Titanium Nitride Nanotube Electrodes Used In Neural SignalRecording Application And Neurotransmitter Detection

Gui Chen
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TITANIUM NITRIDE NANOTUBE ELECTRODES USED IN NEURAL SIGNAL RECORDING APPLICATION AND NEUROTRANSMITTER DETECTION

by

GUI CHEN

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

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2020

MAJOR: ELECTRICAL AND COMPUTER ENGINEERING

Approved By:

Advisor Date

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DEDICATION

Every work needs self-efforts as well as guidance and encourage of people who were very close to our heat.

I dedicate to my family and alone with all hard working and respected Advisors:

Dr. Mark Ming-Cheng Cheng and Dr. Yang Zhao
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CHAPTER 1 INTRODUCTION AND PROBLEM STATEMENT

1.1 Introduction

Neural probes are devices used for stimulating and recording brain and peripheral nerve signals, which can convert the ion potential generated by electrochemical activities into an electronic potential that can be measured by the external instrument systems. Since the 1950s, the research and development of neural probe devices have attracted much attention in both industrial and academic fields. Over the past few decades, the research and fabrication of these probes have given rise to probes that can be used for various applications, such as electroencephalography (EEG) readings, diagnosis of Parkinson’s disease, and Tourette syndrome, retinal prosthesis, epilepsy, and cochlear implants. Many neural probes have been developed in the commercial market. These probes were designed to minimize tissue damage for superior signal quality. There are also continuous research efforts to develop novel materials and designs of neural probes. The mechanical, geometric, and electrical characteristics of each probe are precise and reproducible for consistent, high-quality results. A review of these fields is presented below.

1.2 Types of Commercial Neural Electrode Probes

The NeuroNexus neural probes adapt micromachining to fabricate multiple electrodes on shanks. The standard silicon probe is fabricated using microelectromechanical systems (MEMS) technology, and the applications of the probe can be seen in single and multiple-unit recording and stimulation, along with local field potential recording and stimulation. These probes are often referred to as the ‘Michigan Probe’ as the prototype was pioneered by the University of Michigan. Figure 1.1 shows the types of neural probes fabricated by NeuroNexus.
Figure 1.1 Neural probes fabricated by NeuroNexus [1] : (a) Michigan Probe (b) Silicon Probe (c) Smart Probe (d) Optoelectrode Probe (e) Electroencephalography Probe

An advantage for the standard probe (Figure 1.1 (a)) is that it can be used in either acute or chronic applications. These probes have also been manufactured to connect easily with a head stage, as in Figure 1.1 (b). The low cost of using silicon makes this probe favorable over wire electrodes.

The fabrication of the Smart Probe (Figure 1.1 (c)) allows for the integration of the head stage and accelerometer, leading to reduced noise from electrode connectors and movement. Using modular components, the head stage can be removed from the used probe and connected to another testing probe in order to reduce spending, making this integrated probe favorable.

The optoelectrode uses optical fibers laminated onto silicon probes (Figure 1.1 (d)). It is possible to use single or multiple fibers on a single probe and target different brain areas. The fabrication of the integrated fibers allows for testing facilities to create an ideal optoelectrode by selecting the electrode array design and the fiber type. The smallest fiber outer diameter measures to 65 um, leading to minimal tissue damage when in use.

The EEG probe is fabricated as surface grids, which are optimized for applications with EEG (Figure 1.1 (e)). These probes are fabricated with polymer MEMS technology and flexible. This allows for the probe to be adhered to the human skull by small drops of water. Since these
probes are made of high quality and durable materials, the probes can be left in place for months while still recording data. One of the other ultra-flexible surface grids is the electrocorticography (ECoG) probe, which is designed to conform to the brain surface in applications of ECoG.

NeuroNexus also offers a low-cost 4-channel probe designed to replace tetrodes and wires. The Qtrode is ideal for acute or chronic experiments that do not require high channel counts. Qtrodes can be combined with various electrodes to potentially enhance the data yield. An example of combining the Qtrode with optical fiber would allow the researcher to combine electrophysiology with optogenetic stimulation.

The rDBSA or research -Deep Brain Stimulation Array allows for large amounts of flexibility in microelectrode positioning. This leads to current selective delivery and stimulation programming. The rDBSA probe can be manufactured for both acute or chronic applications [1]. Located on the tip of the electrode, the elliptical sites allow for tunable stimulation.

Another notable company producing neural recording arrays is the BlackRock Microsystems Utah Array (Figure 1.2). This array is said to be able to obtain stable, long-term recordings and action potentials in the brain and surrounding nerve tissue. The Utah arrays allow for large populations of neurons to be monitored, it is easily sterilized for multi-use purposes. It can provide micro-stimulation, and the neural recordings are available immediately after the device is implanted. The Utah array has been tested successfully for recording and stimulation of the motor cortex, sensory cortex, spinal cord, and peripheral nerve fibers.

Figure 1.2 Utah Probe [2]
Ellab Validation Solutions produces a flexible probe (Figure 1.3), which is a good choice for low cost and quick design probe. The flexible probe is designed for measurements in the ears and nose and has a long length. The probe has an inactive silicone cable that does not irritate the skin and can be easily disinfected and sterilized.

![Flexible Probe](image1)

**Figure 1.3** Flexible Probe [3]

The ActivaRC Neurostimulator (Figure 1.4) produced by Medtronic is a dual-channel rechargeable deep brain stimulation device. The ActivaRC can deliver bilateral stimulation via the extension leads, which are implanted into the brain. The greatest application of the device is with use for patients with Parkinson’s disease. The bilateral stimulation has shown results of helping with better motor control while unilateral stimulations have shown results of improved function with suppressing tremors associated with parkinsonian tremors, which have not been improved by medications. The ActivaRC device can have a battery performance of 15 years, and the advanced programming capability of the device can allow patients to optimize settings at a quicker rate.

![DBS Medtronic Probe](image2)

**Figure 1.4** DBS Medtronic Probe [4]
Electrode arrays can also be used in applications of the prosthesis, such as the Argus 2 produced by Second Sight (Figure 1.5). This visual prosthesis system is created by the implanted electrode array bypassing the damaged photoreceptors of the eye and stimulate the remaining retina cells to translate signals along the optic nerve to the brain. The system of the Argus 2 uses special glasses with a small video camera which records the outside world and sends the recording to a small patient-worn computer. This computer can then connect via the antenna to the implant in the eye and stimulate the embedded electrode. Over time, the user will relearn to see using the signals emitted by the electrode array.

![Figure 1.5 Second Sight Argus II Probe](image)

Table 1.1 shows the above commercial neural probes specifications in detail, including the electrode materials, electrode size (thickness and length), and the channel count. The minimum electrode size is around 15um. And the popular materials are Iridium, Platinum and PTFE.
Table 1.1 Commercial Neural Probe Specifications

<table>
<thead>
<tr>
<th>Probe</th>
<th>Material</th>
<th>Electrode Thickness</th>
<th>Electrode Length</th>
<th>Channel Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>NeuroNexus Standard [1]</td>
<td>Iridium</td>
<td>15 um – 50 um</td>
<td>2-15 mm</td>
<td>Varies by design</td>
</tr>
<tr>
<td>NeuroNexus SmartProbe [1]</td>
<td>Iridium</td>
<td>15 um – 50 um</td>
<td>2-15 mm</td>
<td>128,256</td>
</tr>
<tr>
<td>NeuroNexus EEG [1]</td>
<td>Platinum and Polymide</td>
<td>20 um</td>
<td>10 mm</td>
<td>30,32</td>
</tr>
<tr>
<td>NeuroNexus ECoG [1]</td>
<td>Platinum and Polymide</td>
<td>20 um</td>
<td>Varies by design</td>
<td>Varies by design</td>
</tr>
<tr>
<td>NeuroNexus Qtrodes [1]</td>
<td>Iridium</td>
<td>15 um, 50 um</td>
<td>3-10 mm</td>
<td>4</td>
</tr>
<tr>
<td>NeuroNexus rDBSA [1]</td>
<td>Platinum and Polymide</td>
<td>0.75 mm</td>
<td>Max 45 mm</td>
<td>40</td>
</tr>
<tr>
<td>Utah Array [2]</td>
<td>Platinum Iridium Oxide</td>
<td>25 um</td>
<td>20 – 130 mm</td>
<td>Max 128</td>
</tr>
<tr>
<td>ellab MAA Flexible [3]</td>
<td>PTFE</td>
<td>0.8 mm</td>
<td>500 mm</td>
<td>NA</td>
</tr>
<tr>
<td>ellab MAC Flexible [3]</td>
<td>PTFE</td>
<td>0.7 mm</td>
<td>170 mm</td>
<td>NA</td>
</tr>
<tr>
<td>Medtronic ActivaRC [4]</td>
<td>NA</td>
<td>54 mm</td>
<td>54 mm</td>
<td>2</td>
</tr>
</tbody>
</table>

1.3 Stimulation/recording electrodes

Neural electrodes over the past few decades have been created from various materials, each with their own specific uses dictated by the properties of fabrication, charge injection, and biocompatibility. Electrodes are used as a tool of which facilitates the flow of electrons within the electrode to the tissue of which the electrode is being connected to. The electrochemical reactions occurring can either be capacitive, meaning that the electrode is involved in charging and discharging cycle, or faradaic in which surface-level species undergo an oxidation or reduction process [6]. Electrodes created of materials Platinum (Pt), Platinum alloys (PtIr), Tantalum Oxide (Ta₂O₅), Titanium Nitride (TiN), Iridium Oxide (IrOx), Carbon Nanotubes (CNT), Tungsten (W), and Gold (Au) will be discussed within this review for the electrode mechanism and ability to be used for neural electrode applications.

As Cogan [6] stated, materials that involve capacitive charge-injection are more favorable as there do not have chemical interaction of the oxidation or reduction process at the
surface of the electrode. Chemical reactions at the electrode to tissue interface can potentially lead to irreversible damage, either the electrode itself or the tissue surrounding it. Table 1.2 summarizes the mechanism and maximum charge injection of the research electrodes with different materials.

Table 1.2 Electrode materials mechanism [6]

<table>
<thead>
<tr>
<th>Material</th>
<th>Mechanism</th>
<th>Maximum Q_{inj}</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt and PtIr Alloys</td>
<td>Faradaic/ capacitive</td>
<td>0.05-0.15</td>
<td>[7]</td>
</tr>
<tr>
<td>Tantalum/ tantalum oxide</td>
<td>Capacitive</td>
<td>~0.5</td>
<td>[8, 9]</td>
</tr>
<tr>
<td>Titanium Nitride</td>
<td>Capacitive</td>
<td>~1</td>
<td>[10]</td>
</tr>
<tr>
<td>Carbon nanotubes</td>
<td>Capacitive</td>
<td></td>
<td>[11]</td>
</tr>
<tr>
<td>Iridium Oxide</td>
<td>Faradaic</td>
<td>1-5</td>
<td>[12, 13]</td>
</tr>
</tbody>
</table>

1.4 Comparison of different electrode materials

1.4.1 Platinum electrode

The electrochemical characteristics of Platinum (Pt) make it a favorable material for neural electrodes. However, the use of an electrode directly injecting current into the surrounding tissue raises concerns for potential tissue damage. Brummer and Turner [14] reviewed the possible problems that may occur and the expected behavior of Pt electrodes. The significant components of extracellular fluids that the electrode may react with are water (H₂O), Sodium Chloride (NaCl), Bicarbonate (HCO₃), Carbon Dioxide (CO₂), as well as other organic materials such as glucose molecules. If Pt is made an anode in a solution of which these components are found, the following harmful reactions have the potential to occur:

Electrolysis of water: $2H_2O \rightarrow O_2 \uparrow + 4H^+ + 4e^-$

Oxidation of saline: $Cl^- + H_2O \rightarrow ClO^- + 2H^+ + 2e^-$

Oxidation of metal: $6Cl^- + Pt \rightarrow PtCl_2^{2-} + 4e^-$

Oxidation of organics: $C_6H_{12}O_6 + 6H_2O \rightarrow 6CO_2 + 24H^+ + 24e^-$

Figure 1.6 Possible Reactions of Pt electrode with extracellular fluid [14]
The electrolysis of water is to be avoided due to the potential damage to the increase of gas produced during the reaction. This may also cause a change in the local pH of the electrode. The oxidation of certain components such as the metal itself or organic substrates (i.e., glucose) may prove to cause special problems as the oxidation products may be toxic or the surrounding tissue maybe damaged. Brummer and Turner give the following processes as possible solutions to the above problems [14].

Double layer charging: \( Pt(-) \text{repels } Cl^- \iff Pt(+) \text{attracts } Cl^- \)

Surface oxidation: \( Pt + H_2O \iff Pt \text{surface oxide} + 2H^+ + 2e^- \)

**Figure 1.7** Possible Solutions of damaging the surrounding tissue by the Pt electrode [14]

Here double layer charging involves the redistribution of ions between much of the solution and the local area of the electrode. In this solution, no chemical reaction is taking place. Thus the potential for tissue damage is minimized. The option of oxidation and reduction of the surface of the electrode is attractive as the chemical reactions taking place are reversible [14]. The size of the electrode must also be taken into consideration as seen in research completed by McCreery et al [15]. It was found that surface electrodes fabricated with platinum smaller than 0.01 cm\(^2\) were not efficient as connective tissue would grow beneath the disk and push the electrode away from the desired area. This paper also showed specifics of the consequences of the interaction of charge density and charge per phase. It was determined that both parameters must be known in order to predict if the neural injury is going to occur.

**1.4.2 Titanium Nitride**

Titanium nitride is a material that has capacitive charge injection makes it favorable for use as a neural electrode. Cogan [6] stated that the charge injected by the electrode-electrolyte double layer is obtained by fabricating electrode with higher surface roughness. Weiland et al. [10] discussed the many advantages of titanium nitride electrodes, such as low power consumption, availability in small sizes, and the capability for safe tissue stimulation. This
research has also shown that the impedance amplitude of titanium nitride was 15% less than iridium oxide for frequencies larger than 10 kHz, as well as stating that the impedance amplitude is frequency-dependent at frequencies lower than 4 kHz.

![Cyclic voltammogram TiN IrOx](image)

**Figure 1.8** Cyclic voltammogram TiN IrOx [10]

Figure 1.8 shows the cyclic voltammogram results of the TiN and IrOx from -0.6V to 0.7V. The CV traces show that the iridium oxide has peaks that indicate the oxidation-reduction reactions occurring while the titanium nitride does not show such peaks. From this, it is clearly seen that TiN is dominated by capacitive current flow which makes it safer for use as a tissue electrode. Titanium nitride has relatively good conductivity (Electrical Resistivity \(\approx 20\ \mu\Omega\cdot\text{cm}\)).

Zgrabik and Hu [16] studied the metallic behavior of TiN for plasmonic applications from visible into near-IR wavelengths. They found that TiN exhibits a tunable metallic behavior dependence on the substrate and deposition details, which showed TiN can be dielectric, intermediate or metallic material. Titanium nitride can be made into nanotube arrays, which have high surface area to volume ratio due to the columnar structure of the nanotubes.

### 1.4.3 Tantalum Oxide

Tantalum/tantalum oxide capacitor electrodes are the most favorable and extensively researched option for nerve electrodes. The self-organized porous material has a high potential for use in nanoscale-based applications. Sieber and Schmuki [17] discussed the parameters that affect the pore morphology, such as HF concentration, the time duration of oxidation, and
anodization potential. Within their experiments, single pore diameters of 20 nm (Figure 1.9) with the spacing of 15 nm were achieved.

![Figure 1.9 Ta$_2$O$_5$ cross-section [18]](image)

Other uses of tantalum/tantalum oxide include the electrode being used as a low-cost substitute in the fabrication of Dye-sensitized solar cells (DSCs) [18]. Here, Yun et al. demonstrated that the tantalum oxide used as a counter electrode in DSCs showed superior electrocatalytic activity as well as high-power conversion efficiency. Disadvantages of using the Ta/Ta$_2$O$_5$ electrodes include difficulty in achieving ESA/GSA ratios, pore resistance limiting the charge injection of the electrode, and the high bias voltage [6].

1.4.4 Iridium Oxide

The many advantages of using iridium oxide, such as having high charge carrying capacity (unless being used at high frequencies) are what allows for this material to be favorable for electrodes that need an increased storage capacity [10]. The injectable charge was measured as 4 mC/cm$^2$, which is larger than the injectable charge of titanium nitride. Iridium oxide has a porous structure, which increases the effective surface area of the electrode, however, not to the extent that titanium nitride does.

Iridium oxide films have also been formed from the sputtering from Ir metal in an oxidizing plasma [6]. These films have been researched for use in neural stimulation electrodes where charge injection capacities of 100µC cm$^{-2}$ have been reported for safe injection using 10 ms pulses. Microelectrodes of 1.5 mm length and 75 µm diameter were constructed to test the
ability of high charge density with low charge per phase [15]. From these experiments, the Ir microelectrodes did not identify damaged neurons near the tip of the electrode.

1.4.5 Tungsten

One of the key disadvantages of using Tungsten (W) is the material’s susceptibility to being oxidized. Chen et al. [19] have previously reported on the potential problems that this issue can cause in relation to device operating cycle in MEM relays. Oxidation rate increases exponentially as temperature increases, thus when in use with on/off cycles of the relay the temperature built up will cause the exposed surface of the electrode to be susceptible to the oxidation.

Prasad et al. [20], worked on the abiotic and biotic effects on a 50 µm diameter tungsten microwire. They also studied the short-term and long-term effects of the wires on rat tissue. The results of the experiments showed that the electrodes caused persistent injury biomarkers to be released even after long periods of time, which can potentially suggest that the implantation of tungsten electrodes can cause persistent tissue damage.

![Figure 1.10 Tungsten microwire arrays in chronic neural implants [20]](image)

1.4.6 Gold

Gold electrodes have been reported to be used in high sensitivity applications such as gene detection with modified electrodes [21] and as a glucose biosensor [22]. Previous research completed by Gu et al. [23] reported on the immobilization of hemoglobin on nanometer-sized
gold particles associated with the cysteamine monolayer of a gold electrode (Figure 1.11). The fabrication process of the gold electrode included sealing a 0.5 mm diameter gold wire in glass tubes and polishing with abrasive paper and micro-cloth pads. The electrode was then soaked in 0.1 M deoxygenated cysteamine solution and dipped into colloidal gold for the gold colloid-cysteamine modified monolayer. The clusters of gold nanoparticles are connected in a continuous layer. It was observed that the hemoglobin molecules of size 5.2 nm were bound to the gold nanoparticles surface. Similar results were found by Zang et al. [22] in which glucose oxidase molecules attached cysteamine modified gold nanoparticles.

![AFM images of a colloidal gold immobilized cysteamine-modified gold film (a) without the assembled Hb; (b) with the assembled Hb.](image)

**Figure 1.11** AFM images of a colloidal gold immobilized cysteamine-modified gold film (a) without the assembled Hb; (b) with the assembled Hb.

1.4.7 Carbon Nanotubes (CNTs)

Fattahi et al. [24] worked on the specifics of the use and fabrication of carbon nanotubes (CNTs) in neural electrodes. CNTs possess attractive properties, such as high rates of mechanical strength and electronic current, as well as being a great thermal conductor. These properties allow the CNTs to be used in fields of biotechnology, such as biosensors of DNA and proteins. The structure of CNTs is that of graphite sheets rolled into a seamless nanotube shape, of which these can either be single or multi-walled structures. The functionality of CNTs within neural science relates to the ability of CNTs to be applied with surface-level polymers for improvement of biocompatibility, which can then be used for modulation of neural behavior.
Experiments performed by Wei et al. [25] found that even at high current densities (>10⁹ A/cm²) the structure of the CNTs had shown no observable collapse of the nanotube structure as well as no measurable change in the resistance at high temperatures. These factors contribute to the long-term stability of the CNTs as a choice for effective electrode materials. Further experiments completed by Chen et al. [26] complete the analysis of CNTs as a favorable material for electrode involved in electrochemical double-layer capacitors (Figure 1.12) due to the high capacitance found during the CV.

One of the disadvantages of using CNTs is the complex fabrication process [26]. The following steps show the general preparation method: (1) nanotubes are harvested and chemical functional groups are added to the surface of the electrode; (2) the hydrophilic nanotubes are dispersed in a solvent; (3) the individual nanotubes need to be entangled and assembled into a freestanding and stable structure. It is important to note that many studies have reported that nanotubes need to be directly grown on a substrate to minimize the contact resistance between the nanotubes and the substrate of which the electrode is fabricated. The possible toxicity of CNTs is another concern with the use of neural electrodes [24], as there is a potential of cytotoxicity with the material. While toxicity has not been observed for CNT coatings, the potential of decomposition and corrosion of the electrode still must be fully investigated for further analysis for the medical application of the electrodes.

![Figure 1.12 SEM images of carbon nanotubes. (a) Low magnification (b) High magnification](26)
1.4.8 Titanium Nitride Nanotubes (TNTs)

Titanium nitride nanotubes have attracted much attention due to its high specific surface area to volume ratio and the controllable preparation of the morphology. It also inherited some good material properties of TiN. Liu et al. [27] fabricated the TNTs and measured the open-circuit potentials to evaluate the TNTs electrode related to pH sensitivity, which showed good selectivity for H\(^+\) ions in the presence of cations and anions. These made TNTs electrode a promising candidate as a pH electrode sensor. The hollow titanium nitride nanotubes also used as high-performance catalyst supports for the oxygen reduction reaction. Xiao et al.[28] developed a robust Pt/TiN NT catalyst, which demonstrates high activity and durability for the oxygen reduction reaction. The Pt/TiN NT catalyst shows much higher stability than a commercial Pt/Carbon catalyst owing to the unique hollow structure and porous walls of TNTs.

1.5 Literature about failing modes

Each of the above probes has advantages for their specific uses. They also have drawbacks. They are either very expensive or may irritate or damage the tissue. Figure 1.13 shows the possible mechanisms of neural-probe failure modes. In this section, I am going to investigate the parameters which cause these probes to fail in terms of effective applications.

![Figure 1.13](image)
The material of which the probe is fabricated is very important for the charge injection stimulation of the tissue, as the mechanism of which the electrode operates will determine how the tissue reacts to the stimulus. The following material properties should be considered: biocompatibility, good mechanical stability, corrosion resistance, smaller geometry size, reversible reaction, as well as low polarization and impedance. Electrode is a metallic conductor, acting as a bridge, and reactions at the electrode-tissue interface are for mediating the transition from electron flow in the electrode to ion flow in the tissue. The electrodes fabricated with Platinum will work under a pseudocapacitive mechanism, while those fabricated with Iridium will work under a faradaic mechanism. And the Ta$_2$O$_5$ electrode works under a capacitive mechanism. Looking at three different types of injection mechanisms, one can see that an electrode that works under a capacitive mechanism (i.e., TiN) is most favorable for low tissue damage and high potential storage.

Failure modes of neural probes were defined as a loss of neural stimulating/recording capability. The failures can be classified into device design and foreign-body response. Table 1.3 summarizes failure modes of neural probes, including the design failure mechanisms and the biological failure mechanisms.

<table>
<thead>
<tr>
<th>Design failure mechanisms</th>
<th>Biological failure mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical failure of interconnects</td>
<td>Initial tissue damage during insertion</td>
</tr>
<tr>
<td>Degradation and cracking of the insulation</td>
<td>Breach of the blood–brain barrier</td>
</tr>
<tr>
<td>Electrode corrosion</td>
<td>Elastic mismatch and tissue micromotion</td>
</tr>
<tr>
<td>Delamination of probe layers</td>
<td>Disruption of glial networks</td>
</tr>
<tr>
<td></td>
<td>Formation of a glial scar</td>
</tr>
<tr>
<td></td>
<td>Neuronal death</td>
</tr>
<tr>
<td></td>
<td>Materials neurotoxicity</td>
</tr>
<tr>
<td></td>
<td>Chemical mismatch</td>
</tr>
</tbody>
</table>
Figure 1.14 shows how each of the described mechanisms works. Capacitive mechanisms work by being either electrostatic, thus being involved in purely double-layer ion-electron charge separation, or they can be electrolytic, meaning charge is stored across a thin oxide layer at the electrode-electrolyte interface. In practice, materials that use capacitive charge injection are more favorable as there is no chemical changing of electrons in the charging and discharging of the electrode. For materials to work effectively with capacitive charge injection, the electrode must be porous.

![Capacitive (TiN) charge-injection mechanisms](image)

**Figure 1.14** Capacitive (TiN) charge-injection mechanisms [29]

Pseudocapacitive mechanisms (Figure 1.15) can be described as a faradaic reaction occurring at the surface monolayer of the electrode. However, there is still the action of electron transfer across the interface. The amount of pseudocapacitance depends on the surface area, the material, and the structure of the electrodes. Pseudocapacitance may contribute more capacitance than double-layer capacitance for the same surface area by 100x [30]. The faradaic mechanism would suggest that there is a transfer of electrons across the electrode-electrolyte interface and requires that some element on the surface of the electrode is either oxidized or reduced.
Figure 1.15 Three-dimensional faradaic (iridium oxide), and pseudocapacitive (Pt) charge-injection mechanisms [29]

1.6 Objectives of the research

According to the above investigation, in the neural implant application, a long-term electrode monitoring is very important for the robust recording of the activity of the neural signals. Metallic electrodes have a reaction with the approached tissue interface, which may lead to the corrosion of the electrode for long-term use. A reliable corrosion-resistance electrode is necessary for the neural signal detection. Until now, there are several material candidates, including platinum, tungsten, iridium, iridium oxide, carbon derivatives (graphene and carbon nanotubes), conductive polymers, and titanium nitride. Among these electrodes, a few of them have already been commercialized for specific applications. Titanium nitride is the most widely encountered barrier material. It was introduced by Nicolet in the 1970’s. Titanium nitride as the neural implant electrode can have broad applications owing to its super electrical conductivity, biocompatibility, chemical stability, and good hardness. TiN also has unusual optical properties, including an attractive gold-tinged appearance when pure, and high infrared transmission.

Research has been done on the TiN electrodes for the neurotransmitter detection and other chemical compound examination based on the film or even bulk structures. Since Titanium Nitride nanotubes have high surface area to volume ratio and controllable morphology during the growth. In this research, we focus on the applications of TiN nanotubes
as neural probes. We fabricated the TiN nanotubes using Ti films and Ti wires. The corrosion resistance of the TiN nanotube is unknown when the TiN nanotube electrode is used for the long-term recording neural signal in the body. In this work, the corrosion performance of Titanium Nitride nanotubes is first studied using microwire electrodes with different pore sizes. The corrosion characterization was discussed in the 0.9% phosphate-buffered saline (PBS) electrolyte at the temperature 37°C, which is similar to the normal human body temperature. The corrosion resistance was compared between the tungsten electrode and the TiN nanotubes electrode with similar geometric dimensions.

Considering the TiN nanotubes have a high surface area to volume ratio, it could accommodate more space for the ions contact and exchange. This will lead to much better performance in the examination speed and sensitivity when it is used as electrodes. In this research, TiN nanotubes electrodes are further studied as neurotransmitters for the detection of dopamine and serotonin. A neurotransmitter is a kind of chemical messenger that transmits signals across a chemical synapse from one neuron to another selected neuro. Major brain neurotransmitter systems are including the noradrenaline system, the dopamine system, the serotonin system, and the cholinergic system, among others. Noradrenaline and serotonin have functions to modulate the appetite, sleep-wake cycles [31], memory and learning, temperature, mood, and anxiety [32]. Dopamine has functions to regulate motor behavior, pleasures related to motivation, and also emotional arousal. It has a big effect on Parkinson’s Disease [33], drug addiction and reward pathways [34], and schizophrenia [35]. It will be interesting to perform quantitative concentration determination of dopamine and serotonin in the brain for the understanding of the neurotransmission processes.

Applications of Ti in wireless LC sensors are also studied owing to its biocompatible and good conductivity (Electrical Resistivity = 42 uΩ·cm). Intracranial pressure (ICP) monitoring is so critical to detection or treatment of cerebral trauma, especially in the injured
head and diseased brain. The most existing clinically established ICP measurement methods require catheter insertion in the cranial cavity with narrow ventricles. On the one hand, these setups can just be used in the hospital at the instance of physicians. On the other hand, this increases the risk of infection and hemorrhage. Thus, noninvasive methods but accurate techniques are more and more attractive. There are several groups who have already made contributions to this work by designing a battery-free implantable sensor using copper with polyimide substrate. In this work, we present a novel and implantable LC tank sensor simulation estimation for continuous ICP monitoring. The implantable sensor comprises a helix coil with a series-connected spiral coil connected in series to a cylindrical capacitor, all of them made by Titanium metal. The device can detect pressure signals caused by the adjustable capacitance and wirelessly transfer the signal out through the mutual coupling with an external RF reader out coil. The ICP variation can be detected wirelessly through measuring the reader antenna’s scattering parameter $S_{11}$. 
CHAPTER 2 FABRICATION OF TITANIUM NITRIDE NANOTUBE AND ELECTRODES CORROSION PERFORMANCE STUDY

2.1 Introduction

TiN electrodes have been studied for the neurotransmitter detection and other chemical compound examination based on the film or even bulk structures [6, 10]. The corrosion resistance of the TiN is still unknown when the TiN electrode is used for the long-term recording neural signal in the body. In this section, the corrosion performance of Titanium Nitride nanotubes is studied using microwire electrodes with different pore sizes.

2.2 Mechanisms of synthesis of TiN nanotubes

2.2.1 Anodization in an Organic Electrolyte

Highly ordered TiO$_2$ nanotubes were firstly prepared by using a two-step anodization technique [36-38]. A two-electrode electrochemical cell, with a working electrode of Ti wire (purity 99.9% trace metals basis, diameter 0.5 mm from Sigma-Aldrich) and a counter electrode of Pt foil with the hollow cylinder structure, was used for the preparation of TiO$_2$ nanotube arrays (TNTs) (Figure 2.1). The anodization solution used was an organic solution containing ethylene glycol (EG) electrolyte containing 0.5 wt% NH$_4$F and 2 vol% deionized water under different voltages for two hours. This mixture is proven to support improved nanotube structure as well as a strong porous layer [3, 6, 37]. Organic solutions that contain fluoride ions make sure to keep a low concentration of F- ions to minimize the amount of dissolution performed at the oxide layer, while also ensuring that enough of the ions are available for the formation of the desired nanotubes. The presence of the fluoride ions is crucial to the beginning steps of creating the porous layer as well as the continual growth of the walls during the formation of the nanotubes. Continuous flow or stacking of the TiO$_2$ creates the presence of a porous tube structure, from which the flow is created by F- ions continuously meeting with Ti$^{4+}$ ions at the base of the tube. Then the as-prepared TiO$_2$ nanotubes were
removed by ultrasonication in the deionized water. Finally, the well-patterned titanium wires had second-step anodization in the same electrolyte at the same voltage for 30 mins.

![Figure 2.1](image)

**Figure 2.1** The two-electrode electrochemical cell for the preparation of TiO$_2$ nanotube arrays

2.2.2 Creation of oxide layer

When the potential is applied, the oxidization of the Ti metal begins. Titanium valence electrons are released, creating the following form of Ti ions [38].

\[ Ti \rightarrow Ti^{4+} + 4e^- \]

The applied potential will also aid in the splicing of water molecules, resulting in the following formation of free oxygen and OH$^-$ molecules. These molecules can then form with titanium ions to form the oxide layer. The formation of TiO$_2$ is created by a condensation reaction of the Ti(OH)$_4$.

\[ H_2O \rightarrow OH^- + O^{2-} \]
\[ Ti^{4+} + 2O^{2-} \rightarrow TiO_2 \]
\[ Ti^{4+} + 4OH^- \rightarrow Ti(OH)_4 \]
\[ Ti(OH)_4 \rightarrow TiO_2 + 2H_2O \]

Seeing from above equations, each titanium ion can be converted into an oxide molecule as well as the formation of a water molecule that can continue the formation of the oxide layer.
At the cathode, hydrogen evolution is occurring on the platinum ring forming hydrogen bubbles, which can be seen during the anodization process.

\[ 4H^+ + 4e^- \rightarrow 2H_2 \]

The overall process at both the anode and the cathode can be given by the following formula.

\[ Ti + 2H_2O \rightarrow TiO_2 + 2H_2 \]

### 2.2.3 Creation of the Nanotubes

The applied electric field causes the Ti\(^{4+}\) ions to move towards the electrolyte, where they are met with F\(^-\) ions forming a stable titanium complex. This is due to the positive charge on the anode connected to the titanium. The negative fluoride ions will be attracted to the metal oxide and from porous sections and dissolving the oxide layer.

The following main equations show that fluoride ions can interact with the various forms of titanium in the system.

\[ TiO_2 + 6F^- + 4H^+ \rightarrow TiF_6^{2-} + H_2O \]

\[ Ti(OH)_4 + 6F^- \rightarrow TiF_6^{2-} 4OH^- \]

\[ Ti^{4+} + 6F^- \rightarrow TiF_6^{2-} \]

The formation of the nanotubes can be explained in the following three steps. The first step is that when a potential is applied to the system, the current will fall to an almost zero value as the oxide barrier starts to form. This is due to the increased resistance that is now forming within the system. Fluoride ions can move through this resistive barrier and induce pores within the oxide film. Second, as a larger number of pores are formed in the oxide layer, the current is seen to increase as the resistance decreases. The increased number in pores is thus an increase in the number of paths for Ti\(^{4+}\) ions to move into the electrolyte and create nanotube walls. In the third stage, the rate of oxide layer formation, as well as the rate of dissolution of the oxide, reach an equilibrium as can be seen as being in a steady-state.
It is important to note that various factors can affect the growth and formation of the nanotubes. It is thought that changes in the potential applied to the system do not affect the morphology of the tubes. However, it can affect the number or more sites in the oxide film. The amount of water in the solution has the potential to affect the shape of the nanotubes, as an increase in the amount of water added to the organic solution can leave nanotubes with ridges or ribbing instead of a smooth surface. As these ridges would be connected to neighboring tubes, the electrolyte cannot pass through the wall barriers and cannot create gaps between individual nanotubes.

2.2.4 Nitration of the TiO$_2$ Nanotubes

The prepared TiO$_2$ NTA were placed in the Thermo furnace with the gas Ar flow for 30 mins at room temperature, then calcined at 800°C in an ammonia atmosphere for hours with a progressive, slow, heating ramp (room temperature to 300°C, 5°C/min; 300 to 700°C, 2°C/ min; 700 to 800°C, 1°C /min; 800 to 800°C for 1 hour ). After that, cooling to room temperature naturally, TiN nanotubes were finally obtained.
2.3 TiN nanotube arrays Growth on Ti foil

2.3.1 Electrolyte Preparation

The 400mL electrolyte solution was mixed by ethylene glycol (EG) electrolyte, 0.5 wt\% NH$_4$F, and 2 vol\% deionized water. Ethylene glycol ((CH$_2$)$_2$(OH)$_2$), density(1.11g/ml), is 392mL. And the mass of the 0.5wt\% NH$_4$F is 2.23g. 2% volume DI water, density(1g/ml), is 8mL.

Mix all the components into a brown bottle, which is cleaned and dried in the heater chamber at 90°C (Figure 2.4). Then stir the electrolyte on the pot with a magnetic stirrer for 12 hours.

Figure 2.3 Nitration of TiO$_2$ nanotubes Progress

Figure 2.4 Electrolyte Mixture by the magnetic stirrer
2.3.2 Ti foil cleaning preparation before growth

Ti foil (purity 99.9% trace metals basis, thickness 0.5 mm from Sigma-Aldrich, Figure 2.5 (a)) was polished by two different friction of sandpapers. The coarser sandpaper is 120 grit (Figure 2.5 (b)), and the other finer sandpaper is 240 grit (Figure 2.5 (c)). Ti foil was polished by the larger roughness sandy paper first to remove the native TiO$_2$ layer, then polished by the smaller roughness sandy paper to eliminate the coarse sandpaper scratches left and also make the surface of the Ti foil more meticulous.

(a)                                                          (b)                                              (c)

Figure 2.5 Polished Ti foil by sandpaper

Ti foil was cut into smaller pieces (1cm*2cm) by the cutter (Figure 2.6). Then these small Ti pieces were ultrasonic in the Ethanol solution for 15 mins and then in the deionized water for 15 mins. Finally, the Ti foils were dried on the filter paper, and the tapes were put to cover the entire reverse sides.

Figure 2.6 1cm *2cm Ti pieces by the cutter
2.3.3 First-step in anodization of TiO$_2$ nanotube arrays

The as-ultrasonic Ti foil was connected by the anode, and the same sized Platinum foil was face-to-face connected by the cathode to form a two-electrode electrochemical cell in the well-prepared anodization solution for 2 hours with three different supplied voltages, 30V, 45V, and 60V. After the step, the part in the anodization solution of Ti foil become a golden appearance, seen in Figure 2.7 (c).

![Image](a): Planarized Ti foil  (b) TiO$_2$ nanotube growth setup  (c) TNTs for first-step anodization

**Figure 2.7** First-step in anodization of TiO$_2$ nanotube arrays

The as-anodized TiO$_2$ nanotube arrays were treated by ultrasonication (Figure 2.8) in DI water for some time until the golden layer was totally removed.

![Image](Figure 2.8 Remove TiO$_2$ nanotube arrays by ultrasonication)

2.3.4 Second-step in anodization of TiO$_2$ nanotube arrays

The setup of the second-step anodization of TiO$_2$ nanotube is the same as the first-step anodization, in Figure 2.7 (b). And the growth time of the second-step anodization is 30 mins.
2.3.5 Nitration of TiO$_2$ nanotube arrays

TiN nanotube array was synthesized by nitridizing as-anodized TiO$_2$ nanotube arrays. A nitration treatment of TiO$_2$ nanotube array was conducted at 800°C for two h in a Thermo furnace in an ammonia atmosphere, Figure 2.9. The progressive heating rates included 5°C min$^{-1}$ from room temperature to 300°C, 2°C min$^{-1}$ from 300°C to 700°C, and 1°C min$^{-1}$ from 700°C to 800°C. Finally, the TiN nanotube array was obtained after cooling down to room temperature.

![Nitration treatment of TiO$_2$ nanotube array](image)

**Figure 2.9** Nitration treatment of TiO$_2$ nanotube array

2.3.6 Surface morphology and microstructure by SEM

The morphologies of the samples were characterized by field emission scanning electron microscopy (FE-SEM) (Tescan LYRA 3, Version 1.1) at an acceleration voltage of 20 kV. The surface morphology of as-anodized TiN nanotube arrays was in Figure 2.10 by SEM. With the different growth times, the length of the nanotube is different, 5um for 10 mins, 10um for 30 mins, and around 18um for 1 hour.
### Figure 2.10 The surface morphology of TNTs

#### 2.3.7 Elemental Analysis by Energy-dispersive X-ray spectroscopy (EDX)

EDX is an analytical technique used for the elemental analysis or chemical characterization of a sample. EDX is used to measure the degree of nitridizing of TNTs. The TiN sample of the second anodization for 30 mins is analyzed by EDX, as Figure 2.11. It shows the element composition ratio of N and O is around 1:1. It indicates that the nitration of TNTs is inadequate through the above conditions.
Elemental analysis of TiN by EDX

<table>
<thead>
<tr>
<th>Element</th>
<th>Atomic %</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32.21</td>
</tr>
<tr>
<td>O</td>
<td>27.93</td>
</tr>
<tr>
<td>Ti</td>
<td>39.86</td>
</tr>
<tr>
<td>Total:</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 2.11 Elemental analysis of TiN by EDX

2.3.8 Improved Nitriding Method of TiN

Since TiO₂ nanotube array was not completely nitrided in the above nitriding condition, it needs to be changed for enhancing the conductivity of the TiN nanotube electrode. The melting point of TiO₂ is 1843°C, and that of TiN is 2930°C. Therefore, the higher nitriding temperature and the total longer nitriding time are used to achieve better nitriding of TiO₂ nanotubes. A nitriding treatment of TiO₂ nanotube array will be conducted at 1000°C for three h in the Thermo furnace in an ammonia atmosphere. The progressive heating rates included 5°C min⁻¹ from a room temperature to 300°C, 2°C min⁻¹ from 300°C to 700°C, and 1°C min⁻¹ from 700°C to 1000°C. Then, cool down to room temperature. Finally, the surface morphology of TiN nanotube array and EDX will be measured through this nitration condition compared to previous samples. This part of the work will be emphatically analyzed in Chapter 3.4.3.

2.3.9 XRD Measurement of TiN

X-ray diffraction is a technique used for determining the atomic and molecular structure of a crystal, in which the crystalline atoms cause a beam of incident X-rays to diffract into many specific directions. By measuring the angles and intensities of these diffracted beams, a crystallographer can produce a three-dimensional picture of the density of electrons within
the crystal. From this electron density, the mean positions of the atoms in the crystal can be
determined, as well as their chemical bonds, their disorder and various other information. The
XRD spectra of the TiN nanotubes shows the three diffraction peaks corresponding to the TiN
(111), (200) and (220) crystal planes (Figure 2.12).

![XRD spectra of Ti substrate and TiN nanoarray](image)

**Figure 2.12** XRD patterns of Ti substrate and TiN nanoarray [39]

### 2.3.10 Bandgap Measurement of TiN

The bandgap of all the TiN samples by UV-Vis at the Lumigen Center of Department of Chemistry (Figure 2.13) was measured. Figure 2.13 shows the diffuse reflectance spectrum of TiN nanotubes. Using the Kubelka-Munk (K-M) equation,

\[
F(R) = \alpha = \frac{K}{S} = \frac{(1 - R)^2}{2R}
\]

where K is the K-M absorption coefficient, S is the K-M scattering coefficient, R is the
reflectance of the material (R=\%R/100), and \(\alpha\) is the optical absorption coefficient. Then using the transformed K-M function,

\[
(F(R) \times h\nu)^n = A(h\nu - E_g)
\]

where \(n\) is 0.5 for an indirect allowed transition or 2 for a direct allowed transition.

For the indirect transition, \(E_g = 1.6\).
2.4 Fundamental Limitation ---- Shannon criteria

According to Shannon criteria, an empirical rule in neural engineering for the possibility of tissue damage from electrical stimulation, the recommended limit density of a stimulation pulse is 30µC/cm² for a geometric surface area of 0.06cm² [6]. An empirical rule in neural engineering evaluates the possibility of damage from electrical simulation to nervous tissue [40]. The Shannon criteria relate three parameters for pulsed electrical stimulation, charge density per phase $D$ (µCoulombs/(phase•cm²)), the charge per phase $Q$ (µCoulombs/phase), and dimensionless parameter $k$. The relationship of these three parameters is the below equation.

$$\log D = k - \log Q$$
According to the rule, the stimulation parameters that yield \( k \geq 1.85 \) can cause damage to the adjacent nervous tissue. Currently, this empirical law is applied in neuromodulation for the development of implants for cortical, cochlear, retinal [41, 42] and deep brain stimulation [43]. Shannon categorizes the relationship between stimulating electrode and target neural tissue as either Near Field, Mid Field, or Far Field, and discusses how equation parameters may be chosen in each case. In the case of spinal cord stimulation [44], the Far Field category would apply. The data on which the Shannon model was built [15, 45] are restricted to experiments performed in cat cerebral cortex with 7 hours of stimulation under light anesthesia at 50 PPS with 400 \( \mu s \) pulses (charge-balanced, symmetric, biphasic, anodic-first) using platinum surface disc electrodes of 1 mm\(^2\) or larger, recessed, anodized sintered tantalum-tantalum pentoxide pellet electrodes of 1 mm in diameter, or Iridium penetrating microelectrodes of 6500 \( \mu m^2 \). As a result of these restricted methods, Shannon states, "A more comprehensive model of safe levels for electrical stimulation would also account for the effects of pulse rate, pulse duration, stimulus duty cycle, and duration of exposure."[46] Additionally, further study has demonstrated that microelectrodes do not obey the Shannon criterion, and new approaches may be proposed to address these limitations [40].

2.5 TiN nanotubes electrodes for chronic neural stimulation

Based on the good understanding of the TiN nanotubes growth and properties, it is expected that TiN could avoid reduction and oxidation reaction, which causes tissue damage by capacitive charge injection. TiN can also be corrosion-resistance for chronic stimulation applications. Experiments were designed to verify my hypothesis.

2.6 TiN nanotube arrays Growth on Ti wire

Titanium wire (purity 99.9% trace metals basis, diameter 0.5 mm) was purchased from Sigma-Aldrich company. In order to get a specific surface area for cyclic voltammetry and Electrochemical Impedance Spectroscopy measurement, the approximating disc electrodes
were fabricated by the prism glass capillaries (LE16, OD=1.65mm, ID=1.10mm, softens at 785°C). The Ti wires were placed in the glass capillaries and then heated the structure above the hydrogen nozzle (Figure 2.15).

**Figure 2.15** Seal the Ti wire in the prism glass capillary above the hydrogen nozzle

With glass sealed tightly around the wire, one end-surface was polished with SiC sandpapers, and the other end was secured to a gold connector with silver epoxy (Figure 2.16).

**Figure 2.16** Sealed and Polished (a) (c) Tungsten and (b) (d)Ti microdisk on Ti wire under Microscope
Then these Ti wires were ultrasonic in the Ethanol solution for 15 mins and then in the deionized water for 15 mins.

2.6.1 First-step in anodization of TiO$_2$ nanotube arrays

The as-ultrasonic Ti foil was connected by the anode, and the same sized Platinum foil was face-to-face connected by the cathode to form a two-electrode electrochemical cell in the well-prepared anodization solution for 2 hours with three different supplied voltages, 30V, 45V, and 60V.

![Figure 2.17 First-step anodization of TiO$_2$ nanotube arrays](image)

(a) Ti wire  
(b) TiO$_2$ nanotube growth setup

The as-anodized TiO$_2$ nanotube arrays were removed by ultrasonication in DI water for some time until the golden layer was totally removed.

![Figure 2.18 Remove TiO$_2$ nanotube arrays by ultrasonication](image)

2.6.2 Second-step in anodization of TiO$_2$ nanotube arrays

The setup of the second-step anodization of TiO$_2$ nanotube is the same as the first-step anodization, in Figure 2.7 (b). And the growth time of the second-step anodization is 30 mins.
2.6.3 Nitration of TiO$_2$ nanotube arrays

TiN nanotube array was synthesized by nitriding as-anodized TiO$_2$ nanotube arrays. A nitration treatment of TiO$_2$ nanotube array was conducted at 800°C for two hours in a Thermo furnace in an ammonia atmosphere, Figure 2.19. The progressive heating rates included 5°C min$^{-1}$ from room temperature to 300°C, 2°C min$^{-1}$ from 300°C to 700°C, and 1°C min$^{-1}$ from 700°C to 800°C. Finally, the TiN nanotube array was obtained after cooling down to room temperature.

![Figure 2.19 Nitration treatment of TiO$_2$ nanotube array](image)

2.6.4 Surface morphology and microstructure by SEM

The morphologies of the samples were also characterized by field emission scanning electron microscopy (FE-SEM) (Tescan LYRA 3, Version 1.1) at an acceleration voltage of 20 kV. With the increase of the supplied voltage, the pore size of the nanotube is increased linearly. The range of the pore size is from 45nm to 85nm with the supplied voltages, 30V, 45V, and 60V. During the experiments, 20V and 80V were also tried for the growth of the nanotubes. However, for the 20V supplied voltage, the nanotube could not stand upright and ununiformed. For the above 80V, the Ti material had a chemical reaction with the electrolyte. The current was growing quickly. This chemical reaction also released ammonia gas, which consumed the Ti material without forming nanotubes.
Figure 2.20 The surface morphology of TNTs

The different sizes of TiN nanotubes were formed by the different supplied voltages (Figure 2.20).

Figure 2.21 The relationship of the nanotube size and the applied voltage

EDX is also used to measure the degree of nitriding of TNTs on the Ti microwires. The TiN sample of the second anodization for 30 mins is analyzed by EDX, as Figure 2.22. It shows the element composition ratio of N and O is around 2:1. It also indicates that the nitration of TNTs on Ti microdisk is inadequate through the above conditions.
2.7 Cyclic voltammetry characterization of TNTs on wires

Cyclic Voltammetry (CV) is an electrochemical technique, which measures the current that develops in a three-electrode electrochemical cell by cycling the potential of a working electrode. The three-electrode electrochemical cell includes a working electrode, a non-current-carrying reference electrode, and a counter electrode. The potential provides the driving force for reactions at the working electrode, while the current is proportional to the rate of these reactions. CV identifies the presence of electrochemical reactions and provides information on the reversibility of the reactions, the quantity of electroactive material on the electrode, and the stability of the electrode. It is important to appreciate that the CV response, for any electrode material, can appear very different depending on the sweep rate, the geometric area of the electrode, and the roughness of the electrode, even though the electrochemical reactions are unchanged.

2.7.1 Cyclic voltammetry measurement

The electrical characterization of all TiN samples will be performed using cyclic voltammetry curves from -0.8V to 1V in x1 PBS solution at a scan rate of 100 mV/s.
Figure 2.23 CV curve measurement setup by Gamry Instrument

During the CV experiment, the supplied potential condition is from -0.8V to 1V, and the scan rate is 100mV/s. Since the diameter of the wire is 500um, the specific surface size of the electrode is $0.625\pi \text{ mm}^2$. The phosphate-buffered saline (PBS x1, salt concentration, pH7.4) is used as the electrolyte. The electrolyte was heated up to 37°C to simulate the normal human body temperature. And the three electrodes system is used as measuring the CV curve, including AgCl/Ag reference electrode, Pt counter electrode, and TiN wires work electrode.

(a)  (b)

Figure 2.24 (a) CV curve measurement of Tungsten (b) CV curve measurement with the different growth voltages of TiN with nanotubes and without nanotubes

Matlab program was used to calculate the area of the CV curve. The following equation gives the calculation method of the charge density. For the specific charge density, some research divides by 2 but some don’t divide. Singh[47] explained that for symmetric capacitors, when you use two electrode system which has same capacitance we divide by 2, whereas while
using a three electrode system using reference electrode and/or counter electrode we don’t divide by 2. Here, for TiN nanotube electrode, we used the three electrode system to measure the CV characteristics. We didn’t divide by 2 to calculate the charge density.

\[
\text{Charge Density} = \frac{\text{Area of CV curve}}{\text{Scan rate} \times \text{Area of the electrode}}
\]

<table>
<thead>
<tr>
<th>Type of the electrodes</th>
<th>Area of CV curve (uA*V)</th>
<th>Scan Rate (mV/s)</th>
<th>Area of the electrode (um^2)</th>
<th>Charge Density (mC/cm-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tungsten</td>
<td>3.2551</td>
<td></td>
<td></td>
<td>1.6586</td>
</tr>
<tr>
<td>40nm pore size TiN</td>
<td>5.4198</td>
<td>100</td>
<td>196250</td>
<td>2.7617</td>
</tr>
<tr>
<td>60nm pore size TiN</td>
<td>4.2408</td>
<td></td>
<td></td>
<td>2.1609</td>
</tr>
<tr>
<td>80nm pore size TiN</td>
<td>3.7558</td>
<td></td>
<td></td>
<td>1.9138</td>
</tr>
<tr>
<td>Flat TiN</td>
<td>1.1164</td>
<td></td>
<td></td>
<td>0.5689</td>
</tr>
<tr>
<td>Pt</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.05 ~ 0.15</td>
</tr>
<tr>
<td>SIROF</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1 ~ 5</td>
</tr>
</tbody>
</table>

Compared the results to the published research [6], the Charge Density of the TiN is around 0.8 mC/cm^2. With the high aspect ratio of the TiN nanotube, the surface area of the TiN nanotubes will be larger. So the performance of the TiN nanotubes will be better owing to its super surface to volume ratio.

2.7.2 CV measurement with different scan rates

The electrical characterization of all TiN samples will be performed using cyclic voltammetry curves from -0.8V to 1V in x1 PBS solution at different scan rates of 50mV/s, 100 mV/s, 200mV/s, 300mV/s and 500mV/s (Figure 2.25). During the CV experiment, the supplied potential condition is from -0.8V to 1V, and the scan rate is 100mV/s. Since the diameter of the wire is 500um, the specific surface size of the electrode is 0.625π mm^2. The phosphate-buffered saline (PBS x1, salt concentration, pH7.4) is used as the electrolyte. The electrolyte was heated up to 37°C to simulate the normal human body temperature. And the
three electrodes system is used as measuring the CV curve, including AgCl/Ag reference electrode, Pt counter electrode, and TiN wires work electrode.

![CV curve with different voltage rates of TiN nanotubes array](image)

**Figure 2.25** CV curve with the different voltage rates of TiN nanotubes array

### 2.8 Comparison of Tungsten Wire and TiN Nanotubes Microdisk Electrode

Tungsten wire (purity 99.9%, diameter 0.5 mm) was purchased from Sigma-Aldrich company. Tungsten electrode was selected for the comparative study because we can get the probes with similar geometric dimensions as TiN nanotube electrodes. The study was focused more on the corrosion performance of TiN nanotube electrodes in 0.9% phosphate-buffered saline (PBS) electrolyte.

#### 2.8.1 Impedance response in Phosphate-buffered saline (PBS)

Figure 2.26 shows the Nyquist plot of the impedance of tungsten and TiN electrodes in 37°C PBS over a period of time. The tungsten electrode shows a drastic charge in impedance
while TiN remains stable. For the long hours, the real part impedance of the tungsten electrode becomes smaller.

![Nyquist plot (EIS) of Impedance response of tungsten and TiN electrodes in PBS over a period with elapsed time as a parameter](image1)

**Figure 2.26** Nyquist plot (EIS) of Impedance response of tungsten and TiN electrodes in PBS over a period with elapsed time as a parameter

### 2.8.2 Optical Photographs under SEM

![SEM pictures of tungsten electrodes (a) before and after immersion in PBS for (b) 12 hours, (c) 24 hours, (d) 36 hours, (e) 48 hours, (f) 60 hours](image2)

**Figure 2.27** SEM pictures of tungsten electrodes (a) before and after immersion in PBS for (b) 12 hours, (c) 24 hours, (d) 36 hours, (e) 48 hours, (f) 60 hours
The above two figures present the SEM pictures of tungsten and TiN electrodes cycling in PBS solution (a) before (b) 48 hours, and (c) 60 hours. After 60 hours, the tungsten electrode was corroded. However, the TiN nanotubes electrode maintained similar surface topologies. The result shows the feasibility of using TiN nanotubes electrode in the neural implants for long term detection.

2.9 Conclusions

This work shows the great corrosion-resistant and high charge density of TiN nanotubes using microwire electrodes with different pore sizes. The specific charge capacity of nanoporous TiN correlates proportional to the surface area and pore size. In the published research [6], the charge density of the TiN is around 1 mC/cm$^2$. With the high aspect ratio of the TiN nanotube, the charge density is around 2.3 mC/cm$^2$, which is two times higher than the published research. Compared to the flat TiN without nanotubes, its charge density is just 0.57
mC/cm². This result fully explained the advantages of the TiN nanotubes owing to its super surface to volume ratio. The corrosion characterization was further discussed in the 0.9% phosphate-buffered saline (PBS) electrolyte at the temperature 37°C, which is similar to the normal human body temperature. After 60 hours, the tungsten electrode was visibly oxide based on the SEM morphology features. However, the TiN nanotube electrode stayed intact. After the tungsten and TiN electrodes in 37°C PBS over a period of time, the tungsten electrode shows a shift in impedance, while TiN almost remains stable. For the long hours, the real part impedance of the tungsten electrode becomes smaller. Compared to tungsten electrode, the impedance and morphology of nanoporous TiN shows more stable over the long-term. The result shows that the TiN nanotubes electrodes have a promising application in the neural probe stimulation.
CHAPTER 3 TITANIUM NITRIDE NANOTUBE ELECTRODES FOR BIOSENSOR APPLICATION

3.1 Introduction

The medical applications of electrodes range from small glucose sensors used by patients with diabetes to neural stimulators and recorders for neuron binding sites. The capability to stimulate neurons and to measure its response in-situ is essential for brain-computer interfaces (BCI). Selective detection of neurotransmitters has gained great attention as they strongly influence functions of the central nervous system and has been linked to various diseases such as schizophrenia, dementia, and Parkinson’s disease [48, 49]. Abnormalities to the concentration of neurotransmitters can provide information of mental disabilities and disease diagnosis. For a patient with Parkinson’s disease, the loss of motor control is due to the depletion of neurons producing dopamine (DA) [50]. Alternatively, the use of opioids has been found to increase the production of DA while also inhibiting the reuptake of the overproduced neurotransmitter leading to higher than normal DA concentrations [51]. The ability to continuously monitor dynamic behaviors of neurotransmitters would be a powerful tool for treating patients with neurological brain disorders. Since TiN nanotubes has a high surface area to volume ratio, they could accommodate more space for the ions contact and exchange. This will lead to much better performance in the examination speed and sensitivity when it is used as electrodes. In this research TiN nanotubes electrodes are further studied as neurotransmitters for the detection of dopamine and serotonin. In this section, I first review the electrodes that are currently being used for medical applications.

3.1.1 Dopamine Detection

DA is an electrochemically active compound, which is why the detection of DA using microelectrodes has gained such popularity. However, the measuring of DA has many inert challenges [48]. Within biological tissues, DA is found in very low (nM) concentrations, while
Uric acid (UA) and ascorbic acid (AA) are found in relatively high concentrations (0.2-0.5 mM) [52, 53]. The overlapping oxidation peaks of these compounds makes it very difficult for the simultaneous selective detection of DA using a bare electrode, and the electrochemical reactions can be irreversible [52, 53]. One solution is to cover the electrode with an ion doped thin film coating, which would attract DA while rejecting AA or other anionic interfering agents [48, 53].

Numerous studies have been completed for discovering the best type of microelectrode coating for DA detection. Palladium nanoparticle-loaded carbon nanofibers modified carbon paste electrode (Pd/CNF - CPE) [53] (diameter 1.2 mm, length 1 cm) fabricated by electrospinning and thermal treatment process showed excellent electrochemical catalytic activities towards DA by decreasing the oxidation over potential and enhancing peak current. Boron-doped diamond (BDD) microelectrodes [54] are fabricated with BDD deposited on tungsten wires using microwave plasma-assisted chemical vapor deposition. The BDD microelectrode showed low background current and selective oxidization of DA in the presence of AA. BDD microelectrodes have also shown to exhibit excellent performance for the oxidative detection of serotonin. This oxidation was found to occur with very low and reversible adsorption of quinone oxidation product [55]. Characteristics of the BDD microelectrode is a distinctly small electrode tip diameter (5 µm, tip length 250 µm) with a polycrystalline diamond grain size of 2 µm. Chrysanthemum-like titanium nitride (CL-TiN) nanostructure modified glassy carbon electrode [56] was fabricated using solvothermal and ammonia annealing methods. The modified electrode showed improved electrocatalytic activity toward AA and UA over the bare glassy carbon electrode.

Carbon-based materials have been recognized for the advantages of adsorptive characteristics when used with organic solvents [57]. The experiments completed by Pihel et al. [58], utilized thin films of overoxidized polypyrrole coated to carbon fiber microelectrodes
for the selective detection of dopamine with fast-scan Cyclic Voltammetry (CV) at a rate of 300 V/s. Characterizations of the Polypryrrol polymer revealed that the oxidation of the coating resulted in the addition of carbonyl and carboxylic groups that attract DA cations while rejecting AA anions. The experiment concluded that the coated electrode was 3 times more sensitive to DA than the uncoated electrode and proved to be as effective as electrodes coated in Nafion. Separate work had been completed by Bath et al. [57] where two different glass encased carbon fiber electrodes (T560 and P55) were constructed and polished on a diamond coated wheel. Using in vivo experimentation, results showed that temporally accurate voltammetric responses are obtained through fast scan rates at high frequencies. The bare carbon electrode showed a delayed response to concentrations of species that adsorb at the electrode surface. Later work completed by Heien et al. [59] showed that the degree of adsorption is a function of the rest potential and by increasing the anodic potential limit during a scan from 1.0 V to 1.4 V there is an increase in sensitivity for dopamine. Here, a glass-encased carbon fiber (T560) was constructed by aspirating individual fibers into glass capillaries. A multiwalled carbon nanotube modified platinum electrode has successfully been used for the determination of serotonin in plasmatic serum samples using differential pulse voltammetry (DPV). The physical characteristics of the electrode included compact layers of a globular shape, each globule being an average size of 400 nm [60].

Wightman et al. [61] shows obstacles that one may encounter when trying to read the concentration levels of dopamine in extracellular fluid of the brain, one of which being the low concentration levels of dopamine. Electrodes being used for the recording of dopamine are much larger than the synapse where the neurotransmitters are located thus the measurements of dopamine are taken from the overflow of the synaptic region. However, dopamine can only diffuse small distances, and most overproduced dopamine neurotransmitters are brought back into the neuron in a re-uptake process. This leaves a very small concentration of free dopamine
in the extracellular fluids. Nafion, a cation-exchange material, has been described for the use of achieving sensitivity for glucose, it can also be used for improving the sensitivity of dopamine.

![Figure 3.1 CV detection of dopamine with different electrodes](image)

**Figure 3.1** CV detection of dopamine with different electrodes

Research presented by How and Soon [49] explained how dopamine levels could be assessed by using highly exposed facets of titanium dioxide (TiO₂) that have been modified with reduced graphene oxide (rGO). With the issue of low dopamine concentration and DA and AA having similar oxidation potentials, many other electrodes are inefficient in the detection of DA. The above image shows the electrochemical oxidation of 0.5 mM DA with variations of titanium oxide or graphene oxide electrodes. It is clear to see the high oxidation of DA with the rGO/TiO₂ electrode. The results showed that dopamine and AA had an overlapping voltammetric response on a bare GCE while the modified electrode was able to exhibit separation potential between the two elements of about 0.2 V.

3.1.2 Serotonin Detection

Serotonin (5-hydroxytryptamine), another type of neurotransmitter, has been known for influencing physiological systems such as cardiovascular and thermoregulation as well as a variety of behavioral functions including appetite, sensorimotor reactivity, and pain sensitivity. Changes in serotonin levels can be linked to a range of psychiatric disorders,
including depression, anxiety, and obsessive-compulsive disorder (OCD) [62]. In recent years, glassy carbon electrodes (GCE) have been widely used for the serotonin detection. Filik et al. [63] used the modified GCE for the detection of serotonin in human serum. The GCE was modified by an electrooxidative polymerization of safranine O with applying potential from −0.8 to 1.2 V vs. Ag/AgCl at a scan rate of 50 mV (15 cycles). Liu et al. [64] fabricated a 5-HT biosensor based on a Nafion membrane-coated colloidal gold screen printed electrode (Nafion/CGSPE) to monitor serotonin levels in depressed and anti-depressant-treated rats. Bliem et al. [65] developed an ion-selective electrode based on a plasticized PVC membrane. To fabricate this potentiometric sensor, a cobaltabisdicarbollide anion was embedded in a plasticized PVC as an ion-pair generator, and the formation of an ion pair complex between the protonated serotonin and a carborane anion leads to the determination of serotonin levels.

3.2 TiN nanotubes electrodes for neurotransmitter detection

Among various implantable electrodes, including platinum (Pt), tungsten (W), iridium oxide (IrOx), titanium nitride (TiN) is very attractive thanks to its large specific capability, CMOS compatible process, and biocompatibility. The non-reactive, non-absorptive, and non-additive properties satisfy the FDA guidelines set forward by 21 CFR 211.65 [66]. Briggs et al. [67] have successfully fabricated CMOS-compatible titanium nitride nano-scale antennas for information processing applications. Previous research included corrosive resistance of TiN nanotube microwire electrode with different pore sizes. This proved that the TiN nanotube electrode has high biocompatibility, high strength, and reduced corrosive behavior. The nanotube morphology supports a smaller microwire diameter (0.5 mm) while increasing the surface area of the charge injection [38]. This morphology also increases biocompatibility as a biomimetic surface topography, thus not disrupting surrounding tissues when implanted. The fabricated electrode can be used for dual purposes in both electrochemical stimulation of
surrounding tissue as well as for reaction recognition and recording. To the best our knowledge, 
TiN nanotubes electrode has not been demonstrated to measure chemical neurotransmission. 
For the first time, TiN nanotube electrodes were synthesized for evaluation of neurotransmitter 
detection. This work demonstrated the detection of different biological compounds: dopamine 
and serotonin.

3.3 Materials and Reagent for the Experimental

3.3.1 Carbon Fiber Electrode

Carbon Fiber microelectrode was purchased from Kation Scientific (P.O. Box 14674 
Minneapolis, MN, USA), and used as a reference to evaluate the performance of the TiN 
nanotube probes. Exposed microelectrode tip length of 100 µm and a tip diameter of 34 µm. 
Carbon Fiber was encapsulated in the thick borosilicate glass for durable mechanical support 
and electrical insulation.

3.3.2 Titanium Wire

Titanium wire (purity 99.9% trace metals basis, diameter 0.5 mm) was purchased from 
Sigma-Aldrich company. In order to get a specific surface area for the various electrochemical 
characterization’s measurement, the approximating disc electrodes were sealed in prism glass 
capillaries (LE16, OD=1.65mm, ID=1.10mm, softens at 785°C).

3.3.3 Electrode Comparison

Two different types of wire electrodes were used for the experimentation of the detection 
of dopamine and serotonin. The purpose of including Carbon Fiber electrode is to serve as the 
reference material to the efficiency of our fabricated TiN nanotube electrode. The size of the 
electrode is very important for in vivo testing as a smaller tool size decreases the amount of 
tissue damage when implanted. Comparing the size of each electrode, while our electrode is 
larger compared to the Carbon Fiber, we believe that the added surface area of the nanotube 
will allow for decreasing wire diameter while keeping electrochemical detection capabilities.
Table 3.1 Dimensions of the carbon fiber electrode and TiN nanotubes (TNTs) electrodes.

<table>
<thead>
<tr>
<th>Material</th>
<th>Diameter</th>
<th>Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiN microdisk</td>
<td>0.5mm</td>
<td>12.6um</td>
</tr>
<tr>
<td>Carbon Fiber</td>
<td>34um</td>
<td>100um</td>
</tr>
</tbody>
</table>

3.3.4 Electrolyte for Ti microdisk Anodization

The 400mL electrolyte solution was mixed by ethylene glycol (EG) electrolyte (392 mL, 1.11g/mL), 0.5 wt% NH₄F (2.23g) and 2 vol% deionized water (8 mL, 1g/mL). All components were added to a sterilized and dry brown bottle to reduce light interaction with the electrolyte. Then stirred the electrolyte with a magnetic stirrer for 12 hours to make them mix completely.

3.3.5 Tris Buffer (1 M, pH 7.4) recipe and preparation

Tris buffers are critical in the extraction and electrophoresis of DNA from cells. Tris aids in the destabilization of cell membranes, as well as protecting the exposed DNA from pH changes in a buffer solution. Tris base (molecular weight: 121.14 g/mol) is required. 1 M of tris buffer was configured with the tris buffer mass 121.14g. Then 800 mL of distilled water was prepared in a suitable container. 121.14 g Tris base was added to the solution. The solution was adjusted to the desired pH using HCl (typically pH ≈ 7.4). The volume of HCl is around 70mL. Finally, the distilled water was added until the total volume is 1 L.

3.3.6 Dopamine preparation

Dopamine solutions were prepared by dissolving dopamine HClO into the Tris-buffer prior to each experiment. 3-Hydroxytyramine Hydrochloride (99%, ACROS Organics™) was purchased from the Sigma-Aldrich company. 10mM dopamine in the 30mL Tris-buffer was first configured. Then the 10mM dopamine was diluted into smaller concentrations by the addition of tris buffer. Solutions were purged by pure Nitrogen gas for 15 minutes prior to the start of experimentation. The surface is blanketed with nitrogen gas to prevent atmospheric oxygen dissolving into solution.
3.3.7 Serotonin Configuration

Serotonin, 3-(2-Aminoethyl)-5-hydroxyindole, 5-HT, 5-Hydroxytryptamine was purchased from Sigma-Aldrich company. The formula of the Serotonin is C_{10}H_{12}N_{2}O. And the molecular weight is 176.22g/mol. The serotonin was configured into the Phosphate Buffered Saline (PBS x1, salt concentration), pH 7.2 with 1 mM, then diluted to 500 µM, 250 µM, 125 µM 62.5 µM and 31.25 µM. The serotonin was detected by the carbon fiber electrode and TiN nanotubes wires. Each solution was purged for 15 minutes prior to the start of experiment by Nitrogen. Blanketed the surface with nitrogen gas to prevent atmospheric oxygen dissolving into solution.

3.3.8 Apparatus

The well-fabricated TiN nanotubes electrodes were characterized by field emission scanning electron microscopy (FE-SEM) (Tescan LYRA 3, Version 1.1, USA) at an acceleration voltage of 20 kV. Tube Furnace, (Thermo Fisher Scientific Lindberg/Blue), was used for nitrating as-anodized TiO$_2$ nanotube arrays. Various electrochemical characterizations, including Cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS), were performed on a Gamry electrochemical Analyzer (CyberResearch, INC. Branford, Connecticut, USA). 34 um Carbon Fiber microelectrode and 500 um diameter TiN nanotubes working electrodes were individually combined with Pt-wire reference electrode (CH Instruments, Inc.) and saturated Ag/AgCl reference electrode (CH Instruments, Inc.) into a three-electrode electrochemical cell.

3.3.9 Fabrication of TiN nanotubes electrode

The glass capillaries were used by placing the wires into glass tubes and then heating the structure above the hydrogen nozzle. The uniform shape was completed by rolling the glass capillary delicately as it was heated. With the glass sealed tightly around the wire, one end-surface was polished with SiC abrasive paper (CarbiMet™, Buehler Company, USA,
and the other end was secured to a gold connector with silver epoxy. The cleaning process of the sealed Ti wires was a two-step ultrasonic bath. The wires were immersed in ethanol for 15 minutes, followed by DI water for 15 minutes. The wires were completely dried before the development of nanotubes. Highly ordered TiO$_2$ nanotubes were prepared by using the above two-step anodization technique.

### 3.3.10 Nitriding of TiO$_2$ nanotubes electrode

TiN nanotube array was synthesized by nitrating as-anodized TiO$_2$ nanotube arrays. TiN without nanotube was also nitrated in the same condition. A nitration treatment of TiO$_2$ nanotube array was conducted at the different highest temperatures, 800°C, 900°C, 1000°C, 1100°C for 2 h in the Thermo furnace in an ammonia atmosphere. The beginning progressive heating rates for these four samples were the same, including 5°C min$^{-1}$ from room temperature to 300°C, 2°C min$^{-1}$ from 300°C to 700°C, and 1°C min$^{-1}$ from 700°C to 800°C. From 800°C to 1100°C, all the heating rate is 1°C min$^{-1}$. Then the highest temperature was kept for two hours. Finally, the TiN nanotube array was obtained after cooling down to room temperature. The mechanical properties of the wire changed at different temperatures. Wires that were nitrated above 900°C were very fragile and easily broken during the experiment. The fragility of the wire samples potentially is caused by the reaction of the carbon with titanium at high temperatures. When heated together, titanium carbide (TiC) is formed – a black powder with high tensile strength. However, the formation of TiC leads TiN to weaken as titanium complexes are broken.

### 3.3.11 Electrochemical Characterization

CV and EIS measurements were completed using Gamry Instruments. CV was used to measure the current by cycling the potential of a working electrode. The potential provided the driving force for reactions at the working electrode, while the current was proportional to the rate of these reactions. CV identified the presence of electrochemical reactions and provided
information on the reversibility of the reactions, the quantity of electroactive material on the electrode, and the stability of the electrode. It is important to appreciate that the CV response, for any electrode material, can appear very different depending on the sweep rate, the geometric area of the electrode, and the roughness of the electrode, even though the electrochemical reactions are unchanged. EIS, known as dielectric spectroscopy, could determine the dielectric properties of the material. This method gauged the system impedance over a series of frequencies, and the data gathered was graphically conveyed in Nyquist. For each configuration, the following procedure was used to ensure a good, clean surface of the foil or wire. When the CV and EIS measurements had been completed for a sample, it was then rinsed repeatedly and cautiously with DI water to remove surface-level contaminants. Samples were then placed in a 100°C oven for 10 minutes to completely remove DI water from the surface as well as any molecules that may have entered nanotubes.

3.3.12 Measurement and algorithms for DA and serotonin detection

The reaction taking place during cyclic voltammetric testing has a simple electrochemical mechanism, shown as follows:

\[ A + e^- \rightleftharpoons B \]

The redox potential is \( E_0 = 0V \), and the heterogeneous rate constant, \( K_{\text{het}} \), is assumed to be \( 10^{-2} \text{ m/s} \) with diffusion coefficients for both oxidized and reduced specie to be \( 10^{-9} \text{ m}^2/\text{s} \). The transport process can be described through Nernst Planck equations.

\[
R_i = \frac{\partial c_i}{\partial t} + \nabla * ( - D_i \nabla c_i - u_i z_i F c_i \nabla \phi + c_i \mu )
\]

Here, \( c_i \) is the concentration, \( D_i \) is the diffusion concentration, \( u_i \) is mobility, \( z_i \) is charge, \( F \) is Faraday constant, \( \phi \) is electric potential, and \( \mu \) is velocity field. The terms due to migration and convection are neglected due to the presence of the electrolyte and absence of convection. The reaction term, \( R_i \), can also be neglected as we can assume no chemical reactions occurring
for the bulk of the electrolyte. Thus, the above equation can be reduced to the following:

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (D_i \nabla c_i) = 0$$

The effects of subsequent phenomena only occurring at the electrode surface, such as charge transfer and adsorption, can be described by the Butler-Volmer equation.

$$i = i_0 \left[ \exp \left( \frac{\alpha_A nF}{RT} \eta \right) - \exp \left( - \frac{\alpha_c nF}{RT} \eta \right) \right]$$

Where, $i_0$ is the exchange current density, $\eta$ is the overpotential $(V - E_0)$, $n$ number of electrons, $\alpha_A$ is the anodic transfer charge coefficient, and $\alpha_c$ is the cathodic charge transfer coefficient. Since the above equation is expressed in terms of charge densities, it is not suitable for use with mass transport. Rearranging, it is possible to find the following:

$$M = C_{ox} K_f - C_{red} K_b$$

$$K_f = K_{het} * e^{\frac{\alpha_A nF}{RT} \eta}$$

$$K_b = K_{het} * e^{-\frac{\alpha_c nF}{RT} \eta}$$

Here, $M$ is the mass flow density expressed as the number of mol crossing the unit surface in the time unit [68]. While the charge-transfer process is important to the spectrum of chemical reactions, it is seldom occurring alone. In contrast, electron-transfer reactions are frequently coupled with the creation or breaking of bonds. Various methods can be used to theoretically analyze cyclic voltammetry, the simplest being the $EC_{irr}$, which is composed of electron-transfer with subsequent first-order, irreversible chemical follow-up reaction. In this mechanism, the initially formed anion decays and a new species is created, with only a small amount of the primary anion available for oxidation within the reverse sweeping process. The anodic current and the CV curve decreases until it is fully disappeared [69].

3.4 Results and Discussion

3.4.1 Morphological Characterization of TiN Nanotubes Electrodes

Scanning electron microscopy (SEM) was used to identify the structural differences of
nanotube growth at each TiN nitration temperature. Through this process, it was discovered that foil samples nitrated at and above 1000°C showed cracking in nanotube surface and poor alignment morphology. Figure 3.2 displays the SEM images of sample surfaces as well as nanotube morphology and cross-section. The progression of surface cracking can easily be detected from images (a) to (e). Large cracking leads to non-uniform nanotube morphology, potentially disrupting efficient detective procedures. The average length of nanotubes, shown in the image (f), is 12.6 μm with a pore size of 87 nm. Thermal annealing practices, studied by Varghese et al. [70], showed that elevated temperatures of dry and humid argon environments decrease the stability of titanium oxide nanotube arrays. Pore diameter shrinkage and the full collapse of nanotube structure were found in samples annealed at temperatures around 880ºC. It is possible that at high temperatures, nanotube structures are collapsing, forming what can be seen as cracks in nanotube surface morphology. Cracked areas show titanium substrate intact.

![Figure 3.2 SEM images of TiN nanotubes: the surface morphology of TiN foil at different nitration conditions (a) 800°C, (b) 900°C, (d)1000°C, (e)1100°C; (c) the porous structure of TiN nanotubes with diameter 65 nm, (f)cross-section of TiN nanotubes with length 12.6 um.](image)
Figure 3.3 SEM images of the porous structure of TiN nanotubes with cross-section of TiN nanotubes: the surface morphology of TiN foil at different nitration conditions (a) 800°C, (b) 900°C, (c) 1000°C, and (d) 1100°C.

Matlab programmer was used to analyzing the pore size distribution (Figure 3.4) according to the SEM images.

Figure 3.4 SEM images of the porous structure of TiN nanotubes with cross section of TiN nanotubes: the surface morphology of TiN foil at different nitration conditions (a) 800°C, (b) 900°C, (c) 1000°C, and (d) 1100°C.
According to the analysis of the porous structure, the average pore size is around 85 nm from 800°C to 1000°C. And the pore size of the 1100°C is a little bit larger than others. It may be caused by the high temperature.

**Table 3.2** SEM images of the porous structure of TiN nanotubes with cross-section of TiN nanotubes

<table>
<thead>
<tr>
<th></th>
<th>800°C</th>
<th>900°C</th>
<th>1000°C</th>
<th>1100°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porosity</td>
<td>0.2262</td>
<td>0.1571</td>
<td>0.1691</td>
<td>0.2513</td>
</tr>
<tr>
<td>Average Pore Radius</td>
<td>0.0831</td>
<td>0.0844</td>
<td>0.0870</td>
<td>0.0944</td>
</tr>
<tr>
<td>Standard Deviation of Pore radius</td>
<td>0.0252</td>
<td>0.0132</td>
<td>0.0144</td>
<td>0.0186</td>
</tr>
</tbody>
</table>

3.4.2 Pore size distribution of TiN Nanotubes Electrodes

Figure 3.5 shows the N\textsubscript{2} adsorption/desorption isotherms of TiN nanotube with a diameter of 65 nm and length 12.6 µm. The nanostructure exhibited a type IV isotherm, according to IUPAC, and indicated the existence of a pore size range from mesopores to macropores [71]. At relative pressure of above 0.1, the sample shows almost no increment in N\textsubscript{2} adsorption capacity, which shows that the limited amount of mesopores [72, 73]. While the final increased tails in the curves at a relative pressure from 0.9 to 1.0 suggest the increment of macroporosity [73]. The specific surface area of the TiN nanotube sample is 38.8873 m\textsuperscript{2} g\textsuperscript{-1} for 87 nm. The nanotube arrays lead to an increased surface area, which could in turn provide more electrochemical active sites to enhance chemical reactions and mass transport.

![N\textsubscript{2} adsorption/desorption isotherms of TiN nanotube with a dimension of length 12.6 µm, diameter 87 nm and specific surface area 38.8873 m\textsuperscript{2}/g.](image.png)

**Figure 3.5** N\textsubscript{2} adsorption/desorption isotherms of TiN nanotube with a dimension of length 12.6 µm, diameter 87 nm and specific surface area 38.8873 m\textsuperscript{2}/g.
3.4.3 Element Analysis of TiN Nanotubes Electrodes

The introduction of the nanotube morphology has proven to increase the surface area of the electrode and create a morphology that manipulates how compounds can adsorb to the electrode surface, thus influence the detection of different biological materials. This foundation is very important. For the first time, surface modification of TNT growth has been used for the specific detection of micro-concentration biological compounds.

X-ray photoelectron spectroscopy (XPS) is an analytical technique used for the elemental analysis of a sample. Using the XPS for analyzing samples of TiO$_2$ without nitration, TiN nitrated at 800ºC, and TiN nitrated at 1000ºC it is possible to compare the surface-level elements present. Each sample shows the detection of carbon, titanium, and oxygen. As expected, TiO$_2$ foil only shows trace amounts of nitrogen, 1.37%, which is presumably from the electrolyte.

<table>
<thead>
<tr>
<th>Element</th>
<th>TiN 800ºC At%</th>
<th>TiN 1000ºC At%</th>
<th>TiO$_2$ At%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti2p</td>
<td>28.31</td>
<td>27.93</td>
<td>18.17</td>
</tr>
<tr>
<td>C1s</td>
<td>18.80</td>
<td>19.20</td>
<td>31.89</td>
</tr>
<tr>
<td>N1s</td>
<td>24.56</td>
<td>28.56</td>
<td>1.37</td>
</tr>
<tr>
<td>O1s</td>
<td>28.33</td>
<td>24.31</td>
<td>41.39</td>
</tr>
<tr>
<td>F1s</td>
<td>-</td>
<td>-</td>
<td>7.18</td>
</tr>
</tbody>
</table>

Surprisingly, the sample that had not been nitrated and left as TiO$_2$ showed the detection of residual fluoride ions left from the nanotube growth electrolyte, 7.18%. Fluoride ions present to create an inadequate sample and should be fully removed in a cleaning process. Fluoride ions present in ammonium environment at the time of nitration would form ammonium-fluoride (NH$_4$F), a crystalline powder soluble in water that decomposes at the temperature of 100ºC. For this reason, high nitration temperatures used in the experiment, from 800ºC to 1100ºC, would fully eliminate residual fluoride ions left on samples and thus are not detected in XPS data. TiN nanotube array nitrated at 1000ºC shows higher content of carbon and nitrogen at 19.20% and 28.56%, respectively. Previously, for the samples of 800ºC, the carbon
and nitrogen content are 18.80% and 24.56%, respectively. Oxygen content decreases with an increase in nitration temperature, going from around 28.33% at 800°C and decreasing to 24.31% at 1000°C.

High oxygen contents are worrisome, as this reveals an impure TiN surface. Recent theories have been examined for an explanation of the surface oxide phases formed during high temperature treatments, such as the high nitration temperatures greater than 800°C. One such study found that high oxygen exposures and increased temperatures would lead the TiN surface to become partially oxidized to a mixture of TiO₂ and TiNₓOᵧ [74]. During oxidation of nitrides, the oxygen substitutes the nitrogen, which then leaves the substrate as gaseous N₂. An intermediate step before the completion of oxidation occurs at which there is an N-O bonding taking place either on the growing oxide layer or at the TiO₂/TiN interface [75]. Flushing techniques with argon suggest that possible trapped N₂ within the solid metal accumulates and then reacts with formed oxide to create titanium oxynitride [75, 76]. Increased temperatures are also causing an increased amount of oxygen to be adsorbed to the TiN surface – then to be oxidized to TiO₂. The process associated with nitrogen-oxygen exchange highly endothermic (2.84 eV), meaning that a large amounts of heat are needed for the exchange to occur [77]. However, at such high temperatures, we hypothesize that large amount of oxygen gas would be released from the surface, which explains the decreasing At% with increased nitration temperatures. The TiN sample is only partially oxidized, not fully.

It is predicted that environmental carbon is leading to increased levels on the electrode surface. Further, XPS measures were taken before and after an argon etching process to remove surface-level carbon. Results are shown in Figure 3.6. Samples of both TiN and TiO₂ were used for comparing the effects of etching 5 nm of the surface using argon. Using both nitration and argon etching will produce samples with the lowest carbon concentration present on the electrode surface.
Figure 3.6 Elements compound of TiO$_2$ and TiN nanotubes using XPS: (a) before etching (b) after etching 5 nm electrode surface by argon.

Table 3.4 Elements compound of TiO$_2$ nanotubes using XPS before etching

<table>
<thead>
<tr>
<th>Peak</th>
<th>Type</th>
<th>Position</th>
<th>FWHM</th>
<th>Raw Area</th>
<th>RSF</th>
<th>Atomic Mass</th>
<th>%</th>
<th>Conc %</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>1s</td>
<td>Reg</td>
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<td>6</td>
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<tr>
<td>O</td>
<td>1s</td>
<td>Reg</td>
<td>527</td>
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<td>15.999</td>
<td>45.82</td>
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<tr>
<td>Ti</td>
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<td>Reg</td>
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<td>47.878</td>
<td>20.32</td>
</tr>
<tr>
<td>N</td>
<td>1s</td>
<td>Reg</td>
<td>397</td>
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<td>6632.5</td>
<td>0.477</td>
<td>14.007</td>
<td>0.91</td>
</tr>
<tr>
<td>C</td>
<td>1s</td>
<td>Reg</td>
<td>282</td>
<td>3.281</td>
<td>108260</td>
<td>0.278</td>
<td>12.011</td>
<td>26.95</td>
</tr>
</tbody>
</table>

Table 3.5 Elements compound of TiO$_2$ nanotubes using XPS after etching 5 nm electrode surface by argon

<table>
<thead>
<tr>
<th>Peak</th>
<th>Type</th>
<th>Position</th>
<th>FWHM</th>
<th>Raw Area</th>
<th>RSF</th>
<th>Atomic Mass</th>
<th>%</th>
<th>Conc %</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Reg</td>
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<td>230345</td>
<td>1</td>
<td>18.998</td>
<td>11.13</td>
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<tr>
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<td>Reg</td>
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<td>15.999</td>
<td>50.22</td>
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<tr>
<td>Ti</td>
<td>2p</td>
<td>Reg</td>
<td>456</td>
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<td>1039449.9</td>
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<td>47.878</td>
<td>31.83</td>
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<tr>
<td>N</td>
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<td>3.96</td>
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<tr>
<td>C</td>
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<td>Reg</td>
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<td>11855</td>
<td>0.278</td>
<td>12.011</td>
<td>2.87</td>
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</table>

Table 3.6 Elements compound of TiN nanotubes using XPS before etching

<table>
<thead>
<tr>
<th>Peak</th>
<th>Type</th>
<th>Position</th>
<th>FWHM</th>
<th>Raw Area</th>
<th>RSF</th>
<th>Atomic Mass</th>
<th>%</th>
<th>Conc %</th>
</tr>
</thead>
<tbody>
<tr>
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<td>18.998</td>
<td>1.36</td>
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<tr>
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<td>Reg</td>
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<td>756794.9</td>
<td>2.001</td>
<td>47.878</td>
<td>23.34</td>
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<tr>
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<td>1s</td>
<td>Reg</td>
<td>396</td>
<td>3.196</td>
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<td>0.477</td>
<td>15.999</td>
<td>11.06</td>
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<td>Reg</td>
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<td>42.42</td>
</tr>
<tr>
<td>C</td>
<td>1s</td>
<td>Reg</td>
<td>284</td>
<td>3.229</td>
<td>89530</td>
<td>0.278</td>
<td>12.011</td>
<td>21.82</td>
</tr>
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</table>
Table 3.7 Elements compound of TiN nanotubes using XPS after etching 5 nm electrode surface by argon

<table>
<thead>
<tr>
<th>Peak</th>
<th>Type</th>
<th>Position</th>
<th>FWHM</th>
<th>Raw Area</th>
<th>RSF</th>
<th>Atomic Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>BE</td>
<td>(eV)</td>
<td>(eV)</td>
<td>(cps eV)</td>
<td>Mass Conc</td>
<td>%</td>
<td>Conc %</td>
</tr>
<tr>
<td>F</td>
<td>1s</td>
<td>Reg 686</td>
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<td>14010</td>
<td>1</td>
<td>18.998</td>
</tr>
<tr>
<td>O</td>
<td>1s</td>
<td>Reg 531</td>
<td>3.369</td>
<td>1352735</td>
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</tr>
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<td>Ti</td>
<td>2p</td>
<td>Reg 456</td>
<td>9.902</td>
<td>1361375</td>
<td>2.001</td>
<td>47.878</td>
</tr>
<tr>
<td>N</td>
<td>1s</td>
<td>Reg 397</td>
<td>3.181</td>
<td>176370</td>
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<td>14.007</td>
</tr>
<tr>
<td>C</td>
<td>1s</td>
<td>Reg 282</td>
<td>4.808</td>
<td>6867.5</td>
<td>0.278</td>
<td>12.011</td>
</tr>
</tbody>
</table>

3.4.4 Dopamine Detection

The detection of dopamine was studied at varying concentrations. A range of concentrations was used for collecting data on the limit of detection, or the lowest concentration that was detected with the working electrode. All concentrations were tested with each nitration temperature TiN foil and wire and Carbon Fiber electrode as reference data. Figure 3.7 is showing the CV curves of four TiN foils nitrated at 800°C, 900°C, 1000°C, and 1100°C in electrolyte configured to 2.5 mM dopamine. The curve representing foil with no nanotube growth (green, nitrated at 800°C) signifies that TiN without modified surface fabrication cannot be used for biological compound detection. The foil without modified nanotube growth showed a significantly smaller charge capacitor in 1 mM dopamine. All foils with added surface modifications of nanotube structural growth expressed a greater affinity for dopamine and increased charge density. It is possible that the charge density is affected by the nitration temperature, as the trend of nitration temperature and charge density has a somewhat linear relationship. Prominent oxidation peaks can be found for the foil nitrated at 1100°C (blue). This is surprising, as the surface morphology for foil nitrated at 1100°C is not uniform in nanotube growth and produces cracking and unstable structure of the surface, however, the increased charge density resulted in increased sensitivity. Detection peaks can be seen around 0.4V. These peaks become smaller as the nitration temperature and charge density are decreased.
Figure 3.7 CV curves in the 1mM Dopamine with the different nitration temperatures. Figure 3.8 shows the progression of each sample in decreasing dopamine concentrations. From here, it is possible to find a limit of detection for the tested samples, as each sample shows a decreased affinity for dopamine at lower concentrations.

Figure 3.8 CV curves in the different concentrations of Dopamine (a) Carbon Fiber electrode (b) TiN wire at 800 °C.
Carbon Fiber electrode (a) showed the lowest affinity for dopamine detection, with no good results for the highest concentration of 100 uM. TiN wire nitrated at 800ºC (b) showed stable progression in decreasing concentrations of dopamine. The decrease in the sensitivity of the electrode with lower dopamine concentration is due to the slowing of electron transfer at the electrode/electrolyte interface. Small concentrations of dopamine cause a sluggish electrochemical response, which cannot be easily detected by CV generating the diminished oxidation peaks.

3.4.5 Serotonin Detection

Results of testing of serotonin configurations showed similar trends with that of testing dopamine. With the decreased concentration, the affinity of serotonin detection decreased linearly. Figure 3.9 shows the CV results for TiN foil in a 1 mM concentration of serotonin. The electrodes with higher nitration temperatures had an increased affinity for the detection of serotonin, as was the case with dopamine. This, again, can be attributed to the increased charge density with higher nitration temperatures. The foil without modified nanotube growth also showed a significantly smaller charge capacitor in 1 mM serotonin. Titanium has a melting point of 1,660ºC and it can be assumed that high nitration temperatures over 1000ºC are causing structural bonds to be broken. From these results, a nitration temperature between 900ºC and 1000ºC showed the most effective for the detection of serotonin.

![Figure 3.9 CV curves in the 1mM Serotonin with the different nitration temperatures](image)

**Figure 3.9** CV curves in the 1mM Serotonin with the different nitration temperatures
Figure 3.10 shows the limit of detection for all samples in serotonin. Carbon Fiber (a) showed the least affinity for serotonin with a limit of detection around 31.25 µM, whereas TiN wire has a limit of detection around 62.5 µM.

![Figure 3.10 CV curves in the different concentrations of Serotonin (a) Carbon Fiber electrode (b) TiN wire at 800 °C.](image)

3.4.6 Hydrogen Peroxide Detection

Hydrogen Peroxide ($H_2O_2$) was tested as a reference data point to the above tests. When a sample is submerged into the $H_2O_2$, reactions immediately take place as gas bubbles can be seen coming off from all electrodes used for electrochemical cell. This is due to the corrosive nature of the solution. Hydrogen Peroxide results were very similar to the results found by Si & Song [50] for the CV images.
Figure 3.11 CV curves in the 30% H₂O₂ (Hydrogen Peroxide) for TiN wire

Figure 3.11 shows the CV curves in the H₂O₂ for TiN wire. It is interesting to note that increasing the nitration temperature has a little influence on the found chemical reaction at the surface of the material. The higher temperatures of 1000°C and 1100°C were not tested for H₂O₂ detection as these wires were not stable enough for further testing.

3.5 Other potential applications

3.5.1 Glucose Detection

It is important to note that many electrochemical glucose sensors created from metals or alloys can potentially lose activity due to the poisoning of chloride ions. Carbon nanotube electrode remained to have a high sensitivity even with the presence of high concentration of chloride ions. However, this electrode has limitations with being in concentrations of Ascorbic Acid (AA) or Uric Acid (UA), which are present in real biological samples. Experiments were studied for the detection of glucose molecules involve using electrode materials that have a uniform porous structure, the large surface area for better detection, or glucose enzyme encapsulation methods. Ye et al. [78], reported results of recording 30 mM glucose at the speed of 100 mV/s using multi-wall carbon nanotubes (MWNTs) electrode. Wang et al. [79] achieved similar results using a Zinc oxide (ZnO) nanocomb biosensor. For these experiments, the electrodes were coated with Nafion in order to select against AA and UA in the sample. The ZnO nanocoms are a favorable choice for the glucose biosensor for reasons of high surface area and excellent biocompatibility properties. The same properties can also be seen in TiN,
which allows us to believe that a TiN biosensor would have similar results. Yu et al. [80] worked on glucose detection where a glucose sensor was fabricated by immobilizing enzyme glucose oxidase.

TiN may have some of the same or similar characteristics of the described electrodes. The porous structure created with the TiO$_2$ nanotubes gives the large surface area and porous structure needed to effectively record changes in glucose concentrations. TiN is also biocompatible and has the electrocatalytic capabilities [49] needed for the oxidation of glucose molecules.

### 3.5.2 Opioid Detection

Drug abuse associated with opioids are a hot topic currently with the rise in associated deaths from opioid use. Opioids increase dopamine production and inhibit the reuptake of overproduced neurotransmitters [51]. Colantuoni et al. [81] explained that increased amounts of glucose might also have effects on the mu-opioid receptors in the brain. Many of the same behaviors are exhibited by those exposed to high amounts of glucose as with high amounts of abused drugs. There is also the extra production of dopamine and mu-receptors. TiN nanotube electrode is also a good candidate for opioids detection.

### 3.5.3 Brain signal detection by the Nano-scale Ti needle electrode

An electrode introduced into the brain of a living animal will detect electrical activity that is generated by the neurons adjacent to the electrode tip. Continuous and long-term recording of single-neuron electro-physiological response is very important for understanding neuronal functions in brain tissue. If the electrode is a microelectrode, with a tip size of about 1 micrometer, the electrode will usually detect the activity of at most one neuron. Recording in this way is in general called "single-unit" recording. Recordings of single neurons in living animals have provided important insights into how the brain processes information.
However, traditional electrodes incline to damage the brain tissue because their dimensions are relatively large, the width (e.g., > 80 µm for Si needles [82-85] and > 30 µm for metal electrodes) and the diameter (e.g., > 40 µm for Si needles [16, 86, 87]), which makes long-term recording of single-neuron activity very difficult. After that, some research was done with the needle-electrode arrays with a tip diameter of < 7 µm using the vapor–liquid–solid (VLS) process [88, 89]. A large size electrode may destabilize brain tissue [90], increase the risk of infection [91], and damage the brain tissue and blood vessels underneath the bone [92]. Therefore, miniaturization of the device to allow the needle electrodes to approach various cortical areas in vivo is a priority, particularly when it comes to testing on animals. Based on this information, we tried the electrochemical method to fabricate the miniature sharp needle electrode, less than 1 µm, even around 150 nm.

1. Ti Tips Fabrication Method (DC)

A pure 1.5 cm long Ti wire was attached to a W rod using Ag conductive epoxy. The end of the Ti wire was electrochemically etched to make a sharp point in 1 M NaCl in stock ethylene glycol solution. Pt wire used as the reference electrode. Using a DC power supply ca. 50 V was applied to the Ti wire for ca. 5 s. The sharpened wire was washed with deionized water. The size of the Ti tip is around 3 µm.

Figure 3.12 Ti needle electrode by DC power supply

2. Ti Tips Fabrication Method (AC)
With a similar method, a pure 1.5 cm long Ti wire was attached to a W rod using Ag conductive epoxy. The end of the Ti wire was electrochemically etched to make a sharp point in 1 M NaCl in stock ethylene glycol solution. Pt wire used as the reference electrode. Using an AC power supply Vpp 20V was applied to the Ti wire with different frequencies for the different time. The sharpened wire was washed with deionized water.

Table 3.8 Ti needle electrodes fabrication results by sin wave AC power supply with different frequencies

<table>
<thead>
<tr>
<th>Frequency(Hz)</th>
<th>Amplitude (V)</th>
<th>Tip size</th>
<th>Time(mins)</th>
</tr>
</thead>
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<tr>
<td>50</td>
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<td>0.42um</td>
<td>2mins20s</td>
</tr>
<tr>
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<td>0.14um</td>
<td>2mins11s</td>
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</tr>
<tr>
<td>550</td>
<td>20</td>
<td>NA</td>
<td>3mins22s</td>
</tr>
</tbody>
</table>

Figure 3.13 Ti needle electrodes fabrication SEM image results by sin wave AC power supply with different frequencies. In Figure 3.13 (b) the sharp tip is slightly bent by the handling manipulation error during the experiment.

(a) 50Hz
(b) 110Hz
(c) 150 Hz
(d) 220Hz
(e) 300Hz
(f) 550Hz
Based on the SEM measurement results, when the frequency is higher than 300 Hz, it will show some residues around the Ti needle electrode. And for the 150 Hz, the Ti tip is smallest around 140 nm. In Figure 3.14 (b), the sharp tip slightly bent by the handling manipulation error during the experiment. For the further application of this Ti needle electrode, we could design the Ti needle sharp array electrodes with 3D printing and parylene-c coating, seen in Figure 3.15.

![Image](image)

**Figure 3.14** Ti needle sharp array electrodes used for the brain neural signal detection with 3D printing substructure and parylene-c coating

**3.6 Summary and Conclusions**

Many useful characteristics that attribute the success of TiN for stimulation can also enable TiN nanotubes as a good material for biosensors. The proposed method of using TiN nanotube has allowed the expansion of applications for recording the oxidation and reduction processes taking place within an electrochemical cell using neurotransmitters dopamine and serotonin. Compared to the carbon fiber electrode, the TiN nanotubes electrode has 10 times higher current density, which has increased sensitivity for neurotransmitter detection. The experiments showed how the improved surface area ratio and surface structure contributed to the ability for detection at small concentrations. The minimum concentration of detection for dopamine is around 100 nM. For the serotonin, it is around 31.5 uM, which is in the range of the normal concentration in the brain. These results provide a good guideline for the in-vivo
experiment of dopamine and serotonin detection. Based on the study of the Ti needle electrode, we can conclude that the best condition to make sharp Ti needles is the AC power supply with Vpp of 20V and frequency of 150 Hz. The miniature tip diameter of the Ti needle electrode can be as low as 150 nm, which allows the needle electrodes to approach various cortical areas in vivo, particularly when it comes to testing on animals.
CHAPTER 4 WIRELESS LC SENSOR WITH TITANIUM ELECTRODES

4.1 Introduction

Wireless sensors do not require any physical connection between the sensors and the external instruments for signal recording and processing. Therefore, they can be advantageous for continuous in-vivo sensing of biomedical signals. The wireless sensing system can be dated back to LC passive wireless sensors, which were proposed by Collins in 1967 [93], utilizing a pair of flat spiral coils to realize a miniature pressure sensor. However, they did not draw much attention until the 1990’s [94] with the development of microelectromechanical system (MEMS) technology. With the help of this MEMS technology, small size, long lifetime, and low-cost battery-free sensors can be made easily to adapt to a variety of harsh and extreme environments like high-temperature, high-pressure, biocompatible or corrosive and chemical environment, etc. [95, 96]. In the meanwhile, the rapid development of Internet of Things (IoT) [97] for applications such as implantable sensors and wearable devices [98] makes the LC passive wireless sensor a hot research field.

4.2 The operation principle of the LC sensor

The total circuit model of the battery-free and wireless LC sensor is the same as an LC circuit in which the capacitance can be used as the detecting parameter. As we can see in Figure 4.1, the capacitance of the LC sensor is related to the permittivity of the dielectric material, the area and the distance between the two plates. So when the parameter of the environment regarding the temperature, pressure, humidity, or gas component changes, the capacitance is simultaneously altered, thereby changing the resonant frequency and the output resistance of the LC sensor. Then another inductive coil can be used to couple with the inductor inside the LC sensor to extract the impedance characteristics, including phase and magnitude of the sensor. Therefore, we can easily measure the parameter change of the environment though checking the change of the inductive coil output impedance. Figure 4.1
gives us the procedure to perform the measurement of the LC sensor.

**Figure 4.1** Construction of an LC Passive Wireless Sensor

According to Kirchhoff’s law, an analytical model for the inductive circuit can be represented as

\[ U_0 = j\omega L_0 i_0 + j\omega M i_s \]  
\[ U_s = j\omega L_{sis} + j\omega M i_0 = -Rs i_s - is/j\omega C_s \]

where \( U_0, U_s, i_0, \) and \( i_s \) are defined as shown in Figure 4.1. The mutual inductance \( M \) of the coupled coils can be written as

\[ M = k \sqrt{L_0 L_s} \]

where \( k \) is the geometry-dependent coupling coefficient with a value between 0 (no coupling) and \( \pm 1 \) (maximum coupling). The equivalent input impedance \( Z_{in} \) at the terminals of the readout coil is derived using Eqs.(1) and (2) as

\[ Z_{in} = \frac{U_0}{i_0} = j\omega L_0 + Z_R = j\omega L_0 + \frac{\omega^2 M^2}{R_s + j\omega L_s + 1/j\omega C_s} \]

Using the following substitutions,

\[ f_s = \frac{1}{2\pi \sqrt{L_s C_s}}, \]
\[ Q = \frac{1}{R_s \sqrt{\frac{L_s}{C_s}}} \]

where \( Q \) is the quality factor of the LC sensor, and \( f_s \) is the resonant frequency of the sensor, then the real part, the imaginary part, and the real part maximum of \( Z_{in} \) can be written as
\[ Re(Z_{in}) = 2\pi f L_0 k^2 Q \left( \frac{f}{f_r} \right)^2 \left( 1 + Q^2 \left( \frac{f}{f_r} - \frac{f_s}{f_r} \right)^2 \right), \]
\[ Im(Z_{in}) = 2\pi f L_0 \left[ 1 + k^2 Q^2 \left( 1 - \left( \frac{f}{f_r} \right)^2 \right) \right] \left( 1 + Q^2 \left( \frac{f}{f_r} - \frac{f_s}{f_r} \right)^2 \right), \]
\[ Z_{max} = Re(Z_{in})_{max} \mid f = f_s = 2\pi f_s L_0 k^2 Q. \]

**Figure 4.2** Characteristic curve of (a) Re (Zin) and (b) Phase (Zin) of an LC sensor interrogating system

In practical detection, the input impedance will undergo a phase rotation when one moves along the line from the terminals of the readout coil to the port of the measurement equipment due to the transmission line effect at a higher frequency. Actually, it has little effect on the input impedance detected when the testing frequency domain is of tens megahertz. The Q factor detected at the measurement device is not the unloaded Q factor in Eq.(5) but a loaded Q factor as

\[ Q_L = \frac{Q}{1 + \kappa}, \]

which is dependent on a coupling factor \( \kappa \) of the transmission line. The resonant frequency \( f_s \) can be obtained from the maximum of Re(Zin) as shown in Figure 4.2,

\[ f_{\text{max}(Re)} = \sqrt{\frac{2Q^2}{2Q^2 - 1}} \times f_s \approx (1 + \frac{1}{4Q^2}) f_s. \]

It is noticing that \( f_{\text{max}(Re)} \) is only related to \( f_s \) and \( Q \) which are intrinsic parameters of the LC sensor. In normal circumstances, i.e., \( 1/4Q^2 << 1 \), \( f_{\text{max}(Re)} \) is approximately considered as
fs. The phase $\angle Z_{in}$ can be expressed as

$$\angle Z_{in} = \arctan \frac{Im(Z_{in})}{Re(Z_{in})}.$$ 

By solving the equation:

$$\frac{\partial \angle Z_{in}}{\partial f} = 0.$$ 

The frequency at which the impedance phase minimum occurs is derived as

$$f_{phase-dip} \approx (1 + \frac{1}{4}k^2 + \frac{1}{8Q^2})f_s.$$ 

It is observed that $f_{phase-dip}$ is not only dependent on the intrinsic parameters $f_s$ and $Q$, but also the coupling coefficient $k$, which is affected by the location of the readout coil and the sensor inductor. Hence there are two points to note when the phase dip measurement is used: one is to fix positions of the readout coil and the sensor inductor to ensure a constant $k$, and the other is to keep $\frac{1}{4}*k^2 << 1$ to ensure that $f_{phase-dip} \approx f_s$.

In the formula, $f_s$ is the sensor resonant frequency, and $f_{phase-dip}$ is the frequency of the lowest point of the phase angle [99]. $K$ parameter means the coupling coefficient between the inductance coils of the inductive coil and the sensor, and $Q$ is the quality factor of the sensor. In this case, if we can optimize the design to make the $k$ is low enough and the $Q$ is sufficiently high, the $f_s$ of the system can be easily determined by analyzing the output $f_{phase-dip}$.

In this case, as I mentioned before, in order to receive high-performance readout coil and LC sensor coupling, several parameters need to be paid much more attention like the $Q$ factor and the shape of the LC sensor, and the coupling distance or condition between the readout coil and the LC sensor. When it comes to the shape of the coil, the square planar spiral inductor attracts more interest since it can be easily integrated on the PCR chip and even in the future MEMS design. Right now, when the researchers make the design regarding the coil, they prefer to use the more accurate method proposed by Lee T. [100] to calculate the inductance of the square planar spiral inductor.
\[ L = \frac{\mu_0 n^2 d_{avg} c_1}{2} \left( \ln\left(\frac{c_2}{\rho}\right) + c_3 \rho + c_4 \rho^2 \right) \]

\( \rho = \left(\frac{d_{out} - d_{in}}{d_{out} + d_{in}}\right) \) is the fill ratio. \( d_{out} \) is the coil outer diameter, \( d_{in} \) is the coil inner diameter, \( \mu_0 \) is the permeability of free space, and \( n \) is the number of turns of the inductance coil [101]. Where \( c_1, c_2, c_3, \) and \( c_4 \) are constants determined by the shape of the inductance coil. If the construction area, line width, line thickness, and materials of the inductance coil are given, the quality factor can be improved by improving the ratio of the inner and outer diameters of the inductance coil. The quality factor can be expressed as follows [102]:

\[ Q = \frac{w u d_{out} h l (1 - \alpha)}{4 \pi \rho_r s} \left( \ln \frac{1 + \alpha}{1 - \alpha} + 0.2235 \frac{1 + \alpha}{1 - \alpha} + 0.276 \right) \]

where \( w, u, h, l, \rho_r, \) and \( s \) are the angular frequency of the sensor, relative permeability of air, the height of the inductance coil, width of the inductance coil, resistivity of the inductance coil, and spacing between adjacent turns of the inductance coil, respectively. \( \alpha \) is the ratio of the inner and outer diameters of the inductance coil, which can be improved to achieve a maximum \( Q \) value.

**4.3 LC sensors for pressure and chemical detecting**

It is very important to detect the pressure in many fields, and the battery-free wireless LC sensor has its own advantages such as operating in high-temperature environment to monitoring the pressure of turbine engines or compressors in the industry or detect the pressure change inside the human body with the biocompatible capabilities. The two applications mentioned above fall into two main applications of this LC sensors: the pressure sensor for the industrial and environmental monitoring and for the implantation with biocompatibility in biomedical monitoring. The main difference between these two categories are the substrate of the sensors. The solid semiconductor substrate is preferred for the industrial use due to its high
temperature tolerant and large scale [103-107], while the flexible or wearable substrate like PET tends to be used for the biomedical part because of its biocompatible and small size.

4.3.1 Pressure sensors for biomedical use

When it comes to biomedical use, several experiments have been carried out regarding important pressure sensors like blood pressure, intraocular pressure (IOP) monitoring sensor, and intracranial pressure. In 2005, Shin [108] developed the chip embedded flexible packaging (CEFP) technology, which includes the thin silicon chip and antenna to monitor the blood pressure. They made the capacitance type sensor and wrapped it around the blood vessel, which would expand or shrink when the blood inside changes, thereby altering the capacitance and the resonant frequency of the system. In their experiment, while the applied pressure changes from 0 to 213.3 kPa, the resonator frequency changes correspondingly. The sensitivity of the implantable blood pressure is 11.25 kHz/kPa [108]. The schematic illustration of this wireless blood pressure sensor is below,

![Blood pressure sensor schematic](image)

**Figure 4.3** The blood pressure sensor to biomedical use

For pressure sensor used in biomedical applications, the other important one is the intraocular pressure (IOP) monitoring sensor. In 2000, Puers [109] developed a novel distributed parallel-resonant inductive–capacitive circuit to detect the intraocular pressure with Q factors of 30 at 45 MHz and inductance values of 0.4 µH for 3 × 3 mm2 structures [109]. In 2008, Chen [110] fabricated two surface-micromachined sensor designs incorporating variable capacitor and variable capacitor/inductor resonant circuits that have been implemented to
realize the pressure-sensitive components. Pressure responses of the microsensor have been characterized to demonstrate its high-pressure sensitivity (> 7000 ppm/mmHg) in the microsensor designs, which confirms the feasibility of pressure sensing with smaller than 1 mmHg of resolution for practical biomedical applications [110].

Figure 4.4 The eye pressure sensor to biomedical use

The fabrication process of this IOP sensor started with thermally growing and patterning a 0.75-µm-thick oxide. Then several nanofabrication methods, including e-beam evaporation, metal etching techniques, oxygen plasma and DRIE have been used step by step to produce the sensor. Then they used this IOP sensor to do some in vivo experiment with live rabbit eyes for as long as six months and have the Ex vivo data on the right side [110]. In 2014, Chen [111] reported a wireless, real-time pressure monitoring system with passive, flexible, millimetre-scale sensors, scaled down to unprecedented dimensions of 2.5 X2.5 X0.1 cubic millimeter to
monitor in vivo intracranial pressure continuously in proof-of-concept mice studies. The fabrication structure design is on the left [111].

**Figure 4.5** The IOP sensor to biomedical use

Among the biochemical sensors for in vivo and in vitro applications, the LC passive wireless sensors present advantages of operation without wires in the miniature invasion, continuous and long-term monitoring, and reduced dimensions.

In 2009, Lei [112] reported a high-sensitivity capacitive pressure sensor coupled to a stimuli-sensitive hydrogel that is confined between a stiff porous membrane and a thin glass diaphragm and with a pH-sensitive hydrogel inside, the sensor displayed a sensitivity of 1.16MHz/pH for pH3.0–6.5, and a response time of 45 minutes [112]. They have also reported a chemical sensor by embedding superparamagnetic nanoparticles into the hydrogel and laminating the hydrogel on a planar coil [113]. In [114], a hydrogel was sandwiched by a folded coplanar dual spiral coil. The mutual inductance between the two aligned coils was dependent on the gap, which was modulated by the hydrogel. The swelling of the hydrogel changed the permeability of the coil to cause the inductance to change. Besides the hydrogel, an electrolyte-insulator-silicon (EIS) capacitor is capable of converting pH to capacitance as well [115]. To achieve a high Q factor, a double-electrode scheme was developed [116]. In addition to the reference electrode, the second electrode is a low resistance electrode and consists of a set of parallel polysilicon tracks that are interdigitated with another set of EIS capacitor strips.
Based on the investigation of LC sensor, this section presents a miniaturized, wireless, biocompatible, real-time pressure sensor with built-in inductor and capacitor made of Titanium for the intracranial pressure (ICP) monitoring. ICP is so critical to detection or prevention of cerebral trauma, especially in the injured head and diseased brain, that potentially treatment can be operated in advance. The most existing clinically established ICP measurement methods require catheter insertion in the cranial cavity with narrow ventricles. On the one hand, these setups can just be used in the hospital at the instance of physicians. On the other hand, this increases the risk of infection and hemorrhage. Thus, noninvasive methods but accurate techniques are more and more attractive. There are several groups who have already made some contributed to this work by designing a battery-free implantable sensor by the material copper with polyimide substrate. In this work, we proposed a novel and implantable LC tank sensor for continuous ICP monitoring. The implantable sensor comprises a helix coil with a series-connected spiral coil connected in series to a cylindrical capacitor, all of them made by Titanium metal. The implantable sensor is inductively coupled to an external RF reader coil, and the detected signal can be displayed on a portable antenna analyzer. The ICP variation can be detected wirelessly through measuring the reader antenna’s scattering parameter $S_{11}$.

### 4.4 Battery-free and miniature wireless sensors for pressure detection

The ingenious device can be fabricated by metallic 3D printing, which is a rapid prototyping manufacture method with high resolution. It is a better technique than MEMS for
making miniature sensors with various 3D shapes. Based on the specific structure, the spiral inductor, and cylindrical capacitor, the device can detect pressure signals caused by the adjustable capacitance and wirelessly transfer the signal out through the mutual coupling with a reader out coil (Figure 4.7).

![Figure 4.7 The illustration of the implantable ICP sensor continuous monitoring.](image)

### 4.4.1 Description of the New Method or System

The LC circuit structure for ICP sensors is shown in Figure 4.8. It consisted of a helix inductor, a spiral inductor, and a cylindrical capacitor. The T-shaped structure is chosen so that it can easily be implanted to the cerebral for continuous ICP monitoring. It also can be used as a smart screw/nail for fixing the artificial limb and monitoring the pressure of the prosthetic joint.

![Figure 4.8 (a) Bird view of the 3D modeling ICP sensor. (b) Cross-sectional view of the ICP sensor, showing the designed structure including two inductors and one capacitor. (c) A pressure loads to the tip of the LC sensor. (d) The illustration of the sensing principle with equivalent circuit diagram.](image)
The size information is showed in Figure 4.9. The diameter of the helix inductor is 6.6 mm, and the number of turns is 4. The outside diameter of the spiral inductor is also 6.6 mm, and the number of turns is 4. The outer conductor diameter of the cylindrical capacitor is 1 mm, and the inner conductor diameter is 0.5 mm. The length of the cylindrical capacitor is 10 mm. The design is optimized by evaluating the effect of wire thickness on the overall sensor performance.

![Figure 4.9 Dimension information of (a) top view of the 3D modeling LC sensor; (b) side view of the LC sensor; (c) backward view of the LC sensor](image)

### 4.4.2 Simulation for the sensitivity study of the different designs

When the pressure was loaded onto the end tip of the sensor, the helix structure will be compressed, which changes the inductance of the inductor. At the same time, the capacitance of the cylindrical capacitor will be changed because of the position shift of the inner conductor. Both of them will affect the resonant frequency of the LC sensor. However, the amount of the changes will depend on the flexibility of the helix structure, which is related to the thickness of the wire. In the LC sensor, the Q factor is also a very important parameter, alternatively defined as the ratio of a resonator's center frequency to its bandwidth when subject to an oscillating driving force.

\[
Q = \frac{f_0}{\Delta f}
\]

For the series RLC circuit, Q factor is defined below:

\[
Q = \frac{1}{R \sqrt{C}}
\]
where R, L, and C are the resistance, inductance and capacitance of the tuned circuit, respectively. The values of these components are all related to the designed wire diameter in the LC sensor. When the pressure is loaded, the resonant frequency changes. This change value should be larger than the bandwidth of the resonance $\Delta f$ for detection. Based on these information, Ti wires with different diameters were simulated by the Comsol software to evaluate the performance of the LC sensor. And the sensitivity was also analyzed by the different parameters.

We designed 7 different diameters of the helix inductor and spiral inductor from 100 um to 500 um. In order to keep receiving the same force from the pressure, the dimension of the cylindrical capacitor is designed the same values. And the resistance, inductance and capacitance, Q factor, and resonant frequency were all calculated.

**Table 4.1** Parameters of the LC sensor with different wire diameters

<table>
<thead>
<tr>
<th>Wire Diameter (um)</th>
<th>R (Ohm)</th>
<th>Helix inductance (H)</th>
<th>Spiral inductance (H)</th>
<th>Capacitance (F)</th>
<th>Q factor</th>
<th>Resonant Frequency (MHz)</th>
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The normal adult ICP is defined as 5 to 15 mm Hg (7.5–20 cm H₂O) [117]. ICP values of 20 to 30 mm Hg represent mild intracranial hypertension; however, when a temporal mass lesion is present, herniation can occur with ICP values less than 20 mm Hg. We simulated the ICP from 5 mmHg to 25 mmHg with the 5 mmHg interval value by Comsol structural mechanical module. Figure 4.10 shows some results of the different wire diameters.
Figure 4.10 The simulation results of different wire diameters with a fixed pressure 25mmHg by Comsol software

With the decreasing of the wire diameter, the displacement of the inner conductor of the cylindrical capacitor increases with a fixed pressure 25mmHg.

According to the simulation results, the new inductance, capacitance and resonant frequency were calculated (Table 4.2).

<table>
<thead>
<tr>
<th>Wire Diameter (um)</th>
<th>Helix inductance (H)</th>
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<th>Capacitance (F)</th>
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<tbody>
<tr>
<td>500</td>
<td>7.70E-08</td>
<td>4.10E-08</td>
<td>8.02E-13</td>
<td>5.1756E+08</td>
<td>1.2950E+04</td>
<td>4.841E-02</td>
</tr>
<tr>
<td>400</td>
<td>8.50E-08</td>
<td>4.10E-08</td>
<td>8.02E-13</td>
<td>5.0095E+08</td>
<td>1.8971E+06</td>
<td>4.4534E+00</td>
</tr>
<tr>
<td>300</td>
<td>9.50E-08</td>
<td>4.10E-08</td>
<td>8.01E-13</td>
<td>4.8237E+08</td>
<td>5.1172E+06</td>
<td>7.1896E+00</td>
</tr>
<tr>
<td>230</td>
<td>1.07E-07</td>
<td>4.10E-08</td>
<td>8.01E-13</td>
<td>4.6288E+08</td>
<td>1.2268E+07</td>
<td>1.0664E+01</td>
</tr>
<tr>
<td>220</td>
<td>1.09E-07</td>
<td>4.10E-08</td>
<td>8.00E-13</td>
<td>4.5954E+08</td>
<td>1.3918E+07</td>
<td>1.1148E+01</td>
</tr>
<tr>
<td>210</td>
<td>1.11E-07</td>
<td>4.10E-08</td>
<td>7.98E-13</td>
<td>4.5715E+08</td>
<td>1.4639E+07</td>
<td>1.0760E+01</td>
</tr>
<tr>
<td>200</td>
<td>1.13E-07</td>
<td>4.10E-08</td>
<td>7.97E-13</td>
<td>4.5463E+08</td>
<td>1.5504E+07</td>
<td>1.0410E+01</td>
</tr>
<tr>
<td>100</td>
<td>1.48E-07</td>
<td>4.10E-08</td>
<td>7.40E-13</td>
<td>4.2579E+08</td>
<td>2.5782E+07</td>
<td>4.6909E+00</td>
</tr>
</tbody>
</table>
Figure 4.11 (a) Inductance changes of helix inductor with the different pressure (b) Capacitance changes of cylindrical capacitor with the different pressure

Figure 4.11 shows the capacitance and inductance relationship with the loaded pressure range from 5 mmHg to 25mmHg. With the increasing of the pressure, the inductance of the helix inductor increases linearly and the capacitance of the cylindrical capacitor decreases linearly.

Considering the shift frequency should be larger than the bandwidth of the LC sensor, which means the value of $SF/\Delta f > 1$. From the above results, we found the 500 um diameter is less than 1. And the best performance of the diameter value is 220 um. This information provides good instruction for the design of the LC sensor with Ti material (Figure 4.11).

Figure 4.12 The simulation result of the shift frequency over the bandwidth of the LC sensor in the different wire diameters with a fixed pressure 25mmHg

The different pressures from 5mmHg to 25mmHg were also simulated with the
different wire diameters to estimate the limitation of the detection. We simulated the 100 um, 200 um, 300 um, and 400 um. It is found that with the increase of the pressure, the frequency shift is around linearly increasing. And compared the frequency shift frequency to the bandwidth of the LC sensor, the limitation of the detection (LoD) of the 100 um diameter is 6mmHg. For 200 um, the LoD is around 4mmHg. And the LoD of the 300 um is around 7.5 mmHg. The 400 um, is 12 mmHg. For the best performance dimension, 220um is 3.5mmHg. The 220 um diameter has the best sensitivity.

**Figure 4.13** The simulation results of the shift frequency and the bandwidth of the LC sensor in the different wire diameters with different pressures

**4.4.3 Coupling simulation of the LC sensor with the external reader coil**

Based on the above analysis of the sensitivity, we continue to simulate the $S_{11}$ and frequency characterization of the LC sensor with the wire diameter 220 um by an external
reader coil (Figure 4.7). The simulation of the LC tank’s frequency response was performed by the CST software. Figure 4.13 shows the relationships of the S-parameter (Magnitude in dB) and frequency were obtained by changing the distance between the spiral reader coil and the sensor. The resonant frequency of this device is around 800 MHz.

**Figure 4.14** The simulation results of S-parameters vs. frequency response based on the different distances between the spiral reader coil and the sensor by CST studio software.

Table 4.3 shows the performance of other research work’s ICP sensor and our proposed device.

**Table 4.3** The performance comparison of the existing different wireless ICP sensors

<table>
<thead>
<tr>
<th>ICP sensors</th>
<th>Material</th>
<th>Size (mm)</th>
<th>Frequency (MHz)</th>
<th>Sensitivity (KHz/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexible-Coiled LC Sensor [4]</td>
<td>Ti/Au</td>
<td>1.5<em>4</em>4</td>
<td>350</td>
<td>159.25</td>
</tr>
<tr>
<td>“S-shape” sensory coil [5]</td>
<td>Ti and Copper</td>
<td>15.5<em>19.5</em>23.5</td>
<td>395</td>
<td>57</td>
</tr>
<tr>
<td>Ultra-small Cubic Sensor [3]</td>
<td>Copper</td>
<td>1<em>1</em>0.1</td>
<td>2777</td>
<td>2254</td>
</tr>
<tr>
<td>Capacitive ICP sensor [6]</td>
<td>Copper</td>
<td>10<em>22</em>26</td>
<td>400</td>
<td>102</td>
</tr>
<tr>
<td>Planar spiral coil and pressure sensor (Murata SCB10H-B012FB) [2]</td>
<td>N/A</td>
<td>11<em>13</em>13</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Piezoresistive sensor with an oscillator and a chip antenna [1]</td>
<td>N/A</td>
<td>9<em>12</em>12</td>
<td>2429</td>
<td>300</td>
</tr>
<tr>
<td>Copper-clad Liquid Crystal Polymer Sensor [7]</td>
<td>Copper</td>
<td>10*10</td>
<td>35.675</td>
<td>5.76</td>
</tr>
<tr>
<td>The Proposed Device</td>
<td>Titanium</td>
<td>7.6<em>7.6</em>12.65</td>
<td>810</td>
<td>337.5</td>
</tr>
</tbody>
</table>

**4.4.4 Evaluation of the LC sensor fabrication**

An ICP sensor with 300 um wire diameter was tried to be fabricated by the 3D printing machine EOSINT M290 with material Titanium Ti64, which is biocompatible. The fabrication time was 1h 43mins. After the 3D printing, post-processing of the structure with the substrate was dealt with by 650°C for less than 5 minutes to lessen the residual thermal stress during the building process. Figure 4.14 shows the real-scale fabricated device by the 3D printing.
manufacturing method. The optical microscope and SEM pictures illustrate the detailed information of the fabricated devices. However, the surface of the fabricated LC sensor is not very smooth which will affect the values of the resistance, capacitance and inductance, and some of the helix wires even connected with each other which leads to the failure of the flexibility when the pressure is applied to the inner conductor of the cylindrical capacitor. For this problem, we need to try the higher resolution of the 3D printing for the better printing result of the LC sensor.

![Figure 4.15](image)

**Figure 4.15** (a) The physical real-scale parts of the fabricated devices; (b) The optical microscope picture of the fabricated devices; (c) The SEM picture of the fabricated devices.

### 4.5 Conclusions

The designed Ti LC sensor has a potential application in the long-term ICP monitoring, thanks to the biocompatible material Titanium and wireless signal detection in the noninvasive way. The LC sensor consisted of a helix inductor, a spiral inductor, and a cylindrical capacitor. The T-shaped structure is chosen so that it can easily to be implanted to the cerebral for continuous ICP monitoring. We have analyzed the detection capability and sensitivity of the different designs based on the simulation results to get the best parameters, which provides a good guideline for the fabrication. It is found that the wire diameter of 220
um was the best choice for the design of the LC sensor. The sensitivity of the sensor could be found to be 337.5 KHz/mmHg for the 220 um wire diameter. The coupling simulation of the LC sensor with an external RF reader coil was also studied. As a whole system, the $S_{11}$ and frequency characteristics are related to the distance of the LC sensor and reader coil. With the increase of the distance, the center frequency will be decreased until 3 mm. This LC sensor could be fabricated by the 3D printing technology in an integral form, which is easier than the MEMS technology.
CHAPTER 5 CONCLUSIONS AND FUTURE WORKS

5.1 Conclusions

In this thesis, we have developed TiN nanotubes electrodes for neural chronic stimulation/recording and neurotransmitter detection, and designed a wireless LC sensor with Ti for ICP monitoring. Compared to traditional planar metal films or carbon films, the TiN nanotube is more advantages in these applications because of unique material characteristics. Titanium Nitride is biocompatible and has high corrosion resistance, super electrical conductivity, and good hardness, which is important for effective and long-term neural stimulation/recording. The TiN nanotubes also have a high surface area-to-volume ratio, and can accommodate more space for ions exchange. In additional, Ti can be 3D printed, which can lead to the fabrication of Ti-based sensors with various shapes and dimensions for many long-term and noninvasive implantable potential applications.

In Chapter 2, we studied the growth mechanism of TiN nanotubes and the corrosion resistance of TiN nanotubes using microwire electrodes with different pore sizes. The corrosion characterization was discussed in the 0.9% phosphate-buffered saline (PBS) electrolyte at the temperature 37°C, which is similar to the normal human body temperature. After 60 hours, the tungsten electrode was corroded. This work shows the great corrosion-resistant and high charge density of TiN nanotubes electrodes. The specific charge capacity of nanoporous TiN correlates proportional with the surface area and pore size. Compared to tungsten electrode, the impedance and morphology of nanoporous TiN show more stable over long-term. The result shows that the TiN nanotubes electrodes have a promising application in the neural probe stimulation.

In Chapter 3, The proposed method of using TiN nanotube has allowed the expansion of applications for recording the oxidation and reduction processes taking place within an electrochemical cell using neurotransmitters dopamine and serotonin. Compared to the carbon
fiber electrode, the TiN nanotubes electrode has 10 times higher current density, which has increased sensitivity for neurotransmitter detection. The experiments showed how the improved surface area ratio and surface structure contributed to the ability for detection at small concentrations. The minimum concentration of detection for dopamine is around 100 nM. For the serotonin, it is around 31.5 uM which is in the range of the normal concentration in the brain. These results provide a good guideline for the in-vivo experiment of dopamine and serotonin detection. Based on the study of the Ti needle electrode, we can conclude that the best condition to make sharp Ti needles is the AC power supply with Vpp of 20V and frequency of 150 Hz. The miniature tip diameter of Ti needle electrode can be as low as 150 nm, which allows the needle electrodes to approach various cortical areas in vivo, particularly when it comes to testing on animals.

In Chapter 4, the designed Ti LC sensor has a potential application in the long-term ICP monitoring, thanks to the biocompatible material Titanium and wireless signal detection in a noninvasive way. The LC sensor consisted of a helix inductor, a spiral inductor, and a cylindrical capacitor. The T-shaped structure is chosen so that it can easily be implanted to the cerebral for continuous ICP monitoring. We have analyzed the detection capability and sensitivity of the different designs based on the simulation results to get the best parameters, which provides a good guideline for the fabrication. It is found that the wire diameter of 220 um was the best choice for the design of the LC sensor. The sensitivity of the sensor could found to be 337.5KHz/mmHg for the 220 um wire diameter. The coupling simulation of the LC sensor with an external RF reader coil was also studied. As a whole system, the S11 and frequency characteristics are related to the distance of the LC sensor and reader coil. With the increase of the distance, the center frequency will be decreased until 3 mm. This LC sensor could be fabricated by the 3D printing technology in an integral form which is easier than the MEMS technology.
5.2 Future works

Although this work gives good proof-of-concept results for TiN nanotubes corrosion resistance and biosensing applications. There are still a number of problems that need to be addressed:

1) Long-term (months and years) corrosion resistance experiment of TiN nanotubes

Use the higher electrolyte temperature to accelerate the reaction of corrosion to simulate the long-term corrosion resistance research, like months and years. Then we could extend the cycle time of the electrochemical measurement. After that, we can do some in-vivo animal studies for further clinical application in the future.

2) Multi analyte detection

The TiN nanotube structured electrodes have been proved to be an efficient dopamine and serotonin detector. Our next step is the detection of multiple analytes, like glucose and opioids. Recently, a covalent functionalization strategy to modify surface with specific molecules in controlled densities for CV applications has been reported [118-120]. It was an effective method to integrate selective components to the electrode surfaces without compromising the fast response time of CV. In the future work, different channels of a microelectrode array will be modified with certain selective molecules, for the purpose of simultaneous detections of different targets.

3) Fabricate the 3D printing LC sensor for experimental measurement

After the simulation studies of the LC sensor, the LC sensor can be fabricated by a higher resolution 3D printing machine. Once the LC sensor could be fabricated, experiments can be conducted to evaluate the performance of the sensor. The frequency and $S_{11}$ characterization could be measured by the network analyzer, which could be compared with the simulation result. And the effect of the changed LC values caused by the external pressure could be measured by the load cell experiment setup.
APPENDIX

TiN nanotube growth on Ti foil

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Steps</th>
<th>Parameters</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti foil</td>
<td>Purchase Ti foil from Sigma</td>
<td>Thickness: 0.5mm</td>
<td></td>
</tr>
<tr>
<td>Preparation</td>
<td>Polish Ti foil by two kinds of sand papers</td>
<td>Coarser sandpaper: 120 grit; Finer sandpaper: 240 grit</td>
<td>The Ti piece is shining.</td>
</tr>
<tr>
<td></td>
<td>Cut the Ti foil into small pieces</td>
<td>Length: 2 cm; Width: 1 cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrasonic 15 mins</td>
<td>Ethanol</td>
<td>The Ti foil is clean and shining.</td>
</tr>
<tr>
<td></td>
<td>Ultrasonic 15 mins</td>
<td>DI water</td>
<td>The Ti foil is clean and shining.</td>
</tr>
<tr>
<td></td>
<td>Dry the Ti foil</td>
<td>Filter paper</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check Morphology under Microscope or SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-step</td>
<td>First-step anodization</td>
<td>2h 30V, 45V, 60V, Cathode: Pt, Anode: Ti foil</td>
<td></td>
</tr>
<tr>
<td>anodization</td>
<td>Electrolyte: Ethylene glycol, NH₄F, DI water</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check Morphology By SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrasonic 15-20 mins</td>
<td>DI water</td>
<td>Remove the TiO₂</td>
</tr>
<tr>
<td></td>
<td>Check Morphology By SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-step</td>
<td>Second-step anodization</td>
<td>30min 30V, 45V, 60V, Cathode: Pt, Anode: Ti foil</td>
<td>Form TiO₂ nanotube on the Ti piece</td>
</tr>
<tr>
<td>anodization</td>
<td>Electrolyte: Ethylene glycol, NH₄F, DI water</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check Morphology By SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiN growth</td>
<td>Ar</td>
<td>30min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ammonia room temperature ----- 300°C</td>
<td>5 °C/min 54min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300°C ----- 700°C 2 °C/min</td>
<td>3h20min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>700°C ----- 800°C 1 °C/min</td>
<td>1h40min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>800°C ----- 800°C 0 °C/min 1h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cool naturally</td>
<td></td>
<td>Form TiN nanotube on the Ti piece</td>
</tr>
<tr>
<td></td>
<td>Check Morphology By SEM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## TiN nanotube growth on Ti microdisk

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Steps</th>
<th>Parameters</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti wire Preparation</td>
<td>Purchase Ti wire from Sigma</td>
<td>Diameter: 0.5mm Ti Wire</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cut the Ti wire into short sticks</td>
<td>Length: 4–5cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cut the capillary glass into short sticks</td>
<td>Length: ~3cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insert the Ti wire into capillary glass</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seal it in the Hydrogen fire under Ar</td>
<td></td>
<td>The Ti microdisk is totally sealed without bubbles.</td>
</tr>
<tr>
<td></td>
<td>Polish it to exposure the top tip by two kinds of sand papers</td>
<td>Coarser sandpaper: 120 grit, Finer sandpaper: 240 grit</td>
<td>The Ti microdisk is shining.</td>
</tr>
<tr>
<td>Capillary seal</td>
<td>Ultrasonic 15 mins</td>
<td>Ethanol</td>
<td>The Ti microdisk is clean and shining.</td>
</tr>
<tr>
<td></td>
<td>Dry the Ti microdisk</td>
<td>Filter paper</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check Morphology under Microscope or SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>First-step anodization</td>
<td>2h 30V, 45V, 60V, Cathode: Pt, Anode: Ti microdisk Electrolyte: Ethylene glycol, NH$_4$F, DI water</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Check Morphology By SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultrasonic 15-20 mins</td>
<td>DI water</td>
<td>Remove the TiO$_2$</td>
</tr>
<tr>
<td></td>
<td>Check Morphology By SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second-step anodization</td>
<td>30min 30V, 45V, 60V, Cathode: Pt, Anode: Ti microdisk Electrolyte: Ethylene glycol, NH$_4$F, DI water</td>
<td>Form TiO$_2$ nanotube on the Ti microdisk</td>
</tr>
<tr>
<td></td>
<td>Check Morphology By SEM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiN growth</td>
<td>Ar</td>
<td>30min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ammonia room temperature ----- 300°C</td>
<td>5 °C/min  54min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500°C ----- 700°C</td>
<td>2 °C/min 3h20min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>700°C ----- 800°C</td>
<td>1 °C/min 1h40min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>800°C ----- 800°C</td>
<td>0 °C/min 1h</td>
<td></td>
</tr>
<tr>
<td>Check Morphology By SEM</td>
<td>Form TiN nanotube on the Ti microdisk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------------------</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **CV curve measurement** | Potential: -0.8V – 1V  
Scan rate: 100mV/s  
Size specify: 0.625π mm²  
Reference Electrode: AgCl/Ag  
Counter Electrode: Pt  
Work Electrode: TiN Wire  
Electrolyte: phosphate-buffered saline (PBS x1, salt concentration, pH7.4)  
Temperature: 37°C |
| **EIS measurement** | Frequency: 0.1Hz—100000Hz  
Electrolyte: phosphate-buffered saline (PBS x1, salt concentration, pH7.4)  
Temperature: 37°C |
REFERENCES


[50]. Si, B., & Song, E., Recent advances in the detection of neurotransmitters. Chemosensors, 2018. 6(1).


ABSTRACT

TITANIUM NITRIDE NANOTUBE ELECTRODES USED IN NEURAL SIGNAL RECORDING APPLICATION AND NEUROTRANSMITTER DETECTION

by

GUI CHEN

August 2020

Advisor: Dr. Yang Zhao

Major: Electrical and Computer Engineering

Degree: Doctor of Philosophy

Electrode probes are devices widely used for stimulating and recording neural cell signals in the neuroscience field, which can convert the ion potential generated by electrochemical activities into an electronic potential that can be measured by the external instrument systems. A stable neural interface that effectively communicates with the nervous system via electrode is much important for the robust recording and the long-term monitoring of the activity of the neural signals. These probes are designed to minimize tissue damage for superior signal quality. Each probe’s mechanical, geometric, and electrical characteristics are precise and highly reproducible for consistent, high-quality results. There are several material candidates, including platinum, iridium, iridium oxide, carbon derivatives (graphene and carbon nanotubes), conductive polymers, and titanium nitride. Titanium nitride as the neural implant electrode can have broad applications owing to its super electrical conductivity, biocompatibility, chemical stability, and good hardness. In this work, a highly ordered TiN nanotube electrode is fabricated and studied by the two-step anodization technique. The corrosion characterization was studied in the phosphate-buffered saline (PBS). The result shows that the TiN nanotubes electrodes have a promising application in the neural probe stimulation. In addition, the TiN nanotube electrodes are further studied as a biosensor for the neurotransmitter detection of dopamine and serotonin. The result provides a good guideline
for the in-vivo experiment of dopamine and serotonin detection.

The application of Ti in wireless LC sensors is also studied owing to its biocompatible and good conductivity. We present a novel and implantable LC tank sensor simulation estimation for continuous ICP monitoring. The implantable sensor comprises a helix coil with a series-connected spiral coil connected in series to a cylindrical capacitor, all of them made by Titanium metal.
AUTOBIOGRAPHICAL STATEMENT

GUI CHEN

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2016-2020 Doctor of Philosophy, Wayne State University, Detroit, MI, USA

2012~2015 Master in Signal and Information Processing, University of Chinese Academy of Sciences, Beijing, P.R. China

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Selected Publications


