

NOVEL DIGITAL HOLOGRAPHIC MICROSCOPY FOR BROAD SPECTRUM OF APPLICATIONS

Holographic interferometric metrology technology is becoming one of the established analytical tools in several industrial sectors including life sciences and medicine. Digital holographic microscopy (DHM) provides quantitative phase and intensity imaging, and delivers high-resolution and multifocus representation of living cells and engineered surfaces (for example, inspection and imaging of life cells). It is useful for performing investigations on reflective surfaces and marker-free analysis of living cells. Advances in solid state image sensors have enabled high-speed recording of holograms using CCD camera (charge couple device).

Conventional microscopy has limited depth-of-field, which restricts from observing thick semi-transparent objects, leading to complicated and expensive device mechanics. Phase contrast imaging with conventional microscopes used for life sciences application to obtain the desired information has certain limitations. With this approach, the sample may be destroyed; acquiring quantitative information might be difficult; and there could be issues while dealing with image analysis software. Phase imaging digital holography is considered to be a promising technique attributed by lack of coherent noise and precision leading to enhanced resolution. Currently DHM products are being offered only by a few companies across the globe. Such DHM products should deliver high-quality images for investigations (for example, life sciences application). Working along these lines, Brussels-based Ovizio Imaging Systems provides a novel DHM platform device, which uses partially coherent light (patented technology) to generate high-quality base (fundamental) images for various applications, such as life sciences, biotechnology, semiconductor, and water quality control.

Ovizio founded in 2009, is a spin-off from the "Université Libre de Bruxelles" (ULB). The business model of the company (main revenue streams) involves: sales of DHM products; technology licensing; and microscopy as a service (on a monthly basis). Ovizio offers two products in the DHM space--one for laboratory use and the other one for multipurpose applications. The oLine product is a desktop type DHM intended mainly for laboratory applications. The iLine product is a small form factor device based on differential digital holographic microscopy (DDHM) that can be used for various applications, such as life sciences and bioreactors. The DDHM is a next generation holographic microscopy, in which the optical set-up is much simpler compared to classical DHM, resulting in a high speed, low cost multipurpose device.

According to Philip Mathuis, CEO, Ovizio Imaging Systems, "In the differential DHM set up, the interference process takes place after the sample unlike the DHM, and hence the set up is simpler and it is possible to realize devices with small footprint." Mathuis added that Ovizio's DHM solutions combine the benefits of traditional flow cytometry in terms of speed and classical microscopy in terms of resolution. The DHM solutions are completely noninvasive and it is characterized by low phototoxicity.

The horizontal resolution of Ovizio's DHM products is 200 nm (nanometer), while the vertical resolution is 2 nm. For 3D (three dimensional) investigations, the depth of investigation increases 100-fold compared to classical microscopy. High-quality 3D images can be obtained with nanometric precision. Mathuis mentioned that the large depth of focus, facilitates reliable counting, and analyzes of particles in fluids that are out of the focus plane. Fluorescent holograms generated using DDHM, enable complete analysis of the sample under investigation. This is one of the key distinguishing aspects of Ovizio's DHM technology.

Mathuis expounded that Ovizio's DHM products employ partially coherent light (based on patented technology) to produce high-quality base images compared to its competitors. The partially coherent light eliminates the background noise and can be obtained by using lasers or light emitting diodes (LEDs). He added that it is possible to record movies based on several holograms per second, making it a 4D inspection device. High-quality images obtained from using partially coherent light are extremely useful for examining transparent objects, for example cell culture monitoring, particle analysis, and so on (cell biological applications). Blurred images pose difficulty in distinguishing cells from the background noise. Since the image obtained from Ovizio's DHM is of high quality, there is no need for post-image treatment (image processing) or sample preparation unlike competitor's technology. Since, image processing or sample preparation is not required; the acquisition time is fast compared to competing solutions (since Ovizio's DHM does not analyze single particle, but flow of particles). This makes it extremely suitable for real-time applications compared to competitor's technology. One of the most interesting applications is the use of the technology as a real-time on line viable cell counter in biological applications.

Some of the applications include: cell-counting, morphology analysis, size distribution, density monitoring, and culture monitoring. Mathuis indicated that currently there is an increasing demand for DHM from the pharmaceutical sector

followed by the bioreactor sector. Ovizio intends to concentrate on life sciences (which would cover pharmaceuticals and life sciences sector) market while developing applications for water quality control applications (concrete results/output is expected in two years). Currently, the majority of sales are to research and development (R&D), institutes/universities, and global pharmaceutical and biotechnology companies.

Mathuis indicated that commercial penetration is taking up despite the fact that it is a new technology, for which the interest has to be created. Ovizio's activities are strongly backed by funding from the Universities' venture fund and local authorities. Due to the increasing demand for their DHM solutions Ovizio is planning a second round of funding in the next six months. The need for DHM in the pharmaceutical and biotechnology sectors is driving the growth of Ovizio's DHM solution. Mathuis mentioned that Ovizio is evaluating the opportunity of opening an office in the US due to the strong interest of local pharmaceutical and biotechnology companies in that region.

In 2006, Ovizio's DHM was implemented in the International Space Station, and the first commercial version was available in 2010. In 2011, Ovizio anticipates a miniaturized and multipurpose version of the DHM system. Mathuis denoted that Ovizio has plans to develop a DHM device, which could be integrated into existing microscopes. Some of the other R&D areas would include: shape recognition; development of intelligent; and stand-alone devices for specific industries; expanding the fluorescent channels; exploring cost-effective light sources; and integration of stand-alone modules with software for industrial processors--to identify wanted and unwanted particles and triggering an alarm based on the response.

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