DEVELOPMENT OF MICROFULUIDIC DEVICES FOR HIGH-THROUGHPUT BIOLOGICAL AND CHEMICAL ANALYSIS

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I will describe recent studies that are focused on exploiting the spontaneous formation of droplets in microfluidic systems to perform a variety of analytical processes and the use of novel optical techniques for the interrogation of small volume environments. Specifically passive, functional components for droplet merging and dilution are presented, along with their application in high-throughput biological and chemical processing.

Introduction

The past two decades have seen considerable progress in the development of microengineered systems for use in the chemical and biological sciences. Interest in such microscale technologies has in large part been driven by concomitant advances in the areas of genomics, proteomics, drug discovery, high-throughput screening and diagnostics, with a clearly defined need to perform sensitive measurements in short times and on small sample volumes. Put simply, microfluidic activities have been stimulated since physical processes can be more easily controlled when instrumental dimensions are reduced to the micron scale [1].

The relevance of microfluidic technology is significant and characterized by a range of features that accompany system miniaturization. Such features include the ability to process small volumes of fluid, enhanced analytical performance, superior control of fluid flow, reduced instrumental footprints, low unit costs, facile integration of functional components and the ability to exploit atypical fluid behaviour to control chemical and biological entities in both time and space. Based on these beneficial characteristics, microfluidic systems have been successfully used in a wide variety of applications including nucleic acid separations, proteomic, process control, small-molecule synthesis, DNA amplification, immunoassays, cell manipulations, nanomaterial synthesis, DNA sequencing, and diagnostics.

Herein I summarize recent studies that are focused on exploiting the spontaneous formation of droplets in microfluidic systems to perform a variety of analytical processes. Specifically passive but functional components for droplet merging and dilution are presented, along with their application in high-throughput biological and chemical processing.

Droplet-based microfluidics

Droplet-based microfluidic systems allow the generation and manipulation of discrete droplets contained within an immiscible continuous phase [2]. They leverage the immiscibility of the two phases to create discrete volumes that reside and move within a continuous flow.

In liquid-liquid segmented flow microfluidics, droplets of the dispersed phase are produced as a result of the shear force and interfacial tension at the fluid-fluid interface. Droplet generation can be achieved using a variety of strategies. A co-flow microfluidic device generates droplets of one fluid in another immiscible fluid using two coaxial capillaries. In a T-junction microfluidic device, two immiscible fluids intersect perpendicularly and form an interface at the junction where the droplets are created. Finally, in a flow-focusing microfluidic chip the two phases are forced in parallel through a narrow nozzle (or channel constriction) where the dispersed phase can be pinched off. Significantly, such segmented-flows allow for the production of monodisperse droplets at rates in excess of tens of KHz and independent control of each droplet in terms of size, position and chemical makeup. These unique features have significant potential in biomedical engineering, high-throughput screening and massively parallel experimentation.

The use of droplets in complex chemical/biological processing relies on the ability to perform a range of integrated, unit operations in high-throughput. Such operations include droplet generation, droplet merging/fusion, droplet sorting, droplet splitting, droplet dilution, droplet storage and droplet sampling.

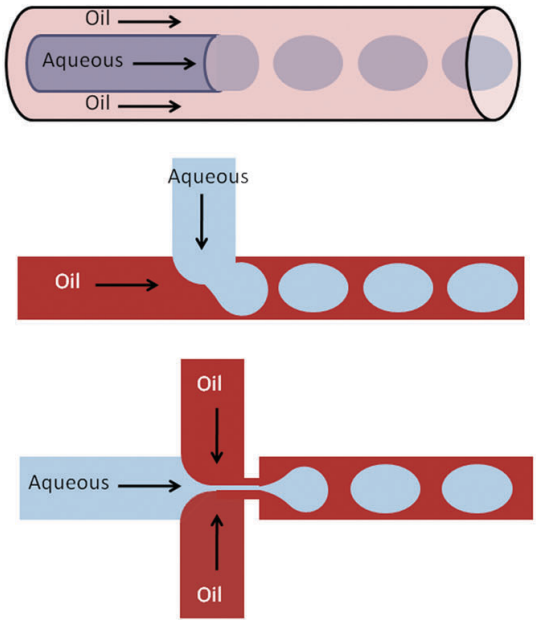

Figure 1 Droplet generation strategies using co-flow in a capillary (top), a T-Junction in a planar chip (middle) and flow focusing in a planar chip (bottom). Taken from reference 2.

Droplet merging is a fundamental process allowing the combination of reagents to initiate or quench a chemical reaction [3]. Merging can be achieved using either passive or active strategies. Passive droplet merging is based on the control of the channel geometry to induce coalescence. Alternatively, active merging is achieved through the application of external stimuli such as electric forces, surface acoustic waves and the thermocapillary effect. Pipetting and dilution are also basic laboratory processes. In microfluidics such operations are equally in demand, but difficult to implement. To this end, we have developed a dilution module for high-throughput screening [4]. Briefly, a nanolitre-sized sample droplet of specified concentration is trapped within an asymmetric microfluidic chamber. Through a process of droplet merging, mixing and re-splitting, this droplet can be combined with a series of smaller buffer droplets to generate a sequence of daughter droplets that define a digital concentration gradient. Importantly, the formed droplets can be merged with other reagent droplets to enable rapid chemical and biological screens. As a proof of concept, we have used the dilutor to perform a high-throughput homogeneous DNA-binding assay using only nanoliters of sample.

We have also used droplet-based microfluidic systems to perform nanomaterial synthesis, cell-based assays and DNA amplification [2].

The Author

Andrew deMello is Professor of Biochemical Engineering at ETH Zurich. His research group is engaged in a broad range of activities in the general area of microfluidics and nanoscale science. Primary specialisations include the development of microfluidic devices for high-throughput analysis, ultra-sensitive optical detection techniques, nanofluidic reaction systems for chemical synthesis and the exploitation of semiconducting materials in diagnostic applications. More recently, a key focus of research efforts in the group has been the development of droplet-based microfluidic systems for the processing of biological systems and live organisms. The primary goal of all these activities is to create high-throughput systems able to perform millions of complex chemical and biological processes in short times and on miniscule sample volumes. Dr deMello has published 200 papers in peer-reviewed journals and given over 250 invited talk in Europe, Asia and North America. Science originating from the group has been recognized through awards that include, the Pioneers of Miniaturization Award (Dow coring, 2012), Corday Morgan Medal (Royal Society of Chemistry, 2009); Clifford Paterson Medal (The Royal Society, 2009); the Clark Memorial Lectureship (California State University, 2007); and the SAC Silver Medal (Royal Society of Chemistry, 2002).

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