SIMONS FOUNDATION

Annual Report

2015 Edition

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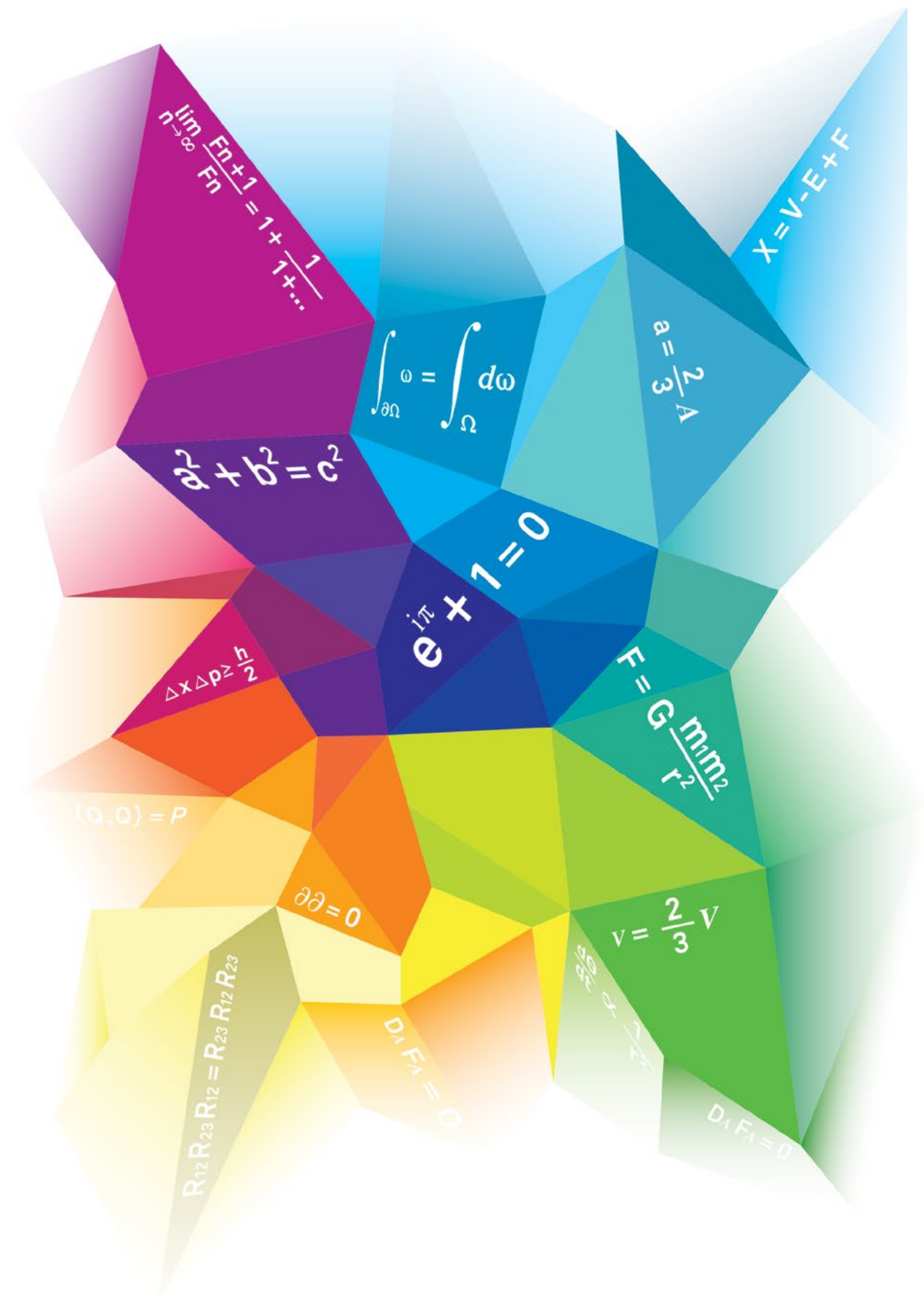
Table of Contents

2015

Cover:

Non-prime numbers are represented
as dots, with prime numbers written
as numerals. Visualizing numbers in
this way can help reveal patterns
in the occurrence of primes.

Letter From the President and the Chair

Numbers, equations and idealized shapes have been an important part of human history for thousands of years. With simplicity and elegance, they express ideas and relationships that can help us make sense of the world around us. As physicist Eugene Wigner observed in his 1960 article "The Unreasonable Effectiveness of Mathematics in the Natural Sciences," the concepts of mathematics, no matter how abstruse, frequently enlighten and magnify even the deepest of scientific theories, often leading to accurate, if unexpected, empirical predictions.

From early formulas such as the Pythagorean theorem to the definition of pi, to Newton's invention of calculus and Maxwell's equations for electromagnetism, to the Dirac equation for the electron and Einstein's equation for the gravitational field, mathematics has shown that it has the power to shape, and to change, the way we see the world. Through the pursuit of mathematical rigor and precision, we have gained insight into the geometry and structure of the universe, made discoveries about the nature of matter and its relationship to energy and invented countless new technologies as a result of these insights: electrical generation and transmission, radio and television, computers, MRI, GPS and cellular telephones, to name just a few. None of these would have been possible without discoveries in mathematics.

Advancing the frontiers of research in mathematics and the basic sciences is the mission of the Simons Foundation, and this annual report highlights our support for mathematics and its myriad applications. You will read about the pure mathematical research we are supporting to try to elucidate homological mirror symmetry, a long-standing puzzle affecting both math and physics. You will also read about research efforts to develop mathematical tools for today's science — algorithms to parse the reams of information being amassed by modern technology. We are hoping to realize an 'unreasonable effectiveness of data,' to rephrase Wigner's idea, to help us understand physical and biological phenomena. As you will see, the applications of mathematics we support are wide-ranging: geology and seismology, theoretical physics, cosmology, systems biology, proteomics, genomics, neuroscience and even microbial oceanography.

Our 2015 annual report also describes our growing portfolio of investigators, grants and collaborative research projects. Through this support we hope to gain insight into some of the most intriguing questions in science today: What happened in the earliest moments of our universe? What is the nature of matter? How does the brain work? How do our oceans support the carbon cycle and life on Earth?

Scientific inquisitiveness goes well beyond the lab, though, extending to the general public. For this reason, the foundation seeks to share the joy and wonder of discovery through its Education & Outreach program and other initiatives. Our public lecture series provides opportunities for scientists to communicate and discuss their ideas not only with peers but with the community at large. Our support for Math for America and programs such as the BioBus seeks to strengthen the mathematics and science skills of the next generation. There is a new generation of budding young scientists delightfully curious about the world!

We would like to add that it is thanks to our outstanding staff that the foundation is able to support this range of programs. It is a pleasure to work with such a smart, creative, purposeful and dedicated group of people. Looking back on 2015, there was a constant buzz of new ideas being presented. We look forward to this continued vibrancy in the upcoming year.

Marilyn Hawrys Simons, Ph.D.
President

James H. Simons, Ph.D.
Chair

Math+X

Maarten de Hoop

Grants to Individuals: Math+X Program
Mathematics is vital to solving problems in many fields of science. Conversely, innovations in those fields may also spur the development of new mathematics. The Simons Foundation's Math+X program supports researchers working at the interface of mathematics and other fields, especially when their work has the potential to benefit both fields.

Half of a Math+X grant goes to a math department and half goes to another department (or departments) at the researcher's university, but the program is flexible and different awardees have chosen to use the funding in different ways. Math+X has so far created four endowed chairs at universities.

Michael Weinstein, professor of mathematics and of applied mathematics at Columbia University, recently received the foundation's first Math+X Investigator award.

Math+X Chairs
In July, Math+X Chair Maarten de Hoop joined Rice University in Houston, Texas, as the Simons Chair in Computational and Applied Mathematics and Earth Science. De Hoop's work has three major components: analysis of inverse problems, particularly as they relate to seismology; development of fast and massively parallel

algorithms that will work on seismic and geophysical data; and deep learning techniques from both points of view. "These are three pillars of the program," he says. "In the middle sits the solid Earth." Geophysics is littered with inverse problems, in which researchers use empirical observations to understand phenomena that cannot be directly observed. De Hoop works on inverse problems related to several different aspects of geology, geodynamics, mineral physics and seismology, including earthquake detection, thermochemical convection and phase transitions in the mantle, and inner-core dynamics. One cannot examine the geomaterial properties of the Earth directly — except by sampling a shallow sliver of its crust — so one must infer them from remote measurements taken on the surface or in space. Determining these properties, he says, gives insight into the physics and dynamics of the Earth.

Rice's location in Houston has led to opportunities to work with energy companies. For these companies, the appeal of de Hoop's work is clear: Finding hydrocarbons, understanding the structures of reservoirs and optimizing production are all inverse problems. "The techniques we are developing can work not only at a planetary scale, but in exploration as well," de Hoop says. In addition to having this obvious use, though, his work can also help the industry understand when its actions may harm others, and how to minimize or mitigate that harm. For example, when an oil field has been used for several decades, it affects the earth around it, and there may be seismic consequences. Can companies do anything that will protect neighboring communities?

De Hoop's work in algorithms and data analysis is applicable not only to Earth science, though. His work could have applications to any number of data-heavy questions in medicine, particularly in imaging and machine learning. He has begun to explore such uses already at Texas Medical Center, across the street from the Rice campus.

Math+X support allows de Hoop to create a unique research group that spans departments. He supervises Ph.D. students in the computational and applied mathematics and Earth science departments and the

"There is a new appreciation by everyone for what mathematics can do."

—Emmanuel Candès

applied physics program at Rice, coordinates a geomathematics seminar and is developing a sequence of graduate courses on geomathematics. Without Math+X, it would be difficult for any school to support such a concentration of research in one specialized interdisciplinary topic. "It is a vital opportunity to really get some breakthroughs in the frontier of unraveling Earth's interior," he says.

Emmanuel Candès, who began as a Math+X chair at Stanford University in 2012, takes a different approach. With a leadership committee of professors from different departments at Stanford, he has helped to support a variety of interdisciplinary projects. Every year, the committee selects several graduate students and postdocs whose work uses mathematical ideas, and funds their research. Over the years, Candès' Math+X grant has funded projects in everything from quantum physics to neuroscience.

Candès himself works on various problems in applied mathematics. "I am mostly a theoretician," he says. "I import into the world of theory problems that come from the outside. If I do anything that is any good, I export my theory and the tools I develop in response to these problems."

Recently, Candès has been concerned with reproducibility in scientific research. Several studies trying to reproduce the results of experiments, particularly in biomedical fields, have found that only a small portion of them can be replicated. There are a few reasons for this problem, but Candès says one of them is a shift in how scientific research is conducted. Before computers could collect and process data as efficiently as they can now, science followed the scientific method: Make a hypothesis, develop an experiment to test it, conduct the experiment. "We've turned things a bit upside down," says Candès. "Now people have large datasets available prior to formulation of scientific theories. They go out and mine these datasets in search of phenomena." Because standard statistical methods are not designed for this kind of data mining, many reported results do not pan out. Candès and his collaborators and students have been working on developing new statistical methods to address this crucial issue.

Candès also works on the mathematics of sparsity and signal processing. Often, it is just too expensive or time-consuming to acquire a complete multidimensional dataset. Candès has designed new sensing protocols so that all the important information is captured in a relatively small number of measurements. Demonstrated success includes the speeding up of magnetic resonance imaging scans.

Candès says Math+X has had a clear and positive impact on the Stanford math department and the other departments involved. Not only has the award allowed them to hire several outstanding applied and computational mathematicians, but it has also affected the culture of the department. "Math+X has helped the math department connect with people in other disciplines," he says. "There is a new appreciation by everyone for what mathematics can do."

Simons Collaborations in Mathematics and Physical Sciences

> "Many things happen just because there's electricity in the air."
>
> —Assaf Naor

The Simons Foundation currently supports four collaborations in mathematics and physical sciences. These projects bring groups of researchers together to tackle problems that have promising paths to near-term progress and whose solutions would represent important research milestones in the field. The Homological Mirror Symmetry collaboration and the Quantum Fields, Gravity and Information collaboration launched in 2015. The Many Electron Problem collaboration and the collaboration on Algorithms and Geometry began the year before.

Simons Collaboration on Algorithms and Geometry

In December 2014, Ran Raz presented a question in linear programming to his colleagues in the Simons Collaboration on Algorithms and Geometry. Linear programming centers on questions of optimization: Given a space of possible outcomes, how can you determine which point in that space maximizes or minimizes an associated linear function — a profit or a loss, for example? Raz, a computer scientist at the Weizmann Institute in Israel who is currently working at the Institute for Advanced Study in Princeton, New Jersey, was hoping to determine whether linear programming is easier if the space of possibilities is fixed while the function to be optimized is changed. While Raz was presenting, Oded Regev, a computer scientist at New York University, realized these questions might be related to his own research. "I saw him immediately have an idea," collaboration director Assaf Naor says. A few months

later, Regev, Raz and co-author Yael Kalai had solved Raz's problem and published a paper about it.

Kalai, Raz and Regev's work is an example of the kind of synergy and discovery the Simons Foundation hoped to facilitate when it gathered this loose conglomeration of pure mathematicians, applied mathematicians and theoretical computer scientists who study a diverse set of problems related to optimization, computational complexity and geometry.

Also by design, the collaboration's participants come from the same geographical region: in this case, the greater New York area. The group sometimes invites guest speakers or long-term visitors to one of their campuses, but the group's monthly meetings are made possible only by the close physical proximity of the participants. Naor, a mathematician at Princeton University, says the fact that there is a critical mass of researchers nearby has been a boon to the group's productivity. "The whole environment is fertile," he says.

All told, collaboration members published many papers this year, with several more now in preparation. Although not all of these projects grew directly from the collaboration's monthly meetings, the frequent meetings encourage creativity. "Many things happen just because there's electricity in the air," Naor says.

Simons Collaboration on the Many Electron Problem

The Simons Collaboration on the Many Electron Problem brings researchers from diverse areas of theoretical physics and chemistry together to work on questions related to the way the properties of a material — magnetism, conductivity and the like — arise from electron interactions within the material.

Members of the collaboration approach these questions from different viewpoints, and before the collaboration started, they had been proceeding independently. The collaboration, which is organized into four broadly defined research groups focused on different classes of methods, has enabled a new level of scientific interaction. The different research groups held meetings throughout 2015, leading to new refinements of existing methods. But the big collaboration-wide effort was a paper that incorporated ideas from all four research groups to do a complete analysis of the single orbital Hubbard model, an idealized version of a lattice of interacting atoms.

In a field where most papers have three authors, this one has 25. "We sat down and found a problem where everybody had something to say about it," says University of Michigan physicist Emanuel Gull, part of the Monte Carlo group. Previously, papers about the Hubbard model were inconclusive, with different approaches yielding contradictory results. The Many Electron group was able to whittle down uncertainty in its model to much less than earlier papers had, reconciling the predictions coming from the four different research groups. Gull says the strength of the collaboration in this work is that the

techniques used by each group work better for some simulated materials than others, so the groups were able to use the approaches that would work best for each situation.

In addition to getting a handle on the Hubbard model with various parameters, the groups were able to learn the limitations to their approaches. "We've identified regimes which remain difficult, and there we understand how the different methods break down, why they break down, and so on," Gull says.

Each year, the collaboration holds multiple workshops and conferences on the physics of the many electron problem, but collaboration members are also working on software. The collaboration is investigating what tools are available for numerical simulations of large numbers of electrons and how to write the new software the researchers need. In the summer of 2016, the collaboration will hold a short course on best practices in large-scale scientific software immediately before its 2016 summer school for graduate students in the collaboration whose thesis research is intensively computational.

As the collaboration's work continues, members hope to move their analysis from the idealized Hubbard model to more realistic systems. "Our big-picture push at the moment is to take these simplified model systems that we have and make them more realistic so that we can say more about actual materials as they appear in nature," Gull says.

Collaboration on Homological Mirror Symmetry

Mathematics could be forgiven for thinking itself a fairy godmother to the other sciences, sprinkling useful theories and theorems into biology, chemistry and physics, enabling them to reach new heights. Sometimes, however, it goes the other way. The Simons Collaboration on Homological Mirror Symmetry, launched in late 2015, works on a field of mathematics inspired by theoretical physics. A successful collaboration would provide mathematicians with a way to translate between seemingly disconnected mathematical realms. The physics inspiration for homological mirror symmetry is string theory, which describes particles as being tiny, vibrating strings. String theory augments our three-dimensional spatial world with an extra six dimensions to make the mathematics of the theory consistent. The extra dimensions are curled up into spaces known as Calabi-Yau manifolds. "Whether this represents the real world is unknown, but there is some fascinating mathematics in there," says Denis Auroux of the University of California, Berkeley, one of the principal investigators of the collaboration.
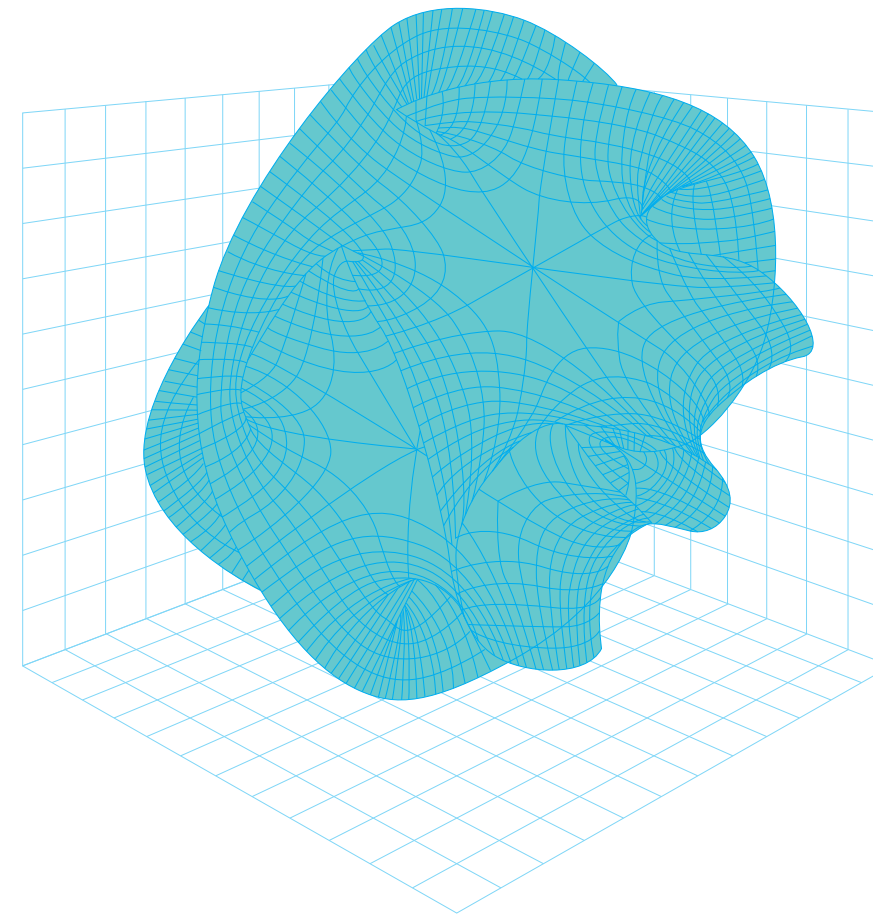
'Mirror symmetry' here refers to an unexpected correspondence between seemingly unrelated space-times: Different Calabi-Yau manifolds described by different quantum theories turn out to encode the same physics. "All the measurable quantities are the same, even though the models governing the interactions look completely different," says Tony Pantev of the University of Pennsylvania, director of the collaboration.

"If you do some kinds of geometric calculations on one and different geometric calculations on the other, you will get the same answer for a reason that is not obvious," says Auroux.

The goal of the Simons collaboration is bold: to prove mirror symmetry in its full generality. Currently, there are three main approaches to homological mirror symmetry that have been developing more or less independently for several years. However, each existing approach can only go so far. "They've gotten quite a lot of momentum," Pantev says, "but it's clear that we have to combine the approaches to get the full solution." The collaboration brings together prominent researchers in each branch to see where they can combine their ideas. "We've gotten enough cross-pollination between these approaches in recent years to understand that we can now really work on the merger," says Pantev.

In 1994, Maxim Kontsevich, who has appointments at both the Institut des Hautes Études Scientifiques in France and the University of Miami, formulated the homological mirror symmetry conjecture, taking mirror symmetry beyond its origin in physics into the world of mathematics. The conjecture he formulated relates objects in two different mathematical worlds, says Pantev. "One is the world of complex geometry, which is fairly robust and rigid and very complicated, the other is the world of symplectic topology, which is kind of flabby and has a lot of wiggle space in it, and is hard to pin down." The conjecture is that every symplectic manifold has a mirror pair in the complex geometry world and that an invariant of the symplectic manifold, known as the Fukaya category, is the same as an invariant called the derived category of its mirror space.

Pantev describes homological mirror symmetry as a dictionary between the symplectic geometry world and the complex geometry world. "There are many questions in both mathematical universes that this dictionary relates that become really accessible and easy once you pipe them through the dictionary," he says. "But first you need to establish the dictionary," or, in other words, prove the homological mirror symmetry conjecture.

In addition to Auroux, Kontsevich and Pantev, principal investigators include Mohammed Abouzaid of Columbia University, Ron Donagi of the University of Pennsylvania, Kenji Fukaya of the Simons Center for Geometry and Physics, Ludmil Katzarkov of the University of Miami and the University of Vienna, Bong Lian of Brandeis University and Shing-Tung Yau of Harvard University. The project launched in November with an inaugural conference at the University of Pennsylvania, and in the coming years it will host several workshops and conferences per year.

A successful proof of homological mirror symmetry would have a large, immediate effect on mathematics. First, it has the potential to make difficult questions in symplectic geometry or complex geometry more tractable by allowing researchers to translate the questions into the other realm and try to solve them there.

A proof of homological mirror symmetry would have surprising and paradigm-changing effects in other areas as well. The Langlands program is another long-standing avenue of research in mathematics that explores surprising relationships between mathematical objects from different realms. One part of the Langlands program, geometric Langlands, is "a special kind of mirror symmetry that descends from electric-magnetic duality in four dimensions," says Edward Witten of the Institute for Advanced Study in Princeton. Thus, a proof of homological mirror symmetry would imply a proof of the geometric Langlands correspondence, a huge breakthrough in the field.

Unlike general relativity, for which the necessary mathematics, Riemannian geometry, had already been developed when Albert Einstein needed it, mathematical research in mirror symmetry was precipitated by physicists. "It's fun because in pure math, usually people work on questions that are very old and very internal. Somehow the answer always comes from within mathematics," Auroux says. "This is a field where physicists came up with this prediction, and we're still playing with it."

Mathematical Modeling of Living Systems

Terry Hwa, professor of physics and of biology at the University of California, San Diego, now specializing in quantitative biology, draws inspiration from an unexpected source: 19th-century thermodynamics, which bridged the gap between molecular interactions within a gas and its large-scale behavior. Hwa seeks to do the same in biology, by first identifying the basic characteristics of cellular behavior and then elucidating the underlying molecular interactions that cause them. This year, he and his group published a paper that takes an important step in that direction. "It's an appetizer for everything else we want to do," he says.

Hwa is an investigator in the Simons Foundation Mathematical Modeling of Living Systems (MMLS) program. The MMLS program seeks to increase the role of theory in biological research, supporting scientists who study a broad range of biological issues, from embryonic development to evolutionary dynamics, by developing and employing sophisticated mathematical models to reveal fundamental concepts and analyze data.

Hwa's team tackled a long-standing question in oncology: Why do cancer cells, unlike most cells in the body, metabolize by anaerobic fermentation instead of the more efficient aerobic respiration, even in an oxygen-rich environment? This phenomenon, called the Warburg effect, has puzzled scientists for nearly a century.

Hwa and his colleagues found that for fast-growing cells, the model organism E. coli in this case, the protein cost of respiration is much higher than for fermentation. "Even though respiration is an efficient way to generate energy on a per-carbon basis, the machinery required is costly," he says. The study was the first to quantify the relative cost to cells of producing the proteins required for respiration and fermentation.

Historically, some had viewed the Warburg effect as a defect in cancer cells' functioning, and hoped to discover what 'went wrong' that caused them to metabolize without oxygen. Hwa's research stands that notion on its head. "Many things can be messed up, but the ability of a cancer cell to grow must be robustly preserved," says Hwa. "Otherwise it would not be cancer." That is, it's highly unlikely that cancer cells' metabolic and growth processes are defective. Instead, his research suggests that a preference for fermentation may be a feature of fast-growing cells in general; therefore, preventing such cells from fermenting may be a way to slow their growth.

Hwa's research bridges the molecular and cellular levels: Instead of plumbing down to proteins and how they work together, his work focuses on functions the proteins are involved in — in this case, waste excretion and cell growth. After measuring their relationship, Hwa's team created mathematical models of cell growth and tested them by varying the environment and the cells' genetics. Their models successfully predicted the resulting changes in overall cellular behavior.

"Usually we think of biological phenomena as being complicated — and very difficult to describe in mathematical terms," Hwa says. "But in the case of the relationship between excretion and growth, we found a straight line. When there is a simple mathematical relation emerging from very complicated parts, that means there is something behind it."

PTOLEMY
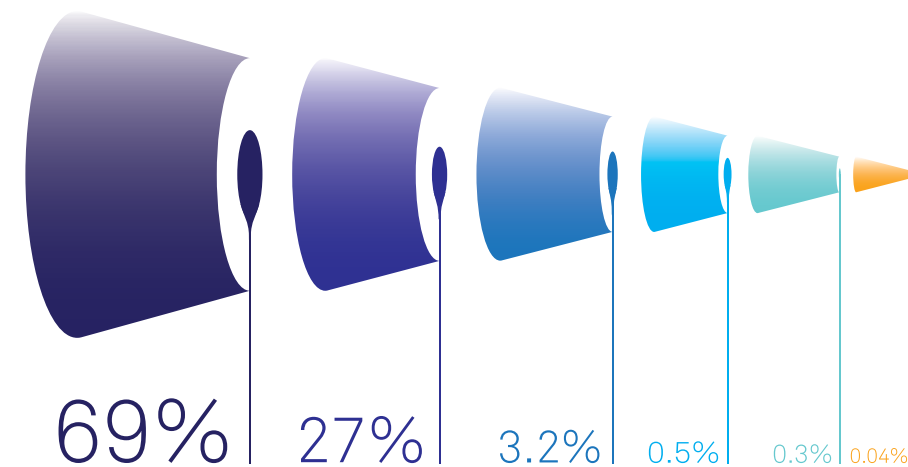
69% – Dark Energy
27% – Dark Matter
3.2% – Free H and He
0.5% – Stars
0.3% – Neutrinos
0.04% – Other Elements

One second after the Big Bang, an unfathomable number of neutrinos were liberated from the surrounding chaos and started traveling through the universe at nearly the speed of light. Cosmologists believe a person is bombarded with something on the order of a quadrillion of these 'relic neutrinos' every second, dwarfing, unbelievably, the number that come from other relatively nearby sources, such as nuclear fusion in the sun or radioactive decay. "You hear this, and you're driven to ask whether it's really true," says Princeton University physics professor Christopher Tully. "How can we know it's true?"

Tully is the principal investigator of the Princeton Tritium Observatory for Light, Early-Universe, Massive-Neutrino Yield (PTOLEMY) project, which aims to accomplish the first direct detection of relic neutrinos. As a byproduct, PTOLEMY may also help answer some questions about the relic neutrinos' properties, such as density and mass.

When physicists first theorized the existence of neutrinos in the 1930s, they believed the particles had no mass. However, work that won Takaaki Kajita and Arthur B. McDonald the 2015 Nobel Prize in physics revealed a surprising behavior: Neutrinos can oscillate between three different types, or 'flavors,' suggesting that they have mass after all.

PTOLEMY is based at the Princeton Plasma Physics Laboratory, a national laboratory on Princeton's Forrestal campus, but over the two-year course of the project, researchers will work with other groups, including the Savannah River National Laboratory, the Goddard Space Flight Center and Argonne National Laboratory, to install, build or improve the sensors and substrates needed to start detecting neutrinos. Unlike current neutrino experiments — which use spectrometry — PTOLEMY will use cryogenic calorimetry to detect relic neutrinos, aided by a key piece of equipment installed shortly after Simons Foundation support began in September: a cryogenic refrigerator that can reach temperatures of 7 millikelvins, just a hair above absolute zero.

Once its detector is in place, PTOLEMY will make precise measurements of the radioactive decay of tritium (hydrogen-3) to helium-3 (an isotope of helium with two protons and one neutron). Usually, tritium decay to helium-3 produces 18.6 kiloelectron volts of energy, an electron, and an antineutrino; however, if the tritium molecule interacts with a relic neutrino from the Big Bang, the amount of energy is slightly boosted. By precisely measuring this increase in energy, PTOLEMY will not only verify the presence and density of relic neutrinos but determine their mass as well.

If PTOLEMY is successful, it will also provide proof of concept for ultra-low-energy electron calorimetry as an effective way to make precise measurements, which could change the way cosmologists do experiments. PTOLEMY's findings could also have far-reaching theoretical implications. They might add to experimental evidence about neutrino masses, which could help cosmologists determine whether neutrinos are Majorana or Dirac fermions. This finding could in turn help explain why there is more matter than antimatter in the universe. The results could even have implications for the quest to understand dark energy. "It's been a huge technical challenge to build up the infrastructure," Tully says. "But once you start on a path of new technologies that can see things you've never seen before, there's no telling what you might learn from it."

arXiv

If you want to read Grigori Perelman's proof of the Poincaré conjecture, arguably the most important mathematical result of the 21st century so far, you won't find it in a book or an academic journal. The iconoclastic mathematician, who famously turned down a Fields medal and a million-dollar prize for his work, published his articles only on the preprint server arXiv, where anyone with an Internet connection can download and read them.

This democratization of access to research is one of the reasons Paul Ginsparg, then a physicist at Los Alamos National Laboratory, started arXiv in the early 1990s. But there was a practical need for it as well. At the time, researchers often shared new results with each other by sending physical copies of preprints to colleagues who might be interested. Creating a centralized system for distributing these papers both sped up the process for researchers and opened up access to the information to graduate students and other less-connected researchers. "That's why arXiv has been very successful," says Oya Rieger, a librarian at Cornell University and program director of arXiv. "Not just because it is an open-access model that levels the field, which is extremely important, but also because it dovetailed very well with the ethos, the norms and the needs of the scientific community."

What began as an electronic bulletin board for about 300 people in a subfield of high energy physics now gets hundreds of thousands of downloads a day from researchers in many areas of physics, math and computer science. In its nearly 25-year history, arXiv has become indispensable to researchers in the fields that use it. "No community that has ever adopted it has relinquished it," Ginsparg says. "In the fields where it was established, it really became the primary source of information for the community."

ArXiv also provides a home for scientific work that might not be published otherwise. Survey articles that summarize the history of a field or student notes about an important theorem wouldn't normally make it into an academic journal, but they can be useful for people learning about a new topic. ArXiv also hosts some offbeat articles. In November, right before the release of the film *Star Wars: The Force Awakens,* a paper titled "It's a Trap: Emperor Palpatine's Poison Pill" analyzed the economics of the Star Wars universe. (The takeaway: Unless the Rebel Alliance has a cache of funds somewhere, "it is likely the Galactic economy would enter an economic depression of astronomical proportions," the authors wrote.)

Peer review is an important part of the scientific process, one that arXiv does not provide. Most researchers still submit their papers to journals in their fields, and peer-reviewed research has a stamp of approval arXiv papers do not. But arXiv allows immediate dissemination of new research at no direct cost to the researchers themselves or to readers, leading to an increased agility in fields that use it. For example, CERN released new Large Hadron Collider data on December 15, 2015. By the beginning of January 2016, there were nearly 150 arXiv papers analyzing and interpreting the data. In fields such as physics and mathematics, where it can be a year or more between submission of a paper and its publication in a traditional journal, the immediacy of arXiv publication is a boon to scientific progress. It allows the research community to act "as a collective organism," Ginsparg says. "All of these articles cite the preceding ones — in some cases written a day earlier."

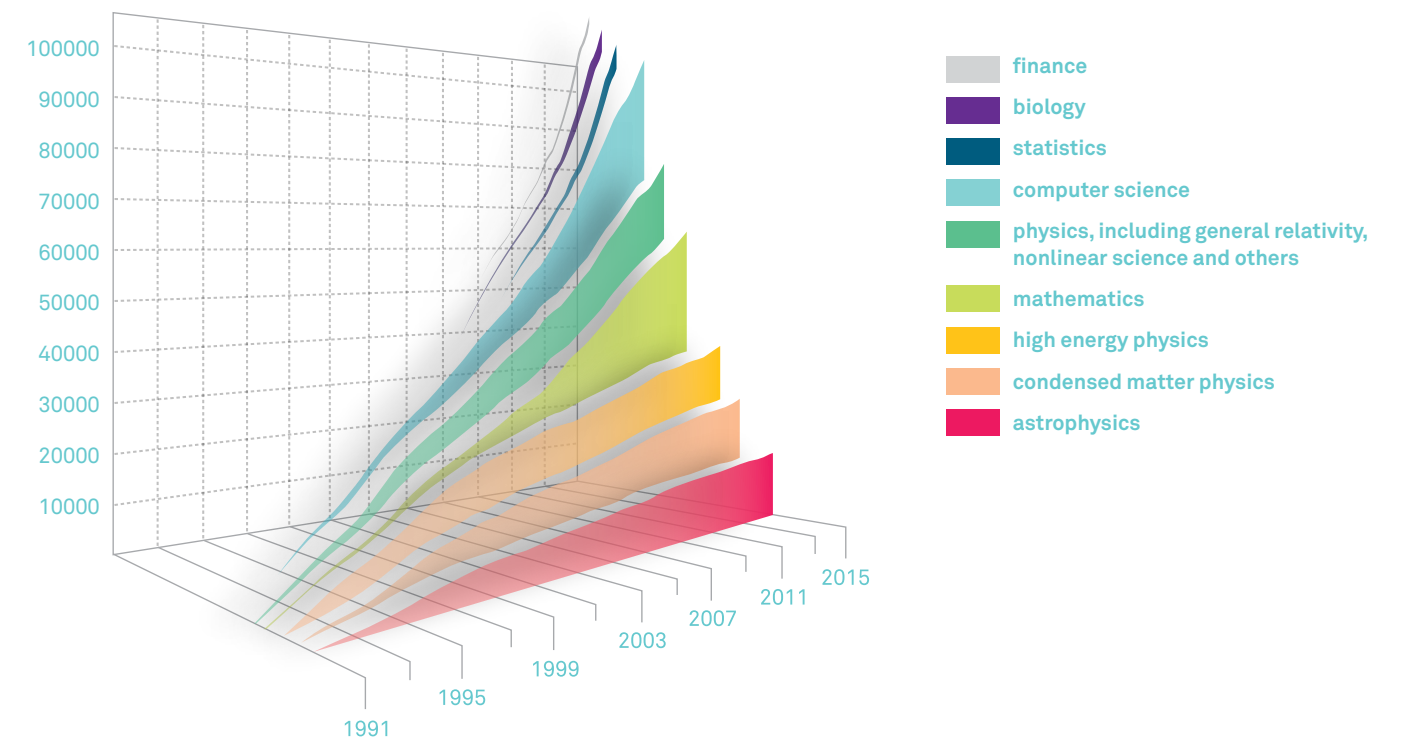Even without peer review, arXiv has managed not to become a repository for bogus proofs of the Riemann

hypothesis or cold fusion. A few sneak through the cracks every once in a while, but arXiv's overall quality remains impressive. Its high standards are due in large part to volunteer moderators for every research area who read through at least the abstracts of all new submissions to weed out illegitimate work. The moderators don't seek to provide peer review, just to check that the papers submitted are plausible as contributions to the field and to ensure that papers are not miscategorized. Recently, some research communities have shown interest in "arXiv overlay journals": Peer review takes place under the auspices of a journal, but the paper lives on arXiv.

When Ginsparg moved to Cornell University in 2001, arXiv traveled with him there, and eventually the Cornell University Library took over the project. It was an unusual arrangement. "Ordinarily, library services are meant to benefit patrons on-site," says Ginsparg. "But arXiv is a unique system in which the vast majority of the benefit is conveyed to the exterior." For about 10 years, Cornell managed and funded arXiv, but that was not sustainable.

"Five years ago, we announced that Cornell University Library could not single-handedly fund this operation and that we would be creating a collaborative model," says Rieger. There are now approximately 190 member institutions that each pay a small membership fee, matched by the Simons Foundation, to support arXiv. The membership program brings in funds, but, more importantly, says Rieger, it precipitated the creation of a member advisory board so arXiv can better understand the needs of its users around the globe.

With the growth of arXiv and recent changes to its organizational model, the arXiv team is eager to find out from users where they would like arXiv to go in the future. Under consideration are changes to quality control methods, new subject categories and even ways to tie arXiv more closely to the peer review process. "Our goal is for 2016, arXiv's 25th anniversary, to be a year of exploration for us," says Rieger. "We will look to arXiv's past and future to decide where to go."

SCDA Computer and Software Groups

Correlations between expression levels for genes obtained from assays of human tissues under different conditions are shown in this figure, derived in a network visualization work flow. This kind of visualization is used to compare experimental expression levels for transcription factors with expression levels for genes they may regulate directly or indirectly. Here, the visualization focuses on the expression level for the 'pter' gene, shown in the lower left column and upper left row, compared with the expression levels for transcription factors such as h2afx, max, rara and others.

At its essence, computation is applied mathematics boiled down to its core elements: ones, zeroes, and some Boolean logic to connect them. But within those narrow confines lies a profound power to accelerate discovery-driven science. The mission of the Simons Center for Data Analysis (SCDA) is to apply this computational power to the deluge of complex experimental data generated by new techniques in bioinformatics and experimental biology. Storing, transmitting and meaningfully analyzing this so-called 'big data' is an emerging research discipline in its own right. In this regard, the computing and software development groups at SCDA are connected to the long line of technologist-scientists whose methodological discoveries — from Robert Hooke's compound microscope in the 17th century to Cooley and Tukey's fast Fourier transform or Greengard and Rokhlin's fast multipole method in the 20th — have both supported and inspired the search for knowledge. "Our job," says Ian Fisk, SCDA's deputy director for computing, "is to make sure that computers are not the limiting factor in terms of scientific progress."

In the past year, SCDA has dramatically expanded its software and computing capabilities. What began in 2014 as a single server running without its own machine room has grown into a high-performance computing network. SCDA can now apply the power of 700 processing cores (about 300 times as many as the average laptop),

nearly a petabyte of high-performance storage (enough to store almost one-fifth of the Library of Congress's digital materials), and a 10-gigabit network infrastructure (fast enough to transfer a 200-gigabyte fully sequenced human genome in less than three minutes) to solving the problems of discovery-driven science. A single specialized node in SCDA's computing cluster has 48 processing cores and 1.5 terabytes of RAM, allowing researchers to quickly find correlations within the extremely large datasets that genomics and neuroscience routinely generate. "It's a lot of power in one box," Fisk says.

The computing and software development groups work directly with SCDA's genomics, neuroscience and systems biology teams as scientific and algorithmic collaborators, not just tool builders. "I certainly consider myself a researcher, and our people are embedded in the science programs here," says Nick Carriero, who leads SCDA's software development group. "A colleague might wander into one of our offices, trying to understand something experimentally, but they don't know quite how to set up the correct in silico apparatus to do it. They're not experts in computation. We meet with them and understand the nature of their problem. That's an important part of having an operation structured like SCDA, which is small, intimate, with a lot of give and take between all parties."
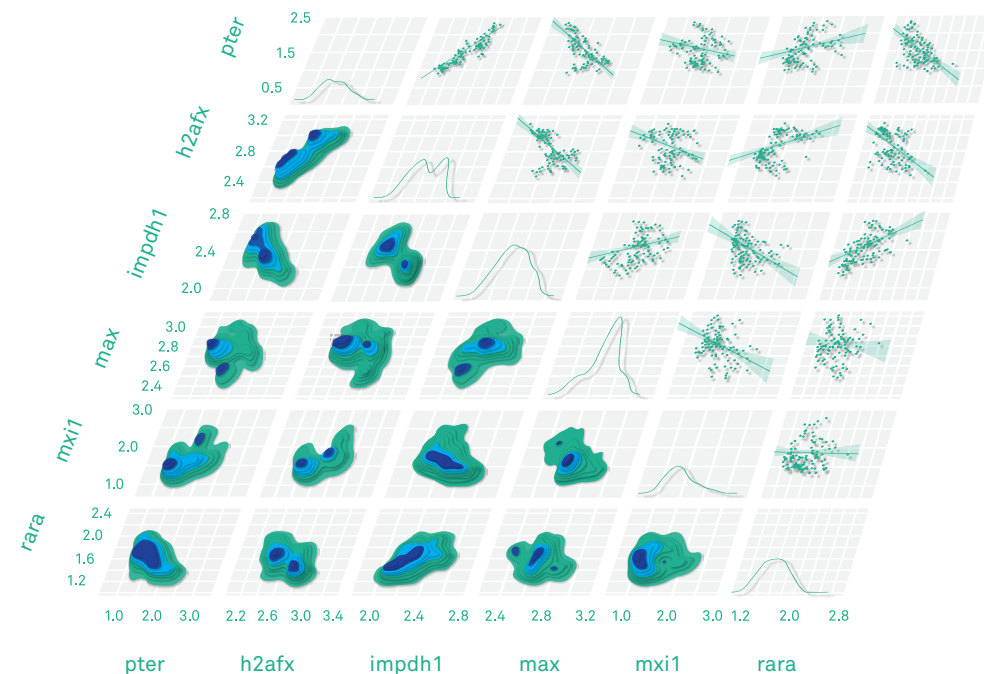
But if computing supports the math at SCDA, the math in turn enables the computing. The center's genomics, neuroscience and systems biology research groups routinely access and manipulate enormously large and complex files, which must be constantly verified to ensure that no data has become accidentally corrupted. SCDA uses a mathematical function known as 'MD5 checksum' to continuously validate the integrity of its files. The MD5 algorithm applies a calculation to each file that converts it into a unique integer (the checksum). This number acts as the file's mathematical 'fingerprint' any time the data are copied or transmitted. Any unintended change in the data will cause the MD5 function to calculate a drastically different value for the checksum, which makes damaged files easy to spot.

SCDA runs this calculation continuously to safeguard against the unavoidable breakdowns that afflict high-performance computing systems. "Once you start working with data at scale, this becomes a problem that you can't ignore," explains Carriero. "It would be an unusual event for the hard drive in an ordinary laptop to fail. But for us, that's a normal event. We exploit this mathematical capability so that we can do the necessary verification of all our data."

Complex real-time analysis is also the purpose of SCDA's 21-million-pixel video wall, which allows researchers to examine ultra-high-definition visualizations of

their data. Unlike pixels in commercial video walls, those in SCDA's screen are individually controlled by four graphics processing units that power the display. This means that resolution — rather than mere magnification — is enhanced in a way that supports detailed visual investigation of complex systems such as protein simulations or genetic regulatory networks.

"These structures can be extremely complicated with hundreds or thousands of features that are essentially impossible to visually resolve on a normal computer monitor," Carriero says. "This highly immersive visualization lets a researcher ask a dynamic series of 'what if' questions about the data: What happens to the network if I remove this gene? What if I switch from thinking about lung to liver tissue? What if I constrain myself to one group of species as opposed to another?" Still, as Fisk says, "The most interesting math comes in

preparing what goes on the wall" — that is, doing the science itself.

Fisk's and Carriero's groups have also been collaborating with SFARI to make genomic data from hundreds (and eventually thousands) of families in the Simons Simplex Collection accessible to autism investigators. The primary hurdle in using this unique collection of data is its sheer size. Each sequenced genome contains approximately 200 gigabytes of information, and analyzing multiple genomes in a cohort can often require unwieldy file transfers. "Some of these files are individually about the size of half of the disk drive inside of your laptop," says Carriero. "A family of four is close to a terabyte of data, and if you have 1,000 families, that's a petabyte of data."

Luckily, most autism investigators aren't interested in comparing whole genomes but rather differences between two or more

discrete sequences. Yet generating even this relatively small volume of variant data requires substantial computation over large amounts of input and — again — more computing and storage hardware. Although transmission of only genetic variants may reduce gargantuan file sizes, because several algorithmic procedures for computing these genetic variations are in use in the field, and because each impacts results differently, researchers may need to perform their own analysis with the full raw dataset anyway.

The arithmetic around adding more storage may be simple, but putting the new systems in place is not. "It's not too hard to call up somebody like Dell, Hewlett-Packard or IBM and order a rack's worth of computing equipment," says Carriero, "but it's surprisingly hard to get a petabyte of storage that's going to be high-performance and reliable enough for scientific computing at scale."
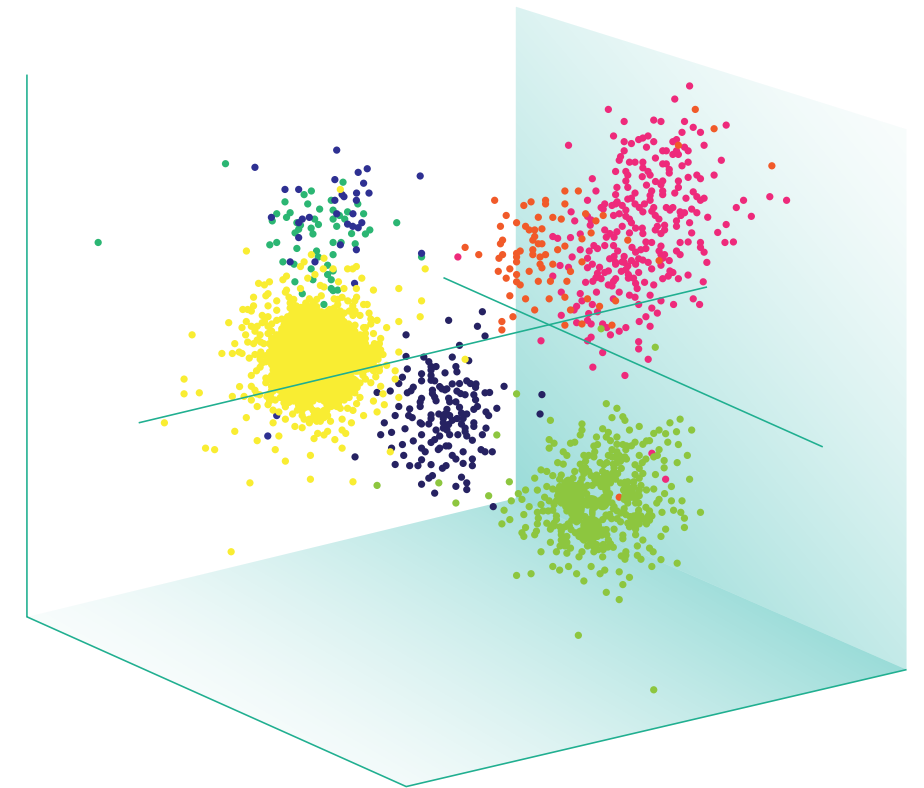
Spike Sorting
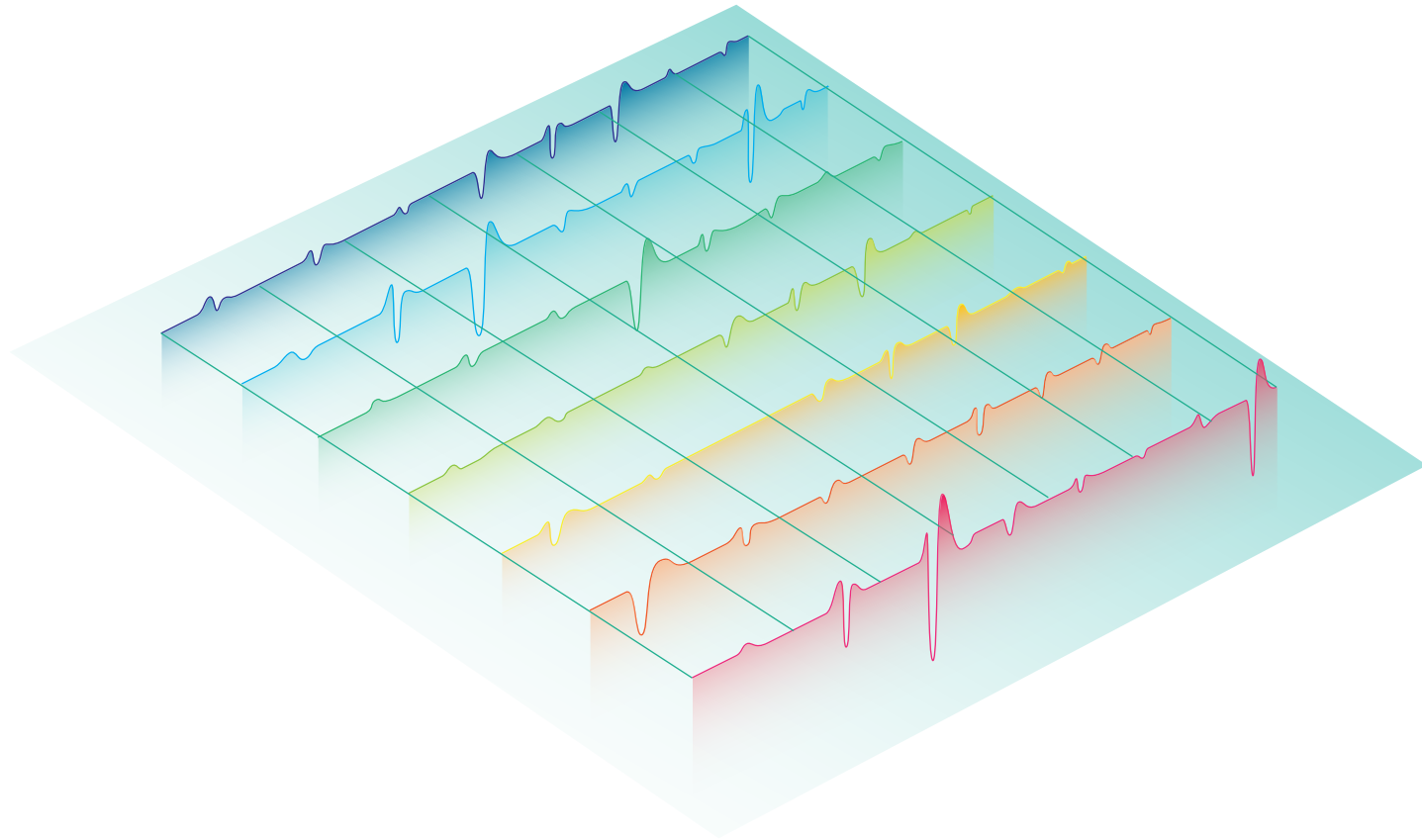
A human brain's 86 billion neurons can fire up to a quintillion times an hour, giving us an incredible ability to process complex information more quickly than most computers. Exactly how our brains use this electrical activity isn't clear, but scientists have spent decades recording and analyzing the signals neurons send, developing better and better tools to track what's going on in our brains. Now, scientists need better algorithms to analyze that data, says Leslie Greengard, director of the Simons Center for Data Analysis (SCDA).

Today, neuroscientists use tiny electrodes inserted into cultures of nerve cells or into the brains of living animals to record electrical signals. Early experiments used just one electrode, then five. Now, some use 18, others use just over 500, and soon some may record with more than 50,000. "That's a lot of data coming into the computer quickly, so we need an algorithm to sort it quickly and accurately," says SCDA senior research scientist Alex Barnett, associate professor of mathematics at Dartmouth College.

Neuroscientists' analysis of neurons' electrical activity is called spike sorting. Neurons' electrical activity comes from changes in concentrations of charged sodium and potassium ions flowing into and out of cells. These changes occur in less than a millisecond and can create slight increases in voltage, which are recorded by the electrodes. A computer displays these voltage increases as 'spikes' rising out of noisy, horizontal traces.

Spike sorting, Greengard says, is all about figuring out which spike comes from which neuron.

Right now, neuroscientists use algorithms that sort spikes by shape. If one spike looks similar in shape to another, an algorithm reports that the spikes came from the same neuron. The current practice is for scientists to use their knowledge of the rules of the brain — principles such as the fact that a neuron has a recovery time of a couple of milliseconds before it can fire again — to make painstaking decisions about neuronal identities. That adds a human bias to the analysis, and it's slow, Barnett says.

Human analysis has another limitation, too. "Sorting by shape is pretty obvious for large spikes, but for smaller ones, it's harder," says SCDA senior data scientist Jeremy Magland. "Two people might look at the same data and come to completely different conclusions." Two different algorithms may also assign the same spike to different neurons. Such discrepancies make it difficult to reproduce spike-sorting results.

In response, Barnett, Greengard and Magland have published a new way to test the validity of current algorithms and are working on a standardized method that will permit neuroscientists to obtain confidence estimates on their results. In 2015, the team also developed an algorithm that efficiently scans data from hundreds of electrodes and sorts the data more accurately, substantially reducing the need for human intervention. Barnett, Greengard and Magland are using signal-processing tools so that the algorithm accurately labels spikes that come from the same neuron and separates those spikes from ones that come from other neurons, even when the neuron's firing amplitude varies over time. They also want to make the algorithm sensitive to smaller and smaller spikes, which are harder to separate from noise.

"The days of human spike sorting," Greengard says, "need to be over."

SFARI Research Roundup

20μm

In 2015, the Simons Foundation Autism Research Initiative (SFARI) supported nearly 200 autism researchers. These SFARI Investigators have pushed forward the frontiers of autism research in many ways, uncovering more and more of the condition's genetic architecture and also elucidating higher-level biological pathways, behavior and cognition. The following pages present some highlights of the past year's research by SFARI Investigators.

Rapid Growth
Brain 'organoids' grown from stem cells derived from skin cells of four boys with autism display shared biological anomalies, a study shows, even though none of the boys have any of the mutations that have so far been associated with autism risk. The research, published in the July 16, 2015 issue of *Cell*, supports the idea that the heterogeneous genetic underpinnings of autism converge on a much smaller set of biological pathways.

The researchers, led by SFARI Investigator Flora Vaccarino of Yale University, grew organoids — three-dimensional neural aggregates that mimic some features of the developing brain — from cells of four boys with unusually large heads, a feature that appears in about 20 percent of individuals with autism. The researchers found that the cells in the boys' organoids divided more rapidly and made more synapses than those in organoids derived from their unaffected fathers. They also had elevated expression of genes involved in cell growth, neuronal maturation and synapse formation.

In particular, the boys' organoids had a higher level of expression of FOXG1, a gene that has been associated with the autism-related condition Rett syndrome. This overexpression, the researchers found, resulted in overproduction of neurons that produce a signaling chemical called GABA that inhibits neural activity.

None of the boys had mutations in FOXG1, but they did have variations in nearby DNA segments, highlighting the importance of understanding autism-related mutations not just in genes but also in regulatory regions of the genome.

Benefits of Early Treatment
Restoring the activity of the gene responsible for Angelman syndrome can greatly reduce symptoms, a new study suggests, especially if the gene is restored early in development.

Angelman syndrome, a condition related to autism that is characterized by a happy disposition, epilepsy, intellectual disability and anxiety and motor deficits, occurs when there is a mutation disabling the maternal copy of the gene UBE3A. In previous mouse model studies, researchers activated the ordinarily silent paternal copy of UBE3A, but found that the mice still displayed repetitive behaviors and anxiety.

The new study suggests, however, that activating UBE3A may prevent some Angelman syndrome symptoms if it is done early enough. A team led by SFARI Investigator Ype Elgersma of Erasmus Medical Center in Rotterdam, the Netherlands, studied mice whose maternal copy of UBE3A had been deactivated. The researchers then turned the gene back on at various stages of development.

They reported in the May 2015 issue of the *Journal of Clinical Investigation* that when they turned the gene on during embryonic development or on the first day of life, the mice did not go on to develop anxiety or motor deficits. By contrast, mice that were treated during toddlerhood escaped only motor deficits, and by adolescence this window had closed as well. Even mice that were treated as adults, however, regained some brain plasticity. The results suggest that early treatment is key, but that treatment at any age may confer some benefits.
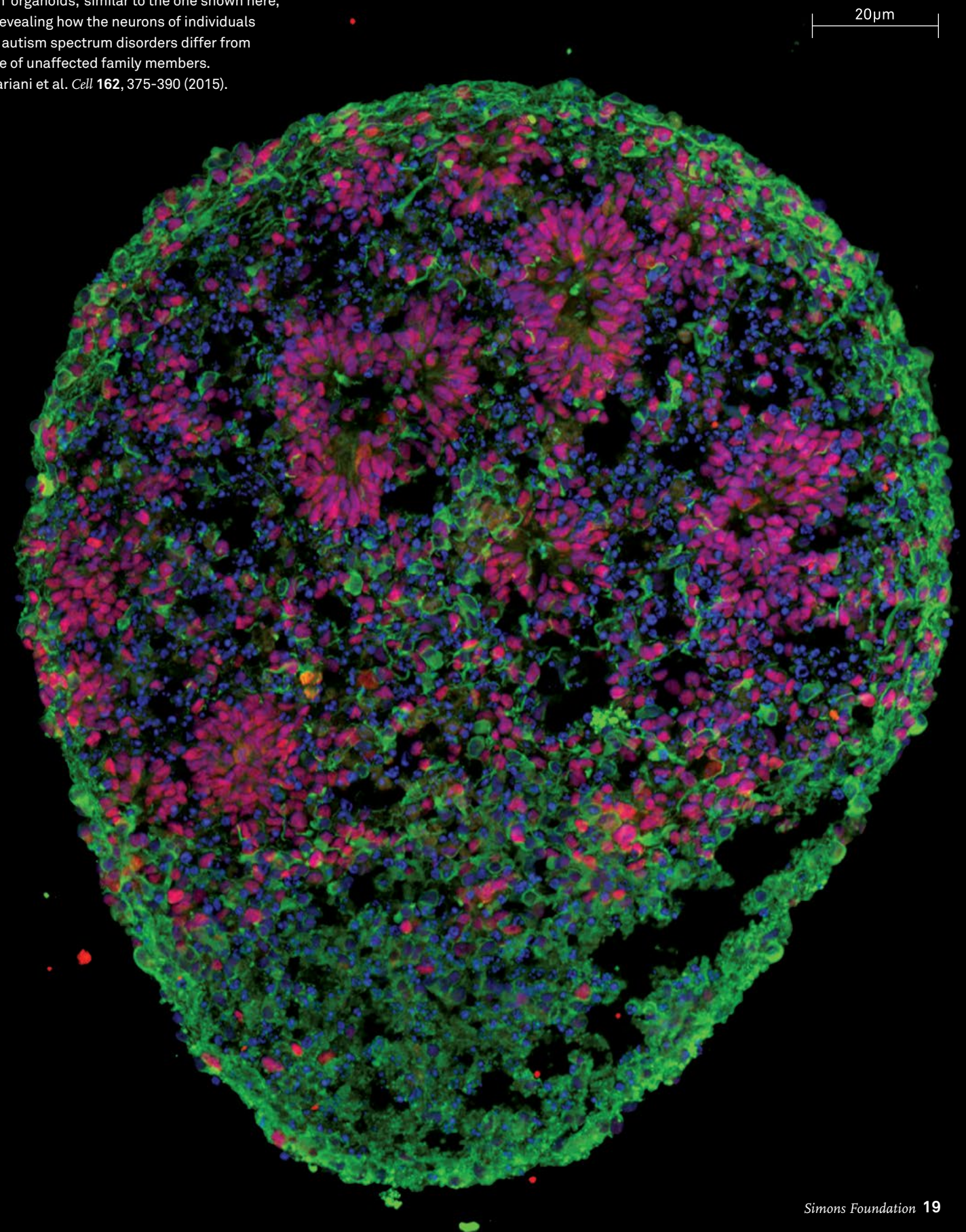
Maternal Mutations

About 10 percent of autism in boys may result in part from rare genetic mutations inherited from their mothers, according to a study published in the June 2015 issue of *Nature Genetics*. SFARI investigators Evan Eichler and Raphael Bernier of the University of Washington and their colleagues examined the exomes — the protein-coding regions of the genome — of 2,377 families from the Simons Simplex Collection, a repository of data from families with one child with autism and unaffected parents and siblings.

The researchers found that even though the mothers in the study did not have autism, they were more likely to have passed down rare mutations to their children with autism than to their unaffected children, at least when it came to 'conserved' genes, ones that are seldom mutated in the general population. The findings are consistent with the idea that women are somehow protected from some of the genetic causes of autism.

On average, the children with the most severe cases of autism had the most of these rare inherited mutations. The researchers estimate that inherited single-letter mutations in DNA contribute to about 7 percent of autism cases; another 3 percent of cases, they propose, result from small copy number variations — regions of DNA that are duplicated or deleted — that contain at least one conserved gene.

Making Connections

Over the past decade, some brain imaging studies of individuals with autism have suggested that their brains are less connected than those of controls, whereas other studies have suggested the opposite. A new study by SFARI Investigator Marlene Behrmann of Carnegie Mellon University in Pittsburgh, Pa., and two co-authors suggests that both findings are correct, and that they are manifestations of a previously undiscovered characteristic of autism spectrum disorders: distorted brain connectivity patterns, often with strong connections in regions where control brains have weak connections, and vice versa.

Behrmann's team, which published its findings in the February 2015 issue of *Nature Neuroscience*, analyzed resting-state, functional magnetic resonance imaging scans from 73 controls and 68 adults with high-functioning autism from the open-access Autism Brain Imaging Data Exchange.

The brain connectivity patterns of the controls adhered fairly closely to a canonical template, yet those of the individuals with autism varied widely, the researchers found, in terms of both intra- and interhemispheric conductivity, observations consistent with the heterogeneity of the disorder. The researchers found that the individuals with the most idiosyncratic connectivity patterns in certain interhemispheric connections had the most severe autism symptoms. These individual alterations in brain organization may be a core characteristic of high-functioning autism, the team proposes.

Hyperactive Protein

Researchers have identified a molecular switch that, when disrupted, locks the UBE3A protein — associated with both autism and Angelman syndrome — in a hyperactive state. Mice with overactive UBE3A, the team found, have an unusually high density of dendritic spines, neuronal protrusions that receive signals from synapses.

The researchers, led by Mark Zylka and SFARI Investigator Ben Philpot of the University of North Carolina at Chapel Hill, began by examining mutations in individuals with Angelman syndrome, who typically have underactive UBE3A. They discovered mutations clustered around a UBE3A region regulated by an enzyme called protein kinase A, which can turn the protein off. In 2014, a whole-exome analysis of the Simons Simplex Collection identified a child with autism who has hyperactive UBE3A and a mutation in precisely this region.

The researchers, who published their findings in the August 13, 2015, issue of *Cell*, found that in mice, the inactive form of UBE3A is most prevalent at birth and then tapers off over the first week of life, suggesting that mutations that make UBE3A hyperactive may disrupt brain development most during this early stage of development. The study hints at a possible role for UBE3A-inactivating drugs such as Rolipram in treating individuals with autism who have UBE3A mutations.

Slower Sound Processing

A new study has linked sound-processing impairment to a copy number variant that is one of the most common causes of autism. Children with deletions in the chromosomal region 16p11.2 process sound markedly more slowly than controls do, researchers reported on February 11, 2015, in *Cerebral Cortex*.

The researchers, led by SFARI Investigator Timothy Roberts of the Children's Hospital of Philadelphia, used magneto-encephalography (MEG) to study how quickly the brain responds to sounds in 51 children with 16p11.2 variants who are part of the Simons Variation in Individuals Project, and 45 controls. They found that children carrying a 16p11.2 deletion produced a particular magnetic response to sound known as M100 about 23 percent later than controls did. Children with a 16p11.2 duplication produced the M100 signal slightly faster than controls did, though this difference was not statistically significant. Less than 20 percent of individuals with 16p11.2 variants have autism, but many of the others show language impairments or developmental delays. The sound-processing delays among children with 16p11.2 deletions occurred across the board, and happened in response to simple stimuli. These delays may have an even greater impact when it comes to processing more complex sounds such as spoken language, which requires rapid, ongoing processing.

LENA Language System

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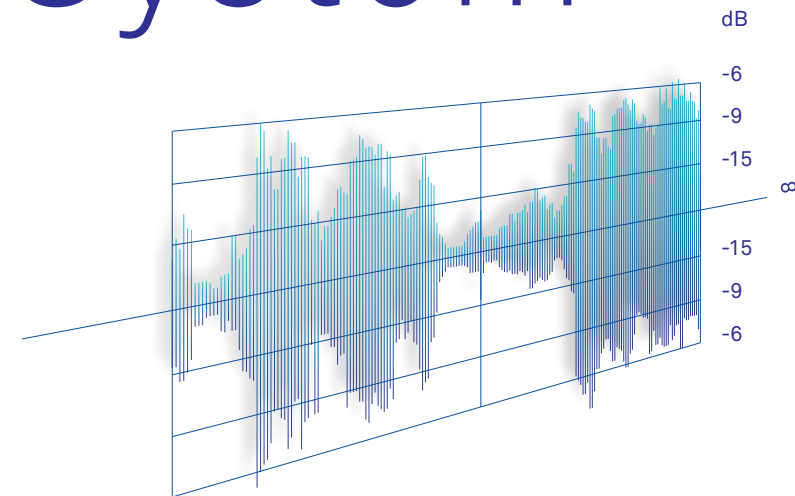
Illustration:

The LENA System allows researchers to record the language an individual with autism uses in everyday life. This spectrogram of a recording made with the LENA System shows the sounds of an excited scream of a child on the autism spectrum. Courtesy of Catherine Lord, Weill Cornell Medical College, Cornell University.

A new algorithmic approach to quantifying language production in individuals with autism has the potential to fill a vexing gap in autism research: the shortage of objective measures of whether a proposed therapy truly improves behavioral outcomes. Mark Clements, an engineering professor at the Georgia Institute of Technology, is building mathematical tools that can analyze audio recordings obtained using a wearable recording device known as the LENA (Language Environment Analysis) System.

The amount and quality of language an individual produces is one of the few behavioral outcomes that all researchers agree is clinically meaningful. But high-quality voice recordings of individuals going about their daily lives are difficult to collect, and then must typically be transcribed by hand, which is time-consuming and expensive. These limitations have greatly reduced the amount of data available to researchers.

Now, Clements and other researchers supported by the Simons Foundation are exploring how to use the LENA system to overcome these obstacles. If their team can automate collection and analysis of language data, "it would mean measurement of language production would be scalable, which is really important in clinical trials," says Pamela Feliciano, senior scientist at the Simons Foundation Autism Research Initiative. "It would be a huge boon."

LENA, created by the LENA Research Foundation, based in Boulder, Colo., attaches to a child's clothing and records his or her sound environment. LENA's developers have created proprietary software that quantifies vocalizations such as squeals and grunts in young children, and that shows promise in identifying toddlers at a heightened risk of developing autism.

LENA has potential for studying older children as well, says psychologist Catherine Lord, director of the Center for Autism and the Developing Brain at New York-Presbyterian Hospital and principal investigator of the current study. But LENA's proprietary software does not perform especially well at analyzing older children's vocalizations. So Clements is developing mathematical techniques for extracting meaningful communication features from recordings of older children with autism.

Most speech-processing programs, such as those available in smartphones, are optimized for adults speaking in well-controlled, quiet conditions. By contrast, LENA recordings capture "competing siblings, parents, TV, all kinds of things," Clements says. Analyzing such complex recordings is "pretty much an untapped research area."

Clements' team has developed software that can identify, with about 90 percent accuracy, when the child with autism is the one speaking, and that can identify laughs and cries. The software also looks at resonant frequencies in the vocal tract to figure out whether the child is happy, sad or angry. "We've had to invent our own mathematics to do that," Clements says.

It's essential, the researchers agree, for psychologists and engineers to work together. Lord was able to tell Clements, for instance, that a simple measure such as how often a child screams might not be that informative, as children with autism often scream from happiness as well as anger. "The psychologists tell us what they think is important, and then we try to make it happen," Clements says.

Genes by the Numbers

Over the past six years, gene sequencing studies have definitively linked spontaneous (or de novo) mutations to autism in children who are the only members of their immediate family to have the condition. Studies of the Simons Simplex Collection (SSC) — a repository of data from families with just one child with autism, and unaffected parents and siblings — have consistently shown that the children with autism have more de novo mutations than their siblings.

In 2014, a landmark sequencing study of the protein-coding regions of the genomes of 2,515 families from the SSC identified about 400 loss of function mutations — ones that indisputably disrupt the function of a gene — in some of the children with autism. Yet that doesn't mean that all 400 mutations are in fact connected to autism; about 200 of the children's siblings also have de novo loss of function mutations. Their mutations, though, are presumably benign, at least with respect to autism.

Assuming, as researchers believe, that the children with autism have benign mutations at about the same rate as their siblings, these numbers suggest that only about half of the 400 loss of function mutations in the children with autism are true autism risk genes, and the other half are red herrings. But which genes fall into which category?

To tackle this question, researchers supported by the Simons Foundation Autism Research Initiative (SFARI) have been developing an array of mathematical techniques to weigh the evidence for each candidate gene. Already, these approaches have highlighted between 65 and 100 high-confidence autism risk genes.

"Five years ago, we had just a handful of genes that we knew contributed to autism risk," says Alan Packer, senior scientist at SFARI. "Now this longer list is acting as a catalyst to the field, and is leading to important insights into the biology of the disorder."

The impact of these new mathematical methods goes beyond autism, says Stephan Sanders of the University of California, San Francisco, who has been involved in many of the sequencing studies and statistical analyses. The creation of these tools has inspired many other studies, he says, on disorders such as congenital heart disease, infant epilepsy, intellectual disability and other diseases whose genetics follow a similar logic to that of autism. "Autism has really been leading the field in putting these methods out there," he says.

Genetic Birthdays

The mathematical techniques being developed vary considerably, but all are based on one underlying principle: Genetic variations most likely to be related to autism are the unusual ones — ones you wouldn't expect to see in the general population.

This principle was first applied to assess the evidence that comes from 'recurrent' copy number variants and mutations: Ones that appear in multiple children with autism. Recurrences should be much rarer among the 200 red herring genes than the 200 true autism genes, as the red herrings are presumably sprinkled fairly randomly among all the approximately 18,000 genes in the genome, while the 200 autism genes are crowded into the much smaller set of genes involved in autism — about 500 to 1,000, researchers estimate. It's as

if you're throwing 200 darts at a dartboard with 18,000 sections, and another 200 darts at a portion of the dartboard with only 1,000 sections: The latter darts are much more likely to hit the same section more than once.

In its simplest manifestation, the dartboard's mathematics is the same as that of the famous birthday problem in probability theory, which asks how likely it is that a group of people will contain at least two with the same birthday: The sections of the dartboard correspond to possible birthdays, and the darts correspond to the people. In reality, though, the picture is more complex. The sections of the genetic dartboard aren't all the same size: Certain genes are more likely to get hit by a dart (that is, have a mutation) than other genes. For example, long genes tend to have more mutations than short genes, just because there are more opportunities to miscopy something. And genes with a high proportion of C-G base pairs are more vulnerable to being miscopied than those with many A-T base pairs.

Sanders is part of a team — with Xin He of the University of Chicago, Kathryn Roeder of Carnegie Mellon University in Pittsburgh, Bernie Devlin of the University of Pittsburgh, and Matthew State of the University of California, San Francisco — that has developed a method called the 'transmission and de novo association test' (TADA) that calculates the size of each gene's section of the dartboard. TADA can analyze recurrences involving mutations whose link to autism is less clear than that of de novo loss of function mutations: for instance, mutations that are transmitted from parents to children, and 'missense' mutations, in which a single base pair
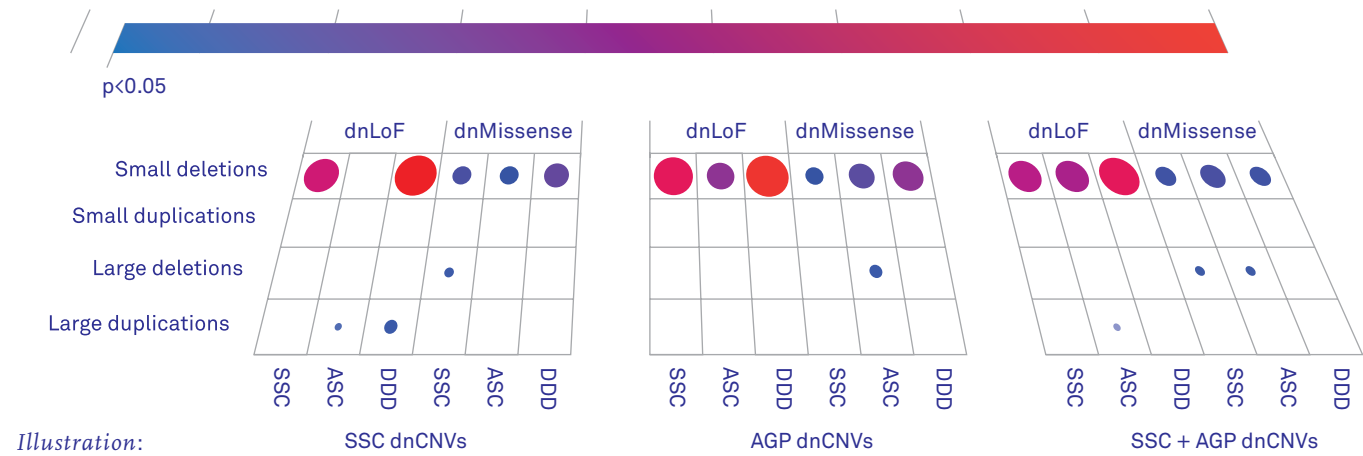
has been miscopied in a way that has not yet been proved to disrupt the working of the gene. In a September 23, 2015, paper in *Neuron*, the team used TADA to identify 65 genes strongly associated with autism.

Intolerant Genes

Recurrences, in which the same gene is mutated in more than one child with autism, are the low-hanging fruit of sequencing studies. But the vast majority of the genes these studies have uncovered are mutated in only one child. Even in these cases, however, it's possible to assess which mutations are most surprising, and thereby prioritize them as candidate autism risk genes.

Michael Wigler and Ivan Iossifov, geneticists at Cold Spring Harbor Laboratory, and David Goldstein, a geneticist at Columbia University, have independently proposed that the key to doing this lies in understanding each gene's mutation tolerance: the extent to which a hit to that gene impairs an individual's ability to survive and reproduce. Because individuals with autism tend to have lower reproduction rates than the general population, these researchers have posited that autism risk genes should be among the less tolerant genes in the genome.

One simple way to measure a gene's tolerance is to observe how many loss of

function mutations appear in that gene in the general population, compared to the gene's length. If loss of function mutations appear often, that means mutations to the gene are largely survivable; if, instead, loss of function mutations are seldom or never seen, that suggests that individuals with mutations to that gene were unable to survive.

Using this tolerance measure, Iossifov compared the loss of function mutations in children with autism with the loss of function mutations in unaffected controls. Sure enough, Iossifov and Wigler's team reported in the September 23, 2015, issue of the *Proceedings of the National Academy of Sciences* that the mutated genes in the children with autism had a lower tolerance to mutation, on average, than the genes that were mutated in controls. Using the genes' tolerance scores, Iossifov and Wigler have identified 239 genes that have at least an 80 percent likelihood of being true autism risk genes.

Meanwhile, Goldstein has developed a different scoring system for genetic tolerance. His system measures a gene's underlying mutability — how easily it breaks — based on physical principles, and then compares that mutability with how many loss of function mutations appear in the general population. In similar logic to Wigler's approach, if a gene has many fewer

mutations than its underlying mutability predicts, then presumably the people with mutations in that gene did not survive to form part of the general population.

As Goldstein and his colleague Slavé Petrovski of the University of Melbourne described in a paper in the September 2, 2015, *PLOS Genetics*, this scoring system offers the potential to shed light on intolerance not only in the 2 percent of the genome consisting of genes, but also in the other 98 percent of the genome, much of which performs important regulatory functions. (Goldstein cautions that extending the scoring method to the whole genome will require a much larger dataset of whole-genome sequences from healthy individuals than currently exists.)

Eventually, this scoring system could help to prioritize mutations that emerge from whole-genome sequencing of the SSC, now under way with support from SFARI and the National Institutes of Health. The New York Genome Center is on track to complete whole-genome sequencing of the entire collection within about another year.

Autism stemming from mutations in the noncoding regions of the genome "virtually has to be happening," Goldstein says. "We want to track those mutations down."

Spectrum Launches

Image above:

The *Spectrum* team in 2015, from left to right:
M. Amedeo Tumolillo, Jessica Wright, Greg Boustead,
Nicholette Zeliadt, Apoorva Mandavilli, Katie Moisse,
Ingrid Wickelgren, Hope Vanderberg, Ashleigh Richardson

In less than a second, a Google search for 'autism research' returns 68 million results. A search for 'autism research news' returns 39 million results. Such an incredible amount of information can be hard to parse when trying to learn more about autism spectrum disorder and what research is revealing about it — even for practicing scientists.

In 2015, confirming its commitment to providing autism scientists — and the interested public — with accurate and comprehensive autism research news, the Simons Foundation launched the editorially independent online publication *Spectrum*.

Spectrum is a sleek, informative news site defined by its ambitious coverage, in-depth articles and eye-catching art. The site's design, developed by Brooklyn-based creative agency Madwell, gives the articles, especially *Spectrum*'s long-form feature stories, called "Deep Dives," room to breathe. "Readers can really immerse themselves in a story," says Apoorva Mandavilli, the site's editor-in-chief.

The site traces its history to autism research news coverage originally appearing on simonsfoundation.org and then on SFARI.org, the website of the Simons Foundation Autism Research Initiative. "The goal of the news coverage was to provide a single place where scientists could keep abreast of their field without having to sift through dozens of scientific abstracts each week," Mandavilli says.

SFARI.org's coverage of autism research news quickly quickly gained attention: The site's traffic doubled each year from 2008 to 2014, as did its output. By 2014, the home page was overflowing with content — journalistic news and opinion pieces were posted alongside announcements for SFARI funding opportunities and research resources.

As SFARI.org grew, Mandavilli started thinking about what a site focused entirely on autism research news might look like and how it could be used to catalyze new research collaborations and novel perspectives on autism. By 2014, it was an idea ready to be made a reality, as SFARI decided that the autism research news coverage deserved its own real estate.

Spectrum launched in September of 2015. Within weeks, tens of thousands of readers came to the new site to read freelancer Ingfei Chen's Deep Dive "Wide Awake: Why Children With Autism Struggle With Sleep." The article's success, just before the site's debut at the annual Society for Neuroscience meeting in Chicago, helped to mark the magazine's auspicious entry into the world of online science journalism, and there were more successes to come. Senior news writer Jessica Wright's feature "The Missing Generation" won third place in public health reporting in the Association of Health Care Journalists' excellence awards contest, and Mandavilli's piece "The Lost Girls" won first place in the trade publication category. Mandavilli's story was also chosen to appear in the 2016 edition of the anthology *The Best American Science & Nature Writing*.

"We are off to an incredible start," Mandavilli says, "and we are excited to continue to establish ourselves as a leading source of autism research news."

Francesca Happé, professor of cognitive neuroscience at King's College London, calls *Spectrum* a beacon on the Internet. "Among autism scientists, it's absolutely the go-to place."

Simons Collaboration on the Global Brain

The secrets to the production of our thoughts, memories and emotions appear to be hidden in the populations of neurons that make up our brains. "Something happens within those sets of nerve cells so that mind and percepts emerge," says Gerald D. Fischbach, chief scientist and fellow of the Simons Foundation. "We want to know how."

Deciphering how memories, emotions and other aspects of cognition emerge requires the best and brightest researchers in neuroscience and, importantly, work and dialogue between them. That is why the Simons Collaboration on the Global Brain (SCGB) has brought together 70 investigators who are using both theory and experiments to understand the neural coding and dynamics that give rise to decisionmaking, thoughts, memories and so much more.

Since the 1950s, scientists have studied individual neurons and made great progress in understanding the mechanics of how a neuron can use electrochemical signals to encode and transmit information. In the SCGB, scientists are now pushing that research further, recording and tracking the signals of hundreds or even thousands of neurons, and searching for patterns in the signals those cells send.

Sifting through the resulting signals is a complex computational task. A single neuron can fire 1,000 times a second — every second — and a single neuron can connect to up to 1,000 other neurons, meaning billions of bits of information move through the brain every second. Analyzing all of this activity requires collaboration: Experimentalists work closely with theorists to develop rigorous statistical analyses of the data, and theorists can use the data to create new models of neural circuits and networks that inform future experiments.

SCGB findings published in 2015 illustrate the intersection of experiment and theory.

SCGB Investigator Michale Fee of the Massachusetts Institute of Technology and his team conducted an elegant series of experiments that explain how young zebra finches learn new songs. This work confirmed many of the predictions in SCGB Investigator Ila Fiete's theory on the same topic. What Fiete previously proposed and Fee confirmed was that neurons in the birds' high vocal center fire in limited bursts, which encode information for a sequence of a few song notes. The brain duplicates the sequence, so that there are two sequences, which then evolve independently as the bird learns more notes for the song. The two sequences are then duplicated and the resulting sequences evolve separately, then duplicate and evolve, until the complete song is encoded in the cells.

Neurons can also encode where an animal is in its environment. These neurons, called grid cells, are good at getting us where we need to go. But, like the GPS navigation systems in our phones and cars, the neurons can sometimes make mistakes and lead us off course. In mice, this happens when grid cells start firing when the animal is far from the space where the cells usually fire. SCGB Investigators Surya Ganguli and Lisa Giocomo of Stanford University, along with Kiah Hardcastle, Giocomo's graduate student, found that grid cells can accumulate errors surprisingly quickly, within two minutes, not the 30 to 40 minutes the team had suspected. The errors arise if the mouse turns too much or too little, or if it miscalculates its speed, and small mistakes add up over time. But, the team found, a mouse's grid cells can correct miscalculations after the animal bumps into a wall or some other boundary. These observations support the

Early Storage Late Storage Response

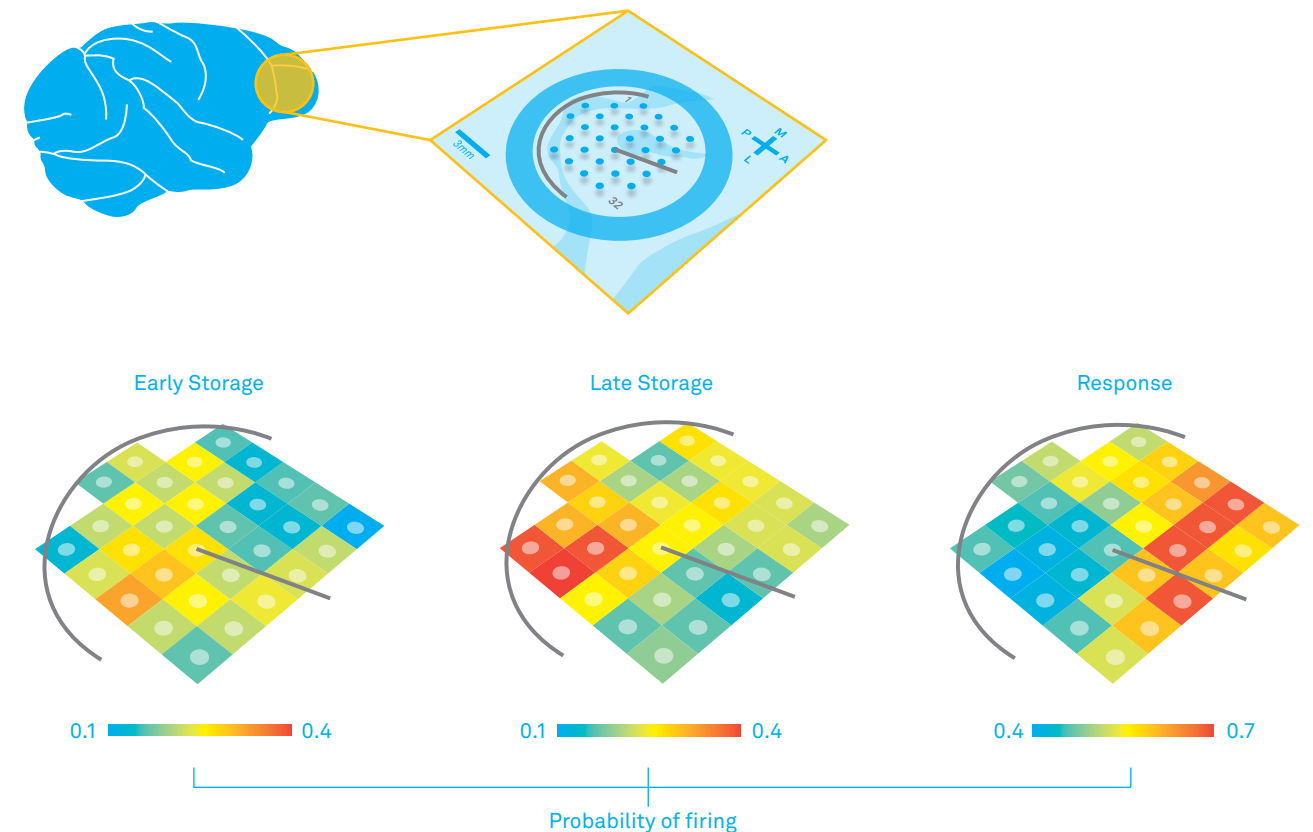0.1 — 0.4   0.1 — 0.4   0.4 — 0.7

Probability of firing

Illustration above:

The prefrontal cortex of the brain is marked in the top, left illustration, with an accompanying pullout depicting an array of electrodes used to record neuronal activity there. The three grids, which depict the activity recorded by each electrode during different stages of working memory, show the probability of neurons in the indicated areas firing. The bars show the likelihood of firing at each stage. There is a remarkably different firing pattern during the late storage stage compared with the early storage stage, and also the late storage stage compared with the response stage. Adapted from D. Markowitz et al, *Proceeding of the National Academy of Sciences* **112**, 11084–11089 (2015).

theory that grid cells use speed and direction to calculate the animal's location and are a first step toward understanding how external environmental cues shape the brain's spatial representations of the world.

Theory and experiment, however, are interactive and can evolve as more information becomes available. SCGB Investigator Bijan Pesaran of New York University and his colleagues found that understanding working memory — the immediate and temporary processing of new information — is more complex than scientists had thought. Theory suggested that a single centralized network of neurons, which all work the same way, support working memory. But Pesaran and his team showed that a monkey's working memory is supported by three specialized yet anatomically distinct networks of neurons that work together to encode information. The results, the researchers write, reveal specific circuit-level neural populations that may hold clues as to how working memory functions, and how it can go awry.

Collaboration is critical to making these kinds of advances. So is an infusion of new minds into neuroscience. In 2015, the SCGB launched a prestigious fellowship program to invite up to 10 promising early career scientists to join the collaboration each year. "The goal is to introduce these students to the mysteries of the brain and have them apply their knowledge of physics, math and other fields to solving the great questions of how our minds work," Fischbach says. "This is the great frontier of the field."

SCOPE Cruise

After much debate over the costs and benefits of spatial versus temporal studies, Simons Collaboration on Ocean Processes and Ecology (SCOPE) researchers decided to investigate temporal variability in ecosystems during their 2015 summer cruise to the Pacific waters north of Oahu, Hawaiʻi.

SCOPE's 16 investigators, assisted by 26 postdoctoral researchers and 11 graduate students, aim to advance our understanding of the biology, ecology and biogeochemistry of microbial processes that dominate Earth's largest biome: the global ocean.

"The 2015 cruise was a tremendous success. We couldn't have planned it any better than we did," said SCOPE co-director Dave Karl at the collaboration's annual meeting at the Simons Foundation's headquarters in December.

Since September 2014, SCOPE scientists have participated in 17 Hawaiʻi Ocean Time Series (HOT) cruises, allowing them to extensively sample the water column of the North Pacific Subtropical Gyre between 5 and 175 meters and, on 10 of those profiles, to survey microbes from the surface to depths of 4,000 meters.

Last summer's expedition, with 46 SCOPE participants, was the highlight of 2015. "This was a very historic event for us here," says microbial oceanographer Edward DeLong of the University of Hawaiʻi at Manoa, a SCOPE investigator and its co-director. "It was the first integrated two-ship operation that has ever been conducted at the University of Hawaiʻi in support of microbial oceanography."

Much of the cruise's success was a result of interaction between experimentalists and mathematicians. "Idealized mathematical models are where you can gain a lot of insight and communicate things really crisply and in a powerful way," says SCOPE investigator and marine biogeochemical modeler Mick Follows, of the Massachusetts Institute of Technology, but "there is another side in the world of modeling — the idea of simulation," he adds. "In oceanography, we have developed our simulation capabilities over the past few decades with the availability of powerful computers."

Ocean simulations — which simulate everything from chlorophyll concentrations to sea surface height and temperature, at both a regional and a global scale — are based on fluid-dynamic models, which, perhaps not surprisingly, originated from weather-forecasting models. For example, in reviewing the sea-surface height of the water around SCOPE field site Station ALOHA, Follows and his team simulated the transport of many thousands of virtual 'floats' by the circulations of cyclonic and anticyclonic eddies. The currents associated with the eddies can be inferred from remote sensing, and run parallel to contours of sea surface height, which is measured by satellites.

Follows' team, along with Dave Karl's group at the University of Hawaiʻi, tracked where the floats were likely to go, to identify which areas were suitable for the experiment. The team was looking for an eddy where the current had both low displacement, where floats remain close to where they started, and low divergence, where two floats that start together stay together, indicating minimal horizontal exchange of water. "You don't want [the floats] to run off to some odd place," Follows says. "Based on the immediately pre-cruise flow, and given that the development of that flow is relatively slow, we could make some useful predictions about how the system near Station ALOHA was going to look." Meanwhile, robotic sea gliders operated by Karl's group provided real-time data, including water temperature, salinity and chlorophyll concentrations in the area, to help validate the computer simulations and refine planning.

In the late-July cruise window, the system around Station ALOHA was not the best for SCOPE cruise objectives. "Station ALOHA was in a frontal region, a highly divergent region. It was not an optimal site for the study," Benedetto Barone of the University of Hawaiʻi reported at the meeting. A launch of a drifter buoy near Station ALOHA confirmed their model predictions; the buoy traveled too quickly to the south, back toward Oahu, for the cruise to take advantage of the currents around the site.

But the satellite data and float simulations had also revealed a promising anticyclonic eddy further north: Two drifters deployed in this region stayed together, indicating an eddy system with low divergence. The buoys circled the

area where they were launched, showing the area also had low dispersion. This provided an ideal system for study, as "the microbial community inside the eddy was composed of spatially cohesive populations that we could track over time," Barone said.

Microbial communities in the ocean coordinate their daily, or 'diel,' rhythms with the sun. These rhythms range from oscillations in gene expression to precisely timed cell division cycles to predator-prey interactions and even to matter and energy transformation. One of the main hypotheses SCOPE researchers test is whether microbial interactions are governed not just by the fact that they are living together in the same current, but by how each species spends and organizes its time. "The idea is that different microbial species line up at precise times during the day, forming a bucket brigade of interspecies matter and energy transfer in organized, predictable ways each day," explains DeLong. "Identifying these interspecies interactions is one of the keys to understanding biogeochemical processes that govern matter and energy flux in and around station ALOHA."

To best investigate these microbial cycles, the oceanographers followed two drifting buoys aboard the research vessel Kilo Moana, which allowed them to track discrete currents and, every four hours or more, to sample water to detect changes in the microbial community. A ship known as KOK tagged along behind, conducting multiple sampling operations along the way.

In order for microbiologists to create simulation models of the microbiome for further testing of community relationships, they need to first collect massive amounts of data. To help accomplish that goal, biochemist Angelicque White of Oregon State University is measuring the diurnal cycle of light absorption and production to estimate community productivity at high temporal resolution. Specifically, her team uses optics as a method for estimating carbon assimilation at daily resolution, from dawn to dusk. This measurement allows the SCOPE team to measure microbial production of organic matter day to day, and link those changes to fine-scale changes in physical and chemical oceanography.

Currently, the gold standard for calculating productivity is to directly measure carbon fixation using radioisotopes (C14 isotopes). White was testing optical methods to measure productivity; the hope is that these methods can be applied to sea gliders, drifters and profiling floats, allowing researchers to quantify ocean production on an unprecedented scale. She says the results are promising. "This method has potential, particularly if we can profile within the mixed layer. It is a practical method for measuring productivity in real time."

"A focus for this cruise was to peer more deeply than ever into the 'days in the life' of oceanic microbial communities," DeLong says. Or, as White put it during the SCOPE annual meeting, to essentially ask the microbes, "How was your day?"

Math for America

Image left:

A crocheted hyperbolic plane from Cornell mathematics professor Daina Taimina's book, *Crocheting Adventures With Hyperbolic Planes*

For hundreds of millions of years, nature has been creating curved corals, ruffled leaves and other hyperbolic objects. In the 19th century, mathematicians figured out how to describe these objects with formulas and equations, but building accurate physical representations of them has always been a challenge. However, in 1997, Cornell University mathematician Daina Taimina, author of *Crocheting Adventures With Hyperbolic Planes,* figured out one way to bring hyperbolic geometry out of our imaginations and into reality: All she needed was knitting needles, crochet hooks and balls of yarn.

This year, inspired by Taimina's work, New York City high school math teacher and Math for America (M*f*A) Master Teacher Dorota Caetano resolved to share this approach to generating and understanding hyperbolic objects with other outstanding teachers in the city.

Caetano is one of about 1,000 teachers in New York City who belong to M*f*A, a nonprofit organization that offers fellowships to outstanding K-12 public school science and mathematics teachers. The fellowships are designed to create a professional community by convening these expert teachers for professional development events and courses, often led by other outstanding teachers in the program as well as by outside scientists, mathematicians and educators.

Approximately 10 percent of all K-12 public school mathematics and science teachers in New York City are now in this prestigious program, whose goal is to make teaching once again a respected and rewarding career choice. "Our vision is to have teachers who are true masters of their subject matter and deeply committed to the craft of teaching," says John Ewing, president of M*f*A.

Caetano's workshop, "From Knit and Purl to Hyperbolic Geometry," was an introduction to the mathematical nature of knitting and explored proportionality, symmetry, pattern recognition and tessellations. Through hands-on activities, participants were able to see how they could help their students visualize difficult, complex part geometry using low-tech tools like yarn and needles. "Crochet and knitting make it possible for some of hyperbolic geometry's most mind-bending concepts to come alive in your hands," she says.

Being a part of M*f*A, Caetano says, has given her new opportunities to explore her teaching philosophy. "I focus on nonroutine investigation more than before and have opportunities to dive deeply into my content area and pedagogy," she says. "More freedom. More creativity. More of what mathematics is really about."

Inspired by her involvement and learning through M*f*A membership, Caetano has begun to challenge her students — and herself — with more creative, open-ended mathematical questions, understanding more than ever that mathematics is ultimately a creative endeavor. Recently, she used some of her own knitted shapes to inspire her geometry students at Vanguard High School in Manhattan to undertake an extended exploration of hexagons. "It's really cool how there are so many possibilities with shapes and yarn," says Yahya Aala, a student in Caetano's class.

"Sometimes," Caetano says, "the students don't even know where to begin. But the process of figuring things out is what mathematics is all about."

Accelerating Science & Math Literacy: An Ideas Workshop

Rarely, if ever, do you hear an educated person say, "I can't read." However, that same person might without hesitation admit that he or she "doesn't get" science or "isn't a math person." And "I'm no scientist" is a refrain, intended to mock empirical evidence, that we hear with alarming frequency from individuals of influence.

These and similar challenges to the public's relationship with science set the agenda for an ambitious two-day gathering at the Simons Foundation on October 26–27, 2015, called Accelerating Science & Math Literacy: An Ideas Workshop.

"How did it become acceptable for so many Americans to profess math and science illiteracy when none of us would find it acceptable to live in a society where many couldn't read or write?" asked Boyana Konforti, director of the Education & Outreach division at the Simons Foundation, during the welcome keynote. In designing the workshop, the Education & Outreach team took a collaborative step toward its goal of bringing scientific thinking to all parts of society by engaging people with the process of science. The team invited scientists, science communicators, policymakers and educators, among others, to the foundation for intensive brainstorming, refinement and iteration of ideas.

"We hope that by bringing everyone together — with their different experiences and perspectives — we can develop and move forward with ideas that none of us could have imagined alone," Konforti told workshop attendees. "But before we can do that, we need to take a step back and ask what it means to be science and math literate."

Indeed, participants began wrestling with this query before the meeting even started. "Science isn't just about the scientific method and a list of facts. It is the tool kit that you want society to adopt," wrote David Ng, director of the Advanced Molecular Biology Laboratory at the University of British Columbia, in a preliminary assignment given to participants ahead of the meeting.

As part of that assignment, Konforti asked participants what a science-and-math-literate society — one that minimizes people's perception of science and math as something difficult and elitist — would look like. Stuart Firestein, professor of neuroscience at Columbia University, volunteered that such a society would foster "an appreciation for the narrative of science, the process of science, the perspective of science."

It would be "a society where science and scientific thinking are assumed to be part of the normal way of doing things," wrote Ben Lillie, co-founder of the live science show and podcast series *The Story Collider*.

During the event, attendees worked in small groups, brainstorming new strategies to present science to the public not as a set of facts but as a tool: a lens through which to view the world. Many of the ideas focused on creative ways to broaden and reframe what it means to be a scientist, and to do science. Encouraging society to 'think like a scientist' and critically assess new information with healthy skepticism, attendees argued, could have a lasting and profound impact on human health, the environment and innovation.

The working groups then shared their ideas with everyone at the workshop. Their presentations, followed by a lively question-and-answer period, allowed participants to give and receive pointed feedback, which helped to make each initiative stronger and more attainable. "It was, without question, one of the most productive meetings I have attended, maybe ever," says Donna Cohen Ross, who was a senior policy adviser at the U.S. Department of Health and Human Services at the time of the meeting.

Konforti says she is grateful for the hard work of the attendees, and inspired by their innovative ideas for making scientific thinking part of everyday life. Her team's next step is to put some of those ideas into action; programs that foster scientific learning in informal and unexpected ways will become a specific focus and grant-making priority.

BioBus
and BioBase

Image below:

Ben Dubin-Thaler, founder and executive director of BioBus, shows a group of students a pipette of water containing *Daphnia*.

A tiny crustacean called Daphnia wriggles across a TV screen. Its legs twitch and its sub-millimeter-sized heart beats rapidly. Such an intimate look at the critter's insides makes it easy to imagine that you're in a high-tech biology lab at one of New York City's top universities. But this is no ordinary laboratory: It's a bus — the BioBus.

The BioBus is a mobile science lab created to show the public that everyone can be a scientist in his or her own way, says Sasha Chait, director of development for Cell Motion Laboratories, which operates the mobile lab. It is a 1974 New York City Transit bus that Ben Dubin-Thaler, founder and executive director of BioBus, bought in 2007, gutted and refurbished with $100,000 of research-grade microscopes.

Since the bus opened its doors in 2008, it has hosted hundreds of thousands of students, from schoolchildren around New York City to curious children and adults living in cities across the country. Students climb aboard BioBus and are immersed in a world where they can experience science in a way they never have before, Dubin-Thaler says. They work side by side with professional scientists, exploring a range of questions, from how Daphnia's body works to what it looks like microscopically when paint dries.

"Exciting students' curiosity for how the world works, that's the goal. And hopefully, we spark careers in science for some of them, too," Dubin-Thaler says. "We also show students that scientists can be young, can be people of color, and are really passionate about their work and interested in making the world a better place."

After building out the BioBus, Dubin-Thaler dreamed of something even bigger: a space where students could continue to pursue their scientific curiosity after their BioBus experience. The BioBase opened in January of 2014 at the Lower Eastside Girls Club in Manhattan. Students can go there to dig deeper into scientific questions and develop projects and ideas of their own. "We really want to empower a new generation of scientists and foster greater public understanding of science," Dubin-Thaler says.

Watching students work at the BioBase is incredible, Chait says. "These kids are asking questions and going after the answers, working alongside formally trained scientists." What's even more inspiring, she adds, is to watch the kids come with their parents for Science Cafes or other public events and see the parents' curiosity get piqued as well.

With support from the Simons Foundation and other donors, Cell Motion Laboratories will begin operating a second BioBus by the fall of 2016, and a second BioBase is slated to open in Harlem in 2017. And the organization may not stop there: Dubin-Thaler, Chait and others would like to see a BioBase in nearly every New York City neighborhood. "We really want to keep going, to give more people an opportunity to be excited by science," Chait says.

Patterns in the Primes

If your favorite number is 712, mathematician Andrew Granville will quickly compute that 712 is 2 times 356, 4 times 178, 8 times 89, or 2 times 2 times 2 times 89. "Every number has a unique way of being written down as a product of primes," Granville says. "When we study an object in chemistry, we go to atoms; in biology, we go to DNA. For number theorists, it is prime numbers."

Granville, a professor of mathematics at the University of Montreal, specializes in analytic number theory and properties of prime numbers. On November 18, he delivered the Simons Foundation Lecture "Patterns in the Primes" as part of the foundation's Math and Its Applications lecture series. The foundation began hosting public lectures in 2013 as a way to convene scientists from diverse backgrounds and the interested public. The Math and Its Applications series was launched in 2015 to explore the usefulness of pure mathematics as a tool both to describe empirical reality and to drive human progress.

"The next really great breakthroughs for the progress of humanity often come because brilliant people have read deep mathematical ideas and make startling new connections with them," Granville says.

An example is the mathematics behind the theory of relativity. When, with no particular practical application in mind, Albert Einstein wanted to rework existing ideas in physics, he employed some mathematics that was developed decades earlier to better understand abstract notions in geometry. The resulting work ultimately upended the way we conceive of the universe.

In his lecture, Granville discussed prime numbers as another example of a deep mathematical idea with the potential to transform. A principal reason primes are
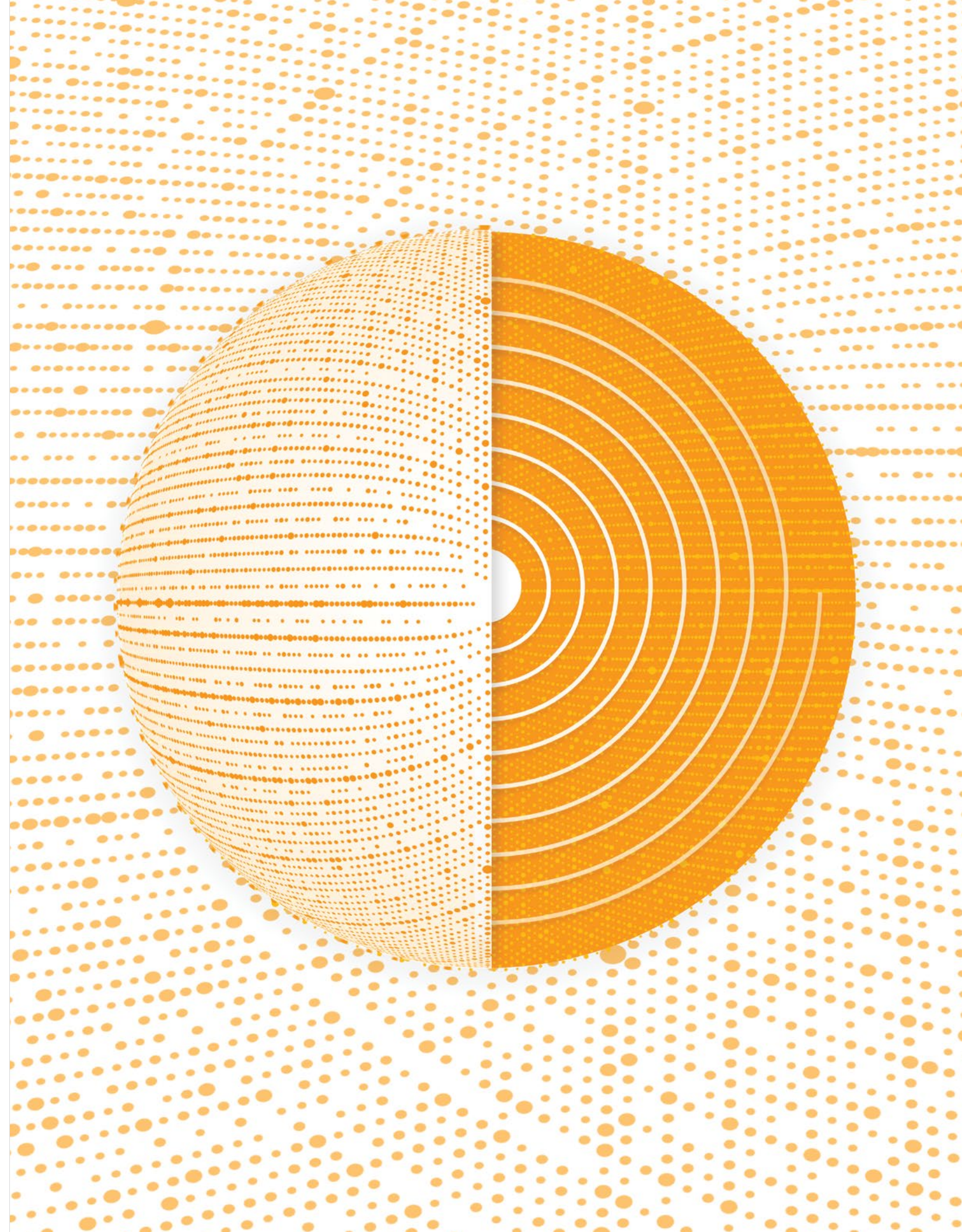
mysterious, he says, is that they are defined in terms of what they are not: They cannot be divided by any number, aside from one. That makes primes difficult to systematically identify and leads to one of the big questions in studying them: Are there patterns in primes? Ancient Greeks asked such questions more than 2,000 years ago, but we don't have answers to many of those questions even today. Still, Granville says, there have been remarkable breakthroughs recently.

Yitang Zhang of the University of New Hampshire made one of these breakthroughs. Prime numbers become rarer as numbers get bigger. But Zhang wanted to know if larger primes cluster, as smaller primes do, so that there are gaps of length two between them, as with the primes 3 and 5, 5 and 7, and 11 and 13. In 2013, Zhang was able to prove that there are infinitely many such pairs of primes that differ by less than 70 million. Other mathematicians have since pushed the work further, showing there are infinitely many pairs of primes with a maximum gap of 246. Such progress brings mathematicians much closer to solving the famous twin prime conjecture, which states that there are infinitely many pairs of primes that differ by two.

Even though understanding primes can have practical applications — for data encryption, for example — Granville cautions that we should not place too much emphasis on practicality in mathematics. "It's a very dangerous question: 'What is this useful for?'" he says. "There is an interesting story to be written about how practical impracticality can be."
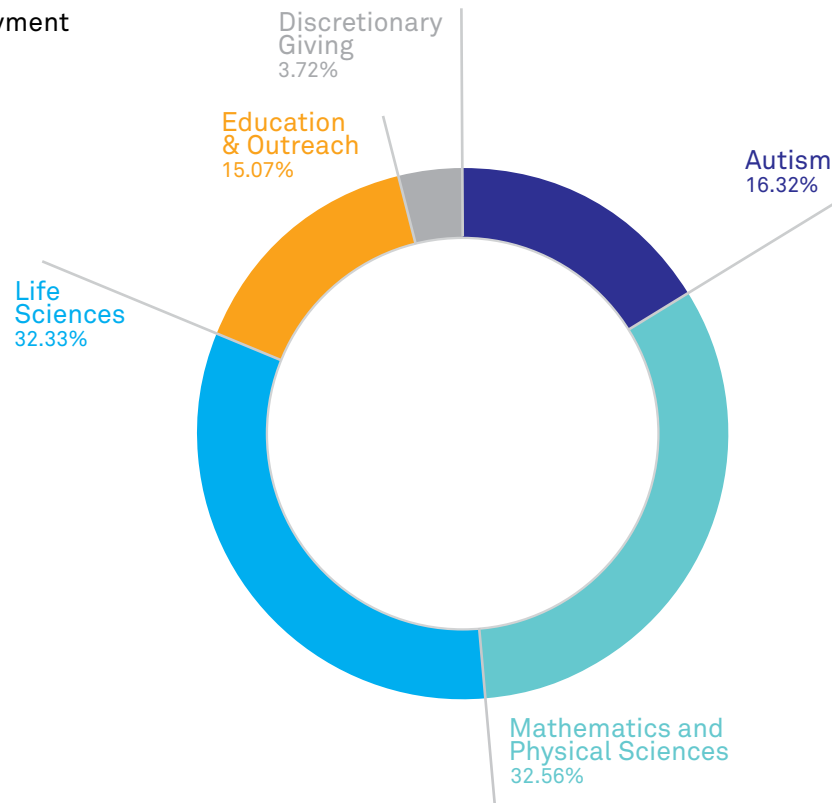
Illustration right:

When written on a number spiral, primes — represented as darker dots — appear to cluster along certain curves, revealing patterns in the positions of the primes.
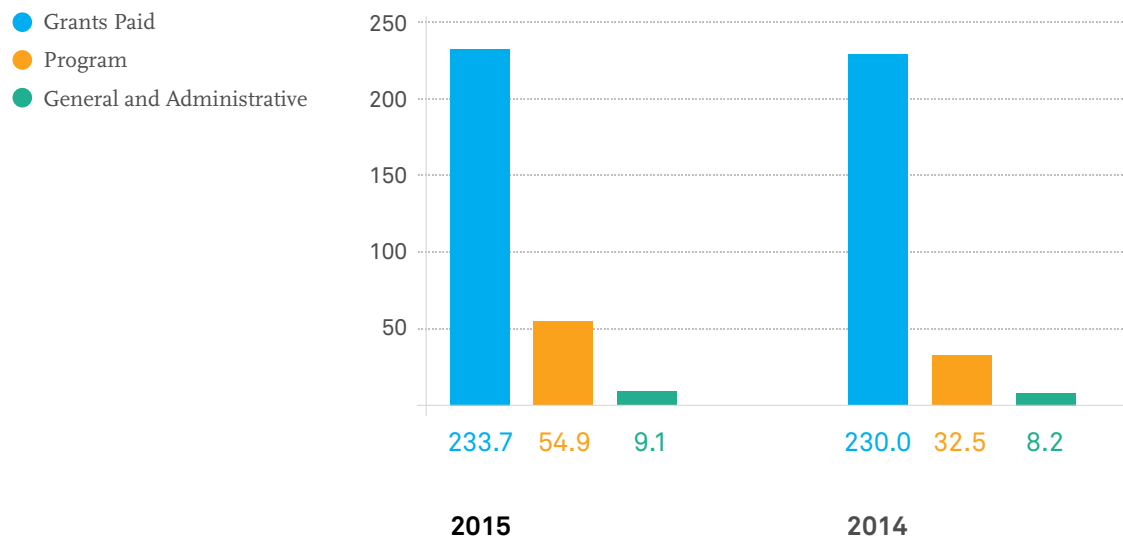
Financials

2015 Grant Payment by Category

- Discretionary Giving 3.72%
- Education & Outreach 15.07%
- Autism 16.32%
- Life Sciences 32.33%
- Mathematics and Physical Sciences 32.56%

Proportions of Expenses

(Cash Basis) $'s in Millions

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

2015	2014
233.7 54.9 9.1	230.0 32.5 8.2

Balance Sheet

Assets	12/31/15	12/31/14
Cash and Cash Equivalents	169,844,932	80,565,538
Investment Portfolio	2,433,730,987	2,257,634,705
Property and Equipment, Net	20,931,788	20,702,903
Other	3,520,672	3,228,187
Total	**2,628,028,379**	**2,362,131,333**
Liabilities		
Accounts Payable	8,819,630	5,003,493
Deferred Rent Liability	4,159,666	4,651,676
Grants Payable	544,379,877	387,212,315
Deferred Excise Tax Liability	17,894,155	14,435,381
Total	**575,253,328**	**411,302,865**
Net Assets	**2,052,775,051**	**1,950,828,468**

Income Statement

	For 12 months ended 12/31/15	For 12 months ended 12/31/14
Revenue		
Contributions	53,625,419	23,637,304
Investment Income	503,566,630	429,995,355
Total	**557,192,049**	**453,632,659**
Expenses		
Grants Paid	233,732,495	229,979,051
Change in Grants Payable	155,716,367	40,553,118
Program	51,778,126	30,552,373
General and Administrative	4,970,054	5,795,055
Depreciation and Amortization	2,840,331	2,500,252
Taxes	6,208,094	3,800,214
Total	**455,245,467**	**313,180,063**
Net Income	**101,946,582**	**140,452,596**

Mathematics & Physical Sciences Investigators

Simons Investigators

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Rajeev Alur
Sanjeev Arora
François Baccelli
Ngô Báo Châu
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Awardees

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Stanislas Leibler
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Kalin Vetsigian

Simons Collaboration on Algorithms and Geometry

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Amit Singer
David Steurer

Simons Collaboration on Homological Mirror Symmetry

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Bong Lian
Ludmil Katzarkov
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Shing-Tung Yau

Simons Collaboration on the Many Electron Problem

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Emanuel Gull
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Evgeny Kozik
Olivier Parcollet
Nikolai Prokof'ev
Mark van Schilfgaarde
Guifre Vidal
Steven R. White
Shiwei Zhang

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

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Dorit Aharonov
Vijay Balasubramanian
Horacio Casini
Patrick Hayden
Matthew Headrick
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Hong-kun Zhang

Theoretical Physics

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Benjamin Davidovitch
Eugene Demler
Andrei Derevianko
Charles Doering
Veit Elser
Glennys Farrar
Steven Furlanetto
Charles Gammie
Paul Ginsparg
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Patrick Lee
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Jacqueline Crawley
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Graeme Davis
Karl Deisseroth
Orrin Devinsky
Bernie Devlin
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Gabriel Dichter
Scott Dindot
Karen Dobkins
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Mayada Elsabbagh
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David Goldstein
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Alessandro Gozzi
Ann Graybiel
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Mady Hornig
Z. Josh Huang
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Jun Huh
Lilia Iakoucheva
Ivan Iossifov
Daoyun Ji
Peng Jin
Rebecca Jones
Zsuzsanna Kaldy
Stephen Kanne
Nancy Kanwisher
Nicholas Katsanis
Raymond Kelleher
Tal Kenet
Jonathan Kipnis
Margaret Kjelgaard
Eric Klann
Alexander Kolevzon
Kenneth Kosik
Gabriel Kreiman
Abba Krieger
Kenneth Kwan

Anthony-Samuel LaMantia
Rebecca Landa
Gary Landreth
David Ledbetter
Jason Lerch
Matthew Lerner
Christa Lese Martin
Bo Li
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