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REVIEW

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Laser processing for bio-microfluidics applications (part I)

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Abstract This paper reviews applications of laser-based techniques to the fabrication of microfluidic devices for biochips and addresses some of the challenges associated with the manufacture of these devices. Special emphasis is placed on the use of lasers for the rapid prototyping and production of biochips in particular for applications in which silicon is not the preferred material base. Part I of this review addresses applications and devices using UV lasers for laser ablation and surface treatment of microchannels, in particular in polymers.

Keywords Laser · Micromachining · Bio-MEMS · μTAS · Microfluidics · Polymers

Introduction

Microfluidics is an emerging technology for advanced analytical chemistry, biology, diagnostics and biomedical research. Traditional approaches largely rely on the use of conventional inorganic substrates such as glass and silica, because of their well-established and extensive usage in the semiconductor and chromatography industries, their well-understood and adapted physical and chemical properties, and the long history of well-characterized surface derivatization chemistries. They dominated the early development of microfluidics because of the ease of transfer of existing macroscopic technologies and protocols to miniaturized systems, and the availability of fabrication techniques for the construction of networks of channels and other features adapted from microelectronics technologies such as photolithography and etching techniques. However, these materials have disadvantages due to a variety of factors, some due to their bulk-material properties such as their inherent brittleness or the lack of optical transparency of silicon, but mostly due to the limitations of the associated fabrication methods, such as the time-consuming multistep processing of these microfluidic chips, the low aspect ratios obtained through chemical etching, and the slow and low-yield annealing process for the enclosure of their microfluidic channel network. In addition, the cost associated with their processing is too high to make disposable devices on a cost-effective basis. The recent trend towards the use of polymeric substrates, in particular for mass-fabricated single-use products, has been primarily driven by the fact that these materials are less expensive and more adapted to mass-production techniques than silica-based substrates. In particular, "dry" techniques, such as replication technologies adapted to smaller scales from macrofabrication methods like injection molding, hot embossing or casting, allow the production of large batch sizes while new fabrication techniques are also being developed, such as laser ablation and plasma etching. The development of polymer substrates is also fuelled by the increasing development and commercial availability of a diverse range of polymer materials and a wide range of polymer chemistries that can be tailored to the chemical and physical needs of specific applications.

We refer to the recent review of Verpoorte and de Rooij [1] for an overview of micromachining methods for microfluidics, in particular in silicon, glass and quartz, and transparent insulating materials such as silicon nitride or oxide. Concerning the fabrication of polymer microfluidics, Becker and Gärtner [2] and Becker and Locascio [3] have reviewed mainly the microfabrication methods for thermoplastics polymers, while Heckele and Schomburg [4] have reviewed more specifically the hot-embossing process.

This review, which includes parts I and II, focuses on the challenges of prototyping and manufacturing microfluidic devices with particular emphasis on polymeric materials and biological applications. It presents the applications of lasers in direct manufacturing and microjoining techniques to construct biodevices, as well as use of laser treatment to modify the chemistry and/or topography of polymeric microchannels to increase their functionality. Developments in laser structuring of microtools for volume

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replication of microparts as well as in laser-based processes, such as laser-LIGA, are also reported. Part I of this review first addresses challenges associated with producing microfluidic devices and summarizes the principles and applications of laser micromachining. It then describes applications taken from the open literature using UV lasers for laser ablation in polymers and glass and surface treatment of polymeric microchannels.

Challenges of laser micromachining for microfluidic applications

The need for flexible and rapid processes is increasing in all fields of microsystem technologies, in particular in lab-on-chip applications in order to meet the demands of great flexibility, rapid turn-around time and lower cost in developing products. The techniques of rapid prototyping, rapid tooling and rapid manufacturing, which are fairly standard in modern manufacturing, gain more and more significance. Rapid prototyping is a big advantage during the design stage of these elements, since flow characteristics of complex structures are difficult to model and are dependent on dimensions. Consequently, there is also a growing interest in the development of a number of alternative serial fabrication techniques based on the removal of materials and adapted to prototyping polymeric devices, such as micro-milling and laser micromachining. These direct fabrication techniques are reasonably straightforward and do not require access to clean-room facilities. In particular, they do not require the generation of masks, like photolithographic techniques, or molds, like the transforming techniques, which adds an additional step to the microchannel fabrication process and reduces flexibility as minor modifications to the design then require the fabrication of a completely new mask or mold.

Micromilling is a well-established technique that is very flexible and fast for the manufacture of single microstructures, but presents limitations with regard to throughput of large batch sizes, as well as to design freedom and quality due to the size and controllability of the milling tool. The chip cost is also comparatively high due to slow machining speeds and considerable tool wear. Laser micromachining is a highly precise, fast, and contactless alternative to classic machining. The great flexibility of the materials deployed and the geometries attainable qualifies these processes in particular for the rapid prototyping of microfluidic structures. Making more complex systems of channels with more sophisticated fluid-handling capabilities through the fabrication of true 3D microstructures gives laser micromachining some key benefits over other, more established micromachining techniques that would require multilayer and multistep processes including stacking and joining substrates. One of the most evident trends is the increasing level of complexity of microfluidic-based systems and integration of individual elements, not only fluidic, but also electrical or electrochemical, chemical or biochemical, optical, etc., in a single device to impart higher levels of functionality, which results in the fabrication of features in different materials and at different levels. An important drawback of many microchip technologies is the post-processing that must be undertaken after the fabrication of the microstructures. Laser-based techniques are compatible with a high level of integration through complementary and post-processing, which allows a unified fabrication approach and can also provide integrated solutions for manufacturing. For example, microelectrodes in thin metal film can be patterned inside the channels to provide electrokinetic pumping for fluid transport within the microchannels; some surface properties after fabrication can be controlled by laser modification and patterning; and concerning fluidic and electrical interconnection, access holes and vias can easily be formed by direct laser ablation.

Another important aspect of microfluidic devices is the ability to enclose the fabricated features so as to allow fluid flow through the device. A usual approach for fabrication of microchannels and fluidic access holes to generate a microfluidic circuit first involves the formation of "open" microstructures, such as channels and reservoirs, into the base layer of polymer, then sealing of the features in the base layer to a cover layer. This last step can be accomplished using an adhesive interlayer or by chemical or thermal techniques that join the two layers (laminating, direct and thermal bonding, plasma activation, ultrasonic and laser joining). The combination of microstructuring by means of direct laser ablation and laser welding offers the advantage of being able to produce closed biodevices. These techniques can be applied over a wide range of materials.

Although an array of techniques is available for the manufacture of polymeric microfluidic structures, issues such as the control of surface chemistry still remain to be addressed as many polymers do not possess all the desired properties for biochip operation, and in many cases the walls or surfaces of polymeric microstructures need be modified to suit the particular application. Unlike glass, for which the surface chemistry is well known, processes need to be developed to change the chemical nature of the polymer surfaces and increase their functionality to (1) establish local hydrophilic or hydrophobic areas, (2) modify charges on microchannel surfaces through precise control of the type and density of ionizable surface groups to tune the magnitude of the electro-osmotic flow (EOF) and control the movement of solutions in microchannel networks, e.g. to optimize separations and ultimately lead to more reproducible device performances, and (3) treat specific areas to control adsorption and nonspecific binding of biomolecules, or increase the biocompatibility of materials, or control and precisely pattern functional molecules and materials of biological origin, which are critical to the further development of many technologies. Polymer surfaces are generally modified by wall coatings, surface chemistry, plasma treatment, or energetic radiation. However these techniques require additional fabrication and characterization steps and raise issues about the stability of the surface after modification and during use. Laser treatments offer advantages over both chemical and other physical methods as they enable precise surface modifica-

tion and surface charges during the fabrication process with little surface damage. They are rather simple techniques, easily controlled, and they are environmentally clean and safe processes. Moreover, laser-based techniques can offer an alternative to other microfabrication techniques such as photolithographic-based methods or micro-contact printing for precise surface patterning of functional molecules, critical to the development of many technologies.

The advantages of laser-based techniques for microsystem manufacturing are numerous. Any solid can be laser machined under the appropriate conditions and processes have been established to machine with high precision a very large variety of materials, such as ceramics, metals, and polymers. Laser-machining covers a wide range of techniques, such as macro- and microscale structuring, drilling, fine cutting, joining, and surface modification, that can be used to fabricate a device in its entirety or can be integrated in a hybrid processing chain with other techniques. In particular it can be used to shape materials both laterally as well as into the depth of the material, hence allowing the manufacture of structures with complex geometries including three-dimensional shapes or structures with varying wall shapes and etch depths, and various aspect ratios on the same substrate, which represents a great difficulty for planar clean-room techniques. Another situation favoring the use of laser micromachining is the use of non-planar substrates. Laser-based techniques allow a high level of flexibility in the chip layout because they directly use digital data generated during the design of the chip; thereby allowing a design to be changed easily and rapidly and iterations with a new prototype with incremental improvements to be made in a microfluidic design. Using a focused laser for direct writing patterns avoids the need for the photo-mask to demonstrate proof of concept, enabling fast turnaround, compared with conventional processes. The process is therefore especially suited for rapid prototyping.

For using a new material it is more straightforward to develop a laser ablation process, compared with the effort to develop other processes, such as a reactive ion etching process, for example. Due to the good beam-shaping properties (focusing capability), laser beam energy may be concentrated on microscopically small areas, allowing for precise control of the laser energy in the focal spot, enabling precise controllability of the energy deposition and very localized materials-processing with minimum affect on the overall part, resulting in a low heat deposition in the workpiece. Moreover, the operating set-up does not require very special conditions like clean rooms and there is no wet etching involved. Many process steps can also be carried out on the same machine. Laser processing technology can be advantageously combined through hybrid processing with other micro-and nano-machining techniques, such as high-resolution techniques derived from clean-room technologies like lithographic methods and plasma etching, or from mechanical machining, such as electro-discharge machining and ultra-precision milling. It can also serve as a complementary tool to slower production techniques such as replication technologies, for example hot embossing. The customization of generic structures that have been fabricated by other techniques is also possible, enabling the fabrication of devices that derive their characteristic properties from small modifications in the overall structures. Laser processing is also used in a chain of hybrid technologies for packaging applications.

Laser micromachining: principles and advantages

Lasers are established, efficient, and flexible tools in many areas of industrial production, from product development to finishing. They are unique energy sources characterized by their spectral purity, spatial and temporal coherence, and high peak intensity. While most of them, being vastly more expensive than traditional tools, only slowly found niche uses, their advantages made up for the added cost and complexity. Laser micromachining is a field that has developed rapidly over the last decades.

All laser micromachining techniques use the process of laser ablation, where the interaction of the laser energy with the sample leads to material removal observed above a certain threshold that is material-, wavelength-, and pulse-duration-dependent. Laser ablation usually relies on the strong absorption of laser photons by the sample material, which means that the wavelength of the laser has to be chosen carefully for maximum absorption. The use of ultrafast lasers, however, has circumvented this approach since ablation takes place as a result of multi-phonon absorption at high peak intensities, which means that even materials normally transparent to the laser wavelength can be machined.

The ablation mechanism is a complex combination of photochemical and photothermal processes and is dependent on the laser characteristics and materials properties. Generally speaking, the high photon energies of UV lasers are capable of direct bond breaking in an organic material strongly absorbing at the wavelength of the laser emission, leading to ablative photodecomposition, a relatively ‘cold’ process with minimum collateral thermal damage to the substrate, while longer wavelengths mainly initiate thermal reactions that will first melt and then decompose the material, leaving a void in the workpiece. The laser wavelength therefore plays an important role in the minimization of the heat-affected zone. Laser pulse duration also plays a critical role in the laser–material interaction and significantly affects the quality of the microfeatures created and also the material removal rate. Absorption mechanisms in the case of ultrashort laser pulses (subpicosecond and femtosecond duration) differ from those involved when longer pulses are used. The potential of ultrashort laser pulses for material processing is based primarily on the possibility to localize energy deposition to dimensions smaller than the diffraction limit of the focusing optics on the surface or in the bulk of materials through nonlinear absorption mechanisms, and to reduce residual damage by minimizing thermal effects. Another important characteristic of femtosecond laser ablation is its capability to machine any kind of material,

in particular transparent materials. The physical aspects of lasers and details of laser micromachining processes are beyond the scope of this review and can be found in various books and articles dedicated to the subject. Some general features concerning modes of operation and types of lasers will, however, be recalled for the sake of clarity.

There exist two modes of laser micromachining: (1) a serial mode for direct writing, also called scribing, and (2) a parallel mode for batch process using a mask-imaging technique where the laser beam is imaged through a mask onto a workpiece, generally using a demagnifying projection lens. In general, serial machining is good for prototyping because there is no requirement for a mask. Data from a file can be used to generate a tool path for the laser beam. On the other hand, mask projection is generally preferred for large-scale production.

The choice of wavelength depends on the optical properties of the substrate material such as absorption and reflection characteristics and on the minimum structure size to be achieved. Theoretically, minimum feature sizes down to the minimum achievable focal spot (about twice the laser wavelength) or the optical diffraction limit $\lambda/2$ are possible.

A variety of different laser sources offering a broad wavelength spectrum from deep UV (157 nm) to IR (10 μm), and pulse durations from microseconds to femtoseconds can be utilized to process specific material types effectively:

- UV lasers, excimer and frequency-converted Nd:YAG lasers, which are typically operated in pulsed mode:
  - Excimer lasers operate at various wavelengths depending on the gas composition used in the laser cavity, such as F_2 (157 nm), ArF (193 nm) , KrF (248 nm), and XeCl (308 nm). The excimer laser produces low coherence beams with high pulse energies (0.01–1 J) and relatively low pulse frequencies (<1 KHz). This combination of parameters makes them ideally suited to the mask projection mode. Excimer lasers can machine a very wide range of materials. However, they are particularly suited to polymers as, for most polymers, strong absorption at excimer wavelengths ensures efficient laser–target coupling, while relatively low thermal conductivity ensures minimal thermal diffusion during the ablation process and a very small heat-affected zone. Furthermore, strong absorption at UV wavelengths leads to low material removal rate in most materials, allowing a precise control of the etched depth. Therefore, in many cases, excellent surface finish and minimum collateral damage (melting and/or debris) can be achieved.
  - The pulsed solid state (Nd:YAG) lasers emitting in their third and fourth harmonics at 355 nm and 266 nm have high pulse frequency (5–100 KHz), low pulse energies (<1 mJ) and highly coherent beams that can therefore be focused directly to very small spot sizes. These lasers tend to be operated for direct writing in serial scanning mode. Pulsed solid-state lasers are becoming increasingly attractive as they can offer (1) a wide choice of wavelengths (either through direct tunability and via harmonic generation), (2) a variety of temporal pulse widths (ranging from milliseconds to a few femtoseconds), (3) high pulse repetition rates (from tens to hundreds of kilohertz), (4) a large choice of output powers and (5) economically favorable running costs.
  - Frequency-converted copper vapor lasers also produce lines in the UV at 289 nm, 271 nm and 255 nm.
- Lasers with longer wavelengths such as Nd:YAG lasers, frequency-doubled in the visible (532 nm) or in the fundamental mode at 1,064 nm, the visible lines of copper vapor (511 nm and 578 nm) lasers, Ti:sapphire (775 nm), CO_2 lasers in the deep infrared range (10.6 μm), and diode lasers emitting between 808 and 980 nm. IR lasers are most often used for cutting and welding or micromachining metals and ceramics.

The remarkable properties of lasers make them stand out as excellent tools for microengineering and their use in microsystems manufacture is increasing. In particular, Holmes [5] reviewed the use of high-power lasers for MEMS manufacture.

Micromachining microfluidic devices with UV lasers

Several groups used UV laser micromachining to directly pattern microchannels and modify the resulting surface, especially for polymer-based devices.

The Laboratory of Electrochemistry of the Federal Polytechnic Institute of Lausanne (EPFL), Switzerland, pioneered the use of UV laser ablation for the production of microfluidic chips in polymer substrates and thoroughly studied multiple aspects of laser ablation of polymers, in particular poly(ethylene terephtalate) (PET). Roberts et al. [6] demonstrated the fabrication of channels with micrometer-sized features, straight side walls and high aspect ratios in a variety of polymer substrates including polystyrene, polycarbonate, cellulose acetate, and PET using an ArF excimer laser (193 nm) radiation projected through a mask with a demagnification factor of 10. Efficient sealing of the resulting photoablated channels was accomplished using a low-cost two-layer PET/polyethylene film lamination technique. Numerous works have highlighted the increase in the surface roughness induced by the photoablation process, in particular the dependence on the laser fluence. It is also known that the photoablation process is not only able to create structures within polymer substrates but also can substantially change the surface properties of the resulting surfaces, such as wetting properties, surface charge, and formation of new functional groups, compared to the surfaces of the original material. This work reported that, relative to the original polymer samples, the photoablated surfaces showed an increase in

their rugosity and hydrophilicity as a group, as well as possessing a negative charge capable of generating capillary flow or even electroosmotic flow when filled with a buffer and placed in high electrical fields. These results showed the compatibility of the laser-machining process with various liquid-handling operations based on electrosmotic flow control and outlined their potential for miniaturized diagnostics systems and micro-scale total analysis systems (μTAS) applications such as capillary electrophoresis.

Rossier and Bercier [7] pointed out that most of the physical characterization studies of photoablated polymers had been performed on surfaces of structures fabricated in a static photoablation mode where the laser beam is focused on the surface of the polymer in the absence of a translational motion of either the beam or the substrate. However, fabrication of microfluidic devices is performed in a dynamic mode, i.e., implying motion of the polymer target relative to the laser beam. They exemplified differences in the surface states of PET induced between these two modes of ablation. The surface characterization studies revealed a homogeneous surface with a high degree of crystallinity and a poor wettability for PET ablated in the static mode, whereas dynamic ablation provided an inhomogeneous and hydrophilic surface. These differences were attributed in part to the effects of redeposited fragments.

Bianchi et al. [8] extended this work and showed the possibility of controlling the surface modification in a microchannel by alternating dynamic and static ablation procedures. They also demonstrated that well-defined static patterning in a microchannel can significantly reduce the electroosmotic flow and that this patterning could be used as an alternative to photochemical treatments to locally modify the surface potential. Rossier et al. [9] reviewed the new concepts developed at EPFL fulfilling the demands of both prototyping and mass production of polymer microfluidic chips for electrochemical and biochemical analyses that are based on two complementary technologies, laser photoablation and plasma etching. They were able to produce microsystems with integrated electrodes in a polymer microchannel system using a combination of UV ablation and carbon ink deposition [10].

Another requirement concerns the possibility of controlling some surface properties after fabrication, which is indeed critical to the development of many technologies. Laser-induced changes in the chemical properties of polymer surfaces, if sufficiently controlled, can be engineered on the microscale to affect protein adsorption or to introduce functional groups allowing easy covalent attachment of particular affinity reagents, for example, generation of two-dimensional arrays of microspots to carry out affinity assays. Schwarz [11] demonstrated that UV laser ablation could be combined to protective surface blocking methods to pattern biomolecules on polyimide and pPET surfaces. Two techniques, low-temperature laminates or protein (BSA) layers, were explored to block the adsorption of labelled proteins from bulk solutions. UV-excimer (193 nm) was used to create laser-defined openings in those protective blocking layers, which opened the underlying polymer substrate surface and allowed physical adsorption of biomolecules. The ablation process produced well-defined patterns with feature sizes of 10–1,000 μm. Enhanced hydrophobicity and roughness of ablated surfaces in comparison to native surfaces enhanced the adsorption of hydrophobic proteins up to three-fold in the ablatively patterned region. The simplicity of the demonstrated patterning technique showed the possibility of biomolecule patterning within polymer-based microanalytical systems. Finally, a preliminary characterization of protein adsorption and immunosorption kinetics was carried out in the photoablated PET channel sealed with a PET/polyethylene layer [12].

NIST also pioneered the use of excimer lasers for generating microchannels and modifying their surfaces. Waddel et al. [13] utilized a KrF laser (248 nm) to create channels in a number of polymer substrates: poly(methyl methacrylate) (PMMA), poly(vinyl chloride) (PVC), poly (ethylene terephthalate glycol) (PETG), and polycarbonate (PC). They studied the parameters affecting the ablation, such as laser fluence and laser repetition rate, as well as the local ablation atmosphere to control the topography and surface state of the channel. Smoother channels were obtained by using slower velocities, lower fluence, and higher firing repetition rates. It was determined that the physical morphology of the ablated region was dependent on the temporal profile, the spatial profile, and the wavelength of the laser pulse. The longer the laser pulse length, the greater the fluence required to ablate the substrate. Similarly, for a given substrate material, different ablation wavelengths afford different limiting aspect ratios. The physical morphology of the channels was also found to be a function of the local atmosphere at the ablation site. In addition to these physical changes, they also observed changes in the surface chemistry and surface charge of ablated polymer substrates. For example, ablation of PMMA under nitrogen or methanol resulted in a rectangular channel profile, whereas ablation under water resulted in a wedge-shaped profile. Ablation of polycarbonate under different atmospheres yielded different electroosmotic flows.

Johnson [14] used a KrF laser (248 nm) to modify the surface charge on the sidewall of microchannels fabricated in a PMMA substrate by hot-embossing. Sub-ablation level fluences were used to prevent ablating or changing the physical dimensions of the preformed channel. The authors showed that the electroosmotic mobility induced by an electric field applied along the length of the channel increased by an average of 4% in the regions that had been exposed to UV laser pulses compared to nonexposed regions. Furthermore, they suspected that laser modification could be applied to decrease band broadening of electroosmotic flow around the turn of a microchannel.

Johnson and Waddell [15] compared surface modification in hot-embossed and UV laser-photoablated microchannels within a PMMA substrate. Using a 248-nm excimer laser system to modify the PMMA surface, they confirmed that changes in the surface properties were not limited to ablation-level laser pulses, but that a measurable

change in the surface chemistry of the polymer occurred when the surface was exposed to UV pulses below the ablation threshold, which induced an increased surface charge. They monitored fluorescently labelled carboxylate groups, which are responsible for the surface charges, and showed that the amount of charge present in hot-embossed PMMA microchannels was significantly less compared with laser-ablated microchannels where charges appeared to be distributed uniformly. Surface charges were also dependent on the irradiation strategy and atmosphere of ablation (nitrogen and oxygen) and post-treatment. The authors also confirmed that this surface modification technique could be applied to reduce the band-broadening effects due to the dispersion in electrokinetic flow around turns by increasing the surface charge on the outside wall of the turn to compensate for the decreased electric field and increased path length between the inside and the outside of the turn, as an alternative to altering the channel geometry. Their study showed that lasers can spatially modify surface charges to allow for fine control, adjustment, and modulation of the wall properties and to obtain the desired electrokinetic flow profiles without using wall coatings or changing the geometry of the channel to achieve the desired flow profile.

Henry et al. [16] studied this aspect of laser ablation and chemical surface modification in more detail, manufacturing channels in PETG under various atmospheric conditions and comparing the control of EOF within these channels. They showed that laser-ablated channels had EOF rates similar to hot-embossed channels that were base-hydrolyzed, which in turn demonstrated a somewhat higher flow rate than as-produced PETG hot-embossed channels. These studies demonstrated that surface-bound carboxylate species could be used as a template for further chemical reactions in addition to changing the EOF mobility within microchannels.

Finally, Pugmire et al [17] investigated changing the ablation atmosphere during the excimer laser ablation of polymer microchannels for fabricating the microchannels as well as controlling their surface properties and associated electroosmotic mobility in a one-step process. The studied substrates that exhibited nonnegligible absorption at this energy, namely poly-(ethylene terephthalate glycol), poly(vinyl chloride), and poly(carbonate), showed significant changes in surface chemical composition and EO mobility with varying ablation atmospheres, with ablation under nitrogen or argon resulting in low EO mobilities with a loss of the well-defined chemical structures of the native surfaces, while ablation under oxygen yielded surfaces that retained native chemical structures and supported higher EO mobilities. In contrast, the ablated surfaces of PMMA were very similar to the native material, regardless of ablation atmospheres due to the negligible absorption of 248-nm light by that polymer.

The Industrial Research Institute of Swinburne (IRIS) in Australia has also been actively involved in using excimer lasers for the manufacture of microfluidic devices and developing new strategies for specific applications. In particular, Suriyage et al. [18] used excimer laser ablation in projection mode (at 248 nm) and hot-embossing techniques to produce microchannels and reservoirs in some commonly used polymer substrates, PC, PET and SU8. They modelled and visualized species transportation with respect to electroosmosis and electrophoresis under different conditions of plug concentration and location of the injection point and reported that laser-ablated polycarbonate channels had the highest mobility among the three materials, and that hot-embossed microchannels in both PC and PET had a lower electroosmotic mobility than their respective values for laser-ablated channels. The authors attributed this result to the fact that the excimer laser ablation process by mask dragging produced a hydrophilic surface chemistry [19], which had improved the electroosmosis in the channel.

Thissen et al. [20, 21] developed a method for use as an effective tool for a number of in vitro and in vivo applications. They combined a unique surface chemistry, based on the deposition of an allylamine plasma polymer on silicon wafer and perfluorinated poly(ethylene-co-propylene) substrates followed by grafting of a protein-resistant layer of poly(ethylene oxide) (PEO). The generation of a spatially controlled surface chemistry allowed control over protein adsorption, a process that mediates cell attachment. The production of two-dimensionally controlled patterns of specific proteins with a resolution circa 1 μm and a nanometer-precise thickness control was accomplished using a fast, one-step laser ablation at 248 nm (KrF). Thissen et al. [22] also used a combination of plasma deposition followed by laser ablation to spatially modify the surface chemistry of surfaces in a controlled manner. They exemplified this method by creating surfaces with controlled wettability in 2D on top of silicon wafers where a first coating of n-heptylamine and a subsequent perfluoro-1,3-dimethylcyclohexane coating were plasma-polymerized, each polymer coating being respectively hydrophilic and hydrophobic. Excimer laser ablation was used to remove a defined thickness of the two-layer coating conferring the appropriate wetting properties.

Wright et al. [23] described a direct-write laser-based method to create narrow channels in a bilayer system consisting of a UV-sensitive polymer, acetophenone O-acryloyloxime (AAPO), layered with bovine serum albumin (BSA), the latter acting as a common blocking agent to prevent nonspecific binding of other biomolecules. By using a focused pulsed nitrogen laser emitting at 337 nm, channels 1 μm wide and 0.15 μm deep were etched into the BSA-coated polymer. AAPO was used here as a sacrificial layer that was selectively ablated from beneath a transparent substrate when irradiated at 337 nm, thus removing as well the attached protein and producing regions that were sufficiently hydrophobic to promote binding of biomolecules. The addition of myosin to the base of these channels provided tracks on which actin filaments could move exclusively. This process, a variant of the method used by Schwarz et al. [11], consisted of patterning from the top down by selectively removing the protecting protein layer then the underlying polymer.

Atkin et al. [24] demonstrated the suitability of a direct-write method using a frequency-tripled Nd :YAG laser at 355 nm to machine polyethylene-teraphtalate film. This method allowed for rapid prototyping of biochip fabrication and for complex geometric shapes to be realized with channel dimensions as small as 10 μm. Untreated PET is hydrophobic compared to glass, the traditionally preferred biochip substrate. The authors showed that the cutting process provides an increase in the hydrocarbon content at the surface, resulting in a decrease in surface charge, hence reducing electroosmotic flow. However, with chemical treatment (saponification), it was possible to render the ablated surface more hydrophilic, improving electroosmotic flow and providing an increase in carboxylate ions that allow a tethering platform for DNA oligonucleotides. This methodology provided a cost-effective process for constructing PET biochips with tailored surface chemistry. Thomson et al. [25] demonstrated the possibility of modifying the internal surfaces of polymer microfluidic devices by the addition of plasma polymers and graft polymers, and subsequent patterning of that material. Channel structures in polycarbonate were first coated by plasma polymerization of allylamine followed by grafting of polyethylene oxide, a protein-repellent surface. Excimer laser ablation was then used to pattern PEO to control protein adhesion in the microfluidic channels.

Many other groups employed UV lasers to develop microfluidic systems. In particular, at the University of Wales at Bangor, Pethig et al. [26] used excimer laser-ablation techniques to manufacture a biofactory-on-a-chip device based on dielectrophoretic transport capable of performing a wide range of complex diagnostic tasks for the electro-manipulation and characterization of cells, microorganisms and other particles. The biochip was constructed from multilayer thin films. Electrodes, typically 10 μm in width, were patterned at a wavelength of 248 nm and accurately profiled interconnecting via holes were produced in the insulating layer. Gray scale micromachining was used to produce channels and manifold structures in polycarbonate as well as for the fabrication of molding tools for hot embossing. Laser micromachining was also applied to the creation of mold tools for casting microfluidic interconnection ports in PDMS [27].

At the Pacific Northwest National Laboratory, the manufacture of polymeric microfluidic analytical devices in polycarbonate and polyimide using a stacked architecture incorporating multiple functional layers, each performing a specific function, such as a double-layer microdialysis unit to purify and desalinate DNA and protein samples for mass spectrophotometric analysis, was accomplished using a KrF laser at 248 nm in combination with a lamination process [28–30].

Lin et al. [31] used UV excimer laser micromachining in bulk polyimide or polycarbonate substrates and a lamination process to fabricate a complete microfluidic analytical device including a microfluidic motherboard, a dual-stage microdialysis chip, and a micro-capillary isoelectric focusing device incorporating an electrospray ionization tip and interfaced on-line with electrospray ionization/mass spectrometry (ESI-MS) to provide a rapid and automated tool to concentrate, separate, and analyze complex protein mixtures. Electrosmotic flows in the laser-ablated channels were typically lower than in fused silica capillary and were compatible with the ESI-MS.

The Fraunhofer Institute of Laser Technology in Aachen, Germany [32], developed a membrane-actuated microreactor array for combinatorial solid-phase chemistry. The microreactor matrix in polytetrafluoroethylene (PTFE) was microstructured by an F_2 laser at 157 nm whereas the PFA membrane was laser welded. The Xerox Wilson Center for Research and Technology [33] manufactured a range of microfluidic structures such as a particle micro-pore polyimide filter, fluid manifold, channels, and nozzles and incorporated them in a picoliter droplet dispenser for integrated thermal inkjet printheads. They used a KrF laser at 248 nm for densely packed feature sizes smaller than 50 μm with tolerances below 5 μm, whereas the adhesive interface with a multi-layer fluid seal between macrofluidic and microfluidic regions was patterned by a low cost CO_2 laser.

Excimer lasers have also been used to machine various polymers for a number of different microfluidic applications. One can mention for example the manufacture of novel composite membranes as an effective transducer for the selective transfer and sensing of molecular ions [34]. The membrane consisted of an upper layer of PET film, UV laser-photoablated at 193 nm (ArF laser) with a microhole array supporting the ion-sensing layer of hot-cast plasticized polyvinylchloride film. Matson et al. [35] also employed excimer laser direct patterning at 248 nm to produce membranes for solvent separators by a step-and-drill method, but they also developed a mask patterning process to create multiple pores of small size. McNeely et al. [36] developed a rapid prototyping technique to fabricate passive hydrophobic, microfluidic device systems integrated with macro, external devices aimed at highly parallel sample analysis. They used KrF excimer laser to perform bulk laser ablation of fluorocarbon polymers compounded with carbon black to be absorptive in the 248-nm-wavelength region.

Sabbert et al. [37] machined cycloolefin copolymer (COC) with no redeposition effects, smooth surface and ablation rates smaller than for PMMA using an ArF excimer laser (193 nm). Numerous works have reported that polyimides, including Kapton, the most popular polyimide, have better photoablation properties than those of PMMA at the wavelength of the KrF excimer laser for applications such as drilling of ink-jet nozzles and production of filters; for example, Gower and Rizvi [38] investigated the use of frequency-tripled Nd:YAG lasers to machine inverse taper nozzles in polyimide. Gillner et al. [32] used F2 lasers at 157 nm to pattern poly(tetrafluoroethylene) microstructures for microfluidic and medical components. They also laser-structured silicone microimplants. Killeen et al. [39] used direct-write laser ablation to fabricate a polymeric microfluidic device with integrated mass-spectrometer interface that included linear arrays of electrospray tips with concentric fluidic channels, a seamless fluid path from liquid sample to electrospray tip,

as well as an interface to microtiter plates with no dead volume.

Kim et al. [40] used the fourth harmonic Nd:YAG at 266 nm to modify the surface of silicon and polytetrafluoroethylene (PTFE) to improve their wettability and adhesion characteristics. They also performed direct writing of copper lines by pyrolytic decomposition of copper formate films using a focused argon ion laser at 514 nm. Kim and Xu [41] used a KrF laser (248 nm) to machine the diffuser and chamber of a diffuser polymer micropump in Kapton. Pfleging et al. [42] used various UV lasers, KrF (248 nm) and ArF (193 nm) excimer and frequency-tripled and frequency-quadrupled Nd:YAG laser sources emitting at 355 nm and 266 nm, respectively, to directly ablate and locally modify polymers, in particular PMMA. The best surface quality was obtained for 193 nm, which induced a pure photolytical ablation, superior to that of the frequency-quadrupled Nd:YAG at 266 nm, though in the latter case the higher repetition rate made the process faster. They also reported direct ablation of polyimide channels with a frequency-tripled Nd:YAG laser.

Yoshida [43] used UV laser micromachining (Nd:YAg at 266 nm and KrF at 248 nm) to create 3D channels and connections in various laminates of heat-hardening resin films. Grooves with slopes and differences in levels could also be produced [44]. Yao et al. [45] used a KrF laser at 248 nm to manufacture a flow-through PCR chip in PMMA. Finally, Yu et al. [46] manufactured embedded channels by multi-step inclined exposure in a single-layer SU8 film using a scanning laser direct-write system (third harmonic of Nd:YAG laser at 355 nm). This technique takes advantage of the flexibility of the laser system in controlling the in-depth laser manufacturing process precisely and quantitatively by adjusting the laser energy or varying the laser focus level. This technique greatly simplifies the process and is well adapted to the 3D manufacture of microstructures and devices.

An area where laser surface modification of polymers is critical is the biocompatibility of biomaterials since surface chemistry and topography ultimately affect the nature and strength of the interactions occurring at the interface between the biomaterial and the biological environment and control, e.g., water and ion sorption, protein adsorption, cell adhesion, mobility, spreading, and proliferation. Several methods of surface modification including UV exposure lead to the introduction of functional groups correlated with, in particular, a higher hydrophilicity; these methods have been studied by many groups. Concerning the use of UV lasers, Nakayama and Matsuda [47] used an excimer laser microsurface-processing method to fabricate microporous polymer films, which may serve as micro-architecturally well-defined substrates in biomedical fields for a number of functional biodevices such as artificial organs. They used a KrF excimer operating at 248 nm to etch well-defined micrometer-sized pits into several polymers to increase the biocompatibility of surfaces of segmented polyurethane, polyimide, and polycarbonate.

Khorasani et al. [48] carried out a series of works using laser treatment to induce surface modifications, thus improving the performance of existing biomaterials. In particular they studied various surface modifications of PDMS using a CO_2-pulsed laser. They showed that laser treatment induced chain ordering and porosity onto PDMS surface, resulting in a super-hydrophobic surface [48, 49]. They also made PDMS surfaces hydrophilic by laser-induced graft polymerization of HEMA, which showed a higher blood compatibility than untreated PDMS but not as high as super-hydrophobic PDMS surfaces [50]. Duncan et al. [51] used a high energy KrF excimer laser (248 nm) to machine poly(ethyleneterephtalate) (Mylar) in order to create well-defined and reproducible surface microstructures at the micron and submicron level and to evaluate their effects on osteoblast-like cell behavior.

Bremus-Kobberling et al. [52] used a technology based on excimer laser treatment of polymer surfaces at 193 nm (ArF) with different fluences and cumulated energies to study the influence of four different topographies (regular ripplings, scales, wells and pillars) with dimensions from 50–250 μm to modify the surface properties with respect to the wettability and controlled cell behavior. They reported that the natural tendency of the polymers was enhanced: naturally hydrophobic polymers like poly(dimethylsiloxane) and perfluoro-aloxy-copolymer became superhydrophobic (lotus effect), while polymers with polar functional groups like poly(etheretherketone), polycarbonate, poly (methylmethacrylate), and poly(ethylenterephtalate) or polymers with aromatic groups like polystyrene strongly increased in hydrophilicity. This technique was applied to tailor the surface properties for medical implants with respect to wettability and controlled cell growth as well as to control and direct cell growth or to guide cells for tissue engineering. The authors also locally modified the chemistry of polymer surfaces by UV photochemical immobilization of azides from solution as an anchor for further modification steps and by immobilization of biologically active molecules for biochips. Heitz et al. [53] successfully modified hydrophobic surfaces of poly(tetrafluoroethylene) by UV irradiation using sources emitting below 200 nm (172 nm excimer lamp, 193 nm ArF laser or 157 nm F2 laser) in a reactive (NH_3) atmosphere. The modified PTFE surfaces, both on large surfaces or selectively on small spots exhibited a good wettability, good adhesion towards metal coatings and a high degree of compatibility with cell adhesion and proliferation.

Laser micromachining is also used to fabricate biodegradable microdevices for biomedical applications as a rapid, flexible and chemical-free process that does not deteriorate the bulk properties of the material. Kancharla and Chen [54] employed excimer laser Xe-Cl at 308 nm and a frequency-quadrupled Nd:YAG laser at 266 nm to direct-write microchannels and holes for ultra-filtration membranes in poly-D-lactic acid and poly-vinyl-alcohol with minimum thermal damage. Chen et al. [55] reviewed the advancements of laser micromachining for etching biodegradable polymers and concluded that deep UV lasers such as 193 nm were a better choice to minimize photothermal effect. Aguilar et al. [56] used a Ti:sapphire femtosecond pulsed laser and ArF excimer laser to direct-

write micron-sized channels and holes in poly(ε-caprolactone) and poly(glycolic acid) and reported that both lasers could successfully pattern biodegradable polymers.

Several groups have also investigated the use of lasers to machine glass substrates with application to microfluidic devices. One of the difficulties is the brittleness and poor thermal properties of most glasses, making the fabrication of finely machined features a challenging task with a risk of laser-induced microcracking and other laser-induced collateral damage such as debris and poor surface quality. The two main ways to overcome these limitations are to use short wavelengths (UV) that can be focused down to smaller spot sizes and thereby produce smaller spot sizes or use lasers with ultra-short pulse duration to reduce thermal effects. Well-defined surface microstructuring of transparent fused silica glass was performed by laser-induced backside wet etching using a nanosecond-pulsed excimer laser irradiation at 355 nm [57, 58]. Nikumb et al. [59] investigated the direct-write laser machining of glass using short pulses from nanosecond (Nd:YAG at 355 nm) to femtosecond (Ti:sapphire at 775 nm) lasers for precision glass machining; they were able to produce crack-free, clean microfluidic devices. They also used laser-induced plasma machining (with a Nd:YVO_4 at 532 nm) to produce shallow features with a superfine surface finish within the channels. Karnackis et al. [60] conducted a comparative study machining borosilicate glass using two types of high repetition rate pulsed lasers, a nanosecond UV (255 nm) frequency-doubled copper laser and a femtosecond Ti:sapphire (800 nm) laser.

Three-dimensional structures have also been produced in photoetchable glass-ceramic. Helvajian and coworkers [61] used pulsed UV lasers to machine various fluidic components and a microthruster subsystem in the photostructurable glass Foturan. Brokmann et al. [62] investigated exposure below threshold energy density of photosensitive glass using pulsed UV lasers of various wavelengths, excimer lasers at 193 nm, 308 nm and 351 nm and a tripled-frequency Nd:YAG laser at 355 nm. Kim et al. [63] compared laser machining of Foturan using a KrF laser and a femtosecond laser [64]. Excimer laser was also used to machine microstamps in a photoetchable glass, which were subsequently replicated in a polymer such as PVC by hot embossing to produce microchannels [65].

Conclusion

Laser micromachining is a mature and versatile technique that presents some key benefits over other more-established microfabrication techniques, in particular for applications in which silicon is not the preferred material base. It offers great process flexibility as well as the ability to micromachine a wide range of materials and substrates, including non-planar ones, and produce structures with complex three-dimensional geometries in a single substrate, which finds increasing use in microfluidic-based applications. It can be used on its own or easily combined in a processing chain of hybrid technologies and is particularly well suited for rapid prototyping, optimizing concepts and during production-development stage of a microfluidic chip to reduce development time. It is also utilized for rapid fabrication of small and medium lot sizes. Direct ablation using UV lasers is particularly attractive in the case of polymers as it provides a very flexible and fast fabrication procedure that, when associated with laser-assisted modification of polymer surfaces, allows tailoring of the characteristics of the surfaces to particular needs. Glass micromachining has also been explored using UV lasers but still presents challenges.

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