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Rapid methods and sensors for milk quality monitoring and spoilage detection

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ABSTRACT

Monitoring of food quality, in particular, milk quality, is critical in order to maintain food safety and human health. To guarantee quality and safety of milk products and at the same time deliver those as soon as possible, rapid analysis methods as well as sensitive, reliable, cost-effective, easy-to-use devices and systems for process control and milk spoilage detection are needed. In this paper, we review different rapid methods, sensors and commercial systems for milk spoilage and microorganism detection. The main focus lies on chemical sensors and biosensors for detection/monitoring of the well-known indicators associated with bacterial growth and milk spoilage such as changes in pH value, conductivity/impedance, adenosine triphosphate level, concentration of dissolved oxygen and produced CO_2. These sensors offer several advantages, like high sensitivity, fast response time, minimal sample preparation, miniaturization and ability for real-time monitoring of milk spoilage. In addition, electronic-nose- and electronic-tongue systems for the detection of characteristic volatile and non-volatile compounds related to microbial growth and milk spoilage are described. Finally, wireless sensors and color indicators for intelligent packaging are discussed.

1. Introduction

Foodborne bacterial outbreaks remain one of major causes for disease and mortality throughout the world. While the majority of bacteria are harmless or even useful for humans, several others are pathogenic in nature and can cause extremely serious threats to health and safety and consequently, inflict enormous financial burden on health care and socio-economic systems (Singh et al., 2013). In spite of quality control, pasteurization and ultra-high temperature (UHT) treatments, numerous outbreaks of foodborne illnesses due to the consumption of contaminated/spoiled dairy products were reported. According to the WHO (World Health Organization) report 2015, every year as many as 600 millions people in the world (http://www.who.int/mediacentre/news/releases/2015/foodborne-disease-estimates/en) fall ill after consuming contaminated food. Of these, 420,000 people die, including 125,000 children under the age of 5 years. Health experts estimate that the yearly costs of all the food-borne diseases are approximately 5–6 billion US$ (Arora et al., 2011). On the other hand, bacterial contamination in processed food has led to many large-scale recalls of food. Such massive recalls result in huge financial losses as well as the disposal of valuable food.

Monitoring of food quality, in particular, milk quality, is critical in order to maintain food safety and human health. Therefore, there is an urgent need for the development of fast, sensitive, reliable and cost-effective methods and sensor systems for food quality monitoring and detection/identification of bacteria at an early stage. Pathogen detection has emerged as the highest technological priority for the dairy industry. According to the FoodMicroSystems project report (FoodMicroSystems, 2013), the microbiological quality control of food represents a global market of ~800 M€, growing at 4–6% per year.

In this paper, we review different rapid methods, sensors and commercial systems for milk spoilage and microorganism detection. The major focus lies on chemical sensors and biosensors for the detection of the established indicators associated with bacterial growth and milk spoilage, like changes in pH value, conductivity/impedance, adenosine triphosphate (ATP) level, concentration of consumed O_2 and produced CO_2, volatile and non-volatile compounds. In addition, wireless sensors and color indicators for intelligent packaging are discussed.

In planning this review, we have chosen to select articles mostly from the last seven years (from 2012 to the beginning of 2019). However, the paper also encompasses key developments of former

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Table 1
The composition of milk from cow (source: Guetouache et al., 2014).

Fat	3.7%
Total protein	3.5%
Casein	2.8%
Lactose	4.9%
Mineral salts	0.72%
Water	87.2%

works, information from websites and catalogs of leading companies producing techniques for milk quality monitoring.

2. Milk spoilage

Milk is a highly complex medium and contains carbohydrates in the form of milk sugar (lactose), milk fat, citrate, nitrogen in the form of a milk protein (casein) and non-protein nitrogenous compounds, and mineral salts (Table 1). These components make milk as a perfect food. Unfortunately, milk is also an ideal medium for the growth of microorganisms that can spoil this product.

Microorganisms most frequently found in milk can be divided into two basic groups: pathogenic and spoilage microorganisms, though some of those (e.g., *Bacillus cereus*) can play a dual role. Pathogenic microorganisms (e.g., *Escherichia coli, staphylococcus, streptococci*) cause food poisoning and disease in man, and should not be present in the milk. The acceptable pathogen concentrations in milk are presented in Table 2.

Spoilage is a term commonly utilized for describing the deterioration of food to the state, where it is unsuitable for human consumption (Sowmya, 2017). Microbial spoilage of milk occurs as a consequence of either microbial growth or release of extracellular and intracellular enzymes (Chove et al., 2018; Ledenbach and Marshall, 2009). Usually, spoilage by microbial growth occurs much faster than spoilage by enzymes in the absence of viable microbial cells (Nura et al., 2016; Ray and Bhunia, 2014). The commercial sterility of UHT-processed milk products depends on microbial contamination caused from two main sources (http://www.rapidmicrobiology.com; UHT Food and Beverage Microbiology):

1. Due to the presence of heat-resistant spores prior to UHT processing. The UHT treatment destroys most bacteria in milk, but some heat-resistant bacteria can survive.
2. Post-process bacteria contamination due to a failure in the integrity of the aseptic filling system, a poor sanitation or caused from packaging.

Spoilage microorganisms or their enzymes (e.g., oxidases, polymerases, proteases, esterases, lipases) are capable of degradation of milk components such as proteins, fat and carbohydrates in order to yield compounds suitable for their growth (Sowmya, 2017). The quality of milk for human consumption is determined by the number of bacteria present in milk at a given time. In principle, any microorganism that can multiply to reach a so-called spoilage detection level is able to cause food spoilage. Depending on the specific nature of spoilage and microbial types, the spoilage detection level can range from 10^6 to 10^8 cells/ml. In the following bacteria are listed, which are mainly involved in the milk spoilage process as described in (Ledenbach and Marshall, 2009; Lu et al., 2013; Murphy, 2009; Ranieri et al., 2012; Sowmya, 2017):

- **Acid-forming bacteria:** Lactic acid bacteria (LAB, e.g., *Streptococcus lactis*, *Lactobacilli, Lactococus*) will ferment lactose to lactic acid (Lu et al., 2013; Sowmya, 2017). This will cause acidification of the milk and a decrease in pH value from 6.7 to a pH of ~4.6. Lactic acid causes milk proteins to coagulate at pH < 4.6 (Lu et al., 2013), resulting in a jellylike substance. Many other bacteria will produce acids to ferment milk if the conditions are not favorable for LABs. Both yeasts and molds enjoy the milk acidification and begin to metabolize the lactic acid into non-acid products as spoilage continues. Finally, *Bacillus* bacteria begin to metabolize remaining proteins into ammonia compounds, slightly increasing the pH value. At this point, the spoilage is evident by the odor of the milk.
- **Coliform bacteria:** Coliforms can produce a mixture of acids, gases, and alcohols and also degrade milk proteins (Lu et al., 2013). They are destroyed by pasteurization or UHT. Typically, the detection of any coliforms in pasteurized/UHT-treated milk indicates the post-processed contamination and potentially shortened shelf-life.
- **Gas-forming bacteria:** Lactose fermentation by these bacteria causes a considerate amount of gases (e.g., CO_2, H_2) (Ledenbach and Marshall, 2009).
- **Psychrotrophic bacteria:** These bacteria are able of growing at temperatures of 7 °C or less and cause spoilage, often resulting in off-flavors. Psychrotrophic bacteria are killed by pasteurization/UHT treatment. However, some bacteria, like *Pseudomonas fluorescens* and *Pseudomonas fragi*, can produce heat-stable extracellular enzymes capable of causing spoilage (Ledenbach and Marshall, 2009). In addition, psychrotrophic bacteria may occur in milk from contamination after pasteurization or UHT. They represent a major concern because one psychrotrophic bacterium with a doubling time of 6 h may spoil 1 L of refrigerated milk in ~10 days due to the resulting high bacterial concentration of > 10^7 CFU/ml (Murphy, 2009).
- **Thermoduric psychrotrophs:** Thermoduric bacteria are those that survive pasteurization or other heat treatment procedures. Some thermoduric bacteria (thermoduric psychrotrophs) are able to grow and spoil milk at refrigeration temperatures (Murphy, 2009) and represent one of the most limiting factors for an increase of milk shelf-life.

Milk spoilage is an indefinite complex parameter and difficult to measure with accuracy. Currently, consumers determine milk spoilage by checking the “sell by”- and “best if used by” dates on milk cartons provided by suppliers. These data are simple estimates of milk shelf-life and are often inaccurate due to the variable processing, shipping, and storage conditions of milk (Lu et al., 2013). In order to avoid the legal and economic consequences of consumers experiencing illness from drinking spoiled milk, milk producers often use overly conservative expiration dates. Retailers and consumers discard billions of pounds of unspoiled milk each year while relying on unreliable expiration dates. Generally, at least a third of the total food production intended for human consumption globally is currently wasted. The quantity of food wasted annually in Europe is 89 million tons that is equivalent to 180 kg per capita (source: http://www.barillacfn.com). According to

Table 2
Acceptable pathogen concentration in milk as specified in the CommissionRegulation No.2073/2005 and analysis time (adopted from Mortari and Lorenzelli, 2014).

Microorganism	Milk category	Acceptable concentration	Analysis time, days
Enterobacteriaceae	Pasteurized milk	< 1 CFU/ml	6.5–7.5
	Milk powder	< 10 CFU/g	
Escherichia coli	Raw milk	< 10 CFU/g	1
Listeria monocytogenes	Ready-to-eat food	Absence in 25 g	3–5
Salmonella	Raw milk	Absence in 25 g	4.5
Staphylococci	Milk powder	< 10 CFU/g	2.5

CFU: colony forming unit.

the report of the Rockefeller Foundation 2014 (http://www.rockefellerfoundation.org), solving food spoilage problems would feed 1 billion more people by 2050.

The milk product quality is generally determined by sensory, chemical and microbiological analyses. The list of specific indicators used in dairy industry to predict expected shelf-life and estimate stages of microbial spoilage is large and diverse. Examples are:

- cell counting of microorganisms;
- detection of specific microorganisms (e.g., pathogens);
- detection of contaminants/residues (antibiotics, mycotoxins, etc.);
- composition of the product (e.g., lactose, fat, protein content);
- detection of gases;
- control of pH, conductivity, temperature, viscosity, color, etc.

3. Methods, sensors and systems for milk quality monitoring and spoilage detection

3.1. Conventional methods

The analysis of milk for the presence of both pathogenic and spoilage bacteria is a standard practice for ensuring food safety and quality. However, detecting the presence of microorganisms in milk before they could multiply exponentially is not easy at all. To date, the detection/identification of microorganisms in the dairy industry rely mainly on conventional standard methods such as plate count and culturing, microscopy, flow cytometry, or on advanced immunological techniques (e.g., biochemical kits, enzyme-linked immunosorbent assay (ELISA)) and polymerase chain reaction (PCR) (Mandal et al., 2011; Law et al., 2015; Zhao et al., 2014). Usually, the conventional plate count and culture techniques are very sensitive (10–100 CFU/ml), inexpensive, can give both qualitative and quantitative information on the number and the nature of microorganisms and serve as the golden standard. However, they are laborious, time-consuming (the required time for microorganism detection is typically between 24 and 72 h and more than a week for identification of the pathogens (Wang and Salazar, 2016; Zhao et al., 2014)) and incapable for real-time, on-site applications.

Immunological methods using automated and robotic ELISAs are widely applied since they can reduce detection time after enrichment to as low as 1–3 h. However, due to sample pre-processing and enrichment steps, the results can be only obtained in 2–3 days. The limit of detection for immunoassays is approximately 10^4–10^5 CFU/ml depending on the type of antibody used and its affinity (Lopez-Campos et al., 2012; Wang and Salazar, 2016).

PCR-based techniques enable identification of bacteria via their genetic material and do not require a bacterial culture step (Law et al., 2015; Mortari and Lorenzelli, 2014; Wang and Salazar, 2016). However, although the time required to perform a PCR is between 30 and 90 min, the whole process, including sample preparation, DNA extraction and amplicon analysis, may take time from 6 to 8 up to 48 h. A major drawback of PCR-based techniques is the inability to distinguish between viable and dead cells, which may lead to an over-estimation and false-positive answers. The limit of quantification of real-time PCR with food samples is around 10^3–10^4 CFU/ml (Lopez-Campos et al., 2012; Wang and Salazar, 2016). If the number of target microorganisms is low and a small volume of sample is used (many PCR methods require 0.1 ml or less), there is a risk that this sample may not include the target organism of interest.

Generally, above listed methods often require fully equipped laboratories and skilled personnel, need extensive sample preparation steps, are time-consuming, represent still off-line laboratory approaches and are unsuitable for real-time continuous monitoring of milk quality/spoilage.

3.2. Rapid methods and tools based on chemical sensors and biosensors

To guarantee quality and safety of milk products and at the same time deliver those as soon as possible, more rapid analysis methods, in-line solutions (real-time continuous measurements) as well as portable, cheap, fast, accurate, easy-to-use on-line- or on-site devices and fast feedback systems for process control are needed. The main goal of rapid methods is to reduce sample preparation and detection time and thus, to minimize the time interval between the filling and detection of microorganisms before release from several days to hours or even to minutes (Adley, 2014). This would allow the food company to decrease product loss by early removal of suspected batches and to early response to production problems. In addition, these tests will help producers to predict product shelf-life.

In this context, chemical sensors and biosensors have been intensively studied as attractive alternatives to existing conventional milk-quality detection methods. According to definitions for chemical sensors and biosensors recommended by a IUPAC (International Union of Pure and Applied Chemistry) working group (Thevenot et al., 1999, 2001): “A chemical sensor is a device that transforms chemical information, ranging from the concentration of a specific sample component to total composition analysis, into an analytically useful signal. Chemical sensors contain usually two basic components connected in series: a chemical (molecular) recognition system (receptor) and a physico-chemical transducer. Biosensors are chemical sensors in which the recognition system utilizes a biochemical mechanism. The biological recognition system (bioreceptor) translates information from the biochemical domain, usually an analyte concentration, into a chemical or physical output signal with a defined sensitivity”.

Chemical sensors and biosensors can be classified according to the analytes to be detected or the biochemical recognition element that is used for detection, or the transducer type. The transducer principles used in chemical sensors and biosensors include electrochemical (e.g., potentiometry, semiconductor field-effect platform, amperometry, conductometry, impedance spectroscopy), optical, acoustic, piezoelectric, gravimetric, thermal transducers, etc. (Ahmed et al., 2014; Das et al., 2018; Lazcka et al., 2007; Velusamy et al., 2010; Narsaiah et al., 2012; Poltronieri et al., 2014; Sharma and Mutharasan, 2013; Wang and Salazar, 2016). These sensors offer several advantages such as high sensitivity, fast response time, small sizes and minimal (or no) sample preparation. They could be implemented in on-line- or in-line systems for the real-time milk-quality monitoring directly in processed milk.

As discussed above, milk spoilage is a result of growth of microorganisms that alter the composition of the medium with their metabolic products, change the pH value, ionic content, conductivity, odor, color, viscosity and other physicochemical parameters of milk. The produced metabolic by-products associated with the spoilage may include: lactic acid, acetic acid, diacetyl, acetoin, ethanol, bicarbonate, urea, H_2S, NH_3, CO_2, H_2, H_2O_2, etc. (Ledenbach and Marshall, 2009; Brosel-Oliu et al., 2015a; Satake et al., 2018). In the following, some chemical sensors/biosensors and commercial systems for the detection/monitoring of well-known indicators related to bacterial growth and milk spoilage, like changes in pH value, conductivity/impedance, ATP level, concentration of consumed O_2 and produced CO_2, volatile and non-volatile compounds, are described and evaluated.

3.2.1. pH sensors for milk spoilage detection

Measuring the pH value of milk in dairy industry is a preliminary quality control step to identify microbiological spoilage as well as chemical contamination. The pH of fresh bovine milk is about 6.7 (Lu et al., 2013). As it was discussed in Section 2, many of the bacteria found in milk create lactic acid as a by-product, which causes a drop in pH value. Since milk is a buffer solution, considerable amount of acid should be produced before those pH changes will be detectable. Depending on the initial concentration and type of microorganisms and temperature, the pH of UHT milk inoculated with probiotic bacteria can

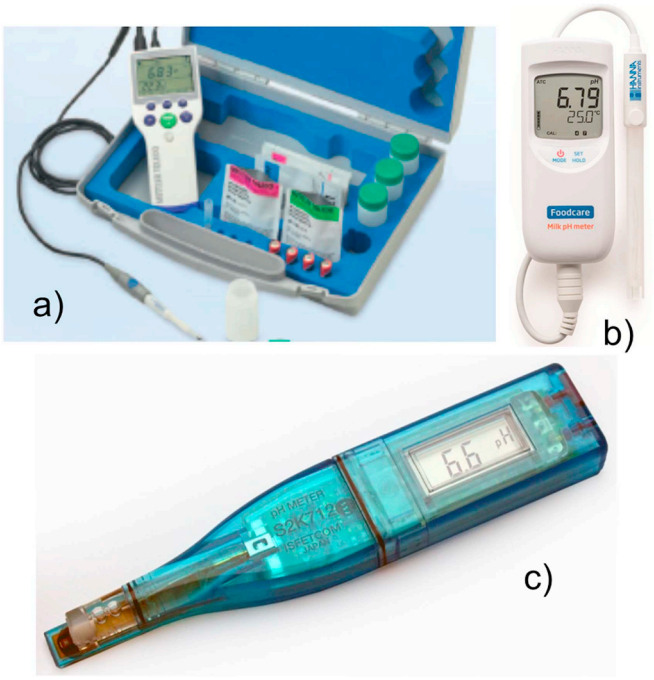

Fig. 1. Portable pH-meter from Mettler-Toledo for pH measurements in milk (a), pH/temperature meter for milk analysis from Hanna Instruments (b) and pocket ISFET pH-meter from ISFETCOM (c). Reprinted with permissions from Companies Mettler Toledo (http://www.mt.com), Hanna Instruments (http://hannainst.com) and ISFETCOM Co., Ltd. (http://www.isfet.com/new).

decrease up to pH 3.9–4.4 after 24 h of incubation (Lu et al., 2013). Thus, the pH value is an important indicator that can be used to test milk quality or identify milk spoilage.

Commercial pH-glass electrodes and pH-ISFETs (ion-sensitive field-effect transistor) are available from many companies (e.g., Hach, Mettler-Toledo, Hanna Instruments, Horiba, Orion, BioControl, etc.). Mettler-Toledo, Hanna Instruments and other companies produce portable pH meters with glass- and pH-ISFET electrodes suitable also for pH measurements in milk samples with an accuracy of < 0.01 pH (see Fig. 1). Moreover, several companies (e.g., Hach, DeltaTrak, ISFETCOM) have realized miniaturized pocket-sized pH meters with an ISFET sensor for pH measurements in a single droplet. As an example, Fig. 1c shows a photo of the Pocket ISFET pH-Meter from the company ISFETCOM with an accuracy of ± 0.05 pH in the range of 2–12 pH and automatic temperature compensation.

pH-glass electrodes are commonly used in dairy laboratories for pH measurements in milk samples. However, pH-glass electrodes are bulky, fragile, expensive and unsuitable for an application in miniaturized detection systems. Recently, several types of non-glass electrodes have been developed. For example, a pH-sensitive polymeric membrane-based electrode has been tested for pH measurement in milk samples (Upreti et al., 2004). A miniaturized semiconductor-based "non-breakable" pH sensor using Ta_2O_5 thin-films as pH-sensitive material has been developed in (Schöning et al., 2005). These sensors showed a nearly-Nernstian sensitivity of 57 ± 1.5 mV/pH in the range of 3–10 pH, small drift (0.01 pH/h), fast response and were suitable for cleaning-in-place applications (Schöning et al., 2005) as well as for pH- and penicillin measurement in commercial milk samples (Poghossian et al., 2018). Potentiometric planar pH sensors based on IrO_x- and Ta_2O_5 films with an integrated screen-printed Ag/AgCl pseudo-reference electrode have been tested to detect *Escherichia coli* cells in undiluted culture medium with a detection limit of less than 10^3 CFU/ml in just 5 h (Uria et al., 2016a). A theoretical detection limit of 20 CFU/ml for *Escherichia coli* in water samples by using a pH-sensitive hydrogel nanofiber LAPS (light-addressable potentiometric sensor) has been reported in (Shaibani et al., 2016). LAPS devices were also applied for cell acidification detection in culture medium (Werner et al., 2012; Dantism et al., 2016). Finally, mixed metal oxide- (Xiansheng and Jing, 2014) and Ir/IrO_x-based (Bhadra et al., 2013; Bhadra, 2015) pH sensors were applied for wireless monitoring of milk spoilage in a container.

The Milkmaid smart jug is a relatively new development that detects milk spoilage using a pH- and temperature sensors (Parrack, 2012). The pH sensor is incorporated into a container, which should be filled with milk. The Milkmaid informs users about spoiled milk via a change in the color of the jug's light-emitting diode. Information about commercialization of the Milkmaid is, however, not given yet.

There are several rapid commercial systems (e.g., BacT/Alert from BioMerieux, Germany, MicroFoss from Foss Analytical, Denmark) for microorganism detection based on pH changes during bacterial growth using colorimetric pH sensors (see Section 3.2.5 for details). Wireless pH sensors and color pH indicators for intelligent packaging are discussed in Section 3.3.

3.2.2. Impedimetric sensors

Among different electrochemical techniques, impedance spectroscopy is one of the most widely used methods for bacteria detection. The impedance microbiology is based on impedance changes that occur in a medium due to bacterial growth. These are:

1) Changes in conductivity of the sample (e.g., bovine milk has a conductivity of 4–6 mS/cm that corresponds to an electrolyte concentration of about 40–60 mM) due to charged ionic metabolites produced by bacterial growth, which can be measured and related to the overall bacterial concentration. Conductivity measurements can be as potential alternative for direct detection/prediction of milk quality (Conte, 2013; Yanthi et al., 2018).

2) Changes in the interfacial impedance due to bacteria adhesion to the electrode surface, which include changes in the charge-transfer resistance (Faradaic process) and/or in interfacial capacitance (non-Faradic process) (Felice et al., 1999; Yang and Bashir, 2008).

The first method is simpler but requires low-conductivity samples. The second method may be very fast and sensitive, particularly if it is accompanied by pre-concentration steps (Brosel-Oliu et al., 2015a). Usually, the impedance technique is preferred over the conductivity method because it takes into account both the double-layer capacitance of the system and the electrical resistance of the medium (Liu et al., 2015; Varshney and Li, 2009). Since only living bacteria cells yield metabolic activity and are able to cause changes in the conductivity of the medium, impedance microbiology is also used for differentiating living and dead cells (Brosel-Oliu et al., 2015a). In addition, since the impedance growth curves have been found to be characteristic for various bacteria species, bacteria may be identified by monitoring of the microbial growth kinetics.

Impedance measurements are usually performed using a pair of metal electrodes or more sensitive interdigitated electrodes (IDE). There are numerous reports in literature dealing with the development and application of impedimetric sensors for rapid bacterial detection by applying different sensor designs and electrode materials (Gómez-Sjöberg et al., 2005; Munoz-Berbel et al., 2008; Yang and Bashir, 2008; Wang et al., 2012; Brosel-Oliu et al., 2015a, 2015b; Liu et al., 2015; Das et al., 2011; Durante et al., 2016; Flint et al., 2014). As discussed in (Uria et al., 2016b), reported techniques using impedance to detect viable cells show detection limits between 10^4 and 10^8 CFU/ml after 8 h and 5 h of incubation (the larger the microbial population, the shorter the detection time) or up to 8 CFU/ml, but after about 15 h of incubation. In addition, several commercial impedimetric systems are available such as Bactometer (BioMerieux, Germany), Malthus systems (Malthus Instruments, UK), Rapid Automated Bacterial Impedance Technique (RABIT) (Don Whitley Scientific, UK) and BacTrac (Sy-Lab, Austria) for bacteria detection (see Table 3).

These commercial systems can also be applied for predicting the shelf-life of milk (White, 1993). For example, the commercial

Table 3
Commercial automated systems (source: Puttaswamy, 2013). TTD: time to detection.

Commercial name	Method employed	Initial load	Microorganisms	TTD
RABIT (Don Whitley Scientific, UK)	Conductance change	1 CFU/ml	Coliforms	16.1 h
Bactometer (Bio Merieux, Germany)	Impedance microbiology	10^5 CFU/ml	*Escherichia coli*	4 h
Malthus systems (Malthus Instruments, UK)	Conductance change	500 CFU/ml	*Clostridium Sporogenes*	15.5 h
BacTrac (Sy-lab, Austria)	Impedance analyzer	100 CFU/ml	*Pseudomonas aeruginosa*	30 h

Bactometer was used for predicting the potential shelf-life of packaged pasteurized milk (Zhiyong et al., 2003). The milk was incubated at 30 or 37 °C for 6 h before the sample is placed into the commercial Bactometer. Test results were available within 14–20 h. However, since these commercial systems are usually not suitable for in-line- or on-line applications, so many efforts have been made to miniaturize the impedimetric instruments. For example, an automated small system for impedance measurements in milk was developed in (Fourie et al., 2007). The planar IDE sensors were used to quantitatively detect *Escherichia coli* O157:H7 in cow milk samples from supermarket without any enrichment medium (Liu et al., 2015). The detection time in *Escherichia coli*-spiked milk with an initial cell concentration between 7.2 and 7.2×10^8 cells/ml was between 10.6 and 1.4 h, respectively.

Recently, a new type of miniaturized impedimetric sensor based on a capacitively coupled contactless conductivity detection (C^4D) transducer (Huck et al., 2014a, 2014b, 2015) and 3D IDE separated by an insulating barrier (Bratov et al., 2008; Bäcker et al., 2014) were developed for the contactless measurement of electrolyte conductivity and label-free biosensing, respectively. Moreover, the C^4D sensors were applied for non-invasive on-line monitoring of bacterial growth (*Escherichia coli*) (Zhang et al., 2018, 2019). The obtained characteristic growth-rate curves for *Escherichia coli* were more accurate than those obtained with contact conductivity methods. The IDE using a Pt thin film as electrode material were tested for a quantification of *Escherichia coli* in diluted milk samples with bacteria concentrations between 10^2 and 10^6 CFU/ml in only 6 h (Uria et al., 2016b). By immobilization of bacteria on the IDE arrays covered with a polyelectrolyte multilayer, the detection limit and TTD of the IDE sensors in culture medium could be improved as low as 10 CFU/ml and around 20 min, respectively (Brosel-Oliu et al., 2015b). The main drawback of these sensors was the non-specificity, because other negatively charged species that might be present in the sample would adhere to the sensor surface modified with a positively charged polyelectrolyte layer as well. Nevertheless, the reported results demonstrate the possibility of IDE arrays to achieve very fast, cheap and robust impedimetric sensors for bacteria detection.

Microfluidics techniques are a good strategy for improving the performance of impedimetric bacteria sensors. For instance, a high-density interdigitated electrode array immobilized with monoclonal anti-*Salmonella* antibodies was used to detect *Salmonella typhimurium* cells inside a microfluidic chip (Fig. 2, Dastider et al., 2015). The impedance sensor provided qualitative and quantitative results in 3 h without any enrichment steps. Lower detection limit was found to be 3×10^3 CFU/ml compared to 3×10^4 CFU/ml of the non-microfluidic sensor.

Advantages of the impedance technique are relative simplicity, rapidity, sensitivity, reusability, portability and comparatively low cost of the experimental equipment, ease of miniaturization, label-free detection, the possibility of remote sensing and more importantly, the potential for on-line measurements or directly in a milk container (miniaturized system). The drawbacks of impedance methods are the interferences from food matrices and possible electrode fouling. In addition, in general, impedance microbiology is not a selective method. However, some selectivity may be achieved by:

- modification/functionalization of the impedimetric sensor surface with high-affinity recognition molecules (e.g., antibodies, aptamers), which selectively bind target microorganisms;
- utilizing selective culture media;
- separation of the target bacteria from the rest of microorganisms present in the test sample and their pre-concentration.

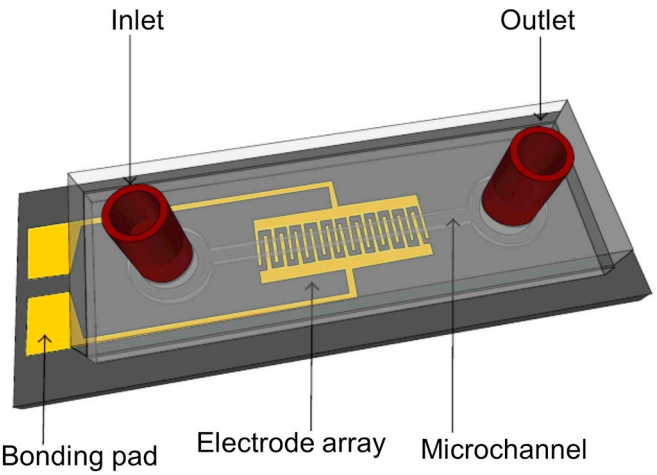

Fig. 2. Three-dimensional schematic of the impedance sensor showing the electrode array embedded under a microchannel with inlet and outlet. Reprinted with permission from Dastider, S.G., Barizuddin, S., Yuksek, N.S., Dweik, M., Almasri, M.F., 2015. J. Sensors, Article 293461. Copyright (2015) Hindawi, Open Access. Creative Commons Attribution License (CC-BY).

The impedimetric method measures a global impedance change, which can be caused from changes of one or all components of the equivalent circuit, making it very difficult to distinguish, which parameter was changed. As a consequence, different authors use different parameters of the equivalent circuit model (sample conductivity, surface resistance, charge transfer resistance, Warbung impedance, double-layer capacitance, etc.) for the interpretation of experimental results that sometimes does not reflect the real changes of a particular parameter.

3.2.3. Amperometric oxygen sensor technology: DOX system

The DOX 60F instrument manufactured by Bio-Theta Ltd. (Japan) is a rapid system for bacterial respiration monitoring and based on an amperometric oxygen sensor technology (http://www.bio-theta.co.jp/en). In the presence of dissolved oxygen in the sample, the following chemical reaction will occur in the DOX cell cartridge equipped with electrodes (see Fig. 3):

$$O_2 + 4\,H^+ + 4\,e^- \rightarrow 2\,H_2O \quad (1)$$

This reaction generates an electrical current at the working electrode. The amount of current depends on the dissolved oxygen concentration in a sample. If bacteria consume dissolved oxygen, the amount of electrical current sharply drops. The DOX system can automatically evaluate the number of microorganisms via their respiration rate by measuring the dissolved-oxygen consumption rate and is considered as a rapid, convenient, and simple method for the detection of bacterial contamination in milk (Numthuam et al., 2009). Total viable cells, coliform counts, *Escherichia coli*, *Staphylococcus aureus* and

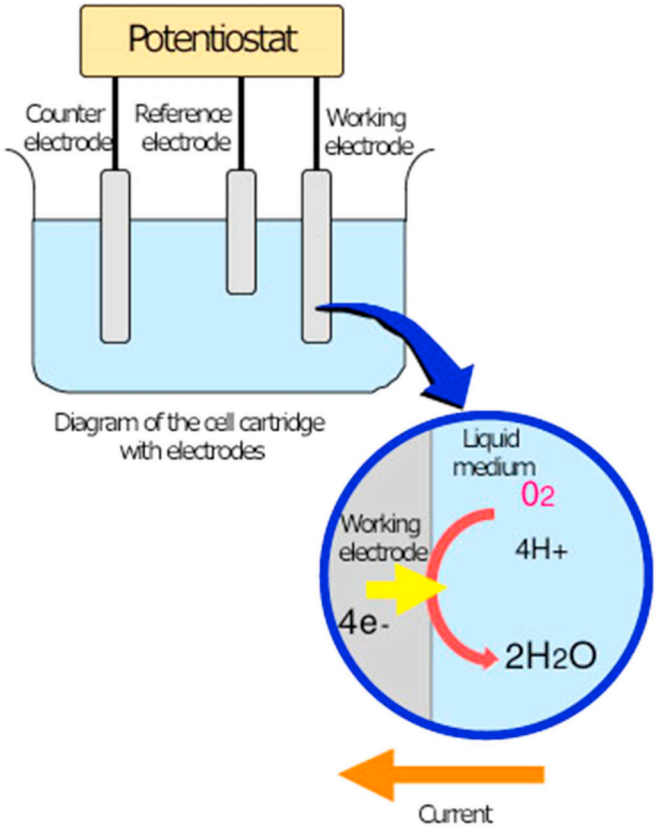

Fig. 3. Working principle of a DOX system Reprinted with permission from Company Bio-Theta (http://www.bio-theta.co.jp/en).

Salmonella can be evaluated with the DOX system with a reduced detection time of about 6 h (for viable counts of 10^5 CFU/g), while conventional tests take more than 24 h (http://www.bio-theta.co.jp/en).

3.2.4. ATP detection methods

3.2.4.1. ATP bioluminescence. One of the most widely-used rapid methods for contamination detection in UHT products is ATP bioluminescence (Niza-Ribeiro et al., 2000; Caprita and Caprita, 2005; Dostalek and Branyik, 2005; Carrascosa et al., 2012; Chollet and Ribault, 2012; Shama and Malik, 2013; Cunha et al., 2014). ATP is the principal energy carrier and is found in all living organisms. The concentration of ATP is directly related to the number of viable bacteria cells present in a sample. Luciferin/luciferase bioluminescence is the most popular and highly sensitive ATP detection method. The ATP bioluminescence technique measures the emission of light produced by an enzymatic reaction between luciferin and luciferase that requires the presence of ATP (Shama and Malik, 2013):

$$\text{D– Luciferin} + \text{ATP} + \text{O}_2 \xrightarrow[\text{Mg}^{2+}]{\text{Luciferase}} \text{Oxyluciferin} + \text{AMP} + \text{PP}_i + \text{CO}_2 + \text{photon} \quad (2)$$

In the presence of O_2 and Mg^{2+} ions, the enzyme luciferase catalyzes the conversion of D-luciferin to oxyluciferin, and ATP is converted to adenosine monophosphate (AMP) with the release of pyrophosphate (PP_i) and the emission of light with a wavelength between 470 and 700 nm and a peak at 562 nm (Shama and Malik, 2013). The amount of light emitted during the reaction – measured by means of a luminometer – is directly proportional to the concentration of ATP, and therefore the number of microorganisms in the sample.

Bioluminescence-based ATP testing has become well established in food processing industry as part of general hazard analysis and critical control points (HACCP) measures (Mandal et al., 2011; Shama and Malik, 2013). The technique is widely used to measure the cleanliness of surfaces that come into contact with food. The ATP-bioluminescence technique can be applied as a presence/absence test to screen a multitude of UHT food products, in particular, milk samples after a considerably reduced pre-incubation time. A number of hygiene monitoring systems and low-cost, hand-held luminometers are commercially available. These include, for instance, the PallCheck (Pall Corporation), Hygiena SystemSURE Plus (Hygiena), Milliflex (Millipore Corporation), RapiScreen (Celsis Rapid Detection), Accupoint (Neogen), Novalum (Charm Sciences), Microbial Luminescence System (3M Food Safety), ATP Detection Kit (Promicol), Lighting MVP ICON (BioControl Systems), etc. The Lighting MVP ICON can be combined with a pH/temperature probe, where an ISFET is used as pH sensor (ICON Brochure, 2013; http://www.biocontrolsys.com). Recently, the characteristics (linearity, sensitivity, repeatability, accuracy) of five leading commercially available, portable ATP hygiene monitoring systems were compared (http://www.hygiena.net). Results of this study showed that the best system on the market is Hygiena's SystemSURE Plus with good linearity, lower detection limit of 0.17 fM ATP, and repeatability (coefficient of variation) of 9%.

The ATP bioluminescence measurement is one of the quickest tests but it is not very specific. It can be used to detect as few as 10^4 CFU/ml of bacteria in milk providing results within a few minutes (Dostalek and Branyik, 2005). The ATP bioluminescence testing system is very simple in handling and it is no need for laboratory facilities.

Major disadvantage of the ATP method is the presence of non-microbial or extracellular ATP generating a background signal and an overestimation of the contamination. As a consequence, total ATP does not always correlate with the number of alive microbial cells. Therefore, to accurately determine bacteria levels, background ATP must first be removed by sample pretreatment (Moon et al., 2010). Another problem is that the ATP content of microbial cells is variable (e.g., the ATP content of laboratory cultivated microorganisms ranges from 0.4×10^{-18} to 16.7×10^{-18} M/CFU (Shama and Malik, 2013)) depending on their nature, the type of microorganism and their physiological state. A further drawback is the quenching of emitted light that can strongly affect the measured results (Dostalek and Branyik, 2005).

ATP bioluminescence measurements may be utilized to enumerate the total number of microorganisms present in a sample, if it is sufficient high ($> 10^4$ CFU/g) (Lopez-Campos et al., 2012). Therefore, ATP methods require substantial sample enrichment in order to be detectable. On the other hand, detection limits of 1 pg ATP, which corresponds to approximately 10^3 bacterial cells was also reported (Mandal et al., 2011; Narsaiah et al., 2012).

3.2.4.2. Other methods of ATP detection. Beside the ATP bioluminescence method, other techniques for the detection of ATP have been proposed and studied. For example, an ATP biosensor based on a pH-sensitive Ta_2O_5-gate ISFET modified with the enzyme apyrase (ATP diphosphatase) has been developed (Migita et al., 2007). The working principle of this sensor is based on the detection of local pH changes, resulting from the hydrolysis of ATP catalyzed by the enzyme apyrase:

$$\text{ATP} \rightarrow \text{ADP (adenosine diphosphate disodium salt)} + \text{HPO}_4^{2-} + \text{H}^+ \quad (3)$$

$$\text{ADP} \rightarrow \text{AMP (adenosine monophosphate salt)} + \text{HPO}_4^{2-} + \text{H}^+ \quad (4)$$

This measurement principle was proposed already in 1986 (Gotoh et al., 1986), where a differential measurement setup between a pH-sensitive ISFET and an ATP-sensitive ISFET has been used to detect ATP in a linear concentration range of 0.2–1 mM and with a detection limit of 0.2 mM.

An aptamer-based ATP-sensitive LAPS for extracellular monitoring of ATP locally secreted from a single taste receptor cell has been

developed (Wu et al., 2012). The biosensor was able to detect ATP in the concentration range from 10 nM to 100 μM. Enzyme-based ATP microelectrode biosensors were developed for the long-term in-vitro monitoring from gastrointestinal tissue (Patel et al., 2011). An amperometric ATP biosensor based on polymer-entrapped enzymes with a lower detection limit in the nM range was reported (Kueng et al., 2004; Weber et al., 2009). An inkjet-printed bioactive-paper ATP sensor was described in (Zhang et al., 2014). The working principle of this sensor is based on the enzyme-catalyzed hydrolysis of S-methyl-L-cysteine generating an odor (methyl mercaptan) that is easily detectable by the human nose with a threshold concentration of 0.2 ppb.

However, most of above-described sensors for ATP detection were tested only in buffer solutions; they are complicated in handling and not able for continuous or real-time in-line/on-line monitoring, or are insufficiently sensitive.

3.2.5. Commercial systems based on colorimetric detection of pH changes, CO_2 production and O_2 consumption

3.2.5.1. MicroFoss (FOSS Analytical A/S, Denmark). MicroFoss is a computer-controlled analysis system for the detection and enumeration of a wide range of microorganisms in food. The MicroFoss system provides microbiological screening for the TVC (total viable count), coliform count, *Escherichia coli*, *Enterobacteriaceae*, mold and yeast in raw materials, during the production process and in finished products (http://www.foss.dk, MicroFoss brochure). MicroFoss is based on the colorimetric detection of microbial metabolites. Growth of microorganisms results in a change of pH and redox potential of media. The color changes are detected by a photodiode at the bottom of a vial; the detection limit is down to 10^3 CFU/ml and shelf-life estimation is possible (e.g., for fresh milk) (White et al., 2006). Specifications of MicroFoss can be found in Table 4. With MicroFoss the microbiological testing process is reduced from 2 to 3 days to about 7 h. For the majority of food spoilage tests, the presence/absence results are possible within 18 h (http://www.foss.dk, MicroFoss brochure).

3.2.5.2. BacT/ALERT (bio Merieux, Germany). BacT/ALERT represents a system allowing the microbial growth and consists of an incubation chamber with different measurement cells, computer systems and flasks with sensor and nutrition medium (http://www.biomerieux.de). The sensor optically detects the pH change in the culture medium due to CO_2 generation or formation of organic acids, respectively. The colorimetric detection principle works comparably to that of the MicroFoss.

3.2.5.3. Soleris (Neogen, USA). The Soleris rapid microbial detection system from Neogen Corporation (http://www.neogen.com) is an automated system which utilizes an LED and a photodetector to monitor color changes caused by bacterial growth in a specially designed ready-to-use vial containing the growth medium and color indicators. The vial is inoculated with a sample dilution and as bacteria grow they produce changes in pH and other biochemical indicators (e.g., CO_2) leading to a color change in the vial. The instrument monitors each vial every 6 min and records the time taken to produce a detectable color change, which is related to the initial microbial count (http://www.neogen.com). The higher the number of organisms, the faster the detection time.

The Soleris system has applications for: TVC, spoilage detection, shelf-life prediction, sterility testing of raw materials and finished products. Neogen offers Soleris tests for coliforms, *Escherichia coli,* yeast and mold, *Enterobacteriaceae*, lactic acid bacteria, *Staphylococcus, Pseudomonas* and *Alicyclobacillus*. The technology offers the quickest and easiest spoilage organism detection ranging from a single organism per vial to 10^8 CFU/ml. For example, Soleris is capable of producing a result for TVC within 18 h (see Table 5). Yeast and mold tests produce accurate results in only 48 h; in comparison, conventional yeast and mold methods can take up to 5 days. Various dyes serving as indicators of metabolic activity (e.g., pH, redox, CO_2 production and enzymatic activity) can be utilized in the system.

3.2.5.4. BioLumix (Neogen). BioLumix (now part of Neogen) has developed a simple rapid microbiological method for the detection of various groups of bacteria, yeasts and molds in UHT samples (http://www.neogen.com, BioLumix brochure). Many products (including milk) can be introduced directly into the BioLumix disposable test vial without the need of a dilution step. A disposable test vial contains a transparent solid sensor located at the bottom of the vial that changes color when CO_2, generated by microbial metabolism, diffuses into the sensor and reacts with a reagent. The system utilizes CO_2 since it is a universal metabolite produced by all microorganisms. Only gases can penetrate the sensor that blocks liquids, microorganisms and particulate matter.

The BioLumix system is capable of quickly distinguishing clean UHT samples from samples containing bacteria, yeast or molds with a high degree of accuracy. For example, the coliform or *Enterobacteriaceae* results can be available within 12 h; yeast- and mold results are achieved within 48 h rather than 5–7 days using plate methods (http://www.mybiolumix.com). The BioLumix has developed a vial specific for testing of *Pseudomonads* that are known as a major cause of bacterial spoilage of pasteurized milk due to post-process contamination. The BioLumix vial was capable for a rapid detection of *Pseudomonas* in commercial milk products within 16–24 h (http://www.mybiolumix.com). Early detection of *Pseudomonas* can be as an indicator for the prediction of product shelf-life, as it belongs to the predominant psychotropic bacteria.

3.2.5.5. GreenLight (MOCON, USA). In contrast to the Solaris- or BioLumix systems, the GreenLight system available from MOCON (USA) uses the fluorescence detection of oxygen consumption by the microorganisms present in a food sample for a rapid enumeration of TVC (http://www.mocon.com, GreenLight brochure: Rapid Microbial Detection and Growth Assay). As bacteria in a sample multiply and respire, they consume oxygen. The GreenLight system uses a unique oxygen sensor (fluorescent oxygen-sensing dye) to continuously monitor bacterial respiration in food samples. The change in oxygen concentration as a function of time (similar to a typical growth curve) is used to calculate the original sample's colony forming unit (see Table 6). GreenLight systems offer high throughput testing with a detection range of 1-10^8 cells and a lower limit of quantification < 15 CFU/vial. It can provide results at very low

Table 4
Examples of microorganism screening with the MicroFoss system (adopted from the MicroFoss brochure, http://www.foss.dk).

Type of food products	Microorganisms	Test time (h)	Reference method test time
A variety of dairy products, meat products, eggs, sauces, fruit juice, vegetables, salad dressings, cakes, confectionary, wines	Total viable count	Up to 18	48–72 h
	Coliforms	Up to 12	24 h
	Enterobacteriaceae	Up to 18	24 h
	Escherichia coli	Up to 18	24–48 h
	Yeast	Up to 18	5–7 days
	Mold and yeast	Up to 18	5–7 days

Table 5
Comparison of Soleris system with traditional methods (source: http://www.neogen.com, Soleris brochure: Automated microbiology for food safety and product quality).

Test type	Typical specification levels	Traditional methods –time to results	Solaris total test time to negative or below specification results	Solaris early alert time for positive results
Total viable count	< 10,000	48 h	18 h	6–8 h
Coliforms	< 10	24 h	14 h	6–10 h
Escherichia coli	negative	24 h	20 h	6–10 h
Yeast and mold	< 100	5 days	48 h	14–24 h
Lactic acid bacteria	< 100	3–5 days	48 h	30–35 h

Table 6
Estimated time to result (http://www.mocon.com, GreenLight brochure: Rapid Microbial Detection and Growth Assay).

CFU/g	10^8	10^7	10^6	10^5	10^4	10^2	10^1
Time (h)	< 1	< 3	< 5	< 9	< 11	< 13	< 15

bacterial loads in less than 24 h without in-carton pre-incubation; for comparison, the conventional standard plate count method requires 48–72 h.

The tests in UHT milk using the GreenLight demonstrated (Lehotová et al., 2016) that if TVCs were lower than 100 CFU/ml, the time to result was obtained within less than 10 h. On the other hand, if the samples contained a higher number of microorganisms (higher than 10^6 CFU/ml), the time to result was achieved within 2–6 h. Milk samples can be tested directly or with nutrient medium added into the barcoded APCheck vials with integrated oxygen sensor. In contrast to plate count methods, no dilution of milk samples is necessary.

It should be noted, however, that most of commercial equipments and methods discussed in this section are end-point assays providing temporally restricted information.

3.2.6. Electronic noses and tongues

3.2.6.1. Electronic noses. There is an increased interest in the development of technology based on the use of gas-sensor arrays, so-called electronic noses (e-nose) for food-quality monitoring applications, among them rapid detection of food spoilage. An e-nose is the analytical device used for the fast detection and identification of mixtures of odorants, which mimics the principle of operation of the human smell. The e-nose consists of two major parts: the detecting system representing an array of gas sensors (usually, non-selective) and a data processing unit. The e-nose generates a characteristic odor profile, a so-called fingerprint, in response to the interaction with a gaseous mixture. Then, the signal is sent to the data recognition system, which mimics brain function. Patterns or fingerprints from known odors are used to create a database and train a pattern recognition system so that unknown odors/mixtures can be subsequently classified and/or identified. Gas sensors based on metal-oxide semiconductors (MOS) (e.g., SnO_2, TiO_2, WO_3, ZnO, ZrO_2) and conductive polymer (CP) films (e.g., polypyrole, polyaniline, polythiophene) were often applied in e-noses (Gomes, 2016; Kalit et al., 2014). The MOS and CP sensors rely on the changes of conductivity in the sensing films induced by the adsorption of gases that are produced during spoilage processes. The selectivity and sensitivity of MOS sensors can be influenced by the operating temperature, which is typically between 200 °C and 650 °C. CP sensors, on the contrary, require a low operating temperature, but usually they are very sensitive to moisture. In addition, the sensitivity of CP sensors is generally one order of magnitude lower than the sensitivity of MOS sensors (Gomes, 2016). Other gas sensors based on metal-oxide-semiconductor field-effect transistors (MOSFET), amperometric gas sensors (AGS), quartz-crystal microbalance- (QCM), surface-acoustic wave- (SAW) and bulk-acoustic wave (BAW) transducers as well as hybrid sensor arrays including different transducer principles were also applied in e-noses (Sliwinska et al., 2014; Gomes, 2016; Mahmoudi, 2009; Persaud, 2016). Pattern recognition techniques (e.g., principal component analysis, artificial neural networks, fuzzy logic) have been employed to analyze e-nose data. Some of commercially available e-noses and applied sensors are summarized in Table 7.

Table 7
Commercial e-noses and applied sensors (Casalinuovo et al., 2006; Matindoust et al., 2016).

E-nose	Type and number of gas sensors
FOX 2000 (Alpha MOS, France)	6 MOS
FOX 3000	12 MOS
FOX 4000	18 MOS
Airsense portable E-Nose (Airsense Analytical, Germany)	10 MOS
MOSES II (Lenmartz Electronic, Germany)	8 MOS, 8 QCM, 4 AGS
Cyranose C320 (Cyrano Sciences, USA)	32 CP
BH-114 (Bloodhound Sensors Ltd., UK)	14 CP
Diagnose-II e-nose system (eNose Company, Netherlands)	12 MOS
NST 3210 (AppliedSensor, Sweden)	10 MOSFET, 5 Taguchi MOS, 1 infrared (IR) CO_2 sensor

Odor is one of the most important parameters for evaluating the freshness of food. Each product has a characteristic profile of volatile organic compounds (VOC) and therefore, its own characteristic odor. Likewise, spoilage will result in a different but still characteristic profile of VOCs in the same product. For example, some bacteria in milk produce VOCs such as ethyl butyrate, acetaldehyde, acetic acid, ethanol, etc., which can be used as an indicator of bacteria growth and therefore, as markers for the early detection of milk spoilage (Kalit et al., 2014). For instance, an e-nose consisting of Taguchi (TGS, Figaro, Japan) gas sensors and a radio-frequency identification (RFID) wireless unit was developed to detect milk spoilage due to bacterial contamination via the detection of VOCs present in the headspace of a milk container (Shinde et al., 2017). A commercial e-nose BH-114 (Bloodhound Sensors Ltd., UK) consisting of 14 conducting polymer sensors was used to differentiate between unspoiled milk and that containing spoilage bacteria or yeasts (Magan et al., 2001). Other examples for the use of e-noses in the dairy sector include: the classification of milk by trademark and type, determination of the off-flavor in UHT milk, shelf-life prediction of milk, freshness control and differentiation of spoilage-causing microbial species, etc. For the details of these applications, see Table 8 and reviews (Baldwin et al., 2011; Casalinuovo et al., 2006; Matindoust et al., 2016; Kalit et al., 2014; Falasconi et al., 2012; Gomes, 2016).

3.2.6.2. Electronic tongues. Concepts similar to e-nose, but for use in liquid media, have also been developed for the food sector. These systems are related to the sense of taste in the same way that the e-nose relates to olfaction and are usually known as taste sensors or electronic tongues (e-tongue) (Winquist et al., 1998; Baldwin et al., 2011; Ciosek, 2016; Hruškar et al., 2009; Kalit et al., 2014; Riul et al., 2010; Wadehra and Patil, 2016; Wei et al., 2013; Sliwinska et al., 2014; Lvova, 2016).

Table 8
Selected examples of commercial e-nose applications for milk quality/spoilage detection (source: Gomes, 2016; Sliwinska et al., 2014).

Sensor type	Number of sensors	Purpose
CP	14	Differentiation of unspoiled from microbially spoiled milk
CP	12	Classification of milk according to microbial counts
CP	28	Grouping milks by the season
MOS	4	Milk quality control by detecting off-flavor
MOS	18	Milk shelf-life
MOS	4–5	Differentiation of UHT and pasteurized milk
MOS	10	Separation of UHT milk in normal and anomalous odor
MOS	7	Differentiation of milk from different dairies and by fat content
MOS	6	Discrimination of milk origin
BAW	6	Discrimination of contaminated milk
BAW	2	Discrimination of milk origin
MOSFET/MOS/IR CO_2	10 MOSFET, 12 MOS, 1 IR CO_2	Differentiation of healthy milk from mastitis cow milk

Electronic tongues consist of an array of sensors, data collectors and data analysis tools. The electronic tongue generates a signal pattern, which can be related to certain features or qualities of the sample. This has a similarity to how the human sense organs produce signal patterns to be qualitatively interpreted by the brain. Similar to e-noses, multivariate pattern recognition techniques (artificial neural networks, principal component analysis or fuzzy logic method, etc.) are applied for data processing.

In the design of e-tongues, different sensor arrays such as potentiometric (including ISFETs), voltammetric, amperometric, impedimetric, conductimetric, optical, mass-sensitive and enzyme-based sensors have been suggested (Lvova, 2016; Persaud, 2016). Until now, there have been numerous attempts to analyze milk by means of e-tongue systems (see Table 9) as they are a very attractive alternative to traditionally used techniques, because of the low cost of analysis, the simplicity of measurements and the possibility to perform the analysis in real-time and on-line. Such applications include the analysis of taste and flavor, microbial growth monitoring, adulteration detection, quality control and process monitoring. Examples are: the simultaneous determination of ethanol, acetaldehyde, diacetyl, lactic acid, acetic acid and citric acid content in probiotic, fermented milk; monitoring the deterioration of milk quality due to microbial growth, monitoring of the aging processes of various milks; discrimination between UHT and pasteurized as well as between fresh and spoiled milk; distinguishing milk from different sources having different quality properties; detection of antibiotic residues in bovine milk. There are commercially available e-tongue systems in the market such as the Taste Sensing System (Intelligent Sensor Technology Inc., Japan) or the a-Astree e-tongue (Alpha MOS, France); the latter is consisting of seven ISFETs covered with different organic materials.

Although human olfactory- and taste systems and sensory assessment of food cannot be replaced by any device, numerous works have shown that e-nose- and e-tongue devices represent excellent non-destructive methods for the determination of volatile and non-volatile food compounds.

Their major advantage is the possibility of continuous monitoring of product quality from the very beginning across all processing stages up to the final product. In addition, the combination of an e-nose and e-tongue (hybrid e-nose/e-tongue systems) can result in better correlations with sensory data and would more closely reflect the complexity of the human sensory system (Baldwin et al., 2011). Compared with the e-nose and e-tongue, classical instrumental analysis employed for the determination of volatile and non-volatile compounds (i.e., gas and liquid chromatography, spectrometry techniques) is much more expensive, time-consuming, needs highly qualified personnel, and cannot be used for on-line production monitoring.

The drawbacks of the currently available e-noses and e-tongues are the sensors' drift, influence of temperature and humidity (for e-noses),

Table 9
Application of e-tongues for the analysis of milk samples (source: Ciosek, 2016; Sliwinska et al., 2014).

Potentiometric tongues		References
Taste sensor: set of electrodes with lipid membranes	Taste of UHT milk after various exposure to light	Mizota et al. (2009)
Integrated array of solid-state ion-selective and partially selective electrodes	Milk classification according to brand/dairy origin	Ciosek and Wróblewski, 2008
Ion-selective electrode array	Discrimination between milks from healthy and infected with bovine mastitis glands	Mottram et al. (2007)
ISFET array: a-Astree e-tongue (Alpha MOS, France)	Recognition of different milk samples from different producers, discrimination between various dairy products from one manufacturer	Hruškar et al. (2009)
ISFET array: a-Astree e-tongue (Alpha MOS, France)	Monitoring of changes in probiotic-fermented milk during storage, classification of probiotic-fermented milk according to flavor and taste	Hruškar et al. (2010a)
ISFET array: a-Astree e-tongue (Alpha MOS, France)	Determination of ethanol, acetaldehyde, diacetyl, lactic acid, acetic acid, and citric acid content in probiotic-fermented milk	Hruškar et al. (2010b)
Voltammetric e-tongues		
Voltammetric cell with 2 working electrodes (Au and Au modified with a Prussian blue film)	Evaluation of milk adulteration, discrimination between milks of various fat content	Paixão and Bertotti (2009)
Voltammetric cell with 5 working electrodes (Au, Pt, Ag, Pd, Ti)	Detection of antibiotic residues in bovine milk	Wei and Wang (2011)
Voltammetric cell with 4 working electrodes (Au, Ag, Pt, Pd)	Monitoring of quality change and storage time of pasteurized milk, estimation of bacterial count, acidity and viscosity changes during storage	Wei et al. (2013)
Hybrid e-tongue and e-nose systems		
Combined e-tongue (SAW sensors) and e-nose (ISFET system)	Discrimination of milks according to fat level	Cole et al. (2011)
Combined e-tongue (voltammetric cell with 4 working electrodes: Pt, Au, glassy carbon, Ag) and e-nose system (8 MOS sensors)	Determination of aging time and brand of milks	Bougrini et al., 2014
Combined e-tongue (Taste Sensing System SA402 (Intelligent Sensor Technology, Japan) and e-nose system (Fox 3000, Alpha MOS, France)	Sensory attributes of raw milk and UHT milk	Mizota et al. (2008)

poor reproducibility, missing standard calibration procedures, lengthy and laborious training procedure and incapability of detecting very low concentrations of bacteria as well as high costs.

3.3. Wireless sensors and color indicators for intelligent packaging

The important parameter of food quality is the expiration date, which is estimated by the producer assuming standard packaging- and storing conditions. Poor storage conditions may spoil food before the expiration date, but conversely, impeccable food may be discarded because the expiration date has passed. It is estimated that about 25% of the world's food supply is lost as a result of microbial spoilage (Pushparajan et al., 2013). The detection of spoilage at an early stage with sensors built inside food packages would enhance food safety, quality and significantly reduce waste. Therefore, there is an urgent need for so-called smart/intelligent packages containing sensors, identification tags (e.g., RFID) or indicators which are capable to evaluate (without complex tests) the actual quality of milk in containers and give a signal about the remaining shelf-life. Intelligent milk containers are becoming an increasingly challenging issue in dairy industry. Many companies and research institutes are directly involved in this field by developing wireless sensors and color indicators that could be used directly in milk or its environment (Antonacci et al., 2016; Brockgreitens and Abbas, 2016; Dumitru et al., 2016; Rossi et al., 2017). Such sensors, RFID tags and indicators must be simple and cost-effective, and must not contaminate the product itself.

3.3.1. Wireless sensors

Application of remote-query (wireless, passive) sensors to detect milk spoilage is an emerging research field. These sensors don't require power source on the sensor or physical connection with the data acquisition system (Tan et al., 2007; Segura-Quijano et al., 2010; Nguyen et al., 2015; Kant et al., 2017; Kassal et al., 2018). Most of works on wireless sensors for milk spoilage detection represent still proof-of-principle experiments. Some examples are described below:

- A wireless passive, sterilizable potentiometric pH sensor made of an iridium/iridium oxide electrode and an Ag/AgCl reference electrode were developed for real-time, milk quality monitoring in a container (Bhadra et al., 2012, 2013, 2015). The resonance frequency of the sensor was monitored at a distance of 5 cm using an interrogator coil and an impedance analyzer (see Fig. 4). As the pH value of milk changes during spoilage, the voltage across the electrodes varies, shifting the resonance frequency of the sensor. A similar principle, but using mixed metal oxides as pH-sensitive material was reported in (Xiansheng and Jing, 2014). In addition, a wireless, printed LC (inductor-capacitor) sensor covered with a polymer layer was applied for monitoring of bacteria growth in milk samples (Ong et al., 2002).
- A 3-D printed “smart cap” with embedded wireless circuit for milk spoilage detection in cartons (see Fig. 5) was developed (Wu et al., 2015a, 2015b). With a flip of the carton, a small amount of milk becomes trapped in the capacitor gap within the cap. The resonance frequency of the LC circuit changes as the dielectric constant of the milk deteriorates over time. The signal was detected wirelessly via an inductively coupled reader. In preliminary tests, a 4.3% frequency shift was observed for milk stored at room temperature for 36 h.
- RFID sensors for monitoring the freshness of milk were constructed using commercial RFID tags from Texas Instruments (Potyrailo et al., 2012; Kant et al., 2017). These RFID sensors were attached to the side wall of the milk cartons (see Fig. 6). The sensor detects changes in the dielectric properties of milk due the milk spoilage as a function of storage time. The sensor response was readout with a pick-up coil. The disposable RFID sensors were successfully tested for real-time monitoring of whole and fat-free milk samples at room temperature. However, since working of these sensors is based on penetration of the electromagnetic field through the thin wall of the cartons into the milk sample, the presence of any metal layer in the milk carton will prevent a successful measurement.
- A magnetoelastic thick-film sensor coupled with a biochemical sensing layer is another platform for wireless monitoring of bacterial contamination and milk spoilage within hermetically sealed containers (Huang et al., 2008). The sensor responds to mass loading due to bacterial adhesion and changes in milk viscosity. A non-contacting pickup coil is then used to remotely detect the magnetic field generated by mechanical oscillations of the sensor. Disposable magnetoelastic sensors can be fabricated from strips costing 300 US $ per kilometer. The possibility to apply a wireless magnetoelastic sensor for real-time identification of spoiled milk samples was studied via the detection of *S. aureus* (Huang et al., 2008). Concentrations of *S. aureus* between 10^3-10^7 cells/ml in milk could be quantified.

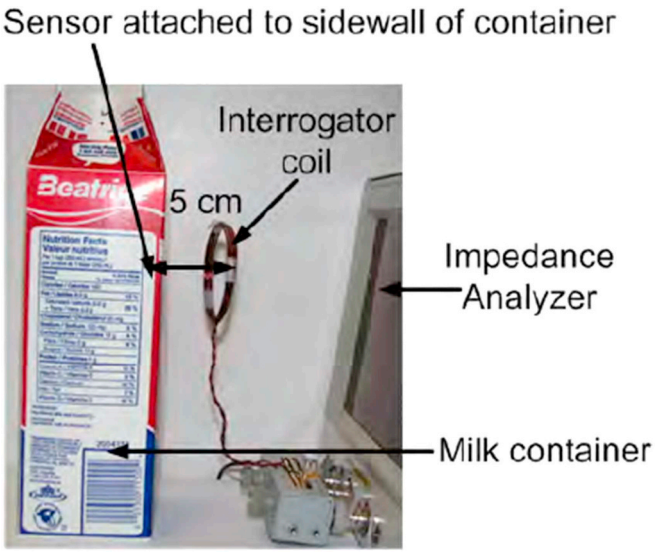

Fig. 4. Measurement setup with wireless, passive pH sensor implemented inside the milk container. Reprinted with permission from Bhadra, S., Thomson, D.J., Bridges, G.E., 2012. In: IEEE Sensors Proceedings, pp. 769–772. Copyright (2012) IEEE.

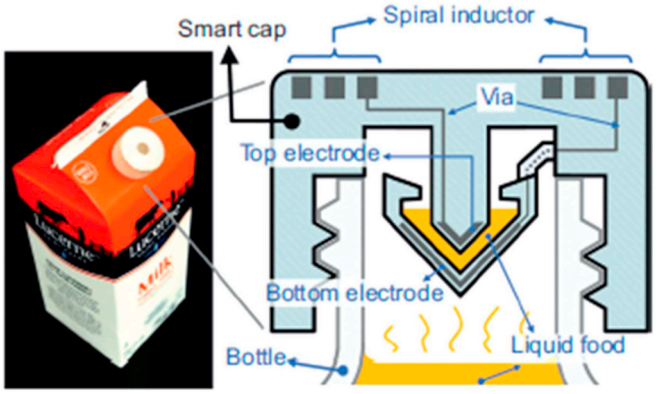

Fig. 5. “Smart cap” for rapid detection of liquid food quality featuring wireless reading: photo of a milk container and schematic diagram showing the cross-sectional view of the cap. Reprinted with permission from Wu, S.-Y., Yang, C., Hsu, W., Lin, L., 2015b. Microsys. Nanoeng. 1, Article 15013. Copyright (2015) Springer Nature Publishing. Creative Commons Attribution License CC BY 4.0.

The main disadvantage of all wireless sensors built inside milk packages is an undesired adsorption of proteins and other milk

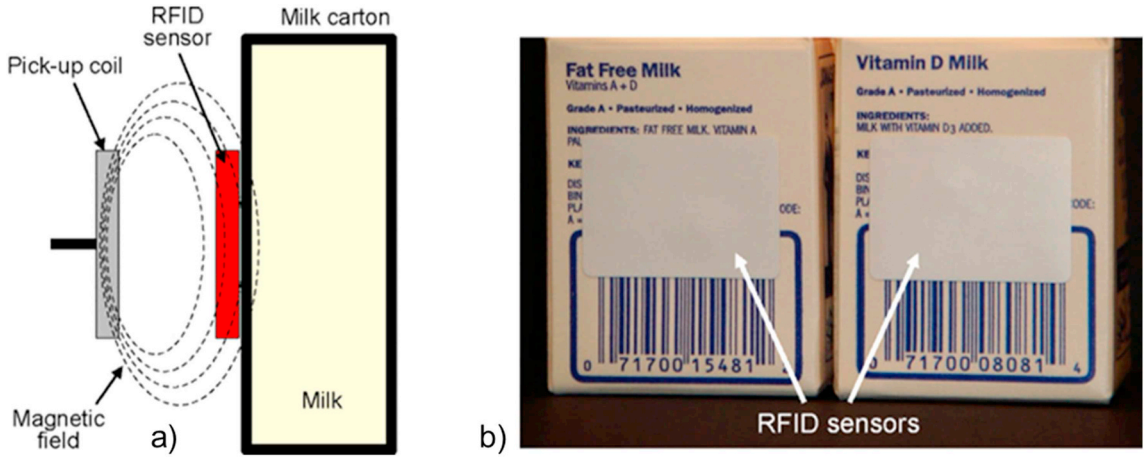

Fig. 6. RFID sensor layout for demonstration of determination of milk freshness: (a) schematic of sensor positioning onto a milk carton and sensor-response readout with a pick-up coil; (b) photo of milk cartons with attached RFID sensors. Reprinted with permission from Potyrailo, R.A., Nagraj, N., Tang, Z., Mondello, F.J., Surman, C., Morris, W., 2012. J. Agric. Food Chem. 60, 8535–8543. Copyright (2012) American Chemical Society.

components onto the sensor surface (which is in direct contact with the milk), resulting in drift effects. Common disadvantage is the small distance (3–5 cm) between the sensor and interrogator coil. Here, Bluetooth technology should be useful to expand this distance.

3.3.2. Color indicators

The role of these indicators is to warn the consumers about the freshness of the food by a color change. The spoilage-indicating milk cartons could have strong market potential as food industries increasingly adopt intelligent packaging designs. Some types of color indicators are shortly described below:

- **pH-sensitive color indicators:** Several research groups studied the possibility of incorporation of pH-sensitive color indicators into milk cartons to detect milk spoilage and replace stamped expiration dates. As pH-sensitive color-changing dye, bromothymol blue immobilized into a polyacrylamide hydrogel that can be added to existing packaging for milk (Blackmon et al., 2013), mixed bromothymol blue/methyl red (Guggilla et al., 2016) and hydroxyethyl cellulose/polyaniline film (Mustapha et al., 2016) have been tested.
- **Time-temperature indicators (TTI):** One of the most important environmental factors determining food preservation is the variation in temperature. The spoilage rate depends on temperature, which has resulted in the development of various TTIs. There is increasing interest in the application of TTIs as cost-effective and user-friendly indirect shelf-life indicators (Pavelkova, 2013; Rahman et al., 2018). Colorimetric TTIs are commercially available (e.g., 3M Monitor Mark (3M, USA); Timestrips (Timestrip UK Limited, UK), Fresh-CheckTTI (Temptime Corp., USA), CheckPointTTI (VITSAB A.B., Sweden), OnVu TTI (Ciba Specialty Chemicals, Switzerland)) and are based on different working mechanisms (Pavelkova, 2013). Most of TTIs utilize an irreversible color change due to exposing of food to room or high temperatures. There is increasing interest in the application of TTIs as cost-effective and user-friendly indirect shelf-life indicators (Pavelkova, 2013). However, because milk could be contaminated with various bacteria having different optimal temperature ranges for their growth and since some bacteria can spoil milk at temperatures even $< 7\,^{\circ}C$, a wide application of those TTIs for milk spoilage detection or accurate shelf-life prediction seems to be questionable.

4. Summary and outlook

In food microbiology, the major objectives are to detect and often identify microorganisms as rapid as possible. Commercially available fast detection methods have substantially shortened the total TTD when compared to conventional methods. However, many detection systems need additional enrichment and are off-line laboratory instruments. Unfortunately, most of the rapid methods still lack from sufficient sensitivity for direct testing and require $\sim 10^3$ CFU/ml (or more) target organisms to be present before detection can be accomplished. The dairy industry needs for in-line solutions as well as for portable, rapid, cheap and easy-to-use devices for an early detection of milk spoilage. These should be able to detect spoilage bacteria directly in milk samples, should require no enrichment, a minimal sample preparation and low interferences from sample components. In addition, TTD, range of detection, accuracy and reliability of results are critical factors to determine the optimal method for milk spoilage detection.

Fig. 7 shows a roadmap of technologies for microorganism detection starting from the methods and technologies that are commonly used in laboratory up to automated in-line systems (Mortari and Lorenzelli, 2014). The goal is to achieve in-line analysis with less than 1 CFU/ml detection limit in less than 1 h by 2030. Moreover, intelligent packaging that can monitor the deterioration of milk in containers and provide information to the consumer on the quality of the product inside is also an interesting innovation. In this regard, a chemical/biological sensor platform is very attractive. However, its use is still often limited to research laboratories and the reported works often represent proof-of-concept approaches rather than systematic studies. In real samples (e.g., in UHT milk), interferences from the very complex food matrix as well as sensor fouling could have a drastic role, preventing correct functioning of such sensors.

Finally, there are fundamental limitations of microorganism- or spoilage detection via metabolites, which should be overcome before chemical/biological sensors and miniaturized systems could found a widespread use in milk-spoilage monitoring. The consumption or release of the metabolites changes the pH value, conductivity, concentration of dissolved or produced gases and other parameters in the sample. However, the amount of metabolites consumed/produced by a single bacterium is extremely small. For example, the oxygen consumption rate for *Escherichia coli* is only 2×10^{-14} mol/h, while the concentration of dissolved O_2 in an oxygenated suspension is in the order of 10^{-6} mol/ml (Puttaswamy et al., 2017). Thus, there has to be an adequate large number of bacteria present in the sample before a measurable sensor signal is produced. If the initial concentration of bacteria in the original sample is small ($< 10^3$ CFU/ml), one must wait for cells to grow to some threshold concentration (often $\sim 10^6$ CFU/ml or higher) before a noticeable change in the properties (e.g., pH, O_2, CO_2 concentration, impedance, etc.) of the sample can be observed. Thus, new strategies or novel transducer principles are needed in order

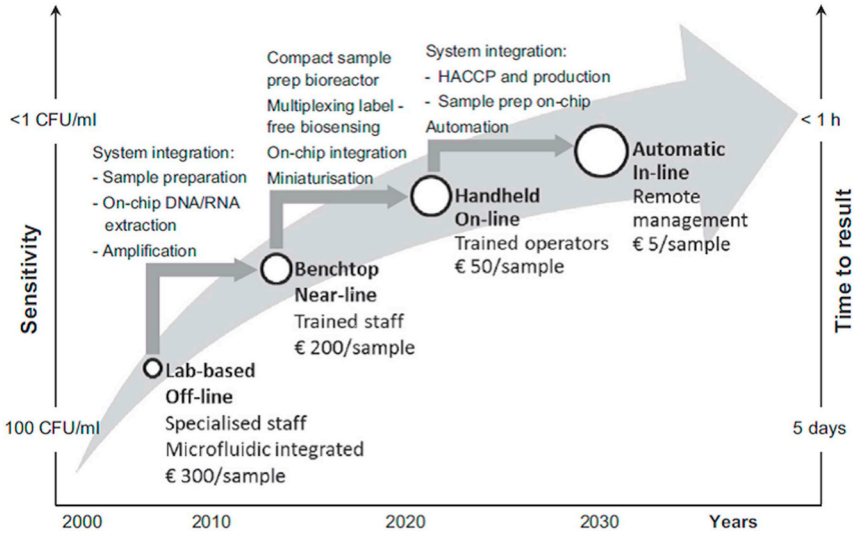

Fig. 7. Roadmap of technologies for microorganism detection. Reprinted with permission from Mortari, A., Lorenzelli, L., 2014. Biosens. Bioelectron. 60, 8–21. Copyright (2014) Elsevier.

to enhance the device sensitivity or reduce the TTD.

One strategy is the separation of microorganisms from the food matrix and their concentration in a very small volume prior to detection. Here, physical entrapment in microstructured compartments, dielectrophoresis, immunomagnetic beads and electrostatic coupling can be employed to concentrate microorganisms in a microfluidic channel above the sensor surface (Gomez-Sjöberg et al., 2005; Heo and Hua, 2009; Jiang et al., 2014). In this way, the effective microorganism concentration is increased without raising the initial number of microorganisms. A microfluidic device capable of concentrating bacteria from a sample could completely eliminate the need for amplifying the bacterial population by a long growth step. Performing the detection at the microscale can result in drastically reduced TTD and lower detection limit.

From our point of view, for increased reliability of measurements and clear interpretation of results, parallel measurement of different spoilage-specific parameters and a combination of more than one method/transducer principle is preferred. In addition, the use of a logic YES/NO principle (e.g., whether signal changes of all applied sensors are in the expected direction, or not; Katz et al., 2017) could be very helpful in order to give a statement about milk freshness or possible spoilage. Such a multi-parameter sensor system could be miniaturized into chip level format and integrated with a microfluidic device or into a “smart cup” for RFID detection.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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