Discovery

Research at Princeton

Predicting the next one:

Could a global disease-forecasting service warn us of approaching pandemics? **10**

2020-21

PRINCETON UNIVERSITY

Highlighting the resilience of research

The image of the brilliant researcher working alone in the lab is a staple of popular culture, but it is more the exception than the rule. In most disciplines, research is collaborative and highly social. Large teams have cooperated to decode the human genome, detect gravitational waves, piece together historical documents and excavate archeological sites. Today, research is more often than not a team sport.

COVID-19 has challenged that norm. In March 2020, researchers at Princeton, like those at universities across the country, switched off computers and equipment, cleaned out lab refrigerators, and shuttered their labs and offices. They went home to bedrooms, basements and dining rooms to spend the next few months staring at lab mates and collaborators through a two-dimensional screen.

Despite these challenges, Princeton research continued. Princeton researchers continued. They crunched data, wrote up their results, and shared their ideas and insights via videoconferencing. They maintained the social side of science. I cannot help but be impressed and inspired by how well Princeton research thrived throughout the roughly three-month stay-at-home period.

In June, we were fortunate to welcome back a portion of our research community, those whose work requires on-campus equipment. As of this message's writing (early November), we continue to operate under the principle that work that can be done remotely should continue to be done remotely. We are working to bring back additional researchers as soon as it can be done safely.

If I was impressed by our researchers' orderly shutdown in March, I am even more impressed with how our community has reopened the labs with thoughtfulness and consideration for one another's health and safety. Our survey of researchers who have returned to campus showed very high compliance with mask wearing, social distancing, staying home when sick, and other public health measures.

What is more, our research enterprise continues to thrive. Our sponsored research expenditures for fiscal year 2020 were the highest on record, and our faculty continue to submit proposals and obtain funding for COVID-19 research and for other projects. In fact, proposal submissions during this period were the third highest on record. Our faculty and research teams continue to publish high-impact findings in major journals.

PHOTO BY FRANK WOJCIECHOWSKI

I'm particularly proud of how our scientists and scholars are contributing to confronting the pandemic. Early on, Princeton awarded nearly half a million dollars in COVID-19-related research funding that has already led to insights on ways to prevent infection as well as on how the pandemic is affecting the economy and our everyday lives.

COVID-19 is not the only challenge facing our nation in 2020. We continue to confront racial injustice, a major economic crisis, and the undeniable effects of anthropogenic climate change. Several stories in these pages address how research and scholarship at Princeton are helping to address some of these challenges.

The Princeton spirit is indomitable. Our creativity and resourcefulness, not to mention our intellectual leadership, mean that the brilliant researcher, even if working at home due to COVID-19 public health restrictions, is never alone. Princeton is many brilliant researchers working together, for new knowledge, in the nation's service and the service of humanity.

Pablo G. Debenedetti
Dean for Research
Class of 1950 Professor in Engineering and Applied Science
Professor of Chemical and Biological Engineering

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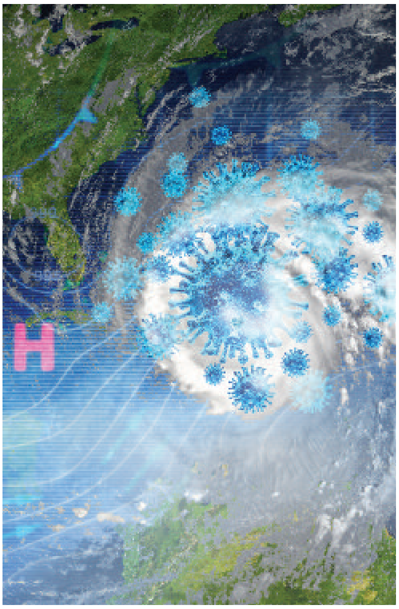

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Just as forecasters warn of hurricanes, a proposed global disease-surveillance service could monitor emerging outbreaks and warn the public of impending pandemics. Illustration by John Opet

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In the Nation's Service and the Service of Humanity

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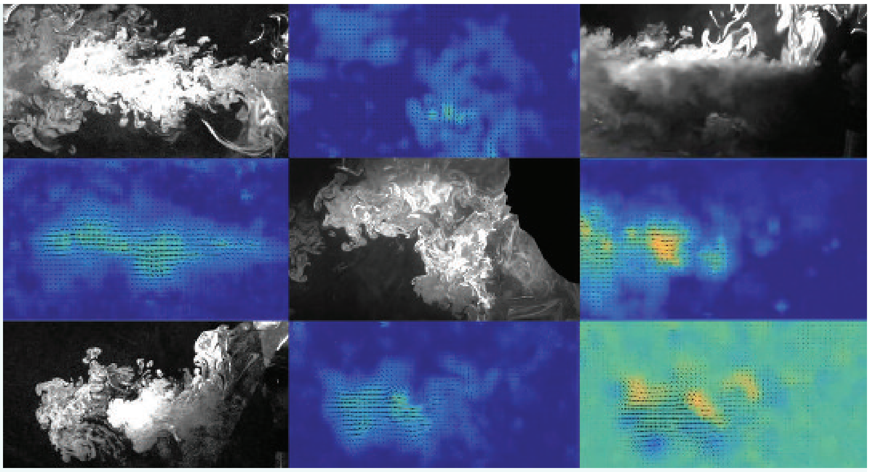
COVID-19

Conversation spreads droplets more than six feet indoors



COURTESY OF HOWARD STONE

With implications for the transmission of diseases like COVID-19, researchers have found that ordinary conversation creates a conical, "jet-like" airflow that carries a spray of tiny droplets from a speaker's mouth across meters of an interior space.

Howard Stone, the Donald R. Dixon '69 and Elizabeth W. Dixon Professor of Mechanical and Aerospace Engineering, and co-lead researcher Manouk Abkarian, a senior scientist at the University of Montpellier in France, led experiments to learn how widely and quickly exhaled material could spread.

In an article published Sept. 25, 2020, in the *Proceedings of the National Academy of Sciences*, the researchers concluded that normal conversations can spread exhaled material at least far as, if not beyond, the social distancing guideline of six feet. The research was funded by a National Science Foundation Rapid Response Research grant.

The researchers also said that while masks do not completely block the flow of aerosols, they play a critical role in disruption of the spray of droplets from a speaker's mouth.

"This identifies why [most] masks play a big role," Stone said. "They cut everything off." ***—John Sullivan***

HUMANITIES

Magic Grant sparks interactive map of treasures

With the pandemic limiting in-person visits to libraries and archives, Princeton's Humanities Council began offering Rapid Response Magic Grants for projects that spark innovation and collaboration amid social distancing. One such project is Mapping Eastern Europe in the 13th–17th Centuries, which offers simple and intuitive engagement with the art and history of the culturally rich, yet often enigmatic and neglected, territories of the Balkan Peninsula, the Carpathian Mountains and early modern Russia. Led by Maria Alessia Rossi, an art history specialist in the Department of Art and Archaeology and the Index of Medieval Art, and Alice Isabella Sullivan at the University of Michigan, the project website features an interactive map offering case studies, historical overviews, and notices about ongoing projects, as well as reviews of recent books and exhibitions. ***—Humanities Council***

ICON GALLERY-OHRID, N.I. INSTITUTE FOR THE PROTECTION OF THE MONUMENTS OF CULTURE AND MUSEUM-OHRID, MACEDONIA

Virgin from the Annunciation

ENERGY

Public-private partnerships propel fusion research

The quest to develop a safe, clean and virtually limitless source of energy for the future has brought the U.S. Department of Energy's (DOE) Princeton Plasma Physics Laboratory (PPPL) into partnership with private companies. PPPL has teamed with five technology companies in the United States, Canada and Great Britain to unlock the potential of fusion, the process that powers the sun and stars, to meet humanity's ever-growing electricity needs. The DOE sponsors the partnerships under its nationwide Innovation Network for Fusion Energy (INFUSE) program, with Ahmed Diallo, a PPPL physicist, as the program's deputy director. ***—John Greenwald***

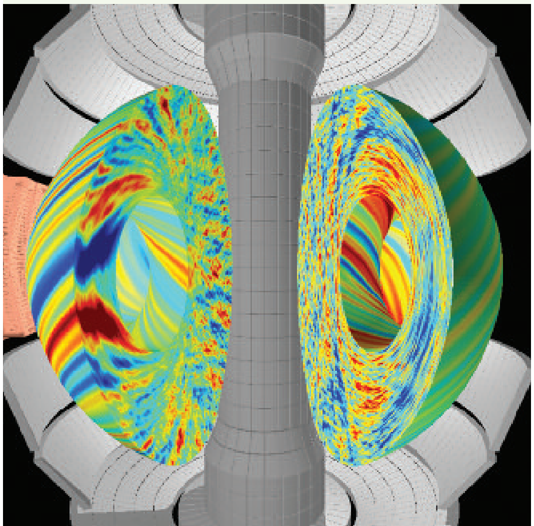


IMAGE PROVIDED BY WALTER GUTTENFELDER, PPPL, AND FILIPPO SCOTTI, LAWRENCE LIVERMORE NATIONAL LABORATORY

HEALTH AND MEDICINE

Bacterial anti-infective defense systems could aid humans

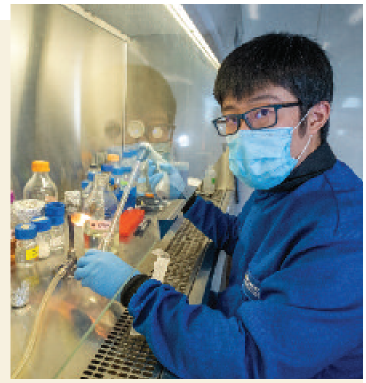


PHOTO BY C. TODD REICHART

The search for new antibacterial and antiviral drugs, including those that could fight COVID-19, is being aided by bacteria themselves. The strategy, pioneered by Mohammad Seyedsayamdost, associate professor of chemistry, exploits bacterial self-defense mechanisms: When bacteria are under attack by other microorganisms, they produce antibacterial and generally toxic compounds, which the researchers collect and study for their suitability to protect humans. "More than half of the anti-infectives used clinically come from nature, from natural products synthesized by bacteria, fungi or plants," said Seyedsayamdost, who in 2020 was named recipient of a John D. and Catherine T. MacArthur Foundation fellowship, considered one of the most prestigious grants in the nation. "These molecules have been honed by evolution to kill a competitor or a virus, exactly the type of thing we want to do in medicine." ***—Wendy Plump***

QUANTUM COMPUTING

Princeton to help lead new quantum science center

Princeton University will play a major leadership role in a new multi-institution center for the advancement of quantum science research announced by the U.S. Department of Energy. The Co-design Center for Quantum Advantage (C^2QA), headquartered at Brookhaven National Laboratory, will develop quantum technologies to serve as the platform for the computing innovations of the future, promising benefits for national security, pharmaceutical development, optimization of resources and more. With involvement from 24 research institutions and over 70 lead investigators, C^2QA will include several Princeton faculty members in major leadership roles. The deputy director and second in command is Princeton Professor of Electrical Engineering Andrew Houck. ***—Catherine Zandonella***

CANCER RESEARCH

New "recycler" protein kicks cancer to the curb

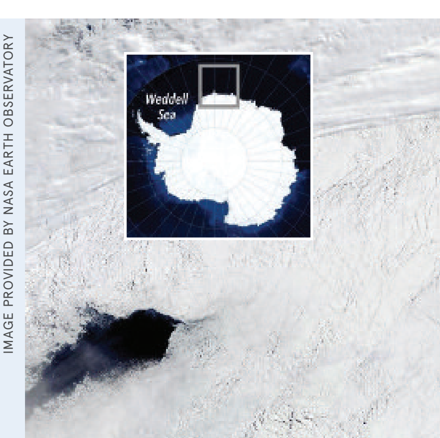
A dangerous protein called SNAI2 helps cancers spread and hide from treatment, but now researchers at Princeton have found two keys to controlling it: A "recycler" named ASB13 that tags SNAI2 for shredding, and a molecule named USP20 that removes those tags. While SNAI2 is notoriously hard to attack directly, ASB13 and USP20 are controllable by medications, providing possible new paths to treatment, said Yibin Kang, the Warner-Lambert/Parke-Davis Professor of Molecular Biology. The team published the result online Sept. 17, 2020, in *Genes and Development*. ***—Liz Fuller-Wright***

UNDERGRADUATE RESEARCH

Antarctic sea ice retreat spurs plankton blooms

Lauren von Berg, Class of 2020, is first author of a peer-reviewed paper studying the role of Antarctic sea ice in regulating the growth of the tiny algae known as phytoplankton. Published in the journal *Geophysical Research Letters* online May 24, 2020, the study found that the retreat of sea ice can significantly influence phytoplankton activity, and, thus, the amount of carbon dioxide the organisms can remove from the atmosphere. Von Berg, who majored in computer science, used her coding skills during her High Meadows Environmental Institute internship at the Scripps Institution of Oceanography to analyze data from floats deployed by the Southern Ocean Carbon and Climate Observations and Modeling project based at Princeton. "My computer science knowledge helped me jump right in," von Berg said. "It was very exciting to see my work result in a peer-reviewed paper." ***—Morgan Kelly***

IMAGE PROVIDED BY NASA EARTH OBSERVATORY



Princeton pivots toward COVID-19

Within days of shutting down their laboratories in response to the COVID-19 pandemic in March, Princeton researchers were asking how they could help.

"Many members of the Princeton faculty reached out with requests for opportunities to use their knowledge, ideas and skills to assist in combating the COVID-19 pandemic," said Dean for Research Pablo Debenedetti, the Class of 1950 Professor in Engineering and Applied Science and a professor of chemical and biological engineering.

In response, the University created a fund of over half a million dollars to support research on COVID-19. The projects, which are still ongoing, range from vaccines and treatments to policy, social and economic topics.

The manual of physical distancing

In the early months of 2020, professors of architecture Paul Lewis and Guy Nordenson realized that the COVID-19 pandemic would make a significant and long-lived impact on cities. New strategies would be needed to rework the design of cities during peak infection and after restrictions are eased.

"The city's density, historically its greatest asset, is now perceived to be at odds with the realities of the pandemic, and is now a crippling vulnerability," Lewis said.

Lewis and Nordenson teamed with David Lewis of the Parsons School of Design, Marc Tsurumaki of Columbia University, and a team of architects and designers to create the Manual of Physical Distancing, an online visual tour of how the virus affects the areas where we live, learn, play and work. The manual distills information from universities, institutes and governments into easily understandable graphical explanations.

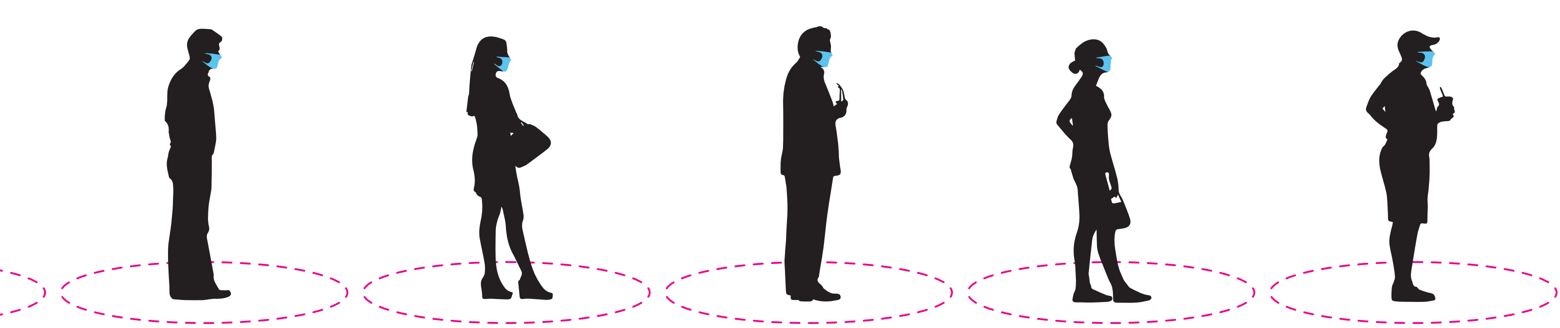
"We sought to negotiate the incompatibility between the functional density of urban spaces and the protection of health," Nordenson said.

Domestic violence and the pandemic

As unemployment rose and large numbers of people began working from home, Maria Micaela Sviatschi, assistant professor of economics and public affairs in Princeton's School of Public and International Affairs, recognized the potential for an increase in domestic violence. Roughly 12 million people in America report experiencing domestic violence annually and 35% of the worldwide population has reported at least one incident.

Sviatschi and collaborators quickly assembled a survey of 8,000 women to assess their attitudes and access to information about domestic partner violence, including interventions such as hotlines and counseling. The research team included economist Sofia Amaral of the ifo Institute at the University of Munich, as well as graduate student Lindsey Buck and Associate Professor of Economics Nishith Prakash of the University of Connecticut.

Although the study is not yet complete, some women reported abusive behaviors such as having their phone constantly checked, being



isolated from their friends and family, and being told what they can or cannot wear. A small number of women reported physical abuse, and a high proportion of the women reported self-blaming.

COVID-19's economic impact

To study the effect of business shutdowns and government stimulus on consumer behavior, assistant professors of economics Natalie Cox and Arlene Wong, with coauthors at the University of Chicago, examined credit card and bank account data from millions of customers. They found that household spending plunged similarly across all income levels in March and April, and that government payments appear to have benefited low-income households, which despite job losses, showed faster rebounds in spending than higher-income households.

The uniform spending cuts across all income levels suggest that the economic shutdown, rather than job losses, were likely the primary driver of spending declines. "Overall declines in spending were much larger than what could be explained by the rise in unemployment," the authors wrote in a paper published in the summer 2020 special edition of the *Brookings Papers on Economic Activity*.

The team also concluded that stimulus programs likely played a sizable role in helping to stabilize spending and savings, especially for low-income households.

Therapeutics and vaccines

To make SARS-CoV-2 safer for handling in the laboratory, Alexander Ploss, associate professor of molecular biology, and his team are developing a less virulent version of the virus. The strain, developed by reverse engineering the virus, lacks components needed to infect cells. Researchers can use this non-infectious version to test new therapies.

To search for treatments for SARS-CoV-2 acute respiratory distress syndrome, the team collaborated with scientists at Boston University to develop new mouse models that contain human lung tissue. The Ploss lab and their collaborators in Boston are working on a vaccine against the virus modeled on a successful vaccine against yellow fever.

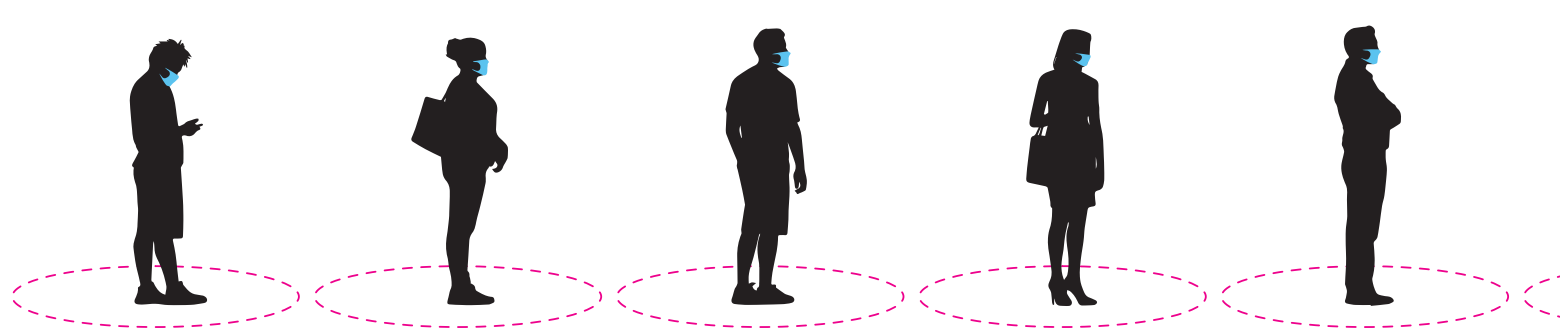
"In addition to these lines of experiments, we have been able to establish very productive collaborations with others at Princeton to identify components that are essential for SARS-CoV-2 entry and replication," Ploss said.

Closing the door on COVID-19

When the virus SARS-CoV-2 attacks the body, the virus's spike proteins must latch onto the human protein ACE2 on the surface of cells to open the door for the virus to enter. Clifford Brangwynne, the June K. Wu '92 Professor of Chemical and Biological Engineering, and colleagues are testing small molecules to see if they can block this process.

The researchers' first step was to develop a way to identify small molecules that thwart the fusion of the virus spike protein with ACE2. The test involves labeling the proteins with colorful fluorescent markers that light up when a molecule successfully stymies spike-ACE2 fusion.

The team is collaborating with colleagues on campus, and around the country, to understand the biophysics of how ACE2 and spike proteins interact, and to study promising small-molecule candidates as treatments for COVID-19. "We are also excited about the potential broader application of this drug-screening approach for other types of common viral infections, particularly those that affect children," Brangwynne said.
—Catherine Zandonella



Not JUST data:

Ruha Benjamin exposes the injustice behind the numbers

W

When Ruha Benjamin was 14, she moved from South Carolina to the South Pacific with her parents, educators tasked with curriculum development and teacher training in Majuro, the capital of the Marshall Islands. To keep the family entertained, her father brought boxes of VHS tapes filled with "Star Trek" episodes.

"It was my only entertainment for nine months," Benjamin said. "I became a real Trekkie."

Later as a graduate student at the University of California, Berkeley, Benjamin realized that many of the scientists and engineers she met shared her love of science fiction. Shows like "Star Trek" weren't just fiction — they were inspirations that led to real innovations and discoveries.

She also noticed that only a small sliver of humanity had the resources and power to translate sci-fi visions into reality — to boldly go where no one has gone before. The rest of the world is forced to "live inside someone else's imagination," Benjamin said.

> The rest of the world is forced to "live inside someone else's imagination," Benjamin said. "What motivates me is to radically expand that imagination."

"What motivates me is to radically expand that imagination," she said.

As the novel coronavirus infiltrates communities of color, and protests erupt over the nation's long history of police violence against Black Americans, people are increasingly aware that institutions have long failed people of color. Benjamin, professor of African American studies, envisions a path to structural changes and a more equitable future by recognizing the failures of the past. Those failures, she believes, are written in data.

Evidence of prejudice and racial inequality are baked into the numbers coming from institutions such as banks, hospitals, schools and prisons. But data can be misinterpreted or intentionally twisted through stories and narratives. In this era of misinformation, if data are to be used for justice, Benjamin argues, the data alone are not enough. Researchers need to be "as rigorous about the stories as they are the statistics," she said.

In 2018, when Benjamin created the Ida B. Wells JUST Data Lab, her goal was to shrink the space between data and interpretation by providing context, limiting the ability for stories and narratives to deflect the truth.

"The concept of JUST Data is to highlight that no data are actually objective," said Cierra Robson, Class of 2019 and a mentee of Benjamin's. "Instead we need to find ways to make it just — as in justice. We need to identify ways to use data for the social good."

The disproportionate number of hospitalizations and deaths due to COVID-19 among people of color, for example, should ideally lead to a greater allocation of resources in those communities to help curb the disparity. Instead, at a press conference in early April, a government official called for people of color to "step up" and avoid tobacco, alcohol and drugs — placing the blame not on systemic failures, but on the very people who are suffering.

"People likely see those numbers and think, 'What are those people doing to get infected at such a high rate?'" Benjamin said. "It becomes even greater fuel for pathologizing and blaming people who are most affected."

Benjamin's efforts are not the first attempts to use data to upend racial injustice. The lab's namesake is Ida B. Wells, the civil rights leader, suffragette and investigative journalist. In 1895, in the midst of intense racial violence targeting African Americans in the post-Reconstruction era, Wells published the Red Record, a historic effort to quantify lynchings in the United States after slavery.

"This was an early example of using data for anti-racist ends," Robson said. "It is the tradition from which we come and an exemplar of the work we do."

Robson is the associate director of the JUST Data Lab's new Pandemic Portal, which collects, examines and distributes data on the impact of COVID-19 on communities of color. The team formed the portal in response to what Benjamin calls the converging crises of SARS-CoV-2 and police brutality.

"Forty-million-plus people have lost their jobs, but the top millionaires have made money this year," Benjamin said. "And we've deputized police to manage that powder keg of inequality."

Powered by undergraduates

In summer 2020, about 40 undergraduates worked on the Pandemic Portal with Benjamin, whose goal is to mentor 100 students every year. The students partnered with community organizations working to address racial inequality in the context of the pandemic. They gathered data on the racial dimensions of the pandemic across 10 domains: arts, mutual aid, mental health, testing and treatments, education, prisons, policing, work, housing and health care. The resulting data-based tools and resources are available on the Pandemic Portal website.

"One of the beautiful things about the Pandemic Portal has been realizing that each of these categories, which seemed very separate — police violence and prisons on one hand, and education, hospitals and health care on the other — are actually deeply connected," Robson said.

Masha Miura, Class of 2021, investigated policing for the Pandemic Portal. Her group worked with Stop LAPD Spying, a coalition of community members in Los Angeles, to investigate how government efforts to track COVID-19 cases could feed harmful forms of surveillance, like predictive policing, or lead to deportations of undocumented people.

This practice can erode trust in medical providers, leading people to avoid seeking care. The researchers created data visualizations that showed how some government contractors had misused data in the past, and provided resources to inform the community about how to protect themselves.

"Ruha has given me a lot of hope for what it means to be a student activist," Miura said, "and shows how research at Princeton can actually give back to these communities."

—Jerimiah Oetting

PHOTO BY CYNDI SHATTUCK

Ruha Benjamin, professor of African American studies, created the Ida B. Wells JUST Data Lab to explore how data are misinterpreted or intentionally twisted through stories and narratives.

Tempest in a laptop:

Ning Lin's hurricanes help planners brace for the big one

Ning Lin denies she predicted Hurricane Sandy, the massive storm that made landfall in New York City in October 2012, causing widespread coastal flooding and wind damage.

"When people say that, I correct them," Lin said. "I don't predict specific events, I predict probabilities. The probability of New York City being hit by strong storms and flooding was higher than most people expected."

But the timing was uncanny. Just months earlier, while a postdoctoral fellow at the Massachusetts Institute of Technology (MIT), Lin co-authored a study projecting that climate change would drive significant coastal flooding on a frequency of once a decade rather than once a century. New York City, the authors said, was highly vulnerable.

It was a startling prediction at the time. New York City experiences far fewer hurricanes than southeastern states like Florida. With little historical data to go on, predicting future extreme storms seemed far-fetched. But Lin's postdoctoral mentor was MIT's Kerry Emanuel, a veteran in the study of hurricanes in the age of climate change, and from him Lin had learned how to solve the problem of too few historical storms — she would generate her own.

Lin, who today is an associate professor of civil and environmental engineering at Princeton, compensates for the lack of historical storms by conjuring hurricanes on her computer. Consisting of bits and bytes, these storms leave behind no damage, but are quite handy at helping predict the destruction these tempests are likely to wreak, especially under future scenarios.

The practice of generating synthetic storms got its start with simple statistical models that civil engineers have used since the 1980s to design skyscrapers to resist extreme winds. But hurricanes are a lot more complicated, and they may change significantly in a warming climate. They create not only high winds but also rainfall and storm surges. And much about how hurricanes behave is still unknown.

> Consisting of bits and bytes, these synthetic storms leave behind no damage, but are handy at helping predict the destruction these tempests are likely to wreak under future climate scenarios.

"The formation of hurricanes is actually quite a complex physical process that is not well understood," Lin said.

However, we do know the ingredients. They include warm surface temperatures, high humidity levels, low wind shear and high vorticity, which is the tendency for the air to move in a rotational pattern. When these factors combine in just the right way at the right time, hurricanes result.

Knowing the relationships between the makings of a hurricane and the resulting storms allows researchers to write software to simulate new storms and predict their path and strength. The engineers don't calculate every step — that would take supercomputer-level capabilities. Instead, researchers study the likelihood that combinations of ingredients — such as wind direction and strength, humidity and high ocean temperature — give rise to storms. It is a bit like knowing that eggs, flour and sugar, combined in certain ratios in a specific sequence, can make a cake, but not knowing every step in the process. By studying enough combinations of inputs and outcomes, researchers can predict which mixtures are likely to stir up a storm.

The resulting synthetic storms are all perfectly plausible. Each could spring up off the coast of Africa and traverse the Atlantic making aim for the Caribbean islands. Some might swing northward and scuttle up the East Coast, swerving inland over Manhattan. Some might move slowly, dumping copious rain, while others whip along wreaking destruction with high winds.

Since 2012, when she joined the faculty at Princeton leading her own research team, Lin has continued to improve the methods for generating realistic synthetic storms. Earlier this year, with graduate student Renzhi Jing, Lin published a new and more accurate hurricane model that incorporates a type of artificial intelligence known as machine learning. Rather than human engineers scrutinizing past ingredients to make projections of future storms, computers do the work.

The model running on Lin's laptop can whip up thousands of storms over the course of a few hours. For each storm, the model outputs movement and direction, intensification over time, and likelihood of making landfall.

To find out what kind of the damage the storm could do, the team connects the storm models to hazard models that predict the amount and location of rainfall, the strength and direction of wind, and the height and spread of storm surge.

With these predictions in hand, engineers can design infrastructure resilient to the extreme winds, rainfall and coastal flooding wrought by hurricanes. For example, engineers can build seawalls, elevate houses, rezone residential areas and reinforce buildings.

Where extreme storms are rare, as in New York City, synthetic storms are especially valuable for illustrating these risks. In a typical year, the Atlantic Coast experiences roughly six hurricanes, about two of which are Category 3 or higher, meaning they are especially large or severe. That isn't much of a record on which to make a decision about building a seawall or relocating residents at a particular coastal location. But Lin's laptop can generate 500 years of hurricanes — or about 3,000 storms — in a few hours. Roughly a third, or 1,000, will be severe, and that is a sample large enough for evaluating the potential damage.

Lin's career at Princeton began as a graduate student in civil and environmental engineering. While earning her Ph.D., she completed courses in environmental policy in Princeton's School of Public and International Affairs, where she met Michael Oppenheimer, the Albert G. Milbank Professor of Geosciences and International Affairs and the High Meadows Environmental Institute, who later became a co-author on the 2012 paper that came out prior to Hurricane Sandy. When Lin finished her fellowship at MIT, she wanted to find a place where she could couple civil engineering with science and public policy, so she chose Princeton.

In a recent study, Lin and her team employed their synthetic hurricane models to estimate the risk of storm surge along the East and Gulf coasts. The team, whose work is supported by the National Science Foundation and the National Oceanic and Atmospheric Administration, found that historical 100-year floods could become annual occurrences in some northern coastal towns.

Whether Lin will be right about this prediction, time will tell. ***—Catherine Zandonella***

Ning Lin, associate professor of civil and environmental engineering, and her research group use computers to whip up virtual hurricanes that help policymakers evaluate the risks of severe storms in regions such as New York City, where such storms are rare but potentially devastating.

PHOTO BY DAVID KELLY CROW

Forecasting the next COVID-19

Could a global disease-surveillance service warn us of approaching pandemics?

By Jerimiah Oetting

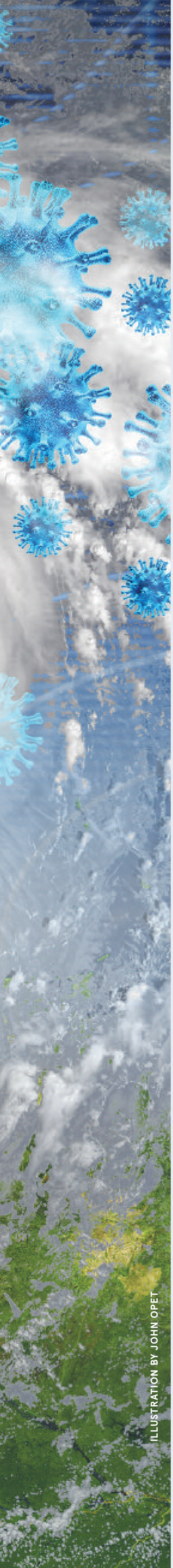


ILLUSTRATION BY JOHN OPET

Princeton disease ecologist C. Jessica Metcalf and Harvard physician and epidemiologist Michael Mina say that predicting disease could become as commonplace as predicting the weather. The Global Immunological Observatory, like a weather center forecasting a tornado or hurricane, would alert the world, earlier than ever before, to dangerous emerging pathogens like SARS-CoV-2.

In late October 1859, one of the century's most devastating storms struck the British Isles. Winds, estimated at over 100 mph, howled across the Irish Sea. The storm destroyed 133 ships and caused at least 800 deaths, more than half on the Royal Charter, a steam clipper built to handle the increased gold rush traffic to Australia.

Despite early signs of the impending storm, the captain pushed forward instead of seeking shelter. He was caught off guard by a gale, which overpowered the ship and sent it careening into the rocky shoreline. Any warning of the storm's strength would have prevented the tragedy.

Storm prediction was thought to be impossible at the time, even considered sacrilegious by some. But in the aftermath of the Royal Charter disaster, one scientist was convinced it could have been averted.

Robert FitzRoy, best known as Charles Darwin's salty captain aboard the HMS Beagle, was the head of a new program to catalog weather observations made by ships at sea. Using his growing knowledge of weather patterns and his arsenal of charts, barometers and thermometers, FitzRoy demonstrated that he could have predicted the storm, allowing time for ships to change course. Weather forecasting — a term FitzRoy coined — could save countless lives.

FitzRoy's early methods pale in comparison to the global, unified effort that now produces our hourly weather forecasts. Thousands of buoys, distributed across the world's oceans, measure sea-surface temperatures. Weather stations and satellites feed data into complex computer models. Anyone with a computer or smartphone can gain a (mostly) accurate picture of current and future weather, anywhere in the world. We take for granted our ability to check the forecast.

Today, we find ourselves in a different kind of storm. Like the captain and crew of the Royal Charter, the world has been caught off guard — this time, by a devastating illness.

COVID-19 isn't the first global pandemic, and it won't be the last. The emergence of disease, from the Black Death to the novel coronavirus, is as unpredictable as the weather was in past centuries. Now, scientists at Princeton, in collaboration with others, are working toward a future where pandemics are predicted, prepared for and — in some cases — prevented.

"If this pandemic has made one thing obvious, it's that the health of any of us is the health of all of us," said C. Jessica Metcalf, a disease ecologist at Princeton University.

Metcalf, together with epidemiologists and immunologists from Princeton, Harvard University, the Wellcome Trust and the National Institutes of Health, pitched an idea for a new and revolutionary approach to global health — a way to make predicting disease as commonplace as predicting the weather.

They call it a Global Immunological Observatory, or GIO. Like a weather center, it would monitor the world's health by compiling data in a systematic and cohesive way. And, like a weather center forecasting a tornado or hurricane, a GIO could alert the world, earlier than ever before, to a dangerous emerging pathogen like SARS-CoV-2.

Had such an approach been in place, countries could have initiated a more cohesive and global response early in the coronavirus pandemic, potentially saving countless lives.

"We're going to do our damnedest to try and make it happen, because it would be crazy not to," said Metcalf, associate professor of ecology and evolutionary biology and public affairs in Princeton's School of Public and International Affairs.

What's today's health forecast?

It's December. You're packing for a trip home for the holidays. Your smartphone informs you to expect subzero temperatures in Minneapolis, so you pack your heavy winter coat. You scroll down and learn your home zip code is experiencing a particularly high caseload of seasonal flu. You add a few masks to your bag, just in case.

"Every day, we have parents looking at their kids and saying, 'You have a runny nose, I wonder what it is? Maybe it's the flu,' said Michael Mina, a physician and assistant professor of epidemiology at Harvard T.H. Chan School of Public Health. "We go to the doctor. But most of the world doesn't have that as an option."

> "If this pandemic has made one thing obvious, it's that the health of any of us is the health of all of us."
>
> —**C. Jessica Metcalf**, Princeton University School of Public and International Affairs

A GIO would provide parents with a way to check local disease conditions. Maybe the parent learns there is a local outbreak of the common cold, not the flu, and so skips the trip to the doctor. Staying home saves time, resources and prevents spreading the disease further.

Metcalf and Mina were the two leading authors of an article pitching the GIO in the June 2020 edition of the journal *eLife*. The other co-authors were leading immunologists and disease ecologists: Adrian McDermott and Daniel Douek of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases; Jeremy Farrar, director of the Wellcome Trust; and Bryan Grenfell, the Kathryn Briger and Sarah Fenton Professor of Ecology and Evolutionary Biology and Public Affairs in Princeton's School of Public and International Affairs.

Mina, who prior to joining Harvard conducted postdoctoral research at Princeton in infectious disease dynamics with Grenfell, envisions the GIO as an open and accessible resource for everyone, providing immunity data by zip code.

But its usefulness in "peacetime" — what epidemiologists call the time between pandemics — is just a bonus. Its true power is detecting novel pathogens and acting as an early warning system.

"Had we had this running, we would have definitely been able to detect SARS-CoV-2," he said.

With the earliest reports out of China, scientists would have been on high alert for strange signals in the stream of immunity data pouring into the GIO. They would have been able to detect a unique pattern emerging across the regions hit early by the pandemic — like New York, Washington and the San Francisco Bay Area. The first detection of those signals would have given Gov. Andrew Cuomo of New York the data-driven firepower to shutdown New York City a month earlier, Mina said.

"And that would have saved tens of thousands of lives," he said.

A GIO would require an unprecedented level of collaboration between scientists and doctors, governments and citizens across the planet. And it would require blood.

"I think of the body as a constantly recording pathogen-detection device," Mina said. "All we have to do is tap into the hard drives, which are the plasma cells and antibodies, to better understand what's happening in our environment."

Blood would provide the data that would drive the observatory. Antibodies, the y-shaped proteins responsible for detecting and neutralizing invaders, are found in our blood serum. They're produced in response to infections, but each antibody can bind only to a specific pathogen.

The types and quantities of antibodies contained in our serum reflect our immune system's past and present battles — a catalog of pathogens it has encountered, whether through infection or vaccine.

Until recently, most blood-serum tests detected antibodies for a single pathogen at a time. But recent breakthroughs have expanded that capability enormously. One example, a method developed at Harvard Medical School in 2015 called VirScan, can detect over 1,000 pathogens, including all of the more than 200 known viruses to infect humans, from a single drop of blood.

Using drops of blood collected from people spanning the globe, methods like VirScan could quickly paint a picture of humanity's collective immune system. The more diverse that blood, the better resolution that picture will have.

"We just want to throw everything at it," Metcalf said. "A lot of the work will be interpreting what we see."

There are already robust methods for collecting blood serum at large scales — think of existing blood banks, supported by individual donations. For people who opt to contribute, they could learn about their own immunity and to which diseases they might be susceptible.

Once data from enough individuals is amassed, scientists could glean important insights about the threats facing humanity's immune system. What demographics are hardest hit by the seasonal flu in Taiwan? What virus is responsible for this year's cold outbreak in North Dakota?

The GIO concept is in a development phase, somewhere between idea and reality. Mina is pursuing the funding and construction of a flagship lab in Boston. Its first project will begin through a partnership with a company that has plasma donation sites across the United States.

By processing tens of thousands of samples, donated by people across the United States, the GIO's first project will be an example, in miniature, of its global potential.

"We're operating on the 'build it and they will come' logic," Metcalf said.

The dark matter of epidemiology

For a given disease, a population can be categorized into three groups: those who are susceptible, those who became infected and those who have recovered. Most of what we know about COVID-19 is derived from active cases and mortality. But that describes only the middle category. The other two comprise what Metcalf and Mina call "the dark matter" of epidemiology. During a disease outbreak, a GIO would illuminate those poorly understood categories.

Susceptibility is difficult to assess, but it is critical for describing a disease's progression through a population. As more people acquire immunity, either through infection or vaccination, the number of susceptible people shrinks. But identifying the populations that remain vulnerable can help prevent an unexpected resurgence of infections.

Princeton disease ecologist C. Jessica Metcalf, associate professor of ecology and evolutionary biology and public affairs.

PHOTO BY SAMEER A. KHAN/FOTOBUDDY

Michael Mina, physician and assistant professor of epidemiology, Harvard T.H. Chan School of Public Health.

IMAGE PROVIDED BY HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

It indicates to public health experts if, and where, new outbreaks may occur.

This is precisely what the scientists in Metcalf's lab aimed to investigate in Madagascar. Amy Winter, now a postdoctoral researcher at the Johns Hopkins Bloomberg School of Public Health, led an effort to investigate blood serum samples to explore the portion of Madagascar's population that was susceptible to measles.

There were tens of thousands of annual cases of measles in the country until 2004, when widespread vaccinations successfully decreased the caseload to just a handful. Despite this successful mitigation, public health officials lacked data on the portion of the population that remained susceptible because they hadn't been vaccinated.

The researchers thought the drop in cases might reflect a honeymoon period, where vaccinations significantly slowed the spread of the virus despite many susceptible individuals remaining in the population. To find out, Winter investigated existing blood serum samples that had been gathered a few years prior, to test if immunity was truly as widespread as the low caseload suggested.

The serum samples were far from ideal — they weren't from a representative sample of the population, for instance. Metcalf said any classical epidemiologist would have been frustrated with the data. Yet, however imperfect, the data overwhelmingly revealed that many in the population lacked protection from the disease.

"Unequivocally, whatever we threw at it, we just kept seeing that there was an outbreak coming," Metcalf said.

Unfortunately, their prediction was correct. A measles outbreak occurred in fall 2018, leading to an epidemic particularly among young children. Ongoing surveillance of blood serum antibodies would have described the extent of susceptible individuals long before the outbreak occurred. Vaccination efforts then could have targeted the demographics found to be susceptible, and yet another tragedy may have been averted.

Patchwork in tatters

The COVID-19 pandemic has caused a confused and uneven response around the world. Some governments, particularly those on the frontlines of previous pandemics, effectively coordinated a response in the early days. Perhaps nowhere was the patchwork response exemplified, and its consequences felt more acutely, than in the United States. Despite suffering the world's highest mortality, even simple interventions like mask mandates cause political divisions.

"Public health and infectious disease surveillance has been decreasingly funded for decades — people didn't recognize the need," Mina said. "It took one massive pandemic to bring our country to its knees. Having systems in place beforehand is just essential."

As COVID-19 has displayed, many U.S. systems lack cohesion, from states disagreeing about lockdown rules like mask wearing to our lack of universal health care. Pioneering a GIO — a revolutionary effort to build cohesion in public health at a global scale — might be a tall order for a country that currently struggles to provide tests or basic health care for its citizens.

"The irony is not lost," said Matthew Ferrari, an associate professor of biology at the Center for Infectious Disease Dynamics at Pennsylvania State University, who is not involved in the project. But Ferrari thinks this is exactly why the United States should lead the effort.

"We'll benefit by creating equity within our borders as well as creating equity globally," he said.

Although supportive, Ferrari has concerns about the GIO's implementation. He points out that governments don't always work well together, and people are bad at preparing for the future.

"There is real power in this kind of proactive investment," he said. "What I'm skeptical of is the ability to put in place the global coordination for response."

Knowing that a catastrophe is looming doesn't always inspire people to change their behaviors. Consider climate change, for instance. Somewhere between optimism and pessimism, there exists the most likely human behavior: ambivalence.

"I think that history has shown that ambivalence rules, more often than not," Ferrari said. The West African Ebola outbreak between 2014 and 2016 threatened a global pandemic. But despite efforts by scientists to implore governments to invest in preventing the next one, "here we are in 2020," he said.

"The humanity of the people in West Africa should have been enough to keep us engaged last time," he said.

Maybe this time will be different. Maybe with a disease threatening the world's wealthiest nations, this catastrophe will encourage investment in the infrastructure to prepare for the next one.

If the GIO is successful at preventing pandemics, it could make the threat of disease seem less severe. In the case of COVID-19, some virus-deniers point to flattened curves as evidence that the virus isn't as infectious or deadly as public health experts claim.

"It's like putting your umbrella up and all the clouds go away," Metcalf said.

The COVID-19 pandemic is a stark reminder that the ravages of disease aren't only the harsh reality in far-off impoverished lands, she said. The complacency of wealthy nations demonstrates that immense resources alone cannot compensate for a lack of cohesive leadership and robust infrastructure.

"It took one massive pandemic to bring our country to its knees. Having systems in place beforehand is just essential."

—**Michael Mina**, Harvard T.H. Chan School of Public Health

A GIO would help the world prepare for the next great pandemic, but it can also chip away at the "background of tragedy," to which Metcalf says we've all become desensitized.

"There's a host of infections from which we should no longer be dying," Metcalf said.

We can't always avoid nasty weather, but forecasts can help us prepare. Some storms might only require an umbrella or a raincoat. Others might send us seeking shelter. A GIO can't prevent the next disease from emerging, nor the next outbreak. But with the immense information it provides, accessible by all — public health officials, politicians and parents alike — the ability to prepare for our next encounter with an infectious disease could be at our fingertips.

The next terrible storm could be developing just over the horizon. We should be ready for it.

ILLUSTRATION BY JOHN OPET

Race and policing in America

Countering bias with data

By Bianca Ortiz-Miskimen

Last year, a widely cited research paper on racial bias in policing caught the attention of Jonathan Mummolo, an assistant professor of politics and public affairs, and his collaborator, computational social scientist Dean Knox. The study, which made national headlines and was cited in congressional testimony, claimed to find no evidence of anti-Black or anti-Hispanic disparities across fatal police shootings. The study concluded that, "White officers are not more likely to shoot minority civilians than nonwhite officers."

Although the study was peer-reviewed and published in a respected journal, Mummolo and Knox immediately noticed a flaw in the authors' logic. The authors of the original study tallied only fatal shootings, not all encounters, and they implicitly assumed that white and nonwhite officers encounter minority civilians in equal numbers. When police officers involved in fatal shootings were nonwhite, the study found that the person fatally shot was more likely to be nonwhite.

Yet, without accounting for the races of the officers and civilians in all encounters, whether fatal or not, Mummolo and Knox said, it is impossible to determine the role that race played in officer shootings. If white officers have few encounters with minority civilians, a small number of fatal minority shootings might translate to a large proportion of the total encounters with minorities. *(See Box: A thought experiment, p. 19.)*

"Data on fatal shootings alone cannot tell us which officers are more likely to pull the trigger," Mummolo said, "let alone account for all relevant differences between incidents to allow us to isolate the role of race."

Studies on police racism are difficult to conduct and often controversial. One of the challenges is how to isolate race to see if, in cases where all else is held equal, officers treat civilians of one race different from civilians of another.

Mummolo's work aims to improve how we measure and understand the potential for racial bias in policing. The ability to amass credible evidence on the relationship between race and officer behavior, Mummolo said, has been hindered by two issues — methodological errors and a lack of reliable data.

Much of the existing literature on policing uses flawed statistical reasoning and inadequate or biased data, Mummolo said. To rectify this issue, he and his co-authors propose statistical methods that more faithfully evaluate police behavior and call on law enforcement agencies to keep detailed records of civilian encounters. His hope is that improved accuracy and transparency of police data will encourage policymakers, officers and civilians to work together to develop a fairer law enforcement system for the nation.

To respond to the flawed policing study, Mummolo and Knox, an assistant professor of operations, information and decisions at the Wharton School of the University of

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> —**Jonathan Mummolo**, Princeton University School of Public and International Affairs

PHOTO BY EGAN JIMENEZ

Jonathan Mummolo, assistant professor of politics and public affairs and the Arthur H. Scribner Bicentennial Preceptor, researches the role of race in police-civilian encounters.

Pennsylvania, co-authored a letter to the journal, the *Proceedings of the National Academy of Sciences*, explaining why the study’s claims were mathematically unsubstantiated. At first, the journal editors rejected the letter, stating that the errors were merely a matter of preference over how to study the issue, and calling its tone “intemperate.” Frustrated, Mummolo and Knox turned to Twitter, sparking a fiery debate among academics.

“Sometimes errors are very nuanced or even debatable, and these disputes can exist in gray areas where it’s not clear who is right and who is wrong,” Mummolo said. “But sometimes, errors are very clear-cut, provable, and simple matters of logic, and as scientists we need to be able to tell the difference.”

After several months of academic arguments, the authors of the original study ultimately retracted their report, admitting that the language they used was not careful enough, which “directly led to the misunderstanding of [the] research.” Although at least one conservative news outlet claimed the retraction was politically motivated, the authors said their decision was strictly because of issues in the content of the study.

“Policing is receiving unprecedented attention from policymakers and the public, but the scholarship is lagging behind,” said Knox, a frequent research partner of Mummolo’s. “There are a lot of important questions that we don’t have answers to, and a lot of work that’s less careful than it should be. Our aim is to put rigorous research front and center in ongoing policy debates, push back on flawed science, quantify the limits of existing approaches, and do the most statistically sound research possible.”

Along with flawed approaches, Mummolo, Knox and colleagues found that published studies often rely on incomplete data. Incomplete data make it difficult to compare situations that are equal in all relevant factors except for race.

Police administrative records often do not include essential information for research, such as the total number of individuals that officers encounter. Without accounting for the total number of potential police-civilian interactions, the records may not be able to shed light on the role of race in officers' decisions to engage civilians, which can skew estimates of subsequent events, like racial bias in the use of force.

With no federal standardized reporting requirements for law enforcement in the United States, data are inconsistent among different departments and agencies. The lack of federal regulation also allows for the persistence of practices that reduce transparency. For example, many police departments purge their data after five to 10 years, and some law enforcement agencies impose high fees to access their records.

These issues directly inhibit research, Mummolo said.

"Right now, policing remains a very difficult thing to study across many jurisdictions," Mummolo said. "We often have to keep our scope of research limited to places where we can actually get the data we need."

Mummolo hopes the government will play a more prominent role in improving the accuracy of police data. He suggests that the federal government should mandate police departments to adopt a standard set of practices and report basic data in a centralized way that is easily accessible to the general public.

He also hopes that others will use a discerning eye when it comes to research. Studies that rely on biased data can underestimate the role of race in police-civilian encounters, leading researchers to conclude an absence of racial bias or even an anti-white bias. Unless these errors are addressed in a meaningful way, a broader audience of people unfamiliar with the issues may continue to cite studies that do not reflect reality. "It's hard to blame people for being misinformed when flawed studies continue to be published," Mummolo said.

> "There are a lot of important questions that we don't have answers to, and a lot of work that's less careful than it should be."
>
> —**Dean Knox**, Wharton School, University of Pennsylvania

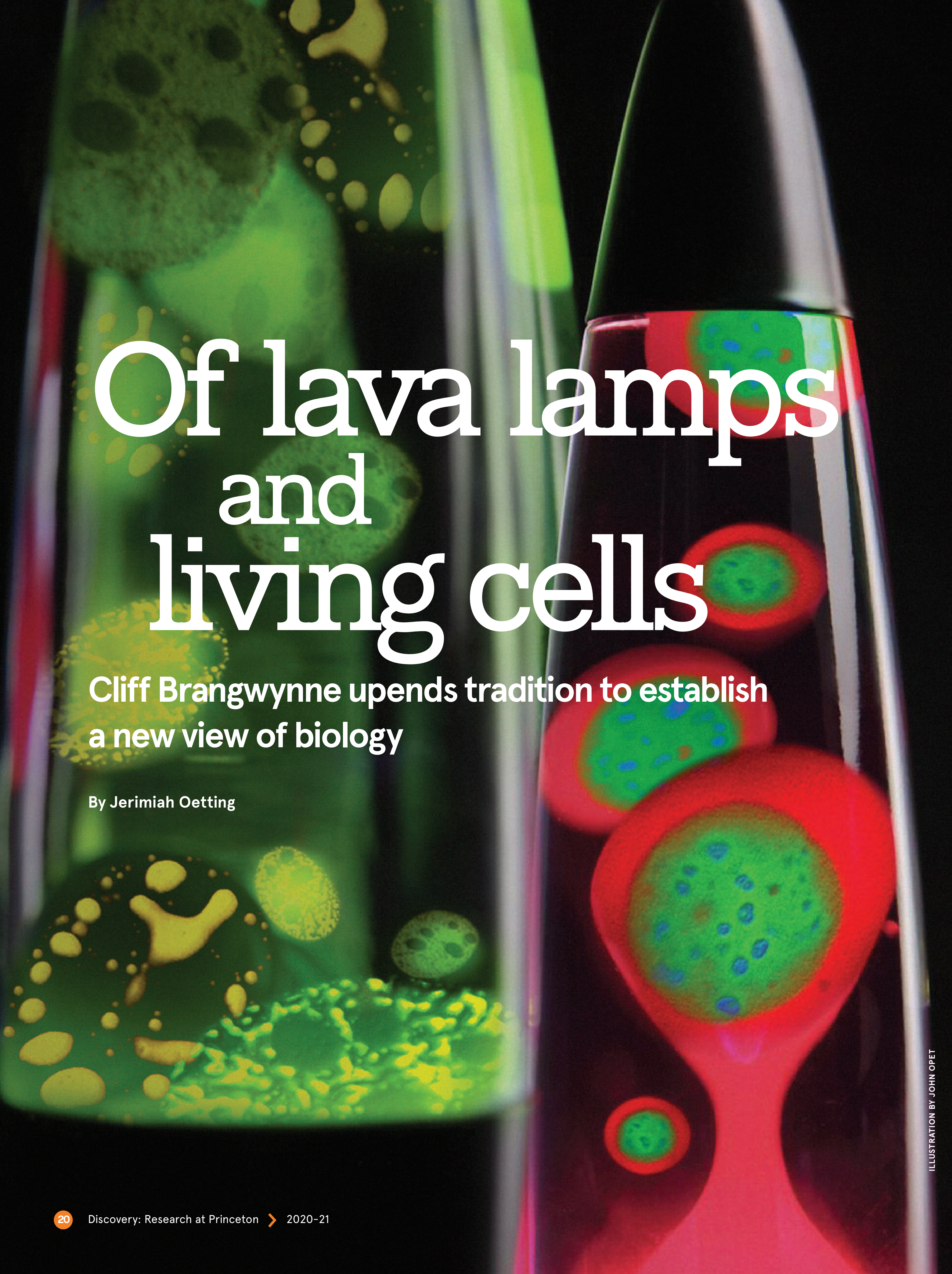
Improvements in police data collection, combined with better research methodologies, can help leaders and politicians gain a more complete understanding of how race affects policing and help to change long-standing disparities in how people of color are treated by law enforcement. Mummolo's research is furthering the national conversation on accountability in law enforcement.

"We are at a time when there is both intense interest in these topics and increasing data availability that are going to allow us to test ideas in better ways than we have in the past," Mummolo said. "But we still have a long way to go in terms of having the data we need — science needs to keep pushing for more."

A thought experiment

Imagine a white officer encounters 90 white civilians and 10 Black civilians, while a Black officer encounters 90 Black civilians and 10 white civilians, both under identical circumstances. If both officers shot five Black and nine white civilians, the results would — according to the reasoning of the original study — appear to show no racial bias.

However, once encounter rates are taken into account, one would see that the white officer shot 50% of the Black civilians he or she saw while the Black officer shot 5.6%. Failing to incorporate information on encounter rates could mask racial bias.



Of lava lamps and living cells

Cliff Brangwynne upends tradition to establish a new view of biology

By Jerimiah Oetting

ILLUSTRATION BY JOHN OPET

C

Cliff Brangwynne was seeing cells in the sidewalk again.

It was another long day in the lab at Harvard Medical School, where Brangwynne would often work late nights, staring at cells. Sometimes he spent so much time staring at cells through the microscope that the cells would follow him home, their shapes imprinted on his vision. Walking late at night, he'd see them dancing over the buildings and the empty streets and sidewalks.

Though Brangwynne was in his college years, he wasn't a student — in fact, some would call him a drop-out. He'd been enrolled at Carnegie Mellon University, a first-generation college student, when a mixture of burnout and wanderlust prompted him to take a year off midway through his degree. At first he thought he would take a yearlong trip to Latin America. But he was interested in materials science —

Structures within living cells can form and dissolve depending on changing conditions, more like the undulating interior of a lava lamp than the fixed parts of a table lamp.

he liked how it described the world in terms of math and physics. He also loved biology: he loved that innumerable cells could self-assemble into organisms that eventually walk around and talk about philosophy.

Brangwynne suspected that his two interests, biology and materials science, were more connected than his coursework suggested.

"I knew the two fields were related, because cells are doing all these crazy things that reflect weird material properties and states — flowing and oozing and moving around," said Brangwynne, now the June K. Wu '92 Professor of Chemical and Biological Engineering at Princeton. "But the biologists I would talk to knew nothing about the materials, and the materials people I talked to knew nothing about biology."

A *Scientific American* article would finally connect the dots. Written by Harvard scientist Donald Ingber, "The Architecture of Life" described the structure of a cell in the same way that an engineer might explain the architecture of a building, down to the biological materials of its construction. Ingber brought together materials science and biology in a way that resonated with Brangwynne's interests. He was so excited about Ingber's ideas that he wrote him a letter. When Brangwynne took the year off from college, instead of heading south on his yearlong trip, he headed to Harvard to take a job in Ingber's lab. As Brangwynne recalls, the experience was nothing short of magical.

"I was really, for the first time, deeply engaged with the science," he said. "Turning knobs, seeing what happened, at the microscope until midnight."

Maybe it was all the late nights staring through a microscope, pondering the materials of cells. Or perhaps it was the work-induced hallucinations that followed — the soft, squishy building blocks of life, stuck in his vision, superimposed on the cold and rigid bricks of Boston. Whatever caused it, Brangwynne saw cells and their structures a little differently than other scientists, and it would lead him to a major discovery that had been hiding in plain sight.

All shook up

Oil and vinegar don't mix. Even a vigorously shaken bottle of vinaigrette dressing will eventually separate into two distinct layers. The two layers are both liquids, so this separation is known as a phase separation — two liquids, segregating from each other because of their characteristic chemistries.

Phase separation, so well-known in salad dressings, was unheard of in cellular biology. But Brangwynne, with his background in materials science, knew that everything, including cells and salads, adheres to the same laws of physics. If phase separation could happen in a bottle at dinner, why not within a cell?

That's the question Brangwynne asked himself when, once again, cells appeared to be playing tricks on his vision. He had returned to Carnegie Mellon to finish his undergraduate degree in 2001, and then went back to Harvard where he earned his Ph.D. working with David Weitz, a pioneer in the field of soft-matter physics — the physics of "squishy materials." Then he headed to Max Planck Institute of Molecular Cell Biology and Genetics to work with Tony Hyman, a leader in the study of cellular structures.

Although made from proteins and other molecules, the structures form in a manner similar to the condensation of water on a windowpane on a rainy day, or a dewdrop on a blade of grass.

After squashing some cells from a roundworm and looking at them under a microscope, Brangwynne observed a structure, which scientists had long assumed to be a solid, instead blobbing apart and coalescing in lava lamp fashion. The supposedly solid structures were behaving much like droplets of oil in vinaigrette dressing. Despite the liquid environment of the cell, the droplets remained distinct from their surroundings. They came together to form bigger blobs and broke apart into smaller ones.

With Hyman and colleagues from the lab, Brangwynne published this observation in the journal *Science* in a 2009 paper, which described the liquid-like behavior of the structures. He correctly suspected that the droplets he saw weren't just a curiosity specific to roundworms — they were an entirely overlooked form of cellular organization.

Today, these structures are known as "biomolecular condensates," because, although made from proteins and other molecules, they form in a manner similar to the condensation of water on a windowpane on a rainy day, or a dewdrop on a blade of grass. When concentrations of certain proteins disperse in the cell's liquid, they begin to stick together, forming larger and larger droplets. But unlike normal condensation, they don't glob together randomly. The proteins bind together in specific ways that create a functional structure.

The most well-studied cellular structures are bound by membranes, which separate their inner machinery against the milieu inside the cell. But these droplets don't need a membrane; they exclude their surroundings the way that oil droplets exclude water. By foregoing the complications of a membrane, the cellular structures can form and dissolve depending on changing conditions, revealing the cell as a much more dynamic and malleable environment than previously thought — more like a lava lamp with its undulating interior than a table lamp with fixed parts.

Since 2009, the droplets have been discovered as key parts of dozens of processes, including cellular division and gene expression. They've been implicated in degenerative diseases, like Alzheimer's and ALS. Some scientists even speculate that these blobs of molecules, simpler than any cell or structure that requires a membrane, may have been the precursors to the earliest forms of life on Earth.

Much like the blobs themselves, the research spawned by their discovery defies boundaries. A growing number of scientists, at Princeton and beyond, are coalescing around Brangwynne and his discovery, finding condensates within their own study systems by collaborating over methods that cross disciplines.

"I don't think this has been oversold in any way," said Ned Wingreen, a professor of molecular biology at Princeton who also trained in physics. "This is a real revolution. It is truly, literally rewriting the textbooks."

Clifford Brangwynne, the June K. Wu '92 Professor of Chemical and Biological Engineering and inaugural director of the Princeton Bioengineering Initiative, sees similarities between living cells and salad dressing, in which oil and vinegar separate according to the laws of physics. The idea has caught on, and now many scientists are exploring how such physical processes can drive the formation of the cell's structures and play key roles in cellular division and gene expression.

PHOTO BY SAMEER A. KHAN/FOTOBUDDY

Glomming onto the next big thing

Crack open a biology textbook, and you invariably will find an illustrated version of a cell: a central nucleus, surrounded by colorful squiggles and bean-shaped capsules. In this picture-perfect universe, globular proteins float dutifully through the cell's liquid interior to find their perfectly shaped counterparts. They connect, perform their function, then separate, drifting off into the cartoon sunset.

"We're absolutely kidding ourselves with those diagrams," said Wingreen, the Howard A. Prior Professor in the Life Sciences, and professor of molecular biology and the Lewis-Sigler Institute for Integrative Genomics.

Wingreen studies the physics underlying biological systems. In contrast to those neat diagrams in textbooks, everything inside the cell is constantly bouncing around randomly. In this complicated soup of moving and shaking proteins and molecules, it's no wonder that biologists assumed a membrane was critical to exclude all the cellular riffraff from the work happening inside the cell's most important structures.

But many cellular processes occur only if the right proteins are in the right place at the right time. How this happens inside a cell's busy interior remains a mystery.

"Here comes phase separation to the rescue," Wingreen said. When the cell produces enough of a specific protein, they begin to glom together. As they do, the droplet that forms contains a high concentration of those proteins, making it much more likely that they will accomplish their task.

Wingreen uses the example of DNA repair — a process that occurs within the cell's nucleus. Sometimes, DNA suffers a double-stranded break. The repairing proteins could form a droplet around the break, repair it, and then dissolve.

For a theoretical biophysicist like Wingreen, studying this process is "a theorist's dream." But he was only mildly curious about Brangwynne's blobs until he attended a 2015 meeting held by the Princeton Center for Theoretical Science that was focused on condensate research. Many consider it the fledgling field's first important workshop.

"It was definitely a who's who of people in the field," Wingreen said of the meeting, which he co-organized with Brangwynne and Mikko Haataja, professor of mechanical and aerospace engineering. The list of attendees and speakers included many scientists who have since made big discoveries involving the cellular droplets, including many currently working at Princeton.

"It was like when a band plays a small venue before they got cool," Brangwynne said.

The number of researchers was still small and "cultish" back then. But after the workshop, the idea started to gain traction across cellular biology. Citations for Brangwynne's 2009 paper skyrocketed. Brangwynne says he knew his discovery was important, but "it became a really big deal. And it's hard to claim I knew that was going to happen — of course I was passionate about the science we were doing, but I didn't realize the whole world would become similarly obsessed with it."

For Wingreen, the meeting proclaimed in no uncertain terms that these liquid droplets were going to be transformative for cellular biology.

"I've got to be working in this field," he recalled thinking.

Wingreen wasn't alone. Countless other scientists would soon find blobs of proteins in their study systems, offering new and exciting ways to understand mysterious cellular processes.

"Brangwynne brainwashed me!" said Mike Levine, the director of Princeton's Lewis-Sigler Institute for Integrative Genomics. Levine has studied gene regulation, the "most interesting biological process on Earth," for more than 40 years. Now, he thinks condensates play a pivotal role in that process.

Turning genes into proteins requires a series of steps involving enzymes, which first transcribe double-stranded DNA into single-stranded RNA, and later translate RNA into proteins. But how do these enzymes know which genes to transcribe and which to ignore? How does the whole process operate with such precision?

The old idea was that one by one, RNA polymerase, the enzyme responsible for transcription, would swoop in, transcribe a gene, and swoop away. But recent innovations in imaging techniques, pioneered by Princeton's Thomas Gregor, professor of physics and the Lewis-Sigler Institute for Integrative Genomics, showed that there were actually great distances between all of these pieces of cellular machinery. Somehow, genes were being activated from afar, and the enzymes were still finding the right places to go.

"I believe Brangwynne-style liquid condensates will be the explanation to these observations," said Levine, Princeton's Anthony B. Evnin '62 Professor in Genomics and a professor of molecular biology.

Instead of a single RNA polymerase finding its DNA partner, Levine thinks a large droplet full of the enzymes likely forms around areas of the genome that are activated for transcription. In other areas, droplets exclude those RNA polymerase

Coming together and branching out

Princeton's small size and range of expertise give it an advantage in working fluidly between fundamental science and engineering. Its buildings are close together, and there is a spirit of collaboration that encourages this interdisciplinary work, said Associate Professor Sabine Petry in the Department of Molecular Biology.

Petry studies microtubules — the skeletal strands that make up the scaffolding that provides the cell's shape and structure. Microtubules play an important role in cellular division because they form the mitotic spindle, a structure that segregates copies of chromosomes between newly formed cells.

Petry devised a way to study a mitotic spindle outside of the cell, where she could more clearly image its formation. She and her team discovered that the linear microtubule strands, in fact, give birth to new microtubule strands from their sides, branching out like the limbs of a tree.

Understanding how microtubules branch could have implications for new therapies, such as targeted cancer treatments and ways to promote cellular growth after a spinal injury. Petry found that one protein, called TPX2, was responsible for the branching of microtubules.

Petry was curious if TPX2 might also behave like a liquid. Sure enough, outside of the cell, TPX2 readily glommed together into a blob. But its liquid properties didn't stop there. Once TPX2 was in the wet environment of a cell, Petry said it preferred to organize into droplets along the length of the microtubules, following the same physical laws by which "dewdrops form on a spider web." Droplets of TPX2 indicated where the microtubule would branch.

Petry says this discovery is at the intersection of physics and biology. The paper, which is currently a pre-print, was co-authored by graduate students Sagar Setru in Princeton's Lewis-Sigler Institute for Integrative Genomics and Bernardo Gouveia in the Department of Chemical and Biological Engineering.

"It's a big discovery, and it only could have been done by having all of these people come together and look at it from different angles," Petry said.

Much like the blobs themselves, the research spawned by their discovery defies boundaries.

enzymes, like oil excludes water, repressing transcription and effectively shutting off those genes.

The implications of this discovery, according to Levine, would be enormous.

"The key to how genomes are organized in functional units may all be driven by these dynamic condensates," he said. "This is going to have a lot of legs, and a lot of impact on the future of genomics."

Levine is careful to say these ideas are still "wildly speculative" at this point. But recent experiments in his lab have resulted in videos of "clear-cut condensates," formed during transcription — blobs that can fuse together and break apart in a dynamic, liquid fashion.

To study these processes requires leveraging the expertise of many Princeton faculty members, combining classical genomics, computational biology and biophysics.

"Phase separation is really in the sweet spot of what Princeton is all about, in terms of encouraging interdisciplinary research," he said. "Princeton is a powerhouse in the field."

The explosion of work in the area also underscores Princeton's strength in building from fundamental discoveries in basic science toward innovations in bioengineering that could have wide benefits for human health and the environment.

Brangwynne, for example, is collaborating with Assistant Professor José Avalos, who is jointly appointed in the Department of Chemical and Biological Engineering and the Andlinger Center for Energy and the Environment. Their work seeks to engineer synthetic condensates that help turn yeast cells into chemical factories, including potentially the production of advanced biofuels.

Across several departments in the School of Engineering and Applied Science, faculty members are bringing computational approaches to studying condensates, including Athanassios Panagiotopoulos, the Susan Dod Brown Professor of Chemical and Biological Engineering, and Professor Mikko Haataja and Assistant Professor Andrej Košmrlj in the Department of Mechanical and Aerospace Engineering. In the Department of Chemistry, Assistant Professor William Jacobs adds to the deep bench of Princeton theorists interested in this problem.

A future phase

With much attention focused on this new way of looking at the biological world, it is not surprising that Brangwynne, who in addition to his appointment at Princeton is a Howard Hughes Medical Institute investigator, has received some attention. He has won numerous awards, including a MacArthur Foundation fellowship.

One of Brangwynne's favorite sayings is that biological systems are the most richly textured forms of matter in the universe.

"Black holes, quasars, supercomputers — nothing can compete with the complexity of even the most basic bacterial cell," he said.

Cellular droplets have revealed the strange and dynamic ways that cells organize themselves. They defy the notion that important cellular processes depend on the trappings of a membrane. How these delicate processes evolved is an open question.

"The cell is like a universe," Brangwynne said. "Any place you point to with a very fine needle, you could spend a lifetime studying it. And people do."

But despite centuries of scientists looking at cells under microscopes, Brangwynne's blobs had evaded discovery until a decade ago. Seeing them required a more fluid view of science, and demanded a vision unfettered by the boundaries of scientific disciplines. It required thinkers, like Brangwynne, who see things a little differently.

How many mysteries still remain in the blind spots?

"Phase separation is one foundational physical principle," Brangwynne said. "I think it's probably one of many that have yet to be discovered." ●

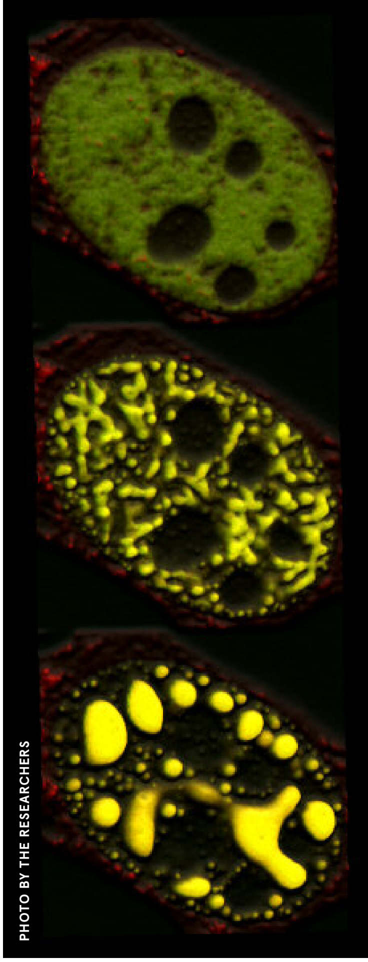


PHOTO BY THE RESEARCHERS

In recent papers in the journal *Cell*, Princeton research teams reported the development of new tools that harness light to accurately probe intracellular phase separation — the process by which the chaotic liquid matter inside cells transforms into functioning cellular compartments called membraneless organelles.

Deemed unfit for freedom

Judith Weisenfeld explores psychiatry, race and religion in the post–Civil War era

By Catherine Zandonella

In 1883, a small news item appeared in the *Richmond Dispatch*: "Mary Judah … (colored) charged with being disorderly and using profane language on the street. Fined $2.50."

Although the fine was modest compared to the $20 speeding ticket given that day to the driver of a horse-drawn buggy, it was probably a significant sum for Mary, a 21-year-old domestic servant. She paid the fine, but two years later found herself in court again. This time she faced a new charge: lunacy.

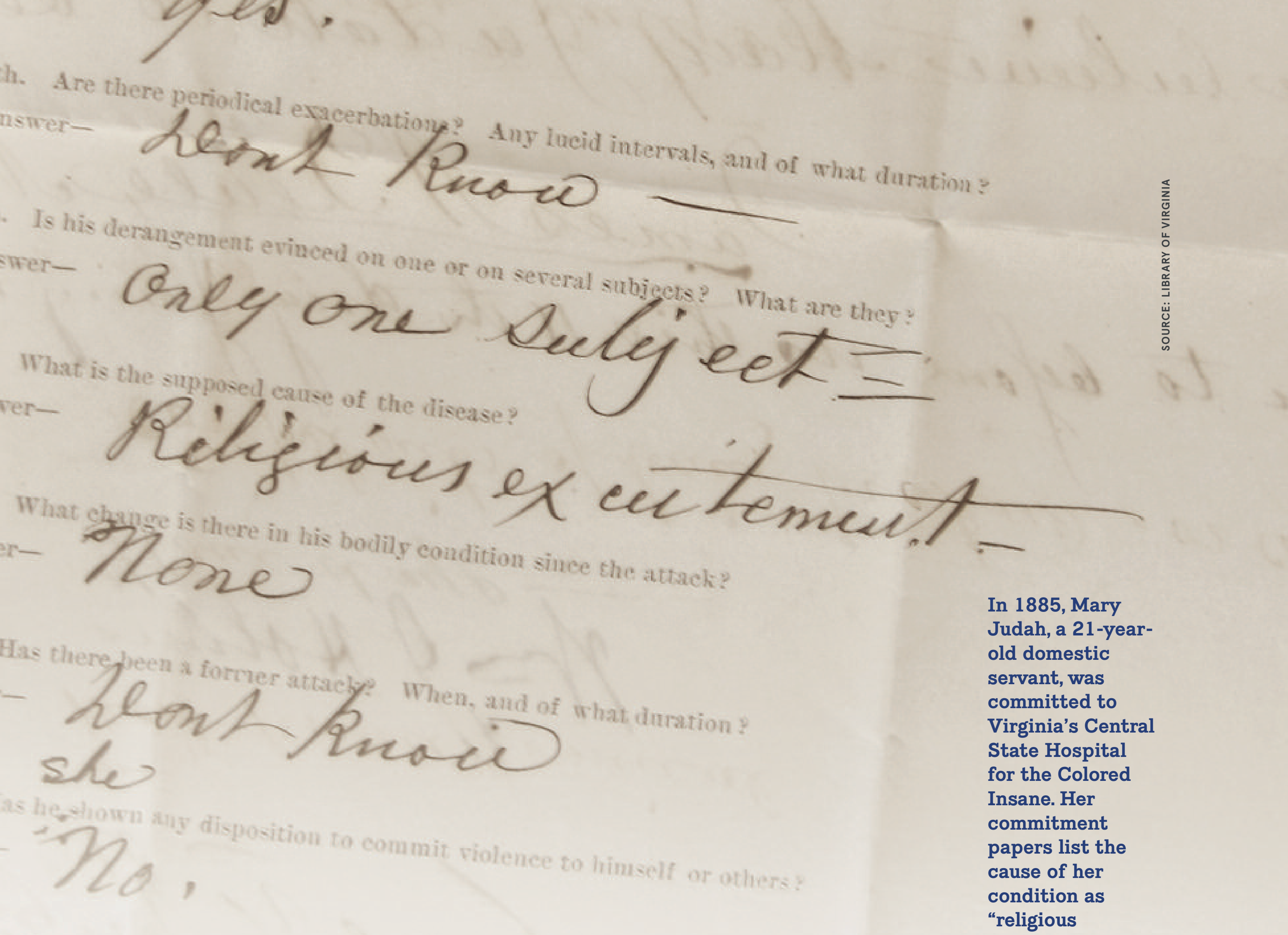
At her hearing, white physician James Beale testified that the defendant was "noisy, filthy and quarrelsome." What was more, Beale said, Mary claimed she was the victim of supernatural forces: She'd been "tricked or conjured" by someone who meant her harm. The all-white panel of three judges declared Mary insane due to "religious excitement" and committed her to Virginia's Central State Hospital for the Colored Insane.

Although Mary may not have deserved the diagnosis — she was discharged within two years — her case was by no means unique. In the decades following the Civil War, the number of African Americans committed to asylums in the South increased significantly. By some accounts, the number of "colored insane" in the United States rose tenfold from 1850 to 1890.

The cause of this apparent upsurge in mental instability was, prominent white Southern psychiatrists of the day claimed, that African Americans were by nature "unsuitable for freedom."

Judith Weisenfeld, a historian of religion at Princeton, has been tracing the stories of African Americans like Mary Judah and others declared insane over the century following Emancipation. Weisenfeld's research tracks the rise in psychiatry as a field of science and the parallel ascent of the discipline's racialized theories about African Americans, theories that helped fuel continued subjugation after the end of slavery. Her work reveals that racialized theories persisted among influential white psychiatrists well into the 20th century. What is more, our national conversation about the cause of racial disparities in COVID-19 victims suggest that these theories likely influence us still.

"At the same time that psychiatry was emerging as a distinct medical specialty in the mid-1800s, physicians were lending medical authority to the idea that Black people were unfit for freedom," said Weisenfeld, the Agate Brown and George L. Collord Professor of Religion, and chair of the Department of Religion, who is writing a book on the topic with support from a grant from the National Endowment for the Humanities.


yes.
Are there periodical exacerbations? Any lucid intervals, and of what duration?
Dont Know
Is his derangement evinced on one or on several subjects? What are they?
Only one Subject
What is the supposed cause of the disease?
Religious excitement
What change is there in his bodily condition since the attack?
None
Has there been a former attack? When, and of what duration?
Dont Know she
Has he shown any disposition to commit violence to himself or others?
No,

SOURCE: LIBRARY OF VIRGINIA

In 1885, Mary Judah, a 21-year-old domestic servant, was committed to Virginia's Central State Hospital for the Colored Insane. Her commitment papers list the cause of her condition as "religious excitement," a justification listed far more commonly for Blacks than whites.

"That was one of the things that was most striking to me."

Many respected mid-19th-century psychiatric journals promoted the idea of African Americans' racial predisposition to emotional states and superstitions, and thus to mental illness. J.D. Roberts, a physician at North Carolina's Eastern Asylum for the Colored, wrote in the *North Carolina Medical Journal* in 1883 that African Americans were "superstitious; fearful of hidden dangers; fond of the marvelous and religious to an extent almost approaching fanaticism."

This racial predisposition toward religious excitement existed, according to white doctors, whether the religion was Christianity, Islam or traditional beliefs with roots in Africa. In the post-slavery era, many African Americans increased their participation in various forms of religion, including Pentecostalism, which was also popular with whites and featured divine healing and speaking in tongues.

In addition, some African Americans engaged in spiritual practices with roots in Africa, including beliefs that combining ingredients and incantations could create potions or talismans with the power to protect, heal or harm. The reliance on traditional practices, known by names such as conjure, voodoo and rootwork, is perhaps not surprising given that enslaved African Americans were often denied conventional medical care, and sought such remedies to treat real physical and mental suffering.

Weisenfeld's research tracks the rise in psychiatry as a field of science and the parallel ascent of discipline's racialized theories about African American religious practices and mental health.


PHOTO BY DENISE APPLEWHITE

Professor Judith Weisenfeld exposes ways in which white Southern physicians' prejudices regarding African American religious practices in the years following Emancipation fueled the rise of theories about race-based susceptibility to mental illness.

But to white Southern psychiatrists, beliefs in supernatural remedies and extreme expressions of Christianity alike fit the racist mindset that "the Negro race" was unable to cope with the challenges of freedom. According to this theory, African Americans' uncivilized nature and mental inferiority made them incapable of surviving in a complex society.

"Early psychiatrists made presumptions about what authentic, reasonable religious practices looked like, and some of what African Americans were practicing did not look reasonable to judges, police and doctors," Weisenfeld said. "These practices were in some contexts criminalized, and certainly stigmatized and marginalized."

As a scholar, Weisenfeld views both mainstream and supernatural practices as fitting the definition of religion. "Religion is determined by its context," she said. "It has political and economic consequences. It is significant that white courts, white medical professionals, white police and white religious authorities had the power to say what was and what was not religion."

Not only did white authority figures adjudicate Black religious expression, but they applied the "religious excitement" standard differently to Black versus white mental patients. Both Black and white individuals admitted they feared being harmed, poisoned or plotted against, according to Weisenfeld's research at the Library of Virginia and other archives. Yet religious excitement was a top cause of insanity among Black patients but not among white patients. About one-fourth of the Black patients admitted to the "colored" hospital with Mary Judah in 1885 had religion listed as a factor in their insanity, versus 5% of whites admitted to the asylum for whites.

Cascade of blame

The cure for these manias and melancholies, as they were called, was a soothing environment far from the travails of civilized life. For whites, this "moral therapy," which was adopted widely in the United States in the mid-1800s, included hot baths, art classes and various amusements. However, treatment was not equal.

Black patients were more likely to be prescribed labor in the fields of the institution for men, or sewing and washing for women. Patients who demonstrated the ability to work and attend church services might eventually be discharged. "The treatment was labor," Weisenfeld said. "It was: How do we make them productive for the larger white society?"

As the 20th century dawned and the field of psychiatry matured, the role of race in the diagnosis of mental instability persisted, Weisenfeld found. In 1910, psychiatrist Arrah Evarts at the Government Hospital for the Insane in Washington, D.C., one of the most prominent asylums in the nation, repeated many of the erroneous and racist ideas developed decades earlier.

"As to the religion of the native African, it is but a belief in witchcraft," Evarts wrote. "Of ethics he has no conception. During its years of savagery, the race had learned no lessons in emotional control, and what they attained during their few generations of slavery left them unstable. For this reason we find deterioration in the emotional sphere most often an early and a persistent manifestation."

Although the field of psychiatry has since evolved, the national discourse on race and societal fitness retains shadows of these racialized theories, Weisenfeld said.

The COVID-19 pandemic has provided evidence that beliefs persist today about Black predispositions to illness, both mental and physical.

Initial public reactions to news that Blacks and Hispanics were disproportionately likely to get sick and die from COVID-19 often focused on supposed physical predispositions and moral weaknesses. In fact, the disparity stemmed from a range of socioeconomic determinants of health, including the fact that, in many parts of the country, people of color are more likely than whites to work in jobs deemed "essential" for which working at home is not an option, and are less likely to have paid sick leave and adequate health care.

"When we first heard, 'Black people are more likely to get COVID-19,' the news was often conveyed in a manner to suggest that it was due to something in the bodies of Black people," Weisenfeld said. "It took a long time for other arguments to come to the fore. I think people fell back quickly on a kind of racial essentialism that I see in psychiatry and a variety of medical specialties in the 19th and early 20th century."

A related factor, Weisenfeld said, is that people are quick to cast poverty as a moral failing. "People are blamed for being poor," she said. "There has been a kind of moral judgment about who gets COVID-19, and why the infection and death rate among people of African descent is higher. And that's certainly similar to, in the late 19th and early 20th centuries, white psychiatrists saying that there is something essential about the Black mind that is leading people to become mentally ill, and that slavery protected them from the worst outcomes of this."

Moral therapy

A similar attitude pervades the discussion around susceptibility to COVID-19 among people with preexisting conditions, she said. "The COVID-19 co-morbidity discussion, I think, really connects to that as well. The narrative is that people are diabetic because they lack self-control, and they lack self-control because they're poor, and they're poor because they lack initiative. There's a whole cascade of blame. And with that sensibility, why treat someone?"

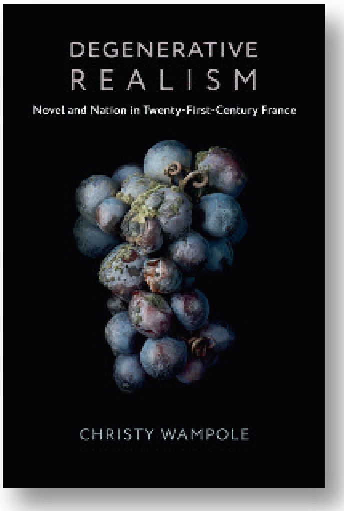
"When we first heard, 'Black people are more likely to get COVID-19,' the news was often conveyed in a manner to suggest that it was due to something in the bodies of Black people."

—**Judith Weisenfeld**, Princeton University Department of Religion

The cascade of blame, Weisenfeld said, legitimizes inaction and reinforces existing systems that keep marginalized groups from claiming the same rights to health as whites. "There are ways in which American medicine and broader society have discounted entire populations as not meriting support or even adequate medical care," Weisenfeld said. "And I think we saw some of those intersections early in the COVID-19 pandemic.

"I see parallels between people today and the people I'm finding in the archives of the asylums.

"Achieving racial equity and justice in mental health care requires that we understand the historical entanglement of ideas about race, religion and mental normalcy in psychiatry," Weisenfeld said, "and I hope my work can help contribute to that." ●



Degenerative Realism: Novel and Nation in Twenty-First-Century France

Columbia University Press, June 2020

Christy Wampole, associate professor of French and Italian

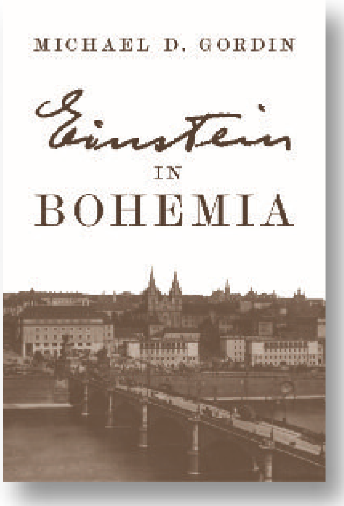
A new strain of realism has emerged in France. The novels that embody it represent diverse fears — immigration and demographic change, radical Islam, feminism, new technologies, globalization, American capitalism and the European Union — but these books, often bestsellers, share crucial affinities. In their dystopian visions, the collapse of France, Europe and Western civilization is portrayed as all but certain. Wampole maps how degenerative realist novels explore a world contaminated by conspiracy theories, mysticism and misinformation, responding to the internet age's confusion between fact and fiction.

Life Magazine and the Power of Photography

Yale University Press, April 2020

Katherine Bussard, the Peter C. Bunnell Curator of Photography, Princeton University Art Museum, and **Kristen Gresh**, the Estrellita and Yousuf Karsh Senior Curator of Photographs at the Museum of Fine Arts, Boston

Offering an in-depth look at the photography featured in *Life* magazine throughout its weekly run from 1936 to 1972, this volume examines how the magazine's use of images fundamentally shaped the modern idea of photography in the United States. Contributions from 25 scholars in a range of fields, from art history to American studies, provide insights into how the photographs published in *Life* — used to promote a predominately white, middle-class perspective — came to play a role in cultural dialogues in the United States around war, race, technology, art and national identity.



Einstein in Bohemia

Princeton University Press, February 2020

Michael Gordin, the Rosengarten Professor of Modern and Contemporary History

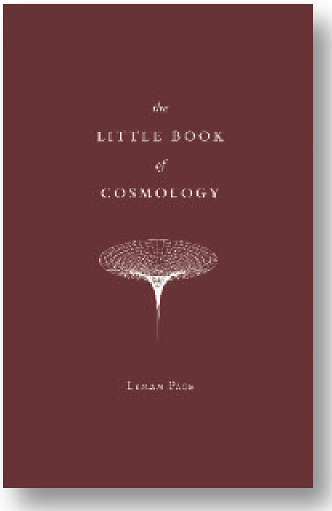
In the spring of 1911, Albert Einstein moved with his wife and two sons to Prague, the capital of Bohemia, where he accepted a post as a professor of theoretical physics. He lived there for just 16 months, an interlude that his biographies typically dismiss as a brief and inconsequential episode. *Einstein in Bohemia* is a spellbinding portrait of the city that touched Einstein's life in unexpected ways — and of the gifted young scientist who left his mark on the science, literature and politics of Prague.

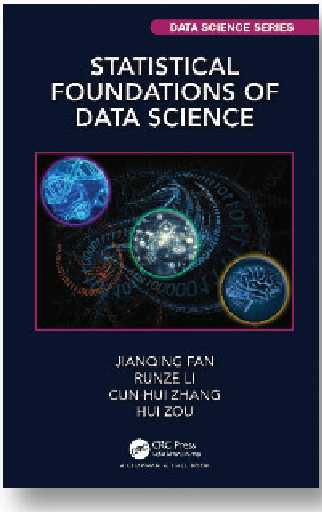
The Little Book of Cosmology

Princeton University Press, April 2020

Lyman Page, the James S. McDonnell Distinguished University Professor in Physics

Written by one of the world's leading experimental cosmologists, this short but deeply insightful book describes what scientists are revealing through precise measurements of the faint thermal afterglow of the Big Bang — known as the cosmic microwave background, or CMB — and how their findings are transforming our view of the cosmos. Yet much remains unknown, and this incisive book also describes the search for ever-deeper knowledge at the field's frontiers — from quests to understand the nature of neutrinos and dark energy to investigations into the physics of the very early universe.





Statistical Foundations of Data Science

Chapman and Hall/CRC, August 2020

Jianqing Fan, the Frederick L. Moore, Class of 1918, Professor in Finance, and professor of operations research and financial engineering; **Runze Li**, Eberly Family Chair, Pennsylvania State University; **Cun-Hui Zhang**, distinguished professor of statistics and biostatistics, Rutgers University; and **Hui Zou**, professor of statistics, University of Minnesota

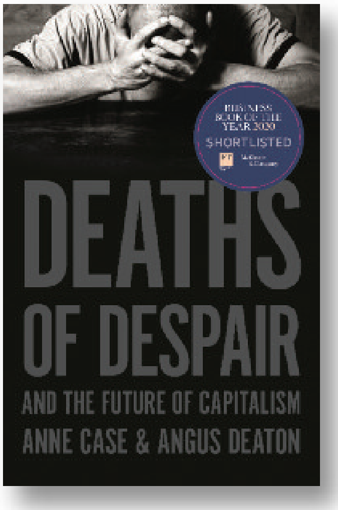
Statistical Foundations of Data Science gives a thorough introduction to commonly used statistical models and contemporary statistical machine-learning techniques and algorithms, along with their mathematical insights and statistical theories. It aims to serve as a graduate-level textbook and a research monograph on high-dimensional statistics, sparsity and covariance learning, machine learning and statistical inference. It includes ample exercises that involve both theoretical studies as well as empirical applications.

Deaths of Despair and the Future of Capitalism

Princeton University Press, March 2020

Anne Case, the Alexander Stewart 1886 Professor of Economics and Public Affairs, Emeritus, and **Angus Deaton**, the Dwight D. Eisenhower Professor of International Affairs, Emeritus, and professor of economics and international affairs, emeritus, both in the Princeton School of Public and International Affairs

In the past two decades, deaths of despair from suicide, drug overdose and alcoholism have risen dramatically, now claiming hundreds of thousands of American lives each year — and they're still rising. Anne Case and Angus Deaton, known for first sounding the alarm about deaths of despair, explain the overwhelming surge in these deaths and shed light on the social and economic forces that are making life harder for the working class. They demonstrate why, for those who used to prosper in America, capitalism is no longer delivering.



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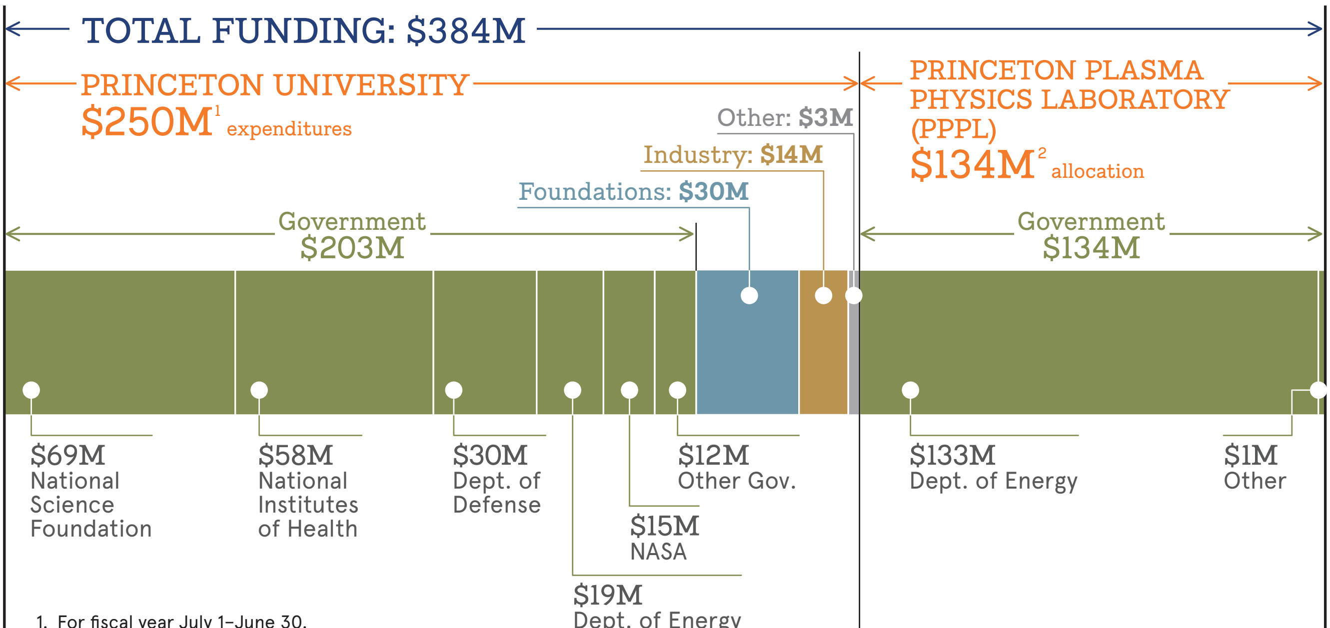
Princeton University is renowned for advancing the frontiers of knowledge across the disciplines, from the natural sciences and engineering to the social sciences, humanities and arts. This snapshot indicates the primary funding sources and amounts spent on research for fiscal year 2020.

MAJOR FUNDING SOURCES



1. For fiscal year July 1–June 30.
2. For fiscal year Oct. 1–Sept. 30.

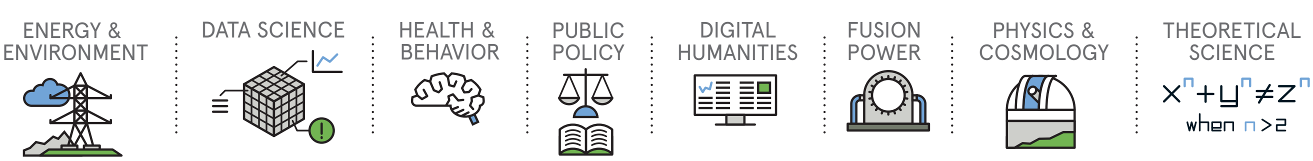
PATENTS AND TECHNOLOGY LICENSING ACTIVITY

6	STARTUPS FORMED FROM PRINCETON DISCOVERIES
124	INVENTION DISCLOSURES FILED
182	PATENT APPLICATIONS FILED
57	PATENTS ISSUED
25	LICENSE AND OPTIONS AGREEMENTS

SPONSORED RESEARCH PROJECTS

1,146	GOVERNMENT-SUPPORTED (INCLUDES PPPL)
99	INDUSTRY-SUPPORTED
284	FOUNDATION-SUPPORTED
63	PRIVATE/OTHER-SUPPORTED
1,592	TOTAL

SELECTED RESEARCH AREAS



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Princeton Innovation is a new initiative that aims to advance innovation and entrepreneurship for societal benefit. Visit our website to learn more about how you can engage with Princeton faculty and their research teams through investment in University startups, research collaborations between industry and University scientists, technology licensing, and entrepreneurial engagement.

innovation.princeton.edu

PHOTO BY SIGRID ADRIAENSSENS

Combining dance and structural engineering, Rebecca Lazier, senior lecturer in dance in the Lewis Center for the Arts, and Sigrid Adriaenssens, associate professor of civil and environmental engineering, are collaborating on a project involving the interactions of dancers with nets to explore materials for resilient building facades and impact barriers. The project, supported in part by the Dean for Research Innovation Fund for Collaborations Between Artists and Scientists or Engineers, aims to create choreographic works that generate a new understanding of how nets turn rigid when loaded and soften when unloaded. At the same time, dancers will explore the interaction between net and human.

Princeton Research › Office of the Dean for Research

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Psychiatry in the 19th and 20th centuries was infused with racist notions that African Americans were mentally unfit for the challenges of civilization. "Religious excitement" was considered a cause for commitment to an asylum for Blacks far more often than for whites, found Judith Weisenfeld, Princeton's Agate Brown and George L. Collord Professor of Religion. Pictured: Black female patients at work in the laundry at St. Elizabeths Hospital, formerly the Government Hospital for the Insane, in Washington, D.C., in 1918.

SOURCE: NATIONAL ARCHIVES