using oxygen plasma etching, as shown in Figure 2d, followed by PEDOT:PSS deposition using either spin-coating or electroplating method. An optical microscope image of the spin-coated PEDOT:PSS microelectrode using spin-cast processing is shown in Figure 2e. To confirm the structural integrity of the PEDOT:PSS/underlying Au-nr and Au substrate/parylene C interfaces, we performed FIB slicing at the center of the microdot of Figure 2e. The confinement of the PEDOT:PSS layer in the 3D Au-nr structure is demonstrated in the SEM image of Figure 2f, highlighting the intimate contact between the different layers of the device.

The \(-0.6–0.6 \text{ V versus Ag/AgCl} \) CV cycling window discussed above was used to characterize the adhesion and mechanical stability of the PEDOT:PSS on Au-nr and Au-pl, at a scan rate of 0.1 V s\(^{-1}\). The electrochemical impedance (1 Hz–10 kHz) and electrode surface alteration, as determined by optical microscope imaging, were monitored periodically.
During CV measurements to assess the adhesion and stability of the PEDOT:PSS coating on different underlying metal substrates. The PEDOT:PSS film was deposited potentiostatically on the Au-nr electrode with a 500 μm diameter. Figure 3a shows the intact electrode prior to cycling, highlighting the uniform electrodedeposited PEDOT:PSS film over the entire Au-nr electrode surface.

Optical inspection of the same electrode of Figure 3a indicates the gradual change in the polymer color (colorimetric change) under CV stressing, as shown in optical images of Figure 3b–d which correspond to 3000, 7000, and 11 000 CV cycles, respectively. This progressive color change can indicate overoxidation of the PEDOT:PSS film which can occur during irreversible electrochemical oxidation reactions rather than overoxidation of the PEDOT:PSS film which can occur during cycles, respectively. This phenomenon of Au electrode dissolution was observed as a control experiment for the enhanced stability of PEDOT:PSS/Au-nr, PEDOT:PSS was also electrodeposited on planar Au conductors (PEDOT:PSS/Au-pl) with 500 μm diameter, as shown in Figure 3h. A similar color alteration of the polymer was observed across the PEDOT:PSS/Au-pl electrode surface over the course of cycling tests, as shown in optical images Figure 3i–k after CV cycles of 1000, 2000, and 2500 cycles, respectively. However, after 2500 CV cycles, the as-fabricated versus up to 10 000 CV cycles. A slight upward shift of the impedance traces below 40 Hz can be attributed to a slight decrease in the PEDOT:PSS thickness (color change in Figure 3a–d and additional transparency under electron beam on top of the Au-nr array in SEM, Figure 3e,f) which reduces the capacitance and increases the electrode impedance. At and above 11 000 CV cycles, we observed an increase in the series resistance manifested by an upshift of the impedance plateau at high frequencies, as shown with the purple trace in Figure 3g. This result was counterintuitive because any morphological changes for the PEDOT:PSS, such as the thinning process illustrated in Figure 3e,f should result in a change of the electrode capacitance or Faradaic impedance. To investigate the origin of the increase in the series resistance, we inspected the overall device morphology and observed a partial dissolution of the Au metal lead, as illustrated in the inset optical image of Figure 3g. This phenomenon of Au electrode dissolution was observed with multiple device experiments and is likely due to the local exposure of the Au surface during oxide formation/reduction as well as oxygen evolution upon cycling voltammetry. Therefore, to exclude the effect of metal lead dissolution from our PEDOT:PSS stability study, a maximum count of 10 000 CV cycles was set as the end point of the adhesion test protocol.

As a control experiment for the enhanced stability of PEDOT:PSS/Au-nr, PEDOT:PSS was also electrodeposited on planar Au conductors (PEDOT:PSS/Au-pl) with 500 μm diameter, as shown in Figure 3b. A similar color alteration of the polymer was observed across the PEDOT:PSS/Au-pl electrode surface over the course of cycling tests, as shown in optical images Figure 3i–k after CV cycles of 1000, 2000, and 2500 cycles, respectively. However, after 2500 CV cycles,
PEDOT:PSS/Au-pl electrodes experienced a severe polymer film delamination near the electrode edge. For further examination, FIB slicing was performed on both a reference electrode that did not undergo CV cycling and the electrode of Figure 3k that underwent 2500 CV cycles. The cross-section of the reference electrode in Figure 3l displayed an intact interface between the PEDOT and the underlying Au conductor, as shown in Figure 3m, and in agreement with the wrinkled morphology observed in the optical image of Figure 3k that we associated with PEDOT delamination. Additionally, the electrode degradation under cyclic load for PEDOT:PSS/Au-pl is manifested in a progressive increase in the impedance magnitude and shift in impedance phase of Figure 3n with increasing cycling counts, in contrast to the nearly stable spectra of the PEDOT:PSS/Au-nr. The magnitude of the impedance at 1 Hz increases by tenfold after 2500 CV cycles.

Another method for depositing PEDOT:PSS from solution is the spin-coating technique that offers monolithic integration and scalability benefits over electrodeposited PEDOT and has been recently used in high-density neural probe electrophysiology. We characterized the stability of spin-cast PEDOT:PSS film on the 500 μm diameter conductor (Figure 4a, see the Experimental Section) in a similar experimental convention to electrodeposited PEDOT:PSS. Figure 4b–h demonstrates a surface morphology change of the same PEDOT:PSS/Au-nr electrode at different CV cycles (up to 11 000 cycles). Similar to the electrodeposited PEDOT:PSS, progressive alteration of the PEDOT:PSS color was apparent under electrochemical stress by showing rapid changes during the first 3000 cycles’ course (Figure 4d). It should be noted that after 7000 cycles (Figure 4f), the contact interface between the PEDOT and the underlying Au-nr layer rearranges, presumably due to volumetric changes, resulting in strong color changes particularly at the dot edges (see Figure 4g,h). Inspection by SEM (Figure S5, Supporting Information) showed a completely different dot profile for the PEDOT:PSS/Au-nr macrodot (Figure 3g), significant EIS changes observed at or above 11 000 cycles, shown as purple traces in Figure 4l, were confirmed with inspection by optical microscope as the result of wiring failure rather than being related solely to the polymer stability. In contrast to the PEDOT:PSS/Au-nr electrode, the...
PEDOT:PSS/Au-pl contact (Figure 4i) showed delamination from the planar Au conductor starting from the electrode edges at only 500 CV cycles, as shown in Figure 4j. PEDOT:PSS/Au-pl macroelectrode undergoes a full detachment from the substrate at 1000 CV cycles (Figure 4k), as can also be observed with the noticeable impedance shifts in EIS spectra of Figure 4m. These results suggest at least tenfold improvement in the adhesion of spin-coated PEDOT:PSS/Au-nr which endured 10 000 CV, as discussed above. Electrodeposited PEDOT coating on Au-nr substrates (Figure 3) did show a slight EIS variation over the course of 10 000 CV cycles, but no sign of film delamination from the substrate was observed. In contrast, spin-coated PEDOT film on Au-nr substrates (Figure 4) demonstrated partial film detachment due to cycling stress but fully stable electrochemical characteristics not by measuring identical EIS spectra upon 10 000 CV cycles. From these experiments, we found that the adhesion of the PEDOT:PSS on Au-nr film is the strongest with electrodeposition (Figure 3a–f) compared to spin-coating (Figure 4a–h). We also found that the electrodeposited PEDOT:PSS on Au-nr film underwent a slight thinning process that we associated with a slight reduction of the capacitance and increase in the impedance (Figure 3g).

The fixed electrochemical impedance spectra for spin-cast PEDOT:PSS/Au-nr microelectrode indicate absence of such thinning and stronger cohesive forces in the PEDOT film. We also found that the adhesion of electrodeposited PEDOT:PSS on planar Au conductors (Figure 3h–k) is stronger than that of spin-cast films (Figure 4i–k).

We have focused so far on large diameter (0.5 mm) electrodes, consistent with earlier studies on improving the adhesion strength and stability of PEDOT.[8,10,19] But microelectrodes are desired for advancing neurophysiological recordings both from the surface and the depth of brain tissue in a chronic setting.[11a,20] Therefore, we evaluated the stability of PEDOT:PSS films on 50 µm diameter Au-nr (Figure 5a) and Au-pl (Figure 5i) microelectrodes. For spin-cast PEDOT:PSS/Au-nr, the microelectrodes display an earlier onset of color change (>1000 cycles, Figure 5c) compared to the macroelectrodes (>3000 cycles, Figure 3c). While this color change was notable but not dramatic for macroelectrodes (11 000 cycles, Figure 3d), a dramatic color change (>2000 cycles, Figure 5c–h) and PEDOT delamination from the microelectrode edge (>5000 cycles, Figure 5e–h) prevailed. Despite these morphological changes, the corresponding magnitude and phase
of the EIS spectra measured after different CV cycling intervals (Figure 5l) did not indicate a significant electrochemical degradation of the electrode up to 8000 cycles. However, at 9000 CV cycles, a significant shift in EIS spectra was measured, as illustrated with the purple traces in Figure 5l, which we attribute to wiring failure as we discussed above. On the other hand, PEDOT:PSS/Au-pl microelectrode exhibited a relatively compromised stability upon CV cycling that was evident from the ring-shaped delamination in the optical images of Figure 5j,k after only 400 and 800 CV cycles, respectively. In addition, significant electrochemical degradation is perceptible from the impedance magnitude and phase spectral shifts, as shown in Figure 5m by dark-red (after 400 CV cycles) and light-red (after 800 CV cycles) traces. Nevertheless, the Au-nr anchoring layers also offer a stabilizing capability for microelectrodes by offering at least tenfold enhanced durability for the PEDOT:PSS/Au-nr microelectrode compared to PEDOT:PSS/Au-pl microelectrode. The mechanistic electrochemical studies discussed above elucidated the success of Au-nr conductors for stabilizing PEDOT:PSS under electrochemical stress. Another test that must be passed is the durability of the PEDOT:PSS in wet mediums that can be characterized with accelerated aging and in vivo experiments. We performed both types of experiments. Venkatraman et al.\cite{19} have shown that PEDOT:PSS/Pt macroelectrodes were stable after an accelerated aging test in PBS for 5 weeks, whereas the microelectrodes experienced a significant degradation after 4 weeks.

Given this and the interest in microelectrodes for electrophysiology applications, we performed accelerated aging experiments on microelectrode arrays with $D = 50 \mu m$ that were prepared with spin-coated and electroplated PEDOT:PSS on both Au-nr and Au-pl conductors (four total devices). The four types of PEDOT:PSS devices were immersed into the PBS solution for 5 weeks at 60 $^\circ$C. This temperature is recommended as a safe temperature for aging polymer films,\cite{13a,21} above which internal polymer films were reported to crack and exhibit unexpected effects that are beyond the scope of this study. Based on the Arrhenius' law, Equation (1) is used to estimate the simulated age upon accelerated aging temperature $T$. According to the ASTM international guidelines, the reference standard equation\cite{19} provides an accelerated aging factor of 4.92 with respect to the body temperature (37 $^\circ$C), resulting in equal simulated age of 25 weeks (=6 month chronic implants).

Figure 5. Spin-coated PEDOT:PSS/Au-nr and PEDOT:PSS/Au-pl microelectrode stability tests under cycling stress. Optical images of the same spin-coated PEDOT:PSS/Au-nr microdot ($D = 50 \mu m$); a) as-fabricated and after sequential b) 1000, c) 2000, d) 3000, e) 5000, f) 7000, g) 8000, and h) 9000 CV cycles, highlighting the progressive colorimetric change of polymer coating along with partial PEDOT:PSS film delamination upon CV cycling, happening at or above 5000 CV cycles. Optical images of the same spin-coated PEDOT:PSS/Au-pl microdot ($D = 50 \mu m$); i) as-fabricated and after sequential j) 400, k) 800 CV cycles, demonstrating ring-shaped PEDOT film delamination and its expansion, respectively (scale bars are 15 $\mu m$).

l) The measured magnitude and phase impedance spectra of the PEDOT:PSS/Au-nr microelectrode at different cycling states; as-fabricated and CV cycled for 1000, 2000, 3000, 5000, 7000, 8000, and 9000 cycles, which correspond to the left side optical images. The purple traces show the measured EIS spectra of electrode after 9000 CV cycles, indicating a noticeable impedance change due to the wiring failure at that cycle count. m) The measured magnitude and phase impedance spectra of the PEDOT:PSS/Au-pl microelectrode; as-fabricated (black) and after different cycling states of 400 (dark-red) and 800 (light-red) CV cycles, which demonstrate obvious impedance shifts due to the ring-shaped PEDOT film delamination upon charge injection.
The results of the accelerating aging experiment are summarized in Figure 6a which shows the changes in the impedance magnitude normalized to values measured directly prior to aging for the four sets of PEDOT:PSS devices at three different frequencies of 10, 100, and 1000 Hz as a function of accelerated aging period in PBS at 60 °C. b) Numbers of “nonfunctional” channels per device type; defined upon exceeding threshold impedance value of 100 kΩ by microelectrodes 1 Hz impedance value, as a function of accelerated aging period. Black, red, blue, and green colors correspond to the Aunr_SC, Aupl_SC, Aunr_ED, and Aupl_ED PEDOT:PSS-based microelectrodes, respectively. The light-blue histograms present the total numbers of functional channels per device type at the beginning of the aging experiment. c) Different delamination behaviors of spin-coated PEDOT:PSS film ranging from partial delamination (scenario I or II) to a full delamination (scenario III) and detachment (scenario IV) from the Au-pl substrate.

\[ t_{17} = t_1 \times 2^{(10^{-17})/10} \]

The number of nonfunctional channels that exceeded the 100 kΩ threshold is also plotted in Figure 6b as a function of aging time. The overall trends of impedance changes over the course of 5 weeks of accelerated aging indicate a stable impedance for the electrodeposited PEDOT:PSS on the Au-nr conductors (Figure 6a) with 2 nonfunctional channels out of 26 (92% survival, Figure 6b). The spin-cast PEDOT:PSS on Au-pl conductors degraded significantly where the impedances increased by over 18× (Figure 6a) and 19 channels became nonfunctional out of 25 (24% survival) after 5 weeks of accelerated aging time. The absence of covalent bonds at the interface of PEDOT /underlying metal deems the interface unstable in extended presence in wet media. The delamination behaviors are manifested in either partial or complete detachment from the Au-pl surface under accelerated aging, as demonstrated in Figure 6c. In agreement with CV results, the Au-nr structure supported enhanced adhesion and mechanical stability for both spin-cast and electrodeposited PEDOT:PSS. Additional examples of degraded morphology for electrodeposited PEDOT:PSS/Au-pl electrodes after soaking test are presented in Figure S7 (Supporting Information). In contrast, both spin-cast and electrodeposited PEDOT on Au-nr substrates were stable, as demonstrated in Figure S8 (Supporting Information).
In different studies, PEDOT:PSS coating has been deployed as an electrode material where the electrodes were chronically implanted for electrophysiological recordings over the course of a month. \[19,22\] In most cases, the impedance of the electrodes increased significantly after the first week of implant due to either adverse effects of tissue inflammatory response on the electrode or possible degradation of the PEDOT:PSS coating upon implant. In these studies, the quality, morphology, and adhesion/stability of the electrodes have not been reported. For spin-coated PEDOT:PSS electrodes, only two studies have reported the implantation of this type of electrodes with their corresponding stable and long-term action potential recording upon implant. The long-term stability of the coated PEDOT:PSS film was not reported. To translate our success in stabilizing PEDOT:PSS in benchtop electrochemical experiments to in vivo, we chronically implanted two sets of PEDOT microelectrodes including spin-cast i) PEDOT:PSS/Au-nr and ii) PEDOT:PSS/Au-pl onto mouse cerebral cortex for 10 weeks. For implantation, a craniotomy surgery was performed involving removal of the bone overlaying the barrel cortex, while leaving the dura mater intact. The array was placed on top of the dura mater and covered with a glass “window” (Figure 7a). The window served a double purpose; first, it replaced the bone, second, it allowed visualizing the integrity of the brain tissue, including imaging of blood flow using single- and two-photon microscopy (Figure 7b). After the implantation, the mouse was returned to its home cage and allowed to move freely in the cage for 10 weeks. After device explanation, FIB slicing and SEM imaging were performed on the PEDOT arrays to examine the electrode morphology. Figure 7c demonstrates the tilted view SEM image of a explanted PEDOT:PSS/Au-nr microelectrode, showing overall stable mechanical condition for spin-cast PEDOT film. To examine the PEDOT/metal interface, a FIB cut was performed at the electrode edge. The following cross-sectional SEM image at the FIB cut, shown in Figure 7d, reveals a tight confinement of PEDOT film within the 3D structure of the Au-nr film, preventing polymer film delamination. In contrast, conventional PEDOT:PSS film on Au-pl electrodes experienced significant morphological changes illustrated with either partial or full polymer delamination, as shown in SEM images of Figure 7e,g, respectively. To verify the partial and full PEDOT film delamination on Au-pl electrodes, FIB cuts were performed at the electrodes edge. Cross-sectional SEM image, shown in Figure 7f, demonstrates retained (intact) polymer film on Au-pl substrate, while PEDOT film delaminated at another electrode side, as highlighted in Figure 7e by white dashed line. FIB cut also was performed at an electrode edge shown in Figure 7g which showed absence of PEDOT film as the worst PEDOT stability case. The Au-pl substrate exposure was perceptible upon continuous extension of metal substrate underneath parylene C passivation layer, shown in cross-sectional SEM image of Figure 7h. Indeed, full exposure of Au-pl underlying substrate indicates a PEDOT:PSS film delamination from the Au-pl substrate after the 10 week chronic implant. The surface morphology of all 32 channels per device type are
presented in Figure S9 (Supporting Information, PEDOT:PSS/Au-pl) and Figure S10 (Supporting Information, PEDOT:PSS/Au-nr). It should be noted that similar morphological changes or delamination of spin-coated PEDOT film from Au-pl substrate (Figures 6c and 7e,g), observed in both in vivo and soaking tests, could correlate their degradation mechanism on polymer film.

Finally, to assess potentially aversive biological responses such as tissue inflammation beneath the implanted electrodes, we performed a histological evaluation 10 weeks after implantation. Therefore, hematoxylin and eosin (H&E) staining as well as immunohistochemical staining with antibodies that label neurons neuronal nuclei antigen (NeuN), astrocytes glial fibrillary acidic protein (GFAP), and microglia ionized calcium-binding adapter molecule 1 (IBA1) were performed on brain slices. An overview of the H&E staining is shown in Figure 8a, including an enlarged view of the cortex; location of the implantation site on the left hemisphere as well as the contralateral site (right hemisphere, no implant) for control, are highlighted. Figure 8b shows representative stainings of neurons, astrocytes, and microglia of the (left) cortex underneath the implant and the contralateral (right) side. The staining with NeuN did not reveal any changes in neuronal density beneath the implant. In comparison to the contralateral hemisphere, the antibody staining of GFAP and IBA1 showed a 40–45% or 18–20% increase of astrocyte and microglia densities, respectively. However, astrocyte and microglia densities are known to increase after craniotomy,[23] therefore, they may not indicate a tissue reaction to the implant itself, but to the implantation procedure, in particular the craniotomy.

The biological applications of PEDOT:PSS materials are rapidly accelerating for in vitro diagnostics[11a,24] and for in vivo electrophysiology[13c,11a] The adhesion and mechanical stability of PEDOT:PSS electrophysiology devices are imperative for their transition for chronic implants and for neural stimulation. In this study, we introduced the fabrication and integration of the Au-nr film with standard PEDOT:PSS neural probe fabrication on flexible parylene C substrates to improve its adhesion and stability. By providing larger interface area and serving as a mechanical anchor for the PEDOT:PSS layers, a Au-nr adhesion layer improved the stability of the PEDOT:PSS-based electrodes (both spin-coated and electrodeposited PEDOT:PSS devices), under both active CV stressing and passive accelerated aging experiments, contingent on polymer coating thicknesses studied in this work. The Au-nr adhesion layer demonstrated tenfold stability improvement of PEDOT:PSS-based electrodes compared to that of Au-pl substrates under CV stress for both macro- and microscaled electrodes. Furthermore, 92% of electrodeposited PEDOT:PSS electrodes remained electroactively functional after 5 weeks of accelerated aging experiments that is equivalent to ~6 month chronic implants. The adhesion-promoting effect of Au-nr film was verified under in vivo conditions where the PEDOT film was stabilized within the 3D structure of Au-nr film, but coated polymer on Au-pl electrodes delaminated after a 10 week chronic implant. The adhesion improvement strategy reported here might also benefit other CP neural interface materials for chronic implants or neural stimulation applications where the long-term stability of the CP film is critical.

3. Experimental Section

Device Fabrication—Spin-Coated PEDOT:PSS-Based Electrodes: The fabrication of the PEDOT:PSS device on Au-pl conductors was similar to previously established protocols and was identical to that of the PEDOT:PSS devices on Au-nr conductors discussed here. Glass slides (Siality Glass Products Inc.) or Si wafer were used as substrate carriers for deposition of parylene C layers. The glass or Si substrates first were cleaned with acetone/isopropanol (IPA)/deionized (DI) water/IPA, which was followed by ultrasonic agitation in IPA for 5 min. To facilitate detachment of the device after the process was completed, diluted Micro-90 (0.1%); an antiadhesion layer, was spun-cast at 1500 rpm on the substrate. A first parylene C layer (~1.9–2.5 µm) was deposited by chemical vapor deposition using a PDS 2010 Parylene coater system. Prior to metalization, metal lead patterns were defined using a Karl Suss MA6 mask aligner using NR9-3000 negative resist and subsequently developed. 15 nm Cr adhesion layer and 100 nm Au contact layer were then deposited using Temescal BJD 1800 electron beam evaporator, and metal leads were defined by a liftoff process in
acetate. Then, patterns of the electrode sites were defined using NR9-6000 negative resist and a Karl Suss MA6 mask aligner for exposure. A 15/100 nm Cr/Au layer was sputtered followed by deposition of ~0.5 µm thick AuAg alloy using a co-sputtering technique performed at 400 W radio frequency (RF) and 60 W (DC) power for the codeposition of Ag and Au, respectively. A lift-off process in acetone followed shortly after. To realize Au-nr film on electrode sites, dealloying was performed in nitric acid at 60 °C for 2 min. O2 plasma (Oxford Plasmalab 80 RIE) was then applied for 2 min (150 W RF power) to activate the surface of parylene C for enhancing the adhesion of the subsequent encapsulating parylene C layer. A layer of ~1.9–2.5 µm parylene C was then deposited and followed by coating another Micro-90 antiadhesion layer; with slightly higher concentrated Micro-90 (1% as opposed to 0.1% for the first layer) to facilitate the separation of the subsequent layers. Then, a third parylene C layer was deposited as sacrificial layer. To define the patterns on electrode sites, a thick 2010 SU-8 photoresist layer was exposed and developed using Karl Suss MA6 mask aligner and SÜ8 developer. Prior to deposition of PEDOT:PSS film, O2 plasma was used to etch the openings in the third and second parylene C layers. 20 µL aqueous dispersion of PEDOT:PSS (pH 1000 from Clevios) was mixed with ethylene glycol (5 mL), dodecylbenzene sulfonic acid (DBSA, 50 µL), and 1 w/v% of (3-glycidyloxypropyl)trimethoxysilane (GOPS), and the solution was spun-cast at 650 rpm for 30 s and prebaked at 95 °C for 1 min. Then, to define the PEDOT:PSS film on top of Au-pl or Au-nr electrode sites, the sacrificial parylene C layer was mechanically peeled off. Finally, the devices were cured at 140 °C for 1 h and then immersed in DI water to remove any Micro-90 residue from the device surface.

Device Fabrication—Electrodeposited PEDOT:PSS-Based Electrodes: First, Au-pl and Au-nr macro- and microarrays were fabricated following a similar procedure to that of spin-coated PEDOT:PSS devices up to PEDOT:PSS coating step. At the final step, PEDOT:PSS film was electrodeposited rather than spun-cast. Prior to the PEDOT:PSS electrodeposition, 20 CV cycles were performed on all channels within −0.6–0.6 V versus Ag/AgCl in PBS as an electrochemical cleaning step. Then PEDOT:PSS was electrodeposited from 0.01 M EDOT in 2.0 g L−1 × 1000E was used to perform EIS in 0.01 M 1× PBS) solution, interface 1000E was used to perform EIS in 0.01 M 1× PBS) solution, using a three electrode configuration, i.e., PEDOT:PSS electrodes as the working electrode, Ag/AgCl electrode as a reference electrode, a large platinum electrode as a counter electrode, and the target microarray/macrodot arrays as the working electrode, at a constant temperature of 27 °C using a GAMRY interface 1000E.

Polymerization was driven for 20 s at or below current density of 0.9 V versus Ag/AgCl in a three electrode setup, i.e., Ag/AgCl electrode as a reference electrode, a large platinum electrode as a counter electrode, and the target microarray/macrodot arrays as the working electrode, at a constant temperature of 27 °C using a GAMRY interface 1000E.

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Supporting Information


Monolithic and Scalable Au Nanorod Substrates Improve PEDOT–Metal Adhesion and Stability in Neural Electrodes

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Figure S1: Nanoporous vs. nanorods Au structures: (a) Top view SEM image of different nanoporous Au structures as the result of using different DC powers of 200 W/ 100 W for Ag/Au and 400 W/ 100 W for Ag/Au during co-sputtering of the AuAg alloy. As expected, a larger DC power for Ag deposition results in more Ag in the film that in turn is selectively etched leaving more voids in the final Au nanoporous layer. (b) Top view SEM image of Au nanorods (Au-nr), realized by de-alloying of co-sputtered AgAu alloy with DC power of 400 W/ 50 W for Ag/Au. The rods are arranged in bundles/islands across the surface. (c) Cross-sectional and top view illustration of 3-D confinement of PEDOT film (green highlight) within 3-D structures of the Au-nr (yellow highlight).
Figure S2: Extracted small signal components for different electrodes: (a) Equivalent circuit model. (b) Extracted small signal components for Au-nr, Au-pl, micro and macro spin-cast PEDOT:PSS electrodes. (c) Measured and fitted EIS magnitude and phase for various electrode materials including macro Au-nr, Au-pl, micro and macro PEDOT:PSS electrodes.

<table>
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<tr>
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<th>Au – nr (D = 500 µm)</th>
<th>Au – pl (D = 500 µm)</th>
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Figure S3: Stability of Au-nr electrode (D=300 µm) under CV stressing test: (a) Optical image of the tested electrode (ch 12) before and after cycling and control electrode (ch 11) before and after soaking in PBS. (b) Impedance magnitude and phase spectra of the tested Au-nr electrode (ch 12) as a function of frequency before and after 1,000 CV cycles.
**Figure S4:** Fabrication flow of PEDOT:PSS/Au-nr electrodes: a) Solvent cleaning of Si or glass substrate. b) First parylene C deposition. c) First Cr/Au metallization to define the meal leads. d) Sputtering Cr/Au adhesion/base layers. e) Co-sputtering AgAu alloy. f) De-alloying of AgAu alloy to realize Au-nr. g) Deposition of second parylene C layer. h) Etching the parylene C layer on top of electrode sites. i) PEDOT:PSS deposition and releasing the device from the carrier substrate.

**Figure S5:** Top-view (a) SEM and (b) optical image of spin-coated PEDOT:PSS/Au-nr macro electrode (D=500 µm) after 11,000 CV cycles. c) Top-view SEM image at highlighted black box, showing partial delamination of PEDOT film from the Au-nr substrate after 11,000 CV cycles.
Figure S6: Accelerated aging results for spin-coated (SC) and electro-deposited (ED) PEDOT:PSS microelectrodes with Au-nr and Au-pl substrates: Scatter values and average of impedance of different PEDOT:PSS-based microelectrodes; (1) spin-coated on Au-nr (Au-nr_SC, black), (2) electro-deposited on Au-nr (Au-nr_ED, blue), (3) spin-coated on Au-pl (Au-pl_SC, red) and (4) electro-deposited on Au-pl (Au-pl_ED, green), at 1000 (a), 100 Hz (b) and 10 Hz (c) 100 Hz as a function of accelerated aging period in BPS at 60 °C.

Figure S7: a) Top view SEM image of electro-deposited PEDOT:PSS on Au-pl substrate, survived after 5 weeks aging test. b) Some examples of morphological changes for degraded electrodes after 5 weeks aging experiment.
Figure S8: a) Top view SEM image of stable spin-coated PEDOT:PSS on Au-nr substrate and stable condition of the whole electrodes on the same array (b) after 5 weeks soaking test without any sign of film delamination or degradation. c) Top view SEM image of stable electro-deposited PEDOT:PSS on Au-nr substrate and stable condition of the whole electrodes on the same array (d) after 5 weeks soaking test, showing no morphological changes nor film delamination from the Au-nr substrate.

Figure S9: In vivo implantation effect on spin-coated PEDOT:PSS/Au-pl micro-electrodes: Top view SEM image of PEDOT:PSS/Au-pl array and all 32 electrodes after 10 weeks of cortical implant in a mouse, showing a full PEDOT film detachment from 29 Au-pl sensing sites and 3 partial PEDOT film delamination from 3 Au-pl electrodes.

Figure S10: In-vivo implantation effect on spin coated PEDOT:PSS/Au-nr micro-electrodes: Top view SEM image of PEDOT:PSS/Au-nr array and all 32 electrodes after 10 weeks of cortical implant in a mouse, showing a full survival of all coated PEDOT:PSS films on 32 Au-nr electrodes.