Electron transfer processes occurring on platinum neural stimulating electrodes: pulsing experiments for cathodic-first/charge-balanced/biphasic pulses for $0.566 \leq k \geq 2.3$ in oxygenated and deoxygenated sulfuric acid

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Abstract

The application of a train of cathodic-first/charge-balanced/biphasic pulses applied to a platinum electrode resulted in a positive creep of the anodic phase potential that increases with increasing charge injection but reaches a steady-state value before 1000 pulses have been delivered. The increase follows from the fact that charge going into irreversible reactions occurring during the anodic phase must equal the charge going into irreversible reactions during the cathodic phase for charge-balanced pulses. In an oxygenated electrolyte the drift of the measured positive potential moved into the platinum oxidation region of the $i(V_e)$ profile when the charge injection level exceeds $k = 1.75$. Platinum dissolution may occur in this region and $k = 1.75$ defines a boundary between damaging and non-damaging levels on the Shannon Plot. In a very low oxygen environment, the positive potential remained below the platinum oxidation region for the highest charge injection values studied, $k = 2.3$. The results support the hypothesis that platinum dissolution is the defining factor for the Shannon limit, $k = 1.75$. Numerous instrumentation issues were encountered in the course of making measurements. The solutions to these issues are provided.

Keywords: platinum electrochemistry, electrical stimulation, neural stimulation

(Some figures may appear in colour only in the online journal)

Introduction

The Shannon [1] Plot, generally speaking, is the de facto touchstone for setting the upper limit for neural stimulation with platinum electrodes. Our goal is to find a way to extend the $k = 1.75$ limit, established for safe neural stimulation. The $k = 1.75$ limit was established by histological data collected from cat brain,
and \( k = 1.75 \) was chosen as it defines a line slightly below the first datum point for stimulation-induced damage.

The cause of tissue damage during neural stimulation is unresolved. Two candidate theories are: cell death brought on by a large number of cells being unnaturally stimulated for long periods of time (hyperactivity) and toxic products due to electron transfer processes (electrochemical reactions). These candidates are not mutually exclusive. The work in this report focuses on the products of electron transfer occurring during the anodic phase of a cathodic-first, charge-balanced pulse. We foresee that a better understanding of electron transfer processes occurring on platinum stimulating electrodes will lead to ways to increase the charge injection levels beyond those currently permitted for safe neural stimulation.

Several empirical studies evaluated the tissue response to electrical stimulation. Using data from stimulation of cat cortex published by Pudenz et al 1975 [2], McCreery and Agnew et al [3, 4] of the Huntington Medical Research Institutes, Shannon [1] found that histology data showing damaged cells could be separated from those showing no damage when the data were plotted as \( \log (Q/A) \) on the horizontal axis and \( \log (charge/density) \) on the vertical axis. Data deemed not damaging by McCreery [4] lay to the left of a line defined by

\[
\log (Q/A/\text{phase}) = k - \log (Q/\text{phase})
\]

Shannon [1] proposed a value of \( k = 1.5 \) to add a factor of safety; he, thus, defined regions to the left of the line as safe. In the course of building neural prostheses, many of us found the limit defined by \( k = 1.5 \) too restrictive and have chosen to use a value of \( k = 1.75 \) as it defines a line that approaches closest to the lowest datum point deemed injurious. In addition, if McCreery’s data are examined more closely, the limit between damaging and non-damaging stimulation is very close to \( k = 1.75 \) (Merrill 2005 [5]).

The data regarding the boundary separating damaging and non damaging levels came entirely from experiments carried out on cat brain with the platinum stimulating electrode placed below the dura and on the pial surface; i.e. close to the target tissues for neural stimulation (Pudenz [2]; Yuen [6]; McCreery [3]). Further, these data were acquired using platinum electrode contacts on various areas of the brain surface with a distant counter electrode. The data forming the basis of the Shannon Plot are an excellent set to work with for situations where the electrode is in close contact with the target tissues, i.e. any electrochemical reaction products are in their highest concentration at close proximity to cells of interest.

The work reported here focuses on the processes involved with electron transfer as charge injection increases from values accepted as safe into the range where safety is less well accepted, i.e. from \( k < 1.75 \) to \( k > 1.75 \). In figure 1, we show a Shannon-type plot derived from experiments performed with platinum electrodes of differing sizes and 10 mm² stainless steel stimulating electrodes used in intra-muscular applications. We include the stainless steel data because of the insights gained in extending stainless steel electrodes’ safe range of stimulation, which will benefit our understanding in experiments focused on platinum.

Consider first the platinum experiments, shown as gray-outlined symbols in figure 1. The black-filled symbols represent histological results that suggested neural tissues had been compromised by stimulation at that level. Open gray symbols represent histological results that suggested neural tissues had not been compromised by stimulation at that level. When a line \( k = 1.75 \) is drawn, all open gray symbols are separated from the black-filled symbols, forming the basis for making \( k = 1.75 \) the upper limit for safe stimulation. Added to this plot are the red and green-filled data points (Robblee [7]): the red-filled triangle indicates that platinum was found in the stimulated brain tissue and the green-filled datum point indicates that no platinum was found in the stimulated brain tissue. Finding platinum dissolution products in the tissue at a charge injection \( k > 1.75 \) calls to mind that the upper limit for stainless steel was also caused by corrosion.

Experience with stainless steel stimulating electrodes (shown as blue-outlined symbols in figure 1), with an estimated surface area of 10 mm², taught us that the limit imposed by charge-balanced/biphasic pulses was 40 \( \mu \text{C cm}^{-2} \). At charge injection levels above that, the electrode would corrode and dissolve (brown-filled circles in figure 1). At 40 \( \mu \text{C cm}^{-2} \), the potential during the anodic phase of the balanced-charge biphasic pulse reached 0.43 V(Ag/AgCl), the corrosion potential for 316 LVM stainless steel (Lan [8]). Perhaps platinum follows a behavior like stainless steel? At charge injection levels below 40 \( \mu \text{C cm}^{-2} \) muscle tissues did not show indications of injury, and no sign of electrode corrosion was noted (Mortimer et al [9], Scheiner 1990 [10]). Plotting the stainless steel results on the Shannon Plot for the 10 mm² electrode yielded an upper limit on a \( k \) value of 2.2 for 316 LVM stainless steel. Further, metal dissolution could be avoided and no added trauma to muscle cells occurred if less charge was injected during the anodic phase of the cathodic-first biphasic pulse (Scheiner [10]). Such a stimulation waveform is said to be charge-imbalanced, biphasic stimulation. Charge injection with imbalanced biphasic stimulation was increased by a factor of six, from \( k = 2.2 \) to \( k = 3.16 \) (open blue squares) without causing tissue injury.

Turning to the platinum results, graphed on the Shannon Plot (gray outlines in figure 1), we note the following anecdotal evidence for platinum dissolution products:

1. They have been reported in brain tissue when the \( k = 1.75 \) line is crossed (filled red triangle, Robblee [7]).
2. They have been reported in \textit{in vitro} studies at charge injection levels in excess of \( k = 1.75 \) (McHardy [11]).
3. They have, in the form of platinum salts, been injected into brain and produced results similar to that seen in stimulated brain tissue at \( k \) values greater than 1.75 (Agnew [12])

- Points one through three have languished in the background since the mid 1980s.
4. They have been shown to be toxic to bacteria (Rosenberg [13]), and Rosenberg’s findings have been refined and subsequently employed to kill tumor cells, specifically testicular cancer4.

Cognizant of the stainless steel experience and suspecting that platinum dissolution may participate in the neural tissue injury reported when charge injection levels exceed \( k = 1.75 \), we undertook electrochemical measurements on platinum electrodes to study the electron transfer reactions occurring under pulsed conditions like those employed in neural stimulation conditions.

Sulfuric acid may at first seem like an odd choice for an initial study related to neural stimulation involving living cells; however, its relevance can be established. It is a well-understood system for platinum electrochemistry and the reactants in a 0.15 M sulfuric acid solution are: water, protons, hydroxide ions, and oxygen—the same as in a living system with the absence of chloride. In the living system, organic matter will be present, which can be oxidized but not likely reduced. The main differences are: (1) the pH is five or six units lower than in the body, the primary consequence of which is an overall shift in the potentials at which reactions occur, not a change in the reactions themselves; (2) no chloride is present.

We use \( k \) as an indicator of charge injection because it indicates the stimulus level, independent of electrode area, under consideration. Thinking in terms of ‘\( k \)’ will turn out to be quite informative when the electron transfer processes are plotted for electrode areas that cover the range used in devices such as cochlear prostheses and spinal cord stimulation. As a thought exercise, look at figure 1 and follow the \( k = 1.75 \) line, moving from right to left. As you follow this pathway you are moving from large platinum electrodes to smaller platinum electrodes. This means that if you know how one electrode behaves on the \( k \) line, you know how all other platinum electrodes of differing sizes behave (at least within the macro-size electrode range for which data are plotted in figure 1).

**Materials and methods**

A significant portion of this communication deals with instrumentation issues encountered while making the measurements we report on5. The details presented should help

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4 It was in 2011 in a conversation with Professor John Mieyal, Department of Pharmacology, at CWRU, that I, JTM, was introduced to the work of Rosenberg and saw that Pt dissolution could very well be the problem and our experience with stainless steel stimulating electrodes may find an additional application for platinum electrodes.

5 The group working on this project involved more than a dozen engineers with diverse training but all working in the area of neural stimulation devices. A lot of head scratching went on when trying to understand the recorded data. Only after we delved into the data recording instrumentation, saw the problems, and solved the problems were we able to derive useful data. The detail presented in Materials and methods may be tedious for some, but for anyone attempting these measurements it is presented here to underscore the importance of starting with a knowledge base rather than to labor as we did to develop it.
To electrochemically clean the platinum electrode, its potential was held at +1.7 V versus Ag/AgCl for ∼900 s.

The current pulse-capacitor discharge instrument (CP-CDi) measurements were made on electrodes that had only been polished and rinsed with ultrapure water, not electrochemically cleaned. Experiments were carried out where the electrolyte was exposed to atmospheric oxygen, (oxygen available for electron transfer), and oxygen purged, where the electrolyte had 100% nitrogen (Airgas, NI 300) bubbled through it for about 30 min prior to collection of data, and nitrogen gas was discharged over the solution surface throughout data collection.

After CP-CDi measurements, the $i(V)$ profile (aka cyclic voltammogram or CV) was acquired by cycling the platinum electrode between −0.3 V (Ag/AgCl) and +1.2 V (Ag/AgCl) ∼90 times with the Autolab Potentiostat (PGSTAT128N), equipped with the linear scan generator module (SCAN250) at 100 mV s$^{-1}$; or until the $i(V_e)$ profile became stable (as shown in figure 9) starting and stopping at the open-circuit potential (OCP). OCP was recorded 20 min after the end of the CP-CDi experiments. The $i(V_e)$ profile was then scanned with OCP as the starting potential.

**Pulsing experiments**

The CP-CDi was used to generate neural stimulation type pulses at 50 Hz. A functional schematic for the instrument is shown in figure 3.

The two basic elements of the measurement setup are the CP-CDi and the electrode–electrolyte test cell. The regulated current pulse generator provides the stimulus pulse. All current flowing through the electrochemical cell is stored on the series capacitor, $C$, within the CP-CDi. That capacitor can then be discharged, with a predetermined delay, back through the electrode–electrolyte system to provide a balanced-charge, biphasic pulse to the electrode–electrolyte cell.

The CP-CDi generates a current pulse or train of identical current pulses (see figure 4).

These pulses were injected into the electrode–electrolyte system. The parameters used in these experiments were a cathodic–first (100µs duration) regulated current pulse followed by a 100 µs delay and then an anodic capacitive discharge. The magnitudes of the cathodic currents were increased according to Shannon $k$ values of 0.566 (1.7 mA, cathodic), $k = 1.24$ (3.7 mA, cathodic), $k = 1.66$ (6.00 mA, cathodic), $k = 2.0$ (8.9 mA, cathodic) and $k = 2.3$ (12.6 mA, cathodic) (see figure 2).

**Using $k$ instead of $Q$ and $Q/A$**

We have introduced $k$ as a way of describing the level of charge injection relative to the upper limit as forecasted by the Shannon Plot. When $k$ is used, the area of the electrode no longer needs to be indicated. Table 1 provides a perspective of the data collected in these experiments. $Q_k/Q_{k=1.75}$ is independent of electrode area, while magnitude of the cathodic current, $I_c$, applies only to these experiments, a disk electrode with a geometric area of 0.785 mm$^2$.

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**Figure 2.** This figure shows the Shannon Plot based on experiments in animals using balanced charge bi-phasic pulses. The $k$-values marked indicate a disk electrode used to obtain the data shown in this communication. The line for $k = 1.75$ (dashed blue) separates charge injection levels that have been deemed safe, to the left of the line, from those deemed unsafe, to the right of the line. Researchers and practitioners in the neural prosthesis field to be more at ease with electrochemical considerations of neural stimulating electrodes.

Experiments were carried out on a model electrode, a 1 mm platinum disk electrode, and focused on the electron transfer processes that occur for three $k$ values less than 1.75 and for two $k$ values greater than 1.75. We use $k$ values rather than charge and charge density because a value for $k$ tells the reader where, with respect to Shannon’s $k = 1.75$ line (the boundary between damaging and non-damaging charge injection) the electrode is operating, independent of electrode area. Figure 2 shows the five stimulus values tested. This range of values was chosen in order to look for correlations of tissue damage, $k > 1.75$, and unique electron transfer reactions occurring on the platinum electrode at charge injection levels above $k = 1.75$.

The working electrode was a Pt disk electrode, (platinum purity 99.5%, eDAQ ET075-1) with diameter of 1 mm, disk area = 0.785 mm$^2$, referred to as the model electrode. The reference electrode was a commercial Ag/AgCl electrode (Gamry, 930-00015). All reported potentials are referenced to the Ag/AgCl potential scale. The counter electrode was a carbon rod (Alfa Aesar 40765). The electrolyte was 0.15 M H$_2$SO$_4$ (Fisher Scientific; Certified ACS Plus concentrated sulfuric acid dissolved in 18.3 MΩ cm ultrapure water, EASYpureUV system, Barnstead). It should be noted that even with high-grade reagents and high quality water, it is extremely difficult to avoid organic contaminants in the measurement system. The reference electrode used for data collection was checked against a similar reference electrode that was used for validation purposes only. Validation occurred at the beginning and end of each data collection session.

Prior to making measurements, the model electrode was polished on an aluminum oxide tile for about 10 min, rinsed with acetone (Fisher Scientific; Certified ACS), sonicated in ultrapure water (18.3 MΩ cm, EASYpureUV system, Barnstead) for 5 min, and then further rinsed with ultrapure water.
Measurement of potential at the electrode–electrolyte interface.

An equivalent circuit, as shown in right-hand panel of figure 3, represents the electrode–electrolyte interface. The variable of interest was the potential across the working electrode interface, $V_{we}$ (i.e. the potential across $C_{we}$ and $R_{we}$).

Table 1. Numerical relationship between $k$ value and charge injected in relation to maximum charge specified by the Shannon Plot. Catholic current employed is shown in the right-hand column.

| $k$ value | $Q_i/Q_{k=1.75}$ | $Q$ ($\mu$C) | $Q/A$ ($\mu$C cm$^{-2}$) | $I_c$ (mA) |
|-----------|-----------------|-------------|-----------------|--------|
| 0.566     | 25.8%           | 0.170       | 21.7            | 1.70   |
| 1.24      | 56.1%           | 0.370       | 47.1            | 3.70   |
| 1.66      | 90.9%           | 0.600       | 76.4            | 6.00   |
| 1.75      | 100.0%          | 0.660       | 84.1            | 6.60   |
| 2         | 135.0%          | 0.890       | 113             | 8.90   |
| 2.3       | 191.0%          | 1.26        | 161             | 12.6   |

Figure 3. This figure shows a functional schematic of the instrumentation used to make the current pulse-capacitor discharge instrument (CP-CDi) measurements and the electrochemical cell. The right-hand panel shows an equivalent circuit used to represent a three-electrode system, working electrode (we), reference electrode (re), and counter electrode (ce). $C_{we}$ represents the double layer capacitance of the working electrode, and $R_{we}$ represents the electron transfer processes associated with the working electrode, governed by the Butler–Volmer equation. $R_{\Omega}$ represents the unavoidable ohmic component of the measured interface potential, and $R_{sol}$ represents the solution resistance. $V_{we}$ is the potential of interest and it is calculated by subtracting $V_{\Omega}$ from $V_{re}$. The current flowing through the electrode is $i(t)$. The left-hand panel shows the functional schematic for the CP-CDi. A regulated current pulse generator creates a positive current pulse that passes through the pulse switch, the ce, the solution, the we, the 100 $\Omega$ current monitor resistor, $R_i$, the inline capacitor $C$ and returns to the negative terminal of the regulated pulse generator. All charge flowing through the electrodes is stored on the inline capacitor. During the delay phase the switch is positioned to the OFF or delay terminal to create an open circuit. Following the delay phase, the switch is moved to the discharge terminal, allowing the inline capacitor $C$ to create a discharge current back through the electrodes, the anodic phase. All measured potentials are referenced to the working electrode, which is also connected to building/instrument ground. The current flowing through the electrode, $i(t)$ is given by $V_i(t)/R_{\Omega}$.

Figure 4. This figure shows the current waveform with the three phases, cathodic, delay, and anodic identified. The duration of the cathodic pulse was 100 $\mu$s and the delay between the end of the cathodic pulse and the onset of the anodic phase was 100 $\mu$s.
The interface potential will mandate the electron transfer processes that are possible at the electrode–electrolyte interface [14].

All potential measurements are referenced to earth ground, the working electrode. The Ag/AgCl reference electrode is placed in the electrolyte, and the potential between it and the Earth ground yields the interface potential, \( V_{\text{wec}} \), and an added ohmic potential, \( V_{\Omega} \). The ohmic component is an unavoidable element of \( V_{\text{re}} \) because it contains the voltage drop arising from ion migration in the electrolyte medium but has nothing to do with the potential associated with electron transfer and must be corrected for in order to obtain the true interface potential. \( V_{\Omega} \) is recognized as the abrupt change in \( V_{\text{wec}} \) on the leading and lagging edges of the measurement, because \( V_{\text{wec}} \), the potential across a capacitor, cannot change instantaneously. The current \( i(t) \) injected into the electrode–electrolyte cell is recorded by measuring the voltage across a 100 Ω current-sense resistor, \( R_i \), in series with the CP-CDi and the electrode–electrolyte cell, referenced to earth ground. \( V_{\text{ij}} \) can be estimated by calculating the ohmic value and multiplying that by \( i(t) \), which can then be subtracted from \( V_{\text{re}} \) to yield \( V_{\text{wec}} \). Assuming the potential across the electrode-electrolyte cannot change instantaneously, the proper choice for the value of the resistance will result in a potential that is the same value just prior to the application of the current pulse and just after it has been applied.

**Correction for digital oscilloscope offset, current recording.**

The current waveform also exhibited an offset voltage. Correction for this offset is demonstrated in figure 6. First, the current-versus-time waveform is plotted by dividing the voltage across the current resistor, \( V_i(t) \), by the resistor value \( (R_i) \)

\[
i(t) = V_i(t)/R_i.
\]

In the upper panel is shown the current waveform in its entirety. The lower panel shows an expanded view of the regions just before and just after the application of the regulated current pulse. The region just prior to the application may contain the tailing edge of the previous pulse and so is not a reliable reference. The current during the delay period, by the design of the CP-CDi, is zero because all switches (see figure 3) are open. Any non-zero value measured in the delay period is the offset and is subtracted from the entire recorded current measurement.

**Calculation of interface potential from \( V_{\text{re}} \) measurement.**

Figure 7 shows an example of the recorded \( V_{\text{re}}(t) \), \( i(t) \), after correction, and the estimate of the interface potential

\[
V_c(t) = V_{\text{re}}(t) - V_{\Omega}(t) = V_{\text{re}}(t) - i(t)R_i.
\]

Panel A shows the recorded \( i(t) \) and panel B shows \( V_{\text{re}}(t) \). The effects of the ohmic component are noted as ohmic component, the abrupt change in potential corresponding to the two edges of the current pulse. The correct value of \( R_\Omega \) was determined through an iteration process. Panel C shows \( V_{\text{re}}(t) - i(t)R_{\Omega} \) for three values of \( R_\Omega \): too large, too small, and correct \([V_c(t) = V_{\text{re}}(t) - i(t)R_{\Omega}]\). Panel D shows, magnified on the time axis, \( i(t) \) (blue), \( V_{\text{re}}(t) \) (black), and \( V_{\text{re}}(t) - i(t)R_{\Omega} \) when \( R_{\Omega} \) is too large (magenta), too small (green), and deemed the correct value to be used (red). \( V_c \) and \( V_{\text{wec}} \) are used interchangeably when referring to the electrode–electrolyte interface potential.

**Results**

**Steady-state recordings**

The electrode–electrolyte interface potential, at 20 ms after the application of a pulse, exhibited a positive creep when a train of pulses was applied at 50 Hz, e.g. the starting potential for the next pulse was positive to the starting potential of the previous pulse. The starting potential exhibited a ratchet
effect that was most pronounced in the first few pulses but reached a steady-state value after a number of pulses. We chose to record measurements for the 1000th pulse. The positive creep, ratchet up, phenomenon is illustrated in figure 8 and has also been described in other literature (Merrill 2005).

**CP-CDi measurements**

The focus of this study is on the electron transfer reactions occurring during the anodic phase of the cathodic-first/balanced-charge stimulus. Of particular interest are changes in the potentials that might produce potentially toxic reaction products as the charge injection is increased from levels generally accepted as non-damaging, below \( k = 1.75 \) to levels above \( k = 1.75 \), where damage has been reported in cat cortex. The reactions occurring on the platinum electrode during the secondary phase can be estimated by comparing the measured potentials occurring during the anodic phase to the \( i(V_e) \) profile [14] for the electrode–electrolyte system (see figure 9). The measured variables are shown in figure 9: (1) oxygen purged from the electrolyte by bubbling nitrogen gas into the electrolyte, and (2) electrolyte open to atmospheric oxygen (\(~21\%)).

Consider first the oxygen-purged electrolyte. As shown in the bottom panel of figure 9, the start potentials (filled black circles) were close to 0 V(Ag/AgCl) and the anodic potentials (filled red and blue circles) increase positively as the charge injection levels increase from \( k = 0.566 \) to \( k = 2.3 \). Projecting these potentials onto the \( i(V_e) \) profile (black line) indicates that at no time during the anodic phase of the pulse does the interface potential enter the platinum oxidation region, greater than \(~0.6\) V(Ag/AgCl). The double layer charging region is between \(~0.1\) and \(~0.6\) V(Ag/AgCl) and, if the electrode is only exposed to potentials in this region, no electron transfer reactions occur in a dilute sulfuric acid electrolyte.

When oxygen is present in the electrolyte, all recorded interface potentials (\( V_e(t = 20\text{ ms}) \)) are measured positive to

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**Figure 5.** Correction for offset in recording from digital oscilloscope. The measured potential was corrected for an inherent offset that was a function of the gain setting on the oscilloscope. The gain settings employed were, 0.5, 2.0, and 5.0 V per division. Two voltage standards were used at each setting, 0.0 V or ground and 2.47 V for reference. Assuming a linear fit at each gain setting, a plot was made and an equation was generated, equations shown in black (0.5 V/div), red (2.0 V/div), and blue (5.0 V/div).
values recorded in the oxygen purged system. The potential measured prior to the onset of the train, start potential (open black circles), is approximately 0.46 V(Ag/AgCl) compared to ∼0 V(Ag/AgCl) for the oxygen purged experiment. When the charge injection levels exceed \( k = 1.75 \), the magnitude of the anodic potentials increases very little with increasing charge injection. This behavior caught our attention because it suggested an electron transfer reaction was occurring that can accommodate the increased levels of charge with little change in interface potential (that is, the \( i(V_e) \) curve is steep on the charge injected axis). Two dashed vertical lines have been drawn at voltage levels where the estimated anodic potentials (red and blue open circles) cross the \( k = 1.75 \) value. Translating these lines to the \( i(V_e) \) profile for oxygen present indicates that the anodic potentials are at a range where platinum metal surface oxidation occurs and platinum dissolution may also occur.

Discussion

The data shown in the Shannon Plot tell us that, when charge injection levels exceed \( k = 1.75 \), something begins to occur that can cause injury to neural tissues in the vicinity of the platinum stimulating electrode. These data were generated in one laboratory (HMRI) with nearly the same team members involved in each experiment. Platinum electrodes were employed in all cases and various sizes were used. These consistent attributes make this a very useful set of data. The
Robblee [7] data (solid red datum point in figure 1) provided a hint that the problem may be platinum dissolution when the charge injection level exceeds \( k = 1.75 \). Also, the same laboratory reported that the stimulation-damaged tissues appear similar to the neural tissues subjected to injected platinum salts (Agnew [12]). Furthermore, platinum dissolution products are employed to kill cancer cells [15, 16]. We hypothesize that platinum dissolution products are produced at accelerated rates when the charge injection limits exceed 1.75, and balanced-charge biphasic pulses are applied.

The positively ratcheting electrode–electrolyte potential values achieved during the delivery of a train of pulses are a critical\(^7\) finding in this study. There are two sources for the positive increase in the electrode–electrolyte interface potential when a train of pulses is delivered: (1) charge delivered to electron transfer reactions that cannot be recovered and (2) processes involved in the CP-CDi/electrode–electrolyte interface reaching steady-state, which could produce an error.

When a train of cathodic-first/charge-balanced/biphasic stimuli are delivered to an electrode and some of the charge injected during the first phase (cathodic) is NOT recoverable during the second phase (anodic), the potential at the beginning of the next pulse will be more positive than the starting potential for the previous pulse (see figure 8). The interface potential will ratchet positive because more charge will be delivered during the anodic phase than is required to return the electrode to its starting potential (Merrill 2005 [5]). Were all of the reactions occurring during the cathodic phase perfectly reversible, the positive ratchet would not happen. After a series of balanced-charge biphasic pulses have been applied, a steady state will be achieved where the charge in the unrecoverable cathodic reactions is equal in magnitude to the charge in the

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\(^{7}\) Here, ‘critical’ does not imply an original finding, but, one that has been neglected by our community.
unrecoverable anodic reactions. One would expect that, as the electrode is required to accommodate more charge at higher $k$ during the cathodic phase, more unrecoverable reactions will necessitate a greater amount of charge to be consumed during the anodic phase, and hence, more anodic reaction products. The likely unrecoverable reactions occurring during the cathodic phase are formation of diatomic hydrogen accompanied by electron transfer to oxygen as oxygen becomes available. Adsorption of monatomic hydrogen is assumed to be perfectly reversible. Candidates for unrecoverable reactions during the anodic phase are oxidation of adsorbed organics and/or platinum dissolution.

Storing the stimulus pulse on a capacitor and then discharging the capacitor as a way to create a charge-balanced-biphasic stimulus can introduce an error in the balance. This error only becomes important first, if the data are collected before the potential waveform has reached a steady state, i.e. the unrecoverable reactions on the anodic and cathodic sides have become equal, and second, when the time constant for the discharge becomes nontrivial in relation to the 20 ms interpulse interval used in these experiments. In regard to the first possibility, we have performed a simulation to evaluate the number of pulses required to establish steady-state. Referring to figure 3, values of $C$, the series capacitor, ranged from 0.01 to 10 $\mu$F; $R_s$ was 100 $\Omega$; $C_{\text{we}} = 0.157$ $\mu$F (from 20 $\mu$F cm$^{-2}$ and calculated for our WE); $R_{\text{we}} = 10,000$ and 100 $\Omega$; $R_0 = 10000 $ $\Omega$. Under worst-case conditions, $C = 10 $ $\mu$F and $R_{\text{we}} = 10,000 $ $\Omega$. Steady state was deemed to have been established by the time 25 pulses had been delivered at 50 Hz. Regarding the second possibility, at no time did we record a current that was greater than zero at $t = 20$ ms. That is, for the pulses and discharge capacitors used in these experiments, the capacitor was fully discharged by the time the next pulse in the train was applied. These results support the conclusion that the reported measurements are an accurate representation of the interface potential, during the anodic phase, at steady state.

We chose to record the interface potentials for the 1000th pulse delivered to the electrode, because the recorded data always appeared to be in a steady state. Merrill [17] reported a ‘steady-state’ had been achieved at or near ten pulses at 50 Hz.

Platinum dissolution is known to occur when the interface potentials move into the region of the $i(V_c)$ profile where platinum oxidation occurs [18]; this region is slightly positive to the resting OCP in an oxygen containing medium. We used the interface potential at 20 ms, $V_r(t = 20$ ms), as an indicator that a net anodic charge transfer reaction was occurring if that potential exceeded the potential at the onset of the pulse train, OCP. For all $k$ values studied, the $V_r(t = 20$ ms) for the 1000th pulse was positive to the OCP. This observation was interpreted to mean that there was a net anodic charge transfer reaction occurring and platinum dissolution was a candidate reaction. As the charge injection level increased, $V_r(t = 20$ ms) increased until $k > 1.75$, implying that the electron transfer reaction became easier, requiring less overpotential. As $V_r(t = 20$ ms) entered into this region of the $i(V_c)$ profile, platinum oxidation became the dominant reaction. These results suggest that if platinum dissolution products prove to be the major toxic reaction product, and these results also hold in a living system, then the living system can tolerate a level of platinum dissolution up to the point where $k = 1.75$, but not at generation rates that result when $k > 1.75$.

**Oxygen available in electrolyte—the case of an electrode operating in a living system**

Our hypothesis for the distinction between $k < 1.75$ and $k > 1.75$ levels of stimulation is that it is related to the rate that reaction products are created during the anodic phase of the charge-balanced, biphasic stimulus. Initially the electrode would have been at an OCP where there is no net anodic or cathodic reaction but a balance between the two. Rand et al [19] have identified the anodic reactions to be platinum dissolution, impurity oxidation and oxygen adsorption and the balancing cathodic reactions to be oxygen reduction. Once charge is injected, a net reaction happens which might or might not be reversible. The reaction products of interest could be platinum compounds in cases where oxygen is available, as in a living system. As the charge density for the stimulus pulse is increased (as $k$ is increased), both the peak overshoot (anodic) potential and the end potential (at 20 ms after the onset of the pulse) increase to higher positive values (see figure 10, lower panel).

Importantly, the steady state anodic potentials are all more positive than the potential at the start of the pulse train. This observation indicates that there is a net anodic electron transfer process that balances the net cathodic electron transfer processes in the steady-state pulse train. Therefore, identifying the anodic reaction products may lead to an understanding of the stimulation induced mechanism for tissue damage. Aligning the potential axes of the $i(V_c)$ profile and the CP-CDi results (see figure 10 middle and lower panels) indicates that the steady state anodic reactions involve platinum oxidation and oxidation of organic contaminants. The charge transferred in these reactions counters the charge transferred on the cathodic side to oxygen reduction and diatomic hydrogen formation. Also, the positive potentials occurring during the anodic phase appear to change very little as the $k$ values move from levels of $k \simeq 1.75$ to levels of $k > 1.75$. These later findings imply an increased availability of reactants to satisfy the increased charge injected at these potentials, consistent with the increased current measured at these potentials for the $i(V_c)$ profile.

If these results hold in the living system, then some level of reaction products can be tolerated since under all stimulation conditions, even at the smallest $k$ value, there is a net unrecoverable anodic reaction. But, one could speculate that, at higher values of $k$, the rate at which reaction products are generated is such that it cannot be tolerated. However, the requirement that the interface potential be held at a potential much greater than those recorded in these experiments to oxidize organics suggests that the primary irreversible anodic reaction occurring during steady state is platinum dissolution. These ideas can be tested in living systems, e.g. cell-culture and/or animals.
Similar to the case when oxygen is available, the electrode potential ratchets up to values positive to the potential at the beginning of the train of 1000 pulses. This behavior indicates that an unrecoverable electron transfer process occurs during the cathodic phase. Candidate reactions during the cathodic phase are residual oxygen, diatomic hydrogen generation, and an unrecoverable electron transfer process must occur during the anodic phase to balance the cathodic charge loss. The electron transfer reaction during the anodic phase is not clear because the interface potential never exceeds the double-layer charging region (see middle panel in figure 9). However, because the interface potential (filled red and blue data points) was never recorded at levels that can support platinum oxide formation, it is unlikely that platinum dissolution would occur in the nitrogen purged electrolyte. Interestingly, Rosenberg et al [13] reported the negative effect of electrical stimulation on cells was not observed in the oxygen purged system.

**Significance of platinum dissolution**

Stimulation in the deaerated media at $k \leq 2.3$ did not result in potentials positive enough for significant Faradaic reactions to occur, such as Pt oxide formation and dissolution; see the peak anodic potentials (filled blue symbols in figure 9) and potentials at the end of 20 ms (filled red symbols). However, when oxygen is available, charge-balanced, biphasic stimulation type pulses resulted in electrode potentials where platinum oxide formation and dissolution are possible, specifically when the charge injection exceeds $k = 1.75$. The work done by Rosenberg [13] (although on E. coli bacteria) directly points to platinum dissolution products causing cell damage. This was verified by Rosenberg [13] when he and his coworkers inoculated the bacterial chamber with a solution of a 0.051 mM Pt(IV) salt for two hours, which resulted in abnormal filamentous growth. Rosenberg [13] also reported that for experiments carried out in oxygen-free media, no cell damage was recorded, possibly because the electrode potential in their experiments never reached a level sufficient to create a toxic concentration of platinum dissolution products. McHardy et al [11] reported that platinum dissolution took place more rapidly in an air-saturated solution than it did in a deaerated solution. The implication of the Rosenberg [13] and McHardy [11] findings for our work is that we were operating in a potential region (i.e. interface potential value), where platinum dissolution products were produced. In the sulfuric acid experiments,
steady state $V_e$ potentials crept positively to a potential where platinum dissolution is plausible, particularly in a chloride-containing medium. In figure 9, the end and peak potentials when oxygen is present are in the region ($> \sim 0.7 \text{ V}$) where platinum oxide formation and dissolution are likely as stimulation levels cross beyond the $k = 1.75$ value.

**Open circuit potentials**

A central element of our analysis is projection of the electrode interface potential measurements made with the oscilloscope onto the $i(V_e)$ profile, indicative of which electron transfer reactions are possible during neural pulsing. The electrode interface potential measurements are made with two devices: one for $i(V_e)$ profiles with an input impedance of $10^{13}$ $\Omega$ (Autolab Potentiostat PGSTAT128N), and the other for pulse potentials with an input impedance of $10^7$ $\Omega$ (Tektronix DPO 4034 oscilloscope). We noticed that the interface potentials we measured with the oscilloscope ($A$ and $B$ in figure 10) at the beginning of the pulse train, prior to the first pulse, were different from those measured with the potentiostat ($A'$ and $B'$), shown as bars to illustrate range of values just prior to connecting the oscilloscope to the electrochemical cell. The difference can be accounted for by the different input impedance values for the two devices. The following analysis accounts for the differences.

**Impact of input impedance on OCP measurements**

The fact that the interface potential is different when measured with the two devices can be explained by analyzing the circuit shown in figure 11. The electrode interface we have been using has been modified by replacing the dynamic representation for charge transfer by the circuitry shown in on the right hand side of figure 11. The voltage equation around the instrument loop is then

$$V_{\text{measured}} + i(R_{12}) E_{\text{ocp}} + i(R_{\text{source}}) = 0,$$

$$V_{\text{measured}} = E_{\text{ocp}} - i(R_{12} + R_{\text{source}}).$$

$R_{12}$ is in the range of $10^2$ $\Omega$ and $R_{\text{source}}$ is in the range of $10^6$ $\Omega$

$$V_{\text{measured}} = E_{\text{ocp}} - i(R_{\text{source}}) = i(R_{\text{instrument}}),$$

$$i = (E_{\text{ocp}})/(R_{\text{source}} + R_{\text{instrument}}),$$

$$V_{\text{measured}} = i(R_{\text{instrument}}),$$

$$V_{\text{measured}} = (E_{\text{ocp}}R_{\text{instrument}})/(R_{\text{source}} + R_{\text{instrument}}).$$

When $R_{\text{instrument}} \gg R_{\text{source}}$

$$V_{\text{measured}} \approx E_{\text{ocp}}.$$

Otherwise

$$V_{\text{measured}} < E_{\text{ocp}}.$$

We can estimate values for $E_{\text{ocp}}$ and $R_{\text{source}}$ using measurements made with instruments having input impedances of $10^2$, oscilloscope, and $10^{13}$, potentiostat, in electrolytes exposed to atmospheric oxygen and purged with nitrogen to yield a low oxygen concentration. See table 2 for values.

**Impact of input impedance on CP-CDI potential measurements**

The oscilloscope probes used throughout these experiments were probes with a $10 \text{ M}\Omega$ input impedance. A common way to determine how much the input impedance of the measurement device is altering the measured value is to halve the input impedance by adding a second probe in parallel with the first probe, making the instrument load on the cell $5 \text{ M}\Omega$. This was done and the observed recording is shown in figure 12. The red trace was made using a $10 \text{ M}\Omega$ probe and the black trace was made with two $10 \text{ M}\Omega$ probes in parallel. The difference in the recordings was deemed insignificant, so either probe would provide a reliable measure of the potentials during pulsing experiments.

**Conclusions**

Unrecoverable reactions occur during the first phase of cathodic-first/charge-balanced/biphasic-pulses over all $k$ values studied ($k = 0.566$ to $k = 2.3$); the ratcheting up of the potential during the anodic phase was evidence of this. The anodic potential
reaches a steady state that increases with increasing charge injection (increasing $k$), and more positive potential excursions are attained with oxygen present than without oxygen present. As more charge is injected above $k = 1.75$ (the Shannon limit for non-damaging stimulation), the rate of potential rise decreases, indicating that new electron-transfer reactions become available in this potential range. The $i(V)$ profile suggests the likely reaction is platinum oxidation, and platinum dissolution accounts for the irreversible anodic current transfer that occurs, which increases with increasing charge injection levels. Other studies have demonstrated that certain platinum species can damage cells. An important hypothesis emerging from this work is that platinum dissolution products generated at a rate that living systems cannot tolerate, may explain the relevance of the Shannon Plot and $k = 1.75$ as an upper limit. Drawing on the experience with stainless steel stimulating electrodes [10] we hypothesize that injecting less charge in the anodic phase is a way to lower the anodic potentials and may be a way to safely inject more charge than the limits imposed by the Shannon Plot for balanced charge biphasic pulses.

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## Authorship statements

Dr Mortimer designed the project, secured funding, and took the primary role in analyzing data, writing the manuscript, and managing the study. Dr Doe 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; Mr Fred Montague managed instrumentation, circuit modeling, and was an important contributor to solving instrumentation issues. Dr Eric Hudak developed data processing methods, prepared figures, and was involved in the interpretation of the results. He also contributed to designing the specifications of the CP-CDi built for these studies.

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