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REVIEW

The future point-of-care detection of disease and its data capture and handling

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Abstract Point-of-care detection is a widely studied area that attracts effort and interest from a large number of fields and companies. However, there is also increased interest from the general public in this type of device, which has driven enormous changes in the design and conception of these developments and the way data is handled. Therefore, future point-of-care detection has to include communication with front-end technology, such as smartphones and networks, automation of manufacture, and the incorporation of concepts like the Internet of Things (IoT) and cloud computing. Three key examples, based on different sensing technology, are analyzed in detail on the basis of these items to highlight a route for the future design and development of point-of-care detection devices and their data capture and handling.

Keywords Biochips · High - throughput screening · Biosensors · Biotechnological products · Clinical · Biomedical analysis · Electrochemical sensors · Mass sensitive sensors · Process analysis

Introduction

Point-of-care testing diagnosis systems are devices that are capable of providing non-trained individuals with real-time diagnostic results in a particular scenario, eliminating the need for waiting time between the test and the results. Because point-of-care devices are commonly used by non-experts, the "sample-to-answer" format, in which the user loads a sample and in return gets a diagnosis, is commonly preferred [1]. The most common commercial point-of-care devices include electrochemical detection methods and immunoassays used for diabetes self-monitoring and home pregnancy tests.

Many efforts are being made to increase the availability of devices that provide patients with point-of-care detection. For instance, the emergence and propagation of antibiotic resistance has created a concern about the intake of antibiotics by patients that do not require them [2]. A successful point-of-care test could differentiate a viral infection from a bacterial one, reducing the unnecessary use of antibiotics in conditions known to be principally viral [3]. Moreover, patients with chronical diseases such as diabetes need to be constantly monitored. Providing them with a point-of-care detection device reduces their dependence on clinical diagnoses which improves their quality of life. In addition, if the information acquired from the device is easily transferred to the patient's doctor, a more accurate monitoring of the condition can be performed. Lab-on-a-chip (LoC) devices and microfluidics are currently being targeted because of their low sample and reagent volume requirements, easy integration, and rapid response [1].

Different types of diseases are of interest in terms of point-of-care detection and diagnosis. In general, diseases that usually require a long time between the test and the results are of special interest. These can be classified in terms of the target analyte as proteins, cells, nucleic acids, and metabolites.

The presence of proteins, generally in the bloodstream, can be used for the diagnosis of diseases [4]. Target proteins are usually detected by immunoassay, in which antigen–antibody binding reactions are used in the analysis because of their high

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specificity and sensitivity. Usually, immunoassay-based LoC systems involve microfluidic channels that take the sample from a sample preparation stage to a sample reaction and delivery section to a final analysis module [1]. Besides, magnetic particles have been studied as a way of immobilizing antibodies on a solid phase or labeling them for further detection [5]. The sample is exposed to the modified antibodies, which are then detected by means of an electromagnet to get information about antibody binding with the target protein.

Counting white blood cells, red blood cells, and platelets is commonly used in the diagnosis of immune system diseases and leukemia. Nowadays, blood cell count is mainly performed by means of a bench-top hematology analyzer, which still faces preanalytical, analytical, and postanalytical issues like requiring a central laboratory [6]. Creating a point-of-care hematology analyzer involves a change in the environment in which the sample is analyzed, which introduces an uncontrolled environment in terms of temperature and humidity, affecting accuracy and precision [7]. For instance, Zhu et al. [8] created a device for counting red and white blood cells by installing three imaging components on a cell phone. The method involved fluorescent labeling and PBS dilutions for counting white and red blood cells, respectively. In addition to optical detection methods based on the staining of blood cells, single cell impedance spectroscopy has been studied as a label-free method, which measures a cell membrane's capacitance and resistance to differentiate between white blood cells subtypes [9].

Cell counting has also been addressed for the detection and monitoring of HIV patients by observing a decrease in CD4-expressing T-helper cell numbers [10]. Normally, this is achieved by using a cytometer, making the test not portable and too expensive. Efforts have been made to obtain a point-of-care HIV monitoring device like the CyFlow® miniPOC by Sysmex which provides absolute CD4 counts for HIV monitoring by using dry monoclonal CD4 antibody reagents [11].

Being the backbone of DNA, nucleic acids provide information about gene encoding and expression in accordance with their sequence order. This is why obtaining information about nucleic acids sequencing could provide specific information about the presence of a disease. Since a complete DNA analysis should take place, nucleic acid amplification is often used to accelerate the process. However, this type of detection regularly requires expensive devices and reagents, trained personnel, and long processing times [1]. Many efforts have been made to integrate the procedure into a microfluidic LoC point-of-care detection device [12, 13]. Nevertheless, several specialized user interventions are still required for the analysis of the sample, which makes it far from being a point-of-care device. This explains the common trend of dividing the steps of nucleic acid analysis between independent devices that interconnect the whole process.

Metabolites are often used as biomarkers to detect diseases such as diabetes, liver disease, and acid base homeostasis [1]. Among all the existing point-of-care metabolite-based detection devices, glucose biosensors account for more than 80 % of the market [14]. Metabolite-based point-of-care devices use a reference and a working electrode connected to a specific enzyme that produces a chemical reaction in the presence of the target metabolite and results in electron transfer between the electrodes. The created current can be detected to determine the presence of the desired metabolite [1].

Despite the wide range of present sensor technology, modern society demands yet faster, more reliable, and cheaper diagnostic information. In addition to this, the market drives producers to optimize the supply chain, the manufacturing process, and the delivery. Fortunately point-of-care devices are not a large market like other types of sensors, such as those used in smartphones, where the location of the manufacturer is heavily dependent on large foundries and clusters. In any case, there are important challenges that anyone deciding to do research or to produce sensors and devices for point-of-care and disease detection has to consider.

Besides the aspects related to the experimentation for developing sensing technology, this critical review focuses on communication with front-end technology such as smartphones and networks, automation of the manufacture, and the incorporation of concepts like the Internet of Things (IoT) and cloud computing. Three key examples, based on different sensing technology, are analyzed in detailed on the basis of these items to highlight a route for the future design and development of point-of-care detection devices and their data capture and handling.

Point-of-care architecture

The architectural basis of a point-of-care device comprises (a) a recognition element and a transducer to an electrical signal; these two are commonly known as biosensors; (b) an electronic signal processing unit for the instrumentation and the integration to a user-friendly interface, also known as the end-user device (Fig. 1).

Recognition element

Some of the most common recognition elements are DNA [15, 16], antibodies [17, 18], aptamers [19, 20], enzymes [14, 21], and nanostructured materials [22–25] such as metallic nanoparticles, polymeric nanocapsules, carbon nanotubes (CNTs), and graphene.

DNA-based sensors use functionalized DNA strands or catalytic DNA molecules to detect a specific analyte on the basis of cleavage and ligation [15]. Functional nucleic acids used for this purpose are obtained through the SELEX

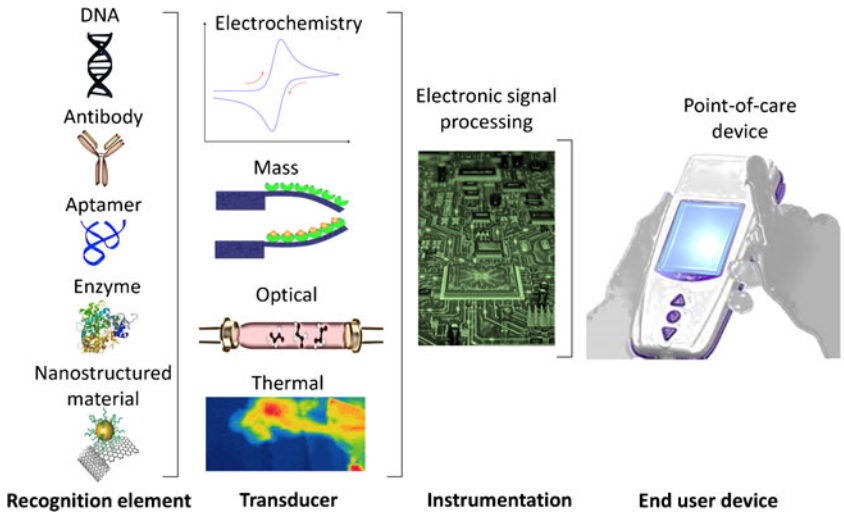

Fig. 1 Point-of-care device architecture

process, in which a chromatography column is used to selectively separate the nucleic acids of interest. These nucleic acids are usually attached to a nanomaterial that serves as a transducer element, increasing the sensitivity of the system [16]; graphene oxide appears to have generated particular interest in this context. DNA-based sensors can be used for the detection of several analytes such as DNA mutations, proteins, metal ions, and cysteine, among others [16].

Antibody-based sensors are functionalized substrates that contain an immobilized antibody specific to a target analyte [18]. These sensors can be used for detecting the presence of specific substances in a fluid, studying the binding and kinetics characteristics of an antibody and its antigen, and determining the concentration of a substance. This category of sensors includes those based on surface plasmon resonance, surface-enhanced Raman spectroscopy, quantum dots, and nanowire FETs, among others [17].

Aptamers are chemically synthesized oligonucleotides with high specificity and sensitivity towards a specific target. Their length is usually between 35 and 100 nucleotides [26, 27]. Aptamers use their geometrical configuration to specifically bind with the target molecule; in terms of applications, food allergens have been detected by using this technique [28].

Enzymatic sensors are known for their high selectivity, by "wiring" an enzyme to the electrode [21]. The immobilized enzymes work as mediators effectively facilitating the transport of electrons, produced by enzyme-specific reactions, from the enzyme active site to the electrode. Because they are immobilized, they cannot escape the biosensor film and leach into the surroundings, thereby allowing sensor use for in vivo measurements [14]. The applied electrode can be operated at the desired voltage, eliminating background interference. This design also lends itself to repeated and prolonged measurements because there are no reagents to replace. There are currently a fair amount of enzyme-based biosensing companies like OptiEnz Sensors, Lamdagen Corporation, and the Gwent group that provide different modes of detection and enzyme stabilization with an average life of a working month per sensor [29].

Nanostructured materials such as CNTs and graphene have often been used as intermediates between glassy carbon, gold, or platinum electrodes and enzyme biorecognition components that confer higher sensitivities, faster response times, and lower detection limits compared with glassy carbon electrodes [30]. The three-dimensional shape and large surface area of CNTs allow large enzyme loading that is accessible within a very thin layer [21]. CNTs are also popular in sensor applications other than electrochemical biosensors owing to their unique optical, chemical, thermal, and mechanical properties [30]. In addition, metallic nanoparticles, especially gold, and polymeric nanocapsules are usually used to increase or enhance biorecognition. In many cases, these nanostructures are used in combination with one of the aforementioned biorecognition elements [23, 25, 31].

Transducers

There are several ways to transduce the biorecognition signal into an electrical signal. These includes electrochemical responses, mass changes, optical absorption or transmission, and thermal readings. Depending on the type of bioreaction or the desired degree of invasion of the technique, one can choose the best transducer. In general, the chosen transducer will define the way in which the end user will interact with the point-of-care device. Some of the most commonly used transducers for point-of-care devices are those related to electrochemical readings and optical detections.

The first ones are usually composed of two basic components, a chemical (molecular) recognition system, which is the

most important part of a sensor, and a physicochemical transducer that is a device that converts the chemical response into a signal that can be detected by modern electrical instrumentations. Biosensors are chemical sensors in which the recognition transducer utilizes a biochemical mechanism [32].

Optical biosensors are normally non-invasive methods and exploit the combination of different molecules to produce a change in the absorbance at a specific wavelength. In some cases, the biorecognition element is bonded to a secondary metabolite that produces a side reaction which can be detected. In some other cases, the target is directly recognized at a specific wavelength in accordance with its composition or chemical bonds. These methods include UV/VIS/IR spectrophotometry, quantum dots, colorimetry, and fluorescence, among others. Some of the first point-of-care devices based their operation on amperometry [33] and colorimetric transducers [34].

Case studies

Three examples of point-of-care devices are described and analyzed according to their advances in communication with front-end technology such as smartphones and networks, automation of the manufacture, and the incorporation of concepts like IoT and cloud computing. All three cases are based on the use of a small sample of body fluids from the patient to determine blood glucose concentration, blood chemistries and electrolytes, and the human papilloma virus (HPV) on portable devices. The first two are already available as commercial devices, whereas the last one is not yet on the market.

Glucose detection

Blood glucose biosensors have been a growing market since their first commercial appearance in 1973 from Yellow Springs Instruments [33]. With the main goal of monitoring the levels of glucose in the blood, nowadays glucose biosensors mostly use an invasive technique that integrates electrochemical transducers and microprocessors to generate an electrical signal in accordance with the analyte concentration [35]. Their popularity increased owing to their relatively cheap and easy manufacture, in addition to their fast response [36]. It is estimated that this market will be worth US$18 million by 2018 [37]. In order to evaluate the state of the art of commercial blood glucose biosensors, the latest devices from Roche Diagnostics, LifeScan, and Bayer are described and analyzed.

Roche Diagnostics was the first company to release a strip-free blood glucose meter in 2010 named Accu-Chek® Mobile. This system has been updated through the years up to the Accu-Chek® Aviva Combo, which represents the latest device from the company. This strip-free glucose biosensor requires a blood sample of 0.6 μL and has a test range of 0.6–33.3 mmol/L [38]. It contains a Bluetooth module with a range of almost 2 m that can be paired with different devices, five preset time blocks to manage insulin, and the possibility to set alarms and reminders [38]. However, no mobile applications have been released by the company, limiting the possibility of communication of the Accu-Chek® Aviva Combo with other devices from the Accu-Chek® family only.

On the other hand, LifeScan's OneTouch® devices are claimed to be the most prescribed brand by primary care physicians. Inside this family, the OneTouch® VerioSync is perhaps the latest version of the glucose biosensor. It uses a color indicator to communicate the blood's glucose level which is displayed in a backlit LCD colored screen [39]. The device also gives the possibility of pairing via Bluetooth with an Apple device where data can be processed and exported to a logbook, which can be shared via text or email [40]. Nevertheless, running the iOS application tends to drain the battery of the device on which it is running because the OneTouch® VerioSync uses regular Bluetooth rather than low-energy Bluetooth [33].

Similarly, Bayer has its own family of devices for measuring blood glucose levels based Contour Next test strips. Their latest device includes a micro USB and allows the user to set reminders and markers. A Bluetooth module connects the device to a Medtronic insulin pump which allows it to provide personalized therapy [41]. However, Bayer's devices experience high interference in the presence of xylose which might cause false results. In addition, the LCD display screen is not backlit which, even when producing a lower energy consumption, introduces a difficulty in night tests.

Roche Diagnostics, LifeScan, and Bayer are the leading companies in terms of self-sampled glucose biosensors. All of them provide a relatively good solution for the monitoring of blood glucose levels by diabetes patients. However, different improvements can be considered. For instance, according to the US Food and Drug Administration, all current strips used for the measurement of blood glucose levels seem to suffer from high interfere in the presence of xylose after food consumption [42]. Moreover, some of the strips may also present false results in the presence of high concentrations of cholesterol and triglyceride, bilirubin, uric acid, ascorbic acid, and acetaminophen [35]. The fact that glucose biosensors are not entirely selective may end in a false diagnosis which might lead to an incorrect dosing of insulin. Current solutions include the need for the patient to request a second or even third test or algorithms in the data processing that try to evidence the presence of an error. However, this may end up in an increment of costs, which includes the extra strips used, an increase in the number of tests performed by the device without an increment in the number of results acquired, and higher computational costs. Future devices might consider multiple sensor systems instead of a single sensor system to help in the detection in the presence of an interfering analyte.

On the other hand, the number of devices that allow a long-term analysis is still low, as is the number of devices that provide wireless communication with a computer or smartphone. The possibility of having the acquired data outside the measurement device can facilitate the communication between the patient and the doctor, which might also improve the response time towards a medical condition that might require an intervention. Furthermore, the actual commercial devices that provide a wireless communication require high levels of energy while failing in providing a real-time data transfer [39]. Improvement in these matters should be addressed.

Likewise, glucose measurement is based on the necessity of blood sampling. According to Pelika Sun [43], 60 % of the lances are either too deep or too shallow. A shallow lance will result in too little or no blood sample, whereas a deep lance will cause bruises and pain. As a consequence, patients tend to avoid the glucose test, resulting in a lack of diagnosis. This is why a pain-free lancer or non-invasive tests should be studied. Many efforts have been made with the second ones which include GlucoWise™ (MediWise Ltd), the Symphony™ CGM (Echo Therapeutics), and the Grove Glucometer, among others [35]. Nevertheless, none of these is yet commercial. Even so, a non-invasive point-of-care detection will greatly reduce the lack of accuracy that rises as a consequence of skin pigmentation, body water content, hydration, temperature, and the presence of interfering analytes as stated above. Xu [44] developed a portable non-invasive device based on a cyclic pattern between the amount of light absorbed by the finger and a heartbeat, which can then be used to determine the amount of glucose in the bloodstream.

Moreover, an improvement in terms of the IoT should be considered. A growing industry is emerging around the need to connect devices and users via a wireless interface. The IoT is a network of interconnected devices that reduce the presence of human error in different systems and processes. The application of this in glucose biosensors can lead to a more precise diagnosis as well as a faster emergency warning system [35].

Blood gas analysis

Point-of-care detection devices for blood gas analysis have been produced in response to the needs of intensive care units, emergency departments, and cardiac surgery [45]. In addition, blood gas analysis has been used in the diagnosis of chronic respiratory failure and long-term oxygen therapy owing to the decrease in testing times and costs that it provides [46].

The i-STAT® point-of-care blood analyzer is an Abbott Point of Care device that uses two drops of the patient's blood on a disposable cartridge to perform diagnosis tests such as cardiac markers, lactate, coagulation, blood gases, chemistries, and electrolytes, and hematology [47], among others. It also provides its own calibration procedure for each of the tests as well as a barcode recognition region where patient and operator can be identified. In addition, Abbott Point of Care has released the i-STAT® Wireless System, which allows one to upload the obtained results to the electronic medical record (EMR) of the patient [48].

A study was conducted in the Cheyenne Regional Medical Center [48] which showed the improvements of including the i-STAT® Wireless System in their diagnosis procedure, which included the possibility of testing at the bedside, an acceleration in patient care decision making, a reduction on sample handling errors, and an improvement in patient management at the emergency department. Likewise, Veldhoen et al. [49] studied the possibility of using the i-STAT® analyzer on intraosseous samples instead of venous ones for situations in which intravenous samples are difficult to obtain. The results showed that the point-of-care device is a suitable solution for measuring pH, base excess, sodium, ionized calcium, and glucose. Moreover, results showed that analysis of intraosseous samples with the i-STAT® blood analyzer is a suitable procedure for aiding emergency decisions in both adult and pediatric patients.

The i-STAT® System works with disposable cartridges that require a correct refrigerated storage facility to avoid false results. It provides a wide range of analyses that are easily performed without the requirement of a technician. It also includes data management software that allows one to take notes with the device that are transmitted wirelessly to the EMR with the test results.

The company Epocal has released the epoc® blood analysis point-of-care device. As with the i-STAT, this device provides a wireless bedside measurement that interfaces with the facility's system to transfer the results from the device to the patient's EMR [50]. In contrast, results from epoc® are obtained in 30 s after the acquisition of the sample and require 100-μL blood samples on their test cards, which do not need any refrigerated storage. It also provides a barcode recognition of the patient and the operator and allows the measurement of pH, sodium, potassium, calcium, glucose, lactate, hematocrit, and partial pressure of oxygen and carbon dioxide [50].

Point-of-care devices have been of special interest owing to their improvement in the turnaround time (TAT) in comparison with clinical laboratory procedures [51]. In the case of blood gas analysis, a difference in TAT of 1 min for the point-of-care device versus 79 min for the clinical laboratory procedure has been observed [46]. Moreover, the greatest expenditure of time in the clinical laboratory procedure is due to the need to transfer the sample to a location, rather than the procedure itself; nevertheless, the intralaboratory TAT is still greater than the point-of-care device TAT. In addition, it is important to emphasize that blood gas analysis is highly dependent on the time between the acquisition of the sample and its measurement [52].

Nevertheless, the cost per measurement of a point-of-care analysis is almost 2.5 times greater than a clinical laboratory analysis [46, 53, 54]. However, if the clinical costs of hospital stays and the number of future medical visits are considered, an overall cost per process reduction of 24.7 % is observed as stated by Oliver et al. [46].

Point-of-care blood gas analyzers have appeared in response to the need to decrease the TAT to aid more effective decision making as well as to decrease false results due to changes in the sample during the transference between the acquisition location and the clinical laboratory. However, they still require the operator to be a physician because of the need to use intravenous samples. This means that there is still a challenge for point-of-care devices to be easily used by patients and connect their results through the IoT.

HPV detection

The HPV is a double DNA chain virus and the most common sexually transmitted viral pathogen. It is associated with cervical lesions, condylomas, and cervical cancer [55]. There are more than 100 types of HPV, some of which are low risk types that are associated with the production of genital warts (e.g., HPV 6 and HPV 11), and others are of high risk that are associated with the development of cervical cancer (e.g., HPV 16 and HPV 18), the most prevalent being HPV 16 [56, 57]. About 35 and 100 deaths per 100,000 women are attributed to HPV in developed and developing countries, respectively; however, between 50 and 80 % of sexually active women worldwide have been infected at least once in their life by a type of HPV [56]. Statistically, each year about 500,000 new cases are diagnosed with condyloma and cervical cancer, causing approximately 240,000 deaths [58].

Two molecular assays are currently implemented in laboratories to diagnose and classify HPV, hybrid capture (HC) and polymerase chain reaction (PCR) [59]. In HC, the cells are denatured and hybridized with a probe of highly specific RNA where hybrids are captured on a plate with specific antibodies. The signal is amplified by the use of an enzyme and a chemoluminescent compound, and the reading process is performed in a microplate luminometer [60]. In contrast, in PCR, several million copies of a target DNA sequence are generated by DNA polymerases to facilitate the virus detection.

Despite the widespread use of standard laboratory techniques, there are several approaches aimed at detecting HPV in the early stages of cancer, in order to develop the appropriate treatments. Several approaches have been studied in order to detect HPV, some based on electromechanical microsystems [61], others on DNA recognition and microfluidics [62]. Although these increase the sensitivity of the measurement, they involve high cost of manufacturing as well as non-automated fabrication processes. Similarly, the use of CNTs for enhancing the selectivity through electrochemical detection has been studied [31, 63]. In some non-traditional methods, surface acoustic wave (SAW) technology has made its entrance by improving the signal processing and allowing easy integration into microelectronics, though without a high selectivity [64]. All these alternatives have so far experimented with DNA strains of the HPV, showing great advances in new possibilities of portable measurements, although far away from real sample experimentation. On the other hand, an antibody-based design with an electronics coupling for a rapid readout has been reported and compared to HC and PCR using real samples for the detection of HPV [65]. This device can contain almost 100 independent biosensors in a microfluidics platform the size of a glass slide. The readout process has been included by the use of front-end electronics that can be plugged into a cell phone for direct file exchange and the possibility to use its connectivity to communicate with third parties, such as the medical doctor or a clinic to follow the patient [66].

This whole system, BMS mobile, consists on a disposable biomicrosystem, which is a set of biosensors placed on a microfluidic platform that is placed onto an electronics reader (Fig. 2). This reader can determine the validation of the test in 60 min and show the result via an LCD display, or, it can be plugged into a smartphone to show detailed information about the test and the HPV, recharge batteries, and contact medical personnel or store historical data [66, 67]. Each test cost was calculated as US$2 [65] compared to US$10–25 for the clinical tests, which are also more time consuming [57, 65].

Nevertheless, this device is far from having all the key aspects that a future point-of-care detection should include. The BMS mobile solution includes the use of smartphones, not only as a source of energy, but also as a communication hub that can incorporate the use of Internet and Internet-related platforms. This device includes a battery that can supply enough energy to establish a Bluetooth communication with the smartphone and perform the test without draining the smartphone's battery [66].

The manufacture of the BMS mobile biomicrosystem allows the selective immobilization of monoclonal antibodies in every well to make an independent biosensor per well after the manufacture of the platform. This can be easily automated with standard high-throughput procedures that are commonly used in the production lines of pharmaceutical companies. There are few examples of diagnosis microsystems that allow one to introduce or immobilize the recognition element after the whole platform is fabricated, promoting the automation of its manufacture path. Some of these cases include the use of microfluidics, though with the use of highly precise and coordinated pumping systems [62], and DNA microarrays, using nanoparticles, for the detection of multiple HPV types [68]; however, in both cases, manipulation of the recognition material is very time consuming. In order to ease the manipulation and localization of certain nanoparticles and nanosized

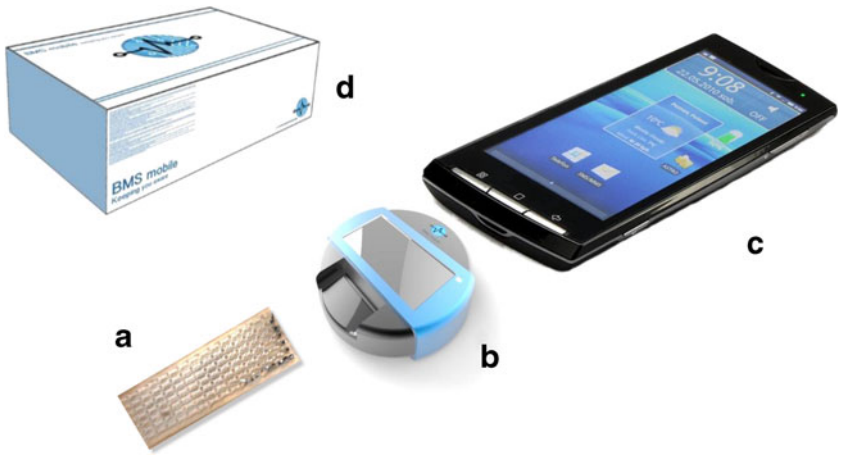

Fig. 2 BMS mobile system: **a** Biomicrosystem, **b** electronic reader, **c** smartphone, and **d** product package

material into sensing devices, magnetic response strategies have been demonstrated to be feasible, precise, and low-invasive techniques to place complex structures or even to locate and orientate DNA strains [69–71].

The fabrication of the microfluidic platform has also been a highly debated issue. The use of PDMS and related polymers for soft lithography [72–74] eases the rapid experimentation for research institutes and is presumed to be a cost-effective technology. This might not be true if you consider mass production where the processes automation is a strong determinant of the final production cost. In some cases, milling, drilling, injection, laser or simply 3D printing might overcome the costs for mass production. In this sense, the BMS system might have a better chance than soft lithography technologies of being scaled up into mass production because the manufacturing process of the microfluidic platform does not take place at a research laboratory but by using the local manufacturing chain based on polymer laser cutting technology.

Other fluidic microsystems for detection inside microenvironments can include the use of enzymes for the detection [75, 76]. The two cited cases illustrate two different approaches; the first cases [75] describes the use of fluorometric equipment already present in many laboratories to exploit the use of fluidic microsystems. The manufacturing process is easily scalable because it is based on drilling and coupling different layers; however, not including the possible immobilization of the enzymatic content after manufacture makes it necessary to have a more complex chain of fabrication. The second case [76] allows the immobilization of the recognition element after the whole fabrication of the microfluidic platform in a similar way as the BMS system; nevertheless, the manufacture of this platform requires the introduction of several techniques that are not always compatible when automated, such as physical evaporation and polymeric coating. Despite the remarkable differences in these microsystems, they share a common characteristic with the BMS mobile system; polymeric 3D printing can be a possible solution for a ready-to-go manufacture process.

In addition to factors related to the connectivity to smartphones, manufacturing processes, and automation of the manufacture chain, a relevant topic to address in future point-of-care detection is IoT. The biggest incentive for businesses, including point-of-care, to move ahead with IoT is arguably the potential financial returns from its "productisation" [77]. Therefore, financial returns are key for IoT to be fully adopted by businesses [78] as forecasts have predicted 26 billion IoT units by 2020, having a major portion based on wireless sensors [79] including wireless enabled point-of-care detection systems. As point-of-care detection is a changing market highly influenced by the new technology discoveries and release, IoT presents an added value that has to capitalize on future developments. It is remarkable that IoT applications enable a reliable and robust device-to-device interaction [79], but more importantly human-to-device interaction; this is a driving force for market entry of point-of-care devices. Nowadays, there are countable examples of IoT included into sensors; moreover, there is a growing interest in the possible connections between healthcare devices and IoT. Recently, Dressler and Fisher [80] reviewed the main challenges for in-body and wearable IoT devices. They stated that IoT for in-body and wearable devices has become an established research field especially for medical and fitness applications, while control of these devices strongly depends on the careful management of the information. In addition, the possibility to link IoT with the cloud computing monitoring and analysis of raw data from sensors and detectors has been identified [81, 82]. Unfortunately, real commercial examples that really exploit the possibilities of IoT and the opportunity to run a heavy data analysis through cloud computing for point-of-care devices are some way off.

Finally, after including cloud computing, the next frontier is its extension to machine learning algorithms, opening the possibility to create configurable point-of-care devices for each patient, in other words, customized point-of-care and disease detection systems. Once again, examples are still scarce, and some of the few running examples are those related to facial recognition

Table 1 Comparative features of example technologies

Feature	Glucometer 1 Accu-Chek Aviva Combo	Glucometer 2 Onetouch VerioSync	Glucometer 3 Contour Next	Blood Analyzer 1 i-STAT® system	Blood Analyzer 2 epoc®	BMS mobile
User-friendly interface	Yes, it is based on the "sample-to-answer" format	Yes, it is based on the "sample-to-answer" format	Yes, it is based on the "sample-to-answer" format	Yes, it contains an easy-to-follow menu and test procedures. The obtained results show the normal ranges which help the post-analysis	Yes, it provides a digital interface that allows the user to choose between the different tests and observe the obtained results	Yes, it incorporates an interface without the need for more equipment
Energy independence	It has a stand-alone rechargeable battery	It has a stand-alone rechargeable battery. However, it drains the battery of the device it pairs to via Bluetooth	It has a stand-alone rechargeable battery	It requires two 9-V lithium batteries	It has a stand-alone ultralife lithium ion rechargeable battery	It has its own energy source without draining the smartphone energy
Wireless connectivity	Yes, via Bluetooth with devices of its own family	Yes, via Bluetooth	Yes, through Bluetooth with an insulin pump	The system provides both wireless and cable connectivity	Yes, it communicates via Wifi or Bluetooth	Yes, through Bluetooth
Pairing with cell phones	No, it does not have any pairing possibility	Yes, but only with Apple devices	No, it does not have any pairing possibility	No, but it can be easily developed	Yes, but the cell phone must have Microsoft Windows Mobile 6.0 Premium Edition	Yes, it can be paired through Bluetooth with any smartphone
Proprietary application for smartphones	No App has been conceived for the system	Yes, it has an iOS App	No App has been conceived for the system	No App has been conceived for the system	Yes, it has an android App	Yes, it has an android App
Use of Internet of Things	No, it does not have connectivity therefore no IoT capability	No, but it can be incorporated via the smartphone connectivity	No, it does not have connectivity therefore no IoT capability	No, but it can be incorporated through the computer connectivity	No, but it can be incorporated via both the smartphone and the computer connectivity	No, but it can be incorporated via the smartphone connectivity
Use of cloud computing	No, and it is not a nearby possibility due to the lack of connectivity	No, but it can be incorporated via the smartphone connectivity	No, and it is not a nearby possibility due to the lack of connectivity	No, but it can be incorporated through the computer connectivity	No, but it can be incorporated via both the smartphone and the computer connectivity	No, but it can be incorporated via the smartphone connectivity
Manufacture automation	Yes, it is a commercial product	Yes, it is a commercial product	Yes, it is a commercial product	Yes, it is a commercial product	Yes, it is a commercial product	It is possible through standard technology
Possible mass production	Yes, it is already mass produced	Yes, it is already mass produced	Yes, it is already mass produced	Yes, it is already mass produced	Yes, it is already mass produced	Yes, for every part of the system without difficulties
Ease for the new point-of-care features	It can be adapted to new point-of-care features	It can be adapted to new point-of-care features	It can be adapted to new point-of-care features	It has been constantly changing to adapt to new point-of-care features	It has been constantly changing to adapt to new point-of-care features	It can easily incorporate other detectors by placing other antibodies in different wells without a dramatic change in the manufacturing process

using machine learning over cloud computing for social networks [83], and some initiatives from pharmaceutical companies to use machine learning techniques to study large databases of compounds to prioritize certain mixture experimentation.

Conclusion

Every case that has been analyzed in this review presents strengths and weaknesses. Some of them presented a good interaction with other components such as computers, smartphones, or other point-of-care devices; however, in some cases the interaction included the rapid drain of the energy source of the other component making the design unfeasible. In some cases, they included user-friendly interfaces as part of their development, but in almost every case, the possibility to handle the information by means of the user was extremely limited.

In terms of manufacture, all examples have a lot to be redesigned and improved. In general terms, glucose-meter manufacturers lack proper strip printing methods, thus leading to an important number of false positives by the interference of xylose and high concentrations of cholesterol, triglycerides, bilirubin, uric acid, ascorbic acid, and acetaminophen. The HPV BMS mobile systems requires a better microfluidic platform manufacturing process. The drilling process of layers that are then assembled can be easily substituted by an injection method that can reduce the cost and time of manufacture while improving the physical appearance of the device. Finally, blood gas analyzers still face the challenge of expanding their users not only to physicians but also patients. Table 1 summarizes the features that every example exhibited and detailed the information for future perspectives in each topic.

To the date, none of the point-of-care examples nor references included in this review fully integrated the use of IoT or cloud computing for each patient's needs. An interesting configuration of smartphones or tablets integrating accelerometers to provide quantified feedback and classify appropriate and inappropriate usage of a cane for patient recovery [84] is clearly heading in the right direction. Therefore, there is a long track to be covered by any existing development to fully integrate all key aspects for future point-of-care technology.

Compliance with ethical standards

Conflict of interests In this work, there are no potential conflicts between or related to any author.

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