



Reconstitution of Cell-cycle Oscillations in Microemulsions of Cell-free *Xenopus* Egg Extracts

Researchers in Qiong Yang's lab have developed an experimental framework that allows them to reconstitute 30-40 self-sustained mitotic cell cycles in oil droplet-based artificial cells over multiple days until the energy runs out. The ability to manipulate and track the dynamics of a biological oscillator is crucial for elucidating its complex mechanisms. However, it is challenging to characterize an oscillatory circuit in live cells due to the noisy signals resulting from the continuous cell growth and cell division at each cell cycle and the lethality of modulating key clock components. They have developed a high-throughput cell-free system to overcome these challenges by encapsulating *Xenopus laevis* egg extracts into water-in-oil emulsion microdroplets (JoVE 2018; eLife 2018). Microdroplets containing cytoplasmic-only cycling extracts function as artificial cells constantly undergoing over 30 self-sustained mitotic oscillations. When adding demembranated sperm chromatin to trigger nuclei self-assembly in the system, they observed a periodic progression of chromosome condensation/decondensation and nuclei envelop breakdown/reformation, as in real cells. Due to its easily-accessible nature, the cell-free oscillatory system can be quantitatively manipulated with the addition or depletion of recombinant mRNAs, proteins, or inhibitors, and is highly tunable to varying droplet size, temperature, and energy levels. Such innate flexibility and robustness are key to uncover clock properties like tunability and stochasticity that would otherwise be difficult in intact cells.



Modulating the Evolution of Drug Resistance

Researchers in Kevin Wood's lab are looking at new ways to optimize the use of currently available drugs to develop new therapies. Drug resistance is a serious and growing threat to public health. Discovering new drugs is an expensive and difficult task, so there is an urgent need for out-of-the-box approaches to optimize the use of currently available drugs. One idea that's received recent attention is to dose the drug in specific temporal patterns, aiming (for example) to maintain the cell population at some manageable level rather than exterminate it. Our work takes a different approach. What if it were possible to dose the drug in specific ways over space, giving rise to spatial regions with high drug concentrations and others with low drug concentrations? If we tuned that spatial profile carefully, could we slow the evolution of resistant cells in the population and potentially prolong the efficacy of the drugs? Max, a PhD student in physics, addressed this question using a very simple mathematical model, and he found something interesting: non-uniform spatial profiles of drug can either speed or slow resistance--so from a practical perspective, spatial dosing could work really well or fail miserably. Why? It has to do with how fast the cells can move--that is, how fast they can migrate to explore the environment--and the rate at which mutations arise, something more or less set by genetics. Non-uniform profiles dramatically slow resistance when cells move slowly or mutate rapidly--intuitively, small pockets of resistant cells arise but are spatially isolated and struggle to get a foothold in the population. The work is entirely theoretical, but it makes a number of explicit predictions that we are currently testing in laboratory populations of bacteria. It's important to note that the model is a clear oversimplification of the complex clinical situation, and it ignores potentially important effects from, for example, the host immune response. The advantage of this simplicity is that the model can be analyzed in detail using tools from statistical physics. I'd like to stress that the work wouldn't have been possible without Max's strongly analytical and mathematical skills (not to mention some real determination during times when the calculations seemed intractable). Even given the idealized nature of the model, the results point to interesting proof-of-principle dynamics and enrich our understanding of ecological-evolutionary trade-offs in cell populations. More generally, the results underscore the need to consider evolutionary outcomes, not merely instantaneous drug efficacy, when designing effective long-term therapies.

WELCOME FROM THE DIRECTOR



Greetings Alumni, Friends, and Prospective Students:

I am delighted speak to you in this second edition of the Biophysics Newsletter. Firstly, let me thank everyone for your continued support of Biophysics over the years, as many of you have watched the unit transform in 2007 from a Research Unit within the Office of Research to a unique graduate and undergraduate program within the College of Literature, Science, and the Arts. Marking the beginning of our second decade I am excited to share with you recent news and events from Biophysics.

As you are aware, Biophysics has established a strong and growing undergraduate curriculum, with new Biophysics majors successfully journeying to the next stage of their career development in academia, medicine and industry. We have also continued our tradition of excellent graduate and post-graduate training in the laboratories of more than forty faculty across a dozen departments and more than three schools. We are committed to our educational mission across all of these levels, continuing to build a community that is diverse, inclusive and equitably providing an environment the enables students, faculty and staff to thrive in achieving their life goals.

As I noted in last year's message, I am very proud of the excellent faculty we have and of the young faculty we have recruited to Biophysics at U of M. We have hired tremendous young faculty members who address biophysical questions from the holistic system level as well as those whose research focus is at the molecular level. Joining our faculty in the fall was Professor Markos Koutmou. Professor Koutmou's research interests are in the area of structural biology of proteins that are essential for human health. Our most recent hire, Dr Jordan Horowitz joins us on January 1, 2019 after completing a prestigious Physics of Living Systems Postdoctoral Fellowship at MIT. Jordan's research interests will strengthen our focus in biological physics and bring an exciting new area of work in nonequilibrium statistical thermodynamics to study information processing and control in living systems. We are excited to announce that Dr Horowitz was very recently awarded the 2019 Oppenheim Award from the American Physical Society. Dr Horowitz's recognition emphasizes the excellent faculty we have and adds to their growing list of achievements. The broad and rich research interests of these new faculty, as well as our more senior core faculty members, are presented in the following pages of this newsletter.

Our faculty continues to evolve in their career development and the research areas they are pursuing. As I noted in last year's letter to you, Professor Ari Gafni is now an emeritus member of our faculty. Additionally, after Professor Veatch's promotion and tenure, she has agreed to join me as the Associate Chair and Director of Graduate studies, taking over from Michal Zochowski, to whom I am deeply indebted for his service in this position during the past three years. Professor Randy Stockbridge will transition her appointment from Biophysics and MCDB fully to MCDB to better align with her strong research interests ion channel biology. Professor Stockbridge has established a tremendous base for her continuing development at U of M during her tenure in Biophysics and we look forward to her continuing affiliation with us. Finally, it is noteworthy that President Mark Schlissel's commitment to research at the interfaces of biology, medicine and quantitative sciences is in its first phase with the Biosciences Initiative. Biophysics is playing a strong role in its participation of efforts to deepen our research bases in the areas of RNA Biomedicine and Cryo-Electron Microscopy. We will participate with these directed efforts to identify future faculty in Biophysics.

Our undergraduate program continues to thrive, with the recent introduction of new two major tracks, Biological Physics and Structural Biology, and strong foundational training in the quantitative aspects of biological structure and function.

Our graduate students are at the core of the outstanding research being carried out in our laboratories, and are being recognized for their accomplishments through awards and recognitions, including NSF pre-doctoral fellowships, HHMI Gilliam Fellowships and a host of other acknowledgments of their ongoing excellence in science and citizenry. In our efforts to maintain our strong and diverse graduate program, Biophysics was excited to host its first "preview visit" for diverse students to explore Michigan Biophysics as they moved toward application for and matriculation into graduate school. We hosted an excellent group of six students during this inaugural preview visit, and they participated in our annual fall retreat to learn about our program and the process of applying for graduate school.

In closing, I note that it is truly my honor and pleasure to serve as the Director of our Biophysics Program. I remain extremely excited by the developments of my faculty colleagues and their co-workers, as well as the achievements of our students. I look forward to a new year that exceeds our expectations from the last.

We benefit enormously from your help and support and encourage you to share with us what you are doing. Finally, if you find yourselves in Ann Arbor, please take a few minutes and visit us. We look forward to hearing from you and seeing you in the future.

Charles L. Brooks III

Director and Professor of Biophysics

Cyrus Levinthal Distinguished Professor of Chemistry and Biophysics

Warner-Lambert/Parke-Davis Professor of Chemistry

BIOPHYSICS PROGRAM NEWS

Biophysics Hosts First “Preview Weekend”

The Biophysics Program hosted the first annual “Biophysics Preview Weekend” for prospective students to explore the graduate program. Six prospective students were able to meet faculty, socialize with current students, and tour the campus. Held offsite at Cobblestone Farms, the prospective students were also treated to research presentations by the various labs, poster presentations and a round table discussion on applying to graduate school. The day also included a wonderful picnic lunch with outdoor games and activities with bonding as the goal. We hope to grow our “Preview Weekend” each year and bring in more prospective students to the program.

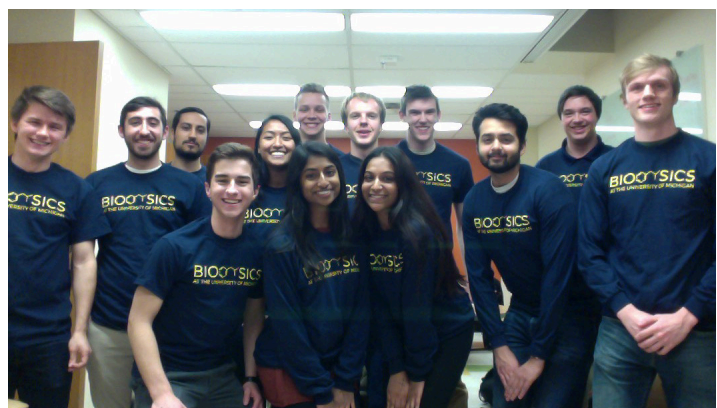


Welcome New Staff!

Biophysics welcomed two new staff members this year. Chief Administrator, Cornelius Wright, who joins us with 20 years of experience at the university. He has held previous positions in student services, most recently as the Student Service Manager in the Department of Chemistry.

Liz Michalski also joined the staff as the new Communications and Events Coordinator. Liz joins us from the nonprofit world with experience in event planning, marketing and fund development.

Welcome, Cornelius and Liz!



UM Biophysics Club Becomes Student Chapter

We are happy to announce that our undergraduate Biophysics Club has been accepted as a Student Chapter of the Biophysical Society! The Biophysical Society was founded in 1958 to lead the development and dissemination of knowledge in biophysics. It does so through its many programs, including its meetings, publications, and committee outreach activities. The Society’s members, now over 9,000, work in academia, industry, and in government agencies throughout the world.

Biophysics Students Awarded Rackham Predoctoral Fellowships

The Rackham Predoctoral Fellowship committee recently announced their winners for the 2018-2019 scholarship, and two Biophysics students were on the list- Katie Gentry (working in the Ramamoorthy lab) and Quinton Skilling (working in the Zochowski lab), pictured left.

The Rackham Predoctoral Fellowship supports outstanding doctoral students who have achieved candidacy and are actively working on dissertation research and writing. The selection committee seeks to support students working on dissertations that are unusually creative, ambitious and impactful. Fellowships are awarded to students who will complete an outstanding dissertation in the year in which they hold the fellowship.

Three non-Biophysics students with Biophysics affiliated faculty were also awarded Rackham Predoctoral Fellowships. These students are Zhengda Li (Bioinformatics- Qiong Yang lab), Xinqiang Ding (Bioinformatics- Charlie Brooks lab) and Amy Farley (Medicinal Chemistry- Janet Smith lab).

Congratulations to Katie and Quinton - a worthy recognition to them and to the program! Cheers also to Zhengda, Xinqiang, Amy and all of the students who received these fellowships!



CORE FACULTY NEWS



Biophysics is pleased to welcome Jordan M. Horowitz to our faculty. Jordan joined us in January 2019 as an Assistant Professor of Biophysics and a faculty in the Center for the Study of Complex Systems.

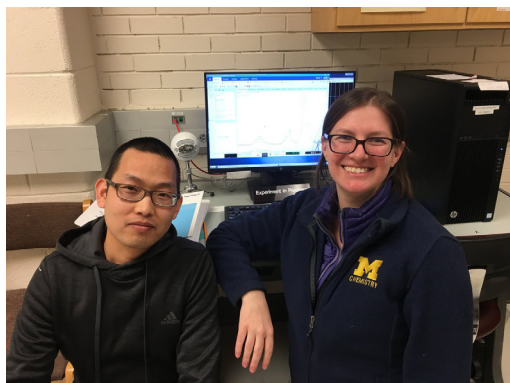
He completed his postdoctoral studies at the Massachusetts Institute of Technology where he worked on non-equilibrium thermodynamics and entropy production. Dr. Horowitz will initiate his research program in the theoretical studies of systems far from equilibrium, where he will explore the tradeoffs between information processing and thermodynamic work.

Biophysics is proud to announce that Jordan Horowitz has also been awarded the 2019 Irwin Oppenheim Award from the American Physical Society. This award recognizes outstanding contributions to physics by early career scientists who publish in Physical Review E (PRE).

We are excited to have Jordan aboard!

Markos joined our faculty ranks in Fall 2018. He received his undergraduate degree in Chemistry from the University of Athens, Greece, and his Ph.D. in Chemistry from the University of Michigan under Dimitri Coucouvanis. He then did his postdoc work at UofM in Biophysics under Martha Ludwig, and continued as a postdoc at the Life Sciences Institute (LSI) under Biophysics Affiliated Faculty Janet L. Smith, and Rowena G. Matthews. After serving as a Research Investigator at LSI, he became an Assistant Professor of Biochemistry and Molecular Biology at the Uniformed Services University of the Health Sciences in Bethesda, Maryland.

Markos' research focuses on examining how biomolecular structure contributes to the processing pathways of two classes of molecules essential for human health: mitochondrial RNAs ((mt)RNAs) and vitamin B12. His work aims to uncover the molecular level details necessary to understand, and ultimately treat, diseases linked to dysfunctional biomolecular maturation mechanisms. He is also studying Methionine Synthase (MS), a large multi-domain protein responsible for generating methionine from homocysteine, and his work will provide an understanding of the relationship between MS function and B12 metabolism, and ultimately lay the groundwork for the development of therapeutics against diseases affected by modulations in the MS action.

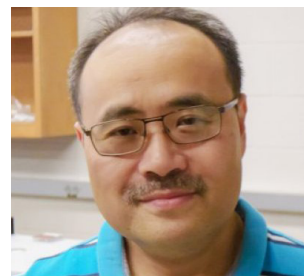


Sarah Keane's lab added a new Bruker 800 MHz magnet to their lab space. Keane and postdoc, Huaqun Zhang, are pictured here after their first experiment using the new magnet.

Core Faculty Highlights

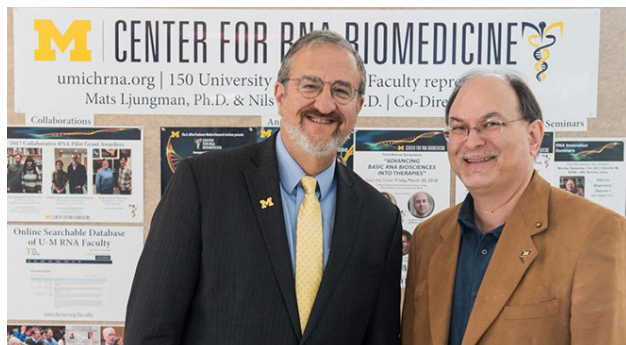
- Kevin Wood's lab was awarded a 5-year NIH R35 (MIRA) to support their ongoing work on collective antibiotic resistance.
- Charles Brooks and his lab recently had articles published and mentioned in the press concerning their work on protein design using rigorous free energy based methods and high throughput in silico drug refinement. Brooks is a Warner-Lambert/ Parke-Davis Professor of Chemistry, Cyrus Levinthal Distinguished University Professor of Chemistry and Biophysics, Director, Department of Biophysics, Professor of Chemistry and Professor of Biophysics.
- Randy Stockbridge, Assistant Professor of Biophysics and Molecular, Cellular & Developmental Biology (MCDB), will be retreating to MCDB full time and staying on board as a Biophysics Affiliated Faculty. We are excited to have Randy as part of our Affiliated Faculty ranks!

Core faculty member Ayyalusamy (Rams) Ramamoorthy (left) and affiliated faculty member Zhan Chen (right) were recently honored by the Royal Society of Chemistry (RSC.) Becoming an RSC Fellow is a recognition of not only making notable contributions to one's field but also to the greater scientific community. Both Chen and Ramamoorthy were delighted and humbled to learn of this recognition. The RSC is the top professional organization of chemical scientists in the U.K. with over 54,000 members. Chen was also recently named an American Association for the Advancement of Science (AAAS) Fellow.



AFFILIATED FACULTY NEWS

Affiliated faculty member and Director of the Center of RNA Biomedicine, Nils Walter, received part of the \$45M Biosciences Initiative to focus on expanding the center. Recent discoveries in biomedicine have revealed that ribonucleic acid, or RNA, is critical to most aspects of human health and that its misregulation is responsible for many diseases. This project seeks to rapidly expand U-M's nascent Center for RNA Biomedicine through the hiring of five faculty members, the creation of three core laboratories, and the funding of pilot and fellowship programs. "We envision that these investments will propel U-M to the forefront of RNA biosciences in the nation," according to the project proposal.



Affiliated Faculty Highlights

- Professor Nicolai Lehnert recently had his paper, "Reversing nitrogen fixation," published in Nature Reviews Chemistry, highlighting the enzymes involved in NH₃ oxidation and N₂O production and degradation in the nitrogen cycle. They also focus on the active site structures, the associated coordination chemistry that enables the chemical transformations and the reaction mechanisms. Nicolai also was recognized with the Harold R. Johnson Diversity Service Award for D-RISE for his efforts to expand a diverse participation in Chemistry.
- Margaret J. Hunter Collegiate Professor of Life Sciences and Professor of Biological Chemistry Janet Smith and her lab group had several papers published highlighting their work in protein structure and function while using crystallography as a structure tool.
- Jennifer Ogilvie, Professor of Physics and Professor of Biophysics, and her lab recently had their work on "Spatially-resolved Fluorescence-detected Two-dimensional Electronic Spectroscopy Probes Varying Excitonic Structure in Photosynthetic Bacteria" published in Nature Communications.

Angela Violi recently received funding from the newly introduced Blue Sky Initiative through Michigan Engineering's Research Pillar of the 2020 Strategic Vision. Her project focuses on a faster response to biothreats, since it has been 30 years since the introduction of the last new class of antibiotics. While bacteria are increasingly developing resistance to existing antibiotics, it can take 14 years and billions of dollars to bring a new antibiotic to market. Her project seeks to develop nanoparticles as a basis for the next generation of antimicrobials. It will use machine learning, molecular simulations and biological experiments to streamline the process of identifying promising nanoparticles and developing treatments with them. Her team believes they can dramatically increase the percentage of proposed drugs that make it to market from the current 14 percent, saving time, money and lives. Violi is a Professor of Mechanical Engineering, Professor of Chemical Engineering, Professor of Macromolecular Science and Engineering, College of Engineering, Professor of Biomedical Engineering, College of Engineering and Medical School and Professor of Biophysics.

Julie Biteen, Associate Professor of Chemistry and Biophysics, and her lab, are working on an element of the starch-metabolizing process, which will ultimately help both in the development of probiotics and more targeted antibiotics. Biteen is working with one type of gut bacteria that breaks down dietary carbohydrates like starch, called *Bacteroides thetaiotaomicron*, or Bt. Bt is a member of a dominant group of bacteria that live in the gut and are essential parts of your microbiome—the community of microorganisms that live in your body. "For example, after you take antibiotics for an ear infection, you might have an upset stomach. That's because the antibiotic is not selective. It's just wiping out all the bacteria—the good and the bad—in your gut," said Biteen. "So what we're studying are the good bacteria, and focusing on the proteins on the surface of the Bt cell that recognize starch, break it down into simpler sugar units, and then internalize these nutrients into the cell." Their work brings them one step closer to developing more effective probiotic therapies, or more targeted antibiotics.



We'd like to congratulate the following for joining our ranks as Biophysics Affiliated Faculty!

- **Assistant Professor Anthony Vecchiarelli**, *Molecular, Cellular and Developmental Biology* - affiliated as of Fall 2019
- **Research Assistant Professor Michael Cianfrocco**, *Life Sciences Institute and Biological Chemistry, Medical School*

GRADUATE PROGRAM NEWS

Graduate Program General Updates

The Biophysics Graduate Program currently has 33 students who are doing research in 19 different labs within the departments of Chemistry, Physics, Molecular, Cellular, and Developmental Biology (MCDB), Cell & Developmental Biology (CBD), Biophysics and the Life Sciences Institute.

The Biophysics Program is excited to announce that we are no longer requiring a GRE to apply to the graduate program! In order to attract a more competitive, diverse candidate pool, we are excited to be among the leaders in the trend of placing higher importance on other components of the application above the GRE.



(Students 1-r)
Efrosini Artikis, Aaron Bart, Maral Budak, Chu Chen, Ziyuan Chen, Kamirah Demouchet

(Students 1-r)
Jeffrey Folz, Christina Freeman, Guoming Gao, Katie Gentry, Elizabeth Gichana, Keanu Guardiola-Flores

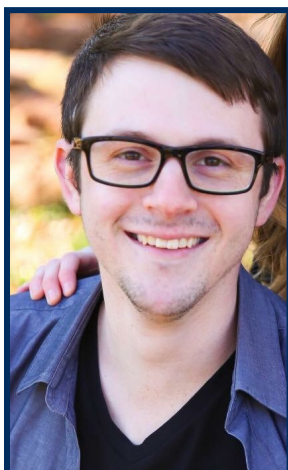
(Students 1-r)
Kelsey Hallinen, Anh Huynh, Minjun Jin, Usha Kadiyala, Jason Karlake, Josh Karlake

(Students 1-r)
Alex Kukreja, Brian Linhares, Desmond Liu, Christian Macdonald, Jeffrey Maltas, Nigel Michki,

(Students 1-r)
Hayden Nunley, Marcos Nunez, Quinton Skilling, Nirupama Sumangala, Zhenyu Tan, Zhaowen Tong,

(Students 1-r)
Logan Walker, Shiyuan Wang, Kevin Wu

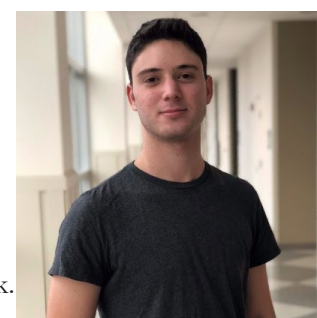
Graduate Student Highlight - (Hayden Nunley - 4th Year in David Lubensky's Lab)



Hayden Nunley is a fourth year Biophysics PhD Candidate from Oklahoma City, OK. He participated in an undergraduate research program with Dr. David Lubensky as an undergrad and realized that he was very interested in studying biological systems in a quantitative way, choosing to pursue his PhD in Biophysics. Nunley was awarded a NSF graduate research fellowship in the Physics of Living Systems. Nunley also teaches Physical Chemistry for undergraduates in Biophysics and is also a member of the Biophysics Graduate Student Council. His advice to students considering a major in Biophysics? "Biophysics is a big field. I recommend finding a few faculty members whose research interests you in particular. Dig into some of their papers, and check if you could do research with one of them. Don't get distracted by how broad Biophysics is. Choose a particular topic, and dive in." Nunley hopes to work in scientific policy or become a professor after graduation.

We are thrilled to have two honorees at the the Office of Graduate and Postdoctoral Studies Outstanding Graduate Awards. Josh Karlake was nominated for the Excellence in Teaching Award, while Katie Gentry was nominated for the Excellence in Research Award. Thanks for being such a bright part of our program!

Biophysics student Itai Palmon is serving as an editor-in-chief for the University of Michigan's Undergraduate Research Journal. Palmon helps lead a staff of 20 students (in conjunction with faculty and sponsor support) to review and publish important undergraduate work.



UNDERGRADUATE PROGRAM NEWS

Undergraduate Program General Updates

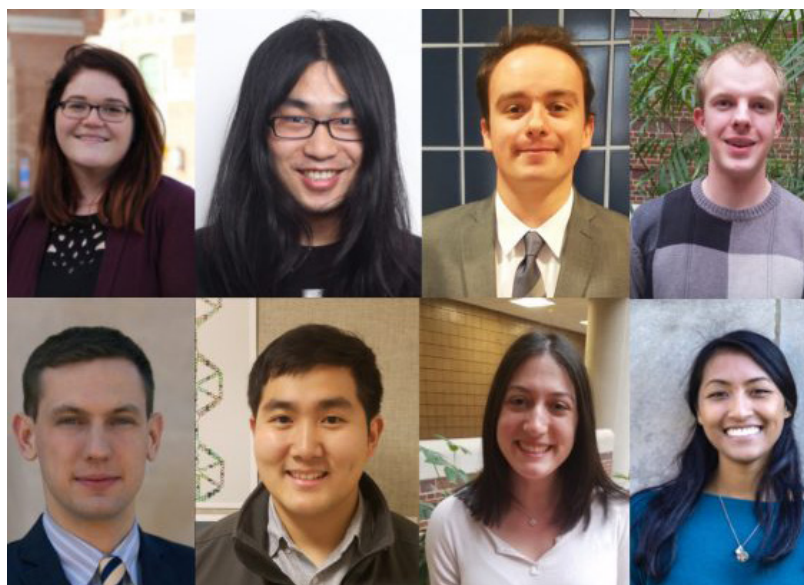
The Biophysics undergraduate class currently has 20 students who are excelling not only in the classroom, but the laboratory setting as well. We are proud to have so many talented undergraduate students in our program and cannot wait to see where their careers take them!

We are also excited to be bringing back the Summer REU Program next year. The REU Program provides selected non-University of Michigan undergraduate students from around the U.S. an opportunity to conduct ten weeks of summer research with some of the country's leading biophysicists in a range of biophysical fields at the University of Michigan. The program is conducted in concert with the NSF Research Experience for Undergraduates Program and is supported by funds from the National Science Foundation.

Undergraduate Student Spotlight -

(Lindsay Ma - Biophysics Junior)

Have you ever found a job you love completely by accident? This is what happened to Lindsay Ma, third year Biophysics major from Grand Rapids, Michigan. Lindsay was applying for research based work study positions at the VA Ann Arbor Healthcare System in Ann Arbor and accidentally applied for a non-work study position. She got the position and has been doing the research that is the topic of her recently published paper, "Design Analysis and Optimization of a Single Layer PDMS Microfluidic Artificial Lung." Ma, along with her lab mentors and co-authors, Alex Thompson, Thomas Plegue and Joseph Potkay had their work published recently. Ma says she likes that research is a major part of being at the University of Michigan. "My research feels very purposeful." Along with her publication, Ma has also done poster presentations at the 2017 and 2018 Microfluidics Symposium, hosted by the University of Michigan department of Biomedical Sciences annually. Ma also lead an oral presentation at the 2017 annual American Society for Artificial Organs Conference, where she was presented with an ASAIO Fellowship award sponsored by the ASAIOfyi and Paul S. Malchesky Fund. Ma, along with her lab, are currently working on rabbit bench top tests with nitric oxide sweep gas and PEG (polyethylene glycol) coated devices, in partnership with the ECMO lab at the University of Michigan hospital. In the future, Ma hopes to attend medical school to focus on surgery.



We'd like to recognize our Biophysics students who graduated in May 2018!

Julia Bourg (Ph.D.)
Yilai Li (Ph.D.)
Eric Bastien (B.S.)
Daniel Evans (B.S.)
Thomas Garton (B.S.)
Hu Lee (B.S.)
Meredith Meyer (B.S.)
Victoria Rai (B.S.)

We wish them the very best of luck in all their future endeavors! We know they will do well!

We'd also like to recognize the two Biophysics

students were recommended to the LSA Honors Program and graduated with high and highest honors.

Daniel Evans, worked in the lab of Yang Zhang as well as Charlie Brooks alongside Troy Wymore and received the distinction of "Highest Honors." Victoria Rai received the designation of "High Honors," and was in the Walter lab. Rai worked with research fellow Julia Widom.



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Thank you to those who participated in Giving Bluesday this year!

If you are still interested in giving to the Biophysics program, visit leadersandbest.umich.edu.

Join us for our upcoming events:

April 12, 2019 - Oncley Lecture

April 15, 2019 - Krimm Lecture

May 4, 2019 - Spring Commencement

Want to be featured in an upcoming newsletter or e-newsletter? We want to know what our alumni have been doing! Send us any recent publications, awards or family news to biophysics.events.communications@umich.edu and you could be featured in our publications, website or social media!

Just want to receive our e-newsletters and updates? Don't forget to update your alumni profile on our website!

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