

Grand challenges in nanomaterial-based electrochemical sensors

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Electrochemical sensors have an enormous potential in a wide variety of environmental, industrial, and medicinal applications. Apart from the immense success of glucose sensors, much more work is still needed in order to make electrochemical sensors have a widespread impact and application. For example, the current circumstances of the COVID-19 pandemic demonstrated the importance and urgency of having accurate and rapid diagnostic devices ([Jiang et al., 2020](#)). The advancement of sensors could truly help stop the spread of many infectious diseases ([Vermisoglou et al., 2020](#)) and detect the early onset of various illnesses such as neurodegenerative diseases ([Kim et al., 2020](#)). Compared to other diagnostic tools currently available, electrochemical sensors have many advantages such as low-cost, rapid and real-time detection with simple operation ([Idili et al., 2019](#) ; [Ligler and Gooding, 2019](#)). They can also be mass-produced and miniaturized into portable devices ([Li et al., 2017](#) ; [Idili et al., 2019](#) ; [Ligler and Gooding, 2019](#)).

The number of research groups reporting the development of novel electrochemical sensors is growing exponentially. Most of the reported sensors have carbon- and gold-based surfaces. These surfaces are popular amongst researchers because they are stable, biocompatible, and provide good electron transfer kinetics. Unfortunately, the unmodified surfaces often lack the sensitivity and selectivity required for the electrochemical detection of trace analytes. To overcome this challenge, nanomaterials have been incorporated within the electrode surfaces ([Quesada-González and Merkoçi, 2018](#) ; [Muniandy et al., 2019](#)). Nanomaterials range from 1-100 nm in size and are extremely beneficial due to the large surface-to-volume ratio and

surface area ([Quesada-González and Merkoçi, 2018](#) ; [Muniandy et al., 2019](#)). Modification of nanomaterials on sensor surfaces allows them to have enhanced interfacial adsorption with improved electrocatalytic activity, biocompatibility, and faster electron transfer kinetics. All these advantages give the sensor a better selectivity and sensitivity toward the detection of specific analytes as well as a superior overall performance ([Quesada-González and Merkoçi, 2018](#) ; [Ligler and Gooding, 2019](#) ; [Muniandy et al., 2019](#) ; [Jiang et al., 2020](#) ; [Kim et al., 2020](#) ; [Vermisoglou et al., 2020](#)).

Recently, some of the most reported nanomaterials used in the fabrication of electrochemical sensors have been different forms of graphene, such as graphene nanoribbons ([Ismail et al., 2017](#)) and graphene flowers, which allow for good conductivity and fast electron transfer rates ([Ismail et al., 2017](#) ; [Quesada-González and Merkoçi, 2018](#) ; [Muniandy et al., 2019](#) ; [Jiang et al., 2020](#) ; [Vermisoglou et al., 2020](#)). Carbon nanotubes (CNTs) have extraordinary metallic/semiconducting properties, which significantly enhance the electrocatalytic performance of sensors ([Musameh et al., 2002](#) ; [Banks et al., 2006](#) ; [Sljukic et al., 2006](#)). Metallic nanoparticles and quantum dots possess remarkable conductive and optical properties that give a higher sensitivity to electrochemical sensors ([Ismail et al., 2017](#) ; [Ponnaiah et al., 2018](#) ; [Ligler and Gooding, 2019](#)). Although nanomaterials have been proven to be remarkably valuable in sensors, their synthesis as well as visual and chemical characterization often require skilled technicians to operate the sophisticated instrumentation. As for metallic nanoparticles and quantum dots, a common challenge is maintaining the stability of these materials, because they are prone to aggregation along with sensitivity to

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environmental factors such as thermal heating, UV exposure and ionic strength of aqueous media. Efforts to overcome this problem often involve the synthesis of core-shell structures and capping with stabilizing agents in order to preserve the colloid from aggregating or degrading. Similarly, researchers frequently try to control the configuration of the ligand shells to protect quantum dots from degradation ([Ismail et al., 2017](#) ; [Ponnaiah et al., 2018](#) ; [Quesada-González and Merkoçi, 2018](#)).

Briefly, the biggest challenges encountered in the development of electrochemical sensors can be listed as follows: (1) obtaining a low limit of detection (LOD); (2) suppressing the non-specific adsorption of interfering species, and (3) maintaining the reproducibility and stability of the sensor in complex real matrices.

An essential property to investigate when developing an electrochemical sensor is the LOD. This value entails the lowest concentration or quantity of a specific analyte that can be reliably detected within an acceptable signal-to-noise ratio. Developing a sensor with a low LOD is crucial because often analytes exist at trace concentrations in real samples. Due to the innovation of nanomaterial-modified surfaces, LODs with values as low as picomole and femtomole levels have been achieved in the case of some ultra-sensitive sensors ([Suherman et al., 2017](#) ; [Li X. et al., 2018](#) ; [Ponnaiah et al., 2018](#) ; [Alizadeh et al., 2019](#) ; [Wu et al., 2019](#) ; [Gupta et al., 2020](#)). For example, a sensor modified with open-ended CNTs was reported to have picomolar levels of sensitivity for the detection of neurotransmitters ([Gupta et al., 2020](#)). An ultrasensitive sensor for the detection of Hg^{2+} was developed by

modification of a glassy carbon electrode with silver nanoparticles resulting in picomolar level LOD values ([Suherman et al., 2017](#)). Yet, these modified surfaces remain challenging as they are not often as reproducible as one would hope. For example, since it is difficult to control the synthesis and immobilization of nanoparticles with varying populations of size and shape, the conformation and topology of these nanomaterials might differ between each sensor ([Wu et al., 2019](#)). In addition, as mentioned previously, nanoparticles tend to alter their behavior under varying environmental conditions. The trade-off associated with increased complexity of the modified surfaces is the reproducibility issues that unfortunately arise. Sensor-to-sensor reproducibility is extremely important in the manufacturing stages since it is not feasible to test every sensor produced in mass-production facilities. Instead, once the sensors are fabricated, statistical sampling of a sub-population of the sensors is performed, and the testing and calibration results should be applicable to the entire batch.

Arguably, the most important test to confirm the validity of a sensor is the “real sample” application. If the sensor is not stable or functional in real samples then it cannot be validated as a diagnostic tool. A wide variety of real samples are often used with electrochemical sensors, the most common ones being urine, blood serum, sweat, saliva, tear, and interstitial fluid ([Li et al., 2017](#) ; [Lipani et al., 2018](#) ; [Tseng et al., 2018](#) ; [de Castro et al., 2019](#) ; [Idili et al., 2019](#) ; [Karpova et al., 2019](#) ; [Sempionatto et al., 2019](#) ; [Azeredo et al., 2020](#) ; [Baghelani et al., 2020](#)). The matrix effect tends to negatively interfere with the detection of a specific analyte which lowers the recovery values and the sensitivity of the sensor. To help overcome the matrix effect,

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researchers frequently dilute the samples in order to shift the effect of interferences below a tolerable threshold. However, the more the sample is diluted, the further it is from reality. Ideally, sensors should be able to function effectively in pure real samples such as whole blood without any sample dilution or processing ([Li et al., 2017](#)). Saliva samples are also quite rich and complex and often need filtration or dilution to be successfully be used as a real sample ([de Castro et al., 2019](#)). For urine samples, the main challenge is the different pH ranges found which can impact the position of peak potential and the height of current intensity as well as cause stability issues ([Azeredo et al., 2020](#)). Tear fluid has also recently gained significant interest because it has lower complexity with easy access for non-invasive sampling techniques. Tear fluid is often used to investigate the progression of ocular diseases and diabetes ([Tseng et al., 2018](#) ; [Sempionatto et al., 2019](#)). Some disadvantages with tear fluid include that the pH can vary, the sample volume is low and the tears from emotion and irritation may differ in composition ([Tseng et al., 2018](#) ; [Sempionatto et al., 2019](#)). Real samples often contain many species that can easily adsorb onto the surface. Non-specific adsorption has been one of the main roadblocks against utilizing electrochemical sensors in real-life applications because it tends to significantly decrease sensitivity, specificity, and reproducibility of the sensors. In the point-of-care, researchers are tackling this challenge with innovative materials and methods to improve sensor performance ([Li Y. et al., 2018](#) ; [Lichtenberg et al., 2019](#)). Both passive and active methods have been used. Passive methods aim to create a hydrophilic and non-charged layer to obstruct protein adsorption on the surface by using different organic

materials such as polymers. Conversely, the aim of active methods is to produce surface shear forces that are stronger than the adhesion forces of the bound non-specific biomolecules on the surface ([Li Y. et al., 2018](#) ; [Lichtenberg et al., 2019](#)).

Notably, the stability of sensors has also been a challenge limiting their applications in remote locations under varying temperature conditions. Sensors are often characterized by their shelf-life; hence, it is important to develop sensors that can work for a relatively long period of time. When using nanomaterials, long-term stability might become a major concern due to issues related to aggregation and flaking of nanomaterial-modified layers. Recently, incorporation of sol-gel materials and ceramics along with nanomaterials has been proven to increase the stability of sensors ([Kim et al., 2018](#) ; [Li et al., 2019](#) ; [Meng et al., 2020](#)). Moreover, designing sensors that are stretchable, self-healing, water-processable and wearable has recently been a major advancement in the sensing field ([Kim et al., 2018](#) ; [Li et al., 2019](#) ; [Meng et al., 2020](#)). These types of miniaturized sensors, which have great stability, are often made with rubber-like composites, hydrogels, organogels and novel polymers. Combining these highly stretchable materials with the excellent electrical conductivity of nanomaterials makes for remarkable sensors with superior analytical performance characteristics ([Kim et al., 2018](#) ; [Li et al., 2019](#) ; [Meng et al., 2020](#)).

Electrochemical sensors have demonstrated a great potential for the future of diagnostic tools. However, the challenges outlined above, not only apply for clinical applications, but also across other fields such as environmental

monitoring, food safety, forensic analysis, agriculture, defense, and military applications as well as electronics industry. Fortunately, the breakthrough created through the applications of nanomaterials represents a significant advancement that impacts across all the fields mentioned above. To continue advancing in the right direction, it is important for researchers to keep on developing innovative solutions in order to introduce more smart sensors in our everyday life.

Author Contributions

CF wrote the original draft of the manuscript. KK revised and edited the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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