Chapter 5
Biosphere

Adela Maghear and Robert Săndulescu

5.1 Chemical and Electrochemical Sensors in Living World

Living world offers a lot of examples of sensors consisting in biological receptors (proteins, nucleic acids, signaling molecules) located everywhere, in the cell (nucleus, mitochondria, cell membrane), in all the tissues, in organs, or even in the circulating bloodstream. Muscular and nervous activities are accompanied by electrical currents which can be measured by electrocardiography or electroencephalography, for example. The transmission of the nervous stimuli represents in fact a true electrochemical process, during which an electrical current is carried all along the neuronal axon to the synapse, where a chemical entity (acetylcholine, adrenaline, etc.) is released. This chemical species passes through the synapse space where it is discharged to the next neuron, generating a new electrical current, in picoseconds, or even in a shorter time. In fact, the whole metabolism, cell division, growth and apoptosis, immune response by antibody synthesis, or even pathologic processes like inflammation are controlled by an outstanding network of receptors and signaling molecules in a sensor-actuator manner. This extremely important feature is common to all living organisms, from microorganisms like viruses and bacteria, to the plant and animal world. In other words, one can say that electrochemistry is surrounding and controlling us in every moment.

Mitochondria are the power plants of the living cell; their most important roles are to produce the energy of the cell, adenosine triphosphate (ATP) (i.e., phosphorylation of adenosine diphosphate (ADP) by a chain of reactions known as the citric acid cycle or the Krebs cycle) through respiration, and to regulate the cellular metabolism (Fig. 5.1).[1]

A. Maghear (✉) • R. Săndulescu
Faculty of Pharmacy, Analytical Chemistry Department, "Iuliu Haţieganu" University of Medicine and Pharmacy, 4 Louis Pasteur St., Cluj-Napoca 400349, Romania
e-mail: rsandulescu@umfcluj.ro

L.M. Moretto, K. Kalcher (eds.), *Environmental Analysis by Electrochemical Sensors and Biosensors*, DOI 10.1007/978-1-4939-0676-5_5

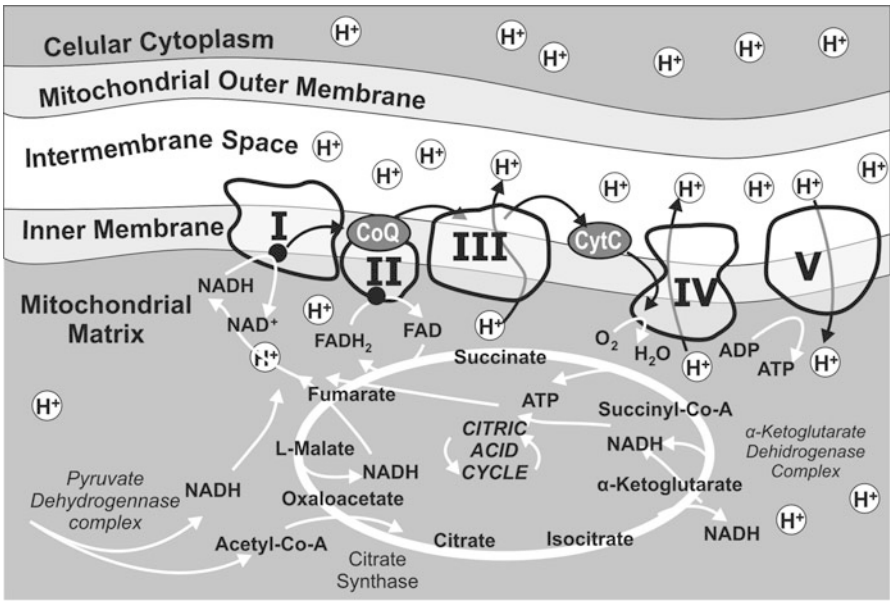

Fig. 5.1 Mitochondrial tricarboxylic acid (TCA) cycle or Krebs cycle

The outer protein-phospholipidic mitochondrial membrane contains a large number of integral proteins called porins, which form channels that allow relatively small molecules (5,000 Da or less in molecular mass) to freely diffuse from one side of the membrane to the other.[2] Larger proteins are transferred by the protein of the outer membrane called translocase which binds a signaling sequence at their N-terminus, and actively moves them across the membrane.[3]

The intermembrane space situated between the outer membrane and the inner membrane has the same composition as the cytosol, because the outer membrane is freely permeable to small molecules. Large proteins (cytochrome *c*) must have a specific signaling sequence to be transported across the outer membrane.[4]

The inner mitochondrial membrane contains proteins[2] that perform the redox reactions of oxidative phosphorylation, generate ATP in the matrix (ATP synthase), regulate the metabolite passage into and out of the matrix by specific transport, and allow the protein passage across the inner membrane (inner membrane translocase), the protein fusion, and fission.

The production of ATP is achieved by glucose, pyruvate, and NADH oxidation in the presence of oxygen (aerobic respiration). In the absence or in the presence of limited amounts of oxygen, the glycolytic products will be metabolized by anaerobic fermentation using alternative substrates such as nitrite.[5]

Pyruvate produced by glycolysis is actively transported across the inner mitochondrial membrane into the matrix where it is oxidized and combined with coenzyme A to form CO_2, acetyl-CoA, and NADH.

During Krebs cycle acetyl-CoA is oxidized to carbon dioxide. The reduced cofactors (three molecules of NADH and one molecule of $FADH_2$) that result from the Krebs cycle are a source of electrons for the electron transport chain, and the molecule of guanosine triphosphate (GTP) is converted to ATP.[1]

Protein complexes in the inner membrane (NADH dehydrogenase, cytochrome c reductase, and cytochrome c oxidase) transfer the redox energy from NADH and $FADH_2$ to O_2 in several steps via the electron transport chain. The released energy is used to pump H^+ into the intermembrane space. Electrons may also reduce oxygen, forming reactive oxygen species such as superoxide, which is a cause of oxidative stress associated with the aging process.[6]

A strong electrochemical gradient occurs across the inner membrane, as the proton concentration increases in the intermembrane space. The protons can return to the matrix through the ATP synthase complex, their energy being used to synthesize ATP from ADP and inorganic phosphate.[1]

Living organisms developed outstanding and very complex networks of biological sensors distributed all over, from single cells and tissues to specialized organs like the eyes, ear, skin, nasal mucous, or tongue. The skin-sensitive fibers are in fact the dendrites of the sensitive neurons that emerge from spinal ganglions and receive external signals like pressure, coldness, or heat. These signals are sent to and from the brain through efferent and afferent neurons. Transmission of nerve impulses constitutes the most convincing example of electrochemistry in the living world.

Neurons do not touch each other; a gap called a *synapse* or *synaptic cleft* separates the axon of one neuron and the dendrites of the next neuron. All the signals must cross the synapse to continue on its path through the nervous system. In the brain, the nervous impulse is carried across synapses by electrical conduction, while in other parts of the body impulses are carried across synapses by an electrochemical process. When an impulse comes, the membrane at the end of the axon depolarizes, opening the gated ion channels, and calcium ions are allowed to enter the cell. The presence of calcium ions determines the release into the synapse of a chemical species called neurotransmitter which moves across the synapse and binds to specific receptors (different proteins serve as receptors for different neurotransmitters) on the postsynaptic neuron membrane that is about to receive the impulse.

Excitation or inhibition depends on the neurotransmitter and the receptor. For example, if the neurotransmitter causes the opening of the Na^+ channels, the neuron membrane becomes depolarized and the impulse is carried through that neuron. If the K^+ channels open, the neuron membrane becomes hyperpolarized and inhibition occurs.

When a neuron is not stimulated its membrane is polarized; the outside of the membrane containing Na^+ ions is positively charged while the electric charge on the inside of the membrane containing K^+ ions, negatively charged proteins, and nucleic acid molecules is negative. The neuron is inactive and polarized until a stimulus comes. Then, the Na^+/K^+ pumps on the membrane pump the Na^+ back outside the membrane and the K^+ back inside.

When a stimulus occurs, the neuron is depolarized; the gated ion channels on the resting neuron's membrane open suddenly and allow the Na^+ that was outside the membrane enter the cell, which becomes positively charged. Polarization is removed and the threshold level is reached. When the stimulus goes above the threshold level, more gated ion channels open allowing more Na^+ inside the cell. Like this, complete depolarization of the neuron is achieved, an action potential is created, and the stimulus will be transmitted.

Once the inner space of the cell is occupied by Na^+, the Na^+ gates close and the K^+ gated ion channels of the cell membrane open allowing K^+ to move to the outside space. Thus, the electrical balance (the repolarization of the membrane) is restored, but at this time the repolarized membrane has Na^+ on the outside and K^+ on the inside.

The membrane potential when K^+ gates finally close is lower than the resting potential, and the membrane is hyperpolarized because the neuron has slightly more K^+ on the outside than it has Na^+ on the inside. After the impulse has passed through the neuron, the action potential is over, and the cell membrane returns to the resting potential.

The Na^+/K^+ pumps will return the ions to their rightful side of the neuron's cell membrane; the neuron returns to its normal polarized state and stays in the resting potential until another impulse occurs. During this period called refractory period, the neuron does not respond to any incoming stimulus.

Signals are sent along the neuronal axon as electrochemical waves (called action potentials) producing cell-to-cell signals where axon terminals make synaptic contact with other cells. Synapses may be electrical or chemical, the last ones being much more common and diverse in functions.[7,8] The neuron that sends the signals is called presynaptic neuron, and the one that receives the signals is called postsynaptic neuron. In the presynaptic area are located numerous microvesicles containing chemical molecules, called neurotransmitters. When the presynaptic terminal is electrically stimulated, the contents of the vesicles are released into the synaptic cleft. The neurotransmitter binds to the receptors located in the postsynaptic membrane, which will be activated. As a consequence, the resulting effect on the postsynaptic cell can be excitatory, inhibitory, or modulatory, depending on the type of receptor (Fig. 5.2). For example, the release of the neurotransmitter acetylcholine at a synaptic contact between a motor neuron and a muscle cell induces rapidly the muscle contraction, the entire synaptic transmission process taking only a fraction of a millisecond.[7]

Over a hundred neurotransmitters are known nowadays, many of them having multiple types of receptors. Among the well-known neurotransmitters are monoamines (dopamine, norepinephrine, epinephrine, histamine, serotonin), amino acids (glutamate, aspartate, D-serine, gamma-aminobutyric acid (GABA), glycine), peptides (somatostatin, P substance, opioid peptides like endorphins), and some others, such as acetylcholine, adenosine, anandamide, nitric oxide, hydrogen sulfide, and carbon monoxide.[9]

Acetylcholine (Ach) can be found in the central nervous system, neuromuscular junctions, spinal cord, and preganglionic and motor neurons. Neurological and

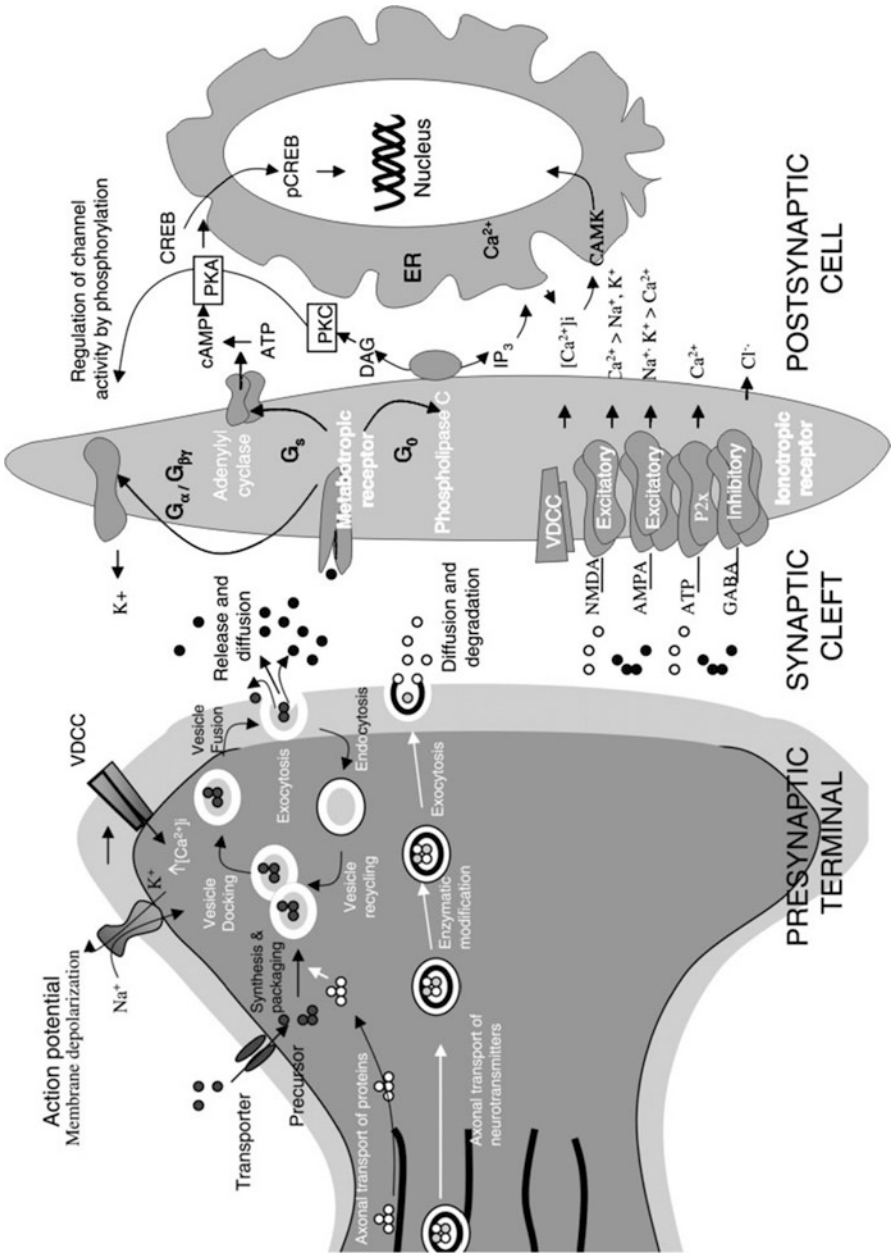

Fig. 5.2 Synaptic nervous transmission

neuropsychiatric diseases, such as Alzheimer's disease, Parkinson's disease, progressive dementia, and schizophrenia, may occur due to acetylcholine accumulation in nervous tissue without being metabolized. This fact explains the considerable interest for its determination in vitro and in vivo, but unfortunately, Ach is neither easily oxidizable/reducible, nor possesses structural characteristics (electroreactive, chromophore, or fluorophore groups) in order to allow a sensitive detection by electrochemical, spectrophotometric, or fluorometric methods. Sattarahmady et al. investigated the electrocatalytic oxidation of Ach by cyclic voltammetry, steady-state polarization measurements, and chronoamperometry on a nickel nanoshells-carbon microparticles-Nafion nanocomposite.[10] The nanocomposite-based Ach biosensor showed a sensitivity of 48.58 ± 0.52 mA M^{-1} cm^{-2} and a limit of detection of 49.33 nM. The same group reported the electrocatalytic oxidation of Ach on two different copper-based transducers, a copper microparticle-modified carbon paste electrode (CPE) and a copper nanoparticle-modified CPE.[11]

Generally, synapses use more than one neurotransmitter, in most cases a fast-acting small-molecule neurotransmitter, such as GABA or glutamate, together with one or more neurotransmitters with slower acting modulatory like peptides.[7,8]

Receptors can be divided into two main types: chemically gated ion channels and second messenger systems. When a chemically gated ion channel is activated, it allows specific types of ions to flow across the membrane, the effect on the target cell being excitatory or inhibitory, depending on the ion type. When a second messenger system is activated, a chain of molecular interactions starts inside the target cell, resulting in a wide variety of complex effects (i.e., the increase or decrease of the cell sensitivity to stimuli).

Both glutamate and GABA have several widely occurring receptor types, but all of them are excitatory or modulatory for glutamate and inhibitory for GABA.[12]

Axonal transport occurs along the cellular cytoskeleton, which is the neuron structural support, allowing the cell to grow or change in size and shape over time. There are three major components of the neuronal cytoskeleton: microtubules, actin, and intermediate filaments. Neurons are uniquely dependent on the microtubule-based transport and the deficits in axonal transport contribute to pathogenesis (neurodegenerative diseases, like amyotrophic lateral sclerosis). The motor, cytoskeletal, and adaptor proteins involved in the axonal transport, in the disruption of axonal transport, and the pathways that may cause neuronal dysfunction and death are described in a review by Chevalier-Larsen and Holzbaur.[13]

An electrochemical strategy to investigate the 1,4-naphthoquinone effect on voltage-gated potassium channels was recently reported by Rodríguez-Fernández et al.[14] Naphthoquinone (NQ) was tested on voltage-gated ion channels expressed in *Xenopus laevis* oocytes by cyclic voltammetry. A typical two-stage mono-electronic reduction mechanism was observed in dimethylsulfoxide (DMSO), while a one-stage bielectronic reduction process was found in physiological supporting electrolyte ND-96 (NaCl, 96 mM; KCl, 2 mM; $CaCl_2$, 1.8 mM; $MgCl_2$, 1 mM; and HEPES buffer, 5 mM; pH adjusted to 7.0 with NaOH). The structural features, such as aromaticity and substituents, prone to hydrogen

bond formation of NQs, are important, together with the NQ interactions with some channel residues which favors their reduction process in the protein surroundings.

5.2 Electrochemical Sensors for Flora and Fauna on Earth

Biosphere comprises all living organisms on earth; this is why it represents the most dynamic and fragile "sphere" of our planet, being strongly influenced by all other "spheres," soil, water, and air. Terrestrial flora and fauna are the main components of the biosphere, but it can be considered that microorganisms (bacteria, viruses, etc.) and human community have their particular features and should be treated separately. Human community brings its main contribution to the pollution of all spheres through industrial and domestic activity, but in the same time one of its main concerns is fighting against environmental pollution by coordinated actions.

Biosphere represents also the most complex and heterogeneous sphere by comparison with air, water, and soil, which are relatively "homogeneous," and, therefore, it makes it difficult to characterize. The great variety of living organisms (microorganisms, plants, animals) makes the assessment of both normal and abnormal "composition" of this sphere almost impossible. So each case should be treated separately and set in the general context of the biosphere and the whole environment. The normal behavior and environmental conditions for a particular living species, plant or animal, in relation with other environmental factors (soil, air, or water) represent an interesting topic. Another topic consists in either the environmental factors or pollutants that affect or damage the living species, or in how the environment is affecting particular species. Some important features here are the continuous deforestation (especially in equatorial areas, such as Amazonia) and desertification caused by intensive agriculture which seriously affect terrestrial atmosphere. Another worrying matter is represented by carbon dioxide emissions caused by the intensive cattle livestock and the so-called greenhouse effect (taking into consideration the important amount of CO_2 that a single cow "produces" per year).

Two different approaches describe the electrochemical sensors for vegetal and animal organisms: sensors able to detect the presence, the movement, and the number of organisms in a given environment, or sensors able to detect a large variety of normal or pathologic parameters in living organisms.

The representative techniques currently applied for an efficient, specific, rapid detection of viruses are described by Caygill et al.[15] Among them, electrochemical biosensors based on amperometric, potentiometric, and impedance measurements, optical biosensors that use surface plasmon resonance, optical fibers and piezoelectric biosensors based on microcantilevers, and recently the use of nanoparticles and novel nanomaterials as alternate recognition surfaces have been widely applied.

Cheran et al.[16] reported the current techniques employed for the transduction and processing of cellular signals, both for single-cell behavior and populations of cells. Electrochemical methodology (transistor and impedance methods), optical (light addressable potentiometry), and vibrational methods (transverse acoustic wave

methodology and Kelvin nanoprobe) were employed for examining populations of neurons, smooth muscles, and human red blood cells on a substrate in a label-free manner.

The use of microtechnology to develop new micro-fabricated electrode structures able to manipulate sub-micrometer particles by means of a nonuniform AC electric field was described by Abonnenc et al.[17] The microchip could integrate manipulation of living cells under software control without affecting the viability of living organisms, and allowed their recovery after having performed complex operations, offering like this a powerful tool for the development of new diagnostic and therapeutic protocols.

The sensors able to detect a great variety of normal or pathologic parameters in living organisms are designed for three main types of pollutants: chemical, microbiological, and genetic.

Some examples in this way are the electrochemical microsensors for Cd(II) and Pb(II) detection in plants[18]; the real-time electrochemical detection of extracellular nitric oxide in tobacco cells as a potent regulator of major processes including germination, root growth, stomatal closure, flowering, and adaptive responses to biotic and abiotic stresses[19]; a DNA electrochemical biosensor based on 2,6-pyridinedicarboxylic acid film and gold nanoparticles on the glassy carbon electrode (GCE) for electrochemical impedance spectroscopic detection of the sequence-specific DNA related to the PAT transgene in transgenic plants[20]; or an electrochemical sensor array for monitoring the proliferation effects of *Cissus populnea* plant extracts on TM4 Sertoli.[21] Some organisms, such as blue-green algae (cyanobacteria), can produce and deliver in water toxic metabolic products for the aquatic organisms and humans, which can be detected and quantified by a phycocyanin sensor.[22]

Environmental monitoring based on whole-organism bioassays and biological early warning systems (BEWS) is lately considered to replace standard expensive chemical analysis. The tests must accomplish some basic conditions like to be simple, based on standardized protocols, predictive, low cost, and applicable to species, populations, and communities. They also need to be sensitive to a wide range of chemicals with minimal matrix effects.[23]

Whole-organism bioassays are based on the measurement of the biological response (acute or chronic toxicity) of a test organism to contaminants present in a water sample (e.g., drinking, ground, surface, or wastewater effluent) in a standardized test usually conducted in the laboratory.[24] Several test species covering most of the different trophic levels in freshwater and/or estuarine/marine environments may be employed, the use of multiple test species and trophic levels being usually recommended because each species shows specific sensitivity to different chemicals or classes of compounds.[24,25]

The usually measured parameters are bioluminescence, metabolic status, or growth, when microorganisms at the base of the trophic chain, such as *Vibrio fischeri* or *Pseudomonas putida*, are used.[26]

Other parameters, like the reduction in photosynthetic activity (by measuring fluorescence) or the growth rate inhibition, can be considered if phototrophic

organisms, such as green algae (*Selenastrum capricornutum* or *Pseudokirchneriella subcapitata*), are employed. The use of dormant organism technology (e.g., algae or daphnid *Daphnia magna*) allows a simplified, rapid, and cost-effective test without the inconvenience of cell cultures, which are much more expensive.[27,28] Thus, the detection of specific effects of herbicides which can affect either photosynthesis systems I or II[29] can be achieved.

Chronic toxicity testing using invertebrates is usually based on growth rate or survival of amphipods (e.g., *Hyalella azteca* or *Gammarus*), chironomid larvae (*Chironomus riparius*), daphnids, oysters (*Crassostrea gigas*), and many other organisms under controlled conditions.[26,30] Bigger organisms such as fish are used for risk assessment, larval/embryonic development rate, fish lethality, or growth rate being the toxicity endpoints used in these assays.[24]

Biomonitoring using BEWS is based on the toxicological response of an organism to a contaminant or mixture of contaminants.[31] Many organisms, including fish species,[32,33] daphnia, midge larvae, microorganisms (e.g., algae and bacteria),[34] bivalve mollusks (e.g., various species of mussels), or even combinations of these test organisms[35] have been used as BEWS.

BEWS applications include monitoring of drinking water intakes, water distribution systems, wastewater effluents, effluents from contamination sites,[36,37] or river basin monitoring,[38] and provide a rapid evaluation of water quality and toxicity that cannot be achieved through other analytical methods.

Generally, BEWS consist of a living organism, a sensing element to detect changes in the test organism, and a processing element to translate the signal from the sensing element into a warning response system. The species commonly used are the rainbow trout (*Oncorhynchus mykiss*) or the bluegill (*Lepomis macrochirus*).[39] The secondary sensing system is composed of electrodes immersed close to the fish to monitor changes in electrical voltage associated with gill muscle activity.[32] Swimming and positioning behavior, or the ability to swim against current and ventilation frequency, are regularly employed.[33,39] Algal monitors are based on fluorescence, oxygen production measurements, and growth rate monitoring and can detect the effects from herbicides or other toxicants that interact with chlorophyll photosynthetic systems.[34] Measurements based on respiration, pumping, and heart rates of bivalve mollusks, such as the freshwater zebra mussel (*Dreissena*) or the marine blue mussel (*Mytilus edulis*),[40] have been tested, even though valve closure or movement responses are defense mechanisms used by bivalves to avoid stress such as contaminated water.[41] Behavioral changes of *Tubificids* worms have also been undertaken.[42]

The exploitation of BEWS depends on the data treatment and coordination of response measures to pollution events in order to mitigate their environmental impact,[43] but also on the improvement in data transfer and on personal computers, the use of online chemical monitoring systems (e.g., SAMOS) being a crucial factor.

A particular category of electrochemical sensors is the sensors able to detect the great variety of normal or pathologic parameters of living organisms. They can be designed either for analytical laboratory conditions, like any other type of sensor, or to be used in vivo, like implantable sensors. In the latter case, issues like their size,

shape, biocompatibility, and lifetime are crucial and will be discussed together with some examples of implantable sensors recently reported in scientific literature.

A broad variety of pharmaceuticals relying on nanoparticles has been reported for both drug delivery and diagnosis tasks.[44] Pharmaceutical products gave rise to new opportunities in directions such as topical and transdermal delivery owing to their ability to penetrate through human tissues, implantable release systems for tissue engineering applications, and ophthalmic delivery in which drug release can be externally controlled by stimuli-responsive nanocomponents.[45–49]

Microdialysis is known as a powerful sampling technique that makes it possible to continuously monitor the concentrations of biological molecules and other substances both in vivo and in vitro.[50] Microdialysis sampling was first applied in the area of neuroscience research,[51] and then it has been extensively employed for other pharmaceutical applications, such as the investigation of the transdermal delivery of drugs,[52] tissue pharmacokinetics,[53] and regional metabolism of drugs in tissues.[54,55] Microdialysis probes have been placed in virtually every tissue and organ in the body, including the liver,[56,57] heart,[58,59] skin,[54,60] blood,[61,62] placenta,[63] stomach,[64,65] and ear.[66]

The mechanism of microdialysis sampling was also explored. Therefore, the probe containing a dialysis membrane with a specific molecular mass cutoff, implanted in the physiological region of interest, is perfused with a fluid that is similar in ionic strength and composition to the extracellular fluid being sampled. Small molecules in the extracellular fluid can diffuse across the membrane based on their concentration gradient and are then transported to the analysis system. In this way, the compounds in the perfusate that are not present in the extracellular fluid can be delivered directly to the physiological site of interest.[50] Therefore, compounds from a single tissue site can be both delivered and recovered. This was proved to be very useful for looking at site-specific release of neurotransmitters,[50] observing regional metabolism of neuropeptides,[67,68] or comparing the metabolism of antineoplastic agents in tumor vs. healthy tissue.[69]

For neurochemical studies, probes are generally composed of stainless steel and are implanted into the specific brain region of interest using a guide cannula. Typical probes used for rat brain studies are normally 15 mm long with a diameter between 200 and 500 μm. The dialysis membrane, from 1 to 4 mm in length, is located at the end of the concentric cannula.[50]

A probe designed for blood sampling was first described by Telting-Diaz et al.[70] and consisted of two pieces of fused silica tubing attached to the dialysis membrane. This probe was so flexible that it could bend when the animal moved, minimizing any blood vessel damage. Online microdialysis–biosensor systems need low sample volumes (μL) if high temporal resolution is required.[50] Also, high sensitivity and specificity for the analyte(s) of interest in the presence of other endogenous electroactive analytes are mandatory.[71] A flow-through biosensor was reported for direct coupling to continuous low-flow microdialysis. Analyte selectivity for glucose and lactate could be achieved by using immobilized oxidoreductase enzymes followed by amperometric detection of hydrogen peroxide.[72]

Online microdialysis sampling coupled to biosensors was reported for analytes such as ascorbate,[73] glucose, lactate,[74,75] and glutamate.[74,76,77] The simultaneous monitoring of glucose and lactate in rats under hypoxic conditions was also achieved.[78] An online system for multianalyte in vivo monitoring was described by Yao et al. and consisted of a triple-enzyme electrode that selectively detected glucose, L-lactate, and pyruvate without significant cross-reactivity.[79] Similar flow injection-based online systems were reported for L-glutamate, acetylcholine, dopamine,[80] and D-/L-lactic acid.[81]

An online system for glucose and lactate to monitor ischemic events in freely moving rats was also developed. The analytes were monitored by flow injection analysis with enzyme-based amperometric detection.[82] Glucose monitoring was achieved in an awake rabbit using a flow-through sensor with chemiluminescence detection.[83] Online monitoring of glucose and lactate from rat brain was also performed following ischemia and reperfusion. In this case, the sensor employed methylene green adsorbed on single-walled carbon nanotubes for detection.[84]

Few studies have used carbon nanotube sensors in biological samples. By reducing the size of the electrodes, as many are based on larger GCEs or CPEs, so they are compatible with tissue implantation or the size of cells; more applications can be found in this direction. Due to the fact that dopamine and other catecholamines are not expected to be present at high levels in plasma or urine, studies should focus on examining tissue from the nervous system or investigating release from cells. Moreover, the low basal levels of dopamine (10 nM) and other neurotransmitters make sensitivity a particular challenge.[85]

Another concern for in vivo use of carbon nanotube-based sensors is their toxicity. Even carbon nanotube toxicity has not yet been fully characterized; many present studies find that CNTs aggregate together, generally in the liver, spleen, and lung tissue. CNT aggregates might have similar carcinogenic properties to asbestos fibers.[86–88]

The extracellular recording of bioelectric signals was proved to be widely achieved by microelectrode electrophysiology. By replacing the traditional electrode conductors with highly flexible electroconductive polymers, non-cytotoxic and biostable all-polymer microelectrode arrays able to reliably capture action potentials and local field potentials from acute preparations of heart muscle cells and retinal whole mounts, in vivo epicortical and epidural recordings, as well as during long-term in vitro recordings from cortico-hippocampal cocultures could be achieved.[89]

By using organic conjugated polymers that use both electrons and ions as charge carriers of the nervous system, a series of novel communication interfaces between electronic components and biological systems was developed. An organic electronic ion pump made of the polymer–polyelectrolyte system poly (3,4-ethylenedioxy thiophene):poly(styrenesulfonate) able to translate electronic signals into electrophoretic migration of ions and neurotransmitters was described.[90] Therefore, it was demonstrated how spatiotemporally controlled delivery of ions and neurotransmitters can be used to modulate intracellular Ca^{2+} signaling in neuronal cells in the absence of convective disturbances. In this way, the amplitude and frequency of Ca^{2+} responses can be strictly controlled due to the

electronic control of delivery, which can be used to generate temporal patterns mimicking naturally occurring Ca^{2+} oscillations. By developing an electrophoretic chemical transistor, an analog of the traditional transistor used to amplify and/or switch electronic signals, the further control of the ionic signals was enabled. Finally, the organic electronic ion pump could be used in a new "machine-to-brain" interface by modulating brainstem responses in vivo.[90]

In spite of its disadvantages, platinum has been used for nonenzymatic detection of blood glucose. One of the drawbacks of the platinum electrode is its catalytic activity for the electrochemical oxidation of glucose drops which can be seriously affected by the chloride ion present in physiological fluids.[91,92] On the other hand, amino acids,[93,94] biochemicals like ascorbic acid, creatinine, epinephrine, and urea[94] in blood can destroy the platinum electrode. In this way, if blood proteins occupy the catalytic sites on the platinum surface, the detection of glucose on platinum will be deteriorated.[96] Due to the fact that glucose oxidation can be inhibited by many biochemicals and amino acids in blood,[95] this can lead to a loss of sensitivity when glucose is detected with platinum.[96]

A system for continuous estimation of blood glucose in fish was developed by Yonemori et al.[97] The eyeball scleral interstitial fluid (EISF) was used as the site of sensor implantation and the relationship between EISF and blood glucose concentrations was evaluated, revealing that blood glucose concentrations were closely correlated with the EISF glucose concentration. A needle-type enzyme sensor for implantation in the fish sclera using a flexible wire electrode was then prepared. The sensor provided a rapid response, good linearity, and reproducibility. Continuous glucose monitoring could be carried out by implanting this needle-type glucose sensor onto the eye. An accurate glucose monitoring could be achieved for over 160 min.

A hybrid biological fuel cell (HBFC) comprising a microbial anode for lactate oxidation and an enzymatic cathode for oxygen reduction was developed and then tested in a marine environment. A laboratory-cultivated *Shewanella oneidensis* DSP-10 was fixed on a carbon felt electrode via a silica sol–gel process in order to catalyze anodic fuel cell processes. The cathode electrocatalyst consisted of bilirubin oxidase, fixed to a carbon nanotube electrode using a heterobifunctional cross-linker, and then stabilized with a silica sol–gel coating. The HBFC maintained a reproducible open-circuit voltage >0.7 V for 9 days in laboratory settings and sustained electrocatalytic activity for >24 h in open environment tests.[98]

A chitosan-modified carbon fiber microelectrode for in vivo detection of serotonin was described. It was demonstrated that chitosan has the ability to reject physiological levels of ascorbic acid interferences and facilitate selective and sensitive detection of in vivo levels of serotonin. In vivo results demonstrated that the chitosan-modified electrode could measure serotonin produced in the zebrafish intestine with high spatial and temporal resolution. A serotonin concentration of 30.8 ($\pm$3.4) nM could be recorded in vivo with the implanted chitosan-modified microelectrode in normal physiological conditions. Due to its inherent biocompatibility and remarkable adherence, chitosan was proved to be an excellent coating for use in implantable sensors, able to selectively detect and monitor levels of in vivo neurotransmitters.[99]

5.3 Sensors for Monitoring Agriculture, Food, and Drug Quality

In order to provide accurate information on crop, soil, climate, and environmental conditions, modern agricultural management relies strongly on many different techniques.[100] For more information on soil and agricultural analysis, see Chap. 2.

5.3.1 Remote Spectral Sensing

An important tool in this direction is the remote spectral sensing of crops, which refers to imagery taken from above a field where the incident electromagnetic radiation is generally sunlight.[101] The difference in color, texture, or shape of the contacted bodies is due to the amount of the reflected, absorbed, and transmitted energy of a specific wavelength.[100] The ratio of reflected energy to incident energy, known as spectral reflectance, is measured as a function of wavelength[102] and its recorded images represent a spectral signature, which is unique to plant species and conditions.[100] Food quality and food contaminants could be detected in food industry by using remote spectral sensing.[103–106] A sensor system that measures induced fluorescence or scattered reflectance is used in food-processing plants when an artificial light source is needed to illuminate the food as it passes on a conveyor belt.[100] The wavelengths measured in food quality cover generally the ultraviolet (10–400 nm), visible (400–750 nm), and near-infrared range (750–2,500 nm).[103] Some studies used also three-dimensional hyperspectral images for accurate detection.[107–111]

5.3.2 The Electronic Nose

Each plant releases a specific volatile organic compound (VOC) as a result of its everyday biological processes and the quantity of this compound represents an indicative of crop and field conditions. VOCs can be affected by the different environmental conditions, but also by insects or plant diseases. Electronic noses are used in agriculture to detect crop diseases, identify insect infestations, and monitor food quality. The electronic nose generally contains two components: an array of gas sensors with a broad and partly overlapping selectivity and an electronic pattern recognition system with multivariate statistical data processing tools.[100] The electronic nose is typically able to compare the profile of VOCs released by healthy plants/fruits with diseased plants/fruits.[100] In the food industry the electronic nose was used to assess the freshness/spoilage of fruits and vegetables during the processing and packaging process.[112,113] The detection of VOCs that indicate fruit ripeness and/or compounds that trigger fruit ripening, such as

ammonia,[114,115] ethanol,[115] ethylene,[115,116] and *trans*-2-hexenal[117] was also achieved. Even they are in preliminary stages of feasibility, studies reported the monitoring of the changes in the aroma profile during storage of apples,[118] to assess the postharvest quality of peaches, pears, bananas,[118–120] and nectarines[118,120] and to detect spoilage in potatoes.[121] Electronic noses were also used to determine the coverage area of pheromone traps set to capture insect herbivores[122–124] or to identify early stages of insect infestations by detecting VOCs secreted by plants that have been attacked.[125–127]

5.3.3 Electrochemical Sensors

The direct measurement of soil chemistry through tests such as pH or nutrient content represents an important application of electrochemical sensors. Due to the importance of soil testing results in obtaining optimal crop production yields and quality food, two types of electrochemical sensors were employed to measure the activity of selected ions (H^+, K^+, NO_3^-, Na^+, etc.) in the soil: ion-selective electrodes and ion-selective field effect transistors. These two types of sensors were also used to monitor the uptake of ions by plants, thus enabling farmers to design fertilization strategies that optimize production.[100] Ion-selective sensors were applied in nitrogen monitoring in soil and crops, such as potatoes,[128,129] and vegetables for fertilization management.[130,131] The investigation of plant metabolism and nutrition, and also the toxicological effects that heavy metals have on plants,[132–135] could also be achieved with these sensors by measuring concentrations of ions, such as iodide, fluoride, chloride, sodium, potassium, and cadmium, in plants or soils. Electrochemical sensors also found their applications in the greenhouse industry.[100] Systems that inject liquid fertilizers based upon ion-specific concentration measurements[136,137] which automatically ensure that the nutrient demand of the plants is satisfied were also developed.[100]

5.3.4 Biosensors

Rapid detection of target chemicals or pathogens in the agricultural field by minimally skilled personnel[138–140] is the main target in nowadays biosensor development.[100] The main bioprobes include nucleic acids (DNA/RNA), proteins, enzymes, antibodies, and phages.[141,142,145] Due to their robust structures and their resistance to heat (up to 80 °C) and chemicals, such as acid, alkali, and organic solvents,[143] filamentous and lytic phages have attracted the interest of researchers as biomolecular recognition elements.[144–146] Also, due to their three-dimensional recognition surface, phages can provide multiple binding sites and hence a strong binding to target pathogens.[100] Therefore, they found their application in the detection of food-borne pathogens.[147–165]

Acoustic wave devices represent an important family of highly sensitive transducers.[100] Phage-based magnetoelastic (ME) biosensors composed of an ME resonator that is coated with genetically engineered phages able to bind specifically with target pathogens[166,167] were described. The mechanism of the ME biosensors has been also explained: the biosensor oscillates with a characteristic resonance frequency under an applied alternating magnetic field and when it comes in contact with the target pathogen, binding occurs.[115] As a result, the mass of the resonator increases and this leads to a decrease in the biosensor's resonance frequency.[1] Various pathogens, such as *S. typhimurium*, *B. anthracis* spores, and *E. coli*,[168–174] could be detected using ME biosensors. Recent studies demonstrated that ME biosensors were able to directly detect bacteria on a fresh food surface without the use of a sampling process (water rinse/stomaching).[175]

Enzyme-based biosensors are said to be very promising tools for highly sensitive and discriminative detection of many chemical threat agents and food contaminants. Organophosphate neurotoxins which have been extensively used as insecticides in agriculture have been detected using biosensors with two types of mechanism approaches[100]: (1) inhibition of particular enzymes such as acetyl or butyryl cholinesterases,[176–179] and (2) organophosphate neurotoxins direct hydrolysis using different hydrolases.[180–184] For more information about biosensors see Chaps. 11, 12 and 13.

5.3.5 *Wireless Sensor Networks*

Wireless sensor networks have been developed to enable new precision in agricultural practice.[100]

Even in their earliest stages of development, wireless sensor networks include already radio-frequency transceivers; soil, water, ion, and VOC sensors; global positioning sensors; microcontrollers; and power sources.[185] See Chap. 14 of second volume for VOC sensors.

The development of this technology aims to provide revolutionary means for observing, assessing, and controlling agricultural practices.[100]

Food represents a very important environmental factor with great impact on "life quality" and, therefore, the need of analytical methods for the assessment of normal constituents, degradation products by alteration, genetic modifications, or chemical (pesticides, hormones, antibiotics, etc.) and biological contaminants.

The great variety of food contaminants and residues at very low concentrations, their various physicochemical features, and the complexity of the food matrix make food analysis a challenging task. Gas chromatography and high-performance liquid chromatography which are commonly employed in food analysis are relatively slow, expensive, and time consuming, and require extensive sample preparation and qualified operators.[186]

Biosensors have demonstrated a great potential for the detection of a large variety of chemical compounds.[187] The high selectivity of the biorecognition

molecule for the target component, the low production cost, the ability to detect analytes in a complex sample matrix with minimal pretreatment, and the potential for miniaturization are the main advantages that recommend biosensors for the specific and rapid detection of biological and chemical components in food, environmental, clinical, and pharmaceutical sector.[187–190]

The microfabrication technologies developed in the last decade have transformed the analytical chemistry research field due to the large surface-to-volume ratios of miniaturized systems, which enhance molecular diffusion and heat transfer, using very small liquid volumes and performing very rapid analyses.[191–193] Microfluidic analytical devices, known as lab-on-a-chip (see Chap. 21) or micro total analysis systems (μTAS), include microfluidic chips as well as non-fluidic miniaturized systems, such as sensors and arrays (biochips), developed for multi-analyte screening in food.[194] Microfluidics technology involves fluid control and small-scale analysis, making possible the integration of multiple steps, multiplexing and parallelization of analyses on a single device, and the achievement of microfluidic analytical systems capable to provide high-throughput and large-scale analysis.[191,195]

Generally, microfluidic analytical devices are made of silica-based materials with channel sizes ranging from 10 to 200 μm, but low-cost disposable microfluidic devices from materials such as polymers or even paper have lately been developed.[196] The most important advantages of microfluidic analytical devices are the low volume of samples and reagents reducing the cost of analysis and the amount of generated waste, the large surface-to-volume ratio, the mass and heat transfer enhancement, short analysis time, portability, allowing on-site analysis, disposability and low cost of fabrication, and integration of multiple processes which allows assay automation and improves analytical performances even when used by unskilled operators.[191,193,197] These devices achieve all the requirements that the food industry and quality control authorities are looking for to maintain the quality and safety of food throughout the entire food chain. Food sample analysis concerning the integration of nanotechnology applications in capillary electrophoresis microchips was reported by Escarpa et al.[198] The rapidly growing number of publications on microfluidics demonstrates the huge interest for microfluidic applications in the field of food and environmental analysis, biotechnology (e.g., fermentation processes in the pharmaceutical and food industry) for online process monitoring and analysis,[199] and homeland security. Microfluidic devices are extensively developed in health care industry for point-of-care diagnostic, high-throughput clinical analysis, and drug screening in pharmaceuticals.[200] The use of biorecognition elements (such as enzymes, antibodies, and DNA) for specific analysis from the sample matrices, and the application of nanotechnology in the detection mechanism of the analytical devices, could be achieved in real sample analysis.

In the same perspective, drugs and pharmaceutical formulations constitute a special issue, especially if we define the internal environment, opposite to the external environment. Detailed aspects will be discussed later (Chap. 9, second volume).

5.4 Future Aspects and Developments

Supposing that plants, just like other forms of life, communicate with other plants and beneficial insects by producing certain chemicals, researchers are trying to develop sensors able to detect the release of particular chemicals in very low concentrations, ignoring other chemicals released by the plant. These new sensors would not only allow farmers to save money, but the decrease in the pesticide concentration would make farmlands more environmentally adequate.

References

1. Voet D, Voet JG, Pratt CW (2012) Fundamentals of biochemistry, 4th edn. Wiley, New York
2. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P (2002) Molecular biology of the cell. Garland Science, New York
3. Herrmann JM, Neupert W (2000) Protein transport into mitochondria. Curr Opin Microbiol 3 (2):210–214
4. Chipuk JE, Bouchier-Hayes L, Green DR (2006) Mitochondrial outer membrane permeabilization during apoptosis: the innocent bystander scenario. Cell Death Differ 13 (8):1396–1402
5. Stoimenova M, Igamberdiev AU, Gupta KJ, Hill RD (2007) Nitrite-driven anaerobic ATP synthesis in barley and rice root mitochondria. Planta 226(2):465–474
6. Huang K, Manton KG (2004) The role of oxidative damage in mitochondria during aging: a review. Front Biosci 9:1100–1117
7. Kandel ER, Schwartz JH, Jessel TM (eds) (2000) Principles of neural science, 4th edn. McGraw-Hill, New York
8. Hormuzdi SG, Filippov MA, Mitropoulou G, Monyer H, Bruzzone R (2004) Electrical synapses: a dynamic signaling system that shapes the activity of neuronal networks. Biochim Biophys Acta 1662(1–2):113–137
9. Rang HP, Dale MM, Ritter JM, Moore PK (2003) Pharmacology, 5th edn. Churchill Livingstone, Edinburgh
10. Sattarahmady N, Heli H, Moosavi-Movahedi AA (2010) An electrochemical acetylcholine biosensor based on nanoshells of hollow nickel microspheres-carbon microparticles-Nafion nanocomposite. Biosens Bioelectron 25:2329–2335
11. Heli H, Hajjizadeh M, Jabbari A, Moosavi-Movahedi AA (2009) Copper nanoparticles-modified carbon paste transducer as a biosensor for determination of acetylcholine. Biosens Bioelectron 24:2328–2333
12. Marty A, Llano I (2005) Excitatory effects of GABA in established brain networks. Trends Neurosci 28(6):284–289
13. Chevalier-Larsen E, Holzbaur ELF (2006) Axonal transport and neurodegenerative disease. Biochim Biophys Acta 1762:1094–1108
14. Rodríguez-Fernández T, Ugalde-Saldívar VM, González I, Escobar LI, García-Valdés J (2012) Electrochemical strategy to scout 1,4-naphthoquinones effect on voltage gated potassium channels. Bioelectrochemistry 86:1–8
15. Caygill RL, Blair GE, Millner PA (2010) A review on viral biosensors to detect human pathogens. Anal Chim Acta 681:8–15
16. Cheran LE, Cheung SL, Wang XM, Thompson M (2008) Probing the bioelectrochemistry of living cells. Electrochim Acta 53:6690–6697

17. Abonnenc M, Altomare L, Baruffa M, Ferrarini V, Guerrieri R, Iafelice B, Leonardi A, Manaresi N, Medoro G, Romani A, Tartagni M, Vulto P (2005) Teaching cells to dance: the impact of transistor miniaturization on the manipulation of populations of living cells. Solid-State Electron 49:674–683
18. Krystofova O, Trnkova L, Adam V, Zehnalek J, Hubalek J, Babula P, Kizek R (2010) Electrochemical microsensors for the detection of cadmium(II) and lead(II) ions in plants. Sensors 10:5308–5328
19. Besson-Bard A, Griveau S, Bedioui F, Wendehenne D (2008) Real-time electrochemical detection of extracellular nitric oxide in tobacco cells exposed to cryptogein, an elicitor of defense responses. J Exp Bot 59(12):3407–3414
20. Yang J, Yang T, Feng Y, Jiao K (2007) A DNA electrochemical sensor based on nanogold-modified poly-2,6-pyridinedicarboxylic acid film and detection of PAT gene fragment. Anal Biochem 365(1):24–30
21. Osibote E, Noah N, Sadik O, Dennis McGee D, Modupe Ogunlesi M (2011) Electrochemical sensors, MTT and immunofluorescence assays for monitoring the proliferation effects of *Cissus populnea* extracts on Sertoli cells. Reprod Biol Endocrinol 9:65
22. Svrcek C, Smith DW (2004) Cyanobacteria toxins and the current state of knowledge on water treatment options: a review. J Environ Eng Sci 3(3):155–185
23. Allan IJ, Vrana B, Greenwood R, Mills GA, Roig R, Gonzalez C (2006) A "toolbox" for biological and chemical monitoring requirements for the European Union's Water Framework Directive. Talanta 69:302–322
24. Keddy CJ, Greene JC, Bonell MA (1995) Review of whole-organism bioassays: soil, freshwater sediment, and freshwater assessment in Canada. Ecotoxicol Environ Saf 30:221–251
25. Gabrielson J, Kuhn I, Colque-Navarro P, Hart M, Iversen A, McKenzie D, Mollby R (2003) A microplate based microbial assay for risk assessment (MARA) and (eco)toxic fingerprinting of chemicals. Anal Chim Acta 485:121–130
26. Farré M, Barceló D (2003) Toxicity testing of waste water and sewage sludge by biosensors, bioassays and chemical analysis. Trends Anal Chem 22:299–310
27. Persoone G, Marsalek B, Blinova I, Torokne A, Zarina D, Manusadzianas L, Nalecz-Jawecki G, Tofan L, Stepanova N, Tothova L, Kolar B (2003) A practical and user-friendly toxicity classification system with microbiotests for natural waters and wastewaters. Environ Toxicol 18:395–402
28. Pascoe D, Wenzel A, Janssen CR, Girling AE, Juttner I, Fliedner A, Blockwell SJ, Maund SJ, Taylor EJ, Diedrich M, Persoone G, Verhelst P, Stephenson RR, Crossland NO, Mitchell GC, Pearson N, Tattersfield L, Lay JP, Peither A, Neumeier B, Velletti AR (2000) The development of toxicity tests for freshwater pollutants and their validation in stream and pond mesocosms. Water Res 34:2323–2329
29. Eulaffroy P, Vernet G (2003) The F684/F735 chlorophyll fluorescence ratio: a potential tool for rapid detection and determination of herbicide phytotoxicity in algae. Water Res 37:1983–1990
30. Schafer H, Hettler H, Fritsche U, Pitzen G, Roderer G, Wenzel A (1994) Biotests using unicellular algae and ciliates for predicting long-term effects of toxicants. Ecotoxicol Environ Saf 27:64–81
31. Kramer KJM, Botterweg L (1991) Aquatic biological early warning systems: an overview. In: Jeffrey D, Madden B (eds) Bioindicators and environmental management. Academic, London
32. Baldwin IG, Kramer KJM (1994) Biological early warning systems (BEWS). CRC, Boca Raton
33. Baldwin IG, Harman MMI, Neville DA, George SG (1994) Performance characteristics of a fish monitor for detection of toxic substances—II. Field trials. Water Res 28:2201–2208

34. Kuster E, Dorusch F, Vogt C, Weiss H, Altenburger R (2004) On line biomonitors used as a tool for toxicity reduction evaluation of in situ groundwater remediation techniques. Biosens Bioelectron 19:1711–1722
35. Gerhardt A, Schmidt S, Hoss S (2002) Measurement of movement patterns of *Caenorhabditis elegans* (Nematoda) with the multispecies freshwater Biomonitor® (MFB)—a potential new method to study a behavioral toxicity parameter of nematodes in sediments. Environ Pollut 120:513–516
36. De Bisthoven LJ, Gerhardt A, Soares AMVM (2004) Effects of acid mine drainage on larval *Chironomus* (Diptera, Chironomidae) measured with the multispecies freshwater Biomonitor®. Environ Toxicol Chem 23:1123–1128
37. Gerhardt A, de Bisthoven LJ, Soares AMVM (2004) Macroinvertebrateresponse to acid mine drainage: community metrics and on-line behavioural toxicity bioassay. Environ Pollut 130:263–274
38. Gerhardt A, Clostermann M (1998) A new biomonitor system based on magnetic inductivity for freshwater and marine environments. Environ Int 24:699–701
39. Van der Schalie WH, Shedd TR, Widder MW, Brennan LM (2004) Response characteristics of an aquatic biomonitor used for rapid toxicity detection. J Appl Toxicol 24:387–394
40. Borcherding J, Jantz B (1997) Valve movement response of the mussel *Dreissena polymorpha* the influence of the pH and turbidity on the acute toxicity of pentachlorophenol under laboratory and field conditions. Ecotoxicology 6:153–165
41. Tran D, Ciret P, Ciutat A, Durrieu G, Massabuau JC (2003) Estimation of potential and limits of bivalve closure response to detect contaminants: application to cadmium. Environ Toxicol Chem 22:914–920
42. Leynen M, Van den Berckt T, Aerts JM, Castelein B, Berckmans D, Ollevier F (1999) The use of Tubificidae in a biological early warning system. Environ Pollut 105:151–154
43. Van der Schalie WH, Shedd TR, Knechtges PL, Widder MW (2001) Using higher organisms in biological early warning systems for real-time toxicity detection. Biosens Bioelectron 16:457–465
44. Torchilin VP (2006) Multifunctional nanocarriers. Adv Drug Deliv Rev 58:1532–1555
45. Papakostas D, Rancan F, Sterry W, Blume-Peytavi U, Vogt A (2011) Nanoparticles in dermatology. Arch Dermatol Res 303:533–550
46. Medeiros SF, Santos AM, Fessi H, Elaissari A (2011) Stimuli-responsive magnetic particles for biomedical applications. Int J Pharm 403:139–161
47. Ganta S, Devalapally H, Shahiwala A, Amiji M (2008) A review of stimuli-responsive nanocarriers for drug and gene delivery. J Control Release 126:187–204
48. Bajpai AK, Shukla SK, Bhanu S, Kankane S (2008) Responsive polymers in controlled drug delivery. Prog Polym Sci 33:1088–1118
49. Domingo C, Saurina J (2012) An overview of the analytical characterization of nanostructured drug delivery systems: towards green and sustainable pharmaceuticals: a review. Anal Chim Acta 744:8–22
50. Nandi P, Lunte SM (2009) Recent trends in microdialysis sampling integrated with conventional and microanalytical systems for monitoring biological events: a review. Anal Chim Acta 651:1–14
51. Bourne JA (2003) Intracerebral microdialysis: 30 years as a tool for the neuroscientist. Clin Exp Pharmacol Physiol 30:16–24
52. Holovics HJ, Anderson CR, Levine BS, Hui HW, Lunte CE (2008) Investigation of drug delivery by iontophoresis in a surgical wound utilizing microdialysis. Pharm Res 25:1762–1770
53. Kim A, Suecof LA, Sutherland CA, Gao L, Kuti JL, Nicolau DP (2008) In vivo microdialysis study of the penetration of daptomycin into soft tissues in diabetic versus healthy volunteers. Antimicrob Agents Chemother 52:3941–3946

54. Bielecka-Grzela S, Klimowicz A (2003) Application of cutaneous microdialysis to evaluate metronidazole and its main metabolite concentrations in the skin after a single oral dose. J Clin Pharm Ther 28:465–469
55. Lanckmans K, Clinckers R, Van Eeckhaut A, Sarre S, Smolders I, Michotte Y (2006) Use of microbore LC-MS/MS for the quantification of oxcarbazepine and its active metabolite in rat brain microdialysis samples. J Chromatogr B 831:205–212
56. Richards DA, Silva MA, Murphy N, Wigmore SJ, Mirza DF (2007) Extracellular amino acid levels in the human liver during transplantation: a microdialysis study from donor to recipient. Amino Acids 33:429–437
57. Davies MI, Lunte CE (1996) Simultaneous microdialysis sampling from multiple sites in the liver for the study of phenol metabolism. Life Sci 59:1001–1013
58. Gilinsky MA, Faibushevish AA, Lunte CE (2001) Determination of myocardial norepinephrine in freely moving rats using in vivo microdialysis sampling and liquid chromatography with dual-electrode amperometric detection. J Pharm Biomed Anal 24:929–935
59. Price KE, Vandaveer SS, Lunte CE, Larive CK (2005) Tissue-targeted metabonomics: metabolic profiling by microdialysis sampling and microcoil NMR. J Pharm Biomed Anal 38:904–909
60. Ault JM, Riley CM, Meltzer NM, Lunte CE (1994) Dermal microdialysis sampling in vivo. Pharm Res 11:1631–1639
61. Huang H, Zhang Y, Yang R, Tang X (2008) Determination of baicalin in rat cerebrospinal fluid and blood using microdialysis coupled with ultra-performance liquid chromatography-tandem mass spectrometry. J Chromatogr B 874:77–83
62. Lin LC, Hung LC, Tsai TH (2004) Determination of (−)-epigallocatechin gallate in rat blood by microdialysis coupled with liquid chromatography. J Chromatogr A 1032:125–128
63. Ward KW, Pollack GM (1996) Use of intrauterine microdialysis to investigate methanol-induced alterations in uteroplacental blood flow. Toxicol Appl Pharmacol 140:203–210
64. Woo KL, Lunte CE (2008) The direct comparison of health and ulcerated stomach tissue: a multiple probe microdialysis sampling approach. J Pharm Biomed Anal 48:85–91
65. Woo KL, Lunte CE (2008) The development of multiple probe microdialysis sampling in the stomach. J Pharm Biomed Anal 48:20–26
66. Zhu T, Cheung BWY, Cartier LL, Giebink GS, Sawchuk RJ (2003) Simultaneous intravenous and intramiddle-ear dosing to determine cefditoren influx and efflux clearances in middle ear fluid in freely moving chinchillas. J Pharm Sci 92:1947–1956
67. Freed AL, Cooper JD, Davies MI, Lunte SM (2001) Investigation of the metabolism of substance P in rat striatum by microdialysis sampling and capillary electrophoresis with laser-induced fluorescence detection. J Neurosci Methods 109:23–29
68. Kostel KL, Lunte SM (1997) Evaluation of capillary electrophoresis with postcolumn derivatization and laser-induced fluorescence detection for the determination of substance P and its metabolites. J Chromatogr B 695:27–38
69. McLaughlin KJ, Faibushevich AA, Lunte CE (2000) Microdialysis sampling with online microbore HPLC for the determination of tirapazamine and its reduced metabolites in rats. Analyst 125:105–110
70. Telting-Diaz M, Scott DO, Lunte CE (1992) Intravenous microdialysis sampling in awake, freely-moving rats. Anal Chem 64:806–810
71. Zhang M, Mao L (2005) Enzyme-based amperometric biosensors for continuous and on-line monitoring of cerebral extracellular microdialysate. Front Biosci 10:345–352
72. Rhemrev-Boom MM, Jonker MA, Venema K, Tiessen R, Korf J, Jobst G (2001) Online continuous monitoring of glucose or lactate by ultraslow microdialysis combined with a flow-through nanoliter biosensor based on poly(m-phenylenediamine) ultra-thin polymer membrane as enzyme electrode. Analyst 126:1073–1079
73. Miele M, Fillenz M (1996) In vivo determination of extracellular brain ascorbate. J Neurosci Methods 70:15–19

74. Boutelle MG, Fellows LK, Cook C (1992) Enzyme packed bed system for the on-line measurement of glucose, glutamate, and lactate in brain microdialysate. Anal Chem 64:1790–1794
75. Kaptein WA, Zwaagstra JJ, Venema K, Korf J (1998) Continuous ultraslow microdialysis and ultrafiltration for subcutaneous sampling as demonstrated by glucose and lactate measurements in rats. Anal Chem 70:4696–4700
76. Berners MOM, Boutelle MG, Fillenz M (1994) Online measurement of brain glutamate with an enzyme/polymer-coated tubular electrode. Anal Chem 66:2017–2021
77. Miele M, Berners M, Boutelle MG, Kusakabe H, Fillenz M (1996) The determination of the extracellular concentration of brain glutamate using quantitative microdialysis. Brain Res 707:131–133
78. Jones DA, Ros J, Landolt H, Fillenz M, Boutelle MG (2000) Dynamic changes in glucose and lactate in the cortex of the freely moving rat monitored using microdialysis. J Neurochem 75:1703–1708
79. Yao T, Yano T, Nishino H (2004) Simultaneous in vivo monitoring of glucose, L-lactate, and pyruvate concentrations in rat brain by a flow-injection biosensor system with an on-line microdialysis sampling. Anal Chim Acta 510:53–59
80. Yao T, Okano G (2008) Simultaneous determination of L-glutamate, acetylcholine and dopamine in rat brain by a flow-injection biosensor system with microdialysis sampling. Anal Sci 24:1469–1473
81. Nanjo Y, Yano T, Hayashi R, Yao T (2006) Optically specific detection of D- and L-lactic acids by a flow-injection dual biosensor system with on-line microdialysis sampling. Anal Sci 22:1135–1138
82. Gramsbergen JB, Skjoth-Rasmussen J, Rasmussen C, Lambertsen KL (2004) Online monitoring of striatum glucose and lactate in the endothelin-1 rat model of transient focal cerebral ischemia using microdialysis and flow-injection analysis with biosensors. J Neurosci Methods 140:93–101
83. Li B, Zhang Z, Jin Y (2001) Chemiluminescence flow sensor for in vivo on-line monitoring of glucose in awake rabbit by microdialysis sampling. Anal Chim Acta 432:95–100
84. Lin Y, Zhu N, Yu P, Su L, Mao L (2009) Physiologically relevant online electrochemical method for continuous and simultaneous monitoring of striatum glucose and lactate following global cerebral ischemia/reperfusion. Anal Chem 81:2067–2074
85. Jacobs CB, Peairs MJ, Venton BJ (2010) Review: carbon nanotube based electrochemical sensors for biomolecules. Anal Chim Acta 662:105–127
86. Poland CA, Duffin R, Kinloch I, Maynard A, Wallace WAH, Seaton A, Stone V, Brown S, MacNee W, Donaldson K (2008) Carbon nanotubes introduced into the abdominal cavity of mice show asbestos-like pathogenicity in a pilot study. Nat Nanotechnol 3:423–428
87. Fraczek A, Menaszek E, Paluszkiewicz C, Blazewicz M (2008) Comparative in vivo biocompatibility study of single and multi-wall carbon nanotubes. Acta Biomater 4:1593–1602
88. Takagi A, Hirose A, Nishimura T, Fukumori N, Ogata A, Ohashi N, Kitajima S, Kanno J (2008) Induction of mesothelioma in p53+/− mouse by intraperitoneal application of multi-wall carbon nanotube. J Toxicol Sci 33:105–116
89. Blau A, Murr A, Wolff S, Sernagor E, Medini P, Iurilli G, Ziegler C, Benfenati F (2011) Flexible, all-polymer microelectrode arrays for the capture of cardiac and neuronal signals. Biomaterials 32:1778–1786
90. Larsson KC, Kjäll P, Richter-Dahlfors A (2012) Organic bioelectronics for electronic-to-chemical translation in modulation of neuronal signaling and machine-to-brain interfacing. Biochim Biophys Acta 1830:4334–4344
91. Giner J, Malachesky PA (1969) Proceedings of the artificial heart program conference, U.S. Department of Health Education and Welfare. p. 839
92. Skou EM (1973) Inhibition of electrochemical oxidation of glucose at platinum at pH 7.4 by chloride ions. Acta Chem Scand 27:2239–2241

93. Gebhardt U, Luft G, Richter GJ, Von Sturm F (1978) Development of an implantable electrocatalytic glucose sensor. Bioelectrochem Bioenerg 5:607–624
94. Gough DA, Anderson FL, Giner J, Golton CK, Soeldner SJ (1978) Effect of coreactants on electrochemical glucose oxidation. Anal Chem 50:941–944
95. Vassilyev YB, Khazova OA, Nikolaeva NN (1985) Kinetics and mechanism of glucose electrooxidation on different electrode-catalysts: Part I. Adsorption and oxidation on platinum. J Electroanal Chem 196:105–125
96. Park S, Boo H, Chung TD (2006) Electrochemical non-enzymatic glucose sensors. Anal Chim Acta 556:46–57
97. Yonemori Y, Takahashi E, Ren HF, Hayashi T, Endo H (2009) Biosensor system for continuous glucose monitoring in fish. Anal Chim Acta 633:90–96
98. Strack G, Luckarift HR, Sizemore SR, Nichols RK, Farrington KE, Wu PK, Atanassov P, Biffinger JC, Johnson GR (2013) Power generation from a hybrid biological fuel cell in seawater. Bioresour Technol 128:222–228
99. Özel RE, Wallace KN, Andreescu S (2011) Chitosan coated carbon fiber microelectrode for selective in vivo detection of neurotransmitters in live zebrafish embryos. Anal Chim Acta 695:89–95
100. Li S, Simonian A, Chin BA (2010) Sensors for agriculture and the food industry. Electrochem Soc Interface 19:41–46
101. Scotford IM, Miller PCH (2005) Applications of spectral reflectance techniques in northern European cereal production: a review. Biosyst Eng 90:235–250
102. Govender M, Chetty K, Bulcock H (2007) A review of hyperspectral remote sensing and its application in vegetation and water resource studies. Water SA 33:145–152
103. Bin Omar AF, Bin MatJafri MZ (2009) Optical sensor in the measurement of fruits quality: a review on an innovative approach. Int J Comp Electr Eng 1(5):557–561
104. Katayama K, Komaki K, Tamiya S (1996) Prediction of starch, moisture, and sugar in sweet potato by near infrared transmittance. Hort science 31:1003–1006
105. Garrido A, Sanchez MT, Cano G, Perez D, Lopez C (2001) Prediction of neutral and acid detergent fiber content of green asparagus stored under refrigeration and modified atmosphere conditions by near-infrared reflectance spectroscopy. J Food Quality 24:539–550
106. Pedro AMK, Ferreira MMC (2005) Nondestructive determination of solids and carotenoids in tomato products by near-infrared spectroscopy and multivariate calibration. Anal Chem 77:2505–2511
107. Ariana DP, Lu RF (2010) Evaluation of internal defect and surface color of whole pickles using hyperspectral imaging. J Food Eng 96:583–590
108. Ariana DP, Lu RF, Guyer DE (2006) Near-infrared hyperspectral reflectance imaging for detection of bruises on pickling cucumbers. Comput Electron Agric 53:60–70
109. Lu RF (2003) Detection of bruises on apples using near-infrared hyperspectral imaging. T ASAE 46:523–530
110. Lu RF, Peng YK (2006) Hyperspectral scattering for assessing peach fruit firmness. Biosyst Eng 93:161–171
111. Kim MS, Chen YR, Mehl PM (2001) Hyperspectral reflectance and fluorescence imaging system for food quality and safety. T ASAE 44:721–729
112. Deisingh AK, Stone DC, Thompson M (2004) Applications of electronic noses and tongues in food analysis. Int J Food Sci Technol 39:587–604
113. Casalinuovo IA, Di Pierro D, Coletta M, Di Francesco P (2006) Application of electronic noses for disease diagnosis and food spoilage detection. Sensors 6:1428–1439
114. Pinheiro C, Rodrigues CM, Schafer T, Crespo JG (2002) Monitoring the aroma production during wine-must fermentation with an electronic nose. Biotechnol Bioeng 77:632–640
115. Ivanov P, Llobet E, Vergara A, Stankova M, Vilanova X, Hubalek J, Gracia I, Cane C, Correig X (2005) Towards a micro-system for monitoring ethylene in warehouses. Sens Actuators B 111:63–70

116. Baratto C, Faglia G, Pardo M, Vezzoli M, Boarino L, Maffei M, Bossi S, Sberveglieri G (2005) Monitoring plants health in greenhouse for space missions. Sens Actuators B 108:278–284
117. Herrmann U, Jonischkeit T, Bargon J, Hahn U, Li QY, Schalley CA, Vogel E, Vogtle F (2002) Monitoring apple flavor by use of quartz microbalances. Anal Bioanal Chem 372:611–614
118. Brezmes J, Llobet E, Vilanova X, Orts J, Saiz G, Correig X (2001) Correlation between electronic nose signals and fruit quality indicators on shelf-life measurements with pinklady apples. Sens Actuators B 80:41–50
119. Llobet E, Hines EL, Gardner JW, Franco S (1999) Non-destructive banana ripeness determination using a neural network-based electronic nose. Meas Sci Technol 10:538–548
120. Brezmes J, Fructuoso MLL, Llobet E, Vilanova X, Recasens I, Orts J, Saiz G, Correig X (2005) Evaluation of an electronic nose to assess fruit ripness. IEEE Sens J 5:97–108
121. Costello B, Ewen RJ, Gunson HE, Ratcliffe NM, Spencer-Phillips PTN (2000) The development of a sensor system for the early detection of soft rot in stored potato tubers. Meas Sci Technol 11:1685–1691
122. Baker TC, Haynes KF (1989) Field and laboratory electroantennographic measurements of pheromone plume structure correlated with oriental fruit moth behaviour. Physiol Entomol 14:1–12
123. Sauer AE, Karg G, Koch UT, Dekramer JJ, Milli R (1992) A portable EAG system for the measurement of pheromone concentrations in the field. Chem Senses 17:543–553
124. Schutz S, Weissbecker B, Hummel HE (1996) Biosensor for volatiles released by damaged plants. Biosens Bioelectron 11:427–433
125. Purnamadjaja AH, Russell RA (2007) Guiding robots behaviors using pheromone communication. Autonomous Robots 23:113–130
126. Henderson WG, Khalilian A, Han YJ, Greene JK, Degenhardt DC (2010) Detecting stink bugs/damage in cotton utilizing a portable electronic nose. Comput Electron Agric 70:157–162
127. Weerakoon K, Chin BA (2010) Detecting insect infestation using a carbon/polymer based sensor array system. ECS Trans 33:85–89
128. Vitosh ML, Silva GH (1994) A rapid petiole sap nitrate-nitrogen test for potatoes. Commun Soil Sci Plan 25:183–190
129. Errebhi M, Rosen CJ, Birong DE (1998) Calibration of a petiole sap nitrate test for irrigated. "Russet Burbank" potato. Commun Soil Sci Plan 29:23–35
130. Warncke DD (1996) Soil and plant tissue testing for nitrogen management in carrots. Commun Soil Sci Plan 27:597–605
131. Kubota A, Thompson TL, Doerge TA, Godin RE (1997) A petiole sap nitrate test for broccoli. J Plant Nutr 20:669–682
132. Rashed MN (1995) Trace element determination in warm-climate plants by atomic absorption spectroscopy and ion selective electrodes. J Arid Environ 30:463–478
133. Rieger M, Litvin P (1998) Ion selective electrodes for measurement of sodium and chloride in salinity experiments. J Plant Nutr 21:205–215
134. Brouder SM, Thom M, Adamchuck VI, Morgan MT (2003) Potential uses of ion selective potassium electrodes in soil fertility management. Commun Soil Sci Plan 34:2699–2726
135. Plaza S, Szigeti Z, Geisler M, Martinoia E, Aeschlimann B, Gunther D, Pretsch E (2005) Potentiometric sensor for the measurement of Cd2+ transport in yeast and plants. Anal Biochem 347:10–16
136. Gieling TH, Van Straten G, Janssen HJJ, Wouters H (2005) ISE and CHEMFET sensors in greenhouse cultivation. Sens Actuators B 105:74–80
137. Gutierrez M, Alegret S, Caceres R, Casadesus J, Marfa O, Del Valle M (2007) Application of a potentiometric electronic tongue to fertigation strategy in greenhouse cultivation. Comput Electron Agric 57:12–22
138. Cass AEG (1990) Biosensors: a practical approach. Oxford University Press, New York

139. Ivnitski D, Abdel-Hamid I, Atanasov P, Wilkins E (1999) Biosensors for detection of pathogenic bacteria. Biosens Bioelectron 14:599–624
140. Jones C, Patel A, Griffin S, Martin J, Young P, O'Donnell K, Silverman C, Porter T, Chaiken I (1995) Current trends in molecular recognition and bioseparation. J Chromatogr A 707:3–22
141. Chambers JP, Arulanandam BP, Matta LL, Weis A, Valdes JJ (2008) Biosensor recognition elements. Curr Issues Mol Biol 10:1–12
142. Leonard P, Hearty S, Brennan J, Dunne L, Quinn J, Chakraborty T, O'Kennedy R (2003) Advances in biosensors for detection of pathogens in food and water. Enzyme Microb Technol 32:3–13
143. Brigati JR, Petrenko VA (2005) Thermostability of landscape phage probes. Anal Bioanal Chem 382:1346–1350
144. Sorokulova IB, Olsen EV, Chen IH, Fiebor B, Barbaree JM, Vodyanoy VJ, Chin BA, Petrenko VA (2005) Landscape phage probes for Salmonella typhimurium. J Microbiol Methods 63:55–72
145. Petrenko VA, Vodyanoy VJ (2003) Phage display for detection of biological threat agents. J Microbiol Methods 53:253–262
146. Petrenko VA, Smith JP (2000) Phages from landscape libraries as substitute antibodies. Protein Eng 13:589–592
147. Neufeld T, Schwartz-Mittelmann A, Biran D, Ron EZ, Rishpon J (2003) Combined phage typing and amperometric detection of released enzymatic activity for the specific identification and quantification of bacteria. Anal Chem 75:580–585
148. Neufeld T, Schwartz-Mittelmann A, Buchner V, Rishpon J (2005) Electrochemical phagemid assay for the specific detection of bacteria using Escherichia coli TG-1 and M13KO7 phagemid in a model system. Anal Chem 77:652–657
149. Yemini M, Levi Y, Yagil E, Rishpon J (2007) Specific electrochemical phage sensing for Bacillus cereus and Mycobacterium smegmatis. Bioelectrochemistry 70:180–184
150. Yang LMC, Diaz JE, McIntire TM, Weiss GA, Penner RM (2008) Direct electrical transduction of antibody binding to a covalent virus layer using electrochemical impedance. Anal Chem 80:5695–5705
151. Yang LMC, Tam PY, Murray NJ, McIntire TM, Overstreet CM, Weiss GA, Penner RM (2006) Virus electrodes for universal biodetection. Anal Chem 78:3265–3270
152. Mejri MB, Baccar H, Baldrich E, Del Campo FJ, Helali S, Ktari T, Simonian A, Aouni M, Abdelghani A (2010) Impedance biosensing using phages for bacteria detection: generation of dual signals as the clue for in-chip assay confirmation. Biosens Bioelectron 26:1261–1267
153. Jia YF, Qin M, Zhang HK, Niu WC, Li X, Wang LK, Li X, Bai YP, Cao YJ, Feng XZ (2007) Label-free biosensor: a novel phage-modified light addressable potentiometric sensor system for cancer cell monitoring. Biosens Bioelectron 22:3261–3266
154. Banaiee N, Bodadilla-del-Valle M, Bardarov S, Riska PF, Small PM, Ponce-De-Leon A, Jacobs WR, Hatfull GF, Sifuentes-Osornio J (2001) Luciferase reporter mycobacteriophages for detection, identification, and antibiotic susceptibility testing of *Mycobacterium tuberculosis* in Mexico. J Clin Microbiol 39:3883–3888
155. Turnbough CL (2003) Discovery of phage display peptide ligands for species-specific detection of Bacillus spores. J Microbiol Methods 53:263–271
156. Goodridge L, Chen JR, Griffiths M (1999) The use of a fluorescent bacteriophage assay for detection of *Escherichia coli* O157:H7 in inoculated ground beef and raw milk. Int J Food Microb 47:43–50
157. Goodridge L, Chen JR, Griffiths M (1999) Development and characterization of a fluorescent bacteriophage assay for detection of *Escherichia coli* O157:H7. Appl Environ Microb 65:1397–1404
158. Edgar R, McKinstry M, Hwang J, Oppenheim AB, Fekete RA, Giulian G, Merril C, Nagashima K, Adhya S (2006) High-sensitivity bacterial detection using biotin-tagged phage and quantum-dot nano-complexes. Proc Natl Acad Sci U S A 103:4841–4845
159. Souza GR, Christianson DR, Staquicini FI, Ozawa MG, Snyder EY, Sidman RL, Miller JH, Arap W, Pasqualini R (2006) Networks of gold nanoparticles and bacteriophage as biological sensors and cell-targeting agents. Proc Natl Acad Sci U S A 103:1215–1220

160. Nanduri V, Balasubramanian S, Sista S, Vodyanoy VJ, Simonian AL (2007) Highly sensitive phage-based biosensor for the detection of beta-galactosidase. Anal Chim Acta 589:166–172
161. Liu FF, Luo ZF, Ding X, Zhu SG, Yu XL (2009) Phage-displayed protein chip based on SPR sensing. Sens Actuators B 136:133–137
162. Balasubramanian S, Sorokulova IB, Vodyanoy VJ, Simonian AL (2007) Lytic phage as a specific and selective probe for detection of *Staphylococcus aureus*—a surface plasmon resonance spectroscopic study. Biosens Bioelectron 22:948–955
163. Zhu HY, White IM, Suter JD, Fan XD (2008) Phage-based label-free biomolecule detection in an opto-fluidic ring resonator. Biosens Bioelectron 24:461–466
164. Olsen EV, Sorokulova IB, Petrenko VA, Chen IH, Barbaree JM, Vodyanoy VJ (2006) Affinity-selected filamentous bacteriophage as a probe for acoustic wave biodetectors of *Salmonella typhimurium*. Biosens Bioelectron 21:1434–1442
165. Fu L, Li S, Zhang K, Cheng ZY, Barbaree J (2007) Detection of *Bacillus anthracis* spores in water using biosensors based on magnetorestrictive microcantilever coated with phage. Proc SPIE 6556:655619
166. Johnson ML, LeVar O, Yoon SH, Park JH, Huang S, Kim DJ, Cheng Z, Chin BA (2009) Dual-cathode method for sputtering magnetoelastic iron-boron films. Vacuum 83:958–964
167. Johnson ML, Wan JH, Huang SC, Cheng ZY, Petrenko VA, Kim DJ, Chen IH, Barbaree JM, Hong JW, Chin BA (2008) A wireless biosensor using microfabricated phage-interfaced magnetoelastic particles. Sens Actuators A 144:38–47
168. Huang S, Yang H, Lakshmanan RS, Johnson ML, Wan JK, Chen IH, Wikle HC, Petrenko VA, Barbaree JM, Chin BA (2009) Sequential detection of Salmonella typhimurium and Bacillus anthracis spores using magnetoelastic biosensors. Biosens Bioelectron 24:1730–1736
169. Lakshmanan RS, Guntupalli R, Hu J, Kim DJ, Petrenko VA, Barbaree JM, Chin BA (2007) Phage immobilized magnetoelastic sensor for the detection of *Salmonella typhimurium*. J Microbiol Methods 71:55–60
170. Lakshmanan RS, Guntupalli R, Hu J, Petrenko VA, Barbaree JM, Chin BA (2007) Sens Actuators B 126:544
171. Wan JH, Johnson ML, Guntupalli R, Petrenko VA, Chin BA (2007) Detection of *Bacillus anthracis* spores in liquid using phage-based magnetoelastic microresonators. Sens Actuators B 127:559
172. Wan JH, Shu HH, Huang SC, Fiebor B, Chen IH, Petrenko VA, Chin BA (2007) Phage-based magnetoelastic wireless biosensors for detecting Bacillus anthracis spores. IEEE Sensors J 7:470–477
173. Shen W, Lakshmanan RS, Mathison LC, Petrenko VA, Chin BA (2009) Phage coated magnetoelastic micro-biosensors for real-time detection of Bacillus anthracis spores. Sens Actuators B 137:501–506
174. Lu QZ, Lin HL, Ge ST, Luo SL, Cai QY, Grimes CA (2009) Wireless, remote-query, and high sensitivity escherichia coli O157:H7 biosensor based on the recognition action of Concanavalin A. Anal Chem 81:5846–5850
175. Li S, Li Y, Chen H, Horikawa S, Shen W, Simonian A, Chin BA (2010) Direct detection of *Salmonella typhimurium* on fresh produce using phage-based magnetoelastic biosensors. Biosens Bioelectron 26:1313–1319
176. Palleschi G, Bernabei M, Cremisini C, Mascini M (1992) Determination of organophosphorus insecticides with a choline electrochemical biosensor. Sens Actuators B 7:513–517
177. Kulys J, D'Costa EJ (1991) Printed amperometric sensors based on TCNQ and cholinesterase. Biosens Bioelectron 6:109–115
178. Starodub NF, Kanjuk NI, Kukla AL, Shirshov YM (1999) Multi-enzymatic electrochemical sensor: field measurements and their optimization. Anal Chim Acta 385:461–466
179. Compagnone D, Bugli M, Imperiali P, Varallo G, Palleschi G (1998) Determination of heavy metals using electrochemical biosensors based on enzyme inhibition. In: Nikolelis DP, Krull UJ, Wang J, Mascini M (eds) Biosensors for direct monitoring of environmental pollutants in field. Kluwer Academic Publishers, Dordrecht

180. Rainina EI, Efremenco EN, Varfolomeyev SD, Simonian AL, Wild JR (1996) The development of a new biosensor based on recombinant *E. coli* for the direct detection of organophosphorous neurotoxins. Biosens Bioelectron 11:991–1000
181. Simonian AL, Wild JR (2006) Detection and remediation of organophosphate contamination. In: Amass S, Bhunia AK, Chaturvedi A, Dolk D, Peeta S, Atallah M (eds) The science of homeland security, vol 1. Purdue University Press, West Lafayette
182. Viveros L, Paliwal S, McCrae D, Wild J, Simonian A (2006) A fluorescence-based biosensor for the detection of organophosphate pesticides and chemical warfare agents. Sens Actuators B 115:150–157
183. Zourob M, Simonian AL, Wild JR, Mohr S, Goddard N (2007) Optical leaky waveguide biosensors for the detection of organophosphorus pesticides. Analyst 132:114–120
184. Ramanathan M, Simonian AL (2007) Array biosensor based on enzyme kinetics monitoring by fluorescence spectroscopy: application for neurotoxins detection. Biosens Bioelectron 22:3001–3007
185. Wang N, Zhang NQ, Wang MH (2006) Wireless sensors in agriculture and food industry—recent development and future perspective. computers and electronics in agriculture. Comput Electron Agric 50:1–14
186. Atalay YT, Vermeir S, Witters D, Vergauwe N, Verbruggen B, Verboven P, Nicolaï BM, Lammertyn J (2011) Microfluidic analytical systems for food analysis. Trends Food Sci Technol 22:386–404
187. Tombelli S, Minunni M, Mascini M (2007) Aptamers-based assays for diagnostics, environmental and food analysis. Biomol Eng 24:191–200
188. Schubert-Ullrich P, Rudolf J, Ansari P, Galler B, Führer M, Molinelli A, Baumgartner S (2009) Commercialized rapid immunoanalytical tests for determination of allergenic food proteins: an overview. Anal Bioanal Chem 395:69–81
189. Tran DT, Janssen KP, Pollet J, Lammertyn E, Anné J, Van Schepdael A, Lammertyn J (2010) Selection and characterization of DNA aptamers for egg white lysozyme. Molecules 15:1127–1140
190. Velusamy V, Arshak K, Korostynska O, Oliwa K, Adley C (2010) An overview of foodborne pathogen detection: in the perspective of biosensors. Biotechnol Adv 28:232–254
191. Li PCH (2006) Microfluidic Lab-on-a-chip for chemical and biological analysis and discovery. Taylor & Francis, New York
192. Manz A, Harrison DJ, Verpoorte EMJ, Fettinger JC, Paulus A, Lüdi H, Widmer HM (1992) Planar chips technology for miniaturization and integration of separation techniques into monitoring systems: capillary electrophoresis on a chip. J Chromatogr A 593:253–258
193. Stone HA, Stroock AD, Ajdari A (2004) Engineering flows in small devices. Microfluidics toward a lab-on-a-chip. Annu Rev Fluid Mech 36:381–411
194. Raz SR, Bremer MGEG, Giesbers M, Norde W (2008) Development of a biosensor microarray towards food screening, using imaging surface plasmon resonance. Biosens Bioelectron 24:552–557
195. Melin J, Quake SR (2007) Microfluidic large-scale integration: the evolution of design rules for biological automation. Annu Rev Biophys Biomol Struct 36:213–231
196. Martinez AW, Phillips ST, Whitesides GM, Carrilho E (2010) Diagnostics for the developing world: microfluidic paper-based analytical devices. Anal Chem 82(1):3–10
197. Squires TM, Quake SR (2005) Microfluidics: fluid physics at the nanoliter scale. Rev Mod Phys 77:977–1026
198. Escarpa A, González MC, Gil MAL, Crevillén AG, Hervás M, García M (2008) Microchips for CE: breakthroughs in real-world food analysis. Electrophoresis 29:4852–4861
199. Schemberg J, Grodrian A, Römer R, Gastrock G, Lemke K (2010) Application of segmented flow for quality control of food using microfluidic tools. Phys Status Solidi A 207(4):904–912
200. Dittrich PS, Tachikawa K, Manz A (2006) Micro total analysis systems. Latest advancements and trends. Anal Chem 78:3887–3907