A COMPUTATIONAL APPROACH TO OPTIMIZATION OF NANOTECHNOLOGY-ENABLED OPTICAL MOLECULAR IMAGING OF CANCER

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Summary: In this proposal, we leverage emerging techniques in computational modeling with our joint expertise in optical imaging, nanotechnology, and medicine to optimize a powerful new approach for detecting molecular specific signatures of cancer in vivo. We take advantage of our existing clinical collaborations in the area of nanoengineered imaging agents to develop a new computationally focused project which will provide guidance to the experimental efforts already underway. It is our view that over the past five years most applications of nanotechnology in medicine have focused on early stage proof-of-principle demonstrations of concepts. Although results in our groups and others have provided much encouragement that a number of these strategies might ultimately prove clinically valuable, we believe it is time to step back and closely examine what is really required to move these nascent technologies forward. This project is predicated on our strong belief that to harness the vast array of potential nanomaterials available requires a more rational and engineering-based approach to determining the design parameters which will provide optimal performance. Specifically, we believe that enhanced computational modeling approaches will be the key advance which allows a more directed approach to optimal design and assessment of nanomaterials for use in biomedical applications. In this proposal, we focus specifically on optimization strategies for optically-based cancer screening, diagnostic, and monitoring applications which rely on the use of scattering and/or absorbing nanomaterials detected using either spectroscopic or direct imaging approaches. We seek to convincingly demonstrate that we can develop a computational model which incorporates enough of the complexity of the actual biology, optical imaging design, and nanomaterial properties that we are able to successfully use the model a priori to predict combinations of imaging design and nanoparticle configurations which provide optimal results as defined based on a series of metrics we create specifically for this project. This project represents an initial effort in this important new area which will be subsequently expanded in future studies. Ultimately, we believe the use of nanoengineered imaging agents will extend the limits of detection of optical technologies, increasing the achievable sensitivity and specificity and promoting improved screening and monitoring approaches. We believe there is tremendous potential for synergy between the rapidly developing fields of computational modeling, biomedical optics, and nanotechnology. Combining the tools of all of these fields—cooperating with the latest advances in understanding the molecular origins of cancer—provides an improved approach to detection and monitoring of cancer, a disease responsible for over one quarter of all deaths in the United States today.

TMC Collaboration: The clinical collaborator on this project, Dr. Kuan Yu, an oncologist at MD Anderson Cancer Center, is actively involved in other seed projects with me which involve both experimental and computational (Monte Carlo) efforts. We both have technical training as biomedical engineers and our training as engineers informs the strategies we focus on to improve our ability to develop nanotechnology-enabled methods for optically detecting and monitoring cancer. Because we are already have a seed grant funded focused on experimental efforts to evaluate fiber probes based on their ability to collect the maximum signal from scattering nanomaterials while minimizing the collected background signal, we are very interested in a parallel modeling project which would provide an improved approach to guiding our experimental efforts by providing insight into both what fiber geometries and nanoparticle geometric configurations we should use. Furthermore, we are both part of a separate one year $75,000 seed project together with another MD Anderson Collaborator using Monte Carlo methods to assess how gold nanoparticles can enhance delivered radiation. In that project, a Monte Carlo approach is used to simulate radiation therapy dosimetry as opposed to collected photons. Although the code and physical processes modeled are completely different, this seed effort does demonstrate we are qualified investigators in the area. Moreover, our already funded joint work shows this is a genuine collaboration we are attempting to build, and we are not faculty simply joining together for purposes of this seed grant.

A number of groups across the country are investigating the use of scattering and/or absorbing nanomaterials (nanoshells, nanorods, gold colloid, etc.) for targeted biomedical optical imaging applications (Sokolov et al, 2003; Loo et al, 2004). Although initial results of such studies have indicated substantial promise of nanomaterial enabled imaging for disease detection and diagnosis, work in this area has been fundamentally limited by the lack of a reliable computational model for a priori predictions of remitted optical signals as a function of nanoparticle physical properties, concentration, and location, inherent tissue optical properties, and optical design system parameters. As a first step towards development of nanoparticles which increase optical contrast, we will create a set of design tools which allow us to optimally configure nanoparticle properties for a particular application and predict a priori the expected gains in contrast. To accomplish this task, we will develop a model (Figure 1) which
allows us to: (1) predict the remitted optical signal given the structural and optical properties of the tissue and the nanoengineered contrast agent, the expected concentration of the contrast agent within the tissue, and the proposed imaging geometry, and (2) determine the physical properties of the nanoparticles which will optimize a particular contrast metric (scattering, absorption, etc.). We believe that the use of such a model will be highly functional in providing an efficient approach to screening the large variety of potential configurations in order to identify those which will provide the optimal results. We will also be able to optimize imaging design, for instance, source–detector separations and numerical apertures, to efficiently collect the nanoparticle optical signals given their expected depth and density distribution throughout the tissue.

In fact, we have preliminary experimental evidence (Figure 2) that in fact one can substantially enhance collected signal through appropriate choice of these design features. Dr. Drezek has extensive prior experience in development of mathematical models of light propagation, including finite-difference time-domain methods (Drezek et al, 1999; Drezek et al, 2000), Monte Carlo methods (Drezek et al, 2001; Pfefer et al, 2004) and the integration of quantitative histologic data into light propagation models (Drezek et al, 2003). Dr. Yu is a radiation oncologist highly familiar with Monte Carlo approaches, the standard method for predicting radiation dosimetry today. Dr. Yu and Dr. Drezek jointly supervise Lissett Bickford, a PhD bioengineering student who is part of the HHMI Translational Cancer Research Program. Through this collaboration, they already have joint meetings to discuss their experimental work. Adding in this new computational project will be a strong addition to their joint program.

The modeling proposed will require that integrating modeling approaches over several length scales including (1) computational electromagnetics methods (FDTD) which are suitable for modeling propagation of light at the nanoscale and cellular levels, and (2) layered and voxel-based Monte Carlo techniques for tissue and organ level modeling of optical imaging. The finite-difference time-domain (FDTD) method is ideally suited to problems where geometry must be defined at the nanoscale. Although Mie theory or other analytical solutions can be used to predict the optical properties of some simple specific...
primary limitation of the FDTD method is its intense computational requirements which limit the overall grid size, and thus, spatial extent of the simulations. In order to simulate light propagation through tissue volumes which exceed the computational limits of the FDTD method, we will develop a hybrid of the FDTD method with commonly used Monte Carlo techniques (Figure 3). Monte Carlo modeling is frequently used to examine photon transport in tissue by simulating a “random walk” of photons in a scattering and absorbing medium (Wang et al., 1995) using an average phase function. When a photon is scattered, its direction changes by an angle in the range $[0, 180]$. Normally, the deflection angle is calculated using the Henyey-Greenstein probability density function (Henyey and Greenstein, 1941). The Henyey-Greenstein function has been shown to adequately describe the angular distribution of scattered light for macroscopic tissue samples. However, it will not be sufficient for modeling the complex phase functions of tissues containing nanomaterials. Thus, it is important to devise a method for incorporating measured or predicted phase functions other than the Henyey-Greenstein approximation into Monte Carlo models. A layered Monte Carlo code capable of sampling phase function based on a tabulated cumulative distribution function rather than a Henyey-Greenstein phase function has already been developed and verified by replicating the simulations of (Mourant et al, 1996). However, to allow more complicated tissue geometries than simply a layered Monte Carlo model, we must allow the phase function and optical properties to vary spatially to capture inhomogeneities present in the tissue and the presence of nanomaterials. Using this model, will replace the aggregate phase function in the Monte Carlo simulations with simulations from the FDTD (or alternative computational electromagnetic) simulations, allowing the phase function to vary spatially to capture different concentrations of nanoparticles as a function of depth within the tissue. We will also incorporate spatial fluctuations in the scattering and absorption coefficients as calculated by the FDTD method. To assess the validity of the model developed, the results of this modeling work will be compared against experimental measurements of nanoshell imaging in vitro and in vivo underway through a separately funded effort (NSF EEC0118007). Specific metrics we will both simulate and measure include: brightness (average signal intensity (dB) in a region of interest), contrast (ratio difference of signal intensities between two ROIs), signal intensity vs. depth, backscattering coefficient, and minimum detectable concentration. A series of progressive experimental measurements (all using scattering nanoshells) will provide a means to evaluate the accuracy of model predictions (funded through a separate seed project). These measurements will use scattering nanoshells in (1) a homogeneous, single layer, semi-infinite phantom containing known nanoshell concentration, scatterers (polystyrene microspheres), and absorbers (hemoglobin); (2) a single layer phantom containing a buried sphere containing nanoshells, (3) a two-layer phantom (nanoshells only in bottom layer) which will be used to simulate nanoshell presence in vasculature, and (4) a cultured skin tissue model (MatTek). Throughout this project, the modeling efforts proposed here will benefit significantly from the experimental projects already underway jointly between our groups. Physically constructing a wide range of proposed nanoparticle configurations and testing each configuration in both non-biological and biological phantoms requires an intensive commitment of time and resources. **Here, we seek to reduce the required number of iterations by developing computational tools which can quickly compare the predicted effectiveness of a large number of nanoparticles in order that experimental groups may concentrate laboratory efforts on those configurations most likely to provide optimum results.** Furthermore, we believe that biomedical applications of nanoparticle-based technologies will expand dramatically in the next decade and the design tools developed for this project will be directly relevant to many other emerging problems.
INNOVATION AND IMPACT STATEMENT

Current State of the Art: Over the past seven years, I have been one of several investigators in our field attempting to leverage computational electromagnetics and Monte Carlo methods to provide new strategies for predicting how light will interact and propagate through tissue at multiple length scales with an ultimate goal of providing a more rational, engineering-based approach to optical system design for in vivo applications. Examples of my work in this area are below:


As nanomaterials became a more significant part of my research program, we began to attempt to adapt our already existing Monte Carlo models to allow incorporation of nanoscale material properties (Lin et al, 2005). Initially, we used computational electromagnetics solutions to compute individual nanoparticle properties which were then incorporated into macroscopic Monte Carlo model absorption and scattering coefficients. However, through experimental validation, we found this was not a sufficient approach to generate model data which matched experiments well enough to be practically useful. By additionally incorporating changes in the anisotropy of the scattering phase function, we found much better agreement with experiments (Lin et al, 2006). Because we now have strong evidence that we can use our models to generate data which match our lab experiments, the type of project we propose to carry out is indeed feasible.

Innovative Aspects: We believe there is currently an imbalance in research efforts with tremendous effort being spent on development a wide array of tunable nanomaterials which offer generally intriguing properties for biomedical applications but almost no effort is being expended in how to sift through the large potential operating space to identify the particles and configurations which offer the most appealing properties for particular imaging and/or therapeutic applications. Moreover, there is very little work on cross-comparisons of the performance of various materials. I believe a computational approach will be the only feasible solution. However, almost all current computational efforts are being directed at predicting nanoscale properties of individual or small collections of nanoparticles. There is a huge gulf between this type of simulation and a simulation which will predict remitted signals from tissues containing these types of materials. What I believe is most innovative about what we are proposing is that if successful, we will not only have a model that enables us to predict the combined influence of optical fiber geometry and nanomaterial properties, but we will be able to actually prove that there is benefit to be derived from such an approach since Kuan and I are involved in experimental work in the same area.
**Interdisciplinary Aspects:** My research program encompasses basic, applied, and translational research at the interface of clinical medicine, biology, engineering, physics, and computational science towards the development of novel photonics technologies for cost-effective, minimally invasive medical diagnosis and therapy with emphasis on oncological applications. I am particularly interested in women’s health, and most of my active research projects involve developing new technologies for detecting and monitoring ovarian and breast cancer. I currently have one of the most interdisciplinary labs on the Rice campus with students with backgrounds in bioengineering, electrical engineering, mechanical engineering, chemistry, materials science, physics, statistics, and medicine working in my group. I believe that the potential for greatest impact over the lifetime of my research career will be in work towards developing the technologies which bridge the gap between our rapidly developing fundamental molecular understanding of disease processes and our ability to rationally harness this understanding to more effectively diagnose and treat disease. Bridging that gap requires developing new tools which can rapidly detect, diagnose, and ultimately, in some way intervene in the disease process based on recognition of specific molecular signatures \textit{in vivo} in point-of-care settings. My lab develops optical imaging tools and complementary engineered nanomaterials to accomplish these tasks. Because there are compelling advantages to using structures engineered at the nanoscale level as a means to achieving optical molecular recognition, much of my present research falls within the realm of nanobiotechnology. During my first several years at Rice, I focused heavily on developing the nano-bio-opto connections within my lab. I believe we are now positioned to begin actively focusing on the information technology aspects as well. In order to be able to truly leverage computational strategies to guide our lab’s experimental efforts, we first needed to have both the experimental components of my research program well-established and the clinical connections firmly in place. In this grant, we focus on development of computational strategies to guide simultaneous optimization of the optical imaging tools and nanomaterials by creating code which can be used to simulate remitted signal from large numbers of potential probe design configurations under varying biological conditions.

**TMC Collaboration:** This research project in this proposal will take place at both Rice University and M.D. Anderson Cancer Center. MDACC has ranked among the two top cancer centers in the country over the past twelve years. Over 465,000 patients were treated at MDACC last year. MDACC is known for its translational clinical research with research spending approaching $200 million dollars per year. The facilities of both institutions will be available for this project. Although I accepted a tenure-track Assistant Professor at Rice in May 2001, I elected to delay the start date of that position for one year in order to spend most of the 2001-2002 year as a M.D. Anderson Odyssey Fellow developing new collaborative research projects. I recently have arranged for my clinical trial costs from MDACC to be directly billed through Rice research accounting. The clinical collaborator for this project is Dr. Kuan Yu (see letter of support). Dr. Yu is an Assistant Professor in Radiation Oncology with extensive expertise in breast cancer treatment. **MDACC is providing Dr. Yu 70% of his paid time for research activities including the work to be conducted in this project.** Furthermore, the development office at MDACC recently successfully acquired a gift to support Dr. Yu’s and Dr. Drezek’s joint efforts to develop a nanomaterial-based approach to intraoperative tumor margin imaging. Dr. Yu and Dr. Drezek are already involved in two small funded seed efforts together. If this project is funded, it will be their most significant funded effort together. Dr. Drezek and Dr. Yu have already submitted a $2.5M joint grant proposal on nanotechnology-enabled optical molecular imaging of breast tissue. We have established that we can successfully use seed projects to build larger grant efforts. If this computational seed project is funded, we will be able to leverage those dollars effectively as well (as described in the section which follows.)
**IMPACT AND EXPLOITATION PLAN**

**Benefit to Rice:** I believe a key to Rice’s future institutional success will be increasing the collaborative links between those areas which already exhibit strength. Although there are portions of Rice’s biomolecular modeling efforts which tie bioengineering, computer science, and the TMC together, in general the Departments of Bioengineering, Computer Science, Electrical Engineering, and CITI are not tied as closely together as they could or should be. I think it is potentially of benefit to all of these programs and to Rice to increase interactions among these individually strong entities. I see strong potential for my work and collaborations to become a part of these interactions for several reasons. First, our computational strategies rely primarily on Monte Carlo strategies which are directly parallelizable. What currently limits us in modeling is (1) the number of photons we can reasonably use in a run and (2) the time required to obtain a solution per photon. There is substantial opportunity to improve the performance of our current codes. The computational electromagnetics portions of our efforts provides separate challenges. Here, we are generally limited by available memory as the code runs in large 3D grids in which we must store a minimum of 6 electric and magnetic field variables in addition to voxel permittivity/conductivity. Although my first years at Rice have focused on establishing my credibility as a research in biomedical applications of nanotechnology, my technical background is largely computationally-oriented. My master’s research provided some of the first applications of finite-difference time-domain solutions of Maxwell’s equation to studying light scattering from biological cells. The paper which resulted from this work (Drezek et al, 1999) remains the most highly cited research paper (67 citations) using FDTD to investigate cellular scattering. My PhD focused on development of a Monte Carlo model use to elucidate relationships between tissue optical properties and clinical measurements of cervical precancers. My lab is actively involved in translational research with a clinical trial currently in progress this fall. I believe computational approaches are crucial to guiding our experimental efforts and that this can become an area of high visibility for Rice. Although there is clearly substantial signal processing, image processing, and algorithm development work we must undertake after generating clinical data, my personal bias is that not enough computational work occurs before running a trial in how we best design the system we will use. When I think about what is really necessary to achieve my research vision, computational modeling is absolutely a central component (see diagram above). My lab is recognized as one of the leading labs in development of Monte Carlo and computational electromagnetics approaches for biomedical optics applications. However, we believe there is substantial opportunity to build collaborations in how we can best improve and use our codes to provide the answers we need to generate the best clinical data we can.

**External Funding Opportunities:** I have had substantial success in leveraging seed funding to create long term funded projects within my labs and with collaborators. Furthermore, both Kuan and I have a history of turning initial seed grant applications into full proposals. At the time I accepted a position at Rice, the word “nanotechnology” was not in my vocabulary nor did nanotechnology appear in any form in my future research proposal at the time I was hired. I was able to move into that area using a $15,000 CBEN seed grant provided as soon as I started at Rice which I used to generate data that then turned into a $500,000 funded NSF proposal. That NSF grant, my first major funded project as a PI, provided the initial drive behind what has become a large component of my research program. My research program has been growing each year since I joined the faculty is 2002, and my Rice report research expenditures last year were ~$685K.

The collaboration between Kuan Yu and myself was not established for purposes of this proposal. We met approximately a year and a half ago when he approached me about potential applications of nanotechnology to cancer treatment. As a biomedical engineering by training himself, Kuan is particularly interested in how new technologies can improve cancer care. We immediately began writing proposals together. A $50,000 seed grant recently funded by the UTHSC/MDACC Translational Science effort is allowing us to begin a project using nanoshells to rapid assess breast tumor margins in HER2+ patients. A $75,000 Concept Award from the DOD Congressionally Directed Medical Research Program between Dr. Yu, Dr. Zhang of MDACC, and myself is funding an effort to assess gold nanoshells as a mechanism to increase delivered radiation dose. A larger grant
between Dr. Yu and I assessing nanotechnology-enabled approaches to optical molecular imaging of breast cancer is currently pending. We currently have a graduate student, Lissett Bickford, who is serving as the link between our two labs on experimental work. She is a graduate student in the new HHMI Translational Cancer Research training program which is joint between Rice and MDACC. Dr. Yu and I already have regular progress meetings to coordinate our efforts. We believe a postdoctoral fellow joint between our groups would be the best approach to jumpstarting the computational efforts proposed here.

There are significant funding opportunities for computationally-driven biomedical applications of nanotechnology through both NSF and NIH. In particular, preliminary data obtained through seed funding could be leveraged in a R21 proposal through the “Nanoscience and Nanotechnology in Biology and Medicine” RFA which has two annual submission dates. NIBIB is a sponsoring institute of that RFA. NIBIB also accepts R21s via a RFA entitled “Exploratory Bioengineering Research” which has three application deadlines each year. Furthermore, NIBIB accepts R03 applications which fund at a rate above the normal agency pay-line. At NSF, biomedical applications of nanotechnology are supported by the NSF BES division which accepts proposals each October 1 and through a BES biophotonics initiative which accepts applications once a year (September 2007 is the next entry point). NSF’s Nanoscale Science and Engineering (NSE) program provides another funding potential funding mechanism; however, due to high application volumes, the funding rates through NSE have been lower than those for the other pathways described. In collaboration with Dr. Zhang of MDACC, we had success last year obtaining a Department of Defense Concept Award from the Congressionally Directed Medical Research Program in Breast Cancer for the Monte Carlo-based radiation dosimetry predictions project. We believe several of the DOD CDMRP RFAs but particularly the breast cancer program offer another potential funding avenue for these efforts. I currently have computational projects funded through NIH so am familiar with how to package this type of research for NIH funding.

Year 1:
- Months 1-3: Assess possible changes to implementation of computational approaches for nanoparticle property prediction in order to broaden the range of nanoparticles code can accommodate. Currently, we are limited to spherical and layered spherical geometries. FDTD (finite difference time domain), DDA (discrete dipole approximation), and T-matrix methods provide approaches to broadening the geometries we can use. If a switch is made, we will need to implement and validate the new code. (We already have validated 3D FDTD code available which works well for single frequency calculations but is currently difficult to use for spectral simulations.)
- Months 4-6: Modification of code to account for arbitrary scattering phase functions. Current implementation uses only Henyey Greenstein (HG) phase functions (that is, changes in anisotropy parameter, g, are implemented through HG phase function only).
- Months 7: Development and coding of metrics for assessment of efficacy of particular geometries/materials configurations
- Months 8-12: Validation and testing of integrated Monte Carlo model

Year 1 Deliverables:
- submission of jointly authored (Drezek/Yu) peer-reviewed manuscript on model developed
- major conference presentation on model developed by postdoctoral fellow
- submission of a joint NIH (or other federally funded grant) generated data/code

Year 2:
- Months 13-24: Use of code to evaluate proposed fiber probe geometries
- Months 13-24: Use of code for nanoparticle configurations which cannot be simulated with code available at start of project (non-spherical particles)
- Months 15-18: Identification of three physically implementable and promising geometries for experimental evaluation and design specification for nanomaterials to be used with these geometries (experiments will be funded separately from this proposal)

Year 2 Deliverables:
- submission of jointly authored (Drezek/Yu) peer-reviewed manuscript on results
- major conference presentation on model developed by postdoctoral fellow
- successful receipt of a federally-funded grant to continue work on the project after the seed project concludes
- generated data/code

Collaborative Interactions: The proposed effort will result in a new collaborative project between the Yu and Drezek labs. At the beginning of the project, each investigator will give a presentation at the other investigator’s weekly group meeting to describe laboratory research directions. After initiating the project, the investigators will meet once every other week to discuss progress. Meetings will include both the postdoctoral fellow who will work on the project described in this proposal as well as the other students from each laboratory involved in the joint experimental projects. The postdoc will attend group meetings for both groups. Involved students will also be invited to attend group meetings for the secondary lab when this makes sense given the topics to be discussed. The labs will submit a joint poster or oral presentation describing preliminary results at next year’s biophotonics Gordon Conference. If preliminary experiments prove successful, the investigators will submit a joint R21 proposal (or alternative external grant) by the end of the first funding year. Dr. Yu is interested in developing more effective clinical strategies for cancer monitoring as part of his laboratory’s research program; Dr. Drezek’s lab has significant strength in optical characterization of materials and in development of novel photonics-based diagnostics tests. There is strong opportunity to build off of the natural synergies between these groups in the proposed GC4R project and through other research endeavors.