The International Journal of Advanced Manufacturing Technology, 2010,
Volume 48, Numbers 9-12, 973-991,

Integration of functionality into polymer-based microfluidic devices produced by high-volume micromoulding techniques

Usama M. Attia* and Jeffrey R. Alcock[a]

** Building 56, Cranfield University, Wharley End, Cranfield, Bedfordshire, MK43 0AL, UK. Tel: +44 (0)1234 750111 ext: 2513; E-mail: u.attia@cranfield.ac.uk*

a Building 61, Cranfield University, Wharley End, Cranfield, Bedfordshire, MK43 0AL, UK. Fax: +44 (0)1234 752473; Tel: +44 (0)1234 754185; E-mail: j.r.alcock@cranfield.ac.uk

Microfluidic devices with integrated functional elements have gained increasing attention in the recent years. Many prototypes covering a wide range of applications have been fabricated and tested, especially in the fields of chemical and biomedical sciences. Nevertheless, integrated microfluidic devices are still far from being widely used as cost-efficient commercial products, often because they are produced by fabrication methods that are not suitable for mass production.

Several methods have been recently introduced for cost-efficient high-volume production of micro-featured plastic parts, such as micro-injection moulding and hot-embossing. These methods have been widely used for fabricating simple disposable microfluidic chips on a commercial scale, but have not yet been similarly applied for producing integrated microfluidic devices.

This review paper aims at presenting the state of the art in integrated microfluidic devices produced by cost-efficient high-volume replication processes. It takes micro-injection moulding and hot-embossing as its two process examples.

Several types of elements are classified according to their functions, defined relative to their physical inputs and outputs. Their level of integration is reviewed. In addition, elements are discussed from a manufacturing viewpoint, in terms of being readily produced by replication techniques or by back-end processes. Current and future challenges in integration are presented and discussed.

Keywords: Integrated microfluidics, micro-injection moulding, hot-embossing, functional elements

1. Introduction

Microfluidic systems have gained increasing interest in the past few years, especially in chemical and biomedical applications, because these systems have potential as easy-to-use, cost-efficient devices that can perform complex tasks. The market volume of microfluidic systems is forecast to grow from approximately US$600 million in 2006 to US$1.9 billion by 2012 [1]. Considerable developments have been made in the manufacture of miniaturized microfluidic devices ranging from simple microfluidic chips up to multifunctional integrated systems, such as lab-on-a-chip (LOC) devices, also known as micro-Total Analysis Systems (μTAS).

Integrated microfluidic devices have been tested for a wide range of applications and have showed high potential for applications such as point-of-care (POC) diagnostics, where rapid clinical tests can be performed with relatively easy handling of samples and minimum volumes of reagents. Relatively simple microfluidic systems are currently being produced on a commercial scale using micromoulding techniques. ThinXXS [2], Micralyne [3], Bartels Microtechnik [4], Abbott [5] and Microfluidic ChipShop [6] are a few examples, and their products are mostly used for biomedical and POC applications. Integrated and relatively complex microfluidic systems, however, are not yet commercially used on a large scale, because the relatively high fabrication costs do not allow for an economical mass-production process. In addition, the complexity of some systems prevents them from being developed beyond lab-based prototyping to the stage where they become suitable for commercial use, especially by non-experts [7].

This review paper presents integration solutions proposed in the literature for microfluidic devices manufactured by high-volume polymer replication processes, namely micro-injection moulding and hot-embossing. The paper focuses on mass-production replication technologies, because they provide a potential for low-cost manufacturing solutions necessary for wider commercialization of integrated microfluidics. This would particularly help in producing low-cost disposable systems usually required in, for example, home health care, developing-country health care and medical analysis microfluidics in general, where cross-contamination should be avoided [8-10]. Thermoplastics offer a great potential for producing integrated microfluidics. They are already being processed commercially at low-cost and fewer manufacturing steps, relative to glass and silicon [11-17]. In addition, the large number of thermoplastics currently available offer a wide range of properties for different microfluidic applications [8,9,14,17,18]. Also, a number of

integration techniques have been successfully tested for replication processes at the micro scale including for example, overmoulding and insert moulding [19,20].

The structure of the paper is made to highlight the relation between the function of the integrated elements and the available integration/manufacturing techniques. The paper aims firstly to review the currently used device elements, categorized into a taxonomy based on their functions. Secondly, the paper aims to identify current potential challenges in developing integrated microfluidics, produced by cost-efficient processes that are directly transferable to industry.

This review concludes with an evaluation of the progress made in integrated microfluidic devices produced by polymer replication techniques in the light of the literature covered within this review. Possible research gaps and potential research areas will be highlighted.

Reviews of several areas, complimentary to the subject of this review paper, can be found in the literature. Gravesen et. al, presented an introductory review of the early stages of microfluidic developments with some examples of basic operations, such as microvalves and micro-pumps [21]. At this stage, integration and mass-production were still presented as potential developments. By the year 2000, polymers had shown great potential for microfluidics, and since then several reviews have covered the relation between polymer properties and microfluidic functions [17,22]. Microfabrication of polymers has also gained special interest in several reviews [23-25] including the microfabrication of polymeric microfluidics by micro-injection moulding [26]. More focus has also been directed towards integrated systems, such as lab-on-a-chip and micro Total Analysis Systems [24,27,28] and comparing different materials and production techniques [29,30]. In addition, the disposability of microfluidic devices has also been reviewed [31] with focus on minimally instrumented diagnostic devices [10]. Regarding applications of microfluidic devices, some reviews are available which discuss applications from a general perspective [32], whereas other reviews focus on specific applications of microfluidic devices, such as DNA analysis [33] and amplification [34].

1.1. Integrated microfluidic devices

Microfluidic devices can be identified as having one or more channels with at least one dimension less than 1 mm [11]. The flow conditions are mostly laminar and rarely turbulent [35]. Integrated microfluidic chips are often referred to as “lab-on-a-chip” (LOC) devices or micro Total Analysis

System (μTAS), because they are designed to perform integrated functions of typical analysis labs. They usually perform standard operations, such as sample preparation, flow control, reaction/mixing, separation and detection [22]. The fluids used depend on the application, but they are usually related to biotechnological applications and hence examples include whole blood or blood components, bacterial cell suspensions and protein or antibody solutions.

A considerable number of microfluidic devices have been discussed in the literature in terms of design, fabrication and testing. However, the majority of such devices are simple in structure, i.e. containing single functions, and used for laboratory prototyping. There is an increasing need for more complex and integrated systems for a set of reasons:

1) To be able to perform a series of laboratory processes such as sample preparation, fluid handling, reaction, analysis and detection on a single device [36].
2) To achieve automation and high processing speed [8,12,37,38].
3) To be able to use the new technology within the physical limits of the existing lab equipment, for example standard holding frames and fluid-delivery systems [39].
4) To produce easy-to-use cost-efficient devices that can perform complex laboratory analyses. This is especially important for, for example, point-of-care applications, lab-on-a-chip and μTAS systems. Integration allows for rapid clinical diagnosis tests, easy usage without complex fluid handling, fewer costly reagents, smaller sample volumes, and shorter assay turnaround systems. In addition, such systems eliminate the often slow, complex and costly preparation techniques of conventional clinical laboratories, such as centrifugal techniques and membrane filtration [8,13,37,38,40-45].
5) To give the microfluidic device the ability to interact with electronic, magnetic, optic and chemical methods to have a chip with broad capabilities [41].
6) To connect microfluidic devices to the outer world by using micro-to-macro interfaces such that an efficient system is obtained [41].
7) To allow for the production of disposable and portable miniaturized devices with potentially low manufacturing costs [12,38,45].

Considerable progress has been achieved in mass-producing relatively simple microfluidic devices. However, similar progress has not yet been achieved for integrated systems, i.e. microfluidic systems that are a combination of the basic, fluid-handling elements of microfluidic chips with other functional units to perform more complex analytical tasks [41]. A

number of reasons have been suggested for this lag in mass-production options for integration. For example, microfluidic devices are often made only for prototyping purposes; so many projects were intended solely for research, not taking into consideration the potentially high costs of commercializing the developed systems. [46,47]. In addition, there are relatively high additional costs for the currently established techniques of insertion of required functional elements and of device encapsulation [18,46]. It has also taken a longer time than estimated for new technologies to successfully compete with an existing, well-established, macro-scale technology [39].

1.2. Review methodology

This paper aims to review the literature from the perspective of progress achieved towards the manufacture of high volume, integrated microfluidic devices via cost-efficient processes. In this regard, micro-injection moulding and hot-embossing were chosen as the replication processes covered in this review. This is because they are commonly used, high-volume, cost-efficient processes. They both have relatively short cycle times, although it should be noted that the cycle time for hot embossing (few minutes to 10 minutes) is generally longer than that for micro-injection moulding (between seconds and minutes). In addition, both processes are similar in terms of polymeric materials used.

Within the context of manufacture by these potential high volume production routes, the review discusses the integration of elements of a microfluidic device. For the purposes of this review, these elements are classified according to their functions, where the selected definition of a "function" is any mechanism of transformation from one basic 'constituent,' to another, in response to environmental stimuli [48]. The three basic 'constituents' are defined as, mass (M), energy (E), or information (I). In this definition, a function is neither the designed purpose of an element, nor the affect of the element on the environment. Instead it is a transformation mechanism [49]. The aim of using this classification system is allow comparison of the state of the art of integration at a fundamental level. This definition results in a set of 9 functions based on the type of input and output constituents as shown in Table 1:

		Outputs		
		M	E	I
Inputs	M	**To move:** e.g. motion of one gear causes another gear to move.	**To power:** e.g. burning fuel gives off energy.	**To activate:** e.g. closing a switch sends a signal.
	E	**To energize:** e.g. the volume of a heated fluid increases.	**To convert:** e.g. a wire carrying a current radiates heat	**To detect:** e.g. a photocell responds to light with a signal.
	I	**To actuate:** e.g. controller signal a robot to move.	**To regulate:** e.g. amplifier output is controlled by received signal.	**To transfer:** e.g. digital to analog conversion.

Table 1: Types of transformation functions [48]

For the purposes of this review, some of these classifications were considered too broad. For example, the "mass to mass" transformation function is described in Table 1 as a motion function "to move", whereas mass-to-mass functions can take different forms such as "to store", "to regulate", "to mix", etc. These forms are referred to here as "function descriptors" and are used as classifiers in the review.

As a second classification, functional elements in micro-fluidic devices are also classified in this review into integrated or non-integrated elements. Integrated elements are defined as elements manufactured as a part of the microfluidic chip, regardless of whether they are fabricated within the micromoulding process itself or added afterwards in a post-moulding process. Non-integrated elements are those external to the microfluidic chip, and therefore generally are those which are, in practise, non-disposable and high in cost.

The complete classification scheme adopted in the review is tabulated in Table 2. The first four columns detail the classification scheme, showing transformation function, input, output and "function descriptor." The fifth column lists categories of microfluidic functional elements which have a particular transformation function. Columns six and seven describe the techniques, noted in the literature, by which these device elements can be integrated into microfluidic devices, either by micromoulding or hot embossing (column 6) or by post-processing (column 7). Columns 8 and 9 describe the techniques by which transformation functions are achieved by functional elements as yet not integrated onto microfluidic chips. Column 8 is allocated for elements

associated with the input functions to the chip (e.g. fluid delivery), whereas column 9 is allocated for output functions (e.g. detection and analysis).

The remainder of this review follows the structure of Table 2. Techniques for achieving integrated transformation functions are reviewed in Section II. Section III reviews the literature for non-integrated transformation functions of micromoulded devices.

Trans-formation Functions	Input	Output	Function Descriptor	Elements	How element are integrated		Non-integrated	
					Micromoulded (Injection or embossing)	Post-processed	Chip-input elements	Chip-output elements
M → M	fluid	fluid	to connect/ deliver	• Fluid connection elements	**Interconnects are moulded with the chip (2.1.1.1):** - Moulded ports. - Capillary features are replicated to deliver the fluid to the chip.	**Interconnects are added in post-moulding steps (2.1.1.2):** E.g. commercial ports, drilled holes with glued tubes, removable silicon adapters, etc.	-	-
			to move, to store, to mix to divide, to regulate, etc.	• Fluid manipulation elements	**Features are machined in the mould and replicated directly on a single chip (2.1.2.1):** - E.g. channels, reservoirs, mixers, dispensers, passive/capillary valves, etc.	**Post-processing is needed after replication (2.1.2.2):** E.g. stacked and bonded, fixed as a module on a standard frame,, etc.	-	-
			to contain	• Sealing elements	**Sealing takes place during moulding (2.1.3.1):** - E.g. "in-line" sealing.	**Sealing is done after moulding (2.1.3.2):** E.g. bonding, adhesives, etc.	-	-
M → E	-	-	-	-	-	-	-	-
M → I	-	-	-	-	-	-	-	-
E → M	Energy/ force	fluid	to move	• Fluid delivery elements.	-	**A miniaturized source of energy is added to the moulded chip (2.2.1):** - E.g. Pressurized-air pump, chemical propellant, gas mixture, etc.	**Fluid-delivery (3.1):** E.g. syringes or pipettes, pumps, high voltage, centrifugal forces, etc.	-
E → E	Electric current	Voltage/ Temp./ Magnetic field, etc.	to convert	• Energy-conversion elements (e.g. heaters, electrodes, electro-magnets, etc.)	**Elements are directly moulded on the chip (2.3.1):** E.g. overmoulding, insert moulding, micro-assembly moulding, embossing, etc.	**Post-processing a replicated chip (2.3.2):** E.g. Sputtering, pressing, mounting, etc.	**Connecting the chip to a power source (3.2):** E.g. Power supply, batteries, Peltier controller for temperature control, etc.	
E → I	Electric signal/ temp./ etc.	info.	to detect	• Data collection elements	-	**Detection device is mounted on the moulded chip:** - E.g. thermocouple, PCB, micro-ammeter, etc.	-	**Detection equipment (3.3):** E.g. optical detection instruments, fluorescence, etc.
I → M	-	-	-	-	-	-		-
I → E	-	-	-	-	-	-	-	-
I → I	Info.	Info.	to analyse	• Data analysis elements	-	-	-	- Analysis device/software

Table 2: Types and categories of functional elements currently applied in replicated microfluidic devices (relevant section numbers of the review in brackets)

2. Integrating Functional Elements in Micromoulded Microfluidics

Integration in polymer processing represents the ability to combine different functional elements on a polymer chip. This can directly be done during the fabrication of the chip, such as in the case of ducts and passive valves. Integration can also be carried out after the production of the plastic chip, particularly if it is difficult to achieve integration in-process, owing to limitations in the replication process. In this case, post processes, sometimes called back-end processes [35], are applied.

This section reviews the current situation of integrated elements for polymer-based, replicated microfluidic devices. Sections 2.1 to 2.4 present integrated elements currently reported in the literature. Following the sequence shown in the first column of Table 2, each section discusses one category of transformation function. For each functional category, sub-sections will compare integration by micromoulding or hot embossing to integration by post-processing. For ease of reference, in Table 2 the different categories of transformation function are marked with the corresponding section numbers of the review.

2.1. Integrated elements involving mass-to-mass transformation functions

Section 2.1 presents the main microfluidic components that perform mass-to-mass functions. They include fluid delivery and fluid manipulation elements, in addition to sealing.

2.1.1. Fluid connection elements

Delivering fluids to a microfluidic chip (or taking them out after processing) requires an interconnection system that allows for a secure and easy-to-plug input and output system. The interaction between the micro and macro world affects the efficiency of the microfluidic systems [41]. In fact, one of the main obstacles that prevents microfluidics from spreading further commercially is the lack of standard interconnects for interfacing the macro-scale environment with the microfluidic channels within the chip [50].

Some requirements for an ideal interconnection system have been mentioned in the literature such as being leak-proof for fluids and gases, possessing minimal dead volume, ease of

use, standard geometry to facilitate interfacing with commercially available devices, reversibility, reliability, lack of contamination and ease of fabrication [36,50].

As an alternative to conventional interconnection, capillary systems are also used in some applications to deliver the fluid sample to the device. The physical phenomena on which they depend are governed by a relationship between surface tension, fluid density, contact angle and the channel size. Therefore, they require the design of the inlet channels to the optimum dimensions in order to deliver the fluid inside the microfluidic chip. Examples are reviewed in the next section.

2.1.1.1. Fluid connection elements produced by micromoulding

Mounting interconnections by post-processing (discussed in the next section) is the commonly used method for most prototypes. There is, nevertheless, an increasing trend towards producing interconnection systems as an integrated part of the moulded chip. An example of micromoulded interconnections has been reported, where a micro-injection moulded chip was sealed by a plastic lid in which connection ports were integrated as one part [50]. The ports are made of a hollow boss with ANSI standard internal 6-32 threads located at each fluid entry point. The use of micro-injection moulding makes the cycle time almost independent of the number of ports. Tube fittings were fitted in a later stage.

Moulded ports were also produced by injection moulding using moving mould-inserts that are shaped like pillars and can be adjusted in length to determine the final depth of the moulded connection port [51].

As mentioned earlier, capillary actions can be used as an alternative fluid-delivery system for interconnects. In an injection-moulded device for monitoring DNA migration, capillary action made the polymer fluid spread in the system, and the subsequent gentle centrifugation flushed the channels [52]. In a similar experiment, a hot-embossed microfluidic device for analysing human sweat applied a propulsion system in which the device was set to collect 600 µl of sweat from human body using capillary action. Afterwards, centrifugation was used to spin the sample out into an analytical container. The sample was finally collected by centrifugation in a standard bench-top swing-bucket centrifuge modified to accommodate the device [44].

2.1.1.2. Fluid connection elements produced by post-processing

Several post-processing connection techniques were mentioned in the literature. For example, access ports were used to connect modular chips together within a frame [41] (more

details about modular designs in section 2.1.2.2). For connecting the chips to the outer world, Luer and Luer-Lok fittings were used, which have gluing edges allowing them to adhere on to the lid surface [39]. Nanoports produced by Upchurch Scientific are commercial examples [53].

In another modular device, where chips were laminated together, a special layer dedicated to connecting the system to the outside world was used. It had a standard format irrespective of the other layers, possessing interface connectors to liquids and electrical/electronics. It also formed the mechanical basis for alignment of the subsequent layers [41]. Self-aligning microfluidic interconnects were also designed and tested for polymer microfluidics that are produced by micro-injection moulding or hot-embossing [54].

For some microfluidic devices, holes are manually drilled in the lid to fit the connection tubes, which are typically connected with glue [40,50,55,56]. In other devices, Luer-Lock syringes were used both as a fluid propulsion system and connection system [57]. Since most devices are produced for prototyping purposes, fluid delivery is usually achieved by manual delivery with syringes or pipettes or with syringe-pumps when flow-rate is an important consideration (section 3.1 for non-integrated methods). Removable silicon adapters were used to connect standard pipette tips into an injection moulded microfluidic chip [58].

Overmoulding was recently tested as a mass-production technique for both packaging and fluidic interconnection [19,59]. The method was applied as a generic interconnection system for microfluidic devices and also for post-packaging of a specific commercial pressure sensor module. This technique provides leak-proof connection between the chip and the fluid-delivery system. However, it requires an extra manufacturing steps in which a chip, with features already produced by a prior process step, is inserted in a special mould and overmoulded by the selected polymer.

2.1.2. Fluid manipulation elements

In medical diagnostics, as a common example for microfluidic applications, complex bodily fluids (e.g. blood) need to undergo a set of preparation steps before being suitable for analysis. Most of the currently demonstrated microfluidic device components pursue single functionality and use, for example, purified DNA as an input sample. Therefore, in the majority of the cases, sample preparation is still performed off-chip [43]. If real samples of bodily fluids are to be inserted directly to the device, e.g. in POC applications, the device has to perform several steps in a single integrated microfluidic system.

2.1.2.1. Micromoulded fluid manipulation elements

Mass-production of integrated subsystems by replication has the advantages of minimizing the cycle time, avoiding post-processing assembly, eliminating opportunities for fluid leakage between different microfluidic stages and reducing fabrication costs. Nevertheless, this method does not have the flexibility of changing the microfluidic feature-shapes or sequences after manufacturing, because this requires the fabrication of a whole new insert. In addition, it is currently limited mostly to "flat", 2½D geometries in order to facilitate part demouldability.

An example for fully integrated circuits is a microfluidic device used for blood typing [60]. The disposable chip, which was micro-injection moulded of COC, comprised a number of fluid-manipulation steps, including flow splitting microchannels, chaotic micromixers, reaction microchambers and detection microfilters. The flow splitter divided the blood sample into four equal amounts, so that several agglutination tests could be performed in parallel, whereas the serpentine laminating micromixer was used to promote efficiency of reactions. The large reaction chambers were introduced to hold the reactant during the reaction time before filtering. Finally, the microfilters are used to effectively filter the reacted agglutinated red blood cells.

Another attempt to integrate several circuits on a single plastic chip was presented in the form of a PMMA CD-like platform [18,61]. Functions integrated included flow sequencing, cascade micro-mixing, and capillary metering.

In another example, an integrated microfluidic device was fabricated by hot-embossing polycyclic olefin. The device was for bacterial detection, and it integrated PCR, valving and electrophoresis on a single plastic chip [45]. Also, a microfluidic device containing a cross-junction channel was used to produce micro-sized beads of Calcium Alginate [55]. The CD-like device was produced by injection moulding PC, and by changing the flow rates of the inputs, the cross-junction was used to produce beads of 20-50 μm in diameter with narrow size distribution (<10% variation in diameter). Micro-injection moulding was also used to produce an integrated disposable microfluidic device for detection of agglutination. The device which was moulded of COC included micro-wells, passive micro-valves and a serpentine micro-mixer [62]. All features were replicated from a nickel mould insert and the device layers were thermally bonded.

Flow control elements, such as valves and dispensers, are usually an essential fluid manipulation element in microfluidic systems. Two main fluid control systems are usually available for microfluidic applications: passive and active. Passive valves operate without the need

for physical actuation, by utilizing energy from the flow and are typically used as check valves [63,64]. Active valves require more sophisticated control systems involving, for example, actuation, which means that multiple inputs, namely mass and information/energy, are involved [63,64].

More attention has been recently directed towards passive fluid control systems, such as passive valves, mixers, diffusion-based extractors, passive filters and membranes. Passive systems have several advantages, including the need for no external power requirement (mass-to-mass function), ease of integration, continuity in substrate material, low cost and, by definition, possibility of use without active control. Nevertheless, some challenges still face passive systems. They are usually application specific and cannot be easily reconfigured. They are strongly dependent on variances in the fabrication process (as will be shown next section) and not suitable for several fluidic mediums [42].

Several types of passive vales have been fabricated and tested. Mechanical valves, such as flap or membrane check valves, and non-mechanical valves, such as capillary valves, have been used for microfluidic devices [65].

The advantages of the passive control systems make them a preferable system for flow control, especially for plastic chips produced by replication techniques, because no back-end processes are needed. For example, in the microfluidic CD platform presented earlier, which was produced by both injection-moulding and hot-embossing [61], a passive capillary-valve that relies on the capillary force to stop the flow in micro-channels, was used [18]. The principle of operation was based on a “pressure barrier” that develops when the cross-section of the capillary expands abruptly. The fluid moves through this valve when the capillary forces are overcome by the centrifugation forces.

Passive valving was also applied in a microfluidic device for point-of-care clinical diagnostics [42]. In this device, a special sequence of flow was required in the microchannels, so the flow was controlled using a so-called “structurally programmable” microfluidic system (sPROMs). sPROMs technology allows fluids to move through a set of valves in designed stages with only an on-chip pressure source. It consists of passive valves and flow conduits, which have different pressure drops depending on the structure and surface properties of the fluidic path [66].

Other types of passive systems can also be found in a variety of fluid handling applications. Capillary metering, for example, is used for delivering precisely metered fluids from

one reservoir to another in a controlled sequence. Bubble snap-off is one technique that has been presented in the literature for sample metering [18]. Here, a gas bubble in the liquid-gas flow passes through a constriction and breaks up into a number of equally-spaced small bubbles. Although metering is not a valving technique, it is still a passive flow-manipulation technique that is dependent on the same principles of geometry change and fluid-surface interaction.

This mechanism can be used in sample metering of microfluidic systems, because a fixed amount of liquid is trapped between two bubbles that are snapped off.

Other fluid control elements have been also tested, such as micro-dispensers in which sample fluid volumes were loaded into a fixed volume micro-dispenser, which in turn dispensed an exact volume of liquid for further biochemical analysis. This was done by designing the geometry of the chamber to contain a specific volume of the liquid between inlet and outlet valves. When the pressure source is released, the metered volume is pushed through the outlet passive valve [42].

As shown in the previous examples, passive fluid-control systems, including valves and dispensers, are a promising technique for fluid manipulation in microfluidic devices. Considering that such systems do not need external actuation or feedback, and that they are readily manufactured as an integrated feature of the substrate, this makes them practical solutions for on-line fluid control systems. The operation principles of the systems are similar, in that they depend on the geometry of the valve (hydrodynamic radius), the fluid properties (viscosity) and the interaction between the fluid and the surface (contact angle and surface tension). Their relative simplicity of principles of operation makes them easy to integrate into devices produced by high-volume replication techniques, as their operation depends primarily on the existence of abrupt change in the geometry of a channel. As the market demand increases for cost-efficient complex systems, more attention is expected to be directed towards passive control systems.

A recently introduced concept of passive fluid control systems is the so-called "lotus surfaces", where sub-μm structures were directly replicated into microfluidic surfaces by hot-embossing [67]. The replicated surfaces had structural gradient that generated driving forces to move liquids in microfluidic channels.

2.1.2.2. Post-processed fluid-manipulation elements

Connecting separate subsystems has been widely used in prototyping microfluidic devices. This is due to the flexibility this allows for modifying of the overall device design.

Furthermore, separate chips can be integrated in standard laboratory equipment, or they allow, by stacking 2.5D chips for example, for 3D designs to be realized.

Several connection techniques have been described in the literature. Stacking, for example, is one well-known technique. In a published experiment, a modular design concept with standard interfaces between each functional module was introduced to present a chemiluminescence experiment [41]. Each module was a discrete microfluidic chip fabricated by hot-embossing for dedicated tasks such as sample preparation, mixing, analysis, etc. Consequently, any new microfluidic design could be incorporated into the system for a specific function as long as some fundamental design rules were adhered to. Elastic averaging, which involves the constraints of the layers using dowel pins, was used to align the different chips together.

The elastic properties of the material and the constraint structure cause deformations in each individual contact feature to average out over the sum of contact features throughout the solid body. The alignment offset measured was between 10 to 20 µm. Better accuracy (10 µm or less) was required for this method [41].

A second example of post-processed integrated subsystems connected from separate chips was a lab-on-a-chip for POC clinical diagnostics, namely a micro biosensor [42,68]. The device was designed for detecting and identifying three metabolic parameters: Partial pressure of oxygen, lactate concentration, and glucose concentration in human blood. The chips were produced by injection moulding using a replaceable insert with micro-features [69], and they were stacked and laminated together using thermal fusion. The same lamination approach was used to integrate injection moulded layers of an integrated microfluidic device for magnetic immunoassay [70].

The integrated functions included chambers and buffer reservoirs, multiplexing channels and a dispenser. Valves and other functional elements were also integrated, and they will be mentioned in more details in the corresponding sections. Stacking was also used to fabricate a pneumatically actuated microfluidic device for bio-analytical applications [71].

Modular structures have been proposed as an alternative method for stacking as a method for both integration and standardization. A microfluidic construction kit was presented, based on modern plastic production technology such as micro-injection moulding and hot-embossing [36]. Chips of different microfluidic functions could be fabricated to the size of a standard microscope slide and connected in a standard frame, used for e.g. POC diagnostics. Modular designs with integrated interconnects were also produced by micro-moulding for continuous PCR [72].

LOC devices integrated modularly can join several laboratory processes, such as sample preparation, fluid handling, reaction, analysis and detection. Since miniaturized systems are likely to be used in parallel with standard laboratory equipment, a modular standard kit has been produced as a method for standardizing microfluidic chips with laboratory equipment [39].

A microfluidic system for DNA sequencing was also reported in the literature in which a set of functional circuits was integrated with micro-fabricated connects. The functional chips were manufactured by hot-embossing PMMA and PC chips. They performed the following functions: PCR amplification of DNA, purification of the PCR products, cycle sequencing using dye-terminator chemistry, purification of sequencing products, solid-phase reversible immobilization and DNA electrophoresis [37]. COC was also injection moulded to produce a laminate-type microfluidic device for PCR application [73].

Both micro-injection moulding and hot-embossing were used to produce an integrated chip for protein analysis [74]. Micro-injection moulding was used to fabricate the COC substrate with micro-channels, while hot-embossing was used to fabricate a polymeric piezoelectric micro-diaphragm. The two parts were bonded together using UV adhesive bonding in a subsequent step.

When it comes to valving, some integrated solutions were presented for micromoulding. Pinch valves, for example, have been recently used as disposable on-chip fluid control elements. A number of designs have been successfully tested for micromoulded integrated chips applied for point-of-care testing of metabolic parameters [75] and PCR analysis [73].

2.1.3. Sealing elements for microfluidic devices

Due to the constraints imposed by the replication processes on the geometrical design of the part, microfluidic devices are replicated as open channels that need to be closed to prevent leakage. From a functional point of view, sealing can be considered as a mass-to-mass function, where the functional descriptor would be to “contain” the fluid. Sealing takes place, either, during fabrication as an integrated step in the processing, or, by post-processing sealing techniques. Section 2.1.3.1 reviews sealing by micromoulding, whereas post-processing sealing techniques will be presented in section 2.1.3.2.

2.1.3.1. Sealing by micromoulding

In the literature covered within this review, a single experiment was reported in which sealing took place as an integrated fabrication step [35]. In this experiment the covering step was

integrated as part of the injection moulding process known as in-line covering. Both the substrate and the cover are injected at the same time with the same material, such that the cover part is attached to the nozzle side of the mould, while the micro-structured substrate is attached to the ejector side. The index plate carrying the cover rotates 180° causing the two parts to be aligned, and the surfaces of the two parts are warmed up, and after renewed closing of the mould the covering process follows. When the mould is opened, the covered part falls finished from the machine after 40 seconds.

2.1.3.2. Sealing by post-processing

Bonding lids to microfluidic substrates is the commonly used post-processing method to close microfluidic channels. The major challenges for bonding are to join the lid to the substrate without clogging the channels, changing their physical parameters or altering their dimensions [17,76]. Several techniques have been developed to seal polymeric microfluidic devices, and they can be grouped into three major categories: Sealing with the use of intermediate material, sealing with the use of energy and mechanical sealing.

Sealing with the use of intermediate material is commonly used for post-processing micromoulded microfluidic systems. Adhesives, for example, have been reported in the literature as intermediate sealing agents for micromoulded microfluidic systems, such as conventional glues [8,17], UV-curable adhesives [13], thermally activated adhesives [38] and copolymer adhesives [12]. In addition to adhesives, polymeric foils, such as PET, have also been tested as intermediate materials to laminate microfluidic substrates together [17]. Solvent-assisted bonding is another technique where microfluidic substrates are wetted with, for example, mixed organic solvents [15] or acetyl acetone [77] and joined permanently under pressure [57,78].

Sealing with energy is based on using one or more types of energy to join the micromoulded devices without the use of an intermediate material. The literature reports a few examples of micromoulded microfluidic devices that were bonded using energy, such as induction heating [76], laser welding [17,76] and thermal-diffusion bonding [8,14,16,50,57,73]. Ultrasonic welding and UV-bonding are other available energy-based techniques for bonding polymers, but very little is mentioned in the literature about using them for microfluidics.

Mechanical sealing is commonly used as a sealing technique, especially for prototyping purposes. A number of examples were mentioned in the literature, where screws [40,52,55] or snap-fit systems [44] were used to seal polymeric microfluidic devices. A

polyethylene/thermoplastic elastomers (PE/TPA) film was used to seal and injection moulded CE chip made of PMMA and PC [51].

Selecting an appropriate packaging technique for polymeric microfluidic devices depends on a number of factors, such as the substrate material, the temperatures involved, compatibility with fluids used and channel size. In addition, the cost of the process is significant to the feasibility of the process for mass-production. A more detailed comparison between packaging techniques for disposable microfluidics is available in the literature [71,79]. A recent review has also been published addressing bonding of thermoplastic polymer microfluidics [80].

2.2. Integrated elements involving energy-to-mass transformation functions

A propulsion force, such as mechanical pressure or centrifugal force is needed to pump fluids throughout the microfluidic channels. Generating forces is usually done by interaction between on-chip elements, e.g. pressure reservoir or capillary channels, and off-chip elements, such as a motor for rotation or a pressure pump. Fluid propulsion systems can, therefore, be considered as “interfacial” integration tools, in the sense that they connect on-chip micro-components to off-chip macro-components.

The amount of energy needed to pump liquids in microfluidic channels vary depending on application. For example, a microfluidic device for chemical analysis was made in which deionised water was pumped at a rate of 730 nl/min with a fixed power of 500 mW [81]. In another application, a microfluidic chip was designed to have a power supply from a commercially available 12V-type MN21 battery [82]. The power consumed for transferring a liquid across the chip ranged between 145 mW initially down to 71 mW after 40 cycles of operation, because the battery was unable to maintain the supply voltage above 75% of the initial output. The experiment revealed, however, that only 8% of the power consumed was consumed in the chip, while the rest was consumed by the electric converter and control circuitry.

Several techniques have been developed for fluid propulsion. In the literature, three main propulsion methods were discussed: mechanical, electrical and thermal [18].

For mechanical propulsion systems, a mechanical pump is often used to provide the driving pressure. It can be as simple as a roller in the blister pouch design, or as complicated as a miniaturized syringe or acoustic pump [18].

For electrically-driven systems, electro-kinetic techniques such as electro-osmosis or electrophoresis, electrodynamics and electrowetting have the advantage that they scale favourably for miniaturization. In electro-osmosis or electrophoresis, the driving forces for flow are generated by the interaction of applied electric fields with ionic species in the fluids. In electrodynamics, the flow is generated by the interaction of electric fields with induced electric charges in the fluids. Electrowetting is based on the principle that the contact angle between a liquid and a solid surface can be changed through the application of an electrical potential. This change may result in capillary forces that provide a driving pressure in small flow channel.

For thermally driven propulsion, it is possible to manipulate the contact angle between a liquid and a solid surface by changing the local fluid temperature. The resulting capillary force is used to drive the fluid as in electro-wetting [18].

2.2.1. Post-processed fluid propulsion elements

The recent trend towards further integration has resulted in the development of techniques in which the off-chip assistance is minimized. One example is a microinjection moulded device used for medical diagnostics applications, which had an integrated air-bursting detonator as a fluid-driving source. This eliminated costly, non-disposable, active microfluidic pumps. As soon as the membrane is broken, the pressurized gas is released pushing the fluid samples into the microchannel through the ruptured membrane [42,68]. The detonator was powered by a 40 mW pulse to power the microheater for 700 ms, which resulted in the release of 650 μJ of stored pneumatic energy to drive a 500 nl sample through microchannels [83]. This technique allows for a relatively higher degree of integrity, since the pressure pump is a cheap and disposable part of the microfluidic device.

On-chip propulsion was also achieved using a chemical propellant, where azobisisobutyronitrile (AIBN) was used as an actuator that releases N2 gas. The gas pressure can then be controlled to accurately control the fluid flow [75]. In another application, a microfluidic system was designed for medical diagnosis, and fluid propulsion takes place using a hydrogen-oxygen gas mixture generated by a sodium polyacrylate-based hydrogel. The gas is created by applying an electric voltage to the water in the hydrogel stored on the chip [84].

Developing integrated energy-to-mass elements will greatly affect the production of integrated microfluidic devices. They have the advantages of mass-to-mass delivery systems in the

sense that they are integrated as on-chip, power-source elements. At the same time they have the potential of supplying relatively large amounts of power comparable to what is offered by non-integrated elements, such as syringe pumps and pipettes.

2.3. Integrated elements involving energy-to-energy transformation functions

Several applications of energy conversion have been used in microfluidic devices, such as microheaters and electromagnets. Electrically conducting structures such as wires and electrodes are the most commonly used elements, especially for applications such as resistive or capacitive sensing, electrophoresis, integrated heaters and electro-hydrodynamic pumping [85]. Magnetic, optical or thermal elements may also be used depending on the application.

The majority of devices with elements performing energy-to-energy transformation functions reported in the literature have external elements that are added by post-processing by, for example, ink-printing or sputtering. Very few devices have been reported having functional elements integrated within the same micromoulding process of the plastic substrate, because integrating such elements requires an additional step of placing them in the mould or the insert. This additional step elongates the cycle time unless a design modification is made in the machine or the mould to integrate and automate the process.

The following sections review integrated elements fabricated by micromoulding and post-processing.

2.3.1. Energy-conversion functional elements fabricated by micromoulding

One of the advantages of micromoulding is the possibility of embedding elements into the plastic during moulding [86]. Conduction paths have been integrated into device structures by hot-embossing a composite polymer/metal material. Paths were first applied to the unstructured substrate and then pressed into the polymer layer during hot embossing so that embedded conduction paths are obtained following the embossed topology [14]. A hybrid structure was also manufactured by integrating a metal insert inside a polymer matrix by hot embossing [20]. In a recent application, conductive polymer electrodes coated with metal were integrated by micro-injection moulding into a polystyrene substrate using over moulding [86]. A similar technique was used to directly emboss a gold nanoelectrode ensemble film into a PMMA based microchip for CE [87]. Hot-embossing was also used to fabricate electro-fluidic polymer microchips [85]. In this

application, electrical wires were integrated by a single-step method into an embossed polymeric microfluidic chip. Using this method, wires could be placed in contact with the flowing fluid or embedded in close proximity to the fluid channels.

For micro-injection moulding, a developing approach for integrating energy-to-energy elements is micro-assembly injection moulding. This process is suitable for producing hybrid micro-structures by injection moulding, such as movable joints, hollow structures and overmoulding wires and optical fibres [88-92]. In this process, electronic connections or optical fibres can be overmoulded within the injection moulding cycle.

In order not to affect the cycle time, the micro-structured cavity is allowed to be exchanged during the machine cycle such that the process steps of demoulding, positioning of insert and heating the cavity for Variothermal processing can be done at an external station. In other words, an external cycle is allowed to take place parallel to the main cycle of the machine.

In order to ensure dimensional stability, the behaviour of different materials for both the insert and the polymer in the injection process should be considered. Additionally, the influence of the flow direction of the polymer is also significant for dimensional stability.

2.3.2. Energy-conversion functional elements fabricated by post-processing

2.3.2.1. Electrodes

Electrodes are commonly used in microfluidic applications, either for electrical measurements or for voltage application. They are particularly important for microfluidic applications that use electroosmotic flow or electrochemical detection [64]. Electrodes are classified as energy-to-energy elements, since they are used to generate voltages in applications such as electrophoresis.

Several post-processing techniques have been used for integrating electrodes onto replicated polymer-based microfluidic devices. Conventional deposition methods such as sputtering and thermal or electron beam evaporation can be used [93]. However, there is limitation on the electrode dimension due to the shadow mask used, which restricts the electrode width to 40 µm and above. Alternatively, laser ablated microchannels can be filled with a conducting ink and act as electrodes [17,45,94,95]. It should be noted that not all metals are equally easily applied to

polymer materials, as some problems might appear such as formation of metal clusters instead of uniform films and formation of micro-cracks in the metal film [64].

For an injection-moulded device used for insulator-based dielectrophoresis (iDEP), platinum-wire electrodes were inserted directly into the syringes used for fluid delivery. A programmable high-voltage sequencer was used to apply voltage [96]. In another micro-injection moulded device for monitoring DNA migration, four holes were drilled in the lid, and platinum electrodes were inserted in the chambers afterwards and fixed in narrow slits [52]. Sputtering by using adapted shadow masks was used to generate electric thin-film electrodes of gold in an injection-moulded electrophoresis separation device [78]. Furthermore, in an injection-moulded device for DNA separation, electrodes of 76-μm-diameter wire were routed to each of the four reservoirs available and terminated at one edge of the chip with a four-prong 2.54-mm-pitch electric header [38]. Gold electrodes were also patterned over a hot-embossed polymeric diaphragm as a part of an integrated microfluidic device for protein analysis [74].

An example for the use of conductive ink printing is a hot-embossed microfluidic device for bacteria detection. Electrodes, with contact pads, function as capillary-electrophoresis driving electrodes. They were integrated by connecting them to high voltage via “pogo” pins. They were manufactured by screen-printing silver/graphite inks onto the polycyclic olefin support film. After being cured at 95°C for 2 hours, the ink pattern on its supporting film was aligned and thermally laminated onto the cover film of the device [45].

2.3.2.2. Microheaters

A common application for energy conversion is microheaters, where localized elevated temperatures are needed in specific places on the microfluidic chip, such as in the case of polymerase chain reaction (PCR) devices. In these devices, thermal cycles consist typically of two steps: a “denaturing” step at 95˚C and an “anneal/extend” step at 60˚C [94].

Installing a microheater on a microfluidic chip is currently done by post processing techniques, since it is technically difficult to integrate microheaters into micromoulding processes. This is because insert-moulding a microheater requires accurate alignment in each cycle, and there is possibility of malfunction in the microheater due to the high pressures associated with micromoulding.

Two examples were reported in the literature. The first example is the microheater used in the air-bursting detonator discussed in the previous section, where electric pulses were applied to heat the thermoplastic membrane causing it to melt and release pressurized gas [42].

The second example for using microheaters is PCR devices, where integrating thermal elements is essential for the function of the device. Heaters were integrated in PCR microfluidic devices produced by hot embossing by mounting electrical resistance heaters to the chip. [56,97].

2.3.2.3. Electromagnets and optical fibres

Examples of integrating functional elements other than electrical parts also appear in the literature. For example, in a magnetic bead-separation device, an external electromagnet was integrated to produce the magnetic fields required for separation. The magnetic forces acting on the beads were different depending on the bead size. For example, for a bead diameter in the order of tens of microns, the magnetic forces were in the order of thousands of pico-Newtons. Magnetic beads in the size of 2-9 μm could be separated from an aqueous solution at the flow rate of 3-7 μl/min [98].

Post-processed elements may also include optical fibres used for fluorescence excitation light. The optical fibre inserted was coupled to a laser fibre that was connected to a diode laser. The laser produced approximately 2.5 mW of power at a wave length of 750 nm. Integrating detection fibres was used for a hot-embossed DNA separation device, where a dual fibre detector was inserted into the assembled device. The fibres were etched and sealed with epoxy [12]. Optical fibres were also integrated into a hot embossed microfluidic device for CE [99,100].

2.4. Integrated elements involving energy-to-information transformation functions

Few examples for integrated detection and measurement systems are presented in the literature. Thermocouples, for example, can be used to monitor the temperature variation on the microfluidic chip for PCR applications [56,97]. Micro-ammeters, of resolution down to 0.1 μA, were also reported to be used for current monitoring in micro-injection moulded devices for DNA separation [38]. However, the complexity of the detection process requires interaction between on-chip sensing elements, e.g. a thermocouple, and external, non-integrated, devices for recording and analysis. Therefore, energy-to-information elements should probably by identified as “interfacial”

elements between what can be integrated on-chip and what is external to the system. More about non-integrated elements is discussed in the following section.

3. Non-integrated Functional Elements

This part of the review is concerned with presenting functional elements that are commonly used with microfluidic devices, yet not integrated on the chip. Non-integrated elements, often expensive and non-disposable, are connected to microfluidic chips to perform relatively complex functions. Such functions are usually related to the input or output elements of the microfluidic system. Input elements, in turn, are usually associated with delivering the fluidic sample to the chip, and include inlet tubes and relevant connections. These input elements are tabulated in column 8 of Table 2. Output elements are associated with the outcome of the microfluidic system, such as detection and data analysis. These input elements are tabulated in column 9 of Table 2. A few non-integrated elements are used for both inputs and outputs, such as a power supply.

These types of elements are usually a source of the high costs often currently associated with microfluidic applications, a fact that limits many microfluidic devices to lab prototyping experiments rather than high-volume commercial purposes. The following sections present some of the commonly used elements.

3.1. Non-integrated elements involving energy-to-mass transformation functions

These elements are usually used for fluid propulsion systems, especially when energy is required for the fluid to either be able to balance capillary forces or to flow into different chambers in a specific sequence.

Several integrated devices covered within this literature review depend on external mechanical pumping equipment, e.g. syringes or pipettes. For example, a hot-embossed microfluidic device for magnetic bead separation was equipped with a syringe pump to deliver the beads in the form of an aqueous solution containing magnetic beads of three different sizes [98]. The same system was applied for an injection-moulded integrated microfluidic device for blood-typing, where the blood and the serum streams were pumped with two separate syringe-pumps to allow for different flow rates [60].

In an injection-moulded device, syringe pumps were also used to control flow inlets in a microfluidic cross-junction to produce beads [55]. Computer-controlled syringe pumps were also used to control the flow of the sample in a micromoulded chip for monitoring of microarray hybridizations [58].

Vacuum pumping was also pointed out in the literature as a possible mechanical fluid propulsion system, where a vacuum-driven system was used in a modularly integrated hot-embossed device [41]. In another hot-embossed device for bacteria detection, vacuum was used to move the sample throughout the device [45]. In addition, vacuum pumping was used for moving blood cells across micro-channels in a micro-injection moulded device used for monitoring DNA fragments [52].

Centrifugation is a developing method for fluid propulsion, where reagents are preloaded in the chip, and centrifugal forces are used to trigger the fluid flow throughout the channels. In centrifugal pumping, fluid propulsion is achieved through rotationally induced hydrostatic pressure. It uses a single low-cost motor, and is capable of fine flow control through proper design of the location, dimensions and geometry of channels and reservoirs based on fluid properties. A device works by spinning a CD-format chip such that the centrifugal forces overcome the capillary forces and the fluid is pumped throughout the channels [18]. However, it should be noted that centrifugation is not only dependent on energy, because the design of the channels themselves play a role in the propulsion of the fluid. The usually-radial configuration of the channels in addition to the sizes of the different channels/reservoirs determines how the fluid will proceed.

An electric field has been applied through integrated electrodes in order to control voltage changes leading to particle separation by electrophoresis [13,101] or electro-osmotic flow [37].

3.2. Non-integrated elements involving energy-to-energy transformation functions

Power supply sources are commonly used to deliver electrical power to different functional elements on the chip. As mentioned previously, with integrated elements for energy-to-energy transformation (section 2.3), an external power source is needed to supply high voltages or to operate heaters. Electrophoresis microfluidic devices reviewed in this paper needed a source of high voltage either from lab-scale power supplies [9,12,15,38,45,52,102] or a voltage-control unit

adjusted by an accompanying software [16]. Electric field values can be in the order of few tens up to few hundreds of volts depending on the application [103,104].

Power supply is also associated with temperature control, where microfluidic systems are required to operate under constant temperature. This can be done by a Peltier controller, for example [58].

3.3. Non-integrated elements involving energy-to-information transformation functions

Device elements performing energy-to-information transformation functions are usually associated with detection and inspection. As an example of a relatively advanced detection element, a detection system was designed in which a circuit converted the output signal from the biosensors to a voltage signal, which in turn was amplified, and the peak value detected and displayed [42].

Inspection is essential for the majority of microfluidic applications, because it is usually required to observe the micro-scale motion of the fluid or to count specific particles.

Conventional microscopes are used to optically observe specific processes inside the microchannels. They can be used, for example, for monitoring cell movements [52]. CCD cameras were also used for monitoring sample movement in channels [15].

In other applications, especially in DNA separation processes, fluorescence is the most popular optical detection method for microfluidics due to its excellent sensitivity down to measuring single molecules [64]. A sensitive technique is often required because of the small sample volumes involved [31,44]. Off-chip fluorescence detection is typically accomplished through the use of lasers for the excitation of fluorescent molecules and CCD cameras or photomultiplier tubes for detection of the emitted fluorescent light [31]. Usually confocal microscopes are used for this purpose [9,52,56,102]. Laser induced confocal microscopes have been used in several microfluidic experiments mentioned in the literature [13,15,16,45,105]. Contactless conductivity detection was also proposed as a detection technique that overcomes some of florescence limitations. It was used within an injection-moulded system for measuring small ions in foodstuff [93].

4. Discussion

4.1. An overview of the current state of integrated micro-moulded microfluidics:

In this review paper, the current state of research was presented for integrated polymeric microfluidic devices produced by two micro-moulding techniques, namely micro-injection moulding and hot-embossing.

The classification system used in this review was intended to link the functional aspects of microfluidic devices together with the degree of integration allowed by current device fabrication techniques. It allowed the review of integrated microfluidic devices from a taxonomical perspective, by combining a physical functional perspective, represented in the nine types of "transformation functions", with a manufacturing perspective, represented in integration technologies. This approach was summarised in Table 2.

The approach used in this paper gave an indication of the level of difficulty involved in integrating each of these generic components and the relationship of this to the elements' transformation function. For example, Table 2 showed that elements of relatively "simple" transformation function, e.g. mass-to-mass, are likely to be directly micro-mouldable (column 6), whereas other transformation functions appear to be currently not-integrated (columns 8 and 9). Most of the elements used for moving or storing masses of liquids, essentially the fluidic subsystem, are able to be incorporated into the chip as part of the operation of micro-moulding, though manifold designs for connection of the devices to the outer world still generally require off-chip integration.

It can be noticed that the majority of non-integrated elements are associated with energy-driven elements (fluid propulsion, for example) and with data collection and analysis. When energy or information are involved as inputs or outputs, the system becomes more complex in structure, because the current level of technology does not easily allow elements involving energy or information transformations to be incorporated into polymer-based chips. Therefore, non-integrated, non-disposable elements are usually needed to ensure the successful overall performance of the chip, with consequences in higher manufacturing complexity and higher costs. This is one of the major reasons why much of the current state of art of microfluidic chips is mainly confined to prototypes that are not easily mass-manufacturable.

Table 2 offered an overall summary of the current state of integrated, replicated, microfluidic devices based on thermoplastic high-volume processes. Hence, the blanks in Table 2 represent examples of one of two possibilities: either research gaps, or applications that are not yet needed. It is possible to separate the two by noting whether the application is currently achieved by non-integrated means. An example of the former is the mass-production of a fluid-propulsion system (energy-to-mass) that is fully integrated in a microfluidic system. This requirement is currently met only by non-integrated syringe pumps and centrifugal forces. An example of the latter is the mass-production of a mass-to-energy system, where there is no indication in the literature of a non-integrated system having been developed.

In this regard, several transformation functions were not discussed in the review as no integrated or non-integrated examples were found in the literature. These are highlighted by the blank rows in Table 2. These were mass-to-energy (as noted above), mass-to-information, information-to-mass, information-to-energy and information-to-information.

The classification method was limited to the transformation from one basic element to another. Therefore, elements that have multiple inputs or outputs were not presented in Table 2. Very few examples of multiple input and output functions exist in the literature. However, those that do exist are worth highlighting, because of their relatively level of sophistication. The main example is that of active micro-valves.

The classification method, represented in Table 2, was mainly directed to the viewpoint of a "designer" wishing to design a microfluidic system consisting of a set of integrated functions, which, at the same time, would be producible by high-volume polymer replication processes. However, for a manufacturer, the focus might be mainly on the integration technique, i.e. how to integrate an external element by high-volume processes.

To attempt to satisfy such a requirement, Table 3 tabulates the literature using integration techniques rather than integrated functions as the basis of tabulation. (It therefore, does not include the literature on non-integrated techniques.)

If the volume of literature references can be taken as a guide, then post-processing appears to dominate integration techniques. On-machine assembly is relatively common, followed by direct integration, with modular integration represented by a small portion of the literature.

However, it should also be noted that some of the integration methods that are used as established techniques for conventional injection moulding have not yet been developed for micro-

moulding. Three-component moulding, for example, is used on the conventional scale to integrate a number of elements in a single moulding cycle using a special mould system fitted with a robotic system [106].

Integration Technique	Applications	Ref.
• Direct integration of fluid-manipulation functions within the mould design	Integrating microfluidic systems, CD-like designs, passive valves and moulded interconnections.	[18,42,45,60,61]
	Passive valves	[18,42]
	Moulded interconnects	[50]
• Modular integration	Integrating microfluidic systems by lamination or modular kits	[36,41,42,71]
• On-the-machine assembly [20]:		
Micro-assembly injection moulding	Integrating movable joints, hollow structures	[88-90]
In-line sealing	Sealing the microfluidic system directly during micro-moulding	[35]
Micro-overmoulding	Integrating fibres and wires or integrating interconnects.	[19,20,59,86,90]
• Post processing	Sealing the microfluidic device	[8,12,15,17,38,55,76, 78]
	Interconnections by ports or drilled holes	[39,41,53,55-57]
	Adding external functional elements, such as electrodes, micro-heaters, magnets and optical fibres.	[12,38,45,52,56,78,96 -98]

Table 3: An example of a classification method based on integration technique

4.2. Potential developments from a low cost, mass manufacturing viewpoint:

As has been shown in this review, micro-moulding techniques have gained increasing interest as low cost manufacturing solutions for integrated microfluidics. Figure 1 shows a schematic diagram of the degree of integration in micromoulded microfluidics based on the reviewed literature. The figure, which presents Table 2 from another viewpoint, shows that micromoulding technologies are still far from realizing fully integrated microfluidic systems capable of covering the required range of transformation functions. This is due to a number of challenges that are discussed below.

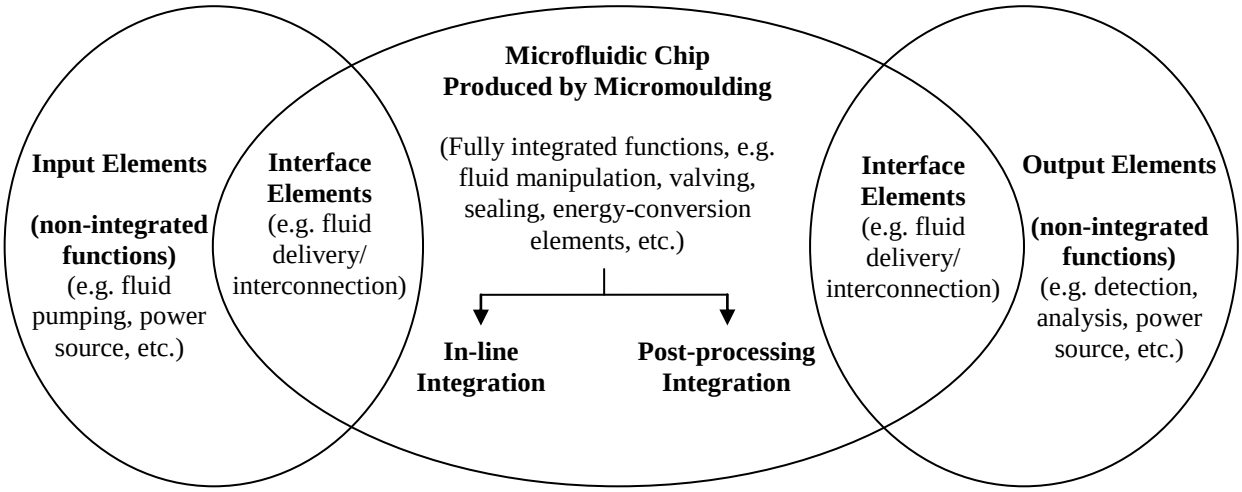

Figure 1: A schematic diagram showing current state of technology regarding the production of integrated elements within micromoulded microfluidic devices.

4.2.1. Geometrical constraints for microfluidic subsystems

Micromoulding has become an established technique for producing microfluidic chips with generally passive integrated functions, such as channels, passive valves and dispensers. However, it is noted from the reported examples discussed in this review that almost all the devices are based on a 2½-D design, which is the simplest geometry producible by injection moulding or hot embossing. This is due to the conventional parallel-movement design of the two platens typical for net-shape manufacturing techniques, which limits the complexity of the manufacturable geometry. In order to produce true three-dimensional geometries with cavities or undercuts, modular lamination is the currently used method. Despite of the number of advantages that such "modular" designs might offer, such systems require additional fabrication steps for bonding or connection. Accurate alignment of different stacked layers can also be challenging. In addition, there is an added cost arising from using frame systems and inter-layer connections.

4.2.2. Energy-conversion functional elements

Post-processing is currently the dominant technique for integrating such elements, but this is time consuming and a considerable bottleneck in mass-production. In addition, they are main sources of raised manufacturing costs, knowing that back-end processing steps can make up to 80% of the device manufacturing cost [25]. In order for microfluidic devices to perform more sophisticated processes, more functional elements will need to be integrated in an efficient

manufacturing process. Micro-overmoulding and micro- insert-moulding are solutions currently under investigation. However, these techniques would require considerable automation to place, accurately, the inserted element in the mould each cycle.

4.2.3. Sealing micro-fluidic devices

Sealing is usually attempted by face-to-face bonding or by adhesives. Several techniques are being established for connecting polymers to similar or dissimilar polymers or to other materials. Nevertheless, sealing is also a process bottleneck from an industrial perspective, because of the time consumed in sealing individual devices and the difficulty encountered in bonding polymers.

In-line sealing has been described, very briefly, within the literature for micro-injection moulding, and remains a challenge for further research. The main advantage of this technique is that it integrates the sealing process in the fabrication cycle making the manufacturing cycle time of the whole device acceptable. The automation of the process can result in accurate alignment and control over bonding parameters such as time and force. In addition the process eliminates the use of external adhesives or back-end processes.

Nevertheless, this technique uses special machine designs and setups in order to undertake the covering process. Furthermore, in cases where it is desired to have the substrate and the lid from different materials, the process will be more complex: two different injection units will be required. This is perhaps the reason why this technology has not yet seen wider adoption.

4.2.4. Fluid delivery to the device

Most of the available interconnection solutions are either not suitable for mass-production, for example drilling and gluing, or too expensive, for example self-adhesive ports. Fluid delivery can be improved by designing a fitting system that can be moulded together with the device substrate (or lid) to allow standard tubes to be attached more easily and securely. However, it is relatively challenging to replicate ports with internal or external threads via plastic replication techniques because of geometrical complexity associated with undercuts and because of the elongated cycle time. Overmoulding is currently being tested as an interconnection technology, and it has the potential of producing a microfluidic substrate where tubes are inserted in the mould and the polymer is injected over them, sealing in place by overmoulding.

4.2.5. Fluid propulsion

Fluid pumping is generally still performed by off-chip sources or at least with the interaction of external elements, because energy-to-mass functions currently require external sources of energy. Pre-installing the required reagents and using capillary motion are suggested alternatives, unless a continuous-flow system is required for specific applications. In mass-production environment, a fluid propulsion element could be manufactured externally, such as air-pressure pumps, and then integrated as an insert within a moulding process.

4.2.6. Fluid control

With regard to fluid regulation, many valving options have been developed for fluid control in microfluidic devices. Active valves form the majority of types and mechanisms, but very little is available in the literature about using active valves within micro-injection moulding or hot-embossing techniques. Passive valves are more promising in terms of manufacturing integration and cost, since several types of them can readily be produced by micromoulding. Passive valves, nevertheless, are not suitable for all applications, and they need further development for applications where more complex flow patterns are required.

4.2.7. Data collection and analysis

Some innovations have been achieved in detection techniques for POC applications [107]. However, detection and analysis systems are likely to remain as non-disposable elements, for the near future, because of the cost and manufacturing complexity associated with them within the currently available technology.

A current trend to overcome this limitation is to integrate relatively-cheap disposable chips with non-disposable, but portable, analysis elements. Several research groups are currently testing the use of a “cartridge” approach, where a disposable chip, either micromoulded or glass-etched, is inserted and operated within a non-disposable, but portable, analysis system [42,108].

The “wristwatch” example is a step forward in this direction. In this system, a disposable chip is inserted and accessed by a portable watch-like analysis device. The disposable chip is designed to be inserted into the analyser unit where the microfluidic sequencing is initiated by a trigger signal from the electronic controller. The electrochemical detection circuitry on the analyser is used to determine the concentration of different analytes [42]. The same principle has

been recently developed for testing metabolic parameters in human blood with a micromoulded disposable chip and a portable analyser [75].

This approach to integration, despite being a practical solution within the currently available technology, has some limitations. It makes use of the disposability and low-cost offered by micromoulding, but it still requires the availability of relatively costly equipment to analyse the collected data. Moreover, very precise positioning and alignment is required between the chip and the analyser system in order to ensure robust contact between their interactive elements, such as electrical components and valves. As suggested in the literature, having the microfluidic chip as just a small part of system in which sample introduction and detection are much more complicated than the chip's operation may be appropriate in some circumstances, but does detract from the potential advantages of microfluidic devices [7].

4.2.8. Power Sources

Some examples of power source solutions were presented in sections 2.2 and 3.2. The majority of the review literature presented conventional sources of power, either main power-supply or batteries. Some examples have been shown where air-pressure or chemical reaction can be used as powers source for fluid propulsion, but even these systems require the existence of an external power source, like a battery, to trigger the release of air or chemical reagents. Power generation is, therefore, likely to remain a non-integrated functional element until more convenient integrable solutions are developed.

5. Conclusion

This paper aimed to critically review the state-of-the-art of technology for producing integrated polymeric microfluidic chips by high-volume micromoulding techniques. In this regard, micro-injection moulding and hot-embossing were chosen as the replication processes covered in this review.

The current state-of-the-art of integration of functional elements into moulded polymer microfluidic devices was assessed. Levels of integration were classified by two methods. Firstly, by "transformation function" of the element, i.e. transformations between mass, energy and information. Secondly, by the current level of integration of these elements into microfluidic devices, whether integrated via moulding, by post-processing or, as yet, not integrated. The review gave detailed examples of elements used to perform the transformation functions and their current level of integration.

The review showed considerable differences between the level of integration of elements, dependant on the elements' transformation function. In particular, non-integration was found for elements with either energy-driven, or data collection and analysis transformation functions. At the present time, analysis systems with disposable microfluidic cartridges, represent the state of the art for the latter. Certain transformation functions, for example mass-to-energy showed no elements currently under development.

The review also assessed the options for integration of elements by such high volume processes. Post-processing appeared relatively common, followed by on-machine assembly, direct integration and then modular integration.

Potential developments in several key areas were assessed. Overmoulding, insert-moulding and in-line sealing all have potential for improving the direct integration of elements.

References

[1] Becker H (2008) Microfluidics: a technology coming of age. Med. Device Technol. 19:21-24.

[2] ThinXXS Microtechnology AG. Available at: www.thinxxs.com Accessed 2008

[3] Micralyne Inc. Available at: http://www.micralyne.com Accessed 2009

[4] Bartels Mikrotechnik GmbH. Available at: www.bartels-mikrotechnik.de Accessed 2008

[5] Abbott Laboratories. i-STAT. Available at: http://www.abbottpointofcare.com/istat Accessed February 2009

[6] Microfluidic ChipShop GmbH. Lab-on-a-Chip Catalogue 01/2009. 20. Available at: http://www.microfluidic-chipshop.com Accessed February 2009

[7] Whitesides GM (2006) The origins and the future of microfluidics. Nature 442:368-373.

[8] Boone TD, Hugh Fan Z, Hooper HH, Ricco AJ, Tan H, Williams SJ (2002) Plastic advances microfluidic devices. Anal. Chem. 74:78A-86A.

[9] Tan W, Fan ZH, Qiu CX, Ricco AJ, Gibbons I (2002) Miniaturized capillary isoelectric focusing in plastic microfluidic devices. Electrophoresis 23:3638-3645.

[10] Weigl B, Domingo G, LaBarre P, Gerlach J (2008) Towards non- and minimally instrumented, microfluidics-based diagnostic devices. Lab Chip 8:1999-2014.

[11] Gottschlich N (2004) Production of plastic components for microfluidic applications. Business Briefing: Future Drug Discovery. Available at: http://www.touchbriefings.com/pdf/855/fdd041_greiner_tech.pdf Accessed February 2007

[12] Qi S, Liu X, Ford S, Barrows J, Thomas G, Kelly K, McCandless A, Lian K, Goettert J, Soper SA (2002) Microfluidic devices fabricated in poly(methyl methacrylate) using hot-embossing with integrated sampling capillary and fiber optics for fluorescence detection. Lab Chip 2:88-95.

[13] Sassi AP, Paulus A, Cruzado ID, Bjornson T, Hooper HH (2000) Rapid, parallel separations of D1S80 alleles in a plastic microchannel chip. J. Chromatogr. A 894:203-217.

[14] Heckele M, Guber AE, Truckenmüller R (2006) Replication and bonding techniques for integrated microfluidic systems. Microsyst. Technol. 12:1031-1035.

[15] Zhou X-M, Shao S-J, Xu G-D, Zhong R-T, Liu D-Y, Tang J-W, Gao Y-N, Cheng S-J, Lin B-C (2005) Highly sensitive determination of the methylated *p16* gene in cancer patients by microchip electrophoresis. J. Chromatogr. B 816:145-151.

[16] Sung W-C, Lee G-B, Tzeng C-C, Chen S-H (2001) Plastic microchip electrophoresis for genetic screening: The analysis of polymerase chain reactions products of fragile X (CGG)n alleles. Electrophoresis 22:1188-1193.

[17] Becker H, Gärtner C (2000) Polymer microfabrication methods for microfluidic analytical applications. Electrophoresis 21:12-26.

[18] Madou MJ, Lee LJ, Daunert S, Lai S, Shih C-H (2001) Design and fabrication of CD-like microfluidic platforms for diagnostic: mircofluidic functions. Biomed. Microdevices 3:245-254.

[19] Webb DP, Hutt DA, Hopkinson N, Palmer PJ, Conway PP (2007) Integration and packaging of microsystems by polymer overmoulding. Proc. ESTC 2006 - 1st Electronics Systemintegration Technology Conference (5 - 7 September 2006) 1:567-574.

[20] Tosello G, Hansen HN (2006) In-process assembly of micro metal inserts in a polymer matrix. Proc. 4M2006, pp. 83-86.

[21] Gravesen P, Branebjerg J, Jensen OS (1993) Microfluidics - a review. J. Micromech. Microengineering 3:168-182.

[22] Song S, Lee KY (2006) Polymers for microfluidic chips. Macromolecular Research 14:121-128.

[23] Becker H, Locascio LE (2002) Polymer microfluidic devices. Talanta 56:267-287.

[24] Vilkner T, Janasek D, Manz A (2004) Micro total analysis systems: recent developments. Anal. Chem. 76:3373-3386.

[25] Becker H, Gärtner C (2008) Polymer microfabrication technologies for microfluidic systems. Anal. Bioanal. Chem. 390:89-111.

[26] Attia UM, Marson S, Alcock JR (2009) Micro-injection moulding of polymer microfluidic devices. Microfluid. Nanofluid. 7:1-28.

[27] Reyes DR, Iossifidis D, Auroux P-A, Manz A (2002) Micro total analysis systems. 1. Introduction, theory, and technology. Anal. Chem. 74:2623-2636.

[28] Auroux P-A, Iossifidis D, Reyes DR, Manz A (2002) Micro total analysis systems. 2. Analytical standard operations and applications. Anal. Chem. 74:2637-2652.

[29] Abgrall P, Gué A-M (2007) Lab-on-chip technologies: Making a microfluidic network and coupling it into a complete microsystem - A review. J. Micromech. Microengineering 17:R15-R49.

[30] Li S, Xu Z, Mazzeo A, Burns DJ, Fu G, Dirckx M, Shilpiekandula V, Chen X, Nayak NC, Wong E, Yoon SF, Fang ZP, Youeef-Toumi K, Hardt D, Tor SB, Yue CY, Chun J-H (2008) Review of production of microfluidic devices: Material, manufacturing and metrology. Proc. of SPIE 6993. Article number 69930F

[31] Fiorini GS, Chiu DT (2005) Disposable microfluidic devices: Fabrication, function, and application. BioTechniques 38:429-446.

[32] Erickson D, Li D (2004) Integrated microfluidic devices. Anal. Chim. Acta 507:11-26.

[33] Sun Y, Kwok YC (2006) Polymeric microfluidic system for DNA analysis. Anal. Chim. Acta 556:80-96.

[34] Zhang C, Xu J, Ma W, Zheng W (2006) PCR microfluidic devices for DNA amplification. Biotechnol. Adv. 24:243-84.

[35] Bourdon R (2003) Short cycles for injection moulded microfluidics parts. Kunsts. Plast. Eur. 93:9,11+33.

[36] Brüning H, Stange T (2004) Towards lab-on-a-chip devices for personalised medication and diagnostics. Med. Device Technol. 15:40-41.

[37] Soper SA, Stryjewski W, Zhu L, Xu Y, Wabuyele M, Chen H, Galloway M, McCarley RL (2003) Polymer-based modular microsystems for DNA sequencing. 7th International Conference on Miniaturized Chemical and Biochemical Analysis Systems (October 5-9) pp. 717-720.

[38] McCormick RM, Nelson RJ, Alonso-Amigo MG, Benvegnu DJ, Hooper HH (1997) Microchannel electrophoretic separations of DNA in injection-molded plastic substrates. Anal. Chem. 69:2626-2630.

[39] Gärtner C, Becker H, Anton B, Rötting O (2004) The microfluidic toolbox - Tools and standardization solutions for microfluidic devices for life sciences applications. Proc. SPIE Int. Soc. Opt. Eng. 5345:159-162.

[40] Blattert C, Jurischka R, Schoth A, Kerth P, Menz W (2004) Fabrication and testing of novel blood separation devices based on microchannel bend structures. Progr. Biomed. Opt. Imaging Proc. SPIE 5651:196-203.

[41] Datta P, Hammacher J, Pease M, Gurung S, Goettert J (2006) Development of an integrated polymer microfluidic stack. J. Phys. Conf. Ser. 34:853-858.

[42] Ahn CH, Choi J-W, Beaucage G, Nevin JH, Lee J-B, Puntambekar A, Lee JY (2004) Disposable smart lab on a chip for point-of-care clinical diagnostics. Proc. IEEE 92:154-173.

[43] Grodzinski P, Liu RH, Chen B, Blackwell J, Liu Y, Rhine D, Smekal T, Ganser D, Romero C, Yu H, Chan T, Kroutchinina N (2001) Development of plastic microfluidic devices for sample preparation. Biomed. Microdevices 3:275-283.

[44] Singh V, Desta Y, Datta P, Guy J, Clarke M, Feedback DL, Weimert J, Goettert J (2007) A hybrid approach for fabrication of polymeric BIOMEMS devices. Microsyst. Technol. 13:369-377.

[45] Koh CG, Tan W, Zhao M-Q, Ricco AJ, Fan ZH (2003) Integrating polymerase chain reaction, valving, and electrophoresis in a plastic device for bacterial detection. Anal. Chem. 75:4591-4598.

[46] Bourdon R, Schneider W (2002) A systematic approach to microinjection moulding. Business Briefing: Medical Device Manufacturing & Technology pp. 1-3.

[47] Biehl M, Velten T (2008) Gaps and challenges of point-of-care technology. IEEE Sensors J. 8:593-600.

[48] Bo Y, Salustri FA (1999) Function modeling based on interactions of mass, energy and information. Proc. of the Twelfth International Florida Artificial Intelligence Research Society Conference, pp. 384-388.

[49] Salustri FA (1998) Function modeling for an integrated framework: A progress report. Proc. of the Eleventh International Florida Artificial Intelligence Research Symposium Conference (FLAIRS '98), (May 27, Menlo Park, California: The AAAI Press) pp. 339-343.

[50] Mair DA, Geiger E, Pisano AP, Fréchet JMJ, Svec F (2006) Injection molded microfluidic chips featuring integrated interconnects. Lab Chip 6:1346-1354.

[51] Huang F-C, Chen Y-F, Lee G-B (2007) CE chips fabricated by injection molding and polyethylene/thermoplastic elastomer film packaging methods. Electrophoresis 28:1130-1137.

[52] Klepárník K, Horký M (2003) Detection of DNA fragmentation in a single apoptotic cardiomyocyte by electrophoresis on a microfluidic device. Electrophoresis 24:3778-3783.

[53] Upchurch Scientific: Micro Fluidic Connectors. Available at: www.upchurch.com/PDF/Lit/micro_singles.pdf Accessed March 2007

[54] Puntambekar A, Ahn CH (2002) Self-aligning microfluidic interconnects for glass- and plastic-based microfluidic systems. J. Micromech. Microengineering 12:35-40.

[55] Liu M-K, Huang K-S, Chang J-Y, Wu C-H, Lin YC (2007) Using a CD-like microfluidic platform for uniform calcium alginate drug carrier generation. Proc. SPIE Int. Soc. Opt. Eng. 6465 Article no. 646508.

[56] Lee D-S, Park SH, Yang H, Chung K-H, Yoon TH, Kim S-J, Kim K, Kim YT (2004) Bulk-micromachined submicroliter-volume PCR chip with very rapid thermal response and low power consumption. Lab Chip 4:401-407.

[57] Morales AM, Simmons BA, Wallow TI, Campbell KJ, Mani SS, Mittal B, Crocker RW, Cummings EB, Davalos RV, Domeier LA, Hunter MC, Krafcik KL, McGraw GJ, Mosier BP, Sickafoose SM (2006) Injection molded microfluidic devices for biological sample separation and detection. Proc. SPIE Int. Soc. Opt. Eng. 6109 Article no. 610901.

[58] Noerholm M, Bruus H, Jakobsen MH, Telleman P, Ramsing NB (2004) Polymer microfluidic chip for online monitoring of microarray hybridizations. Lab Chip 4:28-37.

[59] Webb DP, Hsu CC, Hutt DA, Hopkinson N, Conway PP, Palmer PJ (2005) Polymer overmoulding for microfluidic device packaging and system integration. Polytronic 2005, 5th Int. Conf. Polym. Adhes. in Microelectr. Photonics Proc. 2005:134-139.

[60] Kim DS, Lee SH, Ahn CH, Lee JY, Kwon TH (2006) Disposable integrated microfluidic biochip for blood typing by plastic microinjection moulding. Lab Chip 6:794-802.

[61] Lee LJ, Madou MJ, Koelling KW, Daunert S, Lai S, Koh CG, Juang Y-J, Lu Y, Yu L (2001) Design and fabrication of CD-like microfluidic platforms for diagnostics: Polymer-based microfabrication. Biomed. Microdevices 3:339-351.

[62] Choi SH, Kim DS, Kwon TH (2009) Microinjection molded disposable microfluidic lab-on-a-chip for efficient detection of agglutination. Microsyst. Technol. 15:309-316.

[63] De Mello A (2004) Research highlights - Phase change microvalves. Lab Chip 4

[64] Geschke O, Klank H, Tellemann P (2004) Microsystem engineering of Lab-on-a-chip devices. Wiley-VCH, Weinheim

[65] Oh KW, Ahn CH (2006) A review of microvalves. J. Micromech. Microengineering 16: R13-R39.

[66] Ahn CH, Puntambekar A, Lee SM, Cho HJ, Hong C-C (2000) Structurally programmable microfluidic systems. Proc. microTAS, pp. 205-208.

[67] Worgull M, Heckele M, Mappes T, Matthis B, Tosello G, Metz T, Gavillet J, Koltay P, Hansen HN (2008) Sub-µm structured lotus surfaces manufacturing. Microsyst. Technol. 1-7. Article in press. Doi: 10.1007/s00542-008-0744-7

[68] Choi J-W, Puntambekar A, Hong C-C, Gao C Zhu X, Trichur R, Han J, Chilukuru S, Dutta M, Murugesan S, Kim S, Sohn Y-S, Nevin JH, Beaucage G, Lee J-B, Lee JY, Bissell MG, Ahn CH (2003) A Disposable plastic biochip cartridge with on-chip power sources for blood analysis. Proc. IEEE Micro Electro Mech. Syst. MEMS 447-450.

[69] Choi J-W, Kim S, Trichur R, Cho HJ, Puntambekar A, Cole RL, Simkins JR, Murugesan S, Kim K, Lee J-B, Beaucage G, Nevin JH, Ahn CH (2001) A plastic micro injection molding technique using replaceable mold-disks for disposable microfluidic systems and biochips. Proc. micro-TAS 2001, pp. 411-412.

[70] Do J, Ahn CH (2008) A polymer lab-on-a-chip for magnetic immunoassay with on-chip sampling and detection capabilities. Lab Chip 8:542-549.

[71] Schuenemann M, Thomson D, Atkins M, Garst S, Yussuf A, Solomon M, Hayes J, Harvey E (2004) Packaging of disposable chips for bioanalytical applications. Proc. Electron Compon. Technol. Conf. 1:853-861.

[72] Gärtner C, Klemm R, Becker H (2007) Methods and instruments for continuous-flow PCR on a chip. Proc. SPIE Int. Soc. Opt. Eng. 6465 Article no. 646502.

[73] Lee SH, Kim S-W, Kang JY, Ahn CH (2008) A polymer lab-on-a-chip for reverse transcription (RT)-PCR based point-of-care clinical diagnostics. Lab Chip 8:2121-2127.

[74] Li C, Wu P-M, Browne A, Lee S, Ahn CH (2007) Hot-embossed piezoelectric polymer micro-diaphragm arrays integrated with lab-on-a-chip for protein analysis. Proc. IEEE Sens. 462-465.

[75] Do J, Lee S, Han J, Kai J, Hong C-C, Gao C, Nevin JH, Beaucage G, Ahn CH (2008) Development of functional lab-on-a-chip on polymer for point-of-care testing of metabolic parameters. Lab Chip 8:2113-2120.

[76] Yussuf A, Sbarski I, Hayes J, Solomon M. Sealing and Bonding Techniques for Polymer-Based Microfluidic Devices. Available at: http://www.swin.edu.au/iris/pdf/profiles/AbdirahmanYussuf.pdf Accessed 2007

[77] Nugen SR, Asiello PJ, Baeumner AJ (2009) Design and fabrication of a microfluidic device for near-single cell mRNA isolation using a copper hot embossing master. Microsyst. Technol. 15:477-483.

[78] Guber AE, Heckele M, Herrmann D, Muslija A, Saile V, Eichhorn L, Gietzelt T, Hoffmann W, Hauser PC, Tanyanyiwa J, Gerlach A, Gottschlich N, Knebel G (2004) Microfluidic lab-on-a-chip systems based on polymers - Fabrication and application. Chem. Eng. J. 101:447-453.

[79] Garst S, Schuenemann M, Solomon M, Atkin M, Harvey E (2005) Fabrication of multilayered microfluidic 3D polymer packages. Proc. Electron. Compon. Technol. Conf. 1:603-610.

[80] Tsao C-W, DeVoe DL (2009) Bonding of thermoplastic polymer microfluidics. Microfluid. Nanofluid. 6:1-16.

[81] Yoo J-C, Moon M-C, Choi YJ, Kang CJ, Kim Y-S (2006) A high performance microfluidic system integrated with the micropump and microvalve on the same substrate. Microelectron. Eng. 83:1684-1687.

[82] Erickson D, Sinton D, Li D (2004) A miniaturized high-voltage integrated power supply for portable microfluidic applications. Lab Chip 4:87-90.

[83] Hong C-C, Choi J-W, Ahn CH (2007) An on-chip air-bursting detonator for driving fluids on disposable lab-on-a-chip systems. J. Micromech. Microengineering 17:410-417.

[84] Ellis M (2009) Plastic diagnostic lab-on-a-chip. Mater. World 17:12-13.

[85] Datta P, George G, Tiwari S, Goettert J (2009) Monolithic fabrication of electro-fluidic polymer microchips. Microsyst. Technol. 15:463-469.

[86] Gharib NN, Baldock SJ, Economou A, Goddard NJ, Fielden PR (2008) Disposable injection-moulded cell-on-a-chip microfluidic devices with integrated conducting polymer electrodes for on-line voltammetric and electrochemiluminescence detection. Electroanalysis 20:448-454.

[87] Chen C, Chang G, Lin C-H (2008) Performance evaluation of a capillary electrophoresis electrochemical chip integrated with gold nanoelectrode ensemble working and decoupler electrodes. J. Chromatogr. A 1194:231-236.

[88] Michaeli W, Rogalla A, Ziegmann C (2000) Processing technologies for the injection moulding of hybrid microstructures. Macromol. Mater. Eng. 279:42-45.

[89] Michaeli W, Opfermann D (2006) Micro assembly injection moulding. Microsyst. Technol. 12:616-619.

[90] Michaeli W, Ziegmann C (2003) Micro assembly injection moulding for the generation of hybrid microstructures. Microsyst. Technol. 9:427-430.

[91] Michaeli W, Opfermann D, Kamps T (2007) Advances in micro assembly injection moulding for use in medical systems. Int. J. Adv. Manuf. Technol. 33:206-211.

[92] Michaeli W, Kamps T (2008) Micro assembly injection moulding with plasma treated inserts. Microsyst. Technol. 14:1903-1907.

[93] Becker H, Mühlberger H, Hoffmann W, Clemens T, Klemm R, Gärtner C (2008) Portable CE-system with contactless conductivity detection in an injection molded polymer chip for on-site food analysis. Proc. SPIE Int. Soc. Opt. Eng. 6886 Article no. 68860C.

[94] Heller MJ, Guttman A (2002) Integrated microfabricated biodevices: Advanced technology for genomics, drug discovery, bioanalysis, and clinical diagnostics. Marcel Dekker, Inc., New York

[95] Gärtner C, Kirsch S, Anton B, Becker H (2007) Hybrid microfluidic systems - combining a polymer microfluidic toolbox with biosensors. Proc. SPIE Int. Soc. Opt. Eng. 6465 Article no. 64650F.

[96] Nguyen N-T, Wereley S. Fundamentals and applications of microfluidics, 2nd ed. (2006) Artech House, Boston

[97] Hashimoto M, Chen P-C, Mitchell MW, Nikitopoulos DE, Soper SA, Murphy MC (2004) Rapid PCR in a continuous flow device. Lab Chip 4:638-645.

[98] Do J, Choi J-W, Ahn CH (2004) Low-cost magnetic interdigitated array on a plastic wafer. IEEE Trans. Magn. 40:3009-3011.

[99] Hsiung S-K, Lin C-H, Lee G-B (2005) A microfabricated capillary electrophoresis chip with multiple buried optical fibers and microfocusing lens for multiwavelength detection. Electrophoresis 26:1122-1129.

[100] Lin C-H, Hsiung S-K, Lee GB (2004) High-throughput micro capillary electrophoresis chip for bio-analytical application utilizing multi-wavelength detection. Proc. IEEE Int. Conf. Micro Electro Mech. Syst. MEMS pp. 304-307.

[101] Lee G-B, Chen S-H, Huang G-R, Sung W-C, Lin Y-H (2001) Microfabricated plastic chips by hot embossing methods and their applications for DNA separation and detection. Sensor Actuat. B-Chem. 75:142-148.

[102] Wainright A, Nguyen UT, Bjornson T, Boone TD (2003) Preconcentration and separation of double-stranded DNA fragments by electrophoresis in plastic microfluidic devices. Electrophoresis 24:3784-3792.

[103] Sun Y, Lim CS, Liu AQ, Ayi TC, Yap PH (2007) Design, simulation and experiment of electroosmotic microfluidic chip for cell sorting. Sensor Actuat. A-Phys. 133:340-348.

[104] Sabur R, Matin MA (2006) Study of electro-osmotic flow in microfluidic devices. Proc. IEEE-EMBS Int. Summer Sch. Symp. Med. Devices Biosens. pp. 126-129.

[105] Wang Y, Vaidya B, Farquar HD, Stryjewski W, Hammer RP, McCarley RL, Soper SA, Cheng Y-W, Barany F (2003) Microarrays assembled in microfluidic chips fabricated from poly(methyl methacrylate) for the detection of low-abundant DNA mutations. Anal. Chem. 75:1130-1140.

[106] ARBURG GmbH (2007) Integrating functions in the injection moulding process. Today, the ARBURG magazine, Issue 36, pp. 10-11. Available at: http://www.arburg.com/com/common/download/today/today36_2007_EN_GB.pdf. Accessed 2009

[107] Myers FB, Lee LP (2008) Innovations in optical microfluidic technologies for point-of-care diagnostics. Lab Chip 8:2015-2031.

[108] Meagher RJ, Hatch AV, Renzi RF, Singh AK (2008) An integrated microfluidic platform for sensitive and rapid detection of biological toxins. Lab Chip 8:2046-2053.

Integration of functionality into polymer-based microfluid devices produced by high-volume micromoulding techniques

Attia, Usama M.

2010

The original publication is available at www.springerlink.com

U.M. Attia and Jeffrey R. Alcock, Integration of functionality into polymer-based microfluid devices produced by high-volume micromoulding techniques, International Journal of Advanced Manufacturing Technology, 2010, Vol. 48, Nos. 9-12, pp. 973-991

http://dspace.lib.cranfield.ac.uk/handle/1826/6865