Collaboration Highlight:
Visual Analytics Team Makes Complex Genetic, Health Data More Digestible, page 4
Interactions highlights the collaborative activities of the Mayo Clinic & Illinois Alliance for Technology-Based Healthcare.

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On the cover:
Colleen Bushell, PhD, (left) and Heidi Nelson, MD (right) have worked together for years on various collaborative projects that utilize visual analytics of high dimensional health data for explorative research and predictive modeling for a wide range of health issues.

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The Knowledge Engine for Genomics Gains Momentum

By Claudia Lutz, Carl R. Woese Institute for Genomic Biology

For the individuals involved in KnowEnG, a Center of Excellence established by an NIH Big Data to Knowledge (BD2K) Initiative award to the University of Illinois in collaboration with the Mayo Clinic, recent activities have highlighted both how much has already been accomplished in the past two years and the promise of the center’s newest directions.

KnowEnG stands for Knowledge Engine for Genomics, representing the center’s mission to develop analytical resources that will allow researchers to better interpret new genomic results by leveraging community knowledge of how genes interact with each other. Advances toward this goal were evident when members of the center’s External Advisory Committee and representatives of NIH visited Illinois to attend a two-day conference at the Carl R. Woese Institute for Genomic Biology, which houses the center.

Presentations by investigators highlighted research achievements, tools developed, plans for collaborator review, refinement, and dissemination, and new connections to related research efforts. Abel Bliss Professor of Engineering Jiawei Han, a program co-director for the center, praised the rapid progress of the center, which was founded in October 2014. Efforts at Illinois and the Mayo Clinic have focused on software development and the creation of resources for bioinformatics education and training tailored to the needs of biomedical researchers, as well as establishing a cycle of feedback and refinement that will ensure the utility and accessibility of the resources under development.

“We need to bring computational genomic science together with biomedical science, and this [KnowEnG] is an excellent effort,” said Richard Weinshilboum, MD, Mary Lou and John H. Dasburg Professor of Cancer Genomics and director of the center’s Pharmacogenomics Translational Program. Weinshilboum praised the productivity of the partnership between Illinois and the Mayo Clinic within the center.

Since the center’s inception, researchers have developed a novel resource, the Knowledge Network, which integrates many different high-quality public genomic information sources into a comprehensive theoretical landscape of gene functions and interactions. By placing their new results into the context of the Knowledge Network, biomedical researchers can produce a high-powered analysis of new genomic and transcriptomic datasets.
Another innovation of the KnowEnG Center is the Knowledge Engine (also called KnowEnG), an analytical platform that takes advantage of algorithms that are used successfully in other data mining endeavors, including Google’s search functions, but have not been previously applied to interpretation of genomic data. KnowEnG enables researchers to include the Knowledge Network, as well as more traditional resources, as part of their analytical workflow.

KnowEnG is being designed with a user-friendly interface and standardized analytical pipelines that guide investigators who are less familiar with computational aspects of bioinformatic analyses, and offers varying levels of customization depending on the user’s expertise. The center has contracted with Amazon Cloud so that researchers can run analyses on the cloud, without requiring local resources, thereby increasing the tool’s usability and making it possible to run multiple variations or aspects of an analysis simultaneously.

“Cloud-based computing can be very helpful,” said Professor of Computer Science and Willett Faculty Scholar Saurabh Sinha, who serves as the second program co-director for the center. “Users would like to run those interactions in parallel and be done with it, and a cloud computing network makes that happen very easily.”

KnowEnG’s user interface will also connect with an extensive online suite of bioinformatics training modules that can improve understanding of both computational and biological aspects of genomic analyses. Founder Professor of Bioengineering and of Physics Jun Song leads training activities of the center, which include a new partnership with Fisk University to provide bioinformatics education and research opportunities to minority undergraduate students.

An important focus of the next phase of work will be ensuring that KnowEnG is accessible to biomedical researchers at all levels of computational skill. Partnership with the Mayo Clinic, as well as bio-focused research groups at Illinois, will provide opportunities for several rounds of user testing and feedback. After one more productive year, the KnowEnG Center is excited to share their progress with the wider world of genomic biomedical research.

One of the main paradigms embraced by the KnowEnG Center is the concept of “knowledge-guided analysis,” in which researchers can analyze their own data in the context of publicly available data. Primary sources include gene expression data sets, gene homology relationships, protein-protein and gene-gene interactions, gene ontologies, and literature-based relationships.

Professor Saurabh Sinha says the eventual idea is that scientists will visit the KnowEnG portal with their own datasets (in spreadsheets) and use KnowEnG to analyze their data in the light of this massive compendium (Knowledge Network) of community-shared datasets.

He gives specific examples of analyses already done, emphasizing novel algorithms that have been developed and applied to the discovery of mechanisms underlying diverse phenotypes such as:

- A technique based on diffusion component analysis that identifies cancer pathways associated with drug response;
- An approach using “network smoothing” of gene expression data and random walks with restart on the Knowledge Network to better rank cytotoxicity-related genes;
- A probabilistic graphic model that integrates genotype, gene expression, and transcription factor-DNA binding data with drug response to identify regulatory mechanisms of drug response variation across individuals; and
- Random walk-based methods for gene set characterization, as an alternative to existing techniques such gene set enrichment analysis, using it to glean systems-level insights about social regulation of aggressive behavior.

For more information on the KnowEng Center, including a list of publications, visit www.knoweng.org.
It really all began thanks to Dr. Edison Liu’s sabbatical. At least, this is how Colleen Bushell, senior research scientist at the University of Illinois’ Applied Research Institute (ARI), explains her visual analytics team’s leap into the genomic and medical data domain.

It was 2010 and Liu, president and CEO of The Jackson Laboratory and adjunct professor of molecular and cellular biology at the University of Illinois, was in Urbana-Champaign on sabbatical and meeting with mathematicians, computer scientists, and fellow biologists at the National Center for Supercomputing Applications (NCSA). As the leader of a world-class, cutting-edge genomic research institution, Liu admitted a struggle: he always had trouble communicating the results of genetic analysis of a tumor to physicians. The information was so complex, he didn’t know where to start.

Michael Welge, long-time colleague of Bushell’s at NCSA and then-director of data-intensive technologies and applications research, heard Liu’s challenge and knew it was not unique. Welge, an early member of the Mayo Clinic and Illinois Alliance, was aware that Mayo Clinic researchers and physicians were dealing with the same difficulty—how to draw out and communicate relevant information from a flood of genomic data. The challenge aligned with the Mayo Clinic Center for Individualized Medicine’s Clinomics Program aim: to transform genomic data into applications and information to guide decisions that ultimately improve patient health care. Members of the newly formed Alliance proposed a pilot project, and Mayo Clinic provided seed funding for the work. Like that, the Alliance’s first visual analytics for precision medicine project was born.

The Gamut to Genetic Variances

Visual analytics has been a widely accepted methodology for decades. Bushell describes it simply as the marriage of information design and data science. It is an outgrowth of information visualization and scientific visualization, and has overlapping characteristics, but can attack problems whose size, complexity, and need for both human and machine analysis makes them otherwise unmanageable.

While Welge brings an analytical and computational point of view to projects, Bushell’s formal training is in graphic design. Prior to her role with ARI, she was a professor in graphic design at the U of I. Her interest was information design, focusing on how to communicate both static and interactive data most effectively. From 1986 to 2004, Bushell was an NCSA research affiliate in data visualization. She designed the interface for Mosaic, the world’s first Web browser, worked on taking numeric data from simulations on a supercomputer to create a visual animation of a thunderstorm developing, and co-developed a visual programming interface for NCSAs data mining software. “We were working with big data long before it was called ‘big data,’” jokes Bushell. “Until about six to seven years ago, my knowledge of microbiology, genetics, and medicine was zero. Nothing. The first book I bought was ‘Genetics for Dummies’—just so I could get the terminology correct,” says Bushell. “But even back in the early NCSA days, I was always working in a space like physics or atmospheric science, where it was always a collaboration and I was simply trying to understand enough to represent it accurately.”

With the formalization of the Mayo Clinic and Illinois Alliance, Bushell, Welge, and other members of their NCSA visual analytics team—mathematicians, information designers, and software developers—came together to focus their expertise on health and medical projects. The ARI team now includes Bushell, Loretta Auvil, Matt Berry, Lisa Gatzke, Peter Groves, Xiaoxia Liao, and Michael Welge.

Clearly Communicating Genetic Complexities

The visual analytics pilot project, an early collaboration of the Mayo Clinic and Illinois Alliance, along with the Genome Institute of Singapore (Edison Liu, founder) was a clinomics success. What started out as a few rough design concepts of genetic analysis of a tumor grew into a prototype genetic report that focused on a comprehensive diagnostic panel of 17 hereditary colon cancer genes using next-generation sequencing technologies. Previously, Mayo Clinic ran individual tests for five genes most frequently mutated in hereditary colorectal cancer cases. Labs around the world could test additional genes that were known or suspected to play a role in the disease, but no other institution could test all 17 comprehensively.

Matt Ferber, co-director of the Clinomics Program at Mayo, enlisted the Illinois team to design a visual report for this genetic colorectal cancer panel, one that helped communicate the results of the panel to physicians. Bushell presented the report at the 2012 Individualizing Medicine Conference, sparking great interest from physicians and investigators—especially colorectal surgeon Heidi Nelson.
**Expanded Visualization Projects Meet Extended Random Forest**

After seeing the results of the Alliance's visual analytics collaboration first-hand, Dr. Heidi Nelson, also a vice chair for research in the Mayo Clinic Department of Surgery and an Alliance collaborator in the microbiome research area, knew it was just the beginning. Nelson sponsored three additional Alliance visual analytics seed projects, each with different goals for the team to achieve.

“Sometimes the goal is to help understand the biological complexity of what's happening, or build a predictive model. Sometimes it is to determine feasible courses of action, given the genetic analysis. Sometimes the goal is to create an interactive visualization tool, too,” says Bushell.

One of Nelson's seed projects that Bushell and the visual analytics team at Illinois ARI has completed for Dr. Jordan Miller's heart disease research lab at Mayo Clinic was analyzing high dimensional mRNA and miRNA data from myxomatous mitral valve heart disease (or mitral valve prolapse). Essentially the weakening or degeneration of the valve's connective tissue, it is the culprit of many a valve replacement surgery. However, despite progress in valve repair, lower mortality rates, imaging, and less invasive approaches, far too many patients undergo unnecessary valve replacement procedures. Additionally, performing open-heart surgery, only to find the mitral valve is not at significant risk for repair or replacement, is unsafe and costly. Mayo Clinic researchers wanted to search for features that could help identify degenerative heart valves.

Traditional statistical analysis notes the top ten up- and down-regulated features. Welge constructed a newer analytical approach to the mitral valve project, aptly named Extended Random Forest (ERF) because it builds off the well-known Random Forest algorithm.

The method constructs hundreds of thousands of decision trees that, together, help determine top features and specific combinations and strengths that are most meaningful to a disease or condition. The process is extended to include stability analysis, which is important when there are many features but small sample sizes. In this case, the ERF method found a different list of most-important features than traditional analysis found—or than what researchers had predicted. “It’s actually good that we’re not all biologists, because we present the results without any preconceived bias,” says Bushell. “With this project, the Mayo Clinic researchers were very excited, because the results showed genes that mapped to three biological pathways they believe to be relevant to this valve disease.”

**Creating New Tools for Medical Discovery and Decision-Making**

Nelson is pleased with the number of projects now underway between Mayo Clinic and the Illinois visual analytics group.

“The work we’re doing together is critically important, because Colleen and her colleagues are able to take large amounts of data and work with it to create two or more levels of visualization. This is more comprehensible to a physician or patient than what we can provide alone,” says Nelson.

Currently, the Illinois team is working with Dr. Nelson to develop a microbiome research and reporting tool. It contains data from several microbiome studies where the microbial DNA have been extracted from stool samples and analyzed to identify bacteria that are relevant to various diseases. The tool uses visualization techniques to characterize the microbiome community and displays important bacteria on an interactive phylogenetic tree. Eventually, doctors could use the software to compare an individual patient's profile with database results.

Bushell says she is particularly interested in the microbiome project on a personal level. Two of her three children have type 1 diabetes, and recent research shows a connection between the autoimmune disease and the microbiome. She says her team's focus remains to find ways to identify relevant features in data and communicate intricate information in a biological context that helps people make decisions. Bushell sees Nelson as an incredibly visionary part of their visual analytics team, especially in moving these projects forward.

“What she wants to do is not just design a report of what we can find now, but push ahead to begin thinking about what we could potentially report on in five years, when we have more data,” says Bushell. “She’s asking, what are the kinds of things that clinicians want to know about the microbiome?” She is engaging and funding these projects, knowing that there is not too much clinically actionable information to report on yet. Dr. Nelson wants to get the dialogue going and move people toward a vision. Our design helps push the vision. It encourages them to say ‘we need to do this’ and ‘here’s how we can do it better.’”

“What an academic institution likes to do is find opportunities for their people to solve problems. And in health care, we have those real-world problems. So it's a perfect marriage of having people with great expertise at Illinois filling the gaps we identify at the Mayo Clinic,” says Nelson.
Challenge One: Detection of Biomolecules from Body Fluids for Early Detection of Disease

This challenge was taken on by a research team comprised of Dr. Patricio Escalante, from the Division of Pulmonary and Critical Care Medicine at Mayo Clinic; Yi Lu, professor of chemistry at Illinois; Rashid Bashir, Abel Bliss Professor and department head of bioengineering at Illinois; and Ryan Bailey, professor of chemistry at the University of Michigan (formerly Illinois). Their project, titled “Novel Biomarkers and Point-of-Care Methods for Latent Tuberculosis Infection” aims to develop point-of-care (POC) diagnostic technologies that detect immune biomarkers for high-risk latent tuberculosis infection (LTBI) in a variety of patient populations and settings, improve diagnosis of LTBI, and individualize patient management.

Tuberculosis is a bacterial infection caused by mycobacterium tuberculosis. According to the World Health Organization (WHO) in its 2016 Global Tuberculosis Report, one third of the world’s population is infected. In 2015 alone, 1.8 million people died from tuberculosis, and in the same year another 10.4 million new cases were estimated, worldwide. Add the complex tuberculosis lifecycle, specifically the reactivation of dormant or latent infection (LTBI), plus vaccine resistance—and fallout of epidemic proportions are possible. Currently, the mechanism of TBI reactivation is unknown, but reactivation from a latent infection is the most prevalent source of transmission. The WHO cites gaps in testing and reporting for TB as a major challenge of this top 10 global cause of death.

The Mayo Clinic and Illinois research group has been working to develop three POC device platforms for LTBI. The first is a POC multiplexed cytokine-chemokine detecting technology. The device uses a silicon photonic micro ring resonator (MRR) assay to detect various immune biomarkers in antigen-activated blood samples. This novel MRR technology has been clinically validated at the Mayo Clinic, and there is currently a manuscript in process detailing this work.

The second device in development utilizes personal glucose meters for POC diagnosis of LTBI. The investigators are in the processes of further validation of this technology. However, they believe this device has great potential for rapid diagnosis of LTBI in resource-limited settings.

The third technology is a POC microfluidics platform that has proven successful for other diagnostic applications, such as early sepsis detection, but is being improved upon to reach the level of detection needed for LTBI.

The Mayo Clinic and Illinois team intends to continue their work to further improve and validate all three LTBI diagnostic technologies. Currently, four papers detailing various pilot studies of these technologies are in the process of publication. Additionally, the group has several grant proposals in preparation to acquire external funding for their continued research and technology development.
Challenge Three: 3-D Cancer Tumor Chip-Avatars for Personalized Drug Therapy

Brendan Harley, associate professor of chemical and biomolecular engineering at Illinois, and Drs. Daniel Ma and Jann Sarkaria from the Department of Radiation Oncology at Mayo Clinic received seed funding to address this challenge. Their project, titled “Chip-based engineered tumor microenvironments for glioma therapy” demonstrated the use of engineered glioma biomaterials to find successful therapies for glioblastoma multiforme (GBM), which is the most common, aggressive, and deadly form of brain cancer and is often resistant to current therapeutic approaches.

The gelatin hydrogel platform developed by the Harley lab is proving to be a versatile tool for studying glioma progression, efficient evaluation of cell processes, and treatment efficacy. The platform can also be adapted to evaluate the response of patient derived samples, making this a promising technology for rapid assessment of personalized treatment strategies for GBM.

Prof. Harley, along with Dr. Sarkaria, Dr. Ian Parney, from the Department of Neurosurgery at Mayo Clinic, and Steven George, professor of biomedical engineering at Washington University in St. Louis, were recently awarded R01 funding from the National Cancer Institute, for their project titled “Biomimetic hydrogel niches to study the malignant phenotype of glioblastoma multiforme.” This award will allow the team to continue their work over the next five years.

This team of inter-institutional researchers has used the biomarker discovery seed program as a launching point to enhance and expand the degree, scope, and external funding potential of their collaborative interactions.

“We have established a pipeline for transferring patient derived xenograft cells with a wide variety of diagnostic and therapeutic trajectory information, gathered from more than 75 glioblastoma multiforme patients,” said Harley.

Additionally, Illinois professors Rohit Bhargava and H. Rex Gaskins have joined the project team. Several publications are in preparation and two NIH grants pending, in addition to the R01 award already received, to round out the research activity. To learn more about the continued glioma avatar project, visit the Harley lab website at harleylab.org.
Abstracts of Recent Publications

Mapping Lung Tumor Cell Drug Responses as a Function of Matrix Context and Genotype Using Cell Microarrays

Kaylan KB, Gentile SD, Milling LE, Bhave KN, Kosari F, Underhill GH

Interactions between epithelial tumor cells and components of their microenvironment influence carcinoma progression and affect how the cells respond to therapy. However, the complexity of the extracellular matrix (ECM) makes it difficult to investigate these interactions. This study takes the ECM environment into account by using a high-throughput cell microarray-based approach to study the impact of defined combinations of ECM proteins on lung tumor cell drug responses. The effects of 55 different ECM environments on the responses of lung adenocarcinoma cells to cancer-relevant small molecule drugs were evaluated with this approach. The researchers also assessed the expression of neuroendocrine transcription factor ASCL1, since there is a neuroendocrine-like subtype of lung cancer that co-expresses ASCL1 and RET and has been associated with reduced patient survival, increased tumor cell proliferation, and expression of anti-apoptotic proteins. The results suggest that co-expression of specific ECM proteins with known genetic drivers in lung adenocarcinoma may impact therapeutic efficacy. The researchers believe this approach could be utilized along with integration of clinical cell samples and genomics data to define the molecular mechanisms by which cell–matrix interactions drive drug resistance.

Prior Oral Contraceptive Use in Ovarian Cancer Patients: Assessing Associations with Overall and Progression-Free Survival


Previous studies have shown that oral contraceptive use reduces the risk of ovarian cancer. With this in mind, the researchers decided to examine the effect of oral contraceptive use on overall and progression-free survival of patients diagnosed with ovarian cancer. A retrospective cohort study was carried out on ovarian cancer patients who were seen at the Mayo Clinic over a span of 13 years. When taking confounding factors into account—like age, smoking, or family history—the data showed that patients who used oral contraceptives at any point prior to being diagnosed with ovarian cancer had better progression-free survival than patients who had never used oral contraceptives. Overall survival did not appear to be affected by oral contraceptives when other factors were included in the analysis. Though this study suggests that prior oral contraceptive use is associated with improved clinical outcomes for ovarian cancer, further investigation is needed to understand how and why this occurs. Understanding the mechanisms behind these data may lead to more effective therapeutic interventions for ovarian cancer patients.
Seizure Forecasting and The Preictal State in Canine Epilepsy
Varatharajah Y, Iyer RK, Berry BM, Worrell GA, Brinkmann BH. 2016. The ability to predict seizures may enable epilepsy patients to better manage their medications and activities, potentially reducing side effects and improving quality of life. But forecasting epileptic seizures remains a challenging problem. Machine learning methods, such as the pipeline presented here that processes intracranial electroencephalographic (iEEG) recordings and generates seizure warnings, have shown promise. Results of this study support the ability to forecast seizures at rates greater than a Poisson random predictor for all feature sets and machine learning algorithms tested. In addition, subject-specific neurophysiological changes in multiple features are reported preceding lead seizures, providing evidence supporting the existence of a distinct and identifiable preictal state.

Impact of Adiposity on Cellular Adhesion: The Multi-Ethnic Study of Atherosclerosis (MESA)
The cellular mechanism for how excess body fat promotes atherogenesis as well as the relationship of adiposity to adhesion molecules that leads to atherosclerosis is largely unknown. This study used data from 5,974 adults who participated in the Multi-Ethnic Study of Atherosclerosis (MESA) to assess sex-specific associations of soluble cellular adhesion molecules and adiposity. Adiposity was measured by body mass index (BMI), waist-to-hip ratio (WHR), and computed tomography (CT) measures of subcutaneous adipose tissue and visceral adipose tissue and compared to levels of adhesion proteins. The researchers found that the relation of adiposity to adhesion proteins was similar across adiposity measures for both sexes, with the exception of two adhesion proteins, sVCAM-1 and P-selectin, that may be modified by sex and the particular adiposity measure used. Based on these results, the researchers concluded that assessment of cardiovascular risk in overweight or obese patients should not only rely on BMI and traditional risk factors, such as cholesterol levels and blood pressure. Measuring adiposity with WHR and CT scans and testing the levels of adhesion proteins may prove to be better predictors of cardiovascular risk and could improve patient outcomes by providing more targeted therapy.

Capturing One of the Human Gut Microbiome’s Most Wanted: Reconstructing the Genome of a Novel Butyrate-Producing, Clostridial Scavenger from Metagenomic Sequence Data
The role of the microbiome in health and disease is attracting great attention, but little is known about some of the most prevalent microorganisms inside our bodies. Several years ago, Human Microbiome Project (HMP) researchers generated a list of “most wanted” taxa: bacteria prevalent in both healthy volunteers and distantly related to any sequenced organisms. Unfortunately, the challenge of assembling high-quality genomes from a tangle of metagenomic reads has slowed progress in learning about these uncultured bacteria. This study describes how recent advances in sequencing and analysis enabled the assembly of “most wanted” genomes from metagenomic data collected from four stool samples. Using a combination of both de novo and guided assembly methods, over 100 genomes were assembled and binned from an initial data set of over 1,300 Gbp. One of the genome bins met HMP’s criteria for a “most wanted” taxa and contained three essentially complete genomes belonging to a previously uncultivated species. This an intriguing species for the study of diseases such as colon cancer and inflammatory bowel disease because it appears to produce butyrate, which is thought to play an anti-inflammatory role. The assembly of essentially complete genomes from stool metagenomic data provides valuable information about uncultured organisms’ metabolic and ecologic niches, which may be useful for culturing these bacteria, and explaining their role in maintaining health and causing disease.

Recent Grants Awarded to Mayo Clinic & Illinois Alliance Collaborations
Translational Molecular and Cellular Imaging Technologies for Quantitative Prostate Tumor Pathology
Pls: Rohit Bhargava (UI), Andrew Smith (UI), John Cheville (Mayo); R33 award from the NIH National Cancer Institute.

Biomimetic Hydrogel Niches to Study the Malignant Phenotype of Glioblastoma Multiforme
Pls: Brendan Harley (UI), Jann Sarkaria (Mayo), Ian Parney (Mayo), Steve George (Wash U); R01 award from the NIH National Cancer Institute.

I/UCRC Center Grant: Computing and Genomics – An Essential Partnership for Biology Breakthroughs
Pls: Ravi Iyer (UI), Gene Robinson (UI), and Liewei Wang (Mayo); Award from the National Science Foundation.
Five of Illinois’ best and brightest undergraduates spent their summer as research fellows in Rochester, Minnesota, supported by the Mayo Clinic and Illinois Alliance. The Alliance’s commitment to this educational program continues to be a popular, competitive opportunity for Illinois undergraduates. When you learn more about the clinically-relevant research projects each student undertook, it is easy to see why the Summer Undergraduate Research Fellowship (SURF) program continues to flourish.

Juhi Gupta
Molecular and Cellular Biology, Class of 2017

Since Juhi is interested in pursuing an MD/PhD in the future, she wanted to gain full-time research experience in a clinical setting. She knew if given the opportunity to participate in the SURF program, she would get training and guidance from some of the most qualified people in the medical field. Additionally, she wanted to be challenged and learn to be autonomous in a research lab, and since the SURF program is centered on completing an independent research project, she knew it would be a good litmus test.

While in Rochester, Juhi’s mentors were both Dr. Isobel Scarisbrick and Dr. Hyesook Yoon in the Scarisbrick Lab of Neuroregeneration and Neurorehabilitation. There, her project was to determine the role of PAR1 and PAR2 in myelination using Oli-neu cells (oligodendrocyte cell line) and to dissect the PAR1 and PAR2 signaling pathway. PAR1 and PAR2 belong to a family of GPCRs that have been implicated as having therapeutic potential to treat demyelinating pathologies, such as multiple sclerosis. By determining how PAR1 and PAR2 mediate changes in expression of gene products associated with myelination, future therapeutic targets may be identified.

Back at Illinois, Juhi continues her research concerning multiple sclerosis, but from a different perspective. She work in the Exercise Neuroscience Research Lab of Professor Emerson Sebastio, which examines the efficacy of exercise intervention on multiple sclerosis prognosis.

Amish Khan
Molecular and Cellular Biology and Chemistry, Class of 2017

Amish was inspired to apply to be a SURF when his research mentor, Dr. Jay E Mittenthal, forwarded the opportunity to him. He says the laboratory he was matched to was a great fit, and just on the periphery of his existing skillset—Dr. Hu Li, in the Department of Molecular Pharmacology and Experimental Therapeutics, was Amish’s mentor.

The goal of his research project at Mayo was to identify and target molecular mechanisms that enable select individuals to tolerate infectious pathogens, whereas others exhibit lethal responses, such as sepsis. Utilizing network-approaches, Amish and his team were able to identify targets that may attenuate host-induced pathophysiology. These genes are implicated in, for instance, tissue repair and cell migration. This work will guide the development of new therapies that will help treat individuals exhibiting lethal responses to infection.

Amish graduated early, in December 2016, and will be returning to Mayo Graduate School with support from the Graduate Research Employment Program to continue with Dr. Li on a multi-institutional, DARPA-funded project on host tolerance.

Jared Madden
Molecular and Cellular Biology, Class of 2017

Like all SURFs, Jared wanted to become acquainted with different and interesting clinically translational research at one of the best research institutions in the world. He definitely experienced this.

At Mayo, Jared worked in the Kogod Center on Aging under Nathan LeBrasseur, PhD. He investigated the resiliency effects of lifespan increasing drugs on aged mice that underwent dehydration. He measured the changes in stress response in blood and urine osmolarity, body composition, and blood hormone levels. Jared hypothesized that after administration of lifespan enhancing drugs, aged mice will show more resilience to a dehydration stress challenge compared to vehicle intervention mice. One of the most interesting experiences of his research was working with an Echo MRI machine that gives the percentage of lean vs fat vs water mass of a mouse in 90 seconds. Jared also used a CT machine that provided a fantastic 3D picture of the skeletal system in mice.

Jared’s advice to future SURFs? “Don’t be afraid to ask your mentor questions mentor and let them know what you want to get involved in or exposed to.”
Madelyn cites the techniques she learned and connections made in Rochester as extremely valuable. She says the SURF program was a huge help in figuring out what she wants to do in the future, and encouraged her about the possibilities for advancement within the medical field.

Akash applied to the SURF program because he wanted to work with recognized scientists and physicians to gain hands-on experience with cutting-edge research projects, develop and promote the information that drives therapeutic applications and physiological studies, and connect his experience with his future goals.

During his ten weeks at the Mayo Clinic, Akash worked with Jason Doles, PhD, assistant professor of biochemistry molecular biology. His project studied cancer cachexia, an energy-wasting syndrome that leads to substantial weight loss, muscle atrophy, and fatigue, primarily from the depletion of skeletal muscle and the interplay between circulating cachectic factors and the microenvironment. While cachectic factors are primarily associated with catabolic muscle breakdown, their effects on anabolic muscle pathways is less defined and poorly understood. The overall goal of Akash’s project was to understand how muscle stem cell dysfunction contributes to cancer-associated muscle wasting (cachexia). Dr. Doles’s research lab at Mayo Clinic plans to utilize the data Akash collected during the project.

Madelyn’s summer project involved engineering and testing new skin therapeutic platforms using gold nanoparticle bioconjugation and small molecule inhibitors applied topically, in the form of a cream. These were used to treat sunburn and prevent long term effects of radiation damage such as metastatic melanoma and skin aging. The platform, once optimized, has the potential to be extended to other more severe skin disorders such as psoriasis or rosacea that currently do not have a cure.

An undergraduate student in Professor Andrew Smith’s bioengineering lab, Madelyn is continuing her research on the creation of a live cell imaging platform for better understanding cancer metastasis. She wants to incorporate some of the therapeutic techniques she learned as a SURF to this cancer-related project.

In 2016, the Alliance funded an additional two SURFs to undertake research projects at the Mayo Clinic campus in Jacksonville, Florida. Maria Mihailescu and Shreya Santhanam were the first Illinois students to spend their summer at the Florida campus, doing research on the biology and genetics related to Parkinson’s disease. Read more about their experience in the Fall 2016 issue of Neuromatters, at healthinitiative.illinois.edu.
Talented Trio Comprises the First Group of Technology-Based Healthcare Research Fellows

Congratulations to Arjun Athreya, Faraz Faghri, and Yogatheesan (Yoga) Varatharajah, recipients of the inaugural Mayo Clinic and Illinois Alliance Fellowships for Technology-Based Healthcare Research.

Beginning in fall 2016, this fellowship gives two years of support for University of Illinois graduate students conducting research on new technologies and clinical tools aimed at advancing individualized medicine. Areas of interest include high performance computing, big data, software development, imaging, nanotechnology, point-of-care diagnostics, bioinformatics, systems biology, genomics, and tissue engineering. Graduate students from the UI departments of computer science, electrical and computer engineering, and bioengineering are eligible to apply. The fellowship includes a $30,000 stipend, coverage of tuition and select fees, a $5,000 research and travel allowance, and requires the student spend one year at Mayo Clinic in Rochester, Minnesota, doing mentored clinical translational research.

One of the three fellows, PhD candidate in electrical and computer engineering Arjun Athreya, is already well acquainted with the Mayo Clinic Center for Individualized Medicine and many of its clinicians and researchers. Athreya has spent two previous summers in Rochester as a biomedical informatics intern, working with Mayo Clinic scientists to support pharmacogenomics research.

Athreya says his goal during his fellowship is to bring about breakthroughs in both science and technology, driven by intricate complexities in biological challenges and important diseases such as depression, cancer, and diabetes.

“From my limited exposure to this domain, it has become very clear to me that central to the success of advancement in healthcare research is a fantastic interdisciplinary team of mentors and access to top quality datasets and computational infrastructure,” says Athreya.

Athreya’s PhD advisor at Illinois, Professor Ravi Iyer, and Dr. Liewei Wang and Dr. Richard Weinshilboum from the Mayo Clinic will mentor and monitor his development of a predictive model that uses a game theory approach to tell whether a patient will respond to drug treatment, given their genetic biomarkers.

“The interaction facilitated by this fellowship is priceless, and early results of this model are very promising, which tell us that we are moving in the right direction,” says Athreya.

Applications for the Fellowships for Technology-Based Healthcare are accepted year-round. Detailed information on how to apply can be found in the UI Graduate College Fellowship Opportunities Database, or at mayoillinois.org.
From this conference’s humble beginnings in 2010, the University of Illinois at Urbana-Champaign has been a collaborating partner and joint sponsor of the Mayo Clinic hosted event. Each year, the conference continues to diversify and grow, and 2016 was no exception. These images give a snapshot of the leading-edge event.

Kathy Giusti spoke about her first-hand experience as a cancer patient, the impact of expediting research, and provided key takeaways she has learned as the founder of the Multiple Myeloma Foundation.

Nearly 20 industry exhibitors were on hand to talk about their individualized medicine expertise, and more than 75 investigators presented a poster summarizing their research.

The conference provides ample space and time to comfortably collaborate with colleagues.

Mark your Calendar
Registration opens this spring. Want to present your research at the 2017 conference? Visit individualizingmedicineconference.mayo.edu for abstract deadlines and details.

Save the Date
Registration opens this spring. Spots are limited! Visit go.illinois.edu/computationalgenomics to learn more.
What Is the Mayo Clinic & Illinois Alliance?
The Mayo Clinic and Illinois Alliance for Technology-Based Healthcare is a group of faculty researchers, scientists, physicians, and students at Mayo Clinic and the University of Illinois at Urbana-Champaign who collaborate in a broad spectrum of health-related research. Established in 2010, the Alliance combines the strengths of both institutions to facilitate unique educational programs and advance clinical and translational research and technology innovation.

The Mayo Clinic & Illinois Alliance Purpose
The Alliance advances the promise of individualized medicine. Precision (or, individualized) medicine is uniquely informed by an individual's genomic make up, environment, and lifestyle. The promises of precision medicine include better diagnoses, earlier interventions, customized treatment plans, and more-efficient drug therapies. Combining expertise in genomics, computing, and nanotechnology, the Alliance pushes precision medicine forward.

Disease and Health Conditions Focus
Mayo Clinic and Illinois Alliance research and technology development teams are focusing on advances in myriad health areas. These are current research areas, though the list is continually expanding.
- **Cancer**—glioblastoma, prostate, colorectal, and breast cancers
- **Autoimmune Diseases**—multiple sclerosis, rheumatoid arthritis, and celiac
- **General Health Conditions**—reproductive health, obesity, aging, and heart failure

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