SIMONS FOUNDATION

Annual Report

2018 Edition

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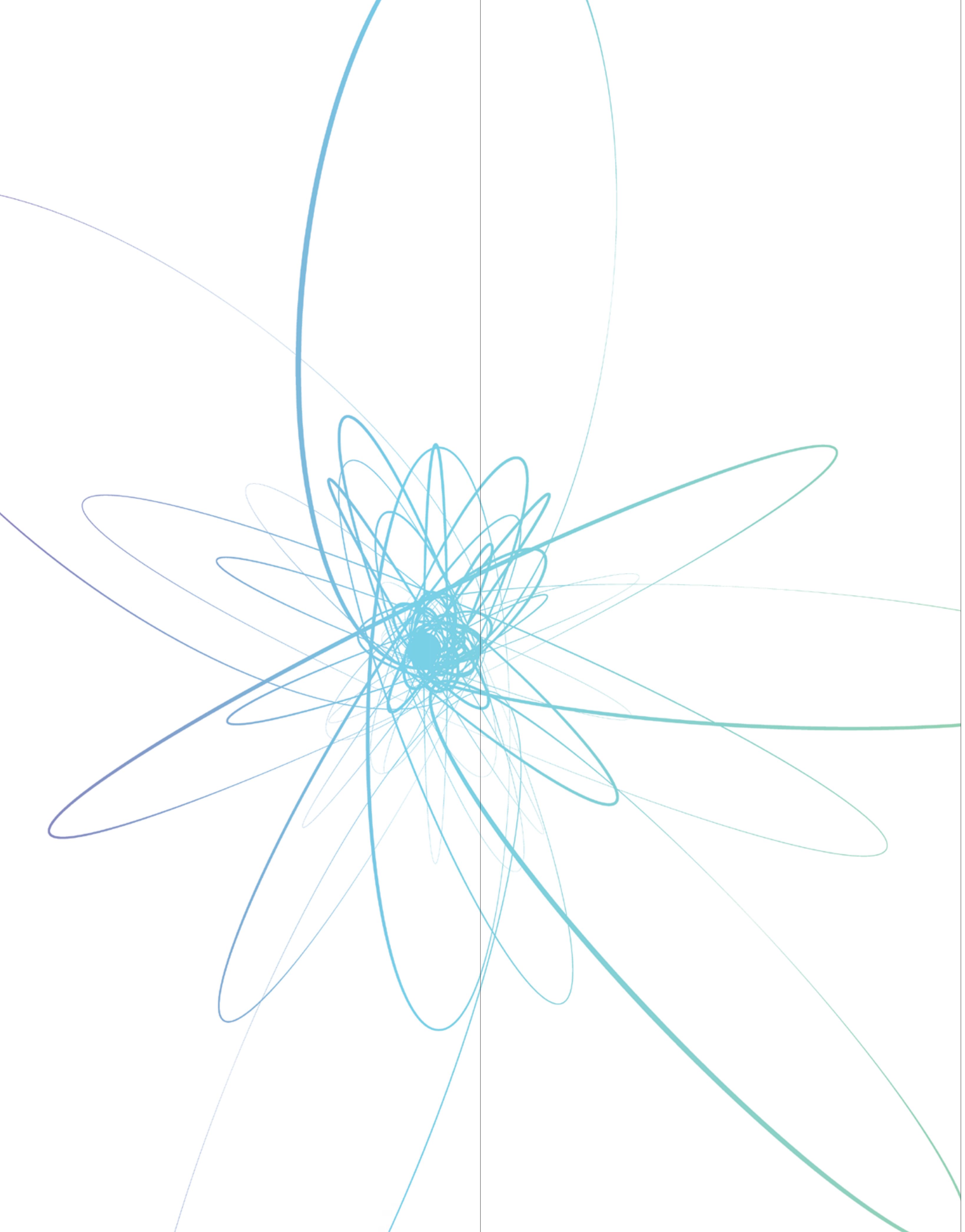


LETTER FROM THE PRESIDENT

As one year ends and a new one begins, it is always a great pleasure to look back over the preceding 12 months and reflect on all the fascinating and innovative ideas conceived, supported, researched and deliberated at the Simons Foundation. Around here, 12 months of seemingly routine work — answering emails, administering programs and attending lectures, workshops and meetings — somehow ends up yielding an amazing amount of intellectual ferment and, ultimately, progress in basic science. From workaday activities and interactions, stunning new concepts and theories emerge — from our grantees and also from staff, taking us in exciting new directions.

In this 2018 annual report, we offer just a few of those thought-provoking ideas being discussed in the hubbub of daily activity at the Simons Foundation. In writing this overview of our work, we use 'emergence' as a central narrative thread and graphic theme. In addition to its popular meanings, the term is used by scientists to refer to individual parts coming together to form a whole, at a new level of complexity. In other words, emergence occurs when the individual's properties differ from the group's properties; e.g., freezing water molecules jumping to alignment to form an ice crystal, ants in a colony together accomplishing work they could never do alone, and interdependent organisms in an ecosystem enabling the whole group's survival. Even electrons in a superconductor join up, forming 'Cooper pairs,' which, in this conjoined state, flow with zero resistance.

At our in-house research division, the Flatiron Institute, astrophysicists are trying to model the emergence of the earliest galaxies in our universe, the biophysical modeling group is trying to understand "how we go from motors and microtubules to collective self-organization," and the neuroscience group is formulating the collective organization of individual neurons into a neural system capable of learning like the human brain. And, satisfyingly, when the smoke clears, mathematics again emerges as the baseline tool for all this groundbreaking science.

In the pages that follow, you will also read about the foundation's grant-making in Mathematics and Physical Sciences, Life Sciences, autism science (SFARI), Outreach and Education, and our Simons Collaborations. Grant recipients work to understand the origins of our universe, explain properties of glass as a system with disorder, model a theory of thought, and comprehend the role of microbes in our Earth's climate and nutrient structure. You can also read about our emerging documentary film efforts, sharing the wonders of science through "The Most Unknown."

Finally, if you're interested in learning more about emergence, *Quanta Magazine*, our editorially independent online science magazine, has explored this phenomenon in articles about quantum gravity, condensed matter physics, consciousness and more.

With more than 330 employees now, the Simons Foundation is a lively center of bright, curious and passionate people working to advance the frontiers of research in mathematics and the basic sciences. It's a pleasure to come to work every day, wondering what new things will be endeavored and learned. If you're in the neighborhood on a Wednesday, please come by for one of our Simons Foundation Lectures. In the meantime, I hope you enjoy reading about our work and that of our grantees in this report, or at simonsfoundation.org.

Marilyn Hawrys Simons, Ph.D. | President

LETTER FROM THE CHAIR

To a large extent, the important developments in 2018 stemmed from the 2012 retreat at the Buttermilk Falls Inn in Milton, New York. In this two-day session, comprising outstanding scientists in a diversity of fields, we decided to add the concept of 'collaborations' to our grant-making activities for individuals and institutions. These would be long-term, goal-driven research projects comprising a substantial number of scientists and postdoctoral researchers from around the country and, indeed, the world. Mathematician Ingrid Daubechies also suggested we establish an institute for computational science. We liked that idea too and decided to build such an institute in-house.

In the subsequent six years, the Simons Foundation has changed dramatically as a result of that meeting. A total of 14 collaborations have been established, and in-house computational science research has grown into the Flatiron Institute, now with more than 150 people and slated to grow to almost twice that. These two areas will constitute at least 40 percent of the foundation's budget and have created a remarkably dynamic atmosphere throughout the organization.

Of the 14 collaborations, let me discuss two.

Origins of Life, established soon after the Buttermilk Falls meeting, is now in its sixth year and going strong. Researchers include chemists, biologists, geologists and astronomers, the last group studying exoplanets to see if any might be conducive to life. A team led by John Sutherland of the MRC Laboratory of Molecular Biology in Cambridge, England, has traced a plausible path from hydrogen cyanide, a chemical common in the early Earth, to the precursor of RNA. Of course, there may be other such paths, and they are being sought, but John's work is very encouraging. Others are studying early geology to discover substrates that may have harbored early life or at least been conducive to it. The problem is being attacked from many angles, and our hopes are high that great progress will be made in the out years of the collaboration.

Hidden Symmetries and Fusion Energy, established in 2018, is an effort to design a functioning stellarator, a device to produce fusion energy, in a manner that the energy output is greater than the energy input. The stellarator was created many years ago but could not be made to work. It was discarded in favor of the tokamak, a device on which much work has been done over many years and which also doesn't work! The Hidden Symmetries group, consisting of a number of outstanding physicists and mathematicians, now believes that an intensive mathematical effort will result in a design that will make an efficient and net energy-producing stellarator. If they succeed, the outcome will be transformative.

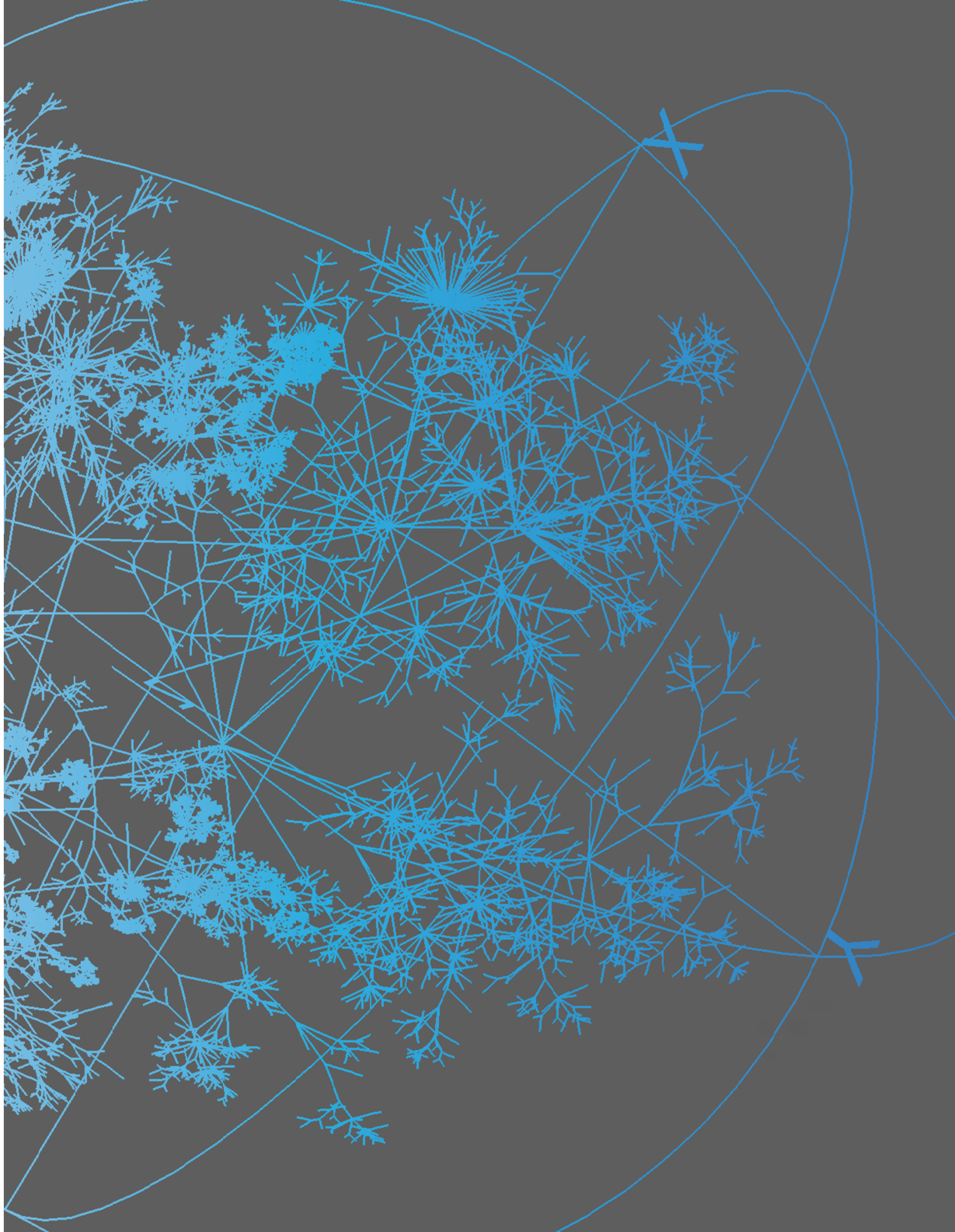
The Flatiron Institute underwent a great deal of change during 2018.

First of all, the building was finally completed. The second-floor auditorium, the 11th-floor dining hall and the rooftop board room and garden have all worked wonderfully. The dining hall especially has been a great addition, where not only do all foundation personnel have lunch, but Flatiron folks also find a nice place to chat (and even work!) during the rest of the day.

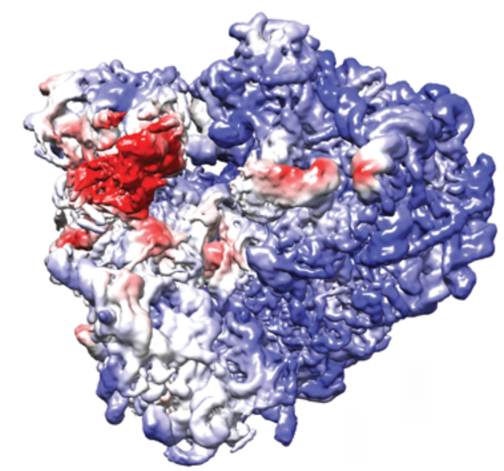
Flatiron was designed for four units, but at the beginning of the year only three were in place: Computational Biology (CCB), Computational Astrophysics (CCA) and Computational Quantum Physics (CCQ). After considerable discussion, we decided that the fourth unit would be Computational Mathematics (CCM). This will consist of such areas as statistics, machine learning, computer science, algorithm development and numerical analysis. Because all these areas can be useful to the other three units, we felt the new unit would act a bit like glue, tying the organization together, with its scientists doing their own work and also interacting with those in the other three units. Leslie Greengard, who headed the CCB, will head the new unit, bringing the CCB algorithm group with him. This required a search for a new director of the CCB, which was finally completed in early 2019 with the choice of Mike Shelley, group leader of biophysics in the CCB. The staff of the CCB was very pleased with this choice, as was Mike himself!

We are proud to report that research emanating from Flatiron has been both copious and excellent, and the institute has acquired a great reputation in the United States and around the world. As time goes on and the units are fully populated, we are confident that its output and reputation will continue to blossom.

Jim Simons, Ph.D. | Chair



DEVELOPING THE COMMON LANGUAGE OF COMPUTATIONAL SCIENCE



The 3-D structure of an 80S ribosome molecule from *Plasmodium falciparum*, a protozoan parasite responsible for around 50 percent of all malaria cases in humans. Researchers reconstructed the shape from electron microscopy measurements. Structures that vary little from molecule to molecule are shown in blue, whereas regions that vary a lot are shown in red and may need additional measurements and analysis to produce an accurate reconstruction. *Image courtesy of Joakim Andén; data from W. Wong* et al./ eLife *2014*

CENTER FOR COMPUTATIONAL MATHEMATICS

The universe has an inherent elegance illuminated by mathematics. A single class of equations can help describe how planets spin around a star, how blood cells flow through a vein, and how electrons travel along a wire.

In October 2018, the Flatiron Institute established its fourth research center to further the computational tools that play a crucial role in modern science and engineering and strengthen their mathematical foundations. The Center for Computational Mathematics (CCM) collaborates with the institute's centers for astrophysics, biology and quantum physics and conducts its own research on problems faced by the scientific community at large.

"Like the other centers, CCM will be a place that builds software tools for the greater academic community," says CCM director Leslie Greengard, who previously directed the Center for Computational Biology (CCB). "The difference is that the other centers typically have a particular application in mind, but the nice thing about mathematics is that often the solutions you develop apply to multiple fields."

The CCM embodies one of the Flatiron Institute's core tenets, "that math is the common language of science," says CCM project leader Christian Müller. That idea has formed a cornerstone of the Flatiron Institute since its inception as the Simons Center for Data Analysis in 2013.

"Since the beginning, there was a desire for people in different centers to interact and work together," says CCM research scientist Eftychios Pnevmatikakis. "But often we were getting lost in the details of the applications. The astronomers couldn't talk biology, and vice versa. With CCM, I see the interactions happen much more organically. We all talk math. CCM looks like it will be a bridge for the different centers and also have a life of its own."

At full capacity, the CCM will house about 50 scientists, mathematicians and programmers. Many of the initial staff transferred from groups at the CCB, taking with them mathematical and computational problems rooted in biology. As the CCM continues to grow, so too will the breadth of the inspirations and applications of the center's work.

"At Flatiron, CCM is surrounded by a problem-rich environment and a diverse set of experts we can collaborate with," says CCM group leader Alex Barnett. "Opportunities like this center only come along once in a lifetime."

"With CCM, I see the interactions happen much more organically. We all talk math. CCM looks like it will be a bridge for the different centers and also have a life of its own."

One of the CCM's areas of interest is leveraging machine-learning techniques. Machine-learning models 'learn' by ingesting large amounts of example training data. After training, the models can produce results not possible through conventional methods.

The problem, though, is that machine-learning algorithms such as neural networks "are black boxes," says Stéphane Mallat, CCM distinguished research scientist and a professor at Collège de France and École Normale Supérieure in Paris. "It works well, but we don't know what's being learned. It doesn't help us understand the phenomena."

The tech companies driving machine-learning development, including Google and Facebook, focus on applications such as image recognition, natural language and marketing. "Right now, machine learning is very much an empirical field," Mallat says. "There are many algorithms which are working well, but we don't understand what type of structures they learn and the mathematics behind them. This means that we cannot interpret results or guarantee their robustness."

At the CCM, researchers will reverse engineer solutions from machine-learning applications to figure out what led to the result. Using that information, the researchers hope to learn more about real-world systems and improve conventional methods. The CCM hosts regular meetups in which researchers from all four centers discuss the latest developments in the field and talk about their machine-learning projects.

"There's a need for new mathematics in this area," Mallat says.

Another research focus for the CCM also involves working backward, so to speak, but using experimental results. Scientists often calculate cause and effect: for example, how light from a lamp will bounce around a room. A trickier question is the reverse, known as an inverse problem. Given the lighting in a room, what can you learn about the light source? Inverse problems crop up in astronomy and neuroscience as well as in medical-imaging applications such as CT and MRI scans.

CCM research scientist Joakim Andén focuses on an inverse problem related to discerning the 3-D layout of a molecule. The experiment involves chilling molecules to extremely low temperatures and bombarding them with electrons. The electrons graze off the molecules, losing some speed. Based on how much each electron slowed down, scientists deduce the molecule's shape. A challenge is that molecules break down when hit by too many electrons, meaning scientists can only get a relatively small number of data points from each experiment.

"It just looks like pure static," Andén says. "If I showed you one of these images, you wouldn't believe that there was anything in there." He and his colleagues at the CCM are working to make sense of the static faster and more accurately.

The CCM also focuses on speeding up basic computational tasks used across many applications. One such task involves solving partial differential equations, which appear in a variety of areas, ranging from acoustics to astrophysics to fluid dynamics. Those equations, dubbed PDEs, arise whenever a quantity depends on more than one independent variable — such as the three spatial coordinates and time — and the rates of change in these variables are coupled in a known way.

Solving PDEs accurately is often incredibly slow, says CCM research scientist Manas Rachh. Much work has focused on removing this computational speed bump. In 1986, Greengard and Vladimir Rokhlin co-invented the fast multipole method — a technique that accelerates the calculation of long-range forces in problems with many components that influence one another. This method has played a pivotal role in the development of fast, robust and accurate PDE solvers. At the CCM, Rachh and others continue to hunt for shortcuts for solving PDEs.

With fast enough solutions, engineers could potentially design, test and optimize devices such as microfluidic controllers and computer chips without the need for the costly hassle of producing and testing prototypes. "That's what we're working towards," Rachh says. "We want tools robust and accurate enough for engineering applications."

The CCM has many other research focuses, each with potential benefits to many research areas. Barnett expects the center to continue taking on new ideas as it expands.

"We shouldn't be scared of leaping into problems that are new to us," Barnett says. "Academia doesn't often reward that risk-taking, or the software development that needs to go along with it, and instead encourages you to do an incremental version of what you did before. Here, we are lucky enough to be able to take such risks, and that can lead to larger breakthroughs."

KAVLI SUMMER PROGRAM IN ASTROPHYSICS

CENTER FOR COMPUTATIONAL ASTROPHYSICS

International collaboration, swirling galaxies and an exploding steam pipe all defined summer 2018 for attendees of the Kavli Summer Program in Astrophysics, hosted at the Flatiron Institute's Center for Computational Astrophysics (CCA).

Over six weeks, 17 graduate students participated in this annual learning and research opportunity that connects students with senior-scientist mentors. The students listened to lectures from experts in the field and worked on research projects that yielded significant discoveries. Participants formed strong bonds, with a diverse group of graduate students, postdoctoral researchers and established faculty members coming together in the spirit of collaboration and scientific discovery.

"Afterwards, we had so much positive feedback from both students and mentors about how invigorating it was and how much they learned," says Greg Bryan. He and Rachel Somerville co-directed the Kavli program and co-lead the CCA's galaxy-formation group. "It was a chance for some of the best students, postdocs and faculty to come together and forge ties, learn about the field as a whole and make real contributions," he says.

The program launched in 2010, with the Kavli Foundation serving as its principal sponsor since 2016. The event's founding director, Pascale Garaud, is professor of applied mathematics at the University of California, Santa Cruz. She modeled the program on one she attended as a graduate student at the Woods Hole Oceanographic Institution in Massachusetts. "That program changed my career, and it changed me on a personal level," Garaud says. "I decided I wanted to do something similar for students in astrophysical sciences."

Hosting duties for the summer program alternate between the University of California, Santa Cruz and other institutions around the world. CCA director David Spergel embraced the idea of bringing the event to the Flatiron Institute, as both the program and the institute emphasize the importance of collaboration.

The 2018 program focused on how galaxies form and evolve, though not all the participants have backgrounds in galaxy formation. "Many of the graduate students come from institutions where this subfield is not well-represented, so they might not have had much opportunity to study or do research on this topic," Somerville says.

“They were the exact feelings I hoped people would get out of the program — that feeling of finding a family.”

Alexander Kaurov *(left)*, a postdoc at the Institute for Advanced Study in Princeton, New Jersey, chats with graduate student Daisy Leung *(right)* during the Kavli Summer Program in Astrophysics.

After a week of lectures on galaxy formation, students partnered with mentors and began working on research projects, the goal being for students to report their results in a peer-reviewed journal.

“It’s one thing to read some papers and do some analysis yourself; it’s another thing for someone to teach you firsthand,” says graduate student Corey Brummel-Smith of the Georgia Institute of Technology in Atlanta.

Graduate student Daisy Leung modeled the emergence of the earliest galaxies in the universe. As a trained observational astronomer, she appreciated the opportunity to work with theorists and further hone her computational skills. “The field can only make progress if observers are talking to theorists,” says Leung, who studied at Cornell University and is continuing her thesis work at the CCA. Her work simulated the small- and large-scale physics that govern how clouds of molecules collapse and evolve to form galaxies. The results provide predictions that future surveys, such as those using the James Webb Space Telescope, can test.

For his project, Yale University graduate student Darryl Seligman explored interactions between gas and dust in space. An outstanding question for astrophysicists is how dust specks coalesce to form an Earth-sized rocky planet. Clusters bigger than a poppy seed shatter when they crash into each other, rather than sticking together. Seligman numerically simulated the long-term evolution of these interactions. Dust faces a headwind as it passes through gas. The dust particles then behave like cyclists in a race, huddling together to minimize drag and creating clusters. Seligman’s simulations showed that the presence of a magnetic field causes the dust to bundle together into sheet-like clumps that might gently combine to form the building blocks of a planet. The results offer insights into the behavior of the dust and gas that surrounds a black hole or that inhabits the void between a galaxy’s stars.

Other projects included how behemoth black holes squelch star formation in galaxies and comparing models of galaxy assembly with real observations. Even though each student had his or her own project, everyone rallied to help one another. “There was no sense of competition except for against the clock,” Bryan says.

“The event was a far more fruitful experience than having 17 projects at 17 different institutions.”

That teamwork was tested on the Thursday before the final week of the program. In the early morning, a steam pipe exploded outside the Flatiron Institute, leaving the building inaccessible for more than a week. Students who had left their laptops inside overnight found themselves computerless and panicking about not being able to complete their projects.

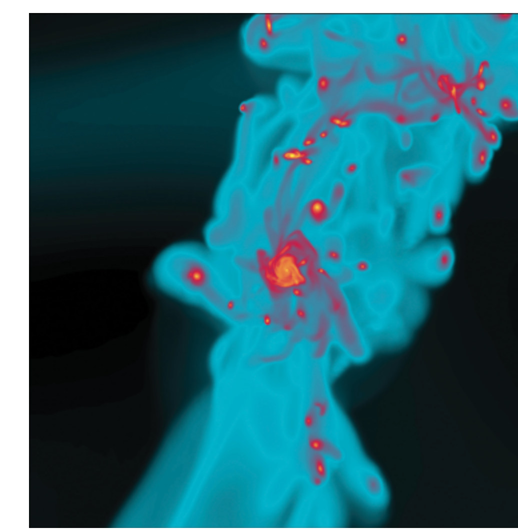
Eventually, the program relocated to New York University’s physics department, which graciously offered space for everyone to work. The Flatiron Institute’s Scientific Computing Core procured loaner laptops so that students could finish their research in time. “It looked like Christmas Day,” as everyone unboxed their computers, Leung recalls.

The experience, although trying, brought the group together, Seligman says. “It felt like an academic family.”

On the program’s final day, after the students presented their results, Leung gave one final presentation on behalf of all the students. She outlined how the summer program and the CCA had inspirited her and others to go forth in science and how much the collaborative and diverse environment meant to them.

“They were the exact feelings I hoped people would get out of the program — that feeling of finding a family,” Garaud says. “It’s going to be hard for any other host institution to top what CCA did.”

The event was such a success that the CCA will host its own, separate summer program for graduate students in 2019, with a focus on black holes, neutron stars and other compact objects. “This is an opportunity to bring people together and encourage the next generation of scientists,” Somerville says.



A density map of the gas in and around Althaea, an early-universe galaxy simulated by Daisy Leung and colleagues. The gas has dense knots and clumps, shown in orange and red. These structures are the birthplaces of young stars and affect the subsequent evolution of galaxies to the present day. *Image courtesy of Daisy Leung*

TOWARD A GRAND UNIFIED THEORY OF SPINDLES

CENTER FOR COMPUTATIONAL BIOLOGY

Biologists in the 20th century broke down the cell into parts, and now 21st-century researchers are figuring out how to put those components back together.

Take the spindle, which lines up chromosomes during cell division before pulling them apart, ensuring that each daughter cell inherits the parent cell's genes.

"The spindle has an infinite number of varieties because it's in all these different types of eukaryotic cells," says Michael Shelley, group leader for biophysical modeling and director of the Flatiron Institute's Center for Computational Biology (CCB). "It's made up of microtubules and motors and crosslinkers but has different structures in different cells."

Exactly how rigid rods and microscopic motors choreograph this fundamental line dance remains unknown, but Shelley and his collaborators aim to find out.

One line of research asks how motor proteins link and move microtubules, the building blocks of the spindle. A question the team is pursuing involves the protein kinesin, which has two heads that can grab one microtubule each, creating a linked pair. The kinesin then 'walks' along these microtubules. If the microtubules have opposite orientations, the walking motion pulls them in opposite directions. If they are aligned, the kinesin's walk has no effect on the pair.

Earlier calculations of interactions in a dilute mixture predicted that a given microtubule's movement would depend on which way its neighbors pointed: Those aligned would stay put, but rebels would be ejected. And yet, real spindles don't display such fickle behavior. Microtubule hordes tens of thousands strong appear to move in lockstep, despite different regions having different average orientations.

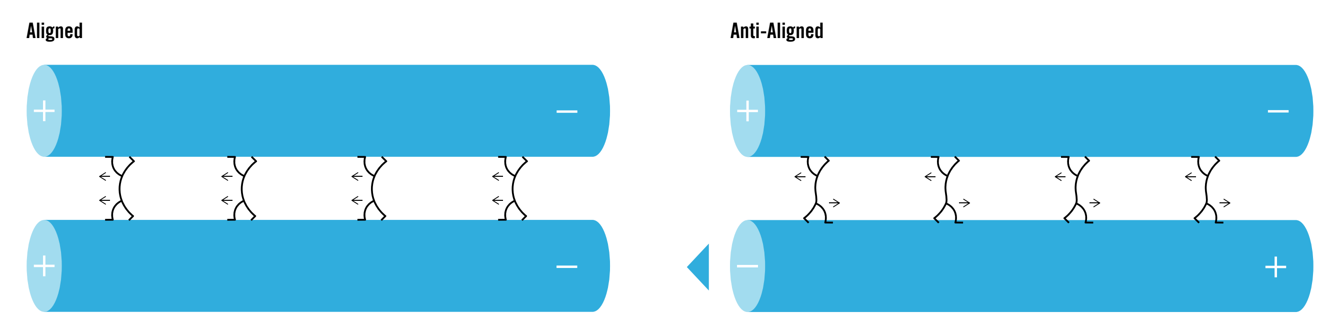
Shelley, along with CCB research scientist Sebastian Fürthauer, CCB visiting scholar and Harvard University applied physicist Daniel Needleman, and their colleagues, investigated what was going on by skipping the complexity of real spindles and using a simple test-tube system with just microtubules and kinesin. In the experiment, the motors linked the rods into a gel. Fluorescent microscopy revealed that although microscopically the rods pointed different ways, macroscopically half flowed to the left, while half went right — a result that suggested the calculations had assumed too much. "What if they're not dilute?" says Needleman. "What if they're really heavily cross-linked?"

Fluorescent microscopy revealed that although microscopically the rods pointed different ways, macroscopically half flowed to the left, while half went right — a result that suggested the calculations had assumed too much.

The research, published as an arXiv preprint in December 2018, presents the group's experimental observations as well as a mathematical framework for the microtubule-kinesin interaction. That framework assumes that both microtubules and motors are more concentrated and therefore more interlinked, which generates predictions that match what happened in the test tube. "It's a natural hypothesis that the same thing is happening in the spindle itself," Needleman says.

A better understanding of how spindles behave could lead to new treatments for cell-division-related health problems, such as infertility. The group has been working on a comprehensive spindle model for several years and hopes to complete it soon.

"What we're working toward is a grand unified theory of the spindle," Needleman says. "This was one of the missing pieces that we needed to understand how we go from the behavior of motors and microtubules to large-scale, collective self-organization."



Kinesin molecular motors *(black)* are part of the microscopic machinery inside cells. The kinesin molecules have pairs of "feet" at either end that latch on to microtubules *(blue)*. The feet march from the negative to the positive end of each microtubule. If the microtubules are aligned, the feet move in the same direction, and the microtubules stay put. If the microtubules are anti-aligned, the feet move in opposing directions, causing the microtubules to slide past one another.

BUILDING A NETWORK THAT LEARNS LIKE WE DO

CENTER FOR COMPUTATIONAL BIOLOGY

At each instant, our senses gather oodles of sensory information, yet somehow our brains reduce that fire hose of input to simple realities: A car is honking. A bluebird is flying.

How does this happen?

One part of simplifying visual information is 'dimensionality reduction.' The brain, for instance, takes in an image made up of thousands of pixels and labels it 'teapot.' One such simplification strategy shows up repeatedly in the brain, and recent work from a team led by Dmitri Chklovskii, group leader for neuroscience at the Center for Computational Biology, suggests the strategy may be no accident.

Consider color. In the brain, one neuron may fire when a person looks at a green teapot, whereas another fires at a blue teapot. Neuroscientists say that these cells have localized receptive fields, as each neuron responds strongly to one hue, collectively spanning the entire rainbow. Similar setups allow us to distinguish aural pitches.

Conventional artificial neural networks accomplish similar tasks, such as classifying images, but these algorithms work completely differently from those in the brain. Many artificial networks, for instance, tweak the connections between neurons by using information from distant neurons. In a real brain, however, the strength of a connection predominantly depends only on nearby neurons.

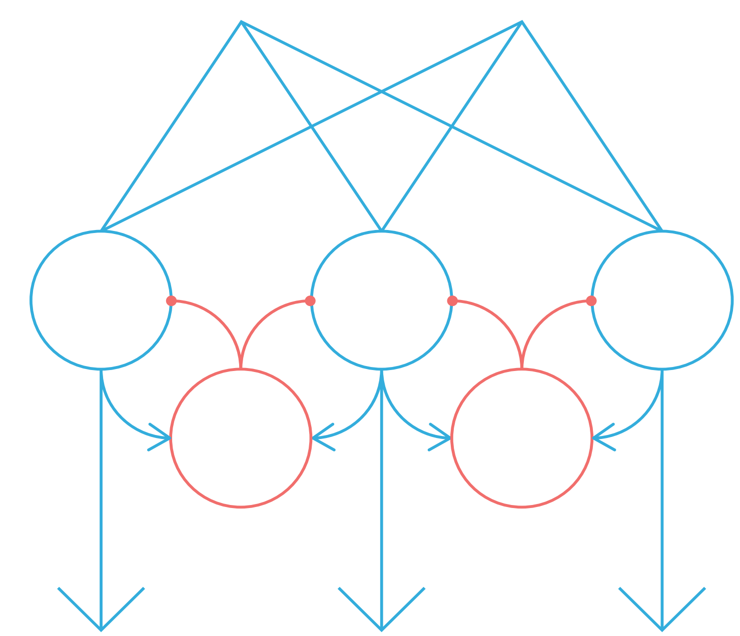
However, by extending a tradition of emulating biological learning, Chklovskii and his collaborators developed an approach that is not only biologically plausible but also powerful. "It basically explains how these systems, even though the agents are doing their own things with little information about others, can collectively organize as a system and learn something," says Cengiz Pehlevan, a theoretical neuroscientist at Harvard University who was a Flatiron Institute research scientist until early 2019.

The typical neural network uses training data to tweak parameters until it churns out correct results, but the new framework — presented at NeurIPS 2018 — starts by expressing three biological truths about how a network ought to function in a mathematical way: Neuronal activity should never be negative. (Real neurons can't do anything less than not fire.) Similar inputs should produce similar outputs. (Put two teapots in, get two teapots out.) Different inputs should yield different outputs. (A teapot and a kettle should not produce two teapots).

The new framework — presented at NeurIPS 2018 — starts by expressing three biological truths about how a network ought to function in a mathematical way.

When the team optimized this mathematical expression, 'the objective function,' the resulting network repeatedly developed the architecture of a human brain: It divided the input space into overlapping sections and assigned one neuron to handle each chunk. In one instance, it learned to recognize a rotating teapot using neurons that fire at specific angles.

In other words, the same localized receptive fields that help people parse what they see and hear had evolved from the team's network. "We had a different expectation of what this algorithm would do," says Anirvan Sengupta, a visiting scholar at the Flatiron Institute and systems neuroscientist at Rutgers University in New Jersey. "It emerged despite us."



Mimicking how the human brain processes information can improve machine-learning techniques. This diagram shows how a biologically inspired neural network can identify data clusters and manifolds. Each neuron outputs a rectified sum of its inputs, in turn influencing its neighboring neurons. Blue circles represent excitatory neurons, whereas red circles represent inhibitory neurons. The strength of the connection between each neuron is adjusted according to biologically plausible local learning rules. *Illustration adapted from A. Sengupta* et al./Advances in Neural Information Processing Systems *2018*

The work is the group's latest in a series deriving optimal networks for learning various tasks. The results hint that the way the brain simplifies inputs is efficient and perhaps borders on inevitable.

Chklovskii's team will continue to reverse engineer learning in biological networks. "The fact that you keep on getting localized receptive fields for many different objective functions representing the same spirit," Sengupta says, "seems to tell me there is something bigger there."

A MANY-METHOD ATTACK ON THE MANY ELECTRON PROBLEM

CENTER FOR COMPUTATIONAL QUANTUM PHYSICS

Uniting our everyday world with the quantum realm requires tackling titanic numbers. A single penny contains 2 billion trillion atoms with a total of 70 billion trillion electrons whizzing around them. The behavior of those electrons produces many of the penny's properties, such as its conductivity and even its shininess.

Taming these electrons would yield society-changing benefits, such as enabling the design and control of materials with desirable properties, such as high-transition-temperature superconductivity. The goal of the Center for Computational Quantum Physics (CCQ) is to help make that future a reality.

The CCQ faces mind-boggling numbers beyond just the plethora of electrons. Particles in a quantum system can exist in many different configurations, called states. Each electron, for instance, can have an upward or downward spin. Completely understanding a quantum system requires calculating the system's wave function, which describes how particles are distributed over all possible states.

For example, even if we consider spin alone, a group of 10 electrons can be in any one of 1,024 states. For a penny's worth of electrons, the number of states would be billions of trillions of digits long. And calculating a material's overall wave function is further complicated by quantum mechanical entanglement, which means that electrons influence one another so strongly that they can't be treated individually.

The CCQ, launched in September 2017, has already established itself as an international leader in developing the computational methods needed to solve the so-called 'many electron problem.' "The center has several angles of attack on this problem," says center director Antoine Georges, who leads the CCQ along with co-director Andrew Millis. "We're bringing together the best methods and people, and I think after a year and a half of existence, we have an impressive set of methods and software." Each method has strengths and weaknesses as well as synergies with other approaches.

CCQ project leader Olivier Parcollet says the center's scientists pursue so many methods "because we don't know which one is best, and we don't even know if any one of them will be the best." For example, Parcollet's work focuses on a method of tackling the many

"We're bringing together the best methods and people, and I think after a year and a half of existence, we have an impressive set of methods and software."

electron problem known as quantum embedding, which originated from research pioneered by Georges in the 1990s. The method leverages the fact that physicists are often only interested in the behavior of a small part of a quantum system. Instead of performing a detailed calculation across the whole system, quantum embedding performs high-level calculation on only the area of interest. The rest of the system is treated more simply, drastically streamlining many quantum problems.

Quantum embedding has limitations, though. The calculations often require experimental validation to ensure that the problem wasn't oversimplified. Also, even a small chunk of a quantum system can be too computationally taxing to compute using conventional methods, requiring the additional use of other methods.

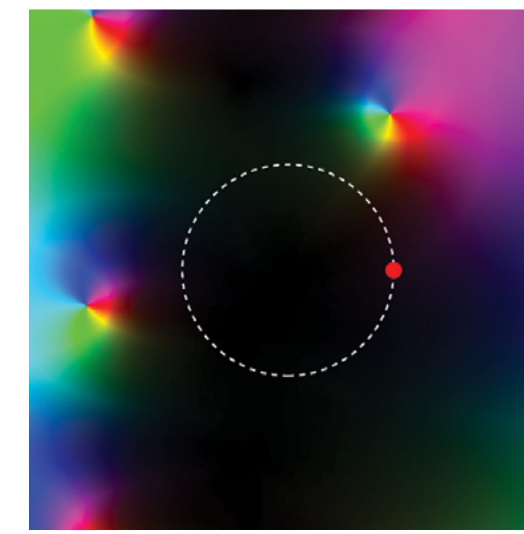
Another approach avoids deterministic computations altogether. Dubbed 'the Monte Carlo method' after the Mediterranean casino, the approach uses random sampling to compute the answer to a problem. A famous example involves randomly throwing stones into a square with a circle inscribed inside. The fraction of rocks that fall within the circle provides a rough estimation of pi divided by four: The more stones thrown, the more accurate the estimate.

Conventional methods such as integration can compute pi more quickly. However, for more complex tasks, such as integrating mathematical equations with many variables, or dimensions, Monte Carlo often wins. "If we do that integration in high dimensions, the clever, faster things suddenly become super slow, and this 'dumb' way wins out," says CCQ senior scientist and group leader Shiwei Zhang, who develops algorithms for Monte Carlo methods.

Quantum physicists run Monte Carlo calculations until they reach a desired accuracy. The method isn't always viable, though. In most quantum systems, the solution requires computing an answer that is the slight difference between large positive and large negative contributions from a quantum system's wave function. In these cases, the time required to compute an accurate solution becomes extremely large.

Whereas Monte Carlo leverages randomness, a relative newcomer directly computes solutions using novel mathematics called tensor networks. The approach compacts quantum problems by bundling information about a system into multidimensional arrays called tensors. Quantum entanglement links these tensors into a network.

Similar to quantum embedding, tensor networks take advantage of the fact that only a small fraction of the states in a large quantum system are relevant to any particular physical situation. The organization of information about the system, therefore, can be streamlined.



The Center for Computational Quantum Physics is developing methods to solve the quantum many-body problem, including predicting the behavior of large groups of fermions such as electrons. The image above represents a color map of two aspects of the self-energy of an interacting fermion system — namely, the modulus and phase (represented by saturation and hue). The red dot indicates the physical solution to be reached. *Photo courtesy of Michel Ferrero of École Polytechnique and Collège de France in Paris*

As an analogy, one might treat a proton and an electron orbiting it as a single atom rather than tracking the details of each particle's motion separately. Tensor-network code leverages patterns in the structure of the wave functions to produce a compact representation of the most important states in a quantum system. This approach makes problems smaller and more manageable, similar to the way streaming websites compress video files.

This approach outperforms other methods in certain situations, such as when the system is large only along one dimension or has relatively simple interactions. In other cases, though, the computational requirements balloon too high to be worthwhile. "Even though we have issues, some of the problems we're tackling can't be touched at all by other methods without making heavy approximations," says CCQ research scientist Miles Stoudenmire, who develops and deploys tensor-network methods.

Tensor networks often take advantage of patterns in a quantum system that are too convoluted and complex for a person to uncover. Artificial intelligence techniques such as machine learning can help uncover such patterns through a complementary set of techniques.

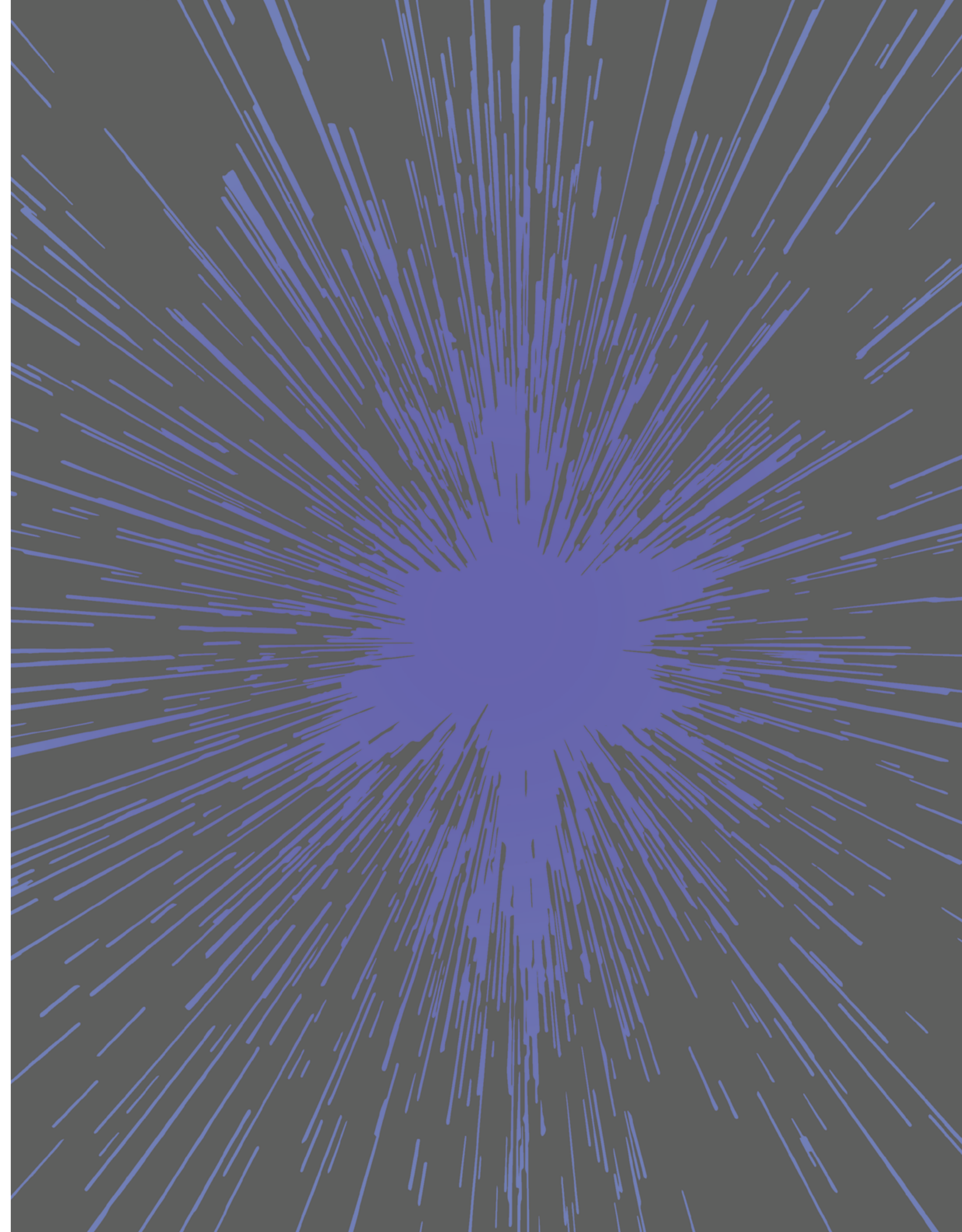
Computer programs that best world champions at board games and train self-driving cars inspired CCQ associate research scientist Giuseppe Carleo to explore artificial intelligence approaches. Similar to those applications, artificial intelligence in quantum physics improves by ingesting information. Over time, the code learns how to impersonate a quantum system. Similar to tensor networks, Carleo's methods create a compact representation of the important states of a quantum system. In February 2018, Carleo and his colleagues published a paper in *Nature Physics* that demonstrated that machine-learning techniques could drastically reduce the time needed to reconstruct a wave function based on experimental results. Systems that would typically require thousands of years to be reconstructed could be thoroughly analyzed in hours.

Sometimes, however, machine-learning techniques take more time than they save. Carleo and others are trying to make the code more efficient. "We're the newborn in the field," Carleo says. "There's an explosion of things going on, but we have a lot left to do."

A crucial part of the CCQ's mission is making its code available to the public via open-source libraries. Carleo shares machine-learning code through NetKet, Stoudenmire maintains a library called ITensor for tensor networks, Parcollet leads the TRIQS project for interacting quantum systems, and Zhang heads the AFQMC library for Monte Carlo codes.

Sharing code helps the whole field advance, Parcollet says. "The complexity of the methods is growing," he says. "We need to minimize the costs of testing new ideas. If a student needs to reinvent the wheel for every new project, the field will slow."

CCQ associate research scientist Giuseppe Carleo gives a talk at the Kavli Institute for Theoretical Physics in Santa Barbara, California, on the uses of neural networks for quantum many-body problems. *Photo courtesy of Miles Stoudenmire*



ARITHMETIC GEOMETRY, NUMBER THEORY AND COMPUTATION

Computation and number theory naturally go hand in hand — one of the earliest examples is a Mesopotamian tablet from 1800 BC that lists 15 sets of integers that satisfy the equation $a^2 + b^2 = c^2$, now known as Pythagorean triples.

The Simons Collaboration on Arithmetic Geometry, Number Theory and Computation continues the legacy of combining computation with theoretical research by focusing on several central problems in the study of numbers and solutions to polynomial equations.

The collaboration, launched in 2018, germinated from a 2015 meeting at the Institute for Computational and Experimental Research in Mathematics at Brown University, titled "Computational Aspects of the Langlands Program" and organized by collaboration investigator John Voight of Dartmouth College and others.

"Our collaboration grew out of the questions: What does computational number theory look like in the 21st century, and what tools should be developed for use by the arithmetic geometry community?" Voight says.

Voight is one of six principal investigators along with collaboration director Brendan Hassett of Brown University, Jennifer S. Balakrishnan of Boston University, Noam Elkies of Harvard University, and Bjorn Poonen and Andrew Sutherland of the Massachusetts Institute of Technology. The principal investigators meet monthly to discuss their research and trade ideas. The collaboration also includes 20 affiliated scientists from around the world, including graduate students and late-career researchers.

Many of those affiliated scientists support the collaboration by developing tools and databases to create and store examples of mathematical phenomena.

"We're really motivated in encouraging the growth of mathematical researchers who are equally comfortable in the computer science side and the math theory side," Hassett says. "That is actually the biggest impact: not just solving particular problems but having a cohort of people who can both do the math and oversee databases of mathematical objects."

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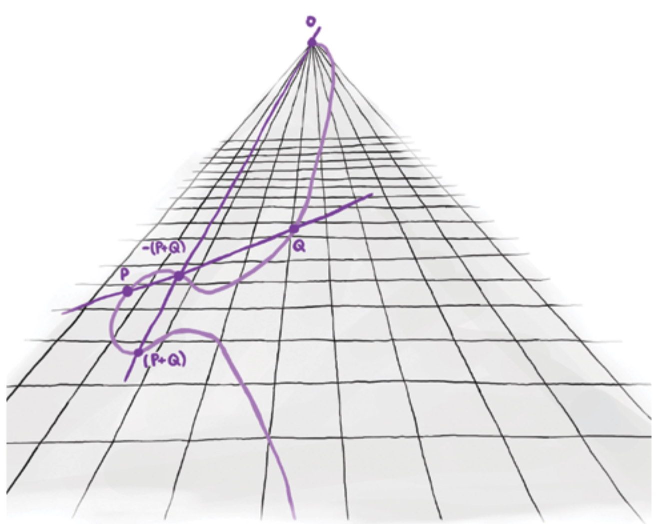
Pulling rank:

Collaboration members used computers to upend a broadly held belief in arithmetic geometry concerning the fundamentals of the field. Basic objects of study in arithmetic geometry are elliptic curves, or solutions to equations in the form $y^2 = x^3 + ax + b$. Researchers want to find points on elliptic curves that are rational — that is, points that have coordinates that can be written as simple fractions. For example, (25/4, −75/8) is a rational point on the curve defined by the equation $y^2 = x^3 - 25x$.



A visualization of the elliptic curve group law, an important concept in number theory, on a projected plane. *Image courtesy of Sachi Hashimoto*

‘Rank’ is a measure of the complexity of the set of those rational points. If an elliptic curve has only a finite number of rational points, it has rank zero. If it has an infinite number of rational points, then it has some positive rank.

For decades, mathematicians have thought that there is no cap on how high this rank can get. In 2006, Elkies used extensive computer experiments to find an elliptic curve with a rank of at least 28, the highest rank seen so far. More recently, Voight, Poonen and their colleagues Jennifer Park of Ohio State University and Melanie Matchett Wood of the University of Wisconsin-Madison developed a heuristic model suggesting that only a finite number of curves defined over the rational numbers have a rank higher than 21. This conclusion implies there must be a cap on rank — at least 28 because of Elkies’ example.

Numerical evidence will be key to progress. If someone could find an infinite number of curves with higher rank, that would disprove the model. Or, if mathematicians could find infinite sequences of curves with growing rank, they’d prove that the existing paradigm of limitless ranks was right. As it stands, the model by Voight and his colleagues has shaken up the world of arithmetic geometry.

Higher genus:

Computational power has also allowed collaboration members to extend research from elliptic curves, which are curves with genus 1, to higher-genus curves given by equations with higher-degree polynomials, such as $y^2 = x^8 + ax^7 + \ldots + gx$.

When finding genus 3 curves with a small discriminant, a number that, like rank, measures the complexity of the curve, Sutherland set a record for the largest computation using the Google Cloud Platform. In one afternoon, Sutherland used more than 580,000 Google computing cores around the world — more than 300 years of computer time — to whittle 10 billion candidate curves down to a list of about 80,000 with particularly small discriminants.

After one of the collaboration leaders’ monthly meetings, Balakrishnan and her co-authors found the rational points of 17,000 curves from Sutherland’s list.

The LMFDB:

Those rational points will be uploaded to the L-functions and Modular Forms Database (LMFDB), an online repository of information about elliptic curves, modular forms and L-functions. L-functions encode a correspondence between certain kinds of elliptic curves, or equations in the form $y^2 = x^3 + ax + b$, and modular forms, a surprisingly useful type of function.

“The L-function encodes the mathematical DNA of these objects,” Sutherland says.

The LMFDB, which is partially supported by the collaboration, is like a modern version of the Mesopotamian tablets. Each encyclopedic page in the LMFDB is dedicated to a mathematical object, such as an elliptic curve, a modular form or an L-function, and its relationships with other objects. Upgrading its infrastructure was one of the first tasks for the collaboration.

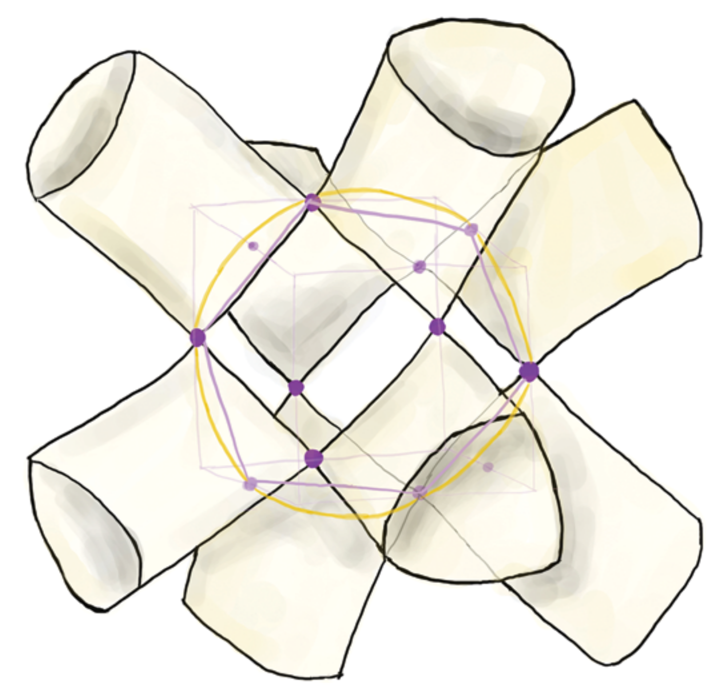
“The LMFDB is a big project, bigger than one university or one department could possibly support alone,” Hassett says.

The mathematical community hopes that numerical data in the LMFDB can help establish a correspondence between higher-genus curves and L-functions, just as elliptic curves correspond with modular forms via their L-functions.

The bigger picture:

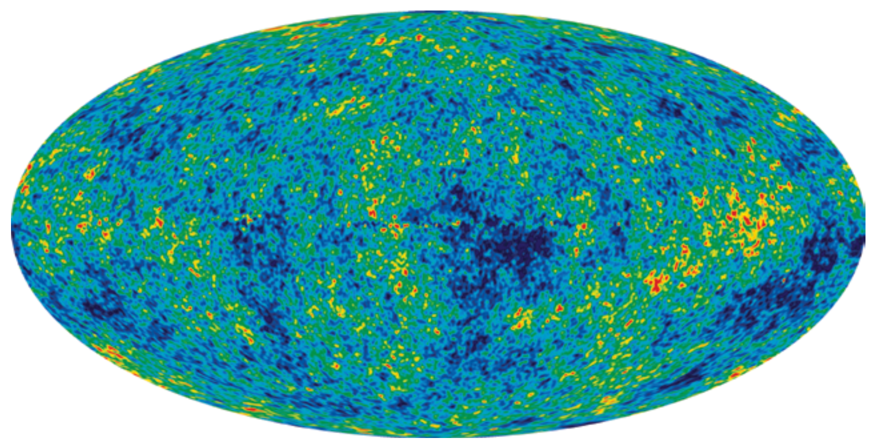
The scope of the collaboration continues beyond these examples to solve computational problems in arithmetic geometry and number theory. Just as we now have the Pythagorean theorem instead of a Mesopotamian catalog of Pythagorean triples, the hope is that more data will lead to more mathematical proofs.

“One of the central premises of our collaboration is to take delight in the wonderful interplay between practical computation and abstract theory,” Voight says. “We’re thinking hard about how computers, algorithmic techniques and big databases can be used to advance number theory. We want to make it easy for researchers to zoom in like a microscope to really dissect a few particular specimens and to zoom out like a telescope to understand large-scale structure of the mathematical universe.”



A visualization of the Kummer surface of a genus 2 curve. *Image courtesy of Sachi Hashimoto*

ORIGINS OF THE UNIVERSE



The oldest light in the cosmos, known as the cosmic microwave background, is the afterglow of the universe's creation. The variation in temperature (shown as a color range) and polarization of the light offers clues about how the cosmos formed. *Image courtesy of the European Space Agency's Planck Collaboration*

The Origins of the Universe program was launched in 2017 to support three teams of researchers investigating three modern theories of the universe and the forces that continue to shape it. The teams operate independently, often exploring avenues of research that directly compete with those of the other teams, but meet for a joint conference once a year. Though their research is theoretical, they all hope to test their predictions at the neighboring Simons Array and Simons Observatory, the latter of which will begin operations in 2020 in Chile.

The telescopes at the observatories will be taking measurements of the cosmic microwave background radiation (CMB), which can provide clues about the early universe. Greg Gabadadze, associate director for physics at the Simons Foundation and a leader, along with Massimo Porrati, of one of the Origins research groups, describes analysis of the CMB as a kind of cosmic archaeology. "Archaeologists go back and dig out artifacts of the Roman Empire or something," he says. "Through those artifacts, they learn how that society was organized." Researchers studying the CMB can likewise excavate information about primordial physics.

The structure of the Origins of the Universe program is unusual in that the research groups are — intellectually — in direct competition with one another. Everyone involved is passionate about their work, and the annual meeting gives them a chance to discuss their competing ideas openly ("and peacefully," one principal investigator affirms), and to broaden their horizons. "These interactions are beyond the interactions anyone could have within their own groups," Gabadadze says.

Eva Silverstein, professor of physics at Stanford University, leads the largest of the groups, the Research in Modern Inflationary Cosmology group. The inflationary model of cosmology is the most widely accepted origin story for the universe. It holds that the universe underwent superluminal expansion — an expansion faster than the speed of light — almost 14 billion years ago.

The structure of the Origins of the Universe program is unusual in that the research groups are — intellectually — in direct competition with one another.

This group is large and sustains many lines of research. One of the group's goals is to unite inflationary cosmology and string theory, in the hopes of explaining quantum gravity. "String theory has led us to ideas for inflationary cosmology that we had not found using classical physics alone," Silverstein says. The project would also move beyond analysis of the CMB and instead examine the large-scale structure of the present universe — how galaxies and other large objects are distributed — to understand the early evolution of the universe.

An Inflationary Cosmology subgroup works to find a mathematical formulation of quantum gravity that is compatible with the accelerated expansion of space-time; such a formulation is demanded by observations indicating that the cosmological constant is positive. The researchers are building from theoretical work in the opposite case, where the cosmological constant is negative, incorporating exciting new tools in quantum theory to make the generalization to the real-world case.

The Cosmological Bounces and Bouncing Cosmologies group's ideas upend the ideas of inflationary cosmology. Lead investigator Paul Steinhardt of Princeton University was himself one of the pioneers of the inflationary paradigm but eventually came to realize that quantum fluctuations spoil the original idea, creating deep problems for the theory. "If you look at the problems with the prevalent idea, they all trace back to the assumption that the universe — space and time — has a beginning," he says. His group instead investigates the possibility of replacing the 'bang' with a 'bounce,' a smooth transition from an earlier period of contraction to the current period of expansion. Furthermore, such contraction and expansion may repeat every trillion years or so, resulting in a cyclic universe with no beginning or end. The group's goal for the Origins project is to develop the mathematical, theoretical and numerical tools to put the 'bounce' on solid footing. After that, they hope to develop predictions that could be tested at the Simons Array or Simons Observatory.

"One of the possibilities when we do the full numerical calculations is we might discover — oops! Something destroys the idea," Steinhardt says. "That's the way it should be in science. You develop an idea, you learn from it whether you win or lose, and it should be killable. If it doesn't have that property, it's not a very good idea."

Gabadadze and Porrati, both of New York University, lead the Cosmology Beyond Einstein's Theory group, which investigates the mathematical foundations of theoretical frameworks that would allow for periods before inflation. "There are a multitude of scenarios which the universe could have followed in the beginning, and we don't know which one is true," Gabadadze says. "That's why we're working on theories that describe those stages and working out predictions of those theories that can be contrasted with observations." Some aspects of their work are more compatible with inflation and some are more compatible with bouncing cosmology or other alternatives, so they work with both groups.

One of the motivations for the group's research comes not from questions about the early history of the universe but from questions in modern cosmology: Their work could help physicists understand dark energy, the mysterious force that makes up about two-thirds of the total energy in the universe and which would also explain the present-day expansion of the universe.

The graduate students and postdoctoral researchers supported by the Origins of the Universe project are in a fortunate position working in such a dynamic area. "Young people who engage in this project get training both in the fundamentals of the field but also in how to conduct research under unusual circumstances, when things are not settled," Gabadadze says. "I believe that is very important for the continuation of the field in general."

Paul Steinhardt of Princeton University presents at the Origins of the Universe program's annual meeting.

CRACKING THE GLASS PROBLEM

Glass has served humankind for millennia and is used in everything from windows to dishes to cell phones and high-speed internet cables. This ubiquitous material is so common that the fact that it is also something of a scientific mystery is surprising. Why don't we have a handle on glass yet?

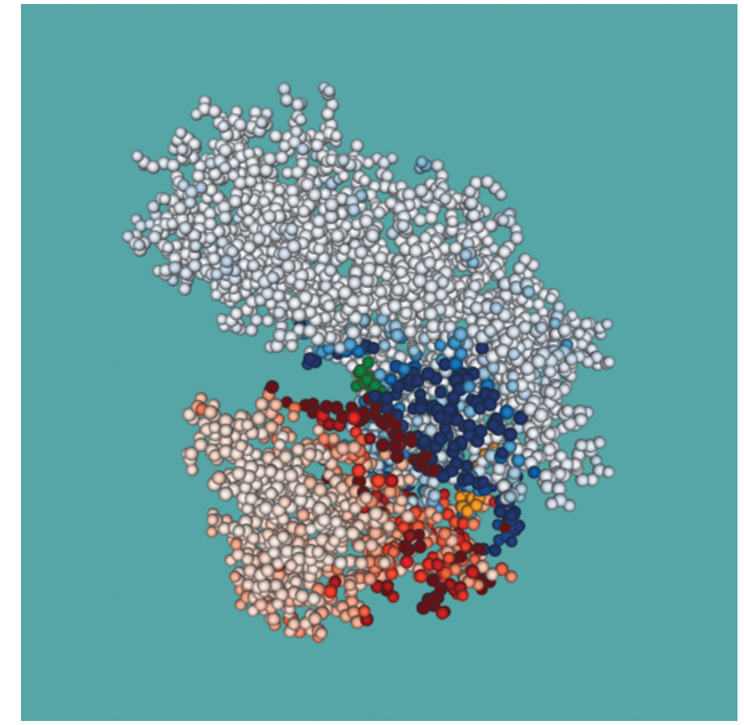
The Simons Collaboration on Cracking the Glass Problem seeks to understand why glass behaves in all the myriad ways it does — rigidly at some temperatures and as a liquid at others — and how its properties might be engineered for everything from building materials to medical devices.

Household window glass is an amorphous solid, meaning it does not have a crystal structure and it exhibits certain property changes when its temperature is raised or lowered. But when collaboration researchers talk about glass, they are referring not only to this familiar silicon dioxide type but also to a host of other materials with two of the same properties: an amorphous structure and a transitional temperature at which its brittle structure becomes pliable and viscous. Non-silicate glasses include, for example, metals that have been heated and then supercooled to prevent them from forming crystals; plastics; the granular materials in between plates at an earthquake fault; and even many biological tissues. All are fair game for the collaboration.

The collaboration is divided into three main research directions. One is tasked with understanding jamming behaviors: When molecules are loosely packed in a space, the material is not rigid. As they are packed more tightly, they become rigid, whether they develop a crystal structure or not. The transition from a loose to a rigid state is called jamming. "There is new physics there, and it's different from the kind of physics you get when a material suddenly becomes a crystal," says Sidney Nagel, a physicist at the University of Chicago and director of the collaboration.

Another strand of research deals with what is called the mean-field transition. Projects in this area look at what happens in theoretical infinite-dimensional arrays of glass, where molecules interact with many more of their neighbors and local effects are not as important. The technique has been common in physics for decades, but with many materials, a lot of precision is lost in the transition from few to many dimensions. Not so with glass. "We found it quite astonishing," says Giorgio Parisi, a physicist at Sapienza University in Rome and a principal investigator in the mean-field group. "These infinite-dimensional computations are much closer in the case of glasses than in other materials." The jamming group and mean-field group study the extremes of glass behavior (zero temperature and

When most of us look out of our windows, we don't realize what a complex substance we are peering through. But collaboration researchers relish the mysteries in this seemingly mundane material.



A model of glucokinase, a glucose-processing protein in the liver and pancreas, produced by collaboration member Jason Rocks of the University of Pennsylvania. Proteins undergo transitions akin to the changes in viscosity and other properties that occur in liquids when they form a glass. This protein's atoms are colored according to a so-called persistent-homology-based analysis. This analysis identifies the two regions of the molecule *(red and blue)* that are most important to the protein's function. *Image courtesy of Jason Rocks*

infinite dimension); combining the two approaches can give insight into how glass behaves in more typical situations.

The final research area is dynamics of glass: how molecules flow past one another at high temperatures or under applied force. Lisa Manning, a physicist at Syracuse University and a principal investigator in the collaboration, says one of the most important avenues of research for the group is understanding how and where glasses are likely to fail. "They fail in interesting and unexpected ways," she says. If members of the collaboration succeed in making better predictions about how glassy materials will behave, they can help materials scientists apply those insights and not only strengthen the materials they are creating but also develop materials with novel functionality.

Over the years, scientists have developed several different methods for understanding and predicting how the structure of glass impacts the dynamics, but until the collaboration was formed, there was little interaction among research groups. Now the collaboration has allowed more than 10 research groups to bring their techniques together to compare their merits and determine which ones are most powerful under which circumstances. For example, Manning's team specializes in looking at vibrational patterns in glassy materials; a group led by collaboration principal investigator Andrea Liu uses machine-learning algorithms to make predictions; and so on. "I think this collaboration is a real breakthrough in our field," Manning says.

Strength from disorder:

"So much of what we have been taught to do as physicists has been to treat ordered systems such as crystals," says Nagel, "but glass's disorder poses a challenge to traditional models of physical objects. Systems with disorder obey different laws of nature not found in ordered crystalline matter." For example, a magnet has only two ground states because all the spins in the system are aligned. For glass, the number of ground states grows exponentially as the number of molecules present increases, requiring a whole new way to address the statistical mechanics of problems involving glass.

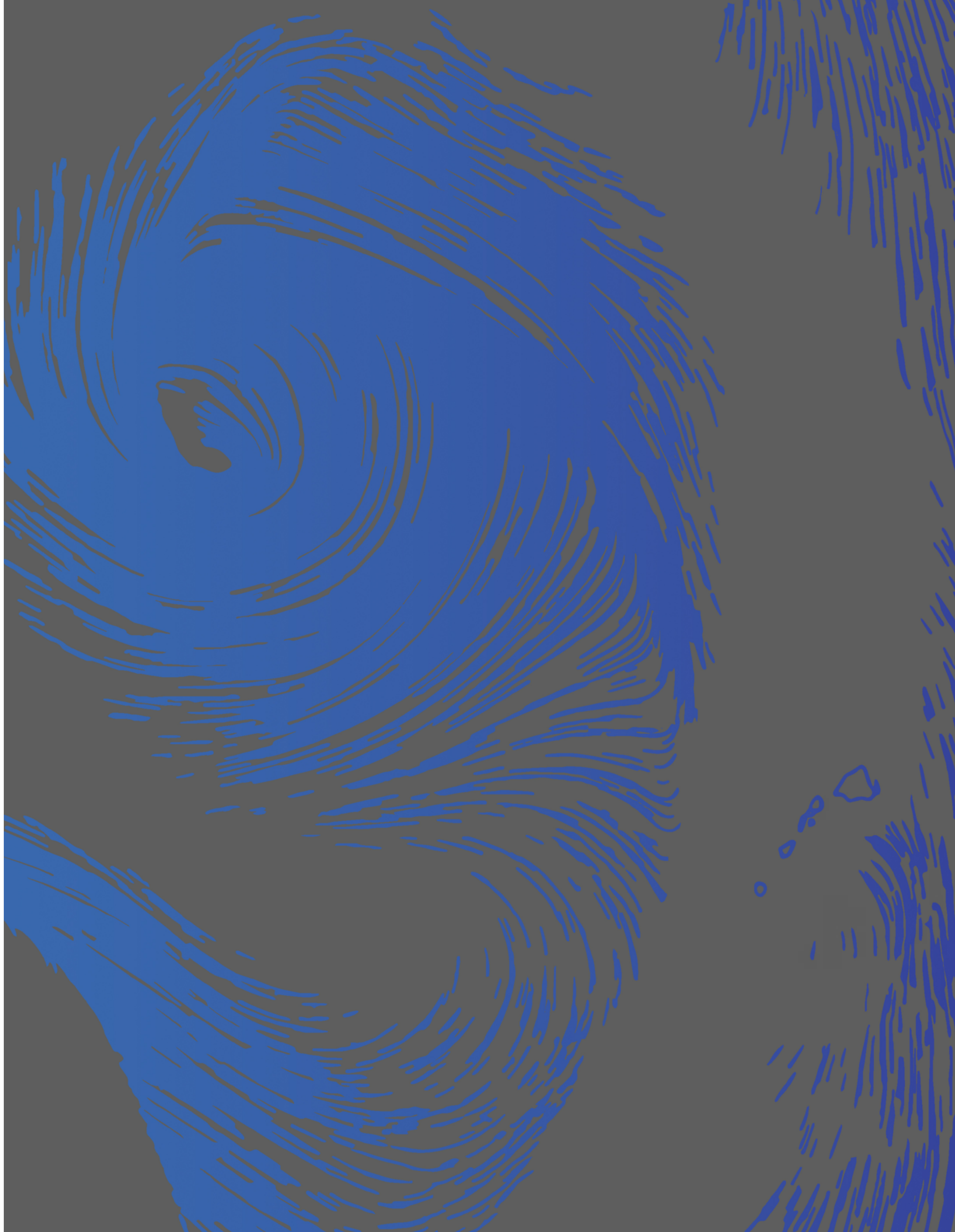
Disordered materials such as glass resist compression and shearing as well. But is the rigidity of glass the same as that of a crystal?

In an ideal setting, crystals are incredibly strong. The uniform structure holds the material together. But in the real world, crystals have slight chemical imperfections that weaken them. One region has a crystal structure aligned with a certain direction that bumps into another region with a crystal structure pointing another way. Along these fault lines, the material is susceptible to breakage or decay. (Perfectly crystalline iron would not rust; oxygen enters through defects in the crystal structure.) Glass, on the other hand, is uniformly disordered, so there are no discontinuities in the structure that can cause weaknesses. Therefore, understanding glass structures and discovering ways to make glass out of particular materials or with particular connections in their molecular structures can result in stronger, more resilient materials for all sorts of applications.

Seeing clearly:

As is often the case in basic research, Cracking the Glass's work will yield knowledge applicable to areas beyond just glass. "We think of understanding this glass state as a hub for understanding many new directions beyond that," Nagel says. Where disorder plays a role in scientific questions, the collaboration's work on disorder in glass could be applicable. For example, work on rugged energy landscapes in glass is relevant to diverse areas, such as questions in biology about cell differentiation and questions in physics about string theory. But perhaps the most unexpected outside connection is to computer science. The collaboration's work on jamming is related to satisfiability problems in algorithms, where a collection of statements, sometimes unrelated to one another, must be simultaneously satisfied.

When most of us look out of our windows, we don't realize what a complex substance we are peering through. But collaboration researchers relish the mysteries in this seemingly mundane material. "We love this kind of problem," Nagel says. "You have things that you've dealt with every day, and then you stop and think about it and realize you don't know how this thing manages to be the way it is. We are at a stage where we can formulate new principles and develop powerful mathematical tools that can be applied widely throughout science."



COMPUTATIONAL BIOGEOCHEMICAL MODELING OF MARINE ECOSYSTEMS (CBIOMES)

Individually, ocean microbes can be as small as one-hundredth the width of a human hair. But collectively, they play an outsize role in the Earth's climate and nutrient cycles. Microbes at the ocean's surface form the base of the food web that sustains ocean life, and they carry out half the planet's photosynthesis. In doing so, these microbes transform carbon dioxide from the atmosphere into organic matter that is drawn down into the deep ocean's giant carbon reservoirs. And the diverse array of ocean microbes also mediates the Earth's cycles of other elements, such as nitrogen and sulfur.

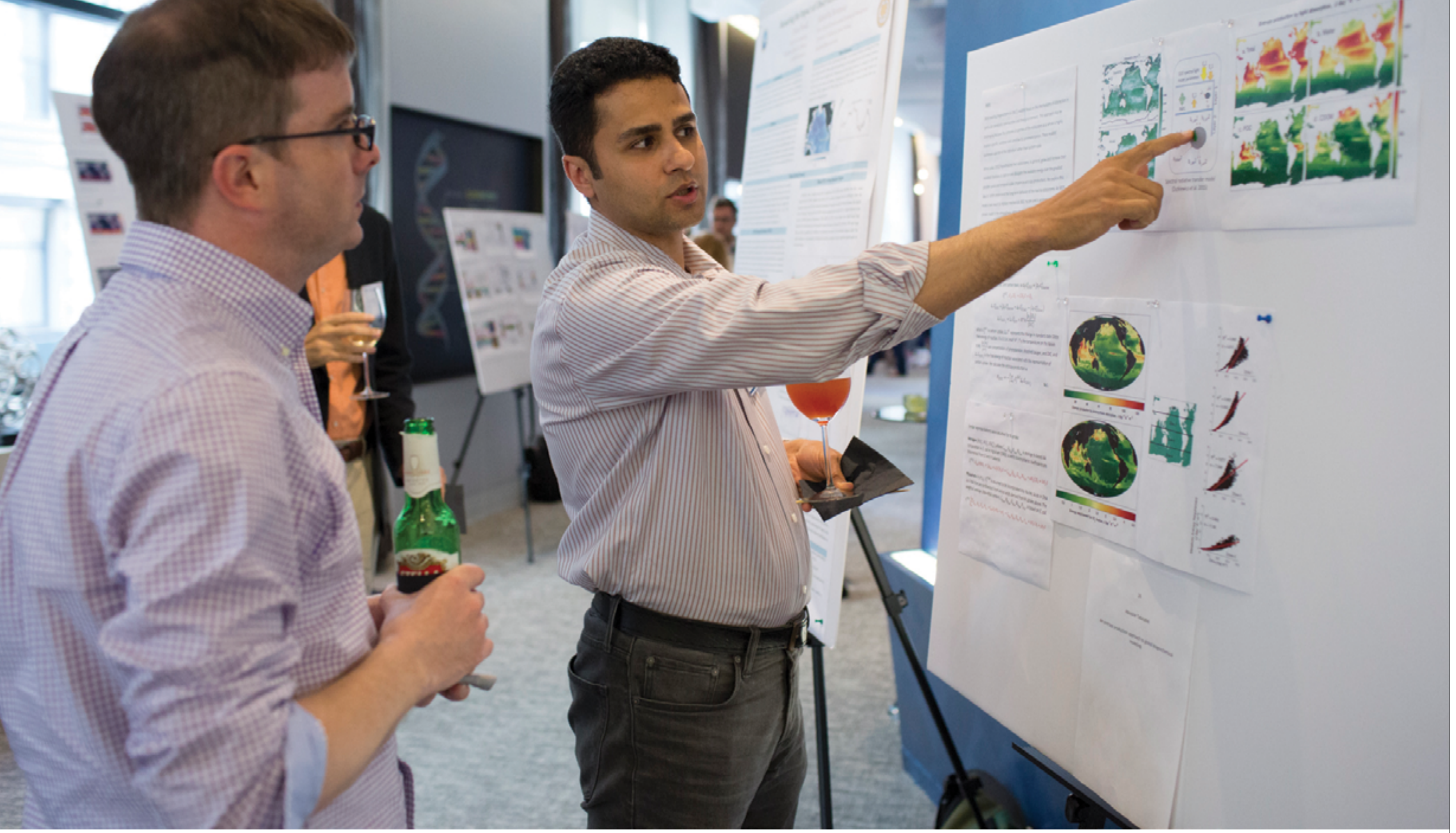
Yet our understanding of the marine microbial ecosystem is spotty at best. "There are large blank areas on the map where we don't really know what's living there," says Michael Follows, an oceanographer at the Massachusetts Institute of Technology (MIT).

Understanding how marine microbes interact with one another and their environment requires a synthesis of empirical measurements, laboratory research, statistics and modeling. To tackle this challenge, in July 2017 the Simons Foundation's Life Sciences division launched the Simons Collaboration on Computational Biogeochemical Modeling of Marine Ecosystems (CBIOMES), a five-year project that unites researchers at nine institutions in the United States, Canada and the United Kingdom. A key objective is to produce a global-scale map showing how the community of marine microbes changes over space and time.

"We have top-level statisticians, people in the lab, people who like big computations, and people who like little bits of clean math," says Follows, the project's leader. "But I think we're all on the same page about the big goals of the project."

Bridging size scales:

To produce a faithful map of ocean microbes, CBIOMES researchers must figure out how to work across vastly different scales — among microbes, ocean regions and time periods.



Research scientist Gaël Forget of MIT *(left)* and postdoc Aboozar Tabatabai of MIT and the Marine Biological Laboratory in Woods Hole, Massachusetts *(right)*, chat at a poster session during the 2018 CBIOMES annual meeting.

Zoe Finkel of Dalhousie University in Halifax, Canada, one of CBIOMES' principal investigators, focuses on some of the smallest scales, uncovering the individual cost-benefit rules that determine which microbes will thrive under which circumstances. Microbes that are adapted to grow quickly, for example, need more phosphorus so they can make RNA, whereas microbes that carry out photosynthesis need more nitrogen so they can make more protein.

"Small differences in the amounts of nitrogen, phosphorus or iron that microbes need determine who wins where," Finkel says. "And if we understand how these things grow and what their needs are, it can tell you about large-scale patterns of nutrients and carbon dioxide. Understanding the small does tell about the large."

Meanwhile, Shubha Sathyendranath, a CBIOMES principal investigator at Plymouth Marine Laboratory in the U.K., focuses on the large: satellite images of oceans across the entire planet. Differences in ocean color, from blue to green, provide a window into the populations of phytoplankton — microscopic marine plants — close to the ocean's surface. Sathyendranath's team is developing methods for turning these images into population estimates both at the surface and in the deeper ocean.

"Since satellites cover the whole globe, typically once every two days, we can map the dynamics of these organisms at the global scale almost on a daily basis," Sathyendranath says.

Uniting the different scales of work such as Finkel's and Sathyendranath's is the role of CBIOMES' modelers, who include Follows and his colleague at MIT Stephanie Dutkiewicz. Their team has created a gigantic simulation of ocean life including up to 300 different functional types of marine organisms that follow Finkel's rules and other assumptions about how they will respond to changes in population distribution, nutrients, temperature and ocean currents. Sathyendranath's satellite analyses then provide a check on how well the model is capturing real marine microbial dynamics, and the models in turn allow Sathyendranath to fine-tune her own methods for understanding phytoplankton below the ocean's surface.

"If we really understand what's going on in the ocean, then one view should compare with another view," Sathyendranath says. "Once we understand such things, we can begin to ask how the ocean ecosystem will respond to climate change."

The MIT group's model currently simulates the Pacific Ocean down to 2-kilometer resolution, a major step forward for simulations that capture both fluid physics and a diverse plankton population. "Just a few years ago I was very proud that we were able to achieve 20-kilometer resolution," Follows says.

Tackling 2-kilometer resolution has been a huge computational challenge. "If you had asked me a few years ago, I would have thought that we wouldn't do it in my career," Follows says. Now, he says, the model "provides a platform for exploring ecological questions that no one else is looking at."

CBIOMES' statisticians, meanwhile, are working to complement the modeling approach with a more data-oriented perspective that aims to learn the rules of microbial interactions directly from the available information from cruises and satellites. "One grand challenge in CBIOMES is, say I have these ocean simulations, how do I match them to actual data?" says Christian Müller, a statistician at the Simons Foundation's Flatiron Institute and one of CBIOMES' principal investigators. Developing a data-driven model to compare with the simulations is "the ultimate statistical question," he says. "Coming up with new analysis techniques for these types of data is really interesting."

Bridging disciplines:

The project is still in the early stages of figuring out how to meld the various teams' different areas of expertise. "We have to find a common language," Müller says.

The project's first annual meeting, in May 2018, was attended by more than 40 researchers. "It's a wonderful group of people who have a really synergistic set of interests and skills," Finkel says.

In addition to the annual meeting, the project carries out monthly online meetings consisting of short research talks and general discussion. And many subgroups of the different teams have met to study joint areas of interest. "There are all sorts of collaborations springing up that I wasn't anticipating," Follows says.

Sathyendranath, for instance, has already started several collaborations and has plans for more. "Some of these are people in different areas whom I might never have met except through this project," she says.

By the time the project is done, "I think we'll have a much better understanding of what controls the biogeochemistry of marine microbes," Finkel says.

For now, the project is "really exciting, but also overwhelming — because the ocean is big," Müller says. "It's uncharted territory, really."

"If we understand how these things grow and what their needs are, it can tell you about large-scale patterns of nutrients and carbon dioxide. Understanding the small does tell about the large."

SIMONS COLLABORATIVE MARINE ATLAS PROJECT

As planning for the Simons Collaboration on Computational Biogeochemical Modeling of Marine Ecosystems (CBIOMES) took off in January 2017, one need quickly became apparent: a database with tools that would allow the project's participants to sift through the mountains of oceanographic data collected from their own work and by other initiatives.

Oceanographic data come in all shapes and sizes: Satellites and numerical models generate enormous datasets, cruises collect water samples of microbes, and sensors measure things such as temperature and salinity across a wide swath of the planet's oceans. Combined, these datasets offer rich possibilities for new discoveries and hypotheses.

But as of early 2017, many of the datasets were not combined. Oceanographic datasets were scattered across a wide range of sources, and using them often required enormous downloads. And each dataset had its own unique internal organization, making the task of comparing information across different datasets a confusing and laborious process.

As a result, researchers who wanted to work across different datasets had to keep reinventing the wheel. "It's this ongoing issue that researchers are forced to solve again and again," says Mohammad Ashkezari, a research scientist at the University of Washington in the laboratory of Virginia Armbrust, one of CBIOMES' principal investigators.

To address this issue, Armbrust's lab has created the Simons Collaborative Marine Atlas Project (CMAP) — an open database that merges CBIOMES data with publicly available datasets from satellites and sensors and, more recently, all the other oceanographic research initiatives supported by the Simons Foundation. The atlas contains more than 10 terabytes of data, Armbrust says, all of it marked with location and time stamps to make for easy comparisons. Cleaning up the data has been a "major undertaking," she says.

Already, researchers at the University of Hawai'i have used the atlas to validate a hypothesis about how the distribution of a particular gene in the ocean correlates with the available nutrients. And Armbrust has used it to compare satellite data on the distribution of chlorophyll with measurements of physical features of the ocean. "Within moments, I could start seeing whether there was a correlation," she says.

Jesse McNichol, a postdoctoral researcher at the University of Southern California in Los Angeles in the laboratory of Jed Fuhrman, a CBIOMES principal investigator, plans to use CMAP to study how the abundance of particular types of bacteria and archaea correlates with variables such as ocean temperature and nutrients. Using new algorithms for denoising genetic data, McNichol has worked with the Armbrust lab to prepare huge amounts of genetic information about ocean microbes for inclusion in the atlas. In the future, this will

The atlas contains more than 10 terabytes of data, Armbrust says, all of it marked with location and time stamps to make for easy comparisons.

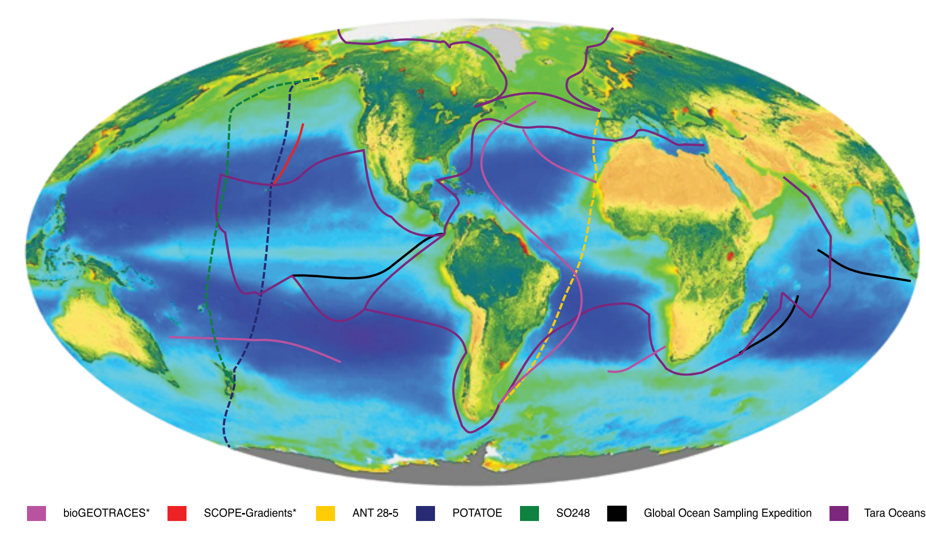
include samples from 2003 and 2016 that cover the Pacific Ocean from Alaska to New Zealand. "We can directly compare datasets that are 13 years apart, across the entire ocean," McNichol says. "Then that data will be out there and accessible to anyone."

In its first months after launch, the atlas was made available only to a few research groups for test runs. But in December 2018, Armbrust's team unveiled an early version of the system at the annual meeting of the Simons Collaboration on Ocean Processes and Ecology. "Eventually, we hope people in the broader community will use it," says Marian Carlson, director of the Simons Foundation's Life Sciences division.

This early version includes online documentation and applications for Windows and Macintosh computers in which researchers can designate the ocean region, time range and type of data they wish to examine, and then download only the data relevant to their query. The application also provides built-in data visualization tools and will eventually include a portal allowing researchers to upload their own data to the archive.

Armbrust's team has moved with amazing dispatch, says Michael Follows, an oceanographer at the Massachusetts Institute of Technology and director of CBIOMES. "I imagined it would take at least a year more than it has before we would see a working ocean atlas," he says. "I'm astonished that we're already there."

Armbrust still considers the project to be in its early stages, but its potential is already clear, she says. "Every time we do a demo to people, they're kind of blown away," she says. "It allows you to do a little dreaming about the kinds of questions you might ask."



A map of research cruise voyages that measured the abundance of certain marine microbes. Data from these cruises will be integrated into the Simons Collaborative Marine Atlas Project. The cruise tracks overlie a map of the magnitude and distribution of phytoplankton chlorophyll in the oceans and vegetation on land. In the oceans, red, yellow and green represent phytoplankton-dense regions. *Image and data provided by Jesse McNichol, the SeaWiFS Project, NASA's Goddard Space Flight Center and ORBIMAGE*

A GLOBAL APPROACH TO NEUROSCIENCE

SIMONS COLLABORATION ON THE GLOBAL BRAIN

An animal foraging for food is engaged in a complex array of mental calculations. It needs to evaluate the smells and sounds in its environment, balancing signs of food with the possibility of predators. It has to recall past foraging jaunts to note which spots have been fruitful or dangerous in the past. It has to weigh the potential reward against risks, given its current state of hunger. And, finally, it has to formulate and execute a plan of action, darting across an open field to grab a desired morsel.

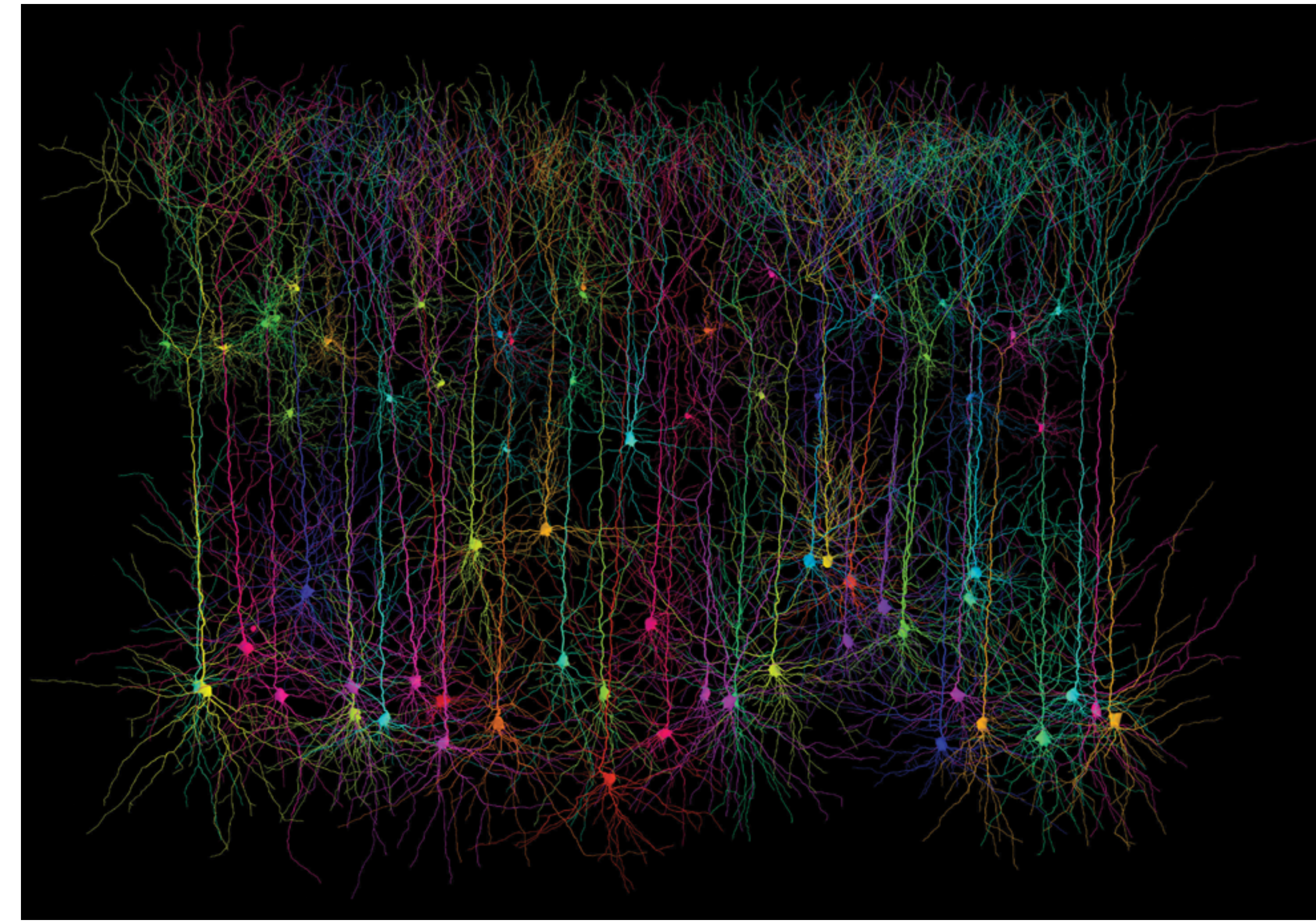
Such computations unfold simultaneously in millions of neurons that interact both locally and across multiple brain regions. Individual neuroscience labs have gained glimpses of how different aspects of cognition function, mostly within specific brain structures. But how multiple brain regions coordinate and interact to produce behavior is still largely a mystery.

Understanding how the brain produces thought requires approaches that are beyond the scope of a single laboratory. The Simons Collaboration on the Global Brain (SCGB) aims to tackle multidimensional problems such as these by bringing together researchers with the diverse expertise needed to decipher the complexities of the brain.

In 2017, the SCGB launched 20 new projects in which teams of experimentalists, theoreticians and computational experts explore some of the biggest questions in neuroscience. The largest of these is the International Brain Laboratory (IBL), a collaboration among 21 labs in four different countries. The scale of the IBL breaks new ground for a field that has typically been the domain of individual labs or a few labs working together.

"The deep problem of how activity across the entire brain produces cognition through neural coding and dynamics is a difficult one that is unlikely to be solved by any single lab," says David Tank, director of the SCGB. "The sheer scale of the number of distinct areas to be investigated and diversity of skills required to do these kinds of experiments — expertise in behavior, animal training, imaging and optics, electrophysiology, and statistical analysis of data — favors collaborations between multiple labs."

The IBL, jointly funded by the Simons Foundation and the Wellcome Trust, will focus its collective talent on the process of decision-making, starting with a task in the lab that mimics foraging. Different labs have expertise in specific brain regions and will record



A network of synthetic neocortical pyramidal cells, which are thought to be involved in cognitive function. *Image courtesy of Michael Häusser of University College London*

neural activity from those regions using a variety of tools, such as electrophysiology and calcium imaging, as a mouse makes a decision. To get a more cohesive picture of how the decision-making process works across the brain, the team will synthesize data from different groups, illuminating how information is transformed as it is transmitted from place to place. Ultimately, the group hopes to reveal how the brain integrates information from the environment, past experience and the animal's internal state to arrive at the most appropriate action, an objective impossible to achieve by studying individual parts of the brain in isolation.

That's an ambitious goal. To collate and compare data from different groups, researchers will need to train mice in four countries to perform exactly the same task. They'll need to standardize the vast amounts of data they collect and figure out how to share it, a challenging prospect for a field that has little infrastructure for such things. Though none of these issues are new to neuroscience, the IBL and other large projects are forcing neuroscientists to tackle them.

"I think the IBL, and the Global Brain collaboration in general, is heralding a partial shift in culture, providing a laboratory for how to make larger-scale collaborations work," says Loren Frank, a neuroscientist at the University of San Francisco and an SCGB investigator. "Creating groups of people who are there to work as a team and need to share data focuses energy on actually solving the problem."

One of the first major challenges the IBL faced was choosing what behavioral task to use in its experiments. With input from theoreticians in the collaboration, the group decided to focus on decision-making, in part because it already has a strong theoretical framework.

Researchers developed a task in which mice rotate a wheel according to the detection and position of a visual cue. The reliability of the visual cue can vary, mimicking the complexity of real-world decisions. "It's rare that you'd have all the facts on hand when making a decision," says Alexandre Pouget, a computational neuroscientist at the University of Geneva and an investigator with the IBL. He and others have developed computational methods for analyzing these types of decisions, which they will apply to the IBL experiments.

Researchers in different labs across two continents now have the task up and running. The next step is to monitor activity across large populations of neurons as animals make decisions. They'll use a

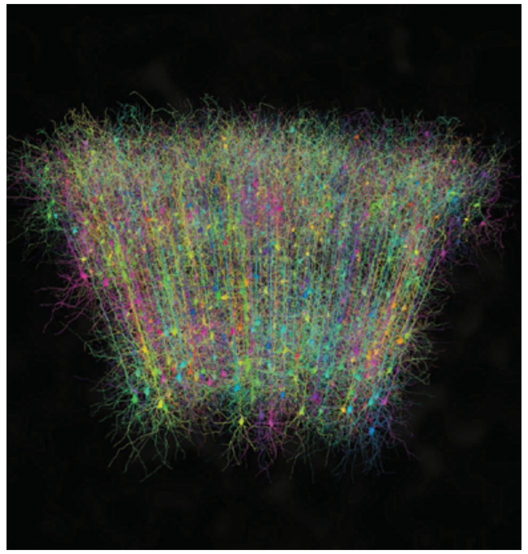
Perhaps the most profound impact that the IBL will have on the field is in providing a framework for standardizing and sharing data.

variety of methods, including a new electrode recording technology called Neuropixels, which can simultaneously record from hundreds of cells in different parts of the brain.

Each of the IBL's decision-making experiments will produce reams of data: terabyte-scale records of neural activity, behavior and other factors. One of the biggest challenges the project faces is how to make these data easily accessible to other labs. Indeed, data sharing is a huge issue for the field as a whole and only grows more urgent with the development of new data-intensive techniques.

"Data sharing in neuroscience is rare and primitive," says Liam Paninski, a neuroscientist at Columbia University and an investigator with the SCGB and IBL. Perhaps the most profound impact that the IBL will have on the field is in providing a framework for standardizing and sharing data.

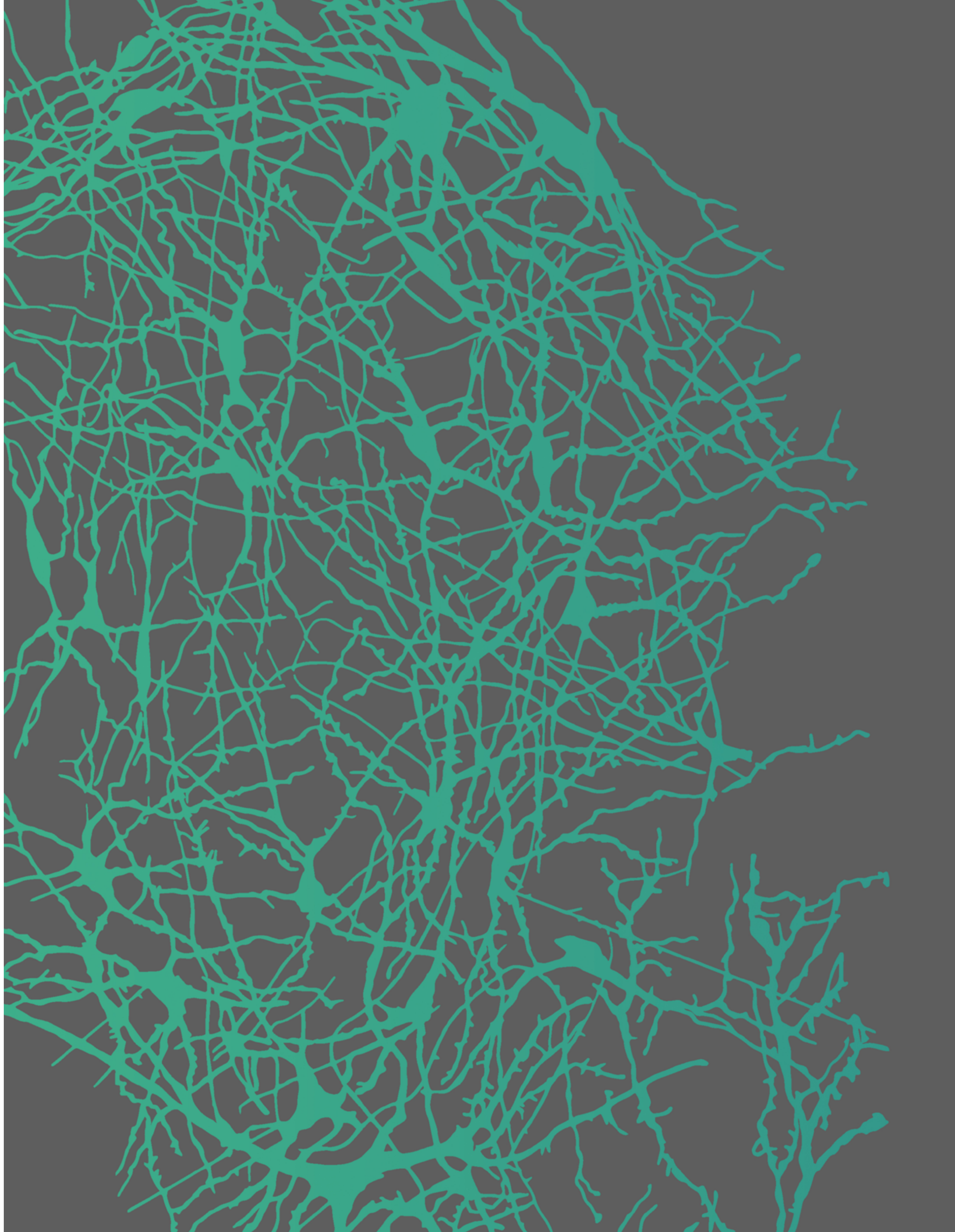
The volume of data that IBL researchers are collecting is too large to share in its raw form, so Paninski's team is developing ways to process data without losing important details, isolating essential signals from calcium-imaging and electrophysiology data so that they can be transferred to the cloud. The IBL plans to eventually make the data public so that theorists around the world can probe them for insight. Paninski hopes the tools his team develops will be adopted much more broadly than just within the IBL. "We want to develop solutions so that no one else has to worry about these problems," he says.



How do millions of neurons work together to support adaptive behavior? A new international collaboration aims to find out. *Image courtesy of Michael Häusser of University College London*

The data the IBL collects will be stored on servers at the Simons Foundation's Flatiron Institute, whose Scientific Computing Core has expertise in handling large datasets from high-energy physics, astrophysics and biology. The Flatiron's neuroscience group is also developing new tools for processing large volumes of data, particularly for electrophysiology and calcium-imaging experiments of the type used in the IBL.

Less than two years in, the IBL has only just begun its efforts. The most exciting outcomes — the first scientific results — are expected soon. But how the project solves data-sharing and other problems could be equally important for the field, providing a model for how to work closely with many labs. "People are reaching out to us all the time about how we use these tools," says Anne Churchland, a neuroscientist at Cold Spring Harbor Laboratory and an investigator with the IBL. "I'm glad we have the opportunity to be leaders in this field."



SFARI'S DATA INFRASTRUCTURE FOR AUTISM DISCOVERY

About 15 years ago, a consensus began emerging that autism is not a single condition but rather a diverse one with hundreds of different subtypes and underlying genes. Given this complexity, the Simons Foundation Autism Research Initiative (SFARI) concluded that the traditional approach to scientific discovery — in which each laboratory collects its own datasets and keeps them close to its vest — would not have sufficient power to map autism. What would be required instead were vast, shared datasets that would allow many different research groups to help fill in the picture of autism.

SFARI took on the task of creating such datasets. Crucially, it made an early decision to administer the datasets itself rather than depend on a governmental entity or an external group of investigators. Over the years, this direct stewardship has allowed SFARI to ensure that the datasets uphold the highest standards of quality and privacy, while simultaneously remaining flexible enough to meet the ever-expanding needs of autism researchers.

Today, a dedicated informatics group within the foundation distributes data from four different autism-related cohorts spanning thousands of families. The Simons Simplex Collection (SSC) is an assemblage of genetic and phenotypic data from more than 2,600 'simplex' families that have one affected child along with unaffected parents and siblings. The Simons Variation in Individuals Project (Simons VIP), recently renamed Searchlight, collects phenotypic data and biological samples from individuals with a mutation in one of more than 50 different autism-linked genes. The Autism Inpatient Collection (the only one of the four datasets that SFARI does not directly manage) is a cohort of individuals whose autism is severe enough to require long hospitalizations. Finally, SFARI's most ambitious project yet, Simons Foundation Powering Autism Research for Knowledge (SPARK), aims to collect genotypic and phenotypic data from 50,000 families.

These datasets have given rise to more than 200 published papers about autism, a figure that is "a testament to the success of these cohorts," says Stephan Sanders, a geneticist at the University of California, San Francisco. "They have had a really massive impact on the field."

The datasets not only provide resources for researchers already studying autism but also lure new researchers into the field. "It's like having very nice flowers for the bees," says Wendy Chung, SPARK's principal investigator and SFARI's director of clinical research.

Over the years, the datasets have launched a new generation of autism researchers. "My research career has been made on the back of the SSC," Sanders says. "When I look at the papers I've published, all the ones with the biggest impact have been as a result of the SSC."

Over the years, this direct stewardship has allowed SFARI to ensure that the datasets uphold the highest standards of quality and privacy, while simultaneously remaining flexible enough to meet the ever-expanding needs of autism researchers.

Mining for research gold:

Researchers can request access to the datasets through an online portal called SFARI Base. Once their requests are approved, the Simons Foundation informatics group stands ready to help them get what they need from nearly a petabyte of data. Researchers can download data to their desktop computers or run computations in the cloud that don't require massive downloads.

SFARI has invested in building a variety of online data-visualization tools to help scientists mine the data for as much research gold as possible. The Genotypes and Phenotypes in Families tool, developed by SFARI Investigator Ivan Iossifov of Cold Spring Harbor Laboratory and his collaborators, helps users search for gene variants and explore behavioral data and medical histories of participants in the SSC, Simons Searchlight and SPARK. SFARI Viewer — developed by the company Frameshift Genomics in collaboration with SFARI's informatics group and a team led by SFARI Investigator Gabor Marth of the University of Utah — allows researchers to interact dynamically with SSC and SPARK data, filtering them according to a wide array of options. Additionally, the cloud-based WuXi NextCODE SSC portal (which was not directly funded by SFARI) offers yet another way for researchers to visualize and analyze SSC data.

The informatics team's role extends far beyond helping researchers access and analyze the datasets. The team is involved in nearly every stage of the process of preparing and distributing the datasets, from filtering out errors to predicting the impact of genetic variants to integrating genomic and phenotypic data. "Many people participate in making sure the datasets are the highest quality we can reasonably make them before they are distributed to the research community," says Alex Lash, the foundation's chief informatics officer.

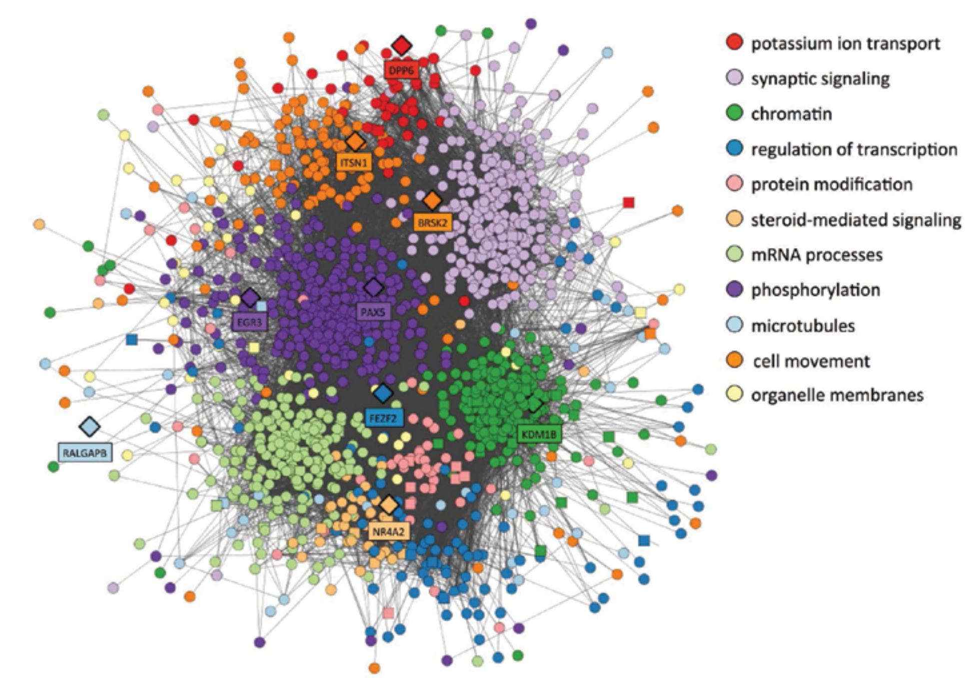
Once a research group has performed a study using SFARI data, the informatics team works to integrate the group's discoveries into the existing datasets, continually enriching each dataset with new information. This process means that even the SSC, which stopped enrolling new families years ago, remains "a gift that keeps giving," says Marta Benedetti, a senior scientist at SFARI. "There's so much that has come out and so much that can still be mined from this dataset."

Although in all cases the identity of the individuals in the datasets is kept strictly private, SPARK participants, if they agree, may be recontacted by researchers if they wish to know about follow-up studies for which they are eligible. So far, "the response from the cohort has been fantastic," Benedetti says.

Recently, this SPARK 'research match' program enabled a team led by Jacob Michaelson, an autism researcher at the University of Iowa, to contact about 5,000 families for a survey on common problems in autism, such as sleep disruptions, eating disorders and gastrointestinal problems.

"Working on our own, I'd probably be at the end of my career before I'd be able to collect this much data," Michaelson says. The research match program is a "game-changer," he says. "It's the kind of infrastructure no lab could hope to have on its own."

SFARI owes a special debt of gratitude to the families who have allowed their data to be used, says Casey White-Lehman, a supervisor and senior project manager for several SFARI cohorts. "Without them, we wouldn't have any of these cohorts," she says. "Some have been engaged with us for a decade, and we're humbled and grateful that they're willing to share their time with us."



A visualization of nine genes — DPP6, ITSN1, BRSK2, etc. — recently discovered to be linked to autism spectrum disorder based on pilot data from SPARK. Genes are colored based on their function, such as potassium ion transport, cell movement and steroid-mediated signaling, and are bundled according to associations between the genes. *P. Feliciano* et al.*/bioRxiv.org 2019*

SFARI RESEARCH ROUNDUP

Since the launch of the Simons Foundation Autism Research Initiative (SFARI) in 2003, the initiative has supported nearly 500 investigators. In 2018, SFARI Investigators studied a wide range of topics — explicating the role of missense mutations in autism, identifying a biomarker for low sociability in monkeys, and understanding how an autism-linked mutation affects brain wiring, for example. Here is some of the work of SFARI Investigators over the past year.

Sociability Boost. For decades, researchers have suspected a link between brain serotonin levels and autism. Yet trials of serotonin-increasing antidepressants as treatments for autism have proved disappointing. An August 8, 2018, study in *Nature* suggests a reason why: These drugs may not target the right brain pathway with enough specificity.

A team led by SFARI Investigator Robert Malenka of Stanford University used light to activate a particular brain pathway in mice connecting the serotonin-producing dorsal raphe nucleus to particular serotonin receptors in the nucleus accumbens, a brain region involved in rewards. Activating the pathway, the researchers found, temporarily made mice far more sociable.

And in a mouse model of autism in which neurons in this pathway lacked the autism-linked chromosomal region 16p11.2, the team again found that activating the pathway made the mice more sociable, 'rescuing' them from the effect of the 16p11.2 deletion. Malenka's team is now studying whether drugs that activate serotonin receptors directly might be more successful than previously studied antidepressants as treatments for mouse models of autism.

A Neural Pacemaker. Even when a case of autism springs from a clearly identified genetic mutation, there's a huge gap between understanding which gene is malfunctioning and repairing the damage it has caused. A new study suggests that it may not always be necessary to make this leap to treat autism. Instead, it might be possible to develop a treatment analogous to a cardiac pacemaker, which helps heart cells coordinate better instead of repairing them.

A team led by SFARI Investigator André Fenton of New York University recorded the electrical activity of neurons in the brains of mice with the autism-related fragile X syndrome. The researchers then observed the mice's "place cells" — cells in the hippocampus that keep track of where the mouse is — as the mice performed a task that involved adjusting to changing locations, something mice and people with fragile X syndrome struggle with.

The researchers reported in the February 7, 2018, *Neuron* that the mice's place cells individually processed spatial information normally but did not coordinate well with each other, often failing to form the temporary coalitions needed to perform cognitive tasks. This result suggests, Fenton said, that neuromodulation, an emerging array of techniques that apply electrical pulses to coordinate brain activity, might be useful for treating this lack of adaptability.

A new study suggests a potential biomarker for social deficits in cerebrospinal fluid: low levels of the molecule vasopressin.

Sociability Marker. Autism researchers have long looked for a stable biomarker of autism — something measurable in a person's bodily fluids or tissues that correlates with autism symptoms. Studies of blood have mostly come up empty, but a new study suggests a potential biomarker for social deficits in cerebrospinal fluid: low levels of the molecule vasopressin.

SFARI Investigator Karen Parker of Stanford University and her colleagues (including SFARI Investigators Antonio Hardan of Stanford and Elliott Sherr of the University of California, San Francisco) reported in the May 2, 2018, *Science Translational Medicine* that in naturally occurring rhesus monkey populations, the least sociable monkeys had markedly lower vasopressin levels in their cerebrospinal fluid than the most sociable monkeys did.

Compared with rodent models, monkey models of autism offer an especially promising way to study the disorder, since primates are so much closer to humans. And indeed, in a small human study, Parker's team found that children with autism also had significantly lower vasopressin levels in their cerebrospinal fluid than controls did. Parker and her colleagues have started clinical trials of inhaled vasopressin as a treatment for low sociability in autism, with encouraging preliminary results.

From Mutation to Miswiring. Recent studies have made enormous strides toward identifying the mutations that underlie autism. But these genetic variants confer autism risk through a wide variety of mechanisms, and little is known about how most of these mutations affect brain connectivity and function.

A new study illuminates this question for one of the most common genetic causes of autism: deletions in 16p11.2. SFARI Investigator Alessandro Gozzi of the Italian Institute of Technology in Genoa and his colleagues examined brain imaging data from children with 16p11.2 deletions in the Simons Searchlight cohort. They report in the July 1, 2018, *Brain* that the children have impaired connections between the prefrontal cortex, a brain region involved in social behavior and cognition, and other brain regions. This weakened connectivity correlates with low social and cognitive skills.

The team also found that mice with a 16p11.2 deletion have flawed connections between the prefrontal cortex and the retrosplenial cortex, which is involved in cognitive functioning. These mice showed a wide suite of brain impairments in the prefrontal cortex, such as miswiring of the neuronal projections connecting the region to the thalamus and a shortage of dendritic spines. The findings suggest that this mouse model may offer a faithful window into the neurobiology of people with 16p11.2 deletions.

Prioritizing Missense. Missense mutations, in which only one amino acid in a protein gets altered, are thought to underlie many cases of autism. Thousands of such mutations have been found among children with autism, but it is hard to know which of these mutations disrupt the function of the gene's corresponding protein. A new framework for prioritizing missense mutations, published on June 11, 2018, in *Nature Genetics*, aims to change that.

The study — led by SFARI Investigator Haiyuan Yu of Cornell University, along with SFARI Investigators Bernie Devlin of the University of Pittsburgh and Kathryn Roeder of Carnegie Mellon University — looked at thousands of missense mutations in children with autism and their unaffected siblings in the Simons Simplex Collection. The researchers found that not only were the children with autism significantly more likely to have a missense mutation than their siblings, but these mutations (unlike their siblings') were 27 percent more likely than chance would predict to affect a region that interacts with other proteins.

By combining experimental methods with machine-learning techniques, the team found that missense mutations resulted in about 2.5 times as many disrupted protein interactions in children with autism as in their siblings. And these disruptive mutations were more likely to impact 'hubs' — proteins that interact with multiple other proteins — than in the siblings. This protein interaction framework, the researchers argue, offers a novel way to identify which missense mutations are most likely to confer autism risk.

A genetic mutation altering just a single amino acid in a protein can affect how that protein interacts with other proteins. This illustration shows the protein interaction interface between two proteins, TRIO *(blue)* and RAC1 *(yellow)*. The orange spheres represent mutations linked to intellectual disability and microcephaly, while the red sphere represents a mutation associated with autism spectrum disorder. *S. Chen* et al./Nature Genetics *2018*

THE SPARK GAMBIT

Three years ago, the Simons Foundation Autism Research Initiative (SFARI) took a leap of faith about how best to spur the next generation of gene discovery for autism. The way forward, the initiative decided, would involve letting go of some of the core methodologies of the previous generation of autism gene discovery.

Studies of the initiative's Simons Simplex Collection (SSC) — a repository of genetic and phenotypic data from families with one child with autism — had uncovered dozens of autism risk genes since its launch in 2006 and indicated that hundreds or perhaps even a thousand different genes underlie the disorder. But these studies had simultaneously made it clear that most of the mutations that cause autism are so rare that they simply can't be pinned down in a cohort the size of the SSC, which has about 2,600 families.

To identify the majority of autism risk genes would require a much larger cohort, potentially on the order of 50,000 families. But scaling an SSC-type cohort up to 50,000 families would be completely impracticable: The SSC had carried out a meticulous deep dive into each of its families, standardizing diagnostic criteria across its many clinics and bringing each family in not just for diagnosis but also for blood samples, brain imaging and a host of phenotypic measures. Carrying this out with 50,000 families would be prohibitively expensive, and it would be impossible to recruit enough families willing to go through such a time-consuming evaluation process.

So when SFARI created SPARK (Simons Foundation Powering Autism Research for Knowledge) three years ago with a goal of recruiting 50,000 families, it dropped some of the most ambitious features of the SSC in favor of a more streamlined approach. Families would report their own professional diagnoses of autism and then just fill out online questionnaires and mail in saliva samples. Through this simplified enrollment process, SPARK has already successfully recruited about 18,000 families, and it hopes to hit its 50,000-family target by 2021.

"No one has ever done anything like this at this type of scale," says Brian O'Roak, a geneticist at Oregon Health and Science University in Portland. "When the SSC got started, it seemed like a phenomenally large number of families, but with SPARK it's a real paradigm shift."

But researchers have wondered: Will a cohort assembled in this way provide as clear a window into autism genetics as a collection such as the SSC does? After all, perhaps some of the families who report autism diagnoses to SPARK would not have satisfied

Thanks to new insights from SPARK data, the Wise family learned more about the genetics underlying their son's autism.

the SSC's rigorous diagnostic criteria. And saliva samples are often contaminated with bacteria, making genetic analyses trickier.

Now, a pilot sequencing study of the exomes — the protein-coding regions of the genome — of 457 SPARK families has suggested, happily, that the leap of faith that went into SPARK's creation was justified. Genetically, the researchers found, the families in the study seem to mirror previous autism cohorts in a host of ways — the types of mutations that appear, the mutation rate, which genes are affected, and which gene networks and biological pathways are implicated.

"I personally needed reassurance that using this form of recruitment would be worth all the energy we're putting into it," says Wendy Chung of Columbia University, SPARK's principal investigator and SFARI's director of clinical research. "The good news is, it looks like this is the case."

And as long as participants provided enough saliva, the team found, the quality of the genetic data was just as high as that from blood samples. It was even high enough in the pilot study to allow the researchers to study mosaic mutations — in which only some of a person's cells are affected by a mutation — which are typically harder to detect than mutations that affect every cell.

"Our philosophy is that as soon as it comes off the machines, we make it available, so that anyone who has a good idea can execute it quickly."

The pilot study, published on bioRxiv.org, was carried out by the SPARK Genomics Consortium, a group that includes members from each of the 25 clinical sites involved in SPARK recruitment.

About 10.4 percent of the families in the study have mutations in one of the approximately 100 genes already known to cause autism. That information has been shared with the families in question. "One of the most exciting things for me is that what we're doing has an immediate impact on families," says Tychele Turner, a postdoctoral fellow at the University of Washington who led some of the consortium's analyses.

The consortium found that approximately 1 percent of the families in the study have deletions or duplications in a chromosomal region called 16p11.2 — roughly the same proportion as in other autism cohorts. And several prominent autism risk genes, such as CHD8, also have mutations in some families.

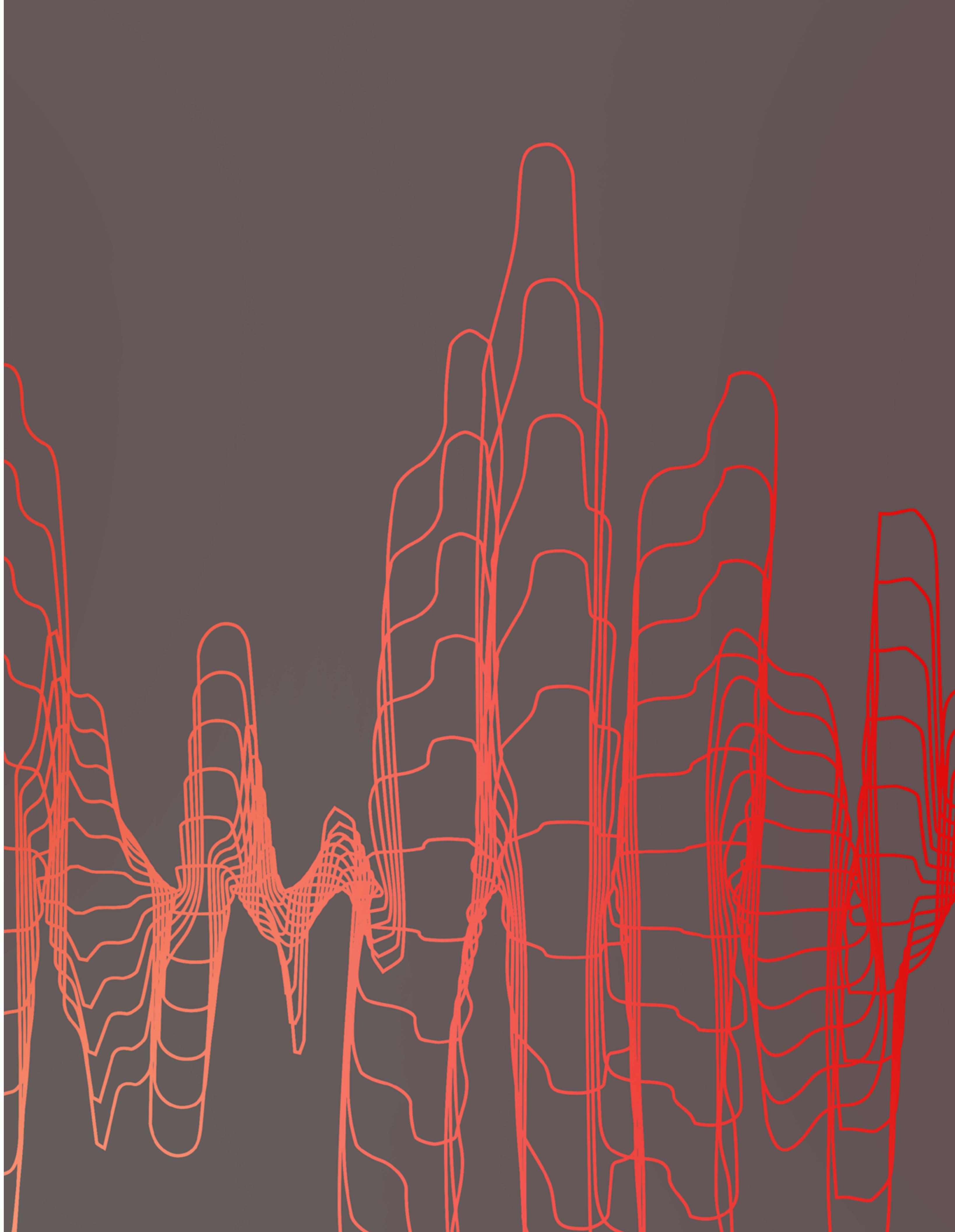
"I was pleasantly surprised at how great the pilot data were, and how similar this cohort was to the traditional, labor-intensive way of creating cohorts," says O'Roak, who led the consortium's study of mosaic mutations.

And the study identified nine new genes that appear to confer risk for autism. Not only do these genes have strong statistical evidence, but an independent systems biology approach showed that the genes have significantly more functional associations with known autism risk genes than chance would predict.

"Even though we just added 450 families, this already allowed us to discover new genetic risk factors," O'Roak says. The rate of gene discovery is likely to ramp up significantly in the near future, as the SPARK Genomics Consortium turns its attention to another 9,000 families who were sequenced in 2018. An additional 10,000 individuals with autism (and, where available, both parents) are slated to be sequenced in 2019. A statistical analysis in the pilot study suggests that sequencing 50,000 families is likely to turn up 70 to 75 percent of all autism risk genes.

SPARK made the sequencing data from 2018 immediately available to the broader autism research community, even before the SPARK Genomics Consortium could complete its own analysis of the 9,000 families.

"Our philosophy is that as soon as it comes off the machines, we make it available, so that anyone who has a good idea can execute it quickly," Chung says. "Because this is all about powering the research engine of autism to get farther faster."



SCIENCE SANDBOX: "THE MOST UNKNOWN"

"*So, this geologist walks into a physics lab ...*" sounds like the beginning of a good joke, but it's actually one of the first scenes of "The Most Unknown," a documentary film produced by Vice Media's Motherboard and funded and co-produced by Science Sandbox, an outreach initiative of the Simons Foundation. The film is not the standard science documentary, in which experts hold forth on complex scientific ideas to a lay audience — "The Most Unknown" will not leave the viewer awash in science factoids. Instead, the creators hope viewers will come away with an appreciation for science as a human endeavor, and with an understanding of the very real passion and curiosity of scientists. (Also, for the record, the geologist's attention does linger on the stalactites growing on the lab walls — and then she buckles down to learn about neutrinos.)

Microbiologist Jennifer Macalady of Pennsylvania State University descends into Italy's Frasassi Caves in search of mysterious slimes created by microbes. In "The Most Unknown," Macalady kicks off a chain of encounters between researchers tackling some of science's biggest questions. *Photo courtesy of VICE/Motherboard*

"I remember being taught science as a process of memorizing all that scientists had already learned, and seeing scientists as experts with all the answers," director Ian Cheney says. "I wanted to craft a film that would instead fill people with a sense of how much we don't know and how wondrous that is."

The creative team took inspiration for the film's structure from their extremely rich subject matter: science itself. After the opening credits, a message appears on the screen: "This is an experiment." Cheney believes science filmmakers lean too heavily on the same few storytelling conventions and that more people would be interested in science movies if

The creators hope viewers will come away with an appreciation for science as a human endeavor, and with an understanding of the very real passion and curiosity of scientists.

During the third segment of "The Most Unknown," physicist Davide D'Angelo of the University of Milan visits cognitive psychologist Axel Cleeremans of the Université Libre de Bruxelles in Belgium. In an abandoned cooling tower in the Belgian town of Charleroi, Cleeremans explains the mysterious connections between consciousness and how we interpret and interact with the world. *Photo courtesy of VICE/Motherboard*

filmmakers took more risks. "I think there is tremendous interest in science," he says. "But I don't think science storytellers are as experimental as the scientists themselves."

Cheney and the producers knew they wanted to show scientists interacting with and learning from one another, but they were concerned that scientists in the same field would end up using too much jargon and leave the audience behind. Then Cheney landed on the idea of the film as a chain of scientist 'blind dates.' One scientist would spend a few days visiting another scientist's lab, learning about the questions that keep that scientist up at night, and possibly even identifying parallels with their own work. Then the scientist who had just been visited, in turn, would pay a visit to another scientist.

Legendary director Werner Herzog served as an adviser on the film and early on suggested some ground rules, one of which was that the film should not cut away to any explainers for challenging scientific concepts. If a scientist started talking about life in a hot spring, there should be no cartoon protozoans to illustrate the point. The filmmakers could not rely on being able to add explanatory scaffolding after the fact; instead, they would extract whatever explanations they needed in situ from the scientists.

Content-wise, the film focuses on three fields of science that offer unknowns on different scales: physics, microbiology and neuroscience. The motivating questions: What is out there in the universe, and how did it get there? What is the origin of life, and where can life flourish? And how are we even able to ask these questions: What is consciousness? There were nine scientist meetings in the film; it turned out that by showing scientists plucked from their fields of expertise, the filmmakers could portray something about the nature of science more broadly.

In the first scientist interaction, geobiologist Jennifer Macalady — freshly emerged from field work in an Italian cave — visits physicist Davide D'Angelo at his subterranean neutrino lab near Milan, Italy, where he tells her about his goal of understanding dark matter. D'Angelo then, in turn, heads to Brussels to meet cognitive psychologist Axel Cleeremans, who explains the challenge of understanding consciousness and puts him in an electrode hat so he can try to control a robotic hand with just his thoughts. This chain of visits works its way across the Atlantic, eventually getting as far as Mauna Kea in Hawai'i before ending in Puerto Rico, where Yale University psychology professor Laurie Santos is studying the cognitive abilities of monkeys that inhabit Cayo Santiago island.

The scientists had no idea what to expect from the project when they first signed on. All were open to new experiences and decidedly passionate about their work, but the creative team gave them information on a 'need-to-know' basis only. They were told where they would be going and what broad field of science they would be learning about, but they didn't learn their host scientist's name or any specifics of their research until they arrived. "We wanted them to be seeing and learning something for the first time, alongside the audience," Cheney says. "I was pretty much in the dark," punned Macalady about her visit to the dark-matter lab.

Though each scientist met only one or two other scientists during filming, they have all been in touch via email since filming concluded. Many met later at screenings, and Macalady and Montana State University astrobiologist Luke McKay have even started a project together. But the main outcome for the scientists hasn't been in collaborations but in sharing the process of science with one another and the broader public, and in coming to a greater understanding of what they have in common as scientists. Cleeremans says he has enjoyed connecting more broadly with scientists who are interested in outreach and seeing how they explain their work.

Macalady agrees. "One of the most exciting things I took away was how much potential there is for better science communication through partnerships with people who are willing to spend a little time and invest a little in each other," she says.

If the film was an experiment, then, what were the conclusions? First, the scientists had fun. "I'd do it again in a heartbeat," McKay says. Also, critical reception was positive, with reviews often citing how the film emphasizes how important curiosity is to the scientific endeavor. And the viewership numbers on Netflix are good. Cheney has participated in several public screenings and is gratified by the audience response. "It's fun to be with an audience who is laughing and learning together, and I think the raw joy of the scientists really comes across," he says. "It's had a much bigger reach than we ever imagined it would."

Microbial residents of scalding hot springs in Nevada's Black Rock Desert produce vivid colors. The heat-tolerant microbes provide insights into where life could survive on other planets. *Photo courtesy of VICE/Motherboard*

"I wanted to craft a film that would instead fill people with a sense of how much we don't know and how wondrous that is."

MATH FOR AMERICA: THE MULLER AWARD

Exceptional math and science teachers in schools across New York City form the close-knit community at the heart of Math for America (M*f*A). The organization, founded in 2004, fosters opportunities for the teachers to learn and share with one another by attending and presenting workshops, traveling to conferences, and building connections with their peers. M*f*A teachers demonstrate leadership not only within the M*f*A community but also in their schools and beyond.

In 2018, M*f*A launched its latest initiative to recognize teachers who make an outsize impact on the profession. The M*f*A Muller Award for Professional Influence in Education, named for board member Peter Muller, goes to one math teacher and one science teacher who have not only become leaders in the M*f*A community but also influenced the teaching profession in exceptional ways.

Seth Guiñals-Kupperman, a physics teacher at the Brooklyn Latin School, and Patrick Honner, a math teacher at Brooklyn Technical High School, were the first recipients of the award. Recipients receive a cash prize, and, to encourage nominations, M*f*A provides a cash award to the institution of each winner's nominator.

Guiñals-Kupperman and Honner "have taken what they've done at Math for America and influenced education in a profound way outside of the Math for America community," says John Ewing, president of M*f*A. "Their influence extends far beyond M*f*A and their schools."

Both Guiñals-Kupperman and Honner are M*f*A Master Teachers — truly expert teachers who enjoy a four-year fellowship awarded after a rigorous selection process. M*f*A Master Teachers receive a yearly stipend and participate in — and in some cases lead — the hundreds of workshops and seminars offered by M*f*A each year on topics ranging from math or science to pedagogy or policy, including equity and social justice in schools. M*f*A Master Teachers also help mentor M*f*A Early Career Fellowship recipients, providing promising public secondary school mathematics and science teachers with the support they need to become top educators. Only M*f*A Master Teachers in their second or higher fellowship are eligible for the Muller Award.

M*f*A Master Teachers hold steady at about 1,000 each year: approximately 10 percent of the public math and science teachers in New York City. M*f*A Master Teachers may apply to renew their fellowships, and some, such as Guiñals-Kupperman and Honner, have participated for multiple cycles.

M*f*A gives its most accomplished teachers 'lateral opportunities' — for example, to write about their work for broad audiences of students and teachers, give presentations, and run workshops — helping them to grow professionally without taking them out of their

The award, to be given annually, goes to one math teacher and one science teacher who have not only become leaders in the M*f*A community but also influenced the teaching profession in exceptional ways.

classrooms. Experienced M*f*A Master Teachers such as Guiñals-Kupperman and Honner often lead M*f*A seminars and workshops and may become involved in the broader national conversation about math and science education, both online and off.

Guiñals-Kupperman has been teaching for 15 years, five of them as an M*f*A Master Teacher. His first experience with M*f*A came before it expanded into science, when he tagged along with an M*f*A Master Teacher to an M*f*A talk. "It blew me away," he says. The next year, when the program opened up to science teachers, he was part of the first cohort of science teachers accepted. Guiñals-Kupperman works on giving his students the tools to explore and discover science for themselves rather than relying on him for answers. "A big part of my focus is making myself somewhat redundant," he says.

At M*f*A, Guiñals-Kupperman has facilitated workshops on modeling instruction, obtaining National Board Certification and understanding energy through graphical representation. He also serves as a mentor and adviser to M*f*A Early Career Teachers of science and is a part of the New York State Master Teacher Program. His influence on physics education across New York City has been substantial.

Guiñals-Kupperman has also participated in teacher-exchange programs with Brazil and India and has visited other countries, such as Iceland and South Korea, to observe teaching there as well. Although pedagogical strategies do not always translate across borders, he found the experiences illuminating: He was particularly struck by the differences in prestige of the teaching profession and the treatment of teachers in different countries. It's rare to feel the same respect here as in other countries with top education systems, he says, but M*f*A gives teachers a place where they receive prestige and respect. Of the Muller Award he says, "I was personally moved that this organization that means so much to me saw what I was doing and recognized its value."

Honner's impact on teaching has taken a different route. Through his popular blog, patrickhonner.com, and his work with M*f*A, Honner started writing for *The New York Times* Learning Network and *Quanta Magazine*, where he shares resources for teachers and students related to recent breakthroughs in mathematics research. He enjoys the challenge of finding ways to fit new math research into the middle and high school curriculum. Now in his 13th year as an M*f*A Master Teacher, Honner appreciates the relationships he has developed with fellow M*f*A teachers and mathematicians. "It's influenced every part of my professional life," he says. "It's a constant source of inspiration for me."

At M*f*A, Honner leads content-focused courses on mathematics and computer science. For example, he ran an M*f*A session on the problem of finding all the types of pentagons that can tile a plane, unpacking the problem for other middle school and high school teachers.

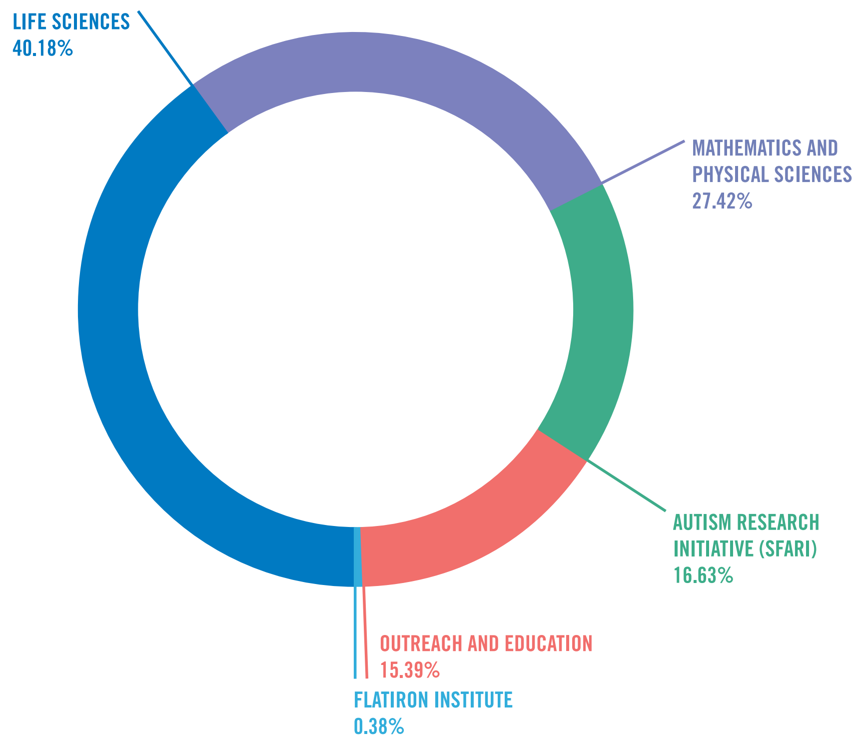
Honner's work in the online math community has led new and prospective teachers around the country to reach out to him for advice. Honner hopes the organization and award will continue to challenge teachers to improve. "What excites me the most about the Muller Award is that I think it will encourage and inspire teachers to think more intentionally about their impact outside of their schools," he says.

He appreciates the leadership opportunity he has been given via M*f*A and more generally the way the organization helps elevate the status of the profession. The career ladder for successful teachers often leads to administration — not ideal for teachers who fundamentally love the classroom. "If you love teaching, you want to be with students," Honner says. That's where he stays.

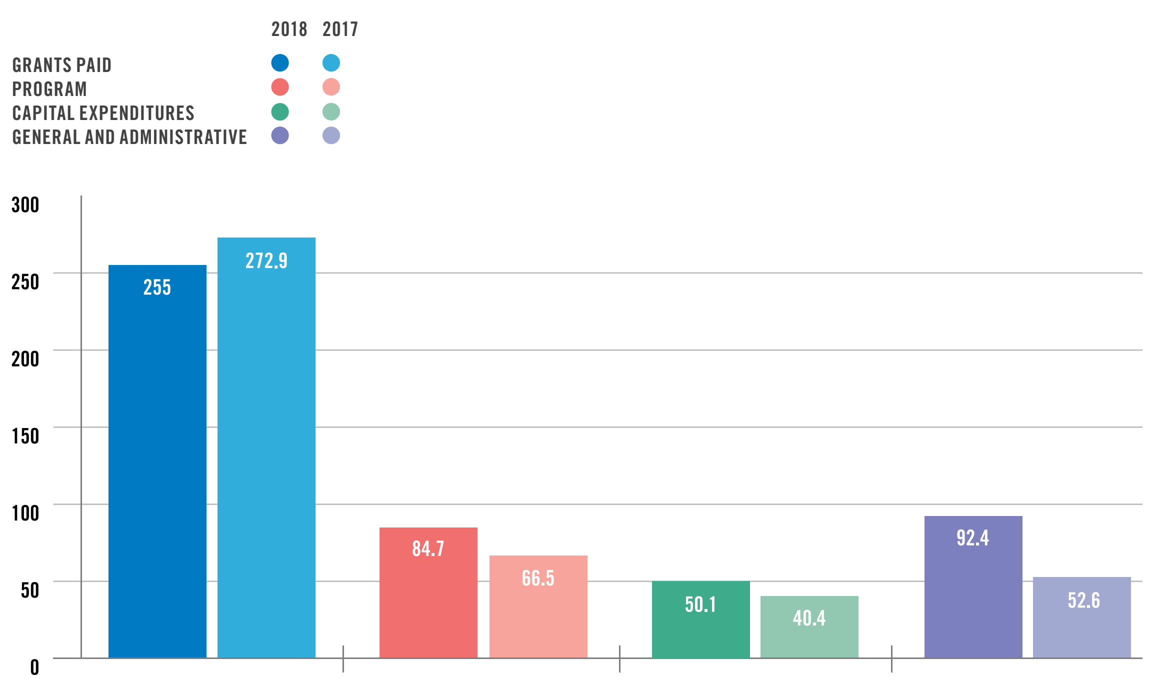
Patrick Honner, a math teacher at Brooklyn Technical High School, accepts the Math for America Muller Award for Professional Influence in Education.

FINANCIALS

2018 GRANT PAYMENT BY CATEGORY



PROPORTIONS OF EXPENSES (CASH BASIS) $'S IN MILLIONS



BALANCE SHEET

ASSETS	12/31/18*	12/31/17
CASH AND CASH EQUIVALENTS	174,076,804	247,842,259
INVESTMENT PORTFOLIO	3,037,424,892	2,821,089,741
PROPERTY AND EQUIPMENT, NET	428,870,518	246,719,463
OTHER	11,530,786	1,679,345
TOTAL	**3,651,903,000**	**3,317,330,808**

LIABILITIES	12/31/18*	12/31/17
ACCOUNTS PAYABLE	16,275,462	13,267,614
TAXES PAYABLE	554,470	10,692,873
GRANTS PAYABLE	493,723,168	545,446,555
MORTGAGE AND LEASE LIABILITIES	263,556,310	153,987,838
DEFERRED EXCISE TAX LIABILITY	11,812,706	11,812,706
TOTAL	**785,922,116**	**735,207,586**

NET ASSETS	**2,865,980,884**	**2,582,123,222**

INCOME STATEMENT

REVENUE	FOR 12 MONTHS ENDED 12/31/18*	FOR 12 MONTHS ENDED 12/31/17
CONTRIBUTIONS	222,000,000	221,459,214
INVESTMENT INCOME	397,963,903	446,263,215
TOTAL	**619,963,903**	**667,722,429**

EXPENSES	FOR 12 MONTHS ENDED 12/31/18*	FOR 12 MONTHS ENDED 12/31/17
GRANTS PAID	255,035,314	272,920,016
CHANGE IN GRANTS PAYABLE	(53,837,678)	19,124,031
PROGRAM	91,113,386	76,602,641
GENERAL AND ADMINISTRATIVE	24,554,323	23,441,724
DEPRECIATION AND AMORTIZATION	15,737,666	11,321,845
TAXES	3,503,230	5,322,414
TOTAL	**336,106,241**	**408,732,671**

NET INCOME	**283,857,662**	**258,989,758**

* Unaudited financial statements

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Aaron Wong
Annie Wong
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