3 MICRO- AND NANOFLOWLIDICS FOR BIOLOGICAL SEPARATIONS

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3.1 INTRODUCTION

Current research on analytical techniques for biological applications is being conducted using micro- and nanofluidic devices fabricated with CMOS processes. Materials such as silicon, silicon nitride, and silicon dioxide are used as device substrates because they are compatible with the lithographic and etching processes required to manufacture nanometer-scale structures. Micro- and nanoscale structures have been fabricated in order to probe and confine molecules on length scales that are comparable to the size of the molecules [1]. At these size scales, advanced separation techniques are possible as are single molecule studies. Micro- and nanofluidic devices have enabled new methods of DNA separation, such as the rapid separation of genomic length DNA. The ability to manipulate, elongate, and detect individual molecules has opened the door for single molecule restriction mapping, directly observing protein binding, and perhaps even single molecule sequencing [2]. Labs-on-chips, of which microfluidics is the key enabling component, hold the promise of facilitating faster biochemical techniques using less reagents with more sensitivity and less variability [3].

This chapter summarizes one subsection of what has become a large field of multidisciplinary research known as microfluidics. Because this chapter is embedded in a book called CMOS Biotechnology, and because one of the author’s expertise is in biological separations in glass- and silicon-based micro- and nanofluidic devices, what follows will be oriented in this direction.
Common fabrication techniques, likely familiar to the CMOS engineering community, will be discussed. DNA and proteins will be briefly discussed as these biological molecules are the primary analytes of most of the microfluidic devices discussed. A brief history of the move from “conventional” microfluidics to chip-based microfluidics will be presented. After the fabrication, the biology, and the history, the remainder of the chapter will describe new micro- and nanoscale systems that have been developed to interrogate and analyze biological samples.

3.2 FABRICATION OF FLUIDIC STRUCTURE

As CMOS fabrication techniques, academic cleanrooms, and advanced lithographic tools have become more available, engineers have increasingly used these techniques for applications other than the manufacture of “classical” CMOS devices. Using CMOS fabrication techniques to manufacture devices for biological applications is now common in the research community. Conventional techniques for separating and purifying biological molecules almost always involve capillary electrophoresis, which is electrically driving molecules through fused silica capillaries [4-6]. Using CMOS fabrication techniques, these capillaries can now be etched directly into silicon or glass wafers.

With creative geometries, wafers can hold hundreds of capillaries, each meters in length. In addition to the miniaturization of existing technologies, CMOS fabrication methods allow features to be made with dimensions of comparable size as biomolecules. Currently, the demands of making features on the order of nanometers or tens of nanometers requires “hard” substrates familiar to the world of integrated circuits such as silicon and silicon dioxide. The lithographic methods and the pattern transfer processes (as described below) will no doubt seem familiar to the general CMOS community. The ability to make channels and structures on the scale of biomolecules has enabled entirely new biological applications as well as elucidated many biological and physical phenomena.

Using standard CMOS fabrication technologies, many types of microfluidic devices can be made (see Figs. 3.1-3). As previously mentioned, capillaries can be easily placed on chips. Channel widths of tens of microns are defined using standard photolithographic techniques. A resist is spun onto a silicon or glass wafer. The resist is patterned with photolithography or electron beam lithography and developed. Once developed, reactive ion etching or chemical etching can be used to transfer the lithographic pattern