RAMS Program Student Projects: Applying Computational Modeling and Analysis to the Biomedical Sciences

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Presented to
Review Committee
Research Alliance in Math & Science

December 3, 2008
Oak Ridge, Tennessee
Outline

- Importance of interdisciplinary research
- Computational biomedical projects
  - Project overviews
  - RAMS students working on project
- Future directions & recruiting efforts
Importance of Computational Biology

• “Computational biology is an interdisciplinary field that applies the techniques of computer science, applied mathematics, and statistics to address biological problems.” (wikipedia)

• “Major diseases like cancer, neurological and cardiovascular diseases are complex in nature involving environmental, life style, ageing and genetic components. One of the future challenges is to integrate the knowledge of all these different components into robust and fully reliable computer models and "in silico" environments that will help the development and testing of new therapies for better prediction and prevention tools in healthcare.” (ICT-BIO 2008)

• To meet this challenge, we need to train:
  – Biologist and medical professionals who understand computer modeling
  – Computational scientists who understand biology and medicine
Computational Biomedical Projects

- **Vascular**
  - Adominal Aortic Aneurysm (AAA) rupture – finite element modeling
  - Intimal Hyperplasia (IH) due to injury
    - Cellular & biochemical mechanisms – hybrid modeling (discrete model + continuous models of PDEs)
    - Population studies – statistical analysis and modeling

- **Obesity**
  - Biochemical cross talk between adipose and skeletal muscle cells – biochemical pathway modeling

- **Seizure Forewarning**
  - Predict epileptic seizures before they happen - Non-linear analysis
Finite Element Modeling of Abdominal Aortic Aneurysm (AAA)

- Collaboration with UT Graduate School of Medicine Department of Surgery and Vascular Research Lab

- CT scans utilized to construct geometrical model of AAA

- Numerical simulations give wall mechanical stress distribution

- Predict AAA rupture site from stress distribution
Rowena Ong: 2004-2005

- Undergraduate: Southern Adventist University
- Major: Computer Science
- Minor: Chemistry, Math
- Graduated: May 2004
- Graduate: Vanderbilt Univ.
- Major: Biomedical Engineering
- M.S.: December 2007
- Ph.D. anticipated: Fall 2010

- RAMS projects (mentor: Kara Kruse)
  - Use C++ and the NURBS libraries to develop a semi-automatic method for patching four surfaces of a AAA together in a C2 continuous manner
  - Using C++, extend a method developed by Antiga and Steinman (2004) to automatically decompose a bifurcation into three branches, construct a parameterized representation of the surface, and from this construct hexahedral meshes of the AAA

- MS thesis:
  - Non-rigid registration methods for breast elastography

- Ph.D. topic:
  - Development of image-guided renal surgery systems
Rowena Ong: 2004-2005

- Impact of RAMS program:
  - “My RAMS internships in some ways were more valuable than my undergraduate experience in introducing me to what science and engineering are actually like. The most important thing I learned was how to ask questions and look for answers. In college, answers were something that I looked for in textbooks, and past internships had focused on accomplishing tasks, so I had not fully understood that science is about asking questions and exploring different possibilities. In RAMS, I was also introduced to practical skills such as literature searches and poster presentations, which I had not had experience with before.”

  - “My project at RAMS was to find better meshing techniques for finite element modeling of abdominal aortic aneurysms, to better understand and predict rupture. The knowledge and skills I gained were a great advantage in graduate school, as I continued in a related area (image-guided surgery/biomechanical modeling) and was able to jump right into research from the beginning. My internships had given me a intuitive knowledge about the modeling, meshing, and visualization, which helped me understand more easily the theoretical side of my graduate courses.”
Erin Lennartz: 2006

- **Undergraduate:** Virginia Tech
  - Major: Engineering Science and Mechanics (Biomechanics Option) / Applied Computational Mathematics
  - Graduated: May 2008
- **Graduate:** Virginia Tech
  - Major: Biomedical Engineering
  - M.S. anticipated: 2009
  - Plans to pursue Ph.D. but undecided on university

- **RAMS project (mentor: Kara Kruse):**
  - Use the ABAQUS finite element modeling software to compute the mechanical stresses on the wall of a bifurcated AAA; search the literature for better parameter values for the model; perform parameter sensitivity analysis

- **B.S. research:**
  - Used finite element software to model stented arteries and cartilage tissues under tensile testing

- **M.S. topic:**
  - Isolation and enrichment of transformed breast cancer using insulator-based dielectrophoresis microdevices
  - Uses the COMSOL and Fluent finite element tools for modeling the electrical field and fluid flow in these devices before fabricating them
Erin Lennartz: 2006

- Impact of RAMS program:
  - “The RAMS program was a pivotal step in where I am now academically and professionally. Before participating I had no research experience, minimal lab experience, and very little computing capability. While my research during RAMS focused on finite element analysis of aneurysms, my research academically has been modeling stented arteries, cartilage tissues under tensile testing, and micro-fluidics for cancer therapy. The area of my research has shifted many times since RAMS but all have required computational components and have all stayed in the biological realm. RAMS opened a door for me I never knew existed; engineering applied in the body and how to use computational models to mimic this. While biologists use cells and microscopes, engineers use models and computing.”
Intimal Hyperplasia After Balloon Injury

- Atherosclerosis (hardening of arteries) results from plaque buildup
- Treated by balloon angioplasty with or without stent placement
- Vessel response can be intimal hyperplasia (IH) and/or restenosis

Can we predict
- Who will be helped or harmed with balloon angioplasty?
- Does hormone replacement therapy affect outcome?
Hybrid Model of Intimal Hyperplasia

- Build vascular smooth muscle cell (VSMC) proliferation/migration model
- Add continuous model of platelet derived growth factor (PDGF) diffusion
- Add enzyme kinetic models for degradation of collagen by matrix-metalloproteinases (MMPs)
- Add other cell types [monocyte (M), endothelial cell (EC)] and biochemicals
Elizabeth O’Quinn: 2005-2007

- Undergraduate: Woffard College
- Major: Biology with Emphasis in Computational Science
- Graduated: May 2006
- Future plans: medical school & interdisciplinary research involving pathology and computational sciences

- RAMS projects (mentor: Kara Kruse)
  - Implement a published model of matrix-metalloproteinase-2 (MMP-2) degradation of collagen I in the JSIM simulation modeling environment and adapt for collagen type IV
  - Implement a published model of MMP-9 degradation of collagen type I in JSIM and adapt for collagen type IV
  - Develop an conceptual model of intimal hyperplasia cellular and biochemical mechanisms using the Java-based object-oriented Unified Modeling Language (UML) software tool ArgoUML

- Current employment:
  - Participating in an interdisciplinary project at Vanderbilt University working with medical biologists, biomedical engineers, and chemical engineers in the study of bone
Elizabeth O’Quinn: 2005-2007

- Impact of RAMS program:
  - “The Research Alliance in Math and Science (RAMS) Program allowed me the opportunity to work with scientists from many different disciplines. I was better able to understand how individuals from different backgrounds and perspectives can come together to communicate and share various ideas toward a common goal. This program served as a gateway for me, studying as an undergraduate at a small school in biology, to participate in this type of research exploring interdisciplinary studies in Biomedical computing with top scientists in this field. This program served as a portal affording me the opportunity for exposure in various novel interdisciplinary research methods, techniques, and principles involving computational biology, modeling, and simulation. This research opportunity has given me a better perspective on current research in the field and potential areas of future research and application of biological modeling in understanding the pathological basis of disease. I was able to better understand how computational modeling and a team of interdisciplinary scientists can use principles of engineering as tools of research for further studies in the pathological basis of disease. This experience gave me the opportunity to participate hand in hand with leading computational scientists, biomedical engineers, physicists, experimentalists, and physicians on novel ideas and concepts in computational biology and medicine.”
Angela Reedy: 2006

- RAMS project (mentors: Kara Kruse & Richard Ward)
  - Implement a model of the Mitogen Activated Protein Kinase (MAPK) signaling pathway critical to vascular remodeling; use the Systems Biology Workbench modeling tool for solving the set of coupled differential equations and plotting results

- Undergraduate: Alabama A&M University
- Major: Biology and Chemistry
- Graduated: May 2007
Abigail Snyder: 2007-2008

• RAMS projects
  – Develop a 1-dimensional finite difference model of the diffusion of biochemicals in a Boyden Chamber; program both the finite difference model and the analytical solution in C++ (mentor: Kara Kruse)
  – Worked on a non-biomedical project form improving the accuracy of the RCSIM radio channel simulation by reformulating the scattering junctions that it uses to propagate a simulated radio wave (mentor: Jim Nutaro)

• Undergraduate: University of Pittsburgh
• Major: Applied Mathematics
• Expected Graduation: May 2011
Katelyn Swift-Spong: 2008

- Undergraduate: Franklin W. Olin College of Engineering
- Major: Electrical and Computer Engineering
- Expected Graduation: May 2011

RAMS project (mentor: Richard Ward)
- Use C++ to develop a 3-dimensional finite difference model of biochemical diffusion and a routine for interpolating the results between grid points; incorporate finite difference model into hybrid model of cell migration in response to a biochemical gradient
Impact of RAMS program:

“My participation in the RAMS program gave me a better perspective on what is involved with doing research and what the possibilities are in research. This experience was helpful since I don't know yet if I want to go into research or industry, and knowing more about this choice is helpful. I also really benefited from the interdisciplinary nature of Biomedical Computing. Before the program I didn't have a clear conception of how computing could be used for biomedical research. Present computing capabilities provide such great ways to do research, and it was great to gain an understanding of how to build models of physical systems. I do not know yet what field I want to go into, but something interdisciplinary would be great.”
Retrospective Statistical Study of Fem-Pop Bypass Grafting

- Correlations established:
  - mental/mood disorders medications
  - high cholesterol

- Trends established:
  - graft type
  - hysterectomy

- Next Steps:
  - Repeat statistical study with prospective data
  - Develop predictive statistical regression model
Sara Wezensky: 2008

- Undergraduate: University of Louisville
- Major: Biology, Genetics
- Graduated: May 2007
- Graduate: Montana State Univ.
- Major: Veterinary Molecular Biology
- Started: Fall 2008

- RAMS project (mentor: Kara Kruse)
  - Use data mining and statistical analysis tools to determine correlations between clinical variables in fem-pop bypass patients; use the ORNL developed Piranha tool for data mining; use JMP software tool for statistical analysis
Sara Wezensky: 2008

- Impact of RAMS program:
  - “RAMS helped me prepare for a multi-disciplinary degree, learn to work with diverse departments, and build my knowledge of the ways that computational tools can fill in gaps in the scientific community. I have promoted the tools derived in CSED as the up-and-coming future in the realm of knowledge data-mining and processing technology.”
Jillian Gauld: 2008

- RAMS project (mentor: Kara Kruse)
  - Use a statistical analysis tool to determine correlations between clinical variables in fem-pop bypass patients; evaluate various software tools and choose one for use in the statistical analysis
  - Future project: Use results from statistical correlation study to develop a statistical regression model for predicting which patients will likely have worse outcome with fem-pop bypass

- Undergraduate: Queen’s University
- Major: Biology
- Minor: Mathematics
- Expected Graduation: May 2012
Jillian Gauld: 2008

- Impact of RAMS program:
  - “I have always been interested in both life sciences and mathematics. While I really enjoyed mathematics, and excelled in it through school, I had always planned to set it aside to pursue a biology related degree. This summer was really beneficial to me because it showed me how to relate the two, by applying computational mathematics to the trends related to modern medicine and science. Seeing how the two work together has inspired me to move toward a more math involved education, while still keeping my foundation in biology. It is really important to keep the links between mathematics and biological sciences strong. Many students think they have to choose between mathematics and science, but they don’t realize the connection these two disciplines share in today’s research.”
Model of Fatty Acid Oxidation in Muscle

- Develop mathematical model describing the effects on skeletal muscle cell fatty acid oxidation (FAO) of biochemicals:
  - Leucine
  - Calcitriol
  - Adiponectin
  - Uncoupling protein 3 (UCP3)
- Fit the mathematical model to Dr. Michael Zemel’s experimental data at 12, 24, and 48 hours
- Next Steps:
  - Develop model for adipose (fat) cells
  - Develop model for biochemical cross-talk between adipose and skeletal muscle cells
Sara Haque: 2008

- Undergraduate: Centre College
- Major: Mathematics
- Expected Graduation: May 2009
- Future Plans: Graduate school in Bioengineering

- RAMS project (mentor: Kara Kruse)
  - Develop a semi-empirical, semi-mechanistic computational model of the effects of various biochemicals on fatty acid oxidation in skeletal muscle cells based on experimental data; use Mathematica programming to develop the model
Sara Haque: 2008

- Impact of RAMS program:
  
  “Participating in the RAMS program has completely changed my outlook on computational sciences and biomedical projects. I have always been interested in the medical field and medical related project and I love my math major so this summer when I had the opportunity to put the two together I was very excited. I had never worked on a biomedical project before and this experience has really helped me realize that I would love to do this again. Biomedical Computing is essential when it comes to understanding how the body works and how external factors may affect the biological pathways; this I learned over the summer. I can definitely say that after participating in the RAMS program and working on a Biomedical project I have seriously considered going into Bioengineering as a career.”
SeizAlert Predicts Epileptic Seizures

- Non-linear analysis approach predicts onset of epileptic seizure
- Implemented in software on a PDA or wearable device to alert wearer to occurrence of seizure
- Code parallelize for analyzing many studies
- Protected by five patents and two pending
- Winner of 2005 R&D 100 award

*Hively, Protopopescu, Munro, Kruse (2005)
Talisha Haywood: 2002-2003

- RAMS projects
  - Develop a parallel implementation of a 3D Symmetric-Galerkin boundary integral method (Mentor: Len Gray)
  - Using MatLab, design and implement a graphical user interface (GUI) for the Fortran non-linear analysis code used in predicting epileptic seizures (Mentor: Lee Hively)

- Undergraduate: Wofford College
- Major: Physics with Computational Emphasis
- Graduated: 2004

- Graduate: North Carolina A&T State University
- Major: Mechanical Engineering
- M.S.: 2007
- Ph.D.: currently pursuing

- Graduate research: Structural and flux-pinning properties of laser ablated YBCO thin films: effects of self-assembled CeO2 nanodots on LaAlO3 substrates
- NSF Engineering Research Center for Revolutionizing Metallic Biomaterials
Travis Whitlow: 2007

- RAMS project (mentor: Lee Hively)
  - Parallelize the SeizAlert non-linear analysis Fortran code using MPI and run on a 260 node distributed cluster machine

- Undergraduate: Alabama A&M University
- Major: Mechanical Engineering
- Graduated: May 2008
Cedrick Collins: 2008

- Undergraduate: South Carolina State University
- Major: Computer Science
- Expected Graduation: May 2010

- RAMS project (mentors: Lee Hively and Jim Nutaro)
  - Implement a Java wrapper to parallelize the SeizAlert non-linear analysis Fortran code for running on a distributed cluster; use ArgoUML to design the Java-Fortran interface; use Java Remote Method Invocation (RMI) to distribute computing jobs to nodes in a computing cluster
Jaron Murphy: 2008

- RAMS project (mentors: Lee Hively and Nancy Munro)
  - Design and implement a Java program for analyzing brain-wave data with the goal of early diagnosis of Alzheimer’s disease

- Undergraduate: Ohio State University
- Major: Computer Science and Engineering
- Expected Graduation: May 2009
New Recruiting Effort – Mentor Protégé’ program in place with Morehouse College

- Morehouse School of Medicine
  - Nerimiah Emmett, Ph.D. – developing models of biochemical pathways involved in vascular remodeling due to high blood pressure (HBP)
  - Find student(s) from Morehouse, Spellman, and/or Clark Atlanta Universities to work on a biochemical pathway model common to vascular remodeling in both HBP and balloon angioplasty
  - Work on project during summer at ORNL and during school year at Morehouse