

# Nanoparticles Treatment for COVID-19

*Northeastern chemical engineer Thomas Webster, who specializes in developing nano-scale medicine and technology to treat diseases, is part of a contingency of scientists that are contributing ideas and technology to the Centers for Disease Control and Prevention to fight the COVID-19 outbreak. [41]*

*According to the Centers for Disease Control and Prevention, common human coronaviruses usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. [40]*

*When diseases reinforce each other, they rapidly accelerate through the population, then fizzle out as they run out of new hosts. [39]*

*It's no coincidence that some of the worst viral disease outbreaks in recent years—SARS, MERS, Ebola, Marburg and likely the newly arrived 2019-nCoV virus—originated in bats. [38]*

*An interdisciplinary team of researchers at Colorado State University has used computational chemistry, biochemistry and virology to uncover new information on how viruses such as West Nile, dengue and Zika replicate. [37]*

*David Baker, Professor of Biochemistry and Director of the Institute for Protein Design at the University of Washington will speak about how algorithmic processes such as de novo design predict protein structures, protein folding mechanisms, and new protein functions. [36]*

*A research team at Kobe University has developed a method of artificially controlling the anchorage position of target proteins in engineered baker's yeast (*Saccharomyces cerevisiae*). [35]*

*Scientists have found a new way to home in on the proteins covering a particular cell's surface. The feat offers insight into how brain cells form intricate networks during development. [34]*

*In a recent report, Mengke Yang and colleagues at the Brain Research Instrument Innovation Center, Institute of Neuroscience, Center for Systems Neuroscience and Optical System Advanced Manufacturing Technology in China, Germany and the U.K. developed a new technique named the multiarea two-photon real-time in vitro explorer (MATRIEX). [33]*

*Measuring optical blood flow in the resting human brain to detect spontaneous activity has for the first time been demonstrated by Wright State University imaging researchers, holding out promise for a better way to study people with autism, Alzheimer's and depression. [32]*

*UCLA biologists report they have transferred a memory from one marine snail to another, creating an artificial memory, by injecting RNA from one to another. [31]*

*Scientists at the Wellcome Trust/ Cancer Research UK Gurdon Institute, University of Cambridge, have identified a new type of stem cell in the brain which they say has a high potential for repair following brain injury or disease. [30]*

*A team of researchers working at the Weizmann Institute of Science has found that organoids can be used to better understand how the human brain wrinkles as it develops. [29]*

*A team of biologists has found an unexpected source for the brain's development, a finding that offers new insights into the building of the nervous system. [28]*

*Researchers discover both the structure of specific brain areas and memory are linked to genetic activity that also play important roles in immune system function. [27]*

*The inner workings of the human brain have always been a subject of great interest. Unfortunately, it is fairly difficult to view brain structures or intricate tissues due to the fact that the skull is not transparent by design. [26]*

*But now there is a technology that enables us to "read the mind" with growing accuracy: functional magnetic resonance imaging (fMRI). [25]*

*Advances in microscopy techniques have often triggered important discoveries in the field of neuroscience, enabling vital insights in understanding the brain and promising new treatments for neurodegenerative diseases such as Alzheimer's and Parkinson's. [24]*

*What is the relationship of consciousness to the neurological activity of the brain? Does the brain behave differently when a person is fully conscious, when they are asleep, or when they are undergoing an epileptic seizure? [23]*

*Consciousness appears to arise naturally as a result of a brain maximizing its information content. So says a group of scientists in Canada and France, which has studied how the electrical activity in people's brains varies according to individuals' conscious states. The researchers find that normal waking states are associated with maximum values of what they call a brain's "entropy". [22]*

*New research published in the New Journal of Physics tries to decompose the structural layers of the cortical network to different hierarchies enabling to identify the network's nucleus, from which our consciousness could emerge. [21]*

*Where in your brain do you exist? Is your awareness of the world around you and of yourself as an individual the result of specific, focused changes in your brain, or does that awareness come from a broad network of neural activity? How does your brain produce awareness? [20]*

*In the future, level-tuned neurons may help enable neuromorphic computing systems to perform tasks that traditional computers cannot, such as learning from their environment, pattern recognition, and knowledge extraction from big data sources. [19]*

*IBM scientists have created randomly spiking neurons using phase-change materials to store and process data. This demonstration marks a significant step forward in the development of energy-efficient, ultra-dense integrated neuromorphic technologies for applications in cognitive computing. [18]*

*An ion trap with four segmented blade electrodes used to trap a linear chain of atomic ions for quantum information processing. Each ion is addressed optically for individual control and readout using the high optical access of the trap. [17]*

*To date, researchers have realised qubits in the form of individual electrons ([aktuell.ruhr-uni-bochum.de/pm2012/pm00090.html.en](http://aktuell.ruhr-uni-bochum.de/pm2012/pm00090.html.en)). However, this led to interferences and rendered the information carriers difficult to programme and read. The group has solved this problem by utilising electron holes as qubits, rather than electrons. [16]*

*Physicists from MIPT and the Russian Quantum Center have developed an easier method to create a universal quantum computer using multilevel quantum systems (qudits), each one of which is able to work with multiple "conventional" quantum elements – qubits. [15]*

*Precise atom implants in silicon provide a first step toward practical quantum computers. [14]*

*A method to produce significant amounts of semiconducting nanoparticles for light-emitting displays, sensors, solar panels and biomedical applications has gained momentum with a demonstration by researchers at the Department of Energy's Oak Ridge National Laboratory. [13]*

*A source of single photons that meets three important criteria for use in quantum-information systems has been unveiled in China by an international team of physicists. Based on a quantum dot, the device is an efficient source of photons that emerge as solo particles that are indistinguishable from each other. The researchers are now trying to use the source to create a quantum computer based on "boson sampling". [11]*

*With the help of a semiconductor quantum dot, physicists at the University of Basel have developed a new type of light source that emits single photons. For the first time, the researchers have managed to create a stream of identical photons. [10]*

*Optical photons would be ideal carriers to transfer quantum information over large distances. Researchers envisage a network where information is processed in certain nodes and transferred between them via photons. [9]*

*While physicists are continually looking for ways to unify the theory of relativity, which describes large-scale phenomena, with quantum theory, which describes small-scale phenomena, computer scientists are searching for technologies to build the quantum computer using Quantum Information.*

*In August 2013, the achievement of "fully deterministic" quantum teleportation, using a hybrid technique, was reported. On 29 May 2014, scientists announced a reliable way of transferring data by quantum teleportation. Quantum teleportation of data had been done before but with highly unreliable methods.*

*The accelerating electrons explain not only the Maxwell Equations and the Special Relativity, but the Heisenberg Uncertainty Relation, the Wave-Particle Duality and the electron's spin also, building the Bridge between the Classical and Quantum Theories.*

*The Planck Distribution Law of the electromagnetic oscillators explains the electron/proton mass rate and the Weak and Strong Interactions by the diffraction patterns. The Weak Interaction changes the diffraction patterns by moving the electric charge from one side to the other side of the diffraction pattern, which violates the CP and Time reversal symmetry.*

*The diffraction patterns and the locality of the self-maintaining electromagnetic potential explains also the Quantum Entanglement, giving it as a natural part of the Relativistic Quantum Theory and making possible to build the Quantum Computer with the help of Quantum Information.*

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Author: George Rajna

## Preface

Where in your brain do you exist? Is your awareness of the world around you and of yourself as an individual the result of specific, focused changes in your brain, or does that awareness come from a broad network of neural activity? How does your brain produce awareness? [20]

While physicists are continually looking for ways to unify the theory of relativity, which describes large-scale phenomena, with quantum theory, which describes small-scale phenomena, computer scientists are searching for technologies to build the quantum computer.

Australian engineers detect in real-time the quantum spin properties of a pair of atoms inside a silicon chip, and disclose new method to perform quantum logic operations between two atoms. [5] Quantum entanglement is a physical phenomenon that occurs when pairs or groups of particles are generated or interact in ways such that the quantum state of each particle cannot be described independently – instead, a quantum state may be given for the system as a whole. [4]

I think that we have a simple bridge between the classical and quantum mechanics by understanding the Heisenberg Uncertainty Relations. It makes clear that the particles are not point like but have a  $dx$  and  $dp$  uncertainty.

## Here's how nanoparticles could help us get closer to a treatment for COVID-19

There is no vaccine or specific treatment for COVID-19, the disease caused by the severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2.

Since the outbreak began in late 2019, researchers have been racing to learn more about SARS-CoV-2, which is a strain from a family of viruses known as coronavirus for their crown-like shape.

Northeastern chemical engineer Thomas Webster, who specializes in developing nano-scale medicine and technology to treat diseases, is part of a contingency of scientists that are contributing ideas and technology to the Centers for Disease Control and Prevention to fight the COVID-19 outbreak.

The idea of using [nanoparticles](#), Webster says, is that the [virus](#) behind COVID-19 consists of a structure of a similar scale as his nanoparticles. At that scale, matter is ultra-small, about ten thousand times smaller than the width of a single strand of hair.

Webster is proposing particles of similar sizes that could attach to SARS-CoV-2 viruses, disrupting their structure with a combination of infrared light treatment. That structural change would then halt the ability of the virus to survive and reproduce in the body.

"You have to think in this size range," says Webster, Art Zafiropoulo Chair of chemical engineering at Northeastern. "In the nanoscale size range, if you want to detect viruses, if you want to deactivate them."

Finding and neutralizing viruses with nanomedicine is at the core of what Webster and other researchers call theranostics, which focuses on combining therapy and diagnosis. Using that approach, his lab has specialized in nanoparticles to fight the microbes that cause influenza and tuberculosis.

"It's not just having one approach to detect whether you have a virus and another approach to use it as a therapy," he says, "but having the same particle, the same approach, for both your detection and therapy."

SARS-CoV-2 spreads mostly through tiny droplets of viral particles—from breathing, talking, sneezing, coughing—that enter the body through the eyes, mouth, or nose. Preliminary research also suggests that those germs may survive for days when they attach themselves to countertops, handrails, and other hard surfaces.

That's one reason to make theranostics with nanoparticles the focus of the COVID-19 outbreak, Webster says.

Nanoparticles can disable these pathogens even before they break into the body, as they hold on to different objects and surfaces. His lab has developed materials that can be sprayed on objects to form nanoparticles and attack viruses.

"Even if it was on a surface, on someone's countertop, or an iPhone," he says. "It doesn't mean anything because it's not the active form of that virus."



That same technology can be fine-tuned and tweaked to target a wide range of viruses, bacteria, and other pathogens. Unlike other novel drugs with large molecular structures, nanoparticles are so small that they can move through our body without disrupting other functions, such as those of the immune system.

"Almost like a surveyor, they can go around your bloodstream," Webster says. "They can survey your body much easier and under much longer times and try and detect viruses."

To do all that, the CDC needs to know the specifics about what kind of structure is needed to neutralize SARS-CoV-2, Webster says. That information isn't public yet.

"You have to identify what we need to put in our nanoparticle to attract it to that virus," he says. "The CDC must know that, because they've developed a kit that can determine if you have [COVID-19], versus influenza, or something else."

An alternative to nanomedicine is producing synthetic molecules. But Webster says that tactic presents some challenges. In the case of chemotherapies used to treat cancer cells, such synthetic drugs can cause severe side effects that kill cancer cells, as well as other cells in the body.

"The same thing could be happening with synthetic chemistry to treat a virus, where molecules are killing a lot more than just that virus," Webster says.

Still, Webster acknowledges that there aren't many researchers focusing on nanoparticles to kill viruses.

One of the main reasons for the lack of those solutions is that the same benefits that make nanoparticles ideal to fight infectious diseases also make them a concern for the U.S. Federal Drug Administration.

Because of their size, nanoparticles are pervasive (too pervasive, maybe) to seep through other parts of the body. To reduce that risk, Webster's lab has focused on using [iron oxide](#). Particles of that make up entail chemistry that is already natural to our bodies and diets.

"Even if you have a viral infection, you need more iron, because you could be anemic depending on how bad the infection is," Webster says. "We're actually developing these nanoparticles out of chemistries that can help your health."

And, he says, iron-based nanoparticles could be directed with magnetic fields to target specific organs in the [body](#), such as lungs and other areas susceptible to respiratory complications after contracting [viral infections](#). That too, Webster says, is something that you couldn't do with a novel synthetic molecule.

"Really, what this all means is that we just have to do the studies to show those iron nanoparticles are not going into the brain or the kidney," Webster says, "that these nanoparticles are going exactly where you want them to go to the virus." [41]

## **Coronavirus: Domestic livestock strains are commonplace**

Many people are hearing about coronavirus for the first time as COVID-19 affecting humans causes concern all across the world. But coronaviruses are not new to livestock and poultry producers, according to a Texas A&M AgriLife veterinary epidemiologist.

According to the Centers for Disease Control and Prevention, common human coronaviruses usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. Most people get infected with one or more of these viruses at some point in their lives.

But the CDC is now responding to an outbreak of respiratory [disease](#) caused by a novel or new coronavirus that was first detected in Wuhan City, Hubei Province, China.

"Coronavirus is a common virus in livestock herds and poultry flocks seen routinely worldwide," said Heather Simmons, DVM, Institute for Infectious Animal Diseases, IIAD, associate director as well as Texas A&M AgriLife Extension Service's associate department head and extension program leader for Veterinary Medical Extension. IIAD is a member of the Texas A&M University System and Texas A&M AgriLife Research.

## **Wildlife in China may be human strain carriers**

"In wildlife, bats are known to carry over 100 different strains of coronavirus, and wild civets are the source of the coronavirus that causes SARS (Severe Acute Respiratory Syndrome), first reported in China in 2002-2003," Simmons said. "Although our understanding is still limited, wild pangolins (a scaly anteater) sold at live markets may be associated with the recently reported coronavirus outbreak in China."

Bats, civets and pangolins are all commonly sold at live markets in China, she said. Coronaviruses from wildlife are dangerous since they have the potential to mutate, adapt and spill over to new species, including humans.

"That is the concern now, this new strain of coronavirus has emerged to cause disease in humans," Simmons said. "It is important to create an understanding of the difference between coronaviruses occurring in domestic livestock and poultry compared to coronaviruses that spill over from wildlife to humans."

## **Coronavirus in domestic livestock doesn't jump to humans**

Simmons said, to date, the coronaviruses in livestock are not considered reportable diseases because their main effect is as an economic burden to livestock producers.

They are known to occur worldwide annually, with some of the most common coronaviruses found in production animals to include the scours and winter dysentery in beef and dairy cattle, porcine respiratory coronavirus in swine and avian infectious bronchitis in poultry.

The World Health Organization has reported that while another coronavirus, MERS-CoV, is known to be transmitted from dromedary camels to humans, other coronaviruses circulating in domestic animals have not yet infected humans.

"That's what is very important to understand at this time," Simmons said. "We have been dealing with these diseases for a long time but as of yet, we have not seen cases worldwide transmitted from livestock to humans or vice versa."

### **What does coronavirus look like in livestock?**

While coronaviruses have a high morbidity, or rate of illness, in livestock and poultry they are generally considered to have low mortality, rate of death, Simmons said. Coronaviruses will affect either the respiratory system or the gastrointestinal system, depending on the species and the age of the animal.

### **Coronavirus in cattle**

In calves, diarrhea commonly occurs in animals under three weeks of age due to a lack of obtaining antibodies when the calf does not get enough colostrum from the mother in order to build up immunity. Clinical signs include severe dehydration and diarrhea. The severity of the [clinical signs](#) depends on the age of the calf and their immune status. This is often seen by producers in the winter months as the virus is more stable in cold weather. The second clinical syndrome, winter dysentery is found in adult cattle. Clinical signs include bloody diarrhea with decreased milk production, loss of appetite with some respiratory signs. Bovine coronaviruses can also cause mild respiratory disease or pneumonia in calves up to six months. The virus is shed in the environment through nasal secretions and through feces.

### **Coronavirus in swine**

There are multiple coronaviruses that affect swine. Like cattle, they affect the respiratory or gastrointestinal tract. In sows and piglets, porcine respiratory coronavirus usually presents with no clinical signs. If clinical signs do occur, it may be a transient cough within the herd and spread of this disease occurs through aerosolized methods.

### **Coronavirus in poultry**

Infectious bronchitis virus, or IBV, is a rapidly spreading respiratory disease in young chicks. Clinical signs in laying hens include reduced production, eggshell abnormalities and decreased internal egg quality.

### **How to treat**

Livestock producers should consult with a veterinarian for treatment, Simmons said. Treatment in [livestock](#) herds and poultry flocks typically includes supportive therapy of fluids. Antibiotics are not indicated for viral infections but may be used if a secondary bacterial infection occurs.

More information can be found through the [Texas A&M AgriLife Extension Disaster Education Network](#). [40]

## When coronavirus is not alone: Team of complexity scientists present 'meme' model for multiple diseases

Interacting contagious diseases like influenza and pneumonia follow the same complex spreading patterns as social trends. This new finding, published in *Nature Physics*, could lead to better tracking and intervention when multiple diseases spread through a population at the same time.

"The interplay of diseases is the norm rather than the exception," says Laurent Hébert-Dufresne, a complexity scientist at the University of Vermont who co-led the new research. "And yet when we model them, it's almost always one [disease](#) in isolation."

When disease modelers map an epidemic like coronavirus, Ebola, or the flu, they traditionally treat them as isolated pathogens. Under these so-called "simple" dynamics, it's generally accepted that the forecasted size of the epidemic will be proportional to the rate of transmission.

But according to Hébert-Dufresne, professor of computer science at University of Vermont, and his co-authors, Samuel Scarpino at Northeastern University, and Jean-Gabriel Young at the University of Michigan, the presence of even one more contagion in the population can dramatically shift the dynamics from simple to complex. Once this shift occurs, microscopic changes in the transmission rate trigger macroscopic jumps in the expected epidemic size—a spreading pattern that [social scientists](#) have observed in the adoption of innovative technologies, slang, and other contagious social behaviors.

### Star Wars and sneezing

The researchers first began to compare biological contagions and social contagions in 2015 at the Santa Fe Institute, a transdisciplinary research center where Hébert-Dufresne was modeling how social trends propagate through reinforcement. The classic example of social reinforcement, according to Hébert-Dufresne, is "the phenomenon through which ten friends telling you to go see the new Star Wars movie is different from one friend telling you the same thing ten times."

Like multiple friends reinforcing a social behavior, the presence of multiple diseases makes an infection more contagious than it would be on its own. Biological diseases can reinforce each other through symptoms, as in the case of a sneezing virus that helps to spread a second infection like pneumonia. Or, one disease can weaken the host's immune system, making the population more susceptible to a second, third, or additional contagion.

When diseases reinforce each other, they rapidly accelerate through the population, then fizzle out as they run out of new hosts. According to the researchers' model, the same super-exponential pattern characterizes the spread of social trends, like viral videos, which are widely shared and then cease to be relevant after a critical mass of people have viewed them.

### Dengue and antivaxxers

A second important finding is that the same complex patterns that arise for interacting diseases also arise when a biological contagion interacts with a social [contagion](#), as in the example of a virus spreading in conjunction with an anti-vaccination campaign. The paper details a 2005 Dengue outbreak in Puerto Rico, and Hébert-Dufresne cites an additional example of a 2017 Dengue

outbreak in Puerto Rico where failure to accurately account for the interplay of Dengue strains reduced the effectiveness of a Dengue vaccine. This in turn sparked an anti-vaccination movement—a social epidemic—that ultimately led to the resurgence of measles—a second biological epidemic. It's a classic example of real-world complexity, where unintended consequences emerge from many interacting phenomena.

Although it is fascinating to observe a universal spreading pattern across complex social and biological systems, Hébert-Dufresne notes that it also presents a unique challenge. "Looking at the data alone, we could observe this complex pattern and not know whether a deadly epidemic was being reinforced by a virus, or by a social phenomenon, or some combination."

"We hope this will open the door for more exciting models that capture the dynamics of multiple contagions," he says. "Our work shows that it is time for the disease modeling community to move beyond looking at contagions individually."

And the new study may shed light on the spread of coronavirus. "When making predictions, such as for the current coronavirus outbreak occurring in a flu season, it becomes important to know which cases have multiple infections and which patients are in the hospital with flu—but scared because of coronavirus," Hébert-Dufresne says. "The interactions can be biological or social in nature, but they all matter." [39]

## **Coronavirus outbreak raises question: Why are bat viruses so deadly?**

It's no coincidence that some of the worst viral disease outbreaks in recent years—SARS, MERS, Ebola, Marburg and likely the newly arrived 2019-nCoV virus—originated in bats.

A new University of California, Berkeley, study finds that bats' fierce immune response to viruses could drive viruses to replicate faster, so that when they jump to mammals with average immune systems, such as humans, the viruses wreak deadly havoc.

Some bats—including those known to be the original source of human infections—have been shown to host immune systems that are perpetually primed to mount defenses against viruses. Viral infection in these bats leads to a swift response that walls the virus out of cells. While this may protect the bats from getting infected with high viral loads, it encourages these viruses to reproduce more quickly within a host before a defense can be mounted.

This makes bats a unique reservoir of rapidly reproducing and highly transmissible viruses. While the bats can tolerate viruses like these, when these bat viruses then move into animals that lack a fast-response immune system, the viruses quickly overwhelm their new hosts, leading to high fatality rates.

"Some bats are able to mount this robust antiviral response, but also balance it with an anti-inflammation response," said Cara Brook, a postdoctoral Miller Fellow at UC Berkeley and the first author of the study. "Our [immune system](#) would generate widespread inflammation if attempting this same antiviral strategy. But bats appear uniquely suited to avoiding the threat of immunopathology."

The researchers note that disrupting bat habitat appears to stress the animals and makes them shed even more virus in their saliva, urine and feces that can infect other animals.



The Egyptian fruit bat, *Rousettus aegyptiacus*, is a host to the Marburg virus, which can infect monkeys and cross over into humans to cause a deadly hemorrhagic fever. Credit: Victor Corman

"Heightened environmental threats to bats may add to the threat of zoonosis," said Brook, who works with a bat monitoring program funded by DARPA (the U.S. Defense Advanced Research Projects Agency) that is currently underway in Madagascar, Bangladesh, Ghana and Australia. The project, Bat One Health, explores the link between loss of bat habitat and the spillover of bat viruses into other animals and humans.

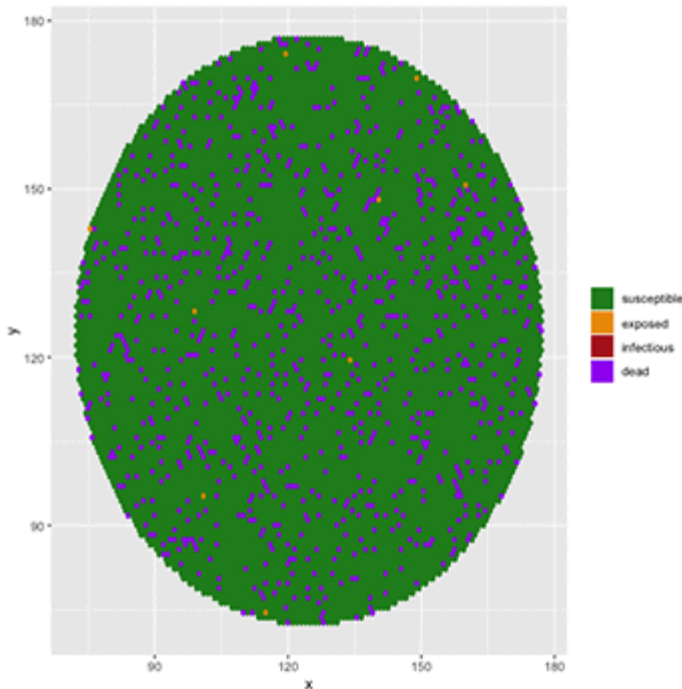
"The bottom line is that bats are potentially special when it comes to hosting viruses," said Mike Boots, a disease ecologist and UC Berkeley professor of integrative biology. "It is not random that a lot of these viruses are coming from bats. Bats are not even that closely related to us, so we would not expect them to host many human viruses. But this work demonstrates how bat immune systems could drive the virulence that overcomes this."

The new study by Brook, Boots and their colleagues was published this month in the journal *eLife*.

Boots and UC Berkeley colleague Wayne Getz are among 23 Chinese and American co-authors of a paper published last week in the journal *EcoHealth* that argues for better collaboration between U.S. and Chinese scientists who are focused on disease ecology and emerging infections.

### **Vigorous flight leads to longer lifespan—and perhaps viral tolerance**

As the only flying mammal, bats elevate their metabolic rates in flight to a level that doubles that achieved by similarly sized rodents when running.



As shown in this model of viral infection, when green monkey (Vero) cells are invaded by a virus, they quickly succumb because they have no interferon response. Susceptible cells (green pixels) are rapidly exposed, infected and killed (purple). Credit: UC Berkeley images by Cara Brook

Generally, vigorous physical activity and high metabolic rates lead to higher tissue damage due to an accumulation of reactive molecules, primarily free radicals. But to enable flight, bats seem to have developed physiological mechanisms to efficiently mop up these destructive molecules.

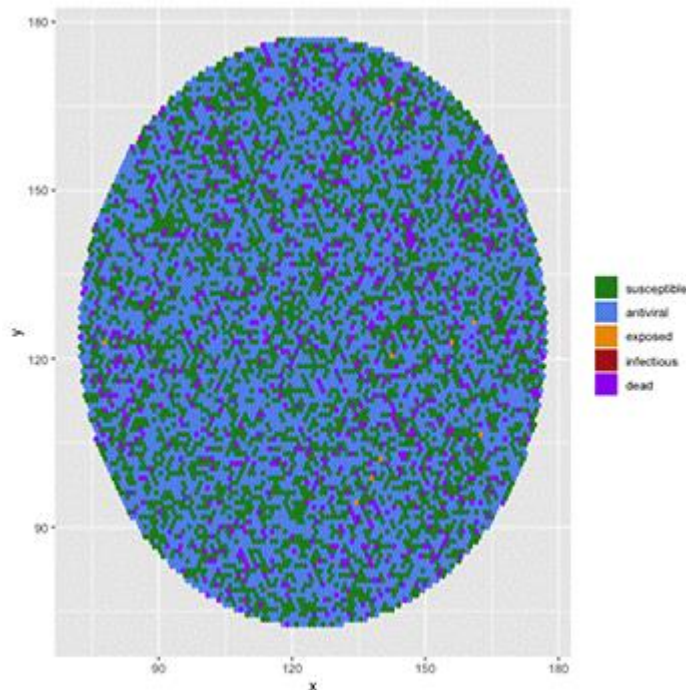
This has the side benefit of efficiently mopping up damaging molecules produced by inflammation of any cause, which may explain bats' uniquely long lifespans. Smaller animals with faster heart rates and metabolism typically have shorter lifespans than larger animals with slower heartbeats and slower metabolism, presumably because high metabolism leads to more destructive free radicals. But bats are unique in having far longer lifespans than other mammals of the same size: Some bats can live 40 years, whereas a rodent of the same size may live two years.

This rapid tamping down of inflammation may also have another perk: tamping down inflammation related to antiviral immune response. One key trick of many bats' immune systems is the hair-trigger release of a signaling molecule called interferon-alpha, which tells other cells to "man the battle stations" before a virus invades.

Brook was curious how bats' rapid immune response affects the evolution of the viruses they host, so she conducted experiments on cultured cells from two bats and, as a control, one monkey. One bat, the Egyptian fruit bat (*Rousettus aegyptiacus*), a natural host of Marburg virus, requires a direct viral attack before transcribing its interferon-alpha gene to flood the body with interferon. This technique is slightly slower than that of the Australian black flying fox (*Pteropus alecto*), a reservoir of Hendra virus, which is primed to fight virus infections with interferon-alpha RNA that is transcribed and ready to turn into protein. The African green monkey (Vero) cell line does not produce interferon at all.

When challenged by viruses mimicking Ebola and Marburg, the different responses of these cell lines were striking. While the green monkey cell line was rapidly overwhelmed and killed by the viruses, a subset of the roussette bat cells successfully walled themselves off from viral infection, thanks to interferon early warning.

In the Australian black flying fox cells, the immune response was even more successful, with the viral infection slowed substantially over that in the roussette cell line. In addition, these bat interferon responses seemed to allow the infections to last longer.



In a model of viral infection, when cells of the Australian black flying fox are invaded by a virus, some quickly wall themselves off from infection, having been forewarned by a rapid release of interferon from dying cells. This allows the cells to survive longer, but increases the duration of infection, maintaining infectious cells (red) until the end of the time series. Credit: UC Berkeley images by Cara Brook

"Think of viruses on a cell monolayer like a fire burning through a forest. Some of the communities—cells—have emergency blankets, and the fire washes through without harming them, but at the end of the day you still have smoldering coals in the system—there are still some viral cells," Brook said. The surviving communities of cells can reproduce, providing new targets for the the virus and setting up a smoldering infection that persists across the bat's lifespan.

Brook and Boots created a simple model of the bats' immune systems to recreate their experiments in a computer.

"This suggests that having a really robust interferon system would help these viruses persist within the host," Brook said. "When you have a higher immune response, you get these [cells](#) that are protected from infection, so the virus can actually ramp up its replication rate without causing damage to its host. But when it spills over into something like a human, we don't have those same sorts of antiviral mechanism, and we could experience a lot of pathology."



The researchers noted that many of the bat viruses jump to humans through an animal intermediary. SARS got to humans through the Asian palm civet; MERS via camels; Ebola via gorillas and chimpanzees; Nipah via pigs; Hendra via horses and Marburg through African green monkeys. Nonetheless, these viruses still remain extremely virulent and deadly upon making the final jump into humans.

Brook and Boots are designing a more formal model of disease evolution within [bats](#) in order to better understand [virus](#) spillover into other animals and humans.

"It is really important to understand the trajectory of an infection in order to be able to predict emergence and spread and transmission," Brook said. [38]

### **New details on how a viral protein puts the brakes on virus replication**

An interdisciplinary team of researchers at Colorado State University has used computational chemistry, biochemistry and virology to uncover new information on how viruses such as West Nile, dengue and Zika replicate. Based on their research, the team said these viruses appear to cripple their own genome replication machinery.

CSU researchers described the results as "surprising," and said the findings have implications for future vaccine and antiviral drug development.

The study, "Motif V regulates energy transduction between the flavivirus NS3 ATPase and RNA-binding cleft," was published in the *Journal of Biological Chemistry* on Feb. 7.

### **How a virus replicates**

Kelly Du Pont, first author of the study and a doctoral candidate in chemistry at CSU, studies Nonstructural Protein 3—or NS3—in flaviviruses, which cause a number of diseases in humans. NS3 is a key enzyme that these viruses use to copy their genomes.

For flaviviruses to replicate, the NS3 helicase—a viral enzyme that binds or remodels nucleic acid—has to unwind the double-stranded ribonucleic acid. NS3 uses adenosine triphosphate or ATP, a molecule abundant in cells, as fuel to power the unwinding.

Du Pont said the unwinding action is similar to what happens with a zipper on a jacket, while the energy produced from ATP driving the unwinding is similar to the transmission system of a car.

"The release of energy from the fuel drives the pistons up and down to turn the transmission and then the wheels, causing the car to move forward," she said. "NS3 uses ATP as its fuel to unwind the double-stranded ribonucleic acid, but we don't know where the crankshaft or transmission is for this machine."



Kelly Du Pont, first author of the study, studies Nonstructural Protein 3 - or NS3 - in flaviviruses, which cause a number of diseases in humans. NS3 is a key enzyme that these viruses use to copy their genomes. Credit: Joe Mendoza/CSU Photography

Du Pont said this research was initially focused on trying to figure out what part of the NS3 protein acts as its molecular transmission. While studying the process, the team identified the part of NS3 that acts as a brake during unwinding.

They also identified mutations that make NS3 unwind the double-stranded ribonucleic acid faster than is normally seen, but also make the [virus](#) replicate more inefficiently in cells.

### **Potential for drug, vaccine development**

If researchers can learn more about how NS3 unwinds the double-stranded [ribonucleic acid](#) and how this process is controlled, they could potentially target areas within the helicase for development of drugs to treat virus-caused diseases.

Brian Geiss, senior author on the study and associate professor of microbiology at CSU, said the findings could also one day lead to improved development of vaccines against these viruses.

"Most vaccines are developed by finding random mutations that slow down virus growth," he said. "By understanding how viral enzymes like NS3 work in great detail, we can use that information to rationally design new mutant viruses that replicate less well and act better as a vaccine, without having to rely on chance to make the vaccine. This can help develop vaccines more rapidly and precisely."

Du Pont, who specializes in creating computational simulations, has been working in Geiss's lab in the Department of Microbiology, Immunology and Pathology. While interdisciplinary work is common at CSU, Geiss said the breadth of Du Pont's project is not typical.

"Kelly represents a true interdisciplinary scientist who can use the tools and knowledge from many different areas of science to answer previously unanswerable questions," he said. "She uses [computational chemistry](#), protein biochemistry and enzymology, and classical virology techniques to study how these viruses work in unprecedented detail. Kelly is what I hope we will see more of in terms of the scientist of the future," he said.

The research team is now taking a closer look at how changes in NS3 affect replication of the virus and how the changes affect the ability of the virus to kill cells. Du Pont and Geiss are also working with the Ebel Laboratory at CSU to see how viruses with altered NS3 proteins infect mosquitoes and alter their survival during infection. [37]

## Scientists can now design new proteins from scratch with specific functions

Proteins are the molecular machines that make all living things hum—they stop deadly infections, heal cells and capture energy from the sun. Yet because our basic understanding of how proteins work has until now remained a mystery, humans have only been able to harness the power of proteins by modifying ones we happen to find in nature. This is beginning to change. Enabled by decades of basic research, the rise of inexpensive computing, and the genomics revolution in reading and writing DNA, scientists can now design new proteins from scratch with specific functions.

David Baker, Professor of Biochemistry and Director of the Institute for Protein Design at the University of Washington will speak about how algorithmic processes such as de novo design predict protein structures, protein folding mechanisms, and new [protein](#) functions.

Computational [protein design](#) is now being used to create proteins with novel structures using iterative structure prediction and experimental structure characterization. These results suggest that new proteins—encoded by synthetic genes—can be designed on computers with atomic-level accuracy.

In April 2019, the Institute for Protein Design (IPD) was selected as part of The Audacious Project, a successor to the TED Prize. As a result, the IPD is expanding its research on vaccine design, targeted drug delivery, 'smart' therapeutics, next-generation nanomaterials and more. [36]

## Novel protein positioning technique improves functionality of yeast cells

A research team at Kobe University has developed a method of artificially controlling the anchorage position of target proteins in engineered baker's yeast (*Saccharomyces cerevisiae*).

The group, consisting of academic researcher INOKUMA Kentaro, Professor HASUNUMA Tomohisa (both of the Engineering Biology Research Center) and Professor KONDO Akihiko et al. (of the

Graduate School of Science, Technology and Innovation) demonstrated that this technique could be utilized to improve the amount of ethanol produced from hydrothermally-processed rice straw by 30%. It is expected that these results will contribute to improved [yeast](#) functionality in cell surface engineering, which is utilized in a variety of fields such as bio-production and medicine.

The journal paper for this research was published in *Metabolic Engineering* on November 9, 2019. This study was conducted in collaboration with researchers from the University of the Western Cape and Stellenbosch University under the JSPS (Japan Society for the Promotion of Science) bilateral program with South Africa.

Cell surface engineering is a technique with applications in a variety of industrial and biotechnological fields. This technique can create microorganisms that can degrade biomass efficiently, allowing biofuels to be produced. In medical fields, cell surface engineering can also be utilized for the screening of antibodies with high antigen-binding capacity. Baker's yeast (or *Saccharomyces cerevisiae*) is often used as a host microorganism for this technique because its characteristics are well understood. This yeast has a [cell wall](#) that is between 100-200 nm thick and consists of a microfibrillar array of glucan chains. The cell wall provides space to display functional proteins.

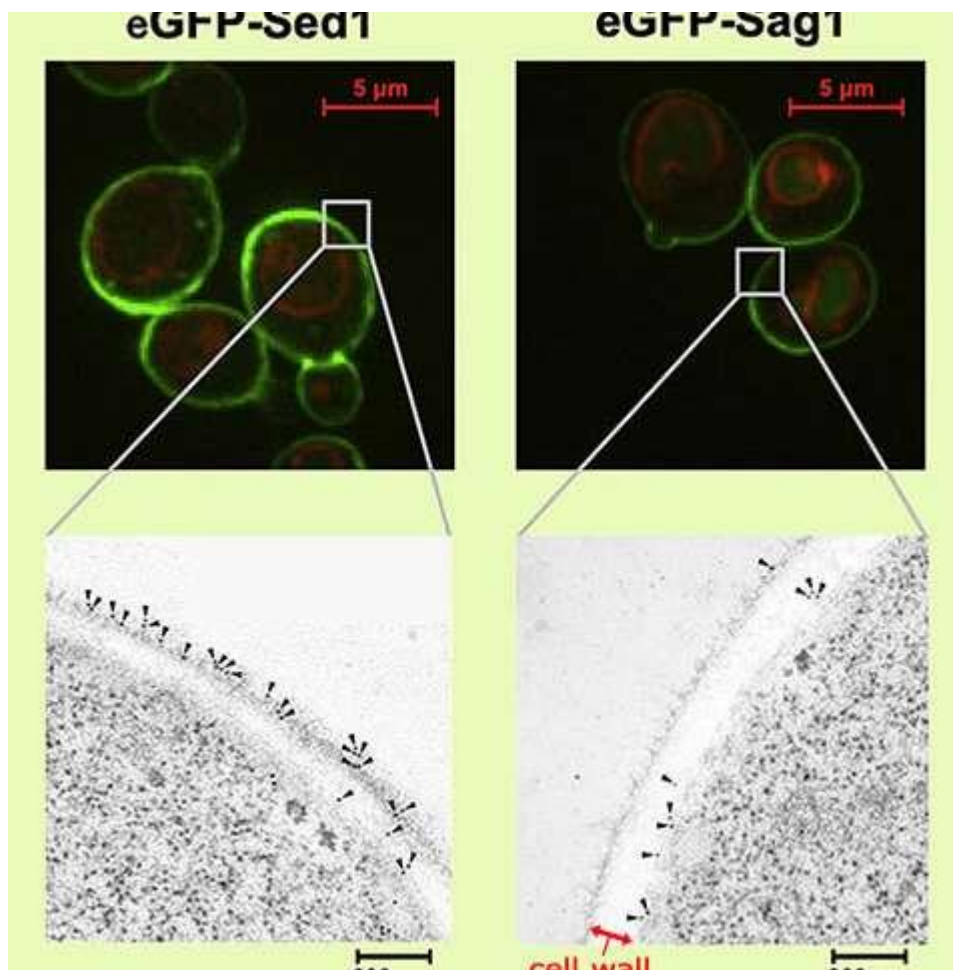


Figure 1. Above

: confocal fluorescence microscope image of yeast cells. Image shows the enhanced green

fluorescent protein (eGFP) (in green) and the vacuolar membranes (in red) in the cells. The Sed1-anchored eGFPs (left) are mainly located on the cell surface, whereas a part of the Sag1-anchored eGFPs are located in the intracellular vacuoles and the amount of Sag1-anchored eGFP transported to the cell surface is comparatively low. Below: Immunoelectron-microscope image showing the yeast cell wall. The arrowheads indicate the location of the eGFP. Sed1-anchored eGFP is mostly located outside the cell wall, whereas Sag1-anchored eGFP is mostly positioned inside the cell wall. Credit: Kobe University

In order to immobilize a target [protein](#) to the yeast cell wall, it is necessary to fuse the target protein to the "anchoring domain," which is a part of the yeast cell wall protein. Selecting the appropriate anchoring domain is important for efficient cell-surface display. A previous study by Inokuma et al. found that the degree to which activity was improved through changing the anchoring domain varied greatly depending on the target protein displayed. From these previous results, the research group hypothesized that changing the anchoring domain affected not only the display efficiency but also the anchorage position of the target protein in the cell wall and conducted the current study to verify this hypothesis.

The experiments were conducted using the two anchoring domains (the Sed1-anchor and Sag1-anchor) often utilized in *Saccharomyces cerevisiae* cell surface engineering. Enhanced green fluorescence protein (eGFP) was used as the [target protein](#). Confocal fluorescence microscopic and immunoelectron-microscopic analyses were performed to investigate how the anchoring domains affected where the eGFP was localized in yeast cell. These analyses revealed that the eGFP that fused with the Sed-1 anchoring domain were mainly located on the outermost layer of the cell wall, whereas the Sag1-anchored eGFP were predominantly positioned inside the cell wall (Figure 1). This result suggested that it was possible to artificially manipulate the location of the proteins on the yeast cell wall by changing the fused anchoring [domain](#).

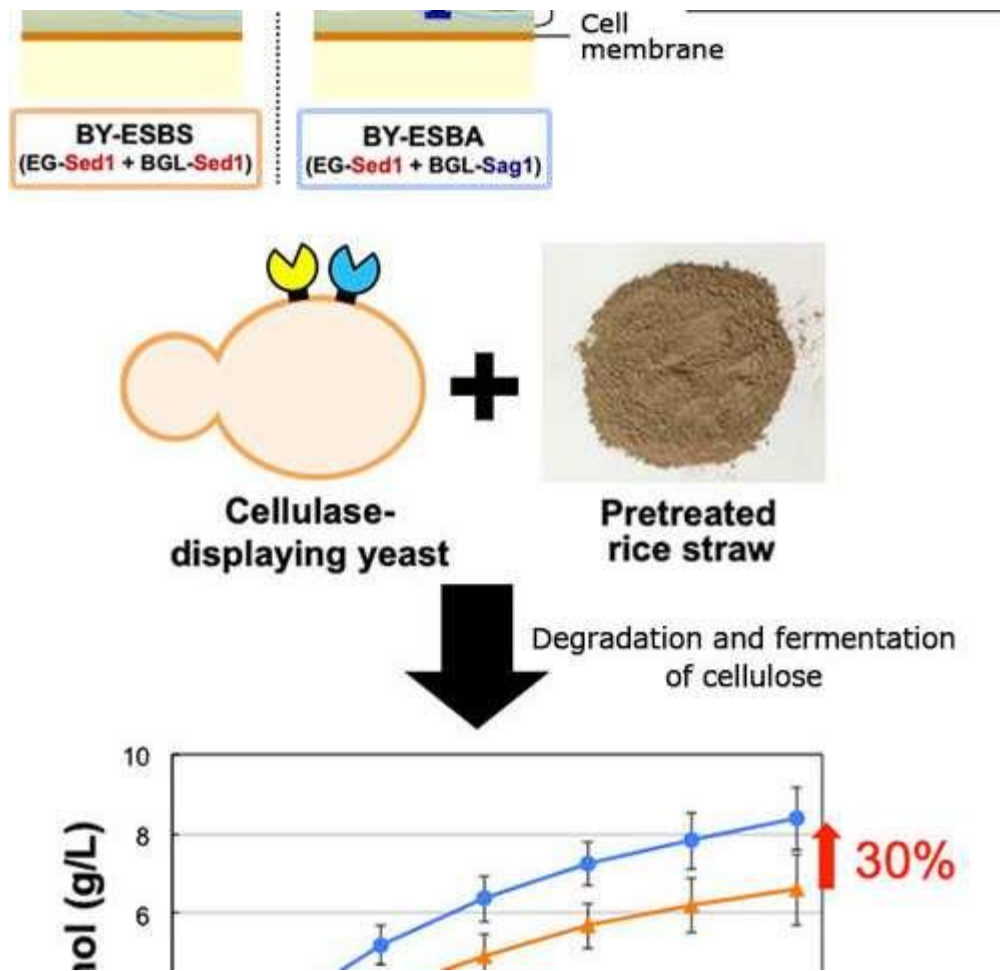


Figure 2:

Improvement of cellulose degradation ability by applying anchorage position control. This technique allowed the enzymes to be placed in the optimal positions for their functions- endoglucanase, which requires direct contact with large cellulose molecules, was anchored to the outside layer of the yeast cell wall, whereas  $\beta$ -glucosidase was anchored to the inside because it doesn't require the direct contact. This allowed more efficient use of the yeast cell wall space and succeeded in increasing the cellulose degradation ability. Credit: Kobe University

Next, an experiment was carried out to demonstrate if this method could be utilized to increase the ethanol productivity from hydrothermally-processed rice straw. *Saccharomyces cerevisiae* [cells](#) were used in the simultaneous saccharification and fermentation of the pretreated rice straw. This process converts the cellulose contained in the rice straw into ethanol. In this experiment,  $\beta$ -glucosidase (BGL) and endoglucanase (EG) were displayed on the yeast cell surface. These enzymes play different roles in breaking down the cellulose. EG breaks down large cellulose molecules at random, whereas BGL dissolves the smaller sugars (oligosaccharide) into glucose. Sed1- and Sag1-anchor domains were used to reposition the enzymes- with EG on the outermost layer and BGL on the interior of the cell wall. This efficient positioning resulted in a 30% greater yield of ethanol (Figure 2).

Discussions on how to improve cell surface engineering efficiency have often centered on anchoring a large number of target proteins to the surface. The current study revealed that controlling the

location of the target proteins played an important role in cell functionality, and this could provide a new strategy for improving this technology. The ethanol fermentation experiment of pretreated rice straw demonstrated in this study indicates that it is possible to position the two enzymes (EG and BGL) in locations suitable for them in the yeast cell wall. In addition, this strategy could also be utilized in other applications; for example in medicine, placing antibodies on the outermost layer of the cell wall could improve their accessibility to large antigens. Therefore, it is expected that this new strategy will improve the functionality of cell-surface engineered yeast across a wide range of fields. [35]

## Surveying all the proteins on a neuron's surface

Scientists have found a new way to home in on the proteins covering a particular cell's surface. The feat offers insight into how brain cells form intricate networks during development.

As if casting a tiny net, a new technique has rounded up all the proteins on the surface of neurons in the brains of fruit flies. The roundup uncovered 20 new molecules involved in wiring the developing [brain](#).

The find furthers scientists' understanding of how neurons in the brain form complex networks, researchers report January 16, 2020, in the journal *Cell*. And it demonstrates for the first time that this [protein](#)-finding method actually works in intact brain tissues—not just [cells](#) grown in the lab, says study coauthor and Howard Hughes Medical Institute Investigator, Liqun Luo.

That's important because the tissue environment is crucial for cells' development, and lab cell cultures can't replicate it. Until now, scientists had no way to monitor all the proteins on cell surfaces in complex tissues like the brain. The new approach provides a way to survey this previously mysterious landscape.

"What really blew me away was the biological follow-up," says biochemist Matthias Mann of the Max Planck Institute of Biochemistry. Luo's team was able to find a trove of proteins whose biological role was previously unknown, says Mann, who was not involved with the work.

Cell surfaces are incredibly dynamic places, especially for [cellular communication](#), says Luo, a neurobiologist at Stanford University. In the [nervous system](#), proteins on the surfaces of nerve cells help the cells find each other and link up. Luo's team wanted a complete view of the proteins that direct connections in the developing fly brain. The researchers focused on proteins involved in forming olfactory networks, which control a fly's sense of smell.

Luo, along with his doctoral student Jiefu Li and collaborators at Stanford and the Broad Institute of MIT and Harvard, modified a method pioneered by study coauthor Alice Ting. In this method, called proximity labeling, researchers use an enzyme to add a molecular tag to a particular protein of interest, plus all the neighboring proteins. Researchers can then identify the tagged proteins using a chemical analysis called mass spectrometry.

Luo's team added a new twist to the technique. They made the enzyme target proteins on fruit fly olfactory neurons at a particular point in brain development: when neurons are making decisions about which connections to form. The team compared the proteins present in adult cells with those present in the developing brain. "The difference is actually very striking," Luo says.

The team identified 20 proteins that were more abundant on the surfaces of developing neurons and knocked them down one by one to see if their absence had an effect on brain wiring. Surprising even to the researchers, all 20 were involved in wiring the fly olfactory network. What's more, many of the proteins they found hadn't even been known to play a role in neural development.

Luo and Li hope their approach will be useful for researchers in other fields as well. Li says it could be applied to immunology as well as to understanding how organs develop or modeling disease. For example, he adds, cell surface proteins are altered in cancer cells, so profiling those proteins could help scientists understand how cancer cells behave within tissues.

"I'd love to use [this technique]," says Joshua Sanes, a neuroscientist at Harvard University who was not involved in the research. Like Luo, Sanes (who is a member of HHMI's Scientific Review Board) is interested in how neurons form the precise patterns of connections that lead to all the complex neural circuitry underlying behavior. But he studies the brains of mammals, not flies. So, first, Sanes says, the method will have to be optimized for mammalian cells—a goal that has so far been elusive. [34]

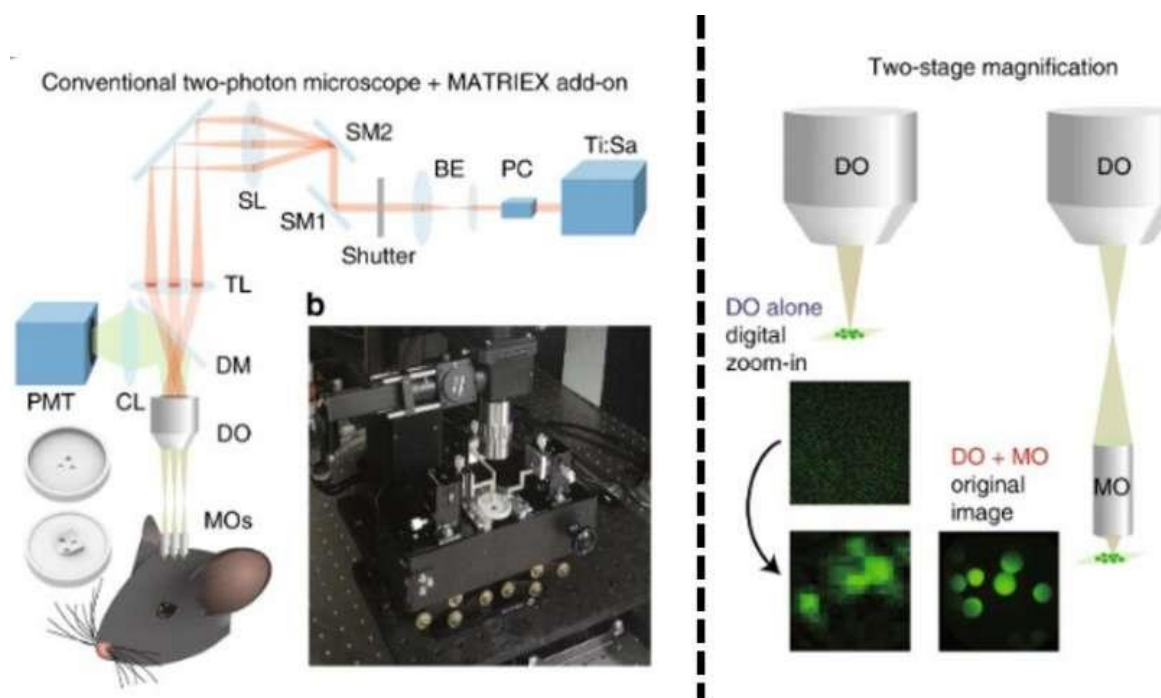
## **MATRIEX imaging: Simultaneously seeing neurons in action in multiple regions of the brain**

Two-photon laser scanning microscopy imaging is commonly applied to study neuronal activity at cellular and subcellular resolutions in mammalian brains. Such studies are yet confined to a single functional region of the brain. In a recent report, Mengke Yang and colleagues at the Brain Research Instrument Innovation Center, Institute of Neuroscience, Center for Systems Neuroscience and Optical System Advanced Manufacturing Technology in China, Germany and the U.K. developed a new technique named the multiarea two-photon real-time in vitro explorer (MATRIEX). The method allowed the user to target multiple regions of the functional brain with a field of view (FOV) approximating 200  $\mu\text{m}$  in diameter to perform two-photon  $\text{Ca}^{2+}$  imaging with single-cell resolution simultaneously across all regions.

Yang et al. conducted real-time functional imaging of single-neuron activities in the [primary visual cortex](#), primary motor cortex and hippocampal CA1 region during anesthetized and awake states in mice. The MATRIEX technique can uniquely configure multiple microscopic FOVs using a single laser scanning device. As a result, the technique can be implemented as an add-on optical module within existing conventional single-beam-scanning, two-photon microscopes without additional modifications. The MATRIEX can be applied to explore multiarea neuronal activity in vivo for brain-wide neural circuit function with single-cell resolution.



Two-photon laser microscopy [originated in the 1990s](#) to become popular among neuroscientists interested in studying neural structures and functions in vivo. A major advantage of [two-photon and three-photon imaging](#) for living brains include the optical resolution achieved [across densely labelled brain tissues](#) that strongly scatter light, during which optically sectioned image pixels can be scanned and acquired with minimal crosstalk. However, the advantages also caused significant drawbacks to the method by preventing the simultaneous view of two objects within a specific distance. Researchers had previously [implemented many strategies](#) to extend the limits, but the methods were difficult to implement in neuroscience research labs. Nevertheless, an increasingly high demand exists in neuroscience to [investigate brain-wide neuronal functions](#) with single-cell resolution in vivo.

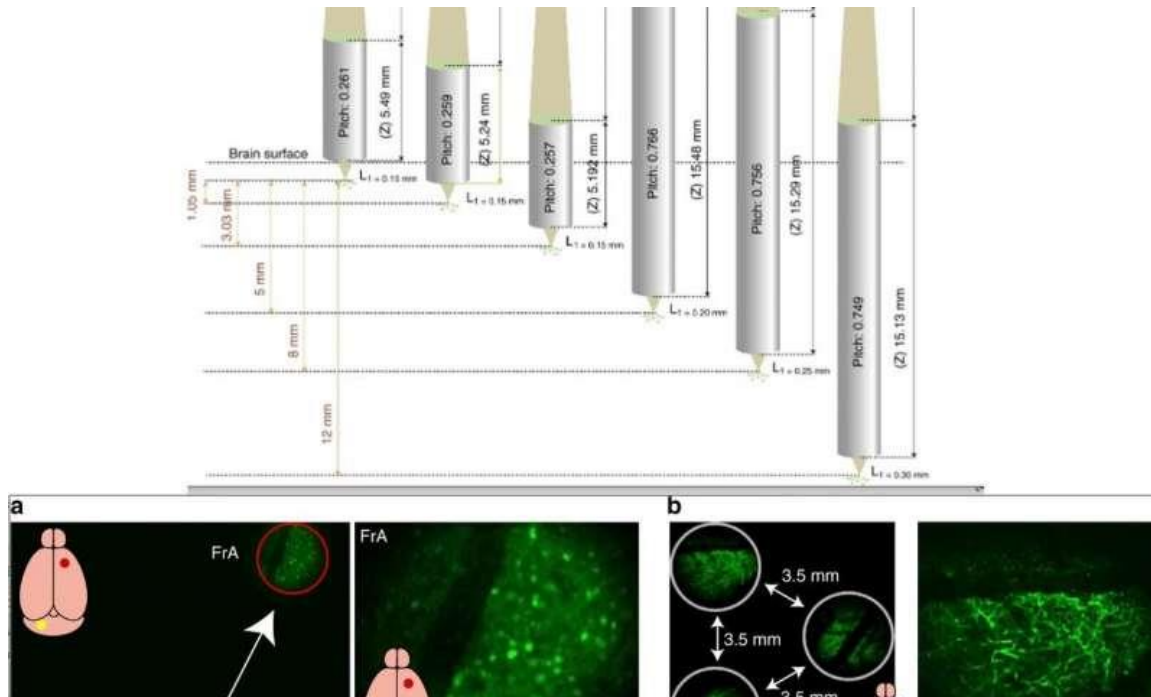


LEFT: Experimental diagram of the Matriex imaging system. The two round 3D objects in the lower-left corner are the top and bottom views of the mouse head chamber used for in vivo imaging. (Ti:Sa): Ti:Sapphire ultrafast pulsing laser; PC: Pockels cell; BE: beam expander; SM1 and SM2: x-y scanning mirrors; SL: scan lens; TL: tube lens; DM: dichroic mirror; CL: collection lens; PMT: photomultiplier tube; DO: dry objective; MOs: miniaturized objectives. RIGHT: Illustrations of the two-stage magnification and multi-axis coupling. The square images are actual two-photon images taken of 20- $\mu$ m beads. Each red circle indicates one FOV. Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0219-x

In a straightforward approach, scientists can [place two microscopes](#) above the same animal brain to image the cortex and cerebellum simultaneously. But such efforts can lead to substantial increases in [complexity and cost](#). The existing high expectations for performance and feasibility therefore pose a highly challenging engineering question on how a

single imaging system can simultaneously obtain live microscopic images from multiple brain regions in vivo. To address the question, Yang et al. introduced a new method that combined two-stage magnification and multi-axis optical coupling.

They realized the method using a low-magnification dry objective (DO), with multiple water-immersed, miniaturized objectives (MOs) under the dry objective. The scientists placed each of the MOs at the desired target position and depth in the brain tissue. The team used the new compound object assembly similarly to the original water-immersed microscope objective without additional modifications to the image scanning and acquisition subsystem.

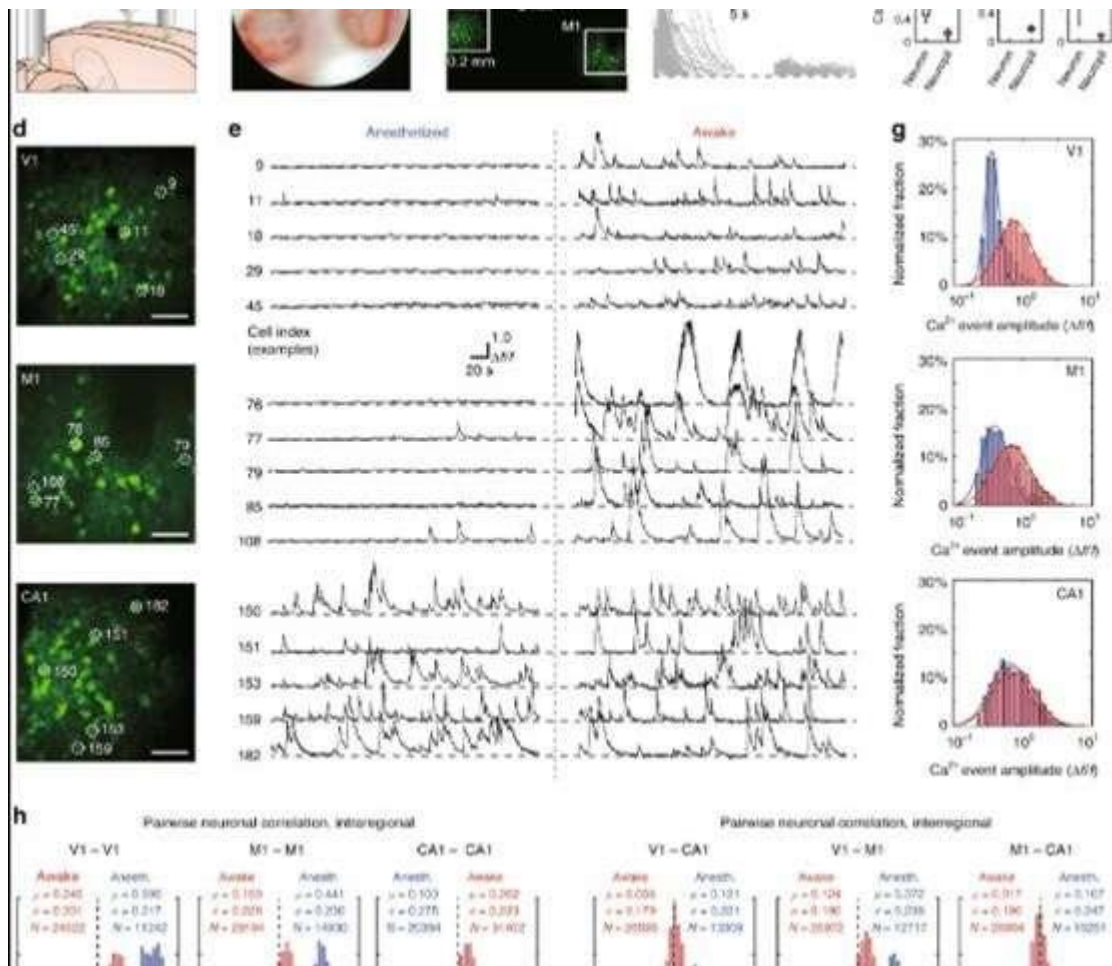


TOP: Configuring the MOs with different parameters to target object planes at different depths to then be conjugated on the same image plane. Each gray cylinder represents one lens with a pitch value, front working distance (L1), back working distance (L2) and length (Z). BOTTOM: Demonstration of MATRIEX imaging: structural imaging in multiple brain areas in vivo. a Left image: a full-frame image including two FOVs in the frontal association cortex (FrA) and the cerebellum. The red and yellow circles indicate two FOVs that are digitally enlarged and shown in the upper-right and lower-right images. A GAD67-GFP transgenic mouse (with the interneurons labeled brain-wide) was used. Two MOs ('standard version') were placed at the same depth under a DO (Mitutoyo  $\times 2/0.055$ ). b Example configuration of three FOVs in the cortex of a Thy1-GFP transgenic mouse (with layer 5 cortical neurons specifically labeled and with tuft dendrites visible near the cortical surface). Three MOs ('standard version') were placed at the same depth under a DO (Olympus  $\times 4/0.1$ ). Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0219-x

The research team first assembled the MATRIEX compound objective. For this, they replaced the conventional water-immersion microscope objective with a customized compound objective assembly, inside a two-photon laser scanning microscope equipped with a conventional single-beam raster scanning device. The compound assembly contained multiple MOs (miniaturized objectives) inserted through multiple craniotomies during which the scientists glued a 3-D printed

plastic chamber to the skull of the mouse model. The chamber roughly aligned the MOs with the same space to adjust lateral position and depth. Yang et al. precisely manipulated the individual MOs to view the objects under all MOs simultaneously in the same image plane.

They implemented the MatriEx method using two principles; two-stage magnification and multi-axis coupling. For example, using two-stage magnification with the dry objective (DO) alone, they observed 20  $\mu\text{m}$  beads as tiny blurry dots while observing crisp, round circles through the compound assembly. During multi-axis coupling, the scientists coupled a single DO with multiple MOs on the same image plane. Using a simple raster scan in a single rectangular frame, the research team acquired a rectangular image containing multiple circular FOVs (Field of Views) – where each FOV corresponded to one MO with minimal inter-FOV pixel crosstalk.



Demonstration of MatriEx imaging: simultaneously acquiring live neuronal activity patterns in V1, M1, and hippocampal CA1 in mice in the anesthetized state or awake state. The neurons were labeled by a genetically encoded fluorescent  $\text{Ca}^{2+}$  indicator, GCaMP6f (a) Illustration showing the positioning of three MOs over the V1, M1 and hippocampal CA1 regions in a model mouse brain. (b) A camera photograph taken through the microscope ocular lens under white light bright-field illumination, in which three FOVs are readily visible. The upper region is V1, the lower-left region is CA1, and the lower-right region is M1. (c) A two-photon image, which is an average of 100 frames, acquired by simple full-frame raster scanning with a two-photon microscope. The solid white boxes show the three parts of the image that are enlarged in panel (d). (d) Digitally enlarged individual

FOVs showing neurons in V1, M1, and CA1, from top to bottom. Scale bar: 40  $\mu\text{m}$ . (e) Time-lapse  $\text{Ca}^{2+}$  signal traces of five example cells from each region, with each labeled by the cell index. Recordings of the same cell in the same animal in the anesthetized state (left side) and in the awake state (right side) are shown. (f) Left: traces showing individual  $\text{Ca}^{2+}$  signal events (split from each onset time and overlaid) from randomly selected example cells. Middle:  $\text{Ca}^{2+}$  signal traces of each of the neuropil zones that are directly adjacent to each of the example cells. Right: three box plots comparing the neuronal  $\text{Ca}^{2+}$  signal event amplitude to the neuron's adjacent neuropil  $\text{Ca}^{2+}$  signal amplitude; paired Wilcoxon rank sum test,  $***P < 0.001$ . (g) Log-normal fitting of the distribution histograms of the spontaneous  $\text{Ca}^{2+}$  event amplitude for data pooled from all animals. The red bars and fitted curve show the distribution of data recorded in the awake state, and the blue bars and fitted curve show the distribution of data recorded in the anesthetized state. (h) Pairwise neuronal activity correlation (Pearson correlation coefficients) for data pooled from all animals. The red bars show the distribution of data recorded in the awake state, and the blue bars show the distribution of data recorded in the anesthetized state. Credit: Light: Science & Applications, doi: 10.1038/s41377-019-0219-x

The scientists credited the magnification of the [numerical aperture](#) (NA) for allowing better resolution with the compound assembly. The associated lenses were also flexible and custom-designed for mass-production at low cost to assist [experimental design](#). The main feature of MATRIEX was its capacity to image multiple objects simultaneously at large depth intervals. To highlight this, Yang et al. designed different MOs with diverse parameters, placing them at a specific depth where the corresponding object planes conjugated on the same axis. In practice, the research team compensated minor mismatches between the desired and actual object depth by adjusting MOs individually along each of the z axes.

Typically, under the DO (dry objective) the maximum lateral size of the target zone is limited by the maximum size of the scanning field. For example, using a DO with a 2x magnification and target zone of 12 mm in diameter, scientists can image an entire adult mouse brain. In this study, Yang et al. simultaneously imaged the frontal association cortex and cerebellum of the mouse. In practice, a 4x air objective was suited to achieve better resolution to [observe fine dendrite structures](#).

# Simultaneous Calcium Imaging in V1, M1, CA1 via MATRIEX

Simultaneous calcium imaging in the V1, M1 and CA1 regions using MATRIEX during anesthetized and awake states in mice. View full movie on Credit: Light: Science & Applications, doi: [10.1038/s41377-019-0219-x](https://doi.org/10.1038/s41377-019-0219-x)

As proof of principle, the research team used MATRIEX to perform simultaneous two-photon  $\text{Ca}^{2+}$  imaging of fluorescently-labelled neurons in the primary visual cortex (V1 region), primary motor cortex (M1 region) and hippocampal CA1 region of mice. In the configuration of the three MOs, the scientists placed two MOs suited for the V1 and M1 region, directly above the cortex and inserted an MO within the hippocampal CA1 region after [surgically removing](#) a cortical tissue. The team then designed the lenses for the object planes corresponding to V1, M1 and CA1 for conjugation on the same image plane. Using a two-photon microscope equipped with a 12 kHz resonant scanner, the scientists scanned the full image to observe three FOVs and their single cells

after enlarging the three different sections to resolve single neurons. Then they noted the laser power to be distributed among multiple FOVs.

While Yang et al. could have obtained these results using conventional single-FOV imaging within a single brain region, the MATRIEX technique provided them data beyond those offered with single-FOV imaging techniques. Taken together, these results allowed a highly inhomogeneous distribution and transformation of spontaneous activity patterns from the anesthetized state to the awake state in mice, spanning a brain-wide circuit level at single-cell resolution.

In this way, Meng Yang and co-workers developed the MATRIEX technique based on the principle of two-stage magnification and multi-axis optical coupling. They simultaneously conducted two-photon  $\text{Ca}^{2+}$  imaging in neuronal population activities at different depths in diverse regions (V1, M1 and CA1) in anesthetized and awake mice with single-cell resolution. Importantly, any conventional two-photon microscope can be transformed into a MATRIEX microscope, while preserving all original functionalities. The key to transformation is based on the design of a compound objective assembly. The researchers can use different, carefully designed MOs to suit diverse brain regions with 100 percent compatibility between the MATRIEX technique and conventional microscopy. The research team expects the MATRIEX technique to substantially advance three-dimensional, brain-wide neural circuit dynamics at single-cell resolution. [33]

## **Researchers demonstrate a novel approach for measuring brain function connectivity**

Measuring optical blood flow in the resting human brain to detect spontaneous activity has for the first time been demonstrated by Wright State University imaging researchers, holding out promise for a better way to study people with autism, Alzheimer's and depression.

Ulas Sunar, associate professor of biomedical, industrial and human factors engineering, and his team of researchers have shown that optical [blood flow](#) contrast measured by Diffuse Correlation Spectroscopy can be used to detect Resting State Functional Connectivity (RSFC) in the brain.

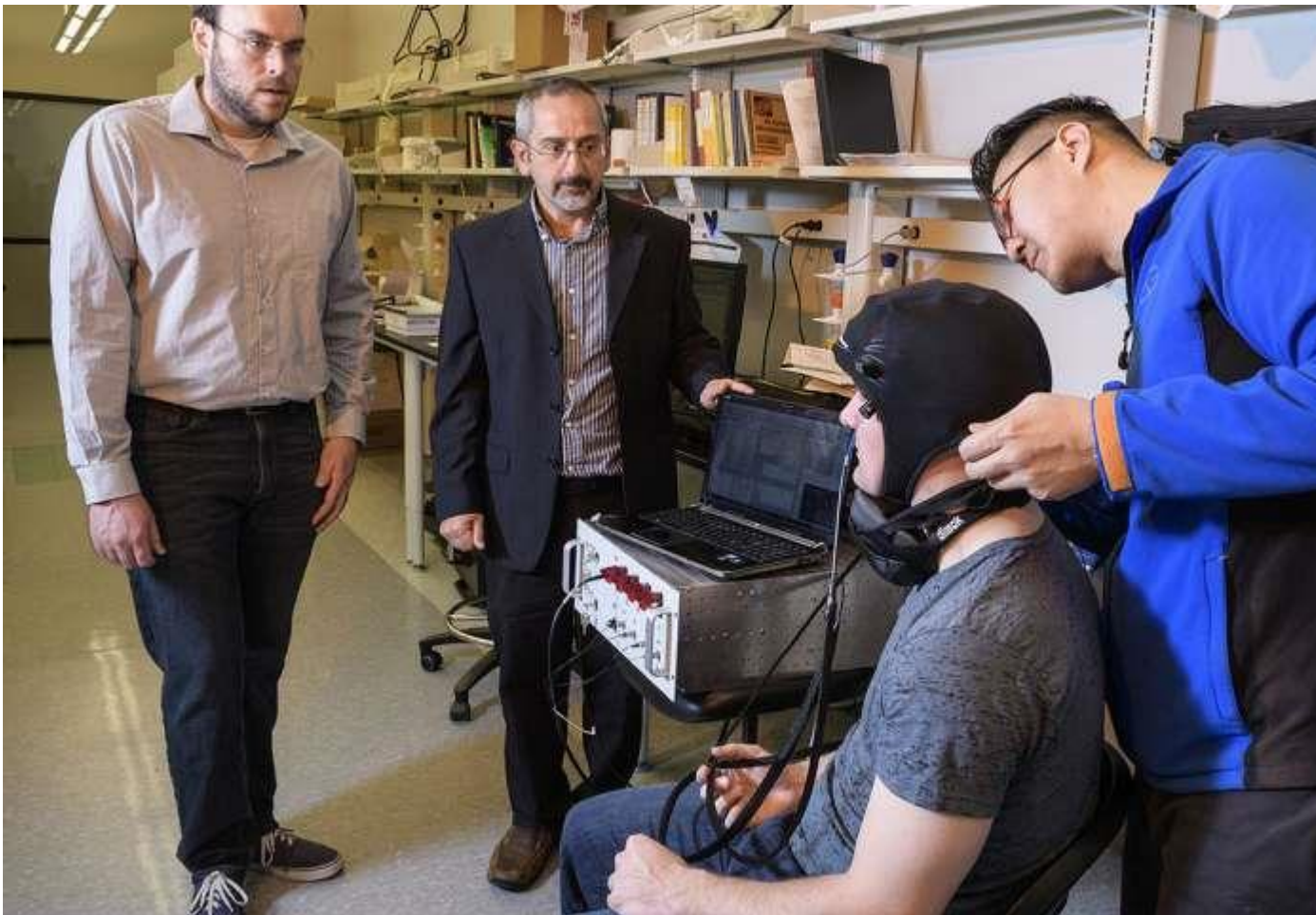
The research team includes Sunar, who holds the endowed position of the Ohio Research Scholar for Medical Imaging at Wright State, and his researchers Chien Poon, Jun Li, Jeremy Kress and Dan Rohrbach.

The team's findings were recently published in one of the top optical journals, the Journal of Biophotonics, covering research on the interactions between light and biological materials. The work has also been featured in the Biophotonics.World, which serves the worldwide biophotonics community as a central access point for the latest news and articles about recent scientific developments in academia and industry.

The team's novel optical approach is based on detecting light scattering from moving blood cells and can quantify absolute cerebral blood flow-related contrast. It is a complementary technique to widely known functional near infrared spectroscopy that measures blood oxygenation.

"We are seeing that blood flow shows higher contrast than oxygenation in our neuroimaging experiments," said Sunar. "Under neuronal firing brain may ask for more blood flow. That's why blood flow is an important parameter for assessing human brain resting state functional connectivity. And also the blood flow imaging technique is relatively new. The custom system was built here, by my Ph.D. student Chien Poon, and we demonstrated the resting state approach for the first time in our field."

The researchers used blood flow parameter to quantify RSFC in nine healthy adult males as a proof-of-concept study. The technique showed high connectivity between certain areas of the brain and low connectivity between other areas. The results match similar studies performed previously with other methods such as functional magnetic resonance imaging (fMRI).



From left: Dan Rohrbach, Ulas Sunar, Ben Rinehart and Chien Poon in the Sunar Research Group lab in the Neuroscience Engineering Collaboration Building. Credit: Wright State University

"These are exciting results in our field since the study has proven the potential of optical blood flow method as a non-invasive mean to assess RSFC in humans," Sunar told Biophotonics.World. "Cerebral blood flow is a very important parameter for neuronal disease characterization due to its high contrast."

RSFC studies are a valuable tool for studying people with disorders that can make performing tasks difficult. But many people, such as young autistic children, are poor candidates for RSFC assessment by fMRI, which requires them to hold still for long intervals inside a confined imaging space with loud noise from the magnet.

Optical imaging is highly suitable for such people because it is fast and can be performed by optical probes that can be worn by the patient. The researchers expect that this will ultimately become a highly useful tool for non-invasively assessing brain function in young and disabled patients.

Sunar said the technology could also be used for assessing human performance to understand if a task increases cerebral blood flow and neural activity.

"When a task is performed, what happens to the blood flow in the brain?" he said. "Is there a relationship? Is the brain network more connected at the resting state and performing state? These are interesting questions to investigate."

The next step for the research team will be to modify the optical system to enable it to show both blood flow and oxygenation.

"We are working on combining multiple imaging contrasts to get a more complete picture of the brain function," Sunar said. "For example, we can quantify cerebral metabolic rate of oxygen consumption by combining blood flow and oxygenation measurements. This approach will have a high impact in many areas, from neurological disease characterization in clinical settings to assessing the human performance relevant to military research." [32]

## **Biologists 'transfer' a memory**

UCLA biologists report they have transferred a memory from one marine snail to another, creating an artificial memory, by injecting RNA from one to another. This research could lead to new ways to lessen the trauma of painful memories with RNA and to restore lost memories.

"I think in the not-too-distant future, we could potentially use RNA to ameliorate the effects of Alzheimer's disease or post-traumatic stress disorder," said David Glanzman, senior author of the study and a UCLA professor of integrative biology and physiology and of neurobiology. The team's research is published May 14 in *eNeuro*, the online journal of the Society for Neuroscience.

RNA, or ribonucleic acid, has been widely known as a cellular messenger that makes proteins and carries out DNA's instructions to other parts of the cell. It is now understood to have other important functions besides protein coding, including regulation of a variety of cellular processes involved in development and disease.

The researchers gave mild electric shocks to the tails of a species of marine snail called *Aplysia*. The snails received five tail shocks, one every 20 minutes, and then five more 24 hours later. The shocks enhance the snail's defensive withdrawal reflex, a response it displays for protection from potential harm. When the researchers subsequently tapped the snails, they found those that had been given the shocks displayed a defensive contraction that lasted an average of 50 seconds, a simple type of learning known as "sensitization." Those that had not been given the shocks contracted for only about one second.



The life scientists extracted RNA from the nervous systems of marine snails that received the tail shocks the day after the second series of shocks, and also from marine snails that did not receive any shocks. Then the RNA from the first (sensitized) group was injected into seven marine snails that had not received any shocks, and the RNA from the second group was injected into a control group of seven other snails that also had not received any shocks.



UCLA Professor David Glanzman holding a marine snail. Credit: Christelle Snow/UCLA

Remarkably, the scientists found that the seven that received the RNA from snails that were given the shocks behaved as if they themselves had received the tail shocks: They displayed a defensive contraction that lasted an average of about 40 seconds.

"It's as though we transferred the memory," said Glanzman, who is also a member of UCLA's Brain Research Institute.

As expected, the control group of snails did not display the lengthy contraction.

Next, the researchers added RNA to Petri dishes containing neurons extracted from different snails that did not receive shocks. Some dishes had RNA from marine snails that had been given electric tail shocks, and some dishes contained RNA from snails that had not been given shocks. Some of

the dishes contained sensory neurons, and others contained motor neurons, which in the snail are responsible for the reflex.

When a marine snail is given electric tail shocks, its sensory neurons become more excitable. Interestingly, the researchers discovered, adding RNA from the snails that had been given shocks also produced increased excitability in sensory neurons in a Petri dish; it did not do so in motor neurons. Adding RNA from a marine snail that was not given the tail shocks did not produce this increased excitability in sensory neurons.



David Glanzman holding a marine snail. Credit: Christelle Snow/UCLA

In the field of neuroscience, it has long been thought that memories are stored in synapses. (Each neuron has several thousand synapses.) Glanzman holds a different view, believing that memories are stored in the nucleus of neurons.

"If memories were stored at synapses, there is no way our experiment would have worked," said Glanzman, who added that the marine snail is an excellent model for studying the brain and memory.

Scientists know more about the cell biology of this simple form of learning in this animal than any other form of learning in any other organism, Glanzman said. The cellular and molecular processes

seem to be very similar between the marine snail and humans, even though the snail has about 20,000 neurons in its central nervous system and humans are thought to have about 100 billion.

In the future, Glanzman said, it is possible that RNA can be used to awaken and restore memories that have gone dormant in the early stages of Alzheimer's disease. He and his colleagues published research in the journal *eLife* in 2014 indicating that lost memories can be restored.

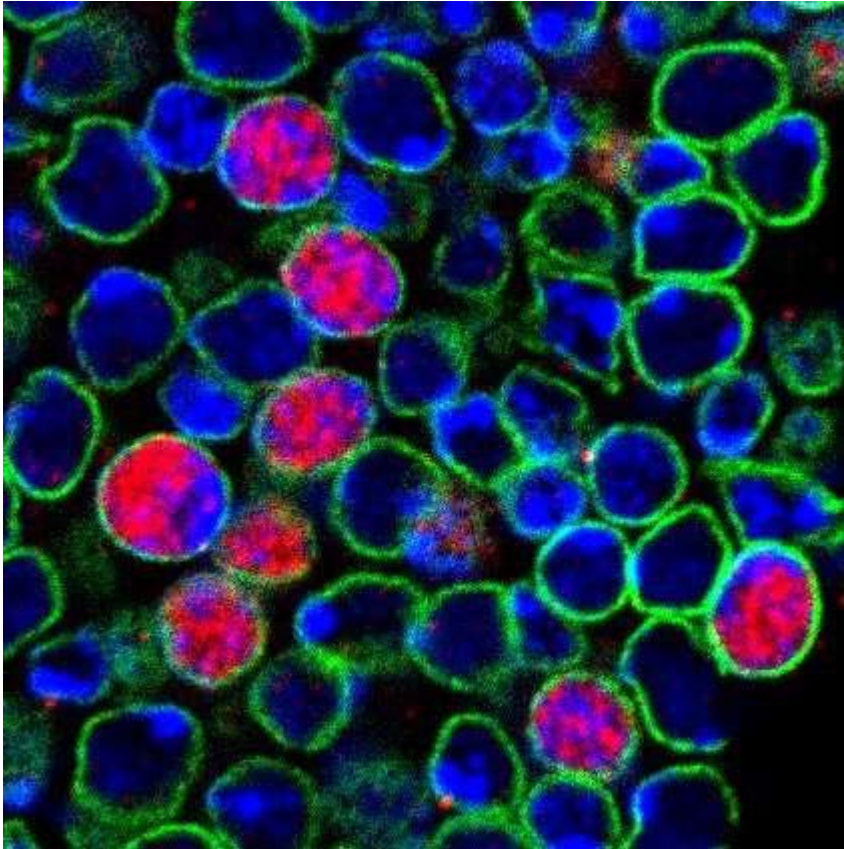
There are many kinds of RNA, and in future research, Glanzman wants to identify the types of RNA that can be used to transfer memories. [31]

### **'Sleeping' stem cells could aid brain repair**

Scientists at the Wellcome Trust/ Cancer Research UK Gurdon Institute, University of Cambridge, have identified a new type of stem cell in the brain which they say has a high potential for repair following brain injury or disease.

A major goal of regenerative research is to repair the brain efficiently following injury, for example due to stroke, Alzheimer's disease or head trauma, disease or ageing. The brain is poor at repairing itself; however, it may become possible to improve repair without surgery by targeting stem cells residing in patients' brains. Stem cells have the unique capacity to produce all of the cells in the brain but are normally kept inactive in a form of cellular 'sleep' known as quiescence. Quiescent cells do not proliferate or generate new cells. Thus, any regenerative therapy targeting stem cells must first awaken them from quiescence.

In a study published today in the journal *Science*, PhD student Leo Otsuki and his supervisor Professor Andrea Brand report the discovery in the brain of a new type of quiescent stem cell (known as 'G2 quiescent stem cell') with higher regenerative potential than quiescent stem cells identified previously. Importantly, G2 quiescent stem cells awaken to make the key types of cell in the brain - neurons and glia - much faster than known quiescent stem cells, making them attractive targets for therapeutic design.



Stem cells are labelled in red, nuclear membranes in green and DNA in blue. Credit: Andrea Brand/Leo Otsuki

"The brain is not good at repairing itself, but these newly-discovered stem cells suggest there may be a way to improve its ability," says Professor Brand. "These stem cells are in a dormant state, but once awake, they have the ability to generate key brain cells."

By studying the fruit fly (*Drosophila*), the authors identified a gene known as *tribbles* that selectively regulates G2 quiescent stem cells. The DNA of fruit flies has many similarities with that of humans, making them a useful model to understand human biology, and 60% of human genes associated with disease are also found in *Drosophila*. The *tribbles* gene has counterparts in the mammalian genome that are expressed in stem cells in the brain. The researchers believe that drugs that target *tribbles* might be one route to awakening G2 quiescent stem cells.

"We've found the gene that directs these cells to become quiescent," adds Otsuki. "The next step is to identify potential drug-like molecules that block this gene and awaken a person's stem cells."

"We believe there may be similar quiescent stem cells in other organs, and this discovery could help improve or develop new regenerative medicines." [30]

## Using organoids to understand how the brain wrinkles

A team of researchers working at the Weizmann Institute of Science has found that organoids can be used to better understand how the human brain wrinkles as it develops. In their paper published in the journal *Nature Physics*, the team describes how they used a modified form of organoid development to study the development of brain wrinkles. Larry Taber with Washington University offers a News & Views [piece](#) on the work done by the team in the same journal issue.

An organoid is an artificially grown mass of [cells](#) meant to replicate human or other animal organs. They are typically much smaller than the organs they are meant to mimic, but allow researchers a unique means of studying how organs develop. In this new effort, the researchers sought to better understand the process by which the [human brain](#) develops wrinkles. Realizing that the standard approach used for creating organoids would not work in such a study, the team tried another tactic—they grew stem cells on platform that resulted in a brain organoid that was much thinner and rounder than it would naturally grow—and it was also grown on a form surrounding a narrow space. The end result, the team reports, was a brain organoid that resembled a pita. This configuration allowed the researchers to take images of folds as they developed and to supply nutrients to all the cells since blood vessels typically do not develop in organoids.

In studying the images of the developing organoid, the researchers found that the folds developed as expected—opposing forces resulting from growth differences in brain material. In this case, it was the cytoskeleton in the organoid's core and the cell nucleus expanding at the organoid's outer edges. Uneven expansion between the two causes one or the other to fold as a means of dealing with the increase in pressure.

To learn more about the development of folds, the researchers ran the same experiment again, but used [stem cells](#) from a patient with smooth brain syndrome, which, as it sounds, is a condition in which the brain develops without folds. As expected, the organoid developed very few folds. A closer look showed differences in elasticity between the cells in the organoid grown with [healthy cells](#) and the those with the mutated genes that are behind smooth [brain](#) syndrome. [29]

## Biologists find new source for brain's development

A team of biologists has found an unexpected source for the brain's development, a finding that offers new insights into the building of the nervous system.

The research, which appears in the journal *Science*, discovered that glia, a collection of non-neuronal cells that had long been regarded as passive support cells, in fact are vital to nerve-cell development in the brain.

"The results lead us to revise the often neuro-centric view of brain development to now appreciate the contributions for non-neuronal cells such as glia," explains Vilaiwan Fernandes, a postdoctoral fellow in New York University's Department of Biology and the study's lead author. "Indeed, our study found that fundamental questions in brain development with regard to the timing, identity,

and coordination of nerve cell birth can only be understood when the glial contribution is accounted for."

The brain is made up of two broad cell types, nerve cells or neurons and glia, which are non-nerve cells that make up more than half the volume of the brain. Neurobiologists have tended to focus on the former because these are the cells that form networks that process information.

However, given the preponderance of glia in the brain's cellular make-up, the NYU researchers hypothesized that they could play a fundamental part in brain development.

To explore this, they examined the visual system of the fruit fly. The species serves as a powerful model organism for this line of study because its visual system, like the one in humans, holds repeated mini-circuits that detect and process light over the entire visual field.

This dynamic is of particular interest to scientists because, as the brain develops, it must coordinate the increase of neurons in the retina with other neurons in distant regions of the brain.

In their study, the NYU researchers found that the coordination of nerve-cell development is achieved through a population of glia, which relay cues from the retina to the brain to make cells in the brain become nerve cells.

"By acting as a signaling intermediary, glia exert precise control over not only when and where a neuron is born, but also the type of neuron it will develop into," notes NYU Biology Professor Claude

Desplan, the paper's senior author. [28]

## **Link Between Immune System, Memory and Brain Structure Discovered**

The body's immune system performs essential functions, such as defending against bacteria and cancer cells. However, the human brain is separated from immune cells in the bloodstream by the so-called blood-brain barrier. This barrier protects the brain from pathogens and toxins circulating in the blood, while also dividing the immune cells of the human body into those that fulfill their function in the blood and those that work specifically in the brain. Until recently, it was thought that brain function was largely unaffected by the peripheral immune system.

However, in the past few years, evidence has accumulated to indicate that the blood's immune system could in fact have an impact on the brain. Scientists from the University of Basel's Transfaculty Research Platform Molecular and Cognitive Neurosciences (MCN) have now carried out two independent studies that demonstrate that this link between the immune system and brain is more significant than previously believed.

### **Search for regulatory patterns**

In the first study, the researchers searched for epigenetic profiles, i.e. regulatory patterns, in the blood of 533 young, healthy people. In their genome-wide search, they identified an epigenetic profile that is strongly correlated with the thickness of the cerebral cortex, in particular in a region of the brain that is important for memory functions. This finding was confirmed in an independent examination of a further 596 people. It also showed that it is specifically those genes that are

responsible for the regulation of important immune functions in the blood that explain the link between the epigenetic profile and the properties of the brain.

### **Gene variant intensifies traumatic memories**

In the second study, the researchers investigated the genomes of healthy participants who remembered negative images particularly well or particularly poorly. A variant of the TROVE2 gene, whose role in immunological diseases is currently being investigated, was linked to participants' ability to remember a particularly high number of negative images, while their general memory remained unaffected.

This gene variant also led to increased activity in specific regions of the brain that are important for the memory of emotional experiences. The researchers also discovered that the gene is linked to the strength of traumatic memories in people who have experienced traumatic events.

The results of the two studies show that both brain structure and memory are linked to the activity of genes that also perform important immune regulatory functions in the blood. "Although the precise mechanisms behind the links we discovered still need to be clarified, we hope that this will ultimately lead to new treatment possibilities," says Professor Andreas Papassotiropoulos, CoDirector of the University of Basel's MCN research platform. The immune system can be precisely affected by certain medications, and such medications could also have a positive effect on impaired brain functions.

### **Innovative research methods**

These groundbreaking findings were made possible thanks to cutting edge neuroscientific and genetic methods at the University of Basel's MCN research platform. Under the leadership of Professor Andreas Papassotiropoulos and Professor Dominique de Quervain, the research platform aims to help us better understand human brain functions and to develop new treatments for psychiatric disorders. [27]

### **Researcher looking to shed light deeper into the human brain**

The inner workings of the human brain have always been a subject of great interest. Unfortunately, it is fairly difficult to view brain structures or intricate tissues due to the fact that the skull is not transparent by design. The reality is that light scattering is the major obstacle for deep penetration into tissue.

Dr. Vladislav Yakovlev, professor in the Department of Biomedical Engineering at Texas A&M University, has been developing a more efficient way of propagating light through an opaque medium. Propagation of light refers to the way that light travels from one point to another, in this case, through a medium, such as human tissue.

The new method involves making a minimally invasive hole within the medium, which is smaller in diameter than needles that are currently being used within the medical field. The process shows a great deal of promise in many uses, including viewing brain structure through the skull and imaging blood through skin tissue.

The technology could even be extended outside the realm of biomedical engineering to develop a more efficient way of seeing through fog while driving. This can be accomplished by deploying a laser pulse that could be sent through fog and evaporate water. This would allow drivers to have a safer experience during hazardous driving conditions and would work exactly as the method used in biomedical engineering applications.

The holes used to pass the light through are a few hundred micrometers in depth and a width of 20 to 30 microns. A micron is one millionth of a meter, and by comparison a single strand of human hair is about 75 microns in diameter. The light is then coupled into the opaque material resulting in an increase of magnitude of optical transmission into the material. The material that light is passed through is also referred to as the scattering medium.

The report documenting the work of Yakovlev was recently published in Proceedings of the National Academy of Sciences of the United States of America and definitively demonstrated that light injected into the scattering medium will remain there for an extended period of time. The amount of time that the photons remained was increased by a factor of 100.

One of the challenges facing researchers is that of optical absorption within tissues. However, because the new method is wavelength independent, the wavelength can be specified to perform measurements in a specific part of the light spectrum. This approach has the potential to yield analytical information about the composition and structure of the medium or tissue. [26]

## **Brain scanners allow scientists to 'read minds'—could they now enable a 'Big Brother' future?**

Are you lying? Do you have a racial bias? Is your moral compass intact? To find out what you think or feel, we usually have to take your word for it. But questionnaires and other explicit measures to reveal what's on your mind are imperfect: you may choose to hide your true beliefs or you may not even be aware of them.

But now there is a technology that enables us to "read the mind" with growing accuracy: functional magnetic resonance imaging (fMRI). It measures brain activity indirectly by tracking changes in blood flow – making it possible for neuroscientists to observe the brain in action. Because the technology is safe and effective, fMRI has revolutionised our understanding of the human brain. It has shed light on areas important for speech, movement, memory and many other processes.

More recently, researchers have used fMRI for more elaborate purposes. One of the most remarkable studies comes from Jack Gallant's lab at the University of California. His team showed movie trailers to their volunteers and managed to reconstruct these video clips based on the subjects' brain activity, using a machine learning algorithm.

In this approach, the computer developed a model based on the subject's brain activity rather than being fed a pre-programmed solution by the researchers. The model improved with practice and after having access to enough data, it was able to decode brain activity. The reconstructed clips were blurry and the experiment involved extended training periods. But for the first time, brain activity was decoded well enough to reconstruct such complex stimuli with impressive detail.



## Enormous potential

So what could fMRI do in the future? This is a topic we explore in our new book *Sex, Lies, and Brain Scans: How fMRI Reveals What Really Goes on in our Minds*. One exciting area is lie detection. While early studies were mostly interested in finding the brain areas involved in telling a lie, more recent research tried to actually use the technology as a lie detector.

As a subject in these studies, you would typically have to answer a series of questions. Some of your answers would be truthful, some would be lies. The computer model is told which ones are which in the beginning so it gets to know your "brain signature of lying" – the specific areas in your brain that light up when you lie, but not when you are telling the truth.

Afterwards, the model has to classify new answers as truth or lies. The typical accuracy reported in the literature is around 90%, meaning that nine out of ten times, the computer correctly classified answers as lies or truths. This is far better than traditional measures such as the polygraph, which is thought to be only about 70% accurate. Some companies have now licensed the lie detection algorithms. Their next big goal: getting fMRI-based lie detection admitted as evidence in court.

They have tried several times now, but the judges have ruled that the technology is not ready for the legal setting – 90% accuracy sounds impressive, but would we want to send somebody to prison if there is a chance that they are innocent? Even if we can make the technology more accurate, fMRI will never be error proof. One particularly problematic topic is the one of false memories. The scans can only reflect your beliefs, not necessarily reality. If you falsely believe that you have committed a crime, fMRI can only confirm this belief. We might be tempted to see brain scans as hard evidence, but they are only as good as your own memories: ultimately flawed.

Still, this raises some chilling questions about the possibility for a "Big Brother" future where our innermost thoughts can be routinely monitored. But for now fMRI cannot be used covertly. You cannot walk through an airport scanner and be asked to step into an interrogation room, because your thoughts were alarming to the security personnel.

Undergoing fMRI involves lying still in a big noise tube for long periods of time. The computer model needs to get to know you and your characteristic brain activity before it can make any deductions. In many studies, this means that subjects were being scanned for hours or in several sessions. There's obviously no chance of doing this without your knowledge – or even against your will. If you did not want your brain activity to be read, you could simply move in the scanner. Even the slightest movements can make fMRI scans useless.

Although there is no immediate danger of undercover scans, fMRI can still be used unethically. It could be used in commercial settings without appropriate guidelines. If academic researchers want to start an fMRI study, they need to go through a thorough process, explaining the potential risks and benefits to an ethics committee. No such guidelines exist in commercial settings. Companies are free to buy fMRI scanners and conduct experiments with any design. They could show you traumatising scenes. Or they might uncover thoughts that you wanted to keep to yourself. And if your scan shows any medical abnormalities, they are not forced to tell you about it.

Mapping the brain in great detail enables us to observe sophisticated processes. Researchers are beginning to unravel the brain circuits involved in self control and morality. Some of us may want to use this knowledge to screen for criminals or detect racial biases. But we must keep in mind that

fMRI has many limitations. It is not a crystal ball. We might be able to detect an implicit racial bias in you, but this cannot predict your behaviour in the real world.

fMRI has a long way to go before we can use it to fire or incarcerate somebody. But neuroscience is a rapidly evolving field. With advances in clever technological and analytical developments such as machine learning, fMRI might be ready for these futuristic applications sooner than we think. Therefore, we need to have a public discussion about these technologies now. Should we screen for terrorists at the airport or hire only teachers and judges who do not show evidence of a racial bias? Which applications are useful and beneficial for our society, which ones are a step too far? It is time to make up our minds. [25]

## **'Latest spoke in the wheel' drives brain-mapping advances**

Advances in microscopy techniques have often triggered important discoveries in the field of neuroscience, enabling vital insights in understanding the brain and promising new treatments for neurodegenerative diseases such as Alzheimer's and Parkinson's. A special section on "Superresolution Microscopy of Neural Structure and Function" in the current issue of the journal *Neurophotonics*, published by SPIE, the international society for optics and photonics, details this work in reports on ground-breaking new research and reviews.

Starting with the Golgi technique at the end of the 19th century, to electron microscopy in the 1950s, to fluorescent confocal and two-photon microscopy at the close of the 20th century, microscopy techniques have driven important breakthroughs in neuroscience, note guest editors Valentin Nägerl and Jean-Baptiste Sibarita of the Université de Bordeaux and the CNRS in their editorial for the special section.

"By providing higher spatial and temporal resolutions, as well as more contrast and specificity, these ground-breaking techniques have greatly informed our view of how the brain works," the editors write.

Super-resolution fluorescence microscopy "is the latest spoke in the revolutionary wheel," the guest editors note. "Recognized with the Nobel Prize in chemistry in 2014 for overcoming the diffraction barrier of light microscopy, it unlocks a new potential to upend biological research at the molecular level. Ten years after their development in a handful of laboratories, super-resolution microscopy techniques have caught on like wildfire and are now routinely used in a large number of biology labs."

While super-resolution microscopy is a relative recent addition to the arsenal of tools available for neuroscientific research, said *Neurophotonics* editor-in-chief David Boas of Massachusetts General Hospital, Harvard Medical School, "the breadth of impactful applications is growing rapidly. This special section provides a snapshot of this growth with a collection of exciting papers illustrating the breadth of applications."

Articles in the section, many of them accessible via open access, help validate and assess new techniques by comparing them with more established approaches. Among them:

In "Filling the gap: adding super-resolution to array tomography for correlated ultrastructural and molecular identification of electrical synapses at the *C. elegans* connectome," Sebastian Matthias

Markert of the University of Würzburg and co-authors describe a new method to correlate molecular information with ultrastructural context. Their aim is to allow researchers to dissect the molecular underpinnings of the ultrastructural organization and function of electrical synapses precisely and confidently.

Producing nanoscale maps of protein organization on cell surfaces or within organelles is another exciting prospect in super-resolution microscopy. In "Counting numbers of synaptic proteins: absolute quantification and single molecule imaging techniques," Angela Patrizio and Christian Specht of École Normale Supérieure describe how single-molecule-based microscopy techniques offer unparalleled opportunities to study protein content and dynamics in key functional compartments.

An early hallmark of neurodegenerative diseases such as Alzheimer's and Parkinson's is the misfolding and self-aggregation of proteins into amyloid structures that are believed to wreak havoc on neurons and synapses. In "Probing amyloid protein aggregation with optical super-resolution methods: from the test tube to models of disease", Clemens Kaminski and Gabriele Kaminski Schierle of the University of Cambridge explain the potential of new optical super-resolution techniques to provide insight on the molecular mechanism of the pathogenic self-assembly process in vitro and inside cells. [24]

## Consciousness and Entropy

What is the relationship of consciousness to the neurological activity of the brain? Does the brain behave differently when a person is fully conscious, when they are asleep, or when they are undergoing an epileptic seizure? A recent study by R. Guevara Erra, D. M. Mateos, R. Wennberg, J.L. Perez Velazquez of the University of Toronto, suggests that consciousness is correlated to a maximum number of neurological connections. In thermodynamics, this quantity, describing the complexity of a system, is entropy. In their paper, published in Physics Letters, they write:

It has been said that complexity lies between order and disorder. In the case of brain activity, and physiology in general, complexity issues are being considered with increased emphasis. We sought to identify features of brain organization that are optimal for sensory processing, and that may guide the emergence of cognition and consciousness, by analysing neurophysiological recordings in conscious and unconscious states. We find a surprisingly simple result: normal wakeful states are characterised by the greatest number of possible configurations of interactions between brain networks, representing highest entropy values. Therefore, the information content is larger in the network associated to conscious states, suggesting that consciousness could be the result of an optimization of information processing. These findings encapsulate three main current theories of cognition, as discussed in the text, and more specifically the conceptualization of consciousness in terms of brain complexity. We hope our study represents the preliminary attempt at finding organising principles of brain function that will help to guide in a more formal sense inquiry into how consciousness arises from the organization of matter.

The authors are rightly cautious about the significance of the correlation. Just because A and B are correlated, does not mean that A causes B. However the recognition that a phenomenon such as entropy may describe consciousness opens a new direction for consciousness research. [23]

## Consciousness is tied to 'entropy', say researchers

Consciousness appears to arise naturally as a result of a brain maximizing its information content. So says a group of scientists in Canada and France, which has studied how the electrical activity in people's brains varies according to individuals' conscious states. The researchers find that normal waking states are associated with maximum values of what they call a brain's "entropy".

Statistical mechanics is very good at explaining the macroscopic thermodynamic properties of physical systems in terms of the behaviour of those systems' microscopic constituent particles. Emboldened by this success, physicists have increasingly been trying to do a similar thing with the brain: namely, using statistical mechanics to model networks of neurons. Key to this has been the study of synchronization – how the electrical activity of one set of neurons can oscillate in phase with that of another set. Synchronization in turn implies that those sets of neurons are physically tied to one another, just as oscillating physical systems, such as pendulums, become synchronized when they are connected together.

The latest work stems from the observation that consciousness, or at least the proper functioning of brains, is associated not with high or even low degrees of synchronicity between neurons but by middling amounts. Jose Luis Perez Velazquez, a biochemist at the University of Toronto, and colleagues hypothesized that what is maximized during consciousness is not connectivity itself but the number of different ways that a certain degree of connectivity can be achieved.

### Many ways of connecting

Perez Velazquez's colleague Ramon Guevarra Erra, a physicist at the Paris Descartes University, points out that there is only one way to connect each set of neurons in a network with every other set, just as there is only one way to have no connections at all. In contrast, he notes, there are many different ways that an intermediate medium-sized number of connections can be arranged.

To put their hypothesis to the test, the researchers used data previously collected by Perez Velazquez showing electric- and magnetic-field emissions from the brains of nine people, seven of whom suffered from epilepsy. With emissions recorded at dozens of places across the subjects' scalps, the researchers analysed every possible pairing of these data "channels" to establish whether the emissions in each case were in phase with one another. They added up the number of synchronized pairs and plugged that figure along with the total number of all possible pairings into a fairly straightforward statistical formula to work out how many different brain configurations that level of synchronicity yields. They then took the logarithm of that number to establish the brain's entropy.

The data were analysed in two parts. In one, they compared the emissions from four of the epileptic patients when undergoing a seizure and when in a normal "alert" state. In the second, they compared emissions from the other five individuals when sleeping and when awake. In both cases, the bottom line was the same: subjects' brains display higher entropy, or a higher value of a similar quantity known as Lempel–Ziv (LZ) complexity, when in a fully conscious state.

### Varying results

Guevarra Erra admits that the results are not watertight. Indeed, the LZ complexity of one of the four epileptic patients in the first analysis showed no change between seizure and alert states (although that person did remain conscious during part of the seizure). In another individual, LZ

complexity actually increased in the second analysis while that person was asleep. Guevarra Erra says that he and his colleagues didn't carry out a statistical analysis of their results in part because of the "very heterogeneous" nature of those results. But he nevertheless remains "highly confident" that the correlations they have identified are real, particularly, he argues, because they were seen in "two very different sets of data".

Peter McClintock, a physicist who works on nonlinear dynamics at Lancaster University in the UK, describes the research as "intriguing" but says that the consciousness–entropy correlation should be confirmed using a larger number of subjects. He also suggests investigating "what happens in other brain states where consciousness is altered", such as anaesthesia.

### **Emergent property**

Perez Velazquez and colleagues argue that consciousness could simply be an "emergent property" of a system – the brain – that seeks to maximize information exchange and therefore entropy, since doing so aids the survival of the brain's bearer by allowing them to better model their environment. On the question of entropy, however, Guevarra Erra is cautious. He says that personally he would like to have a better understanding of the physical processes taking place in the brain before employing the label "entropy", explaining that Perez Velazquez was keen to use the term in their paper. One option, he says, would be to carry out fresh experiments that measure thermodynamic quantities in subjects' brains. He notes, for example, that magnetic resonance imaging can be used to measure oxygenation, which is directly related to metabolism and therefore to the generation of heat.

Guevarra Erra adds that he would like to extend their investigations beyond the hospital to cover more subtle but general cognitive behaviour. The idea would be to monitor a person's changing brain activity as they focus on carrying out a specific task, such as discriminating between musical tones or trying to find their way round a labyrinth. This, he says, should help to establish whether varying "entropy" correlates with degree of awareness as well as simply with the presence or absence of consciousness.

A paper describing the work will be published in Physical Review E and is also available on arXiv. [22]

### **A new study looks for the cortical conscious network**

New research published in the New Journal of Physics tries to decompose the structural layers of the cortical network to different hierarchies enabling to identify the network's nucleus, from which our consciousness could emerge.

The brain is a very complex network, with approximately 100 billion neurons and 100 trillion synapses between the neurons. In order to cope with its enormous complexity and to understand how brain function eventually creates the conscious mind, science uses advanced mathematical tools. Ultimately, scientists want to understand how a global phenomenon such as consciousness can emerge from our neuronal network.

A team of physicists from Bar Ilan University in Israel led by Professor Shlomo Havlin and Professor Reuven Cohen used network theory in order to deal with this complexity and to determine how the

structure of the human cortical network can support complex data integration and conscious activity. The gray area of the human cortex, the neuron cell bodies, were scanned with MRI imaging and used to form 1000 nodes in the cortical network. The white matter of the human cortex, the neuron bundles, were scanned with DTI imaging, forming 15,000 links or edges that connected the network's nodes. In the end of this process, their network was an approximation of the structure of the human cortex.

Previous studies have shown that the human cortex is a network with small world properties, which means that it has many local structures and some shortcuts from global structures that connect faraway areas (similar to the difference between local buses and cross-country trains). The cortex also has many hubs, which are nodes that have a high number of links (like central stations), that are also strongly interconnected between themselves, making it easy to travel between the brain's information highways.

Nir Lahav, the lead author of the study, says, "In order to examine how the structure of the network can support global emerging phenomena like consciousness, we applied a network analysis called Kshell decomposition. This analysis takes into account the connectivity profile of each node, making it easy to uncover different neighborhoods of connections in the cortical network, which we called shells."

The most connected neighborhood in the network is termed the network's nucleus. Nir says, "In the process, we peel off different shells of the network to get the most connected area of the network, the nucleus. Until today, scientists were only interested in the network's nucleus, but we found that these different shells can hold important information about how the brain integrates information from the local levels of each node to the entire global network. For the first time, we could build a comprehensive topological model of the cortex."

This topological model reveals that the network's nucleus includes 20 percent of all nodes and that the remaining 80 percent are strongly connected across all of the shells. Interestingly, comparing this topology to that of other networks, such as the internet, noticeable differences are apparent. For instance, in internet network topology, almost 25 percent of the nodes are isolated, meaning they don't connect to any other shells but the nucleus. In the cortical network, however, there are hardly any isolated nodes. It seems that the cortex is much more connected and efficient than the internet.

Looking at all the shells of the cortical network, the authors were able to define the network's hierarchical structure and essentially model how information flows within the network. The structure revealed how shells of low connectivity are nodes that typically perform specific functions like face recognition. From there, the data is transferred to higher, more connected shells that enable additional data integration. This reveals regions of the executive network and working memory. With these areas, researchers can focus on task performance, for example.

The integrated information then 'travels' to the most connected neighborhood of nodes, the nucleus, which spans across several regions of the cortex. According to Nir, "It's an interconnected collective which is densely linked with itself and can perform global functions due to its great number of global structures, which are widespread across the brain."

Which global function might the nucleus serve? The authors suggest the answer is no less than consciousness itself.

"The connection between brain activity and consciousness is still a great mystery," says Nir. The main hypothesis today is that in order to create conscious activity, the brain must integrate relevant information from multiple areas of the network. According to this theory, led by Professor Giulio Tononi from the University of Wisconsin, if the level of integrated information crosses a certain limit, a new and emergent state is entered—consciousness. This model suggests that consciousness depends on both information integration and information segregation. Loosely speaking, consciousness is generated by a "central" network structure with a high capacity for information integration, with the contribution of sub-networks that contain specific and segregated information without being part of the central structure. In other words, certain parts of the brain are more involved than others in the conscious complex of the brain, yet other connected parts still contribute, working quietly outside the conscious complex.

The authors demonstrate how the nucleus and the shells satisfy all of the requirements of these recent consciousness theories. The shells calculate and contribute to data integration without actually being part of the conscious complex, while the nucleus receives relevant information from all other hierarchies and integrates it to a unified function using its global interconnected structure.

The nucleus could thus be this conscious complex, serving as a platform for consciousness to emerge from the network activity.

When the authors examined the different regions that make up the nucleus, they revealed that, indeed, these regions have been previously associated with conscious activities. For example, structures within the brain's midline, which form the majority of the network's nucleus, were found to be associated with the stream of consciousness, and some researchers, like Professor Georg Northoff from the University of Ottawa, have suggested that these regions are involved with creating our sense of self.

"Now, we need to use this analysis on the whole brain, and not only on the cortex in order to reveal a more exact model of the brain's hierarchy, and later on understand what, exactly, are the neuronal dynamics that lead to such global integration and ultimately consciousness." [21]

## **Network theory sheds new light on origins of consciousness**

Where in your brain do you exist? Is your awareness of the world around you and of yourself as an individual the result of specific, focused changes in your brain, or does that awareness come from a broad network of neural activity? How does your brain produce awareness?

Vanderbilt University researchers took a significant step toward answering these longstanding questions with a recent brain imaging study, in which they discovered global changes in how brain areas communicate with one another during awareness. Their findings, which were published March 9 in the Proceedings of the National Academy of Sciences, challenge previous theories that hypothesized much more restricted changes were responsible for producing awareness.

"Identifying the fingerprints of consciousness in humans would be a significant advancement for basic and medical research, let alone its philosophical implications on the underpinnings of the

human experience," said René Marois, professor and chair of psychology at Vanderbilt University and senior author of the study. "Many of the cognitive deficits observed in various neurological diseases may ultimately stem from changes in how information is communicated throughout the brain."

Using graph theory, a branch of mathematics concerned with explaining the interactive links between members of a complex network, such as social networks or flight routes, the researchers aimed to characterize how connections between the various parts of the brain were related to awareness.

"With graph theory, one can ask questions about how efficiently the transportation networks in the United States and Europe are connected via transportation hubs like LaGuardia Airport in New York," Douglass Godwin, graduate student and lead author on the research, said. "We can ask those same questions about brain networks and hubs of neural communication."

Modern theories of the neural basis of consciousness fall generally into two camps: focal and global. Focal theories contend there are specific areas of the brain that are critical for generating consciousness, while global theories argue consciousness arises from large-scale brain changes in activity. This study applied graph theory analysis to adjudicate between these theories.

The researchers recruited 24 members of the university community to participate in a functional magnetic resonance imaging (fMRI) experiment. While in the fMRI scanner, participants were asked to detect a disk that was briefly flashed on a screen. In each trial, participants responded whether they were able to detect the target disk and how much confidence they had in their answer. Experimenters then compared the results of the high-confidence trials during which the target was detected to the trials when it was missed by participants. These were treated as "aware" and "unaware" trials, respectively.

Comparison of aware and unaware trials using conventional fMRI analyses that assess the amplitude of brain activity showed a pattern of results typical of similar studies, with only a few areas of the brain showing more activity during detection of the target than when participants missed seeing it. The present study, however, was interested not simply in what regions might be more activated with awareness, but how they communicate with one another.

Unlike the focal results seen using more conventional analysis methods, the results via this network approach pointed toward a different conclusion. No one area or network of areas of the brain stood out as particularly more connected during awareness of the target; the whole brain appeared to become functionally more connected following reports of awareness.

"We know there are numerous brain networks that control distinct cognitive functions such as attention, language and control, with each node of a network densely interconnected with other nodes of the same network, but not with other networks," Marois said. "Consciousness appears to break down the modularity of these networks, as we observed a broad increase in functional connectivity between these networks with awareness."

The research suggests that consciousness is likely a product of this widespread communication, and that we can only report things that we have seen once they are being represented in the brain in this manner. Thus, no one part of the brain is truly the "seat of the soul," as René Descartes once



wrote in a hypothesis about the pineal gland, but rather, consciousness appears to be an emergent property of how information that needs to be acted upon gets propagated throughout the brain.

"We take for granted how unified our experience of the world is. We don't experience separate visual and auditory worlds, it's all integrated into a single conscious experience," Godwin said. "This widespread cross-network communication makes sense as a mechanism by which consciousness gets integrated into that singular world." [20]

## **Neuromorphic computing mimics important brain feature**

When you hear a sound, only some of the neurons in the auditory cortex of your brain are activated. This is because every auditory neuron is tuned to a certain range of sound, so that each neuron is more sensitive to particular types and levels of sound than others. In a new study, researchers have designed a neuromorphic ("brain-inspired") computing system that mimics this neural selectivity by using artificial level-tuned neurons that preferentially respond to specific types of stimuli.

In the future, level-tuned neurons may help enable neuromorphic computing systems to perform tasks that traditional computers cannot, such as learning from their environment, pattern recognition, and knowledge extraction from big data sources.

The researchers, Angeliki Pantazi et al., at IBM Research-Zurich and École Polytechnique Fédérale de Lausanne, both in Switzerland, have published a paper on the new neuromorphic architecture in a recent issue of Nanotechnology.

Like all neuromorphic computing architectures, the proposed system is based on neurons and their synapses, which are the junctions where neurons send signals to each other. In this study, the researchers physically implemented artificial neurons using phase-change materials. These materials have two stable states: a crystalline, low-resistivity state and an amorphous, high-resistivity state. Just as in traditional computing, the states can be switched by the application of a voltage.

When the neuron's conductance reaches a certain threshold, the neuron fires.

"We have demonstrated that phase-change-based memristive devices can be used to create artificial neurons and synapses to store and process data," coauthor Evangelos Eleftheriou at IBM Research Zurich told Phys.org. "A phase-change neuron uses the phase configuration of the phase-change material to represent its internal state, the membrane potential. For the phase-change synapse, the synaptic weight—which is responsible for the plasticity—is encoded by the conductance of the nanodevice."

In this architecture, each neuron is tuned to a specific range, or level. Neurons receive signals from many other neurons, and a level is defined as the cumulative contribution of the sum of these incoming signals.

"We have introduced the biologically inspired architecture of level-tuned neurons that is able to distinguish different patterns in an unsupervised way," Eleftheriou said. "This is important for the development of ultra-dense, scalable and energy-efficient neuromorphic computing."

One of the main advantages of these highly selective level-tuned neurons is their improved learning ability. In neuromorphic computing, learning occurs through repeated incoming signals, which strengthens certain synaptic connections. The researchers showed that level-tuned neurons are very good at learning multiple input patterns, even in the presence of input noise.

"Even a single neuron can be used to detect patterns and to discover correlations in real-time streams of event-based data," Eleftheriou said. "Level-tuned neurons increase the capability of a single-neuron network for discriminating information when multiple patterns appear at the input. Level-tuned neurons, along with the high-speed and low-energy characteristics of their phasechange-based implementation, will be particularly useful for various emerging applications, such as Internet of Things, that collect and analyze large volumes of sensory information and applications to detect patterns in data sources, such as from social media to discover trends, or weather data for real-time forecasts, or healthcare data to detect patterns in diseases, etc."

In the future, the researchers plan to further develop the concept of artificial level-tuned neurons in order to design enhanced large-scale neural networks.

"We will be looking into more complex computational tasks based on artificial spiking neurons and their synapses," Eleftheriou said. "We are interested in studying the scaling potential and applications of such neuromorphic systems in cognitive computing systems." [19]

## **IBM scientists imitate the functionality of neurons with a phasechange device**

IBM scientists have created randomly spiking neurons using phase-change materials to store and process data. This demonstration marks a significant step forward in the development of energyefficient, ultra-dense integrated neuromorphic technologies for applications in cognitive computing.

Inspired by the way the biological brain functions, scientists have theorized for decades that it should be possible to imitate the versatile computational capabilities of large populations of neurons. However, doing so at densities and with a power budget that would be comparable to those seen in biology has been a significant challenge, until now.

"We have been researching phase-change materials for memory applications for over a decade, and our progress in the past 24 months has been remarkable," said IBM Fellow Evangelos Eleftheriou. "In this period, we have discovered and published new memory techniques, including projected memory, stored 3 bits per cell in phase-change memory for the first time, and now are demonstrating the powerful capabilities of phase-change-based artificial neurons, which can perform various computational primitives such as data-correlation detection and unsupervised learning at high speeds using very little energy."

The artificial neurons designed by IBM scientists in Zurich consist of phase-change materials, including germanium antimony telluride, which exhibit two stable states, an amorphous one (without a clearly defined structure) and a crystalline one (with structure). These materials are the basis of re-writable Blu-ray discs.

However, the artificial neurons do not store digital information; they are analog, just like the synapses and neurons in our biological brain.

In the published demonstration, the team applied a series of electrical pulses to the artificial neurons, which resulted in the progressive crystallization of the phase-change material, ultimately causing the neuron to fire. In neuroscience, this function is known as the integrate-and-fire property of biological neurons. This is the foundation for event-based computation and, in principle, is similar to how our brain triggers a response when we touch something hot.

Exploiting this integrate-and-fire property, even a single neuron can be used to detect patterns and discover correlations in real-time streams of event-based data.

For example, in the Internet of Things, sensors can collect and analyze volumes of weather data collected at the edge for faster forecasts. The artificial neurons could be used to detect patterns in financial transactions to find discrepancies or use data from social media to discover new cultural trends in real time. Large populations of these high-speed, low-energy nano-scale neurons could also be used in neuromorphic coprocessors with co-located memory and processing units.

IBM scientists have organized hundreds of artificial neurons into populations and used them to represent fast and complex signals. Moreover, the artificial neurons have been shown to sustain billions of switching cycles, which would correspond to multiple years of operation at an update frequency of 100 Hz. The energy required for each neuron update was less than five picojoule and the average power less than 120 microwatts—for comparison, 60 million microwatts power a 60 watt lightbulb.

"Populations of stochastic phase-change neurons, combined with other nanoscale computational elements such as artificial synapses, could be a key enabler for the creation of a new generation of extremely dense neuromorphic computing systems," said Tomas Tuma, a co-author of the paper. [18]

## **Programmable ions set the stage for general-purpose quantum computers**

An ion trap with four segmented blade electrodes used to trap a linear chain of atomic ions for quantum information processing. Each ion is addressed optically for individual control and readout using the high optical access of the trap.

Quantum computers promise speedy solutions to some difficult problems, but building large-scale, general-purpose quantum devices is a problem fraught with technical challenges.

To date, many research groups have created small but functional quantum computers. By combining a handful of atoms, electrons or superconducting junctions, researchers now regularly demonstrate quantum effects and run simple quantum algorithms—small programs dedicated to solving particular problems.

But these laboratory devices are often hard-wired to run one program or limited to fixed patterns of interactions between the quantum constituents. Making a quantum computer that can run arbitrary algorithms requires the right kind of physical system and a suite of programming tools. Atomic ions, confined by fields from nearby electrodes, are among the most promising platforms for meeting these needs.

In a paper published as the cover story in Nature on August 4, researchers working with Christopher

Monroe, a Fellow of the Joint Quantum Institute and the Joint Center for Quantum Information and Computer Science at the University of Maryland, introduced the first fully programmable and reconfigurable quantum computer module. The new device, dubbed a module because of its potential to connect with copies of itself, takes advantage of the unique properties offered by trapped ions to run any algorithm on five quantum bits, or qubits—the fundamental unit of information in a quantum computer.

"For any computer to be useful, the user should not be required to know what's inside," Monroe says. "Very few people care what their iPhone is actually doing at the physical level. Our experiment brings high-quality quantum bits up to a higher level of functionality by allowing them to be programmed and reconfigured in software."

The new module builds on decades of research into trapping and controlling ions. It uses standard techniques but also introduces novel methods for control and measurement. This includes manipulating many ions at once using an array of tightly-focused laser beams, as well as dedicated detection channels that watch for the glow of each ion.

"These are the kinds of discoveries that the NSF Physics Frontiers Centers program is intended to enable," says Jean Cottam Allen, a program director in the National Science Foundation's physics division. "This work is at the frontier of quantum computing, and it's helping to lay a foundation and bring practical quantum computing closer to being a reality."

The team tested their module on small instances of three problems that quantum computers are known to solve quickly. Having the flexibility to test the module on a variety of problems is a major step forward, says Shantanu Debnath, a graduate student at JQI and the paper's lead author. "By directly connecting any pair of qubits, we can reconfigure the system to implement any algorithm," Debnath says. "While it's just five qubits, we know how to apply the same technique to much larger collections."

At the module's heart, though, is something that's not even quantum: A database stores the best shapes for the laser pulses that drive quantum logic gates, the building blocks of quantum algorithms. Those shapes are calculated ahead of time using a regular computer, and the module uses software to translate an algorithm into the pulses in the database.

### **Putting the pieces together**

Every quantum algorithm consists of three basic ingredients. First, the qubits are prepared in a particular state; second, they undergo a sequence of quantum logic gates; and last, a quantum measurement extracts the algorithm's output.

The module performs these tasks using different colors of laser light. One color prepares the ions using a technique called optical pumping, in which each qubit is illuminated until it sits in the proper quantum energy state. The same laser helps read out the quantum state of each atomic ion at the end of the process. In between, a separate laser strikes the ions to drive quantum logic gates.

These gates are like the switches and transistors that power ordinary computers. Here, lasers push on the ions and couple their internal qubit information to their motion, allowing any two ions in the module to interact via their strong electrical repulsion. Two ions from across the chain notice each other through this electrical interaction, just as raising and releasing one ball in a Newton's cradle transfers energy to the other side.

The re-configurability of the laser beams is a key advantage, Debnath says. "By reducing an algorithm into a series of laser pulses that push on the appropriate ions, we can reconfigure the wiring between these qubits from the outside," he says. "It becomes a software problem, and no other quantum computing architecture has this flexibility."

To test the module, the team ran three different quantum algorithms, including a demonstration of a Quantum Fourier Transform (QFT), which finds how often a given mathematical function repeats. It is a key piece in Shor's quantum factoring algorithm, which would break some of the most widelyused security standards on the internet if run on a big enough quantum computer.

Two of the algorithms ran successfully more than 90% of the time, while the QFT topped out at a 70% success rate. The team says that this is due to residual errors in the pulse-shaped gates as well as systematic errors that accumulate over the course of the computation, neither of which appear fundamentally insurmountable.

They note that the QFT algorithm requires all possible two-qubit gates and should be among the most complicated quantum calculations.

The team believes that eventually more qubits—perhaps as many as 100—could be added to their quantum computer module. It is also possible to link separate modules together, either by physically moving the ions or by using photons to carry information between them.

Although the module has only five qubits, its flexibility allows for programming quantum algorithms that have never been run before, Debnath says. The researchers are now looking to run algorithms on a module with more qubits, including the demonstration of quantum error correction routines as part of a project funded by the Intelligence Advanced Research Projects Activity. [17]

## **Realizing quantum bits**

A research team from Germany, France and Switzerland has realised quantum bits, short qubits, in a new form. One day, they might become the information units of quantum computers.

To date, researchers have realised qubits in the form of individual electrons ([aktuell.ruhr-unibochum.de/pm2012/pm00090.html.en](http://aktuell.ruhr-unibochum.de/pm2012/pm00090.html.en)). However, this led to interferences and rendered the information carriers difficult to programme and read. The group has solved this problem by utilising electron holes as qubits, rather than electrons.

A report has been published in the journal *Nature Materials* by a team of researchers from RuhrUniversität Bochum, the University of Basel, and Lyon University; among its contributors were the two Bochum-based researchers Prof Dr Andreas Wieck and Dr Arne Ludwig from the Chair of

Applied Solid State Physics. The project was headed by the Swiss researcher Prof Dr Richard Warburton.

### **Electrons as qubits**

In order to realise qubits in the form of electrons, an electron is locked in a tiny semiconductor volume, the so-called quantum dot. The spin turns the electron into a small permanent magnet. Researchers are able to manipulate the spin via an external magnetic field and initiate precession. The direction of the spin is used to code information.

The problem: the nuclear spins of the surrounding atoms also generate magnetic fields, which distort the external magnetic field in a random, unpredictable manner. This, in turn, interferes with programming and reading qubits. Consequently, the team searched for another method. The solution: rather than locking individual electrons in the quantum dot, the team removed specific electrons. Thus, positively charged vacancies were generated in the electron structure, so-called electron holes.

### **Advantages of electron holes**

Electron holes have a spin, too. Researchers can manipulate it via the magnetic field in order to code information. As the holes are positively charged, they are decoupled from the nuclei of the surrounding atoms, which are likewise positively charged. This is why they are virtually immune against the interfering forces of the nuclear spin.

"This is important if we one day want to manufacture reproducible components that are based on quantum bits," explains Andreas Wieck. However, this method is only applicable at low temperatures, as the holes are more likely to be disturbed by warmth than the electrons.

At Ruhr-Universität, researchers are able to generate quantum dots of outstanding quality. The experiment could be conducted thanks to a structural design developed by Arne Ludwig in Basel and subsequently realised at the RUB Department headed by Andreas Wieck. It enabled the researcher to apply not just individual electrons to quantum dots, but also electron holes. Sascha René Valentin, PhD student from Bochum, utilised the technique for the purpose of the current study. [16]

## **Russian physicists discover a new approach for building quantum computers**

Physicists from MIPT and the Russian Quantum Center have developed an easier method to create a universal quantum computer using multilevel quantum systems (qudits), each one of which is able to work with multiple "conventional" quantum elements – qubits.

Professor Vladimir Man'ko, Aleksey Fedorov and Evgeny Kiktenko have published the results of their studies of multilevel quantum systems in a series of papers in Physical Review A, Physics Letters A, and also Quantum Measurements and Quantum Metrology.

"In our studies, we demonstrated that correlations similar to those used for quantum information technologies in composite quantum systems also occur in non-composite systems – systems which we suppose may be easier to work with in certain cases. In our latest paper we proposed a method

of using entanglement between internal degrees of freedom of a single eight-level system to implement the protocol of quantum teleportation, which was previously implemented experimentally for a system of three two-level systems," says Vladimir Man'ko.

Quantum computers, which promise to bring about a revolution in computer technology, could be built from elementary processing elements called quantum bits – qubits. While elements of classical computers (bits) can only be in two states (logic zero and logic one), qubits are based on quantum objects that can be in a coherent superposition of two states, which means that they can encode the intermediate states between logic zero and one. When a qubit is measured, the outcome is either a zero or a one with a certain probability (determined by the laws of quantum mechanics).

In a quantum computer, the initial condition of a particular problem is written in the initial state of the qubit system, then the qubits enter into a special interaction (determined by the specific problem). Finally, the user reads the answer to the problem by measuring the final states of the quantum bits.

Quantum computers will be able to solve certain problems that are currently far beyond the reach of even the most powerful classical supercomputers. In cryptography, for example, the time required for a conventional computer to break the RSA algorithm, which is based on the prime factorization of large numbers, would be comparable to the age of the universe. A quantum computer, on the other hand, could solve the problem in a matter of minutes.

However, there is a significant obstacle standing in the way of a quantum revolution – the instability of quantum states. Quantum objects that are used to create qubits – ions, electrons, Josephson junctions etc. can only maintain a certain quantum state for a very short time. However, calculations not only require that qubits maintain their state, but also that they interact with one another. Physicists all over the world are trying to extend the lifespan of qubits. Superconducting qubits used to "survive" only for a few nanoseconds, but now they can be kept for milliseconds before decoherence – which is closer to the time required for calculations.

In a system with dozens or hundreds of qubits, however, the problem is fundamentally more complex.

Man'ko, Fedorov, and Kiktenko began to look at the problem from the other way around – rather than try to maintain the stability of a large qubit system, they tried to increase the dimensions of the systems required for calculations. They are investigating the possibility of using qudits rather than qubits for calculations. Qudits are quantum objects in which the number of possible states (levels) is greater than two (their number is denoted by the letter D). There are qutrits, which have three states; ququarts, which have four states, etc. Algorithms are now actively being studied in which the use of qudits could prove to be more beneficial than using qubits.

"A qudit with four or five levels is able to function as a system of two "ordinary" qubits, and eight levels is enough to imitate a three-qubit system. At first, we saw this as a mathematical equivalence allowing us to obtain new entropic correlations. For example, we obtained the value of mutual information (the measure of correlation) between virtual qubits isolated in a state space of a single four-level system," says Fedorov.

He and his colleagues demonstrated that on one qudit with five levels, created using an artificial atom, it is possible to perform full quantum computations—in particular, the realization of the Deutsch algorithm. This algorithm is designed to test the values of a large number of binary variables.

It can be called the fake coin algorithm: imagine that you have a number of coins, some of which are fake – they have the same image on the obverse and reverse sides. To find these coins using the "classical method", you have to look at both sides. With the Deutsch algorithm, you "merge" the obverse and reverse sides of the coin and you can then see a fake coin by only looking at one side.

The idea of using multilevel systems to emulate multi-qubit processors was proposed earlier in the work of Russian physicists from the Kazan Physical-Technical Institute. To run a two-qubit Deutsch algorithm, for example, they proposed using a nuclear spin of  $3/2$  with four different states. In recent years, however, experimental progress in creating qudits in superconducting circuits has shown that they have a number of advantages.

However, superconducting circuits require five levels: the last level performs an ancillary role to allow for a complete set of all possible quantum operations.

"We are making significant progress, because in certain physical implementations, it is easier to control multilevel qudits than a system of the corresponding number of qubits, and this means that we are one step closer to creating a full-fledged quantum computer. Multilevel elements offer advantages in other quantum technologies too, such as quantum cryptography," says Fedorov. [15]

## **Precise atom implants in silicon provide a first step toward practical quantum computers**

Sandia National Laboratories has taken a first step toward creating a practical quantum computer, able to handle huge numbers of computations instantaneously.

Here's the recipe:

A "donor" atom propelled by an ion beam is inserted very precisely in microseconds into an industrystandard silicon substrate.

The donor atom—in this case, antimony (Sb) —carries one more electron (five) than a silicon atom (four). Because electrons pair up, the odd Sb electron remains free.

Instruments monitor the free electron to determine if, under pressure from an electromagnetic field, it faces up or down, a property called "spin." Electrons in this role, called qubits, signal "yes" or "no" from the subatomic scale, and so act as the information bearers of a quantum computer.

The ability to precisely place a donor atom in silicon means that it should be possible to insert a second donor atom just far enough away, in the "Goldilocks" zone where communication is neither lost through distance nor muffled by too-close proximity. Sandia will try to do this later this year, said lead researcher Meenakshi Singh, a postdoctoral fellow. Qubits "talking" to each other are the basis of quantum computing circuits.



The successful Sandia first step, reported in Applied Physics Letters, makes use of electromagnetic forces provided by a neighboring quantum dot pre-embedded in the silicon. The quantum dot— itself a tiny sea of electrons—contains a variety of energy levels and operates like a transistor to block or pass the qubit.

If an available dot energy level is compatible with the electron, the transistor gate is effectively open and the electron jumps into the dot. If not, the qubit stays put. That action is reported back to the surface by a photodiode sensor sensitive to current flows rather than photon movement. Because of the multiple "gates" in the quantum dot, many qubits at different energy levels could pass through the transistor, or be denied passage, theoretically making possible an extremely wide array of information processing.

"Our method is promising because, since it reads the electron's spin rather than its electrical charge, its information is not swallowed by background static and instead remains coherent for a relatively long time," Singh said. "Also, we use silicon as our basic material, for which commercial fabrication technologies are already developed, rather than employing superconducting components that can be expensive."

A third unique quality of the Sandia method is the precise and rapid placement of donor atoms exactly where they should be, placed in microseconds within nanometers of their target, instead of a buckshot approach that places qubits only where they statistically average to Goldilocks distances.

While components of this experiment have been demonstrated before, this is the first time all have worked together on a single chip, with researchers knowing accurately the vertical and horizontal placement of each qubit, instead of mere statistical approximations.

Sandia researcher and paper author Mike Lilly expects "the Sandia technique will allow fabrication of more complicated multi-qubit structures and do so at higher yield than existing donor implant approaches."

Components of the successful silicon device were fabricated in Sandia's Microsystems and Engineering Sciences Application (MESA) facility. The donor atoms were placed at Sandia's Ion Beam Laboratory. Experiment measurements were made at the Sandia/Los Alamos Center for Integrated Nanotechnologies, a user facility supported by DOE's Office of Basic Energy Sciences.

The method in its entirety is straightforward but requires a range of technical expertise and machinery, Singh said. "We used ion beams, silicon fabrication facilities, low-temperature measurements and simulations. It's hard to find a non-commercial place outside of a national lab that can do all of this." [14]

## **Team demonstrates large-scale technique to produce quantum dots**

A method to produce significant amounts of semiconducting nanoparticles for light-emitting displays, sensors, solar panels and biomedical applications has gained momentum with a demonstration by researchers at the Department of Energy's Oak Ridge National Laboratory.

While zinc sulfide nanoparticles - a type of quantum dot that is a semiconductor - have many potential applications, high cost and limited availability have been obstacles to their widespread use. That could change, however, because of a scalable ORNL technique outlined in a paper published in *Applied Microbiology and Biotechnology*.

Unlike conventional inorganic approaches that use expensive precursors, toxic chemicals, high temperatures and high pressures, a team led by ORNL's Ji-Won Moon used bacteria fed by inexpensive sugar at a temperature of 150 degrees Fahrenheit in 25- and 250-gallon reactors. Ultimately, the team produced about three-fourths of a pound of zinc sulfide nanoparticles - without process optimization, leaving room for even higher yields.

The ORNL biomanufacturing technique is based on a platform technology that can also produce nanometer-size semiconducting materials as well as magnetic, photovoltaic, catalytic and phosphor materials. Unlike most biological synthesis technologies that occur inside the cell, ORNL's biomanufactured quantum dot synthesis occurs outside of the cells. As a result, the nanomaterials are produced as loose particles that are easy to separate through simple washing and centrifuging.

The results are encouraging, according to Moon, who also noted that the ORNL approach reduces production costs by approximately 90 percent compared to other methods.

"Since biomanufacturing can control the quantum dot diameter, it is possible to produce a wide range of specifically tuned semiconducting nanomaterials, making them attractive for a variety of applications that include electronics, displays, solar cells, computer memory, energy storage, printed electronics and bio-imaging," Moon said.

Successful biomanufacturing of light-emitting or semiconducting nanoparticles requires the ability to control material synthesis at the nanometer scale with sufficiently high reliability, reproducibility and yield to be cost effective. With the ORNL approach, Moon said that goal has been achieved.

Researchers envision their quantum dots being used initially in buffer layers of photovoltaic cells and other thin film-based devices that can benefit from their electro-optical properties as light-emitting materials. [13]

## **Superfast light source made from artificial atom**

All light sources work by absorbing energy – for example, from an electric current – and emit energy as light. But the energy can also be lost as heat and it is therefore important that the light sources emit the light as quickly as possible, before the energy is lost as heat. Superfast light sources can be used, for example, in laser lights, LED lights and in single-photon light sources for quantum technology. New research results from the Niels Bohr Institute show that light sources can be made much faster by using a principle that was predicted theoretically in 1954. The results are published in the scientific journal, *Physical Review Letters*.

Researchers at the Niels Bohr Institute are working with quantum dots, which are a kind of artificial atom that can be incorporated into optical chips. In a quantum dot, an electron can be excited (i.e. jump up), for example, by shining a light on it with a laser and the electron leaves a 'hole'. The stronger the interaction between light and matter, the faster the electron decays back into the hole and the faster the light is emitted.

But the interaction between light and matter is naturally very weak and it makes the light sources very slow to emit light and this can reduce energy efficiency.

Already in 1954, the physicist Robert Dicke predicted that the interaction between light and matter could be increased by having a number of atoms that 'share' the excited state in a quantum superposition.

### Quantum speed up

Demonstrating this effect has been challenging so far because the atoms either come so close together that they bump into each other or they are so far apart that the quantum speed up does not work. Researchers at the Niels Bohr Institute have now finally demonstrated the effect experimentally, but in an entirely different physical system than Dicke had in mind. They have shown this so-called superradiance for photons emitted from a single quantum dot.

"We have developed a quantum dot so that it behaves as if it was comprised of five quantum dots, which means that the light is five times stronger. This is due to the attraction between the electron and the hole. But what is special is that the quantum dot still only emits a single photon at a time. It is an outstanding single-photon source," says Søren Stobbe, who is an associate professor in the Quantum Photonic research group at the Niels Bohr Institute at the University of Copenhagen and led the project. The experiment was carried out in collaboration with Professor David Ritchie's research group at the University of Cambridge, who have made the quantum dots.

Petru Tighineanu, a postdoc in the Quantum Photonics research group at the Niels Bohr Institute, has carried out the experiments and he explains the effect as such, that the atoms are very small and light is very 'big' because of its long wavelength, so the light almost cannot 'see' the atoms – like a lorry that is driving on a road and does not notice a small pebble. But if many pebbles become a larger stone, the lorry will be able to register it and then the interaction becomes much more dramatic. In the same way, light interacts much more strongly with the quantum dot if the quantum dot contains the special superradiant quantum state, which makes it look much bigger.

### Increasing the light-matter interaction

"The increased light-matter interaction makes the quantum dots more robust in regards to the disturbances that are found in all materials, for example, acoustic oscillations. It helps to make the photons more uniform and is important for how large you can build future quantum computers," says Søren Stobbe.

He adds that it is actually the temperature, which is only a few degrees above absolute zero, that limits how fast the light emissions can remain in their current experiments. In the long term, they will study the quantum dots at even lower temperatures, where the effects could be very dramatic.

[12]

### Single-photon source is efficient and indistinguishable

Devices that emit one – and only one – photon on demand play a central role in light-based quantum-information systems. Each photon must also be emitted in the same quantum state, which makes each photon indistinguishable from all the others. This is important because the quantum state of the photon is used to carry a quantum bit (qubit) of information.

Quantum dots are tiny pieces of semiconductor that show great promise as single-photon sources. When a laser pulse is fired at a quantum dot, an electron is excited between two distinct energy levels. The excited state then decays to create a single photon with a very specific energy. However, this process can involve other electron excitations that result in the emission of photons with a wide range of energies – photons that are therefore not indistinguishable.

### Exciting dots

This problem can be solved by exciting the quantum dot with a pulse of light at the same energy as the emitted photon. This is called resonance fluorescence, and has been used to create devices that are very good at producing indistinguishable single photons. However, this process is inefficient, and only produces a photon about 6% of the time.

Now, Chaoyang Lu, Jian-Wei Pan and colleagues at the University of Science and Technology of China have joined forces with researchers in Denmark, Germany and the UK to create a resonance fluorescence-based source that emits a photon 66% of the time when it is prompted by a laser pulse. Of these photons, 99.1% are solo and 98.5% are in indistinguishable quantum states – with both figures of merit being suitable for applications in quantum-information systems.

Lu told physicsworld.com that nearly all of the laser pulses that strike the source produce a photon, but about 34% of these photons are unable to escape the device. The device was operated at a laser-pulse frequency of 81 MHz and a pulse power of 24 nW, which is a much lower power requirement than other quantum-dot-based sources.

### Quantum sandwich

The factor-of-ten improvement in efficiency was achieved by sandwiching a quantum dot in the centre of a "micropillar" created by stacking 40 disc-like layers (see figure). Each layer is a "distributed Bragg reflector", which is a pair of mirrors that together have a thickness of one quarter the wavelength of the emitted photons.

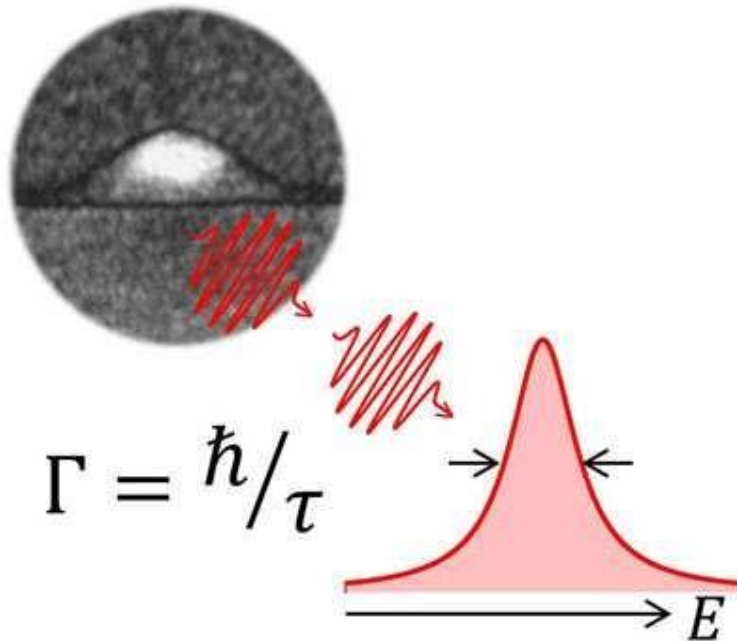
The micropillar is about 2.5  $\mu\text{m}$  in diameter and about 10  $\mu\text{m}$  tall, and it allowed the team to harness the "Purcell effect", whereby the rate of fluorescence is increased significantly when the emitter is placed in a resonant cavity.

Lu says that the team is already thinking about how the photon sources could be used to perform boson sampling (see "'Boson sampling' offers shortcut to quantum computing"). This involves a network of beam splitters that converts one set of photons arriving at a number of parallel input ports into a second set leaving via a number of parallel outputs. The "result" of the computation is the probability that a certain input configuration will lead to a certain output. This result cannot be easily calculated using a conventional computer, and this has led some physicists to suggest that boson sampling could be used to solve practical problems that would take classical computers vast amounts of time to solve.

Other possible applications for the source are the quantum teleportation of three properties of a quantum system – the current record is two properties and is held by Lu and Pan – or quantum cryptography.

The research is described in Physical Review Letters. [11]

## Semiconductor quantum dots as ideal single-photon source



A single-photon source never emits two or more photons at the same time. Single photons are important in the field of quantum information technology where, for example, they are used in quantum computers. Alongside the brightness and robustness of the light source, the indistinguishability of the photons is especially crucial. In particular, this means that all photons must be the same color. Creating such a source of identical single photons has proven very difficult in the past.

However, quantum dots made of semiconductor materials are offering new hope. A quantum dot is a collection of a few hundred thousand atoms that can form itself into a semiconductor under certain conditions. Single electrons can be captured in these quantum dots and locked into a very small area. An individual photon is emitted when an engineered quantum state collapses.

### Noise in the semiconductor

A team of scientists led by Dr. Andreas Kuhlmann and Prof. Richard J. Warburton from the University of Basel have already shown in past publications that the indistinguishability of the photons is reduced by the fluctuating nuclear spin of the quantum dot atoms. For the first time ever, the scientists have managed to control the nuclear spin to such an extent that even photons sent out at very large intervals are the same color.

Quantum cryptography and quantum communication are two potential areas of application for single-photon sources. These technologies could make it possible to perform calculations that are far beyond the capabilities of today's computers. [10]

### How to Win at Bridge Using Quantum Physics

Contract bridge is the chess of card games. You might know it as some stuffy old game your grandparents play, but it requires major brainpower, and preferably an obsession with rules and strategy. So how to make it even geekier? Throw in some quantum mechanics to try to gain a

competitive advantage. The idea here is to use the quantum magic of entangled photons—which are essentially twins, sharing every property—to transmit two bits of information to your bridge partner for the price of one. Understanding how to do this is not an easy task, but it will help elucidate some basic building blocks of quantum information theory. It's also kind of fun to consider whether or not such tactics could ever be allowed in professional sports. [6]

## Quantum Information

In quantum mechanics, quantum information is physical information that is held in the "state" of a quantum system. The most popular unit of quantum information is the qubit, a two-level quantum system. However, unlike classical digital states (which are discrete), a two-state quantum system can actually be in a superposition of the two states at any given time.

Quantum information differs from classical information in several respects, among which we note the following:

However, despite this, the amount of information that can be retrieved in a single qubit is equal to one bit. It is in the processing of information (quantum computation) that a difference occurs.

The ability to manipulate quantum information enables us to perform tasks that would be unachievable in a classical context, such as unconditionally secure transmission of information. Quantum information processing is the most general field that is concerned with quantum information. There are certain tasks which classical computers cannot perform "efficiently" (that is, in polynomial time) according to any known algorithm. However, a quantum computer can compute the answer to some of these problems in polynomial time; one well-known example of this is Shor's factoring algorithm. Other algorithms can speed up a task less dramatically - for example, Grover's search algorithm which gives a quadratic speed-up over the best possible classical algorithm.

Quantum information, and changes in quantum information, can be quantitatively measured by using an analogue of Shannon entropy. Given a statistical ensemble of quantum mechanical systems with the density matrix  $S$ , it is given by.

Many of the same entropy measures in classical information theory can also be generalized to the quantum case, such as the conditional quantum entropy. [7]

## Heralded Qubit Transfer

Optical photons would be ideal carriers to transfer quantum information over large distances. Researchers envisage a network where information is processed in certain nodes and transferred between them via photons. However, inherent losses in long-distance networks mean that the information transfer is subject to probabilistic errors, making it hard to know whether the transfer of a qubit of information has been successful. Now Gerhard Rempe and colleagues from the Max Planck Institute for Quantum Optics in Germany have developed a new protocol that solves this

problem through a strategy that “heralds” the accurate transfer of quantum information at a network node.

The method developed by the researchers involves transferring a photonic qubit to an atomic qubit trapped inside an optical cavity. The photon-atom quantum information transfer is initiated via a quantum “logic-gate” operation, performed by reflecting the photon from the atom-cavity system, which creates an entangled atom-photon state. The detection of the reflected photon then collapses the atom into a definite state. This state can be one of two possibilities, depending on the photonic state detected: Either the atom is in the initial qubit state encoded in the photon and the transfer process is complete, or the atom is in a rotated version of this state. The authors were able to show that the roles of the atom and photon could be reversed. Their method could thus be used as a quantum memory that stores (photon-to-atom state transfer) and recreates (atom-to-photon state transfer) a single-photon polarization qubit. [9]

## Quantum Teleportation

Quantum teleportation is a process by which quantum information (e.g. the exact state of an atom or photon) can be transmitted (exactly, in principle) from one location to another, with the help of classical communication and previously shared quantum entanglement between the sending and receiving location. Because it depends on classical communication, which can proceed no faster than the speed of light, it cannot be used for superluminal transport or communication of classical bits. It also cannot be used to make copies of a system, as this violates the no-cloning theorem. Although the name is inspired by the teleportation commonly used in fiction, current technology provides no possibility of anything resembling the fictional form of teleportation. While it is possible to teleport one or more qubits of information between two (entangled) atoms, this has not yet been achieved between molecules or anything larger. One may think of teleportation either as a kind of transportation, or as a kind of communication; it provides a way of transporting a qubit from one location to another, without having to move a physical particle along with it.

The seminal paper first expounding the idea was published by C. H. Bennett, G. Brassard, C. Crépeau, R. Jozsa, A. Peres and W. K. Wootters in 1993. Since then, quantum teleportation has been realized in various physical systems. Presently, the record distance for quantum teleportation is 143 km (89 mi) with photons, and 21 m with material systems. In August 2013, the achievement of "fully deterministic" quantum teleportation, using a hybrid technique, was reported. On 29 May 2014, scientists announced a reliable way of transferring data by quantum teleportation. Quantum teleportation of data had been done before but with highly unreliable methods. [8]

## Quantum Computing

A team of electrical engineers at UNSW Australia has observed the unique quantum behavior of a pair of spins in silicon and designed a new method to use them for "2-bit" quantum logic operations.

These milestones bring researchers a step closer to building a quantum computer, which promises dramatic data processing improvements.

Quantum bits, or qubits, are the building blocks of quantum computers. While many ways to create a qubits exist, the Australian team has focused on the use of single atoms of phosphorus, embedded inside a silicon chip similar to those used in normal computers.

The first author on the experimental work, PhD student Juan Pablo Dehollain, recalls the first time he realized what he was looking at.

"We clearly saw these two distinct quantum states, but they behaved very differently from what we were used to with a single atom. We had a real 'Eureka!' moment when we realized what was happening – we were seeing in real time the `entangled' quantum states of a pair of atoms." [5]

## Quantum Entanglement

Measurements of physical properties such as position, momentum, spin, polarization, etc. performed on entangled particles are found to be appropriately correlated. For example, if a pair of particles is generated in such a way that their total spin is known to be zero, and one particle is found to have clockwise spin on a certain axis, then the spin of the other particle, measured on the same axis, will be found to be counterclockwise. Because of the nature of quantum measurement, however, this behavior gives rise to effects that can appear paradoxical: any measurement of a property of a particle can be seen as acting on that particle (e.g. by collapsing a number of superimposed states); and in the case of entangled particles, such action must be on the entangled system as a whole. It thus appears that one particle of an entangled pair "knows" what measurement has been performed on the other, and with what outcome, even though there is no known means for such information to be communicated between the particles, which at the time of measurement may be separated by arbitrarily large distances. [4]

## The Bridge

The accelerating electrons explain not only the Maxwell Equations and the Special Relativity, but the Heisenberg Uncertainty Relation, the wave particle duality and the electron's spin also, building the bridge between the Classical and Quantum Theories. [1]

## Accelerating charges

The moving charges are self maintain the electromagnetic field locally, causing their movement and this is the result of their acceleration under the force of this field. In the classical physics the charges will distributed along the electric current so that the electric potential lowering along the current, by linearly increasing the way they take every next time period because this accelerated motion. The same thing happens on the atomic scale giving a dp impulse difference and a dx way difference between the different part of the not point like particles.

## Relativistic effect

Another bridge between the classical and quantum mechanics in the realm of relativity is that the charge distribution is lowering in the reference frame of the accelerating charges linearly:  $ds/dt = at$  (time coordinate), but in the reference frame of the current it is parabolic:  $s = a/2 t^2$  (geometric coordinate).



## Heisenberg Uncertainty Relation

In the atomic scale the Heisenberg uncertainty relation gives the same result, since the moving electron in the atom accelerating in the electric field of the proton, causing a charge distribution on  $\Delta x$  position difference and with a  $\Delta p$  momentum difference such a way that their product is about the half Planck reduced constant. For the proton this  $\Delta x$  is much less in the nucleus, than in the orbit of the electron in the atom, the  $\Delta p$  is much higher because of the greater proton mass.

This means that the electron and proton are not point like particles, but have a real charge distribution.

## Wave – Particle Duality

The accelerating electrons explain the wave – particle duality of the electrons and photons, since the elementary charges are distributed on  $\Delta x$  position with  $\Delta p$  impulse and creating a wave packet of the electron. The photon gives the electromagnetic particle of the mediating force of the electrons electromagnetic field with the same distribution of wavelengths.

## Atomic model

The constantly accelerating electron in the Hydrogen atom is moving on the equipotential line of the proton and its kinetic and potential energy will be constant. Its energy will change only when it is changing its way to another equipotential line with another value of potential energy or getting free with enough kinetic energy. This means that the Rutherford-Bohr atomic model is right and only that changing acceleration of the electric charge causes radiation, not the steady acceleration. The steady acceleration of the charges only creates a centric parabolic steady electric field around the charge, the magnetic field. This gives the magnetic moment of the atoms, summing up the proton and electron magnetic moments caused by their circular motions and spins.

## The Relativistic Bridge

Commonly accepted idea that the relativistic effect on the particle physics is the fermions' spin - another unresolved problem in the classical concepts. If the electric charges can move only with accelerated motions in the self maintaining electromagnetic field, once upon a time they would reach the velocity of the electromagnetic field. The resolution of this problem is the spinning particle, constantly accelerating and not reaching the velocity of light because the acceleration is radial. One origin of the Quantum Physics is the Planck Distribution Law of the electromagnetic oscillators, giving equal intensity for 2 different wavelengths on any temperature. Any of these two wavelengths will give equal intensity diffraction patterns, building different asymmetric constructions, for example proton - electron structures (atoms), molecules, etc. Since the particles are centers of diffraction patterns they also have particle – wave duality as the electromagnetic waves have. [2]

## The weak interaction

The weak interaction transforms an electric charge in the diffraction pattern from one side to the other side, causing an electric dipole momentum change, which violates the CP and time reversal symmetry. The Electroweak Interaction shows that the Weak Interaction is basically electromagnetic in nature. The arrow of time shows the entropy grows by changing the temperature dependent diffraction patterns of the electromagnetic oscillators.

Another important issue of the quark model is when one quark changes its flavor such that a linear oscillation transforms into plane oscillation or vice versa, changing the charge value with 1 or -1. This kind of change in the oscillation mode requires not only parity change, but also charge and time changes (CPT symmetry) resulting a right handed anti-neutrino or a left handed neutrino.

The right handed anti-neutrino and the left handed neutrino exist only because changing back the quark flavor could happen only in reverse, because they are different geometrical constructions, the u is 2 dimensional and positively charged and the d is 1 dimensional and negatively charged. It needs also a time reversal, because anti particle (anti neutrino) is involved.

The neutrino is a  $1/2$  spin creator particle to make equal the spins of the weak interaction, for example neutron decay to 2 fermions, every particle is fermions with  $1/2$  spin. The weak interaction changes the entropy since more or less particles will give more or less freedom of movement. The entropy change is a result of temperature change and breaks the equality of oscillator diffraction intensity of the Maxwell–Boltzmann statistics. This way it changes the time coordinate measure and makes possible a different time dilation as of the special relativity.

The limit of the velocity of particles as the speed of light appropriate only for electrical charged particles, since the accelerated charges are self maintaining locally the accelerating electric force. The neutrinos are CP symmetry breaking particles compensated by time in the CPT symmetry, that is the time coordinate not works as in the electromagnetic interactions, consequently the speed of neutrinos is not limited by the speed of light.

The weak interaction T-asymmetry is in conjunction with the T-asymmetry of the second law of thermodynamics, meaning that locally lowering entropy (on extremely high temperature) causes the weak interaction, for example the Hydrogen fusion.

Probably because it is a spin creating movement changing linear oscillation to 2 dimensional oscillation by changing d to u quark and creating anti neutrino going back in time relative to the proton and electron created from the neutron, it seems that the anti neutrino fastest then the velocity of the photons created also in this weak interaction?

A quark flavor changing shows that it is a reflection changes movement and the CP- and T-symmetry breaking!!! This flavor changing oscillation could prove that it could be also on higher

level such as atoms, molecules, probably big biological significant molecules and responsible on the aging of the life.

Important to mention that the weak interaction is always contains particles and antiparticles, where the neutrinos (antineutrinos) present the opposite side. It means by Feynman's interpretation that these particles present the backward time and probably because this they seem to move faster than the speed of light in the reference frame of the other side.

Finally since the weak interaction is an electric dipole change with  $\frac{1}{2}$  spin creating; it is limited by the velocity of the electromagnetic wave, so the neutrino's velocity cannot exceed the velocity of light.

### **The General Weak Interaction**

The Weak Interactions T-asymmetry is in conjunction with the T-asymmetry of the Second Law of Thermodynamics, meaning that locally lowering entropy (on extremely high temperature) causes for example the Hydrogen fusion. The arrow of time by the Second Law of Thermodynamics shows the increasing entropy and decreasing information by the Weak Interaction, changing the temperature dependent diffraction patterns. A good example of this is the neutron decay, creating more particles with less known information about them.

The neutrino oscillation of the Weak Interaction shows that it is a general electric dipole change and it is possible to any other temperature dependent entropy and information changing diffraction pattern of atoms, molecules and even complicated biological living structures.

We can generalize the weak interaction on all of the decaying matter constructions, even on the biological too. This gives the limited lifetime for the biological constructions also by the arrow of time. There should be a new research space of the Quantum Information Science the 'general neutrino oscillation' for the greater than subatomic matter structures as an electric dipole change.

There is also connection between statistical physics and evolutionary biology, since the arrow of time is working in the biological evolution also.

The Fluctuation Theorem says that there is a probability that entropy will flow in a direction opposite to that dictated by the Second Law of Thermodynamics. In this case the Information is growing that is the matter formulas are emerging from the chaos. So the Weak Interaction has two directions, samples for one direction is the Neutron decay, and Hydrogen fusion is the opposite direction.

### **Fermions and Bosons**

The fermions are the diffraction patterns of the bosons such a way that they are both sides of the same thing.

### **Van Der Waals force**

Named after the Dutch scientist Johannes Diderik van der Waals – who first proposed it in 1873 to explain the behaviour of gases – it is a very weak force that only becomes relevant when atoms

and molecules are very close together. Fluctuations in the electronic cloud of an atom mean that it will have an instantaneous dipole moment. This can induce a dipole moment in a nearby atom, the result being an attractive dipole–dipole interaction.

## Electromagnetic inertia and mass

### Electromagnetic Induction

Since the magnetic induction creates a negative electric field as a result of the changing acceleration, it works as an electromagnetic inertia, causing an electromagnetic mass. [1]

### Relativistic change of mass

The increasing mass of the electric charges the result of the increasing inductive electric force acting against the accelerating force. The decreasing mass of the decreasing acceleration is the result of the inductive electric force acting against the decreasing force. This is the relativistic mass change explanation, especially importantly explaining the mass reduction in case of velocity decrease.

### The frequency dependence of mass

Since  $E = h\nu$  and  $E = mc^2$ ,  $m = h\nu/c^2$  that is the  $m$  depends only on the  $\nu$  frequency. It means that the mass of the proton and electron are electromagnetic and the result of the electromagnetic induction, caused by the changing acceleration of the spinning and moving charge! It could be that the  $m_0$  inertial mass is the result of the spin, since this is the only accelerating motion of the electric charge. Since the accelerating motion has different frequency for the electron in the atom and the proton, they masses are different, also as the wavelengths on both sides of the diffraction pattern, giving equal intensity of radiation.

### Electron – Proton mass rate

The Planck distribution law explains the different frequencies of the proton and electron, giving equal intensity to different lambda wavelengths! Also since the particles are diffraction patterns they have some closeness to each other – can be seen as a gravitational force. [2]

There is an asymmetry between the mass of the electric charges, for example proton and electron, can understood by the asymmetrical Planck Distribution Law. This temperature dependent energy distribution is asymmetric around the maximum intensity, where the annihilation of matter and antimatter is a high probability event. The asymmetric sides are creating different frequencies of electromagnetic radiations being in the same intensity level and compensating each other. One of these compensating ratios is the electron – proton mass ratio. The lower energy side has no compensating intensity level, it is the dark energy and the corresponding matter is the dark matter.

## Gravity from the point of view of quantum physics

### The Gravitational force

The gravitational attractive force is basically a magnetic force.

The same electric charges can attract one another by the magnetic force if they are moving parallel in the same direction. Since the electrically neutral matter is composed of negative and positive charges they need 2 photons to mediate this attractive force, one per charges. The Big Bang caused parallel moving of the matter gives this magnetic force, experienced as gravitational force.

Since graviton is a tensor field, it has spin = 2, could be 2 photons with spin = 1 together.

You can think about photons as virtual electron – positron pairs, obtaining the necessary virtual mass for gravity.

The mass as seen before a result of the diffraction, for example the proton – electron mass ratio  $M_p=1840 M_e$ . In order to move one of these diffraction maximum (electron or proton) we need to intervene into the diffraction pattern with a force appropriate to the intensity of this diffraction maximum, means its intensity or mass.

The Big Bang caused acceleration created radial currents of the matter, and since the matter is composed of negative and positive charges, these currents are creating magnetic field and attracting forces between the parallel moving electric currents. This is the gravitational force experienced by the matter, and also the mass is result of the electromagnetic forces between the charged particles. The positive and negative charged currents attracts each other or by the magnetic forces or by the much stronger electrostatic forces!?

The gravitational force attracting the matter, causing concentration of the matter in a small space and leaving much space with low matter concentration: dark matter and energy.

There is an asymmetry between the mass of the electric charges, for example proton and electron, can understood by the asymmetrical Planck Distribution Law. This temperature dependent energy distribution is asymmetric around the maximum intensity, where the annihilation of matter and antimatter is a high probability event. The asymmetric sides are creating different frequencies of electromagnetic radiations being in the same intensity level and compensating each other. One of these compensating ratios is the electron – proton mass ratio. The lower energy side has no compensating intensity level, it is the dark energy and the corresponding matter is the dark matter.

## The Higgs boson

By March 2013, the particle had been proven to behave, interact and decay in many of the expected ways predicted by the Standard Model, and was also tentatively confirmed to have + parity and zero spin, two fundamental criteria of a Higgs boson, making it also the first known scalar particle to be discovered in nature, although a number of other properties were not fully proven and some partial results do not yet precisely match those expected; in some cases data is also still awaited or being analyzed.

Since the Higgs boson is necessary to the W and Z bosons, the dipole change of the Weak interaction and the change in the magnetic effect caused gravitation must be conducted. The Wien law is also important to explain the Weak interaction, since it describes the  $T_{max}$  change and the diffraction patterns change. [2]

## Higgs mechanism and Quantum Gravity

The magnetic induction creates a negative electric field, causing an electromagnetic inertia. Probably it is the mysterious Higgs field giving mass to the charged particles? We can think about the photon as an electron-positron pair, they have mass. The neutral particles are built from negative and positive charges, for example the neutron, decaying to proton and electron. The wave – particle duality makes sure that the particles are oscillating and creating magnetic induction as an inertial mass, explaining also the relativistic mass change. Higher frequency creates stronger magnetic induction, smaller frequency results lesser magnetic induction. It seems to me that the magnetic induction is the secret of the Higgs field.

In particle physics, the Higgs mechanism is a kind of mass generation mechanism, a process that gives mass to elementary particles. According to this theory, particles gain mass by interacting with the Higgs field that permeates all space. More precisely, the Higgs mechanism endows gauge bosons in a gauge theory with mass through absorption of Nambu–Goldstone bosons arising in spontaneous symmetry breaking.

The simplest implementation of the mechanism adds an extra Higgs field to the gauge theory. The spontaneous symmetry breaking of the underlying local symmetry triggers conversion of components of this Higgs field to Goldstone bosons which interact with (at least some of) the other fields in the theory, so as to produce mass terms for (at least some of) the gauge bosons. This mechanism may also leave behind elementary scalar (spin-0) particles, known as Higgs bosons.

In the Standard Model, the phrase "Higgs mechanism" refers specifically to the generation of masses for the  $W^\pm$ , and Z weak gauge bosons through electroweak symmetry breaking. The Large Hadron Collider at CERN announced results consistent with the Higgs particle on July 4, 2012 but stressed that further testing is needed to confirm the Standard Model.

### What is the Spin?

So we know already that the new particle has spin zero or spin two and we could tell which one if we could detect the polarizations of the photons produced. Unfortunately this is difficult and neither ATLAS nor CMS are able to measure polarizations. The only direct and sure way to confirm that the particle is indeed a scalar is to plot the angular distribution of the photons in the rest frame of the centre of mass. A spin zero particles like the Higgs carries no directional information away from the original collision so the distribution will be even in all directions. This test will be possible when a much larger number of events have been observed. In the mean time we can settle for less certain indirect indicators.

### The Graviton

In physics, the graviton is a hypothetical elementary particle that mediates the force of gravitation in the framework of quantum field theory. If it exists, the graviton is expected to be massless (because the gravitational force appears to have unlimited range) and must be a spin-2 boson. The spin follows from the fact that the source of gravitation is the stress-energy tensor, a second-rank tensor (compared to electromagnetism's spin-1 photon, the source of which is the four-current, a first-rank tensor). Additionally, it can be shown that any massless spin-2 field would give rise to a force indistinguishable from gravitation, because a massless spin-2 field must couple to (interact with) the stress-energy tensor in the same way that the gravitational field does. This result

suggests that, if a massless spin-2 particle is discovered, it must be the graviton, so that the only experimental verification needed for the graviton may simply be the discovery of a massless spin-2 particle. [3]

## Conclusions

The method developed by the researchers involves transferring a photonic qubit to an atomic qubit trapped inside an optical cavity. The photon-atom quantum information transfer is initiated via a quantum "logic-gate" operation, performed by reflecting the photon from the atom-cavity system, which creates an entangled atom-photon state. [9]

In August 2013, the achievement of "fully deterministic" quantum teleportation, using a hybrid technique, was reported. On 29 May 2014, scientists announced a reliable way of transferring data by quantum teleportation. Quantum teleportation of data had been done before but with highly unreliable methods. [8]

One of the most important conclusions is that the electric charges are moving in an accelerated way and even if their velocity is constant, they have an intrinsic acceleration anyway, the so called spin, since they need at least an intrinsic acceleration to make possible their movement .

The accelerated charges self-maintaining potential shows the locality of the relativity, working on the quantum level also. [1]

The bridge between the classical and quantum theory is based on this intrinsic acceleration of the spin, explaining also the Heisenberg Uncertainty Principle. The particle – wave duality of the electric charges and the photon makes certain that they are both sides of the same thing. The Secret of Quantum Entanglement that the particles are diffraction patterns of the electromagnetic waves and this way their quantum states every time is the result of the quantum state of the intermediate electromagnetic waves. [2]

The key breakthrough to arrive at this new idea to build qubits was to exploit the ability to control the nuclear spin of each atom. With that insight, the team has now conceived a unique way to use the nuclei as facilitators for the quantum logic operation between the electrons. [5]

Basing the gravitational force on the accelerating Universe caused magnetic force and the Planck Distribution Law of the electromagnetic waves caused diffraction gives us the basis to build a Unified Theory of the physical interactions also.

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