Gene Constrains DNA Movements

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Scientists have long sought to develop drug therapies that can more precisely diagnose, target and effectively treat life-threatening illness such as cancer, cardiovascular and autoimmune diseases. [37]

Skin cells taken from patients with a rare genetic disorder are up to ten times more sensitive to damage from ultraviolet A (AVA) radiation in laboratory tests, than those from a healthy population, according to new research from the University of Bath. [36]

The use of stem cells to repair organs is one of the foremost goals of modern regenerative medicine. [35]

Using new technology to reveal the 3-D organization of DNA in maturing male reproductive cells, scientists revealed a crucial period in development that helps explain how fathers pass on genetic information to future generations. [34]

According to the Centers for Disease Control and Prevention, Down syndrome is the most common birth defect, occurring once in every 700 births. [33]

Healing is a complex process in adult skin impairments, requiring collaborative biochemical processes for onsite repair. [32]

Researchers at ETH Zurich recently demonstrated that platinum nanoparticles can be used to kill liver cancer cells with greater selectivity than existing cancer drugs. [31]

"PPRIG was set up by NPL in 2012 to progress UK deployment of high-energy proton therapy," explained Russell Thomas, senior research and clinical scientist at NPL and chair of PPRIG. [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 HYPERLINK "https://phys.org/tags/free+energy/" 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 rate and the Weak and Strong Interactions by the diffraction patterns. The Weak Interaction changes the diffraction patterns by moving the electric charge from one side to the other side of the diffraction pattern, which violates the CP and Time reversal symmetry.

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

Gene transcription machinery constrains DNA movements, study suggests

Researchers in Japan have discovered that the DNA inside human cells moves around less when its genes are active. The study, which will be published March 1 in the *Journal of Cell Biology*, suggests that RNA polymerase II (RNAPII)—the key enzyme required to produce messenger RNA molecules from active genes—restricts the movement of DNA by organizing it into a network of interconnected domains.

To fit inside the nucleus of the cell, DNA is organized into chromatin, in which the strands of DNA are wrapped around groups of histone proteins, like thread around a spool, to form structures known as nucleosomes. Nucleosomes can then be folded up into even more compact structures. When a gene is activated, however, its chromatin is thought to open up and, at the same time, become more mobile and dynamic, so that RNAPII can transcribe the gene into messenger RNAs.

Kazuhiro Maeshima and colleagues at the National Institute of Genetics in Mishima, Japan, were therefore surprised when they discovered that the chromatin in human cells becomes more mobile when RNAPII and gene transcription are inhibited.

Maeshima's group used a high-resolution microscopy technique that allowed them to track the movements of individual nucleosomes inside living cells. When the researchers depleted RNAPII from cells, or added drugs that inhibit the enzyme, nucleosomes in the genome clearly became more dynamic, suggesting that RNAPII usually restricts global chromatin movements.

Individual nucleosomes (white dots) are more dynamic when RNAPII is inhibited (right), compared with nucleosomes in a control cell (left). Credit: Nagashima et al., 2019

RNAPII and gene transcription activity are naturally reduced when cells enter a dormant state called quiescence or when their DNA is damaged by ultraviolet light. Accordingly, Maeshima and colleagues saw that chromatin was more dynamic in quiescent or UV-irradiated cells. The researchers speculate that these increased movements may help chromatin recruit factors required to repair DNA or restart gene transcription when quiescent cells are reactivated.

But how does gene transcription affect the global mobility of chromatin when, at any given moment, RNAPII is only transcribing a small fraction of the genome? Based on computer simulations, Maeshima and colleagues propose that clusters of RNAPII and associated factors can bind and connect distant chromatin regions, linking them together in an organized network. These connections are lost when RNAPII is inactivated, breaking up the network and allowing chromatin to become more mobile.

"Our imaging and computational modeling results suggest that chromatin is globally stabilized by loose connections through transcriptionally active RNAPII," Maeshima says. "Our model is compatible with the classical idea of stable transcription factories containing RNAPII, as well as with recent reports that RNAPII and other factors undergo a phase separation process to form dynamic clusters within the nucleus." [43]

New research area: How protein structures change due to normal forces

Proteins made in our cells are folded into specific shapes so they can fulfill their functions. Scientists have discovered the static structures of over 100,000 proteins, but how they change in response to forces on the cell, like muscle contractions, is largely unknown. Matthias Wilmanns and colleagues at the European Molecular Biology Laboratory in Hamburg, Germany, developed methods to study the structure of a protein "strain absorber" as it changes during muscle contractions. They will present their work at the 63rd Biophysical Society Annual Meeting, to be held March 2—6, 2019 in Baltimore, Maryland.

Each muscle unit has a series of highly organized protein rods that are pulled to overlap when a muscle contracts or are pulled apart when a muscle is stretched. Myomesin is a protein that stabilizes and organizes these rods, acting to absorb the strain on stretched muscles to prevent the muscle units from breaking apart. Wilmanns, in collaboration with Matthias Rief's group at the Technical University of Munich, used atomic force microscopy to stretch and measure individual myomesin molecules. Myomesin became 2.5 times longer under force, and their high resolution structure showed this was due to slinky-like linkers in the protein that allow it to stretch without unfolding. However, a key question remains on demonstrating that these mechanisms apply under physiological conditions as well. To address this question, Wilmanns and colleagues are now designing experiments to visualize the changes in myomesin inside muscle cells using super high-resolution imaging.

"Muscle is a good model for looking at how its proteins respond to force, because it experiences extraordinarily high forces, but we have small forces all over the body," explained Wilmanns. "Now we have methods sensitive enough to measure very small forces, so we can start looking at the behavior of different proteins that respond to very small forces. At present there is so little known about mechanisms of molecular elasticity in proteins." [42]

Technique allows researchers to focus the action of drugs via infrared light

Having absolute control of the activity of a molecule in an organism, or deciding when, where and how a drug is activated—these are some of the goals possible with so-called photoswitchable molecules, compounds that change their properties in the presence of certain light waves. The results of a study led by the Institute for Bioengineering of Catalonia (IBEC) together with the Universitat Autònoma de Barcelona (UAB), bring objective this one step closer.

Using pulsed infrared light lasers, scientists have activated molecules located inside neural tissue with an efficiency of almost 100 percent. "It's a development that opens the door to a large number of applications, including drugs that only act at the point of the body that is illuminated and are therefore free from unwanted side-effects in other regions, and the spatial and temporal control of any protein whose function we want to study in the context of an organism," says Pau Gorostiza, ICREA research professor and head of the Nanoprobes and Nanoswitches Group at IBEC. The study has recently been published in the journal *Nature Communications*.

High precision photosensitive switches

The photoswitchable molecule that the researchers used is a new variant of azobenzene, a chemical compound that has a flat shape in the dark, but which bends when exposed to light. Photopharmacology seeks to take advantage of this peculiar property to control the activity of drugs—an inactive drug combined with azobenzene is introduced into the body. The design of the drug only allows its operation when the azobenzene is bent. In this way, the drug will only take effect at the points where the light that stimulates azobenzene is irradiated, thus avoiding the side-effects associated with the drug's action in other areas where azobenzene is present.

Until recently, techniques based on photoswitchable molecules used continuous-wave lasers of violet or blue light (one-photon stimulation) to activate these compounds, a method that does not allow focalizing the stimulus. "We wanted the molecule to be activated at a specific point, not along the whole beam of light that we irradiate. We saw that two-photon transitions using pulsed infrared light could achieve this, but the efficiency was very low, and the applications were limited. The molecules we have developed now achieve this effect with 100 percent efficiency. It is a very robust and precise technology to manipulate neuronal activity," said Jordi Hernando and Ramon Alibés, researchers from the Department of Chemistry at the UAB who have supervised part of this work together with Josep Mª Lluch and Félix Busqué.

Researchers have proven the effectiveness of the technique on mouse neurons and in an animal model for the study of neuronal circuits, the Caenorhabditis elegans worm. "Despite the cells in a neuronal tissue being very close together, we have managed to select those in which we wanted to activate the photoswitchable molecule."

Stimulation via two-photon absorption, predicted by Maria Göppert-Mayer and demonstrated using the pulsed lasers developed by the winners of the Nobel Prize in Physics in 2018, Donna Strickland and Gérard Mourou, has represented a revolution for the visualisation and manipulation of neuronal activity.

The results of this development open the door to new lines of research in the molecular field. With the technique described, scientists will possess unprecedented spatiotemporal control over any photoswitchable molecule they wish to investigate. [41]

Researchers uncover mechanism behind DNA damage control

DNA damage is occurring in our cells all the time due to external agents, such as exposure to sun, or internal agents, like reactive oxygen species. To detect and repair DNA lesions, cells have evolved DNA damage response. Activation of this response underpins genome integrity, which is crucial for preventing the onset of many human pathologies, including hematological disorders, neurodegenerative diseases, and cancer.

DNA damage elicits transient yet profound alterations in cellular gene expression programs. Previous work has established that cells need to shut down gene transcription by RNA polymerase II to facilitate DNA repair and limit the production of abnormal transcripts.

In a study that appeared online on 26 February in the prestigious journal *Molecular Cell*, researchers at the University of Helsinki have now added a new wrinkle to the story. The collaborative effort led

by the Barborič laboratory has uncovered that activating gene transcription is equally important for how cells confront the genotoxic assault.

Transcription of a typical gene in multicellular organisms consists of many phases. Soon after the polymerase starts transcribing, it pauses due to the actions of negative transcription elongation factors. Releasing the pause by the positive transcription elongation factor b (P-TEFb), which is a heterodimeric CDK9/CycT kinase, has emerged as a critical rate-limiting step that enables transcription to the gene's end. Adding yet another layer of regulation, a major fraction of P-TEFb resides within the 7SK snRNP complex in which the kinase activity of CDK9 is repressed, precluding unchecked gene activation.

With the combination of biochemical and genome-wide techniques, the researchers have found that genotoxic stress activates P-TEFb via RBM7, an RNA binding protein that was previously linked to facilitating RNA degradation. Upon activation of the p38 MAPK signal transduction pathway, the phosphorylated RBM7 interacts with 7SK snRNP to trigger the release of P-TEFb.

Subsequently, the active kinase relocates to chromatin, triggering induction of thousands of short coding and non-coding transcription units. Importantly, the authors showed that the transcriptional response is critical for the survival of stressed cells. When they interfered with the RBM7–P-TEFb axis, the cells became hypersensitive to DNA damage-inducing agents, leading to their demise.

"As the results were coming in, the bigger picture began to emerge. We found how and why CDK9 gets activated upon genotoxic stress," says Andrii Bugai, doctoral student in the laboratory and first author of the study.

"In the final analysis there are no alternatives: cells either induce gene transcription or they will die."

"In times of crisis, the gloves are off. Cells de-repress a principal transcriptional kinase, which in turn eliminates the main roadblock to effective polymerase elongation on key pro-survival and DNA damage response genes," says Matjaž Barborič, Sigrid Jusélius Senior Investigator and senior author who spearheaded the work.

"In retrospect some pieces of the story were already there, but with new experimental approaches, we were able to decipher the critical transcriptional pathway and connect the dots."

Emerging body of work shows that prosperity of cancer cells can depend on the addiction to regulators of gene expression, including transcriptional kinases such as CDK9. Highly specific CDK9 inhibitors have been developed, and some are already entering clinical trials. Given that the new study identified CDK9 at the core of cellular DNA damage response, the authors are optimistic about the prospects for novel anti-cancer interventions.

"Because chemotherapeutic drugs can activate DNA damage response, the drug-induced cancer cell killing might be greatly enhanced when combined with specific pharmacological inhibitors of CDK9. This combinatorial approach or its derivatives could be an important way forward in our battle with cancer," says Barborič. [40]

Crowd-sourced computer network delves into protein structure, seeks new disease therapies

When Greg Bowman presents a slideshow about the proteins he studies, their 3-D shapes and folding patterns play out as animations on a big screen. As he describes these molecules, it might be easy to miss the fact that he can't really see his own presentation, at least not the way the audience does.

Bowman, assistant professor of biochemistry and molecular biophysics at Washington University School of Medicine in St. Louis, is legally blind. He also now leads one of the largest crowd-sourced computational biology projects in the world. The effort is aimed at understanding how proteins fold into their proper shapes and the structural motions they undergo as they do their jobs keeping the body healthy. Proteins are vital cellular machinery, and understanding how they assemble and function—or malfunction—could shed light on many of the most vexing problems in medical science, from preventing Alzheimer's disease, to treating cancer, to combating antibiotic resistance.

Appropriately called Folding@home, the project relies on the power of tens of thousands of home computers to perform the complex calculations required to simulate the dynamics of the proteins Bowman and his colleagues are studying. With this networked computing power, Folding@home is, essentially, one of the world's largest supercomputers.

"There are some traditional supercomputing folks who might take issue with that characterization," Bowman said with a laugh. "Rather than a single massive machine, Folding@home is a distributed computing network. Thousands of volunteers all over the world download our software and contribute a portion of their home computer setups to the project. But in terms of raw computing power—the sheer number of calculations it can perform per second—it's on par with the world's biggest supercomputers."

Bowman got started on this work in the lab of Folding@home founder Vijay Pande, Ph.D., of Stanford University. Bowman earned his doctoral degree at Stanford and did postdoctoral research there. After 18 years at the helm, Pande chose Bowman to take over leadership, bringing Folding@home into the next decade and beyond.

"Greg has a unique combination of skills," Pande said. "He has the technical chops to lead this complex project, and he has the people skills to manage the distributed nature of it, especially the fact that it involves so many different kinds of people—scientists and nonscientists alike. Greg also has great vision for the future of this project. He not only will keep the trains running on time, he has a strong picture of where Folding@home should be 10 to 20 years from now."

Folding@home's massive computing capacity is crucial to understanding protein folding, a problem Bowman calls a classic grand challenge in biochemistry and biophysics. Proteins are the raw materials that make up our bodies. But they are also the molecular machines that do the work of building those bodies and making sure they run properly. To do its work, a protein must fold into its proper form. If it doesn't, things go wrong.

Greg Bowman, assistant professor of biochemistry and molecular biophysics at Washington University School of Medicine in St. Louis, is leading a supercomputing project called Folding@home. The project seeks to unravel the mysteries of protein …more

Bowman understands this more than most.

Born with normal vision, Bowman progressively lost sight, becoming legally blind by age nine due to an inherited condition called Stargardt disease. A form of juvenile macular degeneration, it is caused when a protein that removes waste from cells in the retina doesn't fold properly and can't do its job. As a result, light-sensing cells in the retina become overwhelmed with waste and die, causing loss of central vision.

Bowman said the experience lit a passion for biology and a drive to understand what goes wrong when the proteins our body relies on don't work properly. Ultimately, he would like to find ways to fix them. But as a young student, Bowman quickly realized his route into the field might look a little different than that taken by the average biologist.

"I learned that experimental biology is not very accessible to people who are visually impaired," Bowman said. "Essentially, I see at low resolution, mostly with my peripheral vision. I can navigate hallways and laboratories, but I can't read the small dial on a pipette, for example.

"As I came to realize this, I also fell in love with computers," he said. "I saw that the skills of computer science and mathematical modeling could be applied to biological problems. Plus, one of the many beauties of computers is that it's really easy to zoom in on things. I can zoom in to 16 times magnification and scroll around on the screen, so I can read a scientific paper—or even just an email—for example."

With Folding@home, Bowman and his colleagues are zooming in on proteins and how they fold much more than 16 times. Indeed, they are getting as close as physically possible—down to the atomic level. With this networked supercomputer, scientists can model proteins at the level of individual atoms in a fraction of the time it might take even powerful single computers. Many important biological processes that proteins perform take place over milliseconds to a few seconds. That might seem short, but measuring atoms as they bounce off one another requires time scales in femtoseconds—one quadrillionth of a second.

"To model just one millisecond of folding, even for an average-size protein, on a top-of-the-line MacBook Pro, it would take something like 500 years," Bowman said. "But with Folding@home, we can split these problems into many independent chunks. We can send them to 1,000 people at the same time. Running those calculations in parallel, we can take these problems that would have taken 500 years and instead solve them in six months."

Greg Bowman’s team listens to a presentation at their lab meeting. Credit: Matt Miller/Washington University School of Medicine

As of this writing, Folding@home has more than 110,000 volunteer "folders" around the world who have shared a portion of their home computing capacity. According to videos from some volunteers, their reasons for contributing to the project are, like Bowman's, personal. The program gives users some choice in what kinds of projects they contribute to, whether they are interested in boosting cancer research, preventing Alzheimer's disease or fighting antibiotic resistance, among others.

Bowman envisions a future where Folding@home serves as a starting point for new drug design. Right now, scientists often have only one well-known protein structure to study. Beta lactamase, for example, is a protein that some bacteria deploy to protect themselves from antibiotics like penicillin. The protein has a well-documented, long-studied structure. But that structure only represents a single snapshot of beta lactamase at one moment in time.

"That snapshot contains valuable information," Bowman said. "But it's kind of like seeing a picture of a construction vehicle in a parking lot and trying to guess what it does. Really, what you would like is to watch this thing move around and see how it works together with other machinery to, say, build a building. We're interested in watching how every atom in a protein moves—as it's being assembled for the first time and as it goes about its jobs. The atoms in a protein are never still, they're constantly jostling and moving around. And one genetic mutation changes maybe a dozen atoms out of thousands. We want to understand what that does to the entire protein."

Among several projects, Bowman's own lab is using Folding@home to seek new drugs to combat antibiotic resistance. Watching the movement of beta lactamase, for example, already has revealed what Bowman calls "cryptic pockets," weak points in the protein that could be targeted by drugs but

that are not visible in the long-studied snapshot of this protein. The cryptic pockets only reveal themselves when the protein is moving.

As Bowman sees the world a bit differently than most, Folding@home offers scientists a different look at long-studied proteins, revealing solutions to biological problems that might otherwise remain hidden from view.

To put your own computer to work folding proteins, visit the Folding@home website. [39]

Preventing the production of toxic mitochondrial proteins—a promising treatment target

Researchers at the University of Helsinki uncovered the mechanisms for a novel cellular stress response arising from the toxicity of newly synthesized proteins. Activation of the stress response is at the epicentre of the molecular events generated by genetic mutations that cause a complex neurological syndrome.

In all living organisms, the ability to translate the genetic code into proteins is the definitive step in gene expression. Mitochondria are known as the powerhouse of the cell and an indispensable organelle with a unique genome and a dedicated protein synthesis machinery. [KEE1] In humans, mitochondrial DNA is only inherited from the mother and encodes only 13 proteins essential for energy metabolism. Defects in the faithful synthesis of these 13 proteins represents the largest group of inherited human mitochondrial disorders, which display exceptional clinical heterogeneity in terms of presentation and severity. Disruptions to energy metabolism alone do not explain the disease mechanism.

"The ability to treat patients has been stymied because of the fragmented understanding of the molecular pathogenesis and thus, bridging this knowledge gap is critical," says Research Director Brendan Battersby from the Insitute of Biotechnology, University of Helsinki.

AFG3L2 genes act as mitochondrial quality control regulator, preventing the accumulation of toxic translation products and thereby keeps the organelle and cell healthy. Mutations in the genes AFG3L2 and paraplegin cause a remodeling of mitochondrial shape and function, which are one of the earliest known cellular phenotypes in the disease. However, the mechanism by which these events arose was so far unknown. The research group of Brendan Battersby, at the Institute of Biotechnology, University of Helsinki, have now solved a molecular puzzle associated with genetic mutations linked to a multifaceted neurological syndrome.

A recently published research of Battersby's group revealed the etiology for the cellular effects was a proteotoxicity arising during the synthesis of new mitochondrial proteins. The group showed how this proteotoxicity was a trigger for a progressive cascade of molecular events as part of a stress response that ultimately remodels mitochondrial form and function.

Excitingly, a clinically approved drug that can cross the blood-brain barrier was also found to block the production of the toxic proteins and the ensuing stress response.

"Since the mitochondrial proteotoxicity lies at the epicentre of the molecular pathogenesis, preventing the production of toxic mitochondrial proteins opens up a promising treatment paradigm to pursue for patients," says Battersby.

Next step in the research is to test the efficacy of the drug in a double-blind preclinical trial in animal models of these diseases. [38]

New paper provides design principles for disease-sensing nanomaterials

Scientists have long sought to develop drug therapies that can more precisely diagnose, target and effectively treat life-threatening illness such as cancer, cardiovascular and autoimmune diseases. One promising approach is the design of morphable nanomaterials that can circulate through the body and provide diagnostic information or release precisely targeted drugs in response to disease-marker enzymes. Thanks to a newly published paper from researchers at the Advanced Science Research Center (ASRC) at The Graduate Center of The City University of New York, Brooklyn College, and Hunter College, scientists now have design guidance that could rapidly advance development of such nanomaterials.

In the paper, which appears online in the journal *ACS Nano*, researchers detail broadly applicable findings from their work to characterize a nanomaterial that can predictably, specifically and safely respond when it senses overexpression of the enzyme matrix metalloproteinase-9 (MMP-9). MMP-9 helps the body breakdown unneeded extracellular materials, but when levels are too high, it plays a role in the development of cancer and several other diseases.

"Right now, there are no clear rules on how to optimize the nanomaterials to be responsive to MMP-9 in predictable ways," said Jiye Son, the study's lead author and a Graduate Center Ph.D. student working in one of the ASRC Nanoscience Initiative labs. "Our work outlines an approach using short peptides to create enzyme-responsive nanostructures that can be customized to take on specific therapeutic actions, like only targeting tumor cells and turning on drug release in close proximity of these cells."

Researchers designed a modular peptide that spontaneously assembles into nanostructures, and predictably and reliably morphs or breaks down into amino acids when they come in contact with the MMP-9 enzyme. The designed components include a charged segment of the nanostructure to facilitate its sensing and engagement with the enzyme; a cleavable segment of the structure so that it can lock onto the enzyme and determine how to respond; and a hydrophobic segment of the structure to facilitate self-assembly of the therapeutic response.

"This work is a critical step toward creating new smart-drug delivery vehicles and diagnostic methods with precisely tunable properties that could change the face of disease treatment and management," said ASRC Nanoscience Initiative Director Rein Ulijn, whose lab is leading the work. "While we specifically focused on creating nanomaterials that could sense and respond to MMP-9, the components of our design guidance can facilitate development of nanomaterials that sense and respond to other cellular stimuli."

Among other advances, the research team's work builds on their previous findings, which showed that amino acid peptides can encapsulate and transform into fibrous drug depots upon interaction with MMP-9. The group is collaborating with scientists at Memorial Sloan Kettering and Brooklyn College to use their findings to create a novel cancer therapy. [37]

Pioneering study could offer protection to patients with rare genetic disease

Skin cells taken from patients with a rare genetic disorder are up to ten times more sensitive to damage from ultraviolet A (AVA) radiation in laboratory tests, than those from a healthy population, according to new research from the University of Bath.

It is hoped that the work, which has involved designing a brand new molecule with potential to be added to sun cream, could benefit those with Friedrich's Ataxia (FA), as well as those with other disorders characterised by mitochondrial iron overload, notably Wolfram Syndrome and Parkinson's disease, where UVA rays from the sun may pose particular challenges.

Although most sun creams are effective against UVB rays, generally they only protect against UVA rays through the reflective properties of the cream alone. When cells are exposed to UVA rays, the damage caused to cells can be worsened by excess free iron in mitochondria which fuels the generation of 'free radicals', including Reactive Oxygen Species (ROS), which can damage DNA, protein and fats—increasing the risk of cell death and cancer.

Patients with FA have high levels of free iron in their mitochondria. This new research, led by scientists at the University of Bath, King's College London and Brunel University London shows that this excess free iron makes skin cells from these patients up to 10 times more susceptible to UVA damage.

The scientists have custom-built a molecule which acts like a claw to scoop up excess iron particles within mitochondria, preventing them from amplifying UVA-induced damage. The researchers' goal is to see this molecule added to sun creams to enhance their protective effect against UVA rays.

In a series of in vitro experiments using human skin cells called fibroblasts from FA patients, the researchers demonstrated that their claw—termed an 'iron chelator'—reduced damage to mitochondria membranes from realistic doses of UVA rays by a factor of two. In cells pre-treated with the chelator, UVA-mediated cell death was prevented. The chelator is cleverly designed so that it travels to the mitochondria specifically.

Dr. Charareh Pourzand, from the Department of Pharmacy and Pharmacology at the University of Bath, said: "A major function of mitochondria is to produce energy, and iron in the right amount is essential for their function.

Unfortunately because mitochondria are so crucial as the main source of energy, when something goes wrong with them, the consequences can be severe. Mitochondria dysfunction lies at the heart of a growing number of diseases.

"Friedreich's Ataxia is one example of a disease of 'mitochondrial iron overload'. Our results -should they translate to people's skin (in vivo), suggest that patients could be up to 10 times more sensitive to UVA. The damage you and I would get in our skin from for example 2.5 hours' exposure to solar UVA would be 4-10 times higher for a patient with FRDA.

"There's a vicious cycle—excess iron in the mitochondria means more reactive oxidising species and more damage to cell constituents, resulting in cell functions being compromised. This situation leaves cells more sensitive to subsequent oxidative damage notably by environmental factors such as UVA of sunlight.

"We're interested in the biology of iron and how it impacts humans and disease. One of our goals is ultimately to develop new therapies to protect from the sun. Our research shows that adding an iron chelator to sun creams could enhance the photoprotective capability of current preparations and be particularly beneficial to people with acute sensitivity to solar UVA.

"We hope that our findings can be ultimately translated to the people to give them a better quality of life, and that we can inspire other researchers to follow those avenues. We are very thankful to our sponsor the Biotechnology and Biological Sciences Research Council (BBSRC) to have made this project feasible."

The team is now looking to continue the research into the chelator with an in vivo mouse model of the disease.

Friedreich's Ataxia (FA) is a genetic disease characterised by the progressive degeneration of the cells of the nervous system and of the heart. FA has a prevalence of around 1/29,000 in Caucasian populations, and 1/20,000 in south-western Europe. Patients often have to use wheelchairs from a young age and frequently die in early adulthood.

The role of mitochondrial labile iron in Friedreich's ataxia skin fibroblasts sensitivity to ultraviolet A is published in *Metallomics*. [36]

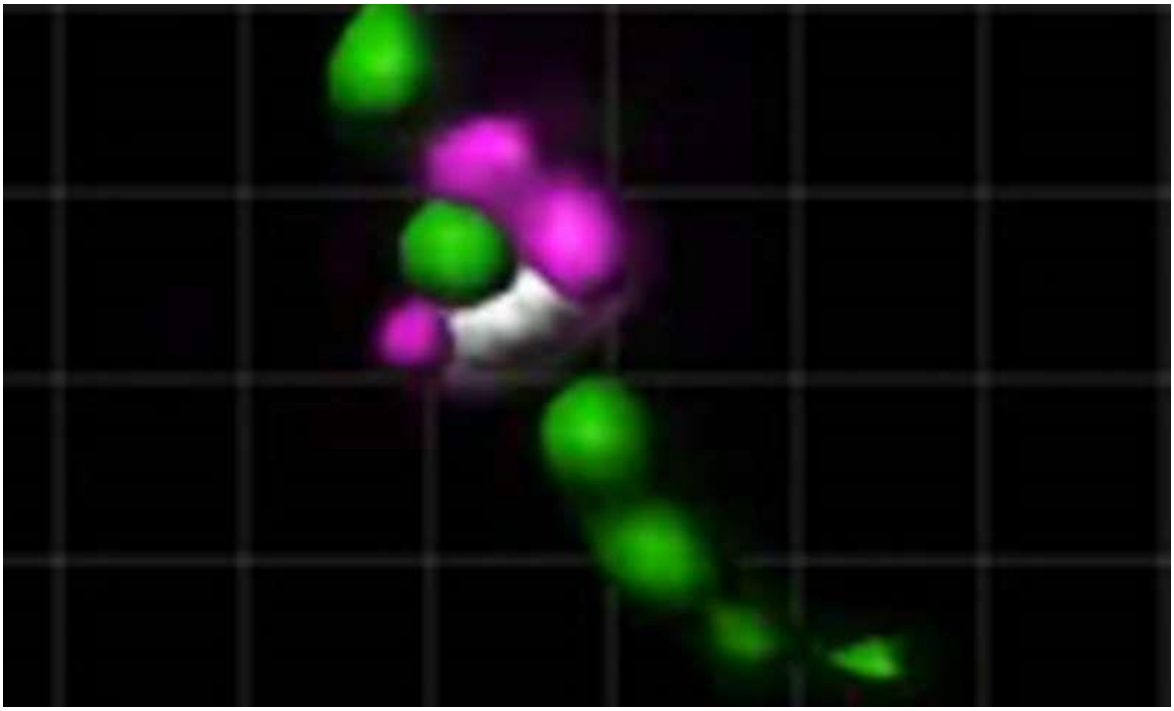
New mechanisms regulating neural stem cells

The use of stem cells to repair organs is one of the foremost goals of modern regenerative medicine. Scientists at Helmholtz Zentrum München and Ludwig Maximilian University of Munich (LMU) have discovered that the protein Akna plays a key role in this process. It controls, for example, the behavior of neural stem cells via a mechanism that may also be involved in the formation of metastases. The study was published in the renowned journal *Nature*.

The research team led by Prof. Dr. Magdalena Götz, director of the Institute for Stem Cell Research (ISF) at Helmholtz Zentrum München and Chair of Physiological Genomics of the LMU Biomedical Center, wanted to identify the factors that regulate the maintenance or differentiation of neural stem cells. To this end, the scientists isolated neural stem cells, which either self-renew and generate additional neural stem cells or differentiate. "We found that the Akna protein is present in higher concentrations in stem cells that generate neurons," explains ISF researcher German Camargo Ortega, first author of the study together with Dr. Sven Falk. "Our experiments showed that low levels of the

Akna protein cause stem cells to remain in the stem cell niche, whereas higher levels stimulate them to detach from the niche, thus promoting differentiation," the author continues.

The scientists were surprised to discover the position of the protein − namely at the centrosome, an organelle in the cell's interior that acts as chief architect for the organization of the cytoskeleton and regulates cell division. "We discovered that an incorrect sequence was originally published for this protein," Sven Falk reports. "However, our work clearly showed that Akna is located directly at the centrosome." The researchers were able to show that Akna recruits and anchors microtubules at the centrosome. This weakens the connections to neighboring cells, and promotes detachment and migration from the stem cell niche.



Akna (here in magenta) is a novel centrosome component regulating the interaction with the cytoskeleton. Credit: Helmholtz Zentrum München"Our experiments show that this function also plays an important role in a process known as epithelial-to-mesenchymal transition, or EMT for short," explains the study leader Magdalena Götz. "In this process, cells detach from a cluster, proliferate and begin to migrate. This occurs, for example when stem cells migrate to form new neurons, but it can also be harmful in disease, for example when cancer cells leave a tumor to form metastases elsewhere in the body. "The novel mechanism that we identified by studying the function of Akna therefore appears to play a key role in a broad range of medically relevant processes." In the next step, the research team plans to investigate the role of Akna in other stem cells and in the immune system. [35]

Scientists reveal how 3-D arrangement of DNA helps perpetuate the species

From fathers to children, the delivery of hereditary information requires the careful packing of DNA in sperm. But just how nature packages this DNA to prepare offspring isn't clear. Using new technology to reveal the 3-D organization of DNA in maturing male reproductive cells, scientists revealed a crucial period in development that helps explain how fathers pass on genetic information to future generations.

The period was captured during a stage of male sperm development called meiosis. This is when reproductive cells, called germ cells, are maturing into sperm that can fertilize a female egg, laying the foundation to make all the cells of a child. Publishing their findings in *Nature Structural & Molecular Biology*, reproductive biologists at Cincinnati Children's Hospital Medical Center say nature prepares the 3-D organization of DNA before packing it into sperm.

By the time the germ cells actually become fertile sperm, the genetic material is tightly arranged. The male germ cell's hereditary material has precise 3-D organization in the cell's genetic control center, the nucleus. Researchers report that this 3-D organization is necessary for a male to help produce the next generation of life.

"We propose that male sperm is not just a carrier of DNA. Our data suggest that the three-dimensional organization in the cell nucleus helps establish a molecular foundation that can reproduce a complete zygote capable of becoming the next generation," said Satoshi Namekawa Ph.D., a principal investigator on the study and member of the Division of Reproductive Sciences.

The findings open the possibility of new research to investigate how the 3-D organization of genetic material affects fertility and issues such as premature birth or stillbirth. Also collaborating on the study was the laboratory of Noam Kaplan, Ph.D. at Technion Israel Institute of Technology, in Haifa, Israel.

Nature's Way

Using the maturing germ cells of male mice for their study, the researchers honed in on meiosis, the stage when male germ cells shed half of their chromosomes while shuffling around genetic material. This is part of nature's rule that male and female mammals each contribute half of their genetic material to generate a genetically whole but diverse member of the next generation. Humans have a total 46 chromosomes, with mother and father each contributing 23.

Using a technology called Hi-C, researchers were able to show the 3-D organization and interactions of chromosomes, as well as the genes in the nucleus of meiotic male germ cells. The authors propose that preparing 3-D organization in meiosis is vital for genes that allow germ cells to regain their ability to produce all the cells of the body after fertilizing a female egg.

"In meiosis, gene expression is extremely high and diverse," said Kris Alavattam, the study's first author and member of the Namekawa laboratory. "Many of these genes are essential for germ cells to develop, and many are expressed nowhere else but germ cells and at no other time."

During this time, the hereditary material in germ cells is organized in spatially related compartments called genomic compartments. In meiotic male germ cells, the researchers noticed genomic compartments are weaker than those in other cells of the body. This weakness helps facilitate what they call a global reprogramming of 3-D chromatin organization. This organization of chromatin—the packaging of DNA with DNA-binding proteins—promotes essential gene expression and germ cell development. After meiosis, genomic compartments of chromatin become stronger and stronger, packing DNA in a highly organized manner as cells ready for procreation.

In order to gain more insight about possible contributions to reproductive health problems in people, the scientists now want to use their laboratory modeling systems to understand how the disruption of 3-D chromatin organization may harm fertility. [34]

Sensitive sensor detects Down syndrome DNA

According to the Centers for Disease Control and Prevention, Down syndrome is the most common birth defect, occurring once in every 700 births. However, traditional non-invasive prenatal tests for the condition are unreliable or carry risks for the mother and fetus. Now, researchers have developed a sensitive new biosensor that could someday be used to detect fetal Down syndrome DNA in pregnant women's blood. They report their results in the ACS journal *Nano Letters*.

Characterized by variable degrees of intellectual and developmental problems, Down syndrome is caused by the presence of an extra copy of chromosome 21. To screen for the condition, pregnant women can have ultrasound scans or indirect blood biomarker tests, but misdiagnosis rates are high. Amniocentesis, in which doctors insert a needle into the uterus to collect amniotic fluid, provides a definitive diagnosis, but the procedure poses risks to both the pregnant woman and the fetus. The emerging method of whole-genome sequencing is highly accurate, but it is a slow and expensive process. Zhiyong Zhang and colleagues wanted to develop a fast, sensitive and cost-effective test that could detect elevated DNA concentrations of chromosome 21 DNA in pregnant women's blood.

The researchers used field-effect transistor biosensor chips based on a single layer of molybdenum disulfide. They attached gold nanoparticles to the surface. On the nanoparticles, they immobilized probe DNA sequences that can recognize a specific sequence from chromosome 21. When the team added chromosome 21 DNA fragments to the sensor, they bound to the probes, causing a drop in the electrical current of the device. The biosensor could detect DNA concentrations as low as 0.1 fM/L, which is much more sensitive than other reported field-effect transistor DNA sensors.

The researchers say that eventually, the test could be used to compare levels of chromosome 21 DNA in blood with that of another chromosome, such as 13, to determine if there are extra copies, suggesting a fetus has Down syndrome. [33]

Skin wound regeneration with bioactive glass-gold nanoparticles ointment

Healing is a complex process in adult skin impairments, requiring collaborative biochemical processes for onsite repair. Diverse cell types (macrophages, leukocytes, mast cells) contribute to the

associated phases of proliferation, migration, matrix synthesis and contraction, coupled with growth factors and matrix signals at the site of the wound. Understanding signal control and cellular activity at the site could help explain the process of adult skin repair beyond mere patching up and more as regeneration, to assess biomechanics and implement strategies for accelerated wound repair in regenerative medicine.

Bioengineers, materials scientists and life scientists who study the intersection of materials and medicine have developed autografts, allografts and xenografts for partial and full wound healing. Limitations of these procedures can delay the healing of large areas of skin defects and is a significant clinical problem in healthcare, due to the potential risk of antigenicity and disease transmission. Tissue engineering strategies for skin regeneration is a practical approach involving the use of bioactive biomaterials for assisted angiogenesis and faster revascularization.
In a recent study, Sorin Marza and co-workers at the interdisciplinary research institutes and faculties of physics, bio-nano-sciences, pharmacy and medicine, developed bioactive glass-gold nanoparticles (BG-AuNPs) to promote the growth of granulation tissue and induce wound healing. In the study, the scientists investigated the impact of BG-AuNP composites as a topical ointment for 14 days on skin wound healing using an experimental rat model. Marza et al. developed a sol-gel of BGs and BG-AuNP composites mixed with Vaseline at concentrations of 6,12 and 18 weight percent (wt%) to understand the repair response of the skin. The scientists observed granulomatous reactions during the process of healing in the wounds treated with the BG-Vaseline ointment. The results are now published in *Biomedical Materials*, IOP Publishing.

Angiogenesis, or the formation of new blood vessels from existing vessels is an important process during skin regeneration. Bioactive glass is responsible for local cellular responses due to in vivo degradation, stimulating the release of growth factors such as VEGF (vascular endothelial growth factor) and bFGF (basic fibroblast growth factor) to cause an angiogenic effect. A variety of studies on tissue engineering have demonstrated the benefits of bioactive glass in wound healing, based on results in animal models in vivo. In its principle of action, scientists have reported that bioactive glass stimulated the process by controlling the inflammation response to enhance the paracrine effect between macrophages and repairing cells.

Gold nanoparticles (AuNPs) are similarly becoming important in medicine due to their chemical and physical properties of biocompatibility, surface modification, stability and optical properties. Despite their challenging early translation in tissue engineering approaches, a low concentration of AuNPs can stimulate cell proliferation during wound repair. Preceding studies by the same research team showed that bioactive glass with AuNPs could stimulate the proliferation of human keratinocyte cells (HaCaT), which constitute 95 percent to 97 percent of the epidermis on the skin surface. In the present study, Marza et al. investigated the potential of dermal tissue regeneration in vivo. By day 14, they observed that both BG and BG-AuNP-Vaseline ointments could stimulate complete skin regeneration in experimental rat models, substantiated with gold standard histopathological analyses.

Marza et al. freshly prepared spherical AuNPs ranging from sizes of 15 nm to 30 nm, confirmed using transmission electron microscope (TEM) micrographs to embed within the glass matrix. Using X-ray powder diffraction (XRD) patterns of the glass samples, the scientists investigated the amorphous structures to identify the crystallization centers and the gold signature. The

characterization studies for the composite samples also included Fourier transform infrared spectroscopy (FTIR), which provided spectra typical for a silicate network. To develop the glass composition ointment, the scientists dispersed the powder composite materials in Vaseline. They then used dynamic light scattering (DLS) to measure particle size distributions and corroborate the difference in sizes between the BG-Vaseline and BG-AuNP-Vaseline sample structures.

After extensive materials characterization, the scientists conducted biofunctionalization studies in vitro with keratinocytes cell cultures to verify biocompatibility prior to conducting surgical procedures in a translational animal model. As before, Marza et al. investigated the proliferation of HaCaT cells on BG-AuNPs and obtained comparable results of good in vitro tolerance during keratinocytes proliferation on both materials (BG and BG-AuNPs). The outcomes substantiated the composites for use as ointments for in vivo investigations.

To assess the healing potential of BG and BG-AuNPs in the Vaseline ointments, Mayer et al. formed composites of 6, 12 and 18 weight percent concentration. For comparison, the scientists used Vaseline as a positive control. In the rat models, the scientists carefully created four skin excision wounds by successfully replicating a previously published small-animal surgery protocol. They used a specific method on each rat when applying the ointment; (1) the upper left excision was kept as the control without ointment, (2) on the left lower excision, the scientists applied the BG-Vaseline ointment, (3) on the upper right excision, they applied Vaseline alone and (4) on the lower right excision, they applied the BG-AuNP-Vaseline ointment.

The scientists used 30 rats in the study with 10 rats assigned to separate groups (6% BG-Vaseline and BG-AuNPs-Vaseline ointment; 12% BG/BG-AuNPs-Vaseline; 18% BG/BG-AuNPs-Vaseline). The working protocol was the same for each group. After ointment application, the scientists added sterile bandages to the wound sites on rats to prevent wound infection postoperatively and administered Tramadol subcutaneously as an analgesic. By day 13, the wounds were closed in all animals. After 14 days, they humanely euthanized the animals and conducted histological examinations to reveal mild inflammatory reactions and wound healing responses in the respective animal groups. In all groups, vascular proliferation was mild to moderate.

Mayer et al. specifically observed largely complete healing with intact epidermis, dermis and skin appendages in the 18 percent BG-AuNPs-Vaseline group. They also observed a lack of vascular proliferation for this group, which they attributed to advanced healing and late vascular remodeling. In this way, Mayer et al. extensively characterized and established bioactive glass-gold nanoparticle based Vaseline ointments as promising materials for wound healing. The research team will conduct further studies to optimize the wound healing ointment for investigations in bench to bedside translation. [32]

Platinum nanoparticles for selective treatment of liver cancer cells

Researchers at ETH Zurich recently demonstrated that platinum nanoparticles can be used to kill liver cancer cells with greater selectivity than existing cancer drugs.

In recent years, the number of targeted cancer drugs has continued to rise. However, conventional chemotherapeutic agents still play an important role in cancer treatment. These include platinum-based cytotoxic agents that attack and kill cancer cells. But these agents also damage healthy

tissue and cause severe side effects. Researchers at ETH Zurich have now identified an approach that allows for a more selective cancer treatment with drugs of this kind.

Platinum can be cytotoxic when oxidised to platinum(II) and occurs in this form in conventional platinum-based chemotherapeutics. Non-oxidised platinum(0), however, is far less toxic to cells. Based on this knowledge, a team led by Helma Wennemers, Professor at the Laboratory of Organic Chemistry, and Michal Shoshan, a postdoc in her group, looked for a way to introduce platinum(0) into the target cells, and only then for it to be oxidised to platinum(II). To this end, they used non-oxidised platinum nanoparticles, which first had to be stabilized with a peptide. They screened a library containing thousands of peptides to identify a peptide suitable for producing platinum nanoparticles (2.5 nanometres in diameter) that are stable for years.

Oxidised inside the cell

Tests with cancer cell cultures revealed that the platinum(0) nanoparticles penetrate into cells. Once inside the specific environment of liver cancer cells, they become oxidised, triggering the cytotoxic effect of platinum(II).

Studies with ten different types of human cells also showed that the toxicity of the peptide-coated nanoparticles was highly selective to liver cancer cells. They have the same toxic effect as Sorafenib, the most common drug used to treat primary liver tumours today. However, the nanoparticles are more selective than Sorafenib and significantly more so than the well-known chemotherapeutic Cisplatin. It is therefore conceivable that the nanoparticles will have fewer side effects than conventional medication.

Joining forces with ETH Professor Detlef Günther and his research group, Wennemers and her team were able to determine the platinum content inside the cells and their nuclei using special mass spectrometry. They concluded that the platinum content in the nuclei of liver cancer cells was significantly higher than, for instance, in colorectal cancer cells. The authors believe that the platinum(II) ions – produced by oxidation of the platinum nanoparticles in the liver cancer cells – enter the nucleus, and there release their toxicity.

"We are still a very long and uncertain way away from a new drug, but the research introduced a new approach to improve the selectivity of drugs for certain types of cancer – by using a selective activation process specific to a given cell type," Wennemers says. Future research will expand the chemical properties of the nanoparticles to allow for greater control over their biological effects. [31]

Proton therapy on an upward trajectory

While proton therapy is becoming a standard treatment option in radiation oncology – there are currently 92 operational proton facilities worldwide and a further 45 under construction – many challenges remain in terms of the fundamental physics, radiobiology and clinical use of protons for the treatment of cancer. Those challenges, and plenty more besides were front-and-centre at the UK's Fifth Annual Proton Therapy Physics Workshop held early in February at the National Physical Laboratory (NPL) in Teddington.

The timing of this year's event was apposite. In 2018, the UK's National Health Service (NHS) opened its first high-energy proton therapy centre at The Christie Hospital in Manchester, with a second facility at University College London Hospital (UCLH)scheduled to come online for patient treatment in 2020. Proton Partners International, a private health provider, is also rolling out a network of four proton-therapy facilities across the UK, with the first of its Rutherford Cancer Centres now treating patients in south Wales.

That upsurge in UK activity – spanning construction, commissioning and clinical go-live of new proton facilities – is being supported by the Proton Physics Research and Implementation Group (PPRIG), a consortium of "interested organizations" that includes NPL, The Christie, Clatterbridge Cancer Centre, University Hospitals Birmingham, UCL and UCLH.

"PPRIG was set up by NPL in 2012 to progress UK deployment of high-energy proton therapy," explained Russell Thomas, senior research and clinical scientist at NPL and chair of PPRIG. "We aim to help coordinate research activities, encourage multicentre collaboration and minimize duplication of effort. Our annual proton-therapy physics workshop is a logical extension of PPRIG's remit, bringing the UK proton-physics community together with leading researchers from overseas."

It's good to talk: delegates at the annual conference on proton therapy (Courtesy: NPL)

Another objective of PPRIG is to promote the work of early-career researchers, helping them to build networks, collaborate on specific research problems, and support their grant applications. “The workshop fosters open, robust, but always good-humoured debate around the hot topics in proton therapy,” Thomas added.

Ana Lourenço, a postdoctoral research scientist at UCL and NPL, agrees that the PPRIG meeting provides a welcoming platform for younger scientists. “The PPRIG workshop was a great opportunity for early-career scientists to present their work and have feedback from world-leading medical physicists and clinical scientists,” she said. “The reduced registration fee for students allowed many to participate, with plenty of time in the programme dedicated to more open, informal discussion to facilitate the interaction between students and senior researchers.”

Standardize and verify

Given NPL’s role as the UK’s national measurement institute, much of the discussion at last week’s meeting eddied around issues of dosimetry and quality assurance (QA). In other words, how to maximize clinical outcomes by ensuring that patients receive standardized and rigorously audited proton therapy – irrespective of where they’re being treated.

With those outcomes in mind, Thomas reported on NPL’s work to develop a code of practice for proton-beam dosimetry in collaboration with the UK Institute of Physics and Engineering in Medicine (IPEM). Underpinning that code is absolute dosimetry for calibration of the proton beam, something that NPL is striving to improve through the development of a primary standard for protons based on a portable graphite calorimeter, in which the temperature rise due to a typical patient dose is measured to quantify the amount of “dose” deposited.

Previously, the only option for proton-beam reference dosimetry was a ^{60}Co-based calibration, which has an uncertainty in terms of reference dosimetry that’s often quoted at 4.6% – but which anecdotally may be somewhat higher. With the increase in patient numbers for proton therapy, it is desirable to bring this uncertainty down to a similar level achieved with the reference dosimetry of conventional photon radiotherapy, which would be closer to 2%.

Thomas says that the NPL calorimeter has been transported to proton-therapy centres in Liverpool (Clatterbridge), Manchester (The Christie), Newport (Rutherford Cancer Centre), Sicily, Prague and Japan, where it has been operated successfully in clinical settings.

“We need to improve the uncertainty of the dose delivered to patients to ensure the best possible consistency across the patient population and to fully understand and interpret the patient outcomes,” he explained. “By bringing the uncertainty on reference dosimetry down to a similar level as that currently achievable in conventional photon radiotherapy, the primary standard will aid in the comparison of the results from high-quality, multicentre clinical trials featuring different treatment techniques.”

Stuart Green, director of medical physics at University Hospital Birmingham, told *Physics World* that the new IPEM code of practice for proton dosimetry relies heavily on calorimetry developments at NPL over the past 15 years. He says the new code will be ready for publication later this year and hopes that UK centres will transfer to the new approach soon after.

“What’s more,” Green added, “the NHS has a significant opportunity with the opening of the two new proton-therapy centres [at Christie and UCLH] to initiate definitive clinical trials. I am sure the rest of the world will watch with interest to see how well these trials are rolled out.”

Other speakers developed the QA theme in terms of reference and in-clinic proton dosimetry. NPL’s Lourenço, for example, reported findings from a team of UK and Danish scientists who compared the response of user ionization chambers at three clinical facilities against NPL reference ionization chambers.

Their study, which involved a low-energy passively scattered proton beam and two high-energy pencil-beam-scanning proton beams, showed “good agreement between the results acquired by NPL and the proton facilities”. Lourenço added that “reference dosimetry audits such as this are important to improve accuracy in radiotherapy treatments, both within and between treatment facilities, and to establish consistent standards that underpin the development of clinical trials.”

In the same session, Antonio Carlino of the MedAustron Ion Therapy Center, Austria, detailed a new approach for end-to-end auditing of the treatment workflow based on customized anthropomorphic phantoms featuring different types of detector. During the dosimetry audit, which was carried out at HollandPTC in Delft, the phantoms followed the patient pathway to simulate the entire clinical procedure, mimicking the human body as closely as possible in terms of material properties and movement. Carlino told delegates that human-mimicking phantoms deployed in end-to-end audits of this type “may serve as dosimetric credentialing for clinical trials in the future”.

Image and adapt

Standardization and QA notwithstanding, there was plenty of focus on new concepts and emerging technologies for the proton-therapy clinic, with imaging at the point of treatment delivery and online adaptive proton therapy very much to the fore.

“It is one thing to deliver the sophisticated treatment dose volumes that proton therapy is capable of, but it is another to be confident that the dose is being delivered to the right place,” explained Thomas. “During a course of treatment lasting up to six weeks, with daily fractions, the anatomy of a patient may change dramatically as a result of weight loss and/or tumour shrinkage. Imaging can ensure the dose is still being delivered correctly, while informing dynamic refinement of the treatment plan over the course of the treatment.”

Central to the success of adaptive proton therapy is a technique called deformable image registration (DIR), the use of powerful image-processing tools that maximize spatial correspondence between multiple sets of images (e.g. CT scans) collected over an extended treatment timeframe, and even across multiple imaging modalities.

> Many developments will take place in the next few years, enabling dose rates to increase and treatment times to reduce
>
> Tony Lomax, Paul Scherrer Institute

However, according to Jamie McClelland from UCL’s Centre for Medical Image Computing, a number of open questions remain around online deployment of DIR in the proton-

therapy workflow: “What exactly do we want DIR to do? How do we know it’s doing it correctly? And how do the errors and uncertainties in DIR impact clinical applications?”

More broadly, what of the longer-term development roadmap for proton therapy? Harald Paganetti, director of physics research at Massachusetts General Hospital (MGH) and professor of radiation oncology at Harvard Medical School in the US, reckons proton therapy is currently at what he calls the “Adaptive 1.0” stage, with CT scans performed daily but treatment plans revised and adapted offline.

MGH’s evolution to “Adaptive 2.0” will see that adaptation taking place online in the proton treatment workflow. Key enablers of the MGH approach include cone-beam CT-based imaging and online measurement of the prompt-gamma emissions from delivery of a “partial dose” to the centre of the target (enabling an initial assessment of range accuracy). This is then followed by a rapid adaptation before the remainder of the dose is delivered for a given fraction.

For protons, it seems, the future is bright, with no shortage of opportunities for progress across core physics, emerging technologies and clinical applications. “Pencil-beam-scanning proton-beam therapy is still in its infancy,” noted Tony Lomax, chief medical physicist at the Paul Scherrer Institute in Villigen, Switzerland. “Many developments will take place in the next few years, [enabling] dose rates to increase and treatment times to reduce.” [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.

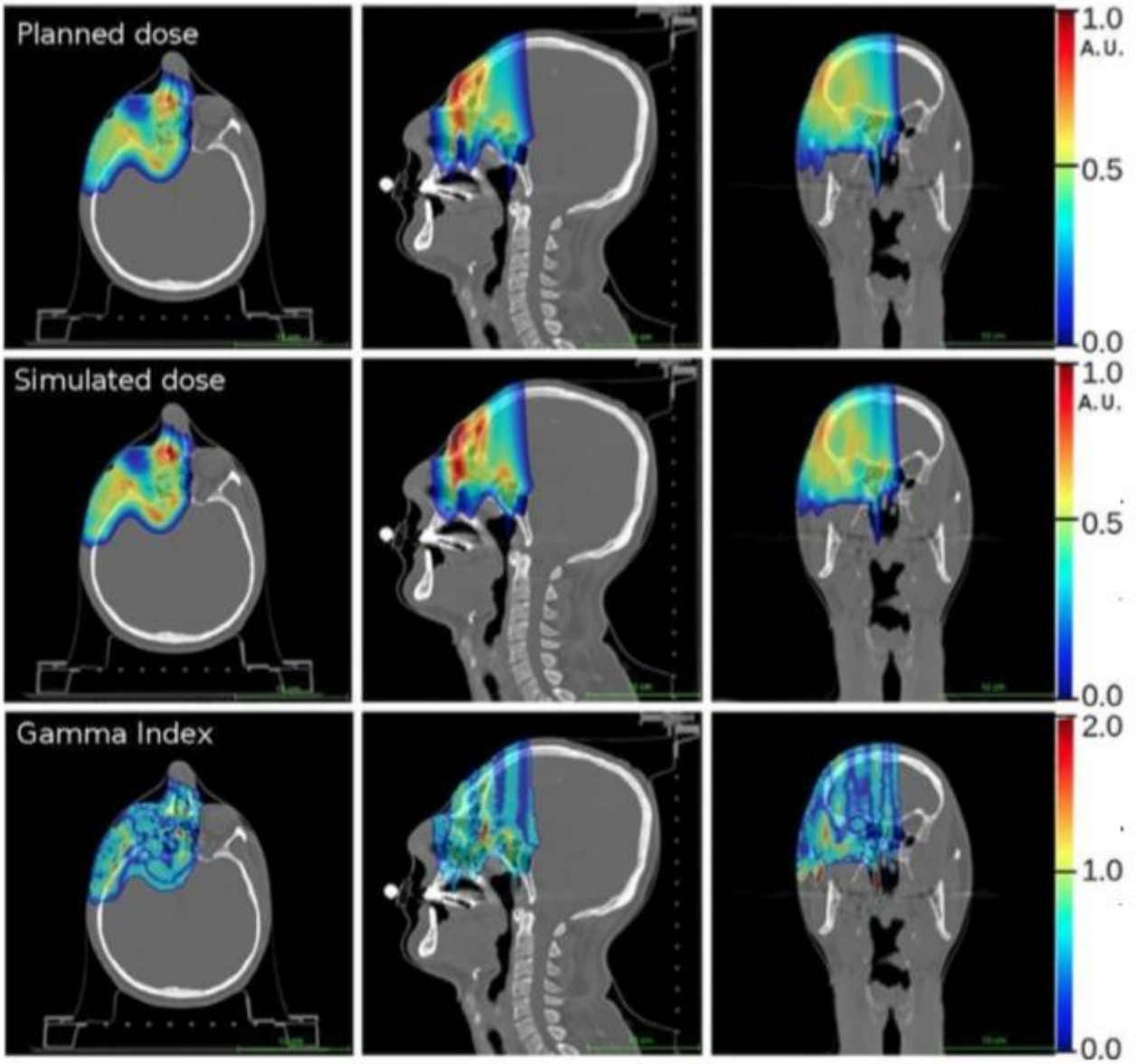
“An accurate Monte Carlo prediction combined with precision imaging would allow the physician to verify the accuracy of the treatment on a daily basis,” said joint first author Elisa Fiorina of the National Institute for Nuclear Physics (INFN) in Turin. In the longer term, the INSIDE technology could 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

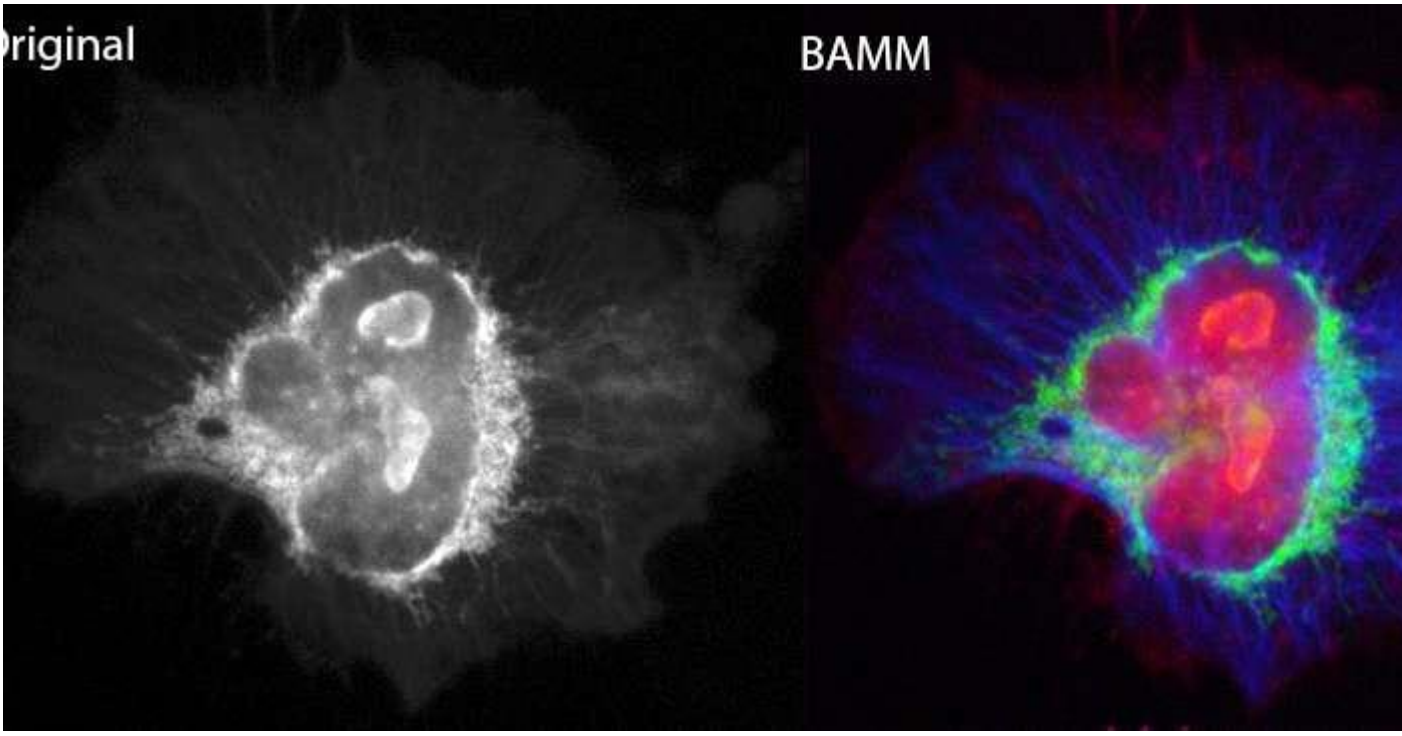
A novel technique developed by researchers at the ARC Centre of Excellence for Nanoscale BioPhotonics (CNBP) will help shine new light on biological questions by improving the quality and quantity of information that can be extracted in fluorescence microscopy.

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."



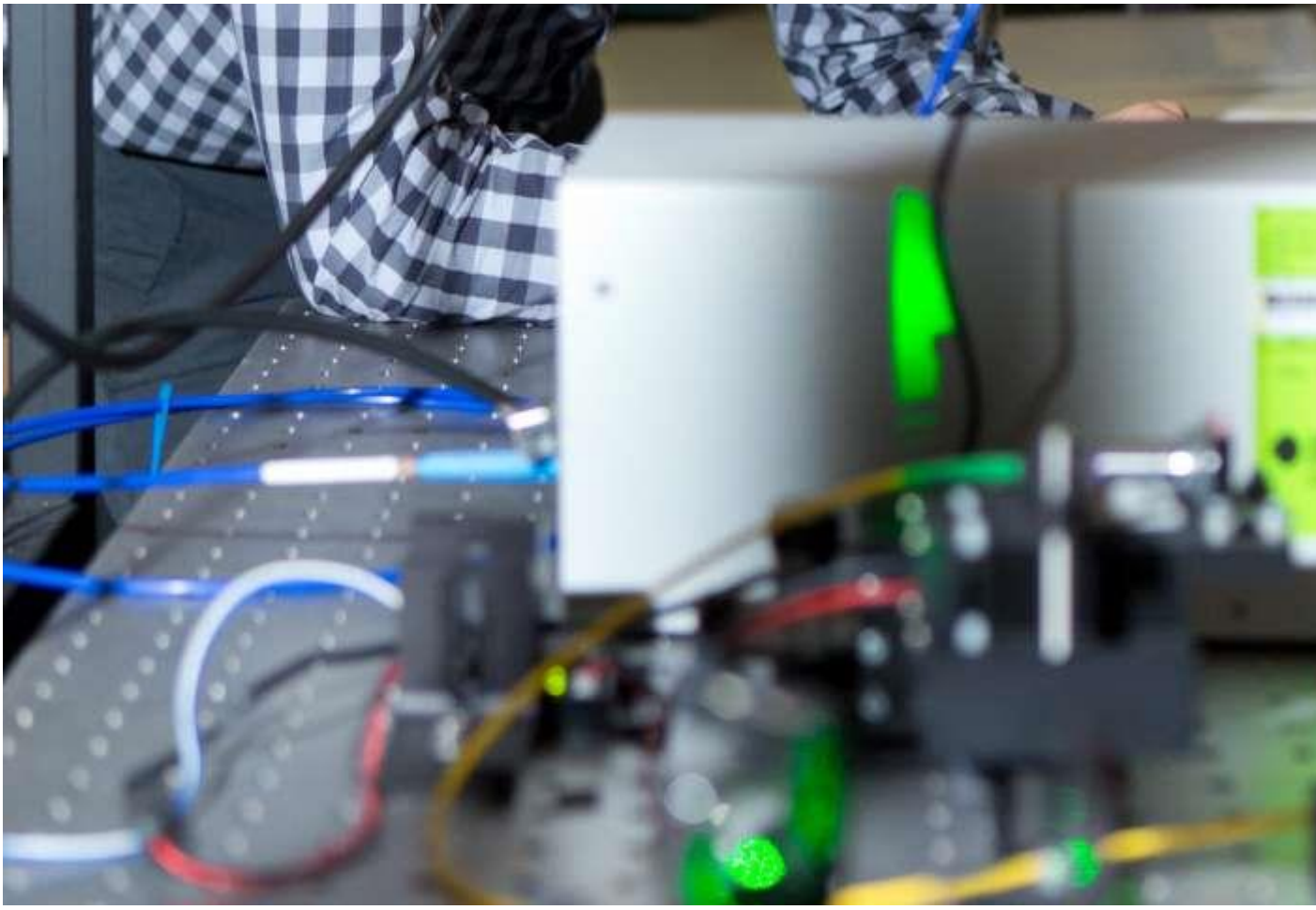
This figure shows the information-rich cellular images made possible by using the newly reported BAMM technique. The 'Original' image shows cells containing multiple fluorescent targets, all having similar colours. This results in a …more

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.

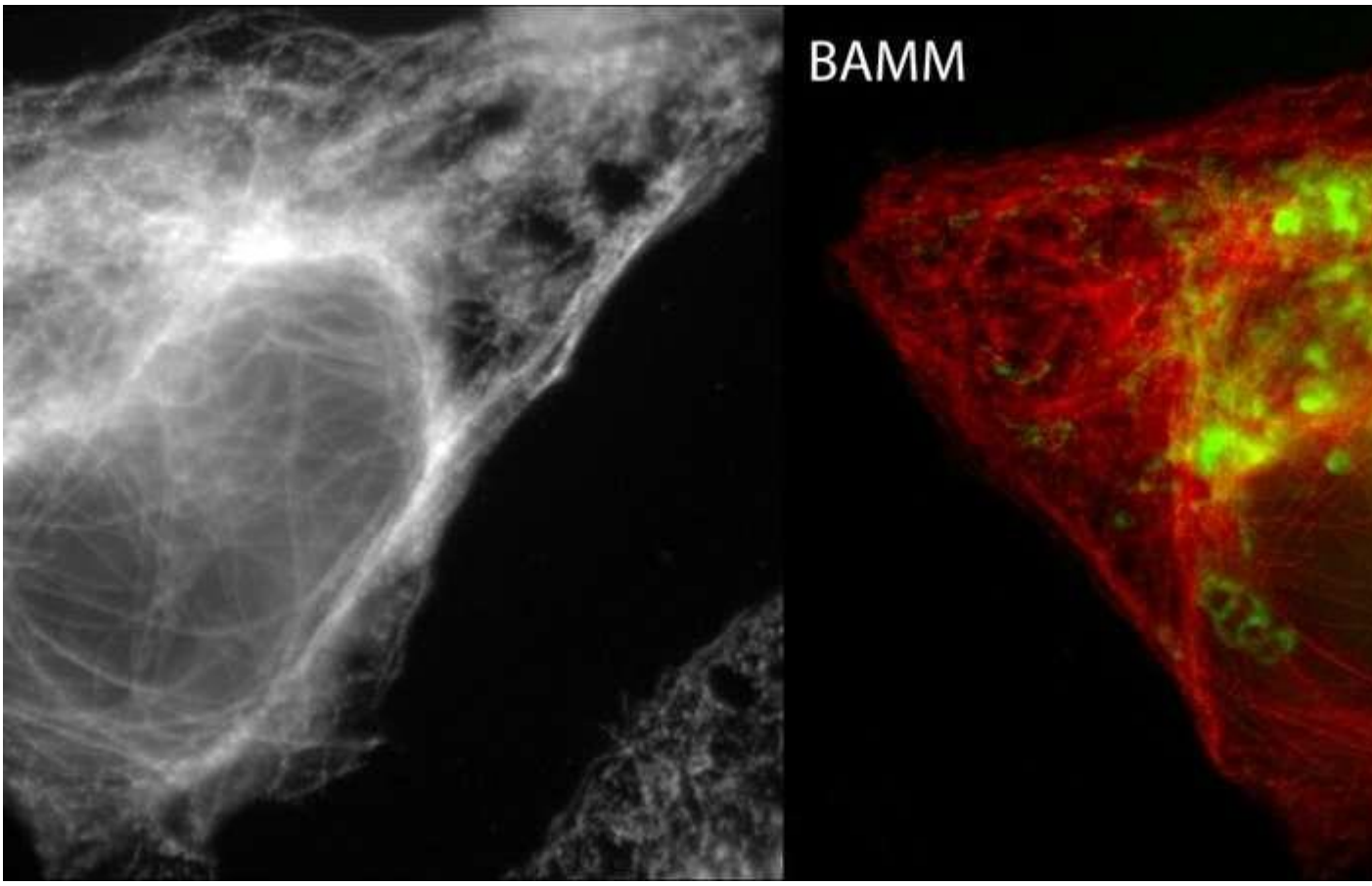
"Typically, most experiments are even less ambitious, incorporating only two or three targets. The heart of the problem is that only one property of the fluorophore – its colour – is being used for identification."

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 specialities 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 hardy 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*.

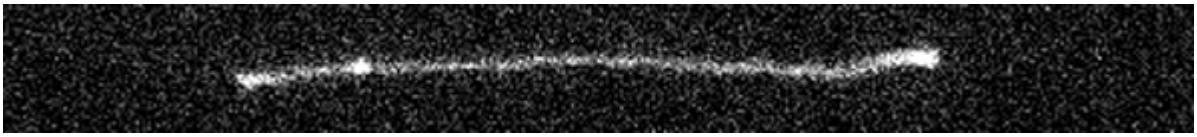
Knots in motion

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 Φ29. "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. Φ29 only needs four.

Composing DNA

Many years ago, researchers working at the Autonomous University of Madrid discovered the DNA replication mechanism of the Φ29 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 cellsfrom 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 lightharvesting 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 selfreproducing 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.

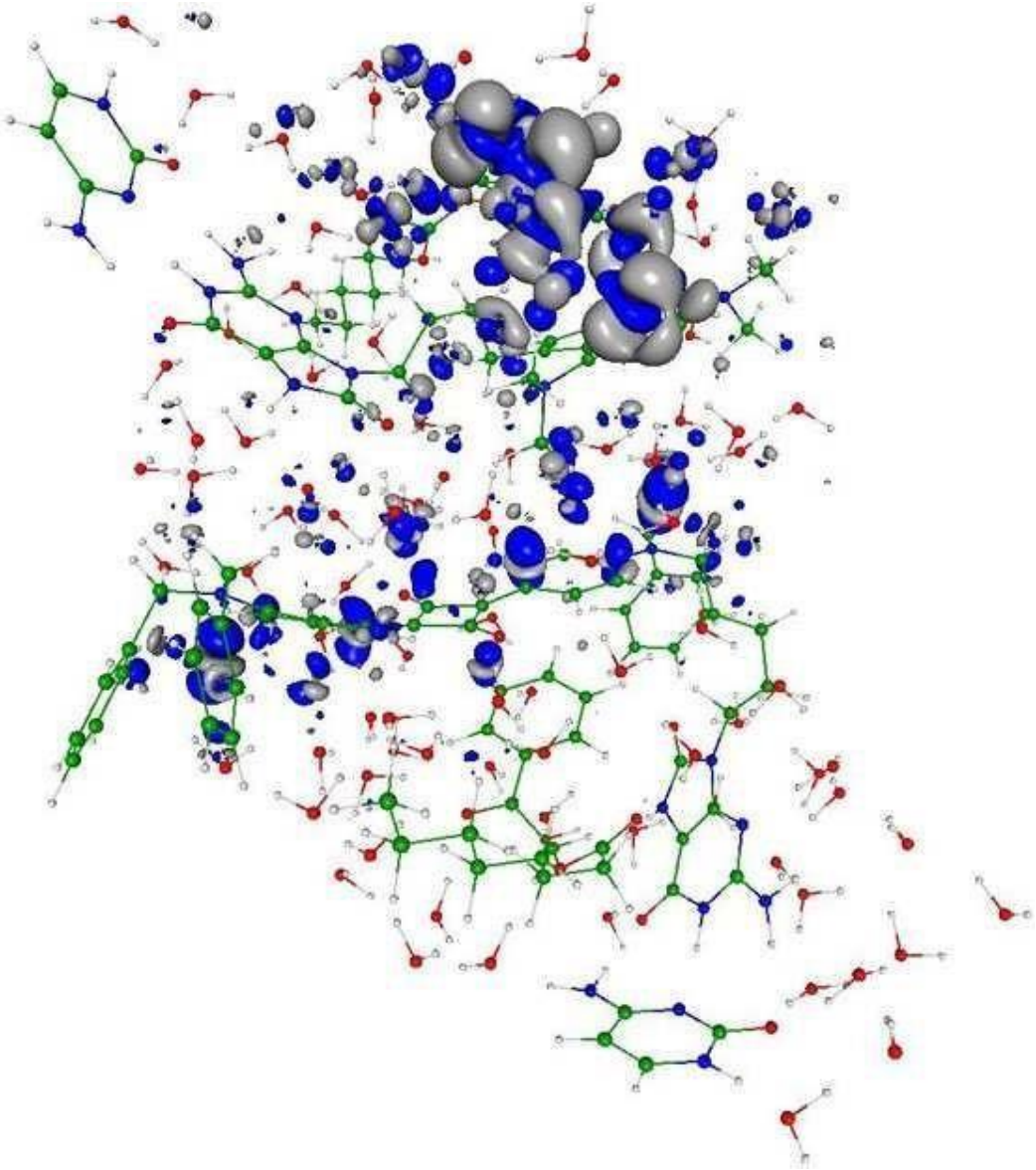
Our discovered phenomenon of the quantum entanglement in the prebiotic systems enhance the photosynthesis in the proposed systems because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states (Tamulis A, Grigalavicius M, Baltrusaitis 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 selfassembled 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 squarine molecule of the first protocell situated in the bottom of this bi cellular 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 squarine 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 electrodynamics 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 enfold 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 delta x position difference and with a delta p momentum difference such a way that they product is about the half Planck reduced constant. For the proton this delta x much less in the nucleon, than in the orbit of the electron in the atom, the delta p is much higher because of the greater proton mass.

This means that the electron and proton are not point like particles, but 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 delta x position with delta p impulse and creating a wave packet of the electron. The photon gives the electromagnetic particle of the mediating force of the electrons electromagnetic field with the same distribution of wavelengths.

Atomic model

The constantly accelerating electron in the Hydrogen atom is moving on the equipotential line of the proton and 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 1/2spin creator particle to make equal the spins of the weak interaction, for example neutron decay to 2 fermions, every particle is fermions with ½ 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 ½ 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 then 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_o inertial mass is the result of the spin, since this is the only accelerating motion of the electric charge. Since the accelerating motion has different frequency for the electron in the atom

and the proton, they masses are different, also as the wavelengths on both sides of the diffraction pattern, giving equal intensity of radiation.

Electron – Proton mass rate

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

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

Gravity from the point of view of quantum physics

The Gravitational force

The gravitational attractive force is basically a magnetic force.

The same electric charges can attract one another by the magnetic force if they are moving parallel in the same direction. Since the electrically neutral matter is composed of negative and positive charges they need 2 photons to mediate this attractive force, one per charges. The Bing 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 rate Mp=1840 Me. In order to move one of these diffraction maximum (electron or proton) we need to intervene into the diffraction pattern with a force appropriate to the intensity of this diffraction maximum, means its intensity or mass.

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

The gravitational force attracting the matter, causing concentration of the matter in a small space and leaving much space with low matter concentration: dark matter and energy.
There is an asymmetry between the mass of the electric charges, for example proton and electron, can understood by the asymmetrical Planck Distribution Law. This temperature dependent energy

distribution is asymmetric around the maximum intensity, where the annihilation of matter and antimatter is a high probability event. The asymmetric sides are creating different frequencies of electromagnetic radiations being in the same intensity level and compensating each other. One of these compensating ratios is the electron – proton mass ratio. The lower energy side has no compensating intensity level, it is the dark energy and the corresponding matter is the dark matter.

The Higgs boson

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

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

Higgs mechanism and Quantum Gravity

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

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

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

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

What is the Spin?

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

The Graviton

In physics, the graviton is a hypothetical elementary particle that mediates the force of gravitation in the framework of quantum field theory. If it exists, the graviton is expected to be massless (because the gravitational force appears to have unlimited range) and must be a spin-2 boson. The spin follows from the fact that the source of gravitation is the stress-energy tensor, a second-rank tensor (compared to electromagnetism's spin-1 photon, the source of which is the four-current, a first-rank tensor). Additionally, it can be shown that any massless spin-2 field would give rise to a force indistinguishable from gravitation, because a massless spin-2 field must couple to (interact with) the stress-energy tensor in the same way that the gravitational field does. This result suggests that, if a massless spin-2 particle is discovered, it must be the graviton, so that the only experimental verification needed for the graviton may simply be the discovery of a massless spin-2 particle. [3]

Conclusions

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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