Implanted devices: the importance of both electrochemical performance and biological acceptance

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Neural interfaces can be implanted throughout the body to restore function, including cochlear implants for severe hearing loss, deep brain stimulation for tremor, and spinal cord stimulation for pain. These devices are intended to remain implanted and effective for the lifetime of the user, which could be several decades. Device performance and longevity can be impacted by the state of the electrode-tissue interface. Electrochemical performance and tissue reaction to implanted electrodes are important factors to consider when testing novel electrodes and materials, and can facilitate understanding of the reactions at the interface. The works summarized in this perspective highlight the significance of evaluating the electrochemical properties and bioreactivity of implanted electrodes in concert through chronic *in vivo* studies. Cochlear implants are used as a case study; however, the results are relevant to all neural interfaces. Electrochemical performance and tissue reactivity must be considered in future studies evaluating electrodes and materials prior to testing in people.

Improving neural interfaces with electrode coatings: Most implanted electrodes are made of platinum (Pt) and/or iridium (Ir), because they are electrochemically stable and biocompatible (Cogan, 2008). Electrode coatings can improve neural interfaces by reducing the impedance and increasing the charge injection limit, which can lead to smaller electrodes and improved specificity (Micco and Richter, 2006; Dalrymple et al., 2019). Additionally, soft electrode coatings are being developed to reduce the mechanical stiffness (Green et al., 2012), as well as coatings with anti-inflammatory drugs or growth factors to reduce bioreactivity (Chapman et al., 2020). Coatings are advantageous, because they can be integrated readily onto existing commercial electrodes. However, coatings carry the risk of delamination from the underlying metal, in addition to bioreactivity challenges.

Extensive bench-top and *in vitro* testing typically precedes *in vivo* testing. Bench-top testing often involves evaluating the coating adhesion and electrochemical properties. For example, a recent study by our group undertook an accelerated aging study to evaluate electrode coating materials (Dalrymple et al., 2019). If a coating material maintained its electrochemical properties (described below), adhered to the base metal, and did not corrode during aging (determined by microscopic inspection), it was considered a viable candidate for *in vivo* testing.

Chronic *in vivo* testing: To translate novel electrode coatings for chronic medical applications, there are three main considerations. First, the coating must adhere to the underlying metal. Second, the coating must have similar or improved charge injection limits compared to the underlying base metal. Finally, the coating material must be biocompatible. Chronic *in vivo* testing allows investigators to analyze the reactions at the electrode-tissue interface in several ways to determine if an electrode material is both safe and effective.

Electrochemical performance: Several electrochemical measurements can inform on the reactions at the electrode-tissue interface in response to an electrical stimulus. Bench-top electrochemical measurements use a three-electrode setup comprised of test, reference, and counter electrodes in a salinated solution (Cogan, 2008; Dalrymple et al., 2019). *In vivo*, a three-cell setup can be substituted to utilize three electrodes on the implanted electrode array; however, the results cannot be compared to bench-top results due to differences in electrode size and materials (Dalrymple et al., 2020a, b) (**Figure 1A**). Electrochemical reactions at the interface can be described as either capacitive or Faradaic (Cogan, 2008). Capacitive reactions involve charging and discharging at the interface double layer. Faradaic reactions involve the conversion of charge carriers from electrons in the electrode to ions in the electrolyte via oxidation and reduction reactions that can be reversible or irreversible. The mode and amount of charge injection for coating materials can be investigated using the following measures.

Cyclic voltammetry (CV) entails sweeping the potential cyclically at a constant rate (scan rate), where the current flows between the test and counter electrodes (Cogan, 2008). The potential is cycled between two limits of the water window, which are the potentials that result in the electrolysis of water (typically 0.8 V and –0.6 V *vs*. Ag|AgCl for Pt and Ir). CV curves provide information regarding the electrode stability, electroactive surface area, and the reversibility of reactions at the interface. **Figure 1B** shows a CV curve recorded from a conductive hydrogel coated electrode *in vivo* (Dalrymple et al., 2020a). The area of the CV curve can be used to calculate the charge storage capacity. The larger the charge storage capacity, the better the electrode can pass charge at low frequencies (Cogan, 2008). However, the scan rate can affect the charge storage capacity and should always be consistent and reported.

Electrochemical impedance spectroscopy uses a small stimulus to measure the impedance over a range of frequencies (Cogan, 2008). The impedance magnitude and phase at different frequencies inform on both electrode and tissue properties. For example, the impedance magnitude at 1 kHz is often reported, because it is related to the duration of an action potential; however, it is more relevant to recording applications. The interface can be modeled by a Randles equivalent circuit; although, other models exist (Lisdat and Schäfer, 2008) (**Figure 1C**). The solution resistance (RS) is due to the electrolyte or tissue and is derived from the high-frequency component of the impedance. This can inform on the extent of tissue growth around the electrode (Cogan, 2008). At low frequencies, the impedance is dominated by a double layer capacitor (CDL). The charge transfer resistance (RCT) reflects the resistance to the current flow produced by redox reactions at the interface. The Warburg impedance (W) is present at lower frequencies and results from the diffusion of ions. Ideally, the impedance magnitude approaches the solution resistance at a lower frequency.

Voltage transient waveforms can be used to calculate the charge injection limit (CIL) (Cogan, 2008). CIL is the charge that produces the maximum cathodal voltage (EMC) equal to the cathodal limit of the water window, which is the maximum amount of charge that can be safely injected during a pulse (**Figure 1D**). Electrodes are stimulated with a biphasic charge-balanced cathodic-first pulse over a fixed pulse width and a variety of amplitudes (Lee et al., 2016). EMC is calculated by subtracting the access voltage (VA) from the maximum negative potential (ΔV). The CIL can be calculated using the current value immediately below the level that went past the cathodal polarization limit (Dalrymple et al., 2019).

Repeating these measures throughout chronic implantation can inform on the ongoing tissue response and charge injection efficacy of the material, which is information that can only be attained in chronic *in vivo* experiments. An increased impedance could indicate an extensive tissue response, rejection of the implant (Foggia et al., 2019), or loss of the coating. Electrochemical measurements should be repeated, if possible, after explant to determine if any changes in electrochemical performance were due to permanent changes to the electrode or coating. For example, in a study by Dalrymple et al. (2020b), the impedance of electrodeposited Pt-Ir coatings increased significantly during the implant period, but upon explant returned to pre-implant values. In a second chronic study evaluating conductive hydrogel coatings, the electrochemical performance remained significantly better than bare Pt throughout the implant period (Dalrymple et al., 2020a). However, there was some delamination of the coating upon explant. Quantifying the tissue response to the coatings helped to explain why there was a change in impedance and when the coating delamination occurred.

Tissue reaction: Implanted neural interfaces evoke a foreign body tissue response. Although cochlear implants have very low complication rates, extensive trauma or tissue response can reduce their efficacy (Foggia et al., 2019). The tissue response to cochlear implants is nearly identical to the response to any peripheral neural interfaces and can be divided into acute and chronic reactions (**Figure 1E**). Immediately after implantation, plasma proteins such as albumin and fibrinogen adsorb onto the implant surface. The acute response is primarily due to insertion trauma and consists of the infiltration of neutrophils into the cochlea (Bas et al., 2015).

During the chronic phase, macrophages and lymphocytes adhere to the implant (Foggia et al., 2019). Macrophages can fuse together to form foreign body giant cells and release factors in an attempt to degrade the implant, including enzymes, acids, and reactive oxygen species. Fibroblasts, in response to macrophage activation, migrate to the implant site and proliferate. Fibroblasts lay down proteins such as collagen to form extracellular matrix around the implant. Foreign body giant cells remain and reside between the implant and the fibrous capsule. Prolonged tissue response to an implant results in an irreversible fibrous capsule around the implant (Lee et al., 2016), without necessarily causing any permanent damage to the implant itself. For example, the tissue response evoked by electrodeposited Pt-Ir was similar to bare Pt; however, it reduced the effectiveness of the high surface area component of the coating (Dalrymple et al., 2020b). Tissue encapsulation increases the impedance of the electrode-tissue interface, reducing the effectiveness of the device by changing the current path (Micco and Richter, 2006). An increased impedance, paired with constant-current stimulation, could result in a potential difference at the interface that approaches or exceeds the water window, as well as increase the power requirements of the device. Increased power usage necessitates more

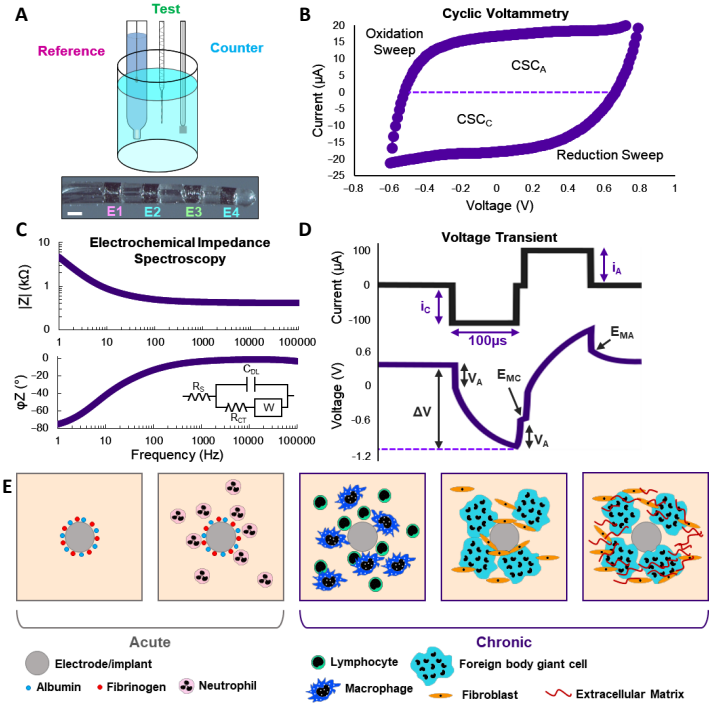

Figure 1 | **Electrochemical measures and stages of the tissue response.**
(A) Bench-top (top) and *in vivo* (bottom) electrode configurations for electrochemical measurements. E1: Reference; E2, E4: counter; E3: test. (B) Cyclic voltammetry curve showing cathodal (CSCC) and anodal (CSCA) charge storage capacity. (C) Impedance magnitude (top) and phase (bottom) from electrochemical impedance spectroscopy. Inset: Randles equivalent circuit. (D) Voltage transient excitation current (top) and response (bottom). EMA: Maximum anodal polarization; EMC: maximum cathodal polarization; iA: anodal current amplitude; iC: cathodal current amplitude; VA: access voltage; ΔV: maximum negative potential. (E) Acute and chronic stages of the tissue response to an implanted electrode in the periphery. Sizes not to scale.

frequent battery changes for implanted pulse generators and limits devices that deliver power wirelessly across the skin.

An abnormal and severe tissue response to a cochlear implant can result in neo-ossification, which can cause poor speech recognition and contribute to the loss of residual acoustic hearing (Foggia et al., 2019). Interestingly, fibrosis and neo-ossification do not correlate with implant duration; rather, it is initiated by trauma during the implant procedure (Bas et al., 2015). Additional factors influencing the tissue response include electrode size and stiffness, as well as micromotion and migration.

Histology can also be used to detect loss of electrode coating during implantation. For example, in our work, coating particulates were phagocytosed by macrophages (Dalrymple et al., 2020a, b) indicating that these particles had been removed from the electrode surface for some time. Conductive hydrogel coatings did evoke a more widespread, yet benign, tissue response than bare Pt (Dalrymple et al., 2020a), which may have contributed to the delamination of the coating from the underlying Pt.

Back to the (more informed) drawing board: New electrode coatings aim to improve safety and biocompatibility by (i) reducing electrode impedance, (ii) increasing charge storage and injection capacity, (iii) reducing implant size, and/or (iv) reducing coating stiffness. Coating materials that can potentially address these aims include electrodeposited Pt-Ir (Dalrymple et al., 2020b) and conductive hydrogels (Green et al., 2012; Dalrymple et al., 2020a), as well as the addition of neurotrophic factors and anti-inflammatory agents onto the implant (Chapman et al., 2020). Chronic *in vivo* testing early in coating development can inform on safety and biocompatibility issues and prompt the redesign of the coating chemistry or process.

If an electrode coating is not performing as expected *in vivo*, both electrochemistry and histology data can be used to understand the reactions at the electrode-tissue interface. Poly(3,4-ethylenedioxythiophene) (PEDOT) is a well-studied electrode coating. Delamination of PEDOT coatings *in vivo* is commonly reported throughout literature and has led to innovations in manufacturing processes and formulations with dopants (Lee et al., 2016; Ganji et al., 2018). Much of the literature describing PEDOT coatings chronically *in vivo* only describe electrochemical performance. Alarmingly, few papers investigate the tissue reaction to PEDOT coatings, limiting the knowledge that material scientists can use to improve the coatings so they can be applied for their intended clinical use. There are many examples of doping PEDOT with anti-inflammatory drugs and growth factors to limit the adverse tissue reaction, but the testing is often done *in vitro* or in acute studies rather than chronically *in vivo* (Chapman et al., 2020). The future of biomaterials needs to include more chronic *in vivo* testing, evaluating material performance and safety using both electrochemical performance, microscopic inspection of the electrode surface, and histology (Dalrymple et al., 2020a, b).

Conclusions: The safety and efficacy of implanted neural interfaces need to be considered from the perspective of electrochemical performance and biological acceptance. Both areas provide information about the electrode-tissue interface that can be used to inform the design of new devices and materials. Ultimately, these areas need to work together to reach for the goal of making safer and more reliable neural interfaces.

I would like to thank Drs. Robert Shepherd, James Fallon, and Douglas Weber for their support and review of this perspective article.

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Date of submission: May 21, 2020
Date of decision: June 27, 2020
Date of acceptance: August 15, 2020
Date of web publication: November 27, 2020

https://doi.org/10.4103/1673-5374.300342
How to cite this article: *Dalrymple AN (2021) Implanted devices: the importance of both electrochemical performance and biological acceptance. Neural Regen Res 16(6):1188-1189.*

Open peer reviewer: *James K Trevathan, University of Wisconsin-Madison, USA.*
Additional file: *Open peer review report 1.*

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P-Reviewer: Trevathan JK; C-Editors: Zhao M, Qiu Y; T-Editor: Jia Y