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CRITICAL REVIEW

Let there be chip—towards rapid prototyping of microfluidic devices: one-step manufacturing processes

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Microfluidics is an evolving scientific field with immense commercial potential: analytical applications, such as biochemical assay development, biochemical analysis and biosensors as well as chemical synthesis applications essentially require microfluidics for sample handling, treatment or readout. A number of techniques are available to create microfluidic structures today. On industrial scale replication techniques such as injection molding are the gold standard whereas academic research mostly focuses on replication by casting of soft elastomers such as polydimethylsiloxane (PDMS). Both of these techniques require the creation of a replication master thus creating the microfluidic structure only in the second process step—they can therefore be termed two-(or multi-)step manufacturing techniques. However, very often the number of pieces to be created of one specific microfluidic design is low, sometimes even as low as one. This raises the question if two-step manufacturing is an appropriate choice, particularly if short concept-to-chip times are required. In this case one-step manufacturing techniques that allow the direct creation of microfluidic structures from digital three-dimensional models are preferable. For these processes the number of parts per design is low (sometimes as low as one), but quick adaptation is possible by simply changing digital data. Suitable techniques include, among others, maskless or mask based stereolithography, fused deposition molding and 3D printing. This work intends to discuss the potential and application examples of such processes with a detailed view on applicable materials. It will also point out the advantages and the disadvantages of the respective technique. Furthermore this paper also includes a discussion about non-conventional manufacturing equipment and community projects that can be used in the production of microfluidic devices.

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Introduction

Microfluidics as a scientific field evolved from classical microstructure technology which has mainly been driven by the intensive work and progress that has been achieved in microelectronics. The classical term microelectromechanical system (MEMS) was defined in the 1980s for systems comprising electrically as well as mechanically actuated or interrogated components. The first MEMS systems of note have been presented in 1982 by Petersen *et al.*[1] and in 1984 by Chen *et al.*,[2] both of which described accelerometers. The most commonly used material in MEMS and semiconductor electronics is to this day still silicon and the processes used for the creation of the first microfluidic devices were photolithography and wet etching processes which had been used at this time in microelectronics for many years. The early development of microfluidics was heavily focused on three technologically quite different application fields:

- Inkjet printing which was mainly driven by IBM and presented by Bassous *et al.* in 1977.[3]
- Process and technology development on integrated circuits (IC) for which Tuckerman and Pease presented first work in 1981 in which they described a heat sink intended for very large scale ICs with microfluidic channels that could be purged with a coolant.[4]
- Analytical applications for which Terry *et al.* first presented work in 1979 describing an integrated gas chromatographic analyzer on two bonded silicon wafers with integrated monolithic microvalves and heat conductivity detection.[5]

As of today inkjet printing is the most relevant commercial application of microfluidics and has been industrially developed to commercial end user devices that are widely available. Microfluidic IC technology is a field with limited market relevance but is still being used for high performance ICs in niche applications. The analytical developments for microfluidics have experienced a major setback after the crucial work of Terry *et al.* and there was no noteworthy scientific continuation to the field until the year 1990 when Manz *et al.* put forward the concept of miniaturized total analysis systems (μTAS).[6] The term and the definition were already introduced by Widmer in 1983 in his seminal paper in which he predicted that "such sophisticated, integrated systems, characterized by their exchangeable modular set-up, will have widespread future applications in industry. They will be part of the analytical impact which is changing the face of the chemical and allied industries".[7] The fact that microfluidics has been and is still closely related to MEMS technology becomes obvious when studying review articles written in the early 1990s where MEMS technology was dominant in the creation of microfluidic devices (see, *e.g.*, the review by Gravesen *et al.* written in 1993[8]). Nowadays microfluidics is considered to be the key discipline for the development of laboratory large scale testing as well as home care diagnostic. The reason why the technology has not yet found the widespread applications for which it is doubtlessly suitable is difficult to find. This has been noted repetitively in the literature; see for example the recent comment by Whitesides.[9] An excellent series of articles has been published over the last two years by Becker who focused on commercialization aspects of microfluidic devices and tried to elaborate why there are still so few successfully commercialized microfluidic products. The series discusses the question whether or not there is one spectacular application for microfluidics (the so-called "killer application"),[10,11] the factors influencing the manufacturing cost and therefore the industrial manufacturability of a device,[12] the importance of intellectual property,[13] and the need (or the lack) for standardization.[14] It also includes a detailed discussion on the industrial requirements for a successful device commercialization.[15,16] However microfluidics promises such immense advantages (such as low sample volume consumption and fast chemical reactions due to short diffusion lengths, strictly laminar flow, *etc.*) that it is one of the most promising evolving technological fields.

Advantages of one-step manufacturing processes

This paper does not intend to give a complete introduction to the theory of microfluidics or the most commonly used microfluidic components. This has been done by others for the most important microfluidic structures such as microvalves,[17] micropumps,[18]

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mixers,[19] as well as the theory of microfluidic flow and fluid mechanics[20] and adjacent fields such as biosensors[21] or, in more specialized form, microfluidic immunosensors.[22] The intention of this article is to line out manufacturing techniques that are currently being used for the creation of microfluidic devices with a strong focus on processes that directly create an applicable microfluidic structure from 3D digital data. These techniques are intrinsically useful for the creation of prototypes as they allow fast and easy adjustment of the structure details and therefore a quick reassessment of a tested structure. These techniques (with few exceptions to the rule) have limited applications in the production in larger scale for which replication techniques are predominant. Technically relevant for a larger scale production of microfluidic devices have been and will most likely always be classical replication techniques such as hot embossing and injection molding. However, in small scale production (as, *e.g.*, in a laboratory environment) the quick and easy fabrication of microfluidic devices is an important aspect. As research progresses different variants of a microfluidic structure may need to be created in order to evaluate the influence of specific feature dimensions on the performance of the overall system. In this stage of the development it is important to decrease the time that is required for implementing a new version of a chip for testing (concept-to-chip). If this time is sufficiently low it becomes increasingly easy to adjust all the important geometrical parameters of a microfluidic structure for a successful functioning in the intended application. Compared to replication techniques (which require the creation of a replication tool), techniques that are able to create the structure directly without the need for an intermediate (such as a replication mold) have enormous advantages. These processes allow for true rapid prototyping, some of them with concept-to-chip intervals as short as a few hours. Such rapid prototyping techniques are the focus of this work. In the scope of this article these techniques shall be referred to as one-step manufacturing techniques, see the section "Term definition". Besides very short concept-to-chip cycles these techniques may offer the advantage of creating true three-dimensional structures directly with embedded channels and therefore may not require bonding techniques for channel sealing. There are a number of very good reviews in the literature that focus on the creation of microfluidic devices by means of classical replication manufacturing processes (see the section "Related work"). However, one-step manufacturing processes are discussed only briefly as additional techniques in a number of reviews. This review intends to give such an overview including all potential techniques that are being used and all the techniques that could potentially be used for the creation of microfluidic devices available in the scientific literature. Although focusing on one-step manufacturing processes we will, where appropriate, point out important process modifications that are not purely one-step techniques in order to provide the reader with information and sources for further reading.

Related work

There are a number of reviews available in the scientific literature that discuss the creation of microfluidic devices with emphasis on aspects such as polymer replication or silicon machining. Verpoorte and de Rooij have not only given an extensive review of current trends and manufacturing techniques in 2003 focusing on classical materials (such as glass and silicon) but also discussed polymers and replication techniques as well as detectors, pumps, valves and similar functional components.[23] Their work does not include one-step manufacturing techniques though.

Abgrall and Gué have provided an extensive review about manufacturing techniques for microfluidic devices focusing on classical materials as well as polymers with a strong focus on the system and peripheral integration. One-step manufacturing techniques are only mentioned in their work but not discussed.[24]

Becker and Gärtner have provided two reviews in 2000[25] and 2008[26] discussing manufacturing techniques for polymer microfluidic devices but focusing on two-step manufacturing techniques such as hot embossing and injection molding. One-step techniques are only briefly discussed in both articles. A similar article has been provided by Becker and Locascio in 2002.[27]

The main focus of this work is the discussion of one-step manufacturing techniques which we found to not be adequately addressed so far by the scientific literature.

Term definition

A couple of defined terms shall be fixed at the beginning of this article in order to clarify the vocabulary used. Within this work a *manufacturing process* is defined as a process that creates a solid physical structure with defined shape and features. A manufacturing process may consist of a number of individual *process steps*. Such steps may include the preparation of a substrate (such as cleaning, mounting to machine, resist application, *etc.*), the actual processing (such as resist exposure during lithography) as well as post-processing (such as removal of expose, cleaning of the processed substrate, *etc.*). A manufacturing process is not disqualified as being a one-step process if it requires more than one process step. One-step relates to the number of transitions that have to be made in order to end up with the usable microfluidic structure. In one-step manufacturing techniques, there is only one transition: from digital data to the finished structure. If this structure can directly be used for a microfluidic application, the manufacturing process used to create the structure is classified as *one-step manufacturing process*. In most cases structures created in a one-step manufacturing process would need to undergo further treatment in order to clean them or to perform application relevant surface treatment processes such as chemical or physical surface modification. Very often microfluidic channels will need to be sealed because the manufacturing process creates an open structure or fluidic interconnections would need to be applied in order to interface the structure with a peripheral system. All of these steps are required in order to obtain a fully functional microfluidic system, however, for the term definition they shall be excluded as this article intends to highlight the manufacturing process of the chip itself not the overall process chain for the respective applications.

In contrast to one-step manufacturing processes, *two-step manufacturing processes* would include all techniques that do not produce the microfluidic structure in one manufacturing step but in two. They therefore require two transitions: from digital data to a primary structure and a second transition from this primary structure to the final microfluidic structure. A good illustration is

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classical polymer replication. In this process a master template is created first from which the later to be used microfluidic structure is replicated. The actual microfluidic structure is therefore created by the second manufacturing process therefore classifying the technique as a two-step manufacturing process. Commonly used techniques that are classical two-step manufacturing processes are injection molding, hot embossing and casting (typically from the elastomer polydimethylsiloxane, PDMS). As a third category, all techniques that use more than two manufacturing processes shall be classified as *multi-step manufacturing processes*. A typical multi-step manufacturing process would be a replication process that uses a lost form. These processes are typically used when a microfluidic structure can be produced with intended physical and feature dimensions but not in the correct material. If, for example, a structure is first created in wax this form can be used to create a molding tool from which the real microfluidic structure is to be created. This process would require three individual manufacturing steps therefore classifying the process as a multi-step technique.

When discussing the dimensional orientation of the object to be created in a manufacturing process a couple of physical orientation definitions shall be introduced (refer to Fig. 1).

The *x*/*y*-plane is commonly referred to as the plane parallel to the substrate on which the microfluidic structure is to be created. Typically such substrates include (but are not limited to) planar sheets of polymers, metals, or ceramics (including silicon). Within this work, the *dimensionality* of a structure is defined as follows: a two-dimensional structure is a structure that is arbitrary in form within the *x*/*y*-plane (but adapted to the application of interest). The height of such a structure is either not physically present (as in case, *e.g.*, of the structure being a projected pattern of light having no physical height and therefore no third dimension) or of no importance (as in case, *e.g.* for a lithographic mask where the physical height of the structure is of course present but has, if kept within reasonable boundaries, no effects on the function of the structure). A *2.5-dimensional structure* is a structure with arbitrary (but again application dependent) structure in the *x*/*y*-plane and a defined physical height. The structure therefore has a top and a bottom plane both of which have identical two-dimensional shapes. For any point on the bottom plane, a corresponding point on the top plane can be found that may be translated in the *x*- and/or *y*-direction and the vector connecting the two points would therefore be perpendicular to the *x*/*y*-plane (in the case of no relative translation between the top and the bottom plane) or under an angle χ (if translated in the *x*-direction) and/or an angle ψ (if translated in the *y*-direction). This vector could be split in a translational component and a normal component to the *x*/*y*-plane, the latter would correspond to the physical height. Such structures can be created, *e.g.*, by means of lithographic methods which would create a nontranslated 2.5-dimensional structure if the lights incident vector is parallel the *z*-axis. A translated structure can be created by setting the incident vector of the light at the angles χ and ψ.

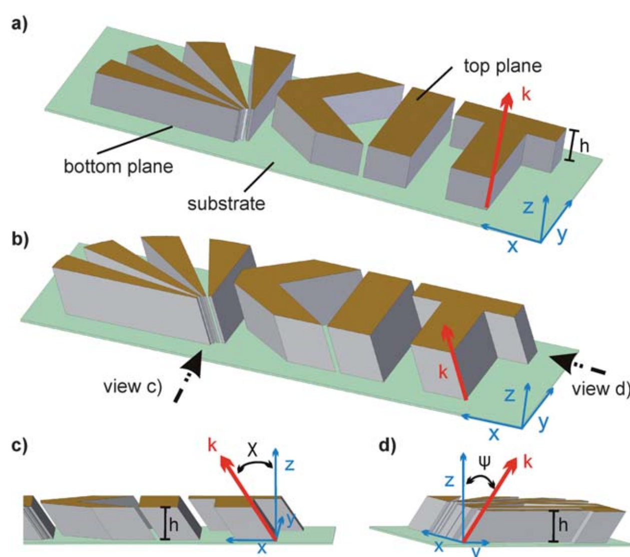

Fig. 1 Three-dimensional view of a structure with and without translation of the top plane with respect to the bottom plane. (a) A structure is created, *e.g.*, by means of lithography on a substrate. The bottom plane of the structure is identical with the top plane of the substrate on which the structure is created; the vector *k* is parallel to the *z*-axis of the chosen coordinate system of the structure. The top plane is parallel to the bottom plane, spaced by the effective height *h* of the structure. (b) Translated structure created, *e.g.*, by means of an exposure under the two angles χ, ψ as denoted in (c) and (d) respectively.

When talking about three-dimensional structures in the scope of this work a distinction needs to be made (refer to Fig. 2). In technical terms a *(technical) three-dimensional object* may be referred to as an object that is stacked from a finite number of 2.5 dimensional layers resulting in a quasi-three-dimensional shape. As most techniques rely on the stacking of such layers this is a commonly found configuration. A *converging three-dimensional object* is an object that gradually reduces its size along a direction (usually the *z*-axis). Such objects are sometimes referred to as being conical. If undercuts are present on the object it is referred to as *non-converging three-dimensional object*. Non-converging objects are typically critical for two-step manufacturing processes such as replication techniques because the mold needs to be split along a symmetry axis in order to release the part. If no symmetry axis is present on the object it cannot be released without mold destruction. One-step manufacturing processes usually do not distinct between these two cases. A *truly three-dimensional object* shall be defined as an object that has arbitrary physical features and structures without a structure derived from stacked 2.5 dimensional layers. There is only a very limited amount of manufacturing techniques that is able to create such objects though.

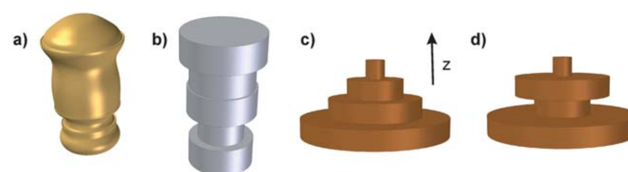

Fig. 2 Terms used in this work to describe dimensionality. (a) A truly three-dimensional object with arbitrary shaping in all dimensions. (b) The structure of (a) interpreted as a (technical) three-dimensional object. The object is assembled from 2.5-dimensional planes that are stacked. (c) Converging three-dimensional object. The object gradually reduces its lateral size along the *z*-axis. (d) Non-converging three-dimensional object. The object does not gradually reduce its lateral size in the direction of the *z*-axis—it features undercuts.

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Materials

Manufacturing strategies are in general inherently linked to the processable materials. There is no simple answer to questions such as "Which material is best?" or "Which material should be used when dealing with cells/protein solutions/*etc.*?" These questions have to be answered while carefully considering the application scenarios as well as the chemicals involved in treating the analyte sample or the microfluidic devices surface. The following section intends to highlight those materials most relevant to microfluidic applications and the techniques discussed in this work. It shall be noted that such a compilation always lacks some materials which may be used only for specific niche applications and have not gained substantial scientific or industrial relevance yet. The most commonly used materials for microfluidic device manufacturing are summarized in Table 1.

Metals

Metals are commonly used materials in microsystem technology. They are used as absorber material on lithography masks (chromium, gold) or as materials for electroplating (gold, copper and nickel) or molding tools for polymer replication. Some of these materials are relevant for microfluidic applications but rarely as materials for the microfluidic chip itself. Gold is an important material for electrodes which are required, *e.g.*, for electrochemical detection such as impedance spectroscopy[28] or surface acoustic waves.[29] However, very few microfluidic chips are created in metals. As microfluidics currently focuses heavily on biochemical, biomedical and biological applications materials are required to exhibit high biocompatibility which is a problem for most conveniently machinable metals (such as chromium or copper). Noble metals (such as gold or platinum) are in principle suitable for these types of applications but disadvantages such as high costs or the lack of optical transparency prevail. However, the literature features some exceptions including work by Salk *et al.*[30] who used a sintered metal microfluidic component as a photoreactor for water purification. Metals remain important materials for special types of fluids and gases, such as plasma in microfluidic channels.[31] The study of the dynamics of microfluidic plasmas and flames inside microfluidic channels has recently been discussed as one of the future fields of research.[32] Another very important field of research where metal (notably stainless steel) microreactors are widely used is flash chemistry which relies on very fast chemical reactions by precisely controlling the heat flux in and out of the reaction. Such prerequisites have (and probably will always) been matched best by metals. Application examples include organolithium synthesis reactions as described by Nagaki *et al.*[33] or the synthesis of palladium nanoparticles as described by Torigoe *et al.*[34] Notable reviews about microreactors have been given by Ehrfeld *et al.*[35] as well as most recently by Frost and Mutton.[36] Classically metals are processed either by mechanical structuring, chemical etching, laser ablation or electrical discharge machining (EDM).

Glass and silicon

Silicon was the first material used for microfluidics.[5] This originates from microelectronics which historically is the parent field of microfluidics. Silicon as well as silicon dioxide and silicon nitride can generally be considered as being decently biocompatible[47] with silicon nitride and silicon oxide exhibiting reduced biofouling compared to untreated silicon which could indicate limits in the materials tendency to allow biological films to settle and proliferate.[48] Silicon is a conveniently machinable material in MEMS technology. Structurally it is typically machined by means of lithographic mask creation and subsequent etching. Etching has been used as a technique to structure crystals for centuries.[49] Silicon is typically etched isotropically by means of reagents such as aqueous solutions of hydrazine or potassium hydroxide (KOH). Anisotropic etching is usually performed by means of reactive ion etching (RIE). Most of the processes used for silicon machining have been textbook science for many years, but, *e.g.*, the work by Delapierre dating back to 1989 still describes the most important processes[50] adequately even today. Because most laboratories that have been focusing on MEMS technology in the past have silicon machining equipment available silicon is still a commonly used material for microfluidics but mostly for the creation of replication molds.

In 1991 Manz *et al.* already discussed the importance of glass alongside with silicon for analytical systems and microfluidics.[51] Glass is still a very important material for microreactors where high chemical as well as temperature resistance are of importance. However, it has to be noted that glass and silicon processing is usually carried out by means of etching *via* an applied mask (usually a polymer of an oxide coating) which makes these processes two-step manufacturing by definition. An exception to this is the use of photostructurable glass which is commercially available (*e.g.* Fotoform by Corning, USA or Foturan by Schott, Germany). Usually these substrates are doped amorphous lithium silicate glass substrates that contain silver ions that will recombine to form silver upon irradiation by the correct wavelength. By annealing the irradiated areas will turn to crystalline lithium metasilicate which can be etched at significant higher etching rates than the amorphous glass. This wet etching is a necessary post-processing step. Photostructurable glasses have been used to create microfluidic hollow three dimensional structures.[52]

Lacking gas permeability, both glass and silicon are not suitable for use in microfluidic systems for cell culturing. Due to their high stiffness these materials are also unsuitable for the creation of mechanically movable microfluidic structures as required for valves and pumps, although in the early years of microfluidics these components have been designed. In fact in their seminal paper in the late 1970s Terry *et al.* already fabricated such microfluidic valves[5] but it is easier and more convenient to use soft materials for these purposes.

Polymers

Since the beginning of the 1990s the choice of material has shifted away from the classical materials towards polymers. This correlates with the increasing demand for cheap and disposable microfluidic devices which are especially important in biomedical and clinical applications. Polymers are suitable materials for larger scale production as they do not necessarily require chemical structuring processes (such as etching) that involve hazardous substances such as HF. In industrial applications polymers are typically structured by means of replication technology,

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Table 1 Chemical compatibility and price of commonly used materials for microfluidic devices.[37–46] Compatibility is given as ranging from good compatibility (+) to medium (short time) compatibility (~) to noncompatible (–) with respect to the given solvent. Please note that for a number of the materials certain variants are available (such as for epoxy polymers or polyurethanes). The properties of individual materials can vary from the indicated values depending, *e.g.*, on the monomers used to create the material

	Solvents									
Material	Hydrocarbons, aliphatic[a]	Hydrocarbons, aromatic[b]	Halogenated hydrocarbons, aliphatic[g]	Mineral acids[c]	Organic acids[d]	Bases[e]	Organic solvents[f]	Plasma, UV irradiation	Swelling in water (mass %), long term exposure	Price
Classical materials										
Glass	+	+	+	+[i]	+	+	+	+	0	Medium
Silicon	+	+	+	+	+	–	~/+	–	0	Medium
Silicon dioxide[h]	+	+	+	+[i]	+	+	+	+	0	Medium
Duroplastic polymers (thermosets)										
Epoxy resins (SU-8)	+	+	~/–	+	~	+	+	–	High	High
TE	n/a	n/a	+	n/a	+	–	+	–	Medium	High
PU	~/+	~/+	–	~/+	–	~/+	–	–	0	Low
Parylene C[j]	+	+	+	+	+	+	+	~	0	High
Thermoplastic materials (thermoplasts)										
PMMA	+	–	–	~/+	~/+	–	–	+	2	Low
PC	~/–	~/–	–	~/+	~/–	–	–	–	0.4	Low
POM	+	+	~/–	~/+	~/+	+	+	–	0.2	Low
PS	–	–	–	~/+	+	+	–	–	0	Low
PSU	+	–	–	+	+	+	–	–	0.6	High
PEEK	+	+	–	~/+	~	+	+	~/+	0.5	High
PE[k]	+	~	~/+	+	+	+	+	–	0.1	Low
PVC	+	–	–	+	+	+	–	–	1.6	Low
PET	~	–	~	~	–	–	–	–	0.5	Low
COC	–	–	–	–	+	+	+	–	<0.1	Low
PP	+	~	–	+	+	+	+	+	0	Low
PTFE	+	+	+	+	+	+	+	+	0	High
Elastomers										
PDMS	–	–	–	~/+	~/+	~/–	–	–	Medium	Medium
PFPE	+	+	+	+	+	+	+	+	Low	High
FFKM	+	+	+	+	+	+	+	+	Small	High
FKM/FPM	+	+	+	+	+	~/+	–	+	Small	High
FEPM	+	+	–	+	+	+	~/+	+	Small	High

[a] *E.g.*, tetradecane. [b] *E.g.*, toluene, ethylbenzene, xylene. [c] Sulfuric acid, hydrochloric acid, nitric acid. [d] *E.g.* lactic acid, acetic acid, formic acid. [e] *E.g.*, potassium hydroxide, sodium hydroxide, calcium hydroxide. [f] *E.g.*, acetone, methyl acetate, ethyl acetate. [g] *E.g.*, trichloroethylene, perchloroethylene. [h] Usually as coating only. [i] Very high solubility in hydrofluoric acid (HF). [j] Details about other types of parylene can be found in the literature.[40] [k] High density (PEHD).

predominantly by injection molding. This process allows for high throughput and comparatively low cost production. A very important aspect to consider is the fact that injection molding is an established industrial process which simplifies commercialization. A distinct advantage of using polymers is the fact that materials with specific chemical and physical properties (such as optical transparency, chemical resistance, stiffness, critical surface tension, *etc.*) can be selected specifically for a target application. Replacing glass and silicon by polymers can be considered a major breakthrough in the development of microfluidics and was fundamental for applications in biology and biochemistry because glass and silicon are materials typically accessible to only those laboratories that have a history in classical MEMS processing. Very often though these labs will lack profound knowledge and experience in biology and chemistry which today are mandatory for conducting application specific research in microfluidics. Polymers can be replicated by processes as simple as thermal replication on a hot plate or by casting with two component materials that cure at room temperature. This convenient way of creating structures has opened up the microfluidic research field immensely and contributed to the high number and diversity of scientific publications in the last decade. Sources for further reading may include reviews about polymer microfluidic devices by Becker and Locascio[27] as well as Boone *et al.*,[53] the latter being an excellent introduction for all readers new to polymeric microfluidics.

Chemical classification of polymers

Polymers are made up of repetitive structural blocks, the so-called monomers. Very often the materials can be directly created from their respective monomer in a pure polyaddition reaction (without cleaving off a substance) by polycondensation (usually cleaving off small molecules such as water or alcohols). Polymers can be classified by the type of chemistry that is used for linking up the individual monomer blocks to form chains. The most commonly used monomer chemistries will be discussed in the following.

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Acrylates and vinyl polymers. Acrylates is the common term used to describe polymers that are created from monomers comprising a prop-2-enoyl (commonly referred to as acryloyl, acrylyl or acryl) group. This group contains a radically curable vinyl group (ethenyl group, *i.e.*, a group comprising a carbon–carbon double bond) which is why acrylic monomers can be referred to as derivatives of vinyl monomers. However, acrylates are technically easier to synthesize than pure vinyl polymers because the simplest acryloyl comprising substance, which is acrylic acid, is a widely used and industrially important synthesis educt. As this substance is readily available monomers are often synthesized by simply using acrylic acid or its methylated form, methacrylic acid. The technically most widely used acrylic acid is poly(methyl methacrylate) (PMMA). In contrast to that, vinyl chloride or similar vinyl modifications are toxic and difficult to handle. The simplest and technically widely used form of a vinyl polymer is polyvinyl chloride (PVC).

The carbon–carbon double bond of the vinyl group can be activated by means of a radical which turns the monomer into a radical thus allowing its interlinkage with the next monomer molecule in order to form polymer chains. The process is referred to as radical polymerization and described thoroughly in textbooks (see, *e.g.*, Braun for a good introduction to radical polymerization[54]). Polymerization is typically induced by means of photoinitiators or thermoinitiators. Commonly used photoinitiators include benzyl derivatives and visible light photoinitiators such as campheroquinone. Typical thermoinitiators are, among others, organic peroxides (such as dibenzoyl peroxide or dibutyl peroxide) and azo compounds (such as azobisisobutyronitrile or azobis(cyano pentanoic acid)). Detailed discussions about radical polymerization as well as initiators have been given, *e.g.*, by Matyjaszewski and Davis.[55]

The scientific literature features a large number of papers on acrylic based (co)polymers. Besides the creation of microfluidic channels the literature features a number of articles that describe the polymerization of acrylates inside microfluidic channels in order to create monodisperse particles.[56] Acrylates are very suitable polymers for surface modifications and the scientific literature lists a number of potential procedures based on chemical (*e.g.*, activation with nitric acid) and physical surface treatment (including plasma activation and corona discharge) techniques.[57] Reports about the synthesis of monomers by means of substances that include a second functional group besides a vinyl or acrylic group have been discussed in the literature. Liu *et al.* have described the synthesis of an acrylate monomer with an accessible epoxy group which allows for easy surface modification on the cured bulk polymer.[58] Priola *et al.* described the synthesis of a fluorinated polymer by means of coupling isocyanate ethyl methacrylate (a molecule that features a methacrylic and an isocyanate group) to a fluorinated alcohol.[59] Other important polymers are acrylic polymers of polyethylene glycol which are usually polymerized from the commercially available polyethylene glycol diacrylate (PEG-DA). This polymer is a hydrogel and swells extensively when in contact with water which makes it a potential candidate for cell culturing and tissue engineering. Multilayer microfluidic devices have been described with this material[60] as well as processes using PEG-DA as molding material.[61] An alternative hydrogel is crosslinked polyvinyl alcohol (PVA) which has been described in the literature for the creation of particles with defined size polymerized inside microfluidic channels[62] as well as being a suitable coating material for microfluidic devices.[63] PVA allows for a robust modification in order to alter the surface properties of the polymer which is described, among others, by Yu *et al.* who coupled PVA to PDMS.[64]

Vinyl and acrylate polymers are per se suitable negative resists for photolithography and their use in photopolymerization techniques has widely been discussed. Suitable precursors for processes such as stereolithography typically consist of modified acrylic oligomers, completed with photoinitiators as well as stabilizers and crosslinkers. The latter are usually used to increase the stiffness of the material and to increase the curing speed. Typical substance groups include diacrylates (such as butanediol diacrylate), triacrylates (such as trimethylolpropane propoxylate triacrylate) or pentaacrylates (such as dipentaerythritol pentaacrylate). The higher the amount of crosslinkers the higher the stiffness of the resulting acrylic polymers will typically be and the higher is their resistance to chemical decomposition due to the tight three-dimensional interlinkage of the polymer network. If crosslinking is low the polymers can usually be melted again which makes the material a thermoplast. Specific acrylic or vinyl monomers can be dissolved in a wide range of solvents including water when not crosslinked. Such water soluble polymers have been discussed, *e.g.*, by Liska *et al.* for potential applications in cell and tissue culturing.[65]

Epoxy resins. Epoxy based chemistry is an important process in the chemical synthesis of organic compounds. The technically most relevant epoxy polymers are typically synthesized from bisphenol A and epichlorohydrin for which synthesis protocols can be found in textbooks.[54] Epoxy groups can be crosslinked by a number of mechanisms which is the main reason why epoxy chemistry is a widely used tool for the creation of polymers. Compounds that add to the epoxy group include amines, amino acids as well as thiols all of which will trigger the curing of an epoxy monomer. Self-crosslinking can be achieved by adding small amounts of an acid or of amines.[54] Commercially available epoxy polymers include widely used two component glues and photoresists specifically engineered for photolithography. Among the latter the negative resist SU-8 has become the most commonly used material for the creation of microfluidic components. The resist was developed by IBM (USA)[66,67] and licensed and commercialized by MicroChem (USA). It is a monomer containing eight epoxy groups which was commercialized under the trade name EPON by Shell (USA) and patented in 1989. Crosslinking is achieved by means of adding substances such as triarylsulfonium salts (*e.g.*, triarylsulfonium hexafluoroantimonate) which undergo photolysis upon irradiation to form an acid that crosslinks the epoxy groups.[68] SU-8 has been used in microsystem technology for almost two decades as a high aspect ratio photoresist that allows flexible micro- and nanostructuring.[69] Besides classical photolithography the resist has found extensive use both for direct creation of microfluidic structures and for the creation of replication molds. Epoxy polymers are typically the materials of choice for prototyping techniques such as stereolithography. We have previously reported the use of the photocurable epoxy resin Accura 60 (3D systems, USA) for microfluidics.[70] Other materials used for

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biomedical applications include DSM Somos WaterShed XC 11122 (DSM Somos, USA) which is a resist with low water absorption especially designed for aqueous solutions.

Thiol–enes. Thiols, which are compounds with sulfur-hydrogen groups, undergo reactions with unsaturated hydrocarbons, most notably substances that feature carbon–carbon double or triple bonds. The reaction was first described by Posner in 1905.[71] The importance of the thiol–ene (TE) chemistry was investigated by Kade *et al.*[72] and Morgan *et al.*, the latter focusing on photocurable thiol–ene systems.[73] Uygun *et al.* presented detailed discussions about initiation mechanisms and properties of polymers created *via* thiol–ene systems.[74] A very good introduction to the history and the mechanisms of thiol–ene chemistry is given by Hoyle *et al.*[75]

Thiol–ene chemistry has become increasingly popular in microfluidics, *e.g.*, for the preparation of porous polymer beads[76] and as material for microfluidic devices in the form of the commercially available thiol–ene polymer Norland Optical Adhesive (NOA). NOA is a transparent UV curable photopolymer commercialized by Norland (USA) that has a wide optical transmission spectrum (ranging across the whole visible spectrum) with low attenuation and low auto fluorescence. The use in microfluidics has originally been suggested by Kim *et al.* who suggested this material for the fabrication of hydrophilic polymer components as oxygen plasma treatment renders NOA hydrophilic for a period of more than a month.[77] Further studies have highlighted the use of the material for microfluidics (see, *e.g.*, the work by Dupont *et al.*[78] or Arayanarakool *et al.*[79]). The chemical resistance of thiol–ene polymers depends largely on the monomers that are interlinked but one important aspect always to consider is the risk of having non-reacted thiol groups still accessible inside the microfluidic channel which could lead to unspecific interaction with target molecules.

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Polyurethanes. Polyurethanes (PUs) are another important class of polymers with high industrial relevance. The chemistry was discovered by Hahn and patented by Bayer in the early 1940s.[80] PU polymers are created by the reaction of an isocyanate group with an alcohol or a polyol. Polyurethanes have been described as suitable materials for the creation of microfluidic devices both as molds[81] and as structures.[82] As the reaction mechanism is very robust a number of polymers with tailored physical and chemical properties can be created from PU which makes the chemistry an important tool in the design of application specific polymers. Furthermore channel creation and sealing (both reversible and nonreversible) is easily achievable in PU components by means of partial curing.[82]

Siloxanes. Siloxanes are a class of polymers that feature an alternating silicon–oxygen polymer backbone. The chains are very elastic therefore rendering mostly elastomers. Among the siloxanes commonly used in microfluidics, polydimethylsiloxane (PDMS) has been of significant importance during the last two decades. Siloxanes tend to form helical structures and the side groups on the main chain (in the case of PDMS these are two methyl groups) shield the polymer main chain thus altering the properties of the overall polymer. Low critical surface tension, flexibility, chemical resistance and hydrophobicity are mainly due to the methyl groups as the main polymer backbone is polar in nature. Polysiloxanes are hybrid organic polymers and inorganic silicates and are typically created from chlorosilanes which are first hydrolyzed to silanols that then polycondensate to form the polymer backbone. If the silanes carry functional side groups these are incorporated as the polymer backbone's side chains. Commercial PDMS usually consists of the polymer matrix (often aromatic siloxanes) and a curing agent which triggers ring opening polymerization or comparable crosslinking. An alternative is the use of a mixture of SiH and vinylterminated polysiloxanes that can be cured (similar to thiol–ene) by means of a mixed catalyst (usually a platinum catalyst). Detailed discussions about the synthesis and characterization of siloxanes are found elsewhere.[54] PDMS is a very versatile material for the creation of microfluidic devices. The method of replicating PDMS against an existing solid master, commonly referred to as casting, was first described in 1993 by the Whitesides group originally as a method to create a polymer stamp for printing inks onto surfaces as selective patterning in chemical etching processes.[83] In one-step manufacturing processes PDMS is not a common material as the typically used curing mechanism relies on the mixing of a two component system and its subsequent hardening against a structured master. The scientific literature features work on the synthesis of UV curable PDMS copolymers which are usually synthesized starting from a PDMS diol which is subsequently modified by isocyanate chemistry to attach an acrylate either to the polymer main chain[84] or as a side group.[85] An alternative is the use of commercially available vinyl terminated polysiloxanes as demonstrated by Tsougeni *et al.*[86] As such materials can be used like a negative resist; they are suitable for one-step manufacturing, *e.g.*, by means of maskless lithography.

Physical classification of polymers

Besides the type of chemistry used for linking up the monomers to form the polymer chains, the physical classification usually subdivides polymers into three categories: duroplastic polymers, thermoplastic polymers and elastomers. This classification describes the extent to which a polymer can change its shape upon exposure to heat. If the individual polymer chains are not interlinked (not crosslinked), the polymer network can be broken by heating which will induce vibration in the polymer network and widening of the spaces between the individual chains. Such a material is a thermoplast. If the individual chains are elastic (as is the case in siloxanes) the polymer can be classified as being an elastomer. Usually these materials have glass transition temperatures well below room temperature. If the chains are interlinked (crosslinked) the network cannot be broken up by heating, thus rendering the material a thermoset. A typical example for a thermoplast is the curing of methyl methacrylic acid (MMA, the monomer of PMMA) to the polymer PMMA. The latter is a typical thermoplast. In a small amount of higher functional monomers (such as a di-, tri- or pentaacrylate) the polymer created is crosslinked and therefore a thermoset. This essentially applies for all crosslinking mechanisms (including epoxy or thiol–ene polymers).

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Duroplastic polymers (thermosets, duroplasts). This class of polymers is typically produced from a liquid polymer precursor or the respective polymer's monomer and undergoes a chemical crosslinking upon triggering of the polymerization. This crosslinking will result in a tight and stable three-dimensional network which is usually temperature stable. Crosslinking can be initiated chemically, *e.g.*, by mixing the monomer with a curing agent, or physically, usually by means of light or heat. In the latter two cases, the monomer or the polymer precursor is blended with a photoinitiator or thermoinitiator, respectively, that create free radicals upon initiation. Curing can either be controlled in order to create a specific shape (one-step manufacturing) or the material can be cured against a mold (two-step manufacturing).[87] Cured once, thermosets are usually temperature stable. Upon heating the material will eventually decompose but it will not melt as the glass transition temperatures are usually in the range of the materials' decomposition temperatures.

Negative photoresists are a typical example of thermosets. Resists are usually classified either as positive or negative resist which refers to an increase (in the case of a positive resist) or a decrease (in the case of a negative resist) of the materials' solubility in a designated solvent after exposure. Commonly used positive resists are S1800 (Microposit, USA) and the AZ resists series (Microchemicals, Germany). Among the negative resists the most frequently used material is SU-8 which is an epoxy based resin. Epoxy based monomers as well as acrylates or thiol–ene based monomers can be classified as negative resists too. Photoresists are usually engineered to result in very stiff and stable polymers which allow the creation of high aspect ration structures. This is usually obtained by creating a monomer with a high number of functional groups resulting in a high degree of crosslinking. As an example, the monomer of SU-8 is a molecule with eight crosslinkable epoxy groups.

Thermoplastic polymers (thermoplasts). Thermoplasts are the most commonly used materials in mass market production of polymer components. Compared to thermosets thermoplastic polymers are not crosslinked which allow the polymer chains to move inside the bulk especially at elevated temperatures. The characteristic temperature for processing is the glass transition temperature which marks the temperature above which a polymer is considered rubber-like and thus easily deformable. Depending on whether the polymer is amorphous or (semi-) crystalline this temperature range is larger (in the case of amorphous polymers) or smaller (in the case of crystalline or semi-crystalline polymers). Detailed introductions to the theory and the modeling of polymers for replication structuring can be found elsewhere.[88]

Replication is by far the most commonly used structuring technique for thermoplasts although direct mechanical structuring, laser ablation or plasma etching are potential methods as well. Scientifically relevant processes are hot embossing, injection molding, micro-thermoforming and injection compression molding all of which are two-step manufacturing techniques that are able to create converging three-dimensional structures. These processes have gained industrial relevance with hot embossing being the least favorable of these four processes due to the higher cycle times.

In hot embossing, a thin sheet of polymer is heated to its glass transition temperature and deformed by means of an equally heated (or slightly hotter) molding tool which is pushed into the substrate preferably under vacuum conditions. After a given time (typically in the range of several minutes) the molding tool and the substrate are allowed to cool and the molding tool is subsequently withdrawn leaving the substrate with the inverse shape. Hot embossing has significant importance in academia due to the comparably reduced demands with respect to equipment. Molding tools do not necessarily have to be created from metals. Processes using cast molds made from epoxy polymers or elastomers (such as PDMS) have been described using the whole range of machining equipment starting from state-of-the-art commercial hot embossing machines[89] to replicating on a laboratory hot plate.[90] Detailed discussions of the process and its application scope can be found elsewhere.[91]

Micro-thermoforming makes use of a thin polymer substrate which is heated above its glass transition temperature and deformed against a molding tool by means of pressurized air. Besides the mere processing of bare polymer substrates the process can also be used to create converging three-dimensional structures comprising metal electrodes.[92]

Injection molding (in MEMS commonly referred to as micro-injection molding) is the process of choice for large scale production. It involves heating a polymer in pellet or granular form by a heated extruder compressing the molten material into an evacuated form. After a short cooling cycle the part is ejected from the mold. The cycle times of this process are in the range of several seconds which makes it suitable for industrial scale manufacturing. Detailed reviews about micro-injection molding can be found elsewhere.[93]

Injection compression molding is a commonly used process for the creation of polymeric structures such as compact discs (CDs). The advantage of this process is the very low cycle time which is even smaller than the typical cycle time of injection molding. In this process preheated polymer is inserted into an open molding form being compressed and formed while the top layer of the form closes. After a very short cooling time the mold is opened and the part ejected. Examples for injection compression molding can be found elsewhere.[94]

The most important thermoplastic polymers for microfluidics are compared in Table 1. Thermoplasts are typically polymerized from their respective monomer:

- Poly(methyl methacrylate) (PMMA, which is the polymer of methyl methacrylate) which has been used for the creation of devices for on-chip electrophoresis[95] and for the separation of DNA.[96] PMMA exhibits very low auto fluorescence which makes the material especially suitable for optical applications.[97]
- Polycarbonate (PC, which is usually created by reaction of bisphenol A and phosgene) which has been used, among others, for the creation of microfluidic mixers[98] and devices for DNA amplification.[99]
- Polyoxymethylene (POM, which is polymerized from formaldehyde) which has been described as suitable material for microfluidic capillary electrophoresis.[100]
- Polystyrene (PS, which is the polymer of styrene) which has been used, among others, as substrate material for cell culture devices[101] and cell growth studies.[102]

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• Polysulfone (PSU, which is a copolymer of bisphenol A and bis(chlorophenyl)) which has been used for the encapsulation of droplets in microfluidic devices[103] and as material for filtration.[104]

• Polyetheretherketone (PEEK, which is created by step-growth polymerization of difluorobenzophenone and hydroquinone salts) which has been used for the creation of microfluidic networks for capillary electrophoresis[105] and fluidic preconcentration of analytes for mass spectroscopy.[106]

• Polyethylene (PE, which is the polymer of ethene) which has been used, among others, for the creation of devices for capillary zone electrophoresis.[107]

• Polyvinylchloride (PVC, which is the polymer of vinyl chloride) which has been used, among others, for the creation of microfluidic pumps[108] and for capillary electrophoresis devices.[109]

• Polyethylene terephthalate (PET, which is polymerized from its monomers terephthalic acid and ethylene glycol or its cyclic di (ethylene terephthalate)[110]) which has been used, among others, for the creation of microfluidic structures for capillary zone electrophoresis.[107]

• Cyclic olefin copolymer (COC, which is produced by copolymerization of cycloalkenes, such as norbornene, and alkenes, such as ethene), which has been used, among others, as material for microfluidic devices in liquid chromatography[111] and for blood typing.[112] COC, sometimes also referred to as cyclic olefin polymer (COP), is considered one of the most important future materials for microfluidics.[113]

• Polypropylene (PP, which is the polymer of propene) which has been used extensively as substrate material for optical biosensors in CD format[114] and is commonly used as a material for membranes on chip.[115]

Besides the classical thermoplastic materials fluorinated thermoplasts have gained increasing interest in recent years due to their high chemical resistance and their low surface tension. There is a wide range of commercially available fluorinated polymers which are typically created from a limited number of monomers or precursors such as tetrafluoroethylene (TFE), chlorotrifluoroethylene (CTFE), hexafluoropropylene (HFP), perfluorinated vinylethers (such as perfluorovinylmethylether PVME sometimes also abbreviated PMVE) and vinylidene fluoride (VDF). The most commonly used fluorinated polymers include:

• polytetrafluoroethylene (PTFE, which is the polymer of TFE),

• polychlorotrifluoroethylene (PCTFE, which is the polymer of CTFE),

• fluorinated ethylene propylene (FEP, which is a copolymer of TFE and HFP),

• perfluoroalkoxylalkane (PFA, which is a copolymer of TFE and PVME),

• ethylene tetrafluoroethylene (ETFE, which is a copolymer of TFE and ethylene),

• polyvinylidene fluoride (PVDF, which is the polymer of VDF) and

• ethylene chlorotrifluoroethylene (ECTFE, which is a copolymer of ethylene and CTFE).

Further material groups include polymers from a specifically engineered fluorinated monomer combined with different combinations of the indicated monomers TFE or PVME. The most prominent material from this group is Nafion by DuPont (USA) which is a sulfonated copolymer of TFE and a perfluorinated vinyl ether. This polymer is a very strong acidic solid state catalyst that allows the movement of cations but hinders the movements of electrons through the bulk.[116] Besides thermoplastic materials there is a number of fluorinated elastomers (see the section “Elastomers”). Fluorinated thermoplasts are commercially available and can typically be processed by classical replication technology only. One-step manufacturing with fluorinated polymers is extremely difficult due to their high chemical resistance. Laser processing is an option[117] as is etching *via* a focused ion beam[118] or mechanical structuring. Commercial fluorinated polymers used in microfluidics include Dyneon THV (3M, USA) which is a polymer consisting of TFE, HFP and VDF which has recently been described as a suitable material for the creation of microfluidic channels for droplet microfluidics.[90] Until now fluorinated thermoplasts are of limited use in microfluidics due to the fact that they require high temperature replication, often at temperatures as high as 300 °C which is only possible if adequate machining equipment is available.

Elastomers. Elastomers are polymers with glass transition temperatures typically well below the operating temperature. They are thus rubber-like and can be deformed without extensive pressure making them ideal material for active microfluidic components such as membrane based microvalves or micropumps. The most commonly used elastomer in microfluidics is PDMS, but other types of elastomers have been described for microfluidic as well, such as linear polyurethanes.[119] Recently, fluorinated elastomers have gained increasing interest in the community. These materials are soft synthetic rubber-like materials with very high chemical resistance. The principal monomers used to create these elastomers are usually classified by their overall fluorination ranging from nonfluorinated (mostly ethylene or propylene) to partially fluorinated (mostly VDF) to fully fluorinated (mostly TFE, HFP). Hence, elastomers containing a fully fluorinated backbone are typically denoted as perfluoroelastomers (FFKM/FFPM), elastomers with a partially fluorinated backbone are denoted with the abbreviations FKM/FPM. The most prevalent commercial polymer of this class is Viton by DuPont (USA) which is used as material for sealing elements and rings. Another member of this group are TFE/propylene rubbers (FEPM) which do not have significant commercial relevance today. Fluorinated elastomers exhibit a number of properties that make them excellent materials for microfluidics. They have very low critical surface tensions, high biocompatibility and outstanding chemical resistance. As most of these elastomers have glass transition temperatures well below room temperature they are soft and flexible which would make them suitable for the creation of deflectable channels, membranes and mechanical valves. However, these materials are typically only available in cured form with given geometries. The individual elastomer precursors are difficult to obtain commercially and efforts have been made recently to create such materials by custom synthesis. Most notable here is work by Priola *et al.*[59] who used a perfluorinated polyether (PFPE) diol which was modified by means of a methacrylate containing side group resulting in a photocurable fluorinated elastomer. This work has subsequently been expanded by Rolland *et al.* for the creation of

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microfluidic components[120] and soft lithography[121] as well as by Hannig *et al.* for droplet microfluidics.[46] Willis *et al.* have shown that membranes created from these materials can be used for valve membranes in devices manufactured from glass.[122] However these materials are still not used on a large scale because of the high price of the precursors especially compared to elastomers like PDMS. A detailed introduction to the chemistry and recent progress on fluorinated elastomers have been presented by Améduri *et al.*[45]

Classification of one-step manufacturing techniques

It seems convenient to apply a general classification scheme for potential one-step manufacturing processes. Within this work a classification is made depending on whether a technique creates a microfluidic structure by removing material (removing techniques) or by depositing material (depositing techniques). An overview of all techniques described and discussed in this work can be found in Table 2.

A technology being classified as material depositing usually involves the application of a certain amount of material at a given location. In order to do so, the material to be deposited needs to be in a form that allows transporting the material volume to an indicated location and turning it into a solid physical form at the given location. Material depositing techniques rely on the material being applicable for deposition. In the case of a polymer this can be achieved by either creating the polymer at the given location typically by locally confined polymerization of the precursor or by bringing the polymer into solution and applying the solution at the current location where the solvent evaporates thus leaving a solid voxel of material.

In contrast to material depositing techniques material removing techniques will create a structure by locally confined removal of material from a bulk. This is achieved, *e.g.*, by laser ablation or mechanical structuring as well as etching techniques. These methods typically do not require materials with specific properties (such as solubility in a given solvent) and are therefore more general in their application range. However, material removing techniques will always cause a loss of material due to the removal from a bulk substrate which may be critical for very expensive substrates.

Material removing techniques

Electrical discharge machining

Electrical discharge machining (EDM) was a process first suggested as a manufacturing technique by Lazarenko and Lazarenko in 1946.[123] In its simplest form it uses the sudden discharge between two differently charged conductive surfaces by means of a spark that creates localized heat zones in which the material melts and eventually evaporates. Besides conductive material EDM can also be used if the electrode (commonly referred to as the tool) is conductive and the part to be machined is nonconductive. The process can be used in ambient conditions but is typically performed within a dielectric fluid in order to guarantee even field distribution and constant dielectric conditions. High electric fields induce dielectric breakdown in this fluid which results in the formation of plasma channels that guide the spark.[124] EDM is suitable to process difficult to machine materials such as titanium or diamond[125] on the micrometre scale. Therefore this process is sometimes referred to as μEDM. In general, two types of EDM processes are used: sinker and wire EDM. Sinker EDM is a two-step manufacturing technique which essentially creates the complementary structure of a primary tool in a metal and is therefore a two-step manufacturing technique. In wire EDM a 2.5-dimensional shape will be cut from bulk material. Wire dimensions as small as 25 μm have been used to create structures such as nozzles and needles with holes as well as tip diameters in the range of 30 μm.[126] In microfluidics EDM is typically used to create molding tools for two-step manufacturing processes.[127] Still, EDM is important for microreactors which commonly require microfluidic structures made from chemically stable but difficult to machine substrates such as diamond, ceramics or catalyst materials.[128]

Laser direct machining

Since the presentation of the first ruby laser in 1960 by Maiman lasers have found applications in numerous fields in science, industry and everyday life.[129] Lasers are routinely used in industry for the creation of structures by means of direct machining. This process relies on the laser spot being scanned over the surface of a part to be processed. Laser machining is an ablation process which results from the absorption of laser photons by the material and thus an increase of the temperature and finally evaporation of the material. The absorption process is typically a multi-photon absorption which allows the ablation of materials which are transparent at the machining wavelength if the peak intensities are high enough. This has been exploited by Ke *et al.* for the creation of microfluidic channels with diameters below one micrometre and several micrometres length by means of a pulsed femtosecond laser in glass.[130] Glass is transparent at the chosen laser's wavelength but nonlinear higher order absorption processes (such as optical breakdown) within the material result in a significant amount of energy being taken up by the exposed voxel allowing very precise machining. The focusing of laser pulses (usually femtosecond lasers) allows the effective three-dimensional structuring of transparent materials such as glass, however, this technique is restricted to materials that are transparent at the laser's wavelength. It should also be noted that usually a post-processing is required after the laser processing, usually a wet-etching process to remove the processed sections of the material. For microfluidic prototyping lasers are typically used to directly machine polymer substrates such as PS or PC,[131] COC,[132] PEEK[133] as well as PET[134] and even PTFE.[135] In recent years excimer lasers have become widely available. Excimers (which is a composed word consisting of "excited" and "dimer") are instable complexes of two molecules which are repulsive in their electrical nonexcited state but will form a complex if at least one of the molecules is in the excited state. Usually noble gas complexes are required for such a process as in ground state these are chemically inert but will undergo dimer formation if excited. The decay of the complexes will result in the emission of light. The wavelength of excimer lasers is dependent on the gas used, *e.g.*, for ArF the wavelength is 193 nm and for XeCl it is 308 nm. Johnson *et al.* have used a UV excimer laser (KrF, 248 nm) to create microfluidic mixers in PC.[98] CO_2 lasers were described in 1964 by Patel and are thus

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Table 2 Comparative overview of the discussed one-step manufacturing techniques. Please refer to the respective section for further details about process properties and applications. Please note that the given values are estimations and may be different from sources found in the literature which may describe specific process variations that result in improved process performance for a certain application or with a certain material

	Process properties							Dimensionality					Miscellaneous	
Process	Lateral size	Resolution	Materials	Cost/ piece	Time/ piece	Channel bonding required	Scalability	2.5	Transl.	3 D	Non-converging	True 3D	Advantages	Disadvantages
Material removing techniques														
EDM	µm–cm	5 µm (sinker) 25 µm (wire)	Polymers, metals, ceramics, diamond	High	Short	Yes	Low	Yes	Yes	Yes	No	No	Wide range of materials	Electrode required (sinker EDM, two-step process), cost for wire (wire EDM)
Laser direct machining	µm–m	1 µm to several 100 µm	Polymers (PTFE), metals, ceramics	Low	Low	Yes[a]	Good	Yes	Yes	Yes	No[b]	No	Wide range of materials, embedded channel design possible if defocused laser spot is used	Serial process
Wet etching	µm–cm	Subµm–cm	Wet (metals, glass, silicon), dry (many substrates)	Low	Low	Yes	Good	Yes	No	Yes	Yes[c]	No	Scalable established industrial process	Harsh chemicals required, expensive machining equipment, masks required
Dry etching, plasma	µm–mm	Subµm–cm	Polymers, metals, glass, silicon, diamond	Low	Medium	Yes	Medium	Yes	No	Yes	No	No	Wide range of materials	Harsh chemicals required, expensive machining equipment
Dry etching, FIB	Subµm–mm	Subµm–cm	Polymers, metals, glass, silicon, diamond	High	High	Yes	Low	Yes	Yes	Yes	No	No	Wide range of materials, no mask required	Expensive machining equipment, serial process
Mechanical structuring	mm–cm	20 µm–cm	Polymers, metals, glass, ceramics (green state)	Medium	High	Yes	Low	Yes	No	No	No	No	Wide range of materials, widely available	Serial process, surface roughness, risk of tool fracture
Material depositing techniques														
Silicon surface micromachining	µm–cm	Subµm–cm	Silicon, silicon nitride, silicon oxide	Medium	Medium	Yes[c]	Good	Yes	No	Yes	Yes	No	Scalable established industrial process	Masks required, usually several repetitive processing steps required
Lithography[d] (mask based)	mm–cm	Subµm–cm	Photoresists, polymers	Low	Low	Yes	Good	Yes	Yes	No	No	No	Scalable established industrial process, wide range of resists available	High costs for the mask
Lithography[d] (maskless, serial)	mm–cm	Subµm–cm	Photoresists, polymers	Low	High	Yes	Good	Yes	Yes	No	No	No	Scalable established industrial process, wide range of resists available, no costs for the mask	
Lithography[d] (maskless	mm–cm	Subµm–cm	Photoresists, polymers	Low	Low	Yes	Good	Yes	Yes	No	No	No	No costs for the mask	Evolving process, equipment not yet widely available

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Table 2 (*Contd.*)

	Process properties							Dimensionality					Miscellaneous	
Process	Lateral size	Resolution	Materials	Cost/ piece	Time/ piece	Channel bonding required	Scalability	2.5	Transl.	3 D	Non-converging	True 3D	Advantages	Disadvantages
projection, parallel)														
Microfluidic tectonics[e]	mm–cm	µm–cm	Photoresists	Low	Low	Yes[f]	Good	Yes	Yes	No	No	No	Creation of devices consisting of several materials possible	
FPP[e]	mm–cm	µm–cm	Photoresists	Low	Low	Yes	Good	Yes	Yes	Yes	No	No	Converging 3D structures can be created in one manufacturing step	Limitations to achievable feature size and depths, strongly material dependant
Layer-to-layer manufacturing	mm–cm	µm–cm	Photoresists, tapes, ceramics, polymers	Medium	High	No	Medium	Yes	Yes	Yes	Yes	No	Arbitrary three-dimensional structures feasible	Depending on the substrates sacrificial materials may be required, processing time linearly dependant on number of layers, depending on material bonding processes required
(µ)STL	mm–cm	µm–cm	Photoresists, light curable monomers	Low	Medium	No	Low (scanner based), medium (projection based)	Yes	No	Yes	Yes	No	Wide choice of materials (almost any photoresist)	Low chemical and biochemical compatibility of the resists, limited choice of materials
Inkjet 3D printing	mm–cm	100 µm–cm	Wax, UV or thermally curable resins	Low	Medium	No	Medium	Yes	No	Yes	Yes	No	Arbitrary three-dimensional structures feasible	Restricted material selection, difficulty removing supportive structures especially from long channels
Powder 3D printing	mm–cm	100 µm–cm	Metals, polymers, ceramics, glass	Low	Medium	No	Medium	Yes	No	Yes	Yes	No	Wide choice of materials	Chemical and physical properties of glue dominate the properties of the constructed part, parts nontransparent, porosity, difficulty removing powder from inner channels
SLS	mm–dm	100 µm–cm	Metals, polymers	Low	Medium	No	Medium	Yes	No	Yes	Yes	No	No glue required, wide choice of materials	Parts non-transparent, porosity, difficulty removing powder from inner channels
FDM	mm–cm	Several 100 µm–cm	Polymers, metals, ceramics (in binder form)	Low	Medium	No	Medium	Yes	No	Yes	Yes	No	Wide choice of materials including all thermoplastic polymers	Very rough and potential porous surfaces, no straight channels possible
Direct writing	mm–cm	Several 100 µm–cm	Polymers, hydrogels	Medium	High	Yes[d]	Low	Yes	No	Difficult	Difficult	No	Easy to implement technique, if structures are used as inverse replication molds creation of complicated channel networks possible	Serial writing process, low chemical and mechanical resistance of structures, instability, channels hard to manufacture
2PP	µm–mm	nm–µm	Photoresists	High	High	No	Low	Yes	Yes	Yes	Yes	Yes	Nanometer resolution structures, smooth surfaces, truly three-dimensional	Serial writing process, large scale patterning difficult

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Table 2 (*Contd.*)

	Process properties							Dimensionality					Miscellaneous	
Process	Lateral size	Resolution	Materials	Cost/piece	Time/piece	Channel bonding required	Scalability	2.5	Transl.	3 D	Non-converging	True 3D	Advantages	Disadvantages
2.5-Dimensional printing	mm–m	100 µm–cm	Polymers, toner, ceramics and metals (in paste form)	Low	Low	Yes	Good	Yes	No	No	No	No	Widely available and established, cheap equipment, smaller structures achievable by means of thermally shrinkable polymer sheets	Costs for masks (mask based techniques such as screen printing)
2-Dimensional virtual channels	mm–cm	µm–cm	Photoresists	Low	Low	No	Good	No	No	No	No	No	Very easy to implement, very little and mostly cheap and widely available equipment required	No real microfluidic channel thus risk of evaporation and contamination

[a] Depending on the substrate or the way the process is carried out bonding may not be necessary—please refer to the respective section of this work for further details. [b] Depending on the substrate or the way the process is carried out this may be possible—please refer to the respective section of this work for further details. [c] This is potentially possible but it requires several separate processing steps. [d] Classical lithography as well as dry film lithography or MF tectonics. [e] Depending on whether or not maskless or mask based processes are used. [f] Depending on the requirements the glass substrate (through which the exposure is carried out) may be directly used as bonded channel ceiling.

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among the first lasers ever used.[136] The laser relies on a discharge in a gas chamber filled with carbon dioxide, hydrogen, nitrogen and helium. The laser wavelength is in the infrared, usually around 10 μm. These lasers have been used for the creation of microfluidic channels in PMMA.[137] Hong *et al.* described the direct laser machining of PMMA by means of a CO_2 laser with channel widths in the range of below 100 μm and depths from a few tens to hundreds of micrometres.[138] Fernández-Pradas *et al.* have used a Nd:YAG 355 nm pulsed laser to create microfluidic channels of several millimeter length in the photosensitive Foturan.[139] The diameters of these channels could be varied from a few micrometres to up to hundreds of micrometres. Laser machining with subsequent wet etching can be used in order to create three dimensional microstructures in such a photosensitive glass as demonstrated by Sugioka *et al.*[140] Using defocused laser beams it is possible to create embedded channel structures in photoresist such as SU-8.[141]

The main drawback of laser direct machining is the risk of material redeposition next to the laser spot and thus the creation of rough surfaces in the microfluidic channels (see Fig. 3). Redeposition can be reduced by precisely adjusting the machining parameters which is an equipment and material specific optimization process. Laser ablation is a serial process but due to high laser intensities and high scanning rates the processing of a microfluidic chip can usually be performed within a few minutes. In general laser machining can be considered a suitable process for large scale production as has been pointed out in the literature.[142] The advantages include a very wide range of materials including metals, ceramics, glass and polymers. Another advantage of laser ablation is the fact that this process can also be used to create electrodes in microfluidic devices by combined polymer and metal ablation. Laser machining is an important process for material processing and can be used to create molding tools suitable for injection molding or hot embossing of microfluidic devices. Sheet metal, which can directly be used for replication[143] or can serve as an electrode for EDM in the creation of a molding tool,[144] as well as bulk material[145] can be processed by laser machining for this purpose.

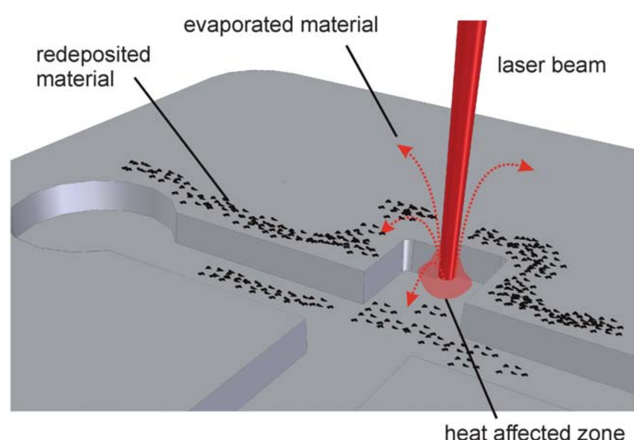

Fig. 3 Principal view for laser direct machining. A laser spot is scanned across the substrate to be machined. Due to photon absorption the laser locally induces heat thus creating a heat affected zone in which the material is heated until evaporation. The material is removed from the machining area in gaseous form which potentially carries the risk of material redeposition on the surfaces around the heat affected zone resulting in an increase in surface roughness.

Besides the mere material removal laser based machining can also be used for changing chemical properties of the surfaces machined in order to influence the electroosmotic flow[146] by modifying the surface charges[147] or to create oxidized surfaces to which silane binding can easily be carried out.[148] Even fluorinated substrates such as FEP can be modified by means of laser treatment assisted by a graft polymer.[149] Laser machining can also be used for laser based welding and thus for bonding of microfluidic devices[135] for which Russek *et al.* have given a detailed review.[150] Further detailed discussions about the potential and the application of laser ablation techniques for the creation of microfluidic devices are given elsewhere.[151,152]

Etching techniques

Etching remains one of the principal processes for the structuring of classical materials such as silicon and glass. Etching techniques are usually classified either as dry or wet etching. In dry etching the substrates are usually processed by means of plasma or particle beams whereas wet etching involves exposing the substrates to solvents in liquid form. Depending on the substrates used and the nature of the etching process the material removal may have preferred directions (anisotropic etching) or it may remove the material equally in all directions (isotropic etching). Etching has been used since the 1950s and can be considered the oldest structuring process. However, most etching processes rely on the application of a mask to product substrate areas that should not be processed. Therefore most etching processes are a two-step manufacturing process with the exception of few. The most prominent of these exceptions is focused ion beam (FIB) etching which is commonly used in MEMS and increasingly in microfluidics. Hug *et al.* etched a microfluidic channel in a silicon cantilever tip for atomic force microscopy (AFM).[153] Besides silicon FIB etching is a viable technique to structure even materials which are difficult to machine classically as, *e.g.*, diamond. This has been demonstrated, *e.g.*, by Imre *et al.* who used FIB lithography to create microfluidic channel structures in diamond layers.[154] Polymers can readily be structured as well as shown by Guan *et al.* who used FIB to directly structure PDMS[155] or Cannon *et al.* who demonstrated the structuring of PMMA.[156] Metals are conveniently etchable substrates. As stated, metal is not a very commonly used material for microfluidic components, however, it is the material of choice for electrodes which can readily be created by etching.[157,158]

Mechanical structuring

Perhaps the most commonly used set of techniques for the rapid prototyping of microfluidic devices is mechanical structuring such as by milling, planing, sawing or drilling. Mechanical structuring relies on the material removal from a substrate by means of a tool typically with a hardened surface. This tool may be nonrotating (as in the case of, *e.g.*, planing) or rotating (as in the case of milling). If suitable tools and machining equipment are available mechanical structuring allows the creation of microfluidic structures in metals, polymers (including PTFE),

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ceramics (usually in the green form) as well as some types of glasses. Glass can be structured, *e.g.*, by means of sawing which has been demonstrated by Szekely and Freitag who created 80 μm wide and 70 μm deep microfluidic channels in glass.[159] Direct mechanical structuring of soft materials such as elastomers (like PDMS) is not possible at room temperature and usually has to be carried out on cryogenic cooled substrates.[160] Mechanical structuring is a viable option for the creation of microfluidic devices as a one-step manufacturing strategy even though the most commonly used application is still for the creation of molding tools for replication processes.[105] Typically CNC machining equipment is used with tools in the range of a few ten micrometers. Even thin and high aspect ratio features down to as few as 20 μm can be machined.[161] Microfluidic channels with widths as small as 30 μm have been described.[162] Typically milled microfluidic channels need to be sealed before use for which Rodrigues and Lapa have suggested the use of a UV curing process in combination with milling[163] but thermal or solvent assisted bonding as well as laser welding are viable alternative techniques depending on the substrate material. Due to the physical shaping of the tools used in mechanical machining the microfluidic structures may display some of the features of the machining tool. For example creating a replication tool for a microfluidic channel intersection will result in radii on the corners due to the radius on the molding tool.[164] For some applications this may limit the suitability of mechanical structuring for microfluidic prototyping. Mechanical structuring can also be used in combination with replication techniques in order to either structure a substrate previously created by the replication technique or to structure a substrate to which microfluidic features are to be added later, *e.g.*, by hot embossing.[165] One very important advantage of mechanical structuring is the fact that microscale features can directly be integrated with larger scale features such as millimetre sized reservoir structures or interconnects. These structures can be almost arbitrary converging three-dimensional shapes which have been widely used for the creation of replication masters in polymers for thermoformed microfluidic systems.[166]

A drawback of mechanical structuring is the risk of tool fracturing during manufacturing.[167] The initial location of the tool with respect to the substrate defines the reference for the machining processes and tool fracture during manufacturing results in the loss of this reference. A subsequently inserted and referenced tool is likely to be shifted with respect to the original reference which will result in deviations of the features to be machined. Another aspect to consider in one-step manufacturing of microfluidic devices is the fact that mechanical structuring always induces surface roughness which is to be considered when the structures are to be used in microfluidic applications. The roughness can be influenced by adjusting the machining parameters such as the rotation and the movement speed of the machining tool. Recently Young *et al.* have shown that by fine adjustment of the machining parameters it is possible to create surfaces with roughness values below 0.5 μm (R_a) in, among others, stainless steel, copper and aluminium.[168] Due to their lower stiffness, roughness values in polymers are typically higher than the ones obtained on metals.

When mainly polymers are to be processed, cutting is a viable mechanical structuring method as well. For this a thin metal blade is moved across a thin sheet of material cutting structures. Commercially available equipment is available for this purpose, *e.g.*, the digital cutter CraftROBO Pro (Graphtec America, USA) which has been used by Do *et al.*[169] The authors created straight and winding microfluidic channels with widths and heights in the range from 20 μm to 150 μm and even larger reservoir structures in COC. Such layers can also be stacked in order to create arbitrary three-dimensional microfluidic structures (see the section "Layer based techniques"). Cutting is a commonly used technique to create masks, *e.g.*, for the etching of glass. Sorouraddin *et al.* have structured self-adhesive polymer sheets *via* the commercially available cutter CX-124 (Roland, Japan) to create such a mask for etching in glass.[170] If no cutting equipment with such fine blades is available, the processing of thermally shrinkable sheets of polymer by means of cutters with thicker blades (or even manual cutting) is an option. This is demonstrated by Taylor *et al.* who cut the polymer sheets with a rough cutter prior to shrinkage.[171] They obtained microfluidic channels with widths in the range of 150 μm to 200 μm and depth of about 700 μm. Microfluidic channels can also be created directly in adhesive tape by means of cutting. Nath *et al.* have created channels with 200 μm width.[172] Yuen and Goral demonstrated gradient mixing structures with channel widths in the range of 400 μm with this method.[173]

Even given the process limitations and the higher cycle times due to the strictly serial processing mechanical structuring may still be considered a very widely applicable one- and two-step manufacturing technique. One of the inherent advantages is the fact that CNC controlled machining equipment may be available to laboratories that have no or limited access to lithography or similar MEMS technology. This is the reason why microfluidics has seen an increasing interest from the engineering community in recent years.

Material depositing techniques

The second group of manufacturing techniques discussed in this work are material depositing techniques. It is important to note that material depositing techniques are often used to complement material removal techniques in order to create sealed microfluidic channels (*e.g.*, by photochemical polymerizing a sealing layer) or truly three-dimensional structures (as, *e.g.*, for layer based techniques where each individual layer is structured by means of a material removing technique).

Silicon surface micromachining

Depositing micromachining techniques for silicon are not very common processes in microfluidic prototyping. They usually involve the deposition of thin layers of sacrificial material (such as silicon oxide) and bulk material (*e.g.*, consisting of polycrystalline silicon), by means of chemical vapor deposition (CVD) processes. The sacrificial layers are used to support the structures created from polycrystalline silicon and are typically removed by means of etching after the manufacturing process. It is possible to create suspended mechanical structures or closed microfluidic channels with this technique. Both sacrificial and bulk material can be repetitively protected and structured by means of lithographically applied etching masks to create the

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structures of choice. Creating a microfluidic structure by these techniques is usually a very time consuming process and can only be carried out if suitable silicon processing equipment is available. However, for institutes and companies specialized in silicon MEMS technology surface micromachining is a viable alternative. Details about the technique can be found, *e.g.*, in the work of Kovacs *et al.*[174]

Lithography

Depending on the resist type, lithography can be regarded as a material removing or a material depositing technique. For one-step manufacturing, the ability to create structures by means of lithography is more relevant which is why, within the scope of this article it is classified as being a primary depositing technique.

The term lithography is derived from the Greek words *lithos* which means stone and *graphein* which means writing or to write. The process in its first technical form was invented by Senefelder around 1800[175] (see the English translation of Senefelder's original manuscript by Muller from 1911[176]). The process was carried out on limestone, thus the allusion to writing with a stone. It involved the application of hydrophilic and hydrophobic surface areas on the stone which would later be used to selectively adsorb printing ink on the hydrophilic areas and rejecting it on the hydrophobic ones. The hydrophobic areas were created by the application of a wax after which the stone was immersed in a lightly acidic solution of a natural gum (usually gum arabic) which penetrates the limestone by means of capillary forces and creates hydrophilic areas on all surfaces not previously protected by the wax application.

Today lithography can be considered the most important manufacturing strategy for MEMS especially in combination with silicon. The process commonly used is photolithography which makes use of a pattern that is created by radiation sensitive material on the surface of a substrate. Commonly used for these processes are photoresists which are applied as thin layers usually by means of spin coating. This thin layer is afterwards exposed to radiation (usually in the UV) *via* a photomask (see Fig. 4). After the exposure the areas of the resist that have been exposed to the radiation will either be more soluble (positive resist) or less soluble (negative resist) compared to the substrate in a designated solvent (see also the section "Duroplastic polymers"). Once a mask is available photolithography is a parallel process (sometimes referred to as parallel data transmission where data indicate spatial structure information). It is of no importance if millions of features on the mask need to be translated to the resist or a single one—the processing time is equivalent. Therefore this process can be regarded as highly scalable and it is only restricted by the size of the substrates that can be processed in one step. Without lithography, microelectronics and semiconductor processing would not exist as we know it today.

Depending on the way the mask is projected a lithography is classified as contact lithography (where the mask is directly located on top of the resist which results in the best projection but usually damages the mask), proximity lithography (where the mask is placed at a certain distance from the resist coated substrate) or projection lithography (which uses a lens system in order to either reduce or increase the size of the projected features). Another important aspect is the type of mask used which is usually either binary (a pixel on the mask is either transparent or not) or grayscale (a pixel has a certain given transmission ranging from transparent to nontransparent with a finite number of increments). The latter is usually referred to as grayscale lithography. Light sources commonly used include mercury-vapor lamp as well as excimer lasers. Recent progress has been made in the field of extreme ultraviolet (EUV) lithography[177] for which typically plasmas are used as light sources with operation wavelengths in the range of 13 nm. For such systems there are no refractive projection systems available and purely reflective optics have to be used.

Mask based lithography is a two-step manufacturing process because it essentially copies the features present on the mask which is the primary structure. Such a mask is usually created by means of a series of (and therefore typically slow) direct maskless lithography techniques, *e.g.*, by electron beam lithography (which uses a focused beam of electrons for resist exposure), some types of X-ray lithography as well as laser lithography. These processes are one-step manufacturing techniques that can, in principle, also be used to create microfluidic devices. However, most of these processes are serial in nature (sometimes referred to as serial data transmission where data again refer to spatial structure information) which means that complicated structures will require more time to be processed than less complicated ones. If frequent design modifications are to be expected the required time and costs for the creation of a mask will dominate the concept-to-chip turnover time and the costs associated with it. For this design phase it may be more suitable to rely on different types of techniques or process modifications such as maskless lithography. Maskless and mask based lithography can be considered complementary: maskless lithography is suitable

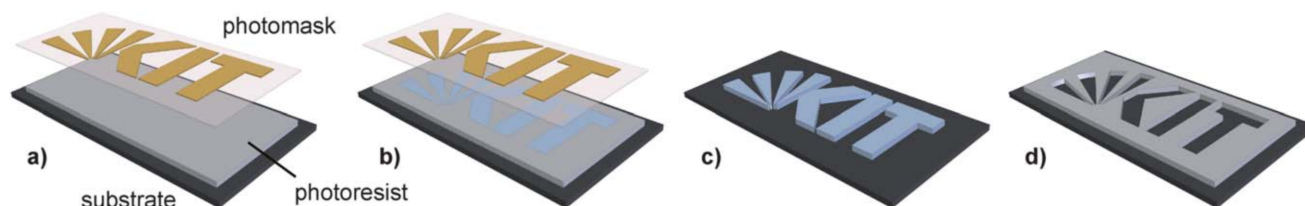

Fig. 4 Classical photolithography process. (a) A substrate is coated with a thin layer of photoresist which is usually applied *via* spin coating. The coated substrate is placed under a photomask which consists of a radiation transparent material with a radiation absorbing material locally confined applied to it. (b) By exposition to radiation (usually UV light) the pattern is translated to the resist layer. Depending on the type of resist the exposed area will either be more soluble in a designated solvent (positive resist) or less soluble (negative resist). After exposure, (c) these areas are removed in the case of a positive resist or (d) these areas will remain on the substrate in the case of a negative resist.

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for short concept-to-chip times and frequent design modifications but unsuitable for large scale production. In contrast, classical mask based lithography is extremely suitable for large scale production but unsuitable for frequent design changes.

In order to combine the best of both technologies, maskless dynamic projection systems have been developed in recent years, namely in the form of digital mirror devices (DMDs) which are also suitable for lithographic applications. The devices were developed by Texas Instruments (USA) and are commonly referred to as spatial light modulator (SLM). The technology was originally patented as an electrostatically deformable printer in 1986[178] and first described in 1991 for use as light modulator.[179,180] DMDs are arrays of electrostatically deflectable mirrors that can be individually addressed in order to set them to an on or an off state. These devices can be used to project different patterns of light without using static masks which is why they are referred to as dynamic mask projection systems. They have found a wide application range from consumer applications in video projectors to maskless lithography in semiconductor processing.

The principal setup of such a maskless lithography system is given in Fig. 5. A light source (typically a mercury-vapor lamp) is equipped with a collimation optics and a filter. The filter is a very important component in these systems as the DMD will serve as a reflective grating which will result in multiple images being projected if the light is not adequately filtered. After filtering and collimation the light is projected onto the DMD which is set to a pattern specified by digital data. Setting a pixel on the DMD to the on state will result in the associated mirror tilting, thus allowing the incident light to reflect from the mirror's surface towards the projection optics. If the pixel is set to the off state the light is reflected towards an absorber, commonly referred to as light dump. The pattern of reflected light is projected *via* a set of lenses (potentially with magnification or demagnification) onto the projection plane which is the substrate with the photoresist. The advantage of this system is the fact that it does not require a static mask (the mask is digital thus easily changeable) and it allows for the full exposure of a larger area (depending on magnification and required resolution, wafer scale level exposure is possible). Typically, DMDs feature extended graphics array (XGA) resolution which means they have 1024 $\times$ 768 individually addressable pixels which can be refreshed at kHz rates. This makes those devices even suitable for stitching individual image sequences in order to pattern larger surfaces. Coupling DMDs with existing optical setups, such as microscopes, has been described as a fast and simple means of setting up a maskless lithography.[181] Using camera optics as projection systems is another alternative.[182]

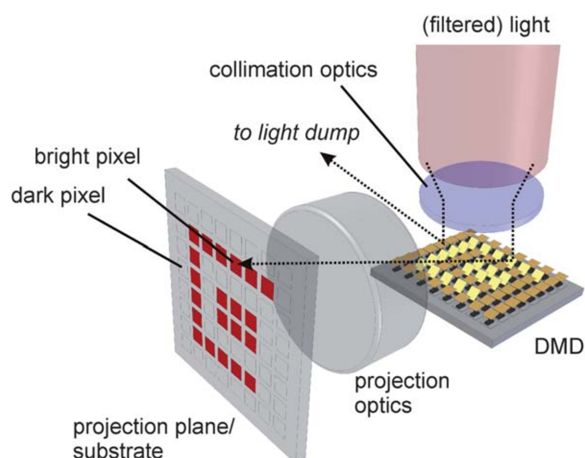

Fig. 5 Principal setup of a maskless projection system by means of a digital mirror device (DMD). A light source is filtered (if required) to a narrow light spectrum (typically passing only one wavelength peak) and collimated by means of a collimation optics. A digital image is translated to the DMD and the mirrors are set accordingly. Depending on whether or not the pixel is in the on or the off state the light is either deflected to a light dump or onto the substrate through a projection optics (usually a set of lenses).

Both mask based and maskless lithography are able to create 2.5-dimensional structures only. By incident light it is possible to create translated structures as well.[183] In order to create truly three-dimensional objects a layer based process using repetitive exposures has to be used (see the section "Layer based techniques"). For microfluidics the negative resist SU-8 is still the most commonly used material for the creation of devices. It is suitable for the creation of high aspect ratio microfluidic channels[184] and as it is widely used in MEMS technology a lot of questions such as sacrificial layer techniques, bonding as well as partial curing or multistep exposure have been addressed already.[185] An important effect to consider when designing microfluidic devices from SU-8 is the mechanical stress within the cured resin layers. Usually SU-8 is applied by means of spin coating, however, due to its surface tension the resist can also be applied in defined volumes on substrates with defined size where the resin will form a layer of homogeneous thickness. Lin *et al.* have shown that it is possible to structure layers of thicknesses in the range of several millimetres by this technique.[186] Besides SU-8 a number of alternative resists have been described such as Loctite acrylates (3108, 3340 or 3525, Henkel, Germany)[187,188] which is a class of commercially available instant adhesives.

Vulto *et al.* have described the use of dry film resists which are commonly used in printed circuit board manufacturing as suitable resists for microfluidics.[189] Usually dry film resist layers are applied on a supporting substrate and can be directly processed without pretreatment. The authors demonstrated microfluidic devices consisting of two structured layers of dry resist, each applied on a glass microscope slide and bonded together. Sufficient biocompatibility as well as an application in capillary electrophoresis have been demonstrated. Other dry film resists have been described for microfluidic devices as well, *e.g.*, TMMF S2000[190] (Tokyo Ohka, Japan) or Ordyl SY330[191] (Elga Europe, Italy). Dry film resists were also demonstrated as suitable replication master for hot embossing in thermoplastic polymers such as PMMA and COC.[192]

Another process which is referred to as microfluidic tectonics was presented by Beebe *et al.*[193] The process uses a fluidic chamber filled with photocurable monomer which is exposed to UV light through a mask. The mask structure is translated to a 2.5-dimensional structure made from cured polymer from which the uncured liquid monomer can be purged. Besides channels, filters and mixer structures can be created.[194] Repeating this process allows the creation of structures consisting of more than one material. The work also demonstrates the polymerization of a pH

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sensitive hydrogel which can be used for blocking channel cross-sections thus creating small microfluidic valves. The process is suitable for the creation of fluidic structures with heights not exceeding a few tens to a hundred micrometres as the light is defocused and the edges of the channels become blurred with increasing depth which results in sloped channel walls. Additionally, light penetration through the cured polymer is limited which results in deeper regions not receiving enough light for sufficient exposure.

A similar technique which has been used for the creation of microfluidic devices is frontal photopolymerization (FPP). In FPP a homogeneous volume of liquid resin is initiated from the top surface creating a propagating polymerization front which moves downwards into the material. Typically, this polymerization is triggered by means of UV radiation,[195] heat[196] or the addition of water.[197] The technique even allows the incorporation of phase-change materials.[198] Cabral *et al.* have suggested this method as a mask based technique for the creation of channel structures as well as microfluidic mixers with channel widths in the range of several 100 μm in NOA.[199] McKechnie and Sinton have used FPP in combination with a fluidic mask consisting of laminar streams of light absorbing and light transparent streams of liquid.[200] Using grayscale masks it is possible to create converging three-dimensional structures as presented by Atencia *et al.* who manufactured channels and even nozzle structures by this technique.[201]

As noted, lithography can be used to create translated or non-translated 2.5-dimensional structures. In order to create truly three-dimensional features, lithography is typically combined with layer based techniques.

Layer based techniques

As pointed out a number of techniques are only suitable to create 2.5-dimensional structures. In order to obtain truly three-dimensional objects such layers need to be stacked. The first task to be carried out is referred to as model slicing (see Fig. 6). For this a numerically modeled three-dimensional geometry which can, *e.g.*, be created by means of CAD is sliced into a finite number of layers which are interpreted as being 2.5-dimensional. For this the three-dimensional model needs to be oriented and a reference plane is selected. This reference plane is usually identical to the bottom plane (see Fig. 1) on which the part is being created and careful selection is required, because the model orientation can in some processes have a significant effect on the quality of the created part (refer to the back side problem, see the section "Layer-on-layer manufacturing"). After the model is oriented, the digital slices are cut such that the individual layers' top and bottom surfaces are parallel to the reference plane and the height of each layer corresponds to the chosen z-increment. The layers are then manufactured either individually (usually referred to as layer-to-layer manufacturing which requires a bonding or lamination process in order to combine the stack of individual layers to the original geometry) or each new layer is created on top of the stack of layers already manufactured (usually referred to as layer-on-layer manufacturing).

Layer-to-layer manufacturing. In layer-to-layer manufacturing individually manufactured layers are assembled by means of solvent or heat supported lamination or bonding processes. Sometimes the use of adhesives is an alternative. This process modification is sometimes also referred to as layer laminated manufacturing (LLM). However, it is only feasible if the individual layers are mechanically resistant enough to sustain the bonding process.

As the individual layers in layer-to-layer manufacturing are created independently the bonding process is of immense importance for the overall performance of the microfluidic component. Besides sufficient adhesion among the layers, correct alignment has to be assured. This can be ensured by geometrical features or by optical markers. Depending on the materials and the bonding process chosen significant efforts have to be put into assembling the individual layers to a complete component which may disqualify the overall process as being a one-step manufacturing technique. Commonly employed bonding techniques include the use of solvents which are applied to the surface of a structured substrate creating a sticky film of dissolved polymer. This layer can readily be bonded to a second substrate

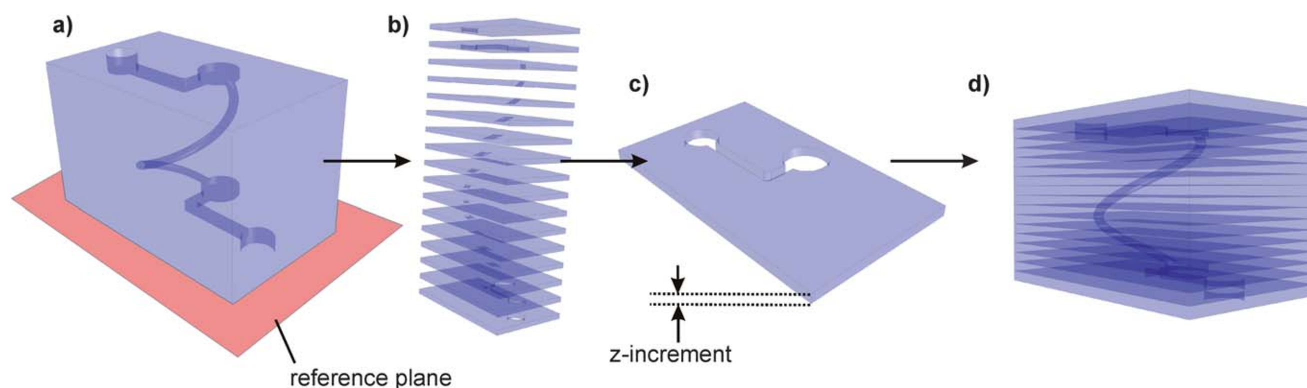

Fig. 6 Model slicing for layer based manufacturing. (a) The three-dimensional object is modeled, *e.g.*, by means of CAD and the reference plane is selected. (b) The model is spliced into a finite number of slices all of which have top and bottom planes parallel to the reference plane. (c) The height of each of these layers is the chosen z-increment, the layers are interpreted as 2.5-dimensional. (d) The individual layers are manufactured either separately and are later assembled to the complete part or the layers are manufactured with the currently processed layer being added to the stack of layers already constructed.

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of the same (or a chemically similar) polymer.[202] An example for such a process is the bonding process of PMMA by using acetone.

Thermal bonding is restricted to thermoplastic polymers. In this process the surfaces of two polymer substrates are heated to near their glass transition temperatures and subsequently pressed together. Upon cooling the polymers will form a bond in the contact zone.[203] Sometimes the substrate surfaces are cleaned and activated, *e.g.*, by means of plasma or corona discharge prior to heating.[204] Ultrasonic bonding uses a similar effect by locally induced heating and subsequent bonding.[205]

Another possibility is the use of chemically interlinked surface modifications, commonly referred to as "chemical gluing". For this process the two substrate surfaces to be bonded are treated with a different surface chemistry which can be applied, *e.g.*, by means of silane chemistry. The silanes used are usually chosen such that they can chemically interlink (*e.g.*, by means of an expoy and an amino terminated silane). Pressing the two substrates together under gentle heating will result in a chemical crosslinking.[206]

Commonly used for the creation of three-dimensional structures is the layer-to-layer manufacturing of SU-8. Individual layers of the cured resist can be laminated to form three-dimensional structures as reported by Abgrall *et al.*[207] SU-8 is usually spun onto a substrate but different methods, including the use of millimetre high fluidic chamber structures to force the resist into the desired thickness, have been reported.[186] Carlier *et al.* have used a multilayer microfluidic device made from SU-8 layers for mass spectroscopy.[208] Bonding SU-8 layers to other substrate materials has also been reported in the literature for PDMS,[209] PMMA[210] as well as silicon and glass.[211] If required for bonding, sacrificial layers can be used to protect channels as reported, *e.g.*, by Sato *et al.*[212] or Bao *et al.*[213] who used an AZ photoresist as sacrificial layer. Spin-on-glass has been reported as a suitable sacrificial layer material as well.[214] These techniques are in general applicable for other epoxy resists as well as they do not inherently rely on specific properties of SU-8; however, sufficient mechanical resilience is generally required.

Besides photoresists, which are inherently facile to laminate due to their ability to cure against a second layer of the same photoresist, almost all thermoplastic polymers can be used which are typically laminated by means of solvents or heat (thermal lamination). The individual layers can be structured by any material removing manufacturing techniques such as mechanical structuring, laser direct machining, *etc.* Paul *et al.* demonstrated devices created from multiple layers of COC by solvent and heat bonding.[215] Mahalanabis *et al.* have shown a device created by 12 thermally laminated COP layers each of which was structured by a commercial cutter.[216] Zhang *et al.* have reported a process that uses the repetitive plasma bonding of PDMS sheets on top of each other.[217] The single sheets of PDMS are replicated from the respective inverse structure created in SU-8 on top of a silicon wafer. Liquid PDMS is cured between the wafer and a second sheet of PDMS which is surface modified with a fluorinated silane, thus creating a nonstick surface. Pressing the fluorinated PDMS sheet onto the silicon wafer will result in a sheet of PDMS in between being cured which can even feature holes. This sheet is released from the wafer and plasma bonded to the last manufactured PDMS layer.

Double sided pressure sensitive adhesive (PSA) has been used as a material for creating microfluidic device prototypes. Typically structures are cut into the tape which is then sandwiched between two polymer or glass plates thus closing the channels. Nath *et al.* have demonstrated the use of this technique for creating microfluidic mixers as well as chip interfaces for microfluidic channels with a width of about 1 mm.[172] These tapes can also be structured by means of a laser as demonstrated by Luo *et al.* who also demonstrated the use of such templates as replication masters for casting.[218] Abgrall *et al.* suggested a method using SU-8 supported by PET substrates.[207] Each SU-8 layer was structured by means of photolithography where the current layer being processed was added to the stack. The layer was resist in dry form supported on a PET substrate which was laminated on the topmost layer. Photostructuring of the layer to be processed is achieved by lithography either through the supporting PET substrate after bonding (layer-on-layer manufacturing) or prior to bonding (layer-to-layer manufacturing). In both cases the supporting PET substrate is removed afterwards. The authors demonstrated microfluidic channel networks with widths in the range of several 100 μm and depths in the range of 50 to 100 μm.

Besides polymers, ceramics can be processed as well. Ibáñez-García *et al.* described the use of the so-called low-temperature co-fired ceramics (LTCC) as a potential material for microfluidics.[219] This material is a ceramic bulk at the green form, which is a mechanically coherent bulk of ceramic particles and binder. This bulk is structurally intact but not yet burned or sintered to its final hardness. The use of ceramics at this stage in thin sheets (which are commonly referred to as ceramic green tape) can offer an alternative approach for layer-to-layer manufacturing of microfluidic devices. The green tape typically consists of a filler material, usually Al_2O_3, glass and organic components such as solvents and binder. The tapes can be structured, *e.g.*, mechanically by means of lasers or cutters, and are subsequently assembled to a stack resulting in a three-dimensional structure prior to burning the part to its final form. Microfluidic systems created by this technique have been used for the detection of chloride in drinking water,[220] the capillary electrophoretic characterization of catechol and dopamine in channels with a width of 100 μm and a depth of 25 μm[221] and the electrochemical detection of pesticides by means of an enzymatic inhibition reaction in a 1.7 mm wide and 430 μm deep microfluidic channel.[222] Once they are burned, ceramic green tapes resemble the respective glass with respect to their chemical and physical properties which makes them extremely appealing for applications that feature outstanding chemical and thermal resistance. Compared to classical glass, processing ceramic green tapes allows the flexibility to create three dimensional structures and does not require harsh chemicals in their creation. A major drawback is the fact that, due to the burning process, shrinkage of the components is unavoidable due to a change of the material's density. This has to be considered in the design phase.

Layer-on-layer manufacturing. The alternative process to using layer-to-layer manufacturing (which requires bonding steps to combine the individual layers) is layer-on-layer manufacturing. In this process a three-dimensional component can be produced by sequential, *e.g.*, lithographic, creation of

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layers on top of each other. An advantage of this process is the fact that the alignment of the component is unchanged; therefore the individual layers being manufactured on top of each other are always correctly aligned. In doing so a common problem which is commonly referred to as the "back side problem" has to be resolved. If for example a microfluidic channel is to be produced by means of lithography, the bottom and the side walls of the channel can be created conveniently. When the ceiling of the channel is to be produced the liquid resin will flood the channel during the exposure. As the penetration depth of the light into the resist is difficult to control precisely the ceiling will result in a very rough surface. There are a number of methods to circumvent this problem. The most commonly used method makes use of a resist exposure at an additional wavelength at which the material has lower absorption and therefore lower penetration. This wavelength is chosen for creating the ceiling whereas the stronger absorbing wavelength is used for the structuring of the channel side walls. This method has so far only been described for SU-8[223] where the strong absorbing wavelength is 365 nm and the weak absorbing wavelength is 254 nm. Similar processes are possible by using different energy levels of a FIB.[224] In both cases the liquid resin then needs to be removed from the channel which can prove difficult for high viscous resins or long microfluidic channels. Usually this process is enhanced by applying vacuum or by increasing the temperature of the substrate thus decreasing the viscosity. Sometimes the use of solvents is required as well. One solution to overcome this problem has been suggested by Hirai *et al.* using a resin that is not completely crosslinked upon the first exposure thus allowing solvent diffusion through the bulk of the material in order to dissolve uncured resin.[225] Final crosslinking is only carried out after the channels have been completely cleared.

A number of techniques make use of layer-on-layer manufacturing, the most important ones for the creation of microfluidic devices will be discussed in the following.

Stereolithography

The classical layer-on-layer manufacturing technique is stereolithography (STL) sometimes also referred to as micro-stereolithography (μSTL) if very fine structures are to be created. STL is one of the most important rapid prototyping processes in industry today. It allows for quick and easy manufacturing of functional prototypes. Depending on the resins used the components can be of considerable mechanical resilience. The basic principle of STL is the use of structured light, usually created by means of a laser beam that scans across the surface of a resin that polymerizes upon exposure. The process was initially described by Hull in 1986.[226] He defined STL as "a method and apparatus for making solid objects by successively 'printing' thin layers of a curable material, *e.g.*, a UV curable material, on top of other"[226] (column 2, line 37). Today, the choice of material is not necessarily restricted to UV curable materials any more. Due to the wide choice of high intensity light sources polymerization can also be carried out at various wavelengths in the visible range by using special types of photoinitiators. STL is a layer based technique so the three-dimensional model to be created again needs to be sliced prior to manufacturing.

There are two important configurations of STL used in academia and industry today: the bath and the layer configuration (see Fig. 7). These variations are also referred to as free surface technique (bath configuration) or constrained surface technique (layer configuration).[227]

The bath configuration is the classical setup for STL and has been used for more than two decades. It uses a liquid bath of curable resin into which a movable stage in the form of a table with a building platform is inserted. This table is used as the z-axis of the object to be created. During the process it is lowered further and further into the polymer bath each time by a distance corresponding to the z-increment. In order to create the first layer the table is placed in such a way that the top of the building platform is located at a distance equal to the z-increment underneath the surface of the liquid resin. An optical scanner (usually one or a set of two tiltable mirrors) is used to scan the laser beam across the surface of the resin which is the x/y-plane. The focus spot of the laser will induce localized polymerization in the resin with a voxel cross-section in the range of the laser spot's focus area and the height of the z-increment. After the laser is scanned across the x/y-plane and the first layer is finished the table is lowered by a z-increment into the resin bath thus creating a second layer of liquid resin on top of the first polymerized layer. This process is repeated until the complete object is built. The bath configuration is a very conveniently implementable setup for performing STL and numerous examples in the scientific literature make use of it.[228] If an optical scanner and a suitable laser or comparable light source are available it is usually straightforward to implement a bath configuration STL. As the resin is polymerized on the surface care has to be taken to reduce contamination and to avoid chemical reactions with the ambient air (such as oxidation which is a potent inhibitor for radically curable resins such as acrylates[229]). Another drawback of the technique is the fact that the height of the resin bath is the z-axis' limitation for the object to be created. Say for example if an object of 20 cm height has to be built a resin bath of at least 20 cm depth has to be provided. This may result in significant costs because of the large amount of resin required from which only a small fraction is effectively used. Modifications for the classical process have been described in the form of a continuous non-layered manufacturing process that uses continuous exposure while lowering the table into the bath.[230]

The second widely used configuration in STL is the layer configuration which is sometimes also referred to as the bat configuration due to the fact that the part is created hanging from the movable table like a bat from a ceiling. It was introduced in 1993 by Ikuta and Hirowatari[231] and Takagi and Nakajima[232] and is especially advantageous when expensive monomers are used as it is only necessary to provide a thin layer of resin for each layer. The process places the optical scanner and the light source underneath the building chamber which is defined by a window which is optically transparent for the wavelengths used. The z-axis is again implemented by means of a movable stage which is located above the window. The table and the window form a narrow slit into which liquid resin is pulled by means of capillary forces. The laser beam is scanned across the surface of the window which is the x/y-plane of the object to be built. This first layer is required to mechanically adhere to the table which is typically guaranteed by mechanically

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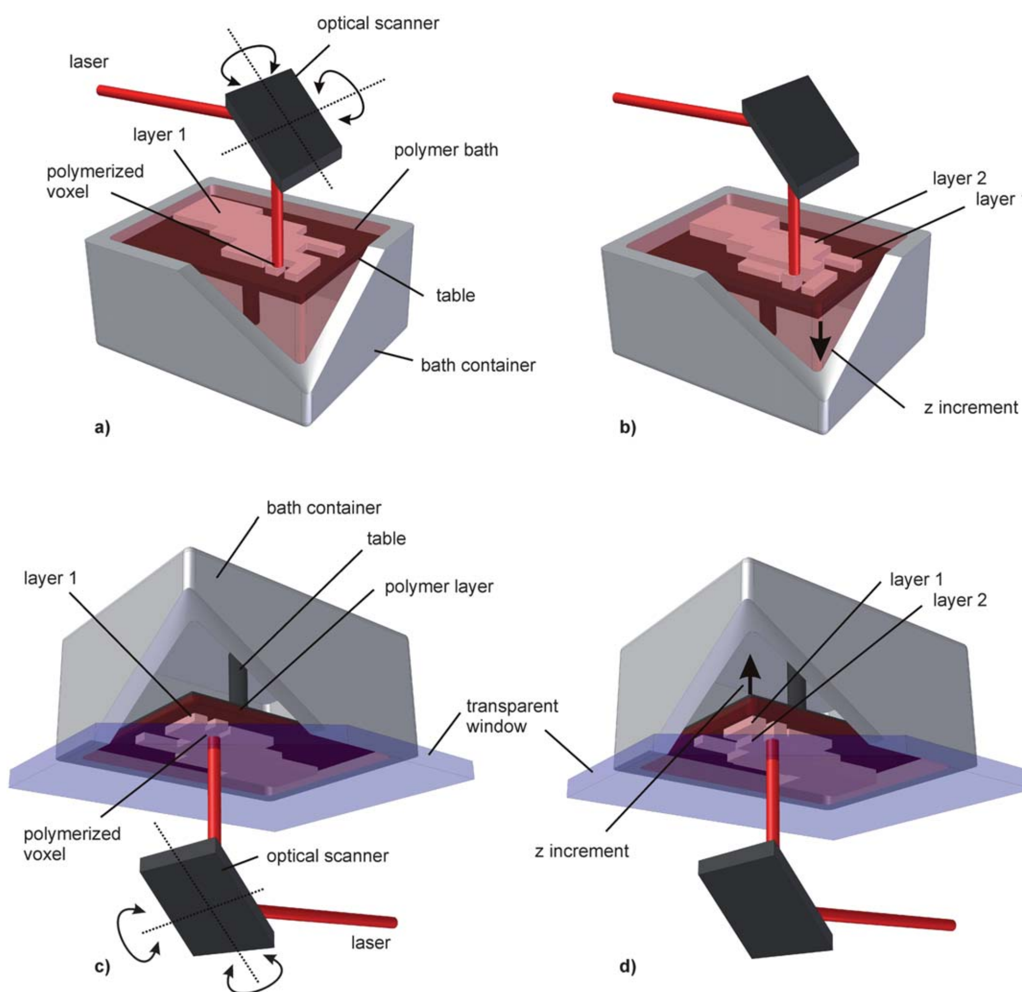

Fig. 7 Principal setup of STL in bath (or free surface) and layer configuration (or constrained surface). (a) The bath configuration consists of a container in which a movable table is located which serves as the *z*-axis. A laser beam (or a split beam) is focused onto the surface of the liquid resin by means of an optical scanner that scans the *x*/*y*-plane. Initially the table is placed by a distance of the *z*-increment beneath the liquid resin's surface. Where the laser beam touches the resin surface a voxel of the laser beam's diameter and the height of the *z*-increment in cross-section and height will be polymerized. The laser beam is then scanned across the *x*/*y*-plane creating the first layer. (b) After the first layer is finished the table is lowered by a distance corresponding to the *z*-increment into the resin bath, thus creating a new layer of liquid resin on top of the first cured polymer layer. This resin layer is then structured repeating this process until the part is completed. (c) The layer configuration consists of a window which is transparent for the laser's wavelength onto which the object is created. The optical scanner is located underneath this window the movable table that represents the *z*-axis is located above it. The resin is provided in the form of a thin layer which is located between the top surface of the window and the movable table. The height of the layer is identical to the *z*-increment. Scanning the laser beam across the *x*/*y*-plane will result in a polymerized layer which attaches (usually by means of a rough surface) to the table. After the first layer is polymerized the table is moved up by a distance equal to the *z*-increment and the gap between the window and the first layer is again filled with liquid resin. The process is repeated until the complete part is built. In this setup the bath container only serves protective purposes.

rough surfaces or undercuts. If the first layer is built the table is withdrawn by a distance equivalent to the *z*-increment. Care has to be taken to ensure that the polymerized layer does not adhere to the window which is usually ensured by means of non-stick coatings or repetitive mechanical tilting of the window with respect to the polymerized layer. The gap which is formed between the window and the polymerized layer is again filled with liquid resin by capillary forces to provide the material for the polymerization of the second layer. This process is repeated until the complete object has been created. As stated the layer configuration is especially suitable for expensive resins; however, it can only be applied if the resin features a sufficiently small viscosity. For highly viscous resins the repetitive filling of the gap can become problematic which makes those materials unsuitable for layer configuration STL.

Besides classical photolithographic materials (such as epoxy resins or acrylates) engineered materials can be used, *e.g.*, to create a biodegradable material. Such materials have been used, among others, by Lee *et al.* who used a biodegradable polymer mixture consisting of poly(propylene fumarate) (PPF) and diethyl fumarate (DEF) to create scaffolds for bone tissue engineering with feature sizes in the range of a few hundred micrometres.[233] Choi *et al.* have shown that STL can also be carried out on more than just one material by simply removing and replacing

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the resin at a given time during the manufacturing process.[234] They have built structures consisting of alternating layers of the commercially available epoxy resins WaterShed 11120, ProtoTherm 12120, and Somos 14120 White (all by DSM Somos, USA). Arcaute *et al.* showed the use of various polyethylene glycol acrylates in a single structure intended for tissue engineering.[235] Rapp *et al.* created microfluidic flow cells with the commercially available epoxy resist Accura 60.[70]

As stated, maskless lithography has been a focus point of recent interest in the development of next generation lithographic devices. In STL, maskless lithography is typically implemented by means of DMDs. Such devices have been used for the creation of three dimensional objects by means of STL in the scientific literature, *e.g.*, by Choi *et al.*[236] who created various shapes with smallest feature sizes in the range of about 70 µm as well as structures created with PPF/DEF polymers.[237] For such systems the use of a UV lamp which is filtered and projected onto the DMD is commonly required. The image reflected by the DMD is collected by a collimation lens with suitable optical transmission characteristics and projected onto the resin bath or layer. A commercially available system for performing maskless STL is the Perfactory system by EnvisionTec (Germany). This system implements a layer configuration STL with a *z*-resolution starting from 15 µm to a few hundred micrometres depending on the resin used.[238,239] As stated, care has to be taken to ensure the created layers do not stick to the window. A number of methods to avoid this have been suggested for this system including the use of flexible membranes[230] and the periodic tilting of the window to mechanically separate it from the constructed part.[240] The system's resolution in the *x*/*y*-plane depends on the chosen magnifying or demagnifying projection objects and can be in the order of a few micrometres to several hundred micrometres. A resin commonly used in combination with the Perfactory system is the resin R11 (EnvisionTec, Germany) although other resins have also been used.[65] The suitability of this system for the creation of microfluidic devices has been demonstrated, among others, by Yang *et al.*[241] Besides a leaf-like microfluidic channel structure, the authors created three-dimensional channel networks with typical channel diameters in the range of 250 µm. Snowden *et al.* have shown the use of this system for the creation of 3.5 mm long, 3 mm wide microfluidic channels with heights varying between 200 µm and 250 µm.[242] The channels were used for the electrochemical characterization of oxidation processes on chip.

STL is a very versatile method for the rapid production of prototypes with low concept-to-chip times. It allows the quick creation of arbitrary three-dimensional structures from 3D-CAD. The techniques can be used either as a one-step manufacturing process in order to directly create structures suitable for microfluidics or as a two-step manufacturing process for the creation of replication molds. There are two important aspects to consider when using STL as one-step manufacturing techniques. First, most STL materials are not designed for applications in liquid environments. This is especially true for epoxy based resins which tend to swell heavily in contact with water. This can be overcome by using nonstandard resins such as specifically modified monomers that will, once cured, be water repellent and hydrophobic in nature. The Somos WaterShed resin series is one of the few commercially available resins that allows for the creation of low water absorbing structures. In order to fully exploit the potential of STL for microfluidics it is usually necessary to use commercially available polymer precursors or monomers as resins.[65] This implies that the user is to blend these materials with suitable photoinitiators, inhibitors and crosslinkers in order to obtain a functional resist. This requires knowledge about the chemistry and the reaction kinetics of such monomers and represents a field of research which is yet to evolve for microfluidics. The second aspect to consider is that in choosing materials one has to be aware of the (potential lack of) biocompatibility and chemical resistance of the polymers created from a certain monomer. For such materials extensive testing may need to be carried out before using them for microfluidic applications. This may represent a significant obstacle for institutes and companies not familiar with these techniques.

3D printing

Another method for the precise application of material by means of layer-on-layer deposition is commonly referred to as 3D printing. Given the fact that a lot of the manufacturing technologies are able to create three-dimensional structures, the name is misleading. In general the term 3D printing is referred to as the layer-on-layer technique creating structures by selectively applying either droplets of glue into a bath of the bulk material in powder form (power printing) or droplets of light curable resin (inkjet printing). The principal component for both processes is an inkjet printing head (thus the allusion to printing), usually in the form of a set of individually addressable nozzles mounted on a movable *x*/*y*/*z*-stage. The nozzles apply liquid (glue or curable resin) onto a building platform according to sliced three-dimensional data.

Inkjet 3D printing. In the simplest form inkjet 3D printers can be considered the three-dimensional equivalent of commercially available paper printers which use light curable resins and wax instead of inks (see Fig. 8a). The wax is usually required to create spatially constrained volumes which are to be filled with the light curable resins. This supporting structure approach is required as the typically spotted resins do not remain confined at the spot where they have been applied to due to their low viscosity. This low viscosity on the other hand is required in order to allow inkjet application *via* an inkjet nozzle in the first place thus the wax is used to compensate for this problem by creating supportive structures to keep the spotted resin in place. If phase change resins are to be used the inkjet nozzle needs to be heated in order to turn the resin liquid and allow for spotting. The resin drop hardens when spotted with increased spatial confinement. However, supportive structures are typically still required. The part to be constructed is usually built on a table with the first layer being laid out in direct contact with it (bottom plane, refer to Fig. 1). An inkjet nozzle or an array of nozzles applies droplets of heated low viscous wax according to the given three-dimensional digital data. The wax hardens almost instantaneously forming cavities into which the resin is spotted. The resin is either cured directly after spotting or the curing is carried out only after a complete layer has been spotted. The second layer is built directly on top of the first layer repeating this process until the complete part is constructed.

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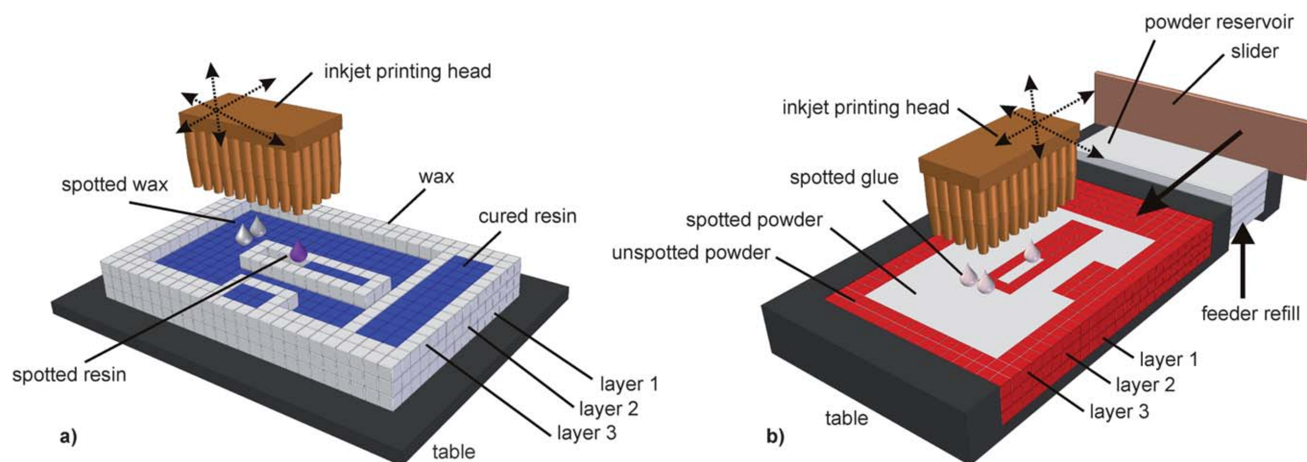

Fig. 8 Principal setup of 3D printing. (a) Inkjet 3D printing—a movable array of nozzles is scanned across a table on which the part is manufactured. The nozzles apply liquid wax in molten form and liquid curable resins. The wax is used to create supporting structures in order to keep the liquid resin locally confined. The resin is cured by means of spatially confined light or heat induced polymerization. After the complete part has been constructed the supportive wax structures are removed by melting the wax and potentially the use of a solvent. (b) Powder 3D printing—a movable nozzle array is used to spot droplets of glue into a bath of bulk material in powder form. This bath is prepared by means of a slider that applies powder from a reservoir. The slider ensures that the powder layer is even before the glue is spotted into it. Where a droplet of glue is applied a voxel of material is created whereas the nonspotted areas remain as loose powder. After a layer is spotted the next layer of fresh powder is prepared and the procedure repeated. After the part has been built completely tempering can be used to ensure complete curing of the glue before the nonspotted powder voxels are removed.

Besides curing *via* light other processes have been suggested such as the use of a single droplet dispenser and the use of chemicals that trigger a chemical reaction when spotted into the resin. Potential chemical reactions include the polycondensation of silane compounds such as acetoxy silanes by the application of water.[243] After the part is constructed the wax is removed by means of heating and potentially the use of vacuum and solvents. Care has to be taken in order to completely clear the constructed microfluidic channels which may be a difficult task due to high capillary forces which may be too high to release the melted wax from the channels.

If structures are to be used as replication molds only the mere application of wax (without the use of a curable resin) may be sufficient. Applications of such pure wax printing are typically in the creation of masters for PDMS replication[244] or to create etching masks, *e.g.*, for selective etching of channel structures into polyimide as demonstrated by Wang *et al.*[245] The same group demonstrated that printed wax is a suitable layer for the thermal bonding of several layers of polyimide. Chan *et al.* manufactured microfluidic channel side walls by applying droplets of paraffin wax onto a glass plate. A second glass plate was used as the channel ceiling with the sandwich being squeezed in a way that the paraffin droplets formed a fluid tight channel structure with channel widths in the range of 100 μm.[246]

One of the most prominent commercial systems available is the Eden printer series by Objet (Israel). This system uses a combined application of photocurable acrylic resins and removable material for the creation of supporting structures. The system features a lateral resolution of about 40 μm in the *x*/*y*-plane and a resolution of 16 μm in the *z* direction. The system has found application in the creation of microfluidic mixer structures as well as sensor cartridges.[247] Another commercial product is the Thermojet printer (3D systems, USA). The system only dispenses droplets of wax which is typically not suitable for microfluidic applications and can therefore only be used to create replication molds. Another commercially available system is the ZPrinter series by ZCorporation (USA). The system is intended as a full 3D color printer with a resolution in the range of 100 μm. The materials are usually not suitable for applications in liquid environment and the resolution would only allow for microfluidic structures of larger size. However, the Thermojet as well as the ZPrinter have been studied for a potential use in prototyping devices for cell culture although the low resolution and the materials have been considered problematic in this study.[248] McDonald *et al.* have suggested using the Thermojet printer as a potential tool for the creation of molds for PDMS replication.[249] Other systems are the V-Flash Personal 3D Printer as well as the ProJet printer series (3D Systems, USA) which both feature resolutions of about 25 μm in the *x*/*y*-plane and of about 100 μm in the *z* direction. The systems are intended for a wide range of application starting from prototyping in industry to the creation of molds for dental implants. They typically print a combination of UV curable acrylic resins and waxes as supporting materials. Solidscape (USA) is another supplier for wax 3D printers and features comparable resolutions.

The main drawback of inkjet printing is the fact that the range of potential materials is limited as the process allows only the processing of resins with sufficiently low viscosities. If the viscosity is too high there is an increased risk to create structures with manufacturing errors or even the destruction of the printing head. For most systems the user loses warranty if the system is used with materials other than the ones provided by the system manufacturer. This limits the choice of materials significantly as the materials developed for 3D printing may not necessarily be suitable for microfluidics directly due to low chemical or biological compatibility.

Powder 3D printing. In powder 3D printing the inkjet printer applies glue at defined locations into a bath of the bulk material which is provided in powder form (see Fig. 8b). The main

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building space is usually a platform onto which a thin layer of powder is spread by means of a slider that ensures a smooth and even surface. The slider is usually fed from a powder reservoir that is continuously fed (*e.g.*, from below) with fresh material. After an even layer has been laid out the inkjet head applies the first layer by means of localized application of small droplets of a glue that will form bulk material voxels when in the powder. After the first layer is created the second layer of powder is applied by means of the slider and the process is repeated. When the part is finished it is usually tempered to allow full curing of the glue. Afterwards the non-bound powder is removed. Again the creation of long and narrow microfluidic channels may be difficult due to the difficulty of removing powder from the channel after the building.

Commercial systems include the R-1 R&D printer by Prometal (USA) which is intended for the creation of parts from metal powder and the TheriForm system by Therics (USA) which has been used, among others, for scaffold manufacturing onto which synthetic skin is applied.[250] Compared to inkjet printing powder printing has the advantage that it does not rely on the bulk material of choice being available in a sufficiently low viscous form. For powder printing the material needs to be provided in a solid, mostly ground form which is feasible for most polymers as well as ceramics and even glass. However, this comes with some disadvantages, the most important one being the fact that the physical and chemical properties of the glue applied will be dominant in the created part. A second point to consider is that most objects created are not transparent due to light scattering by the particles in the bulk. This may also account for potential porosity due to insufficient particle binding or rough inner and outer surfaces.

Despite these concerns, 3D printing (maybe in a slightly adapted form) could well be used as a generic manufacturing technique for microfluidics if further engineering on the applicable glues addresses issues such as biocompatibility and chemical resistance. In general one can see from the literature that 3D printing is still an underrated process for the creation of microfluidic devices. For a lot of applications (such as the creation of replication molds) the process could well be suitable to create larger scale microfluidic structures; the current literature does not feature reports on this, though.

Selective laser sintering. A modified version of powder 3D printing is selective laser sintering (SLS). This process is essentially identical to the process described for powder 3D printing, but uses a laser to selectively warm and thus fuse the powder particles instead of applied glue. This process is able create solid forms from metals[251] as well as ceramics[252] and polymer powder. The latter has gained increasing interest in bone tissue engineering as the processing of materials such as polycaprolactone (PCL) is feasible with SLS.[253] One of the main advantages of SLS compared to the standard powder 3D printing process is the fact that no glue is required and therefore chemical and biological compatibility of the created parts is only defined by the properties of the bulk material. As for powder 3D printing there is no record in the literature for microfluidic applications of this technique yet.

Commercial systems include the Sinterstation HiQ system series by 3D Systems as well as the sPro SLS Centers by the same company. As SLS is a trademark of 3D Systems there are not many alternative suppliers on the market.

Fused deposition modeling

In 1989 Crump filed patents for a method called fused deposition modeling (FDM).[254,255] He cofounded the company Stratasys (USA) to commercialize the technology which is one of the most widely used manufacturing technologies for rapid prototyping and production in small scale today.[256] The technique uses a thermoplastic polymer wire for the creation of free forms. The equivalent term fused filament fabrication (FFF) is also found in the literature as FDM is a trademark of Stratasys. A schematic of the FDM process is depicted in Fig. 9. The main component of a FDM apparatus is a heatable nozzle mounted on an *x*/*y*/*z*-stage. The nozzle is fed with a polymer wire which is heated along its passage through the nozzle to a temperature around its glass transition point. The nozzle applies the melting polymer wire in strings layer by layer onto a substrate table upon which the object is being built. Usually the main polymer wire is used in combination with a second wire which consists of a sacrificial polymer material. This second polymer is used to create supporting structures in order to ensure the stability of the part being constructed. Without this the process could not create free standing structures such as the ceiling layer of a microfluidic channel because the main polymer wire would collapse into it. The material for this supporting polymer is typically either water soluble (in the case of internal supporting structures) or mechanically unstable in order to break it away easily in the case of external supporting structures.

Compared to other one-step manufacturing techniques, FDM can be used to structure almost any type of thermoplastic

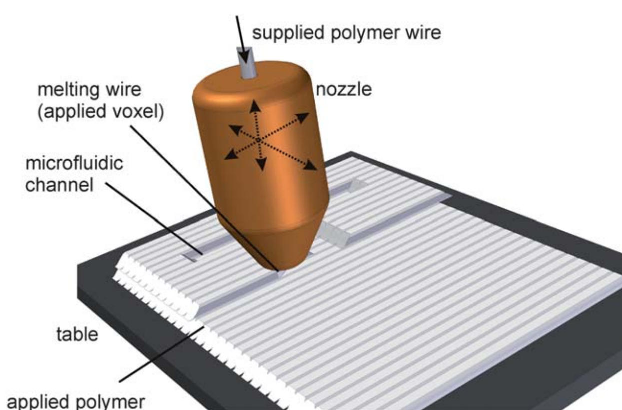

Fig. 9 Principal view of the fused deposition modeling (FDM) process. A nozzle fed with a polymer wire is moved in three dimensions across the building table onto which molten voxels of polymer are applied. The nozzle is heated to a temperature in the range of the glass transition temperature of the respective polymer which turns the wire into a formable voxel at the exit of the nozzle. While moving, the nozzle deposits strains of polymer wire onto the table layer by layer thus creating the part to be manufactured. Typically a set of several nozzles is used each of which is fed by a wire consisting of a different polymer. By this it is possible to create structures consisting of more than one material. One of these materials could be used as a supporting or sacrificial structure that will later be removed from the finished object.

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polymer. This is an important advantage compared to other techniques that require specifically modified polymers. Thus FDM can create components with chemical properties equal to components manufactured from bulk material, *e.g.*, by means of replication technology. It is possible to apply materials with different chemical or physical properties (including stiffness and color) subsequently *via* FDM thus allowing the creation of multi-material components. Typical materials include classical polymers such as PC, PCL, PP or PS as well as acrylonitrile butadiene styrene (ABS) which is the most commonly used material in FDM. Besides these classical materials composite materials have also been used such as glass reinforced polymers,[257] ceramics[258] as well as metals.[259] The latter two are usually particles in a polymer binder containing fiber. Detailed descriptions of the state of science have been given by Lenk for ceramics.[260] Even piezo-composites can be processed by means of FDM.[261] FDM is a commonly used technique for the creation of patient specific implants[262] created, *e.g.*, by computed tomography (CT).[263] Using polymers such as polylactide (poly(lactic acid), PLA) or polyglycolide (poly(glycolic acid), PGA) allows the creation of biodegradable components, *e.g.*, for cell culturing[264] or the embedding of drugs to be delivered to the wounded tissue.[265] Wang *et al.* demonstrated a process modification that used polymer in pellet form instead of a polymer wire.[266] The pellets were melted by means of a small extruder that was used instead of a nozzle. This process allows the application of filaments with diameters in the range of several 100 μm. A similar process is described by Woodfield *et al.* where a bulk polymer is molten in the nozzle prior to deposition in wire form.[267] The authors applied a polyethylene glycol derivative in filaments with typical diameters in the range of several 100 μm.

The most commonly used commercial systems include the Dimension (1200es, UPrint and Elite) series by Stratasys. This series commonly uses a *z*-resolution of 200 μm to 300 μm and allows the creation of models in ABS with the help of break-away or water soluble supporting materials. Another commercially available system is the 3D-Bioplotter by EnvisionTec which has been used, *e.g.*, by Son *et al.* for the creation of scaffolds for PCL.[268]

The main drawback of FDM is the fact that the process creates rough surfaces and the creation of channels with defined side wall geometry and straight walls is difficult. Typically, the final structure still displays the shapes of the polymer wire with which it was created.[269] This results in disturbances in the flow within the channels and leakage flow through the gaps between the single molten polymer wires.[270] Still, FDM has been discussed as a suitable technique for the creation of supporting structures as well as molding forms for two-step manufacturing processes[271] in microfluidics.

Direct writing

A very simple process for the creation of three-dimensional structures from highly viscous liquid or gel-like materials is the direct material deposition usually referred to as direct writing. This technique is applicable for a lot of biologically relevant scaffolding materials such as hydrogels.[272] In this process a nozzle is moved across a surface dispensing a wire of material similar to FDM. However, there is usually no heat involved and often the materials themselves are not mechanically stable which makes the spatially confined application difficult due to the low structural resilience of the applied structure. The simplest version of such a process is a syringe mounted on an *x*/*y*-stage as demonstrated by Vozzi *et al.*[273] The authors applied a mixture of PCL and PLA with line widths down to about 20 μm. Ang *et al.* have used a liquid dispenser mounted on an *x*/*y*/*z*-stage in order to create scaffolds from chitosan–hydroxyapatite for tissue engineering with an applied wire diameter of 150 μm.[274] Yan *et al.* have demonstrated the use of a nozzle array that allows the simultaneous deposition of several materials. Additionally the use of droplet deposition instead of wire deposition (sometimes referred to as extrusion) is discussed as an alternative process variation by the authors. Besides droplet application, spraying is a commonly used techniques as presented, *e.g.*, by Xiong *et al.*[275] The authors demonstrated the suitability of this process for the creation of net-like structures with filament diameters in the range of 500 μm. Such structures especially with engineered filament pitches and thus adjustable porosities are important for tissue and bone scaffold engineering.[276]

The main disadvantage of direct writing techniques is the fact that the physical shape of the material is hard to control once applied which makes the creation of filigree structures difficult. One method to solve this problem is to decrease the temperature of the applied liquid (potentially almost down to the freezing temperature) thus increasing the viscosity as demonstrated by Xiong *et al.*[277] Due to the low chemical and physical resistance of the materials applied direct writing does not support the application of supporting structures such as waxes as commonly used, *e.g.*, for 3D printing. Free standing structures or microfluidic channel structures are therefore hard to create which is the reason why this technique is not commonly used as a one-step manufacturing technique. However, using directly written structures as replication masters is a viable alternative to create three-dimensional channel networks for microfluidic devices. Typically a volatile organic ink is used for the direct writing process creating a network structure that is immersed into a curable resin. After polymerizing the resin the organic ink is removed, thus leaving a complicated three-dimensional microfluidic channel with channel sizes down to a few ten micrometers. Such devices have been used, *e.g.*, for three-dimensional mixing.[278]

Two photon polymerization

Another important technique for the rapid prototyping by means of optical lithography is two photon polymerization (2PP) which is sometimes also referred to as two photon absorption (TPA) polymerization (see Fig. 10). This process usually uses ultrashort laser pulses that are focused into the volume of a liquid resin and trigger photopolymerization by means of two-photon absorption. TPA makes use of the fact that a single photon at low energy may not be sufficient to trigger one photon excitation, but two of them may yield sufficient energy to trigger the excitation of a fluorophore which in turn emits a photon that will trigger polymerization. The emission wavelength of this photon can be of shorter wavelength than the excitation, thus allowing excitation and emission wavelength to be adapted in such a way that only the emission falls within the wavelength at which the resist

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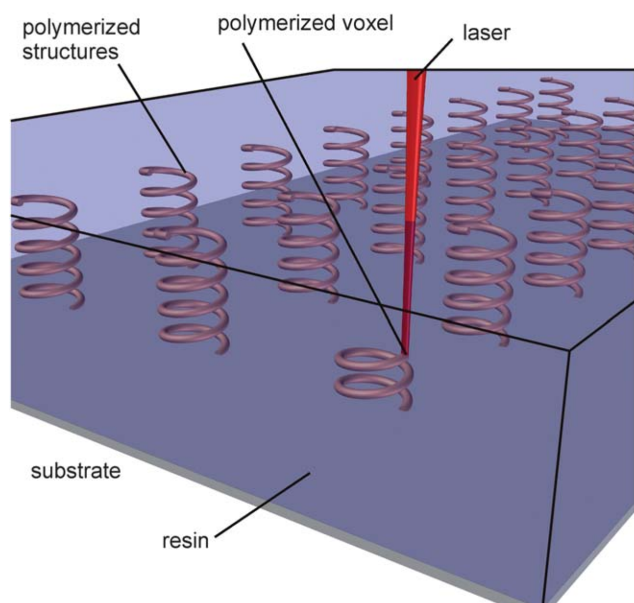

Fig. 10 Principal setup of the 2PP process. A pulsed laser spot is focused and scanned through a liquid resin blended with dyes and photoinitiator. The focused spot will create two photon absorption and thus polymerization in a locally confined volume typically in the range of a few nanometres voxel edge length.

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can be cured. In order to increase the probability of this event the flux of photons is to be kept at a reasonably high level; therefore the use of lasers is usually required. TPA was first described theoretically in 1931 by Goeppert-Mayer[279] and first demonstrated practically in 1961 by Kaiser and Garrett[280] who used an excitation wavelength of 694 nm to obtain fluorescence at 425 nm in a CaF_2:Eu^{2+} crystal and in 1962 by Abella in caesium vapor.[281] 2PP has found a wide application range in microsystem technology and has been described as a suitable technology for large scale structuring.[282] For microfluidic applications typical structures are needles[283] or scaffolds for tissue engineering as well as meshes and porous structures for filtering or purification of analytical fluids.[284,285] Kumi *et al.* describe the creation of replication masters from SU-8[286] which could also be directly used for microfluidic applications. The structures are three-dimensional and feature fluidic channels with widths and heights in the range of a few ten micrometers at high aspect ratios. Such structures have been described by Liu *et al.*[287] Wu *et al.* have discussed the use of this technique for the fabrication of free standing and movable components such as mechanical microvalves, levers and nanoshells in SU-8 and NOA 61.[288] Microfluidic and optical structures combined are described by Reinhardt *et al.*[289] A very interesting approach for microfluidic applications is presented by Coenjarts and Ober.[290] Instead of using classical photoresists the authors demonstrate the potential use of a PDMS based resin that can be cured by means of 2PP thus obtaining complicated three-dimensional channel structures with channel cross-sections of only a few μm^2.

The main drawback of this technique for the creation of microfluidic components is the fact that 2PP is a serial writing technique which means that the voxels are cured one by one. Therefore the process is inherently time consuming when the area of exposure or the number of layers increases. In order to partially compensate for these drawbacks recent contributions to the scientific literature have seen the use of wide field illumination to increase the overall building speed.[291] 2PP is a very interesting process for the creation of structures that, due to their physical structuring, can be used to manipulate the properties of light and thus be of use for optics and plasmonics. Examples of such applications can be found elsewhere.[292,293] Besides the creation of structures, the two photon effect can also be used for applications in microscopy.[294]

Suitable materials for 2PP include classical positive and negative resists. These materials are usually blended with suitable photoinitiators as well as a dye that provides suitable photon emission.[295] Especially suitable for microfluidic applications due to their high biocompatibility are acrylic resins such as polyethylene glycol diacrylate (PEG-DA) or ethoxylated trimethylolpropane triacrylate (commercially available under the trade name SR499 by Sartomer, USA).[296]

2.5-Dimensional printing

In contrast to 3D printing the printing of 2.5-dimensional structures is a widely available technique for the rapid creation of microfluidic devices. It can be performed with almost any type of inkjet or laser toner printer. The most common use for printing technology in microfluidics is the creation of printed photomasks as originally suggested by Duffy *et al.*[297] Besides the creation of replication masters for microfluidics printed masks are also used for the creation of copper electrodes by means of etching *via* protective photolithographic resist layers.[298] However, the creation of microfluidic structures by means of 2.5-dimensional printing is a viable option as well. Do Lago *et al.* as well as Coltro *et al.* have shown the use of an off-the-shelf laser printer for the creation of simple microfluidic channel structures.[299,300] In their work a toner layer was printed onto a planar polymer sheet leaving those areas unprinted that would later form the microfluidic channel. The toner can be used to allow thermal lamination of two structured polymer sheets, thus forming microfluidic channels with a depth corresponding to twice the height of the toner layer (which is about 6 μm, so an overall channel depth of 12 μm can be achieved). The group has demonstrated the process to be usable with a wide variety of polymers (such as polyester) and glass.[301] Liu *et al.* demonstrated that printed grayscale regions within such microchannels can result in rough surfaces that can be used as micromixers.[302] The printed structures can also serve as a replication master (typically for the replication with PDMS) for a two-step manufacturing technique and is generally referred to as "print and peel" (PAP). The method was originally suggested for 2.5-dimensional microfluidic structures by Tan *et al.*[303] Commonly, these printed structures are combined with 3D printed geometries such as passive micromixers.[304] Detailed discussions about potential application scopes of this technique can be found elsewhere.[305] The technique can also be used to deposit electrodes from a metal containing solution inside a microfluidic channel[306] or to pattern cell or protein solutions onto surfaces.[307]

Another potential 2.5-dimensional printing technique suitable for the creation of microfluidic structures is screen printing which involves the application of thicker layers of inks, pastes

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or polymers through a solid mechanical mask which is typically supported by a mesh. This technique is commonly used for the creation of electrodes[308] or insulators but could potentially also be used for the creation of microfluidic channel structures. The main drawback of the technique is the fact that a solid mask is required and the spatial resolution is not very high.

Another printing technique which is commonly referred to as "Print-n-Shrink" uses commercially available heat shrinkable sheets of polymers. After structuring these polymer sheets are exposed to heat in a standard laboratory oven and will experience shrinkage to about a third of the original size in each dimension. These polymer sheets are typically made of PS and are structured either by toner deposition *via* printing[309] or by screen printing of inks or pastes[310] as well as by any material removing technique. Channel widths and depths of about 100 μm are achievable with this technique.

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Two-dimensional virtual hydrophilic channels

Microfluidic devices can be purely two-dimensional if the channels exist as mere virtual channels. On surfaces this is possible by the generation of locally confined hydrophilic and hydrophobic regions. The fluid would flow on the hydrophilic regions being confined by virtual channel walls consisting of hydrophobic regions. Such hydrophilic regions can be created by means of surface modifications or oxidations, *e.g.*, by plasma irradiation. The first technique results in time stable gradients, whereas gradients created by surface oxidation will degrade over time. The recent years have seen an increasing interest in the preparation of inexpensive and simple microfluidic devices that are purely two dimensional. The concept was described by Martinez *et al.* using paper soaked in photoresist that was lithographically structured.[311] The regions where the photoresist remained in the paper exhibited a higher hydrophobicity than the areas where the photoresist was removed thus a two dimensional microfluidic structure was created that was used for demonstrational detection of glucose and proteins.

Another modification of this process is suggested by Abe *et al.*[312] They suggest the use of a hydrophilic paper which was coated with a solution of PS in toluene. The toluene was evaporated leaving a PS coating that could in the next step be selectively removed by printing toluene by means of an inkjet printer at those locations that should reveal the hydrophilic paper and thus create open pathways along which fluids can flow. A commonly used modification of this technique is the so-called FLASH (fast lithographic activation of sheets) process that also implies the use of a paper soaked in photoresist which is covered on the top side with a transparency foil onto which the lithography mask is printed and with a black light absorbing slide on the back side.[313] The latter reduces reflections during the lithography process. The sheets are exposed to UV light after which the transparency foil and the absorbing foil are removed and the fluid guiding structures revealed by removing unexposed photoresist. These processes are able to create fluid guiding structures of widths in the range of 200 μm on inexpensive materials such as standard paper towels. The resolution is mainly influenced by the structure of the paper and the resolution of the inkjet printer.

One drawback of guiding fluids on top of a substrate is the fact that the liquid can evaporate or be contaminated due to pollutants which can be taken up from the ambient air. In order to avoid these problems single layers with virtual channels can be stacked. Paper sheets for example can be stacked by means of hydrophobic adhesive tapes which allows the creation of multilayer microfluidic structures such as complete assays or printing stamps for the application of protein solutions and the like.[314,315] Another technique to reduce this risk of evaporation is to create hydrophilic networks inside a protected chamber which has been suggested by Watanabe.[316] The substrates used are glass slides which are turned hydrophobic by silane treatment with hexamethyldisilazane after which droplets of dimethyl sulfoxide (DMSO) onto the glass are applied which will turn the spotted areas hydrophilic. The glass is placed onto a second substrate spaced at a distance of 100 μm. Fluid entering this gap will flow along the hydrophilic line avoiding the hydrophobic region. In this setup the fluid is partially protected. Rinsing the complete chamber with solvent dissolves the DMSO line which makes the microfluidic network reconfigurable. Later a commercially available inkjet printer was used to apply the hydrophilic ink for which, besides DMSO, ethylene glycol, dioxane and ethanol were suggested as alternatives.[317] If the top layer of the microfluidic channel is modified additionally to the substrate capillary forces can be created to autonomously drive fluid flow.[318]

Community projects

Today the creation of microfluidic systems can be carried out by a number of techniques that are not necessarily restricted to companies or laboratories that have access to state-of-the-art machining equipment. During the early 1990s microfluidics was a scientific discipline only accessible if access to typical MEMS manufacturing technology, such as mask aligners, wet etching processes and replication technology, was available. With the introduction of elastomers such as PDMS microfluidics spread towards application centered laboratories becoming a widely supportive discipline accessible to a great number of people. PDMS casting can be considered the first cheap two-step manufacturing process. Before casting became popular, two-step manufacturing was mainly carried out by means of injection molding or hot embossing. These processes required access to expensive machining equipment both for the creation of the molding tools and the replication.

As stated, one-step manufacturing techniques are the techniques of choice for small scale production. Providing low cost one-step manufacturing techniques could lead to a similar increase in the spread of microfluidics as has been achieved by the introduction of PDMS casting. As highlighted in this work, a number of one-step manufacturing techniques are available today that can be used to create structures using cheap commercially available instruments such as a cutter or a desktop printer. But what about processes that involve more elaborate equipment such as CNC mechanical structuring or 3D printing? Can such techniques be made available as low cost manufacturing alternatives to small laboratories as well? There is a substantial public interest in the development of such processes

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and the impact of these systems on industry and technology has repetitively been discussed as being considerable.[319,320]

This section intends to highlight some of the work currently being undertaken in communities typically organized *via* the internet that aim at providing such instruments at low cost. These instruments are intended to be used by people interested in the technology and could therefore be well suitable for laboratories or companies that have a technical background. As will be seen, some of these projects have been going for quite a long time already and some of the equipment developed can almost compete with commercially available systems but are available at a fraction of the cost. Please note that due to the diverse state of documentation for these systems it is hard to generally state the suitability (or the lack thereof) of these systems for the creation of microfluidic systems and the information given shall therefore be regarded as an estimation. To the best of our knowledge this work is the first contribution highlighting the potential use of these community project systems for microfluidics and there is no published work available that accesses the suitability further.

Mechanical structuring: open source CNC machines

The first noteworthy class of instruments is open source CNC machining equipment. The common goal of the communities around homemade CNC machines is the creation of macroscopic parts in the lateral range of up to several decimetres or even metres. The main focus of the various designs is therefore often to reduce the cost of production and equipment by keeping a certain minimal precision. There is no central hub for open source CNC designs, but most systems use the LinuxCNC software for controlling, their forums are therefore a good place to start.[321]

DIYLILCNC. The DIYLILCNC is a project to create and improve the design of a three-axis CNC milling machine.[322] The project incorporates a low cost hand-held mill as cutting tool. The current version of the system has an estimated total material cost of roughly 700 US$ and can therefore readily be set up at low cost. The mechanics of the system allows for a theoretical positioning accuracy of around 100 μm in the *x*/*y*-plane and 8 μm in the *z*-axis. As the assembly accuracy will have an influence on the overall positioning precision these values will vary from individual machines. This precision is mainly influenced by the resolution of the movable stages used to set up the machine and could potentially be reduced further.

CNCBMO. The origins of many homebuilt CNC machines are derived from an original project by Oltrogge.[323] He mainly used wood to set up the frame for the instrument and distribute the complete construction documentation for around 80 US$. The estimated overall material cost of the CNCBMO is around 3000 US$.

Open source laser direct machining: Lasersaur

Besides CNC machining there is ongoing work on the construction of open source laser cutters, the most notable project being the Lasersaur project.[324] The design of the project is developed closed source by a few individuals who promise to make all designs and software available under an open source license as soon as the project exits the beta stage. They plan to reach this stage within this year. Eventually the parts required to build the machine will be made available as a kit for sale as well. Earlier access to the designs is available through a one time payment (in the range of below 100 US$). The information about the design and specifications of the Lasersaur is hard to come by, but if the laser diode can be pulsed or moved in the *z*-axis, the Lasersaur might be suitable for laser direct machining and would allow the production of 2.5-dimensional microfluidic structures.

Open source FDM: RepRap

One of biggest and most prominent communities of the open source machining community is the one developing the RepRap project.[325] The name represents the design goal of the community: RepRap aims to be a replicating rapid prototyping machine. The aim is that if one machine is available, most of the parts for a second can be printed out quickly with it. This will help spread the technology quickly and cheaply and should make 3D printing available to a wide community. The RepRap is a FDM machine design that was initially started by Adrian Bowyer but is now in community hands: all designs are available under a free license and the further development of the machine is handled by many individuals and groups and is organized over the internet. This community proved very resourceful and entrepreneurial in the way they tackled problems encountered. For example the PLA needed as build material for most RepRap designs was hard to come by for some, so a few people from the community founded a company to distribute it.[326]

The construction of a RepRap is not a trivial task and it typically required to have a first RepRap available in order to create the parts required for a second machine. This led to various companies being founded which sell kits of RepRap derivatives which do away with the design goal of reproducibility and concentrate on easier construction. The most prominent is MakerBot which offers various FDM machine kits based on the RepRap design.[327] A similar European company is Ultimaker.[328] Adopting the RepRap to print ceramics instead of PLA by a direct writing process is the focus of the Belgian Design Studio Unfold ∼fab.[329] As it is the nature with open source projects, all derivatives of the RepRap must also be released under an open source license and are therefore also free projects. In general it seems suitable to start setting up a RepRap from one of the commercially available system kits. A very important advantage of the RepRap project and its derivatives is the fact that data parsing and slicing can usually be carried out with the same system software stack which facilitates matters for the user as there is generally information available online.

The increasing popularity and spreading of open source three-dimensional home fabrication systems brought with it the need for a place to find and share digital designs. The people behind MakerBot instantiated the website Thingiverse to satisfy this need.[330] Thingiverse is now the de-facto standard site for digital designs that are meant to be fabricated in hardware. It is not only limited to MakerBot and RepRap designs but also offers

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templates for laser cutters, commercial FDM machines, 2D printing or plotting, sintering and CNC machines. It also contains new design proposals for various parts of the RepRap machine itself.

As literally no RepRap design or even machine is alike, it is hard to get a fair estimate of machine specifications in order to assess its suitability for the production of microfluidic structures. One example of a RepRap system for which these specifications are available is the MakerBot kit Thing-O-Matic.[327] The website states a resolution of 20 μm in the *x*/*y*-plane and a resolution of 5 μm in the *z*-axis. Again PLA is used as material. These specifications are comparable with commercially available FDM systems and would therefore allow for the creation of structures suitable for microfluidic devices or as molding tool for such devices. In order to expand the specifications towards the creation of even smaller features the open and well documented setup of the system can be changed in order to trade building volume for precision to a certain extent by redesigning some of the mechanical systems.

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Open source SLS

Peter Jansen, an active tinkerer in the RepRap community, started the investigation of open source laser sintering.[331] His approach started out by using the laser from a DVD burner to melt black ABS. His current design is using a low power laser module and a mechanical layout that can laser cut complete sheets of plywood. The stated design goal is the development of a fully functional SLS machine that can also be used as a slow and low energy laser cutter for less than 200 US$ in parts.

One of the described prototype designs is a mini 3-axis CNC stage constructed from three axes taken from commercial CD drives offering very high position accuracy. In order to cut through bulk components Jansen suggests moving the laser's focus spot along the *z*-axis (a process which he refers to as reciprocating laser) which would allow for direct processing and cutting of 2.5-dimensional parts made of black ABS or nylon.[332] Following the traditions of the RepRap community, he regularly posts on the RepRap Builders blog[333] and makes all his designs available on Thingiverse. While he has no fully functional prototype available as of yet, his experiments and studies have spurred great interest in the community already.

Open source 3D powder printing

One of the major problems for open source 3D powder printing is the great number of patents that have been granted for powder and inkjet based 3D printing. To improve the situation, the Solheim Rapid Prototyping Lab of the University of Washington started to make their experiments with nonpatented combinations available for free in a blog.[334] One of the few well documented completely open source projects that provide hardware designs for powder based printing is the HM3DP by Alvaro M. Fogassa.[335] The main component of the machine is an inkjet nozzle mounted onto a *x*/*y*/*z*-stage for spotting adhesive into a powder bath. Most documentation of his work as well as project derivates and the community surrounding it can be found online.[336]

Open source DLP based stereolithography

As stated the use of commercially available DLP projectors can greatly enhance projects intended to set up a stereolithography based on DMDs. One prominent example of such a system is provided by Junior Veloso. He constructed a high resolution 3D printer system using a commercially available cheap DLP projector.[337,338] The system is a layer-on-layer based approach using maskless stereolithography. The resolutions that are achievable are around 50 μm in all axes. Even though the project is not open source, the design and instrument construction were documented in the forum, so redoing it is straightforward. Veloso states that kits containing all parts and software required for his printer including a DLP projector with a suitable lamp will be made available for approximately 1000 US$.

General remarks

As can be seen community projects that intend to design equipment suitable for one-step manufacturing are becoming more and more diverse. As of today there is a number of systems already available for a fraction of the cost of commercial systems. Besides the costs such systems offer another great advantage compared to commercial systems: they are easily adaptable to the needs of a specific application. Even though none of the described systems have been used for microfluidic system manufacturing so far, modifications of quite a few of these systems would well be suitable for doing so and it seems to only be a matter of time until this will be effectively demonstrated.

Summary and conclusion

The intention of this work is to demonstrate and sum up in brief potential manufacturing strategies for microfluidic structures that can be used to create the structure of interest in one step. Thus these techniques are referred to as one-step manufacturing techniques. As can be seen the choice of potential technologies is ample but the number of publications actually describing the creation of microfluidic structures with the individual techniques varies significantly. Some of these techniques may not yet be appropriate for microfluidic device creation because of the insufficient surface qualities or the limited choice of materials that can be processed with the respective techniques. For other technologies it is not so straightforward to see why the scope of applications is yet so small. As the technological progress continues some of these techniques may become a future viable option for prototyping in microfluidics especially on a laboratory scale where small number production of microfluidic devices can be considered the norm. This trend is complemented by the increasing activity in a number of community projects that may also be able to provide, in the not so distant future, low cost processes and equipment for the creation of applicable microfluidic structures available to laboratories and companies that do not have the financial capacities to invest in, *e.g.*, state-of-the-art lithography equipment. The further dissemination and the range of potential applications of microfluidic devices will depend heavily upon such trends and developments and open up the benefit of this discipline to even more researchers worldwide.

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Abbreviations

μSTL	micro-stereolithography
μTAS	miniaturized total analysis systems
2PP	two photon polymerization
ABS	acrylonitrile butadiene styrene
AFM	atomic force microscopy
CD	compact disc
CNC	computer numerically controlled
COC	cyclic olefin copolymer
CT	computer tomography
CTFE	chlorotrifluoroethylene
CVD	chemical vapor deposition
DEF	diethyl fumarate
DMD	digital mirror devices
DMSO	dimethyl sulfoxide
DRIE	deep reactive ion etching
ECTFE	ethylene chlorotrifluoroethylene
EDM	electrical discharge machining
ETFE	ethylene tetrafluoroethylene
FDM	fused deposition modeling
FEP	fluorinated ethylene propylene
FEPM	tetrafluoroethylene/propylene rubbers
FFF	fused filament fabrication
FFKM/FFPM	perfluoroelastomers
FLASH	fast lithographic activation of sheets
FPP	frontal photopolymerization
HF	hydrofluoric acid
HFP	hexafluoropropylene
KOH	potassium hydroxide
LIGA	acronym for the German words *Lithographie* (lithography), *Galvanik* (electro plating) and *Abformung* (replication)
LLM	layer laminated manufacturing
LTCC	low-temperature co-fired ceramics
MEMS	microelectromechanical system
MMA	methyl methacrylic acid
NOA	Norland Optical Adhesive (a thiol–ene polymer)
PAP	print and peel
Parylene C	poly(*p*-xylylene) C
PC	polycarbonate
PCL	polycaprolactone
PCTFE	polychlorotrifluoroethylene
PDMS	polydimethylsiloxane
PE	polyethylene
PEC	polyethylene carbonate
PEEK	polyetheretherketone
PEHD	high density polyethylene
PET	polyethylene terephthalate
PFA	perfluoroalkoxylalkane
PFPE	perfluorinated polyether
PGA	polyglycolide (poly(glycolic acid))
PLA	polylactide (poly(lactic acid))
PMMA	poly(methyl methacrylate)
PMVE	perfluorovinylmethylether
PNB	polynorbornene
PEG-DA	polyethyleneglycol diacrylate
POM	polyoxymethylene
PP	polypropylene
PPC	polypropylene carbonate
PPF	poly(propylene fumarate)
PS	polystyrene
PSA	pressure sensitive adhesive
PSU	Polysulfone
PTFE	polytetrafluoroethylene
PU	polyurethane
PVA	polyvinyl alcohol
PVC	polyvinyl chloride
PVDF	polyvinylidene fluoride
PVME	perfluorovinylmethylether
RIE	reactive ion etching
SLM	spatial light modulator
SLS	selective laser sintering
STL	stereolithography
SU-8	a commonly used epoxy resin
TE	thiol–ene
TFE	tetrafluoroethylene
THF	tetrahydrofuran
TPA	two photon absorption
UV	ultraviolet
VDF	vinylidene fluoride
XGA	extended graphics array

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