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Review

DNA-based bioanalytical microsystems for handheld device applications

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Abstract

This article reviews and highlights the current development of DNA-based bioanalytical microsystems for point-of-care diagnostics and on-site monitoring of food and water. Recent progresses in the miniaturization of various biological processing steps for the sample preparation, DNA amplification (polymerase chain reaction), and product detection are delineated in detail. Product detection approaches utilizing "portable" detection signals and electrochemistry-based methods are emphasized in this work. The strategies and challenges for the integration of individual processing module on the same chip are discussed.
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Keywords: DNA; Bioanalytical microsystem; Lab-on-a-chip; Sample preparation; DNA amplification; Electrochemical detection

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1. Introduction

In the 21st Century, integrated and automated bioanalytical systems are going to play leading roles in medical, food, agricultural, environmental, and biodefense testing. At present, blood glucose and pregnancy testing along with antibody-based infectious diseases and biological warfare agent detection have a major share in this multi-billion-dollar market. In the coming years, thanks to the success of various genome projects and the advancement of nucleic acid (NA)-based molecular techniques, nucleic acid testing (NAT) will bring revolutionary changes to this rapidly growing biochip sector. These NA-based micro/nanoanalyzers are expected to offer much higher sensitivity and specificity than non-NA-based technologies.

Since the early work of deoxyribonucleic acid (DNA) manipulations in microchips by Northrup et al. [1] and Woolley et al. [2], tremendous research activities have been carried out to miniaturize the conventional DNA analytical procedures in microchip platforms. These microdevices enjoy the miniaturization advantages of small size, low sample,

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reagent and power consumption, enhanced analytical performance (e.g. shorter assay time), and high level of integration. An ideal microanalyzer should feature sample in result out kind of automated operation, without any human intervention between individual assay steps. There are three essential components in a complete DNA assay protocol, which include sample preparation, target amplification, and product detection. The implementation of these functionalities on-chip has been individually optimized prior to their final integration. For instance, Northrup et al. developed DNA amplification chips [1,3], whereas Woolley et al. developed capillary electrophoresis (CE) chip [2]. Afterwards, they combined the two modules to form a microfabricated DNA analysis device [4]. Wilding et al. was another example, they studied microchambers for DNA amplification [5–7] and microfilters for cell separation [8,9] separately first. Again, these amplification and preparation functionalities were later integrated onto a single microchip [10].

In the past decade, many integrated DNA analyzers have been developed [11–20]. Of utmost importance, some of these technologies have been successfully commercialized, bringing clinical and on-site NAT into a reality. Companies engaged in this business include Affymetrix (GeneChip® Instrument System [21]), Agilent Technologies (2100 Bioanalyzer [22]), Alderon Biosciences (AndCare 100/800/9600 Portable Electrochemical Instruments [23]), Caliper Life Sciences (LabChip 90 Electrophoresis System [24]), Cepheid (GeneXpert® System [25] and SmartCycler® System [26]), eBiochip Systems (Electrical Array Analyzer [27]), Gen-Probe (Direct Tube Sampling System, DTS™ [28]), Idaho Technology (Ruggedized Advanced Pathogen Identification Device, R.A.P.I.D.® [29] and RAZOR Instrument [30]), IQuum (Liat™ System [31]), Nanogen (NanoChip® Molecular Biology Workstation [32]), Nanosphere (Verigene™ Platform [33]), Roche Molecular Diagnostics (COBAS AMPLICOR™ Analyzer [34]), just to name a few. Most of these instruments have already been widely utilized in central, clinical, and research laboratories, but have not been applied to patient's bedside, doctor's office or battlefield settings yet. This is partly due to the large footprint of these systems, which is attributed to the inclusion of supporting equipment such as pump, thermal cycler, optical detection system, etc.

To date, a number of reviews on micro total analysis systems (μTAS) for NAT have been published [35–45]. These general reviews put much emphasis on the state-of-the-art integrated devices, in particular, CE and microarray technologies, which are not targeted for point-of-care (POC) diagnostics and on-site testing. If future handheld NAT devices would like to gain the acceptance like that of the glucose meter, additional attention should be given to the simplicity, versatility, and multiplexing capability of the systems. In this review, we focus on technologies that are promising in realizing future portable DNA analyzers for POC testing of infectious diseases (e.g. human immunodeficiency and hepatitis C viruses), on-site food and water monitoring (e.g. severe acute respiratory syndrome (SARS)-associated coronavirus in avian stock and *Escherichia coli* O157:H7), as well as bioterrorism agents detection (e.g. *Bacillus anthracis*). The organization of the following contents is based upon the three basic DNA processing modules of sample preparation, target amplification, and product detection. All relevant on-chip techniques will be covered, except that the product analysis is limited only to electrical/electrochemical detection strategies, which are well suited for total system miniaturization. It should be noted that most of the on-chip sample preparation and DNA amplification techniques were developed before year 2001, while many elegant electrochemical detection schemes were developed after 2001. Finally, directions in the future developments of these DNA-based bioanalytical microsystems are discussed.

2. Sample preparation

The purpose of sample preparation in NAT is to obtain nucleic acids, which can be DNA and/or ribonucleic acid (RNA), of sufficient purity and integrity from raw samples for subsequent amplification and detection. In a conventional setting, it consists of quite a number of steps for cell isolation and lysis followed by NA extraction and purification [46]. Depending upon the sample type, NA concentration, and tolerance of the amplification system, different protocols are needed to prepare amplification-ready samples via the simplest and fastest route. A diagram showing these processing flows is given in Fig. 1. The easiest situation is that the sample can be directly added to the amplification mixture, without any pretreatment step. This is only applicable to "clean" samples having negligible amount of substances that inhibit the enzymatic target sequence amplification. The

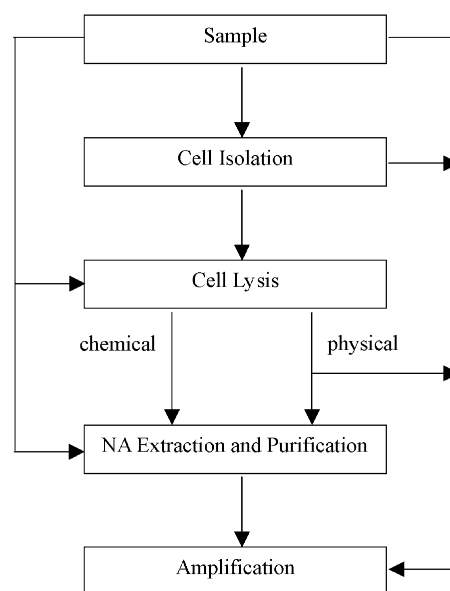

Fig. 1. Diagrammatic representation of the processing flows in sample preparation.

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