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REVIEW PAPER

Lab-on-a-chip: a component view

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Abstract Miniaturization is being increasingly applied to biological and chemical analysis processes. Lab-on-a-chip systems are direct creation of the advancement in the miniaturization of these processes. They offer a host of exciting applications in several areas including clinical diagnostics, food and environmental analysis, and drug discovery and delivery studies. This paper reviews lab-on-a-chip systems from their components perspective. It provides a categorization of the standard functional components found in lab-on-a-chip devices together with an overview of the latest trends and developments related to lab-on-a-chip technologies and their application in nanobiotechnology. The functional components include: injector, transporter, preparator, mixer, reactor, separator, detector, controller, and power supply. The components are represented by appropriate symbols allowing designers to present their lab-on-a-chip products in a standard manner. Definition and role of each functional component are included and complemented with examples of existing work. Through the approach presented in this paper, it is hoped that modularity and technology transfer in lab-on-a-chip systems can be further facilitated and their application in nanobiotechnology be expanded

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1 Introduction

Lab-on-a-chip systems, which are also known as micro total analysis systems, can be defined as integrated micro electromechanical systems that can carry out all stages of biological and chemical processes. They enable miniaturization and integration of complex functions that can automate repetitive laboratory tasks. The portability, compactness, and parallelization features of lab-on-a-chip devices enhance the emerging trends in point-of-care diagnostics.

Currently, most of the developed lab-on-a-chip devices are application specific and their platform design has little consistency from one researcher to another. The absence of standardization in lab-on-a-chip designs can be considered as a bottleneck for their mass production as well as commercialization. The aim of this article is to explore standardization for lab-on-a-chip systems by classifying their integrated components. To date, there exists a set of excellent review papers (Auroux et al. 2002; Haeberle and Zengerle 2007; Lee and Lee 2004) that study lab-on-a-chip devices from different standpoints and cover a subset of their components. Here, we attempt to provide a description of standard functional components found in the existing lab-on-a-chip systems together with an overview of the latest trends and developments in the field. According to our investigation of the available literature, we have established that there exist certain key solutions for each functional component, together with several variations of each key solution. Therefore, in this review, we have attempted to identify and include the main key solutions. Integration of lab-on-a-chip with nanotechnologies is also covered in this article.

The paper is organized as follows. First, we will give an overview of the proposed components in lab-on-a-chip systems. We then provide a detailed description of the

components (injector, transporter, preparator, mixer, reactor, separator, detector, controller, and power supply) followed by a discussion on the integration and standardization of the reviewed components. Then, we describe the advantages of incorporating nanotechnologies in lab-on-a-chip systems, and present examples of how such systems can be used in nanobiotechnology applications. We conclude with a perspective on the future development of lab-on-a-chip technology.

2 Lab-on-a-chip architecture overview

A comprehensive lab-on-a-chip must be able to perform standard laboratory functions which include crude sample handling, sample and reagent mixing and reacting, separation, and subsequently detecting analyte of interest. To implement the stated functions that deal with sample analysis and processing, different standard functional components can be incorporated on a single chip whereby each component has a different role to play. We classify the lab-on-a-chip components into eight major groups as follows: injector, preparator, transporter, mixer, reactor, separator, detector, controller, and power supply. Figure 1 illustrates the proposed component view of lab-on-a-chip systems. The following sections explore details in each formulated component together with a description of the existing implementations.

3 Injector

Injectors ensure precise micro/nanoliter volume delivery of sample or reagent into a lab on-a-chip for analytical process. A symbol that represents injectors is shown in Fig. 1.

Injections can occur in two forms that are either between the external world and the lab-on-a-chip or among the internal components of the lab-on-a-chip. Table 1 summarizes the specification of the developed injectors found in existing lab-on-a-chip systems. Various injectors have been developed and used in conjunction with, or on-board of lab-on-a-chip devices. Syringe pumps and robotic pipettes are the most common injectors used. Daniel and Gutz (2006) used Rainin EDP-Plus electronic pipette as an injector and pump. The length of polyethylene tube connecting the micro-pipette to the microfluidic cell determines the sample volume delivery. A pipette tip guide is incorporated to assist the pipette tip to align itself to the inlet holes of the chip (Oh et al. 2005). A metering chamber based on capillary burst valve is introduced by Steigert et al. (2005) on a centrifugal lab-on-a-chip. Spinning the disc above a critical frequency causing the capillary burst valve to break and a precise metered sample volume is purged out. Precise sample volume delivery among different components in a lab-on-a-chip is required especially for reaction and separation tasks in chemical and biological analysis. Different channel shapes and dimensions are exploited to deliver the desired volume (Fu et al. 2002; Lee et al. 2005). Electrokinetic (Blas et al. 2008), hydrodynamic focusing (Gong et al. 2007), graduated volume measurement (Ahn et al. 2004), and floating sample injection are some of the techniques employed in minute sample dispensement.

4 Transporter

Fluidic transporters control fluids flow sequence, flow duration, flow direction, and flow rate for fluid manipulation

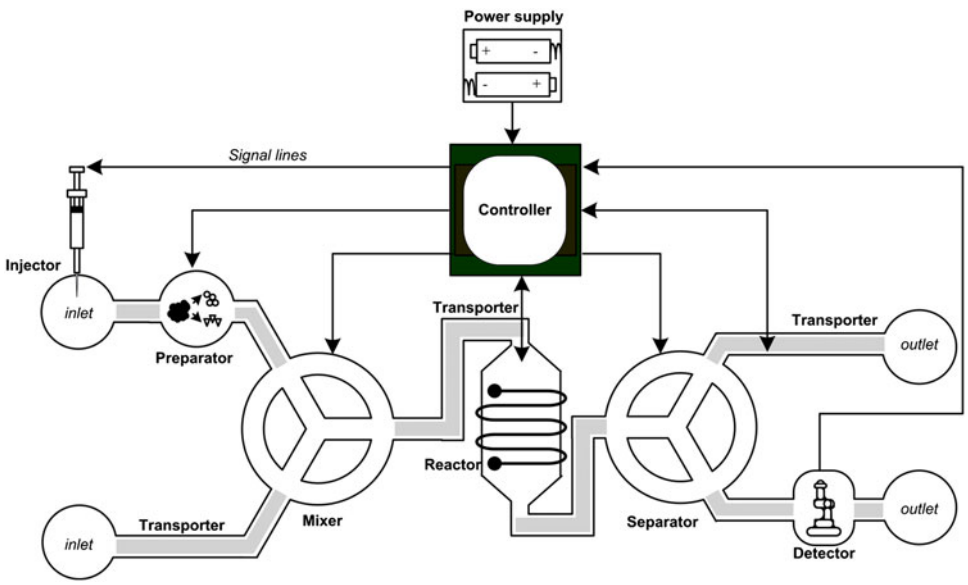


Fig. 1 Component view of lab-on-a-chip

Table 1 Specification of injectors found in existing lab-on-a-chip systems

Injection method	Approach	Remarks	Material	References
Between external world and lab-on-a-chip	Robotic pipette	Delivery volume of 3 μl	Glass	Emrich et al. (2002)
	Electronic pipette	Injection of small volumes of sample in the 100 nl–1 μl range from a pipette loaded with 10 μl	Polycarbonate CD	Daniel and Gutz (2006)
	Syringe pump	Delivery volume of 75 μl	Glass	Perch-Nielsen et al. (2006)
	Metering chamber based on capillary burst valve	Delivery volume of μl range down to nl range	PDMS and SU-8	Steigert et al. (2005)
	Automated dispenser system aided by electrokinetic and pressure difference	Inject sub-microliter sample volumes	PDMS	Futterer et al. (2004)
Among internal components	Graduated volume measurement	Repeatability standard deviation: 0.30% for the 50 nl dispenser 0.45% for the 100 nl dispenser 0.30% for the 150 nl dispenser	Cyclic olefin copolymers (COC)	Ahn et al. (2004)
	Electrokinetic	Delivery volume of 1 pl	Glass	Fu et al. (2002)
	Hydrodynamic focusing	Stable stream-centred laminar flow was readily obtained when the sheath to sample flow ratio was about 2:1	Glass and Su-8	Li et al. (2007)

in a lab-on-a-chip. A symbol that represents fluidic transporters is shown in Fig. 1.

Fluidic transporters can be categorized according to their actuation or driving force which is either active or passive. Active transporters are parts that require energy to actuate or give a driving force while passive transporters are parts that do not require energy to actuate or give a driving force. Table 2 gives a summary of the specification of the developed transporters found in existing lab-on-a-chip systems.

4.1 Active transporters

Pneumatically controlled micro-pumps in peristaltic motion (Fu et al. 2002; Lien et al. 2007; Tai et al. 2007) are commonly used in lab-on-a-chip devices for fluidics control. To ensure pumping rate uniformity, Wang and Lee (2005) introduced the "spider-web" peristaltic micro-pump as an alternative to the conventional "linear" peristaltic micro-pump. Designs based on a thermal actuation approach are presented in (Ahn et al. 2004; Liu et al. 2004; Yoo et al. 2006). Thermal responsive PDMS composite is used along with embedded single-use pumps and valves to achieve fluidic control (Samel et al. 2007). Fluids are transported out of the reservoir as a result of expansion of composite elastomer upon heating via lithographically defined heaters.

Valveless micro-pumps are becoming more popular due to their fabrication simplicity. Nguyen and Huang (2001) manufactured valveless pumps based on the printed circuit board technique. Diffuser or nozzle pump, and peristaltic pump use piezo discs as actuators. The piezo disc is made up of a piezoelectric ceramic layer glued on a brass disc which acts as the pump membrane. Piezo discs arrangements were in a wave-like motion in the peristaltic pump design. Valveless diffuser micro-pump proposed by Andersson et al. (2001) is capable for pumping a wide variety of fluids and is not influenced by the density, ionic strength, or pH of the pumped media. The device includes deep diffusers, a shallow pump chamber, and a thin pump diaphragm actuated by piezoelectric force.

Pneumatic, thermopneumatic, and piezoelectric driven micropumps and microvalves usually involve high driving voltage and high power consumption. Consequently, they require the inclusion of a large voltage source which is usually bulky and inappropriate for point-of-care devices. Electrochemical pumping systems are preferable because they eliminate the design complexity and require a lower fabrication cost compared to their pressure-driven counterparts.

For example, Suzuki and Yoneyama (2003) introduced an on-chip syringe pump controlled by a three-electrode system. This system has low operating voltage around 1 V and low power consumption in the range of micro watts. Meanwhile, a biochip that uses gas, generated by electrolysis of water between two electrodes in saline solution under the influence of current is developed by Liu et al. (2006a).

Table 2 Specification of transporters found in existing lab-on-a-chip systems

Driving force	Parts	Pumping rate (Hz)	Maximum flow rate	Materials	References
Pneumatic	Peristaltic pump and switch valves	50	10 mm/s (GE RTV 615) 14 mm/s (PDMS)	Elastomer GE RTV 615 and PDMS	Fu et al. (2002)
	Serpentine-shaped micro-pump and 4 micro-valves	28	39.8 µl/min (PDMS)	PDMS	Tai et al. (2007)
	Rotary pump with electromagnetic valves	17	170 µl/min at 30 psi	PDMS	Lien et al. (2007)
	"Spider-web" peristaltic micro-pump	15	8.4 µl/min at 150 kPa	PDMS	Wang and Lee (2005)
Thermo-pneumatic	Pump chamber and micro-valves	2	730 nl/min at a power of 500 mW	PDMS	Yoo et al. (2006)
Piezoelectric	Peristaltic pump	50	~1,500 µl/min at 100 V	PCB	Nguyen and Huang (2001)
Hydrodynamic and electro-osmosis	T-shaped microchannels with 4 reservoirs	–	0.2 mm/s	Glass	Gao et al. (2004)
Electrochemical	Micro-pump	–	0.8 ml/min	Polycarbonate substrate	Liu et al. (2004)
	Syringe micro-pump and 2 check valves	–	0.74 mm/s	Glass and PDMS	Suzuki and Yoneyama (2003)
Hydrostatic pressure (gravity driven)	Silica capillary	–	100 µl/min	Polycarbonate	Cai et al. (2006)

4.2 Passive transporters

In the field of reactive cellular and tissues studies, diffusion-mediated transporters are preferable due to their simplicity because no external force or power supplies are involved. Channel dimensions and geometries have been manipulated to achieve various flow rates. This is evident through the fabrication of a liquid-triggered valve consisting of a Y-junction which acts as a geometrical stop-valve (Melin et al. 2004). Meanwhile, Cho et al. (2003) implemented gravity and surface tension as the effluent driving force in their microscale integrated sperm sorter. This gravity-driven pumping system is able to maintain its flow rate regardless of the fluid in the reservoir. Hydrostatic pressure is used to generate gravity driven micro flow injection in the work by Cai et al. (2006). Reasonable liquid level difference and regular sample and solvent aspiration are needed to ensure reproducibility of the micro flow injection analytical signals for two-phase segmented flow. This is because a gravity pump cannot generate steady flows. Absorption and capillary force are also utilized in passive transporter (Schulte et al. 2000).

5 Preparator

Preparators treat and isolate analyte of interest from crude biological sample for downstream analysis. Often, the sample that needs to be analyzed is heterogeneous. A symbol that represents preparators is shown in Fig. 1.

Sample pre-treatment is a mandatory step in molecular analysis especially in DNA/RNA amplification. This is due to the fact that nucleic acid is required to be extracted from the biological cells. In addition, residual material from the samples can inhibit the process and thus reduce the efficiency of PCR amplification. The same applies to environmental and food samples collected for contaminants examination and pathogen detection. Integration of sample preparation on microfluidic devices is challenging because not only the raw sample can exist in different formats, the treatment and preparation of the sample is dependent on the type of analysis to be performed.

A more in-depth account on the challenges related to the usage of real samples in lab-on-a-chip systems can be found in previous publications (Crevillén et al. 2007; Mariella 2008; Mello and Beard 2003). Sample preparation conducted on-chip reduces processing time and requires minimal human intervention. Typical on-chip sample preparation protocols that have been demonstrated so far are filtration, pre-concentration, cell lysis, as well as derivatization. Table 3 summarizes the details of the various on-chip sample preparation techniques used in existing lab-on-a-chip systems.

5.1 Filtration

Filtration is one of the common techniques used to isolate the analyte of interest from the samples. Microfilters are the typical instrument utilized in this protocol. Different

Table 3 Specifications of on-chip sample preparation methods found in existing lab-on-a-chip systems

Sample type	Analyte of interest	Techniques	Performance	Materials	References
Airbone particles (*Escherichia Coli*)	Nucleic acid (rRNA)	Ultra-filtration, pre-concentration cell lysis and extraction	Extraction efficiency 55–70% of 31 s rRNA to 35–40% of 16 s rRNA	–	Chen et al. (2000)
Coumarin dye (C460) solution	–	Pre-concentration	Concentration gain is ~80-fold in <4 min	Glass	Kutter et al. (2000)
Fluorescein and dextran mixture	Dextran	Filtration	98.6% of dextran was retained in the product whereas 43.1% of fluorescein was removed	Laminate layers of plastic sheets (Mylar)	Weigl et al. (2001)
Food pathogens	Nucleic acid (DNA)	Filtration and washing	~15 min	Silicon and PDMS	Cady et al. (2005); Cady et al. (2003)
Haloacetic acids (HAA) in water	HAA	Pre-concentration	Enrichment factor of 54	Polycarbonate	Wang et al. (2005)
Mice blood	Nucleic acid (DNA)	Dilution, cell lysis and pre-concentration	Completed <10 min	Glass	Easley et al. (2006)
NIH/3T3 cells	mRNA	Pre-concentration	Isolation efficiency is 80%	PDMS	Marcus et al. (2006)
Plasma	Red blood cells	Pre-concentration	Extraction time of 20 s	PDMS & SU-8	Steigert et al. (2005)
Protein	BSA, Chymotrypsinogen A, Transferrin, IgG	Derivatization	Protein staining time is 15 min		Suzuki et al. (2006)
Red blood cell	Glutathione (GSH)	Cell lysis	Accomplished within 40 ms	Glass	Gao et al. (2004)
Saliva	Metalloproteinase-8 (MMP-8)	Filtration and pre-concentration	Achieved <10 min	Polymer and glass	Herr et al. (2007)
White blood cells	Viral RNA	Filtration, cell lysis, washing and extraction,	Filtration efficiency >90%	Silicon and glass	Hui et al. (2007)
Whole blood	White blood cells	Filtration	210-fold enrichment with purity of 58%. Throughput of 4×10^3 cells/s.	PDMS	Choi et al. (2007)
Whole blood	Nucleic acid of white blood cells	Filtration, cell lysis and pre-concentration	Pre-treatment process is <50 min	Glass, PDMS, silicon	Chen et al. (2007)
Yeast cells and MS2 bacteriophage	MS2	Filtration	Filtration efficiency is 90%. Sample recovery is 90%	Glass, silicon	Jung et al. (2008)

filter design structures are devised to strain the wanted cells from the sample. Filter can exist in the form of membrane filters with holes diameter of 4–12 μm and thickness of 1–3 μm for airborne particle filtration from airflow (Chen et al. 2000). Filtration using microfabricated silicon structures is reported in (Cady et al. 2005). Chaotropic salt guanidinium isothiocyanate functionalized silicon structures are used to bind DNA to the pillars isolating the nucleic acid from the lysates. Filtration implementing hydrophoretic strategy exploits the differences in size characteristics and deformability of cells and is used in red blood cells filtration (Choi et al. 2007).

Clogging and surface adsorption are the common predicaments faced in filtration systems. Due to the low surface area filtering, acoustic focusing (Jung et al. 2008) is reported to be more robust and effective in manipulating large particles (>2 μm) suspended in liquids. Acoustic standing waves are generated within the microchannel via an integrated piezoelectric transducer (PZT). Focusing efficiency varies with the driving voltage and particle size. Particles above a selected size are removed by adjusting the driving conditions of the transducer.

5.2 Preconcentration

Analyte present in crude sample maybe of very low concentration which may degrade the detection sensitivity of most detection methods except the fluorescence approach. Hence, sample enrichment can play an important role in improving the detector sensitivity. Foote et al. (2005) performed sample pre-concentration by applying a voltage difference between sample reservoir and pre-concentrator reservoirs based on the principle of field-amplified sample stacking. There is a drawback in this design as a small amount of protein leakage can occur in the pre-concentration channel due to electro-osmotic flow of sample through enlarged pores in the membrane. Solid-phase extraction (SPE) involves a mobile phase and a stationary phase for mixture separation. The desired or unwanted analyte is retained at the stationary phase while the portion that migrated through the stationary phase is either collected or discarded. Desired analyte that are trapped at the stationary phase can be collected by rinsing the stationary chamber with the appropriate solution.

Magnetic beads (Inglis et al. 2004; Lien et al. 2008) are used as the solid phase for the capture of antibodies and as carriers of captured target antigen. A magnetic field is created by a DC current to attract the molecule bound by magnetic beads onto the chamber surface. Water flushing is used to purify the target molecule and eradicate any inhibitors. Kutter et al. (2000) described an on-chip solid phase extraction using modified silanes-coated microchannels. SPE can be also seen in the work reported in (Bhattacharyya and Klapperich 2006) for isolation of nucleic acids. Liquid–liquid extraction is one of the crucial sample preparation procedures in organic analysis in chemistry and biology. It is an extraction of a substance from one liquid phase into another liquid phase. (Yu et al. 2005) accomplished three different types of liquid extraction using PZT ultrasonic nanoliter-liquid-droplet ejector. Droplet of nanoliter volume is ejected out without any nozzle, heat or lens but by means of acoustic streaming. Insulator-based dielectrophoresis (iDEP) adapted by Sabounchi et al. (2008) selectively concentrates microparticles of interest based on their electrical and physiological characteristics in the main fluidic channel. Extraction via sedimentation of red blood cells carried out using a centrifugal field is demonstrated in a micro-structured disposable polymer disk in the work by Steigert et al. (2005).

5.3 Cell lysis

Lysing of a cell involves rupturing of membrane cell to access their contents for intracellular and single cell studies. There are numerous cell lysis methods used including mechanical, chemical, physic-chemical, enzymatic, optical, acoustic, and electrical. The selection of lysis method is dependent on the downstream analysis to be performed. Applications and the various cell lysis methods are reviewed in (Brown and Audet 2008).

5.4 Derivatization

Derivatization is a sample preparation protocol frequently employed in chemistry or protein analysis to convert a chemical compound into a product of similar chemical structure. This can improve the detector sensitivity and selectivity in laser-induced fluorescent detection in capillary electrophoresis. Waterval et al. (2000) published a comprehensive report describing different derivatization techniques.

6 Mixer

Mixer mixes multiple streams of fluids in microchannels of a lab-on-a-chip. Due to the low Reynolds numbers in a lab-on-a-chip, mixing of multiple liquids in mixers is performed based on laminar diffusion under normal conditions. A symbol that represents mixers is shown in Fig. 1. Mixers can be divided into two groups: active and passive. Table 4 summarizes the specifications of mixers in existing lab-on-a-chip systems.

Table 4 Specifications of mixers found in existing lab-on-a-chip systems

Operating principle	Performance	Materials	References
Magnetic	Mixing time is 0.5 s	PMMA	Grumann et al. (2005)
Ultrasonic	Turbulence occurred instantaneously after the ultrasonic vibration causing the mixing to spread nearly throughout the entire chamber after 2 s	Silicon and glass	Yang et al. (2000); Yang et al. (2001)
Pneumatic	Mixing index is 96.3%	PDMS	Tseng et al. (2007)
Electrical	Mixing is achieved <10 ms over a length of 200 μm	Silicon and glass	Bottausci et al. (2007)
Chaotic mixing	Complete mixing within <1 ms after the two liquids make contact	Silicon and glass	Wong et al. (2004)
Transverse dispersion	Micro-mixer with 10 modified Tesla cells has a mixing performance of 44% concentration at flow rates of 75 μl/min	COC plastic	Hong et al. (2004)

6.1 Active mixers

Active mixers require the use of external forces to improve the mixing of input fluids. They are more expensive to develop and harder to integrate on a lab-on-a-chip. However, active mixers offer more rapid mixing of liquids in a short time interval. Magnetic actuated mixers incorporate external permanent magnets and magnetic particles in the channel (Suzuki et al. 2004; Wang et al. 2008). Mixing enhancement is achieved through the alternating actuation of magnetic particles suspended in liquid. Grumann et al. (2005) introduced a mixing scheme via inertia of liquids upon acceleration and deceleration in alternate spinning, "shake" mode, in addition to the magnetic beads induced advection Meanwhile, Yang et al. (2001) reported an active mixer that implements a PZT-generated ultrasonic vibration technique to mix water and ethanol. The ultrasonic vibration generates turbulence and cause spreading of mixing. However, the main drawbacks of this approach are the required high excitation voltage of 150 V, and not fully developed turbulence throughout the entire mixing chamber.

6.2 Passive mixers

Passive mixers exploit flow characteristics to mix multiple fluids without application of a force. This makes passive mixers more robust and stable. However, ideal mixing of liquids is attained over a longer period of time. Although it is hard to obtain turbulent flow in the microchannel without external force, mixing can be still enhanced by secondary flow, swirling flow, and vortices. Swirling flow is generated in the presence of a small z velocity component in the flow of liquid in the inlet. Sudarsan and Ugaz (2006) introduced a compact spiral-shaped flow geometries design to promote mixing via diffusion and transverse secondary Dean flows. Mixing in a section can be improved by increasing the lengths of the spiral contour. Mixing at higher flow rates can be obtained by fabricating multiple sections of spirals with fewer arcs.

Chaotic mixers introduced by Xia et al. (2005) implemented two-layer 3D X-shaped crossing channels. Chen and Meiners (2004) presented a multiphase topological mixing scheme that is able to perform fast and efficient mixing by diffusion. In this method, laminarity of the flow is exploited to continuously fold the flow and exponentially increase the concentration gradients. Multiphase mixing method adopted by Garstecki et al. (2006) achieved mixing via periodic oscillation of bubbles inflow into microchannels. In the absence of bubble, liquid flows laminarly at equal rates in both arms of the branch section. When the bubble enters one of the arms, flow of fluid through that particular branch is increased which leads to a decreased in the inflow of liquid to this arm.

7 Reactor

Reactor maintains and controls a chemical or biological reaction in a controlled environment. The reactor is usually equipped with heaters, sensors, or actuators to control and monitor the reaction process. A symbol that represents reactors is shown in Fig. 1.

Miniaturization of reactors has received a great deal of attention from researchers and scientists because it provides improved heat and mass transfer properties in microfabricated structure resulting in a higher yield. Meanwhile, the cost and risk is significantly reduced as only minimal volume of sample and reagent is required for the reaction process.

In times of reactor failure, the hazard of chemical leakage can be considered containable. Reactors are vastly applied in chemical and biological analysis and design considerations are reviewed by Doku et al. (2005). Reactors can be classified into three groups based on the types of reaction they perform: gas-phase, liquid phase, and

Table 5 Specifications of reactors found in existing lab-on-a-chip systems

Reactor type	Task	Remarks	Substrate materials	References
Gas-phase	Hydrogen production	Methanol to hydrogen conversion is 88.19%. It was able to supply hydrogen to a 9.48 watt fuel cell	Silicon and Glass	Pattekar and Kothare (2004)
Liquid-phase	Amide formation	After 1 h, 1.7 g of crude product (90% pure) were obtained. Reaction yield is 81%	Glass	Kikutani et al. (2002)
	Bromination of styrene inside of benzene droplets	Yield for 1,2-dibromoethybenzene is 21 mg at flow rate of 0.16 ml/min for 30 min	Thiolene-based optical adhesive NOA 81 and Glass	Cygan et al. (2005)
Packed-bed	Proteolytic digestion	The protein took 12 min to complete digestion in the device where the digestion pattern is comparable to that attained after 18 h of water bath digestion at 37°C	Glass	Jin et al. (2003)
	Amie N-alkylation process	N-alkylation in ethanol: time taken is 150 s. Reaction yield of N ethylbenzylamine is 85%. Reaction yield of *N*-ethylaniline is 34%	Quartz	Matsushita et al. (2008)
		Tetrahydropyranylations (THP)	Synthesis of 2-	
		benzyloxytetrahydropyran. Conversion 99.997%. Using four reaction channels in parallel: throughput is 50 mg/h. Using a single reaction channel: throughput is 12.5 mg/h	Glass	Wiles and Watts (2007)

packed bed. Table 5 summarizes specifications of a number of reactors found in existing lab-on-a-chip systems.

7.1 Gas phase reactor

A multiplexed reactor capable of eight simultaneous operations was developed by (Szita et al. 2005) for microbial fermentation. Inoculation of *E. Coli* into the reactors was done through the second inlet port with a syringe. Stirring was carried out throughout the inoculation procedure which took about 20 min. Reactors are sealed at the end of inoculation and fermentation parameters are measured. Reactors are also found in microfluidics chips used in hydrogen production for micro-fuel cell (Pattekar and Kothare 2004). Methanol–water mixture was loaded into the reactor via a syringe pump. Argon gas was mixed with reactor exhaust gasses before flowing into gas analyzer to ensure accurate hydrogen production calculation. In contrast, Goerke et al. (2004) developed a reactor for carbon monoxide (CO) reduction in hydrogen production for fuel cells. A HPLC pump fed the water used for reaction into a steel capillary. A resistance wire heated the capillary and caused water to evaporate. Water vapor and N_2/O_2 gasses were pre-mixed and heated to desired temperature in the heated pipes. CO and H_2 were added to the gas/steam mixture in a mixer heated by resistance wire. One thermocouple measured temperature between mixer and upstream of reactor whereas another thermocouple measured gas outlet temperature downstream of reactor and a third thermocouple measured the housing temperature.

7.2 Liquid phase reactor

An example of a liquid-phase reactor is the pile-up reactor consisting of ten levels of microchannel circuits developed for amide formation by (Kikutani et al. 2002). Reagents were continuously fed into the reactor through a double-plunger HPLC pumps with a maximum flow rate of 10 ml/min for 1 h. The resultant organic solution was separated and dried with sodium sulfate, filtered and dried with a rotary evaporator.

Bromination of styrene inside of benzene droplets (Cygan et al. 2005) was realized in a reactor by combining two organic inputs, 1 mol/l solution of bromine in benzene and 1 mol/l solution of styrene in benzene. Droplets of mixture were formed at flow focusing junction and as the droplets flow through down the channel, reaction occurs and orange color of bromine faded to clear. When designing a liquid phase reactor, it is important to understand the behavior of chemical reactions within reactor manifolds. Adequate mixing is the common dilemma faced by liquid-phase reactor designers. (Fletcher et al. 1999) described the theoretical considerations that governs the liquid phase chemical reaction based on electrokinetic fluidics system.

7.3 Packed-bed reactor

The advantage of packed-bed reactors is their higher conversion per weight of catalyst compared to other catalytic reactors. Chemical reaction takes place on the surface of the catalyst and hence, reaction rate is influenced by the amount of catalyst rather than the volume of reactor. (Ukita et al. 2008) fabricated a vertically stacked 3D reactor structure to conduct competition enzyme-linked immunosorvent assay (ELISA). Analyte nonylphenol (NP) and enzyme-labeled alkylphenol (AP) and antibody immobilized polystyrene microbeads were mixed off-chip. The mixture is subsequently injected and retained in the fluid filter for reaction. Reaction was stopped by adding sulfuric acid. N-alkylation of bezylamine and aniline were demonstrated in 300 μm-depth reactor with immobilized Pt-free TiO_2 and TiO_2/Pt. Tetrahydropyranylations employed in a reactor made of borosilicate glass substrate was depicted in (Wiles and Watts 2007). Pre-mixed solution of 3,4-dihydro-2H-pyran and alcohol (1 M, 1:1) is loaded in reservoir A and mobilized through the packed-bed comprising solid-supported acid catalyst. Collection of reaction products is done at reservoir reactor created in (Kataoka et al. 2008) used silicon wafer and borosilicate glass as planar substrates. Mesoporous silica films (MPS) acts as catalyst supports on inner wall of borosilicate microcapillary tubes in reactors. MPS has a highly ordered structure with pore size ranging from 2 to 30 mm.

8 Separator

Separators isolate sample and reagents after mixing or reaction processes. The separator module can be used to perform selection of a pre-determined cell for analysis, or isolation of a large number of single cells where user cannot identify and manipulate a pre-determined cell. A symbol that represents separator is shown in Fig. 1.

Micro-separation technique plays a significant role in system biology for comprehensive profiling of genome, proteome and metabolome, characterization of biomolecules interaction as well as single cell analysis (Liu et al. 2006b). Although capillary electrophoresis (CE) is the famous trend in segregation of desired analyte, other techniques such as optical tweezers, magnetic, dielectrophoresis (DEP), isotachophoresis, chromatography and laminar flow based filter are also emerging. Table 6 summarizes specifications of the separators found in existing lab-on-a-chip systems.

CE is a separation technique that isolates ionic particles by their charge and frictional forces. By applying a voltage across two electrodes placed at the end of the channels, sample is injected into the separation channel and isolation of particles occurs. Ease of implementation, portability, minimal reagent consumption and high speed have made CE (Chen et al. 2006; Kaigala et al. 2008; Vieillard et al. 2007) by far the most popular and matured technique in separation technology. Separation efficiency in CE is often limited by dispersion and this is investigated in (Ghosal 2006). Recently, Ikuta et al. (2008) designed a separator with PAG as the molecular sieve that isolated five different proteins based on their molecular weight. Dielectrophoresis is the motion of particles relative to a fluid under the influence of a non-uniform electric field. Polarization effects in non-uniform electric field allow the manipulation of particles between regions of high and low electric field (Kua et al. 2005). Positive DEP occurs when the particle or cell is more polarizable than the medium surrounding it. Tai et al. (2007) fabricated a biochip, that is capable of performing continuous flow separation of human lung cancer cells utilizing DEP approach. Negative DEP based on trapezoidal electrode array prevents non-specific particle adherence to the electrode surface (Choi and Park 2005). Lately, Vahey and Voldman (2008) introduced the first microfluidic equilibrium separation method called isodielectric separation (IDS). IDS separates particles based upon induced charge and is not limited to low-frequency electric fields with dielectrophoresis as the forcing mechanism. Isotachophoresis is a separation technique that utilizes a discontinuous field to create sharp boundaries between the sample constituents. Liu et al. (2008) developed a transient isotachophoresis/capillary gel electrophoresis (tITP/CGE) for the separation of DNA fragments. tITP/CGE separation was carried out with a single running buffer. tITP is based on the use of discontinuous buffers in respect to ions with different mobility but migrating at the same velocity.

An optical tweezer is a separator that manipulates nanometer or micrometer-sized particles by exerting extremely small forces via a highly focused laser beam. Munce et al. (2004) incorporated both optical tweezers and the capillary electrophoresis technique to demonstrate parallel injection and analysis of calcein-labeled acute myloid leukemia (AML) cells. Optical tweezers examine, select, and analyze a pre-determined single cell and transport them to the injection region for capillary electrophoresis separation by focusing a laser beam marker on the cell. Magnetic separator used antibody-coated magnetic particles, which attach to a specific molecule type and desired analyte, is isolated when a magnetic field is applied (Jiang et al. 2006; Pamme and Wilhelm 2006). Magnetic flux leakage can be prevented by using micro-coils with magnetic pillars and backside plate (Ramadan et al. 2006).

Chromatography refers to the mixture separation technique that involves moving a mixture dissolved in mobile phase through a stationary phase which allows isolation of analyte to be measured from other molecules in the mixture. Various chromatography techniques have been developed: gas chromatography, liquid chromatography,

Table 6 Specifications of separators found in existing lab-on-a-chip systems

Approach	Separation Target	Performance	Materials	References
Optical tweezers	Calcein-labeled AML cells	Throughput is 24 cells/h	PMMA	Munce et al. (2004)
	Leukemia cell lines	Took one and half hours to complete	PDMS and Glass	Lau et al. (2008)
	Colloids	Sorting of 5 cells/s, or 1,000,000 cells in about 2 days	PDMS	Applegate et al. (2006)
	Homogenous mixtures	Count accuracy for homogenous mixture containing only beads for red blood cells is 98–100%, red blood cells and hepatocytes is ~90%	Glass	Seo et al. (2008)
Magnetic	Magnetic microbeads	Spiral micro-coil with magnetic pillar with highest trapping ratio of 84.3% at a flow rate of 20 μl/min	Glass and Silicon	Ramadan et al. (2006)
	ORN 178 *Escherichia coli*	Maximum sorting efficiency is >90% and selectivity is ~100%	–	Shih et al. (2008)
DEP	Human lung cancer cells	Separation accuracy for viable cells is 84% and non-viable cells is 81%	PDMS and Glass	Tai et al. (2007)
	Beads mixture	Purity gained for 15 μm diameter is 96.8 ± 0.6%; Purity gained for 6 μm diameter is 99.5 ± 0.5%	PDMS	Choi and Park (2005)
	Viable yeast cells	At frequency of 500 kHz and flow rates of 1.0 and 1.5 l/min (throughputs of 10^4 and 1.5×10^4 cells/min), separation resolution for viable cells is 1.12 ± 0.15 and non-viable cells is 1.25 ± 0.30	PDMS	Vahey and Voldman (2008)
ITP	Tryptophan enantiomers	Single column ITP yields a high production rate of 2 pmol of pure tryptophan enantiomers per second only suitable for analysis of sample containing high concentration enantiomers	PMMA	Ölvecká et al. (2001)
Capillary electrophoresis	Organic peroxides.	Separation is achieved within 120 s	Glass	Wang et al. (2002)
	Neurotransmitters	Separation is achieved within 140 s	PDMS	Wang et al. (2006)
	Silica particles	99.6% pure silica in the unrestrained first fraction and 95.8% pure polystyrene in the laser retained second fraction. Took 30 min	Glass	Hart et al. (2007)
Acoustic standing wave forces	Lipid particles	Polyamide spheres separation efficiency: ~100%; Triglyceride emulsions separation efficiency: >80%	Silicon	Petersson et al. (2005)
	Blood phantom	90% of particles were successfully gathered in 2/3 of the original fluid volume in the 45° separator design	Silicon	Nilsson et al. (2004)
Laminar flow	Erythrocytes and small fluorescent particles	About 80% of erythrocytes are collected at Branch A3	PDMS	Takagi et al. (2005)

column chromatography (Jindal and Cramer 2004), optical chromatography (Hart et al. 2007), and so on. Another separator design includes using acoustic radiation force from ultrasonic standing wave field to move suspended particles either towards a node or an anti-node of a standing wave depending on their densities and compressibility (Nilsson et al. 2004; Petersson et al. 2005). This exploits geometries of the microchannels to achieve separation of fluorescent microspheres (Takagi et al. 2005) and diffusion-based separation (Schuster et al. 2003).

9 Detector

Detectors identify and quantify analyte via various methods. Detectors consist of transducers that acquire physical signals from analyte and transform them into electrical signals for analysis. A symbol that represents detectors is shown in Fig. 1. There exist several main detection methods including optical, electrochemical, mass spectrometry, capacitance, and magnetic. There are a number of good review articles that describe various detection methods (Kuswandi et al.

Table 7 Specifications of detectors found in existing lab-on-a-chip systems

Technique	Sample	LOD	Materials	References
Fluorescence	Rhodamine 6G	10 nM	PDMS	Banerjee et al. (2008); Klotzkin and Papautsky (2007)
	32-mer molecular beacon DNA probe	10–18 mol of rRNA	Silicon and Glass	Wang et al. (2000)
	Alexa Fluor 633 dye	10 nM	Silicon	Malic and Kirk (2007)
Absorption	Alexa Fluor 633 dye	1 μM	Silicon	Malic and Kirk (2007)
	BSA	15 nM	PDMS	Zhu et al. (2006)
	Uric acid and protein in urine	0.5 mg/dl	SU-8 and Glass	Minas et al. (2005)
	HRP and H_2O_2	0.03 nl	Glass	Chandrasekaran and Packirisamy (2006)
	Ketoprofen	0.27 nl	Silicon	Petersen et al. (2002)
Micro-ring resonator	Avidin/biotin	50 ng/ml	Silicon	De Vos et al. (2007)
Cyclic voltammetry	Salivary mRNA	0.4 fM		Wei et al. (2008)
Chronoamperometry	Response 3 types of recombinant *E. Coli* promoters. (fabA, Dnak and grpE) to phenol (toxic chemical)	1.6 ppm	Silicon	Popovtzer et al. (2006)
Differential pulse voltammetry	Goat IgG	118 fg/ml	Glass	Dong et al. (2006)
Square wave anodic stripping voltammetry	Lead	0.2 ppb	Polycarbonate	Lin et al. (2001)
ESI-MS	Imipramine-d_3.	Electrospray stability with a relative standard deviation of 10%	COC polymer	Yang et al. (2005)
Charge-based capacitance measurement	Dichloromethane and acetone	Resolution of capacitive sensor is 6 bits.	CMOS chip	Ghafar-Zadeh and Sawan (2007a, 2007b, 2008)
Capacitive array sensor	DNA sample	Sensitivity is 90 Hz/fF	–	Kornaros et al. (2008)
Magnetoresistive sensors	Magnetic beads	Able to detect a single 9 μm ferromagnetic bead at a distance of 4.7 μm	SU-8	Jiang et al. (2006)
Laminar diffusion	Phenytoin (small drug molecule)	0.43 nM	Glass	Hatch et al. (2001)

2007; Marta Bally 2006). Table 7 summarizes the specifications of detectors found in existing lab-on-a-chip systems.

9.1 Optical

Optical detection can be considered as the most prevalent detection method in lab-on-a-chip devices due to its integration simplicity. In addition, for optical detection methods, the distribution of the light on the chip enables integration of multiple individual detectors on a single chip (Stanislas 2003). In fluorescence detection, cells that are labeled with fluorescent dye emit light once they are excited with a light source, typically a laser (Ikuta et al. 2008; Pipper et al. 2008). Dye emission light is usually overwhelmed by the excitation light in fluorescence detection. To overcome this setback, a band pass filter (Malic and Kirk 2007; Yin et al. 2007) is used. On the other hand, (Klotzkin and Papautsky 2007) proposed the integration of a polarizer to isolate excitation light from the detector. Currently, the cross polarization strategy is incorporated with organic photodiode detectors in a fluorescence-based lab-on-a-chip reported in (Banerjee et al. 2008). Apart from the fluorescence detection method, absorption spectroscopy (Chandrasekaran and Packirisamy 2006; Zhu et al. 2006) is also widely employed in optical detection due to its label-free environment. In this technique, the intensity of a beam of light is measured before and after interaction with the analyte. Absorption detection shows a lower sensitivity which means a reduced limit of detection (LOD). Although optical waveguides have been incorporated to overcome the abovementioned setback, there are still other complications such as stray light issues as well as detection channel geometry that contribute to the decreased

detection sensitivity (Petersen et al. 2002). Micro-ring resonator (De Vos et al. 2007; Fan et al. 2007) is another label-free optical detection approach. Optical ring resonator is made of a closed loop waveguide coupled to one or more input or output waveguides that measure the change in the refractive index.

9.2 Electrochemical

Electrochemical detection refers to a three-electrode system. Working electrode is dipped into the solution containing the analyte. A voltage is applied to facilitate the electron transfer to and from the analyte. Meanwhile, a reference electrode is used as a reference in measuring and controlling the working electrodes. The counter/auxiliary electrode provides the current needed to balance the current observed at the working electrode. Addition of electrolyte in the system is to provide a conductive environment. The ease of fabrication and integration of electrochemical cells with microfluidic devices has made this technique suitable for biosensor systems that are based upon biochemical reactions for recognition (Chooi et al. 2002).

In cyclic voltammetry (Wei et al. 2008), working electrode potential is ramped linearly versus time. As it reaches a set potential, the working electrode potential ramp is inverted. Meanwhile, the potential of the working electrode is varied, and the resulting current from faradic processes occurring at the electrode is monitored as a function of time in chronoamperometry (Chooi et al. 2002; Popovtzer et al. 2006). A series of regular voltage pulses is superimposed on the potential linear sweep or stair steps in differential pulse voltammetery technique (Dong et al. 2006). Specific ionic species such as lead can apply the square wave anodic stripping voltammetry (Lin et al. 2001) for detection. During deposition step, the working electrode is electroplated with the analyte of interest whereas the species is oxidized from the electrode during stripping step.

9.3 Mass spectrometry

Mass spectrometry evaluates the ratio of charge to mass of particles for identification of chemical composition of a compound. This technique is widely applied in proteomics analysis as it is able to provide molecular weight and structural information. To perform the electrospray ionization mass spectrometry (ESI-MS) detection of concentrated and resolved cytochrome c peptides (Gao et al. 2001), two Spellman high-voltage power supplies are employed for delivering electric potentials of 18 kV to the glass vial and 3 kV to the microdialysis junction to maintain an electric field of 300 V/cm over a 50 cm separation distance as well as induce the electrospray of peptides. The first polymer-based microchip that have direct integration with an electrospray emitter and an internal gold electrode was reported in (Yang et al. 2005).

9.4 Capacitive

Ghafar-Zadeh and Sawan (2007b, 2008) presented a capacitive sensor array as the detector in a lab-on-a-chip. The capacitive sensor was implemented in 0.18 μm CMOS processing. The system features three interdigitated electrodes which are used as sensing capacitors. Meanwhile, Kornaros et al. (2008) introduced a hybridization detector module using a capacitive based microarray structure that encompasses a total of 256 sensing elements. The capacitive sensor is implemented using 0.35 μm CMOS processing technology. Operation of the device was based on the induced stress due to reaction between receptor DNA and the sample. Surface stress change arisen during hybridization and successive bending of ultra thin silicon membrane. Capacitance changes are converted into frequency signal using a special electronic circuit.

10 Controller

Controllers manage all on-chip control, data acquisition, and signal processing operations. They are responsible for issuing control signals to on-chip components such as actuators, heaters, and so on. They also gather data from on-chip sensors. For example, the data acquired from the detector is directed to the controller for processing. The controller also outputs data to external devices such as analyzing instruments via communication interface circuitry. A symbol that represents controllers is shown in Fig. 1.

A typical controller consists of such modules as microcontroller, communication interface, programmable memory, control circuitry, signal preconditioning circuitry, and power interface circuitry. Table 8 provides a summary of the controllers integrated in existing lab-on-a-chip systems.

10.1 Off-chip

Pumps and valves integrated in lab-on-a-chip systems require control circuitry to perform their operations. Control circuits and electromagnetic valves are developed by Wang and Lee (2005) to control the motion of pumps. Tseng et al. (2007) utilized a microcontroller to control the driving of electromagnetic valves to generate pumping and mixing effects. A controller employed by Fu et al. (2002) consisting of 3-way pneumatic switch valves digitally controlled by a National Instruments card via a fast zener diode circuit to generate peristaltic pumping action. A control system is also incorporated in sample concentration and detection based on both insulator-based dielectrophoresis and

Table 8 Summary of controllers found in existing lab-on-a-chip systems

Controller Integration	Elements	References
Off-chip	Electromagnetic valves, SMC Inc., S070M-5BG-32, Japan; Control circuit	Wang et al. (2005)
	8051 Rocontroller; Electromagnetic valves	Tseng et al. (2007)
	National Instruments card AT-DIO-32HS (controller); Zener diode circuit; National Instrument card Lab PC1200 (analog-to-digital converter)	Fu et al. (2002)
	ARM microprocessor	Kornaros et al. (2008)
	Waveform generator (model 33220A; Agilent Technologies, Santa Clara, CA, USA); RF power amplifier (model 325LA; EIN); Labview program	Jung et al. (2008)
	Programmable high voltage power supply, HVS448 (Lab-Smith, Livermore, CA, USA); Laptop; Sequence software program (LabSmith); Modular power supply connections; Instrument communication; Impedance data acquisition and processing; A/D and D/A converters; 8-bit Rabbit 2000 microprocessor	Sabounchi et al. (2008)
On-chip	Sensors and actuators executor	Guo W-p et al. (2005)

electrical impedance measurement on lab-on-a-chips in the work of Sabounchi et al. (2008). A programmable power supply provides feedback to the main system board for active current control. 12-bit analog-to-digital converters were used to interpret power supply currents, impedance signal, and power supply voltage while D/A converters set power supply bias voltages. All control operations such as low-level and real-time microfluidic interface and data acquisition were executed by the microprocessor. A piezoelectric based lab-on-a-chip required a waveform generator and an RF power amplifier to drive the on-chip transducers (Jung et al. 2008).

10.2 On-chip

To achieve lab-on-a-chip concept, it is desirable to integrate all necessary components on-chip instead of off-chip. Guo et al. (2005) have proposed a lab-on-a-chip for human immunodeficiency virus assay with an on-chip controller. The proposed design consists of three modules, microfluidic chip, sensor, actuators, executor, and a CCD imaging device. The sensor and executor precisely manipulate the total system. Currently, there exist a few reports on on-chip integrated controllers. Advancement in both microfluidic and CMOS fabrication technology will make the incorporation of controller in lab-on-a-chips achievable.

11 Power supply

Power supplies energize on-chip components including transducers, actuators, and electronic circuits. They are an essential unit especially in electrokinetic-based lab-on-a-chip systems. A symbol that represents power supplies is shown in Fig. 1. Portable lab-on-a-chip devices usually utilize batteries as their power source. Meanwhile, lab-on-a-chip systems that operate using electrophoresis or dielectrophoresis, require a very high voltage power supply and also the ability to manipulate the voltage values. In this case, high voltage programmable power supplies are needed. Tsai et al. (2006) used a programmable high-voltage power supply to generate the electrokinetic driving forces required for the sample injection and separation steps of the CE process. Alternatively, Erickson et al. (2004) presented a reusable integrated high voltage power supply for electrokinetic transportation of fluids. The power supply was powered by an onboard cell battery and was self-containable and adjustable.

12 Integration and standardization

Lab-on-a-chip researchers are likely to deliberate the rationality of how many functional components should be integrated on-chip. An ideal lab-on-a-chip is to have complete integration of all functional components which includes injector, transporter, preparator, mixer, reactor, separator, detector, controller, and power supply. Injectors and transporters are two components that are essentially found in any lab-on-a-chip. However, existing lab-on-a-chip systems have varying degree of integration. For example, most researchers prefer to perform sample preparation off-chip because raw samples have various composites requiring their own dedicated pretreatment. Apart from that, some laboratory functions do not require all components for analytical process. Therefore, certain components can be omitted from the lab-on-a-chip design. In fact, the degree of integration is dependent on the lab-on-a-chip analytical process, application, and fabrication. The ultimate goal for lab-on-a-chip systems is to be able to accept raw sample and process it without any cross contamination. Table 9 provides some examples of integrated lab-on-a-chip systems to date. The table gives a reference to each work, a visual representation of the lab-on-a-chip system, a description of the functional components found in the system, an explanation of the material used for the fabrication of the system, and a description of the application of the system.

Table 9 Examples of integrated lab-on-a-chip systems

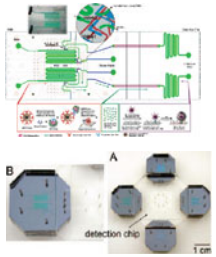
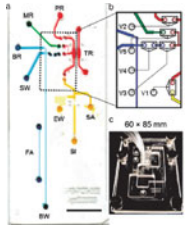
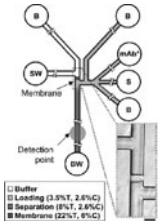
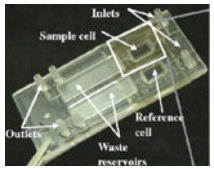
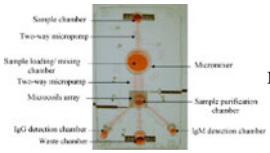
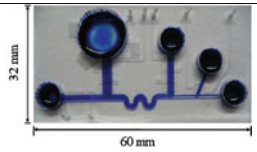
References	Device	Components									Material	Applications
		Injector	Transporter	Preparator	Mixer	Reactor	Separator	Detector	Controller	Power supply		
Renzi et al. 2004		Syringe and T-style injector	Passive (pressure-difference)	–	–	–	CZE and CGE	Optical	On-board (hand-held)	On-board	Fused silica	Protein identification
Shaikh et al. 2005		Pressure driven	Active (pneumatic valves)	–	Passive	Liquid phase	Magnetic	Optical	Off-chip	Off-chip	PDMS	Biochemical analysis
Easley et al. 2006		Syringe	Active and passive (laminar flow and syringe pump)	Dilution, cell lysis and pre-concentration	–	Liquid phase	CE	Optical	Off-chip	Off-chip	PDMS	Genetic analysis
Herr et al. 2007		Electrophoretic	Passive (pressure-difference)	Filtration and pre-concentration	Passive	–	CGE	Optical	On-board (portable reader)	On-board	Glass	Immunoassay

Table 9 continued

References	Device	Components									Material	Applications
		Injector	Transporter	Preparator	Mixer	Reactor	Separator	Detector	Controller	Power supply		
Hui et al. 2007		Syringe	Active (micropumps and microvalves)	Filtration	–	–	–	–	On-board (portable system)	On-board	Silicon and glass	DNA and RNA extraction
Huang et al. 2009		Syringe pump	Active	–	–	–	–	Optical	Off-chip	Off-chip	COC	Biosensor
Lee et al. 2009		Micropump	Active (micropump and microvalves)	–	Active	–	Magnetic	Optical	Off-chip	Off-chip	PDMS and glass	Dengue virus infection diagnosis
Wu et al. 2010b		Micropump	Active (micropump and microvalves)	–	Active	–	Magnetic	Optical	Off-chip	Off-chip	PDMS and glass	Hematopoietic stem cells sorting
Liu et al. 2009		Capillary force	Active (micropump)	–	–	–	–	Electrochemical	On-board (hand-held)	On-board (hand-held)	PDMS and glass	Urinary protein detection

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Although there are increasing research and development of lab-on-a-chip systems to date, still, there exist only little industry standards even for the simplest components. The lack of standardizations leads to issues such as technological incompatibility among different components in lab-on-a-chip systems. This may prevent complete on-chip integration and packaging. The technological incompatibility arises in terms of the materials used for the fabrication of different components as well as the automation and batch processing of the devices for up-scale manufacturing. Early microfluidics components are fabricated using glass and silicon which have well-defined protocols adapted from the semiconductor processes. Using silicon as a substrate material for lab-on-a-chip systems offers benefits such as process flexibility, performance stability and reproducibility. Furthermore, it is compatible with CMOS integrated circuit technology (Popovtzer et al. 2006). Currently, PDMS as a substrate material is used for microfluidic device prototyping in laboratories. This material is gaining popularity due to its ease of fabrication using soft lithography technique. Also, it does not require any elaborate equipment (McDonald and Whitesides 2002) for fabrication. However, the implementations of PDMS technologies for high-throughput fabrication are not yet fully explored and developed.

Lab-on-a-chip systems that are built from various functional microfluidics and microelectronics offer high functionality. However, careful consideration is required to integrate these parts. Leakage and the exposure of electrical points to fluids need to be taken care of during fabrication. One of the proposed approach is to use flexible printed circuit board (PCB) for the incorporation of sub-millimeter size integrated circuits in either glass or PDMS microfluidics systems (Wu et al. 2010a). The microfluidics components are first fabricated using standard procedure and subsequently bonded to the assembled PCB at wafer level. Unlike the previous work, Ghafar-Zadeh et al. (2007) introduced the direct-write fabrication process which enables direct fabrication and integration of microfluidics components, and also fitting connections on top of CMOS chips. The electrical connections and packaging are achieved via wire bonding or flip-chip. This eliminates the need for alignment during the bonding process.

The awareness of the importance of standardization can be seen in the efforts of Shaikh et al. (2005) as well as Rhee and Burns (2008). A modular lab-on-a-chip architecture is introduced by (Shaikh et al. 2005) enabling self-customization of the lab-on-a-chip system. The proposed concept consists of two levels: (1) a single chip level which is further categorized into passive fluidic components (channels and reaction chambers) and active electromechanical control structures (sensors and actuators), and (2) a multiple chip module system level that consists of multiple modules of different lab-on-a-chip functions. Meanwhile, Rhee and Burns (2008) developed standard building blocks for lab-on-a-chip systems to create a development path for assembling a lab-on-a-chip into various custom complex systems. Standardization in lab-on-a-chip systems should not be overlooked to ensure its successful implementation and value. A lab-on-a-chip that is created for a single and specific application can perform limited operations. Through standardization, modularity and technology transfer in lab-on-a-chips can be attained. This will lead to the realization of a single system with an integrated microfluidics networks and circuitry.

13 Integration of lab-on-a-chip and nanotechnologies

Recent trends in lab-on-a-chip systems see the scaling down of their functional components to nanometer dimensions for accommodating nanoscale analysis. Furthermore, nanotechnology tools such as nanotubes, nanowires, nanoneedles, nanopores and nanofluidics are being integrated in the new generation lab-on-a-chip architectures. The term "nanobiotechnology" refers to the application of nanotechnology in life sciences analysis (Jain 2005). The marriage between lab-on-a-chip and nanotechnology (nanochip) offers enormous capabilities in nanobiotechnology by creating bioanalytical devices with exceptional sensitivity and performance. This partnership is driving the advancements in the field of single-molecule diagnostics (Craighead 2006), especially in drug discovery and genetic analysis, leading to the creation of "nanodiagnostics" (Jain 2003).

Cao et al. (2002) introduced an injector component with a gradient fluidic structure ranging from micro to nanometer scales for introduction of long genomic DNA molecules. Long DNA molecules tend to stick to the entrances of nanochannels when drawn by hydrodynamic field or electric field from high-entropy area to confining nanochannels. Therefore, a micropost array is stationed in front of the nanochannels and the gradient structure is designed to pre-stretch long DNA molecules before entering the nanochannels to avoid DNA clogging at the junction. Fabrication of the microposts is achieved via a modified photolithography technique called diffraction gradient lithography. The arrays of nanochannels are fabricated on a silicon substrate chip using nanoimprinting lithography. Lateral and vertical gradient patterns are created using light diffraction. A blocking mask which is a piece of aluminium foil is used to protect the area of desired nanochannels and generate a gradient of light intensity on the surface of the photoresist during light diffraction, thus producing the gradient structure. This technology has potential applications in prenatal diagnosis, pharmacogenomics and forensic medicine.

Nanotechnology also paves the way for exciting developments in sample preparator and separator components.

Continuous flow operation is desirable in preconcentration and separation tasks to enhance detection limit because sampling can be time integrated (Eijkel and van den Berg 2006). There must be some net force generated which is orthogonal to the applied flow field when conducting sieve-type separations in 2D matrix. Conventional membranes, gels and sieves are limited to performing 1D separation in a continuous flow operation due to their isotropic and randomly distributed pore space. This results in a zero net orthogonal separating force with the applied flow field. With nanotechnology, the ability to produce spatially anisotropic sieving structures suitable for continuous flow operation can be achieved.

An example of nanotechnology incorporated filtration strategy is shown in the work of Fissell et al. (2009). The authors developed an ultrathin hemofiltration membrane with monodisperse slit-shaped pores using a sacrificial oxide technique. The slit-shaped pore has the advantages over round-shaped pore in terms of hydraulic permeability and molecular selectivity. The membrane is made up of a 4 μm thick polysilicon diaphragm, consisting of an array of 10 nm × 45 μm slit pores uniformly spaced with 2 μm gaps. The material surface is further modified with polyethylene glycol to prevent protein adsorption, fouling and thrombosis. The authors successfully conducted a 90 h hemofiltration with anticoagulated bovine whole blood using the silicon nanopore membrane. Similarly, Cross et al. (2007) fabricated a microfluidic device coupled to a slit-like nanochannel using standard lithography and etching techniques to perform DNA separation by length. The channels contain no obstacles and sieving matrix and have vertical dimensions of 19 and 70 nm. Electrophoresis was used to drive mixtures of DNA molecules with different lengths. The molecules migrate with a length-dependent mobility when an electric field is applied. However, microfabricated nanofilters/nanopores face volume throughput limitation. This is due to nanochannel small open pore volume which leads to a low throughput compared to traditional membrane materials. To overcome this bottleneck, Mao and Han (2009) presented a novel fabrication strategy to generate massively-parallel, regular vertical nanochannel with high-aspect-ratio. The nanochannels are built with a uniform gap size of 55 nm and an aspect ratio as high as 400 have been demonstrated for membrane applications. Vertical channels are reported to have open pore volume of a few orders of magnitude larger than planar channels which leads to higher sample throughput in the vertical system under similar velocity. The proposed system is employed in continuous flow separation of DNA and yields a higher sampling processing rate of 1 ml/h compared to planar anisotropic nanofilter array developed by Fu et al. (Fu et al. 2007) which produces sample throughput of 1 nl/h.

Meanwhile, the detector component has benefited from the nanotechnology via the integration of nanotube and nanowire (Carlen and van den Berg 2007) to increase its sensitivity. Carbon nanotube is superior in terms of its electron transfer kinetics and strong sorption capacity. Single-walled carbon nanotube (SWCNT) is fabricated by Tang et al. (2006) for label-free detection of DNA hybridization. The SWCNT serves as the transducer that converts and amplifies DNA hybridization on gold surface into a detectable electrical signal. The formation of dsDNA on gold electrodes is found to be the main reason for the acute electrical conductance change instead of DNA hybridization on SWCNT side walls. This is due to modulation of the energy level alignment between SWCNT and gold contact. On the other hand, multi-walled carbon nanotube is used as an electrochemical detector for the determination of isoflavones and major natural antioxidants in a electrokinetic-based lab-on-a-chip platform proposed by Crevillen et al. (2009). The multi-walled carbon nanotube demonstrates analytical reliability, versatility and rapid performance in both flow injection and separation systems. The RSD of isoflavones determination is less than 4% and the peak area repeatability of antioxidant detection has RSD less than 10%. Adaptive nickel nanowires had been introduced by Piccin et al. (2007) on a lab-on-a-chip system to regulate between separation and detection operation. The reversible positioning and orientation of the nickel nanowires at the exit is accomplished via magnetic manipulation. Changing the NdFeB/Ni-coated cube-shaped magnet orientation located on top surface of the microchip behind the channel outlet where the nanowires are positioned, resulting in vertical or horizontal positioning of the nanowires. The detection operation is deactivated via removing the cube magnet from its switching position to the side of the detection reservoir. The authors also demonstrated that the orientation of the nanowire detectors affects the separation performance. The separation efficiency was lowest for horizontal configuration, intermediate for 45° alignment and highest for vertical position. This was due to the postchannel broadening of the analyte zone associated with the different geometries and alignments of the nanowire detector assembly.

Despite the advantages of integration of nanotubes and nanowires in lab-on-a-chip architectures, there exist challenges in converting a prototype nanochip to a device of wide usage in the real world. One of the bottlenecks in this transition is the difficulties in handling and positioning the nanotubes and nanowires on the exact desired location, due to their nature of ultra-small size. In addition, reliable and reproducible fabrication techniques for nanometer-sized structures are yet to be established. Readers can refer to the literature in reference (Lee et al. 2009a, b) for an excellent review of the stated issues, and also the strategies for

integration of nanowires and nanotubes into lab-on-a-chip platforms.

14 Conclusions

Lab-on-a-chip systems enable miniaturization and integration of complex functions that can automate repetitive laboratory tasks. Standardization in lab-on-a-chip development will improve design process, reduce development cost and time, and facilitate technology transfer. With the advancement in micro/nanofabrication technologies and micro/nanoelectromechnical system development, it is anticipated that integration of all components on board of the chip will be attained and subsequently benefit the point-of-care diagnosis. Furthermore, the incorporation of nanotechnology in lab-on-a-chip platforms will bring us a step closer in realizing real-time sensing as well as label-free and non-invasive therapeutic devices.

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