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The Royal Swedish Academy of Sciences has decided to award the Nobel Prize in Chemistry for 2014 to **Eric Betzig**, **Stefan W. Hell** and **William E. Moerner** "for the development of super-resolved fluorescence microscopy".

The Nobel Prize 2014 **in Chemistry**

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Their microscopes crossed the threshold

Optical microscopy had long been hindered by a presumed limitation: that it was impossible to achieve a resolution better than half the wavelength of light. Eric Betzig, Stefan W. Hell and William E. Moerner are awarded the 2014 Nobel Prize in Chemistry for ingeniously bypassing this limitation. Their revolutionary work has taken optical microscopy to nano dimensions.

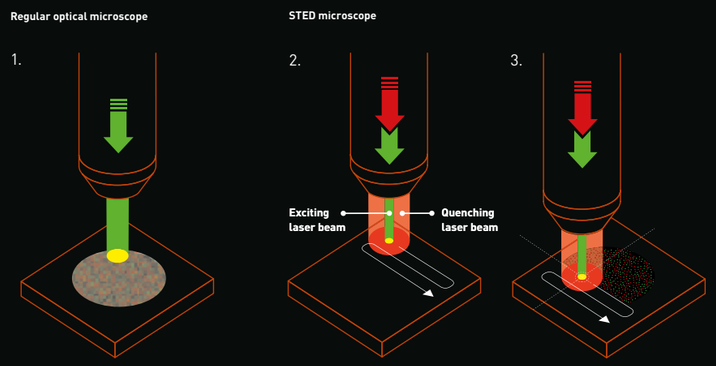
Using what is now called nanoscopy, researchers can see the paths of individual molecules inside living cells. For example, they can see how molecules form synapses between the brain's nerve cells or follow aggregating proteins in cases of Parkinson's, Alzheimer's or Huntington's disease.

Optical microscopy is one of the most important tools in the life sciences, allowing researchers to observe processes inside living cells. However, it had long been thought that it would be impossible to discern a cell in molecular detail. In 1873, microscopist Ernst Abbe determined a threshold for optical microscopy: its resolution would never be better than half the wavelength of light, approximately 0.2 micrometres – but, thanks to the 2014 Nobel Laureates in chemistry, optical microscopy can now be used to observe the nano world.

Two different principles are being recognised and rewarded; both build upon researchers labelling the objects to be studied with fluorescing molecules. The idea for one of the microscopy methods, *stimulated emission depletion (STED)*, came to Stefan Hell in 1993, and he realised it experimentally in 2000.

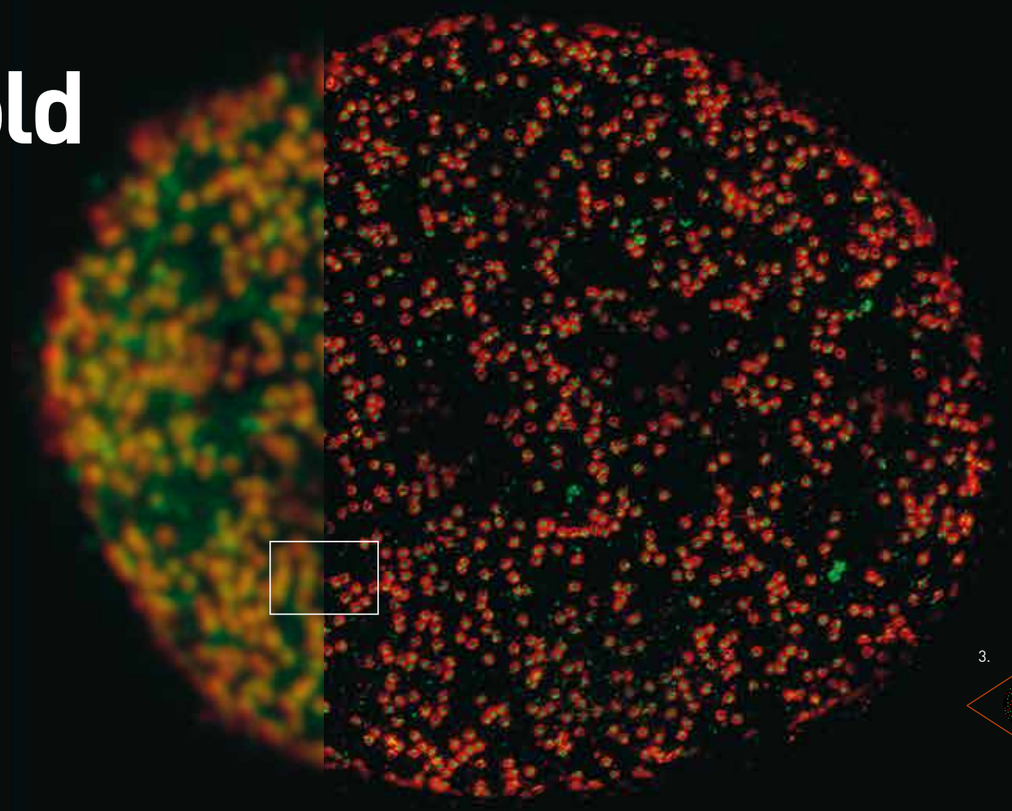
The theory behind the second method, *single-molecule microscopy*, was laid out by Eric Betzig in 1995 – but it was William Moerner who built its practical foundations in 1989, when he was the first person to detect a single fluorescing molecule. The second decisive step was taken by Moerner in 1997, when he developed a tiny molecular lamp that he could turn on and off. Thanks to these successes, Betzig was able to actualise single-molecule microscopy in 2006.

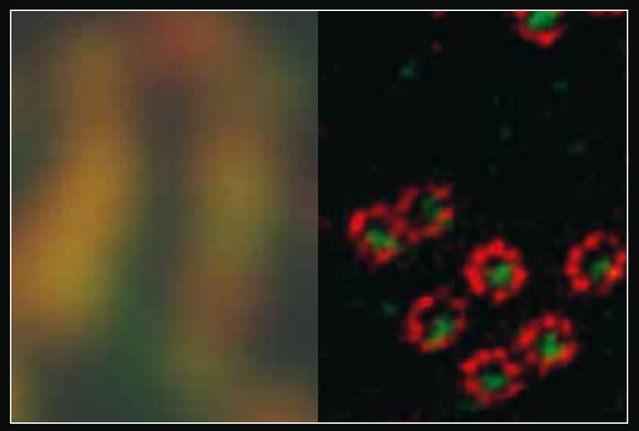
The principle of STED microscopy



2000 – Hell develops STED microscopy

1. In a regular microscope the light beam is broad and the resolution is never better than 0.2 micrometres.
2. Stefan Hell started to use two laser beams in a microscope. One excites all the fluorescing molecules which make them glow. The second, which is ring-shaped, quenches all the fluorescing molecules apart from those within a nanosized volume.
3. The laser beams sweep across the sample, nanometre by nanometre. The researchers know exactly where the beam hits the sample and can use this information to process the image, resulting in a resolution that is far better than 0.2 micrometres.





2006 – Betzig develops single-molecule microscopy

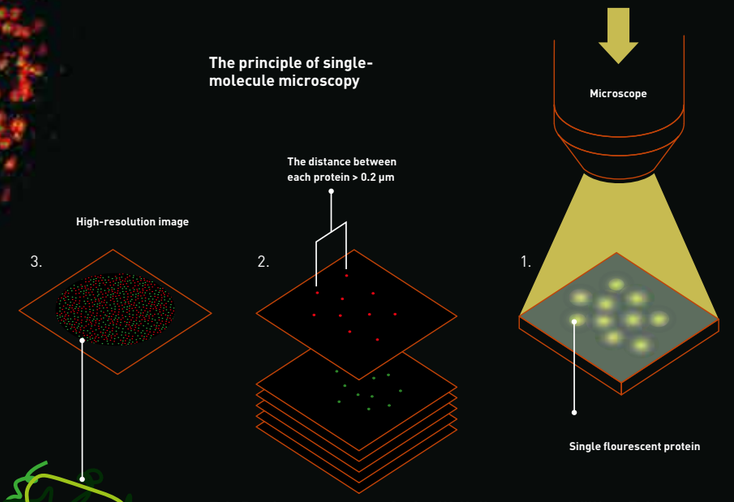
1. In 2006, Eric Betzig circumvented Abbe's limit using a variant of GFP similar to that produced by Moerner. Using a weak pulse of light he turned on a fraction of all the fluorescing GFP in a sample. Because so few were excited the distances between them were large and the microscope could discern every single GFP. They remained lit until they faded while an image was registered.

Betzig then turned on a new subgroup of GFPs and took a new picture. The procedure was repeated until all the GFPs in the sample had been observed and a thousand images had been registered.

2. The blurry images were processed using probability theory so that they became much sharper.

3. When Betzig layered all the images on top of each other, they produced a high-resolution image in which individual proteins could be discerned.

The principle of single-molecule microscopy



↑ The picture shows a cell nucleus and proteins that form pores leading into and out from the nucleus. Important molecules are transported in and out of the nucleus through these pores. The picture was taken using STED microscopy.

1989 – Moerner lays the foundation for single-molecule microscopy ↑

Single-molecule microscopy builds upon a discovery that was awarded the Nobel Prize in Chemistry 2008: the *green fluorescent protein (GFP)*. Using gene technology, researchers couple GFP to other proteins they want to study in a cell. GFP functions as a molecular lamp that shows where the protein is. In 1997, William E. Moerner found a variant of GFP that could be turned on and off, like a tiny molecular lamp with a switch.

Eric Betzig
U.S. citizen. Born 1960 in Ann Arbor, MI, USA. Group Leader at Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, VA, USA.

Stefan W. Hell
German citizen. Born 1962 in Arad, Romania. Director at the Max Planck Institute for Biophysical Chemistry, Göttingen, and Division Head at the German Cancer Research Center, Heidelberg, Germany.

William E. Moerner
U.S. citizen. Born 1953 in Pleasanton, CA, USA. Harry S. Mosher Professor in Chemistry and Professor, by courtesy, of Applied Physics at Stanford University, CA, USA.

FURTHER READING! More information on the Nobel Prize in Chemistry 2014: *http://www.kva.se/nobelchemistry2014* and *http://nobelprize.org* **ARTICLES:** ● **Nair, P.** (2012) QnAs with W. E. Moerner, *Proc. Natl. Acad. Sci. USA*, 109(17):6357 ● **Deffke, U.** (2011) Outsmarting optical boundaries, *www.mpg.de/1039625/Opitcal_Boundaries* **Gewin, V.** (2006) Eric Betzig, group leader, Janelia Farm Research Campus, Howard Hughes Medical Institute, Leesburg, Virginia, *Nature*, 450:578 ● **Howard Hughes Medical Institute** Biography Eric Betzig, *www.hhmi.org/scientists/eric-betzig* **LECTURES AND INTERVIEWS:** ● **Betzig, E.** (2012) Day 2 Distinguished Lecture by Dr. Eric Betzig at MF Symposium, *www.youtube.com/watch?v=UqMIL8-eaxk* ● **Interview with Betzig, E.** (2013) Eric Betzig Sequence, *www.youtube.com/watch?v=RfmgDv46sC8* ● **Interview with Hell, S. W.** (2013) Stefan Hell Sequence, *www.youtube.com/watch?v=WjBPFpVu_6I* ● **Interview with Moerner, W. E.** (2013) Alumni Achievement Award: W. E. Moerner, *www.youtube.com/watch?v=VBmgvlATbCc* ● **More references can be found in the Scientific Background:** *http://kva.se/nobelchemistry2014*

Editors: Sven Lidin and Måns Ehrenberg, The Nobel Comittee for Chemistry. Ann Fernholm/Katalys Media, science writer; Clare Barnes, translation; Jessica Balksjö Nannini, editor, and Emil Kling, Nobel assistant, The Royal Swedish Academy of Sciences. **Graphic design:** Ritator **Illustrations:** Johan Jarnestad/Swedish Graphics **Print:** Åtta45

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