Lab-on-a-Foil: microfluidics on thin and flexible films

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This critical review is motivated by an increasing interest of the microfluidics community in developing complete Lab-on-a-Chip solutions based on thin and flexible films (Lab-on-a-Foil). Those implementations benefit from a broad range of fabrication methods that are partly adopted from well-established macroscale processes or are completely new and promising. In addition, thin and flexible foils enable various features like low thermal resistance for efficient thermocycling or integration of easily deformable chambers paving the way for new means of on-chip reagent storage or fluid transport. From an economical perspective, Lab-on-a-Foil systems are characterised by low material consumption and often low-cost materials which are attractive for cost-effective high-volume fabrication of self-contained disposable chips. The first part of this review focuses on available materials, fabrication processes and approaches for integration of microfluidic functions including liquid control and transport as well as storage and release of reagents. In the second part, an analysis of the state of Lab-on-a-Foil applications is provided with a special focus on nucleic acid analysis, immunoassays, cell-based assays and home care testing. We conclude that the Lab-on-a-Foil approach is very versatile and significantly expands the toolbox for the development of Lab-on-a-Chip solutions.

1 Introduction

Microfluidics is an enabling technology for miniaturisation, integration and automation of laboratory routines like production, purification or analysis of chemical compounds.[1–4] These functionalities are realised in so-called Lab-on-a-Chip systems. Their fabrication usually is inspired by mass production processes known from the polymer processing industry (injection moulding) or semiconductor industry (lithography and etching).

This review, however, discusses the impact of thin and flexible films as functional base materials. This approach is inspired from the huge packaging industries for pharmaceutical[5] or food products.[6] Good packaging not only protects the inside from damage on its way from production to the point of use[7] but also provides information about its content and makes it accessible as well as applicable just as standard beverage cartons with smart mechanisms for opening and closing.[8] In addition, packages

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must always be cost-efficiently mass-producible as well. *So just consider a Lab-on-a-Chip as a "functional package" that encloses valuable contents like microfluidics and biochemistry!* Its function is not limited to storage only—the "functional package" also contains the recipe inscribed in microchannels for how to combine the reagents in a perfect way to perform an assay.

Lab-on-a-Chip is a fast emerging field[9–12] with an expected market volume of 1 to 3 billion dollars by 2013.[13,14] In contrast to the field of Lab-on-a-Chip, conventional packaging is a much bigger business and mature. Hence, we want to point out how development of Lab-on-a-Chip systems can benefit drastically by adopting concepts of functional packaging to the microscale. In packaging technology, it has long been state of the art to equip packages with additional functionalities enabling interaction of the packaging system and its content.[15] Some examples of such additional functionalities are colour changing indicators to display gas concentrations,[16] time–temperature exposure[17] or tampering.[18] Packages can contain integrated oxygen or carbon dioxide absorbers or emitters[19] and even self-heating or cooling mechanisms[20] which have been integrated in military rations or canned beverages, respectively.

Our focus is particularly directed towards foil-based approaches for packaging and their use for Lab-on-a-Chip technology. Foils—often also referred to as films, sheets, laminates, tapes or webs—have been prominent elements in packaging technology since the middle of the 20th century. Several practical reasons make foil-based packages useful: foil packages with barrier functions protect content from degrading by oxidation or vapour transition,[21] as it is for example important in packaging of infant formula or blood plasma. Foils are further characterised by high flexibility and partially by pierceability thus providing easy user interfaces as known from pharmaceutical blister packages to access pills.[22] Certain polymer foils are favoured in other applications than packaging, for example as display panels for mobile phones due to their high transparency which can also be associated with their low thickness.[23]

When the principles of Lab-on-a-Chip are combined with foil technologies to so-called Lab-on-a-Foil systems, it is easy to

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identify several emerging applications that are particularly enabled by the use of thin foils:

- Temperature controlled biological reactions, such as the polymerase chain reaction (PCR), take advantage of fast heat transfer through thin materials.[24] In fact, heat transfer rate through a foil is inversely proportional to the square of its thickness as described by the diffusion equation.[25]
- Valves[26] or pumps[27] can benefit from the inherent flexibility of foils which can complement common elastic materials such as polydimethylsiloxane (PDMS).[28,29] The deflection of a foil under load is proportional to the cube of the foil thickness.
- The use of pierceable foils can provide a sample transfer interface[30] as it is known from aluminium sealing foils for microwell plates.
- Applications such as centrifugal microfluidics in which a microfluidic chip is accelerated can profit from low mass and thus low moment of inertia of foil cartridges.[31,32]
- Assembly or application of microfluidic cartridges can be accomplished by folding or inflating foil compounds. Some examples of this approach will be discussed later in this paper.
- Foil-based Lab-on-a-Chip systems suit perfectly as disposable consumables[33] because they only require a minimum of material volume.
- Several microscale prototyping processes like microthermoforming, hot roller embossing or lamination techniques are adopted from high-throughput macroscale processes. Hence, mass production is conceivable. Many prototyping processes are also upscalable and further expandable, for example by adopting traditional form-fill-seal processes.[34–36]

A recent example of the growing interest in these technologies is the LabOnFoil project that was launched within the scope of the European framework programme 7 in 2008. The project aims at providing dry-resist-based, disposable Lab-on-a-Foil cartridges that can be manufactured in large volume while common smart phones serve as instruments for control and evaluation of the assay.[37]

The first part of this review discusses technological issues like available materials, suitable processes for microstructuring and assembly as well as approaches for integration of microfluidic functions including liquid control and transport as well as reagent storage and release. In the second part, several applications in the fields of nucleic acid analysis, immunoassays, cell-based assays and home care testing are illustrated. Our reviewing criteria are based on key factors for successful development and commercial viability of Lab-on-a-Chip applications comprising the following:

- the capability to implement complex analytical assays[38–40] such as nucleic acid analysis or immunoassays with a broad or even universal range of applications,[10]
- the feasibility of cost-efficient development and perspective of effective mass production,[12,41,42] and
- the capability to provide enhanced utility[4,43] and to enable easy usage for the operator[44] in comparison to rigid, thick and non-flexible substrates.

Since the reviewed literature does not provide any binding definition for the term foil, we suggest the definition that a foil is a semi-finished part of any material that is thinner than 500 μm and of flexible character. All Lab-on-a-Foil systems consist of microstructured foil substrates which play a prominent functional role for the character or behaviour of the system. For simplification, we do not consider plain applications of foils for sealing of microfluidic channels. Membranes are a subclass of foils and are regarded as extremely thin functional layers.[45] Their bare use in a Lab-on-a-Chip system is not considered here, either.

2 Fabrication of Lab-on-a-Foil systems

The choice for a certain material and fabrication method is mainly influenced by the intended application. Take, for example, a chip for nucleic acid analysis by PCR: such a chip must consist of a material that is thermostable during thermocycling as it is exposed to temperatures up to 100 °C. It also should be very thin in order to feature low thermal resistance for fast heat exchange. It must further be compatible with the assay, meaning that a surface modification might be required so that biomolecules do not adhere to surfaces or suffer from degradation due to material incompatibility. In case of an optical readout, a material with high light transmission and low autofluorescence must be chosen. Also mechanical properties such as Young's modulus or tensile strength have to be respected to assure proper geometric and mechanical stability during operation and handling. If the chip development aims at a real market application, an upscalable fabrication process must be chosen in order to enable later mass production. Otherwise, the development may be useless. If the chip is designed as a fully self-contained system with integrated liquid reagent storage, it must feature a fluid encapsulation that prevents liquid or vapour transmission and allows a reasonable long shelf-life.

These and other aspects are discussed in the following section. We first provide an overview over the range of suitable materials and then present fabrication processes for foil-based Lab-on-a-Chip systems. A variety of examples illustrates features for fluid transport and control. We further address issues that are relevant for system integration such as some electronic features, surface modifications, sealing methods and multilayer assemblies. In the end of this section, a form-fill-seal scenario is outlined.

2.1 Materials

Several materials have already been examined in the context of Lab-on-a-Chip applications. Here, we focus on those materials that can meet our definition of foils as semi-finished parts with flexible character. Therefore, the popular PDMS is excluded since it is commonly not used as semi-finished (cured) foil but by primary shaping through casting it into moulds. Apart from that, it is reviewed elsewhere very well.[46] In contrast to such elastic materials, only plastic materials like thermoplastic, thermoset and photosensitive polymers, metals and paper substrates come into consideration as potential foil materials in this review.

Especially polymers offer a broad range of attractive materials and have thus been considered for Lab-on-a-Chip systems since the late 1990s.[47–51] Common thermoplastics such as polyethylene (PE), polystyrene (PS), polyethylene terephthalate (PET), polypropylene (PP), polycarbonate (PC) or cyclic olefin (co)polymers (COC/COP) are widely available as monolayer foils. Also

thermoset polymers like polyimide (PI) have been used for foil applications.[52] Besides such monolayer foils microfluidic applications can also easily benefit from so-called multilayer or compound foils. Two or more different polymers are co-extruded or laminated onto each other so that the resulting foil bears different properties across its cross-section. Such multilayer foils are state of the art in pharmaceutical packaging[53] because optical, mechanical and barrier properties are universally adjustable. One good example is a foil made of the relatively brittle material COC which is covered by a thin PP film on either side.[54] While the optical properties of the COC are only little affected by the opaque PP, the foil becomes more ductile and less tension cracks tend to appear due to the PP fringe. Other applications are multilayer foils with one high and one low melting material.[55,56] The low melting phase acts as a hot-melt adhesive in a thermobonding process while the high temperature melting material remains unchanged.

A different approach is the use of photosensitive polymers in the form of dry film resists which are either provided as rollstock or can be fabricated by spin coating at a laboratory scale. Dry film resists are particularly interesting because they can be lithographically structured and thus allow for patterns within the low- and submicron scale. Monolithic flexible microfluidic systems can be built up by structuring and subsequent lamination of multiple resist layers.[57] Available thicknesses are in a range of up to approximately 75 μm. Their deviation in thickness is as low as 0.01%.[58,59] This is hardly achieved in conventional spin coating processes.

Also foils made of metal, particularly aluminium, can be implemented in Lab-on-a-Foil systems.[54] If an optical readout is not required, such metal foils could solve problems where extreme barrier properties or lateral heat conductance[24] is desired. Their explicit advantage is also to provide a user interface so that an operator can pierce such a foil with a pipette to insert a sample into a chip. The aspects of user interfaces for microfluidic applications are hardly discussed so far but could be attractively addressed by the use of pierceable foils.

Also paper-based materials fall within our definition of foils. In fact, paper is not only a potential Lab-on-Foil candidate, but also it is already successfully used as a base material for lateral flow assays[60] which are sold in billions of units in point-of-care diagnostics. Paper is used when mainly capillary matrices are required.[61] Suitable grades are often made of nitrocellulose such as chromatographic paper.

2.2 Microstructuring

Manufacturing of Lab-on-a-Foil systems requires structuring of semi-finished sheets with microfluidic channels or chambers. It can be performed with different degrees of complexity. The simplest method is patterning a foil substrate with a set of through holes and combining it with a top and bottom layer in order to get a closed channel architecture. Other techniques are not as simple but offer enhanced functionalities in return. In the following, we outline various approaches to structure foils: thermoforming, embossing, photolithographic methods, cutting and wet etching as well as scratching (Table 1). All manufacturing methods are assessed by their applicability and flexibility, their upscalability, robustness and expected cost-efficiency.

2.2.1 Microthermoforming. Thermoforming is a process to form semi-finished polymer sheets into a three-dimensional shape (referred to as blister).[35,36] In the context of Lab-on-a-Chip, this approach has so far been realised as a vacuum supported stretch-forming of thermoplastic foils.[54,62,63] The foils are heated and firmly clamped facing a moulding tool. As soon as the foil is warm and sufficiently soft, a pressure difference over either side of the foil is applied, and the foil is blown onto the mould. Thus, the foil assumes the shape of the moulding tool and replicates its surface structure. After cooling of the foil, it can be demoulded.

It can be differentiated between positive (male) and negative (female) forming (Fig. 1). The elevated structures for positive forming lead to high shape accuracy on the inner surface of the foil substrate which is important for precise moulding of microstructures. The bottoms of the cavities are thick and rims and sidewalls are thin (Fig. 2a). On the other hand, negative forming allows for high shape accuracy on the outer surface which faces the moulding tool. The bottoms of the cavities become relatively thin (Fig. 2b). The obtainable aspect ratios are generally limited for both, positive and negative forming, by the thickness of the foil since the foil is stretched during moulding.[64]

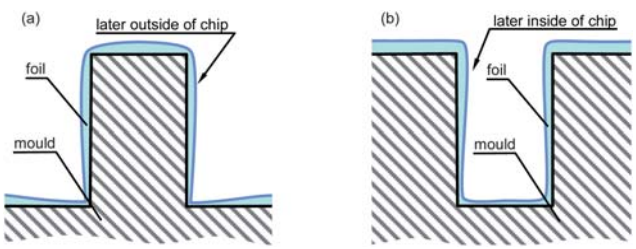

Fig. 1 Schematics of different moulding principles (figures adopted from ref. 35): (a) positive forming and (b) negative forming.

Table 1 Overview of fabrication techniques

Method	Materials	Distinctive feature	Realised applications	Section
Microthermoforming	Thermoplastics	Three-dimensional structures	Cell culture, DNA analysis	2.2.1
Hot roller embossing	Thermoplastics	High-throughput fabrication	DNA analysis in microarrays	2.2.2
Dry resist technologies	Dry resists	Lithographic microstructuring	Microreactors	2.2.3
Laser micromachining	Thermoplastics	Highly flexible structuring	Immunoassays, DNA analysis	2.2.4
Paper-based approaches	Paper	Low-cost wicking substrates	Immunoassays	2.2.5
Xurography	Paper and plastics	Prototyping with knife plotters	Basic fluidic feasibility	2.2.6
Shrinky Dink techniques	Thermoplastics	Shrinking of pre-stretched films	Immunoassays	2.2.7
Lab-on-a-print	Etchable materials	Selective wet etching	Micromixer	2.2.8
Inflatable membranes	Plastic/metal films	Inflation of hollow embodiments	Fluidic microactuators	2.2.9

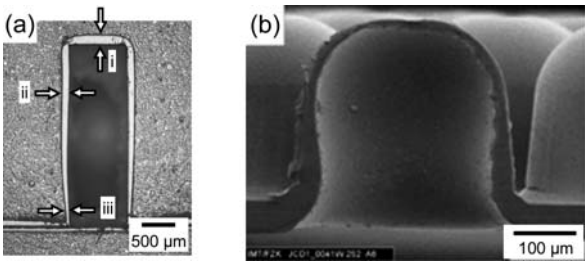

Fig. 2 Cross-sections of foils from positive and negative forming. (a) Cross-section of a channel with a depth of approximately 3 mm and width 1 mm. The positive mould led to thinning of the sidewalls ((i) 160 µm; (ii) 110 µm; (iii) 45 µm).[70] (b) Cross-section of a micro-container for cell culture, upside down.[62] Negative moulding led to a very thin container bottom with approximately 8 µm thickness. (b) Reproduced by permission of The Royal Society of Chemistry.

When the thermoforming process was initially developed for the microscale, negative moulds made of micromachined brass were employed.[65] The use of negative moulds is advantageous because after microstructuring heat-sealing can be done with a flat counter tool and a suitable sealing foil as long as the moulded part is still in its initial mould. Afterwards, the sealed chip can be demoulded. The drawback, however, is that a precise moulding of defined surfaces and sharp edges inside the microfluidic channels is not possible (*cf.* Fig. 1b). This first approach to thermoforming was performed with foils of fairly low thicknesses down to 25 µm. The structures were used to realise cell culture scaffolds with additional surface modifications by various types of irradiation.[62,66]

Our group at the University of Freiburg also performed thermoforming with positive mould inserts featuring microstructures that were obtained from a UV-LIGA process[67] and subsequent electroplating for achieving maximum shape accuracy.[54,68] Further, the concept of thermoforming foil compounds was realised with a 300 µm thick PP–COC–PP laminate.[69] The sample blister was sealed with an aluminium foil to obtain a closed chip.

Usually, moulding tools are made of rigid materials like brass or tool steel and commonly require draft angles of approximately 5° as well as bevels.[62] We recently showed that these requirements for the mould designs can be overcome by employing a flexible, PDMS-based moulding tool (Fig. 3).[63]

This method is an adaptation of the well-established soft lithography technique to microthermoforming and enables rapid prototyping of foil-based microfluidic cartridges. It allows fast design cycles in one day and processing without the need for draft angles for demoulding due to its intrinsic flexibility.

Microthermoforming is usually performed with modified hot embossing presses[62,63] and is still in a prototyping stage. The advantages of thermoforming are their characteristic three-dimensional out-of-plane structures. These allow implementing additional features like manually deformable chambers as known from pharmaceutical blister packages for pills. Such blister chambers promise a broad field of applications from reagent storage and release to means of fluid actuation as will be described later.

Either positive or negative forming can be selected according to specifications of the target application. The choice of moulding technique determines key properties of the obtainable parts as discussed in the preceding section. Critical factors for efficient thermoforming are rapid heating of the foil and fast establishment of vacuum on one side of the soft foil. When these aspects are considered, the microscale process can be rescaled to aim at mass production in order to compete with other technologies like injection moulding.

2.2.2 Hot roller embossing. The technology of hot roller embossing is mainly motivated by the aim of high-throughput production of microstructured foils. This is achieved by large area patterning of polymer foils by a cylindrical roller tool.[71] The heated roller patterns a temporarily softened polymer foil that is in line contact to a backing roller (Fig. 4).[72,73] Unlike the previously described microthermoforming, the foils are not clamped during moulding but are processed in a continuous manner.

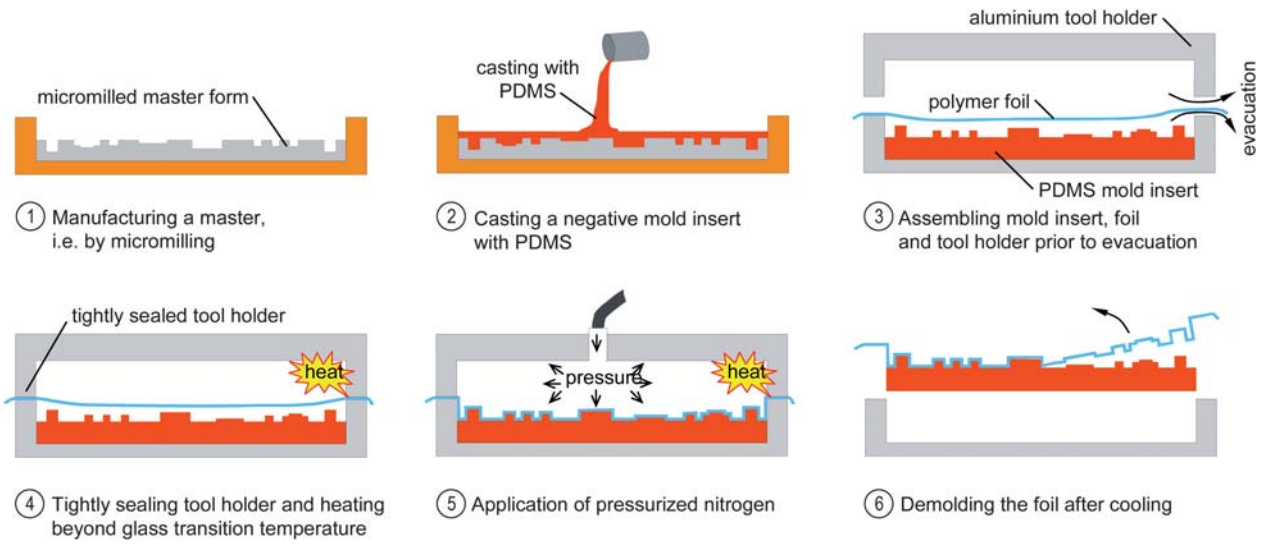

Fig. 3 Cross-sectional view of the rapid prototyping process scheme for moulding of microfluidic foil cartridges.[63]

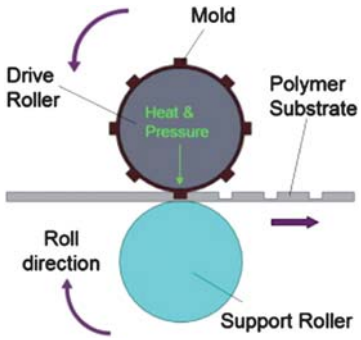

Fig. 4 Roll-to-roll imprinting process.[72] Figure reprinted with permission from Elsevier.

The basic process is well parameterised in literature.[74] Critical parameters are roller temperature, pressure and roller speed. Also preheating of the foil material led to significant improvement.[72] Some variants of the process are for example roller embossing with two structured rolls for double-sided patterning of foils,[75,76] extrusion embossing[77,78] and ultraviolet (UV) embossing.[79] Embossing is also known from conventional batch mode hot embossing with a flat stamp tool. In contrast to the continuous hot roller embossing, the polymer substrate is molten during moulding. There are examples for structuring of foils by a batch mode process applying a rigid[80] or flexible counter tool.[81]

A combination of both, roller and stamp embossing, is extrusion embossing.[77,78] A thin polymer melt is continuously fed on a patterned chill roll. This technique allows very high feed rates to be reached since the roller tool does not need to heat up the polymer but can rather cool it down. A further approach is UV embossing,[79] in which a UV-curable resin film is first roller embossed and then exposed to UV light for curing of the polymer. It is attractive as it can be done at room temperature and thus also allows patterning of temperature-sensitive proteins encapsulated in UV curable hydrogel polymers.[79,82]

Conventional roller embossing at industrial scales can achieve feed rates of several 10 m min^{-1} which allows rapid structuring of large areas and immense throughput.[83] Nevertheless, achievable feed rates in the microscale are still much lower and often less than 0.5 m min^{-1}.[84,85] This is due to the fact that pattern fidelity improves with longer mould-to-polymer contact time.[74]

Tool fabrication for roller embossing poses a challenge since cylindrical tools are required for the roller body. The common approach comprises structuring of large area dry film resists. These are either used themselves as patterning templates[86] or are further upgraded in a subsequent electrolytic plating processes.[74,87]

Compared to all manufacturing processes that are reviewed here, roller hot embossing is closest to mass production capacities due to large area patterning. However, there are also some drawbacks that restrict broad applicability of this process. Roller replication is limited to very small and shallow structures on the high nano- to low microscale or, alternatively, the imprinting patterns require comparatively large draft angles in the range of 10° to 15° if structures with heights in the low millimetre range are replicated. Ng and Wang set up a general rule of thumb that "an aspect ratio of 1 : 1 can be replicated easily, 5 : 1 with care and 10 : 1 only with great difficulty".[87] Apart from this general rule, there are almost no distinctive sources in literature that would describe requirements for sufficient detachment of foils from their moulds.

The strengths of the process are located in the field of micro- and nanoimprinting. Hence, its impact on optical devices could be much bigger than on microfluidic applications where average patterns are larger than in optics.

Roller embossing must directly compete with primary shaping processes like injection compression moulding,[88–90] a variant of standard injection moulding. Injection compression moulding is also used to produce likewise thin and planar parts like CDs and DVDs. In comparison, standard injection moulding is hardly suitable for manufacturing of thin, foil-like Lab-on-a-Chip systems as it is limited by early solidification of the melt front during filling of thin geometries.[91,92]

2.2.3 Dry resist technologies. Structuring processes based on photopolymers enable microstructures on a scale well below conventional machining techniques. There are two approaches of using photopolymers that both allow fabrication of flexible microfluidic chips. In both approaches dry film resists can be used as base materials (see Section 2.1). The first method allows one to monolithically set up a microfluidic chip that is totally made of resist material.[57] The second method makes use of two flexible sheets that enclose a lithographically structured dry film resist.[93]

Dry resist films can either be industrial products or self-made in the own laboratory.[94] Some examples of commercial dry resist systems are Ordyl SY (Elga Europe S.r.l., Italy), Riston (DuPont, USA) and TMMF (Tokyo Ohka Kogyo Co. Ltd., Japan). The common SU-8 negative resist frequently serves as starting material for production of self-made dry resists. SU-8 features remarkable bending characteristics[95] and can be laminated to several 100 μm thicknesses. Dry resists are commonly lined on a backing foil, in order to facilitate handling.

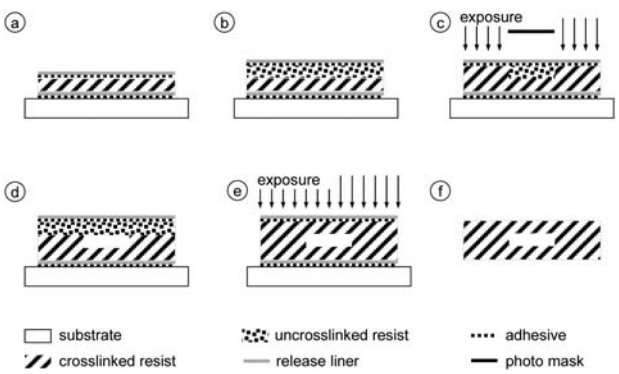

Fig. 5 Basic processing scheme for microstructuring microfluidic chips with dry resist films. (a) Cross-linked dry resist with release liners laminated onto a carrying substrate. (b) Removal of the backing layer and lamination of a second (uncrosslinked) dry resist. (c) Exposure through the transparent liner. (d) After removal of the liner and development (not shown), a third dry resist is laminated. (e) Exposure and enclosing of a channel in a laminated dry resist film chip. (f) The chip can be removed from the substrate.

In the first fabrication approach (Fig. 5), a release liner is affixed to a carrier substrate and a dry resist film is laminated onto it. The backing foil of the dry resist film is on top and must be transparent for UV exposure. Layer after layer is laminated, exposed and developed after removing the respective backing foils which stabilise the assembly in the first instance. After the last layer is completed, the chip can be peeled off from the bottom release liner on the carrier substrate.

The so-called DP^2 Direct Projection has been reported as an out-of-clean room alternative recently.[96] Dry resist films were exposed by a digital light processing projector that was equipped with a camera lens. Eventually, multilayer devices could be fabricated.

Multilayer lamination with dry resist films is reported to be very error-prone if not optimised.[94] Critical parameters are for example duration of soft-bake, UV dose, temperature of post-exposure bake as well as lamination parameters like pressure, temperature and speed. These parameters significantly influence material stress and bonding properties. But once the process is set up, various features can be integrated: micromeshes with pore sizes of 20 μm × 10 μm that fully consist of resist,[97] micro-actuators for manipulation of magnetic particles,[98] as well as chips made of silicon.[94]

In the second fabrication approach,[93] an AF-5075 dry resist film of 75 μm thickness is exposed on a PET backing foil. After development, washing and drying, it is then sandwiched between two slides of PET or PMMA and laminated in a hot roller at a temperature of 110 °C. The top and bottom lamination with two standard polymer substrates serves as stabilisation and allows bending of the chip considerably (Fig. 6). The fabrication method was successfully tested with synthesis of polyaniline in a microfluidic microreactor.

The use of structured dry film resists bears many potentials as it was already demonstrated in several applications. The strengths of the dry resist film approach are the capability to fabricate delicate microstructures which are hardly achieved by conventional machining technologies. However, the process is rather not dedicated for geometries with depths in the millimetre range which can be a disadvantage if larger microfluidic reservoirs are required. The used materials are compatible with many applications as far as biological inertness[99] or chemical resistance[100] is concerned. Thus, the technology of dry resist films is suitable for a broad range of microfluidic applications. The critical aspects of the process, however, have been pointed out: process control and reliability are of utmost importance.

Compared to other thermoplastic materials, the use of dry resist films is more expensive, especially in cases in which clean room facilities are required. Upscaling is certainly a challenge and requires several innovations which can hardly profit from the technology of packaging goods as discussed in the introduction because processing of photosensitive polymers is not found there. Instead, methods of semiconductor fabrication must be employed.

2.2.4 Laser micromachining. The principles and advantages of laser micromachining are well known in the field of microfluidic research and have been pointed out frequently.[101,102] Particularly laser ablation of polymeric substrates is a suitable microstructuring process.[103] Ablation of thin films proved feasible by demonstration of a mask-supported UV laser process for fabrication of polymeric fluidic microchannels with depths < 40 μm.[104] Laser pulses of the UV excimer laser ablate the surface of a substrate. Alignment is achieved by a mask that features the pattern of the later structure. Usually an inert cutting gas is applied concomitantly in order to carry away melt and smoke particles from the kerf.

Another approach for fabrication of microfluidic structures is direct laser cutting of slits into foils and laminate sealing foils on top and bottom. Channel heights would be defined by the thickness of the microstructured middle layer.[105] This laminate-based method also allows assembling chips with 4 to 12 layers for three-dimensional channel architectures. Assembly is facilitated by intermediate adhesive layers that can be structured likewise.

Laser technologies are very attractive due to their great flexibility since expensive and time-consuming toolmaking is not necessary. Varying structural depths are possible with laser ablation technology as depth linearly correlates with the number of laser pulses per area.[104] But laser ablation can change the properties of surfaces[106] as small particles are ejected and deposited on the surrounding surfaces. The ablated areas have an increased carbon/oxygen ratio resulting in decreased charging and thus hydrophobicity. The ejected particles have an increased charge and are thus hydrophilic. This circumstance must be considered for the respective applications.

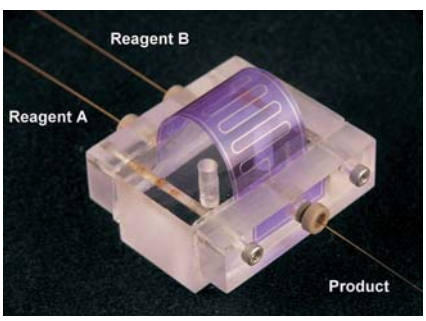

Fig. 6 A flow microreactor system connected to inlet and outlet capillaries.[93] The chip features a structured dry resist film that is sandwiched between two thermoplastic foils. Figure with permission from JCCS.

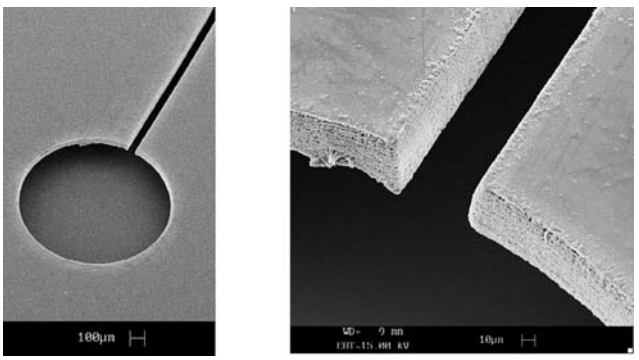

Fig. 7 Polyester foil cut using a femtosecond laser.[107] Left: 1 mm diameter reservoir patterns cut through the whole depth of the foil. Right: close-up view of a 50 μm wide microchannel. Figure and parts of caption with kind permission by EDP Science.

Recent developments report on approaches to integrate laser micromachining technologies in foil-based reel-to-reel fabrication processes.[107] Feasibility of a femtosecond laser system suitable for in-line cutting of 20 μm thick polyester was demonstrated (Fig. 7). Structured foils were subsequently laminated with SU-8 as adhesive intermediate layer at feed rates of 0.4 m min^{-1}.

Laser micromachining is extremely flexible since tooling costs can be saved. This makes the approach attractive for prototyping and small batch productions while in high-throughput production systems, usually replication technologies like embossing are preferred. Nevertheless, integration of laser machining into a production line with subsequent lamination is a highly competitive and versatile approach for fabrication of microfluidic chips.

2.2.5 Paper-based approaches. Fibrous materials are important substrates for diagnostic applications as they are used in various analytical test strips, also known as lateral flow assays. Cellulosic matrices such as paper are made of organic pulp, in which liquids can proceed by capillary forces. Capillary flow is usually directed by defined geometric restrictions that are either the blank edges of the paper device (as in lateral flow strips)[108] or walls integrated in the matrix. In order to generate these walls, a liquid solution is impregnated in the paper and solidified.

In the first approach, chromatographic paper was soaked with the photoresist SU-8.[61] After development of the SU-8, the complete surface of the chip was plasma oxidised to enhance hydrophilicity while the remaining cured SU-8 acted as a hydrophobic barrier. The use of a costly photomask can be avoided by employment of a temporary photomask that is patterned on an adhesive foil layer on the paper substrate (Fig. 8).[109] Patterning can be done with an office printer or manually with a waterproof black pen. By application of a self-formulated negative resist,[109] the impregnated paper can be exposed by any UV source, even sunlight.

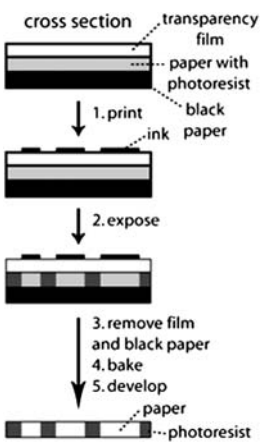

Fig. 8 Schematic process for fabrication of microfluidic devices in paper (cutout from original figure).[109] The paper is soaked with a photoresist and sandwiched between black paper and a transparent film. The temporary photomask is printed on the top film. After exposure, the supporting layers are removed and the resist is developed. The liquid path is defined by the patterned resist. Reproduced by permission of The Royal Society of Chemistry.

A different approach employs molten wax[110] that soaks the paper and solidifies in defined spaces. The wax is patterned on the paper by a commercial wax printer[111] and molten in an oven at 130 to 150 °C for a few minutes. The melting wax then penetrates the paper generating hydrophobic barriers. The pattern resolution is just limited by the capabilities of the applied printer.

These structuring methods can also be used to set up diagnostic multilayer devices[112] with three-dimensional capillary flow paths. Multiple layers of patterned paper are separated by a layer of double-sided adhesive tape.

Connections between adjacent layers are achieved by vias that are laser cut in the adhesive tapes. The capabilities of this technique were demonstrated by a microarray device consisting of 5 layers of paper and 4 layers of tape. Samples of 100 μl each could be fed into 4 separate inlet wells in parallel. Each sample was then distributed by capillary forces into 256 detection zones (that is a total of 1024 spots) in 5 minutes.

The previously described methods are extremely fast ways of setting up a capillary driven microfluidic chip. The described wax printing or lithographic approaches take around 5 to 30 minutes from design to fabricated chip and thus allow very easy and rapid prototyping. Paper-based matrices are commercially applied for lateral flow immunoassays for detection of certain molecules in a sample. Reagents for the assay are pre-stored in the detection zones on the paper device. The use of paper devices is basically limited to the field of immunoassays since these usually work with colour changes that are often visible to the naked eye.

Paper-based devices are already extremely competitive in terms of cost-efficient production due to lowest material costs and simple assembly. In order to further advance their utility, the latest developments like the described multilayer approach were crucial. Only integration of further microfluidic unit operations (such as the described aliquoting) can drive these promising platforms forward to new frontiers with more complex applications.

2.2.6 Xurographic methods. Xurography is a prototyping technique that employs a knife plotter to structure thin foils. Such plotters are state of the art in the graphic design sector and allow very high precision cutting.[113,114] It is possible to cut foils that eventually can be laminated in-between two other substrates.

A superior fabrication protocol with adhesive tapes is adapted from graphic advertisement techniques (Fig. 9). The plotter knife patterns an adhesive film that is kept on its release liner. After patterning, the unnecessary parts of the adhesive film are peeled off the release liner while the relevant pieces remain there. A sticky transfer tape is applied on top of the remaining parts and enables to peel the adhesive film from the release liner without destructing the alignment. Once the adhesive film is applied to the final substrate, the sticky transfer tape can be removed.

Xurography was extensively examined and characterised for several different materials like PET, nitrocellulose and aluminium.[113] The technique allows remarkably high resolutions below 10 μm and thus detailed features. It is very fast and allows low-volume fabrication of microfluidic cartridges in an instant.

2.2.7 Shrinking of pre-stretched films. The application of pre-stretched foils for fabrication of Lab-on-a-Chip devices is a very

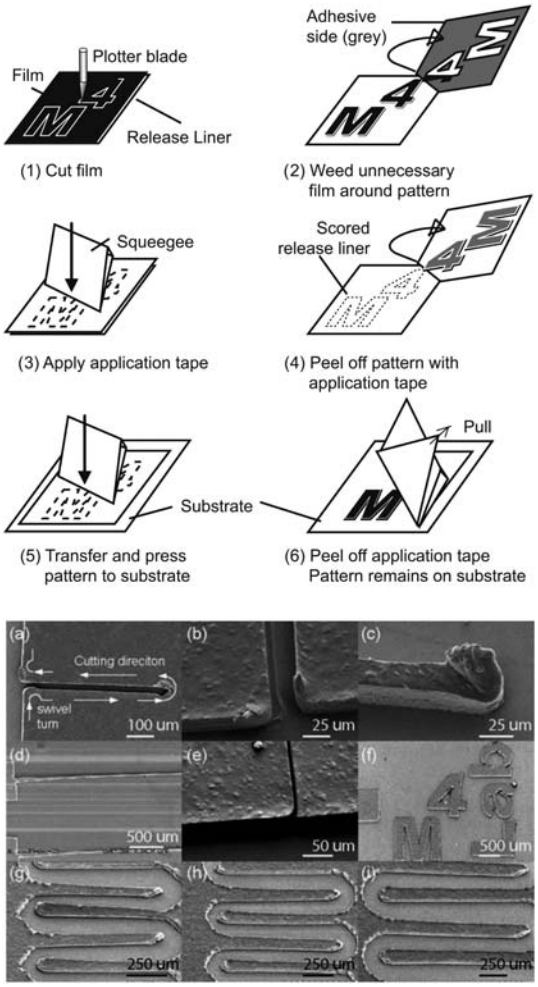

Fig. 9 Process scheme of xurography and results of various patterns at different process parameters (a–i).[113] Figures © 2005 IEEE.

peculiar rapid prototyping approach.[115,116] The so-called shrink films are thermoplastic polymer foils that are stretched during their primary shaping in order to gain an orientation of the molecules.[117] The orientation can be uni- or biaxial. When heated again, the polymer chains undergo a stress relaxation that leads to retraction of oriented molecules into their initial (random) position.[118] Then, reduction of the edge lengths in the biaxial plane goes along with an increase of thickness of the sheet. Shrink films are widely used for tamper-evident and tight wrapping in packaging of food or pharmaceuticals.

One approach in the field of microfluidics is printing of patterns on a biaxially stretched shrink film by laser printing[115] or screen-printing.[116] The pre-stretched and patterned foil is briefly placed in an oven and heated to a temperature around glass transition. Then the foil retracts but the printed pattern is distorted less than the unpatterned areas. This generates a fold or wrinkle along the previously printed channel design. The overall shrinkage depends on the pre-stretched sheet and can amount up to 63%.

In a further approach, several pre-stretched polystyrene sheets are structured by engraving them manually with sharp tools like syringe tips or razor blades. The sheets are then aligned in a multilayer fashion and placed in an oven at 160 °C. Upon

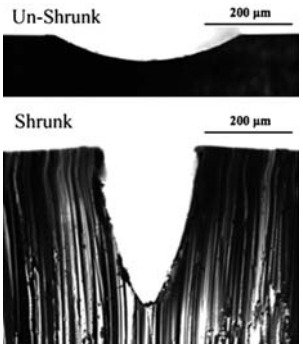

Fig. 10 Cross-sections of structured shrink films.[119] Top: the foil surface is structured by inscribing before heat treatment. Bottom: after shrinking, the structures are far narrower and deeper. Reproduced by permission of The Royal Society of Chemistry.

heating, the engraved patterns become narrower and much deeper (Fig. 10). Moreover, the sheets cross-link and shrink together to a three-dimensional multilayer chip.[119] In an additional study, it was demonstrated that deposited protein spots (monoclonal antibodies) could sufficiently withstand the retraction heat treatment of 30 seconds at 163 °C.[116] Thus, a sandwich immunoassay was feasible on a microfluidic shrink film chip.

The application of shrink films appears primarily to be a simple and fast prototyping method for fabrication of channel geometries that are not very defined. The engraving approach[119] allows fabrication of different depths by inscribing the surface of the shrink film accordingly deep. The printing technique[115] is reported to produce different depths by multilayer printing (feeding the sheet in the laser printer again). But in fact, process control and robustness of the shrinking procedure appear critical. Shrinking depends not only strongly on the stretching temperature during shrink film production, the temperature profile during the relaxation heat treatment[118] but also on the technique of etching where applicable. Small changes in these procedures can add-up and lead to large changes in the final geometries which are critical whenever well-defined geometries are desired. Further, the achievable shrinkage in the range of 60 to 70% is not large enough to provide drastic advantages with the downscaling effect.

2.2.8 Selective wet etching (Lab-on-a-print). Another very creative new approach was introduced as the Lab-on-a-print technology.[120] This technique employs standard solid wax printing with a commercial printer on both sides of a 25 to 125 µm thick polyimide film. The printed pattern omits the later channel routes (Fig. 11). Then the patterned sheet is exposed to a KOH-based wet etching bath. The solid wax serves as an etching barrier. Thus, only the polyimide film is etched where there is no coverage of wax. Finally, the structured polyimide film is folded and, thereby, contacting wax layers can be thermally bonded onto each other.

The Lab-on-a-print technology exhibits a simple but universal chip system made of a polymer foil that can be prototyped in less than one hour. It is obvious that assembly by folding is only possible due to the flexible properties of foil materials. However, due to the thermal bonding of the wax layers there is the risk of delamination when the chip is exposed to increased

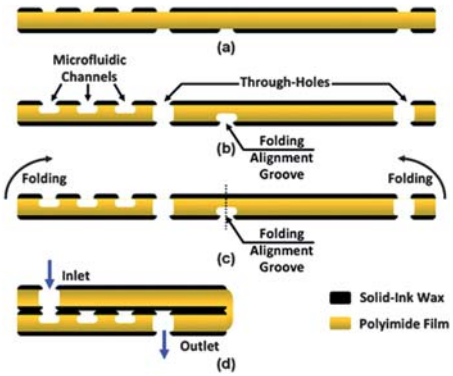

Fig. 11 Schematic illustration of the Lab-on-a-print process:[120] (a) solid-ink wax double-side printed onto a polyimide film using a solid-ink laser printer; (b) wet etching both sides of the film; (c) folding along the folding alignment groove; (d) wax thermal-fusion bonding. Reproduced by permission of The Royal Society of Chemistry.

temperatures. Therefore, broader application is critical, especially outside defined laboratory conditions.

2.2.9 Inflatable warped membranes. The approach to fabricate hollow, three-dimensional parts by inflating thin polymer foils[121] is based on the differential adhesion method[122] which makes use of characteristic adhesion properties of different materials. For example, gold adheres well to chromium and weakly to silicon. Thus, different layers can be deposited in standard clean room processes in order to generate thin layers with different adhesion properties. The above mentioned protocol was carried out with two polyimide foils. The assembly was subsequently connected with air tubes for inflation.

The process of inflating warped membranes has its roots in the development of fluidic microactuators[123] and is hardly upscalable. The approach to inflate a structured foil assembly is unique and only possible with flexible foil materials. The method of inflation, however, has potential to be utilised for microfluidic actuation as it is discussed further down.[124]

2.3 Foil-based fluid actuation

The use of foils in Lab-on-a-Chip systems offers several options for integrating additional functionalities in these systems. This section discusses some approaches on integration of foils for actuation of fluids. Actuation is used for driving a liquid through a channel system and (where applicable) switching, stopping or releasing liquid portions on demand. Here, we present some examples for valving as well as principles for inducing liquid flow that are all based on foils.

2.3.1 Valving. Valving is a delicate issue and relevant for all applications with sequential liquid processing. One simple example is a single-use valve based on foils that can be opened by an increased liquid pressure (Fig. 12).[125] Such valves are often realised with polymer foils that are applied to a carrier substrate but with a reduced bond strength compared to the surrounding areas. This leads to selective, local delamination at the valve interface when it is exposed to a certain liquid pressure.[126] These valves are also termed weak-bonded interface or frangible seal.

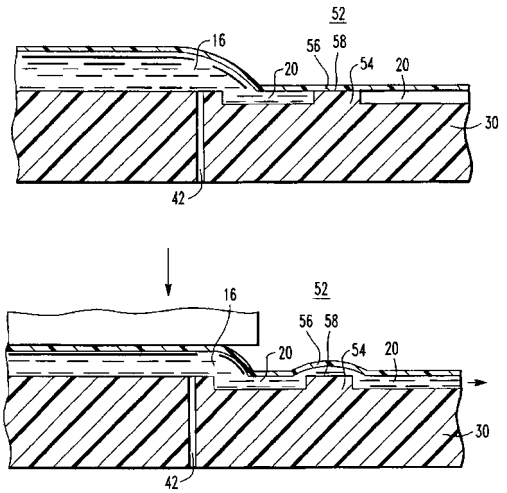

Fig. 12 Patent drawing of a foil-based valve as disclosed by the company Westinghouse Electric Corporation.[125] The valve [54–58] releases liquid reagents that are stored in a reservoir [16]. Upon pressurisation of the liquid, the heat-sealed bond opens a passage to the onward channel [20]. Figures issued by the United States Patent and Trademark Office.

Another valving principle is realised by cold stamping of polymer foils.[127] Cold stamping inserts tensions in the polymer matrix due to stretching at temperatures below the glass transition temperature. Then the tensions are frozen and the polymer structure remains in a non-equilibrium state. Upon heating, the structures can relax and the polymer chains retract to their original position. This can be used to a thermally induced, single-use valve (Fig. 13). This technique is related to the previously discussed technology of pre-stretched films.[115,116]

An alternative single-use valve is extremely universal as it allows a separation layer to be selectively perforated by a laser beam.[128] The separation layer is a foil with a significantly higher absorption at a certain laser wavelength than the other layers. The intermediate layer is embedded in a laminate multilayer assembly and separates two structured and well-aligned microfluidic containers. A laser impulse perforates the intermediate

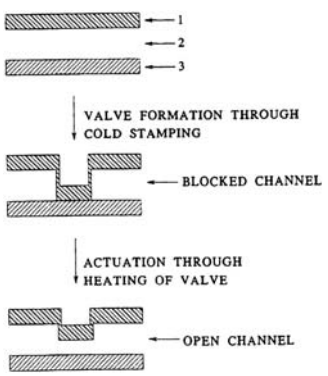

Fig. 13 Patent drawing of a heat-actuated valve as disclosed by the company Tecan Trading AG.[127] The valving principle is single-use only and relies on retracting of inherent tensions in the polymer matrix upon heating. The polymer foil [1] detaches from the bottom layer [3] by contracting and opens a channel [2]. Figure issued by the United States Patent and Trademark Office.

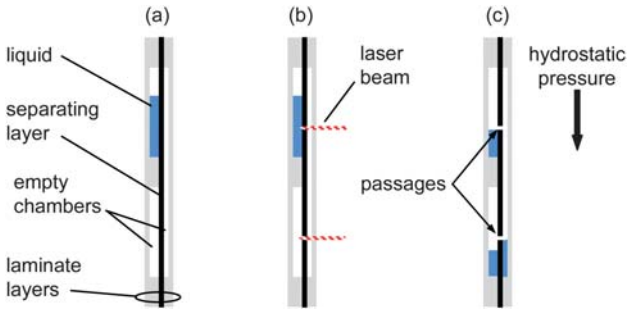

Fig. 14 Valving principle by perforating an intermediate polymer foil with a laser beam (figure adopted from ref. 129). (a) The polymer membrane separates the containers from each other. (b) A laser beam perforates the separating layer and generates a passage. (c) Liquid can flow from one container to the next by actuation of hydrostatic pressure.

layer thus establishing a passage from one container to the other one without affecting the remaining layers (Fig. 14). The fluids can be actuated by hydrostatic pressure that is for example induced by centrifugal forces.[129]

2.3.2 Inducing liquid flow. Lab-on-a-Chip implementations require means to induce liquid transport. In addition to well-established liquid transport methods such as capillary or centrifugally induced liquid transport, foils can enable fluid displacement due to their inherent flexibility when the foil is deformed by an external force. Recently, this principle was realised as a finger-actuated pump in an immunoassay cassette.[27] A foil is bonded on a rigid substrate and gets plastically deformed by a rigid ball at room temperature (Fig. 15). The pouch is then

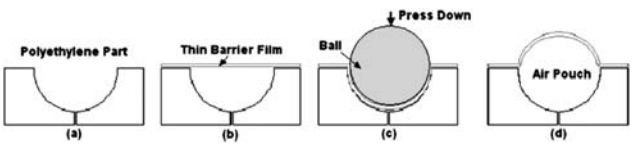

Fig. 15 The fabrication process for a pouch: (a) milling the pouch cavity; (b) bonding a thin film to the surface of the polyethylene; (c) deforming the thin film with a rigid ball; and (d) inflating the pouch with back pressure. Figure and caption[27] with kind permission of Springer Science + Business Media.

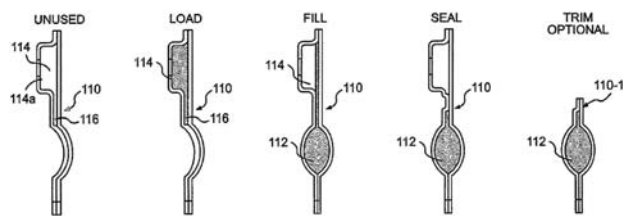

Fig. 16 Drawing of a patent application as disclosed by the company Applied Biosystems.[124] A reservoir [114] is loaded with a liquid by a fill port [114a]. Application of vacuum on the outside of the chip (below marker [116] leads to expansion of the lower chamber [112] and thus creates a vacuum inside [112] resulting in a pressure drop between [112] and [114]. The liquid is sucked through the channel [116] into the chamber. Finally, the lower portion can be sealed and trimmed. Figure issued by the United States Patent and Trademark Office.

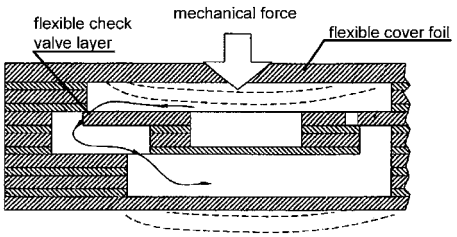

Fig. 17 Manually actuated pump with check valve in a multilayer assembly.[26] Volume is displaced by a mechanical force on the flexible cover foil. The check valve layer bends downward and opens a passage. Back flow is disabled by the laminate valve seats. Figure modified—originally issued by the United States Patent and Trademark Office.

inflated by a back pressure that is applied inside the cavity. By manual pressing on that pouch, the liquid content is transported in the chip. This is a single-use system only as the pouch does not spring back after pressing. Therefore one strike must be sufficient for fluid actuation.

A similar actuation principle for foil cartridges was disclosed in a patent application comprising suction forces.[124] An initially concave chamber wall is switched to a convex position by an external suction force on the cartridge (Fig. 16). The expanding chamber volume creates a pressure drop in the chamber that draws a sample liquid from an inlet chamber into the newly created reaction chamber. Although this application has not become a commercial product yet, it was explicitly designed for reel-to-reel production.

Another patent publication describes how foil-based multi-layer assemblies can integrate manually actuated pumping functions.[26] A flexible foil layer is deformed and thus displaces the liquid (Fig. 17). The flexible layer can move back due to a venting system. Back flow of the liquid can be avoided by integration of a foil-based check valve in the multilayer assembly.

The company Bartels Mikrotechnik GmbH (Dortmund, Germany) offers micropumps whose working principle is based on the flexibility of foils.[130] Piezo-electric actuators deform foils made of polyphenylsulfone (PPSU) that are assembled in an injection moulded case. The deformation leads to a displacement and hence a liquid propulsion. PPSU was chosen as material as it features a very high tensile strength and allows performance of several hundred strokes per second. The beneficial features of the construction is its simple assembly[130] and its capability to use cost-efficient methods like laser welding for fabrication.

2.4 Assembly and full system integration

Full system integration comprises assembly of all relevant units of the chip. There is a broad range of additional elements available, for example electronic features, surface modifications and reagent pre-storage. Apart from that, some techniques for assembly are required, for instance sealing or arrangement in multilayer devices. All units are integrated at different levels of assembly which can be referred to as a packaging hierarchy[51] as known from electronics. Eventually, the complexity of assembly determines later costs, particularly for disposable products. The quality of packaging also influences the shelf-life of a device.[131] Relevant aspects and techniques for assembly and full system integration are discussed in the following sections.

2.4.1 Electronic features. Flexible substrates like foils play a significant role in electronic engineering where they are for example applied in digital cameras or print heads. The main reasons for their application is their ability to be folded into a small three-dimensional installation space and their capability to reduce production costs.[132] More complex, self-contained units can be referred to as System-on-Foil[133] that for example feature polymeric organic light emitting devices (OLEDs), radio frequency identification devices (RFIDs) or sensors.[134]

The technology of flexible printed circuits is also occasionally applied in microfluidics: heating elements were integrated in a chip for performance of PCR[135] by simple adhesive lamination. The main motivation for this study was to examine ways of cost reduction by avoiding expensive materials and fabrication processes associated with silicon/glass. A different report provides perspectives on integration of sensors and opto-electronics by co-extrusion and subsequent lamination of foils.[83] Some other concepts aim at "smart blister packs" for monitoring patient compliance with drug intake. Breakage of the pharmaceutical blister packages can be detected *via* integrated sensor strips.[136] This concept could also support fail-safe operation of microfluidic chips.

However, integration of such additional electronic elements to enhance functionality of Lab-on-a-Foil systems is not very far yet. But this development is likely to benefit from reel-to-reel production as well as from the associated low-cost aspects.

2.4.2 Surface modifications. When specific surface properties are required, surfaces can be modified. Adaptation of wettability[137–139] can enhance or restrict capillary liquid transport. Surface modifications can improve cohesion[140–142] for effective sealing of microfluidic chips. Finally, implementation of biological functions[143–147] is a broad topic. Surfaces are modified for both improving or preventing adhesion of biological molecules on chip surfaces.

Two different modification approaches can be discriminated: local modifications[56,148] that allow selectively changing properties of a chip surface, and global modifications[149] that change the surface properties of the entire chip. Methods of surface modifications are plasma treatment,[150] UV irradiation[151] or laser sources.[152] All these methods have in common that they insert functional groups into the substrate surface thus allowing functionalisation in basically all of the above mentioned applications. Further common methods also include dip coating and local wet deposition.

It is most preferable to get along with as few surface modifications as possible because they increase fabrication complexity and are rather delicate to automate at a later stage. The aspect of reliability of surface modifications that aim at wetting or biological functions may be underestimated during development. But this gets increasingly important as soon as a microfluidic chip is supposed to work properly especially after some months of storage.

2.4.3 Bonding and sealing issues. Microfluidic structures must be sealed to form hollow embodiments. Therefore, bonding of at least two parts is a key factor for almost all microfluidic devices and has been discussed and reviewed frequently.[49,153,154]

Since most foil materials are thermoplastic polymers, the following section focuses on this material group. The available bonding techniques include bonding by temperature,[55,56,141,155–157] solvents,[86,158–165] laser,[55,166–170] microwaves[171–175] and ultrasound.[176,177] Some of these methods are particularly enabled by surface modifications of oxygen plasma[141,155] or UV-ozone pretreatment.[140,142] Apart from these direct bonding methods, adhesives are used for indirect bonding of two surfaces.[178,179]

The choice of bonding technique depends strongly on the specification of the intended application. Certain aspects must be considered, for example bond strengths, feature sizes, thermal restrictions, assay compatibility, transparency, accepted costs and the need for selective (local) bonding.

Thermal bonding is realised by controlling a temperature and pressure regime usually with a laminator or a hot press. Though hot lamination is state of the art to bond dry resist films,[93] deflection of the laminated layers can occur due to the applied line forces. Especially when thermoformed blister cartridges are sealed, a suitable substrate holder must be designed to avoid collapsing of the thin blister walls. However, this does not apply to multilayer laminates. Apart from that, the same principles for thermal bonding apply to foils as to any other rigid substrate: Bond temperatures are usually close to glass transition temperature of the polymer but can be lowered by oxygen plasma pretreatment due to an increased number of hydrogen bonding sites.[158,180,181]

A different approach is to spincoat polymers with low molecular weight and thus low glass transition temperature onto the joint surface to bond at lowered temperatures. This can avoid channel deformation as only the material with the lower softening point melts.[55,56,182] In the case of foils, such low melting layers can easily be co-extruded with high melting layers. If temperature-sensitive reagents are pre-stored, compatibility of the bonding technique must be investigated. Recently, it was shown that sufficient monoclonal antibodies and cellular adhesion proteins withstand heat treatment up to 163 °C for 30 seconds.[116] Nevertheless, the degradation of biological reagents is still a risk factor in individual cases.

Solvent bonding instead is accomplished at room temperature[165] or decreased temperature levels[163] which complies with reagent pre-storage. On the other hand, polymer solvents will very certainly affect pre-stored biological reagents. Furthermore, the chips are usually stored at elevated temperatures for several hours to accelerate solvent evaporation after bonding[163] but this can harm reagents as well. Achieved bond strengths for some materials can be higher than thermally bonded parts.[165] But temperature stability of the bonds significantly depends on complete evaporation of the solvents, since presence of solvents causes stress cracks and cloudiness.

Another interesting approach is laser welding[102] which can be used for bonding of contours, planes and at local spots. This is particularly interesting for applications with pre-stored reagents as the heat affected zone is very narrow in laser welding. But since welding happens at the abutting surfaces, one of the two layers must allow laser light transmittance while the other one absorbs the light and melts. Transparent materials can be equipped with absorbing additives like carbon particles[167] or semi-translucent absorbers like Clearweld® (Gentex Corp., Zeeland, USA) or Lumogen® IR (BASF AG, Ludwigshafen, Germany).[168,169] Such absorbers increase absorbance within the NIR range significantly, while transmission within UV and

visible bandwidth is hardly affected. In the case of Clearweld® the absorber even bleaches out during exposure to laser light at 800–1100 nm thus leaving behind a transparent polymeric material. Most polymers also show natural absorbance within the IR-spectrum which makes them weldable, for example by using IR fibre lasers without the need for additional absorbers. Compared to the intermediate absorber layer this approach can cause increased stress cracks.[170] Selective bonding by laser requires very precise alignment of substrate, lid foil and laser head. When foils are laser bonded, the depth of focus must be very precise.

Ultrasonic welding is a standard technique in polymer mass production but requires sufficient design of the assembly parts. Welding happens by interfacial friction that is realised by spiked energy directors and a suitable sonotrode.[183] Options for prototyping are limited due to the required specific design of the sonotrodes and the associated high fixed expenses. Nevertheless, ultrasonic welding using a standard ultrasonic cleaner as a universal sonotrode in combination with solvents has been reported.[176] Generally, ultrasonic welding suits best for mass production purposes with fluidic structures of low density and complexity.

Adhesive bonding is using an additional intermediate layer which joins the two bond partners. Especially if bond materials do not suit for direct bonding, they still can be linked by adhesives. Adhesives are usually based on chemical effects like polymerisation (*e.g.* acrylics), polycondensation (*e.g.* silicones) or polyaddition (*e.g.* epoxies) and can often be cured at room temperature, at elevated temperatures[184] or using UV light.[185] Beyond that, a broad variety of pressure sensitive or self-adhesive tapes is available but compatibility to the (bio)chemical reaction has to be tested individually in advance. Unspecific bonding of target molecules or interactions between adhesives and reaction fluids can inhibit the assay. In order to minimize the contact area at the interface between the adhesive and the fluid, undesired adhesives can be avoided by using contact printing,[178] or capillary bonding.[186] Techniques like roll to surface print transfer[179] could suit for integration in large production lines though it must be considered that some adhesives contain solvents which must have opportunity to evaporate residue-free.[179] But also thermal properties of adhesives need to be considered. Different thermal expansion rates and decreasing bond strengths at elevated temperatures can lead to undesired deflection of a thin foil substrate. This is critical for those applications that undergo higher temperatures as for example in PCR for nucleic acid analysis.

2.4.4 Multilayer assemblies. Multilayer cartridges allow for production of complex three-dimensional microfluidic channel geometries that are based on stacking of simple two-dimensionally structured layers.[51] The intermediate layers can be structured by techniques like laser machining, xurography or photolithography. Bonding is usually accomplished by thermal,[93] solvent[86] or adhesive methods.[105]

The advantages of such laminate-based assemblies are use of low-cost, disposable materials and their capability for rapid and flexible prototyping.[41] The microfluidic three-dimensional architectures strictly require appropriate alignment of each layer before bonding. This can be achieved by cutting alignment holes in each respective layer for assembly in a suitable registration frame[105] or by simple alignment pins.[113] Alignment tolerances in the range of 1 to 30 μm can be achieved.[41]

2.4.5 Reagent storage and secondary packaging aspects. Reagent pre-storage in a microfluidic chip can enhance operator convenience to a large extent as ideally only the individual sample to be analysed must be inserted into the chip. It further reduces the risk of operator failure and enables to reduce the complexity of base instruments. Reagents can be stored in dry[187] or liquid[188] form. Pre-storage of dry reagents is usually obtained by dehydrating a reagent-containing liquid on a surface or by loading a lyophilised bead. Both can be rehydrated when flushed by liquid which is usually the case when the chip is eventually in use.

Release of pre-stored liquid reagents can be realised by different mechanisms. Weak-bonded valves can be delaminated by centrifugal forces[126] or by compression of the respective chamber.[189] Another method is rupturing of glass ampoules[190] or polymer sacks[191] that contain liquid reagents. This is particularly enabled by the use of flexible foil cartridges.

Whenever reagents are pre-stored in a microfluidic cartridge, it must be ensured that the properties of the reagents may not be altered during shipment and storage:[192] contamination, evaporation, diffusion, outgassing, vapour absorption and certain biological reactions due to oxidation or heat (degradation, precipitation, ligation, Maillard reaction, *etc.*) must be

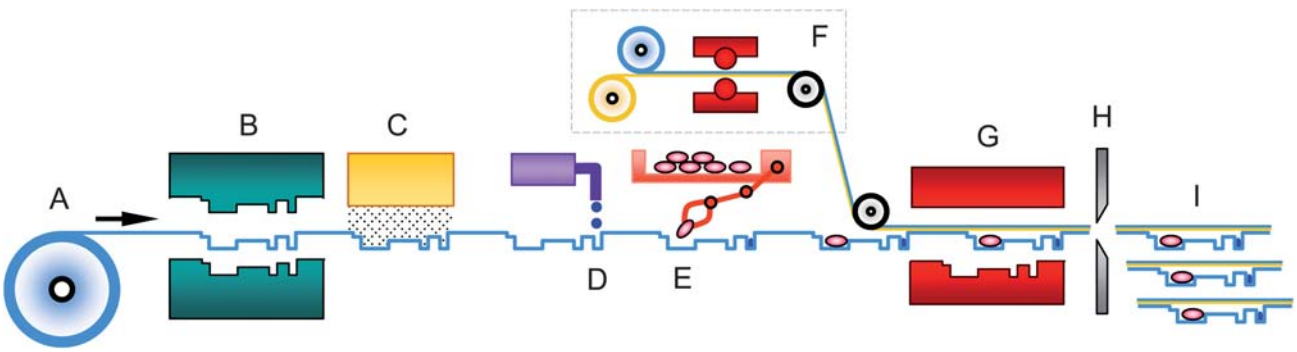

Fig. 18 Schematic of a reel-to-reel processing scenario: (A) rolled foil; (B) structuring; (C) surface modification; (D) liquid dispenser; (E) pick-and-place station; (F) lamination of multilayer sealing foil; (G) sealing; (H) cutting; (I) final product.

considered and prevented. Some elements might even demand a frozen or moist storage as for example integrated hydrogels or agar. Both liquid and dry pre-stored reagents must be encapsulated by materials with extremely low water vapour transmission rates which can be well achieved with aluminium foils. Conventional blister packaging allows an additional permeation barrier layer to be set up with metallised foils that can be pierced to access a liquid reservoir when required.[30,193,194]

2.4.6 Reel-to-reel production. With regard to the packaging industry which was mentioned in the introduction, a continuous reel-to-reel processing scenario (Fig. 18) could be very attractive for a high-volume production of Lab-on-a-Foil systems.[195] In this scenario, the polymer web is provided as rollstock and is continuously driven along stations of the production line.[192] After a structuring station (*e.g.* laser cutting, hot roller embossing, thermoforming, *etc.*), further important manufacturing steps like surface modifications, pre-storage of reagents or filling with extra parts (pick-and-place)[196] can be integrated. In-line sealing can be realised by continuous lamination or application of adhesive layers.[197] Finally, individual Lab-on-a-Foil cartridges could be trimmed, labelled and packed.[35]

3 Applications of Lab-on-a-Foil systems

Within the past years, various microfluidic applications for analysis or diagnostics have been reported which use foils either for fabrication benefits or due to unique foil properties such as enhanced thermocycling capability, flexibility or low mass. The applications are manifold and mainly found in the life science branch within different fields such as nucleic acid analysis, immunoassays, cell-based applications and home care testing. The following sections illustrate applications in these fields that benefit from foil technologies.

3.1 Nucleic acid analysis

PCR is the method of choice to amplify a specific genetic sequence for later detection. The target sequence is copied by enzymatic activity of a DNA-dependent polymerase in multiple thermal cycles. Each of the 30 to 40 thermal cycles comprises a denaturation step at approximately 95 °C for separation of DNA double strands and an extension step at approximately 50 °C for completion of single strands by the polymerase, respectively. In conventional thermocycling devices, one PCR cycle takes approximately 60 to 180 seconds.[198,199] This depends not only on the holding times but also on the duration for heating and cooling. Common heating rates[144,200] are 1 to 3 °C s^{-1} and very few enhanced systems offer 20 °C s^{-1}. Rapid temperature changes can be accomplished very efficiently when the microfluidic cartridges have a low thermal capacity and high thermal conductivity.[135] Particularly Lab-on-a-Chip systems with thin-walled reaction containers can benefit from fast heat transfer through thin material.

In 1993, a distinctive prototype cartridge for PCR[201,202] was demonstrated as a thermoplastic, self-contained blister cartridge with pre-storage of liquid reagents. Fluid transport was accomplished automatically *via* an external roller that sequentially pressed the liquids from one compartment to the next.[203]

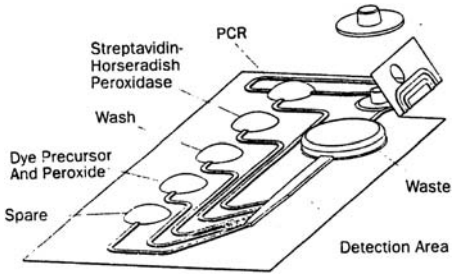

Fig. 19 Self-contained blister cartridge for PCR amplification and detection including pre-filled reagents.[202] The cartridge suits as a disposable. Figure reproduced with permission of the American Association for Clinical Chemistry, Inc.

The system features a thermoformed cartridge made of PE and PET foils with wall-thicknesses of approximately 100 μm (Fig. 19). One thermocycle took typically 60 seconds including dwell times, although PCR amplification with cycle times as fast as 22 seconds per cycle was possible, too. In total, samples of 64 patients were tested successfully for human immunodeficiency virus and a cytomegalovirus with very high sensitivity and specificity.

In 2002 researchers of Motorola Inc. presented an integrated laminate-based device made of PC for amplification of DNA and subsequent hybridisation (Fig. 20).[204] This approach benefited from the use of thermoplastic foils in terms of simple fabrication by multilayer lamination and through the achievable fast heat transfers. Cooling and heating for PCR were accomplished with a Peltier element, allowing for fast heating rates up to 7.9 °C s^{-1} and cooling rates up to 4.6 °C s^{-1} (amounting to approximately 95 seconds per thermocycle including dwell times). PCRs of both,

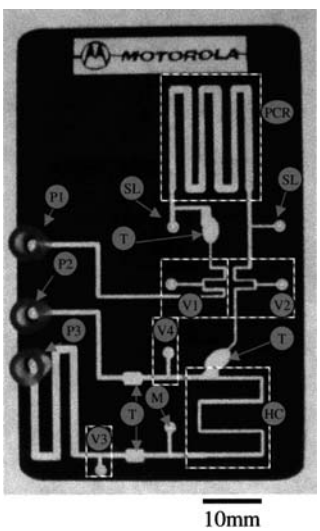

Fig. 20 Monolithic integrated DNA assay device. Serpentine PCR channel (PCR), hybridisation channel (HC), Pluronic valves (V1–V4), Pluronic traps (T), hydrophobic air-permeable membrane (M), PCR reagent loading holes (SL), sample driving syringe pump P1, waste-withdrawing syringe pump (P2), and wash syringe pump (P3). Figure and caption[204] reprinted with permission. Copyright 2002 by the American Chemical Society.

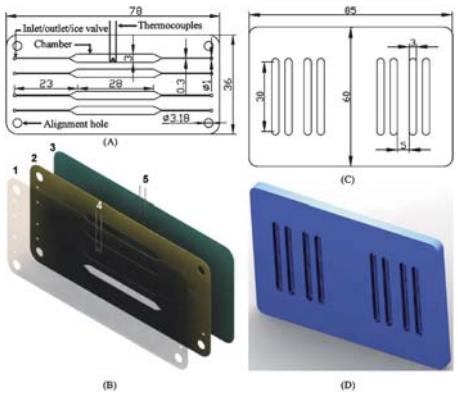

Fig. 21 Design of PCR card and top plate.[24] (A) Layout of PCR card with thermocouples. (B) Rendering of PCR card assembly: (1) PP film; (2) structured PC sheet; (3) Al foil; (4) thermocouple, top; (5) thermocouple, bottom. (C) Layout of top plate. (D) Rendering of top plate. Figures and caption reprinted with permission from Elsevier.

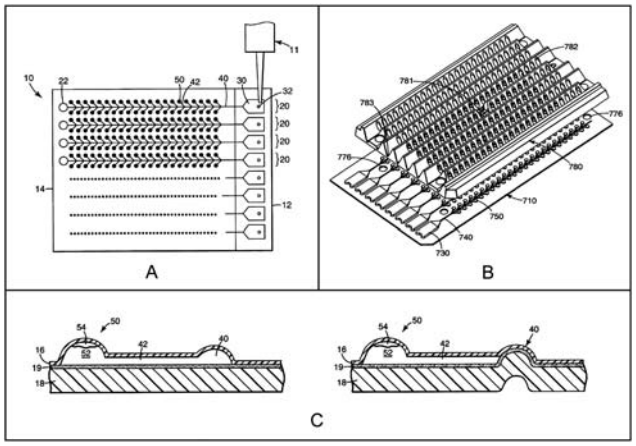

Fig. 22 Schematics of the TaqMan® Array Micro Fluidic card by Applied Biosystems.[187] (A) Overview of how a sample is applied to the cartridge. (B) Assembly of the card (below) in a carrier frame (above) that can be used for PCR and fluorescence readout. (C) Cross-section of a filling channel [40] and a dead end test cavity [50]. The cavities can be separated from each other by pressing the bottom foil into the channel foil by an indentation tool. Figures issued by the United States Patent and Trademark Office.

Escherichia coli and *Enterococcus faecalis*, and subsequent DNA hybridisation to an array were successfully performed.

It was reported that thermal contact between device, thermal coupler, and Peltier surface was difficult. Although oligonucleotide probes were immobilised and pre-stored on the substrate surface, liquid transport had to be done *via* syringe pumps which can be a drawback in terms of operator convenience concerning contamination free connection of tubes and associated dead volume.

In Madou's group, a rapid PCR was performed in a laminated chip made of PP, PC and a 40 μm thick aluminium foil which was facing a thermoelectric module.[24] The aluminium foil was a commercial microplate sealing foil and supported heat conduction due to its superior thermal conductivity (Fig. 21).

An end-point PCR of 10 copies of *E. coli* was successfully conducted. Due to the favourable design of the microfluidic chip and the self-made Peltier cycler, it was possible to perform thermocycles with heating and cooling rates of 10 °C s^{-1}. Amplification took only 27 minutes for 40 cycles (equivalent to 88 seconds per cycle, including dwell times).

In terms of diagnostic utility, the drawbacks of this development are that there are no microfluidic unit operations on the chip yet, and external pumps are required for fluid transport thus leading certainly to unwanted dead volume on the chip yet, and external pumps are required for fluid. Integration of a real-time readout for PCR would make this development even more valuable and could further decrease contamination issues which are related to handling of high copy DNA samples after PCR. However, the described study included a numerical simulation of thermocycling performance for thin-walled cartridges, pointing out their significant potential regarding fast time-to-results.

Another system in the format of a conventional microtiter plate allows fluorescence-based real-time PCR of up to 8 single samples that are aliquoted into 48 reaction wells each.[187] Each well contains specific primers and probes in order to detect various pre-determined genetic targets. The system was originally patented by the technology company 3M (St. Paul, USA) and is now marketed by the life science company Applied Biosystems Inc. (Foster City, USA) under the name TaqMan® Array Micro Fluidic Card. First, the card is filled with the sample liquid (Fig. 22A). Then the card is framed by a light carrier and subsequently centrifuged to fill the 384 reaction wells (Fig. 22B). Finally, the reaction wells are sealed by indenting the carrier foil against an opposing, adhesive sealing film (Fig. 22C).

The functions of the card particularly benefit from the use of a foil: the thin card material allows efficient thermal cycling. Its low mass decreases the risk of unbalance during centrifugation. And its flexibility allows indenting of the backing foil for partitioning of the reaction wells.

This straightforward commercial platform comprises reagent pre-storage, reduces pipetting demands and is implemented in the standard microtiter format.

In another approach by our group at the University of Freiburg, a real-time PCR was conducted in a circularly shaped foil disk (Fig. 23).[63] The microfluidic channel system is designed for fluidic unit operations like metering, mixing or aliquoting of

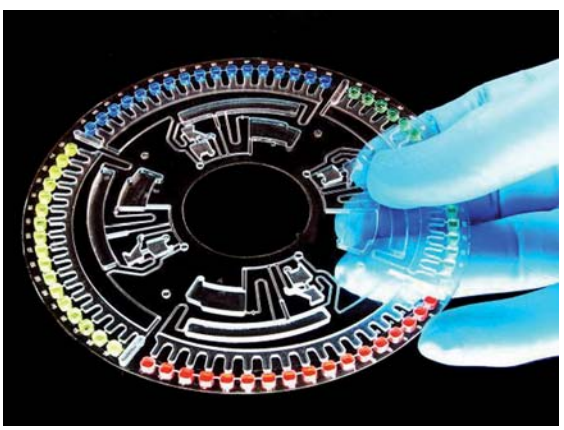

Fig. 23 Foil disk for real-time PCR on a centrifugal microfluidic platform.[63]

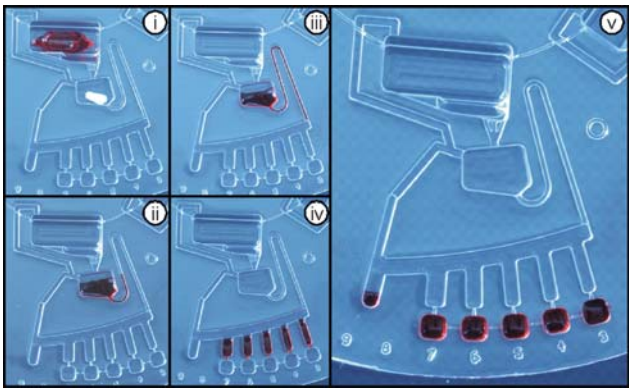

Fig. 24 Microfluidic processing scheme in a centrifugally actuated disk.[205] (i) The disk is ready to be processed. (ii) After the glass capillary is crushed the liquid is spun into the lyophilisate chamber. (iii) A capillary siphon allows valving between lyophilisate chamber and aliquoting structure. (iv) The 50 μL buffer volume is split into 5 × 10 μL aliquots. (v) The fluid fills the reaction chambers *via* a centrifugo-pneumatic valve. To achieve a higher quality of the photographs the buffer is coloured with red ink.

liquid samples that are controlled by the spinning frequency of the disk. The thin walls of the foil disk not only enhance effective thermocycling but also reduce its angular momentum of the disk. This results in an increased angular acceleration for more efficient fluid control during spinning.

The principle of this system was shown with real-time PCR of genes of the antibiotics resistant *Staphylococcus aureus* in a commercial thermocycling device (Rotor-Gene 2000, Corbett Research). The implementation of Lab-on-a-Foil cartridges into already available commercial devices can clearly accelerate their market access and penetration.

Recently, we presented implementation of a new isothermal nucleic acid amplification assay on the previously described Lab-on-a-Foil platform (Fig. 24).[205] Unlike PCR, the amplification of DNA was achieved by an isothermal protocol of the recombinase polymerase amplification (RPA) at a constant temperature of 37 °C.[206] Since no thermocycling is required, this approach does not particularly profit from efficient heat transfer. But it features the pre-storage of reagents in small glass containers in some of the blister chambers (Fig. 24i) that can be crushed by pressing without cracking the foil blister. These glass ampoules hold 55 μl of rehydration buffer that can be released from the respective foil chamber by gently pressing with a finger tip at the beginning of the assay.[190]

Euler forces due to rotational acceleration and deceleration allow sufficient mixing in the cartridge.[32,207] This crucial step is additionally supported by the low moment of inertia of the foil disk. The system proved feasible by demonstrating the detection of less than 10 copies of DNA per reaction well in a time-to-result below 15 minutes.

The company Douglas Scientific (Alexandria, USA) demonstrated a "reel-to-reel" application for performance of foil-based PCR. The so-called array tape is a patented system[208] for high throughput of PCR-based assays like single nucleotide polymorphism genotyping. The array tape contains microwells that are hot roller embossed. The continuous tape is fed from a reel and passes through different stations for liquid loading

Fig. 25 Instrument by Douglas Scientific for continuous reel-to-reel handling of array tape.[30] The wells can be loaded, dried and sealed prior to thermocycling. Figure reprinted with permission from Elsevier.

via pipetting robots, drying, sealing with an adhesive tape and end-point fluorescence readout (Fig. 25). Thermocycling is done by interchanging coiled-up array tapes between water baths of different temperatures.[30,209]

Although the use of array tape is not particularly a real microfluidic application, the advantages become obvious when looking at the potential for reduction of costs and time-to-result.[210] It is reported that use of a microarray tape allows applying down to a tenth of the reagent volumes that are usually required in microplates. It is said that continuous processing of the tape can increase throughput by a factor of five compared to conventional microplate handling. Especially laboratories that perform millions of assays per year can benefit from such technologies in terms of overall efficiency (reduced costs for materials, reagents and handling).

3.2 Immunoassays

Immunoassays are standard laboratory methods for detection of biomolecules, viruses and chemicals. The key elements in immunoassays are antibodies and antigens which are proteins that can specifically bind to each other just as key and lock. Either antibodies or antigens can be immobilised on a solid phase where they can bind with the respective target molecules in the

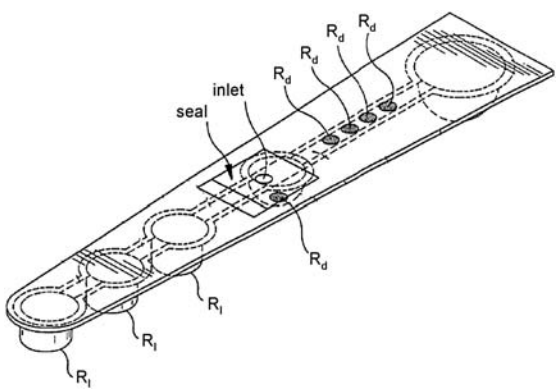

Fig. 26 Patent drawing of a foil-based cartridge as disclosed by the company Becton Dickinson.[211] The unit can be sealed by an adhesive seal after sample insertion through the inlet port. Three wells contain pre-filled liquid reagents R_l and are sequentially flushed through the sample chamber. Spots with dry reagents R_d provide assay monitoring. Figure modified and originally issued by the United States Patent and Trademark Office.

sample fluid. Usually, a labelling enzyme is involved as tracer molecule to indicate the event of binding. Theses markers can eventually be detected, for example by fluorescence, luminescence, colour change or radioactivity. Some immunoassays have been realised in foil-based Lab-on-a-Chip systems. The main reasons for using foils or laminates are due to advantages in fabrication. Immunoassays are widespread commercial tests and must be particularly cost-efficient.

In this regard, a disposable foil-based cartridge for immunoassays was disclosed by the company Becton Dickinson in 1997.[211] The material is a rigid PC film in the range of 200 to 300 μm thickness. The heat-sealed cartridge has five thermoformed wells that are all connected by one channel (Fig. 26).

These wells are aligned in a radial fashion so that liquids can be pumped from well to well by centrifugal actuation. Those three wells that are closest to the centre of rotation contain pre-filled liquid wash buffers that can be flushed sequentially through the adjacent sample chamber by increasing the rotational speed until a certain flow resistance is overcome.

The channel holds four chromogenic spots that change colour when a specific antibody target of the sample binds. All waste liquids are collected in a large waste chamber with a volume of approximately 500 μl. A colour change can be read out by the associated device.

This concept shows how simple a foil-based cartridge can be implemented. The advantages of this approach lie in its low material consumption thus resulting in a light cartridge. This facilitates centrifugal application by reducing the angular momentum. The thermoformed cartridge is a disposable and can be manufactured and pre-filled in large volume production. The circular alignment of several cartridges in the device also allows parallelisation of assays.

The so-called "microfluidic card" developed by Micronics Inc. (Redmond, USA) uses a laminate approach to perform immunoassays in blood type testing.[44] This is particularly vital prior to blood transfusions. The approach of applying laminates is straightforward and promises low production costs. This microfluidic card is disposable after use (Fig. 27), and liquid handling is performed by capillary forces and an integrated pumping bellows that does not require a separate instrument.[212]

Fig. 27 Disposable device for ABO blood typing developed by Micronics, Inc.[44] All fluids are moved and aliquoted through capillary force and manual on-card bellows pumping. Reagents and sample are mixed passively along laminar flow diffusion interfaces in microchannels. The result visible in the viewing window indicates blood type A, Rh positive. Figure and parts of caption reproduced by permission of The Royal Society of Chemistry.

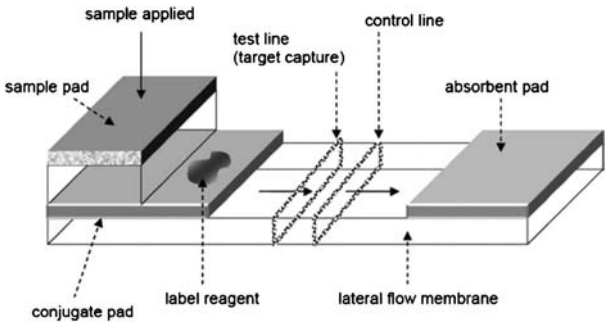

Fig. 28 Lateral flow tests are often constructed from a series of materials that sequentially overlap.[108] The goal is to imbed all reagents in a dried form so that a flowing sample rehydrates and moves all materials along the test strip. Analytes and reagents then interact in zones placed on the strip. The result is a rapid test that provides information easily visible to the eye. Figure and caption with kind permission of Springer Science and Business Media.

There are further blood group assays in paper-based card formats from other companies that have proven feasible in clinical environment.[213] Lateral flow assays,[214] however, do not require specific microfluidic handling. Typical examples for lateral flow assays comprise qualitative or semi-quantitative detection of mycotoxins in food and feed,[215] antigens of the hepatitis C virus[216] and antibodies of the human immunodeficiency virus.[217]

Although test strips contain only most elementary microfluidics, their simplicity, robustness and broad applicability are a prime example for all developers of micro total analysis systems (μTAS). Prototyping of test strips is relatively simple when the appropriate biochemistry is available.[108] Lateral flow assay strips typically comprehend different overlapping layers like a backing foil as carrier, a sample pad for sample uptake and a conjugate pad, in which biochemical reagents like antibodies and label agents are imbedded in dried form (Fig. 28). Often nitrocellulose is used as capillary flow matrix. The different layers are attached to each other by self-adhesive coatings.

3.3 Cell-based applications and sample preparation

Handling of cells becomes an increasingly important topic in Lab-on-a-Chip research.[218,219] Microfluidic technologies are used to cultivate, monitor, analyse or sort cells for various purposes: drug screening, tissue engineering and sample preparation for further analysis are just few examples. The importance of foils in this field of research is comparably small. Nevertheless, foils are used due to their thin walls and advantages in microfabrication.

One example of a foil-based application is tissue engineering which requires particular containers for cell cultivation. Feasibility to fabricate such scaffold systems in thermoplastic foils was demonstrated recently.[220,221] Thin and flexible cell containers for three-dimensional tissue growth are fabricated by thermoforming of afore modified polymer foils. The modification is carried out by heavy ion bombardment and subsequent etching of the ion traces resulting in defined micropores (Fig. 29). These allow for cell nutrient exchange in the scaffolds. As an additional feature multilayer substrates and electrodes can be structured by the same thermoforming process, the latter to enable electrical

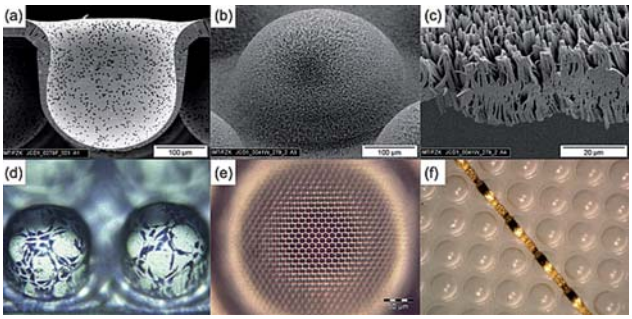

Fig. 29 Microthermoformed containers for cell culture:[62] (a) microporous cell container with pores (cross-sectional view); (b) highly porous microcontainer (back view); (c) part of the highly porous container wall (cross-sectional view); (d) microcontainers with fixed and crystal violet stained L929 cells (back view); (e) microcontainer with X-ray irradiated honeycomb mesh pattern; (f) microcontainers with crack-free conducting path from gold crossing (back view). Figure and parts of caption reproduced by permission of The Royal Society of Chemistry.

stimulation of cells. Various cell types such as embryonic stem cells could successfully be cultivated.[62,222]

In another application developed by Micronics Inc. (Redmond, USA), DNA purification was realised for sample preparation prior to nucleic acid analysis.[223] The laminate-based "lab card" requires an external pump system. Cells of a whole blood sample are first lysed in order to release nucleic acid from the cells. The solution is then flushed through an integrated silica membrane which binds the nucleic acid molecules. After a washing step for removal of contaminates like proteins or salts, an aqueous buffer elutes the bound nucleic acids from the silica membrane and is transported to a sample eluate chamber. Once in this chamber, the sample is ready for further processing. The lab card is a modular system that has interfaces to connect with other microfluidic subcircuits for further sample handling. A subsequent real-time PCR was conducted that showed a matching yield in comparison to reference kits.

The lab card assembly can also be used as microcytometer in a different configuration. Feasibility was shown by automated cell counting and sorting of rare cancer cells.[224] The advantages of the system are a considerably high sensitivity and very fast handling. The particular strength of the laminate-based approach is its ability for modular interconnection between different layers and fabrication for prototyping or larger quantities with relatively low expenditures.

3.4 Home care and near patient testing

In general, analytical chemistry for home care and near patient testing usually employs biochemical reagents to detect the presence of specific target molecules. Common tests are examinations of glucose levels for diabetes management, certain pH-values or co-agulation characteristics of blood. Such tests are frequently performed with paper-based test strips exhibiting simple colour change reactions.

One application of a paper-based chromogenic test was introduced by the Whitesides group in 2008 suggesting to provide such test strips for a telemedicine approach.[225] The authors recognised that mobile telephones are widespread even in resource-poor settings while professional medical care is still quite rare. The simple test strip should be applied by the patient himself, photographed by the integrated camera of a mobile phone at hand and communicated to a suitable health care centre. The test result, a colour change, is interpreted there and a therapy is proposed to the patient in return. The applied assays allowed assessment of glucose and protein content in urine.[225] The assay implementation on a piece of paper also integrates multiplexing. Due to the paper laminate, it is a simple and low-cost approach and thus also applicable for developing countries. The described paper platform also works in difficult environments because dirt particles like dust or plant pollen do not inhibit functionality.[61]

Other test strips are laminate-based and contain electrodes.[226] The lamination assembly defines a capillary channel, in which the sample primes and an exact volume is metered. The arrangement of the electrodes allows detection of sufficiency of sample volume and eventually result generation. Especially test strips for blood glucose tests are widely used successfully.[227] The advantages of thin laminated foils are mainly due to their low-cost mass producibility with costs in the range of 5 to 15 cents per test.[226] With 6 billion assays sold in 2007, no microfluidic platform is used more frequently.

4 Conclusions and outlook

As described in the introduction, packaging of consumable goods is a way of enclosing valuable contents to make them available for the user in a functional way. Packaging provides protection for the content and can allow interaction with it. We pointed out that this concept, and more precisely foil-based approaches, can be applied very effectively to Lab-on-a-Chip systems.

There are various approaches to fabricate foil-based substrates allowing integration of beneficial functionalities. These include first of all efficient heat transfer due to thin walls as well as mechanical flexibility that can efficiently be used for liquid actuation or assembly purposes.

Fabrication of Lab-on-a-Foil systems ranges from prototyping to mass production scale. Multilayer assemblies enable rapid prototyping at relatively low machine expenditures as structuring of the laminate sheets can happen by laser cutting, xurography or the like. Upscaling towards mass fabrication is feasible and of manageable risk. When further dimensional downscaling is required, dry resist processes are available but require very accurate handling and sometimes costly clean room facilities.

When upscaling of fabrication capacities is a target, reel-to-reel processes with hot roller embossing are extremely in favour. A powerful alternative to that is thermoforming which is already widely used for large quantity, macroscale applications. The previously mentioned form-fill-seal lines (Fig. 18) can be an upscaling option for self-contained but cost-efficient products.

We assign those applications best chances for success that can be manufactured by continuous high-throughput fabrication processes and already contain all relevant reagents stored inside the cartridge. Generally, such systems would be disposables and must hence be extremely robust and fail-safe but do not necessarily need to have a microscale footprint since they must be easily manageable by the operator.[228] These demands imply

consideration of highly integrated packaging but also development of convenient user interfaces.

The integration of a striking (bio-)chemical application is also decisive and most challenging. Realisation of simple glucose or alcohol tests will not be sufficient for tapping a new market.[229] Great potential lies in highly parallel genotyping assays, isothermal amplification protocols and ultra-sensitive immunoassays with integrated sample preparation. Many of these functions and applications have already been shown in foil-based microfluidic systems.

However, if the mentioned features and functions are not of prior relevance for a target application, foil technologies have to compete with other processes that are based on rigid materials like silicon or glass. Furthermore, injection moulding is still one of the most capable technologies for polymer cartridges in terms of shaping and upscalability.[230] In the end, foil-based technologies and applications may not be the only solution for successful Lab-on-a-Chip systems. Nevertheless, they enrich the microfluidics toolbox with powerful and versatile additional features and functionalities. In most cases, several years will pass until the potential of foil technologies can be fully exploited but on that way the technology of packaging of consumable goods could be a valuable source of inspiration.

Acknowledgements

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