Progress of Application of Microfluidic Chip

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Abstract. Due to microfluidic chip’s small sample consumption, high detection sensitivity, easy integration, automatic detection and other characteristics, it has been widely used in many fields such as environmental science, chemical detection, and life sciences. This article summarizes the current application and commercial development of microfluidic chips. At the same time, some deficiencies in the technology, problems to be solved and future development directions are also reviewed and prospected.

1. Introduction
Microfluidic chip, also known as Miniaturized Total Analysis Systems (TAS) or Lab on a Chip, refers to a miniaturized, integrated, automated chemistry and biology experiment platform which was established construction on a few square centimetres or smaller chip [1,2]. Microfluidic chip can integrate relevant basic operation units of chemistry and biology fields such as sample preparation, reaction, detection, cell culture, sorting, and lysis in the small chip. As a result, the microfluidic chip can be used to complete different biologic and chemistry reactions, and make microfluidic flow through the entire system via the network formed by micro channels to achieve various functions of conventional chemical or biological laboratories. The microfluidic chip also has broad application prospects in the fields of physics, chemical and biological analysis, pathological diagnosis and environmental monitoring. At the same time, microfluidic chips have been widely used in environmental science, chemical testing, life science and other fields due to their small sample consumption, high detection sensitivity, easy integration and automatic detection. This article summarizes the current application and commercial development of microfluidic chips. At the same time, some deficiencies in the technology, problems to be solved and future development directions are also reviewed and prospected.

2. Environment monitoring
Traditional environment monitoring requires the process of sampling, storage, transportation, determination and so on. At the same time, the operator requires relatively high skills and rich experience. However, current analysed sample of sensor monitoring has relatively small range and many interfering factors. As a result, these sensor monitoring cannot satisfy the needs of contemporary environment monitoring. The microfluidic chip has quick, simple and accurate analysis method and equipment when used for on-site testing to get quick analysis result, reduce cost and contamination risk during sample transportation. Buffi et al [3]. put E. coli coated agarose beads into chip to measure the content of arsenic in the water because the E. coli has different strength of fluorescence reaction to different content of arsenic. Willem Verboom et al. designed a simple v-
shaped microfluidic chip, which can send optical signals through optical fiber to construct a chemical sensor with high relatively high sensitivity. Moreover, this V-shaped microfluidic chip successfully achieved the detection of mercury ion in environmental water samples and the detection limit is 0.5 μm. Guoxia Zheng et al [4] designed and made a microfluidic chip integrated with a pollutant concentration gradient generator and a diffuse algae cultivation unit for the detection of algae toxins in water. Freitas et al [5] used microchip electrophoresis technology to detect Cl⁻, NO₃⁻, SO₄²⁻, NO₂⁻ plasma in fish tank water, biological fertilizer and river water.

Figure 1. Application of microfluidic chip in environmental monitoring; A. Microfluidic devices for arsenic detection [3]; B. Schematic representation of an immunoreaction chip used in the rapid detection of algal toxins [6].

3. Biological science

The high throughput, high sensitivity and high precision are three key technical indicators to the isolation and identification of biological macromolecules such as DNA, protein and other cells. However, current technology is too complicated, and has high consumption of sample along with instability and low sensitivity. On contrary, microfluidic chip has been widely used in cell analysis [7-9], DNA analysis [10-12], protein detection [13-15] and other research fields due to its advantages of high efficiency, fast speed, low sample consumption and so on. Chen et al. [8] developed a microfluidic network hybrid channel for concentration gradient generation in cell culture and drug screening, which further expand the liner range of mass spectrometry of chip and improved the linear index. As a result, Chen’s microfluidic network hybrid channel truly realized chip-mass spectrometry (Chip-MS) and combined qualitative and quantitative detection of cellular metabolites. Wang et al [7] combined microfluidic technology with chemiluminescence technology to establish a high-throughput method for dispersing single cells in water droplets surrounded by an oil phase and cultivating and analyzing them. This method can be used to screen out the only Saccharomyces cerevisiae cell that consumes excessive xylose from 104 cells, and analyze and determine the genomic changes that lead to this high xylose consumption. Woolley et al [11] first used chip capillary electrophoresis to conduct gene sequencing research, which sequenced 150 bases within 10 minute on a microfluidic chip with an effective separation length of 3.5 cm, achieving an accuracy rate of 97%. Gao et al [14] integrated degraded protein on the chip to make an integrated device for protein decomposition, peptide separation and mass spectrometry identification. Figeys et al [15] analyzed the carbonic anhydrase and bovine serum albumin standards degraded by parenzyme using sequential injection with chip capillary electric drive and tandem mass spectrometry. Some applications in the field of biological science are shown in Figure 2.
Figure 2. Application of microfluidic chip in biological science: A Cell analysis [9], B. PCR [12], C. Protein detection [13]

4. POCT

The fast speed, sensitivity and potential to replace conventional biological lab make microfluidic chip become the ideal carrier for the realization of Point of Care Testing (POCT), which is also the publicly recognized as the development direction of POCT. There are wide research and application of POCT from the analysis of pathogenic bacteria, virus detection, to body fluid (including blood, urine, saliva and, etc. [16-19]. The microfluidic chip POCT has obvious advantages in size, scale, and testing flexibility when compared with central laboratory. Moreover, the input of testing equipment and samples is largely reduced, and microfluidic chip POCT is faster, simpler, and more economical, especially for developing countries and regional areas that lack expensive large-scale testing equipment. Wang et al [20]. detected mutations of low-abundance genes (K-ras genes) on a microfluidic chip and used them for early diagnosis of rectal cancer. The microfluidic chip can detect one mutated K-ras gene sequencing from 10,000 normal sequences, which provides a sensitive and accurate detection platform for early diagnosis of rectal cancer. Cao et al [21]. of Boston University in the United States designed a microfluidic chip that can quickly and accurately diagnose seasonal and epidemic influenza strains (Figure 3. (A)). The chip developed by the Cao et al. can integrate a solid extraction and molecular amplification unit, which can achieve the amplification of influenza A virus RNA by reverse transcription polymerase reaction (TR-PCR). This microfluidic chip-based test greatly increases the culture time of virus and sensitivity of rapid immunoassay. At the same time, this chip-based test decreases the frequency of use of DFA and RT-PCR, which makes it become the possible tool to diagnose influenza. Fan et al [22]. established an integrated blood pressure analysis system (Figure 3. (B)) for protein analysis in microliters of blood. This platform can also separate serum in microliters of blood, and test multiple proteins. Easley et al [23]. used an electrochemical pump and a paraffin-type thermostatic valve to make a DNA pattern microfluidic detection system for judicial identification (Figure 3. (C)). Wang et al [24]. used a detection chip made of silicone gel membrane to detect HIV-1 virus. Moreover, the intensity of this system to detect HIV-infected T cells reached the level of a desktop PCR instrument.
In light of the huge application prospects of microfluidic POCT shown in the research development process, currently, many high-tech companies including Abbott, Alere, Abaxis, etc. have launched their own POCT products based on microfluidic chip. These products mainly focus on disease marker protein, infectious virus, and cell detection, etc., which make the entire industry move into a speedy development period around the world. Figure 4 lists common microfluidic equipment used for POCT. As shown in Figure 4 (A), Abbott company’s i-STAT bedside blood monitoring system is a representative product with a relatively early development in this field. The i-STAT entered the FDA (Food and Drug Administration) technical certification stage in the 1980s. The i-STAT system adopts a card structure design to support monitoring of blood gas, electrolyte, coagulation, biochemical and myocardial markers in the blood, and the test results can be obtained within 2 minutes. As shown in Figure 4(B), American company Alere's Triage system is a relatively successful commercial product of immunochromatography POCT. This system can directly detect acute myocardial infarction related markers through whole blood. The results for all analyses are quantified simultaneously within approximately 15 minutes after addition of the sample to the device. The blood analysis instrument developed by the HemoCue and Chempaq companies only require 10µL blood sample to achieve speedy and accurate measurement of blood parameters. This blood analysis instrument can satisfy the medical test requirements of community hospital and clinic. From the tendency of industrial development, microfluidic chip POCT instrument has been developing towards high sensitivity, multifunction, and portability. However, with the increased supervision of the POCT industry in countries such as Europe and the United States, the main commercialization and productization issues facing in this field during the short term are how to establish effective industry regulations and pass increasingly stringent qualification certifications.

Figure 3. Application of microfluidic chip in POCT:  A. Microfluidic Chip for detecting Influenza A RNA [21], B. Integrated barcode chips for analysis of proteins in microliter quantities of blood [22], C. A fully integrated microfluidic genetic analysis system [23]
Figure 4. POCT instrument products: A. i-STAT 1 System& test cartridge[25], B. Triage system, cartridge[26], C. White Blood Cell Count[27], D. Proxima Blood Gas Analyzer[28]

5. Research difficulties
The microfluidic chip has its own advantage in high integration, great accuracy, low cost, and speedy reaction. Moreover, the chip benefits from speedy development of micromachining technology, so it is likely that the chip can provide integrated and complex detection and diagnostic functions. However, limited by stereotype or industry system, there are still some problems those need to be solved for system research and productization. First, the problem of system integration [30]. Currently, the research about system integration mainly focus on breakthrough of single key technology, but design of systems for complex applications is in the ascendant. In order to satisfy clinical needs of early screening of tumour and multi-component detection of body fluid, it is necessary to integrate the micro extraction of sample collection, sequential mixing reaction, separation analysis, detection and other functions on a single microfluidic chip. At the same time, it is important to rationalize the design of valves, fluid channels and reactions pool and other units of microfluidic chip. Second, the ease of use. The microfluidic chip POCT instrument mainly targets at junior technicians or those without technical background. As a result, it is important to further improve the ease of operation to strengthen its adaptability to the environment, and reduce inaccurate or erroneous test results caused by unskilled operation to improve the reliability of the test results. Third, lack of specifications and relevant standards. A mature microfluidic product usually requires supporting reagents, core microfluidic chips, chip drive platform, photoelectric detection module, signal processing module, human-computer interaction software system and other components. However, during the industrialization of microfluidic chip, because of the immaturity of the technology and the lack of relevant specification and standards, there is currently no way to achieve the generalization of components. As a result, it is impossible to form a cooperative development model of upstream and downstream companies. The microfluidic chip product itself is a new combination of many disciplines such as micro-electromechanical processing, life sciences, chemical synthesis, optical engineering and electronic engineering. Consequently, the microfluidic product requires higher technology and longer development period, which result in difficult in making profits for breakthrough product like GeneXpert PCR analyser, due to high cost of research and development in the early stage.

6. Conclusion and Prospect
The microfluidic technology was developed from MEMS, which has many advantages and huge application prospects in single or cross-disciplinary areas such as biology, chemistry and medicine.
In spite of this, the microfluidic technology still requires a high level of integration of basic units such as sample preparation, reaction, separation, and detection in biological, chemical, and medical analysis with components such as power supply, driver, and control to truly its advantages. The various chip manufacturing technology can make relatively mature microfluidic chips, but commercial application is relatively limited and the biggest limit is whether large-scale production can be achieved with low cost.

With the development of new material technology and the improvement of informatization level, the microfluidic chip will have a greater upgrade in function depth and application breadth. First, chips become paper-based. The traditional microfluidic chips usually use photolithography to process matrix materials such as glass, silicon wafers, polymer polymers and other substrates. This process is complicated and has high cost. While the use of wax printing technology to build a micro-channel’s disposable paper-based microfluidic chip can further reduce weight and cost, which has broad application prospects for on-site live diagnosis under conditions of lack of development resources. Second, equipment is informalized. With the rapid spread of consumer electronics and wireless network technology, it provides huge opportunities and challenges for the network of microfluidic chips and home information systems, as well as telehealth and individualized services in the context of big data. Third, microfluidic product can be diversified. The characteristics of new materials such as carbon nanotubes, quantum dots, and gold nanomaterials can help microfluidic chip to further expand the range of current detection and diagnosis such as blood glucose, tuberculosis, HIV, heart markers. As a result, microfluidic chips are expected to cover many fields such as athletic sports, customs ports, emergency assisted medical treatment and so on.

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