# Advanced Development of Chemical Sensors

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**Abstract:** Sensors have received wide attention from scientific researchers since their inception in 1906, and countries worldwide have also invested a lot of human and financial resources in this field. There are more than 1,000 sensor research and production manufacturers in the United States, Europe, and Russia. What's more, according to statistics, the global sensor market exceeded $200 billion last year. The sensor has a history of more than 100 years since its development. During this period, sensors merged with different disciplines, and many different types of sensors were developed—for example, chemical electrode sensors, sensitive film sensors, gas sensors, and optical sensors. In particular, the application of nano-sensors in biomedical domains, which have emerged in recent years, has attracted widespread attention among scientific researchers engaged in sensor research. Although nano-sensors have not been widely used due to their high price and other reasons, their excellent characteristics have been widely recognized by the scientific community. Studies have shown that nanosensors, especially those based on gold nanoparticles, surpass traditional electrochemical sensors in terms of human affinity, measurement accuracy, and feedback speed. This review article aims to summarize the results of sensor development and give a macroscopic reference to the development of sensors. The development history of the sensor will be reviewed in chronological order. In addition, the application of nano-sensors in the field of biomedicine will be introduced in detail. CCS CONCEPTS •Applied computing~Life and medical science.

## 1. Introduction

As a tool to convert original information into available information, sensors improve analyzing and detecting samples [1]. With the improvement of people's requirements for detection technology, sensor production is more and more inclined to be more flexible, smaller, more accurate, more compatible, more energy-saving, more environmental protection. The field of sensor application is more and more extensive.

In 1906, Cremer first discovered the hydrogen ion-selective response of glass membrane electrodes [1, 2]. But in the beginning, the development of sensors was not smooth. It was not until 1960 that chemical sensors began to develop rapidly [3]. From 1970 to 1990, chemical sensors experienced a qualitative leap in the past 20 years and began to form their independent system [4]. Various original chemical sensor synthesis technologies gradually matured and stabilized. With the development of technology, the synthesis of chemical sensors is becoming more and more specialized.

With the rapid development of science and technology, people's demand for health has become higher, and the ability to treat diseases in the field of biomedicine has been improved. At the same time, the development of diagnostic methods for diseases is far behind the progress of treatment methods. So scholars must find new diagnostic methods to meet people's current needs. The biosensors for disease detection are divided into five categories: enzyme sensor, microbial sensor, organallsensor, tissue sensor, and immune according to molecular recognition elements.

Hepatitis C virus is a serious infectious disease, threatening people's safety. Nowadays, people have made great progress in treatment, but the research on diagnosis is a little poor. The new direction of HCV detection - gold nanoparticles, nanoprobes, or sensors may bring some help, showing the advantages that other old methods don't have [5]. Maybe shortly, the diagnosis of HCV will no longer trouble people.

## 2. The development history of chemical sensor

The chemical sensor combines a chemically sensitive layer and a physical converter and is a sensor device that can provide direct information on the chemical composition [1]. The research on chemical sensors is an emerging discipline formed by the interpenetration and integration of multiple disciplines such as chemistry, biology, electricity, thermal microelectronics technology, and thin-film technology in recent years.

### 2.1 The history of chemical sensors

The history of chemical sensors is not long. Still, countries worldwide have invested a lot of manpower, material, and financial resources in the development and research of this new discipline. The number of researchers is increasing, and effective work is being carried out towards industrialization. Chemical sensors are the most active and effective field in the field of sensors today. The important significance of chemical sensors is that they can directly convert chemical components and their content into analog quantities (electrical signals). They usually have many features, such as small size, high sensitivity, wide measurement range, low price, easy to achieve automatic measurement, and online or in-situ continuous detection [6].

In 1906, Cremer first discovered the hydrogen ion-selective response of glass membrane electrodes [1, 2]. With the continuous deepening of research, in 1930, the use of glass film pH sensors entered the practical stage. From then on, the research progress of chemical sensors was very slow. It was not until 1960 that chemical sensors began to develop rapidly [3]. Especially from 1970 to 1990, chemical sensors experienced a qualitative leap in these two decades. They began to form their independent systems, and various original chemical sensor synthesis technologies gradually matured and stabilized [4]. Then, chemical sensors began to differentiate gradually, and many chemical sensors began to change their properties for different application fields. From this development to the present, several different branches have been formed. It shows in the table below [7].

Table.1. Classification of chemical sensors

| Sensor | Chemical sensor type | Specific type |
|---|---|---|
| (1906-1960) Old chemical sensor | Ion-selective electrode | Fluoride electrode |
| (1960-Nowadays) New chemical sensor | Photochemical chemical sensor | Fluorescence sensor; Optical fiber chemical sensor |
| | Chemical electrode sensor | The electronic tongue sensor array |
| | Sensitive film sensor | Metal film sensor |
| | Gas sensor | Sulfur dioxide detector |

## 3. New chemical sensor

### 3.1 Gas sensor

The gas sensor is an important branch of the sensor field. It can feel the change of the external atmosphere and convert it into a usable signal to realize the detection of a specific type of gas [8].

### 3.2 Sensitive film sensor

This sensor is also a simple and portable analysis method, which is more convenient to use and simple to maintain [9]. The electrode sensors make some sensitive membrane sensors based on different ions sensitive to different substances and put them together with standard electrodes.

### 3.3 Chemical electrode sensor

This is a type of electrochemical sensor based on different ion concentrations corresponding to different electrical signals. It works according to the selective characteristics of ions. It is also an earlier type of sensor in chemical sensors. The current technology is quite mature, and many detection methods have regarded it as a standard method for comparison [7].

### 3.4 Photochemical chemical sensor

The photochemical sensor is a kind of latest sensor, but its technology develops very fast, and its application prospect is very broad [6, 10].

3.4.1 Optical fiber chemical sensor.

3.4.1.1 The introduction of Optical fiber chemical sensor.

Optical fiber chemical sensor (FOCS) is also called optrode [11]. This new term is a combination of the two words optical and electrode. It emphasizes the similarity between the sensor and ion-selective electrode in terms of use. However, in principle, they are extremely different. By analogy from the concept of electrodes, the optrode is the optical fiber in contact with the sample. According to the working principle, fiber optic sensors can be divided into two categories. One type of sensor uses optical fibers with the ability to be sensitive to external information and detection functions as the sensor element. This type of sensor is called a functional optical fiber sensor. It uses the transmission characteristics of the optical fiber to change with the detection object so that the characteristics of the light propagating in the optical fiber, such as amplitude, phase, and polarization, also change accordingly. When light is emitted from the optical fiber, its characteristics are modulated. Through the detection of the modulated light, external information can be sensed. In another type of sensor, the optical fiber is only used as a medium for spreading light rays. The function sensitive to external information is accomplished by relying on other functional elements. This type of sensor is called a light-transmitting sensor [10].

3.4.1.2 The advantages of Optical fiber chemical sensors.

Table.2. The advantages of FOCS

| Sensor | Advantages |
|---|---|
| Optical fiber chemical sensor (FOCS) | 1. Both the optical fiber and the probe are miniaturized, with good biocompatibility, combined with good flexibility and uncharged safety, making them especially suitable for real-time and in-vivo testing in biology and clinical medicine. |
| | 2. Optical fiber transmission power loss is small. Transmission information capacity is large, anti-electromagnetic interference, high temperature, high pressure, anti-corrosion, flame-retardant, and anti-explosion to be used for long-distance telemetry and analysis some special environments. |
| | 3. Multi-wavelength and time resolution technology can be used to improve the method's selectivity, and multi-parameter or continuous multi-point detection can be performed simultaneously to obtain a large amount of information. |
| | 4. Appropriate selection of chemical reagents and their fixation methods can detect various substances with great flexibility. |
| | 5. A reference electrode for the potential method is not required, and the cost can be greatly reduced when a cheap light source is used to illuminate the sample. |
| | 6. In most cases, FOCS does not change the sample's composition and is a non-destructive analysis. |
| | 7. It can be used in multiple ways. A spectrometer can be used in conjunction with multiple optical fiber sensors, can be used for multiple wavelengths, and provide instant information. |

Compared with traditional electrochemical sensors, FOCS has many advantages (table2) [1, 12].

Among the many advantages of FOCS, I think the most noteworthy is its instant detection. This high-sensitivity and high-speed feedback feature allow optical sensors to adapt to complex real-world environments more than other types of sensors. This is also the main reason why some scholars believe that optical sensors will replace traditional electrical sensors in the future [10].

The optical fiber sensor has so many advantages that it has been highly valued by academia and research institutions worldwide just after it came out [11].

3.4.1.3 The principle and structure of Optical fiber chemical sensor.

The principle of Optical fiber chemical sensor: Under the action of a certain excitation light source, the intermediate molecules can produce corresponding optical effects with the analyte's concentration so that the analyte's concentration can be measured by the intensity of the reflected light of the optical fiber probe [13].

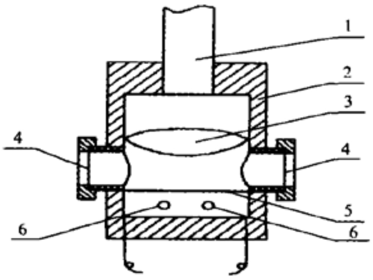


Figure 1. Schematic diagram of optical fiber chemical sensor [6]. 1. Single branch optical fiber 2. Sensor body 3. lens 4. gas-permeable membrane 5. Luminous cell 6. Electrode

3.4.1.4 The disadvantages of Optical fiber chemical sensors.

Since the development of optical fiber chemical sensors, most of them have gone through the stages of principle research and experimental demonstration [10]. However, due to its late development, it is not as mature as the existing electrochemical sensor in terms of technology, and the manufacturing cost is relatively high [14]. In particular, it should be pointed out that the reliability of optical fiber chemical sensors in various complex practical application environments is still to be explored [1].

3.4.2 Fluorescence sensor.

3.4.2.1 The introduction of Fluorescence sensor.

The Fluorescence chemical sensor is another kind of photochemical sensor that extends from the optical fiber chemical sensor [15]. It has been highly specialized since its inception, especially in the field of life sciences and nanoscience. As a means of analysis and detection, it has the advantages of high sensitivity, convenience, quickness, excellent selectivity, real-time online detection, short response time, and high accuracy [4]. These advantages make it widely concerned by scientific researchers from all over the world, making it develop very rapidly in recent years.

3.4.2.2 The structure of the Fluorescence sensor.

Table.3. The structure of the Fluorescence sensor

| Sensor | The structure | Working principle |
|---|---|---|
| Fluorescence sensor | The recognition group | A recognition group is a unit bound by a covalent bond. The relevant part of its structure can chemically react with the detected substance to form a new covalent bond or selectively through weak interactions and different ions and small molecules. Combine to form a supramolecular system of two or more molecules. |
| | The linking arm | Luminescent groups are the information source that emits optical signals and are reporters that convert identification information into fluorescent signals, such as organic fluorophores and rare earth luminescent complexes. The choice of the luminescent group directly affects the expression of the recognition signal. |
| | The luminescent group | The linking arm is a bridge connecting the recognition group and the light-emitting group. After the receptor recognizes the substrate, the linking arm transmits the recognition information to the light-emitting group according to a certain transfer mechanism, promoting the signal response. |

The fluorescent chemical sensor mainly comprises three parts: the recognition group, the linking arm, and the luminescent group [16]. The recognition group can specifically bind to the detection substrate. The luminescent emits an optical signal. The connecting arm is used to connect the recognition group and the luminescent group.

3.4.2.3 The principle of Fluorescence sensor.

There are many working principles of fluorescent chemical sensors. Still, in essence, they convert the substance information to be detected into light signals in a certain way to facilitate analysis and detection. The principle is summarized in the table below.

Table.4. The principle of Fluorescence sensor

| Sensor | The principle |
| --- | --- |
| Fluorescence sensor | Light-induced electron transfer (PET) |
| | Intramolecular Charge Transfer (ICT) |
| | Fluorescence resonance energy transfer (FRET) |
| | Excimer association mechanism |
| | Excited Intramolecular Proton Transfer (ESIPT) |
| | C=N isomerization |
| | Rare earth ion fluorescence emission mechanism |
| | Aggregation Induced Luminescence (AIE) |

PET is currently the most widely used and the most recognized principle of fluorescence sensor recognition in academia [17]. The principle of PET: After the fluorophore is excited by light, the electrons transition from the highest occupied orbital (HOMO) to the lowest unoccupied orbital (LUMO) to generate unpaired electrons; before the acceptor is not bound to the target molecule. The HOMO orbital energy level of the electron-rich group (electron donor) on the acceptor is relatively high. The electron is transferred from the HOMO orbital of the electron donor to the HOMO orbital of the electron acceptor (the excited state fluorophore). When the excited state fluorophore After the HOMO orbital of is occupied by the paired electrons, the unpaired electrons on the LUMO orbital cannot fall back to the HOMO orbital. The fluorescence of the fluorophore is quenched [16].

3.4.2.4 The application of Fluorescence sensor.

The application field of fluorescence sensors is very extensive, and its application field is still expanding rapidly. It can be said that the fluorescence sensor is one of the most valuable and promising research projects in the 21st century [4]. Because its application field almost involves most of the 21st-century hot scientific fields. Therefore, it is unrealistic and unscientific to list its applications one by one. I used the induction method to summarize the main application directions of fluorescence sensors.

Table.5. The main application directions of the Fluorescence sensor

| Sensor | Application directions | Concrete application |
| --- | --- | --- |
| Fluorescence sensor | Inorganic Small Molecule Field | Detection and recognition of ions and small molecules |
| | Biomedicine field | Bioactive substance detection and cell imaging |
| | | Near-infrared fluorescence and time-resolved detection of proteins |
| | Nanotechnology field | Combination of fluorescence sensor with magnetic resonance imaging and nanomaterials |

To the Inorganic Small Molecule Field, Fluorescence sensors are generally used in liquid or gas environments: the Highly Selective and Sensitive Colorimetric and Fluorescent Chemosensors for Rapid Detection of Cyanide Anions in Aqueous Medium [18], the Highly selective fluorescent peptide-based chemosensors for aluminum ions in aqueous solution [19], and the Sensitive and selective detections of mustard gas and its analogs by 4-mercaptocoumarins as fluorescent chemosensors in both solutions and gas phase [20].

Fluorescence sensors are mainly used in the assembly and utilization of nano metal particles or metal compound nanoparticles in the Nanotechnology field. Such as the fluorescent chemosensors for Al3 [21], the Fluorescent Chemosensors for Zn2+ and Pyrophosphate [22], and the Metal ion-responsive fluorescent sensing molecules [23].

To the Biomedicine field, Fluorescence sensors are mainly used in the field of organic synthesis [24, 25] or the activity detection of biomolecules [15, 26]. This field often overlaps with the nanotechnology field. Such as The Ratiometric fluorescence sensor is based on MnO2 nanosheets based on oxidase mimetic enzyme activity to detect reduced glutathione [27].

3.4.2.5 Application of gold nanoparticles

The application of gold nanoparticles belongs to the field of biomedicine. Gold nanoparticles are also one of the metal particles used in fluorescence sensors. But gold nanoparticles are high stability and non-toxicity, and harmlessness to the human body. This allows it to be used in a very special field of biomedicine-the field of human biomedicine. Gold nanoparticles are now widely used in the synthesis of human-related chemical sensors. This makes gold nanoparticles have a transcendent status among many metal nanoparticles.

## 4. Disease detection

With the development of medicine, people treat the obvious diseases and develop to eradicate the diseases that do not pose a threat. Early diagnosis leads to early treatment. To achieve the progress of medicine, it is urgent to design new diagnostic methods. There are a variety of disease detection methods in the clinic. The general method is a laboratory test, but this test method is cumbersome and takes a long time, so it can not meet the needs of modern clinical medicine. The emergence of biosensors has greatly improved this phenomenon.

Sensors using immobilized biological components or organisms as sensing elements are called biosensors. Biosensors can be divided into five categories according to the molecular recognition elements in biosensors: enzyme sensor, microbial sensor, organallsensor, tissue sensor, Immunol sensor.

### 4.1 Enzyme sensor

Enzyme biosensor is a kind of biosensor that uses the amount of substance produced or consumed by the biochemical reaction to convert into an electrical signal through the electrochemical device and selectively determine a certain component.

There are two ways for electrochemical devices to convert electrical signals: the potential and current methods. Potentiometry is a method to further show the concentration of various ions involved in the according to the potential generated by various ions reaction on the induction membrane. The required elements include ammonia electrode, hydrogen electrode, and carbon dioxide electrode. The current method is a method to detect the concentration of the measured substance by the current value generated by the chemical reaction at the positive and negative electrodes of the electrode active substance (such as some ions). The required components include oxygen electrode, hydrogen peroxide electrode, etc.

In clinical diagnosis, the researchers measured the blood glucose levels of fasting subjects by blood glucose detection and then predicted the progression of diabetes through further evaluation [28, 29]. The researchers also measured blood lipid levels to determine metabolism, obesity, and related diseases. In the study of Zaki et al., they investigated the serum levels of NGAL and L-FABP in patients with nonalcoholic fatty liver disease (NAFLD) and their diagnostic value. Some scholars have also studied the correlation between the complications of diabetic patients and body fat content. [29, 30].

### 4.2 Microbial sensor

The microbial biosensor is a biosensor composed of immobilized microorganisms, transducers, and signal output devices.

Microbial biosensors use living microorganisms as sensitive materials to detect and recognize substrates using various enzymes and metabolic systems in the body.

In clinical therapy, researchers can detect leukemia cells and normal cells by identifying leukemia-specific sequences and monitoring disease progression and clonal evolution by this method [31]. Other scholars have studied the relationship between the complications of diabetic patients and serum creatinine level and found that the serum creatinine levels of patients with complications were significantly higher than those without complications [29].

### 4.3 Organallsensor

Organallsensor is a kind of biosensor composed of fixed or unfixed living cells, electrodes, or other converters.

When living cells specifically combine with molecular recognition elements, the generated information is converted into quantitative and processable signals through transducers to achieve the purpose of analysis and detection.

Patch clamp is based on this principle, which plays a key role in studying the mechanism of ion channels and drugs. For example, in studying epilepsy and scorpion drugs, researchers can observe the EEG changes caused by epileptic seizures in mice through patch clamp and the relief effect of drug injection on symptoms. In addition to patch clamp, cell chip is also widely used as an organic sensor. In the article of Sackmann, EK, microfluidic technology is mentioned, and the progress of laboratory on-chip microtechnology and its clinical application in recent years are discussed [32].

### 4.4 Tissue sensor

A tissue sensor is a kind of biosensor composed of tissue slices as molecular recognition elements and corresponding signal elements.

Tissue biosensor uses enzyme in the organism as the catalyst of reaction. Its structure and principle are similar to enzyme biosensors.

The difference between the two is that tissue sensors use organelles as the medium to utilize enzymes, while enzyme sensors use enzymes directly.

Ding, CQ mentioned that carbon dots could be used as sensors or probes for multiple quantitative detections, high-resolution fluorescence imaging, and even long-term real-time observation of tissues [33].

### 4.5 Immunol sensor

Immunosensor is a kind of biosensor based on the recognition function of antigen (antibody) to antibody (antigen).

Once a pathogen or other heterologous protein (antigen) invades an animal's body, the body can produce antibodies that can recognize these foreign bodies and remove them from the body. The combination of antigen and antibody results in immune reaction, high specificity, high selectivity, and sensitivity.

In Farka, Z's article, he summarized the research progress of immunochemical biosensors combined with nanoparticles to improve sensitivity in recent five years. In clinical analysis, immunosensors can be used to detect pathogenic microorganisms, poisons, and pesticides in the field of environment and food [34].

## 5. HCV detection

### 5.1 Antibody test

Hepatitis C virus-specific antibody (anti HCV) in serum or plasma was detected, and positive or negative results were reported. The method has high specificity and sensitivity, but a negative test is not enough to exclude chronic HCV infection. Both hemodialysis patients and immunocompromised patients may have false-negative results, while patients with autoimmune diseases may have false-positive results [35, 36].

### 5.2 nucleic acid test

Two kinds of tests: qualitative and quantitative detection. Both types of tests can be used to identify acute or chronic HCV infection. However, without HCV RNA detection, anti-HCV positive results can be seen in acute infection during the viral clearance period, leading to false-positive results, which may also occur in the recovery of HCV infection and spontaneous remission after HCV infection [37].

### 5.3 gene test

It is clinically used to predict the possibility of response and the duration of treatment. It’s usually used with other methods to detect HCV [38].

### 5.4 The advantage of the gold nanoprobe

Today, 185 million people around the world are suffering from HCV. The demand for HCV diagnosis is very large. However, existing technologies that can detect and quantify HCV in clinical samples are expensive and inaccessible to poor people. So we need to find a rapid and low-cost method to solve this problem. Scholars have focused on gold nanoparticles. The basic principle of HCV detection by gold nanoparticles is to couple HCV-specific probes with gold nanoparticles and then change the behavior of particles by influencing their aggregation and causing color changes according to the presence or absence of HCV. In clinical samples, positive samples usually produce visual or quantitative color changes.

Gold nanoprobe can be used to direct detection of unamplified HCV RNA in clinical samples and DNA repair transcripts from cell lines. It minimizes the factors that may affect the output results, enhance the specificity, sensitivity, and detection limit. Most importantly, this approach allows to achieve quantitative detection of HCV RNA in clinical samples quickly and with reasonable cost, and it could be easily adapted for full automation.

Stability or aggregations of the nanoprobes rely on cationic AuNPs and RNA target folding, which is the advantage of avoiding false-positive results. The assay is simple with a turnover time of ~30 min including RNA extraction, sensitivity, specific, cost effective and could readily be adopted for full automation [5].

Of course, this method also has its defects. Although it has reached a high sensitivity of 93%, it still needs to be improved for HCV, a highly infectious virus that threatens people's lives. Follow-up research will be carried out in the direction of improving its sensitivity.

## 6. Conclusion

For the sensor, the literature shows that its development history is not long. However, the speed of sensor research progress is very fast. According to the summary of the research results of sensors in the literature, we can find that sensors have been fusing with different scientific fields and developing new sensors. For example, electrochemical sensors, gas sensors, and optical sensors. The application environment and application fields of these sensors are different. For example, gas chemical sensors are used in gas environments, while electrochemical sensors are mainly used in liquid environments. The principle of the sensor causes these differences. Although these differences exist objectively, the literature shows that these sensors' manufacturing technology and performance have been continuously improved with development.

For traditional electrochemical sensors, literature shows that emerging chemical sensors (such as optical sensors) have completely surpassed traditional electrochemical sensors in performance. However, due to reasons such as price and technical stability, emerging sensors want to quickly replace the market and position of traditional electrochemical sensors are relatively difficult.

From the macro perspective of sensor development, the literature shows that sensors have been developing in the direction of miniaturization, complexity, and sensitization, and the characteristics of the biomedicine field are just in line with the development characteristics of sensors. The literature shows that the application of nano-sensors in the field of biomedicine is progressing very fast. This is also a microcosm of the development of sensors in biomedicine. It is foreseeable that sensors will develop rapidly in the field of biomedicine.

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