

Shot Noise Sets the Limit of Quantification in Electrochemical Measurements

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Highlights

- A review of literature indicates a linear relationship between the limit of current capable of measuring an entity (e.g., single molecule) or event and the reciprocal of the measurement response time, over > 5 orders of magnitude.
- The minimum charge required to quantify an entity or event is set by the fundamental limit defined by shot noise (~100 electrons).
- The presence of baseline electrical currents raises the shot-noise limit of quantification to ~2,100 electrons, consistent with reported data.
- Amplification strategies in many electrochemical measurements have boosted the current to be well above the shot-noise limit.

Abstract. Detection of single molecules, particles, and rapid redox events is a challenge of electrochemical investigations and requires either an amplification strategy or significant averaging in order to boost the electrochemical current above the noise level. We consider the minimum number of electrons required to reach the limit of quantification in these electrochemical measurements. A survey of the literature indicates that the state-of-the-art limit in current detection for different types of measurements (e.g., voltammetry, single-molecule redox cycling, ion channel recordings of single molecules, metal nanoparticle collision, phase nucleation, etc.) is independent of the nature of the measurement and increases linearly with reciprocal response time, Δt^{-1} , over ~5 orders of magnitude

(from ~ 10 to $\sim 10^6$ s⁻¹). We demonstrate that the practical limit of quantification requires cumulative measurement of $\sim 2,100$ electrons during Δt , and is determined by statistics of counting electrons, i.e., the shot noise in the current.

Keywords

Electrochemistry; Shot-Noise Limit; Limit of Quantification; Signal-to-Noise; Electrochemical Amplification.

Abbreviations

Limit of Quantification (LoQ), scanning electrochemical cell microscopy (SECCM), hydrogen evolution reaction (HER).

Introduction. Electrical current, i , is the rate of passage of charge. For a charge, Δq , passed in a discrete time interval, Δt , this relationship can be written as:

$$i = \Delta q / \Delta t \quad (1)$$

Eq. (1) underpins all electrochemical measurements based on measuring electrical current and indicates that pushing the limits of electrochemistry in both time (faster measurements) and/or current domains (lower currents) requires measurements of smaller quantities of charge, Δq .

The measurement of electrical charge is limited by two fundamental sources of uncertainty[1-4]. Thermal fluctuations of electrons in resistive elements give rise to voltage fluctuations, whose magnitude drives the root-mean-squared (rms) current noise in the circuit [5,6].

$$\sigma_{i,\text{thermal}} = \sqrt{\frac{2kT}{R\Delta t}} \quad (2)$$

In eq. (2) R is the resistance of the electrochemical system, k is the Boltzmann constant, T is temperature and Δt is the time-constant of the measurement. The magnitude of this current noise decreases with the square root of the characteristic resistance of the measurement and can be neglected for low current

measurements measured in highly resistive environments [6]. The quantized nature of electrical charge, $q_e = 1.6 \times 10^{-19}$ C, also introduces statistical limitations on how small a current one can reliably quantify. If i is the average current occurring due to an electrochemical process, then $N = \Delta q / q_e$ is the *average* number of electrons passing in Δt . However, in any particular time interval N will fluctuate about the average with a standard deviation, σ_N . As the samples of electrons from a large population are statistically independent, the number of electrons passing in a time interval Δt is described by a Poisson distribution ($P(x) = \exp(-N) N^x / x!$). This distribution has a variance (σ_N^2) equal to N and thus a standard deviation of [7].

$$\sigma_N = \sqrt{N} \quad (3)$$

Substitution of eq. (1) into eq. (3), and noting that $q_e N = \Delta q$, yields the standard deviation in the current, σ_i [8]

$$\begin{aligned} \sigma_i &= q_e / \Delta t \cdot \sigma_N \\ &= \sqrt{N q_e^2 / \Delta t^2} \\ &= \sqrt{q_e i / \Delta t} \end{aligned} \quad (4)$$

Eq. (4) defines the *shot noise* in any measurement of current, reflecting the uncorrelated random fluctuation in electrical charge per time. Based on the definition of the *limit of quantification* (LoQ) in chemical analyses [9], a signal greater or equal to 10 times the standard deviation of the measurement is necessary to provide a statistically confident measure in quantifying the amount of an analyte. Thus, we define the *limit of quantification of an electrochemical current*, i_{LoQ} , required to detect an event, an entity, or the amount of a species, in terms of the shot noise, eq. (4).

$$i_{\text{LoQ}}^2 = (10\sigma_i)^2 = 100 q_e i_{\text{LoQ}} / \Delta t \quad (5)$$

$$i_{\text{LoQ}} = \pm 100 q_e / \Delta t \quad (6)$$

From eq. (6), one arrives at the conclusion that at least 100 electrons ($N \geq 100$) are required to reliably quantify an electrochemical process, i.e., $i \geq 10 \sigma_i$. To the best of our knowledge, this conclusion has not been explicitly examined within the electrochemical literature.

In this article, we survey diverse electrochemical experiments (e.g., single-molecule ion channel measurements [10], single-nanoparticle electrodisolution [11,12], electrochemical nanoscale imaging[13,14], etc.), which have pushed the limits of what is electrochemically measurable (i.e., faster measurements, lower currents, smaller and/or more subtle phenomena). We assess the smallest currents used to detect a particle, molecule, or an event as a function of the reciprocal response time of the measurement, Δt^{-1} . We find a linear relationship between the smallest values of i with Δt^{-1} that appears to define the state-of-the-art in low current, fast response electrochemical measurements. The linear distribution of these $(i, \Delta t^{-1})$ data pairs covers a five order of magnitude range ($10 < \Delta t^{-1} < 10^6 \text{ s}^{-1}$), irrespective of the electrochemical process or method. We demonstrate that this response limit is well accounted for by the statistical shot noise present in all electrical measurements.

Experimental Measurements of Δi and Δt^{-1}

We surveyed the literature reporting electrochemical experiments based on the measurement of electrical current that appeared to be near the limit of quantification. Here, “limit of quantification” is used to mean that a current i was reported during a response time, Δt , for the purpose of detecting a species or event, or measuring a quantity (e.g., number of molecules or atoms), and that the signal-to-noise was sufficiently high for the investigators to confidently report a “detection” or a specific “value.” As discussed below, Δi generally corresponds to the current measured above a background or baseline current, which may be comparable to or much larger than Δi . We considered 67 values of $(\Delta i, \Delta t)$ reported in 44 electrochemical experiments. These included measurements in which current is measured as a function of time for the purpose of: (i) detection of single molecules and single particles (both metal nanoparticles and vesicles); (ii) detection of single physical or chemical events; (iii) counting small

numbers of molecules; and (iv) observing small surface structures (e.g., single Pt atom and atomic step edges). The methods used included: (a) fast scan cyclic voltammetry; (b) protein and solid-state ion-channel recordings; (c) particle collision electrochemistry; (d) nanoscale electrochemical imaging; (e) redox cycling in nanogaps or nanocells; (f) slow scan “steady-state” voltammetry; and (g) electrochemical scanning tunneling microscopy. The intent of our survey was to obtain representative values of (Δi , Δt) data from modern experiments for our analysis and is not meant to be an extensive review of the literature.

Many of these measurements are based on a physicochemical signal amplification to create a readily measurable passage of charge, thereby pushing an immeasurable phenomenon, e.g., oxidation of a single molecule, well above the limit of quantification. A range of diverse amplification strategies in electrochemistry have been developed in recent years, including, for example, redox cycling in nanogap cells that allows detection of a single redox molecule [15-18], the turn-on of an electrocatalytic reaction that signals the arrival of a single metal atom or nanoparticle at an electrode surface [19], or fluctuations in ion channel currents that record subtle molecular motion within a single molecule [10]. In many cases, the amplification is so large that the observed signal Δi is orders of magnitude above that required at the limit of quantification. We refer the reader to the original literature for details of specific experiments.

A brief summary of six examples from the literature is presented below and in Figure 1 to illustrate the types of experiments and data considered, as well as the generally methodology used to extract Δi and Δt values. Table 1 of the *Supplementary Materials* provides a complete list of experiment data used in this study, as well as comments on how we extracted values of Δi and Δt . Unless stated otherwise, the response time Δt was determined by the measurement filter cutoff frequency stated in the original report, f , using $\Delta t = 1/2f$ [2]. Many of the values Δi and Δt are approximate (within a factor of 2); this limited precision does not alter any of the conclusions of our analysis.

Example 1. Figure 1(a) shows a i - t trace (black trace) where the observed spikes represent single Ag nanoparticle collisions at a microelectrode [12]. Integration of each area under each spike yields a value

of charge passed during the transient collision. The relationship between i and charge in this measurement is clear in the inset trace, where Δi is the peak height above background, ~ 4 pA. The filter frequency of this experiment (250 Hz) is used to determine the response time Δt , ~ 2 ms. Thus, the electrical charge, Δq , associated with this particle collision is estimated as $\sim 50,000$ e, although a value of Δq as small as $\sim 7,000$ e is reported and used below in the analysis. While the baseline current decreases with time in Figure 1(a), we estimate it to be roughly 5 to 25 times larger than the value of Δi used to quantify the charge associated with individual Ag nanoparticle collisions. The importance of the baseline in determining the total shot noise is discussed below.

Example 2. Figure 1(b) illustrates the measurement of base flipping with a single DNA duplex confined in the wild-type α -hemolysin (α -HL) nanopore, and the corresponding i - t trace [10]. The random current fluctuations between two distinct current levels correspond to spontaneous base flipping of a known mismatch in a DNA duplex. The measurable electrical charge used to identify the *shortest* single base flipping event is $\sim 12,000$ e, corresponding to $\Delta i \sim 1$ pA and $\Delta t = 2$ ms. The baseline current in this measurement is ~ 5 times larger than the magnitude of the ~ 1 pA current variation used to identify base flipping.

Example 3. Figure 1(c) shows voltammograms for the hydrogen evolution reaction (HER) at individual Pt_x clusters deposited on a bismuth electrode, where $x = 1$ to 9 [19]. The response time of the voltammetric experiments is calculated using the equation $\Delta t = RT/2Fv$, where R is gas constant, T is temperature, F is Faraday's constant, and v is the scan rate. The total electrical charge associated with a single Pt atom is estimated as 2×10^8 e, based on the limiting current ~ 50 pA and $v = 50$ mV/s. The baseline current in this example is exceptionally low relative to the value of Δi used to quantify the presence of Pt_x , a consequence of the low rate of HER on Bi.

Example 4. As shown in Figure 1(d), the repeated oxidation and reduction of a single molecule between two electrodes, or redox cycling, gives rise to a measureable amperometric response [15]. When a redox mediator enters the detection region in the nanogap, a transient current on the femtoampere level

can be measured. By taking Δt as ~ 1 s in this experiment, Δq is calculated as $\sim 88,000$ e for the signal in Figure 1(d). The baseline current in this example is approximately twice as large as the current associated with detecting a single molecule.

Example 5. Figure 1 (e) shows a scanning electrochemical cell microscopy (SECCM) image of a graphite electrode. In this experiment, a nanopipette filled with a redox species and electrolyte is employed as a scanning probe [13]. A SECCM scan profile corresponding to the black dashed line on the image shows current spikes that correspond to step edges on the graphite sample. The electrical charge of the smallest spike in this current trace ($\Delta i \sim 150$ fA and $\Delta t \sim 10$ ms) corresponds to $\sim 10,000$ e. The baseline current in this example is ~ 25 times larger the current used to detect a graphene step edge.

Example 6. In Figure 1 (f), a cyclic voltammogram recorded at $\nu = 1000$ V/s (200 waveforms averaged) is shown for the oxidation and reduction of an Os complex ($[\text{Os}(\text{bpy})_2(\text{dipy})\text{Cl}]^+$) adsorbed at a Pt nanoelectrode [20]. The peak current of ~ 20 pA and $\Delta t = 50$ μs (using the same method as for Figure 1(c)), were used to compute $\Delta q \sim 6000$ e. The baseline current associated with the charging current is ~ 50 times larger the current associated with the oxidation or reduction of the adsorbed currents (in Figure 1(f), $\sim 90\%$ of the capacitive current has been subtracted in order to see the faradaic current, see ref. [14])

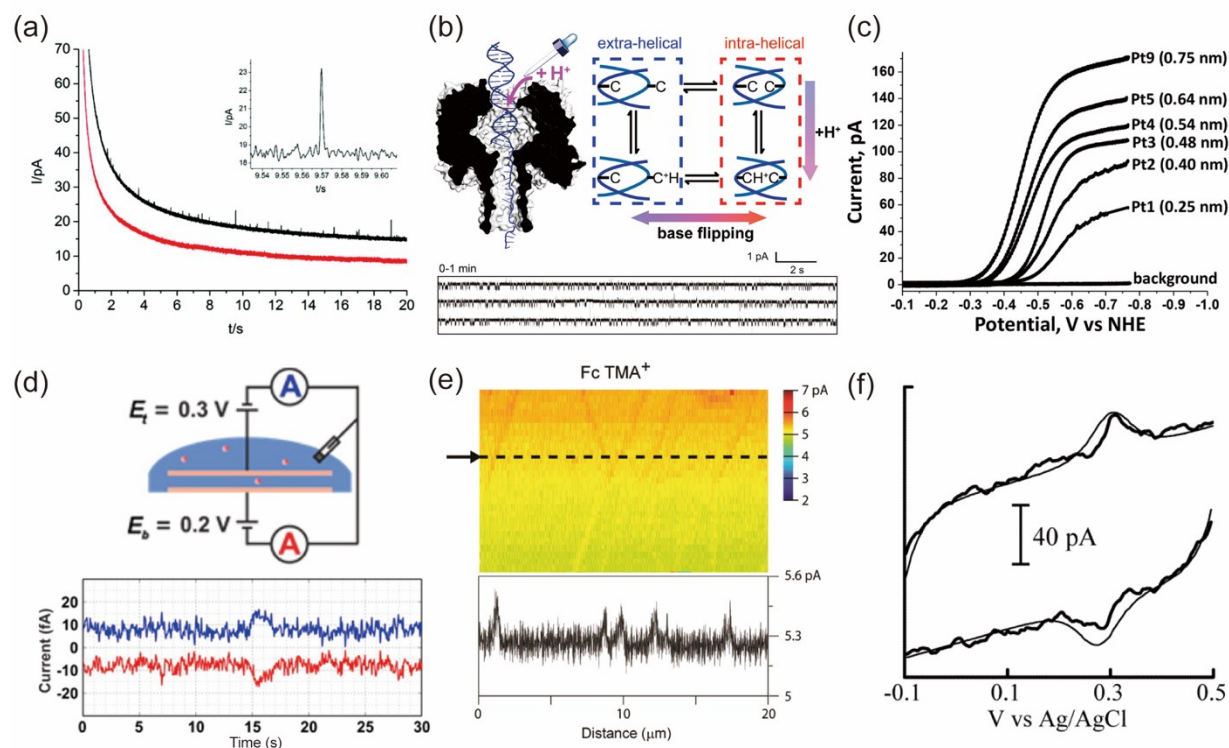


Figure 1. (a) i - t traces of single Ag particle collisions (reprinted with permission from *Analyst* **2015**, *140*, 5048. Copyright 2015 Royal Society of Chemistry). (b) i - t trace for duplex DNA base flipping inside an α -hemolysin protein (reprinted with permission from *J. Am. Chem. Soc.* **2018**, *140*, 5153. Copyright 2018 American Chemistry Society). (c) Voltammograms for HER of a single Pt atom and Pt atom clusters (reprinted with permission from *J. Am. Chem. Soc.* **2017**, *139*, 17677. Copyright 2017 American Chemistry Society). (d) Schematic and i - t traces of single molecule redox cycling in a nanogap cell. (reprinted with permission from *ACS Nano* **2013**, *7*, 10931. Copyright 2017 American Chemistry Society). (e) Image and current-position trace of graphite step edges by scanning electrochemical cell microscopy (reprinted with permission from *ACS Nano* **2015**, *9*, 3558. Copyright 2015 American Chemistry Society). (f) Cyclic voltammogram at 1,000 V/s corresponding to adsorbed redox molecules at a Pt nanoelectrode (reprinted with permission from *Anal. Chem.* **2003**, *75*, 3962. Copyright 2003 American Chemistry Society).

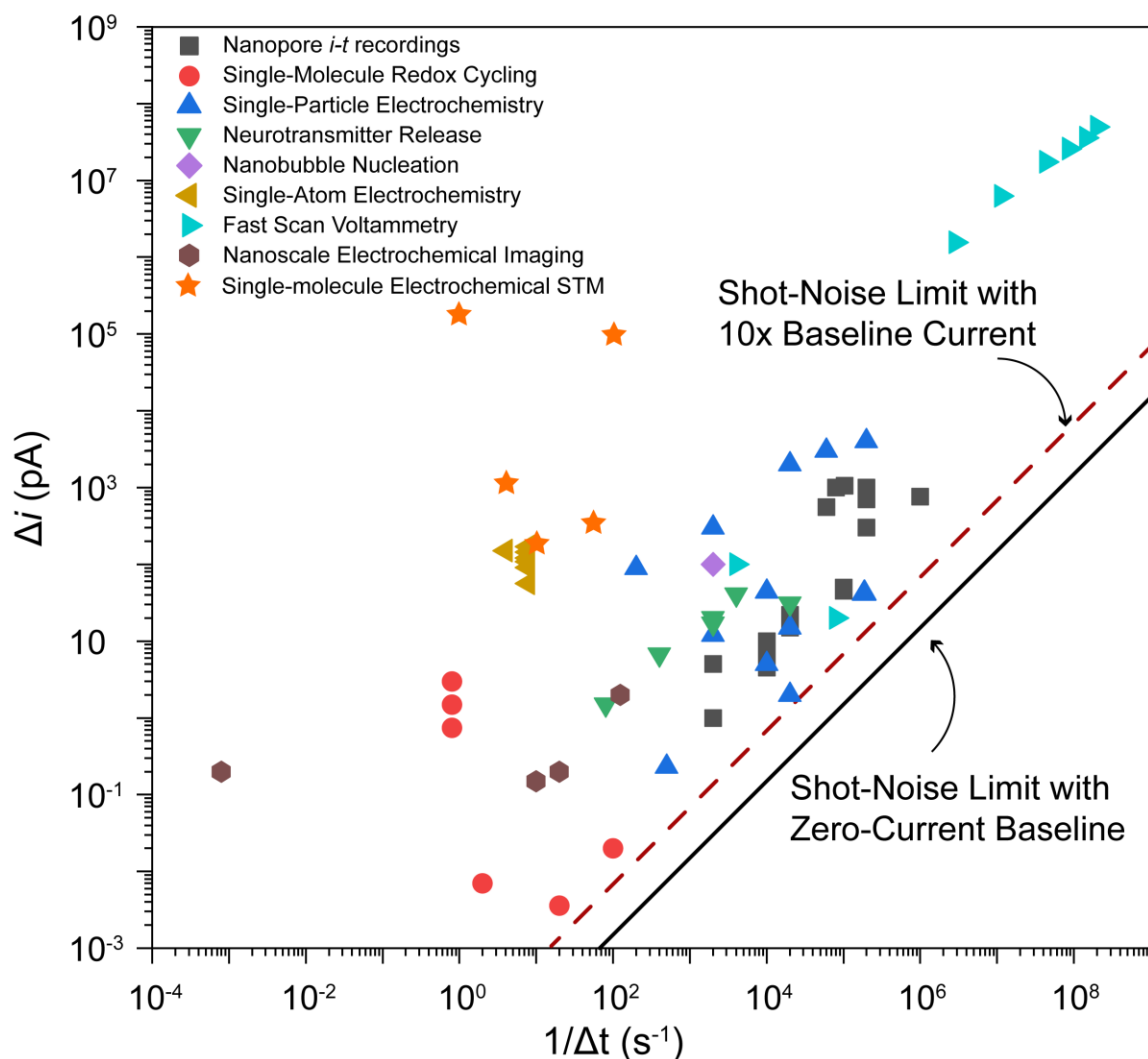


Figure 2. Plot of electrochemical current used to quantify an event or entity, Δi , versus reciprocal response time. The black line corresponds to the shot-noise limit in the absence of baseline current, eq (6). The dashed brown line corresponds to the shot-noise limit in the presence of a baseline current that is 10x larger than the current used to quantify an event or entity, eq. (6) and (10). Table S1 provides the source and values of the $(i, \Delta t^{-1})$ data.

Discussion

Figure 2 shows a plot of $\log(\Delta i)$ vs $\log(\Delta t^{-1})$ of all surveyed data, which varies over 10 orders of magnitude ($10^{-3} < \Delta i < 10^8$ pA and $10^{-3} < \Delta t^{-1} < 10^8$ s $^{-1}$) [10-54]. We observed that all data points lie above a straight line with unity slope (dashed brown line), given by the equation: $\log(\Delta i/\text{pA}) = \log(\Delta t^{-1}/\text{s}^{-1}) - 3.47$. Note, in this work we make no effort to analyze the sources of the variability in these measurements,

which in addition to fundamental noise (shot noise & Johnson noise) could include contributions from other sources (e.g., instrumental, environmental, or 1/f (flicker) noise)[8].

Figure 2 also shows the theoretical i_{LoQ} based on the shot-noise limit, eq. 6 (black line). As previously discussed, shot noise represents a fundamental limit that defines the minimum charge required to quantify an electrical measurement. Eq. 6 assumes that the baseline or background electrical current is zero. However, all electrochemical measurements have a non-zero background current, i_{baseline} , which additionally contributes to the shot noise and, thus, measurement error. The variance in the total measured signal, σ_{total}^2 , is $q_e(i_{\text{baseline}} + \Delta i)/\Delta t$, while that for the baseline alone, $\sigma_{\text{baseline}}^2$, is equal to $q_e(i_{\text{baseline}})/\Delta t$. In determining Δi by subtraction of the signal from the baseline, the error in Δi is computed by the addition of the two variances (i.e., $\sigma_{\Delta i}^2 = \sigma_{\text{total}}^2 + \sigma_{\text{baseline}}^2$), yielding:

$$\sigma_{\Delta i}^2 = q_e(2i_{\text{baseline}} + \Delta i)/\Delta t \quad (7)$$

As noted above, baseline currents in electrochemistry measurements are often comparable or much larger than Δi , ranging from 2 to 50 times larger for the examples shown in Figure 1. Assuming a typical value of i_{baseline} that is $10\times$ larger than Δi , the total variance contained in quantification of an event or entity is given by

$$\sigma_{\Delta i}^2 = 21(q_e\Delta i)/\Delta t \quad (8)$$

Thus, inclusion of the shot noise in the baseline increases the quantification error by a factor of 4.6. The LoQ coming from eq. (8) is plotted in Figure 2 as the dashed line, which corresponds to the theoretical shot-noise limit with the inclusion of a baseline current = $10\Delta i$. Following the derivation of eq. (6), an analogous equation for i_{LoQ} based on Δi that includes shot noise introduced by a finite baseline is derived as follows:

$$i_{\text{LoQ}} = 10\sigma_{\Delta i} \quad (9)$$

$$i_{\text{LoQ}}^2 = (10\sigma_{\Delta i})^2 = 100\sigma_{\Delta i}^2$$

Setting $\Delta i = i_{\text{LoQ}}$ and $i_{\text{baseline}} = 10\Delta i$, yields

$$\begin{aligned} i_{\text{LoQ}}^2 &= 100 q_e (20i_{\text{LoQ}} + i_{\text{LoQ}}) / \Delta t \\ i_{\text{LoQ}} &= 2,100 q_e / \Delta t \end{aligned} \quad (10)$$

Thus, we conclude that a minimum of $\sim 2,100$ electrons are required to quantify any electrochemical event or entity based on measuring Δi with $i_{\text{baseline}} \sim 10\Delta i$, independent of Δt . Taking the $\log_{10}$ of both sides of eq. (10) yields $\log(\Delta i/\text{pA}) = \log(\Delta t^{-1}/\text{s}^{-1}) - 3.47$, which is the equation used to draw the brown dashed line defining the lower limit of experimental values of $(\Delta i, \Delta t^{-1})$ in Figure 2.

It is readily apparent from inspection of Figure 2 that the literature data fall very close to or above the dashed line defining the 10-fold background shot-noise limited current, eq. (10). Thus, it directly follows that many electrochemical measurements reported in the modern literature have reached, or approach, the theoretical shot-noise limit of quantification, corresponding to $\sim 2,100$ electrons for a signal Δi recorded on a $10\Delta i$ background current. This conclusion covers a bandwidth extending over five orders of magnitude. It should be apparent that our choice of $i_{\text{baseline}} = 10\Delta i$ is somewhat subjective and based on literature values that we have surveyed. However, eqs. (5) – (10) may be used to determine i_{LoQ} and the number of electrons required in an electrochemical measurement for any arbitrary value of i_{baseline} .

As noted in the introduction, thermal noise is the other fundamental source of uncertainty in current measurements. With high electrochemical resistances and a relatively short response times, as is typical in the measurements considered in Figure 2, it does not make a major contribution to the uncertainty. This is indicated by data points in Figure 2 approaching the shot noise LoQ

Based on our analysis, there appear to be two strategies to reduce the effects of the fundamental shot noise limit of quantification in electrochemistry. The first is based on simple signal averaging, as used in the example shown in Figure 1(f) where 200 cyclic voltammograms were averaged to obtain a detectable

Δi for counting adsorbed molecules. This approach is suitable for many electrochemical measurements, but is likely limited in electrochemical methods used to detect stochastic events, e.g., the detection of single molecules, particles or events. The second approach is to reduce the baseline or background currents. E.g., a nearly 4.6 fold reduction in i_{LoQ} is obtained by reducing i_{baseline} from $10\Delta i$ to zero.

We note that many of the $(\Delta i, \Delta t^{-1})$ points in Figure 2 are well above the shot-noise limit. As previously discussed, the ability to detect single molecules, particles and events is largely due to redox amplification strategies adopted by the electrochemical community, which result in amplification factors ranging from 1,000 to 100,000. It is interesting to note that these amplification strategies are analogous to amplification schemes used to count photons in spectroscopy, where a photon ejects an electron that causes a cascade of secondary electrons in a photomultiplier or avalanche photodiode. For example, the exceptionally high amplification in some single molecule scanning tunneling microscopy measurements, such as those shown in Figure 2[49,53,54], results from the one-electron oxidation or reduction of the molecule.

Finally, we note that while shot noise prohibits direct electrical measurement of single electron-transfer events, sensitive spectroscopic [55], luminescence [56], and optical [57] amplification strategies have allowed the quantification of individual redox events. Such measurements provide an exciting avenue for electrochemical measurements beyond the limitations highlighted in this work.

Conclusion.

A survey of the literature indicates that the limit of quantification in electrochemical analyses, based on the measurement of current, is determined by the shot noise in the electrical current. This finding appears to hold irrespective of the nature of the measurement, and is in quantitative agreement with a theoretical expression for the *limit of quantification of an electrochemical current*, i_{LoQ} . The fundamental shot-noise limit of electrochemical quantification for a zero-current baseline measurement requires the passage of ~ 100 electrons. Background currents significantly increase the number of electrons required at

the limit of quantification, reaching $\sim 2,100$ electrons for a signal Δi recorded on a $10\Delta i$ background current.

Conflict of Interest Statement

Nothing Declared.

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