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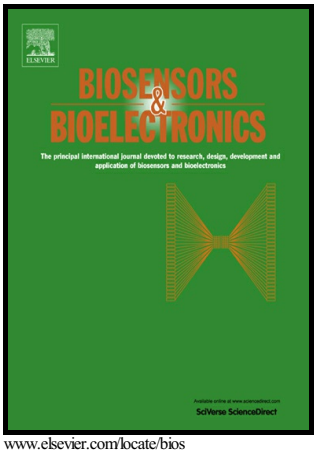

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Recent Advances on materials and methods for sensing salmonella infections

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Abstract

Salmonella infectious diseases spreading every day through food have become a life-threatening problem for millions of people and growing menace to society. Health expert's estimate that the yearly cost of all the food borne diseases is approximately $5–6 billion. Traditional methodologies for salmonella analysis provide high reliability and very low limits

of detection. Among them immunoassays and Nucleic acid-based assays provide results within 24 h, but they are expensive, tedious and time consuming. So, there is an urgent need for development of rapid, robust and cost-effective alternative technologies for real-time monitoring of salmonella. Several biosensors have been designed and commercialized for detection of this pathogen in food and water. In this overview, we have updated the literature concerning novel biosensing methods such as various optical and electrochemical biosensors and newly developed nano- and micro-scaled and aptamers based biosensors for detection of salmonella pathogen. Furthermore, attention has been focused on the principal concepts, applications, and examples that have been achieved up to diagnose salmonella. In addition, commercial biosensors and foreseeable future trends for onsite detecting salmonella have been summarized.

Keywords: Salmonella, detection, infection, biosensor.

1. Introduction

Pathogens are virtually ubiquities, reaching every aspect of life. Between the myriad of bacterial pathogens that cause foodborne diseases and high rate of mortality, the most important are: Salmonella (31%), Listeria (28%), Campylobacter (5%), and Escherichia coli O157:H7 (3%) (Inbaraj and Chen 2015). Among this pathogens the importance of Salmonella bacteria is undeniable, since it is the main cause of foodborne bacterial illnesses in humans in many countries for at least over 100 Years(Crump et al. 2015). Salmonella spp is an anaerobic gram-negative rod-shaped bacteria belonging to the family Enterobacteriaceae and comprises over 2500 serotypes that are medically important pathogens. The most common serotypes associated with human illness are Salmonella enterica Serovar typhimurium (S.

Typhimurium) and S. enterica serovar Enteritidis (S. Enteritidis). The WHO announced salmonella impress about tens of millions of human and 100,000 deaths every year. These estimates indicates that salmonella presents a major ongoing burden to public health and a greet cost for governments (Crump et al. 2015; Inbaraj and Chen 2015).

Infections with salmonella cause clinical disorders including fever, abdominal pain, diarrhea, nausea, and vomiting(Inbaraj and Chen 2015). Pneumonia, Meningitis and Osteomyelitis are other devastating illnesses caused by invading salmonella to bloodstream. However, parallel decreases in incidence of malaria and NTS bacteremia have been reported (Takem et al. 2014). On the other hand, bioterrorism has been put the stress on the need to control the presence of bacterial pathogens that could be used as biological weapons and put the safety of people in jeopardy. Salmonella spp, is one of bacterial pathogens that has been illustrated by contaminated salad bars at the local restaurants in Oregon in 1984, causing illness in over 700 people (Santos 2014). Therefore, importance of food, water, and agricultural safety is undeniable. The millions of infections and thousands of fatal cases every year are an important reason for improving the detection and control of Salmonella Infection. Capacity of the bacterium to tolerate environmental stress, widespread distribution, multiple drug resistance, and adaptability of salmonella has made the detection of pathogen challenging and difficult. Furthermore, the infection diagnosis could be misinterpreted as infection features are quite non-specific and mimic with many other diseases. Moreover, there is no specific treatment available for this disease. Thus, subtle and early diagnosis will pave the way to control and prevent the spread of the infection (Guadarrama et al. 2014). leading to significance of Salmonella, it is essential to sense them with efficient and rapid methods. This review will focus on different biosensor based methods Figure 1 to overcome the drawbacks of conventional methods for identification of salmonella as foodborne pathogen (Lim et al. 2015).

2. Conventional techniques of salmonella detection

Several traditional techniques are available for the diagnosis of salmonella infection, being based the conventional methods on: i) pure culture , ii) immunological and iii) nucleic acid-based techniques. Figure 2 summarizes the steps involved in pathogen identification with an indication about the time involved.

2-1 Pure culture method

Pure culture has always been considered as the gold standard for the diagnosis of salmonella infection. It basically involves four steps that can be applied to any type of food: i) pre-enrichment, ii) selective enrichment, iii) isolation on solid selective media, and iv) complete identification of the colonies through biochemical and serological testing(Mandal et al. 2011). Although the colonies of different Salmonella serotypes can be distinguished by colors with the coliforms on these media, some serotypes are not distinctive and even missed on those media, yielding false negatives and increasing costs for additional tests. Furthermore, this method requires at least 4 or 5 days to give concluding results (Lee et al. 2015; Mandal et al. 2011).

2-2 Immunological techniques

Immunological methods rely on the specific antibody antigen binding. Immunoassay refers to the qualitative and quantitative determination of the presence of antigens in sample specimens through immunological reactions. These methods are more specific than cultural ones, but presents some drawbacks, being necessary to have a polyvalent H-antiserum free of cross reacting antibodies. Additionally, immunological methods are time-consuming,

labor-intensive and typically provide limited information on the biophysical properties of target analytes. Moreover, the labeled reporter (fluorophore, luminophore, enzyme or radio-label) can sometimes alter the specific activity of the binding reagents and result in a less sensitivity procedure and false negative results, or can use aggregation of protein, resulting in false positive results (Benetti et al. 2013; Mandal et al. 2011).

2-3 Nucleic acid-based techniques

The essential principle of nucleic based assays is the specific formation of double strand nucleic acid molecules from two complementary single stranded molecules under selected conditions. DNA probe and PCR are two commercially developed nucleic acid based assays for detecting food pathogens, which can distinguish very low numbers of organisms in the sample (Uyttendaele et al. 2003). Although these systems provide powerful methods, the presence of some inhibitors can dramatically affect the polymerase chain reaction. The major drawback of this technique is the lack of ability to distinguish between live and dead cells hence, providing false negative results (Radhika et al. 2014) .The miniaturization of biochemical assays reduces volumes of reagents, media, and materials, providing a fast characterization of microorganisms like salmonella(Lee et al. 2015). Traditional methods for food born pathogen analysis are regarded as gold standards except for time delay and labor involved. Therefore, they are not fast enough to respond to bioterrorism events and Salmonella outbreak. So that, there is an urgent need for developing analytical biosensors featuring accurate, sensitivity, specificity and usability for detection of salmonella at point-of-care settings (Pan et al. 2014; Tenenbaum and Segal 2015).

3. Principles of bio- and immune- sensors

Biosensors have recently been looked upon as attractive alternatives to the existing conventional pathogen detection platforms. Biosensors have been designed to detect or quantify bacteria(Liu et al. 2016b), virus (Jarocka et al. 2016) or a variety of biochemical molecules including specific DNA sequences(Jia et al. 2016), proteins(Chang et al. 2016), and oligonucleotides(Matsishin et al. 2016). Many biosensors developed to date are affinity-based, meaning in which an immobilized capture probe is adopted to bind the molecule being sensed as target selectively. Therefore transferring the challenge of detecting a target in solution into detecting a change at a localized surface. This change can then be measured in a variety of ways, such as surface plasmon resonance(Vaisocherová-Lísalová et al. 2016), evanescent wave(Taitt et al. 2016) and amperometric measurements (Henao-Escobar et al. 2016). So far, biosensors have found many applications, including biomarker detection for medical diagnostics, pathogen and toxin detection in food and water (Wang et al. 2015b). A typical biosensor encompasses three components (See Figure 3A): the sensor platform, a transduction platform and the amplifier (Mokhtarzadeh et al. 2015). The sensor platform is functionalized with a bio-probe to impart specificity of recognition. Transduction platform generates measurable signals and signals are finally amplified (Geschwindner et al. 2012). Immunosensors are immune reaction-based dependent biosensors, in which immune compounds are utilized as biological receptors. They almost always integrate an immune assay and an associated transducer straightly in a single device (Figure 3B) (Liu et al. 2016a). An integral principle of immunosensors is based on the interaction of an antibody(Ab) with an antigen(Ag), which describes both, specificity and detection limit, of an immunosensor (Justino et al. 2016). The Ab–Ag interaction is determined with association and dissociation reaction rate constants, ka and kd respectively. Most immunosensor devices reported to date conduct indirect measurements by using labels such as enzymes (Fang et al. 2015),

fluorescent (Zhao et al. 2011), and chemiluminescent (Yang et al. 2016b) probes that convert affinity signal in to a measurable response. Apart from their use in clinical analysis, commercial tests are also used in environmental, food and bio threat analysis regarding Salmonella (Bahadır and Sezgintürk 2015) and Bacillus anthracis (Bahadır and Sezgintürk 2015).

4. Salmonella bio- and immune- sensors classification

Given that Salmonella is universal pathogen implicated in food poising (Yang et al. 2016a), bio terrorism and other hazards (Gittinger 2015), it is not surprising that it is one of the hottest topics in immune- and bio-sensing.

Biosensors are usually classified either according to the transduction element (electrochemical, optical, mass sensitive, piezoelectric or thermal) or to the bioreceptor (enzymatic, immune affinity recognition, whole-cell, or DNA). Electrochemical and optical methods are most widely used in the development of salmonella biosensors. Table 1, summarizes some of the characteristics of representative immune- and bio-sensors proposed in the literature for salmonella detection, based on different signaling strategies. This section concentrates on application, advantages and limitations with respect to each signal detection strategy, and a detailed discussion of these different signaling strategies for salmonella detection.

4-1 Optical Salmonella biosensors

Optical biosensors offer powerful analytical techniques which utilize light absorption, fluorescence, luminescence, reflectance, Raman scattering or refractive index changes for detecting analytes. The working principle of an optical biosensor involves the measurement

of changes in amplitude, phase, frequency or polarization of light(Wang et al. 2015b). Optical biosensors include numerous types with enormous potential applications, thus providing beneficial biosensing platforms to investigate DNA, and particularly DNA mutations(Toren et al. 2015) and discriminate lipopolysaccharide (Tenenbaum and Segal 2015) as well as, environmental monitoring and specially food safety(Long et al. 2013).

4-1-1 Colorimetric Salmonella biosensors

The unique optical properties of colorimetric analysis make them very popular for discrimination of microbiological food contamination like salmonella(Yoo and Lee 2016). A variety of colorimetric assays, based on the use of nanoparticles, as gold (AuNPs) and magnetic nanoparticles (MNPs), have been utilized in this filed (Sun et al. 2016). Nanoparticles play curial role in bio sensing as they have a high capture efficiency due to the high surface proportion and the presence of numerous binding domains (Wignarajah et al. 2015)

4-1-1-1 Gold nanoparticles coating salmonella biosensors

The unique properties of gold nanoparticles exhibit novel functions in sensing. Excellent conductivity, catalytic properties and high surface-to-volume ratio of this particles have stimulated the increasing interest in the application of gold NPs in designing biosensors (Li et al. 2010). Prasad et al utilized 23 nm gold nanoparticles for targeting the stn gene of salmonella that was able to produce a detection limit more sensitive than that obtained using gel electrophoresis. In this method the Salmonella enterotoxin (Stn, a putative virulence factor responsible for enterotoxic activity gene)(Nakano et al. 2015) was amplified in order to increase signal strength. An amplified gene can be diagnosed in two different ways, using non-functionalized and functionalized gold nanoparticles. Prasad et al took advantage of

non- functionalized gold nanoparticles in which sensitivity (true positive rate) of 89.15% and specificity(true negative rate) of 99.04% was obtained for salmonella in various food samples (Prasad and Vidyarthi 2011). Fu et al conducted another study in which hut genes of S. enterica was targeted by design thiolated Au probes, and was able to detect salmonella bacteria in contaminated milk samples using 13 nm gold nanoparticles (Fu et al. 2013). In non-functionalized method salt is usually used for the detection of amplified products. If gold nanoparticles aggregate in the presence of salt, their color will alter from red to blue, unless they become fixed by nucleic acids. Fixation of the gold nanoparticles occurs with adsorption of nucleic acids on the surface or reaction with thiol probe, which is hybrid with the target nucleic acids (Figure 4). Another method involves the use of cationic gold nanoparticles, where the interactions between nucleic acids and the surface of gold nanoparticles lead to aggregation of the nanoparticles. In this method gold nanoparticles are not functionalized with a thiol-probe but rather coated with the probe using electrostatic reciprocal action(Verma et al. 2015). Table 2 summarizes some of the main characteristics of gold nanoparticles based methods proposed in the literature for the determination of salmonella microorganisms using functionalized and non-functionalized systems.

Although several nucleic acids based strategies have been presented for the detection of salmonella , it is also possible to detect it by targeting other analytes like antibodies that can target specific sites on the surface of pathogens. This antibody-antigen association leads to aggregation of gold nanoparticles around the pathogen of interest and can thus generate a colorimetric response (Bülbül et al. 2015). Wen-he Wu et al. fabricated aptamer based biosensors (aptasensors) based on label-free aptamers and gold NPs for detection of Escherichia coli (E. coli) O157:H7 and Salmonella typhimurium. Target bacteria binding aptamers captured with the surface of unmodified AuNPs to absorb target bacteria, and the

detection was accomplished by target bacteria induced aggregation of the aptasensor which was associated as red-to-purple color alteration. By employing anti E. coli O157:H7 aptamer and anti S. typhimurium aptamer, they develop rapid approach that could selectively detect bacteria without specialized instrumentation and cell lysis. This device detects as low as 10^5colony-forming units CFU/ml target bacteria within 20 min or less with 100%. Specificity(Wu et al. 2012).

A total of 12 target specific ssDNA aptamers were obtained through ten rounds of Cell-SELEX under stringent selection conditions by Hae-Chul Park and coworkers. Aptamer specificity was investigated using the gram-negative bacteria E. coli and P. aeruginosa and it was found that aptamer specificity was very high towards S. enteritidis and S. typhimurium. The conjugation of individual aptamers to a PDAP confirmed the improvement of binding affinity up to 100-fold relative to the individual aptamer. Therefore, identification of ssDNA aptamers towards S. enteritidis and S. typhimurium should be useful as ultra-sensitive capture and detection probes for the development of an aptamer based biosensor detection system for salmonellosis(Park et al. 2014a). In the particular case of pathogens, combination of aptamagnetic enrichment with the exquisite sensitivity of PCR allows extreme sensitivities even in complex food matrices. The magnetic beads (MB) are ideal for this kind of applications, especially for commercial kits due to easiness of separation and high binding capability. Examples of successful aptamagnetic separation have been reported for Salmonella (Dwivedi et al. 2013).

4-1-1-2 Magnetic nanoparticles coating salmonella bio- and immune- sensors

MNPs possess great potentials for many kinds of applications in the bio-reagent separation and bioassay due to their desirable characteristics of reproducibility, cost-effectiveness, uniformity in size and ease of use for separation(Xiao et al. 2016). Immunomagnetic separation with immune- modified magnetic NPs (MNPs) have been reported for Salmonella. Joo et al discriminated Salmonella in milk by using MNPs and TiO_2 nanocrystals. In this investigation, antibody-immobilized magnetic NPs were employed to select, capture, concentrate and separate Salmonella from solution by antibody-immobilized magnetic NPs. Consequent binding of antibody-conjugated nanocrystals to the MNP–Salmonella complexes was monitored by absorbance measurement. The procedure enabled detection of 100 CFU/ml for Salmonella in milk (Joo et al. 2012). Recently, Ji Young Park et al developed sophisticated magnetic nanoparticles (MNPs) with specific aptamers, and a colorimetric substrate TMB device to deal with the menace of poising with salmonella typhimurium. This novel technique enables simple and rapid sensing with naked eyes. The basic principle of colorimetric detection is shown in Figure 5 (Park et al. 2015). It seems that the DNA aptamers rapidly adsorbed onto the surface of the MNPs and also cause the aggregation of MNPs, considerably reducing the ability of the surfaces and increasing the colorimetric properties (Park et al. 2015).

4-2 Surface plasmon resonance (SPR) salmonella biosensors

Optical affinity biosensors based on surface plasmon resonance (SRP) present one of the most advanced label-free optical sensing technologies since late 1990's (Du et al. 2012). The SPR method is based on optical measurement of refractive index changes associated with the binding of analytes to bio recognize molecules immobilized on the SPR sensor using surface plasma waves to probe bimolecular interactions occurring at the surface of a sensor. (Singh et

al. 2014a). For detection of salmonella, Nitsara et al introduced SPR-based assay, using a Salmonella specific bacteriophage. In this fabrication, bacteriophage M13 was immobilized on SPR sensor surface as probes. To determine the detection limit of this phage based SPR assay, a range of Salmonella concentrations (0, 1×10^7, 5×10^7, 1×10^8, 5×10^8,1×10^9CFU/ml) were tested and detection limit was obtained at 8.0×10^7 CFU/ml using the IUPAC definition (Karoonuthaisiri et al. 2014). In another study, J. R. Son1 et al, evaluated the feasibility of a miniature SPR sensor for detection of Salmonella enterica with immobilized Anti-Salmonella antibodies on the gold sensor surface by using neutravidin. After consecutive and precise analyses they determined that Salmonella can be detected at concentrations below 10^5 CFU/ml (Son et al. 2007). Anu Singh and coworkers fabricated Surface plasmon resonance (SPR) based DNA hybridisation biosensor by generating a self-assembled monolayer of 5-thiolated single-stranded DNA (ssDNA) probe onto gold surface. This DNA biosensor has been investigated for label-free real-time monitoring of Salmonella with 2 fM limit of detection (Singh et al. 2014a).

4-2-1 Evanescent wave salmonella biosensors

The evanescent wave is a phenomenon often poorly understood (Taitt et al. 2016). Schneider et al used an evanescent wave interferometer with a single planar wave of polarized light. Light from a diode laser source was conducted into the wave guiding film as a single wide light. The beam passed per multiple sensing domains on the surface of the chip. An array of integrated optical elements was employed to incorporate light passing through adjacent regions functionalized with specific or non-specific receptors. This technique was utilized to detect Salmonella typhmurium instantly, in the range of 5×10^8 to 5×10^{10} CFU/ml with a detection time of only 5 min. (Ivnitski et al. 1999).

Angela M. Valadez's coworkers developed specific evanescent wave biosensor for Salmonella diagnosis in which anti-Salmonella polyclonal antibody was immobilized onto the surface of an optical fiber using biotin-avidin interactions to capture Salmonella . They performed a test to evaluate low concentrations of pure cultures of S. Enteritidis with the fiber-optic system. S. Enteritidis concentration of 1×10^9 CFU/ml gave the strongest signal, (1,047 ± 92 pA) and the signal decreased with decreasing bacterial concentration. The limit of detection was established to be 10^3 CFU/ml in pure culture and 10^4 CFU/ml in egg and chicken breast samples spiked with 10^2 CFU/ml after 2–6 h of enrichment. The performance of the fiber-optic sensor can be completed in less than 8 h, providing an alternative to the current detection methods (Valadez et al. 2009).

4-2-2 Fluorescent-based salmonella biosensors

Fluorescence spectroscopy is a powerful technique for the detection of very small concentrations of analytes. Fluorescence-based microbial biosensors include in vivo and in vitro type. In the case of in vivo type fluorescent microbial assays, the microorganisms are able to generate the fluorescent substance (e.g., green fluorescent protein) without the addition of an exogenous element. In the invitro type, the metabolic activity of microorganisms changes the surrounding environment, causing exchange in light emission due to the exogenous fluorescent element (Su et al. 2011). Fluorescent dyes have special features they: i) are molecular sensors that integrated both, sensing and response at the molecular level, ii) can be easily integrated into supramolecular and macroscopic devices, although their basic operation does not require this, iii) can be used for homogeneous assays in solution,iv) not require any intermediate signal transduction factor or step in recording the

sensing event(Ding et al. 2015), v). Pyle et al, took advantage of the fluorescent antibody technique followed by incubation with cyanoditolyl tetrazolium chloride (CTC) to asses respiratory activity. Fluorescein conjugate was added and bacteria enumerated after capture of the bacteria and incubation with CTC. This method was enabled to detect E. coli O157:H7 in the range of 10^5–10^9 CFU/ml with an assay time of 4 h. This technique was also employed for distinguishing S. typhimurium and Klebsiella pneumonia (Ivnitski et al. 1999).

4-2-2-1 The Quantum dots labels

The use of QDs as fluorescent labels is emerging as a recent and promising class of fluorescent biosensors because of their distinctive optical properties such as broad excitation spectra together with narrow, symmetric, excellent photo stability, and high water solubility(Huang et al. 2016). For detection of S. typhimurium in chicken carcass, Anti-Salmonella antibody-coated magnetic beads were utilized by Yang and Li to separate the bacteria from wash water and allowed bacteria to react with secondary biotin-labeled anti-Salmonella antibody to facilitate reaction of biotin with streptavidin-coated QDs and measure fluorescence. The linear response between logarithm of bacterial cell number and fluorescence intensity was in the range of 10^3_10^7 CFU/ml with a detection limit of 10^3 CFU/ml (Yang and Li 2005). QDs potency in specific labeling of cells and tissues, long-term imaging and non-cytotoxicity made them vital and significant in bio sensing(Wang et al. 2015a).

The basis of FRET involves an energy transfer from a fluorescent molecule to an acceptor molecule due to dipole-dipole interaction in a close distance interaction. It is a powerful and efficient technique for probing small changes when there is an appreciable overlap between

the emission spectrum of the donor and the absorption spectrum of acceptor(Wang et al. 2015a).

FRET-based studies using QDs as donor are widely applied for bioanalytical chemistry (Freeman et al. 2011), cocaine sensing(Mokhtarzadeh et al. 2015), monitoring botulinum neurotoxin A activity (Sapsford et al. 2011), optical and photo electrochemical sensing (Freeman et al. 2013). FRET system, based on QDs was established with Bei-Bei Wang and coworkers for selective and sensitive Salmonella Enteritidis detection. In this method two color QDs were adopted as donors and acceptors simultaneously because of their large high quantum yield, good photo stability, and size dependent maximum emission wavelength ability(Wang et al. 2015a). In this assay the fluorescence intensity of QDs receptors declined linearly with the increasing concentrations of Salmonella Enteritidis from 75 to 5×10^5 CFU/ml. The limit of detection of Salmonella Enteritidis in this method was 10 CFU/ml without sample enrichment within 1–2 h. This method has been applied for analysis Salmonella Enteritidis in synthetic samples(Wang et al. 2015a).

4-2-2-2 The Phage-Based labels

Bacteriophages have been intensively used as molecular biology tools since their discovery (Lee et al. 2013).In the last decade, several phage-based bioassays have been developed using a variety of output signals as fluorescence and based on both, direct (phage protein fusions or phage DNA staining) (Mosier-Boss et al. 2003) or indirect (phages labeled with antibodies or quantum dots detection(Edgar et al. 2006). Direct detection of S. Typhimurium on spinach leaves using wireless Multiple phage-based magnetoelastic (ME) biosensors that was developed by Suiqiong li et a,. using a wireless biosensor composed of a ME resonator platform that is coated with phage (genetically engineered to bind with Salmonella) (LI et

al.). In this study an alternating magnetic field was used to drive the biosensors into resonance and a pick up coil measures the sensors resonance frequencies. Upon contact with a target pathogen, the phage binds the pathogen to the biosensor, causing an increase in the biosensor mass and a corresponding decrease in resonance frequency. After placing the ME biosensors on the leaves shifts in the resonance frequency of E2 phage ME biosensors were observed, while the change in resonance frequencies of control sensors were negligible. SEM images verified the specific binding of Salmonella to the biosensor surface. This study demonstrated the direct detection of food-borne bacteria on fresh produce (LI et al.). Fernandes et al. developed a phage-based biosensor to detect Salmonella in food stuff using a magnetoelastic platform. Three tested phages were equally able to infect the Salmonella isolates. Among them the PVP-SE1 had the broadest lytic spectrum. The results revealed that PVP-SE1 have multivalent ability and can be an important feature for therapy(Fernandes et al. 2013). Also Nitsara Karoonuthaisiria et al, demonstrated the feasibility of using M13 bacteriophages expressing target-pecific peptides as a binder for salmonella detection(Karoonuthaisiri et al. 2014)

4-2-2-3 The DNA microarray labels

Biosensors based on DNA microarrays are widely used in food safety and quality(Wang and Salazar 2016). This assays have been used to examine poisoning microbes (Clostridium botulinum, Campylobacter spp, Salmonella enterica and Staphylococcus aureus)(Bitaraf et al. 2016), and toxins (cadmium, silver-nanoparticles and tetrodotoxin)(Carter et al. 2016), in different materials including bovine, milk, meat, potato, rice and other analyts (Rusul and Chuah 2015).

DNA microarrays can be classified into those for genotyping and gene expression analyses (Table 3). The sources of microarrays are either custom arrays or microarrays supplied by companies gene expression profiling by DNA microarray assay that are crucial due to their advantages in the evaluation of pathway-based intracellular signaling in response to food materials(Wang and Salazar 2016) . They are also used in evaluating biochemical activities of proteins, due to their binding affinities, specifity and quantitative response (Giles et al. 2015; Mangal et al. 2015). DNA microarrays used for detection of salmonella in foods are summarized in Table 3. Microarray analysis has the inherent quality to become a leading routine detection method for in-depth bacterial analyzes in food and feed environments (Park et al. 2014b).

4-2-2-4 The Aptasensor based labels

The recognition part of biosensor can be composed of antibodies, enzymes, microorganisms, organelles or cells which respond to the presence of the target analyte(Cui et al. 2016). Apart from using mentioned recognition elements short single strand DNA or RNA sequences, called aptamers, have been used as highly specific bioreceptors, which inherently adopt stable three dimensions sequence-dependent structures and bind a target ligand with high affinity. Aptamers have been applied for an extended number of molecules, from small ones such as ions(Jarczewska et al. 2016), or mycotoxins(Liu et al. 2015) to proteins (Erdem et al. 2016) and up to bacteria or viruses(Bitaraf et al. 2016). The development of aptamer- based sensors by systematic improvement of ligands is reproducible and well established, they can be labeled easily without affecting the affinity for their ligands and are more stable than antibodies and many enzymes (Wu et al. 2014). Aptasensors take advantage of aptamers as a recognition element which are illustrated by numerous reviews summarizing data on development of their applications in food analysis (Mokhtarzadeh et al. 2015). Peng Zuo et

al. developed a polydimethylsiloxane (PDMS) hybrid microfluidic system integrated with aptamer-functionalized graphene oxide (GO) nano-biosensors (Figure 6). The integration of aptamer biosensors on the microfluidic biochip was facilitated by paper substrate. This paper avoided complicated surface treatment and aptamer probe immobilization in a PDMS or glass-only microfluidic system. Lactobacillus acidophilus was used as a bacterium model and the system employed for the simultaneous detection of two bacterial pathogens Staphylococcus aureus and Salmonella enterica. After ruling out cross reaction from each other, simultaneous detection of S. enterica from 0–1375 CFU/ml $^{-1}$ and S. aureus from 0–10^6 CFU/ml $^{-1}$ was performed utilizing the microfluidic biochip integrated with aptamer functionalized GO biosensors for Staphylococcus aureus and Salmonella enteric. The calibration curves for the simultaneous detection of S. enterica and S. aureus were generated by plotting the fluorescent intensity against the pathogen concentration. This method enabled one-step, simple, multiplexed pathogen detection without complicated surface modification and probe immobilization. The assay takes only ~10 min once a ready-to-use microfluidic biochip is prepared (Zuo et al. 2013).

4-2-2-5 The Fluorescence resonance energy transfer (FRET) labels

Nanoparticles (NPs) possess several attributes as well as the unique physical and chemical properties that make them promising synthetic scaffold for the creation of novel chemical and biological detection systems (Rosi and Mirkin 2005). Due to their extraordinary high molar extinction coefficients and broad energy bandwidth, these particles serve as excellent fluorescence quenchers for FRET-based assays. The fluorescence-based NP detection strategy relies on the fluorescence resonance energy transfer or the fluorescence change when the system meets the target because of the surface modified fluorescence (Yue et al. 2016). The widely used strategy is FRET, since it consist non-radiative process involving an

excited state donor. For the first time Yang Song et al utilized 16SrRNA and nicking enzyme assisted fluorescence signal-assisted amplification to detect bacteria. Which took advantage of CNPs (carbon nanoparticles) instead of conventional organic dyes to construct molecular beacons (MB) due to their superior chemical inertness and lower toxicity? They have developed a FRET, using nicking enzyme biosensor based on CNPs to detect S. enteritidis. utilizing DNA nicking endonuclease means that each target strand can go through many cycles, leading to cleavage of different molecular beacons (MB). The nicking enzyme recognizes and cleaves the dsDNA fabricated by the interaction between probe and target after adding salmonella. In this sensor, the severity of the fluorescence signal depends mainly on the cleavage reaction. When the aim pathogen is captured, the CNT- DNA sequence can be released and the MB can be cleaved. Since Specificity is equally important as sensitivity in detection, specifity of this biosensor was determined with hybridization between the target sequence and CNT-DNA sequence. Averages of fluorescence intensity (a.u) in milk were 32.987±2.88 (control), 34.277±2.87 (S. typhimurium), 33.27±2.94 (E. coli K88), and 234.447±3.22 (S. enteritidis). The biosensor displays a linear relationship with the concentration of S. enteritidis ranging from 10^2 to 3×10^3 CFU/ml in water and from 1.5×10^2 to 3×10^3 CFU/ml in milk. The LOD of this method was 10 times lower than that of other methods (Song et al. 2014).

4-2-3 Luminescent-based salmonella biosensors

Recent advances in bio-analytical sensors have led to the utilization the ability of certain enzymes to exhale photons as a corollary of their reactions (Mwinyihija et al. 2006). For the first time Ulitzur and Kuhn initiated utilizing the potential applications of bioluminescence for detection of bacteria by developing luciferase reporter phages (Ivnitski et al. 1999). Up to now, many different bioluminescence systems have been used for detection of a wide range of microorganisms. For example, Sarkis et al applied the L5 bacteriophage to detect

Mycobacterium segmantis. Using this bacteriophage has paved the way to detect one hundred cells of M. segmantis in a few hours and 10 cells in two days. Salmonella spp. and Listeria were also detected by Turpin et al in 1993 and Chen and Griffiths in 1996 Using the same approach (Ivnitski et al. 1999). Chemiluminescence assay is field of interest due to high sensitivity, fast reaction, low cost, and simple manipulation (Dai et al. 2013; Mokhtarzadeh et al. 2015). Saem Mun et al fabricated a simple method to detect Salmonella typhimurium using 100-nm antibody- and horseradish peroxidase conjugated magnetic nanoparticles (Ab-HRP-MNPs). In this method bacteria had captured with particles and free particles were removed by filtration. Intensity of light emitted from the chemiluminescence reaction catalysed by bacterium-bound peroxidase in the filter reveal rate of bacteria. The light severity was proportional to the cells in the range of $0\text{-}10^4$ CFU, with a lower detection limit of 10 CFU. These features make this method suitable for commercial applications, the HRP activity of individual Ab-HRP-MNPs was maintained at an optimal level for the reliable measurement of bacterial numbers and particle aggregation was prevented to avoid false positive signals(Mun and Choi 2015)Figure 7.

4-2-3-1 The Aptasensors based labels

All pathogens for which aptamers have been developed have their own aptamer-based detection methodology. The different approaches for aptasensing according to their level of integration have been illustrated in Figure 8 (Amaya-González et al. 2013).

Besides different approaches taking advantage of the nucleic acid character of aptamers, DNAzymes can be utilized in automated synthesis of the aptamer(Miao et al. 2015). These non-protein enzymes were useful for the chemiluminescent detection of Salmonella paratyphy A with mild enzymatic activity. Recently, Yang et al utilized a DNAzyme with

peroxidase activity after binding the hemin cofactor. The DNAzyme-aptamer conjugate wrapping single-wall carbon nanotubes (SWCNTs) was released when both hemin cofactor and target are added. Spiked tap water samples were analyzed, achieving a limit of detection of 10^4 CFU/ml (Yang et al. 2013a). Chemiluminescent immunoassay could become very useful for quantifying Salmonella and for the quantitative detection of chicken interferon-γ (ChIFN-γ), since it provides a flexible ,simple ,rapid and sensitive way (Yang et al. 2013b; Yang et al. 2014). Additionally, Hua Dai et al described an automation-friendly chemiluminescent immunoassay method for the determination of chicken interferon-c (Dai et al. 2013).

4-3 Electrochemical salmonella biosensors

Among widespread variety types of biosensors, electrochemical biosensors present popularity due to privileged merits. These are extremely susceptible in miniaturized detectors and can operate well in opaque media(Diculescu et al. 2016). Their ability to use analytical methods easily and their low economical cost made them considerable(Rotariu et al. 2016). The basis of such devices is the intimate coupling of biological factors and an electron transducer which is responsible to convert desired biorecognition event to an interpretable electrical signal(Rotariu et al. 2016). These sensors are extremely sensitive and have been used widely in commercially available devices ranging from self-testing blood glucose meters to analyzers of various metabolites as well as distinguishing Salmonella and E. coli O157:H7 in less than 90 min. According to type of transducer, electrochemical biosensors are classified as amperometric, potentiometric, conductometric, or impedimetric biosensors (Singh et al. 2014b). Potentiometric and amperometric devices have been expanded, based on enzymatic oxidation such as alcoholic oxidase or formaldehyde dehydrogenase, variation of pH, current and conductivity produced within the sensors (Chiou et al. 2015). A novel field in

electrochemistry issue is nanoelectrochemistry(Castillo-León et al. 2016). It combines benefits of electrochemistry (such as simplicity, high sensitivity and specifity) with distinct features of nanoparticles (such as electronic, optical, magnetic, and catalytic). A wide spectrum of nano electrochemistry subtype in detecting pathogens is electrochemical based nanomaterial biosensors which consist following types:

4-3 -1 Nanoparticles coating salmonella electrochemical biosensors

Dungchai et al proposed a sensitive electrochemical immunoassay for determination of S. typhimurium in which monoclonal antibodies were immobilized on polystyrene for catching bacteria by adding polyclonal antibody conjugate gold NPs to bind the bacteria in the presence of copper-enhancer solution and ascorbic acid.The copper released upon reduction was deposited on GNPs for direct measurement of S. typhimurium concentration by anodic stripping voltammetry, with the limit of detection 98.9 CFU/ml and the anodic current linearly depending on S.typhimurium concentration over a working range of 1.30×10^2 to 2.6×10^3 CFU/ml (Dungchai et al. 2008). Also, a reusable capacitive immunosensor involving ethylenediamine and gold NPs grafted on glass carbon electrode was developed for detection of Salmonella spp by Gong-Jun Yang et al in pork samples(Yang et al. 2009). The interaction of monoclonal antibody conjugated with Salmonella spp. was meticulously measured by electrochemical impedance spectroscopy with a detection limit of $1/0\times10^2$ CFU/ml, the linear relationship between change in capacitance and logarithm of concentration being obtained in the range of $1/0\times10^2$ to $1/0\times10^5$ CFU/ml (Yang et al. 2009). In an attempt to enhance the performance of electrochemical biosensor by CNTs, Jain et al immobilized CNTs functionalized monoclonal antibodies onto a glassy carbon electrode for S. typhimurium detection using electrochemical impedance spectroscopy based on change in charge transfer resistance and impedance. A detection limit of 1.6×10^4 CFU/ml was obtained with a linear

response between 10^1 and 10^6 (Jain et al. 2012). Recently, Huang et al provided amine-functionalized MNPs (AF-MNPs) for quick and high efficiency (88.5e99.1%) capture of both Gram-negative and Gram-positive bacteria from water, food matrices, and urine. A high-affinity adsorption toward myriad bacteria including Salmonella was shown to occur based on the electrostatic interaction between positively charged AF-MNPs and negatively charged sites of the bacterial surface. The amount of AF-MNPs, pH , and ionic strength were shown to be vital in mediating fast and effective interaction. The benefits of this method are short incubation time and high capture efficiency requiring no further modification of biomolecules on AF-MNPs. However, the major hazard is the relative lack of specificity when compared with some other methods using antibody conjugates (Huang et al. 2010).

4-3 -2 Nano wires coating salmonella electrochemical biosensors

Electrons in nanowires are quantum confined laterally and thus occupy energy levels that are different from the traditional continuum of energy levels or bands found in bulk materials. This unique characteristic of nanowire sensors made them significant among bulk or 3-D materials with advantages such as, low analyte volume, real-time detection, possibility to create portable and implantable devices (Hamidi-Asl et al. 2013). Earlier to the aforementioned sensors for Salmonella, Weeks et al developed a silicon nitride cantilever for detection of Salmonella enterica cells by monitoring the cantilever surface bending which was directly proportional to the amount of bacteria bound. This process was easily adapted to batch fabrication, and it can be used for detection of multiple pathogens(Weeks et al. 2003).

4-3 -3 The Amperometric biosensors

Amperometric biosensors are extremely employed in the field of electrochemical biosensors (Tomassetti et al. 2015). These devices evaluate the amplitude of a reduction or oxidation flow at a given particular potential over a fixed period of time (Hayat et al. 2014). Electrochemical biosensors based on amperometric detection incorporating a bienzyme and immunomagnetic beads, were utilized to detect E. coli O157:H7 and S.typhimurium (Velusamy et al. 2010). Immunomagnetic beads enhance the selectivity of amperometric biosensors. In this method Salmonella typhimurium was sandwiched between antibody coated magnetic beads and an enzyme labelled antibody. A magnet was then used to concentrate the beads onto the surface of a disposable graphite ink electrode in a multi well plate format. Cells were distinguished by the oxidation of the electroactive enzyme product and provided a LOD of 8×10^3 cells/ml in buffer in a total analysis time of 80 min(Velusamy et al. 2010). Due to the intrinsic sensitivity of current measurement ultra-sensitive amperometric microbial biosensors can be easily built.

4-3 -4 The Impedimetric biosensors

Electrochemical Impedance Spectroscopy (EIS) is playing a critical role in bio sensing. It was employed for detecting the growth of microorganisms approximately one century ago(Li et al. 2015). Among widespread food borne pathogens detecting Salmonella EIS has reached greet interest since Association of Analytical Communities International (AOAC) has accepted impedance technique as primary screening method for Salmonella in food in 1992 and as a final method of action for Salmonella in 1996 (Arora et al. 2011; Umesha and Manukumar 2015).Yang et al. also developed inter digitized microelectrodes as impedance sensors for swift detection of Salmonella as mentioned in previous section(Yang et al. 2009).

4-3 -5 The Conductometric biosensors

The use of conductive polymers, such as polyaniline, polypyrrole, polyacetylene, and polythiophene, has received considerable interest in the development of biosensors based on electrochemical immunoassay. The conductive polymer acts as the electrochemical transducer to exchange the biological signal into an electrical signal for sensing and industrial purposes. Polyaniline in particular, has been one of the most widely investigated conducting polymers, because of its excellent steadiness in liquid form, consisting electronic properties, and high biomolecular interactions(Alocilja and Muhammad-Tahir 2008; Muhammad-Tahir and Alocilja 2003). The lowest limit of salmonella detection was reported by Muhammad-Tahir and Alocilja as approximately 7.9×10^{1} CFU/ml within a 10 minutes measurement time with development of conductometric biosensor which normally, comprises two metal electrodes separated by a fixed distance and an AC voltage applied across the electrodes. During a bio-recognition event the alter of ionic composition and the change in conductance between the metal electrodes was calculated and enabled specific, low volume and near real-time detection mechanism (Umesha and Manukumar 2015).

4-3 -6 The Electronic nose biosensors

Balasubramanian and coworkers used a Cyranose-320™electronic nose system commercially available to identify S. typhimurium in inoculated beef samples. The volatile organic compounds derived from vacuum packaged beef strip was measured. Their results revealed that the electronic nose system was able to identify contamination of S. typhimurium in meat samples at a population concentration level higher or equal to 0.7 log 10 CFU/g (98). later Arshak et al., used an array of conducting polymer composite sensors, containing poly aniline and carbon black, to identify pathogens such as, Salmonella spp., B. cereus and

V.parahaemolyticus through production of an individual response pattern for each bacterium(Arshak et al. 2007).

Table 4 summarizes the main characteristics of reported electrochemical multiplex biosensors for the detection of pathogens in foods.

5. Commercial salmonella biosensors

Modernizations in biosensor technology have enabled many biosensors to be commercialized and pave the way to detect biomolecules onsite. Moreover, the emerging technologies of lab-on-a-chip microdevices and nanosensors offer opportunities for the development of new biosensors with improved performance. Commercial biosensors have, small size and simple construction that made them perfect for point-of-care biosensing. Apart from their use in clinical analysis, commercial tests are also used in environmental, food, and biothreat/biowarfare analysis (Bahadır and Sezgintürk 2015). Table 5 summarizes data of some commercially available biosensors.

6. Conclusion and future perspectives

An initial warning system for proper recognition of potential infections through foods is required to halt epidemics. The on time and preventive evaluation of bacteria presence in foods can hinder their effect before they become widespread public health concerns. This review shows that salmonella biosensors have been under extensive investigation over decades and that the literature update on recent advances in the development of biosensor systems evidences the tremendous advancements in this field based on their transducer properties as well as biorecognition elements. The suitable biorecognition elements

(enzymes, antibodies or nucleic acids) play a critical role in efficient biosensor configuration. Some biosensors based on antibody fragments evidence the great customizability due to recombinant synthesis methods. If there are enough funds and time is not a limiting factor, aptamers should be utilized as they display the greatest affinity towards their target analytes and are extremely stable. Furthermore, biosensors with high sensitivity can offer excellent tools for point-of-care pathogen testing to detect trace levels of bacteria that cannot be measured by conventional methods. Therefore, it can be concluded that myriad strategies have been developed which are popular in the field of biosensors, resulting in increased sensitivities and low limits of detection. Future researches on developing biosensors for this pathogen may help to fight with the food borne epidemics at a glance and move from the bench to the real world applications.

In order to asses salmonella in foods, Some electrochemical and optical biosensors have been commercialized. Nevertheless, commercial biosensors are just tips of the iceberg compared to the great amount of academic research on them. The intrinsic demerits (slow response, low sensitivity, and poor selectivity) using microorganisms as the biosensing element hider the widespread interest of this biosensors on the market. However, with the development of novel bio-recognition elements; such as aptasensors, salmonella biosensors are becoming really powerful in the field of analytical chemistry.

Salmonella biosensors due to non-specific cellular response to substrates typically suffer from a poor selectivity. With the development of biotechnology and the availability of accurate genome sequence of salmonella, we can genetically engineer them with specific metabolic pathways up-regulated or downregulated, thus providing enhanced selectivity. Another way to improve the selectivity of biosensors is to develop salmonella sensor arrays. The introduction of analyte to the sensor arrays will generate a finger-printed response

pattern. By combining with artificial neural network analysis, the target compound can be distinguished.

With the development of nanotechnology, nanostructured materials have been applied in biosensing because of their good biocompatibility, enhanced electron transfer property, and high surface area. Co- immobilization of salmonella and nanomaterials or nanostructured electrodes could potentially improve the sensitivity of biosensors. The use of micronsized electrodes to develop single devices would provide the insight of how analytes responds to various targets. Furthermore, with the development of lab-on-a-chip technique, the integration of analyte onto a microfluidic chip to develop a biotic-micro electromechanical system would supply a new research aspect in the field of biosensors because such systems only require minimal amounts of sample and provide good sensitivity in the detection of analytes.

Current methods of target immobilization on transducer have limitations which affect cell viability as well as cell function. Physical adsorption suffers from poor stability. A major disadvantage of immobilization is the additional diffusion resistance caused by the entrapment material, which would result in a lost of sensitivity. How to simply and successfully immobilize target without affecting their properties, has become a critical step. We can develop a simple immobilization method to achieve a bacterial monolayer with very strong adhesion to a surface and without losing any of its biological function.

As the world becomes seriously concerned about the effect of food on public health and the safety against bio-war the aforementioned prospects will be a breakthrough in targets immobilization and identification in biosensor field.

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Table 1. Overview of biosensors proposed for salmonella detection divided by the type of transducer.

Transducer		Recognition element	Analyte	Matrix	Analytical range (cfu/ml	LOD (cfu/ml)	References
Electrochemical	Amperometric	Antibody	Salmonella pullorum	_	_	100	(Liu et al. 2013)
		immunomagnetic beads	Salmonella pullorum	_	10^2 to 10^6	89	(Fei et al. 2015)
		Antibody	Salmonella enterica	Milk	_	538	(Brandão et al. 2015)
	Impedimetric	Aptamer	Salmonella	_	75 to 7.5×10^5	25	(Jia et al. 2016a)
		Aptamer	Salmonella Typhimurium	Spiked apple juice	10^2–10^8	3	(Sheikhzadeh et al. 2016)

		Antibody	Salmonella Typhimurium	Chicken	_	10^3	(Kim et al. 2015)
Optical	Fluorescent biosensors	Aptamer	Salmonella enteritidis	_	10^2 to 10^7	60	(Zhang et al. 2016)
		Aptamer	Salmonella paratyphi A	_	$1 _ 10^2$ to $1 _ 10^{11}$	$1 _ 10^2$	(Yan et al. 2015)
		Aptamer	Salmonella enteritidis	Milk	10^2 to 10^5	300	(Liu et al. 2015a)
		Aptamer	Salmonella typhimurium	_	50 to 10^6	35	(Duan et al. 2015)
	Colorimetric	Aptamer	Salmonella typhimurium	_	_	7.5×10^5	(Park et al. 2015)
		Phage	Salmonella typhimurium	fresh juice or milk	_	5×10^8	(Hu et al. 2016)
		Immunoassay	Salmonella pullorum	_	$4.4 _ 10^2$ to $4.4 _ 10^7$	$4.4 _ 10^1$	(Sun et al. 2015)

Table 2. Gold nanoparticles for detecting amplified and unamplified salmonella nucleic acids using non_functionalized or functionalized methods

Method	Microorganisms of interest	Sample type	Analysis time	Detection limit	Working range	References
Non_functionalized (Amplified nucleic acid)	Salmonella enterica	food	3-4h	2.6×10^{4}	2.6×10^{4} - 2.6×10^{11}	Fu et al. (2013)
	Salmonella spp	Culture	<8 h	2×10^{9}	2×10^{9}–2×10^{11}	Prasad et al. (2011)
Functionalizd (Amplified nucleic acid)	Salmonella enterica serovar Typhi	Culture	~1 h post-amplification	10^{3} CFU/mL	10^{3}–10^{5} CFU/ml	Qi et al. (2012)
	Salmonella enterica serovar Typhi	Culture	~8 h	~3.6×10^{11} copies/μL	_	Mollasalehi and Yazdanparast (2012),
Functionalizd (Un amplified nucleic acid)	Salmonella enterica	Nucleic acids	~15 min post-extraction	2.2×10^{4} copies/μL genomic DNA	2.2×10^{4}–3.8×10^{5} copies/μL	Kalidasan et al. (2013)

Table 3. Applications of DNA microarray assay for detection and evalucvation of salmonella in foods.

Food Source or Material	Material Detected	Type of Microarray Used (Source a/Dye)	Reference
Food	69 Salmonella virulence genes	Genotyping (Custom/Cy3)	(Zou et al. 2010)
Food	Salmonella serogroups	Genotyping (Custom, C/SG)	(Braun et al. 2012)
Food	46 Salmonella O serogroups	Genotyping (Custom/Cy3)	(Guo et al. 2013)
Pork	Salmonella enterica pathogenicity genes	Genotyping (Custom/Alexa Fluor 555/647)	(Hauser et al. 2011)
Chicken/Pork	Salmonella enterica probes	Genotyping (Custom/Alexa Fluor 555/647)	(Hauser et al. 2012)
Food	Pathogenic Escherichia coli/Salmonella	Genotyping (Alere/TMB)	(Fischer et al. 2014)

Table 4 .Electrochemical multiplexed detection of foodborne pathogens.

Methodology	Analytes	Sample	Analysis time	Detection limit	Reference
Impedance-based fieldable immunosensor	E. coli O157:H7 Salmonella spp		Response time < 1 min	10 cfu E. coli O157:H7	(Pedrero et al. 2009)
HRP-amplification-based DNA multiwell sensor Strips	Salmonella spp	Natural beach water	3 – 5 h	≤ 1,000 cells Karenia brevis	(Pedrero et al. 2009)
SPE-AP amplificationbased array DNA sensors	Salmonella spp		Total analysis time < 1 h		(Pedrero et al. 2009)

Table 5. Commercially available biosensors for salmonella detection. (Barthelmebs et al. 2010; da Costa Silva et al. 2013)

Company	Biosensor	Country
Michigan State University's electrochemical biosensor	Detection of E. coli O157:H7 and Salmonella in meat products in the USA	USA
Georgia Research Tech Institute	Detection of Salmonella and Campylobacter in the pork industry USA	USA
Molecular Circuitry, Inc.	E. coli O157, Salmonella, Listeria, and Campylobacter	USA
Ambri Ltd	Pathogens such as Salmonella and Enterococcus	USA
ANP Tech, USA	ANP NIDS biothreat/biowarfare handheld assays for biothreat/biowarfare agents like salmonella	USA

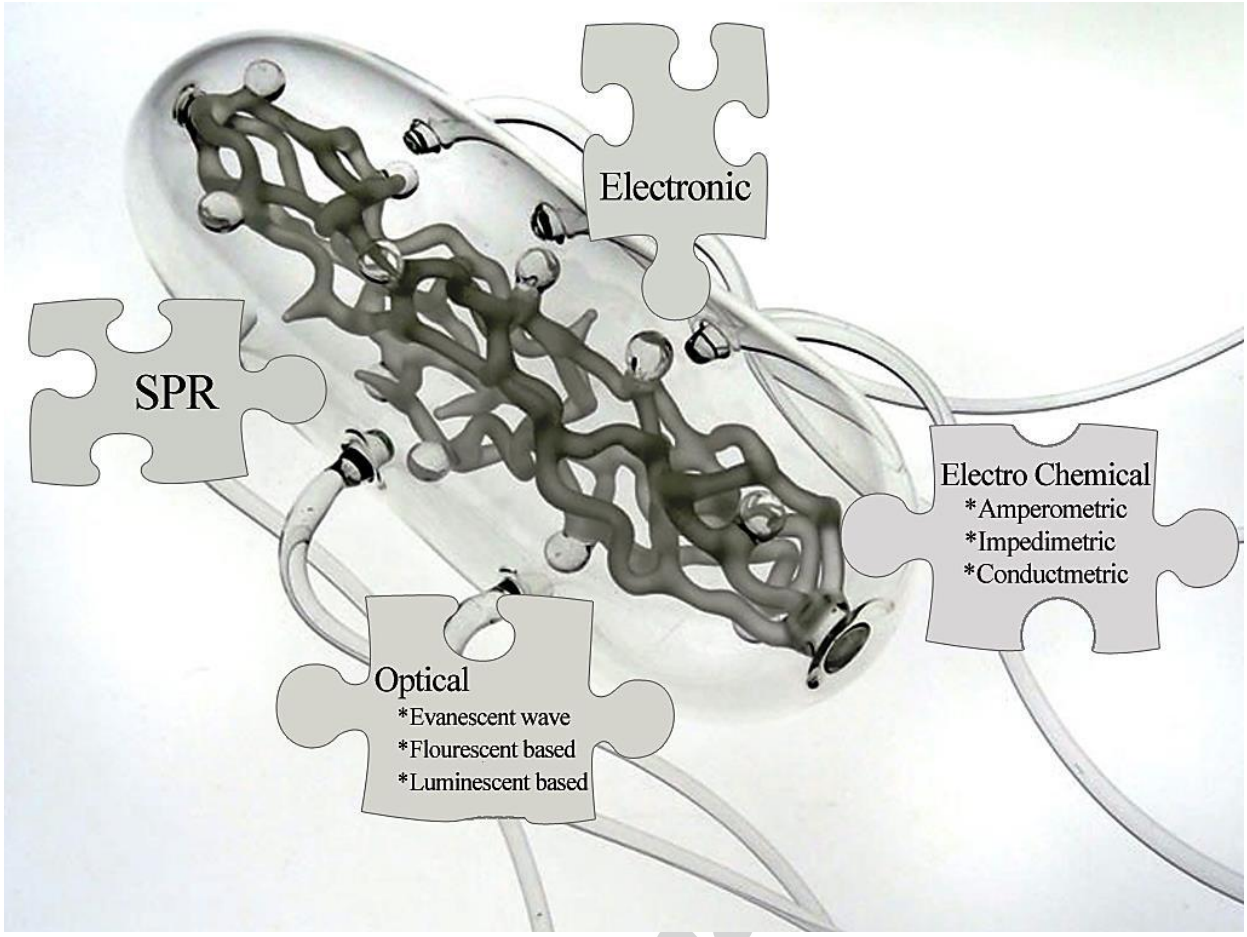


Figure 1. Schematic overview on different biosensor based methods for detection of salmonella infections

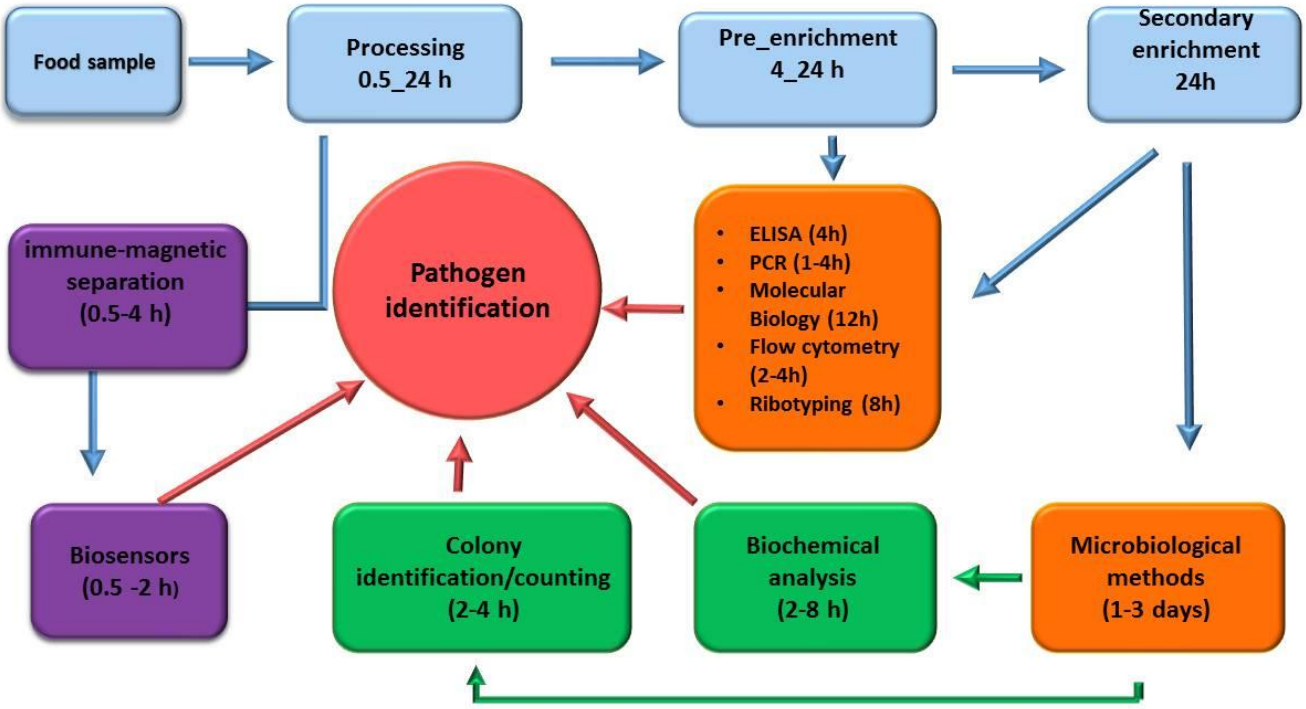
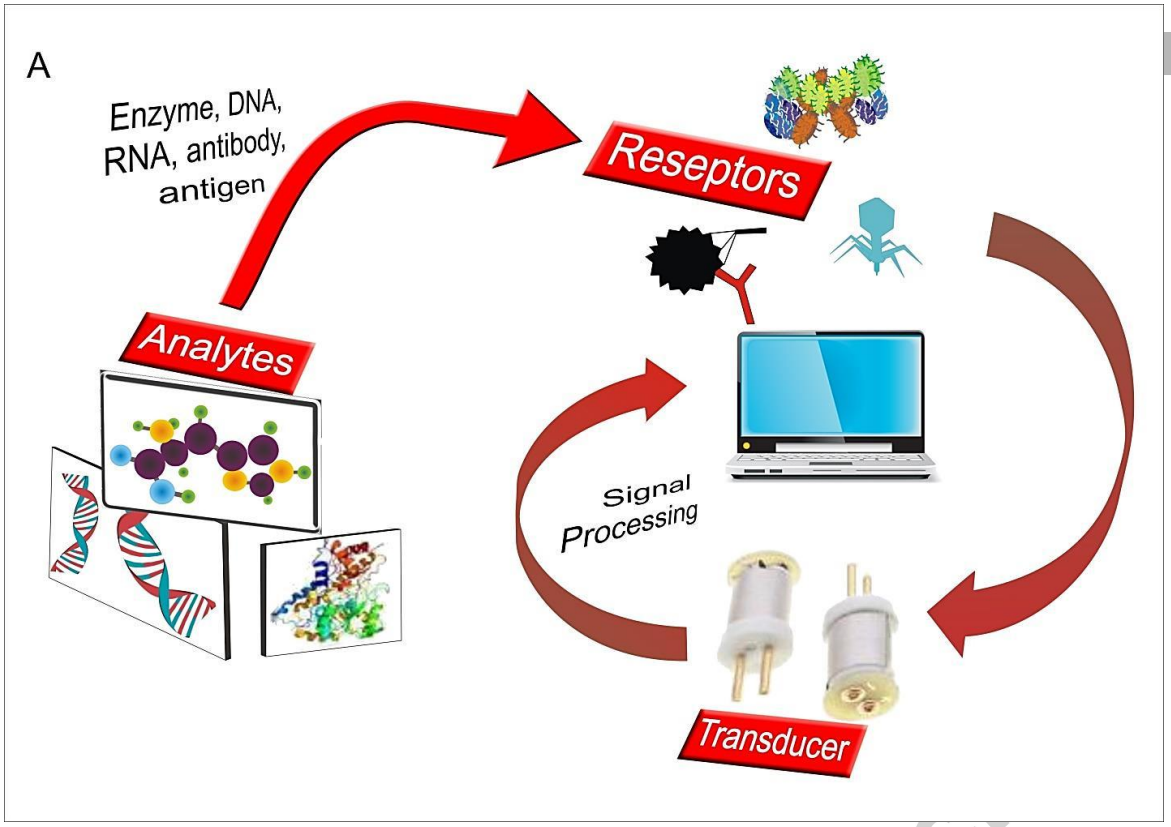


Figure 2. Methods available for pathogen identification


A
Enzyme, DNA, RNA, antibody, antigen
Reseptors
Analytes
Signal Processing
Transducer

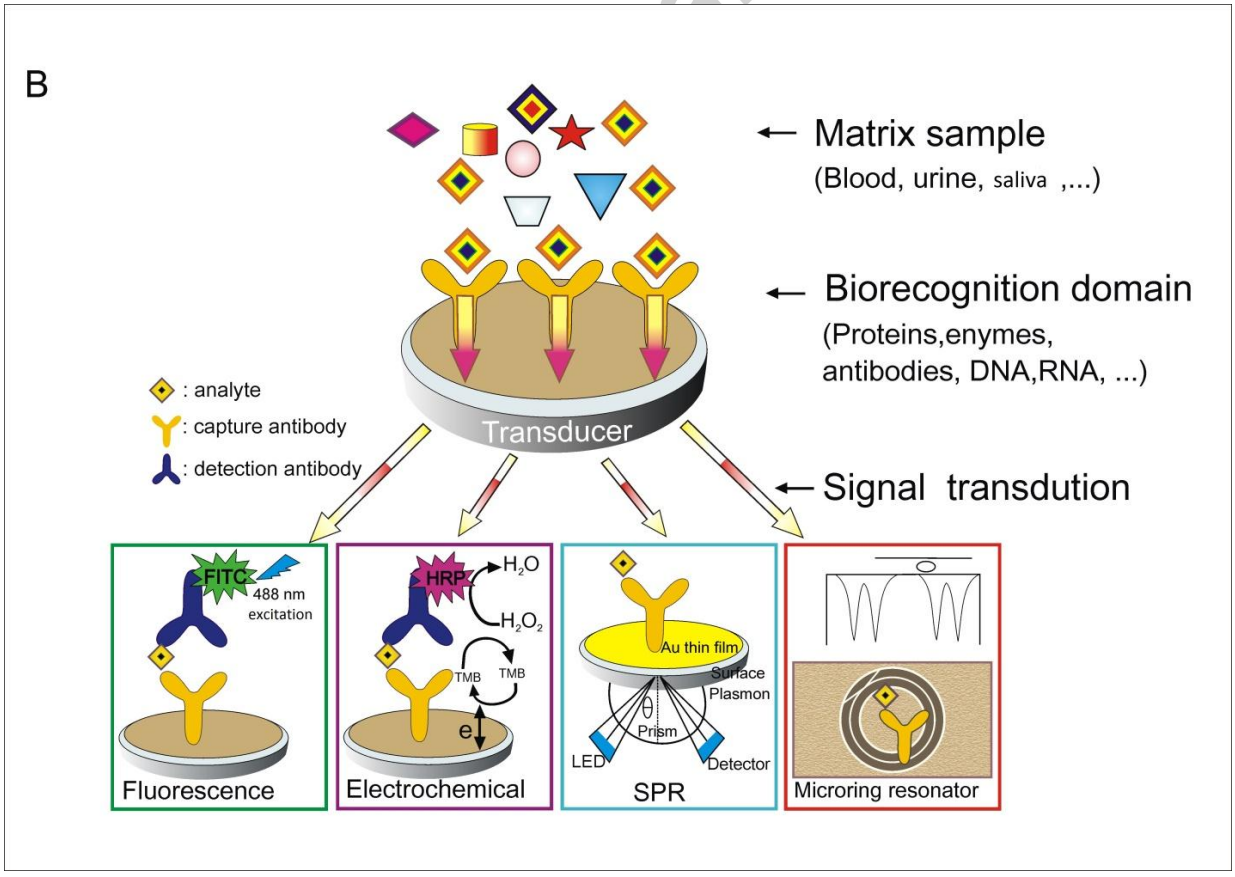

B
Matrix sample
(Blood, urine, saliva ,...)
Biorecognition domain
(Proteins,enymes, antibodies, DNA,RNA, ...)
Transducer
: analyte
: capture antibody
: detection antibody
Signal transdution
FITC
488 nm excitation
Fluorescence
HRP
H_2O
H_2O_2
TMB
TMB
e
Electrochemical
Au thin film
Surface Plasmon
θ
Prism
LED
Detector
SPR
Microring resonator

Figure 3 A) Biosensor structure with a scheme of its three parts: the biomediator sensitive elements, the transducer and the signal processor. B) The steps of the biorecognition process. Adapted from published papers (Liu et al. 2016a)

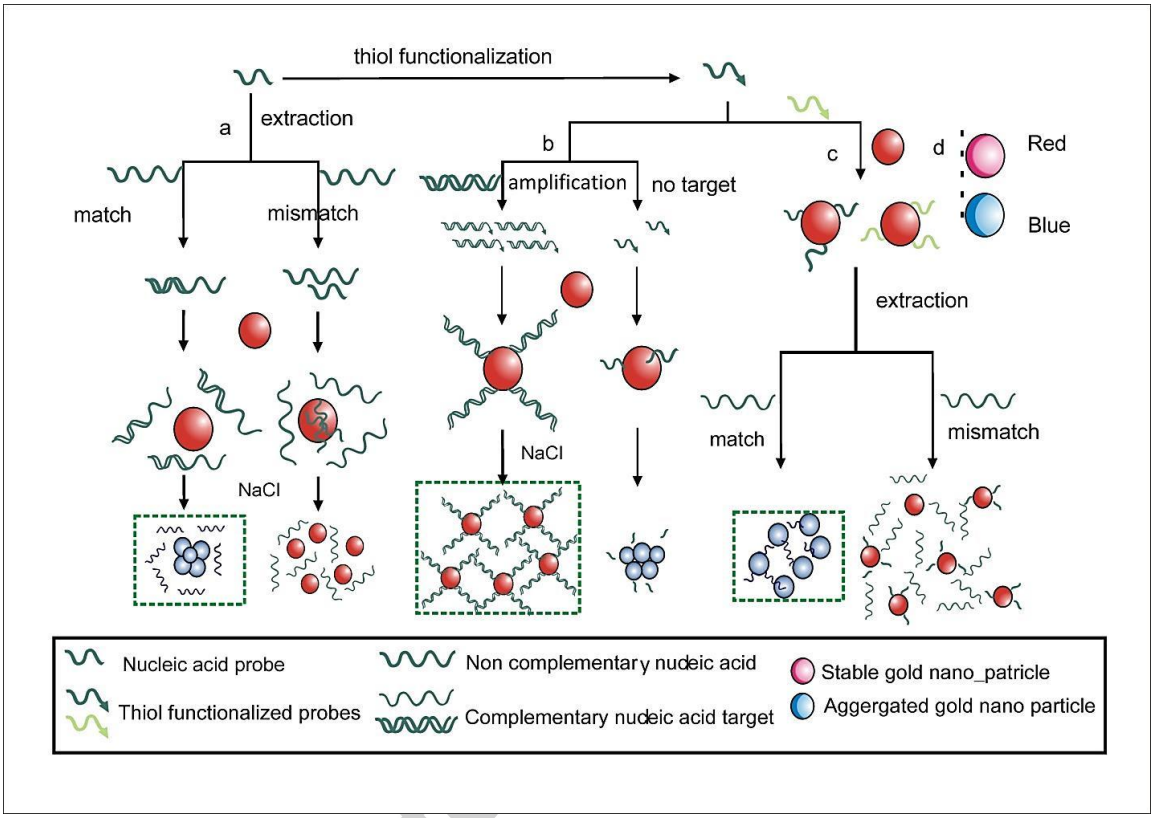


Figure 4. Scheme of the use of non-functionalized and functionalized gold nanoparticles for colorimetric detection of nucleic acids; A) Non-functionalized gold nanoparticles with the use of a single non-thiolated probe, B) Non-functionalized nanoparticles with the use of single thiolated probe, C) functionalizing gold nanoparticles with the use of pair of thiolated probes, D) red and blue digital image of gold nanoparticle. This figure was obtained with permission from reference (Verma et al. 2015).

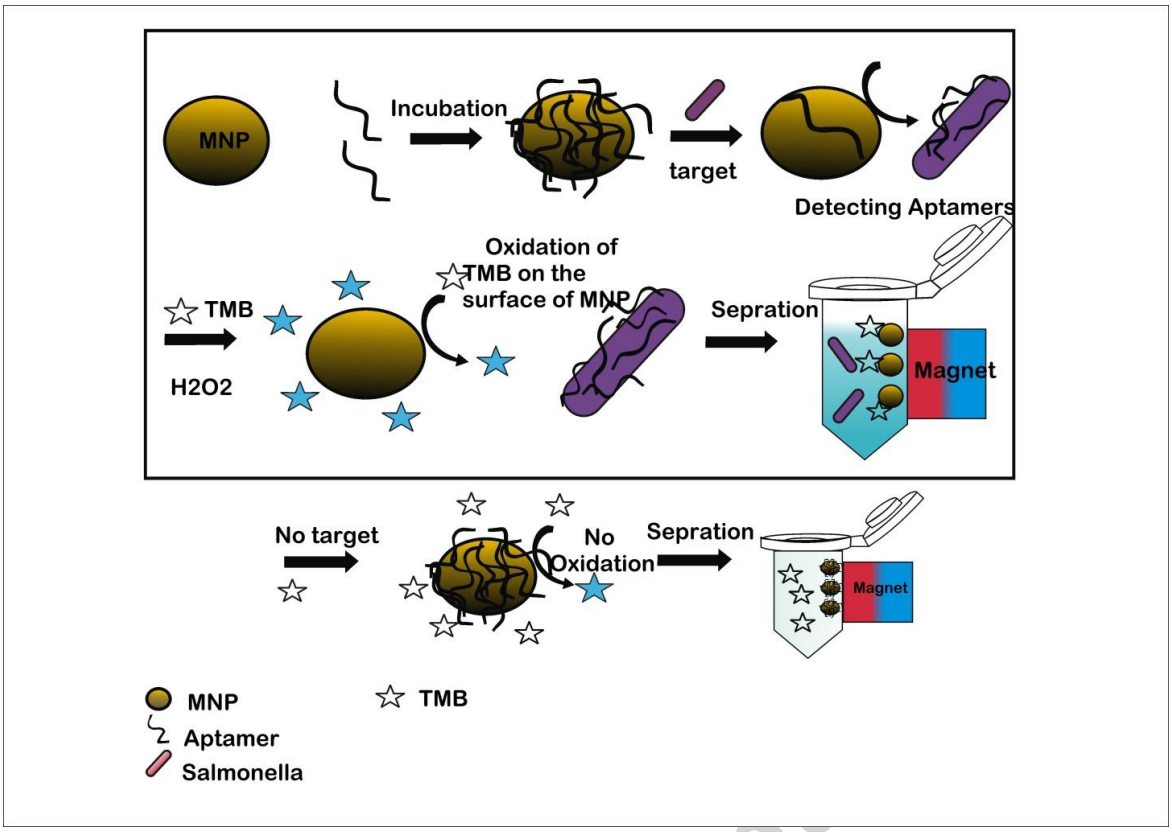


Figure 5. Scheme of the MNP-based colorimetric detection using label-free DNA aptamers and TMB. This figure was obtained with permission from reference (Park et al. 2015).

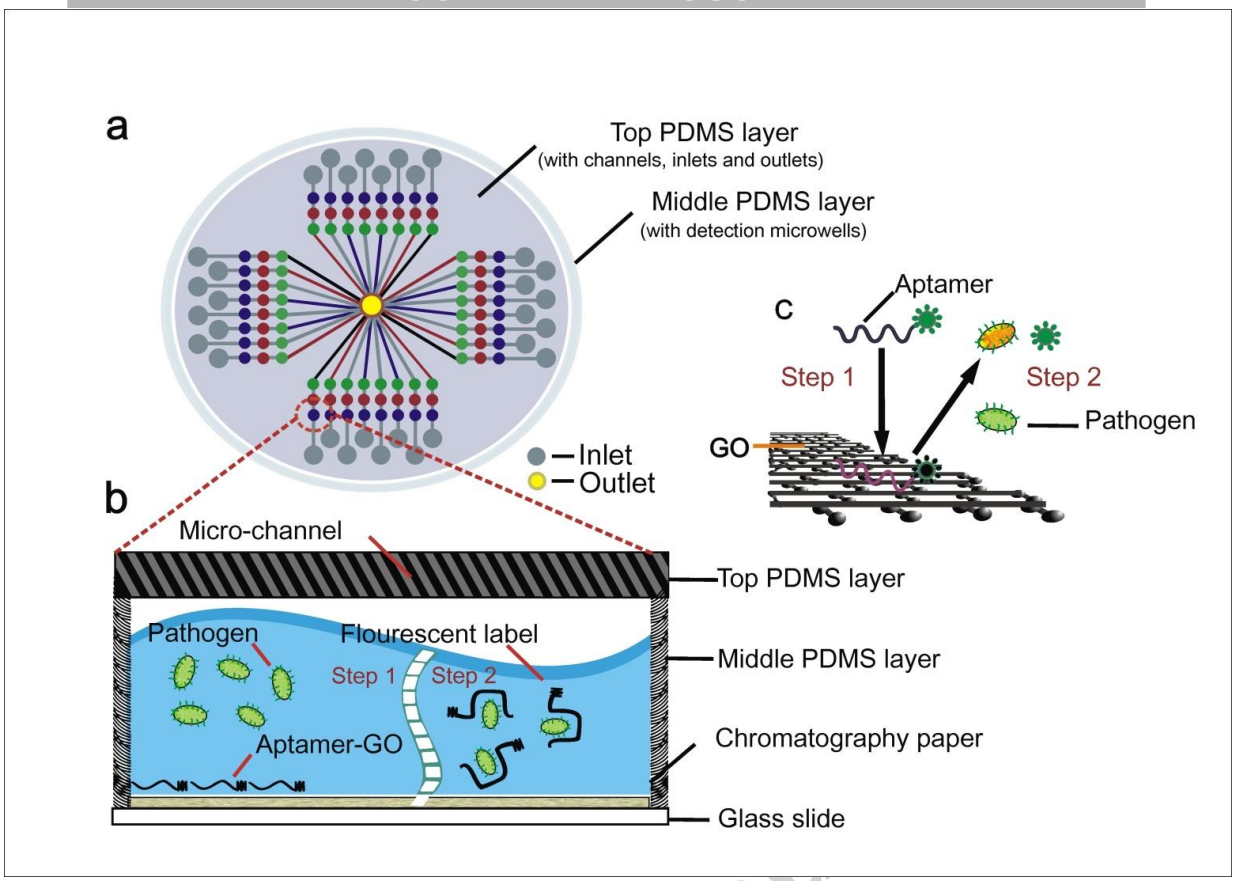


Figure 6. Scheme of the PDMS/paper hybrid microfluidic system for one-step multiplexed pathogen detection using aptamer-functionalized GO biosensor. This figure was obtained with permission from reference (Zuo et al. 2013)

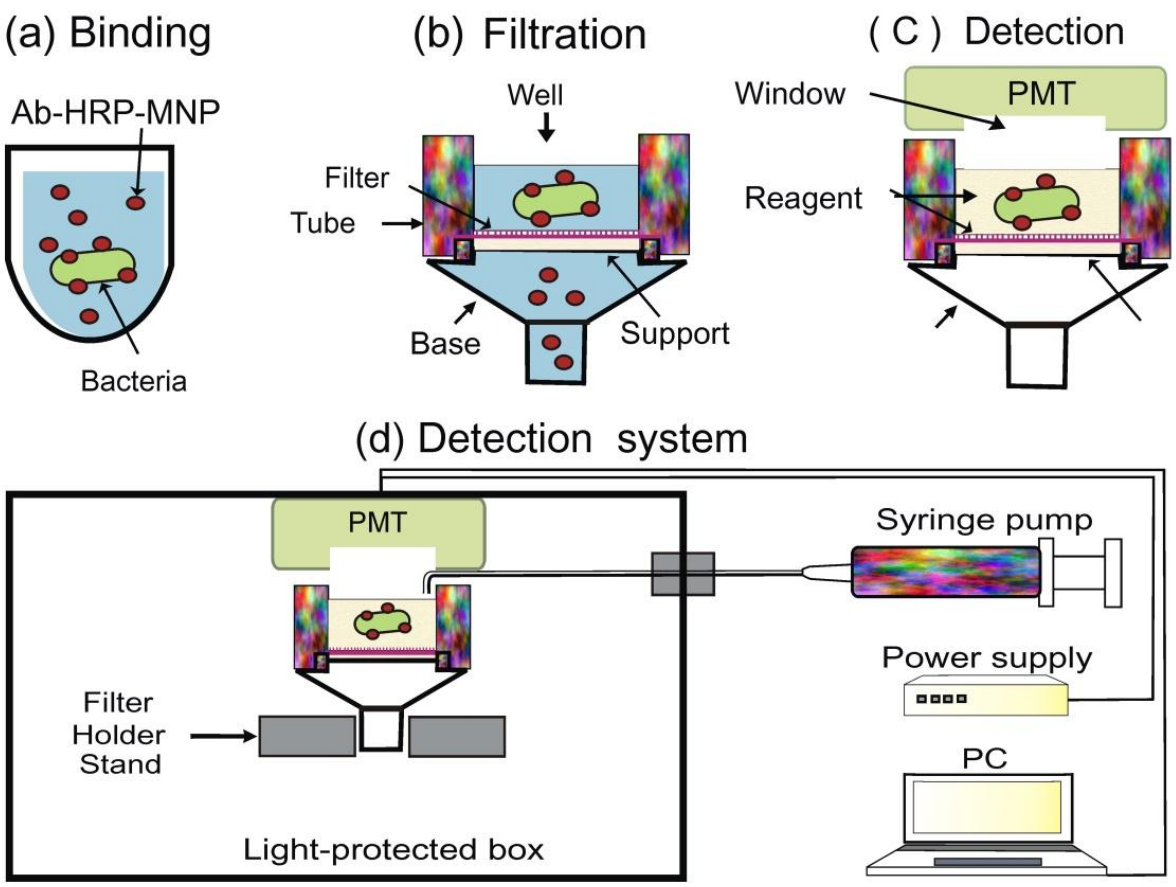


Figure 7. Schematic representation of the detection method and the detection system.This figure was obtained with permission from reference (Mun and Choi 2015)

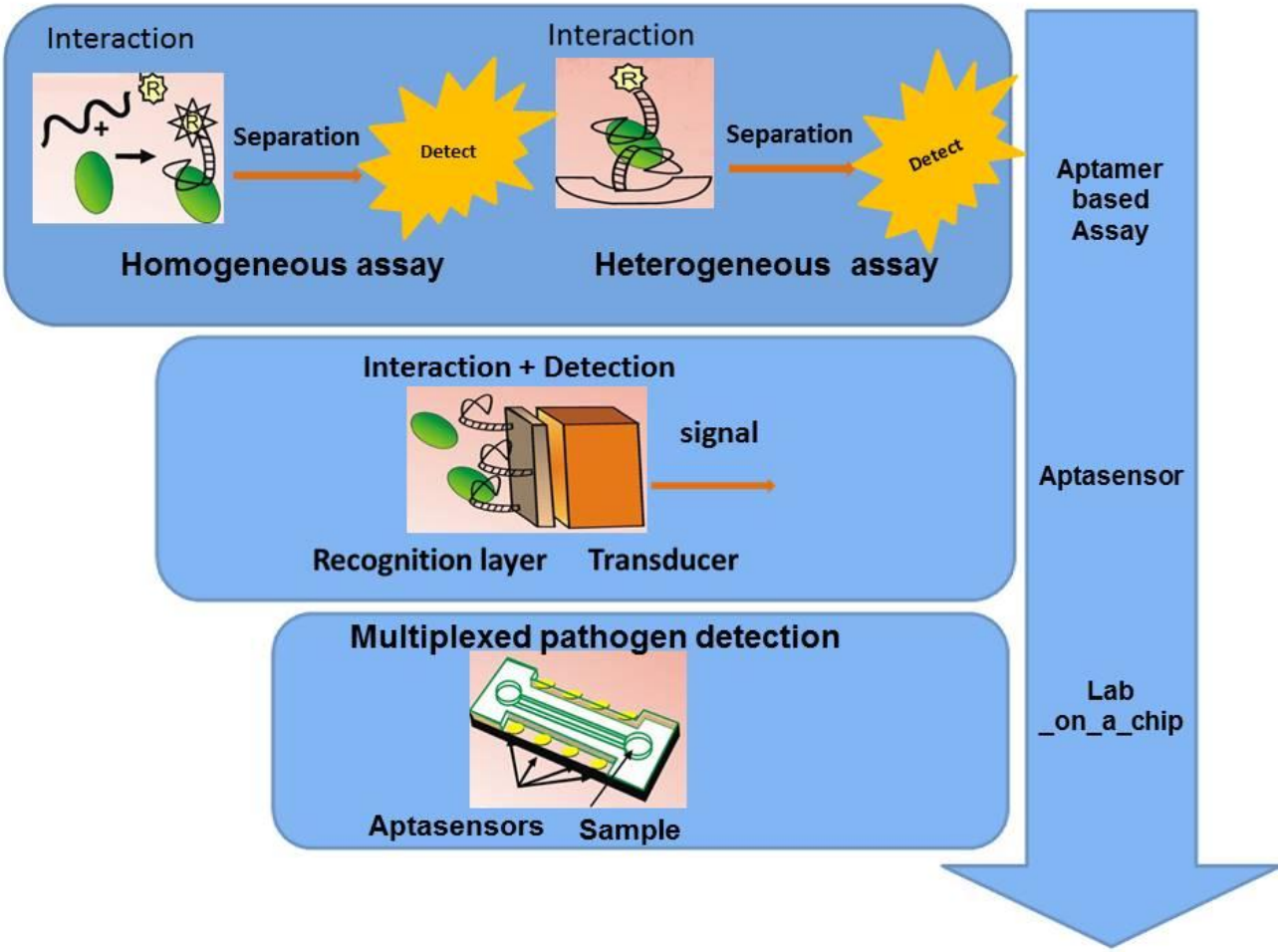


Figure 8. Different approaches of aptasensors. Adapted from published papers (Amaya-González et al. 2013)

Highlights

- A literature update on recent sensing methods to detect salmonella has been made.
- Merits and demerits of conventional salmonella sensing methods have been critically compared.
- Salmonella bio- and immune-sensors have been classified based on the transducer mechanism.
- Optical biosensors were commented, paying special attention to their coating with nano particles.
- Electrochemical salmonella biosensors in the nano and micro scale have been commented in detail.
- Commercial salmonella biosensors indicated the importance of detecting this pathogen.
- The role of nanotechnology and nanostructured materials in salmonella biosensing is undeniable.