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Interface between Two Immiscible Electrolyte Solutions Electrodes for Chemical Analysis

The interface between two immiscible electrolyte solutions (ITIES) plays vital roles in various fields, such as neuroscience, environmental science, analytical chemistry, separation, catalysis, and nanoparticle synthesis. ITIES emerges as a unique approach in chemical analysis due to its sensitivity to both redox-active and redox-inactive analytes. Neurotransmitters, metal ions, drug molecules, and other complex molecules such as proteins have been detected using ITIES. The detection of redox-inactive species at the ITIES has opened a door to understanding a wide range of complex systems that are less suited to probing by solid electrodes. In this feature article, we present the history of electrochemistry at the ITIES; charge transfer reactions, thermodynamics, and kinetics at the ITIES; electrode−solution interfacial structure; and a diverse range of applications enabled by ITIES.

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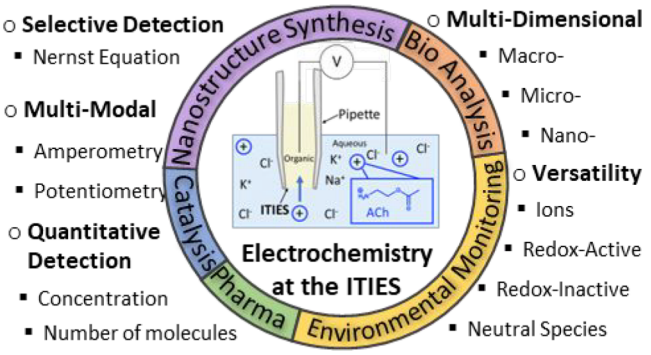

INTRODUCTION

An interface between two immiscible electrolyte solutions (ITIES) is a unique electrode, capable of detecting a wide range of electroactive chemical species regardless of their classification as redox-active or redox-inactive.[1−6] ITIES electrodes have become more prevalent in analytical science due to their sensitivity beyond redox-active analytes and their ease of fabrication down to the nanoscale,[7,8] allowing for high spatial resolution which enables single-entity and nanostructure studies.[9−11] Electrochemistry at the ITIES has enabled researchers to probe fundamental mechanistic processes[1,5,12−40] and a wide range of applications, including catalysis,[41−44] cellular studies,[8−11,15,41,42,45−69] heavy metal detection,[70−74] pharmacological studies,[71,75−93] single-entity studies,[94] environmentally relevant studies,[95,96] and nanostructure synthesis.[26,44,97−118] The versatility of ITIES is summarized in Figure 1.

Electrochemical detection relies on the transfer of charge (ions and electrons) to generate a current, which is one parameter used for quantitative analysis. With solid electrodes such as carbon, charge is transferred via the reduction or oxidation of electrochemical species such as those in the redox couples hexaammineruthenium(III)/hexaammineruthenium(II) or ferrocenium/ferrocene.[119−121] Complementing solid electrodes, which can only probe redox reactions,[122,123] the ITIES allows charged species such as ions to cross it, removing their need to be reduced or oxidized for detection. In addition to ion transfer (IT) at the ITIES, electron transfer (ET) may also occur and has stimulated lots of interest. Mechanisms for charge transfer at the ITIES continue to develop following significant work by several researchers and are discussed later in the text.[2,5,17−21,50,124−126]

In this feature article, we present fundamentals related to chemical analysis with ITIES electrodes. These include the history of electrochemistry at ITIES; charge transfer reactions at ITIES; thermodynamics and kinetics of charge transfer at ITIES; electrode−solution interfacial structure; and also various applications of ITIES such as environmental studies, biosensing, catalysis, and nanoparticle synthesis.

HISTORY OF ELECTROCHEMISTRY AT THE ITIES

In 1902 Nernst and Riesenfeld observed current flowing across an ITIES (a water/phenol/water interface).[127] A traditional

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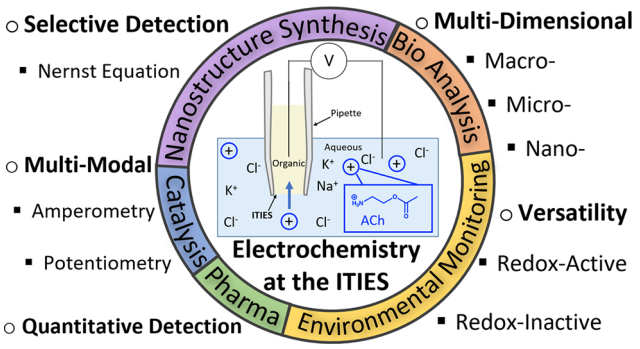

Figure 1. Electrochemistry at ITIES electrodes, as demonstrated by the detection of acetylcholine, plays critical roles in various scientific disciplines, some of which are listed on the center ring. A few of the capabilities of ITIES electrodes are also listed and elaborated.

four-electrode electrochemical cell was later introduced to study the ion/charge transfer occurring in these macro-ITIES (mm- to cm-sized) systems.[21,125,128] In this four-electrode system, two Luggin capillaries are brought close to the interface formed by two different phases, organic (o) and aqueous (w) (Figure 2A). With the use of the Luggin

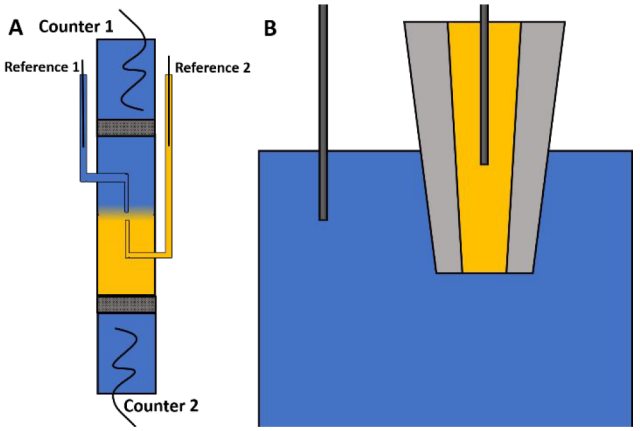

Figure 2. Schematic diagram of a (A) four-electrode electrochemical cell for macro-ITIES system. Reference wires 1 and 2 (Ag/AgCl wire) are inserted into the Luggin capillaries containing each phase, the tips of which are positioned close to the interface. Counter 1 and Counter 2: counter platinum wire electrodes.[125] Modified with permission from ref 125. Samec, Z.; et al. *J. Electroanal. Chem. Interfacial Electrochem.***1979**, *100*, 841−852. Copyright 1979 Elsevier. (B) Nano or micro-ITIES system supported at the tip of a glass pipet. Yellow and blue colors represent the organic and aqueous phases, respectively.

capillaries, the error created by the ohmic potential drop is reduced since reference electrodes can be placed very close to the interface. Two counter electrodes were also inserted into two w phases separated from the working space by glass frits (Figure 2A) to measure the current flowing across the ITIES.

Later in 1986, Taylor and Girault introduced the micro-ITIES, supported at the tip of a micropipette.[45] Micro-ITIES systems have several advantages over a macro-ITIES system, including small ohmic potential drop and charging current and increased spatial resolution due to decreased electrode size.[129] Additional advantages of miniaturizing the ITIES include increased sensitivity, enhanced mass transport, and a lower limit of detection. Since the current measured at a micro-ITIES is considerably smaller (nA to pA scale), Taylor and Girault employed a simplified two-electrode system with an organic phase sandwiched between two aqueous phases in a U tube.[45] Two Ag/AgCl reference electrode wires were inserted at opposite ends of the tube, and a potential was applied between these electrodes to measure current from ion transfer at the ITIES formed at the micropipette tip.[45] The U tube apparatus has been applied to other studies as well, varying the solutions and reference electrodes to meet the study's needs.[7,48,130] Later, this two-electrode system was simplified, where an ITIES was created by immersing the tip of a micropipette filled with an electrolyte solution in another electrolyte solution that the micropipette's solution is immiscible with (Figure 2B).[35,131] A conducting wire was affixed inside the pipet, and another reference electrode was placed outside the pipet; a voltage was applied between the two electrodes.[15] Similarly, two-electrode electrochemical cells have been used for nano-ITIES systems.[12,52,72,132]

CHARGE TRANSFER PROCESSES AT THE ITIES

The faradaic processes at the ITIES are mediated in several different ways, including direct IT, assisted IT (AIT), heterogeneous ET, and coupled ET and IT.[13,14,17,18,124,126,133−135] This versatility enables the detection and manipulation of a wide range of chemical species, allowing for applications in various fields.

Direct Ion Transfer. Ion transfer at the ITIES has been reported by studies pioneered by several groups back to the 1970s.[136,16,137] In a preliminary note published in 1976, Koryta, Vanysek, and Brezina reported the polarization of the interface between two immiscible electrolyte solutions; they also observed the ion transfer at the polarized ITIES.[137] Later in 1979, Koryta presented that, in the absence of current flowing across the ITIES, an equilibrium is established, with the equilibrium potential difference ($\Delta\phi_{eq}$) determined from equations in the Thermodynamics section below.[16] If a potential difference greater than $\Delta\phi_{eq}$ is imposed on the system from an external source ($\Delta V = \Delta\phi_{eq} + \eta$, where η is overpotential), the charge introduced will be used in part for the transfer of an ion across the interface and partially for charging the double layer.[16]

In 1980, Homolka et al. further discussed IT (Figure 3).[18] An ITIES was established between adjacent phases w and o where both phases contain a common ion I^+.[18] This is a poised

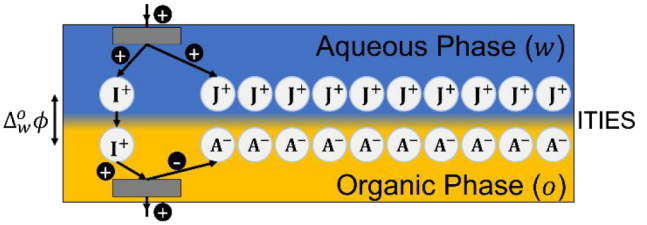

Figure 3. Charge transfer across the interface between two immiscible electrolyte solutions (ITIES). A positive charge is introduced into the aqueous phase (w) by a metallic electrode, which either drives ion I^+ across the ITIES or charges the aqueous side of the ITIES via cation(s) J^+. In the organic phase (o) the current continues with the transfer of I^+ into the bulk of o or with the charging of the organic side of the ITIES via anion(s) A^-.[18] Modified with permission from ref 18. Homolka, D.; et al. *Anal. Chem.***1980**, *52*, 1606−1610. Copyright 1980 American Chemical Society.

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system in which the Nernst−Donnan equation applies.[18] When a charge is introduced into the phases from an external source, two processes occur. The first of these is the charging of the ITIES. The second process is the transfer of ions across the ITIES. When the electrolyte of *w* consists of only very hydrophilic ions (J^+ and a counteranion) and *o* consists of only very hydrophobic ions (A^- and a countercation), there is a potential range in which the ITIES behaves like an ideally polarized electrode and the injected charge is only used to charge the interface (Figure 3).[18] Outside of this potential window, these hydrophilic/hydrophobic ions will be transferred across the interface into their nonideal phases. When semihydrophobic ions (I^+) are present in the system, the charge introduced can cause their transfer across the ITIES within the potential range controlled by J^+, A^-, and their counterions (Figure 3), giving an effect analogous to those shown by redox-active species.[18]

Direct IT at the ITIES has enabled the qualitative and quantitative detection of many chemicals, such as acetylcholine,[9,52,53] various metal ions,[6,35,138] and biological macromolecules.[69,89] A related field making use of ion transfer principles is another type of ion-selective electrodes, i.e., membrane electrodes where ion transfer occurs between solid membranes and solutions. Considering the scope/focus of this feature article on ion transfer between two immiscible solutions, we are not able to provide an in-depth discussion on such electrodes. Instead, we refer readers to reviews in this field with a few examples cited here.[139−142] For the analytes whose detection is not feasible via direct IT, assisted ion transfer offers an alternative option and is explained below.

Assisted Ion Transfer. In 1979, Koryta introduced assisted ion transfer (AIT) to propose a solution to address the challenge in detecting certain chemicals whose IT occurs beyond the potential window.[16] He proposed using ionophores, molecules which can complex with ions and reduce the Gibbs energy of their transfer between phases. For instance, the Gibbs energy of transfer of hydrophilic metal ions such as Na^+, K^+, Li^+, Rb^+, Cs^+, Mg^{2+}, Cd^{2+}, and Cu^{2+} from *w* to *o* is reduced by the presence of an ionophore such as dibenzo-18-crown-6 (DB18C6) in *o*.[7,17,40,67,126,143−145] These crown ether molecules have the ability to chelate the ions at the interface and facilitate their detection. This type of AIT is classified as transfer by interfacial complexation (TIC). Apart from TIC, there are other mechanisms of AIT, including transfer by interfacial dissociation (TID),[126,146] transfer followed by organic phase complexation (TOC),[16,146] and aqueous complexation followed by transfer (ACT).[146,147] Different mechanisms of AIT are described in detail in previous literature.[2,146]

To demonstrate the favorable shift in transfer potential that ionophores induce, we can look at Figure 4, which shows overlapping cyclic voltammograms for an ITIES system where researchers attempted to transfer Cd^{2+} from *w* to *o* with and without an ionophore present.[148] Figure 4 shows that, without the ionophore, Cd^{2+} transfer did not occur in the potential window (dotted line). Once the ionophore was added to the organic phase, Cd^{2+} transfer fell within the potential window and a current increase was observed, corresponding to Cd^{2+} detection (solid line). Further discussion of AIT applications and the theory associated with them can be found in other literature.[16,17,19,20,40,126,143,146,149−151]

One example of a natural ionophore used in AIT is valinomycin. Valinomycin is a naturally occurring antibiotic

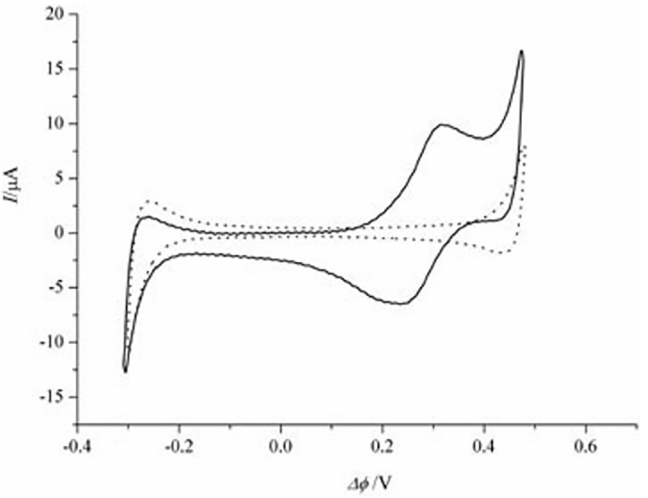

Figure 4. Cyclic voltammograms of the assisted ion transfer of 150 μM Cd^{2+} across the water/1,2-dichloroethane interface, with (solid line) and without (dashed line) 10 mM of the ionophore 4′-morpholinoacetophenone-4-phenyl-3-thiosemicarbazone (MAPPT).[148] Further information about the system is in the original publication. Reproduced with permission from ref 148. Bingol, H.; Atalay, T. *Open Chem.* **2010**, *8*, 1134−1139. Copyright 2010 De Gruyter Open Access.

that transports potassium ions across a cell membrane via complexation. Because of its interior with an environment similar to the hydration shell of an ion in aqueous solution and its strongly hydrophobic exterior, valinomycin at an ITIES can abstract a hydrophilic ion from a hydrophilic environment to a hydrophobic one because of its "hydrophilic" interior and hydrophobic exterior.[152] This is another example in which an ionophore can assist in moving the charge between phases. Beyond valinomycin and DB18C6, other ionophores have been used to aid ion transfer across the ITIES to ensure detection of ions of interest within diverse potential windows.[2,17,40,126,143] These specialized ionophores include cyclic thioethers,[149] ionophores containing thiourea groups,[150] and crown ethers such as diazadibenzo crown ethers[151] and trimeric macrocycle with tris(crown ether) (TriBCE).[143]

Heterogeneous Electron Transfer. While the ion transfer capability distinguishes the ITIES from a solid conductor−solution interface electrode, the ITIES is also able to carry out ET processes. ET processes at the ITIES have gained significant interest due to their fundamental importance and novel applications, like artificial photosynthesis,[153] catalysis,[41−43] nanoparticle synthesis,[97−101] and liquid redox extraction.[4,154] ET kinetics of both charged and uncharged species at the ITIES have been probed using scanning electrochemical microscopy (SECM).[50,51,154] Here, we will not go into depth about ET at the ITIES. Instead, we refer readers to the following articles and the references above.[12,14,50,51,155]

THERMODYNAMICS

The thermodynamics of IT across an ITIES is presented here.[2,47,146,156,157] Consider that an ion, I^z, is in equilibrium between aqueous (*w*) and organic (*o*) phases of an ITIES, where *z* is the charge of the ion, as in eq 1.

$$I^z(w) \rightleftharpoons I^z(o) \quad (1)$$

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Because the system is at equilibrium, the electrochemical potentials ($\bar{\mu}$) of the ion in w and o are equal, as shown in eq 2.[47]

$$\bar{\mu}_{I^z}^{w} = \bar{\mu}_{I^z}^{o} \tag{2}$$

The electrochemical potentials of I^z in w and o can be expressed as in eqs 3 (w) and 4 (o):[2,156]

$$\bar{\mu}_{I^z}^{w} = \mu_{I^z}^{0,w} + RT\ln(A_{I^z}^{w}) + zF\phi^{w} \tag{3}$$

$$\bar{\mu}_{I^z}^{o} = \mu_{I^z}^{0,o} + RT\ln(A_{I^z}^{o}) + zF\phi^{o} \tag{4}$$

In eqs 3 and 4, the variables are the standard chemical potential of species I^z in phase $i(\mu_{I^z}^{0,i})$, the activity of the standard chemical potential of species I^z in phase $i(A_{I^z}^{i})$, inner potential or Galvani potential of phase i (ϕ^i), the universal gas constant (R), temperature (T), and Faraday's constant (F). The Galvani potential difference between w and o ($\Delta_w^o\phi$) can be expressed as

$$\Delta_w^o\phi = \phi^o - \phi^w \tag{5}$$

By rearranging eqs 3 and 4 to describe ϕ^w and ϕ^o, respectively, in terms of I^z and solving we have eq 6:

$$\Delta_w^o\phi = (\mu_{I^z}^{0,w} - \mu_{I^z}^{0,o})/zF + (RT/zF)\ln(A_{I^z}^{w}/A_{I^z}^{o})$$

$$\Delta_w^o\phi = \Delta_w^o\phi_{I^z}^{0} + (RT/zF)\ln(A_{I^z}^{w}/A_{I^z}^{o}) \tag{6}$$

The standard Galvanic potential difference of transfer of I^z from w to $o(\Delta_w^o\phi_{I^z}^{0})$ is defined in eq 7 as[47,146]

$$\Delta_w^o\phi_{I^z}^{0} = (\mu_{I^z}^{0,w} - \mu_{I^z}^{0,o})/zF = -\Delta G_{tr}^{0,w\to o}/zF \tag{7}$$

where $\Delta G_{tr}^{0,w\to o}$ is the standard Gibbs free energy required to transfer I^z from w to o. $\Delta_o^w\phi_{I^z}^{0}$ is specific to the ionic analyte and phases, allowing for qualitative detection of the analyte at ITIES electrodes.[148]

The potential-specific detection of different electroactive species at the ITIES has led to various applications of ITIES electrodes, allowing qualitative identification and quantitative analysis of species in complicated solutions.[2,3,9,52,124,125] One such application lies in neurochemistry and is described by Figure 5. Figure 5 presents amperomograms collected following direct exposure of a nano-ITIES to 2 mM solutions of acetylcholine, gamma-amino butyric acid, glutamate, dopamine, serotonin, K^+, and H^+. Because current spikes are observed only after the introduction of acetylcholine, the detection at a nanoITIES is specific to acetylcholine at the applied potential. Other studies have been carried out to determine transfer potentials for various other species to demonstrate their specific detection in various ITIES systems.[138,158−160]

KINETICS

The determination of the kinetics of charge transfer at an ITIES has been reported.[1,13,40,132,161,162] A recent review article by Amemiya and colleagues presents a very nice discussion regarding kinetics at the ITIES.[163] Given the space limitations, we will not discuss kinetics in detail; instead, to refer readers to these references.

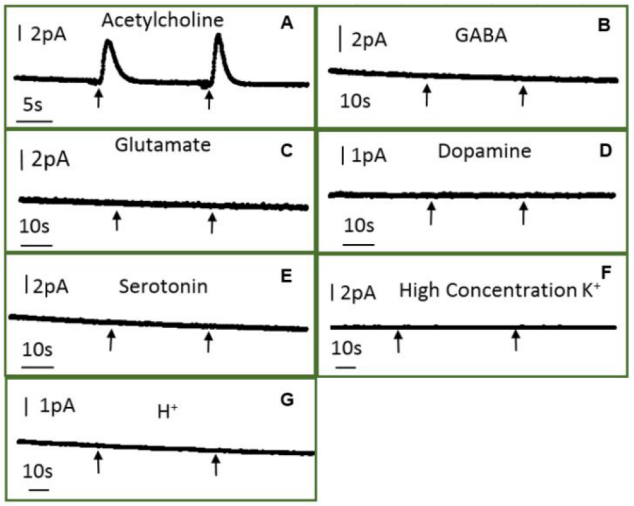

Figure 5. Amperomograms measured at −0.48 V vs the half wave transfer potential of the tetrabutylammonium ion. Amperomograms are measured following the local injection of solutions of 2 mM (A) acetylcholine (noticeable current spikes indicate detection), (B) gamma-amino butyric acid, (C) glutamate, (D) dopamine, (E) serotonin, (F) K^+, and (G) H^+. A lack of any spike in current from the local introduction of the ions shown in B-G indicate a lack of their detection.[9] Reproduced with permission from ref 9. Shen, M.; et al. *J. Am. Chem. Soc.***2018**, *140*, 7764−7768. Copyright 2018 American Chemical Society.

ELECTRODE−SOLUTION INTERFACIAL STRUCTURE

There are two kinds of electrode−solution interfaces: the solid conductor−solution interface and the ITIES. The distributions of ions at these interfaces are shown in Figure 6, with specific schematics for the solid conductor−solution interface (Figure 6A) and the ITIES (Figure 6B).

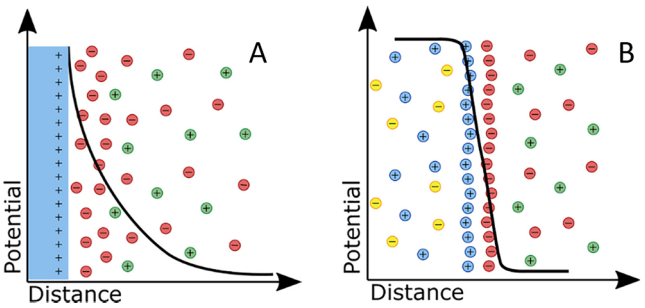

Figure 6. Schematic representation of the distribution(s) of ions at a (A) conductor−electrolyte interface where potential drops across the concentration dependent diffuse layer. Screening is potential dependent as the concentration in the diffuse layer is potential dependent. (B) polarized ITIES where potential drops across a concentration-independent layer. There is no diffuse layer. The bulk charges screen the potential, causing potential independent screening.[169] Modified with permission from ref 169. Gschwend, G. C.; Girault, H. H. *J. Electroanal. Chem.***2020**, *872*, 114240. Copyright 2020 Elsevier.

For the solid conductor−electrolyte interface, the formation of the electrical double layer has been described previously.[47,164−168] In Figure 6A, ions with charges opposite of the conductor's will closely approach the interface, with ionic concentration decreasing with increased distance.[47,169] Because of the distance-dependent ionic concentration, potential also

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decreases with distance.[169] This potential drop is due to charge screening by ions closer to the interface.[169]

At the ITIES it had been thought that a double layer with a diffuse layer falling into each of the two solution phases existed.[165,166] The ITIES has since been further studied and found to be distinct from that of a solid conductor−electrolyte interface and is not considered to have a *true* double-layer structure.[170] The arrangement of ions at the ITIES cannot be considered a double layer due to its lack of distinct Helmholtz and diffuse layers.[2,169] Instead, at the interface of a polarized ITIES there are monolayers of ions constrained in close proximity to the interface.[169] Recently, Girault and colleagues used both a simulation approach and experimental measurements including surface second harmonic generation, surface tension measurements, and high-frequency capacitance measurements to propose that the potential distribution at liquid−liquid interfaces could be visualized by a "discrete Helmholtz" model as in Figure 6B,[169−171] rather than by the Stern−Guoy−Chapman model presented in Figure 6A.[47,164−168] Figure 6B highlights that, at the ITIES, two correlated monolayers of ions are arranged at the ITIES. This ion distribution at the interface leads to a potential drop confined to a thin region near the ITIES from the lack of potential-dependent screening.[169]

APPLICATIONS OF THE ITIES

The unique electrochemical sensing mechanism of ITIES enables tackling challenges in various fields. These include studying the secretion of cholinergic transmitters, cellular toxicity, catalysis, separation, nanostructure synthesis, environmental application, etc. Due to space limitations, only a few examples are highlighted here, and we apologize for not being able to elaborate in detail other application examples.

The ITIES has been applied to environmental purposes such as water quality testing. Recent research has shown that it is possible to detect herbicides in water, potentially leading water quality testing in a new direction.[95,96]

ITIES electrodes have been coupled with scanning electrochemical microscopy (SECM) where SECM is used to position ITIES electrodes at a close distance (down to nanometers) from the secretion sites of biomolecules. In 1995, Bard and co-workers coupled a micro-ITIES electrode with SECM.[15] Since then, several groups used both micro- and nano-ITIES electrodes in conjunction with SECM for various applications.[9,11,15,41,42,45−51] A nano-ITIES electrode is able to perform experiments with nanometer spatial resolution and high temporal resolution down to milliseconds, which enable the study of different dynamic biological processes like chemical transmission.[9,46] Apart from the high spatial and temporal resolution, these electrodes can collect data with a high signal-to-noise ratio since they can be positioned much closer to the substrate compared to a micro/macro electrode.

Another powerful application of ITIES is the detection and quantification of neurotransmitters. Electrochemistry has played a vital role in measuring brain chemicals, revolutionizing our view of brain function and diseases. The conventional electrodes are carbon fiber microelectrode for the detection of redox-active transmitters. Due to space limitations, we will not discuss in detail redox-active neurotransmitter detection. Readers can consult these review articles and book chapters in this area.[172−180] For studying the secretion of nonredox-active neurotransmitters from living neurons, the Shen group has used nano-ITIES electrodes coupled with SECM to measure the concentration and release dynamics of cholinergic neurotransmitters, which are redox-inactive but electroactive, from *Aplysia californica* neurons.[9,46] Using SECM, they were able to position the electrodes as close as ∼140 nm vertically from the release sites on the soma (Figure 7A), where

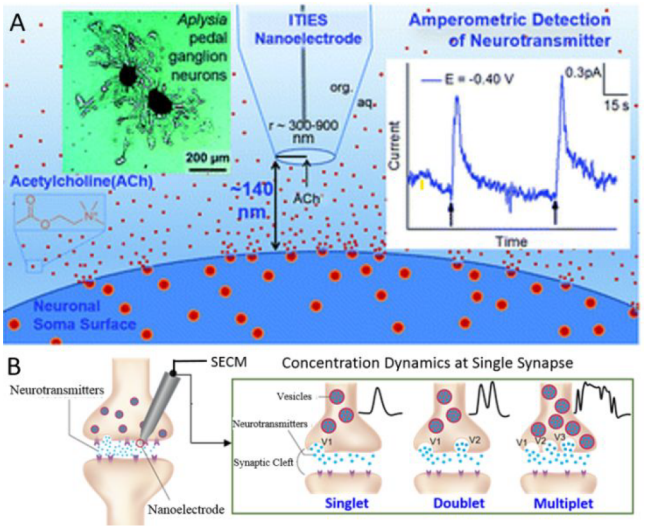

Figure 7. High signal-to-noise ratio study of cholinergic neurotransmitter release dynamics was achieved with nano-ITIES-scanning electrochemical microscope (SECM) platform. (A) Schematic of real-time release dynamics measurement of cholinergic transmitters from *Aplysia californica* soma. Inset: the amperometric trace shows well-defined current increase upon chemical stimulation. Application of chemical stimulation is represented by arrows.[46] Reproduced with permission from ref 46. Welle, T. M.; et al. *Chem. Sci.***2018**, *9*, 4937−4941. Copyright 2018 Royal Society of Chemistry. (B) New exocytosis mechanism, i.e., multiple-vesicular-exocytosis, was unveiled by single synaptic cholinergic chemical transmission study that was achieved with nanoITIES and SECM.[9] Reproduced with permission from ref 9. Shen, M.; et al. *J. Am. Chem. Soc.***2018**, *140*, 7764−7768. Copyright 2018 American Chemical Society.

transmitter release dynamics were studied with millisecond temporal resolution. The amperometric trace (Figure 7A inset) represents the extrasynaptic transmitter concentration and release dynamics simultaneously. A significant response was detected in response to high-concentration potassium stimulation of the neuron. The technique also enabled collection of additional information such as the permeability of the neuronal soma. Besides extrasynaptic transmission, the cholinergic neurotransmitter release dynamics at the synapse between two neurons was studied using a nanoITIES electrode with a radius of ∼15 nm (Figure 7B) by the same group.[9] Authors also proposed a multiple-vesicular-exocytosis mechanism based on the results from the synaptic measurements.

Other examples of biosensing include using a micropipette-supported ITIES tip to detect Ag^+ and study its effects on fibroblast cells. To probe the toxicity of Ag^+ with fibroblast cells, Zhan et al. used a micro-ITIES electrode containing a commercial calixarene-based Ag^+ ionophore, which was positioned near the cell surface using SECM as shown in Figure 8.[49] The Ag^+ ionophore enabled the detection of Ag^+, which allowed researchers to monitor the cells' interactions with Ag^+ via its extracellular concentration. These cellular studies are two simple examples of how the ITIES has facilitated the elucidation of complex biological processes down to the cellular level.

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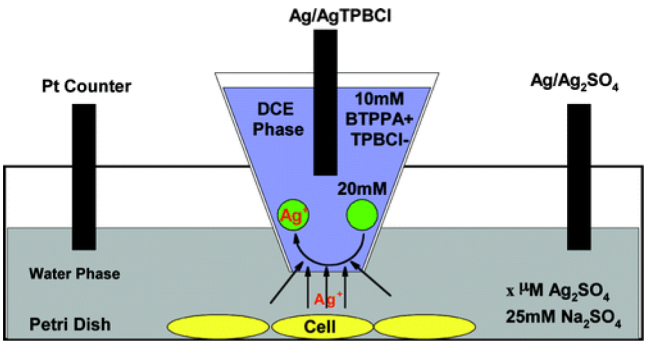

Figure 8. Schematic diagram of SECM for the in situ measurement of the local Ag^+ concentration in the vicinity of fibroblast cells by using the micropipet-supported water/DCE interface as a tip. Aqueous phase: 20 μM Ag_2SO_4 + 20 mM Na_2SO_4. DCE phase: 20 mM silver ionophore +10 mM BTPPATPBCl.[49] Reproduced with permission from ref 49. Zhan D.; et al. *Anal. Chem.***2007**, *79*, 5525−5231. Copyright 2007 American Chemical Society.

Researchers have also used electrochemical measurements at ITIES to elucidate the mechanisms of different biocatalysts. For example, Huang et al. studied the oxygen reduction reaction (ORR) using an ITIES electrode filled with Fe^{III} meso-tetra-(4-*N*-methyl-pyridyl) porphyrin to carry out a catalyzed oxygen reduction reaction at the interface.[181] Through this experiment, the group was able to determine that the reaction mechanism is likely to function via a heterogeneous proton-coupled oxygen reduction route. They suggested that the catalyzed ORR at the water−DCE interface is more likely to proceed via a phase transfer catalysis mechanism by using a nano-ITIES array supported by a silica nanochannel membrane.

Another unique application of ITIES systems is separation. For example, ITIES have been used for the extraction of metals from spent nuclear waste. The Ding group proposed using an ITIES system for the extraction of metal from spent nuclear fuel (the used fuel from a nuclear reactor which still contains radioactive materials) allowing for repurposing of some parts of the spent fuel.[182] For demonstration, they used AIT at the ionic liquid/water interface to extract potassium ions from the water phase. The authors used tetraoctylphosphonium tetrakis-(pentafluorophenyl)borate as the ionic liquid since it exists as an organic ionic plastic crystal which is stable at high temperatures.[182]

Besides biosensing, catalysis, separation, and environmental monitoring, the ITIES has been demonstrated to be a powerful platform for nanostructure synthesis.[97−101] In these studies, precursors (reactants) are added to the two separate phases, aqueous and organic. Electron transfer occurs at the ITIES leading to the formation of particles directly at the ITIES. One example is the study from the Shao group, where Pt, Ag, or Au nanoparticles were synthesized at an ITIES supported by a nanopipette to produce ultramicroelectrodes.[97] The reaction was the electron transfer reaction between chloroplatinic acid, silver nitrate, or $HAuCl_4$ in the aqueous phase inside the nanopipette and decamethylferrocene in the organic phase to synthesize Pt, Ag, or Au nanoelectrodes, respectively.[97] Synthesis at ITIES has great potential for future applications in making nanoelectrodes and studying reaction mechanisms.

CONCLUSIONS AND FUTURE DIRECTIONS

The ITIES has expanded electrochemistry to encompass both redox-active and redox-inactive analytes. While ITIES electrochemistry has a long history of several decades, it remains an evolving field, with the system becoming better understood with each passing year and with more applications being explored. The ease with which ITIES electrodes can be fabricated down to the nanoscale and their capability to monitor a wide range of reactions/analytes make them an excellent tool for the probing of small delicate systems, achieving nanometer spatial resolution. The versatility of ITIES applications includes biosensing, catalytic study, synthesis, separation, mechanistic study, etc. We envision new and exciting applications in the ITIES field in the future.

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Notes

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Mei Shen is an Assistant Professor of Chemistry at the University of Illinois at Urbana−Champaign (UIUC). Dr. Shen is also a faculty member of the Neuroscience Program, the Cancer Center at Illinois, the Center for Biophysics and Quantitative Biology, and the Beckman Institute for Advanced Science and Technology with an affiliation at the Department of Bioengineering at UIUC. Dr. Shen received her Ph.D. from The University of Texas at Austin under the direction of

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Prof. Allen J. Bard and did her postdoctoral work with Prof. Shigeru Amemiya at the University of Pittsburgh. Her research aims to push the limits of electroanalytical chemistry in bioanalysis, especially for the real-time interrogation of multiple groups of chemical transmitters with nanometer spatial resolution. Current research interests in the Shen group interface between nanoscience, electrochemistry, microbiology, toxicology, and neuroscience to tackle pressing societal challenges and to measure fast chemical transmitter release dynamics especially at nanobiological structures, such as the single synaptic cleft, and in vivo. Dr. Shen is committed to creating a diverse and inclusive environment in both classroom teaching and research.

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■ REFERENCES

(1) Samec, Z. *Electrochim. Acta* **2012**, *84*, 21−28.
(2) Girault, H. H.Electrochemistry at Liquid/Liquid Interfaces. In *Electroanalytical Chemistry: A Series of Advances*; Bard, A. J., Zoski, C. G., Eds.; CRC Press, Taylor & Francis Group: Boca Raton, FL, 2010; Vol. *23*.
(3) Suárez-Herrera, M. F.; Scanlon, M. D. *Anal. Chem.* **2020**, *92* (15), 10521−10530.
(4) Velázquez-Manzanares, M. *Procedia Chemistry* **2014**, *12*, 100−107.
(5) Mirkin, M. V.; Tsionsky, M.Charge Transfer Processes at the Liquid-Liquid Interface. In *Scanning Electrochemical Microscopy*, 2nd ed.; Bard, A. J., Mirkin, M. V., Eds.; CRC Press, Taylor & Francis Group: Boca Raton, FL, 2013.
(6) Vanýsek, P.; Ramírez, L.Interface between two immiscible liquid electrolytes: A review. *Journal of the Chilean Chemical Society* **2008**, *53*. DOI: 10.4067/S0717-97072008000200002
(7) Shao, Y.; Mirkin, M. V. *Anal. Chem.* **1998**, *70* (15), 3155−3161.
(8) Shen, M.; Colombo, M. L. *Analytical Methods* **2015**, *7* (17), 7095−7105.
(9) Shen, M.; Qu, Z.; DesLaurier, J.; Welle, T. M.; Sweedler, J. V.; Chen, R. *J. Am. Chem. Soc.* **2018**, *140* (25), 7764−7768.
(10) Chen, R.; Alanis, K.; Welle, T. M.; Shen, M. *Anal. Bioanal. Chem.* **2020**, *412* (24), 6121−6132.
(11) Shen, M.; Ishimatsu, R.; Kim, J.; Amemiya, S. *J. Am. Chem. Soc.* **2012**, *134* (24), 9856−9859.
(12) Cai, C.; Mirkin, M. V. *J. Am. Chem. Soc.* **2006**, *128* (1), 171−179.
(13) Ding, Z.; Quinn, B. M.; Bard, A. J. *J. Phys. Chem. B* **2001**, *105* (27), 6367−6374.
(14) Reymond, F.; Fermín, D.; Lee, H. J.; Girault, H. H. *Electrochim. Acta* **2000**, *45* (15), 2647−2662.
(15) Solomon, T.; Bard, A. J. *Anal. Chem.* **1995**, *67* (17), 2787−2790.
(16) Koryta, J. *Electrochim. Acta* **1979**, *24* (3), 293−300.
(17) Beattie, P. D.; Wellington, R. G.; Girault, H. H. *J. Electroanal. Chem.* **1995**, *396* (1), 317−323.
(18) Homolka, D.; Hung, L. Q.; Hofmanova, A.; Khalil, M. W.; Koryta, J.; Marecek, V.; Samec, Z.; Sen, S. K.; Vanysek, P.; et al. *Anal. Chem.* **1980**, *52* (11), 1606−1610.
(19) Reymond, F.; Carrupt, P.-A.; Girault, H. H. *J. Electroanal. Chem.* **1998**, *449* (1), 49−65.
(20) Reymond, F.; Lagger, G.; Carrupt, P.-A.; Girault, H. H. *J. Electroanal. Chem.* **1998**, *451* (1), 59−76.
(21) Samec, Z.; Mareček, V.; Koryta, J.; Khalil, M. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **1977**, *83* (2), 393−397.
(22) Fang, Y.; Deng, H.; Huang, X.; Wang, L. *Anal. Chem.* **2021**, *93* (7), 3353−3361.
(23) Li, M.; He, P.; Yu, Z.; Zhang, S.; Gu, C.; Nie, X.; Gu, Y.; Zhang, X.; Zhu, Z.; Shao, Y. *Anal. Chem.* **2021**, *93* (3), 1515−1522.
(24) Chen, R.; Xu, K.; Shen, M. *Electrochim. Acta* **2020**, *357*, 136788.
(25) Chen, R.; McAllister, A. B.; Shen, M. *J. Electroanal. Chem.* **2020**, *873*, 114303.
(26) Suárez-Herrera, M. F.; Gamero-Quijano, A.; Scanlon, M. D. *Electrochim. Acta* **2022**, *424*, 140677.
(27) Nieminen, E.; Kazimova, N.; Murtomäki, L. *Electroanalysis* **2020**, *32* (5), 949−957.
(28) Suárez-Herrera, M. F.; Cazade, P.-A.; Thompson, D.; Scanlon, M. D. *Electrochem. Commun.* **2019**, *109*, 106564.
(29) Arooj, M.; Arrigan, D. W. M.; Mancera, R. L. *J. Phys. Chem. B* **2019**, *123* (34), 7436−7444.
(30) Ashida, M.; Hinoue, T. *Anal. Sci.* **2018**, *34* (8), 939−945.
(31) Mareček, V.; Samec, Z. *A mini review. Current Opinion in Electrochemistry* **2017**, *1* (1), 133−139.
(32) Silver, B. R.; Holub, K.; Mareček, V. *J. Electroanal. Chem.* **2017**, *784*, 1−5.
(33) Kummer, S.; Klembt, S.; Ruth, W.; Kragl, U. *J. Mol. Liq.* **2017**, *226*, 85−89.
(34) Duong, Q.; Tan, Y.; Corey, J.; Anz, S.; Sun, P. *J. Phys. Chem. C* **2015**, *119* (19), 10365−10369.
(35) Stockmann, T. J.; Montgomery, A.-M.; Ding, Z. *J. Electroanal. Chem.* **2012**, *684*, 6−12.
(36) Benvidi, A.; Lanjwani, S. N.; Ding, Z. *J. Electroanal. Chem.* **2010**, *641* (1), 99−103.
(37) Rodgers, P. J.; Amemiya, S.; Wang, Y.; Mirkin, M. V. *Anal. Chem.* **2010**, *82* (1), 84−90.
(38) Sisk, G. D.; Herzog, G.; Glennon, J. D.; Arrigan, D. W. M. *ELECTROPHORESIS* **2009**, *30* (19), 3366−3371.
(39) Guo, S.-X.; Unwin, P. R.; Whitworth, A. L.; Zhang, J. *Progress in Reaction Kinetics and Mechanism* **2004**, *29* (2), 43−166.
(40) Beattie, P. D.; Delay, A.; Girault, H. H. *J. Electroanal. Chem.* **1995**, *380* (1), 167−175.
(41) Shao, Y.; Mirkin, M. V.; Rusling, J. F. *J. Phys. Chem. B* **1997**, *101* (16), 3202−3208.
(42) Lin, C.-L.; Rodríguez-López, J.; Bard, A. J. *Anal. Chem.* **2009**, *81* (21), 8868−8877.
(43) Huang, X.; Xuan, Y.; Xie, L.; Su, B. *ChemElectroChem.* **2016**, *3* (11), 1781−1786.
(44) Rodgers, A. N. J.; Booth, S. G.; Dryfe, R. A. W. *Electrochem. Commun.* **2014**, *47*, 17−20.
(45) Taylor, G.; Girault, H. *Journal of electroanalytical chemistry and interfacial electrochemistry* **1986**, *208* (1), 179−183.
(46) Welle, T. M.; Alanis, K.; Colombo, M. L.; Sweedler, J. V.; Shen, M. *Chemical Science* **2018**, *9* (22), 4937−4941.
(47) Bard, A. J.; Faulkner, L. R.*Electrochemical Methods: Fundamentals and Applications*, 2nd ed.; Wiley, 2001.
(48) Shao, Y.; Mirkin, M. V. *J. Phys. Chem. B* **1998**, *102* (49), 9915−9921.
(49) Zhan, D.; Li, X.; Zhan, W.; Fan, F.-R. F.; Bard, A. J. *Anal. Chem.* **2007**, *79* (14), 5225−5231.
(50) Wei, C.; Bard, A. J.; Mirkin, M. V. *J. Phys. Chem.* **1995**, *99* (43), 16033−16042.
(51) Barker, A. L.; Unwin, P. R.; Zhang, J. *Electrochem. Commun.* **2001**, *3* (7), 372−378.
(52) Colombo, M. L.; Sweedler, J. V.; Shen, M. *Anal. Chem.* **2015**, *87* (10), 5095−5100.
(53) Jetmore, H. D.; Milton, C. B.; Anupriya, E. S.; Chen, R.; Xu, K.; Shen, M. *Anal. Chem.* **2021**, *93* (49), 16535−16542.
(54) Rudnicki, K.; Sobczak, K.; Kaliszczak, M.; Sipa, K.; Powałka, E.; Skrzypek, S.; Poltorak, L.; Herzog, G. *Microchimica Acta* **2021**, *188* (12), 413.
(55) Arrigan, D. W. M.; Hackett, M. J.; Mancera, R. L. *Current Opinion in Electrochemistry* **2018**, *12*, 27−32.

https://doi.org/10.1021/acs.analchem.2c01416
Anal. Chem. XXXX, XXX, XXX−XXX

(56) Felisilda, B. M. B.; Arrigan, D. W. M. *Anal. Chem.* **2018**, *90* (14), 8470−8477.
(57) Ribeiro, J. A.; Benfeito, S.; Cagide, F.; Teixeira, J.; Oliveira, P. J.; Borges, F.; Silva, A. F.; Pereira, C. M. *Anal. Chem.* **2018**, *90* (13), 7989−7996.
(58) Iwai, N. T.; Kramaric, M.; Crabbe, D.; Wei, Y.; Chen, R.; Shen, M. *Anal. Chem.* **2018**, *90* (5), 3067−3072.
(59) Arrigan, D. W. M. *Annual Reports Section C (Physical Chemistry)* **2013**, *109* (0), 167−188.
(60) Alvarez de Eulate, E.; Serls, L.; Arrigan, D. W. M. *Anal. Bioanal. Chem.* **2013**, *405* (11), 3801−3806.
(61) Kivlehan, F.; Lefoix, M.; Moynihan, H. A.; Thompson, D.; Ogurtsov, V. I.; Herzog, G.; Arrigan, D. W. M. *Electrochim. Acta* **2010**, *55* (9), 3348−3354.
(62) Collins, C. J.; Lyons, C.; Strutwolf, J.; Arrigan, D. W. M. *Talanta* **2010**, *80* (5), 1993−1998.
(63) Santos, H. A.; García-Morales, V.; Pereira, C. M. *ChemPhysChem* **2010**, *11* (1), 28−41.
(64) Herzog, G.; Roger, A.; Sheehan, D.; Arrigan, D. W. M. *Anal. Chem.* **2010**, *82* (1), 258−264.
(65) Berduque, A.; Zazpe, R.; Arrigan, D. W. M. *Anal. Chim. Acta* **2008**, *611* (2), 156−162.
(66) Berduque, A.; Scanlon, M. D.; Collins, C. J.; Arrigan, D. W. M. *Langmuir* **2007**, *23* (13), 7356−7364.
(67) Beni, V.; Ghita, M.; Arrigan, D. W. M. *Biosens. Bioelectron.* **2005**, *20* (10), 2097−2103.
(68) Arrigan, D. W. M.; Ghita, M.; Beni, V. *Chem. Commun.* **2004**, *6*, 732−733.
(69) Amemiya, S.; Yang, X.; Wazenegger, T. L. *J. Am. Chem. Soc.* **2003**, *125* (39), 11832−11833.
(70) Ahmed, M. M. N.; Bodowara, F. S.; Zhou, W.; Penteado, J. F.; Smeltz, J. L.; Pathirathna, P. *RSC Adv.* **2021**, *12* (2), 1077−1083.
(71) O'Sullivan, S.; Alvarez de Eulate, E.; Yuen, Y. H.; Helmerhorst, E.; Arrigan, D. W. M. *Analyst* **2013**, *138* (20), 6192−6196.
(72) Yuan, Y.; Shao, Y. *J. Phys. Chem. B* **2002**, *106* (32), 7809−7814.
(73) Kitatsuji, Y.; Yoshida, Z.; Kudo, H.; Kihara, S. *J. Electroanal. Chem.* **2002**, *520* (1), 133−144.
(74) Chesniuk, S. G.; Dassie, S. A.; Yudi, L. M.; Baruzzi, A. M. *Electrochim. Acta* **1998**, *43* (14), 2175−2181.
(75) Salman, M.; Lee, S. H.; Jeshycka, S.; Lee, J. S.; Lee, H. W.; Lee, H. J. *ChemElectroChem.* **2022**, *9*, e202200614.
(76) You, Y.; Bai, S.; Ma, Y.; Liu, C.; Wang, L. *Electrochim. Acta* **2022**, *423*, 140568.
(77) Rudnicki, K.; Sobczak, K.; Borgul, P.; Skrzypek, S.; Poltorak, L. *Food Chem.* **2021**, *364*, 130417.
(78) Lamichhane, H. B.; Henares, T. G.; Hackett, M. J.; Arrigan, D. W. M. *Anal. Chem.* **2021**, *93* (26), 9094−9102.
(79) Burgoyne, E. D.; Stockmann, T. J.; Molina-Osorio, A. F.; Shanahan, R.; McGlacken, G. P.; Scanlon, M. D. *J. Phys. Chem. C* **2019**, *123* (40), 24643−24650.
(80) Rudnicki, K.; Poltorak, L.; Skrzypek, S.; Sudhölter, E. J. R. *Anal. Chim. Acta* **2019**, *1085*, 75−84.
(81) Puri, S. R.; Kim, J. *Anal. Chem.* **2019**, *91* (3), 1873−1879.
(82) Jeshycka, S.; Kim, E. M.; Lee, H. J. *Electrochim. Acta* **2018**, *282*, 964−972.
(83) Jeshycka, S.; Han, H. Y.; Lee, H. J. *Electrochim. Acta* **2017**, *245*, 211−218.
(84) Huang, X.; Xie, L.; Lin, X.; Su, B. *Anal. Chem.* **2017**, *89* (1), 945−951.
(85) Vladimirova, E. V.; Dunaeva, A. A.; Petrukhin, O. M.; Shipulo, E. V. *J. Anal. Chem.* **2013**, *68* (3), 253−260.
(86) Petrukhin, O. M.; Kostitsyna, M. V.; Dzherayan, T. G.; Shipulo, E. V.; Vladimirova, E. V.; Dunaeva, A. A. *J. Anal. Chem.* **2009**, *64* (9), 951−957.
(87) Deryabina, M. A.; Hansen, S. H.; Østergaard, J.; Jensen, H. *J. Phys. Chem. B* **2009**, *113* (20), 7263−7269.
(88) Collins, C. J.; Berduque, A.; Arrigan, D. W. M. *Anal. Chem.* **2008**, *80* (21), 8102−8108.
(89) Kivlehan, F.; Lanyon, Y. H.; Arrigan, D. W. M. *Langmuir* **2008**, *24* (17), 9876−9882.
(90) Monzón, L. M. A.; Yudi, L. M. *Electrochim. Acta* **2008**, *53* (5), 2217−2225.
(91) Gulaboski, R.; Cordeiro, M. N. D. S.; Milhazes, N.; Garrido, J.; Borges, F.; Jorge, M.; Pereira, C. M.; Bogeski, I.; Morales, A. H.; Naumoski, B.; Silva, A. F. *Anal. Biochem.* **2007**, *361* (2), 236−243.
(92) Lu, X.; Hu, L.; Wang, X. *Electroanalysis* **2005**, *17* (11), 953−958.
(93) Alemu, H. *Pure Appl. Chem.* **2004**, *76* (4), 697−705.
(94) Laborda, E.; Molina, A. *Current Opinion in Electrochemistry* **2021**, *26*, 100664.
(95) Lu, G.; Despas, C.; Liu, L.; Herzog, G. *J. Electroanal. Chem.* **2020**, *877*, 114745.
(96) García Martínez, H.; de la Garza Rodríguez, I. M.; Colunga Urbina, E.; Amador-Hernández, J.; Velazquez-Manzanares, M. *ECS Trans.* **2018**, *84* (1), 49−55.
(97) Zhu, X.; Qiao, Y.; Zhang, X.; Zhang, S.; Yin, X.; Gu, J.; Chen, Y.; Zhu, Z.; Li, M.; Shao, Y. *Anal. Chem.* **2014**, *86* (14), 7001−7008.
(98) Smirnov, E.; Peljo, P.; Scanlon, M. D.; Girault, H. H. *ACS Nano* **2015**, *9* (6), 6565−6575.
(99) Dryfe, R. A. W. *Phys. Chem. Chem. Phys.* **2006**, *8* (16), 1869−1883.
(100) Binder, W. H. *Angew. Chem., Int. Ed.* **2005**, *44* (33), 5172−5175.
(101) Rao, C. N. R.; Kalyanikutty, K. P. *Acc. Chem. Res.* **2008**, *41* (4), 489−499.
(102) Moya Betancourt, S. N.; Cámara, C. I.; Juarez, A. V.; Pozo López, G.; Riva, J. S. *J. Electroanal. Chem.* **2022**, *911*, 116253.
(103) Al Nasser, H. A.; Bissett, M. A.; Dryfe, R. A. W. *ChemElectroChem.* **2021**, *8* (23), 4445−4455.
(104) Tummino, A.; Scoppola, E.; Fragneto, G.; Gutfreund, P.; Maestro, A.; Dryfe, R. A. W. *Electrochim. Acta* **2021**, *384*, 138336.
(105) Kamyabi, M. A.; Amirkhani, F.; Bikas, R.; Soleymani-Bonoti, F. *J. Mol. Struct.* **2021**, *1228*, 129693.
(106) Moshrefi, R.; Suryawanshi, A.; Stockmann, T. J. *Electrochem. Commun.* **2021**, *122*, 106894.
(107) Zhao, J.; Jiang, C.; Liu, Y. *Aust. J. Chem.* **2020**, *73* (10), 861−867.
(108) Lin, Z.; Liu, C.; Ma, Y.; Wang, L. *J. Electroanal. Chem.* **2020**, *877*, 114520.
(109) Collins, M. C.; Hébrant, M.; Herzog, G. *Electrochim. Acta* **2018**, *282*, 155−162.
(110) Scanlon, M. D.; Smirnov, E.; Stockmann, T. J.; Peljo, P. *Chem. Rev.* **2018**, *118* (7), 3722−3751.
(111) Gschwend, G. C.; Smirnov, E.; Peljo, P.; Girault, H. H. *Faraday Discuss.* **2017**, *199* (0), 565−583.
(112) Rodgers, A. N. J.; Dryfe, R. A. W. *ChemElectroChem.* **2016**, *3* (3), 472−479.
(113) Toth, P. S.; Haigh, S. J.; Rabiu, A. K.; Rodgers, A. N. J.; Rakowski, A. M.; Dryfe, R. A. W. *J. Mater. Res.* **2015**, *30* (18), 2679−2687.
(114) Toth, P. S.; Rodgers, A. N. J.; Rabiu, A. K.; Dryfe, R. A. W. *Electrochem. Commun.* **2015**, *50*, 6−10.
(115) Senthilkumar, S.; Dryfe, R. A. W.; Saraswathi, R. *Langmuir* **2007**, *23* (6), 3455−3461.
(116) Trojánek, A.; Langmaier, J.; Samec, Z. *J. Electroanal. Chem.* **2007**, *599* (2), 160−166.
(117) Platt, M.; Dryfe, R. A. W. *Phys. Chem. Chem. Phys.* **2005**, *7* (8), 1807−1814.
(118) Kowalewska, K.; Sipa, K.; Burnat, B.; Skrzypek, S.; Poltorak, L. *Materials* **2022**, *15* (6), 2196.
(119) Dai, S.; Lu, W.; Wang, Y.; Yao, B. *Biosens. Bioelectron.* **2019**, *127*, 101−107.
(120) Walawalkar, M. G.; Pandey, P.; Murugavel, R. *Angew. Chem., Int. Ed.* **2021**, *60* (23), 12632−12635.
(121) Bernsmann, F.; Voegel, J.-C.; Ball, V. *Electrochim. Acta* **2011**, *56* (11), 3914−3919.

https://doi.org/10.1021/acs.analchem.2c01416
Anal. Chem. XXXX, XXX, XXX−XXX

(122) Compton, R. G.; Banks, C. E.Equilibrium Electrochemistry and the Nernst Equation. In *Understanding Voltammetry*, 3rd ed.; World Scientific Publishing Europe Ltd.: Hackensack, NJ, 2018.
(123) Piela, L.Electronic Orbital Interactions in Periodic Systems. In *Ideas of Quantum Chemistry*, 3rd ed.; Piela, L., Ed.; Elsevier: 2020; pp 1−80.
(124) Girault, H. H.Charge Transfer across Liquid—Liquid Interfaces. In *Modern Aspects of Electrochemistry*; Bockris, J. O. M., Conway, B. E., White, R. E., Eds.; Springer US: Boston, MA, 1993; Vol. *25*, pp 1−62.
(125) Samec, Z.; Mareček, V.; Weber, J. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **1979**, *100* (1−2), 841−852.
(126) Shao, Y.; Osborne, M. D.; Girault, H. H. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **1991**, *318* (1), 101−109.
(127) Nernst, W.; Riesenfeld, E. *Annalen der Physik* **1902**, *313* (7), 600−608.
(128) Samec, Z. *Chem. Rev.* **1988**, *88* (4), 617−632.
(129) Sun, P.; Laforge, F. O.; Mirkin, M. V. *Phys. Chem. Chem. Phys.* **2007**, *9* (7), 802−823.
(130) Stewart, A. A.; Taylor, G.; Girault, H. H.; McAleer, J. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **1990**, *296* (2), 491−515.
(131) Rodgers, P. J.; Amemiya, S. *Anal. Chem.* **2007**, *79* (24), 9276−9285.
(132) Wang, Y.; Velmurugan, J.; Mirkin, M. V.; Rodgers, P. J.; Kim, J.; Amemiya, S. *Anal. Chem.* **2010**, *82* (1), 77−83.
(133) Peljo, P.; Smirnov, E.; Girault, H. H. *J. Electroanal. Chem.* **2016**, *779*, 187−198.
(134) Shi, C.; Anson, F. C. *J. Phys. Chem. B* **1999**, *103* (30), 6283−6289.
(135) Peljo, P.; Girault, H. H.Liquid/Liquid Interfaces, Electrochemistry at. In *Encyclopedia of Analytical Chemistry*; John Wiley & Sons, Ltd., 2000.
(136) Gavach, C.; Seta, P.; Henry, F. *Bioelectrochem. Bioenerg.* **1974**, *1* (3), 329−342.
(137) Koryta, J.; Vaný sek, P.; Březina, M. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **1976**, *67* (2), 263−266.
(138) Ulmeanu, S. M.; Jensen, H.; Samec, Z.; Bouchard, G.; Carrupt, P.-A.; Girault, H. H. *J. Electroanal. Chem.* **2002**, *530* (1), 10−15.
(139) Bakker, E. *Anal. Chem.* **2016**, *88* (1), 395−413.
(140) Meyerhoff, M. E.; Fraticelli, Y. M. *Anal. Chem.* **1982**, *54*, 27−44.
(141) Tani, Y.; Umezawa, Y. *Sensor Letters* **2005**, *3* (2), 99−107.
(142) Lan, W.-J.; Zou, X. U.; Hamedi, M. M.; Hu, J.; Parolo, C.; Maxwell, E. J.; Buhlmann, P.; Whitesides, G. M. *Anal. Chem.* **2014**, *86* (19), 9548−9553.
(143) Chen, R.; Yang, A.; Chang, A.; Oweimrin, P. F.; Romero, J.; Vichitcharoenpaisarn, P.; Tapia, S.; Ha, K.; Villaflor, C.; Shen, M. *ChemElectroChem.* **2020**, *7* (4), 967−974.
(144) Matsuda, H.; Yamada, Y.; Kanamori, K.; Kudo, Y.; Takeda, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64* (5), 1497−1508.
(145) Samec, Z.; Papoff, P. *Anal. Chem.* **1990**, *62* (10), 1010−1015.
(146) Alanis, K.; Alden, S.; Baker, L. A.; Anupriya, E. S.; Jetmore, H. D.; Shen, M.Micro and Nanopipettes for Electrochemical Imaging and Measurement. In *Scanning Electrochemical Microscopy*, 3rd ed.; Bard, A. J., Mirkin, M., Eds.; in production, 2022.
(147) Sinru, L.; Zaofan, Z.; Freiser, H. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **1986**, *210* (1), 137−146.
(148) Bingol, H.; Atalay, T. *Open Chemistry* **2010**, *8* (5), 1134−1139.
(149) Lagger, G.; Tomaszewski, L.; Osborne, M. D.; Seddon, B. J.; Girault, H. H. *J. Electroanal. Chem.* **1998**, *451* (1), 29−37.
(150) Nishizawa, S.; Yokobori, T.; Kato, R.; Shioya, T.; Teramae, N. *Bull. Chem. Soc. Jpn.* **2001**, *74* (12), 2343−2347.
(151) Velazquez-Manzanares, M.; Guerrero-Trejo, G.; Aguilar, J. C.; Amador-Hernández, J. *ECS Trans.* **2007**, *3* (29), 73−81.
(152) Läuger, P. *Science* **1972**, *178* (4056), 24−30.
(153) Volkov, A. G.; Gugeshashvili, M. I.; Deamer, D. W. *Electrochim. Acta* **1995**, *40* (18), 2849−2868.
(154) Liu, B.; Mirkin, M. V. *J. Am. Chem. Soc.* **1999**, *121* (36), 8352−8355.
(155) Li, F.; Unwin, P. R. *J. Phys. Chem. C* **2015**, *119* (8), 4031−4043.
(156) Shao, Y.Electrochemistry at Liquid/Liquid Interfaces. In *Handbook of Electrochemistry*; Zoski, C. G., Ed.; Elsevier: Amsterdam, 2007; pp 785−809.
(157) Koryta, J.; Vaný sek, P.; Březina, M. *Journal of Electroanalytical Chemistry and Interfacial Electrochemistry* **1977**, *75* (1), 211−228.
(158) Scholz, F.; Gulaboski, R. *ChemPhysChem* **2005**, *6* (1), 16−28.
(159) Scholz, F. *Annual Reports Section C (Physical Chemistry)* **2006**, *102*, 43−70.
(160) Ulmeanu, S. M.; Jensen, H.; Bouchard, G.; Carrupt, P.-A.; Girault, H. H. *Pharm. Res.* **2003**, *20* (8), 1317−1322.
(161) Samec, Z. *Pure Appl. Chem.* **2004**, *76* (12), 2147−2180.
(162) Amemiya, S.; Wang, Y.; Mirkin, M. V., Chapter 1: Nanoelectrochemistry at the liquid/liquid interfaces. In *Electrochemistry*; The Royal Society of Chemistry: 2014; Vol. *12*, pp 1−43.
(163) Amemiya, S.; Kim, J.; Izadyar, A.; Kabagambe, B.; Shen, M.; Ishimatsu, R. *Electrochim. Acta* **2013**, *110*, 836−845.
(164) Sposito, G.Gouy-Chapman Theory. In *Encyclopedia of Geochemistry: A Comprehensive Reference Source on the Chemistry of the Earth*; White, W. M., Ed. Springer International Publishing: Cham, 2018; pp 623−628.
(165) Gouy, M. *Journal of Physics: Theories and Applications* **1910**, *9* (1), 457−468.
(166) Chapman, D. L. *London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science* **1913**, *25* (148), 475−481.
(167) Stern, O. *Zeitschrift für Elektrochemie und angewandte physikalische Chemie* **1924**, *30* (21−22), 508−516.
(168) Grahame, D. C. *Chem. Rev.* **1947**, *41* (3), 441−501.
(169) Gschwend, G. C.; Girault, H. H. *J. Electroanal. Chem.* **2020**, *872*, 114240.
(170) Gschwend, G. C.; Girault, H. H. *Chemical Science* **2020**, *11* (38), 10304−10312.
(171) Gschwend, G. C.; Olaya, A.; Girault, H. H. *Chemical Science* **2020**, *11* (39), 10807−10813.
(172) Mellander, L.; Cans, A. S.; Ewing, A. G. *ChemPhysChem* **2010**, *11* (13), 2756−2763.
(173) Perry, M.; Li, Q.; Kennedy, R. T. *Analytica chimica acta* **2009**, *653* (1), 1−22.
(174) Lemaitre, F.; Guille Collignon, M.; Amatore, C. *Electrochim. Acta* **2014**, *140*, 457−466.
(175) Michael, A. C.; Borland, L.*Electrochemical methods for neuroscience*; CRC Press, 2006.
(176) Kim, D.; Koseoglu, S.; Manning, B. M.; Meyer, A. F.; Haynes, C. L. *Anal. Chem.* **2011**, *83* (19), 7242−7249.
(177) Nakatsuka, N.; Andrews, A. M. *ACS Chem. Neurosci.* **2017**, *8* (2), 218−220.
(178) Lama, R. D.; Charlson, K.; Anantharam, A.; Hashemi, P. *Anal. Chem.* **2012**, *84* (19), 8096−8101.
(179) Adams, R. A. *Anal. Chem.* **1976**, *48*, 1126A−1138A.
(180) Venton, B. J.; Wightman, R. M. *Anal. Chem.* **2003**, *75*, 414A−421A.
(181) Huang, X.; Xuan, Y.; Xie, L.; Su, B. *ChemElectroChem.* **2016**, *3* (11), 1781−1786.
(182) Stockmann, T. J.; Boyle, P. D.; Ding, Z. *Catal. Today* **2017**, *295*, 89−94.

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