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The magazine of the European Physical Society

Medical Physics

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the module has landed

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the W boson

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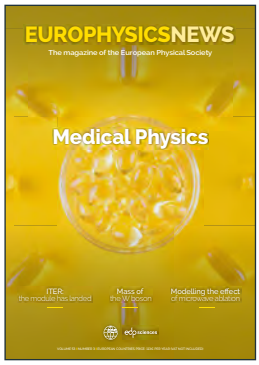

europhysicsnews

Cover picture: Medication in summertimes. In this issue what physics can do for health. ©iStockPhoto

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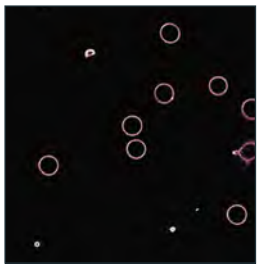
Accelerators for health: from current to dream machines



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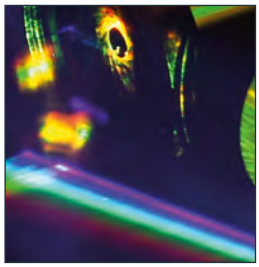
Tiny robots made from biomolecules



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[EPS EDITORIAL]

Towards the EPS 2.0

The European Physical Society (EPS) was founded in 1968 in Geneva through the inspiring leadership of Gilberto Bernardini (1906-1995). Since then, the EPS has grown from 6 to 42 members states. Today it hosts 12 Divisions and 6 Groups, mostly leading the various fields of physics or societal activities ranging from physics for development to technology and innovation. Promoting scientific excellence, the EPS Divisions and Groups organise many of European major conferences and award Europe's most prestigious prizes in their respective areas. This "backbone" of the EPS is reinforced by several committees in charge of the EPS Historic Sites, Equal Opportunities or Young Minds activities. So far, the EPS has also succeeded in attracting more than 40 Associate Members and 30 cooperating societies with whom we have bi-lateral agreements.

Under the guidance of the EPS president, the Executive Committee, elected by the EPS Council, is currently composed of 13 members who meet about 4 times a year in order to pilot activities of the EPS and review its budget. Among the agenda of the last Executive Committee meeting were addressed, among other points, updates on prize charters, the Grand Challenges for Physics on the Horizon 2050 - brightly conducted by Carlos Hidalgo – reports on the activities at our Brussels' office, or the follow up on our actions related to the Russian war in Ukraine. In this respect, the Executive Committee decided to relay initiatives that offer effective assistance to scientific refugees from Ukraine (*e.g.*, scienceforukraine.eu, ERA4Ukraine) and support projects which help children and students to recover decent education infrastructures inside Ukraine (*e.g.*, science4people).

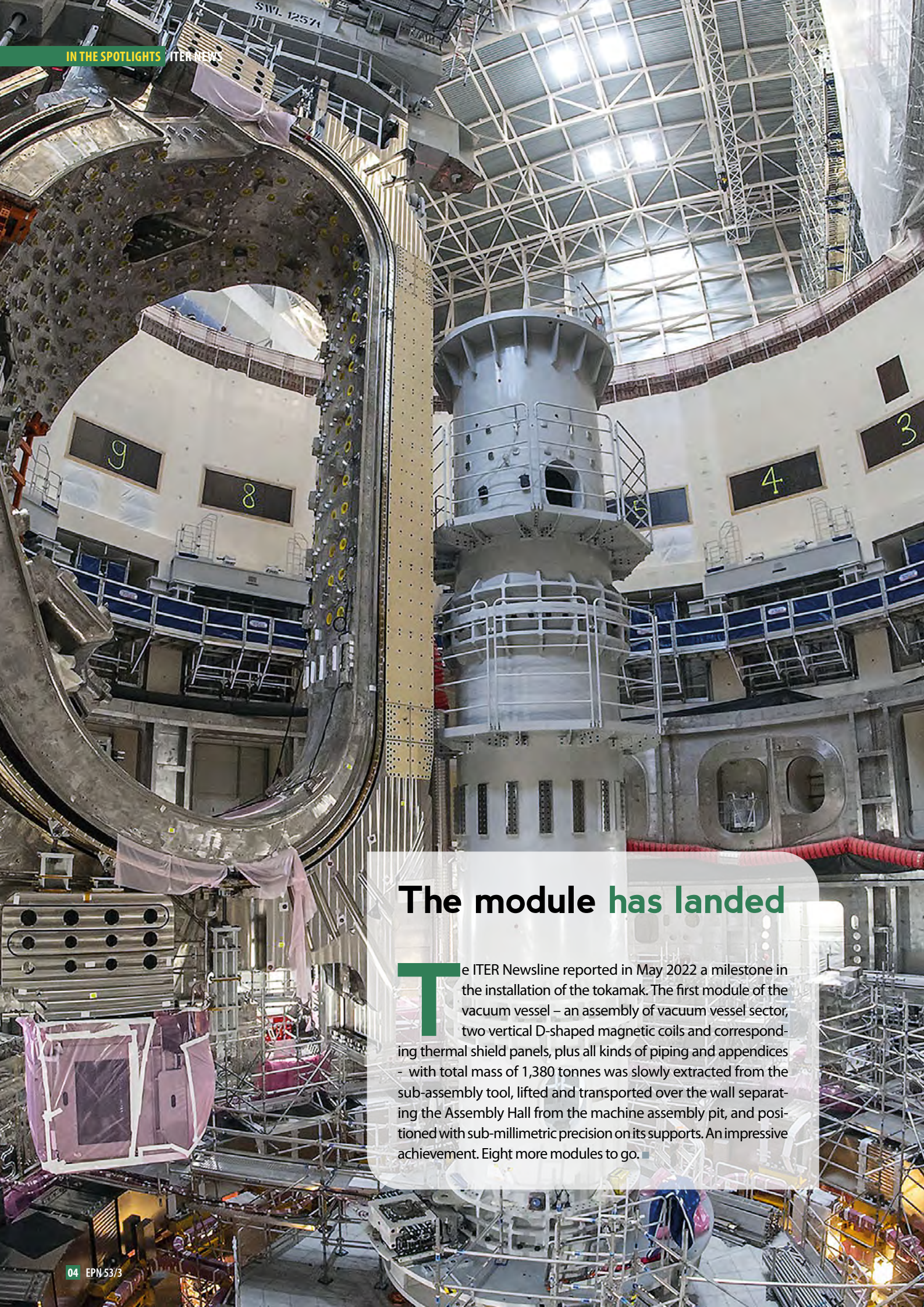
Since its creation, the EPS has known several evolutions and thus successive transformations of its constitution, regularly revised between 2004 and 2016. This necessary evolution inspired the EPS Strategic Plan 2010+ that aimed at reviewing the governance of our learned society and at outlining a possible strategy for its future. Since 2010 our world has, however, rapidly changed too and new priorities occurred. The first priority is to reinforce the link with the industrial sector as more than 50% of our young physicists are employed in industry. This goal is also deeply related to the recruitment of new Associate Members belonging to this community. Specific projects like the EPS Forum, the first edition of which took place in Paris on 2-3 June 2022, will contribute to highlight this new direction and broaden our community. A second objective is to help young physicists. To this aim, the EPS Young Minds Programme was created to accompany and support the next generation of researchers and leaders in physics. Moreover, promoting inclusion, gender equality and helping young professionals who work in low-income countries to keep an excellent academic level have become current objectives in all international learned societies.

Several workgroups have been created to address these new challenges and improve the management of the EPS activities. There are also challenges at the EPS secretariat to distribute and handle the workload generated by these novel activities. Meanwhile, the environment in which the EPS operates has also become more complex. There is generally greater scrutiny of associations, in particular when those receive income from conference organisation and editorial services. There is nowadays a need for greater transparency for any association that wishes to be involved in EU financed projects, in particular for not for profit associations whose financial statutes must be adapted. We already identified new statutory auditors to guide us through these transformations.

Therefore, an extraordinary Council held on 26 January 2022 approved to a large majority the proposal to set up a working group in charge of reviewing the statutes and by-laws of the EPS. This working group will propose recommendations to modernise the EPS constitution and Structures during a further Council Meeting in 2023. In order to pilot these profound structural changes, it was proposed to extend the mandate of all members of the Executive Committee by one year, which was also accepted, considering that enough time needs to be allocated to the examination to each of the EPS components. We deeply thank the Council delegates for placing their trust in us for another year.

The EPS 2.0 is now in progress. ■

Luc Bergé, *EPS President*



The module has landed

The ITER Newsline reported in May 2022 a milestone in the installation of the tokamak. The first module of the vacuum vessel – an assembly of vacuum vessel sector, two vertical D-shaped magnetic coils and corresponding thermal shield panels, plus all kinds of piping and appendices - with total mass of 1,380 tonnes was slowly extracted from the sub-assembly tool, lifted and transported over the wall separating the Assembly Hall from the machine assembly pit, and positioned with sub-millimetric precision on its supports. An impressive achievement. Eight more modules to go. ■

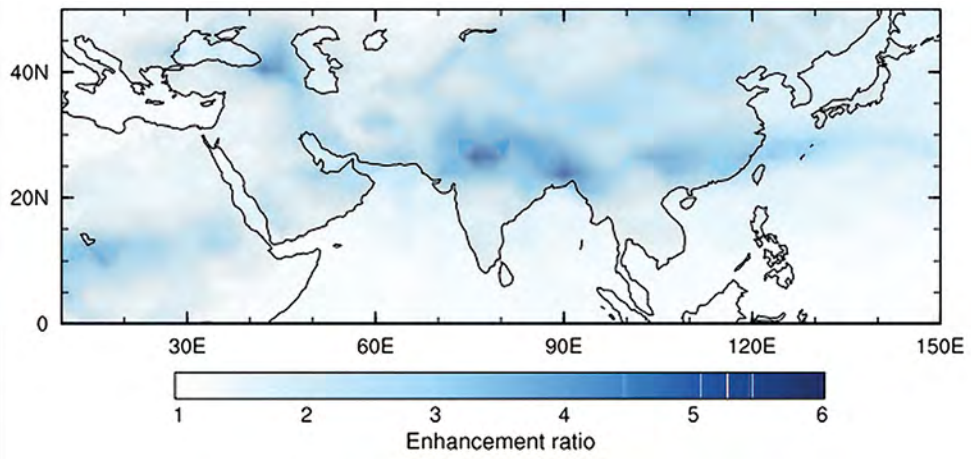
New CLOUD results

The CLOUD experiment at CERN discovered a new way by which aerosols rapidly form and grow at high altitude. The resultant particles quickly spread around the globe, potentially influencing Earth's climate on an intercontinental scale.

The CLOUD experiment at CERN is operated by an interdisciplinary team of atmospheric scientists, cosmic-ray physicists and particle physicists. The scientists aim at studying the influence of cosmic rays on aerosols in the Earth's atmosphere. Aerosol particles are known to generally cool the climate by reflecting sunlight back into space and by making clouds more reflective. However, aerosol formation itself is poorly understood. Measuring the underlying microphysics in controlled laboratory conditions is important to get a better understanding.

In a special cloud chamber aerosols form an artificial cloud, while the Proton Synchrotron at CERN provides an artificial source of "cosmic rays" that simulates natural conditions between ground level and the stratosphere. A beam of particles is passed through the cloud chamber and its effects on aerosol production or on liquid or ice clouds inside the chamber are recorded.

In a paper in Nature in May 2022 [1], the CLOUD collaboration reports that aerosol particles can form and grow in Earth's upper troposphere in an unexpected way. The new mechanism may represent a major source of cloud and ice seed particles in areas of the upper troposphere where ammonia is efficiently transported vertically, such as over the Asian monsoon regions. Using mixtures of sulfuric acid, nitric acid and ammonia vapours in the chamber at atmospheric concentrations, the CLOUD team found that the three vapours form new particles 10-1000 times faster than a sulfuric acid–ammonia mixture, which, from previous CLOUD measurements, was considered to be the dominant source of upper tropospheric particles. Once the three-component particles form, they can grow rapidly to sizes where they seed clouds with ice crystals, comparable to desert dust particles, which are thought to be the most widespread and effective ice seeds in the atmosphere. When a supercooled cloud droplet freezes, the resulting ice particle will grow at the expense of any unfrozen droplets nearby, so ice has a major influence on cloud microphysical properties and precipitation. New models developed by the team of CLOUD showed that although the particles form locally, *e.g.* in Asia, they travel from there to North America in just three days via the subtropical jet stream. In figure 1 a simulation is shown of the aerosol particle formation during the Asian monsoon in a global aerosol model with efficient vertical transport of ammonia into the upper troposphere. Including a mixture of sulfuric acid, nitric acid and ammonia enhances upper-tropospheric particle number concentrations over the Asian monsoon region by a factor of 3–5 compared with the same model with only sulfuric acid and ammonia.



▲ FIG. 1: Simulation of aerosol particle formation during the Asian monsoon compared to the results of an earlier version of the model. (Credit CLOUD Collaboration)

Once again, CLOUD found that anthropogenic ammonia has a major influence on atmospheric aerosol particles. Atmospheric concentrations of sulfuric acid, nitric acid and ammonia were much lower in the pre-industrial era than they are now, and each is likely to follow different concentration trajectories under future air pollution controls. Ammonia in the upper troposphere originates from livestock and fertiliser emissions – which are unregulated at present – and is carried aloft in convective cloud droplets, which release their ammonia upon freezing. The CLOUD results are important for policies for future air pollution regulations. ■

Reference

[1] M. Wang *et al.* Nature, doi:10.1038/s41586-022-04605-4 (2022).

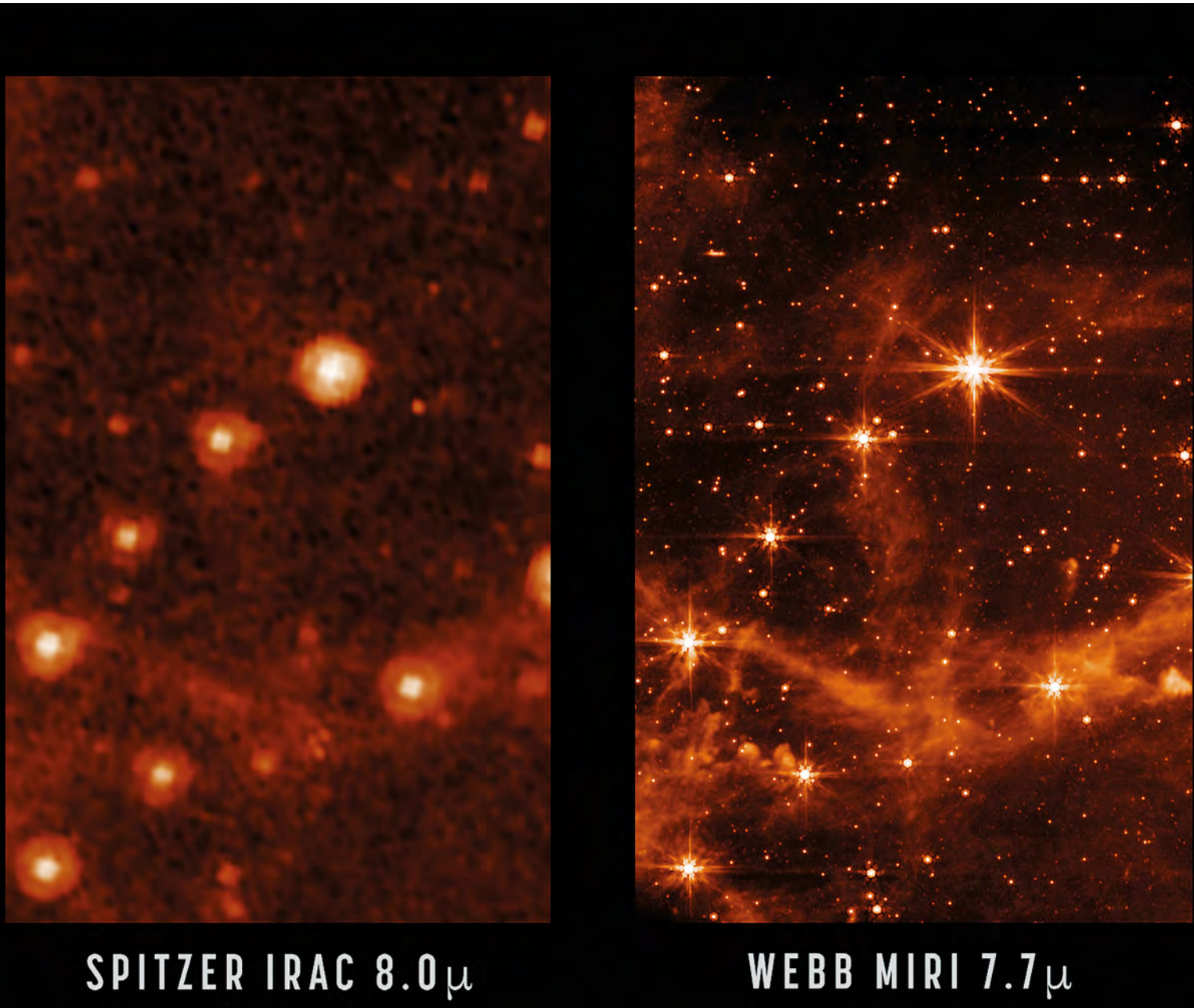
MIRI's Sharper View

The new James Webb Space Telescope is now aligned across all four of its science instruments[1]. A test image of the Mid-Infrared Instrument (MIRI) shows the promising performance of the Webb telescope.

In Figure 1 a comparison between images of the same part of the Large Magellanic Cloud taken by the retired Spizer Space Telescope and by MIRI. The latter shows the interstellar gas in unprecedented details. You can see the emission from "polycyclic aromatic hydrocarbons," or molecules of carbon and hydrogen that play an important role in the thermal balance and chemistry of interstellar gas. When Webb is ready to begin science observations, studies such as these with MIRI will give new insights into the birth of stars and protoplanetary systems. ■

[1] https://www.jwst.nasa.gov

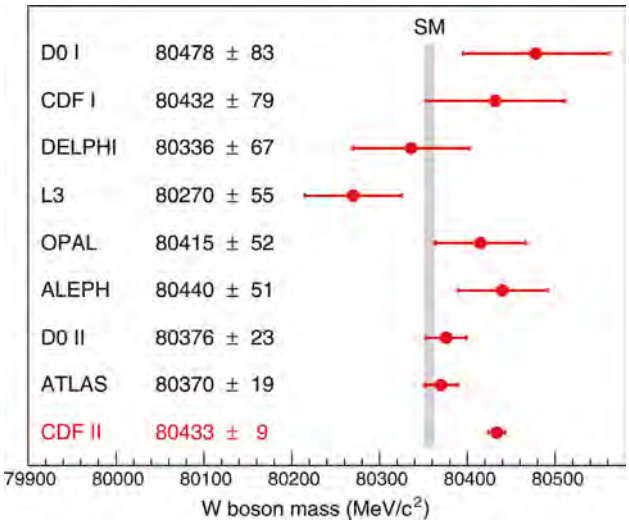
▼ FIG. 1: Infrared image of part of the Large Magellanic by the James Webb Space Telescope (right, NASA/ESA/CSA/STScI) compared to that by the Spitzer Space Telescope (left, NASA/JPL-Caltech).



Mass of the W boson

The mass of the W boson is one of the predictions of the Standard Model. A new - most precise ever - measurement of the W-mass by the CDF collaboration based on the data set from the former Tevatron collider at Fermilab breaks with the prediction.

The Standard Model of particle physics is the theoretical description of nature at its most fundamental level. The W boson is the carrier of the weak nuclear force. In the electroweak theory, the mass of the W boson depends in first order on the mass of the Z boson and the value of the weak mixing angle. At higher order, additional dependencies are introduced, in particular on the mass of the heavy top quark and the Higgs boson. Since its discovery in 1983, various experiments have measured the W-mass with increasing precision. In April 2022, after ten years of analysing the full data set from the former Tevatron collider at Fermilab, the CDF collaboration has published [1] the most precise measurement to date: 80,433.5 ± 6.4 (stat) ± 6.9 (syst) MeV. The value not only stands 7σ above the prediction of the Standard Model, it also deviates from all earlier measurements. This discrepancy must be understood and the value must be confirmed by other experiments such as the D0 experiment at the former Tevatron and the ATLAS and CMS experiments at the LHC collider at CERN. If the new ●●●



▲ FIG. 1: Comparison of this CDF II measurement and past MW measurements with the SM expectation (from [1]).

value for the W-mass will be confirmed, it probably means that the boson feels the influence of unknown particles or unknown forces. Possible extensions of the Standard Model include new Higgs-like particles, dark matter particles or supersymmetry. For particle physicists it is exciting times again. ■

Reference

[1] *Science* **376**, Issue 6589, 170

Run 3 of LHC has started

After a break of more than three years for maintenance and upgrade, particle beams are circulating again in the LHC collider at CERN. Also the experiments underwent major upgrades. Run 3 of LHC operations has begun. Unprecedented number of collisions at record energy will allow physicists to study in even more detail the Higgs boson and put the Standard Model to even more stringent tests. In addition, two new experiments start operation: FASER - designed to search for light and extremely weakly interacting particles - and SND@LHC, that will make measurements of neutrinos produced at the particle collider. ■

LINKS: https://home.cern/news/news/accelerators/large-hadron-collider-restarts
https://op-webtools.web.cern.ch/vistar/vistars.php

Celebration of Higgs@10

Ten years ago, on 4 July 2012, the discovery of the Higgs boson was announced at CERN by the ATLAS and CMS collaborations. Rolf Heuer, then director general of CERN, proposed the audience "As a layman, I would say we got it. Do you agree?" An overwhelming applause was the answer. Francois Englert and Peter Higgs, theoretical physicists who predicted the Higgs particle, were moved by the moment and expressed their gratitude for and admiration of the experimentalists that confirmed their prediction. This year the 10th birthday of the Higgs particle is being celebrated. With a symposium at CERN, with parties in the particle physics institutes, with a series of 'Higgs stories'. ■

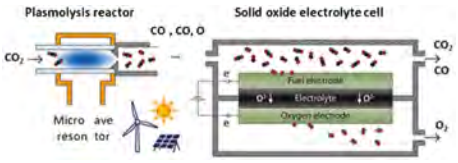
LINK: https://home.cern/news/news/cern/higgs10-save-date

CO_2 conversion via coupled plasma-electrolysis process

Researchers at the Dutch Institute for Fundamental Energy Research DIFFER have demonstrated that electrolysis coupled with plasmolysis leads to a novel route for CO_2 conversion. That is important in the quest for sustainable chemicals and fuels and large-scale, long-term electricity storage.

Production of renewable electricity is making great strides. In 2021 more than 35% of EU electricity production came from renewable source, well underway to reach the EU target of 40% renewable energy by 2030[1]. Or is it? On top of nearly doubling the deployment rate of solar and wind capacity, the grid has to cope with variable input. Intermittency and seasonal mismatch of supply and demand call for long-term (interannual), large scale (PJ) electricity storage, lest power is being wasted by curtailment. Energy storage in high energy density fuels and chemicals could meet requirements. By converting air (CO_2, N_2) and water, powered by (surplus) renewable electricity, high energy density products can be synthesised. This so-called Power-to-X scheme couples the power sector to the chemical, the heating and the fuel sectors thus avoiding the need for fossil fuels in those sectors.

Conversion starts at splitting the strong carbon dioxide and/or nitrogen bond, the most energy intensive step in the process. This provides the basic building blocks CO, N, H_2 for the synthesis of fuels and chemicals. Low temperature plasmas have shown to be effective in splitting CO_2 and N_2 molecules, creating a mixture of highly active atoms, molecules and radicals [1]. The challenge is how to unravel the gas mixture produced. In particular the about equally sized CO and O_2 molecules are difficult to separate. The weak paramagnetic property of O_2 is one avenue to explore. However, electro-chemical separation is a more mature technology applied in electrolysis and fuel cells. A solid oxide electrolyte cell selectively transports negative oxygen ions



from cathode to anode thereby separating the oxygen from the incoming gas mixture.

Researchers of the Dutch Institute for Fundamental Energy Research DIFFER have recently demonstrated that the coupling between electrolysis and plasmolysis leads to a novel route for CO_2 conversion [2]. The researchers are working in the context of the EU H2020 funded project KEROGREEN. The project's ultimate goal is to build a container sized pilot plant for the production of green aviation fuel.

High-temperature electrolysis is characterised by high yield and high energy efficiency. This process results in the direct separation of the reaction products CO and oxygen (O_2). However, challenging requirements on electrode materials are being encountered. CO_2 plasmolysis on the other hand, offers similar energy efficiencies, and no scarce electrode materials are required. However, the mixture of the reaction products cannot be used directly in a chemical synthesis plant. The CO produced remains mixed with O_2 and residual CO_2 and therefore an additional gas separation step is required. DIFFER researchers have demonstrated that the coupling of electrolysis and plasmolysis leads to a renewable-electricity-driven route for CO production, overcoming the main bottleneck of CO_2 plasmolysis. In the coupled process, the CO_2 plasmolysis gas mixture is supplied to a high-temperature electrolyser to separate the product gases electrochemically using solid oxide electrolyte cells (SOEC). Oxygen is transferred to one side of the SOEC, where it is removed. The remaining CO and CO_2 are ready for chemical synthesis of liquid fuel.

In a single pass, the coupled-process product contains 91% less O_2 and 138% more CO compared with bare plasmolysis. "And what is more important: when the solid oxide electrolyte cells operate with the plasma mixture of CO, O_2 and CO_2 in the inlet, we didn't observe any electrode degradation in durability tests", says Michail Tsampas, leader of the DIFFER group Catalytic and Electrochemical Processes for Energy Applications. The synergy between plasmolysis and electrolysis opens up a novel route to efficient CO_2 conversion into valuable building blocks for sustainable chemicals and fuels. ■

[1] https://renewablesnow.com/news/renewables-share-in-eu-electricity-climbs-to-37-in-2020-770744/ or https://www.greentechmedia.com/articles/read/eus-new-2030-climate-target-signals-accelerated-renewable-deployment

Acknowledgement

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Adelbert Goede (DIFFER, Eindhoven, The Netherlands; board member of the EPS Environmental Physics Division)

References

[1] A. Goede and R. van de Sanden, Eur Phys News **47-3**, 22 (2016), http://dx.doi.org/10.1051/epn/2016304

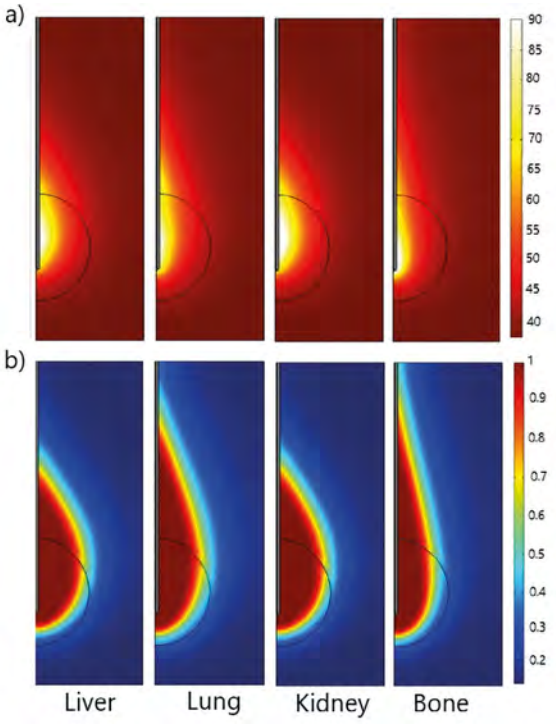
[2] A. Pandiyan, V. Kyriakou, Dragos Neagu, R. Sharma, S. Welzel, A. Goede, M.C.M. van de Sanden and M. N. Tsampas, J. CO2 Util. **57** (2022) 101904 https://doi.org/10.1016/j.jcou.2022.101904

Modelling the effect of microwave ablation

Microwave ablation is gaining popularity as an efficient therapeutic option for treating cancerous tumor cells in patients who are non-surgical candidates. It is a minimally invasive treatment with a short recovery time. Modelling the effect of the treatment helps to minimise damage of healty tissues.

Microwave ablation (MWA) is a material-specific responsiveness procedure with the advantage of faster ablation times, larger ablation volumes, and potentially strong deactivations for tumors compared to other thermal ablation methods. However, the interaction of the medical tools with the tissue may result in healthy tissue damage which can be eliminated by clarifying the causation and conditions of their development. To ensure the destruction of cancer cells with minimal damage to healthy tissue, the elevation of temperature and the evolution of the necrotic tissue need to be controlled. Besides experimental methods, computer modeling is proven to be an effective approach for improving the performance of MWA. Moreover, since the thermal spread in biological tissue is difficult to measure, generating the predictive models from procedural planning to execution may provide a great impact on patient care.

Due to complexity and computational resources consumption, most of the existing numerical models are two-dimensional axisymmetric to emulate actual three-dimensional cancers and surrounding tissue. A mathematical model for the simulation of MWA should consist of three essentials components. The first component includes the model of the antenna that generates a microwave field in the tissue. The second component deals with the heat distribution in the tissue including sources and sinks and the phase changes. The third part describes the effect of heat on tumor cells and their destruction. All these components of the ablation model depend on the dielectric properties and thermal parameters of tissues as well as a variety of material parameters. Additionally, the inclusion of the temperature dependence of dielectric properties, the heat capacity, thermal conductivity, and blood perfusion, is pivotal for establishing the correct model of the ablation process.



▲ FIG. 1: a) Temperature [oC] distribution and b) fraction of damage of liver, lung, kidney, and bone tissue after 600s of exposure to microwave frequency of 2.45 GHz and the input power of 10 W. The black circle shows the boundary of the tumoral tissue.

Although MWA operates in the frequency range from 915 MHz to 2.45 GHz, the antenna system at 2.45 GHz produces greater power deposition and larger ablations in a shorter time due to matching the frequency with water molecule resonance. Microwave power radiated from the antenna is absorbed by surrounding tissue, leading to heating the targeted tissue, consisting of the tumor and a margin of surrounding tissue. It was found that temperatures above 60°C cause relatively instantaneous cell death, while temperatures from 50 to 60°C will induce coagulation and cell death in a matter of minutes, typically 10 min.

In our study, calculations were performed for liver (high perfusion and large heat sinks), lung (low conductivity and large heat sinks), kidney (high perfusion and large heat sinks), and bone (low conductivity) tissue by using the Comsol Multiphysics simulation package. The temperature distribution has an ellipsoidal shape reaching the highest values near the antenna slot as illustrated in Figure 1a. With increasing the distance from the antenna, the heat source becomes weaker and the perfusion of blood limits the extent of the heated area. The highest and the lowest values of the temperature correspond to the kidney and bone tissue, respectively. Ablation zones are concentrated around the tip and slot of the antenna as shown in Figure 1b. The necrotic tissue is mainly located in the tumor with a small amount of surrounding tissue being damaged. Microwaves are less susceptible to perfusion or heat sinks so they successfully penetrate deep into low-conductivity materials such as lungs and bone. The obtained results indicate that the simulation technique can be useful for predicting optimal conditions for MWA and should be considered in treatment planning. ■

Reference

[1] M. Radmilovi-Radjenovi *et al.*, *EPL* **136**, 28001 (2021)

Impact of medical and imaging physics on the COVID pandemic

The COVID pandemic has had a profound global impact, a new collection of papers looks at a multidisciplinary approach to aspects of the pandemic.

The COVID pandemic has impacted every aspect of our lives over the past two years. It is little surprise then that this crisis has united a wealth of disparate fields of science in attempts to mitigate the virus and its effects.

A new focus issue of EPJ Plus collects together invited papers that detail the impact of medical imaging and medical physics technology on various aspects of the COVID pandemic. The focus issue is guest-edited by Evaristo Cisbani and Franco Garibaldi, both from Istituto Superiore di Sanita, Rome, and Istituto Nazionale di Fisica Nucleare, Rome, along with Stephanie Majewski, UC Davis, California, USA, and Andrea Gori, University of Milano, Italy.

"The focus issue deals with Molecular imaging techniques applied to Covid 19. This is just the right time for such a collection, as we believe we have now accumulated enough data and information," Garibaldi says. "We have had the problem of COVID for the last two years and we must be prepared for possible future pandemics."

One particular aspect of the COVID infection looked at by the collection and its authors is inflammation. This is one of the primary causes of severe sickness, especially in those with underlying health conditions such as diabetes.

In their Editorial, the guest editors of the focus issue say that new advanced technologies already available in the research field and undergoing constant improvement could translate into increased sensitivity of early detection and avoiding the long-term side effects of inflammation.

The key to this is understanding what actually needs to be imaged or visualised and what the emerging imaging needs are. Thus, the editors asked experts to address the biomedical issues related to the COVID-19 pandemic and associated inflammatory effects.

The editors lay out the multidisciplinary focus points for the topical collection papers as: the origin and evolution of COVID infection from a biological perspective, diagnosis and early differentiation of COVID-19 from other diseases, and the role of advanced detection technology including medical physics and artificial intelligence. ■

Reference

[1] Focus Point Issue "Progress in medical physics in times of CoViD-19 and related inflammatory diseases", Guest Editors: E. Cisbani, F. Garibaldi, S. Majewski, A. Gori, Eur. Phys. J Plus (2022)

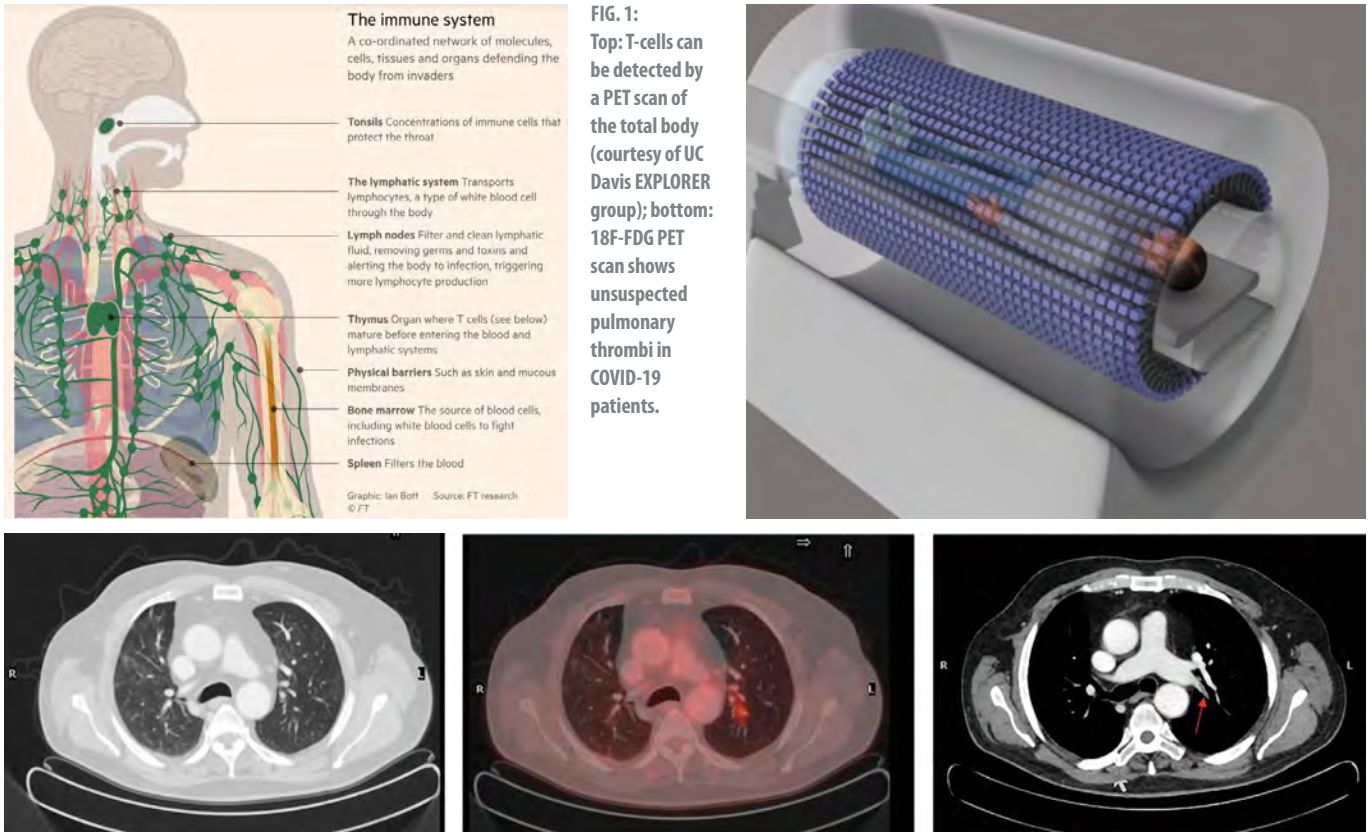


FIG. 1: Top: T-cells can be detected by a PET scan of the total body (courtesy of UC Davis EXPLORER group); bottom: 18F-FDG PET scan shows unsuspected pulmonary thrombi in COVID-19 patients.

International Day of Women and Girls in Science event - Young Minds Groningen

Accelerating progress towards full and equal access and participation of women and girls in science

Stefanie Brackenhoff and Akshara Viswanathan, EPS YM Groningen

"You can't solve a problem until you're asking the right question. Raw data will not solve our problems, asking the right questions will."

Policymakers and faculty boards should consider this approach by Albert Einstein while dealing with diversity issues in science. On the 11th of February 2022, the UNESCO Day of Women and Girls in Science, the Groningen Young Minds Section organized a webinar to discuss the barriers female scientists encounter. The event featured scientific talks by two renowned female scientists, followed by presentations about gender equality by two STEM practitioners, and an open discussion session.

Role models - the agents of change

Stating that "Being a woman in science is a responsibility in itself for the up-and-coming generation." Prof. Irene D'Amico (Full Professor at the University of York) and Prof. Ivone Albuquerque (Full Professor at the University of São Paulo) kicked off the day, while Dr. Francesca Primas (Full astronomer at the European Southern Observatory and former Chair of the International Astronomical Union Working Group on Women in Astronomy) and Dr. Tana Joseph (Postdoctoral Research Fellow at the University of Amsterdam and Coordinator of the Netherlands Astronomy Equity and Inclusion Committee) picked up the gender equality baton for the afternoon.

Prof. D'Amico talked about the use of networks of spins to perform quantum information processing and how evolutionary algorithms may help with this task [1]. Prof. Albuquerque welcomed us to the 'Dark Side' experiment that is designed to directly detect dark matter in the Universe [2]. Dr. Primas discussed a selection of past and ongoing equity, diversity and inclusion efforts in astronomy. Dr. Joseph outlined the advantages and disadvantages she experienced on her journey as an aspiring black female astronomer, and what we can learn from these experiences as a community. Parallel flashbacks between how astronomy in pre-internet South Africa grew versus how Dr. Joseph's astronomy career started inspired the participants. During the open discussion, audience members were able to bring issues they experienced to the table.

A holistic view of equity, diversity and inclusion in astronomy

"Diversity is the mix we want to achieve. Inclusion is what makes the mix work." – Francesca Primas

Dr. Primas discussed the gender gap in astronomy: although the influx of female students is approaching that of male students, women disproportionally experience discrimination (56% of women *vs.* 8% of men) or harassment (30% of women *vs.* 3% of men) [3]. Furthermore, the success rate of female astronomers in winning observing time on the Hubble Space Telescope and other facilities was found to be systematically lower than that of their male counterparts [4, 5, 6]. Preliminary results indicate that implementing dual-anonymous reviews removes this issue [7, 8]. Dr. Primas' talk made ongoing efforts

▼ Top left: Prof. Irene D'Amico. Top right: Prof. Ivone Albuquerque. Bottom left: Dr. Francesca Primas. Bottom right: Dr. Tana Joseph.

heard and kept enough room for improvements in following a principled and pragmatic approach towards making the voice of the underrepresented groups heard.

"Seek first to understand, then to be understood." - Stephen R. Covey

We all have an individual responsibility to make the scientific world a welcome place for everybody. Understanding the humanity, how people operate in targeted communities and keeping an open mind and eye is the key to approaching historically excluded communities. The scientific community must create `cheerleaders' for them. Do not just talk to the children themselves, but also their parents, teachers, and community leaders. Create an environment in which they can thrive. Dr. Joseph also called out on facing 'cultural taxation' – responsibilities placed on faculty of discriminated races without any compensation for their efforts. To get compensated for all her efforts in achieving equity, diversity and inclusion in astronomy, she started her own company 'AstroComms'.

Gender biases in science versus engineering

One participant raised concerns about the field of engineering performing poorly in achieving gender equality. Implementing outreach activities specifically targeted at high school students was proposed as one of the many solutions. Yet the problem is also about how universities promote courses and degrees in engineering and that applied sciences are still perceived as being for 'the stereotypical man' in society.

We conclude with Dr. Joseph's proposal of implementing a scientific approach that unites us. "We can treat diversity issues like a Bayesian optimization problem. Implement an approach, check how well this approach worked, and update it if needed." There is no clear endpoint, but we must converge to a more equal scientific community. ■

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The European X-ray Free Electron Laser: a tool for fundamental research and a wide range of applications

DOI: https://doi.org/10.1051/epn/2022301

X-ray free-electron lasers (XFELs) are the first light sources that are able to routinely generate coherent, ultra-brilliant, tunable laser pulses in the X-ray regime. The European XFEL (www.xfel.eu), is a world-leading large scale research facility, member of EIROforum (www.eiroforum.org), an intergovernamental association of eight of the leading European large-scale infrastructures. Thanks to a 1.7 km long, 17.5 GeV linear electron accelerator based on superconducting resonant cavities and the Self Amplified Spontaneous Emission (SASE) process taking place in very long undulator magnet arrays, high repetition rate ultrashort X-ray flashes with a brilliance that is a billion times higher than that of the best conventional synchrotron X-ray radiation sources are produced. The European XFEL is opening up areas of research from physics to structural biology that were previously inaccessible. Using the X-ray flashes of the European XFEL since the start of its operation in mid-2017, scientists from all over the world are able to map the atomic details of viruses, decipher the molecular composition of cells, take three-dimensional images of the nanoworld, film chemical reactions on the femtosecond time scale and study processes such as those occurring deep inside planets and in extreme conditions of temperature, pressure and applied magnetic field.

The European XFEL is becoming a very efficient decoder, obtaining in a much shorter time and with reduced effort many structures for molecules such as membrane proteins, from which crystals larger than a micrometer in size are hard to obtain. This will advance progress in our understanding of pathogens and the development of pharmaceutical remedies. In addition, biomolecules modify their structure while performing their respective tasks. It would be extremely illuminating to follow these modifications and see the motion of the moving parts in a movie. To make a film of a moving object, it is necessary to take many snapshots. Faster movement requires a shorter exposure time and a greater number of snapshots to avoid blurring the pictures. This is where the ultrashort duration of the FEL pulses will ensure sharp, non-blurred pictures of very fast processes. During the Covid-19 pandemic, XFEL was used to gain insights into protein shape and function at the micro- and nanoscale (SAXS curve). The results from this experiment could improve our understanding of the immune response to coronavirus and help to develop medical strategies to overcome COVID-19.

The European XFEL provides an opportunity to educate a new generation of scientists to address the frontiers of research in an open environment, promoting the European dimension of knowledge and its international mobility. The European XFEL is located in the metropolitan area of Hamburg, Germany, and has a long-standing collaboration agreement with DESY for the accelerator operation. It is organized as a non-profit company with limited liability under German private law (GmbH) that is publicly funded (total construction budget: 1.54 B€; operation budget for 2022: 141 M€) through its international shareholders from 12 European countries. The shareholders' assembly, the so-called Council, is the supreme organ of the European XFEL GmbH, which decides on all important issues of the company (like the annual financial statement and the annual operation budget) and important personnel matters as well as the further development of the facility. The Council meets at least three times a year and is led by a Chair and a Vice-Chair, who are elected from the Council delegations for a total of up to two terms, not exceeding two years each, and who, upon election, leave their delegations and become supra partes.

We note, that Federico Boscherini (in the photo) Professor of Physics at the Physics and Astronomy Department of the University of Bologna, has been elected as the new Chair of the XFEL Council. The appointment starts from July 2022 for a first two year period. ■

Eugenio Scapparone,
INFN Bologna Section director

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ACCELERATORS FOR HEALTH: FROM CURRENT TO DREAM MACHINES

Angeles Faus-Golfe[1] and Elena Benedetto[2] – DOI: https://doi.org/10.1051/epn/2022302

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Any kind of sculpted particle beams from high-energy photons (X-rays and gamma rays), electrons, protons, neutrons to various atomic nuclei and more exotic species have been used to treat cancer. The development of a next generation of accelerators to face the challenges and issues of Particle Therapy is crucial. What are the most promising accelerator techniques, particles or dose delivery modes?

▲ Layout of SEEIIST (South East Europe International Institute for Sustainable Technologies) facility

The potential of accelerator-based Radiotherapy (RT) has increased considerably over the past decades, playing an increasingly important role in identifying and curing affections, such as cancer. Energetic particles of any kind have been used in the past, but nowadays photons (X-rays), low-energy electrons, protons and carbon ions are the most common types of irradiation (Figure 1).

X-rays are the most common method of RT for cancer treatment. Even if the X-rays therapy is a mature technology there is room for improvement. The current challenges are related to the accurate delivery of X-rays to tumours involving sophisticated techniques to combine imaging and therapy. Hadron (*i.e.* proton and ion) beam therapy has growing potential in dealing with tumours close to organs at risks, because the irradiation dose (Figure 1) is mainly deposited at a specific longitudinal position, the Bragg peak, which depends on the energy of the particles. Also, some treatments may benefit from the use of ions that deliver doses with a greater radiobiological effectiveness (RBE), notably Carbon. Helium and Oxygen are also promising candidates for therapy and in particular techniques combining irradiation with multiple ions are getting more interest, to exploit the advantages of the different species[1]. With the recent developments of high-gradient normal conducting (NC) Radio Frequency (RF) linear accelerator (linacs) technology (Figure 2) or even the novel acceleration techniques such as the Laser-Plasma Accelerator (LPA), Very High-Energy Electrons (VHEE) with energies between 50-200 MeV offer a very promising option for anticancer RT.

Whatever RT particle used, the treatment is limited by the toxicity introduced in the healthy tissues surrounding the tumours. A novel paradigm-shifting method for delivering ultra-high doses within an extremely short irradiation time (tenths of a second), known as FLASH-RT is now under study. The technique has recently been shown to preserve normal tissue in various species and organs while still maintaining anti-tumour efficacy equivalent to conventional RT at the same dose level. The "FLASH effect" has been shown

to take place with electron, photon and more recently for proton beams. For details we refer to [2, 3].

Towards a compact and flexible Hadron Therapy facility

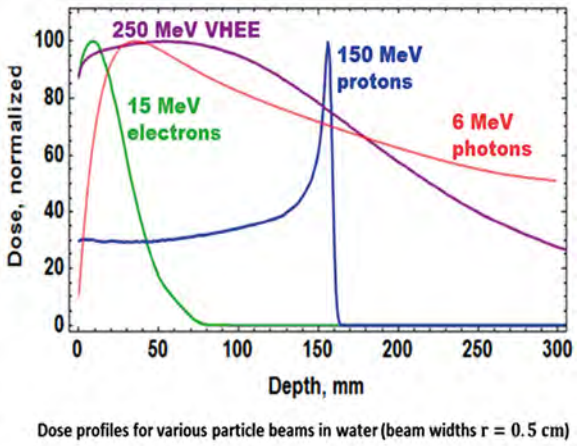
For proton therapy, compact accelerator systems are nowadays available on the market: mostly cyclotrons in Europe and America and synchrotrons in Japan. The irradiation is mainly done via 3D beam-scanning.

Cyclotrons have the advantage that they are very compact and have only a few tuning parameters, thus are simple to operate in a hospital environment. However, scaling to the energies needed for Carbon-ions, which have a factor 3 higher beam rigidity (*i.e.* the resistance to deflection by a magnetic field) is challenging. Another limitation of conventional cyclotrons is their fixed extraction energy, which implies the use of degraders, with associated transmission losses and radioprotection constrains. Current R&D goes in the direction of energy-variable cyclotrons and the use of high-field superconducting (SC) iron free magnets [3].

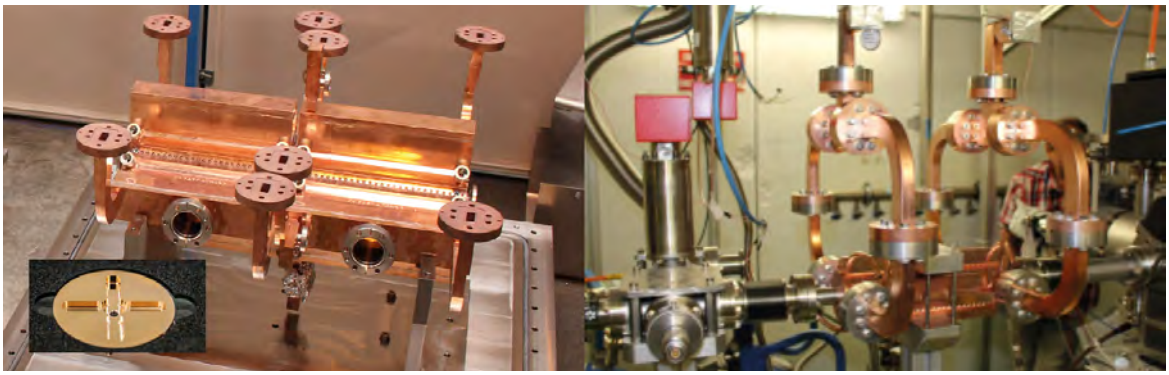
Synchrotrons are easily scalable to ion operation, even if this implies an increase of their footprint, and allow acceleration of different type of ions. The preferred choice for carbon-ions today is a rather large synchrotron (of >20-m diameter compared to the 6-m size for protons). Most important, synchrotrons are flexible with respect to the extraction energy, which can be easily changed between one cycle to the next. A limitation of today synchrotrons, though, is the length of each cycle, of the order of 1s. In Europe, and following what was recently implemented in National Institute of Radiological Sciences (NIRS) in Japan [5], the tendency is to operate synchrotrons with the so-called multi-energy extraction (MEE) scheme, to deliver beams at different energies within the same cycle, thus saving time.

Ultimately, if one could accelerate the total number of ions needed for a treatment session within one cycle (thus a factor 10-20 times higher intensity, accumulated by multi-turn injection), the full dose will be delivered significantly faster. Moreover, this mode of operation will make the use of SC magnets feasible, thus allowing a significant reduction of the dimensions of the ion synchrotron (indeed the SC magnets ramping time is much longer than for NC magnets). The R&D in this sense focus on ions sources to reliably deliver a higher current, on advanced injection and extraction schemes and on strongly curved SC magnets. The development of a SC-magnet carbon-ion synchrotron is precisely one of the main objectives of the Heavy Ion Therapy Research Integration (HITRIplus) [6] and what is being studied by the SEEIIST (South East Europe International Institute for Sustainable Technologies) [7] and the CERN NIMMS (Next Ion Medical Machine Study) initiative [8].

Accelerators other than cyclotrons and synchrotrons are also under study, in particular Fixed Field Alternating gradient (FFA) and linacs. After several years of R&D and developments in research and international laboratories environment, the first linac based proton therapy facilities is under construction and commissioning in Europe. With the use of high-frequency high-gradient copper structures, designed to achieve relatively compact solution and high repetition rate operation, linacs will allow the production of beams with fast energy variation as well as small emittance beams that are potentially suited for the further development of mini-beams dose delivery techniques. Detailed information in [9, 10].



◂ FIG. 1: Dose profile for various particle beams in water (beam widths r=0.5 cm)



▸ FIG. 2: CLIC RF X-band cavity prototype (12 GHz, 100 MV/m)

Towards a VHEE RT facility

Low-energy electrons have historically been used to treat cancer for more than five decades, but mostly for the treatment of superficial tumours given their very limited penetration depth. However, this limitation can be overcome is VHEE (50-200 MeV, Figure 1) are used. Theoretically, VHEE beams offers several benefits. The ballistic and dosimetry properties of VHEE provide small-diameter beams that could be scanned and focused easily, enabling finer resolution for intensity-modulated treatments than is possible with photons beams. Electron accelerators are more compact and cheaper than proton therapy accelerators. Finally, VHEE beams can be operated at very high-dose rates and fast electromagnetic scanning providing a uniform dose distribution throughout the target and allowing for unforeseen RT modalities in particular the FLASH-RT.

Normal Conducting RF linac is the technology being used for most of the VHEE research. The main advantages of the linacs are the flexibility and the compactness. Regarding the linac design in the energy range of interest for VHEE applications there are different possibilities offering the desired performances and compactness with different degrees of technology matureness. The S-band (~3 GHz) technology is the most mature one, High-Gradient compact linacs of this type are already available from various industrial partners. The C-band (~5 GHz) and X-band (~12 Ghz) RF linacs still less mature and are mainly constructed in accelerator laboratories with the help of industries for the machining. Lately a considerable effort is being made from the industrialization point of view [11]. A limited number of accelerators in Europe and USA are available for VHEE R&D. The majority based in NC RF linacs, few of them are based on Super Conducting (SCRF) linac technology at L-band (~1.3 GHz). Finally, a VHEE-FLASH RT facility based on a Compact Linear Collider (CLIC) X-band 100 MeV linac is being designed at CERN in collaboration with *Centre Hospitalier Universitaire Vaudois* (CHUV) to treat large, deep-seated tumours in FLASH conditions. The facility is as compact as to fit on a typical hospital campus.

Recent advances in the high-gradient RF structures, mainly in the material domain (origin, purity, surface treatment) and manufacturing technology in one side and the consistency and reproducibility of the test results in the other side, are transforming the landscape for VHEE RT. Some promising R&D in the next decade are: the distributed coupling accelerator and the use of cryogenic copper that is transforming the linac design offering a new frontier from beam brightness, efficiency and cost-capability. Another approach for the next generation of compact, efficient and high performance VHEE accelerator is the use of higher frequencies millimetric waves (~100 GHz) and higher-repetition rates using THz sources. An important R&D effort to apply these accelerator technologies in the medical has to be made in the next decade to make VHEE RT a clinical reality [2].

Therapy facilities based on Laser-Plasma-Acceleration

As high-performance lasers took big increased enhancements in the last years concerning power and repetition rate their use for particle therapy may be possible in future. The actual limit of about 100 MeV achieved for the highest proton energies driven by ultra-intense lasers using Target Normal Sheath Acceleration (TNSA) depicts a major milestone on the way to the needed energies. But still the broad energy spread of the accelerated protons is not feasible for treatment modalities. The reached energies for laser accelerated ions is still a magnitude lower and thus far from necessary values. The very short dose peaks may be attractive for FLASH therapy, but then the repetition rate of the Petawatt lasers should reach 100 Hz and more, which is not the case nowadays. In addition, the target configuration has to resist this high load on a long-time basis – a therapy facility runs several 1000 hours a year. Furthermore, the reliability of a laser-based proton or ion accelerator must reach 98% or more to be of practical use in a medical facility. But this technique should be explored with high effort in the next decade to identify the long-term potential. Concerning the VHEE there is an intense R&D effort in LPA for being applied in the next generation of VHHE-RT facilities. The major challenge for the LPA technique is the beam quality, reproducibility and reliability needed for RT applications. This R&D is being carried out in some LPA facilities in Europe, Japan and USA, where dedicated beamlines provide

stable experimental conditions for radiobiology and dosimetry R&D. A wide international R&D programme, in particular we highlight the role of the EU network: EUPRAXIA (Compact European Plasma Accelerator with Superior Beam Quality) [12], will be needed in the next decade in order to convert these "dream" facilities into reality.

Final remarks

To enhance the coverage of particle therapy in Europe and worldwide and to enlarge the number of patients, which can profit from this special treatment, the investment costs of such facilities should be reduced as much as possible, which requests smaller and simpler machines to save manufacturing and operating effort. Especially the size of the accelerator has important influence on the building costs. And the amount of beam losses demands more or less concrete for radiation shielding, therefore they should be minimized by design. In addition, the operating and maintenance team needed should be small, but adequate and well-trained, sustained by a modern control system, which predicts pre-emptive maintenance measures through Artificial Intelligence algorithms and thus guarantees highest availability. ■

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Elena Benedetto is Senior Researcher at the SEEIIST Association and is the coordinator of the synchrotron facility design. She works in collaboration with CERN and the European partners of HITRIplus to the development of next generation medical accelerators and gantries.

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PLASMA MEDICINE: THE GREAT PROSPECTS WHEN PHYSICS MEETS MEDICINE

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The research has demonstrated the antimicrobial properties of plasma urging the incorporation of cold atmospheric plasma (CAP) decontamination in current clinical therapies with the aim to improve the benefits on the patients and on society.

Plasma medicine is an innovative and interdisciplinary field of science which has experienced an immense international upswing in the last years. It has emerged two decades ago as a commingling of plasma technology with physics, chemistry, engineering and life science. The final aim of plasma medicine research is to introduce CAPs into clinical medicine and bioengineering fields for human and veterinary therapeutic applications [1].

What is plasma and how it works?

Gas discharge plasma is an ionized gas, composed of free electrons, ions, radicals, excited atoms and molecules, neutral molecules, electromagnetic fields and UV-Vis radiation with no net electrical charge [1] (Figure 1). The features of CAP, according to their non-equilibrium character, include the extremely high concentration of chemically reactive species and a bulk temperature close to the room temperature, which makes it an ideal tool for applications in many fields including agriculture, environment, manufacturing and most of all, medicine. The reactive species, derived from oxygen and nitrogen (RONS - *i.e.* O, $^1O_2$, O_3, $\cdot OH$, $\cdot O_2H$, $\cdot O^{2-}$, $\cdot O^{3-}$, $\cdot NO$, $\cdot NO_2$) are particularly relevant for the medical field as they can diffuse from the gas phase to a solution/biological medium, generating less reactive and longer-lived secondary species, which offer a myriad of potential biological applications [1].

Hence, this has led to the development of two approaches with regards to the putative application methods of plasmas (Figure 2):

i) a direct CAP treatment of the biological target

(*e.g.* microbes, eukaryotic cells healthy or diseased and pathological tissue), which exhibits the synergetic effects derived of all the above-mentioned plasma components on cells.

ii) an indirect CAP treatment consisting on the treatment of biocompatible and biologically relevant liquids (plasma treated liquids - PTLs), which allows for minimally invasive therapy in the target site. The PTLs-based therapy mainly delivers the RONS, which have been reported to be one of the major players controlling biological processes [2,3].

Plasma-generated RONS and their biological relevance

Part of the action of CAP can be explained thanks to advances in redox biology, which can be used as the scientific basis to explain the biological effects related to CAP-generated RONS [3]. Briefly, the two general molecular mechanisms of the RONS to highlight are (i) alterations of the intracellular redox state and (ii) oxidative modification of proteins involved in multiple signalling pathways. According to this, CAP treatment can affect all physiological processes in the human or animal body, where RONS play an important role, such as regulation of blood coagulation, vascular contraction, nerve impulse transmission, angiogenesis, inflammation, and immune system response. In addition, at the cellular level, CAP-derived RONS can alter molecular signalling pathways in both prokaryotic (*e.g.* bacteria) and eukaryotic cells (*e.g.* cancer cells) related to cell-to-cell adhesion, synthesis of growth factors, cell differentiation, division, migration, and apoptosis [3]. The important biological role of RONS in prokaryotic and eucaryotic cells has led to two main capabilities of CAPs targeting both type of organisms with corresponding therapeutical applications.

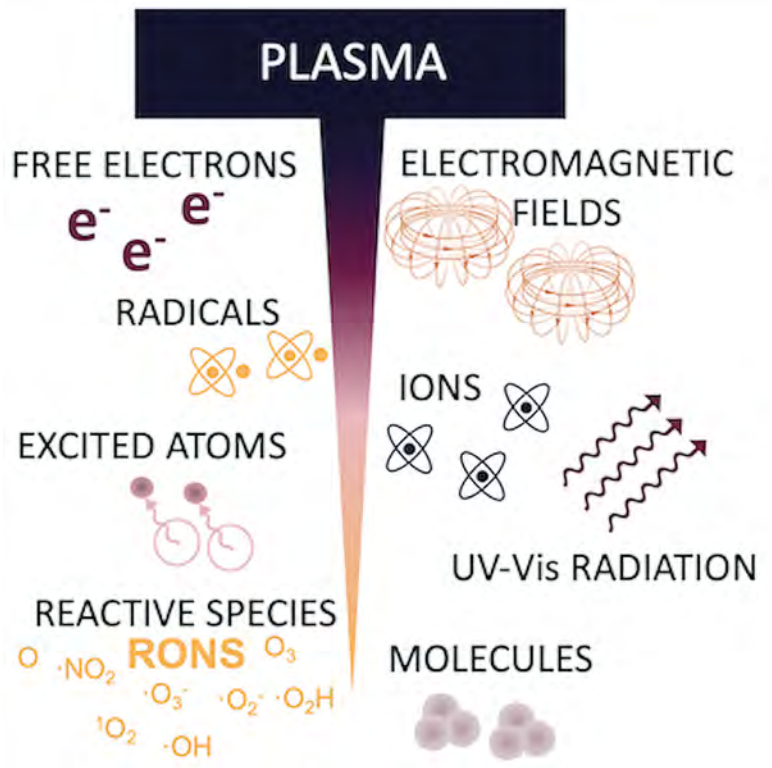
Plasma medicine: CAPs effects on prokaryotic cells

The antimicrobial properties of CAPs have been investigated for over the last two decades, anchoring the concept of plasma decontamination in this field of science. The main medical application of plasma has been focused on the sterilization of surfaces, materials and devices such as prostheses or implants [4]. Nevertheless, the increasingly growing development of atmospheric pressure plasma has promoted the exploration of novel potential applications, especially on living tissues targeting different pathogens such as bacteria, viruses, yeasts and fungi [5].

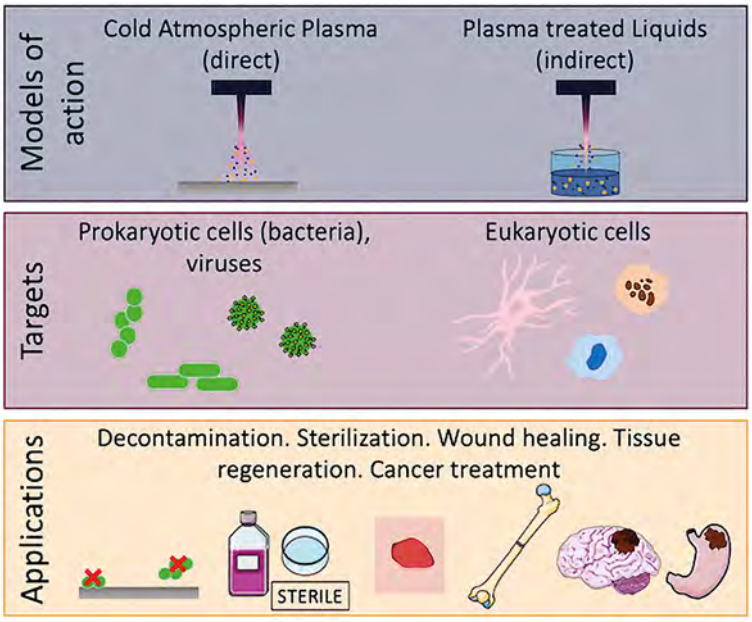
The ever-growing incidence of bacteria with resistance to most antibiotics and the emergence of new unknown pathogens whose transmission is most probably airborne (*i.e.* SARS-CoV-2) has necessitated novel solutions to overcome the handicaps of the available treatments. In this regard, recent research has proved the effectiveness of CAP for inactivation of biofilms and overcoming their acquired resistance to antibiotics [6]. From another point of view, a fundamental finding in this area has been the discovery that under specific conditions, CAP can kill or inactivate harmful microorganisms infecting skin, without causing damage to patient' tissue, thereby facilitating the acceleration of wound healing and treatment of pathogen-based skin diseases [7]. Moreover, CAP has proved to be very effective against bio non-cellular infection-transmitting agents that are resistant to more conventional techniques, like the prions, which are held responsible for neurodegenerative diseases such as transmissible spongiform encephalopathy or Alzheimer's disease, respectively [8]. The research has demonstrated the antimicrobial properties of plasma medicine urging the incorporation of CAP decontamination in current clinical therapies with the aim to improve the welfare on patients and on society.

Plasma medicine: CAPs effects on eukaryotic cells

The recent advances in plasma medicine have shown that CAPs can exhibit the effects on eukaryotic cells and living tissues in the human and animal body evidencing the versatility of plasma treatment. Specifically, it has been demonstrated that the controlled exposure of mammalian cells to different conditions of CAP can lead either to stimulation or inhibition of cellular functions, such as cell proliferation, tissue regeneration, cell detachment, apoptosis, and necrosis [9]. This has opened the door to new therapeutical applications such as tissue • • •



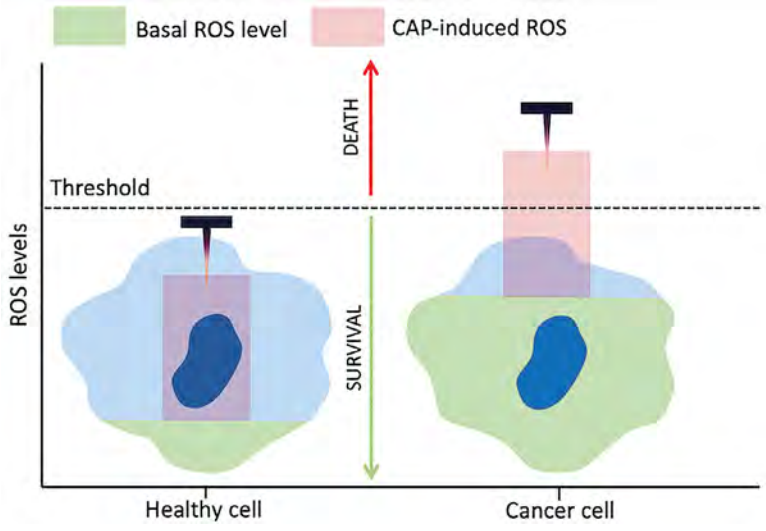
▼ **FIG. 1:** Plasma components include free electrons, ions, radicals, excited atoms and molecules, neutral molecules, electromagnetic fields and UV-Vis radiation with no overall electrical charge.



▲ FIG. 2: Models of action, targets and applications of cold atmospheric plasmas (CAPs).

regeneration and wound healing (*e.g.* diabetic leg healing, ulcers, burns, *etc.*), with potential implications in the cosmetics field (*e.g.* skin regeneration, scar treatment, *etc.*), as well as cancer therapy (*e.g.* melanoma, glioblastoma, colon cancer, *etc.*).

For instance, different atmospheric pressure plasma jets, which have been recently commercialized, have demonstrated their effectiveness at supporting the healing of non-infected acute wounds (kINPen, PlasmDERM, SteriPlas, Plason, PlasmaCare) [10]. To date, these plasma sources have also been applied in the treatment of long-lasting chronic and infected wounds, particularly in cases where conventional treatment have failed, with evidence *in vitro* and *in vivo* with studies in animals, that have led to the initiation of the first clinical trials. In diabetic patients with chronic leg and venous ulcers, plasma-treated patients experienced accelerated wound healing [5]. These results suggest that wound healing may be accelerated due to the simultaneous stimulation of tissue regeneration and angiogenesis. The results observed in such studies enable this vision of CAP technology on its way to becoming a clinical routine for wound healing and skin treatment. This regenerative potential of CAP on skin is currently being explored in the anti-aging and skin-wellness industry. This capacity of plasmas to stimulate tissue regeneration and repair can also be exploited for other tissues [11], opening new avenues that deserve further exploration.



▼ FIG. 3: Treatment with CAP delivers exogenous ROS bringing the metabolically more active cancer cells over the survival/death threshold.

Recent advances in plasma medicine have been exploiting the potential use of CAP in cancer therapies. Cancer is a leading cause of death worldwide and despite the enormous amount of research and rapid developments seen during the past decade, cancer treatment is still challenging. In this sense, one key aspect which is attracting increased attention is the ability of CAPs to selectively kill cancer cells without damaging the surrounding tissues, thus offering a less aggressive solution compared to common anticancer therapies (*i.e.* chemotherapy and radiotherapy). The anticancer effects of CAP have been, at least in part, related to the RONS generated by plasmas, which are important mediators in stem cell biology. In fact, high levels of RONS have long been suggested to be detrimental to cellular health, and adding high amounts of exogenous RONS can induce cell cycle arrest, while higher doses lead to the induction of apoptotic and/or necrotic cell death (Figure 3). In this context, cancer cells are metabolically more active than healthy cells, thereby generating higher amount of intrinsic RONS. For this reason, delivering plasma with low exogenous RONS, triggers cancer cells to surpass the toxicity threshold and activate apoptosis without affecting normal cells of the surrounding healthy tissue. Interestingly, many studies demonstrated that indirect treatment using PTLs exert very similar effects compared to direct CAP treatment what could be particularly favorable in the treatments of areas harder to reach and an injection of PTLs may be a suitable alternative [12].

Quo Vadis, plasma medicine?

Merging physics, chemistry, and engineering with medical science gave rise to plasma medicine, which aims to develop novel and innovative technologies to improve the quality of life of patients and their families. The recent advancements in the field have demonstrated the great versatility of CAP systems and their ability to induce, mainly through RONS delivery, specific biological responses in pathogens (bacteria, viruses, yeasts and fungi), cells (healthy and cancellous), and living tissues. This has opened the door to a myriad of applications on the edge of tissue engineering and regenerative medicine such as eradication of biofilms, wound-healing, treatment of neurodegenerative diseases or cancer therapy. Nevertheless,

there is still much to be done including the rigorous in vivo evaluation of plasma treatments or unravelling the specific molecular mechanisms that are involved on the intra- or inter-cellular level of on living cells and tissues treated with plasmas. Thus, the research community must keep exploring the CAP-tivating versatility, feasibility and therapeutic potential of plasma medicine.

The recently initiated COST Action CA20114 PlasTHER "Therapeutical Applications of Cold Plasmas" (www.plasther.eu) is dealing with all the aforementioned challenges, with the help of a big network of experts in different areas and hopes to bring significant advances to the field forward in the coming years. ■

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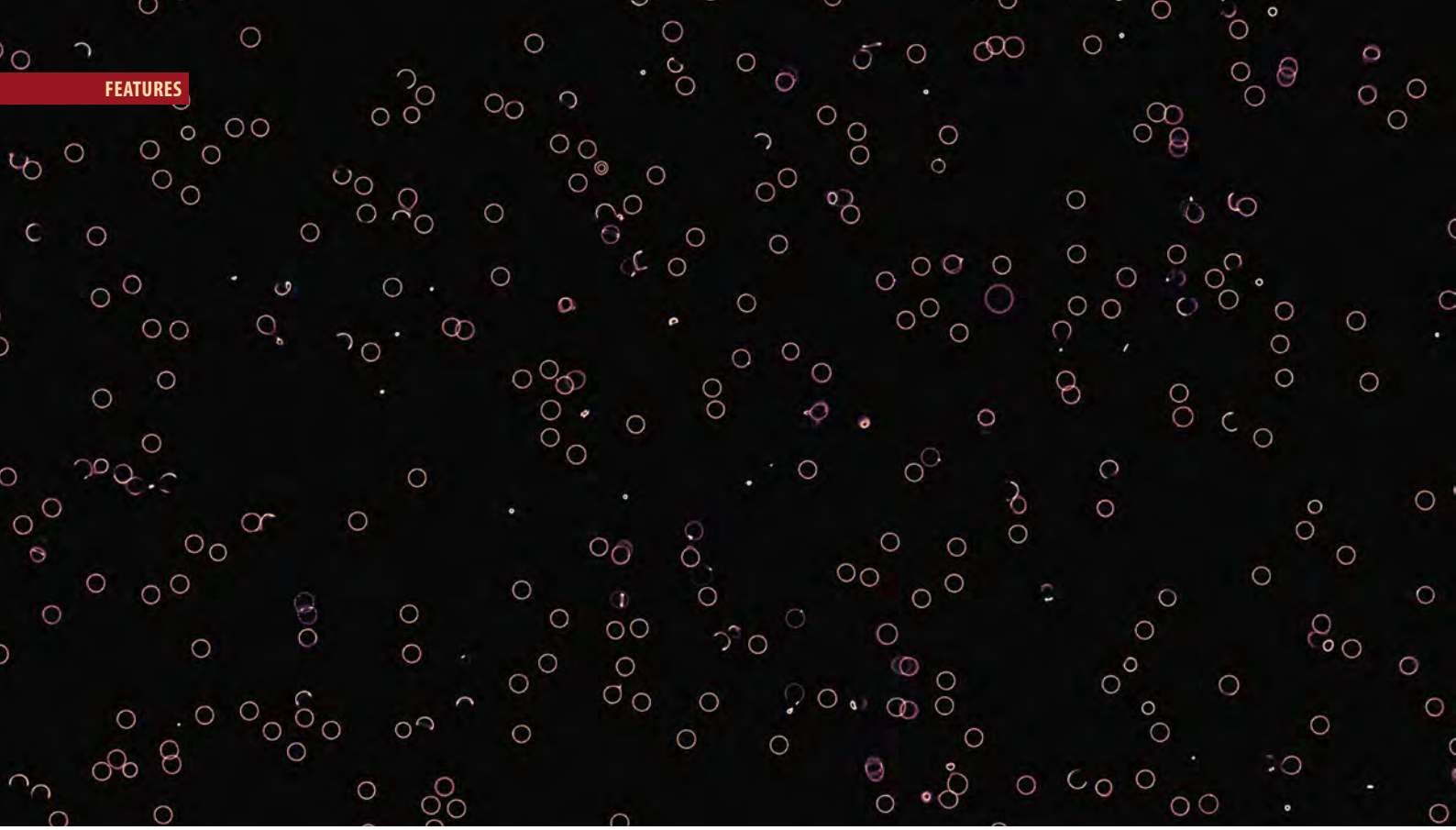

TINY ROBOTS
MADE FROM BIOMOLECULES

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Can we scale down robots to small scales and realize them with self-organizing molecules? As biological cells already act a little like robots – they sense, compute, move, and respond to their environment – the answer is probably "yes". But a wide range of interesting physical challenges have to be tackled.

▲ Fluorescence overlay image obtained from a large number of DNA robot arms such as that on the bottom of Fig. 2 that are rotating (the arms are fluorescently labeled at their tips, resulting in the circular shapes).

Robots have changed the way we work and live, and will continue to do so in the future. Robotic systems speed up and improve manufacturing processes, they assist in many areas such as health care or environmental regeneration. They can work at places which are inaccessible, or whose environments are too harsh or dangerous for humans. In science labs they perform large numbers of experiments in parallel and without getting tired. These robotic systems typically consist of three main units: sensors and actuators, which are coordinated by a computing device. The sensors collect information about the environment or the current state of the robot. This sensory information is then evaluated by a computer and used to decide on the necessary actions carried out by actuators - and these actions often mean mechanical motion. Most robots realized so far are rather large in size and utilize macroscopic mechanical parts and mechanisms combined with electronic control systems and computers.

Interesting questions and challenges arise, when we ask how far we can scale down robotic systems:

Is it possible to realize robots with just a few atoms, molecules, or nanoparticles? Without on-board electronics and power supply? How would one realize sensing, actuation and computation at such small scales? In fact, over the past years researchers in the physical sciences have begun to work on the development of molecular and cell-scale systems, in which robotic functions are realized, at least

up to a certain degree. We are particularly interested in robotic systems based on biomolecules, which have the ability to work in biological environments and interact with biological entities. Among the most prominent goals of this research direction is the realization of nanomedical robots that autonomously detect and cure diseases at the earliest stages, but also the generation of molecular assembly lines that enable the programmable production of chemical compounds is one of its grand visions.

From biological inspiration to molecular and cell-scale robotics

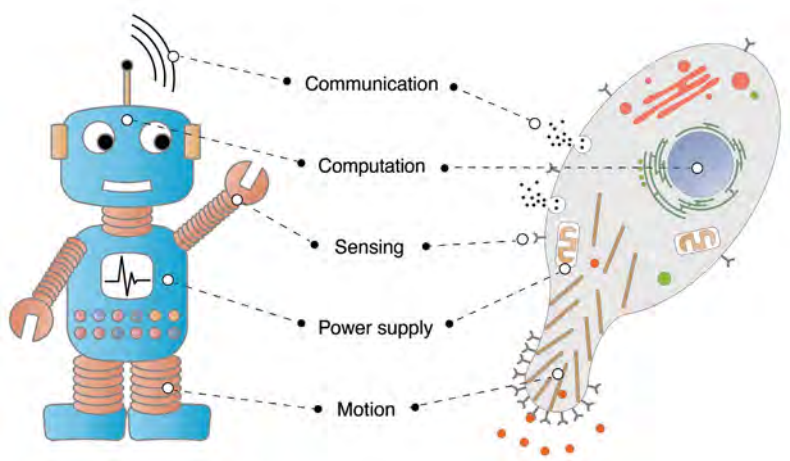
Biology has inspired the development of robotic systems at the macroscale in various ways. Their shapes and appearances are often derived from humans, dogs, or insects, *etc.*, and their movements and actions resemble those of their living counterparts. Roboticists are concerned with "motion planning", "cognition", *etc.* and therefore ask similar questions as neuroscientists. Another exciting example for biomimetics in this context is the field of swarm robotics, which is inspired by the observation of social interactions and dynamics among biological "agents".

At the cellular and molecular level, we can find inspiration for robots as well. Biological cells have sensors and actuators, they store and process information. They move, manufacture and interact with other cells. Other, specific examples are bacterial swimming and swarming, cell-shape changes, cell-cell communication, the immune system, muscle function, *etc.*

In the end, biology is a very different kind of "technology" than electronics and mechatronics. Biological systems are self-organized chemical systems existing far from thermal equilibrium, and if we want to build bio-inspired robots at this tiny scale, we will have to apply to other principles than those developed for "animal-scale" robotics. In the nano world, other physical laws are relevant than in our macroscopic world. For instance, gravity plays no role, but viscous friction is an important player. How should we think of or perform computation at this scale? Should we implement digital computation or develop molecular analog computers?

DNA-based robots

DNA-molecules turn out to be ideal to experimentally explore ideas for nanoscale robotic systems. DNA nanotechnology, especially the so-called "DNA origami" technique, makes it possible to assemble almost arbitrarily shaped molecular objects. Furthermore, various chemical and physical mechanisms have been used to switch these objects between distinct mechanical states. By doing so, linear or rotary molecular motors could be realized. DNA naturally lends itself for information storage and various computational schemes involving DNA have been developed. A wide range of DNA-based sensors – responding to nucleic acids, ions, small molecules or even light – are available. Thus, in principle, all of the aforementioned components of robotic systems can be realized with DNA alone. To name but a few, DNA robots have been created that act as smart drug delivery devices [2,3], DNA walkers have been shown that make decisions, sort, transport and assemble cargo [4-6], and DNA nanomechanical devices have been realized that can be actuated with magnetic or electric fields [1,7], or that themselves actuated soft robotic devices [8].

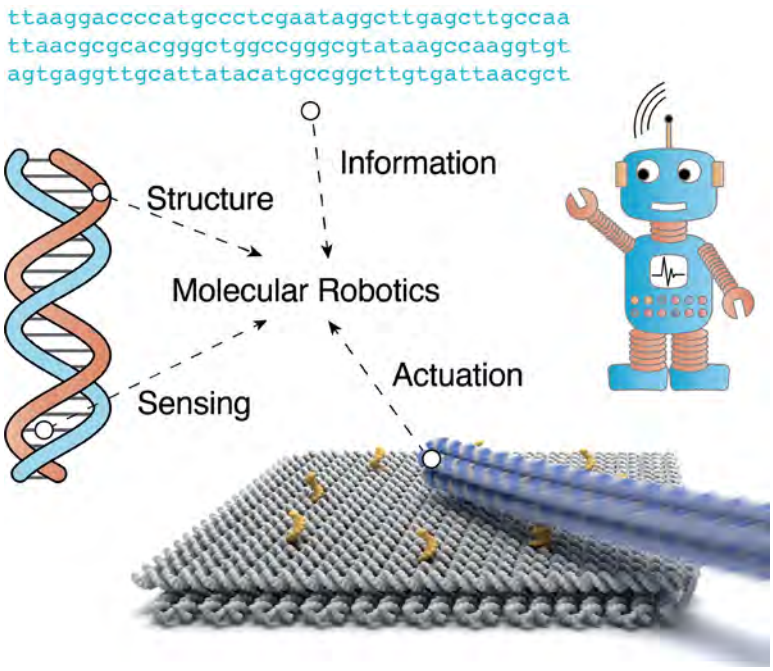


▲ **FIG. 1:** Robots and cells have similar functional modules and capabilities (the image only highlights a few examples). Can we create cell-scale robots that perform non-biological tasks or use biological cells themselves as robots?

While DNA-based robot prototypes are very promising, many challenges remain, and these will also have to be tackled by robots based on molecules other than DNA. First, the information processing capabilities of individual molecular structures are quite limited. Second, most realizations of DNA robots so far are slow and cannot quickly respond to external inputs. Thirdly, molecular robots are, of course, small. This makes it hard to integrate them into larger systems, let them move across larger length scales, and to operate many of them in parallel. Another challenge relates to the question how to best fuel the robots at this scale, whether they can be autonomous or must be externally controlled, *etc.*

Biological molecular motors

Proteins are another promising class of biomolecules which might be used to construct nanorobots. In biology, a plethora of molecular motors exist. For instance, processive motors such as kinesin walking along protein filaments or rotary motors that drive the flagella of bacteria. Protein-based motors on their own or in combination with DNA have already been utilized to create active materials [9,10] and "swarms" [11]. But autonomously moving particles or components alone will not make a robot. The challenge will be to integrate such active behavior with other functions, and it would be desirable to find ways to control and program active behavior. For example, after sensing the environment the output of a sensor module could be used to control a physicochemical parameter that is important for movement. Active particles that move in chemical gradients need to • • •



▲ **FIG. 2:** DNA is an ideal molecule for exploring molecular robotics. It inherently stores information, it is a structural rigid molecule, and it can be used for sensing (*e.g.*, via base-pairing interactions). DNA has already been used to create nanoscale structures and machines (the example at the bottom is an image of a rotatable robotic arm made with the DNA origami technique [1]).

• • • be asymmetric. And this asymmetry could be controlled by a decision-making molecular circuit. Another challenge will be to find the "right chemistry". It should allow active processes and other robotic modules to operate under realistic environmental conditions - *e.g.*, inside a living organism.

Synthetic cells as robots

Maybe there is a "complexity threshold" above which robotic functions can be realistically implemented in molecular systems, and single molecules or small supramolecular assemblies are simply below that threshold. On the other hand, biological cells – more complex assemblies of molecules – really already behave like microscale robots (see above). Biology has successfully tackled the "systems integration" challenge and realized out-of-equilibrium systems that sense, compute and respond to their environment. In cells, various functional modules play together, behave in a context-dependent manner and are controlled by molecular programs.

When envisioning the realization of small robots, we might therefore ask whether we can either build synthetic systems that imitate cells but perform technologically relevant, non-biological functions? Or whether we can engineer biological cells to become more like robots? Essentially both of these approaches to engineer biological systems are already pursued in the (closely related) field of synthetic biology.

The bottom-up approach - putting together all the necessary molecular parts to generate a synthetic life-like system - poses a huge systems-engineering challenge. In order to realize such systems, metabolic processes need to be compartmentalized and coupled to information processing, movement, and other types of actuation, which has not been entirely achieved so far. The second approach circumvents the challenge of realizing a consistent multifunctional molecular system, but engineering of extant cells is difficult due to the sheer complexity of these systems. Engineered modules put additional load on a cell, which compromises their fitness, and they also often suffer from unexpected interactions with other cellular components.

Applications envisioned for micro- and nanorobots

Where can we find applications for such tiny robotic systems? Most likely, micro- and nanorobots will be used when a direct physical interaction with the molecular or cellular world is required. One of the main applications envisioned for such systems will be in nanomedicine, *e.g.*, as highly advanced drug delivery vehicles. Such devices could sense their environment, release drugs on demand, or stimulate cell-signaling events. They may potentially be equipped with simple information-processing capabilities that can integrate more complex sensory information; for instance, to evaluate the presence of a certain tissue or cell type, and thus location in the body, and apply diagnostic rules such as "if condition X is met, bind to receptor Y, release compound Z", *etc.* Given the limited capabilities of small-scale systems, it is not clear how programmable such robotic devices will be. Autonomous robots will have to find their location by themselves, which for some applications may be achieved by circulation and targeted localization in the organism. Alternatively, hybrid approaches are conceivable, which allow for active control from the outside, *e.g.*, by magnetic or laser manipulation. There are many additional challenges for such devices, which are similar to those for conventional drugs, *e.g.*, degradation, allergenicity, dose, or circulation time.

Apart from nanomedical robots, for which the first examples are already emerging, a wide range of applications can be envisioned in biomaterials and hybrid robotics. Hybrid robots (composed of "classical" and molecular components) could use an interface to the environment that is equipped with biomolecular sensor and actuator modules, which would allow, *e.g.*, to release or present molecules in response to an input. Here, the overall robot would be macroscale, but with the ability to act on the microscale. In materials applications, surfaces or particles could be modified with active molecular robotic devices, which can then be programmed and change their properties in response to environmental signals in various ways.

Conclusions

The realization of biomolecular robots is a highly interdisciplinary endeavour with a potentially huge technological impact. First examples of tiny robotic systems have been realized, but real-world applications will require further development. Apart from its more applied aspects, the field is also interesting for physicists, as it touches upon fundamental questions, which are related to the basic robotic functionalities: What are the physical limits of

sensing? What is the computational power of a molecule or a cell? How can we generate autonomous motion at the nano- and microscale, in the presence of Brownian motion? How can we realize collective behaviors and decision-making processes in systems of many interacting agents? How do we supply these systems with energy? These are questions naturally asked also by researchers in biophysics, statistical physics and complex systems. ■

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Tobias Pirzer obtained his PhD in biophysics at the Technical University Munich (TUM) in 2010. Since 2012 he is working as senior scientist in the group of Friedrich Simmel.

Friedrich Simmel obtained his PhD in physics at the Ludwig-Maximilians-University Munich (LMU) in 1999. After a postdoctoral stay at Bell Labs, he started an independent junior research group at LMU Munich and became a full professor of physics at the Technical University Munich in 2007. His research focuses on biophysics and its applications in bionanotechnology and synthetic biology.

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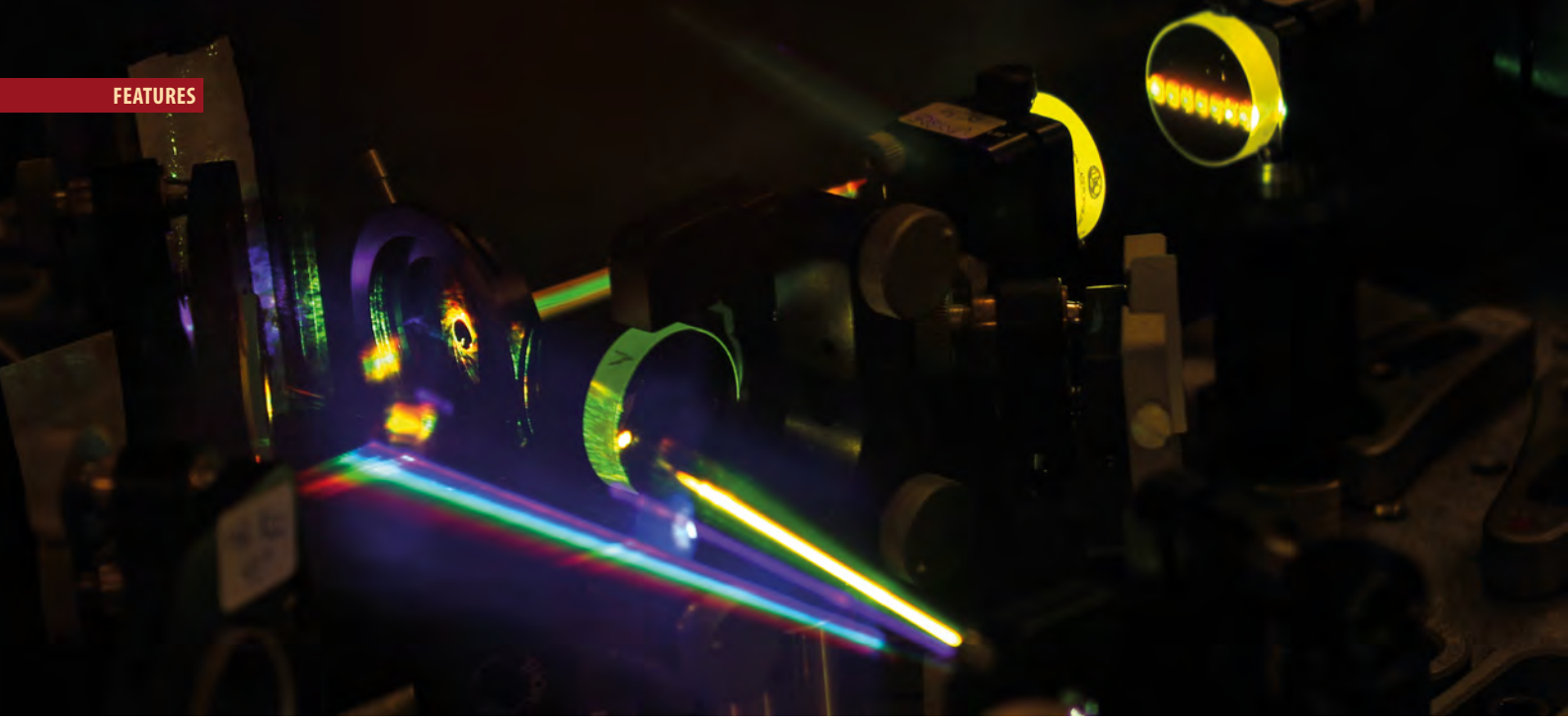

LASERS FOR HEALTH

Giulio Cerullo[1,2] and Renzo Vanna[2] – DOI: https://doi.org/10.1051/epn/2022305
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Thanks to its spatial and temporal coherence properties, laser light lends itself to a wealth of biomedical applications. We review the use of lasers in medical sciences, from microscopy for understanding the origin of diseases, to diagnostics for enhancing the accuracy of therapies to surgery of almost any organ of the human body.

Light for life

Light is intimately linked to life. Many bio-organisms have developed sophisticated molecular machineries to interact with light and exploit it for their functions. In photosynthesis, plants absorb solar energy in light-harvesting complexes and use it to drive charge separation and ultimately convert it into chemical energy [1]. The vision system of higher organisms is based on phototransduction triggered by the isomerization of the retinal chromophore within visual (opsin) proteins [2]. Some animals have learned to generate and manipulate light for improved survival and reproduction. Examples are fireflies and jellyfish which exploit chemical reactions in luciferin compounds to generate bioluminescence, which is used to attract preys, repel predators or to communicate. Other animals, such as peacocks and butterflies, use photonic crystal structures to generate bright color patterns [3].

Light is also intimately linked to medicine, since almost every component of the electromagnetic spectrum can be used for diagnostic and therapeutic purposes [4]. For example, radio waves are employed for magnetic resonance imaging (MRI), infrared and visible light finds application to microscopy and laser surgery, ultraviolet (UV) light is used for eye refractive surgery and for virus and bacteria disinfection, X-rays are employed for computed tomography (CT) and gamma rays for positron emission tomography (PET) and radiotherapy. We will here focus on the medical application of lasers, sources of coherent electromagnetic waves in the optical range of frequencies.

Lasers and medicine

The invention of the ruby laser by Theodor Maiman in 1960 immediately triggered a variety of medical applications. Differently from natural light sources, lasers emit light at specific wavelengths, tunable from the infrared to the UV, and with a high degree of spatial coherence; in addition, mode-locked lasers generate ultrashort light pulses, with picosecond to femtosecond duration [5]. These properties allow to concentrate large amounts of electromagnetic energy into small volumes, resulting in

precise tissue ablation. Early examples of laser therapies were photocoagulation in the retina, destruction of skin lesions and removal of cardiovascular plaque. Nowadays, laser applications in medicine can be broadly classified in three categories: i) microscopy, for studying fundamental biological processes and understanding the cellular mechanisms leading to the development of diseases; ii) optical diagnosis, for real-time visualization of tissues and cells, also in the operating room and inside the body thanks to endoscopic probes; iii) laser surgery and light-activated therapies.

Optical microscopy

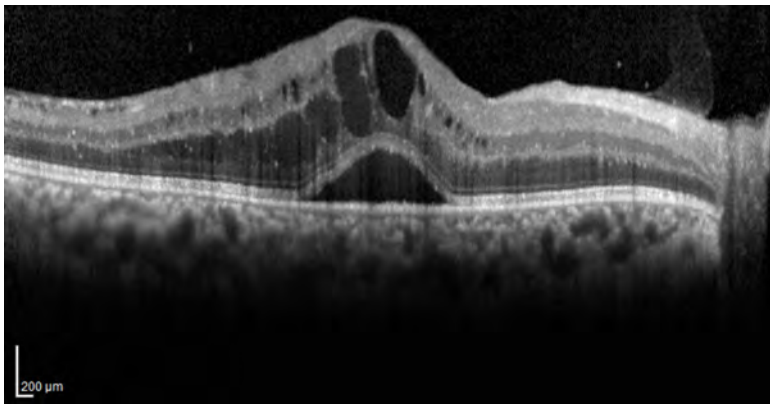
The birth of modern biology goes hand in hand with the invention of the optical microscope. In 1655 the English physicist Robert Hooke used one of the first compound optical microscopes to observe thin cork slices and coined the word "cells", likening their structure to that of cubicles in monasteries. Since then, optical microscopy has gone a long way in imaging the composition of living cells and tissues and studying their dynamical evolution. With respect to other imaging techniques such as MRI, it has the advantage of high spatial resolution; with respect to electron microscopy, it has the advantage of being non-destructive, enabling to operate on living samples. While there are many imaging modalities, the most used, due to its sensitivity, is fluorescence, using either exogenous (such as dyes and quantum dots) or endogenous (such as fluorescent proteins) chromophores [6].

The resolution of optical microscopy is set by diffraction of light and, according to Abbe's limit, is of the order of half of the wavelength of light (or 200-300 nm in the visible range). Recently, super-resolution microscopy techniques such as stimulated emission depletion (STED) [7] and photoactivated localization microscopy (PALM) [8] enabled to overcome the diffraction limit by almost an order of magnitude and to understand biological function at the molecular level.

Lasers for diagnostics

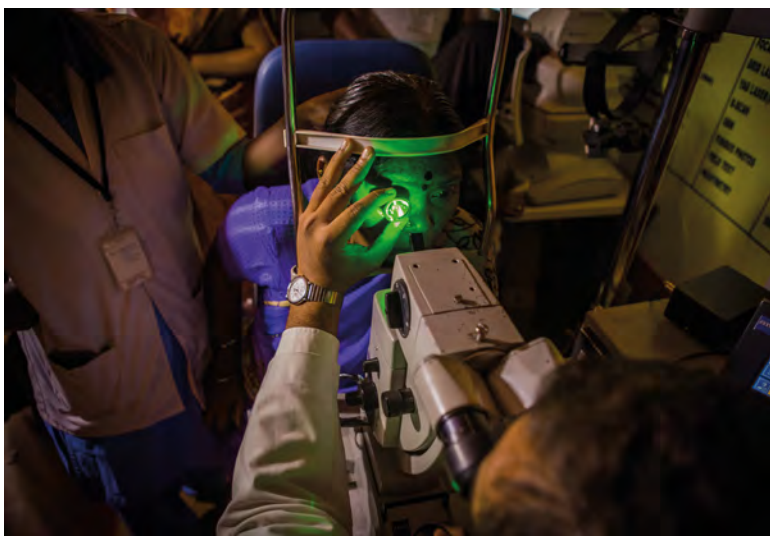
Coherent vibrational microscopies, such as stimulated Raman scattering (SRS), enable to determine the chemical composition of cells and tissues in a label-free and non-destructive way [9]. The current gold standard of tumor diagnosis in histopathology is the century old H&E technique, which requires staining the tissue slices with the hematoxylin and eosin dyes, followed by visual inspection by the histopathologist. SRS promises to improve the diagnostic accuracy by measuring the vibrational response of unstained samples (virtual histopathology) [10] and providing not only morphological but also biochemical information (spectral histopathology).

Many laser-based optical imaging techniques have been developed which are non-invasive and with high spatial resolution, employing a multiplicity of contrast mechanisms. They are used both in diagnosis and in therapy to enhance the precision of surgical interventions, enabling to distinguish between healthy and diseased tissue with • • •



▲ FIG. 1: OCT image of the retina of a patient affected by diabetic macular edema (both intraretinal and subfoveal subretinal fluid are present in the image). Image by Dr. Caterina Toma and prof. Stefano De Cillà

• • • higher accuracy with respect to the naked eye. Fluorescence guided surgery uses the orally administered 5-aminolevulinic acid (ALA) which accumulates in the tumour tissues and is metabolically activated to form protoporphyrin IX, with intense red fluorescence. ALA assisted surgery allows a complete tumor resection with significantly improved outcome. Another successful imaging technique is optical coherence tomography (OCT), which exploits interference of low-coherence broadband light to obtain a 3D image of light back-scattered by a tissue with high spatial resolution (down to a few µm) at depth of up to several mm [11]. OCT has become a standard technique in ophthalmology, as it allows to obtain high resolution images of the retina morphology. It is the standard for diagnosis of pathologies such as glaucoma, diabetic retinopathy (see Fig. 1) and age-related macular degeneration. Time Domain Near-infrared Spectroscopy (TD-NIRS) uses the absorption and scattering of short (picosecond) laser pulses to measure the concentration and localization of various components of tissues, such as oxy- and deoxyhemoglobin, lipids and water. TD-NIRS allows non-invasive monitoring of tissue hemodynamics and oxidative metabolism, for studies of functional activation in our brain [12] and diagnosis of a variety of diseases.



▼ FIG. 2: Laser treatment being done inside a mobile eye van for a patient with diabetic retinopathy. by Rajesh Pandey. Copyright CC BY-NC-SA 2.0.

Lasers for surgery

With respect to the use of a scalpel, laser surgery has the advantage of being a non-contact technique and to enable high precision in tissue removal, limiting the damage to the adjacent tissue and, in some cases, cauterizing the surrounding vascular network. Among the factors that dictate the choice of the wavelength for laser surgery are the absorption coefficient of the tissue and the availability of optical fibers for endoscopic light transport. As tissues are made mostly of water, it is instructive to consider the water absorption coefficient, which peaks in the infrared around 3 µm, where Erbium lasers emit; however, no convenient optical fibers are available at this wavelength. A secondary maximum occurs around 2 µm, where Holmium lasers emit, a wavelength that can be easily guided by optical fibers. Light absorption is also very high in the UV range, where excimer lasers emit.

Lasers find numerous applications in dermatology, for permanent air removal, skin resurfacing resulting in facial rejuvenation and removal of tattoos or port wine stains. An application currently under development is laser lithotripsy for kidney stone fragmentation, using a Holmium laser coupled to an ureteroscope. Similarly, Holmium lasers are used for the treatment of benign prostatic hyperplasia, removing the excess tissue. Erbium lasers hold promise in dentistry for the ablation of hard (dentin and enamel) dental tissue, despite the complication caused by the lack of effective delivery fibers. Low intensity laser light in the red and near infrared is used for photobiomodulation, also known as low level laser therapy, to treat inflammation, chronic pain and sport injuries. The underlying mechanisms, still not fully understood, are related to light activation of the mitochondria in the cells.

Lasers find also numerous applications in ophthalmology, such as *e.g.* in the surgery of retinal detachment, of diabetic retinopathy (see Fig. 2) and of secondary cataract. An established application is refractive surgery for the correction of visual defects, by reshaping of the curvature of the cornea. In laser-assisted in situ keratomileusis (LASIK) a wavefront sensor first characterizes the curvature of the cornea. Subsequently, the corneal epithelium is cut creating a flap which is folded back by the surgeon to reveal the middle section of the cornea, the so-called stroma. At this point an UV excimer laser at 193 nm is used to ablate the stroma, precisely remodeling its curvature. Finally, the flap is folded back in place, and, after a short post-operative care, full visual acuity is recovered accompanied by a correction of the defect. Initially the flap was mechanically cut by a metal blade, but recently a femtosecond laser was found to give better outcomes [13]. With millions of surgeries performed and a very high degree of patient satisfaction, LASIK is an impressive example of how even sophisticated laser technologies have nowadays reached a level of maturity sufficient for their employment in mainstream applications.

Outlook

The future of applications of lasers to health looks bright. More and more sophisticated imaging techniques, both in vivo and ex vivo, can be used to improve the accuracy of the diagnostics and assist during treatment, allowing a personalized, precision medicine. On the other hand, technological progress has made even sophisticated systems, such as femtosecond lasers, robust and reliable enough to allow their use by non-experts in a medical environment. This considerably broadens the range of surgical applications for lasers. Finally, lasers can play an important role in nanomedicine, in which organic or inorganic nanoparticles are used to carry a drug cargo into the body [14]. Light-activated drug release will help to tailor the localization and the dose of the therapy to maximize its efficacy. ■

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Computational Statistical Physics

By Lucas Böttcher and Hans J. Herrmann

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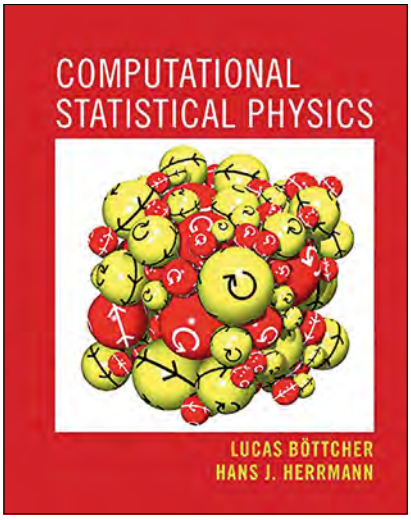

"Computational Statistical Physics" by Lucas Böttcher and Hans J. Herrmann is a textbook for physics students taking a Bachelor or Master course in computational physics and focuses on teaching them stochastic and molecular dynamics methods used in Statistical Physics. The part on stochastic methods covers random numbers, introduces various standard models like percolation or the Ising model, then phase transitions and finite size scaling and finally discusses various methods: Monte Carlo methods, Cluster algorithms, histogram methods, numerical renormalization group, parallelization, and the Gillespie algorithm.

The part on molecular dynamics covers various standard integration algorithms and the cell index method, and then discusses the algorithmic solutions to the specific problems that arise in connection with composed particles, long-range interactions, thermostats, inelastic collisions, and event-driven dynamics as they occur for instance in the simulation of granular matter.

Finally discrete fluid models like the lattice Boltzmann method are briefly touched as well as a short discussion of quantum mechanical ab initio simulations. Apart from the latter two each chapter contains exercises, which ask the reader to implement the discussed algorithm.

The organization and content of the book is very similar to my own lecture on computational physics, and it could very well serve as a textbook for it. It covers a lot of material but has only 250 pages, so a lecturer might have to add additional material or refer to more extensive textbooks on Monte Carlo or molecular dynamics simulations. And she/he would have to add basics of quantum Monte Carlo methods used in computational statistical physics, which is not contained in the book although it could have been straightforwardly integrated into the chapter on the Ising model.

For lecturers as well as students it would have been very useful to provide solutions and computer codes for the exercises, which are unfortunately not included in the book. Very appealing is the layout of the text, the Cambridge University Press textbook style: with blue boxes for highlighted information, grey boxes for additional information, and green boxes for the exercises.

Moreover, many pages display on their marginal column pictures, plus some personal data, of the researcher who made an important contribution to the topic of the chapter. For this reason, it is also fun to scroll through the book and learn about the historic evolution of stochastic methods and molecular dynamics in statistical physics. Therefore, I enjoyed reading it and I can recommend it. ■

■ **Heiko Rieger,** *Saarland University*

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