

# europysicsnews

The magazine of the European Physical Society

## Physics of **Living Matter**

In this special issue the multifaceted research of the most astonishing state of matter.

Nobel prizes  
2020

---

Science diplomacy  
in 1968

---

Young Minds  
survey

---

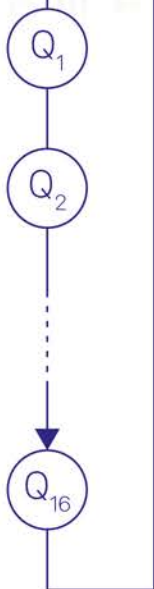


edp sciences

# Your Qubits. Measured.

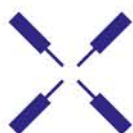
Meet the next generation of quantum analyzers setting new standards for the readout of superconducting qubits.

New



## Your Benefits

- **Compact design**  
Read out up to 64 superconducting qubits in real time: time-staggered or in parallel.
- **Efficient workflows**  
Operate at up to 8.5 GHz in a clean bandwidth of 1 GHz, free of mixer calibration.
- **Strong performance**  
Achieve optimal readout signal at minimal latency using matched filters and multi-state discrimination.
- **Turnkey feature set**  
Characterize and calibrate your system quickly with fast resonator spectroscopy.
- **Scalable system approach**  
Shape your Zurich Instruments Quantum Computing Control System according to your requirements with our latest innovations.



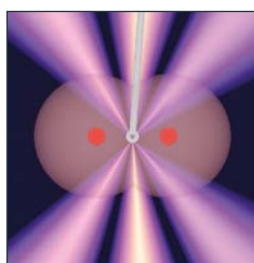
Zurich  
Instruments

Contact us today  
[www.zhinst.com](http://www.zhinst.com)



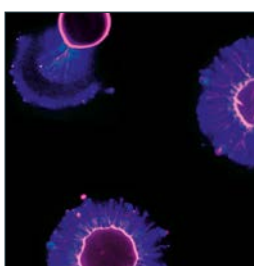
# euromphysicsnews

Cover picture: Living matter, the most astonishing state of matter. ©iStockPhoto



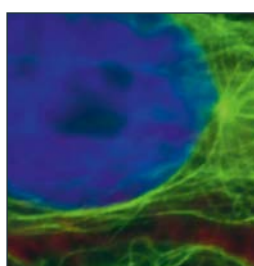
▲ PAGE 12

## Zeptoseconds: new world record



▲ PAGE 18

## Active protein networks



▲ PAGE 28

## Mechanics in biology

### EPS EDITORIAL

- 03 The Physics of Living Matter – C. Beck, K. van der Beek and F. Ritort

### IN THE SPOTLIGHTS

- 04 Personnal Reporte: The Collective Behaviour of Bacteria – C. Douarche  
06 Nobel prize for Physics 2020 – M. Sakellariadou  
08 Nobel prize in chemistry 2020 – R. Seidel  
10 The foundation of the EPS in 1968: a case of science diplomacy – R. Lalli  
11 In memoriam, Robert Pick – M. Ducloy  
12 Zeptoseconds: new world record in short time measurement – E. de Wolf

### HIGHLIGHTS FROM EUROPEAN JOURNALS

- 13 A question of reality  
Impurities enhance polymer LED efficiencies  
14 Effects of time defects in modulated systems  
Avoiding environmental losses in quantum information systems

### YOUNG MINDS

- 16 How YM shapes the physicists of the future – M. Ostinato, C. Martin, R. Zeltner and H. Mkrtchyan

### COLUMN

- 18 Living Soft Matter: active protein networks govern cell shape changes – C. Sykes

### FEATURES PHYSICS OF LIVING MATTER

- 20 Seeing with electrons – A. J. Jakobi  
24 Protein nanomechanics: the power of stretching – M. Mora and S. Garcia-Manyes  
28 Mechanics in biology – T. Idema  
31 Cell differentiation unravelled by single-cell RNA sequencing – A. Alemany  
35 The nonlinearity of life – E. Herrera-Delgado and P. Sollich  
38 Tailored models for COVID-19 – A. Arenas, J. Gómez-Gardeñes, C. Granell and D. Soriano-Paños  
42 On the importance of being critical – M. Marsili  
45 From single particle motion to structure of biological systems – Y. Roichman  
48 What is the temperature of a cell? – K. Hayashi, S. Hasegawa and S. Niwa  
51 Getting started on Twitter as a scientist – E. de Wolf

### ANNUAL REPORTS

- 52 EPS awards and distinctions during the year 2020  
53 EPS directory: summary and website  
55 Annual index volume 51 - 2020

# Control your qubits with Vivace

An all-in-one platform from Intermodulation Products.  
Reach microwaves without analog mixers!



ARBITRARY PULSES

Up to 128 templates with  
250 ps resolution



QUANTUM EVENT ORGANIZER

Place pulses and readout  
on a 2 ns event grid



TEMPLATE MATCHING

Match incoming pulses to stored  
templates to trigger events



MULTIFREQUENCY

Continuous wave modulation and  
demodulation on each port with  
up to 32 simultaneous frequencies



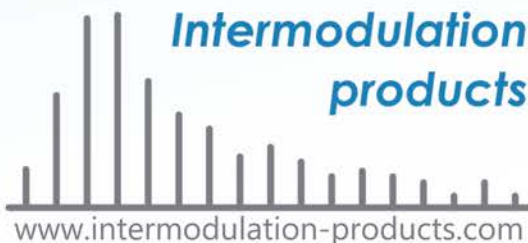
IQ MODULATION / DEMODULATION

Pair-wise length matched outputs  
with DC-bias tuning, perfect for  
driving external IQ-mixers



ALGORITHMS

Simple flexible interface for reset,  
readout, Ramsey, Rabi or your  
own custom algorithm



	Input	Output
Number of ports	8	8
Analog bandwidth [GHz]	4	4
Sampling frequency [GHz]	4.096	6.554
Resolution [bit]	12	14
Lock-in frequencies	32	32



[EDITORIAL]

## The Physics of Living Matter

**Living entities are probably the most astonishing state of matter. They are capable of the most extraordinary feats, from primordial, “defining” tasks at the cellular level such as self-sustainment by feeding from the environment and self-reproduction, to the most sophisticated exercises undertaken at the level of organisms such as thinking, talking, playing...**

**D**espite the enormous knowledge accumulated on the physical and chemical laws governing matter, we still do not grasp the essential difference (if any) between animate and inanimate matter. Biology, the natural science of life, has always benefited from discoveries in physical and chemical sciences. The inventions of the microscope and the telescope in the 17<sup>th</sup> century are examples of how physics has contributed to major developments in the most disparate domains. While the invention of the microscope allowed van Leeuwenhoek to observe the small *animalcules* (microscopic organisms), the telescope led Galileo to discover the big *Medicean stars* (Jupiter moons). During the last century we have witnessed a major change in the way the physical sciences contribute to biology. Biology is now a quantitative science where measurements are ever more accurate, approaching the level attained in the physical and chemical sciences. Biophysics is the natural bridge between biology and the physical-chemical sciences, the latter providing the most advanced instrumentation, tools and methods for an accurate and quantitative assessment of the *behaviour* of living matter. Oppositely, biological systems are ever more used as model systems to test and develop novel physical theories, perfecting a most interesting and highly fruitful interdisciplinary exchange. The ultimate goal of such quests is not only to provide more fundamental and more accurate descriptions of biological processes but also

to unveil hidden physical laws underlying the emergent properties of living matter, if any exist.

In this Special Issue on the ‘*Physics of Living Matter*’, three divisions of the EPS have made the effort to put together a selection of nine features on the most various topics. The goal is to illustrate the collaborative action between physics and biology through a number of examples. The papers are arranged into three main blocks: (i) recent developments in light and force microscopies to study molecules and cells; (ii) developments in statistical and nonlinear physics in genomic, developmental and epidemic systems; (iii) developments in the physics of nonequilibrium systems to understand emergent and collective properties in living matter. The papers are accompanied by a few selected columns on headline and actual topics. We hope that the Special Issue will be enjoyed by our readers and that it will promote further exchange and shared knowledge across the frontiers of these fascinating sciences. ■

■ **Christian Beck,**

*Chair of the Statistical and Nonlinear Physics Division*

■ **Kees van der Beek,**

*Chair of the Condensed Matter Division and member of the EPS Executive Committee*

■ **Felix Ritort,**

*Chair of the Division of Physics in Life Sciences*

## europhysicsnews

2020 · Volume 51 · number 5&amp;6

**Europhysics news** is the magazine of the European physics community. It is owned by the European Physical Society and produced in cooperation with EDP Sciences. The staff of EDP Sciences are involved in the production of the magazine and are not responsible for editorial content. Most contributors to Europhysics news are volunteers and their work is greatly appreciated by the Editor and the Editorial Advisory Board.

Europhysics news is also available online at: [www.europhysicsnews.org](http://www.europhysicsnews.org)

General instructions to authors can be found at: [www.eps.org/?page=publications](http://www.eps.org/?page=publications)

**Editor:** Els de Wolf (NL)

**Email:** [epn.editor@eps.org](mailto:epn.editor@eps.org) - **Twitter** @elsdewolf1

**Science Editor:** Ferenc Igloi (HU)

**Email:** [igloi.ferenc@wigner.mta.hu](mailto:igloi.ferenc@wigner.mta.hu)

**Executive Editor:** David Lee

**Email:** [david.lee@eps.org](mailto:david.lee@eps.org)

**Graphic designer:** Xavier de Araujo

**Email:** [xavier.dearaujo@eps.org](mailto:xavier.dearaujo@eps.org)

**Director of Publication:** Agnès Henri

**Editorial Advisory Board:**

Richard Zeltner (Young Minds), Tracey Clarke (UK), Gonçalo Figueira (PT), Zsolt Fülöp (HU), Manuel Güdel (A), Tero Heikkilä (FI), Agnès Henri (FR), Jo Hermans (NL), Christoph Keller (NL), Antigone Marino (IT), Arnulf Quadt (DE), Laurence Ramos (FR), Chris Rossel (CH), Victor R. Velasco (SP), Sylvain Viroulet (FR)

© European Physical Society and EDP Sciences

#### EPS Secretariat

**Address:** EPS · 6 rue des Frères Lumière  
68200 Mulhouse · France

**Tel:** +33 389 32 94 40 · **fax:** +33 389 32 94 49  
[www.eps.org](http://www.eps.org)

Secretariat is open 09.00–12.00 / 13.30–17.30 CET  
except weekends and French public holidays.

#### EDP Sciences

**Managing & Publishing Director:** Agnès Henri  
**Email:** [agnes.henri@edpsciences.org](mailto:agnes.henri@edpsciences.org)

**Production:** Sophie Hosotte

**Advertising:** Bernadette Dufour

**Email:** [bernadette.dufour@edpsciences.org](mailto:bernadette.dufour@edpsciences.org)

**Address:** EDP Sciences

17 avenue du Hoggar · BP 112 · PA de Courtaboeuf  
F-91944 Les Ulis Cedex A · France

**Tel:** +33 169 18 75 75 · **fax:** +33 169 28 84 91

[www.edpsciences.org](http://www.edpsciences.org)

#### Subscriptions

**Individual Members of the European Physical Society** receive Europhysics news free of charge.

**Members of EPS National Member Societies** receive Europhysics news through their society, except members of the Institute of Physics in the United Kingdom and the German Physical Society who have access to an e-version at [www.europhysicsnews.org](http://www.europhysicsnews.org). The following are 2020 print version subscription prices available through EDP Sciences (Prices include postal delivery cost).

**Institutions - European Union countries:** 113 €  
(VAT not included, 20%). **Rest of the world:** 136 €

**Student - European Union countries:** 54.17 €  
(VAT not included, 20%). **Rest of the world:** 65 €

**Contact:** Europhysics News, EDP Sciences  
17 avenue du Hoggar · Parc d'activités de Courtaboeuf  
BP 112 · F-91944 Les Ulis CEDEX A, France  
[subscribers@edpsciences.org](mailto:subscribers@edpsciences.org) or visit [www.edpsciences.org](http://www.edpsciences.org)

ISSN 0531-7479 · ISSN 1432-1092 (electronic edition)

**Printer:** Fabrègue · Saint-Yrieix-la-Perche, France

**Legal deposit:** November 2020

# The Collective Behaviour of Bacteria

**Biophysicist Carine Douarche has a fascination for bacteria. EPN invited her to write a personal report.**



The surrounding world is extraordinary and life is certainly one of the secrets of the universe that fascinate me most. For example: bacteria. On Earth since nearly the origin of life, these living beings of absolute simplicity consist of one single cell, one single chromosome and yet, are capable of foolproof adaptation. Through the ages, they have drawn their strength from the collective, from their interactions

with their siblings and from their social sense that allows them to perform extremely varied and complex tasks.

## Random walk of bacteria

As a condensed matter physicist by training with a particular focus on soft matter, I became interested in the physics of biological systems at a very early stage of my studies. During my postdoctoral fellowship at the Rockefeller University in New York, I realised the importance of understanding the behaviour of bacteria and their locomotion in heterogeneous environments. Some strains are dotted with flagella - long proteic filaments, attached to the cell membrane through a rotary motor - which allow the cell to swim in aqueous media. Thus, bacteria alternate runs and tumbles, performing a three-dimensional random walk on large spatio-temporal scales. But bacteria can also skew this random walk to find their way in heterogeneous environments, that is to say, in most real situations. Be they gradients of oxygen, of nutrients or temperature, shear stress due to flow, the presence of interfaces, or a high local concentration of cells, bacteria feel a multitude of signals that make them adapt their swimming to their environment. And it's not exclusively a matter of swimming: bacteria consume nutrients and oxygen and release chemicals in the medium. They are entities that are out of equilibrium and locally modify their surroundings, which in turn changes the response of the population to these modified external conditions. The contribution of statistical physics is then to infer from the analysis of microscopic properties of individual cells the behaviour of groups of



**I am convinced that in research, as it is observed in nature, strength and success come from the collective and one's interactions with peers.**

individuals, and to demonstrate how collective properties can emerge from a population.

### Research career

After I obtained a position at the university, my successful grant applications, and in particular to the French ANR “Jeunes Chercheuses Jeunes Chercheurs” programme have enabled me to develop this scientific topic in a biophysics group at the Laboratoire de Physique des Solides of Paris Saclay University, France [1]. While studying the morphogenesis of bacterial biofilms, focusing on the coupling between the role of oxygen and cell motility in these systems, I repeatedly observed convective phenomena in bacterial fluid suspensions. In fact, even when all efforts were focused on designing an experiment in which the fluid was as static as possible, the bacteria, when active and locally concentrated, still managed to set the fluid in motion. Thus, the hydrodynamic component in these low-Reynolds-number systems cannot be neglected. To understand the systems better, I got closer to my collaborators in the field of hydrodynamics, and ultimately moved to the neighboring Fluides, Automatique, et Systèmes Thermiques laboratory.

### Working with peers

I am convinced that in research, as it is observed in nature, strength and success come from the collective and one's interactions with peers. Together with colleagues from the PMMH laboratory at the ESPCI in Paris, we have performed rheology measurements with a low-shear Couette rheometer and demonstrated experimentally that bacteria have the additional ability to modify the viscosity of the fluid which they actively swim in [2]. When the volume fraction of cells in the fluid is increased, the effective viscosity decreases to a value lower than that of water! And, when bacteria are highly active, the viscosity is reduced to near zero. With my colleagues at the University of Edinburgh, we have

observed what happens at the microscopic scale when this phenomenon emerges. During my 6-month sabbatical in Scotland, we performed an extended study of collective motion of bacteria: above a critical density, suspensions of pusher bacteria exhibit a transition to coherent flow and swimmers begin to swarm in a way reminiscent of flocking in birds or fish. A comparison with optical measurements of the bacteria suspension under shear showed that the vanishing viscosity coincides with the appearance of nonlinear flow and the onset of collective motion [3].

### Room for creativity

My curiosity and fascination to the world around me propelled me to an academic career. As a young researcher starting in the field, I have considered academia as an opportunity to fulfill my desire for learning and understanding the physics of biological systems. When one feels free

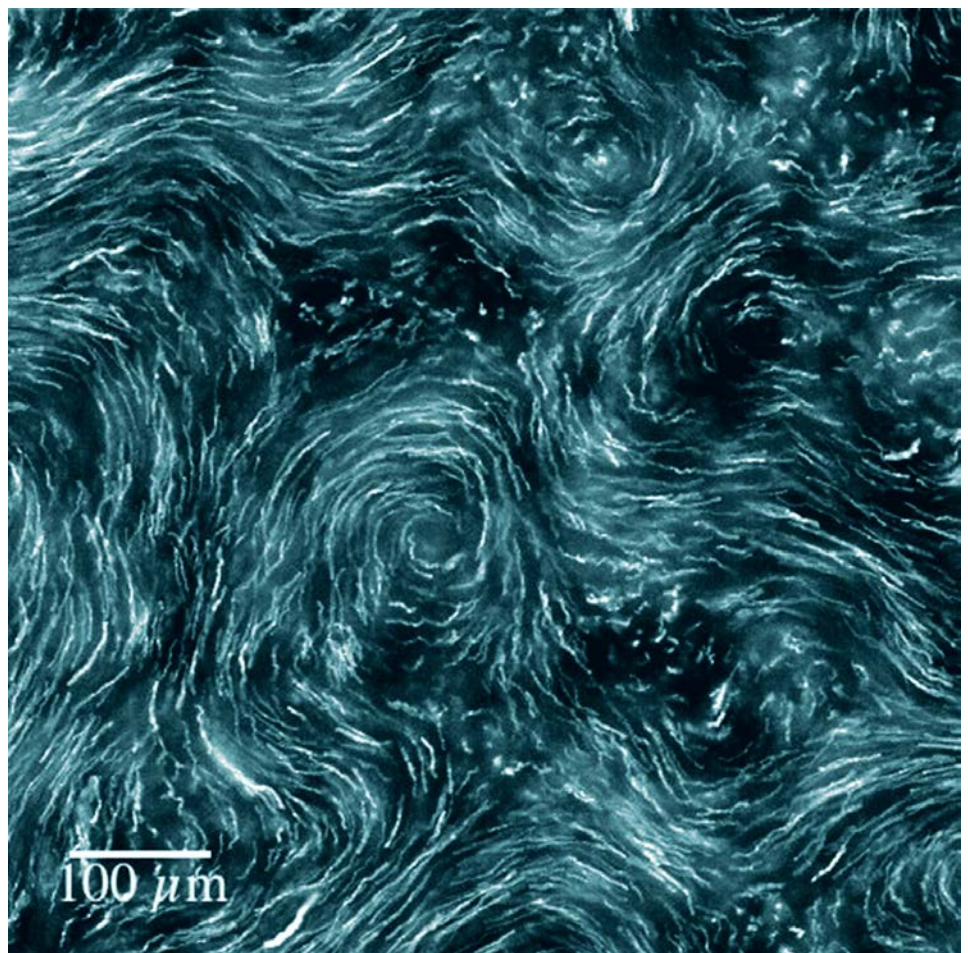
and trusted, then one has room for the all-important creativity that brings scientific breakthrough. I believe it is important to preserve this approach of science today. ■

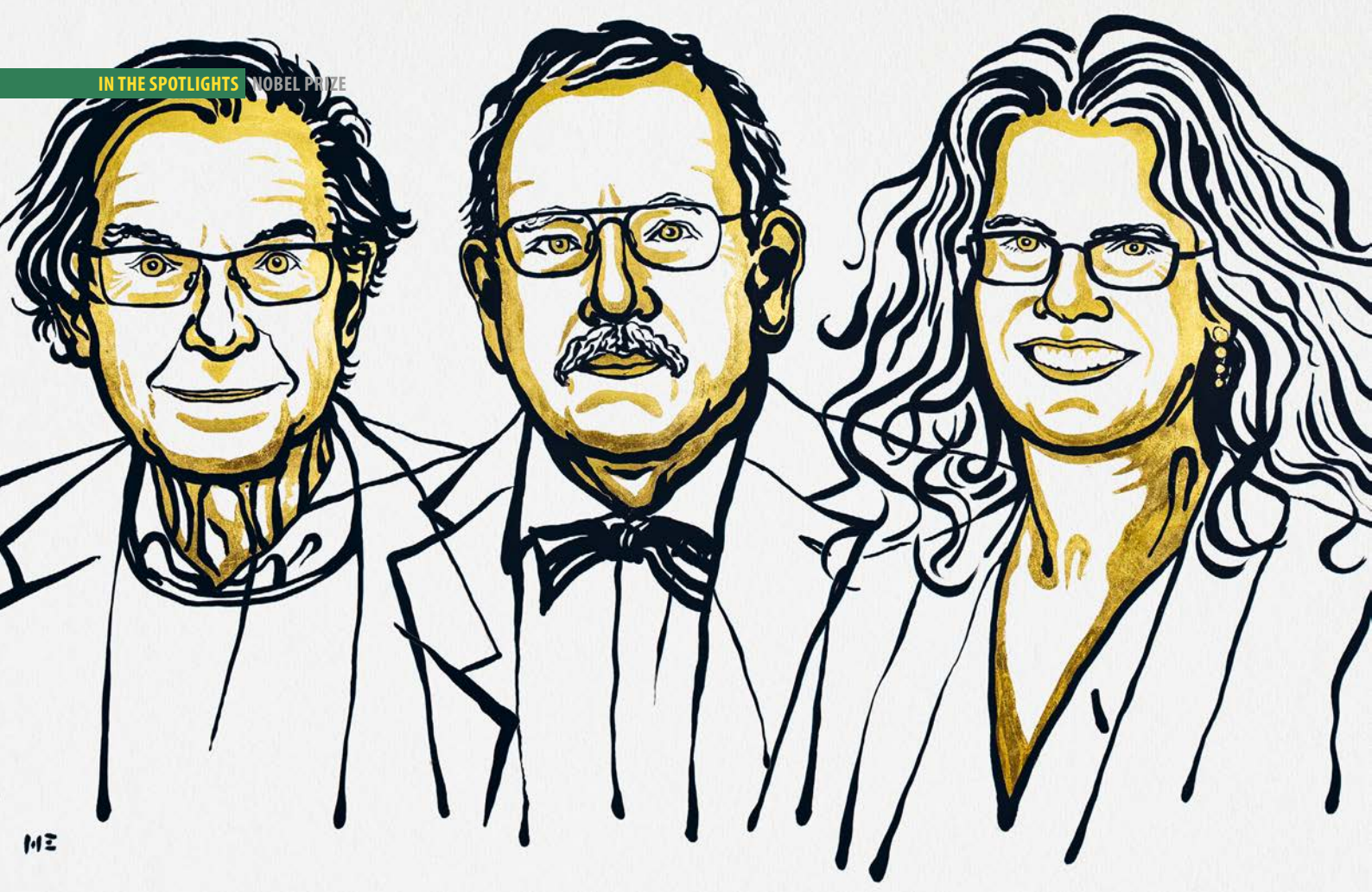
■ **Carine Douarche,**  
*Université Paris Saclay*

### References

- [1] My website:  
<http://hebergement.u-psud.fr/douarche/>
- [2] M. H. Lopez, J. Gachelin, C. Douarche, H. Auradou, E. Clement, *Phys. Rev. Lett.* **115**, 028301 (2015)
- [3] V. A. Martinez, E. Clément, J. Arlt, C. Douarche, A. Dawson, J. Schwarz-Linek, A. K. Creppy, V. Škultéty, A. N. Morozov, H. Auradou, W. C. K. Poon, *Proc. Natl. Acad. Sci. U.S.A.* **117**, 2326 (2020)

▼ Traces, accumulated for 3 sec, of fluorescent bacteria while performing collective motion. Images acquired with V. A. Martinez and J. Schwarz-Linek in Wilson Poon lab at the University of Edinburgh.





## Nobel prize for Physics 2020

**Black holes back to the light. These exotic objects which for long were only inhabitants of a theorist's world, are now the core of the daily activities of observers hunting for them. Gravitational-wave detectors keep recording the spatial disturbances caused by faraway black hole collisions, leaving an imprint in the fabric of space-time. Just a year ago, telescopes immortalised the contour of a supermassive black hole at the centre of a our galaxy.**

**T**he Nobel Prize in Physics 2020 acknowledges pioneering work on black holes. The Royal Swedish Academy of Sciences has decided to award one half to the theoretical physicist and mathematician Roger Penrose "for the discovery that black hole formation is a robust prediction of the general theory of relativity", the other half jointly to the astrophysicists Reinhard Genzel and Andrea Ghez "for the discovery of a supermassive compact object at the centre of our galaxy."

In 1965, ten years after the death of Albert Einstein, Roger Penrose

▲ Left to right:  
Roger Penrose,  
Reinhard Genzel,  
Andrea Ghez.  
© Niklas  
Elmehed for  
Nobel Media

published the "singularity theorem", using the notions of incompleteness and of closed trapped surfaces he had introduced earlier [1]. Penrose's singularity theorem shook the General Relativity community, and led to numerous physical and mathematical developments, with the theory of black holes in the first place. In another seminal paper Penrose defined asymptotic flatness, using the concept of conformal infinity, and then formulated the notion of event horizon as the boundary of the past or future null infinity. In the following decades, a number of exciting ideas have been developed in several physical and

mathematical areas, as the flourishing impact of Penrose's singularity theorem. The research activity that spanned from Penrose's work more than five decades ago, remains as active and vibrant as ever.

Since the 1990s, Reinhard Genzel and Andrea Ghez have both led groups of astronomers that traced the orbits of stars close to the centre of the Milky Way (our galaxy). To do so the two independent teams used some of the Earth's biggest telescopes -- the Keck Observatory on Mauna Kea in Hawaii and the Very Large Telescope on Cerro Paranal in Chile -- and employed cutting-edge



observational techniques. The data they accumulated and analysed, led them to the conclusion that at the centre of our own galaxy a supermassive invisible object resides, known as Sagittarius A\* (Sgr A\*). This is a very compact and bright radio source near the border of the constellation Sagittarius and Scorpius, at 26 000 light-years distance, having a diameter of 60 million kilometres and a mass about four million solar masses. The only plausible explanation is that Sgr A\* is a black hole located at the centre of the Milky Way.

The theoretical foundations for the existence of black holes by Roger Penrose have then been beautifully complemented by the experimental evidence that such an exotic object resides at the centre of our own galaxy. Thanks to these pioneering results, the currently increasing number of detections of black hole

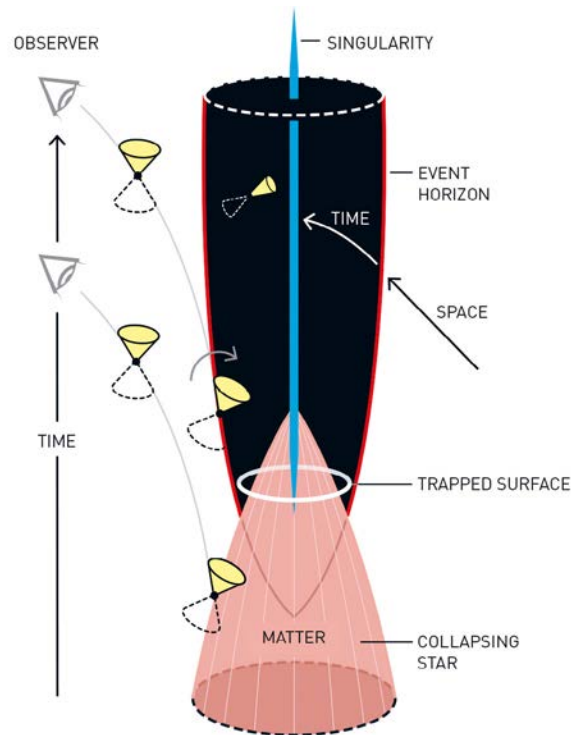
collisions by gravitational-wave detectors, the radio images recently obtained by the Event Horizon Telescope, and the myriad of studies inspired by these developments, black holes cease to be exotic objects and little by little we are able to unravel their mysteries.

**EPS and EPN warmly congratulate Sir Roger Penrose, Reinhard Genzel and Andrea Ghez on the award of the 2020 Noble Prize for Physics.** ■

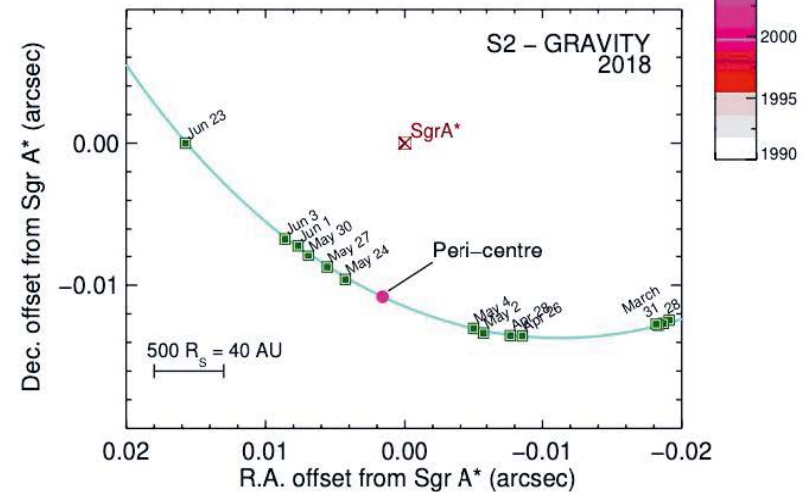
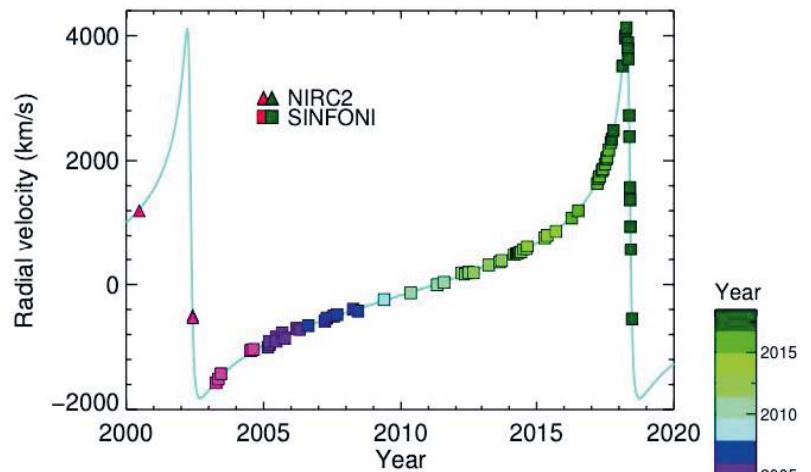
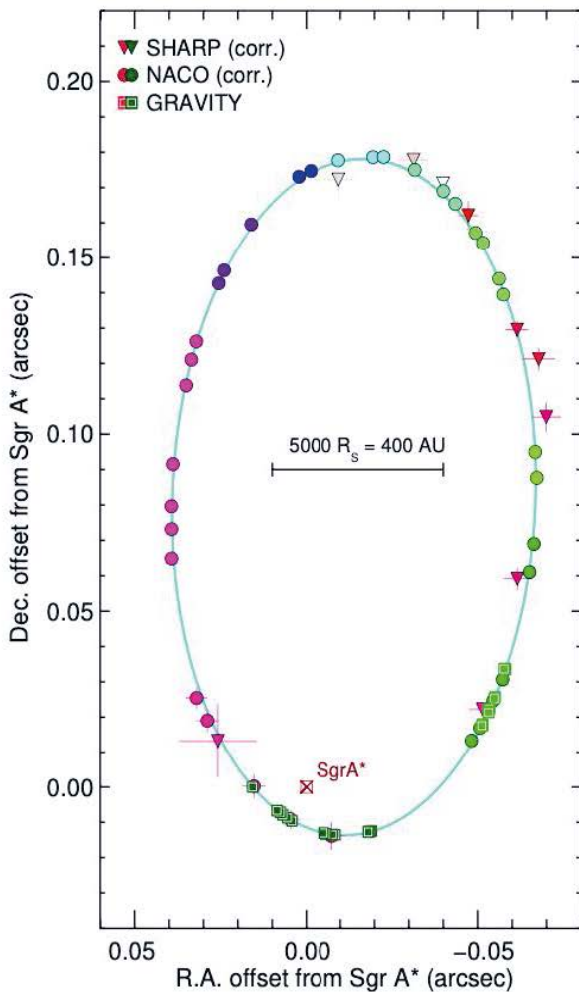
■ **Mairi Sakellariadou,**  
*Chair of the EPS Gravitational Physics Division*

**References**

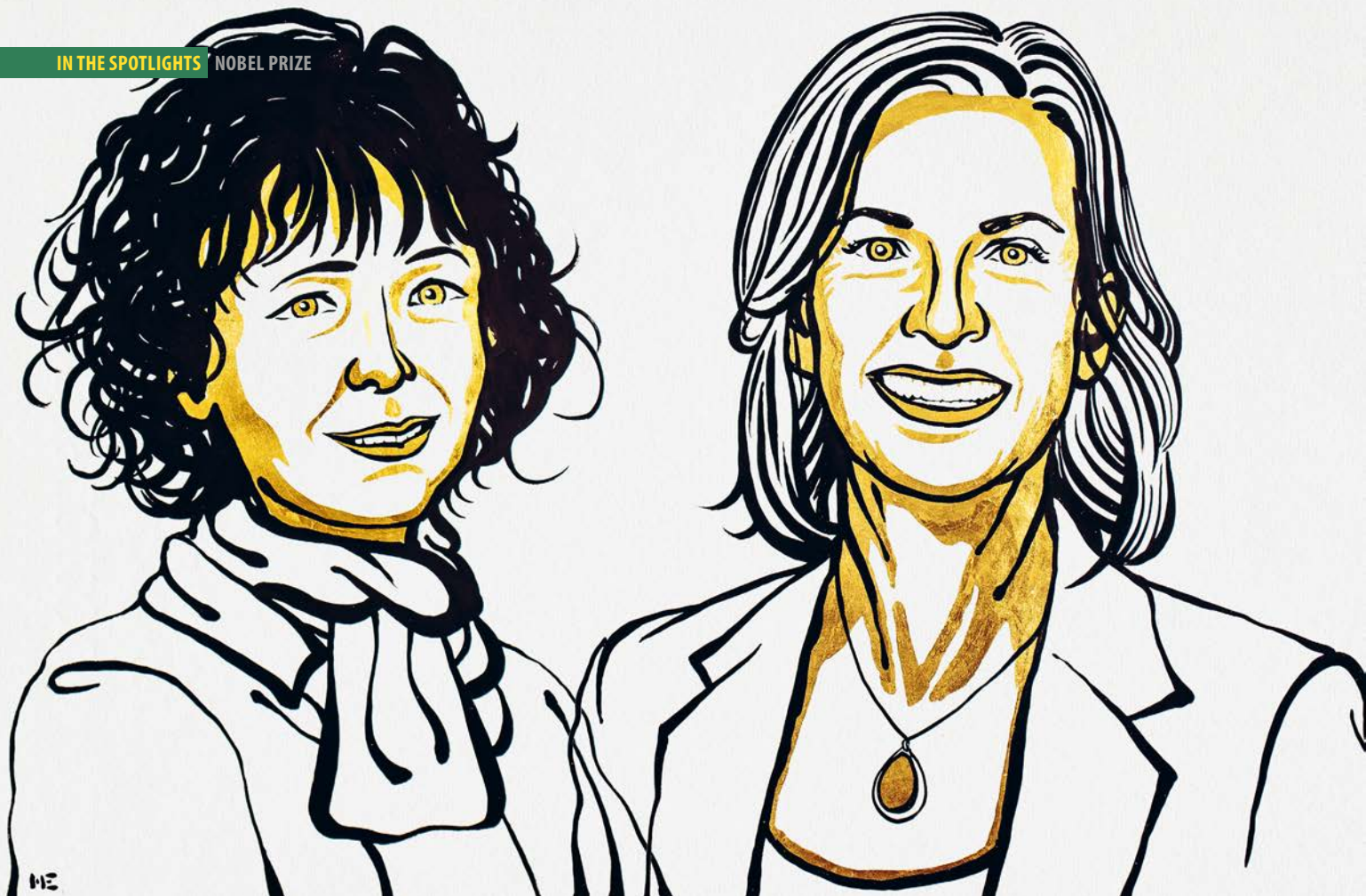
[1] Roger Penrose, *Phys. Rev. Lett.* **14**, 57 – Published 18 January 1965, doi: 10.1103/PhysRevLett.14.57



▲ The diagram is based on Penrose’s paper from 1965 [1] and shows the collapse of matter into a black hole. On a trapped surface all light cones are tipped inwards, and the formation of a singularity is inevitable.



▲ Summary of the observational results of monitoring the S2–Sgr A\* orbit from 1992 to 2018. Pictures from <https://www.nobelprize.org/uploads/2020/10/advanced-physicsprize2020.pdf>



## Nobel prize for Chemistry 2020: Molecular scissors to perturb the genetic code

The Nobel Prize in Chemistry has been awarded this year to Emmanuelle Charpentier from the Max-Planck Institute for the Science of Pathogens in Berlin and Jennifer A. Doudna from the University of California, Berkeley 'for the development of a method for genome editing'.

**T**heir discovery and biochemical reconstitution of the CRISPR/Cas9 genetic scissors allows for conveniently modifying the genetic code in many different types of organisms. Within a short time scale after the corner publication of the two researchers in 2012, it became a wide-spread and essential tool to study the effect of gene modifications and replacements in molecular biology.

The CRISPR/Cas9 genetic scissors are a single protein that harbours an RNA, which is the key component that programs the targeting of a specific gene of interest. Within a cell,

the RNA of the CRISPR/Cas9 complex constantly scans the chromosomal DNA to find a position that is complementary to it, which constitutes the DNA target. Since RNA of practically any sequence can be harboured by the protein complex, binding to any desired genetic locus can be freely programmed. Once bound to the DNA target,

▲ Left to right:  
Emmanuelle  
Charpentier,  
Jennifer  
A. Doudna  
© Niklas  
Elmehed for  
Nobel Media

the CRISPR/Cas9 scissors introduce a double-strand cut, which is, in combination with downstream DNA repair processes, the basis for changes to the genetic code at the target position. The achievement of Emmanuelle Charpentier was the identification of the correct RNA form. She then teamed up with Jennifer Doudna to biochemically



**The CRISPR/Cas9 genetic scissors are one of many other players within natural CRISPR systems. It is a technology that will have major impacts on biotechnology and health care in future** ””

purify and characterise the CRISPR/Cas9 complex to precisely reveal its function. Shortly after their joint publication, the number of studies with applications of this technology started to explode.

Viewing a cell as a large and highly complex signaling or reaction circuit, gene deletions or modifications can be considered as changes to the circuit design. By fusing CRISPR/Cas9 with activator or repressor domains for genes, it is possible to interfere with the circuit function without changing its design. On a systems level, the perturbation of the function of a single gene or multiple genes in parallel can be combined with monitoring the activity of the other genetic elements. This allows for uncovering the complex regulatory network of cells and thus one of the most crucial secrets of life.

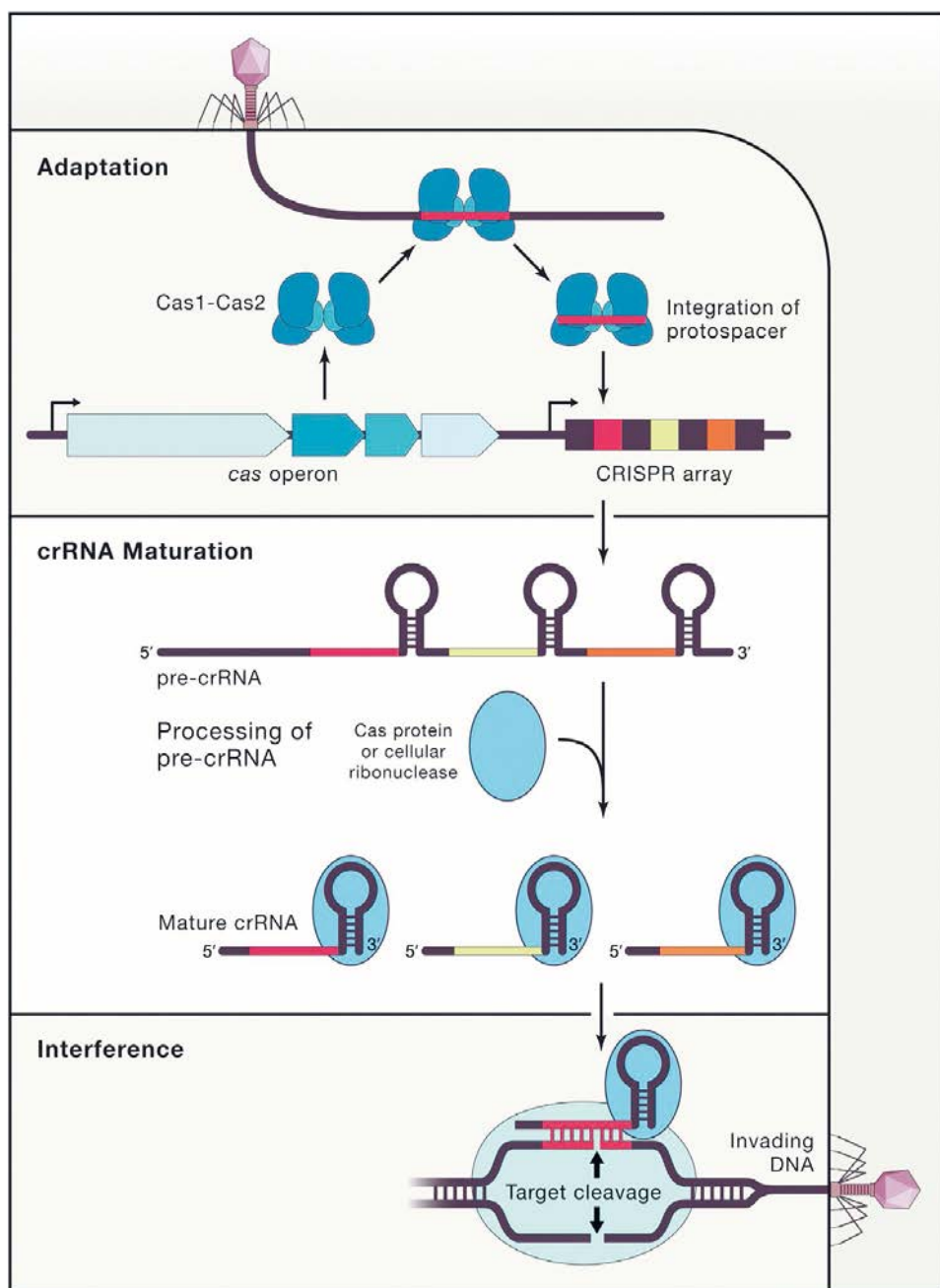
The discovery of the CRISPR/Cas9 technology is also a fascinating story about the importance of fundamental science and the freedom of research. It goes back to the Spanish scientist Francisco Mojica who found unusual sequence repeats in the genome of salt-resistant microbes in the early 1990s. These repeats from which the CRISPR/Cas9 RNA is derived gave rise to the acronym CRISPR, which stands for Clustered Regularly Interspaced Palindromic Repeats. Only in 2005 he found that the repeats contain short sequence stretches from viruses or other invaders of microbes. He concluded that the CRISPR locus encodes a new adaptive immune system for microbes that can, similar to the human immune system, be trained by previous infections. In the following years this idea was confirmed by discoveries of a growing number of groups in this field. The rich branch of CRISPR biology developed and revealed that microbes and invaders use highly complex mechanisms to defeat each other, while constantly changing their weapons in coevolutionary arms races.

The CRISPR/Cas9 genetic scissors are one of many other players within natural CRISPR systems. It is a technology that will have major impacts on biotechnology and health care in future. Whether it will improve our lives or introduce unwanted implications remains to be seen. Like with any new technology, promises and risks need to be carefully balanced as exemplified by the discussions around

reported genetic modifications of human embryos.

**The EPS and EPN would like to congratulate Emmanuelle Charpentier and Jennifer A. Doudna on the award of the 2020 Nobel Prize for Chemistry. ■**

■ **Ralf Seidel,**  
Member of the EPS Division  
of Physics of Life Sciences



▲ A general scheme for the function of the CRISPR-Cas adaptive immune system. Step 1: *Adaptation*: Short fragments of double-stranded DNA from a virus or plasmid are incorporated into the CRISPR array on host DNA. Step 2: *crRNA Maturation*: Pre-crRNA are produced by transcription and then further processed into smaller crRNAs. Step 3: *Interference*: Cleavage is initiated when crRNA recognise and specifically base-pair with a region on incoming plasmid or virus DNA. Picture taken from <https://www.nobelprize.org/uploads/2020/10/advanced-chemistryprize2020.pdf>.

## The foundation of the EPS in 1968: a case of science diplomacy

**Amid social and political unrest, on September 26, 1968, sixty-two physicists gathered in Geneva to found the European Physical Society (EPS). Among them the representatives of the national physical societies of eighteen countries of both Eastern and Western Europe. At the time, EPS was one of the first international scientific institutions that were specifically European and at the same time transcended the Cold War political divide. It was founded at a dramatic historical moment: only one month after the armed invasion of Czechoslovakia by five countries of the Warsaw Pact.**

The recent surge of interest in science diplomacy suggests a new historical perspective to analyse the foundation of the EPS focusing on the interconnections between science and politics within the broader contexts of the Cold War and European integration. That the EPS was supposed to have a political function in international relations was emphasised in the public discourse by the main promoter of the society, Italian physicist Gilberto Bernardini (1906-1995), who became the first EPS president. Bernardini described the EPS as a contribution to the realisation of the “cultural unity” of Europe, and, in this way, to the political unification of all Europe, understood as “a single highly civilised nation.” Taking this political ambition seriously, the foundation of the EPS can be interpreted as a case of science diplomacy where one intends the promotion of international scientific cooperation as a tool to indirectly condition international relations.

The analysis of archival materials of Bernardini and other protagonists in the establishment of the EPS has made it possible to elucidate how the involved physicists came to interpret their role as diplomats amidst particularly turbulent reconfigurations of international political relations. In the mid-1960s, the political ideal of a culturally unified Europe—promoted by supporters of Western European federalism—intertwined with the socio-professional interests of a specific physics community strongly involved with CERN. This interplay established

the idea of physics as a diplomatic tool in the construction of Europe, and this idea became so widespread to lead to the successful proposal of a brand new society. A few weeks before the establishment of the EPS, however, the invasion of Czechoslovakia led many of the Western physicists involved in this process to reframe the role of the society as a tool to diffuse liberal-democratic values, especially in support of physicists who were becoming political dissidents in Eastern Europe. This view of the EPS was actually realised in the early years after its foundation when the society became a translational network that supported Czech physicist František Janouch, who was suffering political discrimination in his home country since 1970. Following pressures

by the EPS, Janouch was allowed to leave Czechoslovakia in 1973 and to accept a permanent position in Sweden, also secured by EPS officials. This development had political consequences: in Sweden Janouch founded the Foundation Charter 77 to provide financial support to the principal opposition group in Czechoslovakia in the latter years of the communist rule.

▼ Participants at the Meeting on European Collaboration in Physics, held in Pisa on April 16-17, 1966. The meeting was a crucial step in the foundation of the EPS. Courtesy Centro Archivistico Scuola Normale Superiore.

### For more information:

Lalli, R. “Crafting Europe from CERN to Dubna: Physics as diplomacy in the foundation of the European Physical Society,” *Centaurus*, <https://doi.org/10.1111/1600-0498.12304> ■

■ R. Lalli,

*Max-Planck-Institut für  
Wissenschaftsgeschichte, Berlin*



## In memoriam, Robert Pick

**Robert Pick, Professor Emeritus at Université Pierre et Marie Curie, passed away on July 28, 2020, at age 87.**

After graduating from the “*École Normale Supérieure*” (ENS Ulm, 1953-7), Robert began his research career at “*Commissariat à l’Energie Atomique*” (CEA Saclay) where he obtained his PhD in 1965, with Jacques Friedel as advisor. He then became Professor at Université Pierre-et-Marie Curie. His major domain of interest was the dynamics of Condensed Matter, mainly studied by spectroscopic approach. In this field he collaborated with the best theoreticians of condensed matter and launched many experimental projects. His work spanned the dynamics of several CM systems, like incommensurable and superionic crystals, molecular crystal plastic phases and vitreous transition, using light scattering. His research was carried out in the “*Département de Recherches Physiques*”, that he led for several years, and later in the “*Institut de Minéralogie, de Physique des Matériaux et de Cosmologie*” (IMPMC). R. Pick was also vice-Director of the “*European Laboratory for Nonlinear Spectroscopy*” (LENS, Florence) for several years.

His activity at EPS started in 1991 when he was elected to the CMD board and stayed until 2000. At that time Maurice Jacob was EPS President (1991-3). They knew each other well from their common studies at ENS Ulm. At the time there was the fear that the US “*Gordon Conferences*” would invade Europe and control the workshop activities in Europe. M. Jacob asked R. Pick to enter the EPS Conference Committee and develop a reply to this impending

threat. He chaired this committee from 1993 and built up strong links with the European Science Foundation (ESF Strasbourg) - which was launching the European Research Conferences (ERC) programme - in order to include physics in it. He made many contributions to the EPS conference programme, introducing the concept of “*Europhysics Conference*” (*i.e.*, organised by EPS Divisions & Groups), distinguishing them from EPS-sponsored conferences (where the main organiser is outside EPS).



EPS Divisions & Groups were asked to nominate one representative in the committee. He also established a funding programme (“*Young Physicists Fund*”) for the participation of young physicists (PhD students/Post-Docs) to those conferences. At the time I was myself EPS President, we built a European network of Physics Summer Schools which was funded once by the European Commission (2003) – but the EC refused to perpetuate it.

During all that time, Robert Pick regularly attended the EPS council where he was very proactive, often intervening in the debates and always with his bright and malicious eyes. He resigned from the EPS Conference Committee in 2003, but continued as interim co-chair up to 2005. During all these years, he never ceased to be a truly European Scientist, fully engaged with EPS. He was elected EPS Fellow in 2006.

We will miss Robert, his communicative enthusiasm, his permanent good mood and kindness. ■

■ **Martial Ducloy**

*EPS past-president (2001-2003)*

# Zeptoseconds: new world record in short time measurement

Atomic physicists from Goethe University Frankfurt together with colleagues at the accelerator facility DESY in Hamburg and the Fritz-Haber-Institute in Berlin, have measured the time that a photon takes to cross a hydrogen molecule: about 247 zeptoseconds for the average bond length of the molecule. It is the shortest timespan that has been measured to date.

The team of Reinhard Dörner, professor at the Goethe University Frankfurt, Germany, used the technique of photoionisation, a fundamental process in light-matter interaction, in which the absorption of a photon leads to the ejection of an electron and the formation of an anion. The technique is a powerful tool to study atoms, molecules, liquids, and solids. Timing in photoionisation usually refers to the time it takes for the electron to escape to the continuum after absorption of the photon. Recently, the team observed a time-difference between electron emissions from the two sides of molecular hydrogen. In a publication in *Science*, the team reports a measured time difference of 247 zeptoseconds between electron emissions from the two sides of molecular hydrogen [1].

For the measurement, the team irradiated hydrogen molecules with 800 eV photons. The energy was chosen such that one photon could eject both electrons out of the hydrogen molecule. During the measurement, the team varied the orientation of the molecular frame of reference with respect to the photon propagation direction and studied the changes in the electron interference pattern. From this, they could calculate the delay between the birth time of the electrons. The measurement was performed using X-rays from the synchrotron light source PETRA III at the accelerator centre DESY in Hamburg. The interference pattern of the first ejected electron was measured using a COLTRIMS reaction microscope [2]. Such a microscope

makes use of an imaging technique to measure the fragmentation of a few body system and thus makes ultrafast reaction processes in atoms and molecules visible. Simultaneously with the interference pattern, the COLTRIMS reaction microscope also allowed for measuring the orientation of the hydrogen molecule.

"Since we knew the spatial orientation of the hydrogen molecule, we used the interference of the two electron waves to precisely calculate when the photon reached the first and when it reached the second hydrogen atom," explains Sven Grundmann whose doctoral dissertation forms the basis of the scientific article in *Science*. "And this is up to 247 zeptoseconds, depending on how far apart in the molecule the two atoms were

from the perspective of light."

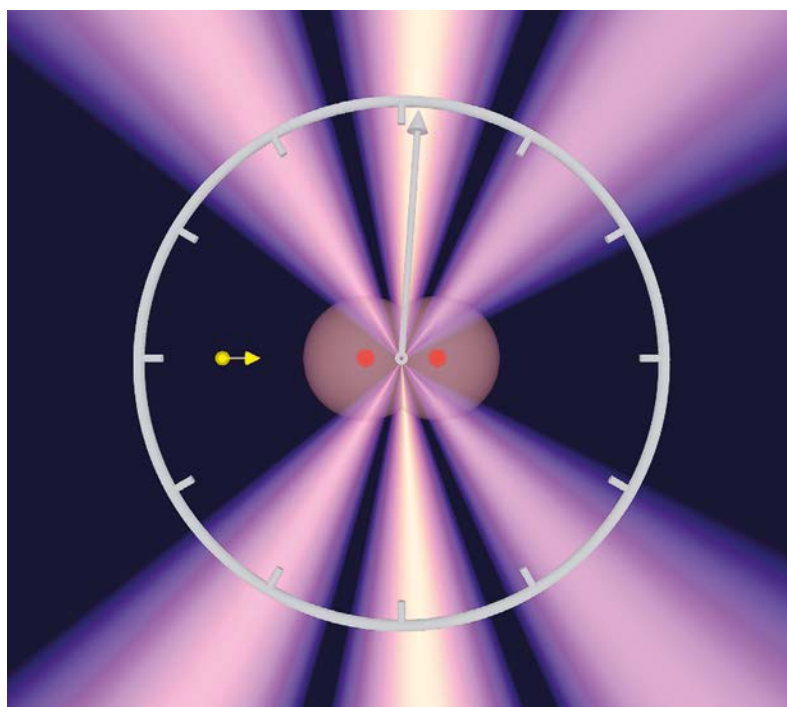
Professor Reinhard Dörner adds: "We observed for the first time that the electron shell in a molecule does not react to light everywhere at the same time. The time delay occurs because information within the molecule only spreads at the speed of light. With this finding we have extended our COLTRIMS technology to another application." ■

■ **Els de Wolf,**  
*EPN Editor*

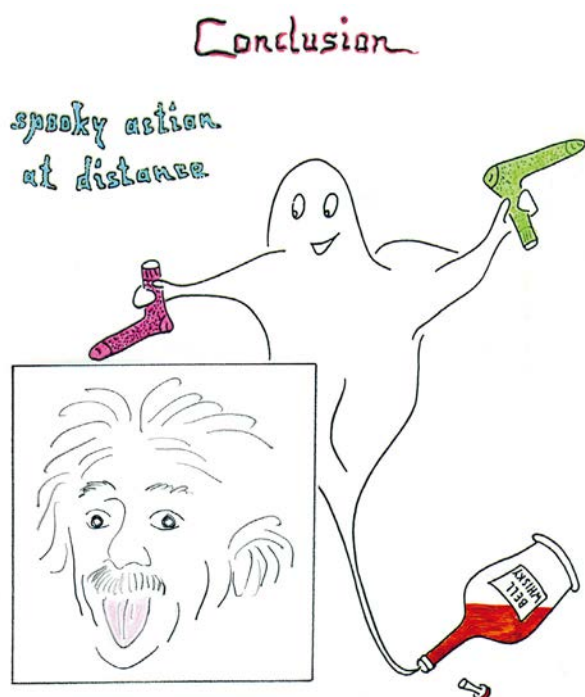
## References

- [1] Sven Grundmann *et al.*, *Science* **370** (6514), 33 (2020), DOI: 10.1126/science.abb9318  
[2] J. Ullrich *et al.*, *Rep. Prog. Phys.* **66**, 1463 (2003)

► Schematic representation of zeptosecond measurement. The photon (yellow, coming from the left) produces electron waves out of the electron cloud (grey) of the hydrogen molecule (red: nucleus), which interfere with each other (interference pattern: violet-white). The interference pattern is slightly skewed to the right, allowing the calculation of how long the photon required to get from one atom to the next. Photo: Sven Grundmann, Goethe University Frankfurt



# Highlights from European journals



▲ Spooky action at a distance: Bell's Theorem in sketch form (Figure 12 in the paper). Credit: Reinhold Bertlmann (1988). Original presented to Bell on the occasion of his 60<sup>th</sup> birthday by R. Bertlmann

## HISTORY

### A question of reality

**John Stewart Bell's eponymous theorem and inequalities set out, mathematically, the contrast between quantum mechanical theories and local realism. They are used in quantum information, which has evolving applications in security, cryptography and quantum computing.**

The distinguished quantum physicist John Stewart Bell (1928-1990) is best known for the eponymous theorem that proved current understanding of quantum mechanics to be incompatible with local hidden variable theories. Thirty years after his death, his long-standing collaborator Reinhold Bertlmann of the University of Vienna, Austria, has reviewed his thinking in a paper for EPJ H, 'Real or Not Real: That is the question'. In this historical and personal account, Bertlmann aims to introduce his readers to Bell's concepts of reality and contrast them with some of his own ideas of virtuality. ■

■ **R. Bertlmann,**

'Real or Not Real: that is the question', *Eur. Phys. J. H.* (2020), DOI 10.1140/epjh/e2020-10022-x

## APPLIED PHYSICS

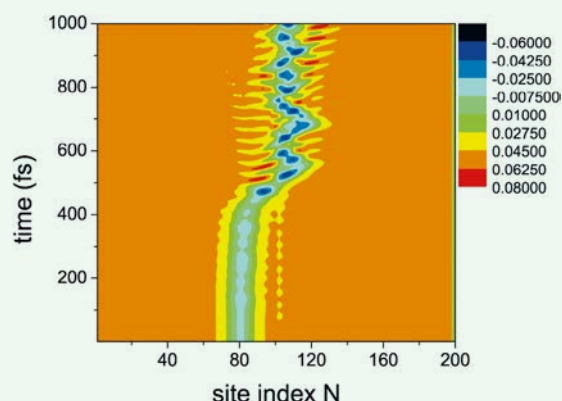
### Impurities enhance polymer LED efficiencies

**Molecular dynamics simulations have shown that the mysteriously high efficiency of polymer LEDs arises from interactions between triplet excitons in their polymer chains, and unpaired electrons in their molecular impurities.**

Polymer LEDs (PLEDs) are devices containing single layers of luminescent polymers, sandwiched between two metal electrodes. They produce light as the metal layers inject electrons and holes into the polymer, creating distortions which can combine to form two different types of electron-hole pair: either light-emitting 'singlets', or a non-emitting 'triplets'. Previous theories have suggested that the ratio between these two types should be around 1:3, which would produce a light emission efficiency of 25%. However, subsequent experiments showed that the real value can be as high as 83%. We found that this higher-than-expected efficiency can be reached through interactions between triplet excitons, and impurities embedded in the polymer. ■

■ **Y. D. Wang, J. J. Liu, Y. X. Liu, X. R. Wang, Y. Meng,**

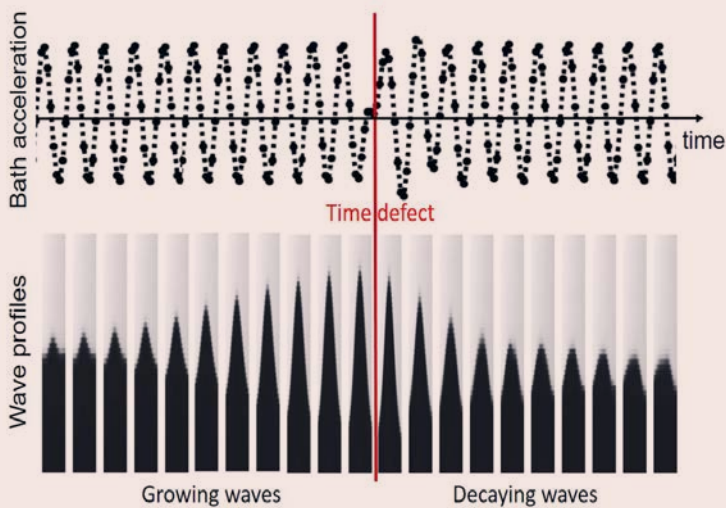
Dynamic Recombination of Triplet Exciton with Trapped Counterion in Conjugated Polymers, *Eur. Phys. J. B* (2020) 93, 173 B 93:173, DOI: 10.1140/epjb/e2020-10310-4



▲ PLED polymers evolve characteristically during operation

CONDENSED MATTER

# Effects of time defects in modulated systems



▲ Waves localised around the time defect

The spatial periodicity in crystals induces energy band-gaps. Similarly, time-modulated systems possess momentum band-gaps. Is there a temporal analogue to the localised edge modes induced by topological defects in spatial crystals?

We show that in a vertically vibrated liquid with a pi-shift in the excitation as a time defect, waves grow exponentially before the defect and decay exponentially after. Because of causality and non-energy conservation, this apparent time localisation must, in fact, be interpreted as a permutation of band-gap modes. However, as such, time defects provide an original way to explore these gaps. ■

■ G. d’Hardemare, A. Eddi and E. Fort, *EPL* 131, 24007 (2020), DOI: 10.1209/0295-5075/131/24007

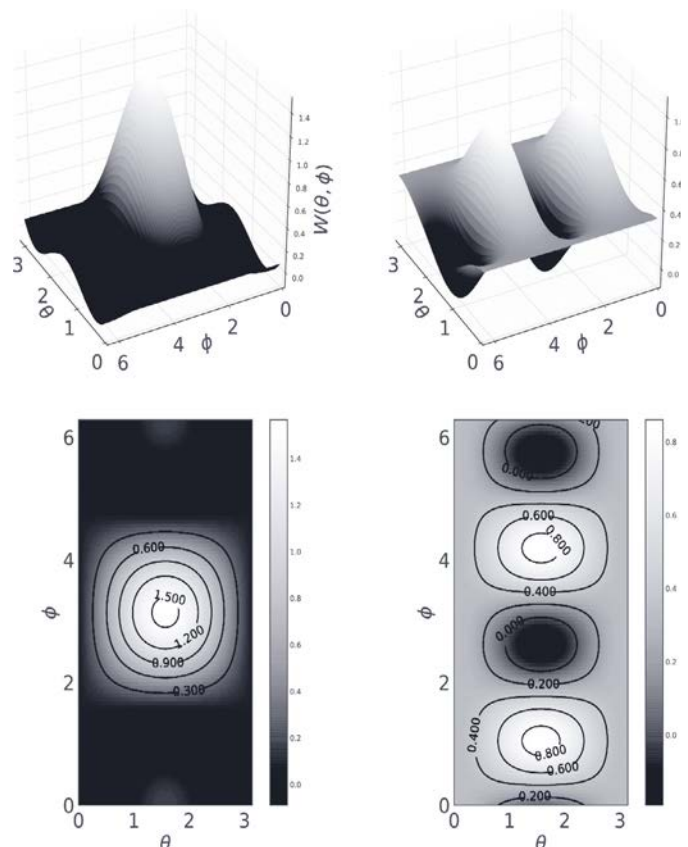
QUANTUM MECHANICS

# Avoiding environmental losses in quantum information systems

Through new techniques for generating ‘exceptional points’ in quantum information systems, researchers have minimised the transitions through which they lose information to their surrounding environments.

Recently, researchers have begun to exploit the effects of quantum mechanics to process information in some fascinating new ways. One of the main challenges faced by these efforts is that systems can easily lose their quantum information as they interact with particles in their surrounding environments. To understand this behaviour, researchers in the past have used advanced models to observe how systems can spontaneously evolve into different states over time – losing their quantum information in the process. We have discovered how robust initial states can be prepared in quantum information systems, avoiding any unwanted transitions extensive time periods. ■

■ R. Ramírez, M. Reboiro, D. Tielas, ‘Exceptional Points from the Hamiltonian of a hybrid physical system: Squeezing and anti-Squeezing’, *Eur. Phys. J. D* 74, 193 (2020), DOI: 10.1140/epjd/e2020-10218-1



▲ Transitioning states in diamond imperfections



## SUBMIT YOUR BOOK PROPOSAL

You have a scientific project  
(Physics, mathematics, Chemistry, biology ...)

In **English** or **French** language

Send a CV, Synopsis and table of contents to:

France Citrini - Head of Books Department  
france.citrini@edpsciences.org



edp sciences

Do you do **MBS**  
**ARPES** measurements?  
Analyse the **Spin** components?

Our state of the art ARPES System with  
**3D ARPES mapping**

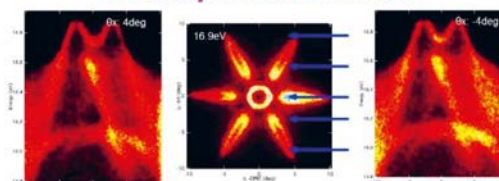
**MBS A-1SYS + L4 lens\***

(\*: Patented by MB Scientific AB : US 9,997,346 B1, SE 539849, JP 3173552.)

ARPES System with **3D VLEED Spin Detector**

**MBS A-1SYS + MBS 3D-VLEED**

Gives you the results!



For more detailed information please contact us!

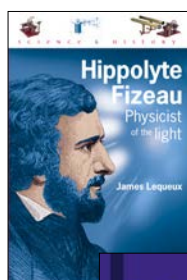
**MB SCIENTIFIC AB**

Address: Fålhagsleden 61, SE-753 23, Uppsala, SWEDEN

Tel: +46 18 290960, Fax: +46 18 572683

e-mail: [info@mbscientific.se](mailto:info@mbscientific.se) Homepage: [mbscientific.se](http://mbscientific.se)

bookstore  
edp sciences

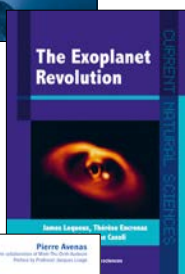


### Hippolyte Fizeau - Physicist of the light

James Lequeux

July 2020 – 148 p. - 29 €

The French physicist Hippolyte Fizeau was the first to directly measure the speed of light in 1849. He discovered the wavelength shift produced by the relative speed of a light or sound source and an independent Doppler observer, and many other discoveries ... This book is the very first devoted to the scientific work of this great physicist.

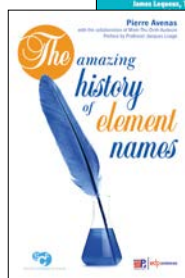


### The Exoplanets Revolution

James Lequeux, Thérèse Encrenaz and Fabienne Casoli

July 2020 – 204 p. color. - 39 €

More than 4300 planets around nearby stars! Who could have imagined this extraordinary harvest only thirty years ago? This book gives a comprehensive vision of this complex and fascinating area of research, presented in a simple and lively way.



### The Amazing History of Element Names

Pierre Avenas With the contribution of Minh-Thu Dinh-Audouin

October 2020 – 272 p. color – 19 €

This book tells the stories behind the naming of the elements, whether they are chemical elements of the Periodic Table, first published by Mendeleev in 1869, or organic elements which are components of DNA and RNA, as well as proteins, themselves elements of living kingdom, plants and animals. The book goes further, into materials and products which became essential elements of modern life.

Order your copy from [bookstore.edpsciences.com](http://bookstore.edpsciences.com)



## Social Engagement, Connections and Growth: How Young Minds shapes the physicists of the future

■ Mattia Ostinato, Carmen Martin, Richard Zeltner and Hripsime Mkrtchyan

The Young Minds (YM) programme of the European Physical Society (EPS) was initiated 10 years ago, with the goal to connect young students and researchers all over Europe and to support their professional and personal growth. The programme now comprises more than 60 sections being active in over 30 countries. In the previous issue of *Europhysics News*, we have asked YM Alumni how the programme affected their career, revealing that the vast majority of them consider engagement in the YM programme as strongly beneficial [1]. In a follow-up survey, we now approached current members of the programme and asked them whether and how they benefit from their engagement in YM.

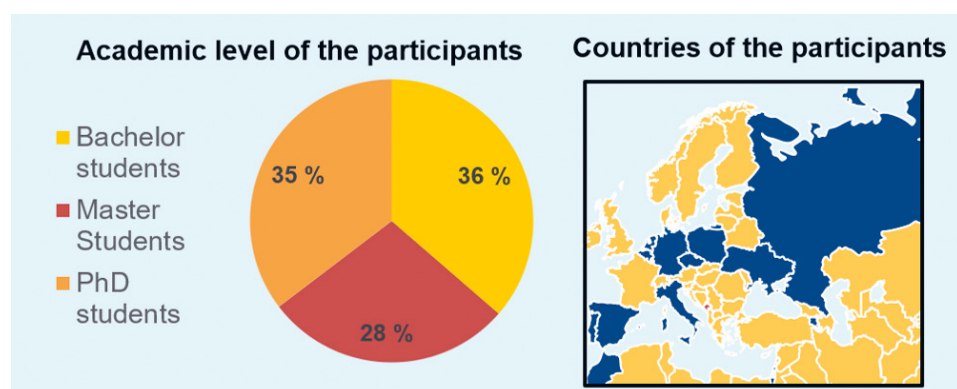
As shown in Figure 1 we have received and evaluated responses from 18 different sections operating in 13 countries distributed from North Africa over central Europe to the Caucasian regions. Most of the participants, approximately 57%, have been engaged with Young Minds for 1 to 3 years. About 36% of the participants are bachelor students, 28% are in their masters and the remaining participants are currently conducting their doctoral studies. Strongly aligned with the findings of the alumni-survey [1] this distribution indicates that local YM sections have a clear appeal for younger students. Strikingly, again aligned with the findings presented in [1], 65% of the

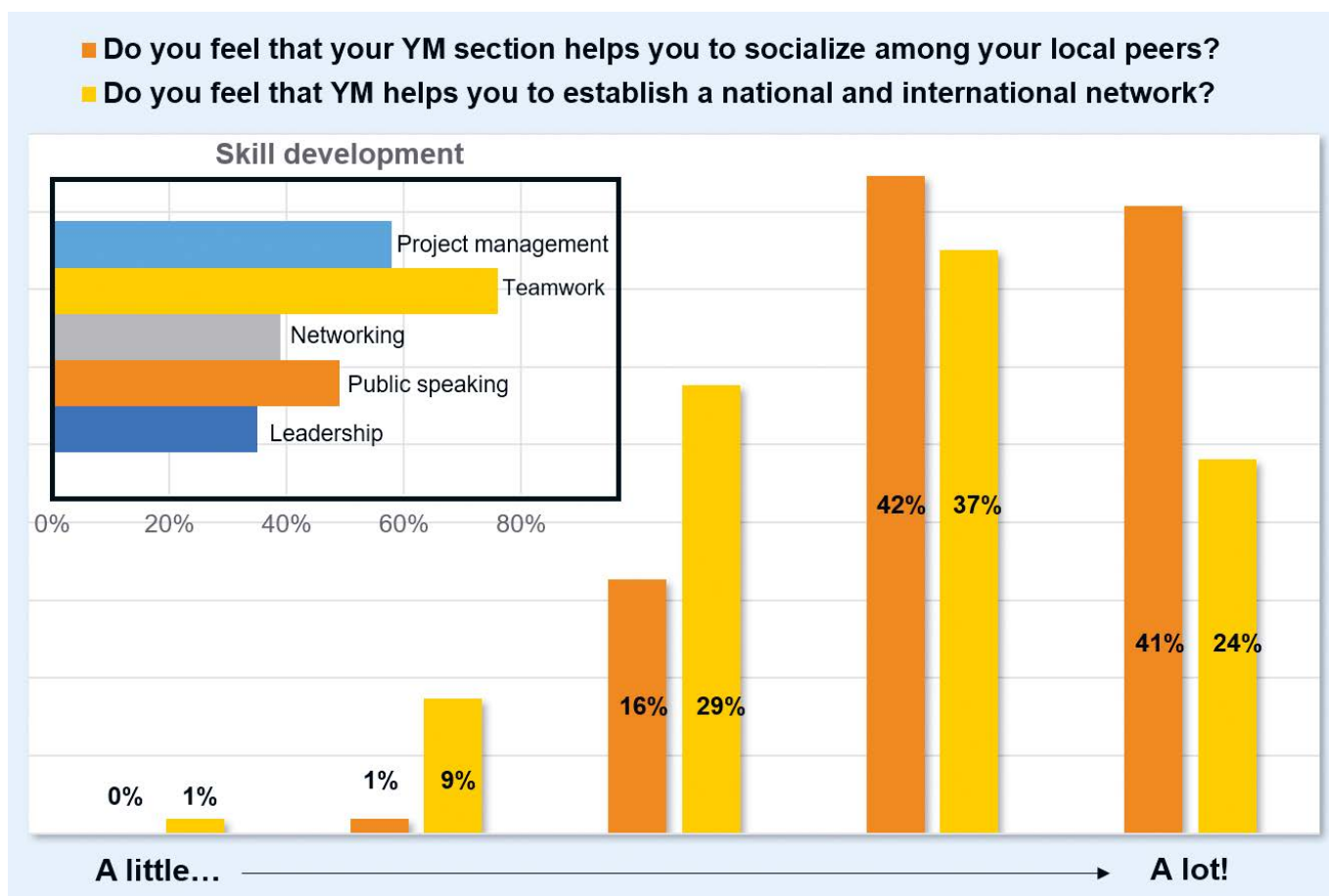
current YM members are convinced that the programme increases their engagement with their national physical society, and, as shown in Figure 2, about 60% report that YM helps them to build a national and international network. This shows that now, 10 years after its birth, the YM programme plays a pivotal role in fostering national and international cooperation, as well as connection and communication between young students. Moreover, while the main ambition of YM is international connection, it seems that the programme plays a major role in bringing students together on the local and regional level as well: more than 80% of the participants reported that their YM section helps to socialise with

local peers. Considering the large number of creative networking and social events that are hosted by sections all over Europe each year, this number is not surprising. What is surprising, though, is that more senior students, e.g. master students and doctoral candidates, report a stronger benefit on their social connection than bachelor students. A possible explanation could be the following: as many young people choose to study at an institution in or close to their hometown, they keep their social network established during childhood and school when entering this new phase of life, such that there is not always a strong need to create new connections. In contrast, the number of students who move to another town or even country after their bachelor's exam is possibly much larger. In the weeks and months after such a move there is unavoidably a lack of social network and a need to connect, which, seemingly, YM can help to ease.

From the survey, it also became clear that outreach is most popular among the YM members: around 68% of the participants listed it when being asked about the type of activity they enjoyed most. While it has

▼ Left: The participants of the survey comprised mainly younger students in Bachelor and Master studies. Right: We received and evaluated responses from 18 sections located in 13 different countries, given in dark blue.





been recognised in [1] that outreach can be a valuable experience and a great way to improve one's communication skills, the current survey adds another possible reason why outreach is so popular: 78% of the participants are convinced that YM makes an important contribution to raising the awareness of science among the public. In this broader picture doing outreach, *e.g.* by giving a talk at a school or explaining an experiment at a science fair, is not only something that makes fun and helps to develop as an individual, but rather an act that contributes to the society, giving deeper meaning to the activity and purpose to those who practice it. In this context it is also worth mentioning that about 80% of the members believe that their activity within YM helps them to engage with the scientific community, *e.g.* by the organisation of scientific talks or conferences. As the techniques and standards of scientific work are often introduced rather late in the

▲ YM connects young people on the local, national and international. Inset: YM fosters the development of various skills among the students participating in it.

academic curriculum, such early interaction with the scientific community is not only helpful when giving outreach, but also eases the transition from the lecture hall to the laboratory.

With outreach being the most favoured activity of YM members it is not too surprising that about 49% reported that engagement within YM positively affects their public speaking skills. Other skills that seem to benefit are teamwork (72%), project management (55%), networking skills (39%) and leadership skills (35%). These numbers underline the positive effects that engagement in a YM section have, helping young students to foster skills in these aspects of professional life, which are usually only merely developed in their academic education yet fundamental both inside and outside academia.

In conclusion, the survey revealed that the ideas and visions of the founders of YM are vividly embraced by the current generation engaged in the project: the programme does not

only support students in the development of a critical skillset, *e.g.* teamwork and networking skills, and to integrate in the connected European scientific community, but it also provides a platform to actually create social and professional networks on various levels. Moreover, the most delighting finding of the survey is perhaps that the students consider their activities within YM not only a means to individual growth but rather as an important contribution to increasing the contact and exchange between science and society, which has never been more important than now. In this sense we are looking forward to the next 10 years of YM and are convinced that the programme will continue to bring young people together and to bring science closer to the public – all over Europe. ■

## References

- [1] R. Caruso, R. Zeltner, A. Marino, *Europhysics News* 51/4, 10 (2020)

by Cécile Sykes

CNRS research director, Institut Curie, France – DOI: <https://doi.org/10.1051/epn/2020501>

## Living Soft Matter Physics : active protein networks govern cell shape changes

A living cell contains flexible, semi-flexible and stiff filaments, forming the cell skeleton, called the cytoskeleton, the detail of which is described in Simon Idema's article. How does this filamentous network rearrange to drive cell shape changes to achieve cell functions such as division and motility?

With the metaphor of a spaghetti bowl, the force you need to apply when tossing with your spoon depends on spaghetti (or filament) density, how much they are cooked (their flexibility), and how they stick together. In particular, cells or cell assemblies are *elastic*, especially at short time scales: when deformed, they recover their initial shape. Pinch your cheek for a few seconds, it will go back. However, at longer time scales, over minutes, days, years, cells can flow: they are *viscous*. Look at your elbow skin and compare it with a baby one: it has flown.

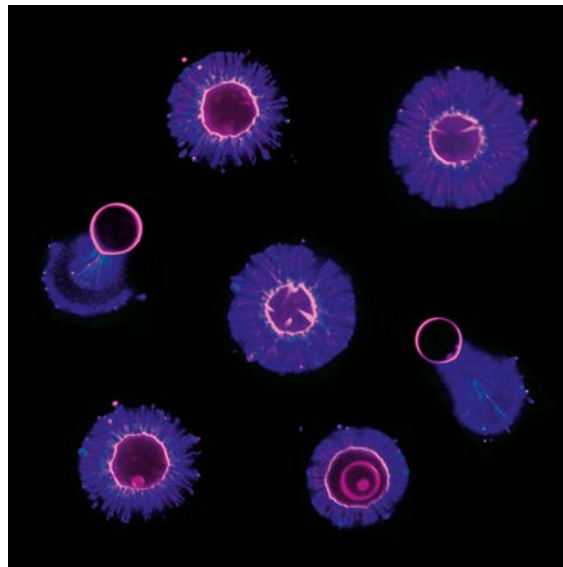
Unlike macromolecular polymer networks (or a spaghetti bowl), living matter is *alive*, consumes chemical energy through hydrolysis of adenosine triphosphate. Proteins in the cytoskeletal network assemble, slide, or change conformation, therefore complexifying the simple picture of passive elasticity and viscosity. These cytoskeletal networks are able to actively deform a membrane, and drive cell shape changes.

The cell membrane separates the cell content from the outside and has a bending energy that amounts to a few dozen times the thermal energy, it is soft and deformable therefore fluctuate at room (or body) temperature. Underneath the cell membrane lies a network of branched and entangled protein

filaments (Blanchoin *et al.*, 2014). Actin filaments have the peculiar property that their growth is activated at the membrane through the formation of new branches in the network.

"Simplicity is complexity resolved" is a quote from the famous sculptor Constantin Brancusi. Likewise, physicists try to make things simple, as a cell is a complex system. Stripped-down experimental systems were developed that reconstitute cell functions with purified components. Whereas one single filament would simply push by growing against the mem-

brane, strikingly, the complex growth of a branched network generates both inward and outward membrane deformations, which is an extraordinary property of these networks. This push or pull depend on the detailed organisation of the network, the growth velocity of their filaments, and membrane tension, as supported by models based either on reaction kinetics or cooperative properties of actin networks (Dürre *et al.*, 2018; Simon *et al.*, 2019). Further modeling, inspired by these controlled experiments, will help to decipher how cells control their membrane deformations for various functions, from virus uptake to cell motility which dysfunction leads to various diseases. ■



▲ Liposomes (membrane marked in pink) on the surface of which the polymerisation of actin is activated and generates the growth of a branched network of actin (purple marks filament ends). Membrane tubes mimic the initiation of endocytosis in cells, and cone shapes mimic dendritic filopodia of neuronal cells. We can also observe actin "comets" propel liposomes and mimic actin-based propulsion of bacteria such as *Listeria monocytogenes*. Liposomes are between 10 and 20 microns in diameter.

### References

- [1] L. Blanchoin, R. Boujemaa-Paterski, C. Sykes and J. Plastino, *Physiol Rev.* **94**, 235 (2014).
- [2] K. Dürre, F.C. Keber, P. Bleicher, F. Brauns, C.J. Cyron, J. Faix and A.R. Bausch, *Nature Communications* **9**, 1630 (2018).
- [3] C. Simon, R. Kusters, V. Caorsi, A. Allard, M. Abou-Ghali, J. Manzi, A. Di Cicco, D. Lévy, M. Lenz, J.-F. Joanny, C. Campillo, J. Plastino, P. Sens and C. Sykes, *Nature Physics* (2019)

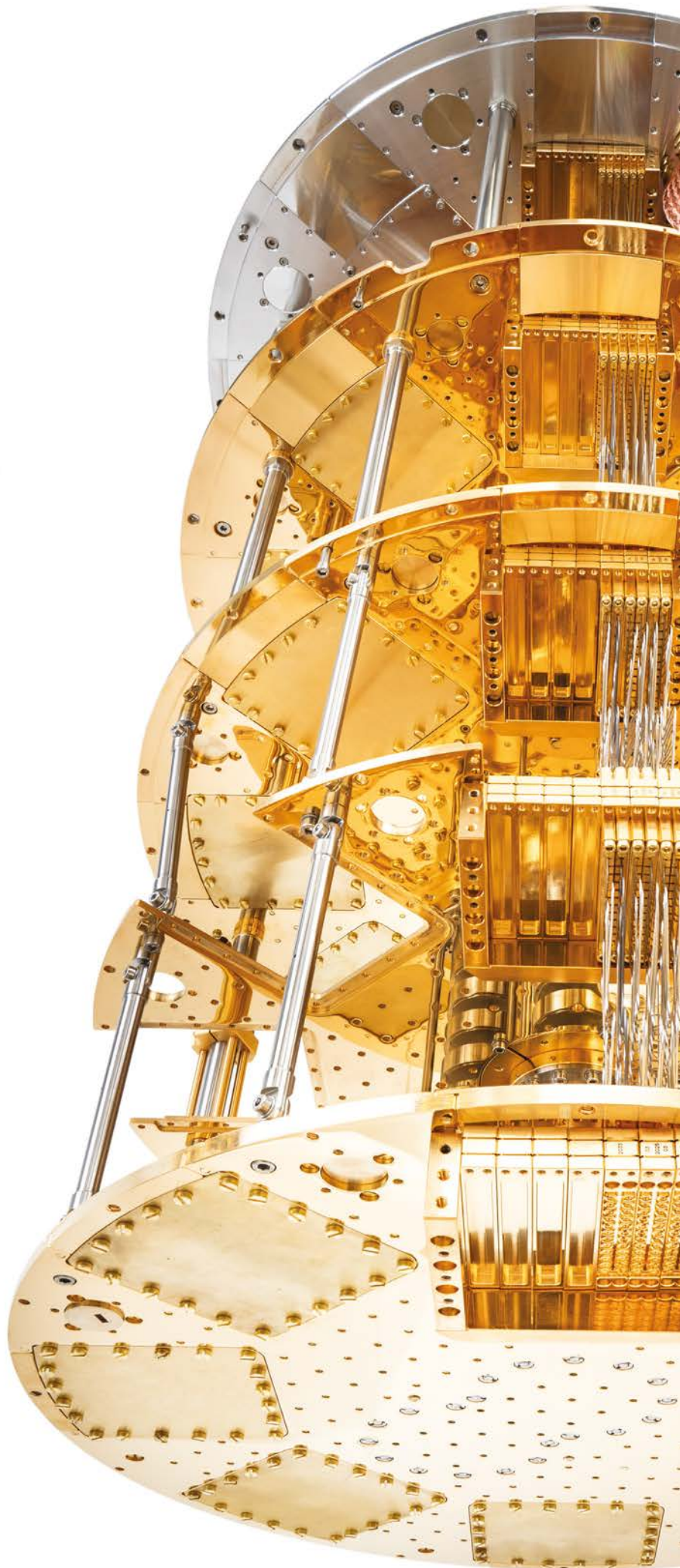
# Cool for Progress.

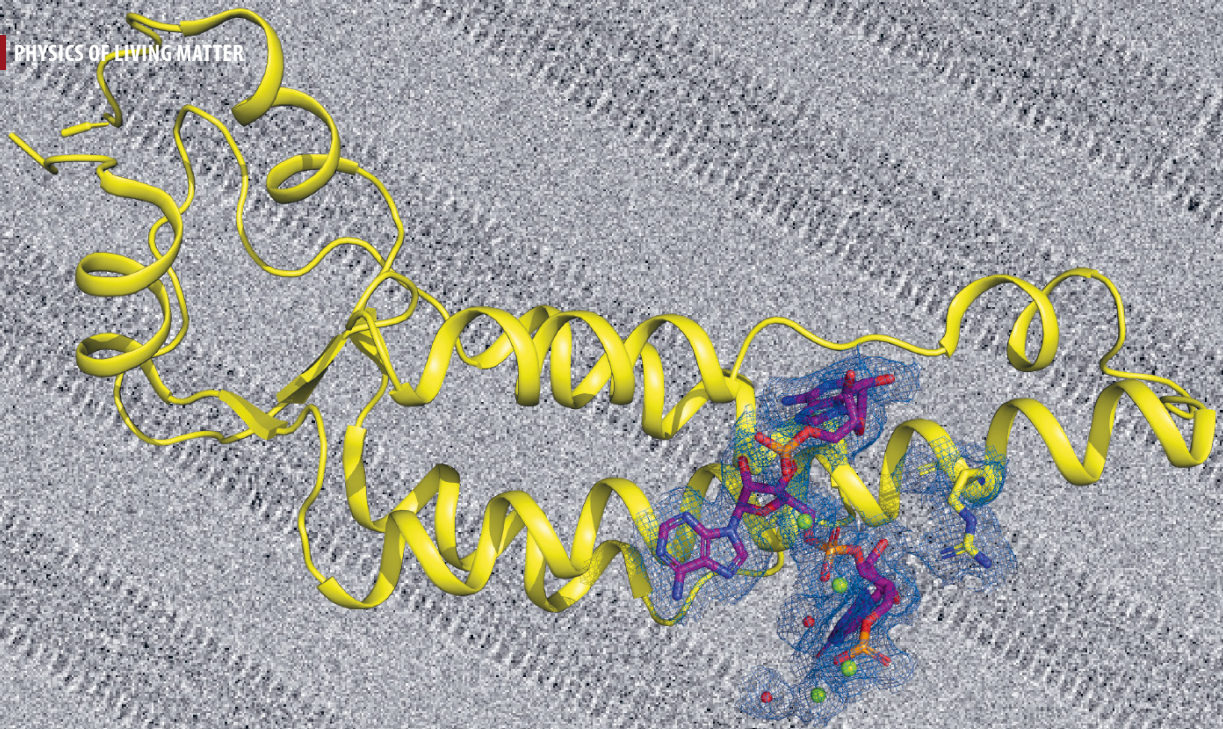
[BLUEFORS.COM](http://BLUEFORS.COM)

## High-density wiring

Our new high-density wiring is a modular option for the Bluefors side-loading XLDsl dilution refrigerator system that enables a large scale-up of the experimental wiring, especially for high-frequency signals. It is easy to install and to maintain.

**BLUE  
FORS**





# SEEING WITH ELECTRONS

■ Arjen J. Jakobi – <https://doi.org/10.1051/ejn/2020502>

■ Department of Bionanoscience, Kavli Institute of Nanoscience, Delft University of Technology, The Netherlands

**Transformative technological advances have propelled cryogenic electron microscopy (cryo-EM) to take center stage in elucidating the intricacies of the nanoscale molecular machinery of viruses, bacteria and eukaryotic cells. Continued developments hold exciting promise for structural biophysicists to move closer to their dream of visualising atomic resolution snapshots of individual molecules at work in their native cellular environment.**

**F**rom its invention in the 1930s by Ernst Ruska and colleagues, the electron microscope has provided biologists with a tool to visualise biological structures at resolutions beyond the limits set by the optical microscope. It has since become an indispensable instrument for determining the structure of biological materials of all kinds, and has greatly contributed to the description of cellular ultrastructure and the molecular machinery underlying cellular function. The central appeal of “seeing with electrons” is that once we can visualise the cellular machinery at a level that allows discerning the structures of its molecular components, we can describe it with the laws of chemistry and physics to answer how and why its molecular components work the way they do.

## Freezing water without forming ice

Despite the early successes, the application of electron microscopy in biology has long been limited by the nature of biological samples. The key issue is that electrons scatter strongly from air, which requires conducting the imaging experiment in a high vacuum. Biological materials, which naturally exist in a watery environment, must therefore be dried or otherwise fixated before they can be imaged. Modern three-dimensional (3D) electron microscopy as it is used today for visualising the architecture of biomolecular assemblies began with the introduction of a unique specimen preparation method by Jacques Dubochet and coworkers in the 1980s. Their method formed the basis for preserving biological molecules in solution while observing them in the electron

microscope [1]. This is achieved by cooling a thin liquid film containing the molecules so rapidly that the layer passes through its glass-transition temperature and forms an amorphous solid phase that is thought to largely preserve the native structure of water. This amorphous ice layer is maintained at liquid nitrogen temperatures during the imaging experiment, from which the technique lends its name: cryogenic electron microscopy, or *cryo-EM*. The molecules suspended in the ice layer are directly visualised by passing high-energy electrons through the sample and recording two-dimensional (2D) phase-contrast projection images on a suitable detector. The images provide rich information, but pose challenges to interpretation because they represent the superposition of the 3D structure onto a single plane.

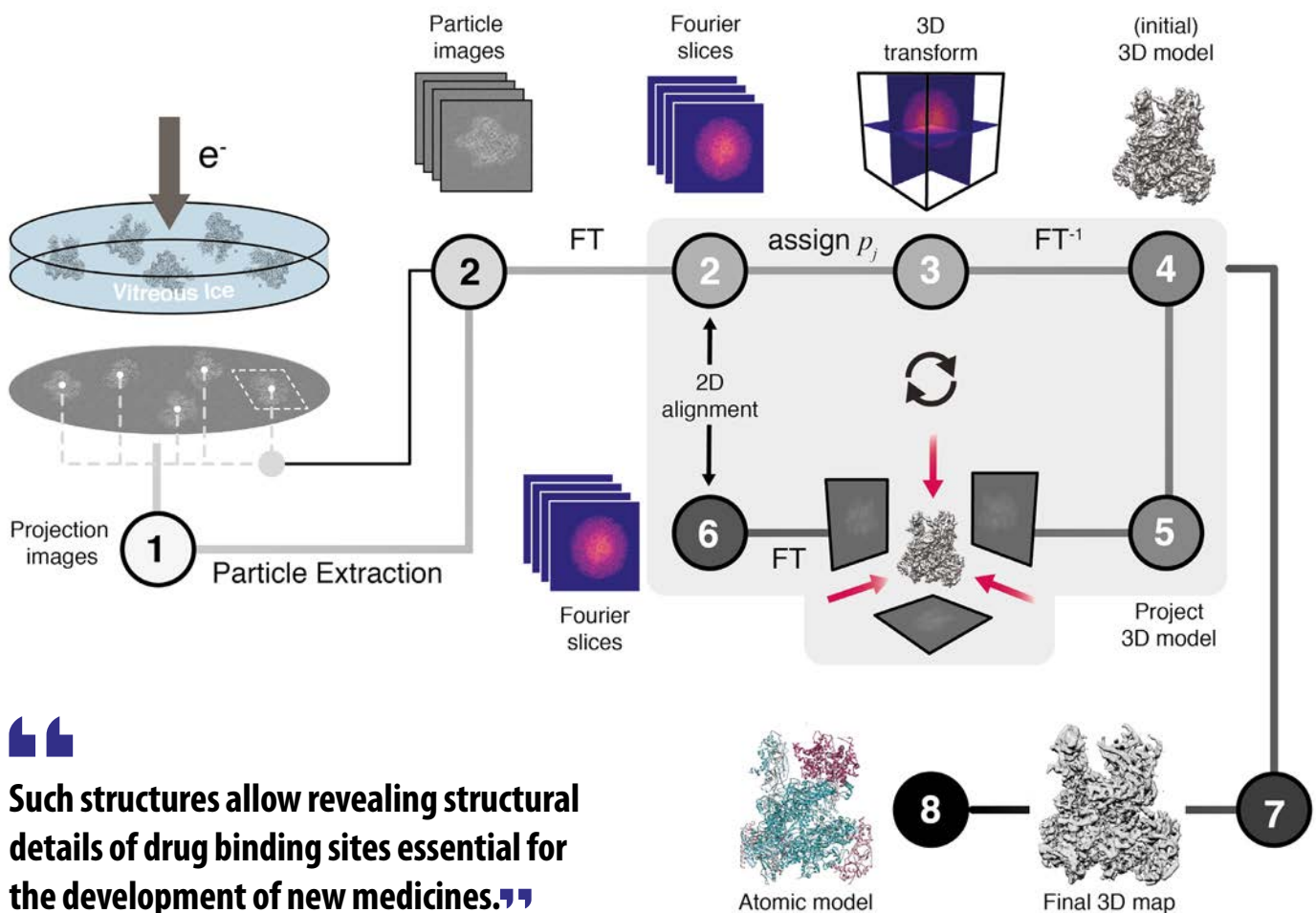
The central goal of cryo-EM is therefore to recover the 3D information by reconstructing a high-resolution estimate of the 3D electrostatic potential of the suspended biomolecules from a set of such images

(Figure 1). Its practical realisation is complicated by two compounding challenges: (1) The three-dimensional location and orientation of the molecules within the ice layer are random and unknown, and (2) the maximum tolerable dose for illumination is severely limited to prevent damage of the radiation-sensitive biological material by the high-energy electron beam. As a result, cryo-EM produces images with extremely poor contrast in which the power of the signal may be more than ten times smaller than the power of the noise. These conditions transform tasks such as the detection and alignment of particles, and the assignment of relative orientations into a formidable challenge. As a result, cryo-EM has long been restricted to the study of large and highly symmetric specimens that, based on their size and symmetry facilitated alignment and reconstruction.

### From blobology to atomic resolution

Due to the limited resolution caused by the poor image contrast, cryo-EM was long referred to as blobology by less

▼ **FIG. 1:** Structure determination by single-particle cryo-EM. A series of images corresponding to 2D projections of individual molecules are localised and extracted from a set of electron micrographs (1). The Fourier transform of each of these 2D projections (2) corresponds to a central section of the 3D transform originating from the 3D structure. Once all 2D transforms have been correctly placed by assigning their relative orientations (3), the original 3D structure can be reconstructed by the inverse Fourier transform leading to an initial 3D model (4). Simulated 2D projections can be generated from this model (5) and used to improve assignment of relative orientations of the original data in an iterative process (2-6) until the process converges (7). If resolution is sufficiently high the resulting estimate of the molecule's 3D electrostatic potential can be used to build an atomic model (8).



Such structures allow revealing structural details of drug binding sites essential for the development of new medicines. ▀▀



## The future looks bright for electron microscopy to help realise the biophysicists' dream to watch, learn and comprehend the inner workings of the molecular machinery in cells and at atomic detail.

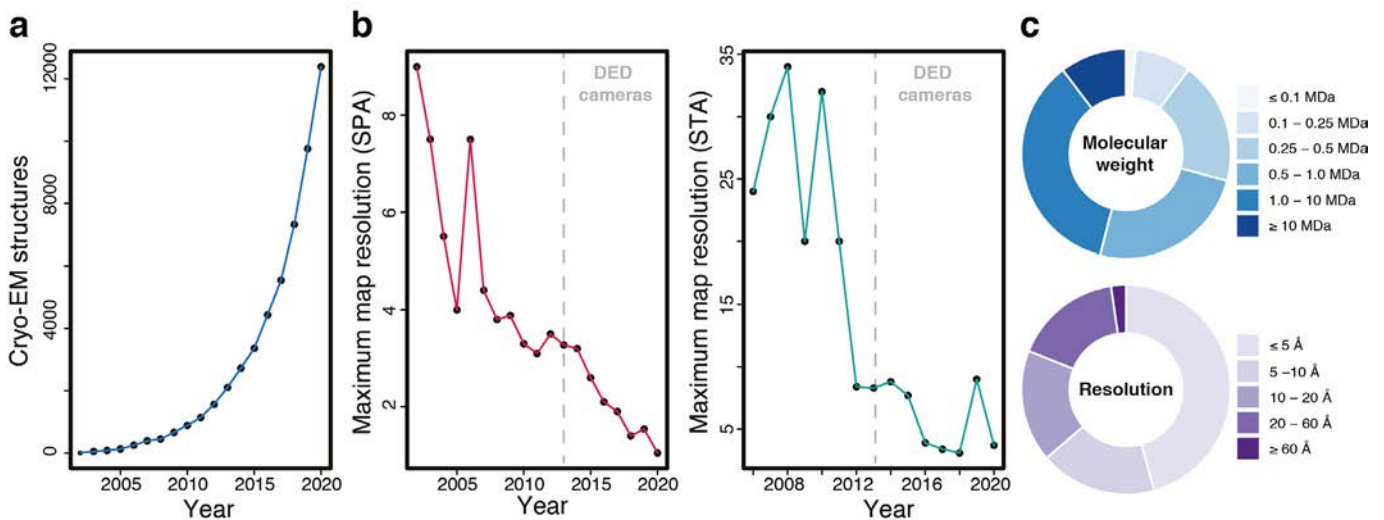
benevolent structural biologists. Unyieldingly, electron microscopists continued to push the development of their technique encouraged by the prediction that, theoretically, it should be able to reach atomic resolution once a number of technical challenges can be overcome [2]. True to this prediction, recent advances in instrumentation and software have led to spectacular improvements of the potential of cryo-EM to produce 3D structures of biomolecular complexes at atomic detail, a realm long reserved to other structural biology techniques such as X-ray crystallography and nuclear magnetic resonance (NMR). The advancement that propelled cryo-EM from “blobology” to a high-resolution technique was largely driven by the development of direct electron detection (DED) cameras based on complementary metal oxide semiconductor (CMOS) technology [3]. These cameras provided two key advantages: (1) they can convert charges of electrons striking the detector directly into signal without first converting the electron charge into photons in a phosphor scintillator as is the case for CCD cameras.

This allows localising the impinging electrons with much higher precision and together with lower read-out noise leads to dramatic improvements in image contrast. (2) Instead of recording a single image per exposure, the large frame rate of the DEDs allows the recording of “movies” which provides the possibility to correct for specimen movement due to drift or charging that lead to blurring of the image and hence loss of resolution.

The quality of a reconstruction also depends on the ability to discern different structural and compositional states of the target molecule(s) captured in the images, and the accuracy of image alignment (*i.e.* the assignment of orientations) of all particles used to reconstruct the 3D density map. The poor signal-to-noise ratio of cryo-EM images poses challenges to deterministic methods for particle alignment because individual particles provide insufficient contrast to allow the assignment of a unique orientation. This realisation has led to the development of probabilistic approaches that can account for such uncertainty by providing Bayesian, or maximum likelihood, estimates of orientation parameters, and proved more robust in classifying subsets of particle images with similar conformations out of a dataset containing many different structural states of the target molecule [3].

These advances have opened up the possibility to approach many challenging biological questions that were considered too difficult to be studied structurally only a few years ago. Foremost, the improved image contrast allows solving biomolecular structures of much lower molecular weight and symmetry than previously deemed possible. This has transitioned cryo-EM away from being a method applicable to only

**FIG. 2:** The cryo-EM “revolution” in numbers. (a) The cumulative number of 3D cryo-EM structures displayed as released entries at the Electron Microscopy Data Bank. (b) Maximum map resolution of cryo-EM structures from single-particle averaging (SPA, left) and sub-tomogram averaging (STA, right). The dashed grey line indicates the year in which DED cameras entered the field. (c) Distribution of molecular weight (top) and average map resolution (bottom) of all entries in the Electron Microscopy Data Bank.





a small subset of specimens to becoming the method of choice for structure determination of a large spectrum of proteins and macromolecular assemblies central to biology. Overall, it has led to an exponential increase in the number of biomolecular structures solved by cryo-EM. It has also opened up a race of solving structures to the highest possible resolution, the record currently held at  $\sim 1.2$  Å (Figure 2). This ambition is well-founded: such structures provide insight that can inform important mechanistic questions of enzymatic reactions, or allow revealing structural details of drug binding sites essential for the development of new medicines. Once such resolutions can be achieved reliably, cryo-EM may take a central role in pharmaceutical drug discovery.

### Beyond static structures

The goal of maximising resolution often comes with the effort to limiting the compositional and structural heterogeneity of the target molecule through biochemically stabilising or physically arresting a particular structural state. With respect to promoting our fundamental mechanistic understanding of biology this effort is unfortunate, as structural variability is often important for biological function and the ability to simultaneously image the full spectrum of functional states is a unique advantage that cryo-EM over other structural techniques. Fortunately, the success of probabilistic methods to efficiently sort structural heterogeneity has led electron microscopists to appreciate this rich information hidden in their data, and it is now common that many uniquely discernible structures are reported from a single cryo-EM experiment. Improvements in sample preparation methods can be expected to facilitate capturing these structural states and movements step-by-step as they interconvert, providing the opportunity to assemble still images into molecular movies that describe the full functional cycle of biomolecular machines at atomic detail.

### Towards structural biology *in situ*

Despite these exciting prospects, single-particle cryo-EM still requires at least partial purification of target molecules away from their native environment inside cells. Another exciting development therefore is the rapid progression of a specialised discipline of cryo-EM, cryogenic electron tomography and the associated method of sub-tomogram averaging. In electron tomography, images containing different views of the same specimen are generated by tilting the sample along an axis perpendicular to the electron beam to create 3D reconstructions of target molecules directly inside cells [5]. Yet, this method suffers from the drawback that an equivalent electron dose must now be distributed over many images of the tilt series, leading to

images with even poorer contrast. In a process called sub-tomogram averaging, different copies of identical molecules retrieved from many tomograms can be aligned in 3D and averaged together to increase resolution. In several cases, this method has yielded structures at resolutions comparable to those achieved in average single-particle experiments, with the key advantage of visualising molecular interactions and modifications as they occur in their native cellular context [6]. To routinely yield high-resolution snapshots of target molecules in this way will require additional technological advances that further improve image contrast and accuracy of reconstruction algorithms, that increase throughput by automation and that facilitate a robust integration of electron microscopy with methods such as single-molecule fluorescence and super-resolution microscopy. Once established, the future looks bright for electron microscopy to help realise the biophysicists' dream to watch, learn and comprehend the inner workings of the molecular machinery in cells and at atomic detail.

### About the Author



**Arjen Jakobi** is an assistant professor at the Kavli Institute of Nanoscience at Delft University of Technology. He and his team develop methods to help cryo-EM realise its full potential.

### References

- [1] M. Adrian, J. Dubochet, J. Lepault and A.W. McDowell, *Nature* **308**, 32 (1984)
- [2] R. Henderson, *Q. Rev. Biophys.* **28**, 171 (1995)
- [3] G. McMullan, A. Clark, R. Turchetta and A. Faruqi, *Ultramicroscopy* **109**, 1411 (2009)
- [4] S. H. W. Scheres, *J Struct Biol.* **180**, 519 (2012)
- [5] O. Medalia, I. Weber, A. S. Frangakis, D. Nicastro, G. Gerisch and W. Baumeister, *Science* **298**, 1209 (2002)
- [6] F. J. O'Reilly, X. Liang, A. Graziade, L. Sinn, S. Lenz, D. Tegunov, C. Blötz, N. Singh, W. J. H. Hagen, P. Cramer, J. Stülke, J. Mahamid and J. Rappsilber, *Science* **369**, 554 (2020)



**The advancement that propelled cryo-EM from "blobology" to a high-resolution technique was largely driven by the development of direct electron detection (DED) cameras. 🗨️**

# PROTEIN NANOMECHANICS: THE POWER OF STRETCHING

■ Marc Mora<sup>1,2</sup> and Sergi Garcia-Manyes<sup>1,2</sup> – DOI: <https://doi.org/10.1051/epl/2020503>

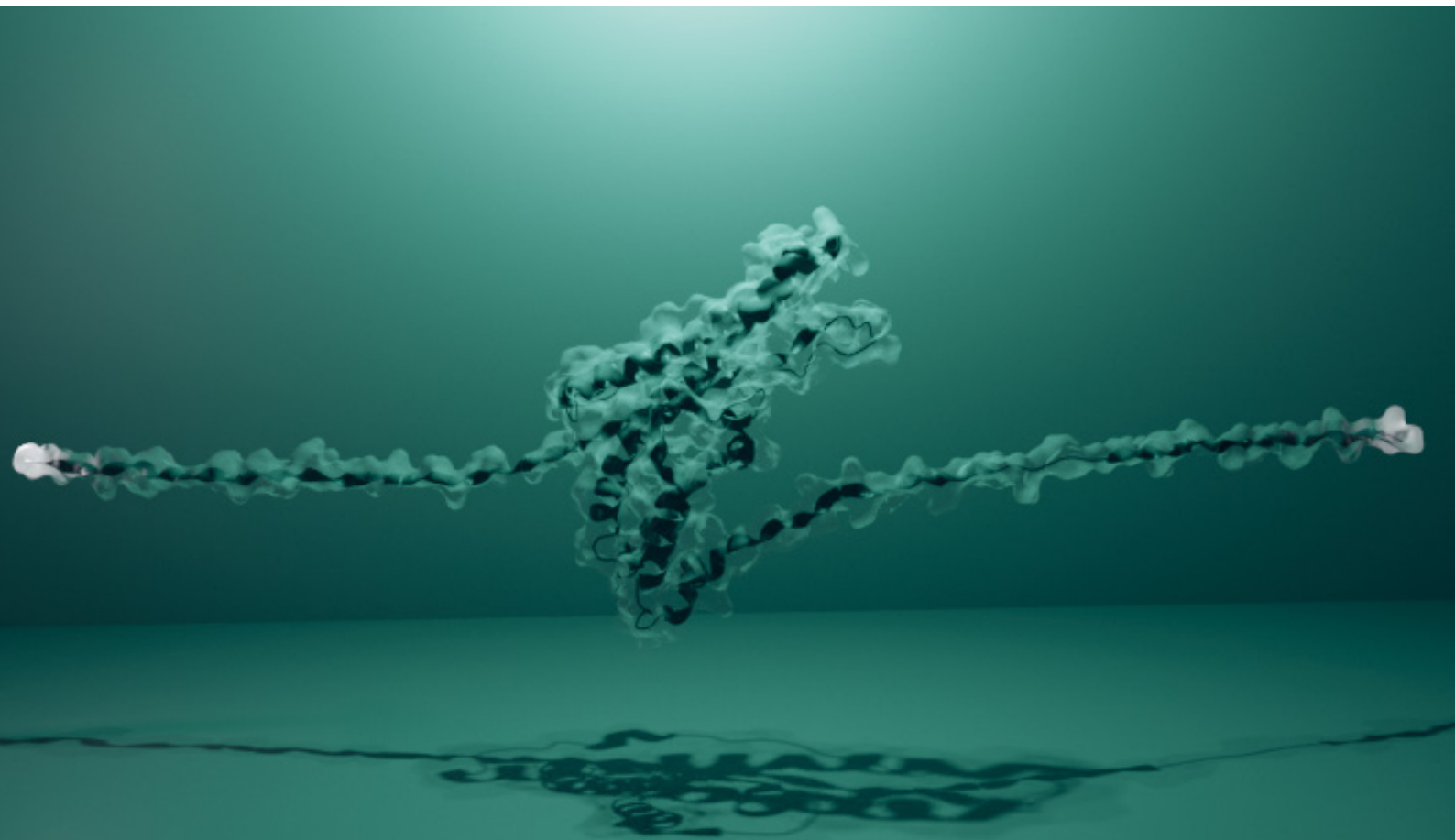
■ <sup>1</sup> Department of Physics and Randall Centre for Cell and Molecular Biophysics, King's College London, WC2R 2LS, London, UK

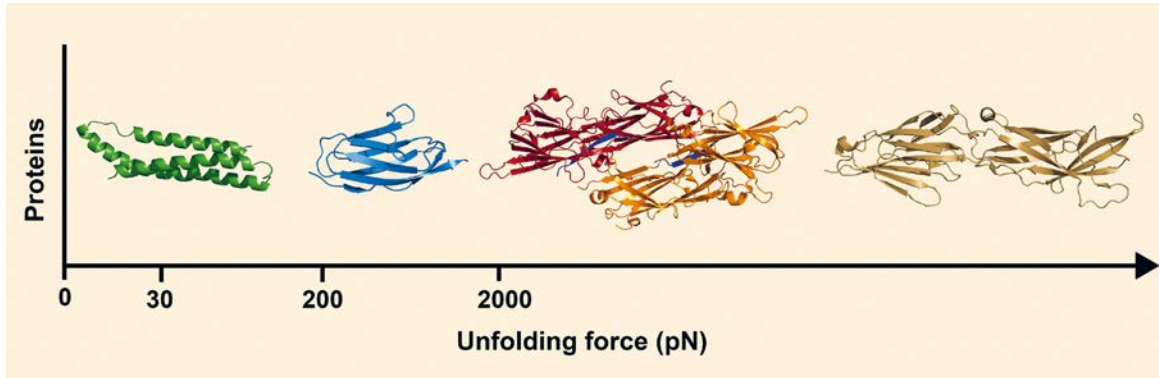
■ <sup>2</sup> The Francis Crick Institute, 1 Midland Road, London NW1 1AT, UK

**Protein nanomechanics is a rapidly evolving field at the intersection of physics, chemistry and biology focused on the characterisation of the conformational dynamics of proteins under force, of common occurrence *in vivo*.**

**M**echanical forces regulate important biological functions, including muscle contraction, differentiation, migration, and even cancer metastasis. Yet, in most cases the underpinning molecular mechanisms remain largely elusive. Those mechanically-regulated cellular processes are often ultimately controlled by the elastic properties of the individual constituent proteins — which need to constantly stretch and recoil under mechanical load under physiological conditions. Capturing the individual unfolding and refolding trajectories of relevant proteins under

force is challenging. Progress in that direction has been mainly halted by the lack of techniques able to probe the dynamics of individual proteins under force. Thanks to the advent of single-molecule technology, we are now in the position of investigating the molecular mechanisms that confer mechanical resistance to proteins. Borrowing concepts from polymer physics, protein chemistry and molecular biology, complemented with innovative technical developments, we are now beginning to understand the molecular basis of protein elasticity, with single-molecule resolution.





◀ **FIG. 1:** Proteins display different mechanical stabilities. From left to right: Spectrin repeat (~30 pN), Titin Ig27 domain (~200 pN), adhesin SdrG:Fgβ complex (~2300 pN) and adhesive pilin Spy 0128 (which is inextensible due to its internal covalent isopeptide bond).

### Force as a denaturing agent

Proteins are essential biological polymers consisting of the covalent linkage of individual amino acids. They are involved in nearly all cellular processes and most of their changes in functionality rely on structural changes, mainly involving the rupture and reformation of their constitutive molecular interactions. In order to be fully functional, the majority of the proteins need to fold into a well-defined three-dimensional structure that defines the natively folded conformation.

Traditionally, characterising protein (un)folding consisted in exposing proteins to harsh environmental changes by using strong chemical denaturants, abrupt changes in pH or temperature. These experiments led to the important observation that protein folding was a reversible process, and overall provided with a thorough description of the folding energy landscape for a large number of studied proteins. However, these experiments cannot probe the effect of mechanical force on the folding energy landscape of elastic proteins. The development of single-molecule force-spectroscopy techniques in the late 90s complemented the classical protein folding field by experimentally testing the implications of using force as a denaturing agent.

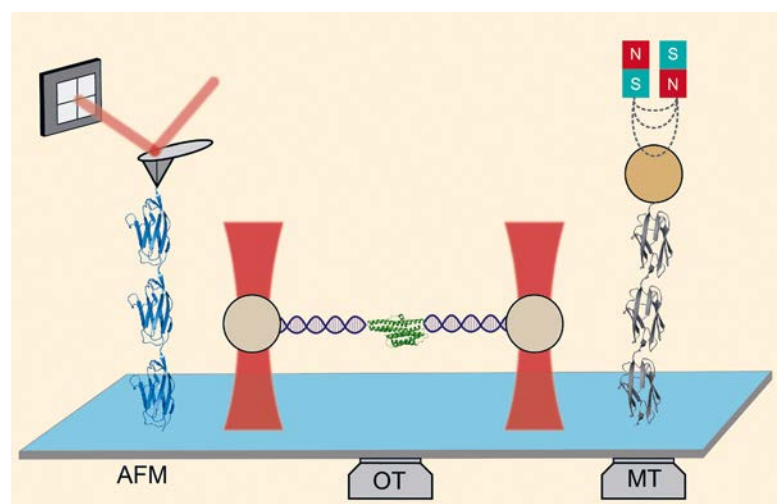
To date, this approach has been used to monitor the force-induced conformational changes of a wide range of proteins. When a stretching force is applied to the protein by a force probe, the protein's restoring force is measured as a function of its end-to-end length. Alternatively, the extension of the protein can be monitored over time. These experiments use the mechanical stability of proteins as their structural fingerprints. Given that proteins exhibit a wide range of mechanical stabilities according to their different structures and topologies (Fig. 1), three complementary main single-molecule techniques (namely optical tweezers, magnetic tweezers and atomic force microscopy) have been developed [1], each of them

excelling at measuring forces with unprecedented resolution within a defined force regime (Box). Combined, the enabling experiments have provided us with a general framework to understand the molecular mechanisms that regulate protein nanomechanics.

### The fundamentals of protein nanomechanics: the mechanical clamp

During the past two decades, an impressive body of literature has unravelled the basic rules governing protein (un)folding under force [2]. The first implication of using force (a vectorial quantity) as a denaturant is that it distributes non-isotropically throughout the protein backbone. Consequently, not all the amino acids forming the polypeptide chain are equally exposed to the stretching force. Accordingly, and in sharp contrast with the isotropic nature of the biochemistry unfolding experiments, mechanical unfolding is a highly localised process, whereby the main barrier to unfold typically lies in the rupture of a few non-covalent bonds between key amino

▼ **FIG. 2:** The three main single-molecule protein nanomechanics techniques. From left to right: single molecule atomic force-microscope, optical tweezers and the magnetic tweezers.



**Mechanical unfolding is a highly localised process, whereby the main barrier to unfold typically lies in the rupture of a few non-covalent bonds between key amino acids that act as the structural force-bearing motif – the so-called mechanical clamp** ”

## BOX: SINGLE-PROTEIN FORCE SPECTROSCOPY TECHNIQUES

### Atomic force microscopy

Developed in 1986 by Binnig and co-workers, the atomic force microscopy (AFM) was initially conceived as an imaging technique to elucidate the topography of both conducting and insulating surfaces with sub-nanometre resolution. By using the sharp cantilever tip as a force probe, it soon became an ideal tool to manipulate individual biomolecules. In a typical experiment, a polyprotein is usually tethered between the substrate (commonly a gold coated cover slide) and the cantilever tip. Protein stretching and unfolding is directly monitored by the deflection of the cantilever tip (Fig. 2 left). The AFM is ideally suited to work with proteins with intermediate to high mechanical stabilities, ranging from  $\sim 20$  pN up to  $\sim 1$  nN. It can work under force-extension and force-clamp operational modes.

### Optical tweezers

Based on the operational principles of the single-beam gradient force trap, optical tweezers (OT) can be used as a force-spectroscopy technique able to apply pN forces to individual biomolecules while recording their position with sub-nanometre resolution. In the particular case of proteins, the experimental strategy consists of tethering a single monomer of interest between two long DNA tethers which are, in turn, attached to two optically trapped dielectric beads (Fig. 2 middle). By controlling the bead displacement and the laser intensity, optical tweezers can apply forces from  $\sim 0.1$  pN up to 100 pN. OT can work both under the force-extension and force-clamp modes, and is typically used to study the unfolding and refolding trajectories of single proteins with low mechanical stability.

### Magnetic tweezers

The magnetic tweezers (MT) technique uses a magnetic field, generated with a pair of permanent magnets placed on top of the sample, to apply calibrated forces to individual biomolecules. In a typical protein-based experiment, individual polyproteins are tethered from both ends. One end is tethered to the cover slide (usually using HaloTag chemistry) and the other terminus is linked to the paramagnetic bead using Streptavidin-Biotin technology (Fig. 2 right). By precisely controlling the position of the permanent magnets — and hence the magnetic field strength — MT can apply forces spanning  $\sim 1$ –200 pN under passive mode conditions. The development of new covalent strategies has enabled the study of protein (un)folding with exceptional stability over long periods of time (of even week-long continuous stretching cycles).

acids that act as the structural force-bearing motif – the so-called mechanical clamp (Fig. 3a). Once the mechanical clamp is disrupted, mechanical unfolding typically proceeds in a downhill manner, without any additional resistance to the applied force (unless further mechanical intermediates are found during the unfolding pathway). A second immediate consequence of the directionality imposed by the applied force is that the mechanical stability of proteins depends on the pulling direction.

## Reconstructing protein energy landscapes with force

Two main operational modes are typically used to study protein unfolding under force: (i) by stretching proteins under constant velocity [3] and, (ii) by applying a constant force [4] – the force-clamp mode. (i) Stretching a polyprotein under constant velocity – as first reported in the seminal paper from Gaub's lab [5] – results in the characteristic saw-tooth unfolding trajectories, where each force peak in the force versus protein extension trajectory corresponds to the independent unfolding of an individual monomer within the polypeptide chain (Fig. 3b). (ii) Alternatively, unfolding a polyprotein under force-clamp conditions results in a staircase-like unfolding trajectory, where each step-wise length increase corresponds to the unfolding of an individual protein monomer (Fig. 3c). The force-clamp approach monitors the time-dependency of protein (un)folding under a constant stretching force, enabling direct extraction of the kinetic parameters defining the unfolding energy landscape.

A qualitative representation of the effect of force on the protein conformation (ultimately dictated by the underpinning (un)folding energy landscape) can be rationalised using simple energetic considerations. In the absence of force, the protein lies in its energy minimum, which typically corresponds to the folded state. The application of a constant force introduces a mechanical work term ( $-Fx$ , where  $F$  is the applied force and  $x$  is the protein's extension), which tilts the energy landscape by reducing the activation energy barrier  $\Delta E$  and introduces a new free energy minimum towards extended conformations that is populated once the protein crosses the  $\Delta E$  barrier upon unfolding (Fig. 3d). The position of this new equilibrium minimum is force-dependent, as predicted by the worm-like chain (WLC) model of polymer elasticity.

A quantitative reconstruction of the protein's energy landscape is accurately obtained by measuring the force-dependent unfolding rates  $\alpha(F)$  at different stretching constant forces. While different models relating  $\alpha(F)$  with the pulling force have been developed, they are ultimately all refinements of the simple phenomenological Bell-Evans-Ritchie model, which describes the exponential relationship between the life-time of individual bonds and the externally applied force:

$$\alpha(F) = \alpha_0 \exp\left(-\frac{F\Delta x}{k_B T}\right) \quad (1)$$

where  $\alpha_0$  is the unfolding rate in the absence of force and  $\Delta x$  is the distance to the transition state. Recent efforts in the field have focused on understanding how well-defined chemical perturbations (such as single-point mutations, protein-ligand interactions and post-translational modifications) affect the (un)folding energy landscapes of proteins under force.

## Conclusions

Force has emerged as a key physical perturbation that precisely controls the conformation of individual proteins, with important implications for the elastic regulation of those proteins that are physiologically exposed to mechanical forces. The advent of single-molecule force-spectroscopy techniques (AFM, OT and MT) has enabled mapping of the conformational dynamics of individual proteins under force with unprecedented force-, length- and time-resolution. While the single protein nanomechanics field is reaching maturity, arguably the main challenge in the field is the translation of these *in vitro* nanomechanical experiments into the cellular context (with potential knock-on effects at the functional level). Despite recent promising achievements, we lack global understanding of whether individual molecules working inside the cell respond to force according to the same fundamental physical laws established by the single-molecule experiments. Closing such a scale gap has become a timely, necessary and unavoidable requirement to enable the natural advancement of the mechanobiology field.

## About the authors

**Marc Mora** is a postdoctoral researcher at King's College London. His research focuses on understanding the effect of chemical reactivity on the mechanical folding of proteins.

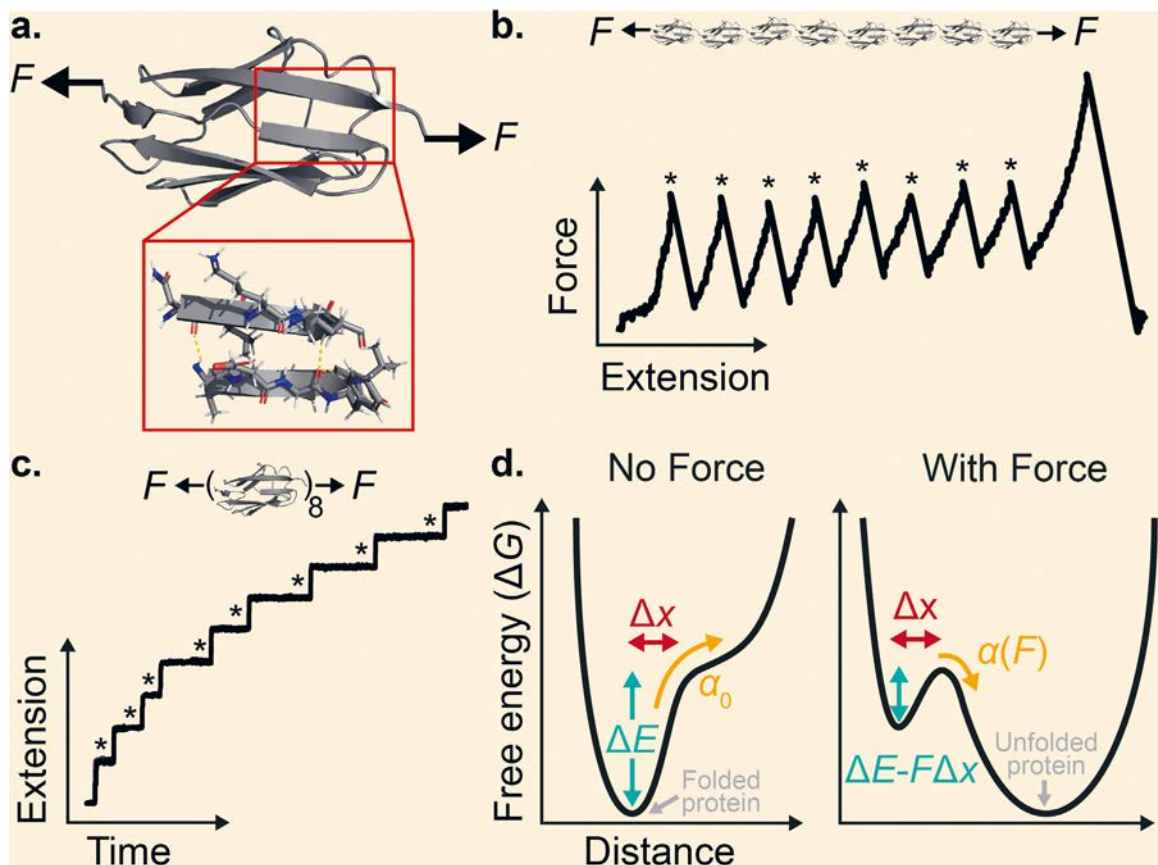
**Sergi Garcia-Manyes** is a Professor of Biophysics at King's College London and a Group Leader at the Francis Crick Institute in London. He is a Royal Society Wolfson Fellow.

## Acknowledgments

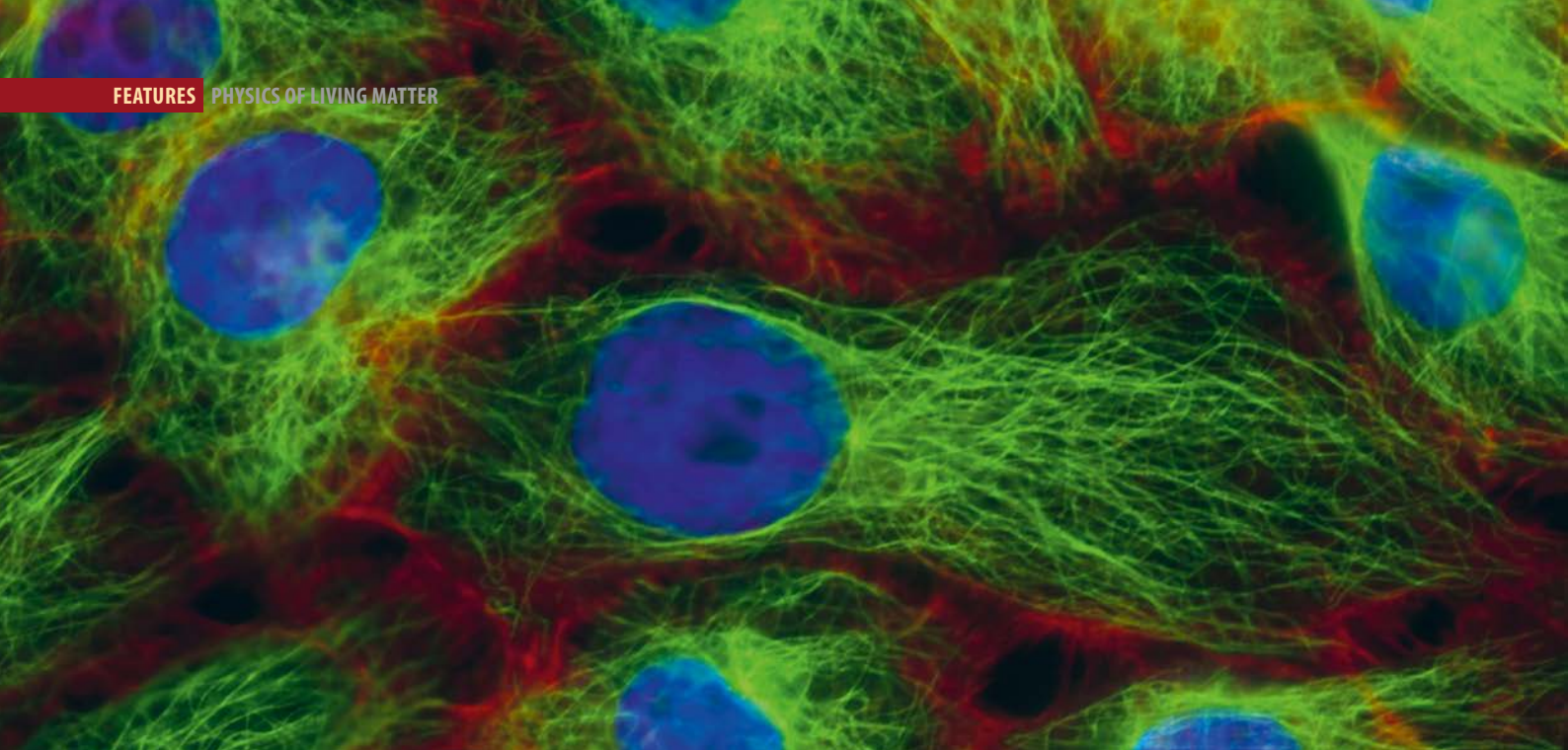
The work is supported by the European Commission (FET Proactive 731957), EPSRC Fellowship K00641X/1, EPSRC Strategic Equipment Grant EP/M022536/1, Leverhulme Trust Research Leadership Award RL-2016-015, Wellcome Trust Investigator Award 212218/Z/18/Z and Royal Society Wolfson Fellowship RSWF/R3/183006, all to S.G.-M.

## References

- [1] S. Garcia-Manyes and A. E. M. Beedle, *Nature Reviews Chemistry* **1** (2017)
- [2] M. Mora, A. Stannard and S. Garcia-Manyes, *Chem Soc Rev* **49**, 6816 (2020)
- [3] K. C. Neuman and A. Nagy, *Nat Methods* **5**, 491 (2008)
- [4] M. Schlierf, H. Li and J. M. Fernandez, *Proc Natl Acad Sci USA* **101**, 7299 (2004)
- [5] M. Rief, M. Gautel, F. Oesterhelt, J. M. Fernandez and H. E. Gaub, *Science* **276**, 1109 (1997)



**FIG. 3:** The nanomechanical characterization of protein unfolding. **a.** The folded structure of the titin Ig27 domain, with a zoom on its mechanical clasp. **b.** Representative force versus extension unfolding trajectory of a polyprotein made of eight identical repeats of the Ig27 protein when stretched at constant velocity. **c.** Representative force-clamp unfolding trajectory of the same polyprotein stretched under a constant force, where each step length increase corresponds to the unfolding of a single protein domain. **d.** Schematic representation of the 1-D energy landscape representation of a protein in the absence and presence of an externally applied constant force.



# MECHANICS IN BIOLOGY

■ **Timon Idema** – DOI: <https://doi.org/10.1051/epn/2020504>

■ Department of Bionanoscience, Kavli Institute of Nanoscience, Delft University of Technology, Delft, The Netherlands

**Mechanics plays a key role in life, from simple tasks like providing protective shielding to highly complex ones such as cell division. To understand mechanical properties on the organism level, we need to zoom in to its constituent cells, then zoom back out to see how they collectively build tissues.**

**W**hen multi-cellularity first evolved, organisms gained an important ability: they could let their cells specialise. In a single-cell organism, the one cell by necessity has to be able to perform all essential functions to stay alive. Driven by evolutionary pressure, it will usually optimise for growth and division. For almost all cells in a multi-cellular organism, however, the current organism represents the end of their road: even though they may divide a couple times more during the organism's life span, when the organism dies, they die as well. However, their genetic information can live on, if the organism as a whole has reproduced. Therefore, the cells have the freedom to specialise in a way that helps the organism thrive, by collecting more and different kinds of food, defending against predators and

invaders, and increasing the chances that the organism will successfully reproduce.

Arguably the most extreme form of specialisation in animal tissues is in their mechanical properties. The Young's modulus of human brain tissue is less than 1 kPa, while that of the cortical bone in the skull protecting it is more than 10 GPa. This huge difference moreover has to be re-developed every time a new organism is created, as all animals develop from a single fertilised egg<sup>1</sup>. To illustrate, let's consider the development of a chicken heart. A chick embryo needs a heart from the second day of development onwards, as at that point it has grown too big for oxygen to diffuse through its entire body. The initial 'heart' is a simple tube, pumping by contracting like you'd pump water through a hose by moving your hand along it. As the chick develops over the next two weeks (when it hatches), the stiffness of the heart goes up by a factor 20 and it develops into the familiar four-chamber structure (similar to the human heart), including the necessary topological changes, all the while pumping blood around [1]. To achieve this remarkable feat, the embryo follows a strongly regulated developmental programme, while maintaining the ability to adopt to unexpected outside effects.

<sup>1</sup> The story for plants is quite different. Plant cells have a cell wall that gives them rigidity, making the difference in stiffness between various parts of the plant, while non-negligible, much smaller than between those of animals. Moreover, plants can also be easily cloned, but when they grow from seeds, they undergo a similar development process including significant changes in mechanical properties.

So how do tissues get their mechanical properties? Ultimately these come from the cells that make up the tissue, through their internal mechanics, their adhesion to each other, and through the extracellular matrix that these cells build around themselves [2,3].

### Internal cell mechanics

Eukaryotic cells (all cells with a nucleus, including animals, plants and fungi, but also simple single-cellular organisms like yeast) have an internal cytoskeleton: a network of several types of polymers that give the cell mechanical structure (see figures 1 and 2). The cytoskeleton mainly consists of three components: microtubules, actin, and intermediate filaments. Microtubules are hollow structures with a persistence length much larger than the size of a typical cell. Actin filaments in contrast consist of two fibers wrapped around each other creating a much more flexible structure. During the growth phase of the cell, the microtubules typically form a radial network, while the actin filaments form a cortical structure along the periphery of the cell (figures 1c and 2a). Both microtubules and actin fibers are polar, allowing for directed transport along them by molecular motors. During cell division, the roles are reversed and motors pull on microtubules connected to chromosomes to divide the duplicated DNA over the two daughter cells (figure 1a); an actin ring around the middle of the cell subsequently contracts, again under the action of motor proteins, to actually divide the cell (figure 2b). While actin and microtubules are found in all eukaryotic cells and have close analogs in bacteria and archaea, there are many different types of intermediate filaments that are more specialised. As their name suggests, these filaments have a stiffness in between those of actin and microtubules. They are nonpolar, making the increase of the stiffness of the cell their primary function.

Unlike the bony skeleton in an adult animal, the cytoskeleton of a cell is highly dynamic. All filaments in it continually grow and shrink by adding or removing monomers. This growth and shrinkage can happen at the same

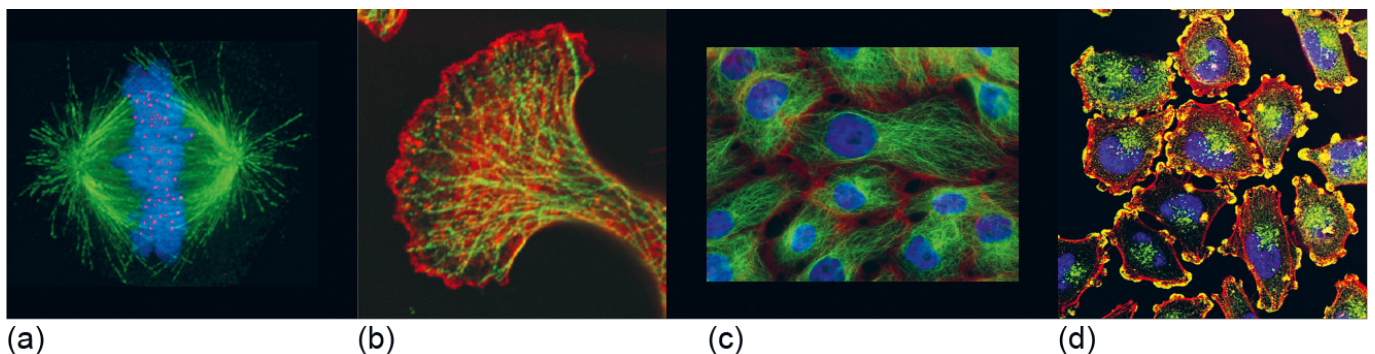
end, but also on opposite ends, leading to treadmilling motion of the filament as a whole. Through branching and crosslinking, the filaments create networks in the cell that give the cell its stiffness [4]. Unlike conventional large-scale materials though, the cell will adapt to its environment; if the cell grows under mechanical load, its elastic modulus goes up, and stem cells placed on substrates of different stiffness differentiate into different cell types matching the outside environment [5,6].

### Mechanics of tissues

Cells don't just have internal mechanics: they also connect to other cells to form tissues. Links to other cells can be made directly through mechanical junctions between molecules protruding from the cell surface. In particular in developing tissues, many of these junctions are reversible, allowing cells to bind more or less strongly depending on the needs of the developmental programme. A currently outstanding hypothesis is that cells may sort due to differential adhesion, which would be a purely mechanics-based mechanism [7].

As tissues develop, cells specialise and become more strongly anchored to their position<sup>2</sup>. In neuronal tissues, these connections remain relatively weak, and continue developing throughout the organism's life, as part of the ever-ongoing learning process. In most other tissues, to increase the stiffness and provide an anchoring platform, cells develop an extracellular matrix of crosslinked polymers, with a many-layered structure (figure 2c). Ultimately all hard structures in the body are made from

**FIG. 1:** Cytoskeletal elements in the cell. Cells get their material properties from biopolymers that continually grow, branch, and shrink, exerting forces as they do so, and providing overall stiffness to the cell. (a) Mitotic spindle in a dividing cell. Microtubules (green) pulling on chromosomes (blue) during cell division. (b) Lamellipodium of a crawling cell, with microtubules (green) and actin filaments (red). (c) Cells in a breast tissue sample, showing the nuclei (blue), microtubules (green) and actin filaments (red). (d) Metastatic melanoma cells, which have broken free from a primary tumor and can invade surrounding tissue. Next to nuclei (blue), actin filaments (red) and actin regulators (green), these cells contain podosomes (yellow), actin-rich structures used to attach the cell to a surface and spread on it. Figure (a): public domain (Wikimedia commons), (b-d) National Cancer Institute (Unsplash).



<sup>2</sup> The most common such transition from motile to polarised epithelial cells is known as the mesenchymal-epithelial transition (MET); together with its reverse process, the epithelial-mesenchymal transition (EMT) it is likely the most studied transition process in biology, as it occurs in development, wound healing, tumor metastasis, and the induced reprogramming of pluripotent stem cells.

such materials [8], including not just the bones, but also the stiffer layer under epithelial tissues, which are found at the boundaries inside the body, in e.g. the skin, the cornea, and the gut. Epithelial tissues have highly nonlinear mechanical properties, as you can test easily for yourself by stretching your skin, which deforms easily at first but stiffens up at the centimeter scale. These properties originate from both the internal mechanics of the constituent cells [9] and the viscoelastic nature of the extracellular matrix [10], combining the elastic response of solid materials on short time scales with a stress-relaxing fluid-like response at longer times.

Because cells in epithelial tissues continually get renewed, they divide relatively frequently. For healthy cells, the number of divisions is limited; once a cell has reached the maximum, it will undergo apoptosis, programmed cell death. Errors in copying the genetic information of the cell can however prevent apoptosis and change the internal structure of the cell, resulting in different mechanical properties, two hallmarks of tumor formation (figure 1d). Fortunately, most of these cells never grow to life-threatening tumors, as they fail to penetrate the surrounding tissue, thanks to a simple but highly effective mechanical mechanism: by building up the hydrostatic pressure around them, healthy cells can keep the tumor in check, causing it to shrink and ultimately disappear. Recent modeling efforts have shown how mechanics can be used to better understand and ultimately suppress tumor development in cases where it does go wrong [11,12], underlining once again the importance of this basic physics concept for the study of life.

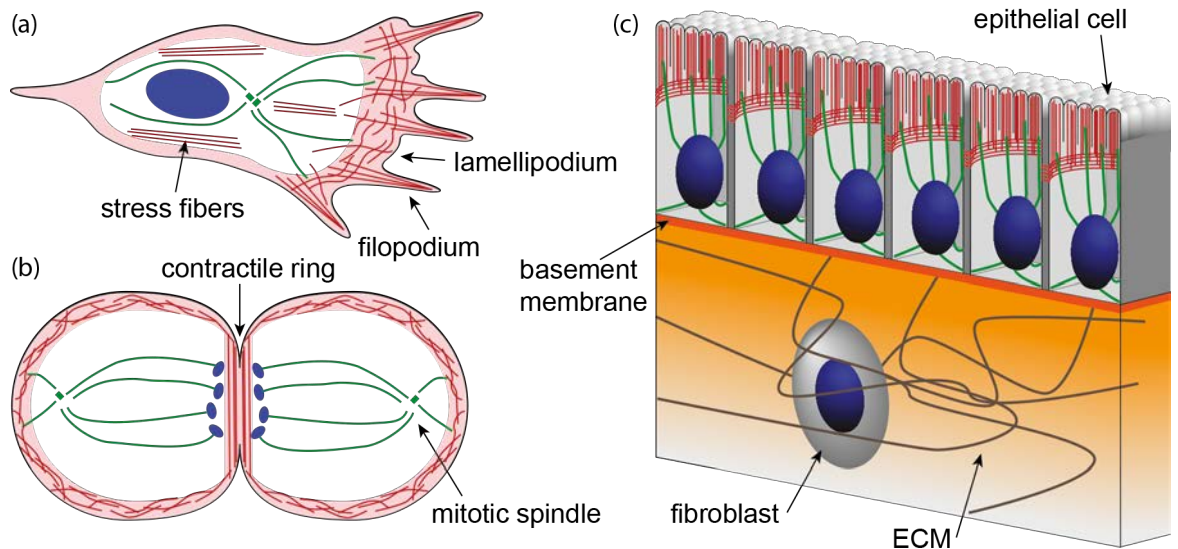
About the author



**Timon Idema** is an Associate Professor of theoretical biophysics at Delft University of Technology. His research focuses on collective dynamics, ranging in scale from molecules to colonies. He has written an open textbook on Mechanics and Relativity and recently received the J.B. Westerdijkprize for his teaching efforts.

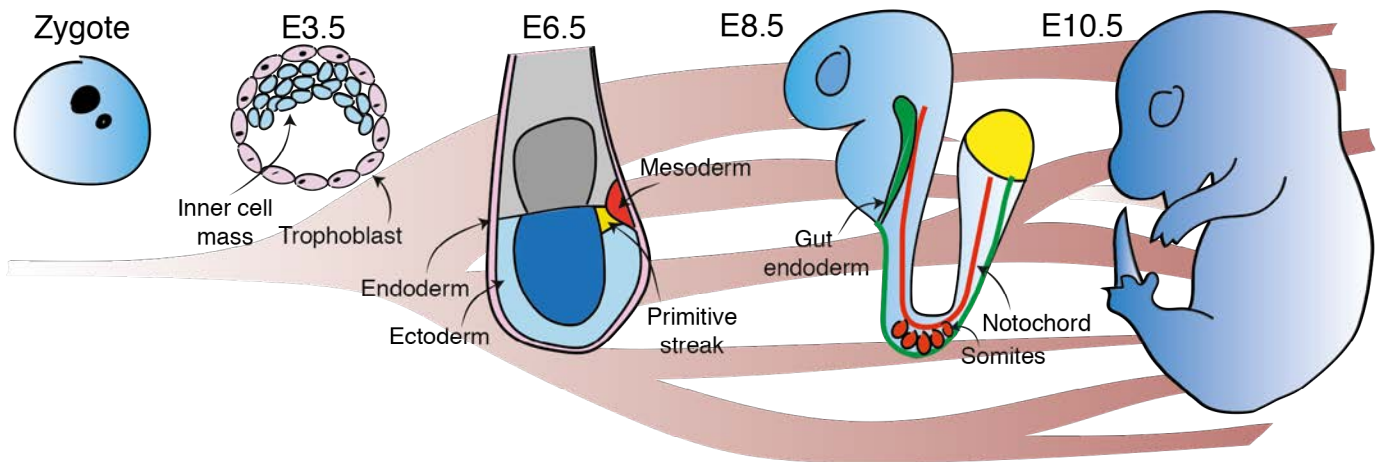
References

[1] S. Majkut *et al.*, *Curr. Biol.* **23**, 2434 (2013)  
 [2] T. J. C. Harris, J. K. Sawyer and M. Peifer, *Curr. Top. Dev. Biol.* **89**, 55 (2009)  
 [3] A. R. Harris, A. Daeden and G. T. J. Charras, *Cell Sci.* **127**, 2507 (2014)  
 [4] D. A. Fletcher and R. D. Mullins, *Nature* **463**, 485 (2010)  
 [5] D. E. Discher, P. Janmey and Y. Wang, *Science* **310**, 1139 (2005)  
 [6] A. J. Engler, S. Sen, H. L. Sweeney and D. E. Discher, *Cell* **126**, 677 (2006)  
 [7] F. Fagotto, *Semin. Cell Dev. Biol.* **107**, 130 (2020)  
 [8] A. Salhotra, H. N. Shah, B. Levi & M. T. Longaker, *Nat. Rev. Mol. Cell Biol.* (2020)  
 [9] N. Khalilgharibi *et al.*, *Nat. Phys.* **15**, 839 (2019)  
 [10] O. Chaudhuri, J. Cooper-White, P. A. Janmey, D. J. Mooney and V. B. Shenoy, *Nature* **584**, 535 (2020)  
 [11] L. A. Harris, S. Beik, P. M. M. Ozawa, L. Jimenez and A. M. Weaver, *Curr. Opin. Syst. Biol.* **17**, 24 (2019)  
 [12] P. Van Liedekerke *et al.*, *PLOS Comput. Biol.* **15**, e1006273 (2019)



**▲ FIG. 2:** Cells in isolation and in tissue. (a) Crawling cell. At the leading edge of the cell, actin filaments form a network that exerts forces on the cell, resulting in the creation of flat lamellipodia (cf. figure 1b) and rod-shaped extrusions known as filopodia. In the cell body, actin stress fibers (red) and microtubules (green) give the cell mechanical structure. The nucleus (blue) is carried along as cargo. Figure by Lucas de Kam. (b) In a dividing cell, the microtubules organise into a mitotic spindle (cf. figure 1a), which exerts forces on the chromosomes (blue), pulling them apart during division. A contractile actin ring (red) then splits the cell. (c) Cells form epithelial tissues at the various surfaces in a body, such as the gut, blood vessels, and the skin. The cartoon shows a simple columnar epithelium with a clear polar structure, in which the cells not only have an internal biopolymer network, but are also laterally connected to other cells, and supported by a basement membrane. Underneath the membrane fibroblast cells build an extracellular matrix (ECM) of other biopolymers, forming connective tissue between one epithelium and the next. Tissues get their mechanical properties from a combination of the intercellular (cytoskeletal) and extracellular polymer networks.





# CELL DIFFERENTIATION UNRAVELLED BY SINGLE-CELL RNA SEQUENCING

■ **Anna Alemany** – <https://doi.org/10.1051/epl/2020505>

■ **Oncode Institute, Hubrecht Institute-KNAW (Royal Netherlands Academy of Arts and Sciences) and University Medical Center Utrecht, Utrecht, The Netherlands.**

All of us originate from a single cell, known as the zygote. Nevertheless, we are made of thousands of cells with different functionalities and morphologies: a skin cell is not the same as a neuron, yet they share the same genetic information. It is during embryo development that, through multiple cell divisions, the zygote gives rise to each of the cell types present in the different organs of each organism. One main challenge of developmental biology is to understand how, when, and where lineage commitment to each cell type takes place.

The differentiation of a cell from an initial to a final state can be viewed as a dynamical process in which the system (*i.e.*, the cell) transits through a sequence of states. This transformation occurs out of equilibrium, typically irreversibly. To characterise how the cell changes during differentiation we can explore modifications in genome architecture, cell morphology or protein content, among others. Here, we describe cellular states using the transcriptome[1], which is the collection of all RNA molecules present in a cell and can be measured using single-cell RNA sequencing (scRNA-seq). These molecules are transcribed from regions of the DNA known as genes, and encode the sequence of amino acids required to make proteins. By measuring the transcriptome of a cell we can infer which genes it is using and hence what is its main function.

## The potential landscape for cell-fate commitment

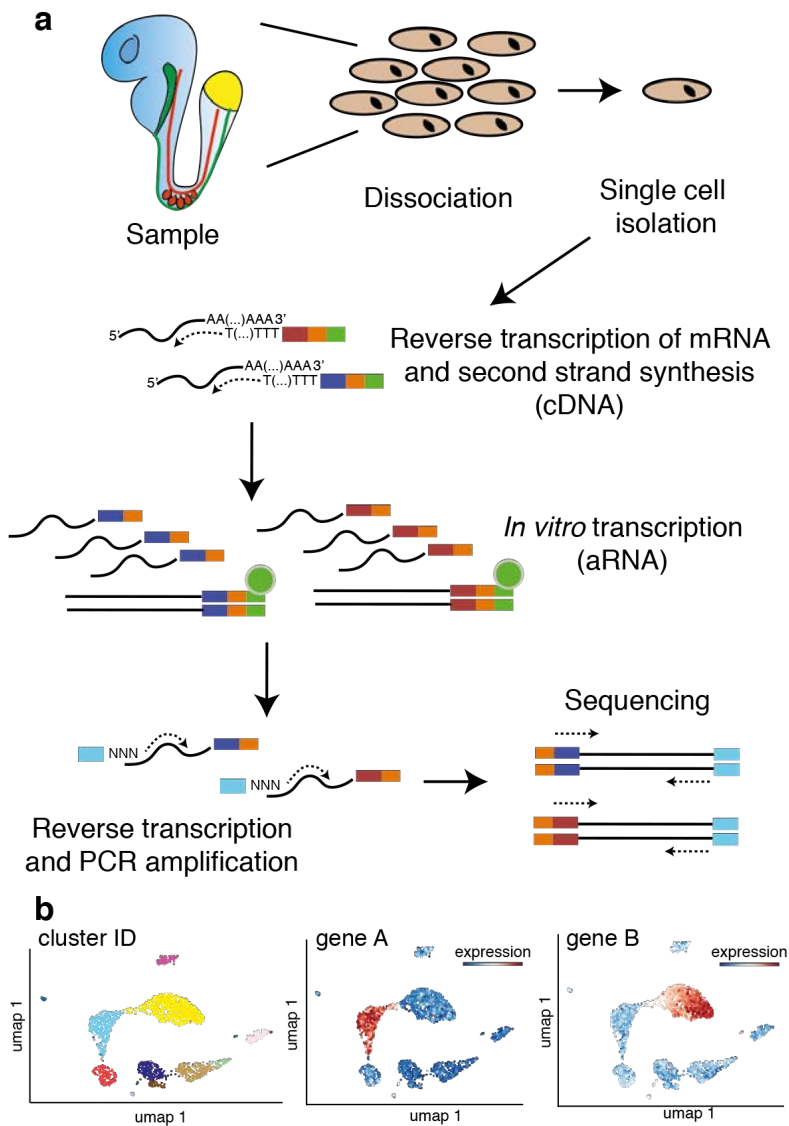
Seminal work in the field of systems biology has set the ground work to mathematically model the molecular mechanisms underlying cellular lineage commitment [2]. A cell is viewed as a Brownian particle whose state is characterised by a vector of RNA expression,  $T = \{m_1, m_2, \dots, m_N\}$ , where each dimension is a gene. The probability  $P(T, t)$  of a cell to have a transcriptional profile  $T$  at time  $t$  time satisfies the Fokker-Planck equation:

$$\frac{\partial P(\mathbf{T})}{\partial t} = \sum_i \frac{\partial^2}{\partial m_i^2} [D(\mathbf{T})P(\mathbf{T}, t)] - \frac{\partial}{\partial m_i} [F_i(\mathbf{T})P(\mathbf{T}, t)] \quad (1)$$

where  $F(\mathbf{T}) = \{F_1(\mathbf{T}), F_2(\mathbf{T}), \dots, F_N(\mathbf{T})\}$  describes the interactions between genes (known as gene regulatory network, Box 1), and  $D(\mathbf{T})$  represents the stochastic diffusion between states. The solution of Eq. (1) is a high-dimensional



## By measuring the transcriptome of a cell using single-cell RNA sequencing, we can infer which genes it is using and hence what is its main function



**▲ FIG. 1:** Single cell RNA sequencing provides a snapshot of the cellular heterogeneity in a sample. a) Single-cell RNA sequencing workflow [1]: the sample (tissue, organ, embryo, etc) is dissociated and single cells are isolated. Protein-coding RNA molecules, which have a poly-A tail, are uniquely labeled with an oligo-dT primer that contains a unique molecular identifier (UMI) and a cell-specific sequence (red/blue boxes), a molecular adaptor (orange) and the T7-promoter sequence (green). Complementary DNA (cDNA) is produced by reverse transcription and second strand synthesis. Next, the cDNA is linearly amplified by in vitro transcription, producing aRNA (amplified RNA). Reverse transcription is performed on the aRNA with a random primer that introduces another molecular adaptor (cyan). Molecules with the two adaptors (orange and cyan) are enriched by a polymerase chain reaction (PCR). Paired-end sequencing, in which both ends of the resulting DNA molecules are sequenced (dashed arrows) is usually performed. b) Two-dimensional projection of the generic scRNA-seq data obtained by uniform manifold approximation and projection (UMAP). Each point is a cell that has been coloured according to cluster identity assigned by hierarchical clustering (left), or by detected gene expression levels (gene A, gene B). Each cell can be assigned to a cell type based on its gene expression patterns.

manifold that connects to the Waddington landscape model (Box 1), in which a differentiating cell is represented by a marble that rolls down a landscape made of hills (transition states) and valleys (intermediate states) until reaching the final state (attractor state). We can also describe the cell state with a set of deterministic dynamic equations to describe RNA expression as a function of  $F(T)$  and  $t$ :

$$\frac{\partial m_i}{\partial t} = F_i(T), i = 1, \dots, N \quad (2)$$

A minimalistic regulatory network comprising two interacting molecules can already produce systems displaying bi-/tri-stability depending on the strength of the interactions (see Box). There, a bi-potent progenitor cell can be seen as an attractor state (red solid dot) whose stability is compromised by a change in its self-activation strength. The bi-potent progenitor then becomes a metastable state (red empty dot) that can differentiate towards two distinct terminal fates (cyan dots). This approach has successfully been applied to qualitatively describe lineage commitment in the blood cell types [2]. However, most models have only been experimentally tested using well-defined *in vitro* differentiation systems where the state of a cell was inferred based on population-averaged ensemble measurements. This reduced the temporal resolution and obscured rare populations and transition states. Hence, a goal in developmental biology is to extract information about the underlying regulatory networks (*i.e.*,  $F(T)$ ) during cell fate commitment *in vivo* with single-cell resolution and genome-wide.

### Cell type identity and RNA dynamics in single cells

In multicellular organisms, cells are specialised and perform a limited set of tasks. The identity of a cell (*i.e.*, the cell type) is commonly defined by its function, and the function can be partly determined by its RNA content. Therefore, scRNA-seq experiments provide an excellent platform to identify cell types present in heterogeneous tissues, since they allow measuring the RNA content in thousands of single cells independently (Fig. 1a) [1]. Overall, scRNA-seq provides a snapshot of the cellular heterogeneity in a sample, and can reveal rare or transient subpopulations usually undetectable by bulk sequencing approaches. Because of the huge number of genes in an organism (both the human and the mouse genome have ~20,000 protein-coding genes), datasets are typically large and sparse. It is a priority to develop analytical methods that exploit these high-dimensional data (each dimension being a gene) to compare transcriptome profiles between different cells. At the moment, there are several pipelines to normalise the data, reduce dimensions, cluster similar cells together, extract differential gene expression profiles, visualise results, and ultimately call cell types (Fig. 1b) [1].

In scRNA-seq, the sample is destroyed when the cells are prepared for sequencing. Therefore, these experiments

are not suitable to measure temporal changes in the transcriptome of the same cell. To circumvent this, experiments are performed on samples where several differentiating cells coexist at different stages (such as embryos), or in biological replicates at different time points, to ensure that all stages of the cellular differentiation trajectory are represented [3].

With the possibility to measure full transcriptomes in single cells undergoing differentiation, new algorithms to investigate the lineage-commitment dynamics have been developed [3]. Usually, it is assumed that cells change their transcriptome continuously as they transit from one state to another. Consequently, cells with similar transcriptomic profiles can be connected together and ordered (Fig. 2a). This gives rise to the concept of pseudo-time as a latent dimension that quantifies the degree of differentiation along a cellular transformation. These approaches are currently challenged by results obtained from lineage tracing studies

in which both the transcriptome and the common ancestry of single cells are simultaneously measured (Fig. 2a) [4]. There, it has been observed that transcriptomically identical cells can derive from ancestors with different RNA profiles, suggesting that cell differentiation has a stochastic component in which fluctuations in gene expression play an important role and cells with similar transcriptome can have different lineages.

In order to assign differentiating cells to a pseudo-time value more accurately, experimental protocols and analysis pipelines have been improved to distinguish newly synthesised (u) transcripts from mature (m) ones (Fig. 2b) [5,6]. Then, we can extract the transcription, degradation and splicing rates,  $\alpha$ ,  $\gamma$  and  $\beta$  respectively, for each transcript, by solving the rate equations:

$$\begin{aligned}\frac{du(t)}{dt} &= \alpha - \beta u(t) \\ \frac{dm(t)}{dt} &= \beta u(t) - \gamma m(t)\end{aligned}\quad (3)$$

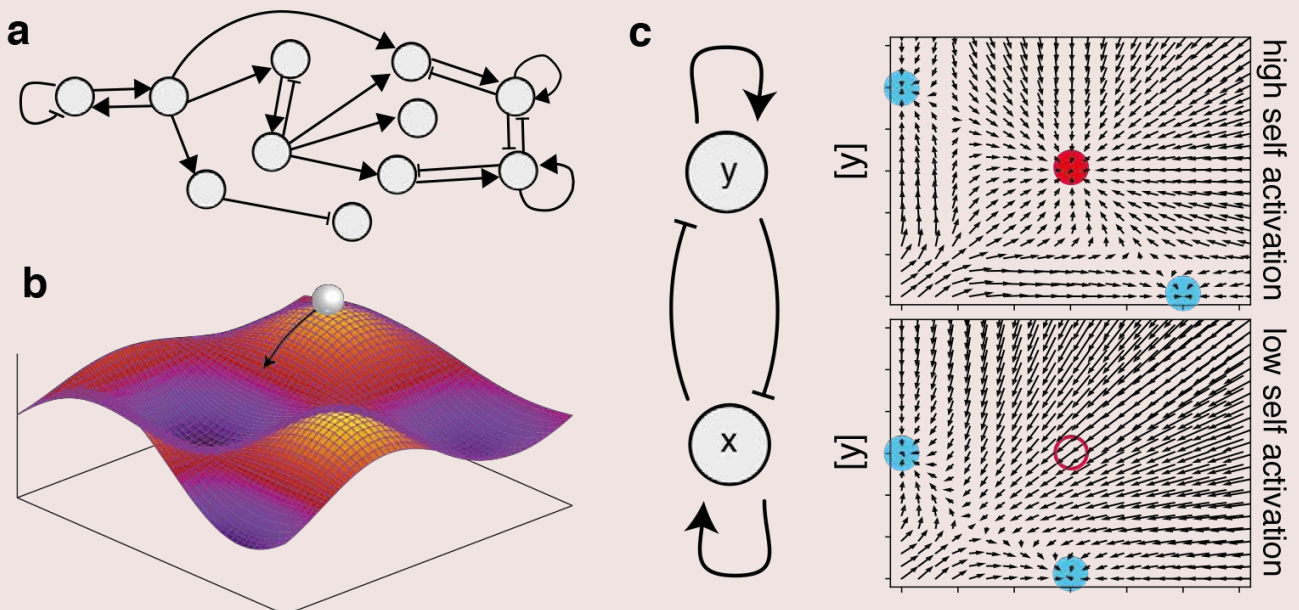
### BOX: CELL DIFFERENTIATION IS REGULATED BY GENE NETWORKS

Mouse embryo development starts right after fertilisation, when the zygote is formed and starts dividing. After ~3.5 days (E3.5) the first commitment event (origination of the inner cell mass and the trophoblast) occurs in the blastocyst. At E6.5 the three germ layers (endoderm, ectoderm and mesoderm) and the three body axes are established via the primitive streak. Around E8.5-E10.5, organ progenitors appear. During these processes, gene expression patterns in single cells are

dynamic and interact with each other via gene regulatory networks.

**a)** Gene regulatory network, where genes are represented as nodes and interactions are represented as edges. Repressive and active interactions are represented with butts and arrows, respectively. **b)** Sketch of the Waddington landscape, in which cell differentiation is illustrated through the position of a ball in a landscape. The ball (*i.e.* the cell) is initially situated at the top of the mountain and it can

only roll down via multiple paths. **c)** (left) Gene regulatory network for two genes  $x$  and  $y$ , that behave as auto-enhancers but repress each other. The dynamic equations for this network can be written assuming  $F_x(x,y) = ax^n / (S^n + x^n) + bS^n / (S^n + y^n) - kx$  and  $F_y(x,y) = ay^n / (S^n + y^n) + bS^n / (S^n + x^n) - ky$  (Eq. 2) [2]; (right) Corresponding phase portrait, obtained for  $S=0.5$ ,  $b=1$ ,  $k=1$ ,  $n=4$  and  $a=1.5$  (top; high self-activation) and  $a=0.5$  (bottom; low self-activation). Solid (empty) dots indicate attractor (metastable) states.



It has been proved that the experimental estimation of the time derivative of the mature RNA —termed RNA velocity— can predict the future state of individual cells on a timescale of hours [5]. RNA velocity can be embedded in the two dimensional representation of scRNA-seq data, in the form of a phase portrait from which one can visualise directions of differentiation at the cellular level (Fig. 2c).

A new challenge of developmental biology is to experimentally connect Eq. (2) and Eq. (3), and link RNA velocity to  $F(t)$  to unravel the regulatory networks that drive cell-fate commitment. This will allow experimentally measuring the Waddington landscape, with the goal to ultimately predict cellular responses to stimuli.

**Future perspectives: lineage tracing, spatial transcriptomics and perturbation assays**

The characterisation of gene regulatory networks and cellular transition states occurring during cell differentiation and their role in cell-fate commitment is a long-standing question in developmental biology. We anticipate that the combination of RNA velocity with theoretical models of molecular phase portraits will help us unravel the

fundamental gene regulatory networks that give rise to new cell fates. With the help of lineage tracing and perturbation studies (such as chemical screens or genetic knock-outs), we will be able to validate our findings and test predictions. In combination with spatial transcriptomics [7], we expect to also unravel underlying principles of intracellular communication.

The ongoing revolution in single-cell sequencing technologies is making it possible to extract other epigenetic properties in single cells, and to integrate them into multi-modal measurements from the same cell. With this, we expect to enhance the characterization of the Waddington landscape of development, with all its epigenetic components. ■

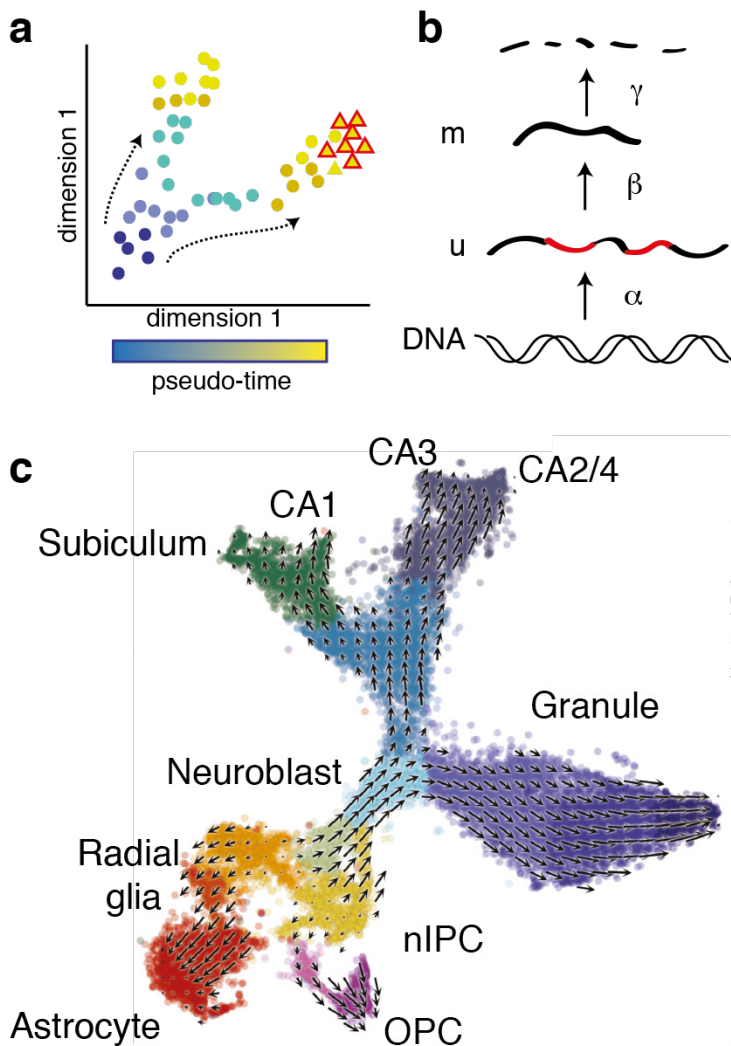
**About the Author**



**Anna Alemany** received her PhD in the group of Prof. Ritort and afterwards joined Prof. van Oudenaarden laboratory for her postdoc. She will start her own laboratory in the Leiden Medical University Center, in the Netherlands. Her goal is to quantitatively characterise the Waddington landscape of development using single-cell RNA sequencing experiments.

**References**

[1] A. Kulkarni, A. G. Anderson, D. P. Merullo and G. Konopka, *Current opinion in biotechnology* **58**, 129 (2019).  
 [2] J. Wang, L. Xu, E. Wang and S. Huang, *Biophysical journal* **99**(1), 29 (2010).  
 [3] D. E. Wagner, C. Weinreb, Z. M. Collins, J. A. Briggs, S. G. Megason and A. M. Klein, *Science* **360**(6392), 981 (2018).  
 [4] A. Alemany, M. Florescu, C.S. Baron, J. Peterson-Maduro and A. Van Oudenaarden, *Nature* **556**(7699), 108 (2018).  
 [5] G. La Manno, R. Soldatov, A. Zeisel, E. Braun, H. Hochgerner, V. Petukhov, K. Lidschreiber, M. E. Kastrioti, P. Lönnerberg, A. Furlan, and J. Fan, *Nature* **560**(7719), 494 (2018).  
 [6] N. Battich, J. Beumer, B. de Barbanson, L. Krenning, C. S. Baron, M. E. Tanenbaum, H. Clevers and A. van Oudenaarden, *Science* **367**(6482), 1151 (2020).  
 [7] P. L. Ståhl, F. Salmén, S. Vickovic, A. Lundmark, J.F. Navarro, J. Magnusson, S. Giacomello, M. Asp, J. O. Westholm, M. Huss and A. Mollbrink, *Science* **353**(6294), 78(2016).



◀ FIG. 2: Reconstruction of differentiation trajectories from scRNA-seq. a) Sketch of a two-dimensional embedding of single cells based on their transcriptome. Each point is a cell and has been coloured according to pseudo-time assignment. Cells labeled as a triangle have a high pseudo-time value. However, lineage tracing studies indicate that they have a different clonal origin from the cells they are connected to in the plot. b) The RNA life cycle starts with transcription from the gene. Newly synthesised RNA is made of nucleotide sequences termed as introns (red) and exons (black). Introns are spliced out to yield mature RNA. Finally, RNA gets degraded. c) Two-dimensional projection of cells isolated from the hippocampus (figure adapted from [5]). Each point is a cell, coloured according to cluster identity. Cell types are annotated. The arrows show the local average RNA velocity, evaluated on a regular grid, and indicate directions of differentiation.

# THE NONLINEARITY OF LIFE

■ Edgar Herrera-Delgado<sup>1,2</sup>, Peter Sollich<sup>2,3</sup> – DOI: <https://doi.org/10.1051/epn/2020506>

■ <sup>1</sup> The Francis Crick Institute, 1 Midland Road, London NW1 1AT, UK

■ <sup>2</sup> King's College London, Department of Mathematics, Strand, London WC2R 2LS, UK

■ <sup>3</sup> Institute for Theoretical Physics, University of Göttingen, Friedrich-Hund-Platz 1, D-37077 Göttingen, Germany

**Statistical physics was originally developed to understand the behaviour of materials like gases, liquids or crystalline solids and the phase transitions between them. But in recent decades, concepts from statistical physics have been applied much more widely, in particular to biological systems.**

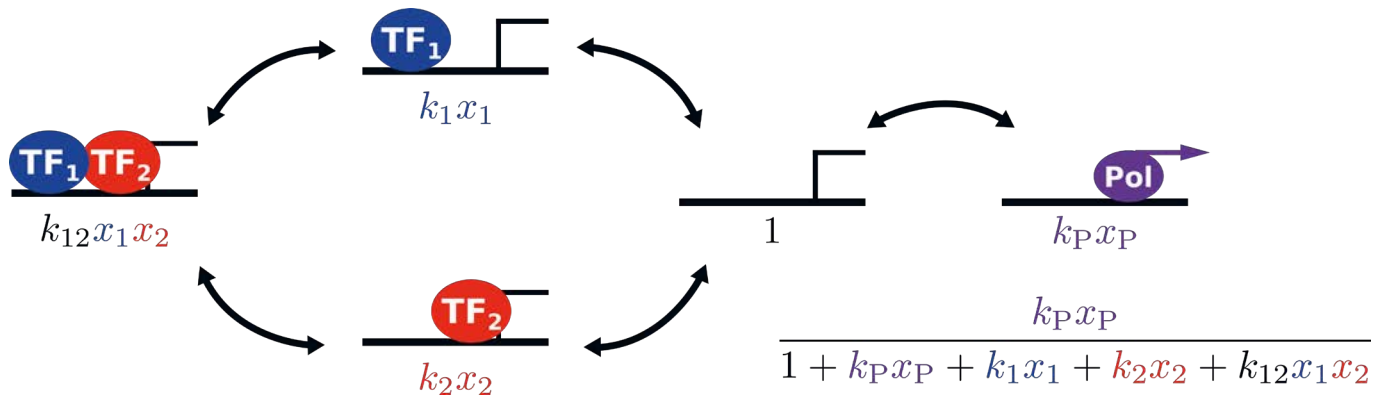
**H**ere they have provided insights into the mechanisms behind some profoundly nonlinear phenomena. One of these is the emergence of patterning in tissues during embryonic development, where cells differentiate from a common initial state into specialised states that are arranged in a highly reproducible fashion. This is achieved in spite of the significant inherent stochasticity in the molecular processes that underpin this behaviour, such as protein production and degradation. In this article we outline how methods from statistical physics can help us understand how biological systems realise this remarkable feat.

## Gene regulatory networks and thermodynamic models

Developing organisms need to specify different cell types in an organised manner to produce the different tissues that form an organism, with the appropriate size and in the correct position. Each cell type is ultimately specified by the proteins that are present within that cell, so the system must ensure that the cells express the right proteins in the right place. This regulation is achieved by Transcription Factors (TFs), which are proteins that

control the production of other proteins, including other transcription factors. TFs therefore interact with each other and can form complex Gene Regulatory Networks (GRNs).

A mathematical description of gene regulation is challenging because of the many nonlinearities involved: TFs can repress or activate the production of other proteins, often with a switch-like concentration dependence, and different TFs can act cooperatively, reinforcing each other's effects, or may compete with each other. Ideas from statistical physics already feature in the construction of models that can incorporate these effects, the so-called thermodynamic models of gene regulation [1]. These models assign thermodynamic weights to the binding states of a piece of DNA. As in mass-action kinetics for chemical reactions, these weights are proportional to the relevant TF concentrations and a binding state-dependent affinity. The protein production rate is then proportional to the relative weight of the states that do produce protein, typically because they have polymerase bound, as illustrated in Fig. 1. The denominator of this fractional weight is the total weight of all states and plays the role of a partition function, a key quantity in statistical physics.

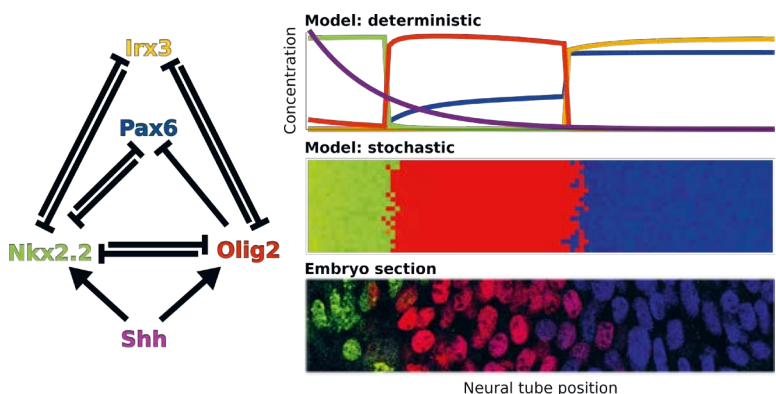


▲ FIG. 1: Sketch of different binding states of a stretch of DNA and transitions between them. Protein will be produced only from the state on the right, where polymerase is bound. When one or both of the transcription factors TF<sub>1</sub> and TF<sub>2</sub> are bound, polymerase cannot bind so these TFs act as repressors. The expressions below each state give its thermodynamic weight in terms of the TF and polymerase concentrations  $x_1$ ,  $x_2$ , and  $x_p$ . The protein production rate is proportional to the relative weight of the relevant states (bottom right). If the affinity  $k_{12}$  is low compared to  $k_1 k_2$ , the transcription factors bind anti-cooperatively: once one is bound the other is unlikely to bind as well.

### Patterning as switching between fixed points

The patterning of the neural tube in vertebrates is a well characterised example of a GRN driving the spatial organisation of a system. A gradient (spatially varying concentration) of the protein Sonic-Hedgehog (Shh, a so-called morphogen) is "interpreted" by cells and this leads to different ultimate cell fates. These fate decisions are made by a GRN consisting of cross-repressive interactions with input from Shh (Fig. 2). The GRN dynamics can be modelled using thermodynamic models of protein production rates as explained above; with appropriate parameters one can then reproduce the experimentally observed timing of protein concentration changes and the final positioning of the cell identity boundaries (Fig. 2) [2]. In more physical language, what this analysis

▼ FIG. 2: (Left) GRN responsible for patterning the ventral vertebrate neural tube. TFs repress each other (lines with bars at end), and input comes in the form of a gradient of Shh (arrows). Colouring of TFs is consistent throughout. (Right) Characteristic concentration pattern of a neural tube, showing discrete spatial domains of gene expression that ultimately lead to distinct choices of neuronal subtypes. Patterns are from deterministic simulation (top), stochastic simulation (middle) and in the mouse embryo (bottom).



shows is that patterning can be viewed as the result of cells switching from one gene regulation fixed point to another in response to an external signal, here given by the spatial variation of morphogen concentration.

### Subnetwork dynamics and memory functions

We have seen that thermodynamic models of GRNs can capture experimentally observed patterning. But can we understand more *qualitatively* how the switching behaviour is generated by the GRN as the pattern is established over time? For this it is helpful to focus on the part of the network driving the dynamics. In the neural tube example this is the pair of TFs Nkx2.2--Olig2, which repress each other and so form a *bistable switch* between two steady states where either one of the TFs has a high concentration and the other a low one. If we want to describe the dynamics of such a subnetwork, we need to account for memory effects: the subnetwork can affect the rest ("bulk") of the network and these effects then feed back at a later time, meaning the subnetwork effectively remembers its past.

The Zwanzig-Mori projection method from statistical physics allows such memory effects to be determined, and we have developed two versions of this to extract information about the mechanisms that lead to emergent behaviour in GRNs.

Focussing firstly on the GRN dynamics near a steady state, the memory effects can tell us about the importance of interactions between TFs. *E.g.* in the neural tube system they identify one such interaction link as ensuring robustness to changes in initial conditions [3], which is important in the noisy world of biological development. We subsequently developed a versatile method that can predict nonlinear memory effects even far from steady states [4]. These are obtained systematically as corrections to a memory-less scenario called quasi-steady state (QSS), where the bulk is taken as adapting immediately to any change in the subnetwork. The approach can correctly capture the choice of cell fate using a subnetwork of just two subspecies, with much greater accuracy than the memory-less QSS approximation (Fig. 3). The memory effects are important also in accounting correctly for the

time delay in final patterning that is characteristic of neural tube patterning (Fig. 3). Importantly, for both of these phenomena one can deduce which specific parts of the network play the biggest role. Nonlinear memory functions thus reveal hidden information that cannot be extracted from *e.g.* directly simulating the GRN dynamics.

## Boundary precision

So far we have ignored fluctuations. But in biology as in physics there is a great amount of randomness, so how can tissue boundaries evolve so precisely? To understand this we can extend the description of GRN dynamics by explicitly including noise, *e.g.* from protein number fluctuations. This gives us Langevin equations, similar to those used in statistical physics to describe the Brownian motion of particles jiggled randomly by a surrounding liquid or gas. Such a stochastic model can then capture the timing, position and, importantly, precision of tissue patterning [5]. We can study in particular how boundary precision is reduced by changes in the GRN such as deleting nodes (TFs) or edges (interactions), and the predicted effects compare well with experiments. An analysis of the model provides an explanation (Fig. 4): boundaries are blurred when cells change stochastically from one fate to another, on the timescale where a tissue pattern is established. Much faster or slower transitions effectively happen always or never, so boundaries stay sharp when transition rates change rapidly from fast to slow as morphogen levels vary across a tissue. These transition rates can be worked out from our stochastic model by generalising Kramers' approach to the thermally activated escape of a particle from a potential well, and this then allows to predict boundary sharpness and its main drivers. We can even perform a systematic screen across a broad class of GRNs, to establish which network structures tend to produce sharp boundaries by the above mechanism [5].

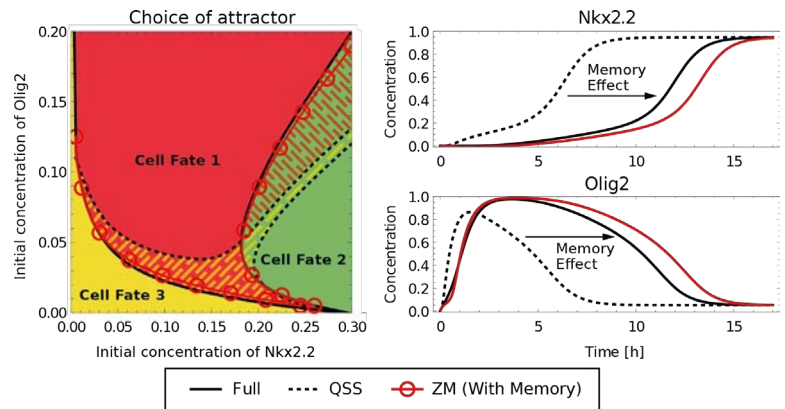
## Concluding remarks

We have only been able to cover a few examples of non-linear physics in biology in this article, yet even so we have encountered a broad range of physical concepts, from thermodynamic weights and reaction kinetics to projection methods, Brownian motion and thermal activation. This suggests to us that there is much potential for future progress in this exciting interdisciplinary effort. ■

## About the Authors



**Edgar Herrera-Delgado** is a post-doctoral researcher in the Mechanics of Mammalian Development group at Institut Curie, having obtained his PhD from King's College London and the Francis Crick Institute. His research focuses on understanding emergent behaviour in biology through modelling, analysis and experiments.



**▲ FIG. 3:** (Left) Basins of attraction for the neural tube network, shown against the initial concentration of the two key TFs. A description of this subnetwork including memory (red circles) captures the true boundaries (black) very well; these mark where cell fate decisions change. Ignoring memory (dotted lines) gives qualitatively wrong predictions (hatched areas). (Right) The timing of patterning is also accurately captured in a subnetwork description with memory, while the memory-less QSS approximation misses the characteristic transient.

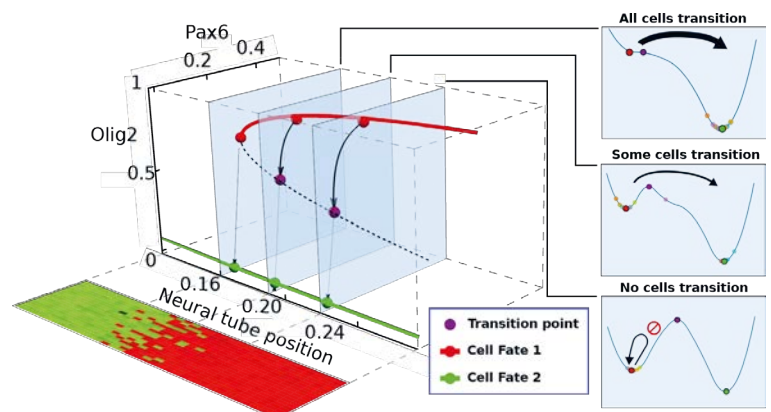


**Peter Sollich** is professor of Non-Equilibrium Statistical Physics at the University of Göttingen and at King's College London, having worked previously at the University of Edinburgh.

## References

- [1] G. K. Ackers, A. D. Johnson and M. A. Shea, *Proceedings of the National Academy of Sciences of the United States of America* **79**(4 I), 1129 (1982).
- [2] M. Cohen, K. M. Page, R. Perez-Carrasco, C. P. Barnes and J. Briscoe, *Development* **141**(20), 3868 (2014)
- [3] E. Herrera-Delgado, R. Perez-Carrasco, J. Briscoe and P. Sollich, *PLoS Computational Biology* **14**(2), 1 (2018).
- [4] E. Herrera-Delgado, J. Briscoe and P. Sollich, *Phys. Rev. Res.* (2020, to be published). arXiv (<http://arxiv.org/abs/2005.04751v1>).
- [5] K. Exelby, E. Herrera-Delgado, L. Garcia Perez, R. Perez-Carrasco, A. Sagner, V. Metzlis, P. Sollich and J. Briscoe, bioRxiv <https://www.biorxiv.org/content/10.1101/721043v1> (2019).

**▼ FIG. 4:** Effect of noise on boundary sharpness. When two cell fates are possible (red/green lines in 3D plot), cells can transition stochastically from "red" to "green"; the rate varies across the tissue. Where transitions are rapid on the developmental timescale they happen always (left on position axis), where they are very slow (right), never. In between the tissue boundary is blurred, so sharp boundaries are produced when transition times change strongly with position.





# Epidemic

## EPIDEMIC SPREADING: TAILORED MODELS FOR COVID-19

■ Alex Arenas<sup>1</sup>, Jesús Gómez-Gardeñes<sup>2,3</sup>, Clara Granell<sup>1</sup> and David Soriano-Paños<sup>2,3</sup>

<https://doi.org/10.1051/epl/2020507>

■ <sup>1</sup> Departament d'Enginyeria Informàtica i Matemàtiques, Universitat Rovira i Virgili, E-43007 Tarragona, Spain

■ <sup>2</sup> Department of Condensed Matter Physics, University of Zaragoza, E-50009 Zaragoza, Spain

■ <sup>3</sup> GOTHAM Lab, Institute for Biocomputation and Physics of Complex Systems, University of Zaragoza, E-50018 Zaragoza, Spain

**A very simple epidemic model proposed a century ago is the linchpin of the current mathematical models of the epidemic spreading of the COVID-19. Nowadays, the abstracted compartmentalisation of the population in susceptible, infected and recovered individuals, combined with precise information about the networks of mobility flows within geographical territories, is the best weapon of the physics community to forecast the possible evolution of contagions in the current pandemic scenario.**

**E**pidemic spreading usually refers to the territorial diffusion of an infectious disease that affects a large fraction of the human population in a relatively short time. The high mortality caused by infectious diseases has boosted mathematical research since the XVIII century. But it took until 1927 for the biochemist W.O. Kermack and the physician A.G. McKendrick to propose what we know today as the "SIR model" [1] and derive one of the main results of epidemiology: the existence of a threshold point that separates the growth of an epidemic from its extinction. Almost a century later, our capabilities for epidemic modeling have been complemented with extraordinary computational resources, which has allowed to tailor the basic models to more sophisticated tools to forecast the epidemic course, but the fundamental idea of the SIR model still remains.

### The linchpin of epidemiological modeling: the SIR model

In epidemiology, compartmental models are those models that assume that the population is divided into groups (compartments) such that individuals belonging to the same compartment are epidemiologically equivalent. The

SIR model divides the  $N$  individuals of a population in three classes: in the "S" compartment people are susceptible to infection (they can get the disease), the "I" compartment consists of people who are infected (and infectious, they can infect others), and the "R" compartment contains those individuals who have recovered from the infection, although "R" can also stand for "removed" to account for people who die from an infection (hence the acronym SIR). Note that at any time  $t$ , it holds that  $N = S(t) + I(t) + R(t)$ .

The SIR model is used to represent the spreading of diseases that yield immunity, no reinfections of individuals are allowed. It specifies the different transitions among these epidemic compartments, according to the most relevant parameters of the particular disease transmission. These transitions can be expressed by a simple *law of conservation of mass*, equivalent to a stoichiometric approach:  $S + I \xrightarrow{\beta} 2I \quad I \xrightarrow{\mu} R$ .

The evolution of these variables is determined by two essential parameters: the probability of infection per contact  $\beta$ , and the recovery rate  $\mu$ . According to the previous expression, if a susceptible individual (S) encounters an infected one (I), the former will transit to the *Infected* compartment with probability  $\beta$ . Additionally, individuals in the *Infected*



compartment will move to the *Recovered* compartment with probability  $\mu$ . These probability rates are specific for each disease, and they depend on so many different factors that it is almost impossible to find accurate values for them by studying the biology of the infection only, making it necessary to rely on statistics once the epidemics evolves.

Despite its simplicity, the SIR model is able to give us some interesting insights. *An essential outcome of the model is the existence of a phase transition whose critical point separates two regimes: one where the epidemic dies out and the other where the epidemic becomes endemic.* Considering the previous simple formulation for the SIR (which assumes a well-mixed population where everybody is statistically equivalent and makes  $\langle k \rangle$  contacts), this critical point happens when  $\beta \langle k \rangle / \mu = 1$ . When this ratio (also known as the Basic Reproductive Number  $R_0$ , indicating the average number of individuals that one infected individual will generate in an otherwise totally susceptible population) is below 1, one infected individual will generate less than one new infected and thus the epidemic dies out. Conversely, when  $R_0 > 1$  the epidemic will grow. The usefulness of this number went unnoticed until 1979, when Anderson and May applied it to study epidemic control strategies ensuring that  $R_0$  is kept below 1. In Figure 1 (top plot) we show this transition, as well as two different temporal evolutions (bottom plots) for two different values of  $R_0$ .

### Including the crucial role of mobility

An important aspect when modeling epidemic spreading is mobility. This is a crucial factor given that the virus is able to travel from one location to another when the host does so. To introduce mobility in the previous model, we adopt the level of description of “metapopulations”, where the full population is decomposed in distinguishable geographical areas named “patches” (see Figure 2). So now, but considering the general quantities  $S(t)$ ,  $I(t)$  and  $R(t)$ , we will have  $S_i(t)$ ,  $I_i(t)$  and  $R_i(t)$ , for each patch  $i$ . Also, the subpopulations are not isolated, instead they are connected through a network of mobility flows  $W$ , where  $W_{ij}$  is the weight of the connection between patch  $i$  and  $j$ . Considering this new scenario, the mobility and epidemic dynamics are as follows: (I) each individual belongs to (or resides in) a patch; (II) an individual will travel outside its patch with probability  $p$  and its destination patch is chosen according to the mobility flows  $W$ ; (III) the individual will contact a fraction of individuals in the destination patch; (IV) the mobility patterns are recurrent, meaning that after traveling, the individual will return to its original patch, implying that the next travel will start out from the same patch of origin. Regarding the epidemics, these mobility dynamics imply that one individual might get infected either if he does not travel and gets infected by someone resident of (or that has traveled to) his origin patch; or if the individual travels and gets infected in the destination patch either by a resident or by somebody that has traveled to that patch. See [2] for the full formulation of this model.

This new scenario allows us to account for a realistic setup in epidemics, one where individuals move across territories; and gives us some non-trivial insights about the role of mobility. Indeed, following the same rationale as with the original SIR model, we can calculate the critical point of the phase transition between epidemic extinction and epidemic growth as a function of the mobility parameters, and therefore learn what interventions in mobility should be enforced if we want to ensure the epidemic is receding. One surprising conclusion that we learn from this model is that a higher mobility probability does not always imply a higher spreading in the epidemic. This is counterintuitive, as higher mobility implies a higher mixing between the subpopulations, and this should foster the spread of the virus. However, despite the higher spatial diffusion, we found that, in some cases, mobility can reduce the number of potential interactions made by infectious individuals, which leads to a higher value of the epidemic threshold needed to observe an outbreak [2,3].

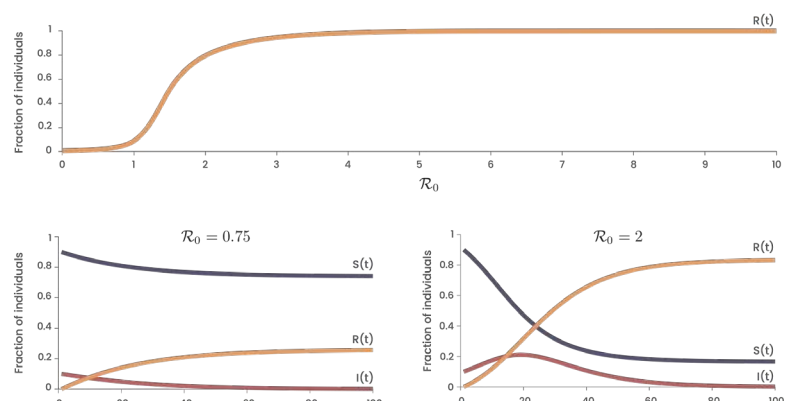
### Towards a tailored model for COVID-19

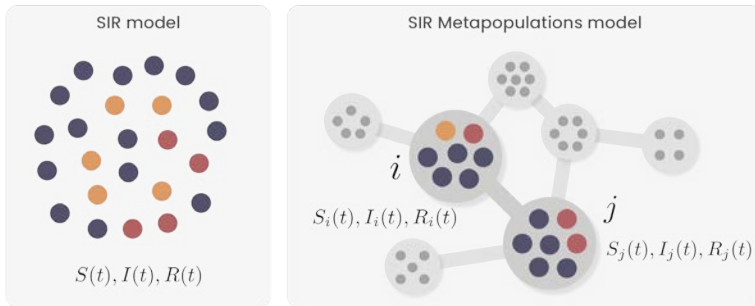
Once we have a basic framework to represent any SIR-like disease and account for mobility, we can move on to the challenge of modeling COVID-19 [7,8]. For this particular disease the epidemic compartments available in the SIR are not enough to capture the complexity of the dynamics and the timescales of transmission of COVID-19, so we start out by including more epidemiological compartments and new transitions among them. The following is a summarised list of the key additions that one has to consider for modeling COVID-19, as exposed in [2-5].

First, we introduce the *Exposed* compartment (E), that accounts for individuals that are in the incubation stage (already infected but not yet infectious). Therefore, when a susceptible individual contacts an infectious one, the former will transit to the *Exposed* compartment, and will remain in this state until the incubation time has passed.

Second, a crucial aspect of the COVID-19 is the existence of *Asymptomatic* individuals (A): individuals that are infected and infectious but that do not show any symptoms. Far from being a clinical feature only, this class is epidemiologically very relevant: an asymptomatic individual is rarely aware of its infectious potential and therefore his or

▼ FIG. 1: Results for the SIR model in a well-mixed population. Top: fraction of recovered individuals in the steady state as a function of  $R_0$ . Bottom: Fraction of individuals in each compartment as a function of time, for two values of  $R_0$ , one below the epidemic threshold ( $R_0=0.75$ ) and the other above the epidemic threshold ( $R_0=2$ ). In both cases the initial fraction of infected individuals is 10%.





**▲ FIG. 2:** Schematic of the SIR metapopulations model compared to the basic SIR model. In the metapopulation model we consider multiple populations so that now the quantities  $S_i(t)$ ,  $I_i(t)$  and  $R_i(t)$  refer to the fraction of Susceptible, Infected and Recovered individuals in patch  $i$ . These quantities can also be interpreted as the probability that a resident of patch  $i$  is in the Susceptible, Infected or Recovered state. The colours are identical to those used in Fig. 1.

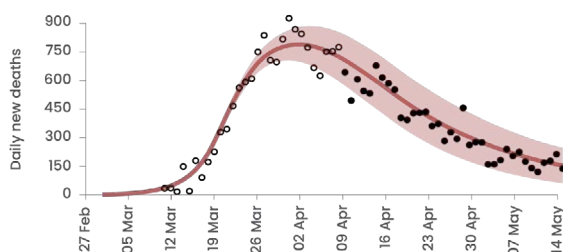
her social and mobility patterns remain unchanged, fostering the spread of the pathogen across the territory.

Third, at variance with usual SIR-like models, we include compartments that capture the clinical evolution of those infected individuals that need hospitalisation in ICU, distinguishing between those that have a favourable prospect and will transit to Recovered after the hospitalisation time has passed, and those having a fatal outcome, transiting to a *Deceased compartment*. This way, besides forecasting the epidemic trajectory, the model allows us to assess different clinical aspects associated to the pandemic such as the health system overload or the number of fatalities.

Another major feature of COVID-19 models lies in the addition of age compartments. Indeed, it is known that age influences not only the symptomatology of the disease, but also the individual's prospect. Besides this clinical factor, the mobility patterns also depend on the age of the individual (e.g. retired individuals do not commute to work). Therefore, we deem necessary to account for age compartments, and we choose to divide the population in three segments: young (Y), adult (M), and elderly (O). To accommodate the age strata, each of the previously mentioned compartments is triplicated, and we use a contact matrix to model the contacts that are established between age compartments.

Once all the aforementioned particularities of COVID-19 are accounted for, the resulting model becomes a very powerful tool for surveillance and policy making. For example, starting out from a completely susceptible population, we can seed infection in certain patches (mimicking the first imported infection cases) and let the system evolve, observing to what other territories the disease spreads to, effectively forecasting community transmission. From this setup, one can calculate the expected amount of new cases, hospitalisations or deaths (see Figure 3). Besides merely observing the outcome of the system, one can also simulate containment measures, like restricting the number of contacts of the elderly population (emulating the confinement of this age

**► FIG. 3:** Daily new deaths for the first wave of COVID-19 in Spain in 2020. The red line represents the outcome of the model, while dots represent real data as reported by the Spanish health authorities. Hollow dots represent the data points used to calibrate the parameters of the model, and solid dots are data used for validation.



segment), and observing if this implies a reduction in hospital load, for example. But most importantly, we can, as we did with the previous simpler models, calculate the critical threshold of the phase transition and discern which values of the parameters drive the epidemic to extinction [6,7].

Summarising, the SIR model established a solid foundation to model the spreading of infectious diseases in a population. Despite its simplicity, it still remains at the core of most of the current tools for epidemic forecasting. *Including the epidemiological traits of the disease we wish to model and considering the role of human mobility, one is able to build very effective tools that reveal us what are the crucial mechanisms behind the spreading of a particular disease, giving us the opportunity to anticipate its outcome and change the course of epidemics.*

### About the authors



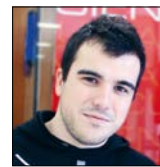
**Alex Arenas** is a full professor at Universitat Rovira i Virgili. His contributions in network science and complex systems -including community detection, synchronization, and multilayer networks- have granted him fellow of the American Physical Society (APS).



**Jesús Gómez-Gardeñes** is an associate professor at the University of Zaragoza. He leads the group of theoretical and applied modeling, specialised in studying the effect of human behaviour in the spreading of diseases.



**Clara Granell** is a junior researcher with a Beatriz Galindo Fellowship at Universitat Rovira i Virgili. The backbone of her research is the study and description of complex systems through the perspective of network science, especially focused on the spreading of infectious diseases.



**David Soriano-Paños** is a PhD Candidate at the GOTHAM Lab in Universidad de Zaragoza, his work focuses on epidemic modeling and human mobility on complex networks.

### References

- [1] A.G. McKendrick, *Proceedings of the Edinburgh Mathematical Society* **13**, 98 (1926). W. O. Kermack and A. G. McKendrick, *Proceedings of the royal society of london. Series A, Containing papers of a mathematical and physical character* **115(772)**, 700 (1927).
- [2] J. Gómez-Gardeñes, D. Soriano-Paños and A. Arenas, *Nature Physics* **14(4)**, 391 (2018).
- [3] C. Granell and P. Mucha, *Phys. Rev. E* **97**, 052302 (2018).
- [4] A. Vespignani, H. Tian, C. Dye *et al.*, *Nature Rev. Phys.* **2**, 279 (2020).
- [5] E. Estrada, *Physics Reports* **869**, 1 (2020).
- [6] A. Arenas *et al.*, medRxiv. <https://doi.org/10.1101/2020.03.21.20040022> (2020)
- [7] A. Arenas *et al.*, medRxiv. DOI: <https://doi.org/10.1101/2020.04.06.20054320> (2020)

# COMPANY DIRECTORY

Highlight your expertise. Get your company listed in europhysicsnews company directory  
For further information please contact [bernadette.dufour@edpsciences.org](mailto:bernadette.dufour@edpsciences.org)

## ADVANCED ENERGY

[advancedenergy.com/trek](http://advancedenergy.com/trek)

Advanced Energy designs and manufactures products for demanding applications in research and industry. High voltage amplifiers from our Trek product line utilize proprietary circuitry to provide a closed-loop amplifier system with exceptional DC stability and wideband performance for driving capacitive loads. Trek's non-contacting electrostatic voltmeters circumvent the charge transfer issues of traditional contacting technology.



## BARTINGTON INSTRUMENTS

[www.bartington.com](http://www.bartington.com)

Bartington Instruments designs and manufactures high precision fluxgate magnetometers, Helmholtz coil systems, gradiometers, magnetic susceptibility instruments and associated data processing equipment, for the precise generation and measurement of magnetic fields around physics experiments, and for calibration of magnetometers in consumer electronics.



## LEYBOLD

[www.leybold.com](http://www.leybold.com)

Leybold offers a broad range of advanced vacuum solutions for use in manufacturing and analytical processes, as well as for research purposes. The core capabilities center on the development of application- and customer-specific systems for creating vacuums and extracting process gases.



## MB SCIENTIFIC AB

[www.mbscientific.se](http://www.mbscientific.se)

MB Scientific AB is a Swedish company which develops and produces state of the art instruments for the photoelectron spectroscopy experiments. Our photoelectron energy analyser MBS A-1 gives you the opportunity to do world leading research together with MBS VUV photon sources, MBS L-1 and T-1, which produce the brightest and narrowest lines existing to be used for this type of experiments.



## MCPHERSON

[www.mcphersoninc.com](http://www.mcphersoninc.com)

McPherson designs and manufactures scanning monochromators, flat-field imaging spectrographs, and vacuum monochromators and measurement systems for reflectance, transmittance, and absorbance testing. Its spectrometers and systems are built for soft x-ray, vacuum-ultraviolet, and UV/Vis and Infrared wavelengths. Applications range from lasers and lithography, solar, and energy to analytical life science and more.



## OPTIGRATE

[www.optigrate.com](http://www.optigrate.com)

OptiGrate Corp is a pioneer and world leader in commercial volume Bragg gratings (VBGs) and VBG-based ultra-narrow band optical filters. BragGrateT Raman Filters from OptiGrate are unmatched in the industry for narrow linewidth, optical density, and optical transmission. BragGrate notch filters enable measurements of ultra-low wavenumber Raman bands in the THz frequency range down to  $4\text{ cm}^{-1}$ .



## PFEIFFER VACUUM

[www.pfeiffer-vacuum.com/en/](http://www.pfeiffer-vacuum.com/en/)

Pfeiffer Vacuum stands for innovative and custom vacuum solutions worldwide, technological perfection, competent advice and reliable service. With the invention of the turbopump, the company paved the way for further development within the vacuum industry. Pfeiffer Vacuum offers a complete product portfolio: backing pumps, leak detectors, measurement and analysis devices, components as well as vacuum chambers and systems.



## TOPTICA PHOTONICS

[www.toptica.com](http://www.toptica.com)

TOPTICA Photonics, founded in 1998 near Munich (Germany), develops and manufactures high-end laser systems for scientific and industrial applications. The portfolio includes diode lasers, ultrafast fiber lasers, terahertz systems and frequency combs. OEM customers, scientists, and over a dozen Nobel laureates all acknowledge the world-class exceptional specifications of TOPTICA's lasers, as well as their reliability and longevity.

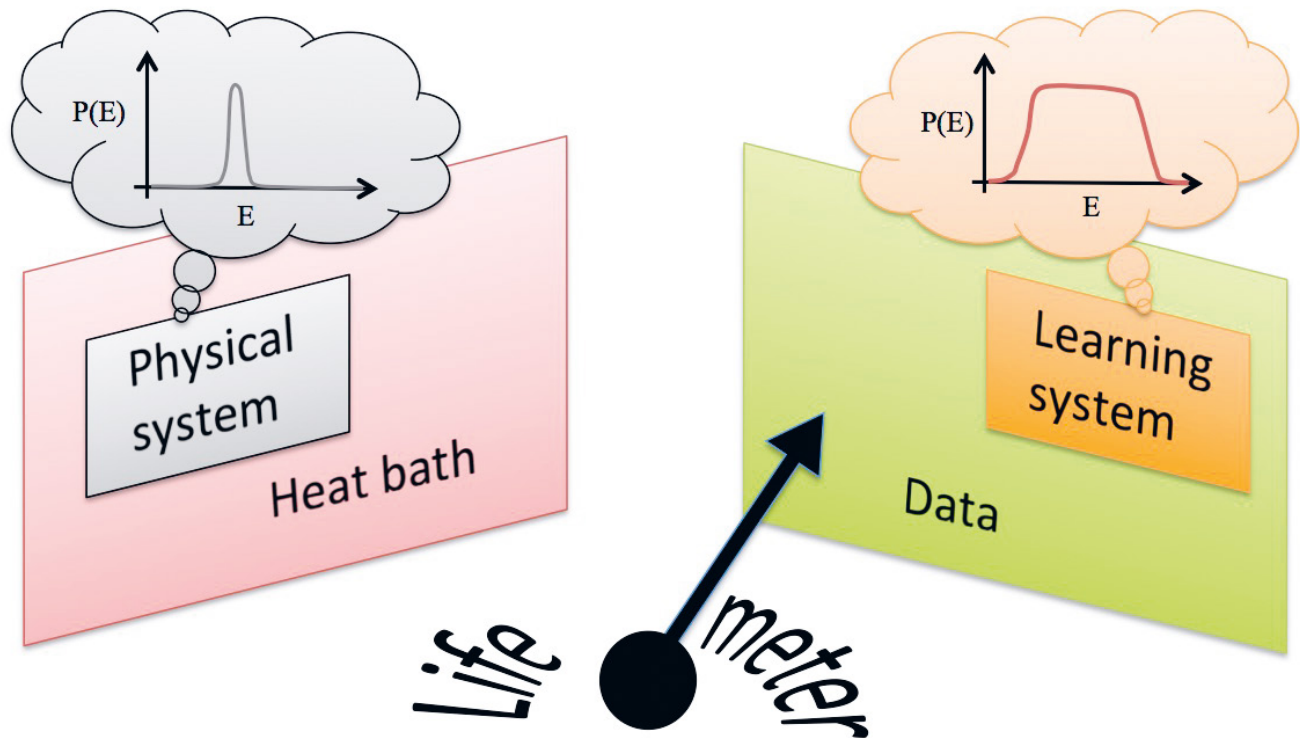


## ZURICH INSTRUMENTS

[www.zhinst.com](http://www.zhinst.com)

Zurich Instruments is a technology leader developing and selling advanced test & measurement instruments for dynamic signal analysis. These devices are used in many fields of application by high-technology research laboratories and industrial development sites. Zurich Instruments' vision is to revolutionize instrumentation in the high-frequency and ultra-high-frequency range by incorporating the latest analog and digital technology into powerful measurement systems.





# ON THE IMPORTANCE OF BEING CRITICAL

■ Matteo Marsili – DOI: <https://doi.org/10.1051/e pn/2020508>

■ The Abdus Salam International Centre for Theoretical Physics – 34151 Trieste, Italy

Being critical, *i.e.* able to process and distill relevant information, is crucial for living systems. Learning distinguishes living from inanimate matter. Quantifying this distinction may provide a "life meter" [1] that, for example, can allow us to detect alien life forms in astrobiology. Living systems also respond in an anomalous manner to perturbations, as compared to inanimate matter, unless the latter is poised at a critical state (in the statistical physics sense). I argue below that these two notions of criticality are only apparently different, because a system that learns is inherently critical, also in the statistical physics sense.

**A**rtificial Intelligence provides an ideal framework to investigate learning in quantitative terms. A learning machine differs in two important respects from a physical system. First, the latter is ruled by the maximum entropy principle, that constrains the distribution to the Gibbs-Boltzmann form and fixes its parameter, the temperature, to that of the environment. Therefore, all a physical

system knows about its environment is just one number. Instead, learning machines, such as deep neural networks, can adjust billions of parameters to shape their internal representations. Second, the "environment" in which learning machines are immersed is the data they learn. This "environment" (*e.g.* digital pictures) generally has a very rich statistical structure of hidden features. After all, there should be something to learn [2]!

Taking this comparison further, one [3,4,5] realises that learning is a dual problem with respect to statistical mechanics. In the latter, the Hamiltonian is given and the distribution over internal states is dictated by the maximum entropy principle. In learning, the Hamiltonian is adjusted in the training process. The energy takes the natural meaning of a coding cost and its average fixes the **resolution** of the representation, *i.e.* the number of bits spent to represent one data point. Physical systems have a very narrow distribution of energies. A learning machine, instead, will make its spectrum of energies (*i.e.* coding costs) as broad as possible to distinguish significantly different structures in the data [3,5]. This is because the **relevance**, which is an entropic measure of the width of the energy range, lower bounds the amount of information that the representation extracts about the hidden features of the data [5]. Therefore, machines that achieve a maximal relevance at a given resolution (*i.e.* those with a broad energy distribution) are those that are maximally informative about the hidden features.

The **principle of maximal relevance** has been verified in learning machines such as Restricted Boltzmann Machines (see Fig. 1) or Deep Belief Network [5,6] and efficient coding [7]. This principle predicts distributions of energy levels that are consistent with the suggested hyperbolic geometric nature of sensory representations [8], and with the (expected) invariance of representations under coarse graining of the data (*i.e.* a picture of a dog should be classified in the same way, both at high and low resolution). This principle also predicts a linear relation between the (micro canonical) entropy and the energy, in the statistical mechanics analogy, which is a signature of criticality [7]. A sample of states from this distribution exhibits statistical criticality, *i.e.* the frequency with which a given state is observed scales with an inverse power law with its frequency rank. The exponent of this law is related to the trade-off between resolution and relevance (see Fig. 1): at high-resolution, the representation is noisy. Further compression extracts more relevant information (*i.e.* the relevance increases). The relevance reaches a maximum at an intermediate resolution and then it decreases.

At the maximum, the distribution of energies is flat, which corresponds to the occurrence of Zipf's law [10]. Hence Zipf's law appears as a signature of maximally informative representations. In this perspective, the occurrence of Zipf's law in the frequency of words in most languages is not surprising. More generally, biological systems are critical not because they are "poised" at a critical point, but rather because their internal states (*e.g.* the immune system) are efficient representations of their environments (*e.g.* the space

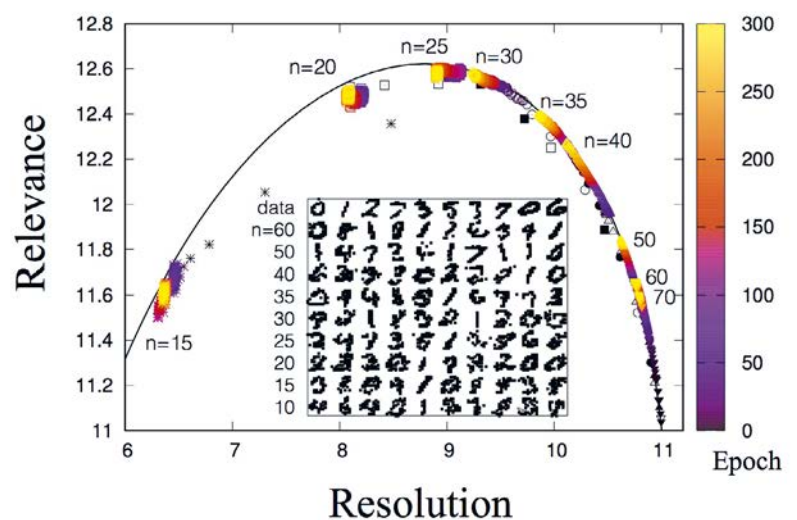


## The relevance lower bounds the amount of information that the representation extracts about the hidden features of the data

of pathogens). This makes criticality a candidate "life meter" [1], because it occurs generically in learning systems, irrespective of what is learned.

The **abundance of experimental data** in life sciences presages remarkable advances in unveiling Nature's code. This requires statistical inference to venture in scarcely explored domains. First, our ignorance of the underlying laws that govern living system requires model-free methods. Second, inference needs to operate in the deep under-sampling regime, where the number of samples is very small compared to the dimensionality of the data. For example, the number of sequences of a protein domain that evolution dispensed us with may be much less than those necessary to estimate parametric models. Life itself operates on very sparse data. A bacterium cannot afford the luxury of estimating changes in gradient concentrations to an arbitrary precision, before mounting the appropriate response. Inference methods need to take into account this trade-off between "chance" and "necessity", to extract information on biological function from data. The concept of relevance provides a guide to explore the under-sampling

▼ FIG. 1: Learning machines converge to representations of maximal relevance at a given resolution. The values of the resolution and of the relevance are reported at different stages of training (from black to yellow) for Restricted Boltzmann Machines (RBM) trained on a dataset of hand-written digits (see Ref. [5] for more details). Different symbols correspond to different number of hidden units, from 15 (left) to 70 (right). The full black curve corresponds to the theoretical limit of maximal relevance. Inset: sample digits in the data (top row) are compared with those generated by RBM's with varying number of hidden units.





## Biological systems are critical not because they are "poised" at a critical point, but rather because their internal states are efficient representations of their environments

regime in a model-free manner, and to detect the signature that "necessity" leaves in biological data. If the internal state of a living system is a maximally informative representation, searching for critical subsets of variables (those with high relevance) in the data, may shed light on how that living system copes with its environment.

The neural code responsible for spatial cognition is a good example of how relevance-based inference differs from standard methods. The Moser's lab [11] deciphered the neural code responsible for spatial cognition in rats, by identifying specialised neurons that fire when the rat visits the vertices of a triangular lattice (see Fig. 2). They did this by correlating neural activity with the rat's position. Evidently, upstream neurons in the cortex don't need to know the rat's position to identify neurons responsible for spatial cognition. This means that one can find these neurons on the basis of their spiking time series alone. Cubero *et al.* [12] have shown that it is possible to identify relevant neurons, without a clue of what they

are coding for, using only data on neural activity. They propose an indicator, called Multi-Scale Relevance (MSR), which characterises the response of a neuron on all time-scales. Neurons with a low MSR are uninformative about navigation covariates (position or direction), whereas all informative neurons have a large value of the MSR (see Fig. 2). The group of neurons with largest values of the MSR allows one to decode the position of the animal as precisely as the group of neurons with the largest spatial information content.

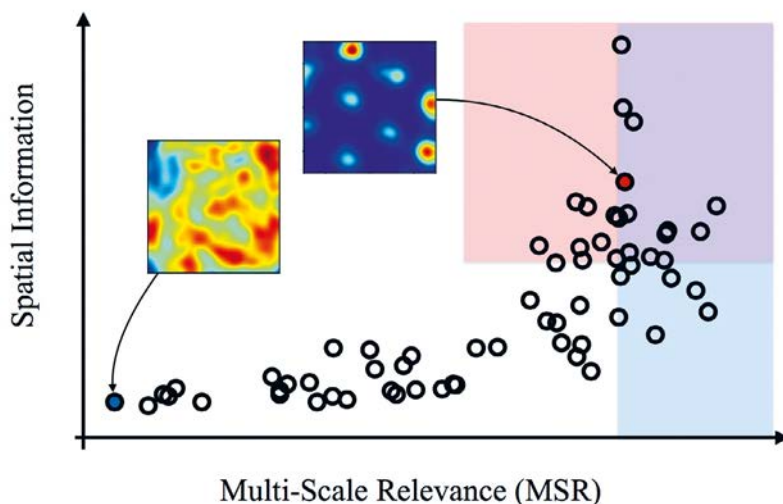
The concept of relevance has also been used to identify biologically relevant sites in protein sequences [13], but it can also be applied to the study of single cell expression data or of DNA methylation, to mention just two examples. In each case, the concepts needs to be declined in appropriate ways, always keeping in mind Doctor Zhivago's warning that "[...] life is never a material, [...] it is infinitely beyond your or my obtuse theories about it".

### About the Author



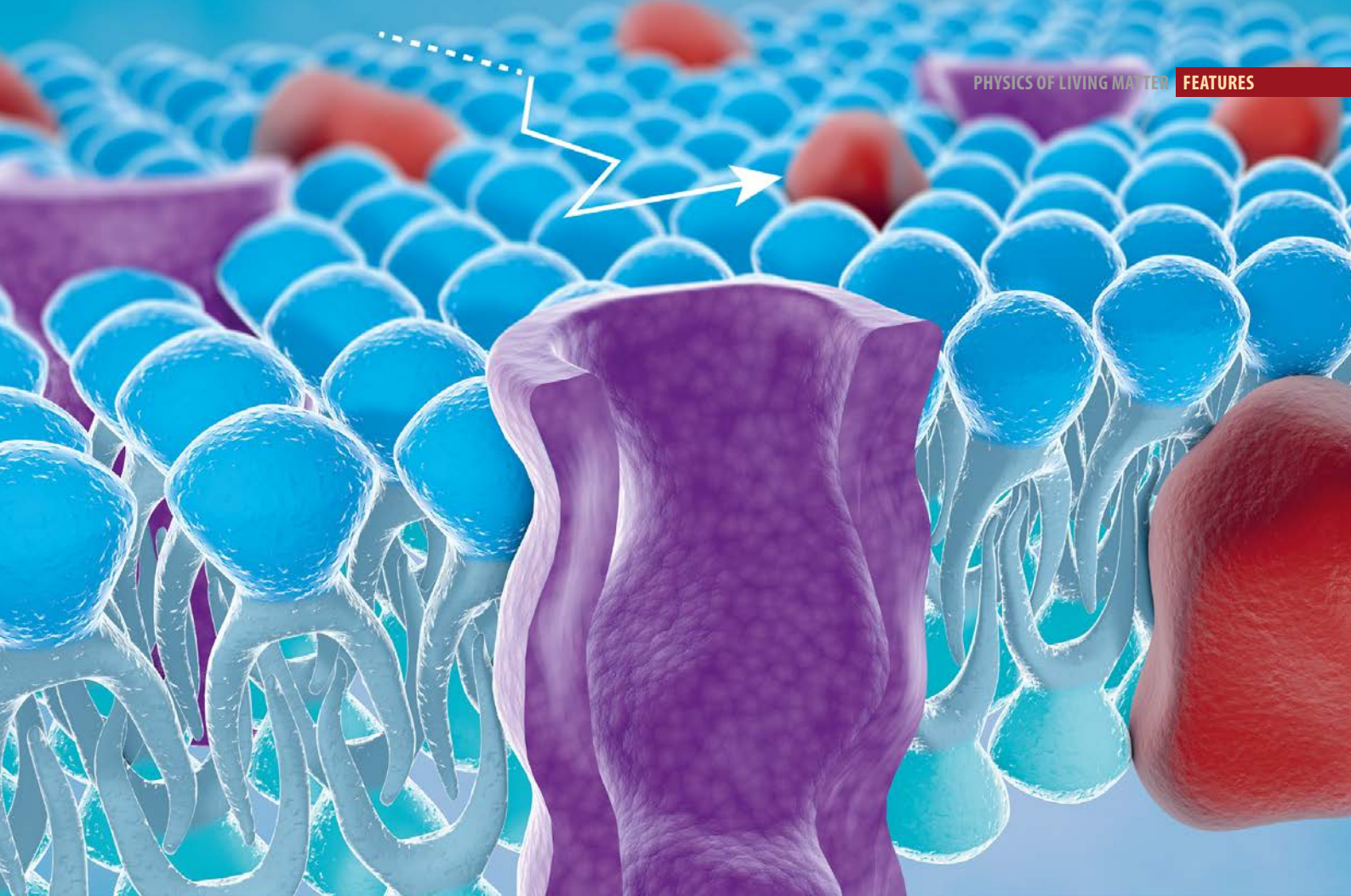
**Matteo Marsili** is a theoretical physicist, leading the Quantitative Life Sciences Section of the Abdus Salam ICTP. He's interested in understanding collective phenomena in different disciplines (physics, biology, economics and finance, statistical inference and learning) with statistical physics methods.

▼ FIG. 2: Multi-Scale relevance and Spatial Information for 65 neurons recorded in the medial Entorhinal Cortex of navigating rats, by Stensola *et al.* [11] (data from Ref. [12]). The spatial information is the mutual information between the rat's position and the neural activity, during the experiment. The insets show the firing rate maps for two representative neurons, that reports the probability of spiking at a given location. The 20 most relevant neurons (in the shaded blue region) can predict the position of the rat at least as well as the 20 most informative ones (red shaded region). Note that identifying the most relevant neurons only requires data on the neural activity, whereas the most (spatially) informative neurons can only be found if also the spatial covariate is known.



### References

- [1] P. Davies, *Physics Today* **73**(8), 34 (2020)
- [2] M. Mézard, *Phys. Rev. E* **95**, 022117 (2017)
- [3] R. J. Cubero, *et al*, *Journal of Statistical Mechanics: Theory and Experiment* **6**, 063402 (2019)
- [4] M. Marsili, *Journal of Statistical Mechanics: Theory and Experiment* **10**, 103401 (2019)
- [5] O. Duranthon, M. Marsili and R. Xie, *Maximal Relevance and Optimal Learning Machines*, arXiv:1909.12792 (2019)
- [6] J. Song, M. Marsili and J. Jo, *Journal of Statistical Mechanics: Theory and Experiment* **12**, 123406 (2018)
- [7] R. J. Cubero, M. Marsili and Y. Roudi, *Entropy* **20**(10), 755 (2018)
- [8] T. O. Sharpee, *Current Opinion in Neurobiology* **58**, 101 (2019)
- [9] T. Mora and W. Bialek, *J. Stat. Phys.* **144.2**, 268 (2011).
- [10] L. Aitchison, N. Corradi and P. E. Latham, *PLoS computational biology* **12**(12), e1005110 (2016)
- [11] H. Stensola, *et al.*, *Nature* **492** (7427), 72
- [12] R. J. Cubero, M. Marsili and Y. Roudi, *J. Comput. Neurosci.* **48**(1), 85 (2020)
- [13] S. Grigolon, S. Franz and M. Marsili, *Molecular BioSystems* **12**(7), 2147 (2016)



# FROM SINGLE PARTICLE MOTION TO STRUCTURE OF BIOLOGICAL SYSTEMS

■ Yael Roichman – DOI: <https://doi.org/10.1051/epn/2020509>

■ School of Chemistry, School of Physics & Astronomy, and the Center for Physics and Chemistry of Living Systems, Tel-Aviv University, Israel

**Single molecule and single particle microscopy opened the door to observing dynamical processes in noisy living systems. Recent studies demonstrate how the stochastic motion of tracer particles can also provide us with information about the structure and flow properties of active and complex biological systems.**

**T**he realization that microscopic particles suspended in fluid move randomly dates back to Robert Brown, a botanist who first observed this phenomenon when watching plant pollen immersed in water under the microscope in 1827. This motion was named Brownian motion and its origin, collisions between water molecules and the suspended particles, was suggested first in 1905 by Albert Einstein [1]. In 1926 Jean Perrin received the Nobel Prize in Physics for using quantitative measurements of Brownian motion as evidence of the

discontinuous nature of matter. In his experiments, Jean Perrin recorded the stochastic trajectories of diffusing particles and related the auto-correlation of their motion to their diffusion constant ( $D$ ),  $\langle \Delta x^2 \rangle = 4Dt$ . The diffusion constant of particles performing Brownian motion in a simple fluid was found to be inversely proportional to the viscosity and linearly proportional to the temperature of the fluid.

The motion of a microscopic particle in a fluid excites long-range flows that affect the motion of other particles immersed in the same fluid. The cross



## Gels of actin and myosin reconstituted in the lab from pure proteins have been studied extensively as a model system for active biomaterials. ”

correlation in motion of two particles embedded in the same fluid arises from such flows, and is proportional to temperature and viscosity in a similar manner to the diffusion constant.

Thermally induced motion, therefore, enables such particles to explore their surroundings and interact with each other over large distances. Turned around, by monitoring the autocorrelation and cross correlation in the motion of colloidal particles, it is possible to characterise the fluid in which they are immersed. The cross correlation in the diffusive motion of two particles at a distance  $R$  is defined as  $D_{\parallel,\perp} = \langle \Delta \vec{x}_i \cdot \Delta \vec{x}_j \delta(|\vec{x}_{ij}| - R) \rangle_{ij}$  in the parallel and perpendicular direction to the vector connecting their centre. This observation is the basis of the field of microrheology [2]; a method to characterise the mechanical properties of materials using extremely small samples of less than a few microliters.

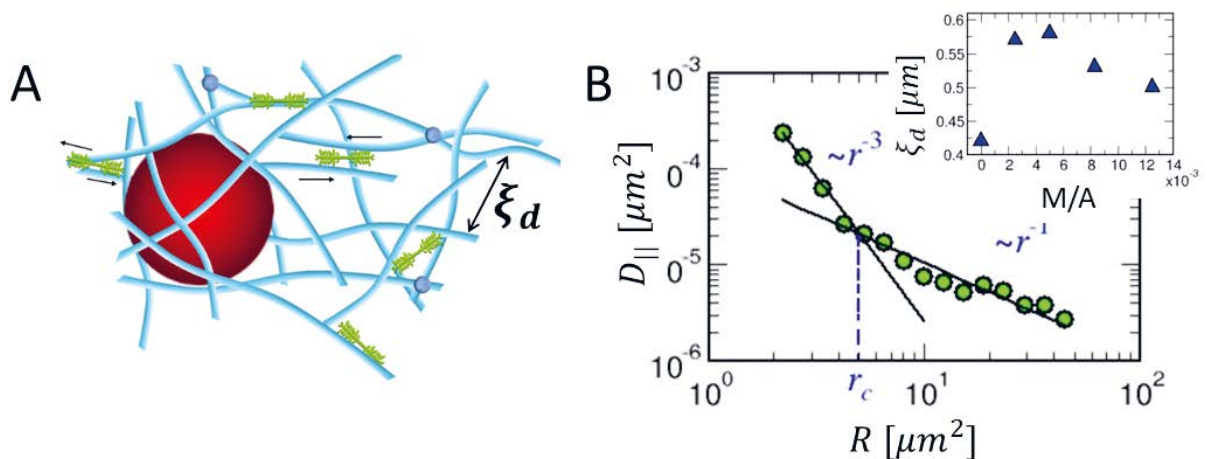
The application of microrheology to characterise biological systems is challenging. First, biological systems are not in thermal equilibrium and therefore the fluctuation of a tracer particle, or biomolecules such as proteins, do not arise solely from thermal motion. This implies that the diffusion constant does not relate to the viscosity of the fluid through the temperature. Second, biological materials, such as the membrane or the skeleton of a cell, are examples of complex fluids, which are materials that respond to mechanical perturbation with a combination of viscous flow and elastic resistance. Complex fluids are comprised of

mesoscopic building blocks, such as the protein chains of the cytoskeleton or the membranal proteins of the cell membrane.

A tracer particle diffusing in a complex-fluid and exploring its neighborhood is affected by the local structure of the fluid. This is reflected in the type of diffusion that it undergoes. Moreover, if the fluid has active components such as molecular motors, the tracer will be affected by them as well. Identifying all the physical processes underlying the motion of tracer particles in such complex conditions remains an ongoing challenge in physics. However, comprehensive analysis tools exist for identifying to leading order structural and dynamical effects have been developed [3]. On the other hand, the flow field a tracer particle produces is affected by the structure of the complex fluid in a completely different manner. Since the functional form of its decay with distance is governed by momentum and mass conservation laws [4], it depends significantly on the interparticle distance. For example, at large inter-particle distances the correlated diffusion reflects the bulk properties of the complex fluid compared to the fluid's typical structural features. The question then arises, what can we infer from the fluctuation of a tracer particle in biological systems?

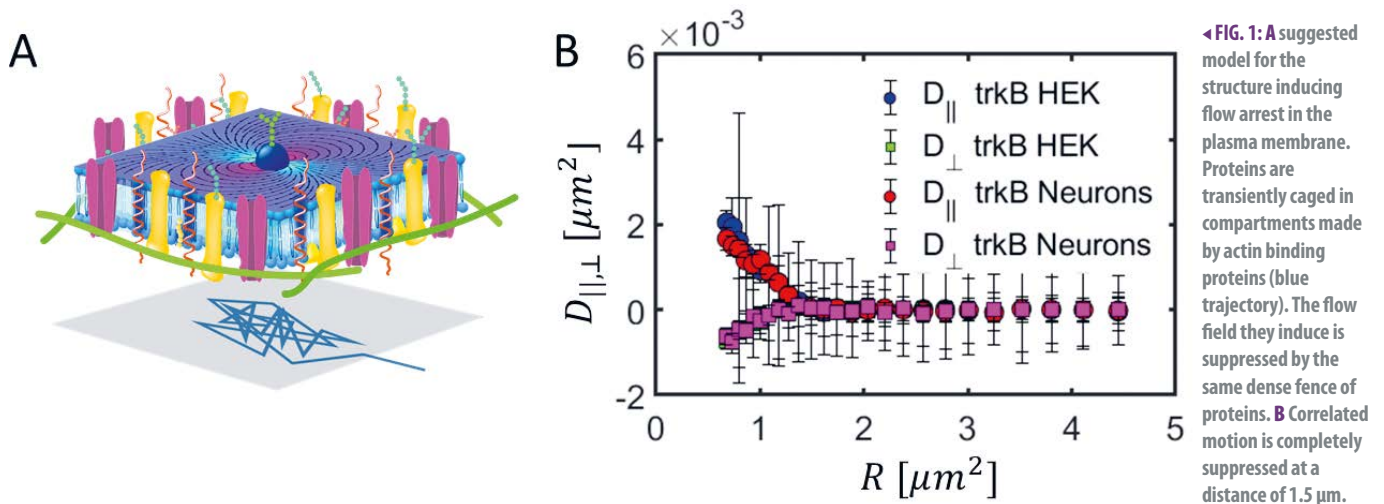
### Structural features affect flow in biological gels

One of the ubiquitous proteins in cells is actin, the polymer that acts to maintain the shape of the cell, that helps to resist external stresses and plays a major role in cell motion. In the cell, actin self-organises into many different structures, one of which is a network supporting the outer membrane of the cell. Myosin II is a molecular motor that can slide two actin filaments one against the other by consuming chemical energy and converting it to motion (Fig. 1A). Gels of actin and myosin reconstituted in the lab from pure proteins have been studied



**▲ FIG. 1:** The structure of actin and myosin networks. **A** Illustration of an actin network (light blue) with myosin motors (green), cross linkers (circles) and a large tracer particle (red sphere). **B** A distinct cross-over in the decay rate of the correlated diffusion is observed at  $r_c$ . From  $r_c$  we extract the mesh size of the network  $\xi_d$  and plot it as a function of myosin to actin (M/A) concentration (inset).





◀ **FIG. 1:** A suggested model for the structure inducing flow arrest in the plasma membrane. Proteins are transiently caged in compartments made by actin binding proteins (blue trajectory). The flow field they induce is suppressed by the same dense fence of proteins. **B** Correlated motion is completely suppressed at a distance of 1.5  $\mu\text{m}$ .

extensively as a model system for active biomaterials. The large difference, *i.e.* two orders of magnitude, between the mechanical properties inferred from the single particle diffusion and the correlated diffusion are a signature of the complex structure of these gels [4].

We examine a range of actin networks with varying typical mesh size. Single particle trajectories allow us to characterise the local environment of the particle and specifically the network structure in terms of the network pores. The correlated motion of tracer particles allows us to measure the flow field at different length scales (Fig. 1B). At intermediate distances, the correlations and induced flow field decay fast ( $\sim 1/r^3$ ) with distance. At asymptotically large distances they decay slowly as  $1/r$ . The typical network mesh size is related to the cross-over distance,  $r_c$ , through the ratio of auto to cross correlated motion of the tracers [5].

In the presence of myosin motors, the fluctuations of the actin network include both thermal and active contributions [6]. Nonetheless, these complex fluctuations induce a similar type of random motion that provides the opportunity to measure the local structure of the actin network and induced flow field within them. The same telltale of the distinct transition in the correlated diffusion of tracer particles is observed in such acto-myosin networks and demonstrates the change in structure due to the introduction of the myosin motors to the network (inset Fig. 1B).

### Flow arrest in the plasma membrane

The plasma membrane forms the interface between a cell and its environment. It controls the incoming traffic of signals and nutrients and the outflux of signals and waste. The plasma membrane is made of a bilayer of phospholipids, molecules that have a hydrophilic charged head and hydrophobic tails. The complex function of the membrane relies on embedded proteins that constitute approximately half of the mass of the membrane. It is also supported by and transiently connected through proteins to the underlying actin network.

Measurements of the motion of fluorescently tagged single molecules within the plasma membrane reveal caged motion (Fig. 2A). Moreover, the correlated motion shows that the membrane flow is local (Fig. 2B) [7]. Combined, these results support the “picket and fence” model with a high density of proteins forming the fences (Fig. 1A).

### Conclusions

The combination of the auto and cross correlation in the motion of tracer particles in biological systems provides insight into details of their structure and flow properties, even far from equilibrium. Using this technique, we were able to show that the mechanical response of the cell is local, which supports the notion of the importance and location selectivity of mechanical signals at the cellular level.

### About the author



**Yael Roichman** is a professor of Physics and Chemistry in Tel Aviv University. She is an expert in microscopy, holographic optical trapping, and single particle tracking, which she uses to study biophysics, soft matter, and non-equilibrium statistical mechanics.

### References

- [1] A. Einstein, *Ann. Phys.* **14**, 182 (1905)
- [2] T. G. Mason and D. A. Weitz, *Phys. Rev. Lett.* **74**, 1250 (1995)
- [3] Y. Meroz and I. M. Sokolov, *Phys. Rep.* **573**, 1 (2015)
- [4] A. Sonn-Segev, A. Bernheim-Groswasser, H. Diamant and Y. Roichman, *Phys. Rev. Lett.* **112**, 088301 (2014)
- [5] A. Sonn-Segev, A. Bernheim-Groswasser and Y. Roichman, *Soft Matter* **13**, (2017)
- [6] D. Mizuno, C. Tardin, C. F. Schmidt and F. C. Mackintosh, *Science* **315**, 370 (2007)
- [7] M. Chein, E. Perlson and Y. Roichman, *Biophys. J.* **117**, 810 (2019)

$$T = \left( \frac{\partial S}{\partial U} \right)^{-1} ?$$

$$D = k_B T / \Gamma ?$$



$$m \langle v^2 \rangle = k_B T ?$$

$$P_c(E) = \exp\left(-\frac{E}{k_B T}\right) / Z ?$$

# WHAT IS THE TEMPERATURE OF A CELL?

■ Kumiko Hayashi<sup>1,2</sup>, Shin Hasegawa<sup>1</sup> and Shinsuke Niwa<sup>3</sup> – DOI: <https://doi.org/10.1051/epn/2020510>

■ <sup>1</sup> Department of Applied Physics, Graduate School of Engineering, Tohoku University, Sendai, Japan

■ <sup>2</sup> Precursory Research for Embryonic Science and Technology (PRESTO), Japan Science and Technology Agency (JST), Tokyo, Japan

■ <sup>3</sup> Frontier Research Institute for Interdisciplinary Sciences and Graduate School of Life Science, Tohoku University, Sendai, Japan

■ Correspondence: [kumiko@camp.apph.tohoku.ac.jp](mailto:kumiko@camp.apph.tohoku.ac.jp)

**Equilibrium temperature is classically defined based on thermodynamics using entropy and internal energy: how then can we describe temperature in non-equilibrium living systems such as cells, whose states are not well described by existing thermodynamics?**

**F**rom the viewpoint of physics, temperature ( $T$ ) is defined from several theoretical standpoints. With respect to thermodynamics, temperature is defined as the inverse of a partial derivative of entropy ( $S$ ) with respect to internal energy ( $U$ ) of a system ( $\partial S / \partial U$ ). Reaching back to statistical mechanics, temperature then follows the canonical distribution as  $p_c(E) = \exp\left(-\frac{E}{k_B T}\right) / Z$ , where  $E$  is energy of a state,  $k_B$  is the Boltzmann constant, and  $Z$  is the partition function. Application of the canonical distribution to a Hamiltonian particle system connected to an equilibrium thermostat then provides the equipartition law regarding the energy of motion:  $m \langle v^2 \rangle / 2 = k_B T / 2$ . Further, temperature is included in the fluctuation–dissipation theorem, such as the Einstein relation and the Green–Kubo relation, in which the temperature of a system is a proportionality constant between the correlation and response functions.

Thus, the temperature of equilibrium systems is perfectly defined by many physical laws. However, the definition is less straightforward when considering a non-equilibrium system, including living organisms.

## Effective temperature under non-equilibrium conditions

A non-equilibrium state is the state of a system with energy injection, such as driving forces, thermal conduction, and chemical reactions. Thus, almost all systems we are exposed to are non-equilibrium systems, since living matter such as the cells constituting our bodies require continuous energy input, and are thus in non-equilibrium states. Given the much greater complexity of living matter compared to an ideal gas, the statistical properties cannot be well described by the existing thermodynamics and statistical mechanics theories described above. This

poses a challenge in defining the temperature of such systems that are so far from the equilibrium in which thermodynamics, statistical mechanics, and linear response theories are valid.

In the case of a simple driven system (*i.e.*, a non-equilibrium system), in which a Brownian particle in a periodic potential in a medium at  $T$  is driven by an external force, it was proved that the Einstein relation,

$$D = k_B T / \Gamma, \quad (1)$$

where  $D$  is the diffusion coefficient, and  $\Gamma$  is the friction coefficient of the particle), was violated based on theoretically calculating the transport coefficients  $D$  (diffusion coefficient) and  $\Gamma$  (friction coefficient) of the particle [1]. Then,  $T_{\text{eff}} = D / k_B \Gamma$  is called the effective temperature of the non-equilibrium system because  $T_{\text{eff}}$  has a dimension of temperature though  $T_{\text{eff}} \neq T$ .

### Intracellular cargo transport

Indeed, the Einstein relation (Eq. 1) is violated in the real world when considering the state of living matter. Cells contain driven particle systems such as the above-mentioned driven Brownian particle, which is referred to as intracellular cargo transport, in which cargo particles are driven by motor proteins (Fig. 1). Motor proteins generate the transport force by a chemical reaction: hydrolysis of adenosine triphosphate (ATP) molecules. The violation of the Einstein relation (Eq. 1) was clarified experimentally in the intracellular cargo transport by measuring the diffusion coefficient ( $D$ ) and frictional coefficient ( $\Gamma$ ) of cargos [2].

In eukaryotic cells, cargos—which pack biomaterials required for sustaining life activities—are transported by the motor proteins kinesin and dynein along microtubules acting as the “roads” for transport spreading across a cell (Fig. 1) [3]. In particular, neurons, which have long axons (ranging from 0.1 mm to 1 m) to connect a cell body to the synaptic region, require fast cargo transport (Fig. 2a) [3]. In addition to neuronal communication, intracellular cargo transport is used by fish to change the colour of their body surfaces (Fig. 2b). Melanin pigments aggregate as cargos in cells on the scale of fish by motor proteins to drive a colour change from dark to light depending on environmental cues. Thus, intracellular cargo transport by motor proteins is a significant function of eukaryotic cells.

Because intracellular cargos are typically several hundred nanometres in size, they can be observed by optical microscopes with a spatial resolution of approximately 200 nm (Fig. 2a,b). Fluorescent proteins and dyes are typically used to label cargos so that they can be readily distinguished in the intracellular environment that is crowded with other vesicles, proteins, and cytoskeletons (Fig. 2a, bottom). By tracking the centre position of a cargo, its trajectory can be obtained (Fig. 2b, bottom). A cargo

transported by motor proteins can be seen over several seconds moving at a constant speed ( $v$ ), while fluctuating due to the effective noise derived from collisions with other vesicles and cytoskeleton components as well as thermal noise in the intracellular environment. This effective noise is considered to be an origin of the effective temperature.

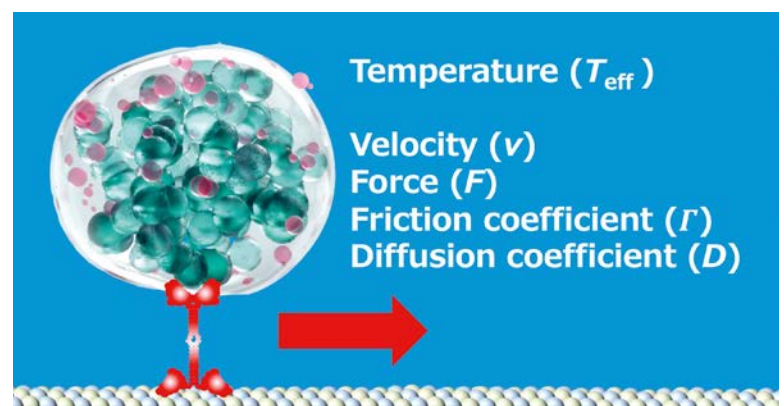
The existence of the effective noise arising in the intracellular non-equilibrium environment causes a problem with respect to physical measurement such as force measurement. The driving force ( $F$ ) acting on cargo transport exerted by motor proteins, can be written as

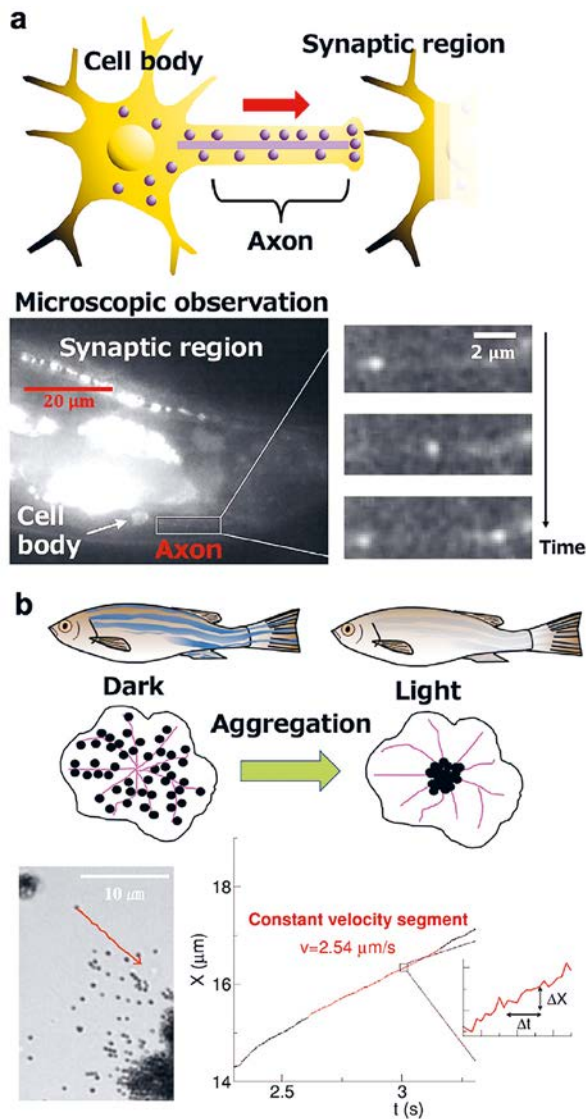
$$F = \Gamma v, \quad (2)$$

where  $\Gamma$  is the friction coefficient of the cargo, however, the value of the friction coefficient ( $\Gamma$ ) cannot be estimated from the diffusion coefficient ( $D$ ), which is easily obtained from the trajectory of a cargo (Fig. 2b, bottom), because of the violation of the Einstein relation (*i.e.*,  $\Gamma \neq k_B T / D$ ). Therefore, the measurable index  $\chi \equiv v / D$  was recently proposed as a substitute for  $F$ . Using the relation of the effective temperature, the relationship between  $F$  and  $\chi$  is derived as  $F = k_B T_{\text{eff}} \cdot \chi$  [4,5]. In Fig. 2c,d,  $\chi$  for neuronal cargos ( $n = 40$ ) (Fig. 2c) and melanin pigment cargos ( $n = 62$ ) (Fig. 2d) is plotted as a function of  $\Delta t$  [note that  $\Delta t$  dependence comes from  $D (= \langle \Delta X^2 \rangle / 2\Delta t)$ ] [4,5]. The index  $\chi$  was found to be discrete, representing the number of motor proteins carrying a single cargo together and generating a driving force. Accordingly, a cargo is transported by multiple motor proteins, similar to the way that many ants work collectively (Fig. 2e).

Using the known force value (approximately 5 pN) of a single motor protein and the relationship  $F = k_B T_{\text{eff}} \cdot \chi$ ,  $T_{\text{eff}}$  was estimated to be approximately  $10 k_B T$  for neuronal cargo transport [4] and  $2 k_B T$  for melanin transport in pigment cells [5]. The reason for this large difference in  $T_{\text{eff}}$  between different cell types has not yet been clarified; however, variations in noise properties and cell structures may affect the value of  $T_{\text{eff}}$ . Taking into consideration that the amount of energy provided by the hydrolysis of

▼ FIG. 1: Schematic of intracellular cargo transport. A motor protein (red) generates driving force ( $F$ ) to carry a cargo (green) moving at velocity ( $v$ ) along a microtubule.



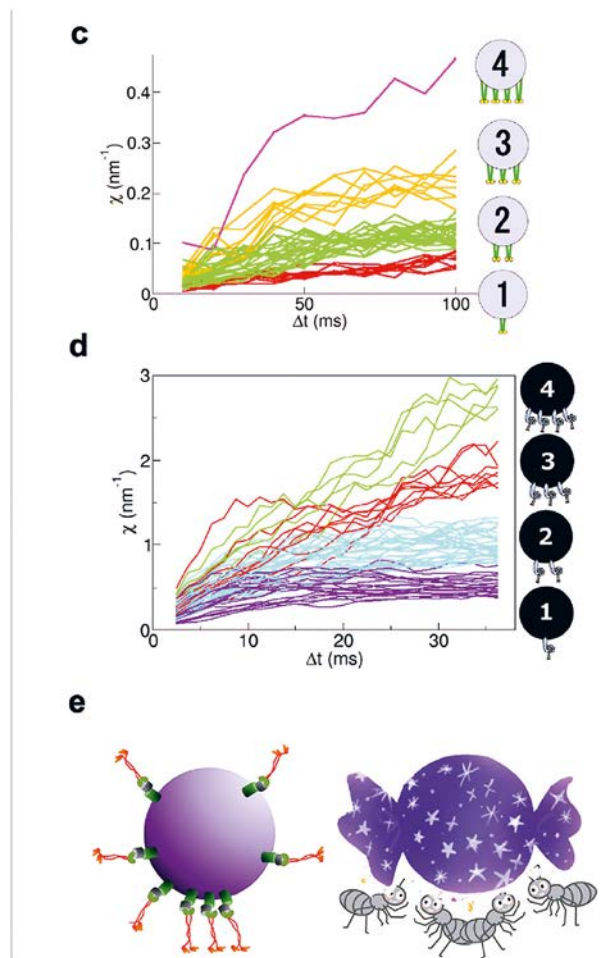


**FIG. 2:**  
 (a) Synaptic vesicle precursor transport in a neuron [4]. (b) Melanin pigment transport in a pigment cell [5]. Measurement of the force index  $\chi$  in the case of neuronal cargo transport [4] (c) and melanin pigment transport [5] (d). (e) A single cargo is carried by multiple motor proteins, akin to ant-like transport.

one ATP molecule is also of the order of  $10 k_B T$ , the energetic meaning of  $T_{\text{eff}}$  is an important issue to be solved for realising force measurement of the intracellular environment.

### Application of $\chi$

Although the exact value of the proportionality constant  $k_B T_{\text{eff}}$  between  $F$  and  $\chi$  is unknown [note that  $F = k_B T_{\text{eff}} \cdot \chi$ ], the qualitative property of  $\chi$ , namely its discreteness (Fig. 2c,d), is significant, as the discreteness implies the number of motor proteins carrying a cargo, which represents the stability of material transport and can therefore serve as a good barometer of healthy transport. Indeed, a decrease in the number of motor proteins observed in synaptic cargo transport was found to result in the mislocation of synapses [4,6]. In neurons, deficits in axonal transport are strongly related to neuronal diseases, including Alzheimer's, Parkinson's, and Huntington's diseases. Therefore, the measurement of  $\chi$  has potential to be more widely applied in the field of neuroscience as a helpful index to monitor disease progression and severity.



### About the Authors



**Kumiko Hayashi** is an associate professor of the Applied Physics Department, Tohoku University in Japan. She changed her major from theoretical physics to biological experiments after acquiring a PhD. Currently, she works on both the fields of theory and experiment fields.



**Shin Hasegawa** graduated from the Applied Physics Department, Tohoku University in Japan. He got a master's degree in engineering.



**Shinsuke Niwa** is an associate professor of the Frontier Research Institute for Interdisciplinary Sciences (FRIS), Tohoku University in Japan.

### References

- [1] K. Hayashi and S. Sasa, *Phys. Rev. E* **69**, 066119 (2004)
- [2] K. Hayashi, et al., *Eur. Phys. J. E* **36**, 136 (2013)
- [3] N. Hirokawa, et al., *Nat. Rev. Mol. Cell. Biol.* **10**, 682 (2009)
- [4] K. Hayashi, et al., *Phys. Chem. Chem. Phys.* **20**, 3403 (2018)
- [5] S. Hasegawa, et al., *Sci. Rep.* **9**, 5099 (2019)
- [6] S. Niwa, et al., *Cell Reports* **16**, 1 (2016)

# GETTING STARTED ON TWITTER AS A SCIENTIST

“Using Twitter can be more than just a social media activity. It can be a real career incubator in which researchers can develop their professional circles, launch new research projects and get helped by the community at various stages of the projects”. In a PLOS Computational Biology paper experienced scientific Twitter users share ‘Ten simple rules for getting started on Twitter as a scientists’ [1].

Scientists can use social media platforms such as Twitter to the advantage of their professional work. Early career scientists ask advice from peers and senior scientist and find mentors and jobs; senior scientist announce jobs, find employees and new students and be a role model for young researchers; they all use the platform to reach out and inform their followers about their study, work and ambitions. Here, we quote and summarise the ten simple useful rules from Ref. [1] to get started:

1. *Start somewhere, but show up.* Creating a Twitter-account is easy. You could do it now while reading this EPN Special Issue and start following the EPN account @EuroPhysicsNews. You could share what you have read in this issue and comment on it. Once started, make a habit to regular show up, get informed and post information for example about your research or a conference you are attending.
2. *Discover opportunities in academia.* Twitter has become a valuable source of information. You can follow other scientists, colleagues and your students; or granting agencies, laboratories and dedicated career columns in popular research journals. Early-career scientists can observe the process of creating national or international research projects. Senior researchers can openly share ideas through Twitter which may lead to the development of new concepts before becoming fully-fledged research projects.
3. *Tweet stuff.* The power of Twitter is its potential for interactions with fellow scientists. Ask them their opinion when (re)tweeting their post; and ask scientists questions about their work: they are using Twitter because they intend to interact.
4. *Learn the rules.* Diplomacy is one of the key components to building a scientific reputation. Check the social media guidelines and rules of your institute. Be careful about subtweeting people. Avoid sharing pictures with people, unless they have explicitly given you permission. Do not respond impulsively when someone is critical towards your research on Twitter.
5. *Take care of yourself.* Online conversation can go off the rails and you might need to protect yourself from trolls and nasty discussions. Be selective on whom you follow and be prepared to mute or block people.
6. *Build your own community.* You do not have to follow everyone who follows you and vice versa. You can follow important people in your field or communicate directly with people who would otherwise not find out about your work and field. Share and explain papers that might be interesting for people outside your field.

7. *Interface with real life.* Twitter makes networking more easy and less scary. It is a good way to stay in touch after a conference. Knowing a bit about the interests in research will make it easier to talk to people again on the next conference. Exchange Twitter accounts. You can use the direct messaging option of Twitter to make private contact.
8. *Spread your message.* Whenever you have a scientific accomplishment, you can share the information by sharing a link to a preprint or a vacancy notice. Summarise the content, include an image and an appropriate hashtag.
9. *Be a real person.* Even if you use Twitter only for professional purposes, consider opening up a little bit to show your followers you are a real person. For example you may mention a nice book or a concert that you visited.
10. *Great power and great responsibility.* Once your reach a substantial number of followers, you will need to spend a bit more time to think about what you tweet. You are a role model now. On the other hand, a large Twitter network can help you spreading important ideas and helping people learn about opportunities you know about.

Twitter has trade-offs between quantity and quality. It is a nice and useful tool to communicate with people and organisations in your scientific community. It is also inhabited by bots which tend to follow you and flood you with a lot of unwanted content. Importantly, you should remember that Twitter’s business model is based on advertising and you should be aware that some content aims to sell you products. However, Twitter is still strongly recommended for people who needs to develop themselves in academia and tighten bonds e.g. with researchers overseas. ■

## Reference

- [1] Veronika Cheplygina, Felienne Hermans, Casper Albers, Natalia Bielczyk, Ionica Smeets, PLOS Comput Biol 16(2): e1007513. <https://doi.org/10.1371/journal.pcbi.1007513> (2020)

 EuroPhysicsNews, #EuroPhysSoc, @elsdewolf1

## EPS awards and distinctions during the year 2020

The EPS would like to congratulate the 2020 laureates for EPS prizes and distinctions for their outstanding achievements in physics across Europe and around the world. The EPS would also like to thank the physics community for submitting the truly excellent nominations received. Finally, the EPS would like to recognise the work by the EPS Divisions and Groups in identifying individuals and their research that contribute to the development of physics and our understanding of our world.

### EPS EDISON VOLTA PRIZE

The 2020 EPS Edison Volta Prize for outstanding achievements in physics was awarded to **Dieter Weiss**, University of Regensburg, Germany *“for discovering a most spectacular new quantum phenomenon, the ‘Weiss Oscillations’”*; **Jurgen Smet**, Max Planck Institute for Solid State Research MPI-FKF in Stuttgart, Germany, *“for the demonstration – in cooperation with Dieter Weiss – of the so-called Hofstadter butterfly and the correctness of the Composite Fermion concept, a new quasiparticle consisting of a combination of an electron and two flux quanta, as well as for the exploration of the special properties of composite fermions”*; and to **Klaus Ensslin**, Laboratory for Solid State Physics, ETH Zürich, Switzerland, *“for his discoveries connected with nonequilibrium phenomena in quantum dots including the emission of microwave radiation from double quantum dots and the time resolved tunneling dynamics in the occupation of biased quantum dots.”*

### EPS EMMY NOETHER DISTINCTION

The Summer 2020 EPS Emmy Noether Distinction for the recognition of noteworthy women in physics was awarded to **Hatice Altug**, Institute for Bioengineering, École Polytechnique Fédérale de Lausanne, Switzerland, *“for her seminal contributions to light-matter interaction at the nanoscale, manipulation of light on-chip and application of nanophotonics in biology, and her inspiring role for the next generation of researchers and women.”*

### PRIZES OF THE EPS DIVISIONS AND GROUPS DURING THE YEAR 2020

#### EPS Alfvén Prize

The EPS Alfvén Prize 2020 of the EPS Plasma Physics Division for outstanding contributions to plasma physics was awarded to **Annick Pouquet**, Laboratory for Atmospheric and Space Physics, University of Colorado and National Center for Atmospheric Research, Boulder, Colorado, USA, *“for fundamental contributions to quantifying energy transfer in magneto-fluid.”*

#### Rolf Wideröe Prize

The Rolf Wideröe Prize of the EPS Accelerator Group for outstanding work in the accelerator field was awarded to **Lucio Rossi**, CERN, *“for his pioneering role in the development of superconducting magnet technology for accelerators and experiments, its application to complex projects in High Energy Physics including strongly driving industrial capability, and for his tireless effort in promoting the field of accelerator science and technology.”*

#### Gersch Budker Prize

The Gersch Budker Prize of the EPS Accelerator Group for a recent significant, original contribution to the accelerator field was awarded to **Hideaki Hotchi**, J-PARC *“for his achievements in the commissioning of the J-PARC Rapid Cycling Synchrotron, with sustained 1 MW operation at unprecedented low levels of beam loss made possible by his exceptional understanding of complex beam dynamics processes, thereby laying the foundations for future high power proton synchrotrons worldwide.”*

#### Frank Sacherer Prize

The Frank Sacherer Prize of the EPS Accelerator Group for an individual in the early part of his or her career was awarded to **Johannes Steinmann**,

ANL, *“for his significant contribution to the development and demonstration of ultra-fast accelerator instrumentation using THz technology, having the potential for major impact on the field of electron bunch-by-bunch diagnostics.”*

#### ESPD Senior Prize

The ESPD Senior Prize 2020 of the European Solar Physics Division was awarded to **Eric Priest**, University of St Andrews, UK, *“for long-standing leadership via mentoring, supervising and field-defining textbooks and for fundamental contributions in key topics of solar magnetohydrodynamics, particularly magnetic reconnection in the solar atmosphere and solar coronal heating.”*

#### ESPD Early Career Researcher Prize

The ESPD Early Career Researcher Prize 2020 of the European Solar Physics Division was awarded to **Victor Réville**, IRAP, France *“for fundamental contributions to creating self-consistent multi-dimensional numerical models of coronal heating and solar wind acceleration via wave turbulence.”*

#### ESPD PhD Thesis Prize

The ESPD PhD Thesis Prize 2020 of the European Solar Physics Division was awarded to **Stefan Hofmeister** (PhD carried at Institute of Physics, University of Graz, Austria) *“for outstanding observational analysis of solar coronal holes, their magnetic fine structure and the associated high-speed solar wind streams.”*

#### EPS-CMD Europhysics Prize

The EPS-CMD Europhysics Prize 2020 of the Condensed Matter Division for recognition of a prominent and well-identifiable discovery,

breakthrough, or contribution to condensed matter physics was awarded to **Jörg Wrachtrup**, University of Stuttgart, Germany, *“for his pioneering studies on quantum coherence in solid-state systems, and their applications for sensing, and, in particular, for major breakthroughs in the study of the optical and spin properties of nitrogen vacancy centres in diamond.”*

#### EPS Liquid Matter Prize

The 2020 EPS Liquid Matter Prize of the Condensed Matter Division for outstanding achievements in the fields of Physics of the Liquid State, Soft Condensed Matter Physics, or Granular Physics, was awarded to **Daan Frenkel**, University of Cambridge, UK

#### Olli V. Lounasmaa Memorial Prize

The 2020 Olli V Lounasma Memorial Prize of the Condensed Matter Division for outstanding contributions to advances in low temperature physics and related fields was awarded to **Seamus Davis**, University College Cork and Oxford University *“for his pioneering investigations and applications of exquisite scanning probe techniques for visualization of electronic quantum matter at the atomic scale.”*

#### Lise Meitner-award

The Lise Meitner-award 2020 of the EPS Nuclear Physics Division for outstanding work in the fields of experimental, theoretical or applied nuclear science was awarded to **Klaus Blaum**, **Björn Jonson** and **Piet Van Duppen** *“for their development and application of on-line instrumentation and techniques, for their precise and systematic investigation of properties of nuclei far from stability, and for shaping the scientific program at the on-line isotope separator facility ISOLDE, CERN”*.

# EPS directory: summary and website

## EXECUTIVE COMMITTEE

### President

**P. Rudolf**  
RUG Groningen, The Netherlands  
TEL/FAX +31 50 363 4974  
EMAIL p.rudolf@rug.nl

### President-Elect

**L. Bergé**  
Commissariat à l'Énergie Atomique (CEA), France  
TEL +33 (0)169 26 7376 (or - 4000)  
EMAIL luc.berge@cea.fr

### Secretary

**Ian Bearden**  
Niels Bohr Institute, Denmark  
TEL +45 353-25323  
EMAIL bearden@nbi.dk

### Treasurer

**S. Palmer**  
IOP Publishing Inc., Temple Circus House, UK  
TEL +44 117 929 7481  
EMAIL Stuart.Palmer@iop.org

### Executive Committee Members

**R. Caruso**  
Università degli Studi di Napoli Federico II, Italy  
TEL +39 081 676248  
EMAIL roberta.caruso@fisica.unina.it

### U. Fantz

Max-Planck-Institut für Plasmaphysik, Germany  
TEL/FAX +49 89 3299-1958 / +49 89 3299 1313  
EMAIL fantz@ipp.mpg.de

The Secretary General is a member of the Executive Committee and most Committees ex officio (i.e. by virtue of his office).

### E. Nappi

INFN Headquarters, Italy  
TEL +39 32 09232336  
EMAIL eugenio.nappi@ba.infn.it

### T. Peña

Instituto Superior Tecnico (IST), Portugal  
TEL +351 218417533  
EMAIL teresa.pena@tecnico.ulisboa.pt

### E. Rabinovici

The Hebrew University of Jerusalem, Israël  
TEL/FAX +972 - 2-6585673 / +972 2- 6584437  
EMAIL eliezer@mail.huji.ac.il

### M. Sakellariadou

King's College London, UK  
TEL +44 020 7848 1535  
EMAIL mairi.sakellariadou@kcl.ac.uk

### A. Schopper

CERN, EP-LBD, Switzerland  
TEL +41 (0)22 76 73158  
EMAIL andreas.schopper@cern.ch

### K. van der Beek

Lab. des Solides Irradiés, École Polytechnique, France  
TEL +33 (0)62663 7411  
EMAIL kees.vanderbeek@polytechnique.edu

### G. Zwicknagl

Institut für Mathematische Physik, Germany  
TEL/FAX +49 (0) 531 391 5206 / +49 (0) 531 391 8186  
EMAIL g.zwicknagl@tu-bs.de

## COUNCIL

### Individual Members Council Delegates

**W. E. Elsaesser**  
Technische Universität Darmstadt, Germany  
TEL/FAX +49 6151 16 20163 / +49 6151 16 20172  
EMAIL Elsaesser@physik.tu-darmstadt.de

### I. D'Amico

Department of Physics, University of York, UK  
TEL/FAX +44 (0)1904 322215 / +44 (0)1904 322214  
EMAIL irene.damico@york.ac.uk

### A. Fontaine

Fondation Nanosciences, France  
TEL +33 (0)6 86 55 25 58  
EMAIL alain.fontaine@neel.cnrs.fr

### I. J. D. Macgregor

University of Glasgow, UK  
TEL +44 1413 304468  
EMAIL douglas.macgregor@glasgow.ac.uk

### E. Scapparone

IINFN, Sezione di Bologna, Italy  
TEL +39 (0)51 209 1093 / +41 22 767 7589  
EMAIL scapparone@bo.infn.it

### Associate Members Council Delegates

**R. Allenspach**  
IPR, Allenspach, IBM Research GmbH, Switzerland  
TEL/FAX +41 44 72 48267 / +41 44 72 48911  
EMAIL ral@zurich.ibm.com

### K. Borras

DESY - Deutsches Elektronen-Synchrotron, Germany  
TEL +49 (0)40 8998 4488  
EMAIL kerstin.borras@desy.de

### U. Fantz

Max-Planck-Institut für Plasmaphysik, Germany  
TEL/FAX +49 89 3299-1958 / +49 89 3299 1313  
EMAIL fantz@ipp.mpg.de

### S. Freitas

INESC - MN, Portugal  
TEL +351-213100380 / +351-213100237  
EMAIL sfreitas@inesc-mn.pt

### M. Pepe-Altarelli

CERN (EP-LBO), Switzerland  
TEL +41 22 76 74473 and +41 22 76 79278  
EMAIL Monica.Pepe.Altarelli@cern.ch

## PAST PRESIDENTS

**R. Voss**, Switzerland (2017-19);  
**C. Rossel**, Switzerland (2015-17);  
**J. Dudley**, France (2013-15);  
**L. Cifarelli**, Italy (2011-13);  
**M. Kolwas**, Poland (2009-11);  
**F. Wagner**, Germany (2007-09);  
**O. Poulsen**, Denmark (2005-07);  
**M.C.E. Huber**, Switzerland (2003-05);  
**M. Ducloy**, France (2001-03);  
**A. Wolfendale**, UK (1999-01);  
**D. Weaire**, Ireland (1997-99);  
**H. Schopper**, CERN, Germany (1995-97);

**N. Kroó**, Hungary (1993-95);  
**M. Jacob**, CERN, France (1991-93);  
**R.A. Ricci**, Italy (1988-91);  
**W. Buckel**, Germany (1986-88);  
**G.H. Stafford**, UK (1984-86);  
**J. Friedel**, France (1982-84);  
**A.R. Mackintosh**, Denmark (1980-82);  
**A. Zichichi**, Italy (1978-80);  
**I. Ursu**, Romania (1976-78);  
**H.B.G. Casimir**, Netherlands (1972-76);  
**E. Rudberg**, Sweden (1970-72);  
**G. Bernardini**, Italy (1968-70).

## SECRETARIAT

### European Physical Society

6 rue des Frères Lumière  
F-68200 Mulhouse, France  
TEL/FAX +33 389 329 440 / +33 389 329 449  
WEBSITE www.eps.org

### Secretary general

**D. Lee** • EMAIL david.lee@eps.org

### Administrative secretary

**S. Loskill** • EMAIL sylvie.loskill@eps.org

### Conference manager

**P. Helfenstein** • EMAIL patricia.helfenstein@eps.org

### Conference assistant

**O. Fornari** • EMAIL ophelia.fornari@eps.org

### Graphic designer

**X. de Araujo** • EMAIL xavier.dearaujo@eps.org

### IT manager

**A. Ouarab** • EMAIL ahmed.ouarab@eps.org

### Accountant

**O. ALAIWAN** • EMAIL olivier.alaiwan@eps.org

### Communications Coordinator

**G. Gunaratnam** • EMAIL gina.gunaratnam@eps.org

## PUBLICATIONS

### EPL

#### Editor in Chief

**B. van Tiggelen**  
EMAIL Bart.van-Tiggelen@grenoble.cnrs.fr

#### Staff editor EPL

**F. Burr** • EMAIL burr@epletters.net

### EPN

#### Editor

**E. de Wolf** • EMAIL e.dewolf@nikhef.nl

#### Science Editor

**F. Igloi** • EMAIL igloi.ferenc@wigner.mta.hu

## PUBLISHER

### EDP Sciences

#### Managing & Publishing Director

**A. Henri**  
EDP Sciences  
17, av. du Hoggar - BP 112  
F-91944 Les Ulis Cedex A, France  
TEL +33 169 187 575  
EMAIL agnes.henri@edpsciences.org

#### Advertising

**B. Dufour** • EMAIL bernadette.dufour@edpsciences.org

## HONORARY MEMBERS

**V.G. Baryakhtar**, Ukraine; **J. Bell Burnell**, Oxford, UK;  
**S. Bertolucci**, Geneva, Switzerland; **C. Cohen-Tannoudji**, Paris, France; **H. de Waard**, Groningen, Netherlands;  
**P. M. Echenique**, Donostia-San Sebastian, Spain;  
**F. Englert**, France; **G. Gehring**, Sheffield, United Kingdom;  
**T.W. Haensch**, Garching/Munich, Germany; **S. Haroche**, Paris, France; **E. Heer**, Geneva, Switzerland; **S. W. Hell**, Göttingen, Germany; **R. D. Heuer**, Geneva, Switzerland;  
**P. Higgs**, UK; **M. C. E. Huber**, Zurich, Switzerland;  
**N. Kroó**, Budapest, Hungary; **M. Leduc**, Paris, France;  
**L. Maiani**, Trieste, Italy; **S. Myers**, Geneva, Switzerland;  
**P. Nozières**, Grenoble, France; **H. F. Schopper**, Geneva, Switzerland; **G. 't Hooft**, Utrecht, Netherlands; **A. Zichichi**, Lausanne, Switzerland

## COMMITTEES

### Conferences

**CHAIR** M. Reiffers  
FHPV PU / University of Presov  
SK-08116, Presov, Slovak Republic  
**TEL** +421 (0)51 75 70 604  
**EMAIL** reiffers@saske.sk

### Distinctions and Awards

**CHAIR** J. Hermans  
Huygens Laboratory - Leiden University  
NL-2300 RA Leiden, The Netherlands  
**TEL/FAX** +31 71 5275824  
**EMAIL** Hermans@Physics.LeidenUniv.nl

### Equal Opportunities

**CHAIR** K. van der Beek  
Laboratoire des Solides Irradiés,  
École Polytechnique  
F-35000 Palaiseau, France  
**TEL** +33 (0)62663 7411  
**EMAIL** kees.vanderbeek@polytechnique.edu

### European Integration

**CHAIR** R. Constantinescu  
University of Craiova, Faculty of Physics  
RO-200585 Craiova, Romania  
**TEL/FAX** +40 251 415077  
**EMAIL** rconsta@central.ucv.ro

### Historic Sites

**CHAIRS** K. Grandin  
Center for History of Science,  
Stockholm University – KVA  
SE-10405 Stockholm, Sweden  
**TEL** +46 86739616  
**EMAIL** karl.grandin@kva.se

### Forum Physics and Society

**CHAIR** C. Hidalgo  
CIEMAT  
ES-28040 Madrid, Spain  
**TEL** +34 (91)3466498  
**EMAIL** carlos.hidalgo@ciemat.es

### Young Minds

**CHAIR** R. Zeltner  
FAU Erlangen-Nürnberg, Experimental Physik  
D-91054 Erlangen, Germany  
**EMAIL** richardzeltner@gmx.de

## DIVISIONS & SECTIONS

### Atomic, Molecular and Optical Physics

**CHAIR** J. Burgdörfer  
Technische Universität Wien (TU Wien)  
AT-1040 Vienna, Austria  
**TEL** +43-1-58801-13610  
**EMAIL** burg@concord.itp.tuwien.ac.at

### Sections

European Group on Atomic Systems (EGAS)  
Chemical & Molecular Physics Section  
Electronic & Atomic Collisions Section

### Condensed Matter Division

**CHAIR** C. van der Beek  
Laboratoire des Solides Irradiés  
École Polytechnique  
F-35000 Palaiseau, France  
**TEL** +33 (0)62663 7411  
**EMAIL** kees.vanderbeek@polytechnique.edu

### Sections

Liquids Section  
Low Temperature Section  
Macromolecular Physics Section  
Magnetism Section  
Semiconductors & Insulators Section  
Structural and Dynamical Properties of Solids  
Surfaces & Interfaces Section

### Education

**CHAIR** D. Sands  
Department Physics and Mathematics,  
University of Hull  
Hull HU6 7RX, United Kingdom  
**TEL** +44 (0)1482 465826  
**EMAIL** D.Sands@hull.ac.uk

### Environmental Physics

**CHAIR** J. Orphal  
Karlsruhe Institute of Technology (KIT)  
D-76344 Karlsruhe/Eggenstein-Leopoldshafen, Germany  
**TEL** +49 (0)721 608-29120  
**EMAIL** orphal@kit.edu

### Gravitational Physics

**CHAIR** M. Sakellariadou  
King's College London - Strand  
London WC2R 2LS, United Kingdom  
**TEL** +44 020 7848 1535  
**EMAIL** mairi.sakellariadou@kcl.ac.uk

### High Energy & Particle Physics

**CHAIR** T. Gehrmann  
Department of Physics, University of Zurich  
CH-8057 Zurich, Switzerland  
**TEL** +41 44 635 5818  
**EMAIL** thomas.gehrmann@uzh.ch

### Nuclear Physics

**CHAIR** R. Reifarh  
Goethe Universität - Giersch Science Center  
D-60438 Frankfurt-am-Main, Germany  
**TEL** +49 (0)69/798-47442  
**EMAIL** reifarh@physik.uni-frankfurt.de

### Physics in Life Sciences

**CHAIR** F. Ritort  
University of Barcelona  
ES-08028 Barcelona, Spain  
**TEL** +34-934035869 / +34-934021149  
**EMAIL** ritort@fn.ub.es

### Plasma Physics

**CHAIR** R. Dendy  
Centre for Fusion, Space and Astrophysics (CFSA)  
Department of Physics, University of Warwick  
Coventry CV4 7AL, United Kingdom  
**TEL/FAX** +44 01235 466377 / +44 024 7615 0897  
**EMAIL** R.Dendy@warwick.ac.uk

### Sections

Beam Plasma and Inertial Fusion Section  
Dusty and Low Temperature Section

### Quantum Electronics & Optics

**CHAIR** G. Cerullo  
Dipartimento di Fisica, Politecnico di Milano  
20133 Milano Italy  
**TEL/FAX** +39 02 2399 6164 / +39 02 2399 6126  
**EMAIL** giulio.cerullo@polimi.it

### Joint European Solar Physics

**CHAIR** E. Kontar  
School of Physics & Astronomy,  
Glasgow University  
UK-Glasgow G12 8QQ, United Kingdom  
**TEL** +44 (0)141330 2499  
**EMAIL** Eduard.Kontar@glasgow.ac.uk

### Statistical & Nonlinear Physics

**CHAIR** C. Beck  
School of Mathematical Sciences,  
Queen Mary, University of London  
London E1 4NS, United Kingdom  
**TEL** +44 20 7882 3286  
**EMAIL** c.beck@qmul.ac.uk

## GROUPS

### Accelerators Group

**CHAIR** R. Assmann  
DESY  
D-22607 Hamburg, Germany  
**TEL** +49 (0)40 8998 3187 (DESY)  
+41 22 767 5231 (CERN)  
**EMAIL** Ralph.assmann@desy.de

### Computational Physics Group

**CHAIR** C. M. Bertoni  
Università di Modena e Reggio Emilia  
Dipartimento di Scienze Fisiche,  
Informatiche e Matematiche  
IT-41125 Modena, Italy  
**TEL** +39 5920 55288  
**EMAIL** carlo.m.bertoni@gmail.com

### Energy Group

**CHAIR** J. Ongena  
Forschungszentrum Jülich GmbH  
Institut IEK-4  
D-52425 Jülich, Germany  
**TEL/FAX** +49 2461 61-2501 / +49 2461 61-3331  
**EMAIL** j.ongena@fz-juelich.de

### History of Physics Group

**CHAIR** K. Grandin  
Center for History of Science  
Stockholm University – KVA  
SE-10405 Stockholm, Sweden  
**TEL/FAX** +46 86739616  
**EMAIL** karl.grandin@kva.se

### Physics for Development Group

**CHAIR** J. Niemela  
Abdus Salam ICTP  
APP-FDL  
IT-34151 Trieste, Italy  
**TEL/FAX** +39 040 2240 607 / +39 040 2240410  
**EMAIL** niemela@ictp.it

### Technology and Innovation Group

**CHAIR** M. Nordberg  
Development & Innovation (RCS-PRJ-DI)  
CERN - AT Division  
CH-1211 Geneva 23, Switzerland  
**TEL/FAX** +41 22 767 7377 / +41 22 766 9575  
**EMAIL** Markus.Nordberg@cern.ch

## NATIONAL SOCIETIES

Albania, Armenia, Austria, Belarus, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Israel, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Macedonia, Moldova, Montenegro, The Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom

## ASSOCIATE MEMBERS

ALBA-CELLS, AYIMI, CAEN SpA, CEA Saclay, CERN, CNR Roma, CONSORZIO RFX, DESY, DIPIC, EDISON SpA, EDP Sciences, EGO, EPFL SPC, ENEA, ESA-SRE, ESRF, EUROfusion, FOM, GSI, HZB, IBA s.a., IBM Research GmbH, INFN Frascati, IOFFE, IPPLM Warsaw, IST Lisbon, JINR, LSC, MPI Festkörperforschung, MPI Plasmaphysik, MPI Science of Light, CENTRO FERMI (Museo Storico della Fisica), NORDITA, PSI, SINCRONTONE Trieste, SISSA, University of Geneva, University of Zurich

## RECOGNISED JOURNALS

Europhysics news, E-EPS, EPL, European Journal of Physics, Physics Publishing Alliance, ECA & Conference Proceedings, Society newsletters, Recognized Journals, Annual Reviews.  
See website: [www.eps.org/publications](http://www.eps.org/publications)

Complete directory online at:  
➔ [www.eps.org/search/custom.asp?id=298](http://www.eps.org/search/custom.asp?id=298)



# ANNUAL INDEX VOLUME 51 - 2020

## MATTER INDEX

### » Annual Reports

Directory - November 2020 • 51/5 • p.53

EPS awards and distinctions during the year 2020 • 51/5 • p.52

Index - Volume 51 - 2020 • 51/5 • p.55

### » Column

Active protein networks govern cell shape changes **Sykes C.**

For all those not reading this column **de Jong S.**

Loránd Eötvös and Hungary's restructured research network **Sólyom J.**

### » Editorials

An ambitious R&I programme for Europe? **Sánchez-Bautista E.**

Careers with a Physics Degree **Peña T.**

EPS acts for a fair gender balance and no harassment **Bergé L.**

In times of coronavirus **Rudolf P. and de Wolf E.**

The Physics of Living Matter **Beck C., van der Beek K. and Ritort F.**

### » Event

175 years German Physical Society Physics for and in Society • 51/2 • p.06

The 100<sup>th</sup> anniversary of the Polish Physical Society • 51/3 • p.06

The 20<sup>th</sup> anniversary of the Pierre Auger Observatory **Mantsch P.**

### » Famous image

Pillars of Creation • 51/3 • p.32

### » Highlights

51/1 • 11 summaries • p. 14-17

51/2 • 5 summaries • p. 12-13

51/3 • 5 summaries • p. 12-13

51/4 • 6 summaries • p. 12-13

51/5 • 4 summaries • p. 13-14

### » Features

30 years of moving individual atoms **Lutz C. and Gross L.**

A Tribute to Loránd Eötvös **Kubbinga H.**

Moving teaching online during the COVID-19 pandemic **Sands D.**

Accretion disks around young stars: the cradles of planet formation **Semenov D. A. and Teague R. D.**

Arabic Science of Light: The birth of modern optics and of the experimental method **Boudrioua A., Chergui M. and Rashed R.**

Astroparticle, nuclear and particle physicists meet **D'Hondt J., Lewitowicz M. and Montaruli T.**

Carbon capture and storage: making fossil fuels great again? **Smit B. and Garcia S.**

Cell differentiation unravelled by single-cell RNA sequencing **Aleman A.**

Deep Mediterranean turbulent convection **van Haren H.**

Education: defining physical quantities for upper secondary school students **Sands D. and Heanes D.**

EPS Action plans for reducing the gender gap **Bergé L.**

EPS and Open Science: an update **Rossel C. and van Dyck L.**

Extrasolar planets: from dust to new worlds **Ercolano B.**

From Astronomy to the clinic: Adaptive Optics based visual simulators **Vinás M.**

From single particle motion to structure of biological systems **Roichman Y.**

Getting started on Twitter as a scientist **de Wolf E.**

Let's take this discussion online **Akhmerov A., Bonet-Monroig X., Fatemi V., Greplova E., van Nieuwenburg E., Seradjeh B., Varjas D.**

Listening to the quantum vacuum: a perspective on the dynamical Casimir effect **Paraoanu G. S. and Johansson G.**

LUXE: Combining high energy and intensity to spark the vacuum **Heinemann B., Heinzl T. and Ringwald A.**

Mechanics in biology **Idema T.**

Moving teaching online during the COVID-19 pandemic **Sands D.**

On the importance of being critical **Marsili M.**

Planets orbiting other stars, the search for extraterrestrial life **Snellen I.**

Precise control of atoms with MBE: From semiconductors to complex oxides **Suyolcu Y. E. and Logvenov G.**

Protein nanomechanics: the power of stretching **Mora M. and Garcia-Manyes S.**

Scanning geophysical hazards **Baker J.**

Seeing with electrons **Jakobi A. J.**

Status of particle physics **Trócsányi Z.**

Submarine seismic tomography using optical fibres **Fernández-Ruiz M. R., Martins H. F., Martin-Lopez S. and Gonzalez-Herraez M.**

Tailored models for COVID-19 **Arenas A., Gómez-Gardeñes J., Granell C. and Soriano-Paños D.**

The ERIC Consortium, a new type of EU Research Institution **Rizzuto C.**

The nonlinearity of life **Herrera-Delgado E. and Sollich P.**

Vacuum Science and Technology at CERN **Jiménez J. M. and Chiggiato P.**

What is the temperature of a cell? **Hayashi K., Hasegawa S. and Niwa S.**

### » In the spotlights

Artificial Intelligence finds a heliocentric representation of the solar system **Iten R., Metger T., Wilming H., del Rio L. and Renner R.**

Building a neutrino telescope in Europe • 51/2 • p.07

Closing in on CERN's future – the most significant proposals discussed in Nature Physics focus issue • 51/3 • p.08

Doubt cast on 'dark energy' **Sarkar S.**

In memoriam, Robert Pick **Ducloy M.**

The foundation of the EPS in 1968: a case of science diplomacy **Lalli R.**

The Union of Physicists from Portuguese Speaking Countries **Rosenfeld R.**

The Vera C. Rubin Observatory - formerly LSST • 51/1 • p.07

Vitrimers: combining the best of both polymeric worlds **Janssen L. M. C.**

Zeptoseconds: new world record in short time measurement • 51/5 • p.12

### » Interview

Interview with C. Morais Smith **de Wolf E.**

Interview with Hatice Altug **de Wolf E.**

### » Personnel report

Early Career Researcher Prize 2019 of the EPS European Solar Physics Division **Pradeep Chitta L.**

Grant for multi-messenger astronomy studies **de Wasseige G.**

Heinz Billing Prize **Dietrich T.**

The Collective Behaviour of Bacteria **Douarch C.**

### » Prizes - Awards - Medals

Cristiane Morais Smith awarded the Emmy Noether Distinction **Platero G. and Rasing T.**

Nobel prize for Physics 2020 **Sakellariadou M.**

Nobel prize in chemistry 2020: Molecular scissors to perturb the genetic code **Seidel R.**

The 2020 awards of the EPS Accelerator Group • 51/4 • p.08

### » Young Minds

Celebrating 10 years of EPS Young Minds • 51/2 • p.10

How Young Minds shapes the physicists of the future **Ostinato M., Martin C., Zeltner R. and Mkrtchyan H.**

Lockdown, millennials and European networks: how is quarantine in the eyes of a Young Mind? **Caruso R. and Hernández T.**

Young Minds, a career springboard for young physicists **Caruso R., Zeltner R. and Marino A.**

## AUTHOR INDEX

- » **A**
- Akhmerov A.** Let's take this discussion online • 51/3 • p.20
- Alemaný A.** Cell differentiation unravelled by single-cell RNA sequencing • 51/5 • p.31
- Arenas A.** Tailored models for COVID-19 • 51/5 • p.38
- » **B**
- Baker J.** Scanning geophysical hazards • 51/2 • p.14
- Beck C.** The Physics of Living Matter • 51/5 • p.03
- Bergé L.** EPS acts for a fair gender balance and no harassment • 51/3 • p.03 | EPS Action plans for reducing the gender gap • 51/3 • p.28
- Bonet-Monroig X.** See Akhmerov A.
- Boudrioua A.** Arabic Science of Light: The birth of modern optics and of the experimental method • 51/3 • p.14
- » **C**
- Caruso R.** Lockdown, millennials and European networks: how is quarantine in the eyes of a Young Mind? • 51/3 • p.10 | Young Minds, a career springboard for young physicists • 51/4 • p.10
- Chergui M.** See Boudrioua A.
- Chigiato P.** See Jiménez J. M.
- » **D**
- D'Hondt J.** JENAS - Astroparticle, nuclear and particle physicists meet • 51/2 • p.08
- de Jong S.** For all those not reading this column • 51/1 • p.12
- de Wasseige G.** Grant for multi-messenger astronomy studies • 51/3 • p.04
- de Wolf E.** Interview with Cristiane Morais Smith • 51/1 • p.18 | see Rudolf P. | Interview with Hatice Altug • 51/4 • p.04 | Zeptoseconds: new world record in short time measurement • 51/5 • p.12 | Getting started on Twitter as a scientist • 51/5 • p.51
- del Rio L.** See Iten R.
- Dietrich T.** Personal report: Heinz Billing Prize • 51/1 • p.08
- Douarch C.** The Collective Behaviour of Bacteria • 51/5 • p.04
- Ducloy M.** In memoriam, Robert Pick • 51/5 • p.11
- » **E**
- Ercolano B.** Extrasolar planets: from dust to new worlds • 51/1 • p.20
- » **F**
- Fatemi V.** See Akhmerov A.
- Fernández-Ruiz M. R.** Submarine seismic tomography using optical fibres • 51/1 • p.22
- » **G**
- García S.** See Smit B.
- García-Manyes S.** See Mora M.
- Gómez-Gardeñes J.** See Arenas A.
- González-Herreraez M.** See Fernández-Ruiz M. R.
- Granell C.** See Arenas A.
- Greplova E.** See Akhmerov A.
- Gross L.** See Lutz C.
- » **H**
- Hayashi K.** What is the temperature of a cell? • 51/5 • p.48
- Heanes D.** See Sands D.
- Heinemann B.** LUXE: Combining high energy and intensity to spark the vacuum • 51/4 • p.14
- Heinzl T.** See Heinemann B.
- Hernández T.** See Caruso R.
- Herrera-Delgado E.** The nonlinearity of life • 51/5 • p.35
- Hessels J.** See Marcote B.
- » **I**
- Idema T.** Mechanics in biology • 51/5 • p.28
- Iten R.** Artificial Intelligence finds a heliocentric representation of the solar system • 51/2 • p.09
- » **J**
- Jakobi A. J.** Seeing with electrons • 51/5 • p.20
- Janssen L. M. C.** Vitrimers: combining the best of both polymeric worlds • 51/1 • p.04
- Jiménez J. M.** Vacuum Science and Technology at CERN • 51/4 • p.24
- » **K**
- Kubbinga H.** A Tribute to Loránd Eötvös • 51/4 • p.27
- » **L**
- Lalli R.** The foundation of the EPS in 1968: a case of science diplomacy • 51/5 • p.10
- Lewitowicz M.** See D'Hondt J.
- Lutz C.** 30 years of moving individual atoms • 51/1 • p.26
- Logvenov G.** See Suyolcu Y. E.
- » **M**
- Mantsch P.** The 20<sup>th</sup> anniversary of the Pierre Auger Observatory • 51/1 • p.10
- Marcote B.** A Fast Radio Burst localised to a nearby spiral galaxy • 51/4 • p.06
- Marino A.** See Caruso R.
- Marsili M.** On the importance of being critical • 51/5 • p.42
- Martin C.** See Ostinato M.
- Martin-Lopez S.** See Fernández-Ruiz M. R.
- Martins H. F.** See Fernández-Ruiz M. R.
- Metger T.** See Iten R.
- Mkrtchyan H.** See Ostinato M.
- Montaruli T.** See D'Hondt J.
- Mora M.** Protein nanomechanics: the power of stretching • 51/5 • p.24
- » **N**
- Nimmo K.** See Marcote B.
- » **O**
- Ostinato M.** How Young Minds shapes the physicists of the future • 51/5 • p.16
- » **P**
- Paraoanu G. S.** Listening to the quantum vacuum: a perspective on the dynamical Casimir effect • 51/4 • p.18
- Peña T.** Careers with a Physics Degree • 51/1 • p.03
- Platero G.** Cristiane Morais Smith awarded the Emmy Noether Distinction • 51/1 • p.09
- Pradeep Chitta L.** Early Career Researcher Prize 2019 of the EPS European Solar Physics Division • 51/2 • p.04
- » **R**
- Rashed R.** See Boudrioua A.
- Rasing T.** see Platero G.
- Renner R.** See Iten R.
- Ringwald A.** See Heinemann B.
- Ritort F.** See Beck C.
- Rizzuto C.** The ERIC Consortium, a new type of EU Research Institution • 51/3 • p.25
- Roichman Y.** From single particle motion to structure of biological systems • 51/5 • p.45
- Rosenfeld R.** The Union of Physicists from Portuguese Speaking Countries • 51/3 • p.07
- Rossel C.** EPS and Open Science: an update • 51/1 • p.26
- Rudolf P.** In times of coronavirus • 51/2 • p.03
- » **S**
- Sakellariadou M.** Nobel prize for Physics 2020 • 51/5 • p.06
- Sánchez-Bautista E.** An ambitious R&I programme for Europe? • 51/4 • p.03
- Sands D.** Education: defining physical quantities for upper secondary school students • 51/2 • p.29 | Moving teaching online during the COVID-19 pandemic • 51/4 • p.30
- Sarkar S.** Doubt cast on 'dark energy' • 51/1 • p.06
- Seidel R.** Nobel prize in chemistry 2020: Molecular scissors to perturb the genetic code • 51/5 • p.08
- Semenov D. A.** Accretion disks around young stars: the cradles of planet formation • 51/1 • p.29
- Seradjeh B.** See Akhmerov A.
- Smit B.** Carbon capture and storage: making fossil fuels great again? • 51/2 • p.20
- Snellen I.** Planets orbiting other stars, the search for extraterrestrial life • 51/1 • p.23
- Sollich P.** See Herrera-Delgado E.
- Sólyom J.** Loránd Eötvös and Hungary's restructured research network • 51/2 • p.32
- Soriano-Paños D.** See Arenas A.
- Suyolcu Y. E.** Precise control of atoms with MBE: From semiconductors to complex oxides • 51/4 • p.21
- Sykes C.** Active protein networks govern cell shape changes • 51/5 • p.18
- » **T**
- Teague R. D.** See Semenov D. A.
- Trócsányi Z.** Status of particle physics • 51/2 • p.23
- » **V**
- van der Beek K.** See Beck C.
- van Dyck L.** See Rossel C.
- van Haren H.** Deep Mediterranean turbulent convection • 51/2 • p.17
- van Nieuwenburg E.** See Akhmerov A.
- Varjas D.** See Akhmerov A.
- Vinás M.** From Astronomy to the clinic: Adaptive Optics based visual simulators • 51/3 • p.17
- » **W**
- Wilming H.** See Iten R.
- » **Z**
- Zeltner R.** See Caruso R. | See Ostinato M.

# INNOVATION IN MAGNETICS



## MAG900 THREE-AXIS MAGNETIC FIELD SENSORS

- Low power consumption
- Noise  $<10\text{pTrms}/\sqrt{\text{Hz}}$  at 1Hz
- Measuring ranges  $\pm 60$  and  $\pm 100\mu\text{T}$

## HC16 HELMHOLTZ COIL SYSTEM

- Homogeneous field to 0.1% in a volume of  $175\text{cm}^3$
- Orthogonality correction using PA1
- Active compensation using CU2
- Control software available

## MAG690 THREE-AXIS MAGNETIC FIELD SENSORS

- Low cost
- Measuring ranges from  $\pm 100$  to  $\pm 1000\mu\text{T}$
- Unpackaged version available

RANGE OF FLUXGATE MAGNETOMETERS AVAILABLE



 **Bartington**<sup>®</sup>  
Instruments

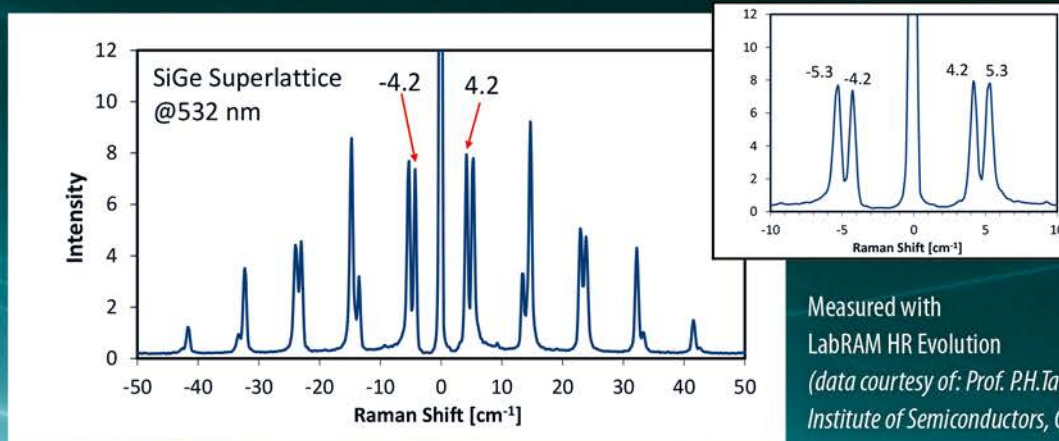
Telephone: +44 (0)1993 706565

Email: [sales@bartington.com](mailto:sales@bartington.com)

Website: [www.bartington.com](http://www.bartington.com)

# Ultra-Low Frequency Raman Spectroscopy

"Extend your Raman system into THz frequency range ( $5\text{-}200\text{ cm}^{-1}$ )"



## BragGrate™ Bandpass and Notch Filters

Spectral and spatial laser line cleaning filters and ultra-narrow line notch filters for low frequency Raman Spectroscopy



### Wavelengths in Production (nm)

405, 442, 458, 473, 488,  
491, 514, 532, 552, 561,  
568, 588, 594, 632, 660,  
785, 830, 980, 1064, 1550

- Frequencies below  $10\text{ cm}^{-1}$  with single stage spectrometer
- Angle tunable for precise wavelength adjustment
- Stokes and anti-Stokes Raman bands
- Unlimited optical life-time
- Custom wavelengths in range 400–2000 nm



INFO@OPTIGRATE.COM  
SALES@OPTIGRATE.COM

**OptiGrate**  
An IPG Photonics Company

WWW.OPTIGRATE.COM  
ORLANDO, FLORIDA, USA