GENOME SCIENCE AND TECHNOLOGY

GROWING TRENDS

ISSUE 05 FALL 2017

Inside this issue

DARK SIDE OF THE MOON

Friends of GST,

Rarely does a new academic year receive a drumroll in the form of a total solar eclipse. For those of you in lands far afield, our region is full of anticipation of an eclipse scheduled for August 21! But I digress. - This Newsletter has a hidden theme. So as not to stretch your patience unduly, let me tell you what it is: Disorder! Our Faculty Spotlight with Dr. Rachel Patton McCord illustrates how mutations as small as a single-base change cause rampant disorder in the three-dimensional organization of the nuclear genome, a defect thought to underlie the premature aging in a disease called progeria. Justin Lindsay explains how his internship at Los Alamos National Lab aims to predict structural parameters for proteins with intrinsically disordered domains. And Ricardo Urquidi reports on a tutorial he recently attended to embellish mathematical models with realistic levels of noise typical for biological data.

While we are probing the unruly disorder in nature, let us also toast to the new academic year with the hope that disorder will remain compartmentalized within our real and virtual test tubes, rather than metastasizing into our academic programs and beyond.

Winners of the Graduate Student Senate Awards (R to L: Arkadipta Bakshi, Sarvesh Iyer, Prashasti, Ann Wells, Khushboo Bafna) with Dr. Albrecht von Arnim. Photo courtesy Shantanu Shukla.

GST is also chipping away at the entropy in the minds of next-generation scientists by gently moving forward with a new initiative in the classroom: Mini-courses. Newly elected GST member Dr. Tian Hong as well as Dr. McCord will be teaching various quantitative methods as parts of two existing first-year graduate courses. Both have agreed to also offer their segments in the form of stand-alone, one-credit courses. See details inside the newsletter.

On an entirely different subject, recently, your GST office collected data on the career trajectories of the program's alumni. The National Institutes of Health in particular are eager to see that graduate training programs publish their outcomes, but arguably, few programs anywhere do it as well as GST. To our alumni, we are grateful that you are sharing this information. It is always a treat to hear from you, and - in light of your impressive track records - share the news when appropriate. Inside the newsletter you will find a graphic that illustrates, in the aggregate, the sectors of the economy in which GST alumni have been leaving their mark.

With best wishes,

Albrecht von Arnim

STUDENT AWARDS

It is our pleasure to announce that seven GST students won Graduate Student Senate Awards for 2016-2017. **Khushboo Bafna, Arkadipta Bakshi, David Foutch, Sarvesh Iyer, Prashasti and Siva Karthik Varanasi** were presented Excellence in Research awards and **Ann Wells** won an Excellence in Teaching award.

Sarah Cooper, a second year graduate student in Dr. Jerry Parks' lab, was selected to receive a prestigious, three year National Science Foundation (NSF) Graduat Research Fellowship.

Siva Karthik Varanasi, from Dr. Barry Rouse's lab, wa awarded UT's Yates Dissertation Fellowship for 201 2018. Karthik also received the Division of Biology' Carolyn W. Fite Award for outstanding scholarl achievement by a graduate student.

Congratulations to all!

THE UNIVERSITY OF TENNESSEE KNOXVILLE

OAK RIDGE National Laboratory

FACULTY SPOTLIGHT: RACHEL PATTON MCCORD
A 'TAD' BROKEN- CLUES TO PROGERIA, CANCER & MORE

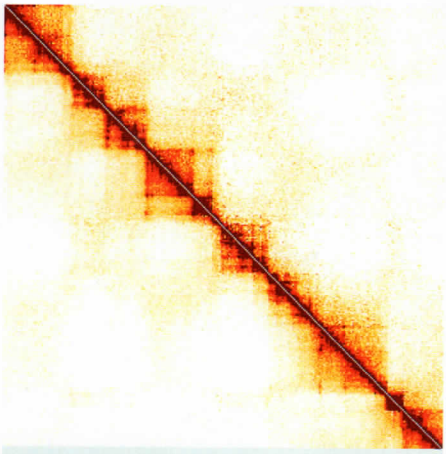
Rachel Patton McCord joined the BCMB faculty as an Assistant Professor in 2016. Since then she has become actively engaged in the GST program as well. Her research area, the three-dimensional organization of the genome in the nucleus of the cell, is attracting much interest in the communities of clinical research as well as fundamental cell biology. Why? Because rare but devastating genetic lesions that disrupt this organization can influence various diseases, including cancer and premature aging.

GT: Thank you, Rachel, for sparing a sliver of your precious time for our newsletter. How did you became interested in nuclear substructure and why?

RPM: As a graduate student I was trying to understand how enhancers activate certain genes, especially when they could lie far apart in the DNA sequence. I had switched over from working with yeast to human muscle differentiation and thought, as many others did, that we would figure out some code in the linear DNA sequence that would program one enhancer to interact with one specific gene and not another, but this concept was really not useful. No combination of proteins or DNA sequence could predictably explain this. It was toward the end of my graduate work that I heard about a technique called Chromosome Conformation Capture to capture the physical evidence for these long-range interactions, where a distant enhancer might contact a promoter by looping. It turned out that the person who had developed the technique, Job Dekker, was just an hour down the road at UMass Medical School. I went and learned this technique from him, really just thinking of it as a way to connect an enhancer to the promoter. We didn't know any of the principles governing that, but I realized that one can get a lot of information out of these interactions. Then the genome-wide version of the method that we use now, the Hi-C method, was published right around the time that I defended my dissertation. That's when I decided to do a postdoc with Job Dekker.

GT: What is the current view of the significance of these interactions?

RPM: We in the field have figured out that there are gene structural units called *Topologically Associating Domains (TADs)* that keep certain parts of the genome interacting with each other and other parts separate. It turns out that's how enhancers 'know' how to activate one gene but not another – they can activate almost any promoter within that domain, but they should not cross the boundary into the neighboring domain. If they do, we get diseases that are quite dramatic; for example deleting one such boundary can cause people to have seven fingers.



A dark-stained region in the graph is evidence of a topologically associating domain (TAD) within a chromosome; image c/o McCord-lab.

GT: You have also had a long-standing interest in biophysical principles.

RPM: Yes. When you can capture all the interactions between all the DNA sequences in a genome you start to think about the folding of the chromosome, the polymer properties of the DNA. It was really appealing to me to be able to say – we have been looking at this DNA sequence just as a sequence of letters, but now we can think about the DNA having a physical shape and structure.

GT: During development, the DNA sequence itself does not change at all, barring a few exceptions, but gene expression changes a great deal, and the TADs are at the nexus between the two. Does the 3-D organization of the genome generally remain stable?

RPM: That was one thing that was surprising. It looks like the TAD structure remains pretty well conserved among a lot of cell types. What tends to change are the proteins that bind within a given TAD. And the individual TADs also move as a unit in the nucleus to different spatial locations where they tend to be either activated or inactivated. It seems like the major changes have to do with large-scale movements of entire TADs at a time, rather than the shifting of boundaries between TADs.

GT: What happens after mutations, such as translocations or inversions, which are generally perceived as being inconsequential?

RPM: Actually it really matters whether they break a TAD or not. It turns out that most benign translocations and inversions happen at the site of a TAD boundary and flip something around, so the TAD units are maintained. But, you can often explain the origin of cancer, because you'll see a break right in the middle of a TAD. In these cases, because of a fusion of two regions you've now got genes from one TAD getting activated by regulatory regions in the other TAD. Indeed, even comparing between mouse and human you find that TAD boundaries are often conserved. It seems as if through evolution, there has been a trend to maintain the TAD boundaries, and if you break those you tend to have disease.

GT: You are one of the few investigators at UT who are well positioned to seek funding from medical foundations, for example, the Progeria Research Foundation. How do the rules of grantsmanship differ in that environment?

RPM: Progeria is a disease characterized by premature aging, and our work has established that the 3D structure of the genome of progeria patients is very disorganized. I worked with the Progeria Research Foundation as a postdoc. This foundation and also the American Federation for Aging Research require you to have a letter of support from someone prominent in the field. UT's Foundation Engagement Office was very helpful in first of all pointing out opportunities to me that I might be interested in, and then also contacting the foundation for me. With our progeria project, there were two different kinds of funding that I could apply for. It was a little ambiguous which one I would

qualify for, so they discussed with the Foundation to find out which one I would best fit in. That was very helpful.

GT: It seems that the software you use to graphically visualize and then analyze your data is pretty specialized, and would be used by only a few people. That must create challenges for example when the person who knows the code in and out gets hired into a different job.

RPM: The software tools that we use are all very specific to the kind of data that we generate, because while genome sequencing is extremely common nowadays, most researchers are doing one of a few things – either sequencing a new genome or ChIP-seq or RNA-seq. Our need is fundamentally different from all of those. From the very beginning, we get sequences where one end of the DNA sequence comes from one place in the genome and the other end comes from a totally different place in the genome. Almost every established pipeline will throw those data out as "not possible". We, for historical reasons, tend to use the tools that I helped develop as a postdoc in the Dekker lab. When I started, I wrote a lot of my own code, simply because not a lot of tools were available. A lot of what (I and other people in) the Dekker lab wrote has been combined into an established pipeline. I have hope that the "4D Nucleome" project sponsored by NIH will streamline and coordinate the efforts within the 3D genome research field. Several groups are completely dedicated to computation and trying to create a set of well-established, well-checked software tools.

GT: What is your experience in training students to use and then eventually co-develop these tools?

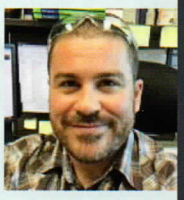
RPM: At this point it is very important for researchers in the field to at least know how to run the tools that are available within anything in genomics. Not being afraid to go in and try things - that is half the battle. In my experience, it is useful to take one or two introductory courses in programming and in statistics. True, a class is never going to teach you exactly what you need to know to do the work you need to do, but it does get you over the 'activation energy' hump. For me, I took a class in Perl, and then most everything else I learned just by saying "I really need to do this, so let me go figure out how to do it". I learned MATLAB and R along the way, but always with the motivation of knowing what I needed to get done. I think that this has also been true for my students. They learn the most when there's a specific task – "we need to select a million random sequences out of this set, can you write something that would do that"? By the time they finish, they'll have learned something. Another key is knowing what search terms to use, which only gets easier with experience once you have assimilated the jargon of your software community. Also, *always* think about what code you can get from other people who have solved a similar problem before. In a way, we are making that kind of connection with Tongye Shen's lab right now, because he works on protein structure and interaction maps, the same way we look at chromatin structure and interaction maps. We are now trying to apply each other's techniques to the opposite kind of data and are learning new and interesting things just by seeing what is analogous and what is not.

GT: Thank you for the opportunity and best wishes for a bright future!

Dr. Rachel Patton McCord

NEW GST FACULTY

Dr. Ahmed Bettaieb is an Assistant Professor in the Department of Nutrition. He joined UT in 2015 coming from a postdoc at the University of California, Davis. Dr. Bettaieb studies the molecular physiology, cell signaling and metabolic (mis)regulation of type 2 diabetes and metabolic syndrome.



Dr. Richard Giannone is a Staff Scientist at Oak Ridge National Lab in the Chemical Sciences Division. His expertise lies in bioanalytical mass spectrometry of microbial proteomes, which he and his team apply to improve the bioconversion of second generation cellulosic biofuels. Rich is a graduate from the GST program (PhD 2008).

Dr. Heidi Goodrich-Blair has been at UT since August 2016, as the new Department Head of Microbiology. Dr. Goodrich-Blair came to us from a position as Full Professor at the University of Wisconsin, Madison. Among many other accomplishments in academic leadership, she led the Microbiology Doctoral Training Program at UW. She is an expert on the microbiology of bacteria that live in mutualistic associations with insect-infecting nematodes.

Dr. Jeremiah Johnson was appointed as an Assistant Professor in the Department of Microbiology in August 2016. He came from a Postdoctoral and Research Faculty appointment at Michigan State University. His research focuses on the microbiology of *Campylobacter jejuni*, a member of the bacterial flora of chicken, which is a primary cause of gastrointestinal infections in humans. He has abundant experience in microbial genome sequence analysis and will join an already strong group of microbial genomics teams at UT-ORNL.

Dr. Tian Hong is an Assistant Professor in the Department of Biochemistry Cell and Molecular Biology. He joined UT in January 2017 coming from a postdoc at the University of California, Irvine . He was hired through a NIMBioS faculty search, his expertise is the mathematical and computational modeling of complex cellular processes, such as cell and tissue differentiation and the underlying gene expression dynamics, as well as cell cycle control. His research has primarily focused on model systems of biomedical relevance such as the epidermal-mesenchymal transition, a key step in cancer development.

CHÉZ ANN: DO MICE PREFER SUSHI, RATATOUILLE, BRIE, OR JUST MEAT & POTATOES?

Ann Wells is completing her PhD with Dr. Brynn Voy in the Animal Science Department. Ann's research has been grounded in experimental work, bolstered by recent metabolomics capabilities available through Dr. Shawn Campagna's core facility in the Department of Chemistry. It has also been transformed by increasingly sophisticated biostatistical and data mining techniques. This is an opportune time to talk a little bit about what Ann has accomplished.

GT: Thanks for agreeing to an interview for the GST Newsletter. Would you please summarize in a nutshell the major project that you are bringing to completion right now?

AW: Yes, my work is part of a large and fairly ambitious project with partners in the Threadgill lab at Texas A&M University. We are studying four different strains of mice across five different diets. The diets were designed to mimic various diets that humans commonly consume in an effort to improve health. So, we have a Western, Mediterranean, Japanese, and a ketogenic, diet, and then we have a standard mice chow to stand in as a reference. On my side of the project I am collecting data on the metabolomes of the three types of tissue that play a major role in energy metabolism- adipose tissue, muscle, and liver. I study how several dozens of metabolites change in concentration in one direction or the other relative to each other for each different diet and how factors like sex and genetic strain interact with diet to influence that shift.

GT: What is the motivation for this work?

AW: Well, in our efforts to help people control their weight we formulate various diets and tell everyone - "Try this diet, or that, exercise more, follow these healthy programs". Our big markers are "Are you losing weight?" or "Are you no longer diabetic?" But we don't really understand how those diets are influencing us on a more immediate level, meaning metabolism and physiology. It is probably important that we tease that out. Essentially, is it possible that certain changes in metabolites, which may be sex-specific or strain specific, may predict certain outcomes, for example weight gain or loss? While I am doing metabolomics, our collaborators at Texas A&M collect a ton of physiological measurements. They look at liver enzymes and inflammatory cytokines and respiratory parameters, etc. These different measurements define if the mice are using fat or carbohydrates as their primary energy source. They also measure behavior, how fast the mice run, how much they just naturally move around, if they are fidgety mice or if they just lay around and do nothing.

Image from http://animals.howstuffworks.com

GT: This type of comprehensive big-data approach sounds innovative.

AW: Yes, this is pretty new, on the scale that we are trying it. In previous studies people have supplemented the diet with something very specific, like methionine, and see how that changes methionine pathways, and they pick a specific tissue, like liver. Or people study how the effects of a specific diet depend on sex. On the other hand, when you get into human nutrition, this is where you see researchers changing whole diets and do food intake studies. But that has its own issues because humans aren't overly compliant! So short of putting them in a box, you are reliant on the study participants telling you what they are doing, And we know from research history that it's generally not very accurate! So this mouse model study is really the first on this scale of how genetics and sex influence these dietary parameters.

GT: Might this type of research eventually influence nutritional guidelines?

AW: Quite possibly. The traditional dietary guidelines were mostly "one size fits all", without considering the possibility that the 'optimal' diet may be different for different people . The new buzzword is "Precision Dietetics", the idea that the composition of a favorable diet may need to be tailored to someone's genetic background.

GT: In this field the stakes are high, because conditions such as obesity and diabetes underlie a lot of other health outcomes. Some might argue that every dollar that is invested into rigorous research would pay dividends? Do you have a sense of the funding climate for this type of research?

AW: I know Brynn's track record has been pretty good and consistent. I think that the Nutrition community is interested, but there is also pull from drug companies to find drugs that will treat these diseases. And I understand both sides, although I have my bias towards the more holistic side. This study was a pilot study and the intention is to try to move it forward, but I don't really know the current status of the project.

GT: What is your opinion about the collaborative environment? Have you experienced that collaborating groups may still have competing agendas?

AW: Actually I have found this to be super easy! I feel like this will be the best collaboration that I will ever have. Rachel Lynch, a former graduate student with Brynn is now a postdoc there and was instrumental in setting up the collaboration. They have been so open and welcoming from the very beginning. I am thinking it may have been very helpful that I visited the lab early on to help with sample collection; that builds trust. On their end they have been very transparent to share their data so that we can try to put our pieces together to make a bigger picture. And they were open to answer my questions and give me samples for the metabolomics analysis at UT. Of course they are interested to discuss our data in the context of their own.

GT: What is your experience with training in mathematical biology, biostatistics, and computational biology? You have been an early proponent among the graduate students here of fully endorsing these kinds of techniques. It is obviously a challenge to absorb these techniques while the experimental data collection is demanding one's full attention.

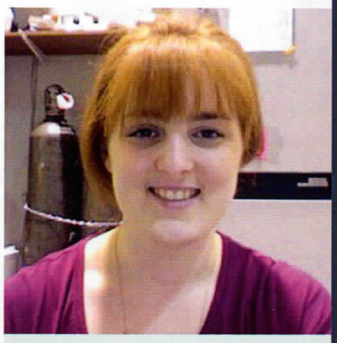
AW: I have been pretty lucky with who I have taken classes from. I am also pursuing a Masters in Statistics besides the PhD,

so I've had to take a lot of statistics courses. The teachers in the statistics department have been very practical. They taught a bit of theory and then showed us how to apply that to a real world experience, so that you get a little breather from the sharp learning curve of coding and implementing the statistics.

GT: It must be hard for the instructor to accommodate the research interests of different students?

AW: What I have really appreciated, in particular in Dr. Saxton's class, is that he takes people's actual research projects, simplifies them for everyone to grasp and works in statistical problems for the class to tackle. Then in Dr. Schmidhammer's class, we also did it the same way, but it was more business oriented, with an occasional biology example. His exams were case studies, and I liked that style. I also took a class from Dr. Petrie, and he taught the 'Probability in Mathematical Statistics' course, which was very good but very intense! That's where we really learned a lot of theory. Outside of taking OIT classes, this class was my first time having to delve deeply into R, and it has been very beneficial. I also found out that I needed to use LINUX. It was fortuitous that I had been a teaching assistant for Dr. Staton's bioinformatics course where I had to learn LINUX on the fly! Plus, Animal Science here has put an emphasis on statistics, which has promoted several office discussions between students. In addition, I also took a lot of math classes when I entered graduate school because I originally wanted to get into computational modeling. Classes like Linear Algebra were the basis for mathematical modeling and now have proved valuable for biostatistics as well.

GT: Thank you for sharing your perspective and best wishes for the home stretch towards graduation and your job search!



Ann Wells

MAKING SENSE OF DISORDER

New Mexico landscape. Photo courtesy Justin Lindsay

First year GST student Justin Lindsay is spending the summer at ORNL's sister lab in Los Alamos, New Mexico. He is conducting computational simulations of protein structure to identify the rules of behavior for an understudied class of proteins, those with intrinsically disordered regions. These are 'floppy' proteins in that they do not adopt a defined three-dimensional structure in realistic biological environments. This summer, Justin arranged for an internship with Dr. Gnanakaran, who happens to be a long-time collaborator of Justin's dissertation adviser, Dr. Tongye Shen.

GT: Justin, please tell us a little about the scope of the work and your experience so far.

JL: Since intrinsically disordered proteins can adopt an almost infinite number of different conformations, sufficient sampling of conformational space becomes especially important for the development of good models. Our method accomplishes this by cutting up the disordered region into short fragments - about 20 amino acids each - and running multiple simulations of each segment from various starting configurations. We then patch together configurations from each segment to reconstruct the entire protein. More specifically, by combining segments obtained from different time points of different simulations, we are able to generate an exponential number of physically relevant conformations (millions to billions) for each disordered region.

GT: How does your approach link the two labs?

JL: We can use these combinatorial structures as an input to Dr. Shen's model. It treats each protein as a polymer to provide distributions of a number of physical variables, such as end-to-end distance and radius of gyration. It does this as a function of variables like temperature, pH, or even denaturant concentration.

GT: What is the longer-term goal of this work?

JL: My current project will help us to refine parameters for coarse-grain simulations, allowing us to better understand the biochemical activities of certain protein complexes that have been difficult to study because large portions of their structures are undetermined. For example, the Syk and Raf kinases are key regulators of metabolic pathways and are heavily implicated in cancer. Being able to provide distributions of properties of these disordered regions, such as end to end distance, will allow parameterization of their interaction forces for building coarse-grain models.

GT: How do you like Los Alamos?

JL: It is a beautiful place. A bear walked by my driveway as I was leaving for work the other day. Aside from that it's been fairly uneventful. That said, being in a new setting has been beneficial for my focus, and while I miss my friends and family from Knoxville, the lack of distractions has been a positive overall. I don't see Gnana much, but his post-docs have been extremely helpful. I also had the opportunity to give a brief talk at the University of New Mexico in Albuquerque at a meeting with the principal investigators on the National Cancer Institute grant, which is funding my time here. It has been a very good experience seeing how other groups conduct research, especially the focus on collaboration and big-picture goals.

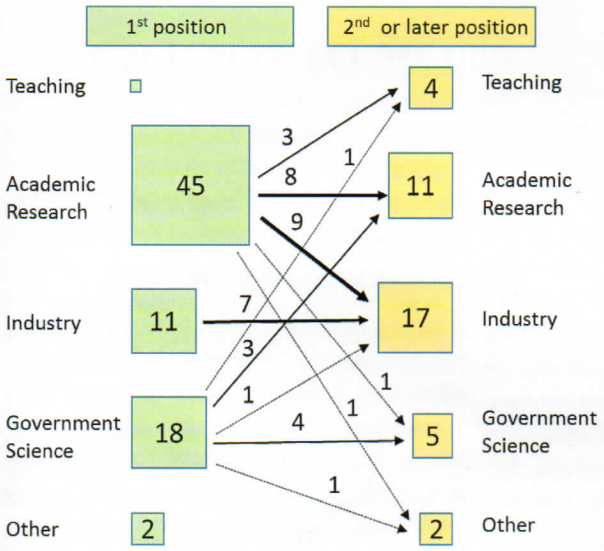
GT: Thank you for providing a glimpse into your summer work and all the best !

Justin Lindsay

MODELERS EMBRACE CLOUDS OF UNCERTAINTY

The National Institute of Mathematical and Biological Synthesis (NIMBioS) at UT offers a host of resources for biologists interested in quantitative methods. One core expertise in NIMBioS is mathematical modeling, that is, representing biological observations in the rigorous language of mathematics. Modeling in biology can be difficult as even relatively simple models can be unwieldy. Parameters can be hard to identify, solutions intractable, and answers to questions about models buried in a sea of literature written by and for mathematicians. This summer, second year GST student Ricardo Urquidi joined other students, post docs, and researchers for a three-day tutorial held at NIMBioS entitled "Uncertainty Quantification for Biological Models". Hidden behind the dry title lie the keys to a mix of new statistical and mathematical techniques to infuse a healthy dose of realism into mathematical models. Ricardo explains: "*The tutorial provided a clear introduction to the topics that tackle the uncertainty inherent to modeling, setting up a scaffold of understanding. This new understanding answered some of my questions directly, while providing a framework to recognize other problems and ask the right questions in the future.*" The topics presented were diverse, covering approaches in both frequentist and Bayesian frameworks. "*Of particular interest to my work were model reduction techniques and methods to propagate uncertainty through models*", says Ricardo. "*The tutorial has allowed me to approach my own modeling in a more rigorous way*". Tutorial materials are available for anyone interested at: http://www.nimbios.org/wordpress-training/uncertainty/.

CAREER TRAJECTORIES OF GST ALUMNI



Career transitions by GST alumni. Of 76 GST graduates between 2003 and 2016, 39 have moved on from their first position to a secondary position. Notably, among 32 moving on from Academic Research or Governmental Science, about half moved into a different sector, often towards industry. Whereas those who started out in industry remained in that sector.

NEW MINI-COURSES IN FALL 2017

Among our major graduate courses each course typically covers a range of diverse topics. And recently, we have begun to integrate more quantitative numerical methods into existing courses. For example, the GST I course on Genetics and Genomics will feature a month-long segment covering data visualization, biostatistics, and mathematical modeling. Meanwhile, the BCMB515 course on Experimental Techniques includes a segment on data visualization, statistics, and mining of public 'omics data. While it is important that junior students absorb these topics early on as part of the core curriculum, this arrangement makes it difficult for more senior researchers to become familiar with this expertise. Therefore, we are now offering several individual course segments in the form of mini-courses. By enrolling in such a course, students can selectively study the given topic, without having to commit to a full semester course with topics that may be less relevant or that they may have learned in an earlier year already. Having piloted this arrangement in Fall 2016, Rachel McCord expressed the sentiment that the students who took her segment as a stand-alone mini-courses were among the most enthusiastic about the new skills being offered.

Coming in Fall 2017

LFSC595 Section 002. Special Topics in GST (1 credit). Topic: Data visualization, statistics, and mining of 'omics data. Instructor: Dr. Rachel Patton McCord. Parent course: BCMB515. Mon Wed and Fri 10:10-11:00 am. Dates: October 2 to October 30. Room: WLS M401.

LFSC595 Section 003. Special Topics in GST (1 credit). Topic: Plant genetics and genomics. Instructor: Dr. Albrecht von Arnim. Parent course: LFSC520. Wed and Fri 9:05-11:00 am. Dates: October 4 to November 1. Room: WLS M415.

LFSC595 Section 004. Special Topics in GST (1 credit). Topic: Biostatistics, data visualization, and mathematical modeling. Instructor: Dr. Tian Hong. Parent course: LFSC520. Wed and Fri 9:05-11:00 am. Dates: August 23 to September 22. Room: WLS M415.

GSO ANNOUNCEMENT

Hello all! As we get ready for a new academic year and semester (and incoming cohort!), I wanted to quickly share some information regarding GST's involvement in the greater graduate community at University of Tennessee. I will be serving as GST's representative to the Graduate Student Senate for the upcoming year to get us both recognized again as a program and have our opinions heard. I'll be sending out monthly emails with updates on what is going on in the GSS after every meeting, and including dates for things such as travel award application deadlines. On a related note, now that GST will be represented again in the GSS, we will be trying to re-start the GST Graduate Student Organization (GSO) for the upcoming year! The GSO is probably going to have monthly meetings, depending on the demand of others and if there are any topics regarding GSS events that people want to discuss further. Casual social events such as picnics, group hikes, or happy hours are also on the hopeful schedule for the GSO.

Input from others on ideas to bring to the GSS or volunteers to get involved with either the GSS or GSO are also very much welcomed! I hope to see us get more involved and active as a program in our campus community. Please get in touch with me about any ideas or suggestions – I'm looking forward to a productive and happy year with everyone. Best, **Alex Teodor.**

SNAPSHOTS OF STUDENT RESEARCH

Terpene-synthase genes in non-seed plants and beyond. Many of the endearing properties of plants such as limes, mint, tomatoes and even Christmas trees are mediated by terpenoids, a class of metabolites that contribute to plants' taste, fragrance, color, as well as their defense against pests. Recently, the Proceedings of the National Academy of Sciences featured two articles from the lab of GST faculty member Dr. Feng Chen. The first paper identified microbial terpene synthase-like genes in non-seed land plants through systematic analysis of transcriptomes of more than 1000 plant species. This extensive research initiative was spearheaded by GST student Qidong Jia from the Chen lab, and involved worldwide collaborations between UT and about a dozen universities and institutes located in the US, Germany, China, Sweden, Canada and Australia. The second paper reported the discovery of terpene synthase genes in amoebae, thereby demonstrating their occurrence in eukaryotes other than plants and fungi. This paper also featured important contributions by two GST students, Qidong Jia and Ayla Norris.

Drug combo may be more effective with oral cancer. A study in human, canine and feline cancer cell lines, published in the Journal of Cellular Biochemistry by three current and former GST students from Dr. Maria Cekanova's lab suggested that anthracycline-based chemotherapy treatments can be more effective for treatment of oral squamous cell carcinomas when combined with inhibitors of the phosphoinositide-3 kinase/AKT signaling pathway.

Anion-quadrupole pairs may maintain protein stability. The first computational characterization of the dynamics of anion-quadrupole interactions formed between negatively charged and aromatic side chains of amino acids, was reported in the Biochemistry journal, by the Baudry, Howell, Hinde and Saxton labs. These studies show the highly dynamic nature of these non-covalent interactions, which play a role in maintaining the structural stability of proteins. These interactions have important implications in structure-based drug discovery.

Thermodynamics reveals clues to enzyme's low promiscuity. If a bacterial infection does not respond to an antibiotic it is quite possibly due to newly evolved resistance engendered by enzymes such as aminoglycoside acetyltransferases. Why do some of these enzymes target different antibiotics and others only a few? Prashasti in Dr. Engin Serpersu's lab compared an enzyme with a very limited substrate profile with highly promiscuous enzymes. She demonstrated experimentally that, despite their strong sequence similarity, the thermodynamics of ligand-protein interactions uncovered clues to this behavior. Her work was published in the journal Proteins.

Novel approach to control virus-induced inflammatory lesions. Ocular infection with Herpes Simplex Virus 1 (HSV-1) causes an inflammatory reaction in the cornea that leads to tissue damage and loss of vision. Researchers in Dr. Barry Rouse's lab, led by GST student Siva Karthik Varanasi, reported that therapy with the DNA methyltransferase inhibitor 5-azacytidine in mice increases the function of regulatory T cells, leading to suppression of the inflammatory lesions. This finding may open up new avenues in the treatment of HSV-induced ocular lesions. The study was published in the Journal of Virology.

SELECTED RECENT PUBLICATIONS BY GST STUDENTS

Jia Q, ... Chen F. (2016) Microbial-type terpene synthase genes occur widely in nonseed land plants, but not in seed plants. Proc Natl Acad Sci USA. 113:12328-12333.

Smolensky D, Rathore K, **Bourn J,** Cekanova M. (2016) Inhibition of the PI3K/AKT Pathway Sensitizes Oral Squamous Cell Carcinoma Cells to Anthracycline-Based Chemotherapy In Vitro. J Cell Biochem. 118:2615-2624.

Kapoor K, Duff MR, **Upadhyay A,** Bucci JC, Saxton AM, Hinde RJ, Howell EE, Baudry J. (2016) Highly Dynamic Anion-Quadrupole Networks in Proteins. Biochemistry. 55:6056-6069.

Dahal S, Poudel S, Thompson RA. (2016) Genome-Scale Modeling of Thermophilic Microorganisms. Adv Biochem Eng Biotechnol. 160:103-119.

Bhojane PP, Duff MR Jr, **Bafna K,** Rimmer GP, Agarwal PK, Howell EE. (2016) Aspects of Weak Interactions between Folate and Glycine Betaine. Biochemistry. 55:6282-6294.

Evangelista W, Weir RL, **Ellingson SR, Harris JB, Kapoor K,** Smith JC, Baudry J. (2016) Ensemble-based docking: From hit discovery to metabolism and toxicity predictions. Bioorg Med Chem. 24:4928-4935.

Bobik K, **McCray TN, Ernest B,** Fernandez JC, Howell KA, Lane T, Staton M, Burch-Smith TM. (2017) The chloroplast RNA helicase ISE2 is required for multiple chloroplast RNA processing steps in Arabidopsis thaliana. Plant J. 91:114-131.

Rempe CS, Burris KP, Lenaghan SC, Stewart CN Jr. (2017) The Potential of Systems Biology to Discover Antibacterial Mechanisms of Plant Phenolics. Front. Microbiol. Review. 8:422.

Kumar P, Serpersu EH. (2017) Thermodynamics of an aminoglycoside modifying enzyme with low substrate promiscuity: The aminoglycoside N3 acetyltransferase-VIa. Proteins. 85:1258-1265.

Chotewutmontri P, Holbrook K, Bruce BD. (2017) Plastid Protein Targeting: Preprotein Recognition and Translocation. Int Rev Cell Mol Biol. 330:227-294.

Zhang Q, Jun SR, Leuze M, Ussery D, Nookaew I. (2017) Viral Phylogenomics Using an Alignment-Free Method: A Three-Step Approach to Determine Optimal Length of k-mer. Sci Rep. 7:40712.

Varanasi SK, Reddy PB, Bhela S, Jaggi U, Gimenez F, Rouse BT. (2017) Azacytidine Treatment Inhibits the Progression of Herpes Stromal Keratitis by Enhancing Regulatory T Cell Function. J Virol. 91: e02367-16 .

Poudel S, Giannone RJ, Rodriguez M Jr, Raman B, Martin MZ, Engle NL, Mielenz JR, Nookaew I, Brown SD, Tschaplinski TJ, Ussery D, Hettich RL. (2017) Integrated omics analyses reveal the details of metabolic adaptation of Clostridium thermocellum to lignocellulose-derived growth inhibitors released during the deconstruction of switchgrass. Biotechnol Biofuels. 10:14.

Adebali O, Zhulin IB. (2017) Aquerium: A web application for comparative exploration of domain-based protein occurrences on the taxonomically clustered genome tree. Proteins. 85:72-77. PubMed Central PMCID: PMC5167639.

Qian C, Hettich RL. (2017) Optimized Extraction Method To Remove Humic Acid Interferences from Soil Samples Prior to Microbial Proteome Measurements. J Proteome Res. 16:2537-2546.

Utturkar SM, Klingeman DM, Hurt RA, Brown SD. (2017) A Case Study into Microbial Genome Assembly Gap Sequences and Finishing Strategies. Front Microbiol. doi: 10.3389/fmicb.2017.01272.

WELCOME, CLASS OF 2017!

GST is excited to welcome the incoming class of 2017. The admissions committee was happy to review a large number of applications this year. Fifteen students were offered admission and nine accepted. The new class brings an amazing 25 years of combined prior research experience. We wish them the very best!

Mang Chang graduated with a BS in Microbiology from Oklahoma State University. She has participated in several prestigious undergraduate and post-bachelor's internship opportunities at Oak Ridge National Laboratory. She has garnered substantial research experience in microbiology and molecular biology, working on diverse research projects in the Morrell-Falvey lab at ORNL. The collaborative research opportunities between UT and ORNL led her to apply to the GST program.

Cheng Chen comes to GST from Georgia Tech., where she earned a Master's degree in Bioinformatics. Prior to this, she graduated with a scholarship from Shanghai Jiao Tong University, China, with a BS in Bioinformatics and Mathematics (minor). She has a strong foundation in research encompassing life science, computer science and mathematics, and seeks to build her skills in the interdisciplinary environment of the GST program.

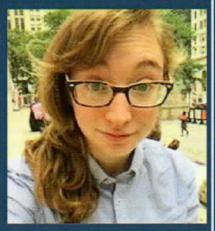
Payal Chirania holds a BTech degree in Biotechnology from the Heritage institute of technology, Kolkata, India and an MS degree in Veterinary Medical Sciences from the University of Maryland, College Park. In her sophomore year, she was selected for a Summer Research Exchange Program at New Jersey Institute of Technology and her research on developing and testing a DNA aptamer for detection of a cancer biomarker was featured in a journal publication. At UMD, she was the recipient of the Dean's Fellowship Award in 2016 and she has continued to expand her research skills during her post-graduate studies.

Viswanathan Gurumoorthy earned a scholarship to pursue a BTech in Industrial Biotechnology at Anna University, Chennai, India. Since graduating in 2012, he has worked as a research assistant at the Indian Institute of Technology, Chennai. His contribution to research on the effect of parental age on somatic mutation rates in the Arabidopsis has been published in a journal article. The multidisciplinary research opportunities in the GST program attracted him and he is keen on augmenting his knowledge and research skills as a graduate student.

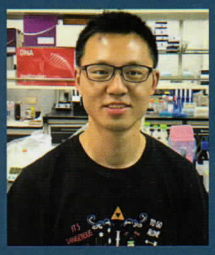
Nicholas Mucci is a recent graduate from the University of Massachusetts, Amherst, where he majored in Biology. He was awarded the Life Sciences Junior Research Fellowship for 2016/17 and he concentrated his efforts on honing his computational skills and working on a microbial genomics project. He seeks to build on his foundations in bioinformatics and genomics, and carve out his research niche in GST.

Samantha Peters holds a BS in Biology from South Dakota State University. Since her graduation, she has participated in many different research projects both in academia and industry. She currently works at a private proteomics company, where her research includes creation and validation of novel DNA-based protein binding reagents. Her search for a graduate program with emphasis on collaborative research led her to apply to GST.

Yue Shen graduated from Shanghai Jiao Tong University, where he earned a BS in Biotechnology. He comes to GST with research experience both at the undergraduate level and after graduation, with published results of his work. He is excited by the state-of-the art resources available to graduate students in the GST program, especially in the fields of high performance computing, genome sequencing and mass spectrometry.



Rebecca Weir is an alumna of UTK, where she earned her BS in Biochemistry, Cellular and Molecular Biology, with a minor in French. She has gained substantial research experience working first as an undergraduate and then a post-graduate research assistant in the ORNL Center for Molecular Biophysics since 2015. Her work in the Baudry Lab on computational prediction of the toxicity of drug candidates has been published and her current research on Insulin Like Growth Factor 1 receptor is also nearing publication.



Yang Xu earned his BS degree in Applied Biotechnology at Huazhong Agricultural University, China, where he was awarded the "National Endeavor Scholarship" in 2012 and the "Merit Student Fellowship" in 2013. After graduation, he has been working as a research assistant in Zheijang University School of Medicine, China, where his research is focused on developing a high-throughput single cell RNA-seq technique. His undergraduate as well as current research has been featured in journal publications. Yang's interests lie primarily in genomics and he is keen on building on his research skills in this field.

Growing Trends is the newsletter of *The UT-ORNL Graduate School of Genome Science & Technology*
1414 West Cumberland Avenue Knoxville, TN 37996. Ph: 865-974-9561 Web: gst.tennessee.edu
Produced by Albrecht von Arnim and Anamika Missra