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Title: Distributed electrochemical sensors: recent advances and barriers to market adoption

Authors: Rafael Hoekstra, Pascal Blondeau, Francisco J. Andrade

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Address: Department of Analytical Chemistry and Organic Chemistry. Universitat Rovira i Virgili, Campus Sescelades, c/. Marcel·lí Domingo, 1, Tarragona, 43007, Spain.

Corresponding author: Francisco Andrade *franciscojavier.andrade@urv.cat*

ORCID of the authors:
Rafael Hoekstra: https://orcid.org/0000-0003-3778-2395
Pascal Blondeau: https://orcid.org/0000-0003-1331-5055
Francisco J. Andrade: *https://orcid.org/0000-0003-1199-2837*

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Abstract

Despite promises of their powerful applications in healthcare and environmental monitoring, electrochemical sensors have yet to be distributed at scale, instead remaining largely confined to R&D labs. This contrasts sharply with physical sensors which are now ubiquitous and seamlessly embedded in the mature ecosystem provided by electronics and connectivity protocols. Although chemical sensors could be integrated into the same ecosystem, fundamental bottlenecks remain in the three key areas of analytical performance, usability, and affordability. Nevertheless, advances are being made in each of these fields, with promise to converge for the deployment of automated and user-friendly low-cost electrochemical sensors.

Here, we present a brief survey of key challenges and advances in the development of distributed electrochemical sensors for liquid samples, geared towards applications in healthcare and wellbeing, environmental monitoring, and homeland security. As will be seen, in many cases the analytical performance is suitable, it is however, the usability that is the major bottleneck in commercial viability at this moment. Were this to be overcome, the consideration of affordability could be addressed further.

Keywords

Electrochemical sensors, autonomous sensing, ultra-low cost diagnostics, remote sensing, distributed sensing networks.

Distributed electrochemical sensors: academic advances and barriers to commercialization

*Rafael Hoekstra, Pascal Blondeau, Francisco J. Andrade**

Department of Analytical Chemistry and Organic Chemistry. Universitat Rovira i Virgili, Campus Sescelades, c/. Marcel·lí Domingo, 1, Tarragona, 43007, Spain.

* e-mail: Francisco Andrade *franciscojavier.andrade@urv.cat*

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1. Introduction

1.1. Scope

With the convergence of cloud computing, mobile devices and global connectivity, information can be now transmitted, stored, shared and accessed at any time, in any point of the planet, at near-zero cost. Combined with artificial intelligence, this technological revolution represents one of the most promising opportunities to solve some urgent global problems in healthcare, security, and environment (Figure 1) worldwide.

Indeed, building networked sensing devices that allow faster, simpler and cheaper decision-making processes has become the new paradigm for the human development in the 21st century. However, leveraging the power of the global network to reshape social systems requires that methods to generate information move from centralized models to decentralized (distributed) approaches. Scientific instruments, traditionally conceived to be produced in small scale, confined in a laboratory and operated by experts, must be now redesigned to be widely deployed, distributed across networks and used by non-experts. The challenge to build new tools that must simultaneously combine robust information, low cost, unsupervised operation (i.e. no user intervention), as well as resilience to changes in the surroundings, requires a compromise, as described by Valcárcel Cárdenas with the notion of "vanguard" analytical tools [1].

Figure 1. Major fields of application for distributed electrochemical sensors (DECSs) and they value they contribute to the field.

Interestingly, the development of tools for decentralized monitoring has moved at an uneven pace. Physical parameters such as heart rate, blood pressure, body temperature, position and speed, etc. can be now monitored using a plethora of portable and wearable systems available in the market. Sensing chemical properties, on the other hand, has moved at a much slower pace. The pioneering work by Diamond *et al.* on chemical sensing networks and body sensing networks provided the first steps on this field and a good overview on the problems to face, such as the 1/f noise, the changes in sensitivity and the cost of the devices [2–4]. More than a decade later, and

despite significant efforts in this area, many of these problems still persist, turning chemical sensing into the Achilles' heel of telemonitoring. For example, despite the clear interest in the remote monitoring of patients (telemedicine), the lack of suitable tools to generate (bio)chemical information outside the lab delays the progress of healthcare. Point-of-Care (POC) devices are a move on this direction since they provide information near the patient, but these instruments are expensive and require trained operators. It should be stressed that the adoption of mass-production criteria in the design of scientific instruments requires a shift in perspective, from the traditional instrument-centred to a user-focused approach. This is one of the main characteristics –and above all the main challenges- of this emerging field of decentralized instruments: the progress does not only depends only on the development of outstanding technology (something that as chemists we know well how to do), but also (and critically) on the successful adaptation of this technology to the users' real needs and contexts[3] (a task that requires truly multidisciplinary approaches)

Gas sensors are the notable exception due to –at least in part- crucial differences in chemical activities in the gas phase. This critical review will not address these, instead focusing exclusively on chemical sensing within aqueous matrices. While it will be seen that analyses within liquids have many inherent challenges, it is pivotal to overcome these in order to access the wealth of chemical information within fluids such as blood, sweat, saliva, urine, and tears, as well as environmental and municipal waters. Furthermore, we will restrict discussion to sensors employing electrochemical techniques. Although there are many excellent sensors being reported based on optical and other techniques- even including a "wearable" mass spectrometer [5]- it is testament to the growth of the field that there is ample material for review even within the limited scope defined. While each analytical technique has both strengths and limitations, electrochemical methods have an inherent advantage particularly relevant to the wide distribution of sensors in the 21st century. Namely, they can connect the electrical to the chemical, to directly transduce chemical information into the digitally connected world.

Although there have been significant efforts in recent years to advance distributed electrochemical sensors (DECSs), with few exceptions, these have remained constrained to academic research and have not yet been proven commercially viable. Developments in this field usually follow different lines. First, the search for alternative detection approaches (since the advantages of lab-based techniques do not necessarily translate into benefits for decentralized settings) and the development of miniaturized autonomous devices. Second, the development of new materials that provide flexibility, adaptability and low cost, and their integration into daily-use objects (wearable devices, embedded sensors, etc.). Finally, the search for applications in different areas. This critical review will discuss both the advances in DECSs and the barriers to their real-world application with a particular focus on the last 5 years.

1.2. Fields of need

1.2.1. Health and well-being

Telemonitoring of patients (telemedicine), i.e. the ability to generate clinically relevant information at home or at a patient´s bedside, is part of the paradigm-shifting transformation of healthcare. DECSs have been recognized as potent tools towards in this area [6]. Telemedicine offers increased patient comfort and peace of mind as well as lowering costs for multiple medical processes: transport, prevention, hospitalization etc. Further to this, it can also facilitate a higher frequency of analyses- from irregular hospital visit testing, to regular monitoring as required- daily, for example. Without a doubt, home-based monitoring of glucose with a handheld glucometer is the archetype of DECSs, having improved the health outcomes and the quality of life for millions of people suffering from diabetes [7–9]. The glucometer offers a good point to reflect on the reasons of its success, what remains to be solved and the existing barriers for further developments.

As a rule, the value of the information generated is directly connected to the decision that it will enable. The glucometer is then a singular case, since glucose levels require frequent monitoring during the day, the number of people suffering diabetes is large and it has been steadily increasing (and is expected to continue growing). This has created a substantial market that has driven decades of research and investment in this area. Thus, analogies with other clinically relevant analytes should be made with caution, since sampling frequencies and decisions associated to abnormal levels might be significantly different. Similar handheld devices *have* in fact been developed for other enzymatically-detected analytes, including creatinine, lactate, ketone, cholesterol, uric acid, and haemoglobin. However, unlike the case of glucose, the need to monitor these is often not strong enough to overcome a poor user experience and high cost (see Table 1). Even within well-established glucose sensing, much room regarding these aspects remains for improvement [10, 11].

Sampling is another significant barrier to the adoption of these tools, particularly when it involves invasive approaches such as the lancing of blood from a finger [12]. Consequently, and as the current medical paradigm primarily references blood, numerous studies are investigating the relationship of analyte levels in blood to other bodily fluids [10]. In the case of glucose, these include interstitial fluid [10], ocular fluid [13], sweat [14, 15], saliva [16], and urine [17]. Moving to detection in other fluids may lower the discomfort of adoption, facilitate incorporation of non-invasive sensors into wearable or otherwise embedded sensors, and possibly extend the sensor´s life time without calibration beyond the maximum recorded time of approximately two weeks (in the case of glucose) [10]. However, significant work still needs to be performed in this area in order to find meaningful correlations with existing parameters.

Table 1 Commercialized devices for medically relevant analytes and their retail prices. (Sources of prices listed in SI)

Analyte	**Device name**	**Device price**	**Price per test strip**
Glucose	Contour Next	$14.75	$0.69

Lactic acid	Lactate scout	$350	$2.42
Glucose, Cholesterol, Uric Acid, Haemoglobin	EasyTouch GCHb Multi Function Monitoring System	$53.50	$0.16 glucose $2.15 cholesterol $0.64 uric acid $0.58 haemoglobin
Glucose beta ketone	Bruno Pharma Innovations MD6	$97.99	$3.00 ketone $0.60 glucose
Creatinine	Statsensor Analyzer XPress	$756.04	$5.70

1.2.2. Environmental monitoring

Natural water systems are rich in data critical to the environment as well as human health. Indeed, regulations such as the European Water Framework Directive require the restoring of water bodies to a 'good status' [18]. Along with this, the environmental metrology market is expected to increase over the coming years. Despite these environmental and economical imperatives, a recent review of the area by Namour *et al.* concluded that *"None of analysed publications present a micro-sensor totally validated in laboratory, ready for tests under real conditions in the field"* [18]. They concluded that the major factor limiting real-use applications was the ruggedness of the receptor towards environmental conditions. Blaen *et al.* have noted that the traditional strategy of *"send a technician, take an isolated sample, send it to the laboratory and analyse it"* will no longer satisfy the need for information to be resolved temporally as well as spatially as studies continue to indicate that nutrient concentrations can exhibit highly dynamic and non-linear behaviour in both time and space [19]. A further consideration is that the integrity of water is vulnerable to contamination when being sampled and transported for *ex situ* analysis [20]. These needs would be best satisfied by the deployment of autonomous chemical sensing units at a scale that would necessitate them having relatively low-cost.

Ions- including heavy metals- are targets of environmental analysis and ion-selective electrodes (ISEs) are the classical analytical tool for this. A recent review by Crespo summarized the key advantage of using ion-selective electrodes (ISEs) for water analysis as *"direct information on so-called free or un-complexed ion activities, even within complex environmental and biomedical matrices"* [20]. While the performance requirements for many cations are already being met, anions- such as nitrate, nitrite, and phosphate- are also important targets for environmental studies, however, ISEs for these are currently inadequate in selectivity, sensitivity, and detection limits.

Amperometric detection using screen-printed electrodes have been reported for nitrate [21, 22], nitrite [22], and phosphate detection [23, 24]. An excellent review of screen-printed electrodes in this context was written by Hayt and Marty, and references multiple electrochemical detection techniques for heavy metals as well as organic contaminants [23].

A further limiting factor impeding deployment is the sensing receptor´s ruggedness towards the environment which currently requires frequent replacement or calibration. Given these considerations, it is clear why the group of Diamond have chosen to use optical methods for their autonomous sensing units of anions in natural waters, compromising on measuring the *direct ion activity* in order to achieve sufficient analytical performance and avoid deterioration of the receptor [25, 26].

1.2.3. Homeland security

In a time of increasing concern for preventing terrorist attacks, there is a growing need for tools that can detect threats early. Where traditional tools have been expensive, bulky and few in number- primarily located at borders such as airports, a modern approach would involve tools that are inexpensive, miniaturized and widely distributed. Electrochemical sensors are well suited to this, and as such are beginning to be explored for homeland security applications.

The 'Solid-state forensic finger', or 'Lab on a finger' reported by the group of Wang is illustrative of this [27]. Their glove-based sensor used a voltammetric method to detect gunshot residue and nitroaromatic explosive compounds upon surfaces. While these measurements were not strictly made in an aqueous solution- instead analysing microparticles in contact with a solid-state electrolyte- they highlighted how electrochemical techniques can bring low-footprint sensors to the frontlines of early threat detection.

2. Challenges and advances in the field of distributed sensors

2.1. Challenges and advances in the *analytical performance* of distributed sensors

2.1.1. Redefining performance: How good is good enough?

The "traditional" analytical parameters, especially the race for the limits of detection, has been the established way to compare techniques. However, when dealing with decentralized systems, sensors need to be as good as required by the intended application, and *only* that good [28]. In this context, *goodness* demands that the sensor can perform determinations in untreated real samples (such as whole blood), that the measurements are *robust*, and that the factors affecting the cost and simplicity are also considered. While soft from a technical point of view, *robustness* is a very useful concept, used it to indicate determinations performed in real samples are impervious to environmental conditions. In this way, the *goodness* results from the combination of

several traditional figures of merit (such as sensitivity, selectivity, limit of detection etc.) *as appropriate to target, matrix and conditions.* Here we divide the question of analytical performance into: what library of targets can we measure; and how robust are our measurements.

2.1.2. What targets should be in our sensing library?

What type of information is needed from decentralized devices? This is a medical, environmental, and security question, rather than an analytical problem, and it is critical for the adoption of these new tools that it is approached as such. Unfortunately, it is not always properly answered. Scientific curiosity may find the search for new biomarkers at ultralow levels more attractive than the determination of potassium or sodium in blood (something that it could be considered a "solved problem"). However, it is clear that at this stage, instead of the detection of cancer or a rare disease, telemedicine is focused on the remote monitoring of chronic conditions or the early detection of acute conditions requiring a fast response (e.g., a heart attack). Thus, while scope remains for expansion of the library of detectable substrates, home-use diagnostic kits for cancer or diagnostics of rare diseases seem still ill-conceived.

Limits of detection remain a very important parameter when dealing with detection of threats or environmental issues. However, many of the species that require monitoring in chronic conditions, such as potassium, creatinine, uric acid, etc., are at relatively high levels of concentration in blood (in the mM to sub mM range). These substances can be determined with high accuracy and precision within the laboratory, but they are extremely challenging to measure in a decentralized context. Monitoring potassium in blood, for example, is important to follow some chronic kidney conditions, hyper or hypokalemic paralysis disorders, etc. In the laboratory, potassium can be determined with ISEs (not to mention atomic spectroscopy), but it is still challenging to find simple, robust and affordable tools to do this determination at home. Interestingly, when using a lancet capillary blood is sampled, while clinical labs normally vein blood is collected. This and other issues –such as the contamination with intracellular potassium due to haemolysis of red cells while passing through the small puncture created by the lancet- may have significant impact in the results, and have to be accounted for when developing a solution for telemedicine. For other analytes, such as nitrate in environmental waters, the limitation is selectivity due to its low concentrations relative to other more lipophilic anions. All in all, beyond the development of a suitable detection scheme, the challenge is of analytical nature–from sampling to reporting of results-.

In general, there are many species for which electrochemical methods already meet the required action standards. Cations such as Ca^{2+}, Na^{+}, K^{+}, and H^{+} can be meaningfully monitored in freshwater and seawater samples [20]. Unfortunately, the case is more challenging for anions, as was exemplified by nitrate. In addition, a variety of clinically relevant small neutral molecules can determined in blood using enzymatic sensors. Several examples are included within Table 1. Beyond ions determined by ISEs and small molecules accessible through enzymatic detection, technologies to track protein levels are being developed, with applications such as cancer diagnostics [29], but, as it

was mentioned above, the relevance of these tools in a distributed context remains unclear.

The reliability of sensors that are already available also requires close scrutiny when medical decisions are in question. While decision-makers across a spectrum of industries remain divided as to wearables could replace routine healthcare services, 55 % of healthcare decision makers from regulatory bodies say these devices are not yet sufficiently accurate or reliable for diagnosis [30]. In this light, the *Vanguard-Rearguard analytical strategy* proposed by Válcarcel and Cárdenas seems conservative [1].

In many cases electrochemical sensors have already demonstrated adequate analytical performance to satisfy the action standards of use cases in the health, environmental, and security spheres. Of course, as with all research, room remains for improvement- however, as will be argued here- it is the questions of usability and affordability that in most cases present the bottlenecks to commercialization and adoption. For this to occur, all three aspects must act in concert, for like a wheel, its utility is ultimately limited by the weakest of its spokes. The key for distribution of chemical sensors is therefore to maintain the analytical performance of laboratory instruments- *at least to the degree that is meaningful within the given context*- while improving the usability and affordability. Additional considerations must be given to the mechanical and chemical wherewithal of the sensors to operate *ex laboratorium.*

2.1.3. How robust are our determinations?

The selection of sensing materials must take several criteria into account in order to align with the needs of distributed sensors. This is especially the case for wearable sensors, whose contact with skin necessitates that materials be non-toxic as well as flexible to conform to the curvature of the body [31]. Furthermore, they must be both resilient in structure and in response to the demands of the stretching and bending associated with bodily motion. Substrates such as plastics and textiles have been established as meeting these requirements, however, only recently did the group of Wang demonstrate the steady performance of sensors undergoing stretching of the sensing material itself, both with inks incorporating elastomeric binders [32] and with carbon nanotube-based sensors [33]. Similarly, their work with temporary tattoo-based sensors has shown the viability of this platform [34]. Comparably robust performance has also been demonstrated by paper-based sensors [35]. Because much of this work relies upon using carbon nanotubes, attention must be given to preventing contact with skin or finding alternative materials. The same applies to other materials that perform well but have associated toxicity issues. Sometimes, miniaturization and encapsulation of a device in a more rigid structure is used in order to avoid deformations and isolate the sensor. A sensing watch to monitor sweat composition has been proposed by *Diamond et al*. [36], and miniaturized devices that can be incorporated into garments have been also developed. In these situations, microfluidics systems must be incorporated to bring the sample to the detection zone. In an interesting twist, Wang *et al.* have recently proposed a wearable potentiostat incorporated into a ring to perform monitoring of chemical compounds in air [37].

As well as the mechanical considerations addressed above, an ideal sensor would also be *chemically robust,* meaning that it would maintain performance without deterioration due to its environment due to *"changes in the chemistry of the sensing surface that inevitably occur through exposure to the real world"*, as Diamond *et al.* put it [3]. This is perhaps the greatest challenge of all in moving from sensors of laboratory scale and expense, to those tailored to distributed applications. Real uses cases typically involve determinations in complex matrices such as whole blood, or water monitoring by un-serviced devices where electrode surface changes limit sensors to a single measurement before contamination becomes prohibitive. One significant advancement in this regard for enzymatic electrodes has been the addition of a diffusion limiting membrane to improve the chemical robustness by protecting the electrode from direct contact with the sample, thereby avoiding fouling (among other functions) [28].

A recent review by Crespo referred to drift values, pointed out that even the best (monovalent) ISE under controlled laboratory conditions experiences voltage drifts correspondent to a 1 % loss in precision per day [20]. It is therefore clear that extended exposure to natural freshwater- let alone seawater- would render such a sensor inviable within a day without recalibration. Constant monitoring would therefore seem impractical.
There are two general approaches to mitigating this dilemma: single-use disposable sensors- as in the case of glucose test strips; or frequent calibration through fluid management- as in the case of ISEs in laboratory autoanalyzers. As far as we are aware, the frequent calibration approach has yet to be demonstrated in a decentralized setting, although it may prove the most practical solution for autonomous remote environmental monitoring.

The use of disposable sensors is a way to avoid problems of modification of the surface due to continuous interactions with the sample. Economic factors are in this case paramount. The choice of commodity materials and mass manufacturing process to build the sensors has become an increasingly important topic, as it will be discussed below.

Challenges and advances in the *usability* of decentralized sensors

1.1.1. Miniaturization

Since it was declared in 1965 [38], the field of electronics has followed Moore´s Law, doubling the density of transistors in integrated circuits every two years until today, where it finds itself hitting the limits of pitch resolution- we shall see if tomorrow these limits can be stretched. Although the field of electrochemical sensors does not have such a law to follow, it does indeed seem to be following a similar trajectory of miniaturization with concomitant reductions in cost (see Figure 2).

The advent of solid-contact electrodes [39], new substrates and modern fabrication techniques, has allowed the miniaturization of electrochemical sensors. Works such as smart bandages [40, 41], paper-based sensors [34, 42–46], temporary tattoo-based sensors [47, 48], and wearable sensor arrays with integrated flexible electronics [15, 49, 50], exemplify the creativity and accomplishment within the realm of

miniaturization. While in theory, amperometric methods lose detectability when miniaturized (where potentiometric methods do not), this has not proven prohibitive to real-use cases, making the question of technique moot to miniaturisation. Indeed, examples of electrochemical sensors using both techniques have been successfully miniaturized, indicating that this is not a bottleneck to the advancement and commercialization of DECSs.

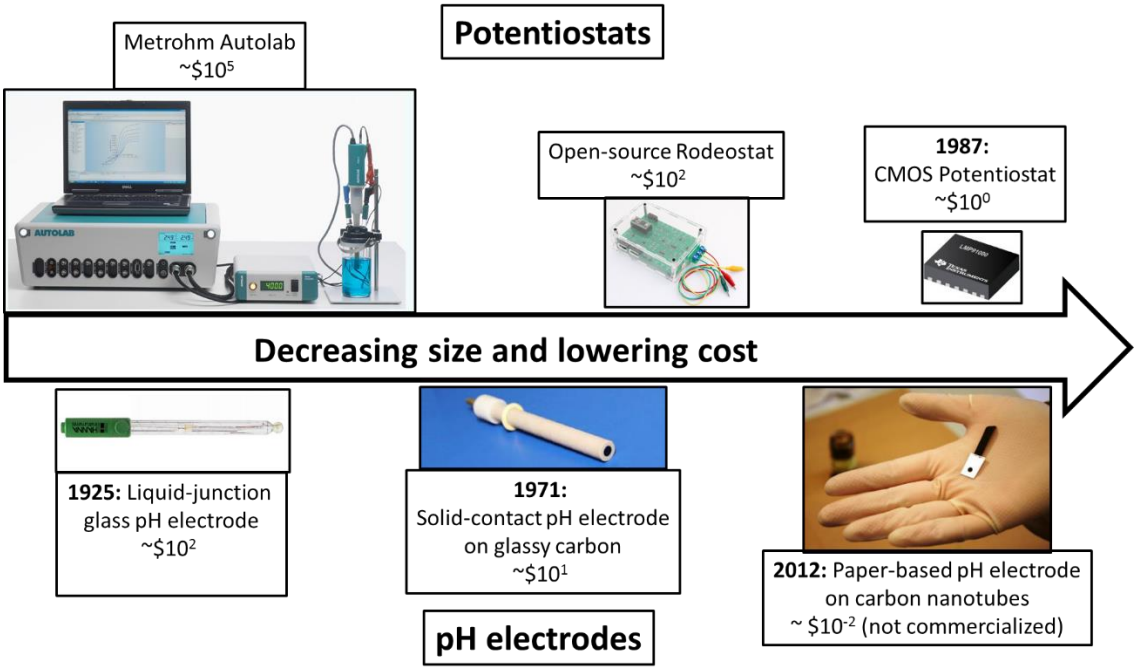

Figure 2. Decreasing size and cost of potentiostats (above) and pH electrodes (below).

1.1.2. The calibration problem and sensor reproducibility

Electrochemical sensors- whether voltammetric, potentiometric, or amperometric- all rely on measuring a current or a voltage. This value can only be translated into meaningful information- such as the concentration or activity of an analyte- in relation to other known values, i.e. the sensor must be calibrated. While physical sensors- such as the ten or more found in today´s smartphones [51, 52] can be manufactured with excellent reproducibility, chemical sensors exhibit far less stability in time and show considerable inter-sensor variability. The origins of this instability are in fact the same environmental processes responsible for signal generation [53], and can therefore likely never be eliminated entirely but rather, minimized below problematic levels. In this regard, the ideal chemical sensor would be highly reproducible and as such, be ready for a direct measurement by the user, without extraneous calibration steps.

In the case of the test strips used for glucose, each batch of sensors is calibrated in the factory and remains stable for a shelf-life of approximately one year. A code particular to each batch of sensors must be entered into the glucometer to calibrate the measurement. This effort is viewed as worthwhile by patients whose health outcomes

depend on regular glucose readings. While some studies still raise serious questions as to their accuracy [11], overall the glucometer is considered a success in terms of analytical performance. This performance has, to a degree, been extended to other analytes such as creatinine, uric acid, cholesterol, lactate, and ketones, using the same analytical principle. However, as it was previously discussed, the lack of the complex combination of factors required to build a compelling business case for monitoring these analytes- in contrast to glucose- have made the combination of calibration hassle and significant cost, un-worthwhile to many potential users.

Potentiometric sensors- despite their many merits- have been even more disappointing in their reproducibility and long-term stability. While work towards improving inter-sensor reproducibility has advanced- the current state-of-the-art being the ISEs upon colloid-imprinted mesoporous carbon with inclusion of a redox couple [54]- long-term stability remains an issue that may make this class of sensors unamenable to factory calibration. As a user-friendly solution to the *'calibration problem'* of potentiometric sensors remains to be found they have yet to find applications without the handling of trained personnel (e.g. the pH meter). Bobacka *et al*. have proposed an interesting experimental approach to minimize these problems [55] that has been preliminarily tested by Parrilla *et al.* in the development of wearable sensors using commercial carbon fibres as a substrate [56].

1.1.3. Compatible electronic instrumentation

While the electronics industry is well advanced, the DECSs market is both very new and very small, and as such, there remains a challenge in bridging existing electronics with emerging sensors. There have been two approaches in response to this: the first is the ad-hoc use of *Maker* electronics platforms such as *Arduino, Yoctopuce* and *Raspberry Pi* (to name just a few) and the second is thee use of purpose-built electronics such as the flexible electronics of Gao and co-workers [15, 49, 50], the custom-designed *Shimmer* board incorporated into the *SwEatch* platform reported by the group of Diamond [36], the miniaturized instrumentation reported by the Wang group [37, 47] or the wireless electrochemical system with radiofrequency reading developed by *GoSense* [40, 57] There is no doubt that electronics of greater suitability and lower cost will continue to be made available as the chemical sensor sector matures and thereby provides the necessary economic pull.

1.1.4. Connectivity and data security

For widespread distribution of electrochemical sensors to be realized, developers will need to address the interdependent questions of connectivity and data security. This has been highlighted by the recent hacking of devices (or *things)* which typically have significantly lower security than personal computers [58–60]. Fortuitously, there is currently a convergence of technologies that provide an optimal environment for the emergence of DECSs: the highly advanced electronics industry complete with flexible and printed electronics, the burgeoning infrastructure stack of IOT, as well as new cryptographic protocols. Major companies such as IBM and Accenture, as well as the government of Estonia are pursuing cryptographically protected blockchains for medical record keeping [61]. Such blockchains are replacing centralized databases to

allow health data to be managed in a decentralized way, have an immutable audit trail, establish data provenance, while being robust and available (without a central point of failure), with improved security and privacy [62]. Second-generation technologies such as *The Tangle,* first exemplified by *Iota* [63]*,* are also posturing for platform of choice of the IOT, which we foresee as including the Internet Of *Chemical* Things. If we add to this mix the emergence of artificial intelligence, it would appear that a fertile ecosystem awaits suitable electrochemical sensors. Significantly, today´s average user has a sophisticated computer in their pocket with multiple connectivity protocols and a native familiarity with data intensive applications- the customer is savvy and ready.

Proof of concepts in connectivity are illustrated by Smart bandages with NFC readings [40] as well as the Bluetooth-enabled *Shimmer board* used in a sodium sensing wearable [36]. In summary, excellent developments are taking place in connectivity and data security and chemical sensors have the challenge of catching up to the mature technologies around them.

1.1.5. Powering the revolution

Unlike the questions of electronics, connectivity and data security, there remain significant issues when it comes to powering distributed sensors. Researchers are addressing the power question both through *evolutionary* and *revolutionary* angles. The evolutionary approach is simply to use established battery technologies. Unfortunately, these can be bulky in wearable uses and more significantly have lifetimes that leave much to be desired. Indeed, although half of consumers consider that wearables can improve healthcare management, they also express concern about their wearable health patches running out of battery [30]. In the case of remote autonomous sensors for environmental applications, battery lifetimes must be on the order of months, if not years, to be viable.

On the revolutionary side, there is a 'demand pull' for elimination of batteries altogether. As noted in a recent market research report, *"…Wireless Sensor Networks … Internet of Things… and embedded sensors cannot achieve 90% of their potential if batteries need to be accessed for charging or replacement. Hundreds of billions deployed is the dream with many inaccessible, e.g. in concrete, underwater and on billions of trees"* [64]. Fortunately, work is underway in energy harvesting and self-powered systems [65–68] as well as paper-based batteries [69]and paper-based fuel cells [70], and it is foreseen that these may converge with electrochemical sensors to form self-powered DECSs. A particularly interesting approach has been proposed by Wang *et al.*, in using the electrical power generated by an enzymatic reaction of naturally occurring lactate in sweat, coupled to an electrochemical sensor [71]. While the approach has not been yet exploited, it depicts the broad range of possibilities to be yet explored in this field.

Challenges and advances in the *affordability* of decentralized sensors

The question of cost is critical to the widespread adoption of DECSs. Even in the oft-touted success story of the glucometer, the sensing strips remain prohibitively

expensive for the majority of the world´s diabetics. Considering that this technology has more than 40 years of optimization behind it and an annual market in excess of $10 Billion [72], lowering the cost of sensing systems for other analytes is an even greater challenge.

Considerations of cost must be holistic, taking into account all previously mentioned aspects: the materials used and manufacturing process, the electronics incorporated, the power consumed, and- if calibration is required- all liquids and fluid management components associated. This can be summarized as the electrochemical technique and associated instrumentation, and the material and manufacturing of the sensor.

Electrochemical techniques themselves each have different requirements in instrumentation and power consumption. Generally, potentiometric methods consume less power and use simpler instrumentation than amperometric methods. That said, complete potentiostats integrated into circuits are now available (as seen in Figure 2), making the instrumentation argument a non-sequitur. However, the passive technique of potentiometry generally consumes less power, and this may be advantageous in designing miniaturised low-cost sensing systems. In any case, it is also true that the target substances and range of applications of these techniques are different, so they must be seen as complementing rather than competing with each other.

Some materials lend themselves to lower-cost fabrication methods. Paper is notable for this, as it lends itself to ink-jet printing. Also, many plastics are amenable to screen printing. Sensors using ultra low-cost electrode substrates have already been showcased. These include paper [28, 29, 35–39, 65–70] textiles [41, 31], rubber [79], cotton yarns [80], and commercial carbon fibres [56]. Alternatives to expensive noble metals such as gold, platinum, and silver are being found in carbon-based materials [81], metal oxides [82–85], conductive polymers and ionic liquids [86]. Films of noble metals on the order or micron thickness have also been used recently by sputtering upon paper [46, 78], or by loading cellulosic material with metal salts before burning off the supporting material [87]. Both of these approaches maintained, or indeed enhanced, the properties of the precious metal while minimising the cost through miniaturisation. A pioneering work into affordable and utilitarian substrates by Wang and coworkers embedded voltammetric and chronoamperometric measurements into underwear by screen-printing carbon inks directly onto the elastic waistbands [31].

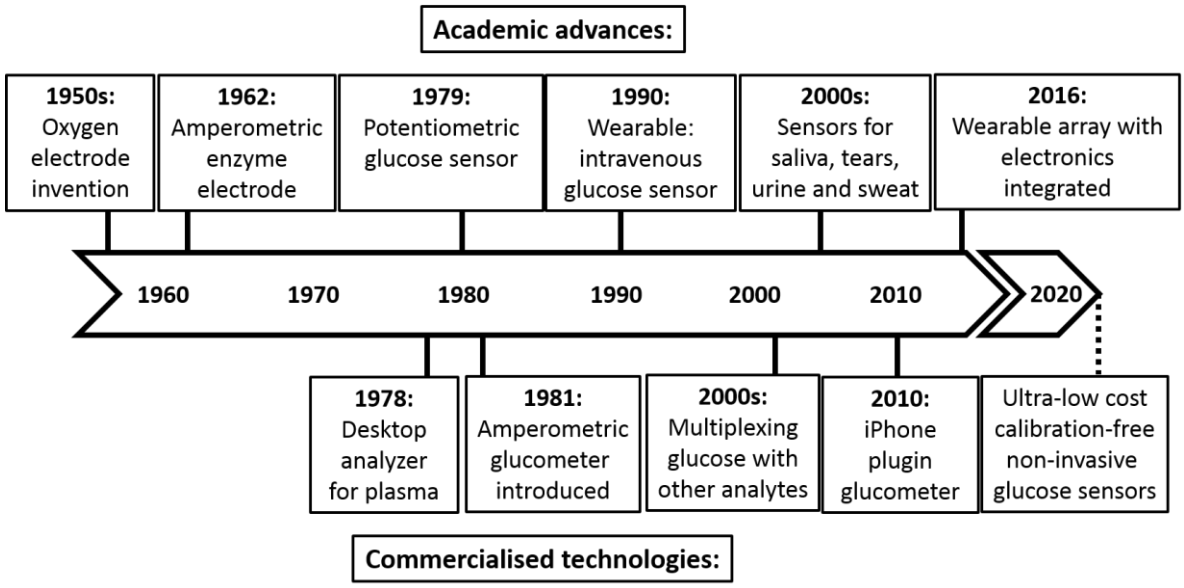

Figure 3. Timeline of major academic and commercial advances in electrochemical glucose sensors. References are included in SI.

2. Summary and outlook

2.1. State-of-the-bottleneck

It is evident that any approach to bringing electrochemical sensors out of the laboratory and into distributed adoption must be holistic, taking into account the materials, the calibration question, power supply, connectivity and instrumentation involved. All aspects of performance, usability and affordability must be addressed in a balanced manner. Nonetheless, a quick survey of the field suggests that current investigations are leaning heavily on the side of advancing analytical performance. As usability seems to be the facet most in need of attention, this review has placed emphasis here. Were usability to be sufficiently addressed, we consider that costs could be subsequently lowered to affordable levels; trying to sell low-cost sensors that are not user-friendly would be putting the cart before the horse.

Putting all of this together and surveying all of the requirements for the deployment of user-friendly electrochemical sensors, the calibration question arises as the major hurdle. Bakker has written an excellent discussion of whether calibration-free sensors can in fact be realized [28]. The alternative- calibration *in situ* appears unattractive due the complications of fluids and fluid management, but remains to be tested extensively.

A further limitation that is perhaps not discussed frequently in the scientific community is the disparity in funding for the sector as compared with IT. While a VC can expect to be reunited with their money within 2-3 years when investing in IT start-ups, a biotech company´s product may need closer to 10 years of development before being approved [88] or indeed ultimately failing, as in the high-profile case of *Theranos* [89]. As the

regulatory question must always be answered, the investment barrier only adds to the argument for ultra-low cost and simple approaches.

2.2. The future is interdisciplinary

The group of Citterio has recently demonstrated the inkjet printing of potentiometric ion-sensing devices upon paper without subsequent conditioning steps [90]. Their sensors demonstrated reproducible Nernstian sensitivities and more impressively, reproducible standard potentials of ± 5.1 mV for the Na^+ sensor and ± 2.8 mV for the K^+ sensor. These features make this the most advanced work in the field of calibration-free single-use potentiometric sensors. While works such as this are excellent from an academic perspective, like most sensor studies, the bubble of specialization limits their realization in practical use. While one group focusses on ultra-low cost chemical sensors, another advances their reproducibility, while yet another optimizes flexible electronics. For DECSs to be truly realized, interdisciplinary collaborations are needed from the initial conception of sensing systems- not merely the fitting together of disparate components after the fact. A survey of 900 cross-industry decision makers in healthcare, insurance, regulatory bodies, app developers, telcos and medical-technology companies considered internet companies, telecom operators and app developers as the top three preferred partners for healthcare [30]. Perhaps the efforts of chemists to incrementally advance analytical performance would be better directed towards forming interdisciplinary collaborations to solve usability issues. This could include for example, collaborations with engineers to automate calibration and industrial designers to integrate chemical sensors with power and instrumentation solutions from conception.

This is perhaps one of the key issues to face in the future of this field. Research -and particularly development- in electronics can be ubiquitously distributed in places that promote the collaborative activity. Even more, during the last decades a real explosion of low-cost electronic tools to build sensing platforms at the mass market level has encouraged and inspired people from all disciplines to explore and expand the field of decentralized sensors. Chemical sensors have not reached the same dynamics. Chemical laboratories are centralized and for many reasons not particularly open to everyone. To build appealing sensing platforms, whether it is a ring, a watch or a patch, a deep understanding of the end-user needs and routines is required. A pioneer work in this field, the *Glucowatch* [91], is an example of how important it is to include industrial designers at an early stage in order to avoid serious market problems [92]. Finding ways to include- from the outset- doctors, nurses, patients and designers for building appealing decentralized chemical sensors is a key priority.

This paper has presented the perspective that while excellent progress is being made towards distributed electrochemical sensors, the major bottleneck limiting their successful deployment is in the usability. Fundamentally new approaches may need to be explored to overcome this barrier, and user-centred thinking is essential to this process. The future is bright for the distribution of electrochemical sensors. To realize this future, as scientists we need to look outside the lab to the brilliant opportunities that are emerging in complementary fields.

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