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THE ROYAL SWEDISH ACADEMY OF SCIENCES

The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry 2017 to **Jacques Dubochet**, **Joachim Frank** and **Richard Henderson** "for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution".

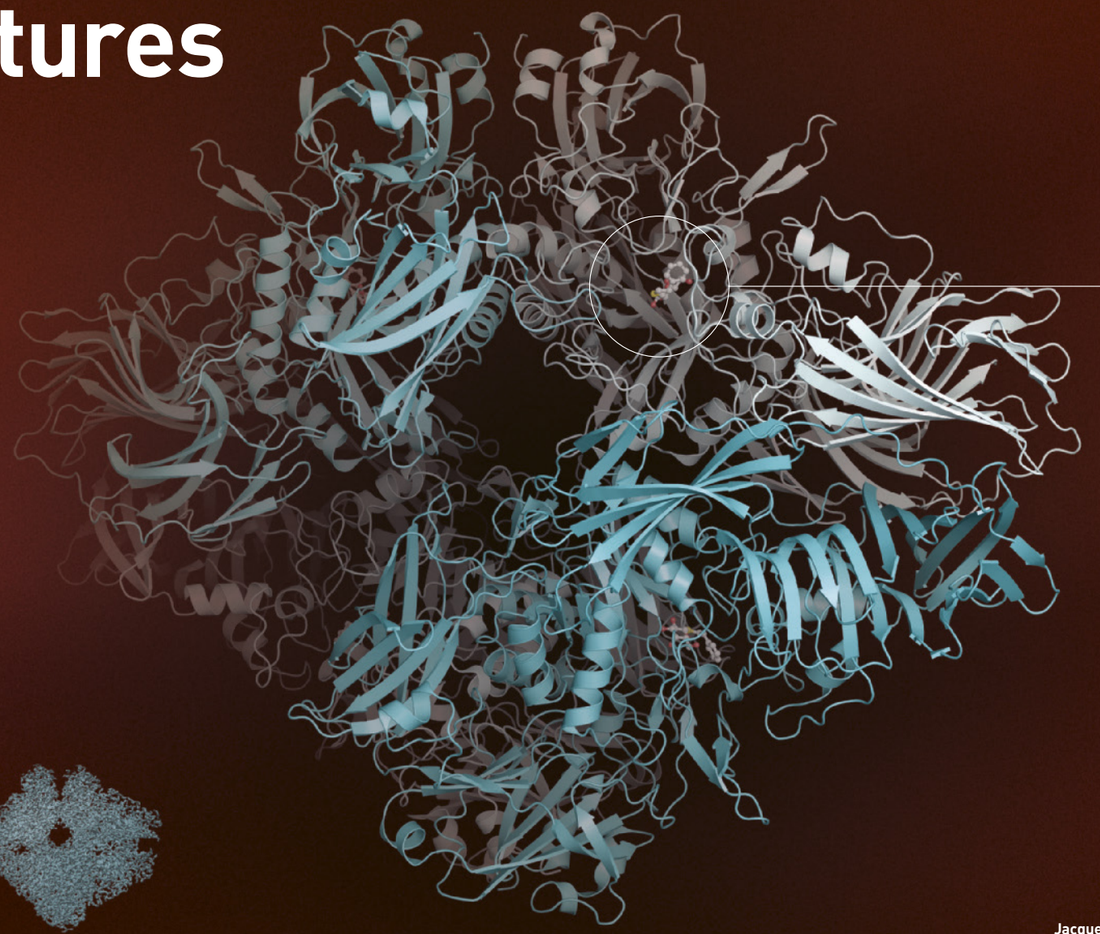
The Nobel Prize 2017 **in Chemistry**

Cool microscopy captures life in atomic detail

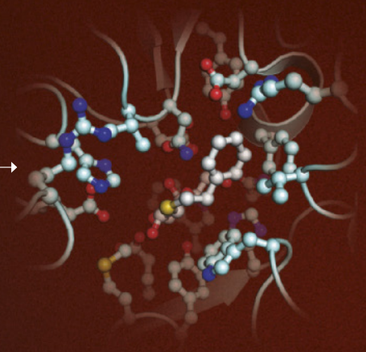
Jacques Dubochet, Joachim Frank and Richard Henderson have been awarded the Nobel Prize in Chemistry 2017 for their development of an effective method for generating three-dimensional images of the molecules of life. Using cryo-electron microscopy, researchers can now freeze biomolecules mid-movement and portray them at atomic resolution. This technology has taken biochemistry into a new era.

A picture is a key to understanding. Scientific breakthroughs often build upon the successful visualisation of objects invisible to the human eye. However, biochemical maps have long been filled with blank spaces because the available technology has had difficulty generating detailed images of life's molecules. Cryo-electron microscopy changes all of this. Scientists can now generate models of the cells' complex machineries at atomic resolution, which is decisive for both the basic understanding of life's chemistry and for the development of pharmaceuticals.

Electron microscopes were long believed to only be suitable for imaging dead matter, because the powerful electron beam destroys biological material. But in 1990, Richard Henderson succeeded in using an electron microscope to generate a three-dimensional image of a protein at atomic resolution. This breakthrough proved the technology's potential and Richard Henderson predicted the revolution that cryo-electron microscopy is currently experiencing. The desired atomic resolution was reached in 2013, and researchers can now routinely produce three-dimensional structures of biomolecules. Biochemistry is all set for an exciting future!

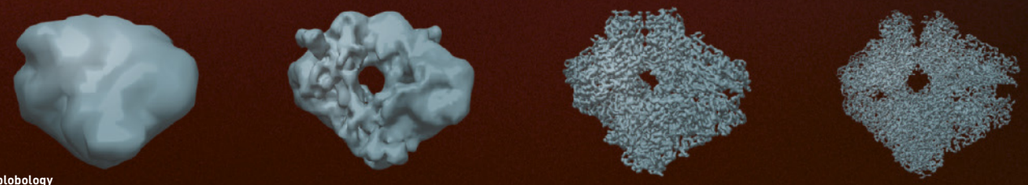


2015: atomic resolution



From blobology to atomic resolution

Over the past 30 years, every nut and bolt of the electron microscope has gradually been optimised. Resolution has improved, Ångström by Ångström, and Richard Henderson has had a central role in this development. The final technical hurdle was overcome in 2013, when a new type of electron detector came into use. Electron microscopy now routinely provides 3D images that show each and every atom in life's molecular machineries, allowing scientists to depict everything from proteins that confer resistance to antibiotics to the Zika virus.



2005: blobology

Cool method protects the samples

In the early 1980s, Jacques Dubochet developed the sample preparation method that has enabled the development of cryo-electron microscopy. The samples are cooled extremely rapidly, so that water solidifies in its liquid form – it vitrifies. Cooling prevents the sample from drying out in the electron microscope's vacuum, and from incineration by the harsh electron beam.

1. The sample to be studied is transferred to a metal mesh and excess material is removed.

2. The sample forms a thin film across the holes in the mesh. It is shot into liquid ethane, which is cooled by liquid nitrogen, –196 °C.

3. The water in the sample solidifies in its liquid form. During the measurements in the electron microscope the sample is cooled by liquid nitrogen.

Many fuzzy pictures form a sharp whole

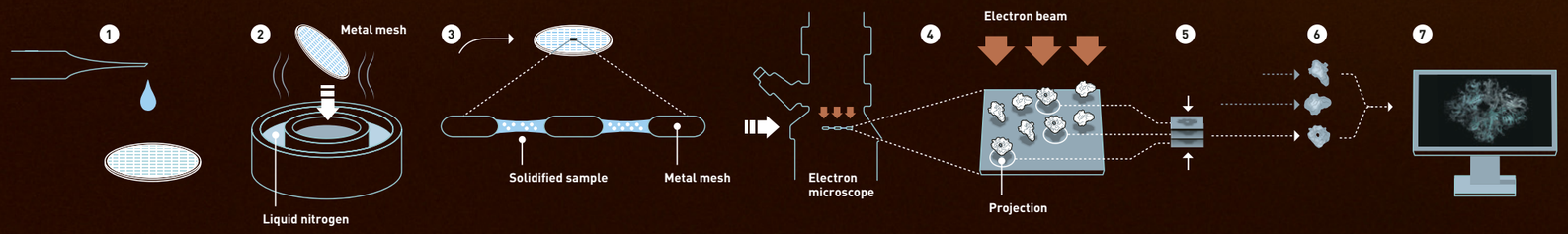
The fuzzy 2D images from the electron microscope are analysed and merged to reveal a sharp 3D structure, using the image processing method developed by Joachim Frank between 1975 and 1986.

4. Randomly oriented proteins are hit by the electron beam, leaving a trace, a projection, on the image.

5. The computer discriminates between the traces and the fuzzy background, placing similar ones in the same group.

6. Using the information gathered from thousands of low-resolution images, the computer generates a high-resolution 2D images.

7. The computer calculates how the different 2D images relate to each other and generates a high-resolution structure in 3D.



Jacques Dubochet
Born 1942 in Aigle, Switzerland. Honorary Professor of Biophysics at the University of Lausanne, Switzerland.

Joachim Frank
Born 1940 in Siegen, Germany. Professor of Biochemistry and Molecular Biophysics and of Biological Sciences at Columbia University, New York, NY, USA.

Richard Henderson
Born 1945 in Edinburgh, Scotland. Programme Leader at MRC Laboratory of Molecular Biology, Cambridge, UK.

Photo: portrait of Jacques Dubochet: Felix Imhof. © UNIL. portrait of Joachim Frank: Brian Wirkowski. © Columbia University Medical Center. portrait of Richard Henderson: Neil Grant. © MRC Lab of Molecular Biology

FURTHER READING More information on the Nobel Prize in Chemistry 2017: *www.kva.se/nobelchemistry2017* and *www.nobelprize.org* **ARTICLES:** ● **Dubochet, J.** (2016) A Reminiscence about Early Times of Vitreous Water in Electron Cryomicroscopy. *Biophys J.*, 110, 756-757. ● **Elmes, J.** (2016) Interview with Richard Henderson. *Times Higher Education, www.timeshighereducation.com/people/interview-richard-henderson-university-of-cambridge* ● **Gelfand, A.** (2016) The Rise of Cryo-Electron Microscopy, *Biomedical Computation Review, http://biomedicalcomputationreview.org/sites/default/files/riseofc-e_bcr-spring-2016-web.pdf* ● **Mossman, K.** (2007) Profile of Joachim Frank, *Proc. Natl Acad. Sci. USA, 104*, 19668-19670. ● **Wilson, R.** and **Gristwood, A.** (2015) Jacques Dubochet. www.embl.de/aboutus/alumni/news/news_2015/20150709_dubochet/ **VIDEOS:** ● **Serious Science** (20 June 2017) *Electron Cryomicroscopy — Richard Henderson*, www.youtube.com/watch?v=L6U--sYUF9s ● **Serious Science** (22 Aug. 2017) *Single-Particle Electron Microscopy - Richard Henderson*, www.youtube.com/watch?v=j_sfs6uwWlc ● **The Franklin Institute** (5 July 2016) *Joachim Frank — 2014 Laureate of the Franklin Institute in Life Science*, www.youtube.com/watch?v=mtvht8Uyh2s ● **More references can be found in the Scientific Background:** *www.kva.se/nobelchemistry2017*

Editors: Peter Brzezinski, Gunnar von Heijne and Sara Snogerup Linse, The Nobel Committee for Chemistry, The Royal Swedish Academy of Sciences; Ann Fernholm, Science Writer; Clare Barnes, Translator; Carl-Victor Heinold, Editor, and Anna Nyhlén, Nobel Assistant, The Royal Swedish Academy of Sciences.
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