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Chapter

Principle and Development of Phage-Based Biosensors

Umer Farooq, Qiaoli Yang, Muhammad Wajid Ullah and Shenqi Wang

Abstract

Detection and identification of pathogenic bacteria is important in the field of public health, medicine, food safety, environmental monitoring and security. Worldwide, the common cause of mortality and morbidity is bacterial infection often due to misdiagnosis or delay in diagnosis. Existing bacterial detection methods rely on conventional culture or microscopic techniques and molecular methods that often time consuming, laborious and expensive, or need trained users. In recent years, biosensor remained an interesting topic for bacterial detection and many biosensors involving different bio-probes have been reported. Compared to antibodies, nucleic acids and enzymes etc., based biosensors, bacteriophages can be cheaply produced and are relatively much stable to elevated temperature, extreme pH, and diverse ionic strength. Therefore, there is an urgent need for phage-based biosensor for bacterial pathogen detection. Furthermore, bearing high affinity and specificity, bacteriophages are perfect bio-recognition probes in biosensor development for bacterial detection. In this regard, active and oriented phages immobilization is the key step toward phage-based biosensor development. This chapter compares different bacterial detection techniques, and introduces the basic of biosensor and different bio-probes involved in biosensor development. Further we highlight the involvement and importance of phages in biosensor and finally we briefed different phage immobilization approaches used in development of phage-based biosensors.

Keywords: biosensor development, bacterial detection techniques, bio-probes, phage-probe, phage immobilization

1. Introduction

The risks due to bacterial contamination and infection to healthcare system and socio-economic stability as well as to environment and food contamination have become global issues [1]. The current approaches are usually not performing well in complex mixtures of opposing microorganisms and environmental conditions devoid of enrichment step. These approaches comprise old-fashioned plating and antibodies-based assays. Therefore, in the skipping of enrichment step, almost all present experiments are not satisfactorily sensitive to sense a distinct or a very small quantity of target bacteria [2]. In contrast, the approaches like hybridization-based assays (ELISA) and polymerase chain reaction (PCR) are sensitive; however, these cannot differentiate the live cells from the dead ones, thus require an augmentation

step for specificity and are laborious and expensive. These restrictions can be potentially overwhelmed by developing a biosensor. Biosensor development needs a specific and sensitive bio-probe that can withstand elevated temperature, extreme pH and remain active in diverse and complicated environment. Bacteriophages being sensitive and specific to host bacterium, and showing activity in diverse ionic concentrations are potent agents in biosensor development for detection of bacteria. Phages naturally deliver specificity in recognition of particular bacterial strain to attach, and specifically sense preferred bacterial spectra. Swift recognition offered by phage-based detection can improve the tracing and remediation of bacterial contamination [3]. The main issue that comes with development of phage based biosensor is active and oriented phages immobilization on substrate surface. The benefit of phage immobilization during biosensor development is that phages remain active for long time period, retain physiological activities with high densities, and having high bacterial cells capture efficiencies. Thus, showing improved detection limits that leads to possible development of phage-based biosensor for rapid and accurate bacterial detection [4]. Bacteriophage based biosensor development involve the following phage related approaches: (i) Observing the released phage particles during lytic cycle in the presence of host bacterium, (ii) monitoring released intracellular lysed cell component in the course of phage-mediated bacterial lysis, (iii) detection of inhibited bacterial growth in the presence of specific phages, (iv) use of stained phages for bacterial capture, and (v) observing the expression of cloned reporter gene in genetically modified phages that is expressed after bacterial infection [5].

2. Bacterial detection approaches

The conventional bacterial detection techniques such as colony count, biochemical and immunological procedures (ELISA) [6], and the modern (PCR) [7] approaches are currently widely in use; however, these approaches are time consuming as these need enrichment step. Consequently, there is a need to develop rapid and sensitive detecting methods. To this end, the use of biosensor, which can sense bacteria at diverse concentrations, are considered well applicable platform owing to their low cost, simplicity, and sensitivity [5]. **Figure 1** shows different bacterial detection approaches and **Table 1** summarizes comparative study of different bacterial detection methods.

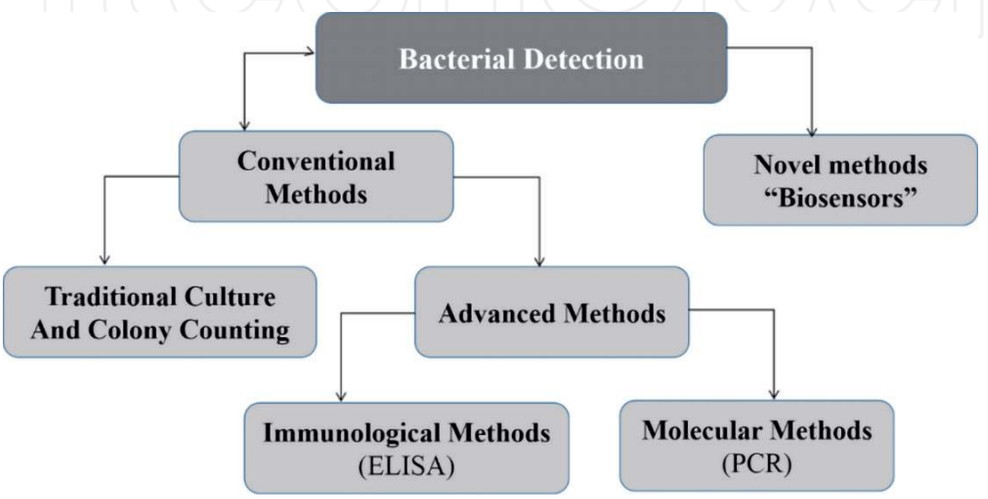

Figure 1.
Representation of various bacterial detection approaches.

Bacterial detection method	Personals	Cost and detection time	Tools	Live and dead cells detection	On spot detection	Ref.
Culture & colony count	Trained users, laborious	Cheap, 5–7 days	Simple	Yes	No	[2, 13, 14]
PCR	Trained users, laborious,	Costly, 1–4 h	Specialized	No	No	
ELISA	Trained users, laborious,	Costly, approx.: 4 h	High-tech	No	No	
Nucleic acids-based-biosensor	Simple, automatic	Expensive, 0.5–2 h	Simple	No	Yes	[2, 15, 16]
Antibodies-based-biosensor	Simple, automatic	Very expensive, 0.5–2 h	Simple	No	Yes	
Phage-based-biosensor	Simple, Automatic	Cheap, 0.5–2 h	Simple	Yes	Yes	

Table 1.
A comparison between culture and colony count, advanced molecular, and novel biosensors-based bacterial screening approaches, adapted and modified from [5].

2.1 Traditional culturing methods

In such methods, bacteria existing in a sample are cultured on different types of media so that to confirm their existence and isolate them. Two main culturing approaches are used, quantitative and qualitative. By qualitative culturing technique, the target bacterial colonies are produced on selective or differential media. In quantitative culturing technique, the specific bacteria are propagated to form specific colonies which can be calculated to evaluate the sum of microorganisms. Finally, different biochemical tests are performed [8].

2.2 Immunological methods

Immunological approaches, such as ELISA, depend upon the reaction of an antigen with a particular specific antibody. This method is unable to differentiate among living and dead cells and also antibodies production is very expensive [6].

2.3 Molecular techniques

Molecular procedures involve the use of DNA for the detection of target bacteria. For example, PCR, first pronounced in 1980s, is nowadays frequently used for detection of bacteria [7]. Molecular approaches are popular for their high sensitivity and rapidity. Dedicated apparatuses, skilled operators and expensive nature mark their rejection.

2.4 Biosensor

According to the proposed definition of biosensor by IUPAC, "Biosensor is a self-controlled imitated device, that is comprise a bio-recognition constituent (bio-prob/bio-receptor), connected to a transducer to translate the biological signal

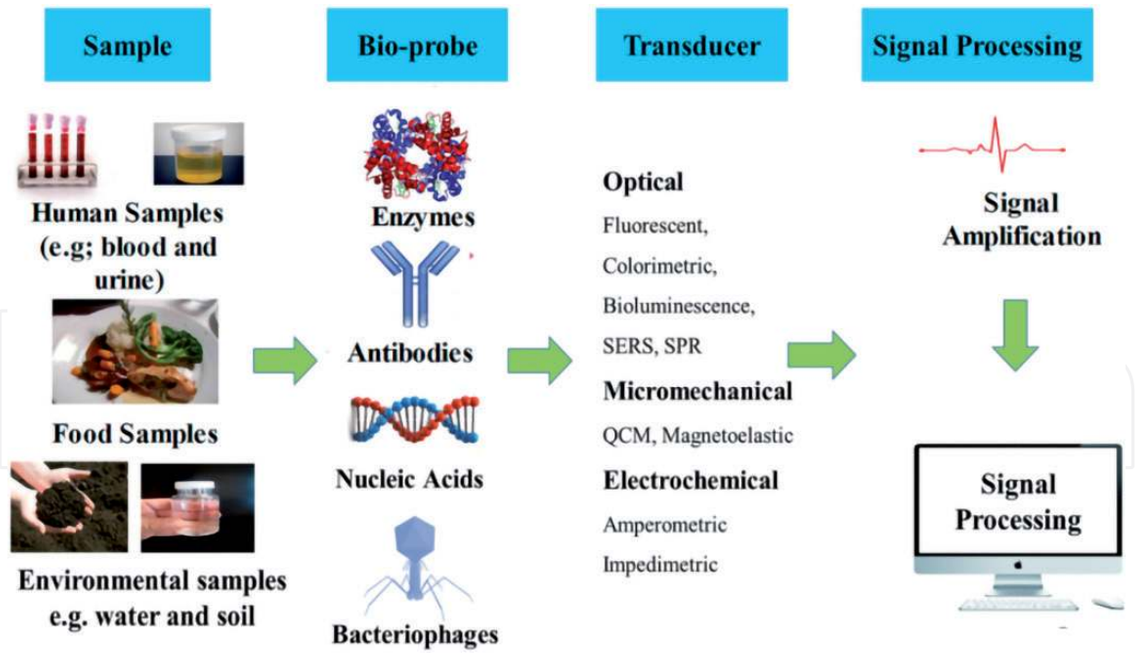

Figure 2.
Schematics representation of a generalized biosensors, reframed from [12].

into a computer readable signal and is then presented on computer and analyzed [9] (**Figure 2**). The bio-probes used in general are bacteriophage, enzyme, whole cell, nucleic acid and antibody. The transducer is electrochemical, optical, or mass based, or combination of these. Typical features of biosensors include; selectivity, reproducibility, detection limit, stability, biocompatibility, sensitivity and linearity [10]. Biosensors are commonly used in medical, diagnostic, quality control, veterinary, food and dairy industry, viral and bacterial diagnostic, agriculture industry, drug production, mining, industrial waste water control, defense and military [11]. Classification of biosensor is based on the recognition element, that is, bio-probe (bacteriophage, enzyme, whole cell, nucleic acid and antibody) used or the type of transducer (electrical, optical, or thermal signals etc.) involved. A representative biosensor is comprised of analyte (target to be sensed), bio-receptor (bio-molecule that identifies the analyte), transducer (responsible for signal transduction) and electronics (display the transduced signal) [5].

3. Bio-probes

As mentioned earlier, biosensor involves some biological recognition elements like bacteriophages [17], enzyme [18], whole cell [19], nucleic acid [20], and antibody [21], etc. These common bio-probe are briefed in the following sections:

3.1 Antibodies

To accomplish the requisite for up-to-date and fast bio-sensing schemes, antibodies (Abs) have become important affinity ligands to detect pathogens in clinical and food samples. Definitely, Abs when immobilized on a surface, these interact with specific antigens present on microbial surfaces, thus inducing a computable signal by an output detector. Abs popularity ascends from numerous benefits, for example, adaptability, ease of incorporation into diverse systems and are highly specific to their target antigens [21].

3.2 Enzymes

From the time of first biosensor (glucose sensor by Clark and Lyons in 1962), enzyme-based biosensors have shown immense progress in many applications. Enzymes are precise competent bioanalytical agents, having the ability to precisely mark out their substrates. This distinctive property mark enzymes potent implements in the development of analytical devices [18]. These biosensors company closely a biocatalyst-comprising a detecting coating with a transducer. Its operational principal is based on the catalysis and binding abilities for specific detection.

3.3 DNA/nucleic acid

The sequence of nucleic acids for a precise detection was established in 1953 and is still developing widely [20]. These biosensors involve nucleic acids as a bio-recognition-prob. The high specific binding between the two single strands of DNA (ssDNA) sequences to make double stranded DNA (dsDNA) sequence is used to develop nucleic acids-based biosensor. This technique validated to develop DNA-built-biosensor from the old-style technique like pairing of radio iso-tropic and electrophoretic separations that are costly, dangerous, and time consuming.

3.4 Cells

These biosensors involve living cells as a bio-probe and detecting component. They are constructed on the basis of living cell ability to sense the physiological parameters, and the extracellular and intracellular micro-environmental conditions, and as a result a response is produced by the reaction between cell and stimulus [19]. Microbial cells, for example fungi and bacteria are commonly used to develop whole cell based biosensors to sense particular molecules or the inclusive "condition" of the nearby environs.

3.5 Bacteriophages

Phages are virus particles, infecting and reproducing only within bacterial cells. Because of their associated evolution along with bacteria, phages have extremely specific machineries to identify and then infect their host bacteria for propagation. Phages generally have two distinctive chunks, the head comprising genetic material while the tail accountable to recognize and attach to bacterial cell [22]. Phages have several biomedical applications, and owing to their specificity they are extensively used for specific and sensitive detection of bacteria [23]. Most significant feature of phages is that they can only identify, and attack living bacterial cells. This exciting feature was well demonstrated by Fernandes et al., to detect viable, viable but not culture-able, or totally dead *Salmonella* cells on a biochip that was bio-functionalized with either phage or antibody as a bio-recognition element [24]. Interestingly dead cells were still capable to interact with the antibody, phage probes enabled a superior difference among viable and dead *Salmonella*. Additionally, some of phages are very specific and infecting only one bacterial specie [25]. This property will permit the recognition of target pathogenic bacterial species in a complex flora. Comprehensive explanation of bacteriophage based recognition elements employed as bio-probes in development of a biosensor to detect pathogenic bacteria, is outlined in the following section.

4. Bacteriophages in biosensor

A phage as a bio-recognition probe offers numerous benefits in rapid bacterial sensing [17] as they are: (•) extremely specific to their host [26], (•) ability of producing extraordinary titers of descendant phages, (•) tolerant to extreme environmental conditions like ultrahigh temperatures, organic solvents and wide-ranging pH compared to Abs, [27], (•) safe handling, (•) discriminating among dead and live bacteria as they proliferate only in live bacterial cells [28], (•) production in bulk are artless and economical. These compensations make phages as leading bio-recognition probes to develop biosensors for bacterial screening [15]. Frequently designed phage-based biosensor schemes comprise the association of whole phage or phage-constituents, infecting/capturing target bacterial cells and ultimately resulting in the production of electrical, colorimetric, fluorescent, or luminescent etc. signals, based on the available biosensing system. Hence, phages are demonstrating themselves as novel troupes for cheap, fast, sensitive and specific bacterial detection in comparison to other available platforms [29].

4.1 Reporter phage-probes

Reporter bacteriophages are genetically edited phages used to import and insert a specific gene into the genome of target bacteria. The foreign gene inserted to host bacteria is expressed, bacteria are marked based on available platforms as a colorimetric, optical, or as a fluorescent marker and thus bacterial screening is permitted [30]. Irrespective of, whether reporter bacteriophages are lysogenic or lytic, both can detect potentially the particular pathogenic bacteria. A number of genes, such as insertion of firefly *luc* or bacterial *lux* gene account for bioluminescence, β-galactosidase-*lacZ* gene, ice nucleation-*inaW* gene, and also green fluorescent protein (*GFP*) gene reported by researchers as reporter phages and detected many of Gram negative and Gram positive bacteria [31, 32].

4.2 Stained phages

Phages stained with different fluorescent dyes have been used for target bacterial detection involving various fluorescence sensing tools. Stained phage-probes can discriminate a target bacterium when they infect and attack host cells [33]. Like, phages were tagged with fluorescent quantum dots (QDs) and *E. coli* was detected at 20 colony forming units per mL in water samples within 1 h [34].

4.3 Lytic phages

Lytic phages infection results in cell burst and consequently intracellular organelles, descendant phages, and cell-lysis materials are released. Both the release of intracellular elements and released progeny phages provide a base to recognize the target bacterium [30]. For example, as a released cell component, adenosine-triphosphate can be detected through bioluminescence just after target bacterial cell lysis [35]. Also the amount of released progeny phages released after cell lysis by a particular phage is directly proportional to the amount of lysed cells and can be used for bacterial sensing [36]. The released progeny phages enumerated by various detection mechanisms such as plaque- or immuno assays, molecular methods like quantitative PCR (qPCR) and, or by isothermal nucleic acid amplification (ITNAA) [37].

4.4 Capturing phages

Phages that are immobilized on solid matrix can be utilized for capturing specific bacterial cell from contained samples. Bacteriophages have a many functionally active groups like hydroxyl group (—OH), aldehyde group(—CHO), carboxyl group(—COOH), etc., on their exteriors, giving them inimitable characteristics permitting their interaction with other materials and to interact with bacterial surface receptor molecules [38]. Consequently phages have been successfully used to capture particular bacterial cells from different samples [39, 40]. Like streptavidin actuated gold nano-particles were used to immobilize GM T4 bacteriophage particles. Delay in impedance was observed due to bacterial cells binding that marked as a sign for the existence of bacterial cells [41].

4.5 Phage receptor-binding-proteins

Some phage components display natural magnetism to host cell for example receptor-binding proteins (RBPs), but they are highly subtle to variations in environmental conditions. Phage tail bears RBPs and helps in binding to host bacterium, proceeding to insert its genetic material within the cell and cell infection is established [42]. RPBs bind to cell surface with help of specific polypeptide or polysaccharide sequences that are present on the cell surface. Poshtiban and colleagues activated magnetic beads by immobilization of RBP protein Gp047 (from phage NCTC12673). These functionally active beads were then utilized for *Campylobacter* cells withdrawal from samples of milk and broth of chicken [43].

5. Phages immobilization strategies

It's obvious from the literature that different approaches have been developed for immobilization of phages on surface of electrodes **Figure 3**. The common phage immobilization strategies on solid surfaces include physical adsorption [44], covalent bonding [45], entrapment of phages in solid matrix [46], etc.

The quantity of randomly oriented phages on solid surfaces is the most straightforward way for enhancing signal in bio-sensing scheme [47]. Deposition

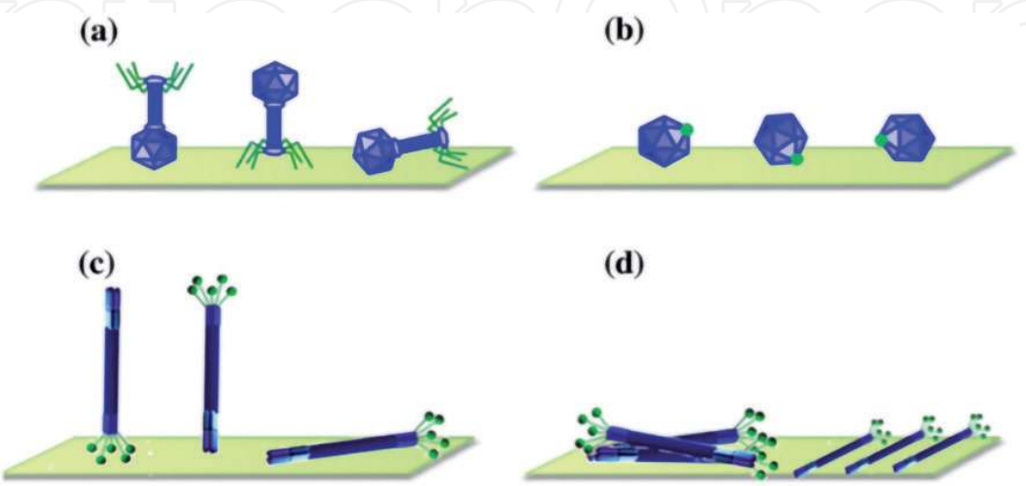

Figure 3.
Different ways to potentially orient phages on solid surfaces. Green highlighted-bacterial binding proteins, (a) tailed phages-side-ways, head-down, or tail-down, (b) asymmetric icosahedral phages, (c) filamentous phages-through either side-ways or, pole, (d) filamentous phages are likely to be bundled or aggregated (left). Oriented typically parallel on the substrate (right), adapted from [5].

of high number of phage particles creates a steric interruption between phage particles [39]. Thus number of phage particles immobilized on solid surface should not surpass a specific threshold per surface area [48]. For T4 phage, estimated optical density was 19 phages/ mm^2 area beyond that clogging was happened, resulting in reduced signal [49]. Phage particles can be simply oriented on the surface of electrode as they bear positive and negative potential on their tail fibers and head respectively. Phage immobilization strategies are briefly highlighted in the following context.

5.1 Immobilization by physisorption, electrostatic bindings and covalent bonding

Most common approach used for immobilization of phages is physisorption [50, 51]. This approach is very artless, but then again the adsorbed phage may possibly detach as of substrate surface because of shear, changes in pH, or temperature, or ionic concentrations caused in the medium that reduces principally their biosensing applications. Subsequently most phage particles having net negative charge at pH 7 [52], a number of investigators successfully used electrostatic binding for phages immobilization **Figure 4,** [52]. Also this methodology suffers due to variability and bacteriophage detachment in turn to the physico-chemical fluctuations in the analyte medium. Covalent bonding of phages offered a more stronger attachment and is not at risk to easy detachment of phages [53, 54]. Proper chemical studies can make easy selection of suitable substrate and then potential application. Covalent attachment resulted in a sophisticated bacteriophage surface mass that is principally necessary for phage application in biosensor development [55, 56]. To design bioactive surfaces with phages, phage infectivity is important or at least phage should be able to interact with host bacteria or analyte; therefore, optimization is needed to reduce the effect on bacteriophage integrity during immobilization.

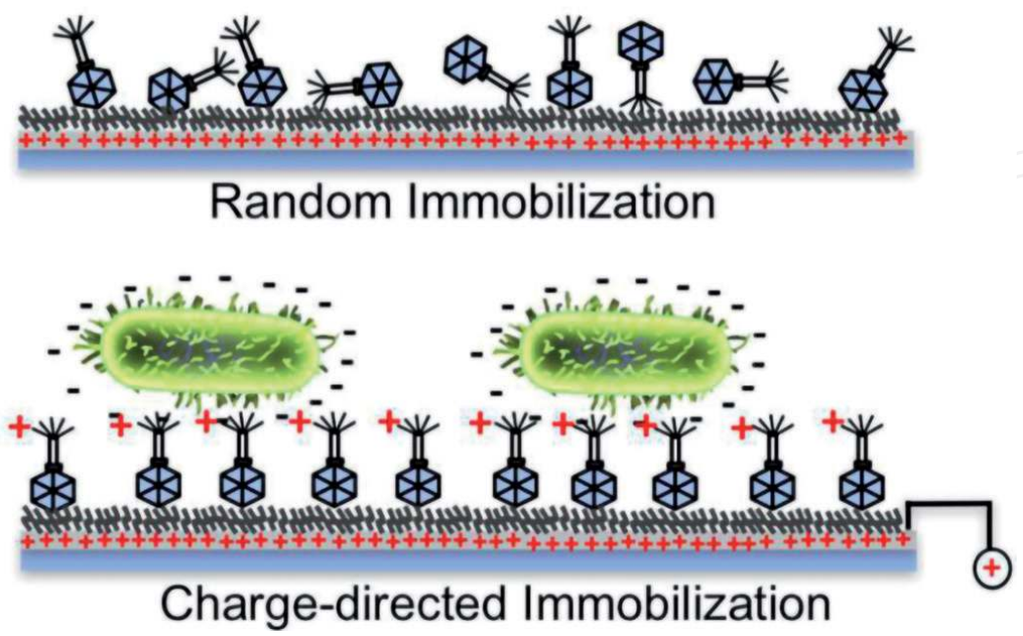

Figure 4.
Graphical representation of bacteriophage random immobilization and electrostatic, charge-directed orientated immobilization of T2 phage onto CNT electrode surface functionalized with polyethyleneimine (PEI) [57].

5.2 Phage display technologies

Bacteriophage-display tools can enable scientist to display peptides of choice present on the phage exterior, that is, phage envelope. Phages expressed peptide can consequently be adsorbed on material surfaces that are coated with peptides specific ligands **Figure 5**. Phage-display-libraries are produced by introducing DNA segments into specific phages to facilitate each phage to display a specific peptide expressed by the DNA segment inserted [58]. Technology of phage display developed as a combined influence of two central thoughts, fusion phage and combinatorial peptide libraries [59]. The first theory allows display of external peptides on bacteriophage surface [59]; while the second idea hires libraries of numerous peptides achieved in corresponding production as contrasting to production of single specific peptides [60]. Merging these two theories stemmed progress in phage-display-tools, multi-billion clone alignments of self-assembled and self-amplified bio-components [54]. It is significant to keep in mind that genetic alteration may alter the characteristics properties of bacteriophages. For example, biotin-carboxyl-carrier-protein (BCCP) gene or the cellulose-binding-module (CBM) gene to the small-outer-capsid-protein (SOCP) gene of T4 bacteriophage was attached, affecting bacteriophage infectivity, and result was decline in burst size, as well as extended latent period [61].

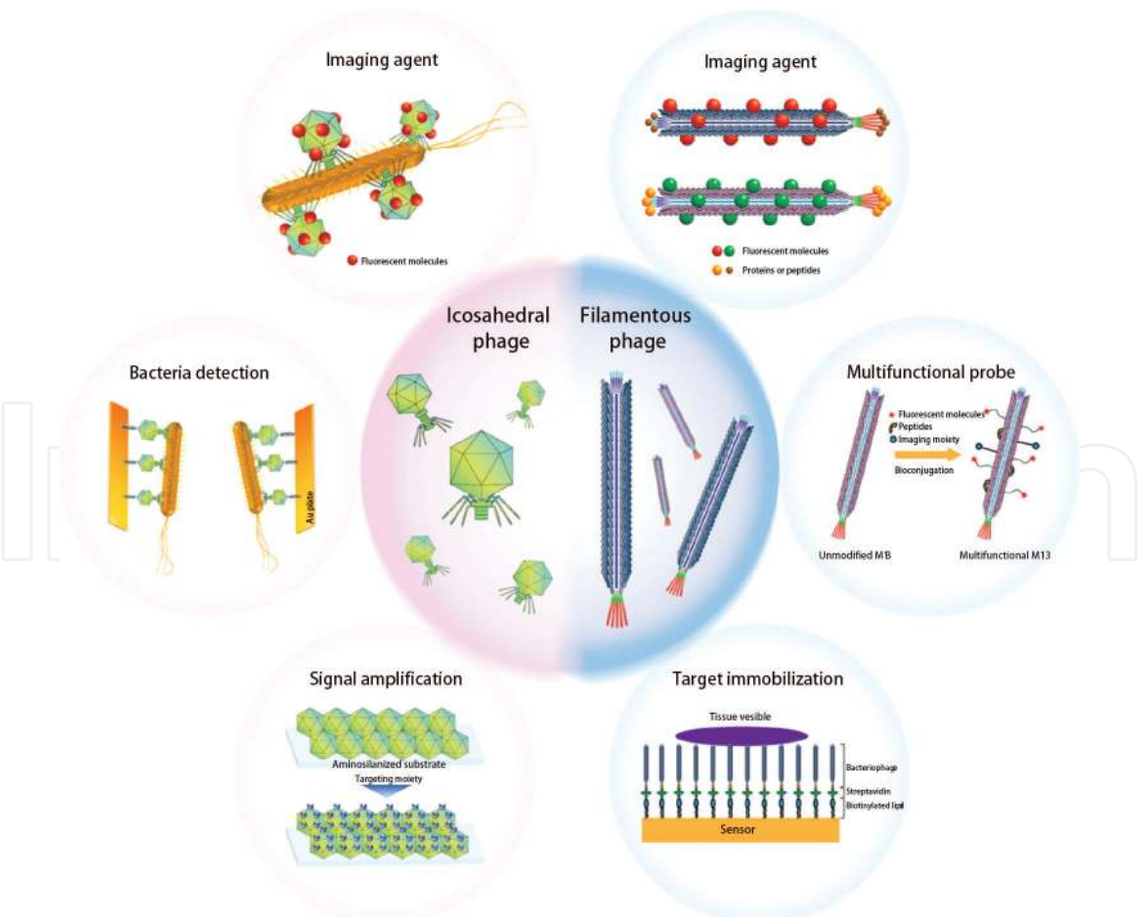

Figure 5.
Current applications of phage display technologies as imaging agents. Icosahedral phages are mostly used as, aiming on moieties for bacterial detection, and substrates for signal amplification. While filamentous phages are mostly used as multifunctional probes, and a variety of sensors [67].

5.3 Phage entrapment in porous matrix

Bacteriophages immobilization in micro-porous matrices permits them functionally and also structurally stable, keeping them active for long time period. Phages immobilization by entrapment in a porous hydrogel, (bio)polymeric agar and alginate matrices, is a tool for selection of applications where protection of phage particles essential against severe environmental conditions [62]. Additionally, entrapment might aid to maintain moisture, which is important for many phages infectivity, or keep phage particles in lyophilized condition [63]. A fruitful marketable case in point of entrapped bacteriophage in matrix is PhagoBioDerm [64] that is 0.2 mm thick, porous-polymeric-wound-dressing saturated with a mixture of biocides and lytic phages [65]. The matrices used for bacteriophage entrapment, that might possibly delay interaction of entrapped bacteriophage particles with host bacterial cells or analytes that are present in the vicinity of medium [66], marking inefficiency of phage bioactive surface.

5.4 Phage layer by layer organization

Many investigators discovered to possibly immobilize phages by alternative layering with polyelectrolytes having oppositely charges, and claimed observation of enhanced phage particle surface coverage [68, 69]. For instance, a layer by layer methodology for M13 bacteriophage was reported, and phage was sandwiched between oppositely charged layers of weak poly-electrolytes, that was capable to diffuse freely form a nearby packed phage monolayer [69].

5.5 Efficiency of immobilized phages in biosensing platforms

The effectiveness of bio-sensing approaches is mostly measured in terms of minimum limit of detection (LOD) of bacterial or other analyte. Thus researchers attempted and focused to improve the bacteriophage surface coverage for pushing detection limits. Significantly keep in mind that the LOD has not been improved biosensors where phages are immobilized by covalent binding, in comparison to the approaches where phage is immobilized by physisorption [22]. Thus, bacteriophage surface coverage is not only the factor to necessarily increase and improve the sensitivity and LOD of bacteriophage-based biosensor. Limit of detection of biosensors, based on various transduction approaches can be different depending on the working principle of selected transduction platform.

6. Conclusions and prospects

Without any doubt, environmental monitoring and food safety are the main universal worries that we humans have to oppose and are constantly struggling to take them over. In this chapter, we evidently demonstrated the principle and development phage-based biosensor. We compared the conventional phage based detection methods and briefed an introduction to different bio-probes involved in biosensors development. Further, we reviewed demonstrative phage/phage-components used in sensors development for pathogenic bacterial detection. Finally, we briefed different techniques to immobilize phages on appropriate substrate that is the major step toward phage-based biosensor development. We intend at thought-provoking and comprehensive explanations in mounting phage-based sensors and enlightening their uses for bacterial detection. By collaboration of engineers and scientists from multidisciplinary area to design a field applicable sensor and make advancements in phage-based sensors for bacterial pathogens diagnosis, we expect that this

chapter might bring together the technologies related to phage-based sensors. In short, phage based biosensors in the fields of food safety, environmental monitoring and infectious disease diagnostics is vital as they are;

- Cheap (based on easy phages production)
- Highly specific
- Very sensitive
- Versatile (based on phage components)

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Acronyms and abbreviations

Abs	antibodies
E. coli	*Escherichia coli*
ELISA	enzyme linked immunosorbent assay
ITNAA	isothermal nucleic acid amplification
IUPAC	International Union of Pure and Applied Chemistry
LOD	limit of detection
PCR	polymerase chain reaction
QDs	quantum dots
qPCR	quantitative polymerase chain reaction
RBPs	receptor-binding proteins
BCCP	biotin-carboxyl-carrier-protein
CBM	cellulose-binding-module
SOCP	small-outer-capsid-protein

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