**NEW WRITING COURSES IN BIOPHYSICS**

Arts & Science majors must fulfill 12 writing credits for graduation. New this year is the ability for Biophysics majors to meet writing requirements with two of our biophysics electives. The spring Advanced Seminar in Biophysics course as well as the Molecular Interactions Laboratory have both initiated a writing component.

**THE UNDERGRADUATE RESEARCH EXPERIENCE**

Bertrand Garcia-Moreno, PhD., Chair

The research experience in biophysics is an integral and very important component of our major and has been so since its inception. Many of our majors begin their research experience at the beginning of their sophomore year. Although only six credits of research are required of our majors, many of them spend as many as three years - including summers - working in our labs under close mentorship by graduate students, postdoctoral fellows and faculty.

Initially the time in a lab is spent trying to understand the problem under investigation, learning background information and doing initial experiments or computations. Eventually the students take off and gain considerable independence. Many undergraduates author papers and some even get to travel to scientific meetings with their labs.

From a mentor's perspective, the joy of undergraduate research rests on being able to observe at close range the budding of our future scientists, and the evolution from grade-driven book-reading student into a knowledge-seeking, question-asking critical thinker driven by the sheer joy and fun of discovery. I believe the undergraduate research experience contributes more towards the growth of our students than any other academic experience at Hopkins. Starting Spring 2012, Biophysics will host an annual poster session where our majors will be able to share the fruits of their research with their peers and with our faculty. I am sure this will develop into one of our most cherished Departmental traditions, where undergraduate, graduate, postdoctoral researchers and faculty together celebrate science and in particular, biophysics.

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**Modeling cell movement**

Jonathan Teo is conducting his undergraduate research in the Cellular Signaling Control Laboratory at JHU. Mobility is one of the key evolutionary features that has helped organisms survive since ancient times. It allows organisms to find food sources, to move to warmer climates, to evade predators, and to move away from toxic waste. This is a universal behavior that can be observed in almost all living organisms, and researchers have spent a lot of time trying to understand the mechanisms behind it.

For large organisms, mobility can usually be attributed to a conscious decision made by the mind. However, for microscopic cells, the mechanism for cell motility is far from trivial. Singular cellular organisms move randomly in the absence of external stimuli or in a uniform chemical concentration. They also travel along chemical concentration gradients, a process known as chemotaxis. What Jonathan finds amazing is really how both a gentle and steep gradient will elicit the same response and how the cells know when to start and stop.

To reconcile mobility behaviors, an understanding of gradient sensing is required along with the translation of such signals into force in cells. Traditionally, researchers would start with biochemical experiments to determine the signaling pathways involved in sensing and motility. This has worked well in simpler organisms like prokaryotes, and it is now known that bacteria employ a temporal means to sense chemical gradients. Based on biochemical experiments, scientists have come up with mathematical models that pretty much simulate what is observed in real life.
In eukaryotes however, the biochemistry is more complicated. Studies have shown that the soil bacterium *Dictyostelium discoideum* senses chemical gradient spatially, which means that the cell exhibits polarizability. The ability to chemotax in a both shallow and steep gradient must indicate that the cell is normalizing external signals through amplification and negative feedback. In addition, the cell adapts to uniform changes in chemical concentration. This is characteristic of a negative feedback component in a signaling pathway that is responsible for adaptation.

Jonathan chose this research area not so much because he was interested in how cells move, but because he wanted to learn more about computational modeling aspects of biophysics. The complexity of the biochemical reactions involved in gradient sensing lends itself to the use of computers and models to simplify and explain the dynamics of molecular interactions. Jonathan says, “I have never really found a liking to working in wet labs, so modeling using computer programs seems like a great alternative. Also, I have always been intrigued by how biological phenomena can be explained by numbers and equations.”

In the Cellular Signaling lab, they propose various mathematical models and use them as a framework to understand the biochemical implications of chemotaxis. Some of the things they have looked at include modeling actin and myosin formation; modeling mitotic spindle formation during cytokinesis; applying new numerical methods used in other fields to cell movement; and Jonathan’s project, modeling chemotaxis in a *Dictyostelium Discoideum*.

Of course, cell motility is just one way Jonathan can use physical models to explain experimental observations. There are many more biological phenomena that have yet to be explained. He feels that his current research will provide him with the fundamentals he will need to tackle those questions in the future.

**LEANNA OWEN, BIOPHYSICS ’12**

**Differentiation in Drosophila**

This summer was the only summer in the past four years that Leanna Owen hasn’t devoted completely to research. She says, “My friends tease me, calling me a lab-rat, but I suppose it’s justified – Even though I truly enjoyed my two months volunteering in Botswana this summer, a large part of me was wishing that I was back in muggy Baltimore working on my research project in the Cell Biology department at JHMI.”

Over the past few years, Leanna Owen has conducted her undergraduate research in Professor Erika Ma’tunis’s fly genetics lab studying the mechanisms that regulate differentiation and competition in Drosophila adult stem cells.

Before coming to college, Leanna would never have guessed that she would be working with flies, since she had hoped that her research would more directly impact human health. However, she says, “I’ve found the relative simplicity of using flies as a model system (having previously worked with mice and rats) enables me to conduct a lot of meaningful experiments in a relatively short time, leading to fundamental conclusions about how stem cells function and interact with other tissues.”

Leanna’s project revolves around the role of Protein Inhibitor of Activated Stat (Pias), a protein whose over-expression during development leads to eyeless or headless flies. When removed from the stem cell niche of the adult male, all of the cells in the niche either die or differentiate. Her current experiments focus on determining how the Pias maintains stem cells in this system. The possibilities include diverse sets of mechanisms: modulating chromatin regulation, activating stem cell maintenance signaling pathways, or acting as a ubiquitin E3 ligase. Leanna’s advise for what to look for in an undergraduate research experience:

Jonathan Teo is a senior from Singapore.
"As Hopkins students, we have the opportunity to study almost any biomedical topic in some of the most influential labs in the world. However, I’ve found that what really makes or breaks a lab experience is having a good mentor. I’m now only able to run my own project because I am being taught how to ask the right questions, how to set up an experiment to yield meaningful results, and how to deal with the challenges that inevitably arise in laboratory research."

When all is said and done, Leanna says, “I’ve found my time in the lab has been the most exciting, frustrating, and ultimately rewarding learning experience at Hopkins.”

Leanna Owen is a senior from Manassas, VA.

Joshua Riback, Biophysics ’13

**Computational analysis of buried ionizable groups in proteins**

Joshua Riback is an undergraduate researcher in the laboratory of Dr. Bertrand Garcia-Moreno. Josh’s research aims at providing a more complete understanding of physical and functional properties of ionizable groups in proteins. Josh is focused on the study of a special subset of ionizable groups, those that are buried in the interior of the protein. These are poorly understood, very different from the exterior-located ionizable groups that are in contact with water, and very important for function. The local microenvironment of an ionizable group in a protein is one of the important determinants of its contribution to the electrostatic potential in the protein-water system. Thus to understand the electrostatic properties of ionizable groups, their local microenvironments have to be examined quantitatively. Josh has been working on this problem using computer algorithms that he develops for this purpose.

Some of the factors that are currently being explored are the static Accessible Surface Area (ASA), which measures the surface area on the atom’s surface that is accessible to a water molecule as it rolls on the surface of the proteins, and the depth of burial (DOB), which measures how far an ionizable group is from bulk water. Many researchers claim that any ionizable atom with an ASA equal to zero can be considered to be buried. Josh disagrees with this assessment of burial, because it falsely portrays the protein as static.

“This disregards the fact that in water the protein is dynamic and fluctuates; therefore, many groups that have low values of ASA can actually establish contact with water.”

The DOB appears to be a better metric for identifying truly buried ionizable groups. Josh is developing an algorithm to identify these truly buried ionizable groups, and a metric for measuring the DOB. His algorithm also identifies many factors that can affect the properties of the ionizable groups, such as proximity to bulk water, to internal water molecules, to polar atoms of the protein, to aromatic residues, and to other ionizable groups. The goal is to learn how to calculate how the different factors affect the properties of the buried ionizable groups. All of these factors will allow better understanding of the molecular determinants of the electrostatic potential of the protein.

During the process of developing and improving a system for classifying internal ionizable groups in proteins, Josh has developed a method for parsing thousands of protein structures from the Protein Database (PDB). He is performing high-throughput calculations on a curated dataset of proteins in an attempt to understand electrostatic contributions to the thermodynamic stability of proteins and to apply the classification system to identify potential residues important for known biological functions. Josh hopes that an algorithm to classify the extent and character of the burial of ionizable groups in proteins will improve our ability to predict function of proteins and to potentially develop a framework to engineer proteins with desired functions.

Josh thanks Dr. Bertrand Garcia-Moreno and Dr. Carolyn Fitch for all of their support and integral involvement in the project.

Joshua Riback is a junior from Livingston, NJ.
Justin Porter, Biophysics ‘12

Protein Docking
Justin Porter’s undergraduate research is in Dr. Jeff Gray’s lab in the Department of Chemical & Biomolecular Engineering. The Gray lab uses computational tools to address the problem of protein-protein complex prediction. In other words, Justin says, “Given the knowledge that protein A and protein B bind, what is the molecular structure of their complex?”

To do this, we generate a random complex using the unbound forms of the two proteins, and iteratively make random small adjustments (like changing a bond torsion angle, or moving one protein partner with respect to the other), assessing the physical plausibility of the adjusted complex. If the adjustment is plausible, we accept it, and if it’s implausible, we throw it out with a probability determined by just how implausible the adjusted structure is. Using a supercomputing cluster, we do this many times. At the end of this process we are left with numerous guess structures, called “decoys,” which we rank.

Justin works on the software that is responsible for ranking structures to determine their ranking, called the “score function.” Given a complex, the score function calculates a numerical score, which is an estimate for the plausibility of that state. It incorporates both information from first-principles physics—like the generic van der Waals attractive force between any two atoms—and empirical/statistical information—like the frequency we observe two amino acids adjacent to one another globally across all proteins.

In particular, Justin uses the score function to separate realistic decoys from unrealistic decoys. We use this score function for our participation in the CAPRI prediction competition. CAPRI stands for Critical Assessment of PRediction of Interactions. This competition has several parts, but in the part Justin participates in, he and his colleagues are given thousands of diverse structures of a single complex, and the goal is to pick out the best; that is, the complex that is closest to the experimentally-determined complex. Justin develops both a software toolchain that sorts, manipulates, and reformats the many differently formatted protein structures, and a new method that combines a two different flavors of score to give it a compound (and more accurate!) rank. On a small test set of structures, this new method is extremely promising, and we are in the process of scaling up our tests of this method.

Justin Porter is a senior from Seattle, WA.

Leah Sibener, Biophysics ‘13

Summer internship at Genentech
This past summer Leah Sibener knew she wanted to experience research in a setting that she could not pursue during the academic year.

“I wanted to see what research was like in a corporate setting”

As a typical Hopkins student Leah applied for many different summer research programs in academia and in biotech. She applied to Genentech on a whim; they were looking for a masters or graduate student to intern in their Early Discovery Immunology Department. Although she was only a rising Junior, Leah’s undergraduate research at Hopkins was in Professor Schneck’s laboratory at JHMI working on immunology, and she had recently taken an immunobiology course. These experiences stimulated a passion for immunology, and an internship at Genentech would allow her to explore this area in a translational setting. The application process involved a few intense telephone interviews, but Leah received the news in March of her selection for an intern position at Genentech.

“Before I started my job I had no idea what to expect. Due to company confidentiality, I knew very little about my project and what type of biomedically related research I would be working on.”

During the interviews the managers (PIs) had inquired about her interests and techniques she would want to learn while at Genentech, but she did not know if she would be getting her own project, would be working with somebody, or even what she would be working on!

Leah arrived at the Genentech campus in south San Francisco in June. Her first impression was and was immediately taken a back by how large it was. There were buildings designated for financial and business divisions, production and purification, basic research,
translational research, operations research, and computation, cafeteria, athletic center, and the clubhouse — essentially an entire university sized campus.

After orientation Leah was immediately thrown into her own project, which was to elucidate the signaling pathway for a Novel Ig protein using different microscopy techniques. The specific goal was to observe its effect on lymphocyte migration in secondary lymphoid tissues. The expectations were high: her task was to learn how to meet the scientific goals by reading the literature and designing her own experiments. Although she had some guidance from other members in the group, she had little direction on how to conduct her experiments. She met with her manager once at the beginning of each week to go over her planned experiments, and once at the end to present her results. These “one on one” meetings were meant for the interns to think about their projects from many different perspectives, to understand each of the experiments and the conditions they planned to run them at, and the purpose of what we were doing.

“I would say the most important skills I learned this summer were how to think through a problem and the ability to design an experiment around it”.

At Genentech they say, “science is done two out of the following three ways: fast, right, or cheap - here, we do it the first two ways.” In comparison to academic labs Leah’s impression is that there are two major differences between academic and industrial science. The first distinction is the means by which they go about their science. A company has huge amounts of resources, and in order to run an experiment all you need to do is order the supplies there really are no limits as to what you can do. For example, she wanted to run a “fun FRET” experiment to see if two proteins were associated; no one had a problem with her ordering the supplies to do so. The second difference she noticed was that there was a clear direction for every project at Genentech. The fact that there was an applicable purpose for all the basic research projects that would hopefully help in the development of a useful therapeutic was an aspect Leah really valued.

“Genentech is not like your typical biotech company”, as Professor Blake Hill described to her, “It’s truly an amazing place.” Leah totally agrees. They reallocate a huge amount of their resources to basic research, and they take great care of their employees. As a biophysics major, Leah felt that her academic courses and independent research at JHMI prepared her extremely well for the Genentech internship. It was interesting to see how many of the managers came from a computational and physical sciences background that eventually got into biotechnology. It was clear that many of the managers valued the quantitative skills we learn as biophys-

ics majors and thought they were “the future of biotechnology.” Leah recommends that all biophysics majors look into industry research internships during the summer — “it’s a unique opportunity to experience research from another perspective and it is something you cannot do during the academic year. “

Leah Sibener is a junior biophysics major from Chicago, Illinois.

DO YOU WANT TO GET INVOLVED IN RESEARCH?
Check out the guide for how to get involved in research written for Biophysics undergraduates at: http://biophysics.jhu.edu/research_in_biophysics.html

Find a couple of Hopkins labs that interest you and meet with your Jenkins advisor to obtain further guidance on selection of your research home.

COURSE NOTES

Molecular Interactions Laboratory 250.383
Taught by Dr. Karen Fleming
Reviewed by Justin Porter, Biophysics ’12
Molecular Interactions Laboratory (MIL) is a hands-on, sweeping survey of some of the most powerful and common techniques in our field, including NMR, x-ray crystallography, circular dichroism, fluorescence and ultracentrifugation. Experiments are performed in Dr. Fleming’s own lab, using her research-grade instruments; as a result, the experimental mechanics match that of true laboratory research. Because it is a class, however, and because enrollment is capped at four students, we have our PI’s full attention at all times.

Working with us in the lab, Dr. Fleming imparts nuggets of “experimentalist wisdom” that I would never have learned by following a protocol in a book. Both implicit—her attitude toward silly mistakes: just have a good laugh at yourself and try again—and explicit—“be absolutely sure your calculations and pipetting are correct, so that when you get an interesting result you don’t doubt your data”—these nuggets are what’s really to be gained by spending time in the lab with an experienced scientist like Dr. Fleming. It is the combination of practically useful laboratory experience with dedicated coaching from Dr. Fleming in how to think about exper-


ments that makes this class the most practically useful lab class I have taken at Hopkins.

250.383 is offered in the Fall.

**Young Alumni News**

Lauren Thomaier ’12 was accepted at the Johns Hopkins medical school and started this fall. She is looking forward to four more years in Baltimore! Siavash Raigani ’12 sent a note from Case Western Reserve medical school sharing how awesome it was that he had learned the basic science behind targeted therapy and drug development in his biophysics classes. Siavash says,

“It was all stuff we had been doing in Computational Biology - I just didn’t realize how fantastic the material we learned about was until I saw it applied to the “patient” in our weekly case study. I completely understood the science behind it and even looked at some crystallographic images of the mutant protein that causes CML and how it differed between the active (bad) state and the inactive-imatinib-bound state. Just awesome!”

Katie (Herbst) Robinson ’06 defended her Ph.D. in Pharmacology in August 2011 from the Johns Hopkins Medical Institute and has moved on to a postdoctoral position at UPenn at the Center for Neurodegenerative Disease Research (CNDR) where she is pursuing drug discovery research for the treatment of Alzheimer’s. Attn: Alumni. Your current and former majors would love to hear the latest. Email your Alumni Updates to be included here.

**Keep in Touch with the JHU Biophysics Group at Linked-In**

Join the JHU Undergraduate Biophysics group on Linked-In to connect with Biophysics majors, past and present. The group was created to facilitate networking connections between current majors and alumni and for staying in touch with Biophysics once students graduate. This group is for current students and Alumni. Be sure to register before you graduate. Check it out online at:

[http://www.linkedin.com/groups?gid=1776717&trk=hb_side_g](http://www.linkedin.com/groups?gid=1776717&trk=hb_side_g)