

# Why Protein Fibers Form

*Alzheimer's disease results from a dysfunctional stacking of protein molecules that form long fibers inside brain cells. Similar stacking occurs in sickle-cell anemia and mad cow disease. [26]*

*Japanese researchers from Osaka University have uncovered a way in which our cells regulate the repair of broken DNA. [25]*

*Scientists at the University of York have used florescent proteins from jellyfish to help shed new light on how DNA replicates. [24]*

*When the molecules that carry the genetic code in our cells are exposed to harm, they have defenses against potential breakage and mutations. [23]*

*A Harvard researcher seeking a model for the earliest cells has created a system that self-assembles from a chemical soup into cell-like structures that grow, move in response to light, replicate when destroyed, and exhibit signs of rudimentary evolutionary selection. [22]*

*New research led by Harvard Medical School reveals a critical step in a molecular chain of events that allows cells to mend broken DNA. [21]*

*Now, Barton's lab has shown that this wire-like property of DNA is also involved in a different critical cellular function: replicating DNA. [20]*

*Researchers have introduced a new type of "super-resolution" microscopy and used it to discover the precise walking mechanism behind tiny structures made of DNA that could find biomedical and industrial applications. [19]*

*Genes tell cells what to do—for example, when to repair DNA mistakes or when to die—and can be turned on or off like a light switch. Knowing which genes are switched on, or expressed, is important for the treatment and monitoring of disease. Now, for the first time, Caltech scientists have developed a simple way to visualize gene expression in cells deep inside the body using a common imaging technology. [18]*

*Researchers at The University of Manchester have discovered that a potential new drug reduces the number of brain cells destroyed by stroke and then helps to repair the damage. [17]*

*Researchers at the University of Connecticut have uncovered new information about how particles behave in our bloodstream, an important advancement that could help pharmaceutical scientists develop more effective cancer drugs. [16]*

*For the past 15 years, the big data techniques pioneered by NASA's Jet Propulsion Laboratory in Pasadena, California, have been revolutionizing biomedical research. On Sept. 6, 2016, JPL and the National Cancer Institute (NCI), part of the National Institutes of Health, renewed a research partnership through 2021, extending the development of data science that originated in space exploration and is now supporting new cancer discoveries. [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**

Preface.....	5
Researchers offer new explanation for why protein fibers form.....	6
The fork in the road to DNA repair.....	7
Jellyfish fluorescence shines new light on DNA copying.....	8
Pioneering.....	9
Human health.....	9
Scientists watch a molecule protect itself from radiation damage.....	9
Researcher creates chemical system that mimics early cell behavior.....	10
Scientists pinpoint critical step in DNA repair, cellular aging.....	12
A plot with many characters.....	12
Averting mischief.....	13
Electrons use DNA like a wire for signaling DNA replication.....	14
Super-resolution system reveals mechanics of tiny 'DNA walker'.....	15
Visualizing gene expression with MRI.....	17
New drug limits and then repairs brain damage in stroke.....	18
When push comes to shove: Size matters for particles in our bloodstream.....	19
Fighting cancer with space research.....	20
IBM lab-on-a-chip breakthrough aims to help physicians detect cancer.....	22
Sorting bioparticles at the nanoscale.....	23

Scientists work toward storing digital information in DNA.....	24
Second layer of information in DNA confirmed .....	27
Mechanical cues .....	27
Simulation.....	28
Quantum entanglement between the electron clouds of nucleic acids in DNA.....	28
Scientists discover secret code hidden within human DNA .....	28
This Physicist Has a Groundbreaking Idea about Why Life Exists.....	29
Photoactive Prebiotic Systems .....	32
Significance Statement .....	32
Figure legend .....	34
Quantum Biology.....	35
Quantum Consciousness .....	35
Information – Entropy Theory of Physics .....	36
Information – Entropy Theory of Life .....	36
Creating quantum technology.....	36
Quantum Entanglement.....	37
The Bridge .....	37
Accelerating charges .....	37
Relativistic effect .....	37
Heisenberg Uncertainty Relation.....	38
Wave – Particle Duality .....	38
Atomic model .....	38
The Relativistic Bridge.....	38
The weak interaction .....	39
The General Weak Interaction .....	40
Fermions and Bosons.....	40
Van Der Waals force .....	40
Electromagnetic inertia and mass.....	40
Electromagnetic Induction .....	40
Relativistic change of mass.....	41
The frequency dependence of mass .....	41
Electron – Proton mass rate .....	41
Gravity from the point of view of quantum physics .....	41
The Gravitational force.....	41

The Higgs boson .....	42
Higgs mechanism and Quantum Gravity .....	42
What is the Spin? .....	43
The Graviton .....	43
Conclusions .....	43
References .....	44

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## 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]

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

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

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

dx and dp uncertainty.

## Researchers offer new explanation for why protein fibers form

Alzheimer's disease results from a dysfunctional stacking of protein molecules that form long fibers inside brain cells. Similar stacking occurs in sickle-cell anemia and mad cow disease.

Scientists know these orderly fibers develop from a wide variety of molecules, but could there be a common reason they form?

In new research, physicists at the University of Chicago and Université Paris-Saclay suggest that such protein fibers are a manifestation of a general physical principle. And that principle offers the possibility of new medicines and tools for engineering desirable protein structures. The findings were published earlier this month in *Nature Physics*.

"We have strong evidence that there's a principle shaping how things aggregate that can be used both to understand disease and modify it and to make things self-assemble in a way that we dictate," said co-author Thomas Witten, the Homer J. Livingston Professor Emeritus of Physics at UChicago.

Proteins aggregate all the time. But mostly they make amorphous blobs similar to those in egg drop soup. "We're trying to find out what makes some molecules assemble to form a fiber instead of a glop," Witten said.

The proteins that form fibers are identical but irregular; they don't fit together cleanly. Witten and his collaborator Martin Lenz, a researcher at Université Paris-Saclay, wondered if that irregularity might hold a key to fiber formation. Using computers, Lenz, lead author of the study, devised a mathematical model to simulate how identical but ill-fitting objects would clump together. He used pentagons and other simple polygons to represent the irregular, fiber-forming proteins.

"We didn't have a lab and test tubes. We just had these little shapes," Witten said.

The researchers made the interaction of the polygons depend on just two attributes without incorporating any other features of real molecules. As in a real fiber, all of the sub-units are identical and irregular. They are also what Witten calls "sticky"—they attract each other but they don't feel the attraction until they touch. They "want" to touch, and they gain energy if they do. But because the shapes don't fit together cleanly, "their surfaces can't touch and feel the stickiness and get that energy unless they distort," Witten said.

Their propensity is to elongate themselves as much as possible to maximize the amount of their surface that is in contact. "But distortion costs them energy," Witten said. "They have to exert forces to get the surfaces to meet. So there is a competition between the energy gained by sticking and the energy cost of distortion."

The simulations done by Lenz embodied that competition. The shapes could attach along any surface. The scientists varied the degree of stickiness relative to the energy cost of distortion for each shape and looked at the various structures that formed across the range of values. The results

were striking: No matter what shape they used, when stickiness and the energy cost of distortion were more or less equal, they got fibers every time.

An additional feature was needed to form the fibers. The growth needed to be irreversible with every surface that sticks needing to stay stuck. Without this irreversible feature, often seen in real molecules, the long fibers would eventually melt into roundish blobs.

The research differs from the approach taken by scientists who study the diseases caused by protein fibers. "They have done a lot of work on the particulars of the molecules involved, and there are strongly held ideas about how those particulars cause the fibers to form," Lenz said.

"We're saying, 'You don't need a specific molecule: it's a general principle.' They're skeptical about that, but despite their skepticism, they acknowledge that our idea deserves a hearing," Witten said.

So far, Lenz and Witten have tried only a small array of shapes in two dimensions. They plan to try to see if the principle holds true for arbitrary shapes, in three dimensions, and abstract the essence of what's going on in the simulations.

"We want to have a theory that predicts things that we can then verify on the computer, a theory that doesn't use specific features of a particular particle shape but just uses the stickiness and the distortion," said Witten. "We may be able to prevent the mad-cow and the sickle cell fibers, if we understand this principle. And we should be able to use the principle to make fibers when they are beneficial. Just put in the right stickiness, put in the right distortion, adjust everything and get the fibers we want." [26]

## **The fork in the road to DNA repair**

Japanese researchers from Osaka University have uncovered a way in which our cells regulate the repair of broken DNA. Their results, published in the journal *Cell Reports* show a common molecule regulates multiple repair mechanisms and help shed light on how the cell maintains the integrity of the human genome when it is damaged.

The human body consists of trillions of cells, and within each are billions of DNA molecules. Strict maintenance of the molecules is essential to maintain a healthy cell and thus a healthy body.

This maintenance is challenged by the daily bombardment of chemicals, UV light, radical oxygen and radiation that can damage the DNA molecules. If left unrepaired, the damage could lead to genomic instability and cell death. Thankfully, evolution has created in the cell innate repair mechanisms to fix any damaged DNA.

"The two mechanisms in the cell are non-homologous end joining (NHEJ) and homologous recombination (HR) for repairing DNA double strand break" explains Chikashi Obuse, Professor at the Osaka University Graduate School of Sciences.

While NHEJ and HR both function to repair damaged DNA, they respond to different situations; types of damage, presence or absence of homologous template or cell cycle stages etc. What has continued to elude researchers is how the cell knows which system to call. Obuse shows in his latest

report that the protein suppressor of cancer cell invasion (SCAI) plays an important role for the selection of HR.

To study the function of SCAI, Obuse and his team of scientists exposed human cells to X-ray irradiation to damage the DNA.

"Our results suggested SCAI bound to 53BP1 to promote the recruitment of HR proteins. When we depleted SCAI these proteins did not accumulate," he said.

In particular, Obuse highlighted the great diminishment of the protein BRCA1 at damage sites when SCAI was depleted. On the other hand, SCAI presence inhibited another protein, RIF1, to promote the recruitment of BRCA1.

"RIF1 is known to inhibit BRCA1 accumulation at DNA damaged sites. It binds to 53BP1. When we looked at confocal imaging of cells, we saw RIF1 initially accumulated at sites of DNA damage but was gradually replaced by SCAI," said Obuse.

This led the scientists to wonder if SCAI and RIF1 competed to bind to 53BP1 and whether this binding determined the DNA repair mechanism.

Indeed, additional experiments showed that the phosphorylation state of 53BP1 determined its binding partner.

"The next question for us is to determine which upstream kinases are responsible for phosphorylating the sites of 53BP1 needed for binding with SCAI," added Obuse. "The upstream signaling molecules will be important for helping to determine the cell's choice for either the NHEJ or HR pathway." [25]

## **Jellyfish fluorescence shines new light on DNA copying**

Scientists at the University of York have used fluorescent proteins from jellyfish to help shed new light on how DNA replicates.

Using these proteins, originally found in jellyfish to make them glow, the team were able to focus laser beams on the brightly lit proteins and track them inside a bacteria that normally lives inside the human gut.

This allowed scientists to watch the molecular machinery of DNA as it replicated inside a cell one molecule at a time. It revealed for the first time that only one component of this process, called DnaB helicase, remains stable - like a molecular anchor to the process.

In most cells, whether human or bacterial, a new cell is created after an existing cell divides in two. This means that a copy of the original sequence of genes coded in its DNA must be precisely copied and placed into the new cell.

This is thought to be a process that occurs slowly and methodically at set points in time. New research at the University of York, in collaboration with the University of Oxford and McGill University Canada, however, has now tracked this replication process in real-time and shown that it



is far more dynamic than the textbooks suggest, occurring instead through a 'stuttering-like process' in short bursts.

## **Pioneering**

Professor Mark Leake, Chair of Biological Physics at the University of York, said: "We pioneered a new method of light microscopy which allowed us to see this fascinating replication process occur molecule-by-molecule.

"We were surprised to find, however, that rather than the organised and methodical way that we expected this process to unfold, it instead happened in a 'stuttering' action, much like driving too slowly in high gear of a car. The big question, of course, was why the cell performs an essential process in such an unstable way?

"The stuttering action provide 'checkpoints' at various stages of the DNA copying process to make sure there is no errors made and, if there is, correct them before it is too late. This means that the cells can pause to fix an error in a small fragment of the DNA rather than attempt an unmanageable correction in one complete and huge strand of it.

"Although the process looks inelegant and almost random, it is actually highly efficient."

## **Human health**

The process of DNA replication is fundamental to all life and the way errors in the process are resolved is especially important to human health. Errors can give rise to forms of cancer and become more prevalent in an ageing population.

This work will help scientists not only understand more fully the basic building blocks of life but potentially also provides new insights into a range of health conditions as well as even shedding new light on how human ageing can give rise to diseases associated with errors in copying the DNA from cell to cell.

Research was conducted using the DNA of Escherichia coli cell, bacteria, but However, the next stage of this research will investigate the same process in more complex cells, ultimately including those from humans.

The research, 'Frequent exchange of DNA polymerase during bacterial chromosome replication', was supported by the BBSRC and is published in the journal, eLife. [24]

## **Scientists watch a molecule protect itself from radiation damage**

When the molecules that carry the genetic code in our cells are exposed to harm, they have defenses against potential breakage and mutations.

For instance, when DNA is hit with ultraviolet light, it can lose excess energy from radiation by ejecting the core of a hydrogen atom—a single proton—to keep other chemical bonds in the system from breaking.

To gain insight into this process, researchers used X-ray laser pulses from the Linac Coherent Light Source (LCLS) at the Department of Energy's SLAC National Accelerator Laboratory to investigate

how energy from light transforms a relatively simple molecule, 2-thiopyridone. This molecule undergoes a chemical transformation that also occurs in the building blocks of DNA. The scientists looked at this process by probing the nitrogen atom in the molecule with X-ray pulses that lasted just femtoseconds, or quadrillionths of a second.

The results, published in *Angewandte Chemie*, are a step toward better understanding what's called "excited state proton transfers" in DNA and other molecules.

"Right now, we want to keep it simple," says lead author Sebastian Eckert, a doctoral student at the University of Potsdam and Helmholtz-Zentrum Berlin. "It's easier to look at the effects of photoexcitation in 2-thiopyridone because this molecule is small enough to understand and has only one nitrogen atom. We are among the first at LCLS to look at nitrogen at this energy, so it's somewhat of a pilot experiment."

This is also the first time the method, known as resonant inelastic X-ray scattering or RIXS, has been used to look at molecular changes involving nitrogen that happen in femtoseconds. This short timescale is important because that's how fast protons are kicked away from molecules exposed to light, and it requires brilliant X-rays to see these ultrafast changes.

"LCLS is the only X-ray light source that can provide enough photons – particles of light," says co-author Munira Khalil, a professor at the University of Washington. "Our detection mechanism is 'photon-hungry' and requires intense pulses of light to capture the effect we want to see."

In the study, the researchers used an optical laser to initiate changes in the molecule, followed by an LCLS X-ray probe that allowed them to see movements in the bonds.

"We look for a resonance effect – a signature that lets us know we've tuned the X-rays to an energy that ensures we're only examining changes related to or near the nitrogen atom," says Mike Minitti, staff scientist at LCLS and co-author of the paper.

These "on-resonance" studies amplify the signal in a way that scientists can clearly interpret how X-rays interact with the sample.

The research team looked primarily at the bonds between atoms neighboring nitrogen, and confirmed that optical light breaks nitrogen-hydrogen bonds.

"We were also able to confirm that the X-rays used to probe the sample don't break the nitrogen-hydrogen bond, so the probe itself does not create an artificial effect. The X-ray energy is instead transferred to a bond between nitrogen and carbon atoms, rupturing it," says Jesper Norell, a doctoral student at Stockholm University and co-author of the paper.

Next, the collaboration will use the same approach to study more complex molecules and gain insight into the wide class of photochemical reactions. [23]

## **Researcher creates chemical system that mimics early cell behavior**

A Harvard researcher seeking a model for the earliest cells has created a system that self-assembles from a chemical soup into cell-like structures that grow, move in response to light, replicate when destroyed, and exhibit signs of rudimentary evolutionary selection.

While the system, developed by senior research fellow Juan Pérez-Mercader, mimics what one might conceive of as early cell behavior, a major caveat is that its main component is a molecule not typically found in living things.

Pérez-Mercader said that is by design. A physicist by training, Pérez-Mercader initiated the work to follow up on a paper he wrote in 2003 discussing mathematical models for some of the basic properties of life. The recent work, described in the open-access journal *Scientific Reports*, is an attempt to use chemistry to translate those mathematical models into the real world, he said.

"I am trying to build something that mimics life in a completely artificial way," Pérez-Mercader said.

Pérez-Mercader came to Harvard to join the Origins of Life Initiative, a University-wide effort involving researchers across Schools and disciplines. Work ranges from investigations into the still-murky processes by which life first arose to study of exoplanets far from Earth.

Life has four main attributes, Pérez-Mercader said. It stores, communicates, uses, and replicates information—as in the data held in DNA. It has metabolism that allows it to make its own parts. It is capable of self-replication. And it is capable of evolving.

"Life ... does all those things based on chemistry. If there is any chemistry that does all of the above, and is not the known biochemistry, we are searching high and low for [it]," he said.

The ability to separate from the surrounding environment is a key component of any living system, Pérez-Mercader said. This allows the chemistry of life to occur in an encapsulated structure, which keeps it from diffusing into the surrounding environment. The work of other researchers in this area has included creating rudimentary cells via fat molecules, which are used in cell-building by living things. Pérez-Mercader sought to strip the process to its essentials to better understand the basics.

"You do need to have something that generates that compartmentalization. So we said: 'Can we build the compartment in a simple way?'" Pérez-Mercader said.

To create the system, Pérez-Mercader worked with Anders Albertsen, an associate of the Department of Earth and Planetary Sciences, and Jan Szymanski, a former postdoctoral fellow at Harvard, to create a chemical soup made up of 2-hydroxypropyl methacrylate. They added ruthenium, a light-sensitive metal, to make the molecule respond to light. The modified molecule tends to link with others into long repeating chains called polymers, with one end repelling water and the other attracting it. That interaction with water causes the polymers to line up, and ultimately form vesicles.

The system is activated by blue light. Over the course of several hours of exposure, the monomers link together to form polymers, and the polymers line up to form spherical vesicles, with some approaching the size of natural cells. They grow due to osmosis until they pop and then begin growing again.

"By five hours the mixture changes," Pérez-Mercader said. "By six hours it becomes turbid. Out of the homogenous mixture develop these containers. The containers implode and grow again, they begin to do these very interesting things."

The regenerative behavior is what led Pérez-Mercader to the description "phoenix vesicles," after the mythical bird that burned up in its nest and was born again.

In addition to the ability to form spontaneously and replicate, the vesicles are attracted to light, and tend to cluster near the light source. Over time, larger vesicles dominate the population, Pérez-Mercader said, indicating that a form of selection is at work.

Aside from any potential lessons about early life, Pérez-Mercader said the findings could be useful in creating a self-assembling delivery system in industry. He said he plans to continue the work with more complex vesicles and include some active chemistry in their interior.

"The implications for the origins of life to me are very interesting, though they still need to be explored," he said. [22]

## **Scientists pinpoint critical step in DNA repair, cellular aging**

DNA repair is essential for cell vitality, cell survival, and cancer prevention, yet cells' ability to patch up damaged DNA declines with age for reasons not fully understood.

Now, research led by scientists at Harvard Medical School (HMS) reveals a critical step in a molecular chain of events that allows cells to mend their broken DNA.

The findings, to be published March 24 in *Science*, offer a critical insight into how and why the body's ability to fix DNA dwindles over time and point to a previously unknown role for the signaling molecule NAD as a key regulator of protein-to-protein interactions in DNA repair. NAD, identified a century ago, is already known for its role as a controller of cell-damaging oxidation.

Additionally, experiments conducted in mice show that treatment with the NAD precursor NMN mitigates age-related DNA damage and wards off DNA damage from radiation exposure.

The scientists caution that the effects of many therapeutic substances are often profoundly different in mice and humans owing to critical differences in biology. However, if affirmed in further animal studies and in humans, the findings can help pave the way to therapies that prevent DNA damage associated with aging and with cancer treatments that involve radiation exposure and some types of chemotherapy, which, along with killing tumors, can cause considerable DNA damage in healthy cells. Human trials with NMN are expected to begin within six months, the researchers said.

"Our results unveil a key mechanism in cellular degeneration and aging, but beyond that they point to a therapeutic avenue to halt and reverse age-related and radiation-induced DNA damage," said senior author David Sinclair, professor in the Department of Genetics at HMS and professor at the University of New South Wales School of Medicine in Sydney.

A previous study led by Sinclair showed that NMN reversed muscle aging in mice.

## **A plot with many characters**

The investigators started by looking at a cast of proteins and molecules suspected to play a part in the cellular aging process. Some of them were well-known characters, others more enigmatic figures.

The researchers already knew that NAD, which declines steadily with age, boosts the activity of the SIRT1 protein, which delays aging and extends life in yeast, flies, and mice. Both SIRT1 and PARP1, a protein known to control DNA repair, consume NAD in their work.

Another protein, DBC1, one of the most abundant proteins in humans and found across life forms from bacteria to plants and animals, was a far murkier presence. Because DBC1 previously had been shown to inhibit vitality-boosting SIRT1, the researchers suspected DBC1 may also somehow interact with PARP1, given the similar roles PARP1 and SIRT1 play.

"We thought if there is a connection between SIRT1 and DBC1, on one hand, and between SIRT1 and PARP1 on the other, then maybe PARP1 and DBC1 were also engaged in some sort of intracellular game," said Jun Li, first author on the study and a research fellow in the Department of Genetics at HMS.

They were.

To get a better sense of the chemical relationship among the three proteins, the scientists measured the molecular markers of protein-to-protein interaction inside human kidney cells. DBC1 and PARP1 bound powerfully to each other. However, when NAD levels increased, that bond was disrupted. The more NAD was present inside cells, the fewer molecular bonds PARP1 and DBC1 could form. When researchers inhibited NAD, the number of PARP1-DBC1 bonds went up. In other words, when NAD is plentiful, it prevents DBC1 from binding to PARP1 and meddling with its ability to mend damaged DNA.

What this suggests, the researchers said, is that as NAD declines with age, fewer and fewer NAD molecules are around to stop the harmful interaction between DBC1 and PARP1. The result: DNA breaks go unrepaired and, as these breaks accumulate over time, precipitate cell damage, cell mutations, cell death, and loss of organ function.

### **Averting mischief**

Next, to understand how exactly NAD prevents DBC1 from binding to PARP1, the team homed in on a region of DBC1 known as NHD, a pocket-like structure found in some 80,000 proteins across life forms and species whose function has eluded scientists. The team's experiments showed that NHD is an NAD binding site and that in DBC1, NAD blocks this specific region to prevent DBC1 from locking in with PARP1 and interfering with DNA repair.

Sinclair said that since NHD is so common across species, the finding suggests that by binding to it, NAD may play a similar role averting harmful protein interactions across many species to control DNA repair and other cell survival processes.

To determine how the proteins interacted beyond the lab dish and in living organisms, the researchers treated young and old mice with the NAD precursor NMN, which makes up half of an NAD molecule. NAD is too large to cross the cell membrane, but NMN can slip across it easily. Once inside the cell, NMN binds to another NMN molecule to form NAD.

As expected, old mice had lower levels of NAD in their livers, lower levels of PARP1, and a greater number of PARP1 with DBC1 stuck to their backs.

After receiving NMN with their drinking water for a week, however, old mice showed marked differences both in NAD levels and PARP1 activity. NAD levels in the livers of old mice shot up to levels similar to those seen in younger mice. The cells of mice treated with NMN also showed increased PARP1 activity and fewer PARP1 and DBC1 molecules binding together. The animals also showed a decline in molecular markers that signal DNA damage.

In a final step, scientists exposed mice to DNA-damaging radiation. Cells of animals pre-treated with NMN showed lower levels of DNA damage. Such mice also didn't exhibit the typical radiation-induced aberrations in blood counts, such as altered white cell counts and changes in lymphocyte and hemoglobin levels. The protective effect was seen even in mice treated with NMN after radiation exposure.

Taken together, the results shed light on the mechanism behind cellular demise induced by DNA damage. They also suggest that restoring NAD levels by NMN treatment should be explored further as a possible therapy to avert the unwanted side effects of environmental radiation, as well as radiation exposure from cancer treatments. [21]

## **Electrons use DNA like a wire for signaling DNA replication**

In the early 1990s, Jacqueline Barton, the John G. Kirkwood and Arthur A. Noyes Professor of Chemistry at Caltech, discovered an unexpected property of DNA—that it can act like an electrical wire to transfer electrons quickly across long distances. Later, she and her colleagues showed that cells take advantage of this trait to help locate and repair potentially harmful mutations to DNA.

Now, Barton's lab has shown that this wire-like property of DNA is also involved in a different critical cellular function: replicating DNA. When cells divide and replicate themselves in our bodies—for example in the brain, heart, bone marrow, and fingernails—the double-stranded helix of DNA is copied. DNA also copies itself in reproductive cells that are passed on to progeny.

The new Caltech-led study, based on work by graduate student Elizabeth O'Brien in collaboration with Walter Chazin's group at Vanderbilt University, shows that a key protein required for replicating DNA depends on electrons traveling through DNA.

"Nature is the best chemist and knows exactly how to take advantage of DNA electron-transport chemistry," says Barton, who is also the Norman Davidson Leadership Chair of Caltech's Division of Chemistry and Chemical Engineering.

"The electron transfer process in DNA occurs very quickly," says O'Brien, lead author of the study, appearing in the February 24 issue of *Science*. "It makes sense that the cell would utilize this quick-acting pathway to regulate DNA replication, which necessarily is a very rapid process."

The researchers found their first clue that DNA replication might involve the transport of electrons through the double helix by taking a closer look at the proteins involved. Two of the main players in DNA replication, critical at the start of the process, are the proteins DNA primase and DNA polymerase alpha. DNA primase typically binds to single-stranded, uncoiled DNA to begin the replication process. It creates a "primer" made of RNA to help DNA polymerase alpha start its job of copying the single strand of DNA to create a new segment of double-helical DNA.

DNA primase and DNA polymerase alpha molecules both contain iron-sulfur clusters. Barton and her colleagues previously discovered that these metal clusters are crucial for DNA electron transport in DNA repair. In DNA repair, specific proteins send electrons down the double helix to other DNA-bound repair proteins as a way to "test the line," so to speak, and make sure there are no mutations in the DNA. If there are mutations, the line is essentially broken, alerting the cell that mutations are in need of repair. The iron-sulfur clusters in the DNA repair proteins are responsible for donating and accepting traveling electrons.

Barton and her group wanted to know if the iron-sulfur clusters were doing something similar in the DNA-replication proteins.

"We knew the iron-sulfur clusters must be doing something in the DNA-replication proteins, otherwise why would they be there? Iron can damage the DNA, so nature would not have wanted the iron there were it not for a good reason," says Barton.

Through a series of tests in which mutations were introduced into the DNA primase protein, the researchers showed that this protein needs to be in an oxidized state—which means it has lost electrons—to bind tightly to DNA and participate in DNA electron transport. When the protein is reduced—meaning it has gained electrons—it does not bind tightly to DNA.

"The electronic state of the iron-sulfur cluster in DNA primase acts like an on/off switch to initiate DNA replication," says O'Brien.

What's more, the researchers demonstrated that electron transport through DNA plays a role in signaling DNA primase to leave the DNA strand. (Though DNA primase must bind to single-stranded DNA to kick off replication, the process cannot begin in earnest until the protein pops back off the strand).

The scientists propose that the DNA polymerase alpha protein, which sits on the double helix strand, sends electrons down the strand to DNA primase. DNA primase accepts the electrons, becomes reduced, and lets go of the DNA. This donation and acceptance of electrons is done with the help of the iron-sulfur clusters.

"You have to get the DNA primase off the DNA quickly—that really starts the whole replication process," says Barton. "It's a hand off of electrons from one cluster to the other through the DNA double helix."

Many proteins involved in DNA reactions also contain iron-sulfur clusters and may also play roles in DNA electron transport chemistry, Barton says. What began as a fundamental question 25 years ago about whether DNA could support migration of electrons continues to lead to new questions about the chemical workings of cells. "That's the wonder of basic research," she says. "You start with one question and the answer leads you to new questions and new areas." [20]

## **Super-resolution system reveals mechanics of tiny 'DNA walker'**

Researchers have introduced a new type of "super-resolution" microscopy and used it to discover the precise walking mechanism behind tiny structures made of DNA that could find biomedical and industrial applications.

The researchers also demonstrated how the "DNA walker" is able to release an anticancer drug, representing a potential new biomedical technology, said Jong Hyun Choi, an associate professor of mechanical engineering at Purdue University.

Synthetic nanomotors and walkers are intricately designed systems that draw chemical energy from the environment and convert it into mechanical motion. However, because they are too small to be observed using conventional light microscopes, researchers have been unable to learn the precise steps involved in the walking mechanisms, knowledge essential to perfecting the technology.

"If you cannot resolve or monitor these walkers in action, you will be unable to understand their mechanical operation," Choi said.

He led a Purdue team that has solved this problem by developing a super-resolution microscopy system designed to study the DNA walkers. The new findings appeared in the journal *Science Advances* on Jan. 20.

Researchers around the world are creating synthetic motors based on DNA and RNA, the genetic materials in cells that consist of a sequence of four chemical bases: adenine, guanine, cytosine and thymine. The designs are inspired by natural biological motors that have evolved to perform specific tasks critical to the function of cells.

The Purdue researchers have designed a DNA walking system consisting of an enzymatic core and two arms. The walker travels along a carbon-nanotube track "decorated" with strands of RNA. The enzymatic core cleaves off segments of these RNA strands as the walker continuously moves forward, binding to and harvesting energy from the RNA. The walker moves in a six-step cycle that repeats as long as there is RNA fuel.

A fluorescent nanoparticle is attached to one arm of the DNA walker, causing it to glow when exposed to light in the visible part of the spectrum. The carbon-nanotube track also fluoresces when exposed to light in a portion of the near-infrared spectrum. Because the new super-resolution microscopy system operates in both the visible and near-infrared spectra, it is possible to track the walking mechanism.

The super-resolution technology allows researchers to resolve structural features far smaller than the wavelength of visible light, which is normally difficult using conventional microscopes because of the Abbe diffraction limit, established by physicist Ernst Abbe in 1873. The limit is about 250 nanometers, which is large compared to the tiny walkers, measuring about 5 nanometers long.

As the DNA walker is exposed to laser light, the nanoparticle and nanotube flash on and off randomly. These flashes are captured as numerous fluorescing dots in thousands of imaging frames. This collection of points is then used to reconstruct the precise motion of the walker, which moves in a six-step cycle that involves cleaving portions of the RNA strand and harvesting its energy before moving on to the next strand.

Findings revealed three primary steps dominate this walking mechanism.



"So, if you can control these three steps within this walking cycle then you can really study and better control these walkers," Choi said. "You can speed them up, you can make them stop and move in different directions."

Whereas it previously would have taken 20 hours or longer to study a complete walking cycle, the new approach speeds the process to roughly one minute. [19]

## Visualizing gene expression with MRI

Genes tell cells what to do—for example, when to repair DNA mistakes or when to die—and can be turned on or off like a light switch. Knowing which genes are switched on, or expressed, is important for the treatment and monitoring of disease. Now, for the first time, Caltech scientists have developed a simple way to visualize gene expression in cells deep inside the body using a common imaging technology.

Researchers in the laboratory of Mikhail Shapiro, assistant professor of chemical engineering and Heritage Medical Research Institute Investigator, have invented a new method to link magnetic resonance imaging (MRI) signals to gene expression in cells—including tumor cells—in living tissues. The technique, which eventually could be used in humans, would allow gene expression to be monitored non-invasively, requiring no surgical procedures such as biopsies.

The work appears in the December 23 online edition of the journal *Nature Communications*.

In MRI, hydrogen atoms in the body—atoms that are mostly contained in water molecules and fat—are excited using a magnetic field. The excited atoms, in turn, emit signals that can be used to create images of the brain, muscle, and other tissues, which can be distinguished based on the local physical and chemical environment of the water molecules. While this technique is widely used, it usually provides only anatomical snapshots of tissues or physiological functions such as blood flow rather than observations of the activity of specific cells.

"We thought that if we could link signals from water molecules to the expression of genes of interest, we could change the way the cell looks under MRI," says Arnab Mukherjee, a postdoctoral scholar in chemical engineering at Caltech and co-lead author on the paper.

The group turned to a protein that naturally occurs in humans, called aquaporin. Aquaporin sits within the membrane that envelops cells and acts as a gatekeeper for water molecules, allowing them to move in and out of the cell. Shapiro's team realized that increasing the number of aquaporins on a given cell made it stand out in MRI images acquired using a common clinical technique called diffusion-weighted imaging, which is sensitive to the movement of water molecules. They then linked aquaporin to genes of interest, making it what scientists call a reporter gene. This means that when a gene of interest is turned on, the cell will overexpress aquaporin, making the cell look darker under diffusion-weighted MRI.

The researchers showed that this technique was successful in monitoring gene expression in a brain tumor in mice. After implanting the tumor, they gave the mice a drug to trigger the tumor cells to express the aquaporin reporter gene, which made the tumor look darker in MRI images.

"Overexpression of aquaporin has no negative impact on cells because it is exclusive to water and simply allows the molecules to go back and forth across the cell membrane," Shapiro says. Under normal physiological conditions the number of water molecules entering and exiting an aquaporin-expressing cell is the same, so that the total amount of water in each cell does not change.

"Aquaporin is a very convenient way to genetically change the way that cells look under MRI."

Though the work was done in mice, it has the potential for clinical translation, according to Shapiro. Aquaporin is a naturally occurring gene and will not cause an immune reaction. Previously developed reporter genes for MRI have been much more limited in their capabilities, requiring the use of specific metals that are not always available in some tissues.

"An effective reporter gene for MRI is a 'holy grail' in biomedical imaging because it would allow cellular function to be observed non-invasively," says Shapiro. "Aquaporins are a new way to think about this problem. It is remarkable that simply allowing water molecules to more easily get into and out of cells in a tissue gives us the ability to remotely see those cells in the middle of the body."

The paper is titled "Non-invasive imaging using reporter genes altering cellular water permeability."  
[18]

## **New drug limits and then repairs brain damage in stroke**

Researchers at The University of Manchester have discovered that a potential new drug reduces the number of brain cells destroyed by stroke and then helps to repair the damage.

A reduction in blood flow to the brain caused by stroke is a major cause of death and disability, and there are few effective treatments.

A team of scientists at The University of Manchester has now found that a potential new stroke drug not only works in rodents by limiting the death of existing brain cells but also by promoting the birth of new neurones (so-called neurogenesis).

This finding provides further support for the development of this anti-inflammatory drug, interleukin-1 receptor antagonist (IL-1Ra in short), as a new treatment for stroke. The drug is already licensed for use in humans for some conditions, including rheumatoid arthritis. Several early stage clinical trials in stroke with IL-1Ra have already been completed in Manchester, though it is not yet licensed for this condition.

In the research, published in the biomedical journal *Brain, Behavior and Immunity*, the researchers show that in rodents with a stroke there is not only reduced brain damage early on after the stroke, but several days later increased numbers of new neurones, when treated with the anti-inflammatory drug IL-1Ra.

Previous attempts to find a drug to prevent brain damage after stroke have proved unsuccessful and this new research offers the possibility of a new treatment.

Importantly, the use of IL-1Ra might be better than other failed drugs in stroke as it not only limits the initial damage to brain cells, but also helps the brain repair itself long-term through the generation of new brain cells.

These new cells are thought to help restore function to areas of the brain damaged by the stroke. Earlier work by the same group showed that treatment with IL-1Ra does indeed help rodents regain motor skills that were initially lost after a stroke. Early stage clinical trials in stroke patients also suggest that IL-1Ra could be beneficial.

The current research is led by Professor Stuart Allan, who commented: "The results lend further strong support to the use of IL-1Ra in the treatment of stroke, however further large trials are necessary."

The paper, 'Reparative effects of interleukin-1 receptor antagonist in young and aged/co-morbid rodents after cerebral ischemia', was published in the journal *Brain, Behavior and Immunity*. [17]

## **When push comes to shove: Size matters for particles in our bloodstream**

Researchers at the University of Connecticut have uncovered new information about how particles behave in our bloodstream, an important advancement that could help pharmaceutical scientists develop more effective cancer drugs.

Making sure cancer medications reach the leaky blood vessels surrounding most tumor sites is one of the critical aspects of treatment and drug delivery. While surface chemistry, molecular interactions, and other factors come into play once drug-carrying particles arrive at a tumor, therapeutic medication doesn't do very much good if it never reaches its intended target.

Anson Ma, an assistant professor of chemical and biomolecular engineering at UConn, used a microfluidic channel device to observe, track, and measure how individual particles behaved in a simulated blood vessel.

The research team's goal: to learn more about the physics influencing a particle's behavior as it travels in our blood and to determine which particle size might be the most effective for delivering drugs to their targets. The team's experimental findings mark the first time such quantitative data has been gathered. The study was published Oct. 4 in the *Biophysical Journal*.

"Even before particles reach a target site, you have to worry about what is going to happen with them after they get injected into the bloodstream," Ma says. "Are they going to clump together? How are they going to move around? Are they going to get swept away and flushed out of our bodies?"

Using a high-powered fluorescence microscope in UConn's Complex Fluids Lab, Ma was able to observe particles being carried along in the simulated blood vessel in what could be described as a vascular Running of the Bulls. Red blood cells race through the middle of the channel as the particles - highlighted under the fluorescent light - get carried along in the rush, bumping and bouncing off the blood cells until they are pushed to open spaces - called the cell-free layer - along the vessel's walls.

What Ma found was that larger particles - the optimum size appeared to be about 2 microns - were most likely to get pushed to the cell-free layer where their chances of carrying medication into a tumor site are greatest. The research team also determined that 2 microns was the largest size that

should be used if particles are going to have any chance of going through the leaky blood vessel walls into the tumor site.

"When it comes to using particles for the delivery of cancer drugs, size matters," Ma says. "When you have a bigger particle, the chance of it bumping into blood cells is much higher, there are a lot more collisions, and they tend to get pushed to the blood vessel walls."

The results were somewhat surprising. In preparing their hypothesis, the research team estimated that smaller particles were probably the most effective since they would move the most in collisions with blood cells, much like what happens when a small ball bounces off a larger one. But just the opposite proved true. The smaller particles appeared to skirt through the mass of moving blood cells and were less likely to experience the "trampoline" effect and get bounced to the cell-free layer, says Ma.

The research was funded by the National Science Foundation's Early-concept Grants for Exploratory Research or EAGER program, which supports exploratory work in its early stages on untested, but potentially transformative, research ideas or approaches.

Knowing how particles behave in our circulatory system should help improve targeted drug delivery, Ma says, which in turn will further reduce the toxic side effects caused by potent cancer drugs missing their target and impacting the body's healthy tissue.

Measuring how different sized particles move in the bloodstream may also be beneficial in bioimaging, where scientists and doctors want to keep particles circulating in the bloodstream long enough for imaging to occur. In that case, smaller particles would be better, says Ma.

Moving forward, Ma would like to explore other aspects of particle flow in our circulatory system such as how particles behave when they pass through a constricted area, such as from a blood vessel to a capillary. Capillaries are only about 7 microns in diameter. The average human hair is 100 microns. Ma says he would like to know how that constricted space might impact particle flow or the ability of particles to accumulate near the vessel walls.

"We have all of this complex geometry in our bodies," says Ma. "Most people just assume there is no impact when a particle moves from a bigger channel to a smaller channel because they haven't quantified it. Our plan is to do some experiments to look at this more carefully, building on the work that we just published." [16]

## **Fighting cancer with space research**

Every day, NASA spacecraft beam down hundreds of petabytes of data, all of which has to be codified, stored and distributed to scientists across the globe. Increasingly, artificial intelligence is helping to "read" this data as well, highlighting similarities between datasets that scientists might miss.

For the past 15 years, the big data techniques pioneered by NASA's Jet Propulsion Laboratory in Pasadena, California, have been revolutionizing biomedical research. On Sept. 6, 2016, JPL and the National Cancer Institute (NCI), part of the National Institutes of Health, renewed a research

partnership through 2021, extending the development of data science that originated in space exploration and is now supporting new cancer discoveries.

The NCI-supported Early Detection Research Network (EDRN) is a consortium of biomedical investigators who share anonymized data on cancer biomarkers, chemical or genetic signatures related to specific cancers. Their goal is to pool all their research data into a single, searchable network, with the goal of translating their collective work into techniques for early diagnosis of cancer or cancer risk.

In the time they've worked together, JPL and EDRN's efforts have led to the discovery of six new Food and Drug Administration-approved cancer biomarkers and nine biomarkers approved for use in Clinical Laboratory Improvement Amendments labs. The FDA has approved each of these biomarkers for use in cancer research and diagnosis. These agency-approved biomarkers have been used in more than 1 million patient diagnostic tests worldwide.

"After the founding of EDRN in 2000, the network needed expertise to take data from multiple studies on cancer biomarkers and create a single, searchable network of research findings for scientists," said Sudhir Srivastava, chief of NCI's Cancer Biomarkers Research Group and head of EDRN. JPL had decades of experience doing similar work for NASA, where spacecraft transmit hundreds of petabytes of data to be coded, stored and distributed to scientists across the globe.

Dan Crichton, the head of JPL's Center for Data Science and Technology, a joint initiative with Caltech in Pasadena, California, helped establish a JPL-based informatics center dedicated to supporting EDRN's big data efforts. In the renewed partnership, JPL is expanding its data science efforts to research and applying technologies for additional NCI-funded programs. Those programs include EDRN, the Consortium for Molecular and Cellular Characterization of Screen-Detected Lesions, and the Informatics Technology for Cancer Research initiative.

"From a NASA standpoint, there are significant opportunities to develop new data science capabilities that can support both the mission of exploring space and cancer research using common methodological approaches," Crichton said. "We have a great opportunity to perfect those techniques and grow JPL's data science technologies, while serving our nation.

Crichton said JPL has led the way when it comes to taking data from raw observations to scientific conclusions. One example: JPL often deals with measurements from a variety of sensors—say, cameras and mass spectrometers. Both can be used to study a star, planet or similar target object. But it takes special software to recognize that readings from very different instruments relate to one another.

There's a similar problem in cancer research, where readings from different biomedical tests or instruments require correlation with one another. For that to happen, data have to be standardized, and algorithms must be "taught" to know what they're looking for.

Since the time of its founding, EDRN's major challenge has been access. Research centers all over the United States had large numbers of biomarker specimens, but each had its own way of labeling, storing and sharing their datasets. Ten sites may have high-quality specimens for study, but if their common data elements—age of patient, cancer type and other characteristics - aren't listed uniformly, they can't be studied as a whole.

"We didn't know if they were early-stage or late-stage specimens, or if any level of treatment had been tried," Srivastava said. "And JPL told us, 'We do this type of thing all the time! That's how we manage our Planetary Data System.'"

As the network has developed, it has added members from dozens of institutions, including Dartmouth College's Geisel School of Medicine; Harvard Medical School's Massachusetts General Hospital; Stanford's NIST Genome-Scale Measurements Group; University of Texas' MD Anderson Cancer Center; and numerous others.

Christos Patriotis, program director at NCI's Cancer Biomarkers Research Group, said the network's members now include international researchers from the U.K., China, Japan, Australia, Israel and Chile.

"The more we expand, the more data we integrate," Patriotis said. "Instead of being silos, now our partners can integrate their findings. Each system can speak to the others."

As JPL and NCI's collaboration advances, next steps include image recognition technology, such as helping EDRN archive images of cancer specimens. Those images could be analyzed by computer vision, which is currently used to spot similarities in star clusters and other astrophysics research.

In the near future, Crichton said, machine learning algorithms could compare a CT scan with an archive of similar images, searching for early signs of cancer based on a patient's age, ethnic background and other demographics.

"As we develop more automated methods for detecting and classifying features in images, we see great opportunities for enhancing data discovery," Crichton said.

"We have examples where algorithms for detection of features in astronomy images have been transferred to biology and vice-versa." [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 0100001.

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 by 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.

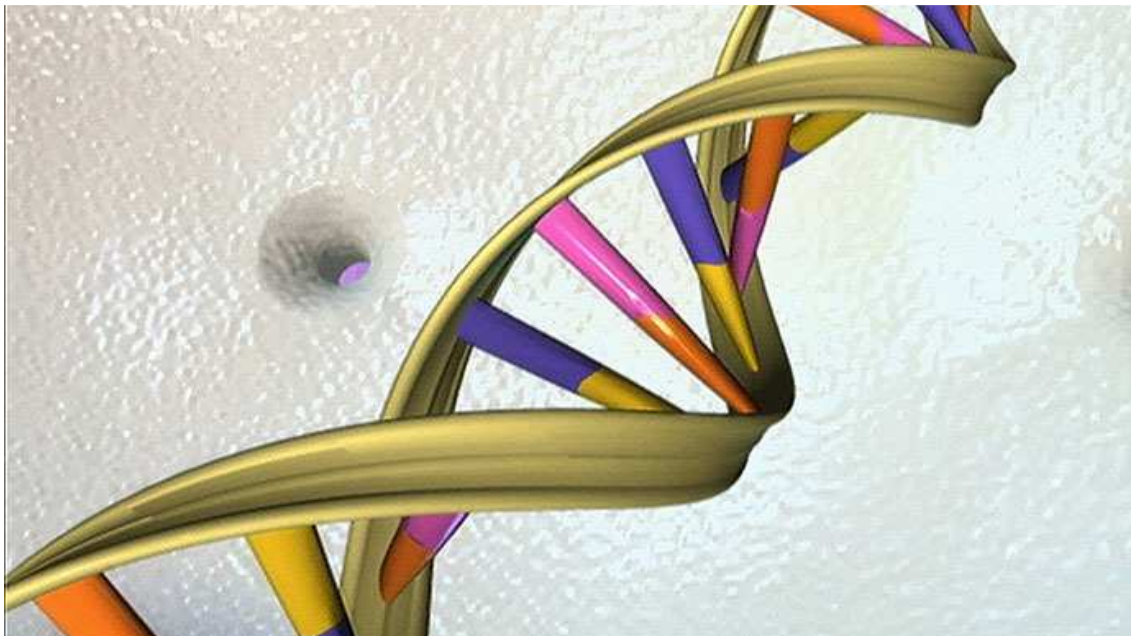
## Simulation

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.

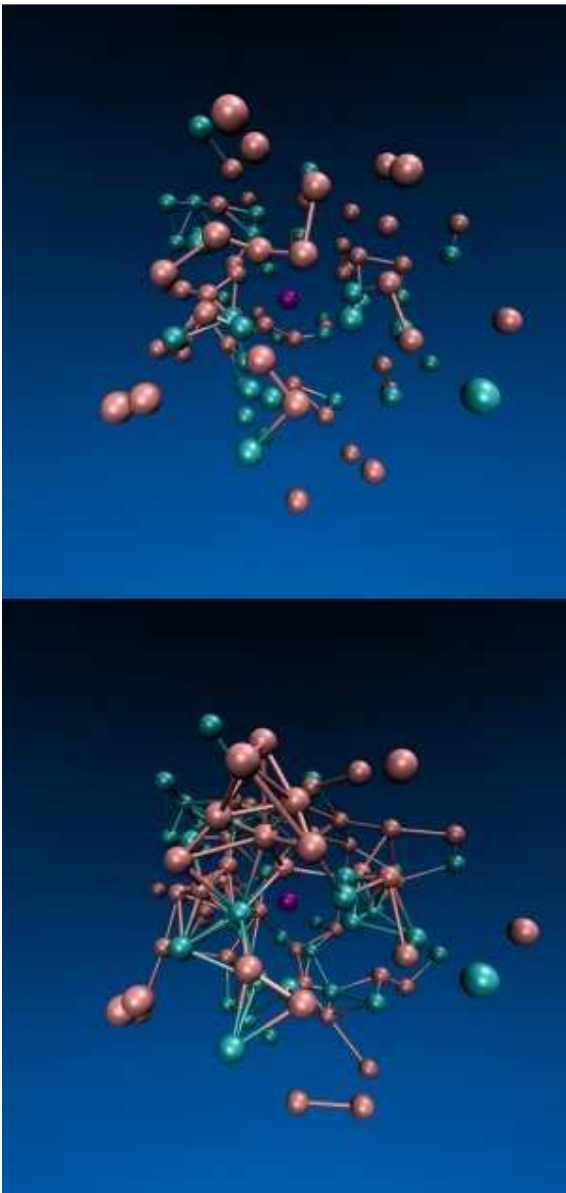
Speaking about the discovery, Stamatoyannopoulos said that the “new findings highlight that DNA is an incredibly powerful information storage device, which nature has fully exploited in unexpected ways.” [10]

## **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.



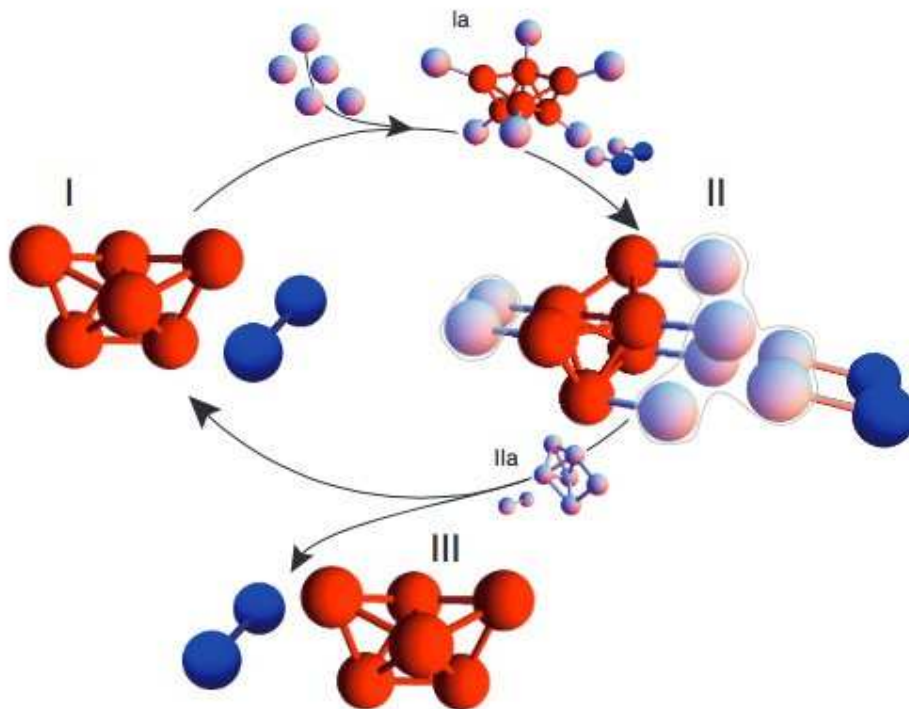
A computer simulation by Jeremy England and colleagues shows a system of particles confined inside a viscous fluid in which the turquoise particles are driven by an oscillating force. Over time (from top to bottom), the force triggers the formation of more bonds among the particles.

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



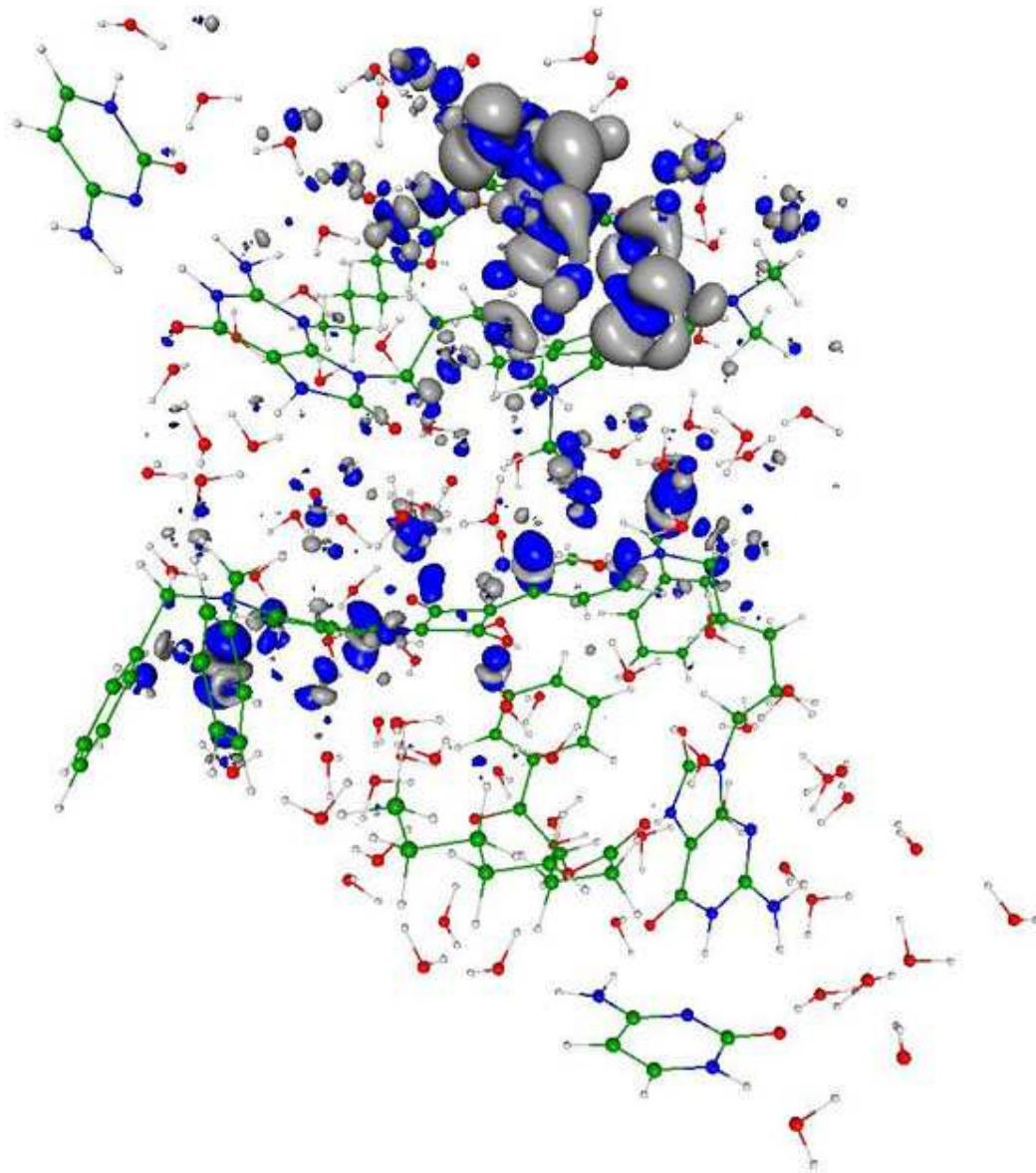
system by appearance of two additional quantum entangled excited states (Tamulis A, Grigalavicius M, Baltrusaitis J, *Orig Life Evol Biosph* 43:49-66, 2013; Tamulis A, Grigalavicius M, Krisciukaitis S (2014), *J Comput Theor Nanos*, 11, 1597-1608, 2014; Tamulis A, Grigalavicius M, 8:117-140, 2014.). 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 squaraine molecule of the first protocell situated in the bottom of this bicellular system to precursor of fatty acid (pFA) molecule of the second subsystem (in the top) and little from the 1,4-bis(N,N-dimethylamino)naphthalene molecule (in the top-right) to the same pFA molecule of the second subsystem (in the top). The electron cloud hole is indicated by the dark blue color while the transferred electron cloud location is designated by the gray color.

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

tunneling of photo excited electrons from the sensitizer squaraine and (1,4-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 unfold information not only for themselves, but for all other organisms, expanding the consciousness of the whole, while at the same time becoming more and more aware of this collective consciousness.

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

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

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

### **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 their product is about the half Planck reduced constant. For the proton this  $\Delta x$  is much less in the nucleus, 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 have a real charge distribution.

## Wave – Particle Duality

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

## The weak interaction

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

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

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

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

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

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

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

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

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

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

## The General Weak Interaction

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

The neutrino oscillation of the Weak Interaction shows that it is a general electric dipole change and it is possible to any other temperature dependent entropy and information changing diffraction pattern of atoms, molecules and even complicated biological living structures.

We can generalize the weak interaction on all of the decaying matter constructions, even on the biological too. This gives the limited lifetime for the biological constructions also by the arrow of time. There should be a new research space of the Quantum Information Science the 'general neutrino oscillation' for the greater than subatomic matter structures as an electric dipole change. There is also connection between statistical physics and evolutionary biology, since the arrow of time is working in the biological evolution also.

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

## Fermions and Bosons

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

## Van Der Waals force

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

## Electromagnetic inertia and mass

### Electromagnetic Induction

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



## Relativistic change of mass

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

## The frequency dependence of mass

Since  $E = h\nu$  and  $E = mc^2$ ,  $m = h\nu / c^2$  that is the  $m$  depends only on the  $\nu$  frequency. It means that the mass of the proton and electron are electromagnetic and the result of the electromagnetic induction, caused by the changing acceleration of the spinning and moving charge! It could be that the  $m_0$  inertial mass is the result of the spin, since this is the only accelerating motion of the electric charge. Since the accelerating motion has different frequency for the electron in the atom and the proton, 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  $M_p=1840 Me$ . 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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