EPJ Web of Conferences **309**, 10003 (2024) https://doi.org/10.1051/epjconf/202430910003
EOSAM 2024

Laser-assisted micromachining: an innovative tool for advancing the multifunctional optofluidic lab-on-a-chip

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Abstract. Ultrafast laser micromachining is a technological innovation with exciting potential for many applications and has led to impressive advances in the study of light-matter interactions. In this context, the laser-assisted wet etching fabrication technique has opened new frontiers in the optofluidic lab-on-a-chip, i.e. complex and easy-to-use microsystems capable of integrating multiple physicochemical processes on a single platform to replicate specific chemical, biological and medical tests typically performed in a laboratory. These miniaturised multifunctional laboratories exploit the synergy between the high sensitivity of optics and the unique ability to manipulate small quantities of microfluidics to develop a new frontier of analytical devices. The chips can be manufactured in monolithic 3D versions with no geometric constraints and are fully embedded in the substrate (typically fused silica). In addition to the advantage of using an inert substrate (strategic for biological applications), the elimination of the sealing step and the high mechanical strength offer numerous advantages. To demonstrate the potential of this new sensing platform, we report on the benefits of integrating in-plane 3D micro-optics to increase the S/N in-chip spectroscopic analysis in two case studies: flow cytometer devices and innovative chips for real-time Raman analysis of bio-samples in flow, even non-transparent ones.

1 Introduction

Arguably one of the greatest human inventions of the last century, lasers have become part of many aspects of our lives, from medicine to advanced industry and even the most innovative areas of research such as nuclear fusion. Their power lies in their ability to generate large electromagnetic fields and to extract large amounts of energy in the form of coherent light. Moreover, their use in micromachining has proven to be extremely versatile, as the principle of their operation is guided by the physics of light-matter interaction: photon energy and wavelength, material band, absorption and energy transfer[1]. Of all the available regimes (cw o pulsed [ns-ps-fs]), femtosecond lasers represent a clear technological breakthrough. As the time scale on which the electrons are excited is smaller than the electron-phonon scattering time (about 1 ps), the thermal effect on the material is minimised by increasing the accuracy of the modification[2,3].

The extremely high peak intensities at the focus of femtosecond laser pulses have paved the way for a wide range of new applications. One of the most promising is micromachining in transparent materials, such as glass[4], crystals[5] and polymers[6] which relies on a non-linear absorption process that leads to a permanent alteration of the material structure. This has opened the possibility of using laser-assisted wet etching to produce Lab-On-a-Chips devices buried in fused silica.

The technique can be identified by several names, although one of its most familiar acronyms is Femtosecond Laser Irradiation followed by Chemical Etching (FLICE) and consists of two steps: (1) the permanent modification of the morphological, physical and chemical properties of the substrate by femtosecond laser irradiation; (2) selective removal of the modified material by chemical etching.

This can be described as a subtractive 3D printing process, with no limitations on the three-dimensional complexity of the mini- and micro-structures produced.

2 Experimental Studies

Lab-on-a-Chips (LOCs) are complex microsystems that can integrate multiple physicochemical processes on a single microfluidic platform to replicate specific chemical, biological and medical tests, typically performed in a laboratory. They have been developed with the aim of being low-cost, compact, portable and “easy-to-use" even by non-expert people, while performing analyses with high accuracy and sensitivity. The current growing interest in studying LOC platforms has been triggered by their ability to achieve the required sensitivity in many applications, particularly for sensors. Optical sensing has proven to be very powerful in advancing this new technology, enabling new

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measurement capabilities never explored before. For these reasons, the integration of different functionalities (fluidic, photonic, biochemical) on the same miniaturized chip can lead to the creation of new devices capable of performing relevant early diagnosis and prognosis or specific analytical functions. The production technology is often a key element in their manufacture.

We report here on two case studies of spectroscopic analysis to demonstrate the potential of combining photonics and microfluidics in chips: flow cytometer and innovative micro-Raman chip devices, for real-time analysis of (bio)samples in flow, even non-transparent ones.

Flow cytometry is considered the gold standard in the statistical analysis of the properties of fluids and individual microparticles. Unlike commercial instruments, which are bulky, expensive, and unsuitable for point-of-care (PoC) testing, microfluidic flow cytometers are small, inexpensive and can be used for on-site analysis. For such a platform to be used in industrial and clinical applications, the requirements of high sensitivity, high throughput and fast response are key elements. To improve the accuracy of optofluidic flow cytometers and thus the minimum detectable particle size at high throughput, two critical factors must be addressed: precise control of the 3D position of the sample in the flow and a high signal-to-noise ratio of the measurement. To meet these requirements, we have developed a new optofluidic flow cytometer, which exploits the integration of an innovative and user-friendly 3D flow cell with an in-plane integrated 3D spherical micromirror on the same glass platform to increase the signal-to-noise ratio by several times.

For the focusing of smaller particles, a new geometry[7] was designed that allows hydrodynamic focusing using only two inputs, exploiting a simple and fast manufacturing process. The same manufacturing tool was used to simultaneously integrate the optical element on the chip, avoiding any misalignment. This smart in-plane optical element has the benefit of picking up useful signals from a non-discrete and wider solid angle, than multiple optical fibers, while reducing background noise by being as close as possible to the sensing core components. As a result, the increased signal obtained enables the detection of micron bio-object (such as cells) and sub-micron particles (including bacteria or plastic fragments) using only low-cost photodetectors[8].

By optimizing the excitation geometry, an integrated optical setup is introduced for high-throughput Raman analysis of various moving fluids, including transparent and non-transparent ones. Raman spectroscopy (RS) is a non-invasive and non-destructive technique par excellence for detecting chemical compounds in an unknown sample. Its characteristics of high sensitivity and non-marking make it particularly interesting for biomedical and biosensing applications, as it allows processes to be studied at the level of individual cells without disturbing the cellular environment. As is well known, the Raman signal is very weak and its detection becomes critical, especially when the object is small, biological and/or moving. As the main drawback result, a very long measurement (integration) time is required, which severely limits its application. To make a positive contribution to this, a special on-chip configuration for Raman analysis in flow was designed, which allowed us to analyse fluids, even non-Newtonian and non-transparent ones such as blood, avoiding deoxygenation and photodegradation even with excitation in the visible range. The increased Raman collection thus obtained allowed us to reduce the integration time to less than one second using an external collection setup. A portable version of the chip was then developed to allow Raman analysis without the use of external objectives, with comparable performance.

3 Conclusion

In our flow cytometry LoC, scatter and fluorescence are collected from the same fiber output: this simplifies the geometry and facilitates the signal processing. This makes the device robust and compact, with valuable advantages in terms of portability, sensitivity, and ease of use.

For the Raman chip, breaking the one-second integration barrier in the portable LoC version bodes well for achieving the ambitious goal of real-time Raman analysis of flowing samples. A number of optimizations have already been implemented to pave the way to this incredible and desirable frontier.

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