Crossdisciplinary Applications of Microscopy Techniques, e.g. Physic-Life Science Interfaces

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Lensless Chip-Microscope for in situ Cell Microscopy

M. Hubl[1], M. Blechert[1], M. Engelhardt[1], S. Seifert[1], A. Ziolkowska[1], E. Jung[1], L. Georgi[2]

[1]Fraunhofer IZM, Medical Microsystems, Berlin, Germany
[2]Technische Universität Berlin, Berlin, Germany

Moritz.Hubl@izm.fraunhofer.de
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Cell Microscopy in new Dimensions: Lensless in situ Cell Microscopy over a wide Field of View

The Lensless Chip-Microscope is a miniaturized microscope tool which uses a new lensless imaging technology in combination with reasonable standard components and a simple and modular assembly. It was initially developed for the characterization of cells and microparticles in microfluidic systems [1]. The technology is based on in-line holography, which allows to image cells and microparticles without lenses or apertures. Combined with a commercial off-the-shelf 10 MP CMOS sensor and a microfluidic chip it is possible to achieve spatial resolution up to a few micrometers on a large-scaled field of view of 4.6 mm x 6.4 mm, which is only limited by the sensor area. “Figure 1.” shows a virtual model and the first prototype of the Lensless Chip-Microscope.

A red laser diode emits coherent light into the microfluidic channel and on the objects of interest. The wave front scatters at the object and overlays with the unscattered laser light and forms unique holograms on the sensor surface. This pattern of the micro-object is dependent on the shape, size, transmission, intercellular elements and distance to the sensor [1]. The microscope image and the corresponding hologram of a threadworm as well as the lensless imaging technology are illustrated in “Figure 2.” The distance between object and sensor is adjustable to achieve less overlapping of the holograms or high-resolving templates for software operations. Template matching algorithms enable identification and counting of certain cell types in a cell solution. The specially programmed software “Lensless” runs the camera in stand-by mode for minimal thermal influence on the sample. Due to its small dimensions of only 4 cm x 4 cm x 6 cm the microscope can be placed into an incubator for observing cells for example in a microfluidic channel. The hologram of incubated cells reveals their type, shape and adherence, sequential imaging also cell mobility and division status. Cells in solution, due to cell division or cell death, show differences in their hologram pattern to attached cells. This fact can be used for continuous monitoring of the cell growth or cytotoxicity tests. “Figure 3.” illustrates the change of the cell holograms during the cell division (left) and the cell adherence and growth of injected fibroblasts after 23 hours (right). With the large field of view of 29,4 mm^2, which is 15-times the field of view of a conventional 10x microscope objective it is possible to detect up to 10.000 of cells within just one image. One crucial benefits of using the Chip-Microscopy is the small investment. It is only a fraction of the cost of a conventional lens based microscope system. Furthermore the Lensless Chip-Microscope can be used for numerous applications in biotechnological microfluidic systems or point-of-care diagnostic tools. Further steps for realization of a stand-alone “Lensless Cell-Microscope” are the implementation of a Peltier cooling to the camera sensor with temperature regulation. The cooling system enables live imaging or video recording and better temperature handling of the sample. A thermoregulated extern incubation chamber around the Chip-Microscope completes the “Lensless Cell-Microscope” for portable cell incubation and simultaneous in situ cell microscopy.

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2. S. Isikman, I. Sencan, O. Mudanyali, W. Bishara, C. Oztoprak, A. Ozcan, “Color and monochrome lensless on-chip imaging of Caenorhabditis elegans over a wide field-of-view”, Lab on a Chip (2010)
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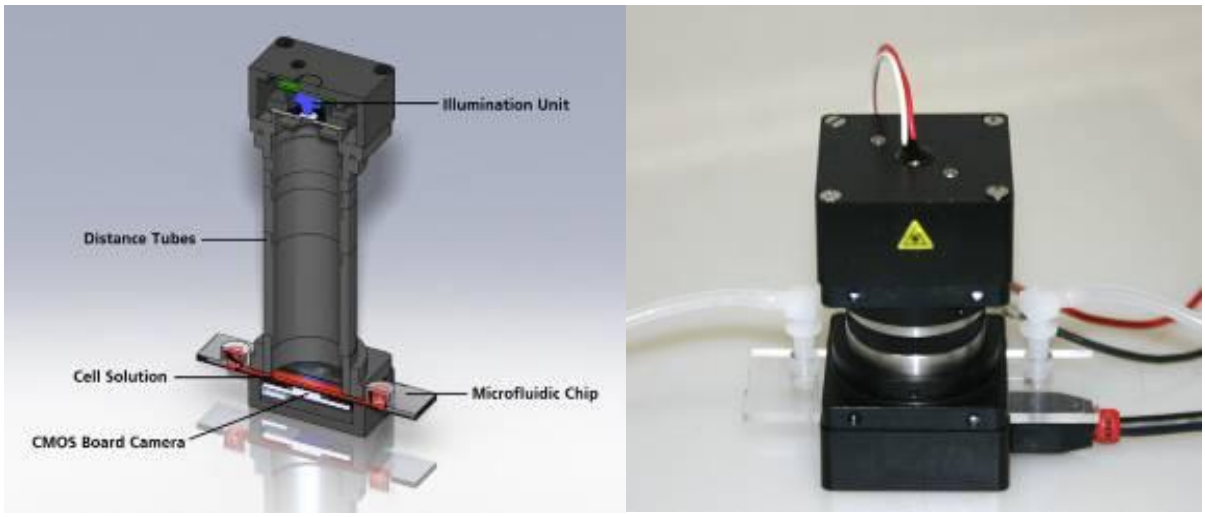

Figure 1. Virtual model (left) and prototype of the Lensless Chip-Microscope (right) with laser illumination and integrated microfluidic chip [1]

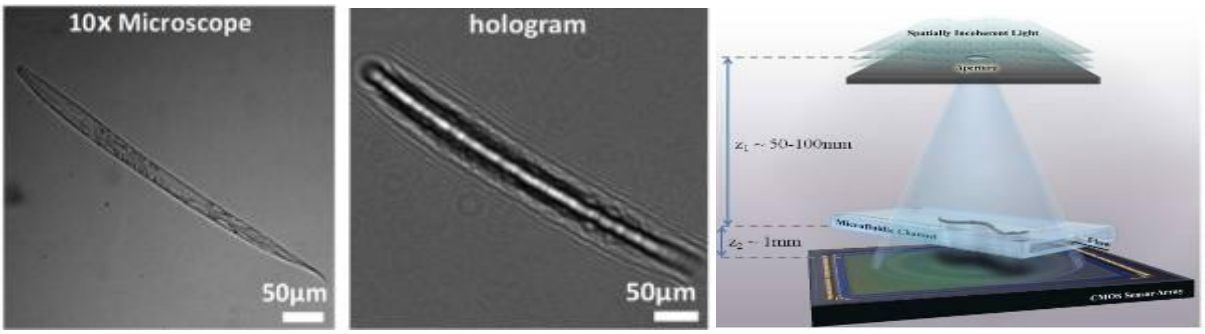

Figure 2. Image of C. elegans under a transmitted light microscope (left) and as hologram under the Chip-Microscope (middle) [2]. On-chip imaging technology of the Lensless Chip-Microscope (right) [3].

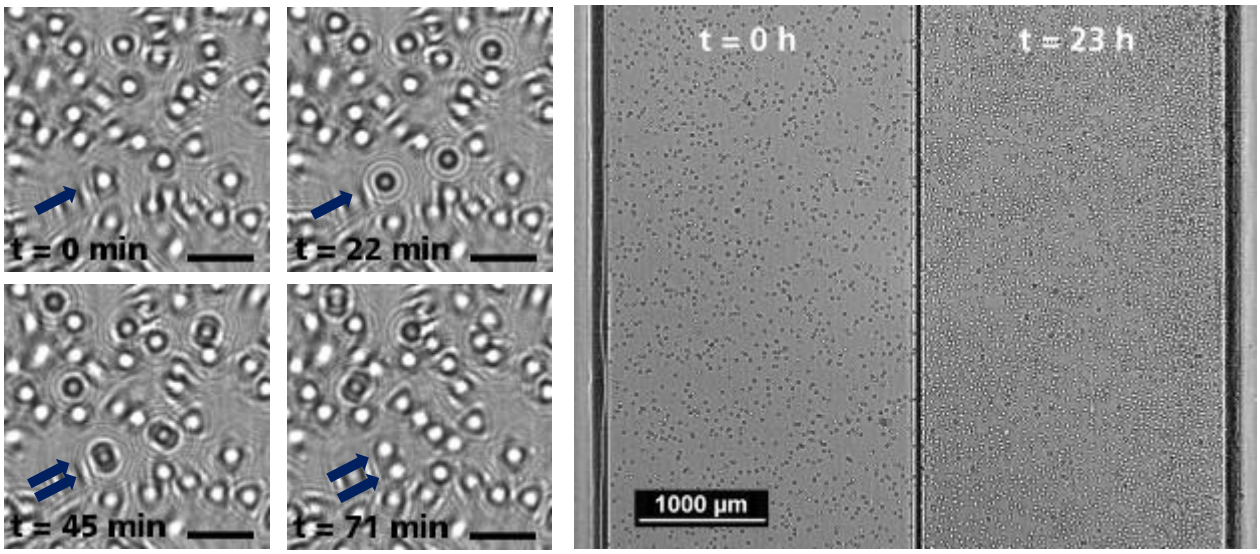

Figure 3. Cell division of incubating fibroblasts cells (left, scale = 100 µm) and fibroblast cell adherence and growth in a microfluidic channel observed over the entire field of view with the Lensless Chip-Microscope (right).