

Nanoparticles Therapy to Brain Tumors

Johns Hopkins researchers report that a type of biodegradable, lab-engineered nanoparticle they fashioned can successfully deliver a "suicide gene" to pediatric brain tumor cells implanted in the brains of mice. [35]

A new study at the University of Georgia has found a way to attack cancer cells that is potentially less harmful to the patient. [34]

Doctors have used focused ultrasound to destroy tumors without invasive surgery for some time. However, the therapeutic ultrasound used in clinics today indiscriminately damages cancer and healthy cells alike. [33]

Scientists in the UK have shown for the first time that focused ultrasound from outside the body can improve the delivery of cancer drugs to tumors in humans. [32]

The discovery could help us better understand aging and eventually could lead to new treatments for cancer. [31]

A research team at the University of Delaware, led by Emily Day, an assistant professor of biomedical engineering, is laying the groundwork for a method to inhibit cancer-promoting genes in cancer cells while leaving healthy cells intact. [30]

Researchers have moved closer to the real-time verification of hadron therapy, demonstrating the in vivo accuracy of simulations that predict particle range in the patient. [29]

A biomimetic nanosystem can deliver therapeutic proteins to selectively target cancerous tumors, according to a team of Penn State researchers. [28]

Sunlight is essential for all life, and living organisms have evolved to sense and respond to light. [27]

Using X-ray laser technology, a team led by researchers of the Paul Scherrer Institute PSI has recorded one of the fastest processes in biology. [26]

A Virginia Commonwealth University researcher has developed a procedure for identifying the source of cells present in a forensic biological sample that could change how cell types are identified in samples across numerous industries. [25]

In work at the National Institute of Standards and Technology (NIST) and the University of Maryland in College Park, researchers have devised and demonstrated a new way to measure free energy. [24]

A novel technique developed by researchers at the ARC Centre of Excellence for Nanoscale BioPhotonics (CNBP) will help shine new light on biological questions by improving the quality and quantity of information that can be extracted in fluorescence microscopy. [23]

Micro-computed tomography or "micro-CT" is X-ray imaging in 3-D, by the same method used in hospital CT (or "CAT") scans, but on a small scale with massively increased resolution. [22]

A new experimental method permits the X-ray analysis of amyloids, a class of large, filamentous biomolecules which are an important hallmark of diseases such as Alzheimer's and Parkinson's. [12]

Thumb through any old science textbook, and you'll likely find RNA described as little more than a means to an end, a kind of molecular scratch paper used to construct the proteins encoded in DNA. [20]

Just like any long polymer chain, DNA tends to form knots. Using technology that allows them to stretch DNA molecules and image the behavior of these knots, MIT researchers have discovered, for the first time, the factors that determine whether a knot moves along the strand or "jams" in place. [19]

Researchers at Delft University of Technology, in collaboration with colleagues at the Autonomous University of Madrid, have created an artificial DNA blueprint for the replication of DNA in a cell-like structure. [18]

An LMU team now reveals the inner workings of a molecular motor made of proteins which packs and unpacks DNA. [17]

Chemist Ivan Huc finds the inspiration for his work in the molecular principles that underlie biological systems. [16]

What makes particles self-assemble into complex biological structures? [15]

Scientists from Moscow State University (MSU) working with an international team of researchers have identified the structure of one of the key regions of telomerase—a so-called "cellular immortality" ribonucleoprotein. [14]

Researchers from Tokyo Metropolitan University used a light-sensitive iridium-palladium catalyst to make "sequential" polymers, using visible light to change how building blocks are combined into polymer chains. [13]

Researchers have fused living and non-living cells for the first time in a way that allows them to work together, paving the way for new applications. [12]

UZH researchers have discovered a previously unknown way in which proteins interact with one another and cells organize themselves. [11]

Dr Martin Sweatman from the University of Edinburgh's School of Engineering has discovered a simple physical principle that might explain how life started on Earth. [10]

Nearly 75 years ago, Nobel Prize-winning physicist Erwin Schrödinger wondered if the mysterious world of quantum mechanics played a role in biology. A recent finding by Northwestern University's Prem Kumar adds further evidence that the answer might be yes. [9]

A UNSW Australia-led team of researchers has discovered how algae that survive in very low levels of light are able to switch on and off a weird quantum phenomenon that occurs during photosynthesis. [8]

This paper contains the review of quantum entanglement investigations in living systems, and in the quantum mechanically modeled photoactive prebiotic kernel systems. [7]

The human body is a constant flux of thousands of chemical/biological interactions and processes connecting molecules, cells, organs, and fluids, throughout the brain, body, and nervous system. Up until recently it was thought that all these interactions operated in a linear sequence, passing on information much like a runner passing the baton to the next runner. However, the latest findings in quantum biology and biophysics have discovered that there is in fact a tremendous degree of coherence within all living systems.

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 ratio 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 understand the Quantum Biology.

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Author: George Rajna

Preface

We define our modeled self-assembled supramolecular photoactive centers, composed of one or more sensitizer molecules, precursors of fatty acids and a number of water molecules, as a photoactive prebiotic kernel system. [7]

The human body is a constant flux of thousands of chemical/biological interactions and processes connecting molecules, cells, organs, and fluids, throughout the brain, body, and nervous system. Up until recently it was thought that all these interactions operated in a linear sequence, passing on information much like a runner passing the baton to the next runner. However, the latest findings in quantum biology and biophysics have discovered that there is in fact a tremendous degree of coherence within all living systems. [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.

Nanoparticles deliver 'suicide gene' therapy to pediatric brain tumors growing in mice

Johns Hopkins researchers report that a type of biodegradable, lab-engineered nanoparticle they fashioned can successfully deliver a "suicide gene" to pediatric brain tumor cells implanted in the brains of mice. The poly(beta-amino ester) nanoparticles, known as PBAEs, were part of a treatment that also used a drug to kill the cells and prolong the test animals' survival.

In their study, described in a report published January 2020 in the journal *Nanomedicine: Nanotechnology, Biology and Medicine*, the researchers caution that for safety and biological reasons, it is unlikely that the [suicide gene](#) herpes simplex virus type I thymidine kinase (HSVtk)—which makes tumor cells more sensitive to the lethal effects of the anti-viral drug ganciclovir—could be the exact therapy used to treat human medulloblastoma and atypical teratoid/rhabdoid tumors (AT/RT) in children.

So-called "suicide [genes](#)" have been studied and used in cancer treatments for more than 25 years. The HSVtk gene makes an enzyme that helps restore the function of natural tumor suppression.

Specifically, the experiments found that a combination of the suicide gene and ganciclovir delivered by intraperitoneal injection to mice killed more than 65% of the two types of pediatric brain tumor cells. The combination was deliberately "transfected" with the gene seven days after the nanoparticle therapy was used to deliver the genetic material. Mice bearing an AT/RT-type tumor lived 20% longer after receiving the treatment—42 days, compared to 35 days for untreated mice. Those with a group 3 medulloblastoma-type tumor implanted in the brain lived 63% longer, surviving 31 days compared to 19 days for untreated mice.

"It's an exciting alternate way to be able to deliver gene therapy to a tumor in a selective fashion that targets only tumor cells," says Eric Jackson, M.D., associate professor of neurosurgery at the Johns Hopkins University School of Medicine. "Our idea now is to find other collaborators who may have a gene therapy that they think would work well to kill these tumors."

Medulloblastoma and AT/RT are two of the most prevalent and deadly pediatric brain malignancies. Traditional treatments, including radiation, can harm healthy tissue as well as the tumor, and can produce long-lasting developmental side effects in growing children, making it critical to find new therapies, Jackson notes.

Gene therapy that targets only cancer cells is a promising treatment avenue, but many gene therapy methods use a modified virus to deliver their therapeutic payloads of DNA, a method that may not be safe or suitable for pediatric use. "A lot of these viruses are safe if you have a mature immune system,

but in very young patients with more fragile immune systems, a virus delivery system may pose additional risks," says Jackson.

To address this issue, Jackson collaborated with Jordan Green, Ph.D., an investigator at the Johns Hopkins Kimmel Cancer Center Bloomberg~Kimmel Institute for Cancer Immunotherapy, director of the Johns Hopkins Biomaterials and Drug Delivery Laboratory and professor of biomedical engineering, to find a different kind of carrier for gene [therapy](#). Green and his colleagues developed the PBAE class of polymeric nanoparticles, which can be engineered to bind and carry DNA.

The biodegradable PBAEs are injected into a tumor mass where they safely release their DNA cargo after being ingested by tumor cells. In previous studies that used similar particles to deliver [gene therapy](#) to adult brain cancers and liver cancers in cell cultures and in rodents, Green and his colleagues found that the nanoparticles preferentially target tumor cells over healthy cells.

The mechanism that allows the particles to target [tumor cells](#) preferentially is still being investigated, but Green thinks "the chemical surface of the particle is likely interacting with proteins that are on the surface of certain types of cancer cells."

Green and his colleagues altered the nanoparticles to target the two pediatric malignancies. "By making small chemical changes to the polymers that make up the nanoparticles, we can significantly change the cellular uptake into particular kinds of [cancer cells](#), and the subsequent gene delivery to the cytosol, in a cell-specific way," Green says.

Jackson says he hopes the nanoparticles can be used to deliver a variety of gene-based treatments—including therapies that alter the expression levels of genes, turn genes on and off altogether, or sensitize [cells](#) to other therapies—depending on the specifics of a patient's [tumor](#). "In some ways, we're still in the discovery phase of what genes to target" in medulloblastoma and AT/RT, he says.

The [nanoparticles](#) "can carry larger genes than what can be carried by a virus, and can carry combinations of genes," says Green. "It's a platform that doesn't have limitations on the cargo size being delivered, or limitations related to immunogenicity or toxicity. And, it is easier to manufacture than a virus." [35]

Study finds salt nanoparticles are toxic to cancer cells

A new study at the University of Georgia has found a way to attack cancer cells that is potentially less harmful to the patient. Sodium chloride nanoparticles—more commonly known as salt—are toxic to cancer cells and offer the potential for therapies that have fewer negative side effects than current treatments.

Led by Jin Xie, associate professor of chemistry, the study found that SCNPs can be used as a Trojan horse to deliver ions into cells and disrupt their internal environment, leading to [cell death](#). SCNPs become salt when they degrade, so they're not harmful to the body.

"This technology is well suited for localized destruction of [cancer cells](#)," said Xie, a faculty member in the Franklin College of Arts and Sciences. "We expect it to find wide applications in treatment of bladder, prostate, liver, and head and neck cancer."

Nanoparticles are the key to delivering SCNPs into cells, according to Xie and the team of researchers. Cell membranes maintain a gradient that keeps relatively low sodium concentrations inside cells and relatively high sodium concentrations outside cells. The plasma membrane prevents sodium from entering a cell, but SCNPs are able to pass through because the cell doesn't recognize them as [sodium ions](#).

Once inside a cell, SCNPs dissolve into millions of sodium and chloride ions that are trapped inside by the gradient and overwhelm protective mechanisms, inducing rupture of the plasma membrane and cell death. When the [plasma membrane](#) ruptures, the molecules that leak out signal the [immune system](#) that there's tissue damage, inducing an inflammatory response that helps the body fight pathogens.

"This mechanism is actually more toxic to cancer cells than normal cells, because cancer cells have relatively high sodium concentrations to start with," Xie said.

Using a [mouse model](#), Xie and the team tested SCNPs as a potential cancer therapeutic, injecting SCNPs into tumors. They found that SCNPs suppressed [tumor growth](#) by 66 percent compared to the control group, with no drop in body weight and no sign of toxicity to major organs.

They also performed a vaccination study, inoculating mice with cancer cells that had been killed via SCNPs or freeze thaw. These mice showed much greater resistance to a subsequent live cancer cell challenge, with all animals remaining tumor free for more than two weeks.

The researchers also explored anti-cancer immunity in a tumor model. After injecting primary tumors with SCNPs and leaving secondary tumors untreated, they found that the secondary tumors grew at a much lower speed than the control, showing a tumor inhibition rate of 53 percent.

Collectively, the results suggest that SCNPs killed cancer cells and converted the dying cancer cells to an in situ vaccine.

SCNPs are unique in the world of inorganic particles because they are made of a benign material, and their toxicity is based on the nanoparticle form, according to Xie.

"With a relatively short half-life in aqueous solutions, SCNPs are best suited for localized rather than systemic therapy. The treatment will cause immediate and immunogenic cancer cell death," he said. "After the treatment, the nanoparticles are reduced to salts, which are merged with the body's fluid

system and cause no systematic or accumulative toxicity. No sign of systematic toxicity was observed with SCNPs injected at high doses."

The study was published in *Advanced Materials*. [34]

Ultrasound selectively damages cancer cells when tuned to correct frequencies

Doctors have used focused ultrasound to destroy tumors without invasive surgery for some time. However, the therapeutic ultrasound used in clinics today indiscriminately damages cancer and healthy cells alike.

Most forms of ultrasound-based therapies either use high-intensity beams to heat and destroy [cells](#) or special contrast agents that are injected prior to ultrasound, which can shatter [nearby cells](#). Heat can harm [healthy cells](#) as well as [cancer cells](#), and contrast agents only work for a minority of tumors.

Researchers at the California Institute of Technology and City of Hope Beckman Research Institute have developed a low-intensity ultrasound approach that exploits the unique physical and structural properties of tumor cells to target them and provide a more selective, safer option. By scaling down the intensity and carefully tuning the frequency to match the [target cells](#), the group was able to break apart several types of cancer cells without harming healthy blood cells.

Their findings, reported in *Applied Physics Letters*, are a new step in the emerging field called oncotripsy, the singling out and killing of cancer cells based on their [physical properties](#).

"This project shows that ultrasound can be used to target cancer cells based on their mechanical properties," said David Mittelstein, lead author on the paper. "This is an exciting proof of concept for a new kind of cancer therapy that doesn't require the cancer to have unique molecular markers or to be located separately from healthy cells to be targeted."

A solid mechanics lab at Caltech first developed the theory of oncotripsy, based on the idea that cells are vulnerable to ultrasound at specific frequencies—like how a trained singer can shatter a wine glass by singing a specific note.

The Caltech team found at certain frequencies, low-intensity ultrasound caused the cellular skeleton of cancer cells to break down, while nearby healthy cells were unscathed.

"Just by tuning the frequency of stimulation, we saw a dramatic difference in how cancer and healthy cells responded," Mittelstein said. "There are many questions left to investigate about the precise mechanism, but our findings are very encouraging."

The researchers hope their work will inspire others to explore oncotripsy as a treatment that could one day be used alongside chemotherapy, immunotherapy, radiation and surgery. They plan to gain a better understanding of what specifically occurs in a cell impacted by this form of ultrasound. [33]

Ultrasound can trigger and enhance cancer drug delivery

Scientists in the UK have shown for the first time that focussed ultrasound from outside the body can improve the delivery of cancer drugs to tumours in humans. In the clinical trial, the team injected 10 patients with heat-sensitive capsules filled with a chemotherapy agent and then heated tumours with ultrasound. The technique could reduce the dose of toxic drugs needed to treat cancers and lead to new ways of dealing with tumours that are hard to treat with conventional chemotherapy, according to the researchers.

Delivering an effective dose of drugs to a tumour while minimizing toxicity elsewhere in the body is a major challenge in cancer treatment. One promising idea involves using drug-filled nano-capsules. These capsules increase the half-life of chemotherapy agents in the body and are designed to accumulate – either passively or through active targeting – in tumours. But they do not always release their payload effectively.

In the latest study, described in [The Lancet Oncology](#), [Paul Lyon](#) and colleagues at the University of Oxford conducted a 10-patient phase 1 clinical trial to test the safety and feasibility of using focussed ultrasound to heat liver tumours and trigger the release of a chemotherapy drug from heat-sensitive, lipid-based carrier.

Temperature-sensitive carrier

All 10 patients had inoperable liver tumours. Under general anaesthetic, they each received a single intravenous dose of the chemotherapy agent doxorubicin encased in a temperature-sensitive liposomal carrier. A focussed ultrasound device, operating at a frequency of 0.96 MHz, was then used to heat the target liver tumour to over 39.5°C – which is the temperature at which the capsule is design to release the drug.

In six patients the temperature of the tumour was monitored using a temporary implanted probe, and tumour biopsies were taken before and after drug infusion, and after ultrasound exposure to estimate drug concentration within the tumour at different treatment stages. In the remaining four patients, biopsies were only taken after ultrasound exposure. The researchers used predictive models to calculate the ultrasound parameters needed to heat the tumours to a temperature in the range of 39.5–43°C. The researchers say this procedure better reflects how the technique might be used in clinical practice.

Following focussed ultrasound exposure, doxorubicin concentrations within the tumours increased by an average of 3.7 times. In seven out of the 10 patients there was at least a doubling of the drug within the tumour. One patient showed an estimated nine times increase in drug concentration within their tumour after ultrasound heating.

Safe trigger

The researchers say that their results build on decades of promising preclinical research to demonstrate that it is possible to safely trigger the release of cancer drugs deep within the body using focussed ultrasound. They add that the several-fold average increase in drug concentration seen highlights the clinical potential of such techniques.

“Only low levels of chemotherapy entered the tumour passively. The combined thermal and mechanical effects of ultrasound not only significantly enhanced the amount of doxorubicin that enters the tumour, but also greatly improved its distribution, enabling increased intercalation of the drug with the DNA of cancer cells,” explains Lyon.

This opens the way not only to making more of current drugs but also targeting new agents where they need to be most effective

“A key finding of the trial is that the tumour response to the same drug was different in regions treated with ultrasound compared to those treated without, including in tumours that do not conventionally respond to doxorubicin,” adds Oxford’s [Mark Middleton](#). “The ability of ultrasound to increase the dose and distribution of drug within those regions raises the possibility of eliciting a response in several difficult-to-treat solid tumours. This opens the way not only to making more of current drugs but also targeting new agents where they need to be most effective.”

Precise anatomical location

[Jeff Karp](#), Professor of Medicine at the Brigham and Women’s Hospital, in Boston, US, told *Physics World* that “this is a very well performed study in human patients”. He adds: “Although some limitations exist, this study demonstrates that by using thermo-sensitive liposomes in combination with ultrasound, it’s feasible to safely enhance the intratumoral delivery of therapeutic molecules to a precise anatomical location in human patients and improve the therapeutic outcome.”

Karp says that the next step in this line of research is to test this approach in other solid tumours and with other drugs. He adds that the development of ultrasound devices that can precisely target different types and sizes of tumours, and ultrasound-sensitive delivery vehicles may further improve drug delivery and reduce side effects. [32]

Scientists find a link between cancer and aging inside our cells

Scientists at Hollings Cancer Center at the Medical University of South Carolina have found that human lung cancer cells resist dying by controlling parts of the aging process, in results published online May 10th in the *Journal of Biological Chemistry*. The discovery could help us better understand aging and eventually could lead to new treatments for cancer.

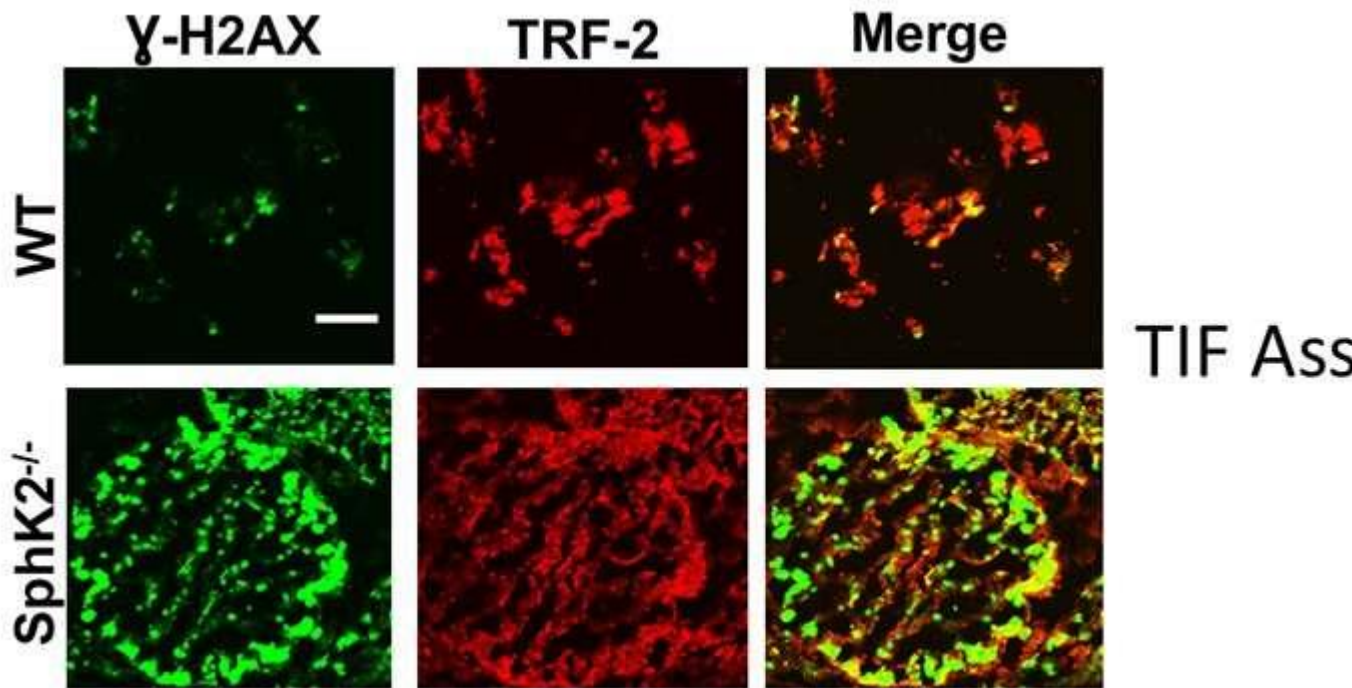
Cancer becomes more common as people get older, but scientists are still searching for answers about why this happens. At Hollings Cancer Center, research into the connections between aging and [cancer](#) is led by Besim Ogretmen, Ph.D., SmartState Endowed Chair in Lipidomics and Drug Discovery. Ogretmen’s team found that cancer cells have specific ways to resist dying the way [normal cells](#) do. They do so by protecting the tips of their chromosomes, which hold our DNA, from age-related damage.

Ogretmen studies how cancer cells are different than normal cells to understand how cancer grows and spreads in the body. His work is part of an \$8.9 million program project grant to research how alterations of lipid metabolism affect cancer therapy. The grant is helping fund a clinical trial of an anticancer medicine to inhibit cellular signaling that helps cancer survive. The drug was found to be useful against cancer in the research reported in the group's new paper.

As normal cells get older, the tips of their chromosomes, called telomeres, can start to break down, which is a signal for the cell to die. This seems to be part of the aging process in normal cells. However, cancer cells have developed a way to prevent their telomeres from falling apart, which helps them to live much longer than normal cells. The long life of cancer cells is part of what allows them to grow and spread throughout the body.

In their new paper, Ogretmen's research group discovered a specific way that cancer cells escape death in response to telomere damage. Scientists have known that various types of cancer cells have low levels of a protein called p16. Ogretmen's group found that, when telomeres become damaged by age or in response to chemotherapy, p16 is a type of cellular decision-maker, where it helps cells decide to grow older or to simply die.

"Telomeres are like a biological clock for our cells," said Ogretmen. "In cancer, this biological clock is broken."



These laboratory images show induction of telomere damage induction (yellow in merged images). Credit: Besim Ogretmen, Ph.D.

The researchers found that p16 became most important to cells when their telomeres began to break down. When that happened, p16 rushed into action and pushed cells toward further aging by inhibiting cell death.

To determine the clinical impact of these data, the researchers used a chemical enzyme inhibitor to cause telomere damage in several types of cancer cells, including lung cancer cells. The inhibitor, ABC294640, acts in a way that prevents cancer [cells](#) from protecting their telomeres, by inhibiting an enzyme called sphingosine kinase 2. This inhibition was shown to force telomeres to break down.

As a result of this enzyme inhibition, telomeres were damaged, resulting in cancer cell death when p16 levels were low or absent. However, [cancer cells](#) with high levels of p16 were able to escape death, and stayed biologically inactive, which was a sign of aging.

"We're excited that there is at least one mechanism that can help us understand how aging is associated with a higher risk of cancer," said Ogretmen. "And then, can we prevent or better treat the aging-related cancers by controlling protective effects of p16 for cancer cell death?"

Ogretmen's group is enthusiastic that the inhibitor in their study might help combat cancer at many levels. The team has already identified the safest dose for use in patients and is planning a phase 2 clinical trial using their inhibitor in patients with a type of liver cancer called hepatocellular carcinoma. The multisite trial will include Hollings Cancer Center, Penn State, the University of Maryland, Mayo Clinic and others.

It is especially important to do this work now, given the predicted forecast by researchers at the National Cancer Institute (NCI) who foresee a 'silver tsunami' of cancer survivors. NCI studies show that by 2040 the number of cancer survivors in the United States will increase by nearly 11 million: from 15.5 million in 2016 to 26.1 million in 2040. A large part of the makeup of the cancer survivor population will shift to older populations. It's estimated that by 2040 only 18 per-cent of cancer survivors will be between ages 50 and 64, and only 8 percent will be younger than 50.

"We hope that maybe we can do both: delay aging and prevent the growth of cancer," said Ogretmen. "That's the ultimate outcome of this." [31]

Shining a light on gene regulation

Cancer treatments—from radiation to surgery to chemotherapy—are designed to remove or kill cancerous cells, but healthy cells often become collateral damage in the process. What if you could use lasers to pinpoint the treatment area and deliver medicine to cancer cells only?

A research team at the University of Delaware, led by Emily Day, an assistant professor of [biomedical engineering](#), is laying the groundwork for a method to inhibit cancer-promoting [genes](#) in cancer [cells](#) while leaving [healthy cells](#) intact. In a new paper published in *Nano Letters*, the team reveals unprecedented insights into this promising method, which involves coating [nanoparticles](#) with gene-regulatory agents and then exposing them to a dose of laser light to unleash that material.

Because the nanoparticles hold the gene regulatory agents inactive until their release is triggered on-demand with light, they have substantial potential to enable high precision cancer therapy while minimizing impact to non-irradiated healthy cells. Day and her team tested their new method against brain tumor cells by using the nanoparticles to silence the expression of green fluorescent protein (GFP) in the cells.

A new way to combine lasers and nanoparticles

Like scalpels and sutures, lasers are often used in medical procedures. Ophthalmologists use lasers to reshape corneas in vision-correcting eye surgery. Dermatologists use lasers to fade scars on skin. Cardiologists use lasers to open clogged arteries. Oncologists use lasers to destroy cancerous cells and tumors.

The Day Lab aims to combine lasers with light-responsive gene regulatory nanoparticles to strategically annihilate cancer cells and minimize collateral damage.

They start with small interfering RNAs, known as siRNAs, which are molecules consisting of complementary strands of RNA that can reduce the expression of certain genes in cancer cells. The siRNAs are coated on nanoparticles made of silica and gold, which measure smaller than the width of a human hair. These particles protect the siRNAs until they reach the desired treatment area. The question is—how do you release them at exactly the right spot?

"Previously, if people wanted to deliver RNA with nanoparticles, they might coat the nanoparticles with a polymer or cell-penetrating peptide, an agent to facilitate cell uptake and delivery," Day said. "The problem is that those agents aren't specific. You end up getting gene regulation in all cells, not just the cancer cells you intended to target for gene regulation."

That's where the precision of lasers comes in.

"Light-triggered siRNA release enables you to silence genes only where the particles and light are combined," Day said. "Since you choose where the light goes, and thus where the siRNA is released, you can achieve very specific gene silencing in tumor cells, reducing the potential for off-target effects."

For these experiments, Day and her team (led by Department of Biomedical Engineering graduate student Rachel Riley) exposed the siRNA-coated nanoparticles to either continuous wave light or short pulses of light administered every one quadrillionth of a second. Both types of irradiation triggered the release of siRNA in double-stranded and single-stranded forms, which came as a surprise since previous studies in the scientific literature suggested that continuous wave irradiation would release only single strands of siRNA (meaning that the two complementary strands of the siRNA separated from each other, rather than the entire duplex releasing from the nanoparticle surface).

"This is the first time anyone has shown that you can get both siRNA duplexes and single strands of RNA to release from nanoparticles using a continuous wave laser as the excitation source," said Day. "However, our studies also reveal that pulsed light is much more efficient at releasing siRNA duplexes than continuous wave light. It is imperative that primarily duplexes be released from the

nanoparticles because only duplexed siRNA will function inside cells to silence expression of the targeted genes."

Day continued, "Further, our studies show that pulsed light doesn't heat up cells like continuous wave light does. This is important since too much heat can cause cells to be damaged by mechanisms other than the desired gene regulation."

Her lab group is well-equipped to uncover such insights regarding the mechanism of light-triggered RNA release from nanoparticles because they perform unique interdisciplinary research.



From left, Margaret Billingsley, Emily Day, and Rachel Riley are shown working on one of their previous research studies, this one on cancer detection. Credit: University of Delaware, Evan Krape, Emily Day and Joy Smoker

"My lab has a lot of expertise in RNA delivery and cancer biology, so we have a lot more molecular biology skills than a traditional nanotechnology lab might have, and this enables us to study the function of RNA nanocarriers with unprecedented detail," she said.

The new insight that Day's research sheds on the use of continuous wave light versus pulsed light for triggered siRNA release from nanoparticles is an important contribution to the field of drug delivery. In addition to demonstrating the functional differences between the two modes of light excitation, the team also showed that siRNA released from nanoparticles upon exposure to pulsed light reduced

the expression of the targeted gene (green fluorescent protein) better than a commercially available material often used to deliver siRNA into cells in lab experiments. This was an exciting observation demonstrating the potential impact of this new system.

This work was conducted in collaboration with Lars Gundlach in the Department of Chemistry and Biochemistry and the Department of Physics and Astronomy at UD, which owns the pulsed laser used in these experiments. Much more research is needed before this could be translated to a viable treatment for cancer patients.

What's next?

"The next step would be to show that we can do this with a more functional and biologically relevant RNA cargo than the siRNA targeting green fluorescent protein that was used in this work," Day said. "There are a lot of different genes that are known to control cancer growth, so we will deliver RNA that targets genes that we know to be important in tumor progression and see if we are delivering enough to have an impact."

The team is particularly interested in studying the delivery of siRNA targeting beta-catenin, which plays an important role in triple-negative breast cancer, and also the delivery of microRNA (which is similar to siRNA, but can regulate multiple genes simultaneously). For example, Day's team hopes to deliver miR-34a, which is considered a master regulator of gene expression in cancer.

In addition to Day and Gundlach, the paper's authors include Rachel Riley, a doctoral student in the Department of Biomedical Engineering; Megan Dang, a doctoral student in Department of Biomedical Engineering; Maggie Billingsley, a senior undergraduate student in the Department of Biomedical Engineering; Baxter Abraham, a doctoral student in the Department of Chemistry and Biochemistry.

Riley, who will soon begin work as a postdoctoral associate at the University of Pennsylvania, started graduate school at UD because she wanted to do science that could make a real impact on the medical field. After losing an aunt to cancer, she was especially motivated to put her talents toward research that could someday help patients.

"The Day Lab's idea of incorporating nanoparticles for specific delivery of therapeutic agents was a really unique approach," she said.

Billingsley has done research in the Day Lab since her first year at UD and wrote three peer-reviewed papers based on her work in the group. In 2017, she was the first author on a paper published in *PLOS One*. Next, Billingsley will attend graduate school at the University of Pennsylvania, where she will study immunotherapy. (She and Riley, a duo Day calls a "dream team," could likely work together in the future.)

"When interviewing with graduate schools, this experience with The Day Lab was the main thing that helped me stand out in interviews and also understand what I wanted out of graduate school," Billingsley said. "I have had so many opportunities to go down my own path and also work with others on new methods, ideas, and areas of research."

This paper also gave Billingsley a taste of an important aspect of scientific discovery.

"We found some results that conflicted with literature, which was a new experience for me," she said. "That was more exciting than just confirming what was expected."

Overall, Day and her team are excited to further pursue this technology to reveal its potential as a high precision cancer therapy. [30]

Simulated PET scans verify proton therapy delivery

Researchers have moved closer to the real-time verification of hadron therapy, demonstrating the *in vivo* accuracy of simulations that predict particle range in the patient. The new Monte Carlo tool is a key component of a system that measures particle range during treatment and compares it with the predictions.

Housed in the synchrotron facility at the National Centre of Oncological Hadrontherapy ([CNAO](#)) in Pavia, the INSIDE system is being developed by an Italian collaboration (See [INSIDE in-beam PET monitors proton range](#)). It combines a PET scanner that maps positron emitters generated during irradiation and Dose Profiler, a new tracking detector that detects signals from secondary charged particles produced by heavy ion beams.

In their latest study, the researchers used their simulation tool in the first analysis of *in vivo* PET data, acquired from a single patient in December 2016 ([Physica Medica 10.1016/j.ejmp.2018.05.002](#)).

By monitoring particle range during treatment, clinics can identify when changes in anatomy produce unacceptable deviations from a patient's planned treatment. For example, tumours may shrink as they respond to treatment, while specific anatomy such as the paranasal sinuses can contain air or higher density mucous. Armed with such information, clinicians can better exploit the sharp dose gradients that protons and heavy ions provide to target the tumour and spare healthy tissue.

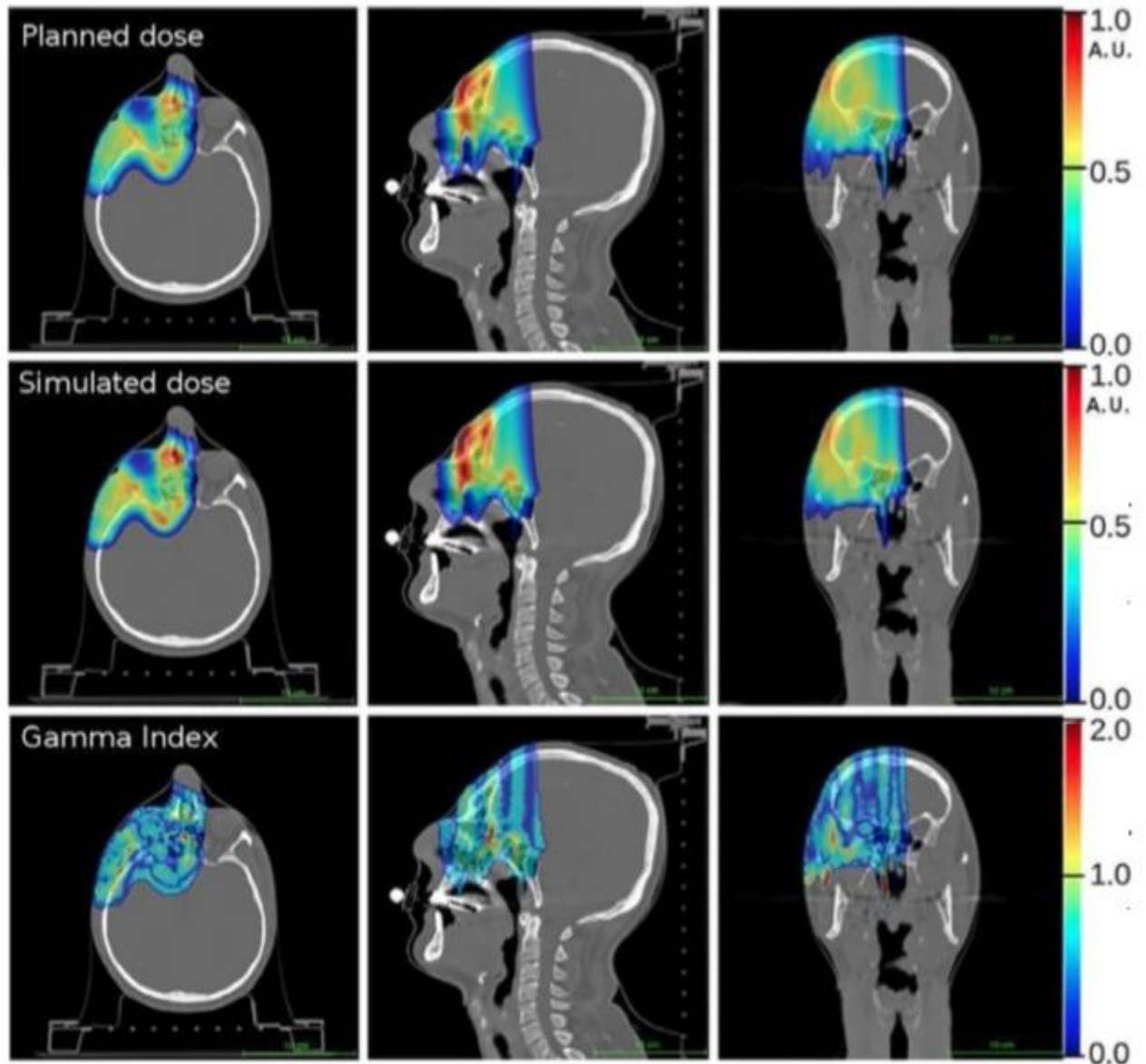
"An accurate Monte Carlo prediction combined with precision imaging would allow the physician to verify the accuracy of the treatment on a daily basis," said joint first author Elisa Fiorina of the National Institute for Nuclear Physics ([INFN](#)) in Turin. In the longer term, the INSIDE technology could potentially be applied for adaptive particle therapy, where treatments are modified for changes in patient anatomy.

The simulation tool generates 4D PET scans using the treatment plan parameters, such as beam energies and spot positions. The patient's geometry and composition is provided by the CT scan acquired for treatment planning. Based on these data, the tool predicts the propagation of therapeutic particles in the patient and subsequent generation and annihilation of positron-emitting isotopes. The resulting gamma rays are used to construct the PET scan. The tool incorporates models of the beamline at CNAO, the spatial and temporal characteristics of the treatment beam, as well as the geometry and composition of the INSIDE system.

Preliminary study

The researchers acquired PET scans during two proton therapy fractions of a 56-year-old patient with carcinoma of the lacrimal gland. Data were acquired over the entire irradiation of one of two fields. Images were updated every 10 s, enabling a visual, qualitative comparison between the measured and simulated data during treatment.

In a comparison with the prescribed treatment plan, dose distributions derived from the simulation proved accurate. Gamma tests demonstrated 91% of voxels agreed to within 3% or 3mm and 98% of voxels to within 5% or 5 mm.



[Comparison of prescribed dose distributions calculated by the treatment planning system with dose predicted by the INSIDE Monte Carlo tool. \(Courtesy: E Fiorina *et al Physica Medica* 10.1016/j.ejmp.2018.05.002 ©2018, Associazione Italiana di Fisica Medica\)](#)

Particle range in the predicted and measured PET images was quantified using iso-activity surfaces corresponding to 10% of the maximum voxel intensity in the scans. The researchers demonstrated that the average distance between the surfaces in the two images was less than 1 mm. The analysis was carried out off-line, but the authors envisage that a real-time implementation will be straightforward, enabling a quantitative analysis while the patient is still being irradiated.

“These first *in vivo* measurements demonstrate that the developed Monte Carlo simulation tool ... is accurate enough to be used as a reference in the PET image analysis,” said Fiorina.

Based on their findings, the researchers are beginning clinical trials later this year, in which the INSIDE system will incorporate a more precise detector positioning system. The trials will include more

rigorous tests of the system's accuracy, including that of the Dose Profiler, using a cohort of around 40 patients. The researchers will also investigate how well the system integrates into routine clinical workflow and potential clinical compliance limits in particle range. The cohort will include individuals with cancers known to respond early to treatment, the group set to benefit most from monitoring. [29]

Camouflaged nanoparticles used to deliver killer protein to cancer

A biomimetic nanosystem can deliver therapeutic proteins to selectively target cancerous tumors, according to a team of Penn State researchers.

Using a [protein](#) toxin called gelonin from a plant found in the Himalayan mountains, the researchers caged the proteins in self-assembled metal-organic framework (MOF) nanoparticles to protect them from the body's immune system. To enhance the longevity of the drug in the bloodstream and to selectively target the tumor, the team cloaked the MOF in a coating made from cells from the tumor itself.

Blood is a hostile environment for drug delivery. The body's immune system attacks alien molecules or else flushes them out of the body through the spleen or liver. But cells, including cancer cells, release small particles called extracellular vesicles that communicate with other cells in the body and send a "don't eat me" signal to the immune system.

"We designed a strategy to take advantage of the extracellular vesicles derived from tumor [cells](#)," said Siyang Zheng, associate professor of biomedical and electrical engineering at Penn State. "We remove 99 percent of the contents of these extracellular vesicles and then use the membrane to wrap our metal-organic framework nanoparticles. If we can get our extracellular vesicles from the patient, through biopsy or surgery, then the nanoparticles will seek out the tumor through a process called homotypic targeting."

Gong Cheng, lead author on a new paper describing the team's work and a former postdoctoral scholar in Zheng's group now at Harvard, said, "MOF is a class of crystalline materials assembled by metal nodes and organic linkers. In our design, self-assembly of MOF nanoparticles and encapsulation of proteins are achieved simultaneously through a one-pot approach in aqueous environment. The enriched metal affinity sites on MOF surfaces act like the buttonhook, so the extracellular vesicle membrane can be easily buckled on the MOF nanoparticles. Our biomimetic strategy makes the synthetic nanoparticles look like extracellular vesicles, but they have the desired cargo inside."

The nanoparticle system circulates in the bloodstream until it finds the [tumor](#) and locks on to the cell membrane. The cancer cell ingests the nanoparticle in a process called endocytosis. Once inside the cell, the higher acidity of the cancer cell's intracellular transport vesicles causes the metal-organic framework [nanoparticles](#) to break apart and release the toxic protein into cytosol and kill the cell.

"Our [metal-organic framework](#) has very high loading capacity, so we don't need to use a lot of the particles and that keeps the general toxicity low," Zheng said.

The researchers studied the effectiveness of the nanosystem and its toxicity in a small animal model and reported their findings in a cover article in the *Journal of the American Chemical Society*.

The researchers believe their nanosystem provides a tool for the targeted delivery of other proteins that require cloaking from the immune system. Penn State has applied for patent protection for the technology. [28]

New technique that shows how a protein 'light switch' works may enhance biological research

Sunlight is essential for all life, and living organisms have evolved to sense and respond to light. Dronpa is a protein "light switch" that can be turned on and off by light. A team of scientists led by Peter Tonge, a Professor in the Department of Chemistry at Stony Brook University, has discovered a way to use infrared spectroscopy to determine for the first time structure changes that occur in Dronpa during the transition from the dark (off) state to the light (on) state. Their findings are reported in a paper published early online in *Nature Chemistry*.

According to Tonge, the technique and their findings will help the researchers understand how this "[light switch](#)" works and enable them to redesign Dronpa for applications in biology and medicine.

"A key challenge in understanding how the switch works in Dronpa is to determine how the initial interaction of light—which happens very, very fast – in less than one quadrillionth of a second – changes the dynamics and ultimately turns the switch on in a process that occurs millions of times more slowly.

In our work we used an instrument that can look at the vibrations of Dronpa over many decades of time so that we could visualize the entire activation process in one experiment," he explained. [27]

Biological light sensor filmed in action

Using X-ray laser technology, a team led by researchers of the Paul Scherrer Institute PSI has recorded one of the fastest processes in biology. In doing so, they produced a molecular movie that reveals how the light sensor retinal is activated in a protein molecule. Such reactions occur in numerous organisms that use the information or energy content of light – they enable certain bacteria to produce energy through photosynthesis, initiate the process of vision in humans and animals, and regulate adaptations to the circadian rhythm. The movie shows for the first time how a protein efficiently controls the reaction of the embedded light sensor. The images, now published in the journal *Science*, were captured at the free-electron X-ray laser LCLS at Stanford University in California. Further investigations are planned at SwissFEL, the new free-electron X-ray laser at PSI. Besides the scientists from Switzerland, researchers from Japan, the USA, Germany, Israel, and Sweden took part in this study.

The molecule retinal is a form of vitamin A and is of central importance to humans, animals, certain algae, and many bacteria. In the retina of the human eye, retinal triggers the process of vision when it changes its shape under the influence of [light](#). In a similar form, certain bacteria also use this reaction to pump protons or ions through the cell membrane. Light energy can be stored in this way, as in the reservoir of an alpine hydropower plant, so that it is available on demand as biological fuel. To ensure efficient utilisation of light, the retinal molecule is embedded in proteins that play a critical role in regulating the process. The [protein](#)-regulated reaction of retinal is one of the fastest biological processes and occurs within 500 femtoseconds (a femtosecond is one-millionth of one-billionth of a second). That is roughly a trillion times faster than the blink of an eye, says Jörg Standfuss, who heads the group for time-resolved crystallography in the Division of Biology and Chemistry at PSI. What happens in the process on the atomic level has now been captured for the first time by PSI researchers, in 20 snapshots that they have assembled into a molecular movie. No one has previously measured a retinal protein at such high speed and with such precision. It's a world record, says Jörg Standfuss, who led the study.

The researchers studied the protein bacteriorhodopsin, which is found in simple microbes. When the retinal molecule embedded in the bacteriorhodopsin traps a light particle, it changes its original elongated shape into a curving form, like when a cat arches its back, explains the PSI researcher. Such changes can also be observed when retinal is examined in a solution without protein. There, though, different reactions, which are also less productive, take place. Proteins are like factories in which chemical reactions run especially efficiently, Jörg Standfuss explains. We wanted to look at how this interplay between the protein and the molecule functions.

In serial crystallography, crystals are injected into an X-ray beam. When the beam and the crystal meet, rays of light are diffracted. The diffracted light rays are recorded by a detector. From the light patterns that many identical crystals produce ...[more](#)

A surprising observation

The researchers discovered that water molecules in the vicinity of the retinal play a critical role. They were able to observe how the water molecules moved aside and made room for the retinal molecule to do its cat-arching-its-back move – in the technical jargon, a trans-cis isomerisation. This detail, which no one had seen before, surprised Jörg Standfuss, as he explains with the help of the cat analogy: You expect that a cat might arch its back to scare another one away. But here the second cat runs away even before the first has arched its back. Computer simulations confirm the measurements, which could be explained by ultrafast quantum processes.

Besides the retinal reaction, the researchers were also able to detect protein quakes that had been predicted by theory. The arching of the cat's back does not require the entire energy of the light that falls on the protein. Excess energy is released, evidently, not in the form of heat but rather in vibrations of the protein.

The film shows the transition between the main states of retinal within the first picoseconds after activation in the binding pocket of the bacteriorhodopsin. Credit: Paul Scherrer Institute/Przemyslaw Nogly and Tobias Weinert

New measurements planned at SwissFEL

For their images, the PSI researchers traveled to California, to the free-electron X-ray laser LCLS at Stanford University. In the future, they will be able to realise such films right at PSI with the newly commissioned facility SwissFEL. For such studies, the sample is illuminated with extremely short and intense flashes of laser-quality X-ray light. The X-ray beams are diverted in different directions by the sample and generate diffraction patterns from which the original structure can be calculated.

As samples, the researchers use tiny crystals in which the bacteriorhodopsin is densely packed in an ordered state. The [light sensor](#) in the bacteriorhodopsin is excited by a short pulse from an optical laser. Afterwards, the X-ray flash hits the crystal and lights up the scene. The time between the optical signal and the X-ray flash determines how far the reaction will have progressed. Individual snapshots taken at different points in time can be spliced together into a movie.

After studying bacteriorhodopsin, the PSI researchers want to use SwissFEL to investigate the retinal in rhodopsin in our eyes. Similar retinal proteins can also be artificially incorporated into nerve cells, so it becomes possible to selectively activate nerve cells with light and study their function. With these retinal proteins, one can activate any region in the brain with the help of light, says Jörg Standfuss, explaining the goal of the new field called optogenetics. Measurements with SwissFEL are expected to contribute to the improvement of optogenetics applications. [26]

Breakthrough in cell imaging could have major impact in crime labs

A Virginia Commonwealth University researcher has developed a procedure for identifying the source of cells present in a forensic biological sample that could change how cell types are identified in samples across numerous industries.

Many traditional techniques for distinguishing between saliva, blood, skin or vaginal tissue in an evidence sample are based on microchemical reactions that can be prone to false-positive or false-negative results, according to the researcher, Christopher Ehrhardt, Ph.D., an associate professor in the Department of Forensic Science in the College of Humanities and Sciences. Additionally, they may be difficult to use on aged or heavily degraded samples.

"The information is often limited," Ehrhardt said. "And when using conventional methods, you have to be prepared to consume part of the sample in most cases, which decreases the value of it."

Ehrhardt's procedure aims to change that. He begins by taking microscopic images of the [individual cells](#) using a benchtop microscope or a flow cytometer—a device used in cell biology that photographs individual cells encased within drops of water. Ehrhardt then makes measurements that capture size, shape and fluorescent properties of the cells. Those measurements are then analyzed using machine learning algorithms—in this case computer software programmed to recognize characteristics of the images—to correlate them with cell type.

"This new procedure can be used to identify different cell types in a sample as well as potentially indicate some attributes of the individuals who deposited the cells, like age, sex and so forth,"

Ehrhardt said. "And the best part is that the procedure is nondestructive. After imaging, the cells can be used to generate a DNA profile. This is really important since many samples are very little biological material, so the more information you can get without consuming the sample, the better."



Ehrhardt's process begins by taking microscopic images of the individual cells using a benchtop microscope or a flow cytometer — a device used in cell biology that photographs individual cells encased within drops of water. Credit: Kevin Morley, University Relations

Brent Fagg, technology manager with VCU Innovation Gateway, said forensic laboratories could use this new procedure to improve the efficiency of their testing.

"Traditional forensic testing methods are time-consuming, destructive to samples, and unable to determine the abundance of cell types in a sample," he said. "Using our new procedure, labs will be able to analyze aged or degraded samples in a quick and nondestructive manner—and with much better results."

Fagg said forensic analysis is just one possible application for this new procedure. It also could be used in areas such as pharmaceutical and health care, and even to monitor exposure to disease.

"There are a number of industries that could benefit from this new cell type identification procedure," he said. "And adopting this technique couldn't be easier, as it uses lab equipment common in biology laboratories."

The [procedure](#) was described in a study, "Rapid differentiation of epithelial [cell types](#) in aged biological samples using autofluorescence and morphological signatures," that was published May 18 in the journal *PLOS One*. [25]

A new way to measure energy in microscopic machines

What drives cells to live and engines to move? It all comes down to a quantity that scientists call "free energy," essentially the energy that can be extracted from any system to perform useful work. Without this available energy, a living organism would eventually die and a machine would lie idle.

In work at the National Institute of Standards and Technology (NIST) and the University of Maryland in College Park, researchers have devised and demonstrated a new way to measure [free energy](#). By using microscopy to track and analyze the fluctuating motion or configuration of [single molecules](#) or other small objects, the new method can be applied to a greater variety of microscopic and nanoscopic systems than previous techniques.

"Scientists have relied on free energy to understand complex systems since the development of steam engines. This concept will continue to be just as fundamental as we engineer and design proteins and other single-molecule systems," noted NIST's David Ross, first author of a new paper on this work in *Nature Physics*. "But the measurements are much harder for those small systems—so approaches like the new one we describe will be of fundamental importance," he added.

By measuring changes in free energy as a system moves or alters its internal structure, scientists can predict certain aspects of how a living system will behave or how a machine will operate—without the impossible task of keeping track of the comings and goings of all the atoms and molecules that make up the system.

An everyday example of free energy is in the [internal combustion engine](#) of an automobile, with a total energy equal to the energy of its motion plus the heat it generates. Subtracting the heat energy, which dissipates from the system, leaves the free energy.

In one method, scientists use a microscopic force sensor to pull on a protein or DNA molecule, which can behave as a miniature spring when stretched or compressed, to measure changes in force and position as a system relaxes and releases energy. However, the attachment of the force sensor can disturb the microscopic system and cannot be used to measure changes in free energy that do not involve a straightforward change in position.

The new method, which can use optical microscopy to track the motion or configuration of small systems, determines free energies without the attachment to a [force sensor](#). The new analysis could prove a powerful way to peer into the inner workings of a broad variety of microscopic systems,

including living systems such as viruses or cells to better understand the processes, such as energy intake, chemical reactions and the movement of molecules that keep living systems functioning.

"We are surrounded by natural systems that take advantage of microscopic fluctuations in free energy, and now we have a way to better measure, understand, and, ultimately, manipulate these fluctuations ourselves," said co-author Elizabeth Strychalski of NIST.

The analysis lends itself to studying microscopic systems that start in a highly excited state with high energy, far from equilibrium with their surroundings, and then relax back toward equilibrium. The properties of [microscopic systems](#) can fluctuate significantly as they relax due to the random motion from continuous jostling by surrounding molecules. The new method, which the team refers to as Relaxation Fluctuation Spectroscopy (ReFlucS), uses measurements of those fluctuations during relaxation to determine the free energy.

"Our approach shows that useful information can be gleaned from observing the random motions of a system as it settles down from a highly excited, far-from-equilibrium state," said co-author Christopher Jarzynski of the University of Maryland.

As an exemplary system, the scientists studied the motion of DNA molecules confined to a nanometer-scale space shaped like a staircase. To squeeze into the top steps, which are the shallowest, the DNA molecules must be compressed more tightly than molecules that occupy the bottom steps. This results in a higher free energy for the molecules at the top. By applying an electric field, the team drove the DNA molecules into the top of the staircase. The researchers then turned off the electric field and observed the movement of the molecules with an optical microscope.

The DNA molecules mostly descended the staircase as they relaxed toward equilibrium, decreasing their free energy. However, due to microscopic fluctuations, the DNA molecules occasionally moved back up the staircase, increasing their free energy. The researchers analyzed the fluctuating motion of the DNA [molecules](#), allowing them to map out the free-energy profile—how much free energy there is at different locations, and where the energy is high and low.

"ReFlucS provides access to information about free [energy](#) that was previously inaccessible," said co-author Samuel Stavis of NIST. [24]

Fluorescence microscopy gets the BAMM treatment

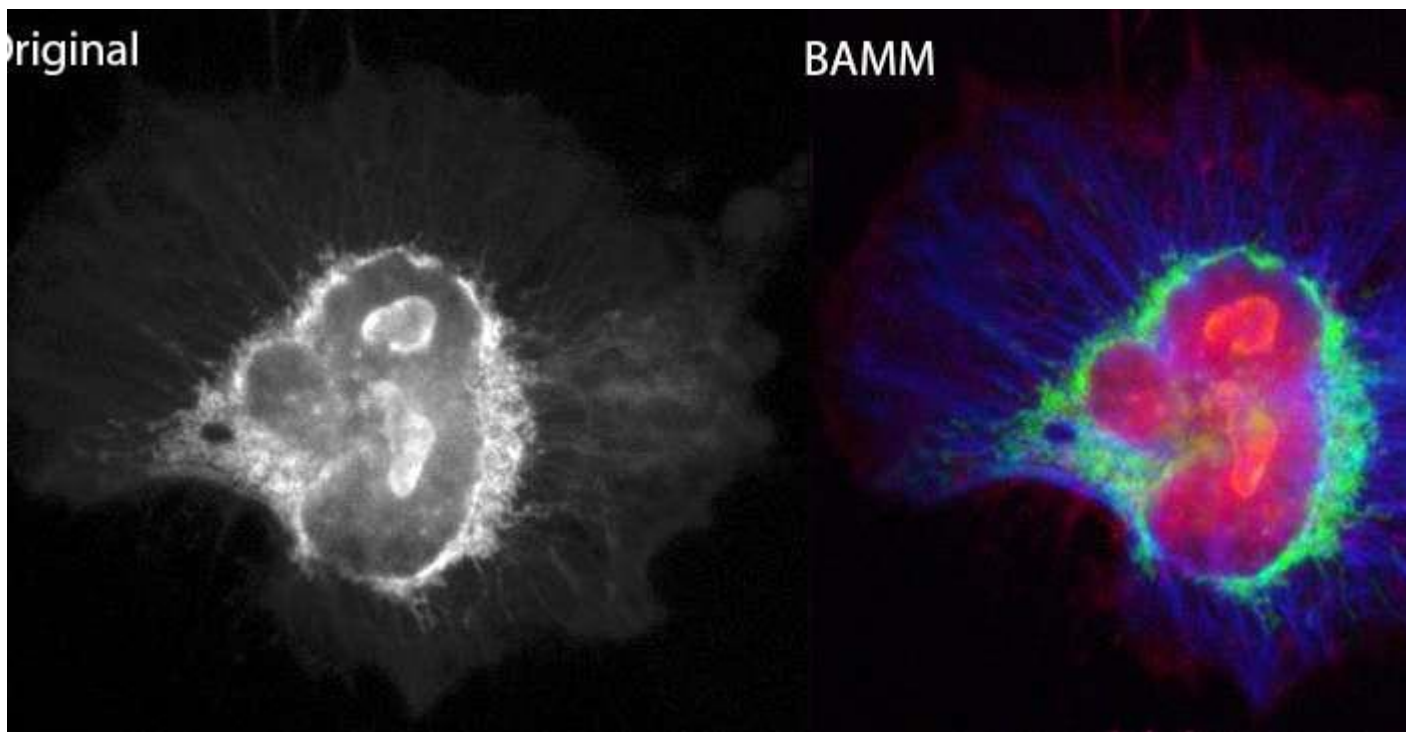
A novel technique developed by researchers at the ARC Centre of Excellence for Nanoscale BioPhotonics (CNBP) will help shine new light on biological questions by improving the quality and quantity of information that can be extracted in fluorescence microscopy.

The technique, 'bleaching-assisted multichannel microscopy' (BAMM) takes a current long-standing weakness of fluorescence microscopy – photobleaching – and turns it into a strength that improves imaging output by up to three times, with no additional hardware required.

Reported in the journal *Biomedical Optics Express*, BAMM will help researchers gain biological insights into the intricate processes taking place within living cells. This includes the interplay between proteins and molecules which have the potential to impact a wide range of health areas from fertility, to pain, to heart disease and more.

"Fluorescence microscopy is one of the most widely used techniques in biology. This is where light emitting molecules called fluorophores are bound to extremely small cellular targets such as proteins, genetic material or other biomolecules of interest," says Dr. Antony Orth, CNBP Research Fellow at RMIT University and lead author of the research paper.

"When the fluorophore is excited by light from the microscope, it reacts by emitting a specific colour signature. Seeing that colour signature under the microscope helps us view, track and understand the cellular target that the fluorophore has been bound to."



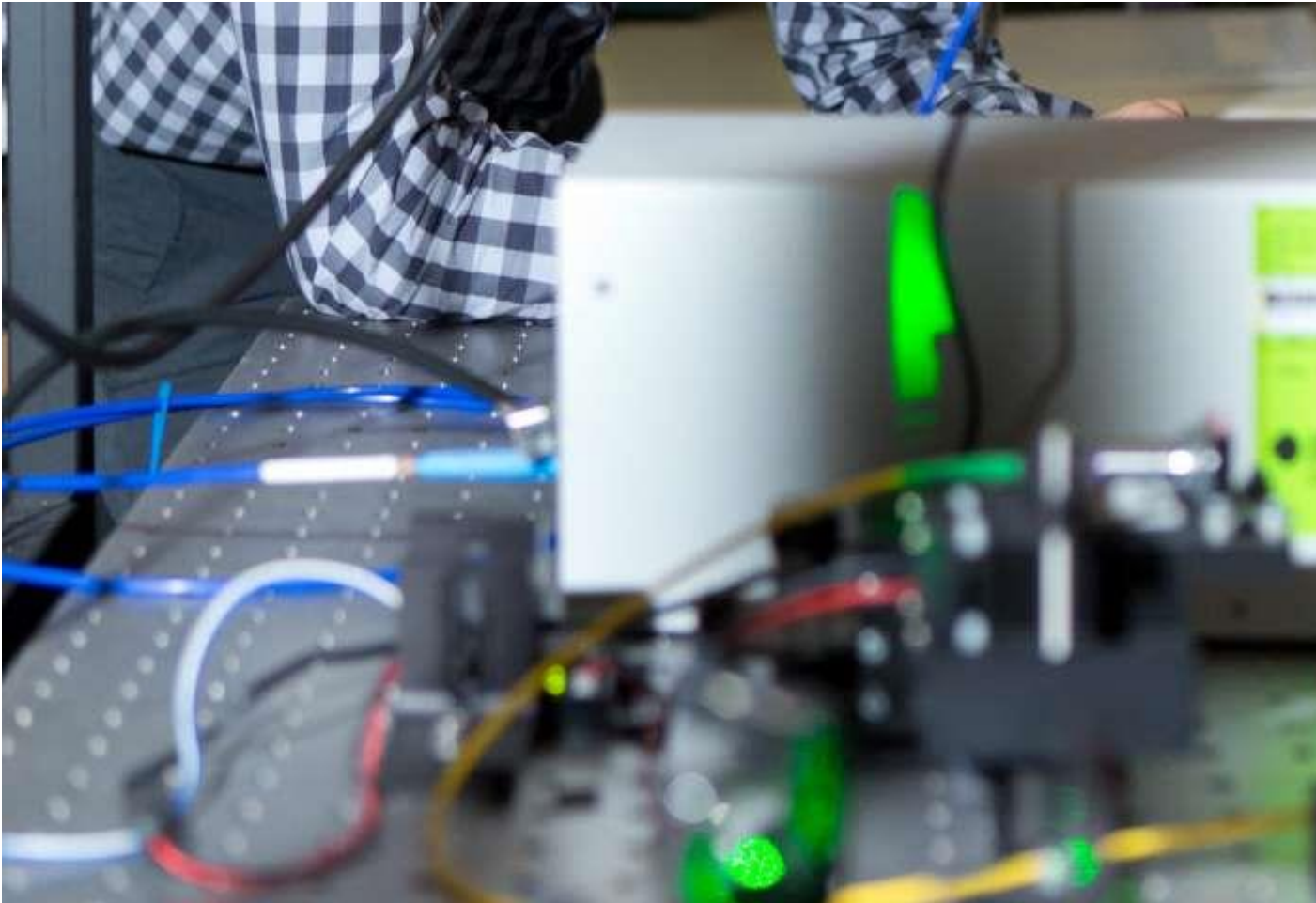
This figure shows the information-rich cellular images made possible by using the newly reported BAMM technique. The 'Original' image shows cells containing multiple fluorescent targets, all having similar colours. This results in a [...more](#)

Notably says Dr. Orth, you can attach different coloured fluorophores to different cell targets, all in the one sample, to maximise the data and imaging information that is received.

This traditional approach to fluorescence microscopy is versatile, but there is a major limitation: the visible (or colour) spectrum, where most fluorophores operate, can get crowded. In an ideal experiment, each target should be chosen to have a distinct colour emission, but this becomes increasingly difficult to arrange as the number of targets increases.

"The visible colour spectrum spans a range of 400 nanometres (nm) to 700 nm and only about 200 nm of this range is available for fluorescence colour emission," explains Dr. Orth.

"A typical fluorophore emits over a 50 nm range of the colour spectrum. Dividing 200 nm of the visible spectrum into 50 nm segments means that the colours of the fluorescent emitters begin to blend together when you attempt to squeeze in more than four colours."



Dr Antony Orth. Credit: CNBP-RMIT

"This is generally limiting researchers to four or fewer fluorescent targets in a sample," says Dr. Orth.

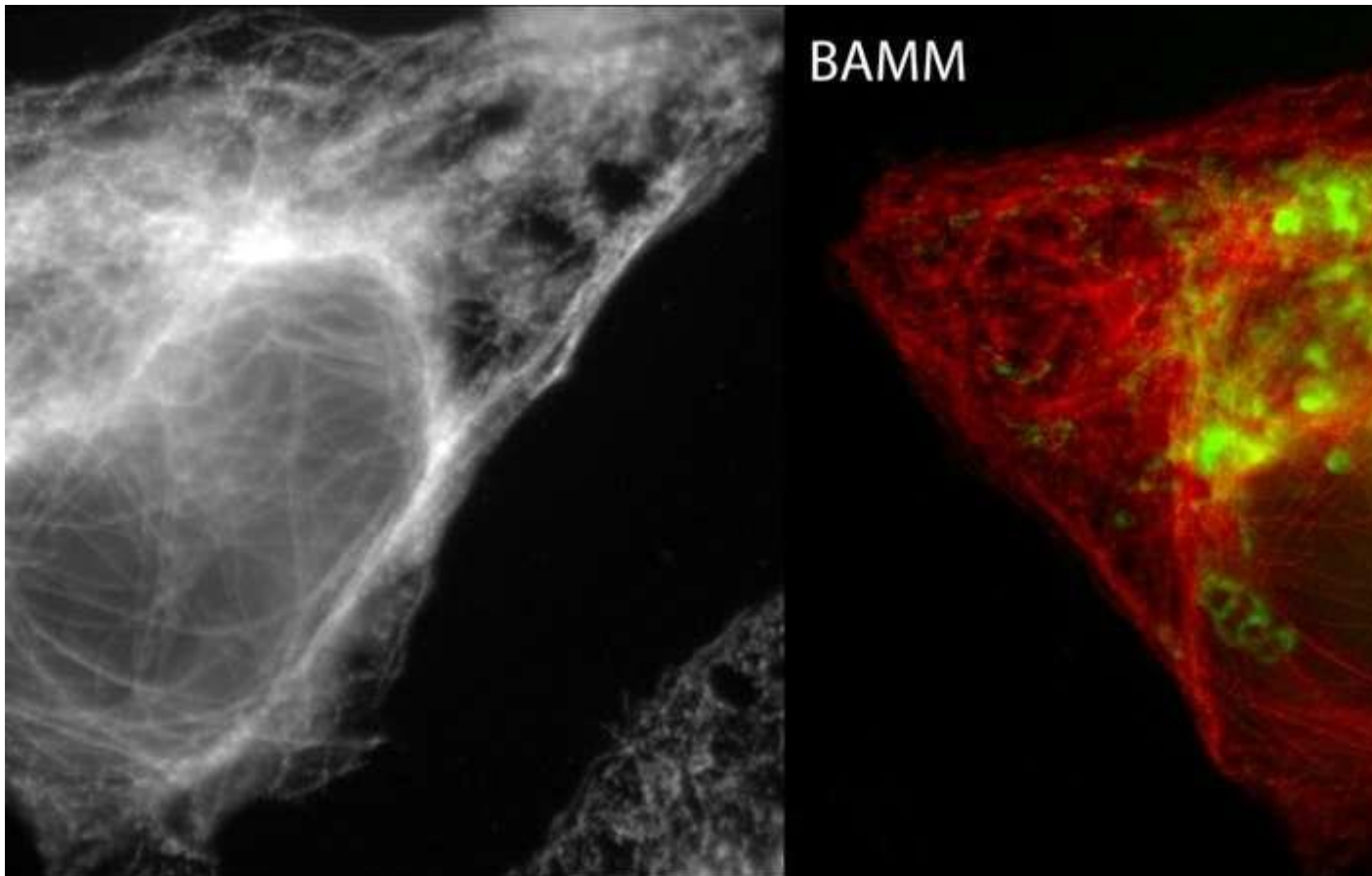
"Typically, most experiments are even less ambitious, incorporating only two or three targets. The heart of the problem is that only one property of the fluorophore – its colour – is being used for identification."

To help overcome this limitation, Dr. Orth and his co-researchers have developed an innovative technique called 'bleaching-assisted multichannel microscopy' (BAMM) to increase their imaging output.

"Instead of using colour to differentiate between fluorophores, we use the fourth dimension of time and exploit a phenomenon called photobleaching—the dimming of a collection of fluorophores or pigments under repeated exposure to light," says Dr. Orth.

"Because each type of fluorophore photo-bleaches at a different rate, we can differentiate between fluorophores without using any colour information. We use the rate of photobleaching as the identifier."

"When paired with traditional colour information, this added dimension of photo-bleaching enables scientists to use 2-3 times more types of fluorescent molecules, all in one sample. This lets us extract far more information from a single investigation."



This figure shows the information-rich cellular images made possible by using the newly reported BAMM technique. The 'Original' image shows cells containing multiple fluorescent targets, all having similar colours. This results in a [...more](#)

"Researchers will be able to design more informative tests – for example, highlighting five targets when only two were previously practical. They will no longer have to avoid using two fluorophores with the same colour, since a difference in photostability alone is enough to distinguish between the two targets," he says.

Traditionally, the phenomenon of photobleaching (or fading) has been detrimental to the fluorescent microscopy process. This is where high-intensity and ongoing illumination from the microscope

permanently destroys a fluorophore's ability to fluoresce so that imaging of the cell target becomes impossible.

"BAMM transforms photobleaching from a long-standing weakness of fluorescence microscopy into a significant strength to allow increased identification of cellular targets," says Dr. Orth.

"BAMM doesn't require any additional hardware, it's comparatively simple to do and doesn't require any specialised sample preparation. It's an extremely exciting new approach which has the potential to benefit all [fluorescence microscopy](#) users and their exploratory science," he says.

Researchers formally involved with the BAMM project were affiliated with CNBP (RMIT University and the University of Adelaide) and Thermo Fisher Scientific. [23]

Speeding up micro-CT scanning

Micro-computed tomography or "micro-CT" is X-ray imaging in 3-D, by the same method used in hospital CT (or "CAT") scans, but on a small scale with massively increased resolution. It enables scientists and engineers to see inside structures and reveal hidden secrets.

Micro-CT imaging is opening up a world of opportunities across industries. Now the EUREKA funded project Xamflow has developed an innovative software application that makes micro-CT examinations more efficient and less labour intensive than before.

"Micro-CT scanning started with human biological materials, but nowadays anything can be scanned, synthetic materials, small animals, food, minerals, and fossils for example," says Tor Hildebrand owner of project partner Imacomp AB based in Sweden.

"Companies want to check the internal structure of their products without having to destroy their samples," Hildebrand explains, "with micro-CT scanning, you can check the microstructures in bone, porosity of food, and search for micro anomalies inside materials".

A time-consuming process

Typically, scanning using [micro-computed tomography](#) is a complicated process that requires the scanning of multiple samples.

"The whole process is complex, time-consuming and involves many manual steps," explains Hildebrand, "there is a lot of switching between applications and tools, slowing the process down and increasing costs and sources of errors," he adds.

Because of this complexity the project needed to bring together a consortium of partners with a range of different specialisations.

"We needed a company that knew the scanning process, a company that developed the hardware, a company that knew how to analyse the images, a company that could build the whole backend system, and a web developer."

We were able to find a team of five different companies and institutes and bring them together to start this project," says Hildebrand. Lucid Concepts AG based in Switzerland handled the visualization and the [image-processing](#) framework.

The Swedish companies ImaComp AB and Capenta AB in Sweden were responsible for the architecture of the full system and the web application development, respectively.

Two Universities, the KTH Royal Institute of Technology in Stockholm and the University of Applied Sciences HSR in Rapperswil, Switzerland supported with clinical analysis and distributed image processing.

Finally, Scanco Medical AG based in Switzerland developed the imaging hardware. "It was a diverse team of people and specialties this helped us to stay focussed and motivated throughout the project," says Hildebrand.

Automating workflows

At its heart, the Xamflow platform is, in fact, a tool for automating complex workflows. Workflow automation is a growing market as businesses look for ways to streamline their processes to save time and money.

Once the system has been fully developed and is ready for commercialisation, it can be modified to support different domains and customer needs.

"Once we have the system ready for sale we can provide specialised modules to help organisations to solve their complex examination problems," explains Hildebrand.

Now that the project is finished Xamflow is moving into a beta test phase with first users having access to the system to give feedback and comments.

The international cooperation was invaluable to the success of Xamflow.

"If you want to build a complex workflow solution like this you need a diverse team of companies and expertise. The funding helped us to build a consortium that could handle the diversity of features needed," says Hildebrand.

The partnership has stayed together after Xamflow applying for and winning a second grant that uses advanced image processing and [artificial intelligence](#) to help find and identify structures in 3-D images for both clinical and research applications.

"When you examine and scan humans and animals one of the most important things is to outline the internal organs and abnormalities like tumours, in a process called segmentation." explains Hildebrand, "You need to extract the information from the scan in order to make a diagnosis or plan radiation treatment for example."

Taking advantage of artificial intelligence

Xamflow is particularly suited to help train artificial intelligence networks to identify different tissue and structures inside human and animal bodies.

"To train the artificial intelligence networks, you need to do lots of scans and analyse a wide range of different tissue samples. Xamflow is well suited to support this type of scenario and then offer a user friendly way of using the trained networks for finding structures," says Hildebrand.

There is no doubt that Xamflow wouldn't be on a path to success without the funding.

"The funding allowed us to bring together a team of specialists from Europe to build a complex but still efficient and user friendly system for advanced 3-D examinations in both industry and academia," concludes Hildebrand. [22]

X-ray laser opens new view on Alzheimer's proteins

A new experimental method permits the X-ray analysis of amyloids, a class of large, filamentous biomolecules which are an important hallmark of diseases such as Alzheimer's and Parkinson's. An international team of researchers headed by DESY scientists has used a powerful X-ray laser to gain insights into the structure of different amyloid samples. The X-ray scattering from amyloid fibrils give patterns somewhat similar to those obtained by Rosalind Franklin from DNA in 1952, which led to the discovery of the well-known structure, the double helix.

The X-ray laser, trillions of times more intense than Franklin's X-ray tube, opens up the ability to examine individual amyloid fibrils, the constituents of amyloid filaments. With such powerful X-ray beams any extraneous material can overwhelm the signal from the invisibly small fibril sample. Ultrathin carbon film—graphene—solved this problem to allow extremely sensitive patterns to be recorded. This marks an important step towards studying individual molecules using X-ray lasers, a goal that structural biologists have long been pursuing. The scientists present their new technique in the journal *Nature Communications*.

Amyloids are long, ordered strands of proteins which consist of thousands of identical subunits. While amyloids are believed to play a major role in the development of neurodegenerative diseases, recently more and more functional amyloid forms have been identified. "The 'feel-good hormone' endorphin, for example, can form amyloid fibrils in the pituitary gland. They dissolve into individual molecules when the acidity of their surroundings changes, after which these molecules can fulfil their purpose in the body," explains DESY's Carolin Seuring, a scientist at the Center for Free-Electron Laser Science (CFEL) and the principal author of the paper. "Other amyloid proteins, such as those found in post-mortem brains of patients suffering from Alzheimer's, accumulate as amyloid fibrils in the brain, and cannot be broken down and therefore impair brain function in the long term."

Scientists are trying to determine the spatial structure of amyloids as accurately as possible, so as to use this information in order to find out more about how the protein fibrils function: "Our aim is to understand the role of the formation and structure of amyloid fibrils in the body and in the development of neurodegenerative diseases," says Seuring in describing the team's motivation. "The structural analysis of amyloids is complex, and examining them using existing methods is hampered by differences between the fibrils within a single sample." The team used the X-ray free-electron laser LCLS at the SLAC National Accelerator Center in the U.S.

One problem is that the strands of amyloids, known as fibrils, cannot be grown as crystals, which is the usual method of performing atomic resolution structural studies using X-rays. Individual amyloid fibrils are only a few nanometres thick and therefore generally too small to produce a measurable signal when exposed to X-rays. For this reason, the usual approach is to line up millions of these fibrils parallel to each other, and bundling them so that their signals add up. However, this means the

diffraction patterns are produced by the entire ensemble, and information about structural differences between the individual fibrils is lost. "A major part of our understanding about amyloid fibrils is derived from nuclear magnetic resonance (NMR) and cryo-electron microscopy data," explains Seuring. "When you are working with samples that are as heterogeneous as amyloids, though, and also when observing the dynamics of fibril formation, the existing methods reach their limits."

In order to gain access to structure information of such heterogeneous samples in the future, the team opted for a new experimental approach. Instead of suspending the individual amyloids in a carrier fluid the scientists placed it on an ultrathin solid carrier made of graphene, in which carbon atoms are arranged in a hexagonal pattern rather like an atomic honeycomb. "This sample support has a double benefit," says Professor Henry Chapman of CFEL, who is a lead scientist at DESY. "For one thing, graphene is just a single layer of atoms thin and in contrast to a carrier fluid hardly leaves a trace in the diffraction pattern. For another thing, its regular structure makes sure the protein fibrils all align in the same direction—at least in larger domains." The diffraction patterns of multiple fibrils overlap and reinforce one another, much like in a crystal, but there is virtually no disruptive background scattering as in the case of a carrier fluid. This method allows diffraction patterns to be obtained from fewer than 50 amyloid fibrils, so that the structural differences emerge more clearly. "We have observed characteristic asymmetries in our data which suggest that our technique could even be used to determine the structure of individual fibrils," says Seuring.

"The CXI instrument at LCLS provided an exceptionally bright, nanofocus beam that allowed us to extract data from such a small number of fibres," reports co-author Mengning Liang, a scientist at SLAC. "Fibrils are a third category of samples that can be studied this way with X-ray lasers, in addition to single particles and crystals. In some regards, fibrils fit between the other two: they have regular, recurring variations in structure like crystals, but without the rigid crystal structure."

The scientists tested their method on samples of the tobacco mosaic virus, also first examined by Rosalind Franklin, and which forms filaments of a structure that is now known in great detail. The test did in fact provide structural data about the virus with an accuracy of 0.27 nanometres (millionths of a millimetre) - corresponding to a resolution almost on the scale of a single atom. The examination of distinctly smaller amyloid fibrils made of endorphin as well as [amyloid fibrils](#) made of the hormone bombesin, which is involved among other things in certain types of cancer, also provided some structural information, with an accuracy of 0.24 nanometres. Although the data was insufficient for calculating the complete structure, the study shows great promise for structural retrieval when more data becomes available, and opens up a new path for the structural analysis of amyloids using X-ray lasers. "It is amazing that we are carrying out very similar experiments as Franklin did, but are now reaching the level of single molecules," says Chapman. [21]

Molecular movies of RNA guide drug discovery

Thumb through any old science textbook, and you'll likely find RNA described as little more than a means to an end, a kind of molecular scratch paper used to construct the proteins encoded in DNA.

But over the last decade, scientists have begun to see RNA as an end in itself.

Research programs and biotech companies have sprung up with the mission of identifying small-molecule drugs that can target RNA to treat a variety of ailments like infectious diseases and muscular dystrophy. The trouble is, RNA is constantly bending, twisting and contorting its shape—often within a few milliseconds. Researchers have found it hard to hit such a moving target.

"When it comes to targeting RNA, the devil is in the details, and the details are in the dynamics," said Hashim M. Al-Hashimi, Ph.D., James B. Duke Professor of Biochemistry and Chemistry at the Duke University School of Medicine.

Al-Hashimi and his team have invented a technique that can capture the many states of an RNA molecule and screen hundreds of thousands or perhaps even millions of potential [drug](#) candidates. In research published May 4 in the journal *Nature Structural and Molecular Biology*, they show that their technique can pick compounds with anti-HIV activity out of a line-up of 100,000 that do not.

"This could present a new paradigm for drug discovery," says Al-Hashimi. "Almost every drug is designed to target proteins. By making it possible to accurately target RNA, we are opening the field up to new and potentially life-saving discoveries."

The "central dogma" of [molecular biology](#) held that genetic information flows from DNA, to RNA, to protein, where the action is. But only about 2 percent of RNAs go on to make proteins. Some research indicates that more than 90 percent of the RNA molecules assembled from the template provided by DNA end up being an RNA as their final state.

But [drug discovery](#) efforts over the last fifty years have overlooked nearly all these "non-coding" RNAs, Al-Hashimi said. One clear reason for this glaring omission is the fact that RNA is one of the most flexible, dynamic molecules around. It doesn't have the typical nooks and crannies that drug developers use to target proteins, and even if it did, a given RNA probably wouldn't sit still long enough for a scientist to capture it on film.

"This is a long-standing problem," says Al-Hashimi. "The motion of life is in these molecules. But nobody can predict which drugs will bind RNA, in large part because we don't have good movies of them."

Most methods that guide the discovery of drugs either rely on a still image captured in the laboratory that doesn't show the molecule in action, or movies generated on a computer that are based on calculations, not real data.

In 2011, Al-Hashimi combined the two, harnessing both nuclear magnetic resonance imaging and computationally generated movies to create the first movie of an RNA molecule—in this case from the virus HIV—as it danced from one shape to another. His group then took individual frames of the movie, each depicting a different shape of the RNA, and ran them through a computer program to identify molecules that bind to the RNA.

"It was a proof of principle that you can conquer the flexibility of RNA," says Al-Hashimi. "That was promising, but it wasn't a rigorous test. A more rigorous test is whether you can fish the needle from the haystack."

In the present study, Al-Hashimi and his team took 78 compounds known to bind that same RNA target from HIV and added them to a chemical library of 100,000 compounds that they had shown incapable of binding. When they used their technique to screen all the compounds, they were able to pull out the 78 with known anti-HIV activity.

"The key in this study is that we know whether the drugs bind or not, which gives us a means to evaluate how accurate the shapes of our RNA are," said lead study author Laura Ganser, a graduate student in Al-Hashimi's lab. "Since it performed so well, we feel that the shapes are accurate, so now we can find and design new drugs."

They also showed that if they used poor-quality movies, the quality of their predictions went down. The more accurate the data, the more accurate the predictions.

"You can always get the right answer for the wrong reasons," Ganser said. "By doing this particular exercise and varying the amount of data that goes into the movie, we were convinced this was real."

The researchers showed that the technique could predict not only what molecules would bind the RNA, but also which particular shape—linear, L-shaped, S-shaped—they preferred. That finding is important because unlike small [molecules](#) that target proteins by competing for a particular binding site, compounds that target RNA work by locking the molecule in an inactive conformation so it can't function properly.

Al-Hashimi and his team are currently using the technique to screen millions of compounds for anti-HIV activity before building smaller libraries for further testing. [20]

Chemical engineers discover how to control knots that form in DNA molecules

Just like any long polymer chain, DNA tends to form knots. Using technology that allows them to stretch DNA molecules and image the behavior of these knots, MIT researchers have discovered, for the first time, the factors that determine whether a knot moves along the strand or "jams" in place.

"People who study polymer physics have suggested that knots might be able to jam, but there haven't been good model systems to test it," says Patrick Doyle, the Robert T. Haslam Professor of Chemical Engineering and the senior author of the study. "We showed the same knot could go from being jammed to being mobile along the same molecule. You change conditions and it suddenly stops, and then change them again and it suddenly moves."

The findings could help researchers develop ways to untie DNA knots, which would help improve the accuracy of some genome sequencing technologies, or to promote knot formation. Inducing knot formation could enhance some types of sequencing by slowing down the DNA [molecules'](#) passage through the system, the researchers say.

MIT postdoc Alexander Klotz is the first author of the paper, which appears in the May 3 issue of *Physical Review Letters*.

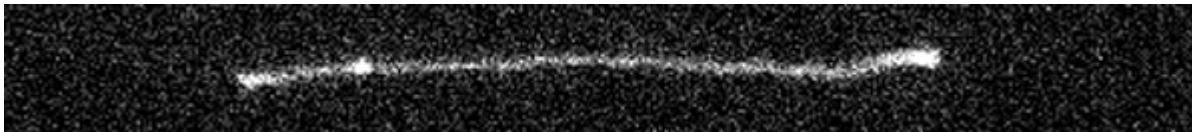
Knots in motion

Doyle and his students have been studying the physics of polymer knots such as DNA for many years. DNA is well-suited for such studies because it is a relatively large molecule, making it simple to image with a microscope, and it can be easily induced to form knots.

"We have a mechanism that causes DNA molecules to collapse into a tiny ball, which when we stretch out contains very big knots," Klotz says. "It's like sticking your headphones in your pocket and pulling them out full of knots."

Once the knots form, the researchers can study them using a special microfluidic system that they designed. The channel is shaped like a T, with an electric field that diverges at the top of the T. A DNA molecule located at the top of the T will be pulled equally toward each arm, forcing it to stay in place.

The MIT team found that they could manipulate knots in these pinned DNA molecules by varying the strength of the electric field. When the field is weak, knots tend to move along the molecule toward the closer end. When they reach the end, they unravel.



A knot near the end of a stretched DNA molecule is driven toward the end and unties, leaving an unknotted molecule. Credit: Alex Klotz

"When the tension isn't too strong, they look like they're moving around randomly. But if you watch them for long enough, they tend to move in one direction, toward the closer end of the molecule," Klotz says.

When the field is stronger, forcing the DNA to fully stretch out, the knots become jammed in place. This phenomenon is similar to what happens to a knot in a bead necklace as the necklace is pulled more tightly, the researchers say. When the necklace is slack, a knot can move along it, but when it is pulled taut, the beads of the necklace come closer together and the knot gets stuck.

"When you tighten the [knot](#) by stretching the DNA molecule more, it brings the strands closer to each other, and this ramps up the friction," Klotz says. "That can overwhelm the driving force caused by the electric field."

Knot removal

DNA knots also occur in living cells, but cells have specialized enzymes called topoisomerases that can untangle such knots. The MIT team's findings suggest a possible way to remove knots from DNA outside of cells relatively easily by applying an [electric field](#) until the knots travel all the way to the end of the molecule.

This could be useful for a type of DNA sequencing known as nanochannel mapping, which involves stretching DNA along a narrow tube and measuring the distance between two genetic sequences. This

technique is used to reveal large-scale genome changes such as gene duplication or genes moving from one chromosome to another, but knots in the DNA can make it harder to get accurate data.

For another type of DNA sequencing known as nanopore sequencing, it could be beneficial to induce knots in DNA because the knots make the molecules slow down as they travel through the sequencer. This could help researchers get more accurate sequence information.

Using this approach to remove knots from other types of polymers such as those used to make plastics could also be useful, because knots can weaken materials.

The researchers are now studying other phenomena related to knots, including the process of untying more complex knots than those they studied in this paper, as well as the interactions between two knots in a molecule. [19]

Researchers build DNA replication in a model synthetic cell

Researchers at Delft University of Technology, in collaboration with colleagues at the Autonomous University of Madrid, have created an artificial DNA blueprint for the replication of DNA in a cell-like structure. Creating such a complex biological module is an important step towards an even more ambitious goal: building a complete and functioning synthetic cell from the bottom up.

Copying DNA is an essential function of living cells. It allows for cell division and propagation of genetic information to the offspring. The mechanism underlying DNA replication consists of three important steps. First, DNA is transcribed into messenger RNA. Messenger RNA is then translated into proteins—the workhorses of the cell that carry out many of its vital functions. The job of some of these proteins, finally, is to perform the last step in the cycle: the replication (or copying) of DNA. After a cell has replicated its DNA, it can divide into two daughter cells, each containing a copy of the original genetic material.

Closing the cycle

Researchers had already realized all of the separate steps mentioned above. Japanese scientists, for instance, created a minimal, stand-alone system for messenger RNA and protein synthesis by taking the relevant components from *E. coli* and tweaking them. But no one had yet been able to combine this system with autonomous DNA replication. "We wanted to close the cycle and be the first to reconstruct the entire flow of genetic information inside a cell-like structure called a liposome," said group leader Christophe Danelon.

Combining the Japanese system with a module for DNA replication proved difficult. "We tried a few approaches, but none seemed to work convincingly," said Danelon. Then, Ph.D. student Pauline van Nies came up with the idea to use the DNA replication machinery of a virus called $\Phi 29$. "Viruses are very intriguing from a molecular biology point of view," said Van Nies. "They are extremely efficient in encoding proteins in a small genome and in robustly replicating their genetic information." In human cells, DNA replication is managed by hundreds of proteins. $\Phi 29$ only needs four.

Composing DNA

Many years ago, researchers working at the Autonomous University of Madrid discovered the DNA replication mechanism of the Φ 29 virus and managed to isolate it. Van Nies and Danelon worked with these researchers to combine the genes that encode for the replication mechanism with the genetic code that is necessary to operate the Japanese module for transcription and translation.

Van Nies composed a unique DNA blueprint that took into account a number of different factors related to the flow of genetic information, such as a suitable binding site for the ribosome, an element that is essential for the production of proteins.

Combining machinery

A goal that now comes into view is combining the new module that regulates the flow of genetic information with other essential cellular functions such as growth and division. Last year, the Danelon group created a way to synthesize the phospholipids that make up liposomes, such as the ones the researchers used in this project. The yield of phospholipids was still too small to sustain growth, but Danelon is confident his group can optimize this process.

Cell division may be a tougher nut to crack. In modern cells, it requires a streamlined process in which copied DNA is neatly packed and then evenly distributed towards the poles of the cell. Concurrently, specialized proteins squeeze the mother cell into two daughter cells. Danelon thinks a simple 'budding' mechanism could also do the trick. "I think we can create liposomes that grow until they start budding. If enough DNA is being produced, hopefully enough of these primitive daughter cells will contain the new DNA to sustain a cell population." This may well be how the very first cells self-reproduced, before evolution equipped them with a more elegant and robust solution.

Building a synthetic cell

The mission that ties together all of the fundamental research described above is the construction of a synthetic cell that can grow, divide and sustain itself. Scientists at Delft University of Technology play a leading role in this exciting new research direction that may ultimately lead to intimate understanding of the inner workings of a cell. Research supporting the initiative could lead to advances in biotechnology, health and energy. [18]

Study reveals the inner workings of a molecular motor that packs and unpacks DNA

DNA is tightly packed into the nucleus of a cell. Nevertheless, the cellular machinery needs to constantly access the genomic information. An LMU team now reveals the inner workings of a molecular motor made of proteins which packs and unpacks DNA.

The genomic DNA of higher organisms is compacted in a highly condensed form known as chromatin. The DNA is tightly wound around a myriad of tiny histone spools called nucleosomes. A single human cell, for instance, accommodates in this manner about two meters of DNA. However, genes must be constantly transcribed into messenger RNAs to direct protein synthesis. Moreover, the entire DNA must be replicated before cell division and DNA damage needs to be repaired. Thus, there must be way to actively grant access to the genome.

This is when chromatin remodelers come into play. Chromatin remodelers have an essential role as they are molecular machines: they unpick and unpack segments of the DNA by sliding nucleosome spools back and forth, replacing individual histones, freeing up the DNA for transcription, and finally compacting it again, when the job is done. Since all of this happens in a highly dynamic fashion, chromatin remodelers enable cells to react rapidly to alterations in their environment – and this holds for brewer's yeast as well as for human cells. In mediating gene accessibility, chromatin remodelers are vital for development and cell differentiation; cell types are defined by the sets of genes they express, remodelers help to determine cell identity.

So far, however, very little is known about what remodeling proteins look like and how they go about doing what they do. In molecular terms, functional remodelers are often very large complexes comprising many different protein components, whose coordinated action makes them akin to molecular machines. These features also make it very difficult to determine their detailed structure. But a team led by Professor Karl-Peter Hopfner, who holds a Chair in Structural Molecular Biology at LMU's Gene Center, has now used cryo-electron microscopy to reconstruct the three-dimensional structure of the nucleosome-sliding remodeler INO80 (which itself consists of 15 subunits) bound to a single nucleosome. "Even with innovative approaches, the best available technology and intensive teamwork, we were always working at the cutting edge," says Dr. Sebastian Eustermann, who worked out the molecular structure of the complex on the basis of electron micrographs of thousands of individual complexes.

By analyzing images of randomly oriented views of the complex formed between INO80 and a nucleosome in the electron micrographs, Hopfner and his team have pieced together its structure at a resolution which has seldom been achieved for a chromatin complex of comparable size. This allowed the researchers to unravel the intricate interaction of the remodeler with its substrate DNA spooled around histones and dissect how the whole machinery works.

From a biochemical point of view, remodelers are responsible for heavy-duty reorganizational tasks. To perform these tasks, they must execute "large-scale conformational changes, which are carried out with astounding precision," says Eustermann. In order to alter the relative positions of nucleosomes, the INO80 complex must first weaken the contacts between the nucleosomal histones and the DNA. A molecular motor which is part of the INO80 complex segmentally detaches the double-stranded DNA from the nucleosome. In doing so, it progressively breaks the contacts that normally keep the DNA tightly wound around the histone particle.

The motor subunit feeds DNA it into the nucleosome. This results in the transient formation of a double-stranded DNA loop that is likely an important intermediate in complex remodeling reactions on the nucleosome. On one hand, the loop exposes some histone proteins that could be replaced by other histones to form a different type of nucleosome. On the other hand, the loop is eventually passed over another subunit and the machine then acts as a ratchet, allowing the nucleosome to "move" on the DNA. Throughout this unpacking process, other subunits in the complex serve to support and stabilize the partially 'denuded' nucleosome itself.

The structure of the complex revealed in the new study sheds new light on the function and mode of action of chromatin remodelers in general. These molecular machines play an essential part in the workings of the cell by maintaining the flexibility of the chromatin, thus enabling the genetic

apparatus to respond dynamically to changing metabolic demands. "Our results provide the first well-founded picture of how they do that," says Hopfner. "Moreover, it has recently become clear that remodelers play a central role in tumorigenesis, because they often misregulated in tumor tissue. So structural and mechanistic insights into their functions will be vital for the future development of new therapies for cancer," he adds. [17]

Biomimetic chemistry—DNA mimic outwits viral enzyme

Not only can synthetic molecules mimic the structures of their biological models, they can also take on their functions and may even successfully compete with them, as an artificial DNA sequence designed by Ludwig-Maximilians-Universitaet (LMU) in Munich chemist Ivan Huc now shows.

Chemist Ivan Huc finds the inspiration for his work in the molecular principles that underlie biological systems. As the leader of a research group devoted to biomimetic supramolecular chemistry, he creates 'unnatural' molecules with defined, predetermined shapes that closely resemble the major biological polymers, proteins and DNA found in cells. The backbones of these molecules are referred to as 'foldamers' because, like origami patterns, they adopt predictable shapes and can be easily modified. Having moved to LMU from his previous position at Bordeaux University last summer, Huc has synthesized a helical molecule that mimics surface features of the DNA double helix so closely that bona fide DNA-binding proteins interact with it.

This work is described in a paper published in *Nature Chemistry*. The new study shows that the synthetic compound is capable of inhibiting the activities of several DNA-processing enzymes, including the 'integrase' used by the [human immunodeficiency virus](#) (HIV) to insert its genome into that of its host cell. The successful demonstration of the efficacy of the synthetic DNA mimic might lead to a new approach to the treatment of AIDS and other retroviral diseases.

The new paper builds on advances described in two previous publications in *Nature Chemistry* published earlier this year. In the first of these papers, Huc and his colleagues developed a pattern of binding interactions required to enable synthetic [molecules](#) to assume stable forms similar to the helical backbones of proteins. In the second, they worked out the conditions required to append their synthetic helix to natural proteins during synthesis by cellular ribosomes. "As always in biology, shape determines function," he explains. In the new study, he introduces a synthetic molecule that folds into a helical structure that mimics surface features of the DNA double helix, and whose precise shape can be altered in a modular fashion by the attachment of various substituents. This enables the experimenter to imitate in detail the shape of natural DNA double helix, in particular the position of negative charges. The imitation is so convincing that it acts as a decoy for two DNA-binding enzymes, including the HIV integrase, which readily bind to it and are essentially inactivated.

However, the crucial question is whether or not the foldamer can effectively compete for the enzymes in the presence of their normal DNA substrate. "If the enzymes still bind to the foldamer under competitive conditions, then the mimic must be a better binder than the natural DNA itself," Huc says. And indeed, the study demonstrates that the HIV integrase binds more strongly to the foldamer than to natural DNA. "Furthermore, although initially designed to resemble DNA, the

foldamer owes its most useful and valuable properties to the features that differentiate it from DNA," Huc points out.

Thanks to the modular nature of foldamer design, the structures of these artificial DNA mimics can be readily altered, which enables a broad range of variants to be produced using the same basic platform. In the current study, Huc and his colleagues have focused on enzymes that are generically capable of binding to DNA, irrespective of its base sequence. However, it may also be possible to use the foldamer approach to develop DNA mimics that can block the action of the many important DNA-binding proteins whose functions depend on the recognition of specific nucleotide sequences. [16]

Simulations document self-assembly of proteins and DNA

What makes particles self-assemble into complex biological structures? Often, this phenomenon is due to the competition between forces of attraction and repulsion, produced by electric charges in various sections of the particles. In nature, these phenomena often occur in particles that are suspended in a medium—referred to as colloidal particles—such as proteins, DNA and RNA. To facilitate self-assembly, it is possible to "decorate" various sites on the surface of such particles with different charges, called patches.

In a new study published in *EPJE*, physicists have developed an algorithm to simulate the molecular dynamics of these patchy [particles](#). The findings published by Silvano Ferrari and colleagues from the TU Vienna and the Centre for Computational Materials Science (CMS), Austria, will improve our understanding of what makes self-assembly in biological systems possible.

In this study, the authors model charged patchy particles, which are made up of a rigid body with only two charged patches, located at opposite poles. They then develop the equations governing the dynamics of an ensemble of such colloidal patchy particles.

Based on an existing approach originally developed for molecular particles, their simulation includes additional constraints to guarantee that the electrical charge "decorations" are preserved over time. In this regard, they develop equations for describing the particles' motion; the solutions to these equations describe the trajectories of these colloidal particles. Such [molecular dynamics](#) simulations lend themselves to being run in parallel on a huge number of particles.

With these findings, the authors complement the lessons learned from experimental observations of similar particles recently synthesised in the lab. Recent experiments have demonstrated that [colloidal particles](#) decorated at two interaction sites display a remarkable propensity for self-organising into highly unusual structures that remain stable over a broad temperature range. [15]

Scientists explore the structure of a key region of longevity protein telomerase

Scientists from Moscow State University (MSU) working with an international team of researchers have identified the structure of one of the key regions of telomerase—a so-called "cellular immortality" ribonucleoprotein. Structural and functional studies on this protein are important for the development of potential anticancer drugs. The results of the study have been published in *Nucleic Acids Research*.

Each cell goes through a DNA replication process before division. This is a precise, fine-tuned process controlled by the coordinated work of a sophisticated enzymatic machinery. However, due to the nature of the copying process, the termini of DNA molecules are left uncopied, and DNA becomes shorter with each replication. However, no important data is lost in the process, as the termini of DNA molecules (telomeres) consist of thousands of small, repeated regions that do not carry hereditary information. When the reserve of telomere repetitions is exhausted, the cell ceases to divide, and eventually, it can die. Scientists believe that this is the mechanism of cellular aging, which is necessary for the renewal of cells and tissues of the body.

But how do "immortal" strains and stem cells that give life to a huge number of offspring cope with this? This is where the enzyme [telomerase](#) comes into play. It can restore telomeric termini of chromosomes and therefore compensate for their shortening during mitosis. The telomerase protein catalytic subunit works together with the RNA molecule, and its short fragment is used as a template to synthesize telomeric repetitions. MSU-based scientists discovered the structure of the telomerase fragment that is in charge of this process.

"Our work is aimed at the structural characterization of the telomerase complex. In a living cell, it includes a catalytic subunit, an RNA molecule, a segment of telomeric DNA, and several auxiliary components. Anomalously low activity of telomerase caused by genetics can result in serious pathogenic conditions (telomeropathy), while its anomalous activation is the reason for the cellular "immortality" of most known cancers. Information on the structure of telomerase and the relationships between its components is necessary for understanding the function and regulation of this enzyme, and in the future, for directed control of its activity," said Elena Rodina, assistant professor of the Department for the Chemistry of Natural Products, Faculty of Chemistry, MSU.

Working with thermotolerant yeast, a model eukaryotic organism, the researchers determined the structure of one of the major domains of the telomerase catalytic subunit (the so-called TEN-domain) and determined which parts of it are responsible for the interaction of the enzyme with the RNA molecule and the synthesized DNA. Based on the experimental data obtained, the scientists constructed a theoretical model of the catalytic core of telomerase.

The activity of the enzyme may be described in a simplified way: Telomerase can be represented as a molecular machine containing an RNA molecule. This machine, with the help of a template part of RNA, binds to the end of a long chain of DNA, and synthesizes a fragment of a new DNA chain along the remaining template fragment. After that, the telomerase machine has to move to the newly synthesized end of the DNA in order to continue to build up the chain. The scientists assume that the TEN-domain allows telomerase to synthesize DNA fragments of strictly defined length, after which the

RNA template should be detached from the DNA strand to move closer to its edge. Thus, the TEN domain facilitates the movement of the enzyme to building up a new region, i.e. the next telomeric fragment, and this is how the synthesis cycle is repeated.

In addition, the researchers identified the structural core of the TEN domain that remained unchanged in a variety of organisms, despite all the evolutionary vicissitudes, which indicates the important role of this core in the function of the enzyme. The team also revealed the elements specific for different groups of organisms, which interact with own proteins of individual telomerase complex.

"The data obtained bring us closer to an understanding of the structure, function and regulation of telomerase. In the future, this knowledge can be used to create drugs aimed at regulating telomerase activity—either to increase it (for example, to increase the cell life span in biomaterials for transplantology) or to reduce (for instance, for immortal cancer cells to lose their immortality)," concludes Elena Rodina. [14]

Custom sequences for polymers using visible light

Researchers from Tokyo Metropolitan University used a light-sensitive iridium-palladium catalyst to make "sequential" polymers, using visible light to change how building blocks are combined into polymer chains. By simply switching the light on or off, they were able to realize different compositions along the polymer chain, allowing precise control over physical properties and material function. This may drastically simplify existing polymer production methods, and help overcome fundamental limits in creating new polymers.

The world is full of long, chain-like molecules known as polymers. Famous examples of "sequential" copolymers, i.e. polymers made of multiple [building blocks](#) (or "monomers") arranged in a specific order, include DNA, RNA and proteins; their specific structure imparts the vast range of molecular functionality that underpins biological activity. However, making sequential polymers from scratch is a tricky business. We can design special monomers that assemble in different ways, but the complex syntheses that are required limit their availability, scope and functionality.

To overcome these limits, a team led by Associate Professor Akiko Inagaki from the Department of Chemistry, Tokyo Metropolitan University, applied a light-sensitive catalyst containing iridium and palladium. By switching a light on and off, they were able to control the speed at which two different monomers, styrene and vinyl ether, become part of a [polymer chain](#). When exposed to light, the styrene monomer was found to be incorporated into the copolymer structure much more rapidly than in the dark, resulting in a single copolymer chain with different compositions along its length. Parts that are rich in styrene are more rigid than those rich in vinyl ether; by using different on/off [light](#) sequences, they could create polymers with a range of [physical properties](#) e.g. different "glass transition" temperatures, above which the [polymer](#) becomes softer.

The newly developed process is significantly simpler than existing methods. The team also found that both types of monomer were built into the polymer via a mechanism known as non-radical

coordination-insertion; this is a generic mechanism, meaning that this new method might be applied to make polymers using a wide range of catalysts and monomers, with the potential to overcome the limited availability of monomer candidates. [13]

Artificial and biological cells work together as mini chemical factories

Researchers have fused living and non-living cells for the first time in a way that allows them to work together, paving the way for new applications.

The system, created by a team from Imperial College London, encapsulates biological cells within an artificial cell. Using this, researchers can harness the natural ability of biological cells to process chemicals while protecting them from the environment.

This system could lead to applications such as cellular 'batteries' powered by photosynthesis, synthesis of drugs inside the body, and biological sensors that can withstand harsh conditions.

Previous artificial cell design has involved taking parts of biological cell 'machinery' - such as enzymes that support chemical reactions - and putting them into artificial casings. The new study, published today in *Scientific Reports*, goes one step further and encapsulates entire cells in artificial casings.

The artificial cells also contain enzymes that work in concert with the biological cell to produce new chemicals. In the proof-of-concept experiment, the artificial cell systems produced a fluorescent chemical that allowed the researchers to confirm all was working as expected.

Lead researcher Professor Oscar Ces, from the Department of Chemistry at Imperial, said: "Biological cells can perform extremely complex functions, but can be difficult to control when trying to harness one aspect. Artificial cells can be programmed more easily but we cannot yet build in much complexity.

"Our new system bridges the gap between these two approaches by fusing whole biological cells with artificial ones, so that the machinery of both works in concert to produce what we need. This is a paradigm shift in thinking about the way we design artificial cells, which will help accelerate research on applications in healthcare and beyond."

To create the system, the team used microfluidics: directing liquids through small channels. Using water and oil, which do not mix, they were able to make droplets of a defined size that contained the biological cells and enzymes. They then applied an artificial coating to the droplets to provide protection, creating an artificial cell environment.

They tested these artificial cells in a solution high in copper, which is usually highly toxic to biological cells. The team were still able to detect fluorescent chemicals in the majority of the artificial cells, meaning the biological cells were still alive and functioning inside. This ability would be useful in the human body, where the artificial cell casing would protect the foreign biological cells from attack by the body's immune system.

First author of the study Dr Yuval Elani, an EPSRC Research Fellow also from the Department of Chemistry, said: "The system we designed is controllable and customisable. You can create different sizes of artificial cells in a reproducible manner, and there is the potential to add in all kinds of cell machinery, such as chloroplasts for performing photosynthesis or engineered microbes that act as sensors."

To improve the functionality of these artificial cell systems, the next step is to engineer the artificial coating to act more like a biological membrane, but with special functions.

For example, if the membrane could be designed to open and release the chemicals produced within only in response to certain signals, they could be used to deliver drugs to specific areas of the body. This would be useful for example in cancer treatment to release targeted drugs only at the site of a tumour, reducing side effects.

While a system like that may be a way off yet, the team say this is a promising leap in the right direction. The work is the first example of fusing living and non-living components to emerge from Imperial and King's College's new FABRICELL centre for artificial cell science. [12]

New interaction mechanism of proteins discovered

UZH researchers have discovered a previously unknown way in which proteins interact with one another and cells organize themselves. This new mechanism involves two fully unstructured proteins forming an ultra-high-affinity complex due to their opposite net charge. Proteins usually bind one another as a result of perfectly matching shapes in their three-dimensional structures.

Proteins are among the most important biomolecules and are the key mediators of molecular communication between and within cells. For two proteins to bind, specific regions of their three-dimensional structures have to match one another exactly, as a key fits into a lock. The structure of proteins is extremely important for their functioning and for triggering the required responses in cells. Now, researchers at the University of Zurich, together with colleagues from Denmark and the U.S., have discovered that unstructured proteins can also have ultra-high-affinity interactions.

One of these proteins is histone H1, which, as a component of chromatin, is responsible for DNA packaging. Its binding partner, prothymosin α , acts as a kind of shuttle that deposits and removes the histone from the DNA. This process determines whether or not genes in specific parts of the DNA can be read. Both proteins are involved in several regulatory processes in the body, such as cell division and proliferation, and therefore also play a role when it comes to a number of diseases, including cancer. Ben Schuler, professor at the Department of Biochemistry at UZH and head of the research project published in *Nature*, says, "The interesting thing about these proteins is that they're completely unstructured—like boiled noodles in water." How such disordered proteins should be able to interact according to the key/lock principle had puzzled the team of researchers.

Notably, the two proteins bind to one another much more strongly than the average protein partners. The research team used single-molecule fluorescence and nuclear magnetic

resonance spectroscopy to determine the arrangement of the proteins. Observed in isolation, they show extended unstructured protein chains. The chains become more compact as soon as both binding partners come together and form a complex. The strong interaction is caused by the strong electrostatic attraction, since histone H1 is highly positively charged while prothymosin α is highly negatively charged. Even more surprising was the discovery that the protein complex was also fully unstructured, as several analyses confirmed.

To investigate the shape of the protein complex, the researchers labeled both proteins with fluorescent probes, which they then added to selected sites on the proteins. Together with computer simulations, this molecular map yielded the following results: Histone 1 interacts with prothymosin α preferably in its central region, which is the region with the highest charge density. Moreover, it emerged that the complex is highly dynamic: The proteins' position in the complex changes extremely quickly—in a matter of approx. 100 nanoseconds.

The interaction behavior is likely to be fairly common. Cells have many proteins that contain highly charged sequences and may be able to form such protein complexes. There are hundreds of such proteins in the human body alone. "It's likely that the interaction between disordered, highly charged proteins is a basic mechanism for how cells function and organize themselves," concludes Ben Schuler. According to the biophysicist, textbooks will need revision to account for this new way of binding. The discovery is also relevant for developing new therapies, since unstructured proteins are largely unresponsive to traditional drugs, which bind to specific structures on the protein surface. [11]

Particles in charged solution form clusters that reproduce

Dr Martin Sweatman from the University of Edinburgh's School of Engineering has discovered a simple physical principle that might explain how life started on Earth.

He has shown that particles that become charged in solution, like many biological molecules, can form giant clusters that can reproduce. Reproduction is shown to be driven by simple physics—a balance of forces between short-range attraction and long-range repulsion. Once cluster reproduction begins, he suggests chemical evolution of clusters could follow, leading eventually to life.

Many biological molecules, like DNA and proteins, might show this behaviour. Even the building blocks of life, amino acids and nucleobases, might show this behaviour. Reproduction in modern cells might even be driven by this simple physical mechanism, i.e. chemistry is not so important.

Dr Sweatman's research uses theoretical methods and computer simulations of simple particles. They clearly show giant clusters of molecules with the right balance of forces can reproduce. No chemistry is involved. However, these theoretical predictions have yet to be confirmed by experiment.

Dr Sweatman said, "Although it will be difficult to see this behaviour for solutions of small biomolecules, it should be possible to confirm this behaviour experimentally with much larger particles that can be seen under a microscope, like charged colloids.

"If this [behaviour](#) is confirmed, then we take another step towards Darwin's idea of life beginning in a warm little pond. A simple evaporation and condensation cycle in a pond might be sufficient to drive [cluster](#) reproduction initially. Survival of the fittest clusters of chemicals might then eventually lead to life."

The research has been published in the international journal *Molecular Physics*.

Experiment demonstrates quantum mechanical effects from biological systems

Nearly 75 years ago, Nobel Prize-winning physicist Erwin Schrödinger wondered if the mysterious world of quantum mechanics played a role in biology. A recent finding by Northwestern University's Prem Kumar adds further evidence that the answer might be yes.

Kumar and his team have, for the first time, created quantum entanglement from a biological system. This finding could advance scientists' fundamental understanding of biology and potentially open doors to exploit biological tools to enable new functions by harnessing [quantum mechanics](#).

"Can we apply quantum tools to learn about biology?" said Kumar, professor of electrical engineering and computer science in Northwestern's McCormick School of Engineering and of physics and astronomy in the Weinberg College of Arts and Sciences. "People have asked this question for many, many years—dating back to the dawn of quantum mechanics. The reason we are interested in these new quantum states is because they allow applications that are otherwise impossible."

Partially supported by the Defense Advanced Research Projects Agency, the research was published Dec. 5 in *Nature Communications*.

Quantum entanglement is one of quantum mechanics' most mystifying phenomena. When two [particles](#)—such as atoms, photons, or electrons—are entangled, they experience an inexplicable link that is maintained even if the particles are on opposite sides of the universe. While entangled, the particles' behavior is tied one another. If one particle is found spinning in one direction, for example, then the other particle instantaneously changes its spin in a corresponding manner dictated by the entanglement. Researchers, including Kumar, have been interested in harnessing quantum entanglement for several applications, including quantum communications. Because the particles can communicate without wires or cables, they could be used to send secure messages or help build an extremely fast "quantum Internet."

"Researchers have been trying to entangle a larger and larger set of atoms or photons to develop substrates on which to design and build a quantum machine," Kumar said. "My laboratory is asking if we can build these machines on a biological substrate."

In the study, Kumar's team used green fluorescent proteins, which are responsible for bioluminescence and commonly used in biomedical research. The team attempted to entangle the photons generated from the fluorescing molecules within the algae's barrel-shaped protein structure by exposing them to spontaneous four-wave mixing, a process in which multiple wavelengths interact with one another to produce new wavelengths.

Through a series of these experiments, Kumar and his team successfully demonstrated a type of entanglement, called [polarization](#) entanglement, between photon pairs. The same feature used to make glasses for viewing 3D movies, polarization is the orientation of oscillations in light waves. A wave can oscillate vertically, horizontally, or at different angles. In Kumar's entangled pairs, the photons' polarizations are entangled, meaning that the oscillation directions of light waves are linked. Kumar also noticed that the barrel-shaped structure surrounding the fluorescing molecules protected the [entanglement](#) from being disrupted.

"When I measured the vertical polarization of one particle, we knew it would be the same in the other," he said. "If we measured the horizontal polarization of one particle, we could predict the horizontal polarization in the other particle. We created an entangled state that correlated in all possibilities simultaneously."

Now that they have demonstrated that it's possible to create [quantum entanglement](#) from biological particles, next Kumar and his team plan to make a biological substrate of [entangled particles](#), which could be used to build a [quantum](#) machine. Then, they will seek to understand if a biological substrate works more efficiently than a synthetic one. [9]

Quantum biology: Algae evolved to switch quantum coherence on and off

A UNSW Australia-led team of researchers has discovered how algae that survive in very low levels of light are able to switch on and off a weird quantum phenomenon that occurs during photosynthesis.

The function in the algae of this quantum effect, known as coherence, remains a mystery, but it is thought it could help them harvest energy from the sun much more efficiently. Working out its role in a living organism could lead to technological advances, such as better organic solar cells and quantum-based electronic devices.

The research is published in the journal Proceedings of the National Academy of Sciences.

It is part of an emerging field called quantum biology, in which evidence is growing that quantum phenomena are operating in nature, not just the laboratory, and may even account for how birds can navigate using the earth's magnetic field.

"We studied tiny single-celled algae called cryptophytes that thrive in the bottom of pools of water, or under thick ice, where very little light reaches them," says senior author, Professor Paul Curmi, of the UNSW School of Physics.

"Most cryptophytes have a light-harvesting system where quantum coherence is present. But we have found a class of cryptophytes where it is switched off because of a genetic mutation that alters the shape of a light-harvesting protein.

"This is a very exciting find. It means we will be able to uncover the role of quantum coherence in photosynthesis by comparing organisms with the two different types of proteins."

In the weird world of quantum physics, a system that is coherent – with all quantum waves in step with each other – can exist in many different states simultaneously, an effect known as superposition. This phenomenon is usually only observed under tightly controlled laboratory conditions.

So the team, which includes Professor Gregory Scholes from the University of Toronto in Canada, was surprised to discover in 2010 that the transfer of energy between molecules in the light harvesting systems from two different cryptophyte species was coherent.

The same effect has been found in green sulphur bacteria that also survive in very low light levels.

"The assumption is that this could increase the efficiency of photosynthesis, allowing the algae and bacteria to exist on almost no light," says Professor Curmi.

"Once a light-harvesting protein has captured sunlight, it needs to get that trapped energy to the reaction centre in the cell as quickly as possible, where the energy is converted into chemical energy for the organism.

"It was assumed the energy gets to the reaction centre in a random fashion, like a drunk staggering home. But quantum coherence would allow the energy to test every possible pathway simultaneously before travelling via the quickest route."

In the new study, the team used x-ray crystallography to work out the crystal structure of the light harvesting complexes from three different species of cryptophytes.

They found that in two species a genetic mutation has led to the insertion of an extra amino acid that changes the structure of the protein complex, disrupting coherence.

"This shows cryptophytes have evolved an elegant but powerful genetic switch to control coherence and change the mechanisms used for light harvesting," says Professor Curmi.

The next step will be to compare the biology of different cryptophytes, such as whether they inhabit different environmental niches, to work out whether the quantum coherence effect is assisting their survival. [8]

Photoactive Prebiotic Systems

We propose that life first emerged in the form of such minimal photoactive prebiotic kernel systems and later in the process of evolution these photoactive prebiotic kernel systems would have produced fatty acids and covered themselves with fatty acid envelopes to become the minimal cells of the Fatty Acid World. Specifically, we model self-assembling of photoactive

prebiotic systems with observed quantum entanglement phenomena. We address the idea that quantum entanglement was important in the first stages of origins of life and evolution of the biospheres because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states, leading to faster growth and self-replication of minimal living cells. The quantum mechanically modeled possibility of synthesizing artificial self-reproducing quantum entangled prebiotic kernel systems and minimal cells also impacts the possibility of the most probable path of emergence of photocells on the Earth or elsewhere. We also examine the quantum entangled logic gates discovered in the modeled systems composed of two prebiotic kernels. Such logic gates may have application in the destruction of cancer cells or becoming building blocks of new forms of artificial cells including magnetically active ones.

Significance Statement

Our investigated self-assembly of molecules towards supramolecular bioorganic and minimal cellular systems depends on the quantum mechanics laws which induce hydrogen and Van der Waals bindings (Tamulis A, Grigalavicius, M, *Orig Life Evol Biosph* 41:51-71, 2011).

In the work presented here, quantum entanglement takes the form of a quantum superposition of the active components in synthesized self-assembling and self-replicating living systems. When a quantum calculation of an entangled system is made that causes one photoactive biomolecule of such a pair to take on a definite value (e.g., electron density transfer or electron spin density transfer), the other member of this entangled pair will be found to have taken the appropriately correlated value (e.g., electron density transfer or electron spin density transfer). In our simulations, the separation distance of supramolecular bio systems changes took place during geometry optimization procedures, which mimic real-world intermolecular interaction processes.

Our discovered phenomenon of the quantum entanglement in the prebiotic systems enhance the photosynthesis in the proposed systems because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states (Tamulis A, Grigalavicius M, Baltrusaitis J, *Orig Life Evol Biosph* 43:49-66, 2013; Tamulis A, Grigalavicius M, Krisciukaitis S (2014) , *J Comput Theor Nanos*, 11, 1597-1608, 2014; Tamulis A, Grigalavicius M, 8:117-140, 2014.). We can propose that quantum entanglement enhanced the emergence of photosynthetic prebiotic kernels and accelerated the evolution of photosynthetic life because of additional absorbed light energy, leading to faster growth and self-replication of minimal living cells.

We can state that: Livings are self-assembled and self-replicating wet and warm stochastically moving supramolecular systems where quantum entanglement can be continuously generated and destroyed by non-equilibrium effects in an environment where no static entanglement exists; quantum entanglement involve the biomolecule inside one living or between other neighboring livings.

This warm quantum coherence is basic for the explanation of DNA stability and for the understanding of brain magnetic orientation during migration in more than 50 species of birds, fishes and insects. Exists experimental evidence for quantum-coherent is used for more efficient light-harvesting in plant photosynthesis. Quantum entanglement exists in supramolecules determining the sense of smell and in the brain neurons microtubules due to quantum vibrations.

In the work presented here, we started to design and quantum mechanical investigations of the molecular logical devices which are useful for construction of nano medicine biorobots against the molecular diseases such a cancer tumors, and against the new kinds of synthesized microorganisms and nano guns.

Figure legend



You can see in the enclosed figure the quantum entanglement phenomenon in the closely self-assembled two synthesized protocell system due to the photo excited electron charge transfer from one protocell to another that leads to closer self-assembly and exchange of energy and information.

Visualization of the electron charge tunneling associated with the 6th (467.3 nm) excited state. The transition is mainly from squaraine molecule of the first protocell situated in the bottom of this bicellular system to precursor of fatty acid (pFA) molecule of the second subsystem (in the top) and little from the 1,4-bis(N,N-dimethylamino)naphthalene molecule (in the top-right) to the same pFA molecule of the second subsystem (in the top). The electron cloud hole is indicated by the dark blue color while the transferred electron cloud location is designated by the gray color.

As a result, these nonlinear quantum interactions compressed the overall molecular system resulting in a smaller gap between the HOMO and LUMO electron energy levels which allows

enhanced tunneling of photo excited electrons from the sensitizer squaraine and (1,4bis(N,Ndimethylamino)naphthalene) to the pFA molecule resulting in its cleavage. The new fatty acid joins the existing minimal cell thus increasing it in size. After reaching some critical size, the minimal cell should divide (i.e. self-replicate) into two separate smaller minimal cells. [7]

Quantum Biology

Researchers have long suspected that something unusual is afoot in photosynthesis. Particles of light called photons, streaming down from the Sun; arrive randomly at the chlorophyll molecules and other light-absorbing 'antenna' pigments that cluster inside the cells of every leaf, and within every photosynthetic bacterium. But once the photons' energy is deposited, it doesn't stay random. Somehow, it gets channeled into a steady flow towards the cell's photosynthetic reaction centre, which can then use it at maximum efficiency to convert carbon dioxide into sugars. Quantum coherence in photosynthesis seems to be beneficial to the organisms using it. But did their ability to exploit quantum effects evolve through natural selection? Or is quantum coherence just an accidental side effect of the way certain molecules are structured? [6]

Quantum Consciousness

Extensive scientific investigation has found that a form of quantum coherence operates within living biological systems through what is known as biological excitations and biophoton emission. What this means is that metabolic energy is stored as a form of electromechanical and electromagnetic excitations. These coherent excitations are considered responsible for generating and maintaining long-range order via the transformation of energy and very weak electromagnetic signals. After nearly twenty years of experimental research, Fritz-Albert Popp put forward the hypothesis that biophotons are emitted from a coherent electrodynamic field within the living system.

What this means is that each living cell is giving off, or resonating, a biophoton field of coherent energy. If each cell is emitting this field, then the whole living system is, in effect, a resonating field—a ubiquitous nonlocal field. And since biophotons are the entities through which the living system communicates, there is near-instantaneous intercommunication throughout. And this, claims Popp, is the basis for coherent biological organization -- referred to as quantum coherence. This discovery led Popp to state that the capacity for evolution rests not on aggressive struggle and rivalry but on the capacity for communication and cooperation. In this sense the built-in capacity for species evolution is not based on the individual but rather living systems that are interlinked within a coherent whole: Living systems are thus neither the subjects alone, nor objects isolated, but both subjects and objects in a mutually communicating universe of meaning. . . . Just as the cells in an organism take on different tasks for the whole, different populations unfold information not only for themselves, but for all other organisms, expanding the consciousness of the whole, while at the same time becoming more and more aware of this collective consciousness.

Biophysicist Mae-Wan Ho describes how the living organism, including the human body, is coordinated throughout and is "coherent beyond our wildest dreams." It appears that every part of our body is "in communication with every other part through a dynamic, tunable, responsive, liquid crystalline medium that pervades the whole body, from organs and tissues to the interior of every cell."

What this tells us is that the medium of our bodies is a form of liquid crystal, an ideal transmitter of communication, resonance, and coherence. These relatively new developments in biophysics have discovered that all biological organisms are constituted of a liquid crystalline medium. Further, DNA is a liquid-crystal, lattice-type structure (which some refer to as a liquid crystal gel), whereby body cells are involved in a holographic instantaneous communication via the emitting of biophotons (a source based on light). This implies that all living biological organisms continuously emit radiations of light that form a field of coherence and communication. Moreover, biophysics has discovered that living organisms are permeated by quantum wave forms. [5]

Creating quantum technology

Another area of potential application is in quantum computing. The long-standing goal of the physicists and engineers working in this area is to manipulate data encoded in quantum bits (qubits) of information, such as the spin-up and spin-down states of an electron or of an atomic nucleus. Qubits can exist in both states at once, thus permitting the simultaneous exploration of all possible answers to the computation that they encode. In principle, this would give quantum computers the power to find the best solution far more quickly than today's computers can — but only if the qubits can maintain their coherence, without the noise of the surrounding environment, such as the jostling of neighboring atoms, destroying the synchrony of the waves. [6]

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 Δx position difference and with a Δp momentum difference such a way that they product is about the half Planck reduced constant. For the proton this Δx much less in the nucleon, than in the orbit of the electron in the atom, the Δp is much higher because of the greater proton mass.

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

Wave – Particle Duality

The accelerating electrons explains the wave – particle duality of the electrons and photons, since the elementary charges are distributed on Δx position with Δp 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 it's 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 it 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 ν 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, their masses are different, also as the wavelengths on both sides of the diffraction pattern, giving equal intensity of radiation.

Electron – Proton mass ratio

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 be 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 be 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

Exists experimental evidence for quantum-coherent is used for more efficient light-harvesting in plant photosynthesis. Quantum entanglement exists in supramolecules determining the sense of smell and in the brain neurons microtubules due to quantum vibrations.

In the work presented here, we started to design and quantum mechanical investigations of the molecular logical devices which are useful for construction of nano medicine biorobots against the molecular diseases such a cancer tumors, and against the new kinds of synthesized microorganisms and nano guns. [7]

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 they 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]

These relatively new developments in biophysics have discovered that all biological organisms are constituted of a liquid crystalline medium. Further, DNA is a liquid-crystal, lattice-type structure (which some refer to as a liquid crystal gel), whereby body cells are involved in a holographic instantaneous communication via the emitting of biophotons (a source based on light). This implies that all living biological organisms continuously emit radiations of light that form a field of coherence and communication. Moreover, biophysics has discovered that living organisms are permeated by quantum wave forms. [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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