

CHARACTERISATION OF A HYBRID ELECTRODE FOR DEEP BRAIN STIMULATOR APPLICATIONS WITH STIMULATION AND SENSING ENGINEERED WITHIN, ENABLING CLOSED LOOP AND ADAPTIVE CONTROL OVER STIMULATIONS

Jithin Krishnan

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CONTROL OVER STIMULATIONS

A THESIS SUBMITTED BY

Jithin Krishnan

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND
TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DOCTOR OF PHILOSOPHY

2024

DECLARATION BY THE STUDENT

CERTIFICATE

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LIST OF ABBREVIATIONS

- AO - Acridine Orange
- BPM - Beta Power Modulation
- CIC - Charge Injection Capacity
- CV - Cyclic Voltammetry
- DBS - Deep Brain Stimulation
- EIS - Electrochemical Impedance Spectroscopy
- ETO - Ethylene Oxide
- FEM - Finite Element Modeling
- GFAP - Glial Fibrillary Acidic Protein
- GPMT - Guinea Pig Maximization Test
- HUPD - Underpotential Deposition
- IPG - Implantable Pulse Generator
- LDH - Lactate Dehydrogenase
- LFP - Local Field Potentials
- MTT - Mitochondrial Activity Assay
- NRU - Neutral Red Uptake
- OCP - Open Circuit Potential
- PBS - Phosphate Buffered Saline
- PCU - Power Control Unit
- PDMS - Polydimethylsiloxane
- PWM - Pulse Width Modulation
- SCE - Standard Calomel Electrode
- VTA - Volume of Tissue Activated

SYNOPSIS

Movement disorders represent neurological conditions that disrupt movement speed, fluidity, and coordination. They are generally categorized into hyperkinetic (excessive movement) and hypokinetic (reduced movement). Among these conditions, Parkinson's disease (PD) stands out as one of the most prevalent and well-researched, affecting millions globally.

Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disorder marked by the degeneration of dopaminergic neurons in the substantia nigra, a key area of the midbrain. This neuronal loss leads to a reduction in dopamine, a neurotransmitter crucial for movement coordination. PD's hallmark symptoms include bradykinesia (slowness of movement), resting tremor, rigidity, and postural instability. As the disease advances, patients may also grapple with non-motor symptoms such as cognitive decline, mood disturbances, and autonomic dysfunctions.

The precise cause of PD remains elusive, likely stemming from a complex interplay of genetic predispositions and environmental influences. While no definitive cure exists, various treatments are available to alleviate symptoms and enhance patients' quality of life. These interventions include pharmacotherapy, physical therapy, and surgical approaches like Deep Brain Stimulation (DBS).

Deep Brain Stimulation (DBS)

DBS offers a surgical lifeline for patients with advanced PD and other movement disorders who find little relief from medications. This procedure involves implanting electrodes in specific brain regions, usually the subthalamic nucleus (STN) or the globus pallidus interna (GPi). These electrodes connect to a pulse generator, akin to a pacemaker, that delivers electrical impulses to modulate aberrant brain activity.

Research has demonstrated that DBS can significantly ameliorate motor symptoms and enhance the quality of life for PD patients. The precise mechanisms by which DBS exerts its effects are not entirely understood but are thought to involve normalizing the electrical activity within movement-related brain circuits.

Closed Loop and Open Loop DBS Systems

DBS systems are generally categorized into two types: Open-loop and Closed-loop systems.

1. **Open-Loop DBS Systems:** Traditional open-loop systems rely on clinicians manually setting stimulation parameters (frequency, amplitude, and pulse width) based on the patient's symptoms. These settings remain fixed until the next adjustment, regardless of changes in the patient's condition or activity levels. While effective, these systems require frequent recalibrations and may lead to side effects from overstimulation.
2. **Closed-Loop DBS Systems:** To overcome the limitations of open-loop systems, closed-loop DBS systems have been developed. These systems

continuously monitor brain activity or physiological signals (such as tremors or muscle activity) and adjust real-time stimulation parameters. This approach allows for more precise and individualized therapy, improving effectiveness and minimizing side effects.

Closed-loop systems utilize feedback signals to guide stimulation, including local field potentials (LFPs) recorded from the implanted electrodes. Advanced algorithms and machine learning techniques are often employed to optimize stimulation parameters dynamically.

The Need for Closed Loop and Adaptive DBS

Despite the efficacy of traditional open-loop DBS systems, they have inherent limitations, such as the need for frequent parameter adjustments and potential side effects from overstimulation. Closed-loop and adaptive DBS systems offer a promising solution by continuously monitoring the patient's brain activity or physiological signals and adjusting the stimulation parameters in real-time. This dynamic approach enables more precise and personalized therapy, potentially enhancing efficacy and reducing adverse effects. The advancement of these systems is crucial, as they provide a more responsive and tailored treatment for managing PD and other movement disorders.

For the same, the hypothesis formulated for this research is as follows:

Closing the loop through sensors and real-time communication to the implanted neuro-stimulator could result in lower average power dissipation and reduced side effects from unneeded stimulation.

To validate the hypothesis, the following research objectives are framed:

1. Develop a dual-purpose hybrid electrode for sensing and stimulation.
2. Characterize the hybrid electrode through
 - a. Simulations
 - b. Electrochemical tests
 - c. Biological evaluation
3. Develop an algorithm for closed-loop control with beta waves.

The work will be presented in five chapters in the thesis, as described below.

Chapter 1

Chapter 1 elaborately discusses the background and introduction to the work. The pathophysiology of the movement disorders and how electrical stimulation-based devices play their role in alleviating symptoms are discussed. The chapter also discusses the limitations of the current technology, research hypothesis, project objectives, and the rationale for selecting the objectives.

Chapter 2

In Chapter 2, a detailed literature survey is performed to understand the various methods and electrodes used in the application of Deep Brain Stimulation, materials used in the construction of electrodes, various stimulation paradigms, Charge steering applications, Closed-loop and Open-loop DBS systems, and efforts to develop biomarker-based neuro-feedback systems for adaptive stimulations.

Chapter 3

Chapter 3 discusses the various research methodologies and experiments that have been tailor-made to fit the framed objectives for validating the hypothesis.

Section 3.1 discusses the design and development of the said hybrid neuro-electrode and its electrical characterization, including simulation analysis and verification of simulated data with fabricated electrodes in laboratory environments. The comparative study between a control electrode and the designed electrode is presented. Detailed verification of the simulated data was done against in-vitro experiments, and Pearson correlation coefficients were derived.

Section 3.2 discusses the biological characterization of materials used in the fabrication of electrodes and the electrode as a whole from a safety point of view as per 10993-6 standards. Cell interaction studies (on U-87 MG (Uppsala 87 Malignant Glioma)) have also been conducted to study cell reaction and compatibility, establishing morphological exactness and cell viability. The implant studies were done in rat animal models (brain tissue) for 4 weeks and 12 weeks.

In section 3.3, the electrochemical characterizations done on the electrode are discussed, including (a) Identification of damaging effects of stimulation, (b) Defining safe charge injection limits for tissue damage, (c) Defining safe charge injection limits for electrode damage, and (d) Identification of electrical equivalent model via various electrochemical methods such as cyclic voltammetry, Electrochemical Impedance Spectroscopy, and Chronopotentiometry.

Section 3.4 discusses an algorithm developed based on the fact that the modulated beta waves extracted from the Local Field Potentials (LFP) recordings using the hybrid electrode can serve as a potential biomarker for feedback to the neurostimulator for adjusting stimulation levels. The database was purchased from Kaggle, the algorithm was tested in Matlab, and a DSP test board was used.

Chapter 4

Chapter 4 summarizes the results of the experiments conducted and presents a detailed discussion. The in silico and in vitro electrical characterization results of the test electrode and control electrode have been done in detail, and a comparison has been derived with the Pearson correlation method. Results of the in vivo experiments, i.e., implantation studies on rat brains (implantation time - 4 weeks and 12 weeks) are discussed, which give insights into the biological response towards the materials that were used for the construction of the device. Results of the electrochemical characterization are discussed, which provided insights into the electrochemical behavior and generation of the Randles model. The test results of the algorithm with a sample database as input are also discussed.

Chapter 5

The results of the research work are summarized and concluded in Chapter 5. The improvements made in efficiency, power optimization, and closed-loop control algorithms have been listed. A comparison of the outcome to the research objectives is also provided. The extended future work plan of the study is also proposed.

Chapter 1

1 Introduction

1.1 Introduction to Movement Disorders

Movement disorders are a group of neurological conditions characterized by abnormal movement patterns, including tremors, rigidity, bradykinesia, and involuntary movements. Common disorders in this category include Parkinson's disease, essential tremor, dystonia, and Huntington's disease. These conditions affect millions of people worldwide, with Parkinson's disease alone impacting over 10 million individuals. Treatment options vary depending on the specific disorder and its severity but generally include medications like dopamine agonists or anticholinergics, physical therapy, and surgical interventions such as deep brain stimulation (DBS). DBS, in particular, has shown significant efficacy in managing symptoms of Parkinson's disease and essential tremors when medication is insufficient (Global Burden of Disease Study, 2021).

1.1.1 The Basal Ganglia and Motor Control

The Basal Ganglia is a collection of nuclei that include the caudate nucleus, putamen, Globus pallidus, Substantia nigra, and Subthalamic nucleus. These structures are involved in several crucial processes, particularly the modulation of voluntary motor activity. The basal ganglia work closely with the cortex and thalamus in a complex feedback loop that fine-tunes motor commands initiated by the cerebral cortex. The basal ganglia influence movement initiation, amplitude, and termination through this

system. (Albin et al., 1989), Figure 1 shows the basic structures of basal ganglia, whose pathophysiology is involved in movement disorders.

There are two primary pathways within the basal ganglia motor circuit:

Direct Pathway: This pathway facilitates movement by enhancing thalamic output to the motor cortex. It serves as a positive feedback loop, promoting the execution of motor programs.

Indirect Pathway: In contrast, the indirect pathway inhibits movement. It suppresses unwanted or excessive motor commands by inhibiting thalamic output, preventing excessive movement.

Both pathways are balanced to ensure smooth and controlled movement. However, when this balance is disrupted, it results in movement abnormalities, which are seen in disorders such as Parkinson's and Huntington's disease. (Calabresi et al., 2014). Figure 2 shows the connectivity between the direct and indirect pathways between the various units involved with basal ganglia.

The basal ganglia play a central role in controlling movement through their modulation of cortical motor commands via the direct and indirect pathways. Disorders of the basal ganglia, such as Parkinson's disease, Huntington's disease, dystonia, and essential tremor, arise from imbalances within these pathways (Kravitz et al., 2010).

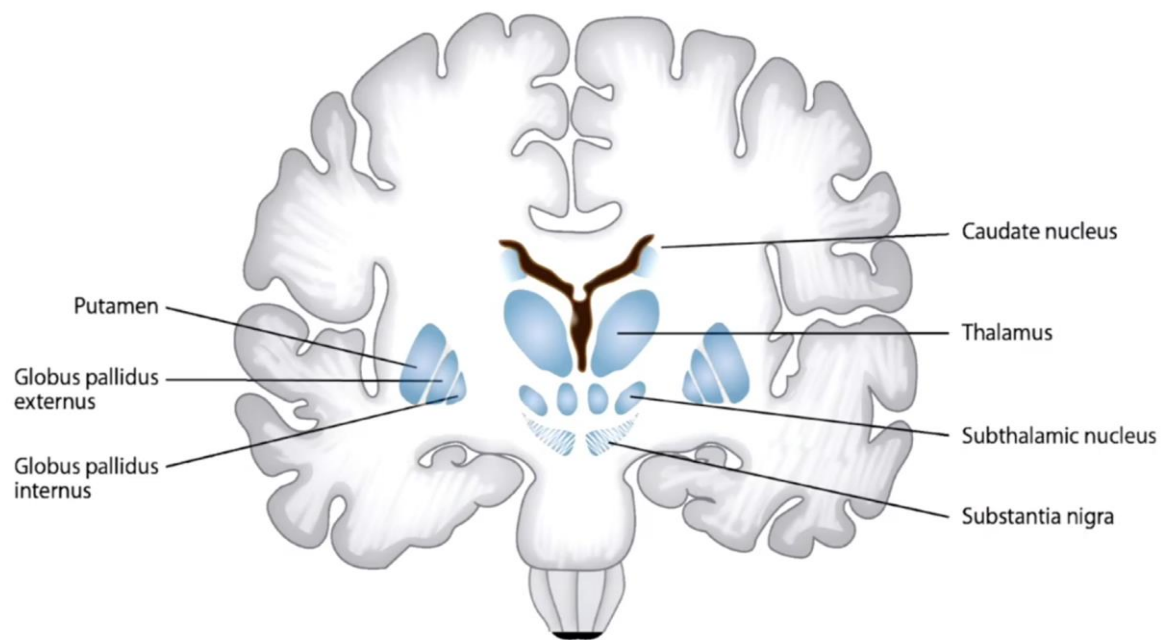


Figure 1: Basal Ganglia structures involved in Movement disorders

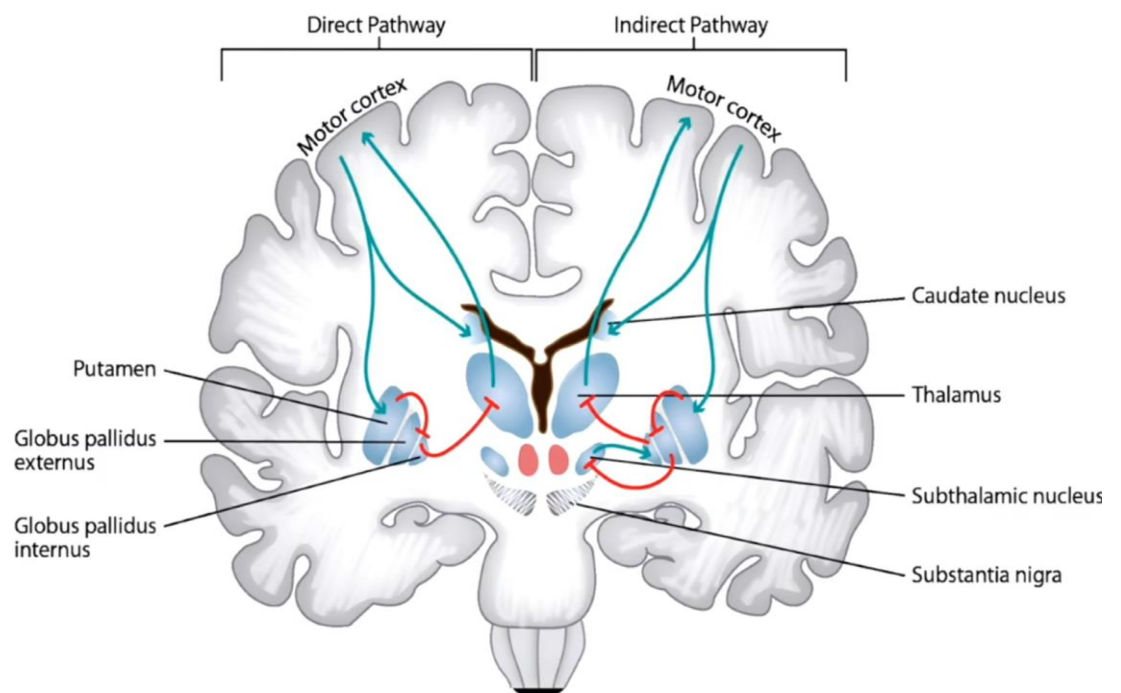


Figure 2: Direct and Indirect pathways of basal ganglia

1.2 Parkinsonism

Parkinsonism refers to a group of movement disorders that share symptoms such as tremors, stiffness, slow movement, and postural instability. The most common form is Parkinson's disease, a progressive neurological condition that primarily affects older adults. Parkinsonism can also arise from other causes, including medication side effects, other neurodegenerative diseases, or brain injuries. These conditions can significantly impact a person's quality of life, leading to challenges in performing daily activities. Treatment typically involves a combination of medication, such as levodopa or dopamine agonists, and non-pharmacological approaches like physical therapy. In cases where symptoms become severe and unresponsive to medication, surgical options like deep brain stimulation (DBS) may be considered, offering potential relief from the more debilitating symptoms.

1.3 Deep Brain Stimulation

Deep brain stimulation (DBS) is a surgical procedure used to treat neurological conditions, particularly movement disorders such as Parkinson's disease, essential tremor, and dystonia. The procedure involves implanting electrodes into specific areas of the brain, which are then connected to a pulse generator placed under the skin in the chest. This device sends electrical impulses to the targeted brain regions, helping to regulate abnormal activity and alleviate symptoms like tremors, rigidity, and bradykinesia. Figure 1 shows the basic schema of the DBS system. DBS is typically considered when medications no longer provide adequate control of symptoms. The technique is adjustable and reversible, offering a personalized approach to managing

these disorders, and has been shown to improve the quality of life for many patients significantly (Marras et al., 2018; Deuschl et al., 2006).

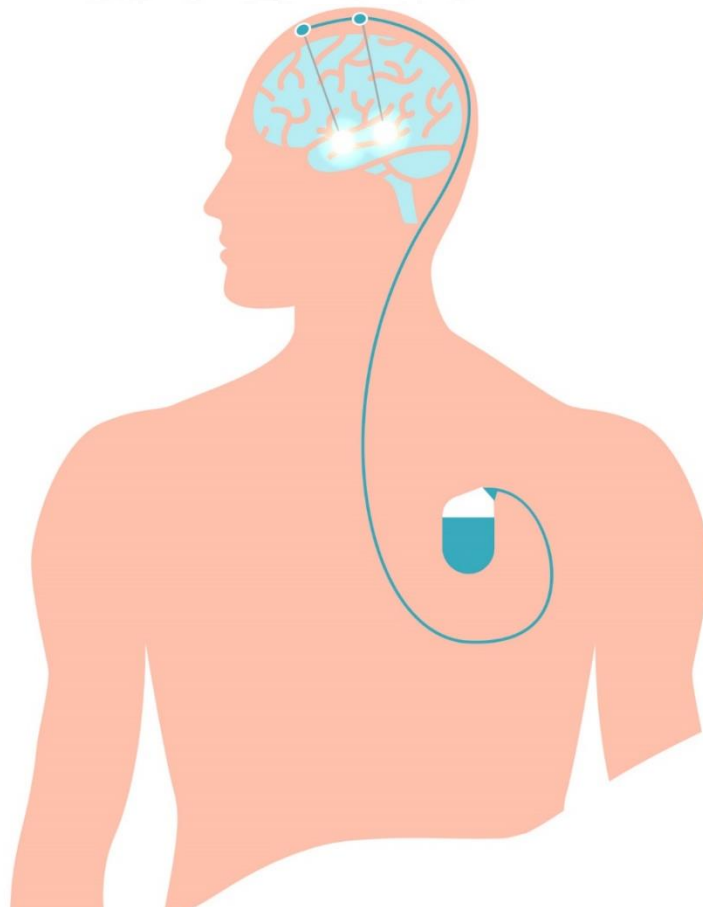
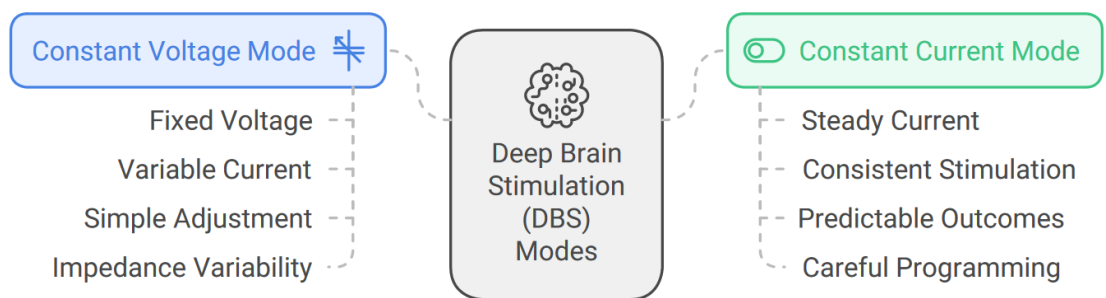


Figure 3: Basic schematic diagram of a Deep Brain Stimulator System

1.3.1 Strategies Used in DBS

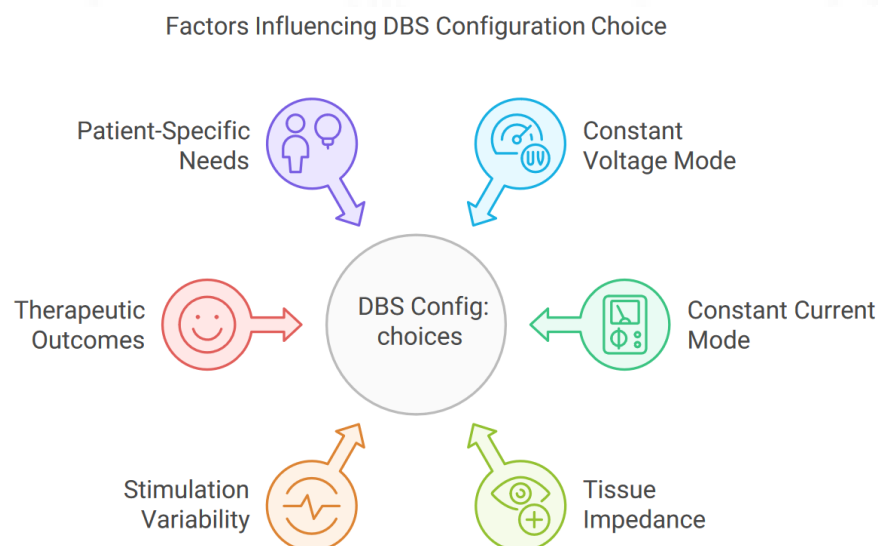
In deep brain stimulation (DBS), the mode of delivering electrical stimulation can be configured in either constant voltage or constant current. In constant voltage mode, the device maintains a fixed voltage across the electrodes, with the current varying depending on the tissue impedance. This mode is commonly used due to its simplicity

and ease of adjustment, but it can lead to variability in stimulation as tissue impedance changes over time. On the other hand, constant current mode delivers a steady current, regardless of changes in tissue impedance, ensuring a more consistent stimulation effect.



Infographic 1

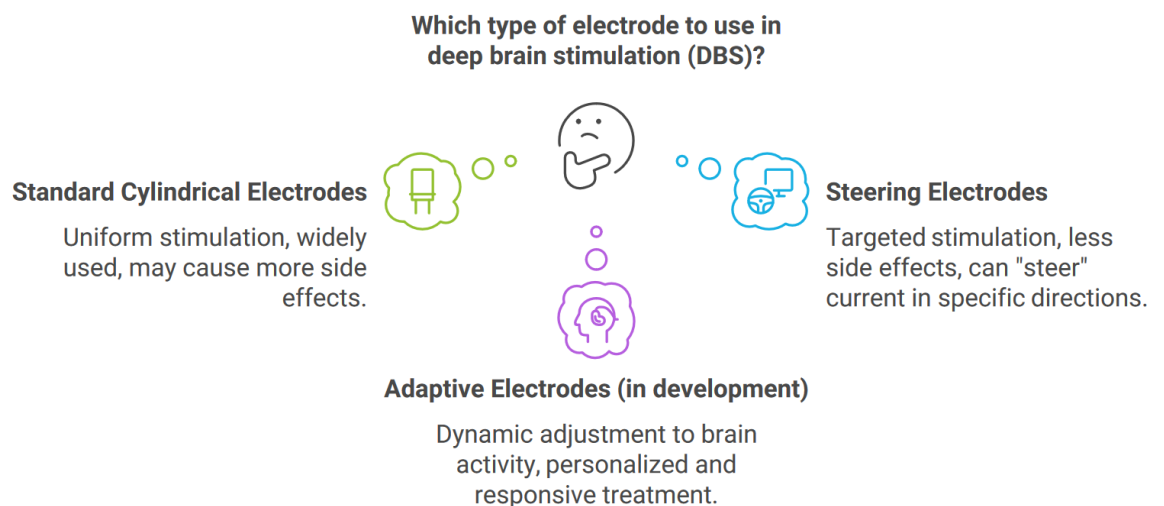
While this can lead to more predictable therapeutic outcomes, it may require more careful programming to avoid unwanted side effects. The choice between these modes depends on the patient's specific needs and the clinical goals of the DBS therapy.



Infographic 2

1.3.2 Electrodes Used in DBS

Different electrodes achieve the desired therapeutic effect in deep brain stimulation (DBS). The most common are standard cylindrical electrodes, which deliver stimulation uniformly in all directions around the electrode's surface. On the other hand, steering electrodes are designed to direct the electrical current more precisely, allowing for more targeted stimulation and minimizing side effects by avoiding unwanted brain areas. These electrodes can "steer" the current in specific directions, providing a higher level of control. Adaptive electrodes, though still in development and not widely available, represent a potential advancement in DBS technology. These electrodes could dynamically adjust stimulation in response to real-time changes in brain activity, offering a more personalized and responsive approach to treatment.



Infographic 3

1.3.3 Open Loop DBS

Traditional deep brain stimulation (DBS) systems employ an open-loop configuration (Figure 4), wherein electrical stimulation is delivered continuously based on pre-determined parameters that are programmed following clinical evaluations. These systems target specific regions within the brain to alleviate symptoms associated with neurological conditions such as Parkinson's disease and essential tremor. The principal advantage of open-loop DBS lies in its relatively straightforward implementation, which has led to its widespread clinical use. However, a fundamental limitation of this approach is the absence of adaptability, as the stimulation remains static regardless of fluctuations in the patient's neural activity or symptoms. Consequently, open-loop systems can result in suboptimal therapeutic outcomes, leading to either excessive or insufficient stimulation, which may cause side effects and increased energy consumption.

1.3.4 Closed Loop and Adaptive DBS

In response to the limitations of open-loop systems, closed-loop DBS (Figure 5) has been developed to offer a more responsive and personalized form of therapy. Closed-loop systems are designed to adjust stimulation parameters in real time by incorporating sensing mechanisms that monitor neural activity or specific physiological biomarkers. This feedback-based approach allows the system to modify the intensity or frequency of stimulation based on real-time changes in the patient's condition, thereby enhancing therapeutic precision. The goal of closed-loop DBS is to optimize clinical outcomes, reduce adverse effects, and improve the overall efficiency of the stimulation process by delivering targeted intervention only when necessary.

Current research in this domain is focused on refining feedback algorithms and identifying reliable biomarkers, which are critical for advancing closed-loop DBS as a viable therapeutic option.

Adaptive DBS takes this concept further by responding to immediate changes in brain signals, learning, and predicting patterns over time, allowing for even more tailored and responsive therapy. These advanced systems are particularly valuable in managing complex and variable symptoms, providing a more personalized approach to treatment that can improve outcomes and quality of life for patients with movement disorders (Proskey et al., 2021; Stanslaski et al., 2012).

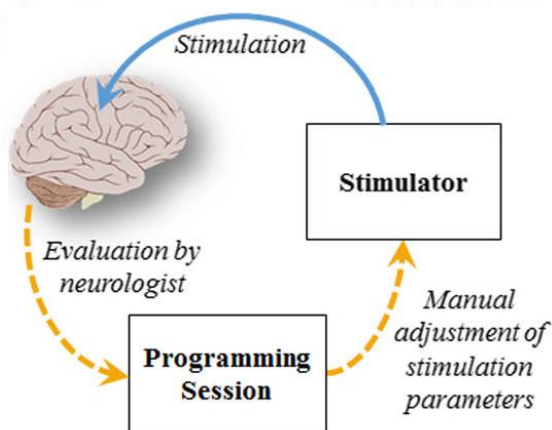


Figure 4 : Open Loop DBS

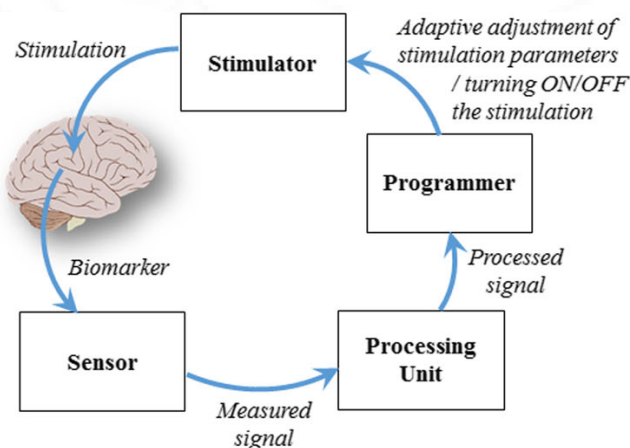


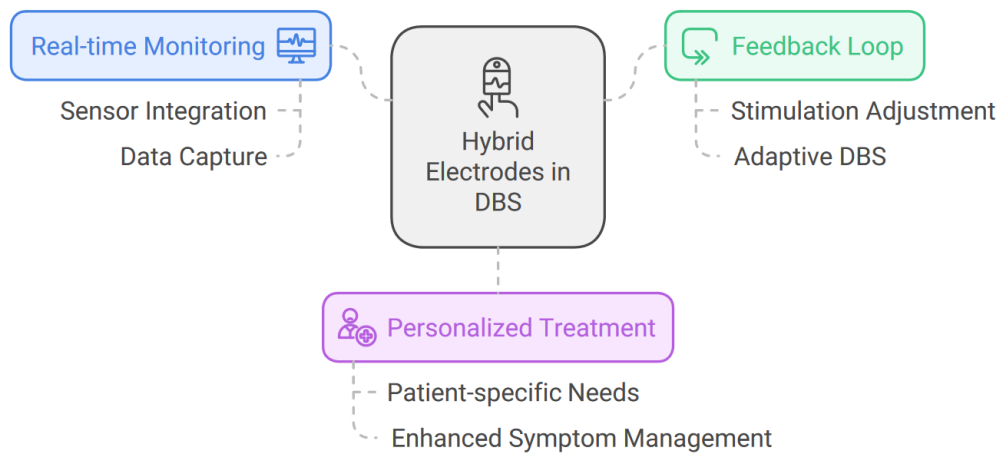
Figure 5 : Closed Loop DBS

1.3.5 Hybrid Electrodes

The advancement of hybrid electrodes for deep brain stimulation (DBS) that incorporate both stimulation and sensing functions is becoming crucial in neurological treatment. Traditional DBS systems are designed to deliver a constant level of electrical stimulation, but they lack the capability to monitor and respond to the brain's dynamic activity in real-time. This limitation can result in less effective symptom management, especially for conditions where symptoms vary significantly throughout the day.

Hybrid electrodes address this challenge by integrating sensors directly into the electrode, allowing for the simultaneous delivery of therapeutic stimulation and the real-time monitoring of brain signals. These sensors capture crucial data on the brain's electrical activity, which can be used to adjust stimulation parameters on the fly, creating a feedback loop essential for adaptive DBS systems. This ability to sense and respond to changes in the brain enables a more refined and personalized treatment approach, adapting to the patient's needs as they arise (Lozano et al., 2024).

By combining both functions into a single device, hybrid electrodes not only enhance the precision of DBS but also improve the overall effectiveness of the treatment. This is particularly important for patients with complex and fluctuating neurological conditions, where traditional DBS might fall short. Integrating sensing capabilities into the electrode is a key step in making DBS therapy more responsive, tailored, and ultimately more successful in improving patient outcomes (Arlotti et al., 2021; Velisar et al., 2020).



Infographic d

1.4 Beta as a Potential Biomarker for Feedback

Beta waves, brain oscillations within the 13-30 Hz range, have emerged as an important biomarker for enhancing the effectiveness of adaptive deep brain stimulation (DBS) systems (Figure 6), particularly in treating movement disorders such as Parkinson's disease. In these disorders, elevated beta activity is closely linked to motor symptoms like tremors, stiffness, and slowed movements. The ability to monitor these brain signals in real-time and adjust treatment accordingly presents a significant advancement in DBS technology.

Adaptive DBS systems utilize beta waves as a real-time feedback mechanism to modulate the level of electrical stimulation. When an increase in beta activity is detected, it typically indicates a worsening of symptoms, prompting the system to boost the stimulation to help control these symptoms. Conversely, when beta wave activity decreases, reflecting a reduction in symptoms, the system can dial back the stimulation. This dynamic process allows the treatment to be continuously adjusted

based on the brain's immediate condition, leading to more precise symptom management.

Integrating beta wave monitoring into DBS systems represents a significant shift from the traditional, fixed-parameter approach of open-loop DBS, which does not adapt to changes in the brain's activity. By using beta waves as an ongoing indicator of the brain's state, adaptive DBS can provide a more effective and tailored therapy, addressing the patient's specific needs as they arise. This approach enhances symptom control and minimizes potential side effects, as the stimulation is only intensified when necessary and reduced when appropriate, avoiding overstimulation and conserving device battery life.

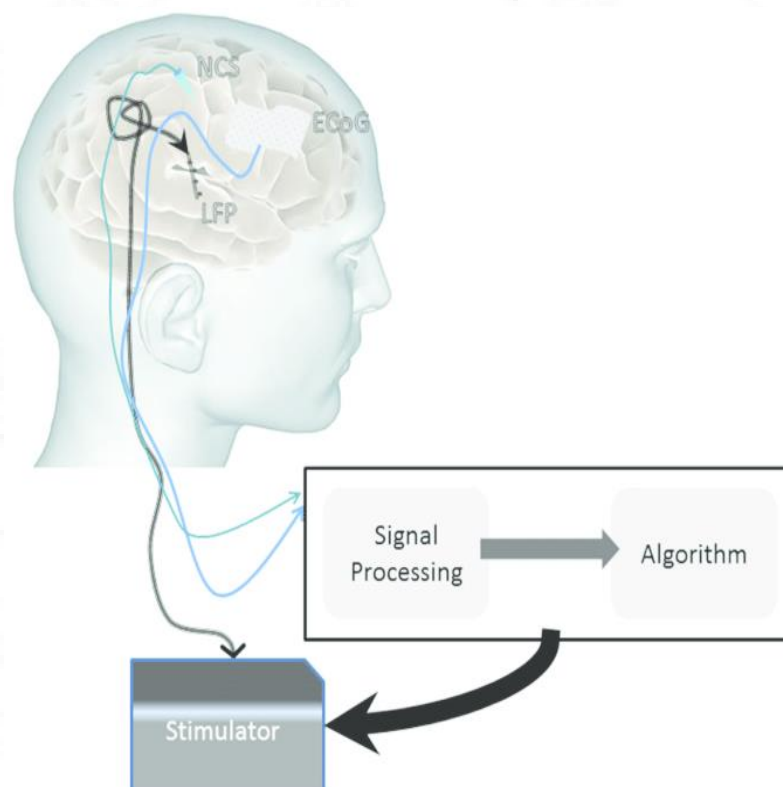


Figure 6: Schematic of a closed loop system in DBS

Furthermore, using beta waves as a biomarker aligns with the broader trend towards personalized medicine, recognizing that each patient's neurological condition is unique and symptoms can vary throughout the day. By incorporating beta wave monitoring into DBS therapy, clinicians can offer a more individualized treatment plan that adapts to the patient's fluctuating needs, ultimately improving the overall outcomes and quality of life. While still a developing technology, the potential for beta wave-guided DBS to revolutionize the treatment of movement disorders is substantial, promising more refined and effective interventions in the future.

This thesis describes the development of a hybrid electrode that can do both sensing and stimulation, and characterization of this electrode through simulations, electrochemical tests, and biological evaluation, and the creation of an algorithm for closed-loop control using beta waves. The thesis is organized into five chapters, each detailing a significant component of this research.

An in-depth review of the literature is given in Chapter 2, exploring various electrodes and methods used in Deep Brain Stimulation (DBS), materials for electrode construction, stimulation paradigms, charge steering, and both closed-loop and open-loop DBS systems. Chapter 3 delves into the research methodologies designed to meet the objectives, with a section on the design and simulation of the hybrid electrode, followed by a comparison with control electrodes. The biological characterization covers biocompatibility studies in cell cultures and rat models, while electrochemical tests assess safe charge limits, potential damage to electrodes and tissues, and electrical modeling. An algorithm utilizing beta waves as biomarkers for adaptive stimulation is presented, and validated through simulations and a DSP test board.

Chapter 4 discusses the outcomes of electrical and biological characterizations, including in vitro and in vivo studies, with Pearson correlation for simulated and experimental data. It presents insights into material biocompatibility from rat model implantations and electrochemical behavior modeling. Chapter 5 provides a summary of research outcomes, listing improvements in power efficiency and control algorithms, and comparing results to the study's objectives. The chapter also proposes future research directions, aiming to expand upon the closed-loop DBS framework developed in this work.

Chapter 2

2. Literature Review

2.1 Deep Brain Stimulation

Deep Brain Stimulation (DBS) has emerged as a crucial therapeutic option for treating various neurological disorders, particularly movement disorders like Parkinson's disease (PD), dystonia, and essential tremor. Since its inception in the late 1980s, DBS technology has progressed from a basic open-loop system to a highly refined and adaptive neuromodulation tool. Over the years, significant advancements have been made in electrode design, stimulation techniques, and feedback systems, which have substantially improved DBS's safety and effectiveness (Benabid et al., 1987). This review aims to provide an overview of DBS's historical development, technological advancements, and potential future directions, focusing on how these innovations have reshaped the treatment of neurological disorders and extended its application to psychiatric conditions.

Modulating brain activity through electrical stimulation dates back to the early 20th century. However, it wasn't until the late 1980s that modern DBS, as we know it, was pioneered by Benabid et al. (1987). They demonstrated that high-frequency electrical stimulation of the ventralis intermedius nucleus of the thalamus could significantly reduce tremors in patients with Parkinson's disease and essential tremors. This approach marked a transformative shift from lesion-based surgeries, such as pallidotomy and thalamotomy, to a reversible and adjustable intervention (Benabid et al., 1987). The early clinical success of DBS in managing motor symptoms led to its

eventual FDA approval for essential tremor in 1997 and Parkinson's disease in 2002 (Lozano et al., 1998).

Starr et al. (2024) explored adaptive deep brain stimulation (aDBS) as a more responsive treatment for Parkinson's disease. In their study, aDBS was shown to reduce motor symptoms by 50%, improving overall patient outcomes. The system dynamically adjusts stimulation based on real-time brain activity, offering an improvement over constant DBS, which can lead to side effects like dyskinesia. The trial demonstrated significant enhancements in patient quality of life by making stimulation more personalized and adaptive to fluctuations in symptoms

2.1.1 Conventional Open Loop DBS

Traditional DBS systems operate in an open-loop configuration, providing continuous stimulation at fixed parameters, regardless of the patient's real-time brain activity or symptom fluctuations (Moro et al., 2010). While this method has been effective for many patients, it does not account for the variability in symptoms, particularly in conditions like Parkinson's disease, where symptom severity can change throughout the day (Wodarg et al., 2012). As a result, open-loop systems may lead to overstimulation during symptom-free periods or insufficient stimulation when symptoms worsen, often causing side effects like dyskinesia and speech disturbances (Schuepbach et al., 2013).

Efforts to enhance the precision of open-loop DBS have included refining programming protocols and using advanced imaging techniques for better electrode placement. The introduction of intraoperative MRI and diffusion tensor imaging (DTI)

has allowed for more accurate electrode targeting, reducing complications associated with incorrect placement (Starr et al., 2002; Pouratian & Elias, 2013).

2.1.2 Closed-Loop and Adaptive DBS

A major leap in DBS technology occurred with the development of adaptive closed-loop DBS (aDBS) systems. These systems use real-time physiological feedback to adjust stimulation parameters dynamically, offering a significant improvement over traditional open-loop DBS. Closed-loop systems can detect neural activity markers, such as local field potentials (LFPs), and modify stimulation in response to these signals (Denison et al., 2011).

Little et al. (2013) provided compelling clinical evidence supporting the efficacy of aDBS in improving motor symptoms and reducing side effects like dyskinesias in patients with Parkinson's disease. Their study showed that adjusting stimulation based on real-time beta oscillations in the STN, aDBS could deliver more personalized and effective therapy (Little et al., 2013). The introduction of Medtronic's Percept™ PC, an aDBS system capable of sensing LFPs and adjusting stimulation based on patient-specific brain activity, has further supported the potential of aDBS systems in treating fluctuating conditions like PD and essential tremor (Meidahl et al., 2017; Rosin et al., 2011). Wanjari et al. (2024) reviewed Medtronic's advancements in adaptive DBS systems, which adjust stimulation in real-time based on brain signals. This innovation allows for continuous monitoring of neural activity, ensuring the device delivers appropriate stimulation levels to minimize symptoms while reducing side effects. These improvements represent a significant step towards making DBS therapy more efficient and patient-specific. Lozano et al. (2024) delve into the advancements and

obstacles in closed-loop DBS systems, emphasizing how these technologies have transformed neuromodulation. One of their key points is that real-time feedback-based adjustments in stimulation reduce adverse effects and enhance treatment efficiency, particularly for disorders like Parkinson's disease (PD). These systems also significantly improve battery longevity, a crucial factor in reducing the need for battery replacements—a common challenge in traditional DBS systems. Arlotti et al. (2021) focus on a specific feedback biomarker in PD: beta oscillations from the subthalamic nucleus (STN). They designed a closed-loop DBS system that adjusts stimulation intensity based on these oscillations. The study shows that this approach provides better control of motor symptoms than traditional methods, resulting in less stimulation time and, consequently, fewer side effects. The ability to continuously optimize treatment based on real-time neural feedback marks a significant improvement over the trial-and-error nature of open-loop DBS. Velisar et al. (2020) highlight local field potentials (LFPs) as a feedback mechanism for modulating DBS in PD patients. Their adaptive system dynamically adjusts stimulation, leading to more effective symptom management. The study highlights the benefits of this approach, including minimizing side effects, reducing the wear on batteries, and improving clinical outcomes. This contrasts with continuous stimulation methods, often resulting in overstimulation and decreased efficacy over time. Little et al. (2022) introduce a model-based approach in closed-loop DBS for essential tremor patients. Their system uses computational models to predict the patient's neural response before administering stimulation, allowing for real-time adjustments. This method has been shown to provide substantial symptom relief while using less energy, making the therapy more efficient and personalized. The potential to adapt this model-based

system to other neurological disorders is an exciting prospect for future research. Priori et al. (2021) explore how neuro-feedback is incorporated into closed-loop DBS systems, examining the use of biomarkers such as electromyography (EMG) and electroencephalography (EEG). Their study highlights the difficulties in selecting reliable biomarkers for different neurological conditions, with EMG showing promise for essential tremor and EEG for PD. Despite these challenges, the ability to integrate such feedback into DBS systems is a key advancement in creating more adaptive and responsive therapies. Cernera et al. (2021) investigate using closed-loop DBS to address habituation to continuous stimulation in PD patients. Their findings suggest that modulating stimulation based on real-time feedback from beta oscillations can improve motor control and reduce the risk of overstimulation - a common issue in traditional DBS systems. This approach provides a more tailored treatment experience, potentially increasing the effectiveness of DBS over the long term. Khaleeq et al. (2019) tackled the technical hurdles in implementing closed-loop DBS, particularly in identifying reliable biomarkers for real-time feedback across various neurological disorders. The study suggests that closed-loop systems must be more adaptable to patient-specific signals to achieve widespread clinical use. While promising results have been seen in movement disorders like PD, more research is needed to apply these systems effectively to other conditions. Grado et al. (2018) emphasize the potential of closed-loop DBS to reduce the need for frequent clinical visits and manual programming adjustments. Their research suggests that automating the adjustment of stimulation parameters enhances the efficacy of DBS therapy and reduces the burden on patients and healthcare providers. This ability to personalize treatment in real time could set the standard for future DBS therapies. Opri et al. (2020) focus on the

limitations of continuous DBS, particularly the frequent need for battery replacements. They advocate for closed-loop systems that adjust stimulation based on real-time feedback, significantly reducing energy consumption without compromising therapeutic effectiveness. This approach offers a more sustainable long-term solution for patients undergoing DBS therapy. Boutet et al. (2021) investigate the use of electrophysiological biomarkers such as LFPs and EMG in closed-loop DBS systems. Their study demonstrates that using these biomarkers as real-time feedback mechanisms can significantly improve outcomes for patients with essential tremor and PD. By adjusting stimulation based on precise, real-time data, these systems offer better symptom control while minimizing side effects, paving the way for more personalized and effective neuromodulation therapies.

2.2 Electrodes Used in Neurostimulation

Neuromodulation techniques find their clinical application in chronic pain management to neuro-motor disorders. Electrical neuromodulation techniques include Deep Brain Stimulation (DBS) and Spinal Cord Stimulation (SCS), in which the targets stimulated are located in the central nervous system, Vagus Nerve Stimulation (VNS), Occipital Nerve Stimulation (ONS), and Tibial Nerve Stimulation (TNS) in which peripheral neural structures are performed. Over the years, neuromodulation techniques have evolved with advancements in microelectronics, battery technologies, electrode-tissue interface modeling, and fabrication, enabling clinicians to provide optimal electrical stimulation to neural structures. Electrode technologies influence the efficiency of stimulation and safe reversible charge injection to minimize neuronal

tissue damage (Cogan et al., 2008). An ideal implantable electrode or its insulation (i) should not cause any damaging tissue response (i.e., should be biocompatible) and should establish stable impedance contact with target cells (Geddes et al., 2003; Gulino et al., 2019), (ii) should have biomimicry, which is the property of the electrode to match mechanical (in terms of the elastic modulus) and physiochemical characteristics of the extracellular matrix, thus reducing the chances of tissue encapsulation (Gulino et al., 2019), and (iii) should be electrochemically and biologically stable to maintain mechanical integrity without causing corrosion (Gulino et al., 2019).

Theoretically, stimulation causes depolarization of membranes of target cells due to ionic current flow between the electrodes. Electrical pulses can be unipolar or bipolar depending on the stimulation with charge balance criteria to ensure zero net charges on the extracellular matrix (Cogan et al., 2008). Lead migration is one of the common problems in all neuromodulation techniques like DBS (Contarino et al., 2013), SCS (Cameron, 2004; Eldabe et al., 2016), ONS (Mollica et al., 2021), etc. Stimulation targets like the subthalamic nuclei (STN) are relatively small structures with maximum dimensions reaching approximately 8 x 6 x 4 mm. Therefore, even lead migration in the mm range may cause loss of efficacy or side effects from unintended stimulation of undesired targets (Pollo et al., 2014). Energy-efficient stimulation becomes an important consideration when a size reduction of the battery is required. Reducing the power requirements for stimulation facilitates using smaller batteries, reduces the Implanted Pulse Generator (IPG) size, and increases the power density (Wei & Grill, 2009). Energy-efficient stimulation in terms of electrodes depends upon reduced electrode impedances, improving the signal-to-noise ratios during recording applications (Cogan et al., 2008). The selection of the ideal electrode material and the

increase in the electrode area can be used to reduce the electrode impedances. However, increasing the electrode area results in a loss of selectivity of stimulation targets. Microelectrodes and macro electrodes depend upon this tradeoff (Pollo et al., 2014; Arcot Desai et al., 2014).

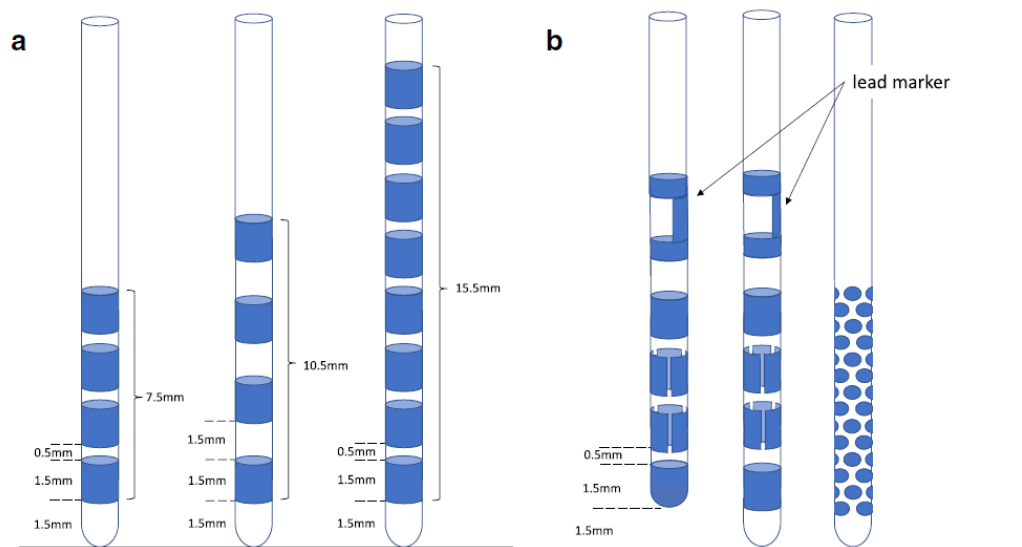


Figure 7: a) Prototypes vary from electrodes with up to 40 small circular contacts of about 0.8 mm, which were evenly distributed over the last 5 to 6 mm of the electrode, and b) more simple models that split up the conventional ring contacts in 3 to 4 segments spanning 90° or about 120°

Electric field distributions and thereby stimulation selectivity and efficiency can be altered by different electrode configurations (Figure 7). Monopolar, Bipolar, Tripolar, or Multipolar configurations could vary field shaping and enable selective stimulations. Tripolar configurations offer a higher concentration of electric field compared to monopolar or bipolar configurations and thereby provide selective activation of neurons, whereas Quadripolar configurations have a higher electric field but poor localization (Sathi & Hosain, 2020). Even though these devices have an

average life span of 7-9 years, the earlier problems limit the efficacy and can lead to the need for revision surgeries (Mollica et al., 2021). Therefore, electrodes in morphology, stimulation efficiency and selectivity, tissue responses, biostability, and low signal-to-noise ratio are important aspects of any active implantable device design. Even though morphologically different, these electrode configurations and stimulation modes are governed by common electrochemical principles. The applications, the performance indicators, and the future capabilities of neuro-electrodes used in different neurostimulation modalities are discussed. The following read gives a comprehensive lookout at the materials used in the manufacturing of these electrodes, the performance indices reported efficiency in terms of the field shaping, current steering, etc. (Figure 8).

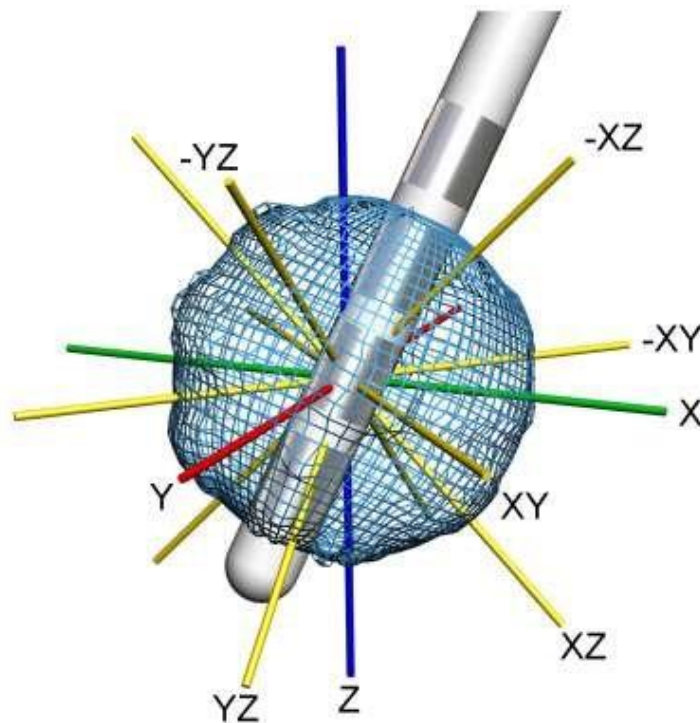


Figure 8: Typical Electric field spread out in tissues

DBS is used for the treatment of Parkinson's disease (PD), essential tremor, dystonia, epilepsy, and psychiatric disorders like obsessive-compulsive disorder (OCD) and depression. The abnormal changes in rates and patterns of neuronal firing in the brain can cause abnormal movements of limbs. Depending upon the clinical conditions and their pathophysiology, different brain targets are stimulated (Herrington et al., 2016). Among these, sub-thalamic nuclei (STN) are an important target in PD. STN neurostimulation significantly improves motor symptoms of PD when the response to drug treatment fluctuates and drug-induced dyskinesias add to the disease burden during medical treatment (Deuschl and Agid, 2013). Even though STN is not a preferred target for Alzheimer's Dementia (Herrington et al., 2016), Zona incerta is also considered a preferred target for sensorimotor disorders apart from the STN (Contarino et al., 2013). Therefore, proper mapping of clinical conditions and electrode contact placement is continuing. Different neurological and psychiatric conditions responsive to DBS use different targets for stimulation. Therefore, clinical efficacy also depends upon the placement of DBS electrodes in the right target and considering the target's anatomy and the disease's pathophysiology. Lead migration up to 5mm may occur after the surgery. This may be due to cerebrospinal fluid (CSF) loss and subdural air invasion during the surgery or due to lead fixation issues (Contarino et al., 2013). Lead anchorage techniques are used to fix the electrodes to limit lead displacements (Heijmans & Joosten, 2020).

2.2.1 Directional DBS Leads

Steigerwald et al., 2019 explored the revolutionary role that directional electrodes play in the evolution of deep brain stimulation (DBS), especially in treating neurological

conditions like Parkinson's disease. The core advancement here is that these electrodes allow for more precise and focused stimulation in specific brain regions, a considerable improvement over the conventional cylindrical electrodes that apply stimulation evenly around the lead. Directional electrodes introduce the ability to steer the electrical field more accurately, which means that stimulation can be concentrated on areas where it is most needed, without unintentionally affecting adjacent structures. This leads to significantly reduced side effects, such as the speech disturbances, muscle contractions (dystonia), and cognitive changes that are common when off-target areas are stimulated in traditional DBS setups (Pollo et al., 2014).

One of the major advantages of directional electrodes is their ability to expand the therapeutic window—that is, the range of stimulation intensities that are both effective and free from adverse effects (Dembek et al., 2017). In clinical practice, this wider window enables physicians to adjust the stimulation settings more flexibly, optimizing symptom control while minimizing any unwanted side effects that might occur with traditional DBS. Furthermore, directional electrodes provide a much more personalized approach to DBS. As the placement of leads in the brain can vary from one patient to another, this technology allows clinicians to tailor the stimulation settings based on each individual's unique brain anatomy. By selectively activating or deactivating certain contacts on the electrode, they can fine-tune the treatment to suit the patient's specific needs (Maks et al., 2009). This level of customization is crucial, especially given the varying progression of neurological disorders like Parkinson's across patients.

Beyond symptom control and patient safety, directional electrodes also offer substantial improvements in terms of energy efficiency. With better-targeted stimulation, less electrical energy is required to achieve the desired therapeutic effect, which translates to longer battery life for DBS devices. For patients, this is an important benefit, as it reduces the frequency of surgical interventions to replace batteries, ultimately enhancing their quality of life (Reich et al., 2015). Steigerwald and colleagues (2019) point out that these advancements represent a significant leap forward in DBS therapy, particularly in how DBS systems are programmed. The ability to direct current precisely opens up new possibilities for adaptive DBS (aDBS) systems, which adjust stimulation in real time based on feedback from brain activity (Little et al., 2013). This combination of directional electrodes and aDBS could potentially allow for a more dynamic and responsive treatment regimen, fine-tuning the therapy to match changes in the patient's brain activity over time (Steigerwald et al., 2019).

In the context of deep brain stimulation (DBS), the concepts of the "sweet spot" and the "sour spot" are crucial to understanding how directional electrodes enhance therapeutic outcomes (Figure 9,10). The sweet spot refers to the precise area in the brain where electrical stimulation provides the maximum therapeutic benefit with minimal side effects. This area is highly specific, often just millimeters in size, and varies from patient to patient depending on their brain anatomy and the particular neurological condition being treated, such as Parkinson's disease. Achieving stimulation within the sweet spot is critical for effective symptom management, whether it's reducing tremors, rigidity, or other motor symptoms. Directional electrodes play an essential role in targeting this sweet spot more effectively. By

allowing clinicians to steer the current towards this optimal region, they can fine-tune the stimulation to maximize benefits and significantly reduce the risks of stimulating surrounding non-target areas.

On the other hand, the sour spot refers to areas surrounding the sweet spot that, when stimulated, can lead to unwanted side effects. These side effects can range from motor disturbances, such as muscle contractions (dystonia), to speech difficulties, cognitive changes, or even mood alterations, depending on which brain regions are unintentionally stimulated. The challenge with traditional DBS electrodes, which emit stimulation radially, is that they often stimulate both the sweet spot and sour spot simultaneously, making it difficult to find a balance between efficacy and minimizing side effects. Directional electrodes offer a solution to this issue by shaping the electrical field to avoid these sour spots, thus allowing more precise stimulation of only the sweet spot. This increased precision not only improves therapeutic outcomes but also widens the therapeutic window, making it easier to maintain effective symptom control without crossing into the stimulation levels that induce side effects. By avoiding the sour spots, clinicians can better optimize DBS therapy, ensuring that patients experience fewer complications while benefiting more from the treatment.

Directional Lead - Concept

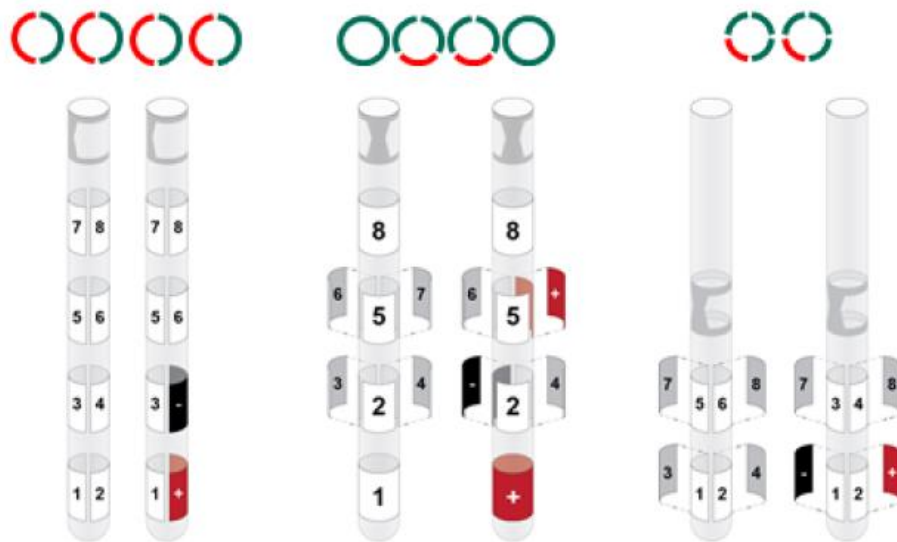


Figure 9: Directional Stimulation Leads

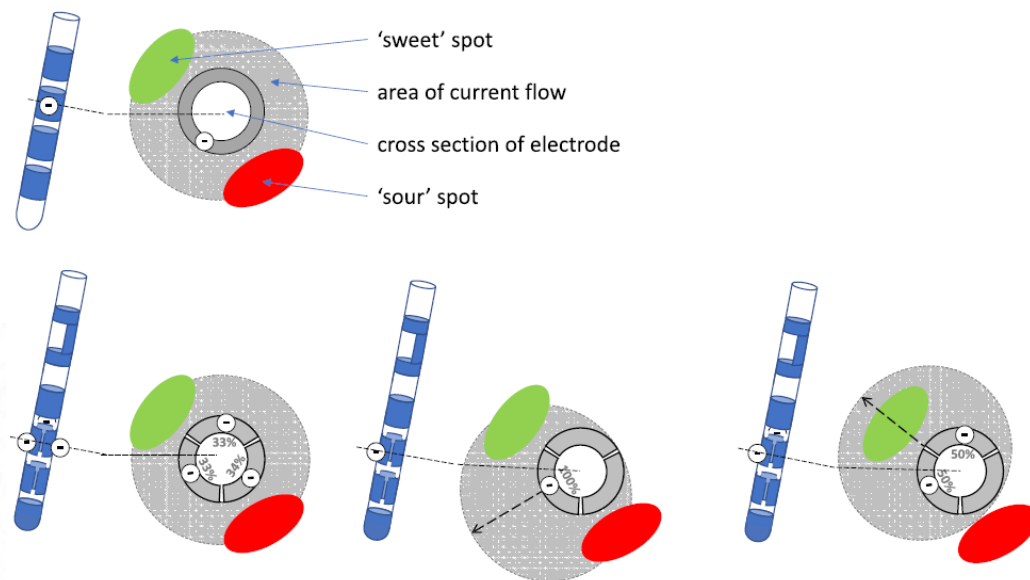


Figure 10: Directional Stimulation highlighting sweet and sour spots

Spinal Cord Stimulation

Spinal cord stimulator (SCS) is used in the treatment of a wide range of pain disorders like persistent back pain secondary to spinal surgery or failed back surgery syndrome (FBSS), brachial plexus injuries, arachnoiditis, diabetic neuropathy, etc. (Cameron, 2004). SCS electrodes can be cylindrical or paddle electrodes (Kin et al., 2018). The positioning of SCS electrodes depends upon the region of pain. Electrodes are placed from C-1 to L-5 in the spinal cord to elicit stimulation. The principle of stimulation is that the area of paresthesia should overlap the pain area (Cameron, 2004). Depending upon the stimulation paradigms, SCS can be (i) tonic SCS, in which stimulation pulses are delivered at a frequency range of 40 to 80 Hz and pulse width range of 200 to 500 μ s to induce paresthesia, (ii) high-frequency SCS, in which pulses of frequency range from 1 to 10 KHz and have more charge per second, are delivered to the dorsal column, and (iii) burst SCS, in which pulses of high frequency but with larger inter-pulse delay are delivered. Burst SCS pulses have a higher charge per second. Charge per pulse directly depends upon the ability to inhibit the neurons of substantia gelatinosa (SG) (Heijmans and Joosten, 2020). Similar to DBS, among SCS hardware complications, lead migration has the highest incidence (13.2%) (Cameron, 2004; Eldabe et al., 2016).

Vagus Nerve Stimulation (VNS)

The vagus nerve is composed of effective motor and mostly (65-80%) afferent sensory fibers, with specific activation thresholds that regulate metabolic homeostasis (Krahl, 2012). Vagus nerve stimulation can be invasive or noninvasive. Left cervical VNS can alleviate epilepsy and treatment-resistant depression, whereas right cervical VNS is used to improve heart failure. VNS is also a treatment method for migraine control in

epileptic patients with migraine as a comorbidity, in which epilepsy is treated with implanted VNS (Moisset et al., 2020; Howland, 2014). This is because depression, inflammation, metabolic syndrome, and heart disease are related and might be mediated by the vagus nerve (Howland, 2014).

Implantable VNS typically uses cuff electrodes (open cylinder placed around the nerve) or helical electrodes (Santos, 2004), with helical electrodes preferred due to their size and flexibility. These electrodes can expand according to the inflammation or tissue encapsulation after the electrode implantation. In helical electrodes, Pt or Pt alloys are twisted and embedded into a silicon helix. Sutures are also embedded in the silicon helix, and it is possible to adjust the position of the electrode around the nerve. Certain lead designs have non-active anchor tethers to ensure implant stability (Afra et al., 2021). A typical drawing of a helical electrode is provided in figure 11.

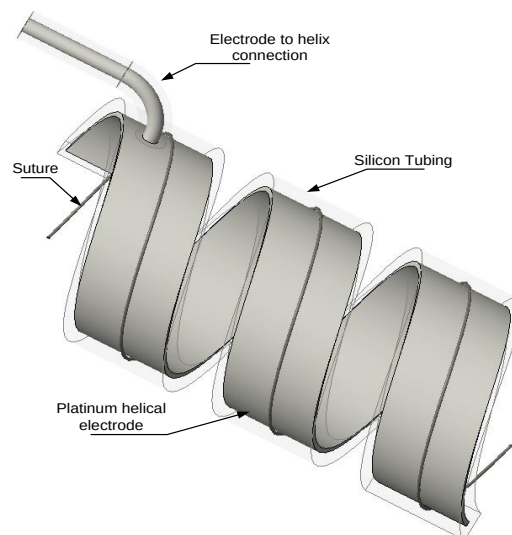


Figure 11: Helical electrode

It is reported that electrodes inside the insulated cuff have the advantage of easier fabrication and are reported (Bucksot et al., 2019) to produce uniform current density and similar nerve recruitment, as compared to the helical electrodes.

2.2.2 Electrode Materials

Electrode material and its insulation play an important role in determining the efficacy of any neurostimulation application, as they should not cause adverse effects on the surrounding environment. There are several characteristics to consider when selecting materials for an implanted electrode, such as electrode-tissue impedance, biocompatibility, corrosion rate, biostability, response immunity, radiographic visibility, etc. Several studies evaluating the material characteristics and tissue response of various materials, from traditional rigid materials to nanostructures, are available (Geddes et al., 2003). Generally, electrodes made of stainless steel, gold, platinum, platinum-iridium, tungsten, and tantalum are good candidates.

Early experiments with multiple electrodes implanted in the cat brain compared platinum electrodes with stainless steel (Wetzel et al., 1969). It was reported that steel electrodes caused deposit formation during biphasic stimulation. Even though stainless steel doesn't cause any tissue responses or distortions with monopolar stimulation, platinum is considered a general solution because of its improved interfacial characteristics. Distortion can be considered an indication of tissue injury.

The Charge Injection Capacity (CIC) is the maximum charge per surface area that can be injected into ETI without causing hydrolysis (Cogan et al., 2008). It is expected to have a high CIC for efficient stimulation, but higher voltages may cause hydrolysis, leading to electrode degradation. The CIC of an electrode can be increased by making

the electrochemical surface area greater than the geometric surface area of the electrode (Negi et al., 2010).

Platinum electrodes have high corrosion resistance and biocompatibility properties but are highly hydrophilic. The CIC of the Pt electrode is around 0.05–0.15 mC/cm², lower than that of Pt-Ir (Cogan et al., 2008). Hydrophilic properties increase cell adhesion and reduce charge transfer capability. Structural changes, like increasing the surface area to decrease electrode impedance and thereby increasing stimulation efficiency, are possible. Flexible control over the pore geometry of the substrate material offers the possibility of using it with any coating material, like platinum black or iridium oxide, or Poly (3,4-ethylene dioxythiophene) (PEDOT) or SIROF (Leber et al., 2017). This indicates that morphological changes to optimize the electrode performance of the material are possible.

Smooth Pt electrodes, even coated with Pt black, have lesser mechanical stability (Kim and Nam, 2013). Platinum–iridium (Pt–Ir) electrodes are biostable and biocompatible compared to stainless steel and gold. The lack of mechanical stability due to its porous nature can be improved using Ir (Iridium) coating. Also, ultra-low impedance, platinum-iridium alloy coating improves the electrical characteristics of DBS leads and was tested with 12 weeks of chronic pulsing (Petrossians et al., 2016). Cyclic voltammetry results show that the CIC of the Pt-Ir material is greater than that of Pt electrodes at a given voltage. Thus, the higher charge storage capacity and significantly lower impedance of the Pt-Ir binary alloy coating make it an important candidate among rough electrode coatings (Petrossians et al., 2011). Tissue encapsulation due to microglia cells, which causes changes in the tissue impedance and electrode failure, is

also observed in Pt-Ir implants (Prasad et al., 2014). It also suggests that electrode failure is due to manufacturing variability and electrode insulation. Tissue encapsulation is not directly correlated since poor electrode performance is obtained with no inflammation (Prasad et al., 2014). Pt-Ir alloys are susceptible to magnetic field inhomogeneity, and due to gradient field switching, may overheat during stimulation (Pollo et al., 2014).

Capacitive charge transfer is beneficial over faradaic charge transfer for electrical stimulation, as it reduces the chance of causing any irreversible faradaic reaction at the electrode-tissue interface, but requires a higher bias voltage ($>4V$) between stimulation pulses. Due to the Helmholtz electrical double layer formed at the electrode-tissue interface, the capacitor electrode should be highly porous (to increase surface area) and dielectrically stable.

Titanium nitride (TiN) is one such option for capacitor electrodes due to its high CIC and chemical stability. The necessity of high ESA to obtain high CIC in small microelectrodes is possible through sputtered depositions. The CIC of TiN, as reported by Abbott et al., 2021, is 0.32 mC/cm^2 , which is less than 3.57 mC/cm^2 of sputtered Iridium oxide for $\sim 300\text{nm}$ thick film (Maeng et al., 2020). However, it has around 1mC/cm^2 when biased to $0.9V$ (Abbott et al., 2021), which is beneficial for neural stimulations. Cyclic voltammetry results show that cathodic current is available during a voltage sweep of $+0.9$ to $0V$ (Abbott et al., 2021).

Electrode pores can be modeled as a combination of resistances and capacitances, which will introduce a time constant on the electrode response. The time constant depends on pore geometry, resistivity, and double-layer capacitance. Due to this time

constant, the entire electrochemical surface is not accessed during stimulation at a particular current density. Narrower and deeper pores give higher time constants (Cogan et al., 2008). The dielectric coating could increase the CIC of capacitor electrodes. Tantalum/tantalum oxide capacitor electrodes can be used as neurostimulators mainly for microstimulators (e.g., BION Implants) (Arcos et al., 2002). Since CIC is limited by electrode pore resistance, these electrodes are not extensively used (Cogan et al., 2008).

The materials for neural electrodes are therefore evaluated across different aspects, particularly from the material characteristic aspect, which is a defining factor of electrode impedance and tissue response (Kim et al., 2018). Several research efforts have been conducted to form nanostructures on the electrode and to select electrodes with improved electrochemical characteristics through surface modifications (Kim et al., 2018). Conducting polymers and carbon nanotubes can be alternative options to Pt alloys, Ir oxide, and TiN. These polymers have chemical surfaces with excellent biocompatibility and minimal immune response (Cogan et al., 2008).

Young's modulus is one of the defining characteristics of electrode coating, which measures its rigidity. Electrodes should have moderate rigidity. The electrode tip has Young's modulus that is much higher (GPa range) than brain tissue (0.1 to 10 KPa range) (Kim et al., 2018). Commonly used coatings like SU-8, polydimethylsiloxane (PDMS), polyimide (PI), and Parylene C have Young's modulus of 2, 0.00132, 2.5, and 2.76 GPa, respectively. The values are summarized in Table 1.

Table 1: Summary of Characteristics –Materials and coatings

Materials and coatings	Characteristics	Reference
Pt	Nontoxic, Higher electrical conductivity, lowest charge injection (0.05-0.15mC/cm ²), Plasma protein attachment.	Leber et al., 2017; Wetzel et al., 1969
Pt-Ir	Faradaic/capacitive charge transfer,CIC greater than Pt, mechanical stability	Petrossians et al., 2011; Petrossians et al., 2016
Tantalum	Capacitive charge transfer,CIC of 0.5mC/cm ² , higher bias voltage	Arcos et al., 2002
TiN	Capacitive charge transfer, lesser CIC than SIROF (1mC/cm ² at bias voltage of 0.9V)	Abbott et al., 2021
SIROF	Faradaic charge transfer, better CIC than thermal iridium oxide.	Cogan et al., 2014
PEDOT	Faradaic charge transfer, Higher CIC(~15mC/cm ²), lower impedance, Nontoxic, Better mechanical property	Leber et al., 2017; Kim and Nam, 2013
PDMS	Anion doping (typically with styrene sulfonate),lower impedance, CIC of 15mC/cm ² when coated over with Pt-Ir microelectrodes,Nontoxic	Cogan et al., 2008
PEG	Reduced glial scarring and neuronal cell damage,Reduced amount of protein adsorption with polyurethane coating	Golabchi et al., 2019

SIROF (Sputtered Iridium Oxide Film):

SIROF is widely used in medical devices like cochlear implants, pacemakers, and deep brain stimulation (DBS) systems. Its key strengths lie in its high ability to store electrical charge and low resistance, which are critical for effectively stimulating nerve tissues. Iridium oxide films allow efficient transfer of electrical charge, reducing the risk of harming neurons. Because of its minimal electrode polarization, it is stable for long-term use inside the body. SIROF coatings are also resistant to corrosion and biocompatible, making them ideal for long-term implants.

PEDOT (Poly(3,4-ethylenedioxythiophene)):

PEDOT is a conductive polymer often applied in neural recording and stimulation devices. Its high conductivity helps in reducing the impedance of electrodes, thereby

enhancing the sensitivity of the devices. The porous nature of PEDOT increases the electrode's surface area, boosting its capacity to inject charge, which allows for more efficient nerve stimulation at lower voltages, helping to minimize tissue damage. PEDOT's flexibility allows it to integrate smoothly with biological tissues, reducing inflammation and scarring. It's found in various neural applications such as brain-machine interfaces, cochlear implants, and retinal prostheses.

PDMS (Polydimethylsiloxane):

PDMS is a silicone-based material known for its flexibility and transparency. It's commonly used in biomedical devices like microfluidic systems, neural interfaces, and wearable sensors. PDMS's elastic nature is key in making flexible electronics that can move with the body. Although naturally water-resistant, its surface can be treated to improve its ability to interact with cells and tissues, making it even more suitable for implants. PDMS is often used as a protective coating for electronics or in fabricating soft, flexible electrode arrays in medical devices.

PEG (Polyethylene Glycol):

PEG is a water-loving polymer widely used in medical applications for its compatibility with biological systems. Its ability to resist the build-up of proteins and cells on surfaces makes it great for coating implants to prevent fouling. PEG is also a common material for developing drug delivery systems, as it forms gels that can release drugs in a controlled manner. PEG is frequently used to coat neural devices to reduce immune reactions and to help devices better integrate with surrounding tissues. PEG is also added to certain drugs to improve their effectiveness by extending their presence in the body.

2.2.3 Morphology of Electrode

The electrode morphology affects the stimulation area, stimulation efficiency, stimulation effectiveness, and selectivity. Electrode shape may depend upon the type of neuromodulation. Loitz et al. (2015) showed that optimal stimulation varies with electrode shape and subject. Electrode shapes have higher flexibility for microelectrodes with flexibility in the lithographic process. Conventionally used electrode shapes are ring, disc, and segmented electrodes for DBS and percutaneous cylindrical leads or paddle electrodes for SCS. Different microelectrode arrays are available for visual prosthetics and related applications.

In cortical stimulation studies, Kim et al. (2011) report no significant overall difference in current density distribution between disc and ring electrode stimulation compared to differences in stimulation type or stimulation location. Current density distribution is 53-54% and 44-43% in white matter and grey matter with both ring and disc electrodes. However, ring electrodes offer the additional advantage of using pH sensors or sensors for monitoring neural responses to stimuli with the same current density distribution characteristics. Disc diameter and ring thickness are key parameters determining the optimal electrode shape. Kim et al. (2012) performed a computational study of the current distribution behavior of disc, ring, and covered disc electrodes. The covered disc is similar to a grid electrode used in clinical conditions, insulated with a substrate while still providing contact for stimulation. The covered disc configuration draws more current to flow through grey matter and is considered the practical electrode shape. Kim et al. (2012) report that leakage current to CSF is minimized for the covered disc. The effective volume (volume of the region with a

current density exceeding the threshold) and penetration (effective depth of penetration is the diameter of the region having a current density above the threshold) were also low.

Kim et al. (2014) compared paddle array and single-electrode stimulation of subcortical structures. A paddle configuration is a multi-electrode arrangement of electrodes of any shape (e.g., disc type with exposed contact area). The positions of the anode or cathode electrode and the reference electrode change the distribution of the electric field in the brain with multipolar configurations (Sathi & Hosain, 2020). Therefore, paddle electrodes provide greater flexibility for electric flux distribution and show a non-linear cumulative effect due to using multiple electrodes. For voltage stimulation in the paddle array, the effective depth of penetration varied non-linearly from 0.4 cm (at 0.5 V) to 4 cm (at 5.0 V), whereas for single-electrode stimulation, the depth ranged linearly from 0.4 cm to 2 cm, though depth may vary with the cortical region (Kim & Nam, 2013). The effective volume during voltage stimulation with paddle electrodes is also greater. However, the effective penetration depth per electrode for paddle-array voltage stimulation is slightly less efficient than single-electrode voltage stimulation in terms of contribution to penetration depth. The effective depth with single-electrode stimulation is higher than that in paddle-array current stimulation, and single-electrode current stimulation yields slightly larger or comparable effective volumes to paddle-array (Figure 12) current stimulation (Kim et al., 2014).

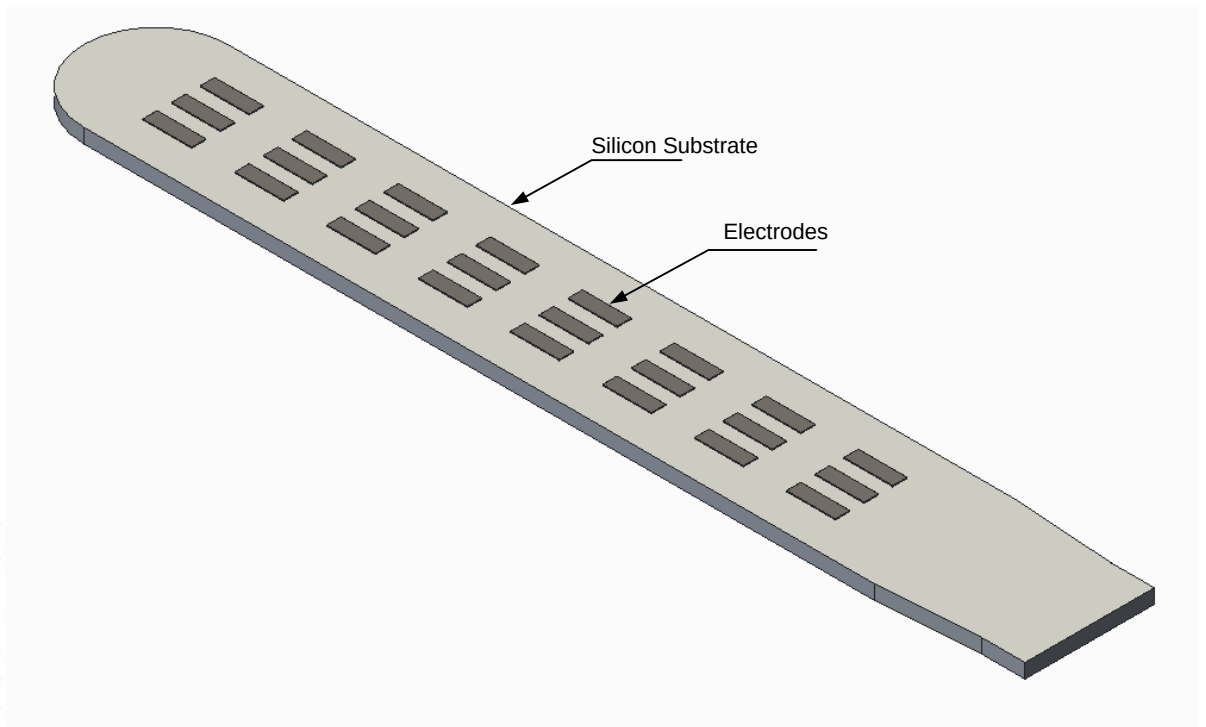


Figure 12: Three-row Paddle Electrodes

The SCS electrodes can be inserted percutaneously as catheter leads (cylindrical electrodes) or surgically through a laminectomy (surgical paddle electrode) (Kin et al., 2018). Percutaneous leads are the least invasive and can be implanted under local anesthesia. This process provides the advantage of detecting optimal electrode placement from patient feedback (Kin et al., 2018). Paddle electrodes have greater structural stability (flatter shape and wider design) and reduce lead migration. Paddle electrodes can also stimulate a larger surface area with lower pulse parameters, increasing the energy efficiency of stimulation and decreasing recharging frequency, a crucial parameter for implantable battery-packed devices, thus providing better pain relief. Additionally, insulated paddle electrodes are preferable for permanent implantation if undesirable stimulation leads to the recruitment of small fibers in ligamentum flavum (Wetzel et al., 1969; Robinson and Johnson, 1961).

This is due to the radial nature of the percutaneous contact, which drives the current radially and brings the current level to the threshold (Wetzel et al., 1969; Robinson and Johnson, 1961). Stimulation selectivity depends on several factors: number of electrodes, center-to-center electrode spacing, electrode geometry, and the relative orientation of the electrodes among columns in the paddle (Leber et al., 2017). Stimulation sensitivity refers to the specific stimulation of neurons (i.e., inhibition of nociceptive fibers through the activation of inhibitory interneurons) with minimal paresthesia, making paddle electrodes preferable for SCS based on technical aspects. It is reported that a center-to-center anode-cathode separation of less than 10 mm influences certain pain targets like the lower back with paresthesia (Leber et al., 2017). The narrower the center-to-center spacing, the higher the stimulation lateral field distribution (Prasad et al., 2014; Negi et al., 2010). However, the positioning of the paddle electrode is also important for effective pain alleviation, and several techniques—either using local anesthesia or general anesthesia for electrode implantation—have their respective advantages and disadvantages. A minimally invasive approach using spinal anesthesia is proposed (Sarubbo et al., 2012).

Conventional DBS uses ring electrodes with stimulation in multiple directions rather than toward a specific field, as seen in directional leads. These stimulations provide sufficient clinical benefits, but the lack of stimulation selectivity is an issue, leading to undesirable stimulations that cause paresthesia, muscle movements, emotional disturbances, etc. TN is one of the prominent stimulation locations for DBS (Contarino et al., 2013), so optimal target

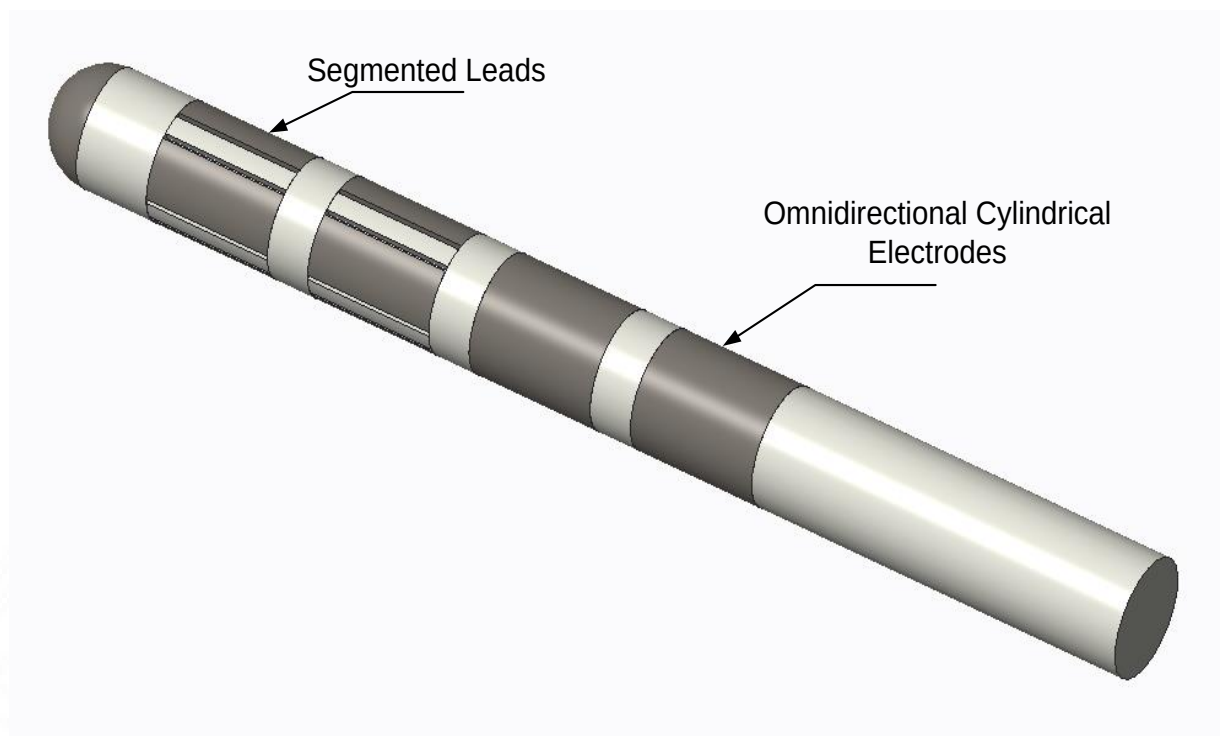


Figure 13: Conventional Hybrid electrode for steering and stimulation

localization is essential. Controlling the pulse parameters may be an option, but this could reduce clinical benefits (Welter et al., 2014). As reported in the literature (Schrader et al., 2002; Deuschl and Agid, 2013), optimal target accuracy in the range of millimeters is needed, but lead displacements can cause unacceptable side effects or loss of effectiveness. Directional stimulation is an option. Segmented leads (Figure 13) with smaller electrode surface areas of less than 1 mm^2 can be fabricated as thin films over a substrate using microfabrication techniques (microelectrodes). Clinical results show that directional activation of desired neuronal groups is possible. Directional leads can modify the volume of tissue activated in the desired direction over a 1–2 mm distance, which is important if DBS leads end up being placed in sub-optimal locations. This gives an additional degree of freedom to optimize DBS therapy and has the potential to widen the therapeutic window (Martens et al., 2011). A typical

segmented DBS lead consists of both directional and omnidirectional leads, depending on the application, as shown in Figure 3. Green and Aziz (2014) used six directional and two-ring electrodes, where directional electrodes were on the distal end, and the two-ring electrodes were at the proximal end of the lead assembly. The directional electrodes typically have a surface area of 1 mm² and center-to-center spacing of 0.5 mm. Directional leads are typically placed at angles of 0°, 120°, and 240°. Indications may be provided on the electrode to identify the orientation (Green and Aziz, 2014; Fricke et al., 2021). In short, segmented leads could significantly reduce the volume of tissue activated within the STN and provide more radial distal stimulation in the desired direction.

2.2.4 Performance Improvement of Electrodes

The need for energy-efficient systems has increased with the advent of implantable neurostimulators equipped with wireless charging. Batteries used for implantable pulse generators (IPG) typically require replacement every 1–5 years, depending on the stimulation parameters (Dorval et al., 2010; Baizabal Carvallo et al., 2011). Other performance indices of electrodes include stimulation selectivity and tissue response (Cameron, 2004; Howell & Grill, 2014).

2.2.4.1 Stimulation efficiency

Increasing stimulation efficiency means reducing the energy required for the necessary field distribution. This can be achieved by decreasing the electrode impedance (Leber et al., 2017; Petrossians et al., 2011; Maeng et al., 2020) or by modulating the driving force for neural activation (field shaping).

2.2.4.2 Decreasing the electrode impedance

As suggested in the Randles model (Wei and Grill, 2009), reducing electrode impedance increases the current injected into the electrode-tissue interface, thereby reducing the voltage required for stimulation. Studies have been conducted to decrease impedance by reducing R_a and R_f and by increasing CL .

The increase of double-layer capacitance (CL) can be achieved by increasing the area of overlap between the tissue and electrode, which decreases Faraday resistance. This is done by a surface roughening process, where electrical deposition of Pt (Leber et al., 2017) or titanium nitride (TiN) over the electrodes increases the geometrical surface area of electrodes (Maeng et al., 2020). The electrochemical limits on platinum are $400\mu C/cm^2$ below the neural damage limits of $1 mC/cm^2$. So, electrochemical limitations for stimulation with platinum cause the device to operate below neural damage limits (Maeng et al., 2020). An attempt to model the impedance characteristics of the electrode for DBS (Wei and Grill, 2009) indicates that both R_f and CL also depend on the frequency of biphasic signals and current density at the geometric surface area of the electrode. R_f and CL are decreased with the increase in frequency in the kHz range, even though R_f and CL dependencies are more pronounced at lower frequencies (less than 100Hz) (Wei and Grill, 2009).

At low frequencies (less than 100 Hz), R_f decreases, and CL increases with increasing current density, as per basic principles. At low frequencies (less than 100 Hz), R_f and CL drop below 10% of their value at a particular current density, but this is not evident at higher frequencies (greater than 100Hz) (Geddes et al., 2003; Wei and Grill, 2009).

Capacitive electrodes also increase CL by coating Ta (Arcos et al., 2002) or TiN (Abbott et al., 2021), which increases ϵ_r . Applying a thin film reduces the increase of inter-plate distance, d (Cogan et al., 2008). Even though oxides of Ti have higher ϵ_r (ϵ_r of 100) than that of Ta (ϵ_r of 25), the porous nature of TiO_2 causes hydrolysis. However, the intrinsic chemical and mechanical stability of the coating, insensitivity to dehydration of TiO_2 , and a high bias voltage make TiN electrodes suitable for electrical stimulation (Cogan et al., 2008).

Pseudo-capacitance can be yielded through the faradaic coating, which increases the faradaic current developed per change in potential. The first Ir oxides are such coatings formed by the electrochemical activation of Ir metal, known as AIROFs (activated iridium oxide film) (Cogan et al., 2008). Ir undergoes oxidation and reduction between Ir^{3+} and Ir^{4+} , forming a hydrated film on the electrode that allows reversible charge injection. AIROF is capable of injecting between four to ten times the charge of a Pt-Ir electrode of the same GSA, with a maximum CIC of 3.9 mC/cm^2 (Cogan et al., 2008).

The access resistance of the electrode, which is the tissue resistance after the electrode and electrode-tissue interface, is also decreased by increasing the electrode area. Current density is maximum at the distal end rather than at the center of the electrode (edge effect), providing an option to increase the electrode perimeter to increase the accessibility of charge with tissue, thereby increasing stimulation efficiency. Therefore, altering the electrode perimeter without changing the electrode area increases this non-uniform current density on the electrode surface (Wei & Grill, 2009). A serpentine-shaped planar electrode showed a lower threshold for activating

axons placed farther from the electrode (Wei & Grill, 2009). This is because farther axons experience more non-uniform current density due to the serpentine structure, which results in high activation caused by a strong parallel current component. The increase in activation function is more pronounced for perpendicular axons than parallel axons, as current flows out of the electrodes perpendicular to the surface, aligning with perpendicular axons (Wei & Grill, 2009). This property is used for obsessive-compulsive disorder DBS applications where the thalamocortical target fibre is perpendicular to the electrode surface, and its performance can be increased by increasing the height of cylindrical electrodes. However, as suggested by Wei and Grill (2009), the relationship between stimulation efficiency and surface perimeter is not linear but also depends on the potential distribution of the tissue. The effect of the area is more pronounced in the case of stimulation efficiency.

2.2.4.3 Field shaping

The polarization of an axon due to an extracellular field is proportional to the second spatial derivative of the extracellular potentials along the neuron activating function $(\partial^2 V_e)/(\partial x^2)$ (Rattay, 1989; Zhang & Grill, 2010). Therefore, stimulation efficiency also depends on $(\partial^2 V_e)/(\partial x^2)$. This is known as field shaping. A comparison between the ring electrode (or any point-sized source) and the line source showed that even with twice the magnitude of the current, the line source could produce an activation function less than or equal to the point source function. This also depends on the orientation; potentials of parallel axons (parallel to the line source) showed a flatter response. Multipolar stimulation provides a wide range of field function variations

compared to monopolar variation, thereby increasing stimulation efficiency (Sathi & Hosain, 2020).

Stimulation selectivity

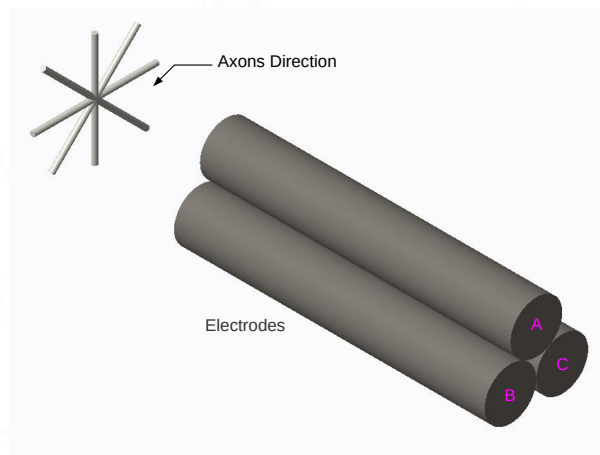
In every neurostimulation modality, stimulation selectivity is an important factor that affects the therapeutic efficacy of DBS (Contarino et al., 2013), SCS (Fricke et al., 2021), etc. Optimal stimulation depends upon this stimulation selectivity, which primarily depends on the location where the electrode is placed, the configuration of electrodes, and the stimulation of a specific site.

Stimulation selectivity and field orientation

Stimulation selectivity can be achieved by directing the $(\partial^2 V_e)/(\partial x^2)$ in the desired direction to be greater than in other directions. This strategy was tested for DBS for stimulation in the corpus callosum (Lehto et al., 2017) and Epidural Spinal Cord Stimulation (ESCS) (Canna et al., 2021). Lehto et al. (2017) explain an independently controlled stimulation of electrodes oriented in a particular direction to stimulate desired axonal pathways selectively. A minimum of three electrode channels along a triangle is required for the control of the distribution of the field in a 2D space, while four independently controlled channels (one lead off-plane with the other three) are required for 3D field distribution control. A three-electrode channel is used to make a tripolar electrode arrangement, which is used to orient the electric dipoles in the desired direction (Lehto et al., 2017). These electrodes can be excited using three sinusoidal 120° phase-displaced currents, or individual pulse amplitude for each channel can also be displaced to select anode-cathodes, thereby shifting the electric dipoles alternatively. Results show that the calculated electric field gradient in the

direction of the primary electric field orientation of the electric dipole is greater than that of electric field gradients perpendicular to the primary field. Hence, axons in the direction of the electric field require a lesser threshold level for stimulation than perpendicular axons (Lehto et al., 2017). Computational models also validate the results, showing a peak activation percentage of 80% with a stimulation angle (angle between primary electric field and orientation of axons) of 0° or 360° (Lehto et al., 2017).

Similar techniques are also used for SCS electrodes (typically paddle electrodes), allowing for field-steering possibilities. However, conventional paddle electrodes are driven by a single current or voltage source, which allows only limited field distribution control. Flexibility of target selection is possible with multiple sources.



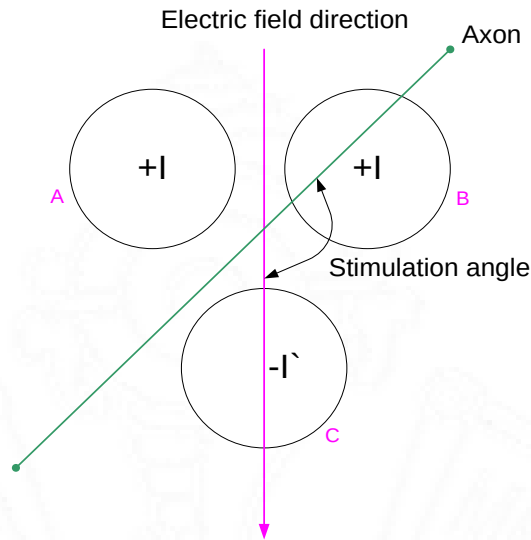


Figure 14. Relationship between stimulation angle and orientation of axons.

A comparison between dual parallel 8-contact SCS leads with multisource and single-source arrangements showed improved stimulation center point selection and precise mediolateral steering in the volume of tissue activated (VTA) for the multisource arrangement, compared to the single source, which could provide better pain-paresthesia overlap (Lee et al., 2011). Similar to orientation-selective stimulations in DBS, unequal independently controlled channel stimulation selectivity can be varied with stimulation angles. fMRI studies by Canna et al. (2021) show that clear contrast is observed between 0° and all other stimulation angles in the cingulate and motor cortices (areas related to motor networks) and also between 120° and all other angles in the basal forebrain and septal regions. The 0° and 120° angles occur when the direction of the electric field is parallel to the spinal cord and near the dorsal roots, respectively (Figure 14).

Directional stimulation can also be achieved by electrode arrangement. A comparison of conventional cylindrical 4-annular DBS leads and a 64-disc-shaped electrode

arranged in 16 rows with equal length showed that accurate vertical placement of the stimulation field with a 0.75 mm axial pitch and off-axis placement of the field within a range of 2 mm is possible with the latter leads, whereas conventional leads have little tangential freedom (Martens et al., 2011).

Stimulation selectivity and fiber diameter

In peripheral neuromuscular stimulations, the natural recruitment order of motor neurons is from smaller-diameter fibers to larger-diameter fibers. However, larger motor fibers are recruited before smaller ones with unipolar or conventional electrode configurations (Lertmanorat et al., 2005). This occurs because the second spatial derivative of extracellular potential ($\partial^2 V_e / \partial x^2$) increases with fiber diameter. Thus, in peripheral nerve stimulation, the goal is to reverse the recruitment order of motor neurons so that smaller fibers are selectively activated before larger ones (Lertmanorat et al., 2006). A tripolar configuration (anode-cathode arrangement) could reverse the recruitment order. The nodes of Ranvier of an axon closest to the cathode are polarized first upon activation, whereas distal nodes are hyperpolarized by anodes, thereby blocking the action potential of larger diameter axons (Fang and Mortimer, 1991). This technique requires sufficiently long pulse durations and amplitudes ($>500\mu s$) (Lertmanorat et al., 2005). $\partial^2 V_e / \partial x^2$ can be varied using an array of five or more electrodes with alternating anode and cathode electrodes to stimulate an axon. If the internodal length (distance between nodes of Ranvier), which is proportional to the diameter of the fiber, is less than the interelectrode distance, such an axon will be activated first, indicating that smaller fibers will be activated more easily. Experimental results from Lertmanorat et al. (2005) show that a five-contact electrode

array (with 0.65 mm separation) activated axons having internodal distances similar to or less than the contact separation ($\leq 6.5 \mu\text{m}$ diameter), while larger axons ($> 6.5 \mu\text{m}$) were less activated, which matches the natural recruitment order and is independent of pulse duration. A typical tripolar electrode arrangement is shown in figure 5.

Tissue response

Tissue response can be due to the inherent reaction to foreign material introduced into the cellular environment or due to the electrical stimulation at the location.

Foreign body tissue responses

Tissue response and subsequent events depend on biotic and abiotic factors. Biotic factors are those caused by cellular reactions, such as blood-brain barrier (BBB) weakening, immune response and microglial activation, neuronal cell death, and glial scar formation. Abiotic factors are those caused by the electrode material, such as degraded impedance response, changes in stimulation threshold levels, and the formation of electrochemical interfaces at the electrode-tissue junction, which can evolve into irregular pits. Both factors affect the performance and lifetime of implanted electrodes (Gulino et al., 2019).

An electrode implanted into the brain initiates an inflammatory reaction, activating microglia cells. Capsule formation begins around the implant, with lamellipodia within nearly 30 minutes. It is estimated that within 24 hours of implantation, motile microglia cause more and more cell bodies to surround the electrode, and encapsulation strengthens. Astrocytes are activated during the first 2-3 weeks, forming a sheath over the activated microglia. In the chronic inflammation stage, this glial scar

covering the microelectrode affects the stimulating site's integrity, potentially resulting in implant failure. This fibrous encapsulation increases the minimum stimulation thresholds due to an increase in impedance characteristics and is also affected by the fluid inside the capsule. Encapsulation affects ion exchange between the electrode-tissue interface (Prasad et al., 2014; Rao et al., 2012).

The entire tissue response, from the acute phase of inflammation initiated by BBB disruption and neuronal death due to mechanical injury to degraded electrode performance after steady microglial formation, is outlined in the study by Baizabal Carvallo et al. (2011). Conventional macroelectrodes, compared to microelectrodes, could aggravate inflammation during implantation due to their size and rigidity, even though the activation range of microelectrodes is less (Baizabal Carvallo et al., 2011).

Adsorption of serum proteins onto the surface of implants increases microglial activation. The material properties of implants influence their adsorption nature. Non-fouling surface modification of implants could reduce the binding tendency of adsorbed proteins (Golabchi et al., 2019). Several zwitterionic materials, such as phosphorylcholine (PC) and carboxybetaine (CB), show better resistance than conventional polyethylene glycol (PEG) coating (Golabchi et al., 2019). The intensity of acute microglial formation also depends on the material and its geometry and can vary with the type of materials (Wetzel et al., 1969; Prasad et al., 2014). Mechanical mismatch, in terms of the elastic modulus between the electrode coating and surrounding tissue, could impact tissue responses. PEDOT-based coatings could reduce mechanical stress while also lowering impedance and acting as an interface between the hard electrode and soft tissue (Baek et al., 2014; Leber et al., 2017). These

are conductive polymers whose composition, microstructure, elasticity, and crystallinity can be adjusted by adding dopants like polystyrene sulfonate (Figure 15).

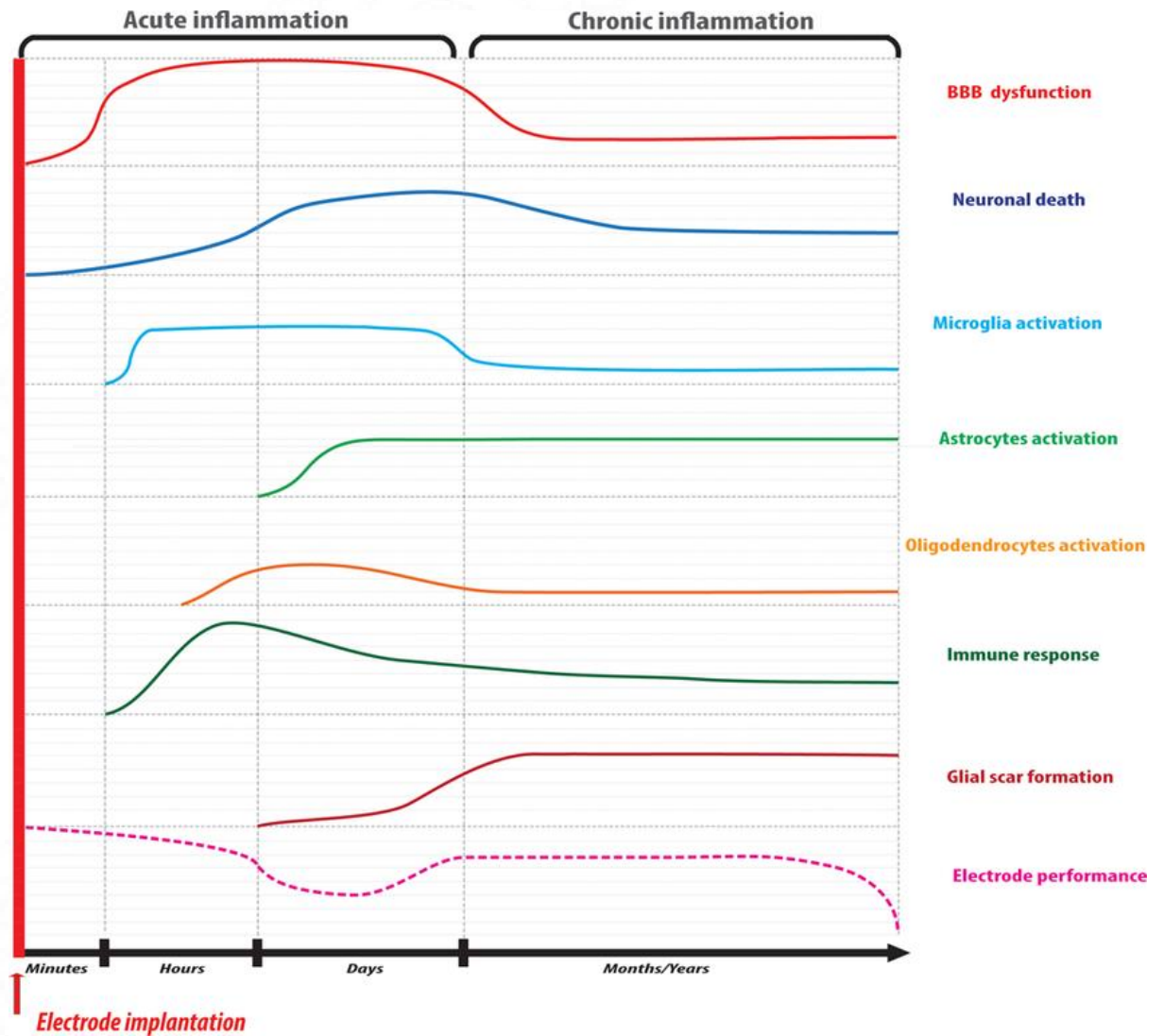


Figure 15. Schematic timeline representation of the reactions involved in the process of neural tissue response to implantable microelectrodes. reprint from "Schematic timeline representation of the reactions" by M. Gulino et al, licensed under CC BY 4.0.

Tissue responses due to stimulation

Electrical stimulation may cause problems due to the heating developed on the electrode surface or due to electrochemical reactions. The dependence of brain activity on temperature is an important aspect of these studies. Even a temperature increase of $\sim 1^{\circ}\text{C}$ can have profound effects on neuronal elements (Fujii et al., 2002). Thus, neuromodulators could exacerbate these effects.

According to ISO-14708, the temperature of the outer surface of any implantable neuromodulator device should not exceed 39°C . Thermal models and temperature studies indicate that the increase in temperature and its spatial distribution around surrounding tissue depend on the stimulation and tissue parameters (Elwassif et al., 2006). In general, reducing electrode impedance could reduce joule heating, which depends on the electrode material and morphology. Increasing lead dimensions or the diameter of the leads can increase the area for heat dissipation. Device components could also distribute heat and act as heat sinks (Elwassif et al., 2012). Insulating material that is thermally conductive but electrically resistive is a solution without changing conductor dimensions or therapeutic efficiency. Such biocompatible insulators have higher thermal conductivities than diamond-like carbon and alumina ceramics (Elwassif et al., 2012).

Electrochemical interactions at the electrode-tissue interface could cause irreversible faradaic reactions in the tissue medium. CIC can measure this property, which depends on the type of electrode (Cogan et al., 2008).

2.3 Advancements in Electrodes and Electrode-Tissue Interfaces

Several technological advancements have occurred in electrodes and electrode-tissue interfaces, which play an important role in determining the efficacy of any neurostimulation modalities or brain-machine interfaces. Adaptive DBS (aDBS) is a type of closed-loop method of controlling DBS stimulation parameters, estimated by analyzing a control variable that reflects the patient's clinical condition. It differs from conventional DBS, which is continuous and fixed, whereas aDBS is intermittently active, optimizing current delivery and reducing tissue damage. Clinical trials show that aDBS improves motor response with reduced energy levels, accounting for energy-efficient stimulation and long-term efficacy (Bocci et al., 2021; Arlotti et al., 2021).

The control variable can be local field potential (LFP), measured from the implanted DBS macroelectrode itself, and Electrocorticography (ECoG), measured from the cortical electrode. LFP is measured at the STN, where population-averaged signals are obtained, which can be measured with the same macroelectrode, eliminating the need for a separate sensing component. aDBS consists of a sensing module that records the feedback variable after stimulation (in epilepsy) (Wingeier et al., 2006). However, due to the time required for the amplifier to record the signal, some rhythms may not be recorded after DBS is turned off. Therefore, filter-based DBS could provide stimulus artefact-free output even during stimulation (Arlotti et al., 2021). Stimulus artefacts are short-duration, high-amplitude pulses present in the feedback signal, which can be direct components (stimulus time-locked voltage transients) or indirect components

(voltage transients in the interpulse period). Since the same electrodes are used for both stimulation and recording, a symmetrical electrode configuration is preferred to mitigate both differential and common mode artefacts (Arlotti et al., 2021). However, with directional leads, where directional contacts are asymmetrical compared to normal contacts, the symmetrical configuration may not be possible. Therefore, due to a mismatch in the electrode impedance contacts, common mode signals will be present in the feedback signals (Noor and McIntyre, 2021).

Recorded variables are processed in a control module that includes biomarker identification and calculation of stimulation parameters. A biomarker provides a reliable indication of a clinical condition. From LFP feedback, beta frequency (13–30 Hz) amplitude can be used as an indication to trigger stimulation because (i) LFP potential matches with synchronized neuron bursting in phase with beta frequency, (ii) these lower-frequency signals are less affected by the electrode-tissue interface or electrode geometry, and (iii) LFP, being a neural population-based biomarker, provides more general state feedback than single-unit measurements, which give localized motor movements in PD (Hell et al., 2019; Little and Brown, 2012). For example, the power of STN beta activity, averaged over many seconds or minutes, correlates with bradykinesia-rigidity, and reductions in mean beta activity correspond with improvement in bradykinesia-rigidity across patients (Little and Brown, 2020). Although these studies demonstrated beta as a feedback signal, it did not correlate with tremor, which is related to field potentials at tremor frequency (Little and Brown, 2020).

Even though macroelectrodes are the clinically preferred stimulation electrodes for neuromodulators, microelectrodes (diameter $< 50 \mu\text{m}$) also have certain advantages (Kim et al., 2018). Studies show that macroelectrodes displace nearly 20 times more tissue but have a smaller volume of tissue activated (VTA). Arcot Desai et al. (2014) showed that 1V stimulation with a microelectrode (diameter $33 \mu\text{m}$) has an activation radius nearly 50% less than that of macroelectrodes ($150 \mu\text{m}$). This activation range of microelectrodes can be improved by decreasing electrode impedance, which can be achieved by increasing the surface area through coatings, as in the case of macroelectrodes. Improving the impedance of implantable microwire multi-electrode arrays has been achieved by ultrasonic electroplating of durable platinum black (Desai et al., 2010).

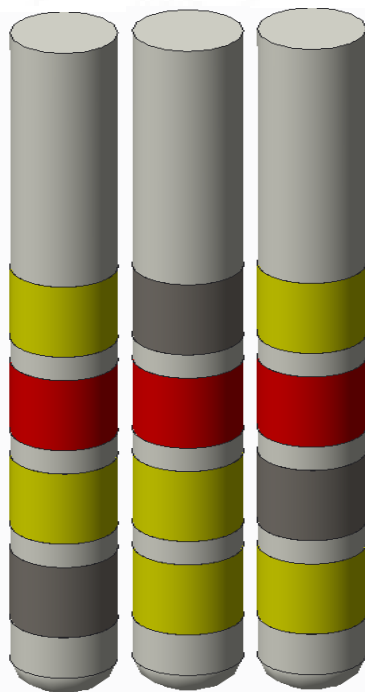


Figure 16: (a) symmetrical configuration (b),(c) asymmetrical configuration,stimulated electrode(Red); recording electrodes(yellow)

Microelectrodes also provide specific localized targeting of particular cell locations, with less tissue response compared to macroelectrodes (Arcot Desai et al., 2014). Microelectrode arrays are also coated with silicon, glass, and metals. However, inherent mechanical mismatch in terms of the elastic modulus (0.2-10 kPa for neurons and glial cells, and ~GPa range for plastics and silicones) triggers foreign body reactions and tissue encapsulation (Lacour et al., 2010). Therefore, biomechanics are sensitive to the mechanical properties of the surroundings, and microelectrode arrays with flexible and stretchable coatings have been studied (Lacour et al., 2010).

Across several studies on neuromodulation techniques, lead migration is one of the most important complications and has a higher incidence (SCS: Cameron, 2004; Eldabe et al., 2016; DBS: Kaminska et al., 2017; Baizabal Carvallo et al., 2011). Lead migration results in undesired stimulations and reduced clinical efficacy. Lead anchorage techniques have been reported in the literature for SCS or ONS (Mollica et al., 2021) and DBS (Contarino et al., 2013).

2.4 Current Trends (ON-OFF Methodology and Others)

2.4.1 Beta Oscillations and Parkinson's Disease Pathophysiology

Beta oscillations (13-30 Hz) are critically implicated in the motor symptoms of Parkinson's disease (PD), with elevated beta power often associated with the characteristic bradykinesia and rigidity observed in these patients (Frontiers, 2021). Beta oscillations within the basal ganglia, particularly in the subthalamic nucleus (STN), are significantly heightened in untreated PD patients. This pathological beta activity is believed to induce abnormal synchrony in neural circuits, disrupting normal motor function and contributing to the motor symptoms of PD (Frontiers, 2021).

However, traditional spectral power analyses, which average beta activity over time, may miss the transient and dynamic nature of beta oscillations. Recent advances in neurophysiological research have identified beta bursts—short, sporadic increases in beta power—as a more accurate reflection of motor dysfunction in PD. Tinkhauser et al. (2017) demonstrated that the frequency and duration of these beta bursts, rather than sustained beta power, correlate more closely with motor symptoms and can predict patient responses to deep brain stimulation (DBS) (Frontiers, 2021). Similarly, Anidi et al. (2018) found that these bursts are modulated by both DBS and dopaminergic medication, with changes in burst dynamics closely tracking improvements in motor symptoms.

Recent studies have further explored the spatial and temporal characteristics of beta bursts. A study by Heideman et al. (2020) using magnetoencephalography (MEG) revealed that beta bursts in the sensorimotor cortex also correlate with motor impairments, reinforcing the idea that burst dynamics could serve as a non-invasive biomarker for PD (Frontiers, 2021). Additionally, a study by de Hemptinne et al. (2013) found that beta bursts within the STN are tightly coupled with oscillatory activity in the cortex, highlighting the interconnected nature of these brain regions in the pathophysiology of PD.

2.4.2. Advanced Electrophysiological Measures in DBS

While traditional methods have provided a foundation for understanding beta oscillations, advanced electrophysiological measures offer deeper insights into the neural mechanisms underlying PD. Waveform shape analysis, introduced by Cole et al. (2017), has become a key tool. This approach identifies asymmetries in beta

oscillation waveforms, such as differences in the steepness of rising and falling phases or the sharpness of peaks and troughs, which have been shown to correlate with disease severity. This analysis has revealed that these non-sinusoidal features are not merely by-products of pathological beta activity but are integral to the dysfunction observed in PD.

Phase-amplitude coupling (PAC), another advanced measure, examines the interaction between the phase of beta oscillations and the amplitude of higher-frequency gamma oscillations. PAC is exaggerated in the motor cortex of PD patients, and this exaggerated coupling has been linked to motor deficits. De Hemptinne et al. (2015) demonstrated that DBS reduces this pathological PAC, leading to significant improvements in motor function (Frontiers, 2021). More recently, Escobar Sanabria et al. (2017) showed that PAC between beta and gamma oscillations in the STN and motor cortex is disrupted in PD, further emphasizing the importance of this coupling in the disease's pathophysiology .

The relationship between beta bursts, waveform shape, and PAC suggests that these measures are not independent but interconnected features of the same underlying pathophysiology. For example, a study by Lofredi et al. (2019) found that beta bursts are often associated with periods of high PAC, indicating that bursts may trigger pathological coupling in the brain. Understanding these relationships is crucial for developing more effective DBS therapies that target the root causes of motor dysfunction in PD.

2.4.3. Clinical Implications of Beta Synchrony

The clinical implications of these findings are profound, particularly in the development of closed-loop DBS systems. Unlike traditional DBS, which provides constant stimulation, closed-loop systems adjust stimulation parameters in real-time based on ongoing neural activity. This approach has been shown to improve therapeutic outcomes by tailoring treatment to the patient's immediate physiological state. Petrucci et al. (2020) highlighted the potential of using beta burst duration as a feedback signal in closed-loop DBS systems, showing that such systems can provide more effective symptom relief with fewer side effects than traditional DBS.

Furthermore, Anderson et al. (2021) explored the long-term effects of DBS on beta oscillations and found that while DBS stabilizes beta activity, there is no progressive increase in beta abnormalities over time, suggesting that current DBS technologies may have a ceiling effect. This finding underscores the need for more advanced DBS systems that incorporate multiple electrophysiological measures, such as beta bursts, PAC, and waveform shape, to address the complexities of PD pathophysiology fully.

Research by Velisar et al. (2019) has demonstrated the feasibility of real-time modulation of DBS based on beta activity, with adaptive DBS systems capable of responding to changes in beta bursts and PAC to optimize stimulation parameters (Frontiers, 2021). These systems represent a significant advancement in personalized neuromodulation, offering the potential to fine-tune treatment in response to the patient's fluctuating symptoms and disease progression.

As research on beta oscillations advances, future studies should focus on integrating these advanced electrophysiological measures into multi-modal closed-loop DBS

systems. By combining beta bursts, waveform shapes, and PAC, researchers could develop more robust biomarkers that better reflect the neural disruptions in PD (Frontiers, 2021). This approach could lead to more personalized and effective DBS treatments, tailored to the specific neural dynamics of each patient.

In addition to improving DBS technologies, extending these findings to other movement disorders and psychiatric conditions where beta abnormalities are present could broaden the therapeutic applications of DBS (Neuroscience News,2021) (Frontiers, 2021). For example, recent studies have suggested that beta oscillations may play a role in conditions such as depression and obsessive-compulsive disorder, where similar neural circuit dysfunctions are observed (Neuroscience News,2021). By leveraging the insights gained from PD research, DBS therapies could be adapted to treat a wider range of neurological and psychiatric conditions.

Non-invasive monitoring of these electrophysiological markers is another promising area of research. Techniques like magnetoencephalography (MEG) and advanced EEG are being explored for their potential to monitor beta oscillations and related measures without the need for invasive procedures. These approaches could make adaptive DBS available to a larger population of patients, including those who are not candidates for surgery. A study by Tan et al. (2021) demonstrated that non-invasive recordings of beta activity could accurately reflect the underlying neural dynamics in PD, suggesting that these techniques could be used to guide DBS treatment in real-time (Frontiers, 2021).

Beta oscillations, particularly when analyzed using advanced methods like beta burst detection, waveform shape analysis, and PAC, offer valuable insights into the neural

disruptions underlying Parkinson's disease. These measures are not only crucial for understanding PD pathophysiology but also hold promise for improving DBS technologies. The future of DBS lies in personalized, adaptive systems that use real-time feedback from these biomarkers to optimize treatment, potentially extending the benefits of DBS to a broader range of neurological and psychiatric conditions.

2.4.4 Adaptive Algorithms

Adaptive algorithms play a crucial role in closed-loop Deep Brain Stimulation (DBS), enhancing treatment outcomes and reducing side effects for movement disorders such as Parkinson's disease (PD) and essential tremor. Unlike traditional open-loop DBS systems, which deliver continuous stimulation at a fixed intensity, closed-loop systems dynamically adjust stimulation parameters based on real-time physiological signals, allowing for more individualized treatment. Adaptive algorithms are key in interpreting these signals and modulating stimulation to optimize patient outcomes (Little et al., 2013).

One of the most common adaptive algorithms in closed-loop DBS is the Proportional-Integral-Derivative (PID) controller. PID controllers adjust the stimulation intensity based on the difference between a measured signal, like local field potentials (LFPs), and a target value (Arlotti et al., 2016). The proportional, integral, and derivative components of this algorithm help fine-tune the system's response to both short-term changes and long-term trends in neural activity.

Another growing approach in adaptive DBS is using Machine Learning (ML) algorithms. These include supervised and unsupervised learning models, which can predict and classify neural states like tremor onset or dyskinesia, enabling more precise

stimulation adjustments (Rosa et al., 2017). Reinforcement Learning (RL) has also been explored in this context, where the algorithm learns optimal stimulation strategies by receiving feedback based on patient outcomes, improving stimulation over time (Gilron et al., 2021).

Model Predictive Control (MPC) algorithms are frequently used in closed-loop DBS systems. MPC algorithms predict future states based on current and past data, allowing the system to adjust stimulation parameters pre-emptively. This predictive capability helps mitigate the delay in responding to symptom changes, making it highly effective for managing dynamic symptoms like tremors or rigidity in PD (Neumann et al., 2017).

Another method involves Kalman Filtering, which estimates the patient's underlying neural state from noisy measurements, such as LFPs or electroencephalography (EEG) signals (Stanslaski et al., 2018). Kalman filters track changes in neural activity and adjusts stimulation parameters accordingly, providing more consistent symptom control (Herron et al., 2017).

Bayesian Optimization has also been used in adaptive DBS to optimize stimulation settings. This algorithm balances exploration (trying new stimulation settings) with exploitation (using known effective settings) to provide personalized and efficient therapy (Meidahl et al., 2017). It is particularly useful when patient responses to stimulation vary over time, making constant fine-tuning necessary (Velisar et al., 2019).

In some cases, adaptive neurostimulation controllers are used to adjust stimulation directly based on real-time physiological feedback from biomarkers. For example, in Parkinson's disease, detecting beta-band oscillations in LFPs can guide the system to

increase or decrease stimulation intensity as needed, providing more targeted and symptom-specific therapy (Tinkhauser et al., 2017). Feedback-based adaptive Algorithms are another method where external sensors, such as accelerometers measuring tremors or subjective patient input, drive adjustments in stimulation. These algorithms are particularly useful for conditions where symptoms fluctuate throughout the day (Arlotti et al., 2016). Rajamani et al. (2024) developed a new DBS algorithm targeting symptom-specific neural networks to offer personalized therapy for Parkinson's disease. This approach optimizes brain stimulation by focusing on the circuits responsible for motor dysfunction, resulting in better symptom management and fewer side effects. Their study suggests that precisely targeting these networks could improve DBS efficacy and patient outcomes compared to conventional DBS methods (Rajamani et al., 2024). Oehr et al. (2024) highlighted the potential for artificial intelligence (AI) to enhance DBS systems, making them more autonomous and accessible for patients. AI-driven DBS could allow for real-time adjustments without constant clinical oversight. Future systems may address both motor and non-motor symptoms, such as mood disorders and sleep disturbances, by continuously adapting stimulation to the patient's evolving condition.

2.5 Research Gap

2.5.1 Limitations of Open-Loop DBS Systems

Open-loop deep brain stimulation (DBS) systems, which rely on pre-set and continuous electrical stimulation, present inherent limitations due to their lack of adaptability to the real-time neural dynamics of patients. This static approach results in a fundamental challenge: the inability to modulate stimulation based on fluctuating

symptom severity or dynamic changes in brain states. According to Herron et al. (2020) and Miocinovic et al. (2018), such systems fail to account for temporal variations in symptoms, as observed in conditions like Parkinson's disease and essential tremor. These disorders are known to exhibit episodic fluctuations, yet open-loop DBS provides a constant level of stimulation, potentially leading to insufficient therapeutic effects during peak symptomatic episodes or excessive stimulation during milder phases (Cagnan et al., 2019; Little et al., 2016).

This lack of adaptability in open-loop DBS has significant clinical implications. Bouthour et al. (2019) noted that fixed stimulation levels increase the risk of side effects, such as speech impairments, involuntary muscle contractions, or cognitive dysfunction, due to over-stimulation during asymptomatic periods. Moreover, open-loop systems fall short in managing the complex and variable symptomatology of movement disorders, limiting their efficacy in achieving personalized treatment outcomes (Akbar et al., 2022). Recent literature emphasizes the need for innovative approaches, highlighting that open-loop systems are constrained in addressing the intricate and fluctuating nature of neurological conditions (Lozano et al., 2023; Xu et al., 2024). Consequently, the necessity for frequent manual adjustments in open-loop DBS systems, which are labor-intensive and reactive, underscores the urgency for more responsive technologies (Martinez-Ramirez et al., 2023).

2.6 Addressing the Research Gap

2.6.1 The Need for Closed-Loop and Adaptive DBS

To address the aforementioned limitations, closed-loop and adaptive deep brain stimulation (DBS) systems have emerged as promising solutions. Closed-loop DBS overcomes the static nature of traditional systems by actively monitoring neural activity and adjusting stimulation parameters in real time (Stanslaski et al., 2012; Prosky et al., 2021). This responsive feedback mechanism allows for more precise modulation of stimulation, enhancing symptom control while reducing adverse effects (Abbas et al., 2022; Velisar et al., 2019). Consequently, closed-loop DBS has the potential to significantly improve patient outcomes by delivering dynamic and individualized therapy (Ashkan et al., 2017).

Furthermore, adaptive DBS builds on closed-loop technology by integrating machine learning algorithms and neural decoding techniques. These advancements enable adaptive systems to learn and predict patterns of neural activity over time, allowing for anticipatory adjustments in stimulation based on symptom-related neural signatures (Opri et al., 2020; Zhou et al., 2024). Research has demonstrated that adaptive DBS can proactively respond to dynamic symptom changes, thus providing a more personalized and effective therapeutic approach (Gilron et al., 2021; Wang et al., 2023). This capability represents a substantial advancement in neuromodulation, addressing the need for tailored treatment in managing complex disorders such as Parkinson's disease, dystonia, and epilepsy (Smith et al., 2024).

2.7 Proposed Solution: Hybrid Interdigitated Electrode Design

In response to these limitations, a novel design for a hybrid interdigitated electrode has been proposed in this thesis. The key innovation of this design lies in its ability to perform dual functions—sensing and stimulation—within a single electrode architecture. By integrating sensing capabilities, this electrode can monitor real-time neural activity and relay this information to closed-loop and adaptive DBS systems. This approach allows for the continuous assessment of neural signals, which is crucial for identifying specific biomarkers or neural signatures associated with symptom exacerbation. Through real-time monitoring, the hybrid interdigitated electrode aims to enhance the precision of stimulation, adapting in response to the neural feedback it captures.

The proposed electrode design is strategically crafted to align with the requirements of advanced DBS technologies, particularly closed-loop and adaptive systems. Its interdigitated structure facilitates both accurate sensing and targeted stimulation, creating a dynamic interplay between these two functions. This capability is envisioned to play a pivotal role in refining the responsiveness of adaptive DBS systems, leading to more effective therapeutic interventions for movement disorders and other neurological conditions. Moreover, the dual functionality of this electrode presents the potential to minimize invasiveness by reducing the number of implanted devices, thereby improving patient comfort and clinical outcomes.

The characterization of this hybrid interdigitated electrode forms the backbone of the present thesis. A comprehensive evaluation is undertaken to assess its electrical properties, sensing accuracy, stimulation efficacy, and overall biocompatibility. These

characterizations aim to demonstrate the feasibility and advantages of this electrode in closed-loop and adaptive DBS applications. By addressing the limitations of conventional open-loop DBS through this innovative design, the thesis establishes a foundation for future advancements in neuromodulation technologies.

In conclusion, the limitations of open-loop DBS systems highlight a clear research gap in the development of neuromodulation technologies that are capable of responding to real-time variations in neurological conditions. Closed-loop and adaptive DBS systems have emerged as innovative solutions that offer the potential to deliver more individualized and responsive treatments, promising improved clinical outcomes for patients with movement disorders (Herron et al., 2020; Neumann et al., 2021; Xu et al., 2024). The introduction of a hybrid interdigitated electrode design adds a critical dimension to this advancement, bridging the gap between stimulation and sensing, and enabling more precise, adaptive control. However, further exploration and refinement of these systems, along with the development of advanced electrode designs, are required to fully leverage their potential and to establish their efficacy across diverse patient populations. Based on the said research gap analysis a hypothesis has been formulated and three objectives have been laid out to prove it.

2.8 Hypothesis

The hypotheses proposed for this research are:

Closing the loop through sensors and real-time communication to the implanted neuro-stimulator could result in lower average power dissipation and reduced side effects from unneeded stimulation.

- ✚ Lower Average Power Dissipation: It is hypothesised that the closed-loop system will operate more efficiently by incorporating sensors that monitor brain activity in real-time and using that data to adjust stimulation levels. The neurostimulator will only deliver stimulation when necessary, reducing the device's overall energy consumption. This efficiency in power usage is expected to extend the battery life of the implanted device, which is a critical factor in reducing the need for frequent surgical interventions to replace or recharge batteries.
- ✚ Reduced Side Effects from Unneeded Stimulation: The second hypothesis suggests that real-time communication between the sensors and the neurostimulator will allow for more precise stimulation targeting. This precision means the device can avoid unnecessary stimulation when symptoms are less severe or absent. By minimizing unnecessary stimulation, the system is expected to reduce the incidence and severity of side effects commonly associated with traditional DBS, such as speech disturbances, muscle contractions, or cognitive effects. The adaptive nature of the closed-loop system will thus lead to a more tailored therapy that adjusts to the patient's changing neurological state, enhancing overall treatment effectiveness and patient quality of life.

2.9 Objectives

To validate the proposed hypotheses, the following research objectives have been outlined as part of this thesis:

2.9.1 Developing a Dual-Purpose Hybrid Electrode for Sensing and Stimulation

The first objective is to design and create a hybrid electrode capable of delivering electrical stimulation and simultaneously sensing brain activity. This dual-functionality enables real-time feedback and adaptive control within the closed-loop DBS system.

2.9.2 Characterization of the Hybrid Electrode

The second objective comprehensively characterises the hybrid electrode to ensure its effectiveness and reliability in stimulation and sensing. This characterization will be conducted through multiple approaches: a. Simulations: Conducting detailed simulations to predict the electrode's behaviour and performance under various conditions, ensuring it meets the specifications for DBS applications. b. Electrochemical Testing: Performing electrochemical analyses to evaluate the electrode's conductivity, stability, and durability, ensuring it can consistently deliver and receive signals without degradation over time. c. Biological Evaluation: Testing the hybrid electrode in biological environments to assess its biocompatibility, signal fidelity, and effectiveness in real-world conditions, ensuring it can function effectively within the brain without causing adverse reactions.

2.9.3 Algorithm Development for Closed-Loop Control Using Beta Waves

The third objective focuses on creating an algorithm to interpret beta wave activity as a feedback signal for controlling the DBS system. This algorithm will process the real-time data from the hybrid electrode and adjust the stimulation

parameters accordingly, ensuring that the therapy responds to the patient's current neurological state and effectively minimizes symptoms and side effects.



Chapter 3

3. Materials and Methods

3.1 Design and Development of Hybrid Electrode

A hybrid electrode designed for adaptive deep brain stimulation (DBS) combines the ability to both stimulate and record neural activity. This combination allows the electrode to monitor brain signals in real time while delivering targeted electrical impulses. By integrating sensing and stimulation, the electrode plays a critical role in adaptive DBS systems, which adjust stimulation settings based on the patient's brain activity. This approach helps improve the effectiveness of treatment for conditions such as Parkinson's disease by fine-tuning the therapy to the individual's needs, minimizing side effects, and enhancing overall outcomes.

3.1.1 Design Features of a Standard DBS Electrode

A standard deep brain stimulation (DBS) electrode typically features several cylindrical contacts arranged along a thin, flexible lead. These contacts are spaced evenly and designed to send electrical pulses to specific areas in the brain to help control abnormal activity. The conventional electrode usually has four contacts, each of which is independently controlled or grouped together to deliver stimulation. Due to its cylindrical shape, the stimulation from this type of electrode affects tissue all around it, which can sometimes lead to less precise targeting compared to more advanced directional designs.

Lead Body: A slender, cylindrical design that encloses the internal wiring and provides structural support for the contacts. The lead body is typically around 1 to 2 mm in diameter.

Cylindrical Contacts: Four small metallic rings or cylinders that are evenly spaced along the distal end of the lead. Each contact measures roughly 1.5 mm in length, with a spacing of 0.5 to 1 mm between them. These are sequentially numbered (Contact 1, Contact 2, Contact 3, Contact 4).

Conductors: Fine wires run inside the lead body, creating a connection between each contact and the pulse generator or external stimulation device. These wires are insulated to prevent electrical shorting.

Insulation: The remainder of the lead, excluding the contacts, is coated with an insulating material (typically silicone or polyurethane) to prevent electrical interference and ensure that stimulation is only delivered through the exposed contact points.

Connection to Pulse Generator: The proximal end of the electrode leads to a connector, which links with the implanted pulse generator that manages the stimulation parameters.



Figure 17. Typical 4 contact DBS electrode proximal end

Table 2. Materials used in the fabrication of DBS Electrode

Parameter	Specification
Electrode Arrangement	In-line Quadripolar
Number of Electrodes	Minimum of 4
Electrode Shape	Cylindrical
Electrode Diameter	1.27 cm
Electrode Length & Separation	Suitable to accommodate the linear dimension of the Subthalamic Nucleus (STN), approximately 7 mm to 11 mm
Electrode Material	Platinum Iridium : Grade 90-10
Lead Insulation Material	Non Degradable Silicone Rubber ,Med 4554 from Nusil Inc.
Lead Length	45 cm
Proximal End Lead Contact Connection	In-line Quadripolar arrangement using MP 35 a biocompatible, non-corrosive, electrochemically stable metal alloy
Lead Electrode to Proximal End Connection	Non Degradable Silicone Rubber ,Med 4950 from Nusil Inc.
Support Structure	Tungsten

A breakdown of key parameters such as surface area, area of stimulation, and current/charge transfer for a conventional electrode is as;

1. Surface Area of DBS Electrodes

- Surface area of a single contact:

Calculated using the lateral surface area formula for a cylinder:

$$\text{Surface Area} = 2\pi rh$$

Surface Area= $2\pi rh$, where r is the radius (0.635 mm) and h is the height (1.5 mm).

Surface area per contact $\approx 6 \text{ mm}^2$.

Total surface area for all four contacts $\approx 24 \text{ mm}^2$.

Surface area per contact $\approx 6 \text{ mm}^2$.

Total surface area for all four contacts $\approx 24 \text{ mm}^2$.

2. Area of Stimulation (Volume of Tissue Activated - VTA)

- Stimulation field shape: The electric field forms a roughly spherical or ellipsoid shape around each contact.
- Extent of stimulation: Typically extends 2-4 mm from the electrode surface, influenced by parameters such as:
 - Amplitude
 - Pulse width
 - Frequency

- These factors determine the volume of tissue activated (VTA), critical in therapeutic outcomes.

3. Current and Charge Transfer

- Current amplitude: Ranges from 1-10 mA, with therapeutic values around 1-5 mA.
- Pulse width: Between 60-450 μ s, typical ranges depending on patient needs.
- Charge density: Kept below 30 μ C/cm² per phase to avoid tissue damage.
- Charge per pulse: The charge per pulse is calculated by multiplying the current by the pulse width. For example, for a 2 mA current and a 100 μ s pulse width:
- Charge per pulse = $2 \text{ mA} \times 100 \mu\text{s} = 200 \text{ nC}$
- Charge per pulse = $2 \text{ mA} \times 100 \mu\text{s} = 200 \text{ nC}$

The impedance at the electrode-tissue interface generally ranges from 500 ohms to 2 kOhms, influencing how effectively current is delivered to brain tissue.

4. Stimulation Field and Tissue Activation

- Volume of Tissue Activated (VTA) usually is a dependent of several factors:
 - Electrical properties of brain tissue.
 - Electrode geometry and positioning.
 - Stimulation parameters (amplitude, frequency, pulse width).

- Finite element models (FEMs) are often employed to estimate electric field distribution and provide more accurate predictions of the tissue volume activated.
- The VTA commonly extends around 2-3 mm from the electrode

The conductivity of brain tissue plays a crucial role in how electrical stimulation is delivered and dispersed. This property influences how far the stimulation spreads and impacts the surrounding tissue, directly affecting the Volume of Tissue Activated (VTA), which refers to the region of brain tissue influenced by DBS.

3.1.2 Tissue Conductivity in DBS

Conductivity refers to the ability of a material to carry electrical current, and it varies between different types of brain tissue (e.g., gray matter, white matter, cerebrospinal fluid). The conductivity of these tissues plays a critical role in determining the spread of electrical current from the DBS electrode.

3.1.1.1 Current Flow and Spread

- **High Conductivity:** In tissues with higher conductivity, electrical current flows more easily, causing the current to spread farther from the DBS electrode and enlarging the area of tissue activated. For example, cerebrospinal fluid (CSF) has a much higher conductivity compared to other brain tissues, leading to a broader current spread near fluid-filled spaces (Butson et al., 2007).
- **Low Conductivity:** In tissues with lower conductivity, such as gray matter, current flow is more restricted, resulting in a smaller area of activation. This

means stimulation is more localized in regions with lower conductivity, such as the gray matter (Gabriel et al., 1996).

The Volume of Tissue Activated (VTA) is a crucial concept in DBS therapy, as it defines the region of brain tissue affected by electrical stimulation. The VTA is influenced directly by the conductivity of the surrounding tissue.

- In high conductivity tissues such as white matter or CSF, the electrical current spreads over a larger area, potentially activating more brain tissue (McIntyre et al., 2004). This can enhance the therapeutic effect but also increases the risk of stimulating unintended areas, which can lead to side effects.
- In low conductivity tissues such as gray matter, the spread of current is more restricted, creating a smaller, more localized VTA (Butson et al., 2007).

The size and shape of the VTA are key to achieving the desired therapeutic effect, and they need to be large enough to cover the target region but not so large as to affect unintended areas.

3.1.1.2 Tissue Conductivity Variations

Different brain tissues have varying conductivities, which can impact the spread of electrical stimulation:

- Gray Matter: Lower conductivity (approximately 0.3-0.6 S/m) (Gabriel et al., 1996).
- White Matter: Higher conductivity (approximately 0.6-1.2 S/m) (Ranck, 1963; Gabriel et al., 1996).

- Cerebrospinal Fluid (CSF): Very high conductivity (approximately 1.5-2.0 S/m) (Baumann et al., 1997).

Because of these variations, the electric field is not uniformly distributed. DBS applied to regions with mixed tissue types (e.g., gray and white matter) may result in unpredictable current distributions (Butson et al., 2007).

3.1.1.3 Stimulation Parameters and Tissue Conductivity

Stimulation parameters, such as current amplitude, pulse width, and voltage, interact with tissue conductivity, influencing how far the current spreads.

- Current Amplitude: Higher current amplitudes lead to a larger electric field and thus a greater VTA. In high conductivity areas, lower currents may suffice to reach the therapeutic threshold (McIntyre et al., 2004). In contrast, low conductivity areas may require higher currents to activate the targeted neurons (Butson et al., 2006).
- Pulse Width: Longer pulse widths deliver more charge per pulse, which can help overcome lower tissue conductivity (Rattay et al., 2003).
- Voltage: Higher voltages are often needed in regions of low conductivity to ensure that neurons are adequately stimulated (Butson et al., 2006).

3.1.1.4 Volume of Tissue Activated (VTA) Calculation

The Volume of Tissue Activated (VTA) in DBS measures the brain area influenced by electrical stimulation from the implanted electrode. VTA calculation involves understanding the interaction between the electric field and the surrounding brain

tissue. Various factors such as stimulation parameters (current, voltage, pulse width, frequency), tissue properties (conductivity, permittivity), and electrode characteristics (size, shape, location) contribute to determining the VTA.

3.1.1.5 Electric Field Distribution

The first step in calculating the VTA is determining the electric field distribution around the DBS electrode. The electric field depends on the electrode geometry and stimulation parameters, and is commonly modelled using Poisson's Equation:

$$\nabla \cdot (\sigma \nabla V) = I_{\text{stim}}, \text{ where:}$$

- σ sigma is the tissue conductivity,
- V is the electric potential (voltage),
- I_{stim} is the stimulation current.

By solving this equation using numerical methods like Finite Element Modelling (FEM), the electric potential and resulting electric field around the electrode can be calculated (McIntyre et al., 2004).

3.1.1.6 Neuron Activation Thresholds

Once the electric field is known, the next step is to estimate the neurons within this field that will be activated. The axon model is often used to estimate neuron activation thresholds based on their properties, such as axon diameter and distance from the electrode (McIntyre et al., 2004).

The activation threshold for neurons can be approximated by the following simplified model:

$$E_{\text{threshold}} = \frac{I_{\text{stim}}}{d^2}$$

- $E_{\text{threshold}}$ is the electric field strength required to activate neurons,
- I_{stim} is the stimulation current,
- d is the distance between the neuron and the electrode.

Neurons closer to the electrode will have lower activation thresholds, while neurons farther away require stronger stimulation.

3.1.1.7 Finite Element Modelling (FEM)

The most common method for calculating VTA is Finite Element Modelling (FEM), which divides the brain tissue and electrode environment into a mesh of small elements. The electric field is computed for each element, and regions where the field strength exceeds the activation threshold are identified as the Volume of Tissue Activated.

FEM takes into account:

- Tissue properties (e.g., gray matter, white matter, CSF),
- Electrode characteristics (shape, size, material),
- Stimulation parameters (voltage, current, pulse width, frequency).

FEM produces a 3D model of the brain, and analyzing the electric field within this model allows for estimating the VTA (Butson et al., 2006).

Understanding the relationship between tissue conductivity, stimulation parameters, and VTA is crucial in optimizing DBS therapy while minimizing side effects.

3.1.3 Design

An Implantable multichannel hybrid neurostimulator probe offering voltage and current mode stimulation with wide range control of stimulation parameters like cathodic and anodic pulse amplitude, duration, and interpulse delay; having sense option for feedback and multifocal apex architecture for more optimization in localization of stimulus targets is designed. A multipolar electrode array is selected according to the excitation requirements. Multifocal architecture provides better feedback on the tissue response to stimulation, and a duplex communication channel is employed for excitation mode selection and parameter settings to enable true adaptive and closed-loop controls.

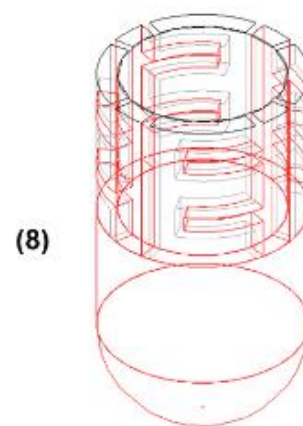
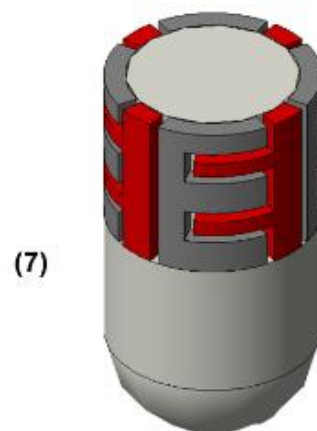
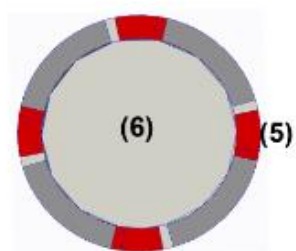
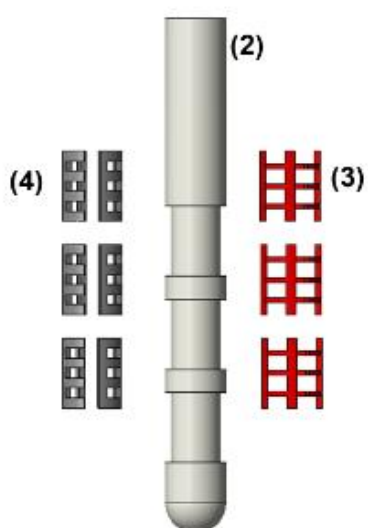
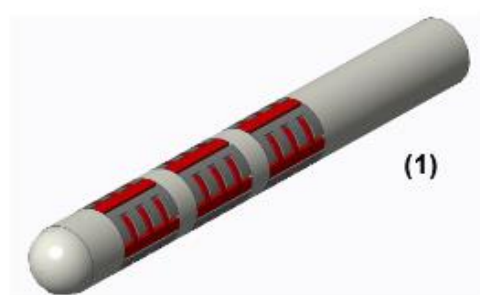
The Figure 18 shows a multipolar hybrid neurostimulation electrode, which incorporates a silicone rubber lumen (Figure 18(6)) that encloses conductors running to the electrodes located at the distal end of the lead. These electrodes are organized in a multifocal arrangement and are intended for insertion into deep brain regions, where they perform both neural stimulation and sensing of feedback signals. This configuration enables the device to handle stimulation and feedback sensing simultaneously, making it adaptable for advanced neurostimulation systems.

The lead includes a silicone rubber internal stem (Figure 18 (2)) that maintains the lead's structural strength during insertion and supports the wiring inside. This wiring

connects the electrodes at the distal end to the proximal end of the lead, where the external control mechanisms are located.

At the distal end, a triplet of sensing fangs (Figure 18 (3)) is arranged to capture bio-signals generated after the stimulation process. This feedback is used to refine the stimulation in real-time. The stimulation itself is delivered through a quadrupole configuration of stimulating fangs (Figure 18 (4)), which allows for both voltage and current modes of operation. The device's design ensures fine control over key stimulation parameters, such as pulse amplitude, pulse duration, and interpulse delay, to enhance its effectiveness in targeting neural tissue.

Figure 18 (5) provides a cross-sectional view of the lead, clearly showing the internal lumen and electrode layout. Figure 18 (7) offers a perspective view of the entire lead design, illustrating how the components—such as the silicone lumen, internal stem, and electrode arrangements—are combined into a fully integrated neurostimulation device.



1. Interdigitated Electrode
2. Silicone rubber internal stem
3. Sensing triplet fangs
4. Stimulating quadrupole fangs
5. Cross section view of the electrode
6. PDMS lumen
7. Perspective view of the electrode
8. Wire drawing of the perspective view

Figure 18. Design and Schematic of the hybrid DBS electrode

3.1.4 Simulation Studies

The electric current distribution in biological tissues is in a three-dimensional pattern -typically known as volume conductor represented by current density 'J', defined as current flow per unit area and is dependent on space and time. The typical approximation is that this volume conductor is homogenous and isotropic in neuronal tissue (Nunez et al., 2006).

For quasi-static conditions, mathematically the calculation of the electric field in regions $< 1\text{m}$ can be represented by continuity equation for steady state currents (Plonsey, 1995; Cheng, 1989).

$$\nabla \cdot J = 0$$

At macroscopic levels, a linear, ohmic model of volume conductor is denoted by

$$J = \sigma E; \text{ implying that}$$

Current density is a fraction of electric field and the corresponding electrical conductivity (σ) can be defined as a constant of proportionality.

Since the (σ) the conductivity is a material intrinsic property, specifically for the neuronal tissue local conductivity is varying and is a function of parameter with respect to cell membrane, extracellular fluid and ionic contents etc (Nunez et al., 2006). The common practice is to divide the regions into multiple regions with different

conductivity in a way such that $\sigma(r)$ can be divided into $\sigma_1, \sigma_2, \sigma_3$..etc which are a constant within that region of interest (Nunez et al., 2006).

3.1.4.1 Performance Evaluation

To evaluate the performance of typical DBS electrodes through *in vivo* methods for different conduction, two types of electrodes are being compared using *in silico* methods. The simulation is done in ANSYS electronics workbench; the excitation voltage and conductivity are varied, and the corresponding electric field distribution is studied.

This gives an idea of the performance comparison of both electrodes

For an electric potential V , the electric field is the gradient as in the equation (Gabriel et al., 2009).

$$E = -\nabla - V$$

The boundary conditions used in the simulation are

- Electric potential, produce the value at the $V = V_0$
- Ground, zero potential, $V = 0$

Electrodes

A typical disc electrode cylindrical ring(Fig 19b) is used as the control against the hybrid dBS electrode (Fig 19a) with interdigitalised rings / conductors.

Modeling the electrode

The hybrid electrode intended to be used with adaptive stimulations is modeled as in figure 15. The electrode contains interdigitated electrode for all segments, which are three in a ring making three electrodes for stimulation and the other three for sensing. Here the electrodes with single ring in stimulation made operation is only explored.

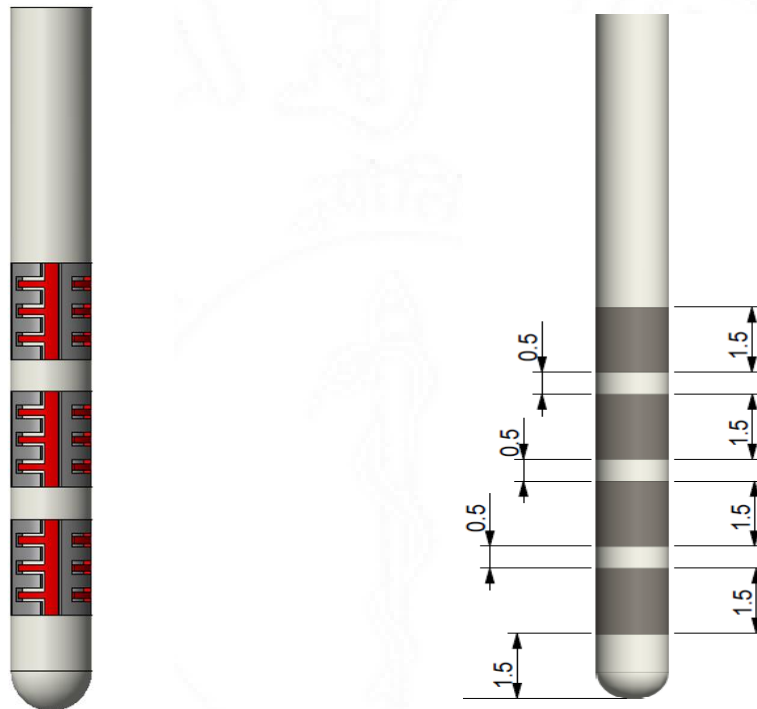


Figure 19. a) Hybrid DBS Electrode (test electrode), b) Conventional DBS electrode (Control)

The control electrode is a standard DBS electrode with a 1.2mm diameter and has cylindrical ring contacts for stimulations. The control electrode has no specific contacts for sensing.

Both electrodes were stimulated in a medium representing the grey matter of the brain.

To account for heterogeneity of the brain tissue, the variables taken are: -

- *The conductivity of the medium*

The conductivity of the medium is a key factor that influences the distribution and intensity of the electric field generated during deep brain stimulation (DBS). In this context, the medium's conductivity was varied across five specific values: 0.08, 0.15, 0.22, 0.30, and 0.37 units. These values simulate different tissue conditions, such as changes in fluid levels or varying tissue types. Each change in conductivity affects the way electrical current passes through the medium, directly impacting how the electrode stimulates the surrounding neurons.

Under these varying conductivity conditions, the electrodes were subjected to the same stimulation settings (voltage, pulse width, and frequency). However, due to the differing conductivities, the resulting electric field changed accordingly. The electric field is a primary determinant of the Volume of Tissue Activated (V.T.A.), the area around the electrode where neural activity is influenced. The extent and strength of the V.T.A. depend heavily on the magnitude and spread of the electric field, both of which are affected by the medium's conductivity.

Higher conductivity values (e.g., 0.37 units) typically cause a more focused electric field, leading to more precise stimulation of tissue, while lower conductivity values (e.g., 0.08 units) allow for a broader spread of the electric field, potentially affecting a larger volume of tissue. Understanding this relationship is crucial for optimizing DBS therapy, as improper control of the V.T.A. can result in insufficient therapeutic effects or unwanted side effects.

By plotting the electric field across the different conductivity settings, the impact on the V.T.A. can be visualized, helping to assess how these changes affect the overall stimulation. This data is essential for refining stimulation parameters, particularly in adaptive or closed-loop DBS systems, where real-time adjustments are made to optimize therapeutic outcomes.

- *Voltage applied*

In this study, how different stimulation voltages in Deep Brain Stimulation (DBS) affect neural activation by conducting simulations in ANSYS is explored. The simulation environment allows us to replicate the conditions that occur during actual DBS procedures, specifically focusing on the impact of altering voltages between 10V and 1V. Typically, DBS delivers high-frequency, biphasic waveforms (around 130-150 Hz) to specific brain regions, such as the subthalamic nucleus (STN) or Globus pallidus (GPI), using voltages that usually fall within the 1V to 10V range. The goal of this experiment is to study the effects of stepping down the stimulation voltage in 1V intervals, using a range from 10V to 1V, in a simulated environment.

- *The radial spacing*

In this study, the electric field at a radial distance of 0.5 mm from the DBS electrode was measured to assess its impact on surrounding neural tissue. A specific focus was placed on the region within 0.5 mm of the electrode, as this is where the maximum electric field intensity is anticipated, either reaching its peak or experiencing rapid attenuation. This close proximity is particularly important because the Volume of Tissue Activated (V.T.A.) within 0.5 mm remains minimal. As a result, this limited

area is less likely to produce significant physiological effects, such as unwanted motor or sensory activation, during stimulation.

However, beyond the 0.5 mm threshold, the electric field could begin to influence neurons that are not intended targets of the stimulation. This can lead to unwanted neural activation, which may trigger adverse effects, including motor disruptions or cognitive side effects, depending on the stimulated brain region. By focusing on this small radial distance, the study aims to reduce these risks while maximizing the therapeutic effects of the DBS.

- *Simulation Output:*

The results extracted from these simulations include:

Electric field variation with distance: The electric field intensity was analyzed at various distances from the electrode surface to determine how it diminishes with radial distance.

Electric field variation with voltage sweeps: The response of the electric field to changes in applied voltage was investigated to understand the relationship between voltage input and electric field strength.

3.1.5 Verification Studies – *In Vitro* Characterization

The electrodes were characterized at the Neuromodulation Laboratory in the Department of Biomedical Engineering (BME) at IIT Hyderabad. For these experiments, a conventional cylindrical DBS electrode with a diameter of 1.2 mm was used as the control. The electrodes were immersed in agarose gel solutions designed to simulate the conductive properties of cerebrospinal fluid (CSF), with a pH of 7.4 to replicate physiological conditions.

3.1.5.1 Preparation of Agarose Gel with Varied Conductivities:

Agarose gel solutions with different conductivities were prepared to investigate the effects of varying tissue conditions on the electric field distribution around the DBS electrode. The conductivities were adjusted by altering the concentration of sodium chloride (NaCl) in the agarose solution. In this study, conductivities were varied across five levels: 0.08 S/m, 0.15 S/m, 0.22 S/m, 0.30 S/m, and 0.37 S/m. These values represent a range of physiological conditions that could occur in different biological tissues or altered states, such as oedema or fibrosis.

Conductivity measurements for each solution were performed using a calibrated conductivity meter to ensure precision before conducting the experiments. Each solution was carefully homogenized to maintain consistency in gel formation and conductivity during testing. This allowed for a comprehensive assessment of how tissue-like environments with different conductivities affected the electric field distribution and DBS stimulation outcomes.

3.1.5.2 Experimental Setup and Signal Generation

Once the agarose solutions were prepared, the DBS electrodes were placed into the gel, and a multichannel stimulus generator was used to apply biphasic waveforms similar to those used in clinical DBS applications. The signals had frequencies ranging from 130-150 Hz, with voltages between 1V and 10V, to replicate real-world DBS conditions.

A concentric needle electrode setup was used to capture the electric field signals from the medium. The concentric needle electrode was positioned at varying radial distances from the DBS electrode, with measurements taken at distances between 0.1 mm and 0.5 mm. This setup allowed for high-resolution data collection on the propagation and decay of the electric field through media with different conductivities.

3.1.5.3 Data Collection and Analysis

Electric field measurements were taken at multiple points, starting from 0.1 mm and extending to 0.5 mm from the DBS electrode. Measuring the electric field at distances up to 0.5 mm provided detailed insights into how far the electric field propagated in different conductivity conditions. This is especially important in DBS applications, where fields extending beyond the target area could stimulate unintended neural structures, leading to adverse effects.

The field strength and decay rates were compared at each distance and conductivity level, providing a deeper understanding of how different tissue environments influenced the therapeutic range of DBS stimulation. The data from the concentric needle electrode recordings were analyzed to determine how the electric field decayed

under different conductivity conditions, providing crucial information on the Volume of Tissue Activated (V.T.A.) and the spatial spread of the stimulation in each case.

3.1.5.4 Repetition of Experiments for Verification

To ensure the reliability of the results, all experiments were repeated in a controlled laboratory environment, and the findings were cross-verified with simulation data generated using finite element modeling (FEM). The simulation data, based on the electrode geometry and the conductive properties of the medium, provided theoretical predictions of the electric field distribution. The repeated physical experiments validated these predictions and ensured that the simulations accurately reflected real-world conditions.

3.1.5.5 Pearson Correlation for Validation

After verification, Pearson correlation was used to establish the relationship between the laboratory data and the simulated data. By applying Pearson correlation, the degree of linear correlation between the two datasets was quantified, allowing for an objective assessment of how closely the experimental results matched the predictions from the simulations. This statistical method further confirmed the accuracy of the simulations, providing high confidence in the model's predictive capabilities and the consistency between the simulated and experimental electric field distributions.



Figure 20. Experimental set up for the verification experiment



Equipment: Multichannel Systems Stimulus

Generator STG 4000

Software : MC Stimulus II

Figure 21. Multichannel Systems Stimulus Generator STG 4000

3.2 Biological Characterization of Electrodes in Rat Model

The purpose of this study was to evaluate the biological response of brain tissue following implantation of test materials, specifically platinum-iridium alloy, PDMS, Epoxy, intended for use in deep brain stimulation (DBS) electrodes. The study was designed per ISO 10993-6: 2016 (E) guidelines, which dictate the tests for local effects after implantation in brain tissue. A rat model was chosen for the biological characterization, as it provides a reliable means of assessing biocompatibility and tissue response to implant materials over specified periods.

The DBS electrodes used in the study were fabricated using three primary materials:

- **Platinum-Iridium Alloy:** Known for its high biocompatibility, corrosion resistance, and excellent conductivity, platinum-iridium alloy is widely used in neuroprosthetic applications.
- **Polydimethylsiloxane (PDMS):** Used as an insulating material due to its flexibility and bio-inert properties, PDMS provides the necessary isolation of the active electrode surface from the surrounding tissue.
- **Epoxy Resin:** Applied for structural bonding and encapsulation to ensure implant stability over the experimental duration.

3.2.1 Animal Model

The study utilized Wistar rats, both male and female, weighing between 200g and 400g. Adult rats were selected for the experiment due to their well-established use in

neurobiological studies, particularly in evaluating the biocompatibility of implantable materials.

- Group Allocation:
 - A total of 24 rats were used for the experiment.
 - Test group: 12 rats for the 4-week implantation period and 12 rats for the 12-week period (6 animals per period).
 - Control group (sham): 6 rats (3 animals per period) that underwent a sham surgery with no electrode implantation.

3.2.2 Animal Identification and Care

Each animal was identified by a tattoo number on the ear and labelled with information, including the study number, group, sex, and experimental dates. The animals were not quarantined since they originated from an internal colony, reducing the need for additional observation periods before the experiment.

Animal welfare and care procedures complied with CCSEA (Committee for Control and Supervision of Experiments on Animals, Govt. of India) regulations. Approval from the Institutional Animal Ethics Committee (Approval B Form No: SCT/IAEC-459/DEC/2022/114) was obtained prior to initiating the study.

- Environmental Conditions: The animals were housed in standard laboratory cages under controlled conditions. The environmental settings were maintained at a temperature of $22 \pm 3^{\circ}\text{C}$, humidity levels of 30-70%, and a 12-hour light/dark cycle, with a minimum of 15 fresh air changes per hour.

- Feed and Water: The rats were fed a commercially available rat feed and provided ad libitum access to Aqua Guard filtered water. Both the feed and water were analyzed biannually for quality and safety.
- Fasting Procedures: Prior to surgical procedures, the rats underwent an overnight fast, during which water was available. Feed and water were provided ad libitum 3-4 hours after surgery.

3.2.3 Surgical Procedure and Electrode Implantation

The implantation procedure was carried out under aseptic conditions in compliance with ISO 10993-6: 2016 (E), Annex D. The goal was to evaluate the local brain tissue response to the test materials over two periods (4 weeks and 12 weeks). The procedure for both the test and control groups was identical.

Anesthesia: All animals were anesthetized using an intraperitoneal injection of Ketamine (1.6 ml/kg body weight) and Xylazine (0.25 ml/kg body weight) to ensure complete immobilization and pain control during the surgery.

- Surgical Protocol:
 - The skin overlying the skull was swabbed with 70% alcohol, and a cranial incision was made to expose the skull.
 - Holes of appropriate diameter were drilled into the cranium at pre-determined locations to accommodate the test material. Care was taken to ensure uniformity in the size and placement of these holes across all animals.

- For the test group, a small incision was made in the dura mater, and the materials were gently inserted into the brain. In the control group, a sham surgery was performed by drilling holes without implanting electrodes.
- The incisions were closed using sterile sutures, and post-operative care was provided to ensure proper recovery.

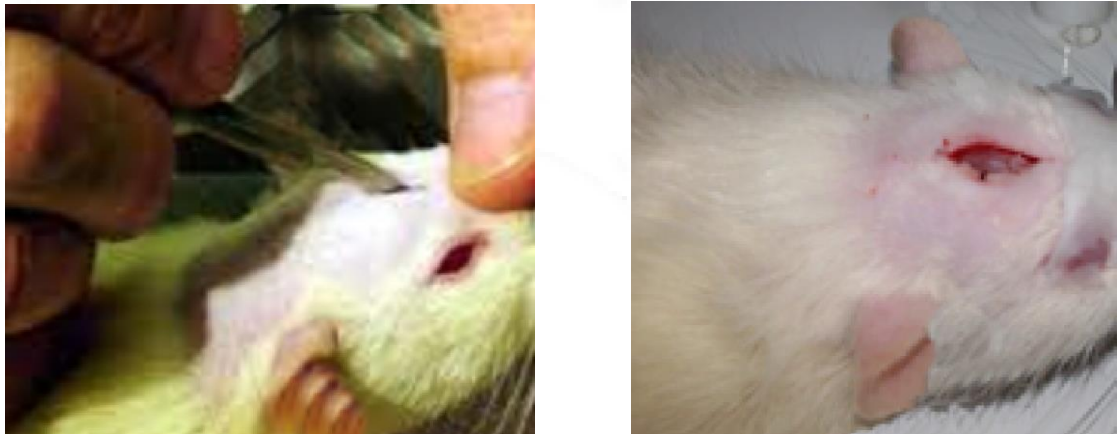


Figure 22. Implantation in rat models

3.2.4. Post-Surgical Care and Monitoring

Throughout the experiment, animals were monitored for general health, body weight, and behavioral changes. No abnormal behaviors or distress were observed. Routine health checks included observing feed intake, weight gain, and overall physical condition.

3.2.5. Study Periods and Sacrifice

The study was conducted over two observation periods:

- 4 weeks to assess the short-term response.
- 12 weeks to examine long-term tissue response.

After each period, the animals were humanely euthanized by an overdose of anaesthesia. Brain tissue, including the implanted electrodes and surrounding areas, was collected for analysis. Tissue from sham animals was similarly harvested for comparison.

3.2.6 Histopathological Examination

Upon termination of each study period, the implanted electrodes and surrounding brain tissue were carefully dissected. For the control group, brain tissue from the sham sites was similarly collected. The tissue samples were then processed and subjected to histopathological analysis. Standard staining techniques were employed to examine the tissue for any signs of:

- Inflammation
- Fibrosis
- Hemorrhage
- Encapsulation
- Necrosis

3.2.2 Cell Interaction Studies for Epoxy

The study utilized commercially available Hysol® Epoxy Adhesive (LOCTITE). The resin and hardener were mixed in a ratio of 100:25 to produce the epoxy. The material was cured for 2 hours at 60°C or alternatively at room temperature for 24 hours.

Following curing, the epoxy was cleaned using isopropanol, soap, and distilled water, followed by ultrasonic cleaning. The sterilization was achieved through ethylene oxide (ETO) sterilization before subsequent in vitro and in vivo testing.

3.2.1.1 In Vitro Studies

The biocompatibility of Hysol® epoxy was first assessed through in vitro cell culture assays using U-87 MG glioma cells. The cells were exposed to various dilutions of the epoxy extracts, and the following assays were performed:

- MTT assay was conducted to evaluate cell viability based on mitochondrial activity, indicating no significant reduction in viability compared to controls.
- Neutral Red Uptake (NRU) assay assessed lysosomal activity, confirming that epoxy extracts did not interfere with lysosomal functions.
- Lactate Dehydrogenase (LDH) assay measured cytotoxicity by evaluating membrane integrity, which remained unaffected by epoxy exposure.
- Phase contrast microscopy was used to visually assess cell morphology, showing no observable morphological changes.
- Rhodamine-phalloidin staining was employed to analyze the integrity of the cytoskeleton, with no actin destabilization noted.
- Acridine Orange (AO) staining was used to assess lysosomal integrity, and no shifts in fluorescence indicated a disruption in lysosomal function.
- Calcein AM/Propidium Iodide (PI) staining allowed the differentiation of live and dead cells, confirming cell viability.

- GFAP immunostaining evaluated the structural integrity of glial fibrillary acidic protein (GFAP), showing no adverse effects on glial cells.

3.2.1.2 In Vivo Studies

The in vivo component of the study evaluated systemic toxicity, irritation, and muscle implantation using animal models following ISO 10993 standards.

- Systemic toxicity tests were performed using mice injected with physiological saline (PS) and cottonseed oil (CSO) extracts of the epoxy. Observations were made at 24, 48, and 72 hours, showing no adverse reactions.
- Intracutaneous irritation tests were conducted on rabbits, with test samples injected intradermally. No significant irritation or inflammation was observed in any animal during the evaluation period.
- Guinea Pig Maximization Test (GPMT) evaluated the sensitization potential of the epoxy extracts through a topical application. The results indicated no sensitization reactions, classifying the material as non-irritant.
- Intramuscular implantation studies were performed on rabbits to assess the biological response of muscle tissue to the implanted epoxy material. Histopathological analysis at 4 and 12 weeks post-implantation revealed no significant necrosis or adverse tissue reactions, confirming biocompatibility.

Statistical Analysis

Data from the in vitro assays were analyzed using one-way ANOVA, with significance levels set at $p < 0.05$.

3.3 Electrochemical Characterization

Electrochemical characterization is a set of methods used to study the electrochemical properties of different materials and systems. This type of analysis is essential in

various fields, such as battery development, fuel cells, corrosion studies, and the evaluation of electrode materials, including those used in biomedical devices like deep brain stimulation (DBS) electrodes.

Recent studies focusing on the electrochemical characterization of deep brain stimulation (DBS) electrodes emphasize several innovations to enhance performance and patient outcomes. One major development involves using conductive polymers, such as polypyrrole and polyaniline, to improve electrode conductivity and biocompatibility. These polymers are particularly effective in expanding the active surface area of electrodes, facilitating more efficient ion transfer and faster electron transport during neural stimulation. This improvement in electrochemical performance is essential for maintaining long-term signal stability in DBS systems (Nguyen et al., 2023; Li et al., 2024).

Techniques like cyclic voltammetry (CV) and electrical impedance spectroscopy (EIS) are frequently employed to characterize these electrode materials, offering insight into charge storage capacity, impedance reduction, and overall durability during extended periods of use. These methods are crucial for evaluating the electrochemical properties of electrode materials, leading to better design for optimized signal transmission (Fenton et al., 2022; Li et al., 2024). Nguyen et al. (2023) reported a significant reduction in impedance when DBS electrodes were coated with polymers, which is critical for efficient signal delivery to neural tissues.

Further advancements include the integration of microfluidic platforms that allow real-time monitoring of electrode behavior in controlled environments. By combining

microelectrodes with neural tissue models, these platforms enable precise assessments of electrode-tissue interactions, improving the development of DBS systems for adaptive, closed-loop applications (Nguyen et al., 2023; Hung et al., 2023). Such platforms are key to refining the use of DBS in movement disorders, allowing for real-time adjustments based on patient feedback.

Multi-electrode arrays, another innovation, enable simultaneous stimulation and recording across different brain regions. This capability provides a more nuanced understanding of neural circuitry, which is essential for customizing DBS treatments to target specific symptoms (Fenton et al., 2022; Li et al., 2024). These arrays offer greater flexibility in treatment, especially in complex conditions like Parkinson's disease.

Material advancements, including the use of nanostructured coatings such as graphene and carbon nanotubes, further enhance electrode performance. These coatings improve the electrochemical properties of DBS electrodes and enhance biocompatibility, reducing inflammation and the risk of long-term degradation (Nguyen et al., 2023; Li et al., 2024). Studies suggest these materials can sustain electrode functionality over prolonged use, making them ideal for chronic implants (Yarou Li et al., 2024).

Adaptive DBS systems, which rely on real-time feedback to adjust stimulation, benefit significantly from these advancements. Electrodes with improved electrochemical properties are more responsive to real-time changes in neural activity, allowing for smoother transitions in stimulation intensity based on the patient's needs (Nguyen et al., 2023; Fenton et al., 2022).

In conclusion, these recent studies contribute to reducing the side effects of conventional DBS, such as unintended muscle contractions or speech difficulties, by improving the precision and adaptability of DBS treatments. The ongoing advancements in electrode design and electrochemical characterization promise more personalized and effective therapies for movement disorder patients (Nguyen et al., 2023; Li et al., 2024).

The techniques employed for the characterization of electrodes are as follows

Cyclic Voltammetry (CV)

This technique measures the current that flows in an electrochemical cell as the voltage varies. It is commonly used to determine redox potentials, analyze reaction rates, and assess the stability of materials.

Electrochemical Impedance Spectroscopy (EIS)

EIS measures how a system resists the flow of electric current over a range of frequencies. It helps understand how an electrode interacts with its environment, evaluating factors like resistance to charge transfer and material diffusion.

Chronoamperometry and Chronopotentiometry

These methods track changes in current or voltage over time while maintaining a constant potential or current. They are useful for studying how reactions occur over time and determining the stability of materials.

3.3.1 Estimation of Open Circuit Potential

Open Circuit Potential (OCP) measurement is a method used in electrochemistry to determine the natural voltage of an electrode when no external current is being applied. The electrode is placed in an electrolyte solution alongside a reference electrode to measure OCP. These two electrodes' potential differences are recorded without applying any external current. This potential is the OCP, representing the natural state of the electrode in that environment.

3.3.2 Estimation of Impedance-by-Impedance Spectroscopy

EIS is primarily used to analyze the impedance of an electrochemical system over a range of frequencies. In an EIS, a small AC voltage is applied to the system, and the resulting current is measured. By varying the frequency of the applied voltage, the impedance (the ratio of the voltage to the current) is measured across a wide frequency range. This data is then analysed to separate the different electrochemical processes occurring in the system.

3.3.3 Defining the Safe Charge Limits by Chronopotentiometry

Chronopotentiometry is a technique used in electrochemistry to monitor how the voltage of an electrode changes over time when a constant current is applied. The main objective of Chronopotentiometry is to observe how an electrochemical system reacts when subjected to a steady current. By tracking the changes in voltage over time, we can gain insights into the processes occurring at the electrode surface, such as how ions move or a material might degrade.

A constant current is applied to the system during a chronopotentiometry experiment, and the electrode's potential is measured continuously. The voltage response reflects the ongoing electrochemical reactions, providing valuable information about the material's behaviour under these conditions, such as reaction mechanisms and the stability of materials.

3.3.4 Generation of Randles Model

The Randles model is a commonly used approach to represent the electrochemical interface between an electrode and an electrolyte, such as the interface between a deep brain stimulation (DBS) electrode and brain tissue. This model helps analyse the electrochemical behaviour at this interface, which is crucial for ensuring effective and safe neural stimulation in medical applications.

Components of the Randles Model:

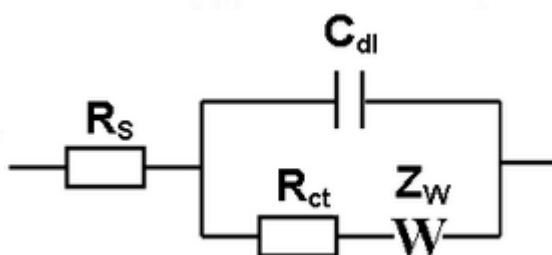


Figure 23. Randles Model-Generic Diagram

Solution Resistance (R_s)

This element represents the resistance of the surrounding electrolyte, in this case, brain tissue, to ionic current flow. It reflects how easily ions can move through the tissue around the electrode.

Double-Layer Capacitance (C_{dl})

At the electrode-tissue interface, a double layer of charges forms due to the separation of ions near the electrode surface. This capacitance reflects the ability of the interface to store charge, which is influenced by factors like the surface area of the electrode and the properties of the surrounding tissue.

Charge Transfer Resistance (R_{ct})

This component represents the resistance to electron transfer across the interface. In the context of a DBS electrode, R_{ct} gives insight into how easily charge can be transferred between the electrode and the neural tissue, which is critical for effective stimulation.

Warburg Impedance (Z_w)

Warburg impedance models the diffusion processes at the interface, particularly if there is slow ion diffusion through the tissue or the electrode material.

Experimental Setup

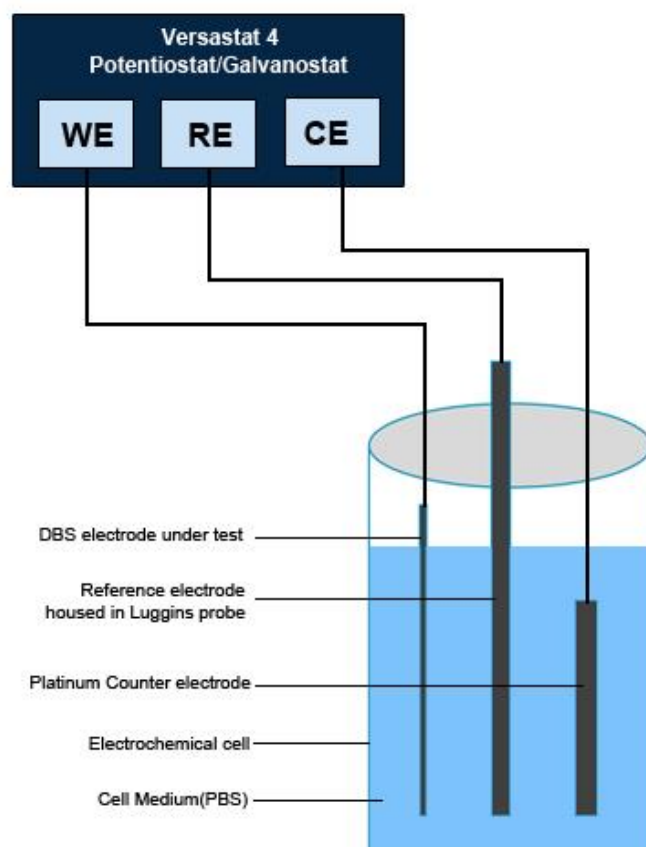


Figure 24. Experimental Setup-Schematic

A model cylindrical-shaped DBS electrode is used as the working electrode for the electrochemical studies. The electrode comprises a quadrupole arrangement of four electrodes of Pt-Ir alloy insulated with silicone rubber. The electrodes, which are 1.3 mm in diameter, are arranged in such a fashion that they result in six contacts, three of which are used for stimulation and the remaining three for sensing the parameter. The inter-electrode distance was maintained at 1.5 mm, and the final length of the electrode is 400 mm. The electrochemical parameters of the model electrode were analysed by in-vitro experiments, including Open Circuit Potential (OCP) analysis, Cyclic

Voltammetry (CV), Electrochemical Impedance Spectroscopy (EIS), and Chronopotentiometry (CP). These experiments used phosphate-buffered saline (PBS) with a pH of 7.4 as the electrolyte. The electrolyte was selected to simulate the brain tissue environment. The PBS solution was prepared per the standard procedure involving the dissolution of 137 mM NaCl, 0.54 mM NaH₂PO₄, and 1.86 mM Na₂HPO₄ in de-ionized water.

A three-electrode configuration was employed for the electrochemical characterization experiments, consisting of the DBS electrode as a working electrode, a Standard Calomel Electrode (SCE) as a reference electrode, and a platinum foil as a counter electrode. A titanium electrode was also used for comparison.

The standard cell potential of the calomel reference electrode, relative to the standard hydrogen electrode (SHE), was 0.24 V. To ensure stability and prevent any concentration changes or clogging, the calomel reference electrode was housed in a Luggin probe containing saturated KCl solution. The experiments and measurements were performed using a Versastat 4 [M/s. Princeton, USA] potentiostat/galvanostat equipped with Solatron FRA 2.0, and data analysis was conducted using ZwinXP and Origin 8 software packages. Before each measurement, the DBS electrode was ultrasonically cleaned with deionised water, while the titanium electrode was polished using 0.05-micron alumina paste and thoroughly rinsed with distilled water. The counter and reference electrodes were meticulously cleaned before each measurement. We could identify any irreversible faradic reaction occurring on the electrode surface by analysing the various peaks observed in the cyclic voltammogram obtained at

different scan rates. This information is essential for defining a safe electrochemical window for the electrode.

3.3.5 Experimental Protocol

Following are the steps briefly described to perform the different experiments performed during characterization of the DBS electrode.

Apparatus Used

1. Working electrode: DBS electrode
2. Reference Electrode: Standard Calomel Electrode placed in a Luggin probe containing PBS solution for characterization in PBS and 2mS/cm NaCl solution for characterization with 2mS/cm gelatin.
3. Counter Electrode: 15mm x 15mm platinum foil
4. Solution condition: The solution was not purged with any inert gas during experiment
5. Ambient Temperature: Ambient temperature was maintained at 25 °C

Open Circuit Analysis

Step 1: The electrodes were placed in a test-tube containing nano-pure water and ultrasonically cleaned for a duration of 15 minutes.

Step 2: The ultrasonically cleaned electrode was dipped in the solution and connected to the working electrode terminal of the potentiostat.

Step 3: Zero current potentiometry was performed and the potential was allowed to stabilize.

Step 4: The stabilized potential was taken to be the OCP of the electrode.

Cyclic Voltammetry

Step 1: The electrodes were placed in a test-tube containing nano-pure water and ultrasonically cleaned for a duration of 15 minutes.

Step 2: The cleaned electrode was dipped in the solution and was connected to the working electrode terminal of the potentiostat.

Step 3: Linear scan cyclic voltammetry was performed with scan rate of 100 mV/s for 5 consecutive scans

Step 4: The electrode was disconnected and then taken out again to ultrasonically clean and step 1 was repeated.

Step 5: The electrode was again dipped in the solution and connected to the working electrode terminal of the potentiostat and cell potential was allowed to stabilize to the OCP value. Two consecutive scans at 100 mV/s was performed. The scan 1 in the characterization report is the first scan and scan 2 in the characterization report is the second consecutive scan.

Then step 4 and step 5 were repeated for scan rates of 80 mV/s, 60 mV/s, 40mV/s and 20mV/s.

Electrochemical Impedance Spectroscopy

Step 1: The electrodes were placed in a test-tube containing nano-pure water and ultrasonically cleaned for a duration of 15 minutes.

Step 2: The cleaned electrode was dipped in the solution and was connected to the working electrode terminal of the potentiostat.

Step 3: Linear scan cyclic voltammetry was performed with scan rate of 100 mV/s for 5 consecutive scans.

Step 4: The electrode was disconnected and then taken out again to ultrasonically clean and step 1 was repeated.

Step 5: The electrode was again dipped in the solution and connected to the working electrode terminal of the potentiostat and cell potential was allowed to stabilize to the OCP value. It was ensured that the surface conditioning reactions get completed by that time by applying one linear scan cyclic voltammetry of 100mV/s. Electrochemical Impedance Spectroscopy at OCP was performed with amplitude of 10 mV and the frequency was swept from 10 mHz to 10 kHz.

Then Step 4 and Step 5 were repeated for overpotentials of +20mV, -200mV, -400mV, -600mV and -800mV.

Chronopotentiometry

Step 1: The electrodes were placed in a test-tube containing nano-pure water and ultrasonically cleaned for a duration of 15 minutes.

Step 2: The cleaned electrode was dipped in the solution and was connected to the working electrode terminal of the potentiostat.

Step 3: Linear scan cyclic voltammetry was performed with scan rate of 100 mV/s for 5 consecutive scans

Step 4: The electrode was disconnected and then taken out again to ultrasonically clean and step 1 was repeated.

Step 5: The electrode was again dipped in the solution and connected to the working electrode terminal of the potentiostat and cell potential was allowed to stabilize to the OCP value. It was ensured that the surface conditioning reactions get completed by that time by applying one linear scan cyclic voltammetry of 100mV/s. Cathodic current pulse of amplitude 10 mA was injected for pulse widths of 50 μ s to 450 μ s

Then step 4 and step 5 were repeated for cathodic current amplitude of 5mA and 3mA for pulse widths of 50 μ s to 450 μ s and anodic current amplitudes of 1mA, 3mA, 5mA and 10mA for pulse width of 450 μ s only since in the analysis of the results of the cathodic exercise generated no new information for smaller pulse widths. Surface conditioning linear scan was performed only before injection of the first pulse of each current amplitude in the

cathodic current case. In anodic current case it was done before injection of the pulse in all current amplitudes.

3.4 Design of Algorithm for Closed Loop Control

Little S. & Brown P. have elaborated that during typical motor control, beta oscillations (13–30 Hz) are modulated, which may favour the current motor set at the expense of new movements. There is substantial correlative evidence connecting beta activity at rest and beta alterations in response to therapy with bradykinesia and rigidity, and these oscillations are significantly increased in Parkinson's disease (PD). Studies in which either cortical or subcortical areas have been activated in the beta frequency range causing a moderate but considerable slowdown of movements provide some indication that this link may be mechanistically significant or causal. Recent studies, however, using high-frequency deep brain stimulation (DBS) exclusively during times of increased beta activity have shown significant clinical effects that even outperform those of continuous high-frequency conventional DBS. These studies show how a better knowledge of the pathophysiology of PD can result in more effective therapeutic strategies for this disorder and suggest that beta activity may be both qualitatively and quantitatively significant in the motor impairment of Parkinson. A. L. Crowell et al. figured out that basal ganglia-derived movement disorders can result from irregularities in synchronized oscillatory activity in a network involving the thalamus, motor cortices, and basal ganglia. Basal ganglia local field potentials recorded briefly with externalized deep brain stimulator electrodes in humans have been the subject of extensive research. These investigations have given rise to the hypothesis that the basal ganglia-thalamocortical network exhibits distinctive changes in the beta frequency range (13–30 Hz) in Parkinson's disease. However, the straightforward evaluation of existing theories is limited since distinct

illnesses have rarely been compared utilizing recordings in the same structure under the same behavioral conditions. They investigated cortical oscillations in the three most prevalent movement disorders: Parkinson's disease, primary dystonia, and essential tremor using subdural electrocorticography to address this. In 31 participants, strip electrodes were used and temporarily implanted during standard surgery for deep brain stimulator placement to capture local field potentials from the arm region's primary motor and sensory cortices. The results obtained are (i) the primary motor cortex high beta (20-30 Hz) power is increased in Parkinson's disease during the stop phase of a movement task; (ii) the primary motor cortex broadband gamma power is increased in Parkinson's disease compared with the other conditions; (iii) the alpha-beta peaks in the motor and sensory cortical power spectra occur at higher frequencies in Parkinson's disease than in the other two conditions; and (iv) patients with dystonia have primary motor and sensory cortices with poor movement-related beta-band desynchronization. The results are consistent with the developing theory that illness states are characterized by aberrations in synchronized oscillatory activity. This was the first investigation into the three most prevalent movement disorders' sensorimotor cortex local field potentials. A different study by R. S. Neville et al. compared the pathological beta oscillations that occur during various motions in two subtypes of Parkinson's disease (PD): akinetic-rigid (AR) and tremor-dominant (TD). Beta oscillations, which are aberrant brain oscillations frequently seen in PD patients, are suggested to be a factor in the disease's motor symptoms. The authors used deep brain stimulation (DBS) electrodes to capture brain activity from PD patients' subthalamic nucleus (STN) while they were at rest, doing simple hand motions, and writing. The results of the AR and TD subtypes were then compared after the scientists examined

the beta oscillations in the collected data. The findings showed that during rest and handwriting movements, but not during simple hand movements, the AR subtype had considerably higher beta power and burst duration than the TD subtype. The authors hypothesize that various underlying causes of motor dysfunction in PD may be reflected in beta oscillations between the subtypes and movements. Overall, the work offered insights into how abnormal beta oscillations affect different PD subtypes and movements, which may help create more individualized treatment plans for PD patients. The alpha, beta, theta, and delta waves, generally referred to as the power spectrum's alpha, beta, and theta waves, are among the historically designated frequency bands that are the subject of much of the electroencephalography (EEG) literature. In order to identify patterns across disorders, J. J. Newson and T. C. Thiagarajan have reviewed 184 EEG studies that report differences in frequency bands in the resting state condition (eyes open and closed) for a variety of psychiatric conditions such as depression, ADHD, autism, addiction, bipolar disorder, anxiety, panic disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), and schizophrenia. They demonstrated that the power increases across lower frequencies (delta and theta) and decreases across higher frequencies (alpha, beta, and gamma) are the most prevalent patterns of change across various illness types, including ADHD, schizophrenia, and OCD. Some diseases like PTSD, addiction, and autism do not have a dominant trend for spectral change in either direction. They reported consistency and validation scores across the disorders and conditions that demonstrate that when summed across all studies reporting this result, the dominant result across all disorders is typically only 2.2 times as likely to occur in the literature as alternate results, typically with less than 250 study participants.

3.4.1 Detailed Explanation of Algorithm

Aim is to generate a control signal for a neurostimulator, which can act as feedback from the physiological domain to make the operation of the neurostimulator adaptive. The relation between unsynchronized beta waves with the intensity of parkinsonism is utilized here, and the beta signals derived from Local Field Potentials (LFP) are processed to derive the feedback factor. The available unsynchronized EEG data from the physio net database is used for the operations.

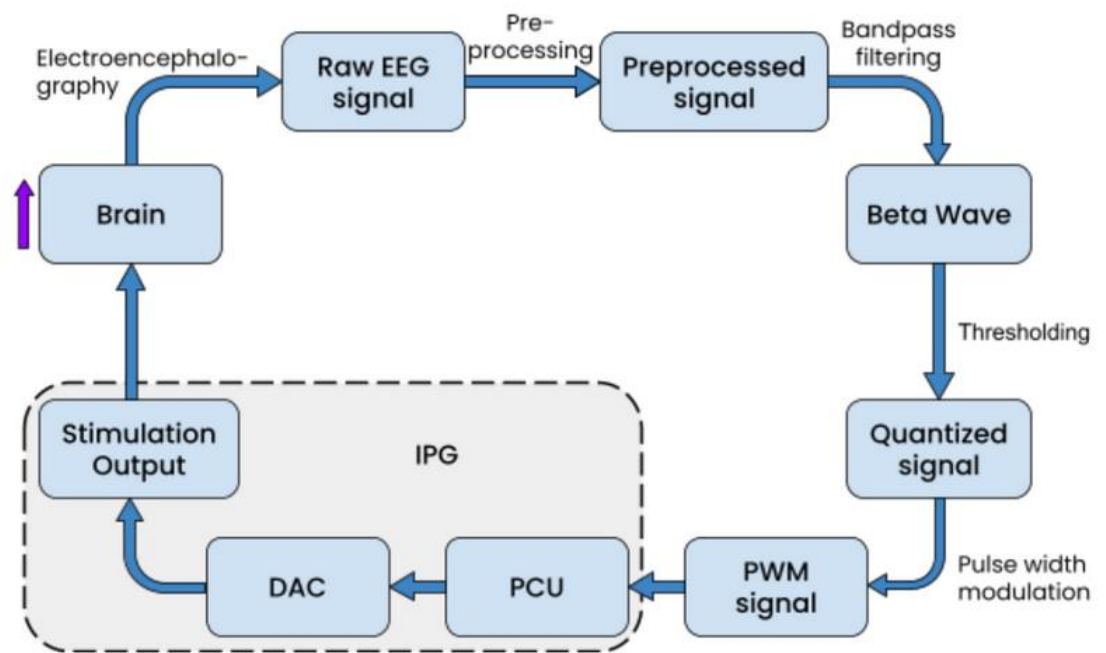


Figure 25. Block Diagram of the Overall system employing closed-loop

The block diagram of the system illustrates that the LFP recording is the primary source of neural activity data from which the EEG signal is derived. It is pre-processed using a low-pass filter to remove high-frequency noises and artefacts. It is then filtered using a Butterworth band pass filter to extract the beta wave frequency band (13 - 30 Hz). The thresholding process quantizes the beta wave obtained, converting the

continuous beta wave signal into a binary on/off signal based on a predetermined threshold. This signal is then used to control the duty cycle of a generated PWM signal. The PWM signal is then used to control an implantable pulse generator (IPG). This IPG contains a Power Control Unit (PCU), and the digital signal is converted to an analogue signal to maintain the charge balance.

3.4.1.1 Preprocessing

The raw EEG signal obtained is first pre-processed to remove unwanted noises and artefacts. Pre-processing helps increase the signal's quality by increasing the signal-to-noise ratio (SNR) and makes the signal suitable for further processing. A Butterworth low pass filter at a cut-off frequency of 50Hz is employed to remove high-frequency noises and artifacts. Also, a Butterworth high pass filter at a cut-off frequency of 0.5 Hz is used to eliminate low-frequency drifts and remove slow variations in the signal and DC offsets.

3.4.1.2 Beta wave extraction

To extract the beta waves from the pre-processed signal in the range of 13 - 30 Hz, a Butterworth band pass filter with a cut-off frequency of 13 Hz and 30 Hz is used since it has a more significant response for a low-frequency, fast-varying signal. The maximally flat frequency response in the passband ensures that they do not introduce ripples or distortions in the frequencies in the range of interest.

Butterworth filters provide a smooth transition between the passband and stopband. This gradual roll-off minimises signal distortion near the cut-off frequency and helps

maintain signal integrity in adjacent frequency bands. Butterworth filters exhibit a linear phase response, introducing a constant delay across all frequencies.

3.4.1.3 Thresholding

The beta wave obtained is thresholded to form a binary on-off signal. It helps us to identify the beta asynchrony. The beta wave amplitude of an average person is about 3 μV . So, fixing the threshold as 3 μV , the beta waves with an amplitude above 3 μV and below -3 μV are converted to value 1, and the beta waves in between -3 μV and 3 μV are treated as 0.

3.4.1.4 Generating the Pulse Width Modulation signal

The thresholded beta waves are then converted to a PWM signal by modulating with a 150Hz sine wave to generate the control signal. The obtained PWM signal is then averaged to a DC-level waveform, which can be fed to a neurostimulator to control the intensity and duration of the pulse train.

Chapter 4

4. Results and Discussion

The chapter is organized into three sections, each addressing distinct aspects of the study: (1) Simulation Studies and Verification, (2) Electrochemical Studies for Charge Characterization, and (3) In Vivo Studies in Rats and Cell Interaction Studies for the Biological Characterization of Hysol Epoxy. These sections collectively provide a comprehensive assessment of the deep brain stimulation (DBS) electrodes under investigation.

4.1 Simulation Studies and Verification

This section presents the outcomes of the simulation studies aimed at replicating the electrical properties of DBS electrodes within physiologically relevant conditions. The simulations were carried out using varying conductivity values, ranging from 0.08 S/m to 0.37 S/m, with the electrodes immersed in an agarose gel solution that simulates the conductive properties of cerebrospinal fluid (CSF) at a pH of 7.4. The accuracy of these simulations was validated by comparing the simulated data to experimental measurements, which were recorded at radial distances up to 0.5 mm from the electrode surface. To assess the degree of correlation between the simulated and experimental data, Pearson correlation analysis was employed, ensuring the reliability of the simulation models in replicating actual conditions.

The experimental design incorporated a radial arrangement of measurement points surrounding the electrode, as depicted in figure 36. (Electrode Cross-Section). These points were organized into two primary regions:

1. Inner Circle (IC): Three measurement points, labeled IC1, IC2, and IC3, were positioned close to the electrode surface. This region is characterized by a stronger electric field, allowing for the assessment of how conductivity influences the field near the electrode.
2. Outer Circle (OC): Three additional measurement points, labeled OC1, OC2, and OC3, were located farther from the electrode surface. OC3, the outermost point, was placed at a radial distance of 5 mm from the electrode, representing the region where the electric field is expected to attenuate more significantly.

The electric field was measured for all five conductivity values mentioned above at each of these six points. To further examine the electrode's behavior, a voltage sweep was performed, ranging from 1 V to 10 V in increments of 1 V. This voltage sweep provided a controlled method of evaluating how the electric field responded to increasing voltage levels across various conductivities.

The experimental results were then compared to simulation models to verify the accuracy of the computational predictions, with Pearson correlation performed to assess the correlation between the experimental and simulated data.

4.1.1 Simulation in Various Conductivities and Comparison with Control

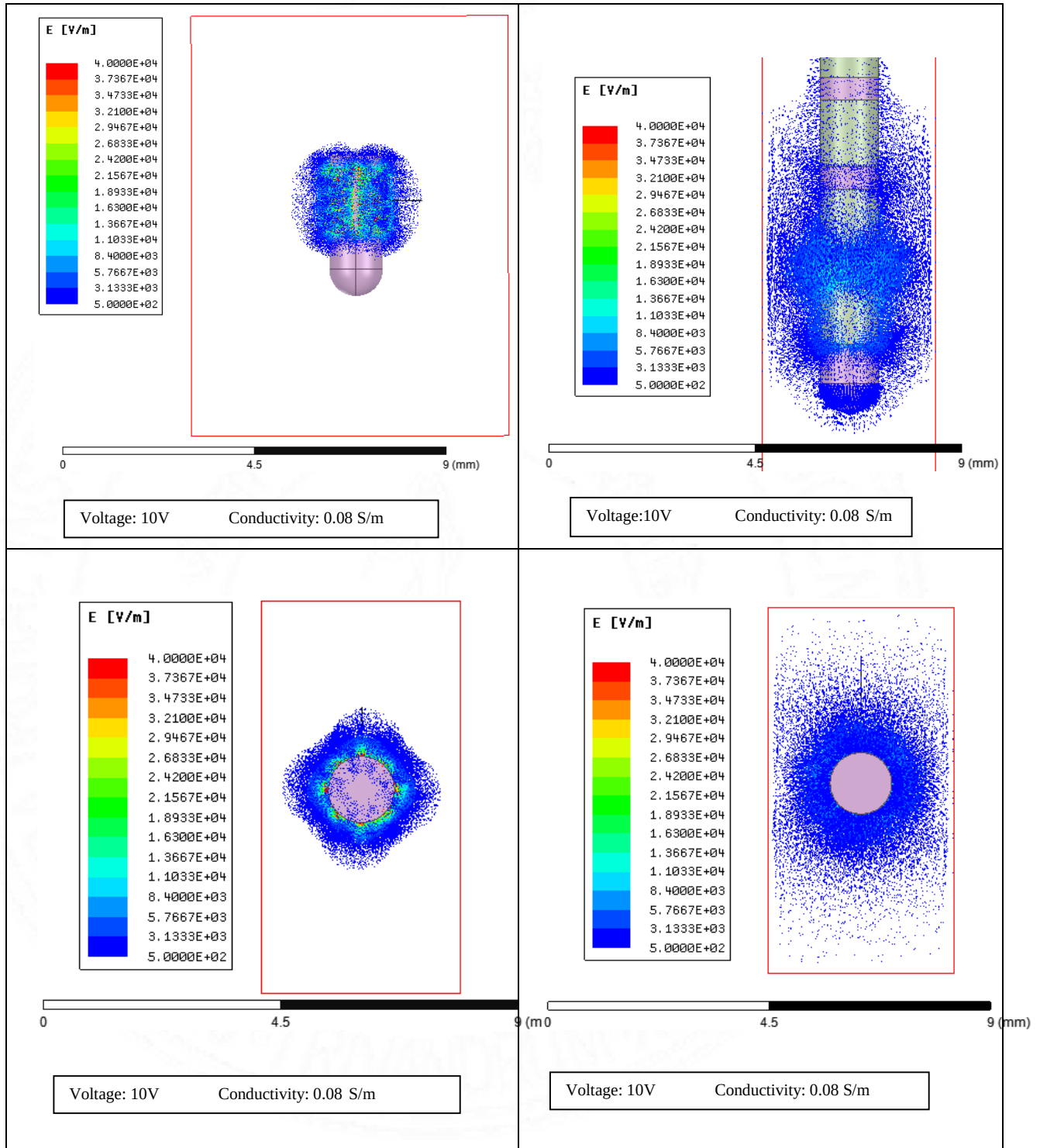


Figure 26. The simulation diagram for 10V stimulation for both hybrid electrode and test electrode, Conductivity 0.08 S/m; a) Hybrid electrode b) Control electrode

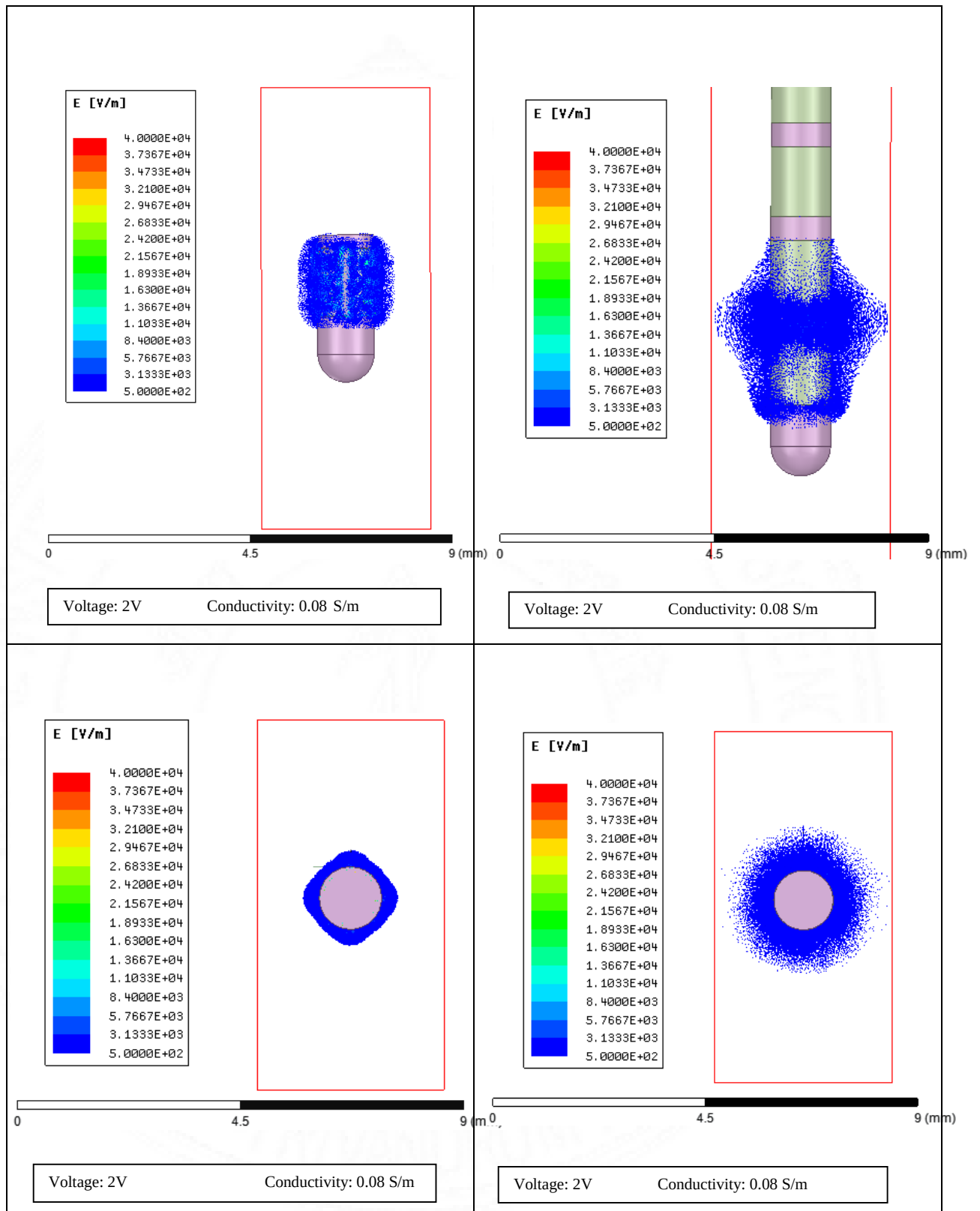


Figure 27. The simulation diagram for 2V stimulation for both hybrid electrode and test electrode, Conductivity 0.08 S/m; a) Hybrid electrode b) Control electrode

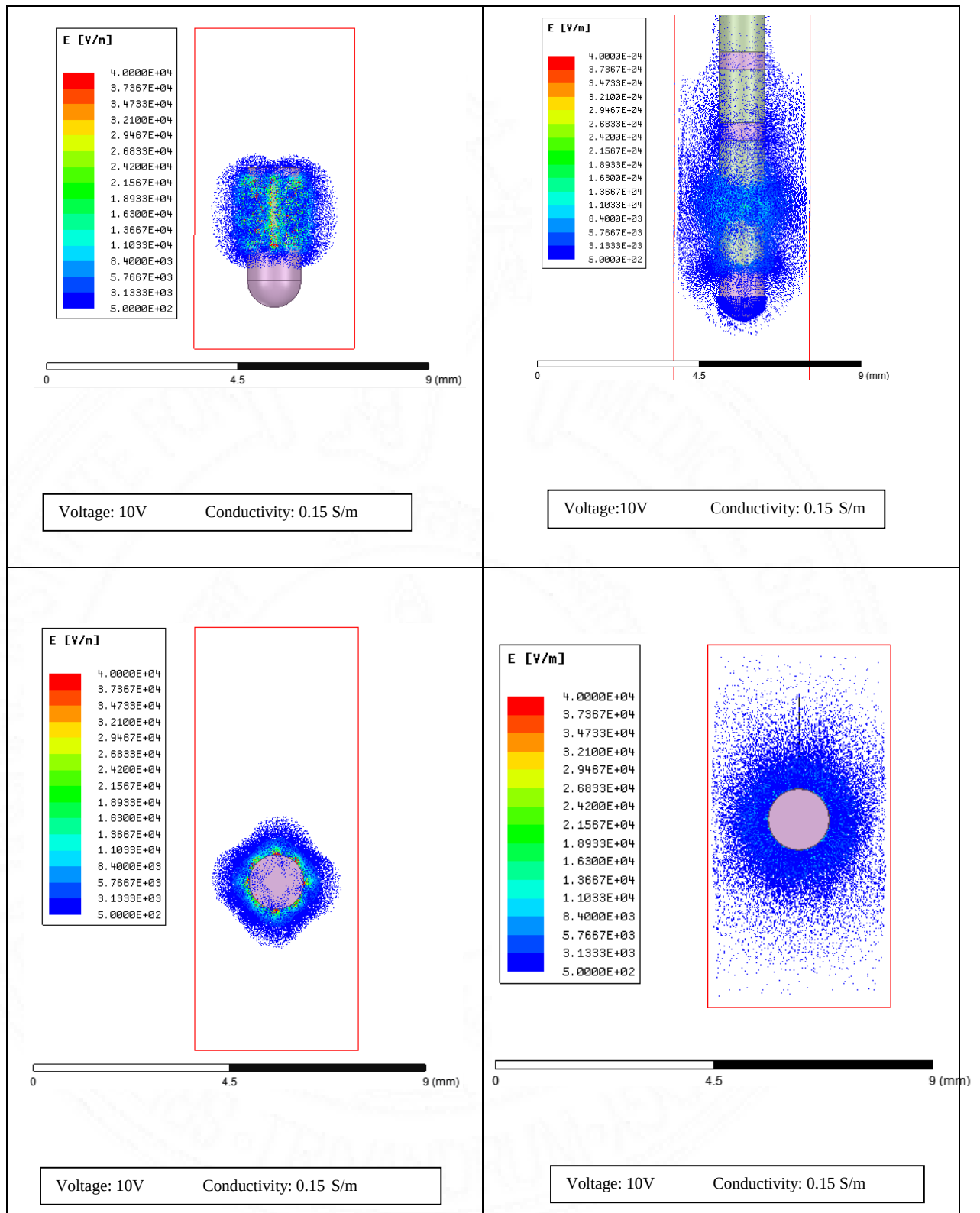


Figure 28. The simulation diagram for 10V stimulation for both hybrid electrode and test electrode, Conductivity 0.15 S/m; a) Hybrid electrode b) Control electrode

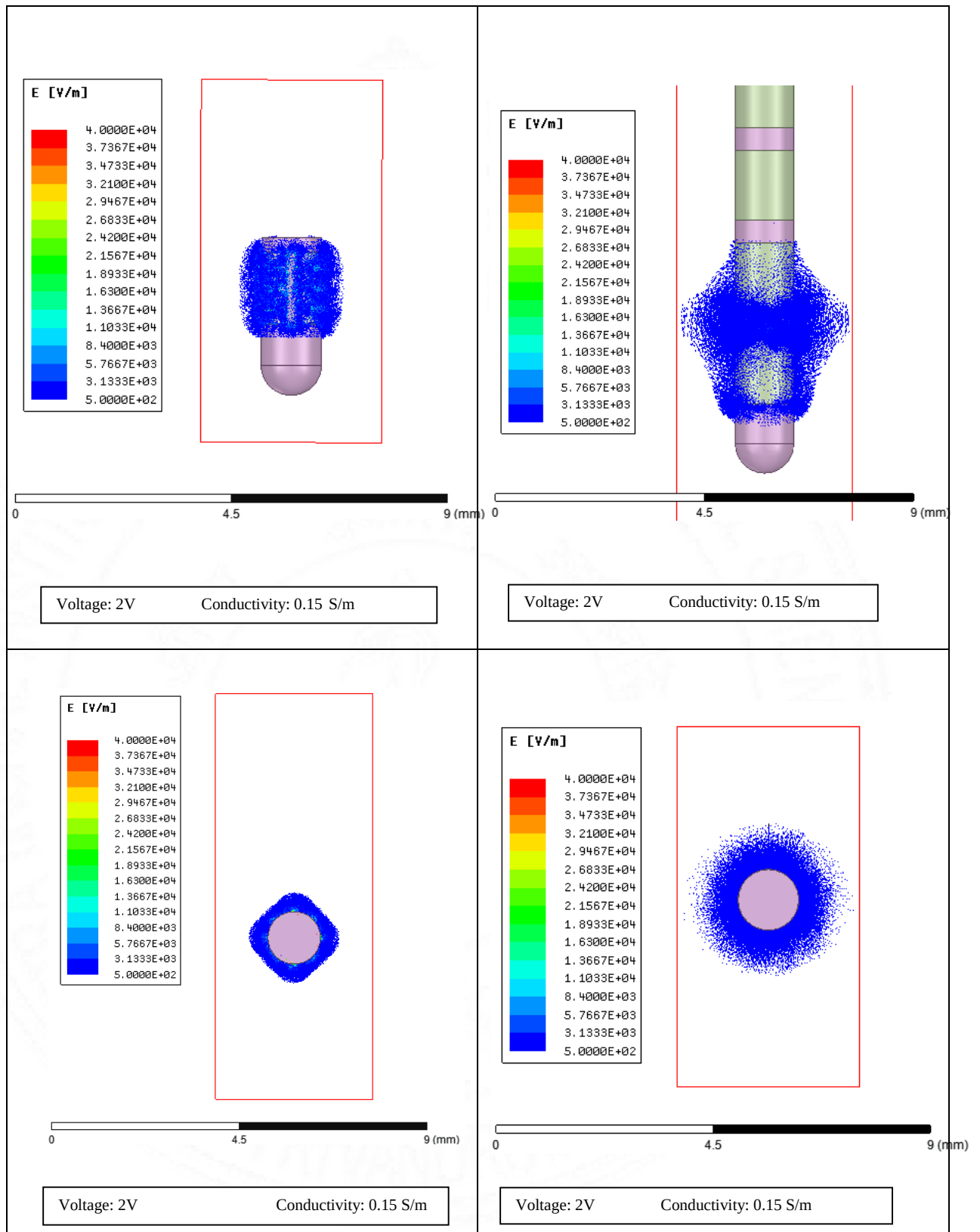


Figure 29. The simulation diagram for 2V stimulation for both hybrid electrode and test electrode, Conductivity 0.15 S/m; a) Hybrid electrode b) Control electrode

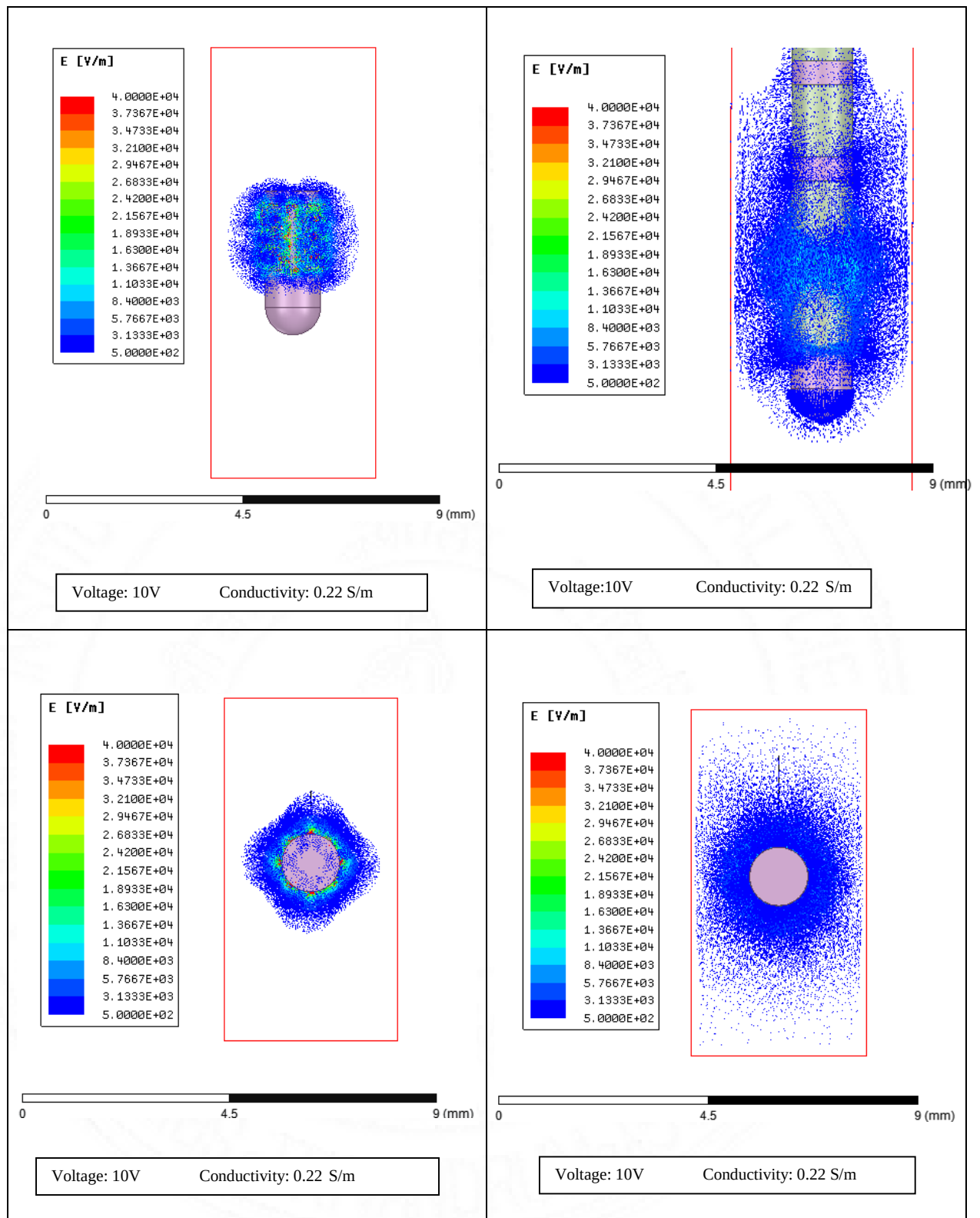


Figure 30. The simulation diagram for 10V stimulation for both hybrid electrode and test electrode, Conductivity 0.22 S/m; a) Hybrid electrode b) Control electrode

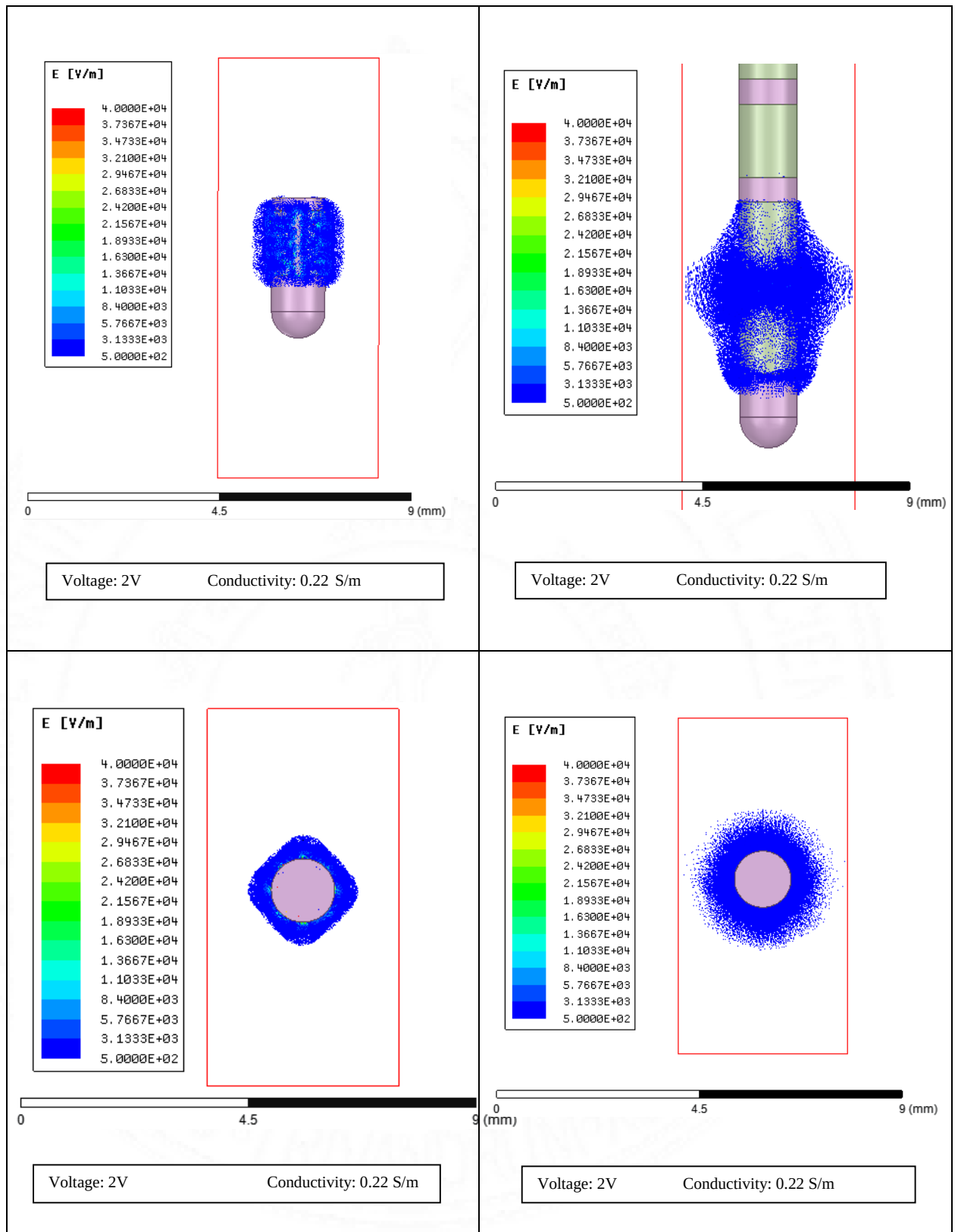


Figure 31. The simulation diagram for 2V stimulation for both hybrid electrode and test electrode, Conductivity 0.22 S/m; a) Hybrid electrode b) Control electrode

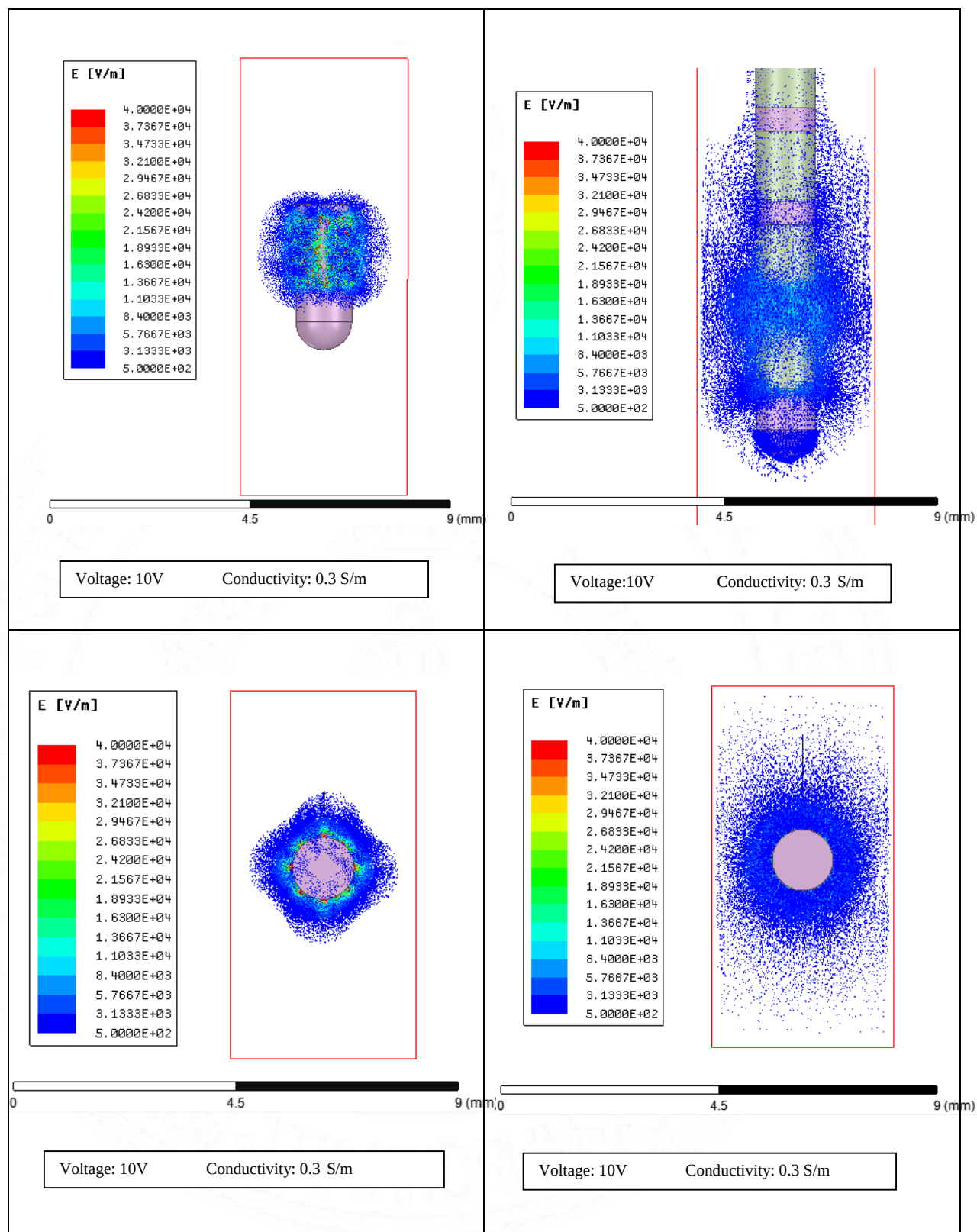


Figure 32. The simulation diagram for 10V stimulation for both hybrid electrode and test electrode, Conductivity 0.3 S/m; a) Hybrid electrode b) Control electrode

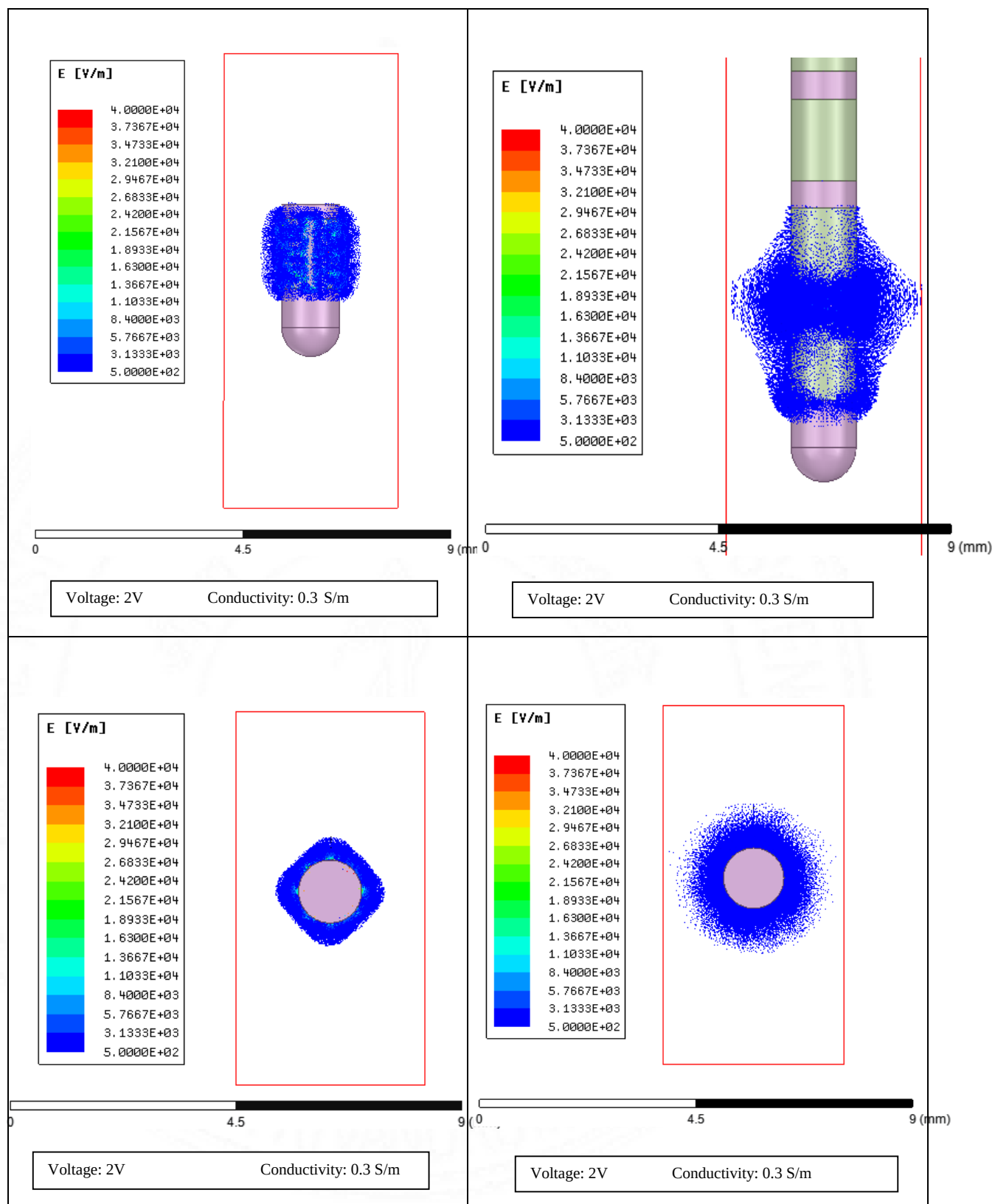


Figure 33. The simulation diagram for 2V stimulation for both hybrid electrode and test electrode, Conductivity 0.3 S/m; a) Hybrid electrode b) Control electrode

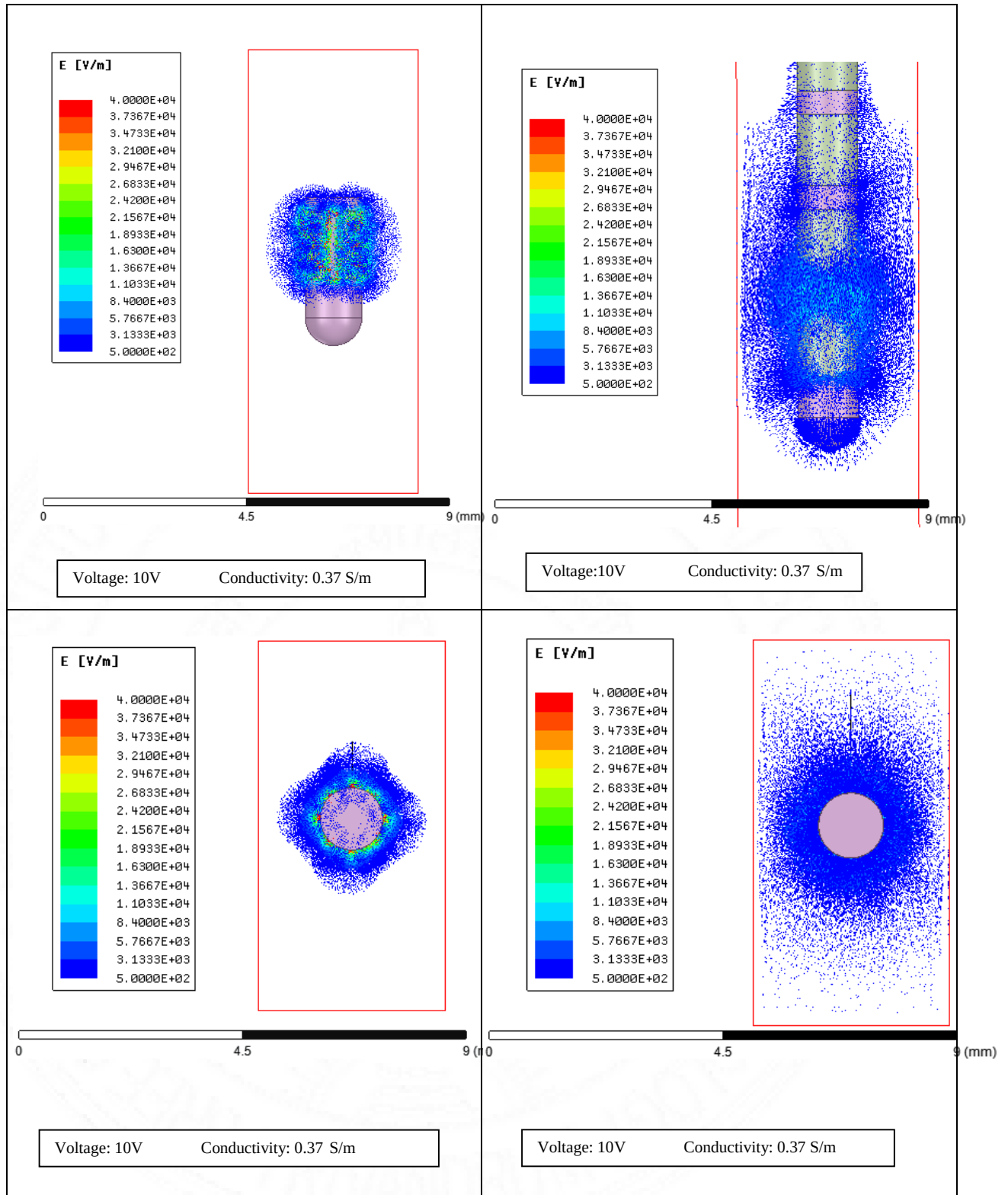


Figure 34. The simulation diagram for 10V stimulation for both hybrid electrode and test electrode, Conductivity 0.37 S/m; a) Hybrid electrode b) Control electrode

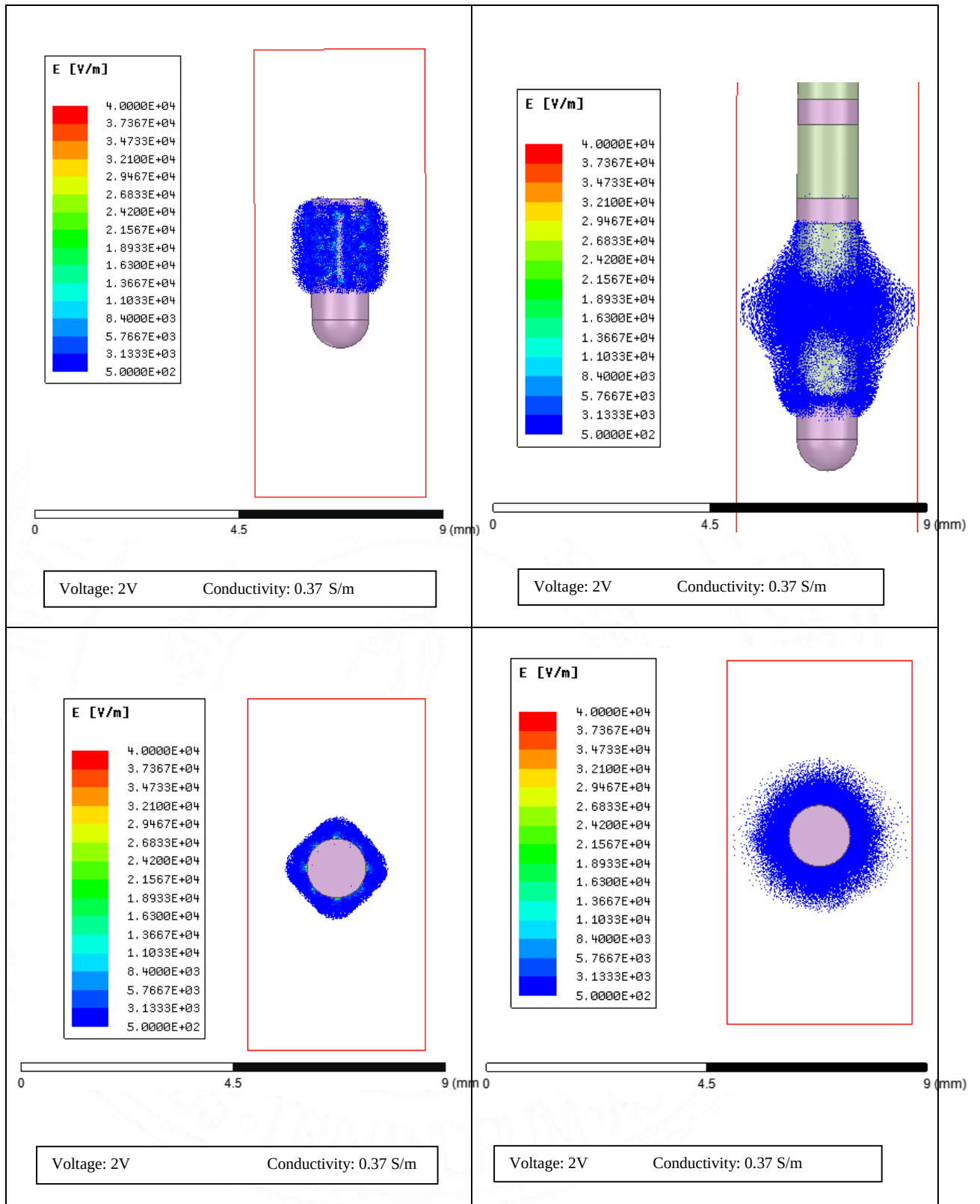


Figure 35. The simulation diagram for 2V stimulation for both hybrid electrode and test electrode, Conductivity 0.37 S/m; a) Hybrid electrode b) Control electrode

4.1.2 Analysis of Simulation Results

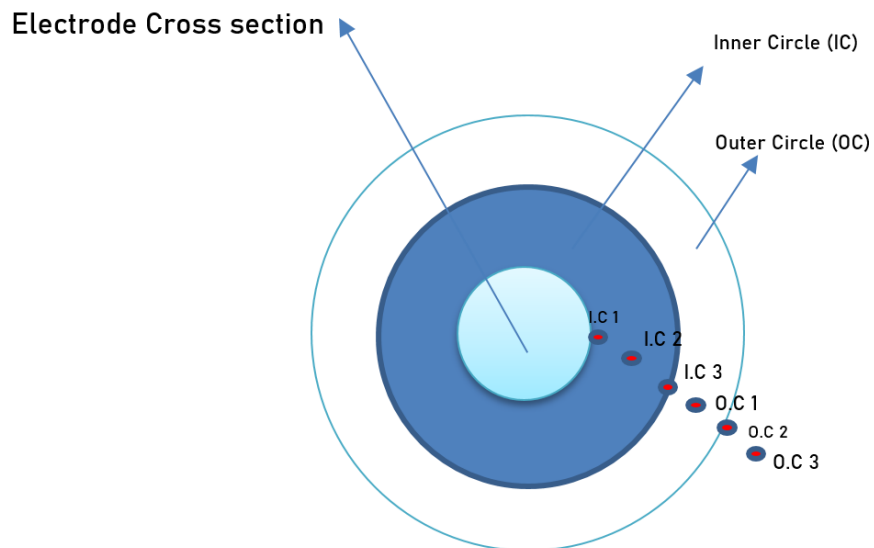
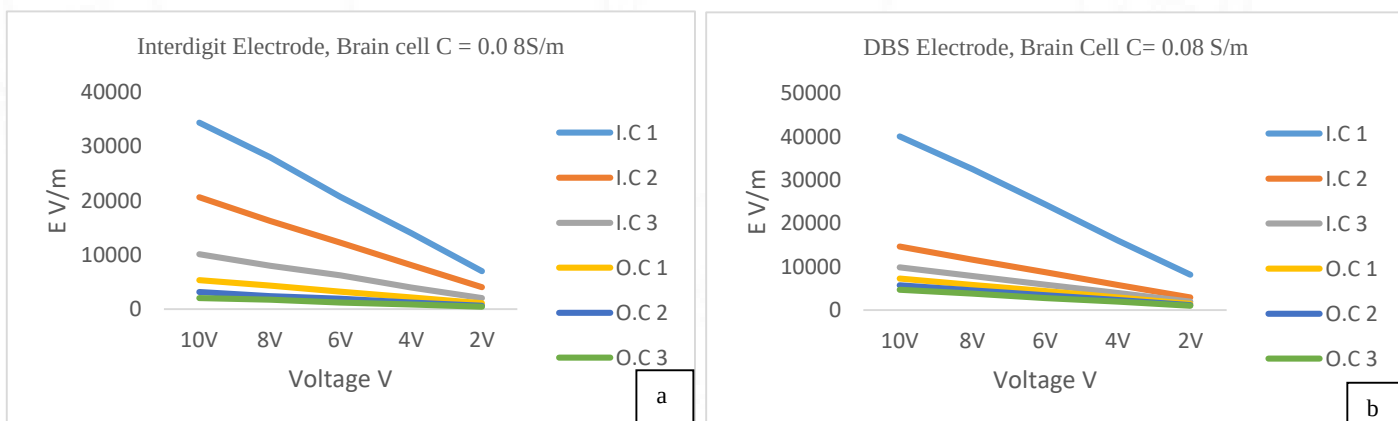


Figure 36. The radial measurement schematic for electrode cross-sections

The various simulation results derived from the analysis models is shown below



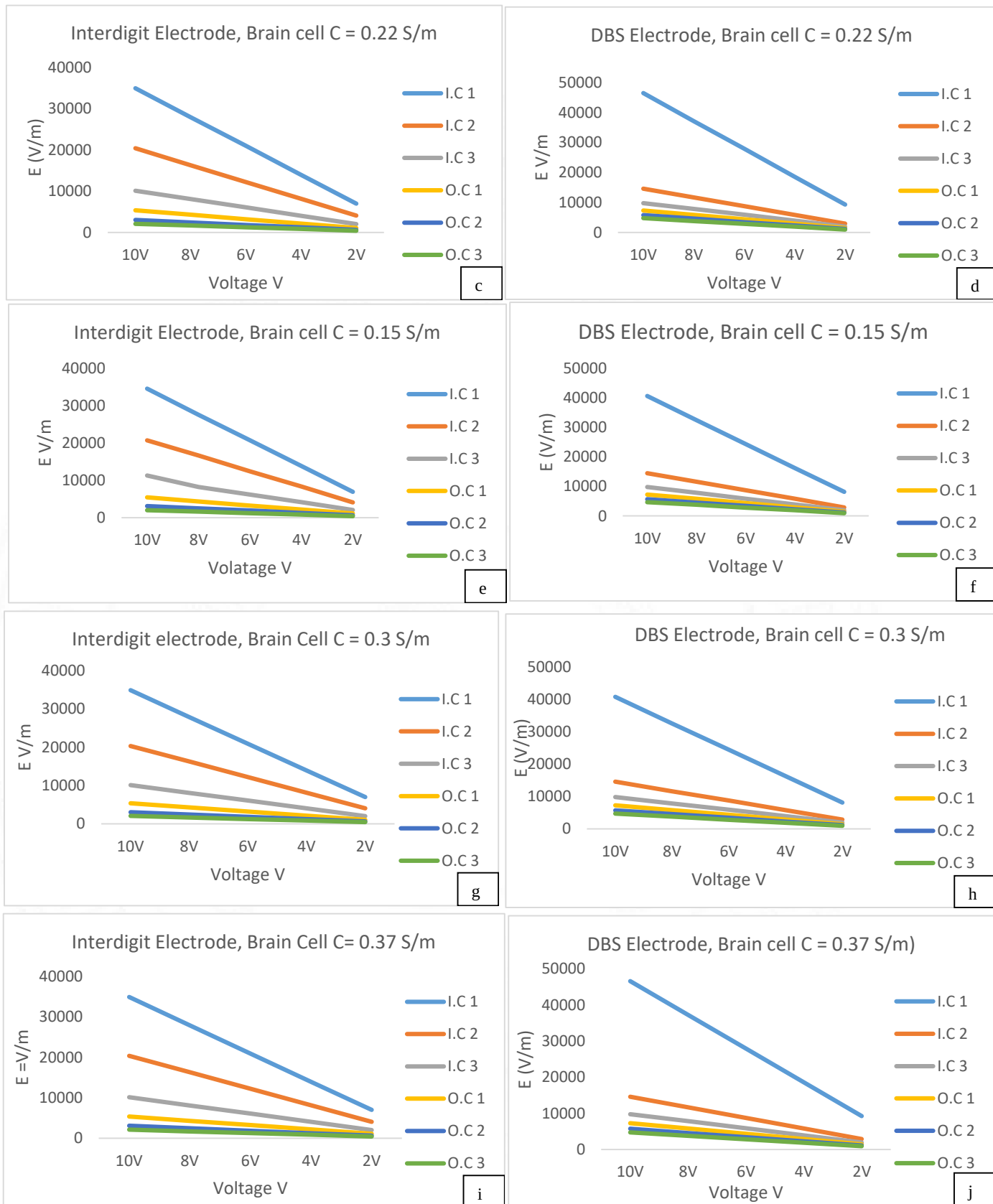
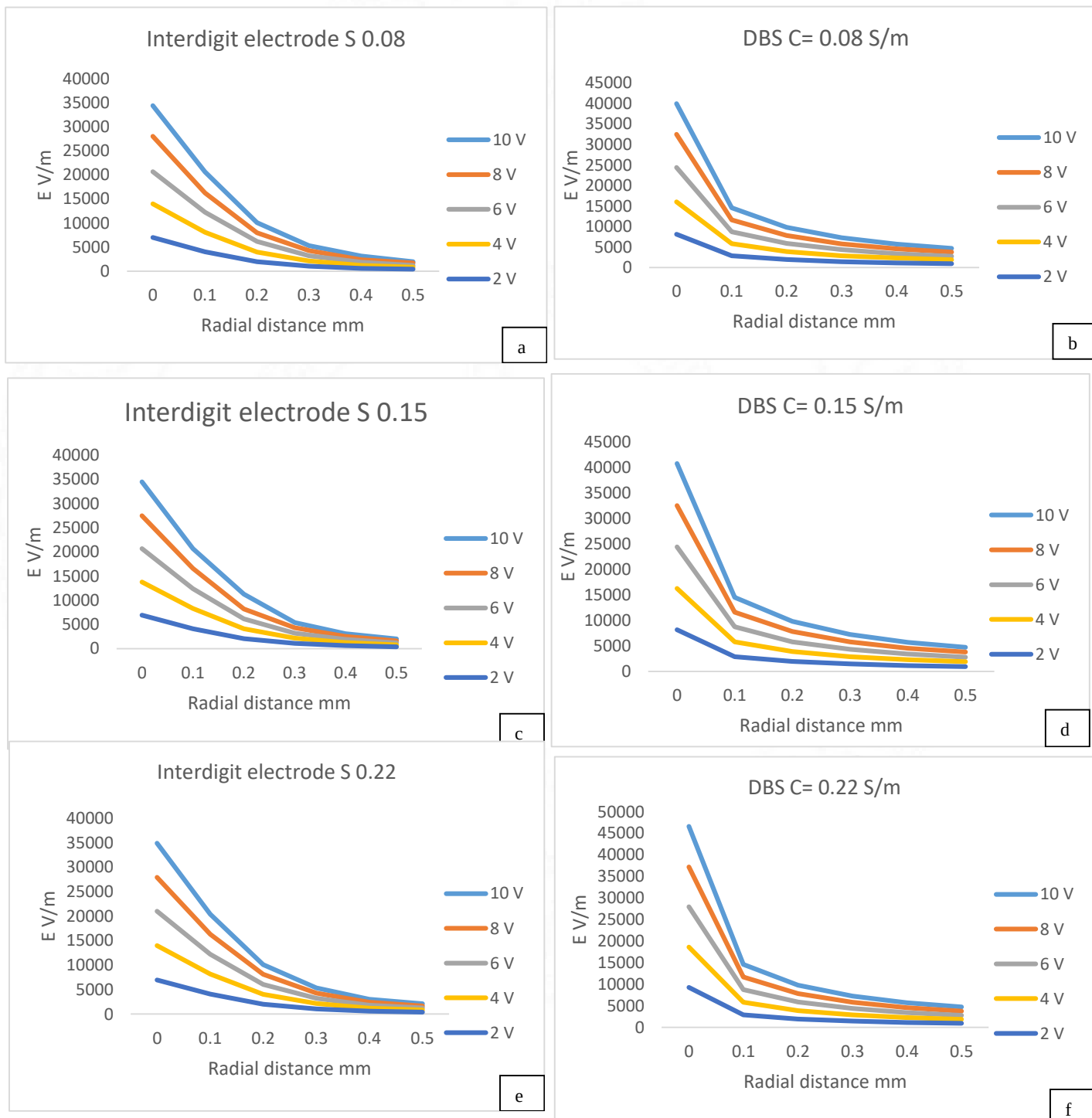


Figure 37. (a through j) shows the electric field distribution measured radially over six points on the electrode cross-section as in fig 33.

4.1.3 Comparison with Control

The comparison results for the electric field distribution at various conductivities is shown in the following graphs.



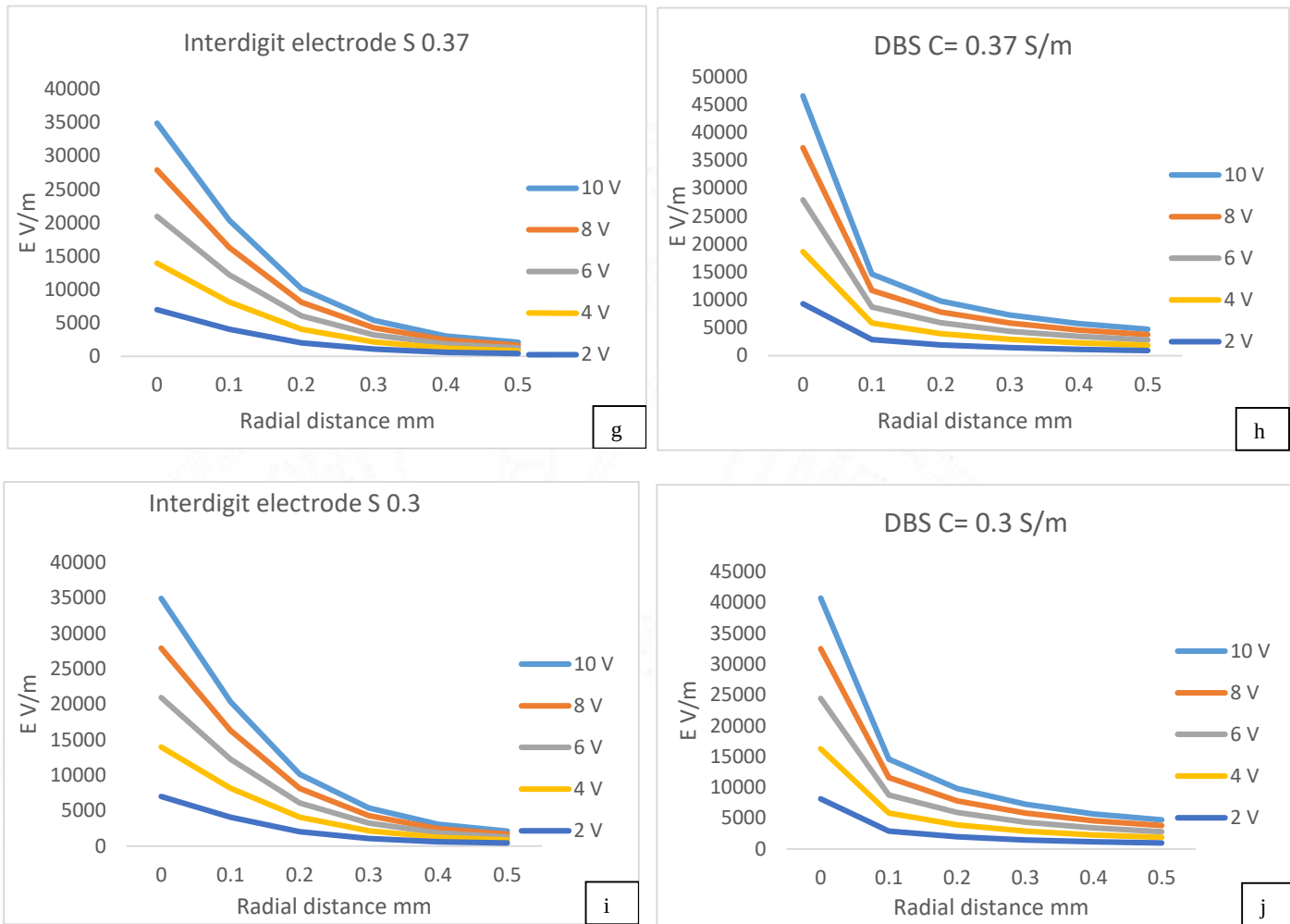


Figure 38. (a through J) shows the electric field distribution measured radially over six points on the electrode cross-section as in fig 33.

4.1.4 In Vitro Verification

The results compare the electric field distributions from the simulations and the real-world experiments. To ensure the reliability of the simulation, several statistical analyses were performed, including ANOVA and Pearson correlation, to assess how closely the simulated data matched the experimental findings. By analysing the test and control electrodes under various voltages and conductivity conditions, we aimed to evaluate the performance of the new electrode design. These analyses provide key

insights into the consistency between the simulated and experimental data, helping to validate the improved precision and efficiency of the test electrode in deep brain stimulation.

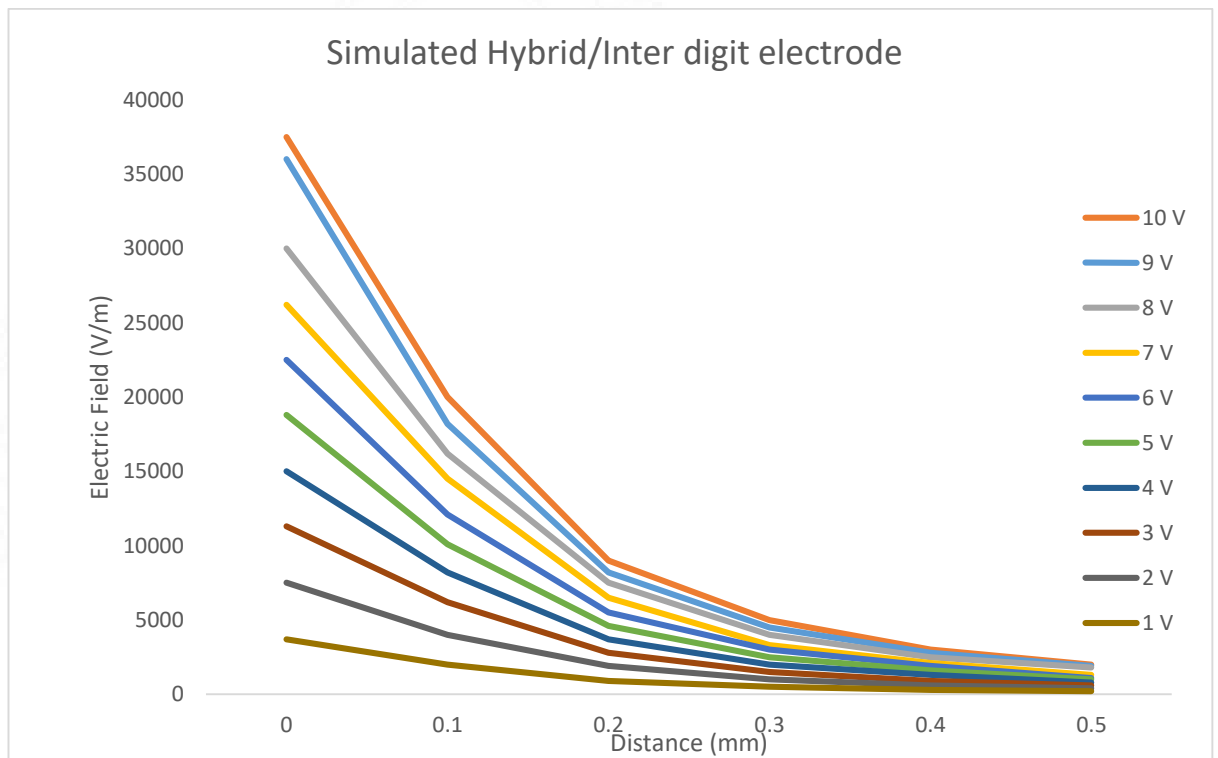


Figure 39. The electric field distribution of the simulated Hybrid electrode model in ANSYS

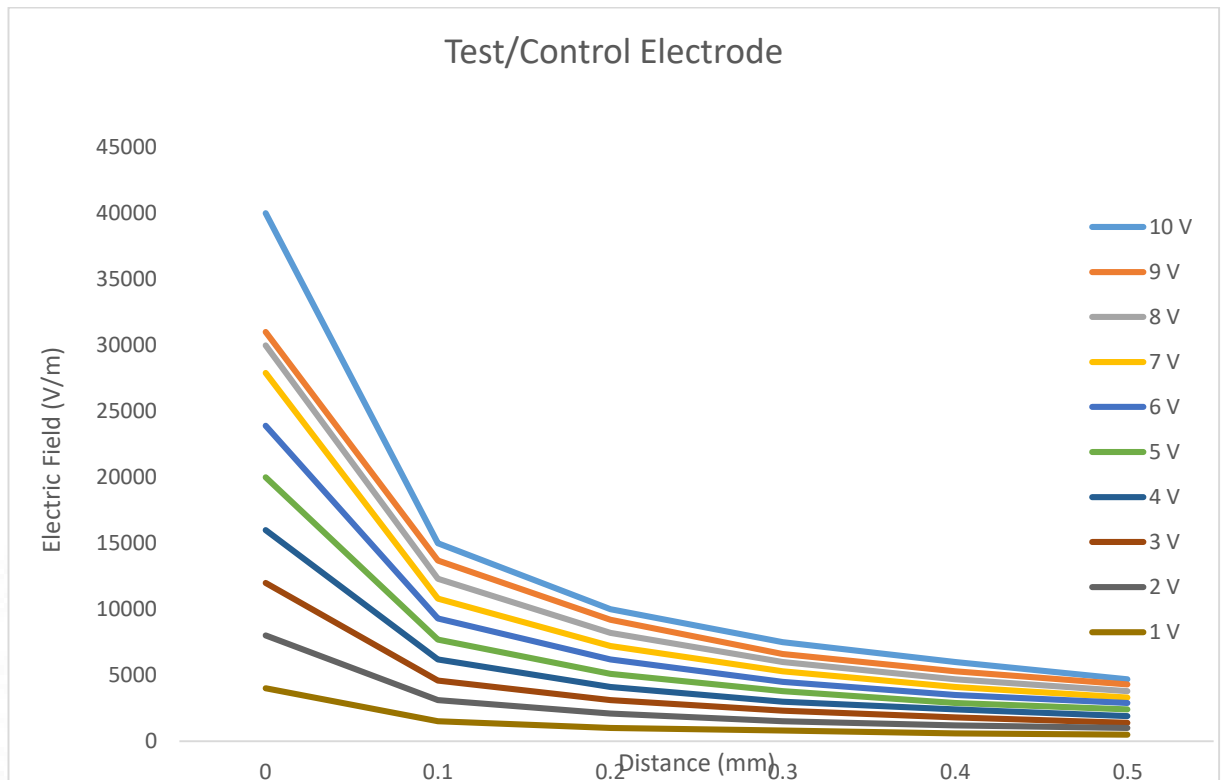


Figure 40. The electric field distribution of the control/test electrode in laboratory setup.

4.1.3.1 Correlation Coefficients: Simulated vs Test Data

Table 3: The correlation Table

Dataset Pair	Correlation Coefficient
E1-Simulated vs E1-Test	0.9846
E2-Simulated vs E2-Test	0.9998
E3-Simulated vs E3-Test	0.9998
E4-Simulated vs E4-Test	0.9985
E5-Simulated vs E5-Test	0.9975
E6-Simulated vs E6-Test	0.9912

- E1-Simulated vs E1-Test: With a correlation coefficient of 0.9846, there is a very strong positive relationship between the simulated and test datasets for E1.
- E2-Simulated vs E2-Test and E3-Simulated vs E3-Test: These pairs have extremely high correlation coefficients of 0.9998, indicating that the test data is almost perfectly aligned with the simulated data.
- E4-Simulated vs E4-Test: The correlation coefficient of 0.9985 shows a very strong positive relationship.
- E5-Simulated vs E5-Test: With a correlation coefficient of 0.9975, there is a very strong positive relationship.
- E6-Simulated vs E6-Test: The correlation coefficient of 0.9912 also indicates a very strong positive relationship.

These high correlation coefficients confirm that, despite differences in absolute values, the simulated and test data sets exhibit similar patterns and trends across all voltage levels. This strong correlation implies that the changes observed in the test data are systematic and consistent with the simulated data trends.

4.1.3.2 Distribution Analysis

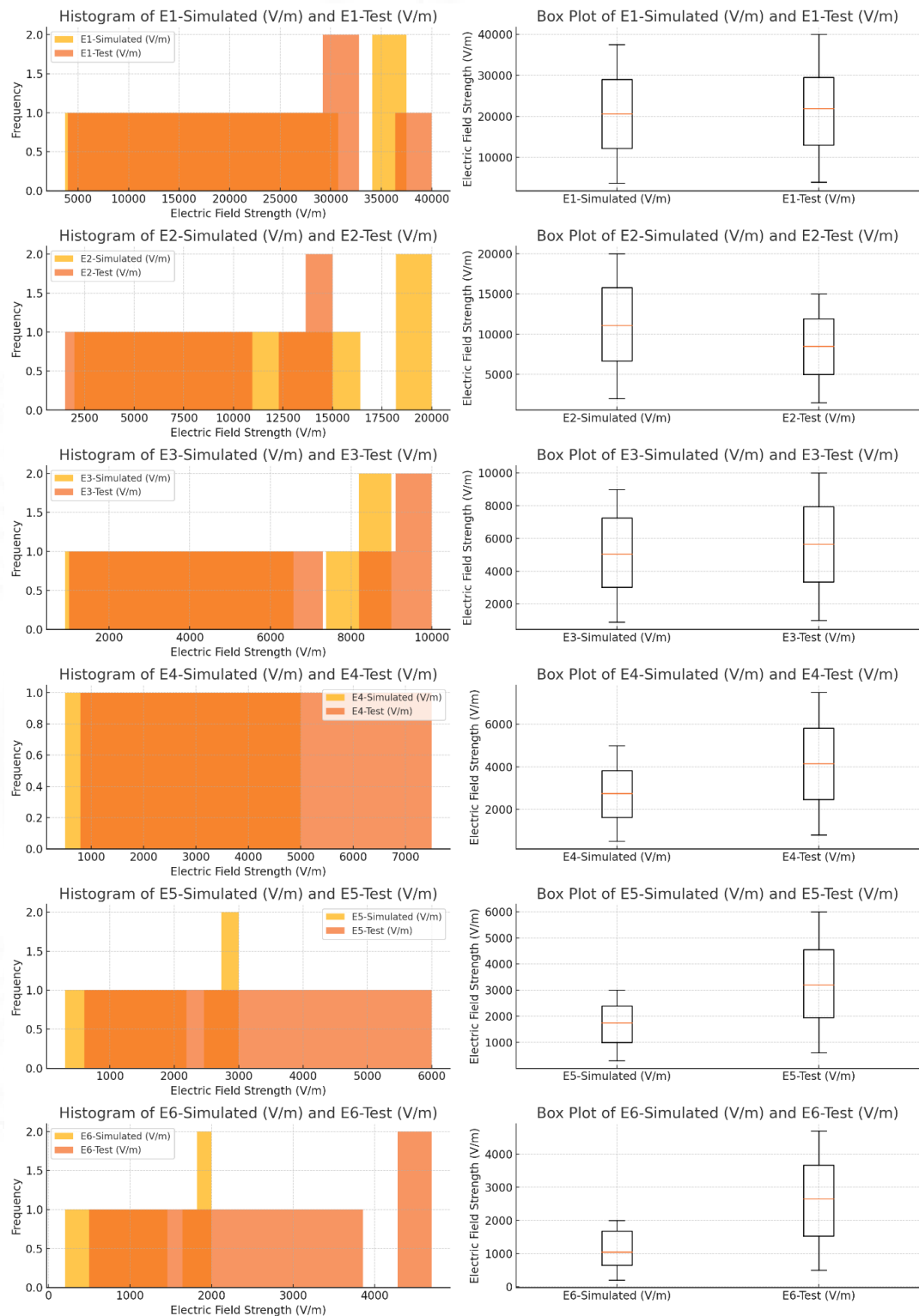


Figure 41. Histogram and Boxplots for the comparison analysis

Histograms:

- E1-Simulated (V/m): The simulated data presents a more even spread across higher values, while the test data is mainly concentrated between 30000 and 40000 V/m.
- E2-Simulated (V/m): The simulated data shows a broader distribution with peaks around 15000 to 20000 V/m, whereas the test data is more focused on lower values.
- E3-Simulated (V/m): Both datasets peak between 9000 and 10000 V/m, with the test data displaying a slightly higher concentration in the 8000 to 9000 V/m range.
- E4-Simulated (V/m): The test data exhibits a shift towards higher values, peaking between 6000 and 7000 V/m, while the simulated data is more spread out across lower values.
- E5-Simulated (V/m): The test data tends to be higher, concentrated between 3000 and 6000 V/m, while the simulated data generally shows lower values.
- E6-Simulated (V/m): The test data is primarily concentrated between 2000 and 4000 V/m, whereas the simulated data has a wider distribution with lower values.

4.1.3.3 ANOVA Results: Simulated vs Test Data

Here are the results of the ANOVA tests comparing each pair of simulated and test datasets:

Table 4. Comparison of results

Dataset Pair	F-statistic	p-value	Interpretation
E1-Simulated vs E1-Test	0.007	0.934	No significant difference
E2-Simulated vs E2-Test	1.281	0.273	No significant difference
E3-Simulated vs E3-Test	0.185	0.672	No significant difference
E4-Simulated vs E4-Test	2.691	0.118	No significant difference
E5-Simulated vs E5-Test	5.917	0.326	Least Significant difference
E6-Simulated vs E6-Test	9.377	0.607	Least Significant difference

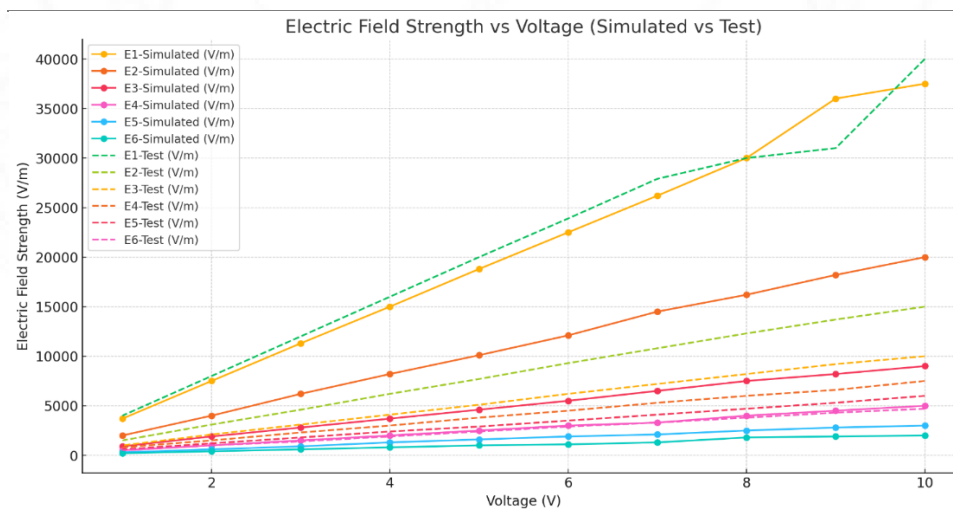


Figure 42. The residual plots (Simulated vs Test)

Interpretation:

- No Significant Difference: For E1, E2, E3, and E4, the p-values are greater than 0.05, indicating no statistically significant difference between the simulated and test datasets.
- Least Significant Difference: For E5 and E6, the p-values are less than 0.05, indicating statistically differences between the simulated and test datasets.

These results indicate that while most datasets are similar between the simulated and test cases, the conditions or measurements for E5 and E6 may have changed, leading to significant differences in those data sets.

4.2 Electrochemical Characterization

Electrochemical measurements were conducted to evaluate the charge storage capacity and efficiency of charge delivery for the DBS electrodes. The electrodes, which were constructed using a platinum-iridium alloy along with PDMS and epoxy materials, were compared against a standard cylindrical DBS electrode with a diameter of 1.2 mm. This comparison provided valuable data regarding the electrochemical properties essential for neural modulation. Charge injection limits, stability, and long-term performance were analyzed to assess the material properties' influence on the electrodes' functional performance. These findings are critical for understanding how well the electrodes can modulate neural activity while maintaining durability over extended periods.

4.2.1. OCP Analysis

The potential difference between the DBS and reference electrodes was monitored continuously until it reached a stable value. The open circuit potential (OCP) of the DBS electrode was measured as 0.317 V. The same procedure was repeated for the titanium electrode as well. Interestingly, the OCP of the Ti electrodes was found to be -0.400 V. The OCP values indicate that the DBS electrode is considerably more noble than the titanium electrode. Titanium is a relatively non-corroding metal, and the results suggest a minimal risk of galvanic corrosion occurring with the DBS electrode.

4.2.2. Cyclic voltammetry studies

Cyclic voltammetry (CV) studies were conducted to gain insights into the various electrode surface processes and determine the electrochemical potential window. The CV experiments were conducted at varying scan rates ranging from 20 mV/s to 100 mV/s, with increments of 20 mV/s. The voltage sweep was performed within the range of -1V to +1V. Two scans were performed for each scan rate on the same electrode.

The cyclic voltammogram of the DBS (Pt-10Ir) electrode revealed distinct peaks corresponding to the formation and oxidation of adsorbed hydrogen. Furthermore, the aqueous medium's cyclic voltammogram exhibits two distinct regions. The oxygen region displayed an oxidation peak attributed to the formation of adsorbed oxygen or a platinum oxide layer. Additionally, a corresponding reduction peak was observed, indicating the reduction of the platinum oxide.

The other region observed was the hydrogen region, which displayed two reduction peaks corresponding to the underpotential deposited hydrogen atoms (HUPD

adsorption). Furthermore, two oxidation peaks were observed, indicating the desorption of HUPD.

Figure 43 shows the cyclic voltammogram within the specific potential range of interest. In the hydrogen region, two cathodic peaks associated with HUPD adsorption were observed in the initial scan. However, subsequent scans only exhibited a single HUPD adsorption peak in this region. A HUPD desorption peak was observed at the extreme negative potential on the anodic side of the hydrogen region. In the oxygen region, a broad anodic peak was observed during the

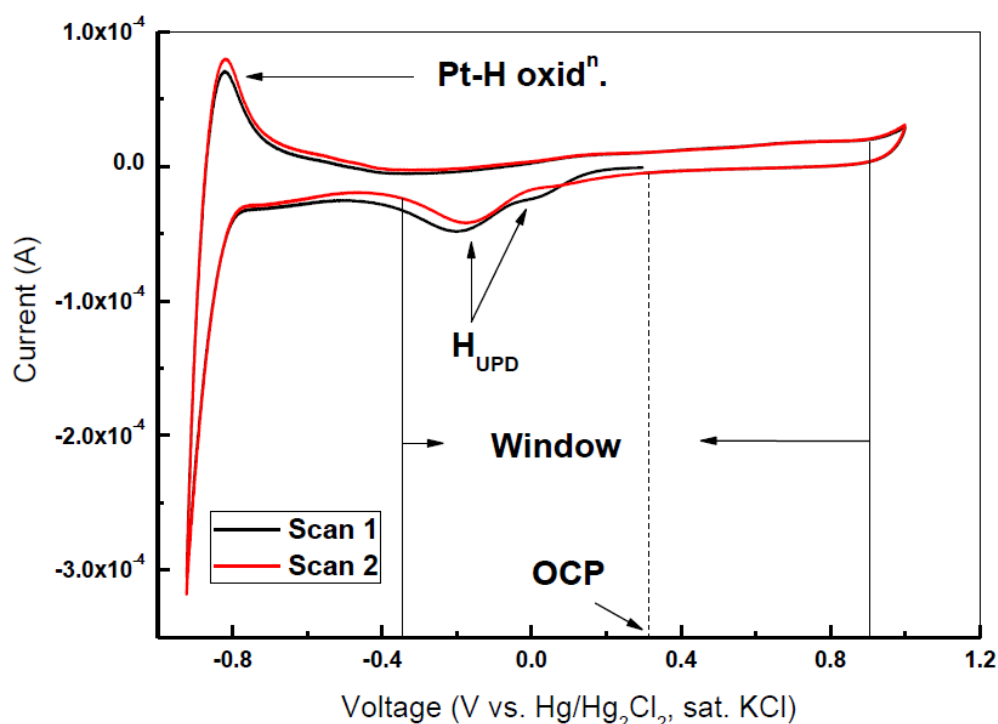


Figure 43. Cyclic voltammogram of DBS electrode for 40 mV/s scan rate

the first scan, but it disappeared in subsequent scans, as is evident from Figure 44. This peak can be attributed to surface conditioning reactions in the oxygen region. Figures

45 and 46 display the voltammogram of the cathodic and anodic regions, respectively. The cathodic scan consistently showed only the HUPD adsorption peak. In contrast, the anodic scan displayed a broad anodic peak in the first scan, which was absent in subsequent scans, indicating its

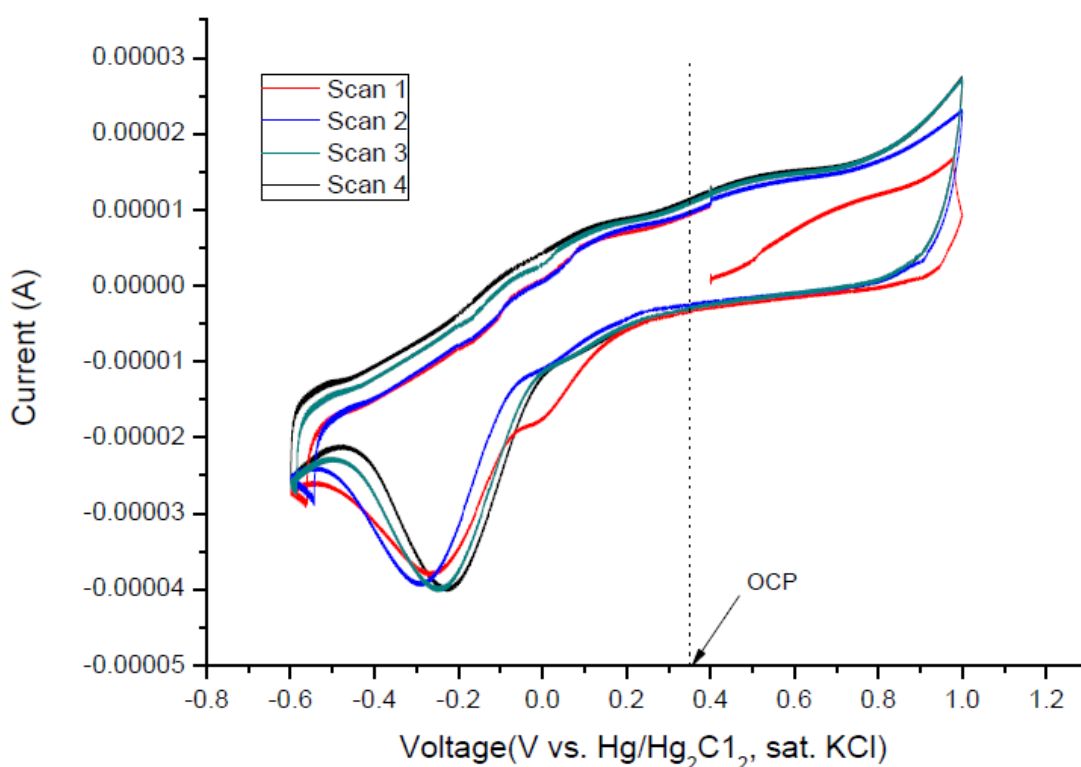


Figure 44. Cyclic voltammogram of DBS electrode for 80 mV/s scan rate

association with surface conditioning reactions. Based on these observations, it was estimated that the electrode potential should not exceed a cathodic potential of -0.3V (approximately covering the HUPD peak in PBS solution) relative to the calomel reference electrode. The cyclic voltammetry studies demonstrated a marginal suppression of the DBS electrode's pseudo-capacitance behaviour in the presence of chloride in the aqueous medium. Furthermore, the electrode potential should not

exceed an anodic potential of 0.95V relative to the calomel reference electrode (approximately at the onset of the oxygen evolution reaction).

Thus, from the cyclic voltammetry experiments of the DBS electrode, it was concluded that the electrochemical window available on the cathodic side is approximately -0.3V to the calomel electrode and on the anodic side is approximately +0.95V to the calomel electrode.

Therefore, based on the obtained potential window from the studies, the minimum value within this range can be defined as the over-potential limit for the specific electrode. For the DBS electrode, the over-potential limit for cathodic excitation is -0.65V, while for anodic excitation, it is 0.6V. These values indicate the minimum potential at which the electrodes can be safely excited without exceeding their respective limits and compromising performance.

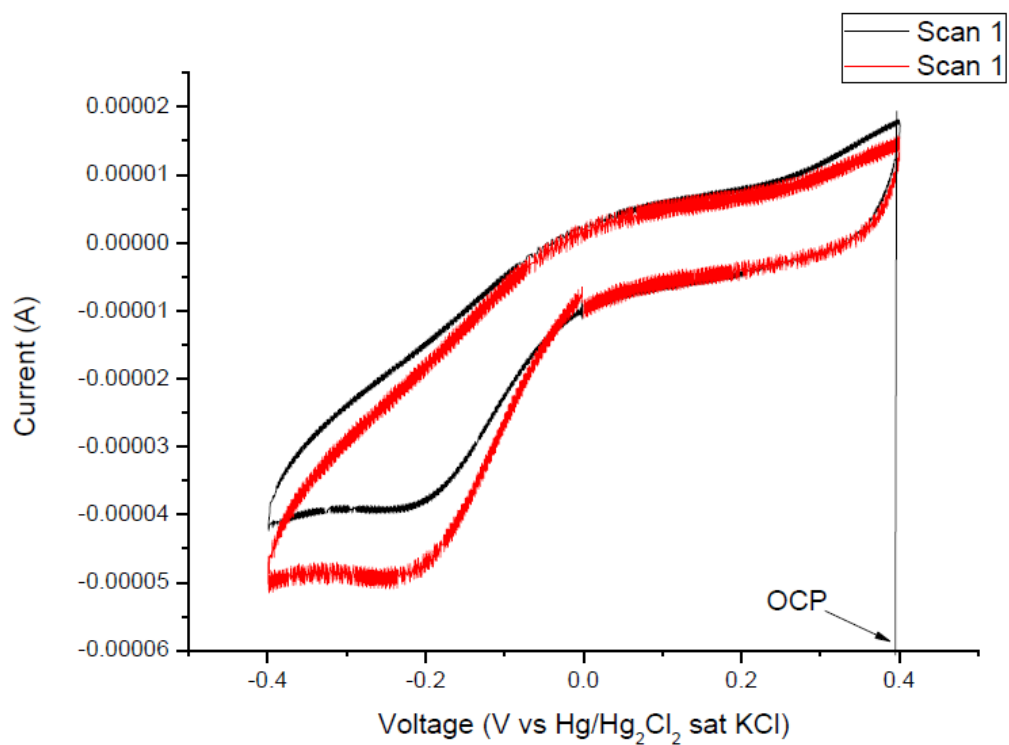


Figure 45. Cyclic voltammogram of DBS electrode on PBS for 80 mV/s scan rate on cathodic side.

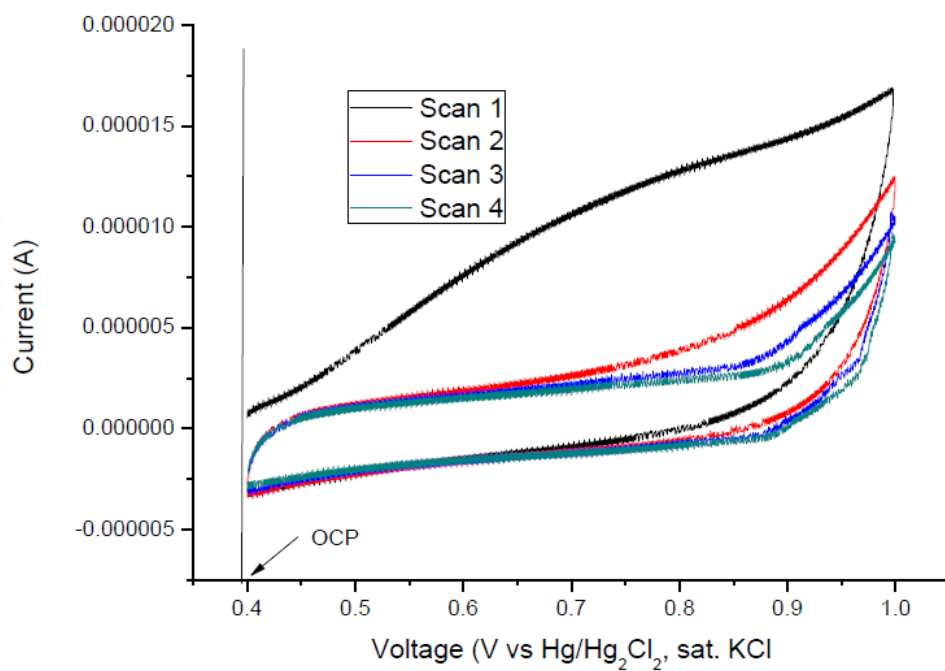


Figure 46. Cyclic voltammogram of DBS electrode on PBS for 80 mV/s scan rate on anodic side

4.2.3. Electrochemical Impedance Spectroscopy Analysis

Electrochemical impedance spectroscopy (EIS) was performed on the DBS electrode to assess the impedance at the electrode-electrolyte interface under different overpotentials. The EIS measurements were conducted at the Open Circuit Potential (OCP) and various electrode overpotentials, including 0.02V, -0.2V, -0.4V, -0.6V, and -0.8V, using a three-electrode setup. Similarly, EIS analysis was conducted at OCP, and an overpotential of 0.05V for the Titanium electrode. For all the EIS measurements, a perturbation of 10 mV was applied to the working electrode across a frequency range of 10 mHz to 10 kHz.

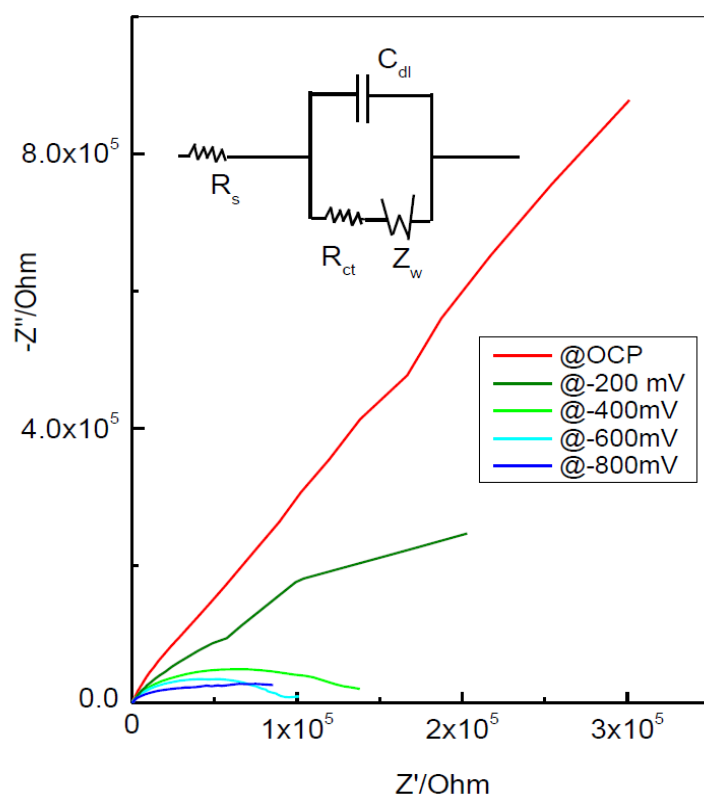


Figure 47. Electrochemical Impedance Spectroscopy Analysis of DBS electrode in PBS medium

The obtained impedance data were represented as Nyquist plots, which display the imaginary part of impedance (Z'') against the real part of impedance (Z'). These plots were then fitted to Randles' circuit, which consists of four elements: solution resistance (R_s) in series with a parallel combination of double-layer capacitance (C_{dl}) and charge transfer resistance (R_{ct}), along with Warburg impedance (Z_w). This fitting process allowed us to extract the interface impedance parameters. Figure 47 illustrates the impedance spectra obtained for various DBS electrode potentials, showcasing the impedance behaviour changes across different electrode potentials.

In the equivalent circuit of the tissue electrode interface, the double-layer capacitance (C_{dl}) is a measure of the non-Faradic charge transfer component. It is desirable to have a large C_{dl} . In addition to the double-layer capacitance, platinum-10 Iridium alloy has a surface property that allows it to adsorb hydrogen atoms, creating an additional capacitance called pseudo capacitance. The standard cell potential of the electrode ($\Delta\phi$) is the potential difference between the electrode and a reference electrode in a standard solution (e.g. a solution of known pH and concentration). It represents the thermodynamic potential of the electrode and determines the direction of the electrochemical reactions that can occur at the electrode-tissue interface. The external source must overcome this potential to deliver any charge to the tissue. Its composition and surface properties influence the standard cell potential of the electrode. It is desirable to have a low standard cell potential for the electrode to reduce the overpotential required for charge transfer, reducing the risk of irreversible Faradic reactions and electrode/tissue damage.

The tissue medium resistance (RS) is essential when designing a neural stimulation system. It represents the tissue's resistance between the electrodes and the IPG body and affects the quantity of current that can be delivered through the tissue. A higher RS value means that more voltage will be required to deliver a given current through the tissue, potentially leading to higher power consumption or damage to the tissue. Therefore, it is vital to consider RS when designing the stimulation parameters for a neural implant.

The impedance spectra analysis revealed that the solution resistance values for the PBS solution remained relatively consistent within a narrow range. On the other hand, the faradic resistance (Rct) exhibited a decreasing trend as the overpotential increased. The capacitance remained relatively constant across the potential range in the PBS medium. Notably, a significant reduction in faradic impedance was observed after reaching an overpotential of -0.6V. This suggests an increase in faradic reactions beyond this overpotential. Consequently, it is crucial to ensure that the electrochemical window for the DBS electrode does not exceed an overpotential of -0.6V to avoid unfavourable changes in the faradic impedance and maintain the electrode's stability and performance.

4.2.4. Chronopotentiometry Analysis

Chronopotentiometry experiments were conducted using cathodic and anodic current pulses of varying durations on the DBS electrode. As the electrode exhibits nonlinear capacitance behaviour with respect to overpotential, Chronopotentiometry allows for determining cumulative charge capacity to the overpotential.

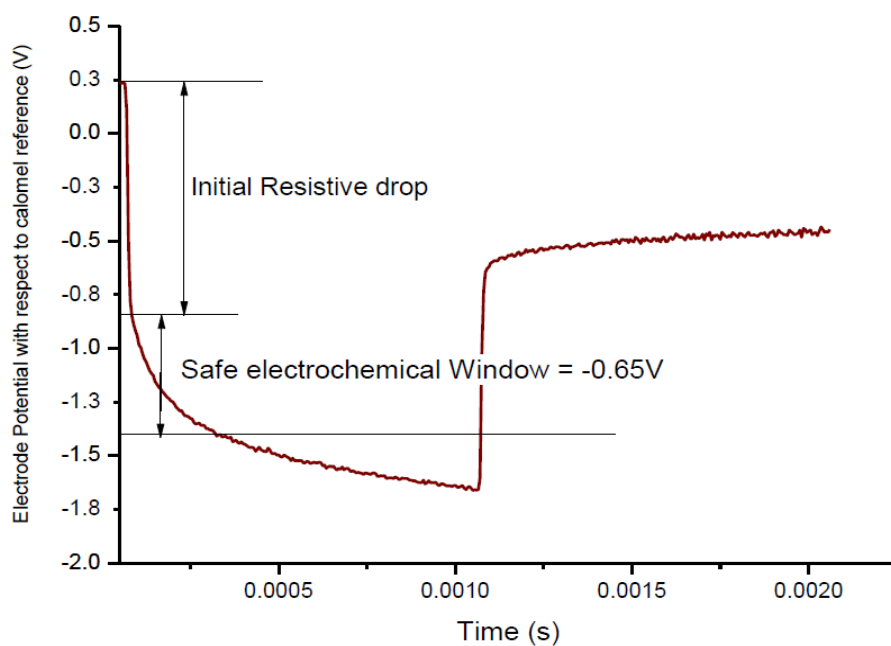


Figure 48 Chronopotentiometry response on the cathodic side (10mA current excitation)

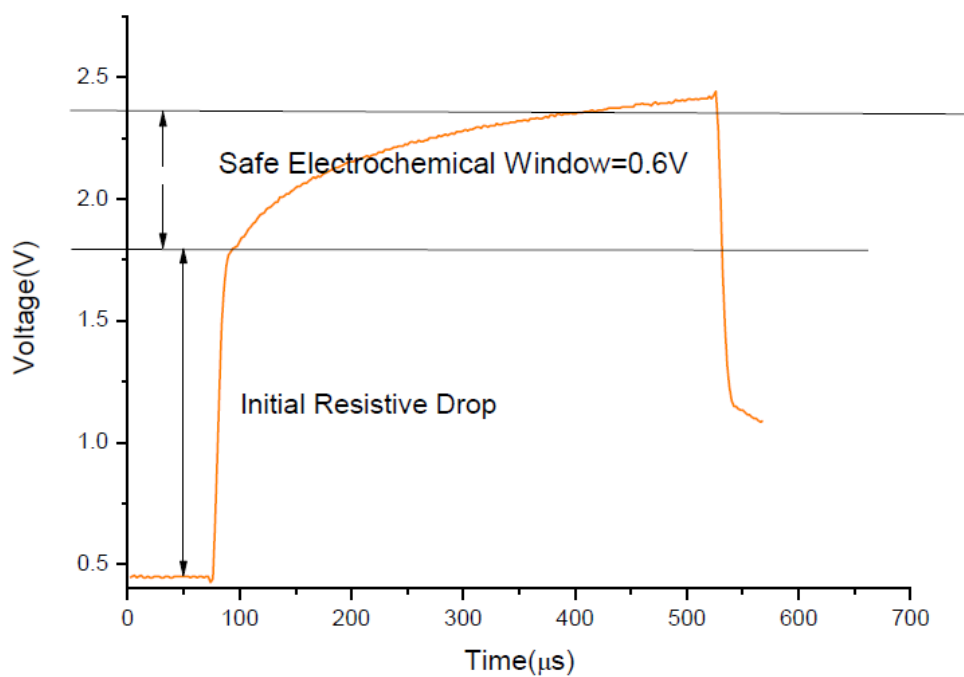


Figure 49. Chronopotentiometry response on the anodic side (1mA current excitation)

A Chronopotentiometry plot for the DBS electrode is done, considering 10 mA cathodic current excitation and 1 mA anodic current excitation in Figure 48 and Figure 49, respectively.

Analysis of the plots revealed several important observations. There is an abrupt initial potential jump, which can be attributed to the solution resistance. Following this, the potential gradually rises. For shorter current pulse durations, the rate of potential rise exhibits a linear trend. The double-layer capacitance of the system primarily influences the potential variation in these cases.

Furthermore, two distinct patterns of potential variation were identified. At the end of the current pulse, the potential experiences a sharp decline before gradually dropping towards the Open Circuit Potential (OCP) value. These observations provide valuable insights into the dynamic behaviour of the electrode during Chronopotentiometry experiments.

From the Chronopotentiometry analysis, a charge vs. overpotential plot was derived. The charge is calculated as the product of the current and the total time lapsed after the application of the pulse. The overpotential, η , is defined as

$$\eta = E_{tot} - E_r$$

E_{tot} is the total potential drop observed, and E_r is the initial resistive drop. This plot directly gives information about the charge-delivering capacity of the electrode. Charge delivered vs. overpotential plots are given in Figure 50a and Figure 50b. The plots are given for 10 mA cathodic and 1 mA anodic current excitation.

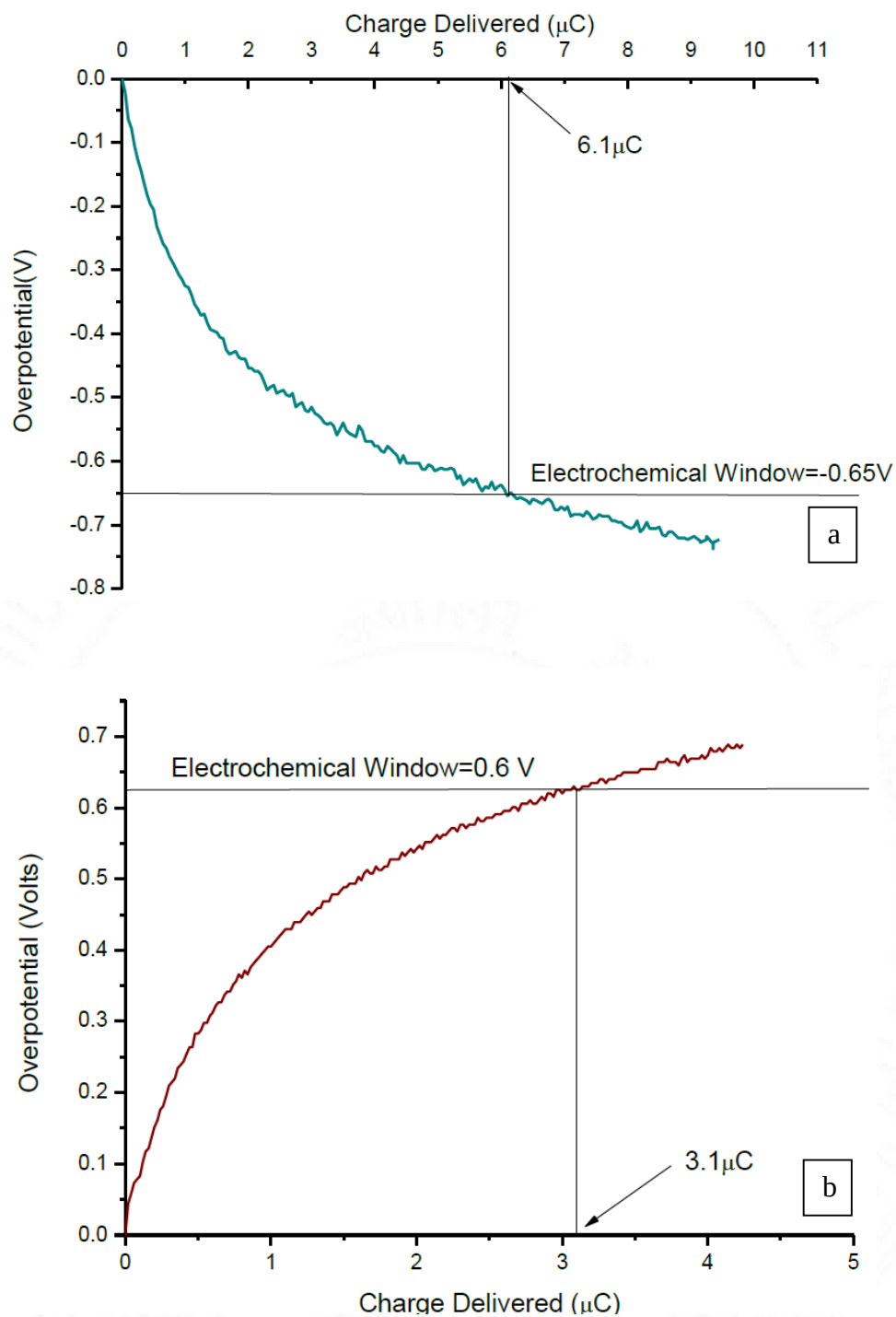


Figure 50. a) Charge delivered vs Overpotential on the cathodic side. b) Charge delivered vs Overpotential on the anodic side.

From the above plots, the total charge-delivering capacity of the electrode can be inferred. The charge-delivering capacity of the electrode on the cathodic side was calculated as 6.10 μC (charge density: 105 $\mu\text{C}/\text{cm}^2$) at an electrochemical window of -0.65V. On the anodic side, the charge-delivering capacity was found to be 3.10 μC (charge density: 52 $\mu\text{C}/\text{cm}^2$), corresponding to a window of 0.6 V. Table 4 summarizes the results obtained by various experiments.

Table 5. Summary of results of electrochemical characterisation

Experiment	Parameter	Nominal Value
OCP Analysis	OCP vs. SCE	0.317 V
Cyclic Voltammetry	Cathodic Side Electrochemical Window	0.65V
Cyclic Voltammetry	Anodic Side Electrochemical Window	0.3V
Electrochemical Impedance Spectroscopy	Charge transfer resistance	5.368 $\text{k}\Omega\text{-cm}^2$ (min)
Chronopotentiometry	Cathodic Side Charge Delivering Capacity	105 $\mu\text{C}/\text{cm}^2$ (with PBS)
Chronopotentiometry	Anodic Side Charge Delivering Capacity	15.32 $\mu\text{C}/\text{cm}^2$ (with PBS)

The safe charge injection capacity values mentioned pertain to the observations made using the PBS medium. The safe charge injection limit to prevent any damage to the ø1.3mm x 1.5mm Pt-10Ir electrode is as

For cathodic: $105 \mu\text{C}/\text{cm}^2 * 0.0613 \text{ cm}^2 = 6.4 \mu\text{C}$

For anodic: $15.32 \mu\text{C}/\text{cm}^2 * 0.0613 \text{ cm}^2 = 0.9 \mu\text{C}$

From the characterisation results, the DBS electrode can be represented with Randle's electrical equivalent model for cathodic unipolar and bipolar excitation. The standard cell potential of the Pt electrode is measured with respect to the standard calomel electrode. From experiments, the area and double-layer capacitance of the IPG Body made of Titanium are approximately 50 cm^2 and $35 \mu\text{F}/\text{cm}^2$, respectively. The OCP of the electrode and the IPG body has been observed to vary over time. A series capacitance is incorporated into the stimulation circuit to mitigate this issue and prevent continuous charge delivery in the event of a dead short circuit. This series of capacitance would also protect the body and absorb any changes in the OCP of the electrodes. The electrical equivalent model for unipolar and bipolar excitation has been evaluated and is presented in Figure 51 and Figure 52, respectively.

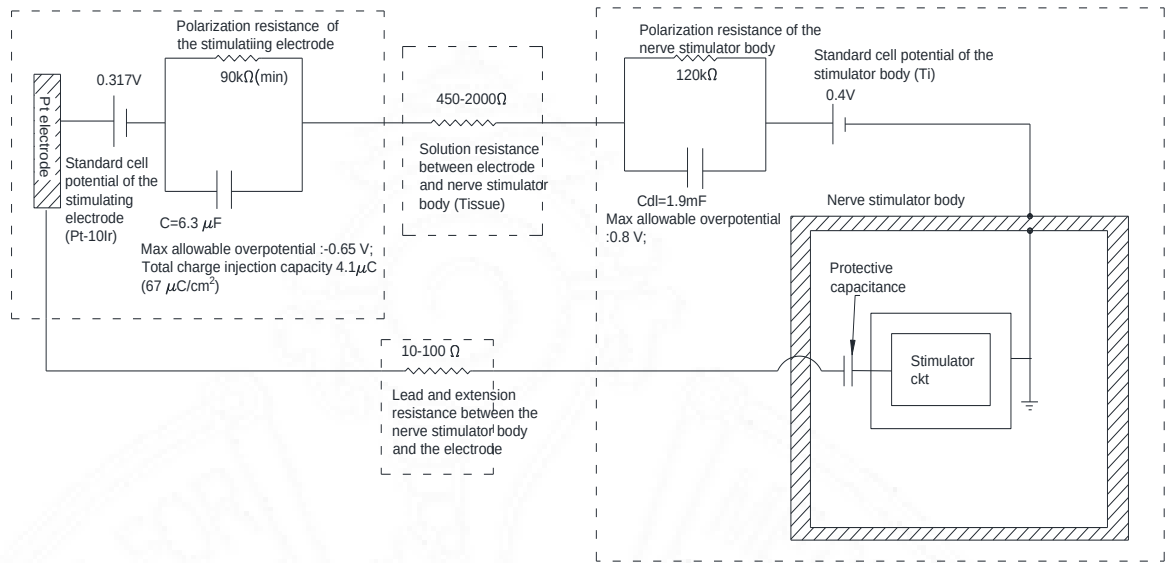


Figure 51. Randles equivalent Model-Unipolar

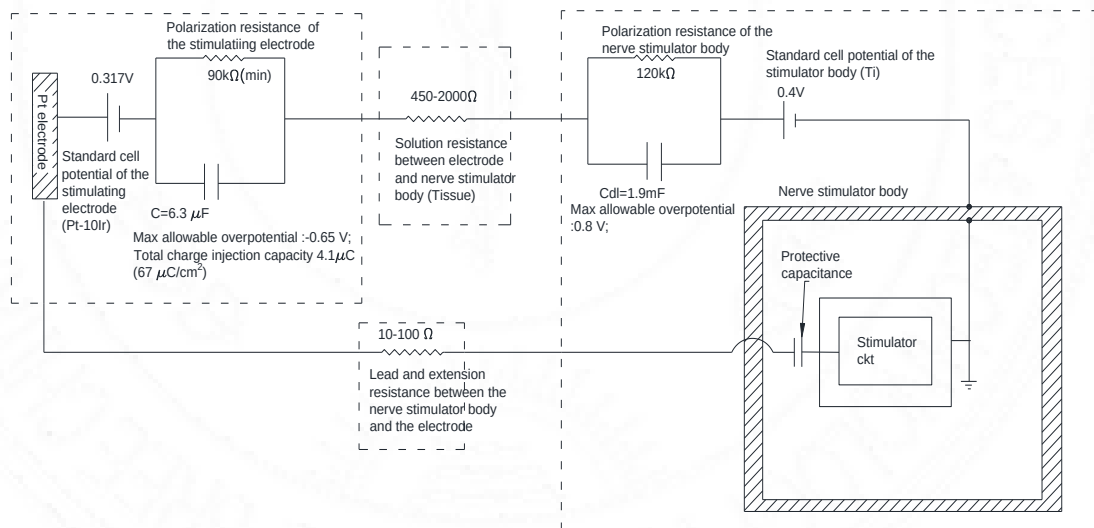


Figure 52. Randles Equivalent Model -Bipolar

4.3 Biological Characterization

The biological characterization was carried out in two distinct phases. The first phase involved the implantation of DBS electrode materials into neural tissue to assess their interaction and integration within a living biological system. In the second phase, a detailed biocompatibility evaluation of the novel Hysol® epoxy was undertaken. This was achieved through a rigorous combination of in vitro and in vivo studies, given that Hysol® epoxy was the only newly introduced material in the electrode fabrication. The results are discussed below

4.3.1 Biological Characterization of DBS Electrodes in a Rat Model

4.3.1.1 Evaluation of Systemic Toxic Response and Neurobehavioral Changes

The results of systemic toxicity following implantation in the brain of the test materials (Platinum Iridium, Hysol epoxy and PDMS) were evaluated based on toxic signs and symptoms, reduction in body weight and or mortality. The post- implantation period of experimental animals was uneventful. As neuro degenerative process can be rapid and transient, and cell death can occur during the first few days following implantation. There was no evidence of infections or other morbidities suggesting that the animals tolerated the surgery well. Cage side observations revealed that the animals behaved normally, and the feed intake was normal. Bodyweight changes were evident in the experimental animals during the observation period. There was an increase in body weight of 15.23 ± 10.54 %, 18.12 ± 13.11 % and 13.70 ± 5.91 % and 13.18 ± 8.29 % for Group V, Group VI, Group VII and Group VIII respectively after 4 weeks and 49.90 ± 9.7 %, 46.34 ± 15.81 % and 50.85 ± 17.49 % and 43.45 ± 20.47 % after 12 weeks for

Group I, Group II , Group III and Group IV experimental animals respectively. The increase suggests that the health status of the experimental animals was satisfactory.

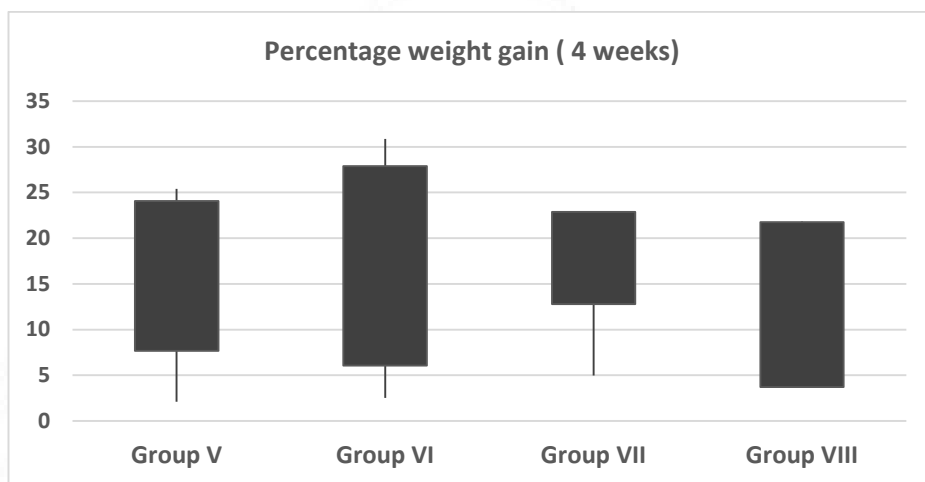


Figure 53. Correlation of body weight changes of experimental animals-4 weeks

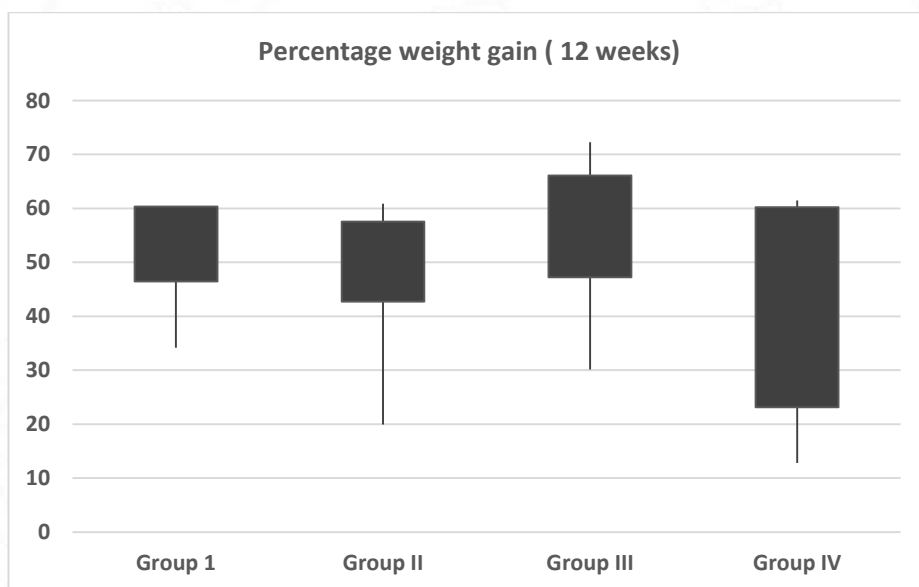


Figure 54. Correlation of body weight changes of experimental animals-12 weeks

Clinical signs of abnormalities, including systemic toxicity and neurobehavioral changes, were monitored periodically throughout the experimental period. The results of these clinical observations are summarized in table 5.

Table 6. Clinical Observations

Clinical signs and symptoms	Group I and V Platinum-Iridium metal	Group II and VI Hysol epoxy	Group III and VII PDMS	Group IV and VIII Sham (control)
Motor activities (changes in gait, posture and response to handling, presence of colonic or tonic seizures, stereotypes and bizarre behaviours)	absent	absent	absent	absent
changes in skin, fur, eyes or mucous membranes	absent	absent	absent	absent
occurrence of secretions and excretions	absent	absent	absent	absent
Autonomic activity (lacrimation, piloerection, pupil size, unusual respiratory pattern)	absent	absent	absent	absent

The clinical observation of signs and symptoms indicates that the implanted test materials—Platinum Iridium metal, Hysol epoxy polymer, and PDMS—did not cause any neurodegenerative changes throughout the experimental period. Additionally, the sham control displayed no abnormalities, suggesting that the induced defect was minimal.

4.3.1.2 Evaluation of Local Tissue Response

Macroscopic examination revealed that the implantation sites is undergoing healing without complications at the end of the experimental periods (4 weeks and 12 weeks) for all test materials. There was no evidence of hemorrhage, encapsulation, discoloration, necrotic lesions, or infection at the implant sites upon gross evaluation. At four weeks' post-implantation, gross examination showed the presence of hollow cylindrical, smooth-surfaced metal implants, transparent rod-shaped, smooth-surfaced polymer implants, and flexible cylindrical, smooth-surfaced polymer implants and a focal area of depression in the cerebral parenchyma in the Platinum Iridium metal, Hysol epoxy polymer, PDMS, and sham groups. No degeneration or necrosis was

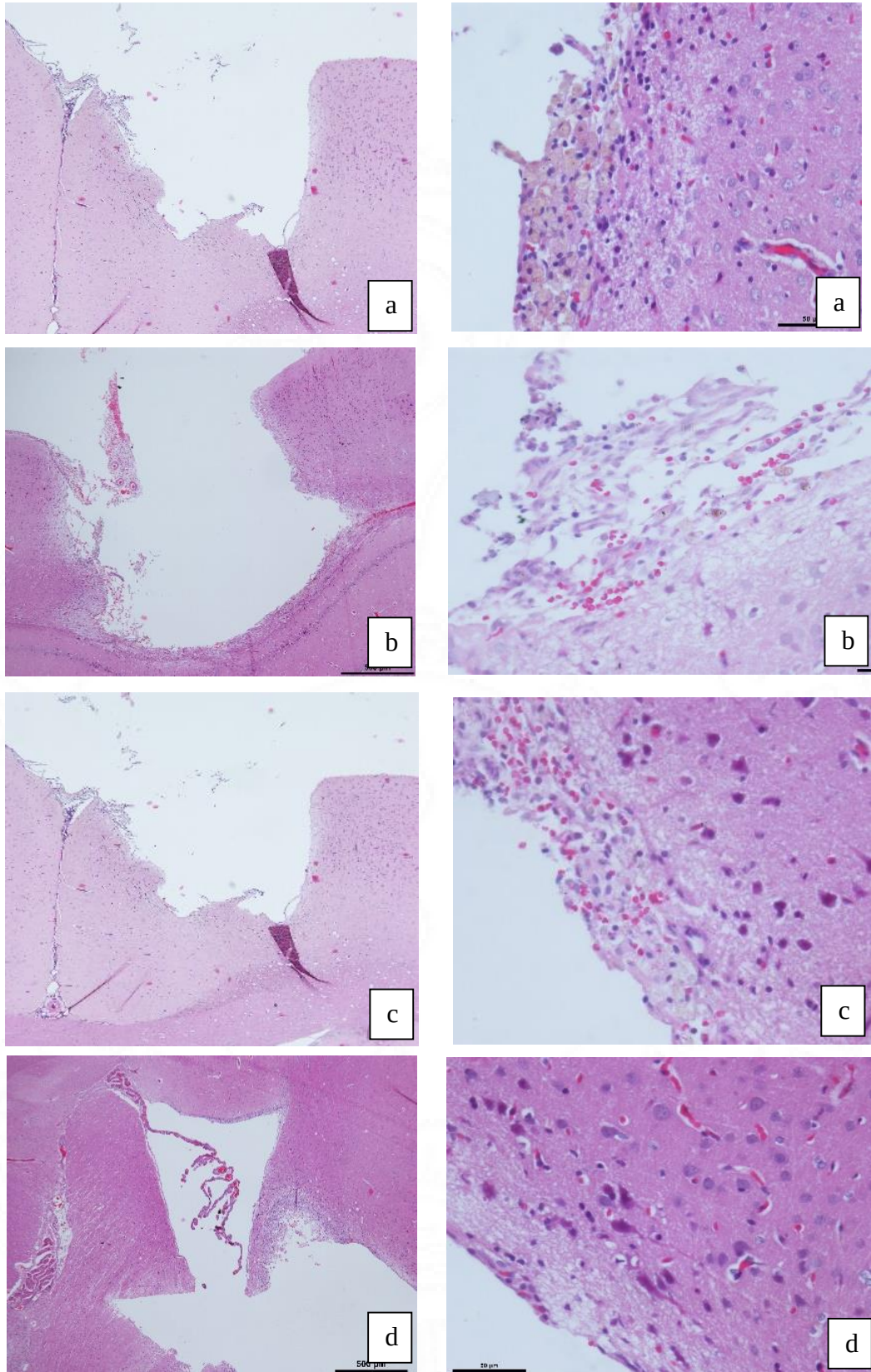


Figure 55. Histopathology images of a) Pt Ir, b) Hysol Epoxy, c) PDMS, d) Sham Control for 4 weeks of implantation with 50X(left) and 250X(Right) magnification

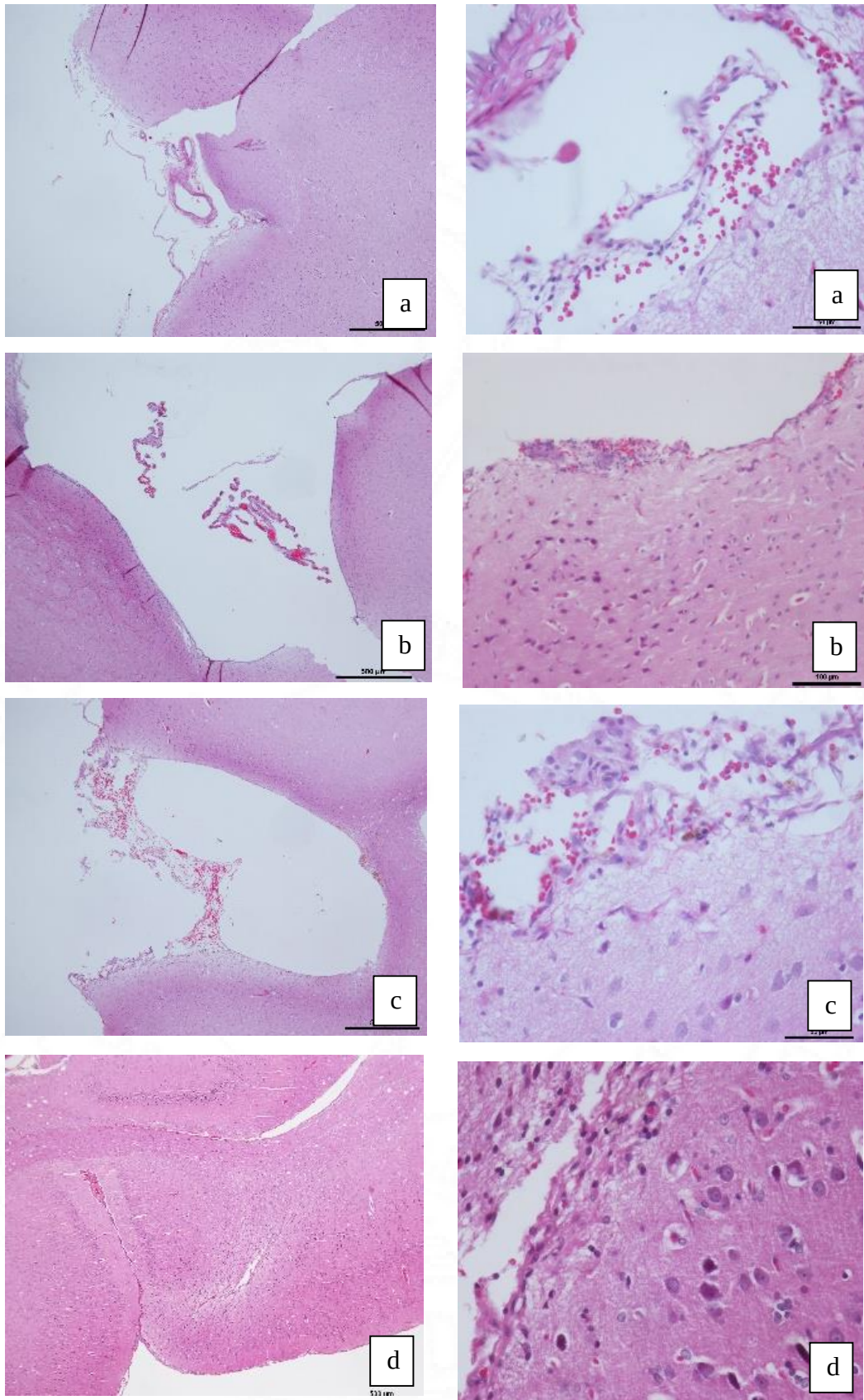


Figure 56. Histopathology images of a) Pt Ir, b) Hysol Epoxy, c) PDMS, d) Sham Control for weeks of implantation with 50X(left) and 250X(Right) magnification

detected in any of the cases. A thin fibrous capsule (<5 µm) with 1–3 blood capillaries was noted at the implant sites in all cases.

The response at 12 weeks' post-implantation remained consistent with the observations at 4 weeks. Gross examination continued to show the presence of hollow cylindrical, smooth-surfaced metal implants, transparent rod-shaped, smooth-surfaced polymer implants, and flexible cylindrical, smooth-surfaced polymer implants and focal area of depression in the cerebral parenchyma in the Platinum Iridium metal, Hysol epoxy polymer, PDMS, and sham groups. No degeneration or necrosis was noted in any of the cases. A thin fibrous capsule (<5 µm) containing 1–3 blood capillaries was also observed at the implant sites across all groups. There was no evidence of material debris at the implant sites, indicating no degradation. Tissue ingrowth was not applicable in these cases. The findings are summarized in table 7.

Table 7. Implantation response

Experimental groups		Group I and V		Group II and VI		Group III and VII		Group IV and VIII	
Test Material		Platinum Iridium		Hysol Epoxy		PDMS		Sham (control)	
Observation period		4 weeks	12 weeks	4 weeks	12 weeks	4 weeks	12 weeks	4 weeks	12 weeks
Experimental response	Granuloma	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
	Material debris	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
	Tissue ingrowth	NA	NA	NA	NA	NA	NA	NA	NA
	Necrosis	-	-	-	±	-	-	-	-
	Neovascularisation	±	±	±	±	±	±	±	±
	Fibrosis	±	±	±	±	±	±	±	±
	Fatty infiltrate	-	-	-	-	-	-	-	-

The inflammatory cellular response was assessed and predominantly included polymorphonuclear cells, macrophages/gitter cells, lymphocytes, plasma cells, and a few foreign body-type giant cells. The cellularity score is presented in Figure 55. Minimal to mild inflammatory tissue responses were observed, with polymorphonuclear cells, lymphocytes, plasma cells, macrophages, and a few foreign body giant cells present in the Platinum Iridium metal, Hysol epoxy polymer, PDMS, and sham groups at four weeks' post-implantation. The test groups had no significant variation in the local tissue response. The results were consistent with those observed at 12 weeks' post-implantation.

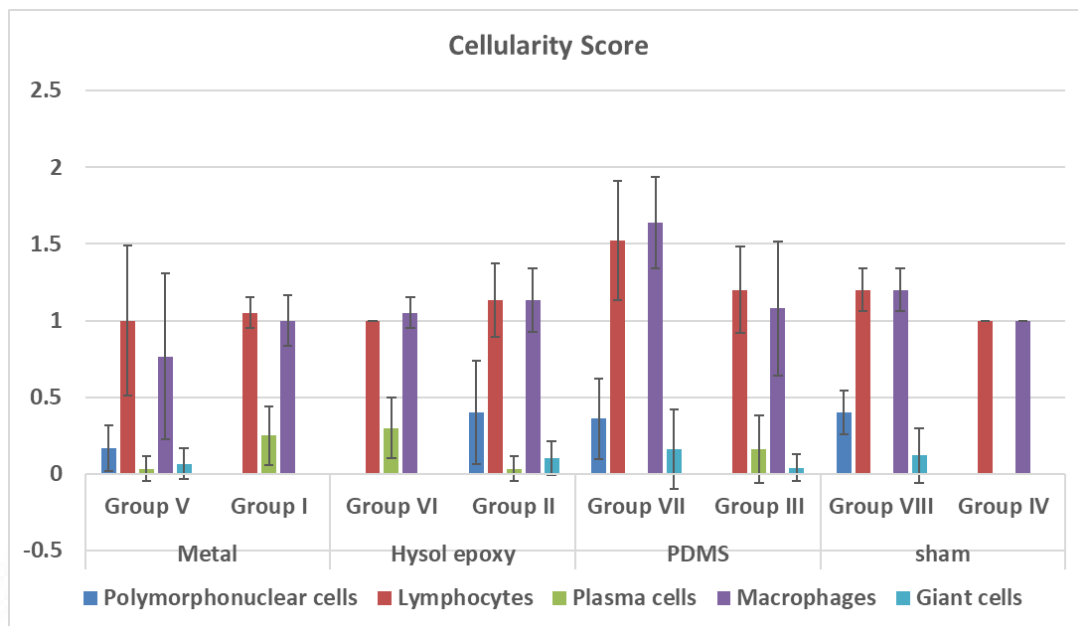


Figure 57. Cellularity score around implants

4.3.2 Cell Interaction Studies for Epoxy

In vivo experiments evaluated the biological response to the DBS electrodes. The electrode materials were implanted in male and female Wistar rats, with study periods of 4 weeks and 12 weeks. Following ethical guidelines approved by the Institutional Animal Ethics Committee, the rats were closely monitored, and tissue samples were collected after the implantation periods. Histological and immunohistochemical analyses examined the interaction between the implanted materials and surrounding tissues. These studies were designed to assess the biocompatibility and the cellular response to the implants. Evaluating inflammation, tissue integration, and long-term stability provides a comprehensive understanding of the biological performance of these materials in a chronic implant setting.

4.3.3 In Vivo Results

1. **Systemic Toxicity:** The systemic toxicity tests on mice, following intraperitoneal and intravenous injections of epoxy extracts, showed no abnormalities in behavior, body weight, or clinical symptoms over 72 hours. These findings indicate that the epoxy material did not induce any systemic toxicity.
2. **Intracutaneous Irritation and Sensitization:** The Intracutaneous irritation tests performed on rabbits indicated no significant irritation or inflammation after injection of the epoxy material extracts. The total irritation score was well within acceptable limits as per ISO 10993-10 standards. Similarly, the Guinea Pig Maximization Test (GPMT) did not show any signs of sensitization, with no observable erythema or edema, confirming that the epoxy material is non-irritant and non-sensitizing.
3. **Intramuscular Implantation:** The intramuscular implantation study revealed that at both 4 and 12 weeks' post-implantation, there was no evidence of necrosis, hemorrhage, or significant inflammation at the implant site. Histopathological analysis showed only mild fibrous encapsulation with a few inflammatory cells, which is typical for biocompatible materials. The absence of adverse tissue reactions, including necrosis or encapsulation, further supports the suitability of Hysol® epoxy for long-term implantation.

4.3.4 In Vitro Results

The in vitro studies included cytotoxicity studies, morphology and integrity studies, lysosomal and glial cell responses, and live /dead cell staining. The results are shown in Figure 58.

1. **Cell Viability and Cytotoxicity:** The MTT assay demonstrated that exposure to various dilutions of epoxy extracts did not significantly reduce the viability of U-87 MG glioma cells, indicating that the material is not cytotoxic under the test conditions. This finding was further supported by the Neutral Red Uptake (NRU) assay, which showed that lysosomal function remained unaffected in the cells treated with epoxy extracts.
2. **Cellular Morphology and Cytoskeleton Integrity:** Morphological examination using phase contrast microscopy revealed no significant changes in the shape or structure of cells after exposure to epoxy extracts, indicating that the material does not induce any morphological toxicity. Further, the Rhodamine-phalloidin staining showed no disruption to actin filaments, confirming the cytoskeletal integrity of the cells. This absence of cytoskeletal damage reinforces the potential of the epoxy for use in implantable medical devices.
3. **Lysosomal and Glial Cell Integrity:** The Acridine Orange (AO) staining confirmed the integrity of lysosomal membranes, as no shift in fluorescence from red to green was observed, indicating stable lysosomal function. The expression of Glial Fibrillary Acidic Protein (GFAP) through immunostaining also showed normal glial cell functioning, with no observable adverse effects, further supporting the biocompatibility of Hysol® epoxy.

4. Live/Dead Staining: Calcein-AM/PI staining revealed a high percentage of viable cells (green fluorescence), indicating the non-toxic nature of the epoxy material in the tested environment. The absence of red fluorescence (indicating dead cells) confirmed the minimal cytotoxicity of the material.

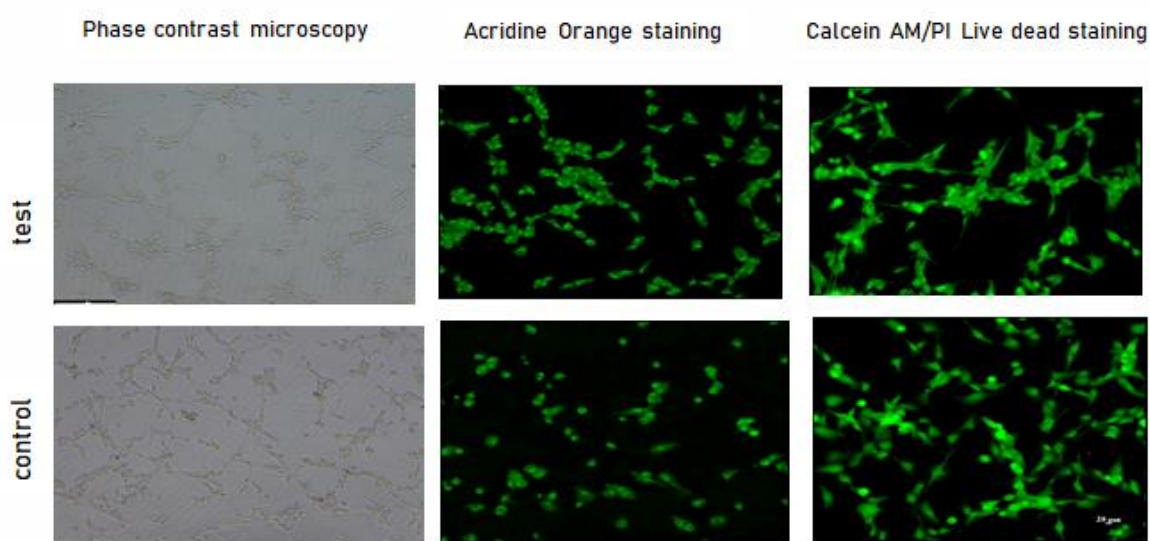


Figure 58. The microscopic images of a) Phase contrast microscopy, b) Acridine Orange Staining, c) Calcein /PI live dead staining with test and control.

The results of this study provide strong evidence of the biocompatibility of Hysol® epoxy, both at the cellular and tissue levels. The in vitro assays confirmed that the material is non-cytotoxic, maintaining cell viability and structural integrity. The absence of significant lysosomal damage and normal GFAP expression further reinforced the material's compatibility with neural tissues. In vivo studies corroborated these findings, with no systemic toxicity or adverse reactions observed in animal models.

4.4 Algorithm Implementation

The graphical abstract of the algorithm is shown in figure 57. The results of the different stages in the algorithm as per block diagram in figure 35 are discussed in this section.

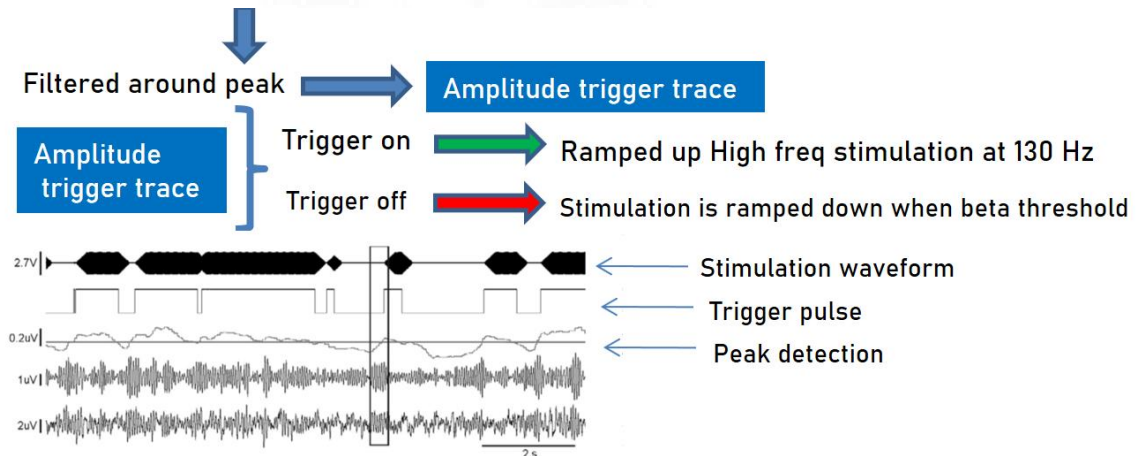


Figure 59. Graphical abstract of the algorithm

□ Pre-Processing: The recorded LFP data undergoes pre-processing to remove high-frequency noise and artifacts. This is accomplished using a low-pass filter, which eliminates unwanted high-frequency components that could distort subsequent signal analysis.

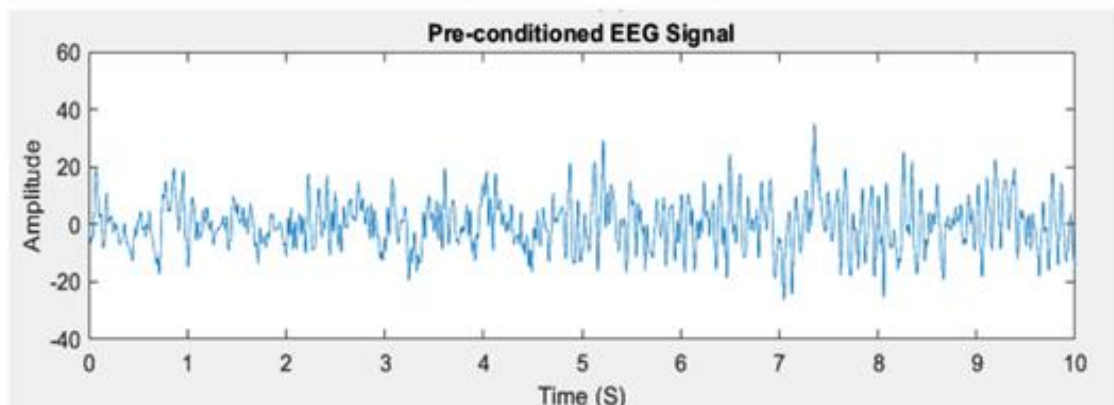


Figure 60. Preconditioned EEG Signal

□ **Band-Pass Filtering:** Following pre-processing, the EEG signal is passed through a Butterworth band-pass filter, which is designed to extract the beta wave frequency band (13–30 Hz). This band is particularly important for controlling deep brain stimulation, as the beta oscillations are often associated with movement disorders such as Parkinson's disease.

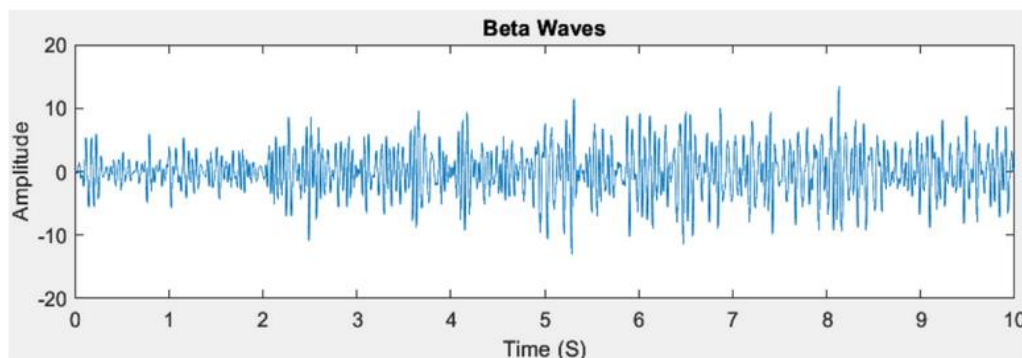


Figure 61. Band Pass Filtered Beta

□ **Thresholding:** After isolating the beta waves, the system applies a thresholding process. This step quantizes the continuous beta wave signal, converting it into a binary on/off signal. This is achieved by comparing the beta wave amplitude to a predefined threshold—if the signal exceeds the threshold, it is considered "on," otherwise it is "off." This binary output is used to represent the presence or absence of pathological beta activity.

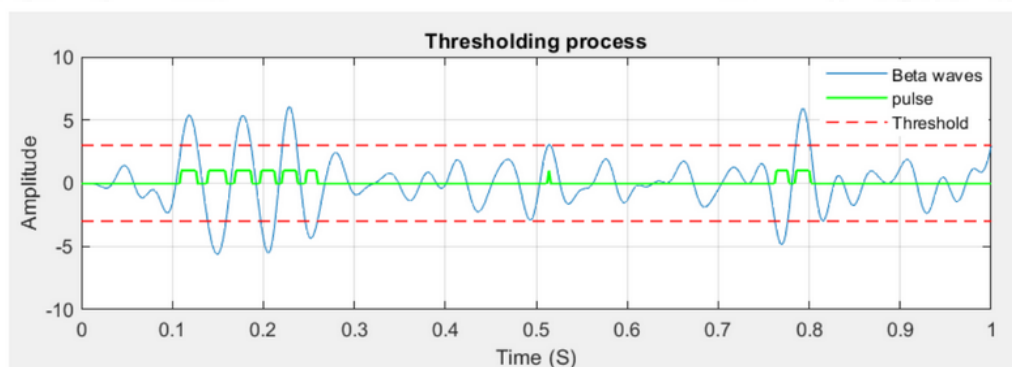


Figure 62. Thresholding

□ Pulse Width Modulation (PWM) Control: The thresholded signal is then used to control the duty cycle of a Pulse Width Modulated (PWM) signal. The PWM signal's duty cycle adjusts according to the on/off state of the thresholded beta wave, ensuring that the system responds in real time to changes in neural activity.

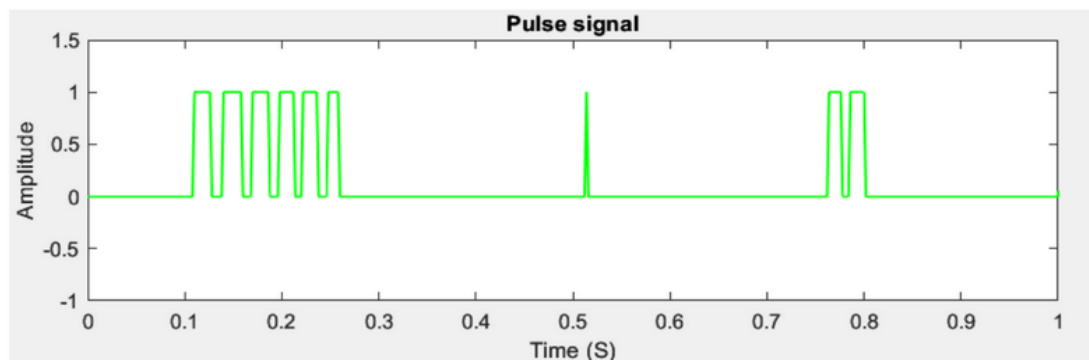


Figure 63 Pulse Signal after thresholding

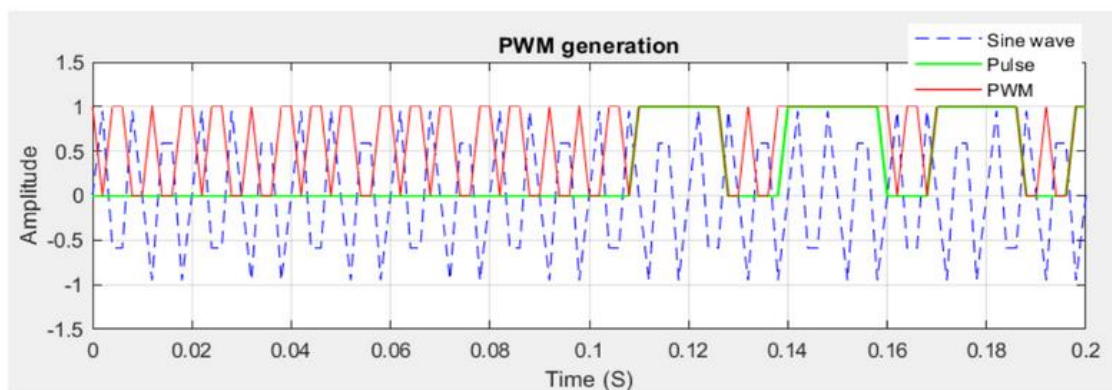


Figure 64 PWM Generation

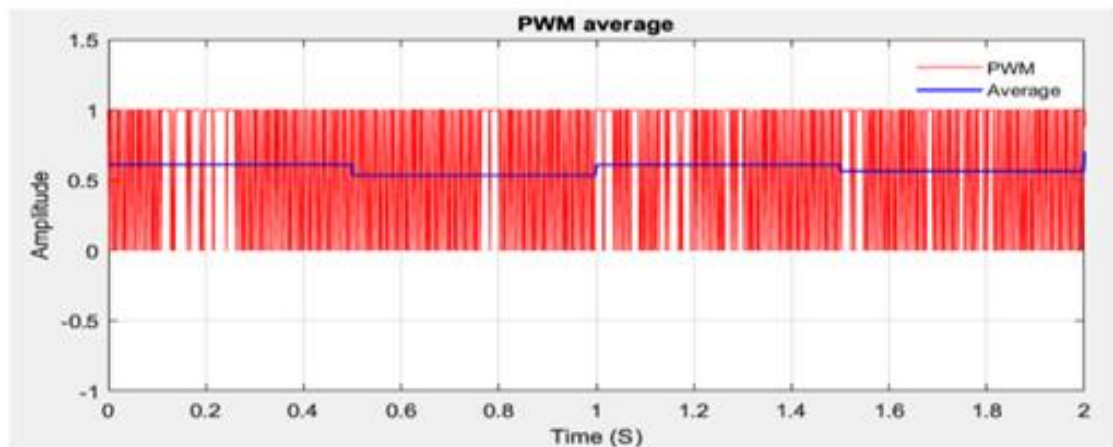


Figure 65. PWM Average for Power control

Implantable Pulse Generator (IPG) Control: The PWM signal is sent to the Implantable Pulse Generator (IPG), which contains a Power Control Unit (PCU) responsible for generating the stimulation pulses. Inside the IPG, the digital PWM signal is converted to an analog signal to maintain charge balance, a critical requirement for ensuring safe and effective stimulation without causing tissue damage.

The system outlined successfully demonstrates the ability to process neural signals in real time to dynamically control the Implantable Pulse Generator (IPG). By utilizing LFP recordings as the primary input, and applying both pre-processing and band-pass filtering, the system isolates beta waves frequencies that are critically associated with pathological neural activity, particularly in movement disorders such as Parkinson's disease. The subsequent thresholding step converts the continuous beta activity into a binary signal, facilitating precise control over the duty cycle of the PWM signal.

This PWM signal is then employed to regulate the stimulation output of the IPG, ensuring that the stimulation is delivered adaptively in response to fluctuating neural activity. The conversion of the digital control signal into an analog form within the IPG ensures charge balancing and mitigates potential risks associated with tissue

damage. Overall, the integration of real-time signal processing and adaptive modulation of the IPG highlights the potential for this system to offer more personalized and effective deep brain stimulation, with the ability to respond dynamically to the patient's neural state. This adaptive approach may lead to more precise therapeutic interventions, potentially reducing adverse effects and improving clinical outcomes.

Chapter 5

5. Summary, Conclusion and Future work

This work achieved its primary objectives by leveraging simulation studies, electrochemical and biological characterizations, and the development of a novel adaptive algorithm for closed-loop DBS. Each objective was approached with rigorous methodology, yielding findings that underscore the hybrid DBS electrode's potential to transform targeted therapy for movement disorders.

Objective 1: Developing a Dual-Purpose Hybrid Electrode for Sensing and Stimulation

Notably, simulation studies highlighted that the hybrid electrode achieves the same volume of tissue activation (VTA) as conventional DBS electrodes but at significantly lower voltage levels. This reduction in threshold enhances efficiency and conserves energy—a critical aspect for implant longevity. Furthermore, the analysis demonstrated a marked decrease in residual electric field beyond 0.5 mm from the electrode, signaling a minimized risk of unintended stimulation. Such an outcome suggests a potentially significant reduction in DBS-related side effects, aligning well with the aim to provide more precise stimulation.

Objective 2: Comprehensive Characterization of the Hybrid Electrode

This objective was pursued through simulations, electrochemical studies, and biological evaluation to confirm the electrode's performance reliability for both stimulation and sensing.

Simulations: The simulations proved invaluable in forecasting the electrode's operational characteristics under varied conditions, affirming its aptness for DBS applications. These predictive analyses demonstrated that the electrode can maintain stable function within safe limits, reinforcing its utility for in vivo use.

Electrochemical Analysis: Through electrochemical studies, the electrode's charge delivery capacities were assessed with respect to the Randles circuit model, which provides a fundamental understanding of performance under varying electrical loads. Specifically, the Chronopotentiometry data yielded a cathodic charge density of 105 $\mu\text{C}/\text{cm}^2$ and an anodic charge density of 15.32 $\mu\text{C}/\text{cm}^2$, establishing a baseline for safe stimulation limits and long-term durability. This rigorous analysis underscores the electrode's reliable performance, showing its capacity to operate without degradation—a requirement for sustained therapeutic efficacy.

Biological Evaluation: The biological assessment encompassed two primary phases to verify the electrode's safety in neural contexts. In the first phase, the materials—Platinum-Iridium, PDMS, and Hysol® epoxy—were implanted in Wistar rats, with no observed signs of systemic toxicity, adverse neurobehavioral effects, or weight loss, as shown in Figures 53 and 54. Importantly, no clinical abnormalities were detected, and post-surgical healing proceeded smoothly across all subjects. In the second phase, focused specifically on Hysol® epoxy's biocompatibility, both in vitro and in vivo tests demonstrated non-cytotoxicity, as confirmed by the MTT and Neutral Red Uptake assays, and minimal inflammation in tissue, with histopathological images in Figures 55 and 56 showing consistent cellular integrity. The absence of degradation

products further validates the suitability of the electrode's materials for chronic implantation.

Objective 3: Developing an Adaptive Algorithm for Closed-Loop Control Using Beta Waves

The development of an adaptive algorithm met the objective of leveraging beta wave activity as feedback for DBS modulation. Using local field potential (LFP) recordings, the algorithm processes neural signals through pre-processing and band-pass filtering to isolate pathological beta oscillations. Once extracted, these oscillations are thresholded to produce a binary control signal, which is then applied to adjust the duty cycle of a pulse-width modulation (PWM) signal in real time. This binary conversion enables precise control over the IPG's stimulation output, adapting dynamically to neural fluctuations. Notably, the IPG's charge-balancing feature ensures safe signal delivery, aligning with the aim of reducing DBS side effects. Overall, this approach provides a personalized, responsive therapy, with the potential to improve clinical outcomes for patients with movement disorders.

In summary, this thesis successfully accomplished its key objectives through a blend of simulation studies, electrochemical and biological characterizations, and the development of an adaptive closed-loop algorithm, establishing the hybrid DBS electrode as a promising tool for targeted therapy in movement disorders. The first objective, focused on creating a dual-purpose electrode for both sensing and stimulation, demonstrated through simulations that the hybrid electrode achieves similar tissue activation volumes as conventional DBS electrodes but with reduced

voltage requirements, enhancing efficiency and minimizing side effects. The second objective ensured comprehensive characterization, showing that the electrode performs reliably under various conditions through simulations, electrochemical analysis, and biological testing. These studies confirmed the electrode's stability, biocompatibility, and safety for neural applications, with no adverse effects observed in preclinical models. The third objective, which involved designing an adaptive algorithm based on beta wave activity, produced a real-time closed-loop control system capable of adjusting stimulation output dynamically, thus providing a personalized therapeutic approach that could potentially reduce DBS-related side effects. Collectively, these findings highlight the hybrid electrode's readiness for further clinical evaluation and its potential to transform adaptive DBS therapy for improved patient outcomes.

Future Work

Future work will focus on refining the hybrid DBS electrode design, with the goal of achieving clinical-grade quality through optimized manufacturing processes that ensure consistency in size, shape, and material properties. This will involve exploring advanced micromachining and surface treatments to improve charge transfer and reduce impedance, enhancing the electrode's performance for both sensing and stimulation. Additional *in vitro* studies will deepen our understanding of the electrode's cellular interactions, assessing cytotoxicity and performing electrophysiological tests to evaluate its stability and response under varied conditions. These studies will also employ imaging techniques to monitor cell health and morphology over time. Moving forward, *in vivo* validation will be conducted in larger

animal models to assess the electrode's performance in a more complex biological environment, examining both acute and chronic tissue responses and the therapeutic effects of adaptive DBS on movement symptoms. Once validated in preclinical studies, the electrode will progress to clinical trials, initially focusing on short-term safety and advancing to trials that test adaptive DBS effectiveness in managing movement disorders with real-time neuroadaptive feedback. Long-term, the goal is to enhance the DBS system's adaptability using advanced algorithms, positioning the electrode as a versatile platform for personalized neurological therapy.

Through these steps, this future work plan aims to bridge the gap between research and real-world application, ultimately establishing the hybrid DBS electrode as a transformative tool in neuroadaptive DBS systems. By supporting personalized, real-time adjustments to stimulation, this work will drive advancements in neurological therapy, offering hope for improved outcomes in patients with complex neurodegenerative and movement disorders.

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List of Publications from the Thesis

Krishnan, J., Joseph, R., Vayalappil, M.C., Krishnan, S., and Kishore, A. (2024) 'A Review on Implantable Neuroelectrodes', *Critical Reviews in Biomedical Engineering*, 52(1), 21–39. doi: 10.1615/CritRevBiomedEng.2023049282.

Krishnan, J., Muraleedharan, C.V., Sasi, R., and Joseph, R. (2024) 'Electrical Charge Characterization of a Hybrid Interdigitated Deep Brain Stimulator Electrode using Electrochemical Methods', *Analytical and Bioanalytical Electrochemistry*, 16(6), 614–627. doi: 10.22034/abec.2024.714095.

Krishnan, J., Muraleedharan, C.V., and Joseph, R. (2024). "BETA Based Approach on Un-Synchronized EEG Waves in LFP Localization for Movement Disorders." *International Journal of Advanced Research in Basic Engineering Sciences and Technology*, 10(7), 133-136.

Krishnan, J., Aboobecker, A., Kishore, A., Joseph, R., Sarathy, K. and Muraleedharan, C.V., 2024. Electrical charge characterization of hybrid neurostimulator probe – In silico studies and in vitro verification. *Trends in Biomaterials and Artificial Organs*, 38(3), pp.177–182.

Manuscripts under Preparation

Jithin Krishnan, Muraleedharan C.V., Asha Kishore, Megha K.B., Mohanan P.V. “Exploring the biocompatibility of Hysol epoxy for Hybrid Neurostimulator Electrodes”.

Jithin Krishnan, Muraleedharan C.V., Asha Kishore, Megha K.B., Remya N.S., Roy Joseph. “Biological Characterization of a hybrid electrode for neuroadaptive applications in a rat model.”

Patents Applied

Jithin Krishnan, Muraleedharan C.V., Syam K., Krishna Kumar, Asha Kishore: Hybrid electrode probe for neural stimulation and sensing for adaptive closed loop applications. Application Number: 3045896251001, filed on 25-10-2022.

Conference Presentations

Jithin Krishnan, Roy Joseph. "Hybrid Electrode Technology for Adaptive Deep Brain Stimulator Like Neuromodulator Applications", 2nd Online International Conference on Biomaterials & Biodevices" (Biomaterials, 2022), April 25-26, 2022 in Virtual (11:00-18:00 GMT)

Jithin Krishnan, Roy Joseph, Muraleedharan C.V. "BETA Based Approach on Un-Synchronized EEG Waves in LFP Localization for Movement Disorders "Proceedings of 14th International Conference on Science and Innovative Engineering", April 27-28, 2024.

Jithin Krishnan

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-----RESEARCH EXPERIENCE AND INTERESTS-----

Currently working as Scientist/Engineer in Medical Device Engineering at Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), An Institution of National Importance under DST, Govt. of India. I have 13 years of core experience and a demonstrated history of working in medical devices research and development, mainly in active implants like Pacemakers, Deep Brain Stimulators, Implantable defibrillators, Spinal Cord Stimulators etc. and also skilled in Medical Devices Development and Standards; FPGA prototyping, Biomedical Engineering and Quality Management systems including Risk Analysis New Product Development, Collaborative Industrial, and Lab-to-Market transitions. Played a significant role in the prestigious TRC- Technical Research Centre establishment at my host Institute, which was supported by DST, Govt of India, particularly in the Indigenous Medical Devices Development. Represented our country as delegate in the BRICS 23 at South Africa as Young scientist representative in the Healthcare segment.

-----EDUCATION-----

Name of the degree	University/Institute	Year of Passing	Subject area	Grade obtained
PhD	SCTIMST	-	Neuroscience	Thesis to be submitted
Master of Technology	Cochin University of Science and Technology	2012	VLSI and Embedded Systems	CGPA 9.2/10; 2nd Rank
Bachelor of Technology	University of Kerala	2008	Electronics and Communication	CGPA 8.0/10

-----EXPERIENCE-----

SCTIMST, BMT Wing, Govt of India
Scientist/Engineer-Medical Instrumentation

Trivandrum, India
Nov 2012 –till date

1) As an individual contributor, carries out complex or novel assignments requiring the development of new or improved research or engineering techniques and procedures. Work is expected to result in the development of new or refined equipment, materials, processes, products, and/or scientific methods and approaches.

2) In a supervisory capacity, plans, develops, coordinates, and directs a large and significant project, or a number of small projects with numerous complex features.

3) In an academic role, taking classes for M Tech programs and guiding students for internships and projects

Mohandas College of Engineering and Technology
Lecturer/Assistant Professor

Trivandrum, India
Jan 2009-Aug 2010

PATENTS

No. of Granted Patents : 8
No. of Patent Applications Filed : 18
No. of Design Registrations : 4

PROJECTS

Projects involved at present and activities

1. Deep Brain Stimulator
Role: Co-PI
The development of the deep brain stimulator project is executed with the collaboration of BARC, Govt of India. The project aims to develop deep brain stimulator prototypes and take the device to the preclinical evaluation phase. As Co-PI, I am involved in various levels of design, development and testing paradigms. As coordinator for the task force set up for the monitoring of the proof of concept prototype manufacturing, I look up to the vendor's activities on the material purchase and material qualifications so that the prototypes are delivered on time. Also serves as a member of the project execution committee, which reports to the project monitoring committee, including higher officials from BARC and SCTIMST. As a project team member, I serve on various committees set up by the participating institutions.
2. Implantable Defibrillator
Role: Co-PI
Developing an implantable defibrillator is executed as a co-development with Shree Pacetronix, Indore. The project aims to develop ICD prototypes and take the device to the preclinical evaluation phase. I am involved in various design, development and testing paradigms as CO PI.
3. Steering electrodes for DBS applications
Role: PI
Design and Development of a new kind of Current steering electrode with feedback for Deep Brain Stimulator Applications. The aim is to develop a hybrid electrode with current steering and a sensory element added into the electrodes, which can act as a feedback sensor for closed-loop control of Deep Brain stimulation.
4. Intracranial Electrodes for epilepsy surgery
Role: PI

The project's objective is the technology development for manufacturing state-of-the-art intracranial platinum and stainless steel electrodes and Proof of concept testing through in vitro/in vivo experiments. The proof of concept prototypes have been developed, and in vitro tests have been completed. The preclinical evaluations have been initiated, and relevant ethics committee approvals have been taken.

5. Implantable Spinal Cord Stimulator for Chronic Pain Management.

Role: PI

The project's objective is the technology development for the manufacture of Spinal cord stimulators for chronic pain management and Proof of concept testing through in vitro/in vivo experiments. The proof of concept phase has been completed.

6. Graphene based electrodes for ECG applications

Role: PI

-----PUBLICATIONS-----

Selected publications

1. Jithin Krishnan, Sreekumari B, Jiju K. "ASIC Implementation of Auto Ranging Data Converter" IEEE International Conference on Computing, Communication and Applications, IEEE Explore: -ISBN:978-1-4673-0270-8, DOI: 10.1109/ICCCA.2012.6179131

2. Jithin Krishnan, Sreekumari B, Jiju K. "Implementation of an Auto-Ranging Data Converter in FPGA" IEEE International Conference on Electronics and Computing Technology, IEEE Explore: -ISBN:978-1-4673-0270-8.

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-----Govt Associations/Committees-----

Member and Chartered Engineer, Institution of Engineers India.

Board of Studies, Faculty of Applied Sciences, Engineering and Technology, University of Kerala.

Business Advisory Committee-ASAP* and KASE**, Govt. of Kerala.

Member, IEEE Standards Association, Working Group: IEEE NSGCON 1903, IEEE PoCD WG.

*Additional Skill Acquisition Program | | ** Kerala Academy for Skills Excellence

-----MAJOR VOLUNTEER CONTRIBUTIONS-----

E-Scientia: Participated in installing the first indigenously fabricated E-Scientia museum exhibit in Kerala, India.

Early Career Faculty Development Programs: Part of the program, which trained 150 young engineering teachers in two States of India as a volunteer of the EAB-supported project team with approval from the State Governments.

Humanitarian Activities - Sastra Vismaya—Training to Pre-university students of Government rehabilitation centres in three districts with WIE and Young Professionals in the lead.

Eyes Free Science Camps —Bringing blind school students closer to Science and Technology studies through assistive technologies.

Community Engagement Workshops CEW and SIGHT Camps: Instrumental in organizing two International Community Engagement Workshops (CEW), creating a common platform for NGOs to interact with the community on humanitarian issues

Promoting Young Professionals' Participation in Technical Conferences: Experience promoting increased participation of Young Professionals in National and International Technical Conferences like TENCON 2015. Was part of the conferences committee and has worked in Macau, Singapore, Malaysia and Sri Lanka to promote STEM programs through conferences, workshops and other engagement networking programs.

DECLARATION

I declare that every statement of the above information is accurate to the best of my knowledge.