

A Megatrend Challenging Analytical Chemistry: Biosensor and Chemosensor Concepts Ready for the Internet of Things

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ABSTRACT: The Internet of Things (IoT) is a megatrend that cuts across all scientific and engineering disciplines and establishes an integrating technical evolution to improve production efficiencies and daily human life. Linked machines and sensors use decision-making routines to work toward a common product or solution. Expanding this technical revolution into the value chain of complex areas such as agriculture, food production, and healthcare requires the implementation and connection of sophisticated (bio)analytical methods. Today, wearable sensors, monitors, and point-of-care diagnostic tests are part of our daily lives and improve patients' medical progression or athletes' monitoring capabilities that are already beyond imagination. Also, early contributions toward sensor networks and finally the IT revolution with wireless data collection and transmission via Bluetooth or smartphones have set the foundation to connect remote sensors and distributed analytical chemical services with centralized laboratories, cloud storage, and cloud computing. Here, we critically review those biosensor and chemosensor technologies and concepts used in an IoT setting or considered IoT-ready that were published in the period 2013–2018, while also pointing to those foundational concepts and ideas that arose over the last two decades. We focus on these sensors due to their unique ability to be remotely stationed and that easily function in networks and have made the greatest progress toward IoT integration. Finally, we highlight requirements and existing and future challenges and provide possible solutions important toward the vision of a seamless integration into a global analytical concept, which includes many more analytical techniques than sensors and includes foremost next-generation sequencing and separation principles coupled with MS detection.



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1. INTRODUCTION

Since its origination in 1999 through Kevin Ashton¹ and since the invention of the first to-the-web-connected device in 1990,² the Internet of things (IoT) sees major attention today not only by all Internet technology-affiliated communities but also by the general industry and science. Its original development was enabled by the hyperexponential growth of computer and Internet technology since the mid-1990s. Today, health technology and even insurance companies seem to have made the first baby steps and indeed profit from wearable health tracking^{3,4} in a basic manner, from step counting and pulse monitoring to ECG control.³ General mobility benefits from

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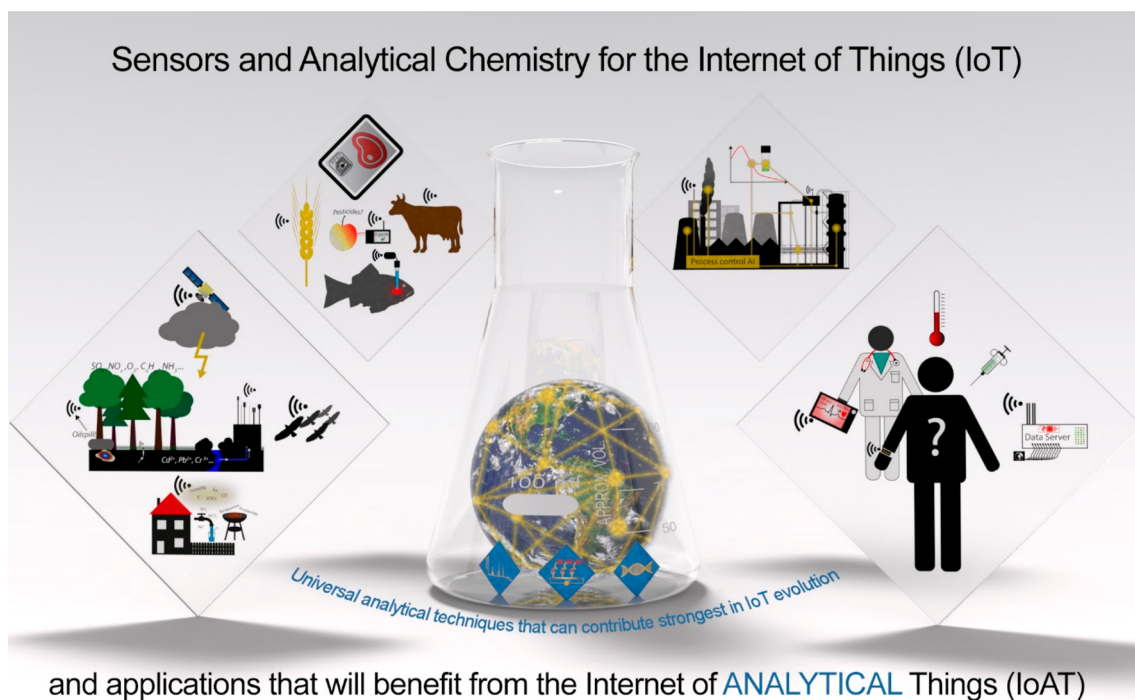


Figure 1. Analytical chemistry and sensors for the Internet of Analytical Things (IoAT).

connected driving^{5,6} and cars evolving to driver-less means of transportation,⁷ albeit still plagued with an abundance of remaining problems.⁸ Also smart homes developed over the last few years into invisible servants for all kinds of imaginable home tasks.⁹ While early contributions from, e.g., geochemical maritime research demonstrated successful sensor design for environmental, long-term, and autonomous deployment,¹⁰ the longest history of connected and self-operating devices has been observed in industrial and automated process control and regulation. Specifically, the idea of closed loop measuring-control cycles with humans serving only as supervisor comes most close to the IoT idea. Analytical examples of these are sophisticated IoT integrations from lab-scaled demo-units such as “LeyLab”¹¹ but also industrial-scale processes commonly contained in the field of process analytical technology (PAT).^{12,13} Yet, the here partly used sophisticated physical sensors cover only a small portion of required information, and significantly more advances in integrating other types of sensors with the IoT are needed, especially as performance requirements are driven by the desired application areas.

Thus, analytical chemistry will be necessary to provide data for the IoT when it addresses complex challenges related to health, environment, climate, food, and water on the local and global scale, on the individual and the population scale. Questions that must be asked are for example: Which technologies lend themselves to answer challenges of global health and disease monitoring, of safe food and water, of optimized industrial processes, of food fraud, of a clean and safe environment that can be integrated in an IoT fashion and not only function in a local, individual manner? Do we need the entire breadth of analytical chemistry, or can we initially chose just a few technologies to succeed in logistical integration as an IoT network? Can we generate an Internet of Analytical Things, IoAT for the IoT?

Typically, the lower the required limit of detection and the more difficult the specific identification in a given matrix, the

more sophisticated sensing platforms are required. Simple examples are blood glucose and pregnancy hormone detection that are routinely done in point-of-care, over-the-counter testing kits, whereas sophisticated analyses reach high-throughput or single-analyte detection limits using FACS,¹⁴ microscopy imaging,¹⁵ mass spectrometry,¹⁶ and next generation sequencing.¹⁷ The level of complexity, which is offered by IoT-linked, autonomously operating sensors is to date however clearly below such gold-standard laboratory methods.

We suggest areas that will be most important and will benefit most from IoT-enabled analytics: (1) Point-of-care sensors are developed today encompassing WHO’s “ASSURED” principle¹⁸ or targeting implantable in vivo sensing and therefore lend themselves in general for in-field and on-site monitoring of individuals in remote locations. (2) Environmental sensing will profit from much higher depths-of-information, more frequent monitoring of standard, and yet uncovered analytes and fewer efforts for human intervention when applied in large sensor networks. (3) Agriculture and food monitoring, closely associated with environmental sensing, is going a step further, considering quality control in a farm-to-fork concept. Starting with regional nutrient and toxicant monitoring down to single plant leaves or production animals to packaged food. (4) Additional, most powerful and versatile lab-based analytical techniques will also benefit from and contribute to an IoT but are beyond the scope of our article. The main performance progress toward being IoT-ready, and the most dramatic change in analytical capabilities has to be achieved for sensors, not for classical lab techniques.

While most of the presented works in this article are very recent (2013–2018), we want to emphasize the groundbreaking work done previously before the term IoT was even invented. Several of these works are highly cited in their field and have inspired later scientists to find their solutions today. This includes a myriad of publications with concepts relevant to all of the here discussed topics, from POC biosensing to environ-

mental monitoring and food sensors, dating back to contributions within the last century.¹⁹ It also includes the concept of remote vegetation mapping, relevant to today's crop yield prediction and farming needs requirements and enabled through recent computing-enabled analysis algorithms and miniaturization of cameras or sensors;²⁰ the very early introduced and continuing concept of combinations of chemo- and biosensors together with neural networks for data improvement and conclusive predictions;^{19,21–24} neural networks in agricultural sensor applications;²⁵ the idea of environmental monitoring via (wireless) sensor networks;^{26,27} wireless sensor networks for food monitoring or in food production;²⁸ early and ongoing research on communication and design of wireless body sensor networks in wearables for diagnostics;^{29,30} and ideas and concepts for in vivo sensors in humans.³¹ All of these examples illustrate quite similar concepts to what is today shown with analytical solutions intended for IoT deployment. In fact, in most cases, recent research benefited through a further level of sophistication among features such as miniaturization, enhanced connectivity, and computing power or increased mobility. As such, more engineering aspects were taken into consideration. On the other hand, deployment into a functioning IoT is yet impeded by persisting grand challenges in basic issues of sensor quality and stability almost throughout. IT innovations have here seemingly surpassed recent analytical and sensor inventions. Specifically, a focus on sensor performance, of long-term stability, specificity, and autonomous operation must return to the center of innovative research so that "IoT-ready" solutions are found.

We conclude the article by proposing future requirements and developments needed to provide a seamless integration to an overall, global analytical concept providing "an answer to everything". Futuristic planning of smart cities such as Quayside, Toronto, may provide a stimulus to nudge analytical chemists toward an IoAT so that analytical data can assist in driving decisions continuously. In such a smart city, driver-less shuttle buses, monitoring and steering of public activity, robots for transport (i.e., delivery) and basic infrastructure support (e.g., waste management), modularity of buildings, self-sustaining energy supply, and ubiquitous sensing come here together.³²

It should be pointed out that this review does not focus on the interface between cloud computing and sensors, such as different architectures for communication to, e.g., wireless sensor networks, machine-to-machine communication and software aspects research as this has been discussed in more detail elsewhere.^{33–35} We focus instead on those critical and common considerations relevant to analytical chemistry.

2. SENSOR SOLUTIONS FOR POINT-OF-CARE AND IN VIVO DETECTION

With the progress of consumer products developed in recent years, body sensors or wearables may be the easiest to envision in an IoAT (Figure 2). Patient data are sent to health centers triggering individual diagnoses and population-wide analyses; a person's health status causes responses by the IoT-house or car; a disease can be controlled before it becomes an epidemic. Prevention, early diagnosis, immediate help, lower costs, availability in all areas, also at the most remote rural countryside are keywords we associate with these principles. The next step, i.e., from wearable to IoAT seems simple—connect the single devices to a network—as advances in recent years relating to miniaturization, connectivity, and power supplies have led to sophisticated devices needed.^{36–38} The stumbling blocks, i.e.,

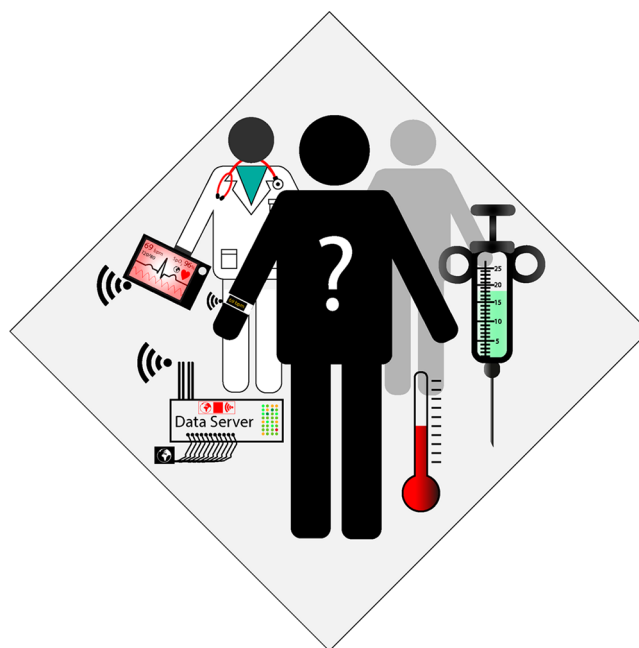


Figure 2. Sensor solutions for point-of care and in vivo detection.

the common analytical challenges, relate to the fact that autonomous/remote/lay-person applications are required and that long-term use is favored.³⁹ The common challenges are: How to prevent electrode fouling,^{39,40} electrode drift, optical transducer blockage, probe degradation in those complex matrices of interest? We present here a few excellent examples that try to address these challenges and have found solutions improving issues toward sensors becoming truly ready for the IoAT. Table 1 provides an overview of sensor solutions and components providing concepts for the point-of-care.

2.1. Appliances/Accessories

Kim et al. presented a mouth-guard-integrated biosensing system to monitor uric acid levels in saliva with wireless data transmission that is only the size of a one cent coin.³⁸ Uric acid is an important marker for diseases (hyperuricemia, gout, renal syndrome) and an indicator for type II diabetes.

A screen-printed, enzyme-modified electrode is integrated with miniaturized electronics and a bluetooth transmitter for wireless data broadcast. The latter requires less energy and has a longer range compared to RFID-based modules.

The use of a mouth guard is highly attractive, similar to nose-pieces of eye glasses, rings, and gloves demonstrated by the Wang group recently, for the detection of lactate and potassium in sweat or the detection of hazardous substances like organophosphates.^{42–44} Reasonably large sensors or multiple sensors can be integrated in such an accessory that is, or can be used daily, for several hours and that can be charged during normal "off times". As with other voluntary wearables, it depends on the consumer's reliance of using it. Also, it requires attention for care or for regular switching of sensing units.³⁸ Kim et al. tested their sensor stability for 2 h, but realistic applications ready for the market must at least have 8 h of continuous usability (e.g., during sleep). Moving toward combined sensor-cure concepts, Liang and colleagues recently went one step further and showed their mouth guard-integrated oral drug delivery module which was designed via 3D-printing. The applicability of their concept was proven in a human study.⁴¹

Table 1. Sensor Solutions for POC and in Vivo Sensing

category	keyword	sensing principle	analyte	ref number
appliances/ accessories	mouth guard	EC	uric acid	38, 41
	eye glasses, ring, gloves	EC...	lactate, K ⁺ organophosphates	42–44
	face mask	EC, flow sensor	breath	45, 46
	contact lens	EC	glucose	37, 47–50
bandages, patches, tattoos	bandage, wristband	impedance, EC, resistance cells/optical	cortisol, Na ⁺ , K ⁺ , glucose, lactate	36, 51–55
	patch	EC, optical, colorimetric	ECG, lactate, blood oxygen level, Cl [−] , glucose, pH, skin melanoma, T	56–60
	tattoo	EC, colorimetric	ethanol, pH, signaling chemicals	61–64
	components	electrodes, connectors, electronics		55, 65–68
in vivo sensing	in vivo (animal)	EC, optical, optofluidic, FET	glucose, lactate, paracetamol, ATP, glutamate, doxorubicin, oxygen	69–83
	in vivo (human)	EC, optical	glucose, cardiac implant, neurodevice	84–89
	foreign body reactions, biobarriers and sensing element stability		bioactive coatings, membranes, biodegradables, probe stability, implantable sensor elements	90–113
microfluidic strategies	sample prep and amplification	EC, microneedles, optofluidics	influenza virus, bacterial strains, glucose, alcohol, nerve agents	114–121
power supplies	batteries, body energy harvesting			122–147

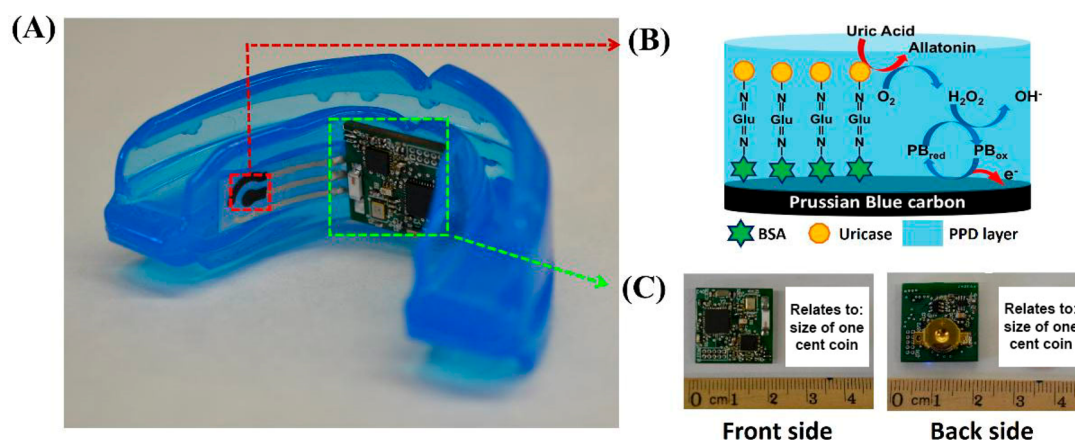


Figure 3. (A) Photograph of the mouth guard biosensor integrated with wireless amperometric circuit board. (B) Reagent layer of the chemically modified printed Prussian-Blue carbon working electrode containing uricase for SUA biosensor. (C) Modified photograph of the wireless amperometric circuit board: front side (left) and back side (right). Adapted with permission from ref 38. Copyright 2015 Elsevier.

The 2001 accepted patent (US 6718982 B2) from Smith, Fasching, and Howard details a face mask with an incorporated respiratory flow sensor.⁴⁵ This opens up interesting possibilities to incorporate gas and breath sensing into such an accessory. Sensors as described above integrated into mouth guards and eye glass pieces can also be integrated into a face mask. They can assist in breath analysis, detection of pathogens such as influenza or seasonal viruses or bacterial infections, and even emerging infectious diseases. Especially in those regions of the world where wearing a face mask is part of the socially accepted or requested habit when people are affected by flu-like symptoms,¹⁴⁸ this will be a valuable approach for comprehensive monitoring not only of an individual but a population as a whole in order to identify outbreaks during typical “flu seasons”. Here, connectivity could be easily established due to the quite large size of a face mask. If used in a densely populated urban area, grids of sensors with large range communication between each other can be established as also proposed by Güder et al.⁴⁶ As well, the associations of “low cost” and “disposable” with simple face masks, are helpful to bypass challenges of sensor long-term stability or fouling. Yet, the complexity of a disposable sensor will be limited by cost, and thus pathogen detection approaches

must rely on a simple assay. A further concept for an IoT-integrated monitoring solution is the diaper-embedded urinary tract infection sensor from Seo et al.¹⁴⁹ Their device is activated automatically when urine is present, and thus sensing at required times can be provided.

A further, yet not much explored, category is textile-integrated biosensing approaches. Already suggested a decade ago by Wang’s group,¹⁵⁰ more work has been discussed recently. Kinnamon et al. show a similar concept with an electrochemical, textile-integrated sensor for the detection of influenza A,¹⁵¹ but the authors do not go beyond the proof of principle. Their approach may make risk-dependent surveillance possible, but textile-unique challenges of long-term stability requirements (people will not change normal textiles as often as other accessories) or required laundry processes render this concept more complicated. Ankhili et al. have presented here a promising approach with their underwear-integrated PEDOT:PSS electrodes for continuous ECG monitoring.¹⁵² Their polyamide fabric-based version could resist 50 washing cycles to still produce a reasonable signal. While integrating all electronic and communication elements in a watertight manner can be imagined, extension of this concept to other biosensing

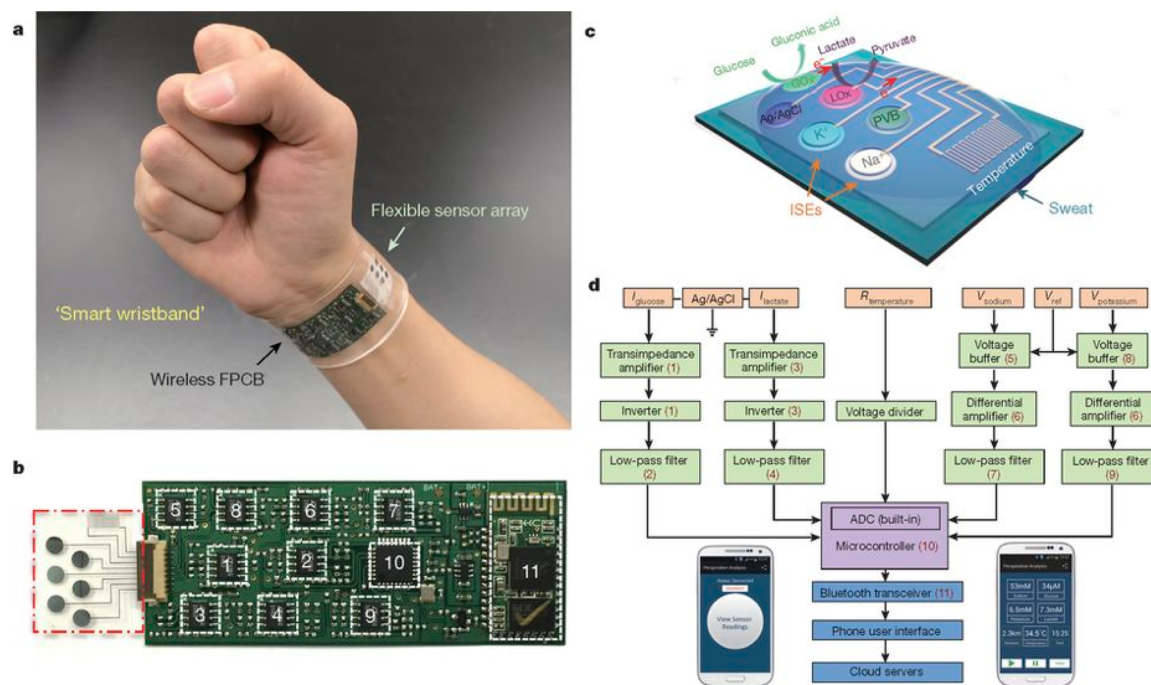


Figure 4. (a) Photograph of a wearable FISA on a subject's wrist, integrating the multiplexed sweat sensor array and the wireless FPCB. (All photographs in this paper were taken by the authors.) (b) Photograph of a flattened FISA. The red dashed box indicates the location of the sensor array and the white dashed boxes indicate the locations of the integrated circuit components. (c) Schematic of the sensor array (including glucose, lactate, sodium, potassium, and temperature sensors) for multiplexed perspiration analysis. GOx and LOx, glucose oxidase, and lactate oxidase. (d) System-level block diagram of the FISA showing the signal transduction (orange) (with potential V , current I , and resistance R outputs), conditioning (green), processing (purple), and wireless transmission (blue) paths from sensors to the custom-developed mobile application (numbers in parentheses indicate the corresponding labeled components in b). ADC, analogue-to-digital converter. The inset images show the home page (left) and the real-time data display page (right) of the mobile application. Reprinted with permission from ref 36. Copyright 2016 Springer Nature.

approaches is yet challenging. Implementing some washing-protection mode, physically shielding more sensible sensing layers can be realized. A different approach for textile-integrated sensors has been presented by Promphet and colleagues. They embedded a colorimetric sensing platform for sweat pH and lactate monitoring.¹⁵³ In general, the suitability of paper-based sensing approaches toward meeting the ASSURED criteria of point-of-care sensing has been critically reviewed by Smith and colleagues.¹⁵⁴

2.2. Bandages, Patches, Tattoos

A significant effort in wearable sensor research focuses on patches, bandages, or tattoos that are worn directly on the skin and provide both sensing as well as data transmission possibilities in a noninvasive mode (no microneedles used). Predominantly electrochemical, enzyme-based, or potentiometric sensors are being developed to identify specific analytes. For example, Munje et al. designed a biosensor for sweat diagnosis based on impedance measurements of the electrical double layer in reaction to antibody–analyte interaction at the semiconductor–liquid interface.⁵¹ Cortisol as a marker for physically induced stress, a relevant parameter for everyday use in sports or at the workplace, was detected. The antibody afforded high specificity but unfortunately also limited the biosensor to single use. AC voltage was preferred over DC voltage, due to the latter causing damage to biomolecules and having significantly higher power consumption. An alternative cortisol-sensing platform, designed as polymeric wearable patch with a nanoporous membrane layer and a transistor using the concentration dependent source-drain current as analytical signal, has been presented by Parlak and co-workers.⁵² Overall, the flexible

substrates, the small size, and the highly specific biosensing suggest that this sensor design is an ideal technology for IoAT as long as power supply, regulation, and transmission units will be integrated within the sensor. Here, important elements for skin-wearable sensing have been introduced by the group of Lu: electronics for RF transmission,⁶⁵ a transparent ITO/Cu mixed material⁶⁶ for control applications or displays, or graphene-based tattoo-like materials for direct biosignal monitoring.⁶⁷ Kassal et al. have reported both a smart bandage for wireless wound-pH monitoring with optical read-out or alternatively a similar approach monitoring uric acid in a bandage, indicating the wound status.^{155,156} Special aspects in such skin-worn approaches to account for include the application time of the bandages, patches, tattoos vs calibration endurance, as well as varying sweat levels in different physiological states (rest phase, sport) and how the sensor response can adapt to that.

All-integrated wearable biosensors patches include the hybrid biosensing system from Imani et al., comprised of an amperometric and a bipolar ECG electrochemical sensor, monitoring lactate levels and the ECG signal. The device is worn directly on the skin and enables wireless signal read-out.⁵⁶ It is especially noteworthy because orthogonal approaches are used to monitor health conditions, hence increasing the reliability of measured data in contrast to the stand-alone pulse oximetry device but which allows for variable placing on the body.⁵⁷ Kim et al. have demonstrated that a biosensor tattoo can detect ethanol by combining iontophoresis of pilocarpine to induce sample collection (sweat) with enzymatic amperometric detection and wireless data transmission,⁶¹ and Sonner et al. presented a sweat stimulation device, helpful for continuous monitoring under rest when sweat production is limited, but

only for 30 min of maximum data acquisition.⁶² Exemplary for a multiple biosensing approach, Gao et al.³⁶ have shown a whole sensor array for the detection of Na^+ , K^+ , lactate, and glucose and additional temperature measurement as an analytical signal and for signal compensation of the other sensing moieties.

The authors use a combination of enzymatic amperometric detection of glucose and lactate, ion-selective electrodes for ion sensing and resistivity-temperature sensing. The internal use of the temperature measurement to compensate for sensor drifts is a highly desirable feature for reliable autonomous sensors. Different coatings of the sensing elements (e.g., chitosan or PEDOT:PSS) provide robustness. All sensors are placed together with circuit components, A/D-converter, further processing elements, and a wireless data transmission function (via Bluetooth to a smartphone app) in a single unit. The whole sensor array with all elements and a Li-ion battery was designed as wristband on a PET support with an additional rayon fabric as skin-contacting and sweat sampling element. Long-term storage was proven for 4 weeks with no obvious change in efficiency, and the longest continuous measuring application tested was over 90 min. This long-term performance is a good starting point in light of requirements needed for actual personal use. Alternative approaches are a colorimetric sensor for sweat chloride, glucose, lactate, and pH sensing which has been presented by Koh et al.⁵⁸ They used a PDMS basis to integrate their capillary and sweat pressure driven microfluidic system leading to chromogenic reactions which indicate analyte abundance. Finally, NFC technology was integrated to facilitate, e.g., smartphone-camera-based signal read-out. In addition, a good overview of the current state of the art for sweat sensor devices is given by Choi et al.⁵⁹ Other wearable sensors include the skin melanoma sensor by Ciui et al., which is presented as a bandage with wireless read-out,⁵³ a sensor that monitors personal UV exposure,¹⁵⁷ and a heart-monitoring sensor which is self-powered.⁵⁴ Bandodkar et al. presented a new concept for skin-worn, self-powered, and wireless multianalyte sensors.¹⁵⁸ The design includes sensing capabilities for sweat rate/loss, lactate, pH, glucose, and chloride in an orthogonal approach bearing potential colorimetric, electrochemical, and volumetric read-outs. The authors outline that their simple and cost-efficient design (e.g., omitted potentiostat) can overcome sensor drift and fouling issues via a disposable application and frequent replacement. The noninvasive principle without microneedles for sampling facilitates that. This might not be a sensor solution for long-term monitoring of chronic conditions, e.g., diabetes, but can be visualized for application during hospitalization. A different approach to cope with fouling issues has been shown by Pifferi et al. with a focus on polymerization fouling of the working electrode employed for amperometric dopamine detection.¹⁵⁹ The authors used a TiO_2 -upper layer on the working electrode, which was exposed to UV irradiation as a cleaning measure, as also proposed for other sensing concepts.¹⁶⁰ This idea might be realized if the electrode is separated far enough and shielded, and energy is provided in a safe manner (low mW range of UV-lamp power and possible heat generation). In the end, it may serve better for environmental applications.

Finally, Zhu et al. have recently presented their capability to directly 3D-print and, with the help of robotics, add electrodes, connectors, and electronic components for different sensing components on moving surfaces. The concept was shown on a freely moving human hand with at least 2 h stability on the hand and being fully removable.⁵⁵ This example shows the capability to provide on-body sensing without the crucial need for support

materials. However, more data on sensor signal quality and stability will be required to reveal to which kinds and durations of sensing such an approach can be applied. Here, an important contribution toward the long-term stability of printed electrochemical devices has been made recently by Bandodkar et al., who presented their version of these devices bearing a capability of magnetic self-healing, irrespective of environmental conditions.¹⁶¹ This is a promising solution for long-term stable wearable on-skin or textile and similar devices. Changes to the material structure and implications on EC-signal responses in a true sensing situation however have to be explored further.

A very early stage, but interesting future idea, has been issued as a patent to Apple Inc. for metal oxide semiconductor chemical gas sensors (e.g., ozone, NO_2 , SO_2 , CO, CH_4 , or VOCs including poisoning species such as water vapor, chlorides, and phosphates).¹⁶² According to the description, the sensing layer can be protected by an adsorbent layer and enclosure, while included heating might refresh the sensor layer. Such a device might be later included into smartphones or even smart watches. The presented mechanisms for poisoning protection, cross response avoidance via a selective adsorbent layer and heating to recover sensing capability, represent promising initial design thoughts for analytical sensor performance. Heating functionality to recover a sensing element (not from electro-/chemical fouling!) might also be imagined in other sensors using liquid systems—providing free convection for “flushing” and thus depicting a further antifouling concept. Practical realization and live performance are yet other issues in any case.

Tattoos can also be applied to fingernails as demonstrated by Kim et al. for pH determination, taking advantage of the simplicity of visual detection and recording with a cell phone camera.⁶³ A PVC membrane containing different pH sensitive dyes was immobilized on tattoo transfer paper and placed onto fingernails. In order to obtain a broad dynamic range, different nails with different indicator dyes were used and provided sensing between pH 3 to 10 and multiple reversible usability (seven times). The backing, which is essentially the fingernails, can be considered a good substrate with less influence on the sensing layer compared to, e.g., skin. Such thoughts are important for placement considerations of wearable body sensors, as long as sampling of the desired analyte remains still possible.

An in vivo application via a patch was presented by Tseng et al. with an on-tooth mounted (2 mm × 2 mm) RFID sensor made of functional materials such as porous silk of PNIPAM hydrogels monitoring the oral cavity (pH and temperature) as well as food intake.⁶⁰ Going a step further, Liu et al. developed a 3D-printable living tattoo made from a patch with genetically engineered, living bacterial cells as active material for sensing.⁶⁴ How these sensors perform over longer durations and cope with unknown interferents is yet to be solved.

2.3. Contact Lenses

Contact lenses are attractive wearables, as, similar to glasses, the user wears them to serve daily needs and tends to forget about their presence after initial insertion and adjustment. Thus, data collection takes place without hampering any daily activities. Yao and later Liao et al. demonstrated a contact lens integrated amperometric glucose biosensor for detection in tear fluid with wireless transmission.^{37,47} Their fully developed system⁴⁷ contains an enzymatic glucose biosensor, detecting physiologically relevant glucose levels in tear fluid, together with a potentiostat, a read-out unit, and a capacitor-driven power

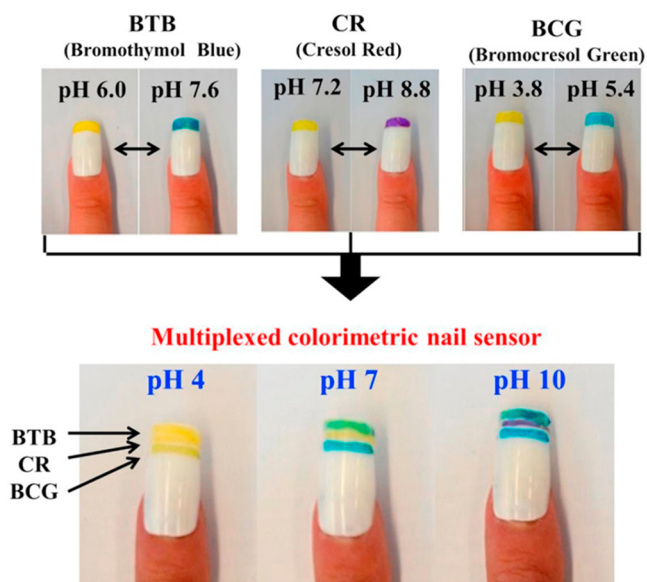


Figure 5. Colorimetric response and application pH ranges of BTB, CR, and BCG dye loaded nail sensors (top) and multiplexed colorimetric response at pH 4, 7, and 10 (bottom). Reprinted with permission from ref 63. Copyright 2016, Elsevier.

supply to enable wireless RF power transmission without the need for batteries or other energy storage units. Transmittance currently is limited to a distance of 15 cm and unfortunately, the authors do not state the performance of their system for long-term use, and no data on electrode fouling or sensor drift are available, which obviously must match the wearing time of the contact lenses.

Park et al. have shown a different strategy through an inductively, wirelessly powered, all-integrated glucose sensing contact lens.⁴⁸ Their approach is different, as the glucose level is directly shown in situ through an embedded LED. This makes

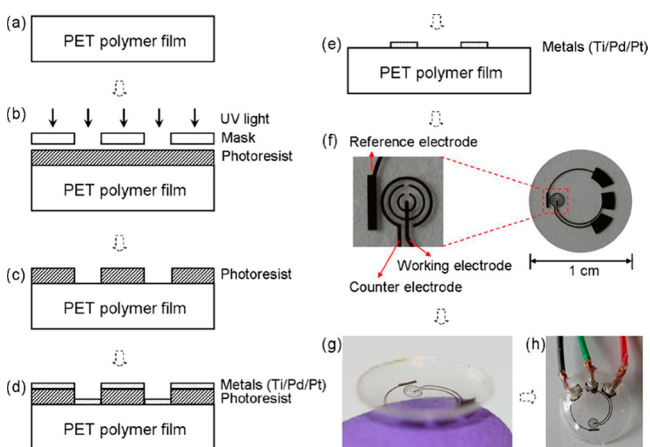


Figure 6. Sensor fabrication process and results: (a) a clean PET substrate is prepared; (b) the substrate is covered by photoresist and exposed to UV light through a mask; (c) the photoresist is developed; (d) thin metal films are evaporated on the sample; (e) after lift-off the metal pattern remains on the surface. After this step, the sensor is cut out of the polymer substrate and heat molded to the contact lens shape and functionalized with enzymes; (f) images of a sensor after it has been cut out of the substrate; (g) image of a completed sensor after molding held on a finger; (h) the sensor may be hardwired for testing. Reprinted with permission from ref 37. Copyright 2011 Elsevier.

their system independent of larger circuits and transmission elements to retain better optical compliance with the eye-vision through the lens.

Typically, contact lenses, glasses, mouth guards, and similar accessories are not worn permanently, implying that continuous online monitoring is not possible. This makes patches or tattoos for these applications more appropriate. If reliable function over longer time frames is ensured, and if these sensors are combined with systems that trigger an action, the next step toward an IoAT is done. Examples here are Google's glucose sensor,⁴⁹ and the concept suggested by Pesl et al.⁵⁰ comprising a real-time insulin bolus calculator, thus enabling a personal advice feature for diabetes patients.

2.4. In Vivo Sensing

The ideal "wearable" biosensor can be an in vivo implanted probe with the sensing element directly exposed to the required biological fluid or tissue, and the whole unit being fully incorporated inside the human body. As these sensors are accompanied by an invasive integration process, their realization is more complicated also in light of medical regulations which slow down innovation significantly.^{163,164} Furthermore, the continuous exposure to the living biological system increases complications of sensor drift, long-term stability, fouling, and internal calibration possibilities. Year's old, industrial research that has provided reasonable concepts for addressing stability by employing membranes and negative control sensor elements for electrochemical approaches points in the right direction.¹⁶⁵ Yet, implantable sensors developed so far are exciting examples of technical innovation. In recent years, various approaches for continuous glucose or lactate monitoring and monitoring of glucose and paracetamol have been shown⁶⁹ or others for single, remote monitoring of ATP or glutamate⁷⁰ and finally those associated with neurodevices.^{71–75} In vivo experiments were done on animal models of rats, rabbits, or pigs, or the respective tissue models throughout. A few human-implanted trial studies are conducted as well.^{84,85} Medical regulatory approval complying with the European AIMD directive⁸⁶ and public market availability is rare (see section 3, Senseonics, Inc.). While medical regulatory institutions approved devices, such as cardiac implantable electronics (i.e., pacemakers et al.), airway-stimulatory units, or neurodevices, besides the Senseonics product, no classical biosensor has been approved yet.^{87,88} It may be noted that an older approach for continuous glucose monitoring from the company Medtronic plc⁸⁹ is not a classical in vivo approach as it is connected to an outside monitoring, pumping, and supply feed unit. However, such semi in vivo approaches might still be the best possible solution for some time. Also, a dual sensing approach for glucose and lactate has been shown in a piglet model,⁷⁸ and a subcutaneous biochip platform, capable of measuring temperature, pH, and incorporating five additional bioelectrodes for further analytes (e.g., suggested: ATP, glutamate, or drugs) was presented by Cavallini et al.⁷⁹ While the latter is not yet comprised of the actual additional sensors, the biochip sets the foundation, and its biocompatibility was tested via 30-day in vivo mouse implants, with good host recoveries after that certain time,⁷⁹ suggesting a compatibility for long-time implants. Thus, the biochip is a good example of a platform capable of bearing multiple in vivo sensing modalities. Taking it one step further, combinations of sensing and medication release elements have been shown as, e.g., for glucose sensing combined with NO release, implanted in pigs.⁸⁰

Expanding the electrochemical sensing approaches to nucleic acids, Arroyo-Currás et al. have published their concept of integrated DNA electrodes for in vivo sensing of small molecules (e.g., doxorubicin) in point-of-care applications in rats.⁷⁶ A DNA probe (aptamer) immobilized on an electrode and modified with a redox marker will undergo conformational changes upon hybridization with the complementary chemical structure. This change will alter the electrode surface and result in a current change that is directly correlated to the concentration of the sample molecules. Furthermore, the same group has modified their method for a calibration-free sensing principle by using the target concentration dependent lifetime changes of the exponential current decay with chronoamperometry, enabling even better compliance with demands of in vivo sensing.⁷⁷ This calibration-free approach is an important example how calibration issues can be bypassed, also for other application areas. Yet, experience must show how this sensing principle can cope with long-term exposure (maximum application test for 8 h^{77,166}), signal response to sensing element fouling, and unknown possible interferents (e.g., drugs in patients) when applied in the human body. Amperometric signal modulation is another strategy, shown years ago by Rocklin et al.¹⁶⁷ This enabled a cleaning of the electrodes. While the authors only increased the long-term stability of the gold working electrodes to 2 weeks, this approach can be an interesting alternative or be imagined as an additional measure to reduce fouling effects. With respect to the reusability of the DNA-based biorecognition element for in vivo applications, Potyrailo and colleagues highlighted the reusability with aptamer-based approaches demonstrating reliable, 365 repetitive bind-release events.¹⁶⁸ This clearly is not sufficient for long-term in vivo use but demonstrates that with possible further sensor advancements, also nucleic acid-based sensors can be considered for such difficult sensing situations.

Also some optical approaches have been demonstrated for in vivo sensing. Chien et al. have shown an implanted, optical oxygen sensor in an in vivo rat model, e.g., for postoperative tissue regeneration studies.⁸¹ Furthermore, an optofluidic approach for optical stimulation of neural regions and microfluidic drug delivery, for “wireless pharmacology and optogenetics” has been shown by Noh et al.⁸² Their system uses soft microfabricated LEDs with a wireless RF power supply, to improve classical fiber-based systems and make the unit independent.

Other optical methods show promise as well. Li et al. and also others presented a nanomaterial technology that can be used for miniaturized, self-powered photodetection systems,^{169–172} Zobenica demonstrated a more sophisticated opto-electrochemical combination with a footprint of only $15 \times 15 \mu\text{m}^2$.¹⁷³ Combination with a nanosized light source for illumination might also be possible.¹⁷⁴ Even eye-implanted optoelectronics for soft retinal implants⁸³ could be envisioned, not only for an eye function supporting mode but also for further sensing applications. Optical approaches can be a suitable alternative to electrochemical methods but have their own set of interference challenges, such as regularly abundant or unknown optical active compounds (e.g., drugs) in the human body.

A key factor for successful in vivo sensing is knowledge and control over body reactions to the implant. Size, shape, and material of the implants but also the extent of tissue trauma generated during implantation have major effects on a successful implant.^{93,95} Exemplary from continuous glucose sensing, Wang et al. have shown the possible effects caused by sizes of implants,

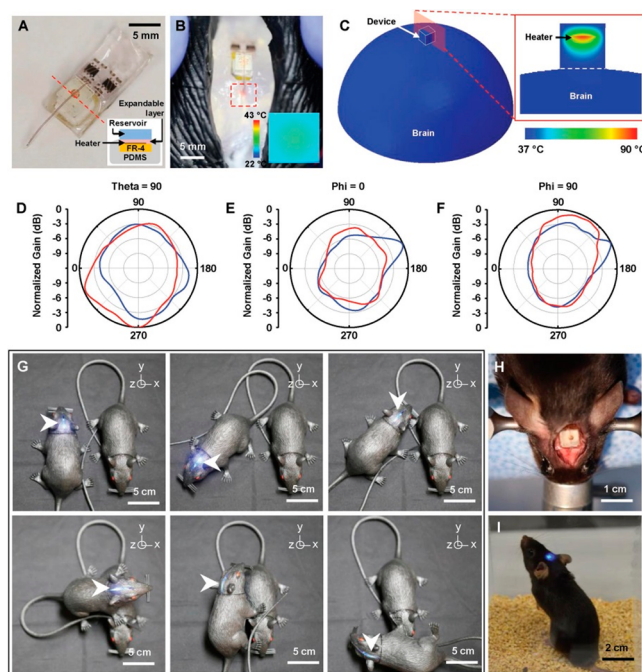


Figure 7. Feasibility study of fully implantable, battery-free, wireless optofluidic systems for operation in freely moving animals. (A) Optical image of a wireless optofluidic device encapsulated with 2 mm thick PDMS for thermally safe operation of the heater on brain tissue. The inset shows the cross-sectional image of the device, defined by the red dotted line. (B) Wireless delivery of red dye into the phantom brain (0.6% agarose gel) in the rat model. The red dotted box indicates the infused dye. IR image in the inset shows surface temperature of the heater's PDMS encapsulant ($\sim 30^\circ\text{C}$) in ambient environment at room temperature when the heater temperature reaches $\sim 100^\circ\text{C}$ during fluid delivery, verifying rapid heat dissipation through the PDMS encapsulant. (C) FEA modeling of temperature distribution at the surface of the 3D model simulating the device operated on the brain surface (left) and that at the cross-section cut by the red plane (right). (D–F) Normalized angular radiation pattern of two-channel antennas in optofluidic systems. Cross-sectional view at (D) $\theta = 90^\circ$, where polar angle θ is the angle measured from the zenith direction of the antenna plane, (E) $\varphi = 0^\circ$, where azimuthal angle φ is the angle measured from the orthogonal projection onto the antenna plane from the direction toward the antenna input, and (F) $\varphi = 90^\circ$. (G) Pictures of a model rat implanted with a wireless optofluidic system, demonstrating wireless operation at various angles. (H) Optical image showing full implantation of an optofluidic device into a mouse's head. (I) Optical image of a freely behaving mouse with an optofluidic device implanted under the skin, on the skull. Reprinted with permission from ref 82. Copyright 2018 Wiley-VCH.

sizes of needles for implantation, and tissue trauma, through model implants in rats.⁹⁵ Using histological evaluations, the sizes of generated foreign body capsules and inflammation factors were determined. The former can lead to a reduction of the biosensor functionality, commonly referred to the biofouling effect. Coating with hydrogels (e.g., PLGA/PVA containing dexamethasone)⁹⁴ can limit foreign body reaction (FBR) and thus sustain sensor performance. Furthermore, the rate of initial tissue trauma (caused by size of implantation needles) was found to control the rate of acute inflammation reactions, while sensor size was mainly responsible for extents of chronic inflammation and FBR.⁹⁵ Following the authors conclusion, the results stress the importance of (1) miniaturization of the biosensors, “the smaller the better” as well as (2) a need for

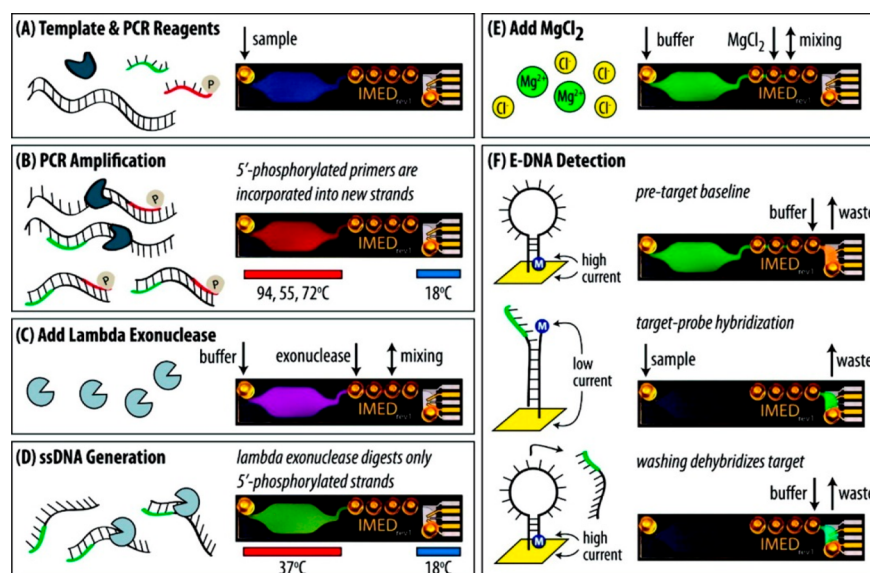


Figure 8. IMED assay overview. (A) Template DNA is added to a PCR reagent mixture containing phosphorylated reverse primers and (B) PCR amplified. (C) Lambda exonuclease is mixed with the product and (D) digests the phosphorylated strands. (E) MgCl_2 is added to optimize hybridization conditions. (F) Before introducing the sample, baseline sensor redox current is measured. Next, the single-stranded DNA product hybridizes with the E-DNA probe, modulating the redox current signal. Finally, the E-DNA probe is regenerated to verify target hybridization. Reprinted with permission from ref 177. Copyright 2009 American Chemical Society.

bioactive, immune-suppressive coatings for long-time body acceptance of the foreign elements. Other coating materials could be silicone or polyurethane.⁹⁰ Furthermore, investigations focus on different materials and techniques used as biofluid barriers¹⁰² of implantable devices or biodegradable silicon-based encapsulation layers and electrical interfaces,¹⁰³ e.g., for temporary in vivo sensors, biodegradable conducting inks,⁹¹ or degradable supercapacitors for energy storage.¹⁰¹

Protecting the sensor is equally important. In the case of enzyme sensors, enzyme molecule stability is often achieved through the use of protective membrane layers. In the case of DNA sensors, DNA probe stability must be ensured,¹¹¹ for which various approaches have been suggested, such as creating different DNA nanostructures,^{96,98,104} origami-like¹⁰⁵ or other,¹¹² by chemically end-sealing the DNA probes^{97,109} or using locked nucleic acids (LNAs)¹¹⁰ as probes. Further probe designs for electrochemical-DNA-based biosensing have been shown by Zhang et al.¹¹³ For all these approaches, long-term functionality of the membrane/coating, i.e., unaltered diffusion of analytes (varying pH, T, ionic strength), no diffusion and retention inside the membrane material, and no biofouling of the membrane material must be provided.

Also allergic potential or skin irritations especially upon medium- and long-term use are of immediate concern. An overview of requirements with transdermal patches has been published by Pastore et al.¹⁰⁸ which must be matched with materials needed for sensing and wireless data transmission. Miyamoto et al. have shown an interesting approach of directly skin-worn electronics as nanomeshes that are stable for at least 1 week of constant wearing and according to the authors are better skin-compatible and reduce itching or similar effects due to their breathability.¹⁰⁶

Finally, patient safety is a most important issue for in vivo sensors, as invasive methods are needed for implantation, and health effects caused by the implant have to be avoided.⁹² Automated insertion or extraction devices for implantable biosensors have been addressed as a patent recently.¹⁰⁷ Wireless

solutions for control and data transfer to the IoAT are mandatory, which ties research for in vivo sensing to research toward wireless integratable potentiostats¹⁰⁰ or data transfer systems.⁹⁹

2.5. Sensing Enhancement through Microfluidic Strategies—Future Visions

In point-of-care sensing, DNA-based detection systems play an important role.^{175,176} However, the inherent need of sample preparation, i.e., obtaining access to intracellular nucleic acid molecules and often amplifying those through a molecular biological reaction, currently prevents their application as a wearable device. Hsieh et al. have shown a promising solution.¹¹⁵ The authors used the concept of before mentioned in vivo aptamer electrode⁷⁶ in a lab-on-a-chip together with microfluidic sample preparation and DNA amplification steps and demonstrated almost online detection of pathogens (influenza virus from throat swabs or bacterial strains from mouse blood).

Clearly, this concept is still far from use as a wearable or in vivo sensor, but it points the way toward body-integrated DNA sensors, from which especially pathogen detection at the point-of-need would benefit. Important tasks to complete include, e.g., to ensure long-term operable sample preparation steps (reagent consumption, in vivo waste disposal) and to discover how long-term stable such a complicated in vivo-assay might be.

In general, microfluidic approaches (in polymers or in paper) are promising concepts as they enable more sophisticated on-skin testing. An interesting sampling approach was shown by Ranamukhaarachchi et al. where a hollow microneedle draws minute accurate sample volumes using optofluidics. It could be employed for wearable, therapeutic drug monitoring in the future.¹¹⁹ Other, less sophisticated approaches use capillary-driven sweat flow.¹¹⁴ The concept of microneedles is an in situ sensing approach but lends itself as well for sampling by implanted in vivo sensors for future developments. Current examples include the detection of alcohol,¹¹⁸ nerve agents,¹¹⁷ generally enzyme-linked assays,¹²⁰ and classical glucose

monitoring or combined with transdermal drug delivery.^{116,121} A further paper-microfluidics, portable sensor for the determination of HIV/HCV in human serum was presented by Zhao et al.¹⁷⁸ Combination of their multiplexed, paper electrode systems with a portable, wirelessly connected potentiostat to obtain an in-field testing system for pathogenic conditions would be desirable. As the authors state, long-term sensor and reagent stability has to be further investigated. Added to that, single sensor cost and intersensor reproducibility as well as functionality with human serum are additional challenges. Also, this approach would not reflect a classical IoT sensor as it still requires human intervention.

2.6. Progress Needed for IoAT in Wearable Point-of-Care Biosensors and IoT Connectivity

A multitude of published biosensor concepts, integrated for wearable detection (or designated as such) demonstrates that analytical chemistry is quickly moving into a direction of an IoAT. Yet, there are several, often disregarded, but major challenges. These belong to all basic sensor design requirements such as recurring calibration needs, robustness, and unanticipated cross-responses. Thus, sensing still remains to be the most important area requiring improvement, while signal read-out and transmission have been accomplished via RF or Bluetooth or cell-phone recordings, and wireless transmission can easily be integrated. In fact, Kang et al.¹²⁹ just demonstrated immense progress in the miniaturization of inductors, which removes some limits in generation of ultrasmall wireless communication systems as possible bottleneck. Additionally, Lopez-Barbosa and co-workers have provided a future perspective article with special focus on data capture and handling of disease-related POC sensing.¹⁷⁹

Aside from the development of (bio)sensors for more and more difficult analytes, attention is needed to provide sufficient power for this level of sensing and its associated data transmission. Batteries are not an ideal solution due to a need for frequent changes, waste generation, additional weight, and wearability issues related to safety albeit LOC device development pushes this area forward as well.¹⁴⁵ Solar power is only possible under sufficient light-conditions and would not allow for permanent day and night monitoring. Hence, much effort is undertaken on the improvement and adaptation of rechargeable batteries,¹²⁸ or as Zamarayeva and colleagues have shown, with their combination of safe and stretchable batteries and solar cells for recharging.¹⁴⁷ Also new power-generation solutions such as via nanogenerators through small mechanical movements (blinking eyes,¹³⁷ muscle movements^{125,132}), power enhancement strategies,¹³⁰ and even in vivo generators^{141,146} are of great interest to amend the power-production strategy of wearable sensors.

In fact, Wang et al. demonstrated a triboelectric generator¹⁴³ harvesting energy through a skin-like structure by employing a cell layer with physiological saline as a transduction- and electrode-layer, together with a silicone rubber layer as triboelectric element. The device can withstand a very high amount of strain of 600%, which makes it very versatile. Furthermore, Fan et al. have investigated the different dynamics of wearable energy harvesting devices (in solar or thermoelectric working modes),¹²⁷ providing deeper insights and allowing for better design of future models. Other solutions have been presented by Wen et al. with a composite textile-based solar-cell, nanogenerator, and supercapacitor combination¹⁴⁴ or Lui et al., with a very low-power consuming wearable device and

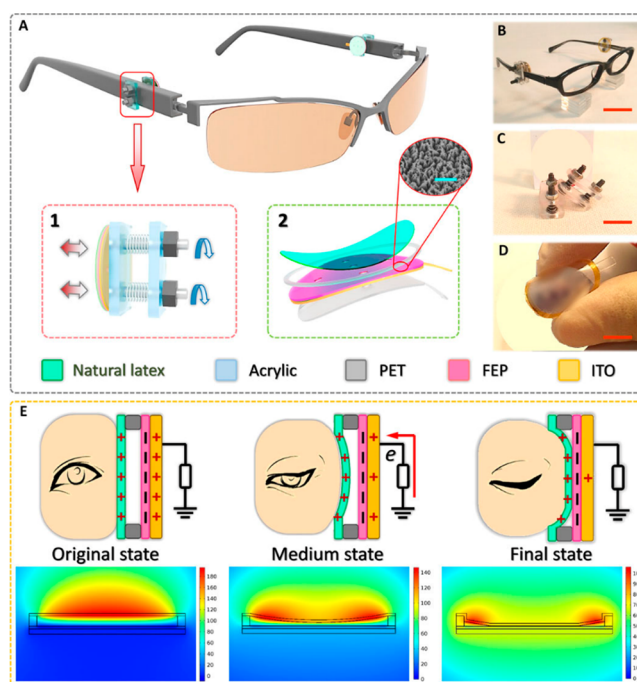


Figure 9. Structure and working mechanism of the msTENG. (A) Schematic structure of a pair of ordinary glasses mounted with msTENG. Bottom left: Structure of the fixing device for convenient adjustment. Bottom right: Schematic diagram of the msTENG. Inset: An SEM image of FEP nanowires. Scale bar, 5 μm . (B) Photograph of an ordinary glasses mounted with an as-fabricated msTENG. Scale bar, 2 cm. (C and D) Modified photographs of the simple fixator (C) and the flexible and transparent msTENG (D). Scale bars, 1 cm. (E) Schematics of the operating principle of msTENG. Top: Charge behavior when the eye is at different states during the blinking process. Bottom: Potential simulation by COMSOL to elucidate the working principle. Adapted with permission from ref 137. Copyright 2017 American Association for the Advancement of Science.

microwave-based, 2 m range, wireless power transmission to the sensor.¹³³ Sanni et al. from the same group have shown induction- and ultrasonic transmission-based approaches for deep tissue implanted devices.¹³⁸ Both variants are interesting for applications requiring low-frequency read-out and those with low-power requiring sensing systems. They provide the possibility to have an easily exchangeable battery system, decoupled from the sensing element. In a very different approach, Pang et al. developed a textile integrated biobattery using *Pseudomonas aeruginosa* as catalysts which can produce up to 6.4 $\mu\text{W}/\text{cm}^2$ usable energy.¹³⁶ This might be a small value compared to the energy storage of today's Li-ion battery cells;¹²⁴ however, power delivery is permanently available. While health concerns with *Pseudomonas* species may arise¹³⁴ upon direct contact to the skin, the idea of microbial fuel cells¹³⁶ as self-sustaining and robust system is an interesting alternative as energy source for body-wearable sensors. A lot of research has been done in this area, including genetic engineering of better microbial systems.^{122,123} A further overview of possible energy harvesting mechanisms is discussed by Shaikh et al. in their review.¹⁴⁰ Misra et al. have presented recent advances regarding the area of energy harvest, storage, sensing, and transmitting elements with low-power consumption,¹³⁵ emphasizing the importance of low-power consumption strategies also for data processing and on-sensor controls.¹³⁹

Table 2. Challenges and Areas Requiring Progress in Wearables and POC Sensing

category	challenges	possible solutions	refs
long-term stability	fragility of biorecognition element, fouling, aging, replacement cycles for in vivo sensors	see section 4	167, 198–210
calibration	sensor drift, calibration reagent consumption and stand time	see section 4, replacement less restrictive	166, 211, 212
multielement sensors	same, uniform calibration over all distributed sensing elements	section 4; network-linked matching and algorithm-based compensation, “bad sensor” voting logic	
portable solutions	robust energy supply	body energy harvesting or batteries	
wireless connection	unified communication standards (WiFi, RFID, Bluetooth), subscription cost	implementation of interoperability and agreed-upon standards, free of charge	
wireless protocols	active & passive, power consumption and range, authentication and encryption, possible topologies, traffic volumes, latency, multiplexing	choice for each application, improvement of capabilities, emerging technologies (5G and 6G), ensure compatibility of the different layers of the network architecture, safe encryption and authentication	184
substrate/sensor material choice	geometrical compatibility, flexibility, stretchability, curvature resistance, stress–strain withstanding to prevent high-noise ratios and bad sensing element/analyte matrix contacts	flexible polymers as, e.g., Ecoflex silicone or parylene	213, 214
biocompatibility	immune and FBR reactions, allergic potential, skin irritation	choice of materials and design, e.g., nanomeshes	106, 108
common influencing factors	seasoning, shelf life, environmental conditions	guarantee stability, sensor concept design with stable components	
personal variations	food preferences, age, body status, drug/medication residues	training on large test groups with AI-based matching (only if interferences are known)	
detection methods	smartphone camera-based detection (see Table 4)	external sensing hardware, reduces weight of sensor unit compared with smartphone (compare to Table 4)	

The power consumption of today's low energy Bluetooth solutions is in the range of microwatts (e.g., 33 μ W, 120 s supply intervals).¹²⁶ Also the power supply of wearable systems of this kind, mostly lies in the low microwatt regime^{132,146} up to greater power values.¹³¹ Exceptions, as shown by Wang et al.¹⁴² are yet still rare. Thus, the provision of and demands for power are approximately on the same level but still require further advances and fit-to-application technology choices to be sufficient in all cases.

As the true power of IoAT comes into play when thousands and millions of sensors are connected, standardized communication protocols and methods are needed, a collective basis should be found and few methods established for successful future market-ready products (to avoid situations such as the USB standards in cell phone charging we face today). This will ensure that new generations of sensors can easily be connected to the network, and data analyses can expand from individuals to entire populations. Data sets must be presented in normed formats, a seemingly simple request that yet at this point is far from being reached, albeit attempts by groups of scientists such as the Allotrope Foundation.¹⁸⁰ Similarly, special considerations regarding the design and layout of sensors have to be kept in mind with implications on their performance as highlighted by Sohbaty and Toumazou exemplary for ISFET CMOS sensors.¹⁸¹ The same is true for data transmission. Jackets with radiation-protecting pouches must be avoided increasing people's exposure to electric smog. Hertleer et al.¹⁸² describe instead a foam-based, clothing-integrated antenna for signal transduction. Also the placement of sensing patches on the body must be carefully studied. Murphy et al. showed that heart beating can affect miniaturized, body-integrated antennas and detune with time.¹⁸³ Thus, antennas have to be placed carefully or interference independent transmission bandwidths must be chosen.

In the case of IoT connectivity,¹⁸⁴ several layers exist, including data link, application,¹⁸⁵ and network layers. Their respective protocols define together how authentication,¹⁸⁶ encryption, quality of service, reliability, or power requirements are approached. Here, data links are the core elements of networking of most importance to sensor design. Several options

are used today, which includes wired Internet protocols (TCP/IP), wireless shorter range representatives e.g., WiFi, Bluetooth (low energy) in the 2.4 GHz frequency range, and NFC. For longer range application, cellular communication protocols are employed. Additionally, several other short- or long-range network protocols exist, e.g., ZigBee, SigFox, or LoRaWAN (Long Range Wide Area Network). The choice between the different options depends on required capabilities as Al-Sarawi et al. have highlighted.¹⁸⁷ Be it power consumption (SigFox very low and suited for communication between single sensors, whereas cellular is thus not ideal between single entities due to high power consumption), range (e.g., SigFox up to 50 km and cellular basically unlimited, NFC very short), security considerations (possible authentication protocols and encryption), or network topologies. Other criteria include, e.g., dynamics of the chosen protocol; i.e. RFID is static, only working with preprogrammed data but up to 200 m, and NFC is suited for active two-way communication but solely on very short-range.¹⁸⁷ Beyond current data link protocols and standards, new cellular networks¹⁸⁸ such as the emerging 5G cellular standard, or an envisioned 6G standard can speed up data sharing¹⁸⁹ and will be important for features like hologram interfaces, ambient sensing intelligence, included AI elements, TeraHertz- (millimeter wave and 60 GHz bands to cope with arising traffic¹⁹⁰) or visible light communications¹⁹¹ and three-dimensional-coverage technologies as Calvanese Strinati et al. have highlighted recently.¹⁹² The obvious possible benefits of higher bandwidths, lower latency, and lower energy requirements are counterbalanced by restricted transmission range, possible subscription prices for users, too much data traffic, too high numbers of sensing entities, and more.^{189,193} In the end, while the classical analytical chemist and sensor developer focuses on challenges associated with creating good, new sensors, with providing sufficient battery life for user acceptance and with deriving joint standards, signal transmission functions of today's and near future capabilities must be considered when designing a sensor.

The obvious next step, directing sensor design for IoT application, is the core idea of sensing data, triggering action without the need for human decision-making. Good examples

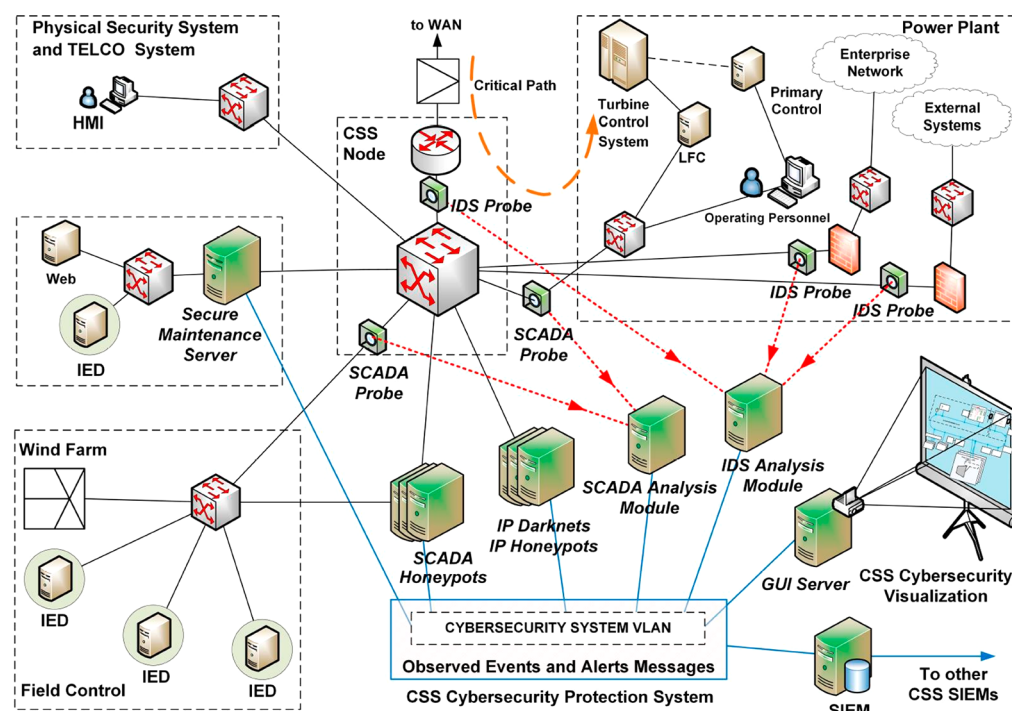


Figure 10. Power grid control system and the designed cybersecurity protection system. Reprinted with permission from ref 220. Copyright 2017 Elsevier.

Table 3. Environmental and Food Sensing Solutions

category	keyword	sensing principle	analyte	refs
global climate and agriculture	climate	birds, GPS, ISFET	humidity, pH, pressure	234–239
local environmental and urban monitoring	gas sensing, mobile & stationary	EC, optical (drones)	T, humidity, BTX gas, H ₂ S, H ₂ , NO _x , NH ₃ , CO, microbial analysis, water flow, contaminants	231, 240–251
local agriculture	precision farming, soil sensing, harvest size	EC, optical (drones)	Cl [−] , image-based, water transport	252–261
livestock monitoring	wearables, in vivo	EC, acoustic, probes	cholesterol, herd monitoring/grazing, T, estrus cycle	262–267
processed & packaged food	freshness	optical, EC, FET, MOX	T, humidity, cadaverine, biogenic amines, gas, ethanol	268–281

are the combination of glucose sensors with insulin dispense units,¹⁹⁴ pacemakers,⁸⁷ antibiotics release devices,¹⁹⁵ warning and alert routines,¹⁹⁶ and preclinical diagnosis-to-cure pathways,¹⁹⁷ and will expand to the integration with smart-home applications for sports or preventative medical nutrition plans and many more. In Table 2 challenges inherent to analytical methods designed for automatic and remote sensing are listed together with proposed solutions where already available. It is important to keep in mind that without solving these basic challenges also new sensing concepts will fail. Ultimately, this implies that the current bottleneck in the progress of sensor research is still to produce good, reliable sensors, which can work flawlessly in an autonomous, distributed environment.

2.7. Safety and Security Considerations

Safety and security considerations will not be addressed in this article as these expand into important and broad discussions of individual rights, protection of personal information, cyber-crime, etc. Possible malicious use²¹⁵ is easily foreseeable and a rise throughout the coming years in cybercrime activities is already predicted.²¹⁶ However, it should be pointed out that extensive research is done toward the protection of infrastructure elements^{217–220} and toward IoT-based systems.²²¹

As a solution for the herein described body sensors or wearables, investigations toward safe authentication protocols for body sensor networks have been done by Wu et al.²²² Also for implantable medical devices, these considerations are especially important.²²³

While today most people seem to be physically linked to their cell phone, direct exposure of the human body to unknown doses of electromagnetic fields and irradiation caused by the wireless transmission techniques in very close proximity to the body or even inside the body must be considered by the scientific community for the IoAT. Here, Lecoutere et al. have introduced a possibility to monitor the individual exposures²²⁴ and deduce possible health effects from that data in a later step.

3. SENSOR SOLUTIONS FOR AGRICULTURE, FOOD, AND ENVIRONMENTAL SENSING

Sensor systems, requirements, and solutions to deal with analytical challenges surrounding agriculture, food, and the environment are met with similar technological requirements, complexities, and challenges and are more often than not intertwined, especially when considering the IoAT. Sensing from farm-to-fork, for personalized food, ensuring food safety, protecting crop from pests, and dramatic climate events play

hand-in-hand and require sensing capabilities at all stages of the supply chain similar to the just-in-time principle of industrial production. We present here only a few examples of this vast research field (Table 3). The first examples of environmental monitoring require label-free techniques for long-term online sensing capabilities, whereas the last examples of packaged food sensing can be solved by single-use sensors and with an end point result (e.g., food is not fresh). In contrast to the point-of-care and in vivo sensors, power supply demands are mostly not an issue here, yet ruggedness and functionality over a large range of scales are major challenges. Hence, the inexpensive and rugged chemo-/physicosensors used in environmental settings are typically accompanied by computational techniques to improve the significance of sensing data. Information related to regional monitoring and toward foresighted predictions is generated in environmental monitoring,^{225–228} for soil quality determination in agriculture²²⁹ and predictive pollution locating.²³⁰ Kelly et al. demonstrated that the same can be used on a small scale, e.g., for home monitoring in single houses or living environments.²³¹ While their platform contains only simple sensors for temperatures and light intensity, it can be expanded toward other analytes (gas sensing, etc.) for smart-home monitoring and control. Further insights into suitable hardware programming for signal processing, data formatting for transmission or an interface for data review—all intended for a wireless building monitoring solution are shown by Jang et al.²³² More generally, Kassal et al. have recently provided a thorough overview of research solutions for wireless chemical sensors from 2007 to 2017.²³³

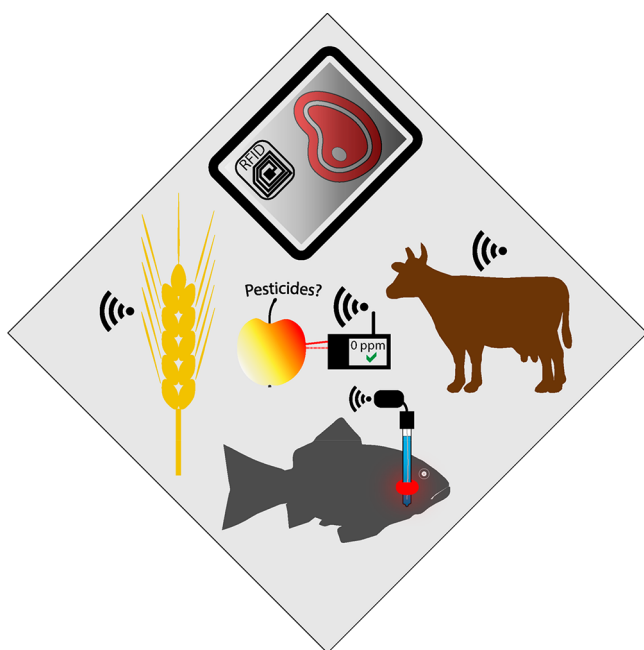


Figure 11. Sensor applications in agriculture and food sensing.

3.1. Global Air Pollution and Large-Scale Agriculture Monitoring

Agriculture relies on regional and global climate conditions and the natural ecosystem; hence large-scale environmental monitoring is an invaluable tool for modern agriculture. New sensor concepts can augment traditional and modern climate prediction strategies and expand much beyond even drones to taking advantage of naturally occurring globetrotters. Mandel et



Figure 12. Sensor needs for environmental sensing.

al. and later Gumus et al.^{234,235} have presented different sensors related to bird research.

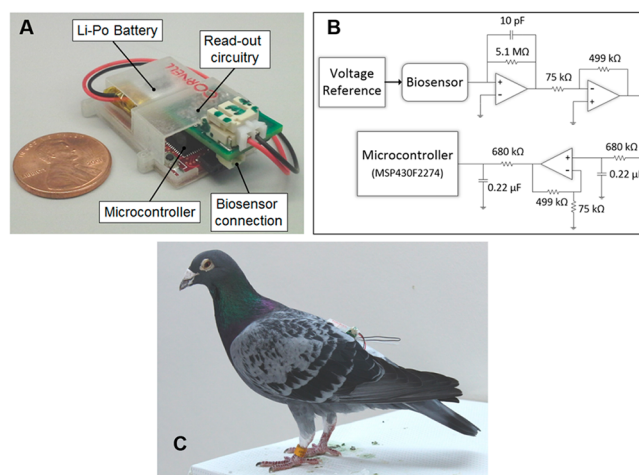


Figure 13. (A) The system consists of microcontroller, read-out circuitry, high capacity lithium polymer battery, and needle-type uric acid biosensor. (B) Two-electrode potentiostat system for driving the biosensor and collecting the data. (C) A pigeon with Lab-on-a-Bird system installed. The entire system weighs approximately 6.5 g, which is well under 4% of an average pigeon's weight and allows for long-term tag-attachment without limiting their motion. Reprinted with permission from ref 235. Copyright 2015 Public Library of Science under the creative commons CC-BY license.

A first version represented GPS modules mounted on birds²³⁴ to study their migratory paths to then inventing a “lab-on-a-bird”²³⁵ monitoring physiological conditions during the birds' flight. Although these sensors are not used for climate monitoring, this concept is a promising avenue for regional or global climate data acquisition combined with already existing wearable sensors for, e.g., monitoring atmospheric pressure, adapted from wearable body position detection²³⁶ or sensors capable of monitoring humidity, adapted from a gum-strain

sensor²³⁷ or small-scale humidity responsive materials.²³⁸ If these are combined to a yet-fictional “bird-sensor-network” with wireless communication and automated transmission to distributed ground stations, a live forecast could be possible—birds replacing drones. Then, even better conclusions about local or larger weather changes can be drawn. As sensors on (semi)wild animals are not really maintainable, solid robustness, covering needs of calibration and stability are most important, while the sensors are required to be designated as disposable. Farming can also benefit through even more precise and in-time weather forecasts, considering the weather’s very different but intense regional implications. It is interesting to note that a ground-based animal-sensor network has already been suggested very early by Li et al.²⁸² A further good example of a new class of global sensor networks for environmental monitoring with a large impact on whole ecosystem processes is the pH-sensing device presented by Johnson et al.²³⁹ Their self-calibrating, pressure-tolerant, and therefore depth-adapting pH monitoring ISFET sensor could be used for a very sensitive, global ocean pH monitoring network from surface to large depths, drawing important data for water ecology and ocean-life insights. Concepts like these, bearing a self-calibration feature, are few albeit most important for all different areas of (environmental) sensors. Earlier work in this area should be reconsidered as well. For example, a self-calibration concept in submersible, osmotically driven seawater nitrate analyzers (conceptual approaches also valid for sensors), with long-term functionality for at least one month was presented 25 years ago.¹⁰ A little bit later, the same group published a similar approach for long-term iron monitoring, bearing an autocalibration feature and working for more than one year in deep sea environments, which manifests true long-term stability.²⁸³ Fritzsche et al. have recently employed optical detection to determine oxygen, pH, and carbonate levels in seawater for long-term deployment together with a smart concept to reduce fouling by use of a separate filtering unit (a copper guard, thus also biocide effect).²⁸⁴ Nevertheless, the authors indicated clogging of the sampling interface to occur upon longer operation, which implies required maintenance. Finally, calibration-free concepts as outlined in [section 1](#) for in vivo sensors have also been previously demonstrated for environmental sensors. In the early 1990s, DeGrandpre et al. presented a calibration-free optical sensing approach.²⁸⁵ Their colorimetric sensor for a determination of the partial pressure of CO₂ in seawater operated for several months. Batteries ensured autonomous operation without interventions needed. Similarly, FT-IR spectroscopy concepts can also be suitable for ocean sensor application as shown by Kraft et al.²⁸⁶ The authors highlighted an advantage of a smooth and hydrophobic antifouling membrane versus rougher, more polar materials. Further analytes of interest, e.g., mercury in seawater, shown for depths down to 300 m by Saviozzi et al.²⁸⁷ can also be important in such a proposed ocean-wide sensor network for, e.g., seafood contaminant surveillance. To conclude, albeit not enough attention is given to calibration issues, workable options that help in the design of reliable sensors, ensuring long-term functionality do exist, and should be taken into consideration for sensing solutions in an autonomous IoT environment.

3.2. Local Environmental and Urban Area Monitoring

For local-scale environmental monitoring, stationary and hence more traditional bio/chemo/physico sensors are easily applicable. In general, for atmospheric or gas sensing humidity/

temperature effects and cross-sensitivities to other gases or volatile species are major challenges. As chemoresistor-based gas sensors share a relative unspecific response characteristic,²⁴⁰ various approaches have been suggested to address selectivity.^{240–242} In computational approaches, a neural network of sensors can be trained on gas mixtures (see Chiesa et al. discussed below) and result in highly selective sensor responses, as long as the sensor output remains constant. Otherwise, specific single sensors can be used, such as the miniaturized toxic gas sensing platform with wireless (NFC) powering and data collection by Ishihara et al. They sense electrophilic gaseous molecules with a combination of wrapped SWCNTs and metallic-supramolecular polymers through conductivity changes.²⁴⁴ Im et al. have shown a potentiometric approach for BTX gas sensing for on-field usage.²⁴³ Fahad et al. presented a room temperature, multi-gas-sensing platform on the basis of a modified nanoscale-silicon field-effect transistor.²⁴⁵ Niggemann et al. have shown a miniaturized, fiber-optics-integrated, surface plasmon resonance spectroscopy-based method for sensing of organic solvent vapors with several months of stability.²⁸⁸ Additionally, miniaturization of SPR sensors is currently realized through combinations with smartphones.²⁸⁹

Chiesa et al. have published 2012 their results on an ammonia gas sensor system, allowing for area monitoring of urban pollution on the scale of a small city.²⁴⁰ They use a carbon-nanotube-based chemresistor gas sensor to monitor ammonia in environmentally relevant concentrations to supervise urban pollution arising from vehicle emissions. The inherent inability to be specific toward just one analyte was overcome by using a fuzzy logic-based algorithm that trained a neural network system and was able to distinguish the analyte from interfering signals (NO_x and ozone). Ceramic was chosen as the substrate for a rugged system, being stable under outdoor conditions resulting in overall low manufacturing and operational costs.²⁴⁰ This combination of a chemosensor with data interpretation using machine learning like algorithms points toward future IoAT applicability, i.e., sensors, wirelessly linked to a central data analysis unit. Such approaches however still have some severe limitations as discussed below. Alternatively, data analysis units on each single sensor can be combined, and sensors communicate with each other yielding a very detailed mapping of urban air pollution on a short time scale. These results can then be used to trigger automatic alarm systems at a specific rate or to actively regulate traffic flow with new automated driving settings or implement bans on driving, when public health is endangered. A similar study was conducted in city parts of Cambridge, UK, with an electrochemical sensor network for CO, NO, and NO₂.²⁴⁶ For metal oxide gas sensors, which are often employed in such applications, Wang et al. have presented a possible solution. The authors used titanium dioxide nanowires as sensor surface and utilized UV irradiation to regenerate the sensor from vapor phase pollutants.¹⁶⁰ This is imaginable to boost long-term stability of such sensors in an autonomous application environment as already discussed above.¹⁵⁹ Additionally, a contribution for handling humidity and temperature variations has been made by Huerta et al. They developed an online decorrelation methodology (nonlinear function of semiconductor energy bands) and applied their method in a sensing experiment for almost one and a half years to provide constant sensor readings.²⁹⁰ A further approach amenable for mobile, localized environmental sensing has been shown by Kassal et al. presenting a paper-based chloride test and a wireless fluorimeter.²⁹¹ Albeit only a proof of principle, the

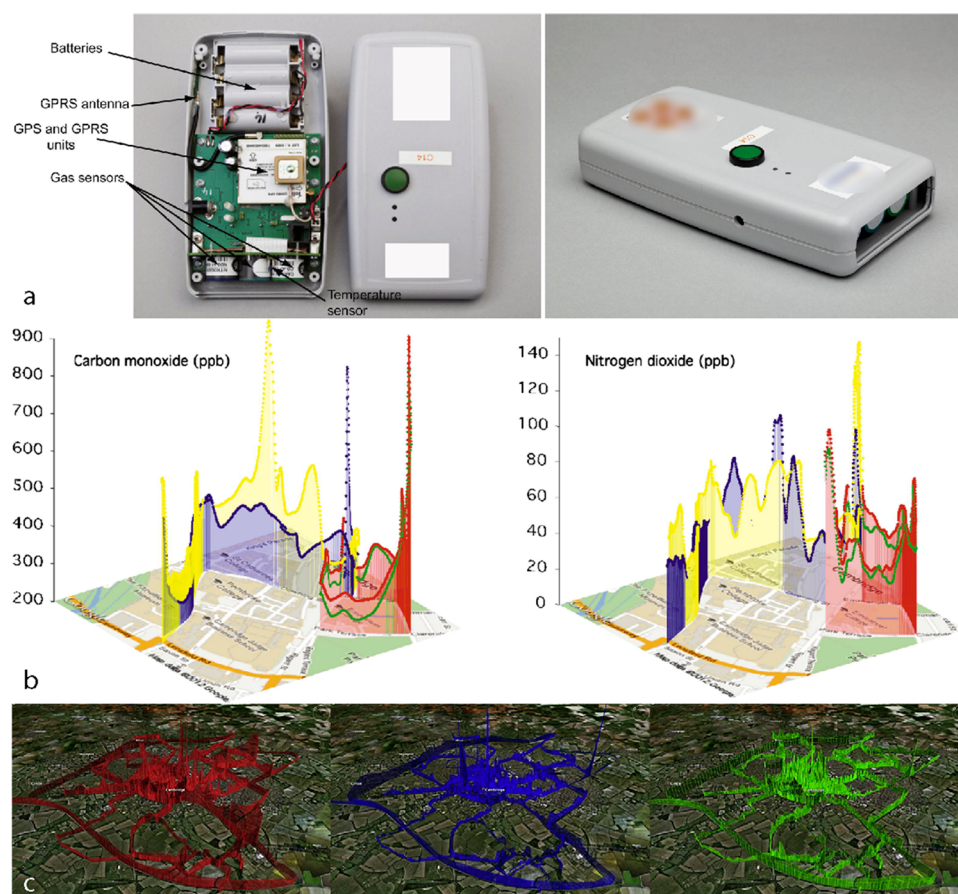


Figure 14. (a) Mobile sensor unit incorporating three electrochemical sensors (for CO, NO, and NO₂ in this case). Various components (GPS/GPRS, batteries etc.) are identified in the left panel. For clarity, the unit is shown without its protective wire mesh, which, during operation, is located in front of the sensors. (b) Selected CO and NO₂ measurements from two sensor nodes in parts of central Cambridge superposed on a roadmap (map data copyright 2012 Google). Data from periods during which volunteers walked together are shown in red and green, and those from when they walked apart are shown in yellow and blue. NO₂ data not corrected for interference with O₃ (see section 3.3 in corresponding reference). (c) 3D plots (left to right respectively) of CO, NO, and NO₂ mixing ratios giving overviews of measurements obtained during a large, mobile sensor deployment. The peak heights correspond to mixing ratio, with maximum values of 7 ppm, 4.5 ppm, and 840 ppb for CO, NO, and NO₂, respectively (map data copyright 2012 Google and 2012 Infoterra Ltd. & Bluesky). Modified with permission from ref 246. Copyright 2013 Elsevier.

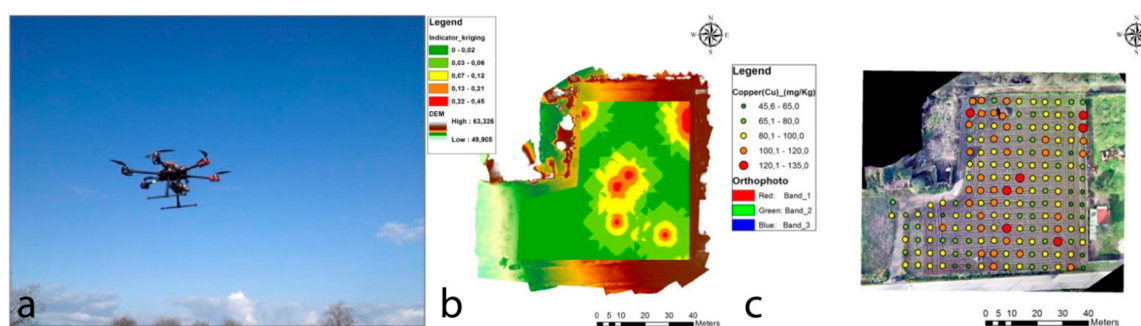


Figure 15. (a) The drone Tarot FY690s equipped with all hardware components and software tools. (b) Map of copper concentration interpolated with Indicator Kriging. (c) Copper concentration classes (in mg/kg) over the obtained orthophoto map. Reprinted with permission from ref 251. Copyright 2015 Elsevier.

authors suggested the sensor for sweat chloride monitoring. While questions of selectivity, calibration, reproducibility, matrix effects, external light protection or resolution have to be answered, the concept of portable fluorescence spectroscopy with paper-based—thus disposable tests is interesting. That approach is maybe even better designated for single-point, on-field applications in environmental sensing problems. Another contribution from Maity and Ghosh is a colorimetric paper-

based ammonia sensor.²⁹² How suited these approaches are for an “autonomous” IoT, especially considering environmental sensing, remains to be seen. Thus, in this application scenario, paper-based approaches are likely of less importance.

Hand-held solutions for localized, point measurements in a monitoring effort can also be envisioned, as, e.g., the approach for detecting hydrogen sulfide with a portable infrared sensor, shown by Guachetá et al.²⁹³ Also, biosensors, using biological



Figure 16. Precision farming in modern agriculture, exemplary in harvest and fertilization control and monitoring. Adapted with permission from CLAAS. Copyright CLAAS.

elements for sensing can be applied for environmental monitoring, e.g., for water quality monitoring using bacteria.²⁹⁴ A further solution toward long-term implemented passive microsensors, e.g., in water lines for hazards detection has been presented by Sanz et al.²⁹⁵

A comprehensive overview of sensing in urban area environments for smart cities was presented by Hancke et al.²⁴⁷ Broday et al. have also highlighted remaining issues and necessary improvements toward a densely stacked, accurate pollution prediction in urban environments.²⁴⁸ Capolupo et al. have presented a drone-based approach, together with predictive modeling to evaluate contamination of soils.²⁵¹ Finally, approaches like those from IBM, receiving a patent for a drone-based microbial analysis system for area monitoring toward possible contamination²⁴⁹ or a system for hydrological evaluation of surface water flows presented by Tauro et al.²⁵⁰ underline the possibilities for sensing from a hazmat or natural disaster protection perspective. Drone-based approaches can be envisioned as a smart solution to bypass sensor design needs for harsh environmental conditions and to avoid some external influences on sensors. However, they come with their own limitations given by optical detection systems and the distance to the sensing area, and are currently restricted to optical detection for ground sensing applications.

Above examples demonstrate a combination of sensor arrays and AI to deconvolute sensor signals and ensure sufficient selectivity. However, a major and yet unresolved drawback of such approaches is the signal stability over time. An AI-based signal analysis only works if the sensor can deliver the same response every time in many instances. This accounts even more for multiplexed solutions covering several analytes without specific sensor response. Practical unpredictable issues that lead to drifting or bad sensor signals including missing or off-scale calibration, sensor fouling and poisoning can likely not be solved through computational approaches alone. It is foreseeable though that AI components will assist when combined smartly with earlier discussed calibration issues.

3.3. Local Agriculture Monitoring

Precision farming refers to the high-resolution spatial monitoring of soil, crop, and plant needs^{296,297} as well as harvest yield prediction. Here, mainly “above ground sensing” is used, and efforts are made for connected, wireless networks of sensors in the farming area, reviewed nicely by Ohja et al.²⁵² Next steps are IoT-like machine systems, driver-less tractors,^{253,254} and research toward intelligent farming robot swarms.²⁵⁵ Obviously, sensors on machines must feature robustness against dirt contamination of the sensing surface and mechanical durability.

In-soil sensing is of equal importance for crop production, which is addressed by Harris et al. through a sensor system to be distributed in soil.²⁵⁶ Screen-printed potentiometric electrodes are used in distributed networks to obtain a spatially resolved

chloride monitoring. This enables the measurement and automated supervision of soil salinity for irrigation cultures, as their sensors transmit information wirelessly and are extended into a network. While the authors tested only distances of sensors of maximally 30 cm, expansion to larger area networks is a desirable future vision. Greenhouse farming with its limited spatial requirements and controlled environmental conditions lends itself well for initial progress and softens the overall needed improvements of autonomous or internal calibration, robustness against varying environmental conditions, mechanical impacts through harvesting machines, etc. When expanding from chloride ion monitoring to other essential soil nutrient ions²⁹⁸ such as nitrate, ammonium, phosphate, or potassium, a more detailed picture of soil nutrient availability and distribution can be drawn. Here, additional persisting chemical challenges are, e.g., cross-responses between ions such as potassium and ammonium in potentiometric sensors.²⁹⁹ Also the quality of nitrate ion-selective electrodes and determination of phosphate with potentiometric sensors³⁰⁰ are critical issues. An interesting concept has been shown already 2002 from Johnson et al.³⁰¹ Arising from ocean research, the authors developed an optical detection method to monitor nitrate, bromide, and bisulfide in deeper ocean regions and surroundings of hydrothermal vents. Their device is able to reliably long-term monitor (for years) these three analytes with high precision and resistance to sensor fouling. Calibration needs and sensor drifts or signal variations (temperature) were covered via the employed optical detection method, data treatment, and by accounting for salinity as correction parameter. Ali and co-workers have recently shown a potentiometric cyanide screen-printed sensor with stated long-term stability for almost half a year employing different ionophores.³⁰² Considering the solid nature of soil, the desirable combination of “above ground” and the “in-soil” sensing systems has a long way to go before it can be efficiently mass deployed and combined for precision agriculture enabled through the IoAT. On the other hand, drone supported monitoring solutions gain in importance such as for evaluation of crop quality and -needs,^{257,258} early stage, highly resolved treatment necessity detection,²⁵⁹ or harvest size prediction.²⁶⁰

A third line of research studies investigates plant sensing to obtain information about climate and soil effects on the crop itself. Oren et al. developed graphene-based plant-leaf “wearable” sensor films to monitor the water transport process and time scale²⁶¹ and hence provide information for irrigation or nutrient needs on a single plant scale. Special demands on such sensors include the energy supply (e.g., small, flexible photovoltaics³⁰³), ruggedness, small sizing, and the tolerance toward weather, mechanical and plant-growth strains, and finally the price of a unit.

with above-described platform with RFID tags or another NFC-based platform with smartphone read-out, that has been published by the same group.²⁷⁸ The latter uses simple, already market-available NFC tags that are manipulated to include chemosensors for gas sensing. Other efforts to the development of amine sensing in food packaging have been made from the industrial side³¹⁰ or shown in patents.²⁷⁹ A general overview of smartphone-based food sensing solutions has been provided by Rateni et al.³¹¹ Kavruk and co-workers have shown a colorimetric, paper-based sensor for the determination of degradation products of organophosphorus pesticides, and retaining 50% activity for 60 days at 4 °C storage, which might be interesting for food packaging.³¹²



Figure 19. Freshness indicator sensing spot on packaged meat showing the food status. Reprinted with permission from ref 271. Copyright 2014 Elsevier.

Finally, in another approach, Abad et al. integrated a gas sensor into RFID tags for food packaging.²⁸⁰ They combined a physical (humidity, temperature, and light) and a chemical gas sensor (MOX), together with memory and energy storage units on a flexible substrate (Kapton). In this last publication, as in many of the above examples, the focus of the authors is on the fabrication methods, the production of the tags, and the combination with transmission and read-out elements. More often, demonstration of actual food sensing (not solely the pure analyte) is missing and with it robustly tested sensing approaches. Many possible disturbing species, either food internal³¹³ or external (food additives, packaging leachants), might be present.³¹⁴ It should be pointed out though, that in some instances, long-term stability is not a major issue, such as for biogenic amine detection in fresh meat. Possible further sensor technologies to be integrated are, e.g., gas sensors described further above, or Sharma's et al. "electronic nose" which is based on the combination of rotational spectroscopy with a wireless EF CMOS transmitter for human breath ethanol detection.²⁸¹ These could be modified to food freshness monitoring. Interesting in this context is the work by Jedermann

et al. The authors studied conceptual requirements for sensor networks in shipped sea containers for food quality control,³¹⁵ which implicates that analytical chemists must obviously emphasize on the development of sensors exhibiting long-term stability, no required maintenance and autonomous operation.

Finally, in Table 4, challenges inherent to analytical methods designed for sensing across the farm-to-fork value chain are listed together with possible solutions. In section 4, topics specifically including calibration issues, long-term stability and fouling versus reliable sensor performance are highlighted again.

4. FACING CALIBRATION ISSUES AND POSSIBLE APPROACHES TOWARD RELIABLE SENSOR OPERATION

In above sections, we highlighted issues referring to the basic analytical challenges of true long-term stability, reliable autonomous operation and calibration and fouling. However, to date, most current IoT-near sensing concepts lack proof of robust performance, and typically miniaturization efforts make such challenges even harder. However, some solutions have been suggested throughout the years that might solve problems in many of the application areas described above. Solutions to provide reliable calibration and to better resist drift or fouling include, e.g., orthogonal approaches.^{316,317} As different detection methods usually have varying susceptibility against the same interference, a rational response can be estimated more reliably from the ratio of both single responses. Alternatively, calibration-free approaches²⁸⁵ are few and might work, depending on the environment, but most have not been tested for very long-term functionality. Bakker has written an interesting opinion regarding the realization of calibration-free sensors.³¹⁸ Concepts to shield the sensing element and sensor from interferences with filters,²⁸⁴ selective membranes^{162,319} (critical points highlighted by Morf et al.³²⁰), with durable solid membranes,^{321,322} and cleaning/renewing of the sensing element/membrane^{159,162} (with irradiation or heat) are realistic contributions toward long-term reliable operation. Yet, complete clogging with time must be prevented and alteration of the membrane, and diffusion to the sensor surface should not impact the sensor response largely. Self-calibration, incorporating calibration reagents¹⁰ or reference items are maybe the best solution for an accurate calibration but also become less realistic the more sensor entities shall be deployed. Cost, replacement or maintenance efforts, and stand time of reagents are issues here. For some applications, drone-assisted autonomous maintenance might be a workable solution. Different autocalibration routines, exploiting special environmental anomalies, where the analyte concentration is intermittently stable, might be also possible in some special cases. This has been shown several years ago by

Table 4. Remaining Challenges for Food & Environmental Sensing

category	challenges	possible solutions
environmental conditions	large temperature differences, humidity, matrix effects	ensure linear response of sensors, regulation capable housing, see ruggedness
cost	low profit margins, investment vs benefit evaluation	inexpensive sensors, single-use, improved production yields outweighing investments
ruggedness	environmental & agricultural settings require ruggedness	design of sensors in accordance to that
supply & maintenance	human and recurrent efforts with large-scale distributed sensors	inventory of reagents, low miniaturization needs, drones for maintenance
optical detection methods	standardization and reproducibility of optical (smartphone camera-based) read-outs: model diversity and their short lifecycle and different filters, cameras (aperture, ISO, bit depth, resolution) and light sources (wavelength/intensity, color profiles) limit these	external camera/light systems, designed as hardware-"smartphone-add-on" but with standardized components (requires agreed-upon standards!).

Table 5. Summarized Approaches To Enhance Long-Term Stability, To Provide Calibration, and To Reduce Sensor Drift or Fouling

method	description	refs
self-calibration	environmental adaptation, exploiting known, stable conditions for referencing and suited calculation model	239
	calculation model (optical detection) together with additional measurement parameter	301
	calibration reagents contained in device and regular calibration with contained standards	10, 283
calibration-free	transduction mode (EC): chronoamperometry, lifetime change of current decay	166
	transduction mode (EC): amperometric signal modulation	167
	multistrategy (colorimetric): (I) renewing sensing solution, (II) reach equilibrium state, (III) ratiometric calculations, (IV) thorough preparation	285
	detection method (EC): exhaustive coulometry	318
orthogonal	colorimetric/potentiometric/volumetric modes	158
	selective binding (mass-based) and column separation	316
	fluorescence/electrochemical/colorimetric	317
membranes/coatings	zwitterionic coating	39
	double membrane layer (adsorbent/enclosure)	162
	ionophores	302
	more stable materials in solid-contact ISEs	321
	PVC membrane	319
	liquid membrane/cellophane membrane	326
	membrane properties: (I) structure (smooth)/(II) surface energy/wettability (hydrophobic) as antifouling strategies	286
filters	copper guard (marine biofouling)	284
additional compensation sensors	interference compensation through negative control sensor units	165
recovery (heat)	heat to refresh sensing layer from adsorbed species (convection)	162
cleaning (UV)	TiO ₂ sensing layer/UV-irradiation for cleaning	159,160
sensing network based	reference-free algorithm in WSNs	324
	voting-logic: truth of the many, "off-scale voting"	
decorrelation methodologies	online decorrelation: via simultaneous temperature and humidity sensing	290
	correction factor: water salinity as separate measure (use salinity bias)	301
exploiting natural anomalies	weather conditions, lead to stable, low analyte concentration to which calibration refers	323
protection approaches	drones: reduce exposure of sensor to environmental conditions, bring sensor to maintenance	

Tsujita and colleagues, for NO₂ gas sensing in a year-long test with recurring autocalibration events in a 2–4 week cycle.³²³ If large enough populations of single sensing modalities are distributed, algorithm-based validation approaches of the response being in- or out-of-range becomes possible to some extent. However, disturbing effects have to be known or be predictable. Another main prerequisite is a densely populated sensor network. Here, Rajan et al. have recently shown an approach for sensor-network calibration with a reference-free algorithm, thus avoiding single-point failures.³²⁴ This can be a solution but still cannot fully eliminate unknown interferents and drifts. "Voting logics", deeming the response of the majority of all sensor entities as correct, seem more reliable the more sensor entities are included. Predeployment (lab-quality) reference-calibration routines in the desired matrix and environment are still necessary and can be kept as reference library, given that the interdevice variation is known. To some account, even correction for drift can be imaginable, if the majority of sensors react the same. Another approach, which is least desirable and practical from the point of view of an IoT, is to employ certain reference-calibration sites. Installing one or few sensors of a network at a convenient location with either calibration reagents supplied or with regular maintenance might be still workable. The as-such validated sensor information can be set as reference working space for all sensors. Yet, the more widespread the single sensors are deployed, the harder to identify unknown influences and the less applicable such a solution may be. Finally, digital approaches have the promise to run inherently calibration-free, as no sensor signal has to be

compared to a standard, but analyte entities are simply counted.³²⁵

In Table 5, all possible approaches are summarized.

5. EXISTING COMMERCIAL TECHNOLOGIES FOR THE IOAT

As the IoT is driving innovation especially in the engineering and IT fields, numerous companies have already demonstrated how analytical systems (beyond the physical sensors ubiquitous in automated industrial processes already) can be integrated. Products exist for all previously discussed application areas. For example, MC10, Inc. uses silicone sensor patches worn on the skin to deliver basic body monitoring data including ECG or pulse monitoring.³²⁷ AgaMatrix, Inc. presents an electrochemical glucose sensor as a connected solution with data presentation, sharing, monitoring, and health report generation.³²⁸ Senseonics, Inc. have presented a 90 day-implantable continuous glucose monitoring biosensor³²⁹ complying with medical regulations in Europe³³⁰ and already in the assessment process at the FDA³³¹ being at the moment the first approved device on the market. Basil Leaf Technologies LLC,³³² evolved from Final Frontier Medical Devices which has won the Qualcomm Tricorder Xprize for the design of an artificial intelligence engine "DxtER" that combines emergency medical and patient derived data for diagnosis together with several noninvasive sensors for health data enquiry.³³³ Noninvasive monitoring of blood glucose, hemoglobin concentration, and white blood cell count is in phase 1 clinical trials, and a urine dip-test connected with a mobile app for urine analysis and wearable

Table 6. Remaining Challenges for IT Infrastructure, -Elements, AI and Algorithms

category	challenges	possible solutions
cloud computing	bandwidth with “a trillion sensors”	implement edge/mist/fog computing concepts.
edge computing	overlap of miniaturization requirements and required computing power	improve miniaturized hardware performance or reduce calculation power requirements
AI & algorithm training	overfitting of data, training on testing data, false matches and conclusions	accuracy, question decision-making, control, large enough training sets
AI & algorithm training	to which extent is AI capable of training itself to new frameworks?	“self-training” capabilities would make AI and algorithms even more operator independent
AI & algorithms	limited algorithm workspace in what it is trained for (boundaries)	capability to make it work outside of narrow frames, more powerful AI
unified protocols and data	communication, data processing, and handling standards needed	“ISO-BUS” alike, joint data format like Allotrope

digital stethoscope and breath sound analysis devices are available.³³² Ontera (formerly Two Pore Guys, Inc.) developed a molecular meter, which is a hand-held device designed as an open system diagnosis and analysis platform.³³⁴ On the basis of silicon nanopores, generating an electrical current, sensing can process various sample forms (e.g., saliva, blood, urine, soil, food) and detect, e.g., DNA, RNA, proteins, or small molecules. Their goal is to develop test stripes from existing assays and adapt them to the hand-held read-out platform.³³⁴ MyDx, Inc. promotes a portable smartphone add-on-style chemical sensing device, using the electronic nose principle. The device is currently able to sense quality or contamination of cannabis and will soon be able to detect pesticides in food, air quality or metal, or other contamination in drinking water according to the manufacturer.^{335,336} Upon connection of many end-user devices, a thorough area monitoring could be envisioned.

In the case of environmental monitoring, the widely available modern precision farming software solutions are a good example. For instance, Cropio³³⁷ can display the on-field gathered nutrient information on soils related to the exact GPS position and therefore suggest interactions, care actions, and harvesting times. Another approach was presented by Bosch with their “Plantect” system for plant disease prediction in greenhouse farming.³³⁸ Software architecture has already been investigated to interconnect technologies from different suppliers and enable communication,³³⁹ demonstrating that in general a basic consensus for interoperability is needed.³⁴⁰ Farmer interaction to steer tractors or machines³⁴¹ or for decision-making³⁴² can be minimized within such IoT setting. Ripe.io provides blockchain technology for the farm-to-fork concept and ties it directly into the IoT.³⁴³

5.1. Business and IT Sector Initiatives Can Drive Innovations in Analytical Chemistry

Innovation in analytical chemistry relevant to the IoT is in part driven by initiatives such as those of the Xprize Foundation or the Trillion Sensors Initiative.³⁴⁴ Where traditionally the chemical, pharmaceutical, and food industries supported innovations in sensor and analytical chemistry developments, new partners and driving forces emerge today, as IT and analytical chemistry develop toward an IoAT. With this vision, predictions about the number of sensors to be employed go into the region of several dozen trillions of sensors during the next approximately 30 years.³⁴⁵ Several projects have been launched and are under development, e.g., the “S in 5” initiative from IBM³⁴⁶ or the CeNSE project from HP.³⁴⁷ New solutions like Intel with context-aware computing³⁴⁸ or Qualcomm, offering newly designed-for-purpose hardware elements (e.g., systems on chips) for IoT sensors³⁴⁹ are on the forefront of innovations. Analytical chemists must also be aware of basic IT infrastructural

development. Examples are the implementation of the IPv6 standard, enabling sufficient IP addresses to be able to connect every single sensor or concepts like edge,³⁵⁰ mist, or fog computing,³⁵¹ saving bandwidths for the enormous data traffic that can be expected for a worldwide IoT network. Much research is done toward IoT-suited edge computing infrastructure, regarding context-aware and real-time data processing as shown by Ren et al.,³⁵² network and architecture design considerations (e.g., P2P- or content distribution networks) as noted by Lopez et al.³⁵³ or how to smartly link edge and cloud computing under safety and security considerations.³⁵⁴ Of immediate interest to analytical chemists are developments such as the Movidius neural compute stick from Intel. It allows edge computing applications for a larger user-base and enables neural networking or deep learning applications with 100 Gflops computing power in the size of a USB stick for a price lower than one hundred dollars. This is well suited for small, stand-alone sensor designs.³⁵⁵ In fact, such components lower the technological hurdle for a broader base of researchers to apply neural computing design considerations to use it, without too much development and programming into their sensor studies. In the future, IT innovations will drive innovation also in analytical chemistry such as enabling through neural networks, deep learning strategies, artificial intelligence, and social- or other predictive and incentive modeling. Successfully applied to environmental sensing improved “user experience” drives people to save drinking water.³⁵⁶ On a larger scale, IBM’s Watson project³⁵⁷ helps in the analytical steps of data treatment, analysis, and results predictions and usage. It thus links detection and decision-making steps and makes them user-independent. AI goes a step further and enables new routes for sensing and detection of analytes that would not be possible without its capabilities. Shaker et al. developed a radar-based, noninvasive blood glucose detection device, using radar waves that allow measurements from outside, through the skin combined their technology with AI-based data evaluation, which could translate the several hundred wave features toward a certain glucose level.³⁵⁸ Mar et al. found that a trained artificial intelligence outperformed experienced dermatologists in reliable diagnosis of melanoma.³⁵⁹ Luechtefeld and his colleagues have just shown that advanced algorithms working from large chemical databases can predict a new chemical’s toxicity better than standard animal tests,³⁶⁰ and Jo et al. used a deep learning approach for anthrax screening.³⁶¹ Deep learning approaches can function well when trained for common pattern recognition tasks, but much still needs to be done in AI development to reach a human emulating intelligence and thinking as Dehaene and colleagues just illustrated.³⁶² Alternative current developments such as “Alexandria” or “Vicarious” will reduce the need for large

training data sets.³⁶³ Other challenges and possible solutions are listed in Table 6.

6. KEY REQUIREMENTS AND CHALLENGES TOWARD A SUCCESSFUL INTEGRATION OF ANALYTICAL CHEMISTRY WITH THE IoT TO GENERATE THE IoAT

The research discussed in this article provides a small overview of the substantial knowledge gained over the last years, and it contains a roadmap of requirements and tasks necessary to synergistically and successfully develop and merge analytical chemistry with the IoT concept. These tasks can be grouped into challenges related to (1) basic analytical challenges, i.e., detection, (2) data processing and issues arising with all data, (3) engineering, and (4) identifying other analytical techniques key to the future of the IoAT.

(1) Each analytical method that is used today for real-world applications must obviously provide highly reliable, accurate, and clear answers to the questions posed. Finding a specific analyte or a group of analytes within a defined sample is likely the least challenging task. Identifying an unexpected analyte in a defined matrix or finding an unexpected analyte in an unexpected sample increases the degree of difficulty immensely. Analytical chemistry has been traditionally very good at providing accurate results even in the most complex testing scenarios. However, this detection success is typically paired with ever-increasing sophistication of the analytical method, training of the operator, and cost and time spent. This trajectory, i.e., addressing complex analytical challenges with highly sophisticated analytical methods, however, is not sustainable for an IoAT. Long-term stability and autonomous stable operation are still posing the most demanding challenges. Here, strategies and requirements that have already been defined for the point-of-care diagnostic tests will likely be adopted by other analytical techniques as well to enable IoAT applications. This includes that sample preparation and detection must go hand-in-hand; orthogonal approaches must be developed to increase specificity and reliability in complex matrices; integrated controls must enable reliable single-point analyses (such as done in current homecare diagnostics), long-term stability and signal drifts must be addressed within the analytical system, e.g., via ratiometric measurements, calibration strategies, and generally more simple methodologies. Very few satisfying concepts toward a sophisticated solution for these challenges have been demonstrated in publications, patents, or products as outlined in this article. An apparent lack of innovation in this area is persisting among all discussed application areas, albeit it did not go unmentioned.³⁶⁴ Thus, while being drawn to the development of new and better sensors, analytical chemists must provide solid fundamentals toward true long-term, autonomous, and reliable sensing functions for all kinds of environments, and this must happen now.

(2) Big data, transmission of data to centralized laboratories, access-free databases are buzzwords when thinking about networking analytical devices and creating more information than achievable with separate devices. The biggest hurdle we face here may be the fact that we do not use a unified strategy for data recording, data presentation, and data interpretation. To create the large databases that we dream of, harnessing for curing diseases, finding sources of food safety concerns, or predicting local agricultural production capabilities, we must use standardized protocols in generating and presenting data, sharing meta data, and have defined and standardized data processing strategies. Organizations such as IUPAC and national chemical

societies have traditionally provided leadership, as have institutions such as the National Institute of Standards and Technology (NIST). The Allotrope Foundation is an example in the right direction, but for an IoAT these standards must be followed across different businesses and research fields, which in itself will be a difficult task for the future.

What we do with the data produced will equally change in the future. Artificial intelligence, machine learning, neural networks, and smart algorithms are part of the future of analytical chemistry as it advances to networked sensing systems that have significantly broader impact than our current locally focused analytical approaches. While this whole progress enables a myriad of useful solutions, we as scientists cannot neglect ethical considerations. Central questions to be asked include: who owns all the data? What to do with the data? How will you (as individual in a worldwide community) feel if the world knows your molecular information? How to ensure a fair and secure usage of that data, toward a better humanity? All these aspects must be discussed among the global society but not solely among circles of governments and the business sector. This is crucial to prevent misuse of these possible, powerful innovations.

(3) Engineering ingenuity and design will continue in their effort to integrate the analytical chemistry and sensor world with its surroundings. For many of the IoAT applications, small, inexpensive, rapid analytical methods are desirable. For others, integration into larger systems requires careful attention to interfaces, and for a few applications no demand for new engineering solution exists as those have been solved already, such as for environmental pollution control stations and for some cell-phone-based point-of-care diagnostics. Also with respect to costs, engineering design will play a major role. For the vast majority of analytical systems, lowering the costs per analysis is not only achieved through the assay components used, but also through the engineering design of transducers, packaging, and interfaces.

(4) The future IoAT will not only need to rely on distributed analytical sensors, but also on even more complex, lab-based techniques that are connected to the IoT through the same mechanisms previously outlined. Already today, the chemical industry is embracing this concept via its process analytical technology (PAT) concept (see Figure 20).³⁶⁵

We predict that the two most consequential technologies are mass spectrometry coupled with separation technologies, and next-generation sequencing (NGS). Mass spectrometry in combination with separation strategies has progressed to be one of the most versatile analytical techniques and provides information on an ever-growing number of analytes in complex matrices.^{366–370} The availability of large databases supports automated and AI-backed data interpretation,^{371–374} and together with smaller, semiportable devices, and advancements in miniaturization^{375–378} it seeks a future in mobile units with great relevance in an IoT environment.^{379–381}

NGS on the other hand can provide an answer to all questions related to genomic information and may make all other molecular biological and microbiological assays obsolete. Also here, databases are populated to take advantage of big data generation, and low-cost, high-throughput sequencing preferably in miniaturized systems^{382–384} will unleash the power of NGS for the IoT^{385–387} in lab-based³⁸⁸ and portable settings.³⁸⁹ Both techniques, MS and NGS however, have to overcome challenges such as the requirement for large, public available

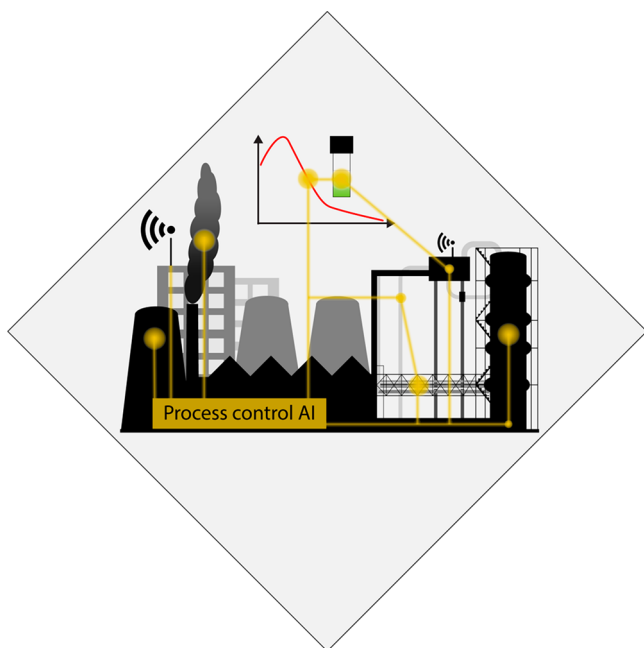


Figure 20. Industrial process monitoring in the field of PAT as model for IoT sensor networks.

databases and for NGS implementation of standardization and reduction of cost for data interpretation.

Finally, sustainability will become an immensely important aspect for analytical chemistry with respect to waste produced, energy consumed, and enabling on-demand local production. Already now, the plastic waste produced by point-of-care devices in remote and resource-limited areas on the globe are a threat to the environment, and new solutions are tepidly sought. For example, moving to recyclable plastic cartridges is not as simple as it sounds, as those severely and negatively affect storage capabilities in hot, humid climates. Therefore, the designation as “disposable” must be reconsidered, and new strategies for sustainable production, use, and recycling must be developed especially when considering a trillion sensor world.

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