

**OPTOFLUIDIC MICROSCOPY AND
WAVEFRONT MICROSCOPY: INNOVATIONS
IN BIOLOGICAL IMAGING**

Thesis by

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This thesis is dedicated to my family.

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Abstract

This thesis presents two new microscopic imaging techniques: the optofluidic microscopy (OFM) and the wavefront microscopy (WM). By integrating optical functionalities onto a single semiconductor chip, these inventions could reduce the cost and improve the efficiency and quality of microscopic imaging in biological research and clinical diagnostics. First, OFM utilizes a microfluidic flow to deliver cellular samples across array(s) of micron-sized apertures defined on a metal-coated CMOS image sensor to acquire direct projection images of the samples. Although the OFM prototype is as small as a dime, it can render high resolution images ($\sim 1 \mu\text{m}$) with comparable quality to those of a bulky standard optical microscope. OFM has great potential in revolutionizing the way we use microscopes. For example, the availability of tens or even hundreds of microscopes on a single chip will allow massively paralleled imaging of large populations of cells or microorganisms; the compactness and low cost of the OFM can enable portable and even disposable biomedical diagnostic tools for future telemedicine and personalized health care. Second, we present a new microscopy concept - WM. Wavefront image sensor (WIS) is the enabling component of WM. By monitoring the tightly confined transmitted light spots through a 2D aperture grid (spacing = $11 \mu\text{m}$, diameter = $6 \mu\text{m}$) fabricated on a CMOS image sensor in a high Fresnel number regime, we can accurately measure both intensity and phase front variations (a measured normalized phase gradient sensitivity of 0.1 mrad under the typical working condition - 1.0 second total signal accumulation time and $9.2 \mu\text{W}/\text{cm}^2$ light intensity on the sensor) of a wavefront separately and quantitatively. Therefore, researchers and clinicians can

incorporate pure phase imaging into their current microscope systems by simply adding the WIS in place of the conventional camera. When combined with adaptive optics strategies, this technology will facilitate deep tissue imaging using multiphoton microscopy.

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LIST OF FREQUENTLY USED ACRONYMS

Acronym	Full name
Al	Aluminium
<i>C. elegans</i>	<i>Caenorhabditis elegans</i>
CMOS	Complementary metal–oxide–semiconductor
DIC	Differential interference contrast
DIC-OFM	Differential interference contrast OFM
FWHM	Full width at half maximum
OFM	Optofluidic microscopy
PSF	Point spread function
N.A.	Numerical Aperture
SA	Structured aperture
SA-DIC	Structure aperture DIC
SAI	Structured aperture interference
SNR	Signal-to-noise ratio
WIS	Wavefront imaging sensor
WM	Wavefront microscopy