Research Statement

Broadly, my areas of research are in the use of numerical solutions to ordinary and partial differential equations to solve questions in medicine and biology. I am currently pursuing two distinct projects of my own initiation and working with students on several other projects.

Airflow

The first project explores airflow patterns in the human respiratory system using computational fluid dynamics. Many questions are unanswered regarding the importance of inter-individual differences in anatomy on flow and particle deposition, the impact of nasal surgery on olfaction, the optimization of drug delivery via the nose or lungs, and the impact of environmental air pollution on respiratory and systemic health. I have found that there are quantifiable differences in flow patterns among individuals that are not predictable by examining medical images [4]. However, total absorption of water soluble gases may not be as variable among individuals as once thought [3]. It is also evident through computational work that surgery can have undesired effects on flow patterns [6]. Open questions remain related to optimizing the construction of computational meshes for complicated human anatomy, improving simulation time and convergence of flow calculations, refining particle transport equations, quantifying the impact of mucous flow on airflow and particle deposition, and handling large volumes of medical images.

I began work in this field while conducting my graduate and postdoctoral research. Since coming to VCU, I have made contact with Worth Longest in Engineering. We are conducting simulations to examine the effect of inter-individual differences in anatomy on deposition of nanoparticles [I]. This research will be relevant to issues regarding the optimal delivery of nasal spray drugs as well as to the impact of air pollution on the respiratory system and extend work done previously [5].

I also initiated collaboration with Richard Costanzo in Physiology to explore the effects of nasal surgery and nasal deformities on airflow patterns as they relate to a loss of sense of smell. The ultimate goal of the work is to predict the impact of nasal surgery on the quality of life for the patient. Dr. Costanzo supplied me with medical images and I developed a 3D hollow model of the nasal airspace. I am working on running flow simulations in this model.

Wound Healing

Currently, my most active area of research involves developing a model for the healing of a tissue wound. This model began development in conjunction with colleagues at the medical school: Kevin Ward (now at University of Michigan), Nathan Menke (now at University of Pittsburgh) and Bob Dieglemann. An extensive series of human subject tests are being conducted to improve the understanding of the complex biochemical and cellular processes which are involved in the mechanics of wound healing. We are hopeful that mathematical models will shed light on which processes are most important in healing and explain why negative outcomes are observed.

An initial model [2] was developed as proof of concept that wound healing dynamics could be captured successfully with an ordinary differential equation model. This model used a generic measure of damage to indicate a wound and also grouped together the entire inflammatory response into one variable. With this model, we were able to show that reduced tissue oxygen has a negative impact on healing rates but that it is possible to manipulate the wound environment (by, for example, increasing the rate of fibroblast recruitment) to improve the healing outcome.

In order to use the ODE model with clinical data, it was necessary to transform the measure of generic damage into a measurable data point. Therefore, in collaboration with Angela Reynolds (VCU Mathematics) we developed a model of wound healing that relies on collagen levels as measure of healing [1]. This refined model was validated using published data on wound healing and will be is applicable in a clinical setting.

The next step in the wound modeling project is to now develop models that account for patient specific information. For example, it is known that high cortisol levels can significantly delay healing. Cortisol has a major impact on the inflammatory response. Since our current wound model groups the entire immune response together, it was not possible to add the effects of cortisol to the existing model. Working the Racheal Cooper (a Ph.D. student) and Shasta Truett (a Masters student – supported by the Jeffress Grant) we are modifying the existing model by separating the inflammatory response into two equations (one for neutrophils and one for macrophages) to allow for more flexibility in applying the effects of cortisol [II].

Estrogen and oxygen have been shown to be beneficial in healing certain wounds. Understanding how these systemic mediators impact the complex relationships in wound healing is an important part in predicting patient outcomes and also in determining when and how to intervene when a patient has significant tissue damage [III]. Current studies are being done to explore the use of both estrogen and oxygen as topical and systemic treatments and we propose the use of mathematical models to help pinpoint the optimal timing of the treatments.

Now that our group has a publication record we are in the process of planning a grant application for submission to the Joint DMS/NIGMS Initiative to Support Research at the Interface of the Biological and Mathematical Sciences (NSF/NIH) to further validate the existing model with data and to look at the broader picture of wound healing to predict successful treatment protocols. We aim to answer questions related to parameter estimation in the absence of data, identification of the parameter space and sensitivity analysis of the parameters. Stability analysis of subsystems of the model will also provide insight into the viability of the model over the entire parameter space.

Work with Students

I have had several productive research experiences with graduate students. Both of my Masters students this year produced work which can be put into publication. Cheri Doucette worked with me on developing a model of urban growth/decay using a cellular automata model [IV]. This work uses a local Richmond neighborhood as a template for

examining the negative impact that the introduction of a major roadway can have on the viability of a neighborhood.

Nicole O'Neil developed an agent based model of cancer cells growing near healthy cells and then modeled the effect of radiotherapy on both the cancer and healthy cells [V]. It is known that cells have different sensitivity to radiation depending on which stage of the cell cycle they are in. Furthermore, the impact of bystander radiation was explored. It is thought that radiated cells effect neighboring cells after the treatment has ended, but this is a large unknown in cancer treatment. I currently have a high school student (Hans Prakash) working on this cancer model with me this summer to fine tune the levels of bystander effects in the model and then the work will be ready for publication.

Gigi Meyer (Ph.D. student) and I are working on developing a model of chronic infection in Crohn's Disease. This work builds on some of the inflammatory dynamics from the wound healing model, but moves it into a new context. The goal of the project is to understand how diet, specifically a diet high in fatty acids, can help to reduce the chronic inflammation associated with Crohn's Disease.

Journal Publications (Referred)

1. RA Segal, RF Diegelmann, KR Ward, A Reynolds "A Differential Equation Model of Collagen Accumulation in a Healing Wound" Bulletin of Mathematical Biology. 2012(74):2165–2182 (IF=1.847)
2. NB Menke, JW Cain, DM Chan, RA Segal, TM Witten, DG Bonchev, RF Diegelmann, KR Ward. An *In Silico* Approach to the Analysis of Acute Wound Healing. Wound Repair and Regeneration. 2010(18): 105–113. (IF=2.445) [Corresponding author]
3. GJM Garcia, JD Schroeter, RA Segal, J Stanek, GL Foureman, JS Kimbell. Dosimetry of nasal uptake of soluble and reactive gases: a first study of inter-human variability. Inhalation Toxicology. 2009, 21(7): 607–618. (IF=1.831)
4. RA Segal, GM Kepler, JS Kimbell. Effects of Differences in Nasal Anatomy on Airflow Distribution: A Comparison of Four Individuals At Rest. Annals of Biomedical Engineering. 2008(36): 1870-1882. (IF = 2.346)
5. J.S. Kimbell, R.A. Segal, B Asgharian, B.A. Wong, J.D. Schroeter, J.P Southall, C.J. Dickens, G Brace, F.J. Miller. "Characterization of Deposition from Current Nasal Spray Devices Using a Computational Fluid Dynamics Model of the Human Nasal Passages." J. of Aerosol Medicine. 2007(20): 59-74. (IF=1.945)
6. D. Wexler, R.A. Segal, J.S. Kimbell. "Aerodynamic effects of inferior turbinate reduction – Computational fluid dynamics simulation" Archives of Otolaryngology – Head & Neck Surgery. 2005(131): 1102-1107. (IF=1.734)
7. R.A. Segal, T.B. Martonen, C.S. Kim, M. Shearer. "Computer Simulations of Particle Deposition in the Lungs of Chronic Obstructive Pulmonary Disease Patients" Inhalation Toxicology 2002(14):705-720. (IF=2.167)
8. Martonen, T. B., Musante, C. J., Segal, R. A., Schroeter, J. D., Hwang, D., Dolovich, M. A., Burton, R., Spencer, R. M., and Fleming, J. S. "Lung models: strengths and limitations" Respiratory Care 2000(45):712-736.
9. X. Guan, R.A. Segal, M. Shearer, T.B. Martonen. "Mathematical Model of Airflow in the Lungs of Children II: Effects of Ventilatory Parameters" Journal

of Theoretical Medicine. 2000(3):51-62.

10. R.A. Segal, T.B. Martonen, C.S. Kim. "Comparison of Computer Simulations and Human Data for Particle Deposition in Healthy Subjects" Journal of Air and Waste Management Association 2000(50):1262-1268.
11. R.A. Segal, X. Guan, M. Shearer, T.B. Martonen. "Mathematical Model of Airflow in the Lungs of Children I: Effects of Tumor Sizes and Locations" Journal of Theoretical Medicine. 2000(2):199-213.

In Process

I. R.A. Segal "Deposition of Nanoparticles in Human Nasal Passages: Effect of Morphological Variation" (in preparation)
II. A.R Reynolds, R.L. Cooper, S. Truett, R.A. Segal "Wound healing under duress: Effect of elevated cortisol" (in preparation for submission to Journal of Theoretical Biology)
III. R.L. Cooper , A.R. Reynolds, R.A. Segal "An ODE Model of the Effect of Estrogen on Wound Healing" (in preparation)
IV. C.C. Doucette and R.A. Segal. "Modeling the Barrier-Effect of Roadways: A Cellular-Automata Neighborhood" (in preparation for submission to Computers, Environment and Urban Systems)
V. R.A. Segal H. Prakash and N.L. ONeil "An Agent Based Model of Tumor Growth and Response to Radiotherapy" (in preparation)