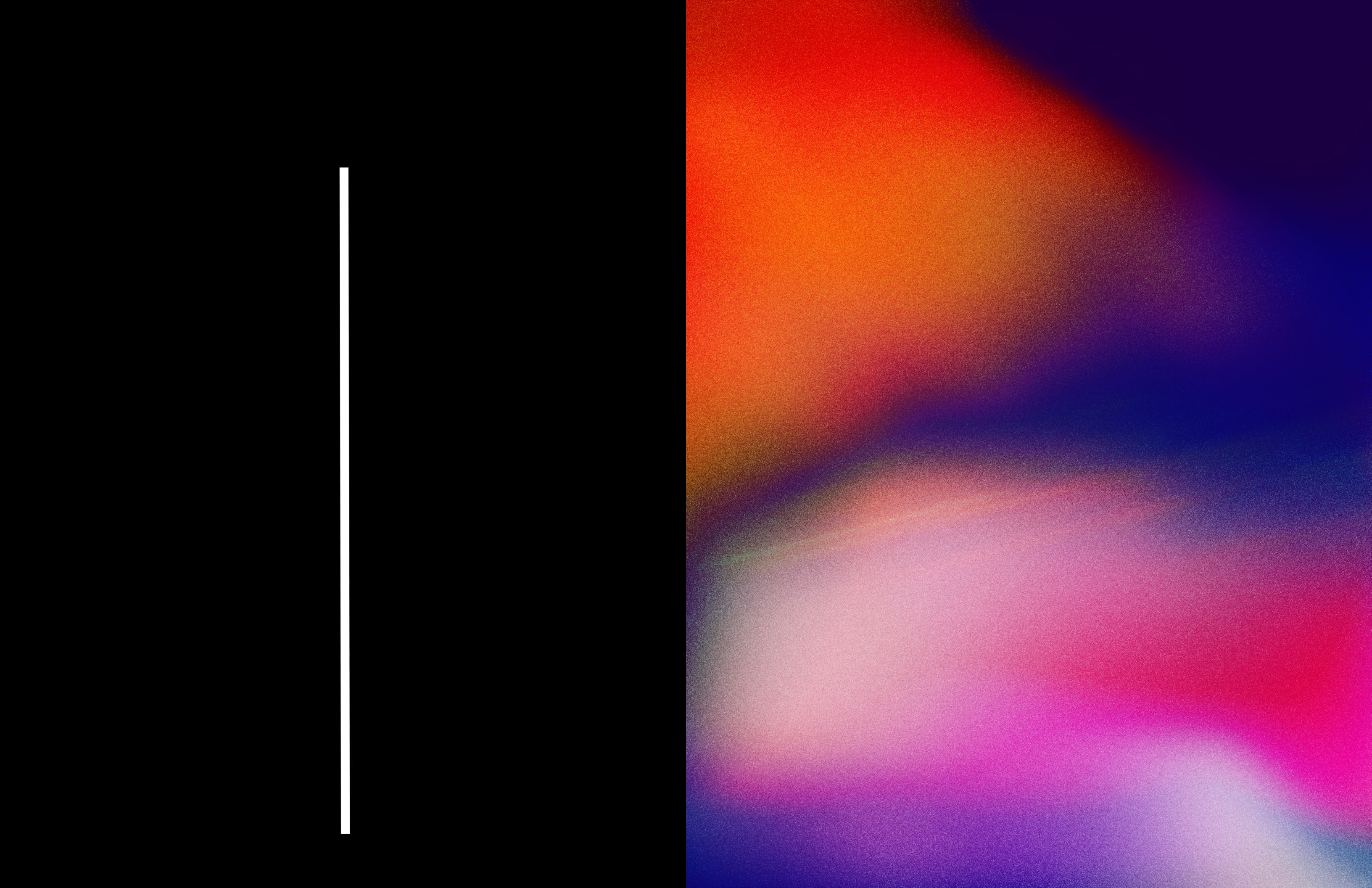


SIMONS FOUNDATION

Annual Report

2019 Edition





Perhaps I could best describe my experience of doing mathematics in terms of entering a dark mansion. One goes into the first room, and it’s dark, completely dark. One stumbles around bumping into the furniture, and gradually, you learn where each piece of furniture is, and finally, after six months or so, you find the light switch. You turn it on, and suddenly, it’s all illuminated. You can see exactly where you were.

— **Andrew Wiles** (“The Proof,” *Nova*, 1997)

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LETTER FROM THE CHAIR

The remarkable thing about basic science — which includes mathematics — is that one never knows where it may lead. Sometimes basic science seems to go nowhere, but more often it goes down a path leading to more discoveries, and more discoveries, and more discoveries. These often result in practical applications of which no one had dreamt, adding to the foundations of our civilization.

In my youth I myself did some mathematics that several years later began to be applied to physics: all kinds of physics! It was a total surprise, but it also gave me the direct experience of seeing how research done purely in the spirit of inquiry may someday be fruitfully applied in an entirely new and unexpected way.

As Marilyn’s letter states, we have just celebrated the foundation’s 25th anniversary, having formed the Simons Foundation in 1994. It’s come a long way: nine years later, in 2003, the foundation determined that its principal focus would be science, primarily basic science. In succeeding years, as the foundation has grown, our work in that area has expanded and flourished, and 2019 was no exception.

The grant-making side of our organization started with our effort to understand the roots of autism. This was followed by the launch of our program in math and physical science, and then a program in life science generally. These grants were primarily given to individuals or their labs, but occasionally to small science-focused institutes such as the Institute for Advanced Study. In 2012 we initiated a program of goal-driven collaborations, each comprising groups of scientists from different institutions, lasting as long as 10 years. At the moment we have 12 ongoing collaborations in math and physical science

and five in life science. Examples of these are the Simons collaborations on the origins of life, the global brain, and hidden symmetries and fusion energy. The last is a mathematically-driven effort to design an apparatus to generate nuclear fusion in a manner that gives off more energy than it takes in. If we succeed, it will be game changing.

In 2013 we embarked on the creation of an in-house computational science program. First came a center in biology, followed by astrophysics, quantum physics and computational mathematics. These are housed in a building across the street and known collectively as the Flatiron Institute. The institute’s growth has been spectacular; it now comprises more than 200 scientists, which is slated to rise to 300 in the next few years. In addition to seminars and workshops attracting people from all over the world, it was the source of almost 1,000 scientific papers in 2019 — all in basic science.

In our annual report we describe some of our grantees’ and scientists’ discoveries. It is our hope that some of them will one day change the world.



Jim Simons, Ph.D. | Chair

LETTER FROM THE PRESIDENT

One of Jim’s stories that I enjoy most in the retelling is about a conversation he had with a relative at his family graduation party when he received his Ph.D. Jim’s uncle asked him what he would do now that he’d finally finished school. When Jim told his uncle that he would probably do math research, his uncle paused thoughtfully for a moment and then asked, “Wait ... isn’t it all done?”

Happily, thanks to innate human curiosity, research is never done. Jim did go on to be a research mathematician and had a distinguished career as well. Given his high regard for research — and mine too — we determined that the mission of the Simons Foundation would be to advance the frontiers of research in mathematics and the basic sciences. This past year we celebrated the foundation’s 25th anniversary, and, to mark the occasion, we created a book focusing on research questions and hypotheses past and present that have intrigued us over the years. We also highlighted some questions we hope will be answered in the next 25 years.

Research is not for the faint of heart, though. This 2019 annual report hopes to convey that uncertain feeling of truly being at the “frontiers of research” — at the very border of human knowledge — and trying to extend the range of our understanding. “Frontiers” is a key word in our mission statement: it conjures up images of standing at the threshold of the unknown and looking out at the dark mysterious expanse of the unfamiliar. That search for knowledge is, as Abel Prize-winning mathematician Andrew Wiles describes it (see opposite table of contents), like groping one’s way through a dark room until one finally finds the light switch and — eureka! — all is illuminated. We hope to share such exploration and inspiration with you in the pages that follow.

In this issue you will read about the science being done by internal researchers at the Flatiron Institute: astrophysicists who are studying black holes and their event horizons, biologists amassing and analyzing large datasets to better understand amyotrophic lateral sclerosis (ALS), mathematicians developing a faster library for computing Fourier transforms, and quantum physicists investigating nonequilibrium quantum phenomena in partnership with scientists at the Max Planck Institute and Columbia University.

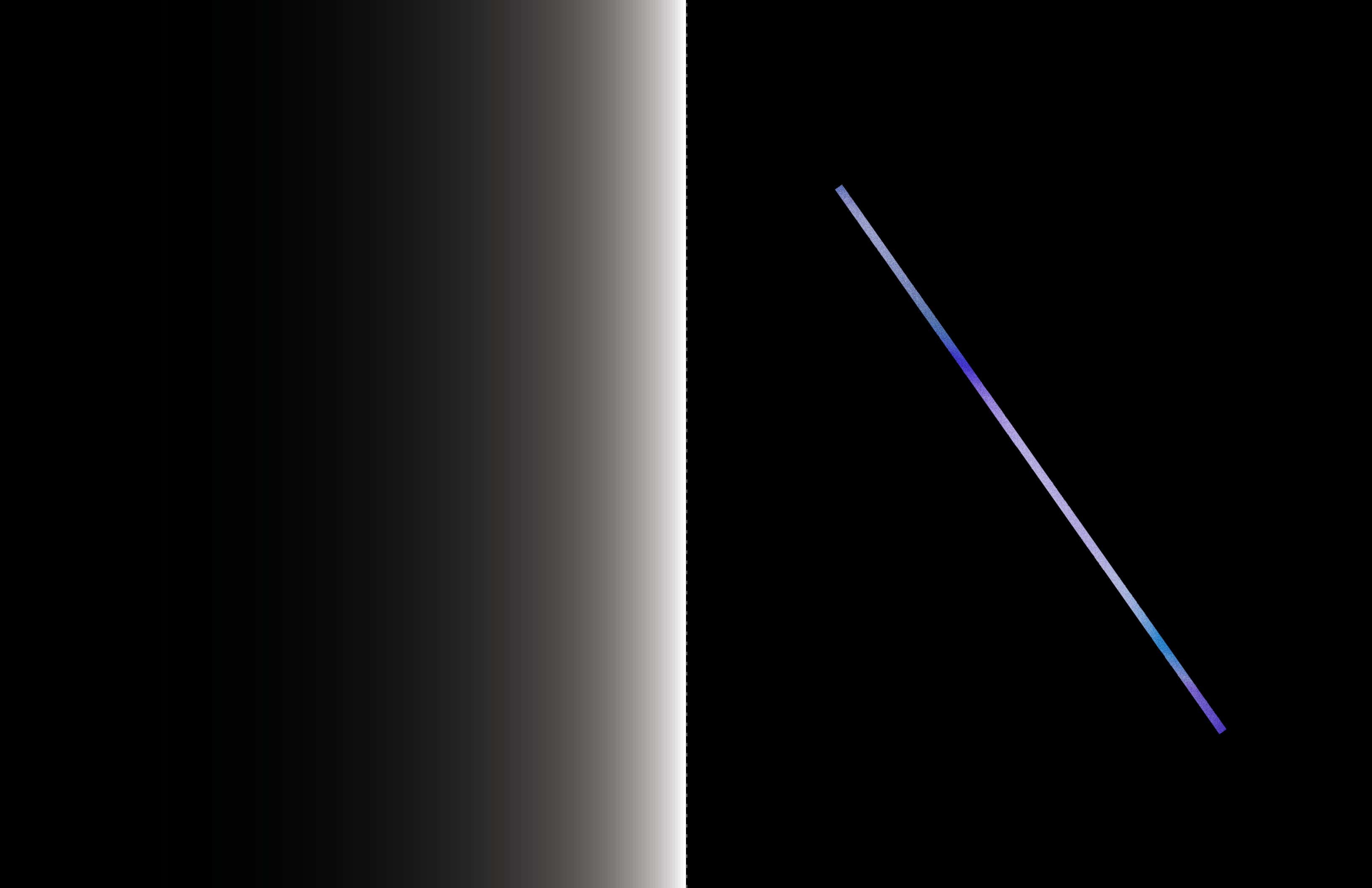
You will also read about cutting-edge research supported by the grant-making side of the foundation. From carrying out experiments in fusion energy to investigating the past and present environment of Mars, to pushing the envelope of our understanding of the workings of our own brains, our grantees are working in incredibly diverse areas to develop new knowledge. And, finally, you will hear about our efforts to disseminate this information to varied audiences with very different levels of expertise.

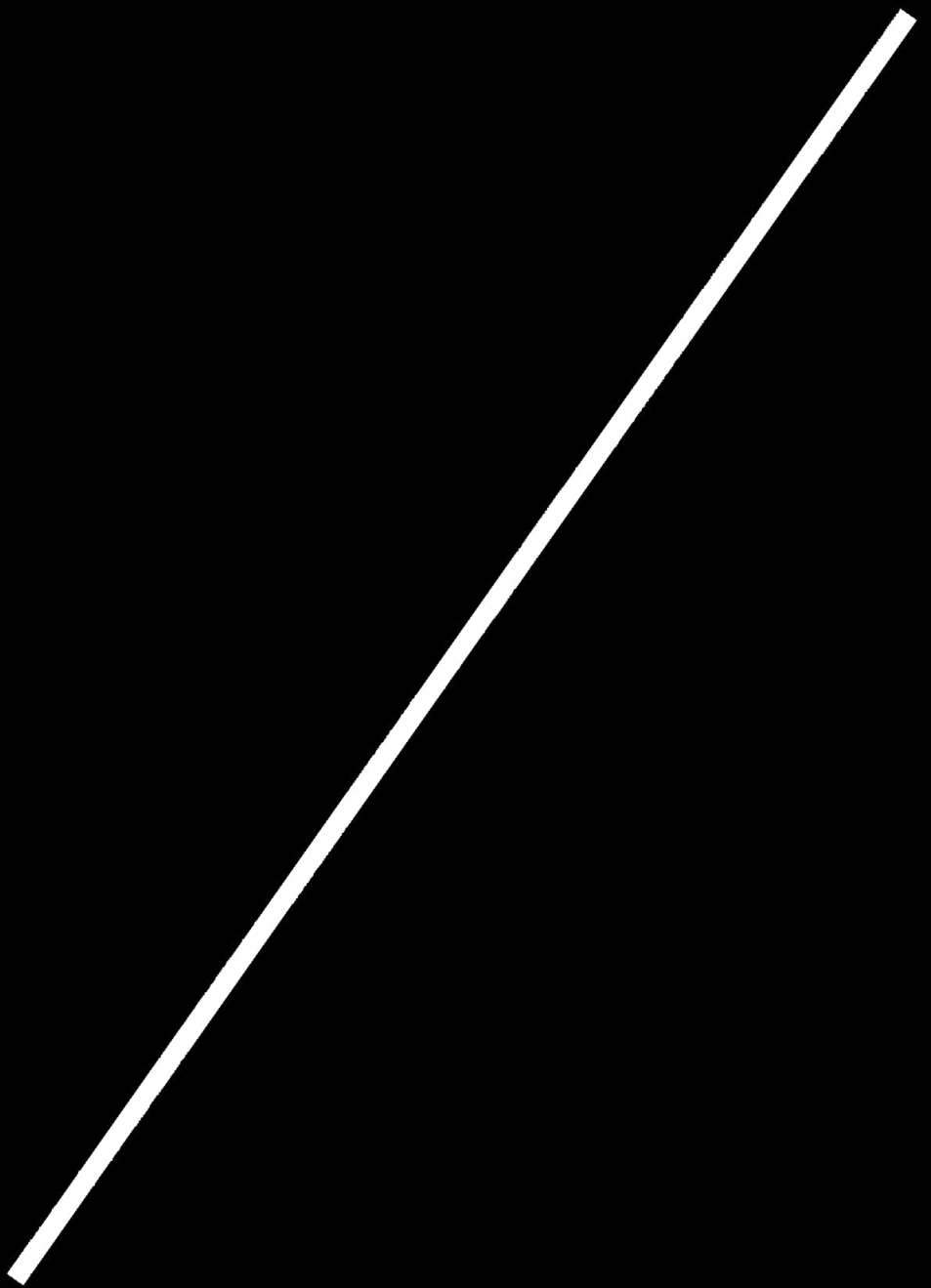
In sum, 2019 was a year of creativity, growth and celebration for us at the foundation. A lot has happened since September of 1994 when Jim and I started a fledgling family foundation with a \$1 million contribution. I am grateful to the many outstanding and insightful people who have helped build the organization through their leadership and commitment, and I feel fortunate to work with such an inspiring and collegial group of people every day.

I hope you enjoy reading about the Simons Foundation’s work.



Marilyn Hawrys Simons, Ph.D. | President





NEW VISTAS FOR BLACK HOLES

CENTER FOR COMPUTATIONAL
ASTROPHYSICS

These are heady times for black hole researchers. A century after physicists first realized that Einstein's theory of general relativity predicts the possibility of black holes, new tools and technologies are enabling astronomers to almost literally hear and see black holes, in ways that previous generations could only dream of. In 2015, the Laser Interferometer Gravitational-Wave Observatory (LIGO) experiment directly detected the very first gravitational waves — ripples in space-time — which emanated from the merger of two black holes. And in April 2019, people around the world gazed in wonder at the first image of a black hole, released by the Event Horizon Telescope after two years of processing data from eight observatories.

Even after a century's worth of research into black holes, in some ways the field is just getting started, says Chiara Mingarelli, associate research scientist at the Flatiron Institute's Center for Computational Astrophysics (CCA). "There will likely be many strange-looking events we can't immediately explain," she says. "Then things will get really interesting."

Flatiron Institute researchers are at the vanguard of this new era of black hole research. The CCA, created in 2016, has quickly become the focal point of astrophysics research in the greater New York City area. "The density of ideas, the level of cross-talk and interaction, is much larger than anywhere else I've been," says Will Farr, the CCA's group leader for gravitational wave astronomy and associate professor at Stony Brook University.

Farr and his colleagues have been studying the spectrum of distinct tones in the gravitational waves emitted when two black holes merge. Einstein's theory of general relativity implies that

the frequencies and decay rates of these tones are completely determined by the black holes' mass and spin, which means that measuring these tones would provide an independent test of general relativity. But until recently, most researchers believed that precise measurements of these tones would have to wait another decade at least, until more sensitive detectors could be built.

But Farr — together with Maximiliano Isi, a Flatiron affiliate at the Massachusetts Institute of Technology, and other researchers — figured out how to reanalyze LIGO data to tease out the frequencies and decay rates of two different tones emitted by a pair of merging black holes. The researchers used one of these tones to calculate the merger's mass and spin, then used that information to calculate general relativity's prediction for the second tone's frequency and decay rate. The predicted and observed values matched closely, offering fresh validation for the theory of general relativity.

The researchers next plan to look for similar phenomena among another 10 black hole mergers LIGO has found in recent years, and, further down the road, another 30 mergers that LIGO has detected but not yet cataloged. "This will rapidly become a precision test of general relativity," Farr says.

As black holes go, the ones LIGO can detect are fairly petite — only about 30 or 40 times the mass of the sun. Mingarelli, meanwhile, studies supermassive black holes, which can be a million or even billion times the mass of the sun. When two such black holes merge, they produce the loudest gravitational waves in the universe, easily a million times louder than those LIGO detects. And unlike weaker gravitational waves, which decay rapidly, these loud waves can linger for 25 million years, collectively forming a gravitational wave background against which all other signals are overlaid.

But just because these waves are strong doesn't mean they are easy to detect. An experiment like LIGO, which measures the wobble when a gravitational wave passes through two hanging mirrors, is good at picking up the high-frequency waves emitted when two small black holes merge. But the waves emitted by merging supermassive black holes are about 10 orders of magnitude lower in frequency than what LIGO can detect, with wavelengths that are multiple light-years long. To measure these, Mingarelli says, "you need an experiment that's the size of the whole galaxy."

Fortunately, the universe itself provides the perfect gravitational wave detectors: rotating neutron stars called pulsars that emit flashing radio waves with such regularity that they are like "radio lighthouses," Mingarelli says. "They're so regular that if you notice a 100-nanosecond change in the arrival of these flashes over 10 years, it's enough to tell you that a gravitational wave is changing the distance between you and the pulsar."

Mingarelli and her team of global collaborators have been monitoring 65 pulsars scattered through the sky. "We think we'll need 15 years of data, and right now we have 14," she says. "So we're very close to making the first detection of the gravitational wave background."

Although a black hole inexorably consumes all energy and particles that fall within its 'event horizon,' jets of particles sometimes escape from just outside the event horizon. These jets are thought to gush forth from a plasma cloud that surrounds and feeds the black hole, but how the particles become energized enough to escape has not been fully understood.

Astrophysicists have had a theoretical framework for jet launching for more than four decades, but until Flatiron researchers recently turned their attention to the problem, there was no way to effectively simulate the plasma and test the theoretical model. That's because plasma simulations traditionally rely on treating the plasma as a unified fluid, but the plasma around a black hole doesn't behave like a fluid: It is 'collisionless,' meaning that its density is so low that its particles don't typically collide with each other.

Jets of particles moving at nearly the speed of light can launch from fast-spinning black holes, as seen in this computer simulation. The particles get a speed boost by stealing some of the black hole's rotational energy, new research suggests.
Credit: K. Parfrey et al./Physical Review Letters 2019

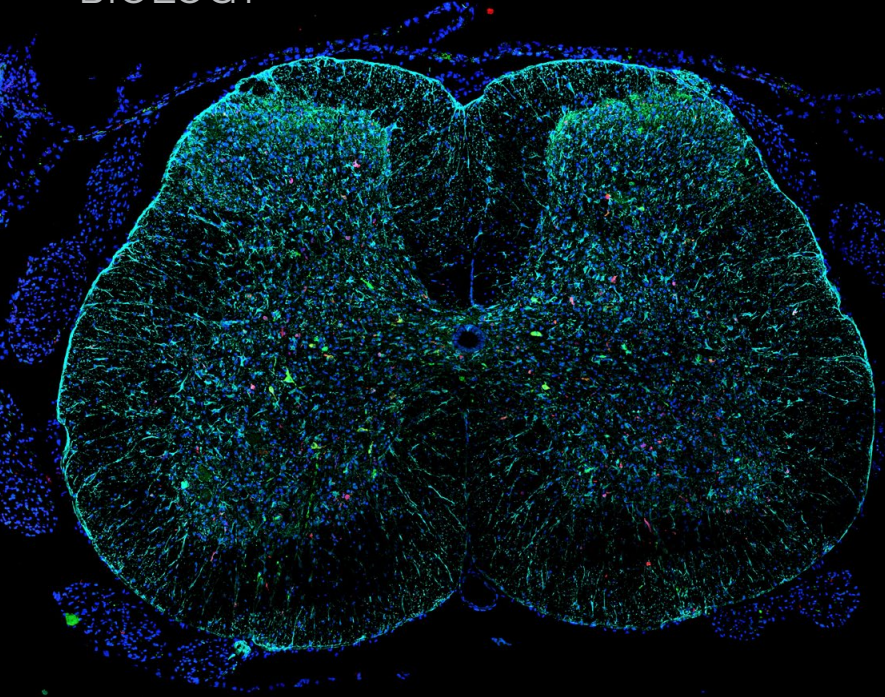
Now, the Flatiron Institute's Alexander Philippov and his collaborators have developed a computational method for simulating collisionless plasma and black hole jets. "Before we started working, there were no algorithms to merge general relativity and plasma physics," Philippov says. "The equations for general relativity and electromagnetic fields are all well known, but the numerical modeling had not been developed, so we had to come up with the algorithms."

The Flatiron Institute, whose mission is to tackle grand scientific challenges from a computational framework, is uniquely positioned to help astrophysicists advance the current understanding of black holes. "The in-house supercomputing facilities and computational expertise are resources that don't exist anywhere else in academia," Mingarelli says.

Black hole research is likely to move forward rapidly in the coming years, Philippov predicts. "There are so many new observational windows that were not available before," he says. "There are tremendous perspectives ahead of us."

AN ENHANCED VIEW OF ALS

CENTER FOR COMPUTATIONAL BIOLOGY



A cross section of a mouse spinal cord stained to highlight components of the autophagy pathway, which is responsible for dismantling damaged cells. A new study suggests that the dysregulation of autophagy is a key aspect of the progression of ALS.
Credit: S. Maniatis *et al.*/Science 2019

Amyotrophic lateral sclerosis (ALS) brutally targets nerve cells. The disease first causes progressive muscle weakness and, typically within three years, results in paralysis and death. Baseball player Lou Gehrig and scientist Stephen Hawking both contracted ALS, and today over 200,000 people worldwide live with the disease. While scientists have linked several genes to ALS, core questions remain about what sets off the cascade of neuron damage and how the disease progresses.

The answers to such questions may be within reach, thanks to a pioneering approach in which researchers are able to examine whole slices of spinal cord tissue — throughout the course of the disease — and to study how the various cell types present there interact and contribute to the disease’s progression. And for the first time, technology exists that allows researchers to see gene expression patterns at a high resolution throughout the spinal cord.

“We use sophisticated computational methods to study human disease,” says Tarmo Äijö, a data scientist at the Flatiron Institute’s Center for Computational Biology (CCB) and co-lead author on a study published in the April 5, 2019, issue of *Science*. Silas Maniatis of the New York Genome Center and Sanja Vickovic of the Broad Institute of the Massachusetts Institute of Technology and Harvard University and the New York Genome Center co-led the study with Äijö.

In this work, Vickovic and colleagues from the KTH Royal Institute of Technology in Stockholm together with Joakim Lundberg’s group at Science for Life Laboratory in Solna, Sweden, applied novel technology they developed for studying spatial gene expression. This technology, along with new computational modeling techniques, enabled the researchers to study the co-expression of different groups of genes throughout the diseased spinal cord and, for the first time, see how the location and extent of gene expression changed as the disease progressed.

Spinal cord tissue from control mice and mouse models of ALS, taken over time as the symptoms progressed, were mounted onto glass slides, each covered with 1,007 tiny spots. The spots contained molecules that captured the tissue’s mRNA; mRNA is used as a measure of gene expression levels. The captured mRNA was then copied and embedded with unique identifiers that recorded its spatial location in the tissue. The researchers then analyzed all the spots together, with gene expression results tied back to the mRNA’s original location within the tissue.

The researchers repeated the process with post-mortem human spinal cord tissue samples from seven ALS patients.

With over 130,000 spatial gene expression measurements from about 1,300 slices of spinal cord tissue, the study far surpassed the depth and scale of the next largest comparable study, which included only a dozen tissue sections from a single time point. “We had multiple time points, genotypes, patients and animals: This was the first use of spatial gene expression analysis at scale,” says Maniatis.

“We know now ‘neighborhood matters’ in ALS,” says Hemali Phatnani, director of the Center for Genomics of Neurodegenerative Disease at the New York Genome Center, referring to how non-neuronal cells can affect neurons’ vulnerability.

Incorporating this spatial component into the data analysis presented significant difficulty. Leveraging his prior work on a time-series analysis of the microbiome, Äijö developed a model for the data in collaboration with Maniatis and Vickovic, which went through multiple iterations and was guided by biology-driven questions: What are the dynamics of ALS pathology across time and space? How does the disease start and spread? And why are only motor neurons impacted? Aiming for a balance between resolution and statistical power, the group settled on defining 11 regions of the spinal cord to guide the spatial interpretation of the data.

The results suggested that microglia — specialized immune cells of the central nervous system that remove damaged or dead cells — show dysfunction near motor neurons even before ALS symptoms begin. When the researchers looked at an array of genes known to be affected in neurodegenerative disease, they saw a sequence of gene expression changes unfold and, for the first time, could see the order in which gene changes occurred. For example, in the mice, an increase in expression of one of the genes, *Tyrbp*, occurred before symptom onset in particular regions of the spinal cord. It was followed by an increase in expression of the gene *Trem2* in the same regions. The expression of both genes increased further as the symptoms progressed. These temporal snapshots are the closest researchers have to real-time video of ALS progression in the spinal cord.

The researchers also identified 31 ‘co-expression modules,’ groups of genes in the spinal cord with similar expression profiles in space and time. “Within the modules, we see the genes in glial cell subpopulations behaving differently at different places in the spinal column, and they seem to be acting in concert,” says Phatnani. The researchers found that in some gene groups, the natural cleaning up of damaged cells — known as autophagy — increased, diminishing the impact of ALS. In other modules, though, autophagy worsened ALS’s impact. “We can now generate testable hypotheses about how autophagy impacts the progression of the disease,” Phatnani says. While the researchers could not study multiple disease time points in the human samples, a spatial relationship between the site of symptom onset and the locations of gene-expression changes in the spine post-mortem was still evident.

Regarding the sheer scale of the data, Maniatis says, “We are continuing to find things in this vast dataset.” He’s most excited, though, by the contribution that this data resource makes to the broader scientific community, via an interactive data browser developed by Äijö that specialists and nonspecialists alike can quickly and easily interrogate.

“In high-throughput biology, genomics and imaging haven’t had a way of connecting until now,” says Richard Bonneau, group leader for systems biology at the CCB. In complicated tissue containing multiple cell types, images are a powerful addition to genomic data, but manual image analysis can be tedious and rate limiting. Aidan Daly, a research fellow in systems biology at the CCB, is developing a two-stage machine learning tool to identify geographic regions in the most complicated tissue, like that found in the spinal cord and brain and in tumors lacking a stereotyped anatomy. “One of the reasons we’re targeting diseases of the central nervous system is because of the inherently challenging tissue. If this can work in these tissues, it can work in any tissues,” says Bonneau.

Patterns in the data consistent with earlier ALS research provide proof of concept for mapping a disease in space and time. However, the identification of potential new ALS mechanisms, through the identification of co-expression modules over the entire spinal cord, adds a dimension of discovery to the work. The next step will be a larger-scale human study, in which the researchers aim to study both the brain and the spinal column, with the hope of uncovering spatially anchored regulatory networks involved in the disease. The ultimate goal is single-cell resolution, says Maniatis. “You would know without ambiguity what cell type is responsible for the signals in the data.”

The scientists agree that without computational and biological scientists interfacing early in the research, this result almost surely could not have occurred. Äijö recalls that hearing Maniatis give a talk at the Flatiron Institute first sparked his interest in solving the computational piece of the puzzle. “This work shows the value of enterprises like the Flatiron Institute and the New York Genome Center,” says Phatnani. “You have the technology, the biology, the computation and the people all together — the research would not have been possible in any other place.”

A HUB FOR QUANTUM INSIGHTS

CENTER FOR COMPUTATIONAL QUANTUM PHYSICS

The equations of quantum mechanics are vastly too complicated to solve in full detail. However, if a system is in equilibrium, general principles such as energy minimization are often enough to guide physicists to good approximate solutions. But for quantum systems that are not in equilibrium — perhaps because they have been pushed out of their comfort zone by bursts of light or electric currents — there is no such road map.

Yet amazing new tools, developed over the past decade, are beginning to allow researchers to investigate and control the remarkable properties of such systems, opening up new frontiers in basic science and the prospect for transformative quantum technologies. “In my view, there’s really a new scientific field forming here,” says Andrew Millis, co-director of the Flatiron Institute’s Center for Computational Quantum Physics.

The newly founded Max Planck-New York City Center for Nonequilibrium Quantum Phenomena aims to put this new field of research on firm footing. Founded in November 2019, the center features a close collaboration between theory and experiment, uniting the complementary strengths of three institutions: the Flatiron Institute and Columbia University in New York City, and the Max Planck Society in Germany (specifically, the Max Planck Institute for the Structure and Dynamics of Matter (MPSD) in Hamburg and the Max Planck Institute for Polymer Research in Mainz).

“We would like to be able to create novel phases of matter on demand,” says Dmitri Basov of Columbia, who will co-direct the center with Millis and Andrea Cavalleri of the MPSD. “When you can do that, that’s the foundation of new technologies.”

Each of the three member institutions brings different expertise to the collaboration. Columbia researchers, for instance, are world leaders in creating new materials by layering extremely thin sheets of graphene and other materials — just a single atom thick — on top of each other. When these layers are positioned at varying angles relative to each other, “all of a sudden you can synthesize new phases of matter completely different from the ones you had on the isolated layers,” says Angel Rubio of the MPSD and the Flatiron Institute, one of the new center’s deputy co-directors.

These thinly layered sandwiches offer a fertile testing ground for studying the phenomena that can emerge when a quantum system is pushed out of equilibrium. Columbia researchers are examining, for example, what happens when such layered systems are placed inside optical cavities, mirrored boxes that are used to make lasers.

The Max Planck Society, meanwhile, has long been a leader in devising new experimental systems. Researchers at the MPSD have built laser systems that can deliver short pulses of extremely intense light and then probe the nonequilibrium phenomena the light stimulates, all in a single device. “From a technical point of view, it’s a remarkable achievement,” Millis says. “It opens up all kinds of directions for turning effects on and off.”

“Building these capabilities has required a decade of dedicated effort,” Basov says. “Now we are in a position to exploit these tools. In combination with the unique materials and structures developed by Columbia scientists, we are poised to make gains.”

MPSD researchers have used their laser-based systems to turn on and off a ‘quantum Hall effect,’ a peculiar phenomenon in which part of an electric current flows sideways from the direction of the applied voltage. Researchers at Columbia and the MPSD have also shown that intense light pulses can briefly turn nonmagnetic materials into magnets, or insulators into superconductors.

“These phenomena were quite unexpected,” Millis says. “If we can understand and control them, that would mean that you can turn fundamentally important electronic properties like superconductivity on and off at the flick of a switch.”

The superconductivity the MPSD researchers reported occurs at a much higher temperature than other known instances of superconductivity, which typically require powerful refrigeration. “If we could figure out how to do this in a steady state, it would revolutionize electrical power transmission,” Millis says.

The third partner in the new collaboration, the Flatiron Institute’s Center for Computational Quantum Physics, brings the theoretical, algorithmic and computational expertise that will help the experimentalists make sense of what they are seeing. “We will be able to develop and implement the theory and concepts that are presently missing,” Millis says.

Flatiron researchers plan to develop algorithms and computer code that will allow the collaborators to model complex nonequilibrium phenomena. The aim of this theoretical framework is to help guide

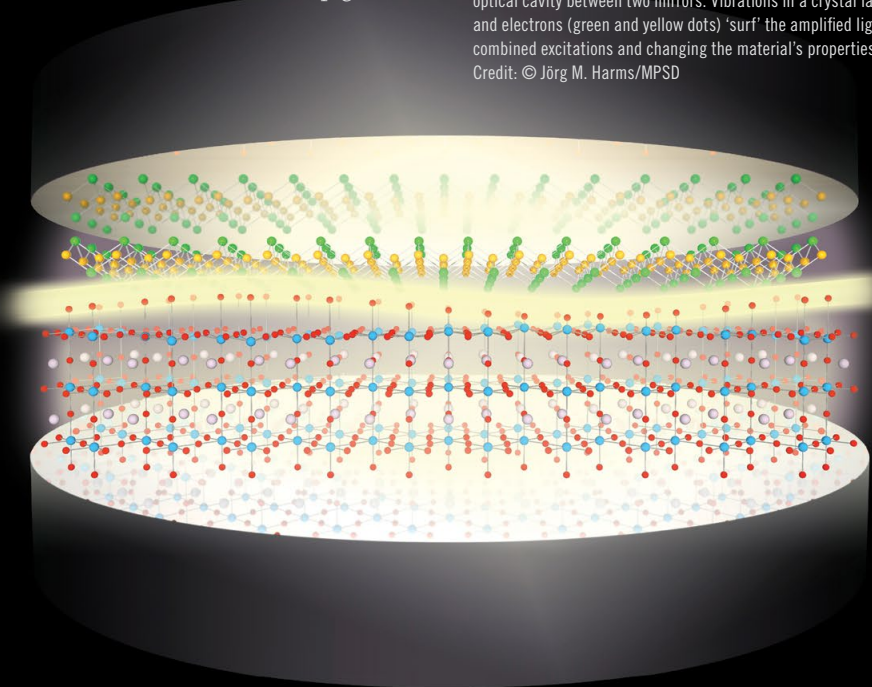
Columbia and Max Planck Society researchers in designing their experiments; the experimental findings, in turn, will keep the theoretical models tethered to reality.

The new center has been funded for five years, with the possibility of being renewed for an additional five years, the maximum allowable time span for a Max Planck Society project. The center aims to promote intense scientific exchange between the institutions, with ample travel support and an annual conference, a summer school and two to four workshops each year. It also plans to support six postdoctoral researchers and three graduate students, to be spread among the member institutions.

And, in an unusual experiment, the center also plans to create two joint junior faculty positions, which will start in Germany and then transition: one to Columbia and the other to the Flatiron Institute. This arrangement will allow the two junior scientists to take advantage of the Max Planck Society’s outstanding technical support and experimental infrastructure, and then segue into long-term career trajectories in New York City. (Most appointments of junior group leaders within the Max Planck Society simply terminate after about five years.) The hope is that these joint appointments will keep the bonds between the member institutions alive long after the center has concluded its activities.

“Science today is about the seamless flow of ideas and people across universities and continents,” Basov says. “That’s what this center will enable.”

Vacuum fluctuations of light (yellow wave) become amplified when trapped in an optical cavity between two mirrors. Vibrations in a crystal lattice of atoms (red dots) and electrons (green and yellow dots) ‘surf’ the amplified light wave, creating new combined excitations and changing the material’s properties.
Credit: © Jörg M. Harms/MPSD



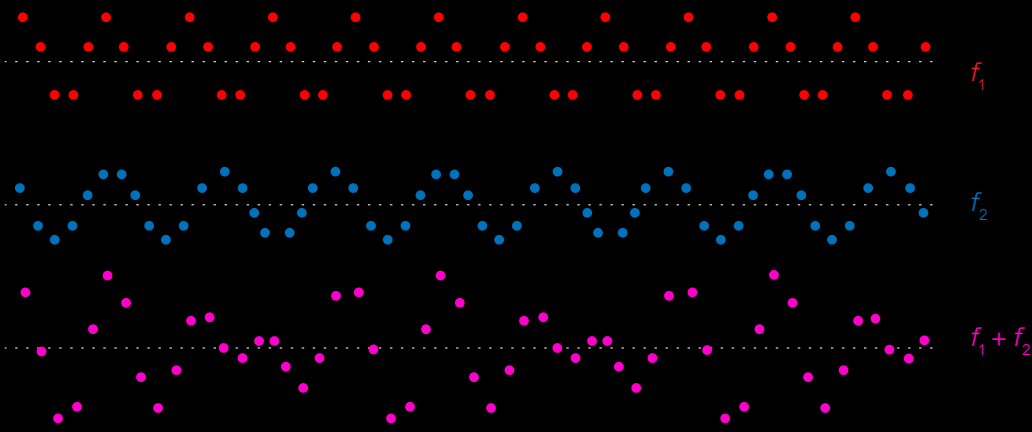
MAKING A FAST COMPUTATIONAL TOOL EVEN FASTER

CENTER FOR COMPUTATIONAL MATHEMATICS

Alex Barnett takes a small silver tuning fork from his backpack, thwacks it against his desk and holds it to a microphone. On his computer, the musical tone appears as a steady succession of identical sine waves.

“It’s an A4, or the A above middle C,” says Barnett, who plays classical and jazz piano in addition to serving as group leader for numerical analysis at the Flatiron Institute’s Center for Computational Mathematics (CCM). “That’s 440 hertz, or 440 oscillations per second.”

A chord — with multiple notes — struck on a piano, however, would yield a distinctly different pattern. Instead of a monotonous series of rises and falls, the microphone would record a mountain range of varying canyons, peaks and plateaus. The various frequencies that make up a chord stack on top of each other, amplifying each other or canceling each other out in different places. This so-called ‘wave interference’ is what produces the complex signal.



Adding two waves (top and middle) together can result in a complex signal (bottom). An algorithm known as the fast Fourier transform can decipher the wave frequencies that make up such complex signals. The algorithm, though, only works when the signal is evenly sampled along a uniform grid.

Untangling the many waves that make up such complex signals appears daunting at first. Thankfully, mathematicians and scientists have the Fourier transform. Invented by Joseph Fourier in 1822, the function takes a signal and churns out a graph with spikes at the signal’s constituent frequencies. For instance, a Fourier transform could reveal that a given chord comprises an A (440 hertz), a C-sharp (277 hertz) and an E (330 hertz).

The Fourier transform has far more uses than just deconstructing harmonies. The transform is used in everything from medical imaging to quantum mechanics to image compression. At the CCM, Barnett and his colleagues have developed and released a new set of software libraries to tackle a thornier subset of applications known as non-uniform discrete Fourier transforms. The software is called the Flatiron Institute Nonuniform Fast Fourier Transform, or FINUFFT, and for many tasks it’s faster than anything else available.

“Tool building is a big part of what CCM is doing, and the Flatiron Institute as a whole is doing,” Barnett says. “We’re building general-purpose numerical tools that people need, are the best quality and, in this case, are the fastest available.”

FINUFFT is “an important mathematical kernel for lots of different applications,” says CCM director Leslie Greengard, who co-wrote one of FINUFFT’s predecessors. Nonuniform Fourier transforms are essential for many applications such as interpreting data from MRI machines, analyzing the distribution of stars across the universe and reconstructing 3D terrain maps using aerial radar.

Such applications can’t be handled solely by the original fast Fourier transform (FFT) algorithm invented in 1965. That algorithm “revolutionized digital signal processing,” Barnett says, but it has limitations. The algorithm requires data inputs that are regularly sampled — meaning they lie on a uniform grid. (CD-quality audio, for instance, records sound pressure values regularly every 22.68 microseconds.)

Many data sources aren’t so orderly, though, with ‘off-grid’ points that don’t align to a uniform structure. Other times, researchers need to switch between regular-grid and off-grid data to run certain calculations. Such was the case for the initial motivator for building FINUFFT: analyzing the unruly data collected by cryo-electron microscopy (cryo-EM) research. Cryo-EM determines the 3D structure of chilled proteins by bombarding them with electrons. In order to rotate a protein model of interest in 3D and accurately match it to hundreds of thousands of noisy images, Fourier transforms need to be evaluated on a variety of grid systems.

FINUFFT generalizes the regular-grid FFT algorithm to handle off-grid input or output data while maintaining a fast processing speed. The code accomplishes this using a so-called spreading function, which controls how the creation of on-grid data points is influenced by the values at neighboring off-grid points: The closer the neighbor, the stronger its influence. The design of this function is crucial to obtaining high accuracy and efficiency. Once all the on-grid points are filled in, the usual FFT can work its magic.

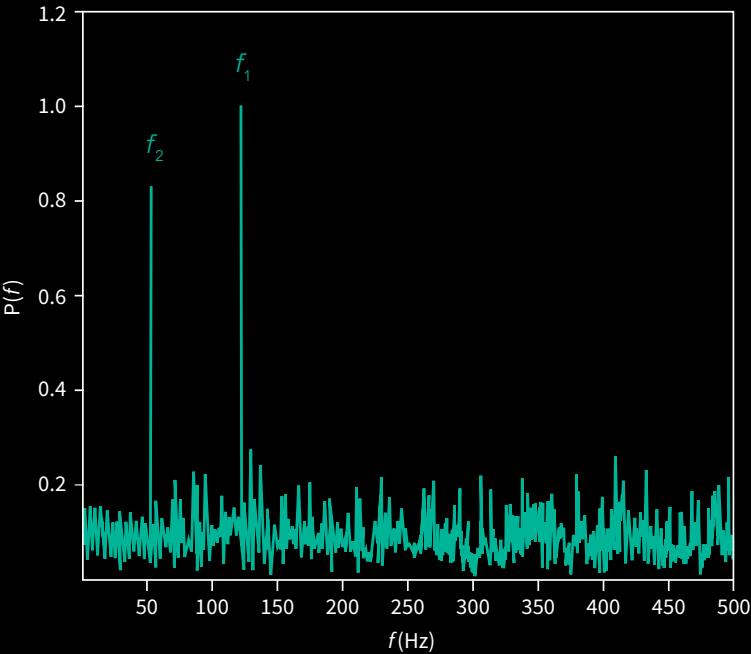
Fourier transforms are crucial to fields such as medical imaging. This mathematical tool breaks down a complex signal into its constituent frequencies, represented by the spikes in this graph.

“The heart of the algorithm is how fast you can do that spreading,” says Jeremy Magland, a senior data scientist at the CCM who contributed to FINUFFT’s development.

FINUFFT users can choose any accuracy level they prefer: Low accuracies run fastest, whereas higher accuracies take longer because more neighboring spreading points are used in the calculations.

Using a spreading function introduces error, though, because it ‘smooths out’ the signal. This smoothing dampens higher frequencies, so FINUFFT boosts higher frequencies after the fast Fourier transform does its work. Since the spreading function is known, the code can directly tweak the final result to compensate for the introduced error.

Although other software libraries exist for non-uniform Fourier transforms, many are made only for specific applications, such as MRI. Barnett, Magland and colleagues designed FINUFFT to be multipurpose, documented and easy to access from all of the major scientific programming languages. FINUFFT works in 1D, 2D or 3D and is entirely open source, so any project can freely use it.



Some scientists are already leveraging FINUFFT in their projects, including in the code used in 2019 to produce the first-ever image of a black hole. At the Flatiron Institute, David Stein, a research scientist at the Center for Computational Biology, uses FINUFFT to convert between the classic Cartesian grid coordinate system and a curved coordinate system that conforms around oddly shaped objects sitting in flowing fluids. Using such custom coordinate systems makes his fluid dynamics calculations more accurate, and FINUFFT allows Stein to move between the two grid shapes freely.

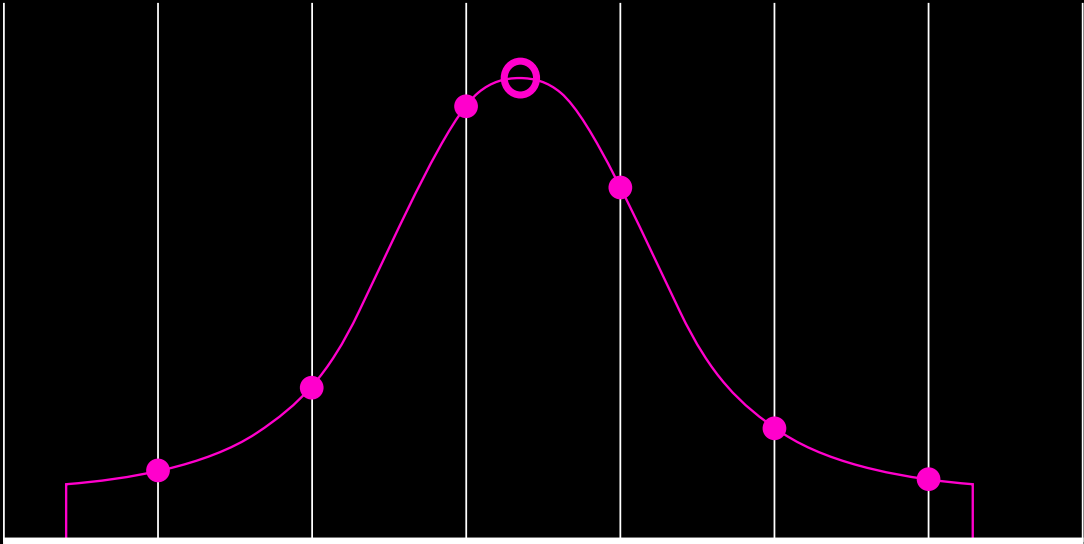
FINUFFT isn't just flexible; it's also blazingly fast. It's designed to remove bottlenecks found in previous code libraries and to take full advantage of the parallel processing capability of a computer's hardware.

In September 2019, Barnett, Magland and collaborator Ludvig af Klinteberg, now of the KTH Royal Institute of Technology in Stockholm, published a paper in the *SIAM Journal on Scientific Computing* showing just how fast FINUFFT is. In tests, FINUFFT was faster than every other tested code at all but the lowest accuracy levels, they found. That included the library co-written by Greengard. "It's one of the codes we beat quite successfully," Barnett says. "He's fine about that."

Barnett and his team are currently working to release an even faster version of FINUFFT written by Flatiron Institute summer intern Yu-Hsuan Shih that runs on graphics processing units (GPUs).

One remaining challenge, Barnett says, is spreading the word about FINUFFT. "You have to rely on some word-of-mouth and people finding it online when they need a tool," he says. Unfortunately, many people don't realize that what they're doing is actually a nonuniform Fourier transform. "It's like making a better hammer, but many people are still hammering with rocks," Barnett says.

At the end of our interview, Barnett scribbles a few outreach ideas on a sticky note, such as including tutorial use cases in FINUFFT's documentation and making installation easier. "Outreach is sometimes as hard as doing new research," he says, "but it's also an exciting part of what we do at the Flatiron Institute. We're trying to make the programs that people need now, and get them out there."



FINUFFT interpolates the values of on-grid points using off-grid data. The tool accomplishes this using a spreading function (pink curve). The function determines how strongly each off-grid point (pink circle) influences values on the grid (white lines). The final value of each on-grid point is the weighted sum of all neighboring off-grid data.

MATHEMATICS AND
PHYSICAL SCIENCES

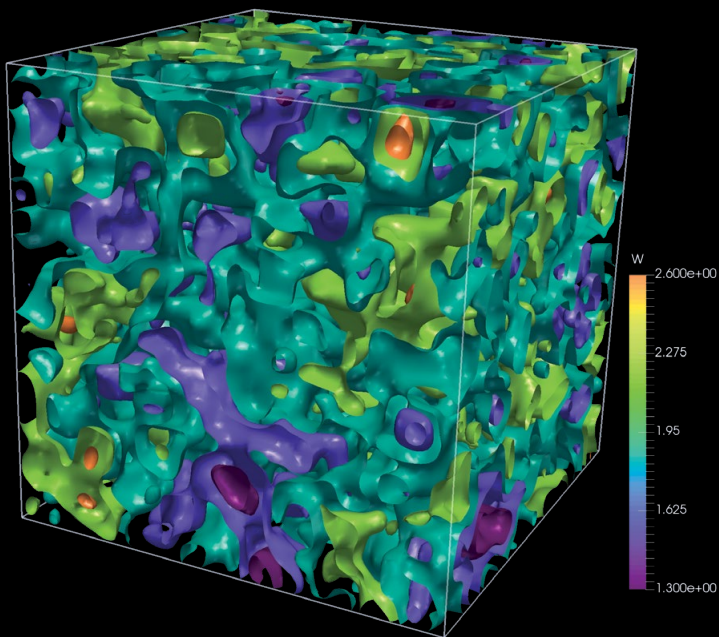


DELVING INTO THE MYSTERIES OF WAVES

SIMONS COLLABORATION ON LOCALIZATION OF WAVES

In the late 1950s, future Nobel Prize-winning physicist Philip Anderson discovered a puzzling phenomenon: In theory, the conductivity of materials could be reduced and even vanish when a sufficient amount of disorder was introduced into the material. Instead of flowing along straight paths, electrons would remain trapped at specific locations. It took decades before this phenomenon, called Anderson localization, was observed in real experiments, and scientists are still trying to understand exactly how and why it occurs.

Anderson localization is just one instance of a broader phenomenon known as wave localization. Wave localization can happen in almost any material in which waves or vibrations carry energy or particles, which includes everything from sound waves to light waves, from vibrations of molecules to quantum properties of atoms or electrons in matter. Waves are said to be localized when they are confined to small areas due to the structure of the ambient medium. Researchers in the Simons Collaboration on Localization of Waves are working to put localization on a mathematically and physically rigorous footing, which could eventually help researchers harness it to create materials with desirable properties.



The roots of the collaboration extend back to 2009, when collaboration principal investigator Marcel Filoche, a physicist at the École Polytechnique, met Svitlana Mayboroda, a mathematician at the University of Minnesota and now also director of the collaboration. Filoche was working on sound localization and absorption caused by geometrical disorder, while Mayboroda was interested in the properties of steady-state solutions to partial differential equations. Soon they realized that their respective projects were deeply connected, and together they began to develop a general theory of wave localization. Their early partnership would eventually expand to become the Simons Collaboration on Localization of Waves, launched in 2018.

The collaboration now has 10 PIs — five mathematicians and five physicists — and dozens of students, postdocs and affiliated scientists from vastly different backgrounds. Participants include mathematicians from the fields of harmonic analysis and partial differential equations (led by Guy David, David Jerison and Yves Meyer), along with experimental physicists working in quantum optics (led by Alain Aspect), semiconductors (led by James Speck and Claude Weisbuch) and organic semiconductors (led by Richard Friend), and specialists in computation (led by Douglas Arnold) to tie it all together.

The cross-pollination between different areas of research has already led to rich cycles of interdisciplinary insights. Physics inspires mathematics, mathematical discoveries spur physical experiments and computational models both validate prior conjectures and lead to new avenues of exploration. “It is absolutely magical,” Mayboroda says. “We created this fantastic team of people who are really the best in each direction of research.”

A 3D representation of the localization landscape for the Schrödinger equation in a random potential. Each colored surface corresponds to a level set of the effective potential. The dark purple regions are candidates for hosting localized quantum states.
Credit: Douglas N. Arnold

The central puzzle of localization is how even a small amount of disorder can effectively hold waves in place. It is not surprising that disorder decreases conductivity. In perfectly ordered materials such as crystals, waves travel in predictable, straight paths, like light rays in the air. Also predictably, disorder interrupts those paths, but the extent to which disorder can cause waves to localize seems disproportionately great. “The physics and mathematics of the previous century is very well equipped to deal with ordered structures,” Mayboroda says. “But localization in particular — and the world in general — is run by disorder.” The collaboration researchers’ challenge is to find the order underlying systems that seem completely disordered so that they can describe and predict them.

The traditional approach to studying disorder-induced localization is probabilistic and statistical in nature. It gives a picture of the most likely behaviors of waves in disordered media, but it does not provide a strong theoretical framework for predicting where and how localization works. The collaboration aims to develop a rigorous mathematical understanding of localization. “We found the same mathematical objects popping up in very different fields,” Filoche says, from the subatomic waves of quantum mechanics to the much larger ones in acoustics. “It seemed like maybe there was a more universal scheme at work.”

Indeed, the original inspiration of Mayboroda and Filoche came from an unexpected area: the study of vibrating plates. Great 19th-century mathematicians, including Ernst Chladni and Sophie Germain, had investigated how waves form on thin plates when different kinds of vibrations are applied. Mayboroda and Filoche, looking at the same problem, discovered that they could dramatically alter the propagation of vibrations by blocking just one point in the plate, thus localizing waves at specific frequencies. They developed a new theoretical tool, called the localization landscape, to describe and predict this phenomenon.

That work, published in 2012, opened the door to an expansion of the research group, in the direction of both mathematics and physics. Mathematicians Douglas Arnold from the University of Minnesota, Guy David from the Université Paris-Saclay, and

David Jerison from the Massachusetts Institute of Technology joined the team; together, their work led to the discovery of ‘effective potential,’ which plays a key role in predicting the quantum energies and densities of states in disordered systems.

At the same time, this theory was immediately applied successfully in semiconductor physics, where Claude Weisbuch, of the École Polytechnique and the University of Santa Barbara, realized that the landscape approach could help physicists understand how localization occurs in light-emitting diodes (LED) and photovoltaic cells. The disorder present in modern LED materials traps the electronic quantum waves, forcing them to concentrate along specific paths and at specific locations and to emit photons. Greater theoretical understanding of localization could help researchers improve the efficiency of LEDs and solve several vexing puzzles, such as why green LEDs are much less energy-efficient than red and blue ones. The collaboration hopes the landscape approach may help solve what researchers refer to as the ‘green gap.’

By the time the group applied for Simons Foundation funding, experimental physicists such as Alain Aspect of the Institut d’Optique in Paris, who studies small systems of atoms at ultralow temperatures, and Richard Friend of the University of Cambridge, who uses high-precision lasers to observe localization at the nanoscale in organic semiconductors, had joined the team, together with Yves Meyer, a mathematician at the École Normale Supérieure Paris-Saclay and an expert in harmonic analysis.

The collaboration is relatively young, but members have already succeeded in building on Filoche and Mayboroda’s localization landscape. A 2019 result of Filoche, Mayboroda and David described the ‘landscape law,’ a breakthrough in understanding the energy levels of localized waves in a mathematically rigorous way.

Mathematics and theoretical physics research sometimes have surprising applications that are only discovered and exploited centuries after the theory is developed. For localization, the timeline is proving much shorter. The theory has already found applications in LEDs and in protein vibrations, and it is about to be developed for solar cells and even for quantum computing. “It is absolutely funny, and a big lesson, that things that were tested on vibrating plates are theoretical tools that could be of help to build the next quantum devices,” Filoche says.

THE SUM OF THREE CUBES

SIMONS COLLABORATION ON ARITHMETIC GEOMETRY, NUMBER THEORY AND COMPUTATION

In the fall of 2019, Andrew Sutherland, a mathematician at the Massachusetts Institute of Technology and one of six principal investigators with the Simons Collaboration on Arithmetic Geometry, Number Theory and Computation, together with his collaborator Andrew Booker, a mathematician at the University of Bristol, published an equation that appealed to both number theorists and fans of *The Hitchhiker’s Guide to the Galaxy*.

$$-80,538,738,812,075,974^3 + 80,435,758,145,817,515^3 + 12,602,123,297,335,631^3 = 42$$

The question of whether a whole number can be written as the sum of three cubes might not generally be “the ultimate question of life, the universe, and everything,” but it is surprisingly tough to answer. And while it may seem like a curiosity, it has deep connections to important areas of research in number theory and algebraic geometry.

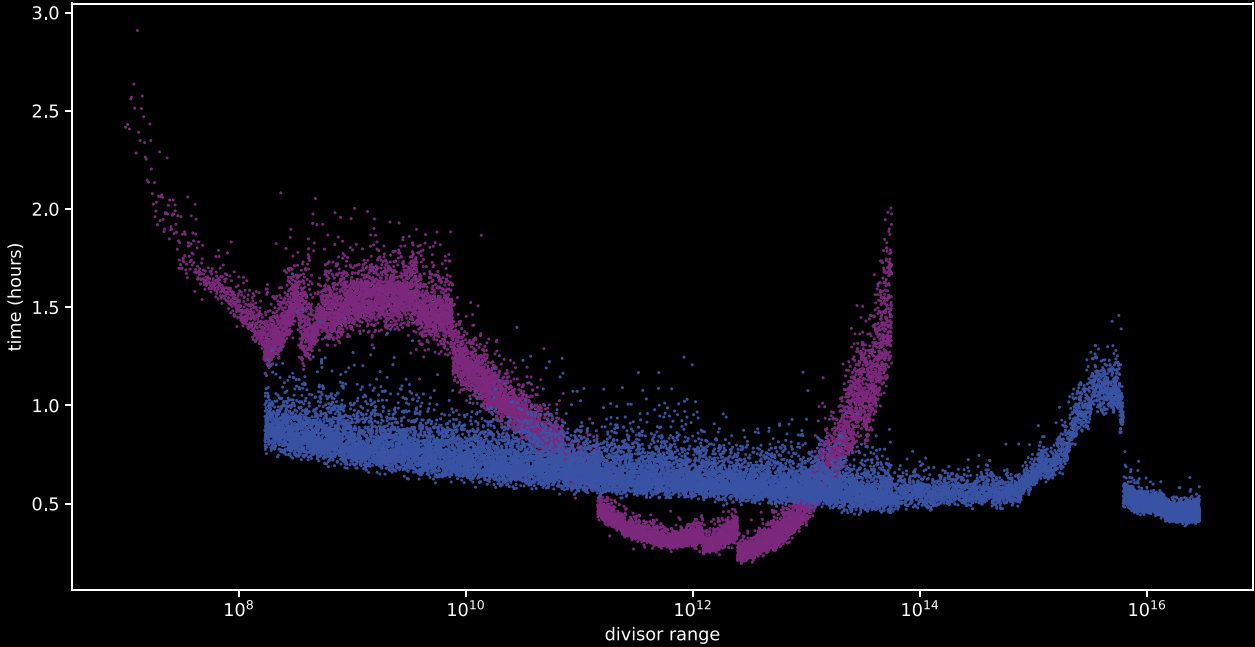
Booker became interested in the sum-of-three-cubes problem after watching a video about it on the popular YouTube math channel *Numberphile*. In 2015, he was perusing the channel looking for activities to do with the math club at his children’s school. He ran into a video, coincidentally featuring his colleague Tim Browning, about the sum-of-three-cubes problem. Browning noted that at the time 33 was the smallest integer for which the problem was unresolved.

It is fairly easy to convince yourself — or, in Booker’s case, an elementary school math student — that a number that has a remainder of 4 or 5 when divided by 9 cannot be written as the sum of three cubes. (Every integer can be written in the form $3n$, $3n + 1$, or $3n - 1$ for some n . If you cube those expressions, you see that every cube is within 1 of a multiple of 9. Add them up, and it’s clear that any sum of three cubes must be within 3 of a multiple of 9.)

In February 2019, Booker used some clever coding and about a week’s worth of time on his university’s computing cluster to find three cubes that sum to 33. The next month, at a conference, he asked Sutherland if he wanted to join the search for three cubes that sum to 42, which was now the smallest number for which the answer was unknown. Sutherland had experience with large parallel computing projects and expertise in the algorithms and programming languages they might use to tackle the problem. Later that year, they used Charity Engine, a crowdsourced network of computers, to show that 42 can be written as the sum of three cubes. That computation finished off the two-digit numbers, leaving 114 as the smallest number for which the problem is open.

Their work extends to a related question: If a whole number can be written as a sum of three cubes, how many ways can it be so written? The number 3 can be written as $1^3 + 1^3 + 1^3$, but it can also be written as $4^3 + 4^3 + (-5)^3$. Both of those representations are fairly easy to find just by playing around with arithmetic. But in 1992, mathematician Roger Heath-Brown conjectured that any number that can be written as a sum of three cubes can be written as a sum of three cubes in infinitely many ways. Sutherland and Booker discovered another representation of 3 as a sum of three cubes, providing one more piece of evidence that Heath-Brown’s conjecture is correct.

The sum-of-three-cubes question lies on what Sutherland describes as the “interesting frontier between what we can do theoretically and what can be turned into a practical computation.” This frontier is the sweet spot for the collaboration, one of whose primary objectives is to build computational tools that can help feed into theoretical understanding of number theory and arithmetic geometry.



A graph showing the computational muscle needed to discover a new representation for 3 as a sum of three cubes. The computation required nearly 4 million hours of CPU time across more than 400,000 PCs. Each dot in the graph represents 50 PCs. The y-axis represents the number of computing hours, and the x-axis represents a key parameter d that partitions the search space. Values of d with no large prime factors are colored blue, while those with a large prime factor are colored purple. Credit: Andrew Sutherland

In this current work, Sutherland was able to adapt algorithms he had previously used to compute zeta functions and L-functions — two important tools used to study problems like the Riemann hypothesis and Sato–Tate conjecture — to the sum-of-three-cubes problem. He is optimistic that the work he and Booker did to speed up the code for this project will have rewards in the world of zeta and L-functions. “There’s a nice synergy there,” Sutherland says.

Although the sum-of-three-cubes problem is simple enough for even young students to understand, it is related to more abstract theoretical work done by members of the collaboration and other mathematicians in the field. For decades, number theorists have pushed the discipline forward by translating problems about discrete entities (whole numbers) into questions about continuous objects (algebraic varieties, which are solution sets to polynomial equations). The sum-of-three-cubes question is another one of these problems. Previous work on the question done by Harvard University mathematician Noam Elkies, also a principal investigator in the Simons collaboration, translates the problem into the question of finding rational points on cubic surfaces, which are defined by polynomials of degree 3.

Every time Booker and Sutherland manage to write a new number as the sum of three cubes, they fit one small piece into the puzzle of which numbers may be written that way. All the same, the puzzle may never be completely solved. The two collaborators’ work is just one part of a more general question researchers have faced for decades: Which polynomial equations have integer solutions? In 1970, mathematicians showed that there is no algorithm that can answer that question for all polynomials.

Collaboration researchers may find a way to answer the question fully for the sum-of-three-cubes problem using theoretical rather than computational tools — or they may not be able to. Far from making Booker and Sutherland feel hopeless, this prospect motivates them to redouble their efforts at approaching the problem from an algorithmic point of view. “It may turn out that our only tool for getting at these kinds of questions is by running computations,” Sutherland says.

EMPOWERING THE FUTURE OF FUSION ENERGY

SIMONS COLLABORATION ON HIDDEN SYMMETRIES AND FUSION ENERGY

Here on Earth, physicists have managed to come up with a few strategies to fuse hydrogen. One method requires heating hydrogen atoms in a container to 100 million degrees to give them enough energy to overcome the mutual repulsion of their nuclei. Under those conditions, hydrogen gas ionizes, which means electrons are stripped from their atoms and float around freely with the nuclei in a mix called plasma.

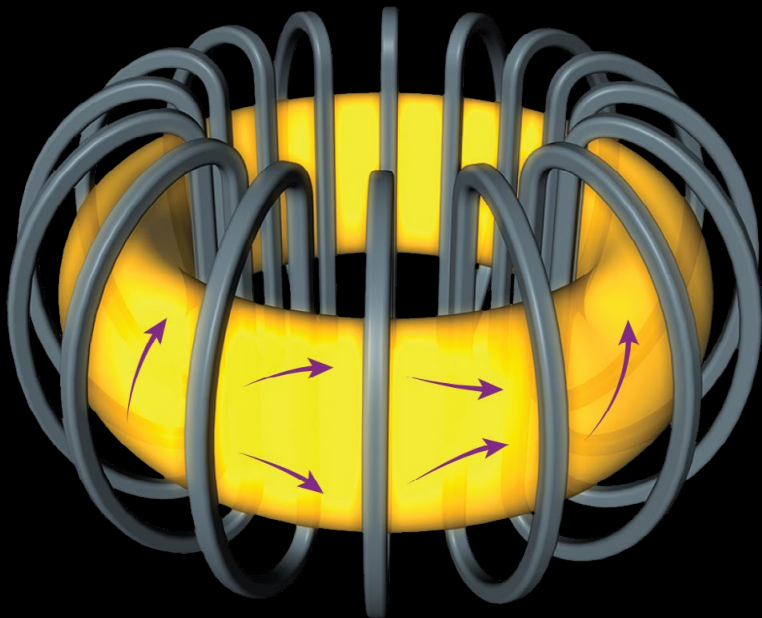
One promising early model was first tested out in 1958. In that design, a doughnut-shaped (or toroidal) tokamak holds plasma by pumping electrical currents through a series of metal coils, which create magnetic fields that contain the hydrogen and squeeze it together, causing fusion.

Tokamaks have a major drawback, however: The magnetic field created by the coils that wrap around the toroidal tokamak also induce a current in the plasma. Researchers usually pulse that current, which makes it difficult to maintain the plasma in the stable steady state necessary for fusion. Furthermore, the system can be disrupted by instability, dissipating the

Since the 1940s, scientists have dreamed of creating fusion energy reactors, which could make energy cheaply and safely, producing less radiation and waste than conventional nuclear-fission reactors. So far, though, no design has managed to generate more energy than was put in, leading cynics to perennially quip that fusion is the energy source of the future — and always will be.

The Simons Collaboration on Hidden Symmetries and Fusion Energy, using a new design approach and fresh insights into the mathematics of symmetry, may yet prove the cynics wrong.

Fusing nuclei together in a controlled way requires creating a starlike environment: In stars, high temperatures result in enough kinetic energy to squash hydrogen nuclei together, forming helium and releasing energy.

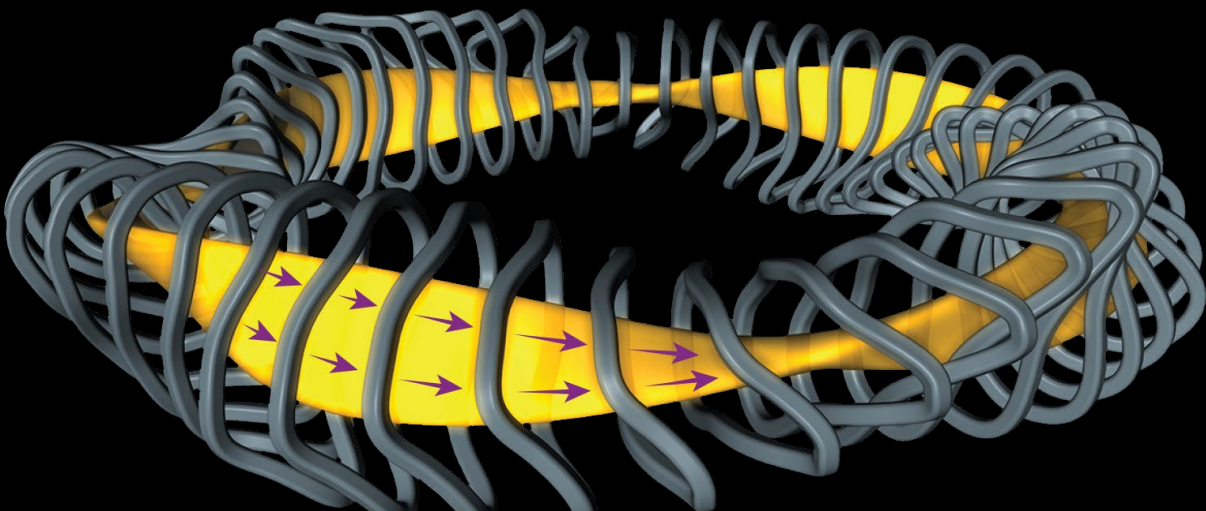


plasma after even a few milliseconds. Scientists have built dozens of experimental tokamaks, but none has yet resulted in a net gain of energy, although research continues.

Princeton astrophysicist Lyman Spitzer thought of another configuration: a stellarator. A stellarator is also torus-like, but because of a complicated helical structure in its coils, the plasma holds no current and hence can operate in steady state devoid of disruptive instabilities, in principle creating ideal conditions for fusion. The challenge is to build an optimum set of coils that will realize the dream of gains in energy via fusion.

The collaboration hopes that new mathematical and numerical techniques will solve that challenge. This collection of 33 mathematicians, computer scientists and plasma physicists from 16 universities across the globe is working on the next generation of stellarators, whose coils test the limits of design and manufacturing precision.

“We are developing novel optimization methods that will enable us to design the stellarator of the future with as much engineering simplicity as possible,” says Princeton University professor of astrophysical sciences Amitava Bhattacharjee, director of the collaboration. “When you put physics and the science of precise optimization together, you can come up with sophisticated designs which were impossible before; the ways to do that is the primary focus of the Simons project.”



Both the tokamak and the stellarator use strong magnetic fields to confine plasma at the high temperatures and pressures needed for nuclear fusion. The tokamak (opposite page) uses an internal transformer to drive a current in the plasma, thereby twisting the magnetic field and containing the plasma. This approach, though, can result in instabilities. The stellarator's contorted design (above) results in a twisted magnetic field without the need for induced current, resulting in improved stability. Credit: © 2020 New Scientist Ltd. All rights reserved. Distributed by Tribune Content Age

THE THEORETICAL SIDE OF HIDDEN SYMMETRIES

Symmetries in objects simplify analyses and allow people to use less energy — think of how circular wheels work better than oval-shaped or square-shaped ones. Unlike those in the doughnut-shaped tokamak, which has an obvious symmetry, the twisting coils of a stellarator don't appear symmetric in terms of the usual x , y and z coordinates. But when their structures are viewed in relation to magnetic fields instead of those axes, in a coordinate system defined by one of the collaboration's founding investigators, Columbia University professor of applied physics and applied mathematics Allen Boozer, stellarators do have an approximate 'hidden' symmetry, or quasi-symmetry.

“The symmetry is hidden in the sense that if you look at one of these magnetic fields it looks like a Salvador Dali painting: It's distorted and wobbly,” says co-investigator Matt Landreman, an associate research scientist at the Institute for Research in Electronics and Applied Physics at the University of Maryland. “But the equations tell us that even if you can't see it by eye, the electrically charged particles in these magnetic fields experience a symmetry. It's sort of like you trick electrons and protons into thinking they're in a symmetric system. That's an exciting and beautiful motivating concept for the project.”

The containing magnetic field of the stellarator can be described using quasi-symmetric equations. Previous numerical research using computers found around 20 possible configurations for the field that minimize the ‘approximateness’ of the quasi-symmetry. But Landreman says that the black-box solution “was emotionally unsatisfying because we don’t know why the computer takes me to this shape. How many possible shapes are out there?”

Instead, the collaborators used different numerical methods to approximate the quasi-symmetry equations. They found all possible configurations, ensuring that future stellarator designs won’t overlook a magnetic field alignment that could optimize energy output.

EXPERIMENTS TO PROVE THE THEORIES

Unlike a constantly tended tokamak, a stellarator is a steady-state system, which means that “you can turn it on in the morning and turn it off in the evening,” says co-investigator Thomas Sunn Pedersen, a professor of physics at the Max Planck Institute for Plasma Physics, where he runs experiments on one of the largest stellarators in the world, the Wendelstein 7-X (W7-X).

Although stellarators such as the W7-X were built and optimized to the best extent possible at the time, the collaboration hopes to use more advanced computing power to better optimize the next generation. Thus far, all the results from the theoretical side have been borne out by data from the W7-X.

“These experiments make me excited,” Pedersen says. “The optimization that was done two decades ago with computers we can laugh about today in terms of computational power works; we can do so much more now.”

THE HUB OF AN INTERNATIONAL COMMUNITY

The collaboration’s shared postdocs are also in on the fun. These eight people embody one of the unusual hallmarks of the project: encouraging travel between multiple institutions, ferrying knowledge and achieving collaboration between departments.

“What I really like about being a shared postdoc is not working by yourself in an office. You really can talk to people and do a lot of interesting problems,” says postdoc Silke Glas, who travels between Cornell University and New York University. “I enjoy the variety I have, and I think it’s a win for the collaboration as well.”

These postdocs help nail down jargon between different fields, a role also played by the biweekly video chats between the theoretical and experimental collaboration members.

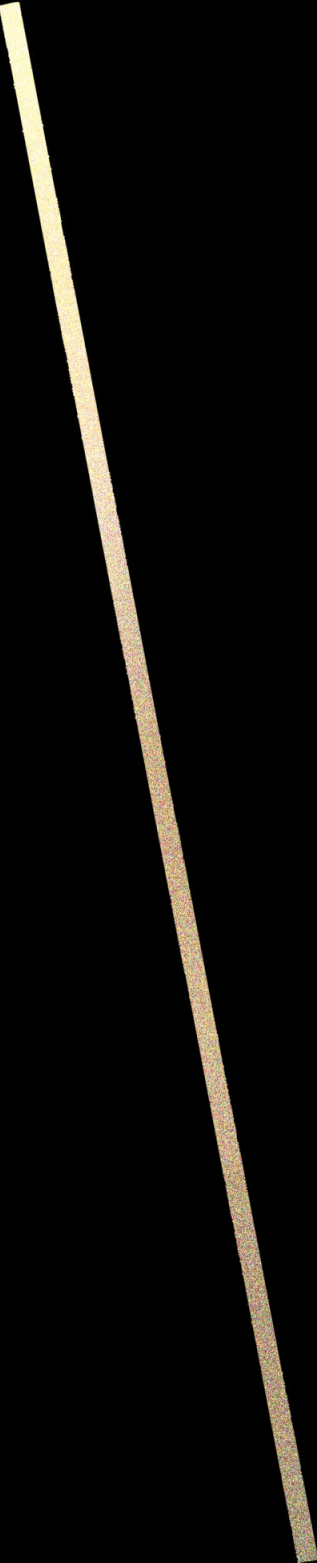
“Another challenge of the interdisciplinary nature of this work is trying to come up with concepts that are interesting to the people in both theoretical and experimental communities,” says Landreman. “One thing we’ve done a lot of this first year is define precisely stated mathematical problems that numerical optimization people can study that are interesting enough from a physics point of view, but don’t have all the complexities of physical experiments.”

Nowadays, nonmembers of the collaboration sit in on the biweekly “Simons Hour” as well. The international research community showed up in droves at the first annual meeting of the collaboration, which took place in late March at the Simons Foundation in New York City. Seventy-five researchers came from around the world for research updates from the collaboration and poster presentations from non-collaboration researchers.

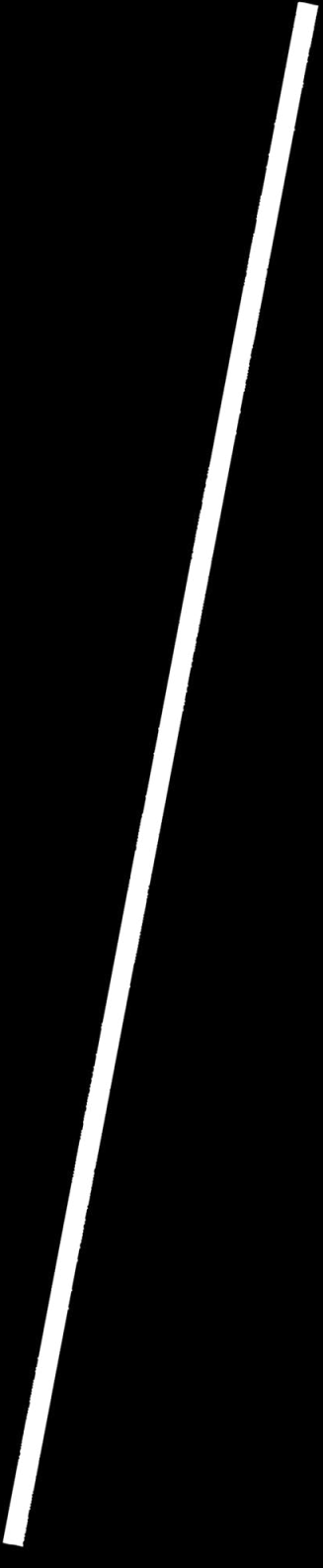
“The general sense of enthusiasm about the hidden symmetries project is very high; I’m very gratified by it,” says Bhattacharjee. “I think what Simons did was support an idea which was very timely in which there were not enough resources invested, and in the process created something that was very much needed by the stellarator community.”

The collaboration also co-hosted a plasma physics summer school at the Princeton Plasma Physics Laboratory for 33 graduate students and postdocs with backgrounds in optimizing magnetic fields, who will hopefully join the community and continue contributing at the frontier of one of the world’s foremost science problems.

“You have here a marriage of fundamental science, wonderful mathematics and physics, dedicated to an engineering cause of great importance,” Bhattacharjee says.



LIFE SCIENCES



NEURAL SIGNALS, FAR AND WIDE

SIMONS COLLABORATION ON THE GLOBAL BRAIN

Neuroscientists have traditionally focused their efforts on discrete brain areas: People interested in vision studied the visual cortex, and people interested in movement studied the motor cortex. Though everyone knew such functions were not actually limited to specific regions, technological limitations made far-reaching experiments infeasible.

But that's rapidly changing. The development of new technologies capable of recording from large populations of neurons in multiple brain regions — simultaneously — is now making it possible to examine how information is represented globally across the brain.

Early results suggest that neural signals for some cognitive functions are more widespread than anyone had predicted. Movement-related information seems to be particularly widespread, encoded all over the brain.

Anne Churchland and her colleagues at Cold Spring Harbor Laboratory have shown that fidgeting — in mice, at least — activates not just the regions typically associated with movement but the entire brain. And a brief, apparently meaningless whisk or kick of a hind limb evokes a burst of neural activity over the entire cerebral cortex.

“It's for sure made me wonder if, for certain organisms, including some humans, part of what it means to think is to move,” says Churchland, an investigator with the Simons Collaboration on the Global Brain (SCGB). “Movements and cognition for those subjects are deeply intertwined.”

“This type of research is essential to the Simons Collaboration on the Global Brain, which aims to understand how neurons work together to produce thoughts,” says David Tank, SCGB's director and director of the Princeton Neuroscience Institute. “Uncovering how populations of neurons encode information across different regions of the brain is the first step in deciphering how these regions collaboratively integrate and process information.”

In Churchland's experiment, published in *Nature Neuroscience* in September 2019, researchers monitored both neural activity and movement as mice learned to press left or right to receive a reward in response to a visual or auditory stimulus. The researchers expected to see just a handful of distinct cortical regions light up. “But what we actually saw was very different,” says Churchland. “Many, many brain structures were engaged. Many more than we anticipated, and to a much greater extent than we anticipated.”

Indeed, neural activity tied to random movements accounted for the majority of variability in neural responses from trial to trial — not just in the motor and somatosensory cortical areas, where fidget-related activity might be expected, but all over the cortex. Neuroscientists have long written off such variability as noise, but Churchland's work suggests a significant chunk of it is actually signal.

The Churchland study followed a paper published in April in *Science* that used both calcium imaging and electrophysiology to monitor the activity of thousands of visual neurons in mice walking on a treadmill with little or no visual stimulation.

Carsen Stringer and Marius Pachitariu, now at the Janelia Research Campus, working with Ken Harris and Matteo Carandini at University College London, both SCGB investigators, found that a mouse's facial movements accounted for a significant amount of neural population activity in its visual cortex. Further experiments showed that this held true across the brain. They also found that the same neurons could encode both visual and behavioral information.

“The findings challenge the idea that the brain is modular. Every brain area contains behavioral information; therefore, sensory areas like visual cortex can no longer be thought of as simply visual,” Stringer says.

These two studies add to an expanding body of research exploring how an animal's behavior profoundly influences the ways its brain processes sensory information and makes decisions. Previous research had mainly shown how single variables — such as running speed or pupil diameter (an indicator of arousal) — could account for changes in activity in sensory areas of the brain. This newer work shows both that movement-related neural activity is broadcast across the whole brain, and that the signals are more complex than previously described.

“Creatures evolved to have a brain to move the body, and cognitive tasks probably borrowed neural dynamics from movements,” Churchland says. She believes researchers should revisit the intersection between movement and thought and figure out how, exactly, the two are linked.

DIFFERENT DISTRIBUTIONS

Other types of information are also found across the brain, though not as extensively as movement-related information. In a study published in *Nature* in November 2019, SCGB investigator Nick Steinmetz, now at the University of Washington in Seattle, and

collaborators found that different types of information can have very different patterns of neural activity distributed around the brain.

Researchers used Neuropixels probes, a newly developed, hair-thin probe densely packed with recording sites, to record from 30,000 neurons in 42 different brain regions in mice as they learned to turn a wheel left or right depending on a visual stimulus. They looked at neural activity linked to different aspects of the task, such as action (when the mouse started to turn the wheel), visual information (the content of the stimulus), choice (whether the animal moved the wheel left or right) and engagement (how likely the animal was to respond to the stimulus).

None of these factors were limited to one part of the brain. As was the case for the Churchland and Harris studies, movement-related information was broadly distributed around the brain. Visual information, however, was more limited, restricted largely to areas known to be involved in visual processing.

Neural activity tied to the animal's level of engagement in the task and its eventual choice had unique representations. Choice-related signals were found in a subset of brain areas, including the prefrontal cortex, basal ganglia and midbrain, but not in the visual or parietal cortex. Engagement also had a distinctive pattern — less activity in the cortex and more activity in subcortical areas.

Researchers now need to figure out how different distributed networks of neurons coordinate with each other. “How is the flow of information controlled across networks?” asks Steinmetz.

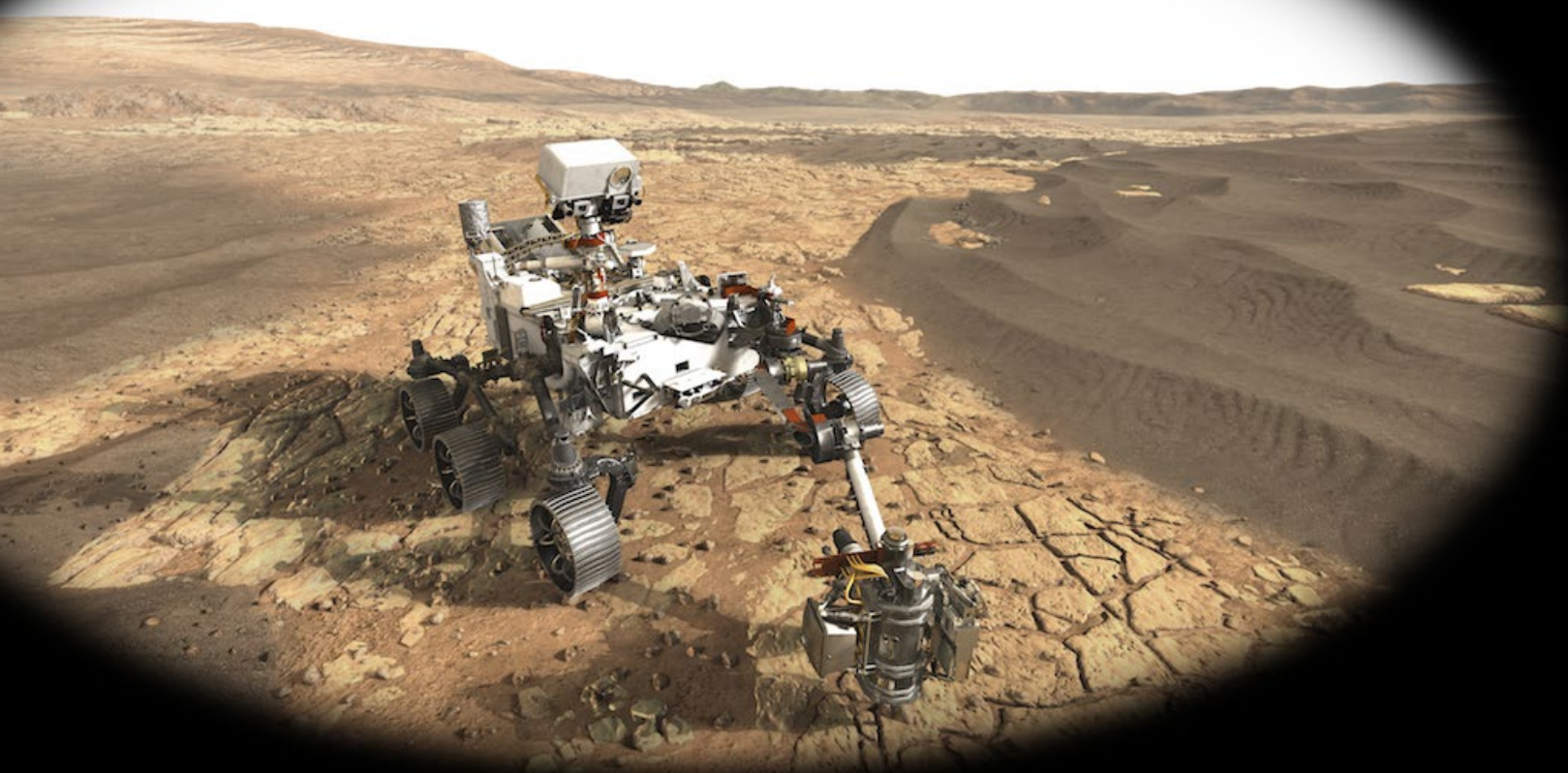
The findings also challenge researchers to reconsider how cortical processing operates and to develop new models that incorporate behavior and the entire cortex. “You have moment-by-moment information about what you're doing across the whole brain,” Stringer says. The question this poses for future research, she says, is: “What does the brain do with that information?”

Even a twitch of a hind leg can produce abundant, widespread and high-dimensional activity in a mouse's cortex. Researchers are investigating why even such small movements can engage the whole brain.
Credit: Peter Diamond



THE HUNT FOR LIFE'S ORIGINS ON MARS

SIMONS COLLABORATION ON THE ORIGINS OF LIFE



Earth's fossil record suggests that by 3.5 billion years ago, life had found a footing on our planet. Yet the very processes that would shape the further evolution of that life — such as plate tectonics, erosion and weathering — also destroyed or muddled the crucial first records of life's emergence, presenting a significant challenge for researchers trying to understand how life arose.

Mars, however, is seemingly inhospitable to life now but may not have always been so. And with nearly half of its surface rocks over 3.7 billion years old, Mars may have retained the records to show it. In short, 4 billion years ago, Earth had oceans and land, while Mars had wet climates and standing water, at least episodically. While one world went on to teem with life, the other may yet hold the key to understanding how life starts.

“On Mars, we have a high-fidelity record of what happened between 3.5 and 4 billion years ago, when the planet looked a lot like Earth,” says John Grotzinger, a professor of geology and geobiology and division chair for geological and planetary sciences at the California Institute of Technology and co-director of the Simons Collaboration on the Origins of Life (SCOL).

Formed in 2013 and now comprising 25 investigators and eight postdoctoral fellows working in geology, chemistry and biology, SCOL seeks to elucidate the origins of life, both on Earth and on other potentially habitable planets. Several collaboration members

are working closely with NASA's upcoming Mars 2020 mission on its goal to determine if Mars ever supported life. “The focus of the Mars missions has gone from the search for water to the search for habitability, and now to the search for life,” says Grotzinger, who was project scientist for the Curiosity rover from 2007 to 2015.

SCOL investigator David Catling, a professor of earth and space sciences at the University of Washington, made a case for where the new rover — recently named Perseverance — should land for the Mars 2020 mission. At NASA's final landing-site selection workshop in October 2018, he suggested landing in Jezero Crater, arguing that it would be the best place to look for signs of prebiotic chemistry. The NASA Science Mission Directorate later chose that location from a list that had started with 60 possible sites. Several other SCOL investigators contributed to the presentation, including Tanja Bosak, Roger Summons and Joel Hurowitz.

Jezero Crater is about 50 kilometers in diameter and contains a 3.8-billion-year-old delta deposit, indicating it was once a lake. The crater may have trapped within its clays and other minerals the vestiges of ancient prebiotic chemistry: the interactions between molecules that directly preceded life. While actual fossils are rare on Earth and could well be even rarer on the exposed surface of Mars, the planet could be a graveyard of materials and chemistries that record the preamble to the emergence of self-replicating organisms, says Grotzinger. If Perseverance discovers such molecular fossils and their origins are determined to be biological or from meteorites, it could reshape our understanding of life's start on Earth. “If Mars' early environment reached a stage of prebiotic chemistry, those chemicals that may have survived can give us a glimpse of a chemistry long erased on Earth,” says Catling.

NASA's Perseverance rover (opposite page) will trek across the red planet's surface, sleuthing out signs of ancient Martian life and collecting rock and soil samples. A future mission could potentially return these samples to Earth. Credit: NASA/JPL-Caltech

The central challenge faced by those who will interpret the Mars samples will be how to distinguish prebiotic signatures from organic matter not associated with life, such as that found in meteorites. “We'll look for molecules that reflect a non-randomness in their chemical structures,” says Summons, the Schlumberger Professor of Geobiology at the Massachusetts Institute of Technology. For example, organic molecules in meteorites often show evidence of being randomly built from additions of single carbon atoms. In contrast, in biology, large and complex molecules are constructed from small sets of common building blocks. In lipids, for instance, carbon atoms are added in twos or fives. However, molecules like ferrocyanides and cell membranes, which are inherently in a reduced state, will require special circumstances to be preserved in Mars' oxidizing environment. “We'll need to look for the magic minerals, like silica, clays and carbonates, that can entomb these molecules and lock them away from oxidation and destruction by ultraviolet light,” says Grotzinger.

In her lab, Bosak, a professor of geobiology at MIT, is working on experimental fossilization of microbes in a Mars-like environment. The rocks on Mars are basalt-based, with more magnesium and iron and less aluminum and silica than most rocks on Earth. “We'll see chemical reactions uncommon on Earth, and this will have consequences for sedimentary features and the kinds of microbes preserved,” says Bosak. One early finding from her lab showed the generation of hydrogen gas from fine-grained basalt and other mixtures of minerals, analogous to those expected in Jezero Crater sediments, when they were mixed into carbonated water. In addition to hydrogen bubbles, surface features like ridges formed along with the precipitation of new minerals. These are the sorts of features Perseverance will be able to capture on camera, says Bosak. Because several kinds of microbes consume hydrogen gas, the gas-related features could be a good place to look for microbial biosignatures.

As a returned sample scientist and a member of the project science team for the mission, Bosak will guide the selection of samples that NASA will send to Earth on a later mission, aiming to optimize the chances of bringing back rocks with prebiotic molecules as

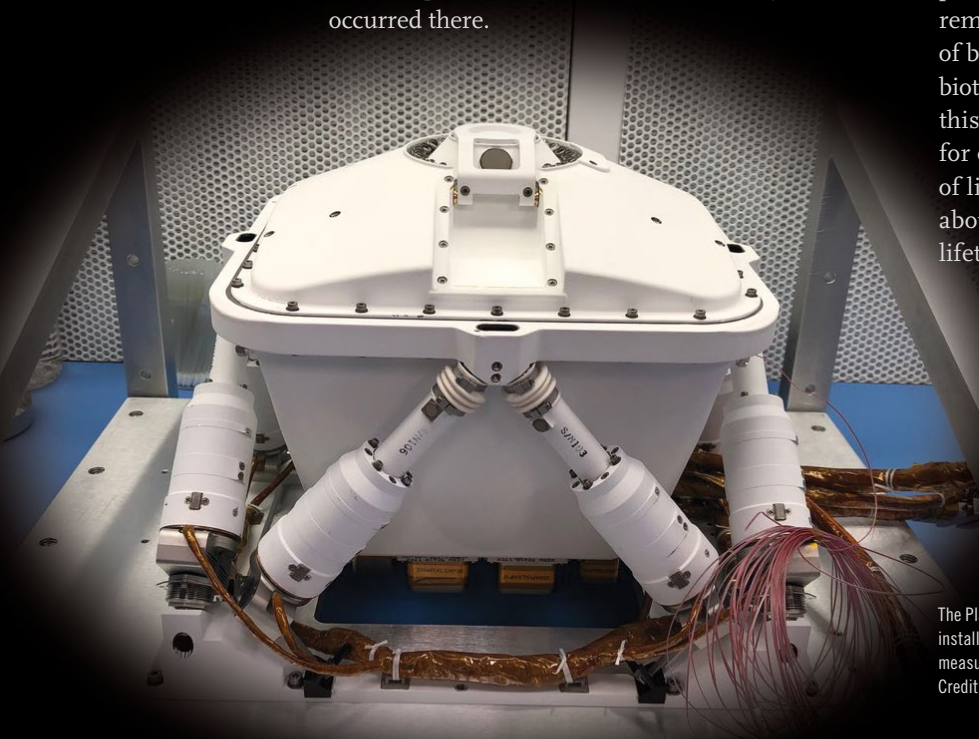
well as microbial fossils. Using the rover's imaging of rock formations and laser spectroscopy that can tell investigators which elements are present, Bosak will help decide where the rover will drill for 20 or more samples, each of which will be the size of a stick of blackboard chalk. Collecting samples with a known geological context will provide a revolutionary opportunity to explore early life on Mars, says Bosak.

For the first time on a Mars mission, chemical information tied to the texture of the rock will be provided by an X-Ray fluorescence instrument called PIXL (Planetary Instrument for X-Ray Lithochemistry), which will be mounted on the rover's arm. SCOL investigator Joel Hurowitz serves as deputy principal investigator for the instrument. Hurowitz, an assistant professor of geosciences at Stony Brook University, has worked on Mars missions since 2004 and hopes the 2020 mission will result in a set of measurements that allow the reconstruction of the ancient environment at Jezero Crater. The identity and composition of the rocks — information provided by PIXL — will be the crucial starting point for experiments. "Then we can go into the lab and try to figure out the range of chemical conditions — pH, temperature, redox state, salinity — that can make those minerals," says Hurowitz. Once his lab has done the astrobiological forensics needed to paint a full chemical picture of the lake 3.8 billion years ago, the researchers can begin to understand what kinds of prebiotic chemical reactions may have occurred there.

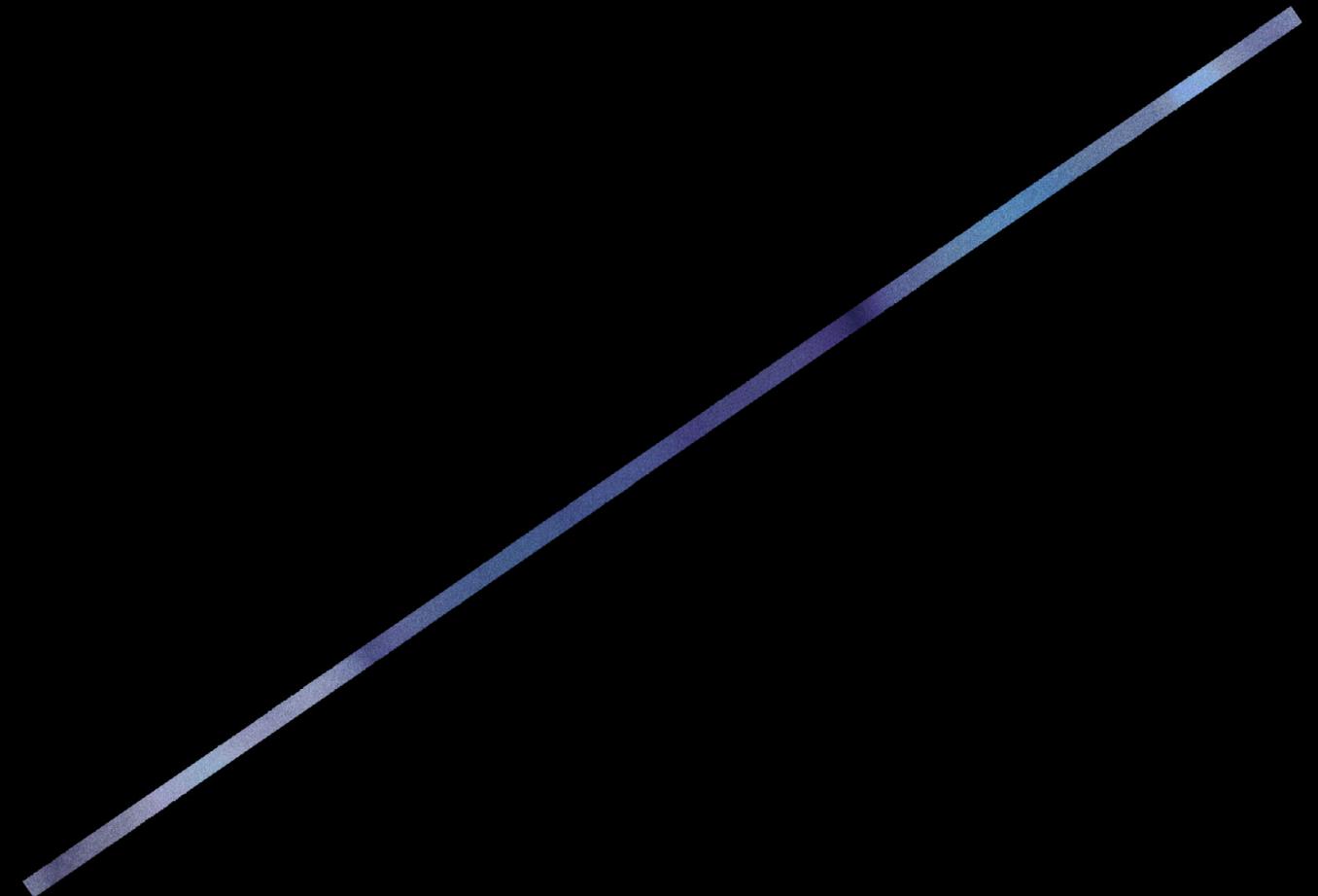
Hurowitz's lab is working now to experimentally precipitate minerals similar to those found in ancient sedimentary rocks on Mars and Earth. For example, spectroscopic analysis of Jezero Crater from orbit shows a predominance of magnesium carbonates. The lab is working to understand what conditions would precipitate magnesium carbonate and what this implies for salinity. The carbonates in other experiments are being used to generate calibration data that can ultimately aid in determining the temperature of the water in Jezero Crater's long-gone lake using a technique that relies on the tendency of heavier carbon isotopes to clump together at lower temperatures.

Mars 2020 researchers credit SCOL with bringing together a large interdisciplinary team to assist with one of science's greatest unsolved challenges. Getting at fundamental questions about life's origins would not be possible without this multidisciplinary group, says Summons.

If the mission finds life on Mars, says Catling, the questions then will be: How different is it from ours? Is there a universal biochemistry? But even if only prebiotic precursors are found rather than biological remnants, scientists will nonetheless reap the reward of being able to refine and possibly expand their prebiotic schemes. "One of the most exciting parts of this work is using a particular planet as a test case for other planets when we consider the emergence of life on Earth," says Hurowitz. And Bosak says about the 2020 mission, "This is a once-in-a-lifetime opportunity."



The Planetary Instrument for X-Ray Lithochemistry (PIXL), shown here before its installation on the Perseverance rover's robotic arm, will use an X-Ray beam to measure the chemical makeup of Martian rocks.
Credit: NASA/JPL-Caltech



AUTISM RESEARCH INITIATIVE
(SFARI)



SPARK: DELIVERING RESULTS

SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Travis King, 15, and his family gathered around the telephone in the living room of their Washington state farmhouse. They were about to get a call from Wendy Chung, the principal investigator of SPARK (Simons Foundation Powering Autism Research for Knowledge). Chung had important news for them: SPARK had found a genetic cause for Travis’ autism.

“Travis sat there listening,” says his mother, Threasa King. “I never know how much he understands, but I wanted him to be a part of it.”

The Simons Foundation Autism Research Initiative launched SPARK four years ago with the goal of analyzing the genomes of 50,000 people with autism and their biological parents (and sometimes siblings). Different rare genetic changes in hundreds of genes are believed to underlie autism, and with a cohort of 50,000 families, SPARK’s researchers hope to uncover most of these.

To date, SPARK has enrolled about 230,000 individuals with autism and family members. More than 22,000 complete families (consisting of an individual with autism and their parents) have submitted their genetic material in the form of mail-in saliva kits. SPARK and its collaborators have sequenced the genomes of more than 45,000 people, with another 23,000 currently in the works. The study now maintains a list of more than 175 genes and segments of chromosomes where a change is known to contribute to autism. SPARK’s sequencing studies have already identified dozens of other statistically significant autism risk genes that will likely be added to this list in the future.

When SPARK finds that a participant has a genetic change linked to autism, it offers the family the option to receive this information through a genetic counselor or medical doctor. In 2019, SPARK provided a genetic diagnosis to nearly 200 people, including Travis — a dramatic increase over previous years. In 2020, the study expects to inform a further 300 participants.

SPARK researchers estimate that 8 to 10 percent of study participants with autism will be diagnosed with one of the genetic changes that have already been identified. The study continues to find more autism risk genes as it sequences more families, so that percentage could gradually rise. Not everyone will receive a diagnosis, however, since a majority of individuals will have autism that is caused by changes to multiple genes rather than by a single genetic change.

Many parents choose to receive their child’s genetic diagnosis in the hope that it will enable them to better manage their child’s care. “We are giving them the tools and information to help them help their child, and also help science,” says Pamela Feliciano, SPARK’s scientific director.

The Kings learned that Travis has a rare change to a gene called *CUL3*, one not inherited from his parents. Threasa King shared the *CUL3* diagnosis with Travis’ doctor and others who work with him.

While there are no specific treatments yet for *CUL3* genetic changes related to autism, the diagnosis has nevertheless influenced Travis’ medical care.

For instance, he had been taking a medication for aggression that requires regular blood pressure monitoring. But because *CUL3* is linked to high blood pressure, the family asked his doctors to reexamine this choice of medicine. “Now his doctors are all on board,” King says.

For some families, receiving a genetic diagnosis from SPARK confirms a long-held suspicion.

Years ago, Cindy and Patrick Badon’s doctor had suspected a genetic cause for their son Reagan’s autism. But Reagan’s symptoms did not fit neatly into any known syndrome, and genetic tests found nothing significant. The doctor said that pinpointing the gene involved would be like “finding a needle in a haystack,” Cindy Badon recalls.

Then SPARK provided the tools needed to comb through Reagan’s haystack. In 2016, the Badons and their sons, Reagan and Chance, joined the study. “I thought maybe SPARK could find what doctors had not been able to [find] so far,” Cindy Badon says.

Even so, she was floored when SPARK told her three years later that Reagan had an alteration in a high-confidence autism risk gene called *MED13*. Like Travis King, Reagan, now 13, is one of very few people worldwide who have been diagnosed with this particular genetic change, which he did not inherit from his parents.

With “disbelief, shock and excitement,” Cindy Badon shared the news with her husband. “It’s a little unnerving sometimes because there’s not a lot of information out there about *MED13* yet,” she says. “But the more I read, the more I feel like this is exactly the piece of the puzzle we’ve been missing.”

In a 2018 article in *Human Genetics*, researchers described the rare developmental disorder connected to changes in *MED13*. Of the 13 people they studied, all had intellectual disability or developmental delays. Many could understand more language than they could speak, as is the case with Reagan. Eight had vision or eye problems, and seven had delays in developing motor skills. Five had autism, and two had heart abnormalities, among other issues.

The genetic diagnosis provides a fresh lens through which to view some of Reagan’s more puzzling symptoms. For instance, he has trouble buttoning a shirt if he has to look down to see the buttons. And he needs to eat frequent, high-protein meals to maintain his energy level. “A lot of the things that we now think are genetic were [previously] written off as being ‘just autism,’” Cindy Badon says.

The genetic diagnosis has given the Badons a path to follow. It confirms their decision to stick with scientifically proven behavioral therapies for autism rather than newer ones that don’t apply to Reagan, says Patrick Badon. The family also plans to ask doctors to check Reagan for the kinds of heart, eye and other problems that have been found in people with a *MED13* change.

To help expand scientists’ knowledge base about *MED13*-related syndrome, the Badons have joined a SFARI program called Simons Searchlight that forms communities of families who have a shared genetic diagnosis. Searchlight participants can share information about symptoms and treatments with each other and take part in additional research studies.

“We would like to see research on what we can do to keep [Reagan] healthy and happy and help him deal with the potential health problems in his future,” Patrick Badon says.

Many of the genetic changes thought to cause autism are almost vanishingly rare, so everyone who joins SPARK and Simons Searchlight increases the likelihood that researchers will discover something new. “Literally every person and every family matters,” Feliciano says.

Through their involvement with SPARK, the King family (opposite page) learned that their youngest son, Travis, has a rare change in his *CUL3* gene that is known to cause autism.



SFARI RESEARCH ROUNDUP

SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Since its launch in 2003, the Simons Foundation Autism Research Initiative (SFARI) has supported the work of more than 550 investigators in the United States and abroad. In 2019, nearly 300 SFARI Investigators studied a broad array of questions about autism, from its genetic basis to new ways to support people with autism and their families. Below are some highlights of the past year’s research.

SENSING AGGRESSION

Some children with severe autism are prone to aggression, which can include hitting, biting and throwing objects. Aggressive outbursts, which are highly stressful for the children and their caregivers, are often hard to predict. A new biosensor, however, offers a warning when a child with autism is likely to erupt within the next minute, giving caregivers a head start on redirecting the child and making the environment safer.

The biosensor, attached to a wristband, measures heart rate, sweat levels, movement and temperature. To teach the device how to recognize when the child is about to become aggressive, SFARI Investigators Matthew Goodwin of Northeastern University in Boston and Matthew Siegel of Maine Medical Center Research Institute in Portland and colleagues collected sensor data from 20 children and teenagers with severe autism who had been admitted to an inpatient psychiatric unit. The researchers then used a machine learning algorithm to figure out which physiological signs indicated an impending outburst.

The sensor’s warnings predicted aggressive outbursts with 71 percent accuracy, provided the sensor had been recording data for at least three minutes before the warning. The accuracy level rose to 84 percent when the model was personalized for a specific child, the researchers reported in the August 2019 issue of *Autism Research*. As more data become available, the researchers say, the model should be able to predict outbursts earlier.

BEYOND THE CODING REGIONS OF THE GENOME

Over the past 15 years, gene sequencing studies have implicated more than 100 genes in autism. But the protein-coding portions of genes represent less than 2 percent of the human genome, and the remaining 98 percent — the ‘noncoding’ genome — may also play a significant role in autism. Teasing out this role is challenging, since the noncoding genome is enormous and nearly everyone has some mutations there. But two recent complementary studies, in the December 14, 2018, issue of *Science* and the May 27, 2019, issue of *Nature Genetics*, have pointed the way forward.

The *Science* paper was the result of work by SFARI Investigators Stephan Sanders of the University of California, San Francisco; Michael Talkowski of Harvard University; Bernie Devlin of the University of Pittsburgh; and Kathryn Roeder of Carnegie Mellon University, and their colleagues. The researchers examined whole-genome sequencing data from nearly 2,000 families in the Simons Simplex Collection, a database of genetic and phenotypic information from people with autism and their unaffected family members. Overall, the study found, children with autism have approximately the same number of spontaneous mutations as their siblings without autism do. But they have significantly more mutations than their siblings in ‘promoter’ regions of the



This wristwatch-style device uses a slew of biosensors to recognize when a child with autism is on the verge of an aggressive outburst.
Credit: © Empatica

SKIN-DEEP TREATMENT

Many people with autism are highly reactive to touch and other sensory stimuli. A mouse study in the August 8 issue of *Cell* suggests that an experimental drug called isoguvacine that dampens the activity of touch neurons beneath the skin can reduce touch hypersensitivity and also alleviate some behavioral traits associated with autism. The finding indicates that sensory reactivity may play a more central, causative role in autism than many researchers had believed.

The researchers, led by SFARI Investigator David Ginty of Harvard Medical School, injected six-week-old mice with a single dose of isoguvacine. They found that the drug moderated reactions to touch in six different mouse models of autism, each of which models a different genetic or environmental cause of autism. The team also gave daily doses of the drug for six weeks to newborn mice missing a copy of either *Shank3*, an autism risk gene, or *Mecp2*, a risk gene for the related neurodevelopmental disorder Rett syndrome. This treatment prevented the development of touch hypersensitivity, anxiety and some social impairments.

genome, which appear just before the start of a gene. Some of these promoter mutations, the team found, are associated with genes involved in developmental delay or neuronal differentiation.

In the *Nature Genetics* paper, Olga Troyanskaya and colleagues at the Simons Foundation’s Flatiron Institute; Robert Darnell of Rockefeller University and colleagues; and Alan Packer of the SFARI science team used a machine learning algorithm that pinpoints how individual noncoding mutations disrupt the way genes turn on and off throughout the body. The algorithm assigns a disease impact score to every nucleotide in the human genome. Among families in the Simons Simplex Collection, the team found, the noncoding mutations in children with autism had significantly higher disease impact scores than the mutations in their siblings without autism.

Combined, these two studies suggest that mutations in noncoding regions of the genome that control gene expression and protein translation significantly contribute to autism.

The team also created mice that lack *Shank3* everywhere except in the peripheral neural system. These mice react normally to touch and don't have anxiety or social difficulties. Their behavior suggests that establishing normal functioning in peripheral neurons may prevent certain autism traits if it is done early in development. The researchers concluded that drugs such as isoguvacine that affect peripheral neurons but cannot enter the brain may reduce autism symptoms, while avoiding the undesirable side effects of drugs that act via the brain.

A WINDOW ON INDIVIDUAL NEURONS

Until recently, researchers studying postmortem brain tissue could analyze alterations in gene expression only at the level of clumps of tissue, not single neurons. Now SFARI Investigator Arnold Kriegstein of the University of California, San Francisco and colleagues have harnessed a new technique to sequence RNA from individual cells in the brains of 15 people with autism and 16 controls. The analysis has identified several types of neurons as playing a crucial role in the condition.

In people with autism, the team reported in the May 17 issue of *Science*, neurons in layers two and three of the cerebral cortex had significantly more altered genes than neurons in the cerebral cortex's other four layers. The new work bolsters earlier studies implicating these two layers in autism. The researchers also saw altered gene expression in other cell types, especially microglia; the brain's immune cells; and astrocytes, star-shaped brain cells that perform numerous tasks, including helping neurons communicate with each other.

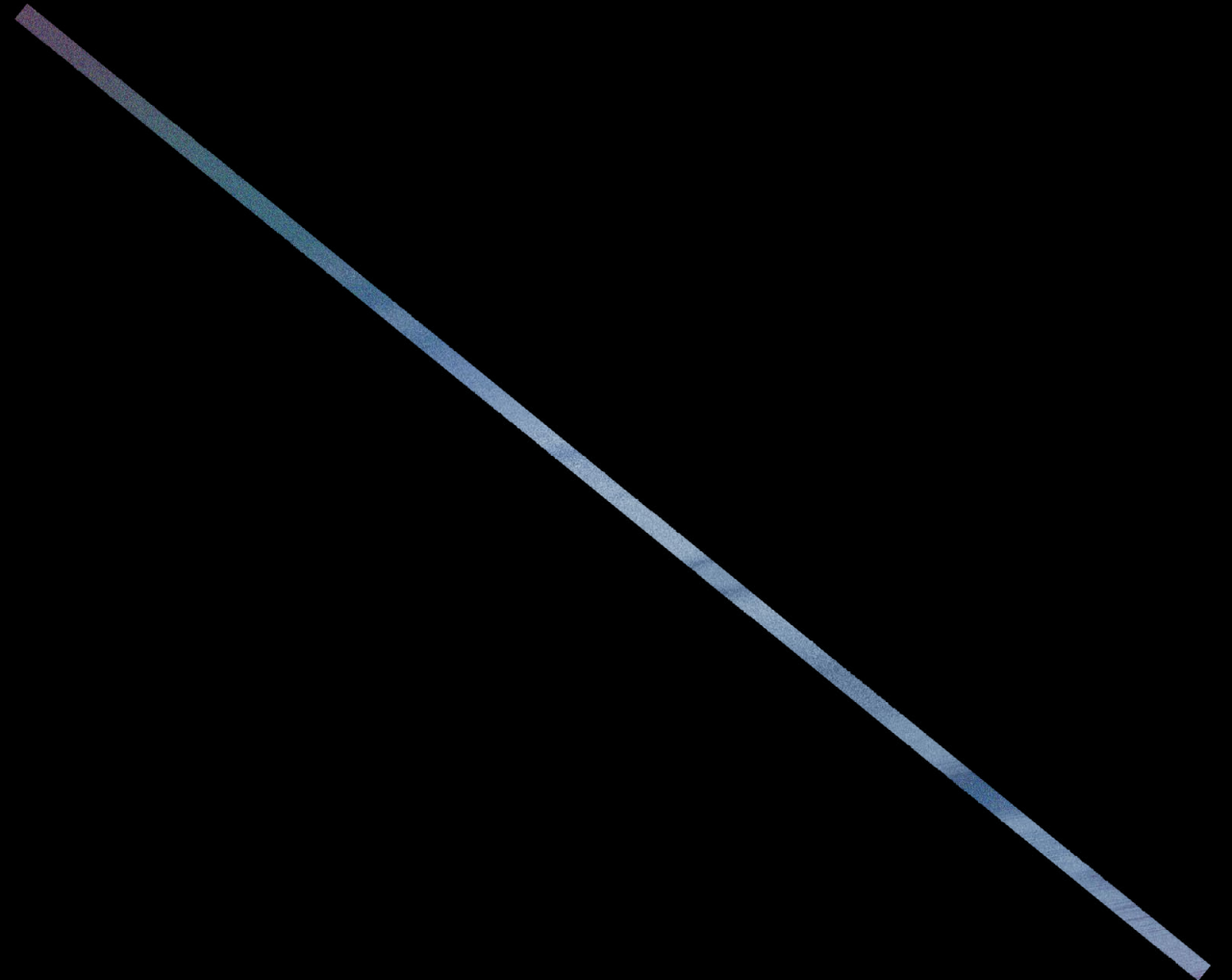
Many high-confidence autism risk genes showed up among those that were expressed differently in the neurons of people with autism. Also, differences in gene expression were most pronounced in people whose autism is relatively severe. The team plans to analyze additional brains and regions outside the cerebral cortex to gather further information about which types of neurons are most important in autism.

A PROTECTIVE IMBALANCE

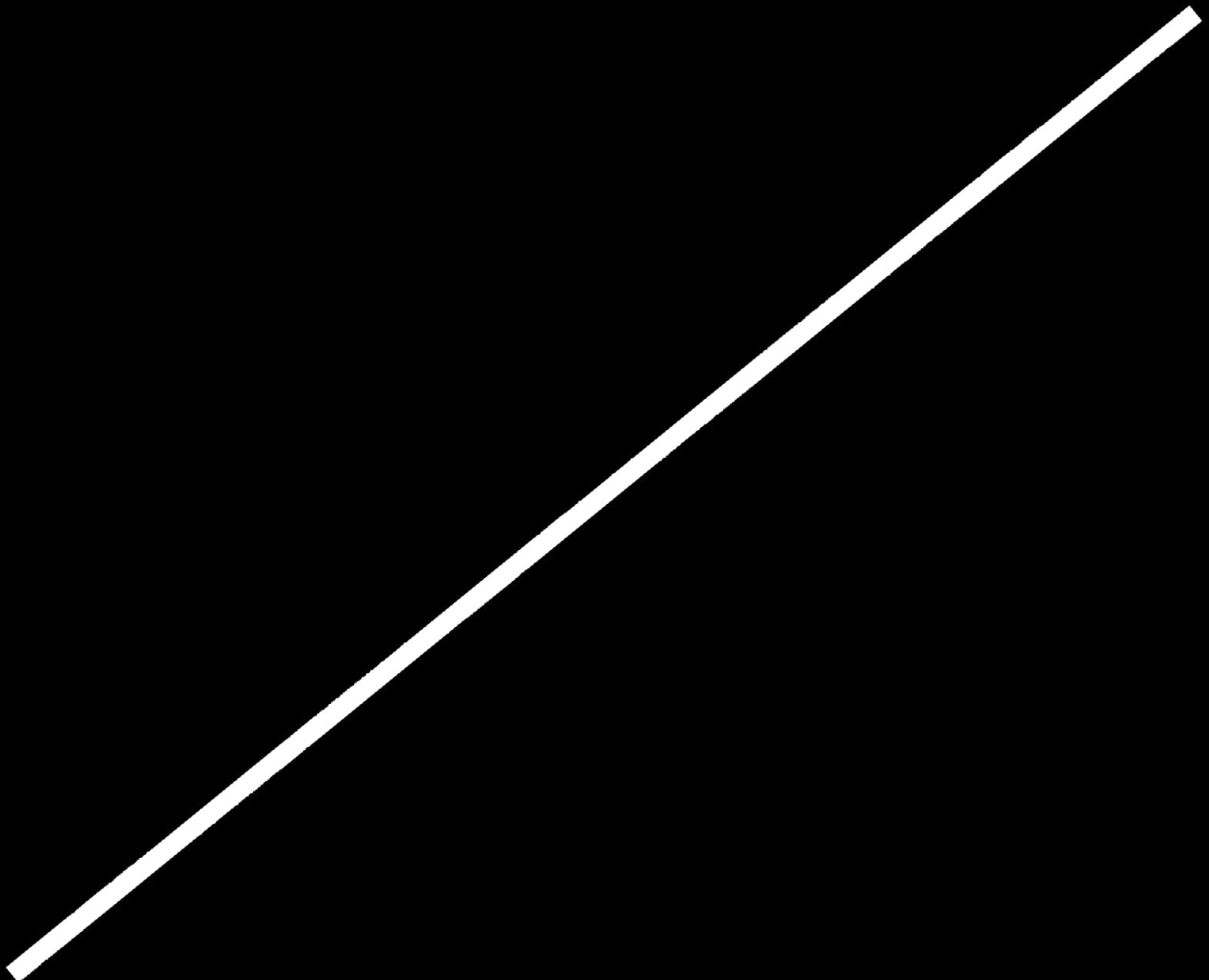
Many studies indicate that the brains of people with autism have too much excitatory activity relative to inhibitory activity. This imbalance, a popular theory proposes, causes neurons to spike too often, leading in turn to problems like sensory hypersensitivity. A new study, however, calls this theory into question, suggesting that the imbalance between excitation and inhibition in autism may in fact compensate for other differences rather than cause them.

The study, led by SFARI Investigator Daniel Feldman of the University of California, Berkeley, examined the somatosensory cortex of mouse models for four different autism-linked mutations. The researchers analyzed both in vitro brain slices and recordings of neuronal activity in live mice. In each of the four models, the researchers did find a higher ratio of excitation to inhibition than in control mice. But to their surprise, the researchers also found that the neurons receiving these signals fired at the same rates as those in the control mice.

This finding, the team wrote in the February 20 issue of *Neuron*, suggests that the skewed ratio of excitation to inhibition may serve as a protective mechanism, helping neurons to spike normally. Some scientists are testing drugs to normalize the signaling imbalance in people with autism, but the new study suggests that such drugs might do more harm than good.



OUTREACH AND EDUCATION



TEACHERS AT THE FRONTIERS OF RESEARCH

MATH FOR AMERICA

When science teacher Vielca Anglin applied for the Math for America (MfA) Master Teacher Fellowship in 2013 — the first year it was open to science teachers — she couldn't have expected that the program would send her three years later to the Amazon Conservatory of Tropical Studies in northeastern Peru. But thanks to an MfA grant, she spent 10 days immersed in environmental science research in the rainforest, measuring wind speed with anemometers to determine microclimates, learning about biomimicry and searching for pink dolphins with researchers.

“It was a really transformational experience for me,” Anglin says. “Even before I arrived, I was getting excited about bringing that experience back to my students. I knew I wouldn't be able to take the students to the Amazon, but my hope was that I could bring a lot of what I learned there back.”

After returning from South America, Anglin searched for relevant curricula and found EcoRise, a program that provides funds and lesson plans to teachers who wish to integrate sustainability into their lessons. Anglin got anemometers for her high school students to measure indoor air quality. After first learning about biomimicry and then using the natural systems they observed to design solutions for human problems, her students put their research into action and won a grant to build a hydroponic garden for the school cafeteria.

Hoping to inspire other master teachers to push the frontiers of environmental knowledge in their own schools, Anglin shared her experiences with nearly 100 other New York City-based MfA fellows through two all-day workshops and an evening workshop on grant writing at MfA.

“Vielca's story is a specific instance of how, when you bring great teachers together who are interested in current science, they figure out how that's going to trickle down to the classroom,” says Michael Driskill,

chief operating officer at MfA. “It can be a powerful, deep learning experience for the students, although this isn't necessarily the kind of learning that you're going to measure with a standardized test score.”

Learning cutting-edge math and science for their own sake, as many researchers do, fuels MfA master teachers. The fellowship program, which was founded in 2004 by Jim Simons, puts the spotlight on excellent, experienced teachers and supports them with stipends, ongoing professional development opportunities and grants.

“We found that investing in accomplished teachers — keeping them in the classroom longer and supporting them in their careers — makes the entire profession better; it's also the best way to attract outstanding people into teaching math and science,” says John Ewing, president of MfA.

New York City STEM teachers with at least four years of teaching experience who make it through MfA's rigorous vetting process receive a yearly stipend for the renewable four-year fellowship, along with access to hundreds of teacher-led workshops and courses on cutting-edge content, pedagogy, educational equity and career development. The average MfA master teacher attends 7 to 15 courses per year, most of which consist of several two-hour evening workshops led by two teachers.

The courses vary based on teachers' own interests. For example, Gary Rubinstein, a 29-year veteran teacher who joined MfA's first master teacher cohort of six math teachers in 2006, spent a year

and a half researching how to apply group theory to permutation puzzles. Afterward, he led a three-week MfA mini-course on the topic, teaching 32 fellow master teachers what he had learned and including puzzle challenges and exercise ideas for their classrooms.

“I hope that the people go and teach this stuff to their students so I get the exponential effects: If I teach it to 30 people, and if even 10 of those people teach it to 30 students, suddenly 300 people are benefiting from this,” says Rubinstein, who sees his course as the culmination of 29 years of teaching — and four decades of solving — Rubik's Cubes.

Rubinstein also recorded 10 30-minute lectures on the content, available on his YouTube channel, and created a free iPhone app of permutation puzzles.

“If I weren't a part of Math for America, I might have still learned this stuff for myself, but I don't know that I would have collected it in such a shareable way,” says Rubinstein, who noted that he'd put in “extreme levels of effort” to create the six-hour mini-course.

That effort pays off in the innovative ways master teachers such as Rubinstein and Anglin engage the next generation of scientists. Anglin recalls that when she taught middle school, her students were always excited about science, but “something along the way happens,” and by the time the students at her transfer high school reach her, they've lost interest in STEM.

“For me, that's the motivating factor with teaching students in the demographic that I teach now,” Anglin says. “I tell them all the time, ‘You're scientists because you're using your five senses; human beings are naturally scientists.’ I teach science because I want to get students connected to the fact that they can see themselves in STEM roles.”

Mentoring the next generation of researchers undergirds one of the basic principles behind MfA: that these dedicated master teachers are mathematicians and scientists in their own right.

“Most people don't think of teachers as people who are immersed in their own fields,” Ewing says. “Our master teachers are passionate about their subject; they always want to learn more themselves; they are deeply engaged. That's what makes them great teachers.”

Anglin agrees and teaches her students every day that they are scientists, as she leads them in collecting data for citizen science platforms, writing grants and asking questions about how to mitigate their community's climate impact.

“I don't have a Ph.D., but I truly believe that I'm a scientist as well,” Anglin says. “As a human being, you're making sense of everything around you by asking questions and using your past experiences to predict outcomes. You say, ‘That may be the answer, but I'm going to investigate to find out if that's the truth.’ The fact that we're always asking questions is part of what makes us scientists.”

A trip to the Amazon inspired Math for America master teacher Vielca Anglin to integrate sustainability into her lesson plans and share her experiences with her fellow master teachers.



SHARING SCIENCE

OUTREACH AND EDUCATION

In the Simons Foundation's early days, Jim Simons and fellow members of the foundation's scientific leadership realized they missed something they had enjoyed during their time in academia: a colloquium series that would give them regular opportunities to hear from top scientists on a wide range of scientific topics. Out of this realization was born the foundation's first lecture series, the Simons Science Series, held monthly from 2010 to 2015.

From this beginning, the foundation has gradually expanded its lecture offerings to reach broader and broader swaths of the science-loving public, from scientists who want to hear high-level talks to nonscientists who simply wish to engage with deep ideas.

The Simons Science Series was invitation-only, but the completion of the 174-seat Gerald D. Fischbach Auditorium in late 2012 prompted the foundation to revise the series and make it open to the public. The first Simons Foundation Lecture was held in March of 2013, and since then the series has met almost every Wednesday during the academic year, for a total of more than 150 lectures on topics in mathematics, the physical sciences, computational science, genetics, autism research and other disciplines. "The lectures are meant to encourage cross-pollination," says Kate Augenblick, assistant to the chairman and an administrator of the program. "They expose people to ideas outside their areas of expertise."

Many attendees are active scientists, but the talks also attract retired scientists, people in finance or technology from the neighboring "Silicon Alley," and the occasional high school or college student. Many of the lectures are broadly accessible; some are more technical. In the latter cases, Augenblick says, "I always get a little worried: How many people will understand this talk? But interestingly enough, a lot of these really specialized people have big followings."

Astrophysicist and Flatiron Institute research fellow Sarah Pearson shares her expertise during a Q&A session following a screening of the documentary "Behind the Curve," which chronicles the flat Earth movement. The event, part of the Simons Foundation Presents series, attracted a diverse crowd of both scientists and nonscientists.

Mathematician Terence Tao presents the Erdős discrepancy problem to a packed house during his October 2017 Simons Foundation Lecture.

Simons Foundation Lectures typically attract 120 to 140 attendees. Even when there are "only" 60 or 70 attendees, the lectures often spark very animated discussions and connections, which are fruitful for the audience and for the lecturers. For instance, when Sonya Dyhrman, a marine microbial oceanographer at Columbia University, gave a lecture in early 2015 as a fairly new arrival in New York City, her talk had comparatively few attendees. But among them were scientists with whom she made deeply worthwhile connections. "Being part of the lecture series helped me to integrate into the local microbiology and genomics community," she says. "I was really thankful to have the opportunity to participate."

While many Simons Foundation Lectures target scientists interested in technical talks, a pilot initiative called Simons Foundation Presents is aimed at a much larger audience. "We want to bring joy and excitement about science to everyone, even people who don't know they like science," says Mariah Roda, civic affairs manager at the foundation.

That series kicked off in May 2018 with a screening of the documentary "Inventing Tomorrow," about teenage scientists around the world who are coming up with cutting-edge solutions to environmental threats. Since then, the series has hosted a variety of events, including another movie night and a lecture by British author Isabella Tree about the rewilding of her farm. "She had a story to tell that was very personal but had a lot of ecological science and chemistry and biology," Roda says. "One of our goals is to bring people tangentially into science; this lecture didn't sound so sciencey, but it was full of science."



Jim and Marilyn Simons speak during TED@NAS, a special collaboration between TED, the Simons Foundation, the Kavli Foundation and the National Academy of Sciences. Credit: Ryan Lash/TED

Recently, the series hosted Peter Winkler — a mathematician at Dartmouth College and the Distinguished Chair for the Public Dissemination of Mathematics at the National Museum of Mathematics in New York City — to talk about a bewildering mathematics puzzle called the Sleeping Beauty problem. “I was really impressed at the size of the crowd and the sophistication of the questions,” says Marilyn Simons, the foundation’s president.

Many Simons public lectures take advantage of the foundation’s rich internal ecosystem. For instance, the Simons Foundation Lectures often feature speakers from one of the Simons Collaborations, each of which holds an annual meeting at the foundation. “Inventing Tomorrow,” meanwhile, was supported by one of the foundation’s outreach initiatives, Science Sandbox. And in November 2018, Simons Foundation Presents held a panel discussion and book signing for two anthologies published by *Quanta Magazine*, the foundation’s editorially independent online popular science publication. The discussion was attended by an overflow crowd, including a *Quanta* fan who drove up from Washington, D.C., just to be there.

“That night we got to talk with students, teachers, artists, filmmakers, writers, philosophers, business-people, engineers, and both amateur and professional mathematicians and scientists,” says Thomas Lin, *Quanta*’s editor-in-chief.

On November 1, 2019, another foundation initiative called TED@NAS, more than two years in the making, came to fruition. This collaboration between the foundation, the National Academy of Sciences, the Kavli Foundation and TED welcomed more than 500 attendees to the academy for a day of scientific talks about topics such as light pollution, micro-robotics and the inner ear’s hair cells, all discussed with the emphasis on big ideas and storytelling that is the hallmark of TED talks.

“There was an almost palpable energy in the room,” Roda says. “There was everything from laughter to wild applause to people holding their breaths for a moment.”

The presenters, gifted scientists and science communicators, had spent months prior to the event working with TED staff to develop their overarching messages and learn how to convey them effectively. “It was an incredible journey of exploration,” says Enrico Ramirez-Ruiz, an astrophysicist (and “certified stellar mortician”) at the University of California, Santa Cruz. He spoke about the stellar materials that underlie life on Earth, binding together cosmic and human history.

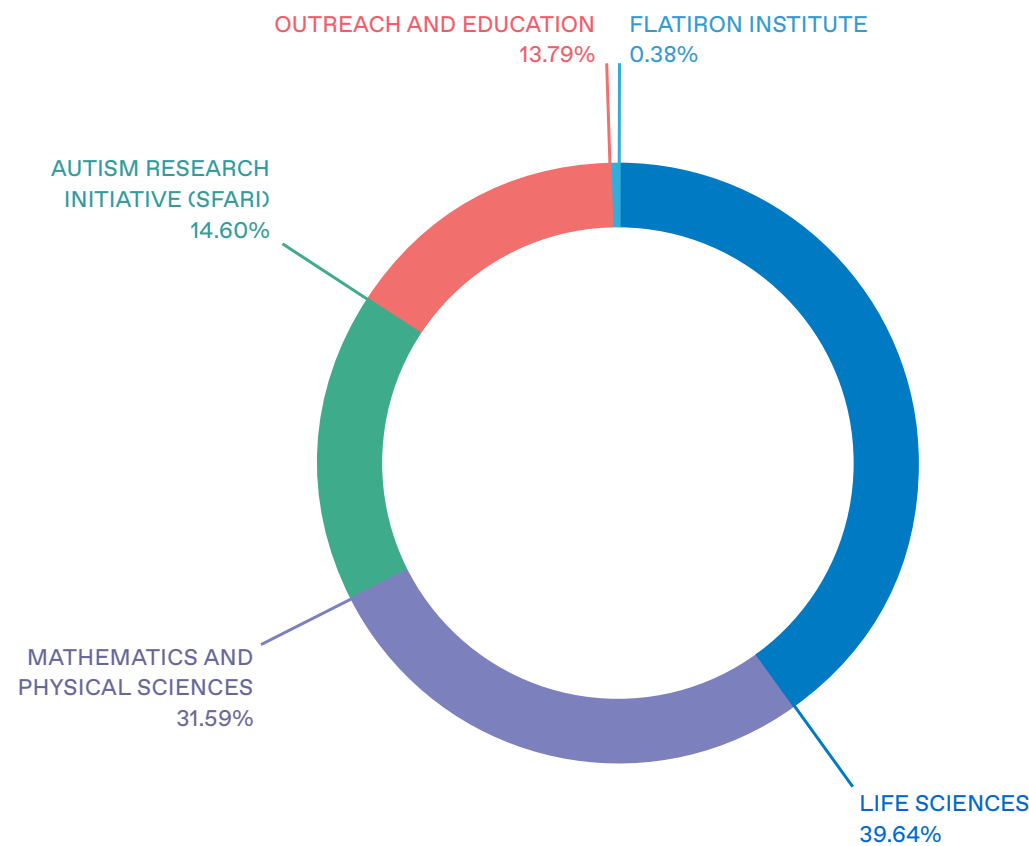
Amanda Schochet spoke about “habitat fragments,” small patches of native plants that can form a network of resources to help an ecosystem adapt to environmental change. She described how this concept gave her the idea of creating “social habitat fragments” to help people cultivate stronger communities — for instance, the tiny science museums that her organization, MICRO, makes. During the break after her talk, she was approached by artists, writers, philanthropists and even a paramedic who all spoke about how this idea resonated with their own activities. “Conversations like that are really exciting to me, because my goal in creating the talk was to share ideas that I thought would be useful to a lot of people in their own work to make the world a better place,” Schochet says.

The speakers, who spent several days in Washington, D.C., rehearsing together, bonded tightly and are still in touch, Schochet says. “I hope that the community that has come out of this will be part of my life for years to come.”

Looking to the future, the foundation plans to continue exploring how its public lectures can enrich the landscape of science events in New York City and beyond. “Talking about science is not one-size-fits-all,” Marilyn Simons says. “There are audiences for challenging material and audiences for fun entertainment. We’re trying to reach all audiences in one way or another and just share the wonderful research going on today in science.”

FINANCIALS

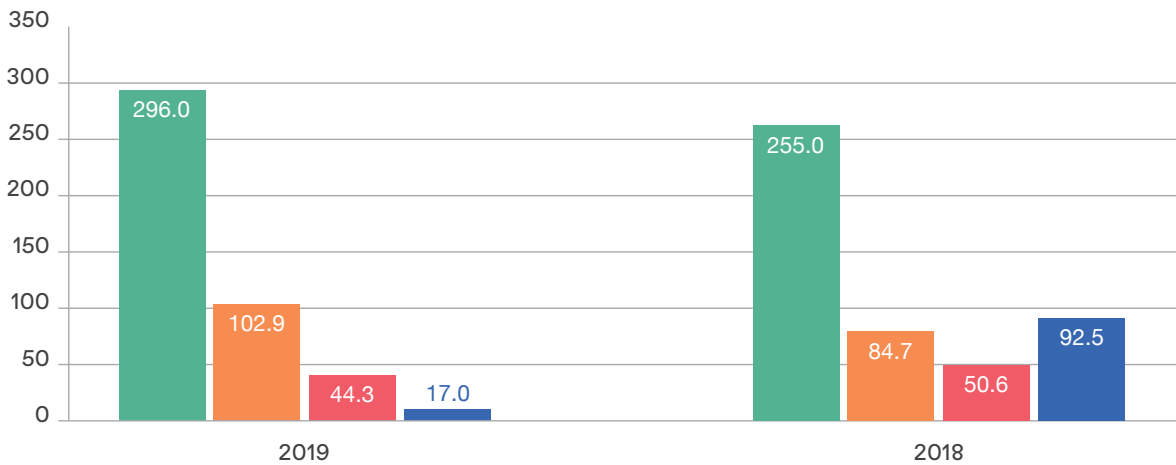
2019 GRANT PAYMENTS BY CATEGORY



PROPORTIONS OF EXPENSES

(CASH BASIS, \$'S IN MILLIONS)

- Grants Paid
- Program
- General and Administrative
- Capital Expenditures



BALANCE SHEET

(UNAUDITED, IN \$)

ASSETS	As of 12/31/19	As of 12/31/18
Cash and Cash Equivalents	151,891,664	174,076,804
Investments	3,407,867,957	3,049,361,841
Property and Equipment, Net	417,989,136	428,870,518
Prepaid Expenses and Other	22,279,414	11,308,487
Total Assets	4,000,028,171	3,663,617,650
LIABILITIES		
Accounts Payable	27,318,378	16,527,873
Grants Payable	541,387,541	520,106,239
Mortgage and Lease Liabilities	265,080,200	263,556,310
Deferred Excise Tax Liability	12,048,974	12,048,974
Total	845,835,093	812,239,396
NET ASSETS		
Beginning Net Assets	2,851,378,254	2,582,123,222
Current Year Change in Net Assets	302,814,824	269,255,032
Total	3,154,193,078	2,851,378,254
Total Liabilities and Net Assets	4,000,028,171	3,663,617,650

INCOME STATEMENT

(UNAUDITED, IN \$)

REVENUE	For the Year Ended 12/31/19	For the Year Ended 12/31/18
Contributions	120,000,000	222,000,000
Investment Income	666,338,856	412,238,682
Total	786,338,856	634,238,682
EXPENSES		
Grants Paid	295,979,745	255,035,314
Change in Grants Payable	16,995,001	(27,454,608)
Program	111,548,113	91,661,508
General and Administrative	28,917,150	24,576,073
Depreciation and Amortization	23,878,283	15,737,666
Taxes	6,205,740	5,427,697
Total	483,524,032	364,983,650
Change in Net Assets	302,814,824	269,255,032

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