Diagnostic Devices with Microfluidics

Edited by
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Šeila Selimović

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Contents

Preface

This book provides insight into the latest developments in point-of-care (POC) and laboratory diagnostic devices that are based on microfluidic principles. Microfluidic techniques and devices have had a steadily growing influence on research in life sciences and bioengineering, leading to their adoption in modern diagnostic solutions. The goal of this book is to highlight this growing field and present a selection of important topics, making it an excellent introductory reading for graduate students in bioengineering and related disciplines. The book is also suitable for advanced researchers, as a review of the latest published studies.

The three sections of the book are devoted to the devices for diagnostics, applications for specific diseases, and practical aspects of developing a diagnostic device.

Chapter 1 provides the description of a handheld microfluidic device for POC in vitro diagnostics. In Chapter 2, recent developments in wearable microfluidic sensors are highlighted, with a special focus on microfluidic devices for monitoring physical and physiological activity and noninvasive collection and analysis of biological fluids, such as breath condensates, sweat, saliva, and tears. The chapter discusses paper-based microfluidics, which is an emerging and rapidly developing technology. It harnesses the material merits of paper as well as the basic concepts of microfluidics. This synergistic combination not only leverages analytical functions and transforms them into a POC technique, but also renders the configuration of the assay as simple as possible. It is advantageous to address technical bottlenecks in current diagnostic assays and to develop novel POC tests. Consequently, paper-based microfluidics is capable of enhancing the delivery of healthcare interventions to patients, especially in resource-limited settings, showing potential to revolutionize first-line clinical practice. Chapter 3 provides a background of paper-based microfluidics, reviews the recent advances in fabrication techniques, and emphasizes its critical applications in a few specific clinical scenarios, including immunoassay, blood typing, and sickle disease detection. Chapter 4 describes a method for fabricating paper analytical devices (PADs) containing wax-ink valves to control the timing of reagent delivery in multistep assays. Wax-ink valves are printed onto membranes in defined patterns and can be actuated by applying localized heat to the valves to allow fluid to flow. Here, the authors describe how to use these valves to enhance the lateral flow immunoassay detection signal water test kit to detect microbiological contamination. Chapter 5 briefly describes some of the established methods of mycotoxin analysis and highlights the limitations of these methods. The need to develop rapid, portable analytical platforms is emphasized. These platforms must be able to compete with the

gold standard techniques in areas such as sensitivity and specificity so that analysis can be moved from the laboratory to "on-site" monitoring. Current research on microfluidics-based devices is examined and examples of devices utilizing microfluidic platforms to offer potential solutions for rapid analysis are described throughout the chapter. Chapter 6 describes a device and its technology underpinnings that are capable of revolutionizing clinical breath diagnostics based on a combination of its small size, low power requirements, ease of use, and applicability to a broad range of clinically relevant biomarker signatures. This technology, based upon the principle of ion mobility spectrometry, generates signature spectral patterns as distinctive as mass spectrometry (MS) but with far greater simplicity and adaptability. The differential mobility spectrometer (DMS) is a portable, handheld device that generates multidimensional biological spectra from volatile compounds found in exhaled breath. Current prototype models of the DMS fit in the palm of the hand, are highly durable, operate at atmospheric pressure, and can be operated with standard batteries.

Due to numerous advantages, there is great potential for microfluidic technology to be applied in the development of disposable, inexpensive, portable, and easy-to-use devices for the detection of infectious diseases in resource-limited settings. Chapter 7 reviews the application of microfluidic device and chips for detecting infectious diseases. While no microfluidic diagnostic platform has been rolled out for TB in endemic countries, significant strides have been made in the development and implementation of molecular diagnostics, which now set the scene for POC microfluidic platforms. Chapter 8 details these molecular diagnostic platforms and follows this with a discussion on the state of the art for TB microfluidic diagnostics that are in development. It also outlines the challenges in scaling up of these interventions and integrating them into healthcare systems.

Chapter 9 highlights considerations for designing a diagnostic device for use on individual patients or populations by assessing and incorporating the answers to two fundamental questions—who is asking for the test and how do test results guide a treatment decision. The methodology described is a best practice for assessing and ensuring that user needs are central to the design, development, and evaluation of a new diagnostic tool. The assessment starts with a clear intended-use statement that is centered on an actionable decision and justifies the time and cost to obtain a diagnosis. This definition is used to frame use-cases and user scenarios that identify users and describe how the test will be implemented, as well as the criteria for generating an actionable test result. All three of these assessments are then used to create a list of product attributes that are required to meet the needs of an end user.

Finally, ensuring that a POC test is designed so that the user can correctly operate and interpret results is paramount to obtaining a correct diagnosis. Designing with end user needs in mind allows researchers to mitigate potential errors and device failures early in the development process. Yet,

too often, a lack of knowledge in how to meaningfully engage device users during the research and design process is a roadblock to progress in early diagnostic development. This is especially true in designing for global health settings where resources to access end users may be limited. Chapter 10 outlines techniques to incorporate the needs of users into device development using a framework of human-centered design (HCD). HCD provides a set of methods to engage with users even before a verified diagnostic device has been created to develop tests that have improved clinical diagnoses, regulatory approval, and commercialization outcomes. Two case studies focused on incorporating HCD into early-stage diagnostic test development provide specific examples of methods in use. Finally, common misconceptions about when and how HCD can be used in diagnostic development are addressed.

We sincerely hope that this book will be a source of inspiration for new applications and stimulate further development of microsystems technologies.

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Series Editor

Krzysztof (Kris) Iniewski is managing R&D at Redlen Technologies Inc., a start-up company in Vancouver, Columbia, Canada. Redlen's revolutionary production process for advanced semiconductor materials enables a new generation of more accurate, all-digital, radiation-based imaging solutions. Kris is also a founder of Emerging Technologies CMOS Inc. (www.etcmos.com), an organization of high-tech events covering communications, microsystems, optoelectronics, and sensors. In his career, Dr. Iniewski held numerous faculty and management positions at the University of Toronto, University of Alberta, SFU, and PMC-Sierra Inc. He has published over 100 research papers in international journals and conferences. He holds 18 international patents granted in the USA, Canada, France, Germany, and Japan. He is a frequent invited speaker and has consulted for multiple organizations internationally. He has written and edited several books for CRC Press, Cambridge University Press, IEEE Press, Wiley, McGraw-Hill, Artech House, and Springer. His personal goal is to contribute to healthy living and sustainability through innovative engineering solutions. In his leisurely time, Kris can be found hiking, sailing, skiing, or biking in beautiful British Columbia. He can be reached at kris.iniewski@gmail.com.

Editors

Francesco Piraino is currently a research scientist at the Swiss Federal Institute of Technology in Lausanne (Switzerland). He uses microscale technologies to develop next-generation microfluidic diagnostics platforms. Following his graduate studies in Biomedical Engineering at Politecnico di Milano (Italy) and at Harvard-MIT Division of Health Science & Technology (USA), he joined the Broad Institute of MIT and Harvard (USA) to develop devices for single-cell genomics. Dr. Piraino is a trained bioengineer who has also attended programs at the Universitat de Barcelona (Spain), the City College of the City University of New York (USA), and the Massachusetts Institute of Technology (USA). His work aims to solve problems at the intersection of biomedical engineering and medicine. His research interests include in vitro diagnostics, tissue engineering, and biomaterials.

Šeila Selimović is director of the NIBIB programs in tissue chips/tissue preservation technologies and biosensors. Her other scientific interests include lab-on-a-chip platforms, paper microfluidics, and point-of-care diagnostics. In 2015, she was selected as one of the "50 Leaders of Tomorrow" from among hundreds of young biotech leaders in the Mid-Atlantic region. Prior to her current position, she was chosen by the American Association for the Advancement of Science to serve as a Science and Technology Policy Fellow at the U.S. Department of State, where she covered science diplomacy issues related to energy security, climate, and innovation. Previously, she was a postdoctoral research fellow at Harvard Medical School and Brigham and Women's Hospital in Boston, Massachusetts. Dr. Selimović's research has focused on the development of microfluidic platforms for applications in biophysics and biological engineering, and her research interests include the physics of microscale flows, protein crystallization, colloidal suspensions, and rheology and microrheology. Dr. Selimović earned her PhD and MSc in physics from Brandeis University, with National Science Foundation support, and her BA in physics and German from Wellesley College. She is a member of Sigma Xi.

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Section I

Microfluidic Devices for Diagnostics

1

*Handheld Microfluidics for Point-of-Care In Vitro Diagnostics**

Baichen Li and Zhenyu Li

CONTENTS

1.1 Introduction

In vitro diagnostics (IVD) influences 70% of all healthcare decisions according to a study (Lewin Group 2005). However, such a universally demanded service is still largely centralized partly due to the fact that current IVD technologies are still too complicated, expensive, bulky, and slow for point-of-care (POC) settings such as emergency rooms, physicians' offices, patients' homes, and ultimately on (or in) human bodies. One important goal of

* Part of this chapter was published in *Lab on a Chip* as a peer-reviewed article (Li et al. 2014).

lab-on-a-chip research is to miniaturize conventional medical diagnostic instruments, including IVD systems (Manz et al. 1992, Whitesides 2006). One common feature of traditional IVD instruments is that they all require complex manipulations of liquid samples such as blood, urine, saliva, and liquid reagents, and so on. Therefore, it is essential for POC IVD systems to have built-in liquid-handling capabilities comparable to robotic pipetting and centrifugation used in conventional clinical labs in order to achieve truly automated sample-to-answer operations. In the past three decades, there have been extensive efforts on miniaturizing liquid-handling components on chip, such as MEMS valves and pumps (Kwang and Chong 2006, Laser and Santiago 2004), elastomeric on-chip valves and pumps (Unger et al. 2000), and droplet manipulation systems (Pollack et al. 2000). However, due to various material, fabrication, integration, and reliability challenges, few handheld (not to mention fully on-chip) self-contained microfluidic systems capable of sophisticated liquid handling exist in the market today except for capillary-driven microfluidics such as lateral flow tests (Wong and Tse 2009). Most lab-on-a-chip systems still rely on bulky off-chip components such as compressed pressure sources, syringe pumps, and electronics to achieve their liquid manipulation functions, which severely limits the applicability of such systems for POC diagnostics, environmental monitoring, and bioterrorism detection. Recently, a handheld instrument was developed that can actuate on-chip elastomeric microvalves using solenoid-containing actuation units (Addae-Mensah et al. 2010). Another promising technique is digital microfluidics, in which droplets are manipulated by electrowetting (Pollack et al. 2000); however, to our knowledge a handheld digital microfluidic system has not been demonstrated. Braille display devices have also been used to build portable microfluidic systems (Gu et al. 2004). In this chapter, we present a smartphone-controlled handheld microfluidic liquid-handling system recently developed by us. It combines elastomeric on-chip microfluidic valves, a handheld pneumatic system, and a smartphone-based control and data processing system. The handheld pneumatic system provides onboard multiple pressure generation, stabilization, and control by using a miniature pump, pressure-storage reservoirs, and small solenoid valves. This system is applicable to both single-layer, pressure-driven microfluidics and multilayer, elastomeric microfluidics (Grover et al. 2003, Hansson et al. 1994, Hosokawa, Maeda 2000, Hansen et al. 2004, Thorsen et al. 2002 and Unger et al. 2000), although the main focus is on the latter. Elastomeric microfluidics refers to microfluidic systems with on-chip valves based on the mechanical deformations of elastomeric membranes or structures, such as multilayer PDMS microfluidics (Hosokawa and Maeda 2000, Unger et al. 2000), glass/PDMS/glass devices (Grover et al. 2003), and other hybrid devices (Hansson et al. 1994).

In a typical elastomeric microfluidic system, often two different pressure sources are needed: one for actuating on-chip valves, which typically require a relatively high pressure level (5–10 psi, depending on the membrane

property and valve geometry); and the other for driving reagents into microfluidic channels (for typical microfluidic channel dimensions, e.g., 10 μm high, 100 μm wide, 1–5 psi is sufficient for many applications). Traditionally, this is achieved by using two pressure regulators connected to a compressed gas (often nitrogen or air) tank (Unger et al. 2000). However, the sizes and nature of these components make them unsuitable for building a handheld system. Although it is possible to use two separate diaphragm pumps to build such a system, the significant fluctuations of the output pressure of a diaphragm pump limit its applications.

To address these challenges, we have recently developed a handheld microfluidic liquid-handling system controlled by a smartphone (Figure 1.1), which can provide two different stable pressure sources and an array of eight pneumatic control lines for operating elastomeric microfluidic chips (Li et al. 2014). One pressure source (P1) is set to above 10 psi (maximum 20 psi) to operate on-chip elastomeric valves, while the other (P2) can be set to any value between 0 psi and P1 to drive liquid flow, with a precision of ±0.05 psi. Eight independent pneumatic control lines are available to handle eight different liquid reagents. The size of the resulting system is 6 × 10.5 × 16.5 cm, and the total weight is 829 g (including battery). The system can operate continuously for 8.7 h while running a sandwich immunoassay liquid-handling protocol when powered by a 12.8 V, 1500 mAh lithium battery. This technology can serve as a general-purpose, handheld small-volume liquid-handling

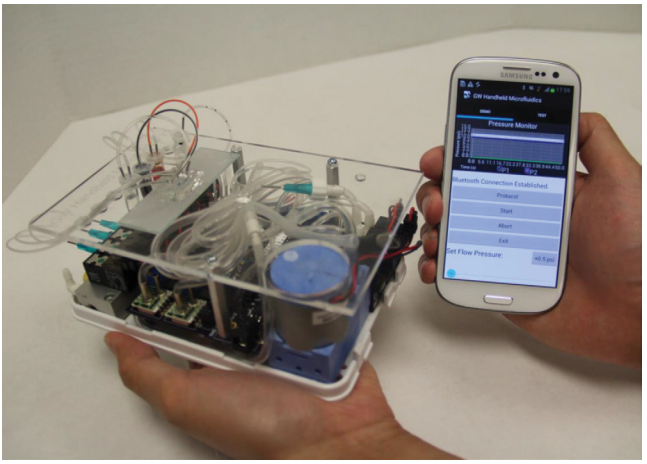

FIGURE 1.1
Picture of the smartphone-controlled handheld microfluidic liquid-handling system. The footprint of the instrument is 6 × 10.5 × 16.5 cm. Powered by a 12.8 V 1500 mAh lithium battery, the instrument consumes 2.2 W on average for a typical sandwich immunoassay and lasts for 8.7 h. A multilayer PDMS device with on-chip elastomeric valves is on top of the handheld instrument.

platform for many biochemical and cell-based assays such as immunoassay, fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), flow cytometry, DNA/RNA/protein microarrays, and sequencing. The integration of this system with biosensors may help realize the long-sought dream of handheld multianalyte in vitro diagnostic (IVD) systems, that is, something that can be called a medical tricorder (Qualcomm Tricorder XPRIZE 2014).

1.2 Design of the Handheld Microfluidic System

The overall handheld microfluidic system consists of three subsystems: (1) a pneumatic pressure generation, stabilization, and control subsystem (*pneumatic* subsystem); (2) an electronic printed circuit board (PCB) with two microcontrollers, a Bluetooth wireless communication module, pressure sensors, and power component drivers (*electronic* subsystem); and (3) an elastomeric microfluidic chip (*microfluidic* chip). The system can be controlled by a Bluetooth-enabled Android smartphone (e.g., Galaxy SIII). Each subsystem will be described in more detail in the following sections.

1.2.1 *Pneumatic* Subsystem

The *pneumatic* subsystem is designed to generate two compressed air pressure sources at different levels (P1: >10 psi; P2: 0 to P1) for operating elastomeric microfluidic chips (or cartridges). Two pressure reservoirs, labeled as Reservoir 1 and Reservoir 2 (Figure 1.2), are used to store compressed air. A miniature DC diaphragm pump is used to pump air into Reservoir 1 to generate the primary pressure source for actuating on-chip elastomeric valves (Grover et al. 2003, Hansson et al. 1994, Hosokawa and Maeda 2000, Unger et al. 2000). A secondary pressure source, stored in Reservoir 2, is derived from Reservoir 1 and stabilized by a feedback control system with a precision of ±0.05 psi for driving liquid reagents through microfluidic channels. The system can be easily extended to have multiple secondary pressure sources of different pressures if needed.

Each pressure reservoir is made of four segments of 1/8″ ID Tygon tubing connected with a four-way barbed cross-connector, leaving four open ports. Each open port of a reservoir is connected to a functional part of the pneumatic subsystem (such as a pump, a solenoid valve, or a pressure sensor, as shown in Figure 1.2 and described in more detail in the following) via a barbed connector. The volume of each reservoir is determined by the total length of tubing used. In this work, the volumes of Reservoirs 1 and 2 are 6.2 and 16.2 mL, respectively.