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3D laser microfabrication of medical devices

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Abstract: Miniaturization is one of the key trends in medical field. In order to keep up with increasing demand novel manufacturing techniques have to be developed. Here we present an approach of using amplified femtosecond laser to realize both additive and subtractive micro-machining in a single workstation. It allows simplification of fabrication workflow as well as allows to produce more complex microdevices. Example structures, such as macromolecule separator and flow meter are demonstrated. We highlight peculiarities, challenges and opportunities that can be exploited using hybrid manufacturing and how it can be employed in medical field.

I. Introduction

During the last decades, femtosecond (fs) laser was established in material processing as an extremely precise and reliable tool. Due to highly nonlinear light-matter interaction in a time frame shorter than heat dissipation from the laser affected zone fs pulses enable "cold processing" yielding processing resolution down to nanometers. Both additive (for instance multiphoton polymerization) and subtractive (for example ablation or laser-assisted selective etching) processing can be realized [1]. It allows to 3D print various polymers (acrylates, hybrids, hydrogels, elastomers, biopolymers, etc) and modify or cut virtually any hard materials from plastics, glasses, to hard metals and ceramics. Thus, the fs laser can process and/or modify any material relevant to science and industry. For this reason, fs pulses were applied to a produced variety of different functional structures, including biomedical implants, microfluidic chips, micro-optical elements, photonic structures, and similar. Nevertheless, in most cases fabrication is carried out using only one interaction regime. Thus only additive or subtractive machining regime is realized in a single processing setup. As a result, achievable architecture and, in extent, the functionality of the final structure is limited. However, modern amplified fs laser systems can be heavily tuned in terms of repetition rate (1 kHz to 1 MHz) and pulse duration (~200 fs to ~10 ps). Thus, a single light source can be used to achieve all relevant processing regimes. Switching between fabrication modes is achieved just by changing laser parameters (which is done using software solutions) and changing focusing optics (form lenses to high-NA objectives). Thus, a hybrid additive-subtractive 3D structuring workstation with a single amplified fs laser source can be created allowing an entirely new way of integrated micro- and nano-device design and manufacturing.

The medical field is in high demand for miniaturized and highly functional devices. In this work, we demonstrate how this field can benefit from 3D hybrid additive-subtractive micro- and nano-processing. To prove the potency of this approach several highly complex microdevices are produced. The examples include flow meter capable of precisely measuring flow down to nl/min. Such a structure is highly relevant for novel treatment methodologies based on extremely precise drug delivery and/or cell therapies. Additionally, microfluidic macromolecule separator is produced with the intent of using it for new generation drug development and production. Polymer, glass, and metal components are chosen and incorporated freely during the manufacturing process, bringing a new level of functionality to the devices. Structure quality is evaluated qualitatively and quantitatively, with a heavy emphasis on performance optimization and how it can be achieved by switching between various processing regimes. We show that the capability of freely choosing appropriate processing mode between additive and subtractive processing in one highly automated workstation simplifies design and fabrication process as it allows to avoid switching between different workstations and use the single tool and single software for all the processing steps. Implications to other fields and practical considerations when realizing hybrid additive-subtractive fs 3D fabrication are also discussed giving an insight on prospects of the approach.

II. Material and methods

The work was performed using "Laser Nanofactory" workstation (Femtika, Lithuania). This setup is based on amplified Yb:KGW laser source "Carbide" (Light Conversion, Lithuania) operating at either 1030 nm fundamental wavelength or 515 nm second harmonic, 200 fs pulse duration and 1000 kHz pulse repetition rate. The laser light is then focused using various objective lenses, with NA ranging from 0.45 to 1.4. Sample positioning is

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realized using Aerotech stages (USA). A linear stage and galvo-scanner synchronization is implemented in the system, allowing rapid translation velocity (up to several cm/s) and stitch-free fabrication in the whole working area of linear stages (16x16x8 cm). The system is controlled by proprietary software "3DPoli" (Femtika, Lithuania). Setup also has built-in machine vision solutions for fast, non-interruptive on-the-fly quality control. More information on the setup can be found elsewhere [2].

III. Results and discussion

One of the keys advantages of miniaturization in medicine is the possibility to approach size ranges close to biological constitutes of the body, such as cells, bacteria, or biomolecules. At these size ranges various simple yet very effective structures can be produced. For instance, one of the concepts in the field is the usage of micro-filters to separate cells or bacteria in bioliquids [3]. Nevertheless, structures demonstrated so far have features in the range of ~µm. Multiphoton polymerization, on the other hand, allows to achieve resolution down to hundreds of nm. Thus, in this work, we set out to integrate nano-level filters inside microfluidic systems to filter out macro-molecules [Fig. 1]. Channels, in this case, are produced using laser ablation, as it offers very fast fabrication (a few minutes for one chip) with adequate quality (surface roughness – up to few µm RMS). The polymerization step can also be relatively fast, reaching production capacity comparable to µ-SLA [2]. Such structures are extremely attractive for applications in drug development and manufacturing because they offer a simple, reliable, passive and cheap way of performing otherwise rather complicated task of macro-molecule separation in liquids.

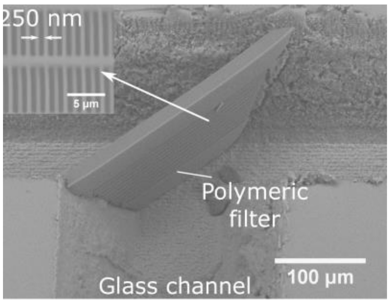

Figure 1: SEM micrograph of 3D polymeric nanofilter in ablated glass channel. Inset shows a zoomed-in fragment of the filter (feature size down to 250 nm).

Alongside passive elements, which require no outside energy source, active micro-devices are also highly promising. Indeed, laser manufacturing and advanced post-processing techniques allow producing complex movable polymeric structures which later can be turned, for instance, conductive *via* chemical metal coating. As it is a selective process, if such a structure is integrated into the glass channel, the channel is not contaminated with metal. Both channels and valves are produced with fs laser using first subtractive then additive processing. It opens up new possibilities in integrating conductive structures to dielectric microfluidic systems. One of the possible applications is slow flow measurement. Then, a valve-capacitor hybrid can be placed into a channel [Fig. 2]. If electricity is connected to the system, the movement of the valve d changes the charge C stored in the system ($C = f(d)$). Because the valve is moved by the flow in the channel, the flow rate can be measured with extreme precision – down to nl/min. Such sensitivity is potentially attractive in medicine and veterinary. Indeed, the delivery of strong drugs used in cancer treatment or treatment of large animals (for instance horses) requires very precise, real-time measurement of flow rate and direction which such flow meter can provide. Thus, it is a good example of how hybrid fs laser additive-subtractive manufacturing can be used to produce active medical devices with unmatched functionality.

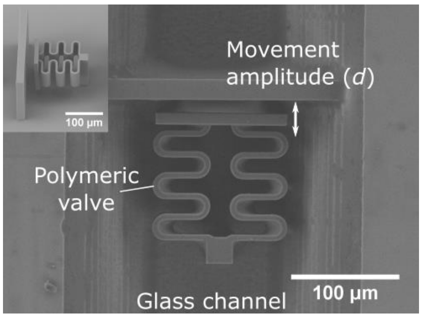

Figure 2: A 3D polymeric flow meter-valve integrated into glass channel. The channel is made using selective glass etching, while the valve is produced via multiphoton polymerization followed by chemical metal coating. The concept is based on metal-coated polymer valve with one part being stationary and other moving as flow is going through it. Then, the electrical capacity C of the system dependent on the movement of the valve d (i.e. C = f(d)). Inset shows side view of unintegrated valve.

IV. Conclusions

In this work, we show how hybrid additive-subtractive fs microfabrication can be used to produce both passive and active medical devices. Furthermore, we provide ideas on how to push the frontiers in the field by demonstrating how higher resolution and supplementary techniques (like selective metal coating). Together this highlights new possibilities for designing elements and devices for highly challenging applications in medicine.

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AUTHOR'S STATEMENT

Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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