Electron transfer processes occurring on platinum neural stimulating electrodes: pulsing experiments for cathodic-first, charge-balanced, biphasic pulses for $0.566 \leq k \leq 2.3$ in rat subcutaneous tissues

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Abstract

Objective. Our mission is twofold: (1) find a way to safely inject more charge through platinum electrodes than the Shannon limit ($k = 1.75$) permits and (2) nurture an interest in the neural stimulation community to understand the electron transfer process occurring on neural stimulating electrodes. Approach. We report here on measurements of the electrode potential, performed on platinum neural stimulating electrodes in the subcutaneous space of an anesthetized rat under neural stimulation conditions. Main results. The results for six platinum electrodes with areas ranging from 0.2 mm$^2$ to 12.7 mm$^2$ were similar to prior results in sulfuric acid, except that the measured potentials were shifted negative 0.36 V because of the pH difference between the two media. The anodic ‘end’ potential, measured at $t = 20$ ms after the onset of the biphasic current pulse, was the primary focus of the data collected because previous results had shown that as charge injection crosses the Shannon limit ($k = 1.75$), this potential moves into a range where platinum surface oxidation and dissolution is likely to occur. The behavior of $V_e(t = 20$ ms) over a range of electrode surface areas studied was consistent with our sulfuric acid study. Implicit, but little noticed, in Shannon’s formulation is that small and large platinum electrodes behave the same in terms of $k$ value; our data supports this idea. Significance. We hypothesize that the $k = 1.75$ Shannon limit for safe stimulation designates a charge-injection boundary above which platinum toxicity becomes a relevant consideration for living cells around an electrode, a possibility that can be directly tested, and is a vital step forward in mission (1).

Keywords: Shannon plot, neural stimulation, electrochemistry of platinum electrodes
Introduction

The Shannon plot [1], generally speaking, is the de facto touchstone for setting the upper limit for charge-balanced/biphasic neural stimulation with platinum electrodes. Our goal is to find a way to extend the charge-injection limits beyond $k = 1.75$, a common limit for safe neural stimulation with platinum electrodes that is often found to be too restrictive for some clinical devices and application. The Shannon plot was constructed on the interpretation of histological data collected from animal studies [2], and $k = 1.75$ defines a line slightly below the first datum point for stimulation-induced damage.

The Shannon plot has been used extensively to establish the separation between what is deemed safe and unsafe levels of charge injection. Here, the words safe and unsafe are shorthand to indicate that the original investigators either could not see or could see damaged tissue in the vicinity of the electrode. It is understood that absolute safety can never be guaranteed in any life endeavor.

In the neural stimulation community, the $k = 1.75$ safety limit has been explained by two candidate theories: hyperactivity/hyperexcitability, injury brought on by a large number of cells being stimulated for long periods of time in an unnatural manner, and toxic products due to electron transfer processes. These candidates are not mutually exclusive. In fact, quoting from Cogan [3], the criteria for electrochemically safe charge injection are that the reactions mediating transfer of charge across the electrode-tissue interface:

1. Do not induce corrosion or degradation of the electrode sufficient to compromise its electrical and mechanical function.
2. Do not produce chemical species that are toxic to cells.

The focus of our work is on the products of electron transfer occurring in vivo on platinum electrodes during the anodic phase of cathodic-first, charge-balanced, biphasic pulses because accelerated platinum dissolution could occur during this phase of a balanced-charge biphasic pulse. Work done at slower scan rates (Sugawara et al [4] and Topalov et al [5]) have shown that Pt dissolution occurs when scanning towards positive potentials forming oxides and also while scanning towards negative potentials reducing the formed oxides. Results from work done using neural stimulation type faster scan rates (Kumsa et al [6]) has shown results that point to a significant minimization of Pt dissolution when inhibiting the formation of Pt oxides, or when blocking those oxides from going through a reduction. Platinum dissolution can also occur at anodic potentials through the formation of platinum–chloride complexes [7–10].

The Shannon limit separating the safe and unsafe regions was based on data from experiments on cat brain where the platinum stimulating electrodes with areas ranging from 1 mm$^2$–50 mm$^2$ were placed below the dura and in the arachnoid surface (i.e. close to the target tissues for neural stimulation) [2]. Further, these data were acquired using disk-shaped platinum electrode contacts with various surface areas. That data set is considered the best available set to work with for situations where the electrode is in close contact with the target tissues. That is, any electrochemical reaction products are in their highest concentration at close proximity to cells of interest. The utility of these data set may be called into question when the separation between the platinum stimulating contact and the target tissue increases beyond that of the original data used in the Shannon plot. Both the stimulating electric field and the reaction product concentrations fall off with separation between the current source and target cells. Nevertheless, even though target tissues may be at a distance, living cells are always adjacent to the electrode and their vitality should not be ignored.

In a previous paper [11], we explored electrochemical reactions occurring during the anodic phase of cathodic-first, charge-balanced, biphasic pulses on a platinum disk electrode (a.k.a. the model electrode, 0.785 mm$^2$) operating in a 0.15 M sulfuric acid electrolyte. These results gave insight into a possible explanation for why the $k = 1.75$ line on the Shannon plot defines the boundary above which stimulation-induced damage was observed in cat cortex [1]. $V_d(t = 20$ ms), the electrode potential just prior to the 1000th pulse at a 50 Hz pulsing rate, was the main parameter of interest in our measurements. The results indicated that with oxygen present, $V_d(t = 20$ ms) increases with increasing charge density. As charge injection exceeded $k = 1.75$, $V_d(t = 20$ ms) moves into a potential range where platinum dissolution products may be generated at an increased rate. Hence, we hypothesized that above $k = 1.75$, platinum dissolution products are generated at a rate that living systems cannot tolerate. This is consistent with data already reported in the literature, where platinum was detected in cat cortex at charge injection levels greater than $k = 1.75$ [12]. Platinum dissolution products are known to be toxic to living cells [13, 14].

For the sulfuric acid studies, measuring the peak positive potential and the potential at 20 ms after the onset of the cathodic phase showed that the platinum electrode potential ratchets positively with succeeding pulses, reaching values that are stable before 1000 pulses have been applied. Under steady-state conditions, with cathodic-first, charge-balanced, biphasic pulses (1000 pulses in these experiments), unrecoverable cathodic charge must be balanced by an equal amount of unrecoverable anodic charge during the balanced recharge phase. The likely unrecoverable reactions during the cathodic phase are oxygen reduction and diatomic hydrogen formation. Monoatomic hydrogen adsorption and desorption is generally considered a very fast reaction that would not contribute to unrecoverable cathodic reactions. During the anodic phase, likely unrecoverable reactions are platinum dissolution and oxidation of organic species.

In a de-oxygenated system over a range of $k$ values from 0.56 to 2.3, the positive potential never reached the place where platinum oxide formation would be predicted to occur, based on a slow $i(V_d)$ profile (100 mV s$^{-1}$ cyclic voltamogram). When oxygen was present, as it is in a living system, all electrode potentials were shifted to more positive values than observed in the de-oxygenated system. The anodic phase potentials moved more positive as charge injection levels were increased from $k = 0.56$ to $k = 1.68$. The rate of change in the anodic electrode potential decreased as the charge injection
Materials and methods

Pulsing experiments

The current pulse-capacitor discharge instrument (CP-CDi) and data processing procedures used were identical to those employed in experiments we previously carried out in sulfuric acid [11]. The experiments reported here can be viewed as replacing the sulfuric acid in the beaker with tissue in a living mammalian system (i.e. the rat subcutaneous space). Refer to the Materials and methods section of our previous paper [11] for additional details.

We chose to conduct initial studies [11] in sulfuric acid because it is a well-understood electrochemical system for platinum. We justified studying the electron transfer processes in sulfuric acid because the reactants in a 0.15 M sulfuric acid solution are the same as in animal (absent chloride): water, protons, and oxygen. Extending the analysis to the in vivo space required choosing an anatomical location that provides a stable, relevant environment in which to compare the electrochemical performance of electrodes meant for different neural stimulation applications. We chose the subcutaneous space of a live animal because it provides a buffered solution with realistic oxygen concentration, ion concentrations, proteins, amino acids, and water. These components are present throughout the body and have been identified as important factors when considering the electrochemistry of neural stimulation [15–17]. Although the electrodes we studied are intended for specific anatomical locations, under chronic implantation all electrodes are encapsulated by fibrous tissue, which acts as an ion/molecular filter, making the environment at the electrode surface more uniform between anatomical locations. The main difference between sulfuric acid and the subcutaneous space is that the pH is five or six units lower in sulfuric acid than in vivo. However, a consequence of this pH difference is an overall shift in the measured potentials at which reactions occur and not a change in the reactions themselves. Also, organic matter will be present in the in vivo environment, which can be oxidized but not likely reduced.

We use k as an indicator of charge injection because it tells the reader the stimulus level under consideration, independent of electrode area, and referenced to the boundary between safe and unsafe stimulation (k = 1.75). See figure 1 for the five stimulus values tested.

Animal preparation and instrumentation

Experiments were carried out in 15 adult Sprague-Dawley rats. The institutional animal care and use committee of Case Western Reserve University approved the experimental animal protocol. Animals were induced with ketamine IP 4–8 mg/100 g, xylazine IP 1 mg/100 g, and maintained with 3% isoflurane and oxygen inhaled to effect anesthesia. Respiration, eye blink, whisker response, and toe pinch response were monitored for anesthetic depth. A SurgiVet® pulse oximeter was used to monitor pulse and oxygenation. A warm water heating pad was placed under the animal to maintain a stable body temperature.

Following anesthesia, the back was shaved, and three ports into the subcutaneous space were created in the back and lateral aspects of the animal. Through these ports, we inserted: (1) one of the six electrodes to be studied; usually a large bore hypodermic needle was used to keep the open space to a minimum; (2) a counter or return electrode (a carbon rod, Alfa Aesar 40765); and (3) an Ag/AgCl reference electrode (Gamry, 930-00015). At the end of the test procedures, animals were euthanized by an overdose of EUTHASOL®. Experiments were carried out on a platinum model disk electrode (diameter of 0.1 cm, A = 0.785 mm², platinum purity 99.9%, EDAQ ET075-1) and five commercially-deployed electrodes of varying geometry: a cochlear implant electrode (A = 0.2 mm², Advanced Bionics HiFocus 1®), a paddle electrode (A = 4.2 mm², Boston Scientific SC-8216), a flattened cuff electrode (A = 4.8 mm², Boston Scientific, 001093), a DBS (Deep Brain Stimulation) electrode (A = 6.1 mm², Medtronic 3387), and a spinal cord stimulation (SCS) electrode (A = 12.7 mm², Boston Scientific SC-2366). All reported electrode potentials are referenced to the Ag/AgCl electrode. No additional fluid or electrolyte was added to the subcutaneous space to ensure the measurements reflected the natural in vivo environment.

Data collection and processing

Our measurements focused on the platinum electrode potential during the anodic phase of cathodic-first, charge-balanced, biphasic pulses. When a train of cathodic-first, charge-balanced, biphasic neural stimulation type pulses is delivered to a platinum electrode, particularly when oxygen is accessible, the electrode potential ratchets positively (in the anodic direction) with each successive pulse, increasing from k = 1.69 to k = 2.3; this behavior suggests that the electrode potential had entered a range where only small changes in electrode potential were necessary to support the increased charge injection associated with increased values of k. This means that a new source of electron transfer (i.e. a new electrochemical reaction) becomes available in this potential range. This behavior occurred in a potential range where the platinum oxidation and platinum dissolution are likely to occur in chloride-containing electrolyte.

Electrochemical experiments carried out in a highly controlled medium, like sulfuric acid, can be very informative but skeptics too easily discount results as irrelevant to living systems. Further, finding a suitable electrolyte that satisfies the skeptics is challenging. In this report, we addressed that challenge by repeating the sulfuric acid experiments in the subcutaneous space of an anesthetized rat model to determine if the electrode potentials behave similarly in an in vivo environment and across the range of macroelectrode sizes. The subcutaneous space of a live animal provides a buffered solution with realistic oxygen concentration, ion concentrations, proteins, amino acids, and water. In addition to the sulfuric acid, the Ag/AgCl reference electrode (Gamry, 930-00015) provided the increased charge injection associated with increased stimulus values tested.

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until the unrecoverable charge in the anodic phase is equal to the unrecoverable charge in the cathodic phase [11]. The electrode potential stabilizes after a few tens of pulses and the 1000th pulse was recorded. While each \( k \)-value measurement was carried out for 20 s (=1000 pulses), each animal experiment averaged about a 6 h implanted-electrode time (table 1). From the recording, the reported values are: the end potential (20 ms after the 999th pulse), the peak cathodic potential, and the peak anodic potential (see figure 2 [11]). Because the potential waveform has stabilized, we assume the end potential is the same as the electrode potential 20 ms after the onset of the 1000th pulse. All reported electrode potential values were recorded versus an Ag/AgCl reference electrode. For all reported peak cathodic potentials and peak anodic potentials, the ohmic component (i.e. IR drop, access voltage) was removed using the iterative process outlined in our previous publication [11]. Hence, the peak cathodic and anodic potentials are due to the electron transfer processes occurring at the electrode-tissue interface during each phase of a pulse. Because net current through the system is virtually zero when the start potentials and end potentials are measured, there is no ohmic component to subtract, so these are raw data values.

**Results**

**Model disk electrode: electrode potentials in rat subcutaneous space**

Electrode potential data from the model disk electrode implanted in rat subcutaneous space are plotted in figure 3. The peak anodic potentials and end potentials were similar to those collected in a sulfuric acid electrolyte with oxygen available as reported in our companion paper [11]. Figure 3 shows the results for the model disk electrode derived from the sulfuric acid experiments (top portion) and from the acute rat experiments (bottom portion). The \( i(V_e) \) profiles for both cases are also included as a reference for what electrochemical reactions are possible at these potentials [18].

Because of the pH difference between the rat (assumed pH of 7.2) and sulfuric acid (measured pH of 1.1), there is a Nernst potential shift of 0.36 V (see appendix for details of calculation). In figure 3, the potential axis for the animal data has been shifted 0.36 V to account for this difference. Correcting this offset emphasizes the similarity in electrode potential behavior for the data collected in sulfuric acid and in the animal. Specifically, the behavior of the end potentials, as \( k \) is increased, is very similar in each medium. The interpolated point where the end potential (red trace) crosses the horizontal \( k = 1.75 \) line has been indicated by the black vertical line spanning all six panels.

In the animal and in sulfuric acid, the end potential (open red data points) increases with increasing charge injection. As the charge injection level crosses the \( k = 1.75 \) line, the rate at which the potential increases slows down. This implies that an electron transfer process has become available that can satisfy the need for increased unrecoverable reactions during the anodic phase with little increase in electrode potential. This behavior occurs in the potential region for platinum oxidation and dissolution on the \( i(V_e) \) profile.

**Model disk electrode: increasing the rate at which charge is returned in the anodic phase**

The rate charge is injected during the anodic phase and can be changed by the choice of the inline capacitor used in the CP-CDi. For the same charge injected during the cathodic
In the anodic phase, the inline capacitor will charge to higher voltages with smaller values of capacitance. Capacitors charged to higher voltages will drive higher currents, and smaller capacitors will discharge more quickly than capacitors with higher values. Insight into the behavior of the electrode potential during rapid and slow discharge rates was gained through experiments using two inline capacitor values: 1.0 µF for low-level slow return and 0.1 µF for high-level rapid return. The current and $V_e(t)$ waveforms for the two capacitor values are shown in figure 4.

Since charge-balanced/biphasic stimuli are often thought of as symmetrical biphasic current pulses, we have included a ghost of a symmetrical biphasic waveform for the anodic phase (gray dashed line, figure 4). Note that the peak of the anodic potential is displaced further from the initiation of the anodic phase when the smaller capacitor is employed as the inline capacitor.

The results of electrode potential measurements during the anodic phase (when a rapid and a slow discharge rate were
The second panel is a vertically expanded version to highlight the anodic sweep of the first panel but on the same horizontal scale. The third panel presents the results for electrode potential measurements made at increasing charge injection values \((k = 0.566–2.3)\) with a 1 \(\mu F\) CP-CDi inline capacitor. The fourth panel shows the results for electrode potential measurements made at increasing charge injection values \((k = 0.566–2.3)\) with a 0.1 \(\mu F\) inline capacitor.

In the panels, the red square symbols represent the potential at the end of 20 ms and the blue round symbols represent the peak anodic potential. The use of the smaller 0.1 \(\mu F\) capacitor produces a higher discharge current compared to the current with the 1.0 \(\mu F\) capacitor, and the anodic phase discharge is faster. Data acquired for the higher, quicker discharge rates produced less positive anodic potentials at 20 ms after the delivery of the 1000th pulse (red open symbols on 0.1 \(\mu F\) plot) than did the lower, slower discharge rate (red open symbols on the 1 \(\mu F\) plot). The peak anodic potentials for the 1000th pulse displayed the opposite behavior; they were greater for the higher, quicker discharge rates. Higher anodic potentials are expected to correlate with higher platinum dissolution rates—the kinetics of platinum dissolution may play a role. The peak cathodic potentials recorded during these experiments are also indicated by open green triangle symbols. It should be noted that at all charge injection levels tested, the magnitude of the peak cathodic potential exceeds the potential for hydrogen evolution as predicted by the \(i(V_e)\) profile, shown in the upper two panels of figure 5. However, this does not necessarily mean that hydrogen evolution was occurring at these pulse levels. Because of kinetic limitations and the diffusion limitation of hydrogen, the hydrogen evolution reaction \([19, 20]\) may not have time to occur during the brief time the potential is in the cathodic region, whereas with an \(i(V_e)\) profile, the slow scan rate allows enough time for the reaction to occur.

**Commercially-deployed electrodes: electrode potentials in rat subcutaneous space**

Figure 5 shows the \(i(V_e)\) profile (top two panels) and CP-CDi potential data recorded in the animal using the same platinum model disk electrode used in our previous studies with sulfuric acid \([11]\). The data presented are from the 1000th pulse in a train of 100 \(\mu s\) pulses at 50 Hz. The first panel shows the \(i(V_e)\) profile recorded at 100 mV s\(^{-1}\). The second panel is a vertically expanded version to highlight the anodic sweep of the first panel and in rat subcutaneous space. The third panel for each set shows the results for electrode potential measurements made at increasing charge injection values \((k = 0.566–2.3)\) with a 1 \(\mu F\) CP-CDi inline capacitor. The fourth panel shows the results for electrode potential measurements made at increasing charge injection values \((k = 0.566–2.3)\) with a 0.1 \(\mu F\) inline capacitor.

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**Figure 3.** Shown in this figure are \(i(V_e)\) profiles and CP-CDi potentials recorded using the model disk electrode in sulfuric acid (top, first panel) and in rat subcutaneous space (fourth panel). The first panel in each set shows the \(i(V_e)\) profile recorded at 100 mV s\(^{-1}\). The second panel is a vertically expanded version to highlight the anodic sweep of the \(i(V_e)\) profile, but on the same horizontal scale. The third panel for each set shows the results for electrode potential measurements made at increasing charge injection values \((k = 0.566–2.3)\). The data are from the 1000th pulse in a train of 100 \(\mu s\) pulses at 50 Hz using a 1.0 \(\mu F\) inline capacitor to produce the anodic phase. The red round symbols represent the end potential \(V_d(t = 20 \text{ ms})\) and the blue square symbols represent the peak anodic potential as defined in figure 2. Because of the pH difference between the rat (assumed pH of 7.2) and sulfuric acid (measured pH of 1.1), there is a Nernst potential shift of 0.36 V (see appendix for details of calculation). The potential axes for the animal and sulfuric acid data were shifted 0.36 V to account for this difference. Correcting this offset emphasizes the similarity in electrode potential behavior for the data collected in sulfuric acid and in the animal. Specifically, the behavior of the end potentials as \(k\) is increased is very similar in each medium. The interpolated point where the end potential (red trace) crosses the horizontal \(k = 1.75\) line has been indicated by the black vertical line spanning all six panels.
out: (1) the similarity in behavior recorded for the end potentials over the group of electrodes and (2) the large values recorded for the cathodic potential. It is unclear why cathodic potentials for certain electrodes (paddle, DBS, and SCS) were much greater in magnitude than the others. It is also noteworthy that the larger $V_e$ (peak anodic) potentials also occurred when the larger cathodic potentials were recorded. We deal with these large cathodic potential issues in the Discussion section.

The $V_e(t = 20\text{ ms})$ data (end potentials) recorded from experiments involving all five commercial electrodes and the model disk electrode are shown in box and whisker plots in figure 7. Data recorded when the inline capacitor was 1.0 $\mu$F (slow discharge) are shown the top panel and 0.1 $\mu$F (rapid discharge) are shown the lower panel.

The slow discharge data (dashed black trace in upper panel) show $V_e(t = 20\text{ ms})$ increasing with increasing charge injection from $k = 0.556$ through $k = 1.66$ for a Tukey–Kramer test with $\alpha = 0.05$. From $k = 1.66$ through $k = 2.3$ the data are not statistically different. (The slow discharge data are replotted in the lower panel for comparison.)

The rapid discharge data (solid black trace in lower panel) show $V_e(t = 20\text{ ms})$ increasing with increasing charge injection from $k = 0.556$ through $k = 1.24$ for a Tukey–Kramer test with $\alpha = 0.05$. From $k = 1.24$ through $k = 2.3$ the data are not statistically different. (The slow discharge data are replotted in the lower panel for comparison.)

**Discussion**

We have studied the electron transfer processes occurring on platinum neural stimulation electrodes *in vivo* with 100 $\mu$s, cathodic-first, charge-balanced, biphasic neural stimulation pulses. Our aim is to understand the electron transfer processes occurring on platinum electrodes. We believe that knowledge of these processes will point to a way to extend the charge-injection limits beyond $k = 1.75$, a common limit for safe neural stimulation with platinum electrodes. Our results apply to the range of commercially deployed electrodes with geometric surface areas from 0.2 mm$^2$ (cochlear prosthesis...
The primary focus was on the end potential, \( V_e(t = 20 \text{ ms}) \), a parameter related to unrecoverable anodic reactions. The important findings of this study are:

1. The limit \( k = 1.75 \) on the Shannon plot defines the boundary where, histological data derived from animal studies, revealed stimulation-induced changes to cells in cat cortex, and this limit coincides with a transition region where platinum dissolution accelerates as the charge injection through the electrode increases, independent of electrode surface area.

2. Increased dissolution rate is predicted by measurements made of the electrode potential, \( V_e(t = 20 \text{ ms}) \). At \( k > 1.75 \), \( V_e(t = 20 \text{ ms}) \) increased very little indicating that an electron transfer process became available that could accommodate increased charge with only slight increases in \( V_e(t = 20 \text{ ms}) \). When \( k > 1.75 \), the \( V_e(t = 20 \text{ ms}) \) coincided with the region of the \( i(V_e) \) profile where platinum oxidation and dissolution are likely.

3. The behavior of \( V_e(t = 20 \text{ ms}) \) in the animal was like that observed in oxygenated sulfuric acid \([11]\). The differences were:
   a. A shift in the potential axis that was accounted for by the pH change.
   b. The presence of chloride, other ions, and organic molecules in the animal.
   c. Electron transfer processes were more easily identified in the sulfuric acid environment because surface contaminants (like organic molecules) were in a much lower concentration \([16]\).
Why platinum dissolution products?

The focus of this project has been on the generation of platinum dissolution products as a candidate explanation for the utility of the Shannon plot. We want to point out the following anecdotal evidence that makes platinum dissolution products a logical candidate to explore:

- Platinum is, by far, the most commonly used metal in neural stimulation devices.
- The results of our *in vivo* and *in vitro* [11] studies indicate that during a train of cathodic-first, charge-balanced, biphasic pulses, the anodic potential reaches a steady state that increases with increasing charge injection (increasing $k$). More positive potential levels...
• Current passage through platinum electrodes has been shown to be toxic to bacteria [14], and Rosenberg’s findings have been refined and subsequently employed to kill tumor cells, specifically testicular cancer [22].

• Platinum compounds, used to treat cancer, are reported to have neurotoxic effects [23].

**Model disk electrode: in sulfuric acid and rat subcutaneous space**

In comparison with Pt in sulfuric acid. During the application of neural stimulation type current pulses, the potential of a Pt electrode reaches the platinum oxidation region in both animal tissue and in a sulfuric acid electrolyte. This was evident after examining the value reached by the end potential during the 1000th pulse, and by seeing what reactions are plausible at that potential, specifically by looking at the \( i(V_e) \) profile (cyclic voltammogram) of the respective media in which the pulsing experiments were carried out. Doing so reveals that the Pt in sulfuric acid with dissolved O\(_2\) present and the Pt in an animal both reach a potential where Pt oxide is forming, seemingly in a region where the Pt oxide formation is still reversible [24]. This lends credence to previous studies done in sulfuric acid to gain insight on how implanted Pt electrodes behave during stimulation [11].

**Anodic phase potentials and platinum dissolution.** Platinum dissolution is predicted to increase with increasing anodic phase potentials. The anodic-phase electrode potential, during a train of cathodic-first, charge-balanced, biphasic pulses ratchets up to a steady-state value that depends on the charge injected into unrecoverable processes during the cathodic phase. Under steady-state conditions with charge-balanced pulses, the amount of charge injected into unrecoverable reactions in the cathodic phase must be balanced with unrecoverable charge in the anodic phase. In the cathodic phase, the likely unrecoverable electron transfer reactions are: oxygen reduction, and hydrogen evolution. Adsorption and desorption of monoatomic hydrogen is assumed to be reversible in these experiments. In the anodic phase, the likely unrecoverable reactions are: platinum oxidation, platinum dissolution, and oxidation of organics. The higher the potential during the anodic phase, the higher the probability these unrecoverable reactions will occur. As charge injection is increased from \( k = 0.566 \) to \( k = 2.3 \), more charge is lost to unrecoverable cathodic reactions. This was clearly evident in the sulfuric acid experiments when nitrogen was used to rid the system of dissolved oxygen [11].

In this study, for charge-injection levels below \( k = 1.75 \), the anodic potentials measured ~20 ms after the onset of the biphasic pulse increase with increasing \( k \) and are significantly different from the means at other \( k \) values (see figure 7). Above \( k = 1.75 \), the anodic potentials were increasing but were not significantly different from each other. This result implies that the electrode potential is in a range where increased electron transfer reactions take place with only a small increase in electrode potential, i.e. reactants are accessible that can be oxidized. On the \( i(V_e) \) profile for the platinum electrode, this
potential range coincides with the onset of platinum oxide forma-
tion. Platinum may be released during oxide reduction [5] and/or through the formation of soluble platinum salts formed in
the presence of the chloride ion (Cl\textsuperscript{−}).
While one might argue that the small increase in 
\(V_e(t = 20 \text{ ms})\) at \(k > 1.75\) could be explained by a plateau in
unrecoverable cathodic reaction products as charge injection
increases, the cathodic potentials for these experiments do not
support this explanation. The de-oxygenated sulfuric acid
experiments indicate that the peak cathodic potentials do not
plateau as \(k\) is increased [11].
Although oxidation of organic molecules is possible above
platinum’s rest potential, platinum dissolution is likely to be
the dominant unrecoverable anodic process [25]. Kumsa et al
[6] provides experimental data showing platinum dissolution
rises in an exponential manner as charge injection approaches
and surpasses \(k = 1.75\). These findings are consistent with the
hypothesis that the \(k = 1.75\) Shannon limit for safe stimula-
tion designates a charge-injection boundary above which plat-
inum toxicity becomes a relevant consideration for living cells
around an electrode.

Tuning the rate of charge return in the anodic phase. With
cathodic-first, charge-balanced, biphasic pulses under steady-
state conditions, the charge involved in the unrecoverable
faradaic reactions during the cathodic and anodic phases
must be equal. For the experiments depicted in figure 5, one
could reasonably expect that the faradaic reactions during the
cathodic phase would be the same for both discharge capacitor
experiments. However, these data do not clearly show that the
anodic faradaic reactions are the same. With the slower return,
1 \(\mu\)F inline capacitor, it is likely that all of the charge going
into the anodic unrecoverable faradaic reactions compensates
for the cathodic unrecoverable faradaic reactions. With the 0.1
\(\mu\)F capacitor, the rapid return could reverse a cathodic fara-
daic reaction (e.g. oxidize a reduced oxygen molecule or ox-
dize diatomic hydrogen), which would require less balancing
charge from an anodic unrecoverable faradaic reaction. If less
charge went into such a reaction, then less anodic reaction
products would be generated than with the slow return. Dis-
solution experiments would indicate if there was an advantage
for a fast anodic return.
Some commercial devices use an in-line capacitor to help
correct charge imbalance because of imprecision in the bal-
anced pulses and to prevent passing direct current. For these
experiments, the CP-CDI was designed to produce precisely balanced charge pulse outputs [11]. A regulated current
pulse generator created a positive current pulse that passed
through an inline capacitor and returned to the negative ter-
minus of the regulated pulse generator. All charge flowing
through the electrodes was stored on an inline capacitor.
After a delay phase, the inline capacitor created a discharge
current back through the electrodes as the anodic phase. This
allowed accurate pulse outputs that were applied to the test
electrodes.
The meaning behind measured electrode potentials. The
measured electrode potential, \(V_e(t)\), contains an ohmic
component that does not contribute to the electron transfer
reactions that cause \(V_e\).
\[ V_e(t) = V_e(t) + V_O(t) = V_e(t) + i(t) (R_O) . \]
The ohmic component must be removed to get an accurate
representation of \(V_e\), the electrode potential. At \(t = 20 \text{ ms}\) after
the onset of the cathodic pulse \(i(t)\) was always zero in these
experiments, so \(V_e(t = 20 \text{ ms})\) is an accurate representation of
the electrode potential, \(V_e\). For other times during the stimulus
pulse, \(i(t)\) is not zero. On these occasions, an estimate of \(R_O\)
would be required to calculate \(V_e(t)\) and that value would be
multiplied by the current as in the equation above. The pro-
cess for removing the ohmic component (i.e. IR drop, access
voltage) was described in detail in our previous publication
[11].

On comparing different sized electrodes implanted in
animals. We are using \(k\) as a measure of charge injec-
tion because it provides an indicator of when an electrode
would cause tissue damage according to the Shannon criteria,
regardless of electrode size. For a macroelectrode of any size,
injecting charge at \(k < 1.75\) is in a range safe for stimulation
as predicted by the Shannon plot, and \(k > 1.75\) is in a range
that resulted in histology that was deemed damaging to cat
cortex. Shannon’s formulation implies that along a specific
\(k\) line (e.g. \(k = 1.75\), large-area and small-area electrodes
behave the same when it comes to tissue damage. If a small
electrode is considered safe at a specific \(k\) value, then a large
electrode is also safe at the same \(k\) value. Our findings support
the prediction.

The data reported in figure 6 show that the end potential
\(V_e(t = 20 \text{ ms})\) data for electrodes in the size range 0.2 to
12.7 mm\(^2\) were very similar, though not exactly alike. The dif-
fferences are more apparent when the \(V_e(t = 20 \text{ ms})\) data are
plotted on an expanded scale as in figure 8.
In an effort to tease out the meaning behind the differences,
we constructed a box and whisker plot for all end potential
\(V_e(t = 20 \text{ ms})\) data as a function of electrode size, shown in
figure 9.

Using a Tukey–Kramer all-pairs comparison test with a
confidence interval of 0.95, a statistical analysis of the end
potential \(V_e(t = 20 \text{ ms})\) data in figure 9 indicated that only the
pair composed of 4.2 mm\(^2\) and 12.7 mm\(^2\) were different from
each other; otherwise, the end potentials were not significantly
different. This is consistent with Shannon’s implicit statement
that large and small electrode behave the same. Considering
the inherent variability in acute in vivo experiments, had
more data been collected from these animals, perhaps no sig-
nificant difference would be found between the end potential
\(V_e(t = 20 \text{ ms})\) data for all electrode sizes.
Shannon’s formulation was derived from histological data
[2] originating from electrically-stimulated cat cortex with
electrodes of a specific size. Additional data showing obser-
vations of damage and evidence for platinum in tissue were
added to the Shannon plot in figure 10 [2, 12, 26–28].
Implicit, but little noticed, in Shannon’s formulation, is
that small and large platinum electrodes behave the
same in terms of \(k\) value. Therefore, we hypothesize that
the dissolution data reported by Kumsa et al [6] (for a 0.785 mm² platinum electrode) would be similar for any platinum electrode with an area between 0.2 mm² and 12.7 mm², which could be proven through additional platinum dissolution experiments over this size range. A correlation between stimulation \( k \) level and an increased platinum dissolution rate above \( k = 1.75 \) would support the hypothesis that platinum dissolution is the underlying reason behind the \( k = 1.75 \) limit for tissue damage. In other words, regardless of electrode size, if stimulation is pushed above \( k = 1.75 \), a toxic level of platinum is released from the electrode, causing the changes deemed by the HRMI investigators to be damaging.

Knowing that large and small electrodes behave the same may also be useful in regard to stimulation safety testing required for new neural prostheses. If it could be shown that the safety of a large platinum electrode in a large subject could be predicted using small electrodes in a small animal, the expense of these experiments and concerns over laboratory animal welfare could be decreased.

On the peak cathodic potential \( V_e(t = 100 \ \mu s) \). Unlike \( V_e(t = 20 \ \mu s) \), the choice of \( R_\Omega \) impacts the plotted \( V_e(t = 100 \ \mu s) \), larger values of \( R_\Omega \) will make the plotted/calculated value of \( V_e(t = 100 \ \mu s) \) smaller. Using the graphical procedure described in the Materials and methods

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**Figure 8.** Electrode potential at 20 ms after the onset of the 999th pulse for six electrodes with areas ranging from 0.2 mm² to 12.7 mm². The data shown here are the same end potential \( V_e(t = 20 \ \mu s) \) data shown in figure 6, but at an expanded potential scale.
Figure 9. Box-and-whisker plots of all end potential data versus electrode area. Shannon’s formulation of the tissue damage data recorded in cat cortex implicitly states that large and small area electrodes behave the same at like charge injection values when viewed in terms of $k$ values. If our data for $V_e(t = 20\text{ms})$ are consistent with this statement, there would be no statistical difference between the data collected for the six electrodes. We tested this hypothesis using the Tukey–Kramer method at a 0.95 confidence level for the five $k$ values used on six electrode areas and found that in the whole data set, only the pair composed of 0.042 cm$^2$ and 0.127 cm$^2$ were different from each other. Considering the inherent variability in acute *in vivo* experiments, had more data been collected from these animals, perhaps no significant difference would be found between the end potential $V_e(t = 20\text{ms})$ data for all electrode sizes. Overlap of circles in the right column indicate degree of lack of significant difference in the means by Tukey–Kramer HSD test.

Figure 10. Shannon plot for safe stimulation parameters derived from animal studies listed in the right-hand side of the figure. The data were derived from studies using charge-balanced/biphasic stimulation on platinum electrodes tested on brain tissue. Open symbols and green filled symbols represent findings where the investigators did not observe damage. Filled black and red symbols represent findings where investigators observed damage.
section depicted on figure 7 in Kumsa [11] for subtracting the ohmic component, the peak cathodic potentials appear too large (in the 6–10 V range) for the paddle electrode, the DBS electrode, and the SCS electrode. At first, we thought the $R_\Omega$ for these electrodes must be too small, but the value chosen using this procedure was found to be nearly identical to the true ohmic value measured with electrochemical impedance spectroscopy (EIS), equating the highest-frequency (100kHz) EIS impedance with the ohmic component. Because of this, we could not rationalize using larger values for $R_\Omega$. The rationale for the graphical method outlined in Kumsa [11] is basically the same rationale as that used in Cogan et al [3] to determine $E_{mc}$. Which is that the solution resistance is modeled after a resistor and will change linearly with the current applied while the electrode–electrolyte interface has a capacitive component that will delay its response to imposed voltage drop.

We considered an idea put forward by John Newman [29] that charge separation occurring beyond the electrode–electrolyte interface gave rise to a measured potential that was not related to $V_e$. The phenomenon Newman described came about in dilute electrolytes (0.001 M KCl) at very high current densities (10 A cm$^{-2}$). Our animal experiments were conducted in the 1.0 A cm$^{-2}$ range, and the concentration of the electrolyte is in the range of 0.1 M, so it may be an unlikely explanation for the large cathodic potentials we measured. Although we have confidence in our experimental setup and data processing methods, the large potentials observed for the paddle, DBS, and SCS electrodes are not likely to be accurate reflections of $V_e$ during the cathodic phase of charge injection.

**On belief and bias.** Some have expressed cynicism of our hypothesis: an increase in platinum dissolution is the defining factor of the $k = 1.75$ Shannon limit for cathodic-first, charge-balanced, biphasic pulses. For instance, one critic commented, ‘Stating that platinum dissolution is the prime mechanism of tissue damage belies decades of research on neural hyperexcitability as a damage mechanism.’ We want to point out that decades of research is actually decades of taking faith in a hypothesis.

‘The results also support the hypothesis of neuronal hyperactivity as a principal cause of electrically-induced injury in the central nervous system’. (Quotation taken from the abstract of the MK-801 paper by Agnew and colleagues [30].)

The only piece of experimental data shown in this work [30] dealing with the excitotoxicity claim in the abstract is a measure of the evoked compound action potential from two cats in figures 10(A) and (B) from Agnew et al [30]. If indeed MK-801 protected neurons by reducing their excitability, then the case with the highest dose of MK-801 administered should show a significant decrease in excitability when compared to the control, but this was not the case. The authors themselves acknowledged this lack of proof in the body of the paper; a statement in the Discussion section reads:

‘Therefore, it seems unlikely that MK-801 protects neurons simply by reducing their excitability.’

Although some members of the neural prosthesis community may not be able to relinquish their long-held belief, we hope that resistance can be lowered enough to consider the testable hypothesis we propose.

**Conclusions**

The results of these in vivo experiments show a compelling correlation between stimulation $k$ level and potentials for platinum oxidation and dissolution, regardless of electrode size. This is consistent with the Shannon plot’s implicit statement that small and large electrodes behave the same in terms of $k$. The behavior of the end potential $V_e(t = 20\text{ ms})$ as a function of $k$ was very similar over a range of surface areas from electrodes for cochlear implants to electrodes for spinal cord stimulators; as the $k$ level of stimulation is pushed past 1.75, $V_e(t = 20\text{ ms})$ enters a potential region where platinum oxidation/dissolution is likely to occur. ICP-MS measurements for dissolved platinum confirmed that when crossing $k = 1.75$, a significant increase in platinum dissolution occurs [6]. These results support the hypothesis that an increase in platinum dissolution is the defining factor of the $k = 1.75$ Shannon limit for cathodic-first, charge-balanced, biphasic pulses.

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Authorship statements

Dr Mortimer designed the project, secured funding, managed the study, and took the primary role in analyzing data and writing the manuscript. Dr Kumsa took primary responsibility for carrying out the electrochemical measurements, managing data collection, processing the data, generating graphs, and secondary responsibility for manuscript development and analyzing data; Dr Bhadra took primary responsibility for the statistical analysis of acquired data and provided guidance on the design of the animal experiments. Dr Hudak was involved in data interpretation, contributed background information/literature on platinum oxidation and dissolution phenomena, and assisted in writing the manuscript.

Appendix

Understanding $\Delta E$ calculation caused by pH shift.

$$T = \text{temperature in kelvin}$$
$$F = \text{Faraday’s constant}$$
$$n = \text{number of electrons transferred}$$
$$E^0 = \text{standard reduction potential}$$
$$R = \text{universal gas constant}$$
$$\text{For the reaction: } 2\text{H}^+ + 2e^- \rightarrow \text{H}_2$$

Let subscripts I and II represent the different concentrations of H$^+$ in the sulfuric acid electrolyte and the rat.

$$E_I = E^0 + 2.3 \frac{F}{RT} \log [\text{H}^+]_I^2$$ Nernst equation for the reduction reaction shown above $E_I = E^0 + 2 \left(2.3 \frac{F}{RT} \log [\text{H}^+]_I\right)$ with $n = 2$ and $E^0$ is the standard reduction potential for the hydrogen reduction reaction, which is 0.

$$E_I = 2.3 \frac{F}{RT} \log [\text{H}^+]_I = -2.3 \frac{F}{RT} \text{pH} \text{ since pH} = -\log[\text{H}^+]$$
$$E_I = -0.059 \text{ pH}.$$

Similarly,

$$E_{II} = -0.059 \text{ pH}$$

$$\Delta E = E_{II} - E_I = 0.059(\Delta \text{pH})$$

$$\Delta \text{pH} = 7.2 - 1.1 = 6.1$$

$$\Delta E = 0.059(6.1) = 0.36 \text{ V}.$$

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