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Review Article

Interpretation of stochastic electrochemical data

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Abstract

Stochastic electrochemical measurement has come of age as a powerful analytical tool in corrosion science, electrophysiology, and single-entity electrochemistry. It relies on the fundamental trait that most electrochemical processes are stochastic and discrete in nature. Stochastic measurement of a single entity probes the charge transfer from a few or even one electroactive species. In corrosion, the stochastic measurements capture either the average amplitude/frequency of many events taking place spontaneously or probe discrete transients, signifying localized dissolution. The measurement principles vary in corrosion, single-entity, and electrophysiology, yet the main quantifiable values are commonly the frequency and amplitude of events. This perspective delves into the methodologies for the analysis and deconvolution of stochastic signals in electrochemistry. Ranging from visual assessment of transients to time/frequency analyses of the data and state-of-the-art machine learning, these methodologies mainly aim at identifying patterns, singular events, and rates of electrochemical processes from stochastic signals.

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Introduction

The umbrella term ‘stochastic’ can take on different meanings depending on context. Physical systems can exhibit randomness due to the inherent graininess of matter. When a stream of particles impinges upon a detector, the exact instant at which each detection event occurs is usually random, even if the average rate of events is perfectly well defined. This is the origin of electrical shot noise, for example. Another form of stochasticity arises from heterogeneities in a population being probed or can result from physically unavoidable intrinsic thermal and quantum fluctuations [1]. In this case, measurements of individual members of the population can yield different results, even though the statistical distribution of the population is well defined. This form of disorder is particularly relevant to studies of, e.g. ensembles of catalytic nanoparticles. Finally, many nanoscale systems exhibit thermally driven fluctuations in time between different internal states that are largely averaged out in macroscopic measurements. The time evolution of the signal then depends on the possible states of the system and the dynamics of the transitions between them. In each case, the observed stochasticity, or ‘noise’ encodes information about a fundamental physical property.

The stochasticity discussed herein is distinct from interference, which is caused by external sources, e.g. power lines or vibrations, and can, in principle, be eliminated from an experiment. However, in practice, a “clean” signal acquisition can become challenging as the data is amalgamated with the instrumental and environmental noise that is generated by the data acquisition instrument, circuitry, interfaces, and electrical and electromagnetic sources of noise. Confusingly, the term ‘noise’ is also often employed to describe both interference and stochastic electrochemical signals. The accuracy of stochastic measurements, particularly in the single-entity domain, relies on proper isolation (e.g. Faraday cages, shielded and triaxial cables, etc.) as well as advanced instrumentation to achieve the amperometric resolution at the sub-picoampere level and the temporal resolution at the sub-microsecond level [2].

Corrosion assessment

The interpretation of stochastic electrochemical signals in corrosion research often serves either as a tool for the assessment of protective coatings, with a range of sensor architectures [3,4], or identifying corrosion patterns. Herein, the stochastic signals are spontaneous potential and current fluctuations generated by the anodic dissolution of metal and the balancing reduction reactions [5]. A unique advantage of the technique is its ability to directly capture the time-varying kinetics of physicochemical processes without perturbation of the system. This is particularly valuable when studying localized corrosion, corrosion inhibition, or re-activation [6,7]. Localized charge-transfer events that are characteristic of localized corrosion are manifested as transient features in the stochastic signal. These transients contain information relevant to the kinetics of corrosion, for example, in the current signals and the thermodynamics via the potential [8]. The accurate extraction of this information is a critical step in the application of stochastic electrochemistry for corrosion assessment [9].

The least stringent data analysis methodology would be to use statistical parameters in the time domain, such as the standard deviation [9]. Parameters in the time domain are relatively straightforward to calculate and can be used for corrosion classification [10] or as inputs for a feature vector in a machine learning algorithm [11]. The charge amplitude and frequency of corrosion events may be connected with the underlying physico-chemical process [9]. Often, however, this is not the case, which limits their applicability to finding correlations between data features and corrosion characteristics [9]. Calculations in the time domain require the prior removal of the direct current (DC) component from the signal, representing either electrode asymmetry or potential shift [12]. This DC drift is often overlooked and, when not removed properly, can result in false frequency components in the remaining data or, otherwise, the removal of data that was representative of the process under investigation [12].

The preferred data analysis methodologies should allow the experimentalist to focus on data transients and, thus, directly on the kinetics of local processes. This is much preferred over indirect statistical analysis methods. Such functionality can be achieved by continuous wavelet- or Hilbert—Huang spectra that show time-resolved frequency information [13]. Figure 1 presents an example of joint time-frequency analysis for a stochastic potential signal. The time-frequency spectra allow a precise selection (Figure 1(**b**)) of the frequency information within any timeframe of interest [14]. Transient phenomena are associated with local maxima in these time-frequency spectra (Figure 1(**c**)) and can be located automatically using pre-defined transient criteria [15]. This results in a more objective study of the localized corrosion process; transient criteria can be kept constant and only relevant information is taken into account, whereas timeframes in between transients can be neglected. Combining time-frequency analysis of stochastic signals with scanning electrochemical microscopy (SECM), or simultaneous, *in situ* optical measurements of the electrode surface, has proven to be a powerful means to locate, classify, and quantify corrosion processes [16,17]. The quantification of the corrosion processes, i.e. the corrosion rate, is possible by measuring the total charge that is associated with the current signal fluctuation, signifying the total anodic dissolution of the metal. The optical assessment complements the electrochemical signals by visualizing the surface changes associated with the transients [17].

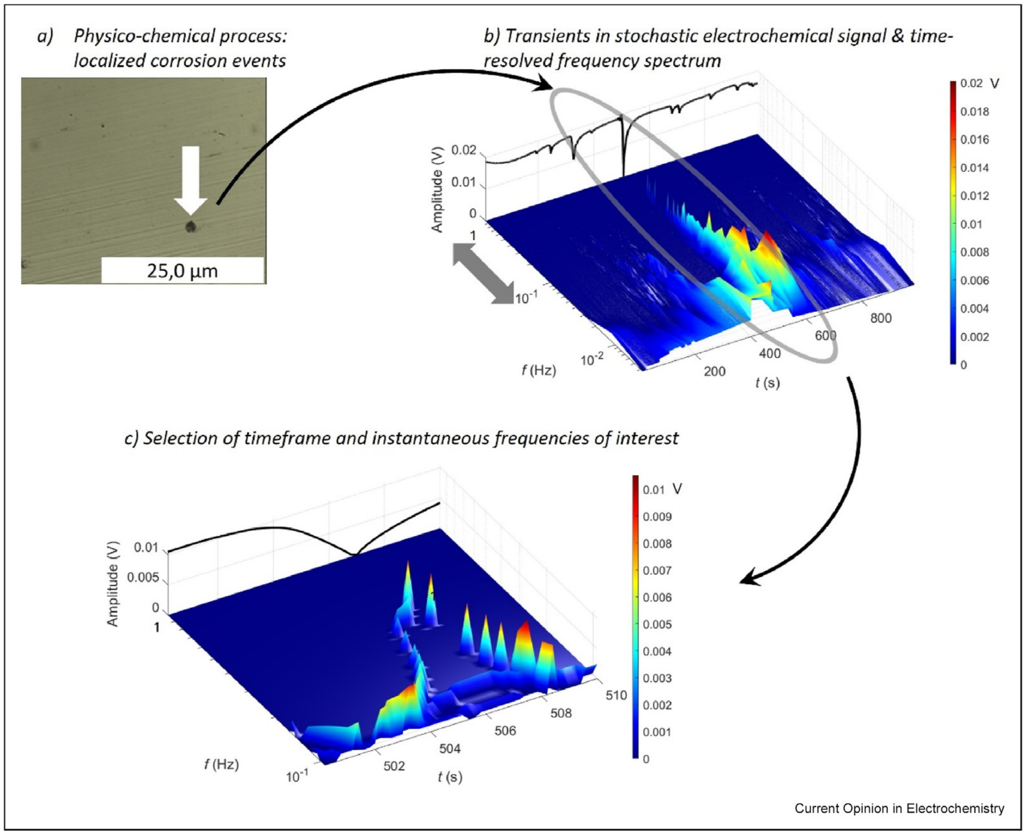
In principle, similar data analysis can be applied to the stochastic signal from battery testing and degradation. The ion-electron transfer via the intercalation or deintercalation processes that drives a typical Li-ion battery is, in nature, analogous to the anodic dissolution and cathodic reduction events in corrosion. Molecular dynamics has been utilized to model these discrete events theoretically and correlate microscopic features with capacitance and impedance [19,20], yet experimental studies that use stochastic signal analysis for battery research have yet to implement tools beyond rudimentary frequency domain analysis [21,22]. While stochastic electrochemistry in corrosion and degradation studies is predominantly concerned with many averaged and/or localized events, the single-entity electrochemistry focuses on the detection of electron transfer across a few or even single electrochemical events. Yet, in both disciplines, the amplitude of the spikes and the frequency of the events are the main quantities of interest.

Single-entity electrochemistry methods

Single-entity electrochemistry [23,24] concerns measurements at the discrete level. Ion channels and nanopores represent the most studied of the stochastic electrochemical systems. It is, however, prescient to consider what information has been gleaned from stochastic signal analysis of other single-entity electrochemistry systems.

(1) Impact electrochemistry methods can, in principle, be employed to (1) infer the concentration of targets via the collision rate and (2) explore population heterogeneities. However, because the former depends on mass transport via diffusion, migration, and convection, all of which are intertwined at the nanoscale, this approach is difficult to apply quantitatively in an analytical setting [25]. Far more interesting have been studies focusing on the microscopic dynamics of individual detection events in oxidative dissolution impact electrochemistry, in which it was revealed that 'single collision events' can in fact involve complex hierarchies of sub-events ruled by the statistical

Figure 1



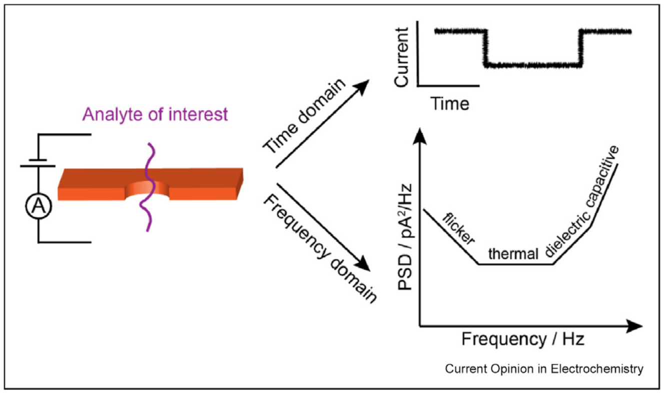
Example of time-frequency transient analysis of corrosion potential signal from AISI 304 stainless steel immersed in 10^{-3} M HCl, using Hilbert−Huang transform. The localized electrochemical process, i.e. the corrosion pit, is indicated by the white arrow in (**a**). The gray circle in (**b**) represents the ability to precisely identify and select transients of interest associated with the localized event. This selection can be expanded and examined in more detail (**c**) or form the basis for further assessment by machine learning [18].

properties of Brownian motion [26,27]. Deconvolving this interplay of mass transport and faradaic processes at short time scales is critical to establishing the actual properties of nanoparticles via these methods.

(2) Redox cycling, in which an electrochemically active species is repeatedly reduced and oxidized, has allowed measurements down to the few-molecule level and even the inference of the current from single molecules [28]. Interestingly, this suggests that reversible adsorption plays a significant role at the nanoscale even for redox cycling by well-behaved, reversible outer-sphere species [29,30]. In addition, dwell-time analysis in nanocavities suggests long-lived adsorption sites not accounted for by purely diffusive dynamics [31]. Finally, it has been predicted from random walk simulations that redox cycling leads to a suppression of shot noise below the classical limit [32]. An experimental verification would be extremely interesting, but this poses a significant challenge due to the low signal levels and dominance of molecule-number fluctuations at low frequencies.

Electrochemical sensing via nanopore architecture is another successful example of single-entity electrochemistry for bioanalytical sensing and sequencing [33,34]. The principle of nanopore sensing is the detection of changes in the ionic current as analyte molecules translocate through the nanopore. Figure 2 illustrates the features of time- and frequency-resolved signatures in the ionic current trace, such as pulse amplitude, width (duration), frequency, and waveform, that reflect abundant information about the translocating analytes, including size, charge, and concentration. Short translocation events are of particular interest as a tool to study small molecules that pass through the pore rapidly. However, it is difficult to detect short pulses, as current noise (i.e. interference) increases with measurement bandwidth. The analyte-induced events are characterized by current fluctuations that can reach single or multiple levels. Various data analysis software, such as Open Nanopore and Transalyzer, has been developed for event identification and feature extraction. The hidden Markov model has been used for characterizing complex signals such as multiconductance levels and detecting events obscured

Figure 2



Schematic representation of electrochemical nanopore sensing and data analysis involving the interpretation of ionic current signals in either the time domain or frequency domain.

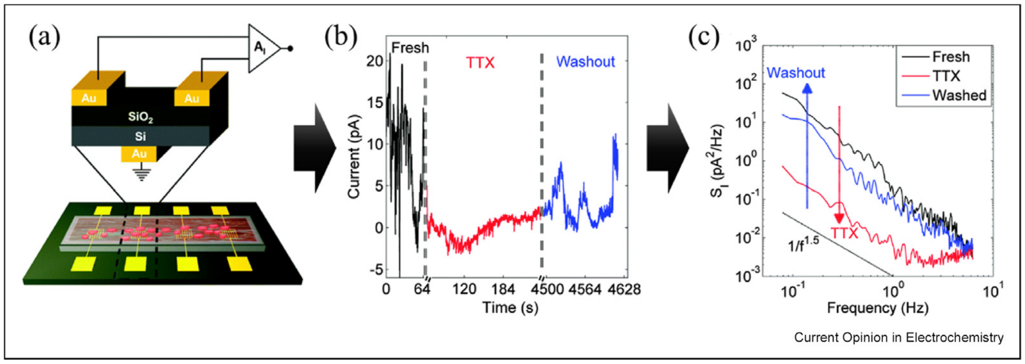
by noise interference. Other methods for detecting multilevel events include threshold-based detection and the cumulative sums (CUSUM) algorithm [35], which characterize the local structures of events by computing their current amplitudes and durations. To facilitate rapid analysis of nanopore data with significantly reduced labeling costs, an active learning method has been introduced to reduce labor costs by selecting the samples that need labeled [36].

A single-entity signal often contains frequency information related to dynamic movements and electrochemical processes. For example, in nanopore experiments, the transport of molecules and ions through biological nanopores is governed by interaction networks among restricted ions, transported molecules, and residue moieties at the pore inner walls [37]. Therefore, in single-entity electrochemistry, the signals often exhibit nonlinear and nonstationary characteristics. These dynamic features of single entities are commonly obscured by noise due to insufficient signal-to-noise ratio (SNR) [38]. One possible approach to extracting multiple features is to utilize time-varying signal processing methods, including the Fourier transform, wavelet transform [39], variational mode decomposition [40], and Hilbert–Huang transform [37]. Analyzing low-frequency noise, particularly 1/f noise, contributes to understanding noise sources, better engineering experimental settings for ionic current recordings and signal interpretation, and unraveling subtle changes embedded in the ionic current traces. For example, a biological nanopore fused with protein receptors as the sensing element exhibited high-amplitude 1/f current noise in the low-frequency domain when reversible captures of a high-affinity protein ligand occurred at the tip of the nanopore. Reversible switches between the ligand-captured and ligand-released substates produce a significant amplification in the low-frequency 1/f current noise, signifying a long-lived binding event. In contrast, low-affinity protein ligands were not sufficient to induce this noise signature, unable to elevate the amplitude of current noise beyond what one would expect for white current noise in the low-frequency domain [41]. Others have investigated how the ionic current noise through solid-state nanopores reflects the adsorption of short, neutral polymers onto the nanopore surface. The power spectral density (PSD) noise exhibited a characteristic change upon polymer adsorption, with the magnitude strongly dependent on both polymer length and salt concentration. For short polymers at low salt concentrations, no change was observed [42].

Stochasticity of bioelectrical data

Stochasticity in biological systems is an inherent characteristic that gives rise to genotypic and phenotypic variations down to the subcellular level. Bioelectrical stochasticity has begun to be appreciated for its essential role in key cellular activities [43]. At the single-cell level, signals can arise from multiple sources, including heterogeneous ion and electron transfers, that generate a stochastic fluctuation of voltage and current. Analysis of bioelectrical signals via PSD functions has been shown to indicate the reversible blockage of voltage gated K^+ and Na^+ channels in an ensemble of glioma cells [44]. Figure 3 shows the data acquisition architecture and data in both time and PSD formats. The blockage of ion channels due to exposure to channel blockers was manifested as a drop in the amplitude of the low-frequency component of the current signal. Another study, similar in nature, examined the bioelectrical signal from voltage-gated sodium channels in an ensemble of human breast cancer cells using histogram and frequency domain analysis [45]. These studies showcase the usefulness of frequency domain and histogram analysis in correlation between

Figure 3



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(**a**) Data acquisition set-up with adherent cells shown as red circles. The current signal is generated by fresh C6 glioma cells (black trace), the C6 glioma cells after exposure to tetrodotoxin (TTX), a potent blocker of voltage-gated Na^+ channels (red trace), and after the TTX washout. The current signal is presented in (**b**) time domain and (**c**) frequency domain formats [44]. (Data reproduced with permission from the Royal Society of Chemistry).

one statistical variable to one biochemical trigger. However, biological systems comprise multiple sources of signal, and a multifactorial analysis requires a more sophisticated data analysis methodology for the deconvolution of data.

AI aided data analysis

Machine learning (ML) has revolutionized the signal processing landscape. The ML algorithms for nanopore data analysis have seen rapid advancements in interference mitigation, spike recognition, feature extraction, and analyte classification [46,47]. The algorithm, once trained with sufficient well-labeled datasets, exceeds the performance of statistical methodology in extracting information from stochastic signals. An example is the implementation of a deep learning methodology based on a bi-path network (B-Net) to acquire prototypical pulses and perform feature extraction without *apriori* assigned parameters. The B-Net was able to process data with a SNR equal to 1, an almost impossible task for threshold-based algorithms [48]. While training the algorithm with raw stochastic data typically requires a large number of data sets, recent work in the field of corrosion has used a two-step strategy to significantly reduce the number of datasets required for training while achieving a 97% accuracy of corrosion classification [18]. Here, the continuous wavelet transform (CWT) spectra and modulus maxima (MM) were first used to generate time-frequency spectral transients, which were then used as input to train a convolutional neural network (CNN) architecture.

Deep learning has also been utilized for analyzing ion channels from patch clamp data, with applications in predicting ion channel functionality and topology, as well as quantifying structure-activity relationships [49,50]. A critical first step in understanding recorded current and voltage traces is event detection, which involves the removal of background noise, reconstruction of underlying signals, and statistical quantification of discrete events. This process, known as "idealization," is particularly challenging for complex biological data containing multiple distinct channels and simultaneous gating events [51]. Therefore, achieving high-quality idealization is often laborious and, in some cases, even infeasible due to subjectivity and the complexity of the biological data. Unsupervised classification of ion and electron transfer events has been successfully performed via the CNN model, a deep learning model with the ability to extract hidden pattern information from the dataset without prior knowledge [52]. With no parameters to set, such as baseline, channel amplitude, or number of channels, the CNN model facilitates unsupervised automatic detection of single charge transition events. Additionally, the CNN model allows for the integration of all prediction tasks into one model, enabling multitask and multitarget predictions with improved classification accuracy. Beyond mere sensing and classification, machine learning architectures have now been successfully tested in closed-loop and feedback-controlled systems to sense the bioelectrical state of the cells and then modulate the bioelectricity via tools such as electrophoretic ion pumps [53—55].

Conclusion

Data acquisition architectures and instrumentations continue to advance and enable stochastic electrochemistry to become a powerful electroanalytical tool. The software of this tool, being the data analysis techniques, needs to catch up with the hardware advancements to allow the technique to reach its full potential. Statistical data analysis techniques are useful for examining smaller datasets with well-defined variables, but more sophisticated methodologies, empowered by artificial intelligence, are required to handle large datasets with multiple variables. The stochastic current and potential signal, whether originated by single-entity detection, corrosion, or biology, share the same nature, where amplitude, pulse, transient duration, and frequency of events are the main analytical values of interest. And therefore, there is much value in interdisciplinary approaches and to learn from advances in data analysis in other branches of stochastic electrochemistry.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Sina Jamali reports financial support was provided by Australian Research Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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