NEW GENERATION OPTOELECTRONICS FOR MEASUREMENT APPLICATIONS (NEGOMA)

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Background and Mission

NeGOMA group focuses on development of solution processable components and systems (sensors and sensor networks, light sources, light detectors, optical components etc) for different kinds of measurement applications. The motivation is to find new ways of applying the new generation optoelectronics to generate high level scientific knowledge but also find solutions which have a real commercial potential in industry and health care. In addition, NeGOMA group members investigate and develop different measurement methods for various applications. NeGOMA group is an active member in PrintoCent as well as a member in More-than-Moore (MtM) RAE consortium. MtM succeeded well in the evaluation, getting 6/6 points in the *Vidi* category.

The wellness and health costs in developed countries are increasing continually. Rapid diagnostics has been seen as one solution to lower the costs. There is a need for an easy to use sensing platform which could be exploited at the doctor's office and in home care. In this study optical polymer detection platforms will be integrated with microfluidic sample handling systems. The aim is to develop an integrated optofluidic sensor platform which meets the criteria for a disposable low cost device with possibility for high throughput manufacturing.

The other direction of current research is investigation of plasmon resonant gold nanoparticles (PRNPs) with variable morphology as contrast agents for optical coherence tomography and confocal microscopy.

Scientific Progress

Inkjet Printed Lens Array for Optical Imaging

An array of microlenses was fabricated with inkjet printing and the applied to an imaging system to examine a biological specimen. Inkjet printed lenses were fabricated on a thin (125 µm) sheet of glass according to Figure 1. The glass was first patterned with photolithography to form shallow (4.5 µm) circular pools into which the liquid lens material was then printed. The shape and the diameter of the lenses are controlled with the patterning. An inkjet printer was used to fill the pools drop by drop, until at wanted shape. By overfilling the pool, surface tension holds the lens in its convex shape until it is hardened with heat and UV-light. The profile of the array was measured with a stylus profilometer and is presented in Figure 2.

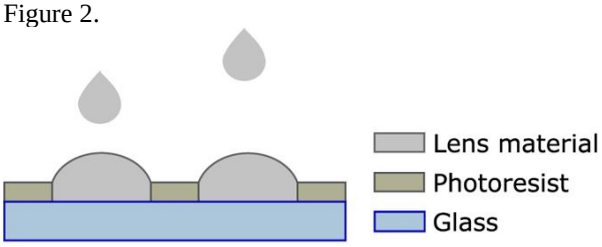

Figure 1. The lenses are printed onto the patterned substrate drop by drop, until the shape is at wanted curvature.

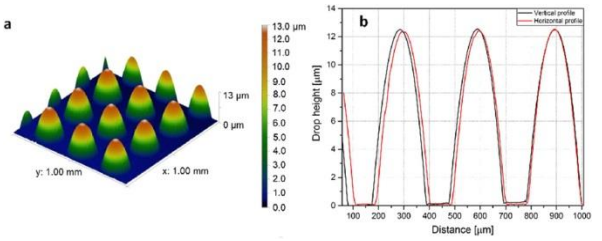

Figure 2. (a) 3D-profile of the printed MLA. (b) Graphs of the vertical and horizontal profiles of the MLA. The average height and diameter of the lenses is 12.4 µm with standard deviation of 0.06 µm and 222 µm with standard deviation of 4.61 µm, respectively.

These lens arrays were combined with a semi-microscopy imaging device to examine a biological sample. The comparison in Figure 3 presents the quality difference between three different kinds of lens arrays; commercial glass lens, hot embossed polycarbonate lens and the inkjet printed lens. As the images show, the quality of the lenses fabricated here is at the same level as with the glass lenses. The maximum obtainable resolution was determined with a USAF resolution target and for glass and inkjet printed lens arrays it was found to be same 128 line pairs per millimeter or 3.9 µm line width. The main difference between these lenses is their price, the glass lens arrays cost about 300 € and the fabrication of the inkjet printed lenses was less than 5 €. This is a great advantage for our lenses.

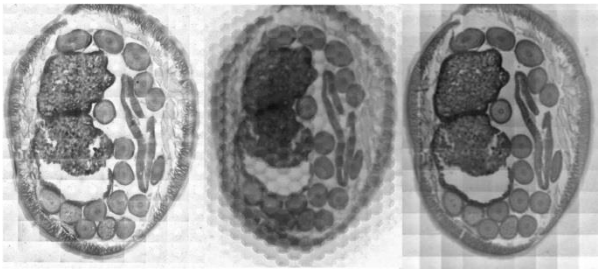

Figure 3. Comparison of images made with different lens arrays. From left to right: glass lenses, hot embossed polycarbonate lenses and the proposed inkjet printed lenses. The polycarbonate lens array produces the lowest image quality. The inkjet lenses produce images with quality comparable to the class lenses.

An Integrated Optofluidic Sensor to Detect Listeria

The detection of food borne pathogens such as Listeria is often difficult and slow. Listeria caused food epidemics as not as common as epidemics caused by many other bacteria, but the fatality rate is around 30%. Because of the high fatality, listeriosis ranks among the most frequent causes of death due to food-borne illness. The traditional way of detecting listeria involves pre-enrichment, selective enrichment, selective plating, biochemical screening and serological confirmation. This process is sensitive and selective, but complicated and slow. It takes a week to get the final results. Recently ELISA detection and molecular techniques such as PCR and DNA hybridization have shortened the time of the detection allowing a test to be completed within 48 h. This is however not adequately fast for prevention of food epidemics.

Our aim in this research is to develop a rapid detection method for Listeria by combining Surface-Enhanced Raman Spectroscopy (SERS) and ImmunoMagnetic Separation (IMS) technique. We studied the detection of one of the Listeria species, Listeria innocua. Many of the current listeria tests do not differentiate between listeria species, because the antibodies used for bacteria recognition usually bind all of the existing species. Additionally the presence of non-pathogenic listeria such as L.innocua often indicates contamination of food with L.monocytogenes.

In our detection process we have combined the use of planar periodic SERS structures with nanoparticle enhancement. Used SERS substrates have been roll to roll fabricated by UV nanoimprint technique. A gold layer has been evaporated on top of the SERS surface. SERS spectrum measured for a highly concentrated sample droplet of L.innocua with nanoparticle enhancement can be seen in Figure 4.

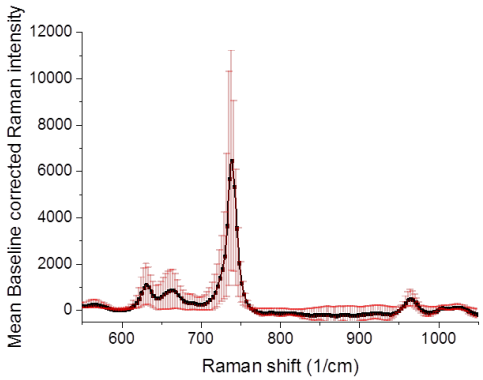

*Figure 4. Raman spectrum and mean absolute deviation of a 6.8*10^9 cfu/ml L.innocua sample droplet on polymer Klarite with nanoparticle enhancement.*

From the results shown in Figure 4 it can be concluded that to gain high enough sensitivity for the Listeria detection, more Listeria should be gathered into the area of the laser detection spot. By using IMS beads to bind the Listeria it was possible to reach higher detection sensitivity. The difference in the sensitivity with and without IMS beads is shown in Figure 5.

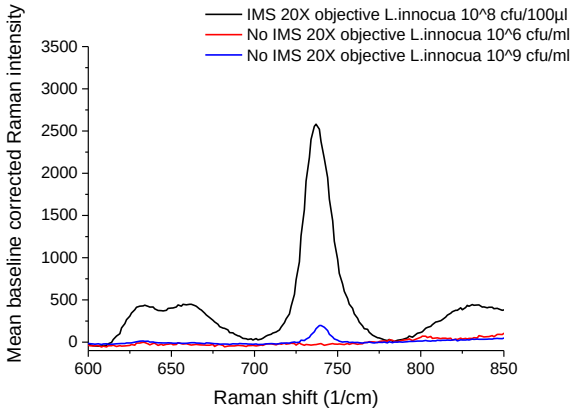

Figure 5. Raman spectra of L.innocua sample droplets on polymer Klarite with and without immunomagnetic separation beads.

To reduce the deviation between measurement-points, the planar SERS surface was integrated with PDMS wells. PDMS wells were cut into a PDMS sheet with a biopsy punch. The hydrophobic nature of the PDMS encourages the sample to dry inside the well onto the SERS surface in sufficiently repeatable manner. The concentration of sample droplet onto the SERS surface during the drying process can be seen in Figure 6.

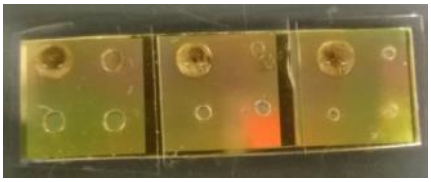

Figure 6. PDMS chambers on top of SERS polymer Klarite surface for concentration and even drying of L.innocua samples.

With the combined SERS and IMS detection the lower limit of detection was around $5*10^4$ cfu/100µl of IMS bound L.innocua, which makes the technique 2 decades more sensitive than the traditional method.

Gold Nanoparticles for Optical Imaging

Optical and contrasting properties of gold nanoparticles (GNPs) were complemented by dark-field and fluorescent microscopy (Figure 7a), light spectroscopy, surface electron microscopy (SEM) (Figure 7b), transmission electron microscopy (TEM) (Figure 7c), and IR-ATR spectroscopy.

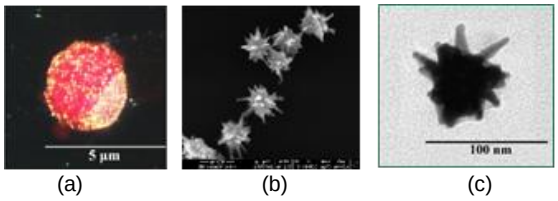

Figure 7. Fluorescent image of mammalian cells covered by nanospheres (yellow dots) (a); SEM image of nanostars on a waveguide surface (b); TEM image of a nanostar on a copper grid (c).

We used nanostars for signal enhancement in infra-red (IR)-spectroscopy in Institute of Analytical and Bioanalytical Chemistry, Ulm University. The plasmonic properties of the GNPs were tested for surface enhanced infrared absorption (SEIRA) on conventional and thin-film waveguides in combination with quantum cascade lasers. We developed a plasmonic chip-based technology by deposition of gold nanoparticle layers onto conventional waveguides. We demonstrated the enhancement of signal from the plasmonic chip both in Raman Spectroscopy and Infrared Reflection-Absorption Spectroscopy (IRRAS) (Figure 8).

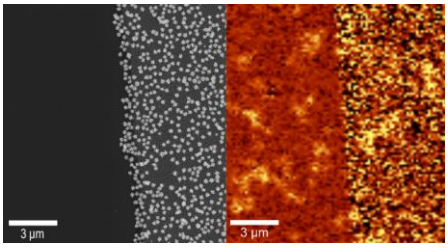

Figure 8. SEM image of the gold nanoparticle layers onto conventional waveguides (a); image of the intensity of Raman signal.

Treatment ability of the synthesized nanostructures was demonstrated by laser-assisted cell optoporation – generation transient pores in the cell membrane. The as-prepared and functionalized PRNPs of different morphology were used for cell optoporation. The cells were irradiated by a CW or nanosecond lasers in presence of PRNPs for enhanced membrane permeabilization and more successful penetration of nanostructures into the cells. We assayed the effect of laser parameters and morphology of different PRNPs on viability of cells and their permeability for extracellular substances (fluorescent markers).

Treatment ability of the nanostructures laser-assisted optoporation of cells was investigated in details. We assessed the effect of laser parameters and morphology of PRNPs on viability of HeLa cells and their permeability for extracellular substances. We evaluated the cell membrane permeability *in-vitro* using continuous-wave (CW) and nanosecond pulsed lasers with weakly focused laser beam or fine-focused nanosecond mutipulsed irradiation in scanning mode. We used nanospheres, nanorods and nanostars with plasmon-resonant peaks at 520, 805 and 800 nm correspondingly depending on the laser operating wavelength to achieve the best performance. For CW irradiation, the laser operated at 808 nm, the dependence between rise of medium temperature and the irradiation time was shown for nanostars and nanorods. Cells samples incubated with gold nanorods showed the highest temperature increase of 72°C. Cell membrane perforation was successfully mediated by gold nanospheres with variable functionalization under nanosecond pulses in wavelength 532 nm as shown by the uptake of a fluorescent dye. Gold nanostars demonstrated perfect optoporation ability under pulsed laser illumination at 1064 in scanning mode: perforated cells was presented exclusively in irradiated area (Figure 9).

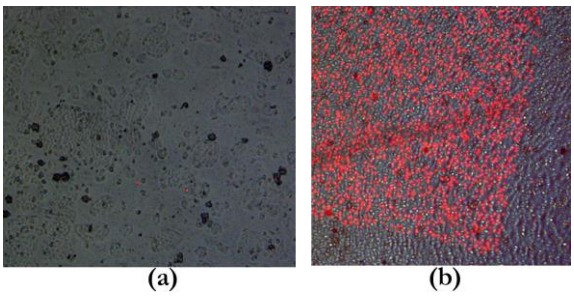

Figure 9. Combination of bright field and fluorescent images of non-irradiated cell samples incubated with NSts (a), irradiated by 30 scans of ns-laser with pulse energy 0.1 µJ (b).

NeGOMA group people participated in several conferences and presented their results during year 2015. These conferences include international and national conferences, for example: The International Conference CTCT-2015: Current Trends in Cancer Theranostics (Jena, Germany); The 3rd International Conference on BioPhotonics2015 (Florence, Italy); The International Conference "BiOS" in frames of SPIE Photonics West (San-Francisco, USA); The 7th

Finnish-Russian Photonics and Laser Syposium PALS'15 (Saratov, Russia).

In frames of CTCT-2015, Ms. Bibikova was awarded with the Bronze Paper Award, in frames of SPIE Photonics West Ms. Bibikova was awarded Newport Research Excellence Award.

Personnel

professors	2
senior research fellows	3
postdoctoral researchers	7
doctoral students	11
other research staff	4
total	**27**
person years for research	20

External Funding

Source	**EUR**
Academy of Finland	114 000
Tekes	137 000
international	45 000
total	**296 000**

Doctoral Theses

Leppänen, K (2015) Sample preparation method and synchronized thermography to characterize uniformity of conductive thin films. Acta Universitatis Ouluensis, Technica C 530.

Apilo, P (2015) Roll-to-roll printing of organic photovoltaic cells and modules. VTT Science 101.

Selected Publications

[1] P. Vilmi, S. Varjo, R. Sliz, J. Hannuksela and T. Fabritius "Disposable optics for microscopy diagnostics", Scientific Reports **5**, 16957 (2015)

[2] M. Uusitalo, J. Hiltunen, P. Karioja, S. Siitonen, V. Kontturi, R. Myllylä, M. Kinnunen, and I. Meglinski, " Performance and flow dynamics studies of polymeric optofluidic SERS sensors," J. Eur. Opt. Soc.-Rapid 10, 15043 (2015).

[3] O. Bibikova, A. Popov, A. Bykov, A. Fales, H. Yuan, I. Skovorodkin, M. Kinnunen, S. Vainio, T. Vo-Dinh, V. Tuchin, and I. Meglinski, "Plasmon-resonant gold nanostars with variable size as contrast agents for imaging applications," IEEE J. Sel. Top. Quantum Electron, DOI 10.1109/JSTQE.2016.2526602.

[4] O. Bibikova, A. Popov, A. Bykov, A. Prilepskyii, M. Kinnunen, K. Kordas, V. Bogatyrev, N. Khlebtsov, S. Vainio, and V. Tuchin, "Optical properties of plasmon-resonant bare and silica-coated nanostars used for cell imaging," J. Biomed. Opt., 20, 076017 (2015).

[5] O. Bibikova, P. Singh, A. Popov, G. Akchurin, I. Skovorodkin, V. Khanadeev, M. Kinnunen, V. Bogatyrev, N. Khlebtsov, S. Vainio, and V. Tuchin, "The effect of laser irradiation on living cells incubated with gold nanoparticles," Proc. SPIE, 9340, 934010 (2015).