A Truly Injectable Neural Stimulation Electrode Made From an In-Body Curing Polymer/Metal Composite

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Abstract

Implanted neural stimulation and recording devices hold vast potential to treat a variety of neurological conditions, but the invasiveness, complexity, and cost of the implantation procedure greatly reduce access to an otherwise promising therapeutic approach. To address this need, we have developed a novel electrode that begins as an uncured pre-polymer that is liquid and can be injected around a neuroanatomical target to minimize surgical manipulation. Referred to as the Injectrode, the electrode conforms to complex target structures such as a foramen or plexus, and within minutes cures *in vivo* forming an electrically conductive interface. The resulting interface has a Young's Modulus of under 100 kPa, which is orders of magnitude less stiff than conventional electrodes. To validate the Injectrode, we performed detailed electrochemical and microscopy characterization of material properties and validated the feasibility of using it to electrically stimulate the nervous system in pre-clinical animal models. Electrochemical testing was performed based off of common FDA preclinical benchtop tests including scanning electron microscopy, cyclic voltammetry, electrochemical impedance spectroscopy, and voltage transient analysis. The metal particle based Injectrode within the cured silicone elastomer performed very similarly to pure wire of the same metal in all measures. Comparisons of charge storage capacity and charge injection limits of the Injectrode to mimics of the clinical LivaNova vagus nerve stimulation electrodes with the same geometric area demonstrated increased charge injection capacity, putatively resulting from the increase in fractal dimension/accessible surface area within the silicone matrix for electrochemical reaction. Acute *in vivo* testing of an Injectrode injected around the complex compound motor nerve branches of the brachial plexus proved low current stimulation induced tetanic activation of the terminal muscles was feasible. Finally, to establish proof of concept in an animal model better matching the scale of human anatomy, direct comparisons of the Injectrode performance to the clinical LivaNova lead were made in evoking heart rate changes via vagus nerve stimulation in swine. By virtue of being simpler than traditional electrode designs, less invasive, and more cost-effective, the Injectrode has the potential to increase the adoption of neuromodulation therapies for existing and new indications.

Keywords: Neuromodulation; Peripheral Nerve; Neural Interface; Injectrode; Biomaterial

1. Introduction

Electrical stimulation of the peripheral nervous system, often known as neuromodulation, Bioelectronic Medicines or Electroceuticals, is an increasingly prevalent clinical therapy. The Federal Food and Drug Administration has approved market applications for myriad new indications for Bioelectronic Medicines in recent years, including diverse conditions such as obesity, sleep apnea, migraine, opioid withdrawal symptoms, dry eye, essential tremor and hypertension. These supplement traditional market indications for Bioelectronic Medicines such as pain and overactive bladder (Figure 1).[1,2] Additional areas of research currently beginning early stage clinical testing include the use of therapeutic electrical stimulation to treat inflammation, metabolism, and endocrine disorders.[3–6] The increasing prevalence of Bioelectronic Medicines has led to a renewed interest in both developing novel devices as well as improving the mechanistic understanding of how neural interface technologies interact with the nervous system. This has resulted in numerous large-scale government funding programs such as the White House BRAIN Initiative, the NIH SPARC Program, and the DARPA HAPTIX and ElectRx Programs.[7]

Existing electrical stimulation devices designed for integrating with the human nervous system can be separated into non-invasive devices, minimally invasive hybrid strategies, and invasive devices. Non-invasive devices apply an electrical stimulation waveform through electrodes placed on the surface of the skin, which are typically intended to electrically interface with deeper neural structures (Figure 2B). Although some impressive therapeutic responses have been demonstrated using non-invasive stimulation paradigms targeted to specific nerves, the unintended stimulation of nerve and muscle fibers superficial to the deep target often lead to therapy limiting side-effects. Additionally, the electric field falls off rapidly with distance from the stimulating electrode, which limits the depth at which structures can be reliably stimulated, at least without intolerable activation of cutaneous pain fibers.[8]

Given the limitations of non-invasive stimulation strategies, implantable neural stimulation electrodes are commonly used to provide more precise activation of a nerve trunk, ganglia, nuclei or other target of interest. One of the most common implantable interfaces to stimulate the peripheral nervous system is the nerve cuff, which consist of multiple electrodes arrayed on an insulating backer that are surgically placed with the electrode contacts surrounding the epineural surface of a nerve trunk (Figure 2F). Although this approach can provide very specific target engagement, the placement of nerve cuffs requires surgical dissection down to the nerve trunk of interest through skin, muscle, smaller nerves and microvasculature. Moreover, cuff surgical placement typically requires 360-degree dissection around the nerve trunk of interest to facilitate placement of the cuff around the nerve. Additionally, stimulation leads must be tunneled to an implantable pulse generator that has a limited battery life. Multiple points of failure and the complexity of the implantation procedure increases both surgical risk and costs, and may contribute to a large amount of variability in therapeutic effectiveness. For example, a 152 patient clinical study recently compared invasive Dorsal Root Ganglion (DRG) stimulation to traditional epidural spinal cord stimulation (SCS) for intractable pain. 81.2% of the DRG patients received a greater than 50% decrease in back pain vs 55.7% with SCS, a significant difference. However, the adverse event rate related to the neural stimulator/device or the implant procedure was significantly higher in the DRG arm (36.8% to 26.4% and 46.1% to 26.3%, respectively).[9] As both DRG and SCS require a complex electrode/lead/implantable pulse generator system,

implant costs ranging from $32k to $58k and annual maintenance costs ranging from $5k to $20k also pose significant barriers to treatment.[10]

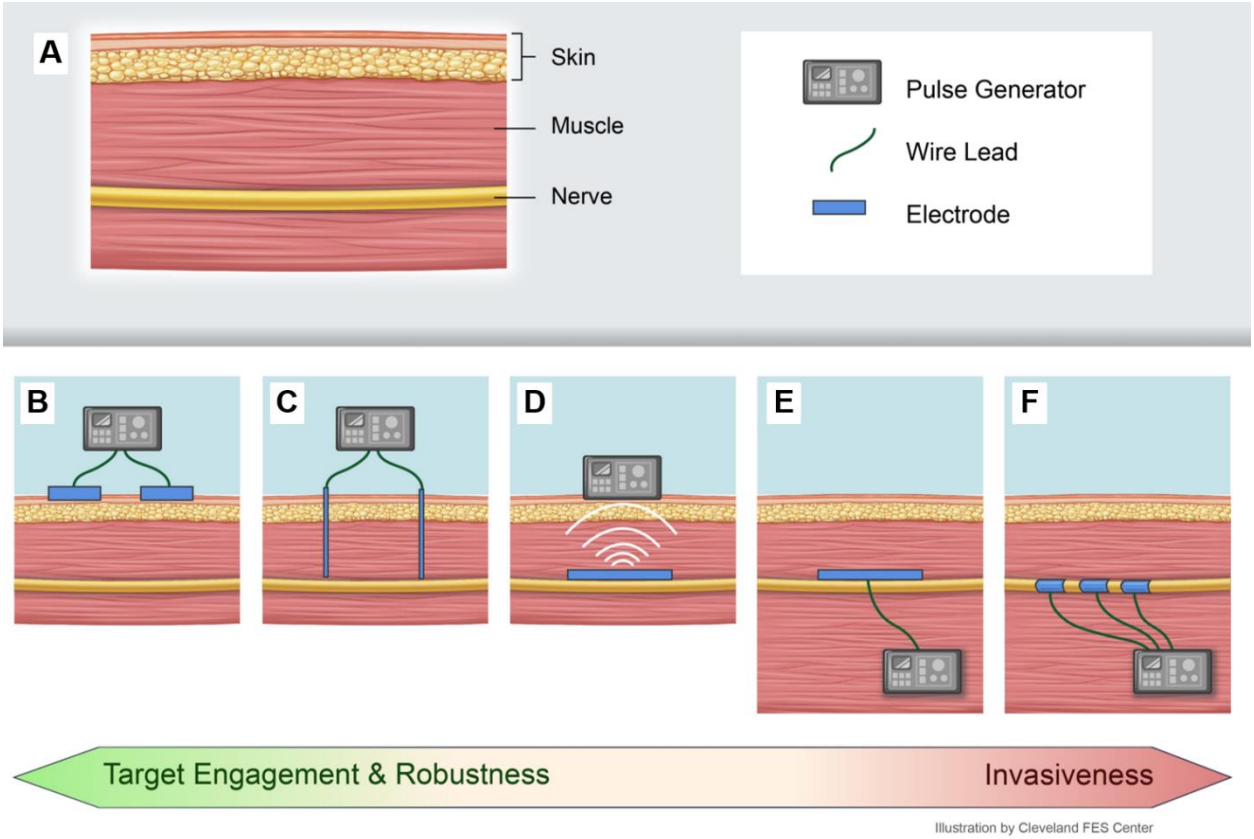

Figure 1: Peripheral nerve stimulation electrode types from least to most invasive, left-to-right. A. *simplified tissue schematic showing distinct layers of the skin muscle and nerve.* ***B****. transcutaneous electric nerve stimulation (TENS),* ***C.*** *percutaneous electric nerve stimulation (PENS),* ***D.*** *injected wireless stimulator (e.g., BION® device),* ***E****. implanted nerve stimulator (e.g. spinal cord paddle electrode),* ***F.*** *implanted cuff electrodes (e.g. vagus nerve stimulator).*

Practically speaking, stimulation device selection involves carefully balancing trade-offs between efficacy and safety – including implantation invasiveness, efficacy, robustness and the cost of the procedure. Although other stimulation and implantation strategies spanning the spectrum from non-invasive to fully implanted (Figure 2) are available, there remains an unmet need for neural interface technologies that can be implanted through a minimally invasive procedure but can maintain a robust connection with complex and difficult to surgically dissect peripheral neuroanatomy.

To meet this need, we have developed a novel electrode, which we call the 'Injectrode'. The Injectrode is a liquid pre-polymer that is injected from a syringe and cures to from a highly conforming, compliant neural electrode *in vivo.* By flowing around the target neuroanatomy, the Injectrode can conform to a variety of targets to form different neural interfaces. For instance, the specificity of an invasive cuff electrode could be mimicked by injection of the electrode into the

sheath around a nerve trunk. Alternatively, the Injectrode could be used to stimulate complex neural structures such a nerve plexus or foramen that are difficult to target with traditional cuff electrodes. Through the injection of this electrode, neural interfaces can be created using a minimally invasive surgical approach that avoids the risks of surgical complication associated with open cut-downs and extensive dissection. In this paper, we present detailed electrochemical and microscopy characterization of material properties of the Injectrode, and validate the feasibility of electrically stimulating through this *in vivo* curing composite material in pre-clinical animal models. Visual assessments were made of the surface morphology of electrodes via light microscopy and scanning electron microscopy. Cyclic voltammetry, voltage excursions, and electrochemical impedance spectroscopy were used to directly compare the electrochemical properties of the Injectrode with pure silver wire, and clinical LivaNova Platinum/Iridium electrodes. Lastly, we also present proof of concept pre-clinical experiments in small and large animal models in order to demonstrate the feasibility of this material as an *in vivo* neural interface.

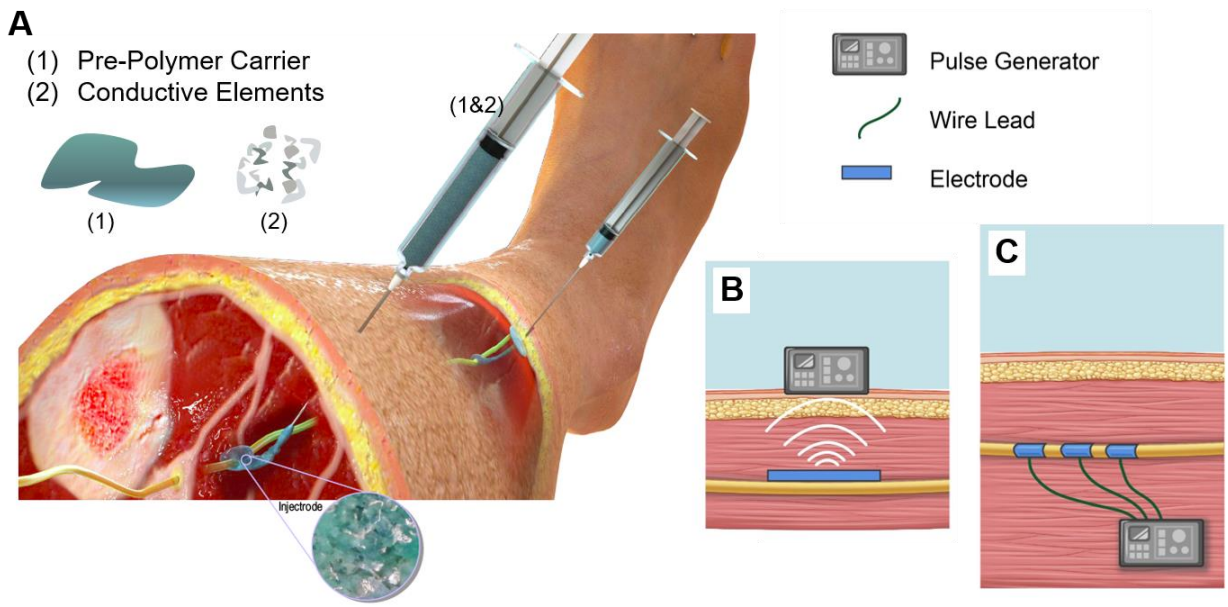

Figure 2: The Injectrode™ Concept. A. *A composite material consisting of (1) a pre-polymer carrier and (2) conductive filler elements, is injected into the body near a target nerve. The mixture cures in place to form an electrically conductive interface.* ***B.*** *wireless configuration (e.g., if connected with a RF antenna circuit),* ***C.*** *wired configuration (e.g. if directly connected to an IPG).*

2. Materials and Methods

2.1. Materials and Equipment

All general supplies, chemicals, reagents and buffers were sourced from Sigma (St. Louis, MO) and used as received. Proprietary Proprietary mixtures of two-part Pt-curing silicone elastomer and metallic silver flakes were prepared according to instructions from Neuronoff, Inc (Valencia, CA). Blend percentages are defined according to a weight/volume (w/v) nomenclature with respect to silver/silicone, where 80% w/v corresponds to 800 mg sliver flakes and 200 mg mixed silicone pre-polymer. The silver flakes (25-50 micron aggregate size) were purchased from Inframat Advanced Materials and used as received. The flakes were additionally pre-treated with the silanization agent (GLYMO) to improve their incorporation into the silicone matrix according to manufacturer recommendations.

To control geometry, for the benchtop characterization experiments, materials were mixed thoroughly and immediately transferred to cure in either a 96-well plate or a 1/16 in. inner diameter silicone tubing for incorporation into a working electrode, as showing in Figure 1. For the *in vivo* experiments, materials were mixed and immediately transferred to a syringe for injection (extrusion) around the nerve of interest.

2.2. Bulk Conductivity (Dry Bench Testing)

Electrochemical testing was performed to determine material characteristics applicable to the use of the Injectrode for neural stimulation. The conductivity of bulk material was determined as a function of w/v with respect to silver/silicone in order to optimize the electrode material so that it was fluid enough to extrude through a standard 1 cc syringe, had a baseline conductivity under 1 ohms at 1 kHz, and would completely cure when injected in surrogate tissue (thawed chicken breast) in under 5 minutes (data not shown).

In order to test the conductivity of the electrode using samples with controlled material properties and geometry, components of the Injectrode composite were combined in a 1cc syringe and mixed for 30 seconds to make the flowable pre-polymer. To control the geometry, the pre-polymer was immediately injected into individual wells of a 96-well plate with coiled silver wire contacts placed at the top and bottom of each Injectrode sample. After allowing 10 minutes for the sample to cure, impedance of each sample was measured using 1kHz sinusoid from a standard LCR meter (DE-5000, DER EE Electrical Instrument).

2.3. Electrochemical Characterization

Benchtop electrical characterization generally followed the techniques described in Stuart Cogan's 2008 review of neural stimulation and recording electrodes.[23] To achieve consistent electrochemical testing, working electrodes with tightly controlled geometric surface area were fabricated. A pre-polymer that was 80% (w/v) silver particles was mixed as previously described and immediately injected into a 1/16" inner diameter (ID) tube (labeled Inner Tubing in Figure 4), which was then cut into 2 cm segments. While curing, a 0.25 mm diameter silver wire was embedded approximately 1 cm deep into each Injectrode sample. After curing, the inner tubing piece was placed into a second piece of tubing (labeled Outer Tubing in Figure 4) chosen with an ID slightly larger than the outer diameter (OD) of the inner tubing. The electrode was then back-filled with silicone, which served to provide mechanical stability and insulate the silver wire. This

yielded an electrode with a 1/16” diameter circular disc Injectrode material exposed at one end, which was used as a working electrode for electrochemical characterization experiments measuring cyclic voltammetry, electrochemical impedance spectroscopy, and voltage transients. A schematic of the fabricated working electrode is shown in Figure 4A and photographs showing both a working electrode sample and magnified cross-section of the electrode surface are presented in figure 4B.

For comparison of Injectrode samples to a pure silver electrode, silver working electrodes were fabricated by removing, under a microscope, insulation from 0.01” silver wire (A-M Systems, Carlsborg, WA) such that the total exposed surface area matched the geometric surface area of the Injectrode. In order to compare properties of the Injectrode to a clinically relevant electrode, platinum working electrodes were fabricated from platinum foil such that the exposed surface area matched that of a LivaNova PerenniaFLEX® stimulation electrode.

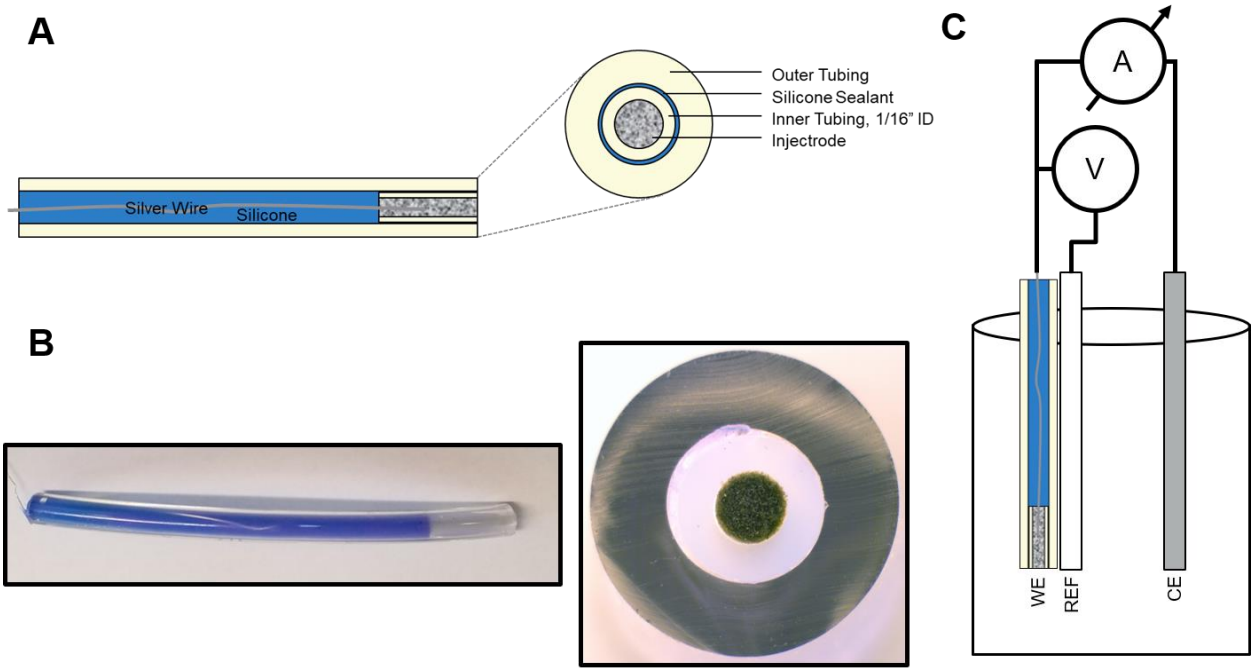

Figure 3: Working electrode fabrication schematic. A. *A short segment of Injectrode material was filled into a 1/16” ID tubing and an uninsulated silver wire was inserted into one end. A larger ID tubing was placed over the smaller tubing to form an insulative outer sheath and filled with silicone. The constructed working electrode provides a consistent 1/16” diameter disk of Injectrode exposed at one end with a silver wire exposed at the other to provide a connection for performing electrochemical experiments* ***B.*** *(left) An image of a completed Injectrode sample fabricated into a working electrode. (right) Cross-section of working electrode tip showing the Injectrode sample with a controlled geometric surface area.* ***C.*** *Diagram of a three electrode electrochemical setup used to perform electrochemical testing.*

Cyclic voltammetry and electrochemical impedance spectroscopy were measured in 0.01 M phosphate buffered saline (PBS) (NaCl 0.138 M; KCl - 0.0027 M; pH 7.4; Sigma, St. Louis, MO) using a three electrode cell consisting of a previously described Injectrode working electrode, a platinum sheet counter electrode (1 cm^2 surface area; Metraohm, Herisau, Switzerland), and a single junction silver/silver chloride (Ag/AgCl) in 3M KCl reference electrode (BASi, West Lafayette, IN). Measurements were performed with an Autolab PGSTAT128N potentiostat (Metraohm).

Cyclic voltammetry was performed with a staircase sweep at 50 mV/s with a step size of 2.44 mV, 15 voltammograms were performed on each Injectrode sample and the final three voltammograms on each sample were averaged to obtain a single measurement. A new working electrode was used for each measurement to minimize effects from previous measurements on any given sample. In order to compare the electrochemical characteristics of the Injectrode to that of a silver electrode with the same surface area fabricated as previously described an extended voltammograms from -1.9 to 3.0V were applied based on the water window of silver in PBS. In order to compare properties of the Injectrode to that of a standard platinum stimulating electrode matching the dimensions of a LivaNova stimulation lead, cyclic voltammograms -0.62 to 0.9 V, a common range for platinum, were applied. From these voltammograms the cathodal charge storage capacity (CSC) was calculated as the time integral of the cathodic current.

To characterize the impedance properties of the Injectrode and compare it to silver wire and platinum stimulation electrodes, electrochemical impedance spectroscopy (EIS) was performed with the same electrodes and electrochemical cell as was used for cyclic voltammetry. Electrochemical impedance spectroscopy was performed following the application of 20 voltammograms from -0.62 to 0.9V. Impedance spectroscopy was performed with 25mV sinusoidal waveforms applied with equal spacing on a logarithmic scale from 0.1 to 100 MHz.

Lastly, voltage transient (VT) measurements were taken, once again, following the application of 20 voltammograms from -0.62 to 0.9V. A cathodic-leading charge-balanced biphasic waveform was used for the VT measurements with pulsewidths of 500 µs, and a 10 µs interpulse delay. Pulses were applied at 50 Hz and VT measurements were made following at least 1000 pulses in order to allow for stabilization. A Keithley 6221 current source (Tektronics, Beaverton, OR) was used for the application of pulse trains used for VTs. Using a Tektronics TBS1154 Oscilloscope (Tektronics, Beaverton, OR), VTs were recorded with the application of increasing amplitude pulses until the maximum cathodic polarization (E_{mc}) was greater than 0.6V. To minimize the effects of noise, VT measurements were recorded as the average of 16 pulses using built in averaging on the oscilloscope. In order to compare properties of the Injectrode to a clinical electrode, a LivaNova PerenniaFLEX® stimulation electrode was used instead of the surface area matched platinum electrode used for cyclic voltammetry and electrochemical impedance spectroscopy.

2.4. Electrode Imaging

Light and electron microscopy of the electrode surface were performed on an unstimulated Injectrode sample from a working electrode that was fabricated as described in the previous section. In preparation for imaging, a cross-sectional slice (Figure 4B) of an Injectrode sample that had not undergone electrochemical testing or stimulation was cut with a scalpel.

Light microscopy was performed with an AmScope ZM-4TW3 stereo microscope, equipped with an 18 MP camera (AmScope, Irvine, CA). The slice was then platinum coated in preparation for SEM. SEM was performed using a Zeiss LEO 1530 (Zeiss International, Oberkochen, Germany).

2.5. Mechanical Testing

ASTM International has specified procedures for evaluating mechanical properties of thermoset plastics under Active Standard D412-16. Specified forms include flat specimens with uniform cross-sectional area, and dumbbell shaped specimens. Molds were designed as closely as possible adhering to the guidelines for creating flat wishbone specimens in SolidWorks. The molds were then cut from acrylic sheets using a laser cutter at ThinkBox (Case Western Reserve University). The mechanical properties of the cured electrodes were then tested using a pneumatically driven universal testing machine (Enduratec) located in the CWRU Department of Materials Science & Engineering Advanced Manufacturing and Mechanical Reliability Center (AMMRC). Specimens were placed into the grips of the testing machine pulled under tension at a rate of 0.5 mm/s. Grip spacing was set to 2 cm, and pulled to a final extension of 2.8 cm or failure.

2.6. Acute Rat Brachial Plexus Stimulation

All animal experiments were approved by the Mayo Clinic Institutional Animal Care and Use Committee (Rochester, MN). Rats were anesthetized with isoflurane, using a 5% for induction and 1-2% for maintenance over the duration of the experiment. The compound motor nerve branches of the rat brachial plexus were exposed and freed from surrounding tissues via careful dissection through the pectoralis muscles. Components of the Injectrode composite were combined in a syringe and mixed for 30 seconds to make the flowable pre-polymer, as previously described. The pre-polymer was injected within 1-2 minutes, to create two circumferential ‘cuff’ electrodes in a bipolar configuration with 5 mm spacing, around the exposed rat brachial plexus. For the purposes of this proof of concept experiment testing the Injectrode in an open surgical site, Kwik-Cast (World Precision Instruments, Sarasota, FL) was used to insulate between and around the two electrodes. Silver wires were inserted into the composite during curing to make direct wired connections to the cuffs.

A biphasic charge balanced waveform at either 30 or 300 Hz (200 µs pulse width, 5mA amplitude) was applied using Master-8 stimulator (A.M.P.I., Jerusalem, Isreal) with Iso-Flex stimulus isolators (A.M.P.I., Jerusalem, Isreal). Effect of stimulation was observed visually as large muscle contractions of the hind limb. Approximate joint angles were calculated using post-hoc video analysis. In brief, Still images were captured from the video every 5 frames (30 fps), and analyzed in ImageJ. Two lines were drawn through the joint. The angle was measured using ImageJ’s built-in toolbox.

2.7. Acute Swine Vagus Nerve Stimulation

Pigs (weight 35-40 kg range) were anesthetized using Telazol/Zylazine for induction followed by maintenance with 1-2% isoflurane for the duration of the experiment. The vagus nerve was carefully dissected free from surrounding tissue and a commercially available bipolar cuff (LivaNova) was placed on the nerve approximately 0.5 to 1.0 cm inferior to the nodose ganglion and 1.0 to 1.5 cm from the carotid bifurication. The cuffs were placed on the ventromedial aspect of the vagus nerve, in a similar fashion to those placed clinically.

A stimulation current-dose-titration curve was generated, with a biphasic charge balanced waveform at 30 Hz (200 µs cathodic pulse width), ranging from 0-5mA. Heart rate was monitored with a pulse oximeter and recorded.

To compare results obtained during stimulation with the Injectrode to those obtained using a clinical LivaNova electrodes, cuff-like electrodes were fabricated using Injectrode material extruded onto a stainless-steel mesh with an insulated backing. The same stimulation current-dose-titration curve was generated and compared to the results obtained while stimulating with the LivaNova electrode.

3. Results and Discussion

3.1. Bulk Conductivity (Dry Bench Testing)

Initial bench testing of electrode impedance at 1 kHz was performed on dry samples using a LCR meter (Figure A,B), and demonstrated that the composite material is low impedance (<10 Ω), above a percolation threshold of approximately 65% w/v mix with respect to silver content. In contrast, samples with silver content below the percolation threshold maintained a high impedance greater than 10 MΩ (Figure 6C). Injectrodes are electrically conductive immediately following placement; curing and cure times of 90-120 seconds were observed with the formulations tested. However, the impedance measurements presented here were all performed after allowing 10 minutes for the Injectrode samples to fully cure. Based on these results a 80% w/v with respect to silver content was selected and used for all of the electrochemical and *in vivo* testing presented in this manuscript.

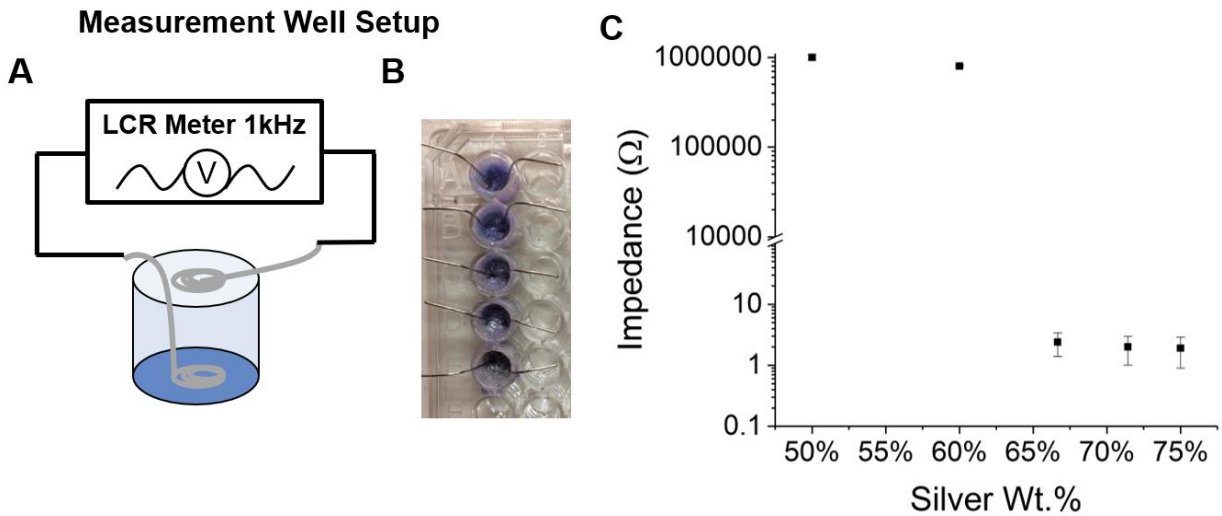

Figure 5: Conductivity Versus Filler Weight Percent. *Composite Injectrode materials were prepared using various filler wt.% from 50-75% of total composition.* ***A.*** *After mixing, each material was extruded into a 96-well plate to control geometry and size. Before extrusion, a silver wire contact was placed in the bottom of each well to serve as one of the impedance meter contacts. A second silver wire contact was placed on top of the material in each well. After curing, impedance was measured using an LCR meter in ambient air conditions with a 1 kHz sinusoidal waveform.* ***B.*** *A photograph of the sample setup.* ***C.*** *A steep inflection point around 65 wt. % is suggestive of achieving percolation (a continuous network) of silver particles in the composite.*

Percolation is a well-studied phenomenon that describes the material percentage required to forms an interconnected network throughout the composite, i.e. metal-to-metal network.[24, 25] The percolation threshold is dependent on the volume of the particulate filler as well as the aspect ratio of the individual particles.[24, 25] For simplicity of measurement during fabrication, weight ratios were the easiest to ascertain and control, but the use of weight ratios for controlling of impedance of the Injectrode is dependent on the use of consistently sized particles with similar distributions and dispersions. While these initial benchtop impedance measurements provided the ability to rapidly iterate through different formulations, they do not adequately represent the electrode performance under physiological use conditions, e.g. hydrated in a saline environment, during the application of electrical stimulation, etc.

3.2. Electrode Imaging

Light microscopy and electron microscopy were performed in order to assess the surface properties of the material. For both types of imaging a thin slice of material was cut from the surface of an Injectrode working electrode sample that had not undergone any electrochemical testing or stimulation. Imaging revealed that the silver particles were well distributed throughout the silicone matrix (Figure 6). Electron microscopy showed surface porosity (Figure 6C,D) as well as a complex arrangement of silver particles within in the silicone matrix.

The porosity of the silicone matrix may act to increase electrolyte permeability, which could enable electrode/electrolyte interactions with particles deeper within the silicone matrix. This in turn would increase the fractal dimension of the material and thus the effective electrochemical surface area. For these reasons, the porosity of the material may be important to the functional capabilities of the Injectrode as a stimulation electrode particularly with respect to increasing the effective surface area available for charge injection. Thus, modifying the porosity of the cured Injectrode is one factor that could potentially be controlled in order to improving the stimulation characteristics of the electrode.

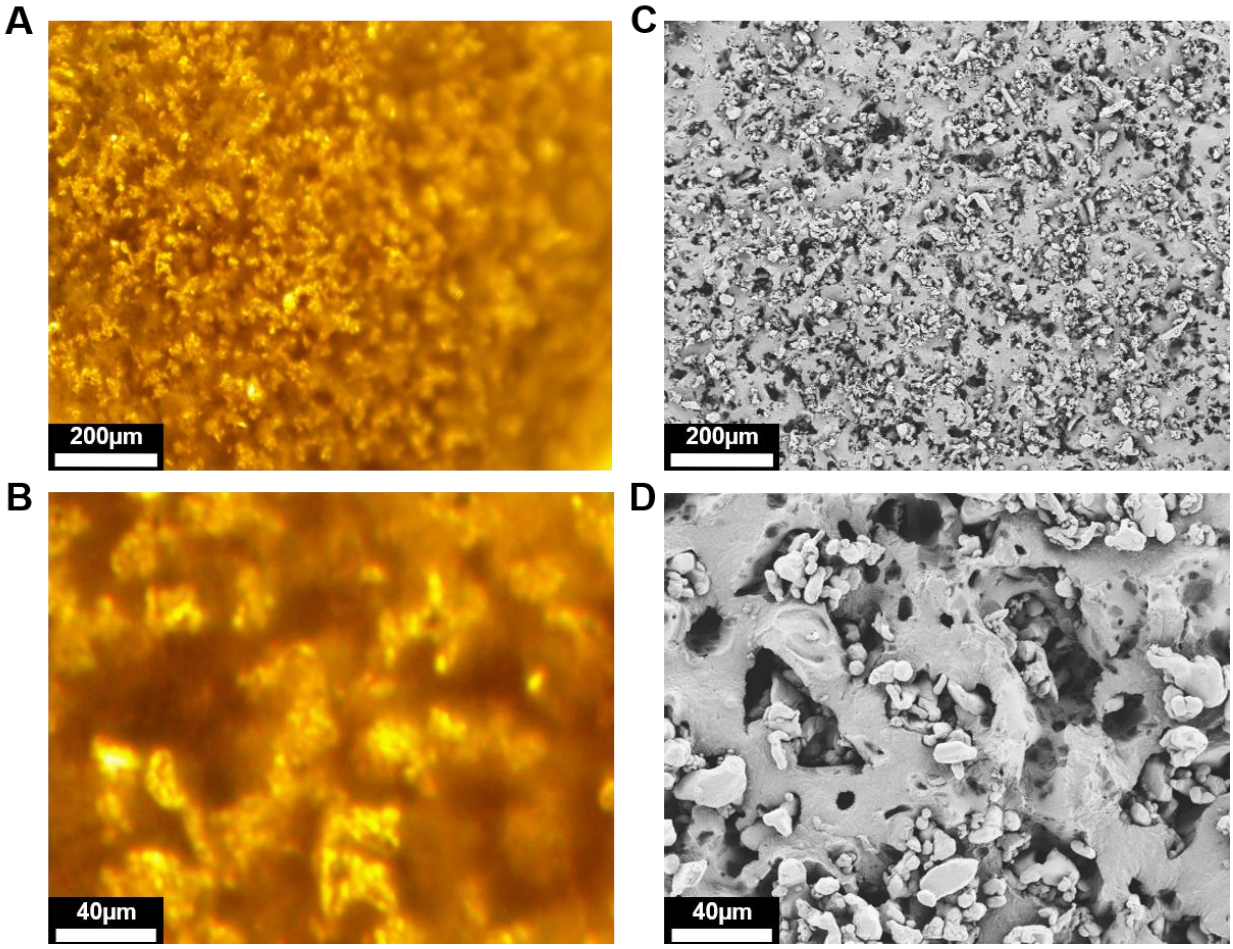

Figure 6: Light microscopy and SEM of the surface of an Injectrode. A-B. *Light microscopy of the Injectrode surface showing distribution of silver particles throughout the sample.* ***C-D.*** *Scanning electron microscopy (SEM) at comparable magnification showing sample topography and revealing porosity of the polymer matrix.*

3.3. Electrochemical Characterization: Cyclic Voltammetry

Cyclic voltammetry is a classical electrochemical method for the characterization of stimulation electrodes. It provides information regarding the electrode interface under electrical load, the electrochemical conversion of species within the solution, and on transient changes due to oxidation or other processes at the electrode surface.[11]

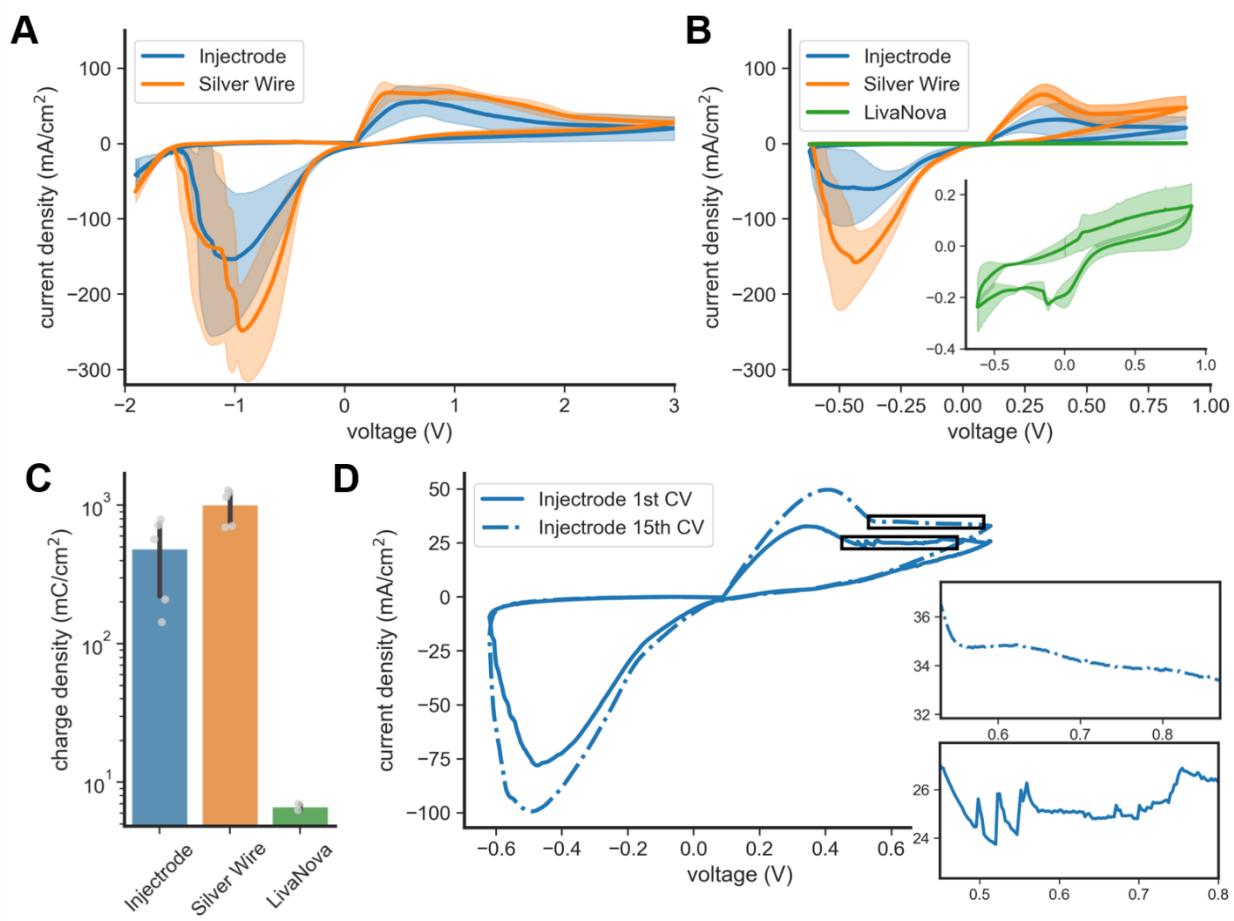

Figure 7: Cyclic voltammetry comparison. A. *Mean cyclic voltammograms of five samples each of Injectrode and silver wire electrodes with matched geometric surface area. Scans were performed at 50 mV/s and over a range from -1.9V to 3.0V.* ***B.*** *Mean cyclic voltammograms of five samples each of Injectrode and silver wire electrodes as well as two contacts of a LivaNova PerenniaFLEX® lead. Voltammograms were scanned from -0.62 to 0.9V at a rate of 50mV/s. Inset show an expanded view of the voltammogram for the LivaNova electrode.* ***C.*** *Cathodic charge storage capacity (CSC) calculated from the -0.62 to 0.9 V voltammograms for each set of electrodes. LivaNova and silver wire electrodes exhibit similar CSCs.* ***D.*** *The 2nd and 15th voltammogram from one representative Injectrode sample showing spiking behavior in early voltammetry sweeps that goes away with the continued application of cyclic voltammograms. Insets show a zoomed view of this phenomenon. Shaded regions in panels A and B represent ± 1 standard deviation. Error bars in panel C also represent standard deviation.*

For assessment of Pt/Ir electrodes it is common practice to perform slow scan (50 mV/s) cyclic voltammetry sweeps in PBS over a voltage range known as the water window; the window between the voltages at which evolution of hydrogen and oxygen occur. Commonly used values for assessment of Pt and Pt/Ir electrodes include -0.62 to 0.9V[12] and -0.6 to 0.8V[11]. These values are a function of the electrode material and the solution within which testing is conducted. For assessment in the context of new materials for neural stimulation, it is important to understand the limits of the water window in physiologically relevant solution. Therefore, we performed an cyclic voltammetry sweep for silver wire and the Injectrode samples with an expanded range from -2V and 3 Volts. It is important to note that, silver particles were used as the conductive filler for the Injectrode due to its high conductivity and low cost for iterating through different Injectrode fabrication and testing methods to establish this early proof of concept. Despite these benefits, silver is not an acceptable choice for the creation of a chronic neural interface as silver and silver chloride have well understood toxic effects[13]. Although testing performed with silver electrodes was sufficient for validating the Injectrode concept, future development will focus on the use of stainless steel, gold, or platinum filler particles that have been well validated in chronic neural interfaces.[12,14] We compared the Injectrode samples to a silver wire with the same geometric surface area to assess equivalency of electrochemical behavior over the expanded voltammogram but did not conduct a detailed study of the electrochemical behavior over this range.

As has been described elsewhere, in PBS, pure silver wire exhibited a large oxidation peak near 0V that has been attributed to the formation of silver chloride (AgCl)[15], while the broadness of this peak and the observation of multiple humps may indicate the formation of other silver oxides[16–18]. Additionally, the reversal of the silver chloride reaction was observed on the anodic side of the CV sweep (see Figure 7A). Putative hydrogen evolution was observed near the anodic limit of the voltammogram (at approximately -1.7V) and visually confirmed through the formation of microbubbles at the surface of the exposed silver wires and Injectrode samples. Interestingly, no clear oxygen evolution was observed even with the upper limit of the voltammogram sweep extended to 3.0V. This phenomenon was not explored further. One of the primary purposes of the electrochemical characterization experiments was to show that the Injectrode behaves similarly to the base metal, in this case silver. This was clearly true via visual inspection, although the Injectrode exhibited slightly decrease peak heights compared to a silver wire electrode with the same geometric surface area, peak shapes and locations for the Injectrode and base metal were similar in shape and location. This was the case for both the truncated sweep within the water window for platinum (Figure 7B) and the expanded sweeps for performed on the silver wire and Injectrode (Figure 7A).

Despite the expanded water window of Ag, a -0.62 to 0.9V voltammogram normally used for assessment of platinum was used instead of the expanded sweep for comparing the Injectrode voltammogram and charge storage capacity to that of platinum stimulation electrodes to provide a more fair comparison. The Injectrode and silver wire electrode both exhibited much larger CSC compared to a platinum electrode. This is largely due to increased charge injection through faradaic mechanisms. However, in light of the decrease in exposed silver available for faradaic reactions when looking at a two-dimensional cross-section of the Injectrode, as can be seen in the SEM imaging shown in Figure 6C and D, the similarity between the CSC of the silver wire and Injectrode samples was unexpected. This suggests that the Injectrode material has greater available three-dimensional surface area due to the previously discussed porosity and permeability of the matrix to the electrolyte to achieve greater SCS. This effect is similar to the

increases in CSC that have been observed with electrode coatings such as sputtering iridium oxide films (SIROF) and activated iridium oxide films AIROF on platinum substrates[11,19–22].

An interesting epiphenomenon was observed that was inconsistent between silver wire electrodes and the Injectrode samples. In extreme voltages of both the anodic and cathodic sweeps of the voltammogram, sharp peaks were initially observed during early CV sweeps (Figure 7D). These peaks are shown in detail in the lower inset of figure 7D and are inconsistent with traditional faradaic reaction mechanisms that lead to 'humps' in the CV, such as those described for silver/silver chloride. Additionally, these spikes appeared at inconsistent voltages on subsequent CVs, and as additional CVs were ran on the Injectrode samples the frequency of these spikes decreased. An example of this is shown in Figure 7D, where extensive spikes are shown on the 1st complete CV scan but are not observed on the 15th scan. These observations suggest the spikes are not caused by reactions occurring at specific voltages but instead may indicate changes in the exposed surface of the Injectrode. We speculate that these spikes may be indicative of dissolution of base silver particles less well-bound within the silicone matrix, or of the exposure of new metal particles available for faradaic reactions through the opening of new pores in the polymer matrix. However, as the overall area under the CV tended to increase over initial sweeps and then settle into a consistent value, this would suggest the loss of particles or changes in exposed surface area would not negatively impact electrical characteristics of the Injectrode, from a neuromodulation perspective. Loss of metal particles from the surface of the Injectrode could be minimized, at least to some extent, through future refinement of the particle sizes, polymer matrix, mixing procedure, or other factors. However, it is worth noting that large chunks of platinum iridium have been reported in post-mortem human tissue from chronically stimulated cochlear implants and that tissue damage is driven by the formation of specific Pt salts during stimulation that lead to local toxicity[23], as opposed to larger chunks of unreacted Pt or Pt/Ir flaking off[24–28]. Whether loss of a small portion of conductive particles during the application of stimulation is an issue for strategies that leverage conductive particles to dope traditionally insulative matrices, such as the Injectrode, should be explored in future studies.

3.4. Electrochemical Characterization: Voltage Excursions

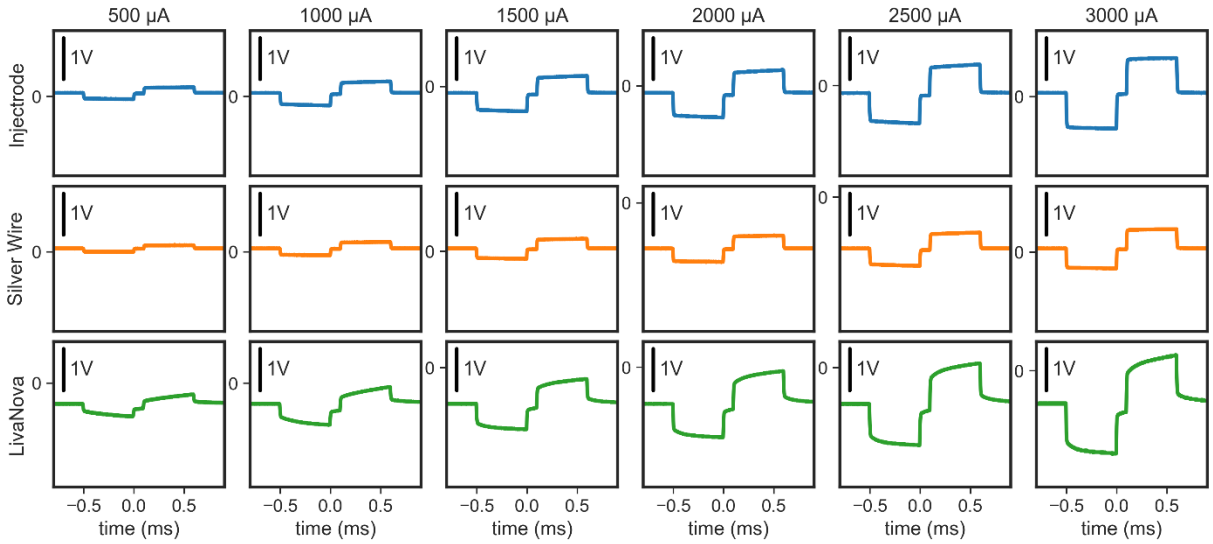

Figure 8: Voltage Transients. *Voltage transients were performed in phosphate buffered saline using a 500µs pulse width and allowing at least 1000 pulses for the response to stabilize.* ***A.*** *Voltage transients performed at 500 through 3000 uA on one Injectrode sample that had previously undergone 20 cyclic voltammogram sweeps from -0.62 to 0.9V.* ***B.*** *The sample measurements shown in panel A but performed with a silver wire working electrode with geometric surface area matched to the Injectrode sample.* ***C.*** *Voltage transients performed with a LivaNova PerenniaFLEX® stimulation electrode.*

Although slow cyclic voltammetry provides unique information about electrochemical reactions that occur at the electrode/electrolyte interface, neuromodulation therapies typically employ charge balanced square wave current controlled pulses ranging from 30 microseconds to 1000 microseconds in duration. For that reason, voltage transients (or voltage excursions) are traditionally used to measure the polarization on the electrode itself during the application of cathodic leading, constant current, charged balanced biphasic pulses at a pulse width within normal clinical neuromodulation ranges[1]. For Pt/Ir electrodes, the current applied is increased until the cathodic polarization on the electrode itself approaches the cathodic limit for the evolution of hydrogen on a Pt/Ir electrode, and this current is adjusted for the geometric area of the electrode to determine the safe charge-injection limit. It is worth noting that for materials that differ from Pt or Pt/Ir - especially materials through which there may be reversible safe electrochemical reactions induced at one level of polarization, and another unsafe electrochemical reaction occurring at a higher level of polarization – the use of voltage excursions to determine unsafe level of polarization needs to be reevaluated on an electrode material by electrode material basis.

Given the extended CVs performed to determine the water window for silver indicated the anodic and cathodic limits before the hydrolysis of water were outside the ranges of traditional Pt electrodes, and the use of silver particles within the composite material of the Injectrode is known to be an issue for direct translation, we decided to perform a conservative comparison of acceptable charge injection limits. This was done by intentionally limiting the acceptable polarization on the pure Ag wire or Injectrode to the established cathodic limit for Pt or Pt/Ir electrodes. By limiting the polarization of the electrode to the safe limits for Pt or Pt/Ir before hydrogen evolution we did not find the maximum charge injection limits of the Injectrode sample.; however, this approach is sufficient to show the Injectrode concept can achieve neuromodulation relevant charge injection limits and is not inherently limited by the properties of the composite material. Given the Injectrode silicone matrix is permeable to water over time, the increased access to interior fractal dimensions during slow scan voltammetry may lead to a large CSC calculation that is not relevant for standard neuromodulation pulses. As such, voltage transient measurements provide an additional method to assess the electrochemical behavior during more stereotypical short neuromodulation pulses. For this reason, it will be important to repeat to determine safe charge injection limits once a more clinically accepted non-faradaic conductor is selected.

As shown in Figure 4a, the voltage transient on the Pt/Ir Clinical LivaNova lead first consists of a very sharp negative voltage deflection at the initiation of the cathodic current pulse, resulting from the voltage generated from the movement of the current through the resistance of the ionic

[1] Cathodic leading pulses are traditionally used for voltage excursion testes, as cathodic leading biphasic pulses require lower thresholds for activation when an electrode is placed directly on a nerve fiber. When there is any separation between the electrode and the fibers, or a group of fibers are being stimulated that cover a span of distances from the electrode, there is less advantage to the use of cathodic first pulsing strategies.

solution. There is then a slow, consistent change in voltage during the remainder of the cathodic current pulse, generated by the polarization of primarily capacitive Pt/Ir electrode. Charge density limits before reaching -0.6 Volts of electrode polarization were between 50 and 150 microCoulombs/cm^2, consistent with the known charge density limits for Pt electrodes (Figure 4C). In comparison to the LivaNova leads, there is almost no polarization of the pure silver wire electrodes or the Injectrodes during the application of a current pulse adjusted to match the same applied current density (See Figure 4A-B). Overall, Injectrodes and Silver wires behaved similarly during the applications of voltage transients, which is another indicator that the Injectrode will behave similarly to metal electrodes made from the same material as the conductive filler in the electrode. Small differences, between electrodes, in the initial voltage caused by the resistance of the solution are expected, as the two electrode types have slightly different geometric areas. The ionic resistance is driven primarily by the ionic resistance at the cross sectional area of the electrode/electrolyte interface; further away from this interface ionic current flow is not limited to the cross sectional area of the electrode/electrolyte interface, and take advantage of the much greater volume for ionic current flow in the bulk solution.

3.5. Electrochemical Characterization: Impedance Spectroscopy

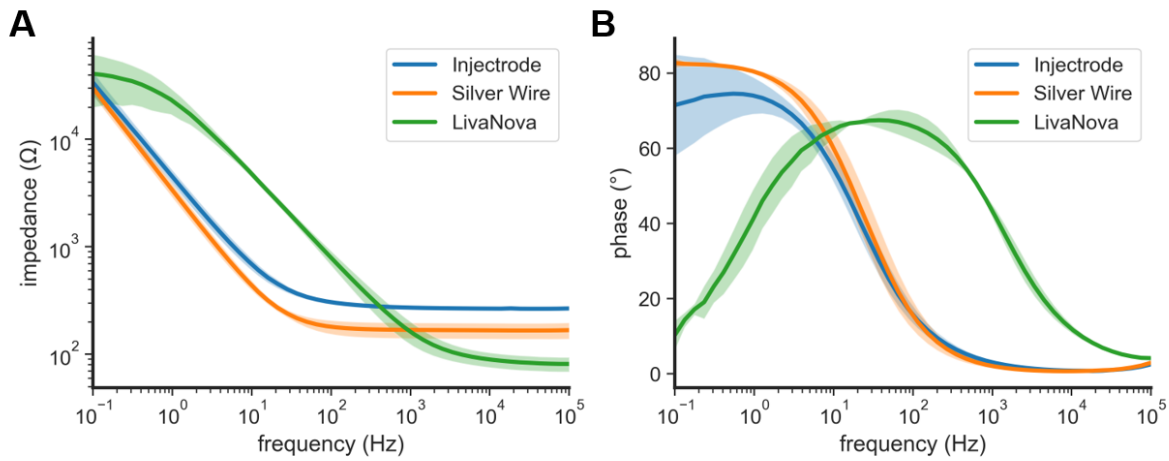

Figure 9: Electrochemical impedance spectroscopy comparison. *Electrochemical impedance spectroscopy of five samples each of Injectrode and silver wire electrodes with matching geometric surface area as well as two contacts of a LivaNova PerenniaFLEX® lead.* ***A.*** *Mean impedance of each set of electrodes as a function of frequency.* ***B.*** *Mean phase of each set of electrodes as a function of frequency. Impedance and phase of Injectrode samples and silver wire show similar behavior across frequencies. Shaded regions represent ± 1 standard deviation.*

In addition to providing a relative measure of impedance at different frequencies for different electrode materials, electrochemical impedance spectroscopy (EIS) provides additional information about the balance of resistive vs capacitive effects dominating current flow. Figure 5a is an EIS sweep between 1 Hz and 50KHz for the Pt LivaNova lead. The Pt electrode EIS results can be explained using a simplified model assuming the Pt electrode/electrolyte interfaces acts as resistor and capacitor in parallel. This interface in turn is in series with the ionic resistance of the solution, and the impedance of the large Pt foil counter electrode is negligible. At very high frequencies in the 10-50kHz range, the capacitive element of the electrode/electrolyte interface is very low impedance with respect to both the resistive element of the electrode/electrolyte interface and the ionic resistance of the PBS solution. Consequently, the ionic resistance of the

solution dominates the overall measured impedance as it is in series with the electrode, and the phase angle measured is 0 degrees indicating of current flow across a resistor. As the applied frequency decreases until another transition point between 10 and 100 Hz, the impedance of the capacitive component of the electrode/electrolyte interface increases, and the phase angle increases towards purely capacitive current flow (90 degrees). As the applied frequency goes below 10 Hz the resistance component of the electrode/electrolyte interface becomes dominant with respect to both the impedance of the parallel capacitive component and the solution resistance, and the overall measured impedance begins to dramatically increase with the phase angle trending back towards purely resistive values (0 degrees).

For a pure silver wire the overall impedance at low frequencies is less than the Pt electrode, and the phase angle stays much closer to zero degrees above 100 Hz indicating current flow through a resistor (Figure 5b). This result is not surprising, as the silver wire has a much more facile mechanism for faradaic (resistive) charge transfer through the formation of AgCl than non-faradaic charge transfer (capacitive). The EIS curves for the Injectrode are very similar to those of a pure Ag electrode. The overall Injectrode impedance is slight higher than the pure Ag wire at high frequencies, and the impedance becomes almost identical to Ag wire at low frequencies. This may suggest that more of the fractal dimensions of the silver particles are accessible to ions in the electrolyte solution through the silicone matrix at low frequencies. This low frequency behavior is a known phenomenon for conductive polymer coating strategies intended to increase the effective fractal dimensions of a stimulating electrode, decreasing pore resistance by providing more time for the ions in solution to permeate the inner recesses of the conductive polymer matrix during each sinusoidal pulse[19–21]. However, given the complex nature of the Injectrode/electrolyte interface caution should be observed in overinterpreting these results.

3.6. Mechanical Testing

The Injectrode was capable of undergoing large reversible deformations, up to 140% strain (Figure 10). As a point of comparison, the ulnar nerve is thought to undergo one of the largest deformations of nerves in the body and is only estimated to stretch by ~29% strain under normal elbow flexion.[29] The Young's Modulus was estimated from the slope of the elastic region in Figure 10B and found to be 65 kPa. This is orders of magnitude less stiff than other materials currently utilized in neural interfaces, e.g., steel (~200 GPa), gold (74 GPa), polyimide (2.5 GPa), and PTFE (400 MPa).[30]

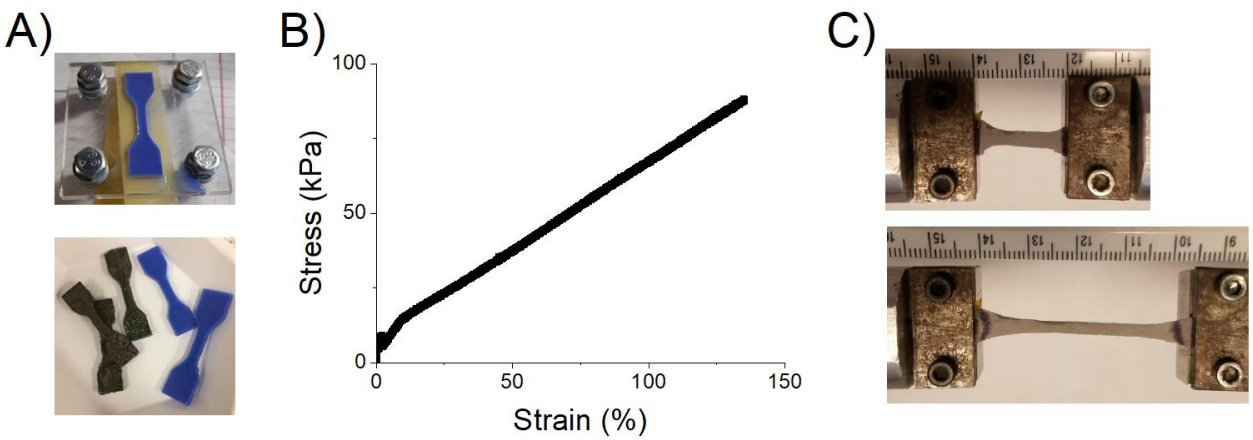

Figure 10: Tensile mechanical testing. A. *Wishbone shaped samples of Injectrode material were prepared in acrylic molds, modeled after ASTM D412-16, standardized testing of vulcanized rubber and other elastomeric materials.* ***B.*** *The elastic region of an Injectrode under tensile testing shown by a representative stress-strain curve.* ***C.*** *Photographs of the Injectrode sample during testing, showing that the material is capable of elastically stretching to over 140% strain – more than double original length – before plastic deformation occurred.*

3.7. Surgical Delivery Proof of Concept

For proof of concept and visualization purposes, we demonstrated the ability to place Injectrodes with an open-cut down approach in a swine cadaver. The materials were easily extruded from 18 gauge needles affixed to syringes and formed cohesive and flexible structures around the nerves (Figure 11A). Importantly, the materials were capable of flowing around complex branched structures and conformed to the anatomy. The materials could also be injected into enclosed areas such as the tissue 'sheath' overlying the neurovascular bundle (Figure 11B). While these procedures were performed with an open incision, the modality could be adapted to a minimally invasive approach mimicking similar endoscopic procedures performed today.

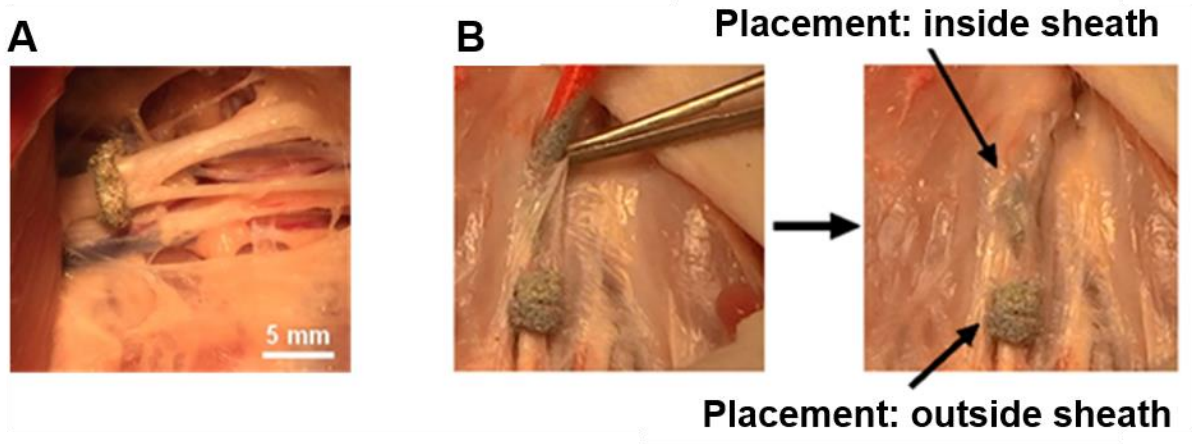

Figure 11: Delivery to Multiple Complex Nerve Anatomies in Swine. *Injectrodes were used to stimulate and block nerves in a rat (N=5) and a swine (N=2) model following extensive cadaver testing to optimize delivery and easy handling under surgical-OR conditions.* ***A.*** *Delivered by syringe, nerve cuff diameters of 1 to 3 mm were achieved around peripheral nerves in a swine model. In addition to encasing a single nerve with an injectable cuff, several nerves running in parallel - either in a bundle or at a neural plexus - were encapsulated and stimulated with a wire that was embedded within the Injectrode cuff.* ***B.*** *Furthermore, nerve bundles were encased by injecting the Injectrode into a nerve sheath commonly surrounding the nerve(s) and then gently manipulating (massaging) the nerve sheath, thereby distributing the Injectrode inside the sheath that functioned as a mold. Injectrodes were placed around nerves on the inside and on the outside of the nerve sheath in swine model.*

3.8. Electrical Stimulation of Compound Motor Nerves (Brachial Plexus)

Injectrode cuffs were placed 360-degrees around the brachial plexus in a rat model, just distal to the location where the nerve visibly branched in to the median, ulnar, and radial segments. A silver wire was embedded into the Injectrode cuff prior to curing and used to connect to the signal generator. A nerve recruitment curve was collected and supramaximal recruitment was determined to be beyond 2mA of current amplitude. To ensure a stable system during tetanic stimulation experiments, the minimum of 2x supramaximal current amplitude was used, in this case 5mA pulses of 200 us pulse width. Complete tetanic muscle contractions resulted from 30 Hz stimulation using a charge balanced biphasic waveform (200 µs pulse width, 5 mA supramaximal amplitude). The simulation effect was quantified by direct measurement of joint angles in captured video.

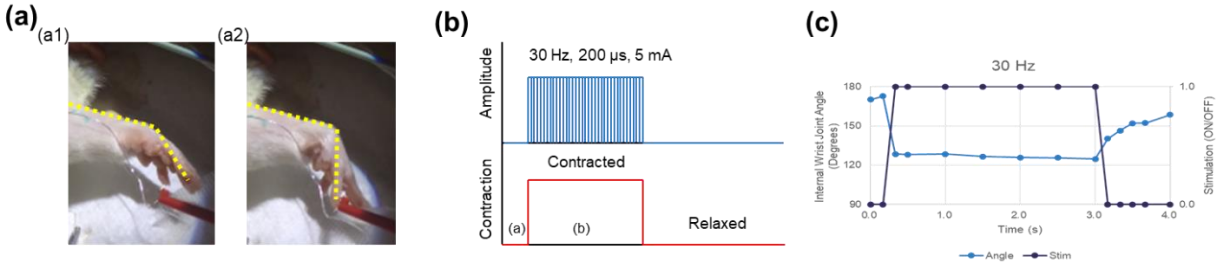

Figure 11: Acute Tetanic Stimulation Rat Brachial Plexus. *Injectrodes were placed in a bipolar arrangement on the left brachial plexus of a rat. Stimulation parameters were established to produce either*

(a) tetanic contraction of the forearm (30 Hz, 200 us, 5mA). Contractions were visually assessed (b) and later quantified by measuring wrist joint angles post-hoc by video analysis (c).

This brief experiment demonstrated that the Injectrode material can form an electrically conductive interface with the nerve and produce activation of the fibers that can lead to a tetanic contraction or an almost immediate relaxation of muscles. In addition, we demonstrated that the material could form an interface with the complex branched nerve structure.

3.9. Electrical Stimulation of Swine Vagus Nerve

In order to directly compare stimulation thresholds with as closely controlled electrode geometries as possible, we formed the Injectrode materials into bipolar cuffs of the same size and electrode spacing as the clinically available LivaNova spiral cuff (Figure 12A). We performed a current controlled dose-titration protocol, where the biphasic waveform was held constant, 200 us pulse width at 30Hz stimulation, and current was ramped up between 0 to 5 mA. The physiological parameter we measured was heart rate (BPM), per previously published protocols.[31] For a given amplitude, the Injectrode induced a proportionally lower change in heart rate compared to the LivaNova cuff electrode (Figure 12B). The approximate voltage was estimated based on recorded cuff impedance values prior to stimulation. Interestingly, though not surprisingly, when corrected for voltage titration, the two electrodes performed nearly identically, as shown in

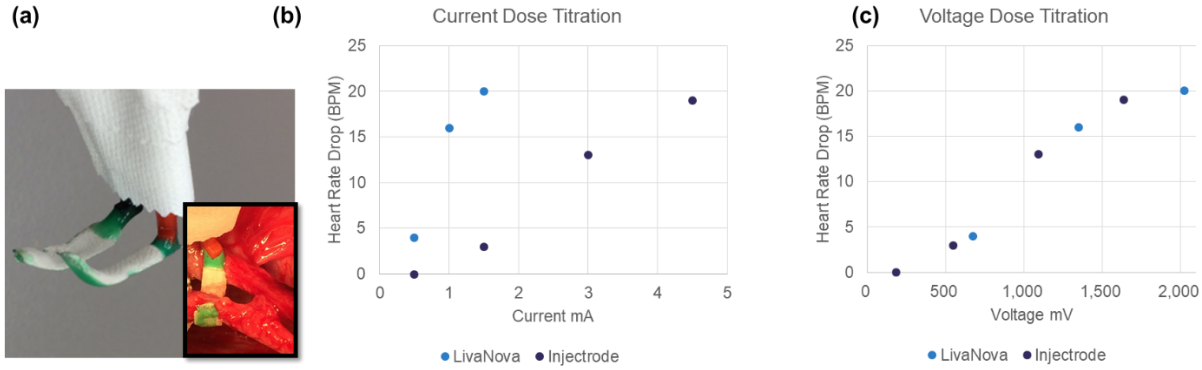

Figure 12: Demonstration of Acute Swine Vagal Nerve Stimulation. *To evaluate effective stimulation parameters of the Injectrode compared to the commercial LivaNova lead to induce heart rate reduction, Injectrodes were placed in an open-cut down procedure on the vagus nerve. To limit variables of the comparison, Injectrodes were fabricated outside the body (a). Stimulation dose-titration was performed with a current-controlled simulator. The experiment was performed first with a standard LivaNova cuff, followed by Injectrode which was placed in the same location and configuration on the vagus nerve. (b) Higher stimulation currents were required with the Injectrode compared to the LivaNova to drive the same heart rate response. (c) However, Impedance of each electrode was measured to be 1350-ohm for the LivaNova and 360-ohm Injectrode. Correcting for lower impedance of Injectrode connection, dose-titration on Voltage-BPM scale was nearly identical with one another, demonstrating a characteristic sigmoidal response relationship.*

3.10. Benefits, Challenges and Future Directions of the Injectable Electrode

The Injectrode is a unique electrode technology that can be injected around a target structure and cures in vivo to form a conductive tissue interface. The fluidity of the pre-polymer material when

it is injected allows for the electrode to conform to the patient's individual neuroanatomy and thus provides a scalable approach to the size and geometry of different target structures. This gives the Injectrode the potential to simplify the surgical approach and eliminate complicated electrode designs needed for difficult neuroanatomical targets such as the stimulation of a nerve plexus presented in Figure 11. Additionally, the elastomeric properties of the cured material has a Young's modulus of under 100 kPa. While this is substantially stiffer than the neural tissues, it is still orders of magnitude less stiff than traditional neural interface materials made from solid wires with polymer insulation. A reduction in the mechanical mismatch between the device and neural tissue may reduce cyclic stains and stresses on the device and surrounding anatomy, and consequently improve the reliability of a chronic neural interface.[32,33] *Despite the benefits derived from the material properties of the Injectrode there are a number of design considerations that will need to be addressed by future studies, including the use of conductive metal particles with known chronic biocompatibility such as gold or stainless steel.*

For the proof of concept experiments presented in this paper, silver particles were used as the conductive filler in the composite material of the Injectrode. The decision to use silver was made in order to reduce the cost of these initial validation studies and allow for fast iteration through Injectrode composites with different ratios of conductive material, particle shapes and sizes, as well as types of composite material. Despite its use as an antimicrobial in certain medical applications, in high doses and during long-term contact with tissue, dissolution of silver metals and the formation of Ag salts, is well known to be associated with cellular and certain organ toxicity[13]. As such, the exact Injectrode formulation used in this paper is not viable as a chronic neural interface. To overcome this limitation, we are currently testing Injectrode formulations based on the use stainless steel, gold, and platinum filler particles to provide conductivity. Due to the need for future changes in the conductive filler used in the composite Injectrode material, we focused the electrochemical testing presented in this paper on demonstrating similarity to the base conductor (silver) and showing that the composite material construct is capable of neuromodulation relevant charge storage capacities and charge injection limits. This was sufficient for this proof of concept demonstration of feasibility, in future studies we intend to emphasize developing the neural interface in terms of both bio-electrochemical compatibility and material flexibility.[26]

Another important point of future development is the Injectrode implantation procedure. While the experiments presented herein were performed through an open cut-down to the neuroanatomical target, the ultimate goal of the Injectrode concept is to enable the completion of these procedures through a minimally invasively surgical approach. Achieving this goal will require development of surgical delivery tools and image guidance tools for accurately injecting the electrode. Non-invasive delivery will require indirect visualization of the nerve target and instrumentation for accurately injecting the electrode around the target. Typical imaging techniques for lidocaine nerve blocks utilize ultrasound imaging surrounding anatomical landmarks, e.g., bony structures and muscle fascia planes. Similarly, the implantation of spinal cord stimulation electrodes utilizes fluoroscopic guidance of the electrode. We envision that similar image guidance and insertion approaches will be applicable for delivery of Injectrodes, although these approaches will need to be optimized for specific indications.

The principal ingredients of the Injectrode were selected to provide rapid proof of concept, and because they have used in different forms within other previously FDA-approved implantable products. Although the FDA does not approve specific materials for implantation, as performance

depends on specific use in the context of an entire system, familiarity for implantable use can streamline the regulatory process. Similarly, surgical glues that cure within the body are not uncommon in clinical use and provide a model to follow for conductive Injectrode based solutions.

4. Conclusion

The Injectrode addresses problems with invasiveness, complexity, and cost of the implantation procedure that hinder the adoption of neuromodulation therapies and reduce patient's access to these otherwise promising treatments. In order to develop the Injectrode into a chronically implanted neural interface, optimization of material properties and surgical approaches will need to be addressed in future studies. Additionally, long-term electrochemical testing of the Injectrode and histological analysis showing chronic stability and biocompatibility of the implant will need to be performed. However, the electrochemical testing and proof of concept experiments presented in this paper demonstrate the feasibility of the injectable electrode approach. Electrochemical testing, performed based on common FDA preclinical benchtop tests, including scanning electron microscopy, cyclic voltammetry, electrochemical impedance spectroscopy, and voltage transient analysis showed that Injectrode, which is conductive due to the incorporation of metal filler particles into a composite material, is electrochemically similar to metal wire of the same material (silver). Additionally, acute *in* vivo testing of an Injectrode, cured around the complex compound motor nerve branches of the brachial plexus, demonstrated stimulation induced tetanic activation of the terminal muscles. Finally, in an animal model better matching the scale of human anatomy, proof of concept comparisons of Injectrode performance to a clinical LivaNova vagus nerve stimulation lead showed stimulation induced heart rate changes in the swine. These experiments suggest the feasibility of the Injectrode for neural stimulation. Additionally, by virtue of being simpler than traditional electrode designs, less invasive, and more cost-effective, the Injectrode has the potential increase the adoption of neuromodulation therapies and enable the treatment of new indications.

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6. Conflict of Interest Statement

MF and AJS are co-founders of Neuronoff Inc. and co-inventors on intellectual property relating to the Injectrode™. JRC and KAL are consultants to Neuronoff Inc.

JW and KAL are scientific board members and have stock interests in NeuroOne Medical Inc., a company developing next generation epilepsy monitoring devices. JW also has an equity interest in NeuroNexus technology Inc., a company that supplies electrophysiology equipment and multichannel probes to the neuroscience research community. KAL is also paid member of the scientific advisory board of Cala Health, Blackfynn, and Battelle. KAL also is a paid consultant for Galvani. None of these associations outside those to Neuronoff, Inc. are directly relevant to the work presented in this manuscript.

7. References

1. Dones, I. & Levi, V. Spinal Cord Stimulation for Neuropathic Pain: Current Trends and Future Applications. *Brain Sciences* **8**, 138 (2018).
2. Heiduschka, P. & Thanos, S. Implantable bioelectronic interfaces for lost nerve functions. *Progress in Neurobiology* **55**, 433–461 (1998).
3. Güemes, A. & Georgiou, P. Review of the role of the nervous system in glucose homoeostasis and future perspectives towards the management of diabetes. *Bioelectronic Medicine* **4**, 9 (2018).
4. Bonaz, B. Is-there a place for vagus nerve stimulation in inflammatory bowel diseases? *Bioelectron Med* **4**, 4 (2018).
5. Pavlov, V. A. & Tracey, K. J. The vagus nerve and the inflammatory reflex--linking immunity and metabolism. *Nat Rev Endocrinol* **8**, 743–754 (2012).
6. Koopman, F. A. *et al.* Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *PNAS* **113**, 8284–8289 (2016).
7. Mosier, E. M. *et al.* Chapter 5 - The Brain Initiative—Implications for a Revolutionary Change in Clinical Medicine via Neuromodulation Technology. in *Neuromodulation (Second Edition)* (eds. Krames, E. S., Peckham, P. H. & Rezai, A. R.) 55–68 (Academic Press, 2018). doi:10.1016/B978-0-12-805353-9.00005-X
8. Plonsey, R. & Barr, R. C. Electric field stimulation of excitable tissue. *IEEE Trans Biomed Eng* **42**, 329–336 (1995).
9. Deer, T. R. *et al.* Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. *Pain* **158**, 669–681 (2017).
10. Kumar, K. & Bishop, S. Financial impact of spinal cord stimulation on the healthcare budget: a comparative analysis of costs in Canada and the United States. *J Neurosurg Spine* **10**, 564–573 (2009).

11. Cogan, S. F. Neural Stimulation and Recording Electrodes. *Annual Review of Biomedical Engineering* **10**, 275–309 (2008).
12. Hudak, E. M., Mortimer, J. T. & Martin, H. B. Platinum for neural stimulation: voltammetry considerations. *Journal of Neural Engineering* **7**, 026005 (2010).
13. Drake, P. L. & Hazelwood, K. J. Exposure-related health effects of silver and silver compounds: a review. *Ann Occup Hyg* **49**, 575–585 (2005).
14. Merrill, D. R., Stefan, I. C., Scherson, D. A. & Mortimer, J. T. Electrochemistry of Gold in Aqueous Sulfuric Acid Solutions under Neural Stimulation Conditions. *J. Electrochem. Soc.* **152**, E212–E221 (2005).
15. Choi, Y.-J. & Luo, T.-J. M. Electrochemical Properties of Silver Nanoparticle Doped Aminosilica Nanocomposite. *International Journal of Electrochemistry* (2011). doi:10.4061/2011/404937
16. Choi, Y.-J. & Luo, T.-J. M. Electrochemical Properties of Silver Nanoparticle Doped Aminosilica Nanocomposite. *International Journal of Electrochemistry* (2011). doi:10.4061/2011/404937
17. Abd El Rehim, S. S., Hassan, H. H., Ibrahim, M. A. M. & Amin, M. A. Electrochemical Behaviour of a Silver Electrode in NaOH Solutions. *Monatshefte für Chemie / Chemical Monthly* **129**, 1103–1117 (1998).
18. Wang, Y.-H. & Gu, H.-Y. Hemoglobin co-immobilized with silver–silver oxide nanoparticles on a bare silver electrode for hydrogen peroxide electroanalysis. *Microchimica Acta* **164**, 41–47 (2009).
19. Cui, X. & Martin, D. C. Electrochemical deposition and characterization of poly(3,4-ethylenedioxythiophene) on neural microelectrode arrays. *Sensors and Actuators B: Chemical* **89**, 92–102 (2003).
20. Cui, X., Hetke, J. F., Wiler, J. A., Anderson, D. J. & Martin, D. C. Electrochemical deposition and characterization of conducting polymer polypyrrole/PSS on multichannel neural probes. *Sensors and Actuators A: Physical* **93**, 8–18 (2001).
21. Ludwig, K. A., Uram, J. D., Yang, J., Martin, D. C. & Kipke, D. R. Chronic neural recordings using silicon microelectrode arrays electrochemically deposited with a poly(3,4-ethylenedioxythiophene) (PEDOT) film. *J Neural Eng* **3**, 59–70 (2006).
22. Weiland, J. D. & Anderson, D. J. Chronic neural stimulation with thin-film, iridium oxide electrodes. *IEEE Trans Biomed Eng* **47**, 911–918 (2000).
23. Merrill, D. R., Bikson, M. & Jefferys, J. G. R. Electrical stimulation of excitable tissue: design of efficacious and safe protocols. *Journal of Neuroscience Methods* **141**, 171–198 (2005).
24. Wilks, S. J. *et al.* Non-clinical and Pre-clinical Testing to Demonstrate Safety of the Barostim Neo Electrode for Activation of Carotid Baroreceptors in Chronic Human Implants. *Front Neurosci* **11**, 438 (2017).
25. Clark, G. M., Clark, J. C. M. & Furness, J. B. The evolving science of cochlear implants. *JAMA* **310**, 1225–1226 (2013).
26. Clark, G. M. *et al.* Biomedical studies on temporal bones of the first multi-channel cochlear implant patient at the University of Melbourne. *Cochlear Implants International* **15**, S1–S15 (2014).
27. Nadol, J. B., O'Malley, J. T., Burgess, B. J. & Galler, D. Cellular immunologic responses to cochlear implantation in the human. *Hearing Research* **318**, 11–17 (2014).
28. Spiers, K. *et al.* An X-ray fluorescence microscopic analysis of the tissue surrounding the multi-channel cochlear implant electrode array. *Cochlear Implants Int* **17**, 129–131 (2016).
29. Tyler, D. J. Chapter 20 - Electrodes for the Neural Interface. in *Neuromodulation (Second Edition)* (eds. Krames, E. S., Peckham, P. H. & Rezai, A. R.) 239–274 (Academic Press, 2018). doi:10.1016/B978-0-12-805353-9.00020-6

30. Young's Modulus of Elasticity for Metals and Alloys. Available at: https://www.engineeringtoolbox.com/young-modulus-d_773.html. (Accessed: 21st March 2019)
31. Premchand, R. K. *et al.* Autonomic Regulation Therapy via Left or Right Cervical Vagus Nerve Stimulation in Patients With Chronic Heart Failure: Results of the ANTHEM-HF Trial. *Journal of Cardiac Failure* **20**, 808–816 (2014).
32. Sridharan, A., Nguyen, J. K., Capadona, J. R. & Muthuswamy, J. Compliant intracortical implants reduce strains and strain rates in brain tissue in vivo. *J Neural Eng* **12**, 036002 (2015).
33. Nguyen, J. K. *et al.* Mechanically-compliant intracortical implants reduce the neuroinflammatory response. *J Neural Eng* **11**, 056014 (2014).