

Application of Microfluidics in Bioprocesses

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What is microfluidics?

Microfluidics is an interdisciplinary area that involves the study of behaviors of fluids, controlled fluid manipulations, and the design of the devices that can effectively perform such manipulations at microscale (tens to hundreds of micrometers). It has been broadly used to miniaturize analytical methods and chemical/biological processes because of its many advantages, such as significant reduction in analysis time, much lower sample and reagent consumption (in the nanoliter range or less), and enhanced system performance and functionality by integrating different components onto individual devices [1,2]. These applications are usually called micro Total Analysis Systems (μ TAS) [3] or lab on a chip (LOC) [4].

One major feature of microfluidic devices is their high surface-area-to-volume ratio, which leads to enhanced heat and mass transfer, and also interfacial phenomena that are not usually observed at macroscale, such as the domination of surface forces instead of inertial and body forces [5]. The fluid flow within a smooth-walled microchannel is typically in the laminar region with a Reynolds number (Re) less than 100 [6]. The Reynolds number is a dimensionless number representing the ratio of inertial to viscous forces, which indicates the relative importance of these two forces under a given flow condition. It is defined as follows:

$$Re = \frac{DV\rho}{\mu} \quad (1)$$

where D is the hydraulic diameter, V is the characteristic velocity, and ρ is the fluid density. For $Re < 2100$, the flow is in the laminar region. Another important feature of microfluidic devices is their capability of integrating multiple steps onto one single device, ranging from sample processing to separation and detection. By mass production, it is possible to develop high-throughput processes using microfluidic devices by parallelization [7,8].

Microfluidic Device Fabrication

Based on the success of Micro Electro Mechanical Systems (MEMS) and microelectronics industry in the 80s, microfluidic devices were initially fabricated with glass and silicon using the well-established photolithographic techniques (Figure 1a). Later on, depending on the process parameters, microfluidic devices have been fabricated with different materials, including ceramic, steel, silicone, and Teflon [9,10]. Polymers are now often used as construction materials to replace glass and silicon because of their lower cost and simpler fabrication process without the need for nasty chemicals. Particularly for biological applications, Poly Dimethyl Siloxane (PDMS) is the most popular material in microfluidic device fabrication because of its many advantages, such as optical transparency, biocompatibility, elasticity, and simple fabrication process ("soft lithography") [11-13] (Figure 1b). More information on PDMS microfluidic devices is available in several reviews and the references cited therein [14-16].

Application in Bioprocesses

Bioprocesses have severed as an important means to support survival and fulfill different needs for thousands of years in the

human history. Early bioprocesses (ca. 4000 BC) employed natural microorganisms, such as yeasts and fungi, to produce different products, including bread, beer, and cheese. The first purification step was ethanol distillation carried out around 2000 BC [17,18]. With advances in science and engineering, bioprocesses increases in both production scale and complexity with integrated processing steps. In addition to nature microorganisms, modern bioprocesses also use other agents, e.g. enzymes and cells from plants, insects, and animals, to produce various products, including organic acids, antibiotics, and therapeutic compounds [19]. Bioprocesses are developed by combining different basic steps (or "unit operations", introduced by Arthur D. Little in 1915), such as fermentation, filtration and drying. For decades, scaling up from benchtop via a pilot plant to a full blown one has been the standard practice of the development of industrial-scale bioprocesses. However, it is faced with challenges from the more stringent requirements, such as size and cost reductions in equipment, lower energy consumption and waste emission, and a safer operation

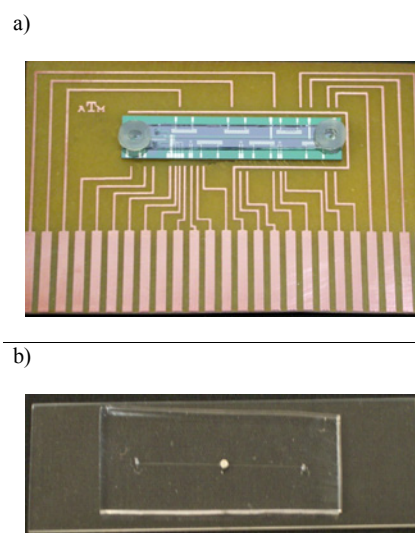


Figure 1: Microfluidic devices for biological applications. a) A device fabricated with glass and silicon using photolithography for microchip DNA gel electrophoresis [29]. b) A device fabricated with glass and PDMS using soft lithography for on-chip enzymatic reactions with derivatized magnetic microbeads [30].

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environment, due to the new trend of using sustainable production schemes in bioprocesses. To address these challenges, an approach called “process intensification” has been used to improve bioprocesses. It focuses on developing new equipment and methods that leads to more cost-effective and sustainable bioprocesses [20,21].

Since its debut in the 90s [22-24], microfluidics has made significant progress through the piling up research results. It has found many biological applications, such as gene/protein manipulation and analysis, cell-based systems, biosensors, and drug discovery and delivery [25,26]. Microfluidic devices have recently come into attention as a powerful tool for bioprocess intensification because of their low fabrication costs and reagent consumption, small form factors for safe operation in a controlled environment, and capability of integrate multiple basic steps onto one chip. A lot of work has been directed to the development of microreactors for enzymatic reactions (e.g. hydrolysis, esterification, oxidation/reduction, and polymerization). For downstream processing, microfluidic devices have been used to develop systems for separation of cells and purification of therapeutic compounds. The results so far are very promising for miniaturized bioprocesses. More information on the miniaturization of bioprocesses can be found in the literature [27,28].

The Outlook

For the past two decades, microfluidics has made great strides and has gradually moved from pure research projects to commercialized products, such as Agilent Technologies’ 2100 Bioanalyzer for biomolecule analysis, Caliper Life Sciences’ LabChip systems for biomolecule analysis and drug discovery, and FutureChemistry’s microreactor systems for process optimization. Although microfluidic systems are still not the dominating ones in bioprocesses, their future is very promising as indicated in reported research results. Along with advances in materials and fabrication processes, new discoveries of fluid behaviors at microscale might lead to new reaction mechanisms that are not possible on conventional macroscale systems.

Microfluidic systems are also potential for industry-scale bioprocesses because of their capability of parallelization. The throughput of such systems can be significantly enhanced by increasing the number of optimized microreactors (“scale out”) instead of the conventional scale-up process that is more expensive and carries more uncertainties. Based on reports in the literature and commercial products currently available, it is foreseeable that there will be cost effective, “plug and play” microfluidic systems with customizable reaction modules for bioprocesses. The user will be able to customize his or her reactions in the desired bioprocess by switching different microreactors, just like what we do today to change our computer configuration by swapping plug and play components.

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