THE KAVLI PRIZE

Science Prizes for the Future

press release

Research in observational X-ray astronomy, inventions of aberration-corrected lenses in electron microscopes, and the discovery of sensory receptors for temperature and pressure win USD 3 million Kavli Prizes

Seven scientists from five countries honoured for breakthrough discoveries in astrophysics, nanoscience and neuroscience

May 27, 2020 (OSLO) — The Norwegian Academy of Science and Letters today announced the 2020 Kavli Prize Laureates in the fields of astrophysics, nanoscience and neuroscience. This year's Kavli Prize honours scientists whose research has transformed our understanding of the very big, the very small and the very complex. The laureates in each field will share 1 million USD.

This year's Kavli Prize Laureates are:

- **Kavli Prize in Astrophysics:** Andrew Fabian (UK)
- **Kavli Prize in Nanoscience:** Harald Rose (Germany), Maximilian Haider (Austria), Knut Urban (Germany) and Ondrej L L Krivanek (UK and Czech Republic)
- **Kavli Prize in Neuroscience:** David Julius (US) and Ardem Patapoutian (US)

"The 2020 Kavli Prize Laureates represent truly pioneering science, the kind of science which will benefit humanity in a profound way, inspiring both current and future generations," says Hans Petter Graver, president of The Norwegian Academy of Science and Letters.

The 2020 Kavli Prize Laureates

Understanding the role of black holes in the 'ecosystem' of galaxies

The Kavli Prize in Astrophysics is awarded to astronomer and astrophysicist ***Andrew Fabian*** for his pioneering research and persistence in pursuing the mystery of how black holes influence their surrounding galaxies on both large and small scales. For decades, researchers have pondered the mechanics and physical processes of galaxies, and many have made discoveries that point to aspects of their inner workings; yet none has the unique vantage point of Fabian: to take a multi-scale understanding and systematically know where to look to put the pieces of the puzzle together and create the bigger picture of this vast ecosystem.

In the current cosmological paradigm, the universe is a 'living' system, in which the flows of gas into galaxies and black holes at their centres, and the subsequent release of energy back into the galaxies and their surroundings, all play vital roles. As the darkest objects in the universe, black holes are observed as their gravity attracts surrounding gas, dust and stars, which swirl into them at high velocities, creating intense radiation, much of it X-rays. Observational X-ray astronomy opened up access to view these and other extremely hot and energetic components of the universe, providing stunning evidence for these processes at work, unveiling how the major constituents of the universe can profoundly influence its overall evolution.

Fabian, a professor at the University of Cambridge, employs X-ray astronomy to explore the physics of the universe. His body of work – from understanding large-scale galactic evolution to the physics of black holes at the centres of galaxies – enabled him to make connections between local conditions around supermassive black holes and the larger gas flows within and between galaxies. This research provided evidence that supermassive black holes at the heart of galaxies are the engines that drive the flow of hot gas out of the galaxy, redistributing energy through the universe and providing the building blocks for future galaxy formation.

"Andrew Fabian is one of the most prolific and influential astronomers of our time," said Viggo Hansteen, chair of the Kavli Prize Committee in Astrophysics. "His research, breadth of knowledge and insights into the universe provided the essential physical understanding of how disparate phenomena in this ecosystem are interconnected."

More details available at the Kavli Prize website: www.kavliprize.org

Enabling scientists to see what was once impossible

The Kavli Prize in Nanoscience is awarded to four scientists for their research and inventions of aberration-corrected lenses in electron microscopes that have created the ability for researchers worldwide to see the structure and chemical composition of materials in three dimensions on unprecedentedly short-length scales: ***Harald Rose*** of the Universität Ulm and Technical University of Darmstadt, ***Maximilian Haider*** of CEOS GmbH, ***Knut Urban*** of the Forschungszentrum Jülich, and ***Ondrej L Krivanek*** of Nion Co.

A major goal of nanoscience is to create materials and devices assembled with atomic scale precision to obtain novel functionalities. The size of an atom is around one ångström (0.1 nanometer), so imaging and analysis of materials and devices at the sub-ångström scale is crucial to illuminate the details of the nanoscale world. The resolution of a classical microscope is limited by the wavelength of the probe used for imaging. Because visible light has a wavelength around 5000 times larger than an atom, optical lenses simply cannot image atoms.

In the early part of the 20th century beams of electrons with atomic-scale wavelength became available, leading to the invention of the transmission electron microscope in 1931. With this type of microscopy, a beam of electrons is transmitted through a thin material, forming an image based on the electrons' interaction with it. The image is then magnified and focused onto an imaging device. But the resulting images were distorted and blurry because making ideal lenses to focus beams of electrons turned out to be a big theoretical and experimental hurdle. The problem persisted for over 60 years as both theorists and experimentalists struggled to find a solution. Thanks to their insights, skills and the increase in computational power in the 1990s, these researchers were able to construct aberration-corrected lenses relying on electromagnetic fields to focus beams of electrons, making sub-ångström imaging (less than one ten-billionth of a metre) and chemical analysis in three dimensions a standard characterization method.

The 1 million USD Kavli Prize is shared by:

- *Harald Rose*, for proposing a novel lens design, the Rose corrector, enabling aberration correction in transmission electron microscopy that can be applied to both conventional and scanning transmission electron microscopes.
- *Maximilian Haider*, for the realization of the first sextupole corrector, based on Rose's design, and for his role in the implementation of the first aberration-corrected conventional transmission electron microscope.
- *Knut Urban*, for his role in the implementation of the first aberration-corrected conventional transmission electron microscope.
- *Ondrej L Krivanek*, for the realization of the first aberration-corrected scanning transmission electron microscope (a type of transmission electron microscope in which the electron beam is focused on a small spot) with sub-ångström resolution, well suited for spatially resolved chemical analysis; obtained using a quadrupole-octuple corrector.

"Their work is a beautiful example of scientific ingenuity, dedication and persistence. They have enabled humanity to see where we could not see before," said Bodil Holst, chair of the Kavli Prize Committee in Nanoscience. "Honouring these scientists and sharing with the world who they are and how they have transformed research, technology, industries and our lives is more important than ever."

More details available at the Kavli Prize website: www.kavliprize.org

Discovering sensory receptors for temperature and pressure

The Kavli Prize in Neuroscience is awarded to ***David Julius*** and ***Ardem Patapoutian*** for their independent discoveries of sensory receptors for temperature and pressure, respectively. While the mechanisms for smell and vision have long been described, a specific molecular understanding for how physical properties like temperature and pressure are detected and encoded into electrical signals the brain can process had been lacking. Over the past two decades, Julius and Patapoutian have independently described the molecular mechanisms that underpin sensitivities to temperature and pressure, as well as pain, and provided new insights into human physiology and disease.

David Julius, a physiologist and professor at University of California, San Francisco used an elegant approach to discover how the body detects high and low temperatures by exploiting the fact that there are chemicals that mimic different temperatures – such as the heat of pungent chili peppers and the coolness of mint. Julius and his team began by employing capsaicin, the compound in chili pepper that elicits the sensation of heat, to identify the gene encoding the first known temperature-sensitive sensor, the ion channel named TRPV1. Julius further discovered that the TRPV1 channel is also activated by high concentrations of protons and chemical compounds generated during the inflammatory response, providing a molecular basis for the pain hypersensitivity observed in damaged and inflamed tissue. This ion channel is a molecular integrator for both temperature sensing and inflammatory signals. Hotness – whether the burn from a spicy chili pepper or the burn from piping hot coffee – is encoded by the same sensor.

Genetic experiments conducted by Julius then showed that mutant mice deficient for TRPV1 have reduced heat sensitivity and a marked reduction in inflammatory and cancer pain. This discovery led to the identification of a family of channels involved in sensing specific ranges of warm and cold temperatures as well as irritants and inflammatory processes that may result in debilitating pain. In other experiments, Julius and collaborators identified these channels as infra-red heat sensors in vampire bats and snakes, and as targets of spider and scorpion toxins, further validating their roles in temperature and pain sensation throughout the animal world. The newly discovered TRPV1 and related channels are now areas for development of new pain-relieving drugs.

Ardem Patapoutian, a professor at Scripps Research and an investigator at the Howard Hughes Medical Institute, discovered a family of pressure-sensitive ion channels, the PIEZOs, with deep evolutionary roots, as they are present in many distantly related species.

Patapoutian and colleagues employed cells from a neuroblastoma cell line, which can be grown in a dish in a laboratory setting. These cells respond to pressure changes from a light touch by generating an electrical signal. With a curated list of over 300 suspected genes (out of the more than 20,000 that exist in our DNA) that might encode for a pressure-sensitive channel, they grew cultures of cells missing one gene at a time. Patapoutian's lab then tested the samples one by one, looking for the gene that, when missing, resulted in cells without pressure-sensing abilities. Candidate gene #72 on the list turned out to be the one.

PIEZOs were soon confirmed by Patapoutian to be essential for pressure sensing in mammals. His work showed that PIEZOs form ion channels and that they are directly responsible for pressure-sensing by Merkel cells and touch sensory terminals in the skin, and by proprioceptors (sensory receptors with endings in the muscle that respond to the body's position and movement in space).

PIEZOs also sense pressure by nerve terminals in blood vessels and in the lungs and affect red blood cell volume, vascular physiology and underlie a broad range of human genetic disorders. The discovery of the PIEZOs opened the door to understanding mechanobiology, an emerging field of science that intersects biology, engineering and physics, and focuses on how physical forces and changes in the mechanical properties of cells and tissues contribute to health and disease.

"The individual discoveries of David Julius and Ardem Patapoutian have given the scientific community the molecular and neural basis for thermosensation and mechanosensation that is revolutionizing our understanding of sensory detection and will have a profound impact on addressing health and disease worldwide," said Kristine B. Walhovd, chair of the Kavli Prize Committee in Neuroscience.

More details available at the Kavli Prize website: www.kavliprize.org

Kavli Prize Committees

Astrophysics
Viggo Hansteen (Chair), *University of Oslo, Norway*
Alessandra Buonanno, *Max Planck Institute for Gravitational Physics, Germany*
Andrea Ghez, *University of California Los Angeles, US*
Robert C. Kennicutt, Jr, *University of Arizona, US*
Irwin I. Shapiro, *Harvard University, US*

Nanoscience
Bodil Holst (Chair), *University of Bergen, Norway*
Gabriel Aeppli, *Paul Scherrer Institut, Switzerland*
Susan Coppersmith, *University of New South Wales, Australia*
Shuit-Tong Lee, *Soochow University, China*
Joachim Spatz, *Max Planck Institute for Medical Research, Germany*

Neuroscience
Kristine B. Walhovd (Chair), *University of Oslo, Norway*
Alexander Borst, *Max Planck Institute of Neurobiology, Germany*
Catherine Dulac, *Harvard University, US*
Mary E. Hatten, *The Rockefeller University, US*
Denis Le Bihan, *NeuroSpin, CEA, France*

About The Kavli Prize
The Kavli Prize is a partnership between The Norwegian Academy of Science and Letters, the Norwegian Ministry of Education and Research and The Kavli Foundation (US). The Kavli Prize honours scientists for breakthroughs in astrophysics, nanoscience and neuroscience that transform our understanding of the very big, the very small and the very complex. Three million-dollar prizes are awarded every other year in each of the three fields. The Norwegian Academy of Science and Letters selects the laureates based on recommendations from three prize committees whose members are nominated by The Chinese Academy of Sciences, The French Academy of Sciences, The Max Planck Society of Germany, The U.S. National Academy of Sciences and The UK's Royal Society. First awarded in 2008, The Kavli Prize has honoured 54 scientists from 13 countries – Austria, Czech Republic, France, Germany, Japan, Lithuania, The Netherlands, Norway, Russia, Sweden, Switzerland, the United Kingdom and the United States.

For more detailed information on The Kavli Prize, the 2020 laureates and their work, visit www.kavliprize.org.

The Kavli Prize Laureates are typically celebrated in Oslo, Norway, in a ceremony presided over by His Majesty King Harald followed by a banquet at the Oslo City Hall, the venue of the Nobel Peace Prize. Due to the COVID-19 pandemic, this year's award ceremony is postponed and will be held together with the 2022 award ceremony in September 2022.

For more information, please contact:

Marina Tofting (Norway)
The Norwegian Academy of Science and Letters
+ 47 938 66 312
marina.tofting@dnva.no

Stacey Bailey (United States)
The Kavli Foundation
+ 310 739 2859
sbailey@kavlifoundation.org

THE KAVLI PRIZE

KAVLI PRIZE IN ASTROPHYSICS 2020

The Norwegian Academy of Science and Letters has decided to award the Kavli Prize in Astrophysics for 2020 to

ANDREW FABIAN
University of Cambridge, UK

"for his groundbreaking research in the field of observational X-ray astronomy, covering a wide range of topics from gas flows in clusters of galaxies to supermassive black holes at the heart of galaxies"

The 2020 Kavli Prize in Astrophysics is awarded to Andrew Fabian for his groundbreaking research in the field of observational X-ray astronomy, covering a wide range of topics from gas flows in clusters of galaxies to supermassive black holes at the heart of galaxies.

X-ray astronomy has opened up access to the extremely hot and energetic components of the Universe. In the current cosmological paradigm, the universe is a living ecosystem, in which flows of gas into galaxies and black holes at their centers, and the subsequent release of energy back into the galaxies and their surroundings all play vital roles. X-ray observations have provided stunning evidence for these processes at work, unveiling how the major constituents of such an ecosystem can profoundly influence their overall evolution.

Andrew Fabian, one of the most prolific and influential astronomers of our time, has been a leading figure in several major research areas in X-ray astronomy. On large scales, he played a vital role in revealing the mystery of and solution to the prodigious heating and cooling mechanisms operating on inter-galactic gas in clusters of galaxies. On small scales, he predicted and co-discovered high velocity X-ray spectral emission from around black holes, which allowed Fabian and his collaborators to develop a powerful method for measuring black-hole spins. These very spinning black holes may provide the energy to heat the inter-galactic gas and affect the evolution of the constituent galaxies. Fabian's breadth of knowledge and insights on vastly different scales have provided key physical understanding of how those disparate phenomena are interconnected.

Andrew Fabian
University of Cambridge, UK.
Photo: © Sam Fabian

ASTROPHYSICS PRIZE 2020 EXPLANATORY NOTES

Black holes as galactic engines

Black holes are among the most enigmatic objects in the universe. Created by imploding massive stars, they are so dense that the gravitational field around them completely warps space-time and prevents even light from escaping their clutches. Anything that passes their event horizon is lost from view forever. And yet we know that black holes exist. That's because the vast amounts of energy given off in their vicinity generate signals that we can intercept, even if those signals take millions of years to reach us.

Figure 2: The active galaxy NGC 1275 is a well-known radio source (Perseus A) and a strong emitter of X-rays due to the presence of a black hole in the center of the galaxy. Credit: X-ray: NASA/CXC/IoA/A.Fabian et al.; Radio: NRAO/VLA/G. Taylor; Optical: NASA/ESA/ Hubble Heritage (STScI/AURA) & Univ. of Cambridge/IoA/A. Fabian

Andrew Fabian, an astronomer at Cambridge University in the UK, has spent his life studying the signals that arrive in the form of X-rays. In particular, he has scrutinised the X-rays emitted by supermassive black holes at the centre of very bright galaxies, revealing that those black holes play an intimate role in the life of galaxies and clusters of galaxies.

A supermassive black hole can be up to billions of times more massive than the Sun, its immense gravity sucking in vast amounts of gas from surrounding space. Because most of that gas arrives off-target having travelled a long way, it overshoots the black hole slightly and then gets pulled back – putting it on a spiral trajectory. The result is a thin "accretion disk" surrounding the black hole within which particles collide and give off energy, much of it at X-ray frequencies.

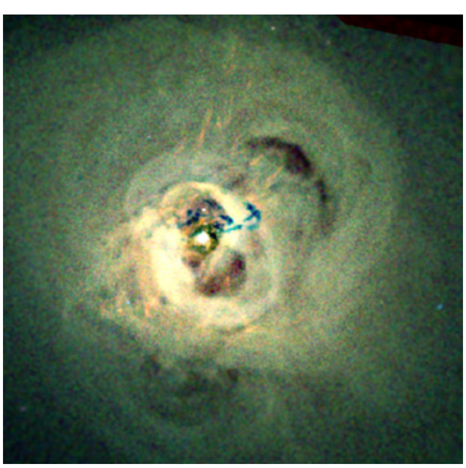
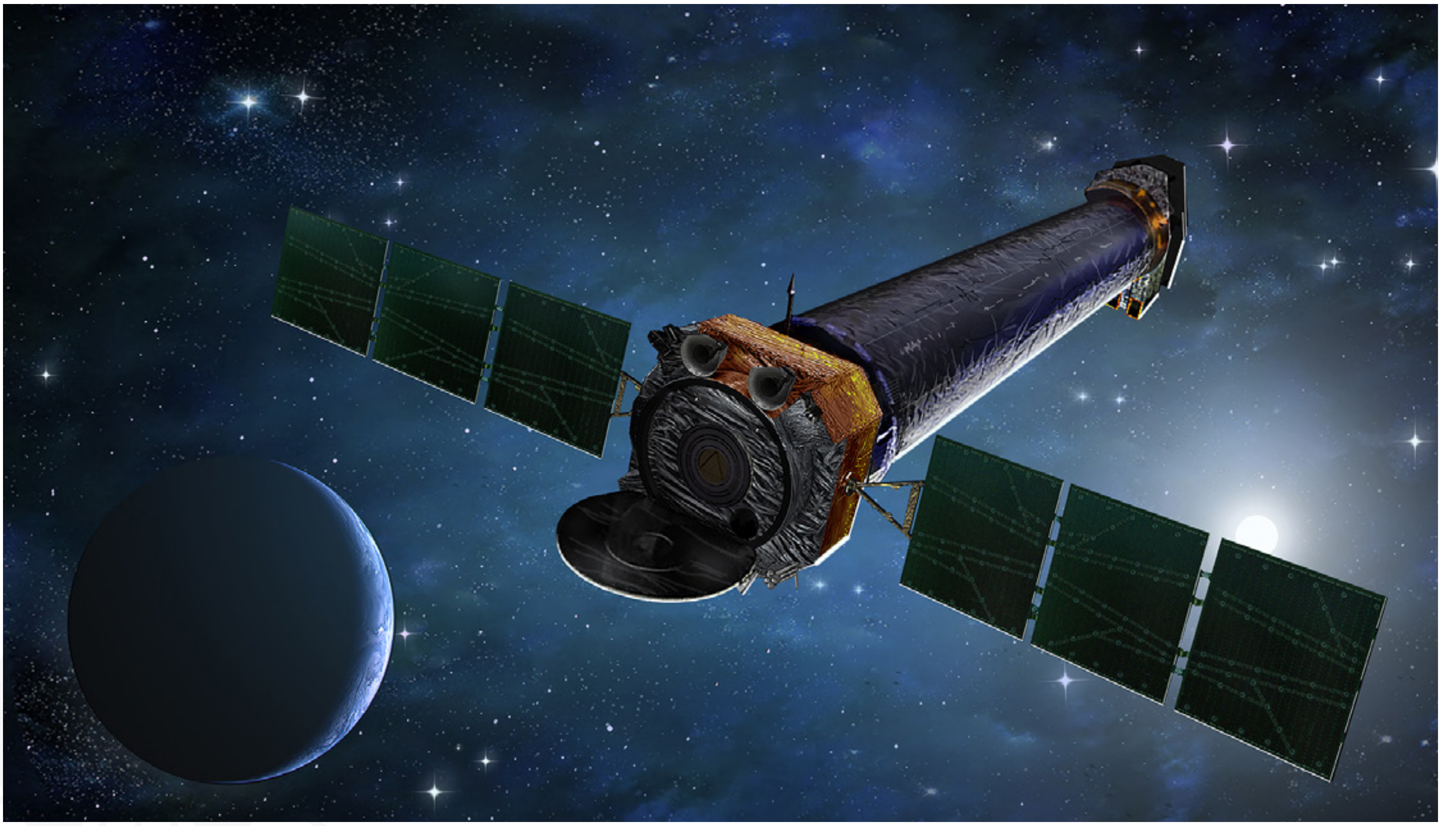


Figure 1: An X-ray image from NASA's Chandra satellite showing heated gas surrounding the centre of the vast Perseus galaxy cluster. Photo: © NASA/CXC/IoA/A.Fabian et al.

These cosmic X-rays can't be seen on Earth because they are blocked by the atmosphere. So scientists instead observe them from space. Having first measured the emission from a black-hole-like source known as Cygnus X-1 in the early 1970s, researchers have since launched a series of ever more sophisticated X-ray satellites.

In 1995, Fabian and colleagues reported having found tell-tale signs of a black-hole powered accretion disk in X-rays gathered by a Japanese-American mission known as the Advanced Satellite for Cosmology and Astrophysics. They discovered that a peak in the energy spectrum due to the emission of X-rays by iron within several very bright galaxies was broader and at slightly lower frequencies than expected. They interpreted this as an effect of Einstein's general theory of relativity, an effect that had been predicted by Fabian and other



Andrew Fabian and colleagues have used NASA's Chandra observatory, seen here in an artist's impression, to make detailed studies of the Perseus galaxy cluster

Credits: NASA/CXC & J.Vaughan

researchers a few years earlier – that time close to a powerful source of gravity slows down when measured from outside.

Building on that research, Fabian found it was possible to measure two distinct sets of X-rays emitted close to a black hole – those generated by the accretion disk directly as well as others produced by very hot electrons close to the black hole that bounce off the disk before travelling out across space. By measuring the short time delays between the two emissions he and his collaborators were able to map the accreting gas and measure the black hole's rate of spin.

But Fabian has also used X-ray data to study the effect of black holes over much greater distances. Indeed, he posed and then found a solution to a problem that has kept astronomers busy for decades – where does intergalactic gas in clusters of galaxies get its energy from? The gas between galaxies in certain bright clusters should be cool enough that it clumps together to form new stars. But astronomers observe no such star formation and measure the gas to be millions of degrees hotter than it ought to be without an extra source of energy.

Fabian and co-workers found clues to help solve the mystery in several X-ray images of the Perseus cluster taken by NASA's Chandra satellite in the first few years of this century. These images showed a range of features within the cluster, including dark patches and ripples of brightness, spaced 30,000 light-years apart, emanating from a central dark region.

Fabian reckoned that these features were created as a result of energy being transferred mechanically from a central black hole to the surrounding gas. The idea was that the dark regions are bubbles formed when jets of material shooting out from the black hole at right angles to the accretion disk push against the gas. The huge pressure generated then propagates outwards as a series of sound waves that heat up the gas.

That work earned Fabian a place in the Guinness Book of Records for having discovered "the deepest note in the universe" – a B-flat, 57 octaves below middle C (a sound, it was pointed out, that no-one would be able to hear). But the research also underlined the central role that black holes play in the lives of galaxies, in this case by generating negative feedback that limits both their own growth and that of surrounding stars. It might also explain why the mass of supermassive black holes is tied to the mass of their host galaxies, as has been observed.

This idea of black-hole feedback is now widely accepted. What's more, Fabian has found that black holes in less massive galaxies than those at the centres of clusters also transfer energy, but do so more directly. In this case, their intense X-rays and ultraviolet radiation simply push dusty gas out of the host galaxy.

A number of details about these processes still remain to be filled in, including the extent to which the spin of a black hole contributes to the heating. But these details aside, says Kavli astrophysics committee chair Viggo Hansteen of the University of Oslo, there is now no doubt that black holes are the central engines heating intergalactic gas. "Every time you solve a problem others emerge," he says. "But the central problem of 'what is heating the gas?' is solved."

By Edwin Cartlidge

THE KAVLI PRIZE

KAVLI PRIZE IN NANOSCIENCE 2020

The Norwegian Academy of Science and Letters has decided to award the Kavli Prize in Nanoscience for 2020 to

HARALD ROSE
Universität Ulm, Germany

MAXIMILIAN HAIDER
CEOS GmbH, Germany

KNUT URBAN
Forschungszentrum Jülich, Germany

ONDREJ L. KRIVANEK
Nion Co., US

"for sub-ångström resolution imaging and chemical analysis using electron beams"

Seeing leads to scientific advancement, understanding and engineering. The 2020 Kavli Prize in Nanoscience honours four pioneers who enabled humanity to see the structure and chemical composition of materials in three dimensions on unprecedentedly short length scales.

A major goal of nanoscience is to create materials and devices assembled with atomic scale precision to obtain novel functionalities. The size of an atom is around one ångström (0.1 nanometer). Therefore, imaging and analysis of materials and devices at the sub-ångström scale is crucial. The resolution of a classical microscope is limited by the wavelength of the probe used for imaging. Because visible light has a wavelength around 5000 times larger than an atom, optical lenses cannot image atoms. In the early part of the 20th century beams of electrons with atomic scale wavelength became available, leading to the invention of the electron microscope in 1931. However, making ideal lenses for electrons turns out to be a big theoretical and experimental problem because lens aberrations limit the resolution. For more than 60 years people struggled! Through persistence, ingenuity and exploitation of the increase in computational power in the 1990s the Laureates constructed aberration corrected lenses and made sub-ångström imaging and chemical analysis in three dimensions a standard characterization method.

Three of the Laureates co-founded two companies and commercialized their lenses contributing further to the major impact of their scientific work. Since then their microscopes have played an enormous role both in fundamental science and technology, where they are used, among others, by semiconductor, chemical and automotive industries.

The 2020 Kavli Prize Laureates in Nanoscience are

Harald Rose, for proposing a novel lens design, the Rose corrector, enabling aberration correction in transmission electron microscopy that can be applied to both conventional and scanning microscopes.
Maximilian Haider, for the realization of the first sextupole corrector, based on Rose's design, and for his role in the implementation of the first aberration corrected conventional transmission electron microscope.
Knut Urban, for his role in the implementation of the first aberration corrected conventional transmission electron microscope.
Ondrej L Krivanek, for the realization of the first aberration corrected scanning transmission electron microscope with sub-ångström resolution, well suited for spatially resolved chemical analysis. This

was obtained using a quadrupole-octupole corrector.

Harald Rose
Universität Ulm, Germany
Photo: © private

Maximilian Haider
CEOS GmbH, Germany
Photo: © "Bilderfest" Germany

Knut Urban
Forschungszentrum Jülich, Germany
Photo: © Research Center Juelich

Ondrej L. Krivanek
Nion Co., US
Photo: © Michelle Krivanek

THE KAVLI PRIZE

NANOSCIENCE PRIZE 2020 EXPLANATORY NOTES

Looking inside matter atom by atom

Manipulating matter at very small scales — even as precisely as moving single atoms — to create particles and devices with new functionalities is the ultimate ambition of nanoscience and nanotechnology. None of this could be achieved without an imaging technique that allows materials and devices to be studied with atomic resolution.

In making their award, the Kavli Prize in Nanoscience committee has selected four scientists who contributed to the development and use of two types of instrument, generally known collectively as aberration-corrected transmission electron microscopes, which can provide information about the structure and other properties of materials with sub-ångström resolution, hence allowing individual atoms to be distinguished.

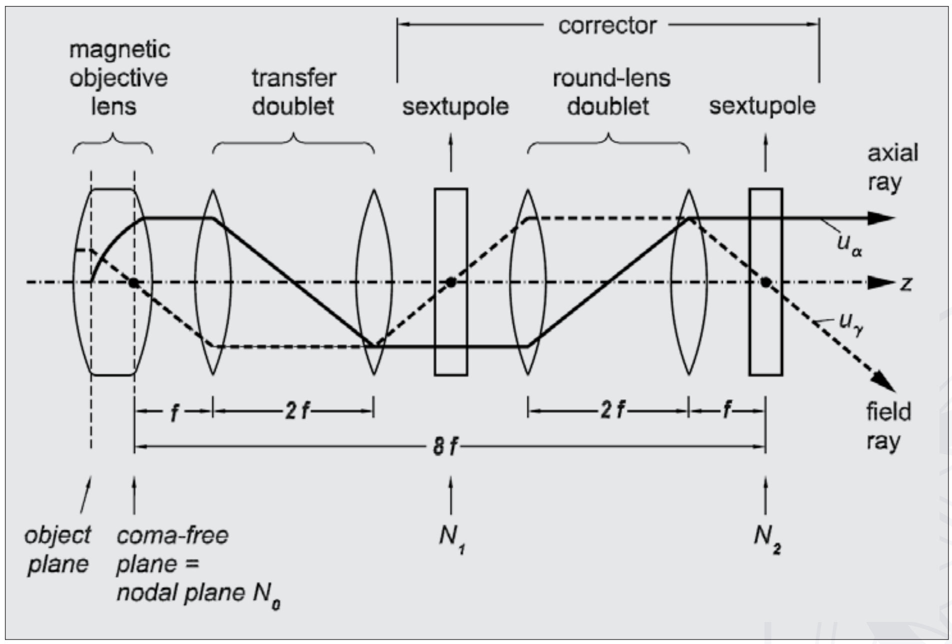
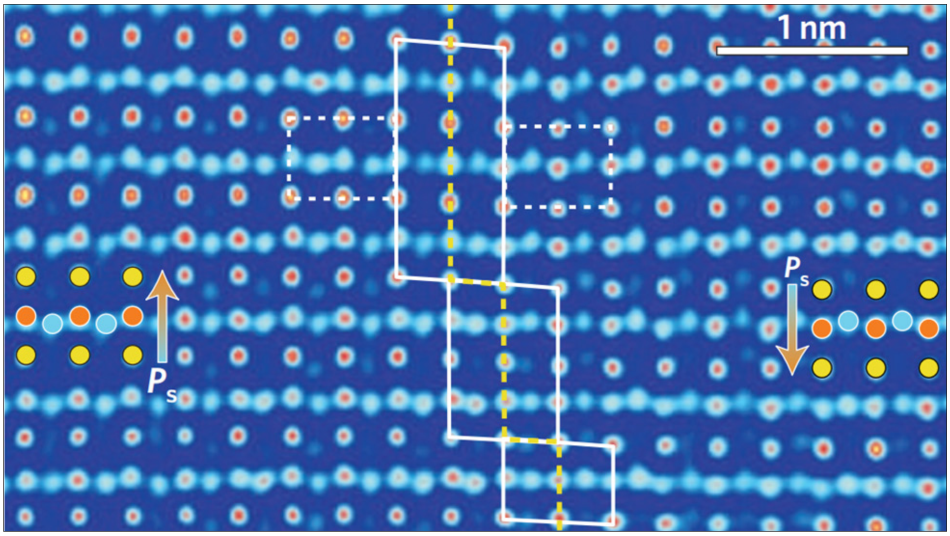


Figure 1. The schematic for an aberration corrector in the 1990 paper by Harald Rose. Optik 85, 19–24 (1990); © Elsevier GmbH

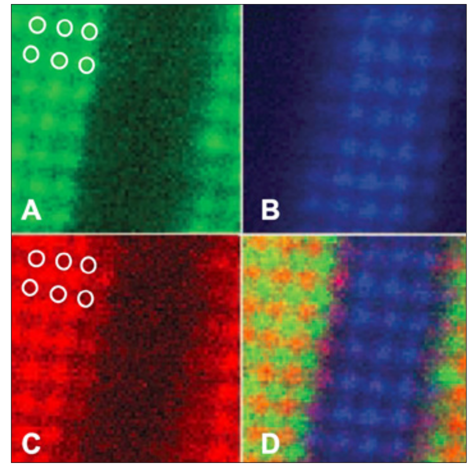
Optical microscopes can at best resolve features a few hundred nanometres across, so a different approach is necessary to distinguish single atoms. The scanning tunnelling microscope and the atomic force microscope, invented in the 1980s, achieved atomic resolution. However, they both work only on exposed surfaces, and for the majority of nanoscale structures it is essential to study the buried interfaces between different materials or different phases of the same material. The most promising route was to optimize the transmission electron microscope, invented in 1931 by Ernst Ruska. The instrument is based on the use of a beam of electrons directed at a thin sample of a given material. Interaction of the beam with the atoms in the material scatters the electrons. Using the scattered electrons the electromagnetic objective lens of the microscope and additional lenses form a magnified image which is recorded with a CCD or a CMOS camera. Ruska's design is today called CTEM, for conventional transmission electron microscope. Conventional" means that, apart from employing electron radiation, CTEM follows the design of an optical microscope. In 1937 Manfred von Ardenne invented the scanning transmission electron microscope, the STEM. In this case, the specimen is scanned with a fine electron beam, collimated by the electromagnetic lenses, and the electrons that have passed through the specimen are collected behind it. The image is then created by displaying the intensity of these electrons on a video screen.

A unique advantage of the STEM is that for each spot of the material that the beam focuses on, it is also possible to analyse the energy lost by electrons when the beam scatters from atoms in the material. This technique, known as electron energy loss spectroscopy, or EELS, can provide information on the atomic composition and electronic states inside the material.

Although for both CTEM and STEM the resolution had reached a few ångströms by the late 1980s, it was impossible to resolve the detailed atomic arrangements in most materials. The problem was that the electromagnetic lenses being used suffered from aberrations much more than optical lenses do. So, for example, electrons passing through the lens far from the centre of it would be focused at a different distance from those traversing it close to the centre, thus blurring the images.



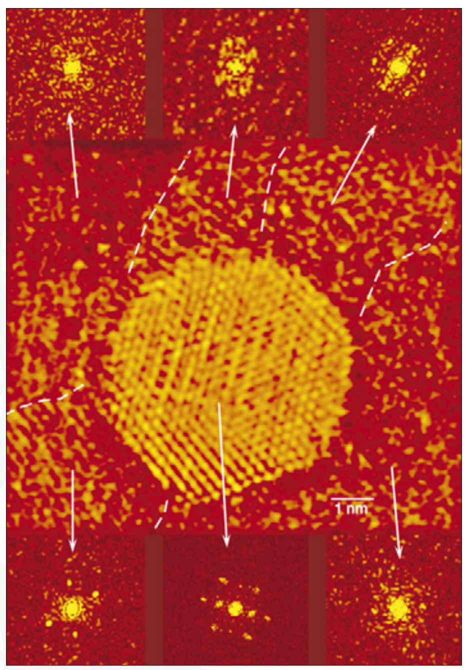
2. *Atomic structure of different ferroelectric domains in the material PZT obtained by aberration-corrected TEM. The positions of the atoms (O, blue; Pb, yellow; Zr/Ti, red) in the two phases can be directly linked to the direction of electric polarization (P_s). Adapted from C.-L. Jia et al. Atomic-scale study of electric dipoles near charged and uncharged domain walls in ferroelectric films. Nature Mater. 7, 57–61 (2008); © Springer Nature Ltd.*



4. *Atomic-resolution chemical map, obtained using EELS on an STEM, of a (La,Sr)MnO_3/$SrTiO_3$ multilayer showing the La (green), Ti (blue) and Mn (Red) atoms; the white circles indicate the position of the La columns; field of view 3.1 nm. From D. A. Muller et al. Atomic-scale chemical imaging of composition and bonding by aberration-corrected microscopy. Science 319, 1073–1076 (2008).*

In 1990, Harald Rose, then at the University of Darmstadt, building on previous work on various ideas for aberration correction, designed a lens system based on electromagnetic hexapoles (Figure 1) that could be tuned to cancel the aberration of a standard electron lens, and that could work with both CTEM and STEM. In the following years, Rose teamed up with experimentalists Maximilian Haider, then based in Heidelberg, and Knut Urban in Jülich, to realize his proposal experimentally for a CTEM. In 1998, the collaboration resulted in the publication of the first images improved using an aberration-corrected CTEM. In 1996 Haider together with Joachim Zach had founded the company CEOS (Correlated Electron Optical Systems) to commercialize the 'Rose corrector', which is widely used today, in both CTEM and STEM.

Aberration-corrected CTEMs have developed substantially in the past 20 years, with the resolution now reaching 0.5 Å. Hence, in comparison with an uncorrected TEM the resolution with respect to the wavelength of electrons could be improved by a factor of 7. The ability to look at single atoms within a lattice has allowed the relationship between the local atomic structure and the properties of the material to be studied. A beautiful example is shown in Figure 2, in which an aberration-corrected TEM has been used to directly link the position of the atoms in a classic ferroelectric material to changes in electric polarization direction.



3. *Atomic resolution image of an island of Au on an amorphous carbon substrate. The island is surrounded by monoatomic clusters of Au. Diffraction patterns from different regions surrounding the island show that these clusters are ordered in various structures adjacent to the built-up islands. Nature 418, 617-620 (2002); © Springer Nature Ltd.*

While Rose, Haider and Urban were developing aberration-corrected CTEM, in 1995 Ondrej Krivanek, a long-time expert in electronic optics and EELS, started working in Cambridge, UK, with Mick Brown and Andrew Bleloch on the development of aberration correction in STEM. In 1997, together with Niklas Dellby, Krivanek started the company Nion to develop aberration-corrected STEM commercially. In 2002, Krivanek, Dellby and their colleague Phil Batson from IBM published sub-ångström resolution images (Figure 3) obtained with the Nion quadrupole-octupole STEM corrector.

The STEM has developed even further in the past two decades. As mentioned previously, the STEM can be used to perform EELS, and this combination has been used to obtain information on the chemical composition of materials (see Figure 4), and even on the type of bonding between atoms.

The pioneering work by Rose, Haider, Urban and Krivanek has now led to TEM and STEM instruments that are used routinely by research laboratories. Thanks to other advances, first and foremost the realization of highly sensitive electron detectors, both instruments can now be used on very delicate samples, including, for example, graphene and other two-dimensional materials. Some instruments are employed as mini-laboratories, where chemical reactions are carried out in-situ under direct atomic-resolution observation. There have also been attempts to go beyond imaging, and manipulate single atoms within a lattice. In industry, the instruments are regularly used to monitor the quality and reliable fabrication of devices. As Professor Bodil Holst of the University of Bergen, and chair of the Kavli Prize in Nanoscience Committee, said "Behind this year's Kavli Prize lies more than 60 years of theoretical and experimental struggle. It is a beautiful example of scientific ingenuity, dedication and persistence. We honour four laureates who have enabled humanity to see where we could not see before".

By Fabio Pulizzi

THE KAVLI PRIZE

KAVLI PRIZE IN NEUROSCIENCE 2020

The Norwegian Academy of Science and Letters has decided to award the Kavli Prize in Neuroscience for 2020 to

DAVID JULIUS
University of California, San Francisco (UCSF), US

and

ARDEM PATAPOUTIAN
Scripps Research, La Jolla, US

"for their transformative discovery of receptors for temperature and pressure"

The 2020 Kavli Prize in Neuroscience is awarded to David Julius and Ardem Patapoutian for their transformative discovery of receptors for temperature and pressure.

While neural mechanisms for sensing chemicals in olfaction and light in vision have been described, a molecular basis for how temperature and pressure are detected and encoded into electrical signals has been lacking. The two Kavli Prize laureates, Julius and Patapoutian, discovered receptors for temperature and pressure, two critical physical features of the environment. These findings revolutionized the field of neuroscience by providing a molecular and neural basis for thermosensation and mechanosensation.

David Julius used capsaicin, the compound in chili pepper that elicits the sensation of heat, to identify the gene encoding the first temperature sensor, the ion channel TRPV1. Julius further discovered that TRPV1 is activated by high temperature, high concentrations of protons found in ischemic tissues and chemical compounds generated during inflammation, thus providing a molecular integrator for both temperature sensing and inflammatory signals. Genetic experiments then showed that mutant mice deficient in TRPV1 have a deficit in heat sensitivity and a marked reduction in inflammatory and cancer pain. This discovery led to the identification of a family of channels involved in sensing specific ranges of warm and cold temperatures and irritants, some of which are mutated in familial pain syndromes. In other experiments, Julius and collaborators identified these channels as infra-red sensors in vampire bats and snakes, and as targets of spider and scorpion toxins, further validating their roles in temperature and pain sensation. TRPV1 and related channels are now targets for development of new analgesic drugs.

Ardem Patapoutian discovered a family of pressure-sensitive ion channels, the Piezos that are highly conserved throughout the animal kingdom. Piezos were soon confirmed by Patapoutian to be essential for pressure sensing in mammals. His work further showed that Piezos form pressure-sensing channels and that they are directly responsible for pressure sensing in skin by Merkel cells, proprioreceptors and touch sensory terminals. Piezos also act to sense pressure by nerve terminals in blood vessels and in the lungs and affect red blood cell volume, vascular physiology and underlie a broad range of human genetic disorders. The discovery of the Piezos opened the door to understanding mechanobiology in health and disease.

David Julius
University of California, San Francisco (UCSF), US
Photo: © UCSF

Ardem Patapoutian
Scripps Research, La Jolla, US
Photo: © Scripps Research

THE KAVLI PRIZE

NEUROSCIENCE PRIZE 2020 EXPLANATORY NOTES

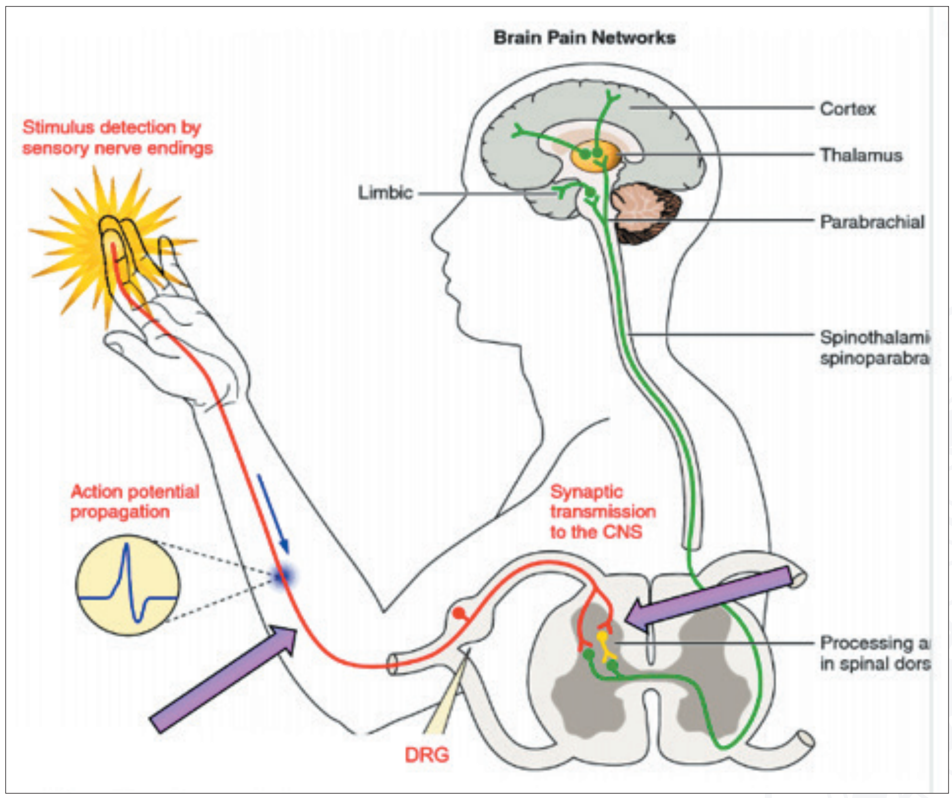
Ouch! When heat and pressure become painful

Picture standing on a beach – warm sunshine, a sea breeze caressing your cheeks, and rough sand between your toes. These are familiar but quite different sensations, yet they all depend on our sense of touch. Whether something feels hot, cold, hard, soft or painful, it is our tactile sensitivity that helps us discriminate between these stimuli. They are all part of our sense of touch, which has been the least well understood of the five senses (compared to seeing, hearing, smell, and taste), until the work of the 2020 Kavli Prize in Neuroscience winners, David Julius and Ardem Patapoutian.

Over the past two decades, they have independently described the molecular mechanisms that underpin our sensitivity to temperature, pressure and pain, and provided new insights into human physiology and disease.

Julius was originally fascinated by how natural products such as hallucinogens used in folk medicine could be used to explore the nervous system. His postdoctoral research focused on receptors for the neurotransmitter serotonin, and drew his attention to sensory neurons that relay sensations to the brain.

Later, as an independent investigator, he came across the work of Hungarian scientists and others showing that a subset of sensory neurons became active in the presence of both heat and capsaicin, the 'hot' ingredient of chili peppers. There was controversy, however, about what the mechanism might be and its significance to pain sensation. It remained a niche area until 1997, when Julius identified the receptor molecule TRPV1 on pain-sensing neurons, and showed that it was activated by both heat and capsaicin, and thus represented a point of convergence for the two stimuli.

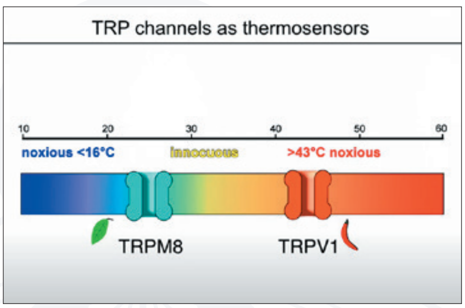


External environmental stimuli such as heat and pressure activate ion channel receptors in the membranes of sensory nerves, resulting in electrical impulses which travel via the dorsal root ganglia (DRG) to sensory regions of the brain. [Illustration adapted from Bourinet et al. 2014]

TRPV1 belongs to a family of ion channels, which sit in the cell membrane and upon activation, open a pore to allow the flow of charged ions (such as sodium and calcium) into the cell. Better understood in fruit flies, this was the first TRP channel to be assigned a physiological role in vertebrates.

"The cloning of the capsaicin receptor was a bit of a landmark moment in terms of understanding a molecular basis for touch and pain sensation… in particular a mechanism by which a physical force can activate these neurons." says Julius. A role for TRP channels in temperature sensation was further confirmed when Julius and Patapoutian independently identified TRPM8 as a receptor responding to menthol and cold.

Capsaicin, the 'hot' ingredient of chili peppers, stimulates the same sensory nerves as heat via the receptor TRPV1. [credit: Marat Musabirov]



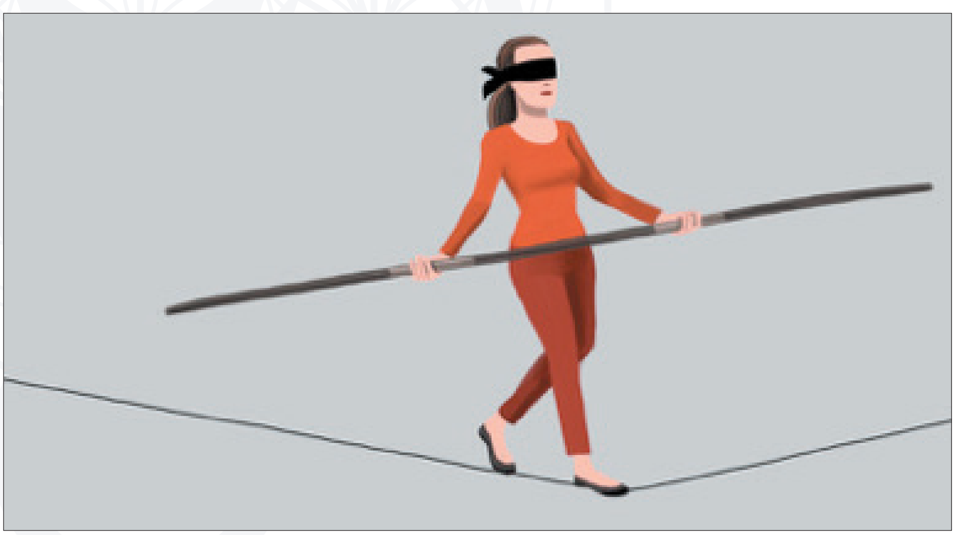
Caption: TRP ion channels respond to changes in temperature by opening pores that allow positively charged sodium and calcium ions to flow through the membranes of nerve cells, triggering a change in voltage across the membrane.

Julius also revealed that TRPV1 was sensitive to chemicals produced during inflammation and mediates inflammatory-related pain hypersensitivity, opening up new potential avenues for the treatment of cancer pain and other conditions.

Julius, Patapoutian, and others have since identified other ion channels that are important to touch and pain. The 'wasabi receptor' TRPA1, for example, responded to wasabi, mustard oil, garlic and a variety of chemical irritants, making this an important receptor for detecting noxious environmental toxins. But its activation by a chemical produced in osteoarthritis signifies a dual role in pain sensation.

Patapoutian's research took a different direction, however, when he started questioning how we sense pressure. In 2010, his team discovered two new ion channels that were activated by mechanical pressure (a gentle poke with a fine rod), to produce electrical activity. They cloned and named the ion channels PIEZO1 and PIEZO2 (from the Greek piezi meaning pressure).

PIEZO1 and PIEZO2 were found on sensory neurons and other cell types, leading to an explosion of research on the role of these ion channels in pressure sensation for touch, pain, blood pressure regulation, lung inflation, and proprioception.



Caption: Proprioception – which enables us to balance and walk blindfolded - depends on PIEZO receptors expressed in 'stretch receptor' neurons. Illustration: Jorge Colombo

Proprioception refers to our ability to sense where our body is in space. It normally enables us to stand and walk, even with our eyes closed or blindfolded, and depends on neurons that signal muscle stretch to the brain. Patapoutian's team and others have shown that PIEZO2 is the key receptor involved, with reports that humans with a rare deficiency in PIEZO2 have difficulty standing and walking in the dark. They also do not experience pain hypersensitivity.

Patapoutian's more recent research in human genetics and mouse models has demonstrated a role for PIEZO1 in controlling red blood cell volume. He found a PIEZO1 gene variant that appears to protect against infection by the malaria parasite, and is carried by one in three people of African descent.

"It's been a very fascinating journey following where PIEZOs take us, from one biology and pathophysiology to another," says Patapoutian.

THE KAVLI PRIZE

BIOGRAPHY
ASTROPHYSICS 2020

Andrew Fabian

Photo: © Sam Fabian

Andrew Fabian

is one of the world's leading X-ray astronomers, having made major contributions to observational and theoretical astrophysics. After graduating in physics from King's College London, he was awarded a PhD from University College London in 1972 for measurements of the diffuse radiation from outside our galaxy known as the X-ray background. Those studies involved analysing data from detectors that he designed and launched onboard two sounding rockets.

A year later he moved to the Institute of Astronomy at the University of Cambridge and he has been there ever since. Starting as a postdoctoral fellow, he was a Royal Society Research Professor from 1982 to 2013 and later also served as the Institute's director. He has supervised over 50 PhD students and was vice-master of Darwin College for 15 years.

Fabian's research has spanned many areas of high-energy astrophysics, notably supermassive black holes and their influence on surrounding space – in the form of active galactic nuclei and the heating of intergalactic gas. His work has led him to participate in many of the X-ray observatories launched over the past half century, from Uhuru in the early 1970s to the currently operating NuSTAR telescope, and he is part of the team preparing the Athena mission for launch in the early 2030s. He complements these X-ray measurements with observations from ground-based observatories at optical and radio wavelengths.

Fabian was president of the UK's Royal Astronomical Society from 2008 to 2010 and a member of the editorial board of the Society's Monthly Notices for 29 years. He is a fellow of the Royal Society and was awarded the Order of the British Empire in 2006. Among his other honours, he received the American Astronomical Society's Bruno Rossi Prize in 2001 for jointly discovering that black holes' gravity can widen the iron lines seen in X-ray spectra from active galactic nuclei.

autobiography

by Andrew Fabian

I was hooked on astronomy by the age of about seven, having read in a children's encyclopedia that astronomers could work out the composition of a star from the light it emits. That seemed wonderful. I recall seeing Comet Arend-Roland when I was nine and I followed the emerging Space Progammes and spent time studying the night sky with a one-inch refractor from our back garden. Asthma meant that I missed junior school several days a month but, provided I sat still, I could read which was the main way my horizons expanded. We had no television till I was about nine. My parents were shopkeepers and not interested in science but left me to experiment, learn the constellations and read by myself.

After the village junior school, I went to the state grammar school in nearby Daventry where I enjoyed most lessons but especially physics and chemistry. My asthma soon disappeared. At home in the evenings I did electronics with crystal sets, thermionic valves and then transistors, which were just becoming affordable. At 15, I ground and silvered a six-inch mirror and assembled a simple Newtonian telescope. The Moon at 200 times magnification was magnificent. Space and astronomy drew me in and I resolved to take study physics. At 17 I spent a couple of weeks at the Jeremiah Horrocks Observatory in Preston, Lancashire, to gain some experience. Much of my time was taken up by measuring and counting sunspots on drawings that had regularly been made a few decades earlier. It was far from exciting but did not dissuade me from wanting to find out more about the Universe.

I studied physics for my first degree at King's College, London. Having lived in a village until then, I felt ready for a city and

Me at the Jeremiah Horrocks Observatory in Preston, Lancashire, aged 17

London seemed right. It was an exciting place at times in the late 1960s, although for a penniless student keen on studying science, opportunities were limited. Astronomy did not feature in my lecture course, although I do clearly remember Professor Herman Bondi giving a lecture on "Why is the Sky Dark at Night?" No visual aids, no black board, just clear speaking – taking something which sounds too obvious to discuss and extracting profound cosmological consequences!

For my PhD I considered several options, including radio astronomy at Cambridge led by Martin Ryle and space astronomy at University College London with Robert Boyd. I chose the latter and started my research in the autumn of 1969 at the Mullard Space Science Laboratories in the Surrey Hills between Guildford and Dorking. By December, I had changed supervisors several times and my new supervisor, Pete Sanford, suggested I write a proposal for a Skylark sounding rocket to observe the granularity of the X-ray Background. He had been at a conference that summer where Martin Rees had discussed the origin of this background radiation in terms of seven radio galaxies per square degree. If true, then the granularity should be measurable. I travelled to Cambridge to meet Martin and was deeply impressed by his friendliness and the generosity with his time to someone who was just starting out. I also consulted David Lindley of the UCL statistics department about how to obtain limits and was told to read his books. A proposal was submitted before Christmas and accepted in January. Things could happen rapidly.

The proportional counter detector was the workhorse of X-ray astronomy back then. The X-ray Background was going to be readily detectable, but what I needed to do was reduce the non-cosmic background in the detector that was due to cosmic rays. Pete Sanford had devised a pulse-shape discrimination method for doing that (X-rays produce a compact cloud of electrons in the detector whereas cosmic rays leave an extended cloud). My immediate task was to design the electronics, using integrated circuits which had not been used for that purpose before at the Mullard Space Science Laboratories. I gave myself a crash course in electronics which was far removed from my home lab work years before. After some months it came together, and by autumn I was testing the assembled equipment on a Skylark payload module.

Weeks were spent trying to suppress radio frequency interference. A transmitter was only a few metres away from the very sensitive preamplifier which detected minute electrical signals from the detector. All sharing the same powerlines. Sometimes I would think it was working well, then step back and everything would go haywire. Eventually it was suppressed and the instrument became robust. At the same time I was learning about X-ray astronomy and astronomy in general. At the time it was reckoned that the total exposure to the X-ray sky by rocket-borne detectors was just a few hours, meaning that I could easily read and digest every paper written on the subject in my spare time.

Skylark SL1001 was launched from Woomera in Australia in late January 1971. I spent six weeks in Australia having flown there on a three-day, Ministry of Defence, turbojet flight to Adelaide followed by train to Woomera out in the desert. (The name Woomera is the indigenous name for a throwing stick.) The flight gave about 15 minutes of exposure to cosmic X-rays during the upper part of its trajectory. Fortunately the data were telemetred down during the flight as the parachutes became tangled and the payload smashed to pieces on hitting the ground. I spent the next day in a helicopter making the recovery, which was exciting at first but, as it was extremely hot outside and the desert was dotted with salt pans, there were strong convection currents: we went up and down like a lift, and I spent the last hours feeling nauseous.

I obtained the telemetry tapes some weeks after my return and read them onto an IBM mainframe in London, analyzing them at the space laboratory. The results became my first publication, "Rocket Observations of the Cosmic X-ray Background" by Fabian & Sanford, Nature Physical Sciences, May 1971. Publication could happen fast back then. I felt that I was in competition with the X-ray astronomy group of Riccardo Giacconi at American Science and Engineering in the US. (Riccardo started cosmic X-ray astronomy with a US rocket flight in 1962.) The American Science and Engineering group had launched a satellite from Kenya named Uhuru which had several proportional counters back in December 1970. By my launch they had buckets of data. Fortunately for me they were making new discoveries every week (X-ray binaries, X-rays from supernova remnants, clusters of galaxies and so on) and didn't get around to the X-ray background. As luck had it, I was generously given and published the Uhuru background data after a visit to them in 1975.

The rocket results showed that the background was very smooth, requiring more than two million sources over the whole sky, and was to be confirmed and extended with a second rocket flight, this time from the European Space Research Organisation (later becoming ESA). Preparation for that meant many trips to the European Space Research and Technology Centre in Noordwijk in the Netherlands, and the launch successfully took place from Sardinia, Italy, in June 1972. In the meantime, I had studied the problem of fluctuations in a background of point sources and found that it overlapped with observations of radio sources in what was known as P(D) – the probability distribution of deflections in the pen recorder as a radio telescope scanned the sky. Through Martin Rees, I was introduced to Peter Scheuer of the Cambridge Radio Astronomy Group who had studied the problem 15 years earlier, and also Dennis Sciama, then at Oxford, who had a student looking at it. Both were interested, friendly and helpful.

A couple of years later I worked on the origin of the X-ray Background with cosmologist Michael Rowan-Robinson and later in the 1980s, Xavier Barcons, with whom I wrote a review on the topic in 1992. In a way we were finding why the X-ray Sky is dark at night. Riccardo Giacconi and others finally resolved most of the X-ray Background into distant active galactic nuclei with the Chandra Observatory in the early 2000s.

My PhD viva was in July 1972 and rather rushed as I thought I was about to head off to Cambridge Massachusetts to work at American Science and Engineering with Giacconi's group. The problem was the visa. They were then hard to get, and I waited and waited until February 1973 and learned that the job no longer existed as the High Energy Astronomy Observatory project I was to be funded on was cancelled by NASA. It was reinstated a few years later, but I was no longer going to the US. I was lucky to remain at Mullard Space Science Laboratories as a postdoc and began working on the small X-ray detectors just launched on the Copernicus satellite. Pete Sanford was the Project Scientist for the instrument and indeed had spent most of his time in the US over the previous two years. I was probably the only person working full time on the X-ray data for the first six months or so. The satellite carried a UV observatory taking spectra of bright O stars. We could choose the pointing direction for about 10 percent of the time. We looked at X-ray binaries, supernova remnants, clusters of galaxies and active galaxies, which led to many discoveries and much reading, studying and understanding diverse processes. I learned an enormous amount of astronomy and astrophysics. One key target we observed was the Perseus cluster of galaxies, showing that its X-ray emission peaked around the central galaxy NGC1275.

I successfully applied for an Semiconductor Research Corp postdoctoral fellowship to work with Martin Rees who was then a professor at Sussex University. A few months later Martin had accepted the Plumian Professorship at Cambridge, so I joined the Institute of Astronomy at Cambridge in October 1973. That summer there was a conference on compact objects that I attended and heard talks from many of the leading theorists on neutron stars and black holes. I was hooked even more.

Over the next eight years I held several postdoc positions at the Institute of Astronomy including the first UK Radcliffe five-year Fellowship in Astronomy. I was using whatever X-ray data I could obtain and also tried theory, finding my math skills were not up to easily solving differential equations and my computer programming was not up to the precise standards necessary for detailed numerical work. I was coming up with lots of questions and ideas and beginning to work with bright research students and my own postdocs on their solution, both observationally and theoretically. I enjoyed the phenomenology of astrophysics.

Around 1980, I was tempted by an offer of a Professorship at Utrecht University, which though attractive would have been a major upheaval. Initially it was at a junior level but that changed in 1981. However, by that autumn I was offered and accepted a Royal Society Research Professorship starting in 1982 and held at the Institute of Astronomy. I retained that post until 2013 and can say it was a great privilege and a dream job. It provided for my professorial salary, research expenses and often a postdoc. I was not obliged to teach but did lecture to final year Physics students on Relativistic Astrophysics initially, and later combined with Cosmology from Anthony Lasenby for the past 20 years. Owing to arcane rules the university classified me until 2003 as an “unestablished research worker,” which is not quite as bad as it sounds. The main thing was that the Institute of Astronomy supported me and my growing research group of students, postdocs and visitors.

The AXAF Science Working Group where I am second from left. Nobelist Riccardo Giacconi (who started X-ray astronomy) is 8th from left

In 1983, I became a Fellow of Darwin College, where I could happily chat to physicists, chemists, biologists and others from the Social Sciences, Arts and Humanities. My delight in exploring everything found an outlet in the annual Lecture Series, starting in 1986 with Origins. I have in total co-organised six of the series. The Lecture Series has become the largest public series in Cambridge and are still going strong; I was recently part of the discussion preparing for 2022. I also did a stint as Vice-Master of Darwin for 14 years.

In 1977, my student Paul Nulsen and I explored the consequences of radiative cooling in the cores of clusters of galaxies, prompted by the Copernicus observation of the Perseus cluster and similar hints from other clusters and workers. This lead to our paper on cooling flows published after similar work by Len Cowie and James Binney. We related the expected cooling flow to the enormous optical H alpha nebulosity seen around NGC1275, which must surely be connected. Under the generosity of Giacconi’s group, I visited the Center for Astrophysics in the other Cambridge for two months in 1979 to work on data from the recently launched Einstein Observatory (the third mission of the revived High Energy Astronomy Observatory program). It was wonderful to see and work on many images from the powerful X-ray telescope that it carried. This included the Perseus cluster, the images of which confirmed and extended the work on cooling flows.

Around 1983, I joined the Science Working Group of NASA’s Advanced X-ray Astronomy Facility, as an Interdisciplinary Scientist with a proposal to study the Perseus Cluster and other cooling flows. This meant that up and until the launch in 1999, after which AXAF was renamed Chandra, I regularly travelled to the US, particularly to Marshall Space Flight Center in Huntsville, Alabama. I was also shifting the main focus of my research onto clusters of galaxies and Active Galactic Nuclei (AGN). I also carried out committee work in the UK (ASR Board of the Space Engineering Research Center) and European Space Agency (AWG and future planning with Horizon then Horizon Plus). In 1979, I joined the editorial board of Monthly Notices of the Royal Astronomical Society dealing with papers in X-ray and Gamma-ray astronomy up until 2008, being managing editor for the final 14 years). I stopped editing when I became President of the Royal Astronomical Society in 2008.

Research funding in the UK for astronomy had been hit hard and we mobilised an Astronomy Forum which included a senior representative from all UK departments researching astronomy and approached government. I found it easier to talk with Science Ministers than with their civil service advisors and gave a Presidential Address on the Impact of Astronomy, at a time when Impact Factors were the centre of funding discussions. I outlined "the impact astronomy has had on our society historically, and at present, in terms of cultural, technological and economic benefits. Also why these benefits are so difficult to quantify in terms of the contribution made by basic science. I hoped to show that we all need to do what we can to promote the worth of our work in the wider world, at this difficult time for public spending" (A&G June 2010). Sometimes it is good to step back and ask why you are doing your science and why someone should pay you to do it! Propagating the scientific method may be a good place to start. My observational work in the early 80s expanded to include optical studies, particularly of clusters cores and the H alpha nebulosities seen there. Theoretically, I explored the possibility of pair plasmas being created around luminous accreting black holes. I picked this up in 2015 in work with Ann Lohfink using data from Fiona Harrison's NuSTAR observatory.

Stimulated by work by my ex-student and postdoc, Paul Guilbert, with Martin Rees, in which they argued that it was plausible for relatively cold gas to occur in accretion flows close to a black hole, in 1988 I considered the X-ray irradiation of a cold accretion disc in that situation. I realised that a fluorescent iron emission line was likely produced, and that it would be relativistically broadened by the strong gravity effects - doppler and gravitational redshifts - close to the black hole. This could explain a puzzling broad iron line seen by Nick White and others from Cyg X-1 using EXOSAT. I discussed it with Nick and he suggested I contact his colleague Luigi Stella who computed the expected line profiles. Our joint paper written together with Martin was published in 1989 and launched what was for me a new path in relativistic reflection.

One of my postdocs, Ian George, and I used Monte-Carlo methods to generate X-ray spectra of X-rays reflected from cold gas. Long-standing collaborator and visitor Randy Ross computed the spectra from gas ionized by the irradiating flux. A theoretical picture had emerged but clear observational evidence was lacking. Ginga spectra from Ken Pounds, Paul Nandra and others showed the expected hard X-ray emission hump from reflection but relativistic effects needed higher spectral resolution. That came after the 1993 launch of the Japanese-US observatory Advanced Satellite for Cosmology and Astrophysics (ASCA), which carried the first charge-coupled device detectors for cosmic X-ray astronomy. I had joined the ASCA team as a science advisor at the generous invitation of Yasuo Tanaka, the Principal Investigator of the mission. My wife, Carolin, and I spent a happy three and a half months in Japan in the summer of 1993 working on ASCA data at Institute of Space and Astronautical Science with other visitors including Richard Mushotzky from Goddard Space Flight Center and MIT student Keith Gendreau. It was an exciting time with many observations yielding new discoveries.

Observations of the bright active galactic nuclei, MCG-6-30-15, showed rapid variability and a strong iron line with a hint of broadening. A long observation was required to substantiate this and was arranged by Yasuo for four days in 1994. A broad iron line with a shape similar to our predictions in 1989 emerged from the spectrum and was published in Nature in 1995. Later that year, I led a paper discussing why alternative origins for the skewed broad shape were either incorrect or implausible. Although instantly accepted by some, it took a long time for others to adopt the model.

At the same time I was working on data from clusters of galaxies, from ASCA and from ROSAT (ROentgen SATellite), which had been launched in 1990. Led by Hans Bohringer, analysis of ROSAT High Resolution Imager data from the centre of the Perseus cluster showed that the double radio source had displaced the hot X-ray emitting gas. The active galactic nuclei was disturbing the inner gas but not necessarily anything else. There was much other work on clusters going on in my group, including the measurement of gas fractions and its implications for the mass fraction of the universe, identification and study of new massive cooling flows clusters from the ROSAT All Sky Survey, and a wide variety of active galactic nuclei phenomena.

Both Chandra and XMM-Newton were launched in 1999 and a fantastic flood of exciting data began. My family and I witnessed the night Shuttle launch of Chandra, when night turned into day. A month later we saw the inverse in the total eclipse of the Sun from Alderney in the Channel Islands. The launch and the eclipse are both 'whole-body' events that have to be experienced rather than viewed in photos. We have seen two further total eclipses but no more launches. I spent much of my Chandra-guaranteed time looking at Perseus and similar clusters, with Jeremy Sanders and others, which rewarded us with immense detail and improving with subsequent longer exposures until we had about a megasecond of data with 100 million photons by 2006. Eugene Churazov had a model for expanding bubbles generated by the central active galactic nuclei matching the ROSAT image and now seen in considerable detail with Chandra. How energy would be spread widely into the hot gas was unclear until we discovered ripples in 2003. They looked to me like sound waves generated by the bubbles. Whether this is the correct interpretation or not still awaits an even longer exposure.

The Reflection Grating Spectrometer (RGS) on XMM clearly showed that although the hot gas dropped in temperature towards the centre of many clusters, it was not radiatively cooling much below ten million K. The energy lost in radiating the X-rays we see was being balanced by heat being supplied, presumably by the central active galactic nuclei. Such clusters became known as cool core clusters and account for about one half of all clusters. The details of the processes involved are still strongly debated. The central black hole controls the behaviour of gas out to a radius a billion times or more its own (event horizon) radius. The overall process is one aspect of black hole feedback and involves jets from matter very close to the black hole blowing bubbles in the surrounding gas.

X-ray spectroscopy capable of measuring the flows of gas in a cool core is a vital step in making further progress. This was taken with the Japan-NASA-ESA observatory satellite ASTRO-H, renamed Hitomi following its February 2015 launch. I was again a scientific advisor eager to look at the spectra expected from the microcalorimeter array, which operated at 50 mK, giving an unprecedented spectral resolution in space of 5 eV. The centre of the Perseus Cluster was the first target and was observed for about 200 ks producing a fantastic spectrum of the emission-line rich intracluster gas. I spent 2 weeks in March at ISAS in Tokyo at the invitation of PI Tad Takahashi working with the Rich Kelley and the Hitomi team on the spectra, revealing that the gas had a mean random velocity of about 160 km/s, with an uncertainty of less than 10 km/s. An amazing result, with a June publication in Nature. This for me emphasised that something more than turbulence was required to transport the active galactic nuclei energy across the core, with sound waves a strong contender. The excitement engendered by the enormous success of this first spectrum was tempered by the loss of the spacecraft, and instruments, a few weeks after the Perseus spectrum was obtained.

I was honoured to give a talk on the results in May at the American Astronomical Society meeting in Naples, Florida. One evening there I saw Hitomi flashing in the dusk sky, reflecting sunlight as it spun rapidly in its orbit and reflected that the path of observational research is not necessarily a straight one.

It has been known for decades that massive black holes are likely to occur in many galaxies: Donald Lynden-Bell discusses dead quasars in his prescient 1969 paper. If gas falls into them they can become very luminous and known as AGN or quasars. In a sense they were seen as more of an ornament in the galaxy centre, almost separate from the rest of the galaxy. In the late 1990s, the black hole mass of a galaxy was found to correlate with the mass of the galaxy (or the bulge part of the galaxy). This sparked the idea, in a 1998 paper by Joe Silk and Martin Rees, that the black hole might control the galaxy, not the other way round. They showed that energy from the black hole can expel gas from the galaxy, stopping star formation and making old galaxies red and dead. A year later I published a paper arguing that momentum was more important for lifting gas out of a galaxy, by analogy with the Eddington limit and the rocket equation which is centred on momentum. A little later I pointed out that this approach led to a relation that agreed well with the observed black hole mass - galaxy mass relation. Radiation pressure on dust might be the active process in such feedback.

I have since continued playing and working on this process with students and postdocs. Wako Ishibashi and I have shown that it can produce outflows resembling those observed and, with Robert Maiolino, that observable stars might form in the outflows. Active galactic nuclei feedback can both stop existing star formation and start new star formation on low angular momentum orbits. It can change the shape of a galaxy.

The action of radiation pressure on dust appears to agree with the column density distribution of absorbing gas in active galactic nuclei as a function of their Eddington fraction. It will be exciting to see whether the shaping of galaxies by active galactic nuclei radiation acting on dust is supported by the ongoing eROSITA X-ray surveys.

Relativistic reflection in active galactic nuclei and black hole X-ray binaries has become commonplace with XMM observations and more recently with NuSTAR and NICER. Relativistic light bending has been needed to explain our XMM data as shown in work with Giovanni Miniutti. Jon Miller showed that reflection is common in X-ray binaries. Reverberation, which was mentioned at the end of the 1989 paper was first spotted in our XMM data of 1H 0707-491 by Phil Uttley. It has been explored further by my students Abdu Zoghbi and Erin Kara and by postdoc Will Alston, as well as by others. It is a strong confirmation of the relativistic reflection interpretation. When 1H 0707 dropped into a low state I found that the spectrum was best interpreted as originating from within two or three gravitational radii around a rapidly spinning black hole. Early work with Kazushi Iwasawa and Anthony Lasenby in the 1990s suggested that we see evidence for black hole spin from the small disc inner radii inferred from spectral fits of broad lines, including MCG-6. Chris Reynolds and Laura Brenneman have more recently systematised this and shown that we have a powerful tool for measuring spin. Together we have explored the observing systematics taking into account the spin dependence of radiative efficiency of accretion and shown that current flux-limited surveys favour rapidly spinning objects.

Recent work with Javier Garcia and others has led to computations and testing of high-density reflection, matching the conditions expected in X-ray binaries and lower mass active galactic nuclei. Much more can be done with current instrumentation such as XMM + NuSTAR but our work is basically photon-starved, particularly in the case of reverberation studies. It is true for both luminous accreting black holes and cool core clusters. It has been great fun and very productive to look at bright Galactic sources with Keith Gendreau's NICER on the International Space Station.

I was very fortunate to have an ERC Advanced Grant to fund my group from 2013-2018. These generous European awards enable a strong focus on the best science for a five-year period and I was able to build a very strong group working well with each other, my students and myself on the topic of active galactic nuclei Feedback. We covered many of the topics mentioned above and benefitted from successful observations with a variety of satellites and telescopes. We exceeded the "critical mass for which the whole exceeds the sum of its separate parts." Most of the postdocs from the group have been awarded fellowships or faculty positions.

I have thoroughly enjoyed my life as an observational X-ray astronomer. Most of the work has been in collaboration with others and I have benefitted greatly from their teaching, mentorship, discussion, hard work and humour. The international spread of collaborators is enormous and highly beneficial. I like to work through the simple theoretical aspects and explanations of the objects and phenomena we have observed. That has often led to further ideas and observations. Although my work has covered a very wide range of objects, I see useful interconnections throughout. A talk on stars or planets can stimulate ideas on quasars and galaxies. There is a tangled web both in the physics and in the interactions with students, postdocs and collaborators.

I'm a firm believer in the value of serendipity in science in the Pasteur sense of "chance favours the prepared mind." I tell my students that I am helping to prepare their minds. I also tell them that I do two things for them: one is to start them off with some good ideas that are do-able but have not yet been done, the other is to tell them when they've done enough on a project, since all projects are semi-infinite. I also like Harwit's concept of Discovery Space in which the coordinates are space, time, resolving power, collecting area, wavelength, etc. When we look ten-fold deeper in any parts of this space then we are likely to discover something really new. I have seen this happen again and again. The success of our telescopes is often measured in terms of new things they discover, yet the proposals for building those telescopes depend on what is already known and how much better that can be measured. There is a tension here that is unresolved. It is also a tension in observing proposals for using a telescope in that you rarely win time by arguing that you just want to look deeper without stating clearly what you will find or test. Maybe there is a parallel here to Churchill's quote on democracy? (No one has come up with a better method of proposal selection). In 2013, I was part of a small team, led by Paul Nandra, that wrote a successful proposal to ESA for the Athena mission, a billion euro orbiting X-ray observatory for studying the hot and energetic Universe. I became a member of the Science Study Team and again made many visits to ESteC, over 40 years after my visits for SL91. Athena is due for launch in the early 2030s, and I look forward to learning of the new discoveries it has made. That is if I last that long!

I am very grateful to my many students, postdocs and collaborators for working and exploring the Universe with me and to Roderick Johnstone and Judith Moss for long-term support. I am indebted to Carolin for love, support and companionship. We share a deep interest in astronomy. Our (biologist) sons, Sam and Laurie, have tolerated many overseas trips with us to the extent that at one stage they preferred to drive to Snowdonia rather than fly to California. Now they view us with bemused good humour. The coronavirus lockdown means that Carolin and I continue to explore the night sky with a small telescope in our back garden. There are always new things to see and new ways to see them.

BIOGRAPHIES NANOSCIENCE 2020

Harald Rose, Maximilian Haider, Knut Urban, Ondrej L. Krivanek

Photo: © private

Harald Rose

Harald Rose is a German physicist. He studied at the University of Darmstadt where he obtained both his diploma and his doctorate, working on theoretical electron optics under the guidance of Otto Scherzer, who had done some seminal work on electron microscopy in the 1930s.

Rose's research career is strongly connected with both Darmstadt, where he worked on his habilitation and was a professor from 1980 to his retirement in 2000, and the United States where he has had a number of appointments. In the early 1970s he spent some time in Chicago in the lab directed by Albert Crewe, the inventor of STEM. Since the late 1970s he has had a number of posts in various US institutions, including the Argonne National Laboratory in Chicago.

His research has widely focused on aberration-correction for electron lenses. In 1990 he designed a feasible system of lenses for improving TEM resolution. He then teamed up with Maximilian Haider and Knut Urban to realize his proposal experimentally, which they achieved in 1998.

Rose has been a ZEISS Senior Professor at the University of Ulm since 2009. He has received a number of prestigious awards including, jointly with Haider and Urban, the Wolf Prize for Physics and the BBVA Foundation Frontiers of Knowledge Award in Basic Sciences, and he is an honorary fellow of the Royal Microscopical Society.

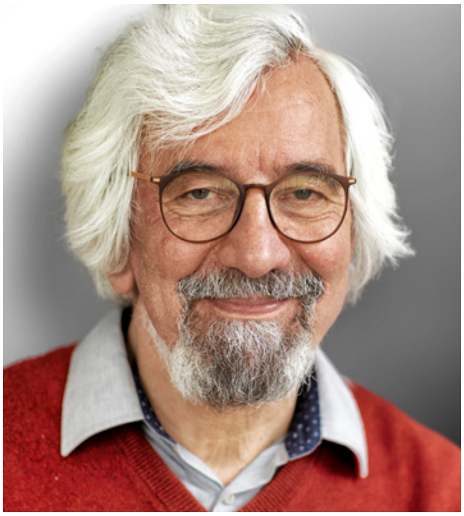


Photo: © "Bilderfest" Germany

Maximilian Haider

Maximilian Haider is an Austrian physicist. After obtaining his degree at the University of Kiel he moved to Darmstadt to work for his PhD, which he obtained in 1987. Only two years later he joined the European Molecular Biology Laboratory in Heidelberg, where he had carried out the experimental work for his PhD, becoming group leader of the Physical Instrumentation Program; he remains there to this day.

His research interests were focused on developing ways to improve the resolution of transmission electron microscopes. While at EMBL he developed a prototype lens system based on the theoretical work by Harald Rose, and started a collaboration with him and Knut Urban that resulted in the first aberration-corrected TEM images of atomic structures in a lattice, with the results published in 1998.

In 1996 Haider co-founded CEOS GmbH in Heidelberg, with the aim of producing aberration correctors commercially. He is still a senior adviser for the company, and since 2008 has also been an honorary professor of physics at the Karlsruhe University of Technology.

He has been awarded a number of prizes for his work, including, jointly with Rose and Urban, the Wolf Prize and the BBVA Foundation Frontiers of Knowledge Award in Basic Sciences, and he is an honorary fellow of the Royal Microscopical Society.

Photo: © Research Center Juelich

Knut Urban

Knut Urban is a German physicist. He studied at the University of Stuttgart where he obtained his PhD in physics in 1972, before moving to the Max Planck Institute of Metals Research in Stuttgart.

In 1986 he was appointed a professor in materials properties at Erlangen–Nuremberg University, and just one year later became Chair of Experimental Physics at RWTH Aachen University and the Director of the Institute of Microstructure Research at Forschungszentrum, Jülich. During this period he collaborated with Harald Rose and Maximilian Haider to obtain the first aberration-corrected transmission electron microscopy results, which were published in 1998.

Urban then worked on the application of aberration-corrected transmission electron microscopy to materials science. In particular he focused on the connection between the precise arrangement of atoms within a lattice and the physical properties of a material.

In 2004 he was chosen as one of the directors of the Ernst Ruska Centre for Microscopy and Spectroscopy with Electrons and since 2012 has been a JARA senior professor at RWTH Aachen University. Urban has been awarded a number of honours. These include the Von Hippel Award of the US Materials Research Society, and jointly with Rose and Haider, the Wolf Prize in Physics, the HONDA prize in Ecotechnology and the BBVA Foundation Frontiers of Knowledge Award in Basic Sciences. He is also an honorary member of several scientific bodies, including the US Materials Research Society, the German Physical Society and the Japanese Institute of Metals and Materials.

Photo: © Michelle Krivanek

Ondrej Krivanek

Ondrej Krivanek is a physicist of Czech and British nationality, resident in the United States. Born in Prague, he moved to the UK in the late 1960s where he obtained a degree at the University of Leeds, before moving to Cambridge to work on his PhD in electron microscopy with Archie Howie.

After Cambridge, Krivanek had postdoctoral positions in Kyoto, at Bell Labs and at UC Berkeley. During his time in Berkeley he became interested in electron energy loss spectroscopy and built his own spectrometer. He became an assistant professor and associate director of the NSF HREM Facility at Arizona State University in 1980, and at the same time started collaborating with Gatan Inc., first as a consultant, before moving permanently to the company and becoming its R&D director.

In 1995 he went back to Cambridge with a grant from the Royal Society to work with Mick Brown and Andrew Bleloch on aberration correction of electron lenses. His advances enabled him and Niklas Dellby to start Nion Co. in 1997, a company of which he is still president. With Niklas Dellby and IBM's Phil Batson, he obtained sub-ångström resolution with a scanning transmission electron microscope, with the results published in 2002.

Ondrej Krivanek is one of the major experts in electron microscopy and electron energy loss spectroscopy. He has received a number of awards, including the Duddell Medal and Prize of the British Institute of Physics, and the Cosslett Medal from the International Federation of Microscopy Societies. He is a fellow of the Royal Society, the Institute of Physics, the Microscopy Society of America, and of the American Physical Society, and an honorary fellow of the Royal Microscopical Society.

autobiography

by Harald Rose

Harald Rose at age 5 (to the right) with his mother Anna-Luise and his two year older brother

I was born on 14 February 1935 in Bremen as the second child of my parents Anna-Luise and Hermann Rose who were both mathematically talented. My father grew up in a house where everybody of his family was playing an instrument, my father the piano. He started to study mathematics but was forced to go into business after his father lost his fortune due to the hyperinflation in the early 1920s. My father was very successful in business and became in 1937 the sales representative of the well-known company Kaffee-Hag for the state of Hessen.

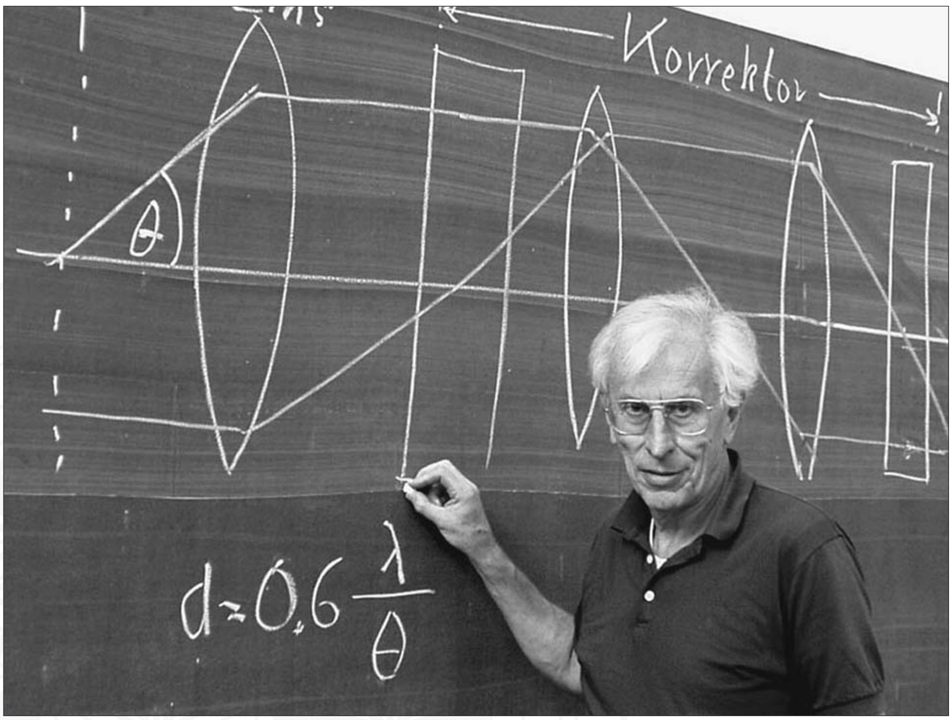
We moved to Darmstadt at this year where my father built a very nice house in an exclusive neighborhood called the Mathildenhöhe, which is the focal point of the German Jugendstiel (Art Nouveau). We moved in the house in 1939. One year later my father was drafted to the German Army after Hitler had started World War II. I saw my father only a few times up to 1944. Shortly after his last visit in February 1944 on the occasion of my 9th birthday he was reported missing in action on the eastern front. We never saw him again. On September 11, 1944, our house was destroyed by an Royal Air Force air raid on the city with a loss of the lives of 12000 civilians. Fortunately, my mother and my brother survived and moved to a small village on the country side where I had been evacuated with my school class half a year earlier. Here the war was over for us when the American soldiers arrived in March 1945.

At the end of this year I passed the examination for admission at the Realgymnasium in Darmstadt where my mother had found a job at the tax revenue office. Because normal housing was not available, we had to live in the damp basement of the ruins of our house. Especially during rainy days, the water was dropping through the ceiling and my mother was moving the beds to a dry spot. Moreover, food was very hard to get and we were quite often very hungry between the end of the war and the German currency reform in May 1948.

Since my mother had to work and taking care to make a living for her two children, she had no time for helping us with the school homework. Fortunately, my mother had not to pay in Hessen tuition fees for the Gymnasium, as it was the case for most other states in Germany. During the time at the Gymnasium I became more and more interested in mathematics. Because we had no money to buy the expensive math books, I went to the Hessische Landesbibliothek in Darmstadt, which was lending scientific books to students for free for a given time. Studying the books helped me to understand easily the mathematics in school. As a result, I did almost never anything for mathematics in school but was always the best in the examinations. At the beginning of 1955, I passed the final examination

(Abitur) with excellent marks in the natural sciences.

Owing to my good grades, I was admitted to study at the Technische Hochschule Darmstadt (today Technical University Darmstadt). At that time there was a strongly restricted admission (numerus clausus) because most of the buildings were not yet restored. At that time the financial situation of my family was still critical because my mother had to take a loan from the bank to rebuild our house. Because studying at a state university was free in Hessen, I could afford to go to the university. I wanted to enroll in the department of mathematics and physics. After my mother asked my grandfather for his opinion, he urged my mother that I should study engineering in order to make a living because “Physik ist eine brotlose Kunst”. Owing to his advice I enrolled in electrical engineering. Because a six-month apprenticeship was required, I was fortunate to be accepted by a local supplier of electricity, where I learned the essentials of electrical craftsmanship. This apprenticeship was helpful for me because I was able to do the basic electrical work at home myself. Although I was able to live in our house, I was forced to earn my own living as a construction worker during the vacations.



Harald Rose explaining the functionality of the hexapole corrector in his seminar room at the Institute of Applied Physics of The Technical University Darmstadt in 1997

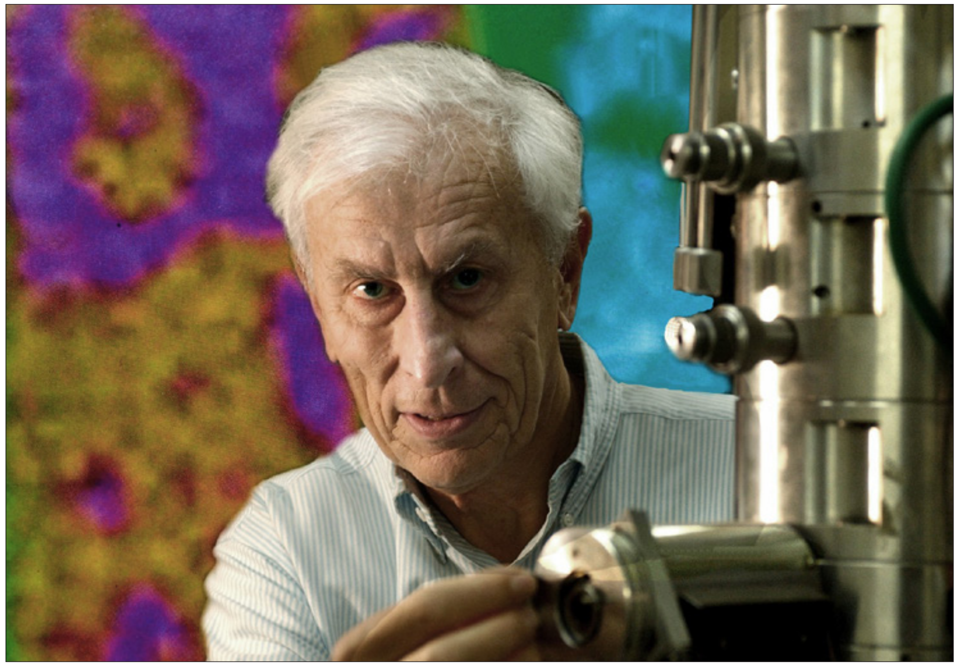
The courses at the university in electrical engineering did not fulfill my expectations because the fundamentals of electricity were hardly discussed. Because I was more interested in the fundamentals of electrodynamics, I decided to follow my own inclinations and changed to physics and mathematics at the end of the semester. My grandfather and my mother were not happy about my decision at that time. The change was not easy for me because I missed the courses of the first semester in physics and mathematics, which always started in April. In order not to lose a year, I acquired the lecture notes of the corresponding courses and studied them during the break before the start of the second semester. This effort helped me to pass in 1957 the examinations for the Vordiplom (roughly equivalent to a bachelor’s degree) after three semesters excluding the semester, which I spent in electrical engineering.

After the Vordiplom I had to decide to graduate either in mathematics or physics because different courses had to be taken for the Diplom examinations (master degree) of each discipline. Because I was not sure which direction to go, I decided to take the courses in both disciplines for some time in order to be sure of my final decision, which I made about one year later due to the fascinating quantum mechanics course given by Otto Scherzer, professor of theoretical physics at the university. Otto Scherzer was a student and assistant of Sommerfeld, who was one of the most famous theoretical physicists in the first half of the 20th century. Like his teacher, Scherzer was outstanding in calculus and had a deep insight into the nature of physical phenomena. In his quantum-mechanics course he showed his excellent pedagogical skills by combining the mathematical formalism with physical explanations of the mysterious nature of the atomic world. Since I managed to solve all exercises correctly, Scherzer offered me a paid position as an assistant for the exercises in theoretical physics. I was very happy for his offer because it gave me enough financial support to make a living on my own without having to work in construction during the brake between the semesters. Moreover, I had free accommodation at my mother’s house, which is in walking distance from the university.

I admired Scherzer for his outstanding abilities as a teacher. Therefore, and because I was already integrated in his institute, I decided to perform my Diplom thesis under his guidance. The topic of my thesis was to find out if it would be possible to detect different atoms in an electron microscope by utilizing their different angular scattering behavior. The result showed that primarily the insufficient technical state of the instruments at that time prevented any realization of this concept. Despite of this frustrating result, my in-depth studies of quantum mechanical scattering prepared the ground for my later work on image formation in the electron microscope. I obtained my Diplom degree at the beginning of 1961. At that time most students and scientists were eager to spend some time at a research institute in the US, which was the center of science. Therefore, I was very glad to obtain an offer from Dr. Fischer, who was on a sabbatical at Scherzer’s institute, to spend a year as a research consultant at the Air Force Cambridge Research Laboratories in Bedford, Mass. My research was focused on the investigation of semi-conductor photodetectors for extremely short light pulses. Although the topic was of practical importance, it did not satisfy my interest.

Returning to Darmstadt in 1962, I was glad that Scherzer offered me to join his institute again for a doctoral thesis. According to Scherzer's suggestion, I agreed to explore in my thesis the imaging properties of non-rotationally symmetric electron-optical systems in detail. The aim was to find feasible systems, which are able to compensate for the spherical aberration in another way as realized in the Scherzer-Seeliger corrector and to find systems corrected for both spherical and chromatic aberration, which are unavoidable for round lenses. This property is known as Scherzer Theorem and prevents atomic resolution in electron microscopes operating at voltages below the threshold of atom displacement. Scherzer derived this result in non-relativistic approximation and it took me some time to show that it stays also valid in the relativistic case. Moreover, I proved that chromatic correction cannot be compensated in any magnetic system with a straight optic axis but that additional electric quadrupoles are indispensable. Although Gottfried Möllenstedt showed in an ingenious experiment that the Scherzer-Seeleger corrector was compensating for spherical aberration, the correction did not improve the resolution of the electron microscope because this was limited by mechanical and electromagnetic instabilities rather than by the optical defects of the lenses. To obtain a real improvement, I calculated the stability criteria, which had to be fulfilled in order that aberration correction is improving the resolution. Nowadays, the effect of the instabilities is known as information limit in contrast-transfer theory. My calculations showed that the number of correction elements must be as small as possible and that they must be mechanically fixed in order to minimize the incoherent aberration resulting from the instabilities. As a result, I designed an electric magnetic multipole corrector consisting of four electric and magnetic octupole elements each of which enabled the excitation of quadrupole and octupole fields and of dipole and sextupole fields compensating for the parasitic alignment aberrations, thus avoiding any mechanical movement.

After I had obtained my doctoral degree, Scherzer offered me a well-paid assistant position to work for my Habilitation, which was required to be granted the "venia legendi", the permission to teach at a



Testing the mirror corrector of the SMART project in 1998

university and to become a professor. In my "Habilitationsschrift", entitled "Properties of spherically corrected achromatic lenses", I showed that all correctors known at that time suffered from large off-axial coma unduly reducing the size of the field of view. Therefore, these correctors are not suitable for the conventional transmission electron microscope (TEM). In order to also compensate for the off-axial coma in addition to the spherical and chromatic aberrations and to keep the number of elements as small as possible, I designed a novel five-element aplanatic corrector utilizing symmetry properties. Imposing symmetry properties has proven later as the key for the design of high-performance energy filters, monochromators, the beam separator in the mirror electron microscope, and the hexapole corrector. The corrector was built and tested successfully at Scherzer's institute within the framework of the Darmstadt Project funded from 1972 until 1982 by the German Research Foundation (DFG). The experiments showed that the corrector introduced an unduly large fifth-order aberration. In order to sufficiently reduce this aberration, Max Haider, who joined my group in 1980, replaced the central octopole element of the corrector by a dodecapole element, which he designed and built in the context of his "Diplomarbeit". However, because computer control was not available, he could not align the system within a time, which was shorter than the duration of stability of the optical system. As a result, the resolution of the microscope could not be improved although the project was successful as far as it went up to its end in 1982 after Scherzer passed away.

One year after my Habilitation in 1970, I was appointed as a H2-Professor of Theoretical Physics at the Technical University (TU) Darmstadt. In 1972 Albert Crewe invited me to spend a year in his group at the University of Chicago. During this time I designed an innovative detector enabling efficient phase-contrast in the scanning transmission electron microscope (STEM). Moreover, I calculated the non-localization in images formed by inelastic scattered electrons. The results were confirmed experimentally by Mike Isaacson and John Langmore using the STEM in Crewe's lab. In the following 20 years I pursued the phase problem related with inelastic scattering in particular with Helmut Kohl, who developed an in-depth quantum-mechanical description of image formation in his Ph.D. thesis.

At the beginning of 1976, I left Darmstadt and moved to the US. I was appointed Principal Research Scientist at the New York State Department of Health in Albany, NY, and Adjunct Professor in the Faculty of Physics at RPI, Troy, NY. During my time in Albany I was confronted with the problem of radiation damage, which decisively limits the resolution of electron-microscope images of biological objects.

To minimize this deleterious effect, one of the main tasks of the electron-microscopy group was to find methods, which provided maximum information about the object for the tolerable electron dose. One possibility was the correlation of many low-dose images of identical particles, e.g., ribosomes. Joachim Frank, who joined the group a few months earlier than me, pursued this method over many years. His successful pioneering work was awarded with the Nobel Prize in Chemistry in 2017. My approach was to find means for improving the optical performance of the instrument to such a degree that all scattered electrons could be utilized. In the course of the project, I designed several novel electron-optical elements, such as the magnetic monochromator, the quadrant STEM detector and the aberration-corrected omega imaging filter, which was constructed and successfully tested by Dieter Krahl in Berlin and later incorporated in the Zeiss TEM. Moreover, I proposed the integrated differential phase contrast imaging in STEM, which has been realized in a commercial instrument by FEI several years ago. Together with my coworker Jürgen Fertig we investigated for the first time the propagation of the convergent electron wave in the STEM through thick crystalline objects showing that strong crosstalk between neighboring atomic columns occurs if the cone angle of the incident wave exceeds the Bragg angle.

I returned to Darmstadt University in 1980 where I became a full Professor in the Institute of Applied Physics and perpetuated the research on aberration correction. I maintained links to Albany by yearly visits of several months till 1986. Shortly after returning to Darmstadt, I found in summer 1980 a surprisingly simple corrector for eliminating the spherical aberration of electron lenses employing symmetry conditions, which I had used for the Darmstadt quadrupole octopole corrector. It was known that hexapoles introduce apart from threefold aberrations also a small spherical aberration whose sign is opposite to that of round electron lenses. Hence, if it would be possible to eliminate in some way solely the large parasitic threefold aberrations, the system could serve as a corrector. The calculations showed that this is indeed possible if the system exhibits double symmetry for the paraxial rays, which are not affected by the hexapole fields. The simplest arrangement, which can serve as a corrector for the STEM consisted of two identical round lenses enclosed by two hexapoles. However, funds to realize the corrector were not available because at that time the resolution of all high-resolution electron microscopes were limited by instabilities rather than by the lens defects. At the end of the 1980s the stability of the instruments had advanced to such a state that it no longer was the prime limitation preventing atomic resolution. By adding, in 1989, another round-lens doublet between the objective lens and the hexapole corrector, I found a system resembling an optical aplanat, which is free of spherical aberration and off-axial coma. According to this property, the corrector enables atomic imaging in a stable TEM for a large field of view. Owing to the high symmetry and the simplicity of the electron-optical aplanat, I asked Max Haider for his opinion regarding the successful realization of aberration correction by means of the novel corrector. Max was developing and testing experimentally the properties of a quadrupole-octopole corrector for the low-voltage scanning electron microscope at the European Molecular Biology Laboratory in Heidelberg and, therefore, had to my opinion the best judgement regarding the feasibility of my proposal. To my surprise, Max was convinced from the very beginning that the corrector would work providing genuine atomic resolution. However, in order to realize the corrector, sufficient funding was necessary. Fortunately, we had a very fruitful discussion with Knut Urban about the prospects of successful aberration correction for materials science during the Dreiländertagung at Salzburg in September 1989. Knut Urban, being aware of the importance of aberration correction, suggested to submit a mutual (Rose, Haider, Urban) proposal to the Volkswagen Foundation because all other funding agencies turned down the proposal primarily on the reason that the US had suspended funding for realizing aberration correction. Contrary to the frustrating decision of the other agencies, the Volkswagen Foundation took the risk and started funding in 1991. This support resulted in one of the most successful projects ever funded by the Volkswagen Foundation after Max Haider succeeded in June 1997 to reduce the point resolution of the basic (uncorrected) instrument from 0.24 nm to 0.14 nm giving genuine atomic resolution, as shown by the pictures taken by Bernd Kabius from Juelich.

In 1997, the Berlin electron synchrotron BESSY II was launched and funds were made available for novel projects exploiting the capabilities of the novel photon source. I was asked by Alex Bradshaw and Eberhard Umbach, the organizers of the ambitious SMART project, to become a member of a group of scientists who were engaged in developing an aberration-corrected electron microscope, which could operate as a low-energy electron microscope (LEEM) using reflected electrons and as a photo-emission electron microscope (PEEM) forming images with electrons emitted from the surface layer by photons. The task of my group was the design, the construction, and the testing of the electric-magnetic objective immersion lens, the aberration-free beam splitter separating the incident and the reflected electron beam, and the mirror corrector compensating for the spherical and the chromatic aberration of the lenses. The successful realization of these ambitious tasks after four years was primarily achieved by my excellent and ambitious students Dirk Preikszas, Peter Hartel, and Heiko Müller. Apart from the SMART project, my group was also involved in the Sub-eV Sub-Angstroem Microscope (SESAM) project, initiated by Manfred Rühle, in developing an electron-filtering electron microscope (EFTEM) with high spatial and high energy resolution. In the context of his doctoral thesis, Stefan Uhlemann designed the high-performance MANDOLINE filter, which was built by Zeiss and incorporated in the SESAM microscope. Up to this day the microscope is operating with outstanding results at the Max Planck Institute in Stuttgart.

Despite the great successes and achievements of my group, its high international reputation, and memorandums from numerous scientists and industry, the Technical University Darmstadt abandoned my field of research by effacing my position after my retirement in April 2000. Owing to my excellent contacts with many colleagues in the US, I followed an invitation to spend a year as a Research Fellow at Oak Ridge National Laboratory. Here, I met Murray

Discussion with professor Hannes Lichte at the M&M Conference in 2009

Gibson from Argonne, who aimed for a high-resolution electron microscope enabling any kind of in-situ experiments. Because this condition can only be met with a large object chamber, the objective lens must be corrected for spherical and chromatic aberration for achieving high resolution of about 0.2nm at medium voltages, which are necessary for reducing radiation damage. I accepted the offer of Murray to design the corrected objective lens and moved to Argonne in September 2001. However, I had to stop my work at Argonne at the end of April 2002 when a biopsy indicated that I had prostate cancer in an early stage. Fortunately, the cancer had not spread so that the chances of survival were very good. After surgery at the University of Mainz, it took me more than a year to recover. In the meantime, upon Murray's change as director to the Advanced Photon Source, Uli Dahmen at Lawrence Berkeley National Laboratory (LBNL) became director of the TEAM project. The aim of the project was changed by DOE by requesting a chromatic and spherically corrected medium-voltage electron microscope providing a resolution of 0.05nm. In September 2003, I moved to Berkeley to become a research fellow at the Advanced Light Source (ALS) of LBNL. Because the ASL is located within walking distance away from the National Center of Electron Microscopy (NCEM), I accepted the invitation of Uli to become an advisor for the TEAM project, which started in 2004 and ended successfully in 2009 with a record resolution of 0.047nm, which is about the radius of the hydrogen atom. I designed the TEAM corrector in cooperation with the company CEOS. By replacing each hexapole of the hexapole corrector by an electric magnetic quadrupole-octopole quintuplet, the resulting corrector compensated for the chromatic, spherical aberration, and the coma by preserving the double symmetry.

In 2007, Professor Ute Kaiser at Ulm University invited me to give a lecture on aberration correction, in particular on the design and the functionality of the hexapole corrector. This corrector was part of her new TITAN electron microscope, which was the first commercial aberration-corrected TEM delivered by the company FEI in 2005. Ute Kaiser was interested in visualizing the atomic structure of two-dimensional (2D) objects such as graphene. However, when operating the microscope at the recommended voltage of 300kV the object was immediately destroyed. Fortunately, thanks to aberration correction, the microscope was also able to provide atomic resolution at 80kV, the lowest adjustable voltage of the instrument. Because this voltage is below the threshold voltage for atom displacement in graphene, she was able to image its atomic structure. This result proved that radiation damage is also limiting the resolution of many objects in materials science. Since the knock-on threshold for many radiation-sensitive 2D objects is in the range between 20kV and 80kV, the need for an aberration-corrected low-voltage electron microscope became obvious. Because at these low voltages chromatic aberration exceeds the spherical aberration of the objective lens and large usable aperture angles are necessary for obtaining atomic resolution, the development of a novel corrector was necessary. The high-performance SALVE corrector was obtained by splitting up the central multipole of the Darmstadt quadrupole-octopole corrector in two spatially separated elements. Using this system as a start, the members of CEOS developed the corrector within the frame of the Sub-Angstroem Low-Voltage Electron microscope (SALVE) project initiated and headed by Ute Kaiser. The SALVE project started in 2009 and was interrupted in 2011 after Zeiss terminated the production of TEMs. In 2013 FEI together with CEOS continued with the project, which ended in 2017 with an unexpected success showing that the resolution of the microscope was almost 30% better than originally required by the contract. I became a member of the group of Ute Kaiser at the start of the SALVE project and, in 2015, I was appointed Senior Professor of Ulm University.

Apart from designing electron-optical components and developing the theory of image formation in the electron microscope on a profound quantum-mechanical basis, I was always interested in understanding the basic nature of the electron. In particular, I tried for more than 20 years to understand the origin of the spin, the charge, and the mass of the electron. For this purpose I employed a novel relativistic quantum-mechanical approach, which is closely related with relativistic electrodynamics and with the Dirac theory. Probably, because I do not belong to the elementary-particle community, my novel theory for explaining the structure of elementary particles was ignored and its publication rejected without reviewing. Nevertheless, I could present on December 10, 2019, my novel theory at a special physics colloquium of the University of Ulm and hope that my talk will initiate fruitful discussions on the topic.

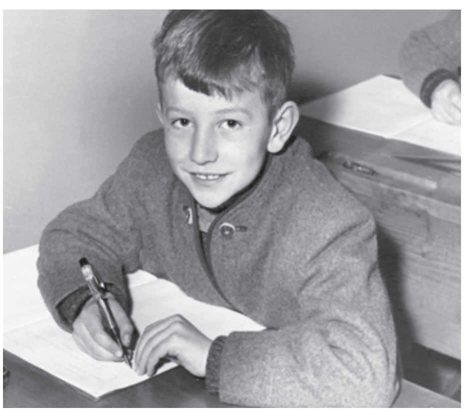
Together with a representative of Zeiss at the 2015 Synposium at Ulm University on the occasion of his 80th birthday, showing one half of the omega filter

A get together with his tennis partners in 2012

Harald and Dorothee on a restaurant celebrating his birthday February 14th, 2012

During all the time after I started with school, I was active in sport playing hockey, skiing in winter, and hiking in the Alps in autumn. Hockey is a very demanding sport but the risk of severe injuries increases with age. Therefore, I had to leave it at age 50 and to look for some other activity. It was quite natural that I chose to learn to play tennis because my wife Dorothee was a very talented tennis player, who played in a team at a local sport club. She was willing to give me tennis lessons because there was nobody else who wanted to play with a beginner. Owing to her help I advanced to a state which enabled me to find partners and to play in a team. Although, I cannot play singles anymore owing to my high age, I still play tennis every week with several double partners. Moreover, Dorothee and I go hiking with former hockey teammates and their wives for several days every year. During my scientific life I have had personal contacts with many colleagues around the world. Many of these contacts have become friendships over the years. I appreciate these friendships very much because I consider them as precious gifts. Finally, I want to thank my wife for her support and her patience when I was working on many weekends for many years.

autobiography



At primary school in 1960, age 10

by Maximilian Haider

In 1950, I was born in a small historic town in Austria, where my parents Maximilian Haider and Anna Haider owned a watchmaker shop. My father had taken over his father´s shop, and my eldest brother stepped into their footsteps and became a watchmaker, too. To expand the business, it was agreed early in my childhood that I should become an optician. Therefore, I started working as an optician´s apprentice in Linz, Austria, when I was 14 years old. After the first optician certification exam I realized that the prospect of working as an optician for my whole life did not satisfy me. Hence, in the following years, I passed several exams to be admitted to university and finally, at the age of 26, started studying physics at the University of Kiel and the Technical University of Darmstadt, Germany. For my diploma thesis I got in touch with the group of Harald Rose that worked in the field of theoretical particle optics. I was attracted by the ongoing aberration correction project due to familiar aberrations in electron optics I knew from my time as an optician. The task I had to carry out was the development of a novel twelve-pole element for an aberration corrector with which the required strong quadrupole and octopole fields could be generated. At the Institute of Applied Physics of TU Darmstadt two groups led by Otto Scherzer and Harald Rose were carrying out a long time project on the correction of the spherical (Cs) and chromatic (Cc) aberration of a conventional Transmission Electron Microscope (TEM) by means of a quadrupole-octopole correction system. The development of such a corrector was

Max Haider is the last person on the right side - when he worked as apprentice in Linz/Austria

Together with Joachim Zach at the European Conference in Budapest, 1984

At the end of the seventies, this was state of the art of aberration correction, however, it could not be demonstrated that this would indeed improve the resolution. Rather than being limited by the aberrations, the proof failed because of the instabilities of the homemade TEM. As the last scientist capable of handling this instrument had left for a position in industry, I had to learn how to operate the complex instrument – the very first functioning aberration corrected TEM – before I could finish my diploma work. A large number of power supplies had to be controlled and, at the same time, the mechanical adjusters of the various lenses had to be kept stable. The alignment of the whole system had to be carried out manually without the help of computers or CCD cameras. In the end, the project was successful in its proof to compensate the two aberrations, but it had failed to show an improvement of resolution. Nevertheless, the project convinced me that aberration correction was the future of resolution improvement, but it was also clear to me that one should only go ahead with enough money to buy a state-of-the-art TEM and to first investigate this TEM to ensure the resolution to be aberration limited. Otherwise one would run into the same problem again.

After my diploma, I continued to work in the Rose group, planning improvements of the existing aberration corrected TEM. Unfortunately, a German Research Foundation (DFG) grant proposal was

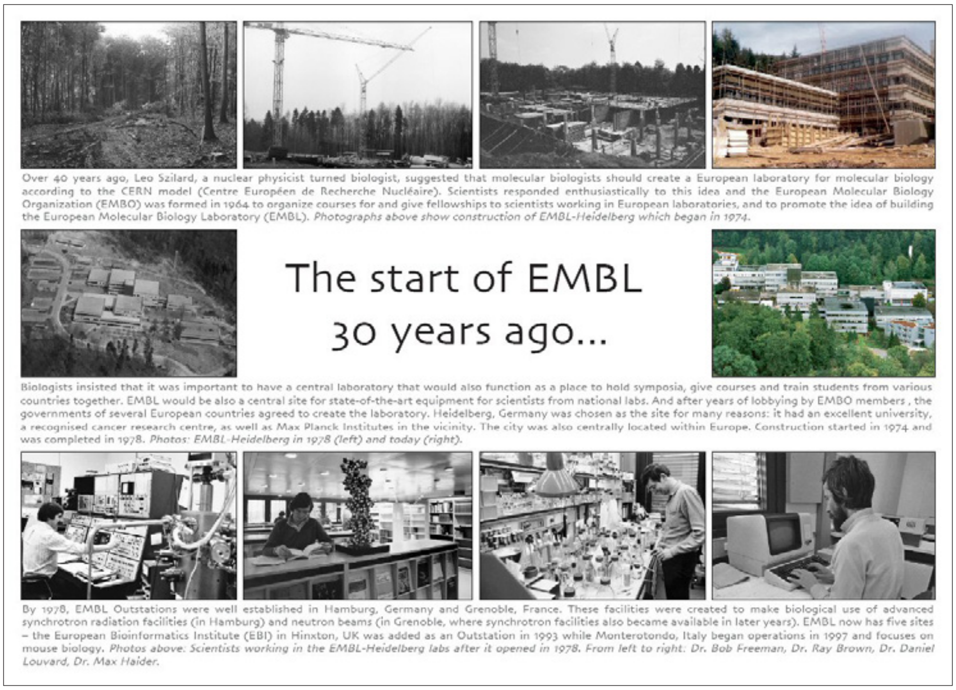
PhD celebration in 1987 with his youngest daughter

rejected because Harald Rose was a theoretician and the project he applied for was an experimentally challenging task. Shortly afterwards, Otto Scherzer, the second "father" of the Darmstadt aberration correction project, died and it seemed impossible to get funding. So I took on a position at the European Molecular Biology Laboratory (EMBL) in Heidelberg with the task to develop an electron spectrometer for a Scanning Transmission Electron Microscope (STEM). Also for this device, the compensation of aberrations was indispensable, and in 1987, with the successful development of a highly dispersive electron spectrometer for a dedicated STEM and in close cooperation with the Rose group I finished my PhD. I then continued the application of the two existing dedicated STEMs for biological applications in the group of Arthur Jones at the European Molecular Biology Laboratory.

The initial experimental work experience with the Darmstadt corrector had inspired my long-standing interest in this field of science. When working in the EMBL environment for biological structure research – knowing that the resolution of biological structures within a TEM is by far not limited by the resolving power of a

EMBL-TEM installation in 1993

TEM – the idea of realizing an aberration correction system to improve the available resolution did not let go of me. However, globally, electron optics lost attraction in physics at that time, and several groups had to close because emeriti were replaced by scientists from other fields. Likewise, the funding agencies lost interest because several aberration correction projects around the world had failed and it was common understanding that the aberration correction for high resolution electron microscopy (EM) would not work and was "unthinkable", particularly for commercial instruments. The only feasible option seemed to decrease the wave length of the electrons used for the imaging of objects by increasing the accelerating voltage. Hence, instruments became larger and more expensive:



already very advanced and the proof of high resolution in materials science went up to 300kV, 400 kV and even 1.2 MV. The resolution could indeed be improved, accompanied, however, by the disadvantage of a strong increase in beam damage of the objects observed in TEM.

Although it was not in vogue to work in the field of electron optics, I could not forget my long-standing idea of compensating the largest and most important obstacle on the way to sub-angstrom resolution. There was little excitement for this idea in my biological environment, with the exception of some cell biologists who were used to working with a Scanning Electron Microscope (SEM) to examine complete cells. However, with some internal money and a cooperation with the semiconductor company ICT (Munich) we were able to start the development of an aberration corrected SEM within the EMBL. Joachim Zach, a graduate student of the Rose group, carried out a theoretical concept of an aberration corrected SEM column with which the resolution should be improved from about 5 – 6 nm down to about 1 – 2 nm. Based on this, we designed and constructed an aberration corrector in cooperation with ICT, including Stefan Lanio, an ICT scientist, working at the EMBL for two years. Within this period of constructing an aberration corrector for a SEM, Arthur Jones retired and I became group leader. Joachim Zach joined my group and continued our development. We did not have the money to buy a modern high resolution SEM; therefore, we started with a used SEM and incorporated a new electron gun with a Schottky emitter that had a higher brightness and smaller energy width. Our aberration correction system consisted of four combined electrostatic and magnetic multipoles (twelve-pole) elements. This system allowed an excitation of all needed quadrupole fields to adjust an astigmatic ray path within the corrector and to have line-foci at the center of elements 2 and 3, at which we compensated the chromatic aberration by exciting strong, almost exactly counterbalancing electrostatic and magnetic quadrupole fields. At these elements we were also able to compensate the spherical aberrations for two sections by exciting strong octopole fields. The third component of the spherical aberration was compensated by additional octopole fields at the elements 1 and 4. In 1995, we were finally able to demonstrate the full compensation of the chromatic and spherical aberration of the objective lens and an improvement of resolution from 5,8 nm down to 1,8 nm at an accelerating energy of 1 keV. This was the first time ever an improvement of resolution by means of a quadrupole-octopole corrector was achieved.

It was clear, however, that our successful correction system for a SEM was designed for very low energies. A solution for TEMs, that use higher energies in order to have mainly single scattering events when electrons are passing through a thin object, still had to be found. At the beginning of the 1990s, novel electron sources (field emission sources) for high resolution TEM and STEM were commercially available. These electron emitters had the advantages of higher brightness and a smaller primary energy width. This matched an idea that had already come up in several discussions with Harald Rose in the 1980s: By concentrating the system only on the compensation of the spherical aberration, the complexity of aberration correctors could be reduced. If the primary energy width can be kept below 1 eV and the objects are imaged with electrons having an energy of about 200 keV, the reduction of contrast due to the chromatic aberration can be minimized. As early as 1981, Harald Rose had proposed a hexapole corrector for STEM that compensated only the spherical aberration. He assumed that this corrector would be sufficient for a probe-forming electron beam, as it would not allow any field of view needed for a TEM.

The 1989 microscopy conference in Salzburg was the starting point for our development of a Cs-corrected TEM, later to be funded by the Volkswagen Foundation: The presentation of a newly ordered 1.2 MeV TEM for the MPI Stuttgart generated discussions of pros and cons of this expensive way to improve the resolving power of a TEM for materials science. Knut Urban, a materials scientist at Forschungszentrum Jülich in urgent need of a high resolution instrument, electron optics theoretician Harald Rose and I discussed possibilities to get funding for a much cheaper project with better resolution and less beam damage of the objects. At the end of 1989, Rose expanded his idea of a STEM corrector and proposed a hexapole corrector with an added transfer system, just behind the objective lens, to achieve an acceptable field of view and to employ this within a TEM. In 1990, he published his idea in the journal Optik as an “outline of a spherically corrected semi-aplanatic medium-voltage transmission electron microscope”. Meanwhile, the three of us kept on discussing the realization of the proposed corrector, and in late 1990, we finalized a grant proposal for the Volkswagen Foundation. Before submission, I needed the Director General´s permission to carry out the project within the EMBL – after all a molecular biology laboratory, not a physics institute. But as all funding was external and perspectively, the instrument could later be used for structure research at the EMBL, permission was given. In summer 1991 the proposal was pre-accepted with the obligation to split the five years into two projects: Task of the first part was a proof of concept, before the state-of-the-art TEM was to be funded. Finally, in January 1992, the development of a hexapole corrector started.

So, our two aberration correction projects were running side by side: the SEM project aiming to correct the chromatic and spherical aberration between 1,5 kV and 0,5 kV, and the TEM project aiming to cancel the spherical aberration from 80 kV up to 200 kV. For the SEM project, a quadrupole/octopole corrector design had to be employed, whereas for the TEM project, a new hexapole corrector was to be developed. At the international conference in Paris in summer 1994, the proof of principle of the hexapole corrector, following the outline of Harald Rose, could be demonstrated. This made way for the funding of the new TEM. In 1995, the instrument was installed and the incorporation of the hexapole corrector began. Already at the end of 1995, Joachim Zach was able to show an improvement of resolution from 5,6 nm down to 1,8 nm by means of the SEM aberration corrector. At the same time, however, the new EMBL Director General stopped the physical instrumentation program, which meant that all contracts of my group, including my own, would terminate in July 1996. It seemed, that we were running out of time so close to the breakthrough.

So our race against time began: In summer 1996, we were able to show the compensation of the spherical aberration with the hexapole corrector in the TEM. But due to instabilities caused by the water cooling of the additional lenses in the objective lens, an improvement of resolution could not be demonstrated. I succeeded in getting money for a project extension by one year by the Volkswagen Foundation and the permission to carry out this extension using the available space without any additional funding by the EMBL. In fall 1996, we managed to get rid of some sources of the instabilities, but in spring 1997, it became clear that one source of instability in the objective lens area remained. The coming months were dramatic: I knew that we had to shut down the TEM and transfer the microscope to Jülich at the end of July. In May, I decided to design a new strong lens below the objective lens to reduce the beam diameter around the area of the instability. We were able to incorporate this new lens in June, but the first test after turning on the new lens still showed the known instabilities. However, after a few hours, at midnight, we suddenly acquired images showing an improved resolution from originally 0,24 nm down to 0,12 nm! So, at the end of June 1997, the project was finished successfully. We shot some images for conference presentations, and in July 1997, the first aberration corrected TEM was transferred to Knut Urban´s laboratory in Jülich.

This major leap would not have been possible without the following two prerequisites: Firstly, in summer 1996, when it became clear that further developments could not be realized at the EMBL, we started the company Corrected Electron Optical Systems (CEOS) in Heidelberg. The strategy to get rid of the instabilities with a specifically designed intermediate lens, within a short time frame, was only feasible with the help of one employee of CEOS who made the design and construction of the new lens his highest priority. Secondly, during the last year of the project, I was able to hire Stephan Uhlemann from the Rose group, who had already worked on the theory of the hexapole corrector during his PhD, to develop an alignment strategy. This method proved very useful to achieve a well aligned state of both the corrector and the whole instrument.

Why was CEOS founded in 1996? Just when the first SEM corrector was finished, we received a request to develop a SEM corrector for a wafer-inspection tool from the Japanese company JEOL. To carry out this task I convinced Joachim Zach (30%) to jointly found our company CEOS. Additional shareholders were Harald Rose (5%) and Peter Raynor (5%), a former electronics engineer in my group. As company, we started a co-operation with JEOL and developed the first commercially available aberration corrector for their inspection tool. While Harald Rose and Peter Raynor acted as mere shareholders, Joachim Zach and I shared the management and started the business with only three additional employees.

The presentation of the novel hexapole corrector for high resolution TEM raised much attention: Laboratories started to raise funds, several companies initiated negotiations with us to secure access to this new technology and to sell instruments including the novel corrector, the German Research Foundation launched an initiative to fund new instruments for various institutes. The growing number of activities made it necessary for CEOS to find new premises in Heidelberg, so we invested our private money for a new building to house four separate labs, one for each of our clients, the EM manufacturers Zeiss, Hitachi, JEOL and Philips/FEI. In 2003, we had secured cooperation agreements with all four companies.

In the year 2000, when the success of the new aberration correction system was apparent, well recognized and appreciated by the materials science community, the US Department of Energy started a discussion to reach further and develop an ultra-high resolution TEM at 300 kV to achieve 50 pm resolution both in TEM and in STEM. The requirement for TEMs was to compensate not only the spherical, but also the chromatic aberration. Subsequently, the TEAM project (Transmission Electron Aberration corrected Microscope) was started in 2005 and had to be finished by summer 2008. When in April 2008, a TEM prototype had been installed at the DOE lab in Argonne, as well as a Cs-corrected STEM in Oak Ridge, we finally managed to ship the whole double corrected 300 kV instrument to the NCEM/Berkeley. For the STEM we developed an advanced hexapole corrector compensating even the fifth-order limiting aberration and showing a resolution of 50 pm. However, for the Cc/Cs-corrector we detected a resolution of 55 pm at 200 kV and of just 65 pm at 300 kV, although the shorter wave length at 300 kV would be expected to show better results. Even though the aberration corrected TEM was accepted, we did not give up investigating the reasons for the loss of coherence at 300 kV and, less strong, at 200 kV. It took us until 2013 to be able to explain the reason of this reduction of resolution by calculations and experimental work (mainly by Stephan Uhlemann): Due to the large diameter of the electron beam within the corrector, free electrons in any

Maximilian and Christa Charlotte in Hawaii after a conference

metal produce small electron currents by correlation, whose small magnetic fields produce magnetic noise. As the strength of the quadrupole fields is limited, the large beam diameter is necessary to produce sufficient focusing power. Solving the riddle of the magnetic noise allowed us to upgrade the existing copy of the TEAM corrector for Jülich and, hence, improve the resolution at 200 kV and 300 kV to 50 pm.

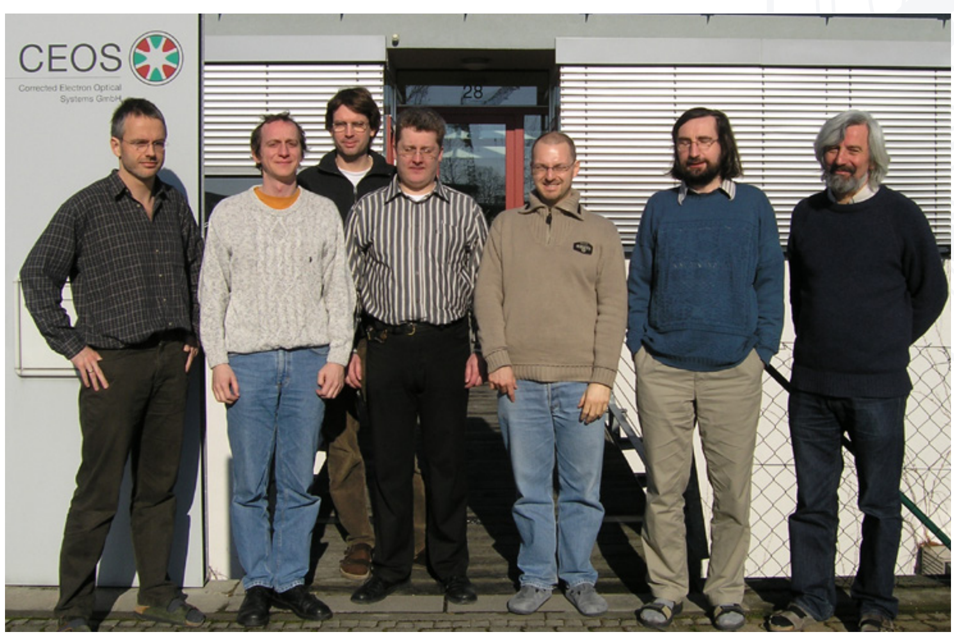
When we had just finished the TEAM project, Ute Kaiser from the University of Ulm asked for a joint project to develop a dedicated low voltage (20 kV up to 80 kV) aberration corrector. The Sub-Angstrom Low Voltage Electron microscope (SALVE) project was started as a joint project with Zeiss, co-funded by the DFG and the State of Baden-Württemberg. However, in 2013 Zeiss stopped the TEM business and a new project partner for the base instrument was found with FEI. We used the time between the negotiations of back-payment by Zeiss and the conclusion of a new agreement with FEI to modify the existing SALVE corrector and to optimize it regarding the magnetic noise. The SALVE project was finished in 2016, with a new landmark of resolution at low energies. As an example, we achieved sub-angstrom resolution even at 40 keV energy, although the wave length of electrons is much larger at this energy than at 200 kV. As figure of merit for the achieved resolution, the wave length of the electrons used for imaging was employed:

With Joachim Frank at an EM-Conference in Davos/Switzerland in 2005

The ambitious goal within the challenging TEAM project was to achieve a resolution 20 times the wavelength. We set the same goal for the SALVE project, but managed to achieve a resolution of about 15 times the wavelength between 20 – 80 kV, and topped the result of the TEAM project in this respect. This is, in comparison with an uncorrected TEM having a resolution of 100 times the wavelength an improvement by a factor of around 7 times.

In addition to these challenging R&D projects, we had to organize the production of Cs-correctors for various companies. So in 2005, when the TEAM project started, we changed the cooperation with FEI for their TEMs and STEMs and granted them permission to produce hexapole Cs-correctors based on our technology. The CEOS company grew over the years, starting as a group of five people in 1996 to an enterprise with almost 50 employees to date. Due to the strong interaction with Roses group in Darmstadt we knew his PhD students and could hire some. Finally, we gathered all together seven former PhD students of Rose all of them having very good knowledge of electron optics. We had to extend the company´s premises in Heidelberg three times, and at the end of 2019, in total around 900 hexapole correctors, based on CEOS technology, have been installed worldwide. This figure stands for about 90% of the global market of aberration corrected electron microscopes.

While my professional career moved from optician to physicist, my life changed dramatically when my wife Brigitte was



The group of former students of H. Rose working at CEOS in front of the building celebrating the 10th anniversary

With K. Urban and H. Rose after the celebration of the Honda Award in 2008

diagnosed with cancer in 1988. In 1989, we moved from Darmstadt to a village near Heidelberg to live much closer to the EMBL, where I worked at that time. She died in 1990 – in the same year when Harald Rose, Knut Urban and I set up our joint Cs-corrected TEM project and were in the middle of securing funding for this project. As Brigitte's illness progressed, she happened to meet Christa Charlotte, a Protestant pastor on maternity leave, whose younger children were about the same age as my two children. In the following months, Christa Charlotte took on the spiritual care for my wife, and after Brigitte´s death, she supported me as single parent. We fell in love, founded a common household in 1995, and are happily married since 2000. I am very happy and feel privileged to have experienced this positive change in my life thanks to my second wife and all children and grandchildren.

With H. Rose at Max's birthday-symposium at the University of Heidelberg

autobiography

by Knut Urban

I grew up in the early post-war period in Stuttgart, Germany. This city is known for its automobile industry and for its large number of small and medium-sized industrial companies.

My father was an electrical engineer and he ran a factory for small electric motors. Over the decades, he set the main accents of the company with a whole series of his own inventions. In my parental home there was a lot of thinking, reading and discussing about science and technology. In addition to parental care, I owe to my father and my mother a critical, open, but cooperative way of thinking. This was later very beneficial to me, not least professionally. Still a young school boy, I used the technical possibilities of the company to build my first optical telescope together with my grandfather. This instrument was followed by a reflecting telescope, which could be used for more serious observations. And a few years later I was accepted as the youngest member of the Stuttgart observatory. That's how I came to physics via astronomy.

After attending high school, I joined Siemens company for a shortened apprenticeship in the field of electrical engineering, which in the sixties, was the prerequisite for studying physics at the university. This was an important time for me, because learning the skills of practical electrical engineering, including design and working in production with ordinary workers not only helped me to acquire important professional knowledge, but also strengthened my social skills. Subsequently I enrolled at the Technical University of Stuttgart to study physics. Inspired by my work in the field of semiconductors at Bosch company already during my studies, I completed university with an experimental diploma thesis in the field of semiconductors. Here I learned a lot about low temperatures, about the optical properties of semiconductors and how these are influenced by crystal lattice defects. This was my entry into solid state physics and especially into the physics of defects in crystals.

A decisive factor for my entire further career was that Alfred Seeger, Professor of Solid State Physics at the University of Stuttgart and Director of the Max Planck Institute for Metals Research, became interested in my results on the optical properties of plastically deformed germanium at low temperatures and offered me a doctoral thesis. Seeger was internationally recognized for his pioneering work in the field of crystal defects, and he was one of the most versatile solid state physicists of his time. Accordingly, the fields dealt with in his institute and the experimental and theoretical methods used were many and varied.

Seeger presented his doctoral students with challenging topics and trusted that they would manage to be successful. The cold water into which I had to jump according to his offer consisted of constructing an object stage for the new high-voltage electron microscope of the Max Planck Institute. The challenge was that the stage should allow samples to be cooled down to the temperature of liquid helium (-269 °C) without impairing the resolving power of the microscope, in order to study atomic lattice defects in metals. This had been attempted by other groups for about a decade without any success. The vibrations of the boiling helium used for cooling and the instability of the low temperature spoiled the optical resolving power. Seeger offered to me to do the design and construction of the system at the Fritz Haber Institute in Berlin under Ernst Ruska, who later won the Nobel Prize as the inventor of the electron microscope. Ruska, who was an engineer through and through, was initially rather skeptical about the young physicist. But my work in the Siemens and Bosch workshops had prepared me for such a demanding job. And when I asked Ruska for an interview a few months later, and approached him with a large bundle of drawings under my arm, he was impressed. From then on, he followed my work with great interest, and he made all the facilities of his institute available to me. As it is not seldom the case, a newcomer who had new and independent ideas could make the breakthrough that had been denied to others.

The helium-cooled object facility in the high-voltage electron microscope then served us for many years as a unique platform for experiments carried out in-situ under direct high resolution observation. The microscope offered an attractive advantage: at high electron energy, atomic defects could be generated by electron-atom displacements, and at low energy, their secondary reactions could be observed at any desired temperature. I myself was rewarded by a number of new observations. The most important of these are certainly the discovery of the radiation-induced diffusion of atomic defects (brought about by electrondefect interaction) and the proof of the spinodal ordering in alloys, a sophisticated process based on special lattice symmetry properties, which had been theoretically treated and discussed for years, but had never been demonstrated experimentally.

In the second half of the eighties I left the Max Planck Institute becoming a Professor for Materials Science at the University of Erlangen. A few years later I moved to Research Center Jülich as Director of the Institute of Solid State Research. This position was combined with a Chair for Experimental Physics at RWTH Aachen University. In the meantime I had begun to take an interest in the new field of quasicrystals, for the discovery of which Dan Shechtman received the Nobel Prize a few years later. I earned my entry ticket into the club of quasicrystal scientists with a paper in which I combined cryo- and high-temperature in-situ electron microscopy to show for the first time that the quasicrystalline phase in alloys developed by itself from the amorphous state at elevated temperatures, whereas previously it was believed that the only access to the quasicrystalline phase would be by quenching from the melt. Some years later, when I discovered by chance dislocations in one of our images, a kind of lattice defect closely related to plastic behavior in crystals, I became very engaged with quasicrystal plasticity and then worked in this field for many years. The discovery of dislocations was so exciting since it was against any expectation. Quasicrystals are based on six-dimensional lattice schemes and understanding the topology of such defects in these lattices turned out to be rather difficult. Similarly complicated was the formulation of a contrast theory for quantitative characterization of these defects in the electron microscope, which kept us busy for a long time. In addition, the observation of dislocations indicated that it might be possible to plastically deform quasicrystalline materials, which are in general very brittle, and we were able to prove this at high temperatures by performing in-situ experiments in the high-voltage electron microscope.

The eighties were exciting years for solid-state physics and materials science. Outstanding was the discovery of high-temperature superconductivity in oxide materials and the invention of scanning tunneling microscopy (STM). The multifaceted interest in new solid-state physics topics, which we learned from Alfred Seeger, and which he exemplified to us, has never left me throughout my professional life. And as someone who had just taken over a research institute at one of Germany's national research centers, which had reasonable financial resources for equipment and personnel, I threw myself into setting up two more working groups, one to set up STM and one to study oxide superconductors. STM had primarily been introduced as a surface physics technique. Following my interest in lattice defects, we built a novel STM, with which we were the first to study single dopant atoms in semiconductors, their electric fields, their diffusion and their behavior in the pn-junctions of devices; highly interesting topics for advanced semiconductor technology. With the oxide superconductors, two things proved to be an advantage for us. We built the facility for the deposition of superconducting thin films and devices ourselves in order to realize our own ideas, and we used our state-of-the art electron microscopes to directly check the quality of the results of film deposition and to continuously improve them. We achieved international records in Josephson-device and high-frequency performance, and our superconducting microwave resonators flew on an international communication satellite mission.

Electron microscopy at that time was more powerful than it had ever been before, and we were proud of our new instruments we were able to put into operation at the end of the eighties. Their resolution of about 2.4 Å at 200 kV and 1.7 Å at 300 kV was fantastic. On the other hand, they still hadn't reached atomic dimensions, which seemed to solid state physicists, including me, at that time to be something like the Holy Grail. It was therefore a great turn of events, that in September 1989 during the 'Drei-Ländertagung' (the traditional quadrennial meeting of the electron microscopy societies of Austria, Germany and Switzerland) at Salzburg, Austria, Maximilian Haider and Harald Rose told me about a project that would decisively change our future professional life, and of course that of electron microscopy in general. Harald Rose had just completed a theoretical study of a new aberration-corrected electron microscope objective lens which, according to a conservative estimate, had a chance of being technically realized with the current state of the art of electronics technology. A few months later we agreed to submit a joint application to the Volkswagen Foundation. The aim was to realize in Haider's laboratory at the European Molecular Biology Laboratory at Heidelberg the new semi-aplanatic corrector lens, known today as the 'Rose corrector', and to implement it into an appropriately modified commercial conventional transmission electron microscope (CTEM). Since in a CTEM one must also correct the off-axial aberrations, this is the more general case, which automatically includes the case of the correction of a scanning transmission electron microscope (STEM).

Due to a decision of the American funding agencies to no longer finance the development of aberration-corrected electron optics due to decades of failure in this field and the lack of interest from industry, the corresponding working groups had been dissolved worldwide.

The Volkswagen Foundation was in general also not prepared to finance pure instrument development. However we thought we had a fair chance to get funded because, as a team consisting of a theoretical and an experimental physicist specialized in electron optics and a materials scientist interested in a variety of fields, we were able to justify our project from the point of view of materials science application. As always after a real change of paradigm, it is today, now that the problem of aberration correction in electron optics is solved and atom-by-atom materials science studies are part of our everyday life, hardly possible to take oneself back in time, to a time when science was quite obviously not prepared for atomic-resolution electron microscopy. Materials science was about to enter the era of nanotechnology for which access to the atomic range of dimensions was highly desirable. But decades of promises, which then electron optics could not keep, the problem of correcting the aberrations of electron lenses was simply too difficult, had destroyed any confidence of materials scientists that electron optics would ever be able to help them. The biggest problem was therefore to convince my own colleagues, the materials scientists, that our concept was better and had a higher chance of eventually making the breakthrough than had been the case with all the earlier attempts.

In this situation I decided to offer and give numerous talks in materials-science oriented institutes in Germany and abroad, and I organized special sessions on conferences in order to advertise the need for atomic electron-optical resolution in materials science. The fact that we were well advised to intensively advertise for our plans became evident when it turned out much later that our proposal was accepted at the final reviewers' meeting with a knife-edge majority of a single vote. In 1997 the world's first aberration-corrected transmission electron microscope demonstrated a record resolution of better than 1.4 Å (at 200 kV), almost doubling the resolution of the original, uncorrected instrument. This allowed us to demonstrate atomic resolution in crystals of germanium.

Every physicist learns in the first years at university that the atomic world obeys quantum physics, and this is in many ways so different from the classical physics we are used to in our everyday lives. So there was still a lot for us to learn if we wanted to understand the images we obtained in atomic dimensions. Contrary to what laypeople (intuitively) assume when they see the high-resolution images, the atoms cannot be seen directly. The electrons react to the atoms' electric fields, and special optical operations are required to obtain an image on this basis. What did we see at all, that was the question that was to occupy us intensively for the coming months. But the effort was richly rewarded; in the meantime the instrument had been moved to Jülich. Under special novel imaging conditions, which nobody had thought of before, we succeeded for the first time in seeing oxygen atoms in oxides.

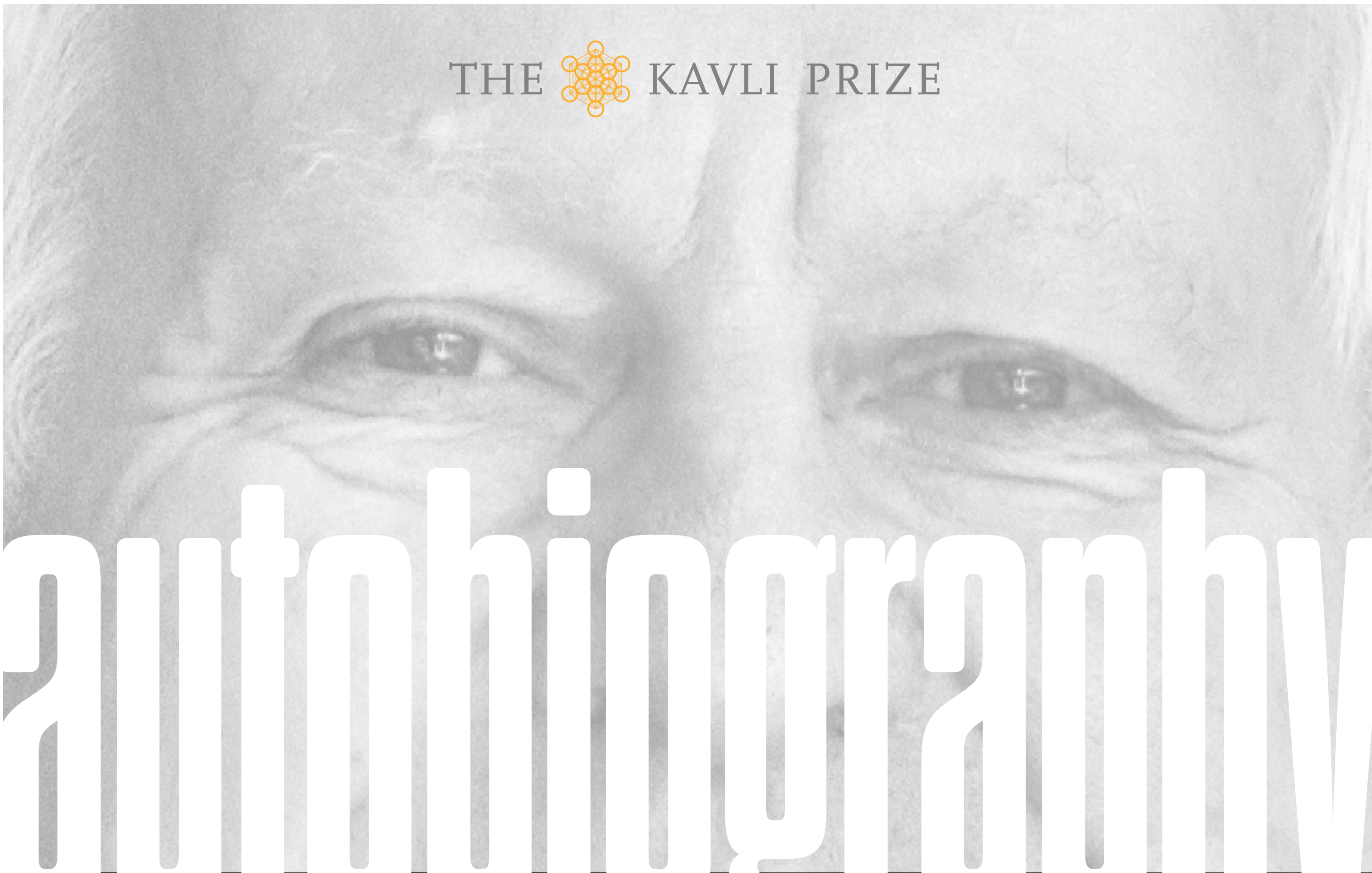
The oxides are forming one of the most significant material classes. But electron microscopy had previously been blind to oxygen, as well as to other light atoms, due to their low scattering power. This now changed suddenly, the oxide chemists were enthusiastic, and we ourselves have been involved in the study of oxygen in materials for many years.

The first significant materials-science problems that were then solved by atomic aberration-corrected electron microscopy are the proof of the order of oxygen atoms in the copper-chain planes of YBaCuO, a phenomenon of fundamental importance for the theory of high-temperature superconductivity. Nobody had been able to directly see the oxygen in these materials before. Furthermore we could not only proof but also measure the understoichiometry of oxygen atoms in lattice defects in BaTiO (and other perovskites), which decided a long-lasting dispute in oxide chemistry. Here again, it turned out to be an advantage that we, as a materials science institute, had the competence in these fields, together with the competence in electron microscopic contrast theory, which allowed us to get the most out of the new instrument developed together with our electron optical colleagues.

What fascinated me from the very beginning is that we found that by combining quantitative aberration-corrected electron microscopy and measurement with quantum-physical and optical image simulations in the computer, in tandem so to speak, we could measure atomic positions and atomic displacements with a precision of better than a picometer. This is actually an unimaginable dimension; it corresponds to one hundredth of the Bohr diameter of the smallest of all atoms, the hydrogen atom. Access to these tiny dimensions means access to where a lot of physics takes place. In addition, this combination of microscopy and computer simulation provides us with analytical information about the chemical nature and concentration of the atoms imaged.

In 2004 I was elected President of the German Physical Society, the oldest physics society in the world and with over 60,000 members also the largest. I have always felt it a special honor to serve this Society, which has had so many famous presidents in its history, personalities whom we can admire, but whose great contributions to the development of physics we can never match. The scientific community is international, and it is a great privilege to be able to meet like-minded people in all nations and to work together across borders. Many of my colleagues have become lifelong friends. This brief excerpt from my scientific life would not be complete without mentioning my years as a visiting professor at the Saclay Research Center near Paris, France, and at Tohoku University in Sendai, Japan, as well as my years of involvement and longer stays at universities in China, namely Tsinghua University in Beijing and Jiaotong University in Xi'an.

I was lucky to be able to work throughout my professional life on fantastic and rewarding projects and to have great and talented people as students, doctor students, staff and colleagues over the years. Working with them has been a great privilege, sometimes a challenge, but always a great pleasure. For this I will always be grateful from the bottom of my heart.



autobiography

by Ondrej L Krivanek

I was born in Prague, Czechoslovakia (now Czech Republic), at a time when the Soviet Union and other socialist countries took pride in their science and technology accomplishments, and in their educational systems. When Yuri Gagarin became the first person to orbit the Earth in April 1961, we were encouraged to form clubs playing at cosmonauts, and I started one with my school friends. Amusingly, our "rocket crew RP-35" got a write-up on the front page of Večerní Praha, Prague's popular daily newspaper.

My parents met soon after the end of WWII, which brought heavy hardships to both of them. My dad was a chemical engineer who specialized in the chemistry of colour photography and an author of books on photography. In his retirement he edited the monthly journal Zpravodaj. My mom studied journalism and later on became a librarian. My paternal grandfather was an expert on school law, and my maternal grandfather designed and built motorcycles, one of which is on display in the Czech National Technical Museum in Prague.

My favourite subjects in high school were math and physics. Students interested in these subjects were encouraged to take part in extra-curricular competitions. We were given challenging problems to solve at home, and I very much enjoyed them. Those who did well progressed to higher rounds, and in my senior high school year, I competed in the national rounds in math and physics, earning prizes in both. In physics I came second, and I was invited onto the national team of three that represented Czechoslovakia at the 2nd International Physics Olympiad, held in Budapest in June 1968. The Olympiads were started in Czechoslovakia in 1959 by Prof. Košťál and other dedicated teachers, and became international in 1967. Our team came second, just behind the "home" Hungarian team. I have since had the pleasure of working with one other former International Physics Olympian – Niklas Dellby, my partner at Nion.
Another major influence was my hobby of building model airplanes using balsa wood and translucent lightweight paper. I enjoyed building them and figuring out how to make them better. Flying them was fun too, but for me, the design and construction phases were more satisfying.

Choosing a field for university studies, I was torn between math and physics. My model airplane building pulled me towards physics as an area that would be more practical, and perhaps allow me to build interesting machines. I took the entrance exam for the Math-Physics Faculty of Charles University in Prague, and then went on a summer vacation I had planned in France and England, intending to come back to Prague in time for the start of the university school year. I was in London when the Soviets and their satellites invaded Czechoslovakia in August 1968, to stop the push towards democracy led by Alexander Dubček, and decided to stay. My parents and sister emigrated at the same time, and settled in Switzerland near Fribourg.

People in the UK were very sympathetic to citizens of a small European country occupied by Soviet tanks. The University of Leeds generously offered five scholarships to Czechoslovak students who wanted to study in England, and I was fortunate to secure one. I had three wonderful years studying physics in Leeds, and I learned to speak English with a Yorkshire accent, which I unfortunately lost later. I graduated at the top of my class, and was accepted for graduate studies at the Cavendish Lab in Cambridge. Professor Archie Howie was my Ph.D. supervisor, and instilled standards of rigour that have stayed with me for my whole scientific career. My research focused on characterizing the structure of amorphous materials using electron microscopes, the latest versions of which were then just able to resolve atomic planes in various materials. I obtained 0.3 nm resolution images from “amorphous” carbon, and used them to show that the carbon contained small graphitic nano-crystals (Krivanek, Gaskell and Howie, Nature 1976). The work made me realize that a clear view of the structure of matter on the atomic scale would only become possible with electron microscopes with better resolving power. I returned to this topic 20 years later, when aberration correction showed promise that the resolving power could be improved substantially. Electron microscopes are incredibly powerful and versatile instruments for exploring the world of atoms, and I was hooked on using them and making them even better.

The world’s highest resolution electron microscope at that time was at Kyoto University in Japan, in the laboratory of Professor Keinosuke Kobayashi: a 500 keV instrument with which Yoshinori Fujiyoshi obtained spectacular images of the copper phtalocyanine molecule, with all the atoms (except hydrogen) clearly resolved. I applied for support for an extended stay there to the UK Royal Society, and was successful. When I got to Kyoto I found that the electron microscope, which on paper was the world’s best, had a rather weak electron source that did not allow us to see images well enough to optimize the microscope set-up. Seiji Isoda and I therefore developed a rapid “assisted tuning” procedure that made it possible to set up the microscope properly without needing to peer at the dim viewing screen. This resulted in a clear image of a complicated defect in a germanium crystal, in which all the projected atomic positions could be simply “read out” from the image. It was also my start on developing methods for improved microscope tuning, which turned out to be an essential component of successful aberration correction.

After the Kyoto stay I went on a three months overland trip through Asia back to Europe, getting a taste of many different cultures, and then started a postdoc at Bell Labs in Murray Hill, New Jersey, USA. Bell Labs was a powerhouse back then, and I worked with people such as Dan Tsui who co-discovered the fractional Hall effect, for which he got the Nobel prize a few years later. The lab had a great variety of interesting materials and devices, but no microscopes able to resolve their atomic structure. The solution was to prepare samples at Bell Labs and to image them at Cornell University in an arrangement facilitated by Professors John Silcox and Steve Sass, with the same type of electron microscope as I had used for my Ph.D. research. Atomic-resolution images of the all-important Si-SiO2 interface in MOSFET devices came out of this work.

My next postdoc was in Professor Gareth Thomas’s group at UC Berkeley. The group was a part of a Materials Science Department, but I was more interested in advancing techniques and instruments than materials. The technique I thought was especially interesting was Electron Energy Loss Spectroscopy (EELS). I got my first taste of it at the 1978 Analytical Electron Microscopy workshop held at Cornell, where I met people who became lifelong friends, such as Phil Batson, Christian Colliex, Ray Egerton, and Mike Isaacson. We were expected to build our own spectrometers in those days – there were no commercial models. I therefore designed and built a compact spectrometer, with major help from Peter Rez, who wrote software for it. It came together in 10 months, from first ideas to a working spectrometer, and it was my first experience of building a complete instrument and applying it to interesting problems. I was guided by five simple rules that proved useful for my later projects too:

1) *Start modestly, with a smaller project that is easier to bring to completion than a big one.*
2) *Think carefully about design choices that will affect the performance and will be hard to change later.*
3) *Move fast and try not to break things.*
4) *Learn lessons from the first design and follow up with a second design that addresses problems that only become clear once the first design starts working.*
5) *Collaborate with others to help the project move faster.*

I added a sixth rule later:

6) *When entering an unexplored research area enabled by the new instrument, investigate it in an industry–university collaboration, with the industrial partner supplying the instrument and the expertise on how to run it, and the collaborating university (or research institute) supplying problems to solve, samples, theoretical expertise, and enthusiastic students and postdocs.*

The principal limitation of my first spectrometer was that it had no aberration correction beyond first order. This limited the entrance aperture size that would give good energy resolution, resulting in a poor signal collection efficiency. I therefore applied rules #4 and #5, and produced a revised design in close collaboration with Peter Swann of Gatan plus Gatan’s consultant Joe Lebiedzik and Mike Scheinfein of Cornell University. The resultant spectrometer had full second order aberration correction, and its signal collection efficiency was about 100x higher than for the first one. This was a powerful lesson about the usefulness of aberration correction. I also learned a lot from Peter, who had an exceptional gift for elegant design, and who became a close friend. The spectrometer became known as Gatan serial EELS model 607, and it was a commercial success.

The design was completed after I moved to a new full-time position, of Assistant Professor and Associate Director of the NSF-funded HREM facility at Arizona State University. Gatan donated one of the new spectrometers to ASU, and with my collaborators we applied it to many interesting problems, and put together the EELS Atlas of all stable elements that is used to this day. ASU was a great place to work, with many experts in electron microscopy either on staff or in long-term visitor posts: John Cowley, Peter Buseck, John Spence, Johann Taftø, Naoki Yamamoto, Channing Ahn, Kazuo Ishizuka, Ray Carpenter, Sumio Iijima (winner of the 2008 Kavli Prize), and many others.

The pull of California, however, proved irresistible when Peter Swann moved the Gatan R&D facility from Pittsburgh to the San Francisco Bay Area, and in 1985 I became the Director of Research at

Gatan. A very productive period followed, during which we introduced a number of successful instruments, including parallel-detection EELS, post-column imaging filters, CCD cameras, scanned image acquisition systems, and DigitalMicrograph and EL/P software. Gatan grew about 10x in size during this time, and I learned that making instruments commercially can be a great way to fund instrumentation research, especially when working with like-minded researchers and lean administrations that understand the value of good science.

The imaging filter we built at Gatan used quadrupole optics and corrected second order aberrations and distortions using sextupoles (Fig. 1). Imaging filters perform two distinct electron-optical tasks: they form an energy-loss spectrum at the energy-selecting slit, acting as a spectrometer, and then they transform the part of the spectrum selected (filtered) by the slit into an image, acting as a projection lens system. This makes their optics very analogous to the optics of a whole electron microscope. The correction principle our filter used was the same as in the aberration correctors Niklas Dellby and I built later: quadrupoles imparted different first-order properties to the beam inside higher-order multipoles, and the multipoles corrected higher order aberration/distortions. Even though the optics seemed complicated at that time, careful attention to the software made the instrument easy to operate.

Later versions of the filter achieved 3rd order aberration correction using octupoles. The straightforward way in which this was accomplished made me think that I had a good chance of correcting the third order (spherical) aberrations of the objective lens of the electron microscope – a classic problem in electron optics since Otto Scherzer's work on the subject in the 1930s and 40s.

There were several successful proof-of-principle correctors built in Germany and the UK in the 1950s to 70s, but no crowning success in the form of practical performance that surpassed what could be achieved with the best uncorrected microscopes. There were also several ambitious and costly corrector projects that failed to achieve their goals, giving aberration correction an aura of a great idea that will never work. This made building an aberration corrector too speculative a project for Gatan. I was keen to build one, and so I explored doing it elsewhere. My first try for corrector funding was a chat with Uli Dahmen, then the director of the National Center for Electron Microscopy in Berkeley, around 1992, but this was not successful.
I had better luck persuading Mick Brown of my Alma Mater, Cambridge University, who had a spare VG (Vacuum Generators) cold field emission (CFE) scanning transmission electron microscope (STEM), that we should try to build a corrector for it. We applied for funding to the British Royal Society, together with Andrew Bleloch in early 1994, and secured £80k from the Paul Instrument Fund. After a few months' delay for the expected arrival of my first-born, in September 1995 I moved to Cambridge with my family for two wonderful years, to work at the Cavendish Lab where I got my Ph.D. Niklas Dellby, with whom I collaborated five years earlier at Gatan and who was then finishing his Ph.D. at MIT, and others joined the project, and Robinson College awarded me a Bye Fellowship.

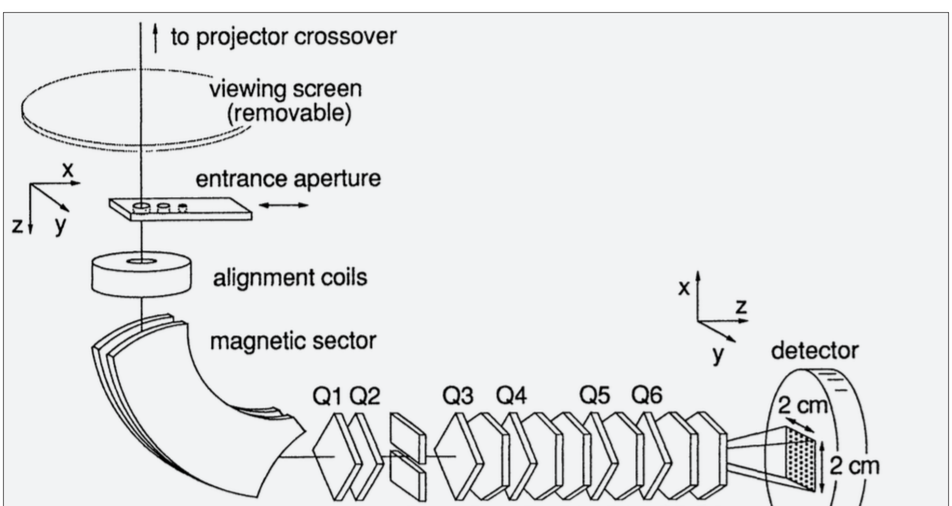


Fig. 1. An imaging filter that used quadrupoles (Q) and sextupoles (S) to correct second-order aberrations and distortions. It worked very well and gave me the confidence that a spherical aberration corrector for a microscope objective lens would not be much harder to build. O.L. Krivanek et al., Microsc. Microanal. Microstruct. 2

We had two key insights. One, aberration correction brings its strongest benefits to STEM, whose operation is less affected by chromatic aberration than the conventional transmission electron microscope (CTEM), and for which the benefits of correction are double: better spatial resolution and more intense beam current in a small probe, giving a major improvement in the STEM's spectroscopic capabilities. This was the reason we focused our efforts on STEM aberration correction right from the beginning, and our hunch turned out to be right: there are now more than two times as many aberration-corrected STEMs in the world than aberration-corrected CTEMs. Two, the correction of spherical aberration requires a complicated piece of electron optics, which is bound to introduce many kinds of "parasitic" aberrations. These cannot be avoided by careful construction, but they can be characterized and nulled one by one. Without taking this step, the corrector may be able to fix the spherical aberration, but strong parasitic aberrations are likely to worsen its overall imaging performance. We focused on developing STEM autotuning algorithms that quantified the parasitic aberrations, using approaches I pioneered in my previous work on characterizing aberrations. We had outstanding help from Andrew Spence for this part of the project, and later on from Andy Lupini.

If electron microscopes could use glass lenses, aberration correction would be very easy: one would simply shape the crucial "objective lens" as required, imparting the right fourth-order parabola shape to it in order to null spherical aberration (Cs). However, unlike light, which passes through glass without much scattering, electrons are strongly scattered by matter and lenses made from a solid material do not work for them (with a few special exceptions). They are instead

Fig. 2. The central part of the first STEM Cs corrector that improved the resolution of the microscope it was built into, with 6 multipole stages containing strong quadrupoles and octupoles, and 96 auxilliary coils for nulling parasitic aberrations. Corrector Ø ~ 12 cm.

Fig. 3. Ondrej Krivanek, George Corbin and Niklas Dellby in front of Nion I building, which featured a large garage that we later converted into a mechanical assembly room. Nion can therefore partly claim that its origins were in the proverbial garage.

focused by magnetic fields that extend into the vacuum in which the electrons travel. The field distributions are subject to the Laplace equation, with the consequence that strong positive spherical aberration cannot be avoided – in a round lens. Our solution was similar to proof-of-principle correctors built in Cambridge UK in the 1960s. It used non-round quadrupole and octupole lenses, in which the electron beam's cross-section is made elliptical, and desirable aberration properties are imparted first in one direction, and then in the perpendicular direction. We also made sure we could measure and fix every important parasitic aberration. We obtained corrected images that improved the resolution of our STEM in the summer of 1997 - the same summer as when the first improved images were obtained by the Heidelberg-Julich CTEM corrector project. We presented our results at the 1997 EMAG meeting held in Cambridge, and the 1998 TARA workshop in Port Ludlow. Our research stay in Cambridge came to its end, and we returned to the USA in October of 1997.

The corrector (Fig. 2) is now displayed in a glass case in the Cavendish Lab, next to Deltrap's proof-of-principle quadrupole-octupole corrector, and not far from the Cavendish's crown jewels that include the apparatus with which J.J. Thompson discovered the electron, and the DNA model built by Watson and Crick. Our Cambridge corrector did not improve on the performance of the best uncorrected STEMs of the time, but our mark II corrector did. Niklas Dellby and I designed and built this corrector as our next project, after I became a Research Professor at the University of Washington in Seattle, and we founded Nion Co., in late 1997. Fig. 3 shows the Nion founders together with Nion's first employee, George Corbin, whom we hired straight out of college, and who has contributed an incredible amount through the 22 years he's been with Nion. We set up a laboratory, bought a second-hand VG STEM for $30k that was a more recent instrument than the STEM we used in Cambridge, and started working on the new corrector. The funding mainly came from Phil Batson of IBM TJ Watson Research Center in Yorktown Heights, NY. The project achieved a double distinction: it was the first commercial corrector, delivered and installed at IBM in June/July 2000, and it led to the first STEM of any kind able to focus an electron beam to <1 Å (0.1 nm) diameter, at 120 keV as set up by Phil. These results were extended soon afterwards when we built a similar corrector into a 300 keV STEM at Oak Ridge National Labs (ORNL), and Matt Chisholm and Pete Nellist resolved atomic columns 0.78 Å apart.

Aberration correction soon became the new frontier in electron microscopy. CEOS GmbH in Germany supplied correctors to established manufacturers of electron microscopes, first for CTEM and later also for STEM, while Nion Co. concentrated on correctors for STEM and did everything on its own. At first we made correctors for VG STEMs, improving their resolution about 2x. Our next "big idea" was an ambitious one: that we could extend our prowess in correctors by designing a whole new electron microscope, and that we would do it better than long-time microscope manufacturers. The microscope that we developed, the Nion UltraSTEM™, went on to establish many performance benchmarks, and it has led to new levels of understanding of the properties of materials. Later on we added many further, often revolutionary capabilities to our microscope, as described below.

To give some examples of the original development, our new STEM produced spectacular images of 2D materials such as graphene and of 1D materials such as nanotubes. We got into this field with samples provided by Valeria Nicolosi of Trinity College Dublin in Ireland, and by Kazu Suenaga of National Institute of Advanced Industrial Science and Technology Japan. Niklas and I brought these samples to Oak Ridge National Laboratory (ORNL), where we worked over a long weekend on the fourth electron microscope Nion had delivered to a customer. The popular wisdom back then was that the imaging technique we were using – high angle annular dark field (HAADF) imaging – could not usefully image light atoms such as carbon. The signal was supposed to be too weak to make the imaging of single atoms possible. Contrary to that "wisdom", we

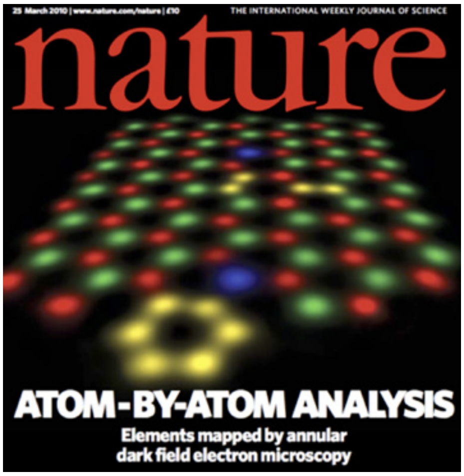


Fig. 4. Cover of the March 25, 2010 issue of Nature. It shows a medium angle annular dark field (MAADF) STEM image of monolayer BN with atomic substitutions. The experimental image was colorized to correspond to the types of atoms that were identified using image intensities, and rendered in a perspective view. Red = B (boron), yellow = C, green = N, blue = O. O.L. Krivanek et al., Nature 464 (2010) 571-574.

started getting spectacularly clear images of nanotubes and graphene at a primary energy of 60 keV, which avoided heavy damage to the samples. I had many hours of operating other electron microscopes under my belt, but I had never seen images as clear as the ones I was getting from the Nion instrument. I am not one given to exclamations, but I remember pausing, pushing my chair back from the control table, and proclaiming: "Niklas, we made a [really] good microscope!"

I was not the only one who thought so. Juan Carlos Idrobo, post-doc at ORNL at that time, walked into the lab one evening, and when he saw the results we were getting, he watched for a long time, as though glued to the spot. He and others began to do similar experiments at ORNL soon after, and a few months later, Matt Chisholm produced an iconic image of a BN monolayer with atomic substitutions that was featured on the cover of Nature (Fig. 4). Results obtained at ORNL later showed how a structure consisting of six silicon atoms anchored in a graphene sheet jumped back and forth between two quasi-stable configurations. EEL spectra with revealing fine structure features were obtained from single Si atoms embedded in graphene, at roughly the same time at Oak Ridge and at the Daresbury SuperSTEM lab, semiconducting MoS2 nanowires were sculpted from a 2D MoS2 sheet also at the lab, and a research group at the University of Vienna, was able to "drive" a single Si atom in chosen directions in a graphene sheet by the electron beam. The increase in the available beam current allowed the elemental composition of materials to be efficiently mapped at atomic resolution both by EELS and by energy-dispersive X-ray spectroscopy (EDXS), precisely as we had expected.

Bonding information can be mapped too, using chemical shifts in EEL spectra of

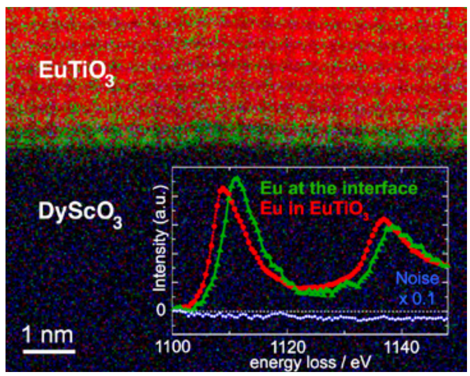


Fig. 5. EELS map of Eu atoms in EuTiO3 crystal leading to an atomically sharp interface with DyScO3. The intensity of each pixel in the map shows the Eu concentration worked out from a spectrum acquired at that pixel, the colour whether the atoms were 3+Eu (green) or 2+Eu (red). Insert shows Eu M4,5 edge threshold peaks from the interface (green) and away from it (red), with chemical shift of 2.5 eV due to the change in the Eu valence.

L. Kourkoutis, D.A. Muller et al., proceedings IMC17 (Rio de Janeiro, 2010).

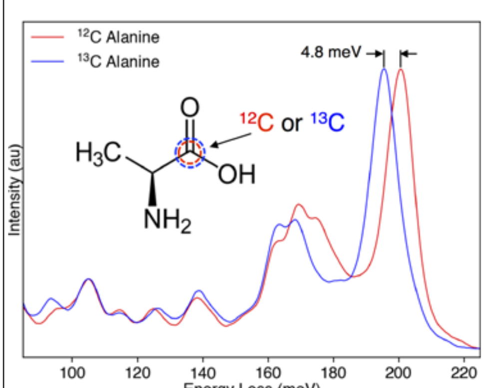


Fig. 6. Experimental vibrational spectra of two forms of the amino acid L-alanine, differing by a single 12C atom substituted by 13C. The 4.8 meV shift of the large peak at ~200 meV, due to the stretch of the C=O bond, can be mapped to reveal where the two types of molecules reside, at about 100 nm spatial resolution. J. Hachtel et al., Science 363 (2019) 525–528.

different elements (Fig. 5). All these capabilities amount to just a small fraction of the different kinds of research enabled by Nion's aberration-corrected STEMs. There are now over 20 of these instruments in the world, and about 700 aberration-corrected STEMs made by other manufacturers. It is no longer possible to cover all the creative work that's being done with these instruments in a single monograph.

Nion's incredibly capable team, led by Niklas Dellby, Tracy Lovejoy, Chris Meyer, George Corbin, and myself, has done many amazing things. Aberration correction is now an established technique of electron microscopy, and we have focused on two new directions: developing flexible and user-friendly open-source software for imaging and analysis, and improving the energy resolution of electron energy loss spectroscopy.

Our software effort augments the advances made by aberration correction, making the instruments more powerful and user-friendly. The improved energy resolution would not have been possible without aberration correction: the monochromator and the electron energy loss spectrometer we have developed both use design principles we first introduced for aberration correction. The optical properties and unsurpassed stabilities of these instruments have pushed the energy resolution of EELS to 3 meV (100x energy resolution improvement relative to an electron microscope not using a monochromator), and 5 meV is attainable on a routine basis. This resolution level allows vibrational spectroscopy to be performed in the electron microscope, and it has opened up major new research areas: 0.2-2 nm spatial resolution imaging of phonons, including acoustic ones, and their interaction with crystal defects; the ability to detect and map hydrogen distributions; distinguishing different isotopes (Fig. 6); and damage-free analysis of organic and biological samples.

The ability to analyse the vibrational signature of biological samples without significant damage in the electron microscope is especially exciting. It relies on the fact that at the vibrational energies that we study (20-500 meV), the dipole interaction that excites optical phonons is delocalized, and it is possible to probe

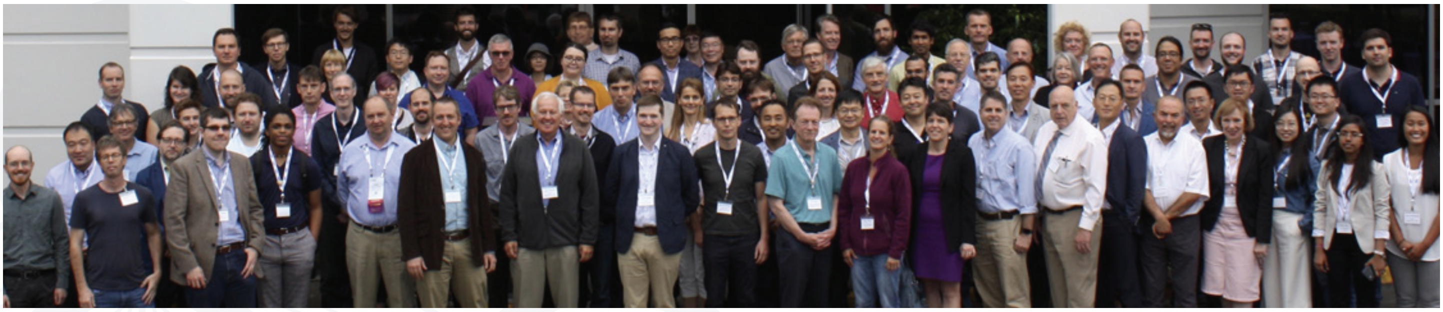


Fig. 7. August 2019 Nion Open House group photo showing the Nion team including Niklas Dellby, Tracy Lovejoy, Chris Meyer, George Corbin, Russ Hayner, Matt Hoffman, Peter Hrncirik, Nils Johnson, Josh Kas, Ben Plotkin-Swing, Lemek Robinson, Zoltan Szilagyi, Dylan Taylor, Janet Willis and Ondrej Krivanek, and Nion collaborators: Toshi Aoki, Nabil Bassim, Phil Batson, Andrew Bleloch, Wouter van den Broek, Peter Crozier, Christian Dwyer, Meiken Falke, Jordan Hachtel, Fredrik Hage, Bethany Hudak, Juan Carlos Idrobo, Demie Kepaptsoglou, Jani Kotakoski, Richard Leapman, Andy Lupini, Alan Maigne, Clemens Mangler, Molly McCartney, David Muller, Matt Murfitt, Xiaoqing Pan, Luca Piazza, Quentin Ramasse, David Smith, Rhonda Stroud, Toma Susi, Luiz Tizei, Kartik Venkatraman, Wu Zhou and many others.

molecular vibrations in sample areas 30-100 nm or even further away from the electron beam. The energy that can be transferred to the sample by each fast electron is typically limited to < 1eV when the beam is that far away, and there is no significant radiation damage. The spatial resolution is not as good as when the electron beam is brought onto the sample and non-dipole signals are utilized, but a technique that can probe what molecules are present where in frozen hydrated biological samples at 30-100 nm resolution should still have plenty of important uses.

I was pursuing this idea in a research stay in Christoph Koch's group at Humboldt University in Berlin, collaborating with Christoph, Benedikt Haas, Zdravko Kochovski, and Johannes Müller at Humboldt University, and Tracy Lovejoy, Niklas Dellby and Andreas Mittelberger at Nion. We had put together all the needed instrumentation and were about to start on experiments when the coronavirus pandemic hit, and I decided to return to Washington State. We plan to resume the work as soon as the pandemic allows. Instrumentation developments resemble probing an uncharted territory, similar to the way the American Pacific Northwest was explored by Alexander Mackenzie and David Thompson over 200 years ago. Best guesses as to what welcoming lands may lie in which direction are followed by the long slog of an expedition, with day-to-day ingenuity in overcoming hardships and obstacles making the difference between failure and success. All the explorers contribute their utmost, and random encounters sometimes bring critical pushes in the right directions. I am deeply thankful to my co-explorers at Nion and in the labs we collaborate with for their incredibly fruitful efforts (Fig. 7).

I am especially grateful to Niklas Dellby, with whom we founded Nion, and with whom I have enjoyed working together for nearly 30 years. Without his brilliance and hard work, the progress described here would not have been possible. What a voyage it has been!

Extended explorations are not easy on those we love, and it is their caring and support that allow us to go on. I thank my daughters Michelle and Astrid, and my nephew David, for their love and understanding, and I am deeply grateful to Eda Lacar (Fig. 8) for her love and support. She expands my horizons in many wonderful and unexpected ways, and makes me into a better person.

Fig. 8. Eda Lacar and Ondrej Krivanek in front of Arizona State University's Southwestern Center for Aberration-Corrected Electron Microscopy. The center houses three aberration-corrected electron microscopes and plays a world-leading role in nanocharacterization.

THE KAVLI PRIZE

BIOGRAPHIES
NEUROSCIENCE 2020

David Julius, Ardem Patapoutian

Photo: © UCSF

David Julius

is an American neurobiologist. He grew up in Brooklyn, New York, and obtained his Bachelor's degree in life sciences in 1977 at the Massachusetts Institute of Technology. He rejected the idea of studying medicine after enjoying undergraduate laboratory research and chose to do a PhD on peptide hormone biochemistry at the University of California, Berkeley, supervised by Randy Schekman and Jeremy Thorner, awarded in 1984.

He then joined Richard Axel at Columbia University where his interest in neuropharmacology led to the cloning of several receptors for serotonin and won him the 1990 NSF Presidential Young Investigator Award. Since 1990 he has held appointments at the University of California, San Francisco, where he discovered a family of ion channels sensitive to temperature and chemical stimuli which provide a molecular basis for touch and pain sensation. He continues this work today as the Morris Herzstein Chair in Molecular Biology and Medicine, and Professor and Chair of Physiology.

Julius was elected to the US National Academy of Sciences in 2004, the American Academy of Arts and Sciences in 2005, and became honorary member of the Hungarian Academy of Science in recognition of his work on the TRPV1 receptor for capsaicin and temperature.

Other recent awards include the 2017 Canada Gairdner International Award, the 2019 Rosenstiel Basic Medical Sciences Award (jointly with Ardem Patapoutian) and the 2020 Breakthrough Prize in Life Sciences.

Photo: © Scripps Research

Ardem Patapoutian

is a molecular biologist specialising in sensory signalling in the nervous system. He was born in Lebanon and attended the American University of Beirut before coming to the USA in 1986 and becoming a US Citizen.

He did his Bachelor of Science at the University of California, Los Angeles, awarded in 1990, followed by a PhD on developmental biology with Barbara Wold at Caltech, Pasadena. In 1996 he went to the University of California, San Francisco for postdoctoral studies on nerve growth factors with Louis Reichardt.

In 2000 Patapoutian joined the faculty of the Scripps Research Institute, La Jolla, where he is now Professor of Neuroscience. He has led the identification of ion channels and receptors involved in sensing temperature and touch, and regulation of proprioception and blood pressure.

Patapoutian's other recent honors and awards include the Alden Spencer Award from Columbia in 2017 (shared with David Ginty) and the 2019 Rosenstiel Award for Distinguished Work in Basic Medical Research (shared with David Julius). He was named an Investigator of the Howard Hughes Medical Institute in 2014, and was elected member of the National Academy of Sciences in 2017 and the American Academy of Arts and Sciences in 2020.

autobiography

by David Julius

By now, I have lived in Northern California for more than half my life, but I remain a native New Yorker in temperament and humor. I grew up in a seaside Brooklyn neighborhood – immortalized by Neil Simon's play 'Brighton Beach Memoirs' – that's been a landing pad for Eastern European immigrants like my grandparents, who fled Czarist Russia and antisemitism in pursuit of a better life. Consequently, my parents are first-generation Americans. They grew up in this NYC enclave, attended public schools, and earned first-class higher educations at tuition-free Brooklyn College, exemplifying what some of us still cherish as the American credo of open borders and opportunity for all.

My father, an electrical engineer, designed and maintained emergency power systems for the telephone company. My mother was an educator and teacher in the NYC elementary school system. Together with my two brothers, Martin and Arthur, we lived on the bottom level of a rather small 'semi-attached' house in Brighton Beach, with the top floor occupied by my maternal grandmother, aunt, uncle, and two cousins, Hope and Rachel. My paternal grandparents lived a few blocks away, in the same pre-war apartment where my father grew up. Quarters were close, but largely convivial, making for a small, close-knit and loving family unit in which modest resources were devoted to providing opportunities and experiences for us kids. My brothers and cousins have pursued careers in research, education, engineering and law. They are fantastic people who, like our parents, are warm, generous and socially minded.

With brother and mom in Brooklyn

Brighton Beach was dense and somewhat gritty, but not a bad place to grow up, with easy access to the beach and just a subway ride from the metropolis of Manhattan. And in the days before 'dynamic pricing,' museums, concerts and Broadway shows were generally affordable, enabling even a middleclass kid to experience transformative culture moments. At the same time, there was plenty of opportunity for pickup games of basketball or summer frolicking at the beach alongside a million or more New Yorkers who would flock to Brighton or nearby Coney Island to catch a breeze on a hot and muggy summer day.

As a child in Brooklyn

Like my parents, we all attended public schools. I was pretty much a reluctant student who often turned in my assignments late (or not at all) and generally tried to stay below the teacher's radar. At some point, around 5th grade, I decided that it was time to put in a little more effort and be less afraid of failure, and then things got easier and more inspiring academically. I attended Abraham Lincoln High School which has a storied past with an impressive list of alumnae ranging from notable writers (Arthur Miller, Joseph Heller, Mel Brooks) and performers (Beverly Sills, Neil Diamond, Harvey Keitel, John Forsythe) to scientists (Arthur Kornberg, Paul Berg, Jerome Karle). In my day, the student body was perhaps not as distinguished, but I met some smart and fun friends with whom I explored the theaters and Greenwich Village clubs of NYC, which is what I remember most about this formative time in my life. Academically speaking, I was exceedingly fortunate to enroll in a physics class taught by Mr. Herb Isaacson, a minor league baseball player turned educator. Mr. Isaacson was a fireball who challenged us with ideas, not facts, and expected enthusiastic participation in return. He made physics fun (and even relevant to baseball) and I credit him for making me wonder whether science could be a career trajectory.

Like my older brother, Martin, I expected to enroll in a NY State college, but a classmate suggested that I apply to MIT, which I had never heard of. No one in my family had attended a private college, but I decided to give it a try and was shocked when a letter of acceptance showed up in the mailbox. MIT wasn't exactly the freewheeling college scene that some of my friends were enjoying elsewhere, but it was an unusual place that I learned to appreciate for its quirkiness and intensity. For me, the magic path was UROP – the Undergraduate Research Opportunity Program – that helped students find laboratories in which they could gain hands-on research experience. In my sophomore year, I worked with Janis Fraser, a graduate student in Joel Huberman's lab who was determining how Okazaki fragments are incorporated into replicating DNA. When Janis stopped doing bench work to write her thesis, I then moved down the hall to work with

MIT graduation

her husband, Tom, in Alex Rich's lab, where I spent the next two years using modified transfer RNAs to study the kinetics and specificity of aminoacylation and how this might influence the fidelity of ribosomal protein synthesis. Working in Alex's lab was a great experience and a sanctuary from classes and problem sets. And I came to realize that designing, executing and interpreting experiments satisfied my intellectual curiosity while also providing an outlet to do something creative at the bench – much like a hobby. I also sensed that science attracted an interesting and eclectic group of people who accepted the uncertainty of discovery for a somewhat more independent and self-determined lifestyle. A case in point was Ned Seeman, at the time a postdoctoral fellow in Alex's lab, who went on to become an originator of nanobiology and a Kavli Laureate in Nanoscience. I was even able to publish a modest paper from my efforts in the lab, providing some evidence that I could be productive in this line of work.

Another great outcome of working in Alex's lab was meeting Simon and Laura Litvak, Chilean nucleic acid biochemists who were on sabbatical from the University of Bordeaux, France. I somehow convinced the Litvaks to let me work in their lab during the summer between junior and senior years, which turned out to be one of the most formative and memorable times in my life. Aside from purifying a couple of enzymes (tRNA nucleotidyl transferase from wheat germ and yeast), I thoroughly enjoyed Bordeaux and its environs, learned something about red wine, and came to appreciate the fact that scientists are privileged to be part of a vibrant international community. Simon and Laura were amazing mentors and we have remained in touch ever since.

Having decided on a career in biomedical research, I applied to several graduate programs but received mostly rejections. However, sometime late in the academic year I got a telegram informing me that I'd been accepted to the Biochemistry Graduate Program at Berkeley, initiating my long-term association with an amazing public institution, the University of

David Julius in the laboratory at UC Berkeley

California. Owing to some unforeseen events and good luck, I came to carry out my graduate studies under the joint mentorship of two young dynamos, Jeremy Thorner and Randy Schekman, who were exploiting Saccharomyces yeast to study pheromone signaling and protein secretion, respectively. I worked on a project at the interface of their two labs that involved understanding how a peptide mating pheromone called alpha-factor is synthesized and secreted by these cells. Like many mammalian peptide hormones, alpha-factor is proteolytically cleaved from a larger polyprotein precursor and thus stood as an excellent model system for identifying enzymes and secretory pathways involved in their biosynthesis. Together with Buff Blair and Tony Brake, we succeeded in this endeavor, with the most exciting discovery emerging in the last few months of my graduate studies when I identified the KEX2 pro-protein convertase as the defining member of a family of furin/subtilisin-like proteases that cleave polypeptide precursors at paired basic amino acids to liberate bioactive hormones, activate viral surface glycoproteins, etc. Such enzymes had been sought for decades, but it was the combined power of yeast genetics and biochemistry that finally brought one to light.

When I was in Alex Rich's lab, Ned Seeman told me that graduate training was a process of gradual maturation leading to a moment of crystallization in which you would suddenly realize that you had reached a state of intellectual clarity and confidence. I think there is some truth to this, which I experienced in my last year or so at the University of California, Berkeley and have witnessed with many of my own students. But this is really a product of daily cumulative influences from all of one's lab mates, collaborators and mentors – and in this regard, I was incredibly fortunate to have come under the tutelage of Jeremy and Randy. They were (and still are) passionate, intense and rigorous in their approach to science, and attracted likeminded students and fellows to their labs. At the same time, they gave us latitude to be creative and make our own mistakes. Both were approachable and have a cutting sense of humor, which helped foster a more informal 'West Coast' atmosphere in the lab that appealed to me and likely influenced my decision to eventually settle in the Bay Area.

After an exhilarating and very productive era at Berkeley, it was time to move on. Yeast was such a powerful system with a bright and broad future, but I decided to use my time as a postdoctoral fellow to explore new and different territory. Two streams of thought converged: my focus on pheromone processing made me wonder about the molecular and physiological actions of hormones and neurotransmitters in the brain; and perhaps influenced by Bay Area history, I became fascinated by the pharmacology of hallucinogens, opiates, and other natural products that societies have used over millennia to alter consciousness and sensory experience. I began reading books and articles from cultural figures and writers like Timothy Leary and Tom Wolfe but was mostly influenced by papers from scientists - notably Sol Snyder and George Aghajanian - who had used LSD and related ergots to probe serotonergic and other endogenous neurotransmitter systems. Their studies suggested that monoamines like serotonin and dopamine each interact with pharmacologically distinct sites in the brain, but there was no understanding of how such receptor subtype diversity might be manifest at a molecular level. This seemed like a fantastic problem to explore, with great relevance to neuropsychiatric disease.

Around this time (1983), a paper from Richard Scheller, Eric Kandel and Richard Axel caught my eye in which they cloned cDNAs encoding precursors for peptide hormones controlling egg laying and related behaviors in Aplysia sea snails. This was relevant to my thesis project, but more importantly enticed me to enter the new frontier of molecular neurobiology. I applied to Richard for a postdoctoral position (not realizing that he was already quite well known for developing methods for gene transfer into animal cells), expressing my interest in cloning a serotonin receptor gene. Richard agreed that this was a worthwhile goal and I returned to NYC in the winter of 1984 to begin my fellowship with him at Columbia University. Richard is a person of intense curiosity and intellect who encouraged his fellows to pursue challenging projects and establish their own scientific persona. Consequently, and especially in the pre-olfaction days of the lab, many of us forged our own trajectories along diverse areas, but often with an immediate goal of cloning genes that define a key cell type or physiological process. Having come to the lab with no experience in neurobiology, vertebrate physiology, or mammalian molecular genetics, I had a lot to learn and spent several years spinning my wheels. But I also had the benefit of advice from great Axel lab friends (Greg Lemke, Moses Chao and Dan Littman) and local collaborators (Amy MacDermott and the late Tom Jessell) and after many false starts, I finally achieved my goal by cloning a serotonin receptor (the 5-HT1c/2c subtype) from a rat brain using a function-based screening strategy. Altogether, my postdoctoral stint lasted six years with a burst of productivity in the last two. Those middle years, fraught with competition, tested my endurance and confidence, but Richard supported me throughout and never (at least to my knowledge) lost faith – something that I have always appreciated and bear in mind when encouraging my own trainees to undertake exciting but risky projects. I also learned from Richard how important (and intellectually rejuvenating) it is to have fellows develop an independent scientific trajectory that they can then take with them. Indeed, no one has a more impressive list of protégés than Richard, which is a part of his legacy that many of us strive to emulate.

Having at long last accomplished my goal, I accepted a faculty position at University of California, San Francisco and moved back to the Bay Area in late 1989 to start my own group. UCSF seemed like a good choice because, in addition to having a stellar reputation in familiar areas (molecular genetics and biochemistry), it was also home to a first-class neuroscience community, which I knew would be essential for my future growth and development. Indeed, the challenge now was to begin thinking more like a physiologist, which can be a tough transition for someone trained as a reductionist biochemist. While intending to spend my time immersed in the vast biology of serotonergic systems, I realized that the world of G protein-coupled receptors was getting immensely crowded and I therefore pivoted to ion channels, transitioning with cloning of 5HT3R (the one ionotropic serotonin receptor subtype), followed by nucleotide-gated (P2X2) channels.

One important outcome of this work was to bring our attention to primary afferent sensory neurons, where these channels are highly expressed. I became intrigued by the idea of studying somatosensation, which was arguably less well understood at a molecular level compared to other sensory systems - and possibly more mechanistically complex in having to detect both chemical and physical stimuli. Moreover, the goal of linking molecular events to behavior seemed more attainable with sensory systems, with the added benefit of possibly finding new inroads to diagnose and treat an unmet clinical problem, chronic pain. Another major selling point was the possibility of exploiting natural product pharmacology to gain a toehold in this area, bringing me back to what had enticed me into neuroscience in the first place. Jancsó and his team in Hungary had famously shown that capsaicin, the pungent principle in chili peppers, was an excitatory agent for a subset of somatosensory neurons, making capsaicin sensitivity a defining functional hallmark of nociceptors. Thus, identifying a mythical capsaicin receptor became something of a Holy Grail in the pain field, but also a frustratingly elusive goal.

For us, the Eureka moment came when Michael Caterina joined my group and successfully spearheaded our efforts to identify the capsaicin receptor (now called TRPV1) using an elegant expression cloning strategy. Together with Makoto Tominaga and others, he then showed that TRPV1 is a heat-activated ion channel, providing a cogent molecular explanation for a widely appreciated psychophysical experience – the 'hotness' of chili peppers. Taking this approach to its logical 'flip side', David McKemy and Werner Neuhausser used menthol to identify a related ion channel (TRPM8) as a cold receptor. These studies revealed a molecular logic of thermosensation while more generally illustrating how somatosensory neurons can detect noxious chemical or physical stimuli. Subsequent discoveries by us and many groups have further highlighted roles for TRP channels (and neurons that express them) in acute and chronic pain and itch, reflecting the ability of these beautifully complex polymodal signal integrators to regulate excitability of the nociceptor in the face of injury or other physiological perturbations. Exploiting these channels to develop non-opioid analgesics remains an important translational goal that has not yet come to fruition, but about which I remain optimistic.

A lot has happened since I started my own lab, but it's still hard to believe that I've been at UCSF for 30 years! No institution is perfect, but I've stayed at this one because it is home to so many energetic and creative colleagues who have expanded my scientific horizons, and with whom I have developed wonderful, long-lasting friendships and collaborations. Chief among these is Allan Basbaum, who has inspired me and our trainees to connect molecular and biophysical findings to pain behaviors and chronic pain syndromes, giving our work greater intellectual depth, impact and translational relevance. Roger Nicoll, my immediate neighbor and legendary neurophysiologist, has been a mentor and role model for me and my trainees - always challenging us to put our hypotheses to the test with the cleanest, most rigorous experiments. Allan, Roger and I also share a similar brand of humor, which is a mainstay of our interactions.

And then there is Yifan Cheng, with whom we have experienced another Eureka moment by leveraging recent advances in electron cryo-microscopy (cryo-EM) to visualize our favorite TRP channels in atomic detail. Seeing is, indeed, believing and the thrill of capturing these channels in various conformational states and in complex with drugs and toxins has been breathtaking. This work began as a synergistic collaboration between two fellows, Erhu Cao and Maofu Liao, and flourished from there over the past seven years to include other channels and trainees. Being part of the cryo-EM 'resolution revolution' has been a thrill as we have watched its impact go far beyond sensory neuroscience. Importantly, our timely contributions to this area were made possible by transformative

Me and my parents

Hiking with family in Thailand

Hiking with Holly in Patagonia

innovations from the Cheng and Agard labs here at UCSF, once again validating this institution as a special place to do science.

The other great collaboration in my life has been with my wife, Holly Ingraham,

The Julius lab enjoys an afternoon of baseball at nearby San Francisco Giants Stadium, circa 2013

also a scientist and professor at UCSF. Holly is well known for her molecular and biochemical studies of neuroendocrine physiology and development, and any appreciation that I may have for integrative physiology comes from watching her intuitive and creative approach to science. Aside from that, she is a talented, generous and loving partner who makes the world a better place for me, our families, friends and colleagues. Together, we have raised a boy, Philip, whose interest cleave more to the arts than science, but I think he is actually the most creative spirit in our household. And both Holly and Philip tolerate my attempt to play trumpet music, which also speaks to their gracious flexibility.

My other family, of course, is the community of superbly talented students and fellows who have honored me by choosing to spend part of their career in the Julius lab doing exceptional and impactful science. My group has never been large (usually around eight members at any given time), but an intense, yet collegial and collaborative atmosphere has created synergy that works to the benefit of all. I am proud to say that many Julius lab alums now head their own successful research groups and are leaders in their fields, thus carrying on the legacy of my own mentors.

In closing, I would like to thank the Neuroscience Kavli Prize Committee for choosing somatosensation and pain as a topic worthy of recognition. Chronic pain remains a largely unmet medical need (as highlighted in this country by the opioid epidemic) and it is only through basic, curiosity-driven research that we will find new mechanism-based solutions to this pressing problem. I've written this autobiography from my home, where we have been 'socially isolating' in the initial phase of the coronavirus pandemic. We live in a paradoxical time when increased access to information is accompanied by a strain of anti-intellectualism and a distrust of those with knowledge and expertise. But it is only through fact-based thinking and decision making that we will navigate through the current situation and other challenges that come our way. The Kavli Prizes hopefully inspire and remind us about the importance that intellectual pursuit, discovery and basic scientific research play in the vibrancy, health and general well-being of our world.

THE KAVLI PRIZE

autobiography

by Ardem Patapoutian

I was born in Beirut, Lebanon, where my mom was an elementary school teacher and principal and my dad was a writer and accountant. The youngest of three kids, I was eight years old when the Lebanese Civil War began. Life was often understandably stressful, with curfews, limited hours of electricity, and the not infrequent explosion. As Armenians, we were usually treated as quasi-neutral parties to the Christian-Muslim strife, and I attended small Armenian schools which continued shrinking in class size as more families escaped the war. By my freshman high school year, we were down to five students, all dear pals, where I was perhaps middle of the pack in my subjects but definitely the shortest in stature. The school closed the next year, and I moved

At four years old, with older brother and sister next to the Mediterranean Sea in Beirut, Lebanon, ca 1970

At age 13, front and center with basketball, Beirut, circa 1980

to a multicultural and academically rigorous private high school where I initially flailed but eventually found a knack for math and science classes, a classic late bloomer.

I had three havens of childhood I remember with fondness: my sports club where I played basketball (not well, see height above) and table tennis (local champ!), our trips to the Mediterranean Sea and the wooded mountains surrounding Beirut, and the beautiful campus of the American University of Beirut, where I attended one year of undergraduate classes as a pre-med major. However, the conflict continued to escalate, and one fateful and terrifying morning, I was captured and held by armed militants. A few months later, I moved to Los Angeles.

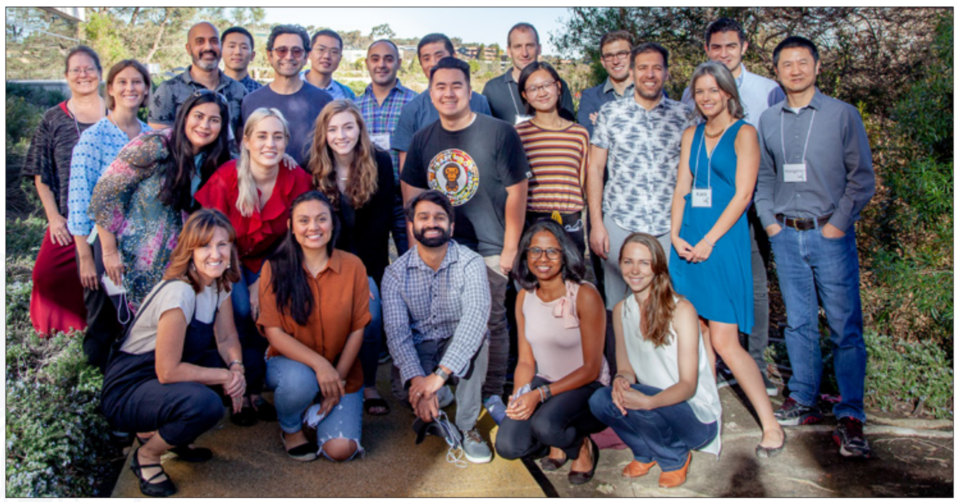
This first year in LA was a different kind of struggle to adapt, perhaps as challenging a year as a young adult as any I had experienced as a child in Beirut. Suffice to say, a highlight was writing horoscopes for the local Armenian newspaper. What a relief it was to gain admission to UCLA to resume my student life. A significant event was joining Judy Lengyel's Drosophila lab and learning molecular biology from her graduate students Eirikur Steingrimsson and Richard Baldarelli. These guys were exceedingly generous and patient in training me, and the work they were doing seemed like so much fun. A gold rush time during fly genetics, we identified the tailless gene responsible for establishing polarity in the developing body plan, resulting in a still-cherished fifth-author publication. And the lab lifestyle – happy hours, crazy hours, flexible hours – these things were so novel to me and such a treat. Working as part of a team, collaborating to contribute to a project, proved to be addictive, indeed a new identity. Having fun and having it together with a tribe of international, curious, oddball nerds became two goals I have kept since those first days as a budding researcher.

A favorite trip with Nancy and Luca to the Galapagos islands in 2009, 200 years after the birth of Charles Darwin

Finding out that graduate school paid a $1000 monthly stipend was the nail in the coffin for medical school, and I made my next scientific home at Caltech. I continued along the path of studying transcriptional regulation in developmental biology, now in the context of muscle differentiation in the lab of Barbara Wold. Barb taught us to think big, rather than getting too bogged down in the smaller details of a mature field of inquiry, another goal in my research life. I also collected more treasured memories of another lovely campus, wonderful colleagues, productive collaborations, and fun times doing photography, cooking at the Prufrock House, and running the famous 24-hour KELROF relay race.

Donning Caltech regalia with Scripps Research President Peter Schultz at the 2019 graduation ceremony in La Jolla, CA

A 2019 lab reunion brought together current and past members of the Patapoutian group to Scripps Research for a symposium



Bertrand Coste, whose postdoctoral research identified PIEZO1 and 2, comes back to San Diego for a visit in 2018

For postdoctoral studies, I joined the lab of Louis Reichardt at UCSF where I shifted to the developmental program driving subtype specificity of the somatosensory neurons that initiate touch and pain. Lou became a key model for me in how to run a lab, granting us a great deal of independence while always being a strong supporter. He allowed me to pursue a slew of projects, many leading to dead ends or fizzling, but three eventually grew into related insights on how secreted neurotrophins drive survival and specialization of these sensory neurons. When not at the bench, we attended so many terrific seminars, all packed, seemingly enough to go to at least one a day, and I soon became a typical San Francisco coffee and food enthusiast.

During this period of studying the development of these sensory neurons, it gradually became more urgent to me that the defining proteins that underlie the function of these cells, the molecules that allow them to detect physical stimuli such as temperature and mechanical force, were largely a mystery. On the temperature front, David Julius across campus had recently cloned TRPV1 as an ion channel activated by heat. Following the visionary Peter Schultz to San Diego, I established my new lab at Scripps Research and set out to test whether other TRP channels were temperature

A 2019 backpacking trip to Evolution Valley in the Eastern Sierras of California with Dorris Neuroscience colleagues Michael Petrascheck (left) and Anton Maximov (right)

channels. My fantastic trainees collaborating with Novartis indeed found TRPM8 and TRPA1 as cold and noxious stimuli sensors. But which channels convert mechanical forces to neuronal signaling, thereby initiating the senses of touch, proprioception (body position in space), and pain? Pete created an environment where I could branch out and scale to tackle these fresh directions.

To identify the proteins that turn pressure into sensory neuronal activity, an amazing postdoctoral fellow in my lab, Bertrand Coste, screened a panel of cell lines to find one responsive to piezo-electrically applied mechanical force, and then proceeded to knock-down candidate genes encoding channel-like proteins. A grueling, low-throughput functional screen, this technical feat identified PIEZO1 and 2, two very large, multiple membrane-pass ion channels expressed in a variety of cell types. Over the following years, Bertrand and other dedicated trainees have fleshed out which of the two channels is responsible for an astonishing number of physiological roles that depend on pressure sensing, while chasing other channels involved in yet more sensory pathways. I hope they are having as much fun as I am in pursuing such science, and I am exceedingly proud of how well they collaborate with each other and with our expert colleagues around the world. Near and dear amongst those colleagues are my fellow faculty of the Dorris Neuroscience Center, who are not only tremendous minds but able bodies who help me enjoy the waters of La Jolla Cove and the wilderness of the Sierra Nevada.

On this occasion of looking back, the role of the Howard Hughes Medical Institute cannot be understated. Their mission of supporting "people not projects" completely aligns with the spirit of modern biology as an integrative and cross-specialty field. The freedom to pursue major innovations, gaining rapid expertise through collaboration, has fueled my research program, and of course I think this is the most fun way to do science. It goes without saying that the role of the National Institutes of Health has been vital to the very existence of basic biomedical research in the U.S., and I sincerely hope our country, and indeed the world, has a newfound level of appreciation for the impact biology research has on human health.

Returning to my appreciation, my family has been a profound source of happiness without which all the science would be hollow. As Kavli Prize Laureate Jim Hudspeth so memorably put it, my first, favorite, and only wife, Nancy, is my intellectual and moral compass, challenging my thinking and ego and reminding me of better angels. Our dear son, Luca, is a constant surprise, who we dare not be too proud of lest we flatter ourselves. My family, including my parents Sarkis and Haigouhie and siblings Ara and Houry, have provided unwavering love and encouragement.

And lastly in gratitude, I acknowledge the extreme privilege to be a scientist. The intellectual nourishment, the richly diverse universe of co-conspirators, the beautiful places around the world where science has taken me, the wonders and mysteries of the human body – what joy, what fortune.