Preface

Over the last several decades, our ability to understand and diagnose disease has dramatically progressed due to advances in quantitative measurements of molecular biomarkers. Techniques such as genetic sequencing, mass spectrometry, flow cytometry, and nuclear magnetic resonance have enabled sophisticated and highly sensitive measurements of biological material that promise improvements in early diagnosis, accurate monitoring of existing diseases, and understanding of the underlying causes and mechanisms of disease. However, the widespread translation of these advanced techniques toward improving patient care has been severely limited by cost and the requisite infrastructure that these technologies demand.

Medical diagnostics at the point-of-care (POC), e.g., performed by a clinician or by a patient without the need for a clinical lab, can greatly improve access to medical diagnosis. Simple POC diagnostics have been available for many years, such as glucose monitors for diabetics and home pregnancy tests, and have provided tremendous benefits for patients. Motivated by the success of these simple tests, there has been a strong push to develop more complex chips that automate and miniaturize advanced diagnostics currently performed in laboratories. These proposed "lab-on-a-chip" devices combine advances in electronics, photonics, microelectromechanical systems (MEMS), and microfluidics to build small, low-cost chips that can perform extremely complex tasks. Much research has gone towards the development of these lab-on-a-chip systems, but only recently has this technology begun to reach the level of maturity for practical use.

It is appropriate that many of the researchers working on developing these biomedical chips have backgrounds in semiconductor physics and engineering. Over the last 50 years, the semiconductor industry, through feats of integration and miniaturization, has turned computers from million-dollar, room-sized machines into the pocket-sized smart phones that are now so globally ubiquitous. Following the example of the semiconductor industry, researchers today imagine handheld devices the size of a cell phone, that with a drop of blood, spit, urine, or sputum

will run a battery of medical diagnostics at a cost and speed that cannot be matched by the manual labs of today.

In addition to the logistical and economical improvements that come from miniaturizing diagnostics, such chips can outperform the larger and more expensive traditional diagnostics tools. Sensors and actuators perform best when they are sized appropriately for the objects that they are measuring. In the case of biology, great improvements in performance come from having micro- and nanometer-sized tools to control and measure cells and molecules respectively.

The invention of new techniques to inexpensively and rapidly diagnose disease at the POC promise enormous impacts on many pressing current health issues. One example of the urgent need for this technology is the emergence of drug resistant strains of tuberculosis (TB). These multi-drug resistant strains (MDR-TB) are mutated strains of TB that do not respond to the standard treatments for the disease. For the effective treatment of this potential pandemic, clinicians need to be able to accurately target the more expensive and more aggressive second-line-of-defense drugs to patients with MDR-TB. However, the best method to rapidly identify MDR-TB in patients is with polymerase chain reaction (PCR), which, despite recent efforts, is still largely unavailable in resource-poor regions where the MDR-TB epidemic is currently localized.

This book consists of chapters by leading researchers working on biomedical chips to bring advanced diagnostics to the point of care. This work is separated into two broad categories: (1) the development of miniaturized chips to control and prepare biological samples and reagents and (2) the development of sensors that can be miniaturized onto chips for the accurate detection of biomarkers.

Beginning with work in fluid handling, Sam Sia describes the work of his group at Columbia University to engineer extremely low-cost microfluidics for POC diagnostics using injection molded chips preloaded with reagents. Sia's work has led to a start-up company Claros Diagnostics Inc. and has recently been used in a clinical trial to diagnose STDs in rural areas of Rwanda. Next, Robert M. Westervelt describes the work by his group to demonstrate a programmable platform to control single cells and pL drops of fluid that utilizes the complexity, small feature size, and low cost of integrated circuits (ICs) combined with microfluidics.

A variety of techniques to measure molecular biomarkers on biomedical chips are described. Peter Kiesel at the Palo Alto Research Center and Aydogan Ozcan at UCLA describe two very different approaches toward miniaturizing optical measurements for the high-throughput bright-field and fluorescence screening of cells. Yang-Kyu-Choi at Korean Advanced Institute of Technology, Toshiya Sakata at University of Tokyo, and Shan Wang at Stanford discuss recent work by their groups to utilize the complexity and small feature sizes of microchip technology to build extremely sensitive microfabricated sensors for molecular biomarkers. Donhee Ham at Harvard University and Hakho Lee at Massachusetts General Hospital describe the work by their groups to miniaturize nuclear magnetic resonance to detect sparse biomarkers in turbid biological samples.

Overall, the work by these researchers paints a very hopeful picture. Through the continuing advancement of miniaturized diagnostic technology, future clinicians and patients will have access to more accurate, timelier, and far less expensive diagnosis of disease.

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