Biological Structure from Limited Data

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A quantum sensor developed by a team headed by Professor Jörg Wrachtrup at the University of Stuttgart and researchers at the Max Planck Institute for Solid State Research in Stuttgart, now makes it possible to use nuclear magnetic resonance scanning to even investigate the structure of individual proteins atom by atom. [24]

Scientists at the University of Nottingham are working with University College London (UCL) on a five year project which has the potential to revolutionise the world of human brain imaging. [23]

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A research team led by Professor CheolGi Kim has developed a biosensor platform using magnetic patterns resembling a spider web with detection capability 20 times faster than existing biosensors. [21]

Researchers at Columbia University have made a significant step toward breaking the so-called "color barrier" of light microscopy for biological systems, allowing for much more comprehensive, system-wide labeling and imaging of a greater number of biomolecules in living cells and tissues than is currently attainable. [20]

Scientists around the Nobel laureate Stefan Hell at the Max Planck Institute for Biophysical Chemistry in Göttingen have now achieved what was for a long time considered impossible – they have developed a new fluorescence microscope, called MINFLUX, allowing, for the first time, to optically separate molecules, which are only nanometers (one millionth of a millimeter) apart from each other. [19]

Dipole orientation provides new dimension in super-resolution microscopy [18]

Fluorescence is an incredibly useful tool for experimental biology and it just got easier to tap into, thanks to the work of a group of University of Chicago researchers. [17]

Molecules that change colour can be used to follow in real-time how bacteria form a protective biofilm around themselves. This new method, which has been developed in collaboration between researchers at Linköping University and

Karolinska Institutet in Sweden, may in the future become significant both in medical care and the food industry, where bacterial biofilms are a problem. [16]

Researchers led by Carnegie Mellon University physicist Markus Deserno and University of Konstanz (Germany) chemist Christine Peter have developed a computer simulation that crushes viral capsids. By allowing researchers to see how the tough shells break apart, the simulation provides a computational window for looking at how viruses and proteins assemble. [15]

IBM scientists have developed a new lab-on-a-chip technology that can, for the first time, separate biological particles at the nanoscale and could enable physicians to detect diseases such as cancer before symptoms appear. [14]

Scientists work toward storing digital information in DNA. [13]

Leiden theoretical physicists have proven that DNA mechanics, in addition to genetic information in DNA, determines who we are. Helmut Schiessel and his group simulated many DNA sequences and found a correlation between mechanical cues and the way DNA is folded. They have published their results in PLoS One. [12]

We model the electron clouds of nucleic acids in DNA as a chain of coupled quantum harmonic oscillators with dipole-dipole interaction between nearest neighbours resulting in a van der Waals type bonding. [11]

Scientists have discovered a secret second code hiding within DNA which instructs cells on how genes are controlled. The amazing discovery is expected to open new doors to the diagnosis and treatment of diseases, according to a new study. [10]

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

From the standpoint of physics, there is one essential difference between living things and inanimate clumps of carbon atoms: The former tend to be much better at capturing energy from their environment and dissipating that energy as heat. [8]

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

The human body is a constant flux of thousands of chemical/biological interactions and processes connecting molecules, cells, organs, and fluids, throughout the brain, body, and nervous system. Up until recently it was thought that all these interactions operated in a linear sequence, passing on

information much like a runner passing the baton to the next runner. However, the latest findings in quantum biology and biophysics have discovered that there is in fact a tremendous degree of coherence within all living systems.

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

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

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

Contents

Author: George Rajna

Preface

Scientists have discovered a secret second code hiding within DNA which instructs cells on how genes are controlled. The amazing discovery is expected to open new doors to the diagnosis and treatment of diseases, according to a new study. Ever since the genetic code was deciphered over 40 years ago, scientists have believed that it only described how proteins are made. However, the revelation made by the research team led by John Stamatoyannopoulos of the University of Washington indicates that genomes use the genetic code to write two separate languages. [10]

Jeremy England, a 31-year-old assistant professor at the Massachusetts Institute of Technology, has derived a mathematical formula that he believes explains this capacity. The formula, based on established physics, indicates that when a group of atoms is driven by an external source of energy (like the sun or chemical fuel) and surrounded by a heat bath (like the ocean or atmosphere), it will often gradually restructure itself in order to dissipate increasingly more energy. This could mean that under certain conditions, matter inexorably acquires the key physical attribute associated with life. [8]

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]

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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.

New algorithms extract biological structure from limited data

Understanding the 3D molecular structure of important nanoobjects like proteins and viruses is crucial in biology and medicine. With recent advances in X-ray technology, scientists can now collect diffraction images from individual particles, ultimately allowing researchers to visualize molecules at room temperature.

However, determining 3D structure from these single-particle diffraction experiments is a significant hurdle. For instance, current data acquisition rates are very limiting, typically resulting in fewer than 10 useful snapshots per minute, limiting the amount of features that can be resolved. Additionally, the images are often highly corrupted with noise and other experimental artefacts, making it difficult to properly interpret the data.

To meet these challenges, a team of researchers from the Lawrence Berkeley National Laboratory (Berkeley Lab) has developed a new algorithmic framework called multi-tiered iterative phasing (M-TIP) that utilizes advanced mathematical techniques to determine 3D molecular structure from very sparse sets of noisy, single-particle data. This approach essentially allows researchers to extract more information from experiments with limited data. Applied mathematicians Jeffrey Donatelli and James Sethian, and physical bioscientist Peter Zwart introduced this framework by expanding on an algorithm that they originally developed to solve the reconstruction from a related X-ray scattering experiment, called fluctuation X-ray scattering. A paper describing the M-TIP framework was published June 26 in the Proceedings of the National Academy of Sciences.

"This approach has the potential to revolutionize the field," says Zwart. "Given that it is hard to get a lot of good data, approaches that reduce the amount of data needed to successfully image 3D nanoobjects are likely to receive a warm welcome."

Donatelli, Sethian and Zwart are all part of CAMERA (The Center for Advanced Mathematics for Energy Research Applications), whose mission is to create the state-of-the-art mathematics required to handle data from many of DOE's most advanced scientific facilities. CAMERA is jointly funded by the Advanced Scientific Computing Research and Basic Energy Sciences programs in DOE's Office of Science.

Single Particle Diffraction

The recent advent of X-ray free-electron lasers (XFELs) has enabled several new experimental techniques for studying biomolecules that were infeasible with traditional light sources. One such technique is single-particle diffraction, which collects a large number of X-ray diffraction snapshots with only a single particle in the beam. By leveraging the extreme power of XFELs, researchers can collect measurable signals even from the tiniest particles.

One big advantage offered by this single-particle diffraction technique is the ability to study how different copies of a molecule vary or change in shape. Since each image comes from a single particle, these variations can be captured in the experiment, in contrast to traditional imaging methods like crystallography or small-angle X-ray scattering, where researchers can only measure an average over all different states of the molecular sample.

However, determining the 3D structure from single-particle diffraction data is challenging. To begin, when each particle is imaged, its orientation is unknown and needs to be recovered in order to properly combine the data into a 3D diffraction volume. This problem is compounded if the molecule can take on different shapes, which requires additional classification of the images. Furthermore, phase information is not recorded in diffraction images and must be recovered in order to complete the reconstruction. Finally, even with powerful XFELs, the number of scattered photons is very small, resulting in extremely noisy images, which can be further contaminated by systematic background and detector readout issues.

Previous approaches are based on solving the reconstruction problem in separate steps, where each individual problem is addressed separately. Unfortunately, a drawback to these serial approaches is that they do not easily leverage prior known features about what the molecule looks like. In addition, any error committed in one step is propagated to the next, resulting in a further increase in error. This "error snowball" ultimately degrades the quality of the reconstruction obtained in the final step.

Best of Both Worlds

Instead of solving the computational problems in separate steps, the team's M-TIP algorithm solves all parts of the problem concurrently. This approach leverages prior information about the structure to greatly reduce the degrees of freedom of the problem in all steps, and consequently reduce the required information needed to achieve a 3D reconstruction.

"Standard black-box optimization techniques can incorporate prior knowledge into the reconstruction but throw away all of the structure of the problem, whereas solving it in completely separate serial substeps exploits the structure of the problem but throws away almost all prior information about what the solution might look like," Donatelli said. "M-TIP leverages the best of both worlds by exploiting the structure of the problem to break up the computation into several manageable chunks and then iteratively refining over all of these chunks to arrive at a solution which is consistent with both the data and any structural constraints."

Using this technique, the team was able to determine 3D structure from extremely low image counts from simulated data, as low as 6 to 24 images for noise-free data and 192 images from highly contaminated data.

Breaking New Ground

This work is part of a new collaboration initiative between SLAC National Accelerator Laboratory, CAMERA, the National Energy Research Scientific Computing Center (NERSC) and Los Alamos National Laboratory as part of DOE's Exascale Computing Project (ECP). The goal of the project is to develop the computational tools necessary to perform real-time data analysis from experiments being conducted at SLAC's Linac Coherent Light Source (LCLS). With upgrades to the beamline, LCLS-II plans to generate several terabytes of data per second, which, for example, will allow scientists to greatly expand upon current single-particle experiments. Analyzing all of this data in real-time will require new algorithms and large computing machines. The M-TIP algorithm will serve as part of this process.

"These are some of the most challenging problems in computational data science," says Sethian. "To tackle them, we need to exploit a range of technologies, including emerging exascale computing architectures, sophisticated high speed networks, and the most advanced mathematical algorithms available. Bringing CAMERA scientists together with exascale application projects has opened the door to building tools to approach some pressing problems in biology and materials sciences."

The researchers note that these are just the first steps. In order for the method to be ready to be deployed, other hurdles have to be overcome.

"Experimental science is messy," says Zwart. "There are additional experimental effects that have to be taken into consideration in order for us to get the best possible results."

"Fortunately, M-TIP is a very modular technique," adds Donatelli, "so, it is well suited to modeling many of these additional effects without needing to change the core algorithmic framework."

The team is currently working on studying these effects as part of the Single Particle Initiative, a large, multi-institutional collaboration dedicated to addressing theoretical and practical issues in X-FEL-based single molecule imaging, ultimately leading to providing the scientific community with the tools needed to break new ground in biology, medicine and energy sciences. [25]

Quantum sensor with improved resolution can now identify individual atoms in biomolecules

Nuclear magnetic resonance scanners, as are familiar from hospitals, are now extremely sensitive. A quantum sensor developed by a team headed by Professor Jörg Wrachtrup at the University of Stuttgart and researchers at the Max Planck Institute for Solid State Research in Stuttgart, now makes it possible to use nuclear magnetic resonance scanning to even investigate the structure of individual proteins atom by atom. In the future, the method could help to diagnose diseases at an early stage by detecting the first defective proteins.

Many diseases have their origins in defective proteins. As proteins are important biochemical motors, defects can lead to disturbances in metabolism. Defective prions, which cause brain damage in BSE and Creutzfeldt- Jakob disease, are one example. Pathologically changed prions have defects in their complex molecular structure. The problem: individual defective proteins can likewise induce defects in neighbouring intact proteins via a sort of domino effect and thus trigger a disease. It would therefore be very useful if doctors could detect the first, still individual prions with the wrong

structure. It has, however, not been possible to date to elucidate the structure of one individual biomolecule.

In an article published in Science, a team of researchers from Stuttgart has now presented a method that can be used in the future for the reliable investigation of individual biomolecules. This is important not only for fighting diseases, but also for chemical and biochemical basic research.

The method involves the miniaturization as it were of the nuclear magnetic resonance tomography (NMR) known from medical engineering, which is usually called MRI scanning in the medical field. NMR makes use of a special property of the atoms - their spin. In simple terms, spin can be thought of as the rotation of atomic nuclei and electrons about their own axis, turning the particles into tiny, spinning bar magnets. How these magnets behave is characteristic for each type of atom and each chemical element. Each particle thus oscillates with a specific frequency.

In medical applications, it is normal for only one type of atom to be detected in the body – hydrogen, for example. The hydrogen content in the different tissues allows the interior of the body to be distinguished with the aid of various contrasts.

Structural resolution at the atomic level

When elucidating the structure of biomolecules, on the other hand, each individual atom must be determined and the structure of the biomolecule then deciphered piece by piece. The crucial aspect here is that the NMR detectors are so small that they achieve nanometre-scale resolution and are so sensitive that they can measure individual molecules exactly. It is more than four years ago that the researchers working with Jörg Wrachtrup first designed such a small NMR sensor; it did not, however, allow them to distinguish between individual atoms.

To achieve atomic-level resolution, the researchers must be able to distinguish between the frequency signals they receive from the individual atoms of a molecule – in the same way as a radio identifies a radio station by means of its characteristic frequency. The frequencies of the signals emitted by the atoms of a protein are those frequencies at which the atomic bar magnets in the protein spin. These frequencies are very close together, as if the transmission frequencies of radio stations all tried to squeeze themselves into a very narrow bandwidth. This is the first time the researchers in Stuttgart have achieved a frequency resolution at which they can distinguish individual types of atoms.

"We have developed the first quantum sensor that can detect the frequencies of different atoms with sufficient precision and thus resolve a molecule almost into its individual atoms," says Jörg Wrachtrup. It is thus now possible to scan a large biomolecule, as it were. The sensor, which acts as a minute NMR antenna, is a diamond with a nitrogen atom embedded into its carbon lattice close to the surface of the crystal. The physicists call the site of the nitrogen atom the NV centre: N for nitrogen and V for vacancy, which refers to a missing electron in the diamond lattice directly adjacent to the nitrogen atom. Such an NV centre detects the nuclear spin of atoms located close to this NV centre.

Simple yet very precise

The spin frequency of the magnetic moment of an atom which has just been measured is transferred to the magnetic moment in the NV centre, which can be seen with a special optical microscope as a change in colour.

The quantum sensor achieves such high sensitivity, as it can store frequency signals of an atom. One single measurement of the frequency of an atom would be too weak for the quantum sensor and possibly too noisy. The memory allows the sensor to store many frequency signals over a longer period of time, however, and thus tune itself very precisely to the oscillation frequency of an atom – in the same way as a high-quality short-wave receiver can clearly resolve radio channels which are very close to each other.

This technology has other advantages apart from its high resolution: it operates at room temperature and, unlike other high-sensitivity NMR methods used in biochemical research, it does not require a vacuum. Moreover, these other methods generally operate close to absolute zero - minus 273.16 degrees Celsius - necessitating complex cooling with helium.

Future field of application: brain research

Jörg Wrachtrup sees not one but several future fields of application for his high-resolution quantum sensors. "It is conceivable that, in future, it will be possible to detect individual proteins that have undergone a noticeable change in the early stage of a disease and which have so far been overlooked." Furthermore, Wrachtrup is collaborating with an industrial company on a slightly larger quantum sensor which could be used in the future to detect the weak magnetic fields of the brain. "We call this sensor the brain reader. We hope it will help us to decipher how the brain works – and it would be a good complement to the conventional electrical devices derived from the EEG" – the electroencephalogram. For the brain reader, Wrachtrup is already working with his industrial partner on a holder and a casing so that the device is easy to wear and to operate on a day-to-day basis. To reach this point, however, it will take at least another ten years of research. [24]

Quantum sensors herald new generation of wearable brain imaging systems

Scientists at the University of Nottingham are working with University College London (UCL) on a five year project which has the potential to revolutionise the world of human brain imaging.

Magnetoencephalography (MEG) is a technique for mapping brain activity - it measures the magnetic fields generated by electrical currents that occur naturally in the brain. A £1.6m Collaborative Award in Science from Wellcome is funding the construction of a new type of MEG scanner which, if successful, could quadruple the sensitivity of current state of the art devices.

Dr Matthew Brookes and Professor Richard Bowtell, in the School of Physics and Astronomy are leading the research in Nottingham, where they have already designed and built a 3-D printed prototype wearable helmet and are in the very early stages of developing the new MEG system. Images are available via this dropbox link.

Dr Brookes said: "Quantum technology has allowed the development of a new type of optical sensor which has the sensitivity to detect the weak magnetic fields from the brain. Unlike current

technology, these new sensors can operate at room temperature, so they can be placed directly on the scalp surface. Our calculations show that by getting the sensors closer to the head we can quadruple the sensitivity of the field detection. This will revolutionise the kind of effect that we are able to detect from the human brain."

Most current MEG systems are cumbersome, built around a small bore into which a participant's head is gently clamped because the sensors, which have to be kept at minus 269 degrees, cannot be moved. It is a static, one-size-fits-all system. This artificial environment restricts both the subject groups that can be scanned and the experimental questions that can be addressed.

Pilot experiments showed potential of new quantum sensors

The collaborative team began working in this area 2 years ago, assessing the potential of quantum sensors in computational simulations. Following this, using pump-priming funding from UCL and the University of Nottingham, the team purchased a small number of quantum sensors, and used them to show, experimentally, that the expected improvement in sensitivity could become a reality. Based on this pilot data, they have now received the Wellcome award to construct a fully functional multi-channel MEG system based on quantum sensors – of which £800,000 is funding the work in Nottingham.

While the physics-based development needed to make the scanner work is being carried out in Nottingham, experts at UCL are carrying out detailed computational and theoretical modelling of the brain to frame the neuroscience and establish what neuroscience questions can be addressed.

A huge and challenging task lies ahead

The research project, 'Moving functional brain imaging into the real world: A wearable, cryogen-free, MEG system', is led by Professor Gareth Barnes, in the Wellcome Trust Centre for Neuroimaging at UCL. He said: "The realisation of this system is a huge, but extremely exciting, challenge, with the potential to revolutionise the brain imaging field. Our simulations and pilot experiments have already shown the unique potential of the new quantum sensors."

Professor Barnes continued: "Our scanner will be worn on the head like a helmet, meaning subjects can undertake tasks whilst moving freely in an open and natural environment."

The new scanner has the potential to revolutionise brain imaging for all subjects, but will be particularly useful in children. Professor Richard Bowtell, grant co-applicant and Director of the Sir Peter Mansfield Imaging Centre in Nottingham said: "Because MEG systems are essentially 'one size fits all', sensitivity is limited for subjects with smaller heads such as infants since their heads are further from the detectors. Room temperature quantum sensors can be mounted directly on the scalp of any subject. This will give us a projected four-fold increase in sensitivity for adults, but the sensitivity could potentially be up to a 15 or 20 fold increase for children or babies."

The first stage of their work has already been published. What the research team really want to do is translate this technology into neuroscience and ultimately a clinical tool for conditions such as drug resistant epilepsy and schizophrenia. [23]

Quantum biometric targets the retina

Scientists in Greece have devised a new form of biometric identification that relies on humans' ability to see flashes of light containing just a handful of photons. The technique involves using very weak laser pulses to measure how a person's sensitivity to light varies across their retina. According to its inventors, such a quantum-based retinal map could provide a more powerful and secure form of identification than is possible with conventional biometrics such as fingerprints or iris scans.

It has been known since the 1940s that humans are able to detect light pulses containing very few photons. However, whether we can actually see single photons is still unclear: one group last year said it had carried out experiments showing this to be the case but others questioned the claim. In the 1940s, Selig Hecht and colleagues at Columbia University in the US showed that variations in our perception of very low light levels are in fact governed by quantum statistics. By exposing several individuals to very dim flashes of light of differing average intensity, they found that the intensity-induced variation in the probability of seeing a flash could be modelled by assuming that the actual number of photons a person sees follows a Poisson distribution.

This result held true across the different people examined, although the specific responses depended on an individual's value of alpha – a parameter describing the fraction of photons arriving at a person's eye that are then detected by their retina. Losses caused by absorption or scattering within the cornea, pupil, lens and body of the eyeball, as well as a finite probability of absorption within the retina itself, means that alpha typically varies between 0 and 0.2. This variation led to a series of curves describing seeing probability versus average intensity, whose precise shape depended on alpha.

Unique variations

In the latest work, Iannis Kominis of the University of Crete and colleagues use these variations as the basis of the new biometric scheme. They say that the value of alpha changes by up to a factor of 100 from one point to another on an individual's retina, while variations between retinas can be up to 50%. As such, they argue that people could be uniquely identified by precisely mapping the variation of alpha across their retinas.

The "alpha map" of a particular individual, who the researchers call Alice, would be created by exposing that person to large numbers of very weak laser pulses. The pulses would have a range of average intensities, and the exercise would be repeated across multiple points on Alice's retina. For each pulse, Alice would be asked whether or not she saw a flash of light. With the map stored on a secure database, Alice could then be identified by examining a subset of points on her retina. Again, she would be exposed to a series of weak laser pulses and asked on each occasion whether or not she sees the pulse. Only if her answers closely match what would be expected from her map would she be allowed to proceed.

As Kominis and colleagues explain in a preprint uploaded to the arXiv server, Alice must be subject to a sufficient number of yes/no interrogations to limit two types of error as far as possible. One type of error is the "false negative", which means that Alice is not recognized as herself. The other type is the "false positive", in which an impostor, known as Eve, successfully fools the system into thinking that she is Alice.

Fifty interrogations

For the scheme to be implemented on a practical timescale, the number of interrogations must be limited. Simply choosing a random subset of points on Alice's retina would involve 2500 interrogations to reach certain benchmarks – generating a false negative less than once every 10,000 identifications and a false positive less than one every 10 billion. However, by refining their technique in a number of ways – choosing only very low or very high alpha regions on the retina, using Bayesian statistics and employing pattern recognition – the researchers calculated that just 50 interrogations would do the job.

In addition, they assessed how well their scheme would cope if Eve was able to measure the number of photons entering Alice's eye as well as monitoring her brain activity. Their conclusion: Eve would need to make extremely precise measurements of both the thermal energy dumped in Alice's eye and the magnetic energy emitted by her head – something that would be very difficult to achieve.

Rebecca Holmes of the University of Illinois in the US praises Kominis and colleagues for having "put a lot of thought into how to optimise" their biometric technique. But she says she is "sceptical" about the scheme's practicality, pointing out that up to half an hour would be needed just to acclimatize Alice's eyes to the very dark conditions required. Holmes also disputes the technique's "quantum" label, arguing that although it involves small numbers of photons, it does not provide a physics-based guarantee of complete security, as quantum cryptography (in principle) can do. [22]

Researchers develop faster biosensor platform using a magnetic field

A research team led by Professor CheolGi Kim has developed a biosensor platform using magnetic patterns resembling a spider web with detection capability 20 times faster than existing biosensors.

The sensing capability of a biosensor is determined by the resolution of the sensor and the movement and reaction rate of molecules. Many research groups in Korea and other countries have been improving the resolution through with nanomaterials innovations, but there improving the sensitivity is challenging due to the low diffusion transport of biomolecules toward the sensing region.

Professor Kim and his research team used a magnetic field to overcome the slow movement of biomolecules such as proteins and DNA is slow when the transport depends on diffusion. Biomolecules labeled with superparamagnetic particles could be controlled with the use of an external magnetic field and detected with an ultra-sensitive magnetic sensor. The research team's biosensor platform uses a spider web-shaped micro-magnetic pattern that improves the sensing ability of the biosensor by attracting biomolecules labeled with the superparamagnetic particles to the sensing area.

DGIST develops 20 times faster biosensor

a. Schematic representation of the sensor-integrated magnetic spider web; b. Scanning electron microscope (SEM) image of the sensor integrated with the spider web net; c. Schematic cross-sectional view of the layered structures of the …more

The first author Byeonghwa Lim at DGIST's Ph.D program of Emerging Materials Science elaborated on the biosensor platform: "When a rotating magnetic field is applied to a spider web-shaped magnetic pattern, it can attract biomolecules labeled with superparamagnetic particles faster to the sensor. The speed is very fast and it can detect the subject 20 times faster than the diffusion method."

The research team also succeeded in monitoring the biomolecules conjugated to the superparamagnetic particles at a distance from the sensing area by utilizing the biosensor platform. In addition, the team found that the superparamagnetic particles not only play the role of biomolecular cargo for transportation, but also act as labels for the sensor to indicate the location of biomolecules.

Professor Kim said, "The existing biosensors require a long time to detect low-density biomolecules, and have poor sensing efficiency as they only depend on diffusion. The magnetic field-based biosensor platform improves the collection capability of biomolecules and increases the speed and sensitivity of the biomolecules movement. Therefore, we are planning to use this platform for early diagnosis as well as recurrence diagnosis of diseases such as cancer. " [21]

New microscopy method breaks color barrier of optical imaging

Researchers at Columbia University have made a significant step toward breaking the so-called "color barrier" of light microscopy for biological systems, allowing for much more comprehensive, system-wide labeling and imaging of a greater number of biomolecules in living cells and tissues than is currently attainable. The advancement has the potential for many future applications, including helping to guide the development of therapies to treat and cure disease.

In a study published online April 19 in Nature, the team, led by Associate Professor of Chemistry Wei Min, reports the development of a new optical microscopy platform with drastically enhanced detection sensitivity. Additionally, the study details the creation of new molecules that, when paired with the new instrumentation, allow for the simultaneous labeling and imaging of up to 24 specific biomolecules, nearly five times the number of biomolecules that can be imaged at the same time with existing technologies.

"In the era of systems biology, how to simultaneously image a large number of molecular species inside cells with high sensitivity and specificity remains a grand challenge of optical microscopy," Min said. "What makes our work new and unique is that there are two synergistic pieces - instrumentation and molecules - working together to combat this long-standing obstacle. Our platform has the capacity to transform understanding of complex biological systems: the vast human cell map, metabolic pathways, the functions of various structures within the brain, the internal environment of tumors, and macromolecule assembly, to name just a few."

All existing methods of observing a variety of structures in living cells and tissues have their own strengths, but all are also hindered by fundamental limitations, not the least of which is the existence of a "color barrier."

Fluorescence microscopy, for example, is extremely sensitive and, as such, is the most prevalent technique used in biology labs. The microscope allows scientists to monitor cellular processes in

living systems by using proteins that are broadly referred to as "fluorescent proteins" with usually up to five colors. Each of the fluorescent proteins has a target structure that it applies a "tag," or color to. The five fluorescent proteins, or colors, typically used to tag these structures are BFP (Blue Fluorescent Protein), ECFP (Cyan Fluorescent Protein), GFP (Green Fluorescent Protein), mVenus (Yellow Fluorescent Protein), and DsRed (Red Fluorescent Protein).

Despite its strengths, fluorescence microscopy is impeded by the "color barrier," which limits researchers to seeing a maximum of only five structures at a time because the fluorescent proteins used emit a range of indistinguishable shades that, as a result, fall into five broad color categories.

If a researcher is trying to observe all of the hundreds of structures and different cell types in a live brain tumor tissue sample, for example, she would be restricted to seeing only up to five structures at a time on a single tissue sample. If she wanted to see more than those five, she would have to clean the tissue of the fluorescent labels she used to identify and tag the last five structures in order to use those same fluorescent labels to identify another set of up to five structures. She would have to repeat this process for every set of up to five structures she wants to see. Not only is observing a maximum of five structures at a time labor intensive, but in cleaning the tissue, vital components of that tissue could be lost or damaged.

"We want to see them all at the same time to see how they're operating on their own and also how they're interacting with each other," said Lu Wei, lead author on the study and a postdoctoral researcher in the Min lab. "There are lots of components in a biological environment and we need to be able to see everything simultaneously to truly understand the processes."

In addition to fluorescence microscopy, there are currently a variety of Raman microscopy techniques in use for observing living cell and tissue structures that work by making visible the vibrations stemming from characteristic chemical bonds in structures. Traditional Raman microscopy produces the highly-defined colors lacking in fluorescence microscopy, but is missing the sensitivity. As such, it requires a strong, concentrated vibrational signal that can only be achieved through the presence of millions of structures with the same chemical bond. If the signal from the chemical bonds is not strong enough, visualizing the associated structure is near impossible.

To address this challenge, Min and his team, including Profs. Virginia Cornish in chemistry and Rafael Yuste in neuroscience, pursued a novel hybrid of existing microscopy techniques.

They developed a new platform called electronic pre-resonance stimulated Raman scattering (epr-SRS) microscopy that combines the best of both worlds, bringing together a high level of sensitivity and selectivity. The innovative technique identifies, with extreme specificity, structures with significantly lower concentration - instead of millions of the same structure needed to identify the presence of that structure in traditional Raman microscopy, the new instrument requires only 30 for identification. The technique also utilizes a novel set of tagging molecules designed by the team to work synergistically with the ultramodern technology. The amplified "color palette" of molecules broadens tagging capabilities, allowing for the imaging of up to 24 structures at a time instead of being limited by only five fluorescent colors. The researchers believe there's potential for even further expansion in the future.

The team has successfully tested the epr-SRS platform in brain tissue. "We were able to see the different cells working together," Wei said. "That's the power of a larger color palette. We can now light up all these different structures in brain tissue simultaneously. In the future we hope to watch them function in real time." Brain tissue is not the only thing the researchers envision this technique being used for, she added. "Different cell types have different functions, and scientists usually study only one cell type at a time. With more colors, we can now start to study multiple cells simultaneously to observe how they interact and function both on their own and together in healthy conditions versus in disease states."

The new platform has many potential applications, Min said, adding that it is possible the technique could one day be used in the treatment of tumors that are hard to kill with available drugs. "If we can see how structures are interacting in cancer cells, we can identify ways to target specific structures more precisely," he said. "This platform could be game-changing in the pursuit of understanding anything that has a lot of components." [20]

Researchers achieve ultimate resolution limit in fluorescence microscopy

It is the holy grail of light microscopy: improving the resolving power of this method such that one can individually discern molecules that are very close to each other. Scientists around the Nobel laureate Stefan Hell at the Max Planck Institute for Biophysical Chemistry in Göttingen have now achieved what was for a long time considered impossible – they have developed a new fluorescence microscope, called MINFLUX, allowing, for the first time, to optically separate molecules, which are only nanometers (one millionth of a millimeter) apart from each other. This microscope is more than 100 times sharper than conventional light microscopy and surpasses even the best super-resolution light microscopy methods to date, namely STED developed by Hell and PALM/STORM described by Nobel laureate Eric Betzig, by up to 20 times. For MINFLUX, Hell used the advantages of STED and PALM/STORM in a completely new concept. This breakthrough opens up new opportunities for researchers to investigate how life functions at the molecular level.

"We have routinely achieved resolutions of a nanometer with MINFLUX, which is the diameter of individual molecules – the ultimate limit of what is possible in fluorescence microscopy," explains Hell, Director at the Max Planck Institute for Biophysical Chemistry. "I am convinced that MINFLUX microscopes have the potential to become one of the most fundamental tools of cell biology. With this concept it will be possible to map cells in molecular detail and to observe the rapid processes in their interior in real time. This could revolutionize our knowledge of the molecular processes occurring in living cells."

The Göttingen physicist, who also works at the Max Planck Institute for Medical Research and the German Cancer Research Center in Heidelberg, has long been convinced that fluorescence microscopy resolution can be increased down to the dimension of individual molecules – with classical use of focused light and conventional lenses.

In fact, the physicist Ernst Abbe had formulated in 1873 that the resolution of light microscopes is limited to half the wavelength of light, which is about 200 nanometers. More than 100 years later,

this Abbe limit is still valid. However, Hell was the first to show that this limit can be overcome with STED microscopy, which he conceived in 1994 and established experimentally five years later.

STED as well as PALM/STORM, developed a few years later, in practice achieve a separation sharpness of about 20 to 30 nanometers – about ten times better than the Abbe limit. For the development of these ultra-high resolution light microscopy techniques, Hell and Betzig together with William E. Moerner were awarded the 2014 Nobel Prize in Chemistry.

Advantages of STED and PALM/STORM combined

Both STED and PALM/STORM separate neighboring fluorescing molecules by switching them on and off one after the other so that they emit fluorescence sequentially. However, the methods differ in one essential point: STED microscopy uses a doughnut-shaped laser beam to turn off molecular fluorescence at a fixed location in the sample, i.e. everywhere in the focal region except at the doughnut center. The advantage is that the doughnut beam defines exactly at which point in space the corresponding glowing molecule is located. The disadvantage is that in practice the laser beam is not strong enough to confine the emission to a single molecule at the doughnut center. In the case of PALM/STORM, on the other hand, the switching on and off is at random locations and at the single-molecule level. The advantage here is that one is already working at the single-molecule level, but a downside is that one does not know the exact molecule positions in space. The positions have to be found out by collecting as many fluorescence photons as possible on a camera; more than 50,000 detected photons are needed to attain a resolution of less than 10 nanometers. In practice, one therefore cannot routinely achieve molecular (one nanometer) resolution.

Hell had the idea to uniquely combine the strengths of both methods in a new concept. "This task was anything but trivial. But my co-workers Francisco Balzarotti, Yvan Eilers, and Klaus Gwosch have done a wonderful job in implementing this idea experimentally with me." Their new technique, called MINFLUX (MINimal emission FLUXes), is now introduced by Hell together with the three junior scientists as first authors in Science.

MINFLUX, like PALM/STORM, switches individual molecules randomly on and off. However, at the same time, their exact positions are determined with a doughnut-shaped laser beam as in STED. In contrast to STED, the doughnut beam here excites the fluorescence. If the molecule is on the ring, it will glow; if it is exactly at the dark center, it will not glow but one has found its exact position. Balzarotti developed a clever algorithm so that this position could be located very fast and with high precision. "With this algorithm it was possible to exploit the potential of the doughnut excitation beam," the young scientist explains. Gwosch, who obtained the molecular resolved images, adds "It was an incredible feeling as we, for the first time, were able to distinguish details with MINFLUX on the scale of a few nanometers."

100 times better resolution

In addition to the molecular resolution, the combination of STED and PALM/STORM offers an additional major advantage: "MINFLUX is much faster in comparison. Since it works with a doughnut laser beam, it requires much lower light signal, i.e. fewer fluorescence photons, per molecule as compared to PALM/STORM for attaining the ultimate resolution," Hell states. Already with STED one could record real-time videos from the inside of living cells. But now it was possible to trace the movement of molecules in a cell with a 100 times better temporal resolution, as Eilers emphasizes.

He managed to film the movement of molecules in a living E. coli bacterium with MINFLUX for the first time, with an unprecedented spatio-temporal resolution. "As far as speed is concerned, we have not made the most of the possibilities with MINFLUX," Eilers says. The researchers are convinced that even extremely fast-occurring changes in living cells can be investigated in the future, like for example the movement of cellular nanomachines or the folding of proteins. [19]

Dipole orientation provides new dimension in super-resolution microscopy

Recently, a new polarization-dipole azimuth-based super-resolution technique has been proposed by a group of researchers in Peking University (China), Tsinghua University (China), and University of Technology Sydney (Australia). It not only provides a new dimension for super-resolution, but also provides a timely solution to a recent hot debate in the field.

Since fluorescence polarization was discovered on 1926, multiple fluorescence anisotropy techniques have been developed to study dipole orientation of fluorophores. However, in the case of super-resolution, while other properties of fluorescence such as intensity, spectrum, fluorescence lifetime, etc., have been well applied, little attention is paid to the direction of the fluorescence dipole (polarization). In 2014, Walla team published an article in Nature Methods to achieve sparse reconstructed super-resolution imaging by polarization-modulating excitation. In early 2016, Keller group published a comment on this article on Nature Methods, which stated that fluorescence polarization adds little additional information to (fluorescence intensity) super-resolution. This raised an interesting debate: whether the polarization modulation can provide super-resolution information or not?

However, both the Walla and Keller groups investigated this problem from a conventional fluorescence intensity point of view. Taking into account fluorescence intensity and fluorescence anisotropy, this work introduces the dipole angle to distinguish fluorescence through the fourth dimension of the fluorescence, and perfectly answers this controversy.

Traditional fluorescence anisotropy techniques are limited to samples of relative uniform polarization. Fluorescence polarization would be affected by a bulk of fluorophores due to Abbe's diffraction limit when it comes to complex samples. SDOM utilizes polarization modulation of excitation laser and demodulation of both intensity and polarization, which improves the spatial resolution as well as the detection accuracy of dipole orientation. With the additional information of fluorescence polarization imposed on the original super-resolution intensity image, Xi group has observed several interesting findings in biological samples. SDOM technology has a very fast imaging speed (up to five frames per second in super-resolution), and the excitation light power requirements are very low (milliwatts level), which is ideal for live cell observation. The observation of living yeast cells was demonstrated in the laboratory. [18]

New tool enables viewing spectrum from specific structures within samples

Fluorescence is an incredibly useful tool for experimental biology and it just got easier to tap into, thanks to the work of a group of University of Chicago researchers.

The group created a new tool as part of a lab class within the Biophysical Sciences graduate program at The University of Chicago, enabling its users to zero in on the spectrum from specific structures within samples.

"The bulk of the work was done by graduate students during their first semester," said Adam Hammond, curriculum director and senior lecturer in the Biophysical Sciences program at the Gordon Center for Integrative Sciences. "Their enthusiasm and creativity made this project possible."

As the group reports this week in the journal Review of Scientific Instruments, from AIP Publishing, the goal of their instrumentation is to observe the spectrum of light that comes from part of a sample on a microscope—but not the entire sample.

"The value of a microscope is that it allows you to observe the variations within a sample," Hammond explained. "We wanted to be able to ask, 'what's the spectrum from that specific structure right there?' This isn't a new desire and instruments that can do it exist, but none, as far as I know, as simply as ours."

During his first year in graduate school, Peter Dahlberg, first author of the article who is now at Stanford University in California, got to build a selective excitation microscope. "Subconsciously, I think the idea started then," he said. "Why not do the same thing, but in reverse?"

How does the group's tool work? First, it splits the light that comes from a sample. Half goes to a camera for normal imaging and the other half goes to a spectrometer. But before it gets to the spectrometer, that half passes through a few optical components that allow users to choose any arbitrary portion of the image and block everything else out.

"There's nothing tricky about these optical components—a spatial light modulator (SLM) between crossed polarizers," Hammond said. "SLMs are common now, with at least three in many modern digital projectors. They have an array of pixels that can each manipulate the phase of the light that passes through them."

Although there are several tricks you can do with a SLM, the group is using the most straightforward one.

"We focus the image from the sample onto the SLM and shift the phase of only those pixels that we want to obtain a spectrum from," he continued. "The shifted light passes through a second polarizer; everything else gets blocked out. Then that light is collected and can be sent to any kind of optical instrument you choose. Right now we send it to a small UV/Vis spectrometer to get a full spectrum."

The group's instrument is, perhaps, best summed up as a "workhorse tool." Its simple concepts and components can easily be adapted for many different purposes and added to existing microscopes easily and inexpensively.

"We set out to build it for one specific use: To measure the spectral shift of fluorescent indicators," Hammond said. "We didn't really think about making it versatile or how to arrange the SLM and polarizers when we started. But we had an enjoyable series of realizations along the way."

One such realization was that their instrument could also be used for absorbance measurements.

"Often, the most important samples are tiny and hard to create or purify—like crystal forms," he said. "It's arduous work to purify the two types away from each other in sufficient quantities to fill a cuvette. When you put the mixture on a microscope slide, it gets easier. Crystals can be measured one at a time, and so can cells that express variable chromophores (molecules responsible for color). This opens up a whole new area that wasn't part of our original plan."

The group's instrument can "take the full spectrum of one or more user-defined regions of interest while simultaneously capturing standard fluorescence images of the whole field of view," Hammond said. "So what you can do with it depends on the sample. We're using it now to follow fluorescent probes for pH and calcium. But an example of a very different application is its ability to identify individual microorganisms within a mixed sample by their absorbance fingerprint."

What's next for the researchers?

"By using a pulsed excitation source, the fluorescence lifetime of a probe could be measured from a select region of interest," said Hammond. "One interesting potential application is within the field of neuroscience for resolving single action potentials with dyes that are sensitive to membrane potential. Fluorescence lifetime measurements provide an advantage over direct fluorescence measurements because they're independent of the concentration of the probe." [17]

Molecular chameleons reveal bacterial Biofilms

Molecules that change colour can be used to follow in real-time how bacteria form a protective biofilm around themselves. This new method, which has been developed in collaboration between researchers at Linköping University and Karolinska Institutet in Sweden, may in the future become significant both in medical care and the food industry, where bacterial biofilms are a problem.

Biofilms are formed when bacteria growing on a surface form three-dimensional colonies in which they survive better than when living alone.

"What characterises biofilms in particular is that the bacteria produce a special slime that binds the bacteria to each other. The biofilm helps the bacteria to withstand external stresses, such as antibiotics, the flow of fluid in a catheter and detergents in the form of dishwashing liquid and other cleaning agents," says Professor Agneta Richter-Dahlfors at Karolinska Institutet, who has led the study together with Professor Peter Nilsson at Linköping University.

The protective biofilm is a problem in, for example, medical care and the food industry. Until now, no specific method to detect biofilms has been available.

"This is the first method that specifically labels the biofilm components. This means that researchers who want to study the mechanisms behind how bacteria form biofilms now have access to a new tool in understanding the process," says Agneta Richter-Dahlfors.

In the present study, published in Nature Journal Biofilms and Microbiomes, the investigators have developed molecules that emit a sort of optical fingerprint that depends on what they bind to. One part of the molecule has the ability to emit light, while another part can bind specifically to a target molecule. In this case, this is a molecule present in the biofilm. When the tracer molecule has bound to the target molecule, the colour of the light emitted changes.

"The molecules that we have developed are unique in that they can emit different colours, depending on their conformation. We call them 'molecular chameleons', since they change colour according to the surroundings," says Peter Nilsson at Linköping University, whose research group has developed these tracer molecules.

The researchers have demonstrated in the project how the method can be used to study Salmonella bacteria, both in cell cultures and in infected tissue. The researchers hope that it will be possible eventually to use the method within medical care and the food industry, where biofilms are a problem. There are, however, also contexts in which the ability of bacteria to form biofilms is positive, for example when bacteria are used to produce biogas to be used as fuel.

"It is possible with the new method to follow in real-time how the bacteria form a biofilm. Now that we have a tool that we can use to see how biofilms are formed, we can also use it to evaluate methods that influence the process," says Peter Nilsson.

The research has been financed with support from the Swedish Research Council, the Swedish Foundation for Strategic Research, the Erling-Persson Family Foundation and Carl Bennet AB. Some of the researchers who work in the study are part-owners in a company that may commercialise the molecules for use within medical care and industry. [16]

Computer simulation breaks virus apart to learn how it comes together

Researchers led by Carnegie Mellon University physicist Markus Deserno and University of Konstanz (Germany) chemist Christine Peter have developed a computer simulation that crushes viral capsids. By allowing researchers to see how the tough shells break apart, the simulation provides a computational window for looking at how viruses and proteins assemble. The study is published in the October issue of The European Physical Journal Special Topics.

"The concept of breaking something to see how it's made isn't new. It's what's being done at particle accelerators and in materials science labs worldwide—not to mention by toddlers who break their toys to see what's inside," said Deserno, a professor in the department of physics and member of the department's Biological Physics Initiative. "With a simulation we can build the virus, crush it and see what happens at a very high level of resolution."

Viral capsids, the protein shells that encapsulate and transport the viral genome, are one of nature's strongest nanocontainers. The shells are made when copies of capsid proteins spontaneously come together and assemble into a round, geometric shell. Understanding how these proteins come together to form capsids may help researchers to make similar nanocontainers for a variety of uses, including targeted drug delivery. Additionally, the simulation could fill a void for virologists, allowing them to study the stages of viral assembly that they aren't able to see experimentally.

Studying the self-assembly of viral capsids is difficult. Most viruses are too small—about 30 to 50 nanometers—and the capsid proteins come together too rapidly for their assembly to be seen using traditional microscopy. As an alternative, Deserno and colleagues thought that a better way to learn about capsid assembly might be to see what happens when an already formed capsid breaks apart.

To do this, Deserno and colleagues created a coarse-grained model of the Cowpea Chlorotic Mottle Virus (CCMV) capsid. In the simulation, they applied forces to the capsid and viewed how it responded to those forces. Their model is based on the MARTINI force field, a commonly used coarse-grained model, with an added stabilizing network within the individual proteins that compensated for the model's shortcomings in stabilizing a protein's folding geometry.

The CCMV capsid is made up of 180 identical proteins. In assembly, the proteins first form pairs, called dimers, and those dimers then join together at interfaces.

While the proteins are the same, the interfaces can be different. At some locations on the capsid, five proteins meet; at others, six. In the simulation, the researchers found that when force was applied to the capsid, the capsid would start to fracture at the hexametric interfaces first, indicating that those protein-protein contacts were weaker than those at the pentametric interfaces. In contrast, the pentametric contacts never broke. Since stronger connections assemble first and weaker ones assemble later, the researchers can use this information to begin to recreate how the capsid formed.

In the simulation, the researchers also found a likely explanation for a strange structural feature found in the CCMV capsid. At the center of the hexametric association site, the tail-ends of the six proteins come together and form a beta barrel. Beta barrels are coiled secondary protein structures. The researchers believe that they act to provide further late-stage stabilization to the weaker hexametric interfaces. [15]

IBM lab-on-a-chip breakthrough aims to help physicians detect cancer

IBM scientists have developed a new lab-on-a-chip technology that can, for the first time, separate biological particles at the nanoscale and could enable physicians to detect diseases such as cancer before symptoms appear.

As reported today in the journal Nature Nanotechnology, the IBM team's results show size-based separation of bioparticles down to 20 nanometers (nm) in diameter, a scale that gives access to important particles such as DNA, viruses and exosomes. Once separated, these particles can potentially be analyzed by physicians to reveal signs of disease even before patients experience any physical symptoms and when the outcome from treatment is most positive. Until now, the smallest bioparticle that could be separated by size with on-chip technologies was about 50 times or larger, for example, separation of circulating tumor cells from other biological components.

IBM is collaborating with a team from the Icahn School of Medicine at Mount Sinai to continue development of this lab-on-a-chip technology and plans to test it on prostate cancer, the most common cancer in men in the U.S.

In the era of precision medicine, exosomes are increasingly being viewed as useful biomarkers for the diagnosis and prognosis of malignant tumors. Exosomes are released in easily accessible bodily fluids such as blood, saliva or urine. They represent a precious biomedical tool as they can be used in the context of less invasive liquid biopsies to reveal the origin and nature of a cancer.

The IBM team targeted exosomes with their device as existing technologies face challenges for separating and purifying exosomes in liquid biopsies. Exosomes range in size from 20-140nm and

contain information about the health of the originating cell that they are shed from. A determination of the size, surface proteins and nucleic acid cargo carried by exosomes can give essential information about the presence and state of developing cancer and other diseases.

IBM's results show they could separate and detect particles as small as 20 nm from smaller particles, that exosomes of size 100 nm and larger could be separated from smaller exosomes, and that separation can take place in spite of diffusion, a hallmark of particle dynamics at these small scales. With Mt. Sinai, the team plans to confirm their device is able to pick up exosomes with cancer-specific biomarkers from patient liquid biopsies.

"The ability to sort and enrich biomarkers at the nanoscale in chip-based technologies opens the door to understanding diseases such as cancer as well as viruses like the flu or Zika," said Gustavo Stolovitzky, Program Director of Translational Systems Biology and Nanobiotechnology at IBM Research. "Our lab-on-a-chip device could offer a simple, noninvasive and affordable option to potentially detect and monitor a disease even at its earliest stages, long before physical symptoms manifest. This extra amount of time allows physicians to make more informed decisions and when the prognosis for treatment options is most positive."

With the ability to sort bioparticles at the nanoscale, Mt. Sinai hopes that IBM's technology can provide a new method to eavesdrop on the messages carried by exosomes for cell-to-cell communications. This can elucidate important questions about the biology of diseases as well as pave the way to noninvasive and eventually affordable point-of-care diagnostic tools. Monitoring this intercellular conversation more regularly could allow medical experts to track an individual's state of health or progression of a disease.

"When we are ahead of the disease we usually can address it well; but if the disease is ahead of us, the journey is usually much more difficult. One of the important developments that we are attempting in this collaboration is to have the basic grounds to identify exosome signatures that can be there very early on before symptoms appear or before a disease becomes worse," said Dr. Carlos Cordon-Cardo, Professor and Chairman for the Mount Sinai Health System Department of Pathology. "By bringing together Mount Sinai's domain expertise in cancer and pathology with IBM's systems biology experience and its latest nanoscale separation technology, the hope is to look for specific, sensitive biomarkers in exosomes that represent a new frontier to offering clues that might hold the answer to whether a person has cancer or how to treat it."

Sorting bioparticles at the nanoscale

Lab-on-a-chip technologies have become an incredibly helpful diagnostic tool for physicians as they can be significantly faster, portable, easy to use and require less sample volume to help detect diseases. The goal is to shrink down to a single silicon chip all of the processes necessary to analyze a disease that would normally be carried out in a full-scale biochemistry lab.

Using a technology called nanoscale deterministic lateral displacement, or nano-DLD, IBM scientists Dr. Joshua Smith and Dr. Benjamin Wunsch led development of a lab-on-a-chip technology that allows a liquid sample to be passed, in continuous flow, through a silicon chip containing an asymmetric pillar array. This array allows the system to sort a microscopic waterfall of nanoparticles, separating particles by size down to tens of nanometers resolution. IBM has already scaled down the

chip size to 2cm by 2cm, while continuing development to increase the device density to improve functionality and throughput.

Much like how a road through a small tunnel only allows smaller cars to pass while forcing bigger trucks to detour around, nano-DLD uses a set of pillars to deflect larger particles while allowing smaller particles to flow through the gaps of the pillar array unabated, effectively separating this particle "traffic" by size while not disrupting flow. Interestingly, IBM scientists noticed that nano-DLD arrays can also split a mixture of many different particle sizes into a spread of streams, much like a prism splits white light into different colors. The continuous flow nature of this technology circumvents stop-and-go batch processing typical of conventional separation techniques.

Leveraging IBM's vast semiconductor expertise with its growing capabilities in experimental biology, IBM scientists used manufacturable silicon processes to produce the nano-DLD arrays for their lab-on-a-chip device. As part of its on-going strategy, IBM researchers are working to increase the diversity of bioparticles that can be separated with their device, and improving the precision and specificity for real-world clinical applications. [14]

Scientists work toward storing digital information in DNA

Her computer, Karin Strauss says, contains her "digital attic"—a place where she stores that published math paper she wrote in high school, and computer science schoolwork from college.

She'd like to preserve the stuff "as long as I live, at least," says Strauss, 37. But computers must be replaced every few years, and each time she must copy the information over, "which is a little bit of a headache."

It would be much better, she says, if she could store it in DNA—the stuff our genes are made of.

Strauss, who works at Microsoft Research in Redmond, Washington, is working to make that sci-fi fantasy a reality.

She and other scientists are not focused in finding ways to stow high school projects or snapshots or other things an average person might accumulate, at least for now. Rather, they aim to help companies and institutions archive huge amounts of data for decades or centuries, at a time when the world is generating digital data faster than it can store it.

To understand her quest, it helps to know how companies, governments and other institutions store data now: For long-term storage it's typically disks or a specialized kind of tape, wound up in cartridges about three inches on a side and less than an inch thick. A single cartridge containing about half a mile of tape can hold the equivalent of about 46 million books of 200 pages apiece, and three times that much if the data lends itself to being compressed.

A tape cartridge can store data for about 30 years under ideal conditions, says Matt Starr, chief technology officer of Spectra Logic, which sells data-storage devices. But a more practical limit is 10 to 15 years, he says.

It's not that the data will disappear from the tape. A bigger problem is familiar to anybody who has come across an old eight-track tape or floppy disk and realized he no longer has a machine to play it.

Technology moves on, and data can't be retrieved if the means to read it is no longer available, Starr says.

So for that and other reasons, long-term archiving requires repeatedly copying the data to new technologies.

Into this world comes the notion of DNA storage. DNA is by its essence an information-storing molecule; the genes we pass from generation to generation transmit the blueprints for creating the human body. That information is stored in strings of what's often called the four-letter DNA code. That really refers to sequences of four building blocks—abbreviated as A, C, T and G—found in the DNA molecule. Specific sequences give the body directions for creating particular proteins.

Digital devices, on the other hand, store information in a two-letter code that produces strings of ones and zeroes. A capital "A," for example, is 01000001.

Converting digital information to DNA involves translating between the two codes. In one lab, for example, a capital A can become ATATG. The idea is once that transformation is made, strings of DNA can be custom-made to carry the new code, and hence the information that code contains.

One selling point is durability. Scientists can recover and read DNA sequences from fossils of Neanderthals and even older life forms. So as a storage medium, "it could last thousands and thousands of years," says Luis Ceze of the University of Washington, who works with Microsoft on DNA data storage.

Advocates also stress that DNA crams information into very little space. Almost every cell of your body carries about six feet of it; that adds up to billions of miles in a single person. In terms of information storage, that compactness could mean storing all the publicly accessible data on the internet in a space the size of a shoebox, Ceze says.

In fact, all the digital information in the world might be stored in a load of whitish, powdery DNA that fits in space the size of a large van, says Nick Goldman of the European Bioinformatics Institute in Hinxton, England.

What's more, advocates say, DNA storage would avoid the problem of having to repeatedly copy stored information into new formats as the technology for reading it becomes outmoded.

"There's always going to be someone in the business of making a DNA reader because of the health care applications," Goldman says. "It's always something we're going to want to do quickly and inexpensively."

Getting the information into DNA takes some doing. Once scientists have converted the digital code into the 4-letter DNA code, they have to custom-make DNA.

For some recent research Strauss and Ceze worked on, that involved creating about 10 million short strings of DNA.

Twist Bioscience of San Francisco used a machine to create the strings letter by letter, like snapping together Lego pieces to build a tower. The machine can build up to 1.6 million strings at a time.

Each string carried just a fragment of information from a digital file, plus a chemical tag to indicate what file the information came from.

To read a file, scientists use the tags to assemble the relevant strings. A standard lab machine can then reveal the sequence of DNA letters in each string.

Nobody is talking about replacing hard drives in consumer computers with DNA. For one thing, it takes too long to read the stored information. That's never going to be accomplished in seconds, says Ewan Birney, who works on DNA storage with Goldman at the bioinformatics institute.

But for valuable material like corporate records in long-term storage, "if it's worth it, you'll wait," says Goldman, who with Birney is talking to investors about setting up a company to offer DNA storage.

Sri Kosuri of the University of California Los Angeles, who has worked on DNA information storage but now largely moved on to other pursuits, says one challenge for making the technology practical is making it much cheaper.

Scientists custom-build fairly short strings DNA now for research, but scaling up enough to handle information storage in bulk would require a "mind-boggling" leap in output, Kosuri says. With current technology, that would be hugely expensive, he says.

George Church, a prominent Harvard genetics expert, agrees that cost is a big issue. But "I'm pretty optimistic it can be brought down" dramatically in a decade or less, says Church, who is in the process of starting a company to offer DNA storage methods.

For all the interest in the topic, it's worth noting that so far the amount of information that researchers have stored in DNA is relatively tiny.

Earlier this month, Microsoft announced that a team including Strauss and Ceze had stored a record 200 megabytes. The information included 100 books—one, fittingly, was "Great Expectations"—along with a brief video and many documents. But it was still less than 5 percent the capacity of an ordinary DVD.

Yet it's about nine times the mark reported just last month by Church, who says the announcement shows "how fast the field is moving."

Meanwhile, people involved with archiving digital data say their field views DNA as a possibility for the future, but not a cure-all.

"It's a very interesting and promising approach to the storage problem, but the storage problem is really only a very small part of digital preservation," says Cal Lee, a professor at the University of North Carolina's School of Information and Library Science.

It's true that society will probably always have devices to read DNA, so that gets around the problem of obsolete readers, he says. But that's not enough.

"If you just read the ones and zeroes, you don't know how to interpret it," Lee says.

For example, is that string a picture, text, a sound clip or a video? Do you still have the software to make sense of it?

What's more, the people in charge of keeping digital information want to check on it periodically to make sure it's still intact, and "I don't know how viable that is with DNA," says Euan Cochrane, digital preservation manager at the Yale University Library. It may mean fewer such check-ups, he says.

Cochrane, who describes his job as keeping information accessible "10 years to forever," says DNA looks interesting if its cost can be reduced and scientists find ways to more quickly store and recover information.

Starr says his data-storage device company hasn't taken a detailed look at DNA technology because it's too far in the future.

There are "always things out on the horizon that could store data for a very long time," he says. But the challenge of turning those ideas into a practical product "really trims the field down pretty quickly." [13]

Second layer of information in DNA confirmed

Leiden theoretical physicists have proven that DNA mechanics, in addition to genetic information in DNA, determines who we are. Helmut Schiessel and his group simulated many DNA sequences and found a correlation between mechanical cues and the way DNA is folded. They have published their results in PLoS One.

When James Watson and Francis Crick identified the structure of DNA molecules in 1953, they revealed that DNA information determines who we are. The sequence of the letters G, A, T and C in the famous double helix determines what proteins are made ny our cells. If you have brown eyes, for example, this is because a series of letters in your DNA encodes for proteins that build brown eyes. Each cell contains the exact same letter sequence, and yet every organ behaves differently. How is this possible?

Mechanical cues

Since the mid 1980s, it has been hypothesized that there is a second layer of information on top of the genetic code consisting of DNA mechanical properties.

Each of our cells contains two meters of DNA molecules, and these molecules need to be wrapped up tightly to fit inside a single cell. The way in which DNA is folded determines how the letters are read out, and therefore which proteins are actually made. In each organ, only relevant parts of the genetic information are read. The theory suggests that mechanical cues within the DNA structures determine how preferentially DNA folds.

Simulation

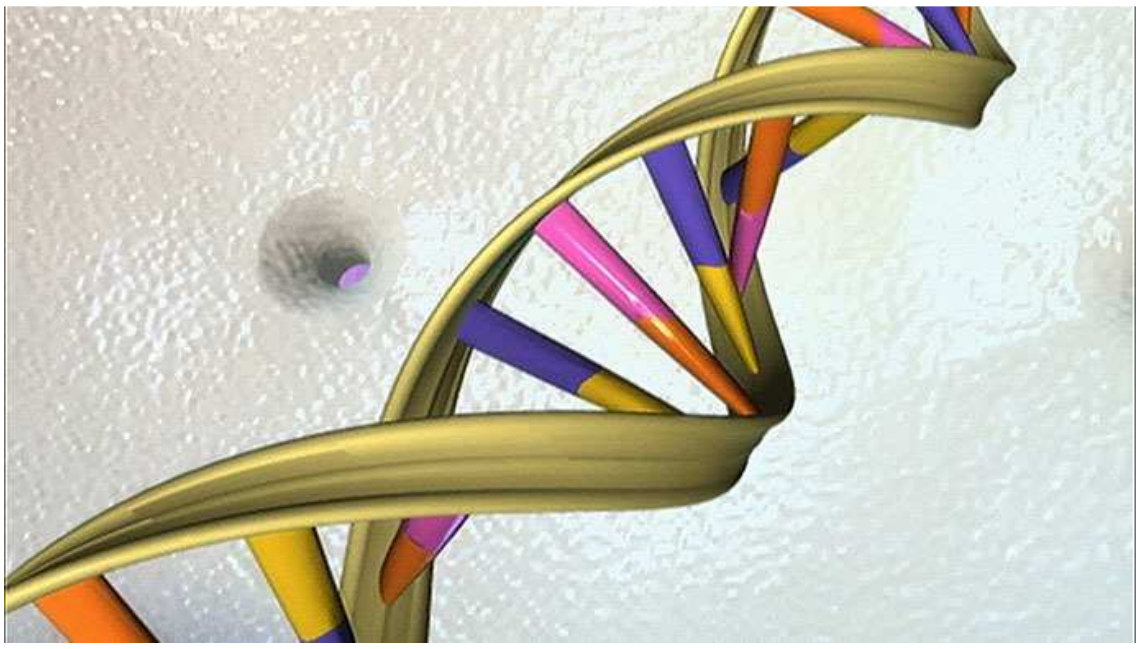
For the first time, Leiden physicist Helmut Schiessel and his research group provide strong evidence that this second layer of information indeed exists. With their computer code, they have simulated the folding of DNA strands with randomly assigned mechanical cues. It turns out that these cues indeed determine how the DNA molecule is folded into so-called nucleosomes. Schiessel found correlations between the mechanics and the actual folding structure in the genome of two

organisms—baker's yeast and fission yeast. This finding reveals evolutionary changes in DNA—mutations—that have two very different effects: The letter sequence encoding for a specific protein can change, or the mechanics of the DNA structure can change, resulting in different packaging and levels of DNA accessibility, and therefore differing frequency of production of that protein. [12]

Quantum entanglement between the electron clouds of nucleic acids in DNA

We model the electron clouds of nucleic acids in DNA as a chain of coupled quantum harmonic oscillators with dipole-dipole interaction between nearest neighbours resulting in a van der Waals type bonding. Crucial parameters in our model are the distances between the acids and the coupling between them, which we estimate from numerical simulations . We show that for realistic parameters nearest neighbour entanglement is present even at room temperature. We quantify the amount of entanglement in terms of negativity and single base von Neumann entropy. We find that the strength of the single base von Neumann entropy depends on the neighbouring sites, thus questioning the notion of treating single bases as logically independent units. We derive an analytical expression for the binding energy of the coupled chain in terms of entanglement and show the connection between entanglement and correlation energy, a quantity commonly used in quantum chemistry. [11]

Scientists discover secret code hidden within human DNA



This undated handout illustration shows the DNA double helix (AFP Photo)This undated handout illustration shows the DNA double helix (AFP Photo)

Scientists have discovered a secret second code hiding within DNA which instructs cells on how genes are controlled. The amazing discovery is expected to open new doors to the diagnosis and treatment of diseases, according to a new study.

Ever since the genetic code was deciphered over 40 years ago, scientists have believed that it only described how proteins are made. However, the revelation made by the research team led by John Stamatoyannopoulos of the University of Washington indicates that genomes use the genetic code to write two separate languages.

“For over 40 years we have assumed that DNA changes affecting the genetic code solely impact how proteins are made,” said Stamatoyannopoulos, according to the press release. “Now we know that this basic assumption about reading the human genome missed half of the picture.”

Scientists discovered that the second language instructs the cells on how genes are controlled, according to findings published in Science magazine on Friday. The study is part of the Encyclopedia of DNA Elements Project, also known as ENCODE.

DNA (Deoxyribonucleic acid) is a nucleic acid that is the main constituent of the chromosomes of all organisms, except some viruses. DNA is self-replicating, plays a central role in protein synthesis, and is responsible for the transmission of hereditary characteristics from parents to offspring.

The second language remained hidden for so long because one language is written on top of the other, scientists said.

Scientists already knew that the genetic code uses a 64-letter alphabet called codons. The research team discovered that some of the codons can have two meanings – one related to proteins, the other to gene control. Those codons were given the name ‘duons.’

And it’s those duons that are expected to change the way physicians interpret human genomes, and give clues for the treatments of diseases.

“The fact that the genetic code can simultaneously write two kinds of information means that many DNA changes that appear to alter protein sequences may actually cause disease by disrupting gene control programs or even both mechanisms simultaneously,” said Stamatoyannopoulos.

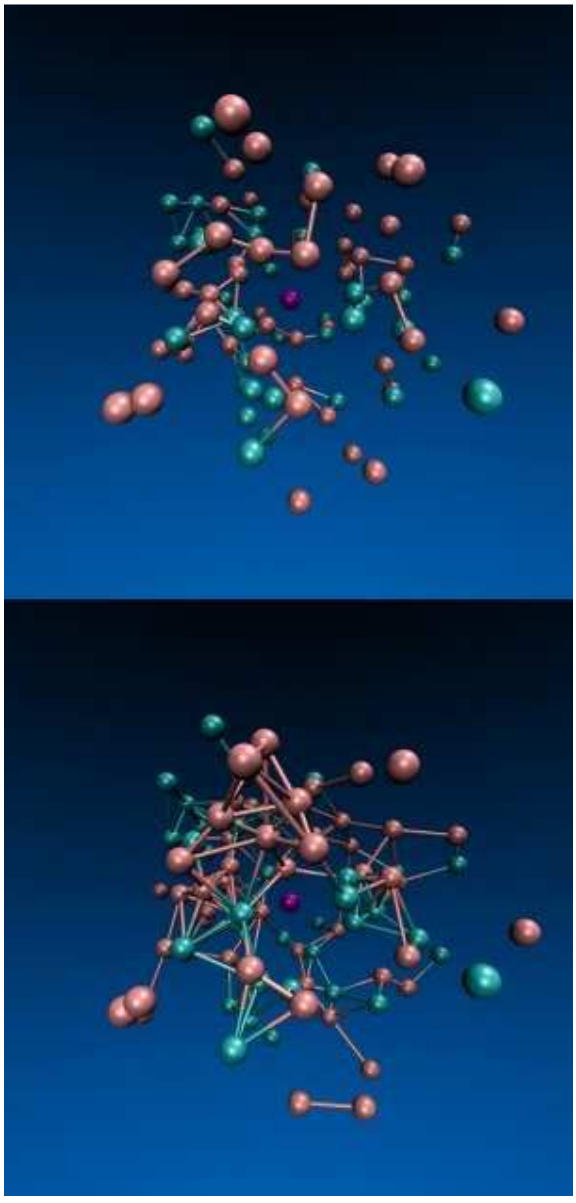
Speaking about the discovery, Stamatoyannopoulos said that the “new findings highlight that DNA is an incredibly powerful information storage device, which nature has fully exploited in unexpected ways.” [10]

This Physicist Has a Groundbreaking Idea about Why Life Exists

“You start with a random clump of atoms, and if you shine light on it for long enough, it should not be so surprising that you get a plant,” England said.

England’s theory is meant to underlie, rather than replace, Darwin’s theory of evolution by natural selection, which provides a powerful description of life at the level of genes and populations. “I am certainly not saying that Darwinian ideas are wrong,” he explained. “On the contrary, I am just saying that from the perspective of the physics, you might call Darwinian evolution a special case of a more general phenomenon.”

At the heart of England's idea is the second law of thermodynamics, also known as the law of increasing entropy or the "arrow of time." Hot things cool down, gas diffuses through air, eggs scramble but never spontaneously unscramble; in short, energy tends to disperse or spread out as time progresses. Entropy is a measure of this tendency, quantifying how dispersed the energy is among the particles in a system, and how diffuse those particles are throughout space. It increases as a simple matter of probability: There are more ways for energy to be spread out than for it to be concentrated.



A computer simulation by Jeremy England and colleagues shows a system of particles confined inside a viscous fluid in which the turquoise particles are driven by an oscillating force. Over time (from top to bottom), the force triggers the formation of more bonds among the particles.

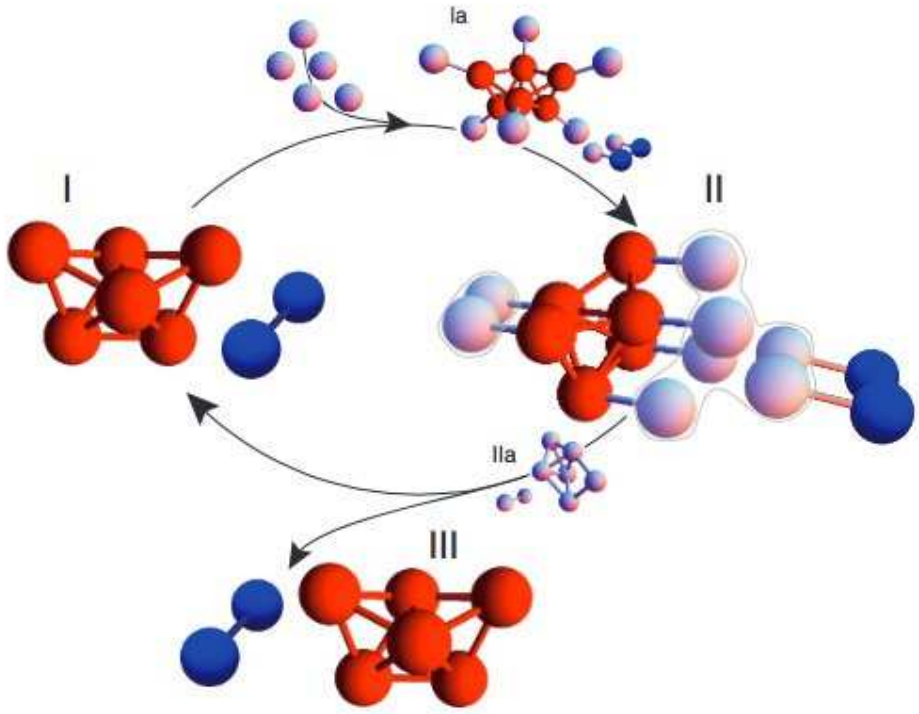
Thus, as particles in a system move around and interact, they will, through sheer chance, tend to adopt configurations in which the energy is spread out. Eventually, the system arrives at a state of

maximum entropy called “thermodynamic equilibrium,” in which energy is uniformly distributed. A cup of coffee and the room it sits in become the same temperature, for example.

Although entropy must increase over time in an isolated or “closed” system, an “open” system can keep its entropy low — that is, divide energy unevenly among its atoms — by greatly increasing the entropy of its surroundings. In his influential 1944 monograph “What Is Life?” the eminent quantum physicist Erwin Schrödinger argued that this is what living things must do. A plant, for example, absorbs extremely energetic sunlight, uses it to build sugars, and ejects infrared light, a much less concentrated form of energy. The overall entropy of the universe increases during photosynthesis as the sunlight dissipates, even as the plant prevents itself from decaying by maintaining an orderly internal structure.

Self-replication (or reproduction, in biological terms), the process that drives the evolution of life on Earth, is one such mechanism by which a system might dissipate an increasing amount of energy over time.

As England put it, “A great way of dissipating more is to make more copies of yourself.”



Self-Replicating Sphere Clusters: According to new research at Harvard, coating the surfaces of microspheres can cause them to spontaneously assemble into a chosen structure, such as a polytetrahedron (red), which then triggers nearby spheres into forming an identical structure.

Scientists have already observed self-replication in nonliving systems. According to new research led by Philip Marcus of the University of California, Berkeley, and reported in Physical Review Letters in August, vortices in turbulent fluids spontaneously replicate themselves by drawing energy from shear in the surrounding fluid. And in a paper in Proceedings of the National Academy of Sciences,

Michael Brenner, a professor of applied mathematics and physics at Harvard, and his collaborators present theoretical models and simulations of microstructures that self-replicate. These clusters of specially coated microspheres dissipate energy by roping nearby spheres into forming identical clusters. “This connects very much to what Jeremy is saying,” Brenner said. [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.

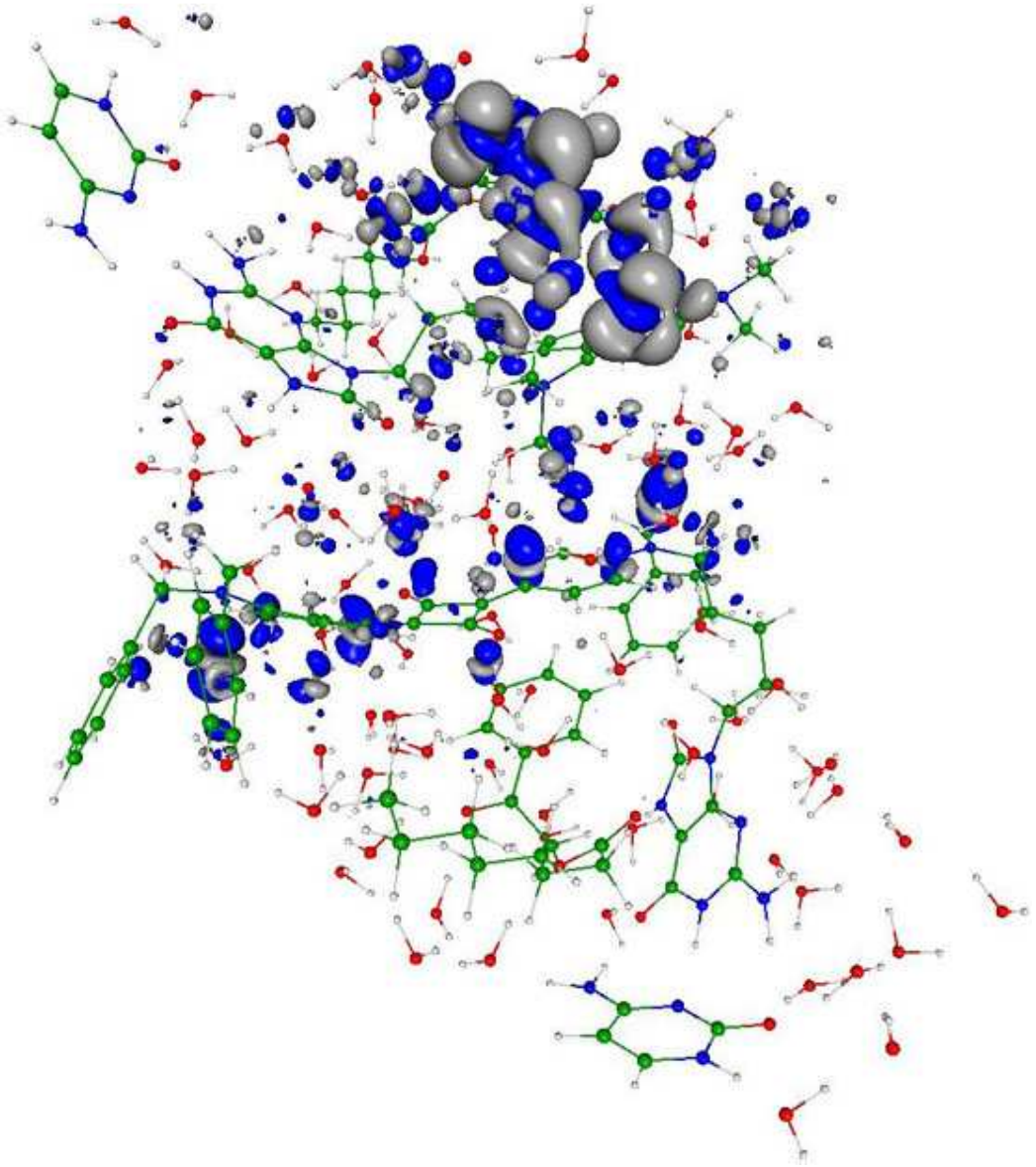
Our discovered phenomenon of the quantum entanglement in the prebiotic systems enhance the photosynthesis in the proposed systems because simultaneously excite two prebiotic kernels in the system by appearance of two additional quantum entangled excited states (Tamulis A, Grigalavicius M, Baltrusaitis 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 squarine molecule of the first protocell situated in the bottom of this bi cellular system to precursor of fatty acid (pFA) molecule of the second subsystem (in the top) and little from the 1,4-bis(N,N-dimethylamino)naphthalene molecule (in the top-right) to the same pFA molecule of the second subsystem (in the top). The electron cloud hole is indicated by the dark blue color while the transferred electron cloud location is designated by the gray color.

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

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

Quantum Biology

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

Quantum Consciousness

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

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

Biophysicist Mae-Wan Ho describes how the living organism, including the human body, is coordinated throughout and is "coherent beyond our wildest dreams." It appears that every part of

our body is "in communication with every other part through a dynamic, tunable, responsive, liquid crystalline medium that pervades the whole body, from organs and tissues to the interior of every cell."

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

Information – Entropy Theory of Physics

Viewing the confined gas where the statistical entropy not needs the information addition is not the only physical system. There are for example quantum mechanical systems where the information is a very important qualification. The perturbation theory needs higher order calculations in QED or QCD giving more information on the system as in the chess games happens, where the entropy is not enough to describe the state of the matter. The variation calculation of chess is the same as the perturbation calculation of physics to gain information, where the numbers of particles are small for statistical entropy to describe the system. The role of the Feynman graphs are the same as the chess variations of a given position that is the depth of the variations tree, the Information is the same as the order of the Feynman graphs giving the Information of the micro system. [9]

Information – Entropy Theory of Life

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.
The living biological systems have also entropy lowering and information growing direction by building more complicated or entangled molecules, governed by the quantum mechanics and the general weak interaction. On the other hand there is the arrow of time; the entropy growing is lowering the information by dissipating these entangled or otherwise connected biomolecules, aging the living systems.

Creating quantum technology

Another area of potential application is in quantum computing. The long-standing goal of the physicists and engineers working in this area is to manipulate data encoded in quantum bits (qubits)

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

Quantum Entanglement

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

The Bridge

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

Accelerating charges

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

Relativistic effect

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

Heisenberg Uncertainty Relation

In the atomic scale the Heisenberg uncertainty relation gives the same result, since the moving electron in the atom accelerating in the electric field of the proton, causing a charge distribution on delta x position difference and with a delta p momentum difference such a way that they product is about the half Planck reduced constant. For the proton this delta x much less in the nucleon, than in the orbit of the electron in the atom, the delta p is much higher because of the greater proton mass.

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

Wave – Particle Duality

The accelerating electrons explains the wave – particle duality of the electrons and photons, since the elementary charges are distributed on delta x position with delta p impulse and creating a wave packet of the electron. The photon gives the electromagnetic particle of the mediating force of the electrons electromagnetic field with the same distribution of wavelengths.

Atomic model

The constantly accelerating electron in the Hydrogen atom is moving on the equipotential line of the proton and it's kinetic and potential energy will be constant. Its energy will change only when it is changing its way to another equipotential line with another value of potential energy or getting free with enough kinetic energy. This means that the Rutherford-Bohr atomic model is right and only that changing acceleration of the electric charge causes radiation, not the steady acceleration. The steady acceleration of the charges only creates a centric parabolic steady electric field around the charge, the magnetic field. This gives the magnetic moment of the atoms, summing up the proton and electron magnetic moments caused by their circular motions and spins.

The Relativistic Bridge

Commonly accepted idea that the relativistic effect on the particle physics it is the fermions' spin - another unresolved problem in the classical concepts. If the electric charges can move only with accelerated motions in the self maintaining electromagnetic field, once upon a time they would reach the velocity of the electromagnetic field. The resolution of this problem is the spinning particle, constantly accelerating and not reaching the velocity of light because the acceleration is radial. One origin of the Quantum Physics is the Planck Distribution Law of the electromagnetic oscillators, giving equal intensity for 2 different wavelengths on any temperature. Any of these two wavelengths will give equal intensity diffraction patterns, building different asymmetric constructions, for example proton - electron structures (atoms), molecules, etc. Since the particles are centers of diffraction patterns they also have particle – wave duality as the electromagnetic waves have. [2]

The weak interaction

The weak interaction transforms an electric charge in the diffraction pattern from one side to the other side, causing an electric dipole momentum change, which violates the CP and time reversal symmetry. The Electroweak Interaction shows that the Weak Interaction is basically electromagnetic in nature. The arrow of time shows the entropy grows by changing the temperature dependent diffraction patterns of the electromagnetic oscillators.

Another important issue of the quark model is when one quark changes its flavor such that a linear oscillation transforms into plane oscillation or vice versa, changing the charge value with 1 or -1. This kind of change in the oscillation mode requires not only parity change, but also charge and time changes (CPT symmetry) resulting a right handed anti-neutrino or a left handed neutrino.

The right handed anti-neutrino and the left handed neutrino exist only because changing back the quark flavor could happen only in reverse, because they are different geometrical constructions, the u is 2 dimensional and positively charged and the d is 1 dimensional and negatively charged. It needs also a time reversal, because anti particle (anti neutrino) is involved.

The neutrino is a 1/2spin creator particle to make equal the spins of the weak interaction, for example neutron decay to 2 fermions, every particle is fermions with ½ spin. The weak interaction changes the entropy since more or less particles will give more or less freedom of movement. The entropy change is a result of temperature change and breaks the equality of oscillator diffraction intensity of the Maxwell–Boltzmann statistics. This way it changes the time coordinate measure and makes possible a different time dilation as of the special relativity.

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

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

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

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

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

Finally since the weak interaction is an electric dipole change with ½ spin creating; it is limited by the velocity of the electromagnetic wave, so the neutrino's velocity cannot exceed the velocity of light.

The General Weak Interaction

The Weak Interactions T-asymmetry is in conjunction with the T-asymmetry of the Second Law of Thermodynamics, meaning that locally lowering entropy (on extremely high temperature) causes for example the Hydrogen fusion. The arrow of time by the Second Law of Thermodynamics shows the increasing entropy and decreasing information by the Weak Interaction, changing the temperature dependent diffraction patterns. A good example of this is the neutron decay, creating more particles with less known information about them.
The neutrino oscillation of the Weak Interaction shows that it is a general electric dipole change and it is possible to any other temperature dependent entropy and information changing diffraction pattern of atoms, molecules and even complicated biological living structures.
We can generalize the weak interaction on all of the decaying matter constructions, even on the biological too. This gives the limited lifetime for the biological constructions also by the arrow of time. There should be a new research space of the Quantum Information Science the 'general neutrino oscillation' for the greater then subatomic matter structures as an electric dipole change. There is also connection between statistical physics and evolutionary biology, since the arrow of time is working in the biological evolution also.
The Fluctuation Theorem says that there is a probability that entropy will flow in a direction opposite to that dictated by the Second Law of Thermodynamics. In this case the Information is growing that is the matter formulas are emerging from the chaos. So the Weak Interaction has two directions, samples for one direction is the Neutron decay, and Hydrogen fusion is the opposite direction.

Fermions and Bosons

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

Van Der Waals force

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

Electromagnetic inertia and mass

Electromagnetic Induction

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

Relativistic change of mass

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

The frequency dependence of mass

Since $E = h\nu$ and $E = mc^2$, $m = h\nu / c^2$ that is the m depends only on the ν frequency. It means that the mass of the proton and electron are electromagnetic and the result of the electromagnetic induction, caused by the changing acceleration of the spinning and moving charge! It could be that the m_o inertial mass is the result of the spin, since this is the only accelerating motion of the electric charge. Since the accelerating motion has different frequency for the electron in the atom and the proton, they masses are different, also as the wavelengths on both sides of the diffraction pattern, giving equal intensity of radiation.

Electron – Proton mass rate

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

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

Gravity from the point of view of quantum physics

The Gravitational force

The gravitational attractive force is basically a magnetic force.

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

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

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

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

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

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

The Higgs boson

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

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

Higgs mechanism and Quantum Gravity

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

In particle physics, the Higgs mechanism is a kind of mass generation mechanism, a process that gives mass to elementary particles. According to this theory, particles gain mass by interacting with the Higgs field that permeates all space. More precisely, the Higgs mechanism endows gauge bosons

in a gauge theory with mass through absorption of Nambu–Goldstone bosons arising in spontaneous symmetry breaking.

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

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

What is the Spin?

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

The Graviton

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

Conclusions

“The fact that the genetic code can simultaneously write two kinds of information means that many DNA changes that appear to alter protein sequences may actually cause disease by disrupting gene control programs or even both mechanisms simultaneously,” said Stamatoyannopoulos.
Speaking about the discovery, Stamatoyannopoulos said that the “new findings highlight that DNA is an incredibly powerful information storage device, which nature has fully exploited in unexpected ways.” [10]
There is also connection between statistical physics and evolutionary biology, since the arrow of time is working in the biological evolution also.
Prentiss, who runs an experimental biophysics lab at Harvard, says England’s theory could be tested by comparing cells with different mutations and looking for a correlation between the amount of energy the cells dissipate and their replication rates. [8]

Exists experimental evidence for quantum-coherent is used for more efficient light-harvesting in plant photosynthesis. Quantum entanglement exists in supramolecules determining the sense of smell and in the brain neurons microtubules due to quantum vibrations.
In the work presented here, we started to design and quantum mechanical investigations of the molecular logical devices which are useful for construction of nano medicine biorobots against the molecular diseases such a cancer tumors, and against the new kinds of synthesized microorganisms and nano guns. [7]
One of the most important conclusions is that the electric charges are moving in an accelerated way and even if their velocity is constant, they have an intrinsic acceleration anyway, the so called spin, since they need at least an intrinsic acceleration to make possible they movement .
The accelerated charges self-maintaining potential shows the locality of the relativity, working on the quantum level also. [1]
The bridge between the classical and quantum theory is based on this intrinsic acceleration of the spin, explaining also the Heisenberg Uncertainty Principle. The particle – wave duality of the electric charges and the photon makes certain that they are both sides of the same thing.
The Secret of Quantum Entanglement that the particles are diffraction patterns of the electromagnetic waves and this way their quantum states every time is the result of the quantum state of the intermediate electromagnetic waves. [2]
These relatively new developments in biophysics have discovered that all biological organisms are constituted of a liquid crystalline medium. Further, DNA is a liquid-crystal, lattice-type structure (which some refer to as a liquid crystal gel), whereby body cells are involved in a holographic instantaneous communication via the emitting of biophotons (a source based on light). This implies that all living biological organisms continuously emit radiations of light that form a field of coherence and communication. Moreover, biophysics has discovered that living organisms are permeated by quantum wave forms. [5]
Basing the gravitational force on the accelerating Universe caused magnetic force and the Planck Distribution Law of the electromagnetic waves caused diffraction gives us the basis to build a Unified Theory of the physical interactions also.

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