Recent Advances in Development of Microfluidic Systems and Applications in Vietnam

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Abstract. Microfluidic technology or microfluidics has emerged as a revolution with major impacts in many research and development (R&D) fields and applications; it deals with the behaviour, precise control and manipulation of fluids that are geometrically constrained to a small, typically sub-millimeter, scale. Microfluidics has applications in many research and industrial areas, including chemical and materials synthesis, biological analysis, biomedical engineering and biosensing. Microfluidic technology and applications, especially microfluidic platforms or systems which provide a set of fluidic unit operations, have been rapidly developed and investigated in recent decades; however, microfluidics is still a new and emerging R&D area in Vietnam, especially in both aspects of R&D investments and commercialization. This paper presents the key points and an overall picture about R&D of microfluidics in Vietnam recently, especially development of microfluidic systems and applications. Issues related to R&D collaborations as well as suggestions for development of microfluidic systems and applications in Vietnam are also highlighted and discussed, aimed to stimulate fruitful collaborations between the UK and Vietnam, especially in the areas of innovative design and developments of smart sensors and devices for medical testing, diagnosis and treatments of diseases and cancers for the low income populations .

Keywords: Microfluidics, Single cell, Immunosensor, Microdroplet, Vietnam

1   Introduction

Microfluidics in general and microfluidic systems in particular have shown its great potential for many R&D areas and industrial applications, especially applications in the biological and biomedical field, which includes molecular biology, cellular biology and drug testing [1], as well as design and developments of smart sensors and devices for medical testing, diagnosis and detections of diseases and cancers. With the capability of manipulating and controlling a very small volume of liquid or reagent in the range of picoliters to nanoliters within microchannels, the microfluidic systems offer the valuable tools of high throughputs, accuracy, sensitivity, automation and cost-effectiveness for the biological analysis [2]. With the latest advancements in micro- and nanofabrication technologies, today's microfluidic systems are able to have various protocols and functional units integrated into a single chip platform to create a lab-on-a-chip (LOC) which integrates and automates multiple laboratory techniques into a system.

The potentials and useful applications of microfluidic systems in biological and medical fields were well documented, including the following ones: (1) LOC devices for the medical diagnosis and early detections of diseases and cancers, (2) Manipulations and analysis of single cells via the micro-channels, and (3) Protein crystallization via the control of a large number of crystallization conditions (temperature, pH, humidity…) on a chip [3].

Microfluidic technology and applications, especially microfluidic platforms or systems which provide a set of fluidic unit operations, have been rapidly developed and investigated; however, microfluidics is still a new and emerging research and development (R&D) area in Vietnam, especially in both aspects of R&D investments and commercialization. This paper presents the key points and an overall picture about R&D of microfluidics in Vietnam in the last decades, especially developments of microfluidic systems. Issues related to R&D collaborations as well as suggestions for further studies about development and commercialisations of microfluidic systems in Vietnam are also highlighted and discussed.

The rest of the paper is organized as follows. Section 2 presents a brief literature reviews about the R&D results and applications of microfluidics from the key R&D groups in Vietnam, including (1) Microfluidic devices for investigations and analysis of cancer cells; (2) DC^{4}D sensors integrated with the functional units of microfluidics; (3) Microfluidic devices for immunoassays which are bioanalytical methods in which the quantitation of the analyte depends on the reaction of an antigen (analyte) and an antibody; and (4) Development of microdroplet devices. Finally, Section 3 presents the key summaries and conclusions, as well as to address the potential R&D collaborations in microfluidics with the R&D institutions in Vietnam.

2 Microfluidic technology and applications in Vietnam

2.1 Microfluidic devices for investigations and analysis of cancer cells

With the latest advancements in micro- and nano- fabrication technology, microfluidic devices were developed for effective investigations and analysis of single cells [4,5]. T.A. Nguyen *et al*. (2013) developed a microfluidic device which was integrated with the electrical cell substrate impedance sensing unit for monitoring the single or multiple cancer cells behaviors, via the dynamic single cell trapping, cell attachments, cell spreading, and cell migrations [4]. Fig.1(a) illustrates the design of the microfluidic chip, in which the mi-croelectrode array (MEAs) and cell capture arrays (CCAs) are arranged inside a microfluidic channel. There are 16 microelectrodes in one channel, which are distributed symmetrically on the opposite side of a large counter electrode (CE). Each V-shaped cell trap structure in the CCAs is aligned with a small electrode to capture single cells from the flow. By utilizing the hydrodynamic trapping technique, single cells are trapped precisely on the microelectrode surface, as shown in Fig.1(b). An image of a packaged sensor chip is shown in Fig. 1(c). The chip can be used for

monitoring the behaviours of a single or multiple cancer cells on the difference micro-electrode sizes and their response to the anticancer drug treatment [4].
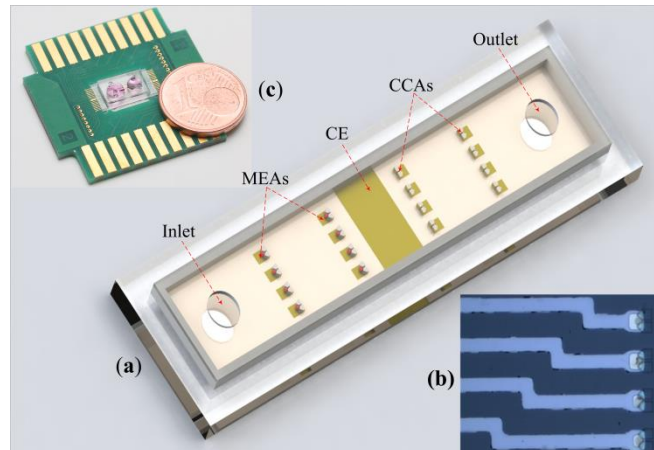

Fig. 1. Microfluidic chip for investigating cancer cells: (a) Design of the chip; (b) The micrograph of trapped single cells on the microelectrodes; (c) The image of a packaged sensor chip [4].

Dielectrophoresis (DEP) is another popular technique, which is used for the cell detection and cell manipulations [6]. This approach allows controlling the single biological cells by utilizing the movement of particles in the non-uniform electric fields that are compatible with the development of microelectronic technologies and fabrication flow of the CMOS (complementary metal-oxide-semiconductor) integrated circuits [13]. C.D. Trinh *et al.* (2017) have developed the DEP microfluidic system with the built-in antibody-based capacitive chip for the tumour rare cells enrichment and detection [7]. The experimental results demonstrated the good effect of the DEP force used for manipulating the living cells to the centre of the working chamber. However, the results need to be improved in order to get a better efficiency.

2.2 DC⁴D sensors integrated with the functional units of microfluidics

In order to detect an object in a microfluidic channel, Trinh C.D. *et al*. (2015) investigated design and development of a differential capacitively coupled contactless conductivity detection (DC⁴D) sensor with the thin polydimethylsiloxane (PDMS) protective layer [8]. The differential capacitance is varied if a micro particle crosses the channel. This sensor has four adjacent electrodes which are arranged to form differential coplanar capacitor structures to offer a high sensitivity. In [9], this group presents a fabrication, and characterization of this sensor. The sensor is fabricated based on a PCB where the electrodes are directly connected to processing circuit. The proposed DC⁴D

sensor can be used for both conductive and non-conductive channels. Various kinds of particles have been tested (i.e air bubbles and tin particles for non-conductive fluidic scenario and plastic particles for the conductive fluidic scenario). On the latter study, they proposed a microfluidic platform with this DC^{4}D technique [10]. This platform has a protective SiO_2 layer in order to insulate the micro electrodes from the electrolyte. Thus, the capacitance varies due to the change of the dielectric permittivity and conductivity of the medium inside the channel.
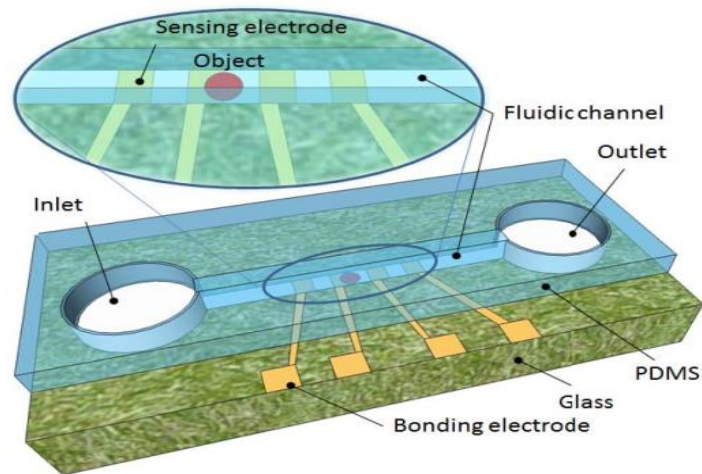

Fig. 2. Design of the DC^4 D sensor [8]

This proposed sensor can be used for both conductive and non-conductive fluid media. This novel design can not only detect the presence of an object but also volume, velocity, as well as electrical property (conduct/non-conduct) of the investigated object.

2.3   Microfluidic devices for immunoassays

There has been a great deal of attention recently to design and development of immunosensor platforms. In comparison to the conventional immunoassay methods, microfluidic immunosensors provide the several advantages, including an increased surface-to-volume ratio, leading to the fast analysis, reductions of the consumption of samples and reagents due to a miniaturized microchannel dimension, and the automated integration with the other functions, such as valves, pumps, mixers, and detectors, in order to achieve a point-of-care goal [11]. Trinh C.D *et al.* developed a low-cost, compact microfluidic chip for detections of proteins. The microfluidic channel enriches the proteins in the sensing area based on the ion exclusion-enrichment effect (EEE) and electroosmotic force created by using low DC voltages at the inlets channel of the fabricated microfluidic system. The immobilized antibody electrodes caught exactly the target proteins in the flux, while the non-target proteins are washed away. The presence

of proteins on the electrode surface causes the change of the impedance between the two sensing electrodes. Consequently, the target proteins can be detected. Schematic of the integrated impedance sensing electrode for the detection of proteins based on the ion exclusion-enrichment effect (EEE) has been proposed as in Fig.3 [12].
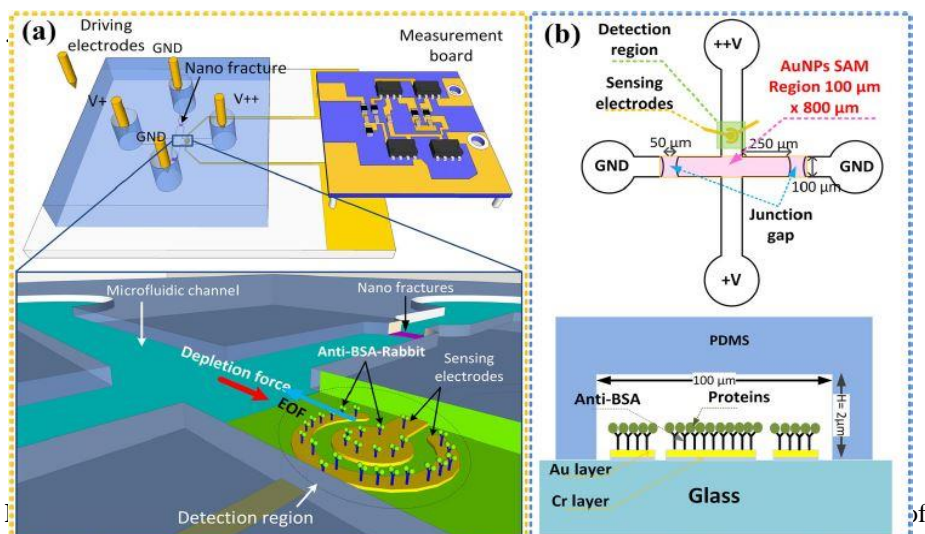

Fig.3. Schematic of the integrated impedance sensing electrode for the detection of Proteins based on the ion exclusion-enrichment effect (EEE). (a) Highly sensitive lock-in amplifier technique is employed for quantitatively recognizing proteins at the designated detection window. (b) Details of microfluidic channels and gold nanoparticle region [12].

Another application of microfluidic immunosensor is investigated by Van Anh *et al.* (2016). They developed a reusable microfluidic device for the rapid and sensitive quantification of a carcino-embryonic antigens tumor marker [13].

2.4   Development of microdroplet devices

Microdroplets are used in many different industries, including the inkjet printing [14] and pharmaceutical industry. Recently, microfluidic has become a popular method due to their ability of generating the highly uniform droplets and the ease of size control [15], compared to the conventional methods. The T-junction is the most popular microfluidic device used for generation of the droplet [16].

Xuan *et al.* (2011) developed the T-junction microfluidic systems to fabricate microdroplets, with the detailed experiments and simulations [17]. The T-junction geometry

is illustrated in Fig.4, consisting of a center channel with width, **Wc,** and a lateral channel with width, **Wd**. The channel is planar with a uniform depth h. The continuous phase (here oil) which the liquid flows at a rate Qc is pumped through the center channel, while the dispersed-phase (here water) which the liquid flows at a rate Qd is pumped through the lateral channel. Size of microdroplet can be controlled by changing the flow rate of continuous and dispersed phases as well as size of channels.
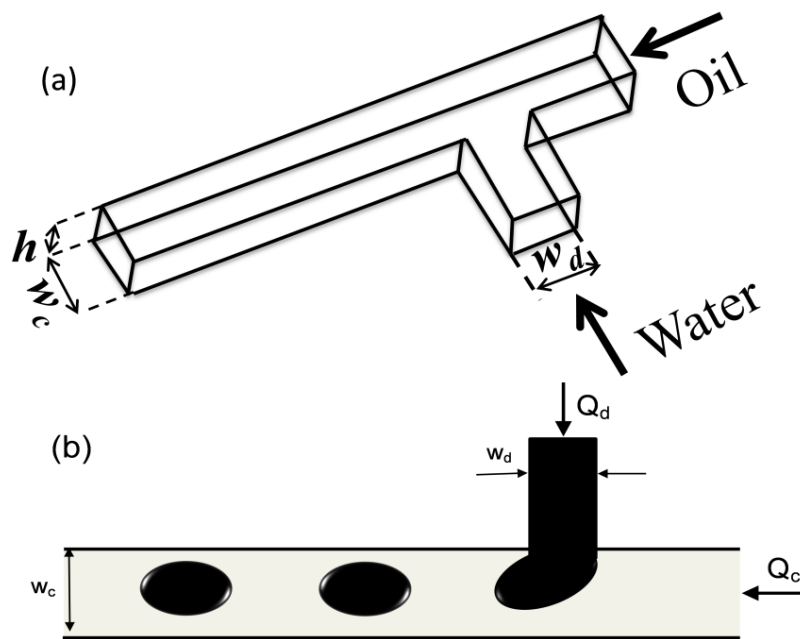

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crofluidic T-junction [17].

3 Discussions and conclusions

In this paper, the key points and an overall picture about the latest developments about the microfluidic technology and applications in Vietnam are reviewed and highlighted. There have been lots of efforts working on R&D activities in the areas of microfluidics, especially innovative and cost-effective design and development of sensors or the LOC devices for different kinds of applications in biology and medicine, with the focus on development of microfluidic-based sensors and devices that provide the remarkable features that outperform those of conventional systems, including the reduced power consumption, diminished consumption of samples and reagents, low-cost system, and compact size.

Since R&D in micro- and nano-manufacturing technologies in general and microfluidics in particular requires multidisciplinary collaborations and big investments. It is necessary and important for developing countries such as Vietnam to take into accounts the following points in order to take advantages of the rapid advancements of the technologies for enhancements of both R&D capability and capacity: (1) Identifications of the right local needs and markets, especially the ones of big impacts such as medical diagnosis and early detections of diseases and cancers; (2) Effective and fruitful collaborations with the international R&D groups via the direct involvements of the collaborative R&D projects and mobility of the researchers, and (3) Innovative and cost-effective design and developments of the products for the low-income populations.

The big scientific and technological (S/T) impacts in the areas of biology and medicine from the micro- and nano- manufacturing technologies in general and microfluidics in particular can be easily recognized via the well-documented applications with the use of smart sensors and devices for medical testing, diagnosis and treatments. In addition, recently, Vietnam government has strongly supported and invested for science and technology via the funding agencies and projects such as National Foundation for Science and Technology Development (NAFOSTED), Fostering Innovation through Research, Science and Technology (FIRST), and National Technology Innovation Fund (NATIF). Together with the funding sources from the UK such as Newton Fund, there are potentials for fruitful collaborations technology for researchers in Vietnam and the UK in the areas of microfluidics and innovative development of smart devices and effective solutions for low-income populations. Especially, Vietnam is ranked the 12_{th} in the incidence (2.6/100,000) and death (1.0/100,000) about cancer diseases; and annually, there are nearly 125 thousand people who are diagnosed with the cancers in Viet Nam [18]. The key points presented in this paper about the recent developments of microfluidic technology and applications in Vietnam could be the good references and update to open fruitful collaborations among researchers in the UK and Vietnam in the areas of micro- and nano-manufacturing in general and microfluidics in particular, to create the big S/T impacts, especially to improve the life quality of the low-income populations.

Acknowledgment

Conflict of interest

The authors declare that they have no conflict of interest.

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