GPS for Chromosomes

A research team from the University of Basel, in collaboration with scientists from Harvard University, has developed a method to trace the chromosomes in individual cells. [34]

A team of UNSW scientists at the School of Biotechnology and Biomolecular Sciences led by Professor Andrew Brown have shown how a key enzyme that contributes to cholesterol production can be regulated—and destroyed—using a particular molecule. [33]

Synthetic proteins have been created that move in response to their environment in predictable and tunable ways. [32]

Bioinspired materials mimic their natural counterparts for characteristic functionality in multidisciplinary applications forming a popular theme in biomaterials development. [31]

MIT engineers have designed tiny robots that can help drug-delivery nanoparticles push their way out of the bloodstream and into a tumor or another disease site. [30]

Researchers have shown that existing optical fibre technology could be used to produce microscopic 3-D images of tissue inside the body, paving the way towards 3-D optical biopsies. [29]

Researchers at MIT, working with surgeons and oncologists at Massachusetts General Hospital (MGH), have now developed a way to improve the accuracy of this surgery, called debulking. [28]

Scientists at the University of Bristol have invented a new technology that could lead to the development of a new generation of smart surgical glues and dressings for chronic wounds. [27]

Elaborate molecular networks inside living cells enable them to sense and process many signals from the environment to perform desired cellular functions. [26]

RNA sequencing is a technique used to analyze entire genomes by looking at the expression of their genes. [25]

Researchers from the University of Chicago have developed a high-throughput RNA sequencing strategy to study the activity of the gut microbiome. [24]

Today a large international consortium of researchers published a complex but important study looking at how DNA works in animals. [23]

Asymmetry plays a major role in biology at every scale: think of DNA spirals, the fact that the human heart is positioned on the left, our preference to use our left or right hand ... [22]

Scientists reveal how a 'molecular machine' in bacterial cells prevents fatal DNA twisting, which could be crucial in the development of new antibiotic treatments. [21]

In new research, Hao Yan of Arizona State University and his colleagues describe an innovative DNA HYPERLINK "https://phys.org/tags/walker/" walker, capable of rapidly traversing a prepared track. [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.

GPS for chromosomes: Reorganization of the genome during development

The spatial arrangement of genetic material within the cell nucleus plays an important role in the development of an organism. A research team from the University of Basel, in collaboration with scientists from Harvard University, has developed a method to trace the chromosomes in individual cells. Using this method, they have now been able to demonstrate that chromosomes reorganize during embryonic development. The study has recently been published in *Molecular Cell*.

Our body is made up of a wide variety of cells with the most diverse functions. Irrespective of being heart, liver or nerve cells, however, they all contain the same genetic information. The reason why cells develop differently is that only parts of their chromosomes are read. This results in some genes being active while others, in contrast, are silent.

For gene activation, both the way the genes are packaged as well as their spatial organization in the cell nucleus play a decisive role. Prof. Susan Mango's team at the Biozentrum of the University of Basel has now investigated this 3-D architecture more closely. Using a novel technique, they were able to trace individual chromosomes during embryonic development in nematodes and show that they rearrange themselves during the early phase.

Chromosome arrangement is not random

If stretched out, all the DNA molecules of a cell would reach about two meters in length. So the DNA must be densely packed to fit into a cell nucleus of only few micrometers in size. The DNA strands are very tightly coiled and twisted to form space-saving structures, called chromosomes. The packaging and the arrangement of the DNA of the chromosomes determines the activity of genes.

In their study, the researchers led by Prof. Susan Mango traced individual chromosomes and investigated their organization during early embryonic development. Embryonic cells of the nematode *C. elegans* served as a model. "Using a novel technique, we were able to follow the spatial rearrangement of chromosomes in single cells at the beginning of embryogenesis," says Mango. "The advantage of this method is that the cells and tissue remain completely intact."

Early chromosomes resemble a barbell

It is well know that chromosome regions with similar functional properties contact each other and interact. This means that chromosome domains segregated into two compartments, active and inactive. "During early embryogenesis, however, the chromosomes are organized differently," says Ahilya Sawh, first author of the study. "In the early embryo, they are organized into an unconventional barbell-like structure, with inactive compartments separated by a central active region." The researchers discovered that the nuclear lamina—a protein mesh lining the inner surface of the cell nucleus—is required to achieve this barbell arrangement. The lamina is attached to the inactive sections and stretches the chromosome.

Chromosomes reorganize during embryogenesis

"Only at a later stage of embryonic development, when the germ layers develop, we actually see the well-known segregation into an active and inactive region," explains Mango. "Using chromosome tracing, we were able to map the whole 3-D chromosome architecture and could show for the first time that chromosomes rearrange during early development, a maturation process that requires the nuclear lamina."

The reorganization of the chromosomes accompanies cell maturation and represents a milestone in the development of a complex organism. The correct chromosomal architecture is crucial to prevent developmental disorders. [34]

Scientists find 'molecular destruction code' for enzyme involved in cholesterol production

A team of UNSW scientists at the School of Biotechnology and Biomolecular Sciences led by Professor Andrew Brown have shown how a key enzyme that contributes to cholesterol production can be regulated—and destroyed—using a particular molecule.

The findings have implications for the development of cholesterol-lowering drugs: knowing how to regulate this enzyme—squalene monooxygenase—may offer a new way to control its abundance in a bid to lower cholesterol levels.

In the paper – published today in the *Journal of Biological Chemistry*—the scientists demonstrated how squalene monooxygenase, when linked to a particular molecule called ubiquitin, gets destroyed and inhibits the synthesis of cholesterol.

The scientists showed that squalene monooxygenase has a "destruction code" that acts to bind ubiquitin when unlocked, initiating its own destruction.

"Knowing the molecular mechanisms of how this enzyme—which plays a key role in cholesterol production—is regulated will allow us to understand how drugs can help maintain healthy levels of cholesterol in the cells of our body," says UNSW Ph.D. candidate Ngee Kiat (Jake) Chua, the paper's lead author.

For nearly twenty years, squalene monooxygenase has been proposed to be an enzyme in the pathway which should be investigated as another drug target to lower cholesterol.

More recently, squalene monooxygenase has also been linked to high cholesterol in human cancers, including liver, breast and prostate cancers.

Cholesterol is an essential component of the membranes that enclose all of our cells. Cholesterol is also the starting material for bile acids that allow us to digest fat as well as for steroid hormones like estrogen and testosterone. But high levels of cholesterol are still a major health concern, given their connection to heart disease.

"What a lot of people don't realise is that our body produces the bulk of cholesterol to meet our metabolic requirements—dietary cholesterol contributes a smaller proportion," Mr Chua says.

Squalene monooxygenase is depicted in blue (top and bottom). Under certain conditions, a helix in squalene monooxygenase (coiled structure, top right) is unravelled to reveal the destruction code (bottom blue squalene monooxygenase). The ubiquitin molecules are shown as purple spheres, linked to squalene monooxygenase in grey rods. Cholesterol is shown as ringed structures (yellow). Credit: University of New South Wales

The body produces cholesterol through a pipeline called the cholesterol synthesis pathway. That's the pipeline that statins—the most common cholesterol-lowering drugs – target. Statins limit cholesterol production by blocking one of the enzymes that is responsible for one early chemical reaction in this pathway.

"Statins are not without their shortcomings—or example, they have been linked to muscle pain in some people who take them and some patients experience statins intolerance.

"That's why researchers are investigating other enzymes in the pathway, with hopes of finding alternative druggable targets to help lower cholesterol.

"Enzymes are proteins that are made up of combinations of about 20 different building blocks called amino acids. In this paper, we reported that joining ubiquitin to a serine amino acid in squalene monooxygenase triggers its destruction. New knowledge of this initial chemical linkage raises new prospects to control cholesterol production. For instance, enhancing the formation of this chemical linkage speeds up the destruction of squalene monooxygenase," Mr Chua says.

The formation of the chemical linkage between ubiquitin and the serine amino acid on squalene monooxygenase is still not well-represented in the scientific literature

"Why biology has introduced such an unusual chemical modification is still not well-understood," Mr Chua says.

"In the entire cholesterol synthesis pathway, which has about 20 steps each carried out by separate enzymes, squalene monooxygenase is the first-known enzyme to possess this unusual chemical linkage with ubiquitin."

With the emergence of newer techniques in modulating enzymes, including gene-editing and chemical molecules to trigger enzyme destruction, researchers are trying new approaches, rather than conventional drugs that simply block enzyme activity.

"While our study has identified the molecular destruction code, future research should focus on identifying ways to unlock it for initiating the destruction of squalene monooxygenase as a strategy to lower cholesterol levels," Mr Chua says. [33]

Designing biological movement on the nanometer scale

Synthetic proteins have been created that move in response to their environment in predictable and tunable ways. These motile molecules were designed from scratch on computers, then produced inside living cells.

To function, natural proteins often shift their shapes in precise ways. For example, the blood protein hemoglobin must flex as it binds to and releases a molecule of oxygen. Achieving similar molecular movement by design, however, has been a long-standing challenge.

The May 17 issue of *Science* reports the successful design of molecules that change shape in response to pH changes. (pH is a chemical scale from basic to acidic.)

The Institute for Protein Design at the University of Washington School of Medicine led the multi-institutional research.

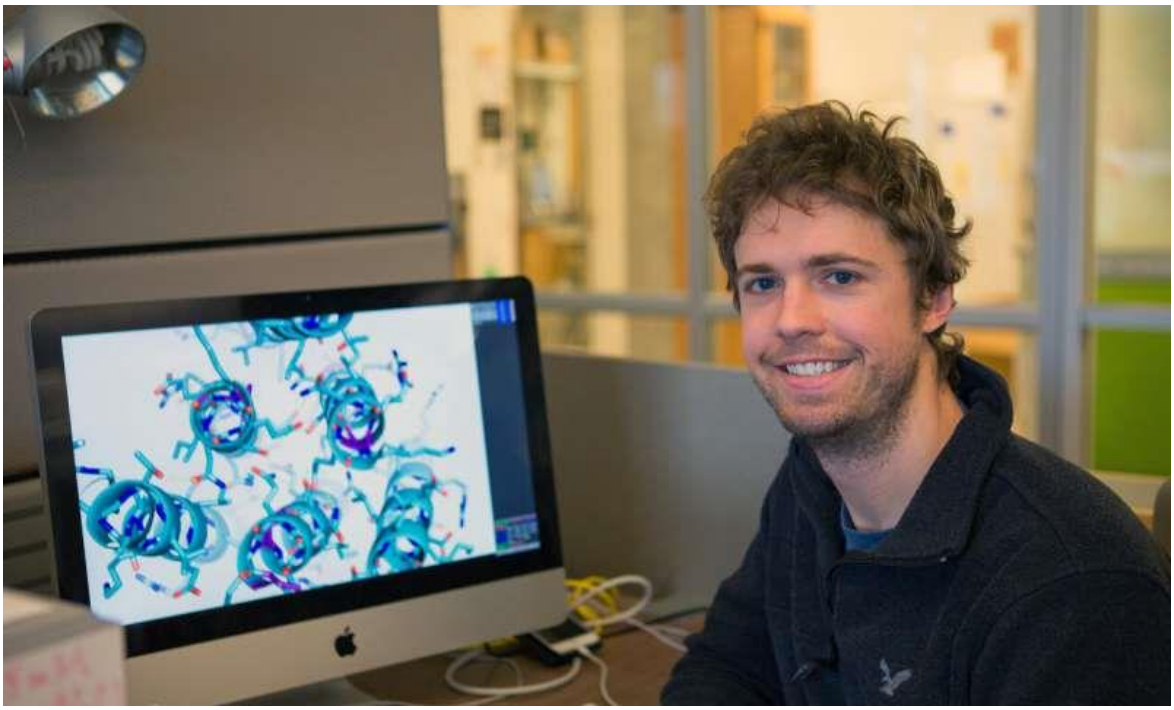
The researchers set out to create synthetic proteins that self-assemble into designed configurations at neutral pH and quickly disassemble in the presence of acid.

The results showed that these dynamic proteins move as intended and can use their pH-dependent movement to disrupt lipid membranes, including those on the endosome, an important compartment inside cells.

This membrane-disruptive ability could be useful in improving drug action. Bulky drug molecules delivered to cells often get lodged in endosomes. Stuck there, they can't carry out their intended therapeutic effect.

The acidity of endosomes differs from the rest of the cell. This pH difference acts as a signal that triggers the movement of the design molecules, thereby enabling them to disrupt the endosome membrane.

"The ability to design synthetic proteins that move in predictable ways is going to enable a new wave of molecular medicines," said senior author David Baker, professor of biochemistry at the UW School of Medicine and director of the Institute for Protein Design. "Because these molecules can permeabilize endosomes, they have great promise as new tools for drug delivery."



Scott Boyken, a recent posdoctoral fellow at the Institute for Protein Design at the University of Washington School of Medicine, designs new protein molecules with moving parts. Credit: Conrado Tapado/Institute for Protein Design

Scientists have long sought to engineer endosomal escape.

"Disrupting membranes can be toxic, so it's important that these proteins activate only under the right conditions and at the right time, once they're inside the endosome," said Scott Boyken, a recent postdoctoral fellow in the Baker lab and lead author on the recent project.

Boyken achieved molecular motion in his designer proteins by incorporating a chemical called histidine. In neutral (neither basic nor acidic) conditions, histidine carries no electric charge. In the presence of a small amount of acid, it picks up positive charge. This stops it from participating in certain chemical interactions. This chemical property of histidine allowed the team to create protein assemblies that fall apart in the presence of acid.

"Designing new proteins with moving parts has been a long-term goal of my postdoctoral work. Because we designed these proteins from scratch, we were able to control the exact number and location of the histidines," said Boyken. "This let us tune the proteins to fall apart at different levels of acidity."

Other scientists from the UW, The Ohio State University, Lawrence Berkeley National Laboratory, and Howard Hughes Medical Institute's Janelia Research Campus contributed to this research.

Those in Vicki Wysocki's Group at OSU used native mass spectrometry to determine the amount of acid needed to cause disassembly of the proteins. They confirmed the design hypothesis that having more histidines at interfaces between the proteins would cause the assemblies to collapse more suddenly.

Collaborators in the Kelly Lee lab at the UW School of Pharmacy showed that the designer proteins disrupt artificial membranes in a pH-dependent manner that mirrors the behavior of natural membrane fusion proteins.

Follow-up experiments conducted in Jennifer Lippincott-Schwartz's lab at HHMI's Janelia Research Campus showed that the proteins also disrupt endosomal membranes in mammalian cells.

Re-engineered viruses that can escape endosomes are the most commonly used drug delivery vehicles, but viruses have limitations and downsides. The researchers believe a drug delivery system made only of designer proteins could rival the efficiency of viral delivery without the inherent drawbacks. [32]

Stimulating the differentiation of bone precursors with organically modified hydroxyapatite (ormoHAP) nanospheres

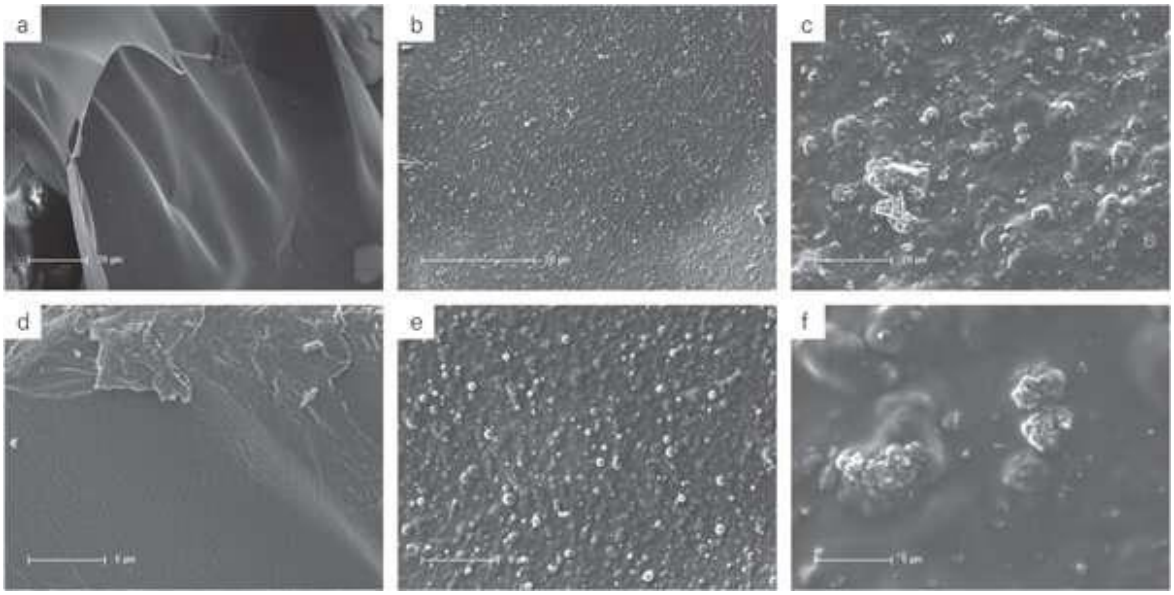
Bioinspired materials mimic their natural counterparts for characteristic functionality in multidisciplinary applications forming a popular theme in biomaterials development. In bone tissue engineering, for instance, researchers focus on the natural composite architecture of bone, organically designed from complex structures of mineralized collagen. The resulting bioengineered constructs include inorganic/organic composites based on native mammalian bone components such as carbonated apatite and collagen. However, microparticle incorporation to material constructs can cause complications during premature in vivo resorbability, due to their brittle nature.

In a recent study, now published in *Biomedical Materials, IOP Science*, Christiane Heinemann and co-workers at the Max Bergmann Center of Biomaterials and Institute of Materials Science in Germany, engineered isolated nanospheres using organically modified hydroxyapatite (ormoHAP) – to form a composite scaffold aligning with preceding work of the same research team. Heinemann et al. engineered the new biomaterial using an electric field-assisted ion double migration process and

embedded the nanospheres thus formed, in the foamed gelatin organic template, to form the composite scaffold.

The scientists tested the biodegradation rates of the biomaterials to show that they correlated with the degree of crosslinking (40%, 80%) conveyed during scaffold preparation and with the mineral content of the scaffolds (0%, 20%, 40%). They used a human cell co-culture model of osteoblasts and osteoclasts derived from bone marrow stromal cells and monocytes, to test the impact of ormoHAP-gelatin scaffolds on cell growth and differentiation for a period of 42 days.

The results confirmed that ormoHAP embedded in the gelatin matrix enhanced TRAP5b bioactivity (Tartrate-resistant acid phosphatase 5b); a group of enzymes synthesized in bone, followed by increased ALP activity (alkaline phosphatase, an osteoblast marker) and increased gene expression of BSPII (bone sialoprotein II – encoding a major structural protein of the bone matrix) in osteoblasts. The scientists proposed a sequence of cell cross-talk interactions, due to the presence and concentration of ormoHAP in the material, to explain the observed behavior in cell co-cultures in vitro.



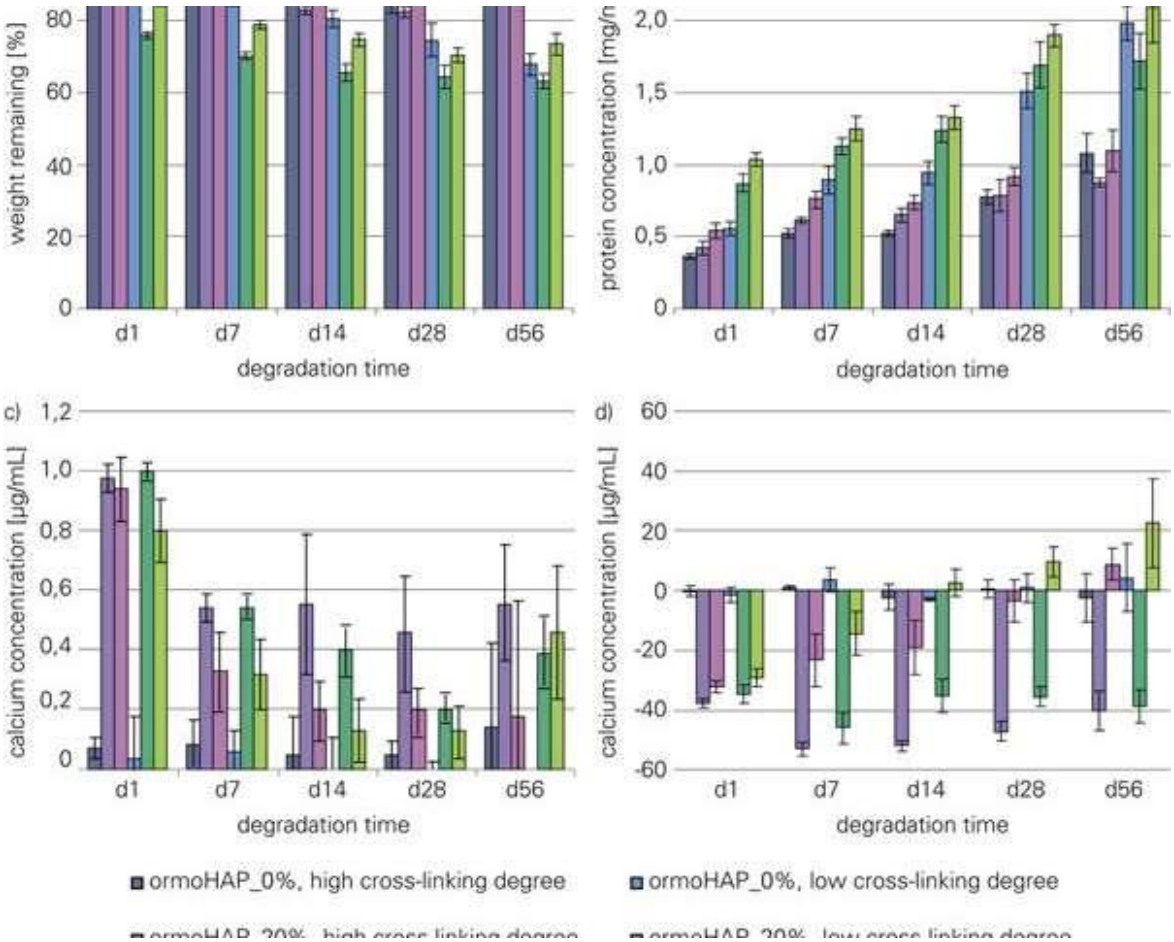
SEM images of foamed scaffolds without mineral (a), (d), with 20% ormoHAP (b), (e) or with 20% commercially available HAP (c), (f). Scale bars represent 20 µm (top column), and 5 µm (bottom column). Credit: Biomedical Materials, doi: 10.1088/1748-605X/ab0fad

The hydroxyapatite (HAP) nanocrystals self-assembled in the organic environment to form hollow spherical agglomerates in the experiments, which the scientists first characterized in depth due to their role in forming the bone substitute materials (BSM). Heinemann et al. chose gelatin as the underlying scaffold matrix material due to its compatibility with the electric field-assisted mineral formation process of nanospheres, while both constituents of the composite (HAP and gelatin)

showed cytocompatibility during cell-material interactions as shown in previous studies in vitro.

Gelatin is a well-suited constituent to form bioinspired materials for bone tissue engineerng, as it is a denaturation product of collagen, with abundant availability, processability, biodegradation and low antigenicity; suited to develop new biomaterials. Materials scientists previously developed similar constructs as gelatin/alginate, gelatin/chitosan, gelatin/βTCP or gelatin/HAP composite scaffolds, where mineralized composites facilitated cell proliferationcompared to monophasic substrates. In vitro experiments with co-cultures of diverse cell types are better suited to test biomaterials as they represent the natural conditions of intercellular interaction to simulate cell regeneration.

To more accurately replicate the conditions *in vivo*, Heinemann et al. previously conducted supplement-free co-cultures with osteoblasts and osteoclasts to test biomaterials during material-assisted bone regeneration. The work indicated the requirement of balanced crosstalk between bone-forming osteoblasts and bone-resorbing osteoclasts either via soluble factors or direct cell-cell contact, for efficient bone remodeling.

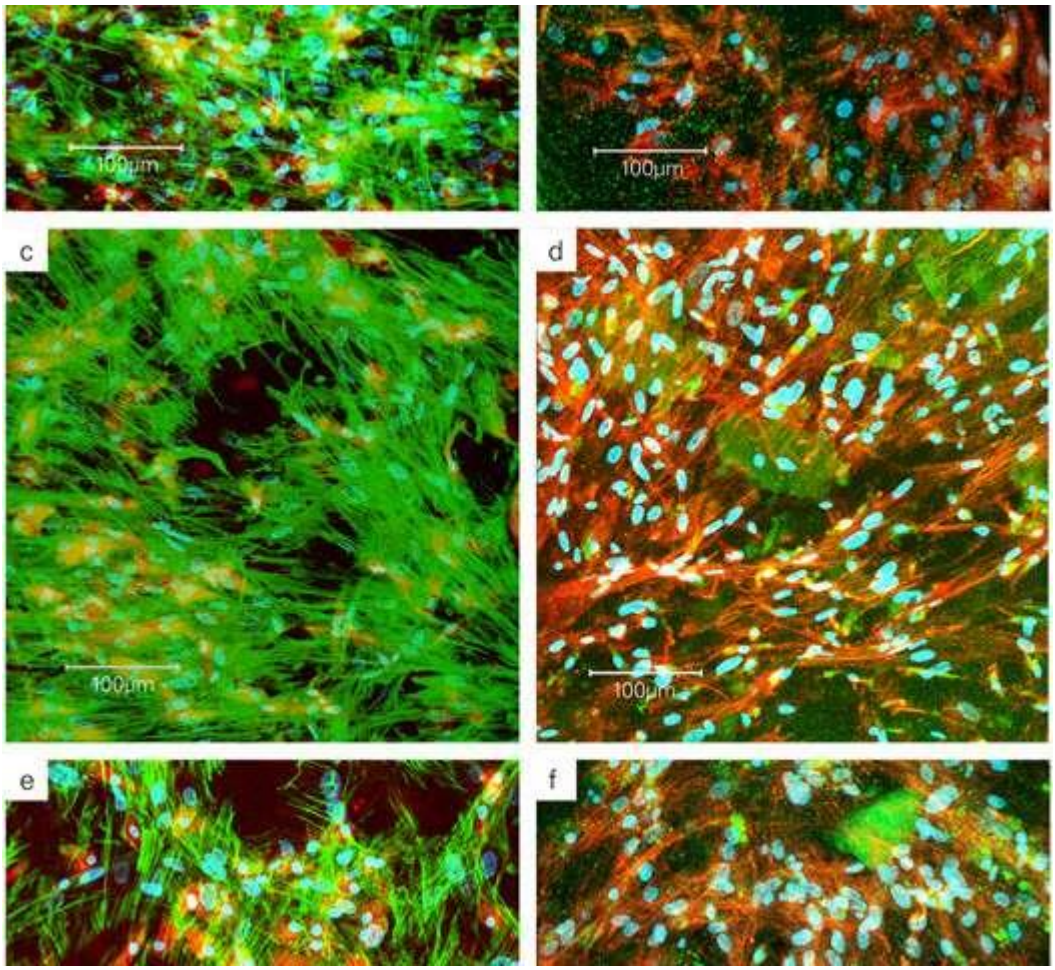


Degradation of gelatin scaffolds in PBS (a)–(c) and SBF (d) without, with 20% and with 40% ormoHAP

as well as high and low cross-linking degree. Mass loss (a) and release of protein (b) as well as calcium (c), (d) in the supernatant were determined. Credit: Biomedical Materials, doi: 10.1088/1748-605X/ab0fad

The scientists therefore unified the results of many previous studies in the present work, to determine the formation of bone-tissue like extracellular matrix deposits guided by the underlying biomaterial. Heinemann et al. co-cultured human bone marrow stromal cells(hBMSC) with human osteoblasts (hOB), and human monocytes (hMc) with human osteoclasts (hOC), without supplements on 3D composite (ormoHAP/Gelatin) scaffolds. They then conducted cell-material characterizations (tests) to investigate the influence of the organically modified HAP nanospheres (ormoHAP) on cell behavior and interactions in the lab.

The scientists first engineered a variety of composites with ormoHAP embedded in gelatin to create multiple scaffolds for cell culture experiments, followed by testing them with scanning electron microscopy (SEM) images to understand the micro-/nano- architecture of the new material. They observed distinct surface patterning on the gelatin matrix due to homogenous ormoHAP distribution. Heinemann et al. produced a variety of such stable scaffolds on chemically crosslinked gelatin organic templates and tested their degradation behavior using buffer (phosphate buffered saline, PBS) or simulated body fluid (SBF) media to closely mimic in vivo biological conditions in the lab.

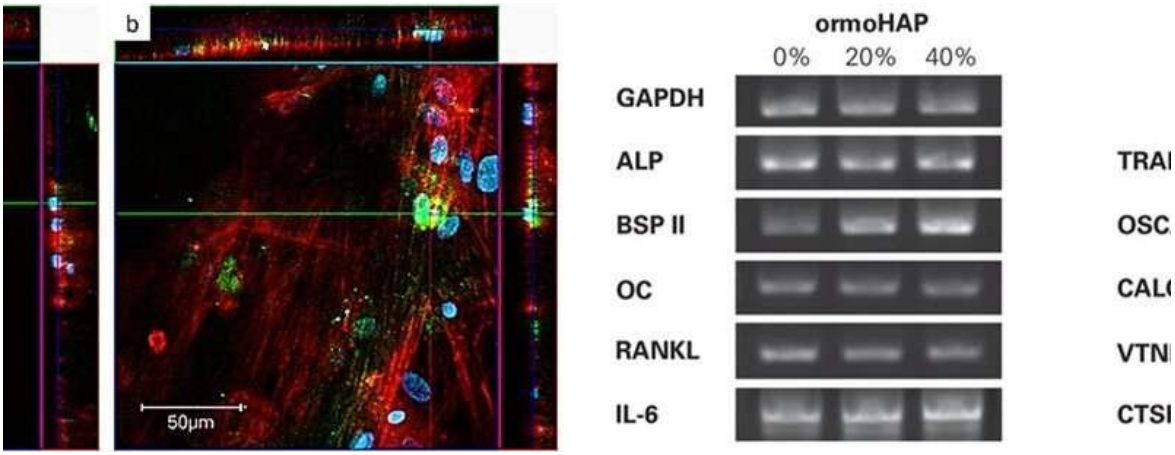


3D reconstructions from confocal laser scanning microscopy (cLSM) image stacks at day 28-42 of hOB/hOC co-cultivation on gelatin scaffolds without (a), (b), with 20% (c), (d) and with 40% ormoHAP (e), (f). In the left column, actin (green), cell nuclei (blue) and CD68 (red) are visible; in the right column, actin (red), cell nuclei (blue) and TRAP (green) are visible. Credit: Biomedical Materials, doi: 10.1088/1748-605X/ab0fad

The scientists determined the effects of the percentage of gelatin cross-linking and the concentration of ormoHAP on the bioactivity and degradation of the new material, with comparative studies. In degradation studies with SBF or PBS, scaffolds with a lower degree of cross-linking degraded much faster, than those with higher cross-linking. By day 56, the scientists observed higher levels of bioactivity on scaffolds with 20 percent ormoHAP; determined by quantifying the levels of surface bound calcium. Although a concentration of 40 percent ormoHAP showed promising results initially, the values of surface-bound calcium decreased with time.

During co-culture experiments Heinemann et al. therefore compared two different concentrations of ormoHAP (20 percent and 40 percent), alongside scaffolds made of pure gelatin alone. The scientists strategically conducted cell culture studies from day 14 to day 28 and up until day 42, then using DNA analysis they quantified the cell nuclei and calculated the rate of cell proliferation to assess the total number of cells on the material surfaces, with no significant difference observed between the surfaces.

They quantified ALP activity, to assess osteogenic differentiation in monoculture and co-culture, which decreased after 14 days as cell maturation increased. To investigate the differentiation of hMc to hOB in co-culture, the scientists quantified TRAP5b activity, which remarkably increased with increasing ormoHAP content in the scaffold composition for material-assisted cell growth. By day 42 however the rates of enzyme activity decreased due to the limited lifespan of osteoclast cells. Heinemann et al. next conducted confocal laser scanning microscopy (cLSM) imaging to investigate co-culture interactions on the scaffold.



LEFT: Ortho-representation of TRAP-positive monocyte-derived osteoclasts after d28-d42 of co-cultivation on gelatin scaffolds with 40% ormoHAP. The images show a single slice of the stack and cross-sections along the colored lines. The actin skeletons (red), the nuclei (blue) and TRAP (green) are visible. RIGHT: Gene expression of the osteoblast-related markers ALP, BSP II, OC, RANKL and IL-6 (left) and the osteoclast-related markers TRAP, OSCAR, CALCR, VTNR and CTSK (right), as well as the housekeeping gene GAPDH, after d42/d28 of co-cultivation of hBMSC/hOB and hMc/hOC on gelatin scaffolds without (0%) ormoHAP, with 20% and with 40% ormoHAP. Credit: Biomedical Materials, doi: 10.1088/1748-605X/ab0fad

They observed the cell co-cultures displaying green actin skeleton, blue cell nuclei using fluorescent makers and used a red cell surface antigen marker (CD68) to detect the monocytes (hMc). Using microscopic images, the scientists observed varying cell morphology from spindle-shape to spherical-shape, detailing how cells interacted with the underlying new material. They detected TRAP, as brightly stained spots of green, increasingly concentrated within cells as the ormoHAP levels on the material surface increased, to highlight the effect of material-assisted cell growth. Heinemann et al. finally conducted gene analysis to determine the upregulation of specific markers related to cell differentiation using quantitative real-time polymerase chain reaction (qRT-PCR).

Notably they investigated BSPII (bone matrix encoding protein), RANKL (receptor activator of NF-κB ligand) involved in bone modeling/remodeling and the osteoclast maker OSCAR(osteoclast associated Ig-like receptor) that resorb bone - essential for bone homeostasis. The results indicated the upregulation of BPSII and OSCAR, verifying material-assisted cell differentiation in the present work.

In this way, Heinemann et al. extensively characterized cell-material interactions to understand the new, bioinspired ormoHAP materials during biofunctionalization . They showed the influence of the new scaffold-geometry on bone forming and resorbing cells, and on inter-cellular interactions with each other, using the cell co-culture study. The results will allow the scientist to achieve optimized production conditions to further improve and develop materials constructs for bioinspired materials engineering. The increased concentration of ormoHAP in the scaffolds stimulated cellular cross-talk between osteoblasts and osteoclasts as evidenced with specific markers of gene upregulation, with promising implications for further investigations of the new materials in bone tissue engineering. [31]

Tiny robots powered by magnetic fields could help drug-delivery nanoparticles reach their targets

MIT engineers have designed tiny robots that can help drug-delivery nanoparticles push their way out of the bloodstream and into a tumor or another disease site. Like crafts in "Fantastic Voyage"—a 1960s science fiction film in which a submarine crew shrinks in size and roams a body to repair damaged cells—the robots swim through the bloodstream, creating a current that drags nanoparticles along with them.

The magnetic microrobots, inspired by bacterial propulsion, could help to overcome one of the biggest obstacles to delivering drugs with nanoparticles: getting the particles to exit blood vessels and accumulate in the right place.

"When you put nanomaterials in the bloodstream and target them to diseased tissue, the biggest barrier to that kind of payload getting into the tissue is the lining of the blood vessel," says Sangeeta Bhatia, the John and Dorothy Wilson Professor of Health Sciences and Technology and Electrical Engineering and Computer Science, a member of MIT's Koch Institute for Integrative Cancer Research and its Institute for Medical Engineering and Science, and the senior author of the study.

"Our idea was to see if you can use magnetism to create fluid forces that push nanoparticles into the tissue," adds Simone Schuerle, a former MIT postdoc and lead author of the paper, which appears in the April 26 issue of *Science Advances*.

In the same study, the researchers also showed that they could achieve a similar effect using swarms of living bacteria that are naturally magnetic. Each of these approaches could be suited for different types of drug delivery, the researchers say.

Magnetically controlled synthetic and living micropropellers stir up nanoparticles for enhanced drug transport. Credit: Schuerle et al., Sci. Adv. 2019;5: eaav4803

Tiny robots

Schuerle, who is now an assistant professor at the Swiss Federal Institute of Technology (ETH Zurich), first began working on tiny magnetic robots as a graduate student in Brad Nelson's Multiscale

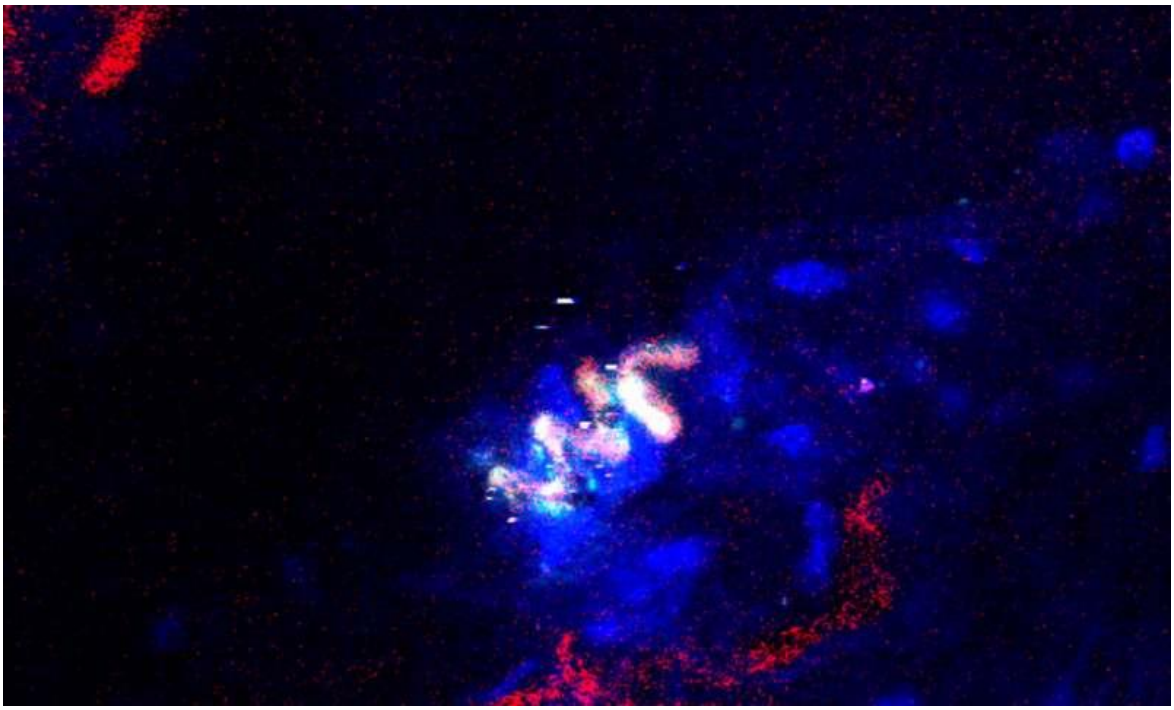
Robotics Lab at ETH Zurich. When she came to Bhatia's lab as a postdoc in 2014, she began investigating whether this kind of bot could help to make nanoparticle drug delivery more efficient.

In most cases, researchers target their nanoparticles to disease sites that are surrounded by "leaky" blood vessels, such as tumors. This makes it easier for the particles to get into the tissue, but the delivery process is still not as effective as it needs to be.

The MIT team decided to explore whether the forces generated by magnetic robots might offer a better way to push the particles out of the bloodstream and into the target site.

The robots that Schuerle used in this study are 35 hundredths of a millimeter long, similar in size to a single cell, and can be controlled by applying an external magnetic field. This bioinspired robot, which the researchers call an "artificial bacterial flagellum," consists of a tiny helix that resembles the flagella that many bacteria use to propel themselves. These robots are 3-D-printed with a high-resolution 3-D printer and then coated with nickel, which makes them magnetic.

To test a single robot's ability to control nearby nanoparticles, the researchers created a microfluidic system that mimics the blood vessels that surround tumors. The channel in their system, between 50 and 200 microns wide, is lined with a gel that has holes to simulate the broken blood vessels seen near tumors.



Detection of synthetic mirpropeller in tumor tissue via multi photon imaging and second harmoincs signals. Credit: Jeffrey Wyckoff

Using external magnets, the researchers applied magnetic fields to the robot, which makes the helix rotate and swim through the channel. Because fluid flows through the channel in the opposite direction, the robot remains stationary and creates a convection current, which pushes 200-

nanometer polystyrene particles into the model tissue. These particles penetrated twice as far into the tissue as nanoparticles delivered without the aid of the magnetic robot.

This type of system could potentially be incorporated into stents, which are stationary and would be easy to target with an externally applied magnetic field. Such an approach could be useful for delivering drugs to help reduce inflammation at the site of the stent, Bhatia says.

Bacterial swarms

The researchers also developed a variant of this approach that relies on swarms of naturally magnetotactic bacteria instead of microrobots. Bhatia has previously developed bacteria that can be used to deliver cancer-fighting drugs and to diagnose cancer, exploiting bacteria's natural tendency to accumulate at disease sites.

For this study, the researchers used a type of bacteria called Magnetospirillum magneticum, which naturally produces chains of iron oxide. These magnetic particles, known as magnetosomes, help bacteria orient themselves and find their preferred environments.

The researchers discovered that when they put these bacteria into the microfluidic system and applied rotating magnetic fields in certain orientations, the bacteria began to rotate in synchrony and move in the same direction, pulling along any nanoparticles that were nearby. In this case, the researchers found that nanoparticles were pushed into the model tissue three times faster than when the nanoparticles were delivered without any magnetic assistance.

This bacterial approach could be better suited for drug delivery in situations such as a tumor, where the swarm, controlled externally without the need for visual feedback, could generate fluidic forces in vessels throughout the tumor.

The particles that the researchers used in this study are big enough to carry large payloads, including the components required for the CRISPR genome-editing system, Bhatia says. She now plans to collaborate with Schuerle to further develop both of these magnetic approaches for testing in animal models. [30]

3-D optical biopsies within reach thanks to advance in light field technology

Researchers have shown that existing optical fibre technology could be used to produce microscopic 3-D images of tissue inside the body, paving the way towards 3-D optical biopsies.

Unlike normal biopsies where tissue is harvested and sent off to a lab for analysis, optical biopsies enable clinicians to examine living tissue within the body in real-time.

This minimally-invasive approach uses ultra-thin microendoscopes to peer inside the body for diagnosis or during surgery, but normally produces only two-dimensional images.

Research led by RMIT University in Melbourne, Australia, has now revealed the 3-D potential of the existing microendoscope technology.

Published in *Science Advances*, the development is a crucial first step towards 3-D optical biopsies, to improve diagnosis and precision surgery.

Lead author Dr. Antony Orth said the new technique uses a light field imaging approach to produce microscopic images in stereo vision, similar to the 3-D movies that you watch wearing 3-D glasses.

"Stereo vision is the natural format for human vision, where we look at an object from two different viewpoints and process these in our brains to perceive depth," said Orth, a Research Fellow in the RMIT node of the ARC Centre of Excellence for Nanoscale BioPhotonics (CNBP).

This study shows existing optical fibre technology could be used to produce microscopic 3D images of tissue inside the body, paving the way towards 3D optical biopsies. Credit: RMIT University

"We've shown it's possible to do something similar with the thousands of tiny optical fibres in a microendoscope.

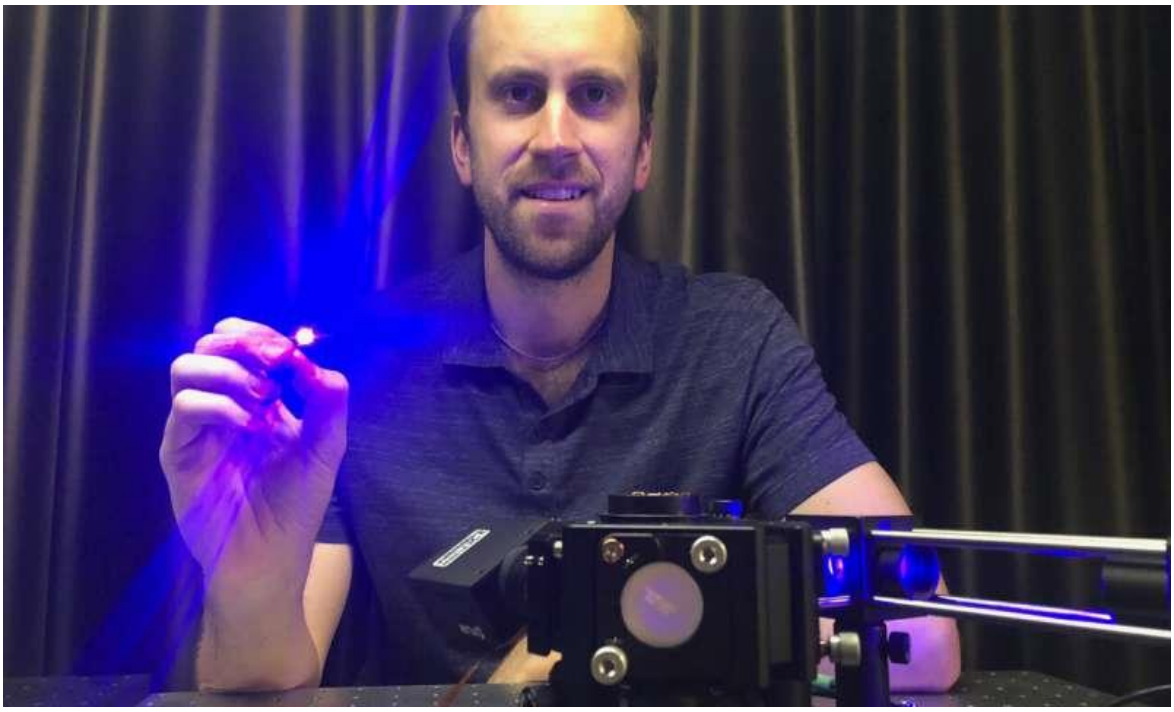
"It turns out these optical fibres naturally capture images from multiple perspectives, giving us depth perception at the microscale.

"Our approach can process all those microscopic images and combine the viewpoints to deliver a depth-rendered visualization of the tissue being examined—an image in three dimensions."

How it works

The research revealed that optical fibre bundles transmit 3-D information in the form of a light field.

The challenge for the researchers was then to harness the recorded information, unscramble it and produce an image that makes sense.



Dr. Antony Orth holding an ultra-thin microendoscope used in the study, which revealed the 3D imaging potential of the existing technology. Credit: RMIT University

Their new technique not only overcomes those challenges, it works even when the optical fibre bends and flexes—essential for clinical use in the human body.

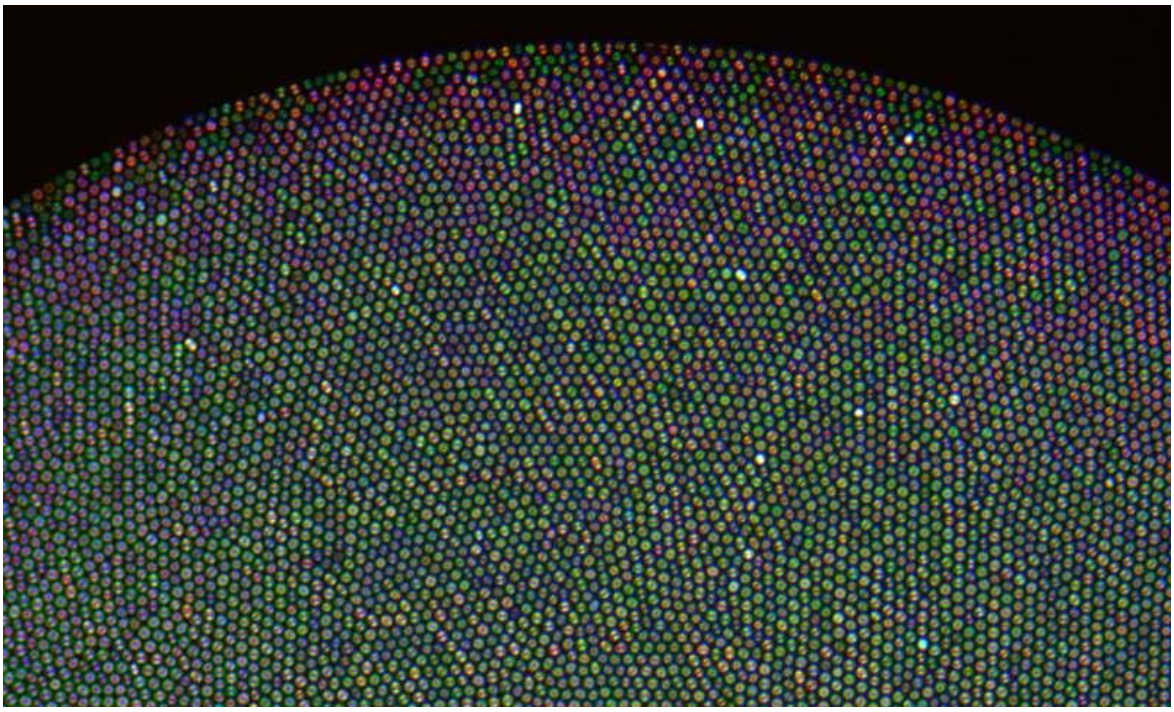
The approach draws on principles of light field imaging, where traditionally, multiple cameras look at the same scene from slightly different perspectives.

Light field imaging systems measure the angle of the rays hitting each camera, recording information about the angular distribution of light to create a "multi-viewpoint image".

But how do you record this angular information through an optical fibre?

"The key observation we made is that the angular distribution of light is subtly hidden in the details of how these optical fibre bundles transmit light," Orth said.

"The fibres essentially 'remember' how light was initially sent in—the pattern of light at the other side depends on the angle at which light entered the fibre."



Modal structure in optical fiber bundles captures light field information, enabling 3D visualization. Credit: Anthony Orth, RMIT University

With this in mind, RMIT researchers and colleagues developed a mathematical framework to relate the output patterns to the light ray angle.

"By measuring the angle of the rays coming into the system, we can figure out the 3-D structure of a microscopic fluorescent sample using just the information in a single image," Professor Brant Gibson, Chief Investigator and Deputy Director of the CNBP, said.

"So that optical fibre bundle acts like a miniaturised version of a light field camera.

"The exciting thing is that our approach is fully compatible with the optical fibre bundles that are already in clinical use, so it's possible that 3-D optical biopsies could be a reality sooner rather than later."

In addition to medical applications, the ultra-slim light field imaging device could potentially be used for in vivo 3-D fluorescence microscopy in biological research. [29]

Imaging system helps surgeons remove tiny ovarian tumors

Ovarian cancer is usually diagnosed only after it has reached an advanced stage, with many tumors spread throughout the abdomen. Most patients undergo surgery to remove as many of these tumors as possible, but because some are so small and widespread, it is difficult to eradicate all of them.

Researchers at MIT, working with surgeons and oncologists at Massachusetts General Hospital (MGH), have now developed a way to improve the accuracy of this surgery, called debulking. Using a novel fluorescence imaging system, they were able to find and remove tumors as small as 0.3 millimeters—smaller than a poppy seed—during surgery in mice. Mice that underwent this type of image-guided surgery survived 40 percent longer than those who had tumors removed without the guided system.

"What's nice about this system is that it allows for real-time information about the size, depth, and distribution of tumors," says Angela Belcher, the James Mason Crafts Professor of Biological Engineering and Materials Science at MIT, a member of the Koch Institute for Integrative Cancer Research, and the recently appointed head of MIT's Department of Biological Engineering.

The researchers are now seeking FDA approval for a phase 1 clinical trial to test the imaging system in human patients. In the future, they hope to adapt the system for monitoring patients at risk for tumor recurrence, and eventually for early diagnosis of ovarian cancer, which is easier to treat if it is caught earlier.

Belcher and Michael Birrer, formerly the director of medical gynecologic oncology at MGH and now the director of the O'Neal Comprehensive Cancer Center at the University of Alabama at Birmingham, are the senior authors of the study, published online in the journal *ACS Nano* this week.

Neelkanth Bardhan, a Mazumdar-Shaw International Oncology Fellow at the Koch Institute, and Lorenzo Ceppi, a researcher at MGH, are the lead authors of the paper. Other authors include MGH researcher YoungJeong Na, MIT Lincoln Laboratory technical staff members Andrew Siegel and Nandini Rajan, Robert Fruscio of the University of Milan-Bicocca, and Marcela del Carmen, a gynecologic oncologist at MGH and chief medical officer of the Massachusetts General Physicians Organization.

Glowing tumors

Because there is no good way to detect early-stage ovarian cancer, it is one of the most difficult types of cancer to treat. Of 250,000 new cases diagnosed each year worldwide, 75 percent are in an advanced stage. In the United States, the five-year combined survival rate for all stages of ovarian cancer is 47 percent, only a slight improvement from 38 percent three decades ago, despite the advent of chemotherapeutic drugs such as cisplatin, approved by the FDA in 1978 for ovarian cancer treatment. In contrast, the five-year combined survival rate for all stages of breast cancer has steadily improved, from around 75 percent in the 1970s to over 90 percent now.

"We desperately need better upfront therapies, including surgery, for these (ovarian cancer) patients," Birrer says.

Belcher and Birrer joined forces to work on this problem through the Bridge Project, a collaboration between the Koch Institute and Dana-Farber/Harvard Cancer Center. Belcher's lab has been developing a novel type of medical imaging based on light in the near-infrared (NIR) spectrum. In a paper published in March, she reported that this imaging system could achieve an unprecedented combination of resolution and penetration-depth in living tissue.

In the new study, Belcher, Birrer, and their colleagues worked with researchers at MIT Lincoln Laboratory to adapt NIR imaging to help surgeons locate tumors during ovarian cancer surgery, by

providing continuous, real-time imaging of the abdomen, with tumors highlighted by fluorescence. Previous analyses have shown that survival rates are strongly inversely correlated with the amount of residual tumor mass left behind in the patient during debulking surgery, but many ovarian tumors are so small or hidden that surgeons can't find them.

To make the tumors visible, the researchers designed chemical probes using single-walled carbon nanotubes that emit fluorescent light when illuminated by a laser. They coated these nanotubes with a peptide that binds to SPARC, a protein that is overexpressed by highly invasive ovarian cancer cells. This probe binds to the tumors and makes them fluoresce at NIR wavelengths, allowing surgeons to more easily find them with fluorescence imaging.

The researchers tested the image-guided system in mice that had ovarian tumors implanted in a region of the abdominal cavity known as the intraperitoneal space, and showed that surgeons were able to locate and remove tumors as small as 0.3 millimeters. Ten days after surgery, these mice had no detectable tumors, while mice that had undergone the traditional, non-image-guided surgery, had many residual tumors missed by the surgeon.

By three weeks after the surgery, many of the tumors had grown back in the mice that underwent image-guided surgery, but those mice still had a median survival rate that was 40 percent longer than that of mice that underwent traditional surgery.

No other imaging system would be able to locate tumors that small during a surgical procedure, the researchers say.

"You can't have a patient in a CT machine or an MRI machine and have the surgeon perform this surgical debulking procedure at the same time, and you can't expose the patient to X-ray radiation for multiple hours of the long surgery. This optics-based imaging system allows us to do that in a safe manner," Bardhan says.

Alessandro Santin, a professor of obstetrics and gynecology and clinical research program leader at the Yale University School of Medicine, described the results as "intriguing."

"These data support the potential use of this novel imaging system in the intraoperative setting for the optical detection of residual malignant tissue at the time of surgical staging, and/or cytoreductive surgery in ovarian cancer patients," says Santin, who was not involved in the study.

Monitoring patients

For most ovarian cancer patients, tumor debulking surgery is followed by chemotherapy, so the researchers now plan to do another study where they treat the mice with chemotherapy after image-guided surgery, in hopes of preventing the remaining tiny tumors from spreading.

"We know that the amount of tumor removed at the time of surgery for patients with advanced-stage ovarian cancer is directly correlated with their outcome," Birrer says. "This imaging device will now allow the surgeon to go beyond the limits of resecting tumors visible to the naked eye, and should usher in a new age of effective debulking surgery."

Now that they have demonstrated that this concept can be successfully applied to imaging during surgery, the researchers hope to begin adapting the system for use in human patients.

"In principle, it's quite doable," Siegel says. "It's purely the mechanics and the funding at this point, because this mouse experiment serves as the proof of principle and may actually have been more challenging than building a human-scale system."

The researchers also hope to deploy this type of imaging to monitor patients after surgery, and eventually to develop it as a diagnostic tool for screening women at high risk for developing ovarian cancer.

"A major focus for us right now is developing the technology to be able diagnose ovarian cancer early, in stage 1 or stage 2, before the disease becomes disseminated," Belcher says. "That could have a huge impact on survival rates, because survival is related to the stage of detection." [28]

Welding with stem cells for next-generation surgical glues

Scientists at the University of Bristol have invented a new technology that could lead to the development of a new generation of smart surgical glues and dressings for chronic wounds. The new method, pioneered by Dr. Adam Perriman and colleagues, involves re-engineering the membranes of stem cells to effectively 'weld' the cells together.

Cell membrane re-engineering is emerging as a powerful tool for the development of next generation cell therapies, as it allows scientists to provide additional functions in the therapeutic cells, such as homing, adhesion or hypoxia (low oxygen) resistance. At the moment, there are few examples where the cell membrane is re-engineered to display active enzymes that drive extracellular matrix production, which is an essential process in wound healing.

In this research, published in *Nature Communications* today, the team modified the membrane of human mesenchymal stem cells (hMSCs) with an enzyme, known as thrombin, which is involved in the wound healing process. When the modified cells were placed in a solution containing the blood protein fibrinogen, they automatically welded together through the growth of a natural hydrogel from the surface of the cells. The researchers have also shown that the resulting 3-D cellular structures could be used for tissue engineering.

Dr. Adam Perriman, Associate Professor in Biomaterials in the School of Cellular and Molecular Medicine, said: "One of the biggest challenges in cell therapies is the need to protect the cells from aggressive environments after transplantation. We have developed a completely new technology that allows cells to grow their own artificial extracellular matrix, enabling cells to protect themselves and allowing them to thrive after transplantation."

The team's findings could increase the possibilities in tissue engineering for chronic wound healing, especially because the process uses fibrinogen, which is abundant in blood.

The researcher's new method of the conversion of natural enzymes into a membrane binding proteins, could pave the way for the development of a wide range of new biotechnologies. [27]

Bioengineers add cooperative molecules to their toolkit for programming signal processing

Elaborate molecular networks inside living cells enable them to sense and process many signals from the environment to perform desired cellular functions. Synthetic biologists have been able to reconstruct and mimic simpler forms of this cellular signal processing. But now, a new toolset powered by self-assembling molecules and predictive modeling will allow researchers to construct the complex computation and signal processing found in eukaryotic organisms, including human cells.

The work by Assistant Professor Ahmad 'Mo' Khalil (BME), Assistant Professor Caleb Bashor of Rice University, BME graduate student Nikit Patel, and other colleagues at MIT, Harvard, the Broad Institute and Brandeis University, has been published in *Science*.

The type of combinatorial signal processing that they've been able to engineer synthetically is what cells naturally and elegantly do to enable intricate tasks, like those in embryonic development and differentiation.

"This work is a tour-de-force of synthetic biology that addresses a major question in how cells process information at the DNA level," says Dr. Tom Ellis, a Reader in the Department of Bioengineering at Imperial College London, who was not involved in the study.

"By taking a common principle that we know exists in nature, the ability for regulatory molecules to collaborate and form higher-order assemblies, you can program cells to execute very difficult computational and combinatorial problems," says Khalil. "This represents a very different way of engineering genetic circuits than is traditionally done and it can open up a new class of cellular functions that we can mimic and control."

First, the researchers built a library of simple, synthetic molecular components that can interact with one another. Each of these components has its own unique chemical and kinetic makeup, which can be used to understand its behavior. Using these known properties, they constructed a quantitative model that can predict how different combinations of those molecules come together to build higher-order assemblies. They could then use that predictive model as a guide to design genetic circuits that take advantage of combinatorial assembly to execute desired signal processing functions.

"Basically, these components bind to one another with extremely weak interactions," says Bashor. "But all of those weak interactions add up, in a bigger complex, to something that's really tight. So, when there's very few of them floating around, they won't form the complex. And when they reach a critical concentration, they see each other, and they can basically come together and form the complex."

The complex itself it made up of three components: a synthetic transcription factor that controls gene activation, the sequence of DNA where that transcription factor binds, and a synthetic "clamp" molecule that secures the three pieces together. That complex can allow them to tune the strength of the cell's response to an input signal, and shut on and off the response at desired times. But it's also much more than that.

"What we are harnessing and trying to build is one of the most powerful and universal features of biology: cooperativity," says Khalil. "One way to think about cooperativity is that it allows for the whole to be greater than the sum of its parts."

"You can think about cooperativity as the same type of signal-processing feature that gives you an analog-to-digital converter," says Bashor. "An analog-to-digital converter takes something that's basically linear and turns it into something switch-like."

Using their system, engineered cells are made to produce assembly components in response to a desired chemical or environmental input. In one experiment, they programmed yeast cells to respond to two different chemicals, and specifically to respond to varying concentrations of the two chemicals in either analog or digital fashion.

In the analog circuits, the response is continuous; if a small concentration of either or both chemicals is present, there is a graded response. But in the digital circuits, there is an all-or-nothing, discrete response—like a signal conversion to binary code, which is only comprised of 0s and 1s, off and on.

By taking advantage of their new ability to adjust the cooperativity between assembly components, they showed that they could convert the cell's response from dull to sharp—the more cooperative the complex, the sharper the response. The sharpness of a response—how acutely and intensely a system responds when a signal reaches a critical threshold—is key for digital signal processing.

"Engineering this type of response into transcription factors was central for allowing us to program cells to perform a diverse array of complex functions, such as Boolean logic, time-dependent filtering, and even frequency decoding," says Khalil.

That upgrade from analog to digital is the culmination of years of research. The analog-to-digital converter and their other synthetic gene circuits can be used to explore and manipulate the regulatory programs that guide immune and stem cell functions with the ultimate goal of developing transformational cell-based therapeutics from engineered human cells.

"It's well known that nature has perfected very powerful information processing with only a small number of parts, but deconvoluting precisely how this works is virtually impossible in human cells due to their complexity," adds Ellis, who was not part of the research. "By recreating the way human cells process information at the DNA level, but in a simple yeast cell model with synthetic parts, they have been able to recreate complex signaling from first principles. This is an excellent example of how thinking like an engineer can unlock a new way to answer major biology questions." [26]

BRB-seq: The quick and cheaper future of RNA sequencing

RNA sequencing is a technique used to analyze entire genomes by looking at the expression of their genes. Today, such genome-wide expression analyses are a standard tool for genomic studies because they rely on high-throughput technologies, which themselves have become widely available.

Nonetheless, RNA sequencing is still expensive and time-consuming, because it first requires the costly preparation of an entire genomic library—the DNA pool generated from the RNA of cells—while the data itself are also difficult to analyze. All this makes RNA sequencing difficult to run, rendering its adoption not as widespread as it could be.

Some new approaches have arrived to help, propelled by the revolution in single-cell transcriptomics, which uses what is known as "sample barcoding" or "multiplexing." Here, individual "barcode" sequences are added to each DNA fragment during library preparation so that each one can be identified and sorted before the analysis of the final data—meaning that this approach only requires a single library that contains multiple distinct samples or cells.

Barcoding reduces both cost and time, and this could extend to bulk RNA sequencing of large sets of samples. But there is still trouble with adapting and validating protocols for reliable and cheap profiling of bulk RNA samples—which is what we're faced with when trying to analyze the transcriptome of cells or tissues.

Now, scientists from the lab of Bart Deplancke at EPFL's Institute of Bioengineering have developed a novel approach called Bulk RNA Barcoding and sequencing (BRB-seq) which is 25 times less expensive than a conventional commercial RNA sequencing technology (Illumina's TruSeq).

Among its many advantages, BRB-seq is quick and preserves strand-specificity—a challenge in the field, having to do with transcribing DNA in the correct direction. As such, BRB-seq offers a low-cost approach for performing transcriptomics on hundreds of RNA samples, which can increase the number of biological replicates (and therefore experimental accuracy) in a single run.

In terms of performance, the scientists found that BRB-seq can detect the same number of genes as "the gold standard" in the field, namely TruSeq Stranded mRNA, at the same sequencing depth, and that the technique produces reliable data even with low-quality RNA samples. Moreover, it generates genome-wide transcriptomic data at a cost that is comparable to profiling four genes using RT-qPCR, which is currently a standard but low-throughput method for measuring gene expression.

In a test, BRB-seq could generate ready-to-sequence genomic libraries for up to 192 samples a day, requiring only two hours of hands-on time. The technique is combined with a user-friendly pipeline for pre-processing and analyzing sequencing data, allowing result acquisition in a single day.

"Since its release, dozens of labs and companies have already contacted us to help them implement the BRB-seq approach," says Bart Deplancke. "Because of BRB-seq's low cost, these researchers realized that they could now analyze many more samples with the same budget, thus vastly increasing the scope and reproducibility of their experiments. We therefore anticipate that BRB-seq or a comparable approach will over the longer term become standard in any molecular biology lab and replace RT-qPCR as the first gene expression profiling option." [25]

New RNA sequencing strategy provides insight into microbiomes

Researchers from the University of Chicago have developed a high-throughput RNA sequencing strategy to study the activity of the gut microbiome.

The new tools analyze transfer RNA (tRNA), a molecular Rosetta Stone that translates the genetic information encoded in DNA into proteins that perform basic biological functions. Developing a clear picture of tRNA dynamics will allow scientists to understand the activity of naturally occurring microbiomes, and study their responses to environmental changes, such as varying temperatures or changing availability of nutrients.

In a new study published in *Nature Communications*, a team of scientists led by Tao Pan, Ph.D., professor of biochemistry and molecular biology, and A. Murat Eren, Ph.D., assistant professor of medicine at UChicago, demonstrated the application of tRNA sequencing to gut microbiome samples from mice that were fed either a low-fat or high-fat diet.

The new software and computational strategy described in the study created a catalog of tRNA molecules recovered from the gut samples, traced them back to the bacteria responsible for their expression, and measured chemical modifications in tRNA that take place after transcription.

Each tRNA in bacteria has an average of eight chemical modifications that can tune its function. The new high-throughput sequencing and analysis strategy detects two of them, but it can also measure the amount of modification on a scale from 0 to 100 percent at each site. The level of one of the modifications, called m1A, was higher in the gut microbiome of mice that were fed a high-fat diet. This is the first time scientists have been able to see any modification level change in tRNA in any microbiome.

"We were working backwards," Pan said. "We had no preconceived notion of why the m1A tRNA modifications were actually there or what they were doing, but to see any modification change at all in the microbiome is unprecedented."

The m1A modification helps synthesize certain types of proteins that may be more abundant in a high-fat diet. The researchers don't know yet if these modification differences occur in response to that diet, or if they are already present and become active to enhance the synthesis of those proteins.

The study is the first of a series of microbiome projects from UChicago funded by a grant from the Keck Foundation. Pan has pioneered the use of tRNA sequencing tools, and the grant will fund continuing work to make them widely accessible through new computational strategies that Eren develops. Large sets of data generated by tRNA sequencing can provide critical insights into microbiomes associated with humans or the environment at a low cost.

"The molecular and computational advances that have emerged during the last two decades have only helped us scratch the surface of microbial life and their influence on their surroundings," Eren said. "By providing quick and affordable insights into the core of the translational machinery, tRNA sequencing may become not only a way to gain insights into microbial responses to

subtle environmental changes that can't be easily measured by other means, but also bring more RNA biology and RNA epigenetics into the rapidly developing field of the microbiome."

Pan and Eren agree that there is much room to improve this novel strategy, and they hope that it will happen quickly.

"There are a number of ways to examine microbiome activities, but nothing is faster and gets you more volume of data than sequencing," Pan said. "Here we have developed a new method that reports activity of the microbiome through tRNA and does so at high throughput. That's really the value." [24]

It looks like an anchovy fillet but this ancient creature helps us understand how DNA works

Today a large international consortium of researchers published a complex but important *study* looking at how DNA works in animals. The research focused on a marine organism, a creature called amphioxus (also known as "the lancelet"), to explore some of the steps that took place as animals evolved from invertebrates (animals without a backbone) to more complex backboned vertebrates, including us humans.

Ozren Bogdanovic is one of the lead authors of the study.

What is this animal, and why do you work with it?

The creature is called Mediterranean amphioxus, or amphy for short (the scientific name is Branchiostoma lanceolatum). Amphy normally lives buried in the sand in the Mediterranean, in the Black Sea and along coastal beaches of the European Atlantic.

Amphioxus looks like a vertebrate (an animal with a backbone, like humans and other mammals) but lacks the specialisations of animals like us, such as a complex brain and limbs. It shares with vertebrates a basic body plan, and has some comparable organs and structures in its body.

So amphy is used in research as an example of one of the simplest animals with a backbone that has some features in common with more complex lifeforms.

Because it "sits in the middle" between invertebrates and vertebrates, it can tell us about some of the steps and developments that took place as animals became more complex over millions of years of evolution.

More simple examples of invertebrates include insects, worms and jellyfish.

What does your new paper tell us about how DNA is used in the body?

For this work we sequenced the amphy genome (all of its DNA) and generated data required to study its genes.

This study gives us an overview of layers and control mechanisms that work around genes, and how these play a role in building more complex animals.

We found that some genes that perform only very general functions in amphy are used in a much more specialised way in vertebrates, particularly in the brain.

As individual animals, both we humans and amphy have two copies of each gene in each cell – one from each of our parents. But in humans, each of those genes further exists in two versions (they are duplicated), whereas in amphy each only exists in one version.

So it seems that the existence of two versions of each gene in vertebrates is linked with the ability to create specialised tissues and functions in our bodies.

What does the research help us learn about how DNA is controlled?

One of the most exciting aspects of this new paper is that – for the first time – it shows us that for some of its genes, amphy uses a similar method to vertebrates to control whether genes are active or not.

This system is called DNA methylation. Small molecules called methyl groups sit on top of a particular part of the DNA and act like signposts that tell genes to switch off.

In more simple animals, such as invertebrates like worms and insects, methylation has been observed at very low levels. Amphy also has low DNA methylation levels in general.

But in this study we found focused sites of dense DNA methylation in the amphy DNA. In these regions, the methylation carries out functions similar to the functions in vertebrates – that is, it participates in gene regulation. This has not been observed before in invertebrates.

For amphy to use DNA methylation to control activities of some of its genes tells us that the regulatory function of DNA methylation might have evolved millions of years earlier than we initially thought.

This new finding may help us understand more about how DNA regulation works, and how it goes wrong in disease. [23]

The origins of asymmetry: A protein that makes you do the twist

Asymmetry plays a major role in biology at every scale: think of DNA spirals, the fact that the human heart is positioned on the left, our preference to use our left or right hand ... A team from the Institute of biology Valrose (CNRS/Inserm/Université Côte d'Azur), in collaboration with colleagues from the University of Pennsylvania, has shown how a single protein induces a spiral motion in another molecule. Through a domino effect, this causes cells, organs, and indeed the entire body to twist, triggering lateralized behaviour. This research is published in the journal *Science* on November 23, 2018.

Our world is fundamentally asymmetrical: Think of the double helix of DNA, the asymmetrical division of stem cells, or the fact that the human heart is positioned on the left. But how do these asymmetries emerge, and are they linked to one another?

At the Institute of biology Valrose, a team led by CNRS researcher Stéphane Noselli, which also includes Inserm and Université Cote d'Azur researchers, has been studying right-left asymmetry for several years in order to solve these enigmas. The biologists had identified the first gene controlling asymmetry in the common fruit fly (Drosophila), one of the biologists' favoured model organisms. More recently, the team showed that this gene plays the same role in vertebrates: the protein that it produces, Myosin 1D, controls the coiling or rotation of organs in the same direction.

In this new study, the researchers induced the production of Myosin 1D in the normally symmetrical organs of Drosophila, such as the respiratory trachea. Quite spectacularly, this was enough to induce asymmetry at all levels: deformed cells, trachea coiling around themselves, the twisting of the whole body, and helicoidal locomotive behavior among fly larvae. Remarkably, these new asymmetries always develop in the same direction.

In order to identify the origin of these cascading effects, biochemists from the University of Pennsylvania contributed to the project too: on a glass coverslip, they brought Myosin 1D into contact with a component of cytoskeleton (the cell's "backbone"), namely actin. They were able to observe that the interaction between the two proteins caused the actin to spiral.

Besides its role in right-left asymmetry among Drosophila and vertebrates, Myosin 1D appears to be a unique protein that is capable of inducing asymmetry in and of itself at all scales, first at the molecular level, then, through a domino effect, at the cell, tissue, and behavioral level. These results suggest a possible mechanism for the sudden appearance of new morphological characteristics over the course of evolution, such as, for example, the twisting of snails' bodies. Myosin 1D thus appears to have all the necessary characteristics for the emergence of this innovation, since its expression alone suffices to induce twisting at all scales. [22]

DNA with a twist: Discovery could further antibiotic drug development

Scientists reveal how a 'molecular machine' in bacterial cells prevents fatal DNA twisting, which could be crucial in the development of new antibiotic treatments.

DNA replication is vital to all lifeforms, but in some organisms it can be prevented by twists in the DNA sequence, called 'supercoils'. If too many supercoils are allowed to build up, cells vital to sustaining life will die.

A molecular machine, called DNA gyrase, which is found in bacterial cells but not human cells, relaxes the twists to allow DNA replication to continue as normal, but until now there was limited understanding of how it does this in real time in actual living cells.

The process is of particular interest to drug developers because if DNA gyrase can be successfully interrupted as it works to stop twists occurring in bacterial DNA cells, the bacteria will die and the threat of infection to the host prevented.

Yellow glow

The team from the University of York, in collaboration with the John Innes Centre, Oxford, and the Adam Mickiewicz University, Poland, used a special laser microscope to shine a light on a fluorescent

protein, which makes DNA gyrase glow yellow. This allowed scientists to see inside a bacterial cell and, for the first time, observe how the molecular machinery prevents twists in DNA.

Professor Mark Leake, from the University of York's Departments of Biology and Physics, said: "By using modified fluorescent proteins the DNA gyrase can be made to glow yellow whereas the cellular machinery, which is used to actually replicate DNA, can be labelled with a different red-glowing protein.

"These separate colours can then be split into different detector channels to enable the precise location of DNA gyrase to be observed relative to the exact point at which DNA replication is actually occurring inside a single living bacterial cell."

The researchers have discovered that the DNA gyrase focuses its twist-relaxation activities just in front of the point at which DNA is being replicated in a cell.

Nanoscale

Professor Leake said: "The molecular machines that perform DNA replication shuttle along the DNA, but this work can result in tiny nanoscale twists of DNA that accumulate in front of the replication machinery, just like tangled up cables at the back of your TV set.

"We have now shown that several tens of DNA gyrase molecules actively bind to a zone directly in front of the replication machinery and relax the DNA nano-twists faster than the replication machinery itself moves along the DNA.

"They essentially prevent a 'twist barrier' from building up which would stop replication machinery from shuttling along the DNA, halt replication, and kill the cell."

Super-bugs

DNA gyrase is a target for a number of different antibiotics, but with several 'super-bugs' emerging that are resistant to antibiotics, there is more urgent need to understand how bacterial cells operate in real time.

Professor Leake said: "Now that we know how DNA gyrase really performs its role inside living bacteria, we can assist in the design of new types of drugs that can stop DNA gyrase from working, which will allow drugs to be more targeted and ultimately kill dangerous bacterial infections in humans.

"Human cells have similar mechanisms to resolve DNA twists but using different molecular machines, and our work on DNA gyrase in bacteria gives us valuable insights into the generalised mechanisms governing the operation of this class of remarkable biomolecules for all organisms." [21]

Built for speed: DNA nanomachines take a (rapid) step forward

When it comes to matching simplicity with staggering creative potential, DNA may hold the prize. Built from an alphabet of just four nucleic acids, DNA provides the floorplan from which all earthly life is constructed.

But DNA's remarkable versatility doesn't end there. Researchers have managed to coax segments of DNA into performing a host of useful tricks. DNA sequences can form logical circuits for nanoelectronic applications. They have been used to perform sophisticated mathematical computations, like finding the optimal path between multiple cities. And DNA is the basis for a new breed of tiny robots and nanomachines. Measuring thousands of times smaller than a bacterium, such devices can carry out a multitude of tasks.

In new research, Hao Yan of Arizona State University and his colleagues describe an innovative DNA walker, capable of rapidly traversing a prepared track. Rather than slow, tentative steps across a surface, the DNA acrobat cartwheels head over heels, covering ground 10- to 100-fold faster than previous devices.

"It is exciting to see that DNA walkers can increase their speed significantly by optimizing DNA strand length and sequences, the collaborative effort really made this happen," Yan said.

Yan is the Milton D. Glick Distinguished Professor of Chemistry and Biochemistry at ASU and director of the Biodesign Center for Molecular Design and Biomimetics.

The study was led by Nils G. Walter, Francis S. Collins Collegiate Professor of Chemistry, Biophysics & Biological Chemistry, founding director of the Single Molecule Analysis in Real-Time (SMART) Center and founding co-director of the Center for RNA Biomedicine at the University of Michigan, and his team, along with collaborators from the Wyss Institute, the Dana Farber Cancer Institute and the Department of Biological Chemistry at Harvard (all in Boston, Massachusetts).

"The trick was to make the walker go head over heels, which is so much faster than the hopping used before—just as you would see in a kung fu action movie where the hero speeds up by cartwheeling to catch the villain," says Walter.

The improvements in speed and locomotion displayed by the new walker should encourage further innovations in the field of DNA nanotechnology.

The group's findings appear in the advanced online issue of the journal *Nature Nanotechnology*.

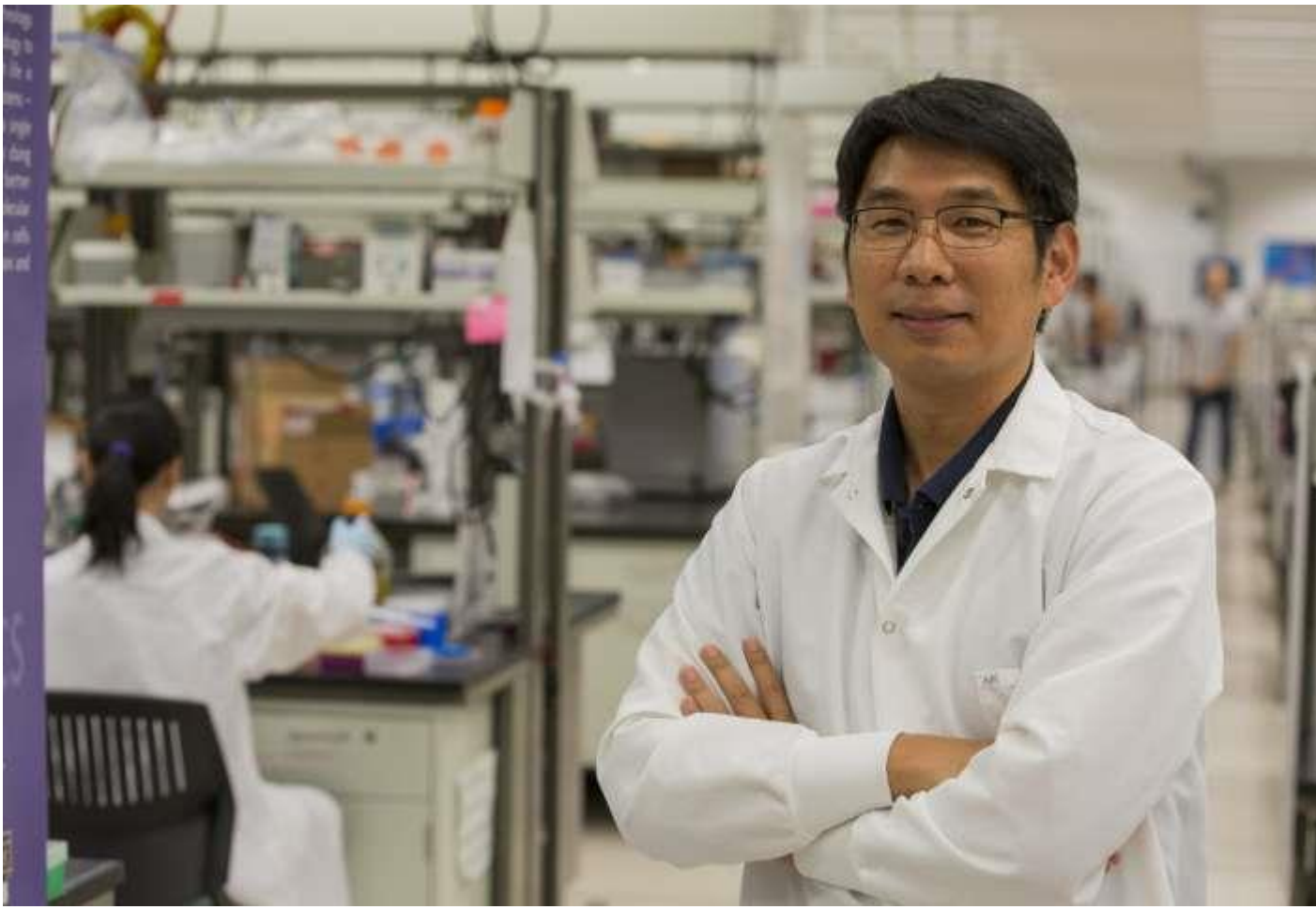
Building with DNA

Nanoarchitects build their DNA structures, motors and circuits using the same basic principle as Nature. The four nucleotides, labeled A,T,C and G, bind to each other according to a simple and predictable rule: Cs always pair with Gs and As always pair with Ts. Thus, varying lengths of DNA may be programmed to self-assemble, snapping together to form an unlimited variety of two- and 3-dimensional nanostructures. With clever refinement, researchers have been able to outfit their once-static nano-creations with dynamical properties.

One of the more innovative applications of DNA nanotechnology has been the design of robotic walking devices composed of DNA strands that successively move in a stepwise fashion across a path. The method enabling DNA segments to stroll across a defined area is known as strand displacement.

The process works like this: One leg of the robotic device is DNA strand 1, which is bound to complementary strand 2, through normal base pairing. Strand 1 contains an additional, unpaired sequence dangling from its end, which is known as the toehold.

Next, DNA strand 3 is encountered. This strand is complementary to DNA strand 1 and includes a toehold sequence complementary to DNA strand 1. Once the toehold of strand 3 binds with the toehold of strand 1, it begins sequentially displacing each strand 2 nucleotide, one by one, until strand 2 has been is completely replaced by strand 3. Strand 2 then dissociates from strand 1 and the process can begin again. (See figure 1).



Hao Yan is the Milton D. Glick Distinguished Professor of Chemistry and Biochemistry at ASU and director of the Biodesign Center for Molecular Design and Biomimetics. Credit: Biodesign Institute at Arizona State University

Toehold-mediated strand displacement, which forms the basis of other DNA nanodevices, allows DNA structures to move from one complementary foothold on the walking surface to the next. As each DNA strand is displaced by a new strand, the nano-creature takes a step forward.

Race walking

Successful DNA walkers of various kinds have been designed and have demonstrated the ability to ferry nano-sized cargo from place to place. Until now, however, the strand displacement reactions they rely on have been slow, generally requiring several minutes to move a short distance. This is much slower than naturally occurring processes in living systems like protein motors, which can perform feats of dissociation similar to strand displacement in much faster time frames.

While theoretical calculations suggest that individual operations by such nanodevices should occur in seconds or less, in practice, such operations typically require minutes or even hours. (A recently designed cargo-sorting walker for example required 5 minutes for each step, with foothold spacings just 6 nm apart. This speed was on a par with similar strand-displacement walkers.)

In the new study, researchers sought to optimize this process to see how quickly a walker designed with speed in mind could move. The limiting factor in terms of speed did not appear to be the strand displacement process itself, but rather the lack of fine-tuned optimization in the overall walker design.

The team redesigned their walker for maximum speed and used a fluorescent imaging technique known as smFRET (for single-molecule fluorescence resonance imaging transfer) to chart the DNA walker's progress and evaluate its subtle kinetic properties.

By altering the lengths of toehold sequences and branching migration points, the stepping rate could be keenly optimized, making for a briskly moving nanorobot that left competitors in the dust, boasting stepping rates a full order of magnitude faster than previous DNA walkers.

Freewheeling nanorobot

Part of the robot's advantage over its competitors is due to its unusual technique of locomotion. Rather than simply stepping from one surface foothold to the next, the acrobatic walker moves head over heels in a cartwheel fashion, while remaining securely bound to at least one foothold at all times.

The stability of the double-stranded sequences anchoring the base of the robot to the track surface, while the free toehold searches out the next complementary sequence, may be one factor improving the walker's speed. The cartwheeling design also allows strand displacement to sequentially proceed in a direction away from the foothold surface, which improves efficiency.

Once the walker was optimized, super-resolved single particle tracking was used to observe the device's movement over a 2-D surface studded with footholds for the walker, covering a range of up to 2 microns. The best walker optimized in the study was able to search ~43 foothold sites per minute with a stepping distance of ~ 10nm. Strand displacement occurred at rates of about a tenth of a second. Analysis suggests the device can take hundreds of steps without dissociating.

Future steps

While still lagging behind naturally occurring protein reactions, the optimized cartwheeling walker offers a marked advancement in performance, representing an order of magnitude improvement over earlier versions, while not consuming any fuel. Borrowing further insights from natural systems may allow dynamical DNA devices like the walker to accelerate even more in the future by converting chemical energy into directed speed.

The study underlines the opportunities for optimization of a range of DNA nanostructures, considerably enhancing their speed and versatility. [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*.

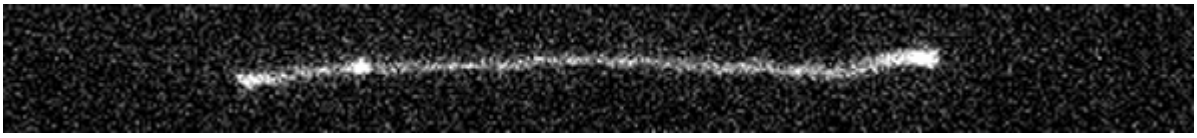
Knots in motion

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.

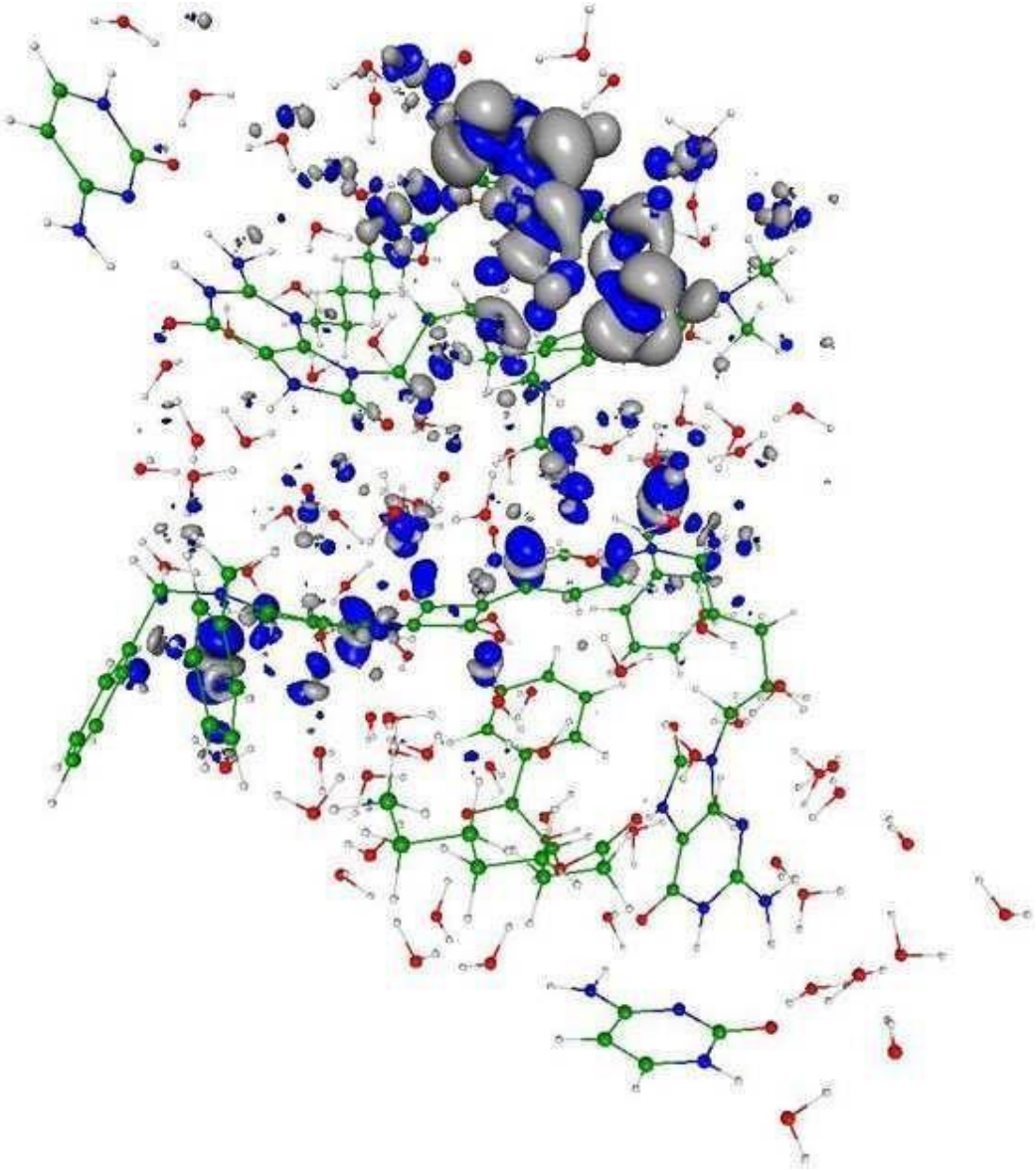
Our discovered phenomenon of the quantum entanglement in the prebiotic systems enhance the photosynthesis in the proposed systems because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states (Tamulis A, Grigalavicius M, Baltrusaitis 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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