Gene Silencing and Transformation

Developing an efficient delivery system for enhanced and controlled gene interference-based therapeutics is an existing challenge in molecular biology. [30]

This fact makes lensless microscopy an ideal tool for medical diagnosis in remote areas since there is no need for the medical doctor to bring and maintain large, heavy and sensitive analysis devices. [29]

The Columbia team behind the revolutionary 3-D SCAPE microscope announces today a new version of this high-speed imaging technology. [28]

The discovery that protein therapeutics can hijack the HOPS complex to gain access to the cell interior should help scientists design therapeutic proteins to treat diseases that are not adequately treated using other approaches, Schepartz said. [27]

DNA regions susceptible to breakage and loss are genetic hot spots for important evolutionary changes, according to a Stanford study. [26]

For the English scientists involved, perhaps the most important fact is that their DNA read was about twice as long as the previous record, held by their Australian rivals. [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 HYPERLINK "https://www.nature.com/articles/s41586-018-0734-6" *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.

Contents

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.

Gold-DNA nanosunflowers for efficient gene silencing and controlled transformation

Developing an efficient delivery system for enhanced and controlled gene interference-based therapeutics is an existing challenge in molecular biology. The advancing field of nanotechnology can provide an effective, cross-disciplinary strategy to facilitate nucleic acid delivery. In a new report, Shuaidong Huo and colleagues in the interdisciplinary departments of Nanoscience, Interactive Materials, Chemistry and Polymer Research in China, Germany and the U.S. used triplex-forming oligonucleotide sequences coupled to its complementary strand to mediate the self-assembly of ultra-small gold nanoparticles.

The resulting sunflower-like nanostructures showed strong near infrared (NIR) absorption and ability for photothermal conversion. When the scientists irradiated the structures with NIR, the larger nanostructures disassembled to generate ultra-small nanoparticles modified with the c-Myc oncogene sequence to directly target the cancer cell nucleus. Huo et al. controlled gene

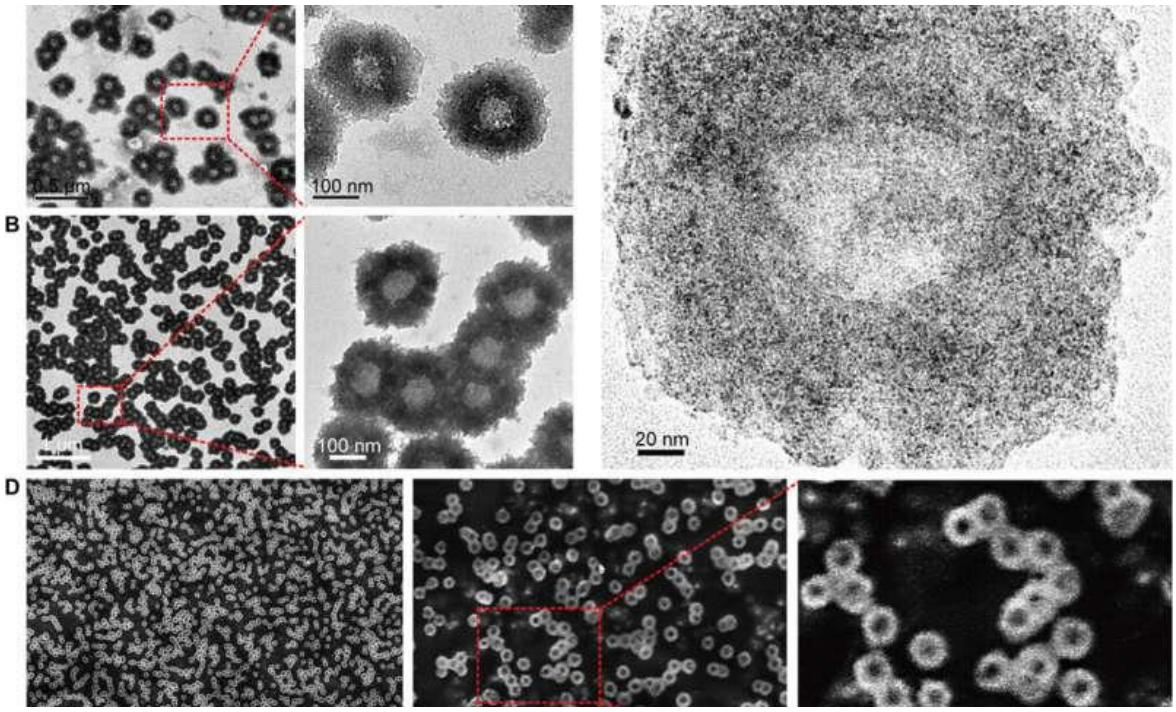
silencing by synergistically controlling the time of preincubating cells with nanoparticles alongside nanostructure self-assembly (in vitro and in vivo) and the time-frame of NIR irradiation. The study provided a new paradigm to construct efficient and tailored nanocarriers for applications of gene interference and therapeutic gene delivery.

Gene therapy has great potential to treat a variety of diseases and complications including infertility, HIV and cancer. Successful gene therapy to alleviate disease symptoms depend on an efficient gene delivery vehicle or vector. During the process, the gene carrier must cross many biological barriers and cell membranes while escaping endosomal entrapment and nuclease-based degradation. Compared to virus-based delivery strategies, non-viral gene delivery approaches face many challenges during the process of loading and releasing DNA/RNA, targeted delivery and intracellular uptake, including incompatibility relative to immune responses in vivo.

Vigorous efforts in nanotechnology are underway to engineer stable and efficient vehicles for gene transfer to cancer cells. Due to their unique physiochemical properties a number of nanomaterials have emerged for gene delivery. Among them, gold nanoparticles (Au NPs) with specific size and surface properties can overcome obstacles in vivo to become one of the most studied gene carrier systems. However, these strategies have encountered a variety of shortcomings and therefore it is important to establish efficient delivery systems or enhanced and controlled gene therapies.

Self-assembly and testing sunflower-like nanostructures

In the present work, Huo et al. were inspired by nature's ability to hybridize DNA by engineering DNA-mediated, self-assembled gold DNA nanostructures (approximating 200 nm). The sunflower-like design showed strong NIR absorption and photothermal conversion properties. Upon NIR irradiation, the structures disassembled to liberate ultra-small gold nanoparticles (2 nm, Au NPs) with potential for oncogene silencing, improved cell and nuclei permeability and enhanced transfection efficiency. The scientists synergistically controlled the cell-nanomaterial interactions based on the time of pre-incubation in the lab, followed by time of circulation in vivo and the timeline of irradiation. The experiments facilitated increased cellular uptake, tunable gene silencing efficacy and controlled tumor inhibition. The transformable nanosunflowers provided an excellent model to design nanovehicles for drug delivery with great potential in biomedicine.

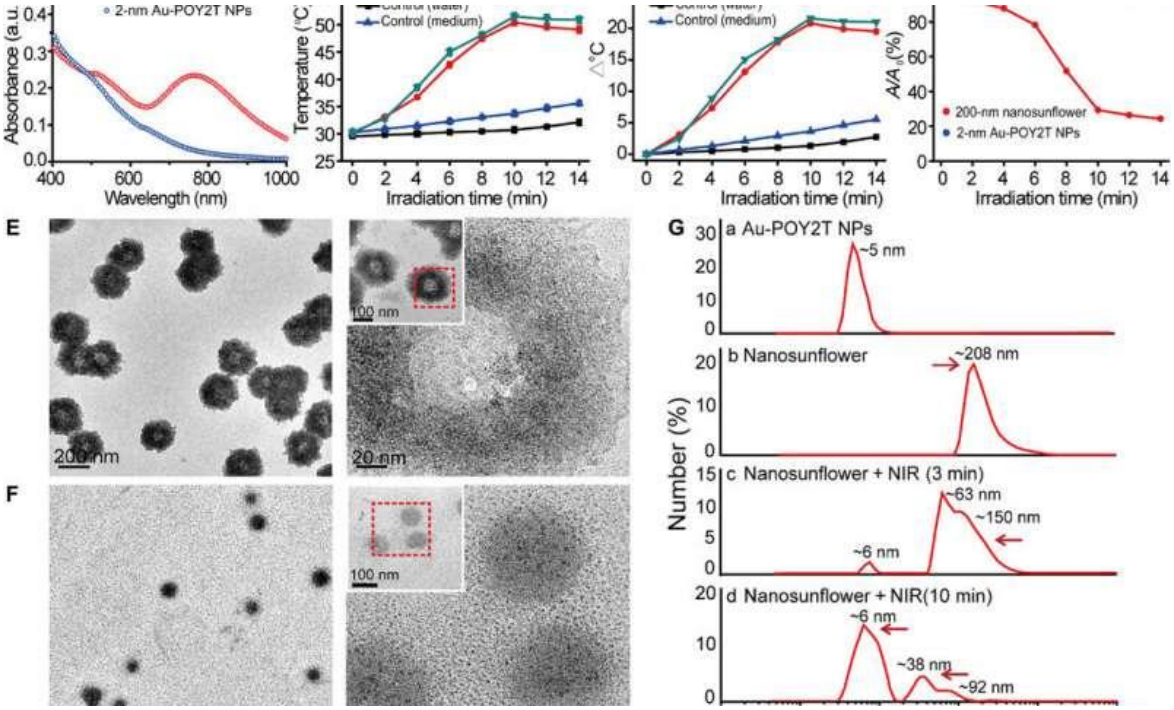


Morphology characterization of the self-assembled nanostructures (nanosunflowers). (A) TEM (200 kV) images of the nanosunflowers with enlarged structural details. (B) Bio-TEM (80 kV) images with enlarged polymer structural details. (C) High-resolution TEM (200 kV) images showing the distribution of ultrasmall NPs on the self-assembled nanostructure. (D) SEM images with enlarged surface topography of the nanosunflowers. Credit: Science Advances, doi: 10.1126/sciadv.aaw6264

Huo et al. first synthesized the two-nanometer Au NPs coated with tiopronin and modified them with thiol-oligonucleotides (SH-POY2T) using an established method of ligand exchange. The 23-nucleotide (nt) POY2T oligonucleotide bound the P2 promoter of the c-myc oncogene to form a triplex structure and downregulate oncogenic c-myc expression. In parallel, they designed and synthesized another single-stranded sequence known as CA to complementarily hybridize to the tail of the POY2T sequence and block its binding to the c-myc oncogene. On completion, the nanostructure self-assembled into sunflower-like structures. The team investigated the nanostructure (200 nm) using transmission electron microscopy (TEM). Additional imaging revealed further details of the DNA moieties of the "sunflower" structure. When the materials scientists used scanning electron microscopy (SEM) to validate the TEM results, they observed consistency between the methods.

They investigated the UV-Vis absorption spectra of the ultrasmall Au NPs prior to DNA-mediated self-assembly. The monodispersed, individual two-nanometer Au-POY2T NPs showed strong absorption in the NIR region to generate heat under NIR irradiation. Huo et al. credited the observed strong NIR absorbance to close interparticle spacing and

nonuniform spatial distribution of individual NPs within the larger nanostructure. They tested the heat response of the self-assembled nanostructures under NIR irradiation and noted the melting point of the complementary DNA sequences (POY2T and CA) to approximate 41 degrees C, dissociating half of the duplex structure between complementary DNA sequences. Huo et al. selected 10 minutes as the optimal time for NIR irradiation in the study.



Photothermal property and disassembly behavior study of the self-assembled nanostructures. (A) Visible absorption spectra of 2-nm core-sized NPs and 200-nm self-assembled nanostructures. a.u., absorbance unit. (B) Temperature response of self-assembled nanostructures, upon NIR irradiation, dispersed in water and cell culture medium. Mean values ± SD, n = 3. (C) Temperature rise of self-assembled nanostructures, upon NIR irradiation, dispersed in water and cell culture medium. (D) Change of maximum absorbance (767 nm) of 2-nm core-sized NPs and 200-nm self-assembled nanostructures upon NIR irradiation. (E and F) TEM observation of disassembly behavior of 200-nm self-assembled nanostructures before (top) and after (bottom) NIR irradiation (808 nm, 10 min). (G) Hydrodynamic diameter of (a) monodispersed 2-nm Au-POY2T NPs and size change of the 200-nm nanosunflowers before (b) and after (c and d) NIR irradiation for different time periods (3 and 10 min). Credit: Science Advances, doi: 10.1126/sciadv.aaw6264

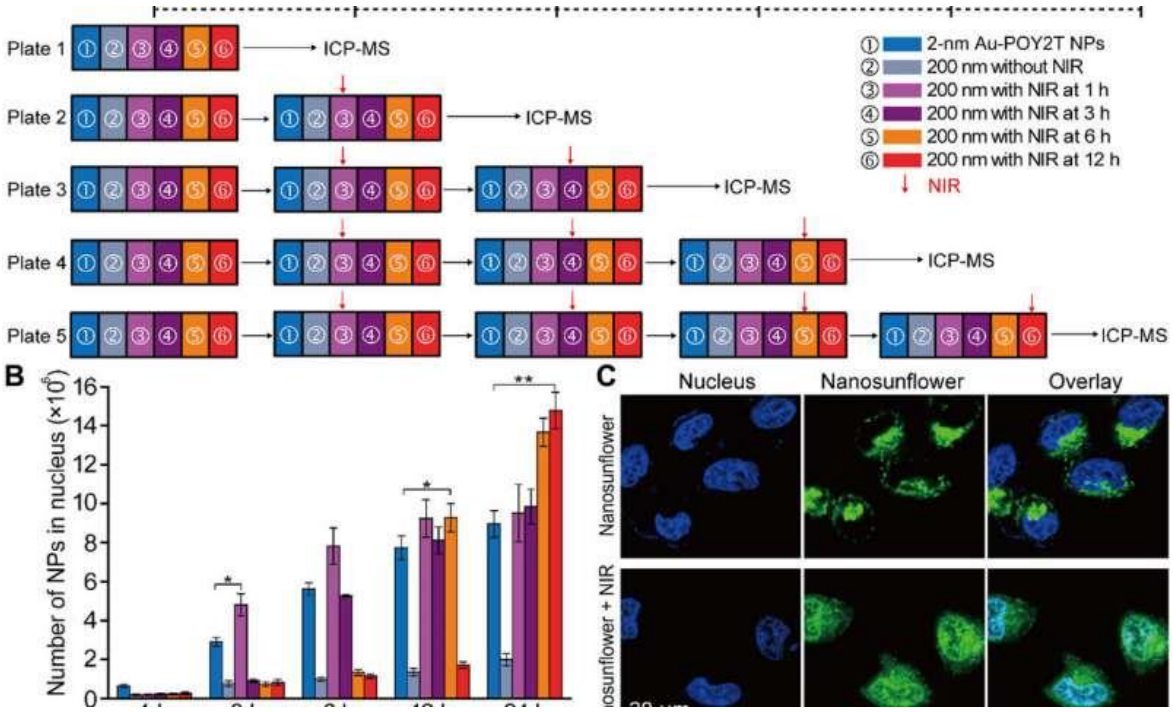
Disassembly behaviour of the self-assembled nanostructures and proof-of-concept

The scientists hypothesized the self-assembled nanostructures would shrink and disassemble into individual ultrasmall Au-POY2T NPs. After 10 minutes of NIR irradiation, the maximum absorption (767 nm) of nanostructures markedly decreased to disassemble the sunflower structure. They followed the experiments before and after NIR irradiation with TEM observations and used particle size analysers to understand the disassembly process and size

transformation of the nanostructures up to six nanometers in size and confirmed the optimal suitability of the 10-minute timeline.

Huo et al. applied NIR irradiation to MCF-7 cells treated with self-assembled gold DNA nanostructures and tested their cellular uptake in vitro as proof-of-concept. They determined the cellular internalization of Au-POY2T (2 nm) across diverse incubation times and quantified their cellular uptake using inductively coupled plasma mass spectroscopy (ICP-MS) and previous methods. They noted increased internalization after six hours of incubation compared to 24-hour incubation timelines. They did not observe inhibitors of endocytosis to influence Au-POY2T NP uptake, suggesting the involvement of an alternative path such as membrane fusion.

Understanding gene silencing behavior of the self-assembled nanostructures



Controlled nucleus localization and gene silencing study in vitro of the self-assembled nanostructures. (A) Schematic of the in vitro cell experimental setup for the controlled NP nucleus localization and gene regulation study. (B) Number of 2-nm Au-POY2T NPs localized in the MCF-7 cell nucleus with treatment of ① individual 2-nm Au-POY2T NPs, ② 200-nm nanosunflowers, and 200-nm nanosunflowers with NIR irradiation (10 min) after different preincubation times (③ 1, ④ 3, ⑤ 6, and ⑥ 12 hours). Mean values ± SD, n = 3. Statistical differences were determined by two-tailed Student's t test; *P < 0.05 and **P < 0.01. (C) Confocal observation of distribution of fluorescein isothiocyanate–labeled nanosunflowers (green) before (top) and after (bottom) NIR irradiation in MCF-7 cells. Nucleus was labeled by 4',6-diamidino-2-phenylindole (blue). (D) Bio-TEM image of the localization of large-sized nanosunflowers (top, red arrow) in the cytoplasm and distribution of released small NPs (bottom, blue arrow) in cytoplasm and nucleus after NIR irradiation in MCF-7 cells. (E) Cytotoxicity evaluation of MCF-7 cells with treatment of 200-nm nanosunflowers after NIR

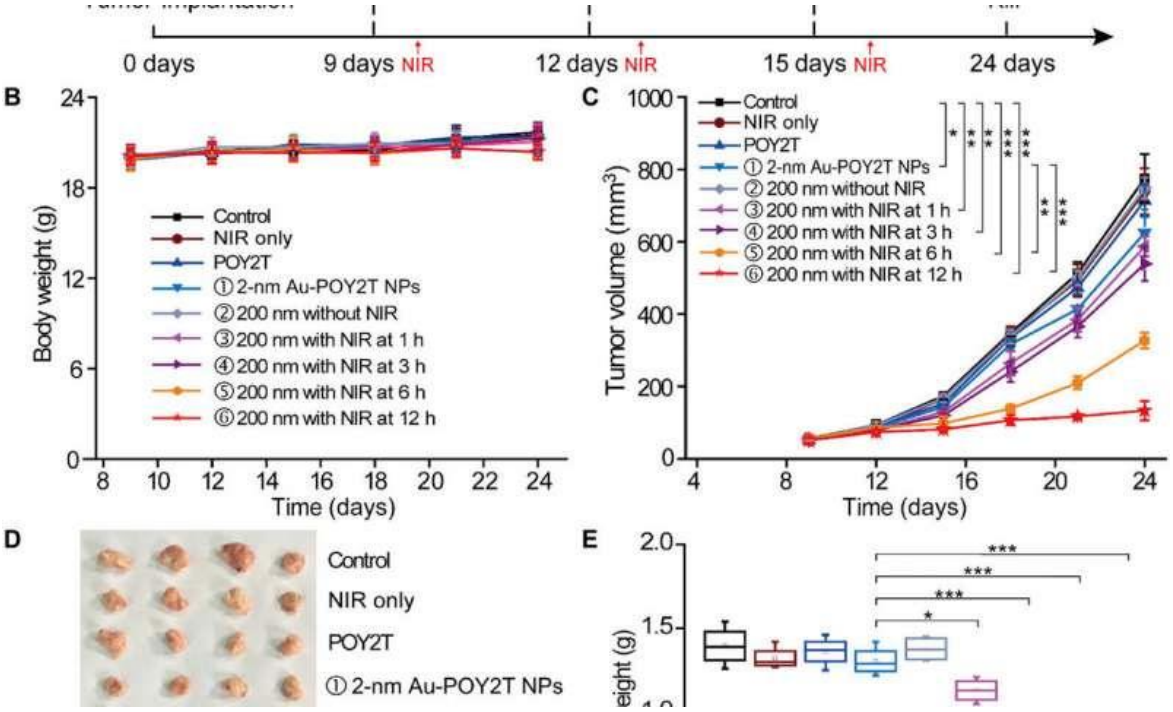
irradiation (after a period of preincubation time: 1, 3, 6, and 12 hours, respectively) compared to control, 2-nm Au-TIOP NPs, POY2T sequence, CA sequence, 2-nm Au-POY2T NPs, 200-nm nanosunflowers without NIR irradiation, and NIR exposure only. All the concentrations of treatments were at or equal to 1 μM in POY2T sequence and were tested after a total of 24 hours of incubation. Mean values ± SD, n = 3. Statistical differences were compared with the treatment group of ① individual 2-nm Au-POY2T NPs determined by two-tailed Student's t test; *P < 0.05 and **P < 0.01. (F) C-myc mRNA level determined by real-time PCR after different treatments as described above. Mean values ± SD, n = 3. Statistical differences were determined by two-tailed Student's t test; **P < 0.01 and ***P < 0.001. (G) C-myc protein levels determined by Western blot and (H) corresponding quantitative histogram after different treatments as described above. GAPDH, glyceraldehyde phosphate dehydrogenase. Credit: Science Advances, doi: 10.1126/sciadv.aaw6264

After enhanced cellular uptake of self-assembled nanostructures in vitro, the research team investigated the distribution of nanoparticles within the cell nuclei using "standby" and "attack" strategies after NIR triggering. For this, they extracted cell nuclei after incubation, for ICP-MS analysis after NIR irradiation across diverse periods of incubation (one, three, six and 12 hours). They noted that the pre-incubation period largely affects nanoparticle internalization within the cell nucleus, and the researchers regulated Au-POY2T NPs in the cell nucleus based on the time of pre-incubation and NIR irradiation.

Huo et al. also investigated NIR-irradiation controlled therapeutic effects of nanosunflowers using cell viability tests; they observed oncogene silencing to increase markedly (80 percent) and kill more cancer cells. The research team controlled the therapeutic impact effectively by changing the timeline of pre-incubation and irradiation efficiently. The results supported a superior ability of the transformable nanosunflowers to silence the c-myc oncogene and oncoprotein. The scientists controlled the gene silencing process by tuning pre-incubation timelines prior to NIR irradiation.

Controlling tumor growth inhibition using self-assembled nanosunflowers

To test the controllable anti-tumor efficiency of nanosunflowers in vivo, the scientists first investigated their blood compatibility to confirm good blood biocompatibility. The research team then established the MCF-7 tumor model using the BALB/c nude mice, allowed the tumor volumes to reach 50 mm^3 and randomly divided the animals into nine groups and treated them with 1000 μl of varying POY2T formulations. After each injection, they irradiated the animal groups with NIR lasers for 10 minutes to reach a local temperature above 41 degrees C.



Controlled tumor growth inhibition study of the self-assembled nanostructures. (A) The MCF-7 tumor BALB/c nude mice model was established at day 0. After tumors were ready, the mice were randomly divided into nine groups and treated with 100 µl of various formulations (equivalent to 10 µM in POY2T sequence; group ① with 2-nm Au-POY2T NPs and groups ②, ③, ④, ⑤, and ⑥ with 200-nm nanosunflowers) at days 9, 12, and 15. In groups ③, ④, ⑤, and ⑥, the tumors were irradiated with a NIR laser for 10 min at 1, 3, 6, and 12 hours after each intravenous injection. Saline, NIR only, and POY2T were used as control groups. The (B) body weights and (C) tumor volumes were measured every 3 days. Scale bar, 1 cm. After the mice were sacrificed at day 24, all tumors were (D) isolated and (E) weighted, respectively. Mean values ± SD, n = 4. Statistical differences were determined by two-tailed Student's t test; *P < 0.05, **P < 0.01, and ***P < 0.001. (Photo credit: Ningqiang Gong, National Center for Nanoscience and Technology, China.) (F) Hematoxylin and eosin staining images of organs including the heart, liver, spleen, lung, kidney, and tumor after different treatments. Scale bar, 200 µm. Credit: Science Advances, doi: 10.1126/sciadv.aaw6264

Of note, mice treated with the nanosunflower-treated group and irradiated at 12 hours showed the most significant anti-tumor effects, indicating efficient delivery of gene silencing units into the tumor site. After 24 days, Huo et al. sacrificed the animals, isolated the tumors and weighed them to demonstrate nanosunflower based NIR-controlled tumor growth inhibition in vivo. Based on histological studies, the team showed the treatment significantly reduced tumor growth and did not affect the morphology of other organs. The results verified the therapeutic efficiency and lack of side effects for nanosunflowers and NIR therapy.

In this way, Shuaidong Huo and colleagues designed, developed and optimized nanoagents for effective anti-tumor therapy. They engineered self-assembled sunflower-like nanostructures to act as multiparticle carriers loaded with many ultrasmall therapeutic units. Upon NIR irradiation, the nanostructures dissociated to release swarms of small NPs to target the cell nucleus. In tumor-bearing mice, the large sunflowers passively targeted the tumor site followed by NIR irradiation to transform

the tumor genetic composition and shrink it. The research team aim to improve transfection efficiency and provide a blueprint for controllable gene silencing at tumor sites using transformable gene interference carriers for intricate theranostics at the level of the single cell. [30]

A multimodal novel lensless microscopy technology for medical applications

Today's state-of-the-art analysis of biological samples by light microscopy includes a vast variety of techniques ranging from conventional bright field microscopy and phase contrast microscopy to high resolution confocal laser scanning microscopy and to recently developed super resolution microscopy techniques like stimulated emission depletion (STED) or stochastic optical reconstruction microscopy (STORM) which abnegate Abbe's limit of diffraction.

Despite the availability of these sophisticated, super resolution techniques, reproducible visualization of cells and identification of subcellular structures in biological samples still requires staining with dyes or immunolabeling by antibodies to specific cellular antigens.

Generally, in-vitro observation of living cells can provide valuable insights into their structure and dynamics including organization of organelles and transduction of chemical signals involved in cell-cell and cell-matrix interactions. Unfortunately, there is a limited use for long term in-vitro imaging as most high-resolution microscopy technologies require processed/fixed tissues or cells. As both high resolution optical microscopy and fluorescence imaging usually require highly skilled users, expensive equipment and maintenance, the presented novel digital in-line holographic microscopy (DIHM) in-vitro imaging technology opens a vast field of applications for standard users. This analytical optical system offers quick and reproducible results at low costs. Moreover, it voids the necessity of referral to specialized labs and is easily implemented as a diagnostic tool for doctors (general practitioners and specialists).

DIHM is based on the numerical reconstruction of a digitally recorded hologram. It allows for the acquisition of both, the amplitude and phase information of a wave front shaped by the microscopic sample. The advantage of the DIHM lies in the simplicity of its setup: the microscope consists of a light-emitting diode (LED) as an illumination source, appropriate filtering for coherence enhancement and an image sensor. The comprehensive data processing algorithm transforms the recorded holograms into a microscope image by angular spectrum approach and digital filtering. In general, the resolution of such a microscope is strongly influenced by the spatial coherence length of the illumination, which can be enhanced via reducing the emitting area, either by cutting a part of the wave front with the pinhole or by use of a point-like nanoLED. The nanoLED arrays developed within the EU Horizon 2020 program ChipScope project will allow enhancement of the imaging resolution compatible to the conventional optical microscopy.

Lensless DIHM microscope

This fact makes lensless microscopy an ideal tool for medical diagnosis in remote areas since there is no need for the medical doctor to bring and maintain large, heavy and

sensitive analysis devices. A simple laptop and a suitcase sized lensless microscope assembly is enough to—for example—make a parasite diagnosis from body fluid samples (e.g. Malaria, Amoeba etc.). The robust construction enables a fast, reliable and automated analysis of the specimen by combining not only high-resolution light microscopy but also implementing modern analysis techniques based on the detection of changes in human DNA, identifying viral genomes and immunological characterization in one device.

To provide the highest light sensitivity and optical resolution, the system is equipped with a normal grayscale camera to work in a multi-cell imaging bright field mode. This novel lensless microscope is equipped with a microfluidic flow channel system for handling living cells and imaging. [29]

High-speed microscope illuminates biology at the speed of life

The Columbia team behind the revolutionary 3-D SCAPE microscope announces today a new version of this high-speed imaging technology. In collaboration with scientists from around the world, they used SCAPE 2.0 to reveal previously unseen details of living creatures—from neurons firing inside a wriggling worm to the 3-D dynamics of the beating heart of a fish embryo, with far superior resolution and at speeds up to 30 times faster than their original demonstration.

These improvements to SCAPE, published today in *Nature Methods*, promise to impact fields as wide ranging as genetics, cardiology and neuroscience.

Why is having faster, 3-D imaging so valuable? "The processes that drive living things are dynamic and ever-changing, from the way an animal's cells communicate with one another, to how a creature moves and changes shape," said Elizabeth Hillman, Ph.D., a principal investigator at Columbia's Mortimer B. Zuckerman Mind Brain Behavior Institute and the paper's senior author. "The faster we can image, the more of these processes we can see—and imaging fast in 3-D lets us see the whole biological system, rather than just a single plane, offering a clear advantage over traditional microscopes."

When Dr. Hillman's team first introduced SCAPE (swept confocally aligned planar excitation) microscopy four years ago, their approach challenged assumptions about how to create an image of living tissues at high speeds.

"Most microscopes that image living samples scan a small spot of laser light around the sample, but the point-scanning approach is slow, giving only a short time to see each spot," said Venkatakaushik Voleti, Ph.D., the paper's first author who developed SCAPE 2.0 as a doctoral candidate in Dr. Hillman's lab. "Our system uses an oblique, or angled, sheet of light to illuminate an entire plane within the sample, and then sweeps this light sheet across the sample to form a 3-D image."

SCAPE 2.0 captures blood flow (purple) in the heart of a developing zebrafish embryo. Credit: Hillman lab/Columbia's Zuckerman Institute

Although imaging samples using sheets of light date back more 100 years, SCAPE's ingenuity lies in the way that it rapidly moves the light sheet and focuses the image of this sheet back to a stationary camera using a single moving mirror—making it lightning fast and surprisingly simple. In addition, SCAPE is gentle on living samples because it uses only a fraction of the light that point-scanning microscopes would need to get images at comparable speeds. SCAPE achieves all this through a single, stationary objective lens, opening up space for a wide array of samples compared to conventional light-sheet microscopes that require complex sample chambers surrounded by many lenses.

"People are often surprised at how compact, simple and easy to use SCAPE is," said Dr. Hillman, who routinely drives SCAPE systems around in the trunk of her car to give researchers hands-on demonstrations.

Dr. Hillman's team is working to help scientists all over the world use SCAPE for their own research, inviting scientists to her lab at Columbia's Zuckerman Institute, or helping them to build their own systems, thanks to grant support from the National Institutes of Health BRAIN Initiative. Dr. Hillman is also working with Leica Microsystems, who have licensed SCAPE and are currently developing a commercial version of the system.

Dr. Hillman attributes broad interest in SCAPE 2.0 to recent major advances in fluorescent labeling, which lets scientists make specific cells in an animal glow different colors, and can even make cells flash on and off when they are signaling to each other. She also notes the growing impact of small, near-transparent animals such a C. elegans worms, zebrafish embryos and fruit flies which can be observed during natural behaviors, or be modified to recapitulate human diseases. SCAPE 2.0 is perfectly positioned to capture the symphony of cellular events, movements and responses playing out in these living systems.

"In our new paper, we show how SCAPE 2.0 can track individual neurons firing in a whole animal as it crawls around, giving us a new window into how neural activity guides behavior," said Dr. Hillman, who is also professor of biomedical engineering at Columbia Engineering.

SCAPE 2.0 captures neurons inside a whole mouse brain. Credit: Hillman lab/Columbia's Zuckerman Institute

Despite being inspired by neuroscience needs, Dr. Hillman notes that many of the aforementioned labeling methods and animal models are now transforming other research areas, letting scientists explore how cancerous tumor cells signal to each other, how immune cells find their targets or how the heart and cardiovascular system are affected by drugs and disease.

"It is really exciting to see techniques, stimulated by the BRAIN initiative, having ever broader impacts on science and medicine" said Dr. Hillman.

Recognizing this opportunity, Dr. Hillman partnered with pediatric cardiologist Kimara Targoff, MD, to put SCAPE 2.0 to work in studying how the heart develops. Dr. Targoff's lab uses zebrafish as an animal model to decipher the genetic mutations that can cause heart malformations in the embryo. Understanding how these mutations lead to disease could inform treatments for children living with congenital heart disease.

"The problem with imaging the beating heart is that it beats fast, changing its shape as blood flows through it in a wide range of directions," said Dr. Targoff. who is an assistant professor of pediatrics at Columbia's Vagelos College of Physicians and Surgeons and a co-author of today's paper. "With SCAPE 2.0, we can image the zebrafish embryo's beating heart in 3-D and in real-time, allowing us to see how calcium signals sent between heart cells cause the heart wall to contract, or how red blood cells flow through the heart's valves beat after beat. Using this knowledge, we can track how a particular genetic mutation affects normal heart development in an environment that most closely recapitulates the heart's natural state."

The desire to follow a single red blood cell as it travels through the beating heart was a driving force behind pushing the speed limits of SCAPE 2.0.

SCAPE 2.0 captures movement and neural activity of a freely moving *C. elegans* worm. Credit: Hillman lab/Columbia's Zuckerman Institute

To reach these unprecedented speeds, Dr. Hillman's team worked closely with Lambert Instruments, leveraging the company's ultra-fast HiCAM Fluo camera. This camera was used to capture images at more than 18,000 frames per second in the zebrafish embryo's beating heart. This new configuration opened the door to recording individual neurons firing in a freely moving C. elegans worms, giving the first view of an animal's complete nervous system in action. SCAPE 2.0's other upgrades include improved light efficiency, a larger field of view and much improved spatial resolution.

SCAPE 2.0's improved resolution also enabled the team to image samples created using tissue clearing and tissue expansion. These methods let scientists see structures and connections deep inside intact samples, from whole mouse brains to tumors and human biopsies. Although these samples are not alive, they are very large and take a long time to image using standard microscopes. Today's paper demonstrates that SCAPE 2.0 could image these types of samples at record-breaking speeds.

Dr. Hillman and her team are continuing to develop and improve SCAPE to further expand its utility, while working with an ever-growing group of collaborators, from Zuckerman Institute neuroscientists to Columbia volcanologist Einat Lev Ph.D., who is using SCAPE to image the way gas bubbles form during volcanic eruptions.

Dr. Hillman's team is also developing a miniaturized version of SCAPE for medical use, to quickly distinguish between healthy and diseased cells within a patient's body, giving doctors a new way to guide how to perform complex surgeries in the operating room.

"The limitations of tools and techniques often constrain what scientists think they can study," said Dr. Hillman, who is also professor of radiology at Columbia's Vagelos College of Physicians and Surgeons. "SCAPE 2.0 opens up a new landscape of things that we can see. I hope our new results will inspire scientists to think of what new questions can be asked, and what new avenues of scientific discovery we can explore next."

This paper is titled "Real-time volumetric microscopy of in-vivo dynamics and large-scale samples with SCAPE 2.0." [28]

Scientists open up new world for biologics—inside the cell

The vast majority of top-selling drugs are biologics—also known as proteins. Proteins are used today to treat many debilitating diseases, including arthritis, Crohn's disease, and several forms of cancer. They have helped to improve the lives of many millions of people worldwide. And proteins have the potential to help many millions more, but they can't, because most are unable to pass through the cell boundary to reach the regions of the cell where they are needed: the cell interior.

"It's been known for decades that proteins can be internalized from the cell boundary into cellular compartments known as endosomes," said Yale's Alanna Schepartz, Sterling Professor of Chemistry and professor of molecular, cellular & developmental biology. "Getting these molecules out of endosomes and into the cell interior was the big problem."

Schepartz and colleagues here at Yale now report the identity of a molecular key that effectively unlocks the endosome, allowing the selective passage into the cell interior of potentially life-saving protein drugs. This discovery was reported in the journal *Proceedings of the National Academy of Science*.

Schepartz—working with graduate students Angela Steinauer, Jonathan LaRochelle, and Susan Knox, postdoctoral associate Rebecca Wissner, and undergraduate Samuel Berry—reports that the endosome unlocking key is the homotypic fusion and vacuole protein sorting (HOPS) complex—a multi-protein assembly that tethers certain endosomes together to allow them to fuse. When the HOPS complex is functional, protein therapeutics escape from endosomes. When it is not functional, they remain trapped within.

The discovery that protein therapeutics can hijack the HOPS complex to gain access to the cell interior should help scientists design therapeutic proteins to treat diseases that are not adequately treated using other approaches, Schepartz said. [27]

Strength in weakness: Fragile DNA regions key to vertebrate evolution

DNA regions susceptible to breakage and loss are genetic hot spots for important evolutionary changes, according to a Stanford study. The findings may lead to new understanding of human evolution.

Regions of DNA susceptible to deletion during replication may have allowed vertebrates to successfully adapt to rapidly changing environmental conditions during evolution, according to a study by researchers at the Stanford University School of Medicine.

The research suggests that some critical evolutionary changes are likely to have occurred in leaps and bounds through the abrupt loss of stretches of DNA, rather than through the slow accumulation and additive effects of many small mutations.

The researchers, who studied a tiny fish called the threespine stickleback, found that such "fragile" DNA regions create genetic hot spots that mutate much more rapidly, and dramatically, than neighboring sequences. The resulting changes can help an organism vault far ahead of its peers in the evolutionary arms race.

Although similar findings have been described in bacteria, this is one of the first studies to show that the same process has occurred in vertebrates to create dramatic changes in body structure. It also addresses a long-standing mystery in evolutionary biology.

"There is a lot of evidence that the same genes across different populations or species are often responsible for similar evolutionary changes," said David Kingsley, Ph.D., professor of developmental biology. "What hasn't been clear is why this is happening. This study describes at a biochemical level, down to the atoms and sequences in DNA, how a particular type of mutation can arise repeatedly, which then contributes to a complex skeletal trait evolving over and over again in wild fish species. It's a great example of how DNA fragility can sometimes contribute to favorable traits rather than diseases in natural populations, and it may give us important insights into the process of human evolution."

Kingsley, a Howard Hughes Medical Institute investigator, is the senior author of the study, which was published Jan. 4 in *Science*. Graduate student Kathleen Xie is the lead author of the work.

Large changes, large effects

Many mutations involve a change in just a single nucleotide, or letter, of DNA. Few of these "point" mutations will confer an evolutionary advantage on their own. Instead, significant change often requires the gradual accumulation of several such mutations. In contrast, sudden, large changes in the genome can have large effects—changing body structure through skeletal modifications or affecting metabolism or brain function, for example. Often, these changes are deleterious, decreasing the chances of an animal's survival. Occasionally, however, the changes are advantageous.

When the last Ice Age ended, about 10,000 years ago, pockets of migratory ocean threespine sticklebacks colonized newly formed lakes and streams in coastal regions, and then evolved independently in response to their new local environments. As a result, many of these populations show significant differences in body structure. Marine sticklebacks, for example, have a hind fin with a large spine projecting down from their pelvic structure. In contrast, dozens of freshwater populations have lost that hind fin; its absence likely reduces their need for calcium and chances of being nabbed and eaten by hungry insects.

Previous studies in the Kingsley laboratory have identified the loss of a specific DNA regulatory region, called the Pel enhancer, as the repeated cause of the missing hind fins in many populations of the freshwater fish. The Pel enhancer drives the expression of a protein necessary to trigger hind fin development. In this study, Xie used marine stickleback DNA to investigate the Pel region that is missing in its freshwater brethren to learn why that region was particularly susceptible to loss.

Xie found that the DNA sequence of the Pel region is unusual in several ways. Unlike surrounding regions, which exhibit the normal, more-stable helical twist associated with most DNA, the Pel enhancer region that was lost formed an alternate DNA structure predicted to be highly flexible and likely to be unstable during DNA replication. The sequence also contains long strings of repeated pairs of nucleotides, like a kind of genetic stutter. Previous studies in bacteria, mice and humans have indicated that these repeats are often associated with deletions of stretches of DNA.

More frequent chromosome breaking

When Xie tested the stability of the missing Pel region by inserting it into artificial yeast chromosomes, she found that the chromosome broke about 25 to 50 times more frequently than typical DNA sequences. When Xie and her collaborators then tested similar DNA sequences in mammalian cells, they observed that the key dinucleotide repeat sequence often led to the deletion of sections of DNA more than 100 nucleotides long.

The increase in the rate of chromosome breakage observed by Xie, coupled with the likelihood that this damage causes deletions of entire sections of DNA, may have been a key factor in allowing the prominent hind fin skeletal trait to emerge over and over again in many different young stickleback populations. Elevated mutation rates may play a similar role when advantageous traits arise in other organisms, the scientists believe.

"Many vertebrates, including early humans, are dealing with a small population size and relatively long generation times," said Kingsley, who is the Rudy J. and Daphne Donohue Munzer Professor in the School of Medicine. "There aren't that many generations available in which to evolve new, potentially advantageous traits. Under these conditions, it may be particularly important for mutations to occur at elevated rates, and to have sweeping effects."

When the researchers investigated known instances of adaptive changes in humans, they found that about half were due to mutations that also arise at elevated rates compared with more typical DNA letter changes.

"What we're learning is that 'arrival of the fittest,' or the relative speed with which a potentially favorable mutation arises, can sometimes be as important as 'survival of the fittest,'" Kingsley said. "The mutation process itself has an important effect on the outcome, and the arrival of the mutation interacts with its effect on the fitness of the organism to bring about major changes in vertebrate evolution." [26]

Record for decoding the longest DNA sequence is impressive – here's what to expect next

Like other professionals, scientists like to be the best at what they do, but they also like to have fun in their job. And in 2018, my colleagues managed just that in claiming a record for decoding the world's longest DNA sequence.

For the English scientists involved, perhaps the most important fact is that their DNA read was about twice as long as the previous record, held by their Australian rivals. The glory of gaining the record is the result of an Ashes-style competition to produce ever longer DNA sequences. The record has exchanged hands several times over the past year, but with this new sequence the trophy seems to be safe in the UK – at least for the moment.

But as exciting as it is to win, the most inspiring thing about this record is the science and the future applications that could become available thanks to our ability to decode ever longer sequences.

Jigsaw jumble

The technology that enables scientists to read runs of DNA sequences has come a long way since the millennium-era race to decode the first human genome. There are lots of ways you can now read DNA, but the problem is that many animal and plant genomes are often billions of base pairs (pairs of DNA building blocks known as A, T, G and C) and so making sense of them is tricky. People have used different methods in the past, but essentially what they do is chop the DNA up into small parts, read each piece and then try to assemble the results back together, a bit like what you would do with a jigsaw puzzle.

Putting the DNA pieces together in the correct order is therefore a major obstacle when it comes to DNA sequencing. This is obviously harder the more pieces you have, especially if they are short and very similar to each other.

Being able to continuously read ever longer pieces – eventually an entire chromosome in one go – would therefore have a huge impact on science and innovation. In my own research, I am interested in finding the genes that determine the left and right sides of animal bodies. And while I can fairly straightforwardly read the genome of snails like "Jeremy" – which has a shell that coils left instead of right – it is very difficult to make sense of it, because the order is almost completely jumbled.

My colleague, Matt Loose, also at the University of Nottingham, led the team behind the new world record , which read 2.3m bases of human DNA in one go. Putting that in context, in the most common form of DNA sequencing only a few hundred bases are read at once, creating millions of pieces to put together. If a few hundred bases are equivalent to once around a grand prix track, then a 2.3m base pair read is twice around the circumference of the Earth. In comparison, the main rival Australian team at the Kinghorn Centre for Clinical Genomics is still some way behind. They have still to get once around the world.

Long reads and small holes

The key technology that is pushing these advances is a very small hole, called a nanopore. DNA bases, or letters, are ratcheted through the nanopore, and the order can be read by monitoring disruptions to an electrical current put through it. If the nanopore were scaled up to the size of a thumb and forefinger pinch, then the scientists would have threaded a rope of over seven kilometres in lenght through the hole, without it becoming tangled or breaking. In comparison, a more typical DNA sequence would be about half a metre in length.

In theory, sequencing a whole chromosome in one go should be possible using this method. This would then avoid the problem of trying to assemble a massive jigsaw. But natural breaks in each chromosome mean that this may not be possible. Whatever the actual limit of read length, the new methods are already being used to more quickly and cost effectively identify pathogens in disease outbreaks. The same methods are also being used to rapidly and accurately characterise the genome rearrangements that take place as cells progress to become cancerous.

A recent proposal to sequence the genomes of 1.5m known animal, plant and fungal species will also benefit from these new long-read technologies. In future, the methods will help enable truly personalised medicine – having our individual genomes sequenced. In the UK, about 85,000 people have already had their entire genetic code read, with an ambition to sequence a million

genomes in the next five years. For the moment, most of this is being done using older, short-read technology, which is still cheaper but misses an important layer of structural information.

In my own laboratory, I plan to use the same methods to find the genes that sometimes enable snails to exist in two mirror-image versions of themselves. The same methods may also be used to further unravel the genetics of human diseases, especially those that are due to structural rearrangements and changes in gene copy number.

The scientists behind the record believe that their record might last for a year or so. And the competition is expanding to include other competitors – just in the last month, a new entrant from the Netherlands came within a whisker of beating the UK record.

But given what's at stake, fierce competition can only be a good thing. [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*.

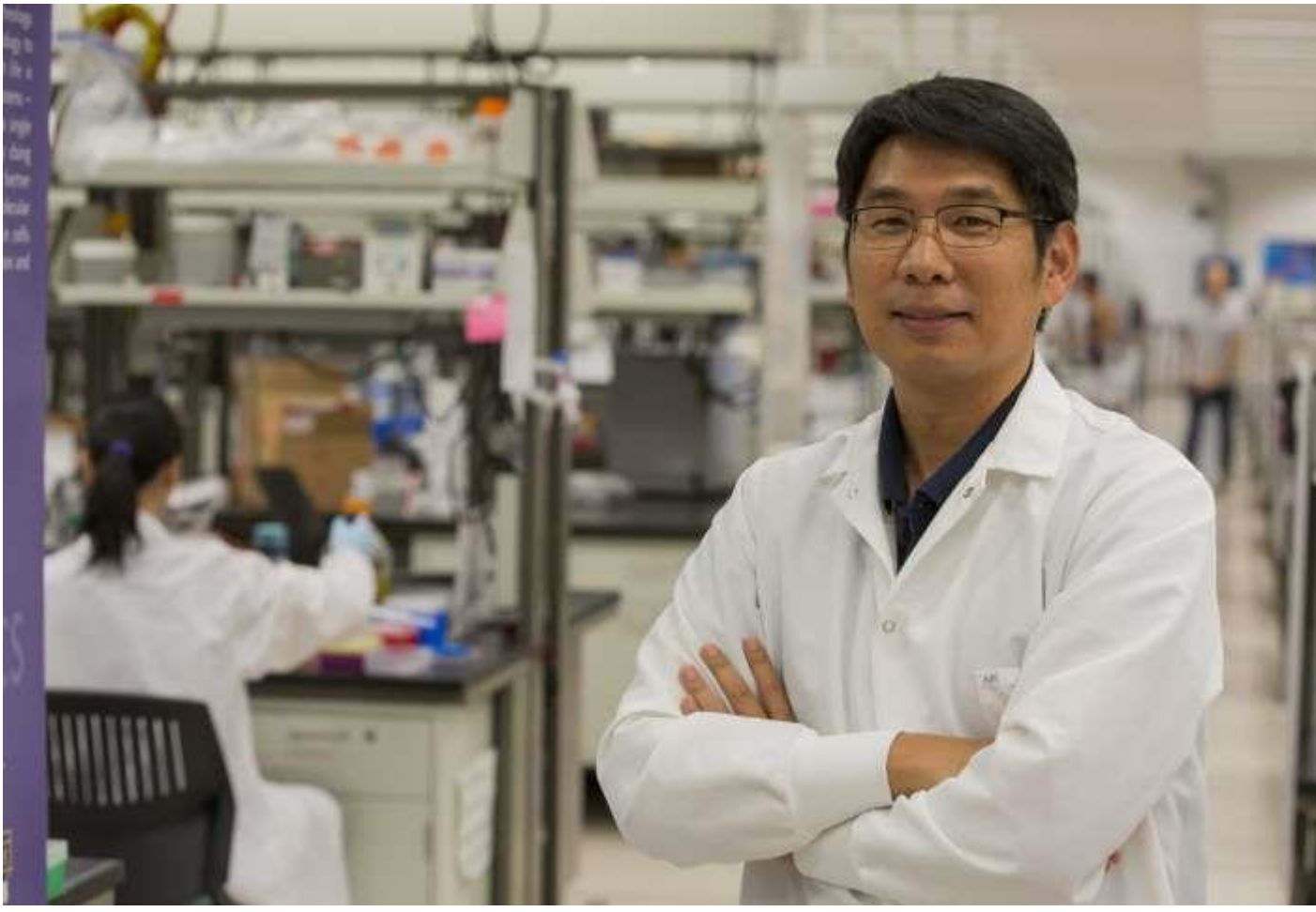
Building with DNA

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*.

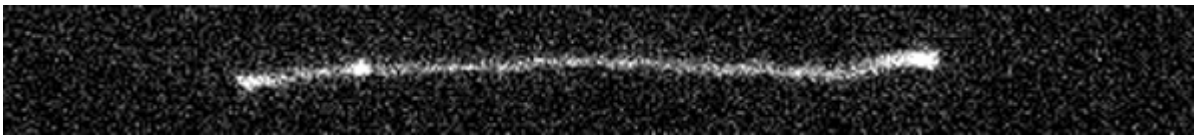
Knots in motion

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.

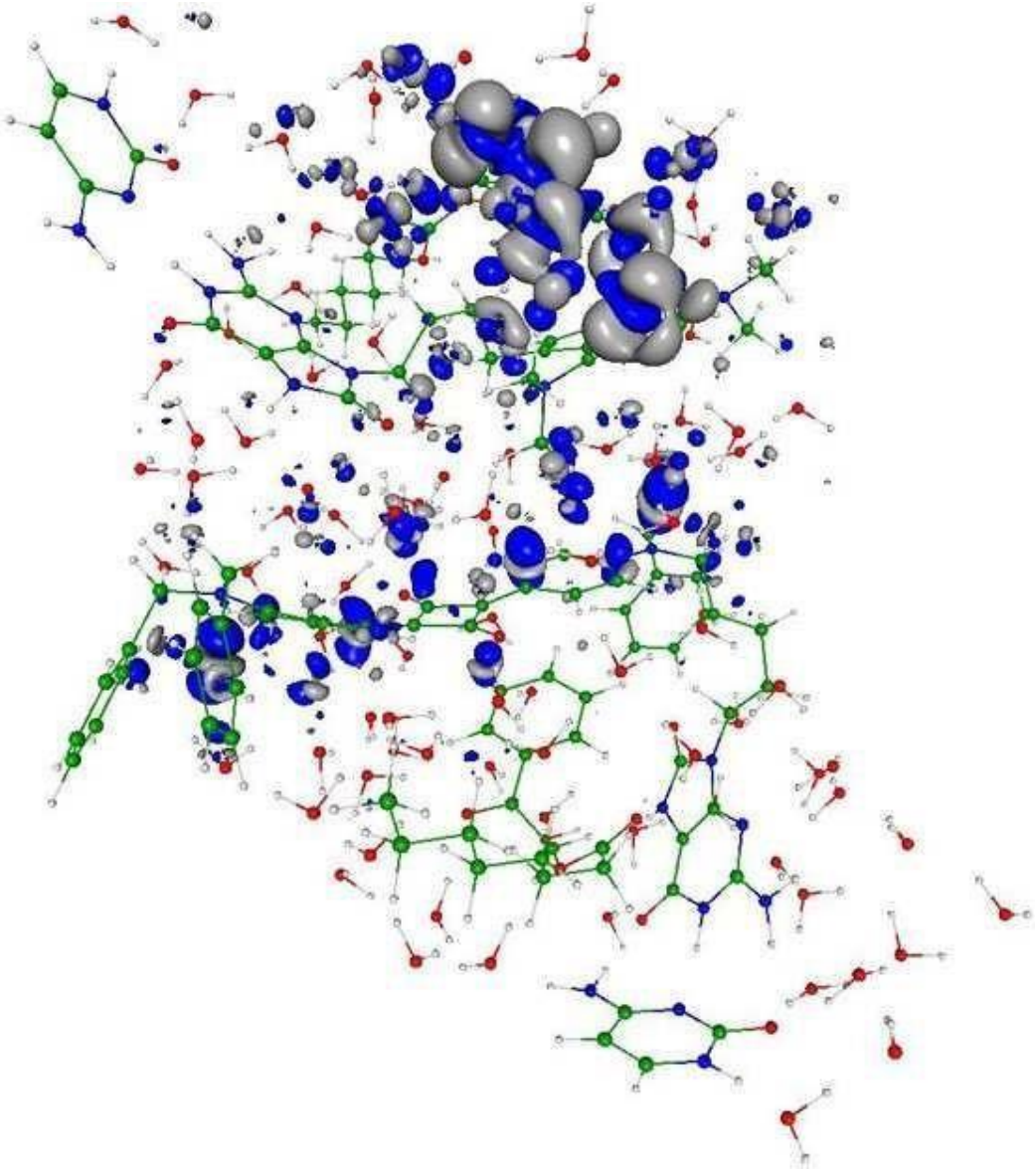
Our discovered phenomenon of the quantum entanglement in the prebiotic systems enhance the photosynthesis in the proposed systems because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states (Tamulis A, Grigalavicius M, Baltrusaitis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