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Application of Electrochemical Methods in Biosensing Technologies

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Abstract

Introducing biochemical factor to electronic devices have created a new branch of science. Recent development in biosensing technology enabled progress in pathogens detection. Currently, wide range of biomarkers (enzymes, peptides, DNA, microorganisms, etc.) recognize various target analytes, starting from basic metabolism changes to serious infections caused by pathogens. Improved sensitivity, selectivity and response time of sensors have instantly replaced traditional techniques. Easy handling, low production costs and miniaturization have met therapeutics need. Biosensing technologies are very strong point in telemedicine in public healthcare. This chapter will focus on electrochemical techniques for pathogens detection and show trending applications in biosensing technologies.

Keywords: sensor, biosensing technology, bioelectronics, electrochemistry, impedance spectroscopy, cyclic voltammetry, immobilized electrode, nanomaterials, noble metal nanoparticles, recognition element, human pathogen, pathogens detection, virus, bacteria, DNA, markers, diseases, telemedicine, point-of-care, lab-on-chip

1. Introduction

The biosensor era have started in 1962 by invention the first glucose meter by Clark and Lyons [1] and speeded up in uncontrollable pace. Currently, it embraces fields such as bio-telemedicine, biology, environmental monitoring, drug discovery, food safety controlling and others. The term 'biosensor' stands for the electronic analytical device incorporated with biological sensing element and physiochemical transducer [2, 3]. The main biosensors success was achieved by transforming technological sophisticated machines to small handy devices.

Especially, electrochemical biosensors are in main interest. Implementation of biological factors to electronic devices have improved sensitivity, selectivity, limits of detection (LODs) and limits of quantification (LOQs). Also miniaturization, simplification and portability have made them user-friendly and available for large audience of non-specialists and patients.

2. Biosensors classification

Biosensors classification mainly relies on the receptor and transducer type and is represented in **Table 1** [2, 4, 5]. Besides the suitable measurement technique used, the biosensor have to meet the requirements, which are detection limit, linear response range, response time, sensitivity and selectivity, stability and reproducibility. New types of biosensors are being developed, transducer hybrids, like photoelectrochemical [6].

Great sensing development can be observed in electrochemical field. Initially detected analytes were basic chemical compounds like glucose, urea, subsequently macromolecules like proteins, whole cells, viruses, bacteria and other pathogens. Currently, it is possible to follow antigen-antibody interactions, detect tumor markers, DNA materials, etc.

BIOSENSORS			
BIORECEPTORS	TRANSDUCERS		
ENZYME	OPTICAL	ELECTROCHEMICAL	MASS-BASED
ANTIBODY			
DNA	RAMAN FTIR	IMPEDIMETRIC	PIEZOELECTRIC
CELL	SPR	AMPEROMETRIC	MAGNETOELASTIC
BIOMIMETIC	FIBER OPTIC	POTENTIOMETRIC	
	OTHER	CONDUCTOMETRIC	
		VOLTAMETRIC	

Table 1. Biosensors classification based on bioreceptor and transducer types.

3. Electrochemical detection

Electrochemical biosensors are devices containing electrochemical transducer. They provide semiquantitative or quantitative analytical information, thanks to biochemical receptor. Electrical changes due to reduction/oxidation reactions of analyte can be analyzed in different ways. In this case, measured properties are current or potential. The principle is the change of solution properties due to production/consumption of electrons that is measured relatively to always stable reference electrode. The process depends on the species activity, not on the solution concentration, because it is focused on the working electrode surface. There are also electrochemical techniques

which do not use direct electron flow and do not focus on the redox reaction. For example, the changes of electrode's surface deriving from surface biofunctionalization and molecular interactions like antigen-antibody, receptor-ligand and others are analyzed. In this case, measured parameters are resistance, capacitance or impedance. The easy way of transforming a biological interaction to simple electrical signal makes it attractive for sensor industry. The strong advantage is a wide range of electrical properties which can be measured and quantified with methods like potentiometry, amperometry, voltammetry, conductometry and impedance (described below). Moreover, multiple electrode materials used as receptors and methods of their immobilization are available [7].

3.1. Electrochemical cell

The conventional electrochemical cell contains three separate electrodes: the working electrode (WE), the counter electrode (CE) and the reference electrode (RE). The WE material must be a chemically stable conductive material, such as carbon, gold, platinum and more. The redox process occurs on the surface, so can be polarized both, cathodic and anodic, depending on analyzed reaction. The electrode material strongly influences the measurement because every material has different parameters, such as potential window, capacity. The WE should have high reproducibility and S/N characteristics. The toxicity and costs are also important. The CE (auxiliary electrode) provides electron flow between WE and CE and closes the current circuit in the cell. The CE surface area must be much larger than WE, to avoid kinetic limit of the process. It can be carbon, platinum wire. The RE produces constant potential in whole cell, balances the WE reaction. Requirements are low impedance and non-polarizability. The most common RE is standard hydrogen electrode (SHE) with a zero half-cell potential or silver wire coated with silver chloride [2, 7].

Except conventional electrochemical cell with three electrodes, there are variations and miniaturized versions. Microfluidic cells concept offers easier sampling and cleaning, enhanced sensitivity and reduced interferences [8]. Obviously fewer reagents are consumed and less waste is generated. For example, the microbial fuel cell (MFC) can convert organic substrates by microbial catabolism to electrical signal [3]. On the lab-on-a-chip devices (LOC), the three electrode system is miniaturized to few centimeters square platform with multiple laboratory functions. It is possible to handle very small fluid volumes (picoliters level) [7]. Screen-printed electrodes (SPEs), three-minielectrodes are deposited or printed onto polymer substrate forming ultrasmall measuring system. They are mass produced with high reproducibility and low costs. This set allows easy modifications of WE surface [2, 9].

3.2. Electrochemical sensor: potentiometric detection

Potentiometric sensors measure the potential change at one electrode referred to another electrode. The electrical potential difference or electromotive force (EMF) is measured at zero current value [4]. For example, the potential is formed when antigen-antibody interaction occurs. The reaction is described by the Nernst equation. Concentration response is logarithmic, allowing very small changes detection [2, 7]. Zelada-Guillén et al. has first applied this technique for *Staphylococcus aureus* detection in real-time. Single-walled carbon nanotubes

(SWCNTs) were used as transducer and functionalized with anti-*S. aureus* aptamers by two approaches. In covalent functionalization, LOD was 8×10^2 colony-forming units (CFU)/mL. Non-covalent approach has had higher sensitivity but LOD was 10^7 CFU/mL level [10].

3.3. Electrochemical sensor: conductometric detection

Conductometric transducers measure variation of the ionic strength of a solution, which changes current flow or electrical conductivity. Despite the few advantages like low-priced thin-film applications [4], direct real-time monitoring [7], no reference electrode need and miniaturization possibilities, this technique gives less sensitive responses than others electrochemical methods [2]. Hnaiein et al. have implemented this technique for *Escherichia coli* detection. Authors have used streptavidin-functionalized magnetite nanoparticles which interact with biotinylated antibodies, anti-*E. coli*. Detection on 1 CFU/mL level causes 35 μ S conductivity change [11].

3.4. Electrochemical sensor: amperometric detection

Amperometric transducers measure the direct current from redox reaction under a constant potential applied on WE. The activity of recognition element varies before and after interaction with a target molecule [4]. The product must be electroactive and undergoes a redox process [12]. The current is a rate of the electrons transferred and is proportional to the analyte concentration [2, 7]. Singh et al. have invented novel DNA-based amperometric sensor for one of the most common human pathogens—*Streptococcus pyogenes*. Gold nanoparticles were functionalized with cysteine, PAMAM and genomic single-stranded DNA (ssDNA). The amperometric response was measured after DNA hybridization, with sensitivity of 951.34 (μ A/cm²)/ng DNA and LOD with 130 fg/6 μ L sample. Sensor was suitable for throat swabs and needed 30 min for pathogen identification [13].

3.5. Electrochemical sensor: voltammetric detection

Voltammetric transducers are the most comprehensive and mostly used by research groups in biosensing analysis. Sensor measures the current-potential relationship. The potential is measured in 'no-current applied' conditions [12]. The potential where the redox peaks appear is specific for the examined species and the current peak size is proportional to the species. It is possible to detect many compounds with different characteristic potentials in one measurement. Voltammetric methods can be further divided into: cyclic voltammetry (CV), differential pulse voltammetry (DPV), stripping voltammetry, AC voltammetry, polarography, linear sweep voltammetry (LSV) etc., however, the most commonly used are CV, DPV and LSV. The difference is in the way of potential application [2]. The simplest is **LSV**, where at WE, the potential applied increases linearly in time. The flowing current consists of the faradaic current (flowing the Faraday laws, means discharging of active compound) and capacitive current (produced due to double electric layer growth between the solution and electrode). Detection limits are at mg/L level. In **CV**, scanning has a triangular shape characteristic. Obtained voltammogram is a closed curve with redox peaks (two if process is

reversible, one if process is irreversible). The low sensitivity makes CV inapplicable for quantitative analysis. **DPV** principle is applying periodical constant potential pulse during linear scanning. Measured is the difference between the current before and after the pulse giving one peak-graph. This technique is very sensitive with detections on 10–100 µg/L limit [2].

3.6. Electrochemical sensor: impedimetric detection

Very strongly exploited are impedimetric transducers. The method, called electrochemical impedance spectroscopy (EIS), characterizes the structure and function of electrodes, especially modified with biological material [14]. It can be further classified as Faradaic or non-Faradaic depending on the presence/absence of redox probe in the solution. The second one is more preferred in point-of-care (POC) devices due to no reagents need. During immobilization of electrode surface, the resistance and capacitance of a double-layer are changing, causing change in the impedance. Thus, the biorecognition process and label-free interactions on the sensor surface can be detected [7]. Two most popular results are expressed as Nyquist and Bode plots. EIS sensors are mainly constructed by self-assembled monolayer (SAM) or a conducting polymer base layer method [12]. Detection limits are worse comparing to potentiometric or amperometric methods. False positive results derived from the electrolytes are the main drawback. It can be overcome by blocking the non-specific binding sites of the electrode surface with, for example, BSA protein [4]. The immunoreaction between antigen and antibody directly indicates impedance changes. Nidzworski et al. have presented the universal biosensor for influenza A virus detection. The principle was attaching appropriate antibodies to gold electrode which detect viral M protein. The difference of electron-transfer resistance was observed before and after influenza virus addition and peptide-antibody interaction. Increasing concentration of peptide causes the increase of resistance. The main advantage was no need for sample pretreatment, just swab suspension in buffer solution. Sensitivity was 80–100 virions/µL [15].

4. Importance of sensing materials choice

The wide range of working electrode materials and the variety of electrode surface bio-functionalization methods [7] make the electrochemistry very strong scientific and industry branch. The choice of active material and functionalization mechanism depends on the type of molecular recognition between the receptor and target analyte. Working electrode materials enhance electroactivity and promote electron-transfer reaction, but differ in reactivity, conductivity and stability so interacts diversely with chemical or biological molecules.

Noble metal nanoparticles (NPs) due to great conductivity, biocompatibility, high surface-to-volume ratio and modification possibilities by hybridization, sol-gel, self-assembly monolayer (SAM) and others methods are very popular and available on the market [16]. Currently, nanomaterials are essential in bio-devices due to enhanced sensitivity and detection limits [17]. Well-known are AuNPs, AgNPs, PtNPs, and their alloys Au-Ag, Au-Pt, Ag-Pt [16]. For example, Liu et al. have used AuNPs combined with *Bam*HI endonuclease

for Hepatitis C Virus RNA detection by DPV technique with LOD 3.1×10^{-22} M [18]. Li et al. have detected gene fragments from Hepatitis B Virus, also by DPV, but introducing AgNPs and LOD was 1×10^{-18} M level [19].

Next appreciated materials are (nano-)carbon components, such as carbon nanotubes [20] or carbon nanowires with high stability, great mechanical strength and good conductivity, glassy carbon materials or graphene-based sensors [21, 22]. Bhardwaj et al. have fabricated cheap paper-based sensor for detection of foodborne pathogens: *E. coli*, *B. subtilis* and *S. epidermidis*. Authors have used single-walled carbon nanotubes (SWCNTs) conjugated with corresponding antibodies (Ab). Covalent attachment of Ab-SWCNTs has increased the stability of a sensor. Measurement technique was DPV. This fast, label-free method had LOD on 13 CFU/mL level with linear concentration range from 10 to 10^7 CFU/mL [23]. Gong et al. have proposed impedimetric DNA biosensor for HIV-1 gene determination. Glassy carbon electrode was modified with graphene-Nafion composite and ssDNA. The decrease in the resistance was proportional to gene concentration in a range from 1.0×10^{-13} to 1.0×10^{-10} M with LOD at 2.3×10^{-14} M [24].

Silica is willingly used due to no toxicity, biocompatibility, significant electronic, optical and mechanical properties [17, 25]. Nguyen et al. have used magnetic silica nanotubes (MSNTs) for label-free *Salmonella typhimurium* detection. A positively charged surface of silica attracted bacteria adsorption. This complex interacted with antibody-immobilized gold electrode. Impedance sensor showed linear signals for 10^3 – 10^7 CFU bacterial concentration. In authors opinion, MSNTs material have a better LOD and sensitivity than other nanomaterials in impedimetric immunosensors [26].

5. Technological comparison

The biosensors will be necessary to provide the consumers with sensing devices having short analysis time, low costs, satisfactory LODs and LOQs, portability possibilities, etc., as it was in the case of glucose meters and pregnancy tests. Electrochemical methods will be compared to optical, piezoelectric and others in reference to technology, detection limits, linear range and specificity.

In optic-based biosensors, single molecule detection, such as DNA, can be done [27]. This technology was later improved due to innovations like combination of biological materials. Also, mixing different optical components on one sensor enables forming multisensing device on a single chip and swift analysis. Hybrids of fluorescence and nanomaterials or biomolecules increase application possibilities and sensitivities. However, the main drawbacks are costs and strict instruments requirements [17]. Optical SPR detection is the most evaluated and calibrated technique for real-time and label-free assays [7]. Piezoelectric devices also offer real-time and label-free analysis, but stand out with the flexibility and low costs, compared to optical methods. Thus, it can be ideal for detection methods optimization [28]. However, from all biosensor types (microbial, electromagnetic, optical and electrochemical), only electrochemical are able to detect both, single or multiple, analytes with the real-time analysis and

satisfying (but not the highest) sensitivity [17]. Thus, the electrochemical transducers seem to be the most beneficial. They are widely used in POC devices which are on-site diagnostic tests accessible to the physicians and patients, thanks to user-friendly handling and portability [29]. Another positive aspects are sensitivity, specificity with real-time analysis. Cost values are fluctuating, however they are not the highest (comparing to optical devices) and available for many laboratory industries. Currently, the electrochemical instruments are being miniaturized to hand-size. Application does not require laboratory conditions; simple instrumentation enables analysis in physician's offices or patient's houses. They are the smallest from all the sensors and with the strongest future perspectives [2, 17]. Biosensors industry offers hybrid-methods, such as photoelectrochemistry. The principle is to activate the species on electrode surface by the light, and received photocurrent is detected. The assay has advantages deriving from both methods. High sensitivity is gained from separated excitation and detection sources. Comparing to whole-optical methods such as fluorescence, exchanging detection to electrochemical lowers the costs and simplifies the instrumentation. Moreover, implementation of photoelectrochemical active nanomaterials can be very beneficial for hybrid assays [7].

6. Non-invasive, wearable biosensors

In everyday life, the superior analysis is with so-called 'non-invasive' biosensors, where there is no interruption in patient's body, what happens in blood or serum collecting. Non-invasive specimens are saliva, sweat and tears. The basic example can be breathalyzer for blood alcohol content from a breath sample. The main promise of non-invasive techniques, such as polarimetry or impedance, is non-stop monitoring with real-time results for optimal health status maintaining and deterioration warning. These solutions can help reduce health care costs and time spent in hospitals [7]. Glucose, alcohol, illness-causing pathogen like influenza virus and others can be detected from the samples [30, 31].

Tears are rich in proteins, lipids, metabolite and electrolytes and are used for diabetes monitoring. Saliva analysis can show changes in metabolic, hormonal or even emotional human body states [2]. For example, Kim et al. have invented the wearable mouthguard sensor for uric acid detection as end product of purine metabolism in saliva specimens. Abnormalities indicate diseases like hyperuricemia, gout or Lesch-Nyhan syndrome. Enzyme-modified printed electrode shows amperometric response and is connected to the platform sending analysis results to smartphones and laptops [32]. By breath analysis, viruses causing respiratory infections can be detected [33]. Others wearable biosensors are blood pressure sensor, temperature sensor, breathing sensor for respiration monitoring or so-called 'smart socks' used to individual step characterization [34].

7. Applications

Many biosensors have found everyday appliance, not only the laboratory usage. The main goal of biodevices is to be implemented in medical field. It means detect human illnesses,

thus mutations, infections at first stages, pathogens, as 'prevention is better than cure'. Pathogens including bacteria, viruses, fungi, protozoa and are one the main human death causes. They have many transmitters like human, animals and plants [35], thus unchecked can cause pandemics. Early diagnosis is one of the strongest prevention method, but still challenging due to high costs, strict sample preparation mechanisms and long-time analysis. Modern technology biosensors can overcome these drawbacks by device miniaturization or rapid data output. Nowadays detection is possible from common illnesses like virus invasions to serious tumors, due to wide range of bioreceptors and measurement techniques mentioned above. Biosensors application, except human health, is in food processing/monitoring, fermentation processes, biodefence in military and many more described in this chapter.

Biological defense sensors are sensitive for organisms posing threat, called biowarfare agents (BWAs), such as bacteria, viruses and toxins. Most used are molecular techniques recognizing BWAs markers, more preferably nucleic acid-based than antibody-based due to higher sensitivity and specificity. An example is detection of genomic DNA of HPV virus by modified surface acoustic wave (SAW) biosensor [36].

Nano-based biosensors are one of the most willingly investigated and applied due to significant properties described in Section 4. For example, nanomaterials are able to detect antibiotics residues in human body which decrease the treatment efficiency [37]. Others specific interactions were carried on porous silicon, for example, for *E. coli* detection [38]. There are also silica-modified materials, by Hg^{2+} ions [39] or Ag/graphene/silica composites [40]. Quantum dots technology can be used for tumor analysis (targeting ligands can be monoclonal antibodies and peptides) and for nano-medicine delivery [17]. Engineered NPs thrive in POC devices. AuNPs combined with magnetic MNPs can detect *mecA* gene which is a biomarker for methicillin-resistant *S. aureus* (MRSA) at concentration 10 pM of targeted DNA. Optical SPR method acts as HBV sensor using AuNPs with LOD 2 fg/mL and 17 min analysis time. Another material, cadmium tellurite QDs conjugated to silica NPs enhanced the signal of Epstein–Barr virus detection. The square wave voltammetry measurements resulted in LOD of 1 pg/mL [29]. For more examples of pathogens nanodiagnostics, view [41], from all nanomaterials, the main interest arouses the gold. Except biosensing application, it is used in drug delivery or photothermal therapy. Gold nanoparticles are the most stable, have activity to biomolecules, significant optical properties depending on environment. In colorimetric methods, it is used for foodborne, waterborne or hospital pathogens detection. The majority of these assays use SPR technique. The peak absorbance of AuNPs highly depends on their shape (nanorods, star-shaped and more) and size. By DNA targeting, it is possible to detect *Salmonella* species, *Bacillus anthracis*, *Chlamydia trachomatis* bacteria or HIV-1 and H1N1 influenza viruses. Another use is *Leishmania major*, a protozoan parasite, detection by gold nanorods. Gold as signal enhancer can be used as non-functionalized or functionalized with nucleic acids and proteins [35]. Simplification of the detection process is required for bringing nanoparticles to POC field. User-friendly devices can be achieved by phone-based, strip-based solutions which already exist on the market.

Except optical detection, gold is often implemented in **electrochemical** techniques.

Davies et al. have developed amperometric biosensor for *Listeria monocytogenes* in food samples. Authors have modified screen-printed carbon electrode with gold nanoparticles and specific antibodies. AuNPs have increased the reaction surface and conductivity of the material and lowering the LOD to 2 log CFU/mL in blueberry samples [42]. Yang et al. have reported a sensor for *Salmonella* spp. detection where AuNPs acted as self-assembled layer on glassy carbon electrode and increased the sensitivity and selectivity. Pathogen presence was recorded by EIS method with LOD 100 CFU/mL [43]. Gaffar and Nurmallasari have invented DNA biosensor with thiol-modified gold electrode for of *M. tuberculosis* oligonucleotide sequence detection. Complementary ssDNA were immobilized on SAM of thiol and further used for target DNA hybridization. DPV was chosen as measurement technique for guanine oxidation signal monitoring. LOD is 2.7046 µg/mL and LOQ is 9.0155 µg/mL with accuracy of 99.22% and precision of 99.86% [44].

Aptamer-based systems have recently gained big potential in bacterial pathogens recognition. This method is applicable for food and clinical probes and offers excellent sensitivity and less time than traditional methods. Aptamers are called nucleic acid analogues of antibodies and are chosen via traditional SELEX technique. Main advantages are high surface density, thus better binding properties, temperature stability, easy chemical synthesis comparing to monoclonal antibodies. Alizadeh et al. have reviewed aptasensors for microbial pathogens. Authors showed detection of Gram-positive bacteria, *S. aureus* (by tyramine signal amplification (TSA) detection method with LOD of 9 CFU/mL in milk sample), *Salmonella* spp. (by non-covalent self-assembly of SWNTs with LOD of 10³ CFU/mL in food, clinical and environmental samples), *E. coli* (by flow cytometric method with LOD of 1.1 × 10³ CFU/mL in pure culture sample), *M. tuberculosis*, *S. mutans*, etc. [45].

Microbial biosensors can monitor fermentation processes. For example, isolated bacteria, like *C. tropicalis*, *G. oxydans* can determine ethanol generated during fermentation. Others, like *L. bulgaricus* or *S. thermophilus* are used for glucose or lactose control [3]. The World Health Organization (WHO) invented a criteria for diagnostic tests development called 'ASSURED' meaning Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment-free, Delivered to those in need. Sensitivity and specificity are required on 85–95% levels [46].

In **viruses**, the main goal is to detect them at very low level, at the beginning of human or animal infection, it allow the doctor for applying appropriate treatment. Currently, viruses are being detected with time consuming methods, like cell culture protocols (2–10 days) or enzyme-linked immunosorbent assay (ELISA) related to viral antigens. Clinical microbiology is limited due long-time process of isolation and detection of microorganisms [46]. Enzyme-linked immunosorbent assay (ELISA) recognizes the antibodies specified to the target antigens with optical response. There are commercially available kits willingly used in clinical laboratories. However, this technique still suffers from long time and multistep analysis, need specialized handling and does not offer satisfying sensitivities. Another technique is polymerase chain reaction (PCR) with nucleic acid amplification for concentration increase of target DNA sequence, thus offering high sensitivities to even single gene copy. Specificity depends on primers design. Interferences from non-targets cause mismatches and non-specific amplifications, but are overcome by newest techniques like real-time PCR, reverse

transcription PCR [5, 35]. The sensitivities between known assays are PCR with 5–100 tissue culture infection dose at 50% endpoint ($TCID_{50}$), cell culture with 104 $TCID_{50}$ and ELISA with 105 $TCID_{50}$. For these reasons a rapid, sensitive, cheap device is pivotal [12]. Virus detection receptors are mainly antibodies, peptides, aptamers and nucleic acids. Antibodies are believed as most common, because are produced as immune response in host organism in the presence of foreign species [2]. They can bind with high affinity (K_d 10^6 – 10^9 M) [12]. Next are peptides, short amino acid monomers chains. They have specific binding properties to viral proteins or antibodies with high stability. Nucleic acids bind specific, complementary viral (also bacterial) RNA and DNA. Viruses can be also detected by electrochemical methods [15]. By CV and DPV techniques, HBV virus can be detected with LOD 1.94×10^{-8} M of target DNA [47]. EIS method is widely used for many pathogens detection, like influenza virus [48], dengue virus [49], HIV [50], rabies virus [51] and others. From optical methods, SPR was the key for many develops in HIV virus issue, like developing new antiviral drugs [52]. SPR has a potential to be portable rapid viral test, however miniaturization is limited. Optical fiber methods were applied for Ebola virus antibodies detection down to 1 ppm or for HCV RNA quantification with LOD at 60 pM [53].

Among all mentioned applications, especially environmental and medical need simple, fast and very sensitive devices, what is available with immobilizers like gold, carbon materials, silica and others. The discovery of electrochemical biosensors became essential in POC [54] and clinical diagnosis [55]. An early disease monitoring is pivotal in adequate treatment.

Lab-on-chip solutions have broad recent scientists' attention, especially fluidic assays due to sample transport improvement, time saving, reduced volumes and dimension of microfluidic channels, making analysis possible in one blood drop. This kind of biosensors includes electrochemical-based, optical-based, micromechanical-based transduction and others. Detection of many pathogens has been reported, like Ebstein-Barr Virus [56], human immunodeficiency virus [57], *Salmonella typhimurium* [58], H5N1 influenza [59] and more. For more examples, please see [60].

Following the newest researches, we have described the most interesting examples. Ganguli et al. have proposed smartphone-based POC sensor for Zika, chikungunya and dengue viruses detection. Blood sample was collected and applied to pre-processing module, where automated mechanism mixed the sample with lysis buffer and RT-LAMP reagents. The mixture next went to the amplification chip where reaction was incubated. After that, the LED from cellphone was switched on for sample illumination. Real-time fluorescence results were displayed on the screen. If the channel lighted up, the pathogen was presented. LOD for Zika was 10 PFU in 25 μ L sample what corresponds to 6250 PFU/mL in blood [54].

A big part of sensing techniques are **smartphone-based** devices as their components are ideal for common analytical readers such as a screen acting as display and controller, a camera as input for signal capturing, a memory for data storing, connectivity modes (Bluetooth, NFC and Wi-Fi) for data transmission. Also, GPS can help track global health in serious cases like pandemic. Wear possibilities and portability makes it powerful branch in biosensing area. The second fact, they are not expensive devices with high accessibility, as there are billions of mobile phone users globally. Smartphone devices are classified as detectors or instrumental

interface for controlling the experiment setup, but this solution is less reported in the literature. This classification means to make a device that can be attached to the smartphone or make independent device and connect it with a smartphone via Bluetooth, etc. Adapters are often required for proper distance maintaining between the sample and the camera or for dark chambers making (in fluorescence). Main attention attracts optical methods, however microscopic, magnetoresistive and electrochemical are also available. The next big advantage is costs reduction. Applications are pH measurements [61], heart rate scanning [62] and others. Noteworthy is that phone's microphone can perform spirometry (lung capacity) by blow-sound measurement. Great idea was to introduce phone sensors platforms to drones for reaching difficult places and providing low weight portable laboratories for human in need [63, 64]. For a critical review, more application examples and commercially available biosensors please see [65].

The point-of-care (POC) diagnostics is the next branch with intention of public health revolution. Rapid disease diagnosis is essential for the accurate treatment. In developed countries, most analysis are performed in traditional way-in specialized laboratories with sophisticated equipment and by qualified personnel. Thanks POC testing allows for in vitro diagnostics with results obtained at ambulances, accident sites or physician's offices. Moreover, self-testing will be provided for patients. The strong advantages are small size, portability and automation, like in smartphones. Actually, smartphones can be classified as POC devices. Many products are currently available on the market, like glucose sensors, pregnancy tests, urine screening and more. The microelectromechanical systems (MEMS) technology is strongly introduced to POC assays. The main advantage is separating, mixing, isolating and more sample treatment steps in one device. Main target analytes are proteins, nucleic acids, cells (blood cells), small molecules (metabolites such as glucose and cholesterol). With features as time-efficiency, easy operating and portability, they are ideal for use in poor countries and difficult geographical regions. Many POC devices use microfluidic assays as paper-based microfluidics are disposable, cheap and easy to storage. However, these microfluidic solutions can only show qualitative answers (yes/no for the presence of target analytes). Challenging is the choice of appropriate marker and optimization of accuracy, sensitivity, speed and more parameters. One of the biggest potential in POC devices is detection of circulating tumor cells for cancer progression monitoring by atomic force microscopy technique. Others common label-free assays are filtration, hydrodynamic chromatography and dielectrophoresis [66, 67]. For more point-of-care sensors, authors recommend reading [68].

The novel pathogen detection method was presented by Waller et al. group. Portable detection of *Bacillus anthracis* spores was done by amperometric immunoassay. Magnetic beads and glucose oxidase, both antibodies-conjugated were used as sensing sandwich-like material on gold matrix. Immunomagnetic spores separation and interferences removal from environmental samples was done. For current signal, samples were incubated with glucose, horseradish peroxidase and electron mediator. Target was captured by polyclonal antisera and signal was generated by monoclonal antibodies. Whole analysis took less than an hour. Authors wanted to increase the sensitivity of available lateral-flow devices and decrease analysis time comparing to ELISA and PCR. LOD was 500 spores and linear quantitative range from 5×10^3 to 5×10^6 CFU/mL [69]. Gouma et al. have introduced novel isoprene sensor for influenza

virus detection. Infected patients generate more volatile products like nitric oxide (NO) and volatile organic compounds (VOCs) which are biomarkers in the disease detection. The secretion comes from the alveolar and airway epithelium and leukocytes infiltrating the lungs. The device is a portable 3-sensor microsystem with rapid non-invasive screening. Measurement must be done as fast as disease symptoms are observed, for biomarkers changes in time observation. The sensor is able to detect three gases: isoprene, ammonia and NO in temperature control. The measurement relies on resistance changes of h-WO_3 matrix with exposure to NO, NO_2 , isoprene and methanol at 350°C [33]. Influenza virus is notably investigated and described in the literature, as it is believed as the mother of all pandemics. Except conventional detection methods, electrochemical techniques attract the scientific and market worlds. Very practical nature of these biosensors makes them applicable for POC [70]. Another electrochemical biosensor was developed for dengue virus. Nascimento et al. have employed gold nanoparticles–polyaniline composite and immobilized with dengue serotype-specific primers. Chosen measurement technique was CV and EIS. Invented system was able to recognize the dengue serotype at picomolar concentration with high specificity and reproducibility [71]. Ishikawa et al. have used In_2O_3 nanowire in their amperometric sensing platforms for SARS virus detection. Authors have used antibody mimic proteins (AMPs), working as antibodies but smaller in size. The biomarker was viral nucleocapsid (N) protein. LOD of 1 nM was achieved in 10 min long analysis [72].

8. Application of biosensing technologies in telemedicine

Telemedicine is a widely used technology branch in patient's healthcare. It exchanges the specialized care information from a distance via electronic communicators, provides health monitoring, increases the access to health services especially in places limited financially, like rural areas, and geographically, enhancing life quality. More specifically it can be video conversation, an email, by smartphone or other device, sometimes wireless tools. Common fields are telepsychiatry, teledermatology and teleradiology. It is definitely safe and effective in adult and pediatric medicine. Telemedicine is no more theory. A big part of implementation attempts succeed. The US survey in 2014 showed 86% of user's satisfaction and 75% of willing attitude to telemedicine formats [73]. Survey from 2011 has reported very high telemedicine application. About 70% of radiology practices in US are in teleradiology form [74]. Treating patients at home seems to be beneficial for the family and the hospital itself. Also the continuous access to patients and physicians is very convenient. Teleconsultations can reduce the costs associated with the transport, waiting time and physical consultation price. Now it is possible to reach more patients with less time with the same or higher consultations satisfactory [75]. Moreover, 'the medicare' is a good marketing and promoting tool for potential new customers wins. Telemedicine cannot act perfectly, obviously. There were many cases of implementation failures, problems connected with operational costs, technology integration lacks, the devices standard quality and safety. The service implementation is affected by factors like financing, technology, society acceptance and more. Necessary are operation trainings, user-friendly simple handlings and the commitment of specialists

(physicians, nurses) and patients. There are few types of services such as telemonitoring, teleconsultations, teleeducation, etc. [74, 76] offering home assistance and psychological support. Nowadays, the telemedicine usage reluctance still is observed, however decreases gradually, because these methods meet users need. Patients, especially elderly, use devices more readily and specialists enhance technology confidence. Helpful are program startups like guidelines published by The American Telemedicine Association (ATA) or The Center for Telehealth [74, 76].

As an example of telemedicine application, Shah et al. have proposed high-intensity model of care for illness care, expanding the access to seriously ill patients using real-time and store-and-forward approaches. Authors have reduced the emergency department visits to 34% over 1 year comparing to control group [77]. Newest Nature reports show a big interest in telemedicine field, to fill the disease's data-gaps, like in inflammatory bowel disease (IBD) case. Authors debate if IBD should be implemented in e-care or not. IBD is a chronic disease and its treatment is suboptimal, however implementation it to e-health may bring some profits. As it is relapsing and remitting disease, traditional clinical approach can be insufficient and not fast enough. By e-health approach, patients are believed to become active part in decisions-making when the first symptom occurs. Moreover, introducing IBD to telemedicine may be important financial impact, cost-saving due to eliminating outpatient visits. However, validation costs must be considered too. Currently available e-cases are very small in numbers, still insufficient for global implementation. Real-life patient's data are lacking [78].

Telemedicine is a great field to show biosensors potential. As their main goal is to be cheap, portable and user-friendly, they can be applied for everyday-based monitoring and in epidemics seasons, like during Ebola outbreak from 2014 in Africa, SARS in 2003 and pandemic influenza in 2009 or in moments where local medical centers suspect the danger and need reference center consultations. The next great appliance is for quarantine patients restricted to isolation [79] or any place with poor economic background or geographically difficult places to reach. Patients will be allowed to examine themselves by different integrated systems, for example, by electronic device with easy to collect specimen and further send the results through mobile phone with specially designed app. For this case, the main target could be Africa with a spread of malaria, tuberculosis, HIV and Human Papilloma Virus (HPV). Current biomedical sensors for resource-limited countries suffering from these diseases are reported in Ref. [80]. Telemedicine have already found appliance in pathogens area. Beste et al. have described telemedicine support in Hepatitis C treatment in the American Veterans (VA) group. The main problem was not willingly prescribed antivirals by primary care providers due to health insurers or providers preference. The new program ECHO for promoting and improving telecare was launched offering video conferences with specialists. After this adjustment, the rate of prescribed antivirals to reviewed patients by VA-ECHO has increased [81]. Telemedicine services have been implemented also in HIV/AIDS case. In literature reported, there was raising awareness in pharmacy trainees to optimize patient care [82] or in forming new systems like 'VIHrtual Hospital' with user-friendly interface [83].

9. Conclusion

The features for biosensors developments are mainly sensitivity, specificity and cost-effectiveness detection. These parameters are critical for the high-quality sensing technology. The modern era requires combination of technological and biological approaches for more and more satisfactory devices. The next level is developing robust multi-task biosensor for long-term use. It is necessary due to therapeutics need, it means never ending patients and newly discovered pathogens. Unfortunately, hygiene and sanitation improvement did not reduce the mortality of infectious diseases. Current use of aptamers, peptides and other biomarkers is a key for accurate affection diagnosis. Sensing approaches are a strong factor for time-reduced and more effective treatment than before. The next success is molecules used not only for disease definition, but novel therapeutics, drug delivery, food and environmental monitoring. Invention of chemical, especially electrochemical, biosensors have found application in many fields, except everyday analysis, in sport medicine, doping control analysis and more, giving information about metabolism and physiology states. They offer rapid, real-time, very sensitive analysis. The next advantages, especially for electrochemical techniques, are miniaturization possibilities connected with reduces costs. Point-of-care devices and lab-on-chip technology win in the run. Electrochemical, mainly voltammetric and impedimetric, techniques are uncompetitive due to wide range of target analytes detection. This kind of biosensors keeps a promise for developing complete automatic sensing systems, with no need of sample pretreatment, fast analysis and interfaces with telecommunication devices (smartphones and tablets) and further with specialists. Telemedicine can be an answer for every patient suffering from lack of medical check-ups. It will be possible to detect many dysfunctions at first stages and prevent them with higher cure-impact than treatment in far advanced infections. The ubiquitous smartphones distribution and connectivity changes the concept of public health. E-health solution meets the market need offering easy to operate system that fits in every pocket. Independent connectivity via Wi-Fi or Bluetooth will enable 24 h availability and updates depending on patient's requirements.

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