We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS

BOOK CITATION INDEX

INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Electrochemical and Optical Biosensors in Medical Applications

Jadwiga Sołoducho and Joanna Cabaj

Additional information is available at the end of the chapter

Abstract

Analysis of many biochemical processes is of great significance for clinical, biological, food, environmental as well as bioterror applications. But, exchanging of the biochemical information to kind of electronic signal is a defiance due to connecting an electronic tool directly to a biological surrounding. Electrochemical detection instrument due to its advantageous to analyze the subject of a biological sample has a great potential in conversion of a biochemical occurrence to an electronic signal.

In this chapter we presented the advancements made in the field of electrochemical biosensors targeted at medical field as well as optical elements used in modern biosensors. This material encompasses the technology, performance and commercialization of this brood of sensors. We have focused on the future development perspectives of this class of sensors, based on the experience gathered by different groups researching this field.

Keywords: biosensors, electrochemistry, optical biosensors, medical applications, nucleic acids, lactate, optical fiber

1. Introduction

Electrochemical detection instrument due to its advantageous to analyze the subject of a biological sample has a great potential in conversion of a biochemical occurrence to an electronic signal [1]. Due to its advances reported earlier [2] they are great alternative for other analytical detection methods used elsewhere, Fig. 1. The connection among quick, sensitive,

selective, precise, miniaturizable and inexpensive electrochemistry-based biosensing [3–5] and areas as genetics, proteomics, biochemistry, and molecular biology, conduct to the development of electrochemical sensing tools of unique selectivity and sensitivity for a mass of the samples being tested on this truck.

As was reported earlier by Almeida et al. [6], since Clark glucose sensor [7], this system was improved highly [6-9], and novel sensing systems for detection i.e. urea [10], creatinine [11], cholesterol [12], insulin [13], cancer cells [14] were developed. Electrochemical biosensors were also found for determination of microorganisms as *Escherichia coli* [15] or *Salmonella typhimurium* [16].

Furthermore, the optical fiber as biosensor part is suitable for rough and unsafe surroundings, because of their notably potent, flexible and persistent arrangements. This is non-electrical; consequently, it may be utilized in varied disrepair electric current adoptions. Optical fibers are usually applied since upstanding quality and the base price for sensing appliances. Especially, the major impressive features of optical fibers may allow transmission of multiple signals synchronously. Due to the fact, it may receive variety capacities for detecting of analyte [17].
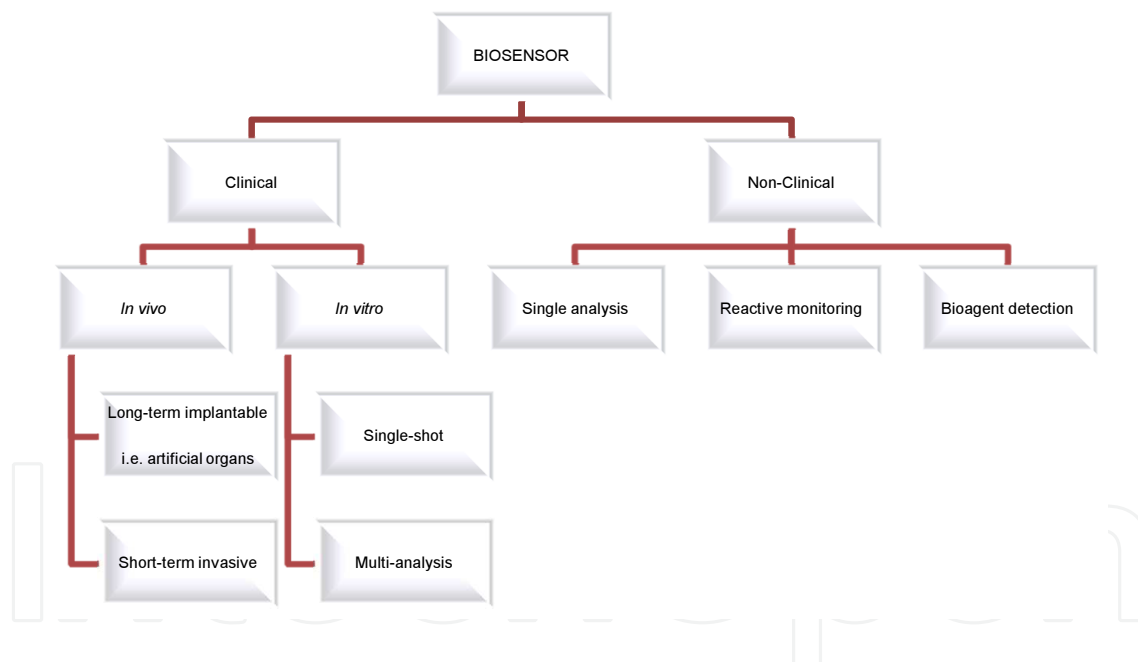

Figure 1. Various applications of biosensors

2. Electrochemical detection in clinical analysis-overview

Electrochemical parameters do not present direct correlations with biological data. However, there are several factors that influence the action mechanisms of drugs, such as stereochemistry, diffusion, solubility, membrane permeability, bioavailability and others, and these

parameters can be related to electrochemical reactions. Electron transfer plays an important role in describing the action mechanisms of many drugs, such as alkylating agents. Other metabolic pathways that involve electron transfer and redox processes include the generation of reactive oxygen species and free radicals and the metabolism of xenobiotics [6,18]. After a brief search of the literature, several biological studies that include electrochemical mechanisms were found. Moreover, it is important to consider the type of the appropriate electrochemical technique that has to be developed to achieve the measurements and the associated parameters.

Among the four common electrochemical techniques, amperometry, pulsed chronoamperometry, differential normal pulse amperometry and differential normal pulse voltamperometry, only the sampled and/or differential techniques permit to determine the analytical signals independent of background and capacitive components [19]. For example, the differential normal pulse amperometry guarantees a stability to the sensor system since this further is polarised at the measurement potential of NO.

The determination of nitric oxide is valid for direct examination of its regulatory roles in biochemical systems. NO assists in the control of crucial cell activities as proliferation or apoptosis. Its unsuitable metabolism can lead to the varied pathologies, as cardiovascular dysfunctions.

One of the NO detection systems was developed by Brunet et al. [19]. The system concerns an appropriate analysis of interfering compounds (hydrogen peroxide, $ONOO^-$, ascorbate) that should be done to evaluate the specificity of the electrochemical sensing of NO in solution. Measuring setup is designed of a nickel porphyrin and Nafion®-coated carbon microfiber. Ames and Kovacic [20] suggested that anti-ulcer agent, as omeprazole could inhibit the H^+/K^+ ATPase from an electron transfer process at the binding site. The electrochemical techniques used in the experiments were cyclic voltammetry and normal pulse polarography.

Liang et al. proposed an electrochemical sensor fabricated by imprinting D- and L-tyrosine on polypyrrole at the surface of Ni electrode [21]. The enantioselectivity of the designed system was determined by coulometry applying positive potential to prompt adsorption of the objective analyte. The L-tyrosine imprinted polypyrrole layer rendered good selectivity for its own template and presented only a minimal relation for the tyrosine derivatives, norepinephrine, epinephrine and dopamine.

Winkler et al. designed catechol-modified chitosan redox cycling system to amplify and detect the electrochemical clozapine signal in undiluted human serum [22]. Clozapine is the antipsychotic ratified by the FDA for treatment-resistant schizophrenia [23]. The authors exemplify the critical function of the reducing mediator in the redox cycling approach, where accurate attention has to be paid to the choice of concentration, contributing up to 1.75-fold to signal reinforcement. The study of electrical potential adoption displays electrophoretic transfer of clozapine playing a similarly significant role in signal amplification, especially in diffusion-limited surroundings, accounting for a factor of up to 2.47 [22]. Recently, Keeley et al. has utilized cyclic voltammetry as well as differential normal pulse voltamperometry in electrochemical biosensing tool for determination of paracetamol in human serum [24]. The

electrochemical active layer was designed as pyrolytic carbon films created using non-catalytic chemical vapour depositionon Si/SiO$_2$ wafers. The proposed sensor was selective, stable and reproducible, with a low detection limit (μM), high sensitivity and broad linear range. Its accuracy has been verified using human serum and commercially available pharmaceutical products. The electroanalytical properties of pyrolytic carbon were found to be competitive with the best available carbon electrodes [24].

Electrochemistry in biosensing/clinical context, as was mentioned earlier [25], has many profits, which make it an appealing choice for clinical analysis. Most electrochemical methods have excellent limits of detection and a wide dynamic range. Electroanalytical techniques require only very small sample volumes, often in the microliter range, coupled with the low detection limits allowing analysis on even subpicogram amounts of analyte [25]. Moreover, the selectivity of electrochemical detection in complex samples is excellent because fewer electroactive interferents are often encountered than spectroscopic interferents.

2.1. Nucleic acid electrochemical biosensors

The rapid detection of nucleic acid sequences (DNA o rRNA) represents a challenging research of bioanalytical chemistry applied to biosensors. Over the last few years, many works have been focused on this aim, with applications ranging from environmental monitoring to food and clinical analysis, developing platforms based on different transduction principles, i.e. piezoelectric, optical and electrochemical [26].

Present clinical diagnostics and monitoring demands rapid and accurate analyses. Vital factors complicating these procedures are often cost of analytical proceedings. Moreover, if it is considered that a qualified personnel is needed for clinical analyses, the natural necessity for alternative analytical technologies is present. For this purpose, biosensors can serve as an option for solving problems mentioned before, or become a helpful in a personalized medicine [27].

Electrochemical biosensors are used to the moment for detection several pathogens (Table 1). These types of detection are the ones that test with complex samples such as tissue, cell culture (without the aid of PCR), or food. It should be noted that many studies utilize synthetic nucleotides [28,29]. Some of the more striking innovations in DNA detection have occurred in the field of virus detection, especially with respect to probe design. Researchers who examined sensing of viruses investigate various capture probes that are tagged with redox species [30].

In one approach, polythiolated DNA probe tagged with ferrocene was evaluated [30]. When the capture probe was not hybridized, the ferrocene molecule on the flexible ssDNA is more mobile and migrates to the electrode surface. When the target DNA hybridizes with the probe, a stiff double helix is formed, which significantly decreases the DPV signal due to relatively immobile ferrocene. Use of peptide nucleic acids (PNA) as capture probes has also been investigated, as it provides for neutral DNA analogs, which lowers electrostatic repulsion, and form "triplex" with dsDNA [31]. In the study reported by Aguilar and Fritsch, an electro-chemical approach targeted 121-mer mRNA of the hsp70 heat shock protein in *Cryptosporidium parvum* [28]. A sample of 2.6×06 oocysts/ml was heat shocked for 10 min to induce transcription

of hsp70. A capture DNA probe was immobilized onto an aminated Au/SiO$_2$ wafer. Then, 500 µl of a 50-µg/ml solution of heat-shocked oocysts was incubated with the functionalized wafer for 1 h for hybridization to be completed. Subsequently, incubation with a reporter probe consisting of 42-base ssDNA conjugated to alkaline phosphatase was used. The modified wafer was rinsed and transferred to a solution containing the substrate for the enzyme, p-amino-phenyl phosphate (PAPP). Over a 12-h period, alkaline phosphatase generated the electroactive species, p-aminophenyl, which was measured by cyclic voltammetry. The authors established that there was very limited cross-reactivity with several common pathogens such as *Cryptosporidium parvum*, *Listeria monocytogenes*, *Campylobacter lari*, *E. coli* O157:H7, and *Salmonella typhi*.

Detection method	Target	Sample matrix	Analysis time (hours)	Detection limit	Ref.
DPV	*Escherichia coli* ssDNA	50 µL sample of separated SSDNA	7	5 cfu/mL	[34]
SWV	*Escherichia coli* ssDNA	1 µL buffer	~1	0.75 amol nucleotide in 1 µL sample	[35]
Potentiometric sensor	*Escherichia coli* rRNA	4 µL buffer	1	10 cfu (0.2 amol 16S rRNA) in 4 µL sample	[32]
Chronoamperometry	*Escherichia coli*	"meat juice" lysate	~7	1 cfu/mL	[36]
Cyclic voltammetry	*Cryptosporidium parvum*	500 µL lysate	16	2 µg mRNA (37 oocysts)/1 mL	[28]
Impedance spectroscopy	*Salmonella choleraesuis* amplicon	PCR mix	~3	1 nM	[37]
DPV	*Staphylococcus saprophyticus* DNA	cell lysate	0.5	1 cfu/µL	[38]
DPV	HBV ssDNA	10 µL buffer	3	0.300 pM	[39]

Table 1. Electrochemical detection of nucleic acids of pathogens

The limit of detection for *Cryptosporidium* is poor in comparison to the femtomol and attomol values in the *E. coli* experiments. The 2 µg/ml limit of detection was established using a synthetic target as in all the work summarized in Table 1, with the exception of Wu et al. [32] where they used bacterial lysate with no PCR. The limits of detection given in Table 1 would be more relevant to food safety and environmental monitoring if they were extracted from experiments that used actual samples of the pathogens as in Wu et al. [32]. Electrochemical sensors, in combination with PCR techniques, are a powerful approach to

detecting nucleic acid sequences in batch assays. The cyclic voltammetry and impedimetric assays also provide characterization of adsorbed monolayers. An alternative sensing approach is to use electromechanical sensors to detect nucleic acids with flow-through sample analysis, where the sample volume is larger than the 1- to 50 μl volumes reported for the electrochemical sensors [33].

2.2. Electrochemical lactate biosensors

L-Lactate plays a vital role in various biochemical processes. Physiological lactate levels are related to the status of anaerobic metabolism associated with muscle contraction. Under normal conditions, healthy persons have lactate concentrations between 0.6 and 2 mM, but during physical activity the value of this parameter can rise up to 20 or 30 mM. That is the reason, L-lactate quantification is vital in i.e. sports medicine [40].

Formation of lactate is followed in the wake of growth in H^+ concentration within the cells; when the rapidity of lactate production is high enough, the H^+ buffering ability may be oversteped, the cellular pH reduces, and the fact may influence on cell acidosis which results on performance of muscles [41].

Even though glucose is usually assumed to be the main energy source for living tissues, there are some evidences that it is lactate, and not glucose, that is preferentially metabolized by neurons in the brain of several mammalian species (i.e. humans) [42], and its monitoring provides a crucial signal in brain stroke and head trauma [43,44]. There was also also revealed that lactate is an indicator for sleep periods [45].

The significance of lactate monitoring in medical diagnostics is indicated by the certainty that blood lactate levels have long been a vital marker of sport as well as clinical states. The facts display the considerable regard in the development of efficient lactate sensors for diagnostics.

2.2.1. Amperometric lactate biosensors

Amperometric transduction is based on the survey of the current appearing from the electrochemical oxidation or reduction of an electroactive species. The resulting current is immediately correlated to the bulk connection of the electroactive species or its production or consumption rate within the adjacent biocatalytic layer. Because of the fact, amperometric sensors alter the concentration of the analyte in their closest vicinity, that is within the diffusion layer [46]. The simplest amperometric biosensors in common usage involve the Clark oxygen electrode.

The enzymes commonly utilized in the development of amperometric biosensors for L-lactate detection are lactate oxidase as well as L-lactate dehydrogenase. In the case of lactate oxidase, oxygen consumption or hydrogen peroxide formation is verified – H_2O_2 provides a current proportional to amount of L-lactate. In dehydrogenase-based sensor, the protein catalyzes the oxidation of lactate to pyruvate in the presence of nicotinamide NAD^+ and the reduced NADH is amperometrically determined. As was reviewed by Rassaei et al. [47] cytochrome b2 [48,49] and lactate monooxygenase [50] have been used in the structure of lactate sensors rarely.

One of the first amperometric lactate biosensor was presented by Faridnia et al. [51]. An amperometric hydrogen peroxide-based biosensor has been developed for non-invasive determination of L-lactate. The biosensor utilizes lactate oxidase immobilized between a polycarbonate membrane and a polytetrafluoroethylene blocking membrane to effectively eliminate electrochemical interferences. The response times were found as 2 min and 10 s, respectively. The biosensor was applied to the analysis of sweat L-lactate content of healthy subjects during physical exercise [51].

Romero et al. has developed [40] biosensor requires only 0.2 U of lactate oxidase, which is immobilized in a mucin/albumin hydrogel matrix. By protecting the platinum surface with a Nafion membrane, typical interference related to negatively charged species such as ascorbic acid has been minimized to practically undetectable levels. A detection limit was found as 0.8 µM. The lactate biosensor presents remarkable operational stability and sensitivity (0.537 ± 0.007) mA M^{-1}. In this regard, the sensor keeps practically the same sensitivity for 5 months.

Because of the fact, the sensors based on L-lactate oxidase involve the electrochemical detection of enzymatically generated H_2O_2. The lactate oxidase based sensors invariably suffers from the interference due to other electroactive compounds such as ascorbate, as the detection of H_2O_2 requires high overpotential. Moreover, the sensitivity of the sensor depends on the oxygen concentration [52]. The method to avoid the oxygen depletion [53] is replacement of lactate oxidase on lactate dehydrogenase, which needs to operate NADH or NADPH.

As was reviewed earlier [47], the character of NAD+/NADH is mediating to shuttle the electrons between the enzyme and the electrode. Nevertheless, hardship in introducing the coenzymes into biosensing device as well as its regeneration, which is connected with high oxidation potential, may frequently cause the need of optimization of collateral parameters. That is the main reason the L-lactate oxidase is mostly used in design and production of amperometric L-lactate sensing devices.

But there are still several models of sensing tools based on L-lactate dehydrogenase as biosensor proposed by Pereira et al. [54]. The amperometric biosensor is based on lactate dehydrogenase and Meldola's Blue. The measured response was based on the electrocatalytical properties of Meldola's Blue to oxidize NADH, which was generated in the enzymatic reaction of lactate with NAD^+ under catalytic activity of lactate dehydrogenase. The amperometric response for lactate using this biosensor showed excellent sensitivity (3.46 µA cm^{-2} mmol L^{-1}), operational stability (around 96.5%) and wide linear response range (0.10–10 mmol L^{-1}). Another example of lactate dehydrogenase-based biosensor was reported by Jena and Raj [52]. The setup was developed using L-lactate dehydrogenase and hydroxylamine enlarged gold nanoparticles (GNPs). Lactate dehydrogenase and GNPs have been integrated with the sol–gel 3-D silicate network derived from 3-(mercaptopropyl)trimethoxysilane. The biosensing of L-lactate is based on the electrocatalytic determination of enzymatically generated NADH by GNPs of the integrated assembly.

As was reported earlier by Rassaei et al. [47] in the design and construction of amperometric lactate biosensor the most attention has centered on electrode, technologies of protein immo-bilization, coenzymes, mediators, the lifetime and biocatalyst stability.

According to IUPAC definition, the sensor sensitivity and selectivity may be improved by using of mediators. Fulz and Durst [55], as well as Nikolaus and Strehlitz [46] reported that the irreversible electrochemical characteristic of several biological species is due to slow heterogeneous electron transport at electrode. This keeps to a sever electrode fouling by adsorption of the bioelement on the electrode or insulation of the active protein center by the surrounding proteins. To avoid these problems the mediators (electroactive agents which operate as an electron shuttle) are utilized. Mediators may also extend the slow rate of electron transfer and reduce the overpotential [46]. In L-lactate detection is suggested to use the polymeric FAD as environment-friendly mediator [56].

As was mentioned earlier by Rassaei et al. [47], enzymes used in lactate biosensor technology may be stabilized on the electrode by a number of different strategies, such as cross-linking [57], entrapment in conductive or nonconductive polymers [58], confinement in a sol–gel [59, 60] or hydrogel [61] matrix, immobilization with another biological component, such as bovine serum albumin [62], or covalent attachment of the enzyme to the electrode [63]. Since the biosensor technologies have emerged, the researches permanently work on the stability, activity as well as efficiency of used enzymes [64].

2.3. Electrochemical biosensors in pharmaceutical assay

Taking into account the fact, that the pharmacological methods are often time-consuming and not cheap, biosensing tools have appeared an entertaining option. Many investigations have been conducted in consideration of the optimization of immobilization procedures as well as the obtaining of the analytical rate. Modern biomimetic identifying setups have been investigated [65]. Moreover, redox properties of drugs can provide insight into metabolic fate, into their *in vivo* redox processes, and their pharmacological effect.

The analytical policy adapted in the expansion of biosensing tools extend from the identification of a signal created by the straight interaction amongst the analyte and the recognizing factor, or indirectly, engaging mediating elements and coupling processes.

The magnitude of biosensors depend on biocatalytic reactions, therewith the essence of the species in the biochemical process, as the molecular features of the analyte, establish the finest group of transducer to be applied [66].

Transport of electron between the enzyme and the electrode surface can arrive by three pathways, qualifying the kind of amperometric tools used, which may be sorted into three classes:

1. The 1st class of electrodes are dependent on the redox proceeding of cofactors (β-NAD(P)$^+$).

2. The 2nd class has included the employment of electron mediators due to reduce potential and rationalize electron transport and sensitivity.

3. The 3rd class of electrodes - the electron transport takes place fairly amongst the active center of protein and electrode [67].

Towards drug specifics inclosing hydrolysable and unstable clusters and/or when proton release is observed, the employment of ion-selective electrodes or potentiometric biosensing tools is the most routinely used variant [68].

Amongst the favorable points of view affected the future of biosensors is the employment of biomimetic systems, which link updated chemical stability with almost identical activity of the particular enzyme [66, 69].

2.3.1. Antiviral drugs

Drug analysis has a large influence on social health. Many analytical techniques have been investigated for the quantitative determination of drugs in both pharmaceutical and biological samples. Even though e.g. chromatographic methods are sensitive and selective, they are tedious and time consuming due to the requisite pretreatment of samples and optimization of chromatogram conditions. Electrochemical methods have been utilized for the determination of wide range of drug compounds, repeatedly without derivatization [70].

Substituted purines represent an important category of compounds actively studied as potential therapeutics against viral infection. Acyclovir is the most commonly utilized nucleoside analog antiviral drug. It is mainly used for the treatment herpes simplex as well as herpes zoster infections. But also may be used for treatment of primary genital herpes or herpetic encephalitis, it is effective in preventing HSV (human herpes virus) infections. This drug provides significant therapeutic benefits in the treatment of viral diseases, and no serious side effects associated with its use have been reported [71]. Based on above description the quantitative determination of ACV become very important and has been widely studied. Several analytical methods have been proposed for individual measurement of acyclovir by fluorometric, high-performance liquid chromatography (HPLC), radioimmunoassay, spectrophotometric methods, GCV by HPLC and PCV by fluorometric [72].

Recently, Heli et al. [70] has reported the electrochemical assay for acyclovir determination by electrocatalytic oxidation of acyclovir on copper nanopartciles-modified carbon paste electrode. Due to investigate simple and time-saving method for the analysis of acyclovir in pure form as well as pharmaceutical formulations, amperometry method was used. Also electrochemical technique coupled with carbon nanotube (CNT) modified electrodes, as was presented by Shah et al. [72] as comfortable and cost-effective. Another example of acyclovir electrochemical analysis was shown by Shetti et al. [73]. The oxidation of acyclovir was investigated at fullerene-C_{60}-modified glassy carbon by cyclic and differential pulse voltammetry. The authors have shown that no reduction peak was observed in the reverse scan, suggesting that the electrochemical reaction was a totally irreversible process. They have assumed also that the oxidation process is located on the guanine moiety in the molecule. It can be concluded that the electrochemical oxidation of acyclovir involves two electron and two proton transfer process to the formation of 8-oxoacyclovir, which is analogous to the initial oxidation product of guanine [73].

2.3.2. Neurotransmitters drugs

The useful in electrochemistry procedures are particularly advantageous in the survey of neurotransmitters and neuronal medicines, not only according to a quality verification, but also for physiological aims. Voltammetry paired to microelectrodes altered with medicine or neurotransmitter receptors are a subservient tool for rating the physiopathological process, clarifying their pharmacological effect, as well as for the extension of novel drugs [74].

Catecholamines

As was reported earlier by de Souza Gil and Rodrigues de Melo, catecholamines apply a great deal of duties at the central as well as autonomous nervous systems [66]. They possess an oxidized catecholic grouping which can be catalyzed by a numerous of oxidases.

The utilization of vegetal material as an origin of oxidases for biosensor destinations images a favorable choice for the quantification of this group of compounds [66, 75-77].

The enzymatic protein - polyphenoloxidase, inherent in coconut fiber material [78], apple tissue [79], avocado pulp [76], zucchini [66], and a lot of sorts of palms [75] have been utilized as source of biocatalysts for biological sensor design concentrating on the assay of particles including catecholic and phenolic groups. Biosensors including palm fruit (*Livistona chinensis*) have been utilized for the test of epinephrine in pharmaceutical formulations when concentration is ranging between 0.05 - 0.35mM. In parallel to classical procedures, the effects rendered significant notability (3.1%) and repeatability [80]. Another palm material-based biosensing tools for catecholamine detection contain the coconut biosensor [81] and the guariroba (*Syagrus oleracea*) biosensor [75].

A biosensor enclosing 25% (p/p) polyphenoloxidase isolated from banana (*Annona muricata L.*), 30% (p/p) graphite, 30% (p/p) silicone oil, and 15% (p/p) of 7,7,8,8-tetracyanoquinodimethane (TCNQ) linked to flow injection systems (FIA) was efficiently employed for the analysis of dopamine in various pharmaceutical species [81].

Benzodiazepines

Benzodiazepines are central nervous system inhibitors, usually utilized for anxiety curing. Since the curing triumph of this group of medicines depends on the support of accurate serum levels, a lot of occurrence can take place regarding to the intake of benzodiazepines. Due to typical antipsychotics, they are not net dopaminergic antagonists but possess other receiver antagonistic activities (e.g. acting on serotonin and/or adrenergic receivers); these specific advantages make them convenient in a wide confine of psychotic diseases (mania, schizophrenia and delirium) with a decreased risk of inducing extrapyramidal effects and acting on negative symptoms of schizophrenia (alogia, anhedonia and avolition) [82].

Thereby, the invention of procedures for benzodiazepines determination is significant in a lot of areas, i.e. quality control, clinical diagnostics and forensic investigations [66].

As was reviewed before [66], reports representing the electrochemical character of temazepam, oxazepam and diazepam on carbon paste electrodes were developed by cyclic and pulse differential voltammetry. For determination of olanzapine (2-methyl-4-(4-methyl-1-pipera-

zinyl)-10H-thieno[2,3-b][1,5]benzodiazepine) Brunton et al. used modified carbon glass electrode with multiwalled nanotubes and layer of TiO_2. The optimal pH for temazepam and oxazepam was found ranging from 3.0 to 5.0, in case of olanzapine it was found as 5.0 as well as no influences of various foreign species on the determination of olanzapine were investigated by square wave voltammetry [82]. On the other hand, Liu et al. reported the combination of electrochemistry and mass spectrometry (nanospray desorption electrospray ionization) as a powerful analytical tool for identification of benzodiazepines [83]. The advantage of the system was found as high sensitivity and the capability of analyzing small volumes of electrolyzed solution. This capability is crucial in analyzing trace amounts of biological samples.

3. Optical sensors

Recently, the optical biosensing devices had been developed rapidly and have been utilized in a numerous of significant fields enclosing food safety, security, environmental monitoring and clinical analysis [47,84]. In clinical analysis, the optical sensor has been used in both regular clinical diagnostic and for clinical research adoptions [85]. The word *optrode* is a fusion of the *optical* and *electrode*. It is used to qualify optical tools [86]. This technique of transduction has been adapted in different kinds of biosensor regarding to the varied classes of spectroscopy [87]. These transduction techniques are efficient to measure another features of the target/ analyte. The optical based biosensor is efficient to supply tab free, real time and parallel determination [88]. The fluorescence or surface plasmon resonance which is united with optical fiber is the most exoteric procedure accessible for optical based biosensors [87]. It occurs that sensing tools based on the optical fiber concept acquire research concern in the area of biosensor design [47].

3.1. Optical fiber sensor

Optical fiber (occasionally named *optrodes*, Fig.2) has acquired substantial concern for investigation as a biosensing element notably in lower detection limit (LOC) sensing surveys. *Optrodes* based sensors are built of few principal constituents: a source of light, a biorecognition factor (immobilized), an optical fiber utilized in light transmission and useful as the base, and a detector (i.e., spectrophotometer) where the output light indicates the operation [89]. As a consequence, when the objective analyte communicates with the biological recognition agents at the surface of the fiber, a biocatalytical process occurs generating the alterations in the optical behavior. These alterations may be compared to the analyte concentration. The biorecognition occurs on the fiber optic, when the light source is transmitted through. The identical or another fiber is applied to direct the output light to the detecting element. The frequent directions of biosensing utilization of optical fiber are acquiring scientist concern due to its principal benefits as a miniaturized fine efficiency sensor, small fiber optical sensors, high sensitivity, rapid result, fine selectivity, and low detection limits [90]. Optical fiber sensors as well possess a number of profits over electrochemical and another biosensing due to their advanced sensitivity, security, independence of electromagnetic involvement and their ability for real time

control [86]. Moreover, this kind of transduction is free of reagent and adaptable, consequently relevant for distant sensing as well as and singular molecule determination [86]. Nevertheless, there are respective disadvantages as the deficient durability of biorecognition agents and sensitivity to surrounding light [86]. Majority of the causes notified in the literature on optical fiber biological sensor appliances have adopted the optic fiber with alternative optical procedures [91]. Moreover, these techniques have been utilized for the determination of numerous biological species as antigen, nucleic acids [92]. Optical fiber biosensing is comprehensive and being commonly utilized for microorganisms identification [91] Leung et al. [93] have described label free determination of DNA hybridization for pathogen testing by applying a fiber optic biosensor.
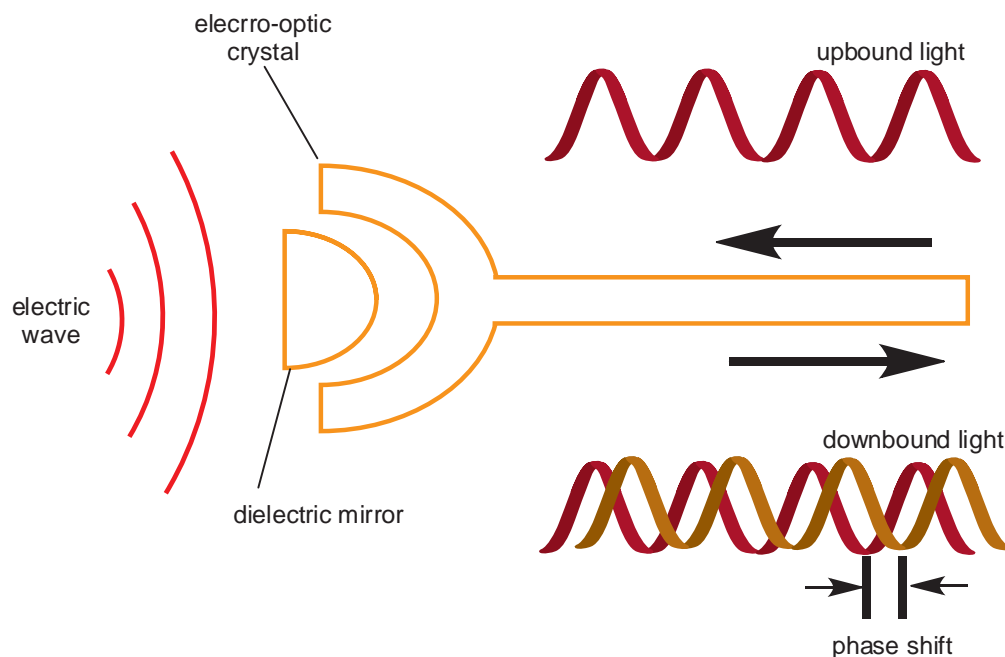

Figure 2. Scheme of optical fiber sensor

3.2. Plasmonic sensors

Surface plasmon resonance (SPR) refers to the collective oscillations of the conduction electrons in metallic nanostructures [94]. Both the intensity and the position of SPR strongly depend on the size, shape and composition of the nanostructures, as well as the dielectric properties of the ambient environment [95,96]. This sundries of responsive variables allows for optical sensors to be created using plasmonic metallic nanostructures. Thereby plasmon-enhanced optical sensors are finding increasing application in detection of analytes in clinical diagnosis, security, food safety and environmental control [97,98]. Herein the expression *plasmonic sensor* refers to sensors that immediately utilize shifts in spectral behavior of the plasmon to operate as the transducer of the sensing signal. Plasmonic sensors are constructed either with 2D chips that support surface plasmon polariton (SPP) mode or with nanoparticles that support localized surface plasmon resonance (LSPR).

3.2.1. Chip-based plasmonic sensors

Planar plasmonic base support expanding SPP course or blended SPP/LSPR course which can be adapted for plasmonic sensing along variations in the refractive index of the ambient environment. SPP may merely be excited utilizing a prism or a grating to provide the extra speed essential to adapt to free-space light. The typical arrangement in chip-based SPP sensing tools is the Kretschmann layout (Fig. 3), [99,100] which allows time- and angle determined reflectivity surveys of a noble metal layer's SPP course through a glass prism. In this collocation, the metal layer is extremely reflective excepting at a concrete angle when the SPP is excited, related to as the SPR angle [101,102]. When target species hinder to ligands immobilized on the plasmonic metal layer, the SPP strand red-shifts regarding to the upper value of refractive index of the species than the water solution, acting as a sensor [98]. The wavelength of the SPR signal differs linearly with the refractive index of the ambient environment due to the Drude pattern [103]. Thereby, the refractive index sensitivity ($S=\Delta\lambda_p/\Delta n$) is signified in entities of nm per RIU, where λ_p is the plasmon frequency of the metal and n is the refractive index of the ambient environment. Figure of merit (FOM=S/FWHM) can be qualified to account the sensing projection of a plasmonic sensor, where FWHM places for the full spread at half-maximum and S is the refractive index sensitivity.
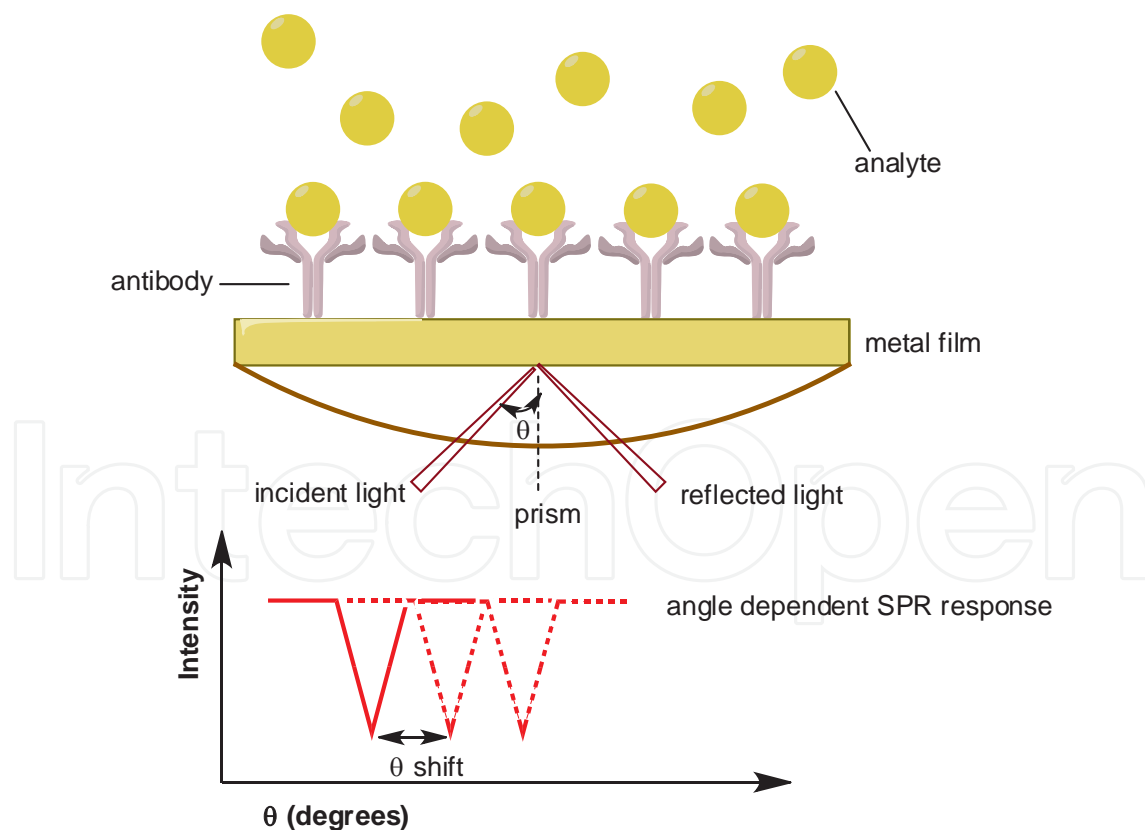

Figure 3. Outline of plasmonic sensing system based on the Kretschmann layout. The incident light is reflected by the metal layer along a prism, and the reflected beam presents a dark line regarding to the SPR absorption. This plasmonic sensing layout can determine time and angle-resolved SPR results upon the binding of analytes.

The method to accomplish the refractive index sensitivity of a plasmonic tool is to decline the SPR signal of the metal layer with the absorption band of the chromophore that ties to the plasmonic metal [104]. Otherwise, the refractive index sensitivity may be increased by exchanging the planar metal layer with a broad-space cyclic nano-array model as a nano-disc array, nanosphere array, or nano-triangle array which assists both a heavier regional EM field and upper sensing plate than planar layers. Conjugated plasmonic nanosized particles may be either combined to a gold layer in a sandwich manner as an analyte linker is prevalent, subsequent enlarging the shift of the SPR signal related to the gold layer alone [105]. Plasmonic chip-based tools possess three clear benefits [99]: (a) label-free determination facilitates the structure and action of the sensor, and excludes the utilization of multiple antibodies as adapted in ELISA, the Au pattern of analytical resolution [106]; (b) real time study of process kinetics as the plasmonic chip is combined with a flow-cell, which supplies a mighty implement for survey the binding incidents [107]; (c) long-range SPP (LRSPP) modes may be created to demonstrate arrangements of size less damping than classic SPP [108]. The smaller damping in LRSPP permits tighter band spreads and higher FOM, as well the penetration deepness of more than 1 mm [109]. It seems to be perfect for study of living organisms [110]. LRSPP modes can be useful when a fine metal layer is settled among two dielectrics with almost identical refractive indexes [111].

3.2.2. Plasmon-enhanced fluorescence (PEF) sensors

The first PEF sensing tool was described in 1991 [112]. As was mentioned before [99], PEF is related either to a surface plasmon-enhanced fluorescence spectroscopy (SPFS) [113], surface-enhanced fluorescence spectroscopy (SEFS), or metal-enhanced fluorescence (MEF). Till now a typical naming convenant for this type of tool does not subsist. The PEF studies were not observable before 2007, but recently, several nanosized elements have been examined to plasmonically enhance fluorescence, compatible with the growth of navigable nanoparticle synthesis and lithography-based formation of nanosized chips. The plasmon-induced fluorescence enhancement agent commonly decreases in the range of 10–100 but may be upper in optimized plasmonic nanosized structures, even rising up to 1340 [114]. The sudden growth of PEF sensors is easy to imagine observed the last tendencies in progress in the idea of PEF [99].

3.3. Optical lactate sensors

A numerous literature reports of optical sensing systems for the determination of lactate reveals that sensor designs largely utilization either fluorometry or (electro)chemiluminescence techniques [115-118]. Also an optrode is capable to classify by the kind of enzymatic protein and the pathway it is combined to the transducer. First time, the optical sensing implement for the determination of lactate in blood was described by Broder and Weil [119] in 1964. The detection tool was relied on a photospectrometric technique, and the relation light/concentration was calculated due to the Lambert-Beer law [119].

Current tendency to miniaturize the analytical tools have led scientists to design optical sensing elements on a chip dually with identification pieces. Wu et al. [120,121], in example, combined optical fibers with a microfluidic tool, which was consisted of an SU-8/poly-

dimethylsiloxane waveguide to monitor online the lactate (Fig. 4). The determination of lactate relied on the absorbance of phenol red (max. 540 nm) through the oxidative reaction of chromogen precursors in the presence of H_2O_2 (produced by the lactate oxidase catalyzed process).

As was reported by Rassaei et al. [47] chemiluminescent biosensing tools are mainly based on incorporation the leading biocatalyzed reaction with a luminescent substrate. Therefore, lactate sensors are based on the chemiluminescent reaction among H_2O_2 formed in enzymatic process and luminol. Still, this reaction demands a basic surroundings (pH 8.5–9) as the light emission intensity decreases severely with pH downfall to inert worth essential for maximal enzyme efficiency. Marquette and Blum [122] invented a fiber-optic flow injection biosensing tool for the monitoring of glucose and lactate concentration employing luminol. The authors immobilized glucose oxidase as well as lactate oxidase on membranes built of polyamide and collagen. Lately, Zheng et al. [123] developed a lactate sensing tool based on an exceptional nanosized optofiber with high spatial resolution to detect the extracellular lactate of a single cancer cell. Their great achievement was to indicating the capability of the biosensor to differentiate higher extracellular lactate planes for cancer cell lines.
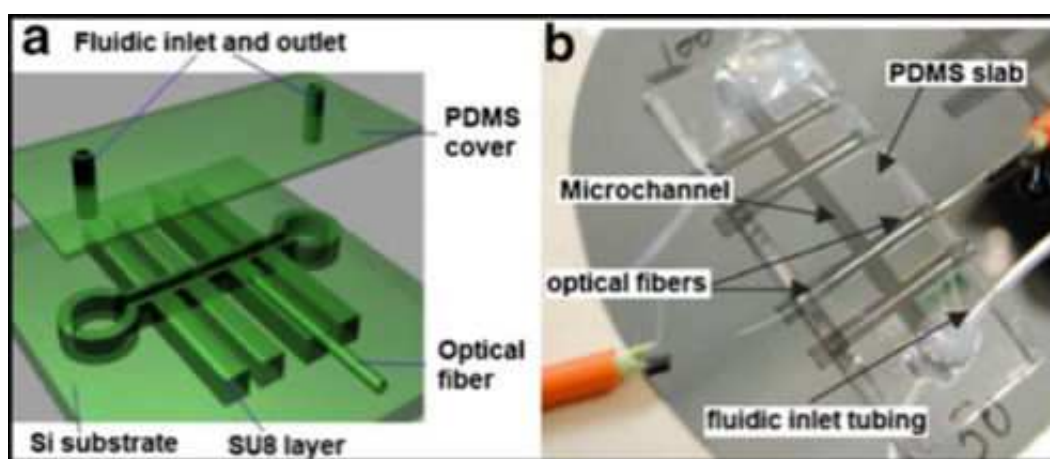

Figure 4. A microfluidic tool built of SU-8/polydimethylsiloxane (PDMS) (a) with incorporated optical fiber as detecting element, and (b) a microfabricated instrument, adopted from [120]

4. Outlook and conclusions

Recently, there has been noticed the significant developments in the area of biosensor. This potent instrument has been employed in a several territories of life. Nevertheless, literature indicates that there are a lot of researches that have been assumed by middle survey with straight clean buffer solutions in place of immediate measurement for real-sample monitoring which is much less crucial. Technological benefits have supplied with the instruments and matters required to fabricate a biosensor which can be combined with a microfluidic arrangement, sound, sampler, detector, amplifier and logic circuitry. This type of implement may be

perspective candidate for label free, reagentless, real time controlling, miniaturization and reasonable adoption cost. For clinical application, this benefit would permit the growth of exceptionally low cost, available biosensors that could be utilized for domestic medical diagnostics without the exigency of transporting analytical samples.

Acknowledgements

Author details

Jadwiga Sołoducho* and Joanna Cabaj

*Address all correspondence to: jadwiga.soloducho@pwr.wroc.pl

Wroclaw University of Technology, Faculty of Chemistry, Wrocław, Poland

References

[1] Stradiotto N.R., Yamanaka H., Valnice M., Zanoni B. Electrochemical sensors: A powerful tool in analytical chemistry, J. Braz. Chem. Soc. 2003, 14, 159-173

[2] Lee T.M.-H., Hsing I.-M. DNA-based bioanalytical microsystems for handheld device applications, Anal. Chim. Acta 2006, 556, 26-37

[3] Drummond T.G., Hill M.G., Barton J.K. Electrochemical DNA sensors, Nat. Biotechnol. 2003, 21, 1192-1199

[4] Mikkelsen S.R. Electrochecmical biosensors for DNA sequence detection, Electroanalysis 1996, 8, 15-19

[5] Palecek E., Fojta E. Detecting DNA Hybridization and Damage, Anal. Chem. 2001, 3, 73A-83A

[6] Almeida M.O., Maltarollo V.G., de Toledo R.A., Shim H., Santos M.C. and Honorio K.M. Medicinal Electrochemistry: Integration of Electrochemistry, Medicinal Chemistry and Computational Chemistry, Cur. Med. Chem. 2014, 21, 2266-2275

[7] Clark Jr, L.C., Lyons C. Electrode system for continuous monitoring in cardiovascular surgery, Ann. N.Y. Acad. Sci., 1962, 102, 29-45

[8] Thandavan K., Gandhi S., Sethuraman S., Rayappan J.B.B., Krishnan U.M. Develop-
ment of electrochemical biosensor with nano interface for xanthine sensing - A novel
approach for fish freshness estimation. Food Chem., 2013, 139, 963-969

[9] Wang J. Glucose biosensors: 40 years of advances and challenges, Electroanal. 2001,
13, 983-988

[10] Barhoumi H., Maaref A., Rammah M., Martelet C., Jaffrezic N., Mousty C., Vial S.,
Forano C. Urea biosensor based on Zn_3Al–Urease layered double hydroxides nano-
hybrid coated on insulated silicon structures, Mater. Sci. Eng., C, 2006, 26, 328-333

[11] Serafín V., Hernández P., Agüí L., Yáñez-Sedeño P., Pingarrón J. Electrochemical bio-
sensor for creatinine based on the immobilization of creatininase, creatinase and sar-
cosine oxidase onto a ferrocene/horseradish peroxidase/gold nanoparticles/multi-
walled carbon nanotubes/Teflon composite electrode, Electrochim. Acta, 2013, 97,
175-183

[12] Ahmad R., Tripathy N., BongHahn Y. High-performance cholesterol sensor based on
the solution-gated field effect transistor fabricated with ZnO nanorods, Biosens. Bioe-
lectron. 2013, 45, 281-286

[13] Xu M., Luo X., Davis J.J. The label free picomolar detection of insulin in blood serum,
Biosens. Bioelectron. 2013, 39, 21-25

[14] Hu Y., Zuo P., Ye B.C. Label-free electrochemical impedance spectroscopy biosensor
for direct detection of cancer cells based on the interaction between carbohydrate and
lectin, Biosens. Bioelectron. 2013, 43, 79-83

[15] Pyun J.C., Beutel H., Meyer J.U., Ruf H.H. Development of a biosensor for *E. coli*
based on a flexural plate wave (FPW) transducer, Biosens. Bioelectron. 1998, 13,
839-845

[16] Prusak-Sochaczewski E., Luong J.H.T. Development of a piezoelectric immunosensor
for the detection of *Salmonella typhimurium*, Enzyme Microb. Technol. 1990, 12,
173-177

[17] Biran I., Walt D.R. Optrode- Based Fiber Optic Biosensors (Bio-Optrode). In: Ligler
F.S, Taitt C.A.R, Ed. Optical Biosensors Present and Future, Elsevier, Amsterdam,
2004

[18] Abreu F.C.D., Ferraz P.A.D.L., Goulart M.O.F. Some Applications of Electrochemis-
try in Biomedical Chemistry. Emphasis on the Correlation of Electrochemical and Bi-
oactive Properties, J. Braz. Chem. Soc. 2002, 13, 19-35

[19] Brunet A., Pailleret A., Devynck M.A., Devynck J., Bedioui F. Electrochemical sens-
ing of nitric oxide for biological systems: methodological approach and new insights
in examining interfering compounds, Talanta, 2003, 61, 53-59

[20] Ames J.R., Kovacic P. Electrochemistry of omeprazole, active metabolites and a bound enzyme model. Possible involvement of electron transfer in anti-ulcer action, Bioelectrochem. Bioenerg. 1992, 28, 443-450

[21] Liang H.-J., Ling T.-R., Rick J.F., Chou T.-C., Molecularly imprinted electrochemical sensor able to enantroselectivly recognize d and l-tyrosine, Anal. Chim. Acta, 2005, 542, 83–89

[22] Winkler T.E., Ben-Yoav H., Chocron S.E., Kim E., Kelly D.L., Payne G.F., Ghodssi R., Electrochemical Study of the Catechol-Modified Chitosan System for Clozapine Treatment Monitoring, *Langmuir*, 2014, 30 (48),14686–14693

[23] Conley R.R., Tamminga C.A., Kelly D.L., Richardson C.M., Treatment-Resistant Schizophrenic Patients Respond to Clozapine after Olanzapine Non-Response Biol. Psychiatry 1999, 46, 73–77

[24] Keeley G.P., McEvoy N., Nolan H., Kumar S., Rezvani E., Holzinger M., Cosnier S. and Duesberg G.S., Simultaneous electrochemical determination of dopamine and paracetamol based on thin pyrolytic carbon films, Anal. Methods, 2012, 4, 2048-2053

[25] Lunte C.E., Osbourn D. Electrochemical detection for pharmaceutical analysis, in: Swarbrick, J. Encyclopedia of Pharmaceutical Technology, 3rd.; CRC Press: New York, 2006

[26] Ermini M. L., Mariani S., Scarano S., Minunni M. Bioanalytical approaches for the detection of single nucleotide polymorphisms by Surface Plasmon Resonance biosensors, Biosen. Bioelectron. 2014, 61, 28–37

[27] Monosık R., Stredansky M., and Sturdık E., Application of Electrochemical Biosensors in Clinical Diagnosis, J. Clinic. Lab. Anal. 2012, 26, 22–34

[28] Aguilar Z.P., Fritsch I. Immobilized enzyme-linked DNA-hybridization assay with electrochemical detection for *Cryptosporidium parvum* hsp70 mRNA, Anal. Chem. 2003, 75, 3890–3897

[29] Sun W., Qi X., Zhang Y., Yang H., Gao H., Chen Y., Sun Z. Electrochemical DNA biosensor for the detection of *Listeria monocytogenes* with dendritic nanogold and electrochemical reduced graphene modified carbon ionic liquid electrode, Electrochim. Acta, 2012, 85, 145–151

[30] Lereau M., Fournier-Wirth C., Mayen J., Farre C., Meyer A., Dugas V., Cantaloube J.-F., Chaix C., Vasseur J.-J., Morvan F. Development of innovative and versatile polythiol probes for use on ELOSA or electrochemical biosensors: application in hepatitis C virus genotyping, Anal. Chem. 2013, 85, 9204–9212

[31] Ahour F., Pournaghi-Azar M.H., Alipour E., Hejazi M.S. Detection and discrimination of recombinant plasmid encoding hepatitis C virus core/E1 gene based on PNA and double-stranded DNA hybridization, Biosens. Bioelectron. 2013, 45, 287–291

[32] Wu J., Chumbimuni-Torres K. Y., Galik M., Thammakhet C., Haake D.A., Wang J. Potentiometric detection of DNA hybridization using enzyme-induced metallization and a silver ion selective electrode, Anal. Chem. 2009, 81, 10007–10012

[33] Rosario R., Mutharasan R. Nucleic acid electrochemical and electromechanical bio-sensors: a review of techniques and developments, Rev. Anal. Chem. 2014; 33(4), 213–230

[34] Anderson M.J., Miller H.R., Alocilja E.C. PCR-less DNA co-polymerization detection of Shiga like toxin 1 (stx1) in Escherichia coli O157:H7. Biosens. Bioelectron. 2013, 42, 581–585

[35] Liao W.-C., Ho J.-A.A. Attomole DNA Electrochemical Sensor for the Detection of *Escherichia coli* O157. Anal. Chem. 2009, 81, 2470–2476

[36] Heidenreich B., Poehlmann C., Sprinzl M., Gareis M. Detection of *Escherichia coli* in Meat with an Electrochemical Biochip. J. Food Prot. 2010, 73, 2025–2033

[37] Berdat D., Rodriguez A.C.M., Herrera F., Gijs M.A.M. Label-free detection of DNA with interdigitated micro-electrodes in a fluidic cell. Lab Chip, 2008, 8, 302–308

[38] Lam B., Fang Z., Sargent E.H., Kelley S.O. Polymerase chain reaction-free, sample-to-answer bacterial detection in 30 minutes with integrated cell lysis. Anal. Chem. 2012, 84, 21–25

[39] Zheng J., Chen C., Wang X., Zhang F., He P. A sequence-specific DNA sensor for *Hepatitis B* virus diagnostics based on the host–guest recognition. Sens. Actuat. B, 2014, 199,168–174

[40] Romero M.R., Ahumada F., Garay F., Baruzzi A.M., Amperometric biosensor for di-rect blood lactate detection, Anal. Chem., 2010, 82, 5568–5572

[41] Kemp G. Lactate accumulation, proton buffering, and pH change in ischemically ex-ercising muscle, Am J Physiol Regul Integr Comp Physiol. 2005, 289(3), R895–R901

[42] Wyss M.T., Jolivet R., Buck A., Magistretti P.J., Weber B. In vivo evidence for lactate as a neuronal energy source, J. Neurosci. 2011, 31(20), 7477–7485

[43] Cureton E.L., Kwan R.O., Dozier K.C., Sadjadi J., Pal J.D., Victorino G.P. A different view of lactate in trauma patients: protecting the injured brain, J. Surg. Res. 2010, 159(1), 468–473

[44] Goodman J.C., Valadka A.B., Gopinath S.P., Uzura M., Robertson C.S. Extracellular lactate and glucose alterations in the brain after head injury measured by microdialy-sis, Crit. Care Med. 1999 27(9), 1965–1973

[45] Naylor E., Aillon D.V., Barrett B.S., Wilson G.S., Johnson D.A., Harmon H.P., Gabbert S., Petillo P.A. Lactate as a biomarker for sleep, Sleep, 2012, 35(9),1209–1222

[46] Nikolaus N., Strehlitz B., Amperometric lactate biosensors and their application in (sports) medicine, for life quality and wellbeing, Microchim. Acta, 2008, 160, 15-55

[47] Rassaei L., Olthuis W., Tsujimura S., Sudholter E.J.R., van den Berg A. Lactate biosensors: current status and outlook, Anal. Bioanal. Chem. 2014, 406,123–137

[48] Shkil H., Stoica L., Dmytruk K., Smutok O., Gonchar M., Sibirny A., Schuhmann W. Bioelectrochemical detection of L lactate respiration using genetically modified *Hansenula polymorpha* yeast cells overexpressing flavocytochrome b2, Bioelectrochemistry, 2009, 76(1–2), 175–179

[49] Smutok O., Dmytruk K., Gonchar M., Sibirny A., Schuhmann W. Permeabilized cells of flavocytochrome b2 over-producing recombinant yeast *Hansenula polymorpha* as biological recognition element in amperometric lactate biosensors, Biosens Bioelectron. 2007, 23(5), 599–605

[50] Romero M.R., Ahumada F., Garay F., Baruzzi A.M. Amperometric biosensor for direct blood lactate detection, Anal. Chem. 2010, 82(13), 5568–5572

[51] Faridnia M.H., Palleschi G., Lubrano G.J., Amperometric biosensor for determination of lactate in sweat, Anal. Chim. Acta, 1993, 278, 35-40

[52] Jena B.K., Raj C.R., Amperometric L-Lactate Biosensor Based on Gold Nanoparticles. Electroanal. 19, 2007, 7-8, 816–822

[53] Makovos E.B., Liu C.C. Measurements of lactate concentration using lactate oxidase and an electrochemical oxygen sensor, Biotechnol. Bioeng. 1985, 27(2), 167–170

[54] Pereira A.C., Aguiar M.R., Kisner A., Macedo D.V., Kubota L.T., Amperometric biosensor for lactate based on lactate dehydrogenase and Meldola Blue coimmobilized on multi-wall carbon-nanotube, Sensor. Actuat. B, 2007, 124, 269-276

[55] Fultz M.L., Durst R.A., Mediator compounds for the electrochemical study of biological redox systems: a compilation. Anal. Chim. Acta. 1982, 140, 1-18

[56] Leonida M.D., Starczynowski D.T., Waldman R., Aurian-Blajeni B., Polymeric FAD used as enzyme-friendly mediator in lactate detection, Anal. Bioanal. Chem. 2003, 376, 832-837

[57] Romero M.R., Garay F., Baruzzi A.M. Design and optimization of a lactate amperometric biosensor based on lactate oxidase cross-linked with polymeric matrixes, Sens Actuat. B, 2008, 131(2):590–595

[58] Rahman M.M., Shiddiky M.J.A., Rahman M.A., Shim Y.B. A lactate biosensor based on lactate dehydrogenase/nictotinamide adenine dinucleotide (oxidized form) immobilized on a conducting polymer/multiwall carbon nanotube composite film, Anal. Biochem. 2009, 384(1), 159–165

[59] Yashina E.I., Borisova A.V., Karyakina E.E., Shchegolikhina O.I., Vagin M.Y., Sakharov D.A., Tonevitsky A.G., Karyakin A.A. Sol–gel immobilization of lactate oxidase

from organic solvent: toward the advanced lactate biosensor, Anal. Chem. 2010, 82(5), 1601–1604

[60] Tsuchiya M., Matsuhisa H., Hasebe Y. Selective amperometric response to hydrogen peroxide at a protein-incorporated sol–gel hybrid film-modified platinum electrode, Bunseki Kagaku, 2012, 61(5), 425–428

[61] Zanini V.P., de Mishima B.L., Solis V. An amperometric biosensor based on lactate oxidase immobilized in Laponite-chitosan hydrogel on a glassy carbon electrode. Application to the analysis of L-lactate in food samples, Sens. Actuat. B, 2011, 155(1), 75–80

[62] Palmisano F., Rizzi R., Centonze D., Zambonin P.G. Simultaneous monitoring of glucose and lactate by an interference and cross-talk free dual electrode amperometric biosensor based on electropolymerized thin films, Biosens. Bioelectron. 2000, 15(9–10), 531–539

[63] Palmisano F., DeBenedetto G.E., Zambonin C.G. Lactate amperometric biosensor based on an electrosynthesized bilayer film with covalently immobilized enzyme, Analyst, 1997, 122(4), 365–369

[64] Campas M., Prieto-Simon B., Marty J.L. A review of the use of genetically engineered enzymes in electrochemical biosensors, Semin. Cell. Dev. Biol. 2009, 20(1), 3–9

[65] Fatibello-Filho O., Lupetti K.O., Leite O.D., Vieira I.C. Electrochemical biosensors based on vegetable tissues and crude extracts for environmental, food and pharmaceutical analysis, Compr. Anal. Chem., 2007, 49, 357-377

[66] de Souza Gil E., Rodrigues de Melo G. Electrochemical biosensors in pharmaceutical analysis, Braz. J. Pharmac. Sci. 2010, 46, 375-391

[67] Oliveira-Neto G., Rover-Junior L., Kubota L.T. Electrochemical biosensors for salicylate and its derivatives. Electroanalysis, 1999, 11, 527-533

[68] Ozoemena K.I., Stefan R.-I., Van-Staden J.F., Aboul-Enein H.Y. Enantioanalysis of S-perindopril using different cyclodextrin-based potentiometric sensors, Sens. Act. B, 2005, 105, 425-429

[69] Kindschy L.M., Alocilja E.C. Development of a molecularly imprinted biomimetic electrode, Sensors, 2007, 7, 1630-1642

[70] Heli H., Zarghan M., Jabbari A., Parsaei A., Moosavi-Movahedi A.A., Electrocatalytic oxidation of the antivirial drug acyclovir on copper nanoparticles-modified carbon paste electrode, J. Solid State Electrochem. 2010, 14, 787-795

[71] Demirtas C., Yilmaz S., Saglikoglu G., Sadikoglu M., Electrochemical Determination of Phenazopyridine Hydrocloride using Poly(p-Aminobenzene Sulfonic Acid) Film Modified Glassy Carbon Electrode. Int. J. Electrochem. Sci. 2015, 10, 1883-1892

[72] Shah B., Lafleur T., Chen A., Carbon nanotube based electrochemical sensor for the sensitive detection of valacyclovir, Faraday Discuss., 2013, 164, 135-146

[73] Shetti N.P., Malode S.J., Nandibewoor S.T., Electrochemical behavior of an antiviral drug acyclovir at fullerene-C_{60}-modified glassy carbon electrode, Bioelectrochem. 2012, 88, 76-83

[74] Crespi F. In vivo voltammetry and concomitant electrophysiology at a single micro-biosensor to analyse ischaemia, depression and drug dependence, J. Neurosci. Meth. 2002, 119, 173-184

[75] Gil E.S., Moraes F.C., Oliveira A., Santana J.C., De-Siqueira E.Q., Machado S.A.S. Development of a modified biosensor by a crude extract of Guariroba (*Syagrus oleracea*) for the analysis of phenolic compounds in environmental samples. In: Spring Meeting of International Society of Electrochemistry, 2008, 6., 148, Book of Abstracts. Lausanne: International Society of Electrochemistry

[76] Fatibello-Filho O., Lupetti K.O., Vieira I.C. Chronoamperometric determination of paracetamol using an avocado tissue (*Persea americana*) biosensor, Talanta, 2001, 55, 685-692

[77] Vieira I.C., Lupetti K.O., Fatibello-Filho O. Determination of paracetamol in pharmaceutical products using a carbon paste biosensor modified with crude extract of zucchini (*Cucúrbita pepo*). Quim. Nova, 2003, 26, 39-43

[78] Lima A.W.O., Nascimento V.B., Pedrotti J.J., Angnes L. Coconut-based plant tissue reactor for biosensing of cathecol in flow injection analysis, Anal. Chim. Acta, 1997, 354, 325-331

[79] Cummings E.A., Mailley P., Linquette-Mailley S., Eggins B.R., Mcadams E.T., McFadden S. Amperometric carbon paste biosensor based on plant tissue for the determination of total flavanol content in beers, Analyst, 1998, 123, 1975-1980

[80] Felix F.S., Yamashita M., Angnes L. Epinephrine quantification in pharmaceutical formulations utilizing plant tissue biosensors, Bios. Bioelec. 2006, 21, 2283-2289

[81] Bezerra V.S., De-Lima-Filho J.L., Montenegro M.C.B.S.M., Araujo A.N., Da-Silva V.L. Flow-injection amperometric determination of dopamine in pharmaceuticals using a polyphenol oxidase biosensor obtained from soursop pulp, J. Pharm. Biomed. Anal. 2003, 33, 1025-1031

[82] Brunton L.L., Blumenthal D.K., Murri N., Dandan R.H., Knollmann B.C. (Eds.), Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill 2011

[83] Liu P., Lanekoff I.T., Laskin J., Dewald H.D., Chen H., Study of Electrochemical Reactions Using Nanospray Desorption Electrospray Ionization Mass Spectrometry, Anal. Chem. 2012, 84, 5737-5743

[84] Tsoka S., Gill A., Brookman J.L., Hoare M. Rapid monitoring of virus-like particles using an optical biosensor: a feasibility study, J. Biotechnol. 1998, 63, 147–153

[85] Caygill R.L., Blair G.E., Millner P.A. A review on viral biosensors to detect human pathogens, Anal. Chim. Acta, 2010, 681, 8–15

[86] Biran I., Yu X., Walt D.R. Optrode-based fiber optic biosensors (bio-optrode). In: Ligler, F., Taitt, C. (Eds.), Optical Biosensors: Today and Tomorrow. Elsevier, Amsterdam, 2008

[87] Abdulhalim I., Zourob M., Lakhtakia A. Overview of optical biosensing techniques. In: Marks R.S., Lowe C.R., Cullen D.C., Weetall H.H., Karube I. (Eds.), Handbook of Biosensors and Biochips. Wiley, Weinheim, 2007

[88] Francia G.D., Ferrara V.L., Manzo S., Chiavarini S. Towards a label-free optical porous silicon DNA sensor, Biosens. Bioelectron. 2005, 21, 661–665

[89] Perumal V., Hashim U. Advances in biosensors: Principle, architecture and applications, J. Appl. Biomed. 2014, 12, 1–15

[90] Lee B., Roh S., Park J. Current status of micro- and nanostructured optical fiber sensors, Opt. Fiber Technol. 2009, 15, 209–221

[91] Atias D., Liebes Y., Chalifa-Caspi V., Bremand L., Lobel L., Marks R.S., Dussart P. Chemiluminescent optical fiber immunosensor for the detection of IgM antibody to dengue virus in humans, Sens. Actuat. B, 2009, 140, 206–215

[92] Brogan K.L., Walt D.R. Optical fiber-based sensors: application to chemical biology, Curr. Opin. Chem. Biol. 2005, 9, 494–500

[93] Leung A., Shankar P.M., Mutharasan R. Label-free detection of DNA hybridization using gold-coated tapered fiber optic biosensors (TFOBS) in a flow cell at 1310 nm and 1550 nm. Sens. Actuat. B, 2008, 131, 640–645

[94] Jones M.R., Osberg K.D., Macfarlane R.J., Langille M.R. and Mirkin C.A. Templated techniques for the synthesis and assembly of plasmonic nanostructures, Chem. Rev., 2011, 111, 3736–3827

[95] Ringe E., Zhang J., Langille M.R., Sohn K., Cobley C., Au L., Xia Y., Mirkin C.A., Huang J., Marks L.D. and Van Duyne R.P. Effect of Size, Shape, Composition, and Support Film on Localized Surface Plasmon Resonance Frequency: A Single Particle Approach Applied to Silver Bipyramids and Gold Nanocubes, Mater. Res. Soc. Symp. Proc. 2010, 1208, O10-02

[96] Ringe E., Langille M.R., Sohn K., Zhang J., Huang J., Mirkin C.A., Van Duyne R.P. and Marks L.D., Plasmon Length: A Universal Parameter to Describe Size Effects in Gold Nanoparticles, J. Phys. Chem. Lett., 2012, 3, 1479–1483.

[97] Sendroiu I.E., Warner and Corn R.M. Fabrication of Silica-Coated Gold Nanorods Functionalized with DNA for Enhanced Surface Plasmon Resonance Imaging Biosensing Applications, Langmuir, 2009, 25, 11282–11284

[98] Mayer K.M. and Hafner J.H. Localized surface plasmon resonance sensors, Chem. Rev., 2011, 111, 3828–3857

[99] Li M., Cushing S.K. and Wu N., Plasmon-enhanced optical sensors: a review, Analyst, 2015, 140, 386-406

[100] Brolo A.G. Plasmonics for Future Biosensors, Nat. Photonics, 2012, 6, 709–713

[101] Liu Y. and Cheng Q. Detection of membrane-binding proteins by surface plasmon resonance with an all-aqueous amplification scheme, Anal. Chem. 2012, 84, 3179–3186

[102] Springer T., Piliarik M. and Homola J. Surface plasmon resonance sensor with dispersionless microfluidics for direct detection of nucleic acids at the low femtomole level, Sens. Actuat. B, 2010, 145, 588-591

[103] Oates T.W.H., Wormeester H. and Arwin H. Characterization of plasmonic effects in thin films and metamaterials using spectroscopic ellipsometry, Prog. Surf. Sci., 2011, 86, 328–376

[104] Zhao J., Jensen L., Sung J., Zou S., Schatz G.C. and Van Duyne R.P. Interaction of plasmon and molecular resonances for rhodamine 6G adsorbed on silver nanoparticles, J. Am. Chem. Soc., 2007, 129, 7647–7656

[105] Law W.C., Yong K.T., Baev A. and Prasad, P.N. Sensitivity improved surface plasmon resonance biosensor for cancer biomarker detection based on plasmonic enhancement, ACS Nano, 2011, 5, 4858–4864

[106] Lahav M., Vaskevich A. and Rubinstein I. Biological sensing using transmission surface plasmon resonance spectroscopy, Langmuir, 2004, 20, 7365–7367

[107] Malinsky M.D., Kelly K.L., Schatz and Van Duyne R.P. Chain Length Dependence and Sensing Capabilities of the Localized Surface Plasmon Resonance of Silver Nanoparticles Chemically Modified with Alkanethiol Self-Assembled Monolayers, J. Am. Chem. Soc., 2001, 123, 1471–1482

[108] Liu Z.D., Li Y.F., Ling J. and Huang C.Z. A localized surface plasmon resonance light-scattering assay of mercury (Ii) on the basis of Hg(2+)-DNA complex induced aggregation of gold nanoparticles, Environ. Sci. Technol. 2009, 43, 5022–5027

[109] Mejard R., Dostalek J., Huang C.-J., Griesser H. and Thierry B. Tunable and robust long range surface plasmon resonance for biosensor applications, Opt. Mater. 2013, 35, 2507–2513

[110] Vala M., Etheridge S., Roach J.A. and Homola J. Long-range surface plasmons for sensitive detection of bacterial analytes, Sens. Actuat. B, 2009, 139, 59–63

[111] Sarid D. Long-range surface-plasma waves on very thin metal films, Phys. Rev. Lett., 1981, 47, 1927–1930

[112] Attridge J.W., Daniels P.B., Deacon J.K., Robinson G.A. and Davidson G.P. Sensitivity enhancement of optical immunosensors by the use of a surface plasmon resonance fluoroimmunoassay, Biosens. Bioelectron. 1991, 6, 201-214

[113] Vasdekis A.E. and Laporte G.P.J. Enhancing Single Molecule Imaging in Optofluidics and Microfluidics, Int. J. Mol. Sci., 2011, 12, 5135–5156

[114] Kinkhabwala A., Yu Z., Fan S., Avlasevich Y., Mullen K. and Moerner W.E. Large single-molecule fluorescence enhancements produced by a bowtie nanoantenna, Nat. Photonics, 2009, 3, 654–657

[115] Galban J., de Marcos S., Castillo J.R., Fluorometric-enzymatic lactate determination based on enzyme cytochrome b2 flurescence, Anal. Chem. 1993, 65, 3076-3080

[116] Zhu A., Romero R., Howard P.R. a sensitive fluorimetric assay for npyruvate, Anal. Biochem. 2010, 396, 146-151

[117] Haghighi B., Bozorgzadeh S., Fabrication of a highly sensitive electrochemiluminescence lactate biosensor using ZnO nanoparticles decorated multiwalled carbon nanotubes, Talanta, 2011, 85, 2189-2193

[118] Han S., Li H., Hu L. electrochemiluminescence of tris(2,2'-bipyridyl)ruthenium(II)/pyruvate system in the absence of cerium(III), Anal. Methods, 2010, 2, 479-483

[119] Broder G,Weil MH (1964) Excess lactate - index of reversibility of shock in human patients. Science 143 (3613):1457–1459

[120] Wu M.H., Cai H.Y., Xu X., Urban J.P.G., Cui Z.F., Cui Z. A SU-8/PDMS hybrid microfluidic device with integrated optical fibers for online monitoring of lactate, Biomed. Microdevices, 2005, 7(4), 323–329

[121] Wu M.H,, Wang J.B., Taha T., Cui Z.F., Urban J.P.G., Cui Z. Study of on-line monitoring of lactate based on optical fiber sensor and inchannel mixing mechanism, Biomed. Microdevices, 2007, 9(2), 167–174

[122] Marquette C.A., Blum L.J. Luminol electrochemiluminescence based fibre optic biosensors for flow injection analysis of glucose and lactate in natural samples, Anal. Chim. Acta, 1999, 381(1), 1–10

[123] Zheng X.T., Yang H.B., Li C.M. Optical detection of single cell lactate release for cancer metabolic analysis, Anal. Chem. 2010, 82(12), 5082–5087