Review: Electrochemical DNA sensing – principles, commercial systems, and applications

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Abstract
Driven by the vision of robust and portable, yet sensitive DNA detection systems for point-of-need applications, the development of electrochemical DNA sensing principles has been of high interest. Many different principles have been developed and these are regularly reviewed. However, the maturity of electrochemical principles and their ability to produce competitive real-world applications is rarely assessed.
In this review, general electrochemical DNA sensing principles are briefly introduced and categorized into *heterogeneous* vs. *homogeneous* approaches, and then the subcategories *label-free* vs. *labeled* and *reagent-less* vs. *reagent-dependent* principles. We then focus on reviewing the electrochemical sensing principles implemented in DNA detection systems, which are commercially available or close to market entry, considering the complete analysis process, automation and the field of application. This allows us to outline and discuss which principles have proved suitable for which kinds of applications, as well as the stage of integration and automation.
Examples from all the identified categories of electrochemical DNA sensing principles have found application in commercial detection systems or advanced prototypes. Various applications have already been demonstrated, ranging from on-site skin care testing, to food safety to the most frequent in vitro diagnostic tests, partially conducted in automated sample-to-answer devices.
Our review is intended to enable researchers in areas related to electrochemistry, biochemistry or microfluidics to assess the commercial state of the art of electrochemical nucleic acid testing, and the interdisciplinary challenges for further improvements.

Keywords: biosensors, electrochemistry, nucleic acids, molecular diagnostics, sample-to-answer

1. Introduction

Electrochemical detection of nucleic acids (NAs), an alternative to the more common optical or early radiological detection methods, has been of high interest – not only for the scientific community, but also for the electronics, semiconductor and medical devices industries. Especially during the genome hype at the turn of the millennium, publications testify to companies' interest in exploiting promising applications of their technologies. An obvious advantage of electrochemical over optical biosensing is the circumvention of optical elements such as light sources, filters, mirrors or lenses. In electrochemical biosensing, electric signals can be generated directly at the electrode, allowing seamless integration with downstream electronics and data processing. Electrochemical biosensing principles allow the realization of small, robust and cost-efficient multianalyte biosensing devices with a broad range of applications, far beyond glucose sensing, which was successfully commercialized in 1975 (Turner 2013; Yoo and Lee 2010). The small size of electrochemical biosensors renders them extremely attractive for mobile applications at the point of need, in particular for infectious disease testing, companion diagnostics, veterinary diagnostics and food testing (Martín-Fernández et al. 2017; Niemz et al. 2011).
Multiple electrochemical sensing principles for NAs have been developed. Several reviews exist have been carried out to examine different aspects of the sensing principles including fundamental DNA electrochemistry (Ferapontova 2017, 2018; Paleček and Bartošík 2012), applications (Campuzano et al. 2017; Patterson et al. 2013; Yu et al. 2017) and miniaturization opportunities (Blair and Corrigan 2019). Our novel review has a special focus on NA detection systems that are currently commercially available or close to market-entry, as well as on these systems' underlying sensing principles, which can be considered a selection of those of principles that have proven particularly advantageous in terms of robustness, maturity and competitiveness. In chapter 2 these sensing principles are systematically categorized into *homogeneous* vs. *heterogeneous* principles, and further subcategorized into *label-free* vs. *labeled* and *reagent-less* vs. *reagent-dependent* principles, following IUPAC standards.
The sensing principles found in commercially available NA detection systems are explained in more detail in chapter 3, together with a brief description of their history, their analysis process and their field of application.
In chapter 4, the status of the reviewed systems is compared and discussed in terms of maturity, degree of automation, portability and competition with optical systems.

2. Basic principles of electrochemical NA detection

This chapter gives a systematic, hierarchical structure of the principles used in electrochemical NA sensing, which is mainly based on recommendations provided by the International Union of Pure and Applied Chemistry (IUPAC) (Labuda et al. 2010), and is extended by additional categories.
The top level divides into *homogeneous* vs. *heterogeneous* sensing. In *heterogeneous* sensing, recognition elements concentrate the analyzed NAs at the surface of an electrode, whereas in *homogeneous* detection the NAs interact with recognition elements in solution.
In the following sections, these two categories are sub-divided into combinations of *label-free / labeled* and *reagent-less / reagent-dependent*. Label-free means that none of the involved NA molecules (targets or probes) are chemically modified with, e.g., an electroactive-molecule. Reagent-less means that no additional molecules that contribute directly to the signal generation are introduced.

2.1 Heterogeneous detection

Heterogeneous NA sensing approaches are based on electrodes functionalized with capture probes. These capture probes are typically synthetic, single-stranded deoxyribonucleic (DNA) or peptide nucleic acid (PNA) probes, often termed oligonucleotides. Hybridization of a target molecule to the capture probe leads to several changes at the electrode surface that can be used for hybridization detection. Firstly, there is an increase in negative charge at the electrode due to the negatively charged backbone of DNA. Secondly, there is a change in conformation from a coiled, single-stranded capture probe to a stretched, double-stranded duplex of probe and target NA. Thirdly, in contrast to the single-stranded probe, the pi-stack of its duplex with the target NA becomes conductive (Kelley et al. 1999; Kelley and Barton 1999), and electrons from intercalating or well-coupled electroactive molecules can be conducted through the duplex, even from its distant end, to the electrode (Gorodetsky et al. 2007; Inouye et al. 2005). Mismatches in the duplex hinder electron transfer, making the method sensitive to single nucleotide polymorphisms (SNPs) (Inouye et al. 2005; Kelley et al. 1999).

2.1.1 Label-free, reagent-less detection

The conformation change and the additional charge that accumulates at the electrode surface due to the hybridization of NAs can be measured directly as a change in capacitance (Berggren et al. 1999) or in charge transfer resistance (Berdat et al. 2008). The change in capacitance can be explained by the displacement of counterions from the surface.
Alternatively, field effect transistors (FET) can be used to detect the hybridization reaction (Souteyrand et al. 1997). Capture probes are immobilized on top of the insulated gate. The charges of the NA strands that accumulate at the gate

Table 1: Categories of electrochemical NA sensing principles.

	Label-free, reagent-less	Label-free, reagent-dependent	Labeled, reagent-less	Labeled, reagent-dependent
Heterogeneous detection	• Change in capacitance • Change in impedance • Field-effect	• Intercalation • Groove-binding • Electrostatic binding • Electrostatic repulsion	• Labeled capture probes • Labeled signaling probes • Labeled nucleotides	• Enzyme labels
Homogeneous detection	• Detection of NA amplification by-product with ISFET	• Consumption of electroactive molecules by interaction with NA	• Release of electroactive molecules	• No principle known
Advantages	• Cost-effective reagents possible	• Enhanced signals	• Specific signal	• Signal amplification
Drawbacks	• Low signals • Risk of unspecific signal changes	• Risk of unspecific signal changes	• Modification of oligonucleotide increases costs	• Additional process steps complicate automation

influence the charge-depleted region of the underlying semiconductor, which can be measured as a change in capacitance or conductivity (Fritz et al. 2002; Huang et al. 2015).
At nanogap electrodes, the hybridization of target NA can bridge the gaps and lead to an increase in conductivity (Zaffino et al. 2014).

2.1.2 Label-free, reagent-dependent detection

The addition of electroactive molecules that interact with the hybridized NA enhances the signal change.
Anionic and cationic electroactive molecules interact electrostatically with the negatively charged NA backbone. The additional charges of hybridized strands thus lead to an increased charge resistance due to repelled anionic molecules (Katz and Willner 2003), or to an enrichment of cationic molecules (Steel et al. 1998).
Other electroactive molecules interact preferentially with double-stranded NAs by binding to a groove or intercalating into the stacked base-pairs (Hashimoto et al. 1994; Millan and Mikkelsen 1993).

2.1.3 Labeled, reagent-less detection

Capture probes, signal probes and nucleotides can all carry an electroactive label.
A label's distance from its capture probe changes upon hybridization, resulting in a change in electron transfer rate (Fan et al. 2003). Signal probes are additional target-specific hybridization probes that can enrich at the electrode in a sandwich-type approach, or can compete for binding sites with target and capture probes (Umek et al. 2001). As an additional alternative, labeled nucleotides can be incorporated during amplification of the target NA (Wlassoff 2002; Yeung et al. 2006).

2.1.4 Labeled, reagent-dependent detection

Enzymatic labels like, e.g., alkaline phosphatase or peroxidase, require the addition of a substrate for the catalytic generation of detectable products (Lumley-Woodyear et al. 1996).
To further increase sensitivity, redox (re-)cycling can be achieved using interdigitated electrodes with typical distances between the electrode fingers of 1 µm and below (Schienle et al. 2004). While one set of electrode fingers is held at reduction potential, the second set is held at oxidation potential, so that a single redox molecule can undergo redox reaction multiple times. This method can generally be used for the sensitive detection of diffusing redox molecules, but is most often used with enzymatic labels like those mentioned above.

2.2 Homogeneous detection

Homogeneous electrochemical NA detection typically involves the release or consumption of electrochemically detectable molecules. The approaches can be subdivided analogously to the heterogeneous approaches. However, to the best of our knowledge there are not yet any examples of labeled, reagent-dependent principles.

2.2.1 Label-free, reagent-less detection

During the amplification of NAs, the incorporation of one nucleotide into the strand leads to the release of one pyrophosphate molecule and one proton. The change in proton concentration can be measured as a pH shift by an ion-sensitive field effect transistor (ISFET) (Pourmand et al. 2006; Purushothaman et al. 2002; Sakurai and Husimi 1992).

2.2.2 Label-free, reagent-dependent detection

Initially freely diffusing electroactive molecules interact with double-stranded NAs. As a result, the diffusion coefficient of these "consumed" molecules decreases, and a reduced signal is measured (Deféver et al. 2009).

2.2.3 Labeled, reagent-less detection

Electroactive molecules can be released from a complex if an NA probe unfolds due to hybridization to the target NA (Aoki et al. 2010; Baek et al. 2019). Furthermore, electroactive molecules can be released through the degradation of a probe upon hybridization due to nuclease activity (Pearce et al. 2011; Xuan et al. 2012). In an alternative approach, uncharged, labeled PNA probes that do not respond to electrode polarization before hybridization are used. Upon forming a duplex with the charged target NA, the duplex is attracted or repelled, depending on the polarization of the electrode (Luo et al. 2008).

3. Commercial NA detection systems using electrochemical NA sensing

Fig. 1. Images of some of the reviewed commercial electrochemical NA detection systems in order of their appearance in the text. A: Cubed Laboratory's NESDEP instrument (copyright: Cubed Laboratory) B: Canon's Genelyzer II instrument (copyright: Canon Medical Systems Corp.) D: GenMark's ePlex instrument (four tower version shown – the device can also be equipped with fewer towers, copyright GenMark Diagnostics Inc.) E: Friz Biochem's envisioned Cycle device (copyright: Friz Biochem GmbH) F: CustomArray's ElectraSense reader (copyright: Custom Array Inc.) F: Elice's Leo instrument (copyright: Easy Life Science) G: Binx's io instrument (copyright Binx Health Inc.). The images are not to scale. All images are published with the permission of the respective companies.

Since the beginning of the 21st century, different electrochemical NA detection systems, especially for pathogen testing, have come to maturity and are now commercially available. This chapter gives a brief description of these commercial systems, their underlying sensing principles, and their application. An overview of the reviewed commercial electrochemical NA detection systems can be found in Table 2. Systems for nanopore (Deamer et al. 2016) and semiconductor sequencing (Shendure et al. 2017) are excluded, as these have been reviewed elsewhere.

The reviewed commercial NA detection systems that rely on *heterogeneous* detection principles are those from Cubed Laboratories, Canon, GenMark, CustomArray and GeneFluidics. Companies with products in a pre-market state are General Atomics and Friz Biochem (Fig. 1 A – E).

Homogeneous detection principles are used in the systems of DNA electronics and Binx, and in the prototypes of Easy Life Science (Fig. 1 F – G).

The chapter is structured according to the sensing principles introduced above. The history of each commercial NA detection system is briefly elucidated. Then the sensing principle is illustrated, and the analysis process is described. Finally, available applications are outlined.

3.1 Heterogeneous, label-free, reagent-less approaches

NA detection systems using label-free sensing principles are advantageous because labeling requires either additional process steps or the modification of NA probes. On the other hand, label-free, reagent-less measurements, namely the measurement of capacitance, impedance, or charge-transfer resistance, are challenging due to the small, specific signal changes involved, and the risk that unspecific adsorption processes could contribute to the signal changes in an unpredictable way. Elimination of this risk demands measures, like e.g. stringent washing procedures, an electrode preparation of high quality and reproducibility and ideally the implementation of an additional control electrode (functionalized almost identical to the sensing electrode, but lacking the target-specific capture probe) to correct for unspecific drifts (Riedel and Lisdat 2018).

3.1.1 Cubed Laboratories (formerly F Cubed)

3.1.1.1 History and sensing principle

Cubed Laboratories, founded in 2010, has implemented in its NESDEP® device a label-free principle that was initially developed at the University of Notre Dame, whose earliest activities relating to this principle are documented in patent applications from 2003.

The sensing principle and its performance is described in (Basuray et al. 2009). The sensor consists of interdigitated electrodes integrated into a flow cell (Fig. 2). Carbon nanotubes (CNTs) are functionalized with capture probes for the hybridization of target NAs. The electrodes are used not only for detection by impedance measurement, but also to create an AC electric field for dielectrophoresis (DEP). The AC field induces a dipole in charged particles like CNTs and NAs. This dipole is used to trap the CNTs at the electrodes and to accelerate NA hybridization. The analysis process comprises the following steps: first, a baseline is recorded by performing an impedance measurement in washing buffer. Then, a mixture of sample (PCR product) and hybridization buffer is introduced for hybridization. Finally, a washing step is performed with washing buffer, in which the subsequent impedance measurement is also performed. A change in charge transfer resistance indicates a positive hybridization event. Measurements are always performed at a constant flow rate, which has several advantages. First, weakly adsorbed or hybridized NA strands which are non-complementary or feature mismatches are sheared off. With this system, specific differentiation of NA sequences that differ in three nucleotides (Basuray et al. 2009) or even better (Cheng et al. 2010) is possible. Second, the influence of double-layer capacitance on the measurement is reduced (Basuray et al. 2009).

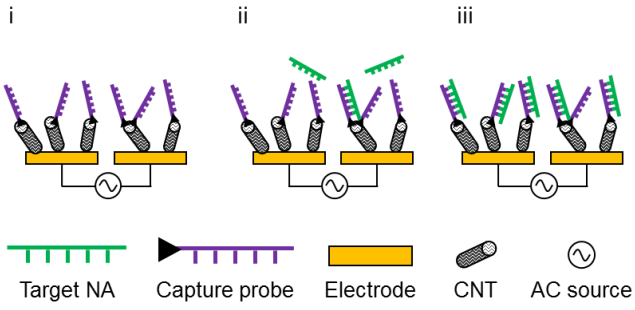

Fig. 2. Heterogeneous, label-free, reagent-less sensing principle. Cubed laboratories use interdigitated electrodes and functionalized CNTs for NA detection. Initially, a baseline impedance measurement is performed (i). Then the single-stranded product of an asymmetric PCR mixed with hybridization buffer is hybridized to the CNT-bound capture probes (ii). After washing with measurement buffer, another impedance measurement is performed (iii). All steps are performed while applying an AC field for dielectrophoresis, which supports specific hybridization.

3.1.1.2 Analysis process and instrumentation

The NESDEP® system (Fig. 1 A) includes modules for all the process steps necessary to analyze a liquid sample (min. 50 mL): sample concentration, homogenization and lysis, two modules for PCR, and one detection module. Single-stranded nucleic acids for the hybridization reaction are obtained using asymmetric PCR, with forward and reverse primers added in different concentrations. Once the primer at lower concentration becomes depleted, the primer in excess is further extended without its corresponding counter-strand. The single-stranded DNA amplicon is then separated from the double-stranded NA by magnetic capture beads. Automated liquid handling is realized by an integrated vacuum source. However, manual interaction is required to transfer the sample between the system's different modules. The complete analysis process requires less than 90 minutes, but the two amplification modules allow new samples to be loaded every 45 minutes.

3.1.1.3 Application

Cubed Laboratories focusses on food safety testing. Available test kits cover *Escherichia coli* O157, *Listeria*, *Salmonella* and *Campylobacter* (Cubed Laboratories). Assays for other applications are in the pipeline. The results of pre-clinical trials for MRSA detection are shown in their whitepaper (Cubed Laboratories 2018). Multiplexing can be realized by electrophoretic sorting of differently sized nanoparticles (Chang et al. 2008). However, information about the degree of multiplexing and performance studies are not available.

3.2 Heterogeneous, label-free, reagent-dependent approaches

The utilization of electroactive molecules for electrochemical NA detection leads to signal changes that are typically higher and more specific than those of label-free detection principles. The approach is relatively simple if the electroactive molecules only interact with double-stranded target NAs, either by intercalation or by electrostatic bonding. However, this interaction is unspecific, i.e. the molecules can also interact with non-target NAs, such as capture probes and unspecific amplification by-products.

The two approaches reviewed in the following both rely on cationic electroactive molecules that interact with the backbone of NAs. It is worth noting that both approaches rely on PNA capture probes rather than DNA probes. PNA capture probes feature a neutral backbone, which leads to several advantages for hybridization-based detection principles (Wang et al. 1996). One of the most important advantages is that cationic electroactive molecules do not interact with the PNA capture probe, and so the background signal can be reduced.

3.2.1 Canon Medical Systems (formerly Toshiba Medical)

3.2.1.1 History and sensing principle

Toshiba's first publication related to electrochemical DNA sensing dates back to 1993 (Hashimoto et al. 1993). Ten years later, a system called Genelyzer™ was introduced, followed by the Genelyzer™ II (Fig. 1 B) in 2015. Both systems rely on immobilized capture probes on the sensing electrodes (Hashimoto and Ishimori 2001), to which the target NA is hybridized. Hybridization is followed by a washing step to remove nonspecifically bound DNA. Then, the electrodes are incubated with the electroactive molecule Hoechst 33258, which binds to the minor groove (Hashimoto et al. 1994). The enrichment of the electroactive molecules is detected by linear sweep voltammetry.

While the initial system was capable of performing just the steps from hybridization to detection, the Genelyzer™ II also includes a step for the amplification of target DNA and pre-stores the required reagents, as described in broad outline in (Okada 2012).

3.2.1.2 Analysis process

NA amplification is achieved with loop-mediated isothermal amplification (LAMP) (Notomi et al. 2000), which has two main advantages over PCR. First, no thermocycling is required. Instead, the reaction volume is heated to about 60 °C for the duration of the reaction. This enables less elaborate instrumentation, fast amplification, and high yield (Zhang et al. 2014). Second, as LAMP products contain single-stranded loop regions, these regions can hybridize directly to the capture probes (Fig. 3 A).

The combination of LAMP with the electrochemical detection of single-nucleotide polymorphisms (SNPs) (Nakamura et al. 2007), as well as with copy number variant detection (Nakamura et al. 2010), has been demonstrated, and a method that allows the analysis of multiple samples with one electrochemical analysis chip (Nakamura et al. 2011) has been developed.

3.1.1.3 Instrumentation and application

After the official launch of the instrument, Toshiba collaborated with different research institutes to demonstrate its versatility. Commercially distributed assays for the early Genelyzer™ instrument targeted human papillomavirus (HPV) detection (Clinichip® HPV) and helicobacter screening (Monigene™) of laboratory animals (Duangchanchot et al. 2014), while those for the Genelyzer™ II targeted bovine respiratory disease detection (up to 9 targets) and rice identification (21 markers to differentiate between 310 rice types). Studies evaluating performance exist mainly for the HPV test (Nilyanimit et al. 2018; Satoh et al. 2013; Torii et al. 2016; Yamada et al. 2015).

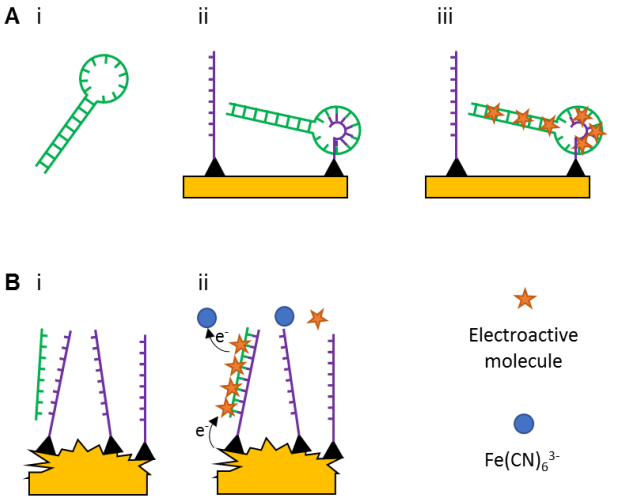

Fig. 3. Heterogeneous, label-free sensing principles that require the addition of electroactive molecules as indicators. A: Canon detects LAMP products (i). Upon mixing with hybridization buffer, the single-stranded loop region of the product can hybridize to the capture probe (ii). After hybridization, the electrodes are washed and then incubated with electroactive molecules, which intercalate into double-stranded DNA (iii). B: Xagenic immobilizes PNA capture probes on nanostructured microelectrodes. Extracted NAs hybridize to the probes (i) and become detectable by their electrostatic interaction with electroactive Ru^{3+}. The reduction signal of Ru^{3+} is electrocatalytically amplified by the presence of $Fe(CN)_6^{3-}$, which oxidizes the reduced Ru during the measurement procedure (ii).

3.2.2 General Atomics (formerly Xagenic)

3.2.2.1 History and sensing principle

Xagenic emerged from developments by Shana O. Kelley and her group at the University of Toronto in 2010. Due to bankruptcy at the end of 2017, Xagenic's assets were acquired by General Atomics. The original chip featured an array of specially shaped micro-electrodes. The fine nanostructures grown on the initially planar electrode increase the effective surface area and lead to beneficial conditions for the hybridization of target NAs to the PNA capture probes (Sage et al. 2014; Soleymani et al. 2009). After hybridization, a buffer containing the redox molecules $Ru(NH_3)_6^{3+}$ and $Fe(CN)_6^{3-}$ is introduced. $Ru(NH_3)_6^{3+}$ interacts electrostatically with the charged backbone of the target NA. The reduction signals of the enriched Ru^{3+} molecules are measured, while the $Fe(CN)_6^{3-}$ in the solution acts as an oxidant, enabling signal amplification through the regeneration and multiple detection of the ruthenium (Fig. 3 B) (Lapierre et al. 2003).

3.2.2.2 Analysis process and instrumentation

Xagenic developed prototypes (Fig. 1 C) for the direct detection of NAs without a prior amplification reaction. The cartridge provides the automated lysis and denaturation of the specimen and the subsequent detection without user interaction within 20 minutes (Xagenic Inc 2014).

3.2.2.3 Outlook

Whether this technology, or parts of it, are brought to market depends on General Atomics. In 2018, a project was started to develop a point-of-use device for biological threat testing in the field, which may use the developments of Xagenic as its basis (General Atomics 2018).

3.3 Heterogeneous, labeled, reagent-less approaches

As described above (2.1.3), there are several ways to introduce labels. Interestingly, the two principles described below both use a labeled signaling probe.

3.3.1 GenMark Diagnostics

3.3.1.1 History and sensing principle

The foundation for GenMark's electrochemical sensors was laid with studies of the electrical conductivity of double-stranded DNA (Meade and Kayyem 1995). Clinical Micro Sensors was founded for further development. This then became part of Motorola before it was traded to Osmetech, which was acquired by GenMark as part of a corporate reorganization. ~~renamed GenMark~~.

Their sensor chips contain electrode arrays that are functionalized with specific capture probes. To improve electron transfer through the functional layer, conductive so-called "molecular wires" are co-immobilized with the capture probe on the electrode surface (Creager et al. 1999). Prior to the hybridization reaction at the electrode surface, a signaling probe is hybridized to the targeted NA. The signaling probe is labeled with ferrocene (Umek et al. 2001) (see Fig. 4 A). The electrodes are then interrogated by alternating current voltammetry (ACV) (Creager and Wooster 1998).

The method has been demonstrated to be suitable for discriminating between point mutations either by using the melting temperature of the target capture probe hybrid (Umek et al. 2000) or by using two SNP-specific signaling probes that have different redox potentials (Yu et al. 2001). For the latter concept, the same capture probe can be used to discriminate between different alleles.

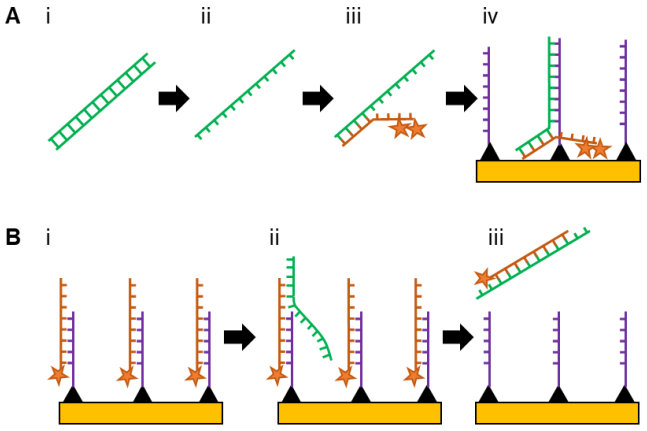

Fig. 4. Heterogeneous sensing principles relying on electroactive labels. A: For GenMark's approach, the double-stranded PCR products (i) become single-stranded via exonuclease digestion (ii). The ssDNA is labeled with a signaling probe (iii) and finally hybridized to the capture probe (iv). B: For FRIZ Biochem's EDDA principle, the signal probe is initially hybridized to the capture probe (i). Since the signal probe's affinity to the target NA is higher, the target NA can displace the signal probe from the capture probe (ii), leading to a decrease in the number of electroactive molecules in the proximity of the electrode surface (iii).

3.3.1.2 Analysis process, instrumentation and application

Two generations of sensors are currently commercially available. The older eSensor XT-8® is used for data acquisition and analysis only. All upstream steps are conducted off-chip. These steps include sample preparation and amplification, single-strand generation through enzymatic counter-strand digestion, and the addition of signaling probes. Six panels are available: a 14-plex respiratory panel (Pierce and Hodinka 2012; Popowitch et al. 2013; Ruggiero et al. 2014), cystic fibrosis genotyping covering 23 disease-related mutations (Johnson et al. 2007), a thrombophilia risk test and a warfarin sensitivity test (all FDA cleared), as well as the research use only hepatitis HCVg (Sam et al. 2013) and cytochrome P450 2C19 genotyping tests (Lee et al. 2011). These panels have been partially evaluated (and also compared to competitive commercial panels ((Babic et al. 2009; Johnson et al. 2007; Maurice et al. 2010; Popowitch et al. 2013; Ruggiero et al. 2014)) in studies by independent groups.

The new ePlex® system (FDA cleared in June 2017) is a true sample-to-answer system that performs DNA extraction and amplification, single-strand generation, and electrochemical detection on a single chip. Liquid transport within the cartridge is realized by electrowetting technology (GenMark). As of November 2019, four panels, targeting respiratory pathogens (Babady et al. 2018; Nijhuis et al. 2017; van Rijn et al. 2018) and sepsis markers (Huang et al. 2019; Maubon et al. 2018) (divided into fungal, gram-positive and gram-negative bacterial tests) have been cleared by the FDA (U.S. Food and Drug Administration). Further tests for gastrointestinal pathogens~~, HCV~~ and central nervous system infections are under development.

3.3.2 Friz Biochem

3.3.2.1 History and sensing principle

Friz Biochem, founded in 2004, started with a low-density electrochemical microarray, on which they run their "electrical detected displacement assay" (EDDA, Fig. 4 B). Different variants of this assay have been proposed (Liepold et al. 2005; Liepold et al. 2008), all of which rely on the competition between the targeted NA, the typically ferrocene-

labeled signaling probe and the capture probe. The target NA either competes with the signaling probe for a hybridization site at the capture probe (Liepold et al. 2005) or displaces the pre-hybridized signaling probe from the capture probe (Liepold et al. 2008). As a result, the number of signaling probes hybridized to the capture probe – and thus also the signal – is lower if competitive target NA is present. Functionality has been tested by detecting the amplification products of an asymmetric PCR with a dipstick 32-electrode array directly in the PCR tube (Liepold et al. 2008), or with a 384-electrode array realized using CMOS technology (Augustyniak et al. 2006; Kruppa et al. 2010). The latest version with an array of 109 electrodes shows optimizations with respect to signal-to-noise-and-offset ratio and user-friendly CMOS integration (Dodel et al. 2019).

3.3.2.2 Outlook

As of November 2019, Friz Biochem has not yet distributed their NA sensing technology, but is working on a sample-to-answer cartridge for the detection of MRSA called Cycle® Diagnostics (Fig. 1 E). Furthermore, the company was included in a survey of technologies that are potentially suited to the detection of infections in low-resource settings (Cantera et al. 2019). The survey's tests aimed solely to assess the amplification and detection performance and were thus conducted with three blind panels of already extracted NA at the facilities of the seven selected manufacturers. Friz Biochem was one of the three candidates that achieved promising results.

3.4 Heterogeneous, labeled, reagent-dependent approaches

This category comprises detection principles that employ enzymatic labels. A single enzyme catalyzes the reaction of multiple substrate molecules, thus enabling sensitive detection. The downside of these approaches is that they require more washing and buffer exchange steps than those described previously.

3.4.1 Combimatrix / CustomArray

3.4.1.1 History and sensing principle

Initially, Combimatrix used an electrode array for the synthesis of oligonucleotides. After synthesis, the chip could be used directly as a DNA microarray. Since the array contains electrodes, electrochemical hybridization detection is a reasonable alternative to fluorescence readout. Their 12K chip features 12,544 CMOS electrodes with a platinum surface. The target NA, which is hybridized to the immobilized oligonucleotides, contains a biotin label. After extensive washing, streptavidin horseradish peroxidase (HRP) is coupled to the biotin labels (Fig. 5 A). Following further washing steps, the enrichment of HRP can be detected by 3,3´,5,5´-tetramethylbenzidene (TMB), which is oxidized by HRP in the presence of H_2O_2. At the electrode, the oxidized TMB is reduced so that an amperometric signal can be measured (Dill et al. 2004; Roth et al. 2006).

3.4.1.2 Analysis process, instrumentation and application

Readout can be performed rapidly (about 30 s for all 12,544 electrodes) by the ElectraSense® reader. Preparatory steps, washing and buffer exchanges are performed manually.

Combimatrix compared the performances of fluorescence and electrochemical detection methods for gene expression and genotyping, using their 12K chip (containing 12,544 electrodes) for both methods. They claimed to reach "at least competitive" performance with the electrochemical approach, and also demonstrated reusability (Ghindilis et al. 2007). Further applications were reviewed in (Rodrigo et al. 2014).

In spite of the good performance data, electrochemical microarrays have remained a niche product in the fluorescence-dominated biochip market. In 2010, Combimatrix (since 2017 part of Invitae) focused on providing diagnostic services and left the development and distribution of microarray technology to CustomArray (part of GenScript since 2017).

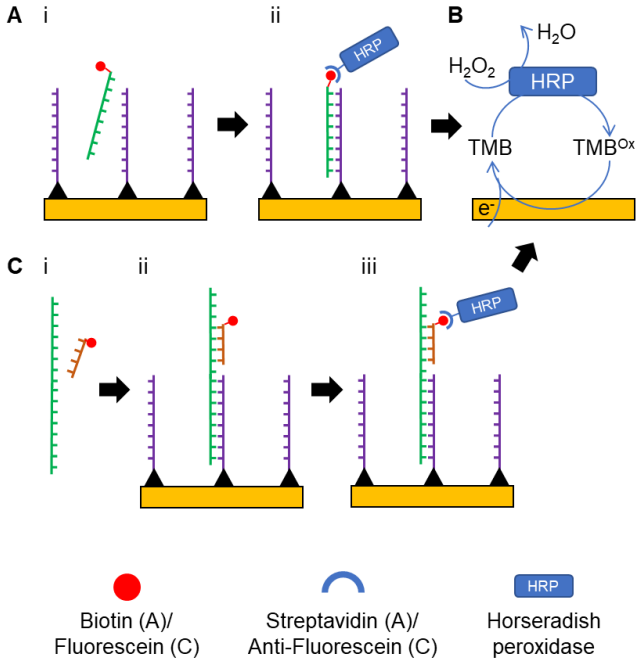

Fig. 5. Heterogeneous, labeled detection principles that require the addition of additional reagents for the detection reaction. A: CustomArray hybridizes biotin-labeled targets to the capture probe (i). After washing, streptavidin-HRP couples to the biotin (ii). The electrodes are washed again and then incubated with TMB, which leads to the catalytic reaction displayed in B. C: GeneFluidics first hybridizes a fluorescein-labeled reporter to the targeted RNA (i), which then hybridizes to the capture probes (ii). Anti-fluorescein HRP couples to the fluorescein. The detection reaction is as displayed in B.

3.4.2 GeneFluidics

3.4.2.1 History and sensing principle

GeneFluidics, founded in 2000, also detects NAs by enriching HRP on an electrode. The targeted NA is first hybridized with a fluorescein-labeled detector probe, before the result is hybridized to the capture probe. After washing, HRP is coupled to the detector probe via an anti-fluorescein antibody (Fig. 5 B) (Gau et al. 2001; Sin et al. 2013). GeneFluidics discriminates between organisms by detecting 16S rRNA, which has several advantages. First, RNA is single-stranded and can thus directly hybridize to its complementary detector and capture probes. Second, multiple copies of 16S rRNA are present in a single cell. This allows the detection of relatively low concentrations of cells without amplification (Liao et al. 2006).

3.4.2.2 Analysis process and instrumentation

The detection reaction is performed on a microfabricated 16-electrode array. A typical analysis time from cell lysis to result is about 50 minutes, mainly consisting of the hybridization (15 minutes) and the HRP coupling, including washing steps (15 minutes) (Liao et al. 2007). The implementation of an electrokinetic technique based on Joule heating leads to improved limits of detection and allows the hybridization reactions of the detector probe, target and capture probe to all take place in one step (Liu et al. 2014b; Ouyang et al. 2013). The technique consists of the application of a 200 kHz square-wave between the counter electrode and the working electrode, with amplitudes in the single-digit voltage range. This results in a local increase in temperature. Another benefit of this technique is the reduction of matrix effects, which improves the detection of 16S rRNA in blood samples (Liu et al. 2014a). The sensor is for detection only. However, ideas exist on how to further integrate automation into the analysis chip (Sin et al. 2013).

3.4.2.3 Application

The literature mainly describes the sensor's application to the identification of urinary tract infections (Liao et al. 2006; Mach et al. 2009; Mohan et al. 2011) and antimicrobial susceptibility testing (Altobelli et al. 2017; Mach et al. 2011). This led to UtiMax™, which was CE-marked in 2017.

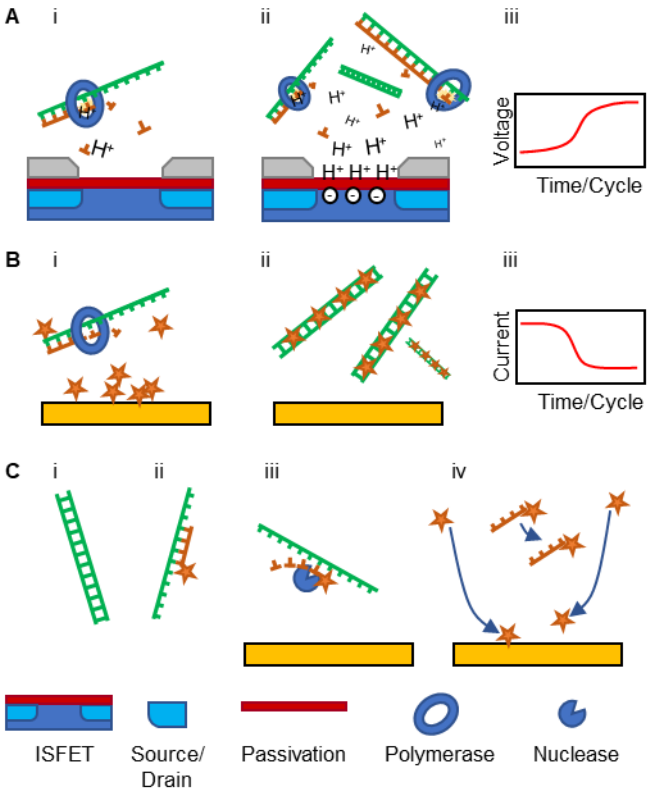

Fig. 6. Homogeneous sensing principles. A: DNAe use ISFETs to monitor the amplification reaction by detecting protons (H^+) that are generated during the incorporation of nucleotides (i). With increasing time (isothermal amplification) or cycles (PCR), the concentration of protons increases. The accumulation of protons at the passivation layer attracts negative charges in the semiconductor (blue), which influence the threshold voltage between the source and the drain (ii + iii). For further details, see SI of (Toumazou et al. 2013) B: Elice detects NAs by monitoring the consumption of electroactive molecules. The initially high concentration of freely diffusing electroactive molecules (i) decreases when double-stranded DNA is generated, into which the molecules intercalate (ii). The signal decreases if the target is present (iii). C: Binx detects double-stranded PCR products (i) by hybridizing a labeled signaling probe to the target (ii), which is then digested by a double-strand-specific nuclease (iii). The released electroactive molecule ~~signal probe label~~ diffuses faster to the electrode surface than the intact signaling probes (iv).

3.5 Homogeneous, label-free, reagent-less approaches

Chapters 3.5 to 3.7 describe NA detection systems that make use of homogeneous sensing principles. Eliminating electrode functionalization facilitates production. However, this is at the cost of losing the ability to specifically discriminate between multiple target sequences using specific capture probes. Other strategies must be implemented if several targets need to be detected within the same reaction volume (Binx (3.7.1) and Elice (3.6.1) provide examples). Additionally, examples of real-time amplification detection, which is useful for the quantification of the initial NA concentration, are described (DNAe (3.5.1) and Elice (3.6.1)).

3.5.1 DNA electronics (DNAe)

3.5.1.1 History and sensing principle

When DNA is replicated, the incorporation of each nucleotide leads to the release of one proton and one pyrophosphate. In weakly buffered reaction mixtures, this leads to a shift in pH that can be detected by ISFETs (Purushothaman et al. 2006; Sakurai and Husimi 1992). The concept of sequencing DNA by sensing the protons generated during the incorporation of nucleotides was published in 2002 (Purushothaman et al. 2002). This concept was transformed into

technology by two companies. Chris Toumazou, one of that paper's authors, founded DNAe and licensed patents to Ion Torrent. Ion Torrent (now part of Thermo Fisher) commercialized sequencing instruments based on this principle (Rothberg et al. 2011). DNAe instead focuses on point-of-care applications by monitoring the amplification reaction (Fig. 6 A) (called "pH-PCR" or "pH-LAMP" (Toumazou et al. 2013), depending on the type of amplification reaction) of target DNA (Kalofonou and Toumazou 2013; Toumazou et al. 2013) or RNA (Gurrala et al. 2016) in real time on a chip that can have the footprint of an SD card, including the required heaters.

3.5.1.2 Application

The first product based on this technology is GeneU, a DNA test used to identify optimized skin care products. Customers' saliva samples are analyzed for SNPs in genes associated with collagen breakdown or susceptibility to oxidative cell damage directly in the store within 30 minutes (Katsnelson 2015; Toumazou et al. 2015).

The next step is to overcome the tougher hurdles of the diagnostic market with the LiDia® system. Its first test will target bloodstream infections. Results presented at conferences demonstrate the detection of nine pathogens at concentrations down to one cell-forming unit (CFU) per mL spiked into a healthy patient's blood sample (Casali et al. 2017). In a study using clinical samples from patients who were being treated with antibiotics, an accordance of 77 % (n=39) with blood culture tests is reported (Bauer et al. 2018). The reduced accordance originates from a larger number of positive results for the LiDia®, which could indicate a higher robustness of the method against the influence of antibiotics. In both studies, the analysis process was semi-automated and required a time-to-result of less than five hours. With further automation, a reduction to three hours can be expected (Casali et al. 2017). In spite of the small footprint of the pH-PCR sensor reported in early works (Gurrala et al. 2016; Toumazou et al. 2013), the LiDia® system, which also integrates sample preparation, is benchtop sized (DNAe).

3.6 Homogeneous, label-free, reagent-dependent approaches

Comparable to its heterogeneous counterpart, in this approach electroactive molecules that interact with double-stranded NAs are used for detection. If these molecules are already present during NA amplification (as described in the following subchapter), it is important to ensure that the amplification reaction is not inhibited. Inhibition is dependent on the kind and concentration of the electroactive molecule and the type of amplification reaction (Martin et al. 2016a).

3.6.1 Easy Life Science (Elice)

3.6.1.1 History and sensing principle

Elice was spun off from the University of Paris Dideridot in 2009. Its detection principle is based on the consumption of electroactive molecules (preferentially osmium complexes $[Os(bpy)_2dppz]^{2+}$ or methylene blue derivatives) during amplification reaction due to their intercalation into double-stranded amplification products (Deféver et al. 2009). Thus, a decrease in signal indicates a positive reaction (Fig. 6 B). This approach allows the real-time measurement of amplification and has been demonstrated for PCR (Deféver et al. 2011; Moreau et al. 2017) and isothermal methods like LAMP (Martin et al. 2016b) and HDA (Kivlehan et al. 2011). Multiplexing can be achieved by performing endpoint melting curve analysis.

3.6.1.2 Instrumentation

The envisioned system is comparable to a typical 48-well plate in combination with a thermocycler (Fig. 1 I), in which the electrodes are interrogated with square-wave voltammetry (SWV). The wells feature electrodes (a three-electrode setup consisting of working, counter, and reference electrodes) at their base. These do not need to be modified with probe molecules, since intercalation happens in liquid phase. The benefit of this system is its flexibility, which could make it a useful tool during the early phases of the development of more integrated solutions.

3.7 Homogeneous, labeled, reagent-less approaches

Principles found in this category rely on labeled signaling probes, which typically increase the specificity of the NA test.

3.7.1 Binx Health (formerly Atlas Genetics)

3.7.1.1 History and sensing principle

Binx was founded in 2005 as Atlas Genetics and spun out by the University of Bath and Osmetech (see also GenMark). The principle (Fig. 6 C) is based on electroactive, labeled hydrolysis probes that specifically detect target DNA (Pearce et al. 2011). If the target is present, the probe anneals, which allows enzymes with 5' → 3' exonuclease activity to digest these probes. After digestion, the Binx system needs to discriminate between electroactive molecules that are bound at an intact probe from electroactive molecules that are only coupled to a single nucleotide cleaved by exonucleases. The smaller molecules diffuse faster to the electrode, where they can adsorb more easily than the bulky intact probes, thus leading to a quickly increasing signal, which is detected by differential pulse voltammetry (DPV).

Ferrocene is used as the electroactive label. For multiplexing, the sample is split into different chambers containing different specific probes. An additional increase in multiplexing capability can be achieved by modifying the ferrocene

labels. It has been demonstrated that by varying the length of an alkyl side-chain, the peak potential of ferrocene is shifted (Marsh et al. 2014). This allows ferrocene molecules to be tailored such that they can be discriminated well enough to detect five different targets (Goggins 2015).

3.7.1.2 Analysis process and instrumentation

The automation level of the analysis process is high: after transferring the specimen with a disposable pipette, all the process steps from NA extraction to PCR to signal detection are performed without user intervention ~~within~~ in about 30 minutes.

3.7.1.3 Application

The technology is applied to the detection of different sexually transmitted infections. A prospective, multi-center study conducted with the io® CT assay (CE marked in 2016, targeting *Chlamydia trachomatis*) resulted in good sensitivity (96.1 %), comparable to other available laboratory-based nucleic acid amplification tests, at a slightly lower specificity (97.7 %) (Harding-Esch et al. 2018). ~~In earlier, smaller studies, a lower sensitivity, but better specificity was reported (Pearce et al. 2015; Widdice et al. 2017).~~ In 2019, Binx received FDA clearance for their CT/NG cartridge that targets *C. trachomatis* and *N. gonorrhoeae.* The underlying clinical data from a prospective, multi-center study demonstrate a sensitivity of 96.1 % and specificity of 99.3 % for the io® CT/NG assay when compared to other FDA cleared assays that were conducted on the Roche Cobas, BD Viper and Hologic Panther platforms (U.S. Food and Drug Administration 2019).

4. Discussion

An overview of the reviewed commercially available systems for electrochemical NA detection can be found in Table 2. It can be seen that sensing principles from all categories have found commercial application. There is no general exclusion of principles from any category, e.g. because of low sensitivity, specificity, or convenience.

Despite the comprehensive representation, it is hardly possible to rank the performance of all the electrochemical principles or systems against each other, since their application scenarios vary largely.

The level of maturity is evolving. As of November 2019, GenMark offers several FDA-cleared tests for two generations of their devices, and Binx Health also received clearance for one of their tests in August 2019. GeneFluidics received CE marks for their tests and are also aiming for FDA approval, and Canon sells the Genelyzer II. Furthermore, there are promising developments, as listed in Table 2.

The degree of automation is evolving as well. GenMark's ePlex instrument and Binx's io device are fully automated sample-to-answer systems, as are the envisioned solutions of ~~Binx,~~ DNAe and FRIZ Biochem.

In this context, it is interesting that the electrification of the analysis chip can serve several purposes besides sensing the detection reaction. For example, GenMark uses electrowetting for liquid manipulation, GeneFluidics uses heat from their electrodes to improve the detection reaction, and Cubed Laboratories uses AC fields to trap and possibly sort particles by dielectrophoresis.

Another push towards further developments in the field of electrochemical NA analysis can be expected from the market model of open systems (like CustomArray, GeneFluidics, Elice) that are or are becoming available. Open systems enable researchers to develop their own assays without developing their own electrodes and all the required processing and readout instrumentation.

The frequently cited controversial prediction that electrochemical readout will enable miniaturized devices must be carefully scrutinized. On the one hand, there are clear examples where electrochemical detection can be performed in handheld and smaller devices: CustomArray's ElectraSense demonstrated that the analysis of a large number of electrodes can be performed in a handheld device, and DNAe's USB stick-like real-time amplification detector demonstrates that even temperature management for NA amplification can be miniaturized (Gurrala et al. 2016; Toumazou et al. 2013). But the integration of sample preparation and liquid handling leads to instruments that are benchtop sized. This enables tests at the point of need, e.g. in hospitals, doctor's offices, or in the food processing industry.

However, in the latter field, the electrochemical systems must compete with optical solutions that have also become smaller and have benefited from the development of robust, high-quality cameras for smartphones. A vivid example of the competition between optical and electrochemical approaches is Insilixa. Insilixa develops CMOS biosensors that can perform voltammetric and impedimetric, but also optical measurements. Heterogeneous, label-free, reagent-less impedimetric measurements that detect the hybridization of targeted NAs at capture probes have been demonstrated on a 10 x 10 pixel CMOS sensor (Manickam et al. 2010; Manickam et al. 2012). Comparably, optical fluorescence detection was demonstrated using 32 x 32 CMOS pixels as photodiodes, with an integrated heater for on-chip thermocycling (Hassibi et al. 2018).

Discussing the state of optical systems in detail and comparing it to the state of electrochemical systems is beyond the scope of this review, because of the high number of systems that are typically reviewed in subsets of application dependent context (Peker et al. 2018; Pinsky and Hayden 2019). Helpful for such discussions are comparative studies, but only few corresponding *clinical* studies have been published: e.g. the GenMark ePlex respiratory panel was compared to tests performed with Cepheid Xpert® (Arbefeville et al. 2017) and BioFire Filmarray® (Babady et al. 2018), Binx

CT assay was compared to BD Viper™ (Harding-Esch et al. 2018), GeneLyzer HPV tests were compared i.a. to results of a Illumina MiSeq™ sequencer (Nilyanimit et al. 2018). These tests show a good agreement between the results of the different systems of typically 95 % or better. Additionally, some reviews perform meta-analyses on published diagnostic studies, but only few have considered electrochemical systems, yet (Vos et al. 2019). Such clinical studies demonstrate the capability of analyzing real samples with the entire system, but it is not possible to derive a statement on the limit of detection or the impact of the underlying sensing principle on that basis. Comparative *analytical* studies would be required to compare the limit of the detection of the entire system, but such studies are hardly available. For non-comparative data obtained with single systems, FDA summaries can be consulted (U.S. Food and Drug Administration), although different units and conditions complicate a direct comparison. In any case, a direct assessment of the impact of the underlying sensing principle in these systems is hardly possible, since the upstream sample treatment like sample volume, sample preparation, but also differences in amplification assay design result in unknown biases.
For future studies, it would be interesting to include handling and economic aspects in addition to the diagnostic validity of the test.
As a conclusion, the available clinical data indicates that systems relying on electrochemical detection have the potential to establish as a sound and competitive alternative in a market that has been dominated by optical systems.
~~To assess their respective technological and economic advantages would require more independent, comparative studies that investigate the competing solutions from a user's point of view.~~
It will thus be interesting to follow further developments and to see whether optical and electrochemical approaches will co-exist, or whether one of these technologies will outcompete the other – at least in a particular niche of applications.

5. Conclusion

A wide range of different electrochemical sensing principles have found application in NA detection systems that are commercialized or close to commercialization. Examples were found for all categories (*heterogeneous / homogeneous*) and sub-categories (*label-free / labeled*, *reagent-less / reagent-dependent*). The applications range from food safety to veterinary to in vitro diagnostics (IVD), with a major focus on the latter.
The degree of integration and automation, which was a point of criticism in 2014 (Díaz-González et al. 2014), has clearly increased, and demonstrates the compatibility of electrochemical principles with sample-to-answer analysis processes for NA detection.
By reviewing the status of commercial electrochemical NA detection systems, the interdisciplinary nature of the challenges that arise from sample to result becomes obvious. The variety of solutions found in this review and the fact that this is just a small portion of all the ideas discussed in scientific papers indicate that further improvements can be expected, e.g. in terms of sensitivity, miniaturization and cost-efficiency.

Table 2: Comparison of the properties of the described electrochemical NA detection systems.

Properties	**Cubed Lab**	**Canon**	**General Atomics**[a]	**Genmark**	**FRIZ Biochem**	**Custom Array**	**Gene Fluidics**	**DNAe**	**Elice**	**Binx**
Device	NESDEP	Genelyzer II		ePlex	Cycle	ElectraSense	[b]	LiDia	Leo	Io
Weight (kg)	18	35	n/a	49[c]	7	0.65	n/a	n/a	25	10.2
Height (mm)	279	450	n/a	590[c]	400	46	n/a	n/a	270	277
Width (mm)	431	490	n/a	480[c]	170	132	n/a	n/a	360	275
Depth (mm)	356	270	n/a	540[c]	300	67	n/a	n/a	490	384
Principle	Heterogen.	Heterogen.	Heterogen.	Heterogen.	Heterogen.	Heterogen.	Heterogen.	Homogen.	Homogen.	Homogen.
Label-free	✓	✓	✓	×	×	×	×	✓	✓	×
Reagent-less	✓	×	×	✓	✓	×	×	✓	×	✓
Electroactive molecule	None	Hoechst 33258	$Ru(NH_3)_6^{3+}$ + $Fe(CN)_6^{3-}$	Ferrocene	Ferrocene	HRP → TMB	HRP → TMB	None	i.a. osmium complexes	Ferrocene
El. chem. method	EIS	Voltammetry	Voltammetry	ACV	Voltammetry	Amperometry	Amperometry	Field-effect	SWV	DPV
Maturity	Development	Product	Development	Product FDA cleared	Development	Product	Product CE-marked	Development	Development	Product FDA cleared
Specimen[d]	Raw sample	Lysate	Raw sample	Raw sample	Raw sample	Prepared target	Lysate	Raw sample		Raw sample
Automated[d]	×	×	✓	✓	✓	×	×[b]	✓	×	✓
Time to result	90 min	90 min	20 min	90 min	30 min	n/a	45 min	3 h	n/a	30 min
NA amplification	PCR	LAMP	None	PCR	PCR	None	None	Real-time PCR/LAMP	Real-time PCR/LAMP	PCR
Markers/chip	n/a	21 [e]	n/a	> 25 [f]	n/a	Up to 12,544	Up to 16 [g]	n/a	> 48[h]	Up to 24 [i]
Applications	Food safety	Veterinary; Food	n/a	IVD	IVD	Various	IVD	IVD	Variable	IVD

[a] State as of 11/2019; the developments since the bankruptcy of Xagenic are unclear. The table lists information available for the Xagenic AuRA technology. [b] GeneFluidics offers a CE-marked test that can be performed with their pipetting robot and their multichannel reader. However, there is no dedicated closed fully integrated device available (11/2019). As of 01/2020, the website shows pictures of new devices for fully automated testing. [c] Data for ePlex 1-Tower instrument. [d] Raw sample specimen and a fully automated analysis process are the features of a sample-to-answer system. [e] Markers in rice identification kit. [f] Blood culture identification panels. [g] One compartment per electrode. [h] One compartment per electrode (48), but melting curve analysis allows multiplexing. [i] Theoretical limit according to (Clarkson 2016): 4 reaction compartments x 6 labels with distinguishable redox potential.

6. Acknowledgements

We acknowledge funding by the German Federal Ministry of Economics and Technology (BMWi) [19364 N].

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