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Super-resolution microscopy of neural structure and function

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Advances in microscopy techniques have a habit of triggering important discoveries in the field of neuroscience, starting from the Golgi technique at the end of the 19th century, to electron microscopy in the 1950s, to fluorescent confocal and two-photon microscopy at the close of the 20th century.

By providing higher spatial and temporal resolutions, as well as more contrast and specificity, these ground-breaking techniques have greatly informed our view of how the brain works in terms of underlying cellular and molecular mechanisms.

The advent of super-resolution fluorescence microscopy is the latest spoke in the revolutionary wheel. Recognized with the Nobel Prize in chemistry in 2014 for overcoming the diffraction barrier of light microcopy, it unlocks a new potential to upend biological research at the molecular level.

Indeed, super-resolution techniques like STED, SIM, and SMLM, which provide unfettered optical access to the inner workings of neurons and synapses and enable nanoscale analyses of their molecular organization and dynamics *in situ*, have quickly become ubiquitous in neuroscience research.

Only 10 years after their development in a handful of laboratories, super-resolution microscopy techniques have caught on like wildfire and are now routinely used in a large number of biology labs. However, in as much as super-resolution microscopy has generated widespread enthusiasm, it is important to validate and assess its various methodological incarnations by comparing them with more established approaches, such as EM or molecular biochemistry.

This special section brings together a series of research papers and reviews presenting and discussing recent advances of super-resolution microscopy and their application to a variety of investigations in neuroscience.

Super-resolution microscopy is helping to close the gap between light and electron microscopy of cellular structure. However, correlating molecular information with ultrastructural context with high confidence is extremely difficult and very challenging. Markert et al. have taken up this challenge and present a new method for correlating EM with super-resolution imaging data from electrical synapses in C. elegans.

In addition to producing nanoscale maps of the protein organization on the cell surface or inside organelles, single-molecule-based super-resolution techniques offer unprecedented possibilities of absolute quantification of protein content and numbers in key functional intracellular compartments, including synapses. This exciting prospect is explained in the review article by Patrizio et al., and an elegant application of such quantitative analysis to study the nanoscale organization of synaptic adhesion proteins is presented in the research article by Chamma et al.

Single-molecule-based techniques also make it possible to reveal the molecular dynamics and subsequent molecular interactions with partner proteins. The review by Compans et al. nicely illustrates how super-resolution microscopy can be used to decipher the organization and dynamics of postsynaptic molecules during synaptic transmission.

Dendritic spines are nanoscale protrusions in the dendritic membrane that mediate most excitatory synaptic transmission in the brain. The research paper by Lauterbach et al. details a powerful new combination of live-cell STED microscopy with holographic photostimulation to study the dynamic structure-function relationship of these mesmerizing postsynaptic specializations.

An early hallmark of neurodegenerative diseases is the misfolding and self-aggregation of proteins into amyloid structures that are believed to wreak havoc on neurons and synapses. The review article by Kaminski et al. explains the potential of new optical super-resolution techniques to better understand the molecular mechanism of the pathogenic self-assembly process *in vitro* and inside cells.

We hope you enjoy the full set of papers in this special section.

U. Valentin Nägerl obtained his PhD in neuroscience from UCLA in 2000, and then worked at the Max Planck Institute of Neurobiology in Munich. Since 2009 he has been a professor of bio-imaging and neuroscience at the University of Bordeaux. His team develops and applies super-resolution imaging techniques like STED microscopy to uncover the nanoscale mechanisms of neural plasticity in the living mouse brain. http://www.iins.u-bordeaux.fr/research-teams-valentin-nagerl

Jean-Baptiste Sibarita holds a PhD in physics and is an expert in live-cell microscopy and image processing and analysis. He headed the Cellular and Tissue Imaging Platform of the Curie Institute in Paris for 12 years, before starting his group Quantitative Imaging of the Cell in 2009 at the Interdisciplinary Institute of Neuroscience, Bordeaux, France. http://www.iins.u-bordeaux.fr/research-teams-jean-baptiste-sibarita.