The Role of Transport Phenomena in Whispering Gallery Mode Optical Biosensor Performance

Thesis by

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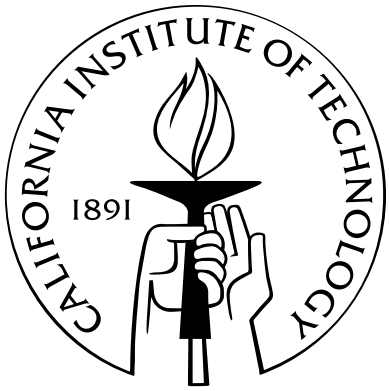

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For Ashley, my wife and friend. Everything changed when I met you.

Acknowledgements

The fact that a single name appears on the title page of a dissertation can be quite misleading. Neither this document, nor the research behind it, could have been completed without the help of a great number of people.

I would first like to thank my advisor, Professor Rick Flagan, who has given me the opportunity to work on a project I truly enjoy. I came to him at the end of my third year of graduate school seeking help from the Executive Officer of Chemical Engineering with finding a new research home on campus. I was looking for a project in a research lab that could support me while I completely rebooted my graduate career, and hoped Professor Flagan could advise me on how to go about my search. After listening to me describe my situation for nearly an hour, he politely asked if I would be interested in hearing about a project available in his own group involving an extraordinary optical biosensor. Within days I was a Flagan Lab member, eager to return to my roots as a chemical engineer by applying the field's core disciplines to the analysis of what was essentially a physicst's toy. Professor Flagan has taught me a great deal about instrument development and validation, and working in his lab has been an excellent education as a researcher.

I am also very grateful to Professor Andrea Armani, who has been a valuable mentor and friend to me since we began working together in 2008. It was her work as a Clare Boothe Luce Postdoctoral Fellow that began the collaboration between the Flagan, Vahala, and Fraser laboratories at Caltech, of which I have been a part. I was fortunate enough to learn this field from her, and benefit from the extraordinary care and patience she put into developing the procedures she used for her experiments. Even after Professor Armani accepted her faculty position at the University of Southern California, she continued to offer her time to answer my (seemingly endless) questions. I cannot express how helpful this was for a researcher trying to

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Andy Downard is another fine groupmate to whom I am indebted. In addition to being a good friend, Andy was of particular help with my efforts to model the fluid flow around sensors. He contributed even more to the daily operations of the lab by generously providing organizational advice and encouraging a multidisciplinary spirit that is too often absent in research environments. Our research group often posed unique challenges, as everyone must quickly develop a broad range of abilities in order to make any progress. I am grateful, however, to *all* the members of the Flagan and Seinfeld groups for creating a cooperative and friendly atmosphere, which should never be taken for granted. You all conduct your research (and yourselves) with class in the face of overwhelming pressure to succeed at any cost.

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Abstract

Whispering gallery mode (WGM) optical resonator sensors have emerged as promising tools for label-free detection of biomolecules in solution. These devices have even demonstrated single-molecule limits of detection in complex biological fluids. This extraordinary sensitivity makes them ideal for low-concentration analytical and diagnostic measurements, but a great deal of work must be done toward understanding and optimizing their performance before they are capable of reliable quantitative measurents. The present work explores the physical processes behind this extreme sensitivity and how to best take advantage of them for practical applications of this technology.

I begin by examining the nature of the interaction between the intense electromagnetic fields that build up in the optical biosensor and the biomolecules that bind to its surface. This work addresses the need for a coherent and thorough physical model that can be used to predict sensor behavior for a range of experimenal parameters. While this knowledge will prove critical for the development of this technology, it has also shone a light on nonlinear thermo-optical and optical phenomena that these devices are uniquely suited to probing.

The surprisingly rapid transient response of toroidal WGM biosensors despite sub-femtomolar analyte concentrations is also addressed. The development of asymmetric boundary layers around these devices under flow is revealed to enhance the capture rate of proteins from solution compared to the spherical sensors used previously. These lessons will guide the design of flow systems to minimize measurement time and consumption of precious sample, a key factor in any medically relevant assay.

Finally, experimental results suggesting that WGM biosensors could be used to improve the quantitative detection of small-molecule biomarkers in exhaled breath condensate demonstrate how their exceptional sensitivity and transient response can enable the use of this noninvasive method to probe respiratory distress.

WGM bioensors are unlike any other analytical tool, and the work presented here focuses on answering engineering questions surrounding their performance and potential.

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