SIMONS FOUNDATION

Annual Report

2017 Edition

TABLE OF CONTENTS 2017

UNCERTAINTY BY DESIGN

The theme of the Simons Foundation 2017 annual report is 'uncertainty': a concept nearly omnipresent in science and mathematics, and in life. Embracing uncertainty, we designed the layouts of these articles using a design algorithm (programmed with only a few constraints) that randomly generated the initial layout of each page.

You can view additional media related to these stories by visiting the online version of the report at simonsfoundation.org/report2017.

COVER

This illustration is inspired by the interference pattern produced by the famous 'double-slit experiment,' which provides a demonstration of the Heisenberg uncertainty principle. That principle, a hallmark of quantum physics, states that there are fundamental limits to how much scientists can know about the physical properties of a particle. The more precisely scientists learn the momentum of a particle, for instance, the less they can know about the particle's position, and vice versa.

LETTER FROM
THE PRESIDENT
AND FROM
THE CHAIR

On September 6, 2017, in a small morning ceremony, the Simons Foundation inaugurated its new in-house research division, the Flatiron Institute. The guest of honor, New York Gov. Andrew Cuomo, stirred the audience of scientists and mathematicians gathered in the institute's lobby with the words, "I'm worried about the world that we're leaving our kids. It's much more complex, the problems are much more difficult, and it's only getting worse, and many of the solutions, I believe, are going to lie in the work that you do." They were inspiring — and motivating — words indeed for a challenging world full of uncertainty.

For tens of thousands of years human civilization has endeavored to reduce uncertainty and unpredictability. The development of agriculture addressed the question of where our next meal would come from, and the taming of fire assured us we would not freeze to death during an unexpectedly cold night. As time went on, the rain god and the witch doctor gave way to the meteorologist and the M.D. In recent centuries, science has played an increasingly large role in reducing uncertainty, and, in fact, to a great extent it is uncertainty itself that has driven science forward.

For the scientist, the concept of uncertainty includes the degree to which something is known. By systematically studying our natural and physical world, scientists chip away at uncertainty, replacing outmoded theories with more accurate ones. As Edwin Powell Hubble depicted this process and its concomitant mindset back in 1939, "The scientist explores the world of phenomena by successive approximations. He knows that his data are not precise and that his theories must always be tested. It is quite natural that he tends to develop healthy skepticism, suspended judgment, and disciplined imagination."

Through our funding of basic science research, the Simons Foundation supports this rigorous process of investigation, this management of uncertainty. We are interested in fundamental questions about our universe, about life on our planet and about the mysteries of our own bodies and brains. And we are always intent on deepening our knowledge of mathematics, the lingua franca of science. By funding our own in-house computational research division, the Flatiron Institute, and by awarding grants to external scientists through their institutions, we strive to advance the frontiers of research in mathematics and the basic sciences.

In this 2017 annual report, you will read about the launch of the Flatiron Institute, and about the research being conducted there to better analyze neuronal activity, to predict the dynamical behavior of materials and molecules, and to analyze important astronomical events. From our grant-making division, you will read about how geoscientists are helping us to piece together the mystery of the origins of life. You will also see stories about the geolocation system of the brain, the basic science of autism, and how three Simons Investigators are grappling with the uncertainties inherent in physics and quantum computing.

The vision and guidance for all of these programs comes from an outstanding leadership team of scientific directors. In a special section, they each reflect on their work and the uncertainties they manage in helping this enterprise to do all that it does. Their deep scientific knowledge and managerial experience is invaluable to the foundation.

Every day, we feel eager to come to work at the foundation because it teems with intellectual activity — and we say that with certainty! We hope that as you read through this report you will enjoy the excitement of learning about the fruits of uncertainty.

Marilyn Hawrys Simons, Ph.D.
President

Jim Simons, Ph.D.
Chair

FLATIRON INSTITUTE INAUGURAL CELEBRATION

Within a brisk five-year period, the Simons Foundation's new Flatiron Institute has grown from the germ of an idea floated at a foundation scientific retreat in 2012 to a large, bustling hub for developing computational methods. In a ceremony on September 6, 2017, Simons Foundation co-founders Jim and Marilyn Simons and keynote speaker New York Gov. Andrew Cuomo joined Flatiron Institute and Simons Foundation leaders to dedicate the new research division of the Simons Foundation. The event, held in the institute's newly renovated lobby, celebrated early progress and hopes for the future.

The Flatiron Institute is located just across the street from the Simons Foundation and was launched to advance scientific research through computational methods, including data analysis, modeling and simulation. At full capacity, the institute will house around 250 scientists and programmers across four research centers and a computing core. "This is a unique place where top people sharing a common interest in the growing impact of computation on science will exchange ideas across scientific fields," says Antoine Georges, director of the new Center for Computational Quantum Physics (CCQ) at the Flatiron Institute. The institute "could lead to big leaps forward in both fundamental understanding and new algorithmic methods."

"We are already becoming a place where people come to learn new algorithms and approaches," says David Spergel, director of the Center for Computational Astrophysics at the Flatiron Institute. "Because of the way we span fields, we have the potential to be a unique place in transferring information, approaches and techniques between areas."

The dedication event capped a year of hiring and startup milestones for the growing institution. Following the ceremony, Cuomo toured the institute's working areas and spoke with Flatiron Institute staff scientists about their work. Although several floors of state-of-the-art workspaces had already emerged from behind construction walls, remodeling continued in the rest of the building. In the offices, researchers have already established the institute's reputation with innovative software releases and important scientific discoveries.

"I couldn't be happier about progress in the Flatiron Institute," Jim Simons says. "The scientific output of Flatiron is remarkable and has exceeded my most optimistic expectations."

The institute's mission is an important one for New York, Cuomo said during the ceremony's keynote address. Computational science "is where we need to grow and flourish," he said. "It's not just what New York state needs, it's what the world needs."

The Flatiron Institute provides a permanent home for professional scientists focused on the development of novel computational, mathematical and analytical techniques and software, says Leslie Greengard, director of the institute's Center for Computational Biology. "Few existing academic institutions have developed a track for such people, especially at the scale of the Flatiron Institute. None have done so with such a broad scope in a single location."

The Flatiron Institute's New York home offers unique opportunities for collaboration, Spergel says. "It's a place where we're surrounded by great universities and where we have the opportunity to partner with them." In fact, many senior researchers within the institute have joint appointments at nearby universities, including New York University, Columbia University, Princeton University and Stony Brook University. "Our unfair advantage is New York," he says.

The institute began as the Simons Center for Data Analysis (SCDA), launched in 2013 under Greengard's leadership. SCDA focused on analyzing the increasingly vast datasets produced by biological research. With the success of this venture, its scope expanded. In 2016, SCDA transformed into the Center for Computational Biology and became the first center of a new organization: the Flatiron Institute. That same year, the Center for Computational Astrophysics launched and began modeling the cosmos and analyzing astronomical datasets.

The youngest center, the CCQ, began operations in September 2017. Led by Georges and co-director Andrew Millis, the center develops new numerical and analytical methods to solve the quantum many-body problem and uses the solutions to predict the behavior of materials and molecules. The Flatiron Institute will name a fourth and final center — focusing on a soon-to-be-decided discipline — in 2018.

A unique and crucial part of the institute's framework is the Scientific Computing Core, which develops the organization's computing infrastructure and collaborates with Flatiron Institute scientists to create and implement new computational and statistical tools for use across the scientific community. Co-directed by Nick Carriero and Ian Fisk, the core hosts an on-site computing cluster comprising 7,000 cores. Two off-site supercomputers at Brookhaven National Laboratory and the San Diego Supercomputer Center at the University of California, San Diego, lend additional processing power, which will continue to grow. In aggregate, Flatiron researchers currently have access to 28,000 processor cores hosted over the three computing facilities, a variety of specialized resources — including general-purpose graphics processing units and visualization walls — and 10 petabytes of storage space.

"The support of the Simons Foundation permits us, as best we can, to ensure that the research community is only limited by their imagination and their initiative, and not by the computing resource requirements and technology," Fisk said during the dedication ceremony.

> "The scientific output of Flatiron is remarkable and has exceeded my most optimistic expectations."


Marilyn Simons, Gov. Andrew Cuomo and Jim Simons cut the ribbon during the Flatiron Institute's inauguration ceremony. Also pictured, from left to right, are center leaders Leslie Greengard, David Spergel and Antoine Georges.

Flatiron Institute researchers don't have to apply for grants, freeing them to pursue long-term projects that might not be possible if continued funding were uncertain. The financial model also means that software developed at the Flatiron Institute is freely available to all scientists and is built to last, receiving long-term support and continued development. That's in contrast to other scientific software that typically is abandoned when funding runs dry or the student responsible for the code graduates.

The institute's rapid growth has already shifted the staff composition of the Simons Foundation as a whole, which, a short time ago, focused only on grant-making. The addition of an in-house research organization has influenced other divisions of the foundation, notes Simons Foundation President Marilyn Simons. Institute scientists regularly mingle with fellow foundation employees at lectures, lunches and staff meetings.

"Adding internal researchers to our organization has been inspiring to all of us working at the foundation," she says. "Their creativity, dynamism and intellectual depth has transformed our environment and given us all the opportunity to share in the experience of scientific research."

CENTER FOR COMPUTATIONAL QUANTUM PHYSICS
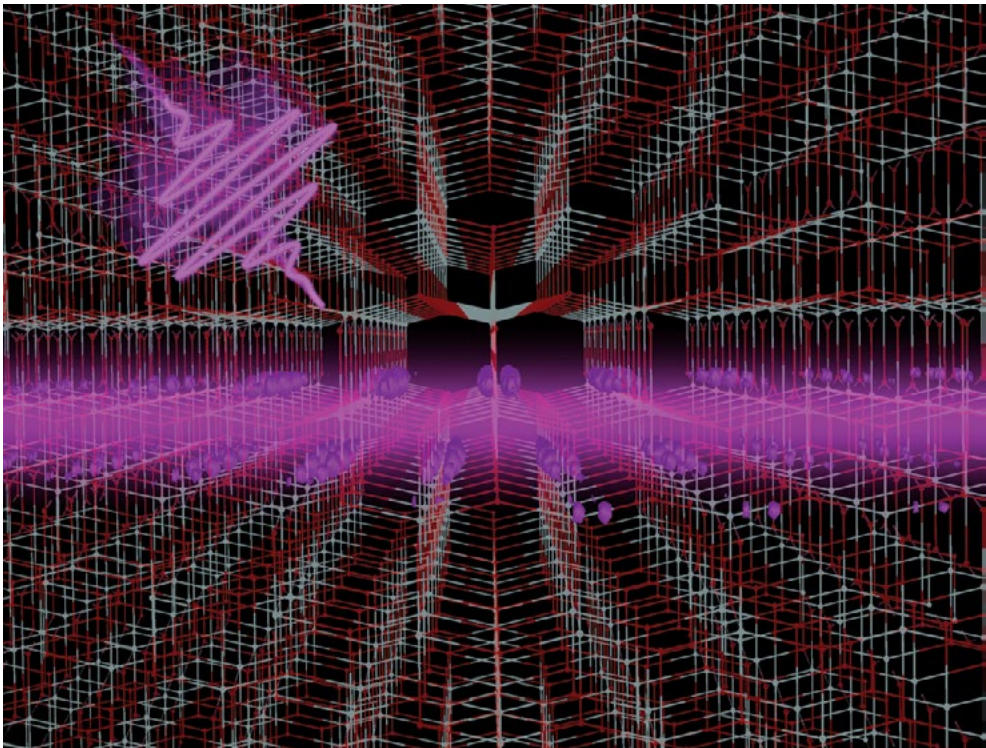
From early stone tools to silicon computer chips, materials have defined humankind's progress. Electrons, discovered in 1897, are chiefly responsible for the physical properties of molecules and materials. The behavior of these charged particles determines why some metals hold an edge whereas others are pliable, why some substances react and others are inert, and why some materials conduct electricity and others insulate.

If scientists could model and predict how large numbers of electrons behave with one another, they could potentially custom-design arrangements of atoms with fantastic properties, such as high-temperature superconductivity, high-density energy storage and high-efficiency hydrogen fuel generation. They might even uncover new properties that defy current understanding.

Overcoming the complexities of the quantum world presents a daunting challenge, which a new research hub aims to meet. The Center for Computational Quantum Physics (CCQ), which launched at the Flatiron Institute in September 2017, is developing the theoretical understanding, algorithms and computational tools needed to bridge quantum mechanics and the behavior of molecules and materials.

"We are not a materials research center," says CCQ director Antoine Georges. "That's what makes us unique in comparison with places that apply existing methods to materials. We're taking the problem from its foundation, from the basic computational, mathematical and physical point of view. We're devising new concepts and new methods."

Understanding and potentially controlling material properties is difficult because of the inconceivable number of electrons involved. A quantum system comprises all possible configurations, or states, of its particles, and the number of quantum states rises exponentially with the number of particles. A teaspoon of copper, for instance, contains more than 10 trillion electrons — that's a lot of potential states.

The CCQ's scientists can't simplify the problem by extrapolating from the behavior of a single electron. In quantum physics, electrons can become entangled with one another. Once entangled, particles can no longer be treated individually, even when physically separate. The collective behavior of entangled electrons therefore drastically complicates the problem. Currently, 'brute-force' methods that incorporate entanglement by considering every potential interaction between every electron can handle only two or three dozen electrons at once. Many useful material properties, such as magnetism and superconductivity, only arise with millions or hundreds of millions of particles.

"There's no way direct, brute-force simulation can work" for this problem, says Georges, who is also a professor at the Collège de France. "It's not a matter of waiting for better computers. You'll perhaps get an additional electron every few years, so you're not going to get to trillions of electrons anytime soon."

Luckily, alternatives to raw computational muscle exist. Under the leadership of Georges and center co-director Andrew Millis, also of Columbia University, the CCQ leverages computational methods to overcome the so-called 'many electron problem' and predict the behavior of molecules and materials. The center's focus on developing new methods and algorithms sets it apart from research universities and government labs, Georges says. Those institutions focus on shorter-term projects, whereas algorithm and code development can take years of continued tinkering and support.

"There hasn't been the right incentive structure in the field to keep the best programmers or algorithm developers around," says CCQ research scientist Miles Stoudenmire. "Programming just isn't as important elsewhere. At CCQ, it's front and center."

The unfulfilled need for an organization such as the CCQ helped drive its selection as the third Flatiron Institute center. The Simons Foundation had already made inroads into the field through the Simons Collaboration on the Many Electron Problem, which Millis directs, and recognized the great need for new computational methods to advance materials science.

Georges and Millis take a project-based approach to the organization of the CCQ. Some of the center's current projects develop machine-learning methods, investigate strong light-matter coupling and build software tools. This structure gives researchers more flexibility as they navigate an uncertain path toward resolving the many electron problem, says Angel Rubio, CCQ distinguished research scientist and managing director of the Max Planck Institute for the Structure and Dynamics of Matter in Hamburg, Germany.

"If you want to be revolutionary and open new avenues, you have to tackle things that are unknown," he says. "Of course, you have an agenda; you know what you want to solve. But in this process, you might deviate toward something that's even more interesting than what you hoped to solve. That's the beauty of CCQ — we're not forcing the people to keep the originally proposed path. We're allowing the exploring of all possibilities."

One promising avenue for overcoming the many electron problem is the use of a mathematical concept called a tensor network. The method organizes information about a quantum system into bundles called tensors. Quantum entanglement connects the tensors into a network. For systems with a simple, regular structure, tensor networks allow researchers to approximate the system using exponentially less computational power. The approach is akin to the compression of video files, says Stoudenmire, who studies tensor networks.

Shortly after the CCQ's launch, Stoudenmire hosted a workshop that attracted tensor network experts from around the world. The event, which included non-physicists, demonstrated that tensor networks offer unexpected potential for technologies such as artificial intelligence, he says. "Physicists have been working in this niche area developing this incredible mathematics just to solve this one tough physics problem that we have. But maybe along the way we've developed something more generally useful."

Fostering collaboration through events such as the tensor network workshop is critical to the CCQ's mission, Millis says. Events offer a chance for CCQ members to mingle with other researchers in the field — both theorists and experimentalists.

"This field needs close contact with experiment, or it becomes sterile," Millis says. "It's a testament to the poverty of our imaginations and the limits of our computational ability. Every few years, the field throws up a complete surprise, a class of materials that do something that nobody expected. With better theory, we're trying to reduce the number of those surprises."

CENTER FOR COMPUTATIONAL ASTROPHYSICS: NEUTRON STAR MERGERS

About 130 million light-years from Earth, the relics of two exploded stars neared the end of a spiraling, dyadic dance around each other. The dance partners were incredibly dense neutron stars: Just a teaspoonful of their neutron-rich star stuff has a mass of about 1 billion metric tons.

Over time, the stars drifted toward each other and picked up speed. Just before collision, each orbit took fractions of a second. Then came the big finale: a final merger that sent ripples through the fabric of space-time and the astrophysics community. On August 17, 2017, scientists at the Advanced Laser Interferometer Gravitational-Wave Observatory (LIGO) in the United States detected the gravitational waves that emanated from that cosmic collision.

The event turned out to be the "cosmic gift that keeps on giving," says astrophysicist Samaya Nissanke, of Radboud University Nijmegen in the Netherlands. Observations of the merger ushered in a long list of firsts: The event was the first direct sighting of two neutron stars slamming together, the first confirmation that such collisions produce vast amounts of heavy elements, such as gold, and the first time scientists identified both gravitational waves and light coming from the same cosmic event. The only previously detected gravitational waves had originated from merging black holes, which scientists don't expect to produce light.

Those discoveries led 44 of the world's top neutron star experts to gather in November at a three-day workshop hosted by the Flatiron Institute's Center for Computational Astrophysics (CCA) to discuss what scientists know — and don't know — about neutron star mergers.

The meeting was the first time experts from around the world were able to assemble following the public announcement of the neutron star merger a mere month before. Flatiron's expertise, facilities and resources enabled the meeting to come together that quickly, says meeting organizer Matteo Cantiello, an associate research scientist at CCA. "We were able to rapidly attract people faster than other groups could, to talk about where we stand in terms of understanding this phenomenon that we've never seen before."

The early fall meeting buzzed with excitement: The neutron star merger marked the beginning of the era of 'multi-messenger astronomy,' in which both gravitational waves and light can reveal insights into the same event.

"This event brought us into a whole new regime of understanding," says Jennifer Barnes, an astrophysicist at Columbia University. "For me, at least, this was the first time I was exposed to some new ideas and interpretations of the event. The meeting highlighted just how many open questions there are. It helped clarify the landscape of uncertainties and questions and ongoing debates."

In the immediate aftermath of LIGO's detection of the neutron star merger, scientists paired the measurements with data from Advanced Virgo in Italy (another hunter of gravitational waves). The combined data allowed scientists to triangulate where in the sky the gravitational waves originated. Within 11 hours of the initial gravitational wave observations, astronomers spotted the afterglow of the neutron star merger in a galaxy about 130 million light-years from Earth. "This was a stupendous event for astronomers," astrophysicist James Lattimer of Stony Brook University said at the Flatiron meeting.

The first day of the meeting at the Flatiron Institute focused on the discovery and the scientific theories it quashed or confirmed. Observations suggest, for instance, that the neutron star merger spewed heavy elements such as silver, platinum and uranium into space, including the equivalent of 10 Earth masses' worth of gold. That abundance of heavy elements points to a previously proposed mechanism called the r-process, in which neutrons cram into an atom's nucleus faster than the atom can undergo radioactive decay. Scientists believe the r-process is responsible for much of the gold on Earth. If neutron star mergers are rare, the gold in a galaxy might be patchy, rather than evenly distributed.

Other observations agreed with theoretical predictions as well, such as that neutron star mergers generate the bright flashes of gamma rays that puzzled scientists for decades. Theoretical astrophysicists, it seemed, had gotten a lot of things right.

"The first day of the meeting, there was a feeling like there's nothing to be done here. We can just pat our backs and head home," Cantiello says. That feeling didn't last, though. "The day after, there were a lot of interesting talks that changed the mood. There was a lot of controversy about how much we understand about aspects of this event."

The uncertainty built over the second day's presentations, culminating in an open discussion that evening. Brian Metzger, an astrophysicist at Columbia University, led the group through a list of significant questions about neutron star mergers, each accompanied by a list of possible answers. After each question, the scientists in attendance voted by a show of hands on which answer they thought was correct.

"This is known to lead to correct scientific hypotheses," joked one of the participants.

Some of the questions had a definite answer. Everyone agreed, for instance, that the event spotted in August was a merger of two neutron stars, rather than something else, like the merger of a neutron star and a black hole.

Other questions, though, lacked clear-cut answers. The observed gravitational waves generated by the merger reached peak intensity 1.7 seconds before the burst of gamma rays. Because both gravitational waves and gamma rays travel at the speed of light, the time gap was a surprise.

"It's an interesting question as to why we had such a delay," says astrophysicist Bruno Giacomazzo of the University of Trento in Italy. "It's not something we expected, and it's not something we can confidently explain right now. We still have a lot of things we don't understand."

That lack of certainty isn't a bad thing, Cantiello says. "At the end of the meeting, people were happy because there seems to be an understanding both that scientists have done an amazing job and that there is more work to be done," he says. "People want there to be stuff to be done. People have a passion for astrophysical puzzles. If everything is understood, you have to move on to another problem."
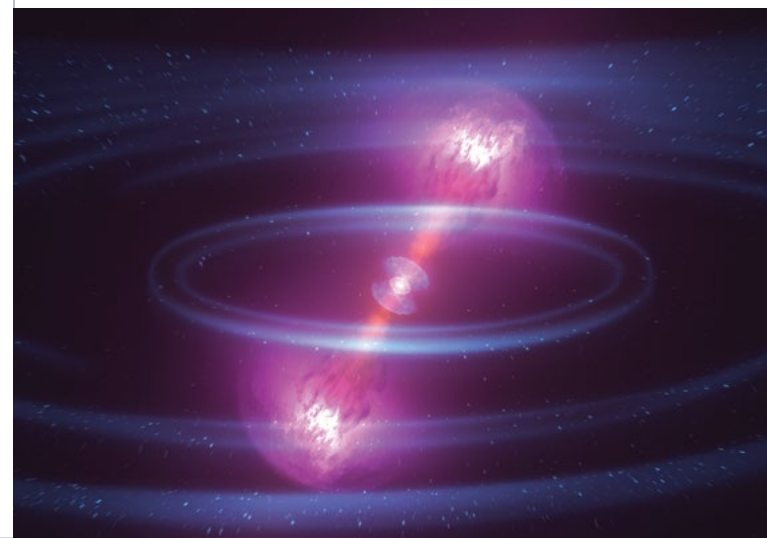
CENTER FOR COMPUTATIONAL BIOLOGY: NEURONAL MOVIES

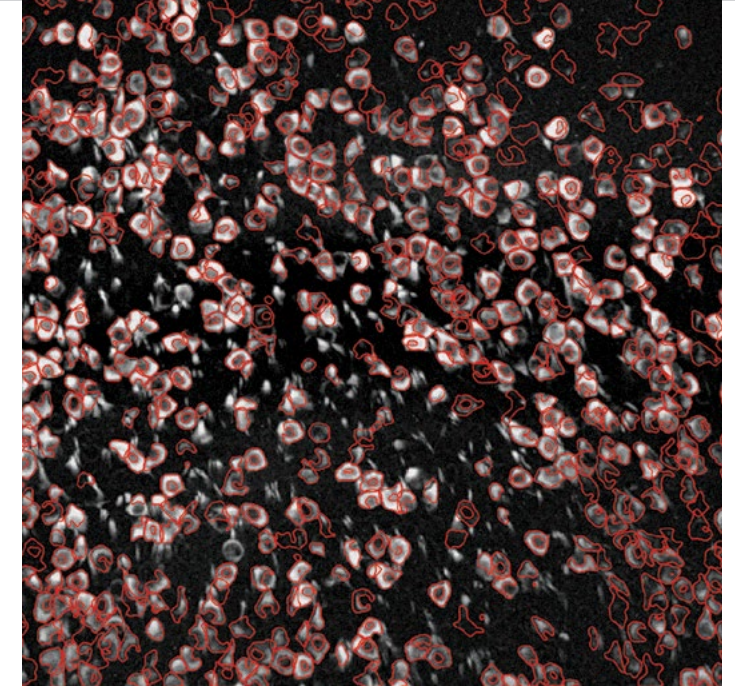In late 2012, Eftychios Pnevmatikakis — then a postdoctoral researcher in statistical analysis of neural data at Columbia University — began working on a challenge he thought would be key to neuroscience research in the coming years: how to handle the flood of data emerging from 'calcium imaging' of animals' brains.

The technology, which makes movies of animals' brains by measuring light emitted from a protein as it binds to calcium ions in neurons, was starting to offer an exciting new window into living brains. The technique noninvasively captures the activity of large brain regions at single-neuron resolution and allows researchers to control exactly which neurons, and even which type of neurons, are being measured. In recent years, the use of calcium imaging has exploded, with neuroscientists making movies of insect, rodent and even primate brains.

Yet Pnevmatikakis was concerned that the technology might soon become a victim of its own success. Until a few years ago, calcium imaging movies were small enough that a laboratory assistant could manually label the neurons, frame by frame. Today, however, it is common to collect 100,000 frames per hour, each containing thousands of neurons.

Pnevmatikakis developed an algorithm that could automatically identify the neurons in certain datasets obtained from his colleagues at Columbia, and in 2014, he came to the Flatiron Institute (then called the Simons Center for Data Analysis, or SCDA) with a mandate to bridge the gap from his algorithm to a broadly useful software platform. "The mission statement of SCDA was to fill exactly this kind of gap, so I thought it would be a good match," Pnevmatikakis says.

Pnevmatikakis soon brought on board Andrea Giovannucci, a neuroscientist who also has a Ph.D. in computer science. Giovannucci had been trying to interpret calcium imaging movies he'd made of mouse cerebellar granule cells, which are tiny and dense. "Recording them is like trying to distinguish specific voices in a full stadium," Giovannucci says. With help from Pnevmatikakis, however, he was able to figure out how to adapt Pnevmatikakis' algorithm to this setting, making it possible, he says, "to single out sentences from the heavy background noise and overlapping voices."

The pair realized that to make a widely useful tool, they would have to look beyond Pnevmatikakis' original tight focus on neuron detection. So they have also examined how to correct for animal motion during filming, and developed tools to benchmark the software's performance.

The resulting software, now called CaImAn, has been freely available to the public since 2015 and has been widely adopted by neuroscientists who do calcium imaging. Meanwhile, Pnevmatikakis and Giovannucci

Neurons found automatically by CaImAn (red) overlaid on an image representing active neurons in a mouse's hippocampus as the mouse navigates a virtual reality environment.
Image courtesy of Eftychios Pnevmatikakis and Andrea Giovannucci; Data provided by Jeffrey Gauthier and David Tank of Princeton University

The pair realized that to make a widely useful tool, they would have to look beyond Pnevmatikakis' original tight focus on neuron detection.

are continuing to improve CaImAn. Most recently, in June 2017, they extended its functionality to identify neurons in real time, as data stream through the software frame by frame. The innovation means that researchers can run CaImAn on ordinary computers that don't have enough storage for the entire dataset. "We like to say that we develop algorithms to do data analysis for the 99 percent," Pnevmatikakis says.

An illustration of how CalmAn detects neuron activity. At left are source data frames of neuronal activity. CalmAn identifies the location of each discrete neuron (Component) within those frames as well as its signal, in red or blue, by differentiating the signal from background activity and noise, at right.
Image courtesy of Eftychios Pnevmatikakis and Andrea Giovannucci

Frames   Component 1   Component 2   Neuropil

CENTER FOR COMPUTATIONAL BIOLOGY: HUMANBASE
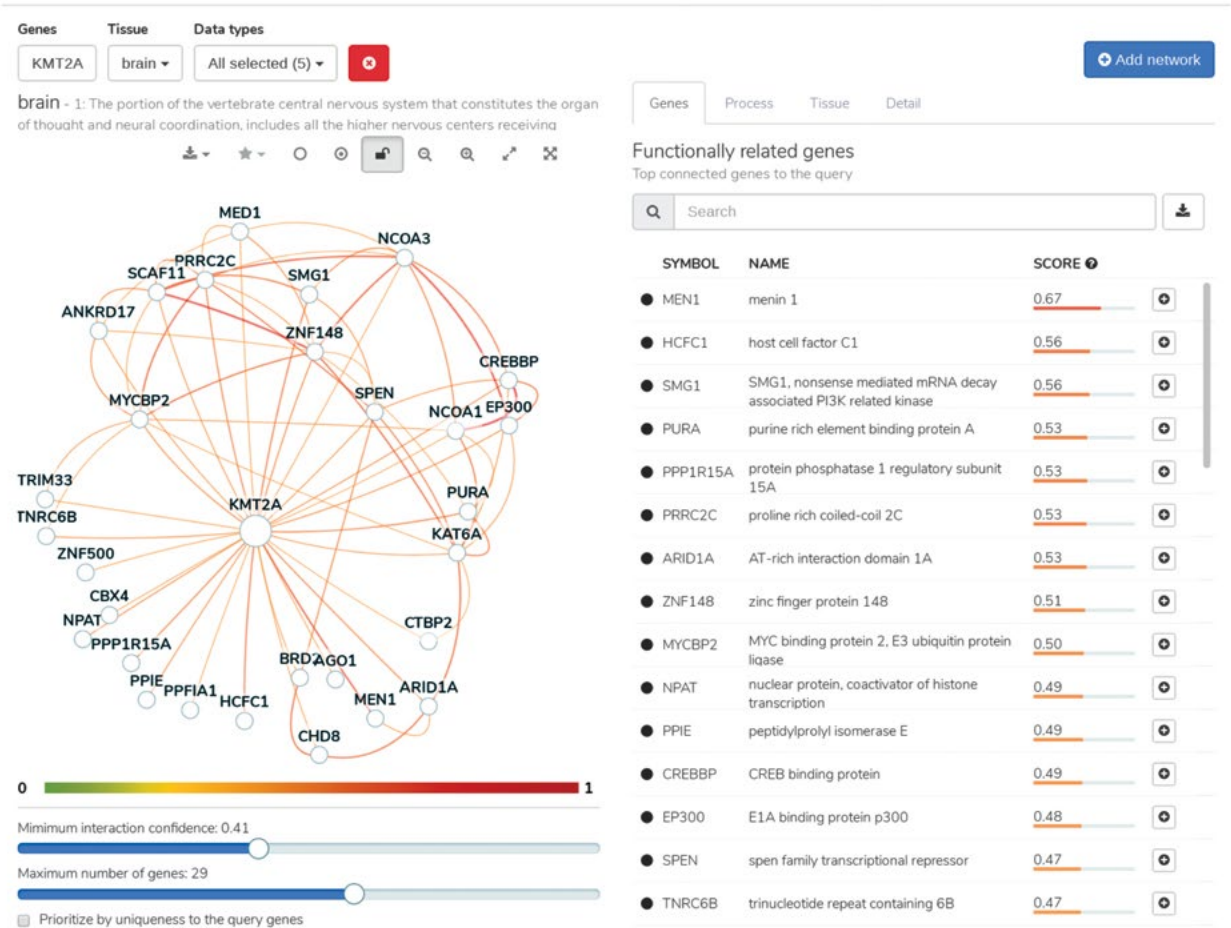

Tissue-specific interactions
Functional networks that capture tissue-specific interactions from large data compendia

An analysis generated by HumanBase displays genes functionally related to KMT2A, a gene associated with autism. Such analyses can help scientists uncover previously unseen connections between genes and disorders.

The human genome contains an estimated 19,000 genes. Those genes encode proteins that allow cells to carry out tasks such as ferrying oxygen molecules, fighting off diseases and communicating with fellow cells. But the function of most genes remains elusive, and scientists are still struggling to crack the human body's full genetic code.

In March 2017, researchers at the Flatiron Institute's Center for Computational Biology (CCB) soft-launched a new tool for decoding the human genome. The cloud-based software, called HumanBase, uses machine learning to trawl through decades of genomic research data for previously unseen potential biological connections. HumanBase can sleuth out how specific genes could potentially control cell functions, influence the expression of other genes, and contribute to disorders such as autism. Researchers can then carry out experiments that verify those potential connections.

"There's a huge wealth of undiscovered knowledge in these data," says Olga Troyanskaya, deputy director for genomics at CCB. "We wanted to build a single resource that could help biologists discover and leverage that knowledge."

Historically, knowledge in the field of genomics largely rested in published findings and the heads of biologists. That's changed, Troyanskaya says. New experiments now generate colossal datasets, but genetic associations are often too faint to uncover with any certainty from any one experimental dataset. Finding those connections requires looking at a much bigger picture, Troyanskaya says.

"A lot of these connections you just cannot see with traditional approaches," she says. "You need computational algorithms that can pick up granules of data across multiple datasets. That's impossible to do just in your head."

HumanBase incorporates data from more than 38,000 genomic experiments and more than 14,000 scientific publications. The software standardizes all of those data before trained algorithms sift through the information looking for biological connections, particularly in the context of specific tissues, cell types and diseases.

HumanBase users can just type in a particular gene or disease and quickly receive a list of genes ripe for experimental scrutiny. For instance, if a gene often expresses alongside genes already associated with increased risk of Parkinson's disease, that gene could be a tempting target for further research. "It's guilt by association," says project leader and CCB data scientist Aaron Wong.

The algorithms that power HumanBase have already proved their prowess. In August 2016, Troyanskaya, Wong and their colleagues reported online in *Nature Neuroscience* a substantial breakthrough in the hunt for genes associated with autism. Using a predecessor to the numerical tools employed in HumanBase, the researchers identified roughly 2,500 genes potentially linked to autism. Several of the most promising candidate genes had no prior genetic research tying them to autism. Scientists had previously identified 65 autism risk genes and predicted that 400 to 1,000 genes are likely involved in autism susceptibility.

> "A lot of these connections you just cannot see with traditional approaches."

HumanBase users are already tapping the software's potential to generate new hypotheses and spark new experiments, but the software's development is far from over. Troyanskaya, Wong and their team plan to add even more datasets to HumanBase's knowledge bank every six months and to continue developing the algorithms powering the software. "We want to build something that biomedical scientists can rely on," Wong says. "We want them to incorporate HumanBase into their research workflow — to drive new hypotheses and follow-up experiments."

# SCOTT AARONSON: QUANTUM AND CLASSICAL UNCERTAINTY

For a quantum computing optimist, Scott Aaronson spends an impressive amount of time trying to figure out what quantum computers can't do. A computer science professor at the University of Texas at Austin and a Simons Investigator, Aaronson pushes the boundaries of both classical and quantum computing to better understand what they can and can't do. "I try to understand the ultimate limitations of algorithms," he says. "It goes hand in hand with understanding what is possible."

Classical computers run on bits. Each bit can be 0 or 1, on or off. Quantum computers instead use quantum bits, or qubits, that can exist in superpositions of states. In a superposition of states, each state has a number called an amplitude associated with it. In some ways, an amplitude is similar to a probability, but instead of the positive probabilities we are familiar with, these numbers are complex. (Complex numbers consist of numbers of the form $x + iy$, where x and y are both real numbers and i is the square root of -1. Complex numbers provide a two-dimensional rather than one-dimensional set of numbers to work with.) By carefully manipulating the amplitudes associated with different states so that correct answers are amplified and incorrect ones cancel out, a quantum algorithm can achieve a massive speed advantage in calculations for some problems compared with a classical computer.

Or so it would seem. But at the heart of any discussion about the relative merits of quantum versus classical computing is a nagging uncertainty called 'P versus NP.' This problem concerns how quickly the amount of time it takes to solve a problem grows as a function of the input size. There are some problems — factoring large numbers is one famous example — that no one knows how to solve in what is known as polynomial time. (That is, the time to run the algorithm is a polynomial function of the size of the input, such as n^2 or $n^{500,000}$.) Instead of polynomial time, the best-known classical algorithms to solve these problems have a number of steps that grows exponentially with the size of the inputs. For large inputs, exponential growth completely overwhelms polynomial growth.

Problems that are known to have polynomial-time solutions are considered 'easier' than problems that don't have such solutions, which computer scientists colloquially call 'hard.' But for some of these hard problems, including integer factoring, it is easy to check whether a proposed solution is correct. The best-known algorithms for integer factoring take exponential time to implement, but it only takes polynomial time to multiply two numbers and check whether their product is the desired number. "We don't have the mathematical tools right now to prove unconditionally that most of the problems we think are hard really are hard," Aaronson says. The P versus NP problem, which has a million-dollar bounty on its head, asks whether the problems that seem hard to solve but easy to check are actually hard to solve at all.

Aaronson and his collaborator Avi Wigderson have also done substantial research on what is known as the algebrization barrier, which they identify as one of the main obstacles to showing that P and NP are indeed different.
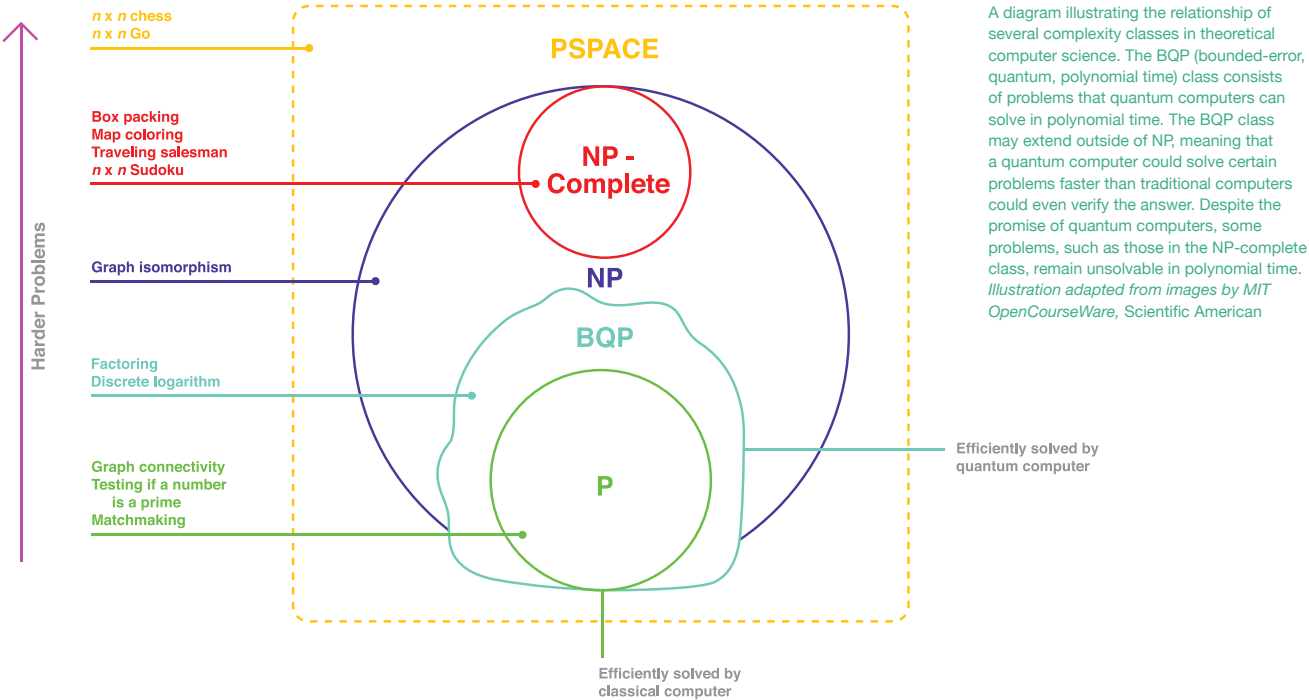
A diagram illustrating the relationship of several complexity classes in theoretical computer science. The BQP (bounded-error, quantum, polynomial time) class consists of problems that quantum computers can solve in polynomial time. The BQP class may extend outside of NP, meaning that a quantum computer could solve certain problems faster than traditional computers could even verify the answer. Despite the promise of quantum computers, some problems, such as those in the NP-complete class, remain unsolvable in polynomial time. *Illustration adapted from images by MIT OpenCourseWare,* Scientific American

PSPACE

NP - Complete

NP

BQP

P

Harder Problems

$n \times n$ chess
$n \times n$ Go

Box packing
Map coloring
Traveling salesman
$n \times n$ Sudoku

Graph isomorphism

Factoring
Discrete logarithm

Graph connectivity
Testing if a number
is a prime
Matchmaking

Efficiently solved by
quantum computer

Efficiently solved by
classical computer

The fact that P versus NP and related questions are still unsettled makes the true extent of quantum advantages difficult to ascertain. In the 1990s, Peter Shor developed an algorithm for factoring numbers in polynomial time using a quantum computer. It is leaps and bounds more efficient than the best-known classical algorithms, but that doesn't necessarily mean there aren't similarly efficient classical algorithms no one has yet been clever enough to find.

Shor's algorithm for factoring large numbers so far seems to be a special case. For most problems, Aaronson and other researchers have found that quantum computers have only a limited, though often substantial, speedup over classical algorithms. So far, other than for factoring, quantum simulation and a few other tasks, quantum algorithms usually cannot take an exponential-time problem and turn it into a polynomial-time problem.

Google, IBM and other research teams have recently built 50-qubit quantum computers, with about twice as many qubits and many orders of magnitude more computational power than what had previously been available. (Data about the performance of these computers may not be available for some time.) Past the 50-qubit point, another uncertainty starts to creep in. If you start using quantum computers to solve computationally expensive problems that aren't easy to check, how do you check your work? "There's a bit of irony here," Aaronson says. "For the problems that we know how to attack in the near future, the only way we know how to verify the quantum computer's results is essentially to simulate the whole computation on a classical computer. But the very fact that you can do the latter calculation means that the quantum computer isn't doing something that's impossible for classical computers." Of course, the

quantum computer will move more quickly. Computations that take seconds to perform on a 50-qubit computer may take days to verify on a classical computer. But verifying the result of computations on a 100-or 200-qubit system could very well become functionally impossible for a classical computer.

When people think about the applications of quantum computing, they often start worrying about the security of current cryptographic systems. For example, RSA (Rivest–Shamir–Adleman), a common public-key cryptosystem, relies on the difficulty of factoring large numbers for its security. Aaronson points out that, although eventually quantum computers could break existing public-key cryptography, there are other cryptographic systems waiting in the wings that we don't know how to break — not even with a quantum computer.

Aaronson is even more excited about another application of quantum computing: simulation. What better to simulate complicated chemical interactions, down to the quantum mechanical level, than a computer that runs on quantum mechanics itself? "Once you're confident the device is working, you can start using it to simulate molecules that have never existed," he says. While some of the problems that quantum computers could solve seem to be hard for the sake of being hard (indeed, much cryptography relies on such questions), simulating complicated chemical interactions could have a tangible impact on a range of questions in physics, chemistry and biology. Although quantum-computing-aided drug discoveries are still a long way off, the next few years could lay the groundwork for the application of quantum physics to several areas of scientific research.

SHARON GLOTZER: ORDER FROM UNCERTAINTY

The second law of thermodynamics says that in a closed system, entropy — colloquially thought of as a measure of disorder or uncertainty — cannot decrease. Generally, higher entropy corresponds to higher temperatures, phase transitions from solid to liquid or liquid to gas, or a general decrease in the order of molecules in a system. Simons Investigator Sharon Glotzer, professor of chemical engineering at the University of Michigan, studies the counterintuitive instances when entropy doesn't work that way. "I'm interested in how entropy can lead to order rather than disorder," she says. "The opposite of what most people think about when they're thinking of entropy."

Entropy appears in different scientific disciplines and in various guises, but Glotzer is concerned with Gibbs, or statistical, entropy. In essence, this is a measure of the number of distinct arrangements, also called microstates, possible in a system. "Typically, the states that we observe in nature are the ones for which there are the most possible arrangements," Glotzer says.

To illustrate: If you put a collection of identical hard spheres — marbles or tiny nanoparticles — in a large container and send it into space to remove the effect of gravity, the spheres will tend to spread out randomly. But if you reduce the size of the container, you'll start to see strange results. When the proportion of the container occupied by the spheres increases to 50 percent, the spheres will form a regular lattice, or crystal structure, even though there is room for them to remain in a less ordered arrangement. "The idea is that when particles are sufficiently crowded, there are more patterns that are crystalline than patterns that are disordered," Glotzer says. Counterintuitively, the particle arrangement with the most entropy is highly ordered. In essence, entropy has driven the emergence of order.

In 2009, Glotzer's research group made a similar discovery for tetrahedrons rather than spheres. While working with semiconducting nanoparticles that happened to have a tetrahedral structure, they found that when the packing fraction got high enough, a quasicrystal structure emerged with 12-fold rotational symmetry. "It was a completely serendipitous discovery that we were never looking for, nor did we expect," Glotzer says. "We didn't believe it for a long time, until we proved to ourselves it was real."

Once again, order had emerged solely as a result of entropy, not from molecular interactions. But this time, the team ended up with a quasicrystal instead of a crystal structure. Unlike crystals, which have periodic structures that repeat precisely, quasicrystals have an ordered structure but no exact translational symmetry and are generally more complicated than crystals. "It was amazing, because here we were looking at one of the simplest three-dimensional solids, the tetrahedron, forming one of the most complicated structures possible — a quasicrystal!" Glotzer says.

Since that discovery, Glotzer's group has been studying different particle shapes to create different crystal and quasicrystal structures using only entropy. "We're marching through the database of crystal structures. We're finding another crystal structure, and then another one, and then another one," she says. They would like to determine whether there are any crystal structures that can't arise solely through entropy. "Just how powerful is entropy as a driving force for order?" Glotzer asks.

In addition to the intellectual curiosity it conjures, this research could someday help people engineer materials with desired properties, such as photonic crystals: materials that trap certain wavelengths of light used in fiber-optic cables. To create these new materials, researchers will need to harness other forces aside from entropy, but Glotzer's research helps explain what role entropy has in the process. "If I want to use only entropy, what shape do the particles have to be?" she says. "Once we understand that, we can combine entropy with other forces to get precisely the material we want."

"I'm trying to argue for elevating the recognition and respectability of the entropic bond."

Another goal is to quantify — and spread the idea of — the entropic bond. Glotzer's work shows that entropy can be thought of as similar to chemical bonds between atoms, such as hydrogen bonds or metallic bonds. Those bonds are based on electron density; entropic bonds are based on entropy density. "I'm trying to argue for elevating the recognition and respectability of the entropic bond," she says. "When you go to 'bond' in Wikipedia, it should list all these bonds, and one of them should be 'entropic bond.'"
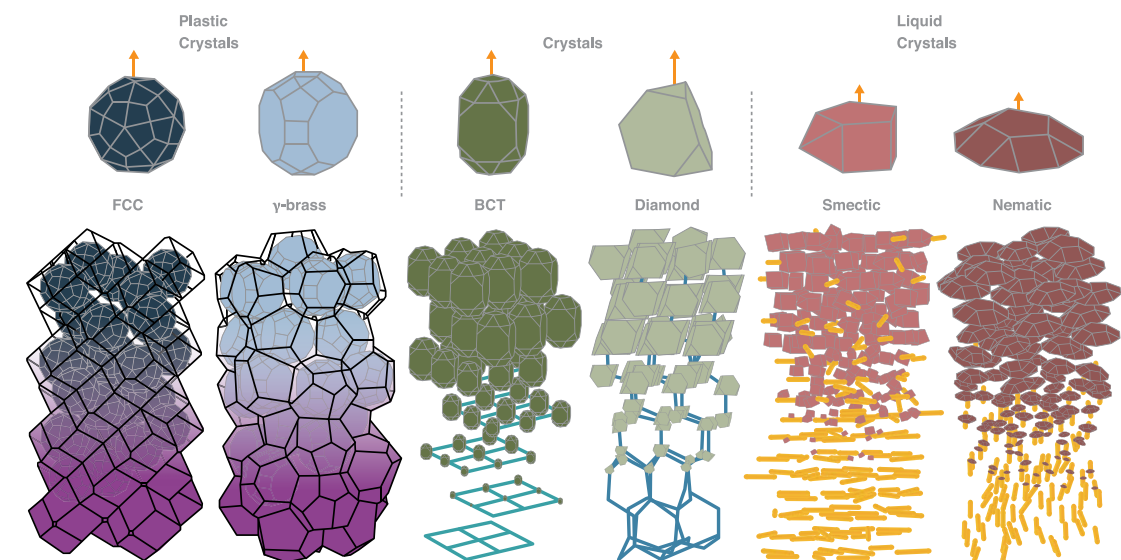
Hard particles can arrange themselves into crystal structures through entropy alone, Sharon Glotzer and colleagues discovered.
Illustration adapted from images by P.F. Damasceno et al./Science 2012

HORNG-TZER YAU: TAMING RANDOMNESS

The matrix is a workhorse of modern math — and of physics, computer science and engineering, for that matter. This mathematical object is an array of numbers that encodes a transformation between mathematical spaces. Matrices can represent the way various elements of a system rely on one another. Among researchers who study social networks, for example, an adjacency matrix that represents the connections between people will use a 1 to indicate that two people in the network know each other and a 0 to indicate they are strangers.

In the 1950s, physicist Eugene Wigner began to use matrices to model the interactions of atomic nuclei. These interactions are so complicated, particularly in a system large enough to represent anything of real-world significance, that it is impossible to discern the exact matrices involved. Instead, he had the insight that random matrices could be used instead. The idea of a random matrix is that instead of looking at a matrix with certain fixed values, one imagines a matrix in which all values are selected randomly from a set of numbers with fixed parameters. Wigner believed these random matrices would behave in particular ways, shedding light on the systems they were modeling.

A few years ago, Simons Investigator and Harvard mathematics professor Horng-Tzer Yau and his collaborators successfully answered key questions Wigner had posed, closing that chapter in the book of random matrices. Yau didn't start his career

studying random matrices. For many years, he worked on a variety of problems related to statistical mechanics, including fluid dynamics and complicated many-body systems that arise in astrophysics. In 2000, he was awarded a MacArthur fellowship, popularly known as a 'genius grant,' in recognition of the contributions he had made to both mathematics and physics in studying those problems.

Shortly before starting to tackle Wigner's conjecture, Yau had been focusing on questions related to the quantum mechanical behavior of semiconductors using random Schrödinger operators. This work built on that of Nobel Prize winner Philip Anderson, who modeled semiconductors with impurities as lattices with randomly distributed obstacles. As Yau was working on Anderson's model, he found that he kept hearing that Wigner's random matrices were lurking in the background. "The question was always mentioned in meetings," he says. Eventually, he and some of his co-investigators decided to alter course and work on Wigner matrices themselves.

In order to say anything meaningful about a matrix full of random numbers — indeed, to say anything meaningful about random numbers at all — the researcher must make assumptions about how the numbers are chosen. Are the numbers distributed normally — the classic bell curve — or taken from some more exotic distribution? Not long after Wigner posed the problem, Freeman Dyson and other physicists were able to successfully probe the case where
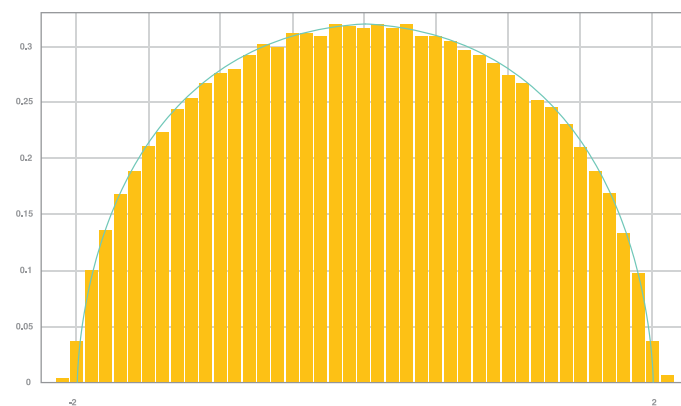
Histogram of eigenvalues of a real symmetric matrix of large size with random entries. The distribution follows Wigner's semicircle law.

the values were distributed normally, but other distributions remained elusive. Wigner and other physicists who studied the question believed that the behavior of these large random matrices would be the same no matter the distribution from which the entries were drawn.

On its face, that was a startling claim. How could properties based on a particular random distribution turn out to be independent of that distribution? But there was a precedent for such a situation: The central limit theorem in statistics asserts an analogous result. In essence, Yau and colleagues showed that Wigner's conjecture was a sort of central limit theorem for random matrices.

These days, Yau is extending his work in several directions. He hopes to circle back to the work on Anderson's model of semiconductors, eventually determining whether they really are governed, as Anderson predicted, by the same rules as random matrices. Yau sees the semiconductor as an important example to study, in part because the randomness of the system is entirely natural rather than imposed by humans. "Most random matrix examples are constructed by something like flipping a coin, a human construction," Yau says. "The Anderson model is so precisely given by a law of nature."

Although some of Wigner's beliefs about random matrices have been confirmed, there are as yet no examples of physical systems that conform to those random matrices. Yau hopes to construct a quantum mechanical model that will actually display the behaviors of Wigner's random matrices.

Whereas Wigner's original vision for random matrices came from his work on quantum mechanics at the level of atomic nuclei, Yau's work has taken that vision on a winding path away from quantum mechanics into pure mathematics. It may well continue into the decidedly macroscopic realms of human social networks and other forms of data analysis. "That's how it happens in science," Yau says. "You sometimes stumble on things in unexpected ways."

His boldest dreams, though, are about finding applications of random matrix theory beyond the quantum world where Wigner's work started. With computing power and dataset sizes at all-time highs, the networks available for analysis are more massive than ever. Yau hopes that the techniques he has developed in random matrix theory will offer insight into the inner workings of neural networks — computer systems that 'learn' by finding patterns in data. So far, even finding an appropriate mathematical language to describe what a neural network does has eluded mathematics. "Mathematicians are not even sure what the right question is yet," he says.

On the other hand, neural networks are large, complicated correlated systems — exactly the type of systems Wigner considered. Although the precise mathematics of how neural networks are related to random matrices is unclear, Yau is hopeful that new insights from the study of random matrix theory will allow his team — or other researchers — to tackle the modern challenges in understanding neural networks and machine learning.

> "You sometimes stumble on things in unexpected ways."

SIMONS COLLABORATION ON THE ORIGINS OF LIFE

Roughly 4 billion years ago, the early Earth was an unfamiliar world. Large-impact craters pitted the planet's surface, the sun glowed dimly, and the atmosphere was almost entirely devoid of oxygen. Yet from this extreme environment, the oldest known evidence of life appeared: Mound-like structures built by microbial communities, crystals containing isotopic traces of biological activity, and microfossils embedded in ancient rocks all hint at when the first earthlings emerged. But how Earth went from lifeless to lush remains uncertain.

"It's the biggest question that science has not been able to come to grips with," says Roger Summons, professor of geobiology at the Massachusetts Institute of Technology. "It's a grand challenge."

That challenge has attracted an international group of scientists, each bringing expertise from disparate fields such as molecular biology, exoplanetary science and geochemistry. The Simons Collaboration on the Origins of Life (SCOL), which started in 2013, explores how life can arise and evolve, whether on Earth or elsewhere in the cosmos.

"We're talking about origins — plural — of life," says Dimitar Sasselov of Harvard University, who co-directs the collaboration with Jack Szostak of Harvard. "We're looking for any plausible pathways, not necessarily for the one and only origin of life here on planet Earth."

The search for life's origins poses a challenge, as it incorporates aspects of many different fields. The breadth of uncertainties involved, from the composition of the ancient Earth's atmosphere to the mechanisms that assembled the first biomolecules, places the subject out of reach for any one research group or lab to fully explore, Sasselov says.

The need for a large, collaborative hunt for the origins of life sparked interest during a 2012 Simons Foundation meeting at the Buttermilk Falls Inn in Milton, New York. That gathering assembled experts from many disciplines to discuss potential Simons collaborations. The next year, SCOL began with 12 founding investigators and one honorary investigator. Over the next several years, the collaboration added more members to bolster its collective expertise and pursue new research paths. As of 2017, the group had 24 investigators and 14 postdoctoral fellows. "We started as a bunch of individuals working on the things that interested us, the things we're capable of doing on our own," says Summons, a SCOL researcher and member of the collaboration's steering committee. "But as we got to know each other and talk and meet and cogitate, people came up with ideas that otherwise would have never happened without this collaboration."

The collaboration is pursuing many potential avenues for the origins of life, and one thread is generating particular interest. In a 2015 paper in *Nature Chemistry*, SCOL investigator John Sutherland of the MRC Laboratory of Molecular Biology in the United Kingdom and his colleagues demonstrated the creation of precursors to nucleic acids, lipids and amino acids — basic building blocks of all known life-forms — from hydrogen cyanide, hydrogen sulfide and a dash of ultraviolet light.

The necessity of ultraviolet light limits where these reactions could have occurred on early Earth, says Sutherland, who will become a SCOL co-director in May 2018. Sunnier spots, such as streams and pools on land, would better facilitate such reactions than dimly lit locations such as hydrothermal vents in the deep ocean. "And at that point, you need to start talking to the geochemists," Sutherland says.

In 2017, SCOL invited several earth and planetary scientists to give presentations at collaboration meetings for consideration to become investigators, signaling the collaboration's appreciation of the necessity of geoscience in work on the origins of life. Insights provided by the collaboration's chemists and biochemists, such as a potential need for ultraviolet light, can help guide the geoscientists toward environmental clues. For instance, exploring the processes and molecules that would have been available in streams and pools on early Earth could help chemists further hone their experiments. "What I like about this is that the chemists on their own couldn't do it, the geochemists on their own couldn't do it," Sutherland says. "We need to work together."

Bridging the gap between pristine laboratory experiments and real-world conditions requires making the experiments "dirtier," says SCOL investigator Dieter Braun, professor of biophysics at the Ludwig Maximilian University of Munich. Inspired by work done by geologists, his group experiments using 3-D-printed rock replicas in the lab. Braun and his colleagues mix powdered minerals such as basalt with printing resin. Using a 3-D printer, they can layer custom shapes of the mixture onto polished rock. The artificial rocks mimic the porous volcanic rocks that were probably abundant on the early Earth. The powdered rocks can catalyze and take part in chemical reactions on the surface, and small pores in the mimic rock can trap water, create air pockets and stash molecules that would otherwise get washed away.

"If we just keep our experiments in glass flasks and clean environments, we will never find these solutions," Braun says. "I think we have to go into those dirty geological settings, and I think we'll learn a lot by doing that."

What rocks on ancient Earth looked like remains somewhat uncertain, though. Plate tectonics, weathering, erosion and biological activity have destroyed nearly all relics of early Earth's surface. Luckily, scientists do know of a treasure trove of remnant rocks — it's just not on Earth.

Mars, unlike Earth, has undergone relatively little resurfacing. The Curiosity rover discovered that rocks from the planet's Gale Crater and surrounding landscape date back between 3.6 billion and 4.1 billion years — making them around the same age as the oldest rocks on Earth. "We can look at sedimentary rocks on Mars that are effectively the same age as the very oldest sedimentary rocks on Earth that may contain life," says SCOL investigator John Grotzinger, who will also become a SCOL co-director in 2018. He is a former project scientist for the Curiosity rover mission and Fletcher Jones Professor of Geology at the California Institute of Technology.

In June 2017, Grotzinger and his colleagues reported in *Science* that geochemical evidence from Curiosity's trek through the Gale Crater suggests the region once hosted liquid-water lakes with layering similar to those found on Earth. Sediments near the top of these ancient lakes contain evidence of more abundant oxygen than what was found in those closer to the lake bed. This division offers further indication that such lakes may have been favorable to life.

"If you find a lake on Mars and you compare it to an ocean on Earth, it's not exactly the same," Grotzinger says. "It's certainly not an identical twin, but it's probably a cousin." The Martian lakes can offer insights into what similar bodies of water may have looked like on the early Earth, he says. Dissimilarities between the two can shed light on why the two planets ultimately diverged in terms of habitability.

"We're looking for any plausible pathways, not necessarily for the one and only origin of life here on planet Earth."

SCOL's ongoing research into all aspects of the emergence of life, from chemical bonds to extraterrestrial lakes, makes Sasselov optimistic that the field is closing in on an origin story. "We are terribly close, it seems to me, to having the whole thing finished for one pathway," he says. "But the jury is still out. It may turn out to completely be a dead end and back to the drawing board, but it doesn't seem like that to me. So many things have fallen into place."

Biophysicist Dieter Braun presents during the Simons Collaboration on the Origins of Life annual meeting.

NURTURING THE NEXT GENERATION OF MARINE MICROBIAL ECOLOGISTS

"If your training is in a physical field, it can be hard to move into ecology. We thought providing funding would encourage people to make that transition."

Oceans cover more than 70 percent of the planet. And within the oceans, it is the microbial ecosystem, made up of bacteria and phytoplankton, that forms the base of the food chain and powers the cycling of carbon, oxygen and other elements. Yet despite its importance, marine microbial ecology remains an underfunded area of science.

To help remedy this situation, in 2017 the Simons Foundation created the Simons Postdoctoral Fellowships in Marine Microbial Ecology. These three-year awards, given out each year to five early-career researchers, were inspired by Sallie (Penny) Chisholm, a marine microbiologist at the Massachusetts Institute of Technology (MIT). "She always gets lists of fellowships that MIT postdocs can apply to, and there's never anything targeted to people in this field," says Marian Carlson, director of the Simons Foundation's Life Sciences division.

"For this area to thrive, we have to get young scientists to find it an area where their careers can flourish," Carlson says.

In choosing fellows, the foundation pays particular attention to whether the applicant's research plan and proposed mentor will help the applicant transition to doing independent research of the highest quality. "This is a career award, not a grant to do a specific project," Carlson says. "We wanted to choose candidates who would move the field forward for the next decade."
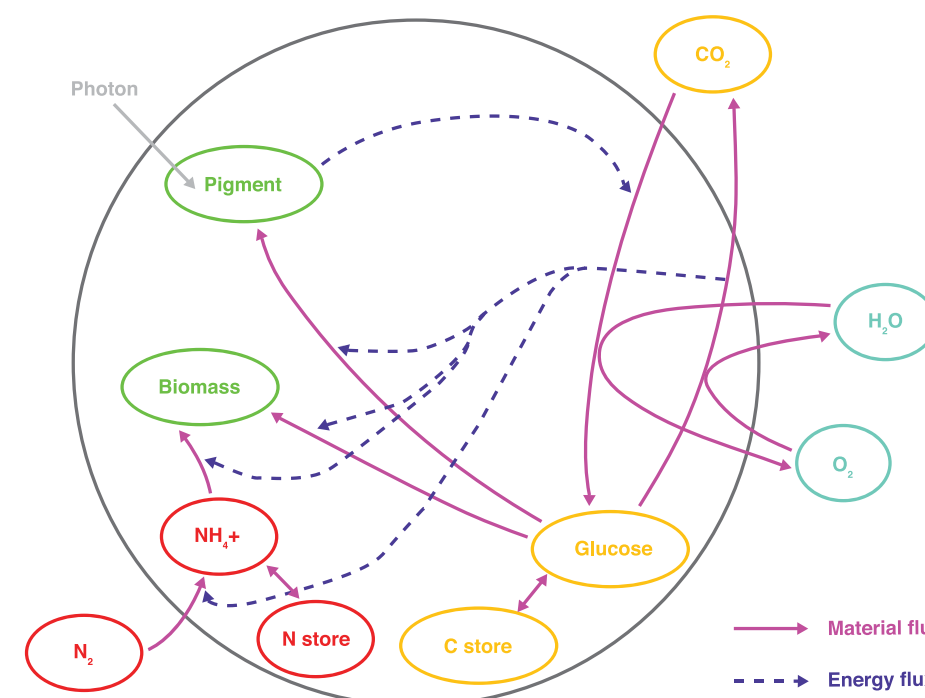
Some of the 2017 awardees have doctoral degrees related to oceanography. But the fellowship also encourages applicants from quantitative areas, such as physics and mathematical modeling, because the interdisciplinary nature of marine microbial ecology means that quantitative research can have a significant impact. "If your training is in a physical field, it can be hard to move into ecology," Carlson says. "We thought providing funding would encourage people to make that transition."

Keisuke Inomura, a Simons Fellow at the University of Washington who is exploring mathematical models of the distribution of different nitrogen-fixing microbes in the ocean, says the fellowship offers him "more possibilities and more degrees of freedom" than he otherwise would have. Many postdoctoral fellowships last only one year, and even in a two-year position, "you have to get results very quickly — like, in one year — if you want to be a strong candidate for an assistant professor job," Inomura says. Having a three-year fellowship essentially doubles that time frame, he says, lifting the pressure and allowing fellows to pursue more ambitious projects.

Natalie Cohen is using her Simons fellowship at Woods Hole Oceanographic Institution in Massachusetts to study how marine microbes adapt to changing supplies of trace metals. The other postdoctoral opportunities she had applied for involved joining existing research projects instead of designing experiments based on her own specific interests, she says.

"The day I got my acceptance letter for the Simons fellowship was the best day of my life, because it meant I could continue to study what I was most passionate about," she says, and three years' worth of funding "means that instead of spending my time writing grants, I can put all my efforts into doing the best science I can."

Natalie Cohen prepares tubing to pump seawater with minimal trace-metal contamination from the northeast Pacific Ocean to examine how phytoplankton respond to rapid changes in available iron.
Image courtesy of Benjamin Twining of Bigelow Laboratory for Ocean Sciences

Keisuke Inomura modeled how material and energy flow through *Crocosphaera*, single-celled marine cyanobacteria. The microbe (circle) accumulates carbon during the day. At night, it uses that carbon to expel oxygen. The resulting low oxygen levels within the organism permit the conversion of nitrogen into ammonia, an important part of the marine nitrogen cycle that has rarely been mechanistically quantified.
Illustration adapted from images by Keisuke Inomura

SIMONS COLLABORATION ON THE GLOBAL BRAIN: MAPPING BEYOND SPACE

Whether you're lost in a new city or driving the most familiar roads, both your hippocampus and your entorhinal cortex are hard at work. Together, these two brain regions create a powerful human navigation system, with diverse cells coordinating to perform different navigational functions, such as tracking the location, speed and direction of your movement. Discovering this navigational system was a huge feat in neuroscience, earning John O'Keefe, May-Britt Moser and Edvard Moser a Nobel Prize in 2014.

But a growing body of research suggests these brain regions may play an even more expansive role in how the brain organizes experience. New findings from David Tank of Princeton University, who is director of the Simons Collaboration on the Global Brain (SCGB), and others show that the cells of the hippocampus and entorhinal cortex can encode much more than physical space: They can also track sound and other factors. And Lisa Giocomo, a neuroscientist at Stanford University and an SCGB investigator, and her collaborators have shown that these cells seem to be capable of rapidly changing their coding properties to respond to a novel environment or task.

Neuroscientists have traditionally defined cells in the hippocampus and entorhinal cortex according to the specific navigational ability they seem to support. Neurons known as grid cells track general location in space. Place cells encode specific locations, firing whenever you pass your house, for example. Still others act as speedometers, encoding how fast you are moving. "People envisioned the system as a GPS: The brain knows the speed and direction you're traveling from specific cells and can then determine distance," Giocomo says.

> "We're trying to break free of a preconceived notion of how the brain is operating."

That approach has drawbacks, however. It requires researchers to hypothesize a priori as to what they believe a cell is doing — such as encoding speed or location — and look for cells that respond to these variables. To find place cells, for example, scientists look for cells that fire most when the animal is in a particular location but grow quiet as the animal moves away. The problem is that most cells in these regions don't behave in such a predictable way and therefore cannot be labeled with a function.

Giocomo and her collaborators developed an assumption-free method to define cells' roles. Rather than looking for cells that code for predefined spatial properties, the researchers have developed statistical models that determine which stimuli best predict whether a neuron will fire. "We're trying to break free of a preconceived notion of how the brain is operating," Giocomo says. "With our approach, you can take a blind perspective."

With this system, Giocomo's team has been able to identify what 75 to 90 percent of cells in the region respond to, compared with less than 50 percent using traditional methods. "We are now capturing a huge percentage of what the entorhinal cortex is doing during behavior," Giocomo says.

The analysis, published in *Neuron* in April 2017, revealed that many cells in the entorhinal cortex are both complex and flexible. A cell might code for one property when an animal is running slowly and another when it runs fast. "That's a fundamentally different way of thinking about how the brain might compute location in space," Giocomo says. "What the field has defined as grid cells is probably on one end of [the] spectrum — it's just the tip of the iceberg in terms of coding features."

Dmitriy Aronov of Columbia University and David Tank have also found striking flexibility in both the entorhinal cortex and the hippocampus. The team showed in 2014 that animals learning to navigate a virtual reality world shifted their internal maps when experimenters shifted that virtual world. They reasoned that if animals can readily adapt to a new spatial reality, maybe they can map other types of experiences as well.

To test that theory, Aronov, then a postdoctoral researcher in Tank's lab, trained rats to traverse an auditory rather than a physical space. The animals used a joystick to move through a sort of soundscape — a defined sequence of frequencies. Moving the joystick to the left, for example, might increase the frequency.

The researchers discovered a set of cells that act very much like place cells. Instead of firing when the animal is in a specific location, these 'sound cells' fire when the animal hears a specific tone. The findings were published in *Nature* in March 2017.

Tank, Aronov and others have also found that neurons in the hippocampus seem to respond not just to space or sound, but to every aspect of the task, firing in a predictable sequence throughout an experiment. "From pressing the lever to traversing the frequency to receiving the reward and starting a new trial — there is a sequence of activation throughout the entire period of behavior," Tank says.

Taken together, the research suggests that cells in the hippocampus and entorhinal cortex are far more flexible than scientists thought. "The findings point to a more general function of the hippocampus," says Aronov. Rather than simply encoding where an animal is or how fast it's moving, the neurons in this brain region map out whatever variables seem to be most important in that context. "If the animal is navigating through space, the sequence [of electrical activity in this group of neurons] tends to correspond to space. If it's traveling through sound, the sequence will correspond to successive sounds."

Researchers theorize that this flexibility, also known as remapping, helps animals encode experiences much more broadly. Remapping helps the brain "distinguish between experiences with strongly overlapping elements, such as parking your car in the same parking lot but in different parking spots each day," Giocomo says.

Giocomo and Tank are now working together, along with Surya Ganguli, Loren Frank, Elizabeth Buffalo, Uri Eden and Ila Fiete, on a new SCGB project that will delve more deeply into the remapping process. Their project will expand on previous research, which focused on how neurons remap in response to visual changes in the environment — if the wall color in a room changes or a wall is knocked down, for example. Giocomo and Tank's work shows that remapping can happen quickly, such as when an animal changes its behavior, and across different modalities, such as sound. "We want to use that as a springboard to understand how neurons remap, what time course this remapping follows and how this information then gets communicated to the rest of the brain to form a memory or drive behavior," Giocomo says.

Giocomo, Tank and their collaborators plan to record electrical activity from the same neurons as animals perform two different tasks — foraging for food in an open environment and finding their way through a maze — and analyze how neuronal activity differs depending on the environment and the task. They aim to uncover how remapping helps the brain encode unique experiences and generalize across different experiences.

Hippocampal formation

Activated neuron
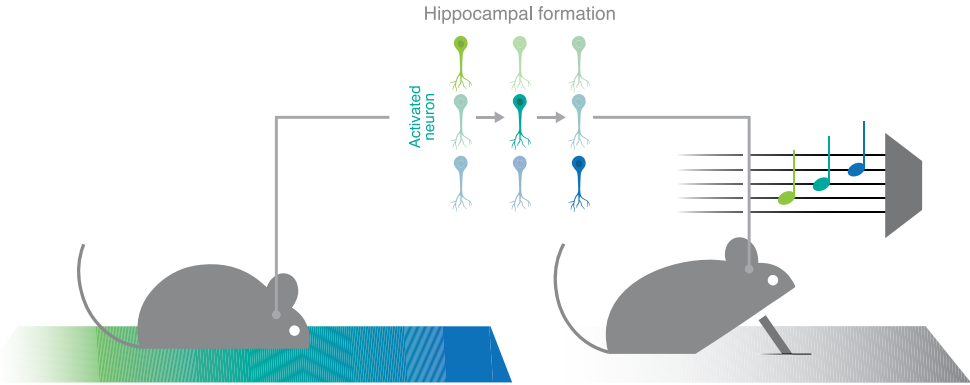
As a rat runs along a straight track, different neurons in the rat's hippocampal region fire. (As the rat enters the green portion of the track, for instance, the green neurons fire.) Researchers later conducted a similar experiment in which rats manipulated a joystick to change the frequency of a tone. The work showed that neurons respond to changes in sound frequency in a manner similar to their response to changes in location. Illustration adapted from J.W. Rueckemann and E.A. Buffalo/Nature 2017

THE HUNT FOR AUTISM GENES

CHROMOSOME RANGE
All

BASE PAIR LENGTH
3095.68Mbp

OF CONNECTIONS
2232

OF GENES
1005

Toggle Type of Protein Interaction
- Protein Binding
- DNA Binding
- RNA Binding
- Protein Modification
- Direct Regulation
- Autoregulation

Toggle Gene Score Categories
- Category S (Syndromic)
- Category 1 (High Confidence)
- Category 2 (Strong Candidate)
- Category 3 (Suggestive Evidence)
- Category 4 (Minimal Evidence)
- Category 5 (Hypothesized)
- Category 6 (Not Supported)

A visualization of the human genetic information contained in the SFARI Gene database. The outer shell displays a curated subset of genes spread across the 23 chromosome pairs. The color of each gene indicates the confidence of the gene's predicted link to autism, with red indicating the strongest links. The shell's interior connects genes associated with the same protein interaction. An interactive version of the visualization is available at gene.sfari.org/database/ring-browser.

Over the past five years, sequencing studies of individuals with autism and their families have led to the discovery of about 100 high-confidence autism risk genes — a remarkable step forward in understanding the genetic basis of the condition. These studies have successfully gleaned many of the mutations most prominently involved in autism: the ones that, though rare, appear frequently enough to have made their role in autism unmistakable. Yet researchers estimate that 300 to 1,000 genes may confer risk for autism. To shake out these additional genes, the Simons Foundation Autism Research Initiative (SFARI) is pursuing a wide range of approaches.

One approach is simply to sequence more families. 'Whole-exome' sequencing — sequencing the protein-coding regions of the genome — remains an effective way to identify new autism risk genes and strengthen evidence for existing candidate genes, says Louis Reichardt, SFARI's director. "It works, and there's a lot more to be discovered there."

To date, researchers supported by SFARI and other institutions have carried out whole-exome sequencing on about 6,000 families. A SFARI initiative called SPARK, or Simons Foundation Powering Autism Research for Knowledge (see page 32), aims to raise that number to 50,000. "It's a certainty that SPARK will enable new risk-gene discovery in autism," says Wendy Chung, the initiative's principal investigator.

Collecting genetic data from 50,000 families should not only reveal new rare autism mutations, but also jump-start the search for the common gene variants that affect autism risk — variants that, by definition, appear in at least 1 percent of the general population. These common variants are often harmless but can be damaging when joined with just the right combination of other common variants. "We know that collectively they impart a significant risk for autism, but for the most part we don't know which ones they are yet," Reichardt says.

Searching for common variants requires tens of thousands of samples. "If we get to 50,000, that dramatically changes what can be done," Reichardt says. "To date we have not been able to find out much about common variants, but our knowledge is going to accelerate over the next year or so."

Diving deeper
Although sequencing tens of thousands of SPARK families is expected to be a key driver of future discoveries, there's still a lot to learn from the roughly 2,600 families in the Simons Simplex Collection (SSC), a data repository launched by the Simons Foundation in 2007. Many of the early sequencing studies of the SSC focused on the exome, where it is most straightforward to find direct links between mutations and autism, but the exome represents only about 1.5 percent of the human genome's 3 billion nucleotides. With support from SFARI, the New York Genome Center has completed whole-genome sequencing of the families in the SSC. Researchers hope this sequencing data will illuminate how the non-protein-coding regions of the genome — such as regulatory regions, which control where and how much a given gene is expressed — affect autism risk.

Researchers supported by the Simons Foundation are also taking a closer look at 'synonymous' mutations among individuals in the SSC — mutations that, by definition, don't change the sequence of amino acids in the coded protein. It might seem, at first glance, that these mutations should not confer heightened autism risk, because they don't change which protein gets created. Yet these mutations do sometimes affect either the 'splicing' or the amount of turnover of the messenger RNA molecules that carry the gene's instructions to the ribosomes, the cell's protein factories. These changes can in turn affect the amount of protein that gets created. "It's important to try to find as many of these mutations as we can," says Alan Packer, a senior scientist at SFARI.

Searching for somatic mutations
SFARI is also supporting research into 'somatic' mutations — ones that occur during development rather than at or before fertilization, and so appear in only a fraction of an individual's cells. Several papers in the past year indicate that somatic mutations contribute significantly to autism risk.

Between 5 and 10 percent of children with 'simplex' autism — autism that affects no one else in their family — may have one of these somatic mutations, says Brian O'Roak of

Between 5 and 10 percent of children with 'simplex' autism may have somatic mutations.

Oregon Health and Science University in Portland, whose team, with support from SFARI, has been combing the SSC for somatic mutations. So far, his research group has uncovered somatic mutations both in known autism risk genes and in novel genes that had not previously been connected to autism, but that are involved in biological pathways linked to the disorder.

Although somatic mutations may sound more benign than mutations that appear in every single cell, it's possible the reverse is true. "Some of the somatic mutations we're finding might be so bad that if they were in every cell, that would not be compatible with life," O'Roak says. Sequencing SPARK families should clarify the role of these mutations, he says.

All told, the mutations identified so far by all methods explain about 20 to 25 percent of simplex autism, Packer says. "It's fair to say that this number will only grow, and probably fairly rapidly."

SFARI RESEARCH ROUNDUP

Over the past 15 years, the Simons Foundation Autism Research Initiative (SFARI) has supported more than 400 researchers studying autism and related disorders. In 2017 alone, SFARI provided funding to more than 200 investigators from around the world, who have studied everything from sex differences in a mouse model of autism to the role of maternal gut bacteria in the condition. The following are some highlights of the research of SFARI Investigators in 2017.

Making sense of missense
Researchers have uncovered 200 candidate risk genes for autism and other neurodevelopmental conditions by examining 'missense' mutations — mutations that change only one nucleotide in a gene, but in a way that alters the resulting protein. Even though missense mutations are thought to account for more cases of autism than more damaging mutations called 'likely gene-disruptive' mutations, they have been studied far less, partly because they are so common in the general population that disentangling their role in autism is tricky.

Now, a team led by SFARI Investigator Evan Eichler of the University of Washington has analyzed missense mutations in 8,477 people with neurodevelopmental conditions, along with 2,178 controls. The team found 200 genes that have significantly more missense mutations in individuals with a neurodevelopmental condition than in controls; 79 percent of these genes have never before been associated with a neurodevelopmental condition. One of the most frequently appearing missense mutations was found in a gene called GRIA1, which encodes a receptor for a neurotransmitter called glutamate.

The study's techniques, described in the August 2017 issue of *Nature Neuroscience*, offer a way not just to identify candidate risk genes, but also to pinpoint just which parts of a gene confer the most risk if they are mutated. This information may prove valuable down the road when it comes to designing targeted therapies for autism and other neurodevelopmental conditions.

Preferred parents
People and animals have two copies of most genes — one copy from each parent — and conventional wisdom says that the two copies are expressed equally in the body. Yet studies of cultured cells have indicated that this may not always be the case. Now a study published March 8, 2017, in *Neuron* has shown for the first time that this conventional wisdom is not true in the brains of mice, monkeys and humans.

SFARI Investigator Christopher Gregg, of the University of Utah in Salt Lake City, and his collaborators found that mouse livers and muscle tissues and a brain region called the dorsal raphe nucleus all have some genes that preferentially express a particular parent's copy. When the researchers mutated one parental copy of one of these genes, they found patches of expression of the mutated gene throughout the mouse brain. The team also found genes with parental preferences in macaque monkeys and in postmortem human brains.

Several of the genes identified in macaques are associated with autism, and others are linked to bipolar disorder, intellectual disability or other neurodevelopmental conditions. Among the autism genes, one of two parental copies of DEAF1 is also preferentially expressed in four human brain regions, the team found. The research may help explain why some mutations linked to autism affect certain people more strongly than they do others: The mutation's effect may depend on which parent it came from.

A light switch
Changing the balance of excitation and inhibition in neurons instantly reduces social deficits in a mouse model of autism, researchers have found. The finding, by SFARI Investigator Karl Deisseroth and others at Stanford University, implies that the wiring in the brains of these mice is still capable of relatively normal social functioning, and suggests that treatments that change the excitation-inhibition balance might alleviate social difficulties in some individuals with autism.

The researchers, who reported their findings August 2, 2017, in *Science Translational Medicine*, engineered mice that lack CNTNAP2, a gene linked to autism, and also express special proteins that turn neurons on or off in response to a flash of light.

Mice lacking CNTNAP2 normally show no interest in interacting with unfamiliar mice. But when the researchers exposed these mice to a flash of blue light that caused inhibitory neurons in the prefrontal cortex to fire, the mice became interested in strange mice placed in their cage; the same thing happened when the team used flashes of light to turn off excitatory neurons. The flashes of light also make the mice less hyperactive, the team found. These results boost the long-held theory that over-excitement in the brain is responsible for many autism symptoms.

Sex differences in learning
Male mice with an autism-related mutation struggle with learning tasks that females with the mutation can perform as well as controls, a new study has found. The work, led by SFARI Investigator Ted Abel of the University of Iowa, illuminates some of the mechanisms that appear to protect girls from autism. Autism is almost five times more common in boys than in girls.

The mice in the new study, which was published October 17, 2017, in *Molecular Psychiatry*, lacked a stretch of DNA called 16p11.2. About 30 percent of people with a deletion in 16p11.2 have autism, and mice with the deletion have cognitive deficits and are hyperactive.

Male mice with the deletion take about three times as long as females with the deletion and controls to learn to poke their noses into a hole for a reward. Males with the deletion also show less perseverance than other mice when the task gets harder.

Abel and his colleagues examined the striatum — one of the brain's reward centers — in the mice and found that compared with controls and female mice with a 16p11.2 deletion, male mice with the deletion have increased activity in a signaling pathway that dampens neuronal activity, and also increased expression of a dopamine receptor that inhibits learning. Abel is planning further work to drill down into the molecular mechanisms underlying this vulnerability in males and resilience in females.

Antibiotic for autism?
Maternal exposure to infection during pregnancy raises the risk that the baby will have an autism-related condition, according to epidemiological studies. And mice exposed to a maternal infection in utero have a higher risk of autism-like behaviors. But pre-treating pregnant mice with an antibiotic protects their pups from developing these behaviors after a maternal viral infection, even though antibiotics don't kill viruses, researchers reported in the September 28, 2017, issue of *Nature*. The study was led by SFARI Investigators Jun Huh of Harvard University, Dan Littman of New York University and Gloria Choi of the Massachusetts Institute of Technology.

The study suggests that infection-induced autism-like features stem from inflammatory immune responses produced by maternal gut bacteria. Previous studies by several of the investigators who worked on the *Nature* paper showed that in pregnant mice with a viral infection, inflammatory molecules made by 'T helper 17' immune cells contribute to the development of cortical abnormalities, social deficits and repetitive behaviors in the mice's pups.

The research may help explain why some mutations linked to autism affect certain people more strongly than they do others.

In the new study, the researchers gave pregnant mice vancomycin, an antibiotic that kills the gut bacteria that spur the growth of T helper 17 cells. Even though the mice were exposed to a virus after antibiotic treatment, their pups developed normally, the researchers found.

Certain bacteria in human intestines also promote the growth of T helper 17 cells. Mice colonized with these bacteria and then infected with a virus gave birth to pups with autism-like features, the researchers found, unless the mothers were pre-treated with an antibody that blocks an inflammatory molecule the T helper 17 cells produce. The researchers hypothesize that women whose gut microbial community is skewed toward the bacteria that generate T helper 17 cells may be more likely than other women to have children with autism if they get an infection during pregnancy.

SPARKING AUTISM RESEARCH

Researchers who want to study autism often face a big obstacle before they even get started: how to track down enough individuals and families who meet the criteria for their studies, and then gain their participation. To overcome this obstacle, in April 2016 SFARI launched SPARK (Simons Foundation Powering Autism Research for Knowledge), an initiative that aims to create a repository of genetic and behavioral data from 50,000 individuals with autism and their families. The effort is well on its way.

A recruitment video delineates the SPARK participation process and underscores the mutually beneficial partnership of SPARK participants and autism researchers in understanding autism. www.sparkforautism.org

Two years into the initiative, SPARK has made substantial progress toward its target: more than 39,000 individuals with autism have already enrolled. "There has been an outpouring of support from the community," says Wendy Chung, the initiative's principal investigator and SFARI's director of clinical research.

SPARK participants complete several online questionnaires and mail in saliva samples from themselves and family members. They then have the option of taking part in future research studies, although such participation is never mandatory.

To boost enrollment from fathers, who are underrepresented among SPARK participants, the initiative ran a three-month-long outreach campaign called "Men of Action," starting on Father's Day 2017. "This was our first attempt to really connect with dads, and it got a very positive response," says Amy Daniels, SPARK's project manager. "We saw a notable increase in the number of fathers who enrolled and sent in saliva samples."

Autism researchers can now apply to SPARK's research match program, which connects them with appropriate SPARK families for their study. In its first year, the program helped researchers recruit thousands of families for more than 10 studies, ranging from assessments of environmental exposure during pregnancy to clinical investigations of brain function.

"It's so exciting to see how engaged SPARK participants are and how they are accelerating the pace of research," says Pamela Feliciano, SPARK's scientific director.

In addition to providing a platform for researchers to connect with potential study participants, the initiative is also in the process of genetically analyzing the saliva samples, which will vastly expand the pool of genetic data from families with autism. "SPARK families' data will help power a new level of discovery," Feliciano says.

To date, SPARK's genetic analyses have focused on the 'exome' — the protein-coding regions of the genome — because those are the regions in which it is easiest to establish a clear causal connection between mutations and autism. SPARK has completed whole-exome sequencing for 488 families and has made the data freely available to scientists. An additional 4,011 families are in the pipeline for whole-exome sequencing.

The initiative maintains a list of high-confidence autism risk genes, and as families are sequenced, they have the option of being notified through a physician or genetic counselor if they have a mutation in one of these high-risk genes. So far, about 5 percent of families have been eligible to receive results, a proportion that is likely to grow as new high-confidence genes are identified. SPARK has already expanded its high-confidence gene list by about 15 percent in the past year, Feliciano says.

Around 10 percent of SPARK participants will receive a result about the genetic cause of their autism, if they elect to receive it. "I had a million questions until we participated in the SPARK study and got the genetic finding," says Lynn Vigo, left, a mother of an adult with autism. "The finding explained so much of what we struggled to understand."

In addition to returning genetic results to families, SPARK is starting to provide families with individualized feedback that shows how their child's social questionnaire score compares with that of other children in SPARK, and it also hosts a series of autism webinars that have attracted more than 4,500 attendees. "An important goal of SPARK is to empower participants with knowledge and access to experts," Feliciano says. "As a parent of a child with autism myself, I know firsthand how helpful a little bit of data or a new insight can be. We aspire to arm all participants with information that will be useful to them."

TRACKING TWINS

New research on twins indicates that the way children look at the social world —
what they look at, when and for how long — is strongly influenced by genetics.
Image courtesy of John Constantino of the Washington University School of Medicine in St. Louis

One of the most immediately apparent traits of many individuals with autism is their diminished eye contact during social interactions. Warren Jones and Ami Klin, researchers at the Marcus Autism Center at Emory University in Atlanta, have spent more than 15 years teasing out the ways in which the gazing preferences of people with autism differ from those of the general population. The duo explores how people on the spectrum look at and learn about the social world — and how differences in these gazing behaviors manifest early in life. And in 2017, in a collaboration with John Constantino of Washington University in St. Louis, they uncovered compelling evidence that gazing differences are tightly tied to genetics.

Many of Jones and Klin's deepest insights into autism have emerged from the unusual and ambitious design of their experiments: Instead of studying children who have already been diagnosed with autism, as most researchers

"This is really how you should be doing science."

do, they focus instead on those children's baby siblings to try to spot the behavioral differences underlying autism at the earliest possible age. 'Baby sibs' of children with autism are 20 times as likely as infants in the general population to eventually be diagnosed with autism.

Such experiments are difficult and expensive, as not only do they typically take years, but they also must include far more children than will ultimately receive an autism diagnosis. Even though baby sibs have an elevated risk of autism, only about one in five of them eventually receives a diagnosis.

"This is really how you should be doing science," says John Spiro, deputy scientific director of the Simons Foundation Autism Research Initiative. "But it's very hard to carry out."

The Simons Foundation was a key early funder of Jones and Klin's work, providing support both for specific studies (including 2009 and 2013 papers in *Nature*) and for the research infrastructure that made the team's long-term studies possible. "That platform has enabled some of our most important insights into the early development of autism," Jones says.

For instance, it allowed them to figure out in 2009 that, unlike typical toddlers, 2-year-olds with autism have no preference for 'biological motion,' an evolutionarily highly conserved and foundational mechanism of socialization. And in 2013, the team reported that gazing differences appear even earlier in development: Baby boys who are later diagnosed with autism start losing interest in looking at eyes sometime between 2 and 6 months — the earliest behavioral marker of autism found to date. This marker is predictive of a diagnosis of autism, and severity of features, at 36 months, they found.

Most recently, Jones, Constantino, Klin and their colleagues reported July 20, 2017, in *Nature* that the way infants view social scenes is highly influenced by genetics. Identical twin toddlers, they found, make strikingly similar decisions about not just what to focus on but even how to shift their gaze in search of social information from moment to moment. "Identical twins effectively synchronized their looking at social content," Jones says. "We found remarkably strong evidence that genes directly shape the way a child sees the world."

The types of gazing that the team found to be most powerfully influenced by genetics — attention to eyes and mouths — are the same ones that are strongly decreased in children with autism. "It's gratifying to see Warren and Ami's early work extended in this really interesting way and starting to make connections to the genetics of autism," Spiro says.

SCIENCE SANDBOX:
THE CHANGING FACE
OF SCIENCE MUSEUMS

Some people aren't comfortable in big, formal science museums. Others face economic barriers to entry or don't have such an institution in their community. Luckily, getting involved in science is becoming more and more apt to happen outside a formal setting. Evolving explorations of what it means to be a modern science museum means that many more people are encountering — and participating in — scientific programming, wherever they may be.

Science Sandbox, a Simons Foundation initiative whose mission is to unlock scientific thinking by engaging people with the process of science, is now helping some of its grantee partners upend the stereotype of the traditional, staid science museum.

MICRO, a nonprofit founded in 2016 by computational ecologist Amanda Schochet and media producer Charles Philipp, works with designers, artists and scientists to pack knowledge into cabinets of curiosity about the size of a vending machine. MICRO increases exposure to science learning by partnering with venues such as the Brooklyn Public Library, Ronald McDonald House and Rockefeller Center to install these tiny museums. The first museum in their 'fleet,' the Smallest Mollusk Museum, can go almost anywhere, from hospital waiting rooms to community centers and malls, reaching people where they already are.

The mollusk museum features a 3-D-printed octopus brain and a glowing holographic aquarium, where visitors can peek inside to see virtual images of mollusks swimming, squid hunting or octopuses squiggling around. Continue around the display to learn how the creatures live, how similar they are to aliens in movies and how they've adapted to survive.

Not only does the Smallest Mollusk Museum teach people about the mollusk world, its compact size physically brings visitors closer together as they learn. While children study the more visual aspects of the exhibit, their parents often

read the copy and share information. After exploring the museum side by side, people who just met sometimes walk away in conversation, Schochet says. One visitor left the museum announcing: "I'm a mollusk person now!"

"It's important for everyone to have access to this kind of knowledge, and for it to be presented in ways that someone with no background in science can jump in and begin to see the big picture," says Schochet. "The dream is to install 6-foot-tall museums all over the country. Even in the Department of Motor Vehicles!"

Another Science Sandbox partner, the New York Hall of Science (NYSCI) — located in Queens — uses science to bridge cultural and economic divides. The museum's NYSCI Neighbors program, an outreach effort in Queens' Corona neighborhood, launched Science Ambassadors in February 2017. The museum opens up after school, free of charge, to students in a network of 20 collaborating schools within walking distance. Children get help with homework, explore exhibits in the museum and take advantage of the Design Lab and Maker Space.

Many schools in the area — where most residents are immigrants — don't provide much access to STEM programming, says Margaret Honey, president and chief executive officer of NYSCI. And if you are an undocumented immigrant, a large museum might be all the more intimidating. So NYSCI Neighbors hopes to build trust within Corona by offering resources and shared experiences that help both parents and children engage in science.

"I think it's a good opportunity for kids and parents to come in and then to get exposed to the rest of the stuff that's in the museum," says Luz Salazar, whose daughter, Camila Melendez, gets homework help through Science Ambassadors. When Camila finishes her studies, she takes part in design-make-play classes that nurture creative problem-solving.

"A place like this can be a game-changer because it can really open up what learning is about," says Honey. "Every learner can find a foothold here that makes them feel successful. We can create experiences here that are designed to ensure that every visitor feels a sense of possibility, a sense of 'I can do this.'"

A third Science Sandbox partner, the Exploratorium, focuses on helping people learn on their own through interactive exhibits. Founded by physicist and educator Frank Oppenheimer in 1969, this highly regarded public science museum and learning laboratory in San Francisco, California, encourages visitors to be curious and ask questions. In the museum's Tinkering Studio, for example, visitors use tools such as pliers, scissors and sewing needles to create projects — such as wearable working circuits — that they can follow up with at home.

The museum also creates science experiences for the people outside its walls: its Studio for Public Spaces places exhibits throughout San Francisco. When people encounter an exhibit or a novel, surprising environment while going about their daily lives, this can create a welcome interaction and learning experience. Some displays foster examination of the physical senses, whereas others bring people together to explore social interactions. Engaging with people outside of the museum often creates a more meaningful experience for them, says Robert Semper, the museum's associate executive director.

"For people who live in this world, in this society, it's critically important for them to both have the skills and the experience to be independent learners," Semper says. "This means providing learning experiences where people live and work day to day, as well as providing them in more formal settings like museums."

Science Sandbox also partners with non-museum organizations that take similarly innovative approaches to communicating science widely.

The Science Festival Alliance's Just Add Science initiative also meets people on their own turf, infusing science into venues such as county fairs, sporting events and Renaissance festivals. Pioneer Works, a cultural center in a restored warehouse in Brooklyn's Red Hook neighborhood, offers programming such as the Scientific Controversies series, which features speakers such as biologist Richard Dawkins and Nobel laureate Rainer Weiss in conversation about provocative topics in science. And the San Francisco Bay Area's Science Action Club, designed by the California Academy of Sciences, is a nationwide out-of-school program for middle schoolers that encourages curiosity about the natural world while providing students with hands-on activities that promote STEM learning.

All these programs further Science Sandbox's goal of helping people realize that they do not have to be a scientist to think like one. "We believe society as a whole benefits when people engage in things like evidence-based reasoning, informed decision-making and critical thinking," says Greg Boustead, program director for Science Sandbox. "It's important to encourage people to be active participants in science, not just tell them that science is important. When they make their own connections — through their own context and their own background — we think it's a powerful way to engage."

The Exploratorium installed this public interactive exhibit in San Francisco, called 'Whispering Dishes.' A pair of curved concrete dishes (just one is shown) focuses sound so that two people around 15 meters apart can hear one another whispering, even over the din of a busy street. *Image courtesy of the Exploratorium*

MATH FOR AMERICA: SUMMER THINK

Engaging students with chemistry sometimes means swapping beakers for spatulas. Math for America (M*f*A) Master Teachers Hayeon Rachel Jun and Laryssa Kramarchuk blend science and the culinary arts in their classrooms. Lessons have students hand-churning ice cream, growing rock candy and quantifying the hotness of peppers, all while studying the underlying scientific properties of these materials.

Jun and Kramarchuk shared these experiences with fellow math and science teachers last July at a three-day M*f*A conference called "Summer Think." Their session, "Kitchen Chemistry," was one of many opportunities at the M*f*A Summer Think for teachers to collaborate and share their ideas on how to engage students with mathematics and the sciences.

This inaugural summer series at M*f*A's New York City headquarters continued the organization's mission of supporting outstanding teachers, which it does by fostering collaboration, offering professional growth opportunities and providing financial support to teachers. Importantly, all the sessions at Summer Think are led by and for teachers.

Jun and Kramarchuk demonstrated one of their chemistry lessons about phase transitions and crystallization. Attendees shook plastic baggies of salt, ice, sugar and cream, periodically pausing to measure the temperature of their solidifying ice cream mixes. Whereas pure water freezes at 32 degrees Fahrenheit, the addition of salt and sugar lowers the mixture's freezing point by a few degrees, as the salt and sugar molecules get in the way of water molecules joining to crystallize.

That session, and many others like it during the meeting, inspired Summer Think participants to try new approaches themselves. Jun and Kramarchuk "were so honest about their experience and how it had gone, including the things that didn't go well," says fellow M*f*A Master Teacher Courtney Ginsberg, who teaches high school mathematics at Humanities Preparatory Academy. "The session made me feel more comfortable to do something seemingly crazy like that in my classroom, where it could be a mess of kids throwing ice cream around."

The 2017 Summer Think was M*f*A's first summer conference. "You can feel the difference in a room full of teachers when it's summer," says Courtney Allison, deputy executive director for M*f*A. "Everyone was a lot more relaxed and casual. Teachers repeatedly tell us how much they love when we do things outside of the normal school year because they have time to think. You're not in the thick of things."

> "We provided the structural support, but the teachers came up with the conference ideas and all of the programming."

John Ewing, president of M*f*A, says the organization is no stranger to doing things differently. "M*f*A was begun with a revolutionary idea — that the best way to improve teaching is to focus first on the most accomplished teachers. Excellence is best built on excellence."

M*f*A's goals are to keep the most accomplished math and science teachers in the classroom, foster teacher-to-teacher professional growth, provide teachers with opportunities for leadership, and influence and build a professional community of accomplished teachers to collaborate and learn from one another. M*f*A now supports more than 1,000 math and science teachers in New York City who are making a lasting impact on their students, schools

and communities. Overall, the organization works to inspire, support and share new ideas that shape policy, practice and the retention of excellent teachers in mathematics and science across New York City's 1,700 public schools and beyond.

M*f*A awards renewable four-year fellowships, which include a stipend and frequent opportunities for teachers to connect with one another. The organization also offers extensive professional learning and growth opportunities, such as courses, workshops and seminars, throughout the school year.

The original spark that led to Summer Think was anything but straightforward. It came from M*f*A Master Teacher Brian Palacios, a high school math teacher at the Bronx Center for Science and Mathematics. Palacios received a grant from M*f*A to attend a summer meeting of teachers who collaborate on Twitter. In his written reflection on that meeting, he proposed that M*f*A host a summer conference. M*f*A staff jumped on the idea and recommended that Palacios spearhead the planning, with their support. "It was just a crazy idea," he says. "I didn't have the slightest clue how to plan a conference. I didn't even know how to start."

After sending out feelers for other M*f*A teachers interested in helping plan the as-yet-unnamed conference, things remained uncertain for a time, Allison says. "We wondered if a large enough group would be interested in a summer event. Twenty teachers showed up for the first planning meeting, which was too many to plan a conference, so they got some ideas and made a smaller planning committee."

Leah Hirsch, a program officer at M*f*A, shepherded the teachers through the uncertainties of the process. "We provided the structural support, but the teachers came up with the conference ideas and all of the programming."

This type of support is what M*f*A does — and it means a lot — says Ginsberg, who also served on the planning committee. "M*f*A had trust in us as teachers to put together and fund this conference," she says. "It feels good to be part of a community where they trust us and believe that we have the best intentions at heart, which is not something we all get in our school communities."

With M*f*A's help, the planning team gathered proposals for sessions. "We got a bunch of proposals, and so we made our own rubric and graded them," says M*f*A Master Teacher Diana Lennon, an environmental science teacher at Columbia Secondary School, who also served on the planning committee. "We were looking for proposals that were outside of the things we could do during the time we

have during the school year — and something that would bridge the divide between science and math teachers."

Summer Think sessions included a 'deep dive' into how to incorporate climate change justice into lesson plans by combining statistics and climate science. Led by M*f*A Master Teacher Peter Mulroy, the session explored analyzing demographic and climate datasets to uncover links between poverty, race and future climate impacts. "It was nice to go beyond just scatter plots related to climate justice," Ginsberg says. Teachers who attended the session are still swapping materials and ideas online, she says.

Master Teacher Jeffrey Horenstein discusses his group's paper craft design during a 'deep dive' session facilitated by fellow Master Teacher Vielca Anglin. The Summer Think session, titled "Curriculum Reboot: Design Challenge as Assessment," explored how integrating math and science into the design process can inspire empathy, critical thinking and real-world problem-solving in students.

Other sessions went beyond curricula. "Facilitation as Leadership" discussed how teachers can embrace their role as leaders to ensure equity and access for all students. Attendees assembled a toolkit of ways to manage group dynamics and give students a voice. The session helped build strong connections among teachers, Lennon says.

"We had to let our guard down," she says. "At M*f*A, I feel like I can do that. At the Summer Think, we shared one of the things we'd like to improve about our teaching or that we didn't think was going well. It's hard as a teacher to put yourself out there and say, 'I don't think I do this well.'"

Facing uncertainties and trying new things as a community were common themes throughout the conference, from the session topics to the meeting's very planning. And they'll be central themes for the 2018 Summer Think, too. "There were a lot of people trying things for the first time at this conference," says Ginsberg. "It's important for teachers to step into that role, because that's what we're always asking our students to do."

SCIENTIFIC LEADERSHIP

The Simons Foundation's research and grant-making divisions are spearheaded by accomplished scientists. These individuals bring expertise, experience and creative thinking to overcoming the uncertainty involved in advancing research in mathematics and the basic sciences.

Marian Carlson

Marian Carlson is director of the Simons Foundation's Life Sciences division. The division supports, alongside more traditional awards programs, collaborations devoted to the study of marine microbial ecosystems and the origins of life. These research areas contain "huge unknowns and great complexity," she says. The rock record from the time life arose on Earth has been erased almost entirely, she says, and marine microbial communities across the world contain incredible diversity.

Carlson's interest in the life sciences comes from a lifelong fascination with the outdoors and the biosphere. She majored in biochemical sciences, examining living cells at the molecular level, and earned her Ph.D. from Stanford University. She is professor emerita of genetics and development at Columbia University and served as senior associate dean and vice dean for research at the medical school. Her laboratory used genetic analysis to identify and study conserved mechanisms of signal transduction and transcriptional regulation.

Nick Carriero

"Ours is a world in which we try to beat out all uncertainty," Nick Carriero says. Carriero co-directs the Flatiron Institute's Scientific Computing Core, which develops, deploys and maintains the institute's computational infrastructure and develops software for the greater scientific community.

Coders, he says, expect the same chunk of code to function the same way even on different hardware. Carriero ensures that the institute's computers and software perform reliably, drawing from his experience managing high-performance computing platforms as co-director of Yale University's W.M. Keck Biotechnology Resource Laboratory. "If you run the same thing designed to be deterministic twice and you get different answers, that's a bad thing," he says.

Sometimes a bit of uncertainty can help drive discovery, though. "Non-determinism and randomness are cousins of uncertainty," he says, "and they both play important roles in computing." Computers can generate random numbers that can help assess an algorithm's efficiency or broaden a simulation's scope. "There's no point running a simulation multiple times if it's deterministic. But by introducing randomness, your simulation will explore something slightly different each run," Carriero says.

Gerald D. Fischbach

"The human brain is the most complex and mysterious object in the known universe," says Gerald D. Fischbach, distinguished scientist and fellow at the Simons Foundation. "Once we understand even a hint about how nerve cells in the brain give rise to thoughts, emotions and behavior, it will break open a whole new world."

Fischbach first wondered how the mind works while taking philosophy courses in college. Seeing few graduate programs in neuroscience, he decided to attend medical school. He went on to Harvard University, where he studied the formation and maintenance of synapses, which play an essential role in communication in the brain. His expertise led to professorships at Washington University and Harvard Medical School. He subsequently served as director of the National Institute of Neurological Disorders and Stroke and then as executive vice president for health sciences at Columbia University.

In 2006, Fischbach joined the foundation as founding director of the Simons Foundation Autism Research Initiative (SFARI). As a founder of the Simons Collaboration on the Global Brain, Fischbach says, "The Global Brain studies internal mental states; SFARI studies how the brain develops. I am optimistic that these projects will enhance one another."

Ian Fisk

Ian Fisk is co-director of the Flatiron Institute's Scientific Computing Core, which manages the institute's computational infrastructure and develops computational software for the scientific community. "We try to make sure that scientific progress is limited by how quickly the people can think and understand, and not by how quickly computers can process and access data," he says.

Fisk majored in mathematics and physics in college before earning his M.S. and Ph.D. from the University of California, San Diego. He later served in several roles overseeing the preparation of the computational infrastructure for the Compact Muon Solenoid experiment within CERN's Large Hadron Collider program. He joined the Flatiron Institute in 2014, then called the Simons Center for Data Analysis, because building up the computational infrastructure for a multidisciplinary research institute "sounded like a great challenge," he says.

The core's work, he says, involves adapting to the evolving challenges of supporting scientific research. "How people need to work to make progress in their fields is always changing," Fisk says. "How to plan for capacity and capability is constantly changing."

Gregory Gabadadze

Gregory Gabadadze joined the Simons Foundation in 2017 as associate director for physics in the Mathematics and Physical Sciences division. He is chair of the physics department at New York University and served as director of the university's Center for Cosmology and Particle Physics.

In high school, he was inspired by an article that explained that a vacuum isn't truly empty but instead is populated by fleeting virtual waves and particles popping in and out of existence due to quantum uncertainty. That germ of wonderment led him to earn a Ph.D. from Rutgers University, after which he began researching the universe at the smallest and largest scales by studying particle physics, gravity and cosmology.

His work, he says, is motivated by the big outstanding questions in physics. "We don't understand about 95 percent of what our universe is made of," he says. "We don't understand the patterns of masses and interactions of the most elementary particles that make the things around us." Those puzzles, he says, "keep me up at night."

Antoine Georges

Antoine Georges is director of the Center for Computational Quantum Physics (CCQ) at the Flatiron Institute and a pioneer of dynamical mean-field theory, a method to determine the electronic structures of materials containing electrons that display collective, rather than individual, behavior.

At the CCQ, Georges continues his innovative research into the behaviors of the unfathomable numbers of electrons that govern the properties of molecules and materials. The quantum mechanical behavior of all those electrons is "simple to formulate but extremely hard to solve," Georges says. Together with co-director Andrew Millis and distinguished research scientist Angel Rubio, he leads the center's efforts to develop ideas, algorithms and code to help tame the complexities of the quantum world.

Georges received his Ph.D. from the École Normale Supérieure in France and is professor of physics at the Collège de France, where he holds the chair in condensed matter physics. He is a member of the French Academy of Sciences and shared the 2006 Europhysics Prize in condensed matter physics for his contributions to the development of dynamical mean-field theory.

Leslie Greengard

"Computational biology is an interesting intersection of problems that come from biology with methods that come from mathematics," Leslie Greengard says.

Greengard has, fittingly, both an M.D. and a Ph.D. in computer science from Yale University. He is director of the Center for Computational Biology (CCB) at the Flatiron Institute and Silver Professor of Mathematics and Computer Science at New York University. Together with Vladimir Rokhlin, he developed the fast multipole method, a mathematical technique with a wide range of applications that speeds up the calculation of long-range forces in the n-body problem. The Institute of Electrical and Electronics Engineers named the method one of the top 10 algorithms of the 20th century.

As director of the CCB, Greengard oversees groups working on modeling frameworks, algorithms and software to help scientists probe large experimental datasets for new insights into the biological world.

Alex Lash

Alex Lash is the Simons Foundation's chief informatics officer. His team helps manage, analyze and disseminate the foundation's extensive scientific datasets and develops software tools to advance the foundation's mission. The work combines his training in anatomic pathology and a lifelong love of computers. He was previously a laboratory member in the computational biology program and then scientific director of the bioinformatics core facility at Memorial Sloan Kettering Cancer Center in New York.

Designing a software tool requires a firm understanding of how people will use the system, Lash says, but developing that understanding can be tricky. "There's always a bit of uncertainty about what users want, even if you have them right in front of you. They can't perfectly foresee how they might use the system, and neither can we," he says.

Lash's team addresses this challenge by putting themselves in users' shoes during pre-launch designing and testing, and then by tracking feedback after a launch and fine-tuning the software accordingly. "That's how you make your users happy," he says.

Andrew Millis

Andrew Millis is co-director of the Center for Computational Quantum Physics at the Flatiron Institute. He formerly served as associate director for physics at the Simons Foundation. Millis is also professor of physics at Columbia University and director of the Simons Collaboration on the Many Electron Problem. In July 2017, he received the Hamburg Prize for Theoretical Physics for his contributions to the field of condensed matter physics.

Millis' research focuses on understanding how interactions between particles influence the properties of molecules and materials. "The intellectual challenge is to understand the quantum mechanics of interacting many-particle systems," he says. "You put large numbers of particles together, and they do crazy and interesting things. We want to understand how and why this happens."

Ultimately, Millis hopes, the center's research will help materials scientists not only understand the properties of known compounds, but also design new materials and molecules with desired properties. "Thanks to a remarkable combination of new experiments, new theoretical and computational methods, and the unique environment provided by the Flatiron Institute, we have the chance to really make progress on fundamental understanding and control of the quantum properties of materials," he says.

Louis Reichardt

Louis Reichardt is director of the Simons Foundation Autism Research Initiative (SFARI), overseeing the group's efforts to study the causes of autism and enhance the quality of life of individuals with the condition and their families.

Reichardt initially intended to study history in college but was inspired by the Sputnik satellite, molecular biologist James Watson, and novelist and physical chemist C.P. Snow to change his major to biology. After attending the University of Cambridge as a Fulbright scholar and completing his Ph.D. at Stanford University, he changed his research interest from genetics and molecular biology to neuroscience as a postdoctoral fellow at Harvard University.

At the University of California, San Francisco, his lab identified the protein synaptotagmin 1, later shown by others to be critical for neurotransmitter release. He completed many studies on neurotrophins and their receptors, which are essential for neuronal survival and function. By combining genetic, cellular and biochemical analyses, his group characterized the impact of cell adhesion molecules on autism-related behaviors. In July 2013, he assumed directorship of SFARI.

David Spergel

David Spergel directs the Center for Computational Astrophysics at the Flatiron Institute. The center, he says, aims to "address some of the basic questions that we have about the universe: How did it begin? How will it end? How did the Earth, stars and our galaxy form? What makes up the universe?"

Spergel has spent his career tackling some of those cosmological conundrums. Since receiving his Ph.D. from Harvard University, he has focused on probing the nature of dark matter and uncovering new physics. He played an influential role in the Wilkinson Microwave Anisotropy Probe project, which mapped temperature fluctuations in the heat left over from the Big Bang.

In December 2017, Spergel and his colleagues received the 2018 Breakthrough Prize in Fundamental Physics for their work on that project. In addition to his directorship, he is Charles A. Young Professor of Astronomy at Princeton University.
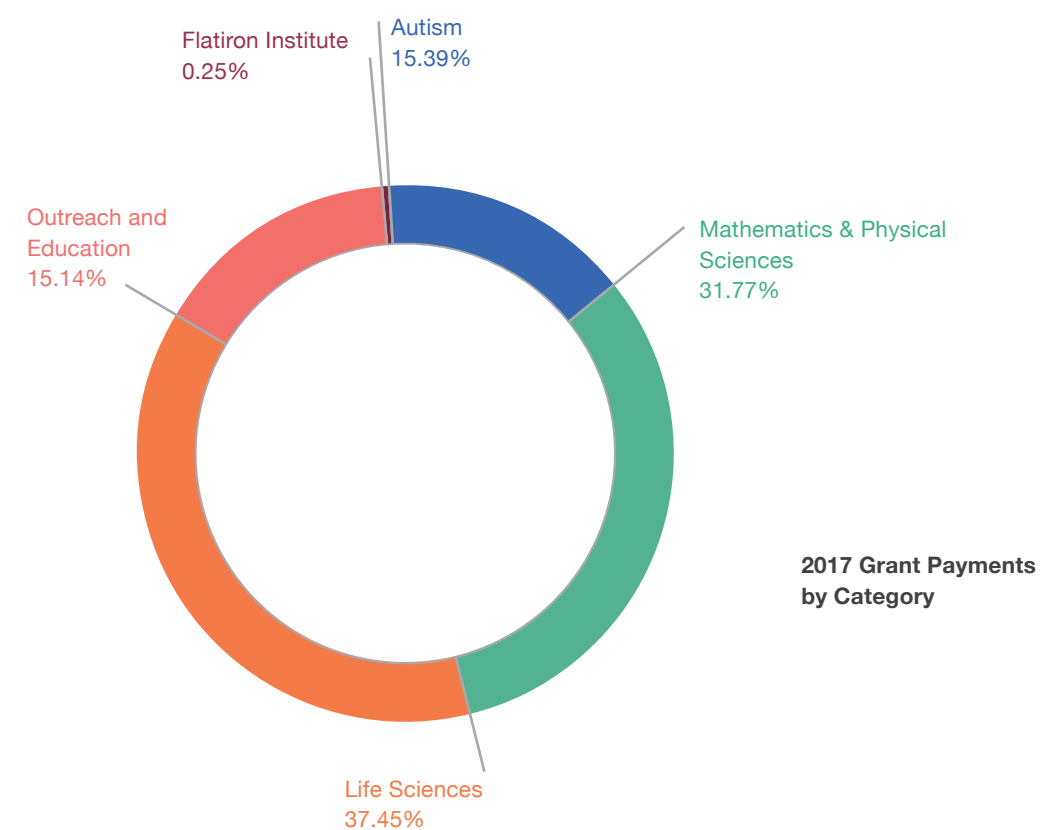
Yuri Tschinkel

At age 15, Yuri Tschinkel picked up a book about number theory, which sparked his enduring interest in the theory of numbers. That interest led him to earn a Ph.D. from the Massachusetts Institute of Technology and pursue a career as a research mathematician, working at the interface of algebraic and arithmetic geometry. Now, as director of the Simons Foundation's Mathematics and Physical Sciences (MPS) division, he is dedicated to supporting mathematics, physics and theoretical computer science on a much broader scale.

Conducting mathematical research and overseeing MPS each provide unique challenges, he says. "In number theory, there is no uncertainty," Tschinkel says. "In decisions on grant applications, there is a lot of uncertainty: Panels sometimes produce divergent opinions; long-term projects may or may not lead to exciting science."

Tschinkel is excited by the utility that computational tools are bringing to areas of pure mathematics. Such methods allow mathematicians to tackle problems that are larger and more complex than ever before. But even with such technological advances, "sometimes one needs just a brilliant idea" to make a breakthrough, he says.

FINANCIALS

2017 Grant Payments by Category

- Flatiron Institute 0.25%
- Autism 15.39%
- Outreach and Education 15.14%
- Mathematics & Physical Sciences 31.77%
- Life Sciences 37.45%

Proportions of Expenses
(Cash Basis) $'s in Millions

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

	2017	2016
Grants Paid	272.9	231.7
Program	66.5	50.3
General and Administrative	40.4	24.4
Capital Expenditures	52.6	39.4
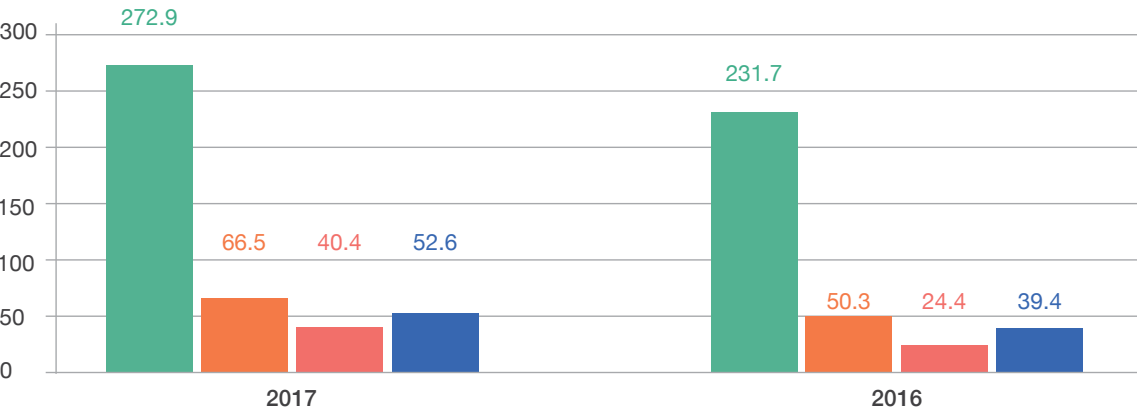
BALANCE SHEET

Assets	12/31/17*	12/31/16
Cash and Cash Equivalents	247,842,261	160,564,011
Investment Portfolio	2,800,626,072	2,663,512,864
Property and Equipment, Net	246,719,463	206,583,733
Other	2,028,544	2,360,299
Total	**3,297,216,340**	**3,033,020,907**

Liabilities	12/31/17*	12/31/16
Accounts Payable	17,157,197	13,505,532
Grants Payable	545,446,555	524,286,998
Capital Lease Obligation	151,135,182	147,834,375
Deferred Rent	2,852,656	3,621,571
Deferred Excise Tax Liability	20,638,967	20,638,967
Total	**737,230,557**	**709,887,443**
Net Assets	**2,559,985,783**	**2,323,133,464**

INCOME STATEMENT

Revenue	For 12 Months Ended 12/31/17*	For 12 Months Ended 12/31/16
Contributions	221,459,214	80,250,000
Investment Income	424,446,359	477,382,475
Total	**645,905,573**	**557,632,475**

Expenses	For 12 Months Ended 12/31/17*	For 12 Months Ended 12/31/16
Grants Paid	272,920,016	231,726,909
Change in Grants Payable	19,124,032	(2,954,477)
Program	76,879,247	52,515,562
General and Administrative	22,006,106	17,386,576
Depreciation and Amortization	11,321,845	3,618,990
Taxes	6,802,007	9,917,523
Total	**409,053,253**	**312,211,083**
Net Income	**236,852,320**	**245,421,392**

* Unaudited financial statements

FLATIRON INSTITUTE SCIENTISTS

Center for Computational Astrophysics

David Alonso
Justin Alsing
Lauren Anderson
Daniel Anglés-Alcázar
Florencio Balboa Usabiaga
Nicholas Battaglia
Megan Bedell
Vasily Belokurov
Jo Bovy
Ramy Brustein
Greg Bryan
Matteo Cantiello
Kelle Cruz
Romeel Dave
Avishai Dekel
Wyn Evans
Glennys Farrar
Stephen Feeney
Daniel Foreman-Mackey
Charles Gammie
Shy Genel
Melanie Habouzit
Chris Hayward
Lars Hernquist
David Hogg
Kenta Hotokezaka
Chia-Yu Hu
Jack Hughes
Fangzhou Jiang
Chang-Goo Kim
Yuri Levin
Miao Li
Yuan Li
Christopher McKee
Chiara Mingarelli
Suvodip Mukherjee
Sigurd Naess
David Neufeld
Jerry Ostriker
Lyman Alexander Page
Tsvi Piran
Bill Press
Eliot Quataert
Ellianna Schwab
Rachel Somerville
David Spergel

Tjitske Starkenburg
Amiel Sternberg
James Stone
Romain Teyssier
Stephanie Tonnesen
Francisco Villaescusa-Navarro
Elijah Visbal
Ben Wandelt
Neal Weiner

Center for Computational Biology

Tarmo Äijö
Joakim Andén
Yanis Bahroun
Alex Barnett
Meet Barot
Richard Bonneau
Nikolai Chapochnikov
Kathleen Chen
Xi Chen
Dmitri "Mitya" Chklovskii
Nicholas Chua
Patrick Combettes
Nick De Veaux
Charles Epstein
Reza Farhadifar
Lisa Fauci
Johannes Friedrich
Julien Funk
Sebastian Fürthauer
Mariano Gabitto
Alex Genkin
Andrea Giovannucci
Vladimir Gligorijevic
Kiley Graim
Leslie Greengard
John Hayward
Shidong Jiang
Jaeyoon James Jun
Eva Kanso
Julia Koehler
Enkeleida Lushi

Jeremy Magland
Cara Magnabosco
Victor Minden
Aditya Mishra
Christian L. Müller
Ehssan Nazockdast
Daniel Needleman
Naomi Oppenheimer
Cengiz Pehlevan
Eftychios Pnevmatikakis
Daniel Podolsky
Aditya Rangan
Anders Rasmussen
P. Douglas Renfrew
David Saintillan
Rachel Sealfon
Anirvan Sengupta
Sebastian Seung
Michael Shelley
Amit Singer
Marina Spivak
David Stein
Mariano Tepper
Olga Troyanskaya
Shravan Veerapaneni
Jun Wang
Aaron Wong
Witold Wysota
Wen Yan
Jian Zhou

FLATIRON INSTITUTE SCIENTISTS

Center for Computational Quantum Physics

Giuseppe Carleo
David Ceperley
Jing Chen
Xi Chen
Martin Claassen
Antoine Georges
Alexandru Georgescu
Gabriel Kotliar
Peter Lunts
Andrew Millis
Olivier Parcollet
Riccardo Rossi
Angel Rubio
Hao Shi
Miles Stoudenmire
Hugo Strand
Steve White
Manuel Zingl

Scientific Computing Core

Nick Carriero
Justin Creveling
Ian Fisk
Andras Pataki
Dylan Simon
Nikos Trikoupis
Aaron Watters

MATHEMATICS AND PHYSICAL SCIENCES SIMONS INVESTIGATORS

Scott Aaronson
Mina Aganagic
Ian Agol
Igor Aleiner
Andrea Alu
Rajeev Alur
Sanjeev Arora
Ngô Bảo Châu
Boaz Barak
Andrei Beloborodov
Andrei Bernevig
Andrea Bertozzi
Manjul Bhargava
Dan Boneh
Simon Brendle
Michael Brenner
Garnet Chan
Moses Charikar
Nigel Cooper
Ingrid Daubechies
Michael Desai
Daniel Eisenstein
Alex Eskin
Jonathan Feng
Paul François
Victor Galitski
Surya Ganguli
Sharon Glotzer
Shafi Goldwasser
Ben Green
Steven Gubser
Larry Guth
Christopher Hacon
Oskar Hallatschek
Patrick Hayden
Chris Hirata
Wayne Hu
Russell Impagliazzo
Piotr Indyk
Shamit Kachru
Randall Kamien
Marc Kamionkowski
Charles Kane

Anton Kapustin
Ludmil Katzarkov
Richard Kenyon
Subash Khot
Alexei Kitaev
Jon Kleinberg
Kirill Korolev
James Lee
Andrea Liu
Madhav Mani
Lisa Manning
Vladimir Markovic
James McKernan
Pankaj Mehta
Maryam Mirzakhani
Joel Moore
Andrew Mugler
Arvind Murugan
James O'Dwyer
Andrei Okounkov
Hirosi Ooguri
Eve Ostriker
Bjorn Poonen
Frans Pretorius
Eliot Quataert
Leo Radzihovsky
Igor Rodnianski
Raphael Rouquier
Anders Sandvik
David Schwab
Paul Seidel
Eva Silverstein
Amit Singer

Christopher Skinner
Allan Sly
Dam Son
Kannan Soundararajan
Dan Spielman
Anatoly Spitkovsky
Iain Stewart
Madhu Sudan
Terence Tao
Daniel Tataru
Shang-Hua Teng
Senthil Todadri
Chris Umans
Salil Vadhan
Mark Van Raamsdonk
Ashvin Vishwanath
Anastasia Volovich
Aryeh Warmflash
Michael Weinstein
Daniel Weissman
Horng-Tzer Yau
Xi Yin
Olga Zhaxybayeva
David Zuckerman

MATHEMATICS AND PHYSICAL SCIENCES INVESTIGATORS

Awardees

Vijay Balasubramanian
Sam Brown
Robbert Dijkgraaf
Tony Ezome
Terrence Hwa
Brian Keating
Christopher Klausmeier
Jane Kondev
Adrian Lee
Simon Levin
Richard Lifton
Edward Lungu
M. Cristina Marchetti
Pankaj Mehta
Surjeet Rajendran
Alvaro Sanchez
Diaraf Seck
Boris Shraiman
Mukund Thattai
Christopher Tully
Massimo Vergassola
Kalin Vetsigian

Simons Collaboration on Algorithms and Geometry

Alexandr Andoni
Sanjeev Arora
Tim Austin
Mark Braverman
Jeff Cheeger
Subash Khot
Bruce Kleiner
Assaf Naor
Ran Raz
Oded Regev
Michael Saks
Amit Singer
David Steurer
Avi Wigderson

Simons Collaboration on Homological Mirror Symmetry

Mohammed Abouzaid
Denis Auroux
Ron Donagi
Kenji Fukaya
Ludmil Katzarkov
Maxim Kontsevich
Bong Lian
Tony Pantev
Shing-Tung Yau

Simons Collaboration on Special Holonomy in Geometry, Analysis and Physics

Bobby Acharya
Robert Bryant
Simon Donaldson
Sebastian Goette
Mark Haskins
Dominic Joyce
David Morrison
Johannes Nordstrom
Simon Salamon
Song Sun

Simons Collaboration on the Many Electron Problem

Garnet Chan
Antoine Georges
Emanuel Gull
Gabriel Kotliar
Evgeny Kozik
Olivier Parcollet
Nikolay Prokofiev
Mark van Schilfgaarde
Sandro Sorella
Guifre Vidal
Lucas Wagner
Steven White
Dominika Zgid
Shiwei Zhang

MATHEMATICS AND PHYSICAL SCIENCES INVESTIGATORS

It from Qubit: Simons Collaboration on Quantum Fields, Gravity and Information

Scott Aaronson
Dorit Aharonov
Vijay Balasubramanian
Horacio Casini
Daniel Harlow
Patrick Hayden
Matthew Headrick
Alexei Kitaev
Juan Maldacena
Alexander Maloney
Donald Marolf
Robert Myers
Jonathan Oppenheim
John Preskill
Leonard Susskind
Brian Swingle
Tadashi Takayanagi
Mark Van Raamsdonk

Simons Collaboration on Cracking the Glass Problem

Ludovic Berthier
Giulio Biroli
Patrick Charbonneau
Eric Corwin
Silvio Franz
Jorge Kurchan
Andrea Liu
Lisa Manning
Sidney Nagel
Giorgio Parisi
David Reichman
Matthieu Wyart
Francesco Zamponi

Simons Collaboration on the Nonperturbative Bootstrap

Christopher Beem
Miguel Costa
Andrew Fitzpatrick
Thomas Hartman
Jared Kaplan
Zohar Komargodski
Joao Penedones
David Poland
Silviu Pufu
Leonardo Rastelli
Slava Rychkov
David Simmons-Duffin
Balt van Rees
Pedro Vieira

Simons Collaboration on Arithmetic Geometry, Number Theory, and Computation

Jennifer Balakrishnan
Noam Elkies
Brendan Hassett
Bjorn Poonen
Andrew Sutherland
John Voight

Origins of the Universe Initiative

Richard Bond
Claudia de Rham
Raphael Flauger
Gregory Gabadadze
Anna Ijjas
Liam McAllister
Rachel Rosen
Eva Silverstein
Paul Steinhardt
Matias Zaldarriaga

MATHEMATICS AND PHYSICAL SCIENCES FELLOWS

Mathematics

Matthew Baker
David Ben-Zvi
Mladen Bestvina
Lewis Bowen
Tobias Colding
Panagiota Daskalopoulos
Aleksandar Donev
Zeev Dvir
Ezra Getzler
Anna Gilbert
Florian Herzig
John Imbrie
Jeff Kahn
Jeremy Kahn
Michael Kapovich
Boris Khesin
Kay Kirkpatrick
Nitu Kitchloo
Alex Kontorovich
Svitlana Mayboroda
Chikako Mese
Tomasz Mrowka
Camil Muscalu
Irina Nenciu
Thomas Nevins
Hee Oh
Julia Pevtsova
Andrei Rapinchuk
Daniel Ruberman
Mark Rudelson
Thomas Scanlon
Natasa Sesum
Gigliola Staffilani
Nicolas Templier
Benedek Valkó
András Vasy
Alexander Volberg
Sijue Wu
Wei Zhang
Maciej Zworski

Theoretical Physics

Philip Argyres
Robijn Bruinsma
Robert Caldwell
Claudio Chamon
Aashish Clerk
Eric D'Hoker
Matthew Headrick
Andrew Jordan
Gabriel Kotliar
Alice Quillen
Lisa Randall
Marcus Spradlin
Neal Weiner

SFARI INVESTIGATORS

Ted Abel
Alexej Abyzov
David Anderson
Dora Angelaki
Michiel Basson
Helen Bateup
Mark Bear
Kevin Bender
Raphael Bernier
Stephanie Bielas
Somer Bishop
Randy Blakely
Benjamin Blencowe
Mark Blumberg
Susan Y. Bookheimer
Joseph Buxbaum
Steven Chance
Moses Chao
Chinfei Chen
Simon Chen
Gloria Choi
George Church
A. Ercument Cicek
Mark Clements
Barry Connors
Edwin Cook
Hilary Coon
Greg Cooper
Rui Costa
Gerald Crabtree
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Lisa Croen
Colm Cunningham
Mark Daly
Sandeep Datta
Graeme Davis
Yves De Koninck
Bernie Devlin
Adriana Di Martino
Ilan Dinstein
Anna Docherty
Catherine Dulac

Kevin Eggan
Evan Eichler
Britta Eickholt
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Mayada Elsabbagh
Cagla Eroglu
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Mady Hornig

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Z. Josh Huang
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Ivan Iossifov
Fulai Jin
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Emily Jones
Rebecca Jones
David Julius
Kristopher Kahle
Raymond Kelleher
Albert Keung
Alexander Kolevzon
Genevieve Konopka
Abba Krieger
Arnold Kriegstein
Smita Krishnaswamy
Chun-Hay Alex Kwan
Kenneth Kwan
Kasper Lage
Anthony Lamantia
Gary Landreth
Markita Landry
Maria Lehtinen
Jason Lerch
Matthew Lerner
Bo Li
Paul Lipkin
W. Ian Lipkin
Dan Littman
Catherine Lord
John Lukens
Liqun Luo
Jeffrey Macklis
Robert C. Malenka
Dara Manoach
Devanand Manoli
Gabor Marth
Thomas Maynard
Sarkis Mazmanian

SFARI INVESTIGATORS

A. Kimberley McAllister
Steven McCarroll
Margaret McCarthy
Emma Meaburn
Vinod Menon
Judith Miles
Alea Mills
Guo-Li Ming
Robi Mitra
Eric Morrow
Philippe Mourrain
Alysson Muotri
Shrikanth Narayanan
Tse Nga Ng
James Noonan
Alex Nord
Gaia Novarino
Cian O'Donnell
Kassandra Ori-McKenney
Brian O'Roak
Theo Palmer
Georgia Panagiotakos
Karen Parker
Kevin Pelphrey
Ben Philpot
Michael Piper
David Pitcher
Christopher Pittenger
Michael Platt
Renato Polimanti
Carlos Portera-Cailliau
Aaron Quinlan
Mani Ramaswami
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Danny Reinberg
Joel Richter
Kathryn Roeder
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Nicole Russo-Ponsaran
Stephan Sanders
Guillermo Sapiro
Celine Saulnier
Christelle Scharff

Robert Schultz
Leah Schust
Ethan Scott
Nenad Sestan
Stephen Sheinkopf
Elliott Sherr
Frederick Shic
Lisa Shulman
Matthew Siegel
Steven Siegelbaum
James Sikela
Pawan Sinha
Stelios Smirnakis
Vikaas Sohal
Hongjun Song
Matthew State
Paul Sternberg
Beth Stevens
Garret Stuber
Thomas Südhof
David Sulzer
Mriganka Sur
James Sutcliffe
Helen Tager-Flusberg
Michael Talkowski
Guomei Tang
Brian Theyel
David Traver
Peter Tsai
Gina Turrigiano
Erik Ullian
Flora Vaccarino
Jeremy Veenstra-VanderWeele
Pam Ventola
Dennis Vitkup

Xiaoqin Wang
Michael Wangler
Zachary Warren
Lauren Weiss
Marius Wernig
Rachel Wevrick
Tonya White
Michael Wigler
Jeremy Willsey
Melanie Woodin
Anthony Wynshaw-Boris
Fei Xu
Lei Xu
Shinya Yamamoto
Je-Hyun Yoon
Haiyuan Yu
Timothy Yu
Chaolin Zhang
Feng Zhang
Mingjie Zhang
R. Suzanne Zukin
Eli Zunder
Mark Zylka

SFARI INVESTIGATORS

LIFE SCIENCES INVESTIGATORS

Bridge to Independence Awards

Renata Batista-Brito
Graham Diering
Michael Gandal
Sung Han
Keren Haroush
Sung Eun Kwon
Yun Li
Thomasz Nowakowski
Rui Peixoto
Aakanksha Singhvi
Holly Stessman
Jason Yi

SPARK Awardees

Leonard Abbeduto
David Amaral
Robert Annett
Raphael Bernier
Eric Butter
Laura Carpenter
Gabriel Dichter
Craig Erickson
Eric Fombonne
Robin Goin-Kochel
Amanda Gulsrud
Melissa Hale
Suma Jacob
Stephen Kanne
Catherine Lord
Christa Lese Martin
Jacob Michaelson
Cesar Ochoa-Lubinoff
Brian O'Roak
Opal Ousley
Juhi Pandey
Karen Pierce
Joseph Piven
Lisa Prock
Cordelia Robinson
Mustafa Sahin
Robert Schultz
Matthew Siegel
Latha Soorya
Zachary Warren
Ericka Wodka

Simons Collaboration on the Global Brain

Larry Abbott
Ralph Adolphs
Misha Ahrens
Emre Aksay
David Anderson
Dora Angelaki
Richard Axel
William Bialek
David Brainard
Carlos Brody
Elizabeth Buffalo
Matteo Carandini
E.J. Chichilnisky
Anne Churchland
Mark Churchland
Thomas Clandinin
Marlene Cohen
John Cunningham
Sandeep Datta
James DiCarlo
Brent Doiron
Shaul Druckmann
Uri Eden
Florian Engert
Adrienne Fairhall
Michale Fee
Ila Fiete
Loren Frank
Jeremy Freeman
Winrich Freiwald
Stefano Fusi
Surya Ganguli
Lisa Giocomo
Mark Goldman
Michael Hausser
Elizabeth Hillman
Mehrdad Jazayeri
Roozbeh Kiani
Adam Kohn
Brian Lau
Andrew Leifer
Nuo Li
Michael Long
Christian Machens

Zachary Mainen
Valerio Mante
Markus Meister
Kenneth Miller
J. Anthony Movshon
William Newsome
Liam Paninski
Joseph Paton
Pietro Perona
Bijan Pesaran
Jonathan Pillow
Xaq Pitkow
Alexandre Pouget
Jennifer Raymond
Fred Rieke
Nicole Rust
Vanessa Ruta
Bernardo Sabatini
Maneesh Sahani
C. Daniel Salzman
Elad Schneidman
Krishna Shenoy
Eero Simoncelli
Spencer Smith
Haim Sompolinsky
Michael Stryker
Karel Svoboda
David Tank
Doris Tsao
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