

Essay

Impact of Interdisciplinary Undergraduate Research in Mathematics and Biology on the Development of a New Course Integrating Five STEM Disciplines

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Funded by innovative programs at the National Science Foundation and the Howard Hughes Medical Institute, University of Richmond faculty in biology, chemistry, mathematics, physics, and computer science teamed up to offer first- and second-year students the opportunity to contribute to vibrant, interdisciplinary research projects. The result was not only good science but also good science that motivated and informed course development. Here, we describe four recent undergraduate research projects involving students and faculty in biology, physics, mathematics, and computer science and how each contributed in significant ways to the conception and implementation of our new Integrated Quantitative Science course, a course for first-year students that integrates the material in the first course of the major in each of biology, chemistry, mathematics, computer science, and physics.

INTRODUCTION

BIO2010 calls for faculty in biology, mathematics, and the physical and information sciences to work collaboratively to find ways of integrating mathematics, the physical sciences, and the life sciences in courses and to recognize that faculty development is a crucial component to doing so. It also calls for increased opportunities for undergraduate research as early in a student's career as possible (National Research Council, 2003). At University of Richmond (UR), we are discovering how undergraduate research can be a driving force in achieving interdisciplinary collaboration. As we increase the number of students participating in undergraduate research, we have observed just how often elements of research projects find their way into the classroom, particu-

larly research projects that have engaged students and/or faculty from different areas to work on interdisciplinary questions. A prime case study at University of Richmond is in the development of our new supercourse called Integrated Quantitative Science (IQS), which combines and integrates the concepts from the first course in each of mathematics, physics, computer science, biology, and chemistry. The course development was funded by a science education grant from the Howard Hughes Medical Institute (HHMI) and is being taught for the first time during the 2009–2010 academic year. Here, we describe four recent undergraduate research projects involving students and faculty in biology, chemistry, physics, mathematics, and computer science and how each contributed in significant ways to the conception and implementation of the IQS course.

UR is a private liberal arts institution of approximately 2800 undergraduate students that is focused on undergraduate research across campus. In summer 2009, there were 150 students involved in undergraduate research in science and mathematics, 35% of whom were funded internally and 65% of whom were funded externally by various grants and awards (e.g., HHMI, Merck-American Association for the Advancement of Science, Beckman, National Institutes of Health, National Science Foundation [NSF], American Chemical Society-Petroleum Research Fund). Richmond fac-

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ulty values the one-on-one interactions and opportunities for teaching outside of a classroom that occur when mentoring undergraduate students in research projects. These opportunities add a new dimension to the students' understanding of the field, providing them with practical skills, opportunities to solve problems, motivation to refine and improve oral and written communication skills, and exposure to the joys and frustrations of scientific research. As one student put it, "Doing research will turn you into a scientist faster than a class will."

Preparing our students to be twenty-first century scientists was also a motivating factor behind the conception and design of IQS. IQS is a two-semester course for first-year students that integrates the material currently taught in the first course of the major in each of biology, chemistry, physics, mathematics, and computer science. Although it is called a course, it is really a new way of teaching the concepts normally covered in these five courses. Students enroll in the course for a full year, and it replaces two courses in their schedules in each of the fall and spring semesters. The course meets for lecture 300 min per week; it has a weekly 3-h laboratory component and a weekly 1-h workshop/laboratory. The course substitutes for the first course in the major in each of the five disciplines involved. After completing both semesters of IQS, the students will complete a traditional major in at least one of the contributing disciplines. These students will have the option to have an interdisciplinary minor in Integrated Quantitative Science by completing additional upper-level courses that combine two of the disciplines and by completing an undergraduate research project. The course development was originally inspired by models from Harvey Mudd's Interdisciplinary Lab (National Research Council, 2003) and the Integrated Science Program at Princeton University (Lewis-Sigler Institute for Integrative Genomics, 2010).

Each semester of IQS is organized around an umbrella theme. The themes were chosen because they related to the research interests of the faculty involved and because of their relevance to all the disciplines. The theme for the first semester is antibiotic resistance, and the theme for the spring semester is signaling and cell-cell communication. Each semester includes a stand-alone, hypothesis-driven laboratory component. The laboratory component of the first semester included creating an agent-based computer simulation model to study the evolution of antibiotic resistance in a macrolevel population, modeling of molecular dynamical behavior of antibiotics, and a semester-long experiment using a novel animal model system to study bacterial symbionts and the selection of antibiotic resistant species. The antibiotic resistance study generated primary research data that allowed students to gain experience using a variety of molecular and bioinformatic techniques. Similar to IQS-1, the laboratory associated with IQS-2 is a discovery-oriented experience composed of both experimental and computer simulation approaches. Students focus on five separate projects during the semester: 1) understanding signaling in the immune system, 2) spot detection/automated generation of protein profiles from two-dimensional gel electrophoresis, 3) Brownian motion: experimental and simulation approaches, 4) kinetics of drug binding to wild-type and multidrug-resistant human immunodeficiency virus-1 protease, and 5) signal propagation and waves.

Student interest in taking the course was strong in our first year. Response from the first class has been for the most part positive and encouraging. We are assessing the first year and making changes for its second offering in 2010–2011. More information about the IQS course as it becomes available can be found at <http://iqscience.richmond.edu>. An overview of its assessment plan is given in the Supplemental Material.

The course is team-taught by five faculty members, one from each of the disciplines involved. The faculty teaching the first semester are different from the faculty teaching the second semester, so in all, 10 faculty are involved. The development of the course was funded by HHMI and was done via a yearlong seminar in 2008–2009, with the 10 faculty members involved. Participation in the seminar and developing the course constituted all of each faculty member's teaching assignment for the second semester. Most of the faculty who participated in the seminar had previous experience directing, collaborating, consulting, or a combination on interdisciplinary research projects. With funding from the NSF, including its innovative Interdisciplinary Training for Undergraduates in Biological and Mathematical Sciences (UBM) program and its Enhancing the Mathematical Sciences Workforce in the 21st Century program and from the HHMI, these faculty had experienced first-hand the power of undergraduate research projects in motivating students to study techniques and methods outside of their majors.

UNDERGRADUATE RESEARCH PROJECTS

Four undergraduate research projects that fed the IQS course development are described below.

Project 1

The first research project described inspired the semester-long experiment used in the laboratory component of the first semester of IQS. The conception of this experiment was a defining moment early in the IQS course development seminar that set the tone of integrating the discipline-specific material by applying it to solve a modern, real-life problem. The experiment uses a novel animal system developed with undergraduates in the lab of the biology member of the first-semester team, Dr. April Hill, as part of an NSF grant. The NSF-funded project is an interdisciplinary endeavor between an evolutionary ecologist, a biochemist, a microbiologist, and a developmental geneticist. One aim of the grant is to develop marine sponges and their microflora as model systems to study host-symbiont associations. Over the past few years, one student (who was originally an HHMI-funded prefreshman in Dr. Hill's lab) piloted methods to use sponge stem cell cultures to study sponge-associated bacterial symbionts. She found that changing the class of antibiotics used in the experiment led to shifts in the bacterial community, often enriching for different bacterial species. Several of the bacterial species that increased in representation after antibiotic treatment belonged to known marine symbiont families. Building on the data from this project, Dr. Hill and her research student developed a hypothesis that some of the novel antibiotic-resistant bacteria

also might be producers of antimicrobial compounds themselves. Thus, they developed protocols for the IQS students to perform investigations on potential new species of antibiotic-resistant bacteria isolated from marine sponge cultures. The IQS students used cell culture, DNA isolation, polymerase chain reaction, and molecular cloning techniques as well as electron microscopy and antimicrobial activity assays to analyze antibiotic-selected marine sponge bacteria. Students used molecular modeling methods based on chemical and physical principles to study the structures and properties of antibiotics used for selection of resistant strains. They used mathematical regression analyses to calculate mutation rates for selected bacteria, and they coded computer programs in Java to compare DNA sequences from newly isolated antibiotic-resistant bacteria. Moreover, this experiment led to further research projects for students in the IQS course. Four of the students from the IQS course along with Drs. Hill and Barry Lawson, a computer science faculty member, continued portions of this interdisciplinary work in summer 2010. Two of the students will pursue genes involved in host/symbiont integration, will further analyze the antibiotic-resistant bacterial species, and will isolate and characterize more species of bacteria from each of the antibiotic selected pools. Two other students will use bioinformatics and other computer science methods to perform analysis on sponge genome sequences as well as symbiont genomes. These two students will also develop and modify bioinformatic software programs to enhance the analysis of the data.

Project 2

The next example occurred during summer 2008 (the summer before the IQS course development seminar began) and contributed to the development of the first semester of the IQS course. Dr. Lester Caudill, biomathematician, directed a team of four undergraduates (three freshmen and one sophomore) in a research project that integrated microbiology, epidemiology, and mathematics. Three of the students were funded by the NSF's Enhancing the Mathematical Sciences Workforce in the 21st Century program, through a grant entitled, "Long-Term Undergraduate Research Experiences (LURE)," and the fourth student was funded by a grant from the HHMI. This project was entitled "Models of Antibiotic Resistance and Hospital-Acquired Infections" and focused on the development and analysis of a mathematical model of bacterial infection dynamics within a hospital ward, including the rise and spread of antibiotic-resistant pathogens. The overall goal was to use this model to test the potential effectiveness of several different strategies (control strategies) proposed in the medical literature for preventing and controlling the rise of antibiotic-resistant bacteria. Like the UBM project, because the students involved were first- and second-year students, Dr. Caudill provided background instruction on key aspects of development and analysis of differential equation models, bacterial growth dynamics, and principles of epidemiology and pharmacokinetics, and training on several salient topics, including the following:

- Principles of mathematical modeling
 - Potential benefits and limitations
 - Basics of model development
- The biology and chemistry of antibiotic-resistant hospital-acquired infections
 - Primer on bacterial infections
 - Mechanisms of antibiotic resistance
 - Ways to combat resistance
 - Principles of antibiotic pharmacokinetics
- Building differential equation systems models via compartment diagrams
- Analysis of differential equation systems models
 - Analytical solution formulas
 - Qualitative analysis of long-term behavior via eigen-analysis
 - Numerical analysis with *Mathematica*

Simultaneously, the students conducted a search of the medical research literature to produce a list of proposed control strategies. The students then read and analyzed a research paper from the *Proceedings of the National Academy of Sciences*. This paper (Lipsitch *et al.*, 2000) provided a differential equation system model that served as the basis for the undergraduate team's original work. This phase began with the student team working through the mathematical analysis conducted by the authors. Then, after some additional analysis, each student selected, for incorporation into this model, one of the control strategies resulting from their literature search. The four control strategies chosen by the students were antibiotic cycling, bacterial vaccinations, patient isolation practices, and control of bacteria in food. The students, working individually, combined their own mathematical and biological knowledge, coupled with additional guidance and instruction from Dr. Caudill, to adapt the basic infection model of Lipsitch *et al.* (2000) to allow for the modeling of their chosen control. Then, using a set of mathematical and computational tools (that varied from one control strategy to another), each student analyzed her own control strategy model, and used the results to draw conclusions regarding the potential for each control strategy to impact the battle against antibiotic-resistant bacterial infections.

Over the course of the project period, the students gained first-hand knowledge of one of the important ways that mathematical modeling can contribute to investigating important public health issues. They also experienced the excitement of seeing their efforts, both individually and as a team, produce results, and the thrill of knowing that they were contributing new understanding and new perspectives on the problem of antibiotic-resistant infections.

The longer-term impact of this project, however, continues to be felt through its influence on the content of the current IQS course. As summer 2008 unfolded, it became increasingly evident that mathematical modeling, meaningfully applied to a modern, real-life problem, could be learned and used by freshmen with prior exposure to calculus. The summer experience helped us to identify the key topics from mathematics, biology, and chemistry that are necessary to set the proper scientific and technical context for this modeling topic. Moreover, it became clear that the field of antibiotic-resistance research is a rich area for connections not only with biology and mathematics but also with chemistry and physics (through the study of antibiotics and their molecular activities), as well as computer science (through simulation studies of infection dynamics). Recognizing this potential, the designers of IQS selected antibiotic resistance as the

theme for the first semester of this two-semester sequence. This theme, in turn, gave rise to several interesting and relevant student activities, including the following:

- A student-developed Java program simulating infection spread in a hospital ward
- A set of wet labs for bioprospecting in marine sponge tissue for new antimicrobial compounds active against pathogenic bacteria
- A computational chemistry study of stable conformations of simple antibiotic molecules

Project 3

The final two examples contributed to the signaling theme of the second semester of the IQS course. Dr. Lipan (mathematics/physics) and Dr. Laura Runyen-Janecky (biology) specially designed a hybrid wet (biology) and dry (mathematics and physics) laboratory. The main laboratory focus is in experimental and theoretical studies of the heat-shock response in mammalian cells. Cells develop a family of proteins that become active after an environmental stress, such as a high rise in temperature. These heat-shock proteins (e.g., HSP70) ensure the survival of the cell. The experimental data collected and analyzed by Lipan *et al.* (2007) show that the mean value response of a cell population to one heat shock can be described by a mathematical expression that is valid for a large range of heat-shock conditions. Students working in this lab are trained to use mathematical models in the early stages of designing their experiments as well as to use basic molecular biology assays to generate experimental data. They developed a nonlinear stochastic theoretical model that explains the empirical law for the mean response. Moreover, the theoretical model predicts a specific biological probability distribution of responses for a cell population. The prediction was experimentally confirmed by measurements at the single-cell level. They studied the response to one pulse of temperature T_1 and duration D_1 ; the next step was to find the response to more complex patterns of input functions.

The response to these complex input functions is the basis of an ongoing project funded by the NSF through the UBM program. Specifically, the first cohort of students participating in the UBM focused on measuring the dynamics of the heat-shock promoter HSP70 under the action of two consecutive pulses: one pulse of temperature T_1 and duration D_1 and the other of T_2 and D_2 . This first cohort consisted of four students: two first-year students from biology, a first-year mathematics student, and a third-year mathematics/computer science student. Because of their varied backgrounds, the spring semester before their first summer of data gathering and analyses was spent teaching all of the students what they needed to know for the project. The mathematics students needed to learn wet lab techniques and the biology students had to become comfortable with the mathematical models.

The mathematical emphasis was on modeling dynamical systems. On the biological side, they compared eukaryotic and prokaryotic biochemical strategies to cope with stress. The students learned the effects of diverse transcription factors on the stress response and the feedback loops that regulate the stress system. The interplay of molecular biol-

ogy and mathematics was readily apparent during these chalkboard discussions. As a parallel activity to the chalkboard meetings, they learned mammalian cell culture and fluorescent activated flow cytometer techniques. The group also met regularly in the genetics laboratory of Dr. Runyen-Janecky to insert a construct in the chromosome of the bacteria *Escherichia coli*. The construct responds to heat shocks and is a basis of the comparative studies between mammalian and bacterial response to heat shocks. For the summer data collection phase, they designed five different combinations of pairs of heat shocks that were delivered to mammalian cell cultures under a variety of temperature and duration parameters. The measurements were taken at single-cell level; by the end of summer, they had accumulated ~14 million data points. During the fall data analysis phase, the data were transferred from the fluorescent activated flow cytometer standard file to a text file and subsequently loaded into MATLAB (The MathWorks, www.mathworks.com). The analysis produced a list of response parameters available for use in developing mathematical models.

As the IQS course was developed, this experience contributed to our understanding of how a research question amenable to multiple discipline perspectives can motivate both lab-adverse and math-phobic students. It also helped to gauge the appropriateness of the level of topics to a course for first-year students. Dr. Lipan is now teaching the mathematical modeling of cell signaling pathway in the second semester of the IQS course. The UBM research helped in choosing one model: the Goldbeter-Koshland enzymatic switch (Goldbeter and Koshland, 1981). This switch appears in many genetic networks, and it is believed to switch on and off the main pathway of the stress response in mammalian cells (Rieger *et al.*, 2005) through a series of phosphorylations. The UBM group of four students, two with no mathematics background beyond calculus, studied this switch in detail, giving us some indication of how to teach it at a level appropriate for a class of 20 first-year students. The UBM activity also helped in understanding the difficulties students have with mathematical modeling. The biology students were skeptical of the power of theoretical thinking, because their previous experience was tightly connected with truth discovered only through experimental techniques. At the end of the data analysis and modeling period, after they went back and forth many times between experimental facts and theoretical predictions, the biology students understood better the power of the method. The mathematics students had difficulties with the fluid way of thinking in constructing the theoretical models. Constructing a model based on observations and revising it based on the results of experimentation is not as simple and well organized as analyzing a model in a mathematics classroom. The frustrations of both the mathematics and biology students better prepared us to accommodate the many different science and mathematics backgrounds of the students in the IQS course. The UBM faculty found during the first year that it is very effective to have a mature (junior or senior) mathematically oriented person in the group who could grasp the mathematical problem faster and help the rest of the group to understand it. Based on this experience, we incorporated several upper-level mathematics and computer science students into the IQS course as teaching assistants. Their duties ranged from trying some of the problems out before they

were given to the class to holding problem sessions for some of the assignments.

Project 4

Whereas the previous project described contributed to the choice of signaling as the unifying theme for the second semester of the IQS course, the final project we describe grew out of questions raised much later in the process of developing the second-semester topics for IQS. What began as simply an idea for a project for a student with strong mathematical skills and an interest in applications subsequently made a significant contribution to the course. This summer project was funded by Richmond's science, technology, engineering and mathematics (STEM) Summer Undergraduate Research (SSUR) program, an undergraduate research program funded as part of a Science Education grant from the HHMI that has as one of its objectives to promote interdisciplinary interactions and collaborations. The project focused on the connection between diffusion and functionality of the G protein-coupled receptors (GPCRs). For the cell-signaling theme in the second semester, the IQS designers decided that GPCRs are an important class of receptors and needed to be taught. On a different note, Brownian motion and diffusion were on the list of essential topics to be included in order to satisfy discipline-specific requirements. Fortunately, it turned out that these phenomena are connected in a nontrivial way: for rhodopsin, a GPCR receptor in retina, diffusion is an important phenomenon (Ramanathan *et al.*, 2005). The summer project extended the approach of Ramanathan *et al.* (2005) from a deterministic model of chemical reactions to a stochastic model. They applied the reaction–diffusion master equation to the GPCR switch in retinal rods and found the effector protein response to different input signals on the light-activated receptor. The response of the GPCR switch depends essentially on both reaction and diffusion and displays the interesting phenomenon of stochastic resonance.

Table 1. Relationship between SSUR project and IQS course

SSUR project	IQS
The master equation for the discrete reaction–diffusion probabilistic model	No master equation; the concept of the probabilistic model and the connection with the concept of Brownian motion covered earlier in the course
Differential equations for the mean and variance	Differential equations for the mean values only plus diffusion (Ramanathan <i>et al.</i> , 2005)
Computation of the systems' behavior from the probabilistic model	Graphical summary of the main results
An extended PowerPoint presentation	Selected PowerPoint slides with pathway animation

The student who worked on this summer project was a highly motivated first-year student, well trained in mathematical approaches to science. However, probabilistic thinking and differential equations were new for him, and only at the end of the 10 wk of research was he comfortable with the stochastic approach. This experience helped us to design lectures that are understandable by the IQS first-year students. To aid in understanding, we represented the computed results with suggestive contour plots, and we created PowerPoint animation of the reaction–diffusion mathematical model for the GPCR pathway. These animations were later used in the IQS class. The differential equations for the GPCR pathway were well received by the IQS students. We did not require them to solve these equations; rather we required them to translate from the qualitative biological description of the pathway to a quantitative model. The creation of the quantitative model using differential equations presented no problem for the IQS students. They later studied the solution to the model with the help of the *Mathematica* software tool. Table 1 relates the main ideas from the original SSUR project to the second semester of IQS.

The impact of novel interdisciplinary undergraduate research programs such as those funded by NSF and HHMI extends beyond the gains of the students involved to major contributions to the kind of faculty development that leads to significant curriculum changes connecting the life sciences with mathematics, computer science, and the physical sciences. It is too early to see the full impact of our experiment integrating the first course of the major of five STEM disciplines at University of Richmond, but it is clear that externally funded interdisciplinary research projects were key in our ability to conceive the integration and in laying the groundwork for the significant faculty collaboration required to implement the idea.

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