

# Microfluidic Monolith Device

*Emerging single-cell diagnostics rely on the potential to rapidly and efficiently isolate bacteria from complex biological matrices. [32]*

*A particularly aggressive, metastasizing form of cancer, HER2-positive breast cancer, may be treated with nanoscopic particles "imprinted" with specific binding sites for the receptor molecule HER2. [31]*

*UNC School of Medicine scientists created a powerful new "directed evolution" technique for the rapid development of scientific tools and new treatments for many diseases. [30]*

*Scientists have been aware of this 'length problem' for a long time, but it was largely overlooked for most of the twentieth century. [29]*

*Such emulsions are similar to the mixture that forms when you shake an oil-and-vinegar salad dressing, but with much smaller droplets. [28]*

*Russian scientists found that nanocrystal tungsten trioxide can be used instead of barium for X-ray examinations and also in cancer treatment. [27]*

*Medical advancements can come at a physical cost. Often following diagnosis and treatment for cancer and other diseases, patients' organs and cells can remain healed but damaged from the medical condition. [26]*

*Tao Sun and colleagues from [Beijing Institute of Technology](#) have described a novel method to incorporate synthetic microfibres containing magnetic beads into self-assembled tissue micro-rings. [25]*

*By testing a variety of gold nanoparticles, researchers at the University of Geneva (UNIGE) and collaborators are providing first evidence of their impact upon human B lymphocytes—the immune cells responsible for antibody production. [24]*

*Researchers at Helmholtz Zentrum Muenchen have developed a method to visualize gene expression of cells with an electron microscope. [23]*

*Researchers at Oregon State University have developed an improved technique for using magnetic nanoclusters to kill hard-to-reach tumors. [22]*

*MIT researchers have now come up with a novel way to prevent fibrosis from occurring, by incorporating a crystallized immunosuppressant drug into devices. [21]*

*In a surprising marriage of science and art, researchers at MIT have developed a system for converting the molecular structures of proteins, the basic building blocks of all living beings, into audible sound that resembles musical passages. [20]*

*Inspired by ideas from the physics of phase transitions and polymer physics, researchers in the Divisions of Physical and Biological Sciences at UC San Diego set out specifically to determine the organization of DNA inside the nucleus of a living cell. [19]*

*Scientists from the National Institute of Standards and Technology (NIST) and the University of Maryland are using neutrons at Oak Ridge National Laboratory (ORNL) to capture new information about DNA and RNA molecules and enable more accurate computer simulations of how they interact with everything from proteins to viruses. [18]*

*The DNA molecules are chiral, which means they can exist in two forms which are mirror images, like a left and right hand. The phenomenon was dubbed "chiral induced spin selectivity" (CISS), and over the last few years, several experiments were published allegedly showing this CISS effect, even in electronic devices. [17]*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Author: George Rajna

## Preface

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

The human body is a constant flux of thousands of chemical/biological interactions and processes connecting molecules, cells, organs, and fluids, throughout the brain, body, and nervous system. Up until recently it was thought that all these interactions operated in a linear sequence, passing on information much like a runner passing the baton to the next runner. However, the latest findings in quantum biology and biophysics have discovered that there is in fact a tremendous degree of coherence within all living systems. [5]

Quantum entanglement is a physical phenomenon that occurs when pairs or groups of particles are generated or interact in ways such that the quantum state of each particle cannot be described independently – instead, a quantum state may be given for the system as a whole. [4]

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

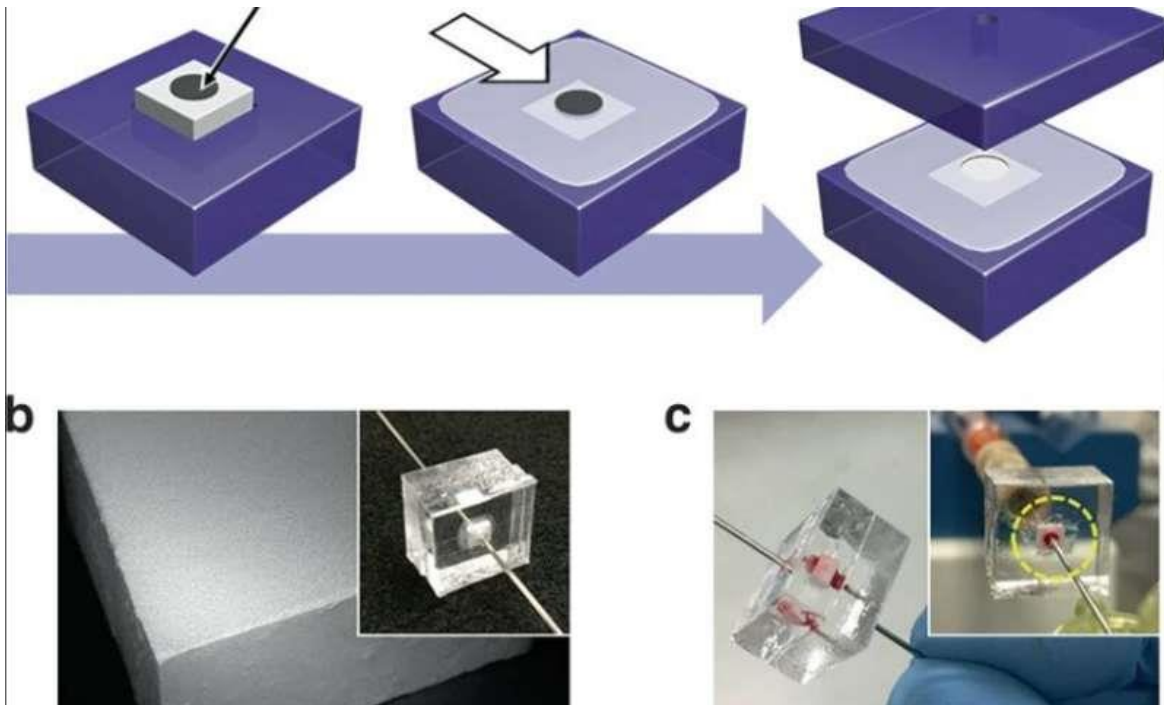
## Isolating intact bacteria from blood using a microfluidic monolith device

Emerging single-cell diagnostics rely on the potential to rapidly and efficiently isolate bacteria from complex biological matrices. In a recent study now published in *Microsystems and Nanoengineering*, Jung Y. Han and colleagues at the interdisciplinary Departments of Mechanical Engineering, Chemical Biomolecular Engineering and Bioengineering in the U.S. developed a device to isolate intact and viable bacteria from whole blood using a microfluidic, porous silica monolith. They achieved mechanical hemolysis while providing passage of intact and viable bacteria through the monoliths for size-based bacterial isolation and selective lysis. Han et al. described a process to synthesize large quantities of discrete capillary-bound monolith elements and millimeter-scale monolith bricks to integrate into microfluidic chips.

They explored the impact of monolithic morphology, geometry and flow conditions on cell lysis and flow regimes that allowed selective cell lysis and selective passage of multiple gram negative and gram positive [bacteria](#). The technique employed by Han et al. allowed rapid sample preparation and bacterial analysis when combined with [single-cell Raman spectrometry](#). The work provides unique sample preparation steps to support rapid and culture-free bacterial analysis for applications in [point-of-care](#) biomedical devices.



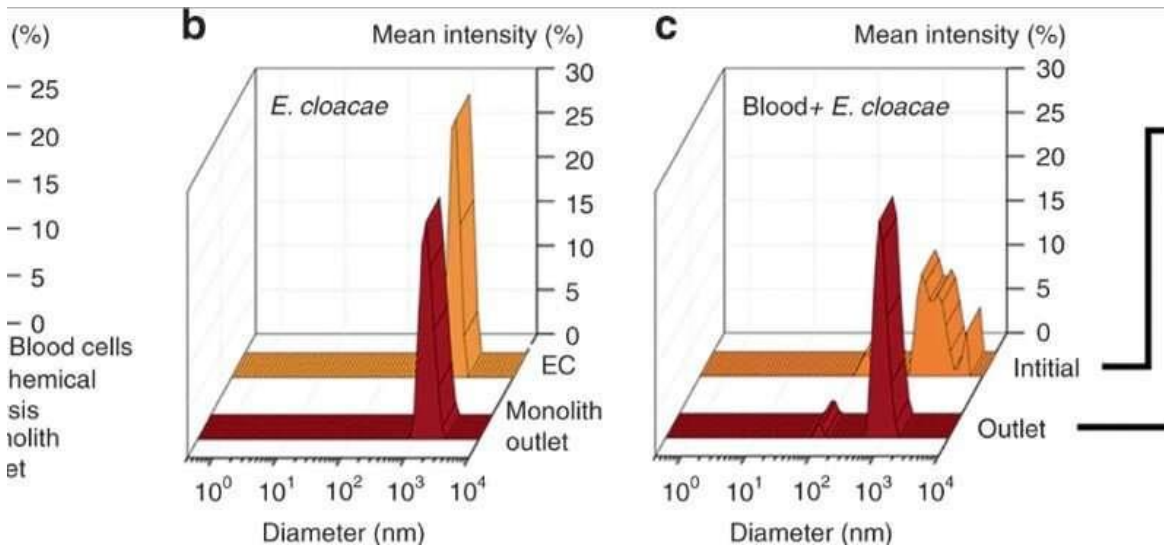
Bacteria in blood can lead to sepsis, infection of tissues and other serious medical conditions, requiring early identification of blood-borne bacteria for effective treatment. The ability to identify bacteria rapidly using point-of-care diagnostics can greatly enhance clinical potential for optimal treatment during early-stage infection. The [existing gold standard for bacterial characterization](#) is based on phenotypic cell culture analysis and requires at least 24 hours to collect samples for culture and analysis in a diagnostic and clinical microbiology lab. The existing technique is robust and inexpensive but cannot generate timely results to guide the initial stages of treatment.



(a) Integration of a silica monolith brick into a thermoplastic chip. A circular tape is placed on a monolith inserted into a COP substrate, and solvated COP is applied to the exposed surface. After partial drying, the tape is removed, the device is enclosed by another COP substrate, and fluid ports are inserted into holes that provide a flow path through the monolith. (b) SEM image of a monolith brick cut by wafer dicing saw. (c) Image of a device during whole blood perfusion. Credit: Microsystems & Nanoengineering, doi: 10.1038/s41378-019-0063-4

In the present work, Han et al. explored microfluidic devices integrated with porous silica monoliths as simple flow-through elements for selective blood cell analysis and the intact isolation of bacteria. Monoliths are highly porous materials composed of [open cell morphology with twisting paths](#) of fluid flow. Scientists can control monolithic pore morphology via high mechanical surface stress during cell perfusion for mechanical hemolysis of blood [cells](#), while allowing intact and viable bacteria to travel the winding flow paths for their culture-free isolation. Han et al. used the approach of selective passage for bacteria in whole blood under flow conditions for gram positive and gram-negative species, despite [differences of the bacterial strains](#). The technique of high-throughput selective monolith lysis combined with powerful analytical methods such as [Raman](#)

[spectroscopy](#) can allow culture-free analysis of bacteria in whole blood at the level of the single cell.

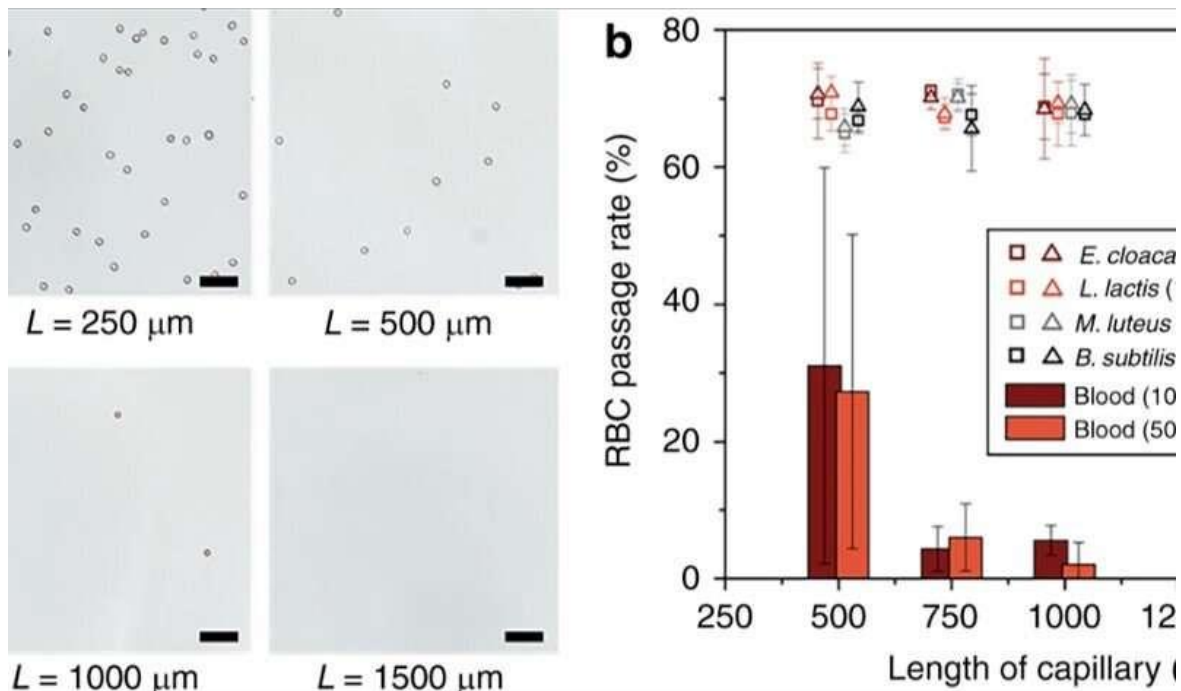


DLS measurement of (a) initial 25× diluted blood, chemically lysed blood, and blood lysed by perfusion through the monolith device, revealing a significant reduction in cell debris size for mechanical monolith lysis over chemical lysis. (b) DLS measurement of *E. cloacae* suspended in 1× PBS, and sample perfused through the monolith device, showing no change in bacteria size. (c) DLS measurement of 100× diluted blood spiked with *E. cloacae*, and sample collected from the outlet of a porous monolith. The broad peak in the inlet sample indicates a mixed population of blood cells and small bacterial cells, whereas the outlet sample showed significant reduction in large (>2 μm) cells, as confirmed in the optical images. Scale bars = 25 μm. Credit: Microsystems & Nanoengineering, doi: 10.1038/s41378-019-0063-4

Han et al. modified [previously reported](#) silica monolith synthesis processes, followed by hydrolysis and condensation of silica to form [silica glass at low temperatures](#). To prepare the silica monolith, the scientists used a precursor solution composed of alkyl silicates, [polyethylene glycol \(PEG\)](#) as a porogen, urea as a source of hydroxyl ions to minimize heterogeneity and acetic acid. When they optimized the synthetic process, the resulting monoliths were homogenous and well-anchored to the silica capillary walls. The scientists measured the thickness of the final skeletal monolith structure and calculated its permeability using [high-performance liquid chromatography](#) to control experimental conditions. To minimize intrinsic variation, Han et al. cut the resulting capillary tubes into 5 cm long segments to test permeability before use.

They then developed two complementary methods for low and high-throughput operation to integrate silica monoliths into microfluidic systems. To allow low throughput operation, the scientists embedded monolith-containing capillary segments within thermoplastic microfluidic chips to protect the monolith during integration. For high throughput-selective lysis they used monoliths with larger cross-sectional areas within the microfluidic devices. The complete method of fabrication yielded excellent reliability for leak-free operation during whole blood perfusion.

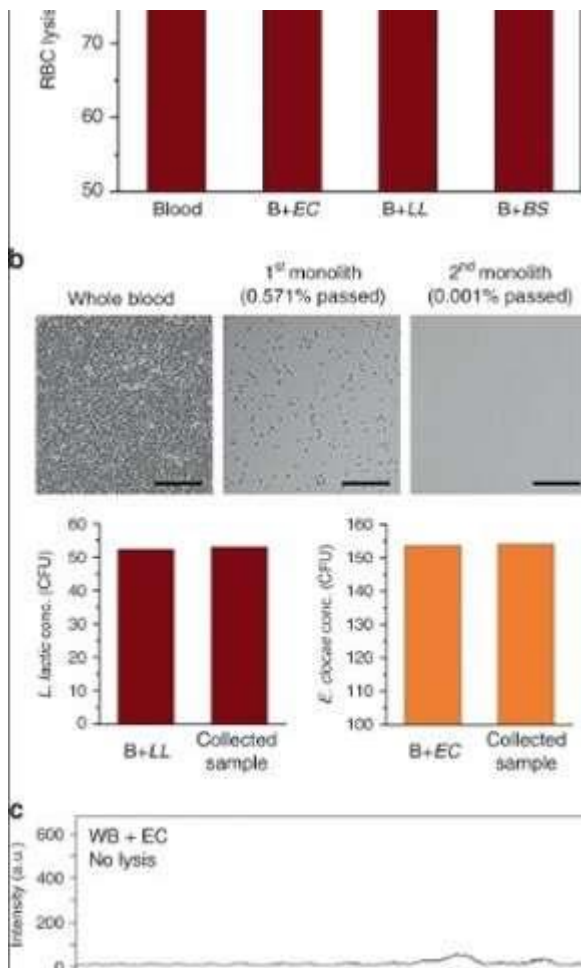




(a) Monolith length dependence of RBC hemolysis. Totally, 50 $\times$  diluted blood in 1 $\times$  PBS was perfused through capillary monoliths of various lengths at a flow rate of 10  $\mu\text{L}/\text{min}$ . (b) Passage rate of RBC and viable bacteria at different flow rates and lengths of monolith-containing capillary. Scale bars = 50  $\mu\text{m}$ . Error bars are  $\pm 1\text{SD}$ . Contrast of optical images was adjusted for visibility. Credit: Microsystems & Nanoengineering, doi: 10.1038/s41378-019-0063-4

As proof-of-principle, Han et al. selected *Enterobacter cloacae* (gram-negative, rod shaped bacteria) to explore their efficacy of passage, alongside three gram-positive bacteria; *Lactococcus lactis*, *Micrococcus luteus* and *Bacillus subtilis*. During the experiments, they perfused bacterial solutions through the microfluidic monoliths with varying geometry and flow conditions to test the passage of bacteria and blood cell lysis using dynamic light scattering (DLS). For instance, the perfusion of purified *E. cloacae* through the monolith did not yield discernable changes in the DLS peaks, indicating the intact passage of bacteria.

The scientists showed the effect of the length of the porous monolith device on the efficiency of red blood cell lysis (RBC). The results indicated that RBC lysis efficiency increased significantly for monolith lengths above 1 mm. Han et al. also studied the fate of white blood cells (WBCs) during operation of the monolith device, the cells could not pass through the monolith without being lysed similar to RBCs. Technically, RBCs deformed to a discoid shape to pass through the monolith, which caused significantly increased membrane tension to result in RBC lysis. Comparatively, bacterial cells had similar dimensions to the monolith pores and therefore required less cell wall expansion for successful passage without rupture. The scientists optimized the parameters of the device for diverse bacteria to tolerate high levels of membrane stress without rupture. Further developments ensured the intact passage of bacteria without degradation and with viability.



(a) RBC lysis efficiency of whole blood in high-throughput devices following perfusion at 10  $\mu\text{L}/\text{min}$  (EC *E. cloacae*, LL *L. lactis*, BS *B. subtilis*). Error bars are  $\pm\text{SD}$ .  $N = 3$  for blood and B + EC, and  $N = 2$  for B + LL, B + BS. (b) Blood cell lysis and bacterial separation following serial operation using two monoliths. Surfaces were passivated with BSA/Tween 20. Over 99.999% RBC lysis was obtained while preserving viability of *L. lactis* and *E. cloacae*. Scale bars = 100  $\mu\text{m}$ . c Raman spectra of whole blood spiked with *E. cloacae* (upper) before and (under) after processing through porous silica monolith. Credit: Microsystems & Nanoengineering, doi: 10.1038/s41378-019-0063-4.

For high-throughput bacterial passage, the scientists diluted the blood in the capillary devices. However, as an alternative, they could also extend the capacity of monoliths for whole blood lysis. The devices processed more than 400  $\mu\text{L}$  of whole blood spiked with bacteria before exhibiting a significant increase in back pressure, due to clogging as a result of cell lysis and also due to intact leukocytes (WBCs) trapped within the porous matrix.

To locate target bacteria, Han et al. obtained a sample deposited on to a glass slide, after it passed through the monolith-process. They conducted single-cell Raman analysis by manually scanning the optical probe across the sample. They expect the use of selective lysis technology, coupled to confocal Raman microscopy in the future to improve the process of detecting bacterial strains of interest at low concentrations in a defined location of interest.

In this way, Jung Y. Han and colleagues developed a microfluidic [monolith](#) to efficiently isolate intact bacteria with wide-ranging [theranostic](#), point-of-care potential for clinical applications. They envision the union of confocal Raman microscopy tools that are currently largely confined to the research lab with emerging miniaturized and handheld systems to pave the way towards rapid and portable point-of-care devices. [32]

## **Inhibition of HER2 on tumor cells by molecularly imprinted nanoparticles**

A particularly aggressive, metastasizing form of cancer, HER2-positive breast cancer, may be treated with nanoscopic particles "imprinted" with specific binding sites for the receptor molecule HER2. As reported by Chinese researchers in the journal *Angewandte Chemie*, the selective binding of the nanoparticles to HER2 significantly inhibits multiplication of the tumor cells.

Breast cancer is the most common form of cancer in women and one of the leading causes of death. About 20 to 30 percent of [breast cancer](#) cases involve the very poorly treatable HER2-positive variety. HER2 stands for Human Epidermal Growth Factor Receptor 2, a protein that recognizes and binds to a specific growth factor. HER2 spans across the [cell membrane](#): one part protrudes into the interior of the cell; the other is on the [cell surface](#). As soon as a growth factor docks, the extracellular parts of HER2 bind into a heterodimer with a second, closely related HER, such as HER1 or HER3. This triggers a multistep signal cascade within the cell, which is critically involved in processes like cell division, metastasis, and the formation of blood vessels that supply the tumor. HER2-positive tumor [cells](#) contain significantly higher concentrations of HER2. One current therapy for early-stage HER2-positive tumors is based on binding an antibody to HER2 to block the dimerization. Researchers led by Zhen Liu at Nanjing University (China) have now developed "molecularly imprinted" biocompatible polymer nanoparticles that recognize HER2 just as specifically as an antibody in order to prevent the dimerization.

Nanoparticles can be molecularly imprinted in that—to simplify—a polymerizable mixture is polymerized into nanospheres in the presence of the (bio)molecules they are supposed to recognize later. The (bio)molecules act as a kind of stamp, leaving nanoscopic "imprints" in the spheres. These then perfectly fit the molecules they were imprinted with and bind to them specifically. In contrast to antibodies, the nanospheres are easy and inexpensive to produce and are chemically stable.

For the imprinting process, the researchers use a special method (boronate affinity controllable oriented surface imprinting) that is particularly controllable and makes it possible to imprint using chains of sugar building blocks (glycans) as templates. Many proteins contain specific "sugar chains." These are unique, like a protein fingerprint. The researchers used this kind of glycan from the extracellular end of the HER2 proteins as their "stamp." This allowed them to produce imprinted nanoparticles that specifically recognize HER2 and selectively bind to it, inhibiting the dimerization. They were thus able to significantly reduce the multiplication of tumor cells in vitro and the growth of tumors in mice. In contrast, healthy cells were essentially unaffected. [31]

## Scientists invent fast method for 'directed evolution' of molecules

UNC School of Medicine scientists created a powerful new "directed evolution" technique for the rapid development of scientific tools and new treatments for many diseases.

The scientists, whose breakthrough is reported in *Cell*, demonstrated the technique by evolving several proteins to perform precise new tasks, each time doing it in a matter of days. Existing methods of directed evolution are more laborious and time-consuming, and are typically applied in [bacterial cells](#), which limits the usefulness of this technology for evolving proteins for use in human cells.

Directed evolution is an artificial, sped up version of the evolution process in nature. The idea is to focus the evolutionary process on a single DNA sequence to make it perform a specified task. Directed evolution can be used, in principle, to make new therapeutics that work powerfully to stop diseases and have few or no side effects. The initial groundbreaking scientific work on directed evolution won the 2018 Nobel Prize in Chemistry.

"What we have developed is the most robust system yet for directed evolution in mammalian cells," said study lead author Justin English, Ph.D., a postdoctoral research associate in the Department of Pharmacology at the UNC School of Medicine.

"The scientific community has needed a tool like this for a long time", said study senior author Bryan L. Roth, MD, Ph.D., the Michael Hooker Distinguished Professor in the Department of Pharmacology at the UNC School of Medicine. "We believe our technique will accelerate research and ultimately lead to better therapeutics for people suffering with many of the diseases for which we need much better treatments."

The broad concept of directed evolution is not new. Researchers have been applying it for centuries in selecting and breeding variants of animals and plants that have desired characteristics, such as crop varieties with larger fruits. Biologists in recent decades also have used directed evolution at the molecular level in the laboratory, for example, by mutating a gene randomly until a variant appears that has a desired property. But on the whole, directed evolution methods for biological molecules have been difficult to use and limited in their application.

The new method developed by Roth, English, and colleagues is comparatively quick, easy, and versatile. It uses the Sindbis virus as the carrier of the gene to be modified. The virus with its genetic cargo can infect cells in a culture dish and mutate quite rapidly. The researchers set up conditions so that the only mutant genes to thrive are the ones encoding proteins capable of accomplishing a desired function within the cells, such as activating a certain receptor, or switching on certain genes. Because the system works in [mammalian cells](#), it can be used to evolve new human, mouse, or other mammalian proteins that would be burdensome or impossible to generate with traditional bacterial cell-based methods.

English and his colleagues call the new system "VEGAS" for Viral Evolution of Genetically Actuating Sequences. In an initial demonstration, Roth's lab modified a protein called a tetracycline transactivator (tTA), which works as a switch to activate genes and is a standard tool used in biology

experiments. Normally tTA stops working if it encounters the antibiotic tetracycline or closely related doxycycline, but the researchers evolved a new version with 22 mutations that allows tTA to keep working despite very high levels of doxycycline. The process took just seven days.

"To get a sense of how efficient that is, consider that a previously reported mammalian directed evolution method applied to the tetracycline transactivator took four months to yield just two mutations that conferred only partial insensitivity to doxycycline," English said.

The scientists next applied VEGAS to a common type of cellular receptor called a G protein-coupled-receptor (GPCR). There are hundreds of different GPCRs on [human cells](#), and many are targeted by modern drugs to treat a wide variety of conditions. Precisely how a given GPCR changes shape when it switches from being inactive to active is of great interest to researchers trying to create more precise treatments. English and colleagues used VEGAS to quickly mutate a little-studied GPCR called MRGPRX2 so that it would stay in an always-active state.

"Identifying the mutations that occurred during this rapid evolution helps us understand for the first time the key regions in the receptor protein involved in the transition to an [active state](#)," English said.

In a final demonstration, the team showed the potential of VEGAS to guide drug development more directly. They used VEGAS to rapidly evolve small [biological molecules](#) called nanobodies that could activate different GPCRs—including serotonin and dopamine receptors, which are found on brain [cells](#) and are targeted by many psychiatric drugs.

The team is now using VEGAS in an effort to develop highly efficient gene-editing tools, potentially for curing genetic diseases, and to engineer nanobodies that can neutralize cancer-causing genes. [30]

## Physicists develop model that describes length growth in biological systems

"Grandmother, why do you have such big ears?" is one of the most well-known questions in literature, posed of course by Red Riding Hood as she hesitantly observes the wolf dressed in her Grandmother's clothes. Had Red Riding Hood been a physicist, she might well have asked: "Grandmother, why are your two ears exactly the same length?"

Scientists have been aware of this 'length problem' for a long time, but it was largely overlooked for most of the twentieth century. Robert B. Laughlin, who won the Nobel Prize for physics in 1998, wrote an interesting paper on the topic. In "Critical waves and the length problem of biology," Laughlin states that for a long period of time no significant progress was made into understanding how organisms regulate their length. He proposed that living things can size themselves and that once they have acquired this information, they can respond accordingly—for example, by ceasing to grow their arms or legs once these limbs have reached their 'desired' size.

Physicists at Saarland University have picked up on these ideas and have developed a mathematical model that can be used to describe how biological systems can measure their length. Graduate

student, Frederic Folz, who addressed the problem in his Master's thesis, has now published the results in the highly ranked journal *Physical Review E* in a paper co-authored by Giovanna Morigi, Professor of Theoretical Quantum Physics, Karsten Kruse, Professor of Theoretical Biological Physics, and Lukas Wettmann, a Ph.D. student in Kruse's group.

The scientists chose to study axons as their [model system](#). Axons are key components of nerve cells ([neurons](#)). Axons act as a link between nerve cells and enable electrical signals to pass from one neuron to another. As the length of an axon can vary from a few micrometres to several metres, organisms must obviously have some means of controlling how long specific [axons](#) should grow. "We have managed to develop a model of a mechanism that explains how an organism can do just that. The model not only explains how neurons can determine their own length, it can also be generalized to other biological systems," explains Frederic Folz.

The chemical signalling molecules that regulate growth in [biological systems](#) behave in the following manner: "The molecules spread through the system as chemical waves until they reach the end of the axon," says Folz. If the frequency at which this 'molecular wave' returns to its point of origin is high, the biological structure through which the wave has passed is short; if the frequency of such a cycle is low, then it has taken longer for the chemical to return and the structure is correspondingly large. A molecule needs less time to travel a few micrometres within a bacterium than it does to travel from the root to the crown of an oak tree. The physicists have described this mechanism using a [mathematical model](#).

The researchers surmise that a biological system, such as a tree, a human or a cell, can 'measure' the frequency of these cycles and can therefore determine and hence control the length of, say, a leaf or a leg.

Their work could be of fundamental importance to future research into a variety of diseases. "Our model can also be used in the electronics sector to regulate different physical quantities," says Folz. The model also incorporates elements that can describe the dynamics of the internet and, more generally, other artificial networks and could well form the basis for further developments and improvements in these areas. [29]

### **'Nanoemulsion' gels offer new way to deliver drugs through the skin**

MIT chemical engineers have devised a new way to create very tiny droplets of one liquid suspended within another liquid, known as nanoemulsions. Such emulsions are similar to the mixture that forms when you shake an oil-and-vinegar salad dressing, but with much smaller droplets. Their tiny size allows them to remain stable for relatively long periods of time.

The researchers also found a way to easily convert the liquid nanoemulsions to a gel when they reach body temperature (37 degrees Celsius), which could be useful for developing materials that can deliver medication when rubbed on the skin or injected into the body.

"The pharmaceutical industry is hugely interested in nanoemulsions as a way of delivering small molecule therapeutics. That could be topically, through ingestion, or by spraying into the nose,



because once you start getting into the size range of hundreds of nanometers you can permeate much more effectively into the skin," says Patrick Doyle, the Robert T. Haslam Professor of Chemical Engineering and the senior author of the study.

In their new study, which appears in the June 21 issue of *Nature Communications*, the researchers created nanoemulsions that were stable for more than a year. To demonstrate the emulsions' potential usefulness for delivering drugs, the researchers showed that they could incorporate ibuprofen into the droplets.

Seyed Meysam Hashemnejad, a former MIT postdoc, is the first author of the study. Other authors include former postdoc Abu Zayed Badruddoza, L'Oréal senior scientist Brady Zarket, and former MIT summer research intern Carlos Ricardo Castaneda.

### Energy reduction

One of the easiest ways to create an [emulsion](#) is to add energy—by shaking your salad dressing, for example, or using a homogenizer to break down fat globules in milk. The more energy that goes in, the smaller the droplets, and the more stable they are.

Nanoemulsions, which contain droplets with a diameter 200 nanometers or smaller, are desirable not only because they are more stable, but they also have a higher ratio of surface area to volume, which allows them to carry larger payloads of active ingredients such as drugs or sunscreens.

Over the past few years, Doyle's lab has been working on lower-energy strategies for making nanoemulsions, which could make the process easier to adapt for large-scale industrial manufacturing.

Detergent-like chemicals called surfactants can speed up the formation of emulsions, but many of the surfactants that have previously been used for creating nanoemulsions are not FDA-approved for use in humans. Doyle and his students chose two surfactants that are uncharged, which makes them less likely to irritate the skin, and are already FDA-approved as food or cosmetic additives. They also added a small amount of polyethylene glycol (PEG), a biocompatible polymer used for [drug delivery](#) that helps the solution to form even smaller droplets, down to about 50 nanometers in diameter.

"With this approach, you don't have to put in much energy at all," Doyle says. "In fact, a slow stirring bar almost spontaneously creates these super small emulsions."

Active ingredients can be mixed into the oil phase before the emulsion is formed, so they end up loaded into the droplets of the emulsion.

Once they had developed a low-energy way to create nanoemulsions, using nontoxic ingredients, the researchers added a step that would allow the emulsions to be easily converted to gels when they reach body temperature. They achieved this by incorporating heat-sensitive polymers called poloxamers, or Pluronic, which are already FDA-approved and used in some drugs and cosmetics.

Pluronic contains three "blocks" of polymers: The outer two regions are hydrophilic, while the middle region is slightly hydrophobic. At room temperature, these molecules dissolve in water but do not interact much with the droplets that form the emulsion. However, when heated, the hydrophobic

regions attach to the droplets, forcing them to pack together more tightly and creating a jelly-like solid. This process happens within seconds of heating the emulsion to the necessary temperature.

### **Tunable properties**

The researchers found that they could tune the properties of the gels, including the temperature at which the material becomes a gel, by changing the size of the emulsion droplets and the concentration and structure of the Pluronics that they added to the emulsion. They can also alter traits such as elasticity and yield stress, which is a measure of how much force is needed to spread the gel.

Doyle is now exploring ways to incorporate a variety of active pharmaceutical ingredients into this type of gel. Such products could be useful for delivering topical medications to help heal burns or other types of injuries, or could be injected to form a "drug depot" that would solidify inside the body and release drugs over an extended period of time. These [droplets](#) could also be made small enough that they could be used in [nasal sprays](#) for delivering inhalable drugs, Doyle says.

For cosmetic applications, this approach could be used to create moisturizers or other products that are more shelf-stable and feel smoother on the skin. [28]

### **Scientists patent new agent for X-ray**

Russian scientists found that nanocrystal tungsten trioxide can be used instead of barium for X-ray examinations and also in cancer treatment. The results of the study are published in *Journal of Nanomaterials*.

Due to the physical-chemical properties of [tungsten](#), in particular, the effective absorptive capacity of X-rays, its compounds are considered as a possible basis for creating a new class of contrast agents. This method can be used in [computer tomography](#). Computer tomography (CT) is a method of visualizing the [internal organs](#). The method is based on one-dimensional or two-dimensional projections obtained by passing of X-rays through tissues, when an X-ray source and a detector opposite to it simultaneously rotate around an object.

To obtain high-quality images, it is essential to have a visually distinct difference in the attenuation of X-rays between the organs. To differentiate organ, normal and pathological structures better, various contrast enhancement techniques are used. Usually this is done with the use of radiopaque agents that are injected in the form of solution. The greatest effect of attenuation of radiation is achieved with the use of chemical elements with a large mass of atoms. When choosing such agents, it is necessary to take into account five criteria for their clinical use in CT: effective radiopacity, selective distribution, lack of pharmacological and/or toxicological effects, in vitro and in vivo stability, and cost and availability.

Today, only iodine and barium are used in radiography. However, in order to obtain a contrast X-ray image of the organ, one needs to take a relatively large amount of agent solution, which can cause discomfort and side effects.

Scientists from Kurnakov Institute of General and Inorganic Chemistry and the Institute of Theoretical and Experimental Biophysics RAS found that tungsten can be used instead of iodine and barium. They showed the biosafety of tungsten nanoparticles for [human cells](#) even in high concentrations, and also developed a scheme for the synthesis of highly crystallized tungsten trioxide nanoparticles, which can form the basis for creating a new radiopaque agent.

"Previously, we synthesized and investigated photochromic tungsten oxide nanoparticles, which have pronounced bactericidal activity against gram-positive and [gram-negative bacteria](#), as well as selective photocatalytic activity against cancer cells, which can be used in perspective for photodynamic therapy of cancer. Our team works in two directions: development of a radiopaque agent and creation of a new class of photosensitizers for photodynamic cancer therapy," comments one of the authors of the study, Anton Popov. [27]

### **3-D body mapping could identify, treat organs, cells damaged from medical conditions**

Medical advancements can come at a physical cost. Often following diagnosis and treatment for cancer and other diseases, patients' organs and cells can remain healed but damaged from the medical condition.

In fact, one of the fastest growing medical markets is healing and/or replacing organs and cells already treated, yet remain damaged by cancer, [cardiovascular disease](#) and other medical issues. The global [tissue](#) engineering market is expected to reach \$11.5 billion by 2022. That market involves researchers and medical scientists working to repair tissues damaged by some of the world's most debilitating cancers and diseases.

One big challenge remains for the market—how to monitor and continuously test the performance of engineered tissues and cells to replace damaged ones. Purdue University researchers have come up with a 3-D mapping technology to monitor and track the behavior of the engineered cells and tissues and improve the success rate for patients who have already faced a debilitating [disease](#). The technology is published in the June 19 edition of *ACS Nano*.

"My hope is to help millions of people in need," said Chi Hwan Lee, an assistant professor of biomedical engineering and [mechanical engineering](#) in Purdue's College of Engineering, who leads the research team. "Tissue engineering already provides new hope for hard-to-treat disorders, and our technology brings even more possibilities."

The Purdue team created a tissue scaffold with sensor arrays in a stackable design that can monitor electrophysiological activities of [cells](#) and tissues. The technology uses the information to produce 3-D maps to track activity.

"This device offers an expanded set of potential options to monitor cell and tissue function after surgical transplants in diseased or damaged bodies," Lee said. "Our technology offers diverse options

for sensing and works in moist internal body environments that are typically unfavorable for electronic instruments."

Lee said the Purdue device is an ultra-buoyant scaffold that allows the entire structure to remain afloat on the cell culture medium, providing complete isolation of the entire electronic instrument from the wet conditions inside the body.

Lee and his team have been working with Sherry Harbin, a professor in Purdue's Weldon School of Biomedical Engineering, to test the device in stem cell therapies with potential applications in the regenerative treatment of diseases. [26]

### **Towards in vitro blood vessel fabrication**

Tao Sun and colleagues from [Beijing Institute of Technology](#) have described a novel method to incorporate synthetic microfibres containing magnetic beads into self-assembled tissue micro-rings. Magnetic force, coupled with a smart usage of surface tension, enabled the adhesion and proliferation of fibroblasts on the micro-rings, as well as subsequent stacking of the rings into tubular structures ([Biofabrication10.1088/1758-5090/ab1ee5](#)).

Finding tissue donors can be a limiting factor in the treatment of several diseases. For this reason, tissue engineering has become a booming field in the last decade, with scientists striving in their quest to replicate functional tissues *in vitro*. Many fundamental structures in the human body display a tubular shape (the trachea, oesophagus and blood vessels, for example) that researchers try to replicate.

Current trends in tissue engineering include the use of hydrogels, which have many advantages but come with a price: inhomogeneous cell distribution, as well as poor mechanical properties and limited nutrient diffusion. Alternative approaches to the direct delivery of cell-supplemented hydrogels to the injury site are already established. Among these is bottom-up structural assembly of biological tubes using tissue rings with incorporated microscaffolds. However, few microscaffolds are currently available as platforms. Therefore, Sun and colleagues examined whether tissue rings with incorporated microscaffolds could be created from microfluidic spun hydrogel microfibres.

In this study, the researchers incorporated magnetic particles in crosslinked calcium-alginate hydrogel fibres, with diameters optimized to provide the best support for cell growth and diffusion. To better hook cells, they coated the microspun fibres with poly-L-lysine residues bound to a fibronectin network.

To align the fibres in a parallel direction, the researchers exploited the surface tension of the fibronectin solution while transferring the rings in a culture dish placed onto a magnet before seeding fibroblasts on them. Thanks to the incorporated magnetic beads, they were then able to avoid floating of the rings, allowing for fibroblast seeding. Cell seeding was successful, with fibroblasts eventually spreading uniformly on the fibres, forming multiple layers and displaying good morphology and viability.

After three days of incubation, the rings self-assembled: the fibres guided the growth of fibroblasts, creating connections between themselves and the microgel, which resulted in the progressive shrinkage of the annular structures. The researchers then used magnetic force to serially assemble the micro-rings on top of each other around an inner pillar. This formed a cylinder that was cultured for five more days to let the cells seal the rings together. The result closely resembled the structure of a blood vessel.

Having provided this important proof-of-concept for bottom-up tissue engineering, the authors plan some important modifications to this platform in their forthcoming studies. These include addressing the observed formation of cell aggregates (possibly due to limited fibronectin coating), as well as the limited guidance of cell orientation. They envision that the substitution of alginate hydrogel microfibrils with methacrylamide-modified gelatin (GelMA) microfibrils will do the job. [25]

## **Polymer-coated gold nanospheres do not impair the innate immune function of human B lymphocytes**

Over the past 20 years, the use of nanoparticles in medicine has steadily increased. However, their safety and effect on the human immune system remains an important concern. By testing a variety of gold nanoparticles, researchers at the University of Geneva (UNIGE) and collaborators are providing first evidence of their impact upon human B lymphocytes—the immune cells responsible for antibody production. The use of these nanoparticles is expected to improve the efficacy of pharmaceutical products while limiting potential adverse effects.

These results, published in the journal *ACS Nano*, could lead to the development of more targeted and better tolerated therapies, particularly in the field of oncology. The methodology also makes it possible to test the biocompatibility of any nanoparticle at an early stage in the development of a new nanodrug.

Responsible for the production of antibodies, B lymphocytes are a crucial part of the [human immune system](#), and therefore an interesting target for the development of preventive and therapeutic vaccines. However, to achieve their goal, vaccines must reach B lymphocytes quickly without being destroyed, making the use of nanoparticles particularly interesting.

"Nanoparticles can form a protective vehicle for vaccines—or other drugs—to specifically deliver them where they can be most effective, while sparing other cells," explains Carole Bourquin, a professor at the UNIGE's Faculties of Medicine and Science, who co-led this study. "This targeting also allows the use of a lower dose of immunostimulant while maintaining an effective immune response. It increases its efficacy while reducing side-effects, provided that the nanoparticles are harmless to all immune cells."

Similar studies have already been conducted for other [immune cells](#) such as macrophages, which seek out and interact with nanoparticles, but never before for the smaller, and more difficult to handle, B lymphocytes.

## Gold is an ideal material

Gold is an excellent candidate for nanomedicine because of its particular physico-chemical properties. Well tolerated by the body and easily malleable, this metal absorbs light and then releases heat, a property that can be exploited in oncology.

"Gold nanoparticles can be used to target tumours. When exposed to a light source, the nanoparticles release heat and destroy neighbouring cancer cells. We could also attach a drug to the surface of the nanoparticles to be delivered to a specific location," explains UNIGE researcher Sandra Hočevár. "To test their safety and the best formula for medical use, we have created [gold](#) spheres with or without a [polymer coating](#), as well as gold rods to explore the effects of coating and shape. We then exposed human B lymphocytes to our particles for 24 hours to examine the activation of the immune response."

By following activation markers expressed on the surfaces of B cells, the scientists were able to determine how much their nanoparticles activated or inhibited the immune response. While none of the nanoparticles tested demonstrated adverse effects, their influence on the immune response differed depending on their shape and the presence of a polymer surface coating.

"Surface properties, as well as nanoparticle morphology, definitely are important when it comes to the nanoparticle-cell interaction. Interestingly, the gold nanorods inhibited the immune response instead of activating it, probably by causing interference on the cell membrane, or because they are heavier," says Martin Clift, an associate professor of nanotoxicology and in vitro systems at Swansea University Medical School, and the project's co-leader.

Uncoated spherical particles easily aggregate and are therefore not appropriate for biomedical use. On the other hand, gold spheres coated with a protective polymer are stable and do not impair B lymphocyte function. "And we can easily place the vaccine or drug to be delivered to the B lymphocytes in this coating," says Carole Bourquin. "In addition, our study established a methodology for assessing the safety of nanoparticles on B lymphocytes, something that had never been done before. "This could be especially useful for future research, as the use of nanoparticles in medicine still requires clear guidelines."

B cells are at the heart of vaccine response, but also in other areas such as oncology and autoimmune diseases. The [gold nanoparticles](#) developed by the researchers could make it possible to deliver existing drugs directly to B [lymphocytes](#) to reduce the necessary dosage and potential side effects. In fact, studies in patients are already being carried out for the treatment of brain tumours. Gold [nanoparticles](#) can be made small enough to cross the [blood-brain barrier](#), allowing specific anti-tumoural drugs to be delivered directly into the cancerous [cells](#). [24]

## Size matters: Color imaging of gene expression in electron microscopy

Researchers at Helmholtz Zentrum Muenchen have developed a method to visualize gene expression of cells with an electron microscope. Although electron microscopy currently provides the most detailed look into cells, it cannot differentiate which genetic programs run inside individual cells. The



new method can now have a closer look by using genetically programmed nanospheres of different sizes as "multicolor" markers, which could even be helpful to investigate how memories are stored in neuronal networks.

What exactly is going on in [cells](#)? This question has kept scientists busy for decades. To label small structures, scientists have been using fluorescent proteins. This method works well but has disadvantages due to the relatively poor resolution of light microscopes. Although [electron microscopes](#) allow a closer look, says Prof. Dr. Gil Gregor Westmeyer, "so far there are hardly any solutions for multi-color genetic labeling of cells for this technology, such that one can directly tell different cells apart." He leads a research group at the Institute for Biological and Medical Imaging (IBMI) of Helmholtz Zentrum München and is Professor of Molecular Imaging at TUM School of Medicine.

### **[Nanocompartments as multi-color labels for electron microscopy](#)**

Westmeyer and colleagues have been working with so-called encapsulins for some time. These are small, non-toxic proteins from bacteria. Encapsulins automatically assemble to nanocompartments in which chemical reactions can run without disturbing the metabolism of the cell. Depending on the experimental conditions, nanocompartments with different diameters are formed within living cells via genetic programming. "Analogous to the palette of colors in [fluorescence microscopy](#), our method turns geometry into a label for [electron microscopy](#)," adds Felix Sigmund from Westmeyer's research group.

To achieve strong contrast in the images from the electron microscopy, the researchers use the enzyme ferroxidase, which can be encapsulated in the interior of encapsulins. If iron ions enter the interior lumen through pores of the nanocompartments, divalent [iron ions](#) are oxidized by the enzyme into their trivalent form. This creates insoluble iron oxides that remain inside. Metals create good contrasts because they "swallow" electrons—comparable to dense bones in an X-ray image, which strongly absorb X-rays. This special material property of encapsulins makes them clearly visible in the images.

### **[Following neuronal tracts](#)**

With their new method, the researchers will now also investigate neural circuits. Despite the impressive resolution of electron [microscopy](#), the method cannot reliably distinguish certain types of neurons within the brain. "With our new reporter genes, we could label specific cells and then read out which type of nerve cell makes which connections and which state the cells are in," adds Westmeyer.

This new reporter technology could thus also help to uncover the exact wiring diagram of brains and to investigate closer how memories are stored in neuronal networks. [23]

## Researchers reach milestone in use of nanoparticles to kill cancer with heat

Researchers at Oregon State University have developed an improved technique for using magnetic nanoclusters to kill hard-to-reach tumors.

Magnetic nanoparticles—tiny pieces of matter as small as one-billionth of a meter—have shown anti-cancer promise for tumors easily accessible by syringe, allowing the particles to be injected directly into the cancerous growth.

Once injected into the tumor, the nanoparticles are exposed to an alternating [magnetic field](#), or AMF. This field causes the nanoparticles to reach temperatures in excess of 100 degrees Fahrenheit, which causes the cancer cells to die.

But for some [cancer types](#) such as [prostate cancer](#), or the [ovarian cancer](#) used in the Oregon State study, direct injection is difficult. In those types of cases, a "systemic" delivery method—[intravenous injection](#), or injection into the abdominal cavity—would be easier and more effective.

The challenge for researchers has been finding the right kind of nanoparticles—ones that, when administered systemically in clinically appropriate doses, accumulate in the tumor well enough to allow the AMF to heat cancer cells to death.

Olena Taratula and Oleh Taratula of the OSU College of Pharmacy tackled the problem by developing nanoclusters, multiatom collections of nanoparticles, with enhanced heating efficiency. The nanoclusters are hexagon-shaped [iron oxide nanoparticles](#) doped with cobalt and manganese and loaded into biodegradable nanocarriers.



OSU researchers Olena and Oleh Taratula's work with magnetic nanoclusters as cancer therapy was featured on the cover of *ACS Nano*. Credit: Tetiana Korzun

Findings were published in *ACS Nano*.

"There had been many attempts to develop nanoparticles that could be administered systemically in safe doses and still allow for hot enough temperatures inside the tumor," said Olena Taratula, associate professor of pharmaceutical sciences. "Our new nanoplatform is a milestone for treating difficult-to-access tumors with magnetic hyperthermia. This is a proof of concept, and the nanoclusters could potentially be optimized for even greater heating efficiency."

The nanoclusters' ability to reach therapeutically relevant temperatures in tumors following a single, low-dose IV injection opens the door to exploiting the full potential of magnetic hyperthermia in treating cancer, either by itself or with other therapies, she added.

"It's already been shown that magnetic hyperthermia at moderate temperatures increases the susceptibility of [cancer cells](#) to chemotherapy, radiation and immunotherapy," Taratula said.

The mouse model in this research involved animals receiving IV nanocluster injections after ovarian tumors had been grafted underneath their skin.

"To advance this technology, future studies need to use orthotopic animal models—models where deep-seated tumors are studied in the location they would actually occur in the body," she said. "In addition, to minimize the heating of healthy tissue, current AMF systems need to be optimized, or new ones developed." [22]

## A better way to encapsulate islet cells for diabetes treatment

When medical devices are implanted in the body, the immune system often attacks them, producing scar tissue around the device. This buildup of tissue, known as fibrosis, can interfere with the device's function.

MIT researchers have now come up with a novel way to prevent fibrosis from occurring, by incorporating a crystallized immunosuppressant drug into devices. After implantation, the drug is slowly secreted to dampen the immune response in the area immediately surrounding the device.

"We developed a crystallized drug formulation that can target the key players involved in the implant rejection, suppressing them locally and allowing the device to function for more than a year," says Shady Farah, an MIT and Boston Children's Hospital postdoc and co-first author of the study, who is soon starting a new position as an assistant professor of the Wolfson Faculty of Chemical Engineering and the Russell Berrie Nanotechnology Institute at Technion-Israel Institute of Technology.

The researchers showed that these crystals could dramatically improve the performance of encapsulated [islet cells](#), which they are developing as a possible treatment for patients with type 1 diabetes. Such crystals could also be applied to a variety of other implantable [medical devices](#), such as pacemakers, stents, or sensors.

Former MIT postdoc Joshua Doloff, now an assistant professor of Biomedical and Materials Science Engineering and member of the Translational Tissue Engineering Center at Johns Hopkins University School of Medicine, is also a lead author of the paper, which appears in the June 24 issue of *Nature Materials*. Daniel Anderson, an associate professor in MIT's Department of Chemical Engineering and a member of MIT's Koch Institute for Integrative Cancer Research and Institute for Medical Engineering and Science (IMES), is the senior author of the paper.

### Crystalline drug

Anderson's lab is one of many research groups working on ways to encapsulate islet [cells](#) and transplant them into [diabetic patients](#), in hopes that such cells could replace the patients' nonfunctioning pancreatic cells and eliminate the need for daily insulin injections.

Fibrosis is a major obstacle to this approach, because [scar tissue](#) can block the islet cells' access to the oxygen and nutrients. In a 2017 study, Anderson and his colleagues showed that systemic administration of a drug that blocks cell receptors for a protein called CSF-1 can prevent fibrosis by suppressing the immune response to implanted devices. This drug targets immune cells called macrophages, which are the primary cells responsible for initiating the inflammation that leads to fibrosis.

"That work was focused on identifying next-generation drug targets, namely which cell and cytokine players were essential for fibrotic response," says Doloff, who was the lead author on that study, which also involved Farah. He adds, "After knowing what we had to target to block fibrosis, and screening drug candidates needed to do so, we still had to find a sophisticated way of achieving local delivery and release for as long as possible."

In the new study, the researchers set out to find a way to load the drug directly into an implantable device, to avoid giving patients drugs that would suppress their entire immune system.

"If you have a small device implanted in your body, you don't want to have your whole body exposed to drugs that are affecting the [immune system](#), and that's why we've been interested in creating ways to release drugs from the device itself," Anderson says.

To achieve that, the researchers decided to try crystallizing the drugs and then incorporating them into the device. This allows the drug molecules to be very tightly packed, allowing the drug-releasing device to be miniaturized. Another advantage is that crystals take a long time to dissolve, allowing for long-term drug delivery. Not every drug can be easily crystallized, but the researchers found that the CSF-1 receptor inhibitor they were using can form crystals and that they could control the size and shape of the crystals, which determines how long it takes for the drug to break down once in the body.

"We showed that the drugs released very slowly and in a controlled fashion," says Farah. "We took those crystals and put them in different types of devices and showed that with the help of those crystals, we can allow the medical device to be protected for a long time, allowing the device to keep functioning."

### **Encapsulated islet cells**

To test whether these drug crystalline formulations could boost the effectiveness of encapsulated islet cells, the researchers incorporated the drug crystals into 0.5-millimeter-diameter spheres of alginate, which they used to encapsulate the cells. When these spheres were transplanted into the abdomen or under the skin of diabetic mice, they remained fibrosis-free for more than a year. During this time, the mice did not need any insulin injections, as the islet cells were able to control their blood sugar levels just as the pancreas normally would.

"In the past three-plus years, our team has published seven papers in *Nature* journals—this being the seventh—elucidating the mechanisms of biocompatibility," says Robert Langer, the David H. Koch Institute Professor at MIT and an author of the paper. "These include an understanding of the key cells and receptors involved, optimal implant geometries and physical locations in the body, and now, in this paper, specific molecules that can confer biocompatibility. Taken together, we hope these papers will open the door to a new generation of biomedical implants to treat diabetes and other diseases."

The researchers believe that it should be possible to create crystals that last longer than those they studied in these experiments, by altering the structure and composition of the drug crystals. Such formulations could also be used to prevent fibrosis of other types of implantable devices. In this study, the researchers showed that crystalline [drug](#) could be incorporated into PDMS, a polymer frequently used for medical devices, and could also be used to coat components of a glucose sensor and an electrical muscle stimulation device, which include materials such as plastic and metal.

"It wasn't just useful for our islet cell therapy, but could also be useful to help get a number of different devices to work long-term," Anderson says. [21]

## By turning molecular structures into sounds, researchers gain insight into protein structures and create new variations

Want to create a brand new type of protein that might have useful properties? No problem. Just hum a few bars.

In a surprising marriage of science and art, researchers at MIT have developed a system for converting the molecular structures of proteins, the basic building blocks of all living beings, into audible sound that resembles musical passages. Then, reversing the process, they can introduce some variations into the music and convert it back into new proteins never before seen in nature.

Although it's not quite as simple as humming a new [protein](#) into existence, the new system comes close. It provides a systematic way of translating a protein's [sequence of amino acids](#) into a musical sequence, using the physical properties of the molecules to determine the sounds. Although the sounds are transposed in order to bring them within the audible range for humans, the tones and their relationships are based on the actual vibrational frequencies of each amino acid molecule itself, computed using theories from quantum chemistry.

The system was developed by Markus Buehler, the McAfee Professor of Engineering and head of the Department of Civil and Environmental Engineering at MIT, along with postdoc Chi Hua Yu and two others. As described in the journal *ACS Nano*, the system translates the 20 types of amino acids, the building blocks that join together in chains to form all proteins, into a 20-tone scale. Any protein's long sequence of amino acids then becomes a sequence of notes.

While such a scale sounds unfamiliar to people accustomed to Western musical traditions, listeners can readily recognize the relationships and differences after familiarizing themselves with the sounds. Buehler says that after listening to the resulting melodies, he is now able to distinguish certain amino acid sequences that correspond to proteins with specific structural functions. "That's a beta sheet," he might say, or "that's an alpha helix."

### Learning the language of proteins

The whole concept, Buehler explains, is to get a better handle on understanding proteins and their vast array of variations. Proteins make up the structural material of skin, bone, and muscle, but are also enzymes, signaling chemicals, molecular switches, and a host of other functional materials that make up the machinery of all living things. But their structures, including the way they fold themselves into the shapes that often determine their functions, are exceedingly complicated. "They have their own language, and we don't know how it works," he says. "We don't know what makes a silk protein a silk protein or what patterns reflect the functions found in an enzyme. We don't know the code."

By translating that language into a different form that humans are particularly well-attuned to, and that allows different aspects of the information to be encoded in different dimensions—pitch, volume, and duration—Buehler and his team hope to glean new insights into the relationships and differences between different families of proteins and their variations, and use this as a way of exploring the many possible tweaks and modifications of their structure and function. As with music,



the structure of proteins is hierarchical, with different levels of structure at different scales of length or time.

The team then used an artificial intelligence system to study the catalog of melodies produced by a wide variety of different proteins. They had the AI system introduce slight changes in the musical sequence or create completely new sequences, and then translated the sounds back into proteins that correspond to the modified or newly designed versions. With this process they were able to create variations of existing proteins—for example of one found in spider silk, one of nature's strongest materials—thus making new proteins unlike any produced by evolution.

Although the researchers themselves may not know the underlying rules, "the AI has learned the language of how proteins are designed," and it can encode it to create variations of existing versions, or completely new protein designs, Buehler says. Given that there are "trillions and trillions" of potential combinations, he says, when it comes to creating new proteins "you wouldn't be able to do it from scratch, but that's what the AI can do."

### **"Composing" new proteins**

By using such a system, he says training the AI system with a set of data for a particular class of proteins might take a few days, but it can then produce a design for a new variant within microseconds. "No other method comes close," he says. "The shortcoming is the model doesn't tell us what's really going on inside. We just know it works."

This way of encoding structure into music does reflect a deeper reality. "When you look at a molecule in a textbook, it's static," Buehler says. "But it's not static at all. It's moving and vibrating. Every bit of matter is a set of vibrations. And we can use this concept as a way of describing matter."

The method does not yet allow for any kind of directed modifications—any changes in properties such as mechanical strength, elasticity, or chemical reactivity will be essentially random. "You still need to do the experiment," he says. When a new protein variant is produced, "there's no way to predict what it will do."

The team also created musical compositions developed from the sounds of amino acids, which define this new 20-tone musical scale. The art pieces they constructed consist entirely of the sounds generated from amino acids. "There are no synthetic or natural instruments used, showing how this new source of sounds can be utilized as a creative platform," Buehler says. Musical motifs derived from both naturally existing proteins and AI-generated proteins are used throughout the examples, and all the sounds, including some that resemble bass or snare drums, are also generated from the sounds of amino acids.

The researchers have created a free Android smartphone app, called [Amino Acid Synthesizer](#), to play the sounds of amino acids and record protein sequences as musical compositions. [20]

## Applying the Goldilocks principle to DNA structure

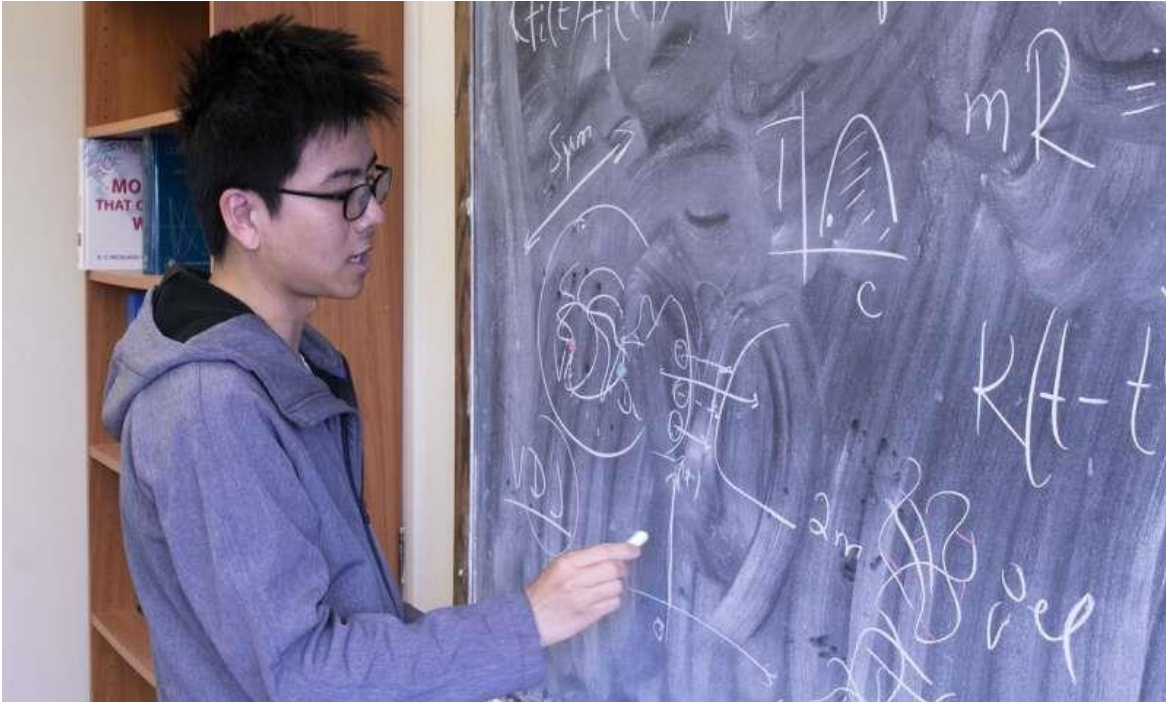
The Goldilocks of fairy-tale fame knew something about porridge. It needed to be just right—neither too hot nor too cold. Same with furniture—neither too hard nor too soft. In a different context, scientists at UC San Diego know something about DNA. They know that the strands of our genetic code, if extended, would measure two meters, or about six feet. They also know that the strands fold into and move within the cell nucleus the size of about a hundredth of a millimeter. But they don't know how and in what state of matter this occurs, so they decided to check.

Inspired by ideas from the physics of phase transitions and polymer physics, researchers in the Divisions of Physical and Biological Sciences at UC San Diego set out specifically to determine the organization of DNA inside the nucleus of a living cell. The findings of their study, recently published in *Nature Communications*, suggest that the phase state of the genomic DNA is "just right"—a gel poised at the phase boundary between gel and sol, the solid-liquid phase transition.

Think of pudding, panna cotta—or even porridge. The consistency of these delectables must be just right to be ideally enjoyed. Just as the "sol-gel" phase transition, according to the scientists, seems just right for explaining the timing of genomic interactions that dictate gene expression and somatic recombination.

"This finding points to a general physical principle of chromosomal organization, which has important implications for many key processes in biology, from antibody production to tissue differentiation," said Olga Dudko, a theoretical biophysicist and professor in the Department of Physics at UC San Diego, who collaborated with colleague Cornelis Murre, a distinguished professor in the Section of Molecular Biology, on the study.

Along with Dudko's former graduate student Yaojun Zhang, now a postdoctoral researcher at Princeton, and Murre's postdoctoral scholar Nimish Khanna, the team collected and analyzed data on DNA motion inside live mammalian B-cells from mice to understand how remote genomic interactions generate a diverse pool of antibodies by the adaptive immune system.



Physics graduate student Bin Wang, who works with Dudko, charts temporal and spatial aspects of the research. Credit: Michelle Fredricks, UC San Diego Physical Sciences

In mammals, such as rodents and humans, immunoglobulin gene segments are arranged in groups of variable (V), diversity (D) and joining (J) segments. These V, D and J segments randomly combine through the process of somatic recombination. This occurs before antigen contact and during B-cell development in the immune system's lymphoid tissue, or bone marrow. These random genetic interactions result in diverse protein codes that match up with antigens which activate lymphocytes.

The scientists examined the various interactions between V and DJ gene segments. While how exactly these interactions occur remains unknown, the UC San Diego researchers developed a strategy to track V and DJ motion in B-lymphocytes. They found that V and DJ segments were trapped in configurations that allowed local motion only—in other words, the segments remained spatially proximal if they were initially close or they remained separate if they were initially spatially distant. The researchers also observed, within a subset of cells, abrupt changes in V and DJ motion, plausibly caused by temporal changes in chromatin.

By comparing experimental and simulated data, the scientists concluded that constrained motion is imposed by a network of cross-linked chromatin chains, or a mesh of bridges between the DNA strands that are characteristic of a gel phase. Yet, the amount of these cross-links is "just right" to poise the DNA near the sol phase—a liquid phase describing a solution of uncross-linked chains.

This pattern suggested to the scientists that a certain organizational principle of genomic DNA exists—proximity to the sol-gel [phase](#) transition—which explains how the genome can simultaneously possess stability and responsiveness within the nucleus.

These results indicate that the packing pattern of DNA within a cell's nucleus has consequences for a cell's fate—whether it becomes a live or diseased cell.

"We have rigorous theories from physics—abstract principles and mathematical equations. We have state-of-the-art experiments on biology—innovative tracking of gene segments in live mammalian cell nuclei," noted Zhang. "It really amazes and excites me when the two aspects merge coherently into one story, where physics is not just a tool to describe the dynamics of gene segments, but helps to pinpoint the physical state of the genome, and further sheds light on the impact of the physical properties of this state on its biological function." [19]

### **Neutrons get a wider angle on DNA and RNA to advance 3-D models**

Scientists from the National Institute of Standards and Technology (NIST) and the University of Maryland are using neutrons at Oak Ridge National Laboratory (ORNL) to capture new information about DNA and RNA molecules and enable more accurate computer simulations of how they interact with everything from proteins to viruses. Resolving the 3-D structures of the body's fundamental genetic materials in solution will play a vital role in drug discovery and development for critical medical treatments.

"A better understanding of both the structure and conformational dynamics of DNA and RNA could help us answer questions about why and how medicines work and help us locate where the key interactions are taking place at the [atomic level](#)," said NIST's Alexander Grishaev, who led neutron scattering research performed at the High Flux Isotope Reactor (HFIR), a Department of Energy User Facility located at ORNL.

The team used HFIR's Bio-SANS instrument to perform small- to wide-angle neutron scattering, a technique not previously performed on DNA and RNA samples in solution because of limited experimental capabilities.

"Capturing a wider range of angles for biomolecules in solution using neutron scattering has not been possible until recently," said Grishaev, "and Oak Ridge is one of the only places you can do this kind of work."

Extending the capabilities of solution neutron scattering is part of an advancing effort toward a more integrative approach in [structural biology](#) that combines crystal studies, solution methods, and other experimental and computational techniques to enhance understanding of DNA and protein structures.

Computer simulations of biomolecules have been well informed by X-ray crystallography. The premier technique uses x-rays to determine the arrangement of atoms in a sample that has been "crystallized" for analysis. To get [high-quality data](#) with this technique, samples of biological materials that are typically dilute in solution are concentrated and solidified into crystals with a uniform structure.

X-ray crystallography works especially well for rigid biomolecules with more or less fixed structures, but flexible biomolecules like DNA and RNA that adopt multiple "conformations" or shapes are less suited to crystallization.

Inside living cells, DNA and RNA can move, change shapes, and respond differently to environmental effects such as pH or temperature, alterations that are important to represent but difficult to characterize.

"Crystallization packs the molecules in tightly, which limits their motions and masks some of the structural information we want to see," said Grishaev.

Several techniques have successfully been applied to DNA and RNA in solution, including solution X-ray scattering and nuclear magnetic resonance (NMR) spectroscopy, both of which yield important data. Yet, significant discrepancies exist between the experimental scattering data and the best available crystal structures of DNA and RNA.

The team turned to neutrons to find out why.

"Neutrons interact with biomolecules differently, so we can use them as an independent source of data for us to either validate or better define the models that we have," said Maryland's Roderico Acevedo.

Whereas x-rays work well to define heavy atoms, such as carbon, oxygen, and phosphorus, neutrons are ideal for examining lighter hydrogen atoms that connect DNA strands, for example. Additionally, neutrons offer an advantage in probing biomolecules because they are nondestructive and do not damage them.

Using the Bio-SANS instrument at HFIR, researchers were able to collect structural information in solution not readily obtainable by other experimental techniques.

The experiment required both a high neutron flux and wide-angle detectors to collect higher precision scattering patterns to reveal the atomic-level structures of DNA and RNA in solution.

Using neutrons to collect structural information on biomolecules is no ordinary feat, says Grishaev. Small biomolecular samples in dilute solutions often produce noisy scattering patterns, making the data difficult to analyze.

"HFIR's Bio-SANS is one of few neutron instruments in the world with the capability to capture small and wide scattering angles simultaneously, combining both global- and local-scale details," said Bio-SANS instrument scientist Volker Urban.

"We were able to get some of the highest-precision solution neutron scattering data ever collected at wide angles, not just on DNA and RNA, but on biomolecules in general," said Grishaev.

By adding the new information collected via solution [neutron scattering](#) to other data from [solution](#) X-ray scattering and NMR spectroscopy, the NIST-Maryland group hopes to get a more comprehensive picture of DNA and RNA structures, as well as to expand avenues for defining molecular structures with [neutron](#)-based techniques. [18]

## Theoretical model may help solve molecular mystery

Spintronics is promising for future low-power electronic devices. Spin is a quantum-mechanical property of electrons that can best be imagined as electrons spinning around their own axes, causing them to behave like small compass needles. A current of electron spins could be used in electronic devices. However, to generate a suitable spin current, you need a relatively large magnet. An alternative method that uses a special type of molecule has been proposed, but the big question is whether it works. University of Groningen Ph.D. student Xu Yang has constructed a theoretical model that describes how to test this new method.

Spin can have two directions, usually designated as "up" and "down." In a normal electron current, there are equal quantities of both spin directions, but using spin to transfer information requires a surplus of one direction. This is usually done by injecting electrons into a spintronic device through a ferromagnet, which will favor the passage of one type of spin. "But ferromagnets are bulky compared to the other components," says Yang.

### DNA

That is why a 2011 breakthrough that was published in *Science* is attracting increased attention. This paper reported that passing a current through a monolayer of DNA double helices would favor one type of spin. The DNA molecules are chiral, which means they can exist in two forms which are mirror images, like a left and right hand. The phenomenon was dubbed "chiral induced spin selectivity" (CISS), and over the last few years, several experiments were published allegedly showing this CISS effect, even in electronic devices.

"But we were not so sure," explains Yang. One type of experiment used a monolayer of DNA fragments, whereas another used an atomic force microscope to measure the current through single molecules. Different chiral helices were used in the experiments. "The models explaining why these molecules would favor one of the spins made lots of assumptions, for example, about the shape of the molecules and the path the electrons took."

### Circuits

So Yang set out to create a generic model to describe how spins would pass through different circuits under a linear regime (i.e. the regime that electronic devices operate in). "These models were based on universal rules, independent of the type of molecule," explains Yang. One such rule is charge conservation, which states that every electron that enters a circuit should eventually exit. A second rule is reciprocity, which states that if you swap the roles of the voltage and current contacts in a circuit, the signal should remain the same.

Next, Yang described how these rules would affect the transmission and reflection of spins in different components, for example, a chiral molecule and a ferromagnet between two contacts. The universal rules enabled him to calculate what happened to the spins in these components. He then used the components to model more complex circuits. This allowed him to calculate what to expect if the chiral molecules showed the CISS effect and what to expect if they did not.



## Convincing

When he modeled the CISS experiments published so far, Yang found that some are, indeed, inconclusive. "These experiments aren't convincing enough. They do not show a difference between molecules with and without CISS, at least not in the linear regime of electronic devices." Furthermore, any device using just two contacts will fail to prove the existence of CISS. The good news is that Yang has designed circuits with four contacts that will allow scientists to detect the CISS effect in electronic devices. "I am currently also working on such a circuit, but as it is made up of molecular building blocks, this is quite a challenge."

By publishing his model now, Yang hopes that more scientists will start building the circuits he has proposed, and will finally be able to prove the existence of CISS in electronic devices. "This would be a great contribution to society, as it may enable a whole new approach to the future of electronics."  
[17]

## Biomimetic chemistry—DNA mimic outwits viral enzyme

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

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

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

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

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

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

## Simulations document self-assembly of proteins and DNA

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

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

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

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

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

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

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

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

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

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

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

The activity of the enzyme may be described in a simplified way: Telomerase can be represented as a molecular machine containing an RNA molecule. This machine, with the help of a template part of RNA, binds to the end of a long chain of DNA, and synthesizes a fragment of a new DNA chain along

the remaining template fragment. After that, the telomerase machine has to move to the newly synthesized end of the DNA in order to continue to build up the chain. The scientists assume that the TEN-domain allows telomerase to synthesize DNA fragments of strictly defined length, after which the RNA template should be detached from the DNA strand to move closer to its edge. Thus, the TEN domain facilitates the movement of the enzyme to building up a new region, i.e. the next telomeric fragment, and this is how the synthesis cycle is repeated.

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

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

## Custom sequences for polymers using visible light

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

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

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

The newly developed process is significantly simpler than existing methods. The team also found that both types of monomer were built into the polymer via a mechanism known as non-radical coordination-insertion; this is a generic mechanism, meaning that this new method might be applied to make polymers using a wide range of catalysts and monomers, with the potential to overcome the limited availability of monomer candidates. [13]

## **Artificial and biological cells work together as mini chemical factories**

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

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

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

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

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

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

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

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

They tested these artificial cells in a solution high in copper, which is usually highly toxic to biological cells. The team were still able to detect fluorescent chemicals in the majority of the artificial cells, meaning the biological cells were still alive and functioning inside. This ability would be useful in the

human body, where the artificial cell casing would protect the foreign biological cells from attack by the body's immune system.

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

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

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

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

## **New interaction mechanism of proteins discovered**

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

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

One of these proteins is histone H1, which, as a component of chromatin, is responsible for DNA packaging. Its binding partner, prothymosin  $\alpha$ , 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  $\alpha$  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  $\alpha$  preferably in its central region, which is the region with the highest charge density. Moreover, it emerged that the complex is highly dynamic: The proteins' position in the complex changes extremely quickly—in a matter of approx. 100 nanoseconds.

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

## Particles in charged solution form clusters that reproduce

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

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

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

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



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

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

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

## **Experiment demonstrates quantum mechanical effects from biological systems**

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## Photoactive Prebiotic Systems

We propose that life first emerged in the form of such minimal photoactive prebiotic kernel systems and later in the process of evolution these photoactive prebiotic kernel systems would have produced fatty acids and covered themselves with fatty acid envelopes to become the minimal cells of the Fatty Acid World. Specifically, we model self-assembling of photoactive prebiotic systems with observed quantum entanglement phenomena. We address the idea that quantum entanglement was important in the first stages of origins of life and evolution of the biospheres because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states, leading to faster growth and self-replication of minimal living cells. The quantum mechanically modeled possibility of synthesizing artificial self-reproducing quantum entangled prebiotic kernel systems and minimal cells also impacts the possibility of the most probable path of emergence of photocells on the Earth or elsewhere. We also examine the quantum entangled logic gates discovered in the modeled systems composed of two prebiotic kernels. Such logic gates may have application in the destruction of cancer cells or becoming building blocks of new forms of artificial cells including magnetically active ones.

## Significance Statement

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

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

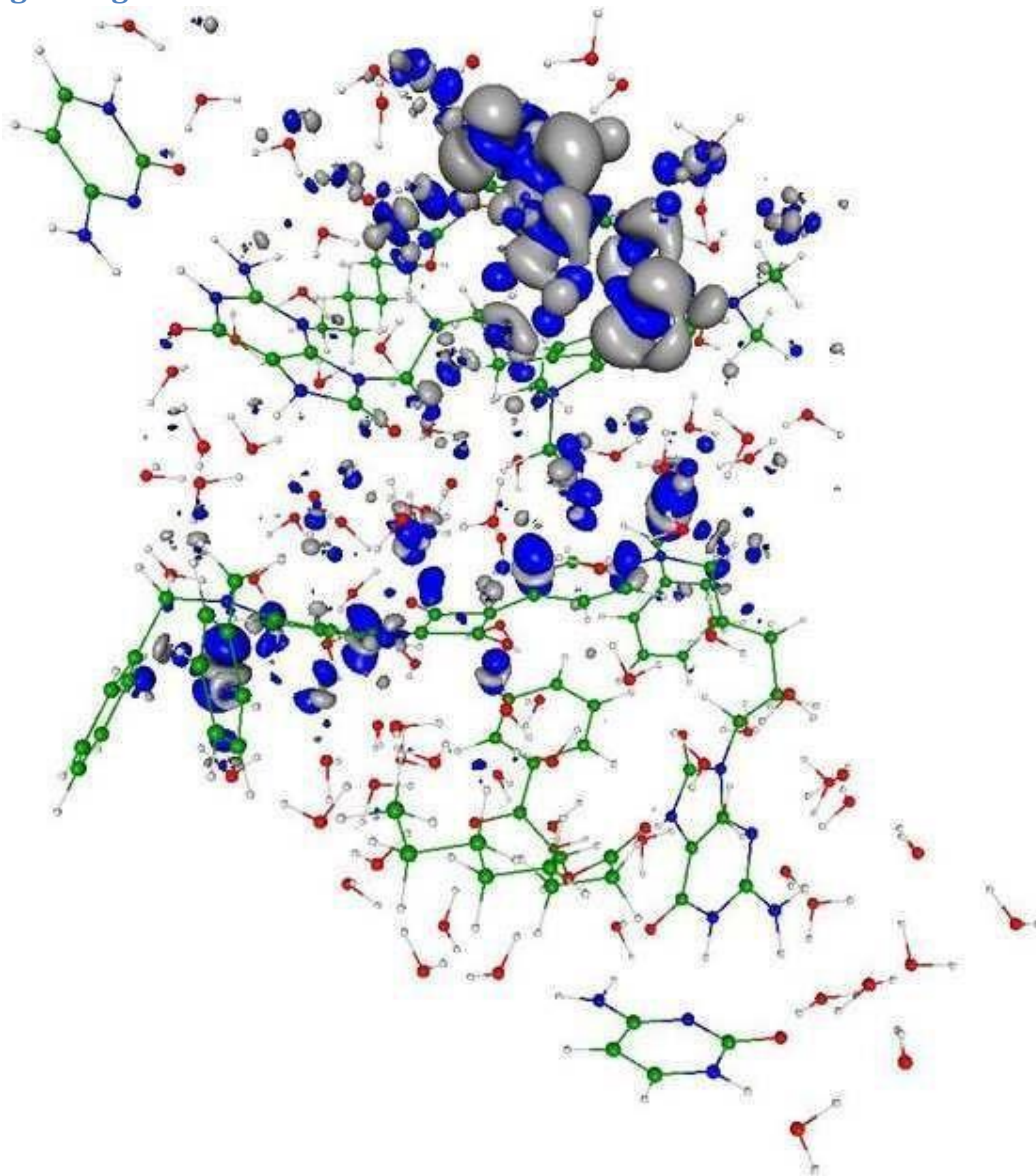
Our discovered phenomenon of the quantum entanglement in the prebiotic systems enhance the photosynthesis in the proposed systems because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states (Tamulis A, Grigalavicius M, Baltrusaitis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

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

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

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

## Figure legend



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

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

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

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

## Quantum Biology

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

## Quantum Consciousness

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

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



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

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

## Creating quantum technology

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

## Quantum Entanglement

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

## The Bridge

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

## Accelerating charges

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

## Relativistic effect

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

## Heisenberg Uncertainty Relation

In the atomic scale the Heisenberg uncertainty relation gives the same result, since the moving electron in the atom accelerating in the electric field of the proton, causing a charge distribution on  $\Delta x$  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  $1/2$  spin creator particle to make equal the spins of the weak interaction, for example neutron decay to 2 fermions, every particle is fermions with  $1/2$  spin. The weak interaction changes the entropy since more or less particles will give more or less freedom of movement. The entropy change is a result of temperature change and breaks the equality of oscillator diffraction

intensity of the Maxwell–Boltzmann statistics. This way it changes the time coordinate measure and makes possible a different time dilation as of the special relativity.

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

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

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

A quark flavor changing shows that it is a reflection changes movement and the CP- and T-symmetry breaking!!! This flavor changing oscillation could prove that it could be also on higher level such as atoms, molecules, probably big biological significant molecules and responsible on the aging of the life.

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

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

## The General Weak Interaction

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

The neutrino oscillation of the Weak Interaction shows that it is a general electric dipole change and it is possible to any other temperature dependent entropy and information changing diffraction pattern of atoms, molecules and even complicated biological living structures. We can generalize the weak interaction on all of the decaying matter constructions, even on the biological too. This gives the limited lifetime for the biological constructions also by the arrow of

time. There should be a new research space of the Quantum Information Science the 'general neutrino oscillation' for the greater than subatomic matter structures as an electric dipole change.

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

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

## Fermions and Bosons

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

## Van Der Waals force

Named after the Dutch scientist Johannes Diderik van der Waals – who first proposed it in 1873 to explain the behaviour of gases – it is a very weak force that only becomes relevant when atoms and molecules are very close together. Fluctuations in the electronic cloud of an atom mean that it will have an instantaneous dipole moment. This can induce a dipole moment in a nearby atom, the result being an attractive dipole–dipole interaction.

## Electromagnetic inertia and mass

### Electromagnetic Induction

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

### Relativistic change of mass

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

### The frequency dependence of mass

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

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

### **Electron – Proton mass ratio**

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

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

## **Gravity from the point of view of quantum physics**

### **The Gravitational force**

The gravitational attractive force is basically a magnetic force.

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

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

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

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

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

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

There is an asymmetry between the mass of the electric charges, for example proton and electron, can be understood by the asymmetrical Planck Distribution Law. This temperature dependent energy

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

## The Higgs boson

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

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

## Higgs mechanism and Quantum Gravity

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

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

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



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

### What is the Spin?

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

### The Graviton

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

### Conclusions

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

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

One of the most important conclusions is that the electric charges are moving in an accelerated way and even if their velocity is constant, they have an intrinsic acceleration anyway, the so called spin, since they need at least an intrinsic acceleration to make possible they movement . The accelerated charges self-maintaining potential shows the locality of the relativity, working on the quantum level also. [1]

The bridge between the classical and quantum theory is based on this intrinsic acceleration of the spin, explaining also the Heisenberg Uncertainty Principle. The particle – wave duality of the electric charges and the photon makes certain that they are both sides of the same thing. The

Secret of Quantum Entanglement that the particles are diffraction patterns of the electromagnetic waves and this way their quantum states every time is the result of the quantum state of the intermediate electromagnetic waves. [2]

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

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

## References

[1] The Magnetic field of the Electric current and the Magnetic induction

[http://academia.edu/3833335/The\\_Magnetic\\_field\\_of\\_the\\_Electric\\_current](http://academia.edu/3833335/The_Magnetic_field_of_the_Electric_current)

[2] 3 Dimensional String Theory [http://academia.edu/3834454/3\\_Dimensional\\_String\\_Theory](http://academia.edu/3834454/3_Dimensional_String_Theory)

[3] Graviton Production By Two Photon and Electron-Photon Processes In Kaluza-Klein Theories With

Large Extra Dimensions <http://arxiv.org/abs/hep-ph/9909392>

[4] Quantum Entanglement

[http://en.wikipedia.org/wiki/Quantum\\_entanglemen](http://en.wikipedia.org/wiki/Quantum_entanglemen)

t

[5] Quantum Consciousness

[https://realitysandwich.com/155783/quantum\\_consciousness\\_0/](https://realitysandwich.com/155783/quantum_consciousness_0/)

[6] Quantum Biology <http://www.nature.com/news/2011/110615/pdf/474272a.pdf> [7]

Quantum entanglement in photoactive prebiotic systems

<https://globalmedicaldiscovery.com/key-drug-discovery-articles/quantum-entanglementphotoactive-prebiotic-systems/>

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

<http://phys.org/news/2014-06-quantum-biology-algae-evolved-coherence.html>

- [9] Experiment demonstrates quantum mechanical effects from biological systems  
<https://phys.org/news/2017-12-quantum-mechanical-effects-biological.html>
- [10] Particles in charged solution form clusters that reproduce  
<https://phys.org/news/2017-12-particles-solution-clusters.html>
- [11] New interaction mechanism of proteins discovered  
<https://phys.org/news/2018-02-interaction-mechanism-proteins.html>
- [12] Artificial and biological cells work together as mini chemical factories  
<https://phys.org/news/2018-03-artificial-biological-cells-mini-chemical.html>
- [13] Custom sequences for polymers using visible light  
<https://phys.org/news/2018-03-custom-sequences-polymers-visible.html>
- [14] Scientists explore the structure of a key region of longevity protein telomerase  
<https://phys.org/news/2018-03-scientists-explore-key-region-longevity.html>
- [15] Simulations document self-assembly of proteins and DNA  
<https://phys.org/news/2018-03-simulations-document-self-assembly-proteins-dna.html>
- [16] Biomimetic chemistry—DNA mimic outwits viral enzyme  
<https://phys.org/news/2018-04-biomimetic-chemistrydna-mimic-outwits-viral.html>
- [17] Theoretical model may help solve molecular mystery  
<https://phys.org/news/2019-02-theoretical-molecular-mystery.html>
- [18] Neutrons get a wider angle on DNA and RNA to advance 3-D models  
<https://phys.org/news/2019-06-neutrons-wider-angle-dna-rna.html>
- [19] Applying the Goldilocks principle to DNA structure  
<https://phys.org/news/2019-06-goldilocks-principle-dna.html>
- [20] By turning molecular structures into sounds, researchers gain insight into protein structures and create new variations  
<https://phys.org/news/2019-06-molecular-gain-insight-protein-variations.html>
- [21] A better way to encapsulate islet cells for diabetes treatment  
<https://phys.org/news/2019-06-encapsulate-islet-cells-diabetes-treatment.html>
- [22] Researchers reach milestone in use of nanoparticles to kill cancer with heat

<https://phys.org/news/2019-06-milestone-nanoparticles-cancer.html>

[23] Size matters: Color imaging of gene expression in electron microscopy

<https://phys.org/news/2019-06-size-imaging-gene-electron-microscopy.html>

[24] Polymer-coated gold nanospheres do not impair the innate immune function of human B lymphocytes

<https://phys.org/news/2019-06-polymer-coated-gold-nanospheres-impair-innate.html>

[25] Towards *in vitro* blood vessel fabrication

<https://physicsworld.com/a/towards-in-vitro-blood-vessel-fabrication/>

[26] 3-D body mapping could identify, treat organs, cells damaged from medical conditions

<https://phys.org/news/2019-06-d-body-cells-medical-conditions.html>

[27] Scientists patent new agent for X-ray

<https://phys.org/news/2019-06-scientists-patent-agent-x-ray.html>

[28] 'Nanoemulsion' gels offer new way to deliver drugs through the skin

<https://phys.org/news/2019-06-nanoemulsion-gels-drugs-skin.html>

[29] Physicists develop model that describes length growth in biological systems

<https://phys.org/news/2019-07-physicists-length-growth-biological.html>

[30] Scientists invent fast method for 'directed evolution' of molecules

<https://phys.org/news/2019-07-scientists-fast-method-evolution-molecules.html>

[31] Inhibition of HER2 on tumor cells by molecularly imprinted nanoparticles

<https://phys.org/news/2019-07-inhibition-her2-tumor-cells-molecularly.html>

[32] Isolating intact bacteria from blood using a microfluidic monolith device

<https://phys.org/news/2019-07-isolating-intact-bacteria-blood-microfluidic.html>

