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The Review of Biosensor and its Application in the Diagnosis of COVID-19

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Abstract. The objective of this article is to summarize the available technologies for biosensing applications in COVID-19. The article is divided into three parts, an introduction to biosensing technologies, applications of mainstream biosensing technologies and a review of biosensing applications in COVID-19. The introduction of biosensors presents the history of inventing the biosensing technology, which refers to the ISFET. The resonant biosensor with the example of MEMS. the principle of optical biosensor, and the thermal biosensor. In the second part, the main use of biosensing techniques, it was discussed the field of the food industry, environmental monitoring, and the medical industry. In the part of biosensor application in COVID-19, it was mentioned that the technique of POCT, the use of RT-LAMP-NBS in the early detection in China, and the use in gRT-PCR for the detection of the DNA code to determine the presence of pathogen of COVLD-19 in the human body.

1 Introduction

According to recent reports from WHO, by 6:02pm CEST, 22 April 2021, there have been 143,445,675 confirmed cases of COVID-19, including 3,051,736 deaths [1]. Moreover, the number of new cases has been increasing for 8 weeks continuously, the number of new deaths increased for 5 weeks continuously by 18 April 2021, 10 am CET [2]. Based on the current situation, there is an increasing demand for the ability to diagnosing COVID-19 to stop spreading. One possible method is the biosensor. It is not the first time that biosensor is used to test the virus: type A influenza virus can be detected by Surface Plasmon Resonance biosensor (SPR) [3]. This makes SPR a possible choice. Another choice may be an electrochemical biosensor (SPR is an optical biosensor) [4]. In fact, not only the two types of biosensor but also many other kinds of biosensors are currently or are going to playing increasingly important roles in preventing the spread of the virus, like point-of-care biosensors (POC) and the requirement have developed from detecting the virus inside the human body through the biological process to various requirements: Chip-based biosensor can produce results instantaneously [5], paper-based electrochemical biosensor has advantages in low cost [6], both 2 biosensors belong to POC [5]. And the target of detection maybe some environment that the virus could survive and spread, like sewage rather than suspected cases [7]. All those requirements ask for research and innovation toward biosensors. In This article, the definition, structure, classification, and application of biosensor would be introduced, and we will analyze and discuss how biosensors would help in the diagnosis of COVID-19.

2 Biosensor introduction

Biosensors are analytical devices that convert a biological response into an electrical signal [8]. In 1962, Clark invented the Clark oxygen electrode, which can be considered as the first biosensor. In general, biosensors are combinations of two parts: a bio element and a sensor element (shown in figure 1). Bio element can be something like enzyme, which interact with specific analyte; sensor element then converts the change of bio element to an electric signal (shown in figure 2). Depending on the transferring mechanism, the biosensors can be separated to many types such as: resonant biosensors, optical-detection biosensors, thermal-detection biosensors, ion-sensitive field-effect transistor (ISFET) biosensors, and electrochemical biosensors [9]. The first biosensor, the Clark electrode, is an electrochemical biosensor using Amperometry to determine the concentration of glucose.

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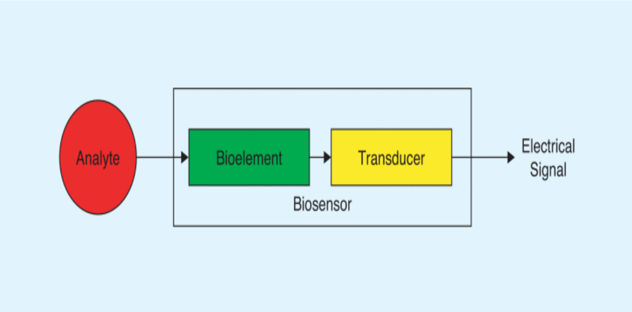

Figure 1. The general structure of biosensors [9].

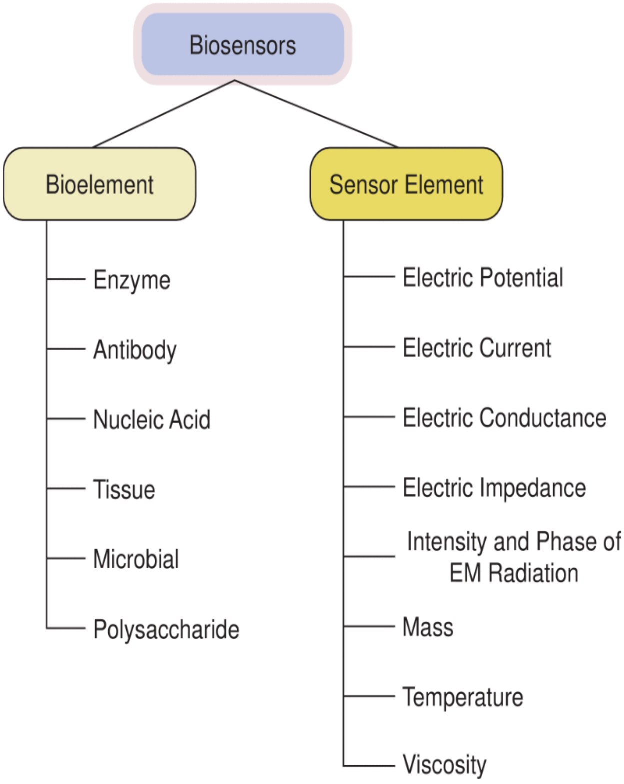

Figure 2. Elements of biosensors [9].

For resonant biosensor, the principle is to let the device coupling with the analyte (antibody or another bio element), then measuring the difference in physical property under the acoustic wave, like resonant frequency, the difference is related to the amount of attached analyte [9, 10]. An advantage of this biosensor is low cost, as it may use quartz in the acoustic sensor. An example is Micro/nano-electromechanical systems (MEMS), which have been used to detect Escherichia coli and vaccinia virus [10-12].

Generally, the principle of the optical biosensor is exploiting the interaction of the optical field with a biorecognition element, generating a signal which is related to the concentration of the analyte. [13]. An example is the Surface plasmon resonance biosensor (SPR), this biosensor was first constructed in research in 1983 [14]. The main advantages of the optical biosensor are that the test is real-time and sensible.

The thermal biosensor is based on detecting and analyzing the heat released during biochemical reactions [15]. The principle is to let the analyte contract the enzyme, causing heat reaction, and measure the change in temperature with temperature sensors, which is related to the amount of analyte that takes part in the reaction [9]. An example is the microelectromechanical systems (MEMS) differential thermal biosensor, which has advantages in thermal detection sensitivities and time responses [15].

Ion-sensitive field-effect transistor (ISFET) biosensor are semiconductor FETs having an ion-sensitive surface. When ions and the semiconductor interact at the surface, the electrical potential would change, which can be measured and is related to the ions (analyte) [9]. An application is using ISFET to monitor the PH change inside the human body, recording the PH change in different position of the digestive system [16].

As mentioned previously, the electrochemical biosensor is the earliest. The general principle of this type of biosensor is to make the analyte a part of an electrochemical cell and analyze its change through the change in some parameters of the cell, like potential or current. Based on that, electrochemical biosensors can be classified as potentiometry, voltammetry, Amperometry, coulometry, conductometry etc. A more current example is research in 2016, using voltammetry to analyze the DNA binding molecule, which is rapid, sensitive and low-cost [17].

3 Biosensor application

Biosensor could be used in many areas. In this paper, we will discuss its application mainly in terms of the food industry, environmental monitoring, and medical industry.

3.1 Food Industry

Food security and quality control are really important in the food industry, and biosensor is a reliable and efficient way. The biosensor can be used to measure many important nutrients in food, like the Tea polyphenols in black tea, protein in pure milk or dairy products, ethanol in alcoholic beverages etc. Or, on the other side, test the possible harmful substances, like bacteria in fresh meat [18]. An example of this is an electrochemical biosensor used to monitor the presence of urea in milk (structure shown in figure 3). This urea biosensor used urease to hydrolyze urea, forming ammonium ion and interact with an ion-selective electrode, then detected by potentiometric transducer [19].

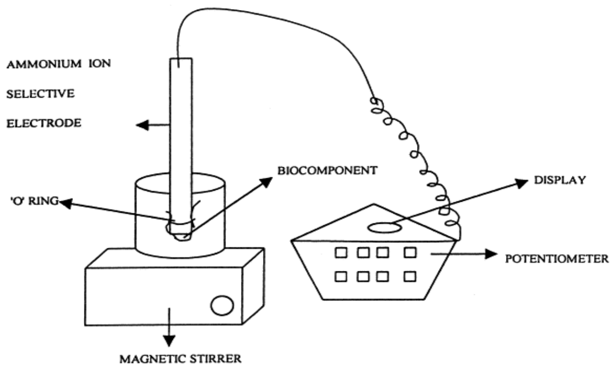

Figure 3. Structure of urea biosensor [19].

3.2 Environmental monitoring

Similar to the food industry, biosensor also has an advantage in terms of cost and efficiency in environmental monitoring, compared to the traditional analytical chemistry method like chromatography [20]. An example of this is the Biochemical Oxygen Demand (BOD) biosensor. BOD is used to measure the oxygen demand of wastewater, indicate the amount of biodegradable organic material (carbonaceous demand) and other important quantitative or semi-quantitative analytical information. The biosensor (as shown in figure 4) makes dissolved oxygen transport through the dialysis membrane and get consumed by the immobilized microorganisms. The remaining oxygen then diffuses through the gas-permeable Teflon membrane and get detected by the oxygen electrode [21].

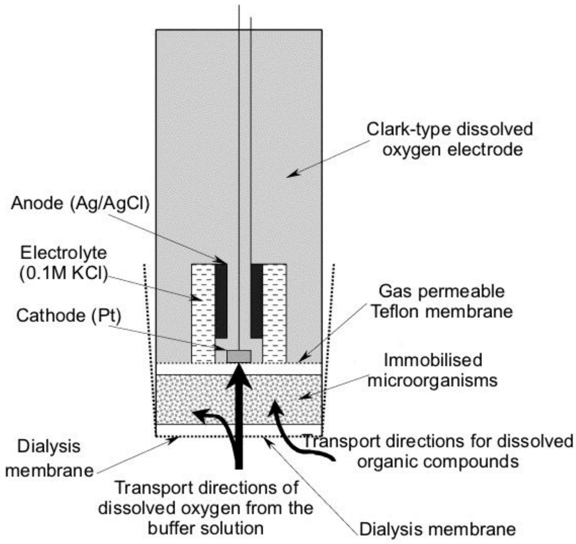

Figure 4. BOD biosensor [21].

3.3 Medical industry

The advantages in cost, like the previous two, also makes biosensor important in medial industry, especially the clinical diagnostics industry. The most common example of this is a single-use glucose strip for diabetic patients. Similarly, the biosensor can be used to monitor important analyte related to diseases, like lactate, urea, creatinine, and cholesterol [22]. Another medical application is the detection of biological agents, which may be not far from people's daily life, like Salmonella, Escherichia coli, Ricin and even some viral pathogens. These may be tested by antibody or some specific DNA fragments [23]. Further discussion will be made relating to COVID-19 in the later part.

4 Biosensor application in COVID-19

COVID-19, which originated in Wuhan, China, in 2019, is extremely widespread and has now been identified by experts as having the potential to become a cyclical epidemic like influenza. Because of the high infection rate, the low number of initial symptoms and the fact that effective agents and vaccines have only been developed in some regions, there is a need for early development of technologies that can easily detect the virus for early medical treatment of patients and to detect the presence of items carrying the virus in important transport channels.

In the early days, before COVID-19 had expanded globally, various inventions were already being developed in China to better detect the virus and to contain its expansion. Blood lactate biosensor used in the diagnosis and treatment of COVID-19. It is proposed that blood lactate level or lactate clearance is an important indicator for COVID-19 stratification, assessment of treatment efficacy and prognosis. The POCT (instant test) blood lactate biosensor is fast, economical, and reliable, enabling rapid and continuous blood lactate testing in clinical patients or individuals (families), facilitating COVID-19 disease severity stratification and assessment of treatment efficacy, as well as enabling patients to identify their condition promptly, relieving psychological concerns and promoting physical recovery [24].

Another invention that played the role in the early detection of COVID-19, is the invention of reverse transcription loop-mediated isothermal amplification combined with gold nano-biosensing in Hainan, China. This invention uses RT-LAMP-NBS for the detection of 2019-nCoV by designing two sets of LAMP amplification primers for the ORF1ab and N genes of 2019-nCoV and labelling the 5' end of the loop primer with a semi-antigen or the two sets of LAMP amplification primers were designed for the ORF1ab and N genes of 2019-nCoV, and the 5' ends of the loop primers were labeled with semi-antigen or biotin to achieve simultaneous detection of both ORF1ab and N genes. The detection system established by the present invention for 2019-nCoV has the advantages of high specificity, high sensitivity, and simple and rapid operation [25].

About a month later, in mid-April, COVID-19 broke out all over the world and became a global infectious disease. More and more comprehensive experiments have been realized, the trend of biosensor for large-scale detection of COVID-19 and the gene detection with qRT-PCR as the diagnostic standard of COVID-19 mentioned in the innovation (shown in figure 5). In RT-PCR, RNA is transformed into complementary DNA, and then the DNA signal is amplified by real-time PCR. In the extension stage of the PCR cycle, when more DNA copies are produced, the fluorescence signal will increase. When it exceeds the set threshold, the test result is positive. If there is no virus in the sample, the fluorescence threshold cannot be achieved, and the detection result is negative. The report also shows Isothermal amplification and point-of-care molecular diagnostics, CRISPR-based diagnosis, and DNA sequencing-based diagnosis of COVID-19 which are based on the bio-sensing technology to detect the antigens in the human bodies [26].

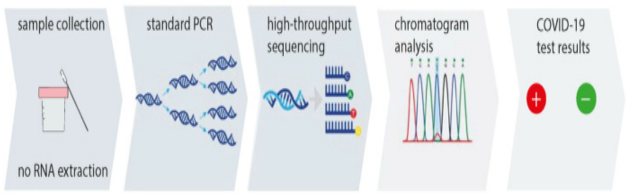

Figure 5. COVID-19 diagnostic whole-genome sequencing workflow [26].

5 Conclusion

To conclude, the biosensing technique becomes more popular in different kinds of fields in this century. There is a trend that the biosensing technique will be used more in the medical aspect and also in the industry aspect which detects the microelements that may affect human health. It will play an important role in the diagnosis, and probably other aspect, of COVID-19. We expect that this article can be helpful to researchers who are interested in this area, give them an basic understanding of biosensors.

Reference

1. “WHO Coronavirus (COVID-19) Dashboard,” World Health Organization, accessed April 23, 2021, https://covid19.who.int/
2. “COVID-19 Weekly Epidemiological Update,” World Health Organization, last modified April 20, 2021, https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---20-april-2021
3. Amano, Yoshihisa, and Quan Cheng. "Detection of influenza virus: traditional approaches and development of biosensors." Analytical and bioanalytical chemistry 381.1 (2005): 156-164.
4. Abid, Suhad Abbas, et al. "Biosensors as a future diagnostic approach for COVID-19." Life Sciences (2021): 119117.
5. Choi, Jane Ru. "Development of point-of-care biosensors for COVID-19." Frontiers in chemistry 8 (2020): 517.
6. Yakoh, Abdulhadee, et al. "based electrochemical biosensor for diagnosing COVID-19: Detection of SARS-CoV-2 antibodies and antigen." Biosensors and Bioelectronics 176 (2021): 112912.
7. Mao, Kang, Hua Zhang, and Zhugen Yang. "An integrated biosensor system with mobile health and wastewater-based epidemiology (iBMW) for COVID-19 pandemic." Biosensors and Bioelectronics 169 (2020): 112617.
8. Mehrotra, Parikha. "Biosensors and their applications–A review." Journal of oral biology and craniofacial research 6.2 (2016): 153-159.
9. Mohanty, Saraju P., and Elias Kougianos. "Biosensors: a tutorial review." Ieee Potentials 25.2 (2006): 35-40.
10. Fogel, Ronen, Janice Limson, and Ashwin A. Seshia. "Acoustic biosensors." Essays in biochemistry 60.1 (2016): 101-110.
11. Gfeller, Karin Y., Natalia Nugaeva, and Martin Hegner. "Micromechanical oscillators as rapid biosensor for the detection of active growth of Escherichia coli." Biosensors and Bioelectronics 21.3 (2005): 528-533.
12. Johnson, Luke, et al. "Characterization of vaccinia virus particles using microscale silicon cantilever resonators and atomic force microscopy." Sensors and Actuators B: Chemical 115.1 (2006): 189-197.
13. Damborský, Pavel, Juraj Švitel, and Jaroslav Katrlík. "Optical biosensors." Essays in biochemistry 60.1 (2016): 91-100.
14. Liedberg, Bo, Claes Nylander, and Ingemar Lunström. "Surface plasmon resonance for gas detection and biosensing." Sensors and actuators 4 (1983): 299-304.
15. Wang, Li, et al. "A MEMS thermal biosensor for metabolic monitoring applications." Journal of microelectromechanical systems 17.2 (2008): 318-327.
16. Duroux, Ph, et al. "The ion sensitive field effect transistor (ISFET) pH electrode: a new sensor for long term ambulatory pH monitoring." Gut 32.3 (1991): 240-245.
17. Diculescu, Victor Constantin, Ana-Maria Chiorcea-Paquim, and Ana Maria Oliveira-Brett. "Applications of a DNA-electrochemical biosensor." TrAC Trends in Analytical Chemistry 79 (2016): 23-36.
18. Meshram, B. D., et al. "Biosensor and its application in food and dairy industry: a review." Int. J. Curr. Microbiol. Appl. Sci 7 (2018): 3305-3324.
19. Verma, Neelam, and Minni Singh. "A disposable microbial based biosensor for quality control in milk." Biosensors and Bioelectronics 18.10 (2003): 1219-1224.
20. Rodriguez-Mozaz, Sara, et al. "Biosensors for environmental monitoring: A global perspective." Talanta 65.2 (2005): 291-297.
21. Liu, Jing, and Bo Mattiasson. "Microbial BOD sensors for wastewater analysis." Water Research 36.15 (2002): 3786-3802.
22. Malhotra, Bansi D., and Asha Chaubey. "Biosensors for clinical diagnostics industry." Sensors and Actuators B: Chemical 91.1-3 (2003): 117-127.
23. Kirsch, Jeffrey, et al. "Biosensor technology: recent advances in threat agent detection and medicine." Chemical Society Reviews 42.22 (2013): 8733-8768.
24. H. Sun, G. Gao, Q. Liu, Y. Ma, J. Li, J. Shi, Exploring the use of blood lactate biosensors in the diagnosis and treatment of COVID-19, 2019
25. X. Wang, X. Zhu, L. Wang, H. Li, X. Fu, Reverse transcription loop-mediated isothermal amplification combined with gold nano-biosensing for the detection of COVID-19, 2019

26. Santiago, Ibon. "Trends and innovations in biosensors for COVID-19 mass testing." ChemBioChem 21.20 (2020): 2880.