

Integration of biosensors based on microfluidic: a review

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Abstract

Purpose – Biotechnology is closely associated to microfluidics. During the last decade, designs of microfluidic devices such as geometries and scales have been modified and improved according to the applications for better performance. Numerous sensor technologies existing in the industry has potential use for clinical applications. Fabrication techniques of microfluidics initially rooted from the electromechanical systems (EMS) technology. **Design/methodology/approach** – In this review, we emphasized on the most available manufacture approaches to fabricate microchannels, their applications and the properties which make them unique components in biological studies.

Findings – Major fundamental and technological advances demonstrate the enhancing of capabilities and improving the reliability of biosensors based on microfluidic. Several researchers have been reported verity of methods to fabricate different devices based on EMS technology due to the electroconductivity properties and their small size of them. Therefore, controlled fabrication method of MEMS plays an important role to design and fabricate a highly selective detection of medical devices in a variety of biological fluids. Stable, tight and reliable monitoring devices for biological components still remains a massive challenge and several studies focused on MEMS to fabricate simple and easy monitoring devices.

Originality/value – This paper is not submitted or under review in any other journal.

Keywords Nanotechnology, MEMS, Biosensors, Nanosensors

Paper type General review

1. Introduction

During the past few years, the use of iteration modeling and miniaturization to define microfluidic devices in elastomers are being rapidly investigated using multiple analyses systems based on electrochemical and biological sensors (Goral *et al.*, 2006). Currently, it is possible to miniaturize all kinds of systems, such as chemical, mechanical, fluidic, electromechanical or thermal, down to sub-micrometric scales (Judy, 2001). Microfluidic devices determine the behavior and manipulation of fluids, which are geometrically chained to small, characteristically sub-millimeter size devices (Janson *et al.*, 1999). It is the science that describes design and construction of the devices being used for miniaturization via chambers and tunnels through which fluids flow in a controlled manner (Nicu and Leichle, 2008). These methods can be used to understand the complete protocols for the purpose of comparing it with traditional protocols, such as reduced reagent consumption, favorable reaction kinetics and the

possibility to be rapidly prototyped, high-throughput potentialities, the ability of integration or mixing and mechanization and reduced analysis periods (Guijt *et al.*, 2002). These advantages are the reason it is utilized in biology, chemistry and medicine by scientists (Figeys and Pinto, 2000). Microfluidics also provide for more accurate *in vitro* environments for small-scale biological species of interest (Prakash *et al.*, 2008). The usage of small stream channels, typically between 1 and 100 μM , is significant when taking into account the networks of microscopic channels in substrates where the analytes are transported, mixed and separated (Stone *et al.*, 2004). Miniaturization allows high-throughput broadcast, portability, and high-density arrays on a small-scale as well. Designs of microfluidic devices, such as geometries and scales, have been modified and improved according to the applications for better performance (Prakash and Gershenfeld, 2014). Further development requires more components to be coupled with the microfluidic system for increased system functionality (Davies *et al.*, 2003). In this review, we place emphasis on the most available manufacturing approaches in fabricating microchannels, their applications and the properties that render them unique components in further studies.

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2. Fabrication technique of microfluidic devices

The fabrication techniques were initially rooted in the electromechanical systems (EMS) technology (Ho and Tai, 1998). Microfabrication is the term used to explain the fabrication of miniature constructions of micrometer scale or smaller devices (Beebe *et al.*, 2002). With further development of microelectromechanical systems (MEMS), whole microfluidic systems were realized, which were made up of multiple elements to realize certain functions (Wu and Gu, 2011). Semiconductor devices were the first to use microdevices in the fabrication of integrated circuits. These integrations have been enclosed by the term “semiconductor manufacturing” or “integration of semiconductor devices” (Lee and Shin, 2001).

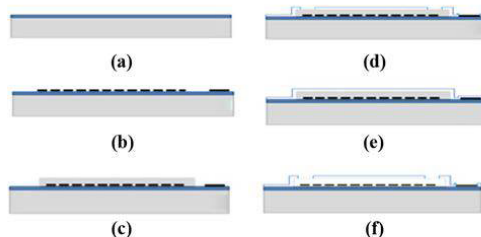
Several approaches and techniques exist for the fabrication of microfluidic devices (Fiorini and Chiu, 2005). Current methods for fabrication of microfluidic devices include prototyping techniques (includes hot embossing, injection molding and soft lithography) and direct fabrication techniques, such as laser photoablation or laser micromachining, photolithography/optical lithography and x-ray lithography (Mescher *et al.*, 2009). Several microfabrication processes are capable of controlling the microfabrication techniques based on different materials, such as silicon (Indermun *et al.*, 2014), polymer (Wu *et al.*, 2014), and glass (He *et al.*, 2014), depending on the specific requirements of the proposed sensor (Shiu *et al.*, 2007). Figure 1 shows some of the conventional methods to fabricate silicon-based microchannel.

Outside biological analysis, other applications of microdevices include chemical analysis, drug synthesis, drug delivery and point-of-use synthesis of risky chemicals. Each method has its respective benefits and difficulties, but the specification of the proposed device will dictate the fabrication method (Shin *et al.*, 2008).

2.1 Micromachining

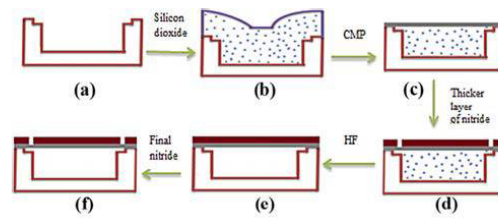
Manufacturing and fabrication techniques are correlated and they are responsible for microminiaturized semiconductor devices used in the industry (Dixit and Ghosh, 2015). Micromachining is commonly used in MEMS (Wan, 2000). Silicon micromachining was one of the first methods used to produce microfluidics. Figure 2 indicates the fabrication of silicon nitride-based microchannels through micromachining

Figure 1 Conventional method of silicon microchannel



Notes: (a) Silicon mold fabrication; (b) parylene deposition; (c) electrode patterning; (d) thermal bonding; (e) flat substrate removal; (f) channel release

Figure 2 Process flow for fabrication of silicon nitride microchannels based on micromachining technique



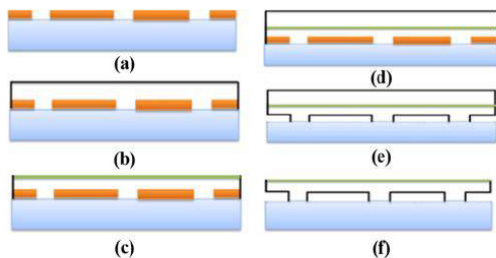
Notes: (a) Silicon nitride; (b) silicon dioxide; (c) CMP; (d) thicker layer of nitride (e) hydrofluoric acid; (f) final nitride deposition

technique. Advances in this method show that it can also be used to fabricate nanometer-sized constructions for microfluidic devices in several applications (Ziaie *et al.*, 2004). Even the technique of micromachining is quite widespread these days, however, due to optical opacity, costs and difficulty in component integration of silicon, it is a good substance for microfluidic applications and the surface characteristic of silicon is well suited for biological applications (Dean and Luque, 2009). Various microfluidic applications are available, with fewer requirements. Furthermore, micromachining methods are costly, labor centralized and require highly specialized expertise, equipment and facilities (Manges *et al.*, 1997).

2.2 Soft lithography

Due to the limits of using the micromachining method, we need a quick, cheap and less specialized technique for the manufacture of microfluidics (Vijayaraghavan *et al.*, 2008). In 1974, scientists in Bell laboratories established a technique of molding soft materials from a lithographic master. The ideas of soft lithography have been used to pattern surfaces via stamping and manufacturing of microchannels using molding and embossing (Gimm and Beebe, 2007). Recently, Whitesides *et al.* (2001) developed the method soft lithography for use in microfluidics. Generally, soft lithography discusses the molding of a two-part polymer (elastomer and curing agent) called polydimethylsiloxane (PDMS) using photoresist masters (Ertaş, 2009). Therefore, the method used to produce multidimensional masters by micromachining or photolithography could also be used to fabricate complex masters for molding PDMS microstructures (Breslauer *et al.*, 2006). Soft lithography is faster, less expensive and more suitable for most organic applications compared with glass or silicon micromachining (Whitesides *et al.*, 2001). The hot embossing techniques can also be described as soft lithography (Forfang *et al.*, 2014). The polymethylmethacrylate, which is the least hydrophobic, is the common plastic for this purpose (Becker and Locascio, 2002). The advantage of hot embossing is that it is less expensive, but does not offer a timely method for changing designs. Hot embossing is usually applied for devices that does not undergo changes, and offers more material opportunities than the aforementioned elastomeric-based soft lithography techniques (Carlborg *et al.*, 2010). Figure 3 indicates the fabrication process of microchannel based on lithography technique.

Figure 3 Process flow for fabrication of microchannels based on soft lithography technique



Notes: (a) Channel structure; (b) polymer coating; (c) polymer curing; (d) polymer removal; (e) relief channel structure; (f) Microchannel

2.3 *In situ* construction

One of the new methods being introduced for the fabrication of microfluidic devices is photo-definable polymers. The technique uses liquid-phase photo-polymerizable materials, lithography and laminar flow (Herold and Rasooly, 2009). The prepolymer polymerizes very quickly, and the exposed polymer forms the channel walls, which is a fixed, flawless and chemically resistant solid (Yang, 2008). Any unpolymerized monomer is flushed out of the channel. Other types of photo-polymerizable materials, once the walls have been formed, can reach into the channel and polymerized through the covers to form components such as valves and filters. According to the fast fabrication process, simple devices can be fabricated in less than a minute. Furthermore, it is not necessary to use cleanroom, specialized facilities or skills (Hawken *et al.*, 2013). *In situ* construction is more advantageous compared with other methods, as it can be done without the need of expensive equipment or facilities (MacGregor *et al.*, 1994). The resolution of the cover and polymerization effects of the polymer limits the dimension of the proposed device. Different materials have been used for *in situ* construction, including an isobornyl acrylate-based polymer, as well as other UV-curable polymers (Jenekhe *et al.*, 1997).

2.4 Micromolding

One of the promising techniques for low-cost fabrication of microfluidic devices is injection molding. Thermoplastic polymer substances are heated past their glass conversion temperature to make them soft and flexible (Ren *et al.*, 2013). The molten plastic is then injected into a cavity containing the master. Due to the fact that the cavity is maintained at a lower temperature than the plastic, rapid cooling occurs, and the molded part is ready in only a few minutes (Bryce, 1996). The only time-consuming step is creating the master that shapes the plastics. This master is often referred to as the molding tool, and it can be fabricated in several ways, such as metal micromachining, electroplating and silicon micromachining. The methods of fabricating the molding tools are similar to those used for making the master for hot embossing, which means that they both share costs issues. However, the injection molding process is considerably faster than hot

embossing, and is the preferred method from a cost perspective for high volume manufacturing. Limitations of injection molding for microfluidics include resolution and materials choices (Au *et al.*, 2014). Methods of microfluidics have been developed rather rapidly. For illustration purposes, laser ablation of polymer surfaces, with subsequent bonding, form channels (Hutter *et al.*, 2013). The process can easily be adapted to create multilayer channel networks. The limitations of this method include throughput, due to the “writing” nature of the cutting process (Bessant and Venables, 2010).

3. Sensor

Sensing and measuring capabilities at the microscale is needed upon the development of microchannels. There are two categories of sensing in microfluidics. First, one needs to measure the output of the device or system. Reducing volumes for chemical or biological assays to the microscale is of very little use if there are no ways to determine the results quantitatively, as in the macro-scale. One of the ways to detect and increase the need for greater sensitivity is by reducing the sample’s size, which means reducing the amount of material (van den Berg and Lammerink, 1998). Constructing sensors or sensing capabilities that are more responsive and smaller in size is the most important goal on the microscale (Satyanarayana *et al.*, 2006).

Second, to realize and develop device and system designs, it is necessary to measure the physics and chemistry of flow in microfluidic devices. The most straightforward technique for determining fluid flow (flow rate) in microchannels is to collect the fluid at an output, measure the volume and divide it by the time over which the sample was collected. The technique is normally quite accurate for obtaining a bulk flow rate measurement. Issues of assembly, evaporation and volume measurement in small scales must be cautiously controlled to retain excellent accuracy.

The field of microtechnology is beginning to influence microbiology (Bruins *et al.*, 2012). Its scale of size is well matched to the physical dimensions of most microorganisms, and micron-scale tools make it possible to manipulate individual cells (Morris *et al.*, 2005), their immediate extracellular environments, and ultimately, their shape and internal organization.

However, electrokinetic flows do not provide any spatial information about flow inside the microchannel, but it is widely used for measuring flow rates (Bayraktar and Pidugu, 2006). Fluorescence is currently one of the most useful approaches of measuring chemical and physical parameters in microchannels. The advantage of using fluorescence is that measuring fluorescence’s intensity is very sensitive, and fluorescently labeled chemicals are widely available (Thomas *et al.*, 2007). The parameters that can be measured by fluorescence are temperature, cell function, flow velocity, flow profiles and polymer dynamics. The progress of particle imaging velocimetry has enabled scientists to quantify the flow patterns inside microchannels with high spatial resolution. Biological responses can also be observed via fluorescence in microchannels (Wheeler *et al.*, 2003; Estrin *et al.*, 2001).

3.1 Classification of microsensors according to the sensing principal

- *Pressure microsensors:* They are typically designed in a linear operation range. For example, piezoresistive is a pressure sensor to reduce fuel consumption by a tight control of the ratio between air and fuel.
- *Position and speed microsensors:* The most significant application for these kinds of sensors is in automobiles, robots and medical instrument applications.
- *Acceleration microsensors:* Acceleration microsensors have generally been used in the automotive industry, and it is usually detected with capacitive and piezoresistive approaches. An elastic cantilever with an attached mass is mostly used. The accelerometers are there to monitor the micromachined surface and its capacitive sensor.
- *Temperature sensors:* The main parameters of temperature sensors are temperature range, sensitivity, output range, linearity and accuracy.
- *Chemical microsensors:* Microelectronic fabrication techniques are beneficial to the manufacture of microsize chemical sensors. These include compact size, reduced sample volume, reduced sensor cost and fast response. Additionally, microfabrication processing produces identical, highly uniform and geometrically well-defined sensor elements (Fleming, 2001).
- *Biosensors:* Biosensors are a special class of chemical sensors for molecular detection that take advantage of the high selectivity and sensitivity of biologically sensitive materials. It is a device incorporating a biological sensing element with a traditional sensor, such as physical or chemical sensors. The biological sensing element selectively size of tin dioxide can be controlled by the fabrication conditions, and are considered critical to the sensor's response (Pitt *et al.*, 1985).

3.2 Classification of microsensors according to the signals

- *Thermal sensors:* The finest and high-quality thermal sensors are thermistors and thermocouples, where these are used to identify the surrounding temperature. The working principles of thermistors and resistive temperature detectors uses the variation in the movements and carrier density when the temperature changes. These variations are shown by coefficients of temperature that might be factors or non-direct temperature functions.
- *Electrical sensors:* This type of sensors can be used to measure quite high voltage values or huge charges. Electrical current flows in accordance to the movement made by charge carriers, which can be electrons, holes, ions and defects in the materials being charged (TermehYousefi *et al.*).
- *Mechanical sensors:* Many mechanical sensors were described in studies and are also available for purchase. There are a total of three mechanical parameters that can be changed to another energy domain, where it can be either sensed or directly measured (TermehYousefi *et al.*). For direct sensing, the mechanical parameters are associated with movements or strain. For example, a brittle material like Silicon can break when the strain is at most around 2 per cent.

- *Magnetic Sensors:* The magnetic microsensor is a small detective device for sensing magnetic effects and transferring it to measurable signals (Hammerschmidt and Leteinturier, 2004). Magnetic microsensors are important in various application areas that are bio magnetism, geomagnetism, nondestructive testing, automobile, field measurement and identification and communication (Bruckl *et al.*, 2005).

4. Integration categories of microfluidics with biosensors

Devices that have the capability to observe physiological variations are called biosensors. These sensors can observe physiological variations that are induced from exposure to environmental agitations (Borkholder, 1998). The current development conducted in cell culture, as well as microfabrication techniques, discovered that the enhancement of sensors benefits the functional description and identification of elements, such as drugs, odorants, toxicants and pathogens (Pérez-Esteve *et al.*, 2013). This type of sensors is useful for huge quantities of drug detection, as well as for medical diagnostics. It is also useful for identifying hazardous (toxic) elements and certain odorants (Liu *et al.*, 2014).

Biosensors consist of dual transducers. The main transducer is essential to transform the existence of substances that are bioactive to cellular signs, while the secondary transducer transforms this cellular signs to electrical signals. The electric signals can be processed and analyzed. An example of secondary transducer is a microelectrode (Ripka and Tipek, 2013). Sensors have different performance characteristics, such as transfer function, sensitivity, dynamic range, linearity, accuracy, bandwidth, hysteresis, noise and resolution. Sensors are classified according to the signals and sensing principal (Patel and Ferdowsi, 2009; Zahn, 1998; Chénais *et al.*, 2004). Figure 4 categorized the microfluidics based on their applications in bioscience.

4.1 Sensors in biotech applications

Biotechnology is thoroughly linked with microfluidics (Kubik *et al.*, 2005). A buffer fluid or carrier fluid are constantly transporting biological targets, whether it is *in vivo* or *in vitro* (Berthier and Silberzan, 2010). For example, in the human body, any bio-MEMS can be transported using body fluids (Grayson *et al.*, 2004). In *in vitro* microsystems, there are some advantages for transporting the target molecules/particles by a buffer fluid: first, most of the time the target molecules/particles are extracted from a liquid such as DNA or cell; second, the biochemical reactions on these targets are performed in an aqueous environment; and third, in liquids, confinement of the targets are easier than in gases (Weigl *et al.*, 2003). Very few examples of biotechnological microsystems exist that do not involve microfluidics. This part shows some of the applications of microfluidic with microsensors in the area of biotechnology.

4.1.1 Biosensors for glucose detection

One of the key medical applications of biosensors is to develop point-of-care for patients suffering from diabetes. In this application, the concentration of glucose is measured using biosensor devices. Using these devices, patients are able to

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