Pharmaceutical Applications of Carbon Nanotube-Based Optical Sensors: Theory and Experiment

By

Daniel P. Salem

Technical Summary

Semiconducting single-walled carbon nanotubes (SWCNTs) are attractive transducers for biosensor applications due to their unique photostability, single molecule sensitivity, and ease of multiplexing. Sensors can be rendered selective via several detection modalities including the use of natural recognition elements (e.g., proteins) as well as the formation of synthetic molecular recognition sites from adsorbed heteropolymers. However, to date, deployment of SWCNT-based biosensors has been limited. The aim of this thesis was to study the design and development of SWCNT-based optical sensors for analytes relevant to the food and pharmaceutical industries including neurotransmitters, proteins, and metal ions. The research described in this thesis spans several levels of nanosensor development including: i) the fundamental study of SWCNT-polymer interactions and their dependence on solution properties; ii) sensor development using existing detection modalities and the use of mathematical modeling to guide sensor design and interpret data; and iii) the invention of a new sensor form factor enabling long-term sensor stability and point-of-use measurements.

Our work on SWCNT-polymer interactions investigates the influence of polymer structure, SWCNT structure, and solution properties on molecular recognition, using single-stranded DNA as a model polymer system. Single-stranded DNA (ssDNA) oligonucleotides have unique, and in some cases, sequence-specific molecular interactions with the surface of carbon nanotubes that remain the subject of fundamental study. We find that specific ssDNA sequences are able to form distinct corona phases across SWCNT chiralities, resulting in varying response characteristics to a panel of biomolecule probe analytes. In addition, we find that ssDNA-SWCNT fluorescence and wrapping structure are significantly influenced by the solution ionic strength, pH, and dissolved oxygen in a sequence-dependent manner. We observe and analyze a generic, ionic strength mediated phase transition exhibited by over 25 distinct oligonucleotides adsorbed to SWCNTs in colloidal suspension. The phase transition occurs as monovalent salts are used to modify the ionic strength from 500 mM to 1 mM, causing a reversible reduction in the fluorescence quantum yield by as much as 90 percent. The negatively charged phosphate backbone increases (decreases) the DNA surface coverage on an areal basis at high (low) ionic strength, and is well described by a two state equilibrium model. We show that the phase transition also changes the observed SWCNT corona phase, modulating the recognition of riboflavin. These results provide insight into the unique molecular interactions between DNA and the SWCNT surface, and have implications for molecular sensing, assembly, and nanoparticle separations.

In addition to our experimental work, we used mathematical modeling to guide sensor design for biopharmaceutical characterization. A mathematical formulation for glycoprotein characterization was developed as well as a dynamic kinetic model to describe the data output by a label-free array of non-selective glycan sensors. We use the formulated model to guide microarray design by answering questions regarding the number and type of sensors needed to quantitatively characterize a glycoprotein mixture. As a second example, we report the design of a novel, diffusion-based assay for the characterization of protein aggregation. Specifically, we design hydrogel-encapsulated SWCNT sensors with a tunable hydrogel layer to influence the diffusion of immunoglobulin G protein species of variable size, and we develop a combined model that describes both the diffusion of analyte and analyte-sensor binding. By measuring the sensor response to a series of well-characterized protein standards that have undergone varying levels of UV stress, we demonstrate the ability to detect protein aggregates at a concentration as low as one percent as measured by size exclusion chromatography.

Finally, we report the development of a new form factor for optical nanosensor deployment involving the immobilization of SWCNT sensors onto paper substrates. Although nanoparticle-based optical sensors are capable of highly sensitive and selective chemical recognition, their incorporation into standardized in vitro assays has been limited, in part due to the incompatibility of existing sensor form factors with many end applications. In this work, we have developed a technique for immobilizing nIR-fluorescent SWCNT sensors on seven paper substrates including nitrocellulose, nylon, poly(vinylidene fluoride), and cellulose. Paper provides a lightweight and inexpensive form factor for nanosensor deployment that is compatible with orthogonal technologies developed in the paper diagnostics field. Sensors remain functional upon immobilization and exhibit fluorescence in non-aqueous solvent systems traditionally inaccessible to many SWCNT-polymer hybrids. Moreover, we pattern hydrophobic regions onto nitrocellulose using the wax printing method and form one-dimensional sensor barcodes for rapid multiplexing. Using a sensor array of select ssDNA wrappings, we are able to distinguish between Cu(II), Cd(II), Hg(II), Pb(II) at a concentration of 100 μM. This work represents a significant step towards the deployment of fluorescent nanoparticle sensors for point-of-use applications.

Thesis Supervisor: Michael S. Strano
Title: Carbon P. Dubbs Professor of Chemical Engineering