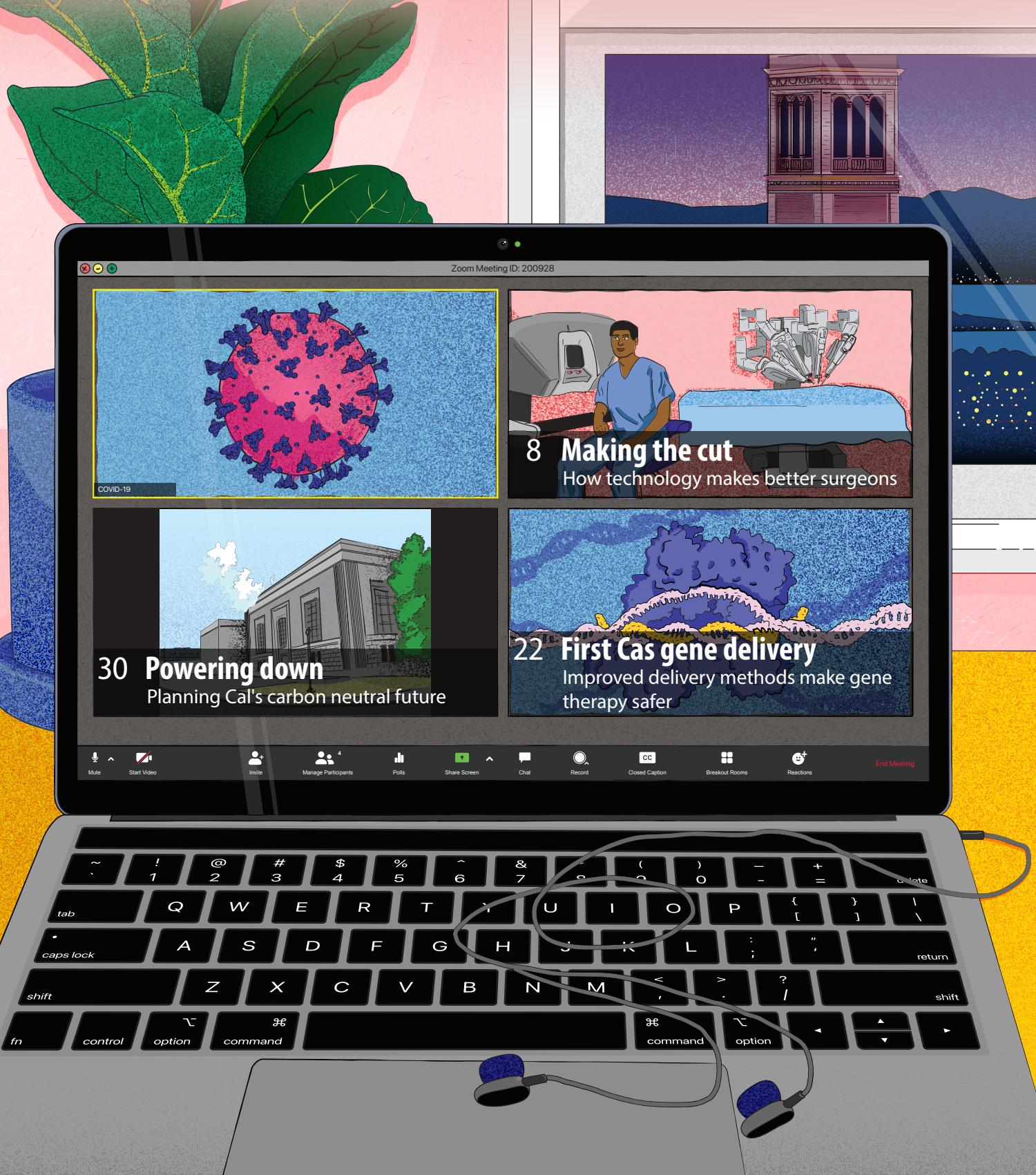


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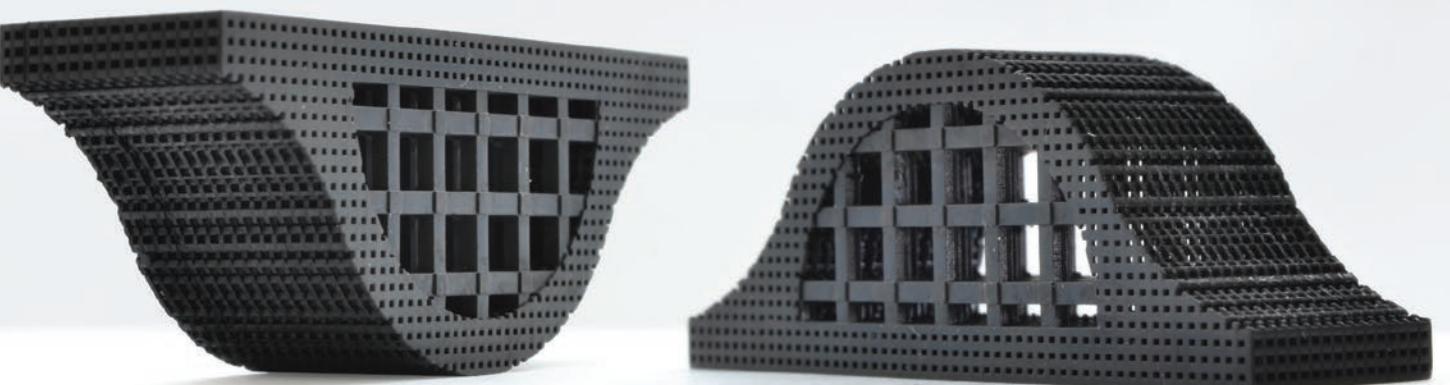
# science review



# from the editor

## INNOVATION WITH A PURPOSE

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DEAR READERS,

This is my ninth issue with the *Berkeley Science Review* over the course of more than four years. With every issue, I am more impressed by the talent and diverse skill set of our team. None of us are professional writers or graphic artists. We are all scientists. But we want to make our world available to our community and strive to make science accessible to anyone who picks up the BSR. That's what motivates a team of graduate students to set aside time to create a beautiful magazine every semester.

This is also the first BSR issue that was produced completely remotely, as the cover art by Santiago Yori Restrepo reminds us. While all of us here at the BSR have gone through our ups and downs adapting to a new way of life, I think it's also

given us a chance to step back, take stock of what's important to us, and tackle changes that the BSR has been meaning to implement for a while. Stay tuned in the coming year for some exciting new updates, especially on our website.

Of course, we aren't the only ones who have been working against the odds in 2020. The scientists doing the work described in the following pages have also had to get creative with their research. This is highlighted in the three articles related to the science behind SARS-CoV-2 and COVID-19: "Putting corona on ice," "Uncovering the pandemic divide," and "Preparing for the next surge." Other creative scientific solutions can be found throughout this issue. Researchers make breakthroughs in gene therapy in "First Cas gene delivery." A graduate student searches for bats in abandoned mines in this issue's "From the field." And old frog DNA finds a new use for frog conservation in "Leaping to a bright new future."

Here at the BSR, we have also been having more conversations about how we can better represent all of the scientists at UC Berkeley. We live and work in a diverse community and want to highlight the accomplishments of scientists from many different backgrounds. In this issue, the faculty profiles highlight three new UC Berkeley faculty members: Zak Al Balushi, Samantha Lewis, and Rediet Abebe, who are changing the long-held ideas of what a scientist should look like and how they should approach their work.

Before you read through this issue of the BSR and enjoy the accompanying illustrations, I'd like to thank a few members of the BSR team for their hard work on this issue. Our Art Director, Santiago Yori Restrepo, rose to the occasion at his new post as head of our design team to produce the beautiful magazine in your hands. Andrew Saintsing, our Managing Editor, juggled the nuts and bolts of the BSR this semester. And a huge thanks to our new Blog Editor in Chief, Maiko Kitaoka, who is revamping the blog and working to create a greater online presence for the BSR.

I would like to extend a huge thank you to everyone who contributed financially to the BSR for this issue. Every donation received from individuals and campus departments helps us maintain our operating costs and make improvements. And of course, thank you to the Karmon family. We are incredibly grateful for your support every year.

Enjoy Issue 39 of the *Berkeley Science Review*!

Sincerely,

Hayley McCausland  
Editor in Chief

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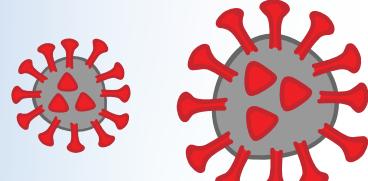
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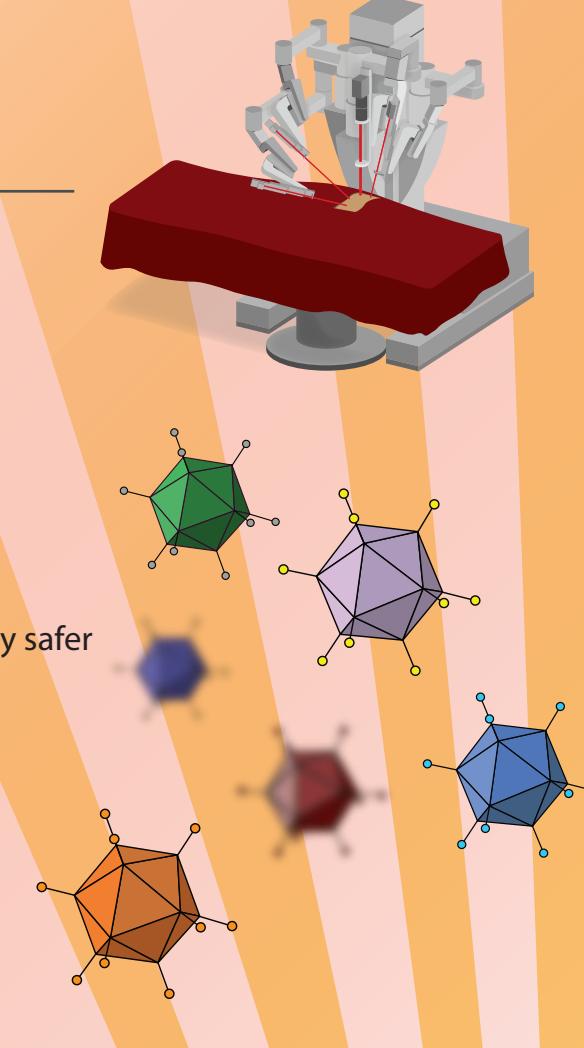


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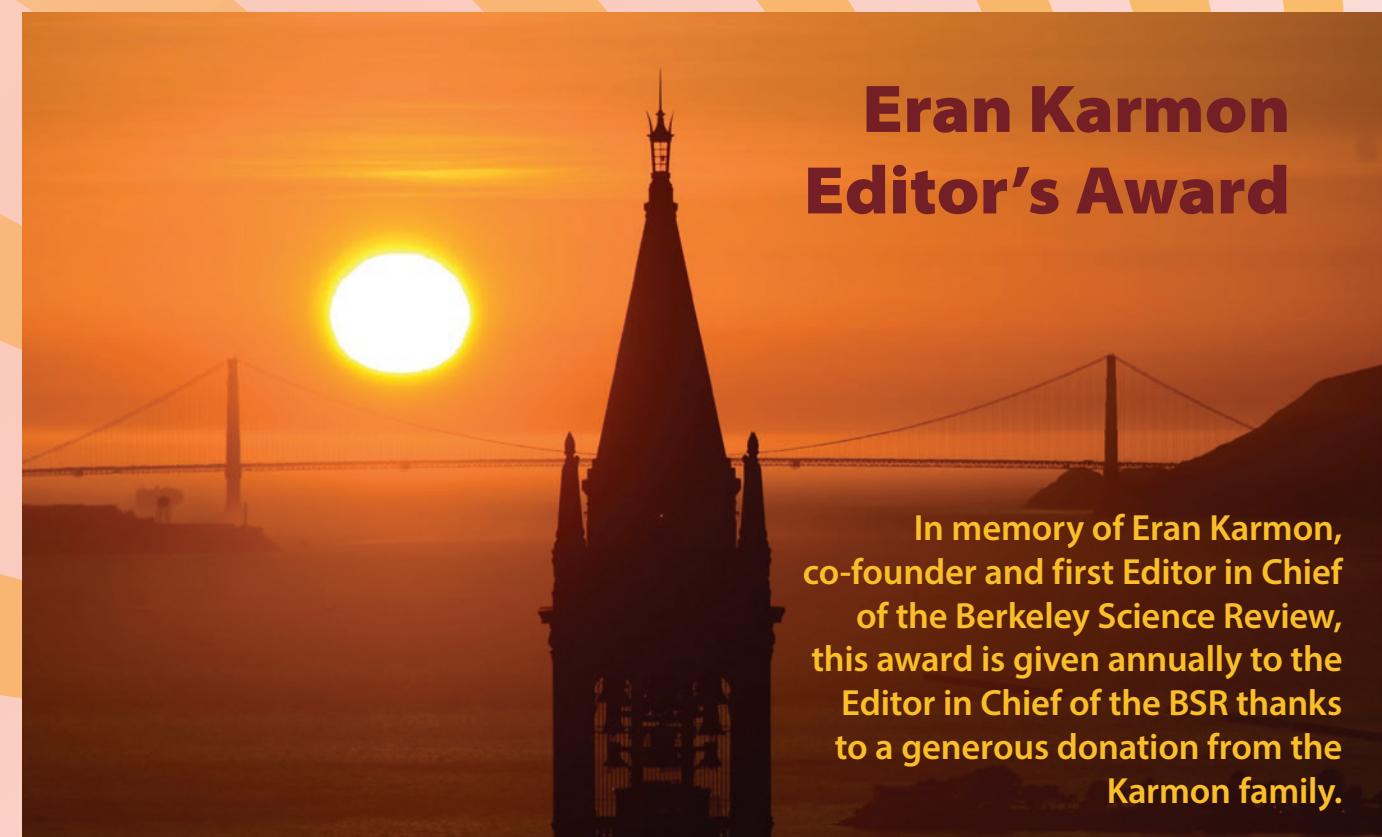
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## Eran Karmon Editor's Award



In memory of Eran Karmon,  
co-founder and first Editor in Chief  
of the Berkeley Science Review,  
this award is given annually to the  
Editor in Chief of the BSR thanks  
to a generous donation from the  
Karmon family.

COVER: Design & Illustration by Santiago Yori Restrepo

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**gratitude** noun  
grat•i•tude | gra-tə-tüd

: the state of being grateful

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**Thank you!**

This issue of the *Berkeley Science Review* was brought to you, in part, by generous support from the Department of Molecular & Cell Biology, the Department of Chemistry, the Helen Wills Neuroscience Institute, and the Office of the Vice Chancellor for Research.

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# faculty profiles



**REDIET ABEBE**  
By Orr Paradise

"What we do here as computer scientists affects real people. Our work comes with a huge responsibility," explains Rediet Abebe, an incoming assistant professor of computer science at UC Berkeley. Abebe tackles problems of social segregation and disparate access to health information—issues typically studied by sociologists, not computer scientists. Her work is interdisciplinary, and even extends beyond the boundaries of academia. "Sometimes we don't realize we are entering a space already occupied by a community, who might have some expertise of their own," she observes.

Abebe's research is also deeply rooted in her own Ethiopian upbringing. "Within computer science, it's not always the case that we embrace our backgrounds and lived experiences as a source of inspiration for our research," says the native of Addis Ababa. "I've found that I am able to work on problems that are meaningful to me and my communities by recognizing the strength that can come from this."

Abebe's personal connection led her

to co-found Mechanism Design for Social Good (MD4SG), a global community of scientists, NGOs, and community leaders researching the problems faced by marginalized communities from a computational lens. It began, she recalls, as a graduate student reading group. These days, MD4SG hosts a yearly conference with over a hundred presentations, and working groups comprised of experts from different fields.

Together with an MD4SG working group, Abebe investigated the origins of poverty cycles and identified a contributing factor overlooked by many welfare models: disruptive shocks to a family's expected income, such as parking tickets and healthcare bills. The result was a way to direct public assistance programs that accounts for a family's susceptibility to such shocks. Abebe and her team are now working with Poverty Tracker, a study following over 2,000 low-income families in New York. They are analyzing how income shocks compound in the real world, and how the resulting snowball effect can be slowed down or even stopped.

Looking forward, Abebe is excited to continue this research on computational

aspects of poverty and inequality alongside colleagues within computer science and in collaboration with the interdisciplinary research centers here at UC Berkeley.

Orr Paradise is a graduate student in electrical engineering and computer science.

## ZAK AL BALUSHI

By Emma Regan

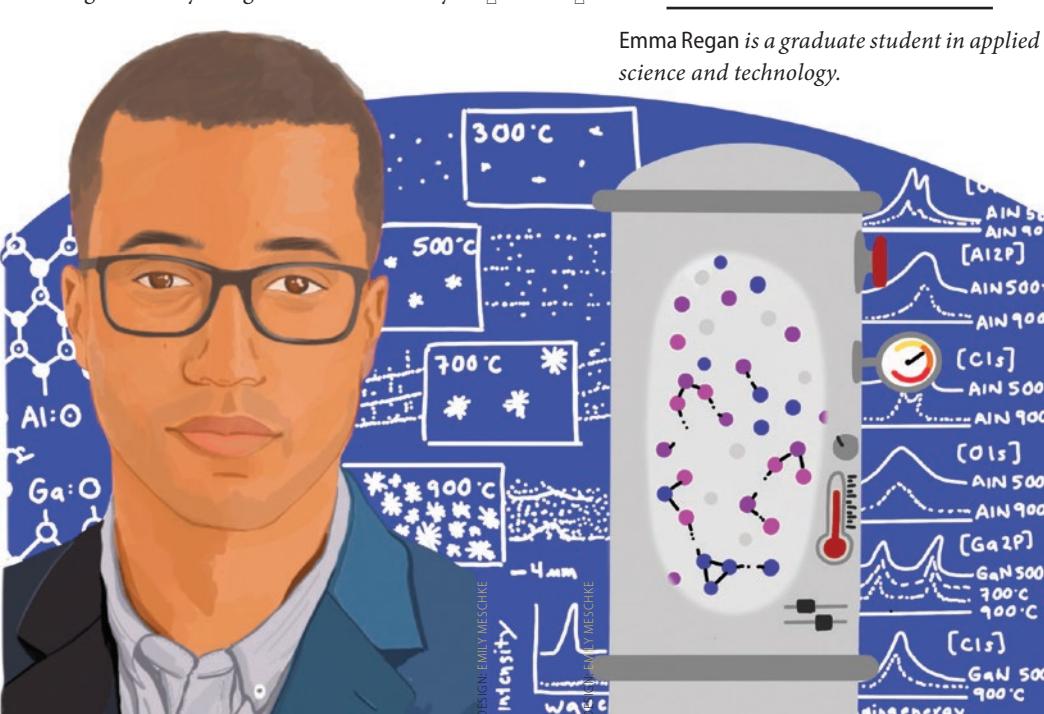
Zak Al Balushi, assistant professor of materials science and engineering at UC Berkeley, has been coaxing atoms into nanoscale patterns, called crystal structures, since he was an undergraduate student. Materials made from the same elements can have dramatically different properties based on how the atoms are arranged. Consider carbon: if the atoms are organized in a hexagonal pattern, they form graphite. But if the atoms are bonded in a more complex structure, the same carbon atoms form diamond. In the lab, Al Balushi uses sophisticated reaction chambers to encourage atoms to build crystals that don't form naturally, with the intention of benefiting next-generation electronics similar to the way that silicon revolutionized microelectronics. "When I have a 3D printing analogue for crystal growth to make any

crystal on demand, that's when I can retire," laughs Al Balushi. "That would change the world."

Al Balushi's lab cannot grow all possible materials, so he collaborates with theoretical materials scientists who predict which crystals might have interesting properties. Then, his team optimizes control knobs like temperature, pressure, and even light exposure in their reaction chambers to guide atoms into the promising arrangement. "I'm excited as soon as the atoms get released in the chamber," Al Balushi gushes, "how they bounce around ... and eventually form crystals."

Al Balushi's love of science motivated him to become the first in his family to earn a PhD, a consistent goal in an otherwise fast-changing childhood as he moved between New York and the Middle East. But Al Balushi's journey to becoming a professor at UC Berkeley was not easy. "Mentoring was not always there when I was younger—I found my mentors sort of by luck," he explains. Now, as a new professor, he is excited for his role in uplifting and educating UC Berkeley's diverse student body: "If people were more active about mentoring, it would change a lot more lives than the few that were lucky enough to find the right people at the right moment in time."

Emma Regan is a graduate student in applied science and technology.



**SAMANTHA LEWIS**  
By Erin Akins

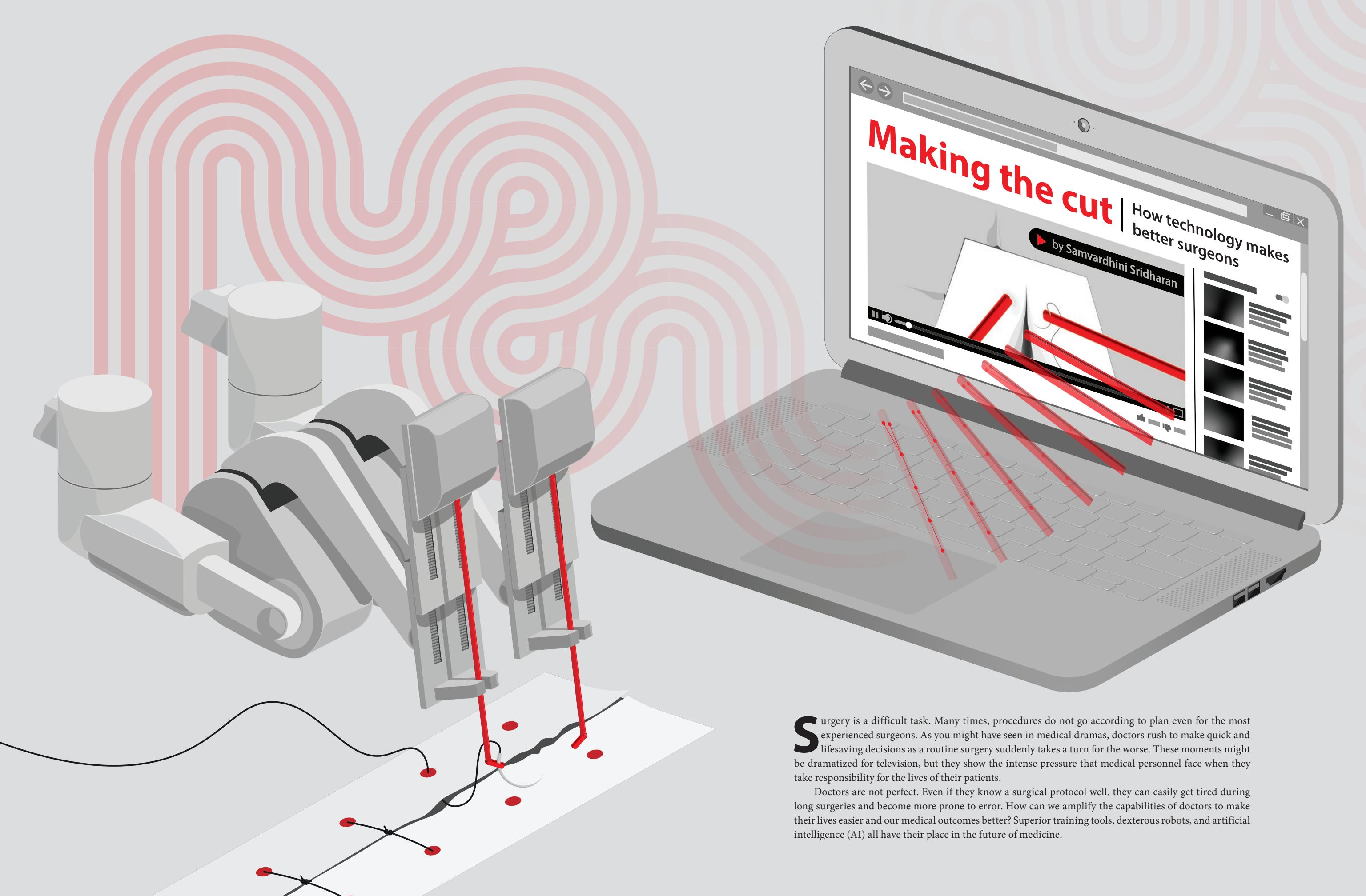
As a first-year undergraduate student at Oregon State University, Samantha Lewis discovered a passion for the life sciences after enrolling in a developmental biology course to fulfill a requirement for her chemical engineering major. Lewis recalls, "The biology course was so interesting that I wanted to know everything. It completely changed my world view." Soon after, Lewis transferred into the zoology department, joined a biology lab, and began to realize her love for research.

Now an assistant professor in the Department of Molecular and Cell Biology (MCB) at UC Berkeley, Lewis studies a genome found not in the nucleus but in a separate organelle: the mitochondrion. Our cells contain thousands of small, circular pieces of DNA called mitochondrial DNA (mtDNA), which encode genes that control processes required for healthy metabolic function. Similar to the nuclear genome, mtDNA can accumulate defects, or mutations, as a person ages that alter cellular function and can result in rare mitochon-

drial diseases. "There is pretty strong evidence that the accumulation of mitochondrial genome defects with age is linked to neurodegeneration and metabolic disease," Lewis explains. Using a combination of molecular biology tools, gene-editing techniques, and super resolution microscopy, Lewis is studying how the mitochondrial genome changes with age and metabolic conditions.

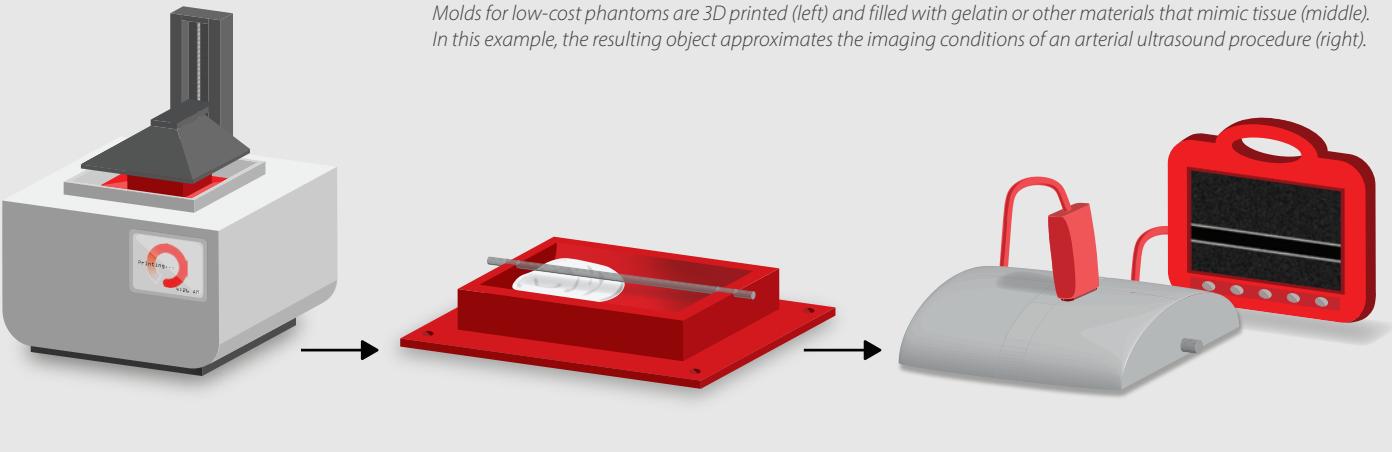
Lewis finds great joy in advising future scientists. She has taken part in multiple formal mentoring workshops and is currently involved with inclusive MCB (iMCB), an initiative to promote an academically enriching and supportive climate for MCB trainees at UC Berkeley. When asked about her greatest accomplishments, Lewis admits, "I am most proud of seeing the students that I have worked with learn, grow, and succeed."

Erin Akins is a graduate student in bioengineering.



**S**urgery is a difficult task. Many times, procedures do not go according to plan even for the most experienced surgeons. As you might have seen in medical dramas, doctors rush to make quick and lifesaving decisions as a routine surgery suddenly takes a turn for the worse. These moments might be dramatized for television, but they show the intense pressure that medical personnel face when they take responsibility for the lives of their patients.

Doctors are not perfect. Even if they know a surgical protocol well, they can easily get tired during long surgeries and become more prone to error. How can we amplify the capabilities of doctors to make their lives easier and our medical outcomes better? Superior training tools, dexterous robots, and artificial intelligence (AI) all have their place in the future of medicine.



### Phantom of the operation

Medical students and new surgeons learn by doing. But with rare or experimental surgeries, hands-on training isn't always an option.

Dr. Neil Long, an emergency physician at the Burnaby Hospital in British Columbia, Canada does surgical research focused on pericardiocentesis, a procedure that removes fluid built up around the heart. At best, this excess fluid can cause the heart to malfunction. At worst, the fluid pressure pushes down on and squeezes the heart, making it stop entirely.

"It's a fairly rare procedure," Long explains. "The classic mantra of surgery is 'see one, do one, teach one,' but the opportunity to practice on patients in the emergency department for this procedure is far less controlled."

Medicine, however, does not look kindly upon blindly inserting needles into chest cavities. An alternative to "see one, do one, teach one" is a skill trainer, called a phantom. Phantoms are physical models that don't necessarily look like real organs but mimic their properties. Surgical phantoms often serve as a proxy to help surgeons learn the rudimentary skills needed before working on actual patients. In real life, the surgery will be new, but because trainees have worked with a phantom, they can go in with more confidence in their abilities.

Such tools seem almost necessary, but cost plays a major factor in accessibility. A surgeon who wants phantoms for a range of surgical procedures would require a menagerie of them since different phantoms are used for different parts of the body. With regards to pericardiocentesis in particular, "there's an existing phantom on the market that's \$3,000," Long recounts. "But everyone's got a tight budget."

Molds for low-cost phantoms are 3D printed (left) and filled with gelatin or other materials that mimic tissue (middle). In this example, the resulting object approximates the imaging conditions of an arterial ultrasound procedure (right).

With many of the phantoms on the market for pericardiocentesis doing a poor job of truly capturing the surgical procedure, it makes it hard to justify the cost. As a result, medical researchers are turning to large corporations for help finding ways to take advantage of new technology and bring prices down. Long maintains a strong research relationship with collaborators at Microsoft. Not only does the company offer its considerable resources, but it also provides fresh eyes for old problems.

Recently, Microsoft engineers worked with the Burnaby Hospital to design a prototype that is cost efficient and easy to scale for other teaching institutions. "At least one version of the phantom is as cheap as possible. It's a relatively small cost that people can afford," Long explains.

Interested surgical trainees would simply need to download code and pay someone to print the phantom's molds on a 3D printer. Materials that mimic tissue are then added to the printout making a better phantom model than what is currently on the market. As the field of 3D printing advances and 3D printers become more affordable, it becomes more possible for medical students to practice life-saving procedures without operating on a real person.

### A call to arms: robotic surgeons

Surgeons are also turning to robotic surgery in order to enhance their skills. "Surgeons' acceptance of robots falls into several camps," explains Dr. Michael Mastrangelo of Bend Surgical Associates. Mastrangelo was an early adopter of minimally invasive laparoscopic surgery in the 1990s and then robotic surgery when the technology became available. "Some feel that robots shouldn't be used at all, and others believe that robotic

surgery is where surgery is eventually going."

Many surgeons were hesitant to move into the age of robotics—robots are bulky, require a protracted setup, add additional cost to the patient, and require a hospital setting as opposed to an outpatient surgery center. As technologies improved, however, it became evident that robotic surgeries could outshine laparoscopic ones in several cases, including prostatectomies, colon resections, and hysterectomies. Furthermore, certain "open surgery" procedures could now become minimally invasive ones. Mechanical improvements were a major factor.

"Imagine you're trying to tie your shoes with your wrist locked," says Mastrangelo. "That's what laparoscopic surgery is like. Laparoscopic instruments don't have wrists, but robotic instruments give you additional freedom to move—more of an intuitive natural movement when you're tying a knot and suturing."

In the last two decades, the invention of new surgical robots has made the promise of robots in the operating room into a tangible reality. The da Vinci Surgical System is behind the famed viral video of "grape surgery" where it successfully reattaches the peel of a tiny grape. Designed to perform delicate and minimally invasive movements, the da Vinci System is quickly gaining traction in many hospitals.

The da Vinci System is operated by a surgeon, who sits at a console looking at an image of the surgical field. The surgeon controls four interactive robotic arms, which perform the surgery. Surgeons like it for many reasons, including improved visualization, dexterous flexibility, and the ability to stay seated throughout the surgery to reduce fatigue.

Even though the surgeon is not standing

above the patient, there is still a team in the operating room. Communication systems are in place so that surgeons can talk to their operation team. And in the rare case that an open procedure becomes necessary, the da Vinci System can be removed very quickly.

### Robotic trainers

The da Vinci System can also be outfitted with two consoles so that two surgeons can operate it simultaneously. A trainee may be seated at one console and an experienced surgeon at the other. If the trainee performs a movement that could cause a surgical issue, the experienced surgeon can take control of the system.

"It's a great tool for training," says Mastrangelo. "When training in laparoscopic surgery you essentially give up the reins. There's a safety factor in having the ability to have more than one console. A lot of [surgical] metrics come out of the da Vinci, too. You learn a lot about how you operate and can work to improve on becoming a better surgeon."

The system even allows for virtual input. A surgeon in another facility, perhaps thousands of miles away, can sit in on surgeries with trainees, observe their techniques, and make recommendations. When today's trainees are full-fledged doctors, an AI may be the one observing their techniques and making recommendations on how to improve. But

before these computer algorithms can evaluate surgeons, they must be trained in surgery. To do so, an AI uses machine learning, in which the computer automatically learns and improves through experience.

In supervised machine learning, an AI learns from a "training" dataset. The AI is given "inputs"—data like videos, pictures, and numerical values—and the "ground truth" or the set of correct predictions the AI is to make based on the inputs. The process is similar to the way students study with an answer key in the back of a textbook. The key is made by the authors, who are certain of what the answers are. Students try to solve questions by plunging into the problems directly, then checking if their responses match with the answer key at the back. They know they are solving the problems correctly if the answers they come up with consistently match. If not, they try to reformulate their theories and try again so the answers do conform.

Translational researchers, who bring bench science to bedside medicine, have found that the da Vinci System can serve as a tool to generate training data that can be used to improve both AI and medical outcomes. Researchers at Johns Hopkins University's Intuitive Surgical Inc. used the robotic surgeon to create the Gesture and Skill Assessment Working Set, known as JIGSAWS.

JIGSAWS was initially created as a training dataset for AIs that evaluate the performance of surgeons during suturing. Eight surgeons of different skill levels used the da Vinci System to complete tasks thought to be the core of surgery: suturing, knot tying, and needle passing. The dataset includes videos of the robot's arms in action and kinematic data describing the arms' motions. In addition, each video has corresponding manual annotations that break down the tasks into discrete actions and that rate the surgeon's performance. Experienced surgeons helped the Johns Hopkins team produce the annotations. AIs using JIGSAWS will treat the videos and kinematic data as inputs and the manual annotations as the ground truth. These AIs will learn to break future surgical videos down into distinct surgical tasks so that they can then evaluate and rate the skill level of the surgeon.

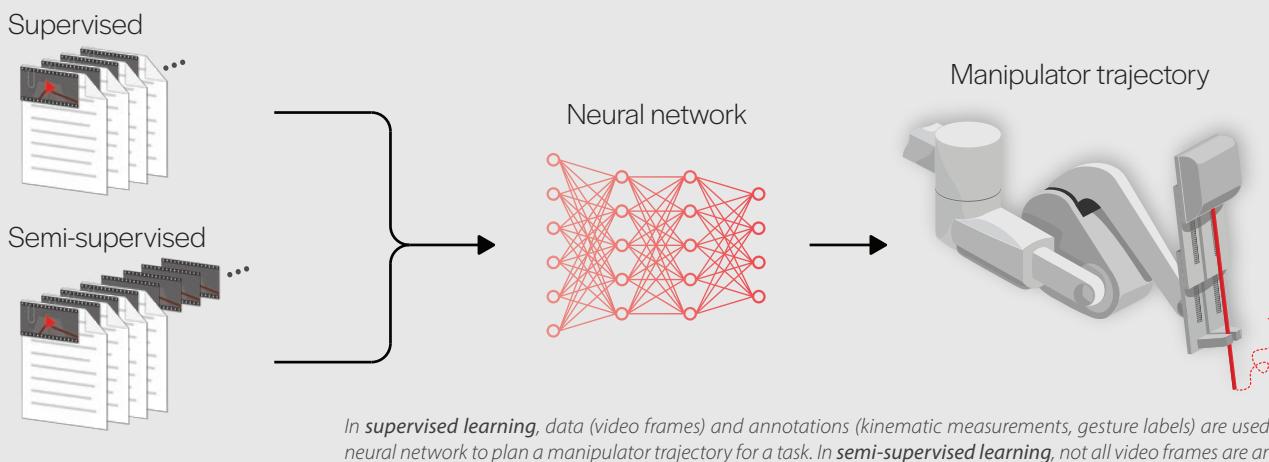
### Artificially intelligent surgeons

Drs. Ajay Tanwani and Ken Goldberg, researchers in the industrial engineering and operations research department at UC Berkeley, found a different use for JIGSAWS. Their team, along with collaborators from Google and Intel, developed the Motion2Vec algorithm that can learn how to operate the da Vinci System by watching human surgeons. The dataset's focus on suturing was fortuitous. Since it's one of the most



DESIGN: GAUTAM GUNJALA

In current clinical practice, a surgeon uses the console of the da Vinci System to perform surgical tasks using interactive robotic arms. Artificial intelligence researchers aim to enable this system to perform some tasks without console input.



foundational tasks in surgery, being able to offload suturing to a surgical AI would allow surgeons to focus on more technical and unpredictable surgical tasks. "Suturing is something that is very tedious," explains Goldberg. "It's delicate work, but we're trying to push that envelope slowly forward."

The problem is that JIGSAWS provides a limited amount of data, and experiencing many surgeries would produce a better surgical AI. Along the same lines, access to varied training cases makes better AI surgeons. The AI may need to choose between various surgical actions, such as needle insertion, needle handoff, or needle extraction. A good medical AI would overcome these issues by being trained on examples from all possible scenarios.

This makes the amount of data required to train a medical AI enormous. Data must not only be supplied in such a way that the algorithm understands it, but also in large enough quantities. That sort of information cannot come from a few minutes of video or a few pictures. Hundreds of hours of data must be spliced together. The best results would come if all of those data were annotated, but annotations take time.

Dr. Danyal Fer, a resident in the

University of California San Francisco East Bay Surgery Program, emphasizes, "Surgeons who are working eighty hours a week find it hard to sit down and accurately annotate what is occurring in a surgical scene [to assist with supervised learning]. Any method you can create to generate a dataset more quickly and accurately is going to be helpful in this space."

To develop Motion2Vec with limited help from surgeons, the UC Berkeley team trained their algorithm on JIGSAWS using "semi-supervised learning." They fed Motion2Vec a small number of videos labeled with the information the robot needed to imitate the actions in those videos. To supplement the annotated videos, they also fed the algorithm video data without labels. It was up to Motion2Vec to group unlabeled videos together with similarly labeled video data so that it could amass enough examples to closely imitate the recorded surgical actions.

If the algorithm grouped videos incorrectly, the movements it produced would fail to match the ground truth, so it would be forced to reevaluate itself and adjust its groupings.

Motion2Vec is not going to be launched into da Vinci Systems in the operating room anytime soon, but the research group has

come up with some promising results. Their AI was able to mimic the movements of skilled surgeons with an accuracy of 85.5 percent, suggesting that the robot can reproduce the motion of a surgeon relatively closely.

Yet, there are still limitations in training an algorithm on JIGSAWS. "These annotations take place in a controlled environment," explains Fer. "In the future, you must be able to accurately describe what the surgeon is doing in an operation with far more detail, in a much more complex, and a much less controlled environment."

Learning from less controlled datasets is not an easy task for an AI. Recognizing a surgeon's skilled hand movements and imitating them requires a thorough understanding of not just the motions themselves, but also differences in lighting, background, and other geometric properties. That makes it important to characterize factors such as position, size of external objects, and the viewpoint of the camera. Still, if researchers can pull it off, the possibilities are limitless. "The world around us is filled with information in the form of videos, images, and text," says Tanwani. "If [AIs] are to make sense of this information—similar to how humans perceive and act in their environments—[they]

can be of tremendous value in everyday life."

### Ethics of artificial intelligence in biomedicine

Although artificial intelligence is steadily becoming more common in medicine, it will not be taking your doctor's job any time soon. A precise algorithm does not replace a seasoned physician. Writing an AI is a highly specialized task which only covers a small fraction of the patient cases and conditions. Doctors and surgeons are capable of looking at hundreds of things at once and drawing conclusions based on a patient's medical and familial history, not just physical symptoms. There will not be an AI in the foreseeable future that can equal a doctor.

"The first real tangible milestone of [AI]-assisted surgery would be to have robots that are semi-operated," Tanwani explains. Surgeons would be in complete control of the robot, but the AI would show them a way to correct erroneous movements. "If we have the right quality of data available," says Tanwani, "we can incorporate [these AIs] as standard models that can be used for training and assisting novice surgeons, as well as providing feedback to experts on how to control these robots."

A full rollout of AI in the surgical force would have serious implications for patients

and clinicians alike. Some ethicists believe that the AI must do a statistically better job than the average medical professional. Others take a stronger stance that AI must do no harm. "The debate parallels that of self-driving cars," comments Fer. "There's a good chance a self-driving car is better than your average driver. But every time a self-driving car has a problem, it is a big deal."

From a societal level, it's unclear what errors would be acceptable from a machine as opposed to a human. Patients may look at it from a place of accountability: who is responsible for surgical or diagnostic error if things were to go awry? In such a situation, does liability fall to the surgeon overseeing the surgery, the physician supervising the diagnosis, the hospital in which the surgery takes place, the doctors involved in creating the training dataset, or the company which created the AI?

"The errors you see in an autonomous system are going to be different from the errors you see occur in a human-driven system," Fer explains. "If I'm suturing a blood vessel, I might not make all the sutures evenly spaced but an autonomous system could completely misread the environment—suturing a centimeter off in a completely different part of the blood vessel."

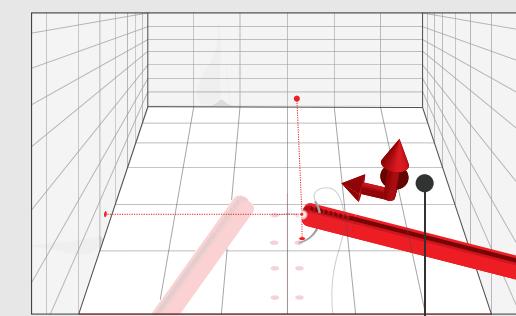
"We do not anticipate replacing surgeons

altogether," concurs Goldberg. "I don't think robots are capable of replacing people. But they can make people's jobs better—just like driver-assist makes drivers better drivers, surgeon-assist would make surgeons better surgeons."

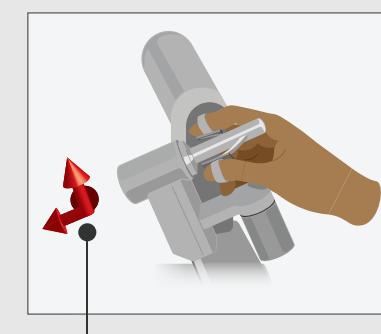
It is possible AI and surgical robots in the operating room will one day factor heavily into the surgical process. There is perhaps even a chance these technologies will feature as a storyline on your favorite medical drama. From correcting erroneous movements to preventing tragic accidents, there is immense promise in using technology in the operating theater. Scientists and clinicians are working hand in hand to create a surgical field that is safer for patients and less risky for doctors. Modern tools including phantoms, AI, and robotic technology are at the disposal of surgeons—giving them confidence before making the cut.

Samvardhini Sridharan is a graduate student in molecular and cell biology.

### Kinematic annotations

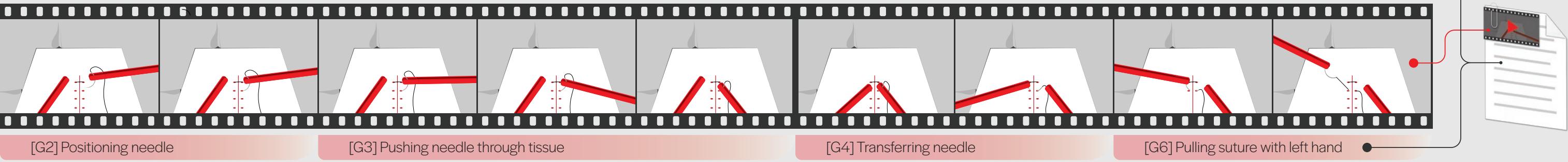


DESIGN: GAUTAM GUNJALA



The JIGSAWS dataset contains videos captured by the da Vinci System during surgical processes, supplemented by two types of annotations. **Kinematic annotations** describe the positions and velocities of the surgeon-side and patient-side manipulators at each video frame. **Surgical activity annotations** break down a complex procedure into sub-tasks, which are associated with sequences of frames.

### Surgical activity annotations (gestures)



# current briefs

## The future is H<sub>2</sub>

Energy resiliency in an age of uncertainty

The last three fire seasons have been the deadliest and most devastating that California has seen. As climate change is a primary culprit, mitigation strategies need to be scaled up and implemented. Energy resiliency—the assurance that electricity will be deployed at any given moment to satisfy the needs of customers—is essential in today's world. But clean energy, which is critical for reducing greenhouse gases and slowing climate change, typically sacrifices resiliency. Common clean energy sources like solar and wind cannot provide round-the-clock power like traditional energy sources including natural gas, oil, and coal. At large refineries, natural gas is burned which causes heat and carbon dioxide to be released as bonds in the gas molecules break. While intermittency can be mitigated by storing excess energy in batteries, batteries alone are not enough to solve our energy problems. Hydrogen may be a solution.

Made up of the most abundant atoms in the world, hydrogen gas, or H<sub>2</sub>, contains a lot of energy in the form of chemical bonds. To convert the chemical energy into electricity, the hydrogen gas must be fed into a fuel cell, where it is split into protons and electrons at an electrode. The protons move through the fuel cell (via an electrolyte) and the electrons move externally through a wire, generating

the electricity. The electrons and protons recombine at the opposite electrode, completing the chemical reaction. This chemical process happens spontaneously and can generate power on the mega- to giga-watt scale. The only byproducts are heat and water!

But there is a catch. Fuel cells mostly use hydrogen that is produced by burning methane, a process that releases a large amount of carbon dioxide. To harness this promising technology for clean energy storage, we can produce hydrogen cleanly using an electrolyzer. An electrolyzer is a fuel cell run backward, using electricity to split water into hydrogen and oxygen.

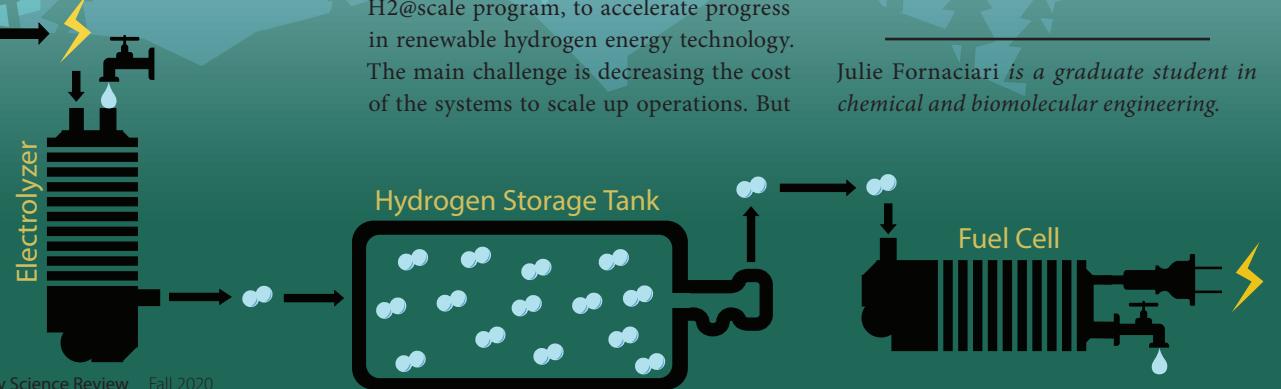
This clean hydrogen can be made during peak production hours when excess energy is generated. Think of a sunny summer day when many people are enjoying their day outside and not using excess energy. By siphoning off some energy during peak production times, hydrogen gas can be made and stored in tanks. According to Zachary Taie, a PhD candidate at Oregon State University, "Two huge incentives for using hydrogen [are that] the energy storage (the tank) is decoupled from the energy conversion (the electrolyzer and fuel cell), and the storage of hydrogen is stable over long time scales—weeks, months, years—which cannot be said for current energy storage technologies just yet."

The Department of Energy is funding multi million-dollar projects, like the H<sub>2</sub>@scale program, to accelerate progress in renewable hydrogen energy technology. The main challenge is decreasing the cost of the systems to scale up operations. But

hydrogen fueling stations are already being approved and the technology development is on its way to meet the demands of the market. Hydrogen fuel cells are replacing the combustion engines in vehicles such as the AC transit buses around the East Bay and heavy-duty trucks, like the ones Nikola Motors is deploying. Fuel cells are also being used as stationary power systems to replace diesel generators, such as Bloom Energy in the South Bay.

Clean and storable, hydrogen may be our best shot at weaning ourselves off of fossil fuels. As Staff Scientist at Lawrence Berkeley National Laboratory, Dr. Nemanja Danilovic puts it, "It is hard to put a value on energy resiliency; renewable energy plus short-term and long-term storage can provide undisrupted energy for hospitals, homes, and towns in the future." Hydrogen is one clean solution for long-term storage. From the perspective of Grace Anderson, a chemical engineering PhD student at UC Berkeley, "The effects of climate change are becoming more apparent, especially here in California. The need to reduce carbon dioxide emissions is great, and I believe hydrogen has a large role to play in eliminating reliance on fossil fuels." It alone is not the silver bullet for addressing climate change, but coupled with batteries, solar energy, wind energy, and other renewables, our dependence on non-renewables can be weakened and a cleaner energy landscape can be achieved.

Julie Fornaciari is a graduate student in chemical and biomolecular engineering.



## DeadLY Inheritance

Sex chromosomes influence lifespan

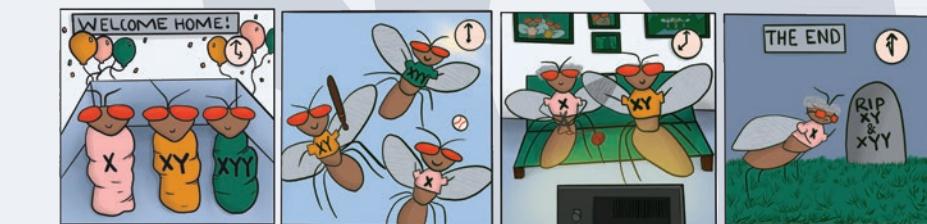
The mutant flies have just enough leg room. The temperature of their incubators is carefully tuned, humidity a comfortable 60 percent. Five thousand fruit flies are enjoying a Goldilocks standard of luxury. Their concierge, biologist Emily Brown, is waiting for them to die.

An alumnus of Professor Doris Bachtrog's lab in integrative biology at UC Berkeley, Brown created this fly spa to study the link between sex and ageing. Female fruit flies enjoy longer lives than their male counterparts. These flies aren't alone—most bird and mammal species have one sex that outlives the other. Researchers like Brown, now a Senior Scientist at New York University Medical Center, suspect this lifespan gap is caused by sex chromosomes.

Proving this, however, is difficult. The different lifestyles of sexes within an animal species affect ageing, but so do genetics. However, unlike eye color or blood type, lifespan isn't a trait that can be pinned down to a handful of genes, which in turn, are only a fraction of an organism's DNA.

The function of genes is well understood. Like books in a library, they hold blueprints for the proteins a cell needs to grow, survive and divide. The remaining DNA, known as heterochromatin, seems to be both library and librarian. Some elements are structural. Others monitor the genome, flagging genes that need to be read or reshelfed. And some heterochromatin isn't helpful. Like rogue librarians scribbling on pages, particularly repetitive sections of DNA can insert nonsense into genes.

As organisms age, they grow worse at stopping this troublesome DNA. Those with a Y chromosome do an especially dismal job, a feature that grabbed Brown's focus during her PhD. "I was interested in the consequences of having different sex chromosomes," says Brown. Rapid ageing might be one consequence—in every species with a



lifespan gap, the shorter-lived sex has the equivalent of a Y chromosome.

This may be due to the composition of the Y chromosome, which contains great swathes of repetitive DNA. In some species, these sections make up almost the entire chromosome. This is risky—if even one element finds its way to a gene, it can do permanent damage. In contrast, the X chromosome is often densely packed with genes, with little space for repetitive elements, and tends to be much better behaved. If both sexes have the same total ability to protect their genomes, those defenses could quickly stretch thin if a Y chromosome is in the mix.

To test this theory, there's no model better than the fruit fly because some variants have incredibly repetitive Y chromosomes. Another advantage is speed. If you want to study ageing, you need to wait for subjects to get old, so a fruit fly's 70-day lifespan comes in handy. But Brown was also drawn to the species by the unusual role its Y chromosome plays in determining sex.

For mammals, an organism with a Y chromosome is male. However, a fruit fly can carry a Y chromosome and remain female. For these insects, sex is determined solely by the number of X chromosomes: one for male, two for female. Through careful cross-breeding, Brown created several strains of fly with abnormal numbers of chromosomes, including females with Y chromosomes and males without.

If the lifespan gap was caused only by differences in lifestyle between the sexes, this meddling would have no effect. But as Brown looked after the flies, checking on their vials daily and counting how many remained alive,

she saw an entirely new relationship between sex and ageing emerge. "There's actually a really dramatic change," says Brown. When she added a Y chromosome to typically long-lived females, the flies aged rapidly. When

she took the Y away from males, leaving them with a lone X chromosome, their odds of surviving shot up. "They just kept on living," says Brown. The worst-off flies were a set of males Brown bred with two Y chromosomes. On average these mutants only made it halfway through the lifespan of the X-only strain.

The Y chromosome is toxic. It's the only way to explain the brief but luxurious lives of Brown's flies. But Brown and her colleagues are quick to acknowledge there is much more to lifespan than one troublesome chromosome. As Alison Nguyen, the PhD student continuing Brown's study, puts it, "We are only really studying one slice of this phenomenon called ageing." An animal's environment, what it eats, and when it mates all influence how long it will live. Since a human's Y chromosome is not quite as repetitive as a fruit fly's (there are just a few more genes to cram in), it likely influences ageing much less than these lifestyle factors do. However, the toxicity of a more sophisticated Y chromosome still needs to be studied, and this is how Nguyen will use the fly spa next.

Andrea Herman is a graduate student in physics.



## Leaping to a brighter future

New tricks increase the value of old DNA

A mountain lake is a classic metaphor for serenity—quiet, still, and calm. But in the High Sierra of Sequoia and Kings Canyon National Park (SEKI), a few hours southwest of Berkeley, the most ecologically healthy lakes are hopping with life. The area is home to birds and snakes, many of which feed on a small frog with a raspy call and brightly-colored thighs: the mountain yellow-legged frog, once the most common amphibian in the Sierra Nevada mountains.

Unfortunately, this species is in trouble. Predation and disease have caused the frog population to shrink to a tenth of its original size. The introduction of non-native trout that feed on frogs and invertebrates has left once-vibrant lakes supporting little else besides gnats and midges. In addition, an insidious fungal disease is rapidly spreading through the frog population. The fungus, *Batrachochytrium dendrobatidis* (Bd), infects the frogs' skin and interferes with their ability to breathe and absorb water, often leading to death. Bd is a likely factor in the decline of hundreds of amphibian species worldwide and its presence in mountain yellow-legged frogs is a bad sign. Between Bd and the non-native trout, these frogs are “very much in danger of going to zero,” says Danny Boiano, aquatic ecologist for the National

Park Service. Because the frogs were once so plentiful, their loss likely has a profound impact on the ecosystem. Isaac Chellman, environmental scientist for the California Department of Fish and Wildlife, explains that the mountain yellow-legged frogs “eat a lot of different invertebrates, and they are also the food source for other animals, including birds and mammals. Undoubtedly they play an integral role in the food web.”

Although the situation seems dire, researchers and field teams are working hard to save this species, and there are signs of hope. Efforts to remove invasive trout have turned previously inhospitable lakes into prime frog habitats. Lakes in which frogs have been eradicated by Bd could be repopulated by the small fraction of frogs that can persist despite the disease. The process of restoring frogs to empty lakes is most successful when the population's genetics are known, since genetically diverse populations are more likely to survive in a new environment. Rothstein determined which populations were most genetically similar. He also found that populations that had been infected with Bd, which might have been expected to have lost genetic diversity as the population declined, were just as diverse as uninfected populations. “We could use that diversity to preserve [this species] in the future,” Rothstein says. “It’s a bit of shining hope.”

Before Rothstein's research was even published, conservation teams were using it to guide decisions about restoring frog populations. “This was a piece that we needed,” says Boiano. “When we’re moving frogs around ... we can pick the best source—the closest or most genetically similar source—so that we’re being as responsible as possible.” In addition to repopulating lakes with frogs of a similar genetic makeup to the original inhabitants, introducing diverse populations to empty lakes could shift the odds in the frogs’ favor. Frog populations are still in decline, and the fate of the species in SEKI remains very uncertain, but with new information of their population genetics, their future looks a little brighter.

Getting a picture of the population genetics across the park, which is larger than Rhode Island and includes thousands of lakes and ponds, was a daunting task. Luckily, as a conservation researcher, Rothstein was well acquainted with the principle of reuse. Hundreds of archived frog skin swab samples already existed in deep freeze but getting useful information from them was no simple matter.

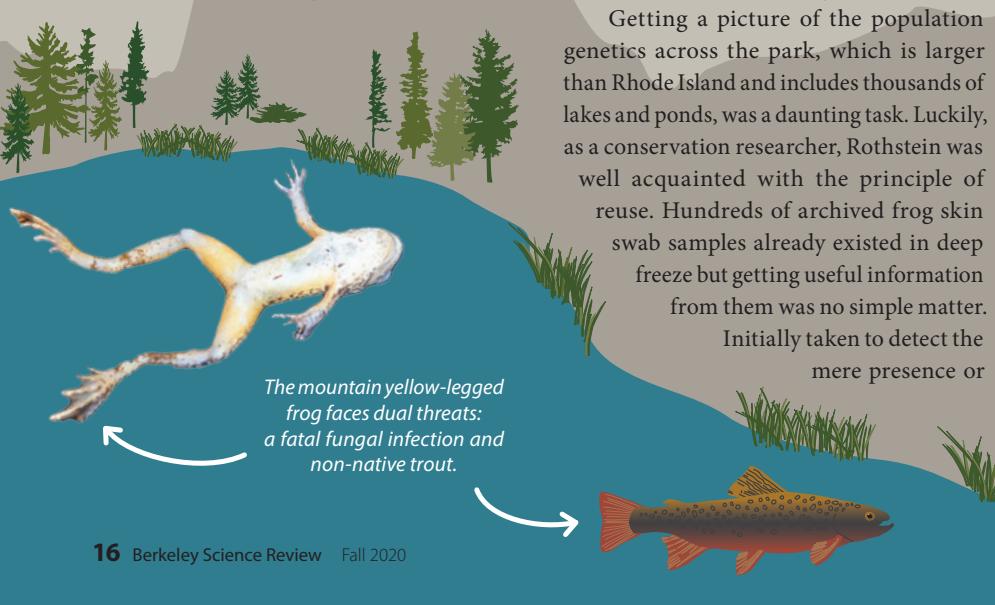
Initially taken to detect the mere presence or

absence of Bd fungus, the samples contained relatively low amounts of frog DNA and included contaminants that made DNA sequencing difficult. Inspired by similar work from Thomas Poorten, a previous frog researcher at UC Berkeley, Rothstein made the most of these low-quality samples by focusing on particularly variable regions of the genome.

This unorthodox data collection paid off. By comparing genetic information from frog populations across the park, Rothstein determined which populations were most genetically similar. He also found that populations that had been infected with Bd, which might have been expected to have lost genetic diversity as the population declined, were just as diverse as uninfected populations. “We could use that diversity to preserve [this species] in the future,” Rothstein says. “It’s a bit of shining hope.”

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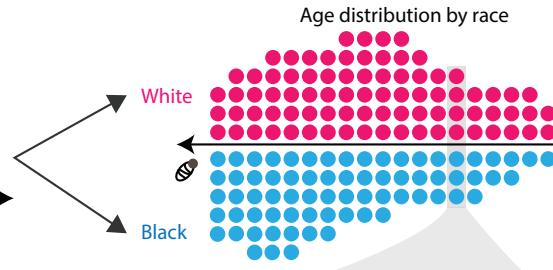
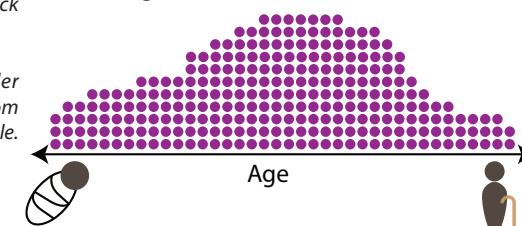
Sophia Friesen is a graduate student in molecular and cell biology.



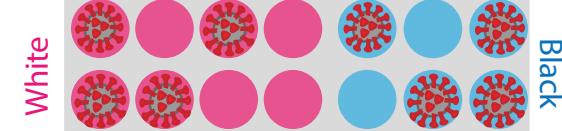
*There are fewer older Black people.*

*Yet, more of those older Black people are dying from COVID-19 than White people.*

Age distribution, combined



Age distribution by race



## Uncovering the pandemic divide

How age reveals COVID-19's hardest hit populations

When the COVID-19 death count surpassed 170,000 in late summer of 2020, the Centers for Disease Control and Prevention (CDC) and major media outlets widely recognized that Black and Hispanic individuals died of COVID-19 more often than White individuals. This trend is not surprising given the countless studies documenting the health disparities affecting minority groups. However, the initial COVID-19 mortality rates from the CDC did not find any major racial differences in COVID-19 death counts. Instead, it was smaller research efforts at UC Berkeley and other institutions that revealed the inequalities surrounding race and COVID-19.

Professor of Demography Joshua Goldstein typically studies social issues related to housing and wages, but when confronted with early statistics that showed no racial disparity in the mortality numbers, he felt he needed to take a deeper look. Goldstein teamed up with postdoctoral researcher Serge Atherwood and together, these two demographers found that the CDC's method for processing mortality data may have grossly underestimated the death rate for Black and Hispanic communities. In fact, they discovered that, when compared to the White population, the death rates for Black and Hispanic populations were 80 percent and 50 percent higher, respectively.

The CDC's mortality rates offer vital insight into the pandemic's progression at a national scale. They are used by public health officials all over the country to see which communities are most vulnerable and to track the efficiency of COVID-19 mitigation efforts. However, mortality rates are not a simple calculation. The raw fatality numbers must be processed to control for confounding factors that may skew the analysis. For example, to account for COVID-19's high density in urban cities, the CDC adjusted the mortality rates for geographical distribution. In other words, the CDC ensured areas with

a dense Black population do not exaggerate the Black mortality rates at a national level. However, Goldstein recognized another important factor not accounted for in the CDC's early analysis: age.

Age is currently the strongest known indicator of COVID-19 mortality, and a population's average age differs significantly depending on race. “Non-Hispanic White people in the U.S. have an older age structure than every other major racial/ethnic group,” explains Atherwood. Accounting for age in the calculation is necessary, as a population with more older people will likely have more COVID-19 deaths. When comparing mortality rates between populations—such as comparing a younger Black population to an older White population—not controlling for age will underestimate COVID-19's impact on Black versus White communities.

By standardizing for age and geography, Goldstein and Atherwood uncovered a pattern of startlingly high death rates for Hispanic and Black communities across multiple states only two months into the pandemic—far earlier than reported by the CDC. “One way to interpret [the higher death rate for Black and Hispanic populations] is that although there are fewer older Black people, a higher proportion of them are dying from COVID-19 than White people,” Atherwood explains.

Acknowledging the racial disparity earlier on in the pandemic would have been invaluable, according to Dr. Rachel Morello-Frosch, a public health professor and environmental health scientist at UC Berkeley. Having the CDC recognize the gap in mortality rates would have not only permitted earlier action, but also would have allowed public health experts to “track the extent to which our interventions may be narrowing that gap,” Morello-Frosch explains.

Atherwood and Morello-Frosch agree

the notable racial difference in COVID-19 death rates is rooted in systemic racial inequality. The results show “a pattern consistent with outcomes seen in other realms of social research,” says Atherwood. Likewise, Morello-Frosch finds that “it’s a mirror on the ways in which inequality and the marginalization of certain groups literally manifest in terms of their health status and how vulnerable they are to the emergence of new diseases.”

Many factors could contribute to a higher minority death rate, including differential access to healthcare, an increased risk of infection due to work conditions and greater public transportation use, or a greater proportion of minorities making up the essential workforce. The “racialized division of labor,” as Morello-Frosch calls it, puts minority groups in more essential, high-risk occupations that may increase their chance of infection.

When the next pandemic inevitably comes, early reporting of precise mortality calculations will be critical, so any underlying racial disparities can be quickly acknowledged and confronted. But ideally, more resources would be focused toward minority communities and their health, as well as educating local health authorities about the most vulnerable communities to diminish or even eliminate the racial disparity in mortality.

Dominik Aylard is a graduate student in molecular and cell biology.

# toolbox

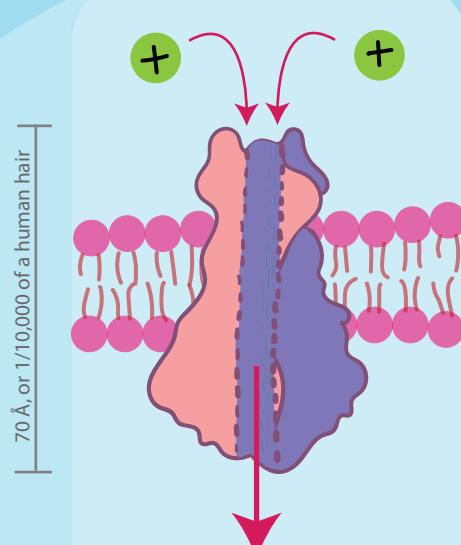
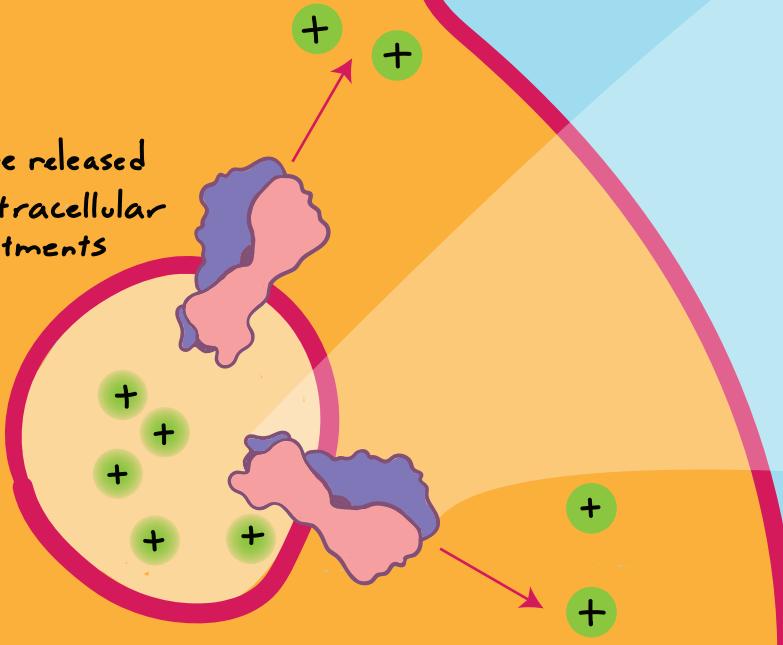
## Putting Corona on ice

The 2011 film *Contagion* became a popular streaming choice in the early days of the COVID-19 pandemic. It was lauded as a realistic depiction of the deadly fallout from a new virus that spreads through respiratory droplets. But David Kern, a postdoc in Steve Brohawn's lab in the molecular and cell biology department at UC Berkeley, keeps thinking about the plot point that seemed least plausible when the movie first hit theaters. "They resolved the structure of a viral [protein] insanely quickly, and I thought: there's no way they would be able to know this so soon," he says. Nine years after *Contagion*'s release, that part seems less far-fetched as his research group shares the results of their rapid characterization of a small protein called 3a, which plays a crucial role in the lifecycle of SARS-CoV-2, the virus responsible for COVID-19.

Kern and Chris Hoel, a graduate student who was also part of the study, are amazed by the "resolution revolution" in

2. Disrupted ion balance can trigger the release of a cell's contents

1. Ions are released from intracellular compartments



The 3a protein makes the host cell permeable to ions, which facilitates the release of viral progeny.

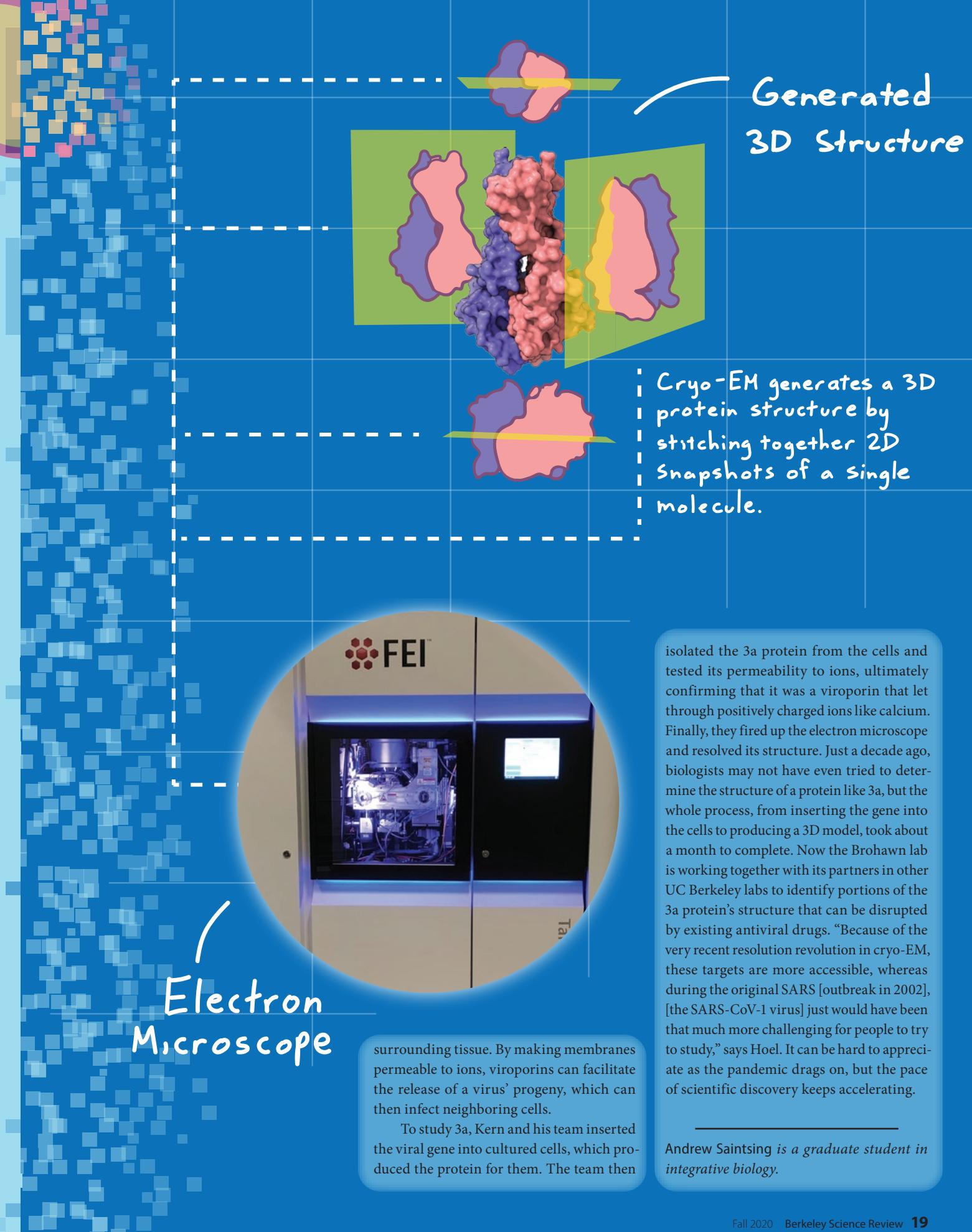
PHOTO: CHRIS HOEL

DESIGN: ALLISON HUNG

cryogenic electron microscopy (cryo-EM) that has transformed their field over the past decade. As structural biologists, they determine a protein's 3D structure, which, in turn, elucidates its function. Before high-powered computers and high-resolution cameras, scientists had to dissolve many copies of a given protein in water and coax them into forming a stable crystal to get a good picture of the molecule. The problem is that some proteins can take months to crystallize, while others, particularly those like 3a that dissolve in fats instead of water, never do. Cryo-EM, on the other hand, generates a 3D protein

structure by stitching together 2D snapshots of a single molecule after it has been flash frozen, circumventing the challenge of crystallization.

The Brohawn lab is one of several research groups around the world that have focused the power of cryo-EM on the proteins of SARS-CoV-2. Their goal is to identify specific viral proteins that are central to a virus' lifecycle, which can be disrupted with antiviral drugs. The genetic sequence of the 3a protein identified it as a potential viroporin, a viral protein that creates a channel through fatty cell membranes and allows ions—charged particles such as calcium—to pass through. The ionic concentrations within a human cell are not homogenous because the cell actively moves ions between distinct subcellular regions separated by membranes. This heterogeneity is essential for healthy functioning. A cell that loses control of its ionic concentrations may die and burst open, releasing its contents into the



Generated  
3D Structure

# from the field



Last winter, I drove from my home in Oakland to Bishop, California to meet up with a back-country cowboy ecologist who would accompany me in my search for snoozing bats.

Along the border between California and Nevada, a large population of Townsend's big-eared bats (*Corynorhinus townsendii*) use the cool, humid mine shafts within the White-Inyo Mountains as safe havens for overwintering. These mines, leftover from the region's history, are appealing locations for hibernating bats. They maintain relatively cool, but above-freezing, temperatures and high humidity, which support lower metabolic rates and reduce evaporative water loss in the bats that roost there. While this species remains active at lower elevations during much of the year to feed on plentiful insects and find mates, only females migrate to elevations ranging from 4,500 to 10,000 feet to hibernate throughout the harsh winter.

Many temperate bat species—like these Townsend's—have unusual patterns of annual reproduction compared to other small mammals. They mate in the autumn months when males and females spend time foraging for food and roosting in the same spaces, but female bats do not immediately become pregnant. Instead, their reproduction is delayed until spring. Female reproductive physiology is adapted to store sperm and delay ovulation while hibernating. When optimal environmental conditions cycle back in the spring, females impressively manage the energetic demands of flight in addition to pregnancy and lactation—hello baby weight! Because they become pregnant almost immediately upon arousing from hibernation, I found myself wondering whether these “future” reproductive costs may affect how female bats manage energy

reserves during hibernation, or influence where they decide to cozy up for the winter.

Digging into this question relied on one very elusive thing: finding hibernating bats. In need of help, I somewhat hopelessly emailed a listserv of chiroptologists (people who study bats) and was amazed by the number of replies that filled my inbox. All were pessimistic, except for one. Dr. Michael Morrison, professor and chair within the Department of Wildlife and Fisheries Sciences at Texas A&M, wrote, “I know where a lot of Townsend's hibernate.”

And so, one year later, I found myself behind the steering wheel of a 4WD rental car filled with field gear and with the windows cracked open just enough to avoid CO<sub>2</sub> asphyxiation from sublimating dry ice. I was making my way to the White Mountain Research Center situated in the Owens Valley just a few miles beyond the Main Street strip of Bishop. There is something about being in the presence of enormous mountains that makes me emotional, and this particular drive down U.S. Route 395 filled me with equal parts nervous energy and sheer joy. Arriving well after dark, I spent the evening counting cotton balls, sterile needles, and small cryovials—a quiet meditation before spending time in the field where everything is a lot less tidy.

Over the next week, I would make myself a large thermos of coffee every morning before throwing my backpack and boxes into Mike's pick-up. We spent the day driving through rocky mountain passes and on gravel paths I hesitate to call roads. To understand how female bats manage their stored energy over winter and the ways that their chosen hibernacula impacts their physiology, we needed to record field measures of body condition and collect samples that I

could bring back to the lab at Berkeley.

As I wiggled, quite literally, through a small hole in a mountain cranny, I immediately understood why so few people know where bats routinely hibernate and tried to focus on my gratitude for being there, rather than the fact that a small earthquake could leave me trapped underground. Once inside, I relied solely on my headlamp to shed light on the jagged rock around me. Confirming the space was just large enough for me to crouch in, I began moving mindfully through the mine, using my lamp like a search light sweeping for something small and fuzzy stuck to the rock. Unlike many biologists who capture bats, we don't need fancy nets or detectors. Our study animals cling quietly to rocks with their delicate toes, their bodies oddly cold to the touch when we find them.

As I recorded mass and body temperature measurements, I remember finding it hard to believe 11-gram bats could be alive with body temperatures hovering around 59°F (over 30°F less than active body temperature). With black leather driving gloves under a pair of nitrile—the biologist's secret to never getting a bite—I carry each bat out of the mine to work on the bed of the truck.

Here I let each bat slowly wake up, uncurling its big ears from over its eyes like a sleeping mask and increasing its metabolic rate and body temperature. Once active, it is safe to take a tiny sample of blood, gently wash out some cells from the reproductive tract, and prepare slides. Later, I will use the slides to look for blood parasites and check for the presence of sperm that would indicate a female has mated. A small sample of fat, about the size of a grain of rice, is carefully removed and frozen over dry ice and a snippet of soft fur taken from its back and saved

in a paper coin envelope. Together, these samples will provide information about diet, immune capacity, mating history, and the biochemical molecules stored for energy during hibernation.

The project will highlight how individual animals cope with physiological and energetic challenges, but will also help us learn more about entire bat populations. Bats are an essential component of ecosystems around the globe, as they help control agricultural pests and play important roles in seed dispersal and pollination. Many bat populations have been decimated due to white nose syndrome, a fungus which predominantly affects hibernating bat species by activating their immune response during a time when energy stores are low. Through my work, we can identify various factors that impact energy use and immune system capacity during hibernation—such as reproductive status or specific hibernacula microclimate—and learn about strategies that permit some individuals to fare better than others. Ultimately, this can inform conservation efforts regarding population susceptibility as well as individual animal health.

After checking off the final boxes for sample collection in my field notebook, I walk the bat back to the portal of the mine from which it came. My fingers loosen their grip around its small body, opening my hand enough for this strong female to rest in the palm of my hand. I raise my arm up high to elevate her, giving her room to drop and catch lift. A few delicate steps to the tips of my fingers, and then I feel her let go, only catching a quick glimpse of wide wings gracefully flapping before disappearing into the dark.

Mattina Alonge is a graduate student in integrative biology.

DESIGN: SHANNON O'BRIEN



# First Cas Gene Delivery

improved delivery methods

make gene therapy safer

by Sierra Lear

Jesse Gelsinger died in November 1999 after receiving experimental treatment for ornithine transcarbamylase deficiency, an obscure disease which prevents the breakdown of metabolic waste products. His death heralded a monumental shift in the aspirations and hopes of researchers and physicians around the world. Just days earlier, gene therapy—modifying the DNA of a patient—was hyped as a miraculous cure for several seemingly incurable and deadly diseases, ranging from Huntington's disease to cancer. However, the field was abruptly quieted following the highly publicized deaths of several patients enrolled in gene therapy clinical trials, including Gelsinger.

Gelsinger's death wasn't caused by the artificial gene injected into his body, but instead by a fatal allergic reaction to the type of virus, known as lentivirus, that was used to carry the gene from the injection site into his cells. Appropriate delivery of DNA cargo via a carrier ship that navigates to the correct destination has been regarded as one of the largest obstacles for gene therapy. Nowadays, thanks to decades of innovations, scientists are finally successfully changing mutated genes in sick patients and generating treatments to countless heritable diseases.

## NUCLEUS

### What is gene therapy?

Gene therapy introduces new genetic material into a patient's DNA to cure disease. DNA contains instructions to create proteins that perform essential functions in the body, and genetic diseases are caused by mistakes or errors in the DNA that lead to missing or dysfunctional proteins. As early researchers discovered this connection, they hoped to create artificial genes or DNA that encoded the dysfunctional protein correctly. Once the artificial DNA was delivered into patients' cells, the cells would have the correct manual for making the appropriate protein.

Yet gene replacement therapy was not without its technical hurdles. Integrating an extra gene into patient DNA, where it was not originally intended to fit, often had unexpected consequences on the surrounding DNA, depending on the size of the artificial gene. In some cases, adjacent genes, or even the integrated gene itself, would suddenly generate more or less proteins than expected. The situation was akin to a young adult who invited their family to live with them. The upheaval in their lifestyle might be minimal if only a single sibling arrived, but would likely increase as more of their extended family decided to move in.

However, in 2012, UC Berkeley chemistry and molecular & cell biology professor Jennifer Doudna found a way to modify DNA that circumvented this obstacle, earning her the Nobel Prize in Chemistry in 2020. She used a new technique called CRISPR/Cas9 genome editing. Cas9 is a protein originally discovered in bacteria that can find a specific DNA sequence and cut it, allowing researchers to more easily delete or edit a specific gene. Cas9 is so specific because it relies on a fragment of RNA, a closely related, single-stranded cousin to double-stranded DNA. This fragment of RNA is aptly named a guide RNA because it guides Cas9 to its cut site by matching and intertwining itself with a complementary piece of DNA targeted for editing. By making precise edits straight into a mutated gene, researchers avoid introducing an entire new copy of the gene.

Whether or not doctors use conventional or CRISPR/Cas9-based methods to treat genetic illnesses in the future, all the materials for treatment must be delivered to the correct cells within a patient. The

Innovative Genomic Institute (IGI), a partnership between UC Berkeley and UC San Francisco aiming to cure disease using gene therapy, has pioneered several solutions to this problem. In particular, researchers affiliated with IGI have made strides by approaching the delivery of gene therapy in two distinct ways: *ex vivo* and *in vivo*.

### Curing sickle cell anemia using *ex vivo* gene therapy

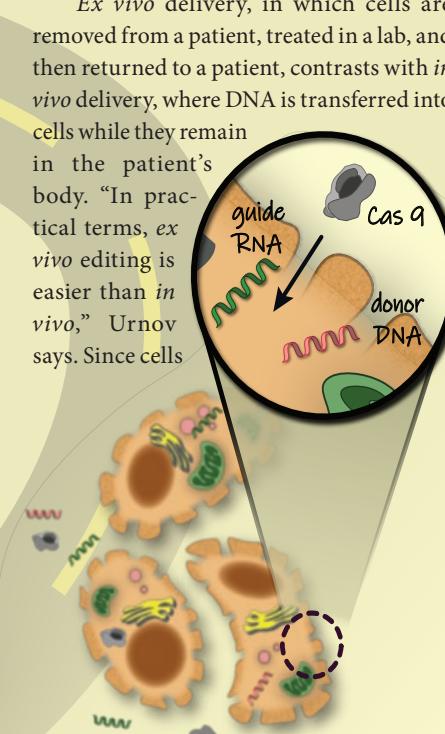
In late 2019, Victoria Gray became the first human to be successfully treated using CRISPR/Cas9-mediated gene therapy. She suffered from a devastating disorder predominantly affecting those of African descent called sickle cell anemia. Her success story was built on the foundation of years of academic research, particularly a 2016 study from the lab of former IGI and UC Berkeley Professor Jacob Corn. They reported on how to cure mice of sickle cell anemia using an *ex vivo* gene therapy strategy, which relies on removing diseased cells from a patient, treating them outside their body, and then reintroducing the treated cells back into the patient. This same *ex vivo* strategy was ultimately used to cure Gray.

IGI scientific director and UC Berkeley Professor of Molecular & Cell Biology Professor Fyodor Urnov describes the first major motivation for targeting sickle cell anemia: opportunity. "When a publicly held company approaches a situation like this, they need to understand how will this be profitable, so you need some number of people," Urnov explains. "Sickle has 100,000 people [in the United States]." As a comparison, around 80,000 people are diagnosed with Parkinson's disease in the United States each year. Urnov continues, "The life expectancy is 40-42 [years], so the unmet medical

need is reasonably high."

Another huge appeal is that sickle cell anemia is especially amenable to *ex vivo* delivery. Sick cell anemia is a blood disorder that transforms healthy blood cells into sickle moon-shaped cells that clog arteries and cannot deliver as much oxygen throughout the body. Researchers are able to siphon and collect the sickened blood cells from the body. Then, they can treat the cells by zapping them with an electric shock. The shock causes the cells to open temporary holes in their cell walls, allowing the CRISPR/Cas9 reagents to move inside and perform the appropriate edits. Scientists observe which of the cells had their DNA correctly edited by Cas9 and transfer only those corrected blood cells back into the patient where they can now function correctly.

*Ex vivo* delivery, in which cells are removed from a patient, treated in a lab, and then returned to a patient, contrasts with *in vivo* delivery, where DNA is transferred into cells while they remain in the patient's body. "In practical terms, *ex vivo* editing is easier than *in vivo*," Urnov says. Since cells



DESIGN: BRITTANY DAWNS

### Apply an electric field

This creates 'holes' in the cell membrane that allow gene editing components to easily cross the barrier.

TITLE SPREAD DESIGN: BRITTANY DAWNS

The cell membrane acts as barrier, blocking the entry of most particles into the cell.

are treated outside the body during *ex vivo* gene therapy, researchers can check that the cells are properly corrected and functioning appropriately before returning them to the patient. Additionally, *in vivo* delivery requires the gene therapy reagents to successfully travel through multiple organ systems in the human body before arriving at the correct tissues. When delivering gene therapy reagents to cells in a petri dish, the chances of successful delivery are much higher.

Despite its advantages, *ex vivo* delivery restricts treatment to very few diseases. Doctors can remove unhealthy blood cells and then inject corrected blood cells into a patient, but they cannot so easily cut away a piece of a patient's damaged brain and replace it with new brain cells. As a result, researchers must pivot to *in vivo* gene therapy to cure most genetic disease.

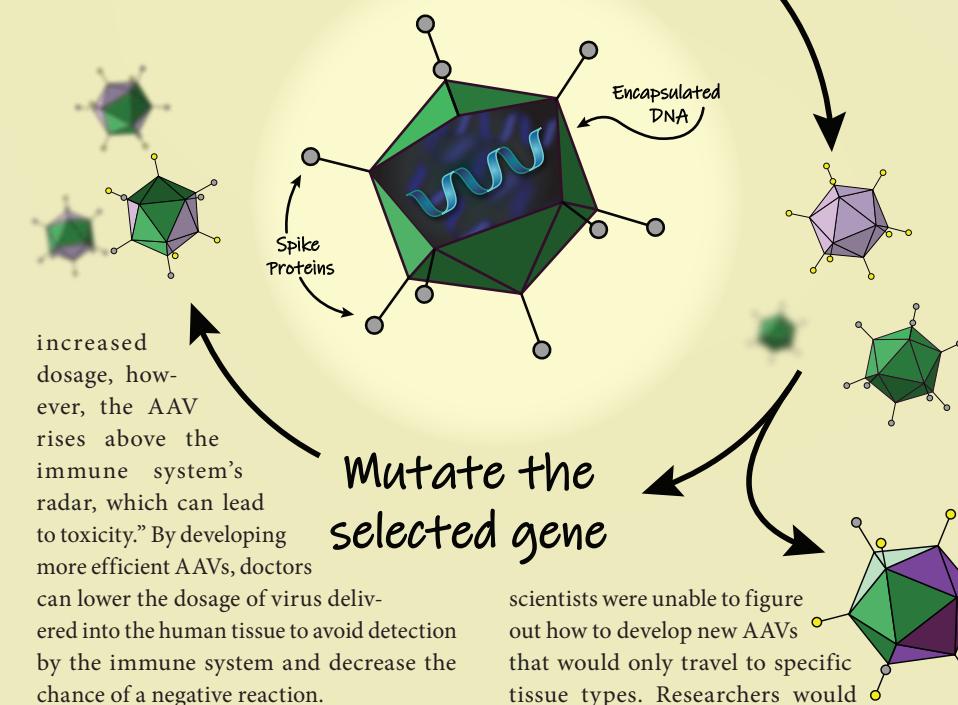
### Changing the destination in *in vivo* gene therapy

Although numerous viral-mediated gene therapy clinical trials failed throughout the 1990s and early 2000s, including the lentivirus that killed Gelsinger, researchers have continued to hijack viruses to deliver gene therapies. They push forward despite the historical failures because viruses have mastered the art of injecting foreign DNA into human cells. In fact, around eight percent of the human genome is estimated to be made of sequences that originated from viruses. The most promising viral carrier is the adeno-associated virus (AAV), a small, naturally-occurring virus that infects humans and other primate species but is not currently known to cause disease.

IGI and UC Berkeley Professor of Bioengineering Dave Schaffer specializes in developing novel AAVs to target specific organs in the body. Viruses that are better at traveling to particular tissues both increase the chance a tissue's diseased DNA will be changed and reduce the chance of any sort of catastrophic allergic reaction. Although these viruses exist in nature, most natural AAVs don't target specific organs. Schaffer explains, "the field has been compensating for that by really amping up the [viral] dose, and still a tiny fraction of the natural AAV makes it to the right tissue. As a result of the

The 'winning gene' from each selection process is mutated to create a new pool. After several rounds, the best genes are isolated and used for further experiments.

## Gene Selection



scientists were unable to figure out how to develop new AAVs that would only travel to specific tissue types. Researchers would redesign specific parts of the AAV

capsid based on their understanding of virus biology to change where it traveled, a technique called rational design or rational engineering. However, the capsid was so complex that researchers were unable to use rational design to successfully determine all the changes they should make. They would inevitably steal away any ability of the virus to deliver gene editing components.

Instead, Schaffer decided to use a different strategy to re-engineer the AAV: directed evolution. Directed evolution was developed by UC Berkeley alum Frances Arnold, who was awarded the Nobel Prize in Chemistry in 2018 for pioneering the use of this technique to engineer enzymes. The strategy of directed evolution emulates natural evolution by creating a large pool of randomly mutated genes before selecting the genes that best survive a particular task. This process is repeated several times by mutating the winner gene from the selection process into a new, diverse pool. Since directed evolution is performed in a controlled lab,

results occur more quickly than they do in nature, where creatures evolve over millions of years. "I began to apply directed evolution towards viruses like AAV for gene therapy applications in 1999, and it's one of those ideas that ended up working even better than I had hoped," Schaffer says. Specifically, his lab would randomly mutate—or perform random mutagenesis on—the capsids of AAVs and then track which AAVs traveled to the tissue where researchers wanted to deliver their therapy.

Directed evolution is ideal for engineering AAVs because, contrary to rational design many capsids can be tested at a time. As Schaffer explains, "With rational engineering, you're basically making one mutation at a time—taking one shot on goal at a time. By doing random mutagenesis, we now have a gene pool of over a billion AAV variants. So, we're not taking shots on goal one at a time. We're taking a billion shots ... all at once."

Those shots on goal have not gone to waste. Fifteen years of hard work have resulted in delivering a virus into the retina to combat several different retinal disorders. Industry connections and collaborations with the Schaffer lab have led to four ongoing gene therapy clinical trials using engineered AAVs in the retina to combat blindness and other eye disorders. The transformation of academic work on wily viruses to direct improvements in human health with clinically tractable treatments that may soon cure patient populations is exactly what Schaffer has always hoped to achieve in his lab. "The fact that we have gotten technology from our lab at Berkeley into multiple human clinical trials is something I'm very proud of," Schaffer says.

### Replacing viruses with gold

Although AAV-mediated gene delivery has had numerous successes, some researchers are pivoting away from using viruses altogether. Instead, they are overcoming the lingering safety concerns of using viruses by creating synthetic carriers to deliver traditional and CRISPR/Cas9-based therapies. One of the most promising non-viral carriers to deliver CRISPR/Cas9 into cells is called CRISPR-Gold, invented in the labs of UC Berkeley Professors of Bioengineering Niren

Murthy and Irina Conboy. Their work has since been catapulted into a start-up called GenEdit founded by Kunwoo Lee, the graduate student in Murthy's lab who spearheaded CRISPR-Gold.

CRISPR-Gold revolutionized CRISPR/Cas9 delivery by showing that it was possible to deliver additional gene editing material that would allow CRISPR/Cas9 to not just destroy, or knock out, a dysfunctional gene, but to correct a dysfunctional gene. The difference between knocking out and fixing is similar to the choice between deleting an entire misspelled word, such as "chocalate", or replacing the misspelled word with the correctly-spelled word "chocolate". While the original only requires Cas9 protein and a guide RNA to tell Cas9 which word to cut out, the latter requires an additional piece of material, called donor DNA, that tells the cell the correct version of the word that needs to be replaced. While some disorders result from the chaotic behavior of a mutated and misbehaving protein, other disorders result from the absence of a protein that is not present in the body. Although knocking out a gene may cure patients that belong to the first category of disease, they cannot treat patients belonging to the second category. Rather, the absence of a functional protein can only be fixed by inserting a correct version of the gene encoding the protein.

Delivering an additional piece of donor DNA along with the rest of the CRISPR/Cas9 was not a trivial task. As Murthy explains, "We focused on a very specific type of problem, which was not just the delivery of the CRISPR protein but also the delivery of the donor DNA. Kunwoo figured out a way to make a nanoparticle that could assemble the Cas9 protein, the guide RNA, and the donor DNA." Specifically, Kunwoo found that gold had a natural affinity to DNA which could be combined

The retrovirus  
Escape membrane to access inside of the cell  
Release from the gold particle and enter the nucleus  
Cas9 directed DNA repair

with other CRISPR/Cas9 components and an additional molecule that helped the whole CRISPR-Gold complex invade cells.

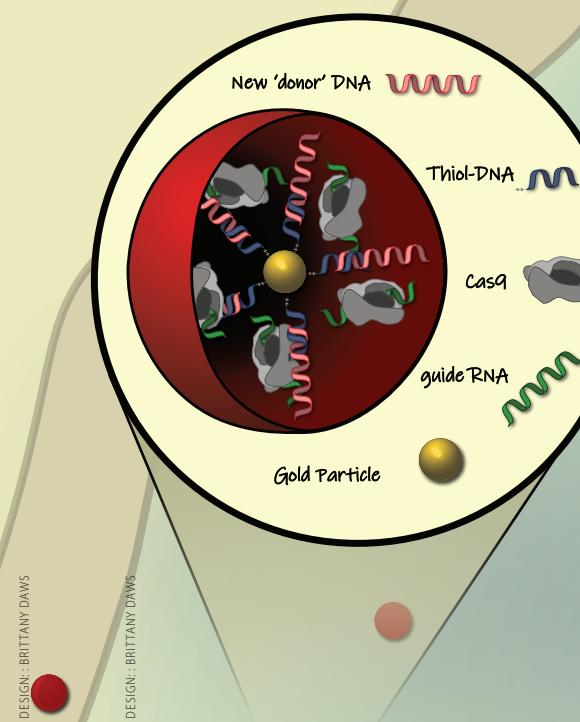
While gold provided an important starting point for delivering DNA along with Cas9, it also created a problem. Gold is not biocompatible, meaning it can accumulate in human tissue and cause people to become sick. However, GenEdit has managed to replace the gold with a synthetic molecule made of repeating molecular chains, called a polymer. This task was not straightforward. "For GenEdit to come up with something that works as well as CRISPR-Gold without the gold, they might have had to synthesize thousands of polymers and invested several million dollars," Murthy says.

Despite these difficulties, investing in non-viral delivery methods such as CRISPR-Gold remains important due to the potential increased safety. AAVs exist naturally in the world, and in people with prior exposure to a specific AAV, there is the chance they will have a harmful immune response, similar to Gelsinger's fatal reaction to lentivirus. Patients are less likely to have been exposed to synthetic nanotechnology, meaning they are less likely to have any sort of allergic reaction.

Most importantly, non-viral delivery can better avoid accidental DNA damage. A couple years after Gelsinger died, another clinical trial in Europe cured eighteen children of severe combined immunodeficiency (SCID) using gene therapy. SCID is better known as bubble boy disease, because if patients are not kept in perfectly sterile environments they will die from a simple cold or infection due to a dysfunctional immune system. While gene therapy cured these children of SCID, following treatment, four of the children developed leukemia, and one of them died from it.

used to deliver the gene therapy had randomly inserted some of the DNA in the wrong place, interrupting a part of the children's genome responsible for preventing cancer.

Unintended manipulation of DNA, similar to what occurred with the SCID cases, is called an off-target effect. While CRISPR/Cas9 gene editing tends to cut DNA more specifically than other viral-based gene editing tools, researchers still worry about Cas9 cutting in the wrong place, especially if it stays around in cells too long. Murthy describes the dilemma: "Gene editing is permanent. Once you corrected a mutation, you don't need the Cas9 protein hanging around afterwards. In fact, having it expressed for long periods of time just increases the frequency of off-target DNA damage, so in the case of gene editing, there are some very compelling reasons to do non-viral gene editing." Viral-based delivery methods, such as AAV, contain a DNA sequence that results in the continuous production of new Cas9, and AAV lingers in some cells for around five years. In comparison, CRISPR-Gold and other non-viral methods do not contain DNA sequences to produce Cas9 but rather add pre-formed Cas9 protein into their carriers. Cas9 is quickly degraded once it is released from its carriers, with half of it being destroyed after six to twelve hours.



DESIGN: BRITTANY DAWES

While potential benefits abound, scientists acknowledge the long battle ahead to elevate non-viral methods to the same status as AAVs. This includes attaining the most coveted prize of all: an FDA-approved treatment using non-viral delivery. AAVs are already FDA-approved, perhaps because they are currently ten to one 100 times more efficient than non-viral delivery methods.

"The big question with non-viral delivery is: is it going to be possible to get the efficiency needed to have therapeutic effects?" Murthy says. "It's an open question whether or not we can improve the efficiency to make it clinically viable." Nonetheless, researchers around the country, and companies like GenEdit, have already achieved great success in improving non-viral methods of gene delivery.

### Other remaining obstacles

Despite the progress in developing delivery methods for gene therapy, several obstacles remain for both *ex vivo* and *in vivo* delivery.

One prominent issue for *ex vivo* delivery is the price and difficulty of introducing DNA or Cas9 into cells. "The only clinical-grade device filed with the FDA to introduce any editing reagent into cells is an electroporator called MaxCyte. It is large, unwieldy, and difficult to work with," Urnov says. A significant problem with electroporation is that it requires that cells from patients are exposed to open air before they are electrically shocked to allow in DNA or Cas9. The consequences of open-air exposure are costly: "If cells are made to see open air, in order to put them back into a subject, you have to utter the three most dreaded letters in all of gene and cell therapy: 'GMP.' Good manufacturing practice. And every time you say 'GMP,' you add three to four zeros to the price of anything," Urnov says.

GMP is a set of standardized procedures to help control the quality of reagents that are used in multiple health products such as pharmaceuticals and medical devices. Although essential for the safety of patients, these practices can often be prohibitively expensive and time-consuming. A patient's own tissue is not subject to GMP when inside a body, but as soon as it is removed from the body and exposed to a laboratory setting, the

strict and pricey GMP rules apply.

Although *in vivo* delivery avoids exposing cells to open air, more work must be done to overcome concerns with AAVs and non-viral carriers. The AAV is only able to carry a small amount of DNA, making it hard to transport whole genes or more complicated treatments to a given cell. Non-viral delivery researchers, meanwhile, are struggling to decrease the size of non-viral carriers made of synthetic molecules. CRISPR-Gold, for example, has mainly been shown to repair DNA in the muscles and brains of mice, because both tissues can be easily targeted using local injections. Most non-viral CRISPR methods are so big that they are unable to be taken up by cells naturally when moving through the bloodstream. Now, labs—including Conboy's and Murthy's—are working on creating smaller, non-viral delivery methods by attaching Cas9 protein with its guide RNA and donor DNA using small molecular linkers.

### The promises of gene therapy

Gene therapy has made incredible progress from its deadly failures in the late 1990s and early 2000s thanks to continuing advances in electroporation, evolved AAVs, and gold nanoparticles. Since the beginning of 2020, at least nine conventional gene therapies have been approved worldwide. The number of traditional and CRISPR/Cas9-based clinical trials and approvals are only expected to increase in the coming years.

Gene therapy has completely changed the lives of those who have been cured by it. Victoria Gray, the sickle cell patient successfully treated using CRISPR/Cas9-based gene therapy in November 2019, has gone from occasionally being unable to move or even feed herself to thriving ten months later. She describes her cure as incredibly fortuitous, as she is now responsible for raising three of her children alone during the COVID-19 pandemic while her husband is deployed out-of-state by the National Guard. Taking care of her family would never have been possible without gene therapy.

Sierra Lear is a graduate student in bioengineering.

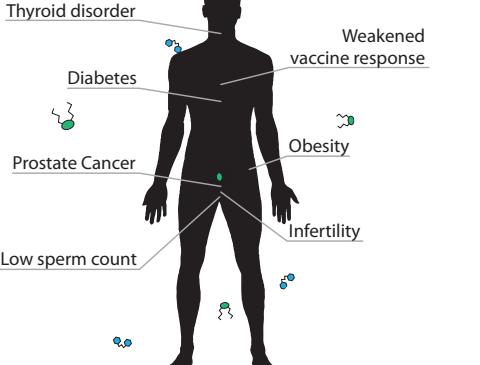
# Labscopes

## No birds and bees with the EDCs

**P**lastic products are everywhere, and we're constantly exposed to the chemicals that make plastic so useful. Many plastics contain endocrine-, or hormone-, disrupting chemicals (EDCs), such as bisphenol A (BPA), which commonly lines food and drink containers. EDCs can alter fertility with chronic exposure, but acute effects are not well studied. Polina Lishko's lab in UC Berkeley's Department of Molecular and Cell Biology recently studied the effects of four EDCs on male fertility. They focused on di-ethyl hexyl phthalate, or DEHP, a chemical found in shower curtains, dolls, and medical tubing. DEHP exposure occurs through ingestion, inhalation, or

skin absorption. It's so ubiquitous that 98 percent of the US population has detectable levels of DEHP in their urine, some at alarmingly high concentrations.

The team, led by graduate student Liliya Gabelev Khasin, discovered that short exposure to physiological levels of DEHP has detrimental effects on male fertility. By fertilizing mouse sperm and eggs in a dish, Khasin found that DEHP-exposed sperm have an impaired ability to penetrate the egg's protective layers. Furthermore, they found that this insufficiency is caused by the sperm's overproduction of damaging radicals. Khasin points out that, despite other varied reasons, "environmental toxins



Impacts of exposure to EDCs on males. Routes of exposure include inhalation, ingestion, and contact with skin.

such as DEHP are a major factor" in the recent drop in fertility worldwide.

While there are still many unknowns regarding DEHP exposure, free radicals, and infertility, this study brings awareness to the impacts of EDC-containing plastics. "It's very difficult to avoid plastic consumption in modern life, but we should reduce it to a minimum," Khasin insists. "Our goal was to increase awareness and hope that the regulation around DEHP will become more stringent, similar to the removal of BPA from kids' toys."

—MAIKO KITAOKA

## PPE to the PPPeople

To handle surges of COVID-19 patients, hospitals must have enough medical supplies. But anticipating which hospitals will need more supplies is like trying to predict the future.

Professor Bin Yu's research group in the Departments of Statistics and Electrical Engineering and Computer Sciences is designing effective ways to predict which counties are going to have a surge of COVID-19 patients. The group has designed an ensemble of predictors known as the Combined Linear and Exponential Predictor (CLEP), to forecast COVID-19 deaths per county two weeks into the future.

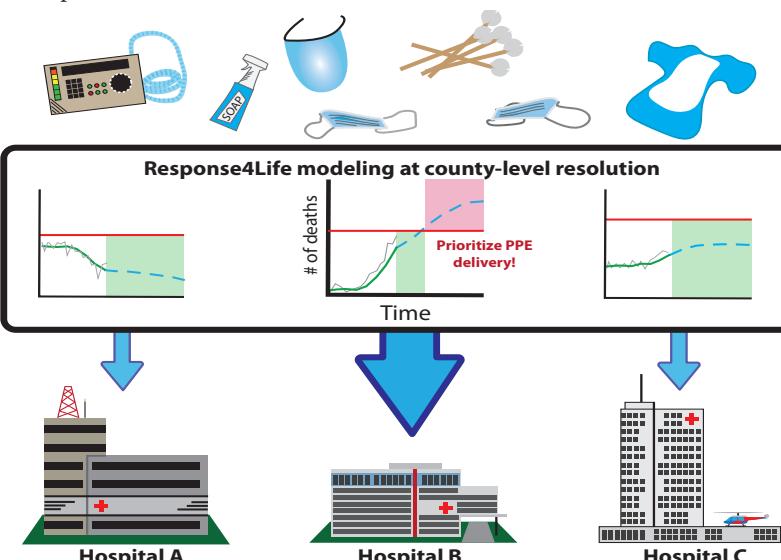
CLEP looks at whether COVID-19 deaths are increasing exponentially or linearly. According to the Yu Group, they used predictors for both exponential growth and linear growth, since they each approximate growth patterns at different phases of the pandemic. For some counties, such as New York county in March, COVID-19 deaths were increasing exponentially. However, as

the outbreak slowed down, most counties' COVID-19 deaths slowed to linear growth. CLEP adjusts its prediction based on which type of growth better fits the data. For instance, if the linear predictor performs better on new COVID-19 data, CLEP will give it more weight over the exponential predictor. Having CLEP update itself dynamically allows the Yu Group to have flexible predictions in the midst of an

incredibly erratic pandemic.

Using their county-level COVID-19 predictors, the group has also developed a method to predict the hardest-hit hospitals. Based on their findings, the group advises Response4Life, a medical supply nonprofit, on which hospitals to prioritize when shipping supplies.

—ALOK TRIPATHY



DESIGN: JOHAN JAENISCH; IMAGE CREDIT: MALE SILHOUETTE AND BRAIN MODIFIED FROM PNGKIT.COM

## Measuring gravity goes mobile

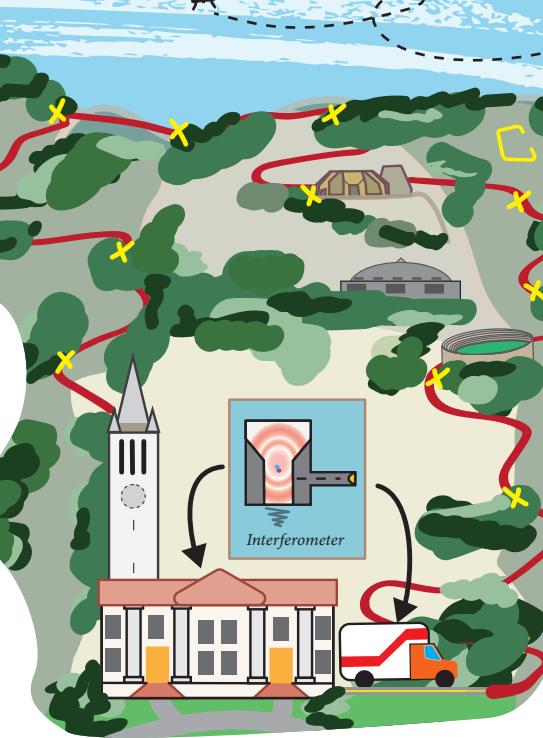
**T**he Mueller lab in the physics department at UC Berkeley uses atom interferometry to precisely measure the Earth's gravitational pull, quantified by the acceleration of objects falling to the ground. For rocket scientists, using 9.8 meters per second squared as the value of gravity might be good enough, but the exact value depends on the earth beneath you. For example, a feather drops minutely slower on a mountain than at sea level. The Mueller group detects these tiny deviations in gravity by studying the interference pattern of carefully dropped atoms.

To visualize interference, consider two rocks dropped in a pond forming ripples. The ripples spread and eventually cross paths. After they meet, a snapshot reveals just a single pattern across the pond, blending the previously separate waves. By carefully studying the interference pattern, one can infer where the rocks splashed. Atom interferometry exploits the wave nature

of atoms to precisely infer the strength of gravity's pull on them.

The Mueller lab's latest breakthrough is their portable gravimeter, an interferometer that measures gravity on the go. They measured gravity in a U-Haul truck driven around the Berkeley hills, and used the measurements to probe the density of rocks below the ground. By freeing the gravimeter from the fragile, expensive environment of traditional laboratories, the Mueller lab has enabled a new generation of scientific applications. There are already proposals to leverage the technology, including monitoring one of the most precious natural resources—ground water.

It's not often that atom-sized experiments are translated to real-world problems. "There are only a few examples of quantum technology leaving the lab," says graduate student Zack Pagel. The group strives to



further simplify the setup and run the next measurement on a drone.

—VINCENT SU

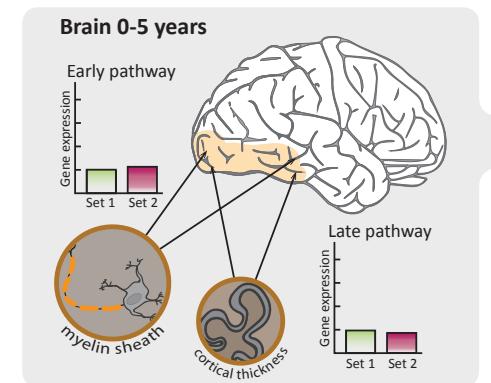
## Build-a-Brain

**T**o tackle questions about the influence of nature versus nurture, some neuroscientists ask why our perceptions of the world are so similar. Is it due to how our brains are wired? Or is it contingent upon having similar visual experiences? At UC Berkeley, the Cognitive Neuroanatomy Lab (CNL), led by Dr. Kevin Weiner, links genetics, brain anatomy, and human behavior to quantify the relative importance of genetics and experience in shaping a person.

In a recent study, postdoc Jesse Gomez focused on the ventral visual pathway.

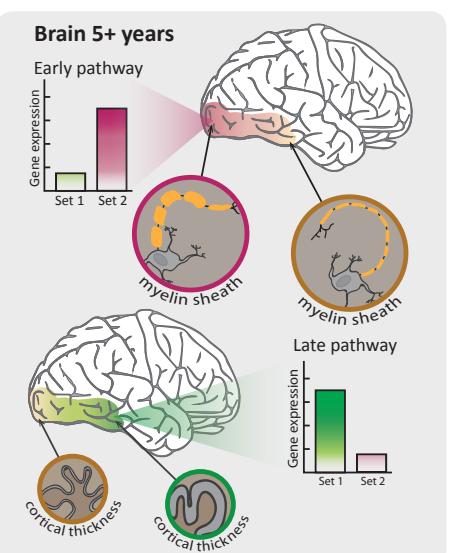
This pathway is organized as a functional hierarchy, meaning early areas process smaller, simpler features—like the edge of an object—and later areas combine these simple features to represent larger, more complex objects—like a face. Gomez discovered two distinct sets of genes whose expression correspond to the thickness of brain tissue and the speed at which neurons fire. These changes in cell structure along the pathway contribute to an increase in the amount of visual space neurons process, explaining why we see an increase in functional complexity.

Gomez also explored how gene expression changes across development. He found that adult-like patterns emerge at age five, not at birth. In other words, even though genetics determine aspects of the structure along the



pathway, experience also shapes anatomy and, consequently, behavior. By probing the influence of genetics versus development on brain anatomy and function, Dr. Weiner and colleagues have begun to unpack how nature and nurture work together to build a brain.

—EMILY MESCHKE



**W**hen plans were first proposed to convert the aging steam plant on UC Berkeley's campus into a combined heat and power cogeneration facility in the late 1970s, it was seen as a major innovation in energy efficiency. Thirty years later, the aging facility is presenting campus leadership with a problem: UC Berkeley is directly responsible for the emissions associated with the cogeneration plant, which, as of last year, accounted for 73 percent of the university's total greenhouse gas emissions. Given UC Berkeley's pledge to reduce greenhouse gas emissions to zero by 2025—and the increasing age of the plant—the university now faces a time-sensitive decision about the cogeneration plant's future. The challenge of how best to provide energy to UC Berkeley's campus involves not only the science of energy, sustainability, and resiliency, but also additional interactions with political and cost-related human factors, making this a particularly complex issue to resolve.

#### What is a cogeneration plant?

In a traditional coal-fired power plant, fuel is burned, emitting heat and greenhouse gases such as carbon dioxide. The heat generated from this process is used to boil water into steam, which then passes through a turbine to produce electricity. However, only around 30-50 percent of the energy released from coal is converted into electricity, and the excess steam is condensed into liquid water and sent back to the plant. On the other hand, cogeneration—or cogen—plants produce both electricity and steam for the community. Cogen plants achieve much higher efficiencies of 65-75 percent by capturing the steam produced while making electricity and using it to heat buildings. This process also reduces the need to burn additional fossil fuels to generate steam from a boiler or steam generator. CO<sub>2</sub> emissions from cogen plants are accordingly significantly lower than separate coal-fired electricity and steam plants per unit of electrical production.

UC Berkeley's cogen plant increases its efficiency even further by using natural gas as its fuel source, which generates roughly half the CO<sub>2</sub> emissions of coal. However, cost, rather than efficiency, motivates this choice of fuel source. Norris Herrington, the manager of UC Berkeley's cogen plant, says,

"You don't have to truck [natural gas] in. It comes in in a pipeline and it's cheap on a per unit basis." He elaborates that the cost of shipping in diesel or coal would be "a heck of a lot more."

Despite being more energy efficient than their counterparts, cogen facilities tend to be less common than traditional power plants because, unlike electricity, it is hard to transport steam over large distances. This transportation difficulty means that any institution using steam generated from a cogen plant needs to be located within "half a mile away maybe, or a quarter of a mile down the road," according to Herrington. The steam generated by UC Berkeley's cogen plant is distributed to approximately 120 buildings on campus for heating and cooling. To reach each building, the steam travels across campus through a series of underground tunnels. Although they are filled with hazards including hot steam, asbestos, and radon gas, these tunnels previously served as a tourist attraction, student haunt, shortcut between lectures, and—allegedly—an escape route for the chancellor fleeing student protests in the 1960s. The steam tunnels have since been sealed off, but students can still see the steam that leaks out from gratings and manholes around campus.

While the cogen plant was initially able to meet 100 percent of the campus's energy needs when it first opened in 1987, due to large increases in the campus population, it now supplies an average of 92 percent of campus' power demand while operating at maximum capacity. Additional electricity is supplemented by Pacific Gas and Electric (PG&E). The plant can occasionally produce more energy than the campus needs at off-peak times, such as nights and weekends, but the capacity to store the excess energy produced is not yet available. As Herrington explains, "You can't really store that amount of energy in a battery" because of current limitations on batteries' maximum storage capacity and lifetime.

#### Cogen versus 2025 carbon neutrality goals

UC Berkeley's cogen plant was initially owned by a third party, which sold its steam to the campus and its power to PG&E. However, after the third party's lease for the

plant expired in 2017, campus leadership made the decision to take over ownership of the plant because UC Berkeley wanted a greater stake in the plant's future. Sally McGarrahah, the associate vice chancellor for facilities at UC Berkeley, explains, "We saw the energy world changing, and locking ourselves into another long-term arrangement with an owner operator would have limited our options for managing our own decisions."

With ownership, however, comes direct responsibility for the emissions associated with the plant. In subscribing to the UC-wide Carbon Neutrality Initiative, the campus has committed to being carbon neutral for building and fleet energy use by 2025. This pledge puts the future of the cogen plant in doubt, given that it runs on natural gas—a fuel which accounts for almost two-thirds of UC Berkeley's emissions. While McGarrahah believes that "the simplest, cheapest thing to do would be to fix the plant we have now," she says that the campus is considering a range of options to meet the campus' energy needs for the future and to fulfill President Napolitano's carbon neutrality pledge.

Not everyone believes that the cogen plant is truly damaging for the environment. While natural gas is a fossil fuel, the carbon dioxide and nitrogen oxide emissions associated with its combustion are much lower than those of coal and oil. As a result, some, including Herrington, consider it a relatively clean fuel. Herrington argues, "California is about the only place that doesn't consider natural gas clean. In every other state in the country natural gas is clean; that's what I grew up hearing." Combustion emissions, however, are not the only source of greenhouse gas emissions associated with natural gas. The drilling and extraction of natural gas from wells and its transportation in pipelines can also result in leakages of methane, a greenhouse gas that traps even more heat than CO<sub>2</sub>. The process of hydraulic fracturing, or fracking, typically used to extract natural gas, is also associated with significant environmental impacts, such as increased erosion, ground and surface water contamination, and earthquakes.

Dan Kammen, professor of energy at UC Berkeley who works on decarbonizing energy systems worldwide, vehemently disagrees

DESIGN: EMILY GONTHIER

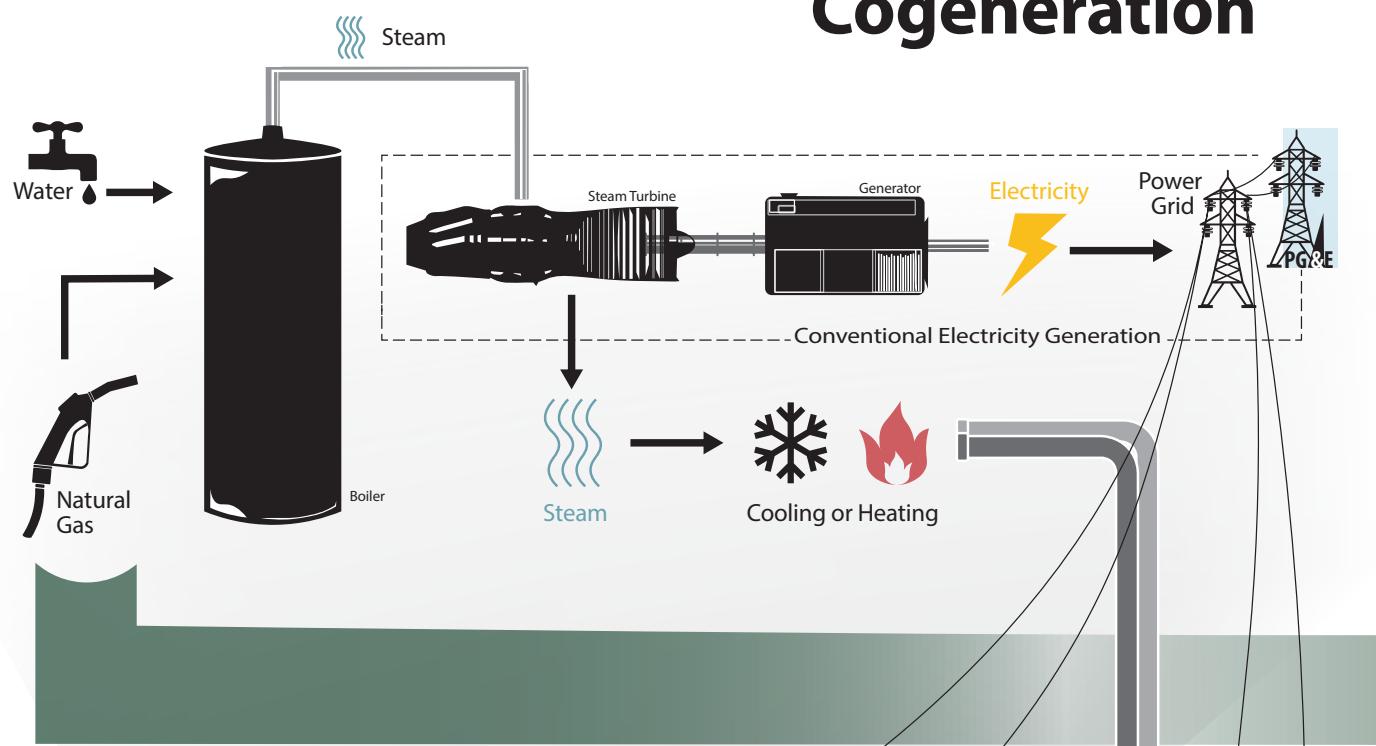
# POWERING



Planning Cal's  
carbon neutral future  
*by*  
Leela Velautham

# DOWN

# Cogeneration



University of California  
**Berkeley** Campus Map

DESIGN: EMILY GONTHIER

with Herrington about the environmental impact of natural gas: "It's not relatively clean—that's just a lie. It's a fossil fuel," citing the greenhouse gases produced from both burning and leaked natural gas.

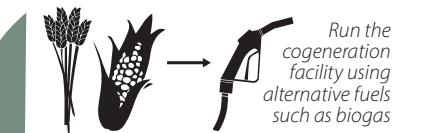
UC Berkeley has already reduced emissions from the plant since reclaiming ownership by making significant changes to its operations, but it's not enough. Reducing the plant's output during the evening when less energy is needed—rather than running it at full capacity all the time—has slightly lowered its greenhouse gas emissions, but far more significant and extensive reductions in natural gas usage and energy generation are required in order to meet the 2025 carbon neutrality goals. As McGarrahan says, "Everything is on the table to figure out how to move towards carbon neutrality under a cost model that we can make happen." Options currently being considered range from keeping the plant open with adaptions to decommissioning it entirely.

## Rethinking the cogen plant

If UC Berkeley continues to use the cogen plant, the campus will have to modify infrastructure in the plant itself to make it more energy efficient. Ideas of reforming the plant are driven by the cogen facility's age. Herrington believes that the 33-year-old plant has around 10 years left: "It's probably getting on up there in age, but personally I think we could make it until 40." As a result of the plant's age, significant and expensive upgrades are necessary to keep it operational at its current capacity, but these upgrades also provide a convenient opportunity to improve the plant beyond its current state. As McGarrahan explains, "We should certainly invest towards the future instead of just thinking of the immediate." UC Berkeley had one of the first cogen plants across the UC system, so the plant is now one of the first to approach the end of its expected life. "We hope to set a path for these other campuses as they come to the end of their cogen's life," she says.

*Upgrade the cogeneration facility and keep operations at current capacity*

Another scenario is to use alternative fuels to power the plant, rather than natural gas. For example, the plant could use biogas, also known as biogenic methane, which is produced from the decomposition of organic materials such as agricultural waste, landfill materials, and solids from wastewater treatment plants. Biogas is made from plants, which naturally remove CO<sub>2</sub> from the air as they grow, so the emissions from burning biogas are typically considered carbon neutral. Once impurities such as water and heavy metals are removed, biogas can be directly substituted for natural gas.



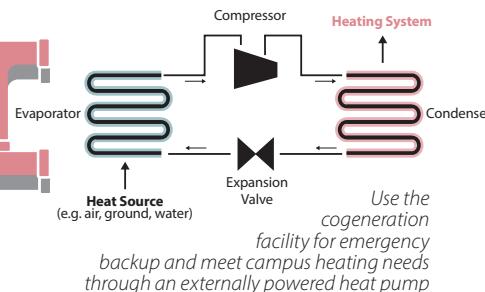
But, just like natural gas, biogas also comes with several disadvantages. The largest concern is the limited availability and transportation infrastructure of biogas nationwide. Biogas currently is not considered a scalable alternative to natural gas, with the National Renewable Energy Laboratory estimating that the current biogas resources in the US would only satisfy 1.5 percent of its natural gas consumption. Herrington also believes that biogas is not a feasible solution from a financial perspective, stating that the UC Office of the President's investments in "some biogas in Louisiana or something ... really aren't economically viable and wouldn't exist if they weren't being subsidized."

Kammen additionally calls the discussion about non-renewable fuels, such as biogas, "unfortunate." He questions the feasibility of switching out natural gas for lower-carbon biofuels: "The more we dig in on [fuel alternatives], the more we discover this is just not a viable pathway." Kamen also explains that biofuels often come at the expense of forests or crops and require high levels of pesticides and irrigation to cultivate, resulting in higher carbon emissions than initially apparent. "It doesn't make any sense to invest in things which we know aren't sustainable," he says.

Alternatively, campus could create a new hybrid heating and electricity system, using the cogen plant only for emergency backup. In such a system, the majority of the

campus' heating needs would derive from a heat pump—an externally powered device that transports heat from one place to another—while electricity would be mainly sourced from the grid. Meanwhile, the cogen plant's operation would be reduced to provide backup power, for instance, in an electricity shutdown, and to serve as a backup source of heat when it is cold. This strategy is similar to the route taken by the natural gas-run cogen plant at UC San Diego, which is now only used as a backup when biogas and solar photovoltaic sources are insufficient to meet the campus' energy needs. Kamen cites the UC San Diego campus as a potential guide for a similar transition to 100 percent clean energy. "We know it can work. UC San Diego essentially already has such a plan—they're not entirely there, but they went to batteries and solar and we need to do a version of that," he says.

However, he also acknowledges that in order to get the Berkeley campus off fossil fuels entirely we "need to push more aggressively." Kamen suggests that reducing the cogen plant to a backup power source would mean that UC Berkeley would still ultimately be reliant on natural gas and fossil fuels. He advocates for fully decommissioning the plant and powering the campus through purchased electricity and renewables alone in order for UC Berkeley to take the bigger, bolder active steps and really "walk the walk."



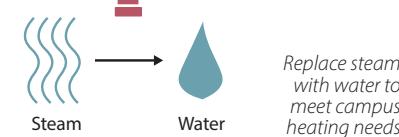
## Shutting down the cogen plant

The most aggressive plan to meet the carbon-neutral pledge is to fully decommission the cogen plant and instead use energy generated from entirely renewable sources. In such a scenario, most of the campus' electricity would come from PG&E, which generates 86 percent of its electricity from greenhouse gas-free sources as of 2019, with an additional contribution from on-site solar and fuel cells. Since the campus is land and sun poor, it

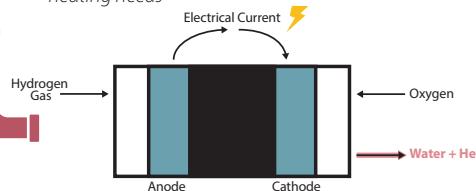
could not rely on its own renewable sources alone to fully meet its electricity demands.

While clean electricity like solar power has become more accessible and cheaper, renewable heat is generally much more expensive and difficult to obtain. Kammen, however, argues that “it’s not that it’s difficult; it’s just that we’re not used to it.” He points to fuel cells as a potential zero-carbon heating solution. Fuel cells work in a similar way to batteries, generating heat and electricity through electrochemical reactions. In a hydrogen fuel cell, the hydrogen molecules are separated into building blocks that can combine with oxygen to produce water and heat. This technology has been used by NASA since the 1970s to generate drinking water for astronauts in space. Kammen argues that the heat generated by a hydrogen fuel cell could be used to meet campus’ more modest heating needs, like warming dormitories. To produce higher temperatures required for more energy-intensive laboratories, Kammen recommends using solid oxide fuel cells, which operate at higher temperatures than hydrogen fuel cells. Overall, he says that the use of both hydrogen and solid oxide fuel

where water is stored in pipes underground and heated when needed using pumps that extract thermal energy from the ground. “There are all sorts of ideas around these super-efficient heating and cooling systems, which UC Berkeley is a potential candidate for,” she says.



*Rely on renewable energy supply for electricity generation and use fuel cells to meet campus heating needs*



cells will give the campus a pathway to skip over biofuels and “really jump to a clean energy system directly.”

Mary Ann Piette, a staff scientist at the Lawrence Berkeley National Laboratory (LBL) whose research focuses on building energy efficiency efforts, also emphasizes the need to transition away from heating via steam, which she calls “very inefficient and very leaky.” She instead cites systems like the district heating and cooling system that was recently installed at Stanford, where stores of hot and cold water are kept and pumped around the campus, because “water is a lot more efficient to pump around than steam.” She also mentions the potential of new systems currently being used in Europe,

cogen will be upfront rather than sustained, and requires a mix of debt, donations, and grants as possible means to finance campus’ future energy landscape.

### Energy resiliency

An additional—and increasingly important—consideration for any future energy scenario on campus is resiliency. A resilient energy system would keep campus powered in emergencies that make external electricity unavailable. The cogen plant is resilient but buying the majority of our electricity from PG&E would not be. Stoll states, “We need to create that same kind of resiliency we have right now with our own plant with whatever system we move to.”

Considerations of energy resilience have become more pressing since the PG&E shutdowns of 2019. As McGarrahan explains, “We were aware, but not with the hyper-awareness we gained last fall, so this has affected our planning.” She shares that one potential option is maintaining the cogen plant to keep serving the southside of campus, with the capability to provide electricity to the whole campus as backup. The rest of campus’s heating needs would be served by the introduction of smaller, more localized nodal thermal plants distributed around the campus. The advantage of localized generation of energy is increased efficiency while phasing the campus toward serving heavier loads if needed. While using the cogen plant as a potential backup source of electricity for the whole campus was not originally considered in this scenario, it is now being included to provide a reliable source of backup power in the case of recurring problems with power delivery from PG&E.

Kammen believes that an energy-resilient campus and a sustainable campus are not incompatible. He suggests that a potential solution would be to use our available physical resources around campus, including the current site of the cogen plant, to house different energy storage technology such as lithium ion batteries, flow batteries, and fly wheels that would provide “several days’ capacity of storage on site.” LBL staff scientist Piette also echoes the call for clean backup in the form of “photovoltaics and batteries for as much as we can,” in combination with a cultural shift to using less energy on campus.

For example, people on campus could limit the use of energy-intensive equipment to the middle of the day when more renewable energy sources like wind and solar are available and electricity from the grid is at its cleanest and cheapest. Additionally, people could be more prepared to enter and emerge from emergency modes. “We could run parts of the buildings and keep things up, but … not turn the entire campus off,” Piette suggests.

### Next steps

Campus leadership and other stakeholders on campus—including financial experts, engineers, and faculty across a range of departments—are currently in the lengthy process of evaluating the proposed energy scenarios from several different perspectives, including capital costs, potential environmental impacts, the type of land use required, cost to update current infrastructure, and how to meet the UC policy around carbon neutrality.

Stoll explains that an additional major challenge of trying to plan for a long-term future without the cogen plant is that

technology in this area, especially energy storage, is constantly evolving and changing. “The other thing we’re looking at is how can we build something that can accommodate new, lower cost technology going forward, as they become available,” Stoll conveys. Plans must be flexible enough to incorporate new technologies as they arise. As McGarrahan says, “We try to be aware all the time of not putting too rigid a box around what we’re doing … fuel cells, hydrogen—you name it, we’re interested.”

Ultimately, the future of UC Berkeley’s cogen plant depends upon a collision of factors: cost, social and political dynamics, and the ever-evolving science behind energy resiliency, technology, and sustainability. The 2025 carbon neutrality goal, however, adds additional pressure for a decision about the future of the cogen plant to be made quickly. As Kammen states, “We either make it or not based on the decision now.”

Leela Velautham is a graduate student in education in math, science and technology.

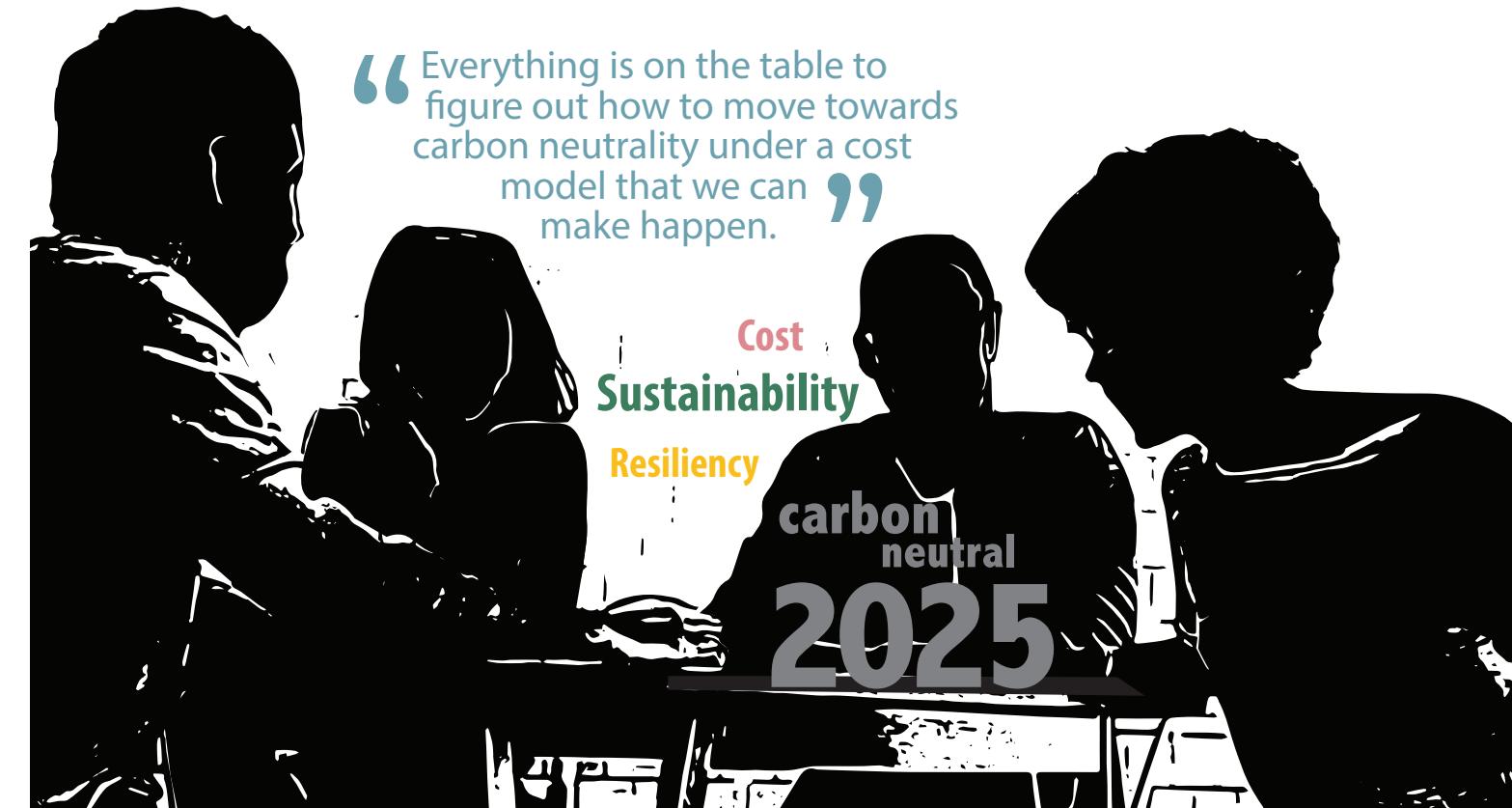


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