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Bioelectronic nose: current status and perspectives

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Abstract

A characteristic feature of human and animal organs of smell is the ability to identify hundreds of thousands of odours. It is accompanied by particular smell sensations, which are a basic source of information about odour mixture. The main structural elements of biological smell systems are the olfactory receptors. Small differences in a structure of odorous molecules (odorants) can lead to significant change of odour, which is due to the fact that each of the olfactory receptors is coded with different gene and usually corresponds to different type of odour. Discovery and characterization of the gene family coding the olfactory receptors contributed to the elaboration and development of the electronic smell systems, the so-called bioelectronic noses. The olfactory receptors are employed as a biological element in this type of instruments. An electronic system includes a converter part, which allows measurement and processing of generated signals. A suitable data analysis system is also required to visualize the results. Application potentialities of the bioelectronic noses are focused on the fields of economy and science where highly selective and sensitive analysis of odorous substances is required. The paper presents a review of the latest achievements and critical evaluation of the state of art in the field of bioelectronic noses.

key words: electronic nose, bioelectronic nose, olfactory receptors, biosensors

1. Introduction

Thousands of years of the evolution made it possible to evolve the senses and accompanying mechanisms characterised by versatility, appropriate efficiency, sensitivity and tolerance with respect to saturation. Humans possess the following senses: sight, hearing, touch, smell and taste. They belong to the fundamental human senses. Three of them (sight, hearing and touch) are responsible for identification of physical stimuli, the remaining two are responsible for chemical stimuli. Knowledge about functioning of the sight and hearing senses is much broader than the knowledge about the mechanisms governing the smell (Lundström et al., 2011). The human sense of smell is less sensitive than that of the majority of animals or insects, this being connected with the type and number of receptors and respiratory tracts (Quignon et al., 2005; Tan et al., 2010; Zhang et al., 2007).

Investigations on odour perception at the gene and protein levels, published by Richard Axel and Linda Buck in 2004, clearly explained the process of reading of odour information by brain (Buck, 2005, 2004). It has been demonstrated that owing to spatial segregation of neurons and axons each odorant excites a defined set of olfactory glomeruli and after reaching the rhinencephalon the signal is converted in such a way that it is recognised as odour. The results of those investigations have shown that the rhinencephalon is a site responsible for odour discrimination. Human genes coding particular receptor proteins are responsible for interception of odorous substances. Differences in the structure of these proteins determine interaction with different odorants. The aforementioned scientists, during independent investigations, revealed that in each cell there was only one type of chemoreceptor. Thousands of olfactory genes were discovered, which belonging to rhodopsin-like family, each of them determining formation of a particular olfactory receptor reacting to a given chemical substance. The olfactory receptor gene (OR) superfamily is the largest in the human genome. The superfamily contains 390 putatively functional genes and 465 pseudogenes arranged into 18 gene families and 300 subfamilies (Olender et al., 2008), which enable identification of thousands of different odours. This type of asymmetry is determined by perfect ability of odour identification by the chemoreceptors, which are capable of discrimination of specific and partial ligands as well as non-bonded molecules. A single odorant activates different types of receptors and at the same time single receptor can be activated by a few odorous substances. In this way numerous combinations of the activated receptors being formed, which are believed to be a unique property of the brain (Firestein, 2001; Gelis et al., 2012; Kay, 2011).

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Combining the odorous molecules with the olfactory receptors results in generation of an electric signal. There are numerous vesicular glands secreting a serous fluid, present in mucous membrane of the olfactory region. The glands secrete odorant-binding protein (OBP), which binds and transports these substances to the membrane receptors of olfactory cells cilia (Tegoni et al., 2000; Vidic et al., 2008). An olfactory tract starts in the bipolar cells, from which the impulses travel along the axons, through the cribriform plate to the olfactory bulb. Smell impulses are transmitted via the axons to the olfactory centre localised in the corner of hippocampus and amygdala situated in the bulk of temporal lobe. Conscious odour perception occurs when the impulses reach the cerebral cortex or when they are transported to the autonomic elements of hypothalamus via other nerve routes. In the case of human sense of smell the threshold level of odour sensing is different for various substances. For example, it is equal to 5.8 mg/L for diethyl ether, whereas for butyric acid it amounts to 0.009 mg/L. The lowest threshold value was recorded for methyl mercaptan – 0.4 ng/L (Olsson and Cain, 2000; Sankaran et al., 2012).

Identification of odours at low concentration levels is a natural feature of biological smell systems. An attempt to mimic the mechanisms of odour identification and the processes responsible for that phenomenon becomes feasible thanks to the elaboration and improvement of devices comprising a sensor array, the so-called electronic noses. First attempts of odours identification employing a set of sensors dates back to the 60s of the twentieth century (Moncrieff, 1961). The subject of the invention was the so-called mechanical nose. The electronic nose was presented for the first time by Wilkens and Hatman (Wilkens and Hartman, 1964) in 1964. However, the concept of an instrument consisting of intelligent sensor matrix capable of odour classification was propagated 20 years later in the papers of Parsaud and Dodd (Persaud and Dodd, 1982) and Ikegami *et al*. (Ikegami and Kaneyasu, 1985; Kaneyasu et al., 1987). Initiation of an emphasis on development of this type of devices took place during the first scientific conference on electronic noses (Table 1). Göpel *et al*. were the first who proposed utilization of particular biomolecules (Göpel, 2000, 1998) as the sensitive elements deposited on the biosensors' surfaces in order to improve some parameters, mainly the sensitivity and selectivity (Göpel, 2000; Ziegler et al., 1998).

The stages of artificial senses development are presented in Table 1.

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Table 1. Historical perspective of sensor-based electronic devices (Gardner and Bartlett, 1994; Vlasov and Legin, 1998)**.**

Year, inventor	Object of the invention	Ref.
1961- Moncrieff	mechanical nose for measuring and classifying odours,	(Moncrieff, 1961)
1964- Wilkens and Hatman	sensors array with redox reactions of odorants at an electrode,	(Wilkens and Hartman, 1964)
1978- Beets	structure–activity relationships in human chemoreception,	(Boelens, 1978)
1982- Persaud, Dodd	first intelligent chemical array sensor system for odour classification,	(Persaud and Dodd, 1982)
1985- Ikegami	olfactory detection using integrated sensors,	(Ikegami and Kaneyasu, 1985; Kaneyasu et al., 1987)
1990- Reykjavik, Iceland	first international conference dedicated to the electronic noses, NATO Advanced Research Workshop	(Gardner and Bartlett, 1992)
1992- Persaud, Dodd	first commercial electronic nose using conducting polymer sensor array	(Hatfield et al., 1994)
1995- Vlasov, Legin, D'Amigo, Di Natale	first electronic tongue,	(Vlasov and Legin, 1998)
1998- Göpel	concept of bioelectronic nose,	(Göpel, 1998)
2000- onwards	more targeted approaches for the design and development of electronic noses for specific problems in medical, food quality and environmental applications,	
2006- Wang	olfactory cell-based biosensor,	(Liu et al., 2006)
2012- Park	first biosensor based on nanovesicles structures,	(Jin et al., 2012)

Progress in the field of electronic nose instruments is closely related to the progress in materials the sensors are made of. Sensitive elements of this type significantly differ from their

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biological counterparts formed in olfactory epithelium of animals. Current knowledge about the biological smell system and the methods of receptor proteins acquisition allows application of materials mimicking biological sense of smell much better (Manuel, 2007; Munger et al., 2009). Achievements in the field of biology, genetic engineering, biotechnology and nanotechnology provide a possibility to construct and implement the devices belonging to the family of bioelectronic noses *(bioelectronic nose, biomimetic electronic nose, bio-enose, b-enose)*. Intensive development of these devices is aimed at elaboration of:

- sensors with a high sensitivity, specificity and shorter response time,
- sensor systems generating the signals similar to those occurring in their biological counterparts,
- electronic systems mimicking human nose or brain.

Dynamic development of those devices has been confirmed by inspection of the recent literature data (Figure 1).

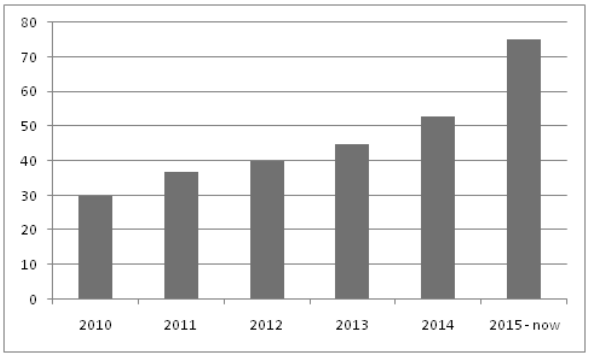

Figure 1. The number of scientific publications in last five years, concerning bioelectronic noses (according to PubMed database).

2. Design and operation principle of bioelectronic noses

A principle of operation of an electronic and bioelectronic nose is based on biological systems. The mechanisms of odorous substances identification implemented in the electronic analogues are very similar to those present in the human nose. The core of the artificial nose is the sensor matrix. Excitation of its sensitive elements in particular types of odour detection and identification systems leads to generation of specific signals. However, it is a suitable method for the generated signal processing and data analysis, which makes it possible to generate unique responses *(odour fingerprints*) for particular odour samples.

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Differences and similarities in the structure of human nose, electronic nose and bioelectronic nose are presented in Figure 2.

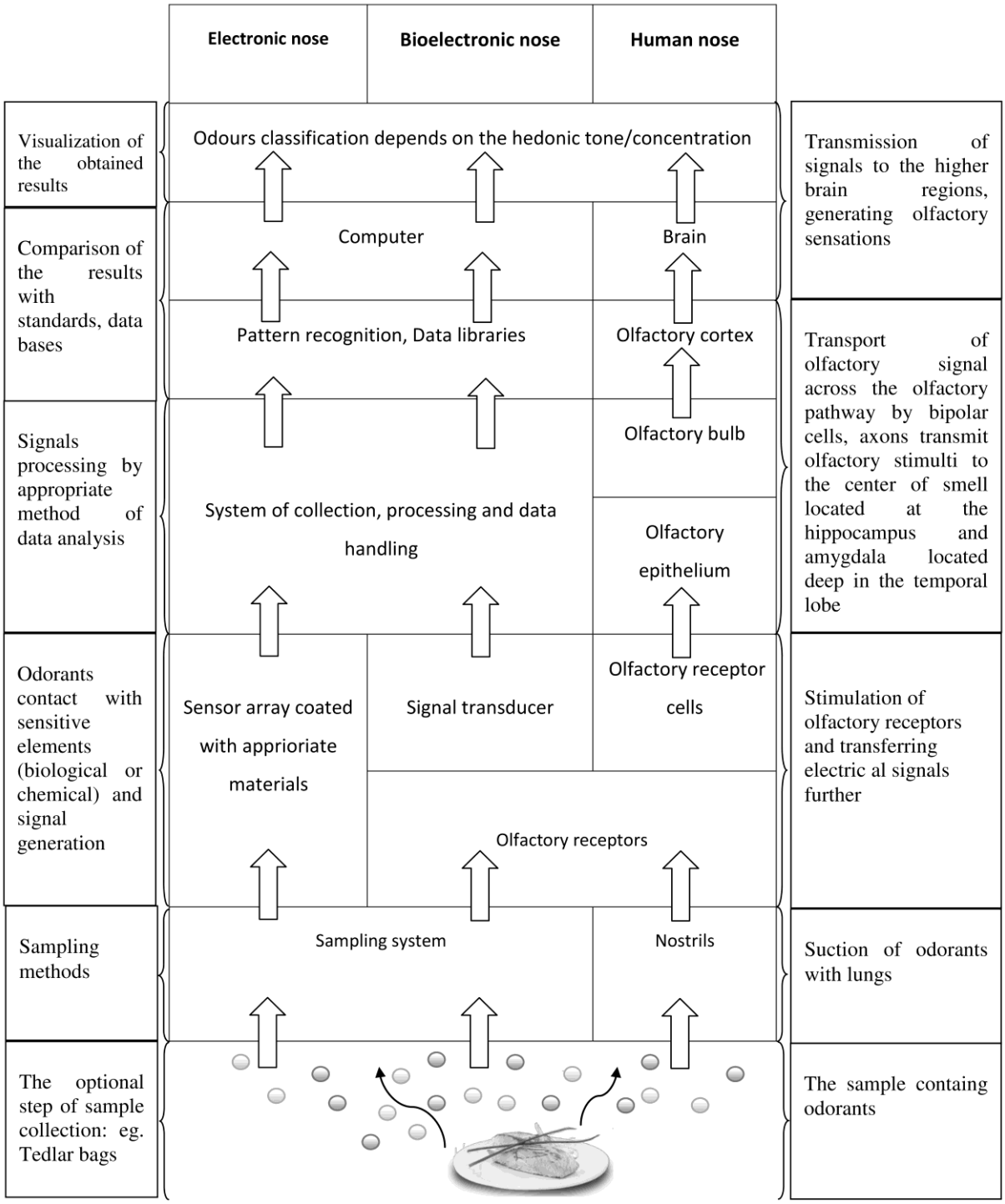

Figure 2. Schematic comparison of structure and operation principle of electronic, bioelectronic and human nose.

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In some aspects the bioelectronic nose differs from conventional electronic noses (Engg and College, 2013) where the active material is made of chemically sensitive elements with a broad response range. It enables detection of complex gas mixtures and the generation of signals characteristic of a particular same. Comparison of obtained odour profiles with the references available in databases allows identification of the odorous compounds occurring in the sample. During the years the ability to analyse complex gas mixtures was improved *via* elaboration of materials for construction of the sensors employed in the electronic noses, mainly metal oxides, conducting polymers, field-effect transistors and quartz crystal microbalances (Chiu and Tang, 2013; James et al., 2005). Effective application of the electronic noses is hindeed by certain problems associated with high cost of equipment, identification of odours at the concentration levels higher than those of the biological counterpart and complicated calibration (Patel and Kunpara, 2011). Additionally, odorants analysis with the electronic noses does not provide an answer concerning concentration of particular compounds in mixture but it rather characterizes the sample as a holistic image of the odours present. The simplest method of presentation of the results of odour identification is graphical representation in the form of histograms. The most frequently applied odour classification methods engulf Principal Component Analysis (*PCA*) and Artificial Neural Networks (*ANN)* (Wilson and Baietto, 2009), (Gebicki et al., 2014). Some limitations originate from the lack of ability of the electronic nose to mimic biological sense of smell, which is due to lack of the adequate biomolecules. Fast operation, non-invasive sample analysis and simple measurement make the electronic nose instruments a real alternative to other popular methods of odour analysis. Moreover, a possibility of more precise mimicking of human sense of smell via implementation of highly selective and sensitive sensors utilised in the bioelectronic noses can significantly broaden the application spectrum of the devices from the electronic senses group (Lee and Park, 2010).

A comparison of basic structural elements of two types of the electronic nose is shown in Figure 3.

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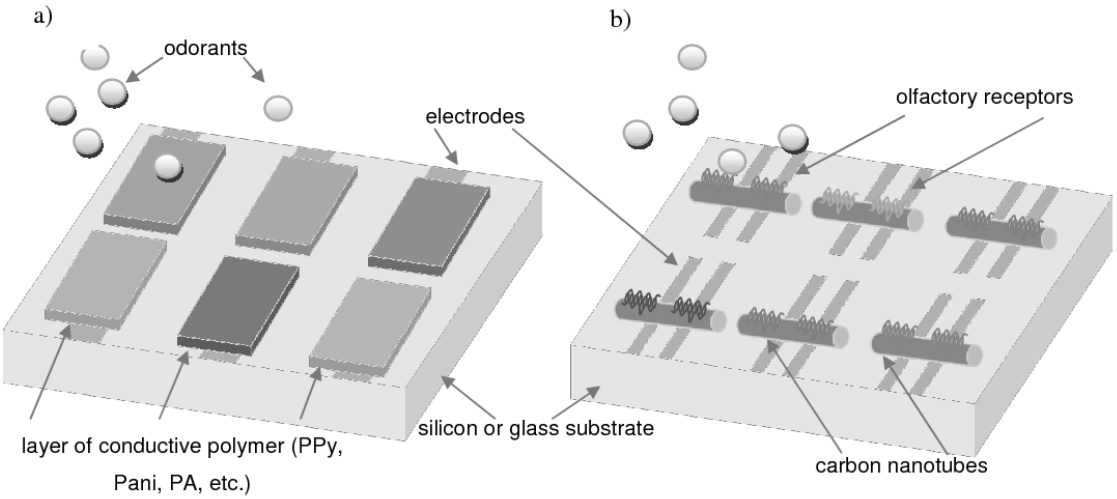

Figure 3. Schematic presentation of electronic (a) and bioelectronic nose (b), the structure of which is based on conducting polymers.

A design concept of the sensors, the principle of operation of which would be based on mimicking biological sense of smell was suggested by the scientists in the 90s of the twentieth century (Göpel, 2000). A principal assumption in the design of bioelectronic noses is application of the proteins of olfactory receptors as the active element of the sensor for odour analysis with high sensitivity and specificity. A sensory part of the bioelectronic nose can be built of olfactory receptors (*OR*) of the cells exhibiting expression of olfactory receptors proteins. The sensitive element made of the biomaterial of that type is directly connected with the sensor intended for odour identification and conversion of biological signal into an analytically useful signal – electrical or optical one. The sensors used in this type of noses are comprised of two elements – a primary and secondary converter. For instance, the first one is built of olfactory receptors cells, for instance, whereas the other (transductor) is a non-biological device. Signal generation occurs as a result of contact between the odorous substance and the receptor, where adenyl cyclase is activated *via* membrane protein G. This activation leads to an increase in cAMP concentration, which combines with channel proteins causing opening of ionic channels, flow of ions and change of potential of the membrane and cilia. Some olfactory receptors activate (*via* protein G) phospholipases C enzyme producing inositol triphosphate. This compound opens the channels for Ca^{2+}, increases concentration of these ions in cytosol, which in turn causes opening of the channels for K^{+} and passing the impulse. The result is generation of action potential in the receptor and depolarization of axon. Then, the generated signal is directed to the non-biological element where it is converted to electrical signal (Su et al., 2009). The mechanism of operation of biological part of the biosensor is illustrated in Figure 4.

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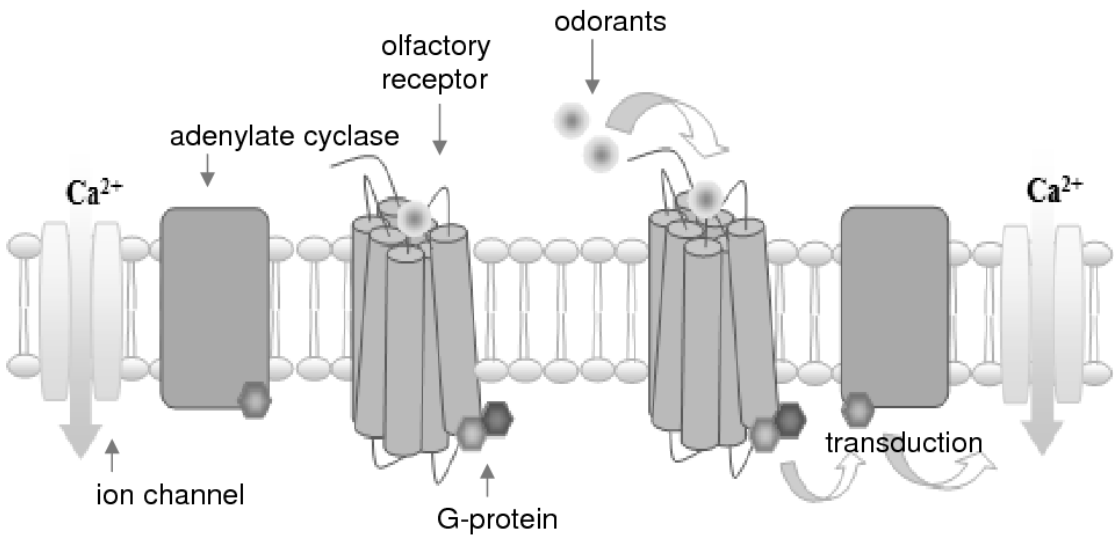

Figure 4. Schematic presentation of mechanism of odour molecules binding and signal generation in biological element of the sensor. Receptor sites are bounded with proteins G. Activation of protein G starts transduction cycle finished with opening/closing of ionic channels. Flow of cations results in membrane depolarization and initiates action potential.

Different types of transducers are utilised for identification of specific biochemical signal and for change into analytically useful ones.

A list of transducers of the signal generated by the biosensitive elements is presented in Table 2.

Table 2. List of transduction technologies utilised for olfactory biosensing.

Class	Technique	Measures	Sensitivity/ Sensitive range	References
Electrochemical	Conductometric/impedance: • EIS Amperometric Potentiometric	Electrical conductance/resistance Current Ion/pH	5×10^{-11} - 5×10^{-2} M 1×10^{-6} M -, MEAs: 1×10^{-15} - 1×10^{-3} M,	(Alvarez-Curto et al., 2010; Dzyadevych et al., 2003; Lojou and Bianco, 2006; Mousty et al., 2007; Reimhult

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	• EOG/EAG, Voltage/current/patch clamps, Microelectrode array, Field effect Transistors, Potentiometric sensor (LAPS) Nanomaterials		FET: $1 \times 10^{-7} – 2 \times 10^{-4}$ M 1×10^{-10} - 1×10^{-4} M 1×10^{-12} - 1×10^{-4} M	and Kumar, 2008)
Resonant	Piezoeletric effect • Bulk acoustic wave (BAW), Quartz Crystal Microbalance (QCM), Surface acoustic wave (SAW), Catilever-based sensor	Mass	BAW: 1×10^{-3} M, QCM: 1×10^{-7} M, SAW: 1.2×10^{-15} M, Catilever: -	(Andle and Vetelino, 1994; Bunde et al., 1998; Ferreira et al., 2009; Jordan and Challiss, 2011; Rocha-Gaso et al., 2009; C. Wu et al., 2012)
Optical	Surface Plasmon resonance (SPR) Fluorescence (including FRET) Luminescence • Bioluminescence (including BRET) • Chemiluminescence Absorbance	Light	$3 \times 10^{-5} \times 10^{-4}$ M - $1 \times 10^{-3} \times 10^{-1}$ M -	(Anker et al., 2008; Dmitri Ivnitski et al., 1999; Homola, 2003; Pancrazio et al., 1999; Passaro et al., 2007; Schmidt et al., 2012)

Usually the detection is based on measurement of different types of signals using:

- microelectrodes,

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- electrochemical impedance spectroscopy (EIS),
- quartz-crystal microbalance (QCM),
- field-effect transistor (*FET*),
- surface plasmon resonance (*SPR*) sensors,
- conducting polymers (for example polypyrrole),
- carbon nanotubes,
- graphene and others.

As far as the sensor structure is concerned there are the bioelectronic noses containing different types of the sensitive element coverage (Figure 5) (Boeker, 2014a; Lee and Park, 2010).

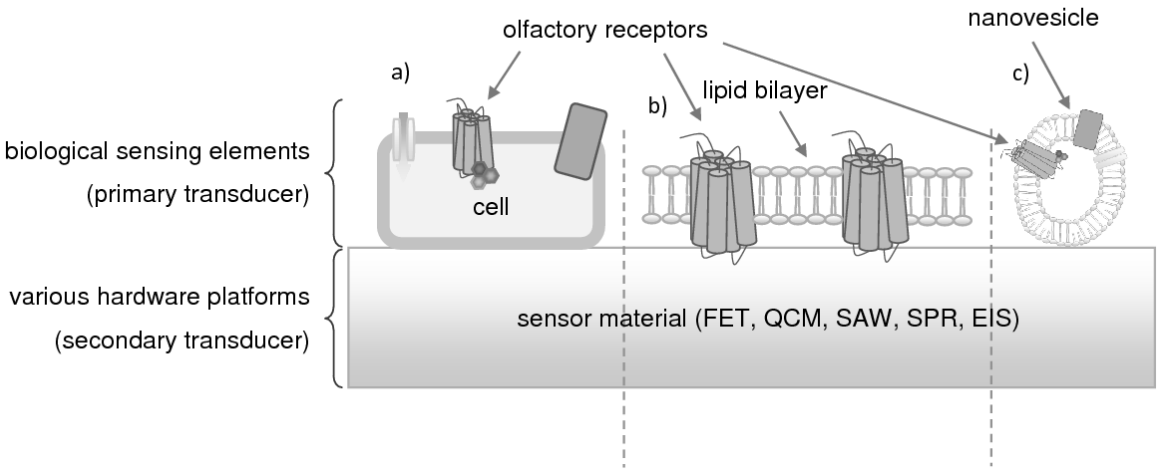

Figure 5. Schematic presentation of sensors design of bioelectronic nose. Three basic types of bio e-noses differ in the elements, which are deposited on suitable substrate: a) cells, b) peptides, c) nanovesicles.

The bioelectronic noses for odour analysis utilize cells or olfactory receptors proteins or specially isolated the so-called nanovesicles. A heterologic variant of the system, employing the olfactory receptors proteins, enables the so-called imitation of the smell system occurring in mammals. This type of biosensors is characterised by non-invasive sample analysis, low cost and long lifetime in the case of measurement of specific cell signals (Gaillard et al., 2004). The olfactory receptors used in the sensors possess the structure of seven helixes penetrating cell membrane. High hydrophobicity of the transmembrane region significantly hinders expression of the olfactory receptors in the heterologic system (Zhang et al., 2007). Achievement of

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functional expression in different heterologic systems is the subject of research of many laboratory teams. Proposed systems include human embryonic kidney cells, which provide relatively high expression level (Ko and Park, 2006; Zhao et al., 1998; Zhuang and Matsunami, 2007). Identification of membrane-targeting tags and additionally the proteins boosting expression through membrane, such as Rho-tag, receptor-transporting protein 1 short *(RTP1S*), facilitate expression at high level in mammal cells (L. Wu et al., 2012; Zhuang and Matsunami, 2008, 2007). Functional expression of the olfactory receptors is also achieved with insect cells, such as *Spodoptera frugiperda 9* (SF9) (Ha and Smith, 2008; Kiely et al., 2007; Matarazzo et al., 2005) and *Cercopithecus aethiops* (COS-7) (Levasseur et al., 2003). Receptor proteins acquisition is also provided by the systems *Saccharomyces cerevisiae* and *Eschericia coli* (Minic et al., 2005; Song et al., 2009; Sung et al., 2006). Details on the methods used for evaluation of expression on cell surface can be found in dedicated protocols and they are also utilised for the measurement of receptors activity level in cells (Zhuang and Matsunami, 2008). Those systems allow for their mass production and effective cleanup, thus they are employed for production of the receptor proteins used in the bioelectronic noses (Du et al., 2013a).

2.1. Bioelectronic noses utilizing peptides or proteins

Immobilization of commercially available sensors (for example semiconductor ones) with suitable materials such as doping with platinum, aluminium, lead, gold, *etc.* has a beneficial influence on their sensitivity, for instance in analysis of volatile organic compounds (Srivastava, 2003). There are many materials and new ones are being developed, which improve sensitivity or other properties of the sensors (Rahman et al., 2008; Shalabney and Abdulhalim, 2011; Sokolov et al., 2010; Wang et al., 2010). The materials to be deposited on the chemical sensors also include olfactory receptors. The bioelectronic noses can be classified with respect to the type of the olfactory receptors – a sensitive layer deposited on the sensor. These elements are the receptor proteins that can be acquired from all types of the expression models. The receptor layer is connected with suitable transducer (Table 2). The bioelectronic noses are characterised by exceptional properties in analytical practice applications. First of all, they exhibit high selectivity, the sensor has the affinity to a particular ligand from a group of numerous analogues. However, additional measurements of the concerning quality control of the developed proteins are required due to complicated structure of the olfactory receptors (Hoover, 2013). Furthermore, mass production of the proteins of olfactory receptors and their easy storage are feasible (Song et al., 2009). It is also important that the proteins of olfactory

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receptors in the *E. coli* expression model are still active, even in dry conditions, which allows construction of the biosensors for detection of gas substances (Lee et al., 2012). In the case of protein olfactory receptors, the presence of double-layered lipid membrane is required for their correct functioning. Production processes of this type of receptors are complicated and time-consuming at some stages. Moreover, complete immobilization of the lipid layer, for example on chips, is so complicated that any possibility of reuse and repeatability is not always provided.

Obtaining high enough repeatability of measurements is possible thanks to application of short synthetic peptides instead of proteins and thanks to a novel method of their immobilization elaborated by Lim et al. (Lim et al., 2013). However, the possibility of sensor reuse with maintaining a reasonable sensitivity and repeatability was limited to 5 attempts only. This could be caused by the washing stages and the interfering substances present the sample matrixes. Optimization of the functionalization process of carbon nanotubes consisted in their deposition on a peptide surface in the form of deionised water suspension, which enabled stable immobilization of peptide receptors and establishing non-covalent interactions (Lim et al., 2013).

Schematic presentation of binding between peptide olfactory receptors and carbon nanotubes is shown in Figure 6.

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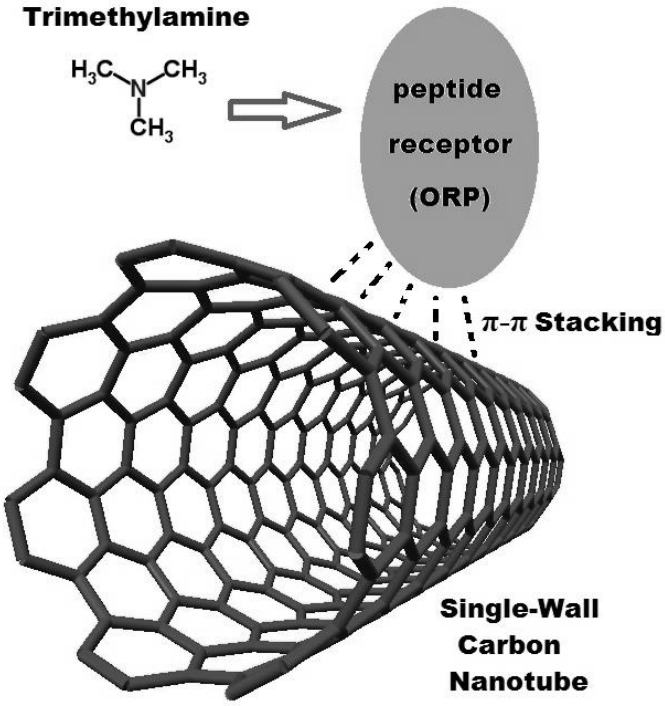

Figure 6. Schematic presentation of self-assembled peptide receptors on the surface of single-walled carbon nanotubes. Receptors are immobilized by π –π bonds at C-terminal. Receptors were self-assembled on the surface of tubes during the treatment of receptor-suspended deionised water (DW) solutions. The receptors were immobilized by p–p stacking of aromatic rings at their C-terminus and attracted TMA molecules very near to the SWNTs (Lim et al., 2013)**.**

2.2. Bioelectronic noses based on cells

The bioelectronic noses based on olfactory cells employ the sensitive element in the form of the cells of olfactory receptors expression, which generate cellular signals. The processes of binding between the odorants and the olfactory receptors result in production of a signals cascade due to ionic transport from outside into inside of the cell (Ko and Park, 2006). Changes of electrical potential in the cell can be measured with different methods such as detection based on fluorescent markers, surface plasmon resonance method or planar microelectrodes (Lee et al., 2006, 2009). One of the most important features characteristic for the bioelectronic noses based on olfactory receptor cells is generation of the signals, which are almost identical with the ones generated by olfactory sensory neurons (*OSNs*). As isolation and *in vitro* growth of the olfactory receptors neuron cells is difficult, their application in practice is limited. Hence, the olfactory receptors (OR) cells are used as an alternative to the OSNs. Functions of particular olfactory receptors have not been fully identified and described in the

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literature. The bioelectronic noses employing olfactory receptors cells can be a useful tool for identification of olfactory receptors' functions, which remain unknown so far.

Figure 7 presents a design scheme of the bioelectronic nose based on microelectrode and olfactory receptors nerve cells as the sensitive element.

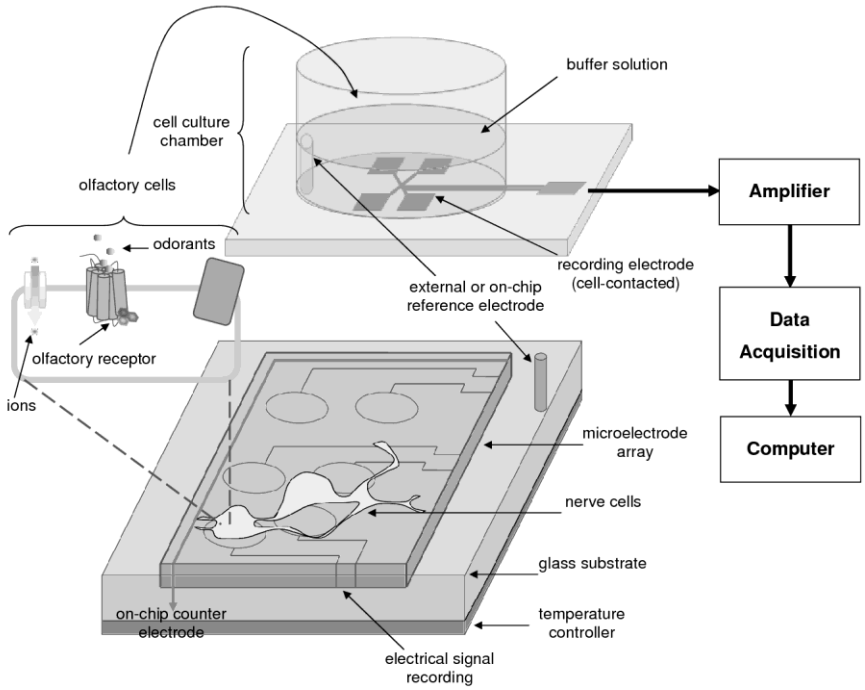

Figure 7. Schematic presentation of bioelectronic nose design. System of microelectrodes is used for measurement of extracellular membrane potential. Interaction of OR with odorants results in a signal, which causes ion exchange and change of potential in cell. Change of membrane potential is monitored by the microelectrodes.

2.3. Bioelectronic noses based on nanovesicles

A concept of utilization of nanovesicles in design of the bioelectronic noses originated from combination of the approaches employing cells and proteins of the olfactory receptors. The nanovesicles can generate the signals similar to those produced by the cells, which arise as a result of reaction with particular odorants via destabilization of cell the membrane (Dushek et al., 2014; Pick et al., 2005). During isolation of the nanovesicles from cells all membrane proteins and cytoplasmic components present in them play a role in signal transduction. Thanks

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to that feature the nanovesicles are characterised by the properties similar to the olfactory receptors cells. Additionally, they exhibit some properties of protein materials such as the possibility of large-scale production and easy storage (Jo et al., 2014). Owing to their small dimensions the nanovesicles can be coupled with nanomaterials in order to functionalize their surface. The bioelectronic nose, the design of which is based on the nanovesicles was elaborated for the first time in 2012 (Jin et al., 2012).

A scheme of formation of the nanovesicles employed for construction of sensor matrix is presented in Figure 8.

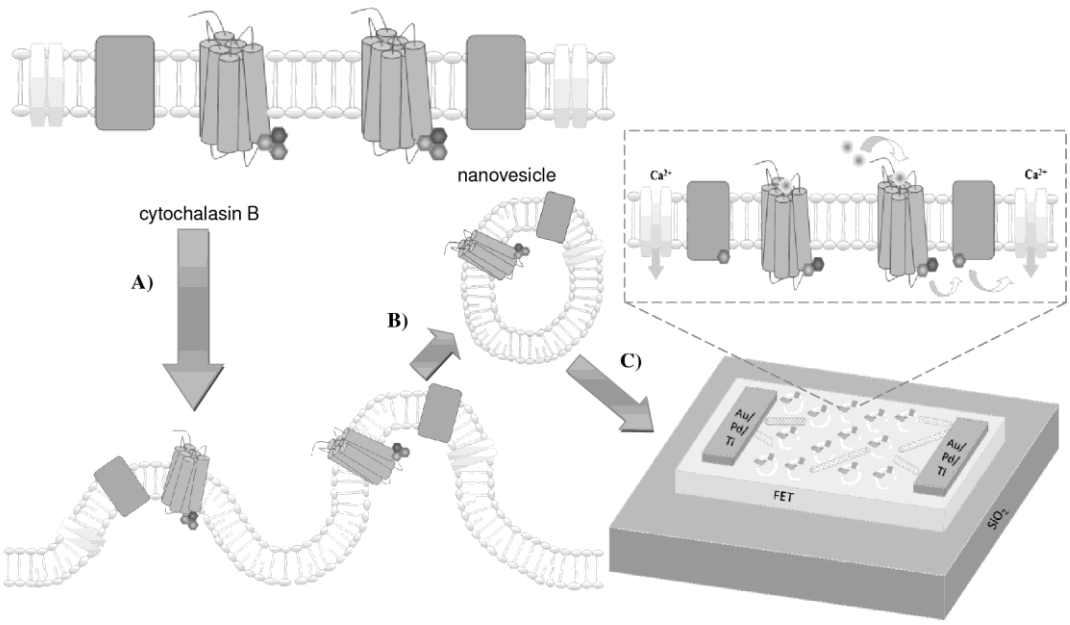

Figure 8. Schematic presentation of signal generation and transmission in cells and nanovesicles. Artificial olfactory cell is comprised of proteins indispensible for signal transmission such as olfactory receptors, proteins G, adenyl cyclases, ionic channels in cell membrane (A). Contact of particular odorant with olfactory receptor generates signal and flow of calcium ions to cell (B). Nanovesicles are produced from the artificial olfactory cells using cytochalasin B (C). The final stage of biosensor design is deposition of the prepared nanovesicles on carbon nanotubes and suitable transducer (D).

Application of the olfactory receptors as the sensitive element in the bioelectronic noses makes it possible to attain a high selectivity of the sensors, at the concentration level occurring in the human counterpart. Accordingly, production of the olfactory receptors or the cells exhibiting olfactory receptors' expression should be a priority for the development of these

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devices. A progress in the field of receptors production using heterologic cell systems employing bacterial, mammal and insect cells will result in elaboration of more efficient sensors for construction of the electronic nose. However, production of the olfactory receptors still remains the most critical stage. A closer mimicking of the natural sense of smell requires improvement of the sensors functionalizing with various biosensitive elements. A progress in application potentialities and successful commercialization depends on solving some technical problems associated with the stability, repeatability and mass production of functional olfactory receptors. Optimum conditions of olfactory receptors production, including their acquisition *via* expression, solubility, purification, immobilization on transducers and others are still the subject of research (Gomila et al., 2006; Sankaran et al., 2012).

Table 3 presents the information on advantages and disadvantages of particular types of biological materials applied as the sensitive element in the sensors utilised in the bioelectronic noses.

Table 3. Advantages and disadvantages of biological elements utilized in bioelectronic noses.

Biological material type	**Advantages**	**Disadvantges**
ORs cells	- generating signals which can be similar to those produced by ORNs, - may facilitate the mechanism of olfactory receptor sensing principles - suitable for physical absorption	- limited applicability to some secondary transducers - hard to manufacture and storage -relatively high cost
ORs Proteins and peptides	- can be acquired from large variety of expression systems: *S. cerevisiae, E. coli,* - Simple to use in practice,	- difficulties with reconstitution of the ORs, inability to guarantee correctness of ORs structures expressed in

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	- very high sensitivity while using the whole protein - possibility to large scale production - relatively easy to storage, - ORs proteins *E.coli* active under dry conditions - possibility of biomimetic approach and virtual design	microbial systems in comparison with the native ones - hard to immobilize onto the secondary transducer
ORs nanovesicles	- generating signals similar to that generated from cells, - production directly from the cells allows to preserve membrane proteins, cytoplasmic components contained in nanovesicles - cell-like properties and protein-like properties in term of long time storage and mass production - highly useful in combination with nanomaterials	- complex process of preparing by treatment with appropriate substances and membrane destabilization - low stability

3. Application of bioelectronic noses

An increasing number of the contributions on theoretical fundamentals of operation and practical application potentialities of the bioelectronic noses can be found in the literature. Due to similarity in function of the bioelectronic nose and its human counterpart numerous applications are possible (Lee and Park, 2010). The bioelectronic noses can be employed in the following fields:

- medical diagnostics: early identification of diseases, infections and metabolic disorders,

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- food products quality control: fermentation processes, level of bacteria, content of main ingredients and additives, odorous substances released,
- branches connected with odours including production of perfumes, cosmetics, wine, coffee: evaluation of usefulness and authenticity,
- environmental analytics and monitoring: outdoor and indoor air quality, surface and underground water, leaks of toxic substances,
- detection of explosives, toxic substances, drugs,
- standardization and visualization of odour,
- identification of the mechanisms of odours perception.

The chemical compounds 'emitted' by human body can be the markers of many diseases, which allows early diagnostics. Classification of some odours with respect to their utilisation as the disease markers was practiced already in ancient times. Volatile compounds released from the organism can also be a source of information about other health problems such as infections, poisonings, metabolic diseases and other (Hill and Binions, 2012; Shirasu and Touhara, 2011; Zhou et al., 2012). The literature describes correlation between particular diseases and identification of odorous volatile substances in biological samples (condensates of exhaled air, urine, blood, sweat, skin, faeces *etc*.). It is necessary to conduct independent investigations in order to evaluate the degree of correlation between the presence of particular compounds and occurrence of given diseases. Many research groups focus on elaboration of non-invasive methods of analysis of the biological samples as far as presence of the biomarkers is concerned (Clark and Patel, 2011; Gao et al., 2005; Schubert et al., 2004).

Exhaled air is rich in different types of compounds, including odorous ones (Zolotov, 2005). Conventional methods of identification of selected odorants occurring in exhaled air include sensory panels (Philpott et al., 2008) and gas chromatographic techniques (Dallinga et al., 2014) coupled with suitable detectors. These techniques are laborious and time-consuming due to complicated stage of sampling of the exhaled air condensates and complicated apparatus (Lourenço and Turner, 2014). Currently, one can observe a tendency to implement the electronic noses as a supplementation of the classic analytical techniques (Röck et al., 2008; Wilson and Baietto, 2009). High sensitivity and selectivity must be ensured because of practical aspects of diseases diagnosis where the majority of patients can reveal a combination of different biomarkers in an odour mixture. Thanks to the bioelectronic noses it is possible to

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identify the odorous compounds at least at a level typical for the human nose (Zheng and Lin, 2012). Different types of biological materials are used as the sensitive element of the sensors in order to achieve appropriate sensitivity and selectivity of particular odorants identification.

Apart from medicine there have been attempts to apply the bioelectronic noses application for quality control of food products (Lim et al., 2013). Nowadays, identification of volatile organic compounds (VOCs) in food products is routinely realised with gas chromatography-mass spectrometry (GC-MS) (d'Acampora Zellner et al., 2008; Duflos et al., 2006; Moldoveanu and David, 2015; Raynie, 2010; Snow and Slack, 2002). Increasing expectations of the customers with respect to quality and freshness of available food products enforce interest in a possibility of practical application of modern measurement techniques in this field. Food products quality control can be enhanced by very sensitive, biological measurement elements (Lim et al., 2014a; Park et al., 2012). Most of the analytical techniques applied so far require complicated stages of sample collection and preparation for analysis, so new concepts of analytes measurement in such matrixes appear (Cifuentes, 2012; Pulkrabová et al., n.d.). Numerous substances present in food products can undergo decay processes due to oxidation, bacterial activity or thermal degradation. On-line measurement of all volatile organic compounds is practically impossible using classic analytical techniques.

The devices, which enable overcoming of some of the aforementioned inconveniences are the instruments from the electronic noses group (Peris and Escuder-Gilabert, 2009). In practice these devices enable skipping the sampling stage and can be used for the measurements conducted in hardly accessible places. Moreover, they can be miniaturised and utilised as mobile devices (Boeker, 2014b). A fundamental limitation of the electronic noses is their inability of selective identification of the odorants responsible for lack of freshness of food products; they can only discriminate fresh and spoilt samples. Different food products are usually combined together, for instance as a dish, so selective and sensitive analysis of particular compounds is not possible with the electronic nose. That is why more advanced instruments are being sought. The bioelectronic nose, as a type of the electronic nose, is characterised by high sensitivity due to application of biological receptor element on the surface of the secondary converter. It allows identification of particular odorants independently of physical properties and degree of sample matrix complexity. This is an important feature in food industry, which can be useful for evaluation of decay degree of food products. Concentration of most aldehydes, especially hexanal, increases due to oxidation of unsaturated

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fatty acids. Hence, it is believed to be an indicator of the decay degree of the food products, which contain fatty acids (Filipiak et al., 2012; Shahidi and Pegg, 1994). The bioelectronic nose, elaborated by the group led by T. H. Park allows identification of hexanal with suitable selectivity and sensitivity at a level of 1 fM (Park et al., 2012).

Apart from the aforementioned examples there are many other fields where the bioelectronic noses can be successfully utilised. First of all, they can become an alternative to the techniques of direct smelling. Currently, odour analytics frequently takes advantage of dogs (Fischer-Tenhagen et al., 2011; Goodwin et al., 2010; Gsell et al., 2010) trained mainly for the detection of hazardous substances (Jezierski et al., 2014). Olfactometric techniques, sensory panels (Eyres et al., 2007; Littarru, 2007; Philpott et al., 2008) are usually used to evaluate odour nuisance and air quality (Brattoli et al., 2011; Gostelow et al., 2001; Sironi et al., 2010). Due to their different limitations new design and apparatus solutions capable of substituting the techniques used so far are being sought, for instance in the field of explosives detection (Brudzewski et al., 2012). One of the solutions is the biosensor elaborated by Kim *et al*. (Kim et al., 2011), which enables the measurement of trinitrotoluene content in the air at the level of 1 fM (Table 4).

Monitoring and analysis of odorous substances with the electronic noses often plays a supplementary role with respect to the classic methods due to fast and easy measurement execution (Dentoni et al., 2012a). Moreover, the sample preparation stage consisting of isolation and enrichment of analytes can be omitted (Capelli et al., 2014; Dentoni et al., 2012b; Littarru, 2007). Despite many advantages and commercial availability of portable electronic noses these instruments are relatively rarely used in environmental pollutants analytics. The sensor matrixes are susceptible to different factors such as humidity, temperature changes and other (Sohn et al., 2008; Vergara et al., 2013). Due to high sensitivity and selectivity the bioelectronic nose can also constitute a supplementary tool with respect to the classic analytical techniques employed in odorous compounds analysis. Utilisation of the bioelectronic noses potential is possible only when the applied sensors are active in dry conditions. Accordingly, the sensors, which use the sensitive elements insusceptible to dry conditions are being elaborated (Lee et al., 2012).

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The examples of technological solutions and fields of application of the bioelectronic noses and the biosensors in odorous substances analysis are presented in Table 4.

Table 4. Examples of bioelectronic noses and biosensors based on olfactory receptors.

Matrix type	Analytes	Sensor type	Sensitivity	Ref.
Milk	hexanal	An olfactory-nanovesicle-fused carbon-nanotube-transistor biosensor including canine ORs (cfOR5269)	1 fM	(Park et al., 2012)
Air samples	n-caproic acide isoamyl acetate, n-decyl alcohol, β-ionone, linalool, ethyl caporate	OR proteins from bullfrogs (Rana spp.) coated onto piezoelectric electrode	10^{-6} - 10^{-7} g	(Wu, 1999)
Mixtures of standards	Ethyl butyrate	Human OR 2AG1 (hOR2AG1) protein expressed in human embryonic kidney (HEK)-293 cells, nanovesicles immobilized on single-walled carbon nanotube-based FETs (swCNT-FETs)	1 fM	(Jin et al., 2012)
Human blood	Heptanal as a lung cancer biomarker	30 types of hORs expressed in HEK-293 cells, nanovesicles immobilized on single-walled carbon nanotubes field effect transistor	10 fM	(Lim et al., 2014 b)
Seafood	Trimethylamine	SWNT- FETs functionalized with olfactory receptor-derived peptides (ORPs)	10 fM	(Lim et al., 2013)

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Fruits	Amyl butylate, helional	Two types of hORs (hOR2AG1 and hOR3A1), immobilized on the Graphene/Diaminonaphthalene/Glutaraldehyde substrate	0.1 fM	(Kwon et al., 2015)
Seafood	Trimethylamine	SWNT-FETs functionalized with olfactory receptor-derived peptides (ORPs) combined with PDMS-based microfluidic system	10 ppt	(Lee et al., 2015)
Food contaminated by moulds, indoor air	R-(–)-1-octen-3-ol (octenol), R-(–)-carvone	Array of five SAW resonators coated with three types of odorant-binding proteins (OBPs): wtbOBP, dmbOBP, wtpOBP	0.48 ppm, 0.74 ppm	(Pietrantonio et al., 2015)
-	2,4,6-Trinitrotoluene	TNT receptors bound to conjugated PDA polymers with SWNT- FET	1 fM	(Kim et al., 2011)
-	Amyl butyrate	hOR 2AG1 (hOR2AG1) expressed in *E. coli* immobilized on CPNTs- FET	10 fM	(Yoon et al., 2009)

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-	Amyl butyrate	2AG1 (hOR2AG1: OR) modified with leading to the formation of the liquid-ion gated FET-type platform	0.04 fM	(Jang, 2012)
-	PBS, diacetyl, isoamyl acetale, acetic acid	Bioengineered OSNs produced by expressing a model OR protein (an olfactory receptor of C. elegances, ODR-10) on the plasma membrane of primary OSNs through transient transfection, coupling with LAPS	0.1-100µM	(Du et al., 2013 b)
	DL-limonene, isoamyl acetate	ORNS cultivated on the surface of 60 channel planar MEA	2.6 g/m^3, 50 mg/m^3	(Ling et al., 2010)
Gummy candies	-	Oligopeptides linked to GNPs by self-assembling, QCM modified sensors by drop of a peptide-GNP suspension	-	(Pizzoni et al., 2013)
-	Isoamyl acetate, acetic acid	Cell-based biosensor with zinc nanoparticles, MEA composed of 64 microelectrodes, coated with platinum black	10^{-15} M	(Hang et al., 2016)
-	Diacetyl	Mixed SAM's funcionalized with Ors (ODR-10), constructed on SAW chip	1.2×10^{-11} mM	(C. Wu et al.,

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				2012)
-	Diacetyl	QCM coated with ODR-10, a sensory receptor of Caenorhabditis elegans heterologously expressed in *E. coli*	-	(Sung et al., 2006)
-	Heptanal, octanal, nonanal, decanal	Olfactory receptor protein of rats 17, expressed on HEK-293 cells coated on QCM	10^{-8} mM	(Sung et al., 2006)
Grains	1-octen-3-ol	OR nanovesicles produced from HEK-293 integrated into SWNT-FETs	1 fM	(Ahn et al., 2015)

LAPS – Light addressable potentiometric sensor, CPNTs – carboxylated polypyrrole nanotubes, SWNT- FET - single-walled carbon nanotube field-effect transistors, PDA – polydiacetylene, SAW – surface acoustic wave, wtbOBP - wild-type OBP from bovine, dmbOBP – double-mutant of the OBP from bovine, wtpOBP – wtpOBP, PDMS – polydimethylsiloxane, HEK293 – human embryonic kidney, hOR – human olfactory receptor, ORNs- olfactory receptore neurons, PBS - phosphate buffer solution, MEA- micro electrode array, GNP- gold nanoparticle, QCM- quartz-crystal microbalance, SAM – self-assembled monolayer

4. Development prospects of bioelectronic noses

The detection and identification of odorants can generate a variety of application potentialities in different fields of the economy such as food and cosmetics industry, environmental monitoring, diagnostics, *etc*. Recent decades witnessed many attempts of standardization of the methods of analysis of odorants present in different matrixes. The

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classical methods of odour analysis including GC/MS, sensory panels, trained animals are still widely applied. However, some inconveniences resulting from degree of the complexity, time of analysis, cost, *etc.* are the incentives to elaborate new devices and techniques of odour analysis. Recently, the instruments form the electronic noses group have gained an increasing popularity as the supplementary ones with respect to the aforementioned techniques. This group also encompasses the bioelectronic noses, which possess a significant development potential. Apart from the examples listed in Table 5, the bioelectronic noses can be employed in the future as the supplementary tools in the fields calling for direct analysis of the odorants emitted at low concentration levels. These instruments can be primarily utilised in the high-risk fields, for instance at the airports, military entities, for detection of hazardous materials and drugs. Although trained dogs are characterised by outstanding sensitivity of odour detection, the cost of their training and maintenance is high. Moreover, natural smell system gets tired and becomes saturated, it can promptly adapt to continuous exposure to odorous substances, which results in a decrease in sensitivity (Kerollos and Chan, 1AD). Analysis of the literature data about the bioelectronic noses reveals a significant growth in interest in application potentialities of such type of devices.

Standardization of odours, which is a correlation of data obtained from the sensor matrix (for example from the bioelectronic nose) and smell perception of particular odorants is especially important in the case of odorous compounds. The legislation concerning odour nuisance introduced in developed countries is based mainly on the investigations performed using sensory analysis, which is still the most popular. However, it is replaced by more advanced techniques, not burdened with the problems characteristic for sensory panels (Brattoli et al., 2011). Currently, different investigations are carried out including digitalization of smell sensations and emotions accompanying particular odours and tastes. Some stages can be accomplished with the bioelectronic noses, which mimic the principle of operation of human sense of smell in most precise way due to utilisation of the olfactory receptors as one of the measurement elements (Sanmartí et al., 2010). It turns out that precise standardization and instrumentation of odour can be realised with qualitative and quantitative analysis employing correlation of the bioelectronic nose and olfactometric data. Potential application of the bioelectronic noses also encompasses detection of hazardous, toxic or explosive substances (Corcelli et al., 2010).

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Recent years bring an increasing number of new prospects of the bioelectronic noses application. They can be implemented in the fields where emitted odours or other types of chemical information call for highly sensitive and selective measurement. New design solutions, for instance the ones supported with micro-flow systems or multi-channel architecture, constitute the latest achievements as far as design and extension of application possibilities are concerned.

4.1. Micro-flow bioelectronic nose

Currently, there are no commercially available biosensors based on the olfactory receptors or they are at the experimental stage. The main obstacles in development of the commercial biosensors are low durability of the sensitive elements (comprised of various olfactory receptors) as well as lack of sufficiently small, portable signal transducers. On the other hand, development of more stable biosensitive materials is still one of the main research subjects in the field of odour sensors. There is a high probability that proteins and peptides will replace tissues and cells as the sensitive elements of the biosensors. A better understanding of odour perception mechanism, identification of odour-binding sites can facilitate development of alternative, synthetic receptors for the biosensors. Moreover, the progress in micro-flow technologies significantly contributes to miniaturization of the biosensors owing to substantially smaller dimensions and limitation of the amount of biosensitive element utilised as well as the reduction of sample volume (Figueroa et al., 2010). Coupling of the bioelectronic noses with the micro-flow systems also belongs to the promising investigation fields and can result in practical application of the bioelectronic noses. An attempt to integrate the bioelectronic nose with the micro-flow system (μBN) for identification of trimethylamine (TMA) was described by Park *et al.* (Lee et al., 2015). A single-walled carbon nanotube-field effect transistor *(SWNT-FET)* functionalised with the olfactory receptors was applied as the signal transducer. Utilisation of the micro-flow system made it possible to obtain sensitivity at the level of 10 ppt and high selectivity of TMA identification in an odour mixture. The designed system was employed for analysis of real seafood samples in order to evaluate their degree of decay. The results confirmed usefulness of the mobile micro-flow systems combined with the biosensors for on-site and on-line analysis of gas samples.

A design scheme of the micro-flow system coupled with the bioelectronic nose is illustrated in Figure 9.

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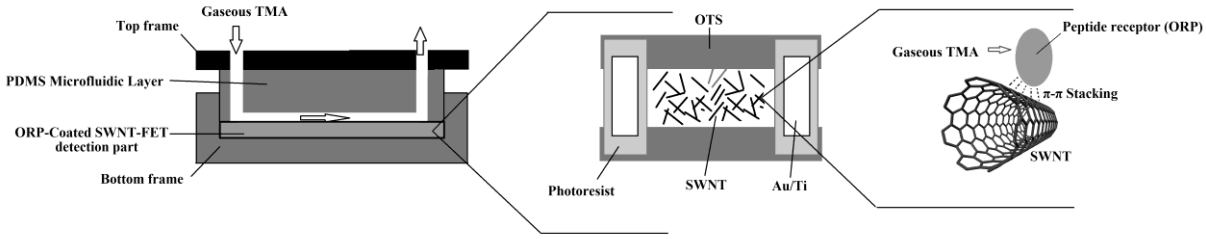

Figure 9. Schematic presentation of design of micro-flow system coupled with bioelectronic nose (µBN).

4.2. Multi-channel bioelectronic nose

Identification of a multi-component gas mixture can be accomplished using a device incorporating a sensor matrix similar to human sense of smell. The type and number of the sensors applied in the matrix depend on the kind of the analysed sample. As opposed to the electronic nose, which can be equipped with a limited number of sensors in the matrix, the bioelectronic counterpart can utilise a multiplatform measurement system comprising, for instance, the olfactory receptors for. It is called the multiplexed or multi-channel bioelectronic nose. Currently, the attempts have been made to integrate a big number of the olfactory receptors on a single matrix to allow simultaneous identification of a larger group of odorants. After processing with suitable data analysis method this information is used to determine an odour profile of gas mixture. The efficacy of this concept has been confirmed by the diagnosis of selected chronic diseases, the detection of which is associated with identification of not only a single but also of a few or several biomarkers in exhaled air. An example of the multi-channel bioelectronic nose design is presented in Figure 10.

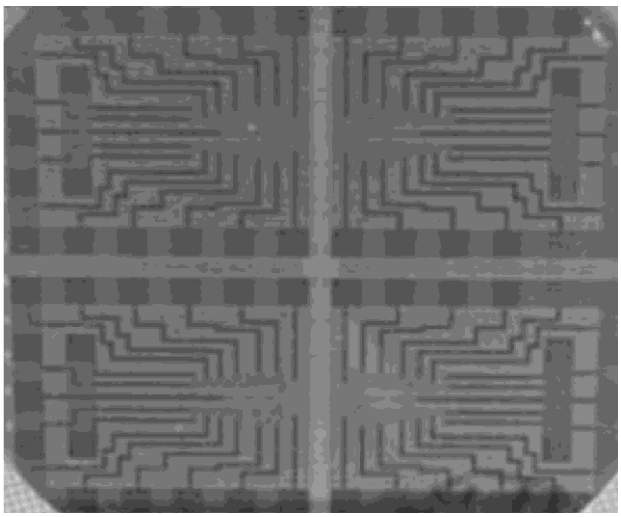

Figure 10. Example of multi-channel bioelectronic nose. Each channel contains different type of olfactory receptor connected with carbon nanotube-field effect transistor (reprinted from (Park, 2011)**).**

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5. Summary

Characteristic features of the olfactory receptors make them a perspective material for construction of sensors. Their unique properties are used for designing instruments from the bioelectronic noses group in order to mimic smell systems in best possible way. Significant improvements in bioelectronic noses design have been done so far, however some problems are still the subject of investigation. The first one originates from existence of only few related ligands available in mammal receptor systems. Low efficiency of acquisition of recombined receptors proteins in heterologic cell systems is also a bottleneck. Many different solutions are used to increase efficiency of products acquisition (Haberstock et al., 2012). In the case of some expression systems effective acquisition of the receptor proteins on cell membrane requires application of additional components, for example the genes-coding chaperones (Ellis, 2013). Another important complication is the problem of receptors anchoring on sensor surface due to the fact that the receptor proteins must be present in lyophilic environment in order to maintain desired structure and functions. A procedure of immobilization of the receptor proteins or the expression cells of receptors on solid surface of the sensor should be performed in mild ambient conditions, proper pH, temperature, *etc*. Moreover, better understanding of the molecular mechanism of odorants binding to specific receptors would enable elaboration of more effective instrument from the bio-enose group. Binding between the odorous substances and the receptors on immobilised surface causes conformation changes in the receptor or signal transduction in the olfactory cells. Effective immobilization of the receptors or cells on the surface can contribute to elaboration of more reliable and repeatable procedure of deposition on a carrier (Wang and Liu, 2015).

Despite significant progress in bioelectronic noses improvement there are still some limitations of their practical application stemming from a constrained mobility, difficulties with provision of appropriate stability and repeatability of measurements. Broadening of the application potentialities of the bioelectronic noses is strongly associated with the progress in design solutions and biological materials deposited on the transducers. New generations of the bioelectronic noses can be capable of overcoming the limitations appearing at different stages of the classical techniques of odorants analysis. The attempts of odour visualisation and standardization can involve the olfactory cells as sensitive material, which allows mimicking the principle of operation of the human counterpart. In this case the biggest difficulty is long-term maintenance of desired properties of the biomaterial. Production of commercially

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available biosensors is associated with deposition of the sensitive elements, such as peptides or olfactory receptors proteins, on the transducers. The bioelectronic noses can find practical application in the fields of odour visualization, coding information about smell stimuli, odour standardisation, medical diagnosis, detection of hazardous substances, quality evaluation of food products, drugs, perfumes, etc..

To sum up, the bioelectronic noses based on biosensors, which employ the olfactory receptors as sensitive element, are the subject of investigation of many scientific groups from various fields including biology, protein engineering, material engineering, electronics, data analysis and processing methods. A progress in the techniques of preparation and implementation of suitable materials can contribute to real practical application and commercialisation of the olfactory receptors-based biosensors. It is expected that upcoming years are believed bring a dynamic improvement of the bioelectronic noses, which will contribute to the development of odour analysis. Commercialisation of these devices and their marketability as an alternative to the classical methods of odour analysis can soon become a real perspective.

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