Published in final edited form as:

Adv Mater. 2009 October 5; 21(37): 3764–3770. doi:10.1002/adma.200900887.

Interfacing Conducting Polymer Nanotubes with the Central Nervous System: Chronic Neural Recording using Poly(3,4-ethylenedioxythiophene) Nanotubes

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Development of advanced chronic, high-fidelity neural interfaces is accelerating research into brain function^[1] and more effective treatments for neurological conditions.^[2–5] The primary functional requirements of these interfaces include recording and/or stimulating from a number of discretely sampled volumes of the brain at requisite spatial resolutions for specific time periods that may extend from hours to years.^[6–9] This translates to a push towards smaller electrodes that are more biologically transparent and biocompatible^[10–12] with a high density of electrode sites that remain functional for long period of time.^[13–15] As electrode size goes to the microscale (higher spatial selectivity), the impedance of electrode site increases, and consequently, the quality of signal recordings decreases (lower sensitivity). Thus, there is a trade off between the size (spatial selectivity) and quality of signal recordings (sensitivity) in neural microelectrodes.^[16–18] Studies have also shown that the response of brain tissue to implanted microelectrodes includes an acute injury and a chronic reactive tissue response. The chronic response is characterized by the presence of both activated microglia and reactive astrocytes, which eventually encapsulate the electrode to some degree.^[10,12,19–21] Consequently, in addition to the initial high impedance of microelectrodes, these reactive tissue responses have been associated with a progressive

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increase in the impedance of the electrode/tissue interface.^[10,12] Therefore, achieving a very low impedance electrode/tissue interface is important for maintaining and improving signal quality.

Signal transduction at the electrode/tissue interface is a complex function of electrode properties and tissue characteristics.^[17] Transduction between the ionically conducting tissue and the electronically conducting electrode is primarily through capacitive currents and/or Faradaic currents from reversible reduction–oxidation reactions at the electrode surface.^[7,17] However, conventional metal electrodes, including gold, tungsten, platinum, and iridium, create a relatively abrupt materials interface that have well defined electrical characteristics, but have few options for dramatic impedance improvement.^[10] Therefore, new materials are required to decrease the electrode impedance, facilitate the ions to electrons signal transduction, and improve the biocompatibility at the electrode/tissue interface.

The recent advances in the application of nanoscience in biology^[22] have enabled the design of nanomaterials such as carbon nanotubes^[23] and silicon nanowires^[24] that can be used for neural interfaces. Nanostructured materials may provide a means to significantly alter the structure/function relationship of microelectrode sites to reconcile the sometimes-conflicting requirements for smaller size, favorable electrical characteristics, and biocompatibility.^[25] Conducting polymers such as poly(–pyrrole) (PPy) and poly(3,4-ethylenedioxythiophene) (PEDOT) have both electronic and ionic conductivity^[26] and have been recently considered as bioelectronic interface materials^[27] for biomedical applications,^[28,29] especially neuronal cell signaling^[30] and neural interfaces.^[31,32] Conducting polymers have favorable reactive tissue responses through attenuation of glial responses and enhanced integration and signaling of neuronal processes.^[30,33] Although PEDOT exhibits higher conductivity and chemical stability than PPy in the oxidized state,^[34] both PPy and PEDOT have been reported to decrease electrode impedance and increase charge injection capacity as compared to metal sites of similar geometric area.^[35–38]

Here, we report for the first time the use of conducting polymer nanotubes for highly selective, chronic neural recording at the microscale. We demonstrate that PEDOT nanotubes enhance quality of recording signals. We measured in vivo electrochemical impedance spectroscopy (EIS), noise level, quality of unit activity, and analyzed local field potentials (LFPs). We show that electrodes modified with PEDOT nanotubes registered high quality unit activity (signal-to-noise ratio, SNR > 4) on 30% more sites than controls (uncoated), primarily as a result of a reduced noise floor. Moreover, we demonstrate that sites modified with PEDOT nanotubes have significantly less low frequency artifact in LFP recordings. The Nyquist plots of in vivo EIS measurements revealed that the PEDOT nanotubes may be used as a novel method for biosensing to indicate the transition between acute and chronic responses in brain tissue. These findings also demonstrate the chronic recording functionality of PEDOT nanotubes. Coupled with the previously demonstrated drug delivery capabilities of PEDOT nanotubes,^[37] this study paves the way for “smart” recording electrodes, which can deliver therapeutic agents to alleviate the immune response or induce neurons to grow toward the electrode.

Eight-channel chronic “Michigan” neural microelectrodes (Center for Neural Communication Technology, CNCT) with $1250\ \mu\text{m}^2$ gold recording sites were used throughout this work (Fig. 1e,f). PEDOT nanotubes were fabricated on the surface of every other recording site by using a nanofiber templating method (Fig. 1). Poly (L-lactide) (PLLA) electrospun nanofiber templates were prepared and collected on the neural microelectrodes (Fig. 1g,h and Fig. 2a,b). The diameter of the PLLA nanofibers ranged from 50 to 140 nm with the majority between 63 and 98 nm (Fig. 2a–d). Figure 1i,j shows the optical micrographs of PEDOT nanotubes on the neural microelectrode sites. The total applied charge density during electrochemical deposition was $1.44\ \text{C cm}^{-2}$ for all samples. This corresponded to the charge density needed to give the minimum impedance at 1 kHz,^[37] which is the relevant frequency typical of neuronal action potentials.^[39] The wall thickness of the PEDOT nanotubes varied from 20 to 35 nm, and the inner nanotube diameter ranged from 50 to 140 nm (Fig. 2e–h). By controlling the polymerization time, we could reproducibly prepare tubular structures with thin walls or thick walls.^[35] The overall thickness of PEDOT nanotubes was between 2.4 and 3.1 μm , depending on the thickness of electrospun fiber mesh on the neural microelectrodes.

Six chronic neural microelectrodes were implanted in the barrel cortex of three rats (See Supporting Information Figure S1, two electrodes per Sprague Dawley rat). Impedances of implanted microelectrodes were monitored after the surgery for 7 weeks. Figure 3a–d show the average EIS data for uncoated (control) and coated (PEDOT nanotubes) sites before implantation (Fig. 3a), right after implantation (Fig. 3b), 8 days after implantation (Fig. 3c), and 49 days after implantation (Fig. 3d). As shown in Figure 3b, the impedance spectrum of both uncoated and PEDOT nanotube sites increased right after implantation over the whole range of frequencies (from 841 ± 7 to $908 \pm 5\ \text{k}\Omega$ for uncoated sites and from 17 ± 4 to $87 \pm 8\ \text{k}\Omega$ for PEDOT nanotube sites at 1 kHz). This increase of impedance may be attributed to immediate protein absorption on the electrode sites coupled with the impedance of neural tissue.^[10,12] Additionally, the impedance spectrum of implanted microelectrodes increased for both uncoated and coated sites in day 8 ($1250 \pm 43\ \text{k}\Omega$ for uncoated and $546 \pm 30\ \text{k}\Omega$ for PEDOT nanotube sites at 1 kHz) and day 49 ($980 \pm 15\ \text{k}\Omega$ for uncoated and $521 \pm 18\ \text{k}\Omega$ for PEDOT nanotube sites at 1 kHz). This increase of impedance can be explained by both the acute and chronic responses of the brain to the implanted electrode over the course of time.^[10,12,20] Although the impedance of both uncoated and PEDOT nanotube sites increased, the PEDOT nanotube sites always had lower impedance than control sites, which should help in the quality of recording signal.^[7,11,17,40] Figure 3e shows the average impedances of PEDOT nanotubes and uncoated sites at 1 kHz over the time course of our recordings (49 days). Over the 1–3 days following surgery, the average impedance of the electrode sites remained relatively stable. During this period, the average impedance for the uncoated sites was $960 \pm 9\ \text{k}\Omega$ while for the PEDOT nanotube sites it was $105 \pm 7\ \text{k}\Omega$ ($p < 0.002$). The impedance of both PEDOT nanotube sites and control sites dramatically increased between days 3 and 9; the average impedance at 1 kHz for control sites was $1220 \pm 15\ \text{k}\Omega$ and for PEDOT nanotube sites was $530 \pm 17\ \text{k}\Omega$ ($p < 0.002$). This increase is most likely due to the initial trauma and edema around the implant after implantation.^[11,19,40,41] Edema remains after 4 days post-implantation, however excess swelling diminishes after 6–9 days due to the action of activated microglia.^[12,20] Consistent with this hypothesis, our

results showed that impedance at 1 kHz increased until day 9 for PEDOT nanotubes and control sites and then decreased. We then observed a reduction of impedance at 1 kHz between day 9 and day 15 for both control (uncoated) and PEDOT nanotube sites most likely due to reduction of acute inflammatory response.^[10,12,20] After day 15, their impedance started increasing and stabilized due to the chronic foreign body reaction.^[10,12,19,20] Across this period the average impedance of control sites was 1133 ± 19 k Ω and PEDOT nanotube sites was 509 ± 8 k Ω ($p < 0.002$) (see Supporting Information Table S1, summary of impedance results across days).

Figure 3f–q shows the Nyquist plot of uncoated electrodes (control) and coated sites (PEDOT nanotubes) over the time course of day 0 (day of implantation), day 3, day 6, day 13, day 29, and day 49 post-implantation. As demonstrated in the Figure 3f–q, the real (Z'), and imaginary (Z'') impedance increased over time after implantation, presumably due to tissue reactive responses. The most interesting results can be seen from the Nyquist plot trends of the PEDOT nanotubes sites. The profile trend was similar between day 0 and day 6 and between day 13 and day 49, however, some event occurred between day 6 and day 13 that caused a shift in the profile of only the PEDOT nanotube sites. This period correlates with the transition between acute and chronic responses.^[10,12,19–21] The Nyquist plots of PEDOT nanotubes suggest that an inflammatory response occurred between day 0 and day 6 and the wound-healing process (chronic response) began from day 13, which is consistent with described immunohistology results.^[10,12] The precision of the low-frequency measurements decreased due to instrumentation limitations.

Over the duration of this 7-week study, signals that regularly exceeded the 3.5 standard deviation threshold were evident on all 40 recording sites. On average, 90% of the PEDOT nanotubes sites recorded waveforms categorized as poor or better from day to day, compared to an 85% mean for the control sites ($p > 0.05$, See Fig. 4b). 65% of the PEDOT nanotubes' sites registered units categorized as high quality (SNR > 4) on a daily basis, whereas only 35% of the control sites registered high quality units ($p < 0.01$) (Fig. 4c). The number of sites demonstrating high quality unit activity decreased notably in the days following surgery, presumably as a result of the acute immune response.^[10,20]

The increase in average number of quality units (Fig. 4c) is likely a result of a decrease in noise (Fig. 4a). As expected, the average noise floor for PEDOT nanotube sites across days was 6.1 ± 0.8 μ V, significantly lower than the control site noise floor of 6.4 ± 0.9 μ V ($p < 0.01$) (Fig. 4a). It should be noted, however, that biological sources of noise, $1/f$ noise, ambient noise, and instrumentation noise, also contribute to the noise in extracellular neuronal recordings.^[42] A reduction in thermal noise diminishes only one of these sources of noise. As a result, there is still a high degree of variability in the noise observed on a given site.^[7,11]

Calculating a meaningful SNR of unit recordings for comparison between PEDOT nanotube and control sites was complicated by the fact that PEDOT nanotube sites registered an overall greater number of discernible units. While the decrease in noise on PEDOT nanotube sites tends to raise the SNR of units that would already be detectable, it also reveals units of low SNR that would have been obscured by the noise. Consequently, comparing the

“average” SNR of all discriminable units is not representative of the true difference in SNR between PEDOT nanotube and control sites. To account for this “threshold” bias, we compared the SNR of the 100 units with the highest SNR on PEDOT nanotube and control sites. Presumably, these 100 units would have been visible with or without the reduction in noise, and therefore, avoid the threshold problem. The average SNR of the top 100 units on PEDOT nanotube sites was 4.58, whereas the average SNR of the top 100 units on controls sites was 4.39 (significant, $p < 0.0001$). Although lowering the initial impedance of the implanted microelectrode resulted in a statistically significant increase in observed SNR as well as number of neurons recorded, these increases were relatively modest. This difference in mean SNR is consistent with the observed mean difference in noise. As noted in previous studies, recorded noise decreased in the days immediately following surgery, and then returned to slightly higher than original levels (Fig. 4a).^[8] Quality unit activity also decreased in the days following surgery, but never returned to the original observed level (Fig. 4c). The time course of these observed changes is consistent with the time course of the acute immune response.^[10,12,21]

LFPs are thought to reflect the synaptic activity of neurons in the vicinity of recording sites, and typically vary in frequency from 3 to 90 Hz. During this experiment, LFP recordings were taken in conjunction with single unit recordings. A low frequency voltage perturbation (<1 Hz) was intermittently evident on the control sites that were not evident on the PEDOT nanotube sites (Fig. 4d). This low frequency drift was sufficient in amplitude to register on the control sites despite the bandpass filter. This low frequency signal has been noted in other studies, and is typically considered an undesirable artifact.^[40,43] Two likely sources of this low frequency noise source are motion related artifact, or low frequency perturbations of the open circuit potential at the recording sites. In a differential recording set-up, these two sources are supposed to be mitigated by the use of a recording reference. Consistent with prior studies, a distal stainless steel bonescrew implanted in the skull was used as a recording reference, with impedance in the frequency range of LFP of ~ 5 k Ω . In an ideal differential recording set-up, the impedance of the recording electrode should match the impedance of the reference electrode as closely as possible to eliminate common noise and transient artifacts. As noted previously, the low frequency impedance of PEDOT nanotubes in vivo was drastically lower than control sites. Consequently, the PEDOT nanotube sites provided a better impedance match to the stainless steel reference screw. Not surprisingly, the low frequency artifact observed on control sites was therefore removed through differential subtraction on the PEDOT nanotube sites (Fig. 4d).

We monitored the change in impedance and signal quality of neural microelectrodes that were coated with PEDOT nanotubes for evaluation of long-term performance over a 7-week period. The response of brain to neural implants^[10,12,19,20] and the time course of our EIS results are consistent with an association between the trend of impedance and reactive tissue responses. Current theories hold that glial encapsulation electrically isolates the electrode from nearby neurons, thereby increasing electrode/tissue interface impedance.^[21,44,45] We found that the lower impedance of PEDOT nanotubes over the course of this study (Fig. 3e) resulted in significantly lower noise (Fig. 4a), and therefore a higher number of discriminable neural units. As noted in prior studies the tissue encapsulation of the electrode

may mitigate the long-term benefit of reducing initial impedance in the 1 kHz range.^[10,12,19] Consequently, an interesting strategy would be to control the foreign body response to the implanted array, while also maintaining normal neuronal density around the electrode, to yield additional long-term benefits. PEDOT nanotubes can provide a mechanism to address these issues through the controlled delivery of therapeutic agents from the electrode sites,^[37] which will be explored in future studies. The results here, however, demonstrate that PEDOT nanotubes can effectively record neuronal signals in a chronic setting, and is therefore suitable for both chronic recording and drug delivery. Furthermore, in vivo impedance spectroscopy of PEDOT nanotube sites indicates PEDOT nanotubes can be used as a biosensor for the transition of acute inflammatory response to chronic response (Fig. 3f–q). Another potential benefit of PEDOT nanotubes is dramatically reduced low frequency impedance in the chronic setting. A recent study by Nelson et al. has demonstrated that larger low frequency impedances can induce increasingly large phase lag biases in the recorded LFP.^[46] As coherencies between the timing of individual neuron firings and oscillations in the LFP are commonly used to elucidate neuronal network activity, these phase lag biases may become a factor in analysis. Here, we demonstrated that PEDOT nanotubes have markedly lower impedances than control electrode sites in the frequency range relevant for LFP chronic setting, and therefore should decrease this problematic phase lag. The results of this study indicate that PEDOT nanotubes provide an incremental benefit for obtaining high quality neural recording.

Experimental

Materials

Poly (L-lactide) (PLLA, RESOMER L 210) with inherent viscosity 3.3–4.3 dl g⁻¹ was purchased from Boehringer Ingelheim Pharma GmbH & Co. (KG, Germany). 3,4-ethylenedioxythiophene (EDOT, BAYTRON M) with molecular weight 142.17 g mol⁻¹ was received from H. C. Starck Inc. (Newton, MA). Lithium perchlorate (LiClO₄) were purchased and used as received from Sigma–Aldrich.

Fabrication of Electrospun Nanofiber Template

PLLA solution was prepared by dissolving PLLA (0.72 g) in dichloromethane (10 mL) at a temperature of 50 °C for 10 h in order to have a homogenous solution with PLLA concentration of 4% w/w. PLLA nanofibers were directly deposited on the six chronic microfabricated Michigan neural electrodes by electro-spinning in an electrical field of 0.6 kV cm⁻¹ with flow rate of 0.25 mL h⁻¹ for 30 s. The neural microelectrodes were held at a distance of 15 cm from the syringe needle.

Fabrication of PEDOT Nanotubes

The electrochemical deposition was performed by an Autolab PGSTAT-12 (EcoChemie, Utrecht, Netherlands) in galvanostatic mode, with a conventional two-electrode configuration at room temperature. PEDOT was deposited on the surface of gold electrode sites that were coated with electrospun PLLA nanofibers. PEDOT was grown on the sites and around the PLLA nanofibers. PEDOT deposition was carried out in 3,4-ethylenedioxythiophene monomer (EDOT) (0.01 M) and LiClO₄ (0.1 M) aqueous solution at a

current density of 0.5 mA cm^{-2} . The amount of polymer coated on the electrode site was controlled by the total charge passed during polymerization. The working and sensing electrodes were connected to the electrode site. The reference and counter electrode were connected to a platinum wire within the EDOT/LiClO₄. After electrochemical deposition was completed, the PLLA core fibers were removed by soaking the probe tips in dichloromethane for 5 min.

Electrochemical Impedance Spectroscopy—In vitro

An Autolab PGSTAT-12 and Frequency Response Analyzer software (Eco Chemie, Utrecht, Netherlands) were used to record impedance spectra of electrode sites for the neural probes. A solution of phosphate buffer solution (PBS, 0.1 M, pH = 7) was used as an electrolyte in a three-electrode cell configuration. The working electrode was connected to the electrode site through a connector. The counter electrode was connected to a platinum foil that was placed in a glass container. An Ag/AgCl reference electrode and the neural microelectrode tip were immersed in a glass container of electrolyte. An AC sinusoidal signal of 5 mV in amplitude was used to record the impedance over a frequency range of 1–10⁵ Hz.

Surgical Procedure and Implantation of Chronic Electrodes

All animal procedures were approved by the University of Michigan University Committee on Use and Care of Animals and were in accordance with the National Institutes of Health guidelines. See Supporting Information Text for details.

Electrochemical Impedance Spectroscopy—In Vivo

Impedance spectroscopy measurements were made using an Autolab potentiostat PGSTAT-12 (Eco Chemie, Utrecht, The Netherlands) with associated frequency response analyzer (FRA) (Eco Chemie, Utrecht, The Netherlands). Impedance measurements were made by applying a 5 mV RMS sine wave with frequencies varied logarithmically from 1 to 10⁵ kHz.

Data Collection

After implantation, neural recordings and impedance spectroscopy for each recording array were taken three times a week for 7 weeks. Animals were anesthetized with ketamine/xylazine throughout the data collection sessions.

Neural Recordings and Data Analysis

Recorded neural signals were acquired using a Multi-channel Neural Acquisition Processor (MNAP; Plexon Inc, Dallas, TX). See Supporting Information Text for details. All statistical analyses of the results were performed using one-factor ANOVA (PEDOT nanotubes versus controls), unless otherwise noted in the text.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank Luis Salas for assistance during surgery and data collections, Eugene Dariush Daneshvar for his valuable comments and edits on the manuscript, Nick Langhals and Greg Gage for their comments. This study was supported by a Rackham Predoctoral Fellowship, the Department of Defense Multidisciplinary University Research Initiative (MURI) program administered by the Army Research Office under grant W911NF0610218, and the Center for Neural Communication Technology that is a P41 Resource Center funded by the National Institute of Biomedical Imaging and Bioengineering (NIBIB, P41 EB002030) and supported by the National Institutes of Health (NIH). The authors acknowledge the University of Michigan Center for Neural Communication Technology (CNCT) for providing the neural microelectrodes. Supporting Information is available online from Wiley InterScience or from the author.

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Figure 1.

Schematic illustration of conducting polymer (PEDOT) nanotube fabrication on neural microelectrodes: a,b) Electrospinning of biodegradable PLLA template fibers. c) Electrochemical deposition of conducting polymer (PEDOT). d) dissolving the electrospun core fibers to create conducting polymer nanotubes. e,f) Optical microscopy images of the entire microelectrode (e) and single electrode site (f) before surface modification. g,h) Optical microscopy images of the entire microelectrode (g) and single electrode site (h) after electrospinning of PLLA nanofibers. i,j) Optical microscopy images of the entire microelectrode (i) and single electrode site (j) after electrochemical deposition of PEDOT and removing the PLLA core fibers.

Figure 2.

Scanning electron microscopy (SEM) images of PLLA nanofibers and PEDOT nanotubes on neural microelectrodes. a–d) SEM images of electrospun PLLA nanofibers from lower (a,b) to higher magnification (c,d). d) Higher magnification image of a single PLLA nanofiber showing the well-defined surface texture on the surface of electrospun PLLA nanofiber. The diameter of the nanofibers ranged from 50 to 140 nm with the majority between 63 and 98 nm. e–h) SEM images of PEDOT nanotubes from lower (e,f) to higher magnification (g,h) on the surface of a single microelectrode site. h) Higher magnification image of a single

PEDOT nanotube showing the well-defined internal and external surface texture. The internal surface texture was replicated from the external surface texture of PLLA nanofibers. The wall thickness of the PEDOT nanotubes varied from 20 to 35 nm, and the nanotube diameter ranged from 50 to 140 nm. The total applied charge density during electrochemical deposition was 1.44 C cm^{-2} .

Figure 3.

Electrochemical impedance spectroscopy. a–d), electrochemical impedance spectrum for PEDOT nanotube sites (PEDOT NTs) and uncoated sites (control) before implantation (a), immediately after implantation (b), day 8 after implantation (c), day 49 after implantation (d). e), impedance magnitude at 1 kHz over time after surgery. f–q), Nyquist plots of uncoated (control) and PEDOT nanotube sites (PEDOT NTs) after implantation in day 0 (f, g), day 3 (h, i), day 6 (j, k), day 13 (l, m), day 29 (n, o), and day 49 (p, q). The data in the graphs was averaged between the 20 uncoated sites and 20 PEDOT nanotube sites. The bars

denote standard error of the data set on a given day ($n = 20$). Day 0 measurements were taken immediately after surgery.

Figure 4.

Average RMS noise, and percentage of sites recording low- and high-quality units. a) Average RMS noise over time. PEDOT nanotube (PEDOT NTs) sites exhibited a significant reduction in recorded noise on a daily basis ($p < 0.01$), presumably resulting in the observed increase in number of quality units on PEDOT nanotube sites. As observed in prior studies, the average noise for both PEDOT nanotube and control sites decreased in the days immediately following surgery, and then returned to slightly higher than original levels. b,c) Units with SNR > 2 (b), quality Units with SNR > 4 (c). Over the course of the experiment, an average of 90% of the PEDOT nanotube sites recorded low quality unit activity from day to day, compared to an 85% average for control sites ($p > 0.05$). PEDOT nanotube sites demonstrated a significant improvement in percentage of sites recording high-quality units on a day-to-day basis (PEDOT nanotubes mean: 65%, control mean: 35%; $p < 0.01$). The bars denote standard error of the data set on a given day ($n = 20$). Day 0 measurements were taken immediately after surgery. d) Local field potential recordings. The above figure is a representative segment of local field potential recordings taken from one animal

immediately following surgery. Note there is a low frequency artifact visible on the uncoated sites that is not evident on the PEDOT nanotube sites.

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