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Application of biosensors to detection of epidemic diseases in animals

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Abstract

Epidemic diseases are the leading cause of animal mortality, resulting in significant losses to the agricultural economy. These economic impacts have generated a strong interest in advancing methods for the diagnosis and control of epidemic diseases in animals. Conventional methods are often time-consuming (typically result is available in 2 ~ 10 days), expensive, and require both large-scale equipment and experienced personnel. However, the advent of biosensor technology has ushered in a new and promising approach for the diagnosis of animal diseases. With advantages that include simplicity, real –time analysis, high sensitivity, miniaturization, rapid detection time, and low cost, biosensor technologies are under active development for the diagnosis of epidemic diseases in animals. Here, we summarize recent developments in biological sensing technologies used to detect infectious viral, bacterial, and parasitic diseases. Additionally, we discuss research challenges and future prospects for this field of study.

Keywords: epidemic disease; animal; biosensor technology; detection

Introduction

Presently, the status of international animal disease epidemiology is complicated by threats of both old and new infectious diseases. These challenges highlight the need for rapid and specific diagnosis, coupled with timely initiation of appropriate treatment in order to prevent and control the spread of these common animal diseases, thereby protecting human health and safety. Currently, a variety of physical, chemical, and biological techniques are employed to detect animal pathogens, and derivative technologies based on previous methods have been rapidly developed in response to the emerging epidemiological threats (Li et al., 2012). Conventional methods for the detection of infectious diseases are time-consuming and require centralized laboratories, large-scale equipment, and experienced personnel. These systems have been widely used and play an important role in the study and prevention of animal epidemics, but there is a need for improved sensitivity, specificity, and detection diversity.

Recent advances in biosensor technologies have the potential to deliver point-of-care diagnostics that match or surpass conventional methods with respect to sensitivity, selectivity, accuracy, and cost. Development of nanomaterials (Singh et al., 2017), electronic technique and microminiaturization accelerate the development of biosensing technique which provides a novel means to employ quick assays for use in basic medical research and clinical diagnostics (Du et al., 2014). Here, we review recent developments in biosensor technologies used for the detection of viral, bacterial, and parasitic infectious diseases in animals (Table1). We also discuss the critical challenges that need to be addressed to facilitate implementation of integrated diagnostic biosensors in real-world settings.

Types of biosensors

A biosensor is an integrated receptor-transducer device that uses a biological recognition element to provide selective, quantitative or semi-quantitative information. Most biosensor technologies employ a transducer that converts a biological recognition event into a detectable signal (Figure 1). The signal can be electrochemical or optical and displays the presence, concentration, or reaction process of the target biomarker in the analyte.

There are two primary mechanisms for classification of biosensor methods. The first level of categorization is based on the signal output and includes electrochemical, optical, piezoelectric, acoustic, and calorimetric biosensors. The second level of categorization is based on the method of detection and includes enzymatic, immunological, microbial, and cellular biosensors.

Detection of viral infectious diseases using biosensing techniques

Viral diseases can spread quickly among animals, leading to devastating economic consequences. Viral infection can cause lasting damage to an organism, and many viruses have high mortality rates in both animals and humans (He et al., 2016; Yu et al., 2012). Traditional methods for viral detection, such as polymerase chain reaction (PCR), enzyme-linked immunosorbent assays (ELISA), and serological assays, are expensive, time-consuming, and require specialized facilities with highly trained staff. As a result of these limitations, novel biosensing techniques have been created to facilitate detection of viral infections.

Avian influenza

Avian influenza is an acute infectious disease that has important clinical, economic, and epidemiological implications (Ginsberg et al., 2009; Huang et al., 2016). Avian influenza is induced by infection with the avian influenza virus (AVI) comprising the H5, H7, and H9 subtypes. Several studies have reported biosensor-based mechanisms for detection of AVI.

A miniaturized gold electrode biosensor was developed by Diouani et al. to facilitate electrochemical detection of the AVI H7N1 virus (Diouani et al., 2008). The sensor was created by immobilizing an AVI-specific antibody on a bio-functionalized gold electrode. Reaction with the AVI virus was characterized by impedance spectroscopy, providing reproducible results with a low limit of detection (LOD: 5 μg/mL). A similar assay using immobilized monoclonal antibodies directed against the H5 hemagglutinin protein was shown to capture AVI H5 subtype viral particles in specimen samples (Qi et al., 2010). In this case, the antibody-virus interaction was detected using an integrated microfluidic reactor system, combined with high spatial resolution imaging ellipsometry (IE). Changing concentrations of

AVI on the surface of the wafers altered the gray-scale on the IE image. A three-dimensional, magnetic bead-based microfluidic chip was also developed that could facilitate electrochemical detection of inactivated AVI H5N1 labeled with CdS quantum dots (Krejcova et al., 2014). Additionally, a low-cost impedance immunosensor was developed for rapid detection of the H5N1 virus in chickens (Lin et al., 2015). Specific monoclonal antibodies directed against the H5N1 virus, which were obtained by fusing mouse myeloma cells with spleen cells isolated from a H5N1-virus-immunized mouse, were immobilized onto electrodes. An electron-transfer resistor then detected changes in flow impedance when different concentrations of the H5N1 virus were captured on the electrodes. The linear range of the biosensor was from 0.2 to 20000 hemagglutination units (HAU)/50 μL with a LOD of 0.2 HAU/50 μL.

In addition to these antibody-based biosensors, DNA-based biosensors are also under development for the detection of AVI. For example, to detect AVI H7N9, Dong et al. developed a novel DNA tetrahedral nanostructure-based electrochemical biosensor that recognized a fragment of the hemagglutinin gene sequence (Dong et al., 2015). The probe DNA was immobilized on a gold electrode surface, where it self-assembled into a tetrahedral shape that ended with a long sequence of complementary oligonucleotides capable of hybridizing with the target ssDNA of AVI H7N9. The target ssDNA was biotinylated, and horseradish peroxidase-conjugated avidin was introduced, along with 3,3',5,5'-tetramethylybenzidine (TMB), to produce an amperometric signal. This electrochemical biosensor could distinguish the target DNA fragment of H7N9 virus from other types of influenza viruses with a LOD of 100 fM.

Porcine circovirus virus disease

Porcine circovirus virus disease is one of the four porcine diseases caused by infection with type 2 porcine circovirus virus (PCV2) (Allison et al., 2015; Chae, 2016). To develop a label-free, antibody-based PCV2 biosensor, Staphylococcal Protein A (SPA) was employed to modify a silanized fiber surface to enhance the proportion and bioactivity of a specific anti-PCV2 antibody (Luo et al., 2016). The resulting sensor could detect different PCV2 titer levels by monitoring the shift in resonance wavelength, resulting in a LOD of approximately

9.371 $TCID_{50}$/mL (TCID: tissue culture infectious dose); the saturation value was approximately 4.801 × 10^3 $TCID_{50}$/mL. A related biosensor was constructed by binding mercaptopropionic acid (MA) to a gold membrane by forming covalent bonds between the gold and the sulfur present in MA (Hu et al., 2014). PCV2 antibodies were then conjugated to the MA through the formation of covalent amide bonds. The LOD for this biosensor was calculated to be 0.04 μg/mL as determined by the observed change in delta response units for the surface plasmon resonance (SPR).

Blister stomatitis disease

Vesicular stomatitis virus (VSV) primarily affects cattle, horses, and pigs, and infection with this virus can cause blister stomatitis lesions. To facilitate real-time, sensitive, label-free visualization of VSV directly in a complex solution, an imaging technique was developed using graphene oxide to enhance the interferometric signal associated with VSV particles (Scherr et al., 2016). This assay combined the advantages of a single-particle reflectance imaging sensor with microfluidics. The sensor was capable of real-time, digital detection of individual 100 nm VSV particles as they bound to an antibody microarray. More recently, an interferometric reflectance imaging sensor was developed based on an N, N-dimethylacrylamide–acryloyloxysuccinimide–3(trimethoxysilyl)-propylmethacrylate composite (Lopez et al., 2011). This biosensor was capable of sensitively detecting intact VSV particles in a real time in a high-throughput setting with a LOD of 3.5 × 10^5 plaque-forming units/mL (PFUs/mL).

Porcine reproductive and respiratory syndrome

Porcine reproductive and respiratory syndrome (PRRS), commonly known as ‘blue ear disease’, can lead to reproductive failure in sows and severe respiratory distress in neonatal pigs (Arruda et al., 2016). This disease costs the swine industry hundreds of millions of dollars each year. To detect the presence of the PRRS virus, an optical biosensor was developed that recognized specific binding between SPA labeled with either a quantum dot or gold nanoparticle and the Fc fragment of the PRRS virus-specific antibody labeled with a fluorescent dye (Stringer et al., 2008). Interaction of the PRRS virus with the virus-specific

antibody results in a conformational change of the biosensor complex, leading to a measurable change in the fluorescence spectrum. The LOD of the proposed sensor was determined to be 3 viral particles/μL.

Infectious bursal disease

Infectious bursal disease, caused by infection with infectious bursal disease virus (IBDV), is an acute infectious disease in poultry that is highly contagious and leads to immunosuppression. A unique bioanalyzer for detecting IBDV was recently developed based on optical SPR (Hu et al., 2012). The analyzer consisted of a micro-flow cell, a temperature regulator, an integrated biosensor, an optical platform, and an electronic control unit incorporated into a photoelectric conversion device, as well as a universal serial bus interface circuit board. IBDV-specific antibodies were crosslinked to the surface of gold film with MA, resulting in a biosensor capable of detection of IBDV over a wide range of dilution factors, from 100 to 1600.

White spot syndrome virus

White spot syndrome virus (WSSV) is a major pathogen that affects the shrimp industry worldwide. This disease causes severe economic losses to the shrimp farming industry and can result in 100% mortality within a 3- to 7-day period. To detect this disease, a label-free, affinity-based immunosensor was developed using the WSSV-binding protein (WBP) immobilized on a gold electrode (Waiyapoka et al., 2015). The biosensor could quantitatively detect WSSV in shrimp pond water by measuring impedance of the biosensing surface, which changes (ΔZ") in real-time as copies of WSSV bind to WBP. The sensitivity of the immunosensor was reported to range from 1.6×10^{1}–1.6×10^{6} copies/μL.

Foot-and-mouth disease

Foot-and-mouth disease is a highly communicable disease caused by infection with the foot-and-mouth disease virus (FMDV) (Elnekave et al., 2015; Keeling et al., 2003). Livestock hosts include cattle, sheep, goats, and pigs. A rapid, label-free method of detection of FMDV has been developed using a surface-immobilized FMDV antibody (Bhatta et al., 2012).

Binding of the antigen to the antibody results in changes in the refractive index monitored within specific sensing channels.

Detection of bacterial infectious diseases using biosensing techniques

Anthrax

Anthrax is an acute, infectious, zoonotic disease that is caused by infection with the bacterium *Bacillus* anthrax. This pathogen affects herbivorous animals such as cattle, horses, and sheep; human infection can occur after contact with sick animals. The main forms of anthrax are cutaneous, gastrointestinal, and the most deadly form-pulmonary anthrax.

Huan et al. developed a biosensor using selective electrochemical detection for the diagnosis of anthrax (Huan et al., 2009). In this method, rather than a conventional antibody, a short chain peptide was immobilized on a gold electrode and used as a bio-detector; the peptide had the advantage of smaller size, improved ease of synthesis, and better biological stability. For comparison, the group tested a biosensor that replaced the peptide with a conventional antibody. Another assay developed for anthrax involves a label-free, real-time nanopore sensing method for the detection of anthrax lethal factor, a component of the anthrax bacterium (Wang et al., 2014). In this method, a complementary single-stranded DNA is used as a molecular probe. Hybridization of the target pathogen gene segment produces a modulation of the ionic current as the molecule passes through a nanopore. This DNA sequence-specific detection approach should prove useful as a model for the development of nanopore sensors for the detection of other pathogens.

Streptococcus suis

Streptococcus suis is a worldwide pathogen that primarily affects suckling and weaning piglets. Importantly, it is also a zoonotic agent, and humans can become infected after contact with diseased pigs or byproducts. Of the 35 serotypes of *Streptococcus suis*, type 2 streptococcus (SS2) causes the most economic damage to the pig industry.

An electrochemiluminescent immunosensor was developed for the detection of SS2 (Wang et al., 2013). To improve the detection sensitivity, a double antibody sandwich model was used in which antibodies were linked by chemicals that could produce a synergistic

catalytic reaction *in situ*. The biosensor was found to have a wide linear range for the detection of luminescence intensity and could detect logarithmic concentrations of SS2 ranging from 0.0001 to100 ng/mL with a LOD of 33 fg/mL.

Johne's disease

Johne's disease (JD), caused by the *Mycobacterium avium* subspecies *paratuberculosis* (MAP), is a chronic, and sometimes fatal, gastrointestinal disease in animals, especially domestic ruminants. The disease causes a significant economic impact on the global bovine dairy industry because infected animals shed viable MAP in their milk, making it unfit for human consumption.

To detect MAP, a conductometric biosensor was developed using purified MAP antigen immobilized on a conjugate membrane and an anti-bovine IgG linked to another membrane with polyaniline (Okafor et al., 2014). A silver electrode detected changes in conductivity that occurred when MAP antibodies found in the serum of infected animals bound to the immobilized MAP antigen. The group compared the sensitivity of their assay with a commercially-available ELISA kit and demonstrated moderate strength of agreement between the two assays.

Salmonellosis

Salmonellosis is a disease that affects many types of animals, as well as humans. It is caused by infection with the *Salmonella* bacterium. Pullorosis, a type of Salmonellosis caused by infection with the *Salmonella pullorum* bacterium, is one of the most serious disease threats affecting the poultry industry.

To detect the presence of *Salmonella* infection, a sandwich electrochemical immunoassay using immune magnetic beads (IMB) and reduced graphene oxide coated with gold nanoparticles (rGO-AuNPs) was developed (Fei et al., 2015). An antibody against the *S. pullorum* bacterium was conjugated to IMBs, and a secondary antibody was linked to rGO/AuNPs. The linear range of sensitivity for detecting the pathogen was from 10^2 to 10^6 CFU/mL with a LOD of 89 CUF/mL.

Detection of parasitic diseases using biosensing techniques

Schistosomiasis japonica

Schistosomiasis is a parasitic infection that is caused by one of three types of schistosome species: *Schistosoma mansoni, Schistosoma japonicum,* or *Schistosoma haematobium. Schistosoma japonica* (SJ) is the most infectious of these species and plagues humans, cattle, sheep, pigs and many other mammals (Wang et al., 2015).

A liquid phase piezoelectric immunosensor (LP – PEIS) was developed to detect SJ (Wen et al., 2011). In this assay, IgG antibodies were collected from rabbit serum after immunization with SJ. The purified IgG antibodies were immobilized on the surface of the piezoelectric quartz crystal of LP – PEIS using SPA. Based upon the change of frequency value in the sensor before and after the immune response, SJAg could be detected in infected serum samples. The positive detection rate of this biosensor was 100%, which was a higher rate of detection than that of a sandwich ELISA (92.8%). SJ antigens could also be detected by an enhanced sensitive biosensor designed to detect biological targets by tailoring the localized surface plasmon resonance properties of core–shell gold nanorods (Huang et al., 2011). After binding of goat IgG and SJ antigens, the gold nanorods were modified with a layer of chalcogenide to retain the bioactivities of the antibodies and enhance the sensitivity of this biosensor. The plasmon resonance wavelength of the gold nanorods could be red-shifted up to several hundred nanometers when attached to the biomolecule and chalcogenide shell. Human serum that was infected with SJ could be diluted to 1:50,000 (volume ratio, serum/buffer solution), and the antigen was still readily detectable with this assay.

Bovine babesiosis

Bovine babesiosis is a tick-borne disease caused by protozoa of the genus *Babesia.* In infected cows, parasitized blood cells may be present in the reticuloendothelial system. An impedance sensor was developed to detect the presence of antibodies to bovine babesiosis in the serum of infected cows (Silva et al., 2008). To create the sensing probe, a recombinant C-terminal portion of RAP-1 (*Babesia bovis* rhoptry-associated protein 1), obtained from the Portuguese strain of *B. bovis,* was immobilized on gold electrodes by the formation of a

self-assembly layer. Changes in the impedance spectra before and after an immune response were measured, and this change was used to determine the concentration of the *B.bovis* antibody in bovine serum. The results obtained using this biosensor were consistent with those obtained using ELISA.

Toxoplasmosis

Toxoplasmosis as a zoonotic parasitic disease is caused by the protozoa *Toxoplasma gondii*. The detection of antibodies specific to the toxoplasma parasite is an effective method for diagnosing toxoplasmosis. Based on detection of the *Toxoplasma gondii* IgM antibody (Tg-IgM), an electrochemical immunosensor was constructed to verify the presence of toxoplasma infection (Jiang et al., 2013). Thionine, used as a mediator, was electrodeposited on a glass carbon electrode modified with nafion-graphene. Next, gold nanoparticles and antigens specific to toxoplasma (Tg-Ag) were immobilized on the biosensing surface. To assess the presence of Tg-specific IgM, an enzyme-labelled antibody was coupled to the nanoparticles, followed by attachment of electrodes used to measure current in response to H_2O_2. Two linear ranges for the biosensor were determined to occur from 0.0375–1.2 AU/mL and 2.0–18 AU/mL; the LOD was 0.016 AU/mL (S/N = 3).

Conclusions and perspective

Animal epidemic diseases not only cause great economic losses to the animal husbandry industry, but they also pose a serious threat to human health and safety. Therefore, development of rapid and sensitive detection technology for early diagnosis is important to control the spread of these diseases. Modern biosensors exploit micro- and nanofabrication technologies using nanomaterials and microfluidics integrated into the techniques. Despite the need for these biosensors, translation of these assays from research laboratories to practical applications has remained limited to a few notable examples. There are many practical challenges, such as sample preparation, working lifetime, matrix effects, and system integration that impede mainstream implementation of these technologies. Addressing these technical problems will allow biological sensing technology to become an effective trace detection method that can be widely used to rapidly identify and diagnose animal diseases.

Competing Interests

The authors have declared that no competing interest exists.

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Figure Legends

Figure 1. A schematic representation of a biosensor. After the analyte contacts a recognition element on the surface of the biosensor, physical or chemical changes yield a reaction that is transformed into an electrochemical, optical, or other type of detectable signal. This information can be further processed to determine the concentration of the pathogen and changes in the composition of the analyte.

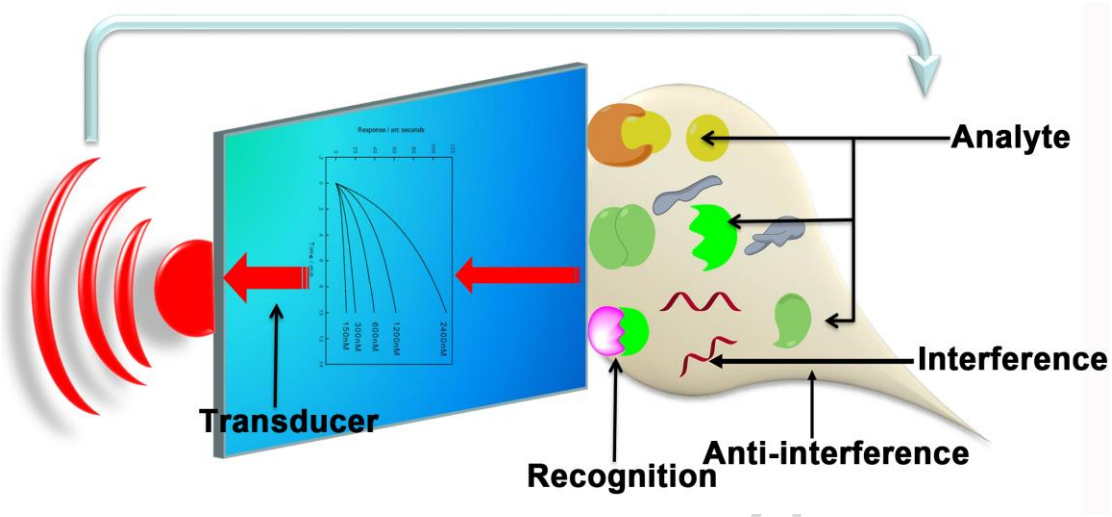

Fig. 1

Table1. Detection of animal epidemic diseases using biosensor technology

Analyst	Detection technique	Materials	Performance	Reference
Babesia bovis	Impedance spectroscopy	Gold electrode	Linear range: 16.7-500 μM	(Silva et al., 2008)
Toxoplasmosis	Electrochemical	Thionine, graphene	Linear range: 0.0375-1.2 AU/mL, 2.0-18 AU/mL LOD: 0.016 AU/mL	(Jiang et al., 2013)
AVI H5N1	Electrochemical	Microfluidic chip, CdS QD	Real sample detection	(Krejcova et al., 2014)
AVI H5N1	Impedance immunosensor	Interdigitated array microelectrode	Linear range: 0.2-20000 HAU/50 μL LOD: 0.2 HAU/50 μL	(Lin et al., 2015)
AVI H7N9	Electrochemical	DNA tetrahedral probe	LOD: 100 fM	(Dong et al., 2015)
PCV2	Optical	SPA modified silanized fiber	LOD: 9.371 TCID50/mL Saturation value: 4801 TCID50/mL	(Luo et al., 2016)
PCV2	SPR	MA modified Au film	LOD: 0.04 mg/mL	(Hu et al., 2014)
VSV	Imaging microscope	Graphene oxide	LOD: 100 PFU/mL	(Scherr et al., 2016)
VSV	Spectral reflectance	Layered Si-SiO_2 substrate	LOD: 3.5×10^5 PFUs/mL	(Lopez et al., 2011)

	imaging			
PRRS	Optical	QDs, Au nanoparticle	LOD: 3 particles/μL	(Stringer et al., 2008)
IBDV	Optical SPR	MA modified Au film	Dilution factor: 100-1600	(Hu et al., 2012)
WSSV	Impedance immunosensor	Gold electrode	Linear range: 1.6×10^{1}-1.6×10^{6} copies/μL	(Waiyapoka et al., 2015)
FMDV	Optical	Multi-channel sensor chip	Detection time: 3-5 minutes	(Bhatta et al., 2012)
Anthrax	Electrochemical	Short chain peptide modified gold electrode	LOD: 5.2 pM	(Huan et al., 2009)
Anthrax	Electrochemical	Complementary single-stranded DNA	Detection time: ～ 1 min.	(Wang et al., 2014)
SS2	ECL immunosensor	Double antibody and enzyme	Linear range: 0.0001-100 ng/mL LOD: 33 fg/mL	(Wang et al., 2013)
MAP	Conductometric	Uniform screen-printed silver electrode	Agree with ELISA	(Okafor et al., 2014)
Salmonella	Electrochemical	IMB, rGO-AuNPs	Linear range: 10^{2}-10^{6} CFU/mL LOD: 89 CUF/mL	(Fei et al., 2015)
SJ	LP – PEIS	SPA modified piezoelectric quartz crystal	Higher than ELISA	(Wen et al., 2011)
SJ	SPR	Core–shell gold	dilutions up	(Huang et al.,

	nanorod	1:50,000 detected	can be	2011)

Highlights

- Recent developments in biological sensing technologies used to detect epidemic diseases were summarized for the first time.
- Types and principle of biosensors were described in this paper.
- The performance of various biosensors were summarized in this paper.
- Research challenges and future prospects for this field of study were discussed.