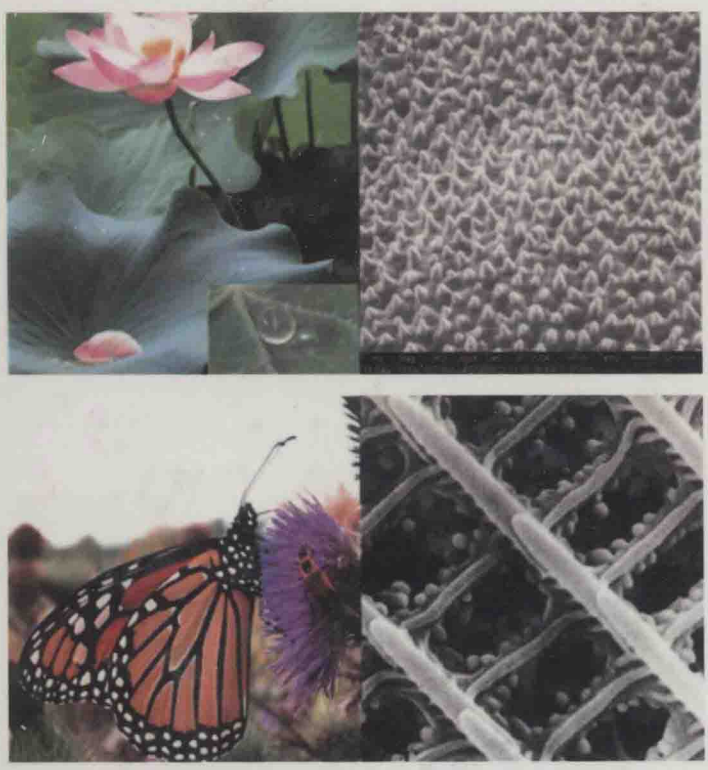
Edited by
Challa S. Kumar

Microfluidic Devices in Nanotechnology

Applications



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MICROFLUIDIC DEVICES IN NANOTECHNOLOGY

PREFACE

I hope you had an opportunity to go through the first volume. It gives me immense satisfaction in placing the second volume of the two-volume book series—*Microfluidic Devices for Nanotechnology: Applications*—in your hands. The second volume is the first book ever to be published that covers nanotechnology applications using microfluidics in a broad range of fields, including drug discovery, biosensing, catalysis, electrophoresis, enzymatic reactions, and synthesis of nanomaterials. While the first volume, *Microfluidic Devices for Nanotechnology: Fundamental Concepts*, in its combined form provides readers an up-to-date knowledge of the fluid and particle kinetics, spatiotemporal control, fluid dynamics, residence time distribution, and nanoparticle focusing within microfluidics, the second volume primarily captures up-to-date applications. The book fills in a long-term gap that existed for the real-time measurement of biomolecular binding in biosensors and justification for incorporating nanoporous membranes into "lab-on-a-chip" biosensing devices. Focusing on lab-on-a-chip systems for drug delivery (also called bio-MEMS), separating bioanalytes using electrophoresis, genomics, proteomics, and cellomics, the book is a must for biologists and biochemists. Highlighting the importance of nanoneuroscience, the book educates the reader on the discipline of microfluidics to study the nervous system at the single-cell level and decipher physiological processes and responses of cells of neural origin. For a nanomaterials chemist interested in novel approaches for synthesis of nanomaterials, this book is an excellent source of information covering a wide variety of microfluidic-based approaches for synthesis of metallic and nonmetallic nanomaterials. Finally, opening a window for the next-generation alternative energy portable power devices, nanocatalyst development for industrially useful reactions in silicon-based microreactors is discussed especially in the context of syngas conversion to higher alkanes, which could solve current difficulties of storage and transportation

by converting natural gas into liquid fuels. Overall, the book contains reviews by world-recognized microfluidic and nanotechnology experts providing strong scaffolding for futuristic applications utilizing synergy between microfluidics and nanotechnology.

Chapter 1 by Drs. Pamela G. Gross and Emil P. Kartalov focuses on the application of microfluidic devices to study the nervous system at single-cell level using nanotechnologies. This chapter describes various aspects of microfluidic chips used to decipher physiological processes and responses of cells of neural origin with examples of novel research not previously possible. Continuing on a similar theme, Chapter 2 by Professor Shalini Prasad et al. provides a detailed account of real-time biomolecular sensing through incorporation of nanoporous membranes, man-made as well as natural, into "lab-on-a-chip" biosensing devices. In addition to nanoporous membranes, simple spherical nanoparticles are finding novel applications when incorporated within the microchannels. Chapter 3 by Professor Giovanna Marrazza reviews the most recent applications of nanoparticles within microfluidic channels for electrochemical and optical affinity biosensing, highlighting some of their technical challenges and the new trends. Chapter 4 by Professors Chunhui Deng and Yan Li presents the recent advances in the field of immobilized microfluidic enzymatic reactors (IMERs), which constitutes a new branch of nanotechnology. In view of the increasing use of lab-on-a-chip systems in the healthcare industry, there is a growing demand for discovery, development, and testing of active nanodrug carriers within the microfluidic environment for controlled drug delivery. Chapter 5 by Professor Clement Kleinstreuer and Jie Li provides a comprehensive treatise on fundamentals and applications of microfluidics and bio-MEMS with respect to nanodrug targeting and delivery.

Capillary electrophoresis (CE) and microchip electrophoresis (MCE) are two promising separation techniques for analyses of complex samples, in particular, biological samples. Not surprisingly, these techniques have been profoundly influenced by the advances in nanotechnologies. Chapter 6 by Muhammad J. A. Shiddiky and Professor Yoon-Bo Shim covers the recent developments and innovative applications of nanomaterials as stationary and/or pseudostationary phases in CE and MCE. This chapter illustrates the importance of various types of nanomaterials, including metal and metal oxide nanoparticles, carbon nanotubes, silica nanoparticles, and polymeric nanoparticles, in enhancing the separation of biological samples using CE and MCE. The examples we have seen so far involve externally fabricated nanomaterials, which are later on utilized for a number of applications within the microfluidic channels. Chapter 7 by Drs. J. Shi and Yong Chen discusses pillars and pillar arrays integrated into microfluidic chips in the fabrication process itself. This chapter demonstrates how such an approach provides a large variety of functionalities for molecule and cell biology studies.

The applications we have seen so far in the first seven chapters range from biology to drug delivery. Chapter 8 by Shihuai Zhao and Professor Debasish Kuila is uniquely placed in the book as it brings out the recent recognition for microreactor as a novel tool for chemistry and chemical process industry, such as fuel industry. This chapter presents silicon-based microreactors for the development of nanocatalysts for

industrially useful reactions. For example, methanol steam reformer to produce H_2 and CO purifier is described in detail for potential microreactor applications in the next generation of alternative energy for portable power devices.

The last example that the book provides is the application of microfluidic reactors for the synthesis of nanomaterials. With the increase in the demand for high-quality metal nanoparticles with narrow size, shape distribution, and homogeneous composition, the continuous-flow microfluidic processes are gaining attention as they are particularly suited for realizing constant mixing, reaction, and quenching conditions necessary for production of high-quality metallic nanomaterials. Chapter 9 by Dr. Ali Abou-Hassan et al. reviews the recent scientific literature concerning the use of microfluidics for the synthesis of the iron oxides nanomaterials. Chapter 10 by Professor J. Michael Köhler and coworkers is a fitting conclusion to the book delineating a number of promising opportunities and challenges for the application of microreaction technology for the synthesis and manipulation of metallic nanoparticles. In combination with the Chapter 9 in Volume 1, this will provide a strong platform from both theoretical and experimental perspectives on synergism between microfluidics and nanotechnology for automated microreactor-based controlled synthesis and engineering of nanomaterials for a number of applications.

In conclusion, the two volumes bring out a clear understanding of theoretical and experimental concepts of microfluidics in relation to nanotechnology in addition to providing a seamless transition of knowledge between and micro- and nanofluidics. The contributors for both the volumes are world-renowned experts exploiting the synergy between microfluidics and nanotechnology. I am very much grateful to all of them for sharing my enthusiasm and vision by contributing high-quality reviews, on time, keeping in tune with the original design and theme of both the volumes. You will not be having this book in your hand but for their dedication, perseverance, and sacrifice. I am thankful to my employer, the Center for Advanced Microstructures and Devices (CAMD), who has been supporting me in all my creative ventures. Without this support, it would be impossible to make this venture of such magnitude a reality. No words can express the understanding of my family in allowing me to make my home a second office and bearing with my spending innumerable number of hours in front of the computer. It is impossible to thank everyone individually in this preface; however, I must make a special mention of the support from Wiley in general and the publishing editor Anita Lekhwani in particular, who has been working closely with me to ensure that this project becomes a reality. I am grateful for this support.

Note: Additional color versions of selected figures are available on ftp://ftp.wiley.com/public/sci_tech_med/microfluidic_devices_concepts

Baton Rouge, LA, USA
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MICROFLUIDICS FOR NANONEUROSCIENCE

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1.1 INTRODUCTION

The nervous system of an organism is like the information technology department of an organization. Each of the billions of building blocks of the nervous system, called neurons, is a multistate device similar to the transistors of a microprocessor. But while transistors are binary state devices, neurons are capable of being in many thousands of states, and this adds many orders of magnitude to the complexity of possible connections within a nervous system. In addition, each neuron has multiple connections with other neurons, and some of these connections are bundled into tracts and nerves that travel within brain and spinal cord, and out to peripheral locations. In computers, disconnection of one network cable, or disabling of the electronic circuits in the server, can seriously compromise the function of the organization. Similarly, traumatic injuries or neurodegenerative processes such as multiple sclerosis, Alzheimer's disease, or Parkinson's disease can significantly impair the functionality of an individual by damaging the neurons, tracts, and nerves. However, unlike computer systems, medical repair processes do not yet exist because we do not yet understand how the system operates in the healthy state. This may change in the near future as cell biologists pursue stem cell interventions to regenerate or remodel

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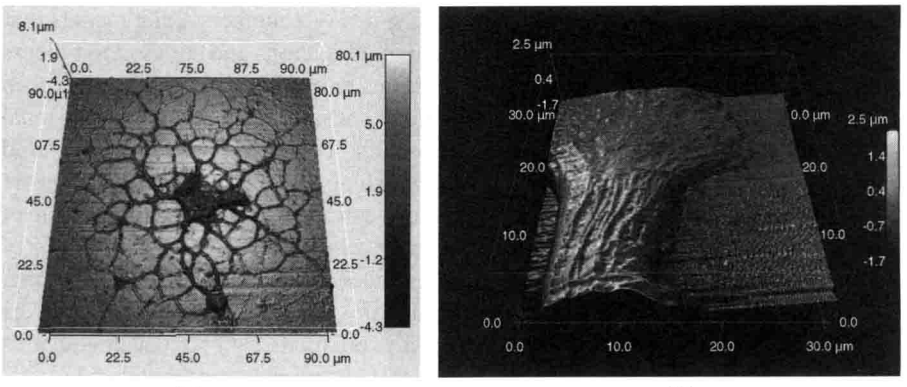
damaged areas of the nervous system. Simultaneously, engineers are teaming up with biologists to design electronic implants and prostheses that can interface with functioning tissue on either side of a damaged connection and act as a bridge to allow restoration of injured neuronal circuits. Pharmaceutical researchers are using nanotechnologies to create novel systems capable of delivering targeted drugs and other agents across the previously impenetrable blood–brain barrier,[1,2] a feature of nervous systems that chemically separates the system from the rest of the organism.

All these advances may be accelerated by knowledge derived from studies of cellular physiology using tools designed to study biological processes at the single cell level. As our ability to fabricate tools on the micro- and nanoscale levels has progressed, we can now study cellular processes at a scale compatible with cell size, and this is revealing new information about their operational responses, including how they respond to physical and chemical cues from their immediate environment. It is important that neuroscience researchers be aware of these new technologies, so that their use can be optimized.

Recent advances in biological applications of micro- or nanotechnology have included novel micro- or nanoscaled carriers for drug delivery,[3–6] quantum dots that operate as nanoscaled sensors at the cellular level,[7–11] and nanoelectrodes.[12] In addition, self-assembled monolayers and scaffolding, as well as carbon nanotubes, have been used as artificial nanotechnology matrices for cell culture.[13–19] In neuroscience specifically, nanoparticles have been used for free radical scavenging in ischemic and neurodegenerative diseases.[20] Scaffolds made of self-assembling nanofibers are being developed to enhance neuroregeneration.[21] The blood–brain barrier has been successfully breached by drugs attached to special nanoparticles.[22] High-resolution studies of the topography and material properties of live nervous system cells are being carried out by atomic force microscopy (AFM) (Figure 1.1).[23,24] Single-molecule tracking using quantum dots has revealed details about the structure and function of membrane receptors.[10,25,26] Finally, nanotubes, nanowires, and nanoneedles are being developed for use as relatively nontraumatic intracellular electrodes.[12,27,28] On a slightly larger scale, microfabrication technology has been used to create microfluidic platforms that have been employed for a variety of nanoneuroscience studies, and these platforms will now be discussed.

Microfluidics refers to a technology that utilizes microscale channels to manipulate fluid and suspended objects in a controlled manner at the nanoliter scale. Most microfluidic chips are designed and constructed using the same techniques as used in the development of microelectronic circuitry. Microfluidics has been advancing rapidly over the past decade and has progressed from basic devices, for example, a channel,[29] a valve,[30] and a pump,[30] to large-scale two-dimensional integration of components,[31] three-dimensional architectures,[32] and nonlinear autoregulatory systems.[32] Simultaneously, the development of the fundamental technology has enabled the advent of a plethora of specialized devices that have miniaturized important macroscale applications such as protein crystallization,[33,34] DNA sequencing,[35] and PCR (polymerase chain reaction), a technique for DNA detection and amplification.[36,37] The same development has also enabled the advent of novel techniques to conduct fundamental research in a scale that was never previously possible.



(a) (b)

FIGURE 1.1 Atomic force microscopy images of neural lineage cells. (a) Three-dimensional rendering of an oligodendrocyte differentiated from a murine neural stem cell. Fixed sequentially with 100% ethanol and 4% PFA, air dried, and then imaged on an Asylum Research MFP 3D AFM using an Olympus AC160 cantilever in AC mode in air. Note the detailed process formation. Scan size is 90 µm × 90 µm. (b) Three-dimensional rendering of a portion of a living astrocyte derived from a human embryonic stem cell on a polyornithine/laminin-coated substrate, imaged in media, in AC mode with an Olympus Biolever, and on an Asylum Research MFP 3D AFM. The image shows cytoskeletal fibrous elements visible through the cell membrane in the proximal thicker area of the cell as they enter a broad, flat attachment area. Scan size is 30 µm × 30 µm (unpublished data, Pamela G. Gross).

More recently, some microfluidic chips incorporate other microtechnology and nanotechnology hardware, such as electrodes,[38–44] magnetic coils,[45,46] and surface-emitting lasers,[47] to enhance their capabilities beyond fluid handling.

Many of the first applications of microfluidic chips involved studying the physics of fluid dynamics at the microscale (characterized by low Reynolds numbers, laminar flow, and fast diffusion), which is quite different from the flow characteristics of bulk fluid at the macroscale (characterized by higher Reynolds numbers, turbulence, and slow diffusion). The unusual behavior of fluid traversing microchannels has allowed creation of new methodologies to manipulate molecules, in order to synthesize novel nanomaterials and chemical/pharmaceutical moieties, and this has been described in other chapters. For biologists, microfluidic platforms have emerged as invaluable tools to study biology at small scales, even down to the single cell level. For neuroscientists, these "lab-on-a-chip" platforms have enabled a novel approach for experiments on the cellular physiology of the nervous system. Their usefulness in deciphering the complicated interactions involved in the differentiation, growth, and maintenance of neurons in health and in disease has become increasingly apparent within the past 5 years, as more research in this field continues to be reported. As more neuroscientists become familiar with this technology, we anticipate a rapid evolution of the field. This chapter will review pertinent contributions in the use of microfluidics to study the physiology and pathophysiology of neurons and their support cells and will hopefully serve as a primer for neuroscientists unfamiliar with this technology, inspiring some to develop new applications of microfluidics to the field of neuroscience.

Microfluidic platforms typically contain a series of chambers and channels that each measure in the range of 1 μm to a few hundred microns and are used to process fluid at a microscopic scale. For *in vivo* applications, microfluidic technology has been integrated with neural implants for precise delivery of solutions.[48] Three-dimensional electrodes with bundled microfluidic channels that can be implanted into severed nerves to guide and monitor their regeneration while allowing infusion of drugs are also under development.[49] However, the most common biological application of microfluidics has been for *in vitro* studies, such as the delivery and processing of biochemical reactants for DNA sequencing[35] and protein analysis,[50] the sorting, counting, and analysis of cells by flow cytometry,[51] the delivery of cell adhesives and cells for substrate micropatterning of cell populations,[52,53] the development of biomimetic three-dimensional tissues, complete with stromal support molecules,[18,19] and the isolation and nurtured maintenance of individual cells to study basic cell physiology and cell–cell interactions on a single (or near-single) cell basis.[54–59] In addition, microfluidic platforms have been used to study the effect of laminar flow and shear forces on the function of endothelial and other types of cells,[60,61] to provide artificial circulation through various organ-simulating cell culture chambers in order to determine the pharmacokinetics of prospective pharmaceutical agents,[62] and to deliver test samples containing potential toxins to cells acting as biosensors (also known as "lab-in-a-cell" technology).[63–65] Finally, microfluidics can be used to study physiology within small organisms, such as the effects of anesthetics on the regrowth of severed axons, or the recovery of axonal synapses after laser ablation in *Caenorhabditis elegans* nematodes that have been captured and immobilized in microfluidic chips.[66,67]

Microfluidic-based cell studies are a useful adjunct to conventional *in vitro* techniques or mini culture systems[68] because microfluidic chambers have the ability to control both the amount of material (media, growth factors, etc.) used for cell study and their exact distribution over well-defined periods. This can permit better control of the experiment by limiting unanticipated extraneous factors and diffusion constraints that can occur in larger systems. The effects of cell population variability will also be more limited in smaller systems and therefore individual differences among similar cells will be less likely to influence results. From an economic standpoint, small culture volumes allow cost savings since the required volume of expensive media, hormones, and growth factors is orders of magnitude less than that used in typical culture flasks. These platforms can also be designed for high throughput and compatibility with automated laboratory equipment such as plate readers. In addition, the hardware is portable and it can be mass produced so inexpensively that it can be very cost-effective to perform massively parallel microfluidic platform-based experiments, in order to confirm results or test the effects of numerous agents simultaneously.

These parallel experiments are necessary to verify results obtained on individual cells since it is known that there can be significant variation in the behavior of particular cells, even if they are cloned from the same precursor cell.[69] Similarly, it will be imperative that the effect of microenvironment parameters such as mechanical forces, shear stress, effective culture volume, and material interfaces be well

understood and controlled before interpreting single cell study results so that these factors do not contribute to misleading conclusions.[70] Nevertheless, observations derived from studies of individual cells in a controlled microenvironment may be much more likely to reveal true cellular physiology responses than those derived from studying the responses of populations of cells simultaneously, as is done with conventional *in vitro* studies.

Although the development of this technology has progressed significantly over the past 5–7 years, its utility as a tool is just beginning to be appreciated by biologists. There are many published reviews on the general topic of microfluidics for biological applications,[69–85] but there have only been a few that have focused on microfluidic applications in neuroscience.[80–82] This chapter will update the reader on the discipline of microfluidics to study the nervous system at the single cell level. Specifically, it will report on microfluidic chips used to decipher physiological processes and responses of cells of neural origin, and it will also focus on examples of systems that combine microfluidic chambers with other technologies for novel research not previously possible.

Section 1.2 will begin with a description of current microfluidic chamber construction techniques, starting with a discussion of the characteristics of the PDMS polymer used in many microfluidic chambers and then moving on to cover step-by-step fabrication processes. Various architectural designs of use for cellular studies will then be introduced, followed by a description of alternative applications of PDMS to create tools that are useful in customizing the substrate of microfluidic chips for specific experiments. Practical limitations of microfluidic techniques will then be discussed to present a balanced view of the topic.

In Section 1.3, gradient-generating designs will be reviewed, along with examples of how they have been used to study cellular responses. Methods of incorporating electrophysiological measurements into chip design, including patch clamping, will be examined and then use of other integrated micro- and nanoscaled analytical devices will be considered. The theory and methodology used for *in vivo* tissue simulation will be evaluated, since the natural behavior of cells is ultimately what most biological research is attempting to discern.

Following this, a literature review of neuroscience research involving microfluidic platforms will be detailed in Section 1.4, starting with cell identification and separation tools, which is essential for researchers requiring specific subpopulations of neural lineage cells. Studies on microfluidic analysis of neuropeptide release will follow, which is of interest to individuals studying synapse formation and function. The use of microchips to study the effects of physical and chemical guidance cues on single cells will then be considered since this is a key to understanding how neural cells interact with their environment and with each other.

Section 1.5 will focus on electrophysiology studies that use multielectrode arrays (MEAs) as microfluidic chamber substrates. This is a popular field of endeavor since these two technologies seem to be complementary and can allow studies on action potential characteristics and propagation in single axons. The effect of growth factors on neuronal responses of microfluidically cultured and isolated cells will be covered after this, given its significance in understanding cell differentiation and maturation.

The use of microfluidic chambers for gene therapy studies on neural cells will be subsequently discussed. Although this is a relatively new area of study, preliminary results are very promising and future research will likely take advantage of the unique capabilities that microfluidic chips offer to this field. The final area of research to be covered involves studies based on the microfluidic isolation of axons and neural cell bodies. This approach to neural research is gaining great interest, given the potential applications for those studying neural degeneration and regeneration processes, in addition to those interested in axonal transport mechanisms, and synapse formation and physiology. A general discussion with consideration of future perspectives will complete the chapter. It is hoped that the reader will gain an appreciation for the future potential of these platforms to uncover previously hidden cell-based interactions in the nervous system, and this will stimulate new applications of microfluidics for their specific research programs.

1.2 PDMS MICROFLUIDIC DESIGN AND FABRICATION

1.2.1 Characteristics of PDMS

Initially, most microfluidic chambers were constructed on silicon wafers using "hard" lithography. Since those early studies, "soft" lithography has been developed and various polymers and fabrication techniques have been investigated.[86] Now, soft-sided chambers made of polydimethylsiloxane (PDMS) are gaining increased popularity, especially for biological applications. PDMS is a silicon-type elastomer and can be purchased commercially as Sylgard® 184 by Dow Corning or RTV by General Electric. It can be molded into many different shapes to form valves, chambers, and channels. PDMS is advantageous for biological studies since it is biocompatible, optically transparent down to wavelengths as low as 280 nm, permeable to gases needed for cellular respiration, autoclavable, and naturally inhibitory to cellular adhesion.[87,88] PDMS has therefore proven very handy for cellular studies by allowing long-term cultures, optical microscopy, and fluorescent/chemiluminescent studies, while the cells are still *in situ* in the chip.[64] A final advantage of this material for use with cell culture systems is that PDMS has been shown to be an excellent protective coating for on-chip solid-state analytical devices (such as surface-emitting lasers), since PDMS is optically transparent yet prevents the detrimental effects of ions migrating from the culture medium into sensitive electrical junctions.[47]

Native PDMS is hydrophobic, and this influences many of its surface properties, including its interactions with fluid and molecules that are in contact with it. These properties can be altered by physical and chemical treatments that can change the hydrophobicity of the surface of the PDMS channels and change its adhesive properties if this is desired.[74] For example, the pretreatment of the PDMS channels with bovine serum albumin (BSA) will assist in blocking cell adhesion to its surface.[54] Alternatively, PDMS can be made hydrophilic and supportive of cell growth by treatment with oxygen plasma,[88] or UV/ozone,[89] that acts by changing the moieties on the PDMS surface to increase the number of silanol groups and decrease the number