Advances in biosensor technology in clinical medicine

Wenzheng Wu¹, Chengzhen Meng²†, Xiaoyi Zhao²†, Jingyi Yun¹, Shihao Wang², Wei Zhao¹, Pufan Shan³,*

¹College of Pharmacy, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province 250355, China;
²College of Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province 250355, China;
³College of Acumox and Tuina, Shandong University of Traditional Chinese Medicine, Jinan, Shandong Province 250355, China.

†These authors have contributed equally to this work and share first authorship
* Corresponding Author Email: 931750604@qq.com

Abstract. With the rapid development of science and technology and medical technology, the development of biosensor technology is on the fast track and is becoming increasingly integrated into clinical care. This phenomenon has revolutionised the healthcare industry, but at the same time, the drawbacks are also becoming apparent. In this paper, we examine the process of integrating biosensor technology with clinical care, discussing the current state of integration and making recommendations accordingly.

Keywords: Biosensor technology; Clinical medicine.

1. Basic overview of biosensors

1.1 Biosensors and their principle, role

1.1.1 Overview of biosensors

A sensor is a special device that can acquire and process information. For example, the sensory organs of the human body are a perfect sensing system that perceives physical information such as light, sound, temperature and pressure from the outside world through the eyes, ears and skin, and chemical stimuli such as smell and taste through the nose and tongue. In contrast, biosensors are a special class of sensors that use biologically active units (e.g. enzymes, antibodies, nucleic acids, cells, etc.) as biosensitive units and are highly selective detectors for the target test substance. Biosensors are characterised by good selectivity, high sensitivity, fast analysis, low cost, and the ability to perform online continuous monitoring in complex systems, especially its high degree of automation, miniaturisation and integration, which has led to its vigorous and rapid development in recent decades. The biosensor is an analytical and detection device resulting from the interpenetration of biology, medicine, electrochemistry, optics, thermodynamics and electronics.

1.1.2 Principle of biosensors

Biosensors are devices that use immobilised biological components (enzymes, proteins, DNA, antibodies, antigens, biofilms, etc.) or the organism itself (cells, microorganisms, tissues, etc.) as sensitive materials, combined with appropriate chemical transducers to produce a rapid detection of various physical, chemical and biological quantities [2, 3].

Sensitive materials are biologically active units that act selectively on the target. The first ones to be used were enzymes with a high degree of selective catalytic activity. Enzymes were either physically (encapsulated, adsorbed, etc.) or chemically (cross-linked, polymerised, etc.) immobilised in the sensitive membrane of the chemosensor, and the concentration of the specific product produced by the enzyme-catalyzed reaction of the target was then measured indirectly by using the chemical electrode as a transducer.
Biosensors are divided into two key components. One is the recognition component from the molecules, tissues, etc. of the organism, which acts as the signal reception or generation part of the biosensor. The other component is the hardware instrumentation component, which acts as a data processing and analysis device, mainly through biological principles. The information conversion component converts a change in the molecular recognition component or a change in the substance to be measured through the selective recognition of the molecular recognition component into an electrical signal and produces the corresponding effect. This is the principle of action of the biosensor.

1.2 Successive generations of biosensors along

Since the first oxygen biosensor was created in 1962, researchers have developed applications for different fields. A biosensor is often defined as a special device that combines a biological component with a physicochemical device for the detection of biologically significant analytes. A key step in the biosensor research process is the immobilisation of biomolecules, and depending on their different forms, biosensors have been developed in three main stages.

1.2.1 First generation biosensors - dielectric amperometric biosensors

The first generation of biosensors is a combination of analyte or enzyme-catalyzed reaction substrate onto the sensor surface, which is then expressed in the form of an electrical signal. The sensing principle is that when the analyte diffuses into the biosensitive membrane layer, a biological reaction occurs through molecular recognition and the information generated by the reaction is converted into a quantitatively processable electrical signal by the corresponding physical or chemical transducer, which is then amplified and output by a detection amplifier to achieve quantitative detection of the measured substance. The first generation of biosensors had numerous drawbacks, such as being limited by the partial pressure of oxygen and its solubility, high overpotential and many interferences. This led to the development of small molecule electron mediators to replace oxygen in the electronic channel between the enzyme activity centre and the electrode, and to detect changes in substrate concentration by detecting changes in the current of the mediator. On this basis, a second generation of biosensors was born.

1.2.2 Second generation biosensors - dielectric amperometric biosensors

Second generation biosensors use chemical mediators or specific biomolecules to replace O2/H2O2 for electron transfer in enzymatic reactions and between electrodes. A good mediator needs to have (1) an extremely easy participation in redox reactions in the presence of biologically active materials and electrodes and rapid electron transfer in both homogeneous and non-homogeneous systems; (2) a reduced state that is not oxidised by oxygen; (3) a low voltage required for regeneration of the oxidised state and is not affected by pH; (4) non-toxic to organisms and not used as a substrate by biocatalysts; (5) easy to co-immobilisation; and (6) sufficiently long stability time during operation or storage. Common second generation biosensors are nucleic acid aptamer sensors and transcription factor sensors.

At present, the second generation of sensors is the most used and widely used sensor, the performance of the product has been greatly improved compared to the first generation, the practicality is significantly improved.

1.2.3 Third generation biosensors - nanobiosensors

The introduction of nanomaterials into second generation biosensors in recent years has improved their detection sensitivity and usability. Nanomaterials in a broad sense are materials that are in at least one dimension in three-dimensional space at the nanometer size (0.1 to 100 nm) or are composed of them as basic units, which corresponds approximately to the scale of 10 to 100 atoms closely aligned together. This size is in the transition region between the microscopic world represented by atoms and molecules and macroscopic objects. Systems based on this size are neither typical microscopic nor macroscopic systems, and therefore have unique chemical and physical properties, such as surface effects, microscopic size effects, quantum effects and macroscopic quantum tunneling.
effects, and present superior properties that conventional materials do not possess. The modification of these new nanomaterials onto the electrode surface can effectively immobilise biomolecules and facilitate direct electron transfer between their redox centres and the electrode, and then use the sub-micron sized transducers, probes and nano-microsystems of the nano-biosensor to develop a third generation biosensor. The third generation biosensor eliminates the electron mediator and achieves direct electron transfer between the enzyme and the electrode, resulting in a biosensor with higher conduction efficiency, less interference, better accuracy and promising applications.

1.3 Current status of application

1.3.1 Applications in the medical field

In clinical medicine, enzyme electrodes were one of the first sensors developed and most used. Using microorganisms with different biological properties instead of enzymes, microbial sensors can be made. Biosensors such as immunosensors can be used to detect various chemical components in body fluids and provide a basis for diagnosis by doctors. In military medicine, the timely and rapid detection of biotoxins is an effective defence against biochemical weapons. In addition to monitoring a wide range of bacteria, viruses and their toxins, biosensors can also be used to measure various amino acids such as acetic acid, lactic acid, lacturonic acid, antibiotics, glutamic acid and various carcinogens.

Biosensors play a major role in the medical field. Biosensing technology not only provides a new fast and simple detection method for basic medical research and clinical diagnosis, but also, because of its specificity, sensitivity and fast response, it has broad application prospects in military medicine.

1.3.2 Application in fermentation production

The detection of a wide range of relevant biochemical parameters (biomass/cellular activity, substrate/nutrients, products/metabolites) during microbial fermentation is an essential prerequisite for researchers and engineers in the field of biotechnology to effectively control the process. Among the various biosensors, microbial sensors are the most suitable for the determination of many chemical and biological parameters in the fermentation industry. Because of the presence of enzyme-disrupting substances in the fermentation process and the fact that fermentation broths are often not clear and transparent, they are not suitable for spectroscopic or other methods of measurement. The application of microbial sensors makes it extremely possible to eliminate interference and is not limited by the degree of turbidity of the fermentation broth. Also, as the fermentation industry is a mass production, the low cost and simple equipment of microbial sensors give them an even greater advantage in their application.

The widespread use of biosensors in fermentation production has led to them being called the eyes of the fermentation plant. For the rapid and sensitive detection of amino acids, alcohols and other substances in the fermentation process, it has the advantages of excellent selectivity and stability, ease of operation, short time required for determination, easy automation of counting and no requirement for the specimen to be optically transparent.

1.3.3 Applications in environmental monitoring

In atmospheric environmental monitoring, SO2 is the main cause of acid rain and acid mist formation, and traditional detection methods are complicated. marty et al. immobilized subcellular lipids on acetate membranes and made amperometric biosensors with oxygen electrodes, which can detect acid rain and acid mist sample solutions.
2. Current status of integration of biosensors with clinical medicine

2.1 Current status of the combination of the two

2.1.1 Integrated application of various nanomaterials to improve the efficiency of clinical detection of biosensors

The application of nanomaterials in the field of biosensors has long been of great interest. They are widely used in the preparation of biosensors because of their unique chemical and physical properties as well as their small size effect, quantum size effect and biocompatibility, which are compatible with the conditions of precision, high speed and high sensitivity required by biosensors.

At present, the more widely used are nano-metal materials, nano-oxides, nano-fiber, etc. Traditional nano-materials such as nano-metal materials are one of the most commonly used nano-materials due to their simple preparation and stable properties. Among them, due to its good physical properties and very high specific surface area, nanogold can make more enzyme-labeled antibodies immobilized to the electrode surface in electrochemical immunosensors, and can better maintain the biological activity of antibodies, in addition, nanogold can effectively reduce the non-specific adsorption of antibodies and improve the sensitivity and reliability of detection. In addition, some new nanomaterials, which have also been proven by a large number of experiments to have greater advantages in the application of biosensors, such as graphene materials. All carbon atoms on the surface of graphene react directly with biomolecules, giving it a higher sensitivity than silicon nanowires or carbon nanotubes (CNTs); the availability of its oxygen-containing groups greatly influences the electrochemical properties in terms of electron transfer rate, as well as the adsorption and desorption of biomolecules during the electrochemical reaction, making it comparable to The availability of oxygen-containing groups allows free electron transfer between graphene and biologically active receptors without passing through any medium, which is important for maintaining the biological activity of the substrate and rapid electron transfer. At the same time, the relatively low price of graphene reduces the cost of clinical assays to some extent.

Biosensors need to develop towards more accuracy, sensitivity, portability and ease of operation to meet the needs of clinical medical detection, and nanoscale biosensors as an important development trend, how to make comprehensive use of various nanoscale materials to improve the needs of clinical detection is an urgent problem to be solved.

2.1.2 Improving the quality of enzyme markers

Enzyme biosensors are now widely used in the medical testing industry for monitoring blood glucose, lactate, uric acid, transaminases etc. If the sample to be tested contains the corresponding enzyme substrate, it can react with and produce certain informative substances which are then converted into electrical signals for detecting the concentration of that substance in the sample. In enzyme biosensors, the enzyme is the main substance of the biomolecular recognition element and to enhance the efficiency of the sensor use, it is converted into an enzyme that can be used repeatedly and continuously by immobilised enzyme technology. Therefore, the quality of the enzyme marker directly determines the efficiency of the clinical application of the sensor, and the prepared enzyme marker should be of high purity, stability and affinity. Based on this, when making enzyme markers, on the one hand, a preparation method with high yield that does not affect the biological activity of the enzyme and is simple and easy to operate should be adopted, and on the other hand, stability protectors for different markers can be developed.

2.2 Effects (advantages) resulting from the combination

Due to the advantages of high selectivity, sensitivity and accuracy in clinical detection, biosensors have a wide range of applications in the medical field. The main biosensors that have been widely used in clinical medical detection include enzyme biosensors, microbial sensors, DNA sensors, protein biosensors, etc.
The advantages of biosensors, such as their high efficiency, specificity and economic practicality, make them play an important role in immediate detection and concomitant diagnosis. In chronic diseases, such as diabetes and kidney disease, patients can conduct real-time, dynamic detection at home, so that they can grasp the evolution of their condition at the first time; with the gradual development of research on biosensors in the medical field, their role in diagnosing tumours has also been, their role in diagnosing tumours has also been mentioned in recent years, especially in the direction of liver cancer, which has made great progress. At the same time, its miniaturisation and integration features are expected to achieve individualised detection in the future, reducing the cost of detection for medical institutions, alleviating to a certain extent the problem of "expensive" and "difficult" patient care, and further promoting the development of preventive medicine and predictive medicine.

3. Prospects for the development of the combination of biosensors and clinical medicine

3.1 Predicted trends in the integration of biosensors with clinical medicine

3.1.1 Improving the efficiency of testing in clinical medicine

The design and application of biomolecular sensors for the monitoring of clinical samples is a common goal of the sensor research community. Surface plasmon resonance (SPR) and other plasmon techniques such as localised surface plasmon resonance (LSPR) and imaging SPR have now reached a level of maturity sufficient for monitoring biomolecules in clinical samples and are increasingly being used for detection in the field of clinical medicine.

Clinical testing is an important driving force in the continuous development of clinical medicine. In clinical medicine, it is important to quickly determine and understand the type and characteristics of a disease, and to determine the exact type of disease so that a treatment plan can be developed in time to free the patient from the pain and suffering. Traditionally, clinical tests were mainly carried out by the "laboratory method", whereby the patient's body fluids or secretions were transported to the laboratory, where they were tested and the laboratory report was then transmitted to the relevant medical personnel. With the development of science and technology, biosensors have been developed and have been widely used in clinical testing. The high sensitivity and selectivity of biosensors to the sample being tested has improved the accuracy of clinical testing and the rapidity of signal conversion. The overall improvement in efficiency has led to an increase in the efficiency of clinical testing and, together with the advantages of ease of operation, the importance of biosensors in clinical testing has been further enhanced. With the potential for real-time analysis, speed of analysis and low cost, biosensors offer exciting opportunities for a multitude of decentralised clinical applications . From emergency room screening to home self-testing and alternative field testing, the embedding of biosensors has allowed the application of clinical medicine to no longer be limited to specific clinical locations; the implementation of continuous and real-time in vivo monitoring has allowed for increased flexibility in the timing of clinical medicine monitoring, as well as increased efficiency in the examination of acute, critically ill patients for real-time monitoring, gaining safety for the continuation of life.

In recent years, SPR sensing has been involved in the field of clinical medicine in the bio-detection of various diseases (Alzheimer's, hepatitis, diabetes, leukaemia and cancers such as prostate and breast) , where bio-fluids collected from patients are precisely analysed for microscopic substances such as antibodies, proteins, enzymes, drugs, small molecules and nucleic acids in bio-fluids by piggybacking on biosensors, and in the microscopic detection and analysis of diseases. Biosensors represented by SPR sensors offer more research opportunities for medical testing in the clinical market. Further advancement in the field of biosensors will complete a good transition from the proof-of-concept stage of local research to the actual clinical application stage of biosensors, providing more diverse options for the implementation of clinical testing applications.
3.1.2 Promoting newer iterations of biosensors

Since their introduction, biosensors have shown a bright future with their rapid development. The current biosensors are summarised into three major directions of development: (1) microsystematic and ultramicroscopic molecular biosensor systems, where the size of ultramicroscopic biosensors has entered the nano level. (2) Multi-parameter measurement biosensors marked by LAPS have become a major development trend of biosensors. (3) With the tremendous progress of optical microelectronics, optical fiber technology, optical signal processing and display technology and optical computer technology and the continuous improvement of the technical level, the superiority of optical technology is increasingly reflected, has become the fastest growing sensing technology. At present, biosensors are currently developing in the following areas: (1) to high-performance, miniaturization, and integration direction. (2) the combination of biosensors and computers, constitutes an intelligent system for biochemical detection, such systems can automatically collect data, database management and data processing with artificial intelligence. (3) The development of bionic biology.

In recent years, research on biomedical sensors has developed rapidly, with researchers researching various aspects of biomedical sensors, mainly in the areas of performance improvement, expansion of application scenarios, integration with new technologies, and the development of new structures and principles. At the same time, researchers are also working to remedy the various shortcomings of existing biomedical sensors through various efforts, including the following. The first is the miniaturisation of biomedical sensor devices. Current biomedical sensors rely on manual fabrication for some of their devices, which poses a challenge in terms of high precision and miniaturisation requirements. Researchers have been able to improve the accuracy and miniaturisation of biomedical sensors by drawing on the best techniques from industrial production, such as flexible circuit board fabrication and 3D printing. Secondly, the cyclic stability of biomedical sensors: on the one hand, the mechanical stability of the devices has to be tested in complex environments; on the other hand, improvements in energy harvesting capacity, energy storage capacity and energy conversion capacity can increase the effective operating time of biomedical sensors. Existing energy harvesting techniques are theoretically adequate, but in practice, they are not as effective as they could be due to attenuation caused by a variety of factors. Researchers have used multilayer, array and composite generator schemes to improve the efficiency of biomedical sensor power generation. The development of biosensors is very attractive and it is believed that with the development of biotechnology, materials science, microelectronics, optoelectronics, and electronic computers and the urgent need for practical applications, the development and application of biosensors will continue to move forward.

4. Outlook

With the development of new technologies, applications such as instant diagnosis and personalised treatment are placing more demands on biosensors. The development of plasma nano biosensors extends their application to arbitrary settings outside the laboratory and integrates them into existing biomedical systems. Therefore, how to improve the reusability of plasma nano biosensors and how to develop integrated devices for diagnosis and treatment that combine the plasma photothermal effect with LSPR sensing needs to be further explored.

New biosensor recognition elements are still being developed and future work in clinical medicine will focus on improving the specificity of biosensor recognition elements for target capture in complex matrices. At the same time, it is important to enhance the ability of the recognition element to resist external interference, to increase the resistance of the recognition element and to extend the lifetime of the sensor. The use of nanomaterials offers new opportunities for the construction of biosensors, and the continued exploration of new properties of recognition elements in combination with nanomaterials to create more clinically applicable biosensors. Currently, many prototypes of
biosensors have not reached the commercialisation stage and the translation of results needs to be further advanced.

With its high sensitivity and sensitivity to small mass changes on the electrode surface up to the ng level, the medical diagnostic testing process is simple to operate and easy to automate; the detector made by the biosensor is small, portable and can achieve real-time detection, which is especially suitable for rapid detection outside the hospital; the detection cost is low; there is no need to mark, avoiding the radioactive material to the human body. It is also inexpensive and does not require labelling, avoiding the risk of radioactive substances to the human body and pollution to the environment. As a result, biosensors have attracted much attention in recent years in the field of medical diagnosis. If biosensors can be successfully used in clinical work for the detection of medical and tumour-related markers, the development of miniaturisation and arrays, multi-channel detection and more sensitive direction will make up for the shortcomings of current detection methods and play an important role in the development of clinical medicine and early diagnosis and treatment of malignant tumours. Biosensor microarrays have already been developed to detect multiple samples or items simultaneously. The next step to be investigated is how to improve the throughput of the sensor detection system and make it more efficient. In addition, the choice of the best fixation method, the relationship between frequency and mass adsorption under different conditions, the design of specific probes, further improvements in sensitivity, and further improvements in automation are also issues that need further consideration. However, as biosensing technology continues to improve, biosensors will become a widely used new detection tool in the medical field. Although there are still many problems to be solved before they can be applied as practical detection tools, with the improvement of preparation techniques and the integration of more and more complementary technologies, it is believed that the future of biosensors in clinical medicine will have a promising future.

References

[1] Li Jing. A review of the progress of biosensors[J]. Science and Education Wenhui (Upper Journal), 2007(08):204.

[2] Campanella L,Cubadda F,Sammartino M P,et al. An algal bio-sensor for the monitoring of water toxicity in estuarine environments[J]. Water Research,2001,35(1):69-76.

[3] Lee Hae-Ok,Cheun Byeung Soo,Yoo Jong Su,et al. Application of a channel biosensor for toxicity measurement in cu Itured A lexandrium tamarenselJ Journal of Natural Toxins,2000,9(4):341-348

[4] Chen Ling. A review of the research progress of biosensors[J]. Sensors and Microsystems, 2006(09):4-7. DOI:10.13873/j.1000-97872006.09.002.

[5] Zhou Yan, Cai Yishan, Zheng Hui, et al. Application of nanomaterials in electrochemical biosensors[J]. Chinese Journal of Health Quarantine, 2015(5): 310-312

[6] DZYADEVYCH S V, ARKHYPOVA V N, SOLDATKIN A P, et al. Amperometric enzyme biosensors: past, present and future[J]. IRBM, 2008,29(2):171-180.0

[7] Zhu Qanyun, Li Lun, Chen Xuelan. Biosensor development and its applications[J]. Health Research,2019,48(03):512-516.DOI:10.19813/j.cnki.weishengyanjiu.2019.03.026.

[8] Han Shubo, Guo Guangmei, Li Xin, et al. Research and application of voltammetric biosensor for total bacterial count[J]. Chinese Medicine, 2000,63(2):49-52.

[9] Jia Shi Ru. Application of biosensors in fermentation and food engineering[J]. Journal of Tianjin Institute of Light Industry, 1986(01):98-105. doi:10.13364/j.issn.1672-6510.1986.01.015.

[10] Han Shubo, Guo Guangmei, Li Xin, et al. Research and application of voltammetric biosensor for total bacterial count[J]. Huaxia Med, 2000,63(2):49-52.

[11] Huang Shanshang, Li Zhonghai, Li Jili, Guo Xiaobing, Geng Mei. Research progress on the application of nanogold in electrochemical biosensors[J]. New Chemical Materials,2014,42(06):219-221.
[12] Li Menghan, Wang Xiaoping, Wang Lijun, Shi Jia. Research progress of graphene-based electrochemical biosensors[J]. Journal of Materials Science and Engineering, 2020, 38(03): 503-508+517. DOI: 10.14136/j.cnki.issn1673-2812.2020.03.027.

[13] Hu Xizizi. Study on the application of biosensors in clinical testing[J]. China Equipment Engineering, 2021 (06): 169-170.

[14] Bansi D. Malhotra et al. Recent trends in biosensors[J]. Current Applied Physics, 2005, 5(2): 92-97.

[15] Masson Jean-Francois. Surface Plasmon Resonance Clinical Biosensors for Medical Diagnostics. [J]. ACS sensors, 2017, 2(1): 16-30.

[16] Lin Quan, Peng Chenglin, Song Wenqiang. Development of biosensors and their applications in biomedicine[J]. China Medical Equipment, 2007, 4(4): 19-22. doi: 10.3969/j.issn.1672-8270.2007.04.007.

[17] Tan Puchuan, Zhao Chaochao, Fan Yubo, et al. Research progress of biomedical sensors[J]. Journal of Physics, 2020, 69(17): 137-148. doi:10.7498/aps.69.20201012.

[18] Duan Ruiqi, Yu Xiuzhang, Lan Zhu, et al. Research progress of LSPR biosensors in clinical medical detection applications[J]. Optoelectronic Engineering, 2017, 44(2): 152-160. doi:10.3969/j.issn.1003-501X.2017.02.005.