Scientific Newsletter

SPRING 2024

At the front page of IRIG

Enzymes react with the bacteria responsible for hospital-acquired pneumonia

The bacterium *Staphylococcus aureus* is one of the pathogens responsible for hospital-acquired pneumonia that has become resistant to antibiotics. Researchers are studying an alternative treatment using Lysostaphin enzyme. The enzyme bacteriolytic property enables to target the vital integrity of *S. aureus* by reacting with the peptidoglycan polymer lining the bacterial wall.

To understand how it works precisely, researchers at IRIG used two enzymes of the same family Lysostaphin and LytM that are evolutionarily related but have different functions

The IRIG team studied the high lytic activity of the enzymes Lysostaphin and LytM against the bacterium *S. aureus*, by targeting the glycil-glycine bridge linking the peptide strands of the bacterial wall polymer. Monitoring of the catalytic reaction revealed these two enzymes acted in a similar way on the polymer fragments but only Lysostaphin was capable of solubilising the entire polymer.

Analysis of the nuclear magnetic resonance (NMR) characterization data led to coherent models for the docking of the enzymes on the polymer.
The researchers have shown that each enzyme reacts distinctly with the polymer depending on the complexity of **cross-linking** and therefore has different biological functions (*cf.* **figure**).

Using nuclear magnetic resonance (NMR) combined with mass spectrometry, this work proposes a model in which peptidoglycan **cross-linking** affects the activity and selectivity of the enzymes Lysostaphin and LytM differently, underpinning the specific role of each structurally related enzyme.

These results highlight the complex interaction between enzymes and their substrates. They pave the way for targeted antibacterial strategies.

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Nature Communications 2023

Jean-Pierre Simorre | IBS |
Institut de biologie structurale

Cross-linking is a linear transformation into a three-dimensional polymer.

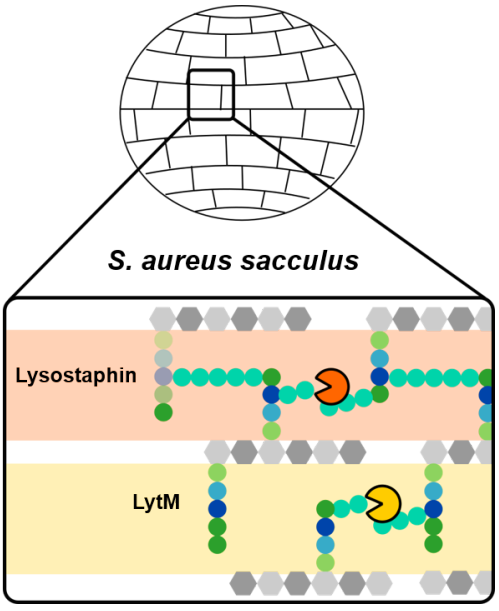

Figure : model of the activity of two enzymes LytM and Lysostaphin belonging to the same family but modulated differently by the state of cross-linking of bacterial peptidoglycan.

Looking for a needle in a nanofibers stack

A team at IRIG is developing a technique called Dynamic Nuclear Polarization (DNP) which significantly increases the detection sensitivity of molecules by Nuclear Magnetic Resonance (NMR) spectroscopy. Its application to the grafting of a drug onto the surface of cellulose nanofibers enabled detection of the drug itself and optimization of its anchoring process at grafting rates below the detection threshold of conventional characterization techniques.

Sabine Hediger | MEM |
Modeling and Exploration of Materials Laboratory

Thanks to their developments in dynamic nuclear polarization, researchers at IRIG were able to push back the detection limit of their technique. Together with chemists from Grenoble's Department of Molecular Pharmacochemistry, they succeeded in optimizing the grafting by green chemistry of a prodrug onto the surface of cellulose nanofibers. Using DNP, different reaction and product washing conditions were tested to maximize the degree of grafting compared with simple adsorption, as well as the efficient elimination of by-products. They also demonstrated an unexpected reaction of cellulose with the grafted prodrug.

By providing a unique insight into surface species, the Dynamic Nuclear Polarization (DNP) technique may well become a key approach for the development of more robust green strategies for drug grafting onto cellulose nanofibers.

Cellulose nanofibers are used in a wide range of applications, including as controlled-release drug carrier. They combine the characteristics of wood, a natural, renewable, biocompatible and mechanically resistant material, with nanometric size and a large specific surface area.

Figure: optimizing drug grafting onto cellulose nanofibers is like looking for a needle in a haystack. This magnifying glass is called nuclear magnetic resonance hyperpolarized by dynamic nuclear polarization.
© miromiro/Getty Images

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The surface chemistry of a nanocellulose drug carrier unravelled by MAS-DNP
Chemical Science 2020

The life of the alga thriving in red snow sometimes called "blood snow"

Researchers at IRIG [**Collaboration**] have shown that the alga grows at the periphery of the ice crystals, inside free water flows circulating in the snowpack. The biologists analysed the alga's cellular architecture using 3D electron microscopy. They revealed the adaptations traits that enable it to live in the snow. For example, they observed that Sanguina's cell membrane is covered by small wrinkles that increase its surface area in contact with the surrounding environment. This enables the algae to extract the ions it needs for its growth from an environment that is extremely poor in nutrients.

Eric Maréchal | LPCV |
Cell & Plant Physiology Laboratory

Collaboration

- Cell & Plant Physiology Laboratory (CNRS-CEA-UGA-INRAE)
- National Centre for Meteorological Research (CNRS-Météo France)
- Modeling and Exploration of Materials Laboratory (CEA-UGA)
- Institut de biologie structurale (CNRS-CEA-UGA)
- Unité d'appui et de recherche Jardin du Lautaret (CNRS-UGA).

The inside of the cell also held some surprises. The alga has a single chloroplast. Inside this chloroplast, the thylakoids, the lamellar structures where photosynthesis takes place, are not oriented in a single direction as in most plants and algae. In *Sanguina nivaloides* they are arranged in all possible orientations allowing the capture of light scattered in all directions. This is an adaptation specific to life in the snow, an environment where light is diffused and reflected as in a hall of mirrors. The mitochondria, the cell's energy centres, are positioned directly on the periphery of the chloroplast to use the starch it synthesises (see image inside the photo).

Finally, the research team looked at the algae's red pigments. They do not, as previously thought, serve to protect the cell nucleus from UV radiation. Consisting of carotenoids, they enable the alga to protect itself against the harmful effects of oxidising free radicals, in an environment bathed in very intense light levels.

After the snow melts, the alga reaches the soil and undergoes a metamorphosis allowing them to adapt to a radically different environment. Scientists now want to understand this unknown process. Time is running out, as the entire ecosystem dependent on *Sanguina nivaloides* is threatened by climate change and the reduction of snowfall in the mountains.

Photo © Jean-Gabriel Valay (UGA-CNRS/Jardin du Lautaret)
Image inside © Gregory Si Larbi (LPCV)

This work supported by the ANR as part of the AlpAlga programme is the first to be published with the help of the Kilian Jornet Foundation.

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Nature Communications, 2023

The current flows inside magnetic insulators

Spintronics concerns the transport of spin for electronics, supported by electrons in metals; but in magnetic insulators, spin is transported by quasi-particles called magnons. Compared with metals, magnetic insulators are better at conducting spin currents.

This field is attracting interest because of the hope that the formation of a quantum condensation of magnons, known as a Bose-Einstein condensation, will lead to a strong increase in conductivity. Researchers therefore seek to control and enhance spin currents in magnetic insulators. Inspired by the analogous electric diode they believe that a spin diode would be perfect for transporting spin currents without friction in analogy to a superconductor that transports electric current without resistance. This would make it possible to produce more efficient, energy-saving non-linear components such as microwave signal amplifiers or rectifiers.

Olivier Klein | Spintec |
Spintronics and component technology

Collaboration

- University of Grenoble Alpes
- University of Paris-Saclay
- University of Lorraine
- University of Bretagne Occidentale

A consortium (CEA-IRIG, CEA-IRAMIS and CNRS/Albert Fert Laboratory) has studied magnetic yttrium iron gar-net (YIG), a material with non-linear current characteristics. The device consists of a YIG film on which two adjacent platinum wires are deposited as magnon emitter and collector, in order to electrically control the chemical potential of the magnons and with very low magnetic damping. However, although the measurements showed a diode-like current-voltage characteristic curve, due to the non-linear increase in the population of low-energy magnons, the gain obtained was small, several orders of magnitude lower than expected (*cf.* **figure**).

In the first article [**1**] the researchers explain this weakness by a rapid saturation of the population of low-energy magnons, which limits the spin diode effect to such an extent that the YIG material is unable to reach a state of infinite spin concentration. The whole material behaves more like a classical liquid of spins, without the quantum effect.

Bose-Einstein condensate
At very low temperatures elements of condensed matter behave as if they occupied a single lower-energy quantum state.

A second article [**2**] explains why the non-linear diode effect can only be observed for large distances between the electrodes. At short distances, spin transport is dominated by high-energy thermal magnons, which produce only a linear response as a function of the voltage applied between the electrodes. However, as their influence decays rapidly with distance, low-energy magnons are able to produce the spin diode effect once the distance between the electrodes exceeds a few micrometers. Furthermore, these experimental observations are corroborated by an analytical model that integrates all the effects of low-energy magnons and thermal magnons.

The results of this study show that it is not possible to obtain the formation of a **Bose-Einstein condensate** in extended YIG films. Nevertheless, in future studies, it would be interesting to determine whether the saturation regime makes it possible to obtain a new condensed state, of the liquid type.

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Non-local magnon transconductance in extended magnetic insulating films. Part I: spin diode effect
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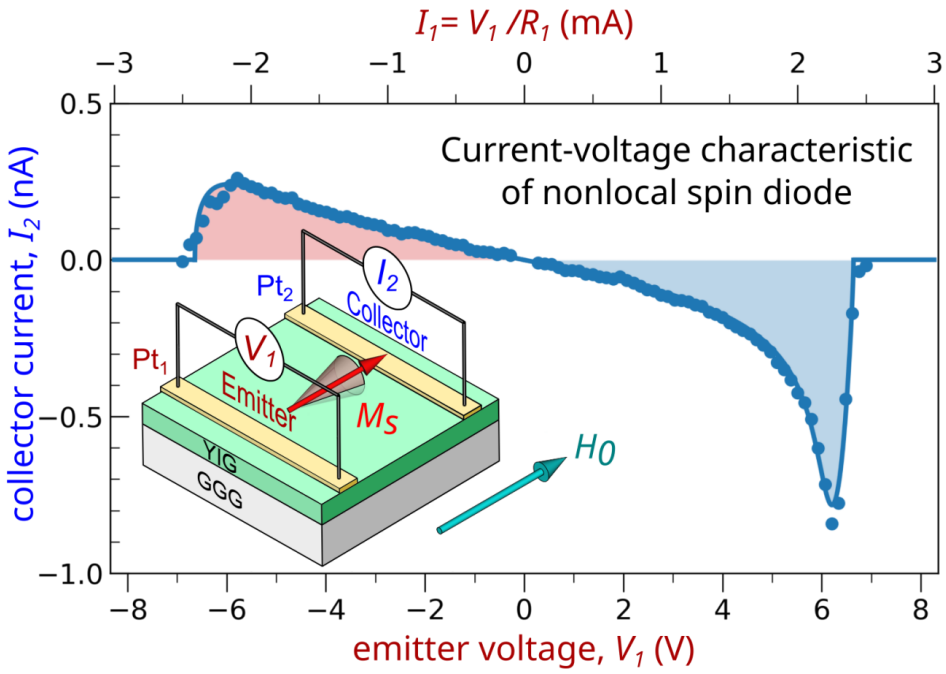

Figure: illustration of the current-voltage characteristic curve I (V) of a spin diode made from YIG material

The mystery of the DNA pyramids solved by Electron Paramagnetic Resonance

Nanotechnologies based on the assembly of DNA - DeoxyriboNucleic Acid - of biological or synthetic origin, are increasingly used in the fields of biotechnology, nanomedicine, nanophotonics and nanoelectronics. Recent progress, based on the predictable pairing properties of nucleobases, has made it possible to create many different oligomeric architectures such as cages, LEGO® or origami. It therefore appeared necessary to have exhaustive characterisation methods to better define these structures in order to improve their design. On the one hand, characterisation techniques such as gel electrophoresis, chromatography and dynamic light scattering determine the average size of nanostructures by volume; on the other hand, atomic force microscopy and electron microscopy enable surface measurements on the nanometre scale. However, these techniques do not provide valuable information about folding products and assembly intermediates. Nor do they address aspects concerning the homogeneity and stability of these biomolecular architectures in different buffers and biological media.

Didier Gasparutto | SyMMES |
Molecular Systems and nanoMaterials for Energy and Health

To supplement this information, researchers at IRIG as part of an international collaboration with the University of Lille, ENS Paris and the University of Padua in Italy, have succeeded in designing and characterising DNA nano-pyramids with unprecedented sub-nanometric resolution. In particular, the researchers have precisely analysed the parameters of the self-assembly process. These results were obtained thanks to the multi-disciplinary expertise brought together within the consortium, combining chemical and biochemical synthesis methods, spectroscopic analyses using pulsed mode Paramagnetic Electron Resonance, and molecular dynamics approaches.

Drawing on the expertise in biomolecular engineering developed over many years within the BIOMade platform at IRIG, the researchers synthesised and assembled tetrahedral DNA nanostructures, which they labelled with two radical probes on precisely selected sites using "Click Chemistry" (see **Figure**).

This bio-conjugation method operates under mild conditions, does not form any by-products, and offers high selectivity and reaction yield.

This work focuses on new predictive synthesis and analysis tools for the preparation of DNA-based self-assemblies, which can be applied to other biopolymers. It involves the design of new functional dynamic architectures, such as chemo-activatable, photo-activatable or bio-activatable molecular nanomachines, for applications in many areas of bio-inspired nanotechnologies.

Fundings: CEA Programme Phare A3DN and Arcane labex

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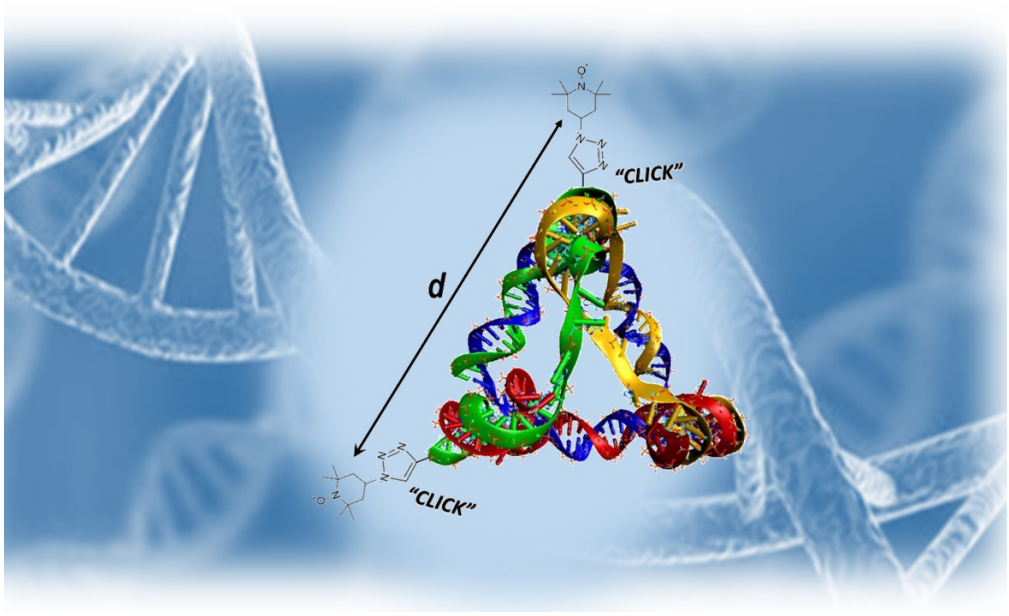

Figure: measurement by pulsed electron paramagnetic resonance of the correlation between two radical centres (here two nitroxide probes) within a DNA tetrahedron. The active centres are introduced into the nanostructure by means of regio-selective multi-labelling (by using 'click chemistry') of the DNA strands used as building blocks. In the case presented here, the measured distance of 5.55 nm (distance between the two probes positioned at the top of a 17-nucleotide edge tetrahedron) is in perfect agreement with the predicted size of 5.6 nm.

Simcryogenics simulation tool for JT-60SA

The JT-60SA **tokamak** is the largest nuclear fusion facility in operation. This research reactor was inaugurated on December 1st 2023 in Naka, Japan. Designed and funded by the European Union and Japan to study hydrogen fusion, the research will run in parallel with the ITER project in France. Magnetic confinement of the plasma is provided by superconducting magnets cooled by a helium cryogenic plant capable to extract 9 kW at 4.5 K.

François Bonne | DSBT |
Low Temperature Systems Department

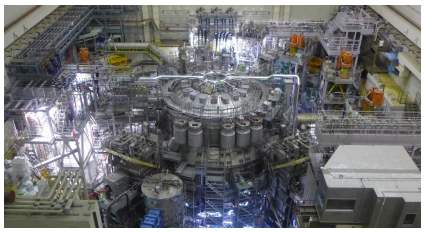

Photo: tokamak JT60-SA

To ensure that the magnets are maintained at a temperature of 4.5 K, teams from the IRIG designed a cryogenic plant, manufactured by the French company Air Liquide and installed in Japan. Following the successful commissioning of the cryogenic system, the scientists contributed to the testing of the superconducting magnets during the first fusion experiments, which led to the creation of a plasma current with an intensity of 10^6 A.

During these tests, rapid discharges of the current circulating in the magnets were carried out to test the magnet system's ability to trip. Rapid discharge of the current dissipates heat, which increases the pressure in the cryogenic loop that cools the magnets and risks causing helium to escape into warm storage. Beforehand, the researchers used the Simcryogenics simulation tool to model the loop, to ensure that the rise in pressure would remain below a safety threshold and thus prevent the helium exhaust.

The simulation tools designed by the IRIG's team were used to test the behaviour of the cooling loop for the superconducting magnets in the JT-60SA tokamak. These calculations ensured the safe commissioning of the fusion reactor.

A **tokamak** is a toroidal experimental reactor for exploring nuclear fusion conditions in a plasma by magnetic confinement.

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The haploinsufficiency model of Rendu-Osler disease revisited

Rendu-Osler disease, also known as Hereditary Haemorrhagic Telangiectasia (HHT), is a rare vascular disorder (1 in 5,000 individuals) characterised by nosebleeds and arteriovenous malformations of vital organs such as the lung, liver and brain. This genetic disease is caused by mutations in two genes, Activin receptor-Like Kinase 1 (ALK1) and endoglin, which encode receptors in the endothelial cells lining blood vessels.

Sabine Bailly | Biosanté |
Biology and Biotechnologies for Health Laboratory

In 2007, an IRIG team identified two Bone Morphogenetic Protein proteins, BMP9 and BMP10, as ligands for these two receptors [**1**, **2**]. ALK1 mutations lead to a loss of function of the protein, suggesting that this disease is due to functional **haploinsufficiency**.

In this new work, the researchers analyzed the transcriptomic of endothelial cells, derived from umbilical cord blood carrying the mutated ALK1 gene, in response to stimulation by BMP9 or BMP10. The results show that a single mutation in the ALK1 gene does not affect the signalling pathway after stimulation by BMP9 or BMP10 [**3**].

The **haploinsufficiency** model of Rendu-Osler disease is thus revisited: This works shows that a second hit (genetic, inflammatory, angiogenic) is necessary to lead to this vascular pathogenesis..

haploinsufficiency: only one of the two copies of the gene provided by the parents is active, but synthesized in insufficient quantities to allow normal cell function.

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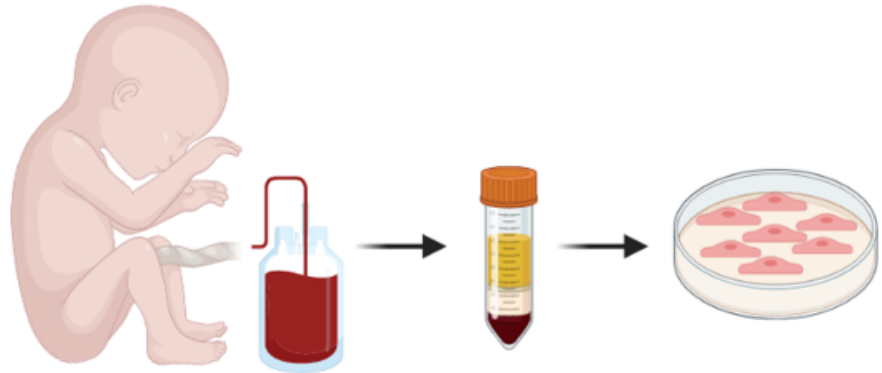

Figure: collection of cells from umbilical cord blood of a newborn baby whose mother or father has Rendu-Osler disease.

DNA-based metalloenzymes to improve the selectivity of an oxidation reaction

Biocatalysis is the biology of sustainable chemical synthesis, where the chiral catalyst can be an enzyme extracted from a living organism or a synthetic enzyme. For example, artificial metalloenzymes are developed by introducing a bio-inspired inorganic complex into a protein, in a cavity. The inorganic complex is the reactive center and the protein is the support for stability and selectivity. The aim is to develop efficient hybrid catalysts for oxidation reactions with a focus on asymmetric oxygen transfers.

Caroline Marchi-Delapierre | LCBM | Chemistry and Biology of Metals laboratory

Two **enantiomers** R and S have the same physicochemical properties in relation to an achiral agent, but behave differently in relation to a chiral agent. The notion of chirality is essential in the molecular recognition processes of living organisms, for example in the functioning of enzymes or the action of drugs. It is therefore important for a chemist to preferentially synthesize a single enantiomer of an asymmetric molecule.

Sulfoxydation adds an oxygen atom to a sulfur atom by a chemical process transforming a thioether into a sulfoxide and creating an asymmetric center on the molecule.

Researchers at IRIG, in collaboration with the Department of Molecular Chemistry – Unité Mixte de Recherche CNRS & Grenoble Alpes University, are studying hybrids formed from various metal complexes (Co, Fe, Mn, Ru) and the NikA protein, which transports nickel in *E. coli* bacteria. These hybrids catalyze oxidation reactions of alkenes (C_nH_{2n}) or thioethers (R-S-R'). However, these reactions are only weakly stereoselective. In order to improve the enantioselectivity of the sulfoxidation reaction (*i.e.* the selection of the R and S forms of both **enantiomers**) the researchers replaced the NikA protein with a G-quadruplex oligonucleotide. Thanks to significant folding polymorphism, these G-quadruplexes, associated with a copper complex, constitute versatile DNA-based catalytic entities for selective asymmetric oxidation reactions.

The enantioselectivity of the catalysis depends on the topology adopted by the G-quadruplex, and therefore on the reaction conditions. The researchers have shown that it is possible to constrain a G-quadruplex in a unique topology by attaching it to a polypeptide leading to the oxidation of thioanisole derivatives with an enantiomeric excess of up to 73% in the presence of hydrogen peroxide as the oxidant.

Comparative studies between the natural G-quadruplex and constrained G-quadruplexes modified at the 3' external tetrad by the addition of one to six thymidines identified the different reaction sites within the artificial enzyme and proposed a reaction mechanism.

The results obtained help to decipher the enantioselective control of the **sulfoxidation** reaction with G-quadruplex type catalysts, highlighting the importance of the nature of additional nucleosides over the 3'-tetrad.

Fundings: ANR CoolCat project.

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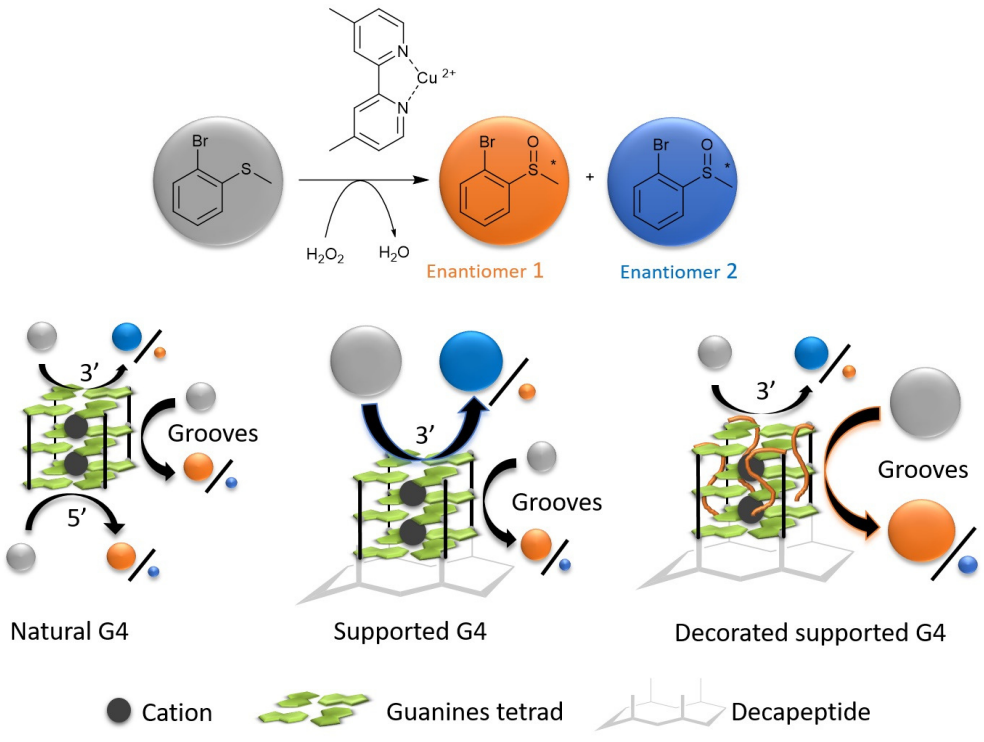

Figure: comparison of the enantioselectivity of an asymmetric sulfoxidation reaction as a function of the nature of the G-quadruplex catalyst.

Giant atomic swirl in bilayer graphene

Graphene is a sheet of carbon atoms arranged on a honeycomb lattice, with remarkable properties, including exceptional electrical conductivity. It is theoretically possible to obtain moiré patterns by stacking two sheets of graphene and exerting mechanical stress on just one of the two sheets. But until now, no one had succeeded in carrying out the experiment, or in studying this new associated physics.

Vincent Renard | Pheliqs | Quantum Photonics, Electronics and Engineering Laboratory

Collaboration
- University of Cergy Pontoise
- University of Manchester
- Universidad Autonoma de Madrid
- Centre de Recherche sur l'Hétéro-Epitaxie et ses Applications CRHEA (CNRS)

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Mesple F, Walet N, Trambly de Laissardière G, Guinea F, Došenović D, Okuno H, Paillet C, Michon A, Chapelier C and Renard V.
Giant Atomic Swirl in Graphene Bilayers with Biaxial Heterostrain
Advanced Materials 2023

By chance, researchers at IRIG [**collaboration**] were able to produce this graphene stack. Their process of freeing the graphene sheets from the silicon carbide substrate proved to be slightly incomplete, and a few carbon atoms of the graphene sheet in contact with substrate remained chemically bonded to silicon atoms in the substrate. This induces a biaxial stress, exerted only on the graphene sheet close to the substrate.

This bilayer graphene, in which one sheet is subjected to a biaxial stress and the other is not, produces a moiré that is different from that of the twisted bilayer (two stacked sheets, one of which is rotated with respect to the other) which has recently made headlines for its superconductivity.

The scientists were able to observe this novel moiré patterns using tunneling microscopy and to link a characteristic length of these patterns (200 nanometres) to the low stress exerted on the sheet close to the substrate. They then used this stress value to calculate the relaxation of some 3 million carbon atoms in the bilayer graphene.

Calculations which reproduce well experiments, show that this reorganisation of the carbon atoms forms a giant atomic swirl!

The atoms rearrange themselves in such a way to minimise the energy of the bilayer graphene, and more precisely, to reduce to a minimum (almost to a point!) the region where the hexagonal lattices of the two graphene sheets are exactly superimposed. The result looks like a cyclone or spiral galaxy whose arms are associated with electronic states that are much sought-after in quantum physics (known as topological states).

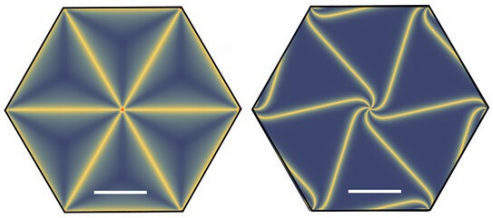

Figure: stacking parameter for a structure relaxed from a moiré induced by a 0.1% purely biaxial heteroformation. Right: low-energy spiral soliton mode; left: metastable right-hand soliton mode. Scale bar: 100 nm.

Fundings: CEA PTC-instrum project DForm, ANR project Flatmoi, and Science and Technology funding Council (UK).

Skin organoids to study Monkeypox

Monkeypox, or Mpox virus, is an infectious disease circulating in tropical Africa. In 2022, an epidemic of Mpox emerged in over a hundred countries, mainly in Europe and the USA. Although this disease appears less severe than smallpox, serious complications, including skin lesions or extensive lesions, cases of superinfection and deaths have been reported. There is, therefore, an urgent need to better understand the pathophysiology of this infection to develop effective treatments.

Karine Raymond-Lebrin | BGE | Biosciences and bioengineering for health laboratory

As this disease affects the skin, researchers at IRIG, in collaboration with a Dutch team from the Universities of Rotterdam and Leiden, have developed cutaneous organoids derived from human stem cells that reproduce the characteristics of the skin. These **organoids** could represent a robust experimental model (ref. **1**, **2**).

In contact with the Mpox virus, they overexpress viral genes that modify the host's genetic information. The researchers' studies show that treatment with the antiviral tecovirimat inhibits the production of infectious particles, confirming the potential of this model.

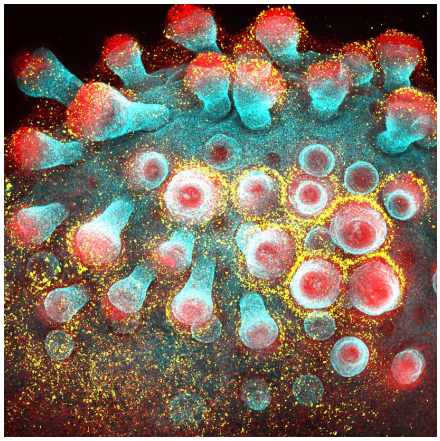

Figure: skin organoids (blue) infected with the Mpox virus (yellow). Red: Cell nuclei

These discoveries contribute to a better understanding of the skin lesions associated with Mpox virus infection. The use of human organoids, therefore, seems an interesting avenue for facilitating, or even accelerating, the discovery of treatments for other emerging diseases in the future.

Organoid
3D structures cultivated *in vitro* that self-organize and reproduce certain functions of the real organ.

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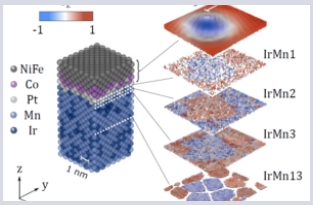
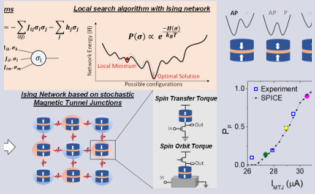
Other scientific news from laboratories



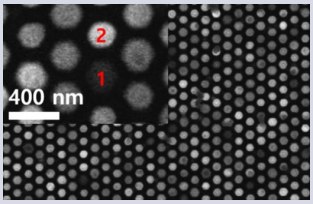
Local setting of spin textures in antiferromagnets

On SPINTEC website



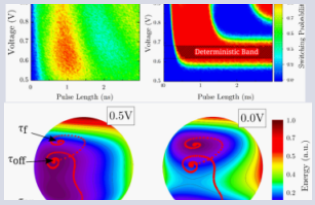
Resistively-coupled stochastic MTJ for energy-based optimum search

On SPINTEC website



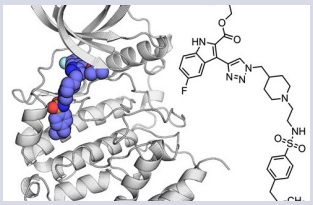
The tree or the forest: A method for the statistical analysis of the optical properties of a range of InGaN nanowires

On PHELIQS website



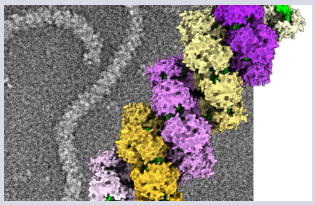
Deterministic switching in Voltage Controlled Magnetic Anisotropy Magnetic at Cryogenic Temperatures

On SPINTEC website



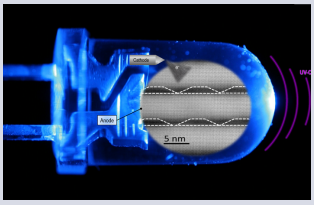
Targeting differently the CK2 protein kinase as an example

On BIOSANTE website



Highlights on the Influenza virus genome organization

On IBS website

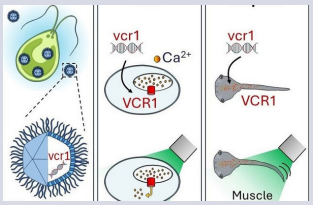


Towards safer UV disinfection with advanced AlGaN semiconductor solutions

On PHELIQS website

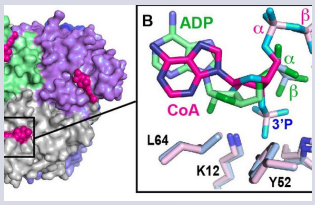
Pressure on solid-state batteries: a breakthrough

On SYMMES website



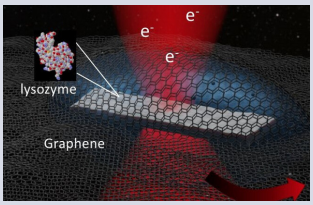
Photocontrol of intracellular calcium by a new class of viral rhodopsins: application to light-mediated restoration of muscle contraction in paralized animals

On IBS website



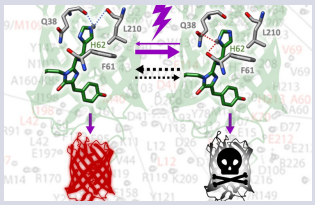
A new link between metabolism and epigenetics

On IBS website



Room temperature protein electron crystallography

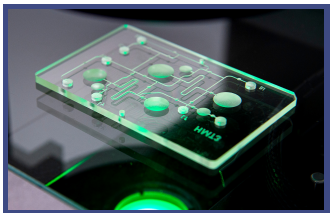
On IBS website



NMR reveals new secrets of fluorescent proteins used in super-resolution microscopy

On IBS website

Press releases – Prizes – Others

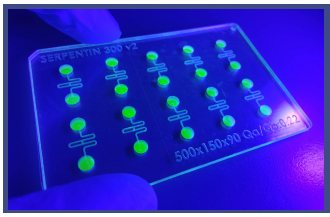


PEPR MED-OOC explores organoids on chip and has been approved by the Plan d'Investissement d'Avenir France 2030

On IRIG website

PEPR SPIN for frugal agile and sustainable digital tech

On IRIG website



Teams at CEA-IRIG and CEA-LETI have developed an innovative microfluidic platform to ensure that organoids are properly vascularized, thus promoting their maturation *in vitro*.

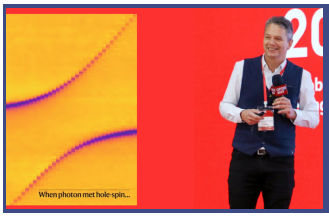
On IRIG website

Collaboration with Vietnam supports solar fuels

On IRIG website

Philippe Sabon is recipient of the CNRS 2023 Collective Crystal for the Repotech project

On IRIG website



The SIF-SFP 2023 Friedel-Volterra Prize awarded to Silvano De Franceschi

On IRIG website

Rebekka Wild and Johan Decelle are 2024 CNRS bronze medals winners

On IRIG website

The Amylen project led by researchers at LCBM is developing new materials for producing electricity from water vapour.

On LCBM website

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Unité Inserm CEA-INSERM-UGA
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