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Nanoscale Electrochemical Sensing and Processing in Microreactors

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electrochemical sensing, electrochemical microreactors, nanoparticles, nanowires, electrocatalysis, electrochemical synthesis

Abstract

In this review, we summarize recent advances in nanoscale electrochemistry, including the use of nanoparticles, carbon nanomaterials, and nanowires. Exciting developments are reported for nanoscale redox cycling devices, which can chemically amplify signal readout. We also discuss promising high-frequency techniques such as nanocapacitive CMOS sensor arrays or heterodyning. In addition, we review electrochemical microreactors for use in (drug) synthesis, biocatalysis, water treatment, or to electrochemically degrade urea for use in a portable artificial kidney. Electrochemical microreactors are also used in combination with mass spectrometry, e.g., to study the mimicry of drug metabolism or to allow electrochemical protein digestion. The review concludes with an outlook on future perspectives in both nanoscale electrochemical sensing and electrochemical microreactors. For sensors, we see a future in wearables and the Internet of Things. In microreactors, a future goal is to monitor the electrochemical conversions more precisely or ultimately in situ by combining other spectroscopic techniques.

1. INTRODUCTION

Although the field of electrochemical sensing has a long history dating back to the 1960s to the first electrochemical sensors for oxygen and later glucose (1), the advent of new micro- and nanotechnological capabilities has surely brought a revival of the field. This is illustrated by three 2017 issues (Vol. 89, Issues 13–15) of *Analytical Chemistry*, the most relevant journal in the field. Of all techniques, it appears that mass spectrometry (MS), in some cases combined with liquid chromatography (LC), is still the most important workhorse in the field (see **Figure 1**). However, optical and electrochemical detection follow closely behind.

In this article, we review and summarize nanoscale electrochemical sensing and microreactor processing. In processing, electrochemistry is used to convert chemical substances in reactions where electron transfer is required. Focus in this area is typically to obtain full conversion of the molecules introduced into the electrochemical cell. As such, the electrochemical cell can be considered as an electrochemical (micro)reactor, with features that resemble the general reactor designs in flow chemistry. Typically, large electrode areas are used to convert as much starting product as possible. This is different from sensing, where the design criteria are completely different. In sensing, a small (ultramicro)electrode can have its benefits in such areas as measuring smaller amounts of molecules or to obtain steady-state currents because mass transport can monitor the consumption of ions at the surface. In both cases, miniaturization can offer specific advantages to enhance mass transport. In the rest of this review, we discuss trends and significant developments in two separate sections for sensing and processing. The sensing section focuses on the nanoscale, whereas in the processing section, designs typically have critical dimensions in the (sub)micrometer range. Our aim is not to give a total overview of the field. Instead, we highlight recent important developments and trends and refer to other review articles for more extensive overviews whenever possible.

2. NANOSCALE SENSING

Developments in nanoscale sensing are driven by a number of different factors. Downscaling electrode dimensions to the nanoscale offers unique opportunities, such as localized probing of

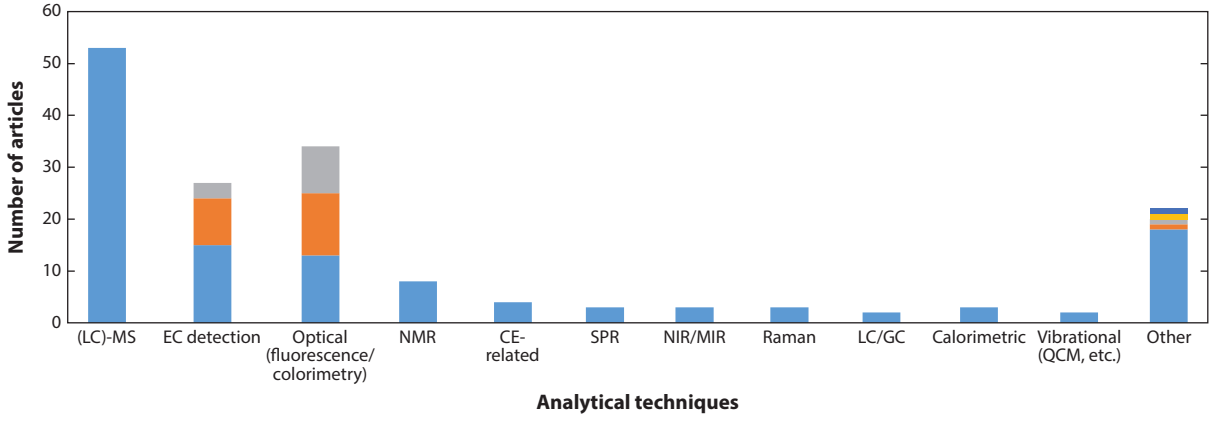


Figure 1

Summary of the techniques used in 164 studies published in issues 13–15 (2017) of the journal *Analytical Chemistry*. Abbreviations: CE, capillary electrophoresis; EC, electrochemical; GC, gas chromatography; LC, liquid chromatography; MIR, mid-infrared spectroscopy; MS, mass spectrometry; NIR, near-infrared spectroscopy; NMR, nuclear magnetic resonance; QCM, quartz-crystal microbalance; SPR, surface plasmon resonance.

cells, catalytic sites, single particles, and the detection of small amounts of molecules or even single molecules. Perhaps the most striking commercially successful example is the DNA sequencing technology from Ion Torrent, which records small pH changes in an extremely small volume upon the inclusion of a nucleotide into the single-stranded DNA (ssDNA) during the copy process (2). However, downscaling comes at the cost of introducing several technological challenges. Smaller electrodes typically generate smaller currents, thereby effectively reducing the signal-to-noise ratio (SNR). Moreover, fabricating sensors with submicron dimensions implies nanofabrication technology, traditionally carried out with relatively advanced and expensive cleanroom processes such as e-beam or nanoimprint lithography. Addressing these technological challenges can be very rewarding, as there is much to gain from a fundamental perspective. Entering the nanoscale provides new insight into physical and chemical processes such as Debye screening, chemisorption and adsorption, and mass transport at the molecular level (3).

The sections below summarize the developments and trends observed in miniaturized nanoscale electrochemical sensors. Most nanoscale sensing is based on nanomaterials such as nanoparticles or nanotubes. In this review, we focus mainly on nanometer-sized devices such as nanowires, nanocapacitive arrays, or nanogaps used for processes such as redox cycling. We observe that nanosensing techniques are also gaining recent interest for the detailed study of catalytic activity, as there is considerable ongoing research effort in the search for alternatives to fossil fuels.

2.1. Nanoparticle-Based Sensing

Nanoparticles have unique properties, in both the optical and the chemical domain, demonstrating exceptional and different behavior from bulk material. Many articles have been published on this topic but are too numerous to discuss in detail here. We therefore only give an overview of the various uses for nanoparticles and refer to other review papers that go into more depth (4–6).

Nanoparticles have found their way into many sensors, carrying out specific roles in the sensing mechanism (4). One of the most straightforward roles is their electrocatalytic activity, which enhances sensitivity and selectivity (5). Attributing this enhanced electrocatalytic activity is a topic of intense debate in the literature. Surely, downscaling particle size will enhance the surface-to-volume ratio, thus leaving more active sites for the reaction. Moreover, mass transport is enhanced by using nanoparticles compared to bulk electrodes. However, there is more at play, as structural effects also play a major role because it is known that different crystal planes display different activity (7). In addition, in many cases, the edge of a plane also demonstrates high catalytic activity. Depending on the method of synthesis, nanoparticles are not just uniform spheres, and for example, transmission electron microscopy images show clear crystal structures that can further explain their enhanced catalytic behavior.

A second use for nanoparticles in electrochemical detection is to enhance electron transfer, for example, in enzymes where the active center is shielded, or in cases where polymer linkers demonstrate poor conductivity between the biorecognition element and the electrode surface. A landmark article in this area was published by Xiao et al. (8, p. 1877), demonstrating nanowiring of redox active enzymes by a gold nanoparticle. In this study, 1.4-nm gold nanoparticles were functionalized with flavin adenine dinucleotide (FAD) groups, using *N*-hydroxysuccinimide as linker to the particle. Next, apo-glucose oxidase (apo-GOx) was reconstituted with the gold-FAD particle. Lastly, the gold-FAD-apo-GOx combination was linked to a macroscopic gold electrode, demonstrating significantly increased electron transfer turnover rates. A similar approach was demonstrated more recently by Yehezkeli et al. (9), functionalizing flavin-dependent glucose dehydrogenase and 3.5-nm gold nanoparticles with thiolaniline and subsequent electropolymerization

on a functionalized gold electrode. The main advantage of their approach is the use of an oxygen-insensitive enzyme, with excellent electron transfer kinetics.

A third application that is widely studied is the use of nanoparticles for labeling molecules such as DNA or antibodies. In this case, the particle can be considered as contrast agent, enhancing the overall signal readout. By using the plasmonic properties of nanoparticles, this readout can be optical; alternatively, by using metallic nanoparticles, the readout can be obtained by various spectroscopic methods, including X-ray spectroscopy or inductively coupled plasma–mass spectrometry (10). Because this review focuses on electrochemical detection, we refer the interested reader to other reviews on this topic (4, 11). Looking at electrochemical techniques, captured metal nanoparticles can be used as a signal by dissolving the metal ions, followed by sensitive detection using techniques such as stripping voltammetry. Dequaire and coworkers (12) have demonstrated this approach for the detection of immunoglobulin G, obtaining an impressive limit of detection down to 3 pM.

Creative use of the photoelectrochemical properties of nanoparticles was recently demonstrated for sensing of cysteine. Heterostructures consisting of gold nanoparticles with perovskite Bi_4NbO_8Cl were used to detect the presence of electron-donating cysteine under irradiation conditions. The resulting differences in photocurrent could be used for sensing purposes (13). Similarly, Molybdenum(VI) oxide (MoO_3) was electrodeposited on an array of titanium dioxide (TiO_2) nanoneedles to obtain a lowered band gap of 2.6 eV instead of the typical 3.2 eV for TiO_2 only. The TiO_2/MoO_3 surface was coated with an antibody and subsequently used to detect the decrease in photocurrent as a measure for the amount of macrophage cells (14). A detailed description of the exact sensing mechanism was not given by the authors, but it is suggested that the decrease in photocurrent is caused by increased steric hindrance when macrophage cells are captured.

2.2. Carbon Nanomaterials

When discussing nanomaterials such as metallic nanoparticles for electrochemical detection, carbon nanotubes (CNTs) and graphene cannot be ignored, as both materials went through a typical hype cycle upon discovery of their existence. For carbon nanotubes, the peak of the hype probably occurred around the year 2000, with researchers from the NASA Institute for Advanced Concepts even proposing that CNTs could help build an elevator to outer space (15). Regardless of such unrealistic claims stated during the peak of inflated expectations, CNTs do have intrinsic properties that make them interesting for sensor applications. CNTs behave as metals in terms of electrical conductance. Moreover, their high surface area enhances signal intensity, sensitivity, and electron transfer. Their electrocatalytic activity toward hydrogen peroxide and nicotinamide adenine dinucleotide (NAD) is also of interest for many sensing applications involving enzymes (16). Later, graphene basically took over the CNT hype, as this two-dimensional material displays unique advantages in terms of high specific surface area, excellent thermal and electric conductivity, and special optical properties. Detailed and highly cited reviews on CNT (17, 18) as well as on graphene and graphene oxide (19–21) research for electrochemical detection have been published over the last decade.

2.3. Redox Cycling Nanosensors

Redox cycling can be described as the effect of a reversible redox molecule cycling between an oxidizing and reducing electrode pair. For each cycle, the same single molecule contributes to the measured current, effectively amplifying the signal by chemical means (22). Meaningful

amplification only occurs when two electrodes are placed in close proximity such that their concentration profiles overlap. Typically, the critical dimensions of redox cycling sensors are well below 5 μm (23, 24). A good tutorial review by Mathwig et al. (25) on nanopores and redox cycling was recently published. In this review, a clear motivation for the use of redox cycling is given from the perspective of downscaling electrode dimensions. The use of nanometer-sized electrodes comes with its own set of difficulties. One of these can be found in measurement equipment, as electronic amplifiers typically need a minimum amount of electrons to measure above the noise level at room temperature. Amplifying the measurement current using redox cycling simplifies the task of designing very sensitive amplifiers to be able to get sufficient signal-to-noise.

Redox cycling is advantageously useful in scanning electrochemical microscopy (SECM) where amplification or the so-called feedback mode between the scanned surface and the tip electrode provides useful insight into the surface potential and morphology (26, 27). An innovative variant of this technique, using a tip containing both the electrode and microfluidic channels to collect samples for mass spectrometric detection, was published by the Girault group (28). With this device, they demonstrate the electrochemical scanning of fingerprints, while simultaneously tracing residues originating from that same finger. Besides signal amplification, redox cycling can also be of particular use to increase selectivity, either by discriminating between reversible or nonreversible redox couples or by tuning into one specific redox couple by setting electrode potentials around its standard potential (29). An extensive overview of literature on the design of redox cycling sensors was recently published by Wolfrum and coworkers (30). Here we discuss only the most recent papers on the topic since 2016.

Adly and coworkers (31) have fabricated a redox cycling sensor using an inexpensive and scalable fabrication method based on multilayer inkjet printing. It consists of a gold bottom electrode and a top carbon electrode separated by porous polystyrene beads. According to the authors, this device (see **Figure 2*a***) demonstrates a current amplification of 30× using ferrocenedimethanol. Using the same printing technique, the same team managed to print planar carbon finger electrodes down to micrometer resolution (32). These planar structures were used to detect HIV-related ssDNA using peptide nucleic acids attached to the electrode surface. The results suggest that approximately 1–10 nM of ssDNA could be detected reliably.

Zafarani et al. (33) recently published a more traditional design based on e-beam lithography (see **Figure 2*c***). Their device consists of a band of 80-nm-thick gold separated into two pieces. A gap is created by lift-off, resulting in two gold electrodes with a spacing of 70 nm. Insulation of the remaining gold is provided by a 500-nm-thick layer of polymethyl methacrylate, which is also opened locally by e-beam exposure to allow electrolyte to enter the nanogap. Unfortunately, the device was not tested for other analytes besides the model compound ferrocene dimethanol.

Steentjes, Sarkar, and coworkers (34) have included poly(ethylene glycol) (PEG) modified with redox-active ferrocene end-groups and immobilized these chains onto facing electrodes from an earlier published nanometer-spaced cell design (24, 34) (**Figure 2*b***). In the absence of an electrochemical mediator, the authors demonstrated that a redox cycling current was established between the oxidizing and reducing electrode by transferring electrons from one PEG chain to the other. For this charge transfer to work it is essential to use polymer chains of sufficient length to allow the ferrocene end-groups to interpenetrate the PEG chain from the opposite electrode. An alternative sensing mechanism can be developed in the future by binding an analyte to the polymer, effectively changing the stiffness, diffusivity, or length of the chain.

The Bohn group (35, 36) has published a redox cycling device based on a nanopore containing an elevated ring with a recessed disk electrode at the bottom, as shown in **Figure 2*d***. Based on these devices, the effect of the electrical double layer on the redox cycling amplification was studied. The group found that the amplification could be increased from 55× to 500× by removing

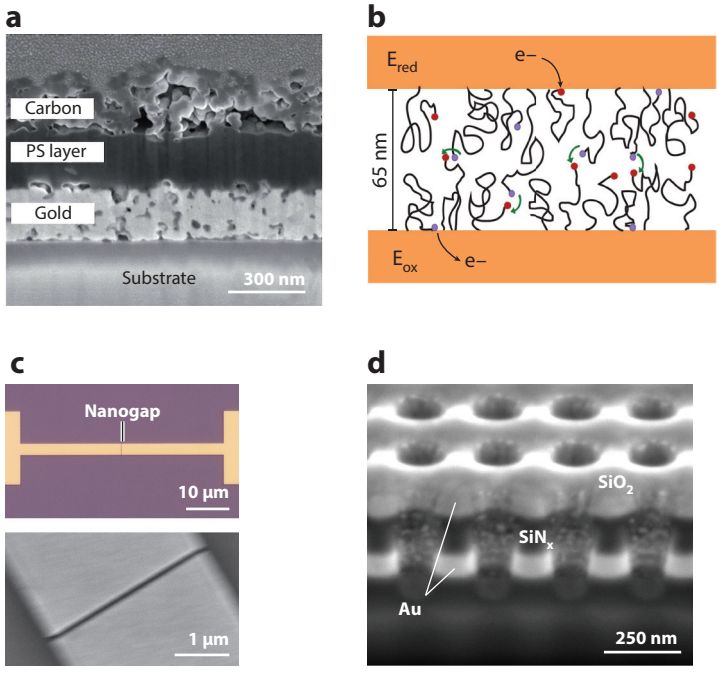


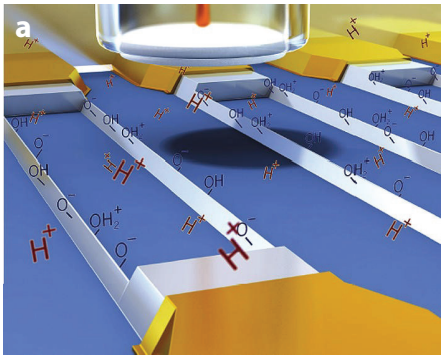
Figure 2

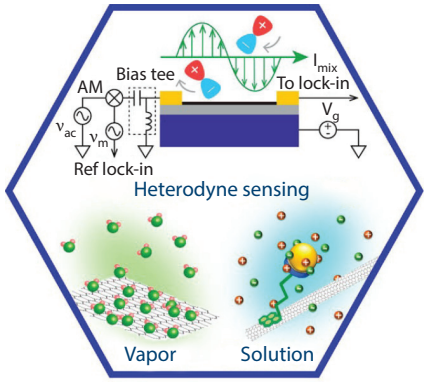
(*a*) Multilayer inkjet printing of nanoparticle-conductive ink (31). Redox cycling occurs between the gold and carbon electrode layers, separated by a porous nonconducting polystyrene (PS) layer. Adapted from Reference 31 with permission from the Royal Society of Chemistry. (*b*) Interpenetrated poly(ethylene glycol) chains with ferrocene groups demonstrating redox cycling (between the red and purple ferrocene groups) in a previously published nanocavity device (24) in the absence of an electrochemical mediator (34). Adapted with permission from Reference 34. Copyright 2016, John Wiley and Sons. (*c*) Nanogap sensor fabricated by a two-step E-beam process. Adapted with permission from Reference 33. Copyright 2017, American Chemical Society. (*d*) Nanogap array with elevated ring and recessed disk-type redox cycling structures. Nanometer-sized dimensions of the pores were exploited as zero-mode waveguides, enabling simultaneous optical and electrochemical readout. Adapted from Reference 38 with permission from the Royal Society of Chemistry.

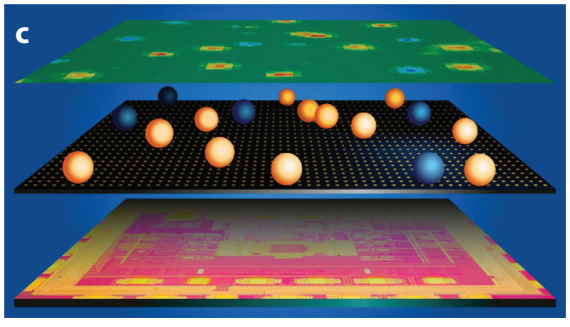
the supporting electrolyte increasing the Debye length (37). In other recent work by this group (38), the nanometer dimensions of the pore were exploited to be used as zero-mode waveguides to enhance fluorescent imaging within the active area of the redox cycling electrodes. Simultaneous optical and electrochemical signal enhancement could be obtained using the redox-active, fluorogenic molecule flavin mononucleotide. The spectroelectrochemical readout allowed the authors to detect the activity of single fluorogenic redox-active molecules.

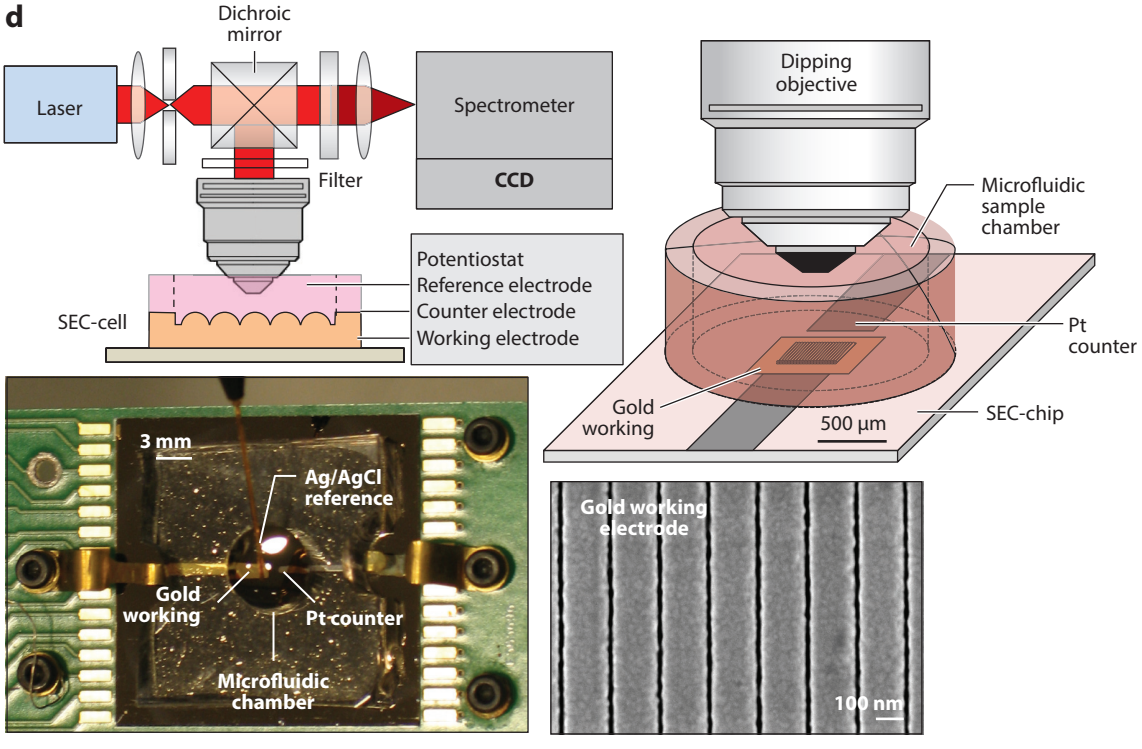
2.4. Silicon Nanowire Sensing

In 1970, Bergveld (39) published his first article describing a field effect transistor (FET) with the gate connection replaced by a reference electrode in contact with a liquid electrolyte. This article marked the invention of the ion-sensitive field effect transistor (ISFET) (40). With the enhanced capabilities for nanofabrication, this concept gained renewed interest after researchers employed silicon nanowires (see **Figure 3*a***). In silicon nanowire sensing, the so-called channel that forms in the depletion zone between the source and drain of a metal-oxide semiconductor









(Caption appears on following page)

Figure 3 (*Figure appears on preceding page*)

(*a*) Artist's impression of silicon nanowires used for the detection of ions. Adapted with permission from Reference 42. Copyright 2011, American Chemical Society. (*b*) Infographic demonstrating the concept of heterodyne sensing using the frequency mixing of ion dipoles and a nanoscale transistor. Adapted with permission from Reference 49. Copyright 2016, American Chemical Society. (*c*) CMOS nanocapacitive sensor array used to image microparticles and track living cells in space and time. Adapted with permission from Reference 48. Copyright 2016, American Chemical Society. (*d*) Raman spectroelectrochemical setup using gold nanowires with a tunable sub-20-nm gap. Shifts in the spectrum of a monolayer of Hemin were recorded upon oxidation/reduction. Adapted with permission from Reference 54. Copyright 2015, American Chemical Society. Abbreviations: CCD, charge-coupled device; SEC, spectroelectrochemical.

FET (MOSFET) is replaced by the silicon nanowire. The amount of charge inside the wire, and therefore the resulting conductivity of the nanowire, depend on the amount and charge of the ions at the nanowire surface/electrolyte interface.

Besides being used in sensing of ions and pH in solution (41, 42), nanowires are popular for sensing of proteins or DNA. In these cases, the nanowire is first functionalized with ssDNA or antibodies (43). Subsequently, binding events can be detected with high sensitivity due to a change of surface charge (44). Zhang & Ning (45) published a more detailed and recent review on this topic.

2.5. Novel Nanosensing Strategies

Widdershoven et al. (46) developed a novel sensing strategy based on modifying a CMOS image sensor with nanometer-sized gold electrodes in direct contact with the electrolyte (**Figure 3*c***). These gold electrodes form one of the two plates of a capacitor. Using two MOS transistors, this capacitor is periodically charged and discharged at frequencies up to 50 MHz. The average charge and discharge current are measured and serve as the sensor output. Using this platform, it was demonstrated that microparticles and living cells could be detected and even imaged and tracked over space and time (47). With ever-decreasing pixel size in CMOS technology, this could be a potentially powerful technique to detect items with submicrometer dimensions, such as nanoparticles, viruses, or even proteins. With further downscaling, the operating frequency could theoretically be increased beyond the dielectric relaxation cut-off frequency of the electrolyte, effectively eliminating the dependence on ionic conductivity (48).

Heterodyning is an old and well-known trick in radio transmission that works through mixing a received radio signal with a local oscillator. As a result, two new signals are obtained at the sum and difference of the received and local oscillator frequencies. Zhong and coworkers (49) have employed this technique by studying the mixing response of molecular dipoles and nanoscale transistors, as shown in **Figure 3*b***. A high-frequency carrier signal (typically in the range of 100 kHz to several megahertz) is modulated with a 1.43-kHz reference signal and fed to a nanowire FET. This AC signal induces oscillations of dipoles of molecules in close proximity to the nanowire. The resulting current is mixed using a lock-in amplifier to obtain the desired mixing current that contains the chemical information. Using a high carrier frequency prevents charging of the double layer and avoids unwanted Debye screening. This technique has not been studied until recently due to the absence of high-gain devices that are required to obtain sufficient SNR. Employing the recent developments in graphene and carbon nanotubes (see Section 2.2) and in silicon nanowires (Section 2.4), researchers demonstrated the recognition of streptavidin binding to biotin beyond the Debye screening length (50) and the sensitive detection of organic solvent vapor down to 1 ppb (51).

Spectroelectrochemistry refers to the in situ study of electrochemical processes using additional spectroscopic techniques. In general, optical methods are used based on absorption of light in the

ultraviolet (UV), visible, or infrared range or on Raman scattering. Additionally, articles have been published on the combination of nuclear magnetic resonance, X-ray absorption spectroscopy, or electron paramagnetic resonance (52). The combination of electrochemistry with spectroscopy is quite powerful and is particularly useful to elucidate reaction mechanisms or identify short-lived intermediates. In most articles describing spectroelectrochemistry, the area of the electrodes is relatively large and well beyond the nanoscale for the obvious reasons of obtaining sufficient spectroscopic readout. Here, we discuss some recent interesting studies that fit the scope of nanoscale sensing covered in this review.

Carlen and coworkers (53) managed to fabricate an array of gold nanowires with a tunable sub-20-nm gap for surface-enhanced Raman spectroscopy, demonstrating an enhancement factor of 1.2×10^7. These gold nanowires could also be interfaced as electrodes to drive electrochemical reactions. A proof-of-concept study showed that it was possible to record shifts in the Raman spectrum upon oxidation and reduction of a monolayer of hemin attached to the gold electrode surface (54), as shown in **Figure 3*d***.

Raman spectroscopy is also commonly used to determine if a graphene sample is actually single layer or multilayer. We have used this property of graphene, combined with its capability as an electrode to do a fundamental study on the reaction mechanism of frequently used model compounds such as ferrocene dimethanol, ruthenium hexamine trichloride (RuHex), and ferrocyanide (55). A shift in the position of the G-peak in the Raman spectrum showed that both ferrocyanide and ferrocene methanol adsorb to the graphene, whereas no shifts were observed for RuHex. These results confirmed that the reaction mechanism for RuHex follows a so-called outer sphere reaction mechanism that does not require strong interaction with the electrode surface. Additionally, the oxidation of ferrocyanide is a reaction that requires adsorption and strong interactions with the electrode surface.

Recently, the surface enhancement effects of gold nanoparticles were used to follow their electrochemical deposition and dissolution on a thin-film boron-doped diamond (BDD) electrode on top of an attenuated total reflectance crystal (56). Using the gold nanoparticle–modified surface, the adsorption of thiocyanide anions was recorded over time. As the authors state, their system could potentially also be used to study the electrocatalytic activity of gold nanoparticles (as discussed in Section 2.1).

3. PROCESSING: ELECTROCHEMICAL MICROREACTORS

The design demands for electrochemical microreactors are in many ways completely opposite to those for sensors. In electrochemical microreactors, the key aim is to get sufficient conversion of the target analyte. As such, designs are optimized to gain a good surface-to-volume ratio by enlarging the electrode surface area and reducing the microfluidic channel volume (57–59).

Electrochemical microreactors are used to drive reactions in which electron transfer plays a role. Driving such reactions inside these reactors offers several advantages over more traditional setups, such as batch cells. Microreactors can be employed to drive green chemistry, as electrons are a relatively clean and cheap source to drive oxidation or reduction reactions, compared to using chemical reductants or oxidizing agents, for example. An additional advantage is that the use of electrodes allows for more precise control over the reaction by tuning the electrode potential, controlled current techniques, or catalytically active surfaces. Another way to tune the reactions occurring at the electrodes is using pulsed potential or pulsed current techniques (60). The importance of precise control over the potential is of particular interest to enhance the selectivity of the desired electrochemical reaction or to prevent fouling of the electrodes. Moreover, there is more control over the electric fields compared to traditional batch reactors due to the enhanced control

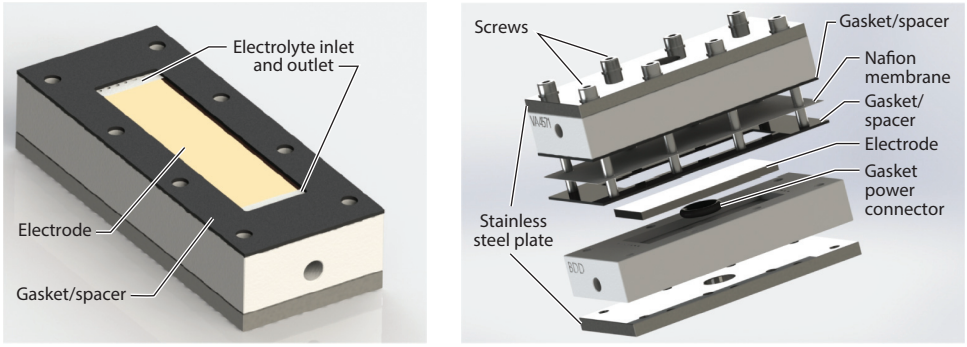


Figure 4

Electrochemical flow-through microreactor, as published by Waldvogel and coworkers (65). It consists of two Teflon parts, with recessed squares for electrodes. Fluidic channels are formed by gaskets. Working and counter electrode compartments can be separated with an optional (Nafion) membrane. Stainless steel plates clamp the whole stack together using screws. Electrode dimensions are 20 × 60 mm, whereas gaskets between 0.12 and 2 mm are used. Adapted with permission from Reference 65. Copyright 2017, American Chemical Society.

over the spacing between working and counter electrodes. Electrochemical microreactors are a special type of flow microreactors. As such, they are typically used in setups well described in the area of flow chemistry (61). Similar advantages to other types of flow microreactors are applicable as well, namely, the precise control over temperature and the possibility to run the system in a continuous manner. One striking advantage is their ability to generate reactive intermediates followed by fast analysis (62) or to drive subsequent reaction steps (63). Microfluidics can be a great advantage in this case by reducing the time required for mass transport and by allowing sufficient intermediates to reach the target molecules or measurement equipment.

However, there are surely some disadvantages. Depending on the reactor design and the type of reaction, the addition of supporting electrolyte to reduce ohmic drop might be required. Reducing the spacing between the electrodes can help in some cases by compensating for ohmic drop and eliminating the need to add additional ions to the mixture. Moreover, these systems are only compatible with a limited amount of solvents. Despite some disadvantages, the many benefits have inspired scientists to use electrochemical microreactors in various applications that are discussed below.

3.1. (Drug) Synthesis

An exemplary reactor design typically used for electrochemical synthesis is shown in **Figure 4**. The dimensions are often rather large compared to sensing applications, with electrode areas in the range of several square centimeters spaced apart by several hundreds of micrometers. For a detailed overview of other cell designs, we refer to another recent and comprehensive review (64).

These reactors are typically used to replace synthesis in large batch reactors. In conventional batch reactors, severe limitations can be found in controlling temperature, which is required to either drive the reaction or remove it to prevent overheating. Moreover, driving synthesis in flow reactors offers unique opportunities to work with short-lived intermediates or chemicals that would otherwise raise considerable safety issues. After optimization, the yield of desired product is typically more than 80%. Recent reviews that highlight this application in detail were written by the groups of Wirth (66) and Atobe (64, 67). In this review, we only highlight some recent

publications, demonstrating the wide range of possible chemical reactions as well as the unique tricks offered by their microreactor design.

In this first highlight, we show the unique benefits of fast mixing by preventing the loss of reactive intermediate. The study (68) demonstrated the electrochemical carboxylation of 1-(chloroethyl)-benzene using a microreactor design containing two compartments, as illustrated in **Figure 5*a***. In the first compartment, 1-(chloroethyl)-benzene is first reduced electrochemically, followed by a reaction with CO_2 to form a carboxylate ion. In the next compartment, acid is added to stabilize the carboxylate ion. The authors studied the effect of electrode distance to the yield and found that, in this case, smaller (20 μm) is better. The fast subsequent mixing with acid helps to stabilize the carboxylate ion intermediate, further increasing the yield of desired product.

In the second example, laminar flow is used to precisely control mass transport, thereby controlling the reaction products forming at both the anode and cathode. The authors demonstrated C-C coupling of naphthalene derivatives and alkylbenzenes in a reactor that employs a laminar coflow of both reactants using two separate inlets (69) (**Figure 5*b***). The naphthalene substrate was oxidized at one electrode, whereas the alkylbenzene nucleophile was reduced at the other electrode. Subsequently, both compounds react at the anode from the cross-coupling product. The coflow prevents the nucleophile compound from unwanted oxidation at the anode.

The third example nicely demonstrates the unique electrochemical behavior of BDD electrodes. A BDD electrode microreactor was employed to generate and prove the existence of methoxy radicals (70). The authors found proof for the existence of methoxy radicals using electron spin resonance spectroscopy. Subsequently, licarin A was synthesized electrochemically from isoeugenol at a yield of approximately 40%, as shown in **Figure 5*c***.

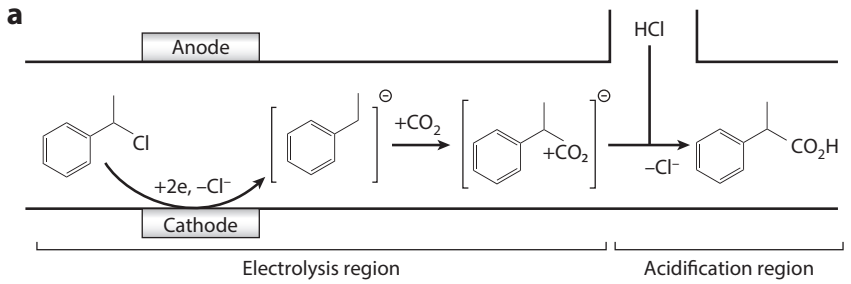
The fourth and last example demonstrates how dangerous reactions can still be conducted safely in microreactors. Renault et al. (58) fabricated a microreactor design with many parallel channels scratched in platinum plates with a homemade needle that simultaneously acted as electrode. This channel/electrode plate was soldered onto a copper heat exchanger. Using this setup, the authors fluorinated deoxy glucose, as shown in the reaction scheme of **Figure 5*d***. In this specific case, microreactor technology assisted in reducing safety hazards caused by the fluorination agents (fluorine gas). Moreover, the efficient heat transfer aided in controlling chemical selectivity.

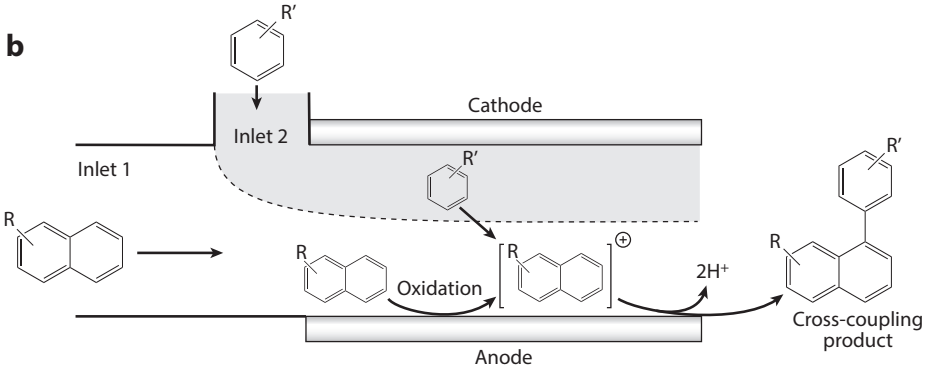
3.2. Biocatalysis

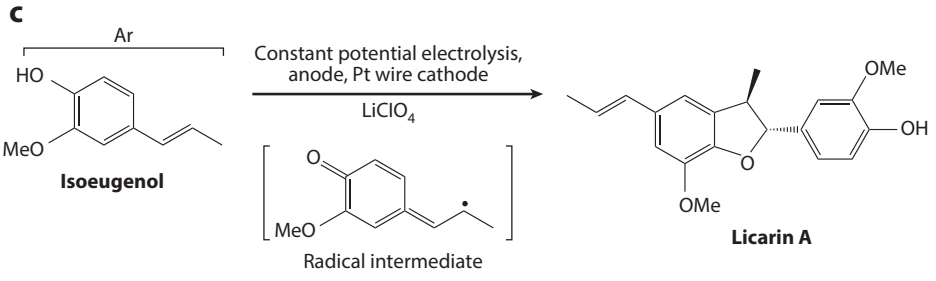
An interesting alternative for direct oxidation or reduction at electrode surfaces for synthesis is the use of enzymes to drive biocatalysis. Redox-active enzymes can offer unique opportunities by demonstrating reaction mechanisms otherwise not possible through direct electrochemistry. Moreover, these enzymes commonly exhibit much higher selectivity. However, in nature, the cofactor NAD is often required to close the catalytic cycle. NAD or its phosphorylated form (NADP) is expensive, which is a major disadvantage for synthesis purposes.

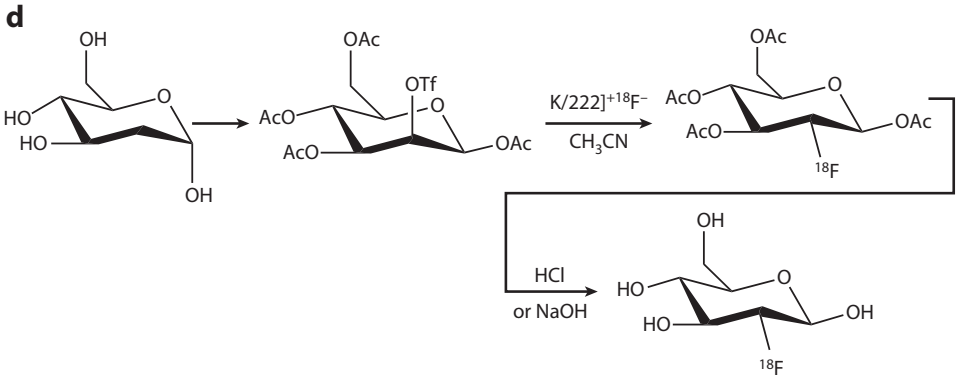
Hollmann et al. (72) wrote an extensive review of currently existing methods to solve this cofactor challenge. These methods typically involve regeneration of the NAD or NADP cofactor using electrodes to provide the necessary electrons.

A recent example using such a system demonstrates the synthesis of carbobenzoxy-β-alanine catalyzed by horse-liver alcohol dehydrogenase through the use of a filter press electrochemical microreactor. NAD was directly regenerated at the gold anode (73). Ruinatscha et al. (74) developed an electrochemical microreactor with reticulated vitreous carbon (RVC) electrodes that were separated by a Nafion membrane for the regeneration of FAD. RVC electrodes were chosen for their large surface area, thereby enhancing the overall FAD regeneration yield. As model reaction, the authors demonstrated the synthesis of (*S*)-styrene oxide catalyzed by styrene monooxygenase.









(*Caption appears on following page*)

Figure 5 (*Figure appears on preceding page*)

(*a*) Carboxylation of benzyl halides using a microreactor with an electrolysis and mixing compartment for subsequent acidification. Adapted from Reference 68 with permission from the Royal Society of Chemistry. (*b*) C-C coupling of naphthalene derivatives to alkylbenzene nucleophiles. Laminar flow is used to prevent unwanted oxidation of the nucleophile compounds. Adapted from Reference 71 with permission from the Royal Society of Chemistry. (*c*) Methoxylation of isoeugenol to synthesize licarin A. The employed microreactor uses a BDD working electrode and Pt counter electrode. BDD was demonstrated to be the most effective material to generate methoxy radicals as measured by ESR spectroscopy. Adapted with permission from Reference 70. Copyright 2012, John Wiley and Sons. (*d*) Fluorination of deoxy glucose using a microreactor with many parallel channels, and a heat exchanger to control chemical selectivity. Adapted with permission from Reference 58. Copyright 2012, Springer. Abbreviations: BDD, boron-doped diamond; ESR, electron spin resonance.

Another interesting example is the enzymatic synthesis of formate accomplished by reducing CO_2 and using formate dehydrogenase (75). It should be noted, however, that in this specific case all reactions were carried out in batch.

Keeping the NAD and enzyme inside the reactor while releasing starting and final product is an additional challenge, especially under flow conditions. An interesting approach that was published two decades ago involved immobilizing NAD onto the electrode surface (76). Subsequently, lactase dehydrogenase was bound to the immobilized NAD. In this specific case, the aim was directed at sensing lactate.

3.3. Water Treatment

Electrochemical oxidation in the treatment of waste water is one of the emerging techniques used to meet stricter regulations in water quality (77). However, challenges in electrode stability and treatment cost need to be resolved before this approach is accepted in mainstream water treatment plants. Water treatment generally demands high throughput of large volumes, and hence, it is not an area where microreactors naturally are employed. However, studies on microreactors used for this purpose have been published to, for example, demonstrate proof-of-concepts in the removal of specific compounds.

Monochloroacetic acid is a compound that is difficult to remove by chemical degradation. Scialdone et al. (78) used a microfluidic cell with a BDD anode and graphite cathode to demonstrate the complete removal of monochloroacetic acid at flow rates around 0.3 mL/min.

A troublesome and emerging class of pollutants that are toxic for ecosystems are formed by pharmaceuticals secreted by humans and the veterinary industry. Even at low concentrations, these compounds can have detrimental effects on such areas as the drug resistance of microorganisms or the well-being of fish and other aquatic organisms. Brillas & Sirés (79) published a detailed review on this topic. The mechanism of electrochemical drug degradation is typically studied by coupling electrochemical reactors with analytical methods such as LC-MS, which is discussed in more detail in Section 3.5.

3.4. Artificial Kidney: Removal of Urea by Electro-oxidation

A special case of water treatment through the use of electrochemical microreactors involves regenerating dialysate in the development of an artificial kidney. A key challenge in this application is the removal of urea, as it is difficult to remove by adsorbing it to sorbents such as activated carbon. A recent review article by Simka and colleagues (80) gives an overview of other techniques to remove urea, which includes hydrolysis, enzymatic decomposition, and the use of biofilters

or strong oxidants. In the same review, the authors present an extensive overview of the various electrode materials used for urea decomposition, which include platinum, titanium, ruthenium, nickel, and multimetal combinations of these materials as well as with iridium, tantalum, and tin.

Wester et al. (81) have compared platinum, ruthenium oxide, and graphite electrodes in a parallel plate reactor designed for urea removal in dialysate. They found that platinum and ruthenium removed more urea compared to graphite. This is most likely due to enhanced catalytic activity of the metal electrodes toward the regeneration of reactive chlorine species and the subsequent reaction of these with urea. In contrast, the graphite electrodes produced less chlorine while maintaining decent urea removal ratios. More importantly, the authors reported the release of potentially toxic metal ions from the metal electrodes. A material that might be studied in more detail in the future for this application is BDD, as studied by Cataldo Hernández et al. (82) in batch cells. These authors showed that only BDD could completely decompose urea compared to other electrode materials such as platinum, titanium–ruthenium oxide, and antimony-doped tin oxide. Moreover, they observed significant differences in the formation of various nitrogen-containing reaction products.

3.5. Electrochemical Microreactors Combined with Mass Spectrometry

Electrochemistry and MS are a powerful combination for resolving a wide range of (bio)chemical analysis problems. This combined approach has been used to study reaction mechanisms, to detect compounds otherwise not ionized (83), to mimic the oxidative (drug) metabolism normally catalyzed by the cytochrome P450 enzyme family (84, 85), or to modify proteins in the field of proteomics (86, 87). We have recently reviewed the design aspects of microreactors for coupling to MS (57). In this review, we emphasize that microreactors for MS coupling need to demonstrate a high turnover rate to be able to detect reaction products at low abundance. As most miniaturized designs resemble a thin-layer configuration, we have introduced the thin-layer plate number to objectively assess the performance of electrochemical microreactors with respect to turnover rates. Moreover, we stress that specific attention should be focused on the choice of materials to prevent adsorption of proteins, for example, or to avoid incompatibility with commonly used solvents such as acetonitrile. A specific advantage of using microfluidics is that it can detect short-living compounds if dead volumes are carefully reduced (62). Because we included a summary of published miniaturized cell designs in our earlier review (57), we therefore only discuss some recent developments since 2015 here.

A disposable and cheap microreactor to study the phase-2 metabolism of acetaminophen and dopamine with glutathione was demonstrated recently using commercially available DropSens electrodes and polycarbonate microfluidic chips made by micromilling (see **Figure 6*a***). The costs of the resulting device were less than £5, thus meeting one of the demands from industry to deliver disposable devices to enhance reproducibility. However, the simplicity of the device likely did not warrant high turnover rates or separation of the products from working and counter electrodes; these issues were not discussed by the authors.

We have recently developed a microfluidic chip with high-quality integrated BDD electrodes and 5-μm-high microfluidic channels (89) (**Figure 6*b***). Counter and working electrodes are separated into two compartments, and the overall volume of the chip was ∼160 nL. Mixing two liquids in microfluidic chips in a thin-layer flow-through cell configuration is not trivial. A novel micromixer based on rotating the gradient profile between two liquids was demonstrated, as shown in **Figure 6*c***. The mixing efficiency was measured to be more than 80% in a mixing volume of 790 pL in 24 ms. This novel device was used to generate reactive metabolites from xenobiotics. Moreover, our group showed that these reactive metabolites can modify proteins such as

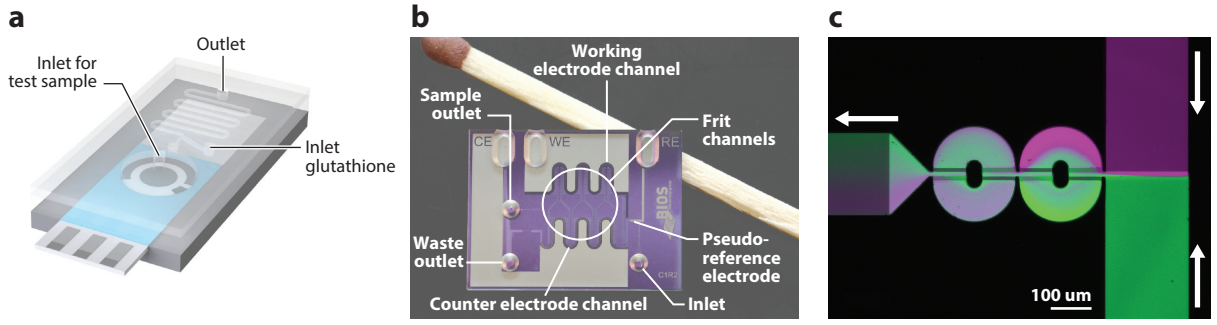


Figure 6

(*a*) Inexpensive and disposable electrochemical microreactor based on commercially available DropSens electrodes and a micromilled polycarbonate chip. Adapted from Reference 88 with permission from MDPI. (*b*) Boron-doped diamond, 3-electrode electrochemical microreactor with 160-nL internal volume. Working electrodes and counter electrodes are placed in two separate channels, whereas a dense array of small frit channels provides sufficient conductivity. Adapted with permission from Reference 90. Copyright 2016, American Chemical Society. (*c*) A 790-pL volume/24-ms gradient rotation micromixer, employing a rotation of the diffusion profile normally present between ceiling and bottom of the microfluidic channel in thin-layer flow cells. Adapted from Reference 89 with permission from the Royal Society of Chemistry.

β-lactoglobulin A. This demonstrates that this microreactor can potentially be used to predict hazards from exposure to environmental pollutants, such as xenobiotics.

The same chip was also used to cleave proteins electrochemically at the C-terminal side to tyrosine and tryptophan (90), which represents an attractive alternative to tryptic digestion that was previously demonstrated in large-scale cells by Permentier and coworkers (91). The oxidative cleavage of bovine insulin and chicken egg white lysozyme was successfully identified by subsequent LC-MS detection. BDD is particularly useful in this application to prevent adsorption of the proteins to the electrode surface. Moreover, we have recently observed that disulphide bonds of insulin could also be reduced electrochemically (92). This opens up exciting opportunities for fully instrumental protein fragmentation, an alternative to the traditional proteomics workflow based on chemical disulphide bond reduction and tryptic digestion.

4. CONCLUSIONS AND PERSPECTIVES

In this review, we have discussed developments in nanoscale electrochemical sensing, including the use of nanoparticles, carbon nanotubes, and graphene; nanoscale redox cycling; nanowire ISFETs; and high-frequency nanocapacitive imaging and heterodyne sensing. Moreover, we discussed microreactor technology for use in (drug) synthesis, biocatalysis, and water and dialysate treatment, and its applications in analytical chemistry, such as drug metabolism and proteomics. We would like to end this review by discussing conclusions and future perspectives.

4.1. The Future of Nanosensing

We see the future of nanosensing development being driven by two forces, namely, the quest for fundamental insight and the wish to develop commercially relevant applications. From the fundamental side, the novel and exciting developments using high-frequency measurements, such as the CMOS nanocapacitive array and heterodyne sensing, show great promise. Yet, further research is required for these methods to become practical for real-world sensing applications.

The nanocapacitive or nanowire array could surely be the next-generation technology for DNA sequencing or the study of viruses and proteins.

On the application side, we see a future in which sensors in food, health, and wellness are used in smartphones as well as wearables, including watches and clothing (93). Moreover, new sensors are required in the Internet of Things, for example, to realize the promise of a refrigerator that can alarm you to either eat your vegetables now or throw them away tomorrow. After all, a simple near-field communication chip that only communicates the product's expiration date will not always give a good indication for product freshness. To fulfill the promise of wearable sensors or sensors in the Internet of Things, two hurdles need to be overcome.

First, it is of utmost importance to deliver cheap and high-quality sensors. Consider global positioning system (GPS) trackers as an analogy: GPS navigation only became accepted by the general public in smartphones after the technology was mature enough to work quickly and reliably and at acceptable rates of power consumption. From that aspect, the points raised by Kissinger in 2005 (94) are still very much relevant 12 years later: The field needs to push itself harder to publish high-quality articles; for example, it is important to demonstrate more than just a proof-of-concept sensor used only in aqueous buffer while the real application requires a much more hostile or dynamic environment.

The second factor that is important for widespread adaptation is to find highly relevant applications with significant real-world impact. Another example from the microelectromechanical systems field illustrates this well: A barometer was not included in smartphones until it became apparent that they can help determine altitude for faster global positioning or for in-building navigation. We do not have a clear sense of what will be relevant applications in electrochemical sensors for wearables or the Internet of Things. However, we predict that the applications will likely be noninvasive, and the sensors will be produced in large volumes.

4.2. Microreactors: In Situ Observations of Electrochemical Processes

Thus far, the research focus on microreactors has mainly been to synthesize sufficient product with subsequent analysis by other equipment off-line or downstream from the reactor. We see a future involving the integration of in situ monitoring of these electrochemical conversions to better track the reaction conditions both spatially and chronologically. Another driving factor is that this integration facilitates fundamental studies of the reaction mechanisms occurring at the electrode surface. Creating such devices would require careful design of the microreactor to allow such steps as optical probing. A potentially attractive method would integrate waveguides or fibers to allow UV, visible, or infrared spectroscopic readout. Interesting developments are also ongoing in the local and in situ monitoring of electrochemical reactions by MS, as recently discussed in a short review by Lu et al. (95). These new techniques offer unique opportunities to unravel reaction mechanisms at nanometer-length scales and at microsecond timescales.

These new hybrid techniques will surely attract more interest in the near future for various fields of study. These possibly include the on-site synthesis of pharmaceuticals (96) and the artificial kidney (81). The most promising area can be found in the field of electrocatalysis, as there are currently increased research efforts to search for catalysts that generate solar fuels. In all of these fields, spectroelectrochemical reactors will surely be an exciting and welcome technological development in the next decades.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Errata

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