Chapter 1

Introduction

1.1 History and Context

The present work represents the first foray into the field of whispering gallery mode sensing, or any biosensing technology, on the part of the Flagan Research Group. During her graduate and post-doctoral research, Dr. Andrea Armani began applying the microtoroidal resonators first created in the Vahala laboratory in Applied Physics to chemical and biological sensing. When the interpretation of these experiments demanded an expertise in biology and heat transfer, Professors Scott Fraser and Rick Flagan were consulted and a collaboration was born that later produced a publication in the journal *Science* [1].

I joined the Flagan Group in January 2008 after it became necessary to find a new laboratory and research project to finish my doctoral work. From January until August I had the privilege to learn from Dr. Armani the methods and theory that she developed in her work with microtoroidal whispering gallery mode (WGM) biosensors. She ordered components and oversaw my construction of a new experimental setup to mimic the one she used in the Vahala laboratory and another being built concurrently in the Fraser laboratory. I was trained on the finer points of pulling tapered optical fiber waveguides, using a CO_2 laser to reflow silica disks into toroids, coupling light into the toroidal cavity, and, finally, performing a sensing experiment in an acqueous environment.

My intentions when I joined the Flagan Group were to bring a chemical engineer's perspective to the evaluation of the nascent WGM biosensor. The single-molecule sensitivity observed by Dr. Armani begged more questions than it answered—especially when it comes to evaluating the future of this technology. How the sensitivity scales with molecular size, laser scanning rate, wavelength, and fluid flow rate all matter when optimizing operating conditions. Additionally, it becomes important to determine the advantages and disadvantages of single-molecule sensitivity when a slightly worse sensitivity is still orders of magnitude better than alternative technologies but does not require as much effort for data analysis.

There was doubt expressed concerning the results in the *Science* paper beginning shortly after its publication, but it did not develop until a recent publication attempted to reconcile the proposed physical model with current models and to address the extraordinary sensitivity. While no evidence has been presented to doubt the validity of the experimental observations, it became clear that fundamental questions remain unanswered concerning the basic interactions between the electromagnetic fields in the resonator and the biomolecules that adsorb to the surface. It was at this point that I began the work in Chapter 4 concerning a full description of the heat transfer that would be a part of the thermo-optical model of WGM sensor performance. My progress was limited by my lack of familiarirty with the theory concerning electomagnetic fields and waves, and I began collaborating with labmate Xerxes Lopez-Yglesias to form a complete model that would allow us to compare Dr. Armani's results to a more thorough theoretical prediction. The problem turned out to be monstrously complex, and so we instead crafted a roadmap to guide future work that itself provided new insight and corrected mistakes propagated in the previous literature.

I continued running WGM biosensing experiments in an effort to demonstrate how these devices could be used to detect pollen fragments that play a role in asthma exacerbation. Unfortunately that project was sidetracked by poor luck; the New Focus Velocity$^{\mathrm{TM}}$tunable laser source at the heart of the WGM sensing experiment was broken when we received it and, after being returned to us 6 months later, immediately began to degrade in performance and cause artifacts in the data until it was no longer functional. I turned my focus back to modeling the effects of mass transport on WGM biosensor performance, yielding the work in Chapter 5. This work has only begun addressing the many interesting problems involved when extraordinarily intense light is present during an equilibrium surface reaction.

The present work is intended to serve as a foundation on which future research into the many physical processes involved in WGM biosensing may build. My original research plans involved expanding the applications for these devices; however, that changed when when I saw opportunities to improve our understanding of WGM biosensors behavior and have a greater impact on the field by modeling the transport phenomena that, until now, have received little attention. This work ultimately addresses fundamental questions that would otherwise hinder the evolution of this technology toward a viable instrument, and, in doing so, presents methods that may be used to address some of the remaining challenges.

1.2 Thesis Structure

This thesis is arranged to serve as a primer for those who hope to conduct WGM biosensing experiments in the future. Chapter 2 introduces the field of biosensors and, more generally, the specific molecular recognition events that go into a successful bioassay. I describe sample preparation and useful surface chemistries, and review some of the current label-free biosensing technologies that one might encounter in the literature. Chapter 3 continues the introduction by focusing on WGM resontors and sensors. Topics in this chapter include fabricating, characterizing, comparing, and modeling these devices.

Chapter 4 explores the significance of fluid flow and mass transfer on the transient data observed using a variety of WGM biosensor geometries. Specifically, that work explores how the asymmetric concentration boundary layers that form around the sensor in the WGM biosensor flow cell enhance the transient early portion of the transient response, giving rise to the surprisingly fast binding time observed by Dr. Armani that had, until now, puzzled those who work with these devices. Chapter 5 includes the work done in collaboration with Xerxes Lopez-Yglesias to model the relevant physical processes involved in WGM sensing of single molecules. As mentioned above, it is a guide for those interested in modeling the entire, complicated process including nonlinear thermal and optical effects. In Chapter 6, I describe experimental work that seeks to advance WGM biosensors toward medically relevant applications for which they pose a unique solution. In particular, I detect a small molecule biomarker for oxidative stress in the respiratory system that can be found at low concentrations in exhaled breath condensate. Establishing that the WGM biosensor outperforms other analytical techniques for this measurement may make help expand into lower-concentration regimes the working library of biomarkers available for use in diagnostic medicine.

Finally, Chapter 7 concludes this document by reviewing findings and discussing the many interesting places this research may lead. I truly hope that those who read this document see the promise in this type of biosensor technology, but also realize that a great deal of work must be done before it can be used in practical analytical or diagnostic applications.