

BREAKTHROUGH



Spring 2014

Volume IV, Issue 2

*Tufts Undergraduate
Science Journal*

Science Abroad in Santiago, Chile

Laboratories, Languages, Latin America

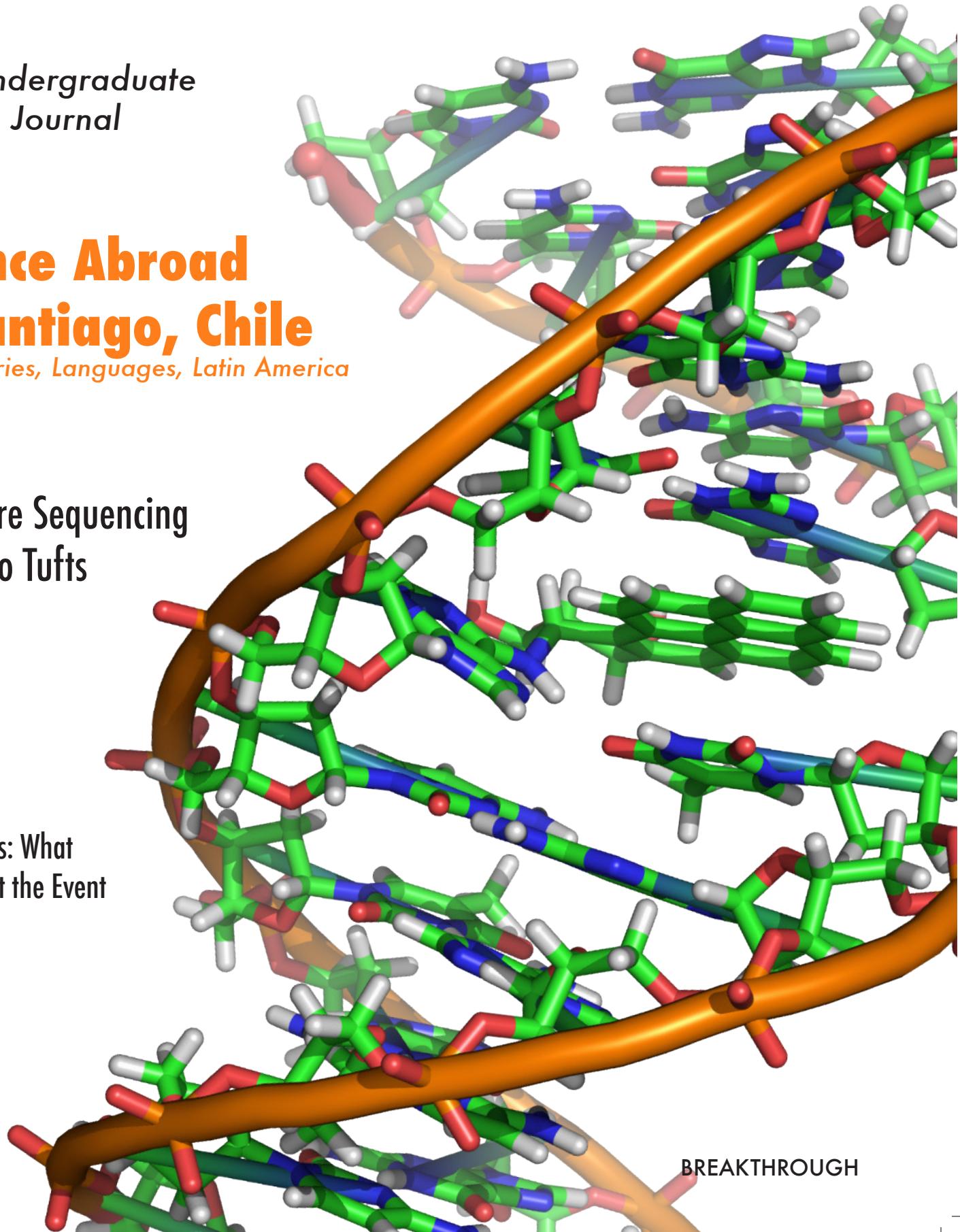
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FROM THE EDITORS

Dear Readers,

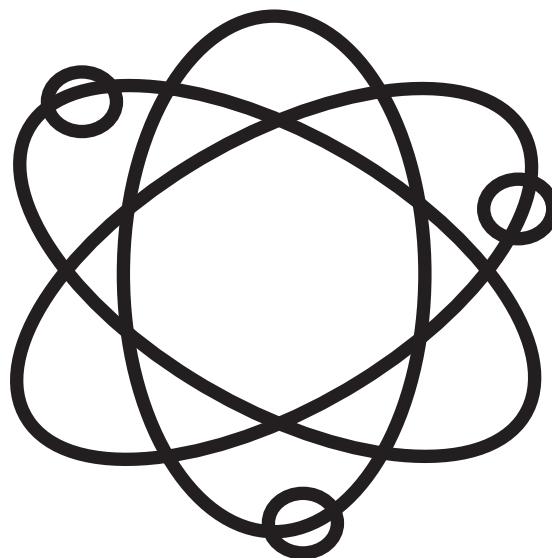
Welcome to our Spring 2014 issue of Breakthrough Magazine! We are happy to share this set of scientific articles, illustrations, and experiences that has been collected over the past semester. Additionally, we are proud to share our first issue printed in full color!

Our group has seen exciting changes in our publication process. Most of the articles' authors have extended their commitment into laying out their own articles. This method has allowed our writers to be in full control of their articles from beginning to end. We are both extremely impressed and thankful to our whole team for the work they have put into this magazine!

Inside this issue, you'll find a larger focus on Tufts research than our Fall publication. Outside of Tufts research, we have also included an article about one student's experience as a science major studying abroad in Chile, as well as an article written and sent to us from a student currently in Hong Kong.

Thanks for grabbing our Spring issue and we hope you enjoy reading it as much as we have enjoyed writing it!

*Julia Hisey and Stephen Walsh
Co-Editors-in-Chief*



*The opinions expressed in each article
are those of the author and do not
necessarily reflect the opinions of the
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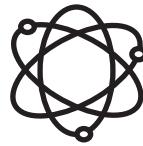
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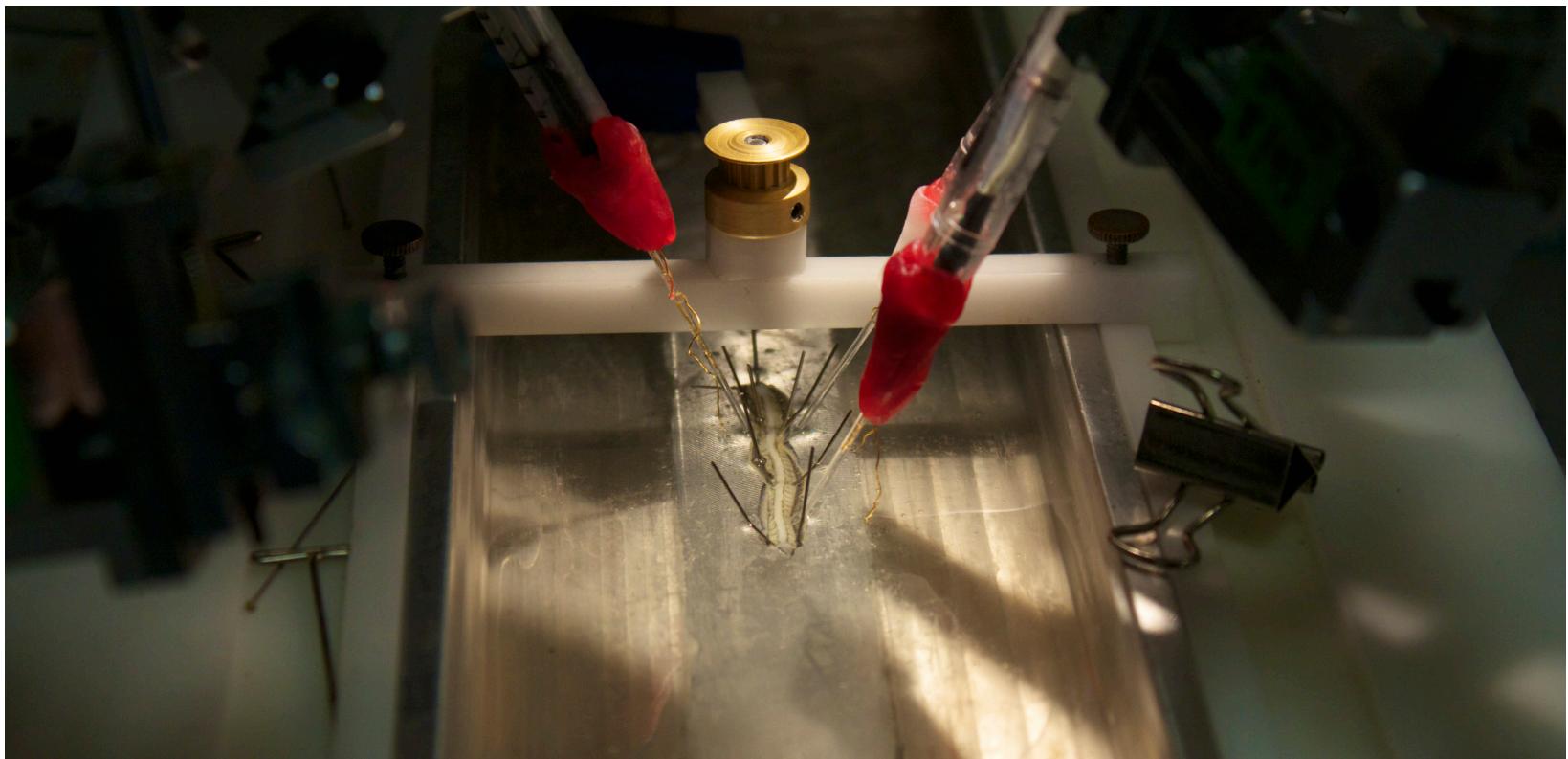


Image Courtesy of Alex Azan

The Science of Swimming

Take a look outside and you will see humans running, birds flying through the air, and fish swimming. Despite how simple it feels to move our bodies, in reality the process of locomotion is a complex concert among systems within the body and between the body and its environment. Dr. Eric Tytell of the Tufts biology department is researching the details of these relationships to better understand the biomechanics of fish and other animals – including humans. Dr. Tytell's research has the potential to benefit a wide range of fields, from robotics to medicine.

Dr. Tytell became involved in biomechanics as an undergraduate at the University of North Carolina when he became interested in the work of Dr. William Kier. He received a fellowship to work at the Woods Hole Oceanographic Institute with Mark Grosenbaugh to study the fluid dynamics of fish swimming. While he was completing his PhD at Harvard University, he realized that while much of the fluid mechanics of fish swimming was understood, the ways in which fish responded to the forces acting on them was still relatively unknown. This led him to his current research: how the nervous system interacts with the mechanics of the body.

To study how fish control their movements in an

unsteady flow, Dr. Tytell's lab has developed a system that creates vortices. Reflective particles are added to the water and a laser beam sheet is used to light the particles. By filming the particles as they move, the lab is able to track how the water moves. He also uses high speed cameras to film fish swimming and is hoping to automate the process for greater efficiency. By implanting electrodes into the fish, the lab is able to measure the fish's muscle activity. Dr. Tytell is also developing accelerometers that can be implanted in the fish. "Like in your phone, how it knows you're moving around, we're hoping to have the same knowledge about our fish. That will help give us some nice data of how the fish is actually moving in three dimensions." Currently, three-dimensional analysis is difficult and laborious to do.

“ The ways in which fish responded to the forces acting on them was still ” relatively unknown...

Dr. Tytell's lab is studying central pattern generators, which activate muscle. These neural circuits are not only present in fish, but also in a wide variety of organisms, including humans. Specifically, he is looking at the spinal cords of lamprey eels, the most primitive existing vertebrate. "What's fun about it is that you can dissect out a lamprey's spinal cord, put it in a dish with oxygenated saline and an excitatory drug and the circuit will start swimming." This enables them to measure the output of neurons. Unlike humans, whose main sensory receptors are in our muscles, lampreys receive sensory inputs through their spinal cords.

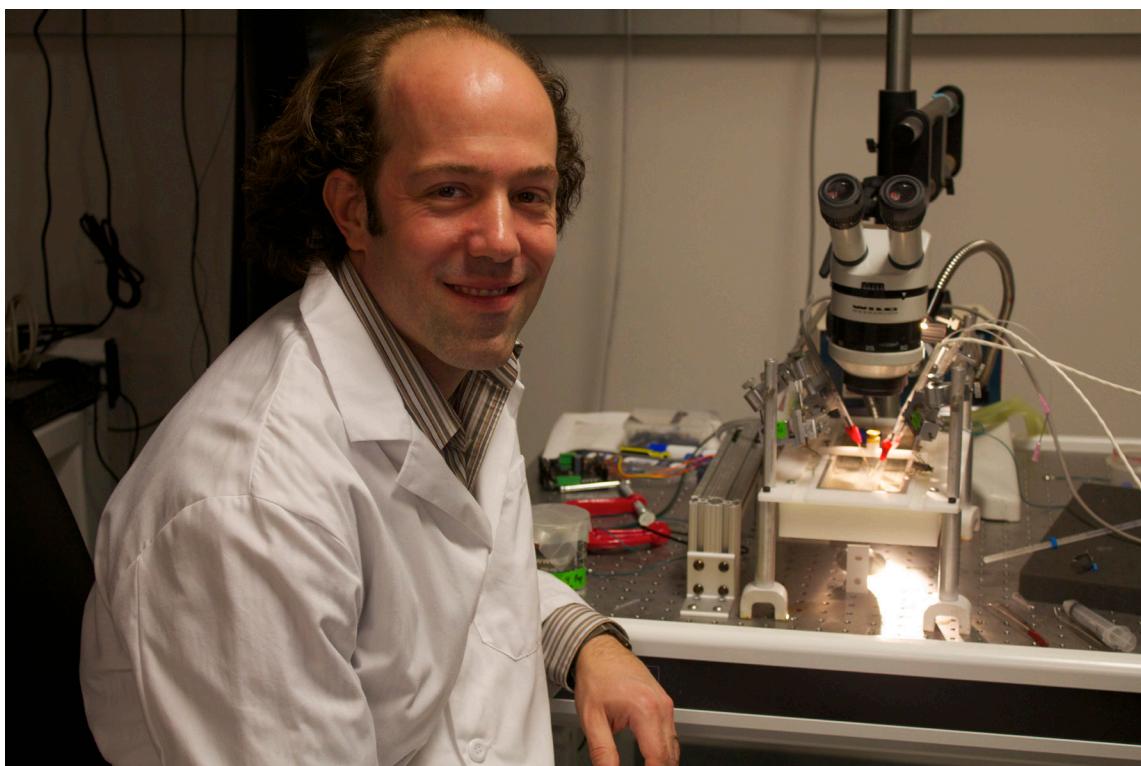
Because of this, Dr. Tytell is able to replicate swimming and see how the spine responds. Dr. Tytell hopes to combine all of these different experiments to give a more detailed understanding of the neural-mechanics of swimming.

However, while they are studying the components of fish biomechanics in isolation in the lab, in reality the process is much more complex. The animal both acts upon and reacts to its environment. "Thinking about these complex feedback loops is really challenging. That being said, it's a really interesting and exciting problem to explore."

In continuing his research, Dr. Tytell is planning on looking at unsteady behaviors in fish. Previous research has looked at how fish behave in flow tanks, but to be more realistic, he is investigating how fish accelerate. Additionally, future research at Dr. Tytell's lab will look at what role does muscle play in stabilization.

Other areas of study are using Dr. Tytell's findings to improve their own research. The "growing field of bioinspiration in engineering" turns to nature for help designing robots. A better model of swimming can help engineers design better aquatic robots. This research also has medical implications. Lamprey larvae can recover from having their spinal cords clipped; Dr. Tytell has been collaborating with Dr. Jennifer Morgan at the Marine Biological Laboratory in Woods Hole to study this phenomenon and how it can be applied to treatments for spinal cord injuries. These are just a few examples of the impact the study of the biomechanics has on science. We continue to make advancements in many areas as we study the how and why of even the smallest motion in the smallest of fish.

Story by Becca Lachs, a freshman majoring in Biology.



Courtesy of Alex Azan

Beyond Rulers:

Measuring the Distance in Protein-Protein Interaction Networks

Proteins are responsible for roughly half of the human body's dry mass (1). These macromolecules perform a variety of functions, including reaction catalysis, DNA replication, transportation of oxygen and other molecules, and hormonal regulation. They participate in almost every cell process and are essential for life.

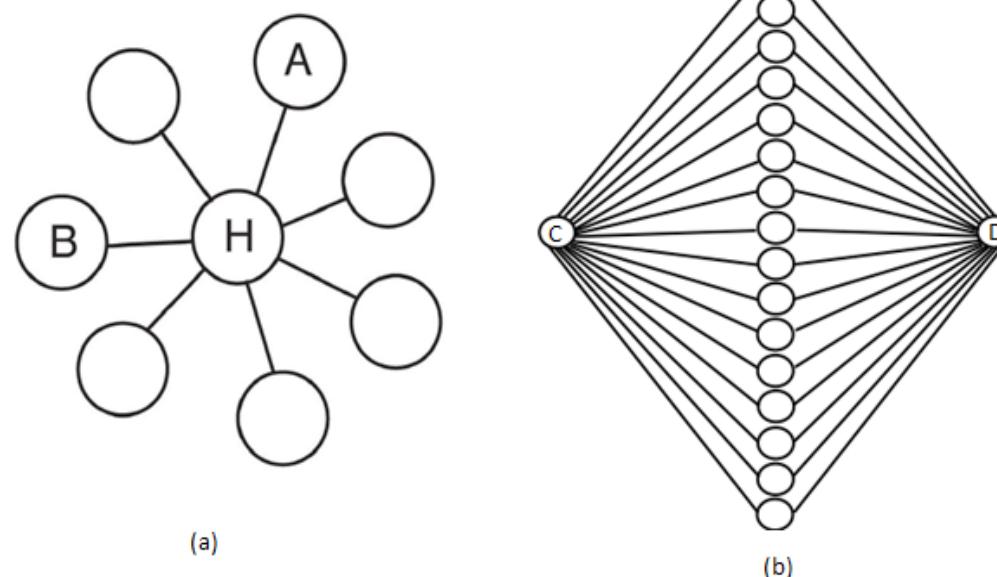
However, a single protein rarely acts alone. When proteins bind together, it is called a physical protein-protein interaction (PPI) (2). Biological research often uses known protein function along with their known interactions to predict the function of proteins whose function is currently unknown. This is called "guilt by association": if two proteins interact with a common protein (or a group of common proteins), they are more likely to have similar functions. Most often, this analysis is done using graph models, where the vertices are proteins and the edges are interactions. Such a graph is called a PPI network (Figure 1).

In their October 2013 article "Going the Distance for Protein Function Prediction: A New Distance Metric for Protein Interaction Networks," a team of computer science researchers from Tufts University and Boston University note that the standard

distance metrics in PPI networks may not paint the best picture of similarity in protein function. Most PPI networks are "small world": a particular protein (vertex) can be reached from any other protein (vertex) via a path consisting of only a few edges. This becomes a problem when trying to predict protein function based on what other proteins are short distances away, since every protein is close to every other protein.

For example, proteins A and B in figure 1a are a distance of two away. Proteins C and D in figure 1b are also a distance of 2 away. Proteins C and D have many common neighbors, meaning that they interact with many of the same proteins and are likely to have similar functions. However, in figure 1a, protein H is a "hub". It interacts with a lot of proteins, including A and B. That doesn't necessarily mean that the function of H is similar to A or B, or that the function of A is similar to B. But, because they are close to each other in the physical sense, protein function predictions based on spatial distance alone would suggest that A, B, and H have similar functions.

To compensate for this, the team of researchers presented a new metric for measuring distances between proteins in a



A simple PPI network. The circles represent proteins, and the lines represent protein-protein interactions (3).

Can a protein's neighbors predict its function?

PPI network. Rather than simply count the shortest number of edges required to get from protein A to protein B, the Diffusion State Distance (DSD) between proteins A and B is based on the similarities in the likelihood of reaching other proteins in the PPI network when taking random paths starting at proteins A and B.

Pretend there are n proteins in a PPI network. In figure 1, $n = 8$. Label each protein in the network from 1 to n – which protein has which number does not matter, so long as each has a unique index. Choose a random path length k . Starting at protein A, count the expected number of times that a random path of length k reaches protein 1. Do the same for protein B. Take the absolute value of the difference between these two numbers. Repeat this process for the expected number of times that random paths of length k starting from proteins A and B will reach protein 2, and protein 3, and so on through protein n . Then add all of these absolute values up. This is the DSD for proteins A and B. The researchers note that $k = 5$ produces results that are close to the limit of the new metric as k approaches infinity.

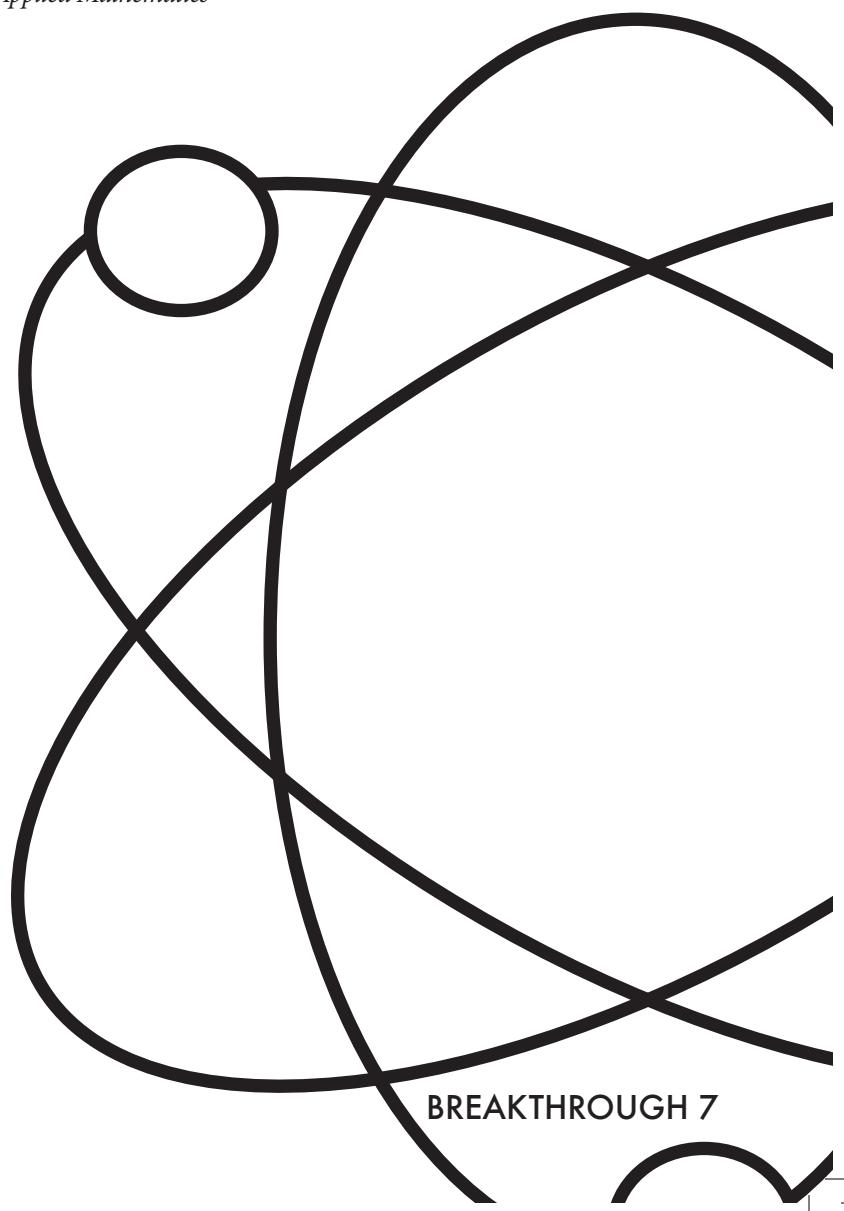
This metric is an improvement upon the shortest path metric because it identifies proteins with many similar neighbors as more functionally similar. If the expected number of times that a

random path of length k reaches protein 1 from protein A is close to that from protein B, then their difference will be small. If all such differences are small for proteins A and B, then their DSD will be small, as well. As the research team pointed out, “DSD recognizes that nodes [proteins] having large common low-degree neighborhoods are highly similar and correctly identifies functionally similar node pairs, and does so in situations where shortest-path distance fails” (3).

The next step in this research is to align graphs to each other to make them as similar as possible. This will allow for more improved protein function prediction, but would also allow researchers to break the privacy settings on social media networks if given access to their friendship networks. Professor Hescott has authored a paper on this, but it is unpublished at this time.

Story by Ashley Hedberg, a junior majoring in Computer Science and Applied Mathematics

“ DSD recognizes that nodes [proteins] having large common low-degree neighborhoods are highly similar and correctly identifies functionally similar node pairs, and does so in situations where shortest-path distance fails ”



Nanopore Sequencing Comes to Tufts

Graduate student in Mirkin laboratory is one of first to use Oxford Nanopore's strand sequencing technology

Ryan McGinty is a third year PhD candidate in the Mirkin Laboratory at Tufts University. After completing his undergraduate education at Boston College, he continued his biology career at the Broad Institute in Cambridge, MA. There, he performed genotyping arrays to find genetic variations linked to diseases in human populations. This experience contributed to McGinty's passion for advances in sequencing technology -- he currently studies the "role of genetic variation in contributing to the expansion of repetitive DNA sequences, which are known to be responsible for numerous human diseases" (Ryan McGinty).

Like many, McGinty had been hearing exciting about Oxford Nanopore's "strand-sequencing" platform and was eager to partake in an opportunity to be one of the first to obtain a Nanopore. Oxford Nanopore's MinION Access Program (MAP) has made the nanopore technology pre-commercially available to scientists for open development of this sensing technology. The structure of MAP is similar to a commonly-used strategy in the software development world, such as when Xbox video games have been given to an exclusive group of volunteers for open testing. Similarly, after an application process, McGinty was one member of an exclusive group invited to take part in the MAP program.

In contrast to the current next-generation sequencing platforms, the Nanopore functions on the order of a single molecule and can sequence much longer DNA fragments than are possible now. One of the most exciting characteristics of the MinION is that it fits in the palm of your hand and can rest on any surface while plugged into your computer's USB port. The nanopores themselves are cylindrically shaped and have a diameter

of only a few nanometers. An array of nanopores are embedded in a synthetic membrane and an electric potential is applied across the membrane. A single DNA molecule is unwound and threaded through each nanopore, one base at a time. Based on the nucleotide-base-dependent differential disruption of the electric potential at each pore, the DNA sequence can be determined. An array chip allows for many DNA strands to be sequenced at the same time (1).

In his proposal to Oxford Nanopore, McGinty touched on the implications this technology could have for scientists who are not focused on sequencing. Like McGinty, many researchers use sequencing technologies in order to answer a larger question, and often send their samples to a core facility or collaborator for sequencing. The MinION can make sequencing much more accessible for these scientists, allowing them to easily perform sequencing in their

own labs. McGinty comments, "With something that's the size of a flash drive, it could potentially wind up on every benchtop in every lab." He also adds that the technology may become accessible to scientists without an extensive background in molecular biology or sequencing, extending the reach of sequencing to other fields.

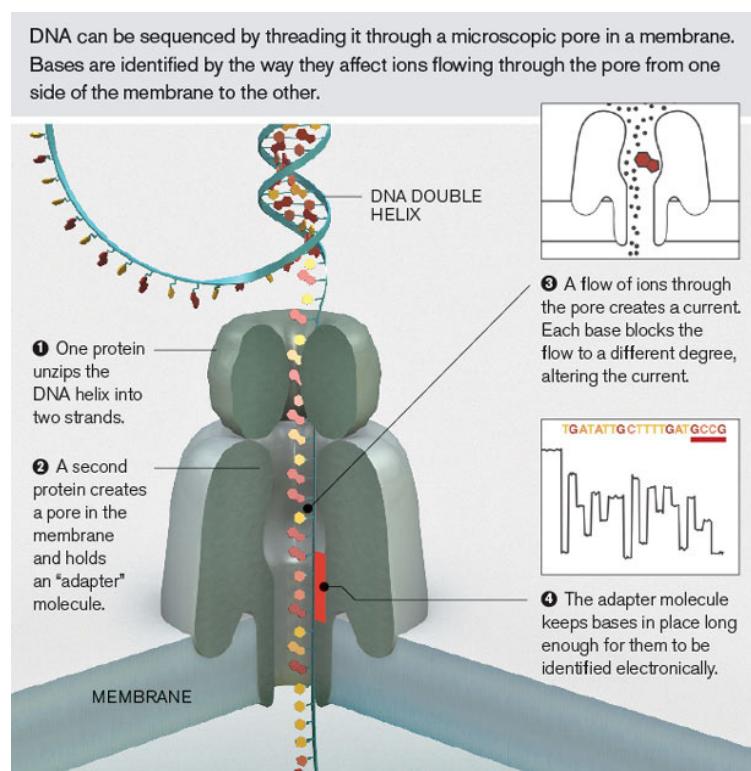
The Mirkin laboratory uses *Saccharomyces cerevisiae* as a model organism to study DNA repeat expansions. Many of the previous generations of sequencing technologies were designed for large scale experiments such as human genome sequencing; however, McGinty's sequencing needs fall on a much smaller scale. To get a sense of the difference in magnitude, the yeast genome is 250 times smaller than the human genome. Oxford Nanopore offers a great technology for individual researchers who lack the manpower of a core facility to conduct sequencing for their specific needs.



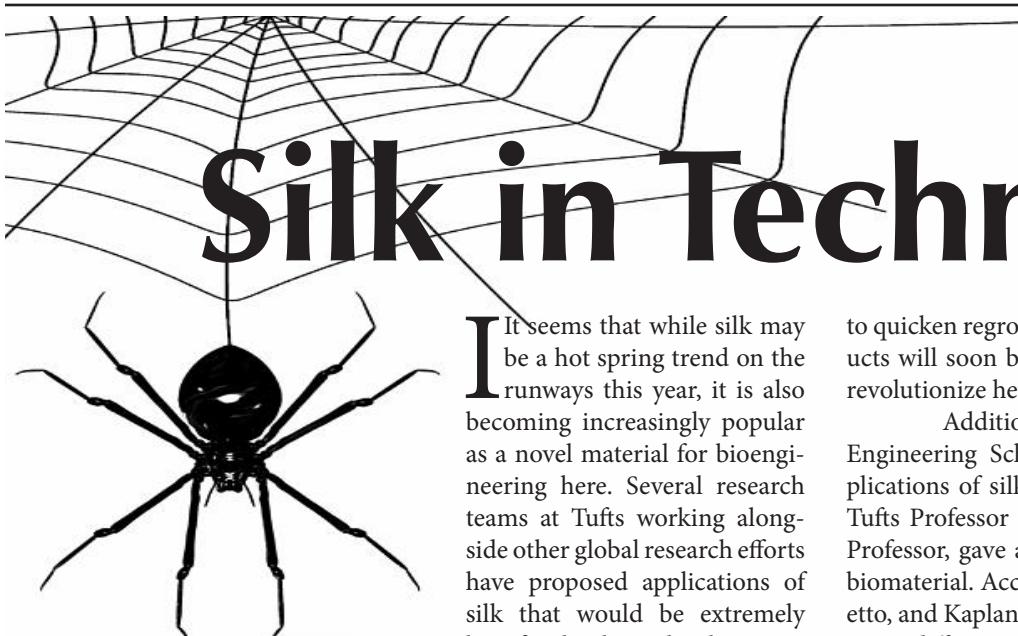
Courtesy of Alex Azan

In addition, most current sequencing technologies produce short DNA fragments around 100 base pairs long, which are then stitched together by looking for short overlapping sequences. Often times, repetitive portions of the genome are longer than 100 base pairs, so researchers like McGinty have no way of knowing exactly how long the sequences are or where they fit into the genome. With the Nanopore, McGinty will be able to read tens of thousands of bases at a time, which will allow him to see how long the repeat sequences are and where they fit into the genome (based on the nonrepetitive DNA flanking the repeats). McGinty plans to use the Nanopore to conduct whole genome sequencing for his studies of genetic modifiers for repeat expansion diseases. The longer "read length" could also ease challenging tasks like assembling genomes or mapping large-scale mutations such as translocations, deletions, or insertions. The potential is enormous; now it's up to MAP to see if the reality lives up.

Story by Julia Hisey, a senior majoring in biology.



Courtesy of Technology Review



It seems that while silk may be a hot spring trend on the runways this year, it is also becoming increasingly popular as a novel material for bioengineering here. Several research teams at Tufts working alongside other global research efforts have proposed applications of silk that would be extremely beneficial to biotechnology.

A team of researchers at the Tufts School of Engineering along with Beth Israel Deaconess Medical Center have developed fixation devices for broken bones out of pure silk protein. Traditional screws and plates for setting broken bones as they heal are made out of metal, which means they are restrictive during the healing process must be removed at the end of treatment (1). The proposed silk screws and plates functionally similarly to the current metal technology, yet would have the added benefit of dissolving naturally so that doctors would no longer have to remove the bone supports with a surgical procedure. David Kaplan, the current Chair of the Biomedical Engineering and Stern Family Professor of Engineering, has been working with silk as a potential biomaterial for many years. According to Kaplan, silk could be used to transfer antibiotics or other pharmaceutical products to the bone

to quicken regrowth and strengthen development (1). These products will soon be tested in clinical trials that if successful would revolutionize healthcare.

Additionally, the Omenetto and Kaplan labs at Tufts Engineering School have been developing the biomedical applications of silk for several years. In 2008, Fiorenzo Omenetto, Tufts Professor of Biomedical Engineering and Frank C. Doble Professor, gave a TED talk on the amazing potential of silk as a biomaterial. According to an article published by Hu Tao, Omenetto, and Kaplan, silk protein can self-assemble and can be used in many different material formats, making it an extremely versatile polymer (2). Much of the research is being done to fully understand the self-assembly process and to better take advantage of the biological phenomena. Furthermore, silk assembles such that it can enclose and maintain the function of other biomaterials (2). Both labs have made significant contributions to research on the biological applications of silk, with the Omenetto lab focusing on silks' optical properties and the Kaplan lab on assembly and tissue engineering.

It seems that opportunities for silk can only become more expansive as further research is focused on the applications of this amazing material. From runways to research, silk is a material that may always be in fashion.

Story by Jennifer Hammelman, a sophomore majoring in computer science and biology.

Science Abroad: Santiago, Chile Edition

Laboratories, Languages, Latin America

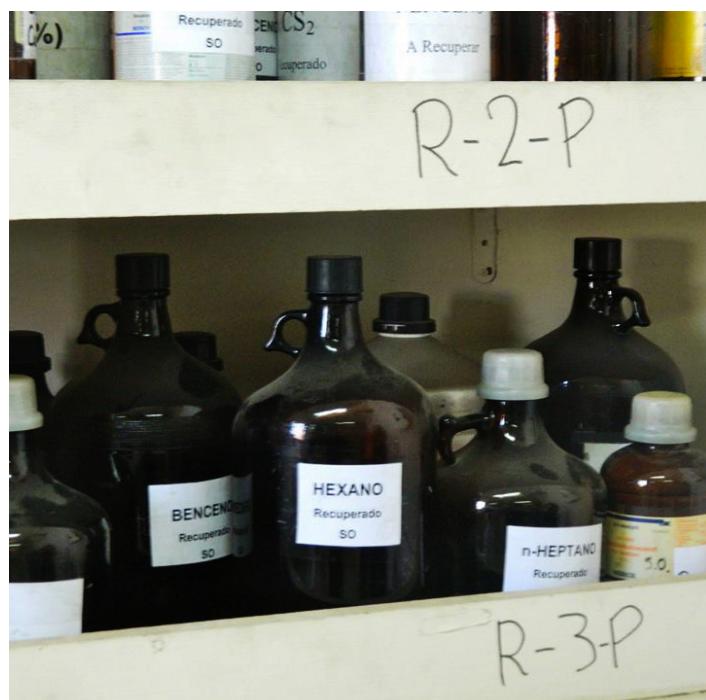


I never thought I would learn so much about science by studying abroad in Santiago, Chile. I was surprised from my first day. My first course, Science Technology and Chilean Society, was an elective in the Engineering Department at the University of Chile. The professor began by posing the question, "How many of you would like to study in the United States or Europe in order to obtain your graduate degree?" At least a third of the students raised their hands. I was stunned. I have always deeply appreciated my education, but after my experience in the Chilean science world I am able to understand my education and career opportunities in a whole new way. During my time abroad, I took two classes in the Engineering Department and worked part-time in an organic chemistry lab in the Chemical and Pharmaceutical Sciences Department. Though I'd heard others say it before, it was still surprising how much learning I did outside the classroom in my time abroad. Throughout my time in the science departments at the University of Chile, I had opportunities to speak to undergraduate and graduate science students, and a lot of what I heard surprised me.

One girl asked me if my parents approved of my decision to pursue a career in the sciences. I was confused, so I asked her why she would say that. She said it was not looked upon favorably in Chile to choose a career in science because it was uncertain as to whether you would find a job, and therefore you almost had to be willing to go overseas to get a job. Throughout Science, Technology, and Chilean Society, I learned a lot about the exportation of science and scientists from Chile (and most of Latin America) to the United States and Europe. This is in part because the so-called Western world has more money which scientific research requires. This idea was echoed by another Chilean friend of mine who switched her career of study from nursing to biotechnology. She told me that though her parents supported whatever she did, it was not a "good" idea in terms of getting a job. She said that she was willing to move outside of Latin America to work, and

really, that she would have to, if she wanted to get the best jobs.

Though I learned a lot by interacting with my classmates on the physical sciences campus, the best science experience I had in Chile was definitely working in the organic chemistry lab. I work in Dr. Bennett's organic chemistry lab here at Tufts, but working in a lab in Chile was a unique experience. The first time I met with the Principal Investigator of the lab, Dr. Ramiro Araya Maturana, a professor of Chemical and Pharmaceutical Sciences, something he said amazed me. He handed me a scientific article written in English. I asked him, "Do you write the papers in English and in Span-





ish?" I was confused that all the papers he read, including the one he gave me, were in English. He responded to my question in a puzzled tone that of course the papers were always written in English. If they were not, they would not be able to be published in the best scientific journals. Though his spoken English seemed proficient at best, his scientific papers were perfect (a million times better than what I could write). Though he had perfected his writing skills necessary for science publication, he rarely practiced his speaking skills.

At first glance Dr. Araya Maturana's lab looked very much the same as the one I work in at Tufts. There were rotary evaporator machines, plates used in Thin Layer Chromatography to analyze compounds, glass columns used for column chromatography, chemical bottles full of organic solvents, and glassware of all sorts. During my time in lab I conducted reactions of 2-methyl-1,4-benzoquinone with aniline in organic solvents, water, and solid phase mediums. One of Dr. Araya Maturana's current research interests is "green chemistry," a relatively new term that refers to a chemical research methods that are sustainable and minimize the use of hazardous substances. Near the end of my stay in Chile, he asked me to assist him in writing an article highlighting the "green" aspects of the experiments I had conducted. The basic reaction mechanisms used in his lab were the same ones I had seen in my introductory organic chemistry courses here at Tufts, and his group's primary aim is to create novel bioactive and medicinally relevant compounds just as we do in the Bennett Lab here at Tufts. At first glance the lab was the same, and in the end, it was the same. The actual materials, equipment, and theory were all the same. The difference, unfortunately, lies in the lack of a history of science cul-

ture in Chile and the related lack of funding. I couldn't have gained this sense of the necessary context for science research by going to Europe, for example, because it is part of the Western world. These problems, and their consequences, are not easily solved.

Despite my sense that not much was very different from Dr. Bennett's lab here at Tufts, Dr. Araya Maturana said as he showed me his lab for the first time, "I'm sure the lab at your university is much nicer than ours." He was joking, and yet, it was not a joke. He may have been embarrassed to show me his older equipment. I told him sincerely, with a smile, that the lab did not look any different from the one I worked at in Boston. He continually joked with me about this throughout my time there, and I don't think he ever really believed me. This reaction to my American perspective was recurrent. In every day life, in various contexts, people would assume I had the best in America and that I looked down on them for having less. It was an uncomfortable feeling, and I expected it to some degree when I chose to study in Latin America, but I never thought this a feeling would be so prominent in science.

One of the most important things I learned from this experience is that ultimately, the science (and pretty much everything else in Chile) is not that different from here in America. The same equipment is used, the same topics studied, and similarly passionate people are making discoveries that positively contribute to society. Though there are fewer resources devoted to science in Chile and less of a science culture in general, the science is the same.

Story by Emily Steliotes, a junior majoring in Chemistry.

Black Holes: What Happens at the Horizon?



Falling into a black hole is the ultimate demise - there is no escape by definition, not even if you could travel at the speed of light. Once you get too close to the singularity, a point of such high density that our laws of physics break down, extreme gravitational forces stretch you into spaghetti and then squash you into an infinitesimally small point. All that remains of you are tiny pieces of radiation released from the black hole. But before you reach this point, you must cross the black hole's event horizon, or the point of no return. Traditionally, it was thought that the event horizon held no special properties and that nothing much would happen to you as you crossed it. However, there is some evidence that you may actually be instantaneously terminated at what is known as a firewall at the horizon.

HISTORY: A PARADIGM IN QUESTION

Albert Einstein's seminal 1916 paper on general relativity proposed that matter warps space-time. Karl Schwarzschild found that if a spherical mass is packed inside a certain radius, the gravitational field has a peculiar behavior where some terms become infinite. In order to escape from the surface of a mass of that radius, you would need to travel at the speed of light. This boundary became known as the event horizon. Anything that enters it is doomed to encounter the singularity.

In 1974, Stephen Hawking applied quantum field theory to black holes (normally in the macroscopic realm) and showed that they should release radiation. His mechanism for this radiation assumed that pairs of quantum particles and antiparticles exist in the vacuum of space. If an antiparticle with negative energy falls into a black hole, the black hole's mass must decrease while the other particle flies off as radiation. This means small black holes decay over time as they release energy.

The discovery of Hawking radiation was paradoxical. It's

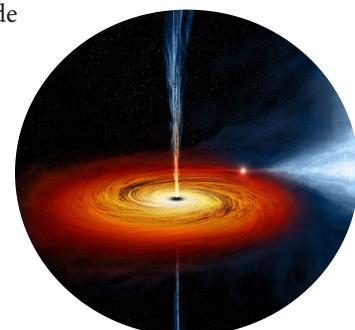
widely accepted that information cannot be lost in the universe. Additionally, a theorem named the "no-hair" theorem states that all black holes are characterized by just three parameters: mass, electric charge, and angular momentum. Any black holes with the same three values are indistinguishable, including the radiation they emit. This means that any information about the particles falling into the black hole is lost.

THE BET

Hawking insisted that his theory was correct and that quantum mechanics should be altered to accommodate it. Other physicists like John Preskill believed that the view of general relativity producing black holes needed to be rethought. The debate led to a public bet in 1997 between Hawking, Kip Thorne, and Preskill. The person who was right about whether information is lost would win an encyclopedia of their choice, from which, unlike a black hole, information is easily retrieved.

Meanwhile, Gerard 't Hooft and Lenny Susskind, while studying quantum gravity in the 1990s, discovered what is known as the holographic principle. This new idea said that the two-dimensional surface of the event horizon could encode information about three-dimensional space inside

it, much like a flat holograph creates a 3D image. When the black hole evaporates, the information is returned. Susskind and 't Hooft thus joined the war against Hawking's solution. In 2004, Hawking declared a rigorous mathematical



solution to the paradox. The mechanism he offered was that radiation escapes the black hole through quantum tunneling and could carry information out. He conceded that he was wrong and gave Preskill an encyclopedia on baseball. However, the information retrieved from a black hole is so garbled that he said it might have been more appropriate to give Preskill its ashes. Our thinking of black holes since then has rested on the principles of complementarity and “no drama”. No drama predicts that an observer falling into the black hole would not notice crossing the event horizon because there is no particularly strong warping of space or other special properties there.

Complementarity is demonstrated through thought experiments with a pair of entangled observers, Alice and Bob, who share all their information.

Because Hawking radiation carries information about the inside of the black hole as it escapes, Bob can sample the radiation and learn about the black hole from outside the event horizon. Say Alice now adventurously jumps inside the black hole and gets the same information. This duplication of information is illegal in quantum physics. Susskind showed that although Alice and Bob have the same information, it is impossible for them to communicate with one another across the event horizon. According to complementarity, information can be seen at two different places as long as it cannot be shared between the two observers.

DOWN THE WORMHOLE AGAIN

In July 2012, Ahmed Almheiri, Donald Marolf, Joseph Polchinski, and James Sully (referred to sometimes as AMPS, according to their initials) published a paper that revived the debate yet again. They claimed that one of three things must happen: information is lost, some new laws of physics are required outside the event horizon, or there is a firewall at the

event horizon and anything falling in would be immediately terminated.

The paradox they describe is this: If information preservation is correct, then outgoing Hawking radiation is entangled with the black hole (in order to carry information out). Now let's say that Alice

is at the event horizon and is about to jump in. Since this is a normal region of space, quantum physics says that Alice should see a bit of radiation entangled with something else on the other side of the horizon. However, this would mean that the radiation is entangled with two separate entities, which is forbidden in quantum mechanics. So either we must give up information, or the equivalence principle actually breaks down at the event horizon and it behaves like a singularity and poor Alice never makes it to the black hole.

Some physicists argue that a stronger version of complementarity, in which Alice's and Bob's observations match,

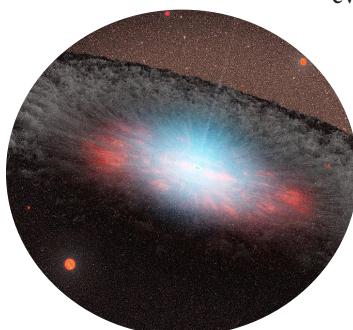
could resolve the paradox. However, it was found that Alice and Bob could, in principle, communicate conflicting measurements and therefore complementarity is not enough.

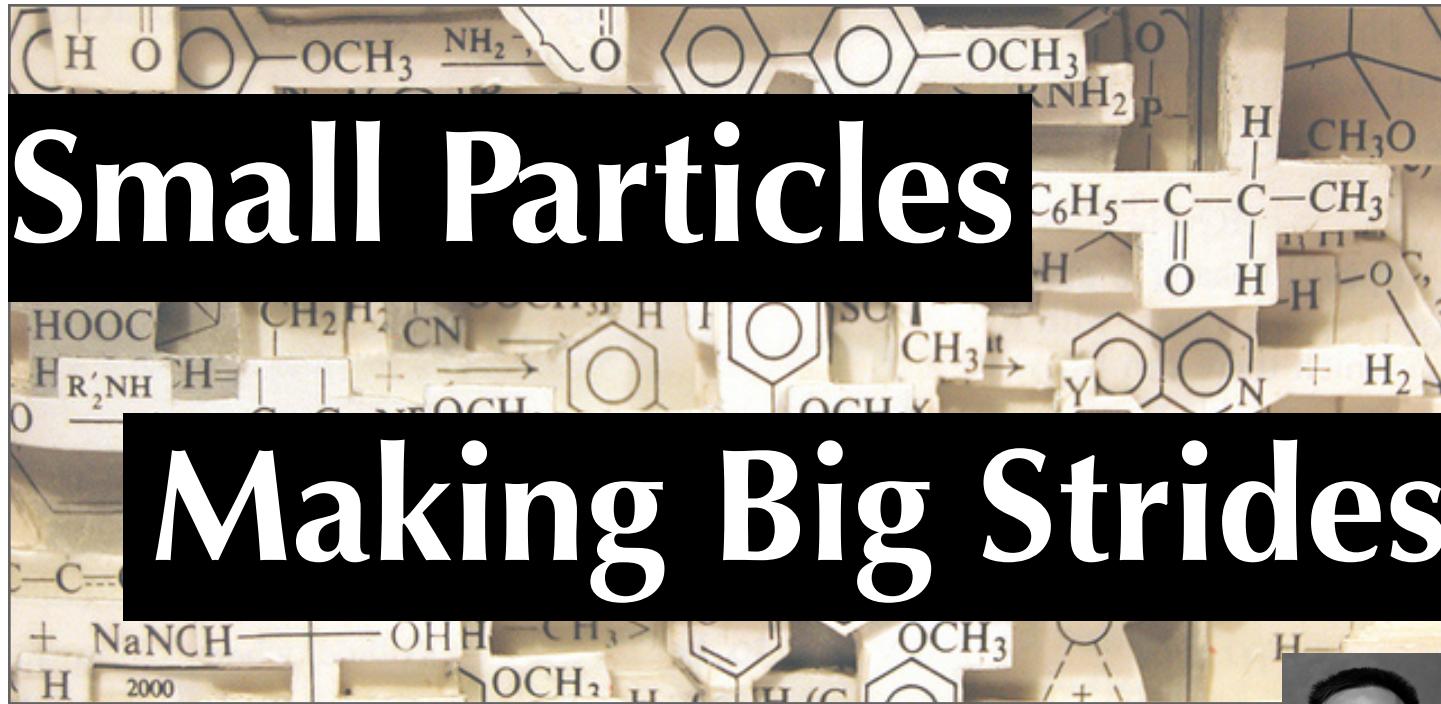
Some, such as Raphael Bousso, would rather modify quantum theory than give up unitarity and allow information to be lost. Alternatively, physicists could give up equivalence and say there is a firewall. Leonard Susskind and Juan Maldacena recently proposed a solution involving wormholes, hypothetical curves in space-time that connect two distant locations. They build on a theory that all entangled pairs are connected by a wormhole, or Einstein-Rosen bridge. Therefore, the black hole is connected to all the Hawking radiation that has left it. They believe that these wormholes would smooth out space-time at the

event horizon enough to avoid the firewall; however, there is no observational evidence that they exist.

PERCHED ON A PARADIGM HORIZON?

The firewall debate is far from over. None of the proposed options seem appealing, since they all involve altering a tenet of physics that had previously been widely accepted. One of the reasons the paradox put forth by AMPS is so difficult is that we do not yet have a unified theory of how gravity works on a quantum scale. Black holes represent a regime where both general relativity, which describes gravity over large areas of the universe, and quantum mechanics, which describes the behavior of tiny subatomic particles, apply and come into conflict. Just as the information paradox clarified our lack of understanding and led to the holographic principle and complementarity, this paradox illuminates the problems that a theory of quantum gravity will need to solve. Whatever the solution is, physicists agree that it will have radical consequences for our understanding of the universe. Story by Isabel Yannatos, a junior majoring in Physics.





Small Particles

Making Big Strides

Professor Qiaobing Xu's Nanoparticles as a Novel and Innovative Platform for Drug Delivery



Cancer treatment has been and remains to this day an arduous and frustrating process, yet has become more and more of a necessity over the years as the human lifespan has increased, thus increasing the likelihood of developing cancer. Cancer cells divide uncontrollably in the body and are extremely resilient, and tumors eat up nutrients that the rest of the body's tissues are then unable to compete for. Currently, chemotherapy drugs target rapidly-dividing cells in the body by using cytotoxic molecules to inhibit key cell-division pathway proteins. However, these drugs often create harmful side effects including hair loss, immunodeficiency, and gastrointestinal problems, since the inhibitors can't differentiate between healthy rapidly-dividing cells and cancerous cells.

Cancer cells overexpress certain proteins and nucleic acids in order to promote their uncontrollable division. Extensive research has been done to uncover the specific protein and nucleic acid sequences overexpressed in common types of cancers, and drug developers are using that knowledge to target those cancer cells, creating a therapeutic technique more specific than the in-

“Data from Xu’s lipidoid library helps gain insight into the design of a nano-carrier that can send specific oligonucleotide sequences into cancer cells.”

discriminately killing off all rapidly-dividing cells. Companies like Amgen and Biogen have developed peptide-based drugs that use antibodies to treat cancers. Other companies are exploring a method to target overexpressed nucleic acid sequences in order to halt translation of the mRNA into proteins that are necessary for tumor

cell growth. These drugs can be synthesized to target any protein or nucleic acid sequence of interest, increasing drug-binding specificity by directing therapeutics to those distinct biomarkers. This allows cancer patients to experience limited side effects.

One challenge that researchers continue to encounter is efficiently delivering therapeutics to the tissue or organ in question. Administration routes include direct injection, oral capsules, and infusion pumping, a method in which drugs are pumped directly into the circulatory system. Unfortunately, cancer cells can go through metastasis, or migration, into another part of the body, which makes direct injection only a short-term treatment. A big obstacle that oral capsules and infusion pumping face is efficiency; as the drug moves through the body trying to find its target, it can flow into or get absorbed by other tissues, lowering the amount of medication delivered to the desired tissue.

Professor Qiaobing Xu in the Tufts Biomedical Engineering Department is pursuing a novel and innovative nanoparticle solution for efficient drug delivery. Xu came to Tufts with a strong chemistry background, having earned his PhD from Harvard University. He completed his post-doctoral work at MIT with Dr. Robert Langer, a pioneer of nanoparticle drug-delivery. Xu joined Tufts in 2010 and started a lab focusing on lipidoid nanoparticle technology, a field that unites chemistry, biology, and engineering to explore novel pharmaceutical technologies. Nanoparticles are small vesicles ranging between 1 and 100 nanometers in diameter that can be used as vessels to transport biomolecular cargo. Current interests in Xu’s group include the synthesis of lipid-based nanoparticle carriers that deliver biomolecules to targeted cancer cells in the body. Their use in biomedical research has skyrocketed in recent years because they can be engineered with specific antibodies attached, allowing them to recognize and bind to cancer cell surface markers.

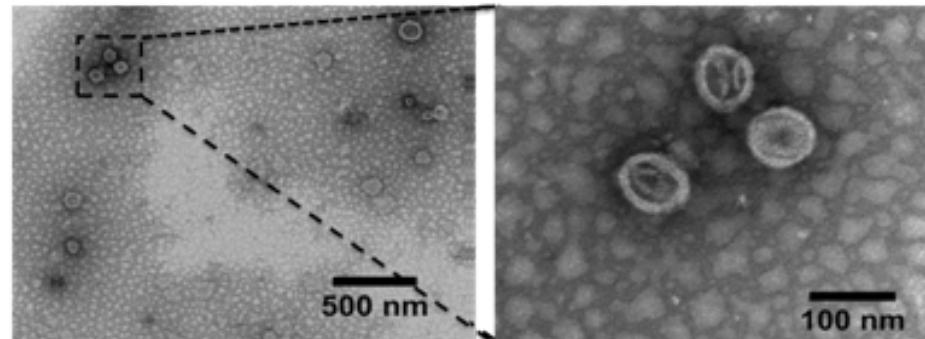
During Xu's first three years at Tufts, his lab generated a "lipidoid library for nucleic acid and protein delivery", which "focused on the chemical sites for carrier design." Lipidoids are particles that have a hydrophobic tail and a cationic head that can bind to negatively charged nucleic acids. They are simple and inexpensive to synthesize, with charged heads that are easily modifiable by different reactive groups. His group found the specific set of parameters for lipidoids that allows the most effective delivery of DNA into cells. Data from Xu's lipidoid library helps gain insight into the design of a nanocarrier that can send specific oligonucleotide sequences into cancer cells. This blocks mRNA sequences that code for essential proteins from being translated, halting the cell's functionality.

Xu's team is currently looking into protein delivery and exploring novel nanoparticle platforms for proteins and peptides, focusing on mechanisms of how the cytotoxic proteins being delivered can cross the cell membrane. His group is exploring the biological therapeutics to "promote more specific binding" in order to inhibit specific enzymatic pathways and cause cells to stop proliferating. Enzymes bind reactant to stabilize the high-energy transition state between substrate and product so that the body can use less energy to make the same reaction happen. Cancer cells overexpress certain proteins that catalyze the formation of the molecules that cause them to proliferate so quickly. These are the proteins that drug developers try to target. "We are trying to make a molecule to mimic the substrate's transition state in the enzyme", says Xu. This would create a competitive inhibitor to render vital proteins inactive. As more drugs are synthesized, they can be coupled with Xu's

carrier technology to even more effectively inhibit protein pathways and kill off tumor cells in the body.

Xu's research could lead to a more efficient and specific platform for cancer drug delivery. His passion for his work can be clearly seen in his desire to be creative and original. He is driven "to use the knowledge gained from literature in order to create new things in the biomedical area to treat diseases that are untreatable," and fueled by a desire to "show the contribution that [he] can bring to society." He hopes that his "innovations and the new technology can be brought to helping the patient." As his lab continues to

research and design, Xu can see the "evolving process in the lab". He is always learning and being inspired by the progress made with each passing day, both in the field and in his own lab. "We are always searching to make a connection between new discoveries and what our group does to see how



Close up of a nanocarrier and its cargo, a cytotoxic protein. Dr. Xu is developing the use of nanoparticle formulations as a more efficient delivery mechanism for targeted drug therapy.

we can contribute," says Xu. Despite the rising cancer rates, the boom in biotechnology and cancer research over the past few decades is helping to increase the quality of life for those diagnosed. Xu continues to pursue nanoparticle research and participate in the increasing point-of-care cancer therapeutics research, and his nano-sized particles are surely making a large impression in drug innovation.

Information taken from Sun S, Wang M, Xu Q. (2012) Combinatorial library of lipidoids for in vitro DNA delivery. Bioconjugate Chemistry (135-140).

Story by Yusi Gong, a sophomore majoring in Biomedical Engineering

Researching for Success

Did you know that not all published papers are listed on Google Scholar and there are better ways of finding the research papers you need and/or want to access? Did you know you can ask the library to request to either borrow or purchase any book, article, DVD, CD or other information source you need?

At college we receive direct access to knowledge through access to primary literature and research journals. But, how do we sift through all the available information as efficiently as possible? How can we minimize the repeated aspect of the search process and find data we need as quickly as possible? How do we identify the right sources to answer and frame our research questions?

How are holes in the current state of the literature identified?

Research for Success, an 8 week Ex-College class I took last year, teaches you the methods to answer these questions and become efficient at research. Taught by the Tisch library research librarians Regina Raboin and Laurie Sabol, this pass-fail half-credit course taught me how to best use the databases and other research resources we have available to us as scholars at Tufts University.

In the past this course has been taken by mainly seniors working on their Senior theses, but since these seniors all said they wished they had learned these skills as freshmen—it's worth taking this course earlier. You'll have the tools

to conduct research efficiently and, I know from experience, that professors in your other classes will notice as the quality and relevancy of your sources increases.

If you're interested feel free to contact Regina.Raboin@tufts.edu, the Science Research Librarian, and Lauri.Sabol@tufts.edu, the Social Sciences Research Librarian or drop by their offices at Tisch library. You can also contact the author with questions at Chinami.Michaels@tufts.edu.

Blurb by Chinami Michaels, a senior majoring in Biology and Studio Art through the Tufts/SMFA dual-degree program.



Out of Spite

How game theory provides possible mechanisms for the evolution of spite

Spite: to deliberately hurt, annoy, or offend. At first glance, the evolution of spite in a population seems to be an anomaly. Yet spite is observable in nature. We see it in the movies, in books, and in our own lives. One common example of spite is in the behavior of fire ants. The workers will kill any infant queens in their colony that do not share their genetic markers. This is harmful to the population as whole and seems to hold no benefit for the spiteful ants, which pay a cost for unnecessarily expending energy (1, 2). This evolutionary puzzle of spiteful behavior has motivated Associate Professor of Philosophy Patrick Forber to choose spite as one of his current research interests. He uses evolutionary game theory to study evolutionary biology, specifically the evolution of spiteful behavior. By representing strategies of different individuals as moves in a game and the fitness of a strategy as game payoff, Forber provides a simple game setup for studying the effects of social interaction on evolution.

Forber's initial interest in spite developed from a reading group, when they "decided to go back and read some seminal papers that were written in the sixties and seventies on group selection in the evolution of cooperation". Among those papers were evolutionary biologist William Hamilton's articles on kin selection. Hamilton investigated altruism in populations, and realized that the same mechanisms for evolving altruism could also be used to evolve spite. Hamilton was the first to propose that

spite is only stable in populations where there are anti-correlated interactions. Anti-correlated interactions are encounters between

two individuals that have different social strategies. Assuming that there is at least one spiteful individual in a finite population, there is always some degree of anti-correlation. Game theoretic models suggest as population size decreases, this anti-correlation effect becomes greater, and spite becomes a stronger strategy. Hamilton believed that the large size of wild populations would deter the natural development of spiteful behavior. He went so far as to claim that "Such trends of selection in small populations, if they occur at all, must act like the final infection that kills failing twigs of the evolutionary tree"(3).

Yet when Forber and his collaborator Rory Smead began to investigate this hypothesis, they found that other factors could make

spite an evolutionarily stable strategy without leading to extinction. Other research in the field investigated conditional spite, where individuals chose to cooperate with certain individuals and spite others. Forber and Smead instead chose to work with unconditional spite, such that individuals are undiscriminating in their harming behavior. They found that high baseline fitness could help support spite in small populations. In other words, if the community is particularly healthy it can tolerate a higher level of spite as long as the population size is sufficiently small. Forber says, "As soon as the population gets big enough, it's not worth spiting individuals anymore, and it will go extinct".



Image Provided by Professor Forber

However, if the population is unable to grow beyond this threshold, spite may be able to remain a stable and viable strategy.

Forber and Smead's research also unveiled further insight into the effects of spiteful behavior on the evolution of cooperation. They began by studying spite within the context of the Prisoner's Delight, a spinoff of Prisoner's Dilemma that favors the stabilization of cooperative behavior. Their model indicated that the greater the benefit to cooperative behavior, the less likely it is to evolve. With a large benefit to cooperation, the average fitness of the population will be lower as spiteful individuals withhold the benefit in their interaction. The lower average fitness creates a smaller difference between the selection coefficients of the spiteful and cooperative

“ If we couple the dynamics of different strategic interactions, spite in one arena may act as a kind of punishment that helps stabilize cooperation in the other ”

strategies in the game of social interaction, therefore making both strategies "nearly neutral" in their reproductive fitness and making the population, with genetic drift, vulnerable to eventual fixation on spite (4, 3). This adds a new complication to the evolution of cooperation: when cooperation is highly beneficial, spite crops up as well. While spite may seem to be the natural counterpart to cooperation, it seems that when used strategically, spite can actually aid in the development of cooperation. In Forber and Smead's article, An evolutionary paradox for prosocial behavior, they say, "If we couple the dynamics of different strategic interactions, spite in one arena may act as a kind of punishment that helps stabilize cooperation in the other"(3).

Forber plans to continue his research with spite. He says, "The idea is to look at more complex and different strategic situations and see what happens when you throw spite into the mix". One way of doing this is to examine populations that exhibit interactions between unconditionally and conditionally spiteful individuals. Forber is especially interested in "[h]ow spite might affect the evolution and stability of fair behavior in various kinds of resource division games". It seems that spiteful behavior is not only evolutionarily possible, but also can be constructive in the development of a cooperative population.

For more information on Professor Forber's research, see
<http://pforber.squarespace.com/>

Story by Jennifer Hammelman, a sophomore majoring in Biology and Computer Science.



Signs of the Heart

A novel look at heart tissue engineering

There are many factors in a progenitor cell's environment that contribute to the path a stem cell will take, whether it be differentiation, senescence, or apoptosis. These stimuli include chemical, mechanical, and electrical signaling. Over the last decade, a lot of progress has been made toward the discovery of these signals, especially in heart tissue engineering applications.

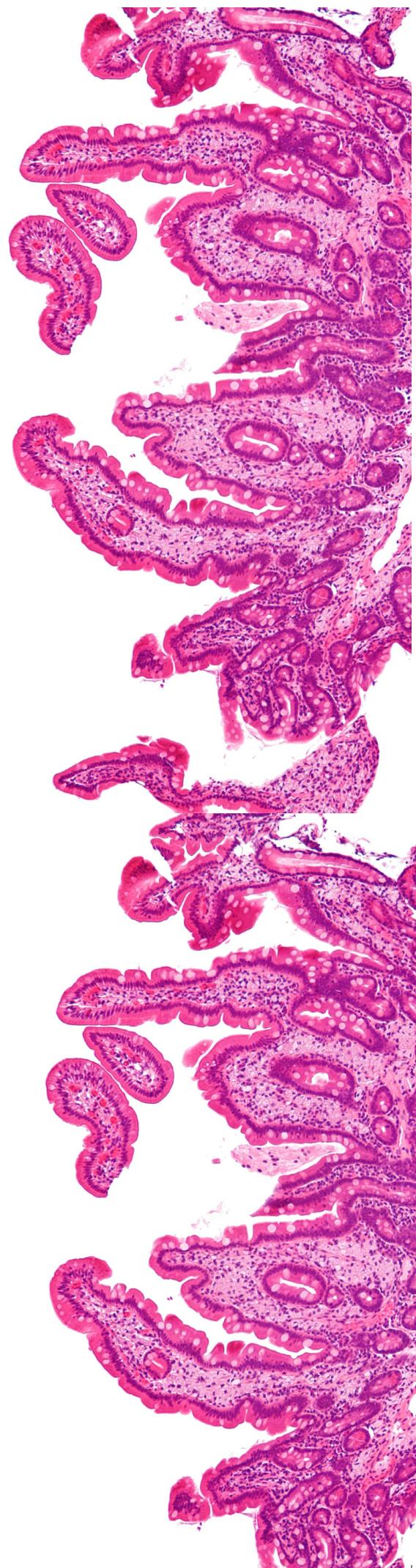
Heart disease has, unfortunately, been the leading cause of death worldwide for almost a century. The ratio of the already-scarce reservoir of viable donor hearts to patients who need heart transplants decreases with each passing year. Furthermore, while new drugs were being synthesized to treat heart symptoms, they could not fix the problem. Thus, it was necessary to come up with a new solution, and scientists turned to tissue engineering.

The first few trials of heart tissue engineering sought to inject stem cells into the site of cardiac infarctions, or where the heart tissue had died. Stem cells had been discovered to mimic the features of cells in their environment, preferentially differentiating into those cells due to signaling molecules that mature cells released. However, this was precisely the problem: the stem cells injected onto the site of the infarction began taking on characteristics of the cells around it—the dead cells. What was originally thought to improve patients' lives caused more damage than improvement.

Researchers then began to look at the extracellular matrix (ECM), a protein structure that acts as a support and signaling structure for tissues. The mechanotransduction aspects of the ECM were extensively studied to see how cells sense the mechanical environment provided by the ECM as well as how signals are transduced to trigger pathways. They discovered that by protein combinations in the ECM differ depending on age of the patient and the type of tissue that the matrix surrounds, and by changing the composition of the matrix, stem cells could be made to differentiate into a different type of tissue altogether. In addition to the chemical environment of the matrix, it was discovered that the mechanical stimulus caused by the matrix also had an effect on stem cell differentiation. Mechanical strain, compression, and shear forces contribute to signals that reach all the way down into the nucleus. These small physical signals can cause a complete change in gene expression.

Professor Lauren Black in the Tufts Biomedical Engineering Department, a leading expert in cardiovascular tissue engineering, has been working to create new methods to study the biophysical stimulation of the extracellular environment and how it can lead to cardiac repair. His group built a bioreactor to mimic how heart cells contract, creating an environment that imitates the electrical signals sent to heart cells. His goal was to combine the mechanical stretching and the electrical signaling and determine the relation of the two stimuli with one another, exploring how timing affects cell growth. Data from his research suggests that applying electrical stimulation a delayed time period after mechanical stimulation to the cells contributed to maximizing cell differentiation into the desired tissue. This emphasizes the vitality of signaling in our body's tissue growth, and with these findings, researchers like Black can better engineer better functioning cardiac tissue.

Story by Yusi Gong, a sophomore majoring in Biomedical Engineering



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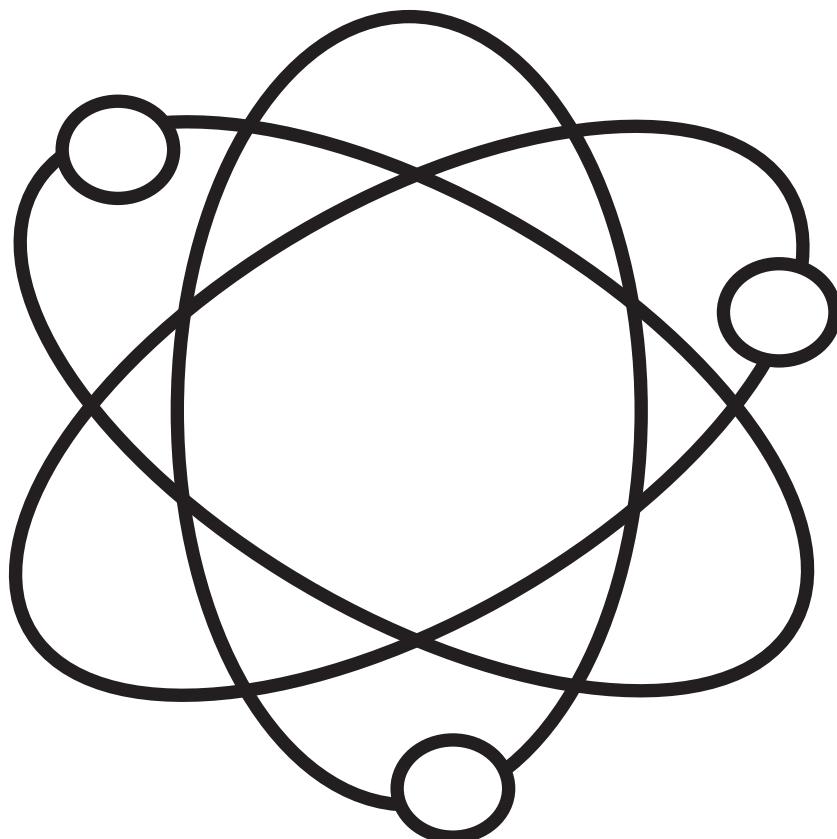
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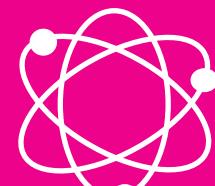
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