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

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Abstract

Objective. Charge injection through platinum neural stimulation electrodes is often constrained by the Shannon limit (Shannon 1992 IEEE Trans. Biomed. Eng. 39 424–6) of $k = 1.75$. By leveraging the tools of electrochemistry to better understand the reactions at electrode-tissue interface, we endeavor to find a way to safely inject more charge than allowed if the traditional Shannon limit were followed. Approach. In previous studies on platinum electrodes using charge-balanced, cathodic-first, biphasic pulses, we noted that during the secondary anodic phase, the electrode potential moves into a range where platinum dissolution is possible when charge injection is greater than $k = 1.75$. Platinum dissolution products are known to be toxic to brain tissues. We hypothesize that by injecting less charge in the anodic phase than the cathodic phase, the anodic potential excursions will decrease, thereby avoiding potentials where platinum dissolution is more likely. Main results. Our findings show that using these charge-imbalanced pulses decreases the anodic potential excursions to a level where platinum oxidation and dissolution are less likely, and aligns the anodic potentials with those observed with charge-balanced stimulation at $k < 1.75$—a range widely accepted as safe for stimulation with platinum. Significance. From these results, we further hypothesize that charge-imbalanced biphasic stimulation would permit more charge to be safely injected through platinum electrodes than would be permitted if the dogma of charge-balanced biphasic stimuli were followed. Testing this hypothesis in cat brain in the same manner as the experiments that formed the basis for the Shannon plot could open the door for safe charge injection through platinum electrodes at levels greater than $k = 1.75$.

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

**Background**

In 2012, we began a journey to find a way to extend the safe limits beyond the Shannon limit of $k = 1.75$ for charge injected through platinum neural stimulating electrodes and to bring a stronger awareness to the neural stimulation community of the importance of understanding the electron transfer processes that take place on neural stimulating electrodes, be they platinum or some other material. Significant progress has been made in understanding how platinum electrochemistry relates to the $k = 1.75$ limit and in identifying a potential way to surpass the limit safely [2–4].

The Shannon plot utilizes an equation to draw lines on a plot of charge density versus charge per phase of stimulus pulse:

$$ \log(D) = k - \log(Q) $$

where $D$ is the charge density in $\mu C \ cm^{-2}$ and $Q$ is the charge per phase in $\mu C$. Shannon’s analysis suggests there are certain values of $k$ where one should expect no tissue damage, and others where damage can be expected. A Shannon plot [1], originally derived from histological data acquired by McCreery et al [1] in studies on cat brain using charge-balanced pulses, is shown in figure 1, supplemented with data from other reports where platinum stimulating electrodes were evaluated in cat brain (gray-outlined symbols). We consider these data to be the best available for relating stimulation parameters to tissue damage with a platinum electrode in close contact with target tissues (near-field stimulation). Recently, a compilation [5] of DBS preclinical and clinical data depicting damage was published, following the trend predicted by the Pudenz [6] and McCreery [7] studies. We draw a line that separates the data deemed as injured (filled black symbols) from non-injured (open, gray-outlined symbols) at $k = 1.75$. From the time Robert Shannon published the plot [1] until now, no one has been able to give more than a graphical construct as a basis for the plot. Evident, but not often noticed in Shannon’s formulation is that large and small-area electrodes behave the same in terms of $k$. In our third report [4], working with cathodic-first, charge-balanced, biphasic pulses, we showed that platinum electrodes, over an area range from 0.2 mm$^2$ to 12.7 mm$^2$, exhibited similar anodic potentials as the charge injection exceeded $k = 1.75$. When platinum is driven to anodic potentials, surface oxidation and dissolution reactions become more likely. In our previous work, we have found that as stimulation surpasses $k = 1.75$, and the electrode is exposed to more anodic potentials, the rate of platinum dissolution accelerates [3]. Several studies have shown that platinum dissolution products are correlated with cell death [8–10].

Also shown in figure 1 are data from studies with stainless steel electrodes in cat muscle (blue-outlined symbols). The stainless-steel data are included to make the point that charge-imbalanced, biphasic stimulation permitted safe injection at charge densities that would have resulted in corrosion if charge-balanced, biphasic stimulation had been used, and that tissue damage did not occur at the higher charge injection levels.

The Shannon plot has been used extensively to establish the separation between what are deemed safe and unsafe levels of charge injection. Here, the words safe and unsafe are short-hand 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 safe is a subjective term, and that absolute safety can never be guaranteed.

Our approach to extending the safe limits was to first develop an understanding of the electron transfer processes occurring on the platinum electrode: the electrochemistry of the electrode-tissue interface.

In our first report [15] we provided a tutorial on the platinum $i(V_c)$ profile, describing the thermodynamic electron transfer processes over an electrode potential range between hydrogen evolution and oxygen evolution. The report was designed to give engineers, working in the neural stimulation arena, a sense of comfort and appreciation for the steady-state electron transfer processes occurring on a platinum electrode. The main message of this contribution was that the electrode-electrolyte interface potential is the key driving force behind electron transfer processes, which is described by the $i(V_c)$ profile, also referred to as the cyclic voltammogram or CV. This message is well known to the hard-core electrochemistry community, but underappreciated by our neural stimulation community. Our hope was to correct this under-appreciation by creating a document(s) that is accessible to the engineers working in neural stimulation.

Our second report [2] detailed the electron transfer processes occurring in a well-controlled electrode-electrolyte environment: a model platinum electrode in oxygenated and deoxygenated sulfuric acid. In an oxygenated electrolyte, the electrode potential, $V_c$, move into the platinum oxidation region of the $i(V_c)$ profile when the charge injection level exceeded $k = 1.75$. This behavior suggests the availability of an easily accessible anodic process, e.g. platinum dissolution. We hypothesized that the reaction product was platinum dissolution and that its presence in tissue could explain why $k = 1.75$ defined a boundary between damaging and non-damaging levels on the Shannon plot [1] (histological data [7]).

In our third report [4] we showed that the predictions derived from the platinum model electrode-sulfuric acid work

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accurately describe the electron transfer reactions occurring in rat subcutaneous space. Further, and most importantly, commercially deployed electrodes with surface areas from 0.2 mm$^2$ to 12.7 mm$^2$ behave the same with respect to the $k = 1.75$ line: similar anodic potentials are exhibited and they increase beyond the $k = 1.75$ line, potentially defining the limiting value for safe stimulation for all electrodes in this size range in close contact with the target tissues. As a result, we hypothesized a physical meaning for the Shannon plot: for cathodic-first, charge-balanced, biphasic pulses, $k = 1.75$ defines a boundary for platinum toxicity to cells in the immediate vicinity of the platinum electrode. Below $k = 1.75$, an insufficient amount of platinum is released to result in damage to cells.

### Introduction

We learned from our previously reported studies [2, 4] that with charge-balanced, biphasic pulses, when the charge injection level exceeds $k = 1.75$, the electrode potential moves into a region where platinum oxidation and platinum dissolution can occur (see figure 5). If platinum dissolution products are toxic to neural tissues—and the goal is to reduce the likelihood of generating platinum dissolution products while increasing the charge injection above $k = 1.75$—the logical solution is to inject less charge in the anodic phase than was injected in the cathodic phase, thus avoiding driving the electrode potential into the range where platinum dissolution becomes likely.

In this report, we repeat the in vivo experiments [4] with neural stimulation type pulses having various amounts of imbalance. That is, we inject less charge in the secondary anodic (positive) phase than in the leading cathodic (negative) phase to show that at charge injection levels exceeding $k = 1.75$ electrode potentials can be kept below levels where platinum dissolution is known to occur.

### Materials and methods

The animal protocols and instrumentation used were the same as those described in our previous paper [4]. The reader is referred to the materials and methods section of that paper [4] for details.

The experiments in this work were carried out with the six Pt electrodes used in our companion paper [4]: a Pt model disk electrode (diameter of 0.1 cm, disk area, =0.785 mm$^2$, platinum purity 99.9%, EDAQ ET075-1), a cochlear electrode ($A = 0.2$ mm$^2$), a paddle electrode ($A = 4.2$ mm$^2$), a flattened cuff electrode ($A = 4.8$ mm$^2$), a DBS electrode...
(A = 6.1 mm²), and a spinal cord stimulation (SCS) electrode (A = 12.7 mm²). All reported potentials are referenced to the Ag/AgCl electrode scale. The electrolyte was limited to the fluid in the rat subcutaneous space.

The current pulse-capacitor discharge instrument (CP-CDi) and data processing procedures used here were also identical to those employed in experiments carried out with the CP-CDi studies in a rat [4].

A schematic of the CP-CDi instrument used is depicted in figure 2. A 100 μs wide constant-current cathodic pulse is followed by a 100 μs open-circuit delay and then a passive capacitor discharge in the anodic phase. When an imbalance is desired, a resistor shown in parallel with the inline capacitor, is switched in. The range of the external resistors used was (900 kΩ–100 kΩ). Smaller-value shunt resistors result in more imbalance.

**Results**

To examine the effect of imbalancing a biphasic pulse, pulse trains of 1000 pulses were injected through electrodes implanted in the subcutaneous space of the rat. The potential excursions during the pulse train were recorded through an oscilloscope and analyzed offline. As in our previous communications, a baseline $i(V_e)$ profile was recorded using a model platinum disk electrode to provide a picture of the electrochemical reactions that are thermodynamically possible over the potential range of study. From the pulse train data, the metric of interest was the steady-state values (999th pulse) of $V_e$ (the electrode potential) during the secondary (anodic) phase of the stimulus pulse. The ratcheting of the $V_e$ towards more positive values reflects the necessity for charge going into unrecoverable reactions in the primary (cathodic) phase to be balanced by charge going into unrecoverable reactions in the secondary (anodic) phase [16, 17]. When less charge is injected in the anodic phase than the cathodic phase, the extent of ratcheting to a positive $V_e$ value decreases. A less positive $V_e$ that is closer to the resting potential means a lower probability of forming platinum oxides and platinum dissolution products. Electron transfer reactions can continue to occur after the application of the current pulse into the interpulse interval.

In the first two panels of figure 3 are $i(V_e)$ profiles of the model platinum disk electrode in the subcutaneous space of the rat, recorded before and after CP-CDi current pulsing experiments. Results from the pulsing experiments are plotted in the third and fourth panels with the following potential measurements recorded: peak anodic potential $V_e$ (peak) (blue symbols), end potential $V_e$ ($t = 20$ ms) (red symbols), and most cathodic potential $V_e$ (cathodic) (green symbols).

The vertical black line drawn through all four panels in figure 3 represents the average open circuit potential (OCP) measured for twenty-seven measurements. This average is
the resting potential where the net current is zero. This does not mean there are no electron transfer processes but that the rate of charge going into the cathodic electron transfer processes are equal in magnitude to the anodic electron transfer processes.

The first and second (high magnification) panels in figure 3 are \(i(V_e)\) profiles for the model platinum electrode used in the bottom two panels as well as the data reported in Kumsa et al [2]. The black trace was the first and only voltage sweep cycle, beginning and ending at OCP before the tests were performed to collect data shown in the two lower panels, meaning the electrode was not subjected to an electrochemical cleaning [18] process prior to conducting the experiments. The blue traces are \(i(V_e)\) data collected after the data shown in the lower two panels were acquired. The potential sweep for the blue trace extended into the anodic region where oxygen (O₂)
evolves; the potential sweep for the black trace was terminated before platinum oxide formation and, by logical consequence, before oxygen \((O_2)\) evolution to avoid altering ambient oxygen concentration.

The plots in the third and fourth panels of figure 3 offer a second point of focus. The line-connected red and blue data points represent \(V_e\) (peak) (blue) and \(V_e\) \((t = 20 \text{ ms})\) (red) for charge-balanced biphasic pulses, using a 1 \(\mu F\) (third panel) or 0.1 \(\mu F\) (fourth panel) anodic discharge capacitor. Red and blue dashed lines are drawn vertically through all four panels to represent the potential value where the red and blue data lines cross the \(k = 1.75\) line (drawing from the 1 \(\mu F\) discharge capacitor data). By comparing the data sets in this manner, it is clear from the \(i(V_e)\) profile that an oxidation process (potentially Pt-oxide formation and/or Pt dissolution) becomes available at potentials above the dashed lines.

Also in the third panel, the open red square and blue circle symbols are \(V_e\) data recorded when less charge was injected in the secondary anodic phase than was injected in the primary cathodic phase. The larger the symbol is, the more charge was imbalanced, resulting in anodic potentials moving less positive with more imbalance. Interestingly, shunting the inline capacitor with a 700 k\(\Omega\) resistor was sufficient to move the anodic end potentials \(V_e\) \((t = 20 \text{ ms})\) to values that match those measured with charge-balanced pulses at \(k < 1.75\). As the magnitude of the shunt resistor was made smaller, there was more imbalance between the anodic phase and the cathodic phase, and the anodic potentials shifted to less positive values, further from the region of the \(i(V_e)\) profile where platinum oxidation and dissolution can occur, but further into the potential region, where oxygen reduction can occur.

The data plotted as green triangles are measured peak cathodic potentials. The utility of these data are not clear as was pointed out in Kumsa et al [4]. They are presented in this figure for completeness and for the curious mind. More information on potential implications of these potentials are covered in the Discussion section.

The plots shown in the fourth, bottom panel displays data similar to those shown in the third panel, except the inline capacitor is 0.1 \(\mu F\), which results in a higher-amplitude, shorter-duration anodic discharge current. As noted in Kumsa et al [4], an electrochemical benefit to the larger/faster secondary current is unlikely since it is the unrecoverable charge occurring during the primary, cathodic, phase that will impact the unrecoverable charge in the secondary, anodic, phase at least for charge-balanced pulses. In this case, the primary, cathodic phase was the same for the two inline capacitors.

The experiments performed on the model platinum disk electrode \((\text{area} = 0.785 \text{ mm}^2)\) were repeated on the five commercially deployed platinum electrodes \((\text{areas ranging from} 0.2 \text{ mm}^2 \text{ to} 12.7 \text{ mm}^2)\). The OCPs (black symbols), end potentials \(V_e\) \((t = 20 \text{ ms})\) (red symbols), and peak anodic potentials \(V_e\) (peak) (blue symbols) were measured and plotted in figure 4.

Increasing the charge imbalance by injecting less charge in the anodic phase than was injected in the preceding cathodic phase resulted in a decrease in the electrode potential during the anodic phase. One goal of the experiment was to demonstrate that by imbalancing the pulse, the anodic potentials for pulses greater than \(k = 1.75\) could be decreased into the region between OCP and \(V_e\) \((k = 1.75)\). This goal was met for all electrodes’ end potentials, \(V_e\) \((t = 20 \text{ ms})\). The goal was not met for \(V_e\) (peak) for the paddle and the SCS electrodes at the \(k = 2.3\) charge injection level. However, it is reasonable to expect that the goal would have been met had shunt resistors with values less than 100 k\(\Omega\) been tested. The main point here is that injecting less charge in the anodic phase than was injected in the cathodic phase will result in less positive values of \(V_e\), moving the electrode potential away from the platinum oxidation/dissolution region of the \(i(V_e)\) profile.

**Discussion**

The hypothesis of platinum dissolution products

The approach to the present study and its previous related journal articles is to take our early observations (and experience with stainless steel) and pose a hypothesis: the primary reason the Shannon plot predicts \(k = 1.75\) as the safe limit for platinum stimulation is that the rate of production of platinum dissolution products accelerates above this limit, and these dissolution products cause cell death at an unacceptable rate. Further described in the section below, platinum dissolution is caused by polarizing the electrode in the anodic direction, hence our rationale for focusing on the anodic-phase potentials in our recent publications.

An alternative explanation for stimulation-induced cell death can be found in the study by Agnew et al, which claimed that prolonged electrical stimulation induced hyperactivity of neurons, resulting in cell death. Subsequent investigators have cited this paper, claiming that hyperactivity/excitotoxicity is the ultimate underlying reason the Shannon plot predicts damage. However, in the publication, Agnew et al state they were not proposing hyperactivity as the only potential cause of stimulation-induced injury, and even suggest, ‘...neurons may be injured by a toxic electrochemical reaction at the electrode-tissue interface’. The results reported in our previous articles have contributed evidence that support the hypothesis of platinum dissolution products. The method of imbalanced stimulation described in this study enable the hypothesis to be tested more definitively in a relevant biological model where tissue damage can be fully assessed with modern techniques. Should such a study disprove the hypothesis of platinum dissolution products, other hypothetical mechanisms of damage can be tested further.

Anodic and cathodic-phase reactions

Testing the hypothesis that an increase in the production of platinum dissolution products at \(k > 1.75\) is the underlying reason why the Shannon plot predicts damage requires special attention to the anodic-phase potentials the electrode is exposed to during cathodic-first, biphasic pulse trains. There are two main modes of platinum dissolution possible, and both are only possible if the electrode polarizes into
The first mode of platinum dissolution is in the reaction of Pt with the chloride ion (Cl\(^{-}\)): oxidation of Cl\(^{-}\) occurs and Pt-chloride complexes are formed, which are soluble species \[19\]. The secondary mode of Pt dissolution occurs because of repeated oxidation and reduction of the platinum surface itself. The further into the anodic region the electrode travels, the more Pt-oxide forms. The vast majority of this oxide layer is reduced during the cathodic phase, but a minute proportion of Pt oxide may remain on the surface. After repeated anodic-cathodic cycles, a small portion of the Pt-oxide complexes may be removed from the bulk electrode due to instability in the surface structure around these complexes \[20–22\].

Several studies have shown that platinum dissolution products are correlated with cell death \[8–10\]. The surmounting supporting data for the deleterious effects of platinum products informed our hypothesis on platinum dissolution products which led to a focus on anodic-phase reactions. Cathodic-phase reactions could have important implications as well, however, it is not thermodynamically possible to cause platinum dissolution when polarizing negative of the open-circuit potential (OCP) if there were no significant platinum oxides created by first going in the anodic direction. Negative to the OCP on platinum, the following cathodic reactions can occur: O\(_2\) reduction, H\(_2\) evolution, and pH changes. Reduction of O\(_2\) results in the production of reactive oxygen species (ROS), which interact

![Figure 4](image-url). Shown in this figure are an \((i(V_e))\) profile and CP-CDi potentials recorded in a rat using platinum electrodes that range in area from 0.2 mm\(^2\) to 12.7 mm\(^2\). The data presented are from the 1000th pulse in a train of 100 µs pulses at 50 Hz. The first panel shows the \((i(V_e))\) profile recorded at 100 mV s\(^{-1}\) on a Pt disk electrode. The rest of the panels show interface potentials from pulsing experiments arranged in increasing order of electrode area (top to bottom). An external capacitor magnitude of 1 µF was used in all the cases shown. The red symbols represent the end potential \(V_e\) \((t = 20\) ms\), the blue symbols represent the peak anodic potential \(V_e\) (peak), and the black symbols represent the start potential prior to pulsing. Larger symbols indicate smaller shunt resistors across the in-line capacitor (figure 2), i.e. more imbalance.
with nitric oxide (NO), resulting in a reduced concentration of NO in local blood vessels [18]. A reduction in NO will result in blood vessel constriction and local ischemia (Pudenz et al [19] and Mortimer, unpublished observations when repeating the Pudenz experiments in an undergraduate lab at CWRU); the risk increases the greater the difference between $V_e$ (secondary or anodic phase) and OCP. Local ischemia may be tolerated in the brain for short periods of time less than a few minutes. Local pH changes are another possibility but work by Balletrassee et al [23] has shown that pH changes are localized to a short distance from the electrode, more specifically a few micrometers for an electrode with a radius of 1 $\mu$m.

**On quantifying the imbalance**

The CP-CDi used in these experiments was designed to produce completely/perfectly charge-balanced, biphasic pulses. The initial (cathodic) phase provides a constant-current pulse to the electrode circuit while simultaneously charging an inline capacitor with the same exact amount of charge. When the secondary (anodic) phase is initiated, this inline capacitor is completely discharged, resulting in a perfectly charge-balanced pulse. By placing a bleed resistor across the inline capacitor, an imbalanced pulse, with less charge in the secondary (anodic) phase, can be delivered. Traditional biphasic, square-wave, charge-balanced stimulators have slight imbalances between phases because two separate current sources are used for each phase, and it is very difficult for these types of circuits to inject the same exact amount of charge in each phase. We wanted to first map out the potential excursions using our perfectly charge-balanced pulses, and then imbalance the pulse to demonstrate control over the anodic potentials. Unfortunately, the CP-CDi did not lend itself to making a reliable quantification of the imbalance. Measuring the current flowing through 100 $\Omega$ current measuring resistor and integrating that over a 20 ms time period was found to be unreliable. The unreliability came from a small, but inherent error in the digital measurement, causing a significant error.
when integrated over the 20 ms period. If a specific imbalance number is desired, it is recommended that a pulse generator be used where the two phases of the biphasic pulse can be controlled, e.g. two rectangular pulses of well-controlled amplitude and duration.

**The right amount of imbalance**

Turning to our stated goal of safely injecting more charge than Shannon’s $k = 1.75$ would allow, the knowledge gained from the studies reported here indicates that for cathodic-first, biphasic stimuli, $V_e (t = 20 \text{ ms})$ and $V_e$ (peak) should not be more positive than the anodic potential values from charge injection at $k = 1.75$. Lowering the anodic potentials will prevent the production of platinum dissolution products at a rate or amount hypothesized to be unsafe for tissue. The presumed safe limit of $k = 1.75$ is supported by decades of evidence with platinum used across numerous neural stimulation applications. Our data show that $V_e (t = 20 \text{ ms})$ and $V_e$ (peak) can be controlled by bleeding off charge on the inline capacitor with a shunt resistor. The smaller the shunt resistor, the more charge is bled off during the secondary phase. If one carried this line of thinking to the extent of making the shunt resistor $0 \Omega$, this would produce a monophasic cathodic pulse, which is widely accepted as a poor idea for stimulation safety. When $V_e$ (peak) is negative to OCP, or if $V_e$ (cathodic) drifts negative to OCP, accelerated oxygen reduction may take place which can result in the increased creation of reactive oxygen species (ROS) as described previously. Keeping $V_e (t = 20 \text{ ms})$ and $V_e$ (peak) less than the red and blue dashed vertical lines (blue shaded region in figure 5) assumes that $k = 1.75$ provides a reliable upper safe electrode potential. Potentials more positive than these limits result in increased platinum dissolution and rates that are hypothesized to be unacceptable to the cells around the electrode.

The hypothesis can be tested by repeating the McCreery *et al* experiments with charge-imbalanced biphasic stimuli. If charge injection levels above $k = 1.75$, with proper imbalance, are found to not cause the histological changes demonstrated by McCreery *et al* [7], our hypothesis will be validated.

**Relationship between pulse design and platinum dissolution**

A logical next step would be to directly examine the electrode surface at high magnification for evidence of corrosion after stimulation in these experiments. However, the pulse trains used in this study lasted only 20s, thus it would be highly unlikely to observe surface changes due to dissolution on the electrodes.

Kumsa *et al* [3] tested the idea behind imbalanced bipolar stimulation as a method to reduce platinum dissolution at charge injection levels above $k = 1.75$. They examined the relationship between pulse design, charge density, and platinum dissolution rate. They reported on *in vitro* platinum dissolution experiments using monophasic pulse trains and biphasic pulse trains over a range of $k$ values ($k = 0.556$ to $k = 2.3$) for 2h at each level. These measurements showed that imbalanced stimulation (deployed using a $100 \Omega$ shunt resistor) kept platinum dissolution below the levels measured at $k = 1.75$ with charge-balanced pulses, (which are accepted to be tolerable by neural tissues).

**Summary**

A study of the electron transfer processes (i.e. electrochemistry) occurring on platinum neural stimulating electrodes has led to:

1. A hypothesis that $k = 1.75$ on the Shannon plot defines the upper level of platinum toxicity that living cells in close proximity to the stimulating electrode can tolerate. This applies to all platinum electrodes with areas between 0.2 mm² and 12 mm².
2. A hypothesis that the Shannon $k = 1.75$ limit for charge injection with charge-balanced, biphasic pulses can be extended if charge-imbalanced, biphasic pulses are employed.
3. A hypothesis that the explanation for cell injury at $k > 1.75$ is a result of hyperactivity/excitotoxicity [24] is not correct.
4. A hypothesis that the Shannon plot with the $k = 1.75$ limit applies ONLY to platinum neural stimulating electrodes, and that other stimulating materials will have to be studied following the template we have described for platinum electrodes [2, 4, 15]. In this regard, we can comment on stainless steel: $k = 2.2$ is a possible limit for stainless steel, and corrosion defines the 10 mm² electrode limit (see figure 1). Keep in mind the corrosion products of stainless steel apparently were not toxic to cells in the vicinity of the stimulating electrode [13].
5. Imbalance can be achieved by placing a shunt resistor across the inline capacitor on the output side of an IPG (implantable pulse generator) similar to the CP-CDi. Many commercial IPGs employ an inline capacitor on the output stage.

**Authorship statements**

Dr Mortimer designed the project, secured funding, took the primary role in analyzing data, writing the manuscript, and managed the study. 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 Hudak was involved in data interpretation, contributed background information/literature on platinum oxidation and dissolution phenomena, and assisted in editing the manuscript. Dr Bhadra took primary responsibility for the statistical analysis of acquired data and provided guidance on the design of the animal experiments.
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