OPTOFLUIDIC MICROSCOPY AND WAVEFRONT MICROSCOPY: INNOVATIONS IN BIOLOGICAL IMAGING

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

2010

(Defended on November 18th, 2009)

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This thesis is dedicated to my family.

Acknowledgments

The successful completion of my thesis has relied on the support from many individuals. I am grateful for their caring and guidance during my enjoyable graduate study at Caltech.

First of all, I would like to express my sincere gratitude to my advisor, Professor Changhuei Yang. Yang is absolutely supportive to my research, and I really enjoy working in the Biophotonics lab. Yang gave me the complete freedom to learn and access any resources that could help the development of OFM. I feel my ability of performing independent research has grown a great deal during my Ph.D. study, and I truly appreciate Yang's belief in me. In addition, Yang has amazing passion for scientific research. He always can bring up a new idea every time I see him. It totally stirs up my zeal to research as well. I am very thankful that Yang has taught me how to think like a creative researcher.

I am also grateful to Professor Demetri Psaltis. He and his students have given me much generous help on the OFM project. The optofluidic center led by him also provided a great platform for me to communicate with experts from other institutes.

I feel deeply indebted to Professor Paul W. Sternberg and Professor Scott E. Fraser. They are always there to provide me precious advice and generous help, and to encourage me to grow.

I would like to thank Professor Harry A. Atwater, Professor Scott E. Fraser, Professor Ali Hajimiri, Professor Yu-Chong Tai, and Professor Amnon Yariv for being my thesis committee and/or my candidacy committee, and providing me their valuable

suggestions. They are all professors I admired. I wish I would accomplish similar achievement someday as they did.

I would also like to thank for the discussion and help from Professor Axel Scherer, Professor Babak Hassibi, Professor P. P. Vaidyanathan, Dr. Guillermo J. Tearney, Dr. C. Thomas Vangsness, Jr., and Dr. Richard J. Cote.

I have enjoyed working in the friendly and creative research group of Biophotonics at Caltech. Dr. Zahid Yaqoob, Dr. Xin Heng, and Dr. Jigang Wu have helped me quickly become involved in the lab when I first came to Caltech. Dr. Xin Heng, Lap Man Lee, Dr. Jigang Wu, and Sean Pang are my teammates on the OFM project, and I am thankful for their generous help and insightful discussions. Dr. Emily J. McDowell and I joined the group at the same year, and we have shared the same office for three years. I could not say enough thanks to express my gratitude to her constant help. Matthew Lew was my SURF student, and now is my great colleague. I really enjoy working with him and being friends with him. I would also like to thank other group members: Dr. Marinko V. Sarunic, Dr. Vahan Senekerimyan, Dr. Meng Cui, Guoan Zheng, Jian Ren, Shuo Pang, Ying Min Wang, Arthur Chang, and Tony Wu for their friendship and enjoyable communications during these years.

Thanks to Dr. Emily J. McDowell, Ying Min Wang, Dr. Meng Cui, Dr. Sri Rama Prasanna Pavani, and Dr. Michael Salvador for reading my thesis. I have learned a lot of from them to improve my writing skill.

Anne Sullivan, Christine Garske, Ya-Yun Liu, and Agnes Tong are our greatest secretaries. They have been extremely helpful to supply my research and take care of me in the lab. They make the lab feel like a home to me.

During my Ph.D. research at Caltech, I have also benefited a lot from the generous help from many collaborators: Dr. Weiwei Zhong (now at Rice University), Dr. Ying Zhou, Dr. Claudiu Giurumescu, Oren Schaedel, Dr. Xiaoyan Robert Bao, and Dr. Zhenyu Li, to name a few.

My final and most important acknowledgements contribute to my Dad, Jun Cui, my Mom, Guihua Wang, my sister, Yanyan Cui, for their love and support. Without their encouragement, I would not have had enough determination to complete my Ph.D. study.

Xiquan Cui

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Pasadena, CA

Fall, 2009

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 (~1 μm) 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 μm, diameter = 6 μm) 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 $\mu W/cm^2$ 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
C. elegans	*Caenorhabditis elegans*
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