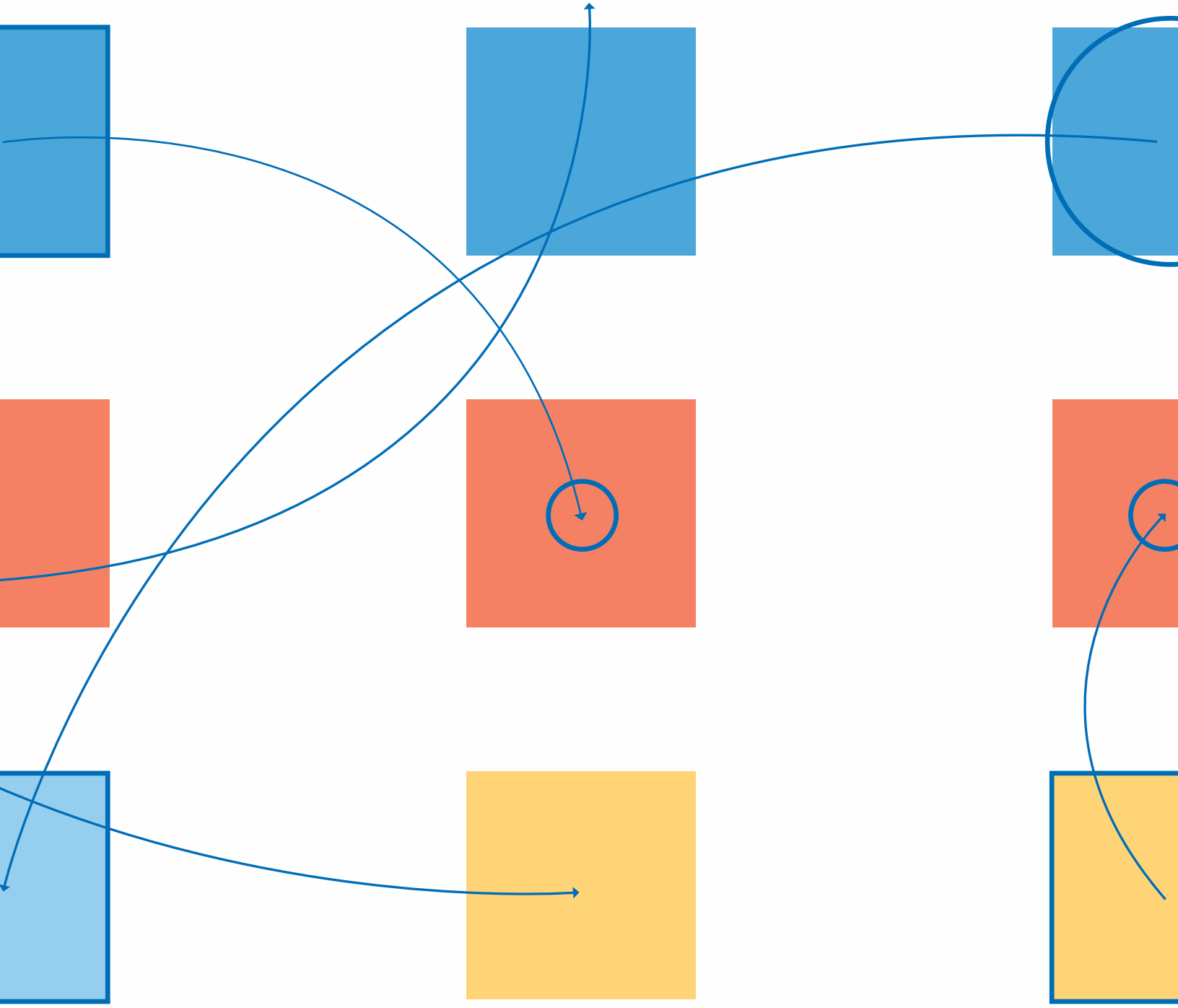
SIMONS FOUNDATION

Annual Report

2020 Edition



The Simons Foundation is pleased to present you with this copy of our 2020 annual report. Staying connected through Zoom, emails and conference calls, our grantees and scientists made groundbreaking advancements over the last year. We hope you enjoy reading about just a few of them.

You can view additional media related to these articles by visiting the report's digital edition at **simonsfoundation.org/report2020** or by scanning this QR code.

Marilyn Hawrys Simons, Ph.D.
President

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Letter From the Chair

2020 was quite a year — the likes of which we have not seen since the "Spanish flu" in 1918. Nonetheless, a remarkable amount was accomplished at the foundation. A few highlights follow.

Early on, we contributed $5 million to Rockefeller University to support COVID-19 research. That inspired an avalanche of such funding from other friends of Rockefeller, and some excellent work was accomplished. This flood of support culminated in an extremely effective monoclonal antibody treatment for COVID-19, recently licensed to Bristol Myers Squibb and now undergoing trials. The presence of vaccines notwithstanding, a highly effective treatment for COVID-19 will have an important role to play around the world.

Back at the foundation, we established a new unit of the Flatiron Institute, the Center for Computational Neuroscience (CCN), which will be housed at 160 5th Avenue instead of across the street at the institute's main site. It will be led by Eero Simoncelli, an outstanding scientist, and will grow to 50 people over the next several years. This is the fifth and last unit to be established at Flatiron. To seed it, the neuroscience group from Flatiron's Center for Computational Biology (CCB) has moved to the CCN, allowing the CCB to expand into other areas.

While working from home and over Zoom, the folks at Flatiron produced over 750 scientific papers submitted for publication this year: a new record. A good deal of recruiting took place, some for senior scientists but most for postdoctoral scientists. Flatiron continues to grow!

Louis Reichardt, who headed our autism research program, stepped down at the end of September after almost seven years of very good work. Until a new director is in place, John Spiro, SFARI's deputy director, is also serving as interim director and doing an excellent job. A search for a director has been underway for some time, and we believe the position will be filled quite soon.

A number of new Simons Collaborations were established, mostly in the Mathematics and Physical Sciences division, but one in Life Sciences — called the Simons Collaboration on Plasticity and the Aging Brain — is particularly interesting, especially to me, whose brain is definitely aging! This effort is overseen by Gerry Fischbach, assisted by Alyssa Schaffer. It is not focused on diseases of the brain such as Alzheimer's, but on the natural deterioration of the brain as we age. A team of great scientists, headed by Coleen Murphy of Princeton, are populating this collaboration, and some interesting ideas have already emerged. If we can get to the bottom of this, it is possible that some interventions may be discovered to slow the aging process. Fingers crossed!

Late in the year, Marilyn and I determined to change our roles at the foundation. I have been overseeing the science we support, with Marilyn overseeing administration as well as the foundation's outreach and education mission. As of July 1, 2021, David Spergel will step in and run the whole show as our new president. Presently David heads the Flatiron's Center for Computational Astrophysics, and he is an outstanding scientist as well as an outstanding leader. The foundation board was unanimous in his selection. Marilyn and I will both assume the title of co-chair. We haven't the slightest doubt that under David's leadership the foundation will thrive.

Onward and upward!

Jim Simons, Ph.D.
Chair

Letter From the President

The coronavirus upended our lives and society in 2020. With COVID-19's rapid spread worldwide, many of us quarantined and socially distanced ourselves, pivoting to the virtual realm. The world turned its hope to science for defense from this pandemic, and in little over a year, two very effective vaccines appeared using an innovative synthetic mRNA technology, and then several quickly followed using a DNA-based adenovirus approach. The quick turnaround in providing these immunizations obscured the fact that decades of research actually went into their production: A huge amount of past investment in fundamental scientific research provided a broad and deep knowledge base that could be leveraged for these acutely important efforts. When we look back on the race to formulate a vaccine, the gains from the previous century's investments in basic science research are undeniable.

Supporting basic science research and mathematics is the work of the Simons Foundation. At our Flatiron Institute, theoretical and computational scientists advance our understanding of natural phenomena in the areas of astrophysics, biology, quantum physics, neuroscience and mathematics. Through our grantmaking programs, we support individual research proposals as well as collaborative projects in mathematics, the physical sciences, the life sciences, neuroscience and autism. And through our outreach and education program, we hope to engage all audiences with science and mathematics.

2020 was a productive year at the foundation, as this report shows. Our feature stories are based on the theme of "connections." They highlight connections of all kinds: research focused on connections between atoms and between neurons; connections between scientists within a field — or collaborating across disciplines; and even connections we have with other funding partners.

2020 was also a particularly challenging year. Our year of remote work lacked the inspiring connection of in-person meetings and serendipitous encounters with new ideas and old friends. The tragic social injustices we witnessed shook our complacency with the status quo. Staff members' urgent calls to action focused us on mobilizing programs to advance diversity, equity and inclusion in our workplace and in science.

As we reflect on this past year, there are many lessons to learn from the triumphs and tragedies of 2020. Relating to science in particular, we've already grasped these salient takeaways: the profound importance of long-term commitment to basic science research, the necessity for greater outreach to the public to promote a deeper understanding of science and the need to build a pipeline of scientists who are representative of our diverse society. Clearly, we've got lots more work ahead!

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Revolutionizing Simulations of the Universe With AI

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But the practicality of simulations is often limited by the sheer amount of computing resources they require. That's where machine learning, or 'deep learning,' is starting to help. Neural networks that mimic the brain's web of biochemical connections can study a handful of simulations and learn to fill in the gaps. Critically, they can do so millions of times faster than it would take to run a continuum of simulations from scratch.

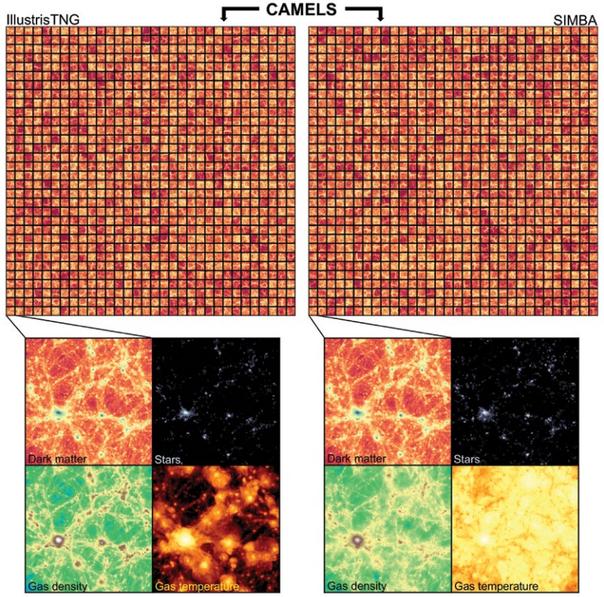
"We usually want to understand some fundamental quantities of the universe; it could be the planets, it could be gravitational waves, black holes, it could be the universe itself," says Shirley Ho, head of the Cosmology X Data Science group at the Flatiron Institute's Center for Computational Astrophysics (CCA). "We want to accelerate simulations to produce the observations we want ... and then compare them to the data."

Researchers at the CCA are using deep learning to speed up simulations of vast volumes of space that enclose millions of galaxies. The goal is to get more out of upcoming telescopes such as the Simons Observatory, whose observations will refine measurements of fundamentals such as the evolution of dark energy, the enigmatic force accelerating the expansion of the cosmos.

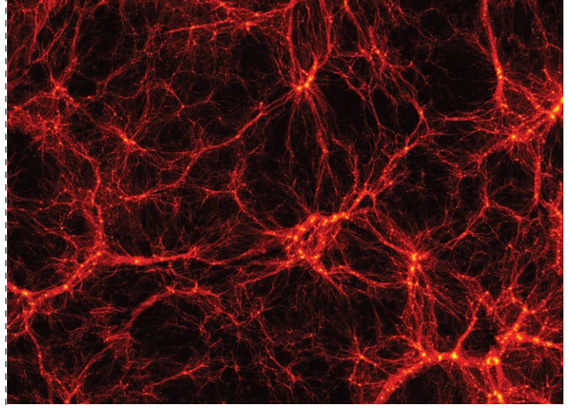
"We've got a new set of tools," says CCA director David Spergel. "Machine-learning tools may let us even recover the initial conditions of the universe."

Cosmological simulations that track the assembly of gargantuan superclusters of galaxies are massively 'multiscale' problems: Cumulative effects from even individual stars can ripple across millions of light-years to alter the fates of entire galaxies. Building and running a simulation that connects all these scales is no small feat, often requiring millions of CPU hours.

But neural networks are good at linking multiscale phenomena, says Stéphane Mallat, a distinguished research scientist at the Flatiron's Center for Computational Mathematics (CCM). What's more, a neural network doesn't need to see simulations of every imaginable scenario. It can study representative samples and then churn out new simulation results without working through all the underlying physics from scratch.



The top panels show the large-scale distribution of dark matter for thousands of simulations performed with the IllustrisTNG (left) and SIMBA (right) galaxy formation models as part of the CAMELS project. The bottom panels compare the distribution of dark matter, galaxies (and their stars), gas density and gas temperature for one representative simulation as performed by each model with the same initial conditions. Credit: Francisco Villaescusa-Navarro, Daniel Anglés-Alcázar and Shy Genel



"We think we can train a neural network to learn the relationship between dark matter and galaxies, or dark matter and gas," says Rachel Somerville, leader of the CCA's Galaxy Formation group. "Then the network is much faster than running this full simulation." Early results are promising, she says. "We've already started doing some tests. We know that it kind of works."

One ongoing test for training a neural network is CAMELS, the Cosmology and Astrophysics with MachinE Learning Simulations. The project is led by CCA associate research scientist Daniel Anglés-Alcázar, CCA associate research scientist Shy Genel and former CCA research fellow Francisco Villaescusa-Navarro. Within CAMELS, CCA researchers recently trained a neural network on thousands of cosmological simulations to accomplish a number of tasks, such as predict the star formation rate of galaxies based on only a few parameters such as the abundance of matter. Another effort, known as dm2gal — for 'dark matter to galaxies' — taught a neural network to add the right amount of stellar mass in virtual galaxies using knowledge of how much dark matter was present.

While these researchers take on the universe, others at the CCA are using machine learning on a smaller scale.

Colliding pairs of black holes are all the rage: Since 2015, astronomers have detected gravitational waves from 46 such mashups, and they'd like to know how these pairings form. Perhaps they come from massive stars paired up since birth, wandering their home galaxy as a lonely duo. Or maybe they're churned out in jam-packed globular star clusters, where hundreds of thousands of stars routinely trade partners.

Flatiron researchers set a neural network loose on the problem. They fed the machine the output from simulations that predicted black hole masses produced in these two scenarios. The network deduced the relevant relationships connecting various parameters of binary stars and globular clusters to the black hole masses that each produces, and determined that globular clusters account for about 80 percent of the known binary black holes.

That result is far from the final word on the matter, partly because the neural network didn't know about other formation options. But it demonstrates the power of machine learning in exploring binary black hole origins, says study author Katelyn Breivik, a research fellow at the CCA.

"The best way to understand all of this would be to just simulate all possible scenarios," she says. "And that's, of course, completely intractable. But you can pick points along the way and then fill in the other points with machine learning, and then it's not intractable."

Remarkably, these machines know nothing about astronomy or physics. But could a machine learn the laws of physics, including some not yet discovered?

That's what Princeton graduate student Miles Cranmer set out to do. Working closely with researchers at the Flatiron, he showed a neural network simulations of particles moving about, subject to typical forces found in nature. Just from watching the particles move, the machine "discovered" physics standbys such as Newton's law of gravity and Hooke's law of spring force.

He then set the network on an astronomical problem: Is there a way to predict how much dark matter gathers in the center of the dark matter "halos" that envelop every galaxy based only on a halo's mass and the mass of halos around it? Although astronomers have come up with such a relationship, its precision is a bit shoddy. Cranmer's neural network cranked out an equation that was far more accurate than the one humans produced.

"It's a long process to unravel these mysteries," says Cranmer. "But with artificial intelligence, we can tether science to Moore's law — the law that says you get an exponential increase in computing power — and maybe get an exponential increase in knowledge, too."

The Flatiron is well poised to lead the way. Connections across fields as diverse as astrophysics and machine learning are opening possibilities for researchers of all stripes.

"We have maximum freedom at Flatiron, and we have this encouraging interdisciplinary atmosphere," Ho says. "Here, it's encouraged to work across fields. It's encouraged to take a little bit of risk and do something different."

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Reverse engineering the universe is a tricky thing. To figure out how dying stars explode, an astronomer can't blow up a thousand stars. But they can create and destroy virtual stars on a computer, where lines of code emulate the laws of physics. Such simulations can predict the fate of not just single stars but also solar systems, galaxies and even the entire universe.

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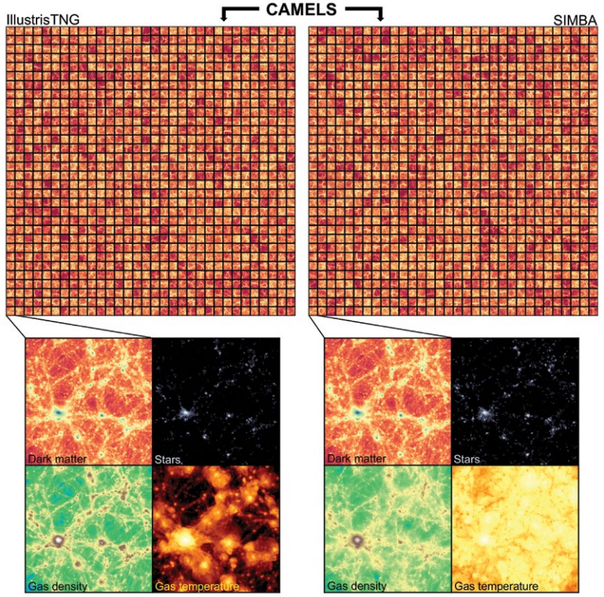

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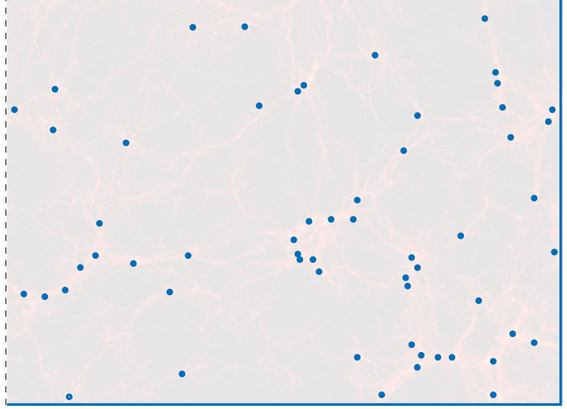

The spatial distribution of dark matter in a region of space roughly 300 million light-years across, taken from one of the Quijote simulations, which astrophysicists use to train neural networks. Dense halos connected by long thin filaments form a cosmic web; the densest regions (dots) house galaxy clusters.

"We think we can train a neural network to learn the relationship between dark matter and galaxies, or dark matter and gas. Then the network is much faster than running this full simulation."

Rachel Somerville

Watch the full video of Shirley Ho at simonsfoundation.org/report2020

"There are many things that we can do with these faster cosmological simulations that we could not have done before. This is one of [the things] that our group has been pushing for, which is to compare the observed cosmological data ... directly with the full prediction of what the universe would be, given all the changes in the theory. ... All [those predictions] will be pushed into a simulator [to] generate a predicted universe, and then we compare it to the observation, so that hopefully we've squeezed all the information we can out of the observed universe."

Shirley Ho

HumanBase Sees Connections Between COVID-19 and Diabetes

When Chandra Theesfeld, a research scientist at the Lewis-Sigler Institute for Integrative Genomics at Princeton University, was starting her career as a biologist, she knew that studying the human genome came with significant challenges. At the time, high-quality curated databases could help those scientists studying smaller organisms, like yeasts and worms, but nothing remotely comparable existed for humans. As a result, human genomic studies tended to be piecemeal and limited in scope, narrowly focused on just one or a few human genes. Scientists often relied heavily on what they remembered from the literature to make meaningful inferences from the available data.

The genomics revolution changed all that. A flurry of advancements in genomic analysis, research computing and data storage yielded a tremendous influx of new data from the human genome, and with it came the promise of a more comprehensive understanding of human biology. But a new problem soon emerged: The data were too vast for individual scientists to dig through. "The traditional forms of analysis in humans just weren't possible anymore," Theesfeld says.

In need of a resource that could help researchers properly sift through human genomic datasets at scale and find the new insights hidden there, scientists at the Center for Computational Biology (CCB) at the Flatiron Institute created HumanBase, an interactive software platform that allows Theesfeld and other biologists to access results of tens of thousands of experiments in one place and make connections in a systematic way that springboard human biological discovery.

Launched in 2018, HumanBase brings robust computing power and advanced algorithms to bear on thousands of genomics datasets, enabling scientists to make connections across genes in ways that are impossible using traditional methods. HumanBase uses machine learning to reach into published and publicly available datasets from tens of thousands of genomics experiments and make predictions about how genes from specific tissues of the body interact with each other. Machine learning is uniquely suited to finding nuggets of biological gold in these large, diverse datasets: A biological signal that is faint in any one dataset may stand out when many datasets are integrated to generate one large network.

"HumanBase is designed around connections, like gene-to-gene, gene-to-disease and mutation-to-disease connections, and draws these connections in a data-driven way, one that can't be replicated by individual scientists mining the literature," says Aaron Wong, a data scientist and project leader at the CCB. Olga Troyanskaya, CCB deputy director for genomics and a professor of computer science at the Lewis-Sigler Institute, describes the power of the networks assembled by HumanBase in a strategy called functional module detection. "By looking at the genes in the context of a network, we can discover the pathways impacted by a disease," she says.

To use functional module detection, scientists first input a list of up to 4,000 genes. HumanBase will take the list and generate a network showing how the genes work together in a particular cell type, such as a kidney cell. The results are displayed in weblike maps showing how each gene is associated with others in the database. Clusters in the maps known as modules contain genes with common functions. For example, one module might consist of genes that promote viral replication. Functional module detection can also suggest a function, or set of functions, for a previously uncharacterized gene. "The networks connect genes that are working together in the same pathway, and the module detection in turn reveals higher-order processes and pathways," says Theesfeld.

In 2020, scientists at the Flatiron Institute and the University of Michigan used HumanBase's functional module detection to examine the mechanics of COVID-19 infection in kidney cells. In work published October 7, 2020, in *Kidney International*, whose initial findings were shared in May on the medRxiv preprint server, the authors investigated why individuals with diabetes are more susceptible to COVID-19. SARS-CoV-2, the virus that causes COVID-19, enters the cell by locking onto a protein on the cell surface called ACE2. The scientists sought to learn what is different in kidney cells that express ACE2 and, specifically, to understand what it is about these cells in people with diabetes that makes them especially susceptible to infection.

In ACE2-expressing kidney cells both from patients with diabetic kidney disease (DKD) and from patients with COVID-19, the scientists found thousands of genes that showed increased expression. They used HumanBase to construct modules from these genes, revealing that in both groups of patients, these modules relate to viral entry, replication and immunity. "HumanBase showed us that [the DKD] cells with expressed ACE2 have a cellular program already activated which makes them exceptionally vulnerable to the virus," says Matthias Kretzler, a nephrologist and professor of medicine at the University of Michigan and co-corresponding author on the study. Troyanskaya adds, "Without any input from the virus, the cells of the diabetic kidney already look similar to cells of patients who have the virus. The diabetic kidney is essentially primed for SARS-CoV-2."

The connections between ACE2 expression and biological processes relating to immunity and viral activity, and between programs in the cells of patients with DKD and COVID-19, could not have been made without HumanBase, says Theesfeld. "You have a list of thousands of genes — you can't make sense of that. You need the sophisticated connection-drawing power of networks and machine learning to find the common threads," she says. Further research is needed to determine definitively if the activation of viral infection pathways in DKD is responsible for the increased susceptibility of patients to COVID-19, and if COVID-19 infection in patients with DKD results in cumulative kidney damage.

The study also showed that common medications for hypertension and DKD do not increase the levels of ACE2, despite initial concerns, and thus patients could continue safely taking these medications. "This was a critical piece of knowledge we could share quickly with our global kidney doctor community, and we could add a mechanistic explanation for why," says Kretzler.

Importantly, the functional modules uncovered by HumanBase are a starting point for exploring new therapeutic avenues to treat COVID-19. Scientists will examine how kidney tissue grown in a lab responds to drugs that target genes and processes that HumanBase shows are activated in cells expressing ACE2. The processes identified by HumanBase suggest roles for particular structures of the cell, such as the ribosomes and cell membrane, during SARS-CoV-2 infection. Theesfeld describes two recent studies in which scientists showed experimentally how SARS-CoV-2 infection upsets the functioning of these very structures, the ribosomes and cell membranes, in kidney cells. "We see different omics [high-throughput molecular analysis] approaches that validate our predictions," she says. "A next step would be to look for drug targets in those pathways."

The COVID-19 study has implications for virus biology in general, too, says Theesfeld. Some viruses use receptors other than ACE2 to enter the cell. If HumanBase were applied to study another virus, "would we find the same processes upregulated in cells that use a different receptor?" she asks. The results could shed light on which viral processes are universal and which might be unique to coronaviruses.

At present, researchers are using HumanBase to reveal the cellular processes activated in lung cells during SARS-CoV-2 infection after treatment with Moderna's vaccine, Troyanskaya notes. "These processes are complex," she says. "The pathways involved and their connections are only revealed at the network level, showing the biological coherence behind large sets of genes." Theesfeld adds, "The HumanBase approach is a powerful and general way to reveal the network effects of dysregulation in human disease."

The long-term support of the Simons Foundation in developing HumanBase was critical to this work, says Wong. "A key mission of the Flatiron Institute is to develop cutting-edge algorithms and make them broadly available, not just to computational people but also to biologists and biomedical scientists," he says. Troyanskaya agrees, emphasizing that HumanBase lets biomedical and clinical scientists make connections formerly in the domain of computer scientists. "The critical connection is between a biologist's insight, the data and advanced computational analysis: HumanBase allows this loop to work without an advanced computer scientist in it."

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> "One really important outcome of what we do is following up on our computational predictions. So, as we say in the field, the proof is in the pudding. It's really important for us to work with biologists and experimentalists to both test and follow up on our predictions."
>
> **Aaron Wong**

> "The HumanBase approach is a powerful and general way to reveal the network effects of dysregulation in human disease."
>
> **Chandra Theesfeld**

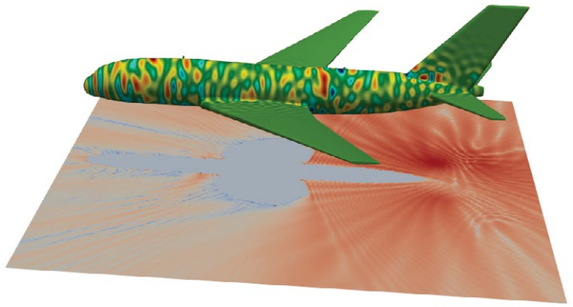
HumanBase Pipeline

Standardized input	Modeling and training	Prediction	Exploration
More than 52,000 genomic experiments are standardized with statistical tools.	Algorithms model patterns, validate and train using the latest biological knowledge.	HumanBase applies what has been learned to derive inferences for new biological connections.	Users query data-driven predictions to identify experimental hypotheses that can guide their research.

Credit: Lucy Reading-Ikkanda/Simons Foundation

Manas Rachh: Building Mathematical Tools That Drive Discoveries

When the Flatiron Institute opened in 2016, one of its goals was to support basic science by funding researchers who develop software and computational tools that can be used by scientists outside the institute. Such software can be crucial for new research, but the emphasis on publication in the academic world sometimes hinders the development and maintenance of these programs. "You don't get as much credit in academia for working on software packages right now," says Manas Rachh, a research scientist in numerical analysis at the Flatiron Institute's Center for Computational Mathematics (CCM).



A calculation of acoustic scattering on a plane-shaped object requiring the solution of partial differential equations; this figure was generated to demonstrate the capabilities of CCM solvers on multiscale geometries.

Rachh grew up wanting to be an engineer like both his parents, but as an undergraduate he realized he was most interested in the mathematical side of the engineering courses he was taking and so he pivoted to applied mathematics instead. Rachh left India for the United States to begin graduate work at New York University. "And at the end of the first two weeks, I was seriously questioning my choices," he says. "The mathematics I had learned as an undergraduate in engineering was nowhere close to the level of rigor and detail required in grad school." With the help of friends in his program and a supportive adviser (Leslie Greengard, now the director of the CCM), he found his footing, earning a Ph.D. in 2015.

Rachh went to work at Yale University as a Gibbs assistant professor of applied mathematics before joining the Flatiron in 2018. Since graduate school, he has focused on developing fast algorithms to find numerical solutions to certain partial differential equations (PDEs), which are equations that describe relationships between partial derivatives of multivariable functions. PDEs are notoriously difficult to solve exactly — or even approximate efficiently — because the complexity of these relationships increases precipitously with the number of variables. PDEs arise in a range of application areas, including chip design, acoustics, plasma physics, fluid dynamics and computational biology.

Researchers can find very good numerical approximations to solutions of PDEs in some cases, but usually the more precise an answer is, the longer it takes to find. Rachh and his colleagues have to balance this trade-off between speed and precision in developing software, while also prioritizing usability for researchers. The fastest code in the world will not have any impact if it is too complicated to garner widespread use. "That's a day-to-day concern," he says, "deciding where we are willing to make sacrifices in speed and efficiency in exchange for usability and attracting a wide audience."

Furthermore, Rachh and his colleagues need to be able to guarantee that their programs are reliable and can produce answers that are within certain accuracy specifications. All PDE models already have uncertainty baked in; researchers do not want to adopt new software that will introduce even more of it, or make their answers less accurate. "We want to make sure there is no error arising from doing a simulation by computer," Rachh says. "All of the errors should be artifacts of the model that they've chosen, not how that model is being solved."

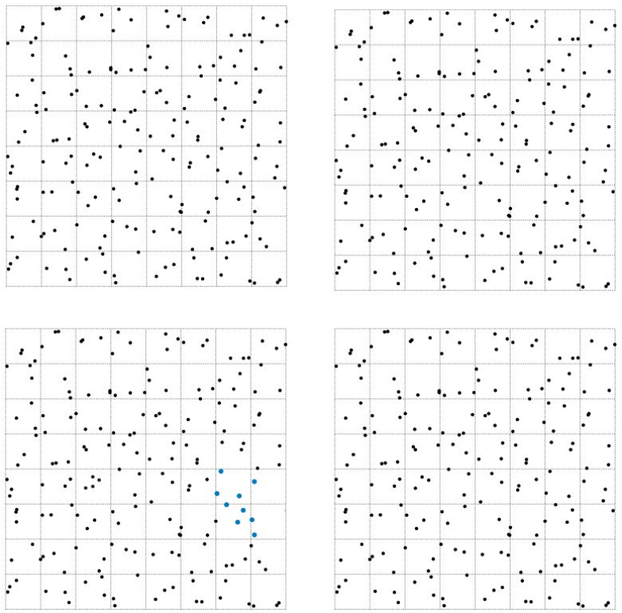
Academic researchers who need specialized software are sometimes poorly served by commercially available software packages because academic clients are often less lucrative than business clients, and they may have very specific and unusual needs. Rachh believes he and other researchers at the Flatiron fill an important niche. "Often, commercial software can solve a much broader class of problems than we can, but the problems that we do solve, we can solve better," he says. "One of our advantages is that we understand researchers' problems better, having worked on similar problems ourselves, whereas a company might be excellent at software development, but they might not have someone who's worked on both the software and the research applications."

Rachh and his colleagues write code in several different programming languages widely used by researchers in the fields they are supporting. For example, his team is collaborating with the Electromagnetic/Radio Frequency team at MathWorks to incorporate one of its tools into MATLAB, a popular programming language for mathematicians and engineers. "We are currently not working on the application itself," Rachh says, "but facilitating other engineers to be able to solve bigger problems faster using the same amount of resources." Deciding what languages and platforms to use, and understanding how to best write for the interfaces their end users will be working with, are challenging parts of the job. "This is not something I was formally trained in," he says of developing user-friendly software interfaces. "We want the things we're building to last for a while, so we have to factor that in at an early stage."

Rachh is especially proud of two programs his team has released recently, FMM3D and fmm3dbie, both of which use techniques called fast multipole methods to solve Laplace, Helmholtz and Maxwell equations. All three are PDEs that arise in several areas of physics, including gravitation, heat conduction, fluid dynamics and electromagnetism. "For me, this has been a project that's been going on for seven to eight years, and for some of the other people in this group, this is something that they've been looking forward to for two or three decades," Rachh says. "Finally having something that's out there and getting a bunch of use has been very satisfying."

Rachh is looking forward to building on these two programs, making them more user-friendly and faster so that researchers can incorporate them into their pipelines for the numerical simulation of their PDE models. "Ideally, four or five years from now we want to get close to computer-aided design." That is, scientists and engineers should be able to design optimal systems or devices for a specified goal or task primarily through the numerical simulation of their corresponding PDE models. "But right now, we are just not there."

Rachh feels great satisfaction in being able to contribute to science by creating and supporting software for a diverse range of application areas, even though such work usually takes place behind the scenes. "Personally, what attracted me to Flatiron is the ability to dedicate time and resources to building these tools so that other people who are better suited and are experts at the modeling side of things can use them and push the frontiers of science faster."



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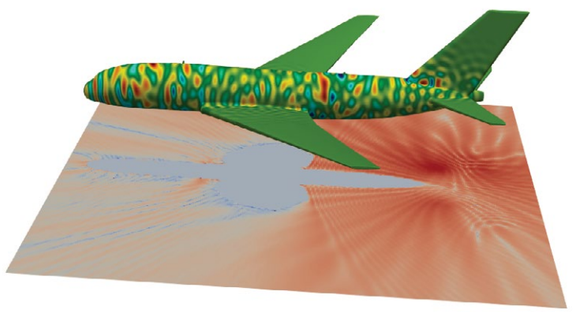

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> "Imagine that you were plucking a guitar string. It creates some sound. So how do you model the vibrations of these strings? One way you could model the vibrations of this string is to understand what the height of the vibration is as a function from one of the endpoints of the guitar as a function of time. So how this height function would vary as a function of distance from the end and as a function of time would be a PDE. ... And you might think that's a very simplistic model, but models like these have been very useful in describing ... [everything from] very large-scale phenomena, like the evolution of galaxies and stars, to very small-scale phenomena, like how microorganisms swim or move in their environments."
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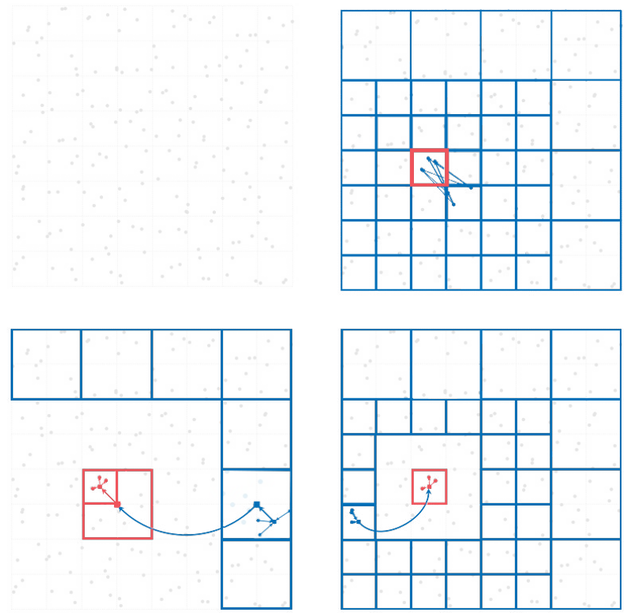
Manas Rachh collaborates with the Center for Computational Neuroscience (page 11) and the Simons Collaboration on Hidden Symmetries and Fusion Energy.



The logo for the Flatiron Institute Fast Multipole Libraries, which was developed by Manas Rachh and his colleagues. The fast multipole method algorithm calculates the dynamics of systems containing many particles, such as planets gravitationally tugging one another as they orbit a star. The logo's quadrants represent how the algorithm considers different collections of particles (blue dots) when calculating the net force acting on a fixed set of target particles (red dots).

The fast multipole method was co-invented by CCM director Leslie Greengard.

New Flatiron Institute Center Aims to Map the Brain's Inner Workings

We have long understood the equations that govern the physical world, thanks to the elegant symbiosis between theory and experiment among physicists. For instance, theoretical physicists provide explanations of how magnetism or gravity operates in different contexts, which experimentalists can then confirm, refine or refute. This iterative process has resulted in a robust understanding of the world's physical forces.

By contrast — and not surprisingly — we have no comparable understanding of the brain. Neuroscientists have determined which brain regions are responsible for complex planning (primarily the frontal lobe) and which regions help us interpret emotions (the amygdala and hippocampus, among others). But despite outstanding experimental achievements, we do not yet have a total picture of how the parts of the brain function together. That's because we still need to develop theories that can guide interpretation of the experimental results.

Enter the newly launched Center for Computational Neuroscience (CCN) at the Flatiron Institute, its fifth discipline-based computational center. The CCN's mandate is to stimulate a collaboration between experimental and theoretical neuroscientists. Headed by Eero Simoncelli, who will also maintain his appointment as Silver professor of neural science, mathematics, data science and psychology at New York University, the center began its work in fall 2020 and will take possession of its physical space by the end of summer 2021.

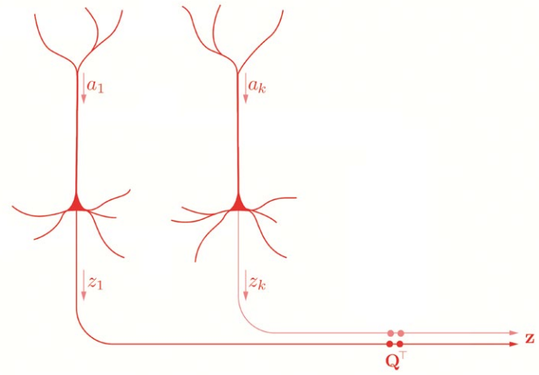
Simoncelli is a leading authority on how human brains process visual information, and he has worked to develop ever-more-powerful computer models that explain this capability throughout his career. He is a Howard Hughes Medical Institute investigator, a fellow of the Institute of Electrical and Electronic Engineers, and an Emmy Award recipient for the development of computational models to assess how viewers perceive the quality of visual images.

"After a thorough search, Eero Simoncelli seemed the perfect person to head the new unit," says Simons Foundation chair Jim Simons. "The other Flatiron directors and I were thrilled that Eero accepted the position."

One useful way to think of the brain is as an extremely powerful computer, but one with a unique set of operations. "Understanding how the brain works is a computational challenge," Simoncelli says. "Sensory input and internal states are continuously combined and transformed to drive thoughts, memories and behaviors. Our goal at CCN is to help decode that complexity."

Simoncelli notes that, especially in recent years, neuroscience experiments have yielded massive datasets that can only be interpreted with powerful computers, such as those at the Flatiron. The CCN will provide fertile ground for theoreticians, computational scientists and experimentalists to collaborate in developing an improved understanding, through data analysis, of how the brain works.

Simoncelli studied physics as an undergraduate and draws inspiration from the time-honored symbiosis between theory and experiment that physicists have developed. Though it might seem evident that neuroscience should have forged a similar path long ago, Simoncelli notes that physicists had the advantage of being able to begin with easily observable forces and objects rather than interpreting the dynamical evolution of ephemeral, internal neural patterns. In addition, the computational power to record and analyze neural activity at scale, in the brains of both animals and humans, has existed for only a decade or two.



The CCN will initially comprise two working groups. Simoncelli, building on his expertise in the neuroscience of vision, will lead the computational vision research group. Group members will use computational theory and models that help interpret how our brain's sensory systems make predictions about the world around us. Their goal is to understand how these processes, at the level of neural populations and circuits, drive visual behavior.

Dmitri 'Mitya' Chklovskii leads the neural circuits and algorithms group, which was previously part of the Center for Computational Biology. Chklovskii, who is also a research associate professor of neuroscience and physiology at New York University, focuses on how the activities of individual neurons and neural circuits generate thought and behavior. "Our goal is to understand the specific function of every neuron," Chklovskii says. This more mechanistic approach will complement Simoncelli's more behavior-centric analysis.

The CCN will ultimately employ approximately 50 people, some of whom will have joint appointments at the CCN and surrounding academic institutions. Visiting scientists will also be part of the mix. Simoncelli expects that everyone associated with the center will come to the physical offices at least some of the time, as circumstances permit.

"In my experience, the pandemic has reaffirmed the value of in-person contact," Simoncelli says. "If a project was already very well established when the pandemic began, then remote work proceeded reasonably well. But starting new projects from scratch has been much harder online than in person."

Toward that end, Simoncelli — the son of an architect (and named after one) — has been heavily involved in the design of the CCN's physical space. Most offices will accommodate a maximum of two people. Simoncelli feels that two people sharing an office can do focused work together in silence, whereas adding a third person tends to impede concentration. There will also be a diverse and distributed set of open work areas where people can discuss joint research at blackboards. And, importantly, Simoncelli's diligent work to find a suitable pro-level espresso maker for the center will help to fuel the quantity and quality of research insights!

The launch of the CCN adds another player to the Simons Foundation's array of efforts to understand the human brain. SFARI — the foundation's first program — and its independent news publication *Spectrum* produce and disseminate new insights about the neuroscience of autism. SFARI's research cohorts, such as the Simons Simplex Collection and the SPARK cohort, will continue to provide readily accessible raw data to scholars of autism and related fields the world over. The Simons Collaboration on the Global Brain (SCGB) seeks to understand the mechanisms of the neural activity that produces cognition. This program funds researchers across the globe, including Simoncelli. A related collaboration launched this year, the Simons Collaboration on Plasticity and the Aging Brain, concentrates on the study of the healthy aging human brain.

The potential for synergy between these groups is significant. "It's extremely exciting to have this new dimension to the study of the human brain in-house," says Simons Foundation president Marilyn Simons. "Understanding how the brain works is one of the biggest intellectual challenges of our time."

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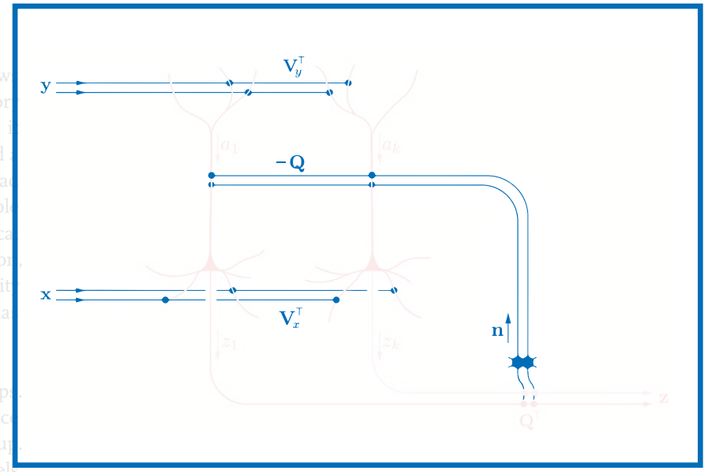
CCN director Eero Simoncelli is also an investigator with the Simons Collaboration on the Global Brain (page 23).



A novel neural network for supervised learning. Unlike existing neural networks based on the backpropagation algorithm, this neural network respects biological constraints and could model computations in the human brain. Credit: S. Golkar, D. Lipshutz, Y. Bahroun, A. Sengupta and D. Chklovskii/NeurIPS 2020

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"There's an explosion of interest around the world ... in artificial intelligence driven by things that were inspired from neuroscience. These are sometimes called deep neural networks. The ideas that are underlying those deep neural networks originally came from neurobiology ... observations about the brain being very different from a traditional computer (a von Neumann architecture). And of course along with that thinking comes the thought that, well, maybe there's something special about the architecture of the brain that allows it to compute things, estimate things, measure things [or] respond to things in a way that is harder to describe in a conventional computer architecture, but more readily described in terms of brain architectures. AI has had a long history of trying to use brainlike architectures to solve problems."

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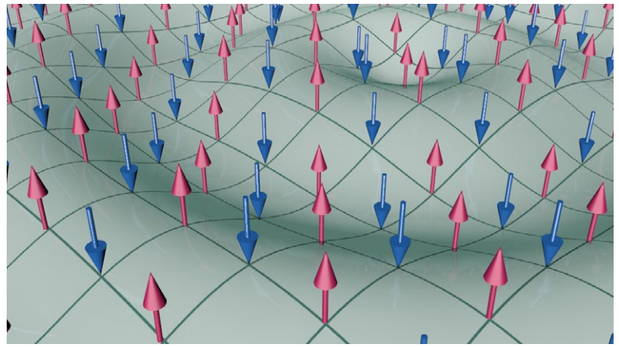
A Collaborative Paradigm for Cracking the Code of Quantum Systems

Every object derives its properties from its electrons, which interact in a scaffold of atoms and whose motion is choreographed by the rules of quantum mechanics. Breakthroughs in areas from computing to energy storage rely in part on understanding these interactions well enough to create materials tailored to specific requirements.

Tracking quantum interactions in real materials is comically complex — a single gram of hydrogen, for example, contains about 10^{23} atoms. Equations with that many variables are intractable to even the most powerful supercomputers. So physicists must come up with ways to analyze the essential physics of these systems without considering every aspect of the motion of the underlying particles, predicting how electrons will dance about their atoms as circumstances change. From these predictions, physicists can deduce, for example, how a material's electrical properties change under pressure. The trouble is that there are many prediction methods, and each approaches the problem differently and communicates the results in its own mathematical dialect.

One method provides snapshots of electrons as they move about. Another calculates the probability of finding electrons in particular configurations. Some methods predict behavior well at high temperatures, some at low temperatures. Some are best suited to describing the evolution of materials over time, while others are better for a material that's sitting still.

Stitching together, from all these techniques, a cohesive picture of how even one material behaves is a conceptual and logistical challenge. "We were sometimes getting consistent results, but more often than not, we were not getting consistent results, or we were computing things that can't be directly compared," says Antoine Georges, director of the Flatiron Institute's Center for Computational Quantum Physics (CCQ).



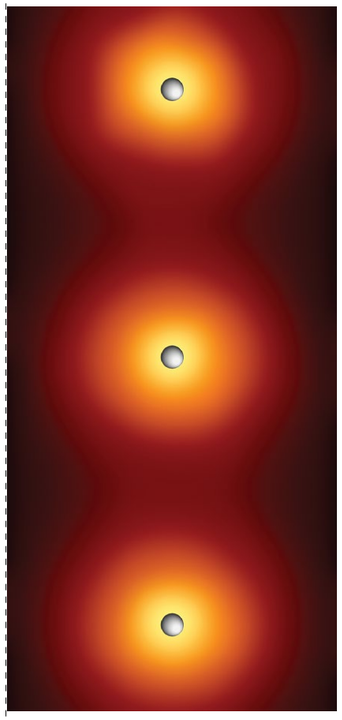
A particle wave passes through a crystal structure containing electrons (arrows). The structure has antiferromagnetic order because its electrons have alternating up and down spins. Credit: Lucy Reading-Ikkanda/Simons Foundation

Georges and colleagues at the CCQ are now changing that with a "multimethod, multimessenger" approach: They take a simple mathematical model of a material and throw every computational method they have at it. By marrying these techniques and resolving their differences, CCQ researchers aim to kick-start a new era of materials design and take on grand challenges such as developing practical superconductors, which conduct electricity with zero resistance at reasonable temperatures.

But getting there requires a culture change, one that the CCQ is leading: Physicists must step out of the silos in which they work and join forces to surmount an overarching hurdle. The payoff is that "you get much more information when you combine different methods with different potential sources of error or systematic biases," says CCQ co-director Andrew Millis.

To that end, CCQ researchers turned to one of the simplest models around: an infinitely long chain of hydrogen atoms. An endless queue of hydrogen may not seem realistic, but it's a perfect theoretical playground for getting all these computational techniques to play well together. "We wanted a system that all the methods can actually handle that also brings out all the complexities of these problems," says CCQ research scientist Miles Stoudenmire.

The scenario goes like this: Line up simulated hydrogen atoms and space them a few tenths of a nanometer apart — just a few times the width of the atoms themselves — and then slowly decrease the distance. As the atoms bunch up, let a crew of computational techniques figure out how the electrons respond and how that response affects the lineup's overall behavior.



Even in this 'simple' situation, a diversity of behavior emerged. The hydrogen chain went through three phases: It started as an antiferromagnet, a state in which the intrinsic magnetic orientation of the electrons alternated direction. As the atoms crowded together, the electrons started spending more time between neighboring pairs of atoms — a state reflective of hydrogen molecules wanting to form. As the spacing shrank further, the whole chain transitioned from being an electrical insulator to a metal.

"As we bring the atoms closer together, the whole electronic structure changes," Millis says. Such insulator-to-metal transitions are intriguing for various applications, and it took many methods to reveal the underlying mechanism.

The lessons learned from this model system can be applied to other, more practical lineups. "Hydrogen is particularly squirrelly; we can't really build this in the lab," Stoudenmire says. "But it's not pie in the sky. It's close to solving other chainlike molecules, like a chain of DNA."

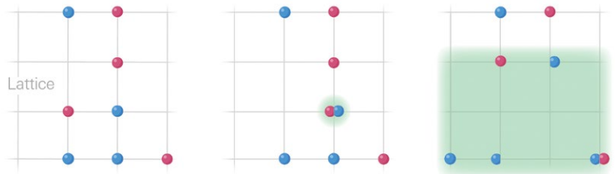
Other well-established physics models have also been getting the multimethod, multimessenger treatment. The Hubbard model is a simple mathematical prescription for how electrons interact in a 2D array of atoms. But fleshing out its physics has remained a challenge.

"The Hubbard model has been the Mount Everest of our field," Millis says. "It's beautiful, it's impressive ... it abstracts away all of the actual complexity of solids while leaving all the difficulty of quantum mechanics."

Here again, CCQ researchers saw an opportunity to set a plethora of computational techniques working cooperatively on the problem. Specifically, they wanted to see how electrons in the Hubbard model responded to plummeting temperature.

As the temperature dropped, the material went through three distinct phases. At high temperatures, it was a soup of electrons dancing every which way. As the temperature decreased, the system became a metal, with electrons moving in a more orderly fashion. And as the temperature continued dropping toward absolute zero, it transitioned to an antiferromagnetic insulator.

Characterizing the various phases of the Hubbard model is a major achievement, setting the stage for further investigations of superconductivity.



"All these studies are guiding us toward how we should develop further the available methods and what the next generation of methods might be," Georges says. "The ultimate goal is to put these methods to good work in applications like design of interesting electronic materials." The work also has connections beyond materials: Some of the models share mathematical DNA with theories of quantum gravity.

"Our vision for CCQ has been to build a place where we have several senior and junior faculty who are experts at certain types of methods," says Georges. "Put all these people under the same roof and have them interact and collaborate and invent the methods of tomorrow through this sort of synergetic effort."

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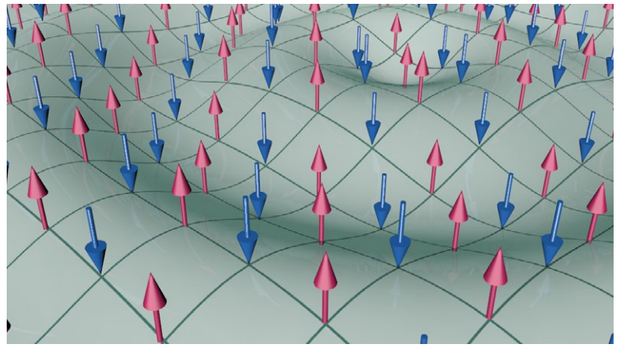

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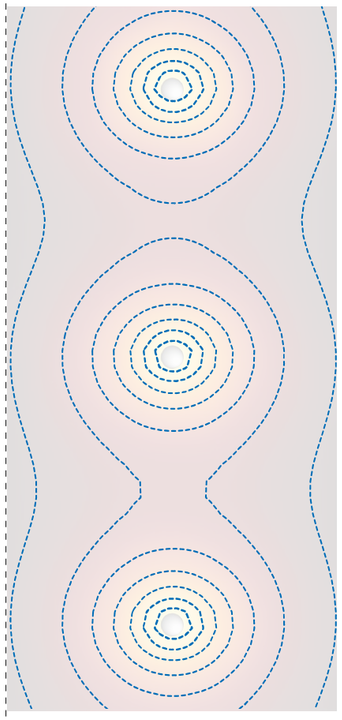
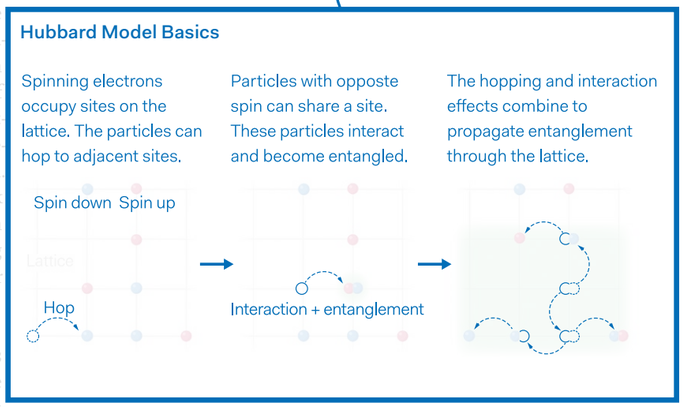
The CCQ works closely with the Simons Collaboration on the Many Electron Problem. The collaboration is led by CCQ co-director Andrew Millis, who previously served as associate director for physics in the Mathematics and Physical Sciences division at the foundation (pages 15–18).



A visual representation of where electrons are most likely to be found around a chain of hydrogen atoms. Brighter colors denote higher probabilities, and dashed lines represent contours of constant probability. At this spacing between atoms, electrons try to link pairs of adjacent atoms to form dihydrogen molecules. Because the protons are fixed in place, these molecules can't form. Instead, each electron 'leans' toward a neighboring atom. Credit: M. Motta *et al.*/*Physical Review X* 2020



Credit: Lucy Reading-Ikkanda/Simons Foundation

"Hydrogen is particularly squirrelly; we can't really build this in the lab. But it's not pie in the sky. It's close to solving other chainlike molecules, like a chain of DNA."

Miles Stoudenmire

The Quest for a Deeper Understanding of Deep Learning

Deep learning enables modern wonders like computer vision, speech recognition and natural language processing. Scientists are applying it to everything from automated audio transcription to robotic locomotion. Still, in 2018, a self-driving car struck and killed a pedestrian in Tempe, Arizona. The woman was walking with a bicycle outside of a designated crosswalk, and the car's programming was not prepared to correctly identify or move to avoid a person in that position. Such outcomes represent a stunning array of possibilities for the various futures for deep learning: Will face recognition programs provide a safer society? A society devoid of individual privacy? Or both?

The term 'deep learning' refers to a suite of machine learning techniques in which algorithms use methods that mimic the way human brains form new connections to make decisions or classify examples; the computing systems underlying these techniques are often referred to as (artificial) neural networks.

Deep learning algorithms are remarkably effective and accurate, but researchers do not have a good handle on exactly what's going on under the hood. The algorithms give answers but do not explain them. "I think the thing that's really exciting from a scientific perspective is that these are techniques that practitioners have advanced," says Peter Bartlett, a computer science and statistics professor at the University of California, Berkeley. "They've engineered systems to perform very well on particular benchmark problems, but without a deep understanding of why they're so successful."

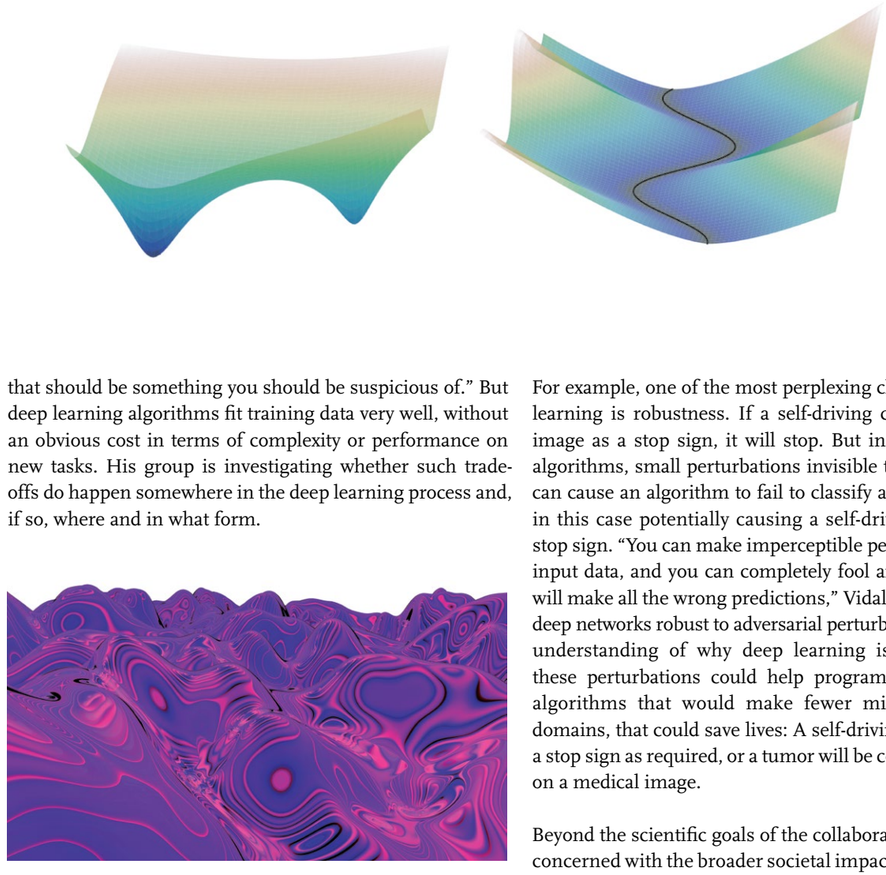
The inexplicability of how and why algorithms make the decisions they do creates several problems for the field, of which perhaps the most troubling is that of fairness and equity, as algorithms are increasingly used to make decisions consequential to our society. If a bail algorithm sets a higher price for one defendant than another without explanation, how can the people affected be sure the decision was not the result of racism or some other human failing, indelibly absorbed into layers of code?

This opacity also means that deep learning algorithms may be more complicated and less robust than they could be, and it hinders progress in improving algorithms in some areas of application.

Responding to the need for more research into how these algorithms work, the National Science Foundation and the Simons Foundation announced a joint call for proposals related to the mathematical foundations of deep learning. Two collaborations were awarded funding and officially began work in September 2020. Bartlett is the director of the Collaboration on the Theoretical Foundations of Deep Learning, whose leadership includes seven principal investigators and three co-investigators at universities in the United States, Israel and Switzerland. The other collaboration, Transferable, Hierarchical, Expressive, Optimal, Robust, Interpretable NETworks (THEORINET), is directed by René Vidal, the Herschel Seder professor of biomedical engineering and director of the Mathematical Institute for Data Science at Johns Hopkins University, who works with four principal investigators and 10 co-investigators in the United States and Germany. Although the two collaborations are separate and have different approaches and areas of focus, their interests overlap enough to permit twice-monthly meetings at which the members of both groups share their work and exchange ideas.

Deep learning algorithms ask questions like: Given a particular collection of pixels, what is the likelihood that the tissue pictured has a tumor? Or: Given a particular audio file, what was the person recorded most likely to have been saying? Bartlett's collaboration believes that although these problems are familiar to classical statistics, deep learning mechanisms are fundamentally different from those used in classical statistics, and hence present different challenges.

"It seems like deep learning is breaking one of the most fundamental rules that we've traditionally taught in our undergraduate classes, that there has to be a trade-off between the fit to the data and the complexity of the prediction rules," Bartlett says. "If you get a perfect fit for the training data, that should be something you should be suspicious of." But deep learning algorithms fit training data very well, without an obvious cost in terms of complexity or performance on new tasks. His group is investigating whether such trade-offs do happen somewhere in the deep learning process and, if so, where and in what form.



An illustration capturing the intricacies of high-dimensional optimization, which is key to training a neural network. Optimization requires identifying the global maximum or minimum value. One of the persistent challenges — spurious local optima that are only locally maximum or minimum values — is on display. Credit: Robert Ghrist

Bartlett and other researchers in the collaboration currently have hypotheses about where the trade-offs are, which they plan to investigate on a mathematical level. They hope to refine their hypotheses and extend them into a robust scientific theory that not only explains deep learning but also allows scientists to create better algorithms. "Our point of view is that having an understanding of how deep learning techniques work, what's underlying their success, is really important to overcoming the issues that surround the application of these methods," Bartlett says.

Vidal's collaboration, THEORINET, has several aims. Researchers seek to obtain a rigorous analysis of several key properties of deep neural networks and then leverage that analysis for further insight into the design of algorithms that can be guaranteed to satisfy particular constraints and into the transfer of deep learning techniques from one domain to another.

For example, one of the most perplexing challenges in deep learning is robustness. If a self-driving car recognizes an image as a stop sign, it will stop. But in computer vision algorithms, small perturbations invisible to the human eye can cause an algorithm to fail to classify an image correctly, in this case potentially causing a self-driving car to run a stop sign. "You can make imperceptible perturbations to the input data, and you can completely fool an AI system — it will make all the wrong predictions," Vidal says. "Why aren't deep networks robust to adversarial perturbations?" A greater understanding of why deep learning is so sensitive to these perturbations could help programmers implement algorithms that would make fewer mistakes. In some domains, that could save lives: A self-driving car will stop at a stop sign as required, or a tumor will be correctly identified on a medical image.

Beyond the scientific goals of the collaboration, Vidal is also concerned with the broader societal impacts of the program. The collaboration has proposed a partnership with the University of Maryland, Baltimore County Meyerhoff Scholars Program to equip undergraduates from underrepresented groups to enter careers related to artificial intelligence and deep learning. They also want to use their work to inform public policy related to the implementation of high-stakes algorithms. "One worry we have is that decision-makers either distrust AI and continue to make decisions based exclusively on human decision-making, or believe everything AI does and don't understand the pitfalls," Vidal says. Either extreme creates problems. To that end, the collaboration has held, and will continue to hold, conferences and seminar talks related to issues of equity and justice in algorithms and how to understand and influence public policy discussions. "Deep learning has great potential to impact our society," Vidal says, "but we need to understand its foundations to make sure its predictions are correct, safe and fair."

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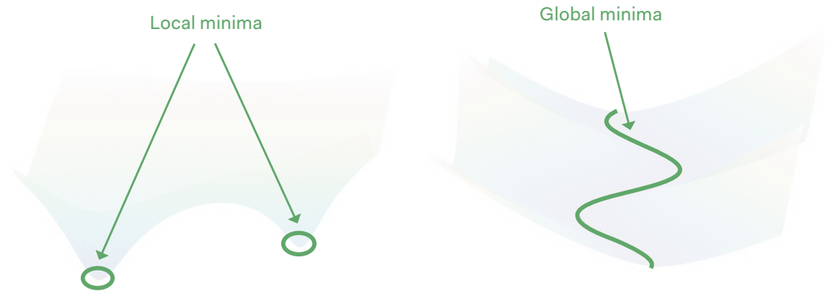

The accuracy of a neural network is gauged by a loss function, which estimates how far off the neural network's predictions are from expectations. The goal is to minimize the loss value by tweaking parameters. Above is a visualization of the loss landscape for an underparameterized 'classical' optimization landscape (left) and an overparameterized 'modern' optimization landscape (right), which occurs in large neural networks. Credit: C. Liu, L. Zhu and M. Belkin

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The Simons Foundation has also partnered with the National Science Foundation on the NSF-Simons Research Centers for Mathematics of Complex Biological Systems.

For more work involving machine learning, see the articles on the Center for Computational Astrophysics (page 5), the Center for Computational Biology (page 7), the Center for Computational Neuroscience (page 11) and SFARI-funded research highlights (page 29).

Leveraging Symmetries to Invent Exotic Materials

For the past two decades the field of metamaterials — the design and fabrication of materials that have properties not found in nature — has been an exciting area of research in physics and engineering. The Simons Collaboration on Extreme Wave Phenomena Based on Symmetries is part of this line of inquiry. Researchers in the collaboration are interested in discovering, exploring and creating materials with exotic properties that will interact with electromagnetic and acoustic waves in unusual and desirable ways. These types of properties are created by leveraging various kinds of symmetries and 'symmetry breaking' in the engineered materials.

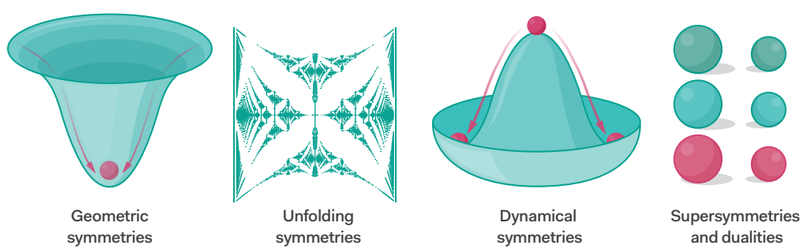
The word 'symmetry' often brings to mind geometrical features: a square, which looks the same when it is rotated 90 degrees or reflected across horizontal, vertical or diagonal lines; a circle, which lines up with itself when rotated by any angle or reflected across any diameter line; or a snowflake, which looks unchanged when rotated by 60 degrees or reflected across one of many lines of bilateral symmetry.

More broadly, a symmetry is a general transformation of an object that, when performed, leaves the object in a state indistinguishable from its initial state. In addition to the more familiar geometrical symmetries, researchers in the collaboration are studying symmetries in three other general classes: unfolding symmetries, dynamical symmetries, and supersymmetries and dualities. Unfolding or scaled symmetries occur in materials whose wave equations are governed by fractal behavior. The dynamical class refers to symmetries that are based on the evolution of properties of the material.

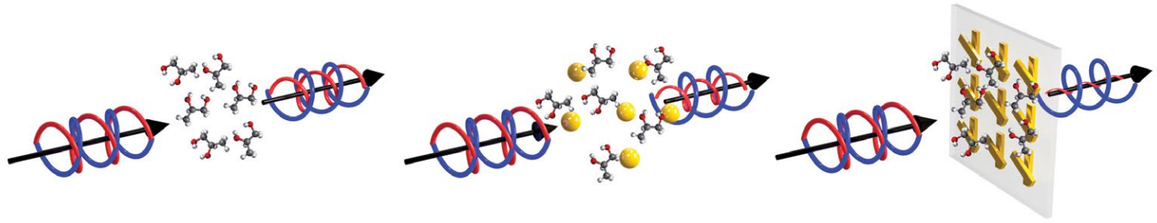
Supersymmetries and dualities, in theoretical physics and mathematics, are phenomena in which seemingly unrelated systems exhibit the same responses. Postdoc Michel Fruchart and his supervisor Vincenzo Vitelli hit upon the potential for using these ideas to generate exotic material properties almost by chance while playing with Lego structures a few years ago. Their tantalizing discovery spurred new research into the physics of dualities in the context of wave phenomena. Vitelli, a principal investigator of the new collaboration and physics professor at the University of Chicago, says, "We just stumbled into this effect, and then we realized that it's a smoking gun for a more general mathematical formalism that occurs in a variety of mechanical, optical and electronic systems."

Researchers are looking at both the properties endowed by particular symmetries in a metamaterial and the exotic behavior that can be created when symmetry is broken. "For me, it's exciting to think about how to design a structure so that I can break symmetry in a specific way or add symmetry-breaking for functionality," says Katia Bertoldi, a principal investigator of the collaboration and engineering professor at Harvard University.

Besides exploring different kinds of symmetry, the researchers are also excited by the potential for combining several types of symmetries in the same metamaterial to control the overall response. "Can we combine different aspects of symmetry to come up with something that's more than the sum of the individual parts?" asks Nader Engheta, a principal investigator and professor in both the electrical and systems engineering department and the physics and astronomy department at the University of Pennsylvania. "That could open the door to a lot of interesting future devices and possibilities."



The Simons Collaboration on Extreme Wave Phenomena Based on Symmetries is exploring and blending four broad symmetry classes: geometrical symmetries, unfolding symmetries, dynamical symmetries, and supersymmetries and dualities. Credit: Lucy Reading-Ikkanda/Simons Foundation



For example, although different types of waves seem very different in day-to-day life — sound and light, for example, are perceived in different ways and have different uses — many of the same principles apply to the study of all waves. "If you look at the problems from a theoretical perspective, they're not that different," says Andrea Alù, collaboration director and Einstein professor of physics at the City University of New York (CUNY) Graduate Center, as well as founding director of the Photonics Initiative at the CUNY Advanced Science Research Center.

For that reason, researchers often build models and devices that work with one kind of wave before trying them in a different setting. "The beauty of this field is that we have a lot of tools at our disposal," says Demetrios Christodoulides, a principal investigator of the collaboration and professor of optics at the University of Central Florida. "We come up with a theoretical discovery, and then we actually have the flexibility to decide how best to demonstrate it." For example, researchers might first fabricate structures that conduct acoustic waves: Because these waves are relatively slow, such structures tend to be large-scale and simple to design. Later, tests of the concepts can be translated to the more complicated microscopic worlds of optical or electromagnetic devices.

Scientists in the collaboration can fabricate prototypes of new materials in a matter of weeks, but perfecting these designs and then applying them in real-world devices of course takes much longer. Nevertheless, researchers are hopeful that their materials could eventually be used to improve technologies as disparate as medical imaging, optical computing and cellular communication networks.

Although the collaboration officially began only in September 2020, it is building on existing research collaborations among several of its principal investigators and their research groups. "The goal of the collaboration is to leverage all these initial efforts that our team members have pioneered, using symmetries to guide the optimal designs of metamaterials for various technologies, and bring them together, connecting the dots to build a unified theory that can enable us to discover new materials and new functionalities for many technologies," Alù says. These earlier projects have allowed investigators to get the collaboration up and running quickly in the short time since their official launch date.

Researchers involved in the collaboration come from a wide range of academic backgrounds. "It's interesting to get perspectives from mathematics, from physics, from engineering, and try to find common ground," Bertoldi says. "It always takes some time to make sure that we understand each other, but that's the fun part."

As is often the case with research that spans theoretical and applied science, inspiration does not flow in one direction, from theory to applications. Instead, "it's a back-and-forth," Christodoulides says. "We have a problem in mind and then we see what kinds of tools we can bring to address this problem. At the same time, we cannot address a problem unless we really know our toolbox." Insights from the theoretical and applied aspects of the collaboration create a complex cycle of gradual progress on all fronts.

"The Simons Foundation gives us the opportunity not only to continue existing collaborations, but also to expand them more broadly," Engheta notes. The new structure will be especially valuable when it comes to cross-disciplinary projects, which can be more difficult in traditional academic collaborations. "When we study a phenomenon, that phenomenon does not just go into a box called physics or a box called mathematics," Engheta says. "It's a combination of everything."

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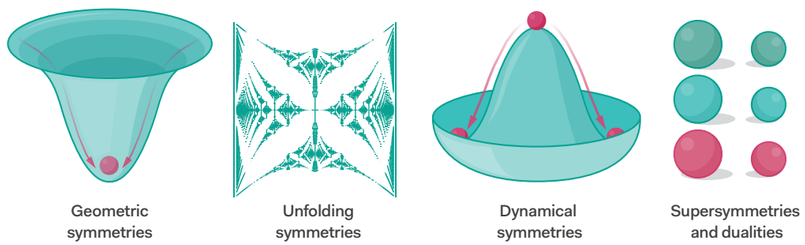

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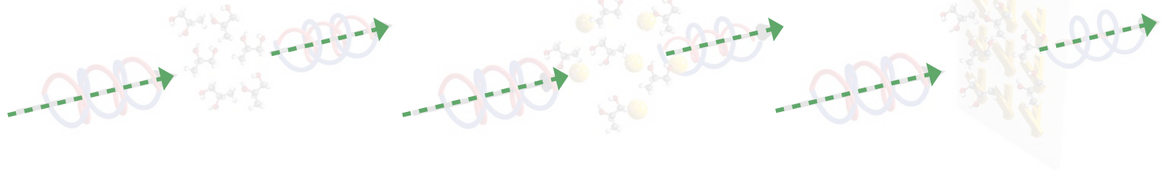

A twisted metasurface bilayer enables the detection of chiral molecules (which have 'right-handed' or 'left-handed' mirror symmetry) at very low concentrations. Credit: Y. Zhao *et al./Nature Communications* 2017

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Other Simons Foundation collaborations also explore symmetries, including the Simons Collaboration on Hidden Symmetries and Fusion Energy and the Simons Collaboration on Homological Mirror Symmetry.

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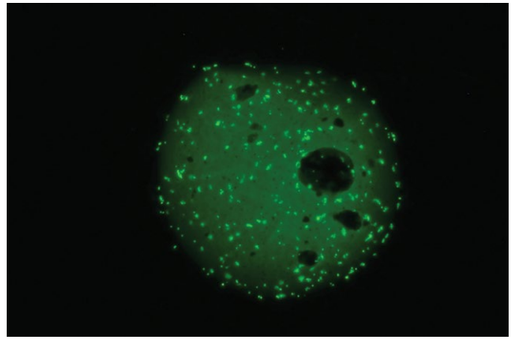
Otto X. Cordero Explores the Relationships Within Microbial Communities

When microbial ecologist Otto X. Cordero describes his approach to understanding complex societies of microbes, he pivots to talking about cars.

"If I ask you how a car works, and you give me a list of parts, I can't do anything with that," says Cordero, an associate professor at the Massachusetts Institute of Technology. "But if you tell me there's an engine that produces movement, and a wheel that can steer, then that makes more sense."



Marine bacteria colonizing and consuming polysaccharide particles. The microbes are stained with a fluorescent dye. Credit: Otto X. Cordero

Likewise, when it comes to microbial communities, biologists understand the parts — the individual species. But Cordero wants to identify the engine and the wheels, to build a more functional description of how the species work together to create microscopic guilds that break down organic matter — a job vital to life on Earth.

"The interconnection between the Earth and microbes is just amazing," he says. "But we understand very little about how these diverse communities of organisms work."

To that end, Cordero co-leads the Simons Collaboration on Principles of Microbial Ecosystems, or PriME. Now entering its fifth year, PriME brings together researchers across many disciplines to understand how microbes assume their well-defined roles — with no 'chief microbe' telling them what to do — and how multispecies microbial communities respond to and influence Earth's ever-changing environment.

Doing so has required breaking from business as usual in microbiology, to approach the problem with an eye to the big picture rather than individual microbes. And although the collaboration employs many researchers worldwide to make that change happen, much of the vision trickles down from Cordero, whose eclectic background helps him approach microbiology from atypical angles.

"He brings a really unique flavor to the research," says PriME co-director Roman Stocker of ETH Zürich. "He's very good at distilling [complex problems] into simplified questions and approaches."

Cordero is a long way from where he started. Growing up in Ecuador in the 1980s and '90s, he had no scientific role models. "I didn't have any idea about what a scientist does or what a scientist looks like," he says. But his grandfather — "a writer, a poet and a bohemian" — had a huge library in his home. "That sparked my interest in knowledge, learning and science."

As an undergrad at the Polytechnic University of Ecuador, Cordero became fascinated with 'artificial life': computer simulations built on simple rules out of which complex collective behaviors emerge. He took this passion with him to graduate school at Utrecht University in the Netherlands. There he met Paulien Hogeweg, a pioneer of artificial life who was using the simulations to study everything from social behaviors to evolution. Under her tutelage, Cordero pivoted to biology.

"He had this eagerness of doing science, of understanding things and using whatever means are available for doing it, and really getting into the subject," Hogeweg recalls.

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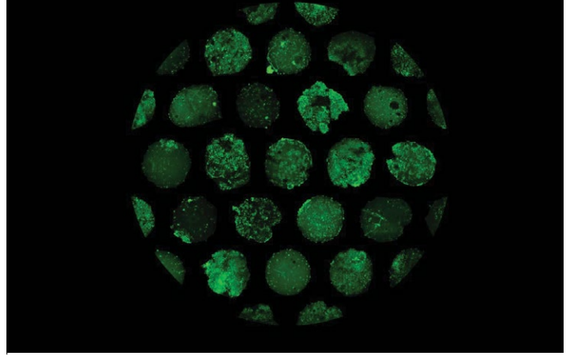

Marine microbes growing on nutrient patches. All the microbes originated from the same liter of seawater, yet the patterns that emerge as they grow vary across the different micro-ecosystems. Credit: Rachel Szabo and Otto X. Cordero

So he once again crossed the ocean, to MIT for postdoctoral work, experimenting in the lab to better understand the microbes themselves. It was here that the seeds for PriME took root. His Ph.D. had been focused on mathematically modeling biological processes. But as an experimentalist, "I learned a lot more about what is actually happening with the lives of microbes," he says. "I learned in more concrete terms how interconnected the planet is with microorganisms."

Microbes en masse wield enormous influence. They produce more than half of Earth's oxygen, form the marine food web's base, and play a key role in recycling carbon throughout the environment. In the ocean, much of this recycling happens on motes of organic matter known as marine snow. When carbon-consuming critters such as phytoplankton die, they tend to stick together and form small, whitish flecks, which then sink. If that were the whole story, much of the ocean's carbon would end up on the seafloor. But these 'snowflakes' are a buffet for microbes, who colonize the particles and scarf up the carbon, eventually returning it to the sea or atmosphere.

"That's what we've been studying in our lab for the last five or so years," says Cordero. "How the microbes assemble into complex communities on these tiny particles, and how their interactions mediate the degradation of organic matter." The rate of that degradation is one of the tuning knobs influencing how much carbon is freely available on Earth.

Though the pandemic slowed things down, it didn't stop the team from making discoveries. One thing they've learned in the past year is that although turnover among microbes on these particles is high, the basic jobs available stay the same. "You can see hundreds of different species coming and going," he says. "The next day, you may see different species coming and going. And the next day, slightly different species."

But all those different species assume similar functional roles, depending on how they obtain food. "Degraders" harvest their food from the marine snow, "cheaters" steal from the degraders' hard work, and "waste scavengers" munch on everyone else's excrement. Identifying those roles has been a major achievement. "This to me is one of the main problems in the field," he says. "How to go from this shopping list of species to a functional description of the system."

The discoveries haven't been limited to Cordero's lab at MIT. The PriME collaboration encompasses nine labs worldwide, each focused on different aspects of marine microbial communities. At the University of Southern California, for example, biologist Naomi Levine and others recently reported on how marine microbes leverage competing evolutionary strategies. And Roman Stocker and colleagues have shown how the fluid flow created by sinking marine snow affects consumption rates.

"We have done a pretty bold experiment with this collaboration," says Stocker. "We've brought in people from a variety of disciplines, including a number of people who have never before worked on the oceans."

Through the efforts of physicists, chemists, mathematicians and microbiologists, the team has established a new research platform by turning marine snow communities into a 'model system,' an archetype for further exploration, much the way that fruit flies are the classic staging ground for genetics research.

"Now we have a platform to do really exciting things," says Cordero. "We're at a stage now where we can actually ask much better questions."

Getting to this stage has required about 40 researchers across disciplines and around the globe to work together and try something new. But some of the success undoubtedly comes from Otto X. Cordero's character — from his being someone who enjoys life and enjoys connecting with people from backgrounds as varied as his own.

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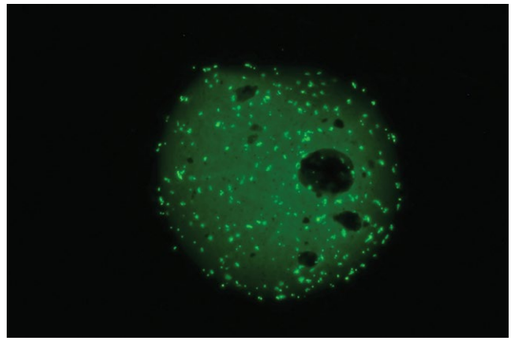
Otto X. Cordero Explores the Relationships Within Microbial Communities

When microbial ecologist Otto X. Cordero describes his approach to understanding complex societies of microbes, he pivots to talking about cars.



Marine bacteria colonizing and consuming polysaccharide particles. The microbes are stained with a fluorescent dye. Credit: Otto X. Cordero

"If I ask you how a car works, and you give me a list of parts, I can't do anything with that," says Cordero, an associate professor at the Massachusetts Institute of Technology. "But if you tell me there's an engine that produces movement, and a wheel that can steer, then that makes more sense."

Likewise, when it comes to microbial communities, biologists understand the parts — the individual species. But Cordero wants to identify the engine and the wheels, to build a more functional description of how the species work together to create microscopic guilds that break down organic matter — a job vital to life on Earth.

"The interconnection between the Earth and microbes is just amazing," he says. "But we understand very little about how these diverse communities of organisms work."

To that end, Cordero co-leads the Simons Collaboration on Principles of Microbial Ecosystems, or PriME. Now entering its fifth year, PriME brings together researchers across many disciplines to understand how microbes assume their well-defined roles — with no 'chief microbe' telling them what to do — and how multispecies microbial communities respond to and influence Earth's ever-changing environment.

Doing so has required breaking from business as usual in microbiology, to approach the problem with an eye to the big picture rather than individual microbes. And although the collaboration employs many researchers worldwide to make that change happen, much of the vision trickles down from Cordero, whose eclectic background helps him approach microbiology from atypical angles.

"He brings a really unique flavor to the research," says PriME co-director Roman Stocker of ETH Zürich. "He's very good at distilling [complex problems] into simplified questions and approaches."

Cordero is a long way from where he started. Growing up in Ecuador in the 1980s and '90s, he had no scientific role models. "I didn't have any idea about what a scientist does or what a scientist looks like," he says. But his grandfather — "a writer, a poet and a bohemian" — had a huge library in his home. "That sparked my interest in knowledge, learning and science."

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"Not enough people know this in the general public, but microorganisms like bacteria, something else called archaea that not many people know about, [and] fungi are key players in all ecosystems on the planet. The planet wouldn't look the way it looks if it wasn't because of these microbes. There wouldn't be any life, in fact. For example, every living form requires nitrogen. ... Nitrogen is in the atmosphere, and the only way it gets into plants — and, therefore, into beings that eat plants, like us — is because there are microbes that converted atmospheric nitrogen into organic nitrogen."

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A New Simons Collaboration Probes How the Brain Ages

The African turquoise killifish is unusual for a vertebrate, especially among those typically found in research labs. All told, it lives about six months, a life cycle adapted to the ephemeral ponds of Zimbabwe and Mozambique. Ironically, their short life span makes these fish ideal candidates with which to study the science of aging: Their life stages appear predictably and rapidly and, as research on aging progresses, will eventually permit quick evaluation of genetic and other interventions.

Bérénice Benayoun knows this. As a postdoctoral researcher with Anne Brunet at Stanford University, Benayoun helped piece together the killifish genome and then edit it to recapitulate known hallmarks of aging-related disorders. Now a Simons Collaboration on Plasticity and the Aging Brain (SCPAB) investigator and a researcher at the University of Southern California, Benayoun continues to collaborate with Brunet to manipulate other under-studied molecular pathways, to understand how they control aging processes including cognitive decline. Given that the world's population of people 65 and older will double in the next few decades, these questions are increasingly relevant.

The killifish is just one of a handful of organisms used to study aging. Coleen Murphy, a Princeton University professor of molecular biology and genomics and director of the SCPAB, has long been interested in using the tiny *Caenorhabditis elegans* roundworm to understand why and how we age. Her team is working to untangle multiple molecular pathways underlying aging, including those involving CREB (cAMP response element-binding protein), a transcription factor involved in neural plasticity whose abundance declines with age in both worms and humans. In 2019, Murphy's team showed that they could manipulate the CREB pathway to rescue the ability of old worms to learn and remember.

Driven by the goal of understanding the aging brain, the SCPAB has so far pledged support to 21 investigators to search for mechanisms underlying aging and investigate whether they can be slowed or reversed. The SCPAB was begun with the belief that cognitive decline and aging are worth understanding per se, as well as for their connections to neurodegenerative disorders. All animals age, and though there is plenty of research on conditions such as Alzheimer's disease, much less is known about the 'normal' aging process that most of us will experience. SCPAB funding is distributed across seven projects, each tackling the question of aging from a different angle. Groups are investigating aging at the genetic, molecular, systems and behavioral levels — and in different species.

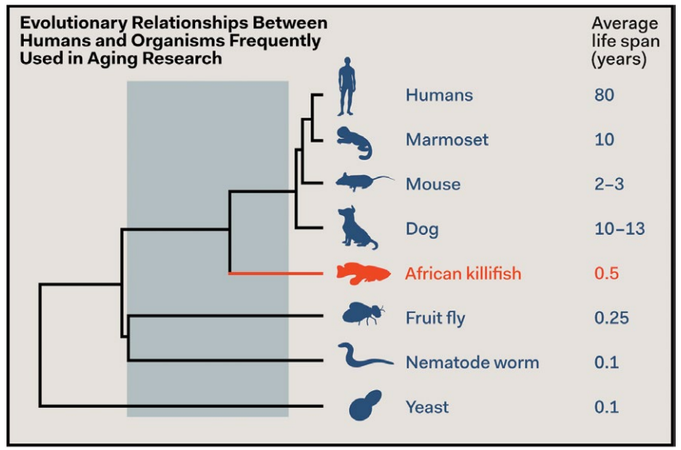
All of the projects rely on animal models that have been underutilized in aging research thus far. Although research on different animal models has thrived, until the SCPAB collaboration, studies were usually performed without reference to one another. "We all knew of each other's work, but there was never an opportunity for us to work together," Benayoun says. "Simons funding gave us a platform and a common project to work on."

Most of the SCPAB projects require expertise across multiple domains. For example, one project focuses on the role of bloodborne factors shown to affect aging processes. To fully understand these mechanisms, the SCPAB team will use multiple approaches: proteomics and RNA sequencing to understand which proteins can cross from blood into the brain, high-resolution imaging to understand structural changes caused in blood vessels, and behavioral assays to assess how these bloodborne factors alter cognition. Injecting such bloodborne factors may be a viable way to extend our healthy, cognitively active years.

A common goal across SCPAB projects is to find similarities and differences across species, beginning with defining what should be considered "old" for each organism. "We want to understand the molecular changes that take place with age in the brains of all these organisms — and which changes are conserved in different species and which are unique," Murphy says.

"It's not going to be enough to say I found one thing that changes with aging," says Gerald Fischbach, distinguished scientist and fellow at the Simons Foundation, who initiated the SCPAB in 2017. "The question is: Are there common features of aging across species?"

To truly compare results between species, one SCPAB project is dedicated to designing a database that will standardize data collected across all organisms studied, as well as from all SCPAB projects, becoming the first database on aging of its kind. The database will also feature data from humans: initially neuroimaging data from the U.K. Biobank, and later many types of human data from other sources.



Males and females age differently. Benayoun's team developed a mouse model to study the influence of hormonal regulation on our aging genomes and brains. But as a trained genomicist, she was a fish out of water when attempting to understand what was happening to the brain as these mice aged. Facilitated by SCPAB workshops intended to harmonize the way researchers collect and annotate data, she traded expertise with fellow SCPAB researchers like Dena Dubal, who specializes in neuroscience and behavior.

This type of collaborative approach, especially starting from the inception of a project, is truly unprecedented. "With traditional funding mechanisms, you are already about 90 percent done with the project in question when you apply for support — which means that your ability to adjust course is really very limited," Benayoun says.

Sometimes, this involves getting into the nitty-gritty about what's working and what's not — even down to specific experimental time points — ultimately saving each other the time and effort of working out the kinks themselves. "This is not something you're going to see at a conference," Benayoun says.

"I've rarely been involved in such a collaborative project where people are so committed at such an early stage," says Fischbach. Importantly, the SCPAB leadership values and listens to everyone on the project, even students and junior investigators. "It's a true collaboration," Benayoun says. "It feels very original."

Ultimately, the goal of this harmonization is to develop clear insight about why we age and how we might reduce cognitive decline. In Benayoun's words, "How do we best design what each lab is doing so that we can learn something that transcends what each lab is doing?"

For octogenarian Fischbach, the scientific and humanitarian implications of the SCPAB work have deeply personal importance. He notes that although the present focus is on using simple organisms to test causality, these findings may ultimately lead to genetic or therapeutic interventions in humans. "It's going to be hard to do such genetic manipulation in higher vertebrates," he cautions, "but it's coming."

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Gerald Fischbach also played a pivotal role in the launch of the Simons Collaboration on the Global Brain (page 23) and SFARI (pages 25–30).

> "One of the really great things about the collaboration on the aging brain has been making new connections between groups that never would have worked together otherwise. I feel like we've been able to bring together a really stellar group of investigators, and some of those investigators didn't know when we met for the first time in a workshop that they would end up collaborating. … But because we had these workshops, and they started talking with each other, they realized they had a great intellectual question that was shared. And so from that sprung a number of collaborations … that never would have happened if the Simons [Foundation] hadn't gotten them together."
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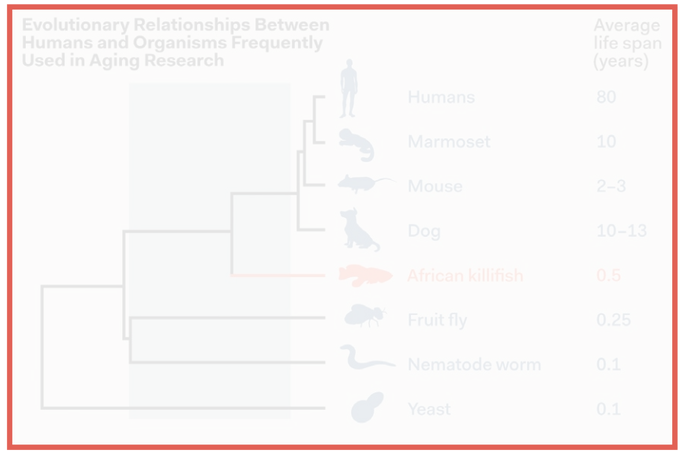

Studying the aging process in animals requires studying an organism throughout its life cycle. African killifish are more closely related to humans than other animals with short life cycles, such as fruit flies and nematode worms, while still having only a monthslong life span. Credit: A. Wang *et al./Cell* 2015

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Neuroscientists Are Tracking How Information Travels Across Our Brains

The brain performs a massive number of complex computations, all day long. In a game of dodgeball, the visual cortex might signal that something is approaching your face — fast! — and promptly alert the motor cortex to duck! from an oncoming sphere. Or, maybe, when you detect the smell of your grandmother's perfume, signals from the olfactory cortex combined with memories stored in your hippocampus might transport you back in time to enjoyable childhood visits. Each area of the brain is like a high-tech command center: taking in information, transforming it with computation and then rerouting it to new cerebral locations.

For decades, scientists have been trying to understand the content of those signals. Adding to the complexity is the fact that researchers are asking not only about the content of the information sent, but also how and where computations happen and how they effect thought and behavior. Tracking the paths and transformations of messages through multiple brain networks may be the key to understanding how the brain processes information so flexibly.

Enter the Simons Collaboration on the Global Brain (SCGB), a network of 76 scientists dedicated to doing just that: understanding how internal brain processes occur and also how they then impact the transformation of sensory information into actions. Now in its seventh year, SCGB is unveiling important lessons about memory, decision-making and the kinds of theoretical frameworks scientists will need to peel away the layers of complexity and reveal the inner workings of the brain in unprecedented detail.

For decades, SCGB investigator and University of California, San Francisco researcher Loren Frank has been interested in the neural circuits active in memory formation. As an animal moves through space, neurons in the hippocampus fire to record the animal's location and to update other areas of the brain, effectively forming a spatial memory. These sequential firing patterns are reactivated during 'sharp-wave ripples,' events thought to act as time-compressed versions of spatial memories that are often replayed during stillness and sleep.

In 2020, Frank's lab published a study in *Neuron* investigating how different regions of the hippocampus broadcast this spatial memory to the nucleus accumbens, an area involved in reward. Before this study, the team knew that both the dorsal and ventral regions of the hippocampus exhibited sharp-wave ripples, but not whether these regions communicated with different or overlapping networks in the accumbens. By recording simultaneously from the hippocampus and the nucleus accumbens, they showed that dorsal and ventral ripples activated mostly separate sets of neurons and had opposing effects when they spoke to the same neurons.

Lead author Mari Sosa, who wrote the paper as a graduate student and now works as a postdoctoral fellow with SCGB investigator Lisa Giocomo at Stanford University, thinks these opposing effects may help the brain tease apart different parts of a memory, such as specific locations or the emotional and social context of an experience. "In order to disassociate specific pieces of information, you might want to have neural circuits dedicated to separately storing and retrieving those different pieces of information," Sosa says. When you're recalling your walk to the coffee shop, you can remember which corner it's on, or the sense of relief after the first sip of your latte, or both. By integrating different sets of inputs, it's likely that the accumbens neurons are able to tease apart these memories.

The actual messages being sent between the hippocampus and the nucleus accumbens, however, are still a mystery. "We don't know what the content of these replay messages are just yet, but one possibility is that the dorsal and ventral hippocampus are routing different types of information during memory storage and retrieval," Sosa says. It's possible that these different messages are what's reflected in the different firing patterns in the accumbens.

Sosa's work adds to an increasing pile of evidence that most information processing happens in neurons distributed across brain areas. "You might have groups of neurons within a brain area that are specialized to process a certain type of information, but that's probably not the only thing they're doing," Sosa says. "They could also be modified to do something a little bit different depending on what inputs they receive from other areas."

Flexibility is indeed a crucial feature of how our brains work — it's how we remember, learn and ultimately change our behavior. It's possible that having different routes for information can help the brain more flexibly compute information based on context, experience, mood and more.

Still, the mechanisms of this flexibility, and their timescales, are a bit of a mystery. "Given that almost everything in the brain is connected to everything else, how do brain regions connect and disconnect?" SCGB and Howard Hughes Medical Institute investigator Karel Svoboda asks. "What are the mechanisms, and how do they enable flexible computation?" To address these questions, Svoboda is working on expanding our capacity to image multiple brain areas simultaneously.

Working with fellow SCGB investigator Liam Paninski, a researcher at Columbia University, Svoboda is developing novel ways to image large swaths of brain activity down to the resolution of synapses. Last year, they helped develop a microscope that can simultaneously image more than 9,000 inhibitory neurons across four different cortical areas, along with callosal projection neurons spanning two hemispheres. The hope is that this technology will shed light on the precise connections that enable behaviors.

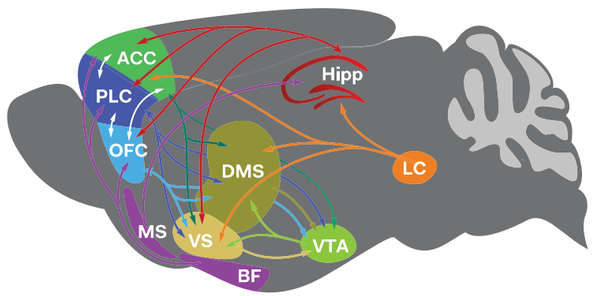
Other researchers are turning to high-yield electrophysiology devices such as Neuropixels recording probes to determine how brain areas work together to route information. Working as part of the International Brain Laboratory (IBL), a 21-lab collaboration funded in part by SCGB, SCGB investigator and University of Washington researcher Nick Steinmetz is using Neuropixels to understand how rodents make decisions. Steinmetz is primarily interested in how an animal's internal state influences its brain activity and ultimately its behavior; researchers at the IBL are determined to figure out what is different in the brain when an animal is paying close attention versus when it's disengaged. He trains mice to make visual decisions and has noticed that an animal's engagement with a task can change how quickly and how well it makes a decision. "The same stimulus on the retina fails to generate a behavior," Steinmetz says. "Somewhere, the activity is different."

Steinmetz and his colleagues believe that changes in the structure of communication between brain regions may be what distinguishes different attentional states. "It's actually by modulating information flow, and via high-dimensional communication patterns, that the behavioral effects of engagement are brought about," Steinmetz says.

But activity happening synchronously through multiple brain regions can be difficult to parse. Most computational theories of brain activity describe the flow of information from one area to another, with many transformations occurring along the way. New theories and methods are needed to tackle the logic of multiple brain regions speaking to many other regions.

This is where SCGB investigators like Byron Yu come in. Yu, a neuroscientist at Carnegie Mellon University, is working with fellow SCGB investigators Adam Kohn of Albert Einstein University and Christian Machens of the Champalimaud Foundation to develop new statistical methods to parse the relationships between brain areas that enable visual perception. In the past two years, their team published two papers showing that different areas in the visual cortex could communicate through specific channels, or subspaces. Their idea is that this works like a lock and key: Signals that match the channel are sent to the next brain area; mismatched signals are not. Identifying this neural mode of signaling relied on new mathematical approaches, including a few that can tease apart feedforward and feedback signals, a crucial distinction in understanding how information is routed.

Frameworks like these underscore the importance of understanding the brain as an interconnected network. "We have a great temptation to draw box-and-arrows diagrams and think that they tell us how the system works," Steinmetz says. "It's pretty clear it's going to be more complicated than that."



Neuroscientists Are Tracking How Information Travels Across Our Brains

The brain performs a massive number of complex computations, all day long. In a game of dodgeball, the visual cortex might signal that something is approaching your face — fast! — and promptly alert the motor cortex to duck! from an oncoming sphere. Or, maybe, when you detect the smell of your grandmother's perfume, signals from the olfactory cortex combined with memories stored in your hippocampus might transport you back in time to enjoyable childhood visits. Each area of the brain is like a high-tech command center: taking in information, transforming it with computation and then rerouting it to new cerebral locations.

For decades, scientists have been trying to understand the content of those signals. Adding to the complexity is the fact that researchers are asking not only about the content of the information sent, but also how and where computations happen and how they effect thought and behavior. Tracking the paths and transformations of messages through multiple brain networks may be the key to understanding how the brain processes information so flexibly.

Enter the Simons Collaboration on the Global Brain (SCGB), a network of 76 scientists dedicated to doing just that: understanding how internal brain processes occur and also how they then impact the transformation of sensory information into actions. Now in its seventh year, SCGB is unveiling important lessons about memory, decision-making and the kinds of theoretical frameworks scientists will need to peel away the layers of complexity and reveal the inner workings of the brain in unprecedented detail.

For decades, SCGB investigator and University of California, San Francisco researcher Loren Frank has been interested in the neural circuits active in memory formation. As an animal moves through space, neurons in the hippocampus fire to record the animal's location and to update other areas of the brain, effectively forming a spatial memory. These sequential firing patterns are reactivated during 'sharp-wave ripples,' events thought to act as time-compressed versions of spatial memories that are often replayed during stillness and sleep.

In 2020, Frank's lab published a study in *Neuron* investigating how different regions of the hippocampus broadcast this spatial memory to the nucleus accumbens, an area involved in reward. Before this study, the team knew that both the dorsal and ventral regions of the hippocampus exhibited sharp-wave ripples, but not whether these regions communicated with different or overlapping networks in the accumbens. By recording simultaneously from the hippocampus and the nucleus accumbens, they showed that dorsal and ventral ripples activated mostly separate sets of neurons and had opposing effects when they spoke to the same neurons.

Lead author Mari Sosa, who wrote the paper as a graduate student and now works as a postdoctoral fellow with SCGB investigator Lisa Giocomo at Stanford University, thinks these opposing effects may help the brain tease apart different parts of a memory, such as specific locations or the emotional and social context of an experience. "In order to disassociate specific pieces of information, you might want to have neural circuits dedicated to separately storing and retrieving those different pieces of information," Sosa says. When you're recalling your walk to the coffee shop, you can remember which corner it's on, or the sense of relief after the first sip of your latte, or both. By integrating different sets of inputs, it's likely that the accumbens neurons are able to tease apart these memories.

The actual messages being sent between the hippocampus and the nucleus accumbens, however, are still a mystery. "We don't know what the content of these replay messages are just yet, but one possibility is that the dorsal and ventral hippocampus are routing different types of information during memory storage and retrieval," Sosa says. It's possible that these different messages are what's reflected in the different firing patterns in the accumbens.

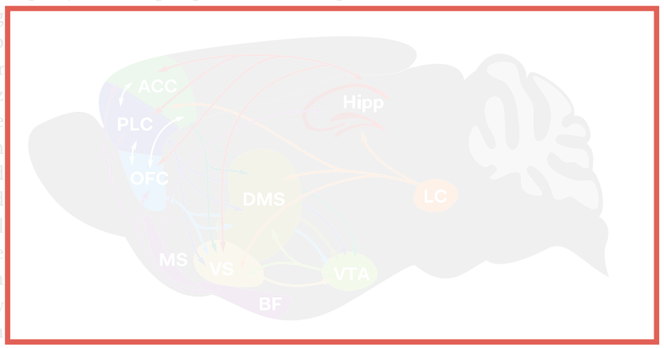
"Given that almost everything in the brain is connected to everything else, how do brain regions connect and disconnect? What are the mechanisms, and how do they enable flexible computation?"

Karel Svoboda

"Certainly, for me, the biggest impact of SCGB has been in their ... visionary support for the International Brain Lab, which is what I'm a part of. The fact that they undertook this sort of massive and ambitious and risky project, and have supported it financially, and also supported it in terms of building a community, I think, has been tremendous."

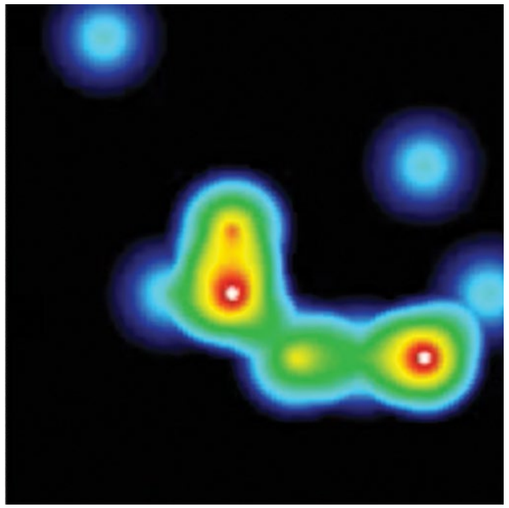
Nick Steinmetz

Watch the full video of Nick Steinmetz at simonsfoundation.org/report2020



Loren Frank and collaborators are exploring how the hippocampus (Hipp) interacts with several brain regions, including the anterior cingulate cortex (ACC), prelimbic cortex (PLC) and orbitofrontal cortex (OFC).
Credit: Adam Kepecs and Loren Frank

Solving for Early-Career Challenges in Autism Research



Spontaneous activity of in vitro cultured neurons recorded through a multielectrode array. Credit: Yun Li laboratory/University of Toronto

One of the most vulnerable stages in a scientist's career is the transition from traineeship to professorship. In the biomedical sciences in particular, a mismatch between the number of doctoral recipients and the number of available tenure-track faculty positions has made this process increasingly difficult in recent years. "There is a logjam of highly trained scientists that can't advance to the next level," says Alice Luo Clayton, a senior scientist at the Simons Foundation Autism Research Initiative (SFARI). "It's a missed opportunity for valuable talent."

To address this issue and attract outstanding early-career scientists into autism research, in 2015 SFARI created the Bridge to Independence (BTI) program, which provides three years of funding to researchers who are finishing a mentored position, to commence as soon as they move into a tenure-track position at a U.S. or Canadian research institution. The program currently includes 31 fellows whose work spans a wide range of approaches to autism research, including genetics, molecular mechanisms and clinical science.

The award makes recipients more competitive in a tough job market, Clayton says. And once they secure a position, it lets them hit the ground running. Early-career scientists typically come under immediate pressure to apply for grants, but the BTI award "gives them breathing room to actually focus on their science for a while," she says.

Besides funding, the program provides less tangible forms of support, from advice on negotiating job offers to an instant community of early-career autism researchers. "When you start in a new place, you don't usually have a cohort of people who were hired at the same time," says Rebecca Muhle, a 2017 fellow who is now an assistant professor at Columbia University. The BTI award is "a nice way to find your peers, even though they are at different institutions," she says. "You're part of the same BTI class."

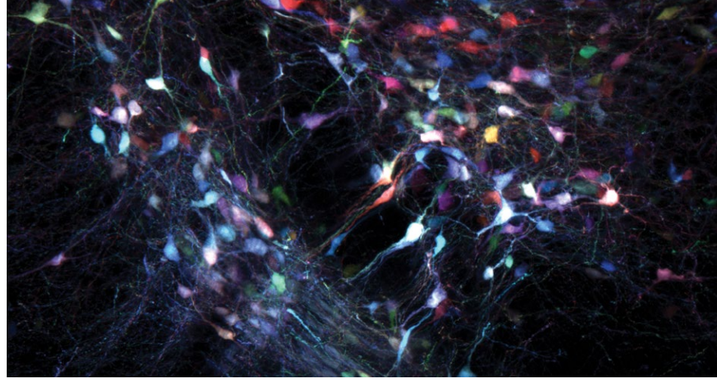
The program hosts an annual meeting at which the fellows explain their research (this year, due to COVID-19, the meeting was spread out over six weeks of virtual sessions). "Some of the talks are over my head, and others are completely in my wheelhouse," Muhle says. "There's such a breadth of experience, and it's great to all come together with a common purpose."

The fellows also exchange wisdom about how to meet the challenges of setting up a lab as a brand-new principal investigator. "We're all in the same boat — we have the same challenges, the same fears, the same excitement, the same roadblocks," says Stephanie Rudolph, a 2017 fellow who is now an assistant professor at Albert Einstein College of Medicine in New York.

Several senior autism researchers also attend the meeting, to advise the fellows on matters such as how to recruit students and postdocs, craft a grant proposal, strategize for collaborations and preserve time for research amid the competing demands of a tenure-track professorship.

"There are all these skills that a young scientist doesn't really have, because no one taught them," Rudolph says. "We were taught as postdocs to be good scientists. But now we're also entrepreneurs and mentors and teachers."

Although some fellows planned all along to do autism research, others were drawn into the field by the BTI program, bringing a diverse array of backgrounds and expertise into autism research. Rudolph, for instance, studied basic synaptic physiology, but she is now examining how disruption in the cerebellum may contribute to autism-associated behaviors. "Writing the BTI grant and thinking about the relevance of my research for autism has profoundly changed how I think about my science," she says. "It has opened up a whole world of thinking about clinically relevant questions."



Multicolor dopaminergic neurons in the mouse ventral tegmental area and substantia nigra pars compacta following systemic delivery of AAV-PHP.eB-Th-VAST vectors. Bridge to Independence fellow J. Elliott Robinson used this technique to study alterations in neuronal morphology in a mouse model of neurofibromatosis type 1, a neurodevelopmental condition that is also the focus of his Bridge to Independence project. Credit: Gerard Coughlin and J. Elliott Robinson/Viviana Gradinaru laboratory at the California Institute of Technology

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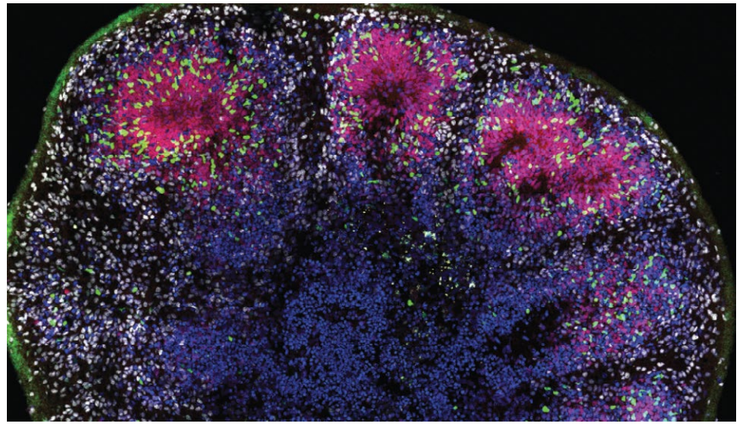
Muhle is now studying how changes in the expression of the autism risk gene CHD8 affect biological pathways and symptoms such as seizures in mice that have only one functioning copy of the gene. She also sees patients with neurodevelopmental disorders in her clinic. "I hope in the future we'll come to a place where we're able to improve things for our patients, in a way that will enable them to live their best lives," she says.



A 70-day-old brain organoid derived from an individual with a mutation in SCN8A, a high-confidence autism risk gene. In his Bridge to Independence project, Ranmal Aloka Samarasinghe will use this in vitro system to study the effects of SCN8A mutations on excitatory-inhibitory balance and neural oscillations in autism spectrum disorder. Credit: Ranmal Aloka Samarasinghe/University of California, Los Angeles

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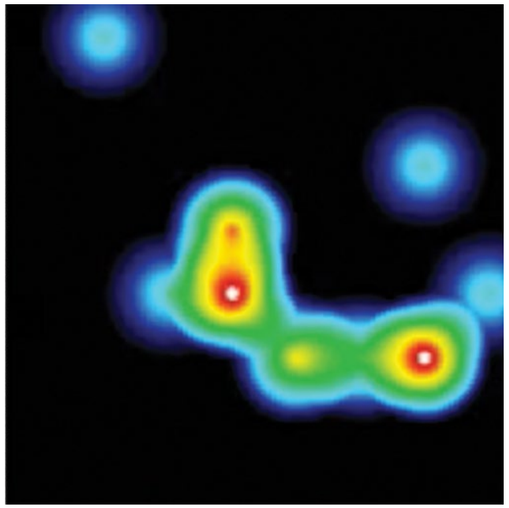

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Securing a long-term research career in academia has become increasingly difficult. In 1973, 55 percent of Ph.D. recipients in the biological sciences received a tenure-track academic position within six years. By 2009, that number had dropped to 18 percent. Source: National Academies of Sciences, Engineering, and Medicine.

Read about all of the SFARI Bridge to Independence Award recipients at www.sfari.org/grant/bridge-to-independence-award-request-for-applications/?tab=awardees

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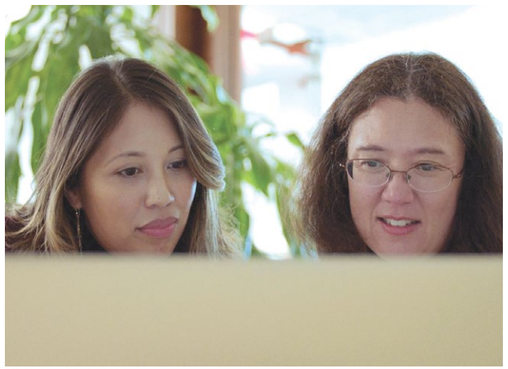
In January 2021, the Simons Collaboration on the Global Brain (page 23) launched its own Bridge to Independence Award program.

Searching for the Genetic Roots of Inherited Autism

Over the past decade, sequencing studies of children with autism and their families have uncovered about 100 high-confidence autism risk genes by searching for de novo variants — spontaneous variants that appear in the child but in neither parent. In one of autism research's most striking success stories, these findings have provided an explanation for about two-thirds of the portion of autism risk that is associated with de novo variants.

Yet even though about 80 percent of autism risk comes from genetic factors, researchers estimate that only about one in five autism cases can be explained by a de novo variant. "That clearly isn't the answer for the majority of individuals," says Wendy Chung, the principal investigator of the Simons Foundation Powering Autism Research for Knowledge (SPARK) initiative. "There's still something missing."



Pamela Feliciano and Wendy Chung review genetic data from SPARK.

When it comes to genetics (as opposed to environmental factors), the "something missing" consists of all the inherited variants that can increase autism risk. This vast portion of the autism risk landscape is much harder to chart than the portion that comes from de novo variants. Whereas an individual typically has just one or two de novo variants in the entire protein-coding portion of their genome, they will typically have tens of thousands of inherited variants, most of which will have nothing to do with autism. "There are so many that it's hard to know which to pay attention to," Chung says.

Sifting through these variants to figure out which ones increase autism risk requires sequencing tens of thousands of families or possibly even 100,000 families. Until recently, such numbers were out of reach. But SPARK, launched in 2016, is in the process of assembling a cohort of 50,000 individuals with autism and their families. Sequencing studies of SPARK families are now starting to illuminate the inherited portion of autism risk.

SPARK researchers analyzed the genomes of nearly 10,000 families from SPARK and other publicly available autism genomic data. Their analysis has uncovered the first gene, NAV3, that confers autism risk only through inherited variants and not through de novo variants. "We have very high confidence that this is a true autism risk gene," says Yufeng Shen, a researcher at Columbia University who carried out the study with Chung and a large group of SPARK collaborators.

Lopsided Transmission. Examining the entirety of inherited autism risk is far too big a task to carry out without a much larger cohort even than the SPARK collection. To make the task more manageable, SPARK researchers restricted their attention to ultra-rare variants — ones that appear in at most 1 in 100,000 people in the general population. The variants that make the strongest contributions to autism risk tend to be these rare ones, since people with autism are less likely than others to have children, which means that their genetic variants are not as likely to be passed down to the next generation.

Rico and Israel Winston participate in the SPARK autism study.

Next, researchers narrowed down the list of ultra-rare variants even further by focusing on those that had been computationally predicted to be deleterious — variants that probably destroy or significantly alter the functioning of the protein that the gene encodes.

To find the genes in this shortlist that are associated with autism risk, the researchers next looked for what they call a "disequilibrium" in how the gene's variants are transmitted to the next generation. Since a parent has two copies of each gene, when one copy has a variant, each child has only a 50 percent chance of inheriting the variant. In the case of an autism-linked variant, the children who inherit it are much more likely to show up in the SPARK data than the children who don't inherit it. This means that within SPARK, transmission of the autism variant will look lopsided: More than 50 percent of parents with the autism variant will have passed it down to their children with autism.

In the case of NAV3, 49 parents had a rare damaging variant, and 40 of them (81 percent) had passed the variant down to their children with autism — much more than 50 percent. "It's very strong statistical evidence," Shen says.

The researchers also found some indications of inherited autism risk for another gene, ITSN1. SPARK is now completing a genetic analysis of an additional 10,000 families, and researchers hope that these added data will bolster the evidence for NAV3 and ITSN1 and bring many other inherited autism risk genes to light. "As of today, we have more than doubled our genomic data since our first analysis," says Pamela Feliciano, SPARK's scientific director. "I'm confident that the data SPARK is generating will yield even more insights."

Specific Pathways. The NAV3 protein, which is involved in neuronal migration, is part of a biological process that has long been known to be involved in de novo autism risk. Although this connection to other autism risk genes bolsters the evidence for NAV3, researchers hope that the search for inherited autism risk genes will ultimately lead them to some pathways that are more specific to autism than the ones that have come up in the context of de novo risk. Many of the known de novo risk genes are associated with autism that is compounded by intellectual disability and other neurodevelopmental conditions. Much less is known about the biology of autism in which only the core traits of the condition are present. "There's a large part of the autism spectrum that we just don't have answers for," Chung says.

The genes underlying this type of autism may turn up more abundantly among inherited risk genes than among de novo risk genes. That's because among people with autism, those who have only the core traits, without intellectual disability, are most likely to have children and pass their variants down to the next generation. Additional research is needed to determine if people with autism spectrum disorder who have inherited mutations in genes such as NAV3 and ITSN1 are less likely to have cognitive impairments.

"How many of the inherited variants we find might elucidate brand-new biology that might have greater specificity to autism?" Chung wonders. "It opens up the possibility that we're just crossing the threshold into a new dimension."

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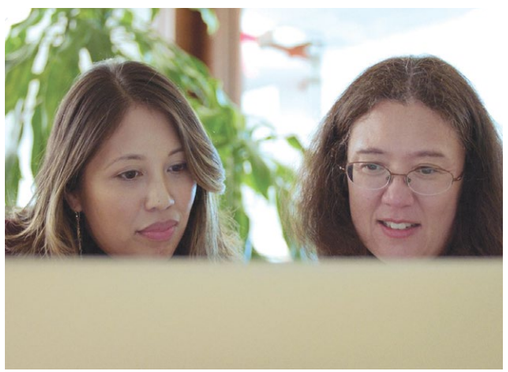

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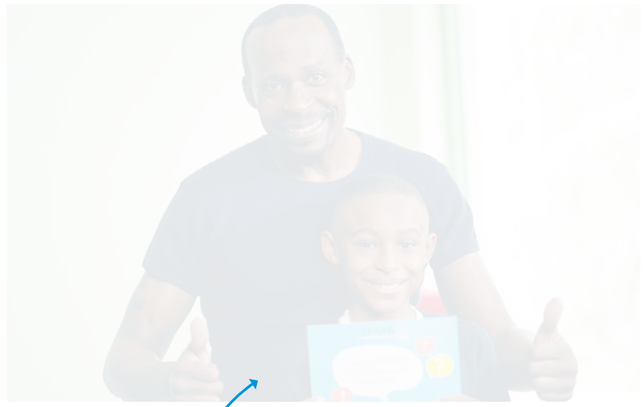

Rico and Israel Winston participate in the SPARK autism study.

Watch Rico Winston talk about his experiences as a SPARK participant at sparkforautism.org/discover_article/community-spotlight-autism-advocate-rico-winston

"Many families have spent a long time trying to understand: Why does their ... family member have the challenges that they have? And getting an answer ... that's grounded in biology and science has been really impactful, in the sense that they can breathe a sigh of relief and understand that it wasn't something they did. It wasn't something that happened or a chance situation. It was because of this biological reason. And I think that a lot of families are happy to receive this information."

Pamela Feliciano

Watch the full video of Pamela Feliciano at simonsfoundation.org/report2020

Highlights of SFARI-Supported Autism Research From 2020

In 2020, the Simons Foundation Autism Research Initiative (SFARI) supported nearly 300 investigators in the United States and abroad who have pushed forward the frontiers of autism research in many directions. The following are some highlights of SFARI Investigators' research in the past year.

Spotting harmful missense. Many families and individuals with autism participate in sequencing studies in the hope of receiving a definitive genetic explanation for their condition. Sometimes, this wish is fulfilled: Genetic sequencing uncovers a mutation that clearly sabotages the protein encoded by a known autism risk gene. But other times, only a "missense" mutation in the gene is found — one that switches a single amino acid in the corresponding protein, perhaps destroying the protein's function, but perhaps not. Missense mutations are thought to underlie many cases of autism, but it's hard to tell which missense mutations are deleterious and which are benign.

A study led by SFARI Investigator Kurt Haas of the University of British Columbia offers a systematic framework for assessing which missense mutations are likely to be damaging. As they reported on April 29, 2020, in *Nature Communications*, the researchers examined 106 mutations in the autism risk gene PTEN in five model systems: yeast, roundworms, fruit flies, rats and human cells. The team tested the functional impact of the mutations in a variety of ways, such as by examining larval development in fruit flies and the structure of neurons in rats.

Many of the mutations had harmful impacts, and these impacts tended to correlate across the different organisms. The correlations were especially strong in the case of mutations that weaken the protein's stability, suggesting that assessing protein stability might be a quick first test for spotting disruptive mutations. The team has since used its testing platform to study missense variants in another autism risk gene, SYNGAP1. As more genes go through this pipeline, the pool of individuals with autism who can receive a conclusive genetic explanation may greatly expand.

Rescuing plasticity. The autism-linked gene SHANK3 is essential to brain plasticity, according to a new study that illuminates the gene's role in enabling neurons to adjust to changes in sensory input. The study, led by SFARI Investigator Gina Turrigiano of Brandeis University, also found that the mood-stabilizing drug lithium mitigates repetitive behaviors and disruptions to brain plasticity in rats and mice missing SHANK3, which is mutated in about 1 percent of people with autism.

The researchers, who reported their findings in the June 3, 2020, issue of *Neuron*, disrupted SHANK3 expression in cultured rat neurons, and then temporarily blocked the neurons' ability to fire. Once the block was removed, the cells failed to return to their normal firing rate, suggesting they were unable to adapt to this change. Lithium restored the neurons' ability to adjust their firing rates.

The team next glued one eye shut in mice lacking SHANK3 and used multielectrode arrays to study their visual cortex. Neurons in the mutant mice decreased their firing rate more gradually than those in control mice, suggesting that they took longer to adjust to the decrease in visual input. And then, while neurons in the control mice compensated for the loss of vision and resumed firing after a couple of days, neurons in the mutant mice never returned to their original firing rates.

The mutant mice also groom themselves excessively, but this behavior was eliminated by lithium treatment. The findings imply that lithium may be useful for treating people with SHANK3 mutations. Although lithium is often poorly tolerated, understanding why it works may also open the door to better treatments.

Mutated motion. A machine learning algorithm that breaks down motion into discrete behavioral chunks can tell the difference between control mice and ones with a particular autism-linked mutation, a new study shows. The algorithm was able to identify hyperactivity in the mutated mice, and it also detected how a widely used autism drug affected their motion.

The study, led by SFARI Investigator Sandeep Robert Datta of Harvard University, used MoSeq, an algorithm Datta and his team developed in 2015 to break down motion into discrete "syllables" without human assistance. The researchers, who published their findings on September 21, 2020, in *Nature Neuroscience*, examined the motion of mice with two mutated copies of the gene CNTNAP2. MoSeq identified 16 motion syllables that are different in these mice than in controls.

The drug risperidone, the team found, restored seven of these syllables to normal, and improved seven others. The researchers also examined the motion of control mice that were given one of 15 different drugs for depression, anxiety, psychosis or other disorders, and found that MoSeq was able to figure out which mice had received which drug. The software might help researchers quickly screen drug candidates to see which ones show promise for alleviating hyperactivity, repetitive movements and other traits linked with autism.

Mapping autism's genetic terrain. A new genetic analysis of people with autism and their families offers the most expansive view yet of the landscape of autism risk genes, identifying 102 genes strongly associated with autism, including 30 that had not been previously linked to the condition. The study — a large collaborative effort that involved SFARI Investigators Stephan Sanders and Matthew State of the University of California, San Francisco, Bernie Devlin of the University of Pittsburgh, Kathryn Roeder of Carnegie Mellon University, and Michael Talkowski of Harvard University, under the auspices of the Autism Sequencing Consortium — looked at the exomes (the protein-coding regions of the genome) of more than 35,000 individuals from the Simons Simplex Collection and other cohorts, making this the largest exome-sequencing autism study to date.

The researchers, who published their findings in *Cell* on February 6, 2020, applied an enhanced version of their previously developed statistical method, called TADA, to determine which gene variants are likely to be harmful. The 102 genes that emerged from this analysis tended to cluster in groups that affect gene expression or neuronal communication. In cells from the human cortex, the team found that the expression of these genes is enriched in both excitatory and inhibitory neurons starting in early development. Some lines of research have suggested that autism stems in part from an imbalance between excitatory and inhibitory signaling, and the new study indicates that there may be multiple biological pathways toward this imbalance.

Editing Angelman syndrome. Altering mouse DNA using CRISPR gene-editing technology can prevent many characteristics of the autism-related condition known as Angelman syndrome, researchers reported in *Nature* on October 21, 2020. The therapy's benefits lasted for the entire 17 months that the researchers monitored the mice, and may be lifelong.

Angelman syndrome, whose core traits include developmental delays, motor dysfunction and speech impairments, typically results from a mutation blocking the maternal copy of the gene UBE3A. The paternal copy of this gene is normally silent, and treatments that activate this copy in mice can ameliorate some traits of the condition. However, these improvements typically wear off over time.

The new study, led by SFARI Investigator Mark Zylka of the University of North Carolina at Chapel Hill, used the CRISPR-Cas9 gene editing approach to deactivate the RNA molecule that ordinarily silences paternal UBE3A. The therapy, which was delivered to the cortical neurons of embryonic and infant mice in two doses, activated the paternal copy of the gene in 58 percent of cortical neurons. Mice that received the therapy showed improved motor coordination and reduced anxiety and repetitive behaviors.

The researchers also found that the therapy activated paternal UBE3A in cultured human neurons, suggesting that it might be effective in people as well as mice. But the approach is considered risky because it can make unpredictable cuts in DNA. So Zylka's team next plans to examine alternate versions of CRISPR therapy that can activate paternal UBE3A without cutting DNA, and thus may be safer for human use.

Highlights of SFARI-Supported Autism Research From 2020

In 2020, the Simons Foundation Autism Research Initiative (SFARI) supported nearly 300 investigators in the United States and abroad who have pushed forward the frontiers of autism research in many directions. The following are some highlights of SFARI Investigators' research in the past year.

Spotting harmful missense. Many families and individuals with autism participate in sequencing studies in the hope of receiving a definitive genetic explanation for their condition. Sometimes, this wish is fulfilled: Genetic sequencing uncovers a mutation that clearly sabotages the protein encoded by a known autism risk gene. But other times, only a "missense" mutation in the gene is found — one that switches a single amino acid in the corresponding protein, perhaps destroying the protein's function, but perhaps not. Missense mutations are thought to underlie many cases of autism, but it's hard to tell which missense mutations are deleterious and which are benign.

A study led by SFARI Investigator Kurt Haas of the University of British Columbia offers a systematic framework for assessing which missense mutations are likely to be damaging. As they reported on April 29, 2020, in *Nature Communications*, the researchers examined 106 mutations in the autism risk gene PTEN in five model systems: yeast, roundworms, fruit flies, rats and human cells. The team tested the functional impact of the mutations in a variety of ways, such as by examining larval development in fruit flies and the structure of neurons in rats.

Many of the mutations had harmful impacts, and these impacts tended to correlate across the different organisms. The correlations were especially strong in the case of mutations that weaken the protein's stability, suggesting that assessing protein stability might be a quick first test for spotting disruptive mutations. The team has since used its testing platform to study missense variants in another autism risk gene, SYNGAP1. As more genes go through this pipeline, the pool of individuals with autism who can receive a conclusive genetic explanation may greatly expand.

Rescuing plasticity. The autism-linked gene SHANK3 is essential to brain plasticity, according to a new study that illuminates the gene's role in enabling neurons to adjust to changes in sensory input. The study, led by SFARI Investigator Gina Turrigiano of Brandeis University, also found that the mood-stabilizing drug lithium mitigates repetitive behaviors and disruptions to brain plasticity in rats and mice missing SHANK3, which is mutated in about 1 percent of people with autism.

The researchers, who reported their findings in the June 3, 2020, issue of *Neuron*, disrupted SHANK3 expression in cultured rat neurons, and then temporarily blocked the neurons' ability to fire. Once the block was removed, the cells failed to return to their normal firing rate, suggesting they were unable to adapt to this change. Lithium restored the neurons' ability to adjust their firing rates.

The team next glued one eye shut in mice lacking SHANK3 and used multielectrode arrays to study their visual cortex. Neurons in the mutant mice decreased their firing rate more gradually than those in control mice, suggesting that they took longer to adjust to the decrease in visual input. And then, while neurons in the control mice compensated for the loss of vision and resumed firing after a couple of days, neurons in the mutant mice never returned to their original firing rates.

The mutant mice also groom themselves excessively, but this behavior was eliminated by lithium treatment. The findings imply that lithium may be useful for treating people with SHANK3 mutations. Although lithium is often poorly tolerated, understanding why it works may also open the door to better treatments.

Mutated motion. A machine learning algorithm that breaks down motion into discrete behavioral chunks can tell the difference between control mice and ones with a particular autism-linked mutation, a new study shows. The algorithm was able to identify hyperactivity in the mutated mice, and it also detected how a widely used autism drug affected their motion.

This research was also funded in part by the Simons Collaboration on the Global Brain (page 23).

The study, led by SFARI Investigator Sandeep Robert Datta of Harvard University, used MoSeq, an algorithm Datta and his team developed in 2015 to break down motion into discrete "syllables" without human assistance. The researchers, who published their findings on September 21, 2020, in *Nature Neuroscience*, examined the motion of mice with two mutated copies of the gene CNTNAP2. MoSeq identified 16 motion syllables that are different in these mice than in controls.

The drug risperidone, the team found, restored seven of these syllables to normal, and improved seven others. The researchers also examined the motion of control mice that were given one of 15 different drugs for depression, anxiety, [illegible] is able to [illegible] movements and other traits linked with autism.

[illegible] brain, a new genetic analysis of [illegible] most comprehensive view yet of the landscape of autism risk genes, identifying 102 genes strongly associated with autism, including 30 that had not been previously linked to the condition. The study — a large collaborative effort that involved SFARI Investigators Stephan Sanders and Matthew State of the University of California, San Francisco, Bernie Devlin of the University of Pittsburgh, Kathryn Roeder of Carnegie Mellon University, and Michael Talkowski of Harvard University, under the auspices of the Autism Sequencing Consortium — looked at the exomes (the protein-coding regions of the genome) of more than 35,000 individuals from the Simons Simplex Collection and other cohorts, making this the largest exome-sequencing autism study to date.

The researchers, who published their findings in *Cell* on February 6, 2020, applied an enhanced version of their previously developed statistical method, called TADA, to determine which gene variants are likely to be harmful. The 102 genes that emerged from this analysis tended to cluster in groups that affect gene expression or neuronal communication. In cells from the human cortex, the team found that the expression of these genes is enriched in both excitatory and inhibitory neurons starting in early development. Some lines of research have suggested that autism stems in part from an imbalance between excitatory and inhibitory signaling, and the new study indicates that there may be multiple biological pathways toward this imbalance.

Editing Angelman syndrome. Altering mouse DNA using CRISPR gene-editing technology can prevent many characteristics of the autism-related condition known as Angelman syndrome, researchers reported in *Nature* on October 21, 2020. The therapy's benefits lasted for the entire 17 months that the researchers monitored the mice, and may be lifelong.

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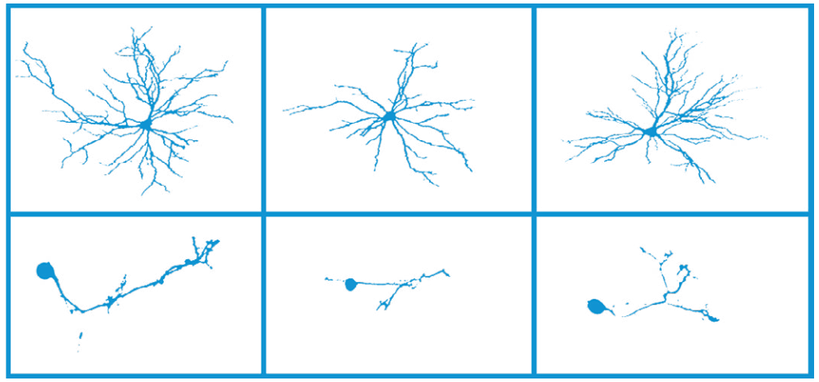
In February 2020, SFARI convened a two-day workshop to explore the possibility of gene therapies for autism spectrum disorder. Mark Zylka's work using the CRISPR gene-editing technology in a mouse model of Angelman syndrome proved an important topic during the event. "This workshop provided a terrific discussion about the challenges in developing targeted gene interventions and their potentially transformative effects as therapies," says SFARI interim director John Spiro. "SFARI looks forward to translating these discussions into focused funding decisions in the near future."

Read more about the workshop at **www.sfari.org/2020/06/24/sfari-workshop-explores-challenges-and-opportunities-of-gene-therapies-for-autism-spectrum-disorder/**

View more SFARI-funded research publications at **www.sfari.org/research/funded-publications**



Representative images of cultured hippocampal (top) and dorsal root ganglion (bottom) neurons expressing the GFP gene alone (left), or with WT-PTEN (middle) or PTEN-C124S (right). Credit: K.L. Post *et al.*/ *Nature Communications* 2020

New York Teachers Rally Spirits, Adapt Techniques During COVID-19 Pandemic

When the coronavirus arrived in New York City, Math for America (M*f*A) chemistry teacher Kimberly Dempsey did not waste any time. She immediately created a Google doc to teach her students about the pandemic, updating it daily with news stories about the virus and organizing the information into about two dozen categories from "Combating Misconceptions" to "Environmental Impact." By March, she had compiled enough information and data in the doc to design a slide deck that she also shared with her students. Dempsey then opened up both resources to her peers in the M*f*A fellowship program. The resources quickly became points of discussion on M*f*A's internal network, which allows more than 1,000 teachers to communicate from hundreds of schools. Soon Dempsey's work was being used in schools across the city.

"What I love about M*f*A is that we're a big community," says Dempsey, an M*f*A Master Teacher. "When you want to do something extra, you need people who will say 'This is awesome' rather than saying 'This is weird and impractical.' Making this resource is not going to help my students pass a test; it's not going to help me get a better rating from my administration. I appreciate the ability to find other teachers at M*f*A who are willing to step out of their comfort zones and expand what it means to be a teacher."

Founded in 2004, M*f*A supports and rewards extraordinary New York City STEM teachers like Dempsey with four-year fellowships. The fellows, who must have at least two years of classroom experience, receive a yearly stipend, the ability to apply for grants for national conferences and workshops, and, importantly, the opportunity to engage professionally with other expert teachers. Before the COVID-19 pandemic, more than 100 Master Teachers might have been at the M*f*A headquarters on any given night in various intensive workshops. When New York City went into lockdown and teachers moved to remote instruction, M*f*A continued its support by moving all its programming — M*f*A teacher-led workshops, workshops by outside experts and the organization's public lecture series — to remote platforms like Zoom.

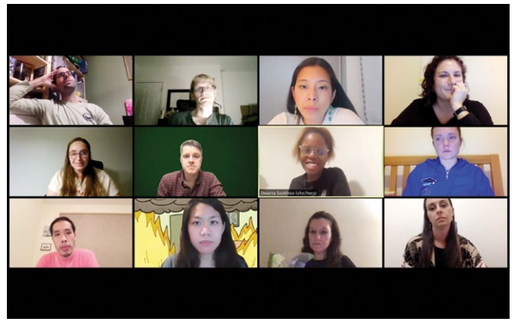
When New York City schools closed, Soni Midha, a 12th-grade math teacher, was in the middle of co-leading a four-session, in-person M*f*A workshop on how mathematics content builds upon itself from the sixth through 12th grades. With the help of M*f*A, she quickly moved the workshop online. "When we went virtual, we were apprehensive about doing the workshop remotely," says Midha, who has been teaching for 14 years and is in her third M*f*A Master Teacher fellowship. "But then we started and it was so nice to still have that community feel, even though we were online."

Moving M*f*A's public lecture series online benefited teachers, and there were even some silver linings that will change the way M*f*A hosts public talks in the future. In person, M*f*A's scientific and mathematics lectures usually reach capacity.

Math for America Master Teachers discuss how to develop challenge puzzles inspired by escape rooms to assess and extend mathematics and science content knowledge. The in-person meeting was held prior to the COVID-19 pandemic. Credit: Michael Lisnet for Math for America

After moving online, the organization found that they could reach a much larger audience and that it was easier to book distinguished speakers to give talks virtually. In December 2020, vaccinologist Florian Krammer of the Icahn School of Medicine at Mount Sinai gave a webinar on COVID-19 vaccines and how they work to over 300 M*f*A Master Teachers and the public, a scale usually impossible in person due to space limitations.

"Florian Krammer's talk gave teachers the chance to interact with a leading scientist around the most up-to-date information about COVID-19 and vaccine development," M*f*A president John Ewing says. "As with other M*f*A programming, teachers brought what they learned back to their schools to the benefit of their students and school communities. That helped many people across the city get crucial public health information at a time when it was needed most."



M*f*A Master Teachers meet virtually through Zoom to talk about how to infuse their teaching with antiracist practices, student-centered instruction and equitable opportunities for student voices to be heard. Virtual gatherings allowed Master Teachers to stay connected and share ideas during the pandemic.

M*f*A also made efforts to share what its teachers were learning about remote instruction with a wider audience. In July M*f*A hosted a virtual forum attended by about 80 M*f*A Master Teachers, who shared promising practices around how to best help all students to learn remotely. M*f*A then worked with specific teachers to produce practical and informational resources that could be disseminated by free download in a new, dedicated section of M*f*A's website addressing four areas: community, content, engagement and assessment.

"What stands out most about our remote teaching resources is that they are written by and for teachers," says M*f*A chief operating officer Michael Driskill. "This is what real classroom teachers are figuring out in their own classrooms. It is highly relevant to that practitioner audience."

"M*f*A responded to the pandemic by adapting our fellowship model and finding new ways to support teachers. We moved workshops to Zoom, redesigned courses and created space for teachers to share and address new teaching strategies," Driskill says. "We were initially worried that teachers would be too overwhelmed to participate, but the opposite turned out to be true — attendance has increased instead."

"All teachers have struggled a lot with remote instruction," says Laura Torres, a 15-year veteran chemistry teacher who joined M*f*A two years ago. "It's been so helpful to have people around you who are similar to you and are tackling the same fears and challenges as you."

Just as M*f*A creates an engaging, collaborative environment for Master Teachers to delve into topics from vaccine development and cutting-edge science research to equity in education and evaluation protocols, M*f*A Master Teachers painstakingly nurture learning communities for their students. Torres' own contribution to M*f*A's remote teaching materials centers on how she builds a welcoming and engaging online community for her students.

"We're very vulnerable when we're learning," Torres says. "Especially if you're a teenager, you may make a fool out of yourself, or you may not look good in front of other people. We have to be so aware of that and make sure that is not going to stop them. That's where it comes back to the community: Can I create a community where it is safe to not know something and to make some mistakes?"

"Professional community is more important than ever as teachers tackle the challenges of the global pandemic and remote teaching and learning," says Ewing. "At M*f*A we will continue to support outstanding teachers as they find their way forward."

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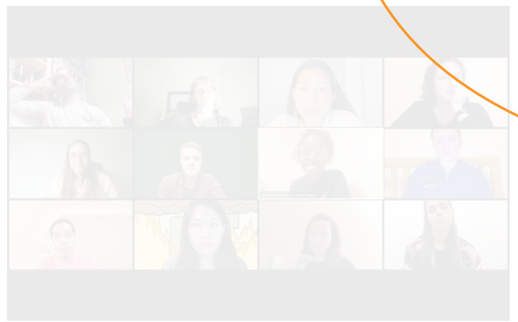

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Jim Simons launched Math for America in 2004. M*f*A is headquartered one block away from the Simons Foundation in New York City.

> "I think that now when we go back, we'll also have a new appreciation for what that community in the classroom really is, and how valuable it is, and how hard it is to replicate otherwise when we're away. Also, a really keen awareness of how different we are and how our different conditions at home really come with us to school. ... That awareness, I think, is going to be better than ever, and really help improve our teaching."
>
> **Laura Torres**

Watch the full video of Laura Torres at simonsfoundation.org/report2020

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> "Before the pandemic, Math for America did such a great job of providing professional development on tech tools that we didn't know we were going to need. ... I had already done workshops. I'd already done [professional learning teams] on the Desmos activity builders. I had already learned about things like Nearpod. And so when we started remote teaching, I already felt like I was prepared for it, and that was all due to Math for America."
>
> **Soni Midha**

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Prior to the COVID-19 pandemic, Math for America Master Teachers gathered for a workshop on the mastery-based learning approach. Credit: Michael Lisnet for Math for America

Sandbox Films Brings the Wonders and Mysteries of Real Science to Cinema

In 1492, a meteorite crashed into a field close to what is today the French town of Ensisheim, its ferocious descent visible and audible across the Rhineland and southwestern Switzerland. The stone was declared a wonder of God by advisers to the Habsburg ruler Maximillian, who saw it as a prophecy of military victory against the French. (He was right about the victory, as it turned out.)

The Ensisheim stone's impact pales in significance, though, to the destruction wrought by an asteroid that crashed into what is now the Yucatán Peninsula of Mexico 66 million years ago. It landed with such force that it extinguished an estimated three-quarters of all species on the planet, including all non-avian dinosaurs. And we continue to live in a cosmic shooting gallery, with an exceedingly low — but not zero! — risk that a large comet or asteroid could destroy the lives of millions of humans, and other life forms, in a single jolt.

Interesting stuff, right?

Sandbox Films thinks so, and is betting that almost everyone else will, too. An independent nonprofit film studio launched in 2020 by the Simons Foundation, the company has big plans to reinvent science documentary film so that audiences of all stripes will pack the houses and clamor for more ... science.

The above stories of meteors are just a few of the juicy chronicles from Sandbox Films' recent release, *Fireball: Visitors From Darker Worlds*. Co-directed by legendary filmmaker Werner Herzog and by Clive Oppenheimer of the University of Cambridge, *Fireball* tells the story of how meteorite impacts have shaped civilizations throughout history, and continue to do so today.

Sandbox Films is an offshoot of Science Sandbox, a grantmaking program of the Simons Foundation begun in 2015, whose mission is to "unlock scientific thinking by engaging

In the latest production by Sandbox Films, *Fireball: Visitors From Darker Worlds*, filmmakers Werner Herzog and Clive Oppenheimer visit the sites of ancient impacts, such as this crater in the Australian outback.

everyone with the process of science." In 2018, program director Greg Boustead, in addition to administering Science Sandbox's grants to outreach organizations, began experimenting with supporting science documentaries; a co-production with VICE Media led to the release of *The Most Unknown* on Netflix later that year. A couple more successful forays into support of independent filmmakers followed, and in 2020 Science Sandbox's film grantmaking efforts led to the birth of mission-driven documentary film company Sandbox Films.

"We have evolved into a full-fledged production company," says Boustead, now also founding director of Sandbox Films.

Sandbox Films seeks to nurture and launch top-grade science documentaries and is committed to supporting the science films — and the diverse voices — that people need to see and hear. The company makes grants to a few projects it identifies each year and later provides outright financing to bring projects to completion, usually in partnership with for-profit companies. Profit is not the central goal of Sandbox Films, but recouping equity from a project's success allows that capital to be reinvested into the next film, perhaps an even more forward-thinking one.

Early on, Boustead recruited Emmy-nominated science documentary filmmaker Jessica Harrop to lead development, production and strategy. Together the duo are off to a tremendous start, forming collaborations with production partners and filmmakers around the world with an eye to telling artful and inclusive stories about science. Sandbox Films wants nothing less than to redefine science documentaries, making them accessible and meaningful to all kinds of audiences, not just those whose interest in science is already assured. In other words, Sandbox Films is fundamentally about engagement, and about inspiration.

The still small company is off to an extremely promising start. Their films have premiered at festivals around the world, including Sundance, SXSW, Telluride, TIFF and CPH:DOX. And they have been distributed by Netflix, Apple Original Films, Neon, the BBC and PBS. The critical reception for *Fireball* has been positive. *Hollywood Reporter* critic Sheri Linden called the film an "elegant fusion of science and awe." Glenn Kenny, in *The New York Times*, proclaimed it "about as transportive as documentaries get."

"Both filmmaking and science are fueled by awe in pursuit of the unknown, of the inarticulable — of something that is dormant inside of us and dormant inside the physical world," says Herzog, who serves as founding adviser to the fledgling company. Herzog's expression of what unites cinema and science — that linchpin of "the unknown" — is what gives films about science such striking potential to attract audiences across cultures, races, education levels and socioeconomic status.

Oppenheimer, an expert on volcanoes, pitched the idea that became *Fireball* to Herzog, who then discussed it with Boustead. The two quickly realized that it was right up Sandbox Films' alley. Sandbox Films signed onto the project, providing partial financing and co-producing the documentary with Spring Films and Werner Herzog Filmproduktion. Later, Apple Original Films acquired the title and released it worldwide in fall 2020 on Apple TV+.

Herzog and Oppenheimer embarked on a filmmaking journey that spanned the globe. In less than 100 minutes, we visit a Day of the Dead procession in the Yucatán Peninsula, the site of the asteroid hit 66 million years ago; travel along the vast icy depths of Antarctica, where many meteorites' remains are still undiscovered; and meet leaders and artists from indigenous communities in Australia, which have incorporated meteors and impact craters into their understanding of the cosmos and eternity. We also come along on expeditions to collect urban micrometeorites in Norway, observe NASA's ongoing surveillance of the skies for threatening asteroids, and even stop by the pope's summer residence to meet the man dubbed 'the pope's astronomer,' whose thinking spans from the intimacy of the human soul to the immensity of the cosmos. By the film's end, we have been to five continents.

The crew who traveled with Herzog, some of them half his age, were stunned by his stamina and drive and his passion for film. Boustead recalls that one night the crew was getting ready to sleep in the Australian desert, and they were short of tents. Herzog allocated the tents that were available to protecting the valuable camera equipment from sand gusts. After all, it's great fun to sleep in the open air anyway!

Near the beginning of the film, Oppenheimer — *Fireball*'s host and co-director — meets Australian aboriginal artist Katie Darkie, whose vivid paintings reflect the ancestral meanings of the desert landscape. She lives near a kilometer-wide crater formed around 120,000 years ago by a battleship-sized asteroid, which vaporized almost completely upon impact. But this is the scientific version of events. "Some say it's a star fell in there," Darkie says. "But the ancestors and the old people were telling us it's the rainbow serpent who fell in the crater. So that's how we got three stories."

"Meteorites have to do with mythologies in human cultures and strange beliefs and premonitions and, of course, deep questions," Herzog says. "How is the universe formed? Could meteorites even carry the building blocks of life within them?"

These and related questions are, of course, the hefty ones that keep us all up at night: no science degree required. How did the universe begin? Why are we here? And why did this comet come? Is it a warning? A message from the divine? Sandbox Films is hoping to tap into exactly that universality to draw everyone in — closer to science and closer together — as we all wrestle with big questions that are ultimately ... science. As science historian Simon Schaffer cannily observes in *Fireball*, "Meteorites have meaning, and the task of humanity is to interpret what that meaning is."

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Sandbox Films is an offshoot of Science Sandbox, a grantmaking program of the Simons Foundation begun in 2015, whose mission is to "unlock scientific thinking by engaging

In the latest production by Sandbox Films, *Fireball: Visitors From Darker Worlds*, filmmakers Werner Herzog and Clive Oppenheimer visit the sites of ancient impacts, such as this crater in the Australian outback.

everyone with the process of science." In 2018, program director Greg Boustead, in addition to administering Science Sandbox's grants to outreach organizations, began experimenting with supporting science documentaries; a co-production with VICE Media led to the release of *The Most Unknown* on Netflix later that year. A couple more successful forays into support of independent filmmakers followed, and in 2020 Science Sandbox's film grantmaking efforts led to the birth of mission-driven documentary film company Sandbox Films.

"We have evolved into a full-fledged production company," says Boustead, now also founding director of Sandbox Films.

Sandbox Films seeks to nurture and launch top-grade science documentaries and is committed to supporting the science films — and the diverse voices — that people need to see and hear. The company makes grants to a few projects it identifies each year and later provides outright financing to bring projects to completion, usually in partnership with for-profit companies. Profit is not the central goal of Sandbox Films, but recouping equity from a project's success allows that capital to be reinvested into the next film, perhaps an even more forward-thinking one.

Early on, Boustead recruited Emmy-nominated science documentary filmmaker Jessica Harrop to lead development, production and strategy. Together the duo are off to a tremendous start, forming collaborations with production partners and filmmakers around the world with an eye to telling artful and inclusive stories about science. Sandbox Films wants nothing less than to redefine science documentaries, making them accessible and meaningful to all kinds of audiences, not just those whose interest in science is already assured. In other words, Sandbox Films is fundamentally about engagement, and about inspiration.

In 2016, the International Astronomical Union named an asteroid after Jim Simons (6618 Jimsimons). Marilyn Simons also has an asteroid named after her, 10701 Marilynsimons.

Werner Herzog is a founding adviser of Sandbox Films and contributed to Sandbox Films' first production, *The Most Unknown*.

The Simons Collaboration on the Origins of Life is investigating craters as possible birthplaces of life on Earth.

"Both filmmaking and science are fueled by awe in pursuit of the unknown, of the inarticulable — of something that is dormant inside of us and dormant inside the physical world," says Herzog, who serves as founding adviser to the fledgling company. Herzog's expression of what unites cinema and science — that linchpin of "the unknown" — is what gives films about science such striking potential to attract audiences across cultures, races, education levels and socioeconomic status.

Oppenheimer, an expert on volcanoes, pitched the idea that became *Fireball* to Herzog, who then discussed it with Boustead. The two quickly realized that it was right up Sandbox Films' alley. Sandbox Films signed onto the project, providing partial financing and co-producing the documentary with Spring Films and Werner Herzog Filmproduktion. Later, Apple Original Films acquired the title and released it worldwide in fall 2020 on Apple TV+.

Herzog and Oppenheimer embarked on a filmmaking journey that spanned the globe. In less than 100 minutes, we visit a Day of the Dead procession in the Yucatán Peninsula, the site of the asteroid hit 66 million years ago; travel along the vast icy depths of Antarctica, where many meteorites' remains are still undiscovered; and meet leaders and artists from indigenous communities in Australia, which have incorporated meteors and impact craters into their understanding of the cosmos and eternity. We also come along on expeditions to collect urban micrometeorites in Norway, observe NASA's ongoing surveillance of the skies for threatening asteroids, and even stop by the pope's summer residence to meet the man dubbed 'the pope's astronomer,' whose thinking spans from the intimacy of the human soul to the immensity of the cosmos. By the film's end, we have been to five continents.

The crew who traveled with Herzog, some of them half his age, were stunned by his stamina and drive and his passion for film. Boustead recalls that one night the crew was getting ready to sleep in the Australian desert, and they were short of tents. Herzog allocated the tents that were available to protecting the valuable camera equipment from sand gusts. After all, it's great fun to sleep in the open air anyway!

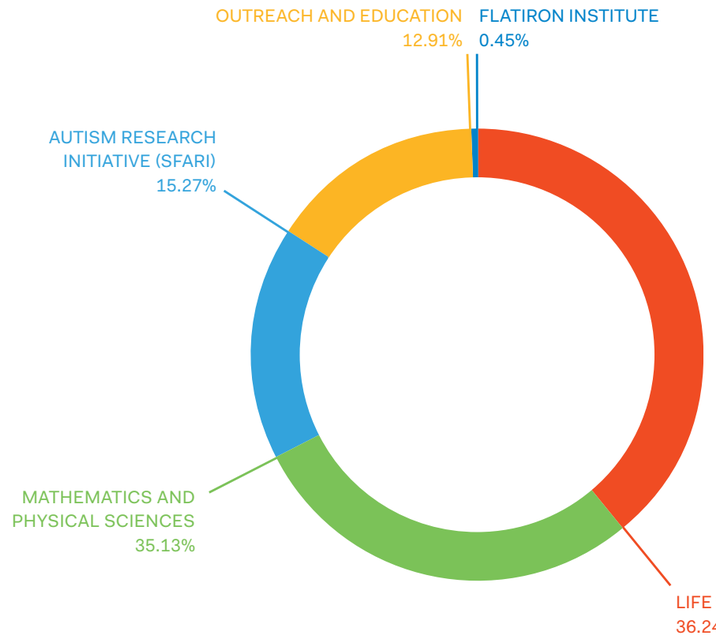
Near the beginning of the film, Oppenheimer — *Fireball*'s host and co-director — meets Australian aboriginal artist Katie Darkie, whose vivid paintings reflect the ancestral meanings of the desert landscape. She lives near a kilometer-wide crater formed around 120,000 years ago by a battleship-sized asteroid which vaporized almost completely upon impact. But this is the scientific version of events. "Some say it's a star fell in there," Darkie says. "But the ancestors and the old people were telling us it's the rainbow serpent who fell in the crater. So that's how we got three stories."

> "Both filmmaking and science are fueled by awe in pursuit of the unknown, of the inarticulable — of something that is dormant inside of us and dormant inside the physical world."
>
> Werner Herzog

Fireball features Paul Steinhardt, a 2012 Simons fellow in theoretical physics and the recipient of a 2019 targeted grant from the Simons Foundation's Mathematics and Physical Sciences division. Steinhardt co-discovered the first known natural quasicrystals in a meteorite found in eastern Russia.

Financials

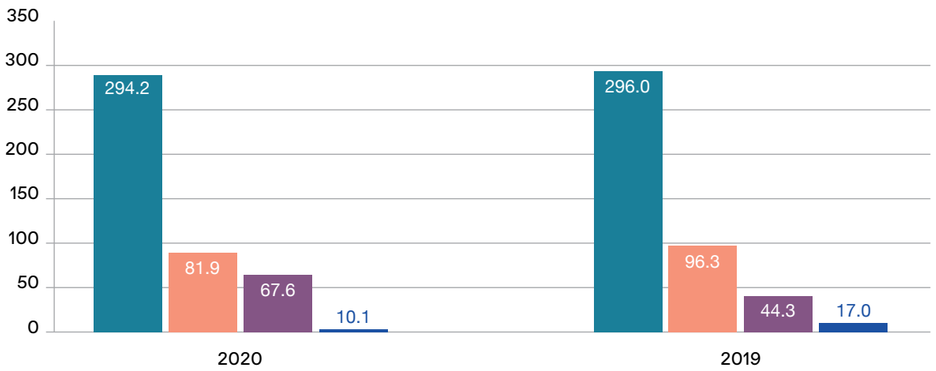
2020 GRANT PAYMENTS BY CATEGORY



PROPORTIONS OF EXPENSES

(CASH BASIS, $'S IN MILLIONS)

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



BALANCE SHEET

(UNAUDITED, IN $)

ASSETS	As of 12/31/20	As of 12/31/19
Cash and Cash Equivalents	111,229,686	151,891,664
Investments	3,696,277,248	3,427,506,267
Property and Equipment, Net	503,455,245	417,989,136
Prepaid Expenses and Other	13,870,166	20,177,353
Total Assets	**4,324,832,345**	**4,017,564,420**
LIABILITIES		
Accounts Payable	5,311,932	24,624,706
Grants Payable	655,524,912	541,966,747
Mortgage and Lease Liabilities	344,069,407	265,080,200
Deferred Excise Tax Liability	15,879,742	15,879,742
Total	**1,020,785,993**	**847,551,395**
NET ASSETS		
Beginning Net Assets	3,170,013,025	2,851,378,253
Current Year Change in Net Assets	134,033,327	318,634,772
Total	**3,304,046,352**	**3,170,013,025**
Total Liabilities and Net Assets	**4,324,832,345**	**4,017,564,420**

INCOME STATEMENT

(UNAUDITED, IN $)

REVENUE	For the Year Ended 12/31/20	For the Year Ended 12/31/19
Contributions	-	120,000,000
Investment Income	718,901,935	685,775,651
Rental Income	3,983,672	-
Total	**722,885,607**	**805,775,651**
EXPENSES		
Program	527,959,943	446,040,800
Management and General	60,892,337	41,100,079
Total	**588,852,280**	**487,140,879**
Change in Net Assets	**134,033,327**	**318,634,772**

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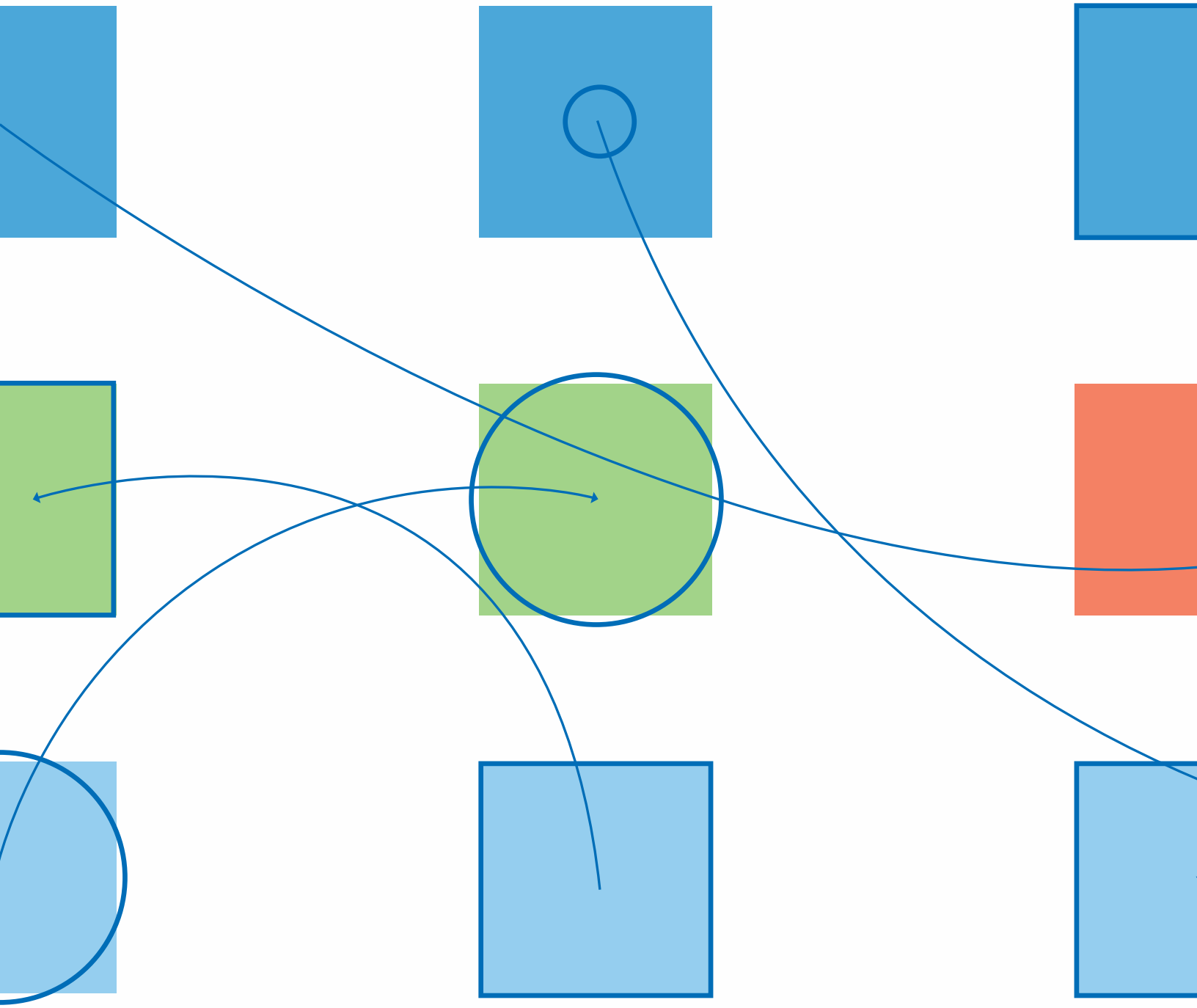

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