Effect of Counter-Ion Ratio on Poly(3,4-ethylenedioxythiophene) (PEDOT) as a Neural Interfacing Material

by

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Abstract

Many problems exist in chronically implanted neural prostheses due to the lack of reliable neural interface. This is due to increased impedance and foreign body response resulting in an inability to record and stimulate. Poly (3,4-ethylenedioxythiophene) (PEDOT) and other conductive polymers have recently emerged as a better material for neural stimulation. PEDOT exhibits larger electrochemical stability and higher charge storage capacity due to the two bonding sites on C2,5 of the conjugated backbone. Previously, PEDOT has been used for neural interfacing applications. PEDOT has been electrodeposited in vitro on micro-electrodes resulting in a decreased impedance magnitude, enhanced charge storage capacity and a stabilized performance as compared to Iridium Oxide (IrOx) coatings [1]. Furthermore, in 2018 Murbach showed decreased impedance magnitude of injectable PEDOT electrodes in excised peripheral nerve [1]. In this study, we use the conducting polymer PEDOT as a neural interface material for microstimulation of platinum iridium (PtIr) microwire electrodes in rodent cerebellum. PEDOT deposition and the effect of varying the counter-ion and concentration counter-ion through electrochemical impedance spectroscopy, histology, and microscopy.

0.1wt% PEDOT:PSS was found to have the lowest impedance magnitude out of the varying concentrations of PSS in the injectable electrodes, whereas there was no significant difference in the impedance magnitude of the agarose polymerization. Furthermore, the smaller counter-ion ClO₄ was found to be inefficient in solubilizing the EDOT monomer in the agarose. Therefore, the polymerization took place at the oxygen-air interface, resulting in a decreased impedance magnitude over all frequencies. The PEDOT clouds also appeared to decrease in size with increasing PSS concentration.
Dedication

The majority of my research has focused on neurodegenerative diseases. This is an area of science that is actively pursued, but often slow in moving ideas or new procedures to clinics and patients. My drive to pursue a PhD in biomedical engineering and focus on moving research from bench to bedside stems from my experience of family and friends who have suffered and succumbed to various neurological diseases. It is these people who motivate me to do more experiments, study harder and ultimately achieve my career goals in the hope that, one day we will be able to provide personalized and effective treatments for patients. Thus, I would like to dedicate this work, as well as all my future efforts to Martha and Aaron Lowder, James Widener, Paula and Steve Widener, Betty Jo Couch, and all others who have experienced the effects of neurodegenerative diseases.
Acknowledgements

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Table of Contents

Chapter 1: Introduction ................................................................................. 6
  Purpose of Study .......................................................................................... 6
    Neurological Diseases .................................................................................. 6
    Neural Prosthetics ...................................................................................... 6
    Conductive Polymers .................................................................................. 9
  Statement of Hypothesis ........................................................................... 11
  Significance of Study .................................................................................. 12
  Limitations/Assumptions of Study .............................................................. 13

Chapter 2: Methods ....................................................................................... 14

Chapter 3: Results ......................................................................................... 18
  Specific Aim #1 ......................................................................................... 18
    Electrochemical Impedance Spectroscopy ................................................. 18
    Histology and Microscopy ........................................................................ 21
    Counter-ion Comparison ........................................................................... 22
  Specific Aim #2 ......................................................................................... 24
    Electrochemical Impedance Spectroscopy ................................................. 24
    Laser Lightsheet Microscopy ................................................................... 25

Chapter 4: Conclusion .................................................................................. 27
  Discussion .................................................................................................... 27
  Future Studies ............................................................................................. 28

References .................................................................................................... 29

Appendix A: Tables and Figures ................................................................. 31

Appendix B: Acronyms ............................................................................... 32
Chapter 1: Introduction

I. Purpose of Study

A. Neurodegenerative Diseases

Today it is estimated that one billion people throughout the world have a neurological disease and each year 6.8 million die from these maladies [2]. Examples of these diseases include Parkinson’s Disease (PD), Alzheimer’s Disease (AD), Multiple Sclerosis (MS), Amyotrophic Lateral Sclerosis (ALS or Lou Gherig’s Disease) and Huntington’s Disease (HD). Neural prosthetics have recently been implanted to ameliorate these diseases through interaction with damaged neural tissue at the neural interface. These connections can occur at multiple levels including peripheral nerves, spinal cord or in the brain [3].

B. Neural Prostheses

Neural prostheses are assistive devices that restore functions lost as a result of neural degeneration. The ability to record activity and stimulate in tissue has been integral to medical diagnosis and the progression of treatments for neurological diseases [4]. Specifically, implantable neural interfaces have shown promising results in recording activity and replacing function [4]. Electrodes used in these implants are typically fabricated from conductive, stable materials such as gold, platinum, and iridium oxide. Although these materials are considered inert, metal electrodes are not conducive to tissue integration [5]. Metal electrodes have a Young’s modulus’ 6 orders of magnitude higher than neural tissue [6, 5], and this mechanical mismatch leads to a foreign body response (FBR) to devices resulting in a glial sheath formation around the implant.
Specifically, an immunological FBR around implants leads to the acute activation of macrophages and the formation of the glial sheath, preventing signal between the tissue and device (Figure 1). When electrodes are first implanted, microglial cells in the surrounding tissue are activated and respond to the injury [7]. Specific plasma proteins in the blood brain barrier (BBB) recruit microglial cells and astrocytes to proliferate around the implant. In chronic studies, the long-term application of microelectrodes is limited by the sustained inflammation. This glial encapsulation is related to increased system impedance and decreased signal-to-noise ratio for recording and stimulating devices [8]. Other factors that contribute to the persistent response are micromotion of the electrode and mechanical compliance mismatch between the implant and neural tissue [9].

Figure 1: Formation of a glial scar around neural prosthetic. (a) Acute inflammatory response after probe implantation. Activated microglia and astrocytes recruited to site of implantation. (b) Chronic inflammatory response, deposition of fibrous scar network. (c) deposition of conductive polymer on neural electrode reduces cellular recruitment and maintains healthy neuronal populations. [21]
The reduction of chronic inflammation around neural implants is consequentially one of the most important obstacles to overcome for neural interface technology to be fully realized [9]. Thus, when designing a neural prosthetic there are four main requirements to consider: decreased foreign body response, improved biocompatibility, soft mechanical properties, and improved electrical conductivity [10]. Many strategies have been investigated for reducing chronic tissue reaction that focus on different factors generating the response. These strategies can be broken down into two main groups: mechanically based and biologically based strategies. The end goals of these strategies both include minimizing neuronal loss, promoting neural regeneration and limiting the formation of the glial sheath. This research will focus on the mechanical and biological advantages of using the conductive polymer PEDOT as a neural interfacing material.

Mechanical approaches for a better neural interfacing electrode consider size, flexibility and material density relative to the tissue. In order to decrease the FBR around the implant, newer electrodes have been considerably smaller and thinner [9]. The reduction in surface area of these electrodes mitigates the initial tissue damage, decreases neuronal loss surrounding the implant and results in reduced chronic inflammation [11]. Similarly, by choosing materials with comparable mechanical properties to neural tissue foreign body response is limited [6]. Therefore, current research has turned to the use of conductive polymers as a neural interfacing material. The reduced modulus of these materials better matches the neural tissue, decreasing foreign body response and inflammation over time. The electrical properties of these
materials at the device-tissue interface have shown to improve recording and stimulation over time versus standard metal electrodes in a biological system [12].

C. Conductive Polymers

Conductive polymers (CPs) are a group of organic materials that show fast charge transfer while maintaining flexibility at the neural interface [4]. The structure of these polymers consists of alternating single and double bonds that allow charge transport to occur across the backbone. Overlapping carbon orbitals, generated by the pi bond of the monomer unit, allows for delocalized electrons to travel across the backbone, creating a current (Figure 2b). The electrical conductivity, wettability, color and volume of CPs can be altered through the manipulation of the electrochemical state of the material by adding dopants to the polymer [13]. This research focuses primarily on the effects of the addition of different counter ions and counter-ion concentrations on the electrochemical properties and diffusion of the conductive polymer, poly(3,4-ethylenedioxythiophene) (PEDOT), in agarose and tissue.

Previously, PEDOT has been used to coat metallic electrodes and demonstrates superior performance at delivering charge at neural interfaces over other conductive polymers [13]. PEDOT has also shown decreased impedance magnitude, increased charge storage capacity and improved recording quality in vivo [14]. In 2013, Richardson-Burns et al, showed the toleration of the monomer, EDOT at a moderate concentration during twelve hours of exposure in vitro neural cell culture tests. In 2011, Ouyang et al, showed that by polymerizing PEDOT in rat brain slices that had been incubated with EDOT monomer solution, PEDOT was diffused into the brain extracellular space (ECS) [15].
PEDOT has also been polymerization by direct delivery of EDOT monomer to the reaction site [15]. In 2018, Murbach et al, injected PEDOT into sciatic nerve and showed decreased impedance magnitude as compared to plain tungsten wire [1]. In 2007, Richardson-Burns et al., proposed the ability of PEDOT to grow filaments that could reach beyond the glial scar creating a PEDOT “cloud” [16]. Following this study, in 2011, Wilks et al., showed the ability to form PEDOT cloud in agarose when 6-10μL was injected into the solution using a PlasticsOne device through in situ electrodeposition [17]. Also in 2011, Ouyang et al., showed PEDOT cloud deposition in vivo demonstrating the ability of PEDOT to diffuse into tissue [8]. Ouyang and Wilks saw a PEDOT polymer cloud grow from the working electrode tip and extend at least 1mm into the brain tissue.

Figure 2: a) Monomer unit of poly(3,4-ethylenedioxythiophene) (PEDOT), bonding sites are seen every third monomer unit due to the electron density pulled away from C2 and C5. This becomes bonding site for counter ions on the backbone. b) Diagram of delocalized molecular orbitals of PEDOT above and below the backbone.
Dopants used for PEDOT are p-dopants and oxidize the polymer, resulting in a dark blue deposition. If the PEDOT over-oxidizes it becomes brown in color. It should also be noted that the CP matrix during redox processes can lead to swelling and de-swelling of polymer as a result of changes in bond lengths, conformation of the polymer and osmotic expansion of the polymer chain. When dopant anions are small, they can be expelled by the application of negative voltages. When anions are large enough, they become immobilized and trapped inside the polymer structure. In this study the following counter-ions will be observed: perchlorate (ClO$_4$), p-toluene sulfonate (pTS) and Poly(styrene sulfonate) (PSS) (Figure 2a).

The effect of dopant on PEDOT as a neural interfacing has only been briefly researched in the past decade. In 2013, Baek observed the biomechanical properties of conducting polymer films on platinum electrodes [13], showing that electrical properties of the materials had a size dependent behavior with smaller counter-ions having highest charge transfer capacity and the lowest impedance magnitude. They also showed by nanoindentation that the modulus of the polymers had a direct correlation to the size of the counter ion.

II. Statement of Hypothesis

The conductive polymer PEDOT has shown potential as a neural interfacing material, however; the electrochemical behavior of PEDOT with dopants is not very well known. This study aims to understand the effect of counter-ion ratio on the electrical, chemical and mechanical properties of PEDOT. I hypothesize that by altering the counter-ion ratio in the conductive polymer PEDOT, 0.1wt% concentration of the counter ion PSS will show improved electrical properties,
stability and diffusion of the polymer into gel as compared to other concentrations and dopants. My hypothesis consists of two specific aims as follows:

(1) The counter-ion and counter-ion concentration affect the electrochemical properties of PEDOT to act as an effective neural interface material. I expect that if you use 0.1 wt% PEDOT:PSS you will see low impedance magnitudes, charge storage capacity and increased chemical stability of the polymer.

(2) The addition of a counter-ion into the monomer solution will affect the morphology and structure of the polymer whilst being injected into the tissue. This will affect the ability of the polymer to diffuse into the tissue. I expect that as the polymer becomes larger with the addition of counter ions, the PEDOT cloud and ability to diffuse into the agarose will decrease.

III. Significance of Study

It has been found that the addition of the dopants have the capacity to increase the stability and solubility of the monomer, EDOT. It can be assumed that altering the dopant concentration will affect these properties as well. Furthermore, by assessing the material properties of PEDOT as a function of the counter-ion and counter-ion ratio, the results will improve our ability to use PEDOT as a chronic neural interfacing material. These results would then open the door to new treatments for neurological diseases. PEDOT could potentially improve conductivity of neural devices, improve ability to diffuse into tissue, reduce
delamination over time, and improve stimulation and recording capabilities. This research could also lead to advancements in drug delivery using conductive polymers by observing the effect of dopant and dopant concentration on the diffusion of PEDOT into agarose. Ultimately, these results could lead to advancements in neural prosthetics to develop personalized and effective treatments for people with neurodegenerative diseases.

IV. Limitations/Assumptions of Study

Although there have been huge advancements in conductive polymers as neural interfacing materials, there is still much we don’t know about the chronic stimulation of PEDOT. Consequently, there are not many studies showing the effect of dopant at neural interfaces over time so much of this work will only be applied for acute stimulations. There is also a lack of information regarding interfacing with materials and neural tissue. Furthermore, the processing used for the Laser Lightsheet imaging is varied and inconsistent, as the method is typically designed for tissues rather than materials of high modulus such as PEDOT.
Chapter 2: Methods

I. Specific Aim #1: Effect of counter-ion and concentration on electrochemical properties of PEDOT

A. In Vitro Electrochemical Polymerization

0.01M of EDOT (97% Sigma Aldrich, St. Louis, Mo, USA) was combined with varying concentrations (0, 0.01, 0.1, 1 wt%) of poly(4- sodium styrene sulfonate) (PSS, Mₐ ~ 70,000 g/mol, Sigma Aldrich, St. Louis, MO, USA) in 1X phosphate buffer saline (PBS, pH = 7.4). The EDOT monomer solution was vortexed and sonicated for 20 minutes prior to polymerization and mixed into a 0.6wt% agarose solution. In vitro polymerization was performed using a three-electrode cell configuration with a 100μm PtIr wire as the working electrode (WE) and counter electrode (CE), and an Ag|AgCl reference electrode (RE). Constant potentiostatic polymerization was performed using the Autolab PGSTAT128N at 2V for thirty minutes.

0.01M of EDOT was then combined with three different dopants: 0.1wt% PEDOT:PSS, 0.5wt% PEDOT:pTS, 0.5wt% PEDOT:ClO₄ in 1X PBS for PBS and De-ionized (DI) Water for pTS and ClO₄. The monomer solution was vortexed and sonicated the same as before, then mixed into a 0.6wt% agarose solution. The polymerization procedure followed the same process as mentioned above.

B. In Situ Electrochemical Polymerization

0.01M EDOT was combined with varying concentrations (0.01, 0.1, 1 wt%) of PSS, in 1X PBS. The monomer solution was vortexed and sonicated for twenty minutes prior to polymerization. In situ polymerization was performed using a
three-electrode cell configuration using a 100μm PtIr wire as the WE and CE, and an Ag|AgCl RE (Figure 3). 0.6wt% agarose gel was deposited over the entire rat cortex. Constant potentiostatic polymerization was performed for thirty minutes using the Autolab PGSTAT128N at 2V whilst 6-10μL of EDOT:PSS was injected into excised rat cortex.

C. Electrochemical Impedance Spectroscopy

Electrochemical Impedance Spectroscopy (EIS) measurements were taken before and after both *in situ* and *in vitro* polymerization using an Autolab PGSTAT128N with a three-electrode cell configuration. Using a 100μm PtIr wire as the working electrode and counter electrode, and an Ag|AgCl reference electrode. EIS measurements were collected by applying a sine wave between WE and Ag|AgCl RE while measuring the current magnitude and phase over a 0.01-10kHz frequency range, using a 15-sine 10mV RMS excitation voltage.
D. Tissue Processing, Histology, and Microscopy

Post polymerization the brains were fixed in 4% paraformaldehyde (PFA), transitioned to 1X PBS, and placed in 30% sucrose for at least 24 hours. Brains were embedded in Optimal Cutting Temperature solution (OCT) and cryosectioned into 30-μm thick sections. Afterwards, select slides were stained with DAPI then imaged at 10x magnification using a 488-nm laser.

II. Effect of counter-ion concentration on diffusion through agarose.

A. Agarose Tubes

The agarose tubes were formed by filling a drinking straw with a mixture of 1wt% Agarose in a solution of 1X PBS and cooled at room temperature until solid. The tubes were then transferred into a solution of 1X PBS and placed in a refrigerator until ready for use.

B. Polymerization

Polymerization was performed with a three-electrode cell configuration using a 100μm platinum-iridium (PtIr) wire as the working electrode and counter electrode, and an Ag|AgCl reference electrode. Constant potentiostatic polymerization was performed using the Autolab PGSTAT128N at 2V, whilst 6-10μL of the 0.01M EDOT monomer with varying concentrations (0.01, 0.1, 1wt%) of PSS was injected into 0.6wt% Agarose for thirty minutes.
C. Laser Light Sheet Microscopy

Polymerized agarose tube were then placed in a 63% 2,2’-thiodiethanol (TDE, Sigma Aldrich, St. Louis, MO, USA) solution for 20 minutes. Brightfield images using Laser light sheet microscopy (Zeiss Z. 1 Light Sheet, Germany) were used to assess the diffusion of PEDOT into the agarose at 5x magnification.

D. Statistics

a. Student’s t-test

Mean 1kHz impedance magnitude values were evaluated for statistical significance using student’s t-tests (p<0.05). Error bars regions represent the standard error mean from n = 3 different counter-ions and counter-ion ratios. The approximate area of each electrode was 78,539 μm².
Chapter 3: Results

I. Specific Aim #1: The counter-ion and counter-ion concentration affect the electrochemical properties of PEDOT to act as an effective neural interface material.

A. Electrochemical Impedance Spectroscopy

The first goal of this project was to determine the effect of dopant concentration on electrochemical properties such as impedance magnitude and phase angle. Figure 5 (1a) is the impedance magnitude of uninsulated PtIr wire compared to PEDOT with different concentrations of PSS (0, 0.01, 0.1, 1.0wt%). All concentrations showed a significant decrease in the impedance magnitude from the PtIr wire, as calculated by the student t-test (p<0.05). The impedance magnitude at 1kHz was taken as the fundamental frequency of the axon potential in Figure 5 (1b). There was no significance in the change between the different counter-ion concentrations, as calculated by the students t-test. The phase angle is seen in Figure 5 (1c), and shows a consistent trend to more resistive behavior (0° phase angle) as frequency increases.

In situ PEDOT was injected into excised rat brain, displayed in Figure 5 (column 2). The impedance magnitude for varying dopant concentration showed a significant difference as compared to the in vitro polymerizations. 0.1wt% PEDOT:PSS shows the largest decrease in impedance magnitude over all frequencies, followed by 1.0wt% and 0.01wt% PEDOT:PSS (Figure 5 (2a)). This may be due to the ohmic impedance of the tissue, for future studies it is recommended to take impedance caused from the tissue from the real impedance and have a corrected impedance value. Figure 5 (2b) shows the 1kHz fundamental
frequency of PEDOT polymerized *in situ*. All concentrations of PEDOT:PSS *in situ* show a statistical significantly difference from the pre-polymerization PtIr wire. 0.1wt% shows a significant difference from both data sets and 0.01wt% PEDOT:PSS is not significant from 1.0wt%.

The phase angle of the *in situ* polymerized PEDOT can be seen in Figure 5 (2c), all concentrations show a trend to a more resistive behavior at high frequencies. Both *in situ* and *in vitro* polymerizations showed a significant decrease in impedance magnitude from the pre-polymerization PtIr wire, this demonstrates lower power required for stimulation at lower current densities with PEDOT [14, 18].
Figure 5: (1a) Impedance Magnitude of PEDOT:PSS at different concentrations (0, 0.01, 0.1, 1.0 wt%) as compared to plain PtIr wire in 0.6wt% agarose. (2a) Impedance magnitude of injected PEDOT:PSS into excised rat cortex as compared to plain PtIr wire. (1,2b) Show the impedance magnitude at 1Khz with standard deviation error. (1,2c) Phase Angle compared to Frequency (Hz), all concentrations show resistive to conductive behavior at high frequencies. Artifacts are seen at 1kHz for PtIr wire, 0% PEDOT:PSS and 1.0wt% PEDOT:PSS (1c). A significant amount of noise is seen at low frequencies for PtIr in tissue (2c).
B. Histology and Microscopy

*In situ* polymerization was initially assessed in 2D cryosectioned brain slices. Figure 6 shows a brain slice containing PEDOT:PSS (0.1wt% PSS) that was polymerized using injected monomer into the brain tissue. PEDOT was imaged under fluorescence microscopy due to its intrinsic fluorescence at 488nm [14]. The brain in Figure 6 expresses green fluorescent protein (GFP) background due to its acquisition from a transgenic rat expressing GFP ubiquitously. *In Situ* injection and polymerization methods have demonstrated precise polymerization of PEDOT in cortex, decreased impedance magnitude post-polymerization for all dopant concentrations.

**Figure 6**: Cryosectioned brain slice 30μm thick, showing intrinsic fluorescence at 488nm. Injected PEDOT in excised rat cortex. White arrow indicates site of insertion.
C. Counter-ion Comparison

Different counter-ions can have varying effects on the material properties such as solubility, stability, and electrical properties of the conductive polymer. Commonly used dopants include p-toluene sulfonate (pTS), Lithium Perchlorate (LiClO₄), Poly(styrene sulfonate) (PSS) and have been studied before by Green, et al in 2014 [13]. This study shows the change in electrochemical properties compared to the change in dopant. Figure 7a shows the change in impedance magnitude for PSS, pTS and ClO₄. ClO₄ shows the lowest impedance magnitude at high frequencies, whereas at low frequencies pTS has the lowest impedance magnitude.

Figure 7: (a) Impedance Magnitude, (b) Phase Angle and (c) 1kHz Impedance Magnitude for PEDOT with varying counter-ions.
Figure 8: PEDOT film deposition on working electrode used in vitro. (a) PtIr wire pre-polymerization. (b) 0.1wt% PEDOT:PSS on PtIr, dark blue coloring indicates polymerization of PEDOT in oxidized state. (c) 0.5wt% PEDOT:pTS on PtIr with mixed patches of oxidized PEDOT (dark blue) and over-oxidized PEDOT (brown). (d) 0.5wt% PEDOT:ClO$_4^-$ deposition on PtIr working electrode agglomerated at the site of the oxygen interface.
PEDOT:ClO$_4$ showed the lowest impedance magnitude at 1kHz, this may be a result to the size of the perchlorate ion. Since PEDOT is a very hydrophobic polymer, its ability to disperse into agarose is limited because of the tendency to agglomerate together. As a counter-ion is added into the monomer solution, it will disperse around the PEDOT chain decreasing hydrophobicity and allowing dispersion through the solution. Since ClO$_4$ is a small ion compared to PSS and pTS its ability to solubilize the monomer EDOT is limited and when polymerized, will flocculate at the air interface because of the hydrophobic nature of the polymer. On the other hand, PSS and pTS are large enough to solubilize the monomer in the solution, allowing for an even dispersion throughout the agarose. Therefore, PSS and pTS will have the effect of impedance from the agarose increasing the overall impedance magnitude over all frequencies, whereas ClO$_4$ does not have the effect of impedance from the agarose and only considers the electrode-air interface allowing a lower impedance magnitude.

**II. Specific Aim #2: Effect of Counter-Ion Concentration on the Ability of PEDOT to Disperse Into Agarose.**

**A. Electrochemical Impedance Spectroscopy**

Figure 9a shows the impedance magnitude of injected PEDOT:PSS at different concentrations post polymerization. 0.1wt% PSS shows the lowest impedance magnitude at high frequencies and 0.01wt% PSS shows lowest impedance at low frequencies. 0.1wt% shows the lowest impedance magnitude at 1kHz in the agarose tube and the lowest impedance magnitude injected in tissue. This may be due to the ability this counter-ion ratio of PSS to solubilize the PEDOT in solution allowing for more charge transfer in stimulation.
B. Laser Lightsheet Microscopy

Laser lightsheet microscopy showed the deposition of a PEDOT cloud at the site of injection (Figure 10). As the counter-ion concentration increased, the size of the cloud decreased. Unfortunately, it was very difficult to mount and image these agarose tubes, so the 0wt% PEDOT:PSS is shown below had the largest PEDOT cloud, 0.01wt% formed in a similar manner. Figure 11 shows an optical image of the cloud formed by 0.1wt% at different focuses along the injection site. The PEDOT cloud appears to be an inverse function of the PSS concentration, this may be due to the ability of the counter ion to solubilize the monomer in the solution. At low concentrations, there is not enough PSS to cover the PEDOT chains leading to flocculation of the monomer around the injection site. At high concentrations, there is extra PSS in the solution, allowing for the over-dispersion of the monomer in the agarose after injection, leaving no visible PEDOT cloud.

Figure 9: (a) Impedance magnitude of injected PEDOT:PSS into agarose at different concentration (0, 0.01, 0.1, 1.0 wt% PSS). (b) Phase angle of injected PEDOT:PSS at different concentrations from 10kHz to 1kHz. All graphs showed a resistive behavior as frequency increases with the exception of 0.01wt% PSS.
Figure 10: Laser lightsheet microscopy at 5x magnification of agarose tube injected with PEDOT. Injection site is indicated by yellow arrow. PEDOT shows brittle cracking behavior, this may be an artifact from the mounting process used for lightsheet imaging.

Figure 11: Optical microscopy of 0.1wt% PEDOT:PSS injected into agarose tube, PEDOT deposition is visible along the site of injection. (b) Shows the distal (closer to the agarose-air interface. (c) Shows the proximal (site into the agarose tube).
Chapter 4: Conclusions

I. Discussion

At the beginning of this research the following hypothesis was made: I hypothesize that by altering the counter-ion ratio in the conductive polymer PEDOT, 0.1wt% concentration of the counter ion PSS will show improved electrical properties, stability and diffusion of the polymer into gel as compared to other concentrations and dopants. The hypothesis also consisted of two specific aims as follows: (1) The counter-ion and counter-ion concentration affect the electrochemical properties of PEDOT to act as an effective neural interface material, (2) Effect of Counter-Ion Concentration on the Ability of PEDOT to Disperse Into Agarose.

The first aim was evaluated by EIS and microscopy to determine the effect of counter-ion and counter-ion concentration in agarose and tissue. It was found that 0.1wt% PEDOT:PSS showed the lowest impedance magnitude for injected systems (Figure 4(2a) and Figure 9a). This may be an artifact due to the impedance of the tissue at high frequencies and should be corrected for in future studies. All polymerizations showed a trend toward more resistive properties as frequency increased.

When comparing the different counter-ions it was found that perchlorate showed the lowest impedance magnitude, but this may be due to the inability of the dopant to solubilize the monomer and the resultant polymerization at the electrode-air interface.
The second aim was evaluated through microscopy of polymerized agarose tubes. It was found that as the concentration of the monomer increased, the PEDOT cloud decreased. Which is important when considering drug delivery systems using conductive polymers.

II. Future Studies

Future studies include the evaluation of diffusion into agarose of the different types of dopants for neural interfacing and drug delivery applications. The effect of different concentrations should also be observed in solution without the effects of agarose or tissue to determine the actual significance in impedance between the different counter-ion ratios. Furthermore, ohmic impedance, or the impedance of the system, should be accounted for when comparing the impedance magnitude of different concentrations. The use of multiple dopants for the polymer would be particularly interesting regarding the crosslinking and stability of polymer for chronic studies.
References


[18] "Poly(3,4-ethylenedioxythiophene) (PEDOT) as a micro-neural interface material for electrostimulation".


## Appendix A: Additional Figures

<table>
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<tr>
<th>Dopant</th>
<th>Chemical Structure</th>
<th>MW (g/mol)</th>
<th>Toxicity (LD&lt;sub&gt;50&lt;/sub&gt;, mg/kg)</th>
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<sup></sup><sup>20</sup>Toxicity of sodium perchlorate.
Appendix B: Acronyms

AD – Alzheimer’s Disease
PD – Parkinson’s Disease
MS – Multiple Sclerosis
ALS - Amyotrophic Lateral Sclerosis (Lou Gherig’s Disease)
HD – Huntington’s Disease
FBR – Foreign Body Response
CP – Conducting Polymer
EDOT – 3,4-ethylenedioxythiophene
PEDOT – Poly(3,4-ethylenedioxythiophene)
PSS – poly(4-sodium styrene sulfonate)
pTS – p-toluene sulfonate
LiClO₄ – Lithium Perchlorate
PBS – Phosphate Buffered Saline
EIS – Electrochemical Impedance Spectroscopy
PtIr – Platinum-iridium
BBB – Blood Brain Barrier
ECS – Extracellular Space
WE – Working Electrode

CE – Counter Electrode

RE – Reference Electrode

CSC – Charge Storage Capacity

PFA – paraformaldehyde

OCT – Optimal Cutting Temperature